The Literature of Heterocyclic Chemistry, Part VIII, 1999–2001

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I. Introduction

This survey is a sequel to seven already published *in Advances in Heterocyclic Chemistry* (66AHC(7)225, 79AHC(25)303, 88AHC(44)269, 92AHC(55)31, 98AHC(71)291, 99AHC(73)295, 01AHC(79)199). It includes monographs and reviews published during the period 1999–2001 as well as some published earlier but omitted in Part VII.

Like Parts III–VII, this survey is based mainly on short bibliographic papers published by the authors in *Khimiya Geterotsiklicheskikh Soedinenii* since 2002 (02KGS404, 02KGS992, 03KGS447, 03KGS776). Sources not only in English but also in Russian, Japanese, Chinese, Czech, and other languages are surveyed and classified. This feature of the survey should cause no problem because some of the sources are available in English translations and practically all others have informative English abstracts as well as quite understandable and useful schemes and lists of references. As before, carbohydrates are not covered. Such compounds are mentioned only in general cases (e.g., anomeric effect) as well as when carbohydrates serve as starting compounds for the synthesis of other heterocycles or they are present as fragments of a complex system including another heterocyclic moiety such as nucleosides.

II. General Sources and Topics

A. General Books and Reviews

1. *Textbooks and Handbooks*

Handbook of Heterocyclic Chemistry: 00MI1.
Applied homogeneous catalysis with organometallic compounds: 96MI7.
Aqueous-phase organometallic catalysis: 98MI2.
Basic principles of drug design: 00MI15.
Biologically active substances of plant origin (a dictionary in 3 volumes): 01MI79.
Chemistry for pharmacologists and biochemists/pharmacology for chemists and biochemists: 01MI71.
Fundamentals of medicinal chemistry: 01MI67.
Fundamentals of organic chemistry of drugs: 01MI68.
Mass spectrometry of heterocycles: 01MI66.
Organic reaction mechanisms: 99MI19.
Palladium-catalyzed organic reactions: 97MI1.

2. *Annual Reports*

a. Comprehensive Reports. 00PHC1, 01MI145, 01PHC1, 02PHC1.

b. Specialized Reports Devoted to Basic Series of Heterocycles.
Three-membered heterocycles: 00PHC57, 01PHC52, 02PHC52.
Four-membered heterocycles: 00PHC77, 01PHC71, 02PHC75.

Pyrrole and its benzo derivatives: 00PHC114, 01PHC111, 02PHC114.

Furan and its benzo derivatives: 00PHC134, 01PHC130, 02PHC139.

Thiophenes, selenophenes, and tellurophenes: 00PHC92, 01PHC87, 02PHC90.

Five-membered heterocycles with more than one N atom: 00PHC161, 01PHC167, 02PHC180.

Five-membered heterocycles with N and S (Se) atoms: 00PHC185, 01PHC188, 02PHC200.

Five-membered heterocycles with O and S (Se, Te) atoms: 00PHC204, 01PHC205, 02PHC222.

Five-membered heterocycles with O and N atoms: 00PHC219, 01PHC217, 02PHC235.

Pyridine and its benzo derivatives: 00PHC237, 01PHC238, 02PHC257.

Diazines and their benzo derivatives: 00PHC263, 01PHC261, 02PHC279.

Triazines, tetrazynes, and fused polyaza-systems: 00PHC294, 01PHC296, 02PHC310.

Six-membered heterocycles with O and/or S atoms: 00PHC317, 01PHC317, 02PHC332.

Seven-membered heterocycles: 00PHC339, 01PHC340.

Heterocycles with eight-membered and large rings: 00PHC352, 01PHC378, 02PHC356.

c. Reports Devoted to Individual Problems.

Alcohols, ethers, and phenols including cyclic ethers, heterocyclic alcohols and ethers: 00JCS(P1)2529.

Applications of stochiometric transition metal complexes in synthesis and transformations of heterocycles: 00JCS(P1)109.

Catalytic applications of transition metals in organic synthesis (particularly, in syntheses and transformations of heterocycles): 00JCS(P1)3335.

Catalytic asymmetric syntheses of heterocycles: 00JCS(P1)275.

Carbon–carbon bond-forming solid-phase reactions: 99CRV1549, 01CRV137.

Cyclizations of imines into aziridines and β-lactams: 00JCS(P1)125.

Functionalized polymers as reagents for transformations of heterocycles: 00S1035.

Heterocycles as ligands in catalysts for asymmetric synthesis: 00JCS(P1)275.

Heterocycles as ligands in catalytic syntheses of alcohols, ethers, and phenols: 00JCS(P1)2529.

Heterocyclic imines, enamines, and oximes: 00JCS(P1)125.

New methods for the synthesis of heterocycles annelated by three-, four-, five-, six-, and seven-membered saturated and partially unsaturated carbocycles: 00JCS(P1)477.

Δ^3-1,3,4-Oxadiazolines as versatile sources of reactive intermediates: 00JCS(P1)2161.

Preparative biotransformations of heterocycles: 00JCS(P1)611.

Protecting groups in the synthesis and transformations of heterocycles: 00JCS(P1)2495.

Rapid analog syntheses of heteroaromatic compounds: 00JCS(P1)2845.

Recent developments in indole ring synthesis: 00JCS(P1)1045.

Saturated oxygen 3–9-membered heterocycles: 00JCS(P1)1291.

Synthesis of cyclic peptides: 01JCS(P1)471.

Synthesis of heterocycles by radical cyclization: 00JCS(P1)1.

Synthesis of thiols, selenols, sulfides, selenides, sulfoxides, selenoxides, sulfones, and selenones (as well as S- and Se-substituted heterocycles, S- and Se-heterocycles): 00JCS(P1)835, 01JCS(P1)335.

Thin-layer chromatography (with special paragraphs devoted to dyes, pigments, pesticides, drugs, alkaloids, purines, pyrimidines, nucleic acids, toxins, and vitamins): 00AC(12)9R.

3. *Nomenclature*

Comprehension and application of its basic principles: 01M1.

Does CIP nomenclature adequately handle molecules with multiple stereo-elements? A case study of vancomycin and cognates: 01AG(E)701.

Glossary of terms used in combinatorial chemistry: 99PAC2349.

NMR nomenclature. Nuclear spin properties and conventions for chemical shifts (IUPAC recommendations 2001): 01PAC1795.

4. *History of Heterocyclic Chemistry, Biographies*

Jacobus Henricus van't Hoff hundred years impact on stereochemistry: 01AG(E)3783.

History of the discovery of stable nitroxide radicals: 00MI19.

Publication list of Prof. H. B. Kagan: 01T2960.

Scientific biography of Prof. Ya. L. Gol'dfarb: 01KGS3.

5. *Bibliography of Monographs and Reviews*

The literature of heterocyclic chemistry, 1997–1999: 01AHC(79)199.

a. *Specialized Surveys*. 01KGS997, 01KGS409, 02KGS404, 02KGS992, 03KGS447, 03KGS776.

B. General Topics by Reaction Type

Activation of unreactive chemical bonds by metal complexes (a general survey): 99MI26.

Activation of the N–N triple bond in molecular nitrogen and its chemical transformation into organonitrogen compounds: 99MI27.

Annular tautomerism of six-membered heterocycles: 01AHC(81)253.

Applying biological principles to the assembly and selection of synthetic superstructures: 01CSR287.

Cyclic aromatic systems with hypervalent centers, in particular, heterapentalenes: 01CRV1247.

Photophysical and photochemical processes in supramolecular systems: 01MI128.

Quantitative measure of aromaticity for mono-, bi-, tricyclic penta- and hexaatomic heteroaromatic ring systems and their interrelationships: 01CRV1421.

Recent advances in computing heteroatom-rich five- and six-membered ring systems: 01AHC(81)1.

Self-assembly *via* multiple hydrogen bonding interactions in synthetic macromolecular systems: 01CSR83.

Structural aspects of aromaticity: 01CRV1385.

Supramolecular chemistry (general monograph): 99MI5.

Supramolecules with properties of molecular recognition: 01CSR158.

Synthetic cyclopeptides, cyclodextrins, crown-containing compounds as models of cation-conducting channels: 01CSR274.

Three-dimensional aromaticity in polyhedral boranes and related molecules: 01CRV1119.

1. *Structure and Stereochemistry*

a. Theoretical Aspects.

Spectroscopy, structure, and photochemical behavior of carbenes in matrices (heterocyclic carbenes and heterocycles as carbene precursors): 01MI61.

b. Molecular Dimensions.

Contribution of X-ray crystallographic analyses of heterocyclic compounds toward organic chemistry: 99YGK1092.

Powder X-ray diffraction for structure determination of heterocycles: 01AG(E)1626.

Structure investigations of new coordination compounds: 01KK243.

c. Stereochemical Aspects.

A survey of supramolecular chemistry (1993–1994): 96MI2.

Atropoisomerism, particularly, in cyclopeptides: 01CSR145.

Control of reactivity in aggregates of amphiphilic molecules: 96MI3.

Design of self-replicating systems: 96MI5.

Metal template control of self-assembly in supramolecular chemistry: 96MI1.

Nuclear Overhauser effect in structural and conformation analysis of heterocycles and biopolymers: 00MI34.

Stoichiometric asymmetric processes, e.g., synthesis and transformations of heterocycles: 01JCS(P1)95.

Synthesis of hetero-bridged syn-facially fused norbornadienes (“[n]polynorbornadienes”) and their topological diversity: 00EJO3363.

Arene complexes of rare-earth metals, among them complexes with heterocyclic ligands: 00UK856.

Enantioselective nucleophilic catalysis with "planar-chiral" heterocycles (sandwich compounds): 00ACR412.

d. Betaines and Other Unusual Structures.

Diazene-derived cyclic azomethine imines: 00JHC541.

Heterobicyclopentadienyl complexes of group-3 metals: 01EJI891.

Heterocyclic nitrones: 00S759.

Heterocyclic phosphorus ylides: 00PHC22.

C_{60} Hexakisadducts with an octahedral addition pattern (particularly, fullerenoheterocycles): 01EJO829.

Metal–carbene complexes stabilized by ring heteroatoms: 01JOM(617–618)56.

Nonbenzenoid cyclopropanes (including cyclopropaannelated heterocycles): 01EJO849.

Stable heterocyclic carbenes: 00CRV39.

Structure and dynamics of cationic organic π-complexes (three-membered π- and σ-complexes with N-, P-, and Hal-cations): 00ZOR479.

Zwitterions with heterocyclic fragments among them those with metals as heteroatoms: 00EJI577.

e. Miscellaneous Substituted Heterocycles.

Chemistry of *N*-(1-haloalkyl)heteroarylium salts: 00AHC(77)183.

Chemistry of vicinal polycarbonyl compounds among them derivatives of heterocycles: 00CRV1121.

Cyclic diaryliodonium ions: 00CSR315.

Heterocyclic guanidines and guanidine-substituted heterocycles: 01MI134.

Monoorganyl derivatives of tellurium(IV) (heterocycles with Te-containing substituents): 00UK940.

Progress in the synthetic methods of phosphonyl heterocyclic compounds: 00MI23.

Recent trends in the chemistry of fluorinated five- and six-membered heterocycles: 01JHC793.

Six-, seven-, and eight-membered heteryladamantanes: 00ZOR329.

Stability of the metal configuration in chiral-at-metal half-sandwich compounds (with heterocycles as ligands at metal atom): 01EJI905.

Synthesis of photochromic dihetarylethenes: 01KGS19.

2. *Reactivity*

a. General Topics.

Activation of racemic and nonracemic catalysts by their binding with chiral additives among them heterocycles: 00AG(E)3532.

Anion recognition by derivatives of heterocycles: 01AG(E)486.

Application of microwave activation in heterocyclic chemistry: 00KGS1308.

Applications of enzymes in organic solvents for transformations of heterocycles: 00AG(E)2226.

Arene-catalyzed lithiation in transformations of heterocycles: 00EJO225.

Arylation with organolead and organobismuth reagents: 01T5683.

Asymmetric cyclopropanation reactions using chiral metal catalysts with heterocyclic ligands: 00MI53.

Carbanionic reactivity of the anomeric center in carbohydrates: 01CRV81.

Chemical reactions catalyzed by DNA polymerases: 00MI45.

Cine- and tele-substitution reactions: 01T1639.

Degenerate ring transformations in heterocyclic systems: 99AHC(74)1, 00JHC427.

Electrochemical reactions and mechanisms: 00MI6.

Electron transfer in covalently linked supramolecular systems based on organic compounds: 01MI39.

Electron transfer in host–guest and cage-type supramolecular systems: 01MI43.

Electron transfer in hydrogen-bonded donor–acceptor supramolecules: 01MI42.

Electron-transfer reactions of heteroaromatic compounds: 01MI33.

Enzyme-catalyzed reactions of heterocycles: 00MI5.

Formaldehyde N,N-dialkylhydrazones as C_1 building blocks in asymmetric synthesis: 00SL1228.

Fragmentation and cleavage of heterocycles mediated by SmJ_2: 01OPP567.

Heterocycles as reagents and ligands in immobilized heterogeneous catalysts: 95MI1.

Heterocycles in encapsulation and assembly: 00H(52)493.

Heterocyclic carbene protonation: 01MI59.

Metal carbenes in organic synthesis (general monograph): 99MI18.

Nitro compounds in synthesis and transformations of heterocycles: 01MI32.

Organoselenium compounds in stereoselective reactions of heterocycles: 00AG(E)3740.

Origin of π-facial diastereoselection in carbonyl addition, application of the exterior frontier orbital extension model to 1,3-diheteran-5-ones (heteroatom = O,S): 00H(52)1435.

Photochemical dimerization in solution of heterocyclic substituted alkenes bearing an electron-withdrawing group: 01H(54)475.

Prototropic tautomerism of heteroaromatics: 00AHC(76)1.

Reactions in high-temperature aqueous media: 01CRV837.

Reactions of alkyl carbonates with heterocycles and use of cyclic carbonates in synthesis: 00T8207.

Reactions of ketone analogs $RR'M=X$ (M = Ge, Sn, Pb; X = S, Se, Te) with heterocycles: 00ACR625.

Reactions of some heterocycles with XeF_2 as fluorinating reagent and radical initiator: 01UK262.

Recent advances in chemo-, regio- and stereoselective hydroformylation: 01S1.

Role of metal–oxygen intermediates in biological and chemical alkane monooxygenations: 01IZV1712.

Selective reactions of amino groups in polyamino compounds (particularly those in heterocyclic polyamines) by metal-chelated or -mediated methods: 01T4801.

Self-assembly of cyclic nanostructures mediated by transition metals: 00CRV853.

α-Silyl ketone controlled asymmetric syntheses with participation of heterocycles: 00SL1371.

Solvent-free organic syntheses among them syntheses with participation of heterocycles: 00CRV1025.

Structures, properties, and synthetic applications of heterocyclic sulfoximines: 00S1.

Supercritical fluids in synthetic organic chemistry (including reactions of heterocycles in supercritical CO_2): 01JCS(P1)917.

Tandem transformations with participation and formation of heterocycles initiated and determined by Michael reaction: 00UK1091.

Tautomerism of five-membered heterocycles with one heteroatom: 00AHC(76)85.

Tautomerism of five-membered heterocycles with two or more heteroatoms: 00AHC(76)157.

Tautomerism involving other than five- and six-membered rings: 00AHC(77)1.

Tautomerism of fused five–six, five–five, and six–six ring systems with heteroatoms in both rings: 00AHC(77)51.

Transition-metal catalyzed multi-component carbocyclization and related reactions with participation of heterocycles: 99YGK912.

Vinylogous aldol reaction of heterocyclic silyloxy dienes and its synthetic application: 00PAC1645.

Water-accelerated organic transformations: 01CC299.

b. Reactions with Electrophiles and Oxidants.

Acetylenic coupling of alkynyl-substituted heterocycles including construction of macrocycles: 00AG(E)2632.

Addition of metal derivatives of five-membered heterocycles to chiral nitrones: 00SL442.

Application of Vilsmeier reagents in organic synthesis including acylation, chlorination, chloroformylation, aromatization, and dehydration reactions of heterocycles: 00MI51.

Reactions of perfluoroalkyl halides with heterocyclic derivatives: 00UK538.

Structure and reactivity of nitrozonium complexes of organic compounds including azines, crown ethers, and heterocyclic cations from NO^+ and olefins or arenes: 01UK241.

Vinylogous Mannich reactions: 01T3221.

c. Reactions with Nucleophiles and Reducing Agents.

Nucleophilic trifluoromethylation reactions of organic compounds (in particular, heterocycles) with (trifluoromethyl)trimethylsilane: 00T7613.

Reactivity of copper(I) complexes with heterocyclic ligands towards dioxygen: 00EJI2311.

Translocation of heteroatoms in rings and its role in Dimroth rearrangement of heterocycles: 00AHC(75)79.

d. Reactions toward Free Radicals, Carbenes, etc.

Cyclic nitroxide radicals: 01MI5.

Cyclization of alkoxyl radicals: 01MI12.

Enantioselective radical-mediated reactions of carbonyl derivatives of some heterocycles with organotin reagents: 01YGK560.

Homolytic aromatic substitution in heterocyclic series: 01MI3.

Hydrogen atom abstraction: 01MI8.

Isonitriles as useful trap in radical reactions leading to heterocycles: 01MI2.

Nitrogen-centered radicals: 01MI11.

Radical cyclizations in alkaloid synthesis: 01MI9.

Radical reactions of heterocycles on solid support: 01MI4.

Rearrangements of epoxides: 01MI7.

Sulfur-centered radicals: 01MI13.

Synthesis of oxacyclic natural products: 01MI10.

Unusual radical cyclizations: 01MI6.

e. Reactions with Cyclic Transition State.

Cycloadditions (including those with participation and formation of heterocycles) under microwave irradiation conditions: 00EJO3639.

Diels–Alder reactions in water: 00PAC1365.

Olefin metathesis and related reactions in carbohydrate chemistry (formation and ring opening of heterocycle): 00CC519.

Recent advances in Lewis acids catalyzed hetero-Diels–Alder reactions in aqueous media: 01EJO439.

Stereoselective 1,3-dipolar cycloadditions to heterocyclic compounds; 00JHC551.

f. Heterocycles as Intermediates in Organic Synthesis.

Asymmetric synthesis by Diels–Alder reaction with participation of (*S*)-N-acryloylindoline: 01PAC283.

Chiral P,N-bidentate ligands in coordination chemistry and organic catalysis with participation of rhodium and palladium (P,N-bidentate phosphorus containing 4,5-dihydrooxazoles as ligands): 00UK721.

Enantioselective catalysts with heterocyclic ligands: 01AG(E)284.

Functionalized polymers (among them polymers with grafted heterocyclic residues, which are used for automated combinatorial synthesis): 01AG(E)650.

Heterocycles as chiral auxiliary substances and ligands in reactions of enolates: 00T917.

Heterocycles as ligands in carbene complexes using as catalysts of olefin metathesis: 00AG(E)3012.

Heterocycles as reagents for introduction of protective groups: 00T2339.

N-Heterocycles, crown ethers and their analogs as additives promoting selectivity and activity of lipases in reactions of esterification and esters hydrolysis: 00T2905.

N-Heterocyclic carbenes in transition-metal-complex synthesis: 00JOM(600)12.

Heterocyclic protective groups: 00T2339.

N-Fluorinated heterocycles as fluorinating agents: 00MI13.

Formylation of carbohydrates using reactions of 2-lithiumthiazole or 2-lithiumbenzothiazole with sugar lactones followed by deoxygenation of ketones obtained and CHO group formation from thiazole fragment: 00PAC1577.

Glyoxylic acid derivatives in asymmetric synthesis (N-glyoxyl-(2*R*)-bornane-10,2-sultam as a key compound): 00PAC1589.

Heterocycles in derivatization reactions in capillary electrophoresis of amino acids: 00CLY347.

Heterocycles in the synthesis of carbosubstituted conjugated dienes: 01UK830.

Heterocyclic acyl and formyl anion equivalents: 01AHC(79)89.

Late-metal catalysts (with heterocycles as ligands) for ethylene homo- and copolymerization: 00CRV1169.

Modelling the hydrodenitrogenation of aromatic N-heterocycles in the homogeneous phase: 01EJI43.

New trends in peptide coupling reagents (heterocycles as reagents): 01OPP203.

Preparation of achiral and enantiopure geminally disubstituted β-amino acids for β-peptide synthesis (heterocycles in synthesis of β-amino acids): 00EJO1.

Preparation of mono-, 1,1-di-, *trans*-1,2-di- and trisubstituted ethylenes by benzotriazole methodology: 01SL458.

Recent advances in catalytic enantioselective Michael additions (catalysts with heterocyclic ligands): 01S171.

Synthetic application of chiral pool derived heterocycles: 00JHC509.

Synthetic applications of electrochemical reduction of allyl ethers in the presence of nickel complexes with bipyridines and tetraazamacrocycles as ligands: 00CCC844.

3. *Synthesis*

a. General Topics, Nonconventional Synthetic Methodologies.

Advances in selenocyclofunctionalization reactions (synthesis of N-heterocycles, selenolactonization, and formation of macroheterocycles): 01T1411.

Application of enzymes in organic solvents for syntheses of heterocycles: 00AG(E)2226.

Application of microwave irradiation in the synthesis of heterocyclic compounds: 01MI136.

Arene-catalyzed lithiation in the synthesis of heterocycles: 01SL1197.

Asymmetric synthesis of heterocycles, in particular, asymmetric epoxidation and hetero-Diels–Alder reactions: 01MI148.

Baylis–Hillman reaction (condensations of aldehydes with α,β-unsaturated carbonyl compounds or nitriles) with participation and formation of heterocycles: 01MI142.

Benzotrifluoride and derivatives as solvents for organic synthesis and fluorous synthesis: 99MI14.

Carbene complexes of transition metals containing 1,3-butadienyl fragment in syntheses of heterocycles: 00EJO17.

Catalyzed asymmetric arylation reactions (with participation or formation of heterocycle): 01AG(E)3284.

Chiral nitrone reagents for cycloaddition reactions: 00JHC481.

Click chemistry (diverse chemical function from a few good reactions): 01AG(E)2007.

Design and management of organic syntheses through free-radical cascade processes: 01AG(E)2224.

Development of general-purpose chiral synthons from carbohydrates: 00CRV4267.

Electrophile-induced 5-*endo* cyclizations: 02PHC19.

Electrophilic nature of carbenoids, nitrenoids, and oxenoids ([1 + 2] cycloaddition reactions): 01CRV697.

Enantioselective organocatalysis (heterocycles as ligands and auxiliary compounds): 01AG(E)3726, 01CRV757.

Formation of heterocycles on insertion of carbenes into C−H bonds of alkoxides: 01MI64.

Hydrogen bonding in noncovalent synthesis of molecular strands, oligomers with heterocyclic fragments: 01T1139.

Increase in intricacy as a tool for evaluating organic syntheses: 01T6855.

Intramolecular free-radical conjugate additions: 01T7237.

Kinetic resolutions by means of cycloaddition reactions: 01EJO2999.

Metal catalysis in water: 99MI12.

Modern solvent systems in industrial homogeneous catalysis: 99MI16.

Multicomponent reactions with participation of isonitriles in syntheses of heterocycles: 00AG(E)3168.

New methodology of electrophilic addition reaction as a method for "assembling" polyfunctional compounds from simple precursors (cyclic vinyl ethers, thiiranium, and thiophanium ions in electrophilic addition reactions): 01IZV1862, 01MI129.

Noncovalent synthesis using hydrogen bonding: 01AG(E)2382.

Novel heterocyclic construction via dipolar cycloadditions to 1,2-dicarbonyl compounds: 00JHC659.

Olefin metathesis in synthesis of heterocycles including macrocycles: 00AG(E)3012.

Organic synthesis (basic principles): 98MI1, 01MI31.

Organometallic chemistry directed towards organic synthesis (heterocyclization of functionalized allenes, carbopalladation of 1,1-dibromoalk-1-enes to give fused heterocycles): 01MI131.

Palladium in the synthesis of heterocycles: 00T5959.

Perfluorinated solvents as novel reaction medium in organic chemistry: 99MI13.

Polymer-supported catalysis in synthetic organic chemistry: 01T4737.

Preparative biotransformations with participation and formation of heterocycles: 01JCS(P1)1475.

Radical translocation reactions in synthesis of heterocycles: 01CSR94.

Reactions in ionic liquids (mainly in N-alkylpyridinium and 1,3-dialkylimidazolium salts): 00PAC1391, 00PAC2275, 01CC2399.

Reactions in supercritical carbon dioxide ($scCO_2$): 99MI15.

Recent progress in the chemistry of multicomponent reactions (syntheses of heterocycles): 01PAC187.

Regeneration of carbonyl compounds from the corresponding oximes: 01S1903.

Ring expansion reactions of phenylnitrene: 01MI63.

Self-assembling of heterocycles: 00CRV3483.

Silica gel in organic synthesis, particularly, in formation and transformation of heterocycles: 01UK1094.

Silylation as new strategy of using of aliphatic nitro compounds in organic synthesis (cyclic silyl nitronates, heterocyclization): 01IZV1850.

π-Shielding in organic synthesis, particularly, in Diels–Alder reactions: 01T7999.

Since 1995 the new chemistry of multi-component reactions and their libraries including their heterocyclic chemistry: 00JHC647.

Solid-phase reactions with C–C bond formation in syntheses of heterocycles: 99CRV1549.

Solvent-free syntheses of heterocycles: 99MI17, 00CRV1025.

Syntheses of cyclic iodonium salts and other heterocycles from alkenyliodonium salts: 00UK118.

Syntheses of diverse and complex molecules, among them heterocycles, on the solid phase: 00ACR215.

Synthesis of heterocycles from molecular nitrogen as a nitrogen source: 00JHC623.

Syntheses of heterocycles induced by microwave irradiation: 01PAC147, 01PAC193.

Synthesis and application of fluorinated heterocycles: 01MI65.

Synthetic methodologies derived from electron-defficient alkynes (with participation and formation of heterocycles): 01MI130.

Transition-metal catalyzed multi-component carbocyclization and related reactions of bifunctional molecules with the formation of heterocycles: 99YGK912.

Three-component Ni-catalysed cyclizations, couplings, and cycloadditions (among them syntheses of heterocycles): 00ACR467.

Various aspects of the reaction of a chiral catalyst or reagent with a racemic or enantiopure substrate: 01T2449.

Water as solvent in organic synthesis: 99MI11.

b. Synthetic Strategies and Individual Methods.

Applications of aliphatic unsaturated non-proteinogenic α-H-α-amino acids (including heterocyclizations): 00JCS(P1)4197.

Asymmetric hetero-Diels–Alder and related reactions: 99MI24.

Development of asymmetric synthesis of heterocycles: 99YZ787.

Diacetylene-based industrially promising syntheses of heterocycles: 00UK642.

Formation of heterocycles in nucleophilic addition to nitrones: 00S759.

Junjappa-Ila heteroaromatic annelation: 01PHC1.

Linkers and cleavage strategies in solid-phase organic synthesis and combinatorial chemistry: 00CRV2091.

Methods for the synthesis of conjugated ω-aminoketones containing heterocyclic fragments: 00UK1111.

Multi-step organic synthesis using solid-supported reagents and scavengers (including synthesis of heterocycles): 00JCS(P1)3815.

New applications of polyfunctional organometallic compounds in synthesis of heterocycles: 00AG(E)4414.

Nucleophilic addition/ring closure sequence for the stereocontrolled synthesis of heterocycles: 99MI2.

Nucleophilic vinyl substitution in the synthesis of heterocycles: 01KGS41.

Palladium-catalyzed heterocyclizations reactions of allenes: 00CRV3067.

Polymeric scavenger reagents in organic synthesis (including synthesis of heterocycles): 01EJO1213.

Preparation of optically active derivatives of heterocycles as a result of autocatalysis: 00CC887.

Protecting groups: 00MI3.

Radical addition of organohalides to multiple bonds in the synthesis of heterocyclic compounds: 01KGS570.

Solid-phase asymmetric synthesis of heterocycles and heterocycles as auxiliary reagents: 01MI126.

Soluble polymer supported synthesis and transformations of heterocycles: 00ACR546.

Synthesis of heterocyclic and carbocyclic compounds via alkynyl, allyl, and propargyl organometallic cyclopentadienyl iron, molybdenium and tungsten complexes: 00CRV3127.

Syntheses of heterocycles using metathesis reactions: 01MI104, 01MI127.

Synthesis of heterocyclic compounds from metallated unsaturated compounds and isothiocyanates: 00KGS1443.

Synthesis of monotrifluoromethyl-substituted saturated heterocycles: 00T3635.

Synthesis of sterically hindered heteroaromatic ketones under conditions of phase transfer and metal complex catalysis: 01KGS8.

Thermolysis of N-vinylimino ylides and syntheses of mesomeric betaines involving back-donated 1,6-cyclization: 00YZ630.

Transannular Diels–Alder strategy applied to total synthesis (transformations of macroheterocyclic trienes): 01T4243.

c. Versatile Synthons and Specific Reagents.

Alkyl 2-substituted 3-(dimethylamino)propenoates and related compounds as versatile reagents in heterocyclic chemistry: 00SL1077.

Chiral acetylenic sulfoxides and related compounds in heterocyclic synthesis: 99MI3.

Derivatives of γ-halocrotonic acids, convenient reagents in the synthesis of heterocycles: 00KGS435.

α-Diazo-β-dicarbonyl compounds in synthesis of heterocycles: 01MI140.

Early transition metal carbenoid reagents in epimetallation and metallative dimerization of unsaturated substrates (synthesis of heterocycles with participation of carbenoid reagents): 01JOM(617–618)148.

α-Halosulfones in the synthesis and transformations of heterocycles: 01SL1.

(Het)aroylpyruvic acids and their derivatives as promising "building blocks": 01UK1039.

Organohypervalent iodine compounds in the synthesis of heterocycles: 01SL565.

α-Silyl ketone controlled asymmetric syntheses of heterocycles: 00SL1371.

Stereoselective syntheses of heterocycles with lithiated methoxyallene: 00JHC597.

Sulfamides in the synthesis of heterocyclic compounds: 00UK239.

N-Sulfonyl imines—useful synthons in stereoselective organic synthesis: 99MI4.

Syntheses of heterocycles by aza-Wittig reaction: 01MI139.

Syntheses and transformations of heterocycles with participation of triflyc anhydride: 00T3077.

Synthetic applications of the dearomatization agent pentaammineosmium(II): 01T8203.

Transition metal reagents and catalysts: 00MI2.

Using ring-opening reactions of oxabicyclic compounds as a strategy in organic synthesis: 99MI1.

d. Ring Synthesis from Nonheterocyclic Compounds.

Acetylenic and allenic sulfones in syntheses of heterocycles by 1,3-dipolar cycloaddition: 01T5263.

Acylic stereocontrol between remote atom centers via intramolecular and intermolecular stereo-communication (formation of heterocycles): 01T2917.

Addition of carbon-centered radicals to imines and related compounds (heterocyclizations): 01T5461.

Aromatic nucleophilic denitrocyclization, particularly, in synthesis of heterocycles: 01CLY540.

Asymmetric 1,3-dipolar cycloadditions for the construction of enantiomerically pure heterocycle: 01OPP103.

Brook rearrangement in tandem bond formation strategies (formation of heterocycles as the result of $C \rightarrow O$ or $O \rightarrow C$ migrations of silyl groups): 01T2065.

Catalytic enantioselective rearrangements and cycloadditions involving ylides from diazo compounds: 01CSR50.

Combinatorial methods for optimization of Diels–Alder aza-reaction, epoxidation and other transformations leading to heterocycles: 01S1431.

Conformations of open-chain compounds favorable for heterocyclization and annelation: 00AG(E)2054.

Diels–Alder reactions on solid supports: 01T7053.

β-Halovinylaldehydes as versatile reactive intermediates in the syntheses of polycyclic fused heterocycles: 00H(53)941.

Metal mediated carbometallation of alkynes and alkenes containing adjacent heteroatoms (reactions are accompanied by heterocyclization): 01T5899.

New routes to heterocycles from unsaturated carbanions, heterocumulenes and thiocarbonyl compounds: 01EJO4569.

4- and 5-Oxocarboxylic acids as versatile synthons for the preparation of heterocycles: 00H(53)1379.

Perfluorinated acyl(aroyl)pyruvates as building blocks for the synthesis of heterocycles: 00H(52)1411.

Radical aryl migration reactions leading to formation of heterocycles: 01T9649.

Reactions of conjugated haloenolates with nucleophilic reagents (formation of heterocycles): 01T2643.

Recent advances in the synthesis of heterocycles from oximes: 00H(53)2285.

Ring closure reactions of suitably *ortho*-substituted maleanilic acids in synthesis of heterocycles: 00H(53)476.

Sulfur ylides in the synthesis of hetero- and carbocyclic compounds: 01UK744.

Synthesis of heterocycles based on ketones of adamantane series: 01ZOR489.

Synthesis of heterocycles based on reactions of acetylacetaldehyde with aromatic and biogenic amines and indoles: 01H(55)1365.

Synthesis of heterocycles by C–C bond-formation and its application: 01MI105.

Ynamines and ynamides in synthesis of heterocycles: 01T7575.

e. Syntheses by Transformation of Heterocycles.

Formation of fused heterocycles from acetylenic or allenic sulfones and pyrroles or furans as dienes: 01T5263.

Syntheses of carbohydrate related compounds by using aldolase-catalyzed reaction, in particular, transformations and syntheses of heterocycles: 00YZ42.

4. *Properties and Applications (Except Drugs and Pesticides)*

a. Dyes and Intermediates.

b. Substances with Luminescent and Related Properties.

Advances and prospects of organic photochromics: 01MI133.

Chiroptical molecular switches (photochromic compounds among them dihetarylethenes, fulgides, and spiropyrans permitting undestructive read-out of information using change of optical rotation: 00CRV1789.

Crown ethers and their analogs as luminescent sensors: 01PAC503.

Diaryl- and dihetarylethenes for memories and switches: 00CRV1685.

Electron-transfer dyads suitable for novel self-assembled light-harvesting antenna/electron-transfer devices (bacteriochlorin-fullerene dyad): 01PAC469.

Fluorescent chemosensors containing polyamine receptors (mainly polyheterocyclic amines: 00EJI2143.

Luminescent iridium(III) polyimine complexes with heterocycles as ligands: 00CSR385.

Organic photochromism (IUPAC Technical Report summarizing data on terminology in the field and classification of photochromic compounds): 01PAC639.

Photoactive molecular wires based on metal complexes with 2,2′-bipyridine, phenathroline, and 2,2′:6′,2-terpyridine as ligands: 00CSR1.

Three-dimensional optical data storage using photochromic materials (spirobenzopyrans, dihetarylethenes, azobenzene derivatives: 00CRV1777.

Use of luminiscence probes for spectral characterization of polymer matrices: 01CLY102.

c. Organic Conductors (Except Polymers).

Electron transfer in molecular wires based on metal complexes: 01MI50.

Heterocycles as conductive molecules: 97MI2.

Oligothienylenevinylenes as a new class of multinanometer linear π-conjugated systems for micro- and nanoelectronics: 00ACR147.

Protonic molecular wires containing metal complexes: 01MI52.

d. Coordination Compounds.

Aromatic interactions in complexes formed by heteroaromatic compounds: 01JCS(P2)651.

Axially chiral bidentate heterocyclic ligands in asymmetric catalysis: 01T3809.

Chiral catalysts with heterocyclic ligands and asymmetric synthesis of heterocycles with participation of metal carbene complexes: 01JOM(617–618)98.

Cyclophosphazenes as scaffolds for the construction of multi-site coordination ligands: 01CSR193.

Electron transfer in covalently linked supramolecular systems containing metal complexes: 01MI41.

Electron-transfer processes in mononuclear polypyridine-type metal complexes: 01MI34.

Enantioselective acyl transfer using chiral cyclic phosphines as ligands in catalysts: 01SL1499.

Heterocycles as ligands in complexes of radioactive elements: 01UK974.

Luminescent carbon-rich rhenium(I) complexes with 2,2′-bipyridine ligands: 01CC789.

Oxygen scavenging metal chelates with heterocyclic ligands: 01CSR205.

Progress in catalytic asymmetric hydrogenation (asymmetric hydrogenation of N- and O-heterocycles, heterocycles as chiral ligands in catalysts: 01MI132.

Strategies for the construction of supramolecular compounds through coordination chemistry (heterocycles as ligands): 01AG(E)2022.

Tris-2,2′-bipyridinecomplex of ruthenium(II) as chlorophyll model in photosystem (II): 01CSR36.

Union of planar complexes with N-heterocyclic ligands to three-dimensional complexes: 01CC509.

e. Polymers.

Foldamers, polymers existing in specific compact conformation, among them are olygopyridines and nucleotide mimics: 01CRV3893.

New polymer synthesis by nitroxide mediated living radical polymerizations: 01CRV3661.

Polyaniline and polypyrrole as representatives of conducting polymers: 01CLY484.

Polymer monolayers and Langmuir-Blodgett films of conducting oligo- and polythiophenes: 00UK963.

Supramolecular polymers with N-heterocyclic monomeric units: 01CRV4071.

Synthesis and molecular electronic properties of oligomers with alternating 2,5-thienylene and ethynylene subunits: 00ACR791.

Synthesis of polymeric enzyme-like catalysts with N-heterocyclic fragments as active centers: 01SL1343.

Synthesis of ultrapure, processable, and high-mobility organic transistor semiconductors (thiophene oligomers, anthradithiophenes, benzodithiophenes, phtalocyanins, polythiophenes): 01ACR359.

f. Miscellaneous.

Bis(ethylenedithio)tetraselenafulvalene (BETS) as a source of molecular magnetic superconductors: 00CSR325.

Electron-transfer approaches to an optically controlled molecular switch: 01MI51.

Electron transfer-based molecular logic gates: 01MI53.

Electron transfer-based molecular antennas: 01MI54.

Electron transfer in molecular memory devices: 01MI55.

Electron transfer in nonlinear optics: 01MI56.

Ionic liquids (mainly pyridinium and imidazolium salts) as new "solutions" for transition metal catalysis: 00AG(E)3772.

Photochromic fulgides, fulgimides and related compounds for memories and switches: 00CRV1717.

Photochromic spiropyrans and spirooxazines for memories and switches: 00CRV1741.

Protein crystals cross-linked by compounds with pyridine and/or succinimide fragments as novel catalytic materials: 01AG(E)2204.

Switching devices based on interlocked molecules, catenanes with heterocyclic fragments: 01ACR433.

Syntheses and properties of functionalyzed dendrimers containing heterocyclic fragments: 00UK699.

C. Specialized Heterocycles

1. *Nitrogen Heterocycles (Except Alkaloids)*

a. General Sources and Topics.

Advances in the chemistry of azatricyclo[4.3.1.1.^{3,8}]undecane (4-azahomoadamantane): 01ZOR959.

Cyclic N-acyliminium salts and related intermediates: 00T3817.

Nitrogen-containing ligands for asymmetric homogeneous and heterogeneous catalysis: 00CRV2159.

Nitrogen pyramidal amides (N-benzoyl-7-azabicyclo[2.2.1]heptanes): 01YZ65.

Sulfonimidic acids and their derivatives (S,N-heterocyclic sulfonimides): 00ZOR167.

Synthesis and chemistry of bridgehead azabicycloalkenes: 01AG(E)820.

b. Structure and Stereochemistry.

Cyclic azomethines and their hydrogenated derivatives: 00KGS579.

Synthesis of neutral π-allylpalladium complexes having bisnitrogen ligands (mainly, those related to 2-(pyrazol-3-yl)pyridine, 2-(imidazol-2-yl)pyridine, and 2,2-bipyridine) and palladium-catalyzed cyclopropanation of ketene silyl acetals with allylic acetates: 00YGK736.

c. Reactivity.

Catalysis of isomerization of amides, derivatives of cyclic amines: 00ACR849.

ortho-, *meta*-, and *para*-Cyclizations in structure modifications of π-deficient azaaromatic compounds: 01MI99.

Cyclic imines with glycine or alanine fragment as templates for asymmetric synthesis of α-amino acids: 00EJO2689.

Exploring the chemistry of 3-substituted 2-azanorbornyls in asymmetric catalysis: 00SL1092.

Reactions of highly electrophilic fluoro-containing compounds with cyclic enamines, isoquinoline, quinoline, pyridine and indole derivatives: 01MI77.

Some aspects of the Lewis base and ligand behavior of N-heterocyclic carbenes: 01JOM(617–618)105.

Strategies of the regioselective N-functionalization of tetraazacycloalkanes: 00SL561.

d. Synthesis.

Allylic boron and zinc derivatives in synthesis of nitrogen heterocycles: 00PAC1641.

Amidoalkylating agents in the synthesis of N-heterocycles: 92MI1.

Annelation of azomethines with β-di- or β,β′-tricarbonyl compounds: 01MI75.

Bis-triazenes as precursors of heterocycles: 01OPP59.

Catalytic asymmetric hetero-Diels–Alder reactions of imines: 00AG(E)3558.

Diels–Alder reactions of 1-azadienes: 00T5259.

Heterocyclizations of trisubstituted formamidines containing aryl or hetaryl substituent at the imine N-atom: 00UK924.

Metallation-based functionalization of azines and azoles: 01EJO3975.

6-Methylenecyclohexa-2,4-diene-1-imines (aza-*ortho*-xylylenes), their syntheses, valence isomerization to benzazetines, and application to the synthesis of heterocycles: 01EJO3587.

Organosilane-induced synthesis and functionalization of sulfur-containing N-heterocycles: 00EJO2171.

Rhodium(II) mediated cyclizations of diazo alkynyl ketones: 01JOM(617–618)3.

Phosphonium reagents for the synthesis of nitrogen heterocycles: 01MI89.

Stereoselective C–C bond formation and cyclizations of biradicals (with formation of pyrrolidine or piperidine rings): 00PAC1623.

Syntheses and applications of optically active N-bicyclic compounds: 00YZ1117.

Synthesis and properties of nitrogen heterocycles containing a spiro cyclopropane fragment: 00UK507.

Synthesis of N-heterocycles by Diels–Alder cycloaddition of α,β-unsaturated N,N-dimethylhydrazones: 01H(54)1095.

Synthesis of lactams using trasition metal catalysis of selective cyclocarbonylation reactions: 00SL161.

Use of polyvalent-iodine compounds in the synthesis of nitrogen-containing heterocycles: 00MI30.

2. *Oxygen Heterocycles*

a. Chemistry of Individual Classes of O-Heterocycles.

Cyclic ethereal oxonium ylides: 00YGK934.

Chemistry of bridgehead oxabicycloalkenes: 01AG(E)820.

b. Reactivity.

Organosilane-induced synthesis and functionalization of sulfur-containing O-heterocycles: 00EJO2171.

c. Synthesis.

Asymmetric synthesis of O-heterocycles: 00JCS(P1)1785.

Catalytic asymmetric hetero-Diels–Alder reactions of carbonyl compounds: 00AG(E)3558.

The effect of ring strain on the ease of lactonization of bifunctional chain molecules: 00EJO3117.

Heterocyclization on alkylation of phenols with terpenoids leading to partially hydrogenated polycyclic fused furans and pyrans: 00KPS198.

Intramolecular [4 + 3] cycloaddition reaction, in particular, with participation of furan derivatives: 01ACR595.

Oxygen-containing heterocyclic compounds on the base of 1,5-diketones: 00KGS1155.

Photoinduced [2 + 2] cycloaddition of double C=O bonds to triplet benzene derivatives: 01ACR1.

Synthesis of lactones by transition metal catalysis of selective cyclocarbonylation reactions: 00SL161.

Syntheses of O-heterocycles by Co-mediated cyclizations, particularly, by Pauson-Khand reaction: 00JCS(P1)1657.

Synthesis of oxygen heterocycles via alkynyltungsten compounds: 01PAC265.

3. *Sulfur Heterocycles*

a. Chemistry of Individual Classes of S-Heterocycles.

Sulfonimidic acids and their derivatives (S,N-heterocyclic sulfonimides): 00ZOR167.

b. Structure and Stereochemistry.

New aspects of hypervalent organosulfur compounds: 99MI9.

Sulfur radical cations: 99MI8.

c. Reactivity.

Cyclic sulfites and cyclic sulfates in organic synthesis: 00T7051.

d. Synthesis.

Asymmetric [4 + 2] cycloadditions mediated by sulfoxides: 99MI6.

Organosilane-induced synthesis and functionalization of S-heterocycles: 00EJO2171.

Synthesis of vinyl sulfoxides, derivatives of S-heterocycles: 00ZOR11.

Thiocarbonyl compounds as specific tools for organic synthesis: 99MI7.

D. Natural and Synthetic Biologically Active Heterocycles

1. *General Sources and Topics*

Bioactive natural products: 00MI33.

Biodegradable polymeric materials based on starch: 00UK494.

Chem-Bioinformatics and QSAR: 01CRV619.

Forensic science: 99AC(12)235R.

Metal ion effects in isotopic hydrogen exchange in biologically important heterocycles: 00ACR672.

Molecular recognition of photoinduced electron transfer fluoroionophores: 00H(52)945.

QSAR and QSPR in nitrogen heterocycles: 01MI90.

Role of metal–oxygen intermediates in biological alkane monooxygenations: 01IZV1712.

Stereocontrolled additions to dihydropyridines and tetrahydropyridines as an access to N-heterocycles related to natural products: 01AHC(78)269.

Structure–property relationships in functional conjugated oligomers: 99PAC2053.

The chelate effect in binding, catalysis, and chemotherapy: 00PAC333.

Three-dimensional database searching of bioactive compounds and their application: 00YGK676.

a. Biological Functions of Natural and Synthetic Bioactive Heterocycles.

Free-radical mechanisms of biological action of nitrofurans: 00MI39.

Hemoglobin as oxygen carrier: 01CRV2797.

Models of hemoprotein active sites: 96MI4.

Nitrogen heterocycles as ligands of serotonin receptors: 01MI85.

Synthetic hydrogen-bonding receptors (heterocycles) for biologically essential monosaccharides: 00YGK1077.

Thermodynamic aspects of molecular recognition in solutions of crown ethers, cryptands and cyclodextrins: 01MI80.

b. General Approaches to Syntheses of Biologically Active Heterocycles.

A novel synthesis of porphobilinogen, synthetic and biosynthetic studies: 00JHC487.

Application of chiral (*salen*)Co in catalytic asymmetric reaction and natural product syntheses: 00MI26.

Biological activity of 5- and 6-membered azaheterocycles and their synthesis based on 5-aryl-2,3-dihydrofuran-2,3-diones: 01KGS291.

Boron Heterocycles as Platforms for Building New Bioactive Agents: 00PHC1.

Carbohydrates in the synthesis of natural products: 01AG(E)1576.

Concepts for the total synthesis of deoxy sugars: 01S507.

Development of synthetic methods for 4-substituted indoles and their applications for the syntheses of natural products: 00YZ363.

Efficient synthesis of organometallics of pyridine quinolines and diazines: new synthetic methodologies for azaaromatic biomolecules: 00JHC615.

Electrophile-induced cyclizations in syntheses of physiologically active azaheterocycles: 00JHC607.

Heterocycles in synthesis of insect pheromones: 01MI69.

Nickel-catalyzed cyclization of 1,3-dienes with a tethered carbonyl group and its application to synthesis of natural products: 01YGK576.

Pauson–Khand reaction and related [2 + 2 + 1] cycloadditions in the syntheses of some natural heterocycles: 00T3263.

Reactions of 1,3-dipolar cycloaddition of nitrile oxides in synthesis of natural compounds and their analogs: 01UK730.

Rearrangements of sulfoxides and sulfones in total synthesis of natural compounds: 01UK1013.

Silyloxy-Cope rearrangement of *syn*-aldol products (formation of tetrahydropyrans and piperidines used in syntheses of natural compounds): 01SL1079.

Solid-phase synthesis of oligosacharides and glycoconjugates: 00UK869.

Stereoselective total synthesis of axially chiral natural products via biaryl lactones: 01ACR615.

Sulfones and sulfoxides including heterocyclic ones in total synthesis and transformations of biologically active natural compounds: 00UK403.

Survey of the most important achievements of the twenty century in the field of total synthesis of natural compounds: 00AG(E)44.

Synthesis of cyclopropane ring-containing natural products: 01T8589.

Syntheses of biologically active azine and azole derivatives: 01MI91.

Syntheses of natural saturated O-heterocycles with bicobalt hexacarbonyl complex of acetylene: 00YGK25.

Synthesis of biologically active natural heterocycles using metal-mediated key reactions: 00YZ1035.

Synthesis of 2-deoxyglycosides; 1988–1999: 00T8385.

Tartaric acid and tartrates in the synthesis of bioactive molecules: 01S1281.

The β-alkyl Suzuki–Miyaura cross-coupling reaction in natural product synthesis: 01AG(E)4544.

The efficient total synthesis of bioactive microbial natural heterocycles: 00YGK828.

Total syntheses of the 1990s: 00AG(E)1538.

2. *Alkaloids*

a. General.

Alkaloids as chirality transmitters in asymmetric catalysis: 00MI7.

Biological activity of alkaloids (a microreview): 01MI103.

Isolation, total synthesis, and biological activity of phenanthroindolizidine and phenanthroquinolizidine alkaloids: 01S2365.

b. Structure.

Structure and synthesis of antimalarial quinazoline alkaloid febrifugine: 01YGK569.

c. Synthesis.

Development of intramolecular oxidative phenolic coupling reactions using hypervalent iodine(III) reagents and their application to the synthesis of *Amaryllidaceae* alkaloids: 00YZ1061.

Efficient stereoselective syntheses of piperidine, pyrrolidine, and indolizidine alkaloids: 99YGK834, 01PAC573.

Enantioselective total synthesis of marine alkaloids, manzamine A, and related compounds: 00JHC567.

New approaches to total synthesis of manzamine A, ircinal A, and related alkaloids: 99YGK1004.

New synthetic methods and strategies for the total syntheses of pumiliotoxin A class alkaloids: 99YGK981.

Recent chemistry of benzocyclobutenes, in particular, their use in the synthesis of alkaloids and other heterocycles: 01T625.

Recent progress in efficient syntheses of *Amaryllidaceae* and morphine alkaloids: 00JHC535.

Synthesis of strychnine: 00CRV3455.

Total synthesis of montanine-type *Amaryllidaceae* indole alkaloids: 00PAC1773.

Vinyl isocyanates as useful building blocks for alkaloid synthesis: 00SL1.

d. Individual Groups of Alkaloids.

Alkaloids containing isoquinolinequinone unit: 00MI9.

Biological activity and new trends in the chemistry of isoquinoline alkaloids: 01MI92.

Biological aspects of aporphinoid alkaloids: 00MI8.

Chemical studies on the analgesic indole alkaloids from the traditional medicine (*Mitragyna speciosa*) used for opium substitute: 00YZ959.

Chemical transformations of tricyclic quinazoline alkaloids: 01MI101.

Cinchona alkaloids and their derivatives as catalysts and ligands in asymmetric synthesis: 01S961.

Diterpenic acid-based alkaloid-like compounds as new group of nootropic agents: 01MI97.

Diterpenoid alkaloids of getizane type: 00KPS345.

Electrochemical determination of alkaloids of the morphine series: 00CLY1075.

Glycosidase-inhibiting glycomimetic alkaloids (piperidine analogs of sugars), their biological activity and therapeutic perspectives: 00YGK666.

Palladium chemistry in pyridine alkaloid synthesis: 00PHC37.

Progress in studies of novel marine bisindole alkaloids: 00MI50.

Quinoline alkaloids of *Orixa Japonica*: 01H(54)1139.

Recent progress on the lupine alkaloids in leguminous plants growing mainly in Japan: 00YZ923.

Sanguinarine (naphto[1,2-*c*]isoquinoline derivative) and related alkaloids: 00CLY15.

Simple indolizidine and quinolizidine alkaloids: 01MI58.

Tebaine-based syntheses of μ-opioide agonists: 01MI102.

The Almaline group of indole alkaloids: 01MI57.

The pharmacology and therapeutic aspects of colchicines: 00MI11.

3. *Antibiotics*

a. General.

Bacterial RNA as targets of carbohydrate-based antibiotics in connection with resistance to the latter: 01AG(E)3508.

Comparison of new natural immunosuppressors with cyclosporine A by the mechanism of action: 00MI36.

Genetic and biochemical studies on the regulatory mechanism of the self-resistance and biosynthesis of antibiotics: 01YZ193.

Use of various antibiotics for the treatment of patient with acute sinusits: 00MI38.

b. Antitumor Antibiotics.

Synthesis and mode of action of azinomycins (antitumor antibiotics with 1-azabicyclo[3,1,0]hex-2-ylidene structural fragment): 01T4467.

Synthesis of benzonaphthopyranone C-glycoside ravidomycin: 00PAC1783.

Synthetic studies on the A 83586 C and bryostatic antitumor macrolides and the monoamycin antibiotics: 00PAC1659.

c. β-Lactam Antibiotics.

Cephalosporines, their significance, and history of discovery: 01MI112.

Cephoperazon (medoceph) in the modern treatment of heavy forms of bacterial infections: 01MI114.

β-Lactams, structure-activity relationship: 00MI24.

Modern significance of cephalosporine antibiotics by treatment of infections in hospital: 01MI113.

Structural aspects of carbopenem antibiotics: 01H(54)497.

d. Macrocyclic Antibiotics.

Cyclic peptide antibiotics produced by bacteria of *Bacillus* genus: 01KPS103.

Macrolide antibiotics with 1-(2-methylthiazol-4-yl)propen-2-yl substitutent, Epothilones A–D, and their thiazole-modified analogs as novel anticancer agents: 99PAC2019.

Main properties and treatment of community acquired pneumonias of Azitromycin (Sumamed, 15-membered macrolide with N-atom in aglycone ring): 00MI43.

Strategy and methodology for the total synthesis of polyether ionophore antibiotics: 00CRV2407.

e. Miscellaneous Antibiotics.

Antimicrobial activity, pharmacokinetics, and clinical significance of Levofloxacin (Tavanik), new quinolone of III generation: 01MI116, 01MI117.

Arthrotoxicity and mechanism of action of quinolones and fluoroquinolones: 00MI40.

Conformational flexibility of cyclosporins: 01CLY9.

Fluoroquinolones in the treatment of pneumonia: 00MI42.

(*E*)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoic (mycophenolic) acid as antibiotic and immunosuppressant: 00CRV3801.

Lomefloxacin (Maxaquin), a broad-spectrum antimicrobial agent, results of its 10-year use in Russian hospitals: 00MI37.

Role of Pefloxacin (Abactal) in modern therapy of bacterial infections: 00MI41.

Spiramicin (rovamicin) in the treatment of toxoplasmose of pregnant women: 01MI115.

Synthetic studies toward pyranonaphthoquinone antibiotics: 00PAC1635, 00T1937.

4. *Vitamins*

Biological activity of oxythiamine synthetic derivatives: 00KFZ(6)8.

Methods for control and standardization of drugs containing liposoluble vitamins: 01KFZ(10)41.

Synthesis and reactions of antimalarial bicyclic peroxides: 00JHC639.

5. *Drugs*

a. General.

Analysis of pharmaceuticals and related drugs: 99AC(12)217R.

Application of bioreduction to the asymmetric syntheses of chiral drugs: 01MI118.

Applications of green chemistry in the manufacture of oligonucleotide drugs: 01PAC175.

Biotransformation of terpenoids from the crude drugs and animal origin by microorganisms: 01H(54)529.

Brazilian phytochemical diversity: bioorganic compounds produced by secondary metabolism as a source of new scientific development, varied industrial applications, and to enhance human health and the quality of life: 99PAC1663.

Chemical aspects of drugs effect on functions of organism: 01IZV1293.

Computer prognosis of biological activity of chemical compounds as starting point for the search and optimization of basic structure of new drugs: 01MI95.

Continuing evolution of the drug discovery process in the pharmaceutical industry: 01PAC67.

Design and development of novel polymeric prodrugs prepared by mechanochemical solid-state polymerization: 00YZ1337.

Detection of drugs and poisons: 01AC2735.

Development of measurement of new quinolones in body fluids by HPLC using column switching and their application to drug interaction: 01YZ319.

Expanded porphyrins as synthetic materials with potential medical utility: 99PAC2009.

Finding drug candidates in virtual and lost/emerging chemistry: 00JHC669.

Importance of biodiversity to the modern pharmaceutical industry: 99PAC1655.

Novel reagents and reactions for drug design: 00PAC347.

Novel routes to chiral drugs: 01MI93.

Pharmaceutical and related drugs: 01AC2805.

Property-based design: optimization of drug absorption and pharmacokinetics: 01JMC1314.

Studies on the efficient syntheses of N-heterocyclic drug metabolites: 00YZ1135.

Targeting RNA with small-molecule drugs: 01ACR836.

Thermodynamic modeling of crystal deposition (particularly, that of xanthine, uric acid, and urates) in humans: 01PAC785.

b. Definite Types of Activity.

Anti-carcinogenic structure modification by fluorine-substitution in azapolycyclic aromatica: 00YZ1373.

Antimicrobial preparations as immunomodulators of biological reactivity of organism: 01MI119.

Anti-tumor activity of some polynitrile derivatives including derivatives of 2-pyrroline, pyrrole, 2,7-dioxabicyclo[3,2,1]octane, pyrido[3′,4′:3,4]pyrrolo[1,2-*a*]-1,3,5-triazine, pyrrolo[3,4-*c*]pyridine, and 1,2,3,4-tetrahydropyridine: 00KFZ(4)11.

Assesment of anti-tremorogenic drugs using nicotine-induced tail-tremor model and elucidation of the mechanism: 01YZ259.

Asymmetric synthesis of an endothelin receptor antagonist (pyridine derivative): 99YGK1016.

C- and N-Substituted mono- and bicyclic piperidines as new synthetic analgesics and anesthetics: 01MI96.

Chemistry, design, and structure-activity relationship of cocaine antagonists (N-heterocycles as antagonists): 00CRV925.

Comparative QSAR analysis of 5α-reductase inhibitors (azasteroids as inhibitors): 00CRV909.

Current and novel approaches to the drug treatment of schizophrenia: 01JMC407.

Design of piperidine derivatives as selective sigma ligands: 01PAC1499.

Drugs used by Alzheimer's disease: 01KFZ(4)3, 01MI120.

From cancer prevention to cancer treatment using some N-heterocycles as drugs: 00YZ987.

GABA-activated ligand gated ion channels: medicinal chemistry and molecular biology: 00JMC1427.

Heterocycles as corticotropin releasing factor (CRF) receptor modulators: 00JMC1641.

Heterocycles as ligands of peroxysomatic proliferationally activated receptors: 00JMC527.

Heterocycles as pain-relieving agents: 99JMC1481.

Heterocycles as platelet glycoprotein IIb–IIIa antagonists: 00JMC3453.

Heterocycles as sodium channel blockers: 01JMC115.

N-Heterocycles as potassium channel modulators: 01JMC1627.

Heterocycles for treatment to cocaine abuse: 99JMC2721.

Heterocyclic ligands for glutamate receptors: design and therapeutic prospects: 00JMC2609.

Histamine receptors and histaminergic substances: 00KFZ(3)3.

Isolation and identification of trypanocidal coumarin derivatives from the *Rutoles*: 01PAC617.

Lipophilic nitrogen heterocycles as prospective class of antituberculosis preparations: 01MI100.

Main directions of search of new anti-tubercular agents including derivatives of heterocycles: 00KFZ(1)12.

Main trends in design of drugs for chemotherapy of AIDS: 00MI44.

The NCI (National Cancer Institute, USA) experience in international collaboration in drug discovery and development: 99PAC1619.

New dermatological agents for the treatment of psoriasis: 01JMC281.

New developments in anti-HIV chemotherapy: 01PAC55.

New developments in A_1 and A_2 adenosine receptor antagonists: 01PAC1411.

Novel strategies for the discovery of plant-derived anticancer agents: 99PAC1611.

Perspectives in animal healh: 01JMC641.

Perspectives of epilepsy treatment by a herbal mixture prescription "saikokeishito-ka-shakuyaku" (SK): 01YZ295.

Physiologically active compounds including heterocycles interacting with glutamate receptors: 00ZOR1273.

Piperidine and pyrrolidine derivatives as arginine mimetics: 01T7073.

Physiologically active compounds interacting with serotonin (5-hydroxytriptamine) receptors: 01UK382.

Policyclic heterocycles as antagonists of opioid receptors: 01JMC2259.

Syntheses of HIV protease inhibitors: 01S2203.

Syntheses of non-nucleoside reverse transcriptase inhibitors (heterocycles as inhibitors): 00S479.

Synthesis of acyclovir, gancyclovir, and their prodrugs (guanine derivatives with antiviral activity): 00S329.

Synthesis of thymidine derivatives as potential drugs against HIV: 01ZOR807.

The use of boron clusters in the rational design of boronated nucleosides for neutron capture therapy of cancer: 00JOM(614–615)37.

c. *Individual Substances and Groups of Compounds*.

Antitumor acridines with diaminoalkyl pharmacophoric group: 01PAC1421.

Application of polymers and copolymers of acrylic acid and ethylene oxide derivatives in pharmacy: 01KFZ(1)33.

Chemistry and total synthesis of natural antitumor terpenoid taxol: 01CC867, 01MI123.

Chemistry of biologically important synthetic organoselenium compounds: 01CRV2125.

1-(Chloromethyl)silatran as regulator of functional activity1of connective tissue: 01KFZ(9)3.

Dibenzoxepines as treatments for neurodegenerative diseases: 99PAC2039.

Discovery and development of novel anticancer drug capecitabine (N^4-amyloxycarbonyl-5′-deoxy-5-fluorocytidine): 99YZ881.

Donepezil hydrochloride, an acetylcholinesterase inhibitor for the treatment of Alzheimer's disease: 99PAC2031.

2-(4-Methyl-1-piperazinyl)-10-methyl-3,4-diazaphenoxazine dihydrochloride (Azafen) as antidepressant: 00KFZ(5)16.

New drugs based on alkaloids and nitrogen-containing terpenoids: 01MI84.

New medical materials on the basis of modified polysaccharides: 00KFZ(11)36.

Pharmacological role of isatin, an endogenous MAO inhibitor: 00YZ352.

Porphyrins in chemical control of cell differentiation of human myeloleukemia: 00YZ104.

Pyrazidol (Pyrlindole, 2,3,3a,4,5,6-hexahydro-8-methyl-1*H*-pyrazino[3,2-*j*,*k*]-carbazole hydrochloride) as antidepressant: 00KFZ(9)12.

Pyrazino[1,2,3-*a*,*b*]-*β*-carboline derivative, Inkazan (Metralindole), as antidepressant: 01KFZ(2)3.

Quinolizidine alkaloids and flavonoids in *Sophora Flavescens* Soland roots: 01MI121.

Rational design and synthesis of homochiral azole antifungal agents: 01PAC1477.

Recent studies on taxol related water-soluble prodrugs: 01MI122.

Research and development of an antiplatelet agent cilostazol: 00YZ1247.

Retinoic acid and its heterocyclic analogs as new promising chemopreventive and chemoterapeutic agents in oncology: 01PAC1437.

Synthesis of {1-[(4-*tert*-butylaminocarbonyl)-2-methoxyphenylsulfonyl]-4′-(2-morpholinoethoxy)-5-ethoxyspiro(quinoline-3,1′-cyclohexane)-2-one, the vasopressin receptor 2 antagonist SR-121463: 01PAC1401.

Targeting of ellipticine drugs on tumor cells: 01CLY549.

6. *Pesticides*

Strigol-type bis-*γ*-lactones as germination stimulants: 99CC2017.

Synthesis of O-heterocyclic pheromones: 00ACR102.

Trends in research of crop protection (heterocycles as insecticides, herbicides and fungicides): 00AG(E)1725.

7. *Miscelaneous*

a. *Enzymes, Coenzymes, and Their Models.*

Angiotensin II antagonists: 00YZ1261, 01CRV2727.

Calix[4]arenes as dinuclear metallo-phosphodiesterase models: 00CSR75.

Zn-Chelates with tripodal ligands containing N-heterocyclic fragments as analogs of zinc enzymes: 00CC1971.

Comparative QSAR study of tyrosine kinase inhibitors: 01CRV2573.

Correlation of three-dimentional structure and mechanism for heme-containing oxygenases and peroxidases: 01MI37.

Cytochrome oxidase, electron transfer in respiration: 01MI36.

Discovery and application in cell biology of Lactacystin, a proteasome inhibitor: 00YZ935.

Electrochemical and photochemical activation of redox enzymes: 01MI49.

Electron transfer conjugated with ATP hydrolysis in nitrogenase: 01IZV1706.

Heme peroxidases, their structure, function, mechanism, and involvement in activation of carcinogens: 00CCC297.

Se,N-Heterocycles as antioxidants with glutathione peroxidase activity: 00CSR347.

Heterocycles as inhibitors of caspases and possible anti-inflammatory and anti-apoptotic drugs: 00JMC3351.

Heterocycles as cyclin-depedent kinase inhibitors, useful targets in cell cycle regulation: 00JMC1.

Heterocycles as protease inhibitors: 00JMC305.

Inhibitors of cyclin-dependent kinases: 01CLY295.

Interaction of structure of protein globule and bioluminescence spectra of firefly luciferase: 01IZV1670.

Investigations of the roles of the distal heme environment and the proximal heme iron ligand in peroxide activation by heme enzymes via molecular engineering of myoglobin: 01ACR818.

Model studies for molecular recognition of carbonic anhydrase and carboxypeptidase: 01ACR171.

New heterocyclic structures from unsaturated aldehyde derivatives. Inhibition of α-fucosidases: 00JHC455.

NMR studies of ligand binding with dihydrofolate reductase: 00AG(E)290.

Plant cytochromes P450 and peroxidases and their role in degradation of environmental contaminants: 01CLY212.

Preparation of novel specific aminopeptidase inhibitors with a cyclic imide skeleton: 00YZ909.

L-Proline as an enzyme mimic and new asymmetric syntheses using small organic molecules as chiral catalysts: 01AG(E)529.

Pyridoxal 5′-phosphate-dependent α,β-elimination reactions of O-acetylserine sulfhydrylase: 01ACR49.

Roles of human cytochrome P450 enzymes involved in drug metabolism and toxicological studies: 00YZ1347.

Structural aspects of catalysis mechanism and inhibition of dihydrofolate reductase: 01IZV1652.

Synthesis of inhibitors of HIV-RT and thrombin: 99PAC2025.

Synthetic studies on N-heterocyclic antagonists of cholecystokinin receptor: 00YGK766.

Telomeres and telomerase (enzyme having RNA subunit and conducting replication of the ends of linear chromosomes, in particular, those of human cells): 00AG(E)33.

Use of inhibitors to study reactions catalyzed by enzymes requiring pyridoxal phosphate as coenzyme: 00PAC373.

b. Amino Acids and Peptides.

Designer cyclopeptides for self-assembled tubular structures: 00PAC365.

Designer hybrid cyclopeptides for membrane ion transport and tubular structures: 01ACR919.

Disulfide-bonded cyclic peptides: 00SL172.

N-Heterocycles in the synthesis of mimetics of polypeptides of β-hairpin group as reagents for drug and vaccine discovery: 00SL429.

Palladium-catalyzed heterocyclizations of amino acid and peptide derivatives: 00SL1523.

Peptide and protein recognition by designed molecules of heterocycles: 00CRV2479.

Peptide-based heme-protein models: 01CRV3165.

Peptide segment coupling by prior ligation with various heterocyclic derivatives and proximity-induced intramolecular acyl transfer: 00T3449.

Reactions, synthesis and biological activities of amino acid derivatives: 01MI124.

Recent advances in study on cyclic peptides from marine sponges: 01MI143.

Substrate dehydrogenation by flavoproteins: 01ACR299.

Syntheses and applications of β-turn mimetics of peptides and proteins: 01T7431.

Synthesis of modified peptides containing α-amino aldehydes on the C-end: 00MI17.

Tryptophan rotamers that report the conformational dynamics of proteins: 01PAC415.

c. Plant Metabolites.

Antihypertensive chromenes and flavones in the leaves of kumis kucing (*Orthosiphon aristatus*) in Java island: 00YZ474.

Asymmetric total synthesis of terpenoids possesing novel structure of macrocyclic ethers with two bibenzyl fragments: 00YGK1167.

Biological and pharmacological activity of lignans: 00CLY111.

Chemical composition of genus *Lamium L.S.L.* species (Iridoids, terpene glycosides of 6-membered cyclic acetals): 00MI48.

Chemistry and biology of plant-leaf movements, N-heterocycles as factors of the movement: 00AG(E)1400.

Distribution, chemistry and activity of anti HIV–1 active *Calophyllum* coumarins: 00H(53)453.

Flavonoids, alkaloids, and vitamins C and E as components of some species of *Elaegnaceae* family plants: 01KPS87.

Flavonoids and methylxantines in cocoa beans and chocolate: 01CLY610.

Indole derivatives in vegetables of the *Cruciferae* family: 00MI46.

Plant O-heterocycles: 01KPS3.

Research of furostanol saponins (steroid saponins with tetrahydrofurane ring E): 00MI25.

Sesquiterpene lactones and acetogenin lactones from the *Hepaticae*: 01H(54)1057.

Stereocontrolled syntheses of unsymmetrically substituted furofuran lignans: 00H(52)1399.

Strategies for the synthesis of ellagitannins (macrocyclic diesters of hexahydroxydiphenyl-2,2′-dicarboxylic acid and sugars): 01S1585.

Structure, biological activities, and total syntheses of macrocyclic ethers with two bisbibenzyl fragments from liverworts: 00YGK654.

Taxanes (tetracyclic terpenoids with oxetane fragment), anticancer drugs with unique mechanism of action: 00CLY226.

d. Heterocycles Produced by Marine Organisms.

Guanidine metabolites of *Ptilocaulis spiculifer* and related compounds (marine alkaloids with tricyclic guanidine fragment); isolation and synthesis: 00CSR57.

Marine cyanobacteria—a prolific source of natural products: 01T9347.

Marine O-heterocycles, macrolides, and alkaloids: 01EJO633.

Marine polar steroids with O- and N-heterocyclic fragments: 01UK763.

Nitrogen-containing metabolites from marine bacteria: 00MI10.

Recent advances in tetrodotoxin research: 00YZ825.

Synthesis and biological activity of the marine metabolite cylindrospermopsin: 01CSR303.

Total syntheses of pinnatoxin (a macrocycle with O- and N-heterocyclic fragments): 00YGK877.

Total synthesis of antillatoxin, an ichthyotoxic cyclic lipopeptide from marine cyanobacterium *Lyngbya majuscula*: 00YGK634.

Total synthesis of marine oxylipins: 01YGK599.

Total synthesis of polycavernoside A, macrolide toxine from red algae *Polycavernosa tsudai*: 99YGK993.

e. Cyclodextrins.

Cyclodextrin-based molecular machines: 01ACR456.

Cyclodextrin host–guest systems containing azaaromatic moieties: 00H(53)1595.

The gas-phase chemistry of cyclodextrin inclusion complexes: 01ACR653.

f. Other Topics.

Absorption and flurescence spectra of 8-aza-(D-homo)-gona-12,17(a)-diones: 01MI73.

Antifungal metabolites (O-heterocycles) produced by micromycetes: 00CLY21.

Cyclohexane epoxides—chemistry and biochemistry of (+)-cyclophellitol: 01EJO1607.

Dendrobatidae frog poisons (hexacyclic systems with N- and N,O-heterocyclic fragments): 00CLY230.

Homogeneous redox catalysis in CO_2 fixation: 01MI48.

Medium and temperature effects on the redox chemistry of cytochromes: 01EJI2989.

Microbial production of colored azaphilone metabolites (6,7-dihydroisochromene-8-one or 6,7-dihydroisoquinoline-7-one derivatives: 00CLY105.

Microtubule inhibitors: 01CLY700.

Novel microbial metabolites, macrospelides (15-membered unsaturated trilactams) and madindolines (tetrahydrofuro[2,3-*b*]indole derivatives): 99PAC1673.

Organotransition metal modified sugars: 01JOM(615–618)119.

Rationally designed bicyclic lactams control different turn motifs and folding patterns in hexapeptide mimics: 00EJO695.

Recent developments in the chemistry of odorants (O-heterocycles including macrocycles): 00AG(E)2980.

Redox modulation by molecular recognition: 01MI47.

Role of the geme active site and protein environment in structure, spectra, and function of the cytochrome P450S: 00CRV407.

Spectroscopic and dynamic studies of the epidermal chromophores, *trans*-urocanic acid and eumelanin: 00ACR307.

Syntheses and biological evaluation of (+)-lactacystin (2-pyrrolidone derivative, a secondary metabolite from *Streptomyces*) and analogs: 00EJO2513.

Syntheses of CP-225917 and CP-263114 (polycyclic saturated O-heterocycles, fungal metabolites with properties of enzyme inhibitors): 00AG(E)1415.

Structure of "endogenous ouabain"(a steroidal γ-lactone): 99PAC1643.

Synthesis of insect pheromones-heterocycles: 01MI69.

III. Three-Membered Rings

A. One Heteroatom

1. *One Nitrogen Atom*

Asymmetric aziridination: 99MI20, 00MI35.

2*H*-Azirines as synthehic tools in organic chemistry: 01EJO2401.

Recent synthetic applications of chiral aziridines: 00S1347.

The use of polypyrazolylborate copper(I) complexes as catalysts in the conversion of olefins into aziridines: 01JOM(617–618)110.

2. *One Oxygen Atom*

a. Reactivity of Oxiranes.

Application of $InCl_3$ in rearrangements of epoxides: 00EJO2347.

Asymmetric catalysis of epoxide ring-opening reactions: 00ACR421.

Asymmetric ring opening of epoxides and related reactions: 99MI25.

Chemical transformations of spirooxiranes: 01ZOR1431.

Coupling of 2,3-disubstituted oxiranes with 2-substituted 2-metallo-1,3-dithianes: 00YGK857.

Epoxide hydrolases in asymmetric synthesis: 00MI20.

Exchange reaction of oxiranes with β-hydroxyalkyl sulfides, selenides, and phosphines: 00IZV575.

Oxygen-directed carbocyclizations of epoxides: 00T8779.

Reactions of epoxides with ester, ketone and amide enolates: 00T1149.

b. Synthesis of Oxiranes.

Advances in the asymmetric epoxidation of double bond using salen manganese(III) complexes as catalysts: 01MI106.

Asymmetric epoxidation of allylic alcohols: 99MI21.

Asymmetric epoxidation of electron-deficient olefins: 00CC1215.

Asymmetric epoxidation of alkenes other than allylic alcohols: 99MI22.

Asymmetric epoxide formation of enones and aldehydes: 99MI23.

Biosynthesis of chiral epoxides: 01MI138.

Chiral ketone-catalyzed asymmetric epoxidation of olefins: 00S1979.

Formation of oxiranes in reactions of organic hydrotrioxides RCOOOH with alkenes and cycloalkenes: 01UK123.

The use of polypyrazolylborate copper(I) complexes as catalysts in the conversion of olefins into epoxides: 01JOM(617–618)110.

3. *One Sulfur Atom*

Catalytic macrocyclizations of thiiranes by metal carbonyl complexes: 00ACR171.

B. Two Heteroatoms

1. *Two Nitrogen Atoms*

Carbene generation from diazirines: 01MI60.

2. *Two Sulfur Atoms*

Chemistry of dithiiranes: 00AHC(77)221.

C. Three Heteroatoms

Formation of thiadioxiranes in reactions of singlet oxygen with sulfides (persulfoxides as intermediates): 01ACR875.

IV. Four-Membered Rings

A. General Topics

Ynolate anions as equivalents of ketenyl anions and their transformations into β-lactones and β-lactams: 00YZ1233.

B. One Heteroatom

1. *One Nitrogen Atom*

Development of catalytic approach to the enantioselective synthesis of β-lactams: 01AG(E)4377.

β-Lactam-based synthesis of complex nucleoside antibiotics and macrocyclic peptides: 00PAC1763.

β-Lactams as versatile intermediates in α- and β-amino acid syntheses: 01SL1813.

Non-classical polycyclic β-lactams: 00T5743.

4-Oxoazetidine-2-carbaldehydes as useful building blocks in stereocontrolled synthesis: 01CSR226.

Progress in the synthesis and application of β-lactams: 01MI144.

Recent progress in the synthesis and reactivity of azetidine-2,3-diones: 01OPP315.

Progress in the stereoselective syntheses of β-lactams mediated by oxazoline N-oxides: 00PAC1721.

The S-thioester enolate/imine condensation as a shortest way to β-lactams: 00EJO563.

2. *One Oxygen Atom*

Paterno-Büchi reaction of N-acyl enamines and aldehydes—the development of a new synthetic method and its application to total synthesis and molecular recognition studies; synthesis of oxetanes and their transformations: 00SL1699.

Progress in the stereoselective syntheses of β-lactones mediated by oxazoline N-oxides: 00PAC1721.

The β-elimination route to stereodefined γ-alkylidenebutenolides: 01CC141.

3. *One Sulfur Atom*

Catalytic macrocyclizations of thietanes by metal carbonyl complexes: 00ACR171.

C. Two Heteroatoms

Chemistry of 1,2-dithietanes, and 1,2-dithietes: 00AHC(77)221.

Formation of 1,2-dioxethanes in reactions of organic hydrotrioxides RCOOOH with alkenes and cycloalkenes: 01UK123.

New mechanistic and synthetic aspects of singlet oxygen chemistry, formation, and transformations of 1,2-dioxethanes: 00T9151.

V. Five-Membered Rings

A. General Topics

Aromatic N-haloazoles: 00AHC(75)1.

Catalytic enantioselective 1,3-dipolar cycloaddition reactions of nitrones: 00CC1449.

Efficient chiral control based on five-membered heterocyclic and related systems: 00YZ1323.

Formation of cumulenes, triple-bonded, and related compounds by flash vacuum thermolysis of five-membered heterocycles: 01EJO2209.

Photochemical isomerization of pentaatomic heterocycles: 01AHC(79)41.

Regio- and stereochemistry of 1,3-dipolar cycloaddition of nitrile oxides to alkenes: 01UK464.

Ring-opening reactions of five-membered nitrogen-containing heterocycles: 01MI107.

Ring transformations of five-membered heterocycles and their fused derivatives: 01EJO3405.

Stereocontrolled asymmetric syntheses of 5-membered N-heterocycles: 00PAC1691.

Stereoselection in 1,3-dipolar cycloaddition reactions of chiral allyl ethers: 01EJO1039.

Syntheses and properties of azafulvalenes: 00AHC(77)115.

Tricyclic azoloquinolines: 01AHC(78)189.

B. One Heteroatom

1. *General*

Synthesis, reactions, and biological activity of furan and thiophene oximes: 01KGS156.

Synthetic utility of furan-, pyrrole- and thiophene-based 2-siloxydienes: 00CSR109.

2. *One Nitrogen Atom*

Phosphorus-containing indole and pyrrole derivatives: 00KGS1587.

a. Monocyclic Pyrroles.

Analytical application of oligopyrrole macrocycles: 01CCC693.

Mechanisms of pyrrole electropolymerization: 00CSR283.

Organometallic compounds of pyrroles: 01AHC(79)115.

b. Hydropyrroles.

Mechanisms and stereoselective syntheses of dihydropyrrolones from iron-substituted α,β-unsaturated imines and organolithium and Grignard reagents: 00EJO3961.

Stereoselective and enantioselective synthesis of chiral pyrrolines via conjugate additions of allylsulfone carbanions: 00PAC1671.

Syntheses and applications in heterocyclic chemistry of pyrrolidinetrione derivatives: 01S811.

Synthesis and properties of dioxopyrrolines of isoquinoline and phenanthridine series: 01MI74.

c. Porphyrins and Related Systems.

Porphyrins and related compounds (general monograph): 00MI4.

Acidic and complex forming properties of tetraazaporphyrines: 01KK483.

Advances in modern synthetic porphyrin chemistry: 00T1025.

Advances in the synthesis of petroporphyrins: 00MI31.

Biomimetic electron-transfer chemistry of porphyrins and metalloporphyrins: 01MI35.

Building molecular wires from the colors of life conjugated porphyrin: 99CC2323.

Carbaporphyrinoids with benzene, azulene, cyclohexatriene, indene or pentalene fragment instead of one or two pyrrole rings: 00SL279.

Electron transfer in covalently linked supramolecular systems containing porphyrin units: 01MI40.

Extracoordination of molecules on metalloporphyrins as a factor of catalytic and enzymatic activity of porphyrins: 01MI81.

Giant porphyrinoids, from figure eight to nanomolecular cavities: 00AG(E)1763.

Macrocyclic effect and biological activity of metalloporphyrins: 01MI83.

Molecular design of porphyrin-based artificial molecular and ion recognition systems with allosteric guest responces: 01ACR865.

Molecular size, length, and the extent of electronic π-conjugation in discrete giant porphyrin arrays: 01SL1663.

Oligomeric porphyrin arrays: 99CC1771.

Photobleaching of porphyrins and chlorins: 01T9513.

Photosynthesis with participation of synthetic porphyrins: 01ACR40.

Porphyrins in high-performance liquid chromatography: 00ZAK1014.

Spectral properties of porphyrines, their precursors, and derivatives: 01UK656.

Synthesis and spectral investigations of diporphyrins bonded on *meso*-positions: 00SL296.

Synthesis and potential applications of porphhyrin derivatives: 00JHC527.

Synthesis of porphyrins from dipyrrolylmethanes: 00UK337.

Synthetic molecular systems on the basis of porphyrins as models for study of energy transfer by photosynthesis: 01UK1059.

Synthetic routes to multiporphyrin arrays: 01CRV2751.

Thermodynamics of molecular complex formation in solutions of natural porphyrins: 01MI82.

The role of the electronic structure of the porphyrin as viewed by EPR/ENDOR method in the efficiency of biomimetic model compounds for photosynthesis: 01EJO4379.

d. Indoles, Carbazoles, Related Systems, and Hydrogenated Derivatives.

Chemistry of sulfur-containing indoles: 02PHC1.

New approach to the annelated 5-hydroxy-substituted indoles based on Nenitzescu reaction: 01MI88.

Nucleophilic aromatic substitution of hydrogen in syntheses of indole derivatives: 01H(54)445.

Organometallic compounds of indoles and carbazoles: 01AHC(79)115.

Recent developments in the synthetic methods of indole ring compounds: 01MI137.

Synthesis and properties of carbazole-1,4-diones: 00H(52)977.

e. Isoindoles (Including Phthalocyanins and Porphyrazines).

A retro Diels–Alder reaction in the synthesis of fused-skeleton isoindolones and saturated hetero polycycles: 00JHC439.

Acetylenic phthalocyanines and phthalocyanine analogues: 01EJO2797.

Phtalocyanines as active materials for optical limiting: 01EJO3759.

Photobleaching of phthalocyanins used in photodynamic therapy: 01T9513.

Phthalocyanine thin films: 99PAC2145.

Phthalocyanines in high-performance liquid chromatography: 00ZAK1014.

Selective synthetic approaches to phthalocyanines: 00EJO2821.

Synthesis, structure, and properties of coordination compounds of iron phthalocyanine series and their analogs: 00UK355.

Synthetic potential of phthalimide SET photochemistry: 01ACR523.

Traditional and electrochemical methods for the synthesis of phthalocyanines and their metal complexes: 00KK323.

f. Polycyclic Systems Including Two Heterocycles.

Indolocarbazoles: 01AHC(80)1.

Indolopyridines with nodal heteroatom: 01KGS1155.

Pyrroloquinolines: 01KGS1587.

Synthesis and biological activity of benzo[*b*]furoindole and benzo[*b*]thienoindole derivatives: 01MI98.

Synthesis of fused 7-azanorbornanes: 01PHC25.

Synthesis of 1,(7)-substituted pyrrolizidin-3-ones: 00T6359.

Synthetic methods for the stereoisomers of swainsonine and its analogs (1,2,8-trihydroxyindolizidines): 00T8579.

3. *One Oxygen Atom*

a. Furans.

Benzylfurans in the synthesis of benzannelated heterocycles: 01IZV1436.

2-Furylphosphines as ligands for transitional-metal-mediated organic synthesis: 01CRV997.

Organometallic compounds of furans: 01AHC(78)1.

Recent advances in metal-mediated synthesis of substituted furans: 00MI22.

Synthesis of furans from sucrose: 01CLY202.

b. Hydrofurans.

Stereoselective construction of the tetrahydrofuran nucleus by alkoxyl radical cyclizations: 01EJO619.

c. Annelated Furans.

New approach to annelated 5-hydroxy-substituted benzofurans, based on Nenitzescu reaction: 01MI88.

Organometallic compounds of benzannelated furans: 01AHC(78)1.

Resveratrol (bioactive 2,3-dihydrobenzofuran derivative): 00CLY602.

Synthesis and biological activity of benzo[*b*]furoindole derivatives: 01MI98.

d. Five-Membered Lactones.

A novel production of γ-butyrolactone catalyzed by homogeneous ruthenium complexes: 00YGK787.

Catalyzed transformations of bisketenes into potentially biologically active compounds, in particular, into 5-alkoxyfuran-(3*H*)-ones: 00SL13.

Effect of ligands on divalent palladium-catalyzed carbon–carbon coupling reactions in highly enantioselective synthesis of optically active γ-butyrolactones: 01PAC247.

2(5*H*)-Furanones: 01AHC(81)107.

4. *One Sulfur Atom*

Thermal reactions of sulfur, hydrogen sulfide and its derivatives with organic compounds (syntheses of thiophenes, benzothiophenes, thienothiophenes): 01ZOB1941.

a. Thiophenes.

Chemistry of thiophene 1,1-dioxides: 99MI10.

Molecular structure of compounds containing 2,2′-bithienyl fragment: 00KGS725.

Organometallic compounds of thiophenes: 01AHC(78)1.

Thermal methods for the synthesis of thiophene and its derivatives: 00KGS3, 00UK90.

b. Annelated Thiophenes.

1,3-Dihydrobenzo[c]thienylium (thiophtalylium) salts: 00KGS147.

Organometallic compounds of benzannelated thiophenes: 01AHC(78)1.

Recent trends in isomeric thienoquinoxalines [1980–2000]: 01JHC809.

Synthesis and biological activity of benzo[*b*]thienoindole derivatives: 01MI98.

C. Two Heteroatoms

1. *General*

Carbene complexes derived from lithiated azoles: 01JOM(617–618)170.

Chemistry of trimethylsilylazoles: 01ZOR165.

Reactions of oxazoles, thiazoles, imidazoles, and corresponding azolines with isocyanates or ketenes including acylation followed by [2 + 2], [2 + 2 + 2], [3 + 2], [3 + 3], and [4 + 2] annelation: 01T6651.

Rigid-chain polybenzobisazoles and molecular composites based on them: 01UK88.

2. *Two Nitrogen Atoms*

a. Pyrazoles.

Organometallic complexes of pyrazoles: 01AHC(80)157.

Organometallic complexes of pyrazolylborates and related ligands: 01AHC(81)167.

Polypyrazolylborate copper(I) complexes as catalysts in the conversion of olefins into aziridines and epoxides: 01JOM(617–618)110.

Pyrazol-3-ones. Synthesis and applications: 01AHC(80)73.

b. Imidazoles.

Chemical properties and application of imidazoline-2-ones and their derivatives: 00MI29.

Packing regularities in structures of chelates based on 3-imidazoline nitroxide radical: 01KK317.

Preparation of imidazolidinone chelated carbene complexes: 01JOM(617–618)182.

Synthesis of chiral imidazolinylidene transition metal complexes and their application in asymmetric catalysis: 01JOM(617–618)70.

c. Annelated Imidazoles.

Benzimidazole-2-ylidenes with ferrocenyl substitutuents: 01JOM(617–618)28.

Properties of 2,3-dihydroimidazo[1,2-*a*]pyridines: 00KGS1011.

3. *One Nitrogen and One Oxygen Atom*

a. 1,2-Heterocycles.

Carbene and radical pathways in pyrolysis of benzisoxazolones: 00JHC631.

Preparation and synthetic utility of 3-isoxazolols: 01OPP515.

Synthesis and biological activity of steroid isoxazoles: 00KGS291.

b. 1,3-Heterocycles.

Fused munchnones in recyclization tandems: 00JHC519.

Hemilability of hybrid ligands and the coordination chemistry of oxazoline-based systems: 01AG(E)680.

Phosphinooxazolines as versatile, modular P,N-ligands for asymmetric catalysis: 00ACR336.

4. *One Nitrogen and One Sulfur Atom*

Thiazolylketoses as a new class of versatile intermediates for glycoside synthesis: 99CC2133.

5. *Two Sulfur Atoms*

New concept in tetrathiafulvalene chemistry: 01AG(E)1372.

New redox materials based on functionalized di-1,3-dithiolyliden 9,10-anthracenediylidenes: 99PAC2137.

Reagents for preparation and cleavage of 1,3-dithiolanes: 00UK1032.

Structure of organic metals on the basis of bis(ethylenedithio)tetrathiafulvalene with photochromic nitroprusside anion, $(BEDT\text{-}TTF)_4M[FeNO(CN)_5]_2$, $(M = Na^+, K^+, NH_4^+, Tl^+, Rb^+, Cs^+)$: 01KK283.

Synthesis and chemistry of dithioles: 01S1747.

Tetrathiafulvalenes as building blocks in supramolecular chemistry: 00CSR153.

D. Three Heteroatoms

1. *Three Nitrogen Atoms*

a. Monocyclic systems.

Selective biotransformation reactions on D-arabino- and D-threo-hydroxyalkyltriazoles: 01PAC167.

Synthesis of chiral triazolinylidene transition metal complexes and their application in asymmetric catalysis: 01JOM(617–618)70.

b. Annelated Triazoles.

Carbene and radical pathways in pyrolysis of benzotriazoles: 00JHC631.

Chemistry of 1,2,4-triazolo[4,3-*c*]pyrimidines: 00AHC(75)243.

Chemistry of 1,2,4-triazolo[1,5-*c*]pyrimidines: 00AHC(77)345.

Efficient synthetic routes to polyfunctional compounds with benzotriazole participation: 00PAC1597.

2. *Two Nitrogen Atoms and One Oxygen Atom*

Monocyclic furazans and furoxans: 01AHC(78)65.

Trichloromethylarenes in synthesis of 1,3,4-oxadiazoles: 01MI87.

E. Four Heteroatoms

Alkylation and related electrophilic reactions at endocyclic nitrogen atoms in the chemistry of tetrazoles: 00H(53)1421.

Methods for the synthesis of mono- and polynuclear NH-tetrazoles: 00KGS867.

VI. Six-Membered Rings

A. General

1-Azabutadienes as dienes in Diels–Alder reactions: 01T6099.

Imines as dienophiles in Diels–Alder reactions: 01T6099.

B. One Heteroatom

1. *One Nitrogen Atom*

a. Pyridines.

Achieving positional selectivity in pyridine synthesis: 00JHC451.

Dendrimers based on electroactive metal complexes with pyridine fragments: 01CCC1.

Dipolar and non-dipolar pyridine metal complexes for nonlinear optics: 00EJI229.

Directed metallation of pyridines: 01T4059.

Enzymatic syntheses of pyridine derivatives: 99YGK1064.

Ring transformation of pyridines and benzo derivatives under the action of C-nucleophiles: 00H(53)1607.

Ruthenium polypyridine complexes as models for the photosynthetic reaction center: 01ACR905.

Selective preparation of pyridine derivatives from two different alkynes and a nitrile: 01PAC271.

Solventless three-phase syntheses of pyridine derivatives: 01CC2159.

b. Pyridinium Compounds, Ylides, Pyridine N-Oxides.

Catalytic reduction of pyridinium salts: 01KGS807.

Redox-tunable pyridinium assemblies and their interactive spin-based functions: 99PAC2079.

c. Applications of Pyridines.

Oligopyridine liquid crystals as novel building blocks for supermolecular architectures based on metal coordination and hydrogen bonding: 00AG(E)2454.

d. Bipyridines and Related Systems.

Molecules comprising at least two 2,2-bipyridine units as ligands: 00CRV3553.

Spin crossover phenomena in Fe(II) complexes with tridentate ligands related to 2,2′:6′,2-terpyridine: 00CSR419.

e. Hydropyridines.

Stereoselective synthesis of piperidines: 00S1781.

Synthesis of new 3-piperidinol-type chiral building blocks and their application to the alkaloids syntheses: 99YGK1075.

f. Biologically Active Pyridines and Hydropyridines.

Enantioselective automultiplication of chiral pyridylalkanols by asymmetric autocatalysis: 00ACR382.

g. Pyridines Annelated with Carbocycles.

Application of $InCl_3$ in the synthesis of quinolines: 00EJO2347.

Directed metallation of quinolines: 01T4059.

Nucleophilic aromatic substitution of hydrogen in syntheses of quinoline derivatives: 01H(54)445.

Photoactive mono- and polynuclear Cu(I)-phenanthrolines: 01CSR113.

Synthesis of 3,4-dihydroisoquinolines: 01MI78.

Synthesis of 1(2*H*)-isoquinolines: 01KGS723.

h. Pyridines Annelated with Heterocycles.

Chemistry of nitronaphthyridines: 00AHC(77)285.

Directed metallation of carbolines: 01T4059.

Indolopyridines with nodal heteroatom: 01KGS1155.

Properties of 2,3-dihydroimidazo[1,2-*a*]pyridines: 00KGS1011.

Pyridopyridines: 01UK345.

Pyrroloquinolines: 01KGS1587.

Structure, properties, and general methods for the synthesis of naphthyridines: 00UK218.

Synthesis of annelated quinolizine derivatives from cyclic Schiff bases by [2 + 4] cyclocondensation: 01MI86.

Synthetic methods for the stereoisomers of swainsonine and its analogs (1,2,8-trihydroxyindolizidines): 00T8579.

Tricyclic azoloquinolines: 01AHC(78)189.

2. *One Oxygen Atom*

Catalytic reduction of pyrilium salts: 01KGS807.

Conformational space and dynamic stereochemistry of dixantylene and its S- and N-analogs: 01EJO15.

Reactions of fluoro- and chlorocontaining chromones with aliphatic mono-, di-, and triamines: 01MI76.

Solventless three-phase syntheses of 3-carboxycoumarins: 01CC2159.

Synthesis of 2,2-dimethyl-4-chromanones: 00JHC1389.
Synthesis of 2,2-dimethyl-2H-chromenes: 00H(53)1193.

3. *One Sulfur Atom*

Catalytic reduction of thiopyrilium salts: 01KGS807.

C. Two Heteroatoms

1. *Two Nitrogen Atoms*

a. 1,2-Heterocycles.
Chemistry of 1*H*-1,2-diazaphenalene: 01MI94.
Chemistry of pyridazines: 00AHC(75)157.
Nucleophilic substitution of hydrogen atoms in pyridazine series: 01KGS1611.

b. 1,3-Heterocycles: Monocyclic Pyrimidines and Hydropyrimidines (Except Pyrimidine Nucleoside Bases and Nucleosides).
Enantioselective automultiplication of chiral pyrimidylalkanols by asymmetric autocatalysis: 00ACR382.
Recent advances in the Biginelly dihydropyrimidine synthesis: 00ACR879.
Recent advances in the synthesis of 3,4-dihydropyrimidinones: 01MI108.
Synthetic applications of the pyrolysis of Meldrum acid derivatives: 01S2059.

c. Annelated Pyrimidines (Except Purines, Pteridines, and Flavins).
Chemistry of 1,2,4-triazolo[4,3-*c*]pyrimidines: 00AHC(75)243.
Chemistry of 1,2,4-triazolo[1,5-*c*]pyrimidines: 00AHC(77)345.
Synthesis of substituted quinazolin-4(3*H*)-ones and quinazolines via directed lithiation: 00H(53)1839.

d. Pyrimidine Nucleoside Bases and Purines.
Combinatorial syntheses of purine derivatives: 01AG(E)339.
Enzymatic syntheses of purine derivatives: 99YGK1064.
Simultaneous determination of theophylline and its metabolites by HPLC: 00YZ1051.
Synthesis and biological activity of 2- and 6-C-substituted purine bases: 00CLY978.

e. Nucleotides and Nucleosides.
Advances in synthesis of sugar-modified nucleosides in past 10 years: 01YGK331.
Bicyclic nucleosides and conformational restriction of oligonucleotides: 00JCS(P1)3539.
Biocatalytic selective modifications of conventional nucleosides, carbocyclic nucleosides, and C-nucleosides: 00CRV4319.
Chemistry and biochemistry of cyclic ADP-ribose and its analogs: 00YGK1144.

Dialdehyde derivatives of nucleosides, nucleotides, and oligonucleotides: 00MI47.

Metal ion-binding properties of the antiviral nucleotide analog, 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA): 99PAC1727.

New nucleoside analogs, synthesis, and biological properties: 00PAC1705.

Purine 8-O and 8-S-cyclonucleosides, synthesis, and properties: 00CLY355.

Syntheses and properties of novel conformationally restrained nucleoside analogs: 99YGK969.

Synthesis and biological activity of 2- and 6-C-substituted purine bases, nucleosides, and acyclic nucleotide analogs: 00CLY978.

Synthesis and biological activity of thionucleosides: 00S1637.

Studies on syntheses of a novel antiherpetic nucleoside A-5021 and related compounds: 00YGK683.

Transformations of β-xylofuranosylnucleosides: 00MI18.

f. Nucleic Acids.

Affine sorbents containing nucleic acids and their fragments: 01UK581.

Analysis of noncovalent complexes of DNA and RNA by mass spectrometry: 01CRV377.

Antisense molecules as nucleic acid mimics: 01CC1419.

Capillary electrophoresis for the analysis of nucleic acids: 00AC(12)111R.

Chemical etiology of nucleic acid structure: 00PAC343.

Construction of reagents for directed cleavage of ribonucleic acids: 01UK562.

Development of functional nucleic acids and peptides by combinatorial chemistry and downsizing methods: 00YGK1133.

Dynamics of photoinduced charge transfer and hole transport in synthetic DNA hairpins: 01ACR159.

Effect of chirality of ribose on nucleic acid structure and function: 99YZ689.

Electron transfer and charge transport process in DNA: 01MI38.

Fluorescence correlation spectroscopy in nucleic acid analysis: 01MI147.

From equilibrium to kinetic footprinting of RNA structure: 01JCS(P2)1263.

Long-distance charge transport through DNA: 01PAC449.

Long-range transfer in DNA transient structural distortions control the distance dependence: 00ACR253.

Mimicking the structure and function DNA, insights into DNA stability, and replication: 00AG(E)990.

Molecular mechanisms of DNA recognition and function by bioactive compounds: 00YZ1409.

Molecular mechanisms of mutations induced by DNA lesions: 00YZ1159.

Nucleic acid conformation diversity: 01CSR70.

Nucleic acid synthesis and molecular recognition: 99YZ625.

Recognition of DNA sequences by pyrrole-imidazole polyamide: 00YGK975.

Strategies for the design of drugs targeting RNA and DNA–protein complexes: 00AG(E)1890.

Study on electron transfer of nucleic acid precursors and their modified structure: 01MI125.

Synthesis of fluorescently labeled oligonucleotides and nucleic acids: 00CSR97.

Synthetic control of DNA triplex structure through chemical modifications: 96MI6.

Use of nucleic acids for construction of nanostructures: 01AG(E)4128.

g. 1,4-Heterocycles: Pyrazines and Hydropyrazines.

Chemistry of pyrazino-bis-steroids: 00MI49.

Complexes of pyrazine, 4,4′-bipyrazine, and similar N-heterocycles with two coordinated ML_n groups: 00ACR755.

(5*S*) and (5*R*)-Ethyl 3,6-diethoxy-5-isopropyl-2,5-dihydropyrazine-2-carboxylates as key compounds in asymmetric synthesis of α-substituted serines: 00YGK756.

Pyrazine functional derivatives in the asymmetric synthesis of α-substituted serines: 00YZ28.

h. Annelated Pyrazines.

Fluorescence correlation spectroscopy of flavines and flavoproteins: 01MI146.

Recent trends in isomeric thienoquinoxalines [1980–2000]: 01JHC809.

New pyrazinone derivatives as chiral reagents in asymmetric synthesis of α-amino acids: 00JHC467.

2. *One Nitrogen and One Oxygen Atom*

New oxazinone derivatives as chiral reagents for the asymmetric synthesis of α-amino acids: 00JHC467.

Preparation of morpholine-2,5-diones: 01CLY22.

Selective biotransformation reactions on (±)-benzoxazines: 01PAC167.

Synthesis and reactions of 2-hetero (RO-, RS- or RR′N)-4H-3,1-benzoxazin-4-ones: 00JHC1369.

Synthesis of heterocyclic compounds on the basis of isatoic anhydrides (2H-3,1-benzoxazine-2,4-diones): 01KGS435.

3. *Two Oxygen Atoms*

Optical spectra and photophysical properties of polychlorinated dibenzo-*p*-dioxins: 00UK1128.

Synthesis and chemical properties of 6-aryl-2,2-dimethyl-1,3-dioxin-4-ones: 01KGS1011.

4. *One Oxygen and One Sulfur Atom*

Stereostructure, peculiarities of physicochemical properties, and some transformations of 1,3-oxathianes: 00MI16.

5. *Two Sulfur Atoms*

Formation of thianthrenes in thermal reactions of sulfur, hydrogen sulfide, and its derivatives with organic compounds: 01ZOB1941.

Generation of 2-substituted 2-metallo-1,3-dithiane derivatives and their coupling with 2,3-disubstituted oxiranes: 00YGK857.

D. Three Heteroatoms

Synthesis of melaminecyanuric/barbituric acid derived nanostructures: 01EJO3191.

E. Four Heteroatoms

Annelated 1,2,4,5-tetrazines: 01JHC541.

Synthesis of new substituted $1\lambda^4$-1,2,4,6-thiatriazines: 00JHC583.

VII. Rings with More Than Six Members

A. Seven-Membered Rings

1. *One Heteroatom*

Introduction of nitrogen atom into six-membered ring and formation of seven-membered N-heterocycles: 00T4317.

2. *Two Heteroatoms*

Synthesis and chemical tranformations of 1,5-benzothiazepines: 00JHC199.

Synthesis and chemical transformations of 1,4-, 4,1-, and 1,5-benzoxazepines: 01JHC1011.

B. Medium Rings

Metal-mediated synthesis of medium-sized heterocycles: 00CRV2963.

New synthetic methods for construction of medium-sized cyclic ethers and convergent coupling of polyether fragments: 01YGK193.

Synthesis of medium-sized heterocycles by the ring-closing metathesis reaction: 00AG(E)2079.

C. Large Rings

1. *General Problems*

Planar chirality—synthesis and transformations of 8- to 10-membered heterocycles bearing (*E*)-olefin units: 01EJO1801.

a. Structure, Stereochemistry, Reactivity, Design.

Changing the reactivity of heterocyclic enediynes by metal-ion coordination: 00EJO381.

b. Synthesis.

Efficient syntheses of rotaxanes and catenanes based on hydrogen bonding: 01YGK206.

Formation of macrocyclic lactones and oxalactones by metal carbene transformations: 01SL1364.

c. Applications.

Macroheterocycles as synthetic receptors: 00JCS(P1)3155.

2. *Crown Ethers and Related Compounds*

s-Block metal inverse crowns: 01CC1049.

Cation dependent pericyclic reactions of crown-containing photochromic compounds: 01IZV1882.

Crown-ethers in radiochemistry: 00UK840.

Development of chiral crown ethers: 01MI109.

Interactions of alkali metals cations (complexed with crown-ethers and kryptands) with aromatic π-systems: 00EJO2967.

Molecular design of crown ethers-based artificial molecular and ion recognition systems with allosteric guest responses: 01ACR865.

Recent highlights in hemicarcerand chemistry: 01ACR95.

Studies on azacrown ether compounds and macrocyclic polyamines: 01MI110.

Studies on crown ethers cyanine dyes: 00H(53)1821.

3. *Miscellaneous Macroheterocycles*

Analytical application of oligopyrrole macrocycles: 01CCC693.

Attractive intramolecular edge-to-face aromatic interactions in flexible organic molecules, particularly, in, heteraphanes: 01ACR885.

Calixarenes bearing azaaromatic moieties: 01H181.

Catenanes and rotaxanes as chemically, electrochemically, and photochemically guided artificial molecular machines: 00AG(E)3348.

Chiral cyclodextrins, crown ethers, and macrocyclic antibiotics in chiral separations using capillary electrophoresis: 00CRV3715.

Cyclodextrins and their derivatives as stationary phases for separation of enantiomers by capillary gas chromatography: 00CLY10.

Development in the research of bridged calix[6]arenes: 00MI28.

Electron transfer processes in pseudorotaxanes: 01MI43.

Electron transfer processes in rotaxanes and catenanes: 01MI44.

Electron transfer processes in metal-assisted catenanes, rotaxanes, and knots: 01MI45.

Electron transfer processes in dendrimers: 01MI46.

From rotaxanes to knots. Templating, hydrogen bond patterns, and cyclochirality: 00PAC2223.

Heteroatom-briged calixarenes: 00EJI2303.

Inner-phase stabilization of reactive intermediates (macroheterocycles as molecular containers, carceplexes): 01EJO423.

Molecular mobility and topological chirality of rotaxanes: 01ACR465.

Rotaxanes. From supramolecular self-organization to molecular devices: 00MI21.

Self-assembling of rotaxanes, catenanes, and molecular knots: 00CRV3483.

Self-assembling nanotubes from cyclic peptides and depsipeptides: 01AG(E)988.

Supramolecular devices based on rotaxanes and polyrotaxanes: 01UK28.

Supramolecular recognition in macrocyclic polyamines: 01MI135.

VIII. Heterocycles Containing Unusual Heteroatoms

A. General

Formation of P-, Si-, and Ge-heterocycles from corresponding heavy allenes E=C=E′: 00CRV3639.

B. Phosphorus Heterocycles

Applications of phosphorus heterocycles in homogeneous catalysis: 01MI30.

Aromaticity of phosphorus heterocycles: 01CRV1229.

1. *Chemistry of Individual Classes of P-Heterocycles*

The birth of phosphorus–carbon heterocyclic chemistry: 01MI14.

Phosphiranes and phosphirenes: 01MI15.

Diphosphiranes and diphosphirenes: 01MI16.

Diphosphetanes, dihydrodiphosphetes, and diphosphetes: 01MI19.

Modulating phospholane ligands in asymmetric catalysis: 00ACR363.
Phosphetanes: 01MI17, 01MI18.
Phospholanes and phospholenes: 01MI20.
Phospholes: 01MI21, 01MI22.
Heterophospholes: 01MI23.
Phosphinanes, dihydro-, and tetrahydrophosphinanes: 01MI24.
Phosphinines: 01MI25.
Six-membered rings with two or more heteroatoms with at least one phosphorus atom: 01MI26.
Phosphorus-containing macro- and spiro-heterocycles: 01MI27.
Bicyclic and polycyclic systems with a ring junction phosphorus atom: 01MI28.
Compounds with phosphorus at the spiro position: 01MI29.
From phosphathiafulvenes to phosphabenzenes and stable six-membered phosphaallenes: 00PAC1769.
Organometallic compounds of phospholes: 01AHC(79)115.
Synthesis and reactions of oxaphospholanes using hydroxyalkylphosphonium salts: 00YGK548.
Zirconium-phosphorus chemistry (metallocycles, P,Zr-heterocycles): 00AG(E)314.

2. *Structure and Stereochemistry*

Vibrational spectra, force constants, and conformations of molecules of trivalent tricoordinated phosphorus compounds including P-heterocycles: 00UK817.

3. *Reactivity*

Amides of trivalent phosphorus acids (including cyclic amides) as phosphorylating reagents for proton-donating nucleophiles: 00CRV3755.
Functionalization of P^{III} phosphocavitandes: 01MI111.
7-Membered cyclic phosphoramidites as ligands in catalytic asymmetric conjugate addition: 00ACR346.

4. *Synthesis*

Flash vacuum thermolysis in synthesis of new reactive heterocycles with P = Si double bonds: 00EJO3253.
Phosphorus ylides containing fluorine atoms bonded to phosphorus (reactions leading to the formation of P-heterocycles): 01SL1065.
Syntheses of cyclophosphanes from silylphosphanes: 00CRV3341.

C. Boron Heterocycles

1. *Chemistry of Individual Classes of B-Heterocycles*

Highly Lewis acidic bifunctional B-heterocycles: 00EJI2131.
Nickel and iron bisdicarbollides: 00JOM(614–615)27.
Organometallic compounds of boroles: 01AHC(79)115.
Small cage C_2B_4-carborane: 00JOM(614–615)10.

2. *Structure and Stereochemistry*

Boron-bridged group-4 ansa-metallocene complexes: 01EJI321.
The structural chemistry of boron-rich derivatives of alkali metals, particularly, salts with cage carbaboride anions: 00EJI1679.

3. *Reactivity*

Metal induced B-H activation of semi-sendwich Cp*Rh-, Cp*Ir- (p-cymol)R-, and (p-cymol)Os-complexes containing 1,2-dicarba-*closo*-dodecaborane(12)-dichalcogenate ligand: 01IZV1444.

4. *Synthesis*

Photochemical reactions with participation and formation of B-heterocycles: 00T7339.

5. *Applications*

Forced *exo-nido* rhoda- and ruthenacarboranes as catalyst precursors: 00JOM(614–615)48.

D. Silicon, Germanium, Tin, and Lead Heterocycles

1. *Chemistry of Individual Classes of Heterocycles*

Anionic chemistry of four- and five-membered silyl-substituted π-electronic systems, formation of polycyclic Si-heterocycles: 99YGK945.
Chemistry of cyclic siloxanes: 00YGK926.
Germatranes and their analogs: 01KGS1451.
Oligoorganocyclocarbosiloxanes: 01MI72.
Organometallic compounds of siloles: 01AHC(79)115.

Silicon heterocycles as starting compounds, intermediates, and reaction products: 00MI32.

Spin chemistry of short-living intermediates in reactions of germanorbornadienes and digermabicyclooctadienes: 01IZV1830.

Stable cyclic silylenes: 00ACR704.

Thermally stable cyclic bis(amino)silylenes: 01JOM(617–618)209.

Unsaturated Si-heterocycles: 00PAC2333.

2. *Structure and Stereochemistry*

Electronic structure of Si-, Ge-, and Sn-heterocycles: 00MI12.

Homoatomic polyhedra as structural modules in Zintl ions $[E_9]^{3-}$ and $[E_9]^{4-}$ (E = Si, Ge, Sn, Pb): 01AG(E)4101.

3. *Reactivity*

Development of reactions of silacyclopropanes as new methods for stereoselective organic synthesis: 00ACR813.

Reactions of 4-sila-2,5-cyclohexadienylidenes investigated by direct spectroscopic methods: 01MI62.

Stereoselective introduction of C_2-units and the ring enlargement reaction of (3-oxa-2-silacyclopentyl)methyl radicals into 4-oxa-3-silacyclohexyl radicals via a pentavalent silicon-bridging radical: 01YGK589.

4. *Synthesis*

Dehydrocondensation of organylsilanes giving Si–Si bonds (formation of Si-heterocycles): 00UK150.

Flash vacuum thermolysis in synthesis of new reactive heterocycles with N = Si, P = Si, and S = Si double bonds: 00EJO3253.

Transition-metal-catalyzed additions of silicon-silicon and silicon-heteroatom bonds to unsaturated organic molecules (particularly, with formation of Si-heterocycles): 00CRV3221.

E. Selenium and Tellurium Heterocycles

1. *General Sources and Topics*

Syntheses of benzo[*b*]telluroles, benzo[*b*]selenophenes and dibenzotellurolo [3,4-*b*]tellurole: 01YGK355.

2. *Chemistry of Individual Classes of Heterocycles*

Tellurium–nitrogen-containing heterocycles: 01AHC(79)1.

Thermal methods for the synthesis of selenophene and its derivatives: 00KGS3.

F. Other Unusual Heterocycles

1. *Metallacycles*

Carbene complexes (Ti and Zr-cycles): 01JOM(617–618)81.

Formation of Ti- and Zr-heterocycles in reactions of titano- and zirconocenes with diynes and polyynes: 00ACR119.

Heck reaction as a sharpening stone of palladium catalysis: 00CRV3009.

Highly polar metal–metal bonds in "early-late" heterodimetallic complexes (metallocycles): 00AG(E)2658.

Inorganic antimony and bismuth 3-, 4- and 6-membered rings with organic substituents: 00CSR403.

Intramolecular *ortho*-palladation of N-donor ligands with formation of N,Pd-cycles: 00MI52.

Metallabenzenes: 01CRV1205.

Metal complex catalysis in the synthesis of organoaluminum compounds (formation of Al-heterocycles): 00UK134.

Organometallic polymers formed by ring-opening polymerization of ferrocenophane: 01MI141.

Organotitanium complexes (including Ti-heterocycles): 00CRV2835.

Palladacycles as intermediates in Heck reaction: 01T7449.

Palladacycles as simple, and efficient catalyst precursors for homogeneous catalysis: 01EJI1917.

Reactions of ruthenium and osmium cluster carbonyls with heteroatom-substituted and functionalized alkynes (metallocycles): 00IZV1.

Ring-opening polymerization of strained metallocyclophanes: 99CRV1515.

Self-assembling of metallacycles: 00CRV3483.

Structures and reaction mechanisms of organocuprate clusters including closed Cu-Li clusters: 00AG(E)3750.

Synthesis and reactivities of cubane-like sulfido clusters containing noble metals: 00ACR46.

Synthesis, structure, and properties of exohedral metallofullerenes M_nC_{60} (M = transition metal): 00ZSK164.

Titanacyclopropanes as versatile intermediates for carbon-carbon bond formation in reactions with unsaturated compounds: 00PAC1715.

Zirconium-phosphorus chemistry (metallocycles, P,Zr-heterocycles): 00AG(E)314.

2. *Metal Chelates and Related Complexes*

Chelate complexes of cyclopentadienyl ligands bearing pendant O-donors: 00CRV1495.

Diimine Ni- and Pd-chelates as highly active catalysts for olefin polymerization: 00MI27.

Ligand oxidation as method of intramolecular activation of metal chelates: 01IZV549.

Liquid-crystal complexes with heterocyclic ligands and chelates: 00KK803, 00KK883.

Metal chelates with N-containing ligands: 00AG(E)468.

Ni, Co, Fe, and Pd Chelates as catalysts for olefin polymerization: 01AG(E)534.

Platinum group organometallic "pincer complexes" as sensors, switches, and catalysts: 01AG(E)3750.

Supramolecular magnetic materials with heterocyclic and chelate structural fragments: 00ACR647.

Synthesis of metal chelates: 00MI14.

Thin copper films from vapor phase of volatile Cu(I) and Cu(II) chelates by chemical vapor deposition (CVD): 00UK1149.

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Annulated Heterocyclo-Purines I. Fused Five-Membered Heterocyclo-Purinediones, -Purinones, and -Purineimines

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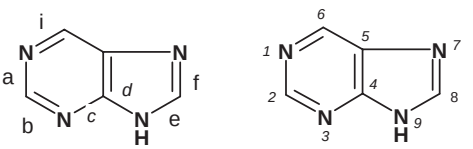
I. Introduction

Various purines have successfully been employed in medicine for some decades. The effort to obtain compounds with a greater selective efficacy without the unwanted side-effects then those of the parent purines, stimulated the study of annulated compounds. One route fulfilling this aim was the annulation of an heterocycle to the purine ring system.

The purine skeleton offers various possibilities for fusion of a further ring; the most studies tricyclic compounds were those with an annulation to bonds a, b, c, f, and i.



This review presents purines annulated with fused five-membered rings, as pyrrolo-, oxazolo-, thiazolo-, imidazo-, pyrazolo-, triazolo-, and tetrazolo-purines. Aiming to eliminate some misinterpretations (numbering of the skeleton in some papers did not match those in Chemical abstracts) atoms of the first scheme in each chapter will be numbered. Each group of compounds includes the synthesis, reactions of the heterocyclic system in question, biological effects, and, if accessible, also references about the detailed spectral data, X-ray analysis and so on. Papers were abstracted up to December 2002, inclusive vol. 137 of Chemical Abstracts.

Purines annulated with six and more-membered rings will be treated in a subsequent review.

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II. Purines Fused with Five-Membered Heterocycles

A. Pyrrolo-purines

1. *Pyrrolo[1,2-a]purines*

A representative of this type of compounds, 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]purine-9-amine (**3**), was accessible by heating 5-amino-imidazole-4-carbonitrile (**1**) with 5-ethoxy-3,4-dihydro-2*H*-pyrrole (**2**) (88JCS(P1)593). Compound **3** shows a *phytohormone effect* greater than that of benzyladenine (89JAP(K)1) (Scheme 1).

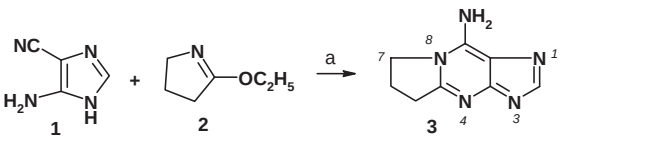
An analogous structure, 1,4,4a,5,6,7-hexahydro-1,4,4a-trimethyl-9*H*-pyrrolo-[1,2-*a*]purin-9-one (**5**), can be prepared by cyclization of a caffeidine homologue, 1-methyl-4-methylamino-imidazole-5-[*N*-(4-oxopentyl)carboxamide] (**4**) in ethanolic hydrogen chloride (Scheme 2). The *vasodilatation activity* of compound **5** was reported in (86CPB36).

2. *Pyrrolo[1,2-b]purines*

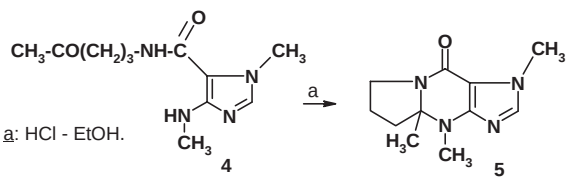
1-*H*-Pyrrolo[2,1-*b*]purin-4(5*H*)-one (**9**) was synthesized from ethyl 4-amino-imidazole-5-carboxylate (**6**) and 2,5-(diethoxy)tetrahydrofuran in heated acetic acid to give ethyl 4-(pyrrol-1-yl)imidazole-5-carboxylate (**7**), which afforded on treatment with hydrazine the required hydrazide. Subsequent reaction with isoamyl nitrite in acetic acid gave azide **8** followed by elimination of nitrogen to produce compounds **9**. Yields are low in all steps (9–26%) (82H(17)405) (Scheme 3).

3. *Pyrrolo[1,2-e]purines*

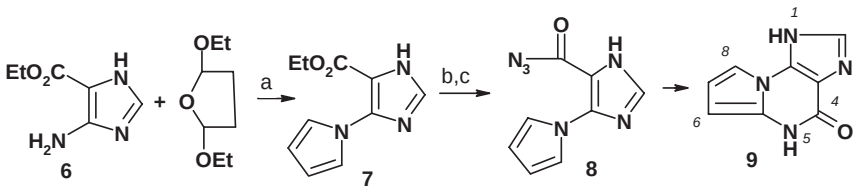
A representative of this group, 3,6,7,8-tetrahydro-4-oxo-4*H*-pyrrolo[1,2-*e*]-purine-8-carboxylic acid and various derivatives were obtained from ethyl 5-ethoxy-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**10**) and amino-cyanoacetamide (**11**) in ethanolic



Scheme 1

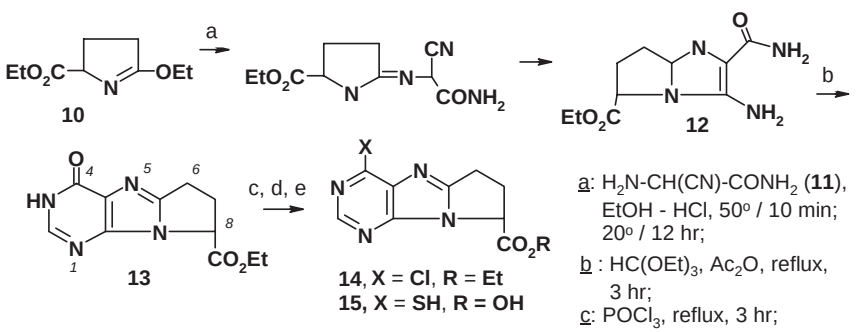


Scheme 2



a: AcOH,reflux / 1 hr; b: $H_2NNH_2.H_2O$, EtOH, reflux / 1 hr; c: AlkONO, AcOH.

Scheme 3



a: H_2N-CH(CN)-$CONH_2$ (**11**), EtOH - HCl, 50° / 10 min; 20° / 12 hr;
b : $HC(OEt)_3$, Ac_2O, reflux, 3 hr;
c: $POCl_3$, reflux, 3 hr;
d: $(H_2N)_2CS$, EtOH, reflux; e: 2N HCl, reflux, 1 hr.

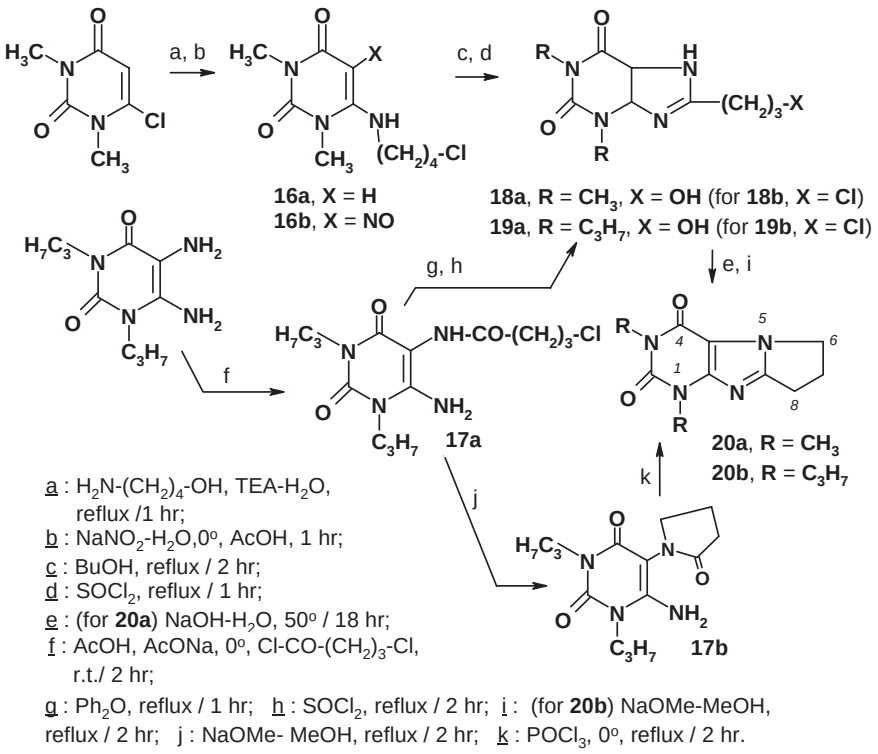
Scheme 4

hydrogen chloride giving pyrrolo-imidazole **12**; its cyclization in a mixture of ethyl orthoformate and acetic anhydride afforded ethyl 1,6,7,8-tetrahydro-4-oxo-4*H*-pyrrolo[1,2-*e*]purine-8-carboxylate (**13**). A stepwise treatment with phosphorus oxychloride and thiourea produced ethyl 4-chloro-7,8-dihydro-6*H*-pyrrolo[1,2-*e*]-purine-8-carboxylate (**14**) and its thiouronium salt, respectively. Acid hydrolysis of this salt gave 1,6,7,8-tetrahydro-4-thioxo-4*H*-pyrrolo[1,2-*e*]-purine-8-carboxylic acid (**15**) (73KFZ(11)14) (Scheme 4).

4. *Pyrrolo[2,1-f]purines*

Displacement of bromine by benzhydrylpiperazine in 8-(3-bromopropyl)-1,3-dimethyl- or 1-isobutyl-3-methyl-3,7-dihydro-1*H*-purine-2,6-diones gave rise to the required product and small amounts of 1,3-dimethyl- or 1-isobutyl-3-methyl-1,6,7,8-tetrahydro-2*H*-pyrrolo[1,2-*e*]-purine-2,4(3*H*)-dione and its [2,1-*f*] position isomer. The structures of both substances were corroborated by ^{1}H-NMR spectra (87EJM243).

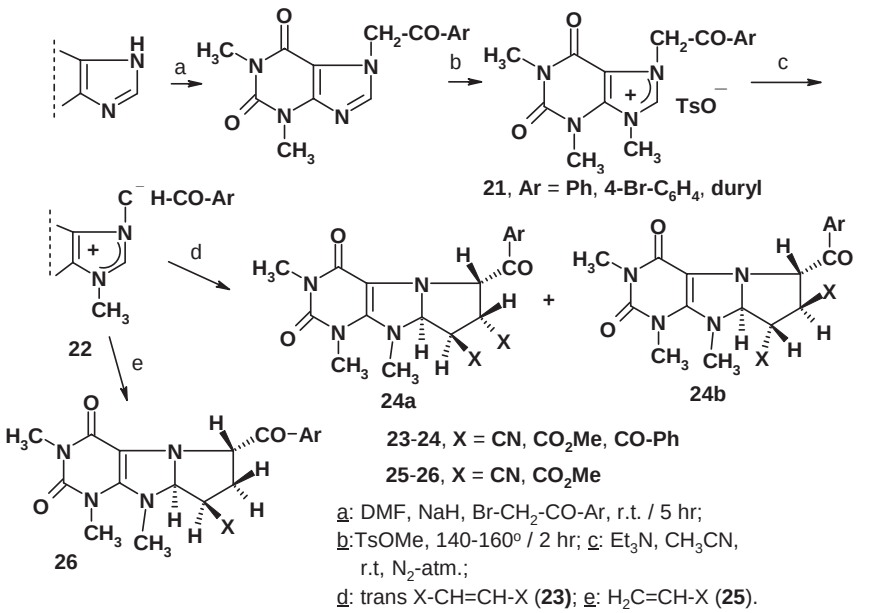
Of preparative importance are the following methods: *the first*, and most simple is based upon intramolecular alkylation of 8-(3-chloropropyl)purine intermediate **18b** in dilute alkali. The key intermediate **18b** was obtained by a four-step synthesis starting from 6-chloro-1,3-dimethyluracil and 4-(hydroxybutyl-amino)-5-nitrosouracil **16b**, its cyclodehydration to 8-(3-hydroxypropyl)-purinedione **18a** and reaction with thionyl chloride (85JHC105) (Scheme 5).



Scheme 5

An alternate method started from 5,6-diamino-1,3-dipropyluracil which reacted with 4-chlorobutyryl chloride to give 6-amino-5-(4-chlorobutyryl)amino-1,3-dipropyl-1*H*,3*H*-pyrimidine-2,4-dione (**17a**) and subsequently underwent cyclization in diphenyl ether under reflux. The water produced in this step hydrolyzed the product into 8-(3-hydroxypropyl)-1,3-dipropyl-7*H*-purine-2,4(1*H*,3*H*)-dione (**19a**). Heating the latter in thionyl chloride led to the appropriate 8-(3-chloropropyl) derivative **19b** which underwent intramolecular alkylation with $NaOCH_3$ to afford the final tricyclic **20b**. Another route started from 6-amino-5-(4-chlorobutyl)amino derivative **17a** by an intramolecular alkylation to 6-amino-5-(2-oxopyrolidin-1-yl)-1,3-dipropyl-1*H*,3*H*-pyrimidine-2,4-dione (**17b**) and its subsequent cyclization by phosphorus oxychloride under reflux to **20b** (94JHC81) (Scheme 5).

The second method was based on a cycloaddition reaction of olefinic and acetylenic dipolarophiles to xanthinium-(N_7) ylides. Xanthinium-(N_7) ylides **22** were generated from 7-substituted 1,3,9-trimethylxanthinium tosylates **21** by deprotonation with triethylamine in dry acetonitrile followed by reaction with dipolarophiles **23** and **25** (dimethyl fumarate, fumaronitrile, methyl acrylate, acrylonitrile and the like). Reaction with dimethyl fumarate afforded the *endo*-(**24a**) and exo-(**24b**) adducts in a 3:2 ratio. The stereochemistry of these compounds was established by ^{1}H-NMR and X-ray analysis (84H2199). With derivatives of acrylic acid **25**, only *endo* adducts (**26**)

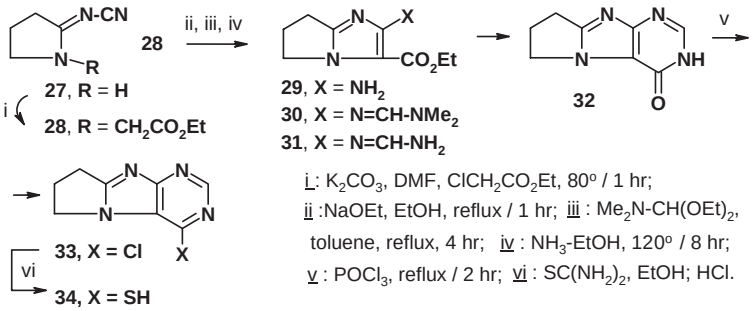


Scheme 6

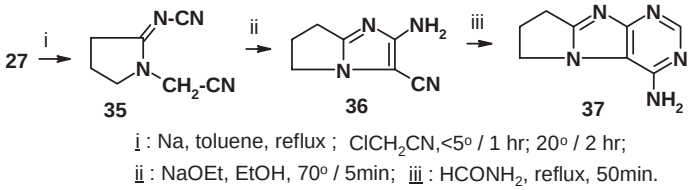
were furnished (87JCS(P1)1211) (Scheme 6). An analogous cycloaddition with dimethyl acetylene dicarboxylate or methyl propiolate led to unsaturated derivatives of **24** and **26** with a $C_{(7)}$–$C_{(8)}$ double bond (86CPB1328).

The previous two methods started from a purinedione derivative and the pyrrole moiety was built up. The following methods start from the pyrrole rings, the purine moiety being fused. Thus, starting from cyclic cyanamidine **27** 1-(ethoxycarbonyl-methyl)-2-cyanoimino-pyrrolidine (**28**) was obtained by alkylation with ethyl chloroacetate. Compound **28** afforded 2-amino-3-ethoxycarbonyl-5,6-dihydro-7*H*-pyrrolo[1,2-*a*]imidazole (**29**) by a cyclocondensation of the Claisen type. Further reaction with *N*,*N*-dimethylformamide diethyl acetal gave rise to 3-(ethoxycarbonyl)-2-(*N*,*N*-dimethylaminomethylenamino)-5,6-dihydro-7*H*-pyrrolo[1,2-*a*]imidazole (**30**) and then ammonolysis at elevated temperature gave amidine **31** which cyclized immediately to 7,8-dihydro-3*H*-pyrrolo[2,1-*f*]purin-4(6*H*)-one (**32**) (Scheme 7).

The enol form of compound **32** can be transformed into 4-chloro derivative **33** by phosphorus oxychloride. Thiourea with the latter produced a 6-mercapto derivative through the respective isothiouronium salt and mild hydrolysis. The last three compounds revealed *antitumor* and *antiviral activities* against Herpes simplex type 1 and influenza virus, respectively (92KFZ(9–10)63) (Scheme 7). 4-Chloro derivative **33** reacted with other nucleophiles to form 4-methoxy-, 4-benzylamino-, and 4-morpholino derivatives. Alkylation of the Na^+ or K^+ salt of 4-mercapto derivative **34** led to 4-benzylthio-, 4-(methoxycarbonyl)methyl-thio, and 4-(1-methyl-4-nitroimidazol-5-yl)thio derivatives. Similarly alkyl-amines with **30** formed 3-alkyl-7,8-dihydropyrrolo[2,1-*f*]purin-4(6*H*)-ones (95KFZ(2)27).



Scheme 7

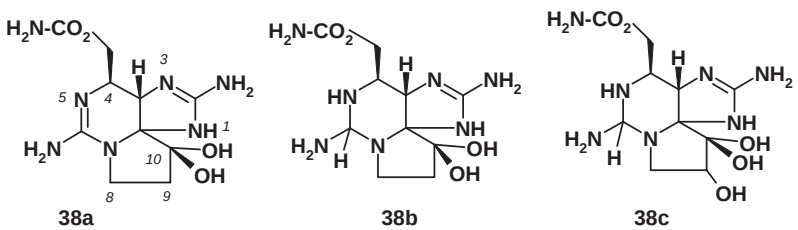


Scheme 8

Alkylation of sodium cyclic cyanamidine **27** with chloroacetonitrile produced 1-cyanomethyl-2-(cyanimino)pyrrolidine **35**. Thorpe-Ziegler reaction of the latter led to 2-amino-3-cyano-5,6-dihydro-7*H*-pyrrolo[1,2-*a*]imidazole (**36**) and cyclization with formamide on heating closed the third ring to 4-amino-7,8-dihydro-6*H*-pyrrolo [2,1-*f*]purine (**37**) (91KGS754) (Scheme 8).

5. *Pyrrolo[1,2-c]purines*

This unusual annulation was reported with *saxitoxin*, 2,6-diamino-4-{[(amino-carbonyl)oxy]methyl}-3a,4,8,9-tetrahydro-1*H*,10*H*-pyrrolo[1,2-*c*]-purine-10,10-diol (**38a**) isolated from tissue of a bullfrog and its derivatives, *neosaxitoxin*, 2,6-diamino-4-{[(aminocarbonyl)oxy]methyl}-3a,4,5,6,8,9-hexahydro-1*H*,10*H*-pyrrolo[1,2-*c*]purine-10,10-diol (**38b**) (91MI1)), *gonyautoxin*, 2,6-diamino-4-{[(aminocarbonyl)oxy]methyl}-3a,4,5,6,8,9-hexahydro-1*H*,10*H*-pyrrolo[1,2-*c*]purine-9,10,10-triol (**38c**) (Scheme 9). Application of these compounds as *local anaesthetics* was published by Kohane (98MIP1).



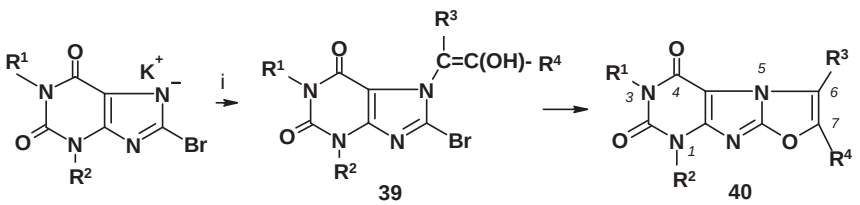
Scheme 9

B. Oxazolo-purines

1. *Oxazolo[2,1-f]purine-2,4-diones*

This heterocyclic skeleton is accessible by four methods: The *first* involves an intramolecular cyclization of the enolform of 8-bromo- or 8-chloro-7-(acylalkyl)-purinedione derivatives **39**, which were prepared from the potassium salt of 8-bromopurinediones and α-bromodialkyl- or α-bromoalkyl aryl ketones **41** under reflux in dimethylformamide giving derivatives of oxazolo[2,3-*f*]-purine-2,4-dione **40** (86KGS1133) (Scheme 10).

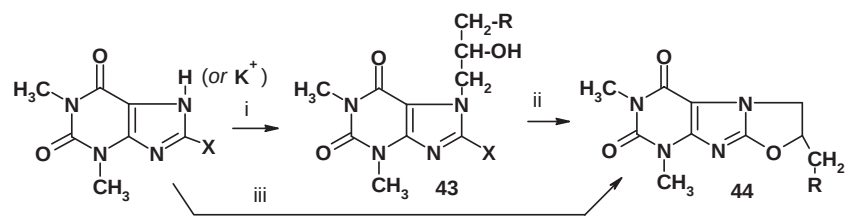
The second method is based on treatment of potassium salts of 8-halogeno-purine derivatives with derivatives of oxirane (e.g., epihalogenohydrin, glycidol, propylene oxide, butylene oxide, alkyl- or aryl-glycidyl ether) (**42**) in the presence of catalytic amounts of pyridine in propanol or aqueous ethanol to produce 8-halogeno-7-(2-hydroxyalkyl) derivatives **43**; intramolecular nucleophilic displacement (without isolation) in dilute hydroxide at room temperature or on heating (64JOC3126, 00EJO3489) furnished 7-substituted methyl-hexahydro-oxazolo[2,3-*f*]purinediones **44** (62MI1, 69M1797, 87KFZ566). Enantiomers formed at chiral carbon-7 can be distinguished by ^{1}H- and ^{13}C-NMR in the presence of dirhodium tetrakis[(R)-α-methoxy-α-(trifluoromethyl)-α-phenyl-acetate] as a chiral auxiliary (00EJO3489) (Scheme 11).



39, **40**, **R¹,R³** = **H**, **Alk**; **R²** = **Alk**; **R⁴** = **Alk, Aryl**

i : Br-CH(R^3)-CO-R^4(**41**), DMF, reflux, 0.5-1 hr.

Scheme 10



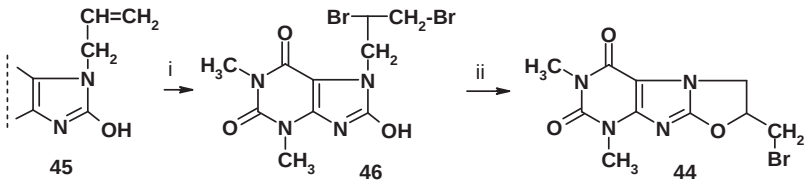
i :  (**42**),

(cat.) pyridine, PrOH *or* H_2O-EtOH;

42-44, **X** = **Cl**, **Br**, **R** = **Cl, Br, OH, H, Alk, AlkO, ArylO**

ii :NaOH-H_2O, (or H_2O-EtOH); iii :  , $Bu_4P^+ Br^-$, 90° / 12 hr, diglyme.

Scheme 11



Scheme 12

Another method involved a reaction of 8-chlorotheophylline with an excess of phenyl or aryl glycidyl ethers, or epichlorohydrin in the presence of tetrabutylphosphonium bromide as a phase-transfer catalyst in diglyme at 90 °C to produce **43** (92TL6307). Also, oxiranes and their precursors such as compounds of 3-halogenopropane-1,2-diol type can be employed with 8-halogenoxanthine (65MI1).

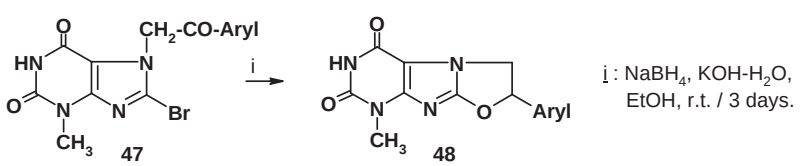
The third method closed the third oxazole ring having a bromomethyl group at $C_{(7)}$ (**44**) by a short heating of 7-(2,3-dibromopropyl)-8-hydroxyxanthines **46** (accessible by addition of bromine to 7-allyl-8-hydroxyxanthines **45** in alkali) (62MI1) (Scheme 12).

Formation of the third oxazole ring can also be realized by a reaction of epichlorohydrin with 8-nitro- or 8-(methanesulfonyl)-4-(2-hydroxypropyl)-xanthine derivatives (75JPR745).

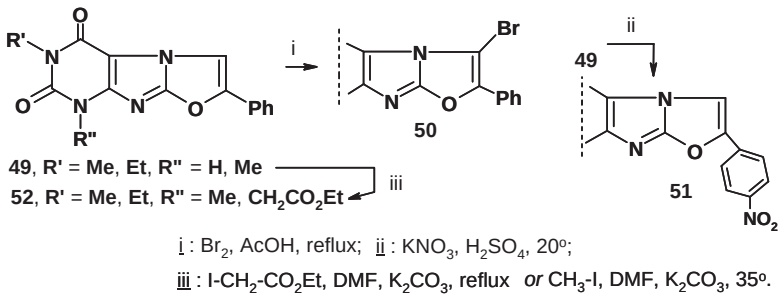
The fourth method was based upon the reduction of 8-bromo-7-(acylmethyl)-purine-2,6-dione **47** with sodium borohydride in alkali at ambient temperature through 8-bromo-7-[aryl-2-hydroxyethyl] derivative to 6,7-dihydro-7-aryl-oxazolo[2,3-*f*]purinediones **48** (90UKZ215) (Scheme 13).

Bromation of 1,3-dimethyl-7-phenyl-oxazolo[2,3-*f*]-purine-2,4-dione **49** (bromine in acetic acid), took place at position 6 (compound **50**). Nitration with potassium nitrate in sulfuric acid did not take place at C_6 but instead gave 7-(4-nitrophenyl)-oxazolo[2,3-*f*]purinedione derivate **51** due of the protonation of the oxazolo-purine ring system by acid. Alkylation at position 1 with ethyl iodoacetate in dimethylformamide in the presence of potassium carbonate gave **52** (90KGS1396) (Scheme 14).

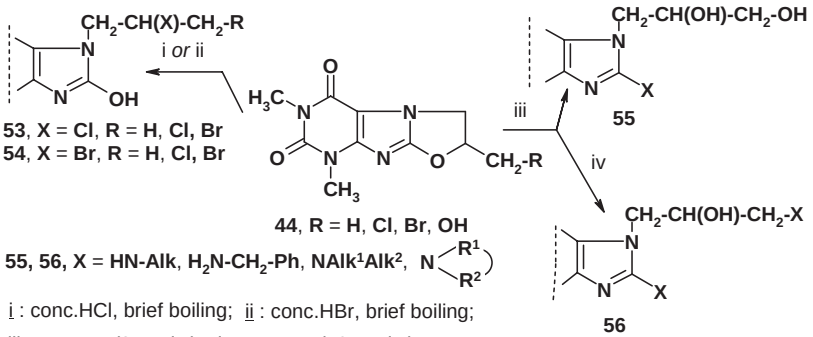
Hydrolytic cleavage of the dihydro-oxazolo ring of **44** with conc. HX gave 8-hydroxypurine-2,6-dione derivatives **53** and **54** (64JOC3126). The oxazole ring of **44 (R = Cl)** (1 mol) was similarly opened on ammonolysis with primary and secondary amines (2 mol); the substituted amino group entered position 7 of the xanthine derivative **55**. Provided the substituent in position 7 of 6,7-dihydro-oxazolo[2,3-*f*]purinediones is a halogenomethyl group and a large excess of amine was used



Scheme 13



Scheme 14



Scheme 15

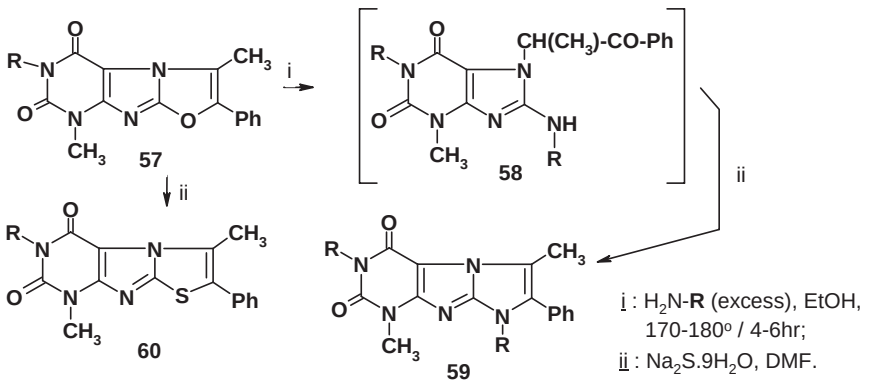
(1:10), two nucleophilic substitutions took place to form 8-substituted amino-7-(3-substituted amino-2-hydroxypropyl)-purinedione **56** (75MI1, 82MI1, 85MI1, 70AP378, 70AP596) (Scheme 15).

It is worth noting that the dihydro-oxazole ring cleavage of **44** with ammonia, alkylamines, aralkylamines, and cycloalkylamines proceeded much easier (reflux in ethanol, propanol) than the nucleophilic displacement of bromine in 8-bromo-7-(2-hydroxyalkyl) **43** (autoclave, 160–170 °C, ethanol) (87KFZ566).

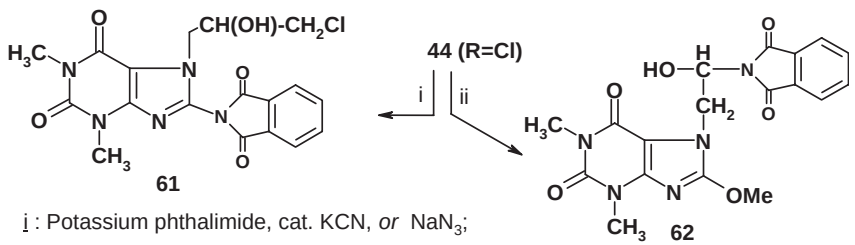
Opening of the oxazole ring of 7-hydroxymethyl, 7-aryloxymethyl or 7-alkoxymethyl derivatives **44** with hydrazine hydrate on reflux in methoxyethanol produced the corresponding 7-(2,3-dihydroxy- or 2-hydroxy-3-methoxy- or 2-hydroxy-3-aryloxy-propyl)-8-hydrazinopurinediones (81KFZ59).

Similar cleveage was encountered with the oxazole ring of unsaturated derivatives **57** with 2-4 molar excess of primary amines at 170–180 °C giving 8-alkylamino-7-acylalkyl-xanthines **58**; these then underwent cyclization to the respective imidazo-purinediones **59** (88KGS534). Thiazolo[2,3-*f*]purinediones **60** were found to be similarly formed with sodium sulfide in dimethylformamide (Scheme 16).

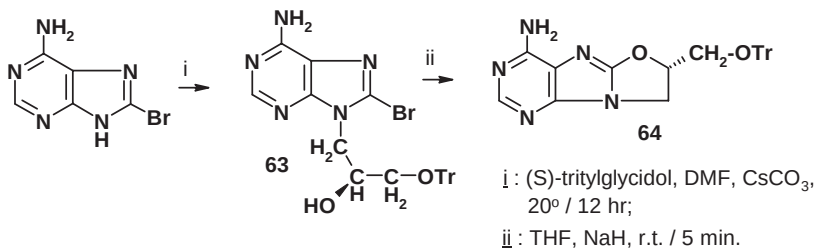
Depending on the catalyst, the dihydro-oxazole ring of 7-chloromethyl-6,7-dihydro-oxazolo[2,3-*f*]purinedione **44** (**R = Cl**) was cleaved in two ways: 8-phthalimido-7-(2-hydroxy-3-chloropropyl)-purinedione **61** and 8-methoxy-7-(3-phthalimido-2-hydroxypropyl)-purinedione **62** were created with KCN or NaN_3 and with $NaOCH_3$, respectively (78TL2049) (Scheme 17).



Scheme 16



Scheme 17



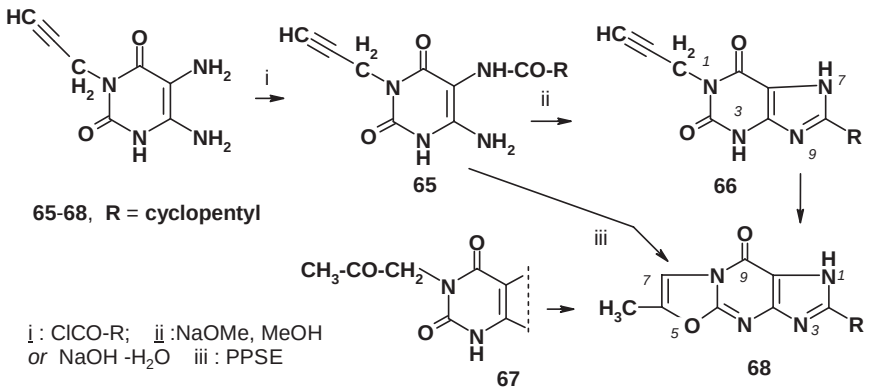
Scheme 18

2. *Oxazolo[3,2-e]purine-4-amines*

Heating 8-bromoadenine with tritylglycidol in formamide in the presence of a base produced (S)-8-bromo-9-[2-hydroxy-3-(trityloxy)propyl]adenine (**63**) which quickly cyclized to (S)-7-[(trityloxy)methyl]-7,8-dihydro-oxazolo[3,2-*e*]purin-4-amine **64** by NaH in an aprotic medium (00CCC1126) (Scheme 18).

3. *Oxazolo[3,2-a]purin-9-ones*

This heterocycle was observed on cyclization of 6-amino-5-(cyclopentane-carboxamido)-3-propargyluracil (**65**) with $NaOCH_3$ in methanol or with dilute



Scheme 19

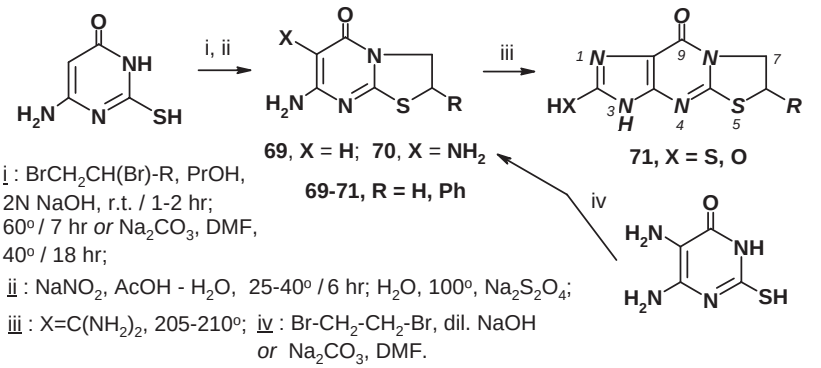
alkali leading to 8-cyclopentyl-1-propargyl-3,7-dihydro-1*H*-purine-2,6-dione (**66**). Concurrent hydratation of the triple bond of the propargyl group took place to give 1-(2-oxopropyl) derivative **67** and a consecutive intramolecular cyclization afforded 2-cyclopentyl-6-methyloxazolo[3,2-*a*]purin-9(1*H*)-one (**68**). Useful preparations employ the trimethylsilyl ester of polyphosphoric acid (PPSE) to cyclize 1-(2-oxopropyl)purinedione derivative **67**, or 3-propargyl-uracil derivative **65**, to their tricyclic derivatives **68** only. These compounds are efficient *antagonists* not only of *A_1 adenosine receptors* (33 times more effective than the reference 8-cyclopentyl-1-propyl-purinedione), but also *A_2 adenosine receptors* (55 times more effective) (94JOC1928) (Scheme 19).

C. THIAZOLO-PURINES

1. *Thiazolo[3,2-a]purine-2,4-diones*

The first synthetic *method* leading to these heterocycles started from 6-amino-2-thiouracil which cyclized with 1,2-dibromoalkanes to 7-amino-2-R-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-5-ones **69**. The latter was nitrosed at C-6 and reduced with sodium dithionite to 6,7-diamino-2,3-dihydro-2-R-5*H*-thiazolo-[3,2-*a*]pyrimidine-5-one **70**. The third imidazole ring was closed by fusion of the diamine **70** with urea or thiourea to 2-hydroxy- or 2-mercapto-6-R-6,7-dihydro-thiazolo[3,2-*a*]purin-9(1*H*)-ones **71**. An alternate route starting from 6-amino-2-thiouracil through 5,6-diamino-2-thiouracil (2 steps) cyclized with dibromoethane to diamine **70**. The annulation site of the thiazolo to pyrimidine rings of the intermediate **69** was corroborated by X-ray analysis. Compounds **71** were tested for *antiviral effect* (Herpes simplex type 1, Vasicular stomatitis virus, Coxsackie virus), but no significant efficacy was found (89JHC1701, 91FES899) (Scheme 20).

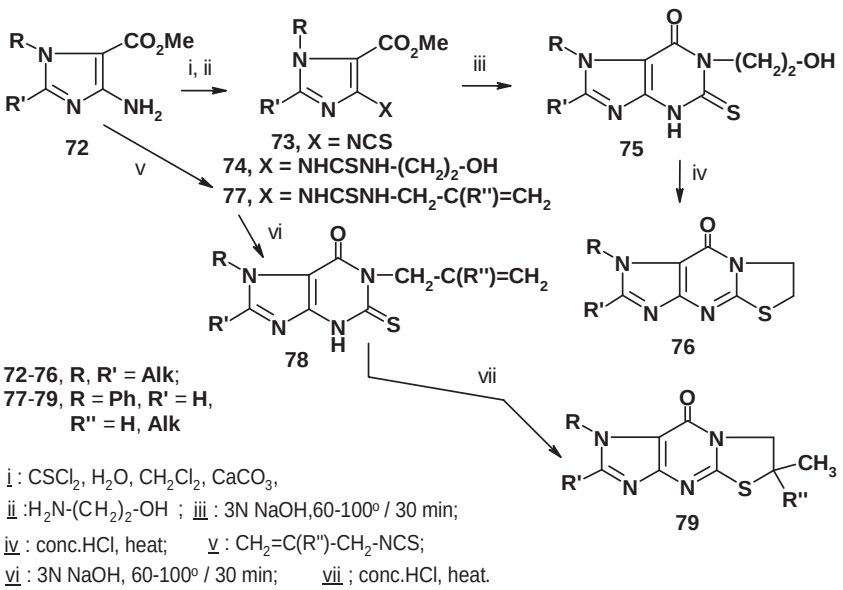
The second method employed methyl 4-amino-imidazol-5-carboxylate (**72**) which gave 1-R-2-R′-4-isothiocyanato-imidazole-5-carboxylate (**73**) with thiophosgene and methyl 1-R-2-R′-4-[1-(3-hydroxyethyl)thioureido]imidazole-5-carboxylate **74** with



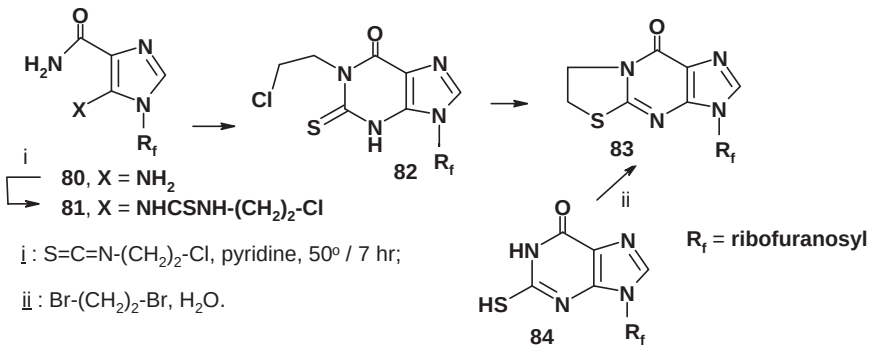
Scheme 20

ethanolamine. Cyclization proceeded with alkali to yield 7-R-8-R′-1-(2-hydroxyethyl)-1*H*,3*H*-2-thioxopurin-6-one (**75**). The third ring of the intermediate **75** was closed by heating with acid giving 1-R-2-R′-6,7-dihydro-thiazolo[3,2-*a*]purin-9(1*H*)-one (**76**).

A variation of this method was based on the same starting material **72**, which reacted with 2-alken-1-yl-isothiocyanate to produce methyl 1-R-2-R′-4-[1-(3-alkenyl)thioureido]imidazole-5-carboxylate **77**. Two similar cyclizations as shown with the previous method (through the intermediate **78**) originated 1-R-2-R′-6,7-dihydro-6-methyl- (with allyl isothiocyanate) and 1-R-2-R′-7-R″-6,7-dihydro-6-methylthiazolo[3,2-*a*]purin-9(1*H*)-one (**79**) (with 2-R″-alken-1-yl isothiocyanate) (89PHA533) (Scheme 21).



Scheme 21



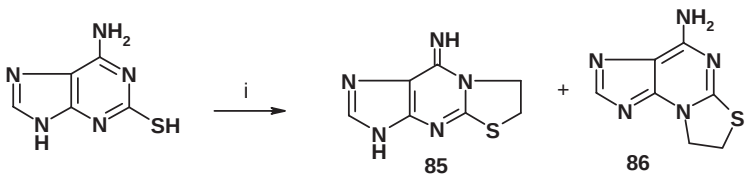
Scheme 22

Annulation of the bond "a" of the purine skeleton was evidenced by desulfuration of compound **76** with Raney-nickel: 1-ethyl derivative of hypoxanthine and 1-(2-R″-propyl) and 1-(2-R-ethyl) derivatives from compounds **79** and **71**, respectively being the products.

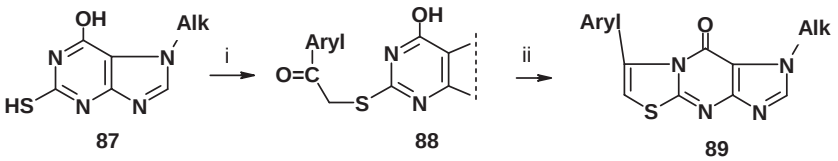
Further variant of this method utilized 5-amino-1-(β-D-ribofuranosyl)-imidazole-4-carboxamide **80**, which reacted with 2-chloroethyl isothiocyanate to afford 5-[3-(2-chloroethyl)-1-thioureido]-1-(β-D-ribofuranosyl)-imidazole-4-carboxamide (**81**), i.e., the reagent attacked the 5-amino group of the imidazole and not the nitrogen of the carboxamide owing to its low basicity. A long heating (3 days) in pyridine gave the required 3-(β-D-ribofuranosyl)-6,7-dihydrothiazolo[3,2-*a*]-purin-9(1*H*)-one (**83**) through the intermediate **82** (91JOC4213) (Scheme 22).

The crystallochemical structure of compound **83** was reported in Ref. 94AX(C)734.

The third access was based on the reaction of 1,2-dibromoethane with 2-mercapto-purin-9-one or 2-mercaptoadenine and their derivatives. Preparation of compound **83** from potassium or sodium 2-mercaptoinosine (**84**) with an excess of 1,2-dibromoethane in water exemplified the first reaction according to Scheme 22. The annulation site of thiazole to purine moieties was proven by desulfuration with Raney-nickel (after previous cleavage of the saccharide grouping) by the appearance of 1-ethylhypoxanthine (74CPB342). An example for the second reaction was the cyclization of 2-mercaptoadenine with an excess of dibromoethane giving a mixture of 3,6,7,9-tetrahydro-9-iminothiazolo[3,2-*a*]purine (**85**) and isomeric 4-amino-7,8-dihydro-thiazolo[2,3-*b*]purine (**86**). Both isomers were separated by their much different insolubility in chloroform (80JHC583) (Scheme 23).



Scheme 23



87 88 89

i : Aryl-CO-CH_2-(Cl/Br), H_2O, iso-PrOH, KOH; ii :conc.H_2SO_4

Scheme 24

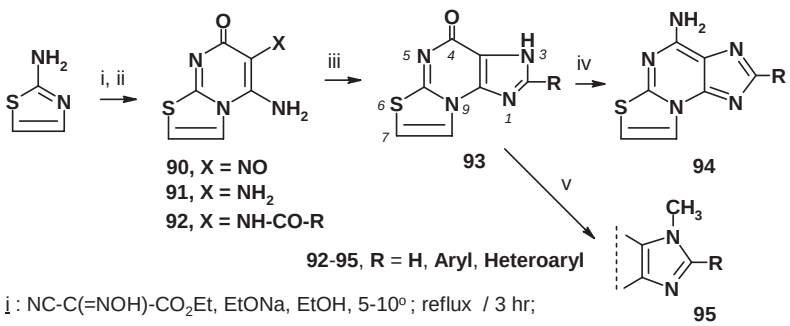
The *fourth method* employed alkylation of 2-mercaptohypoxanthine derivatives (**87**) with aroylmethyl halides to 2-(aroylmethylthio)-7-alkyl-hypoxathines (**88**) and their cyclization to 7-aryl-1-alkyl-thiazolo-[3,2-*a*]purin-9(1*H*)-ones (**89**) with conc. sulfuric acid (89UKZ1076) (Scheme 24).

Compound **71** (R = H; X = O) was shown to have an *immunomodulation* effect (88MIP1).

2. *Thiazolo[2,3-b]purin-9-ones*

In addition to cyclization of 2-mercaptoadenines with dibromoethane to a mixture of [2,3-*b*] and [3,2-*a*] isomers (**86**, **85**) shown in Scheme 23, the method starting from 2-aminothiazole also produced this heterocycle. This compound—a cyclic isothiourea—was condensed with ethyl nitrosocyanoacetate to 5-amino-6-nitroso-thiazolo[3,2-*a*]pyrimidin-7-one (**90**). Reduction of the nitroso group with sodium dithionite to 6-amino derivative **91** followed by acylation with acyl chloride yielded 5-amino-6-acylaminothiazolo[3,2-*a*]pyrimidin-7-one (**92**). Heating **92** with polyphosphoric acid produced 2-aryl- or 2-heteroaryl-thiazolo[2,3-*b*]purin-4(3*H*)-ones **93**.

Known are two of its reactions: Phosphorus oxychloride first chlorinated the molecule to a 4-chloro derivative and methanolic ammonia gave 4-amino-2-aryl- or 2-heteroaryl-thiazolo[2,3-*b*]purines **94**. Alkylation of the sodium salt of **93** with methyl tosylate afforded 3-methyl-2-aryl- or 2-heteroaryl-thiazolo[2,3-*b*]purin-4(3*H*)-ones **95** (95JHC1725) (Scheme 25).



i : NC-C(=NOH)-CO_2Et, EtONa, EtOH, 5-10°; reflux / 3 hr;

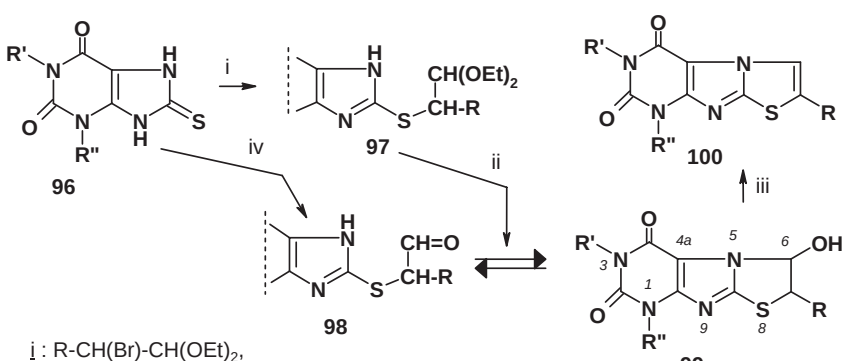
ii : $Na_2S_2O_4$ / 30%NH_4OH, 70-80°; Cl-CO-R, pyridine, 0-5°; r.t. / overnight;

iii : PPA, 100-110° / 6 hr; iv : $POCl_3$; NH_3 / MeOH; v : NaH, DMF, TsOMe

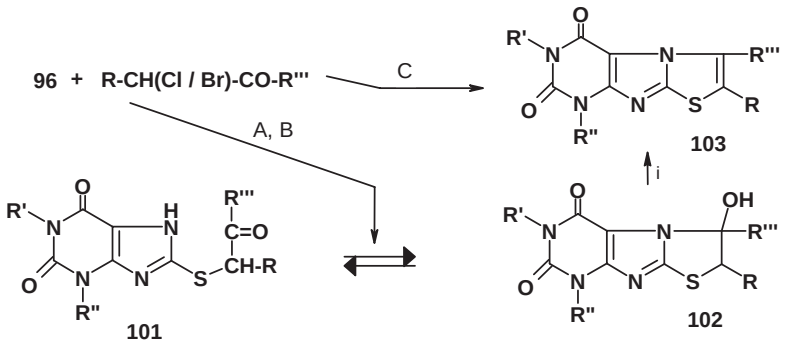
Scheme 25

3. *Thiazolo[2,3-f]purin-4-ones and -2,4-diones*

Purines fused to thiazole ring at bond "f" were the most studied subgroup of thiazolopurines; six methods were described to achieve this heterocycle: *the first* issuing from 8-mercaptopurine derivative **96** and α-halogenocarbaldehyde acetals gave purin-8-ylthiocarbaldehyde acetals **97** which underwent an easy hydrolysis to carbaldehydes **98** appearing together with their tautomeric-cyclic form **99**. The same tautomeric mixture was also prepared from mercapto derivative **96** with α-halogenocarbaldehydes or their acetals. The existence of a cyclic tautomeric form was proven by their IR spectra of the solid reaction product lacking the band belonging to an aldehyde group but revealing that of a hydroxyl group at 3170 cm^{-1}. On the other hand, a solution of this reaction product in alcohols or dimethyl sulfoxide showed an equilibrium between both forms, the aldehyde being corroborated by formation of its dinitrophenyl-hydrazone.The mixture of tautomers **98** and **99** furnished the substituted 7-alkyl- or 7-aryl-thiazolo[2,3-*f*]purine-2,4(1*H*,3*H*)-diones **100** with dehydrating reagents. The annulation site of the thiazole ring was demonstrated by desulfuration of compounds **100** with Raney-nickel giving a 7-substituted purinedione. The 9-substituted purinedione was not formed consistent with the finding that no [3,2-*e*]-isomers were isolated (72KGS996) (Scheme 26). Reaction of 8-mercaptopurine derivative **96** with α-halogenoalkyl aryl- or α-halogenoalkyl heteroaryl ketones or α-halogenodialkyl ketones in alcohols or in the presence of dimethylformamide (methods A,B,C), or in an excess of α-halogenodialkyl ketones (method D) gave 9-(acylalkylthio)purinediones **101** equilibrated with their cyclic tautomeric form **102** just as with tautomeric forms **98** and **99**. The tautomers **101**, and **102** were transformed by various dehydrating reagents into 6-alkyl- or 6-aryl- or 6,7-dialkyl- or 7-alkyl-6-aryl-thiazolo[2,3-*f*]purine-2,4(1*H*,3*H*)-diones **103**, or, when using cycloalkanons into



Scheme 26



Method A : [EtOH, EtONa, 60-65° / 1-13 hr]; *for* **R** = **H**, **CH_3**; **R'''** = **Alk**, **Aryl**, **Heteroaryl** ; Method B : [EtOH or DMF, 5-6 hr / r.t.]; *for* **R** = **H**; **R'''** = **$C(CH_3)_3$**, **Aryl** ; Method C : [EtOH, reflux / 4-7 hr]; *for* **R** = **H**, **CH_3**; **R'''** = **Alk**; **R+R'''** = **(CH_2)n**, **n = 3**,**4**; [for Method A and B] i : - H_2O, cat.H^+.

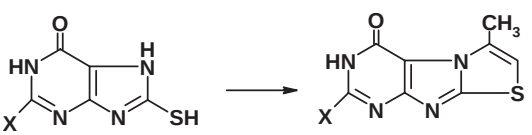
Scheme 27

6,7-trimethylene- or 6,7-tetramethylene-thiazolo[2,3-*f*]-purine-2,4(1*H*,3*H*)-diones **103** ($R + R''' = [CH_2]_{3,4}$) (74KGS693, 87KGS1534). An exceptional case was the appearance of 6-chloromethyl derivative **103** ($R = H$, $R' = R'' = H$, Alk, $R''' = CH_2Cl$) from 1,3-dichloro-acetone (94KFZ(8)21) (Scheme 27).

Method D is illustrated in Scheme 28: The sodium salt of 8-mercapto-xanthine reacted with chloroacetone and the resulting tautomeric intermediates were dehydrated with ethanolic hydrogen chloride to a tricyclic 6-methyl-thiazolo[2,3-*f*]-purine-2,4(1*H*,3*H*)-dione **104**.

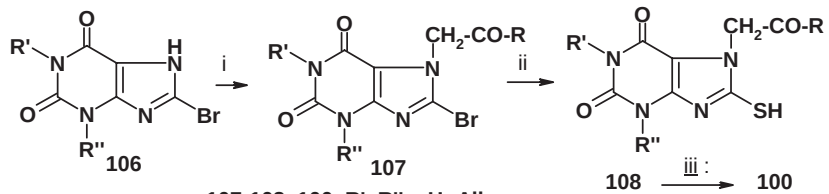
The 8-mercaptohypoxanthine derivatives reacted similarly as the xanthines **96** with halogenated carbonyl compounds to afford 6-alkylthiazolo[2,3-*f*]purine-4(3*H*)-one e.g., **105** (73CPB256) (Scheme 28). The structures of compounds **103** showing the "f"-bond fusion were proven by desulfuration with Raney- nickel yielding the 7-substituted purin-one or -dione.

The second useful preparation of thiazolo[2,3-*f*] purinediones started from 8-bromopurine-2,6-diones **106**, their conversion into sodium salts and reaction with α-halogenated ketones to 7-[(X-benzoyl)methyl]- or 7-(acylmethyl)-8-bromopurine-diones **107**. The following reaction with sodium hydrogen sulfide and elimination of water gave 7-[(X-benzoyl)methyl]- or 7-(acylmethyl)-8-mercaptopurines **108** and



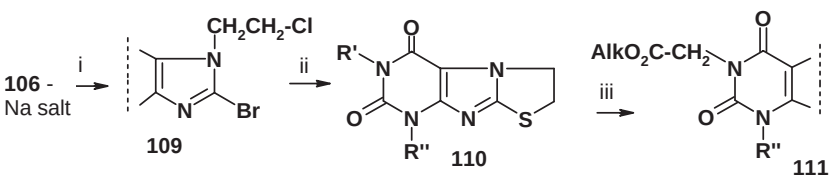
Method D : 1. NaOH-H_2O, 2. Cl-CH_2-CO-CH_3, reflux / 30 min., 3. HCl-EtOH

Scheme 28



i :EtONa, EtOH, R-CO-CH_2(Cl/Br), reflux / 5 hr; ii : NaHS, EtOH, reflux /25 hr;
iii : - H_2O, cat.H^+.

Scheme 29



i : Br-CH_2CH_2-Cl, DMF;
ii : Na_2S, DMF, reflux / 2 hr; iii ; (Cl/Br)-CH_2-CO_2Alk, DMF, K_2CO_3, reflux / 2 hr.

Scheme 30

the required 7-alkyl- or 7-aryl- purine-2,4(1*H*,3*H*)-diones **100** (75KGS1121) (Scheme 29).

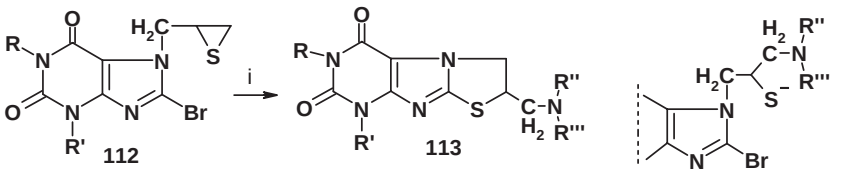
The third method utilized 8-bromo-7-(2-chloroethyl)purine-2,4-dione **109** obtained by alkylation of the sodium salt of 8-bromopurinedione with 1-bromo-2-chloroethane, followed by cyclization with sodium sulfide producing 1,3-dialkyl-6,7-dihydrothiazolo-[2,3-*f*]purine-2,4(1*H*,3*H*)-diones **110** (96KFZ(3)49) (Scheme 30).

Provided R′ = H, compound **110** can by alkylated with halogenoacetates to compounds **111** revealing a *diuretic effect*.

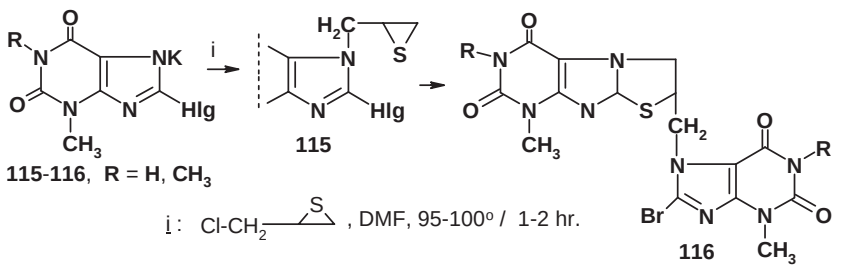
Reaction of 8-mercaptohypoxanthine with 1,2-dibromoethane in liquid ammonia can be taken as a modification of this method. The reaction product was the equimolar mixture of 6,7-dihydrothiazolo[2,3-*f*]-purine-4(1*H*)-one and 7,8-dihydrothiazolo[3,2-*e*]purine-4(1*H*)-one (00ZOK160).

The fourth method consisted in conversion of 1,3-dialkyl-7-aryloxazolo[2,3-*f*]-purine-2,4(1*H*,3*H*)-diones **57** with sodium sulfide to 1,3-dialkyl-7-aryl-thiazolo[2,3-*f*]purine-2,4(1*H*,3*H*)-diones **60** (cf. Scheme 16) (90KGS1396).

The fifth method was based on reaction of 8-halogeno-7-(thiiranylmethyl)-purinediones **112** with primary or secondary amines to generate 7-[*N*,*N*-(R″,R‴) aminomethyl]-6,7-dihydrothiazolo[2,3-*f*]purine-2,4(1*H*,3*H*)-diones **113** (91KGS840, 94KFZ(9)33). This reaction was presumed to proceed through thiolate anion **114** which displaced bromide ion from position 8. Compounds **113** were tested for *diuretic* and *hypoglycaemic effects* without any significant result (Scheme 31).



Scheme 31

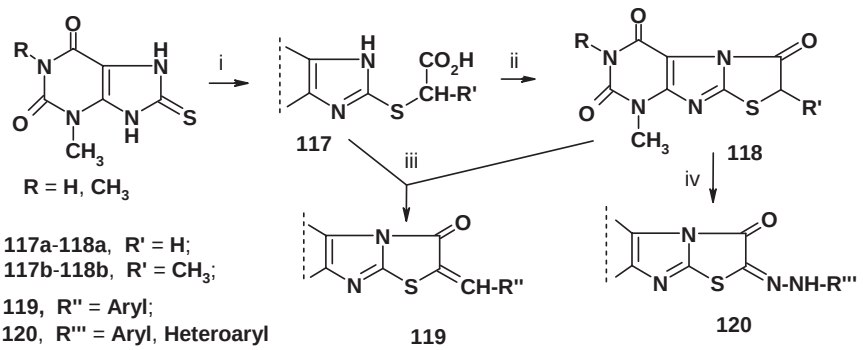


Scheme 32

Also, heating potassium 8-halogenopurinediones with chloromethylthiirane is a reaction of this type. Instead of the expected 8-halogeno-7-(thiiranomethyl)-purinediones **115** compounds **116** were obtained. This reaction course can be explained provided the intermediate 7-thiiranomethyl derivatives **115** first reacted with the potassium salt of the starting xanthines to give a new intermediate with a thiolate side chain, which in turn closed the third thiazole ring. This reaction proceeded also when using an equimolar amount of potassium 8-halogenopurine (88KGS1284) (Scheme 32).

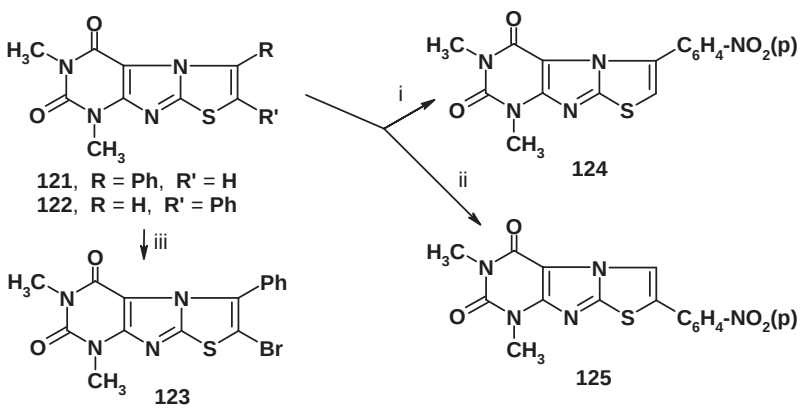
The sixth method utilized the reaction of 8-mercaptopurine-2,4-diones with 2-halogenoalkanoic acid to 8-[(1-carboxy-1-alkyl)thio]purine-2,4-diones **117** and their subsequent dehydratation to thiazolo[2,3-*f*]purine-2,4,6-(1*H*,3*H*,6*H*)-triones **118**. When halogenoacetic acid was applied a tricyclic compound with a methylene group in position 7 (**118a**) was obtained; the latter can undergo condensation with substituted 4-X-benzaldehydes or 5-X-furals to 7-[(4-X-phenyl)methylene]- or 7-[(5-X-furyl)methylene]-thiazolo[2,3-*f*]purine-2,4,6(1*H*,3*H*,6*H*)-triones **119**. The activated methylene group in compound **118a** could also undergo coupling with substituted benzenediazonium fluoro-borates to yield 7-[(X-phenyl)hydrazone]-thiazolo[2,3-*f*]purine-2,4,6,7(1*H*,3*H*)-tetrones **120** (82UKZ514, 88UKZ195) (Scheme 33).

Electrophilic substitutions of thiazolo[2,3-*f*]purinediones were demonstrated by the reaction of 1,3-dimethyl-6-phenylthiazolo[2,3-*f*]purine-2,4(1*H*,3*H*)-dione (**121**) with bromine or N-bromosuccinimide producing the 7-bromo derivative **123**.



i : R'-CH(Cl / Br)-COOH, AcOH, reflux / 30 min, or MeOH, reflux / 2 hr ;
ii : Ac_2O, reflux, 20 min; iii : (*for* **117a**, **118a**) AcONa, Ac_2O, R''-CHO, reflux / 3 hr ;
iv : (*for* **118a**) AcOH, AcONa, Ac_2O, R''-N_2^+ BF_4^- in MeOH, 20° / 18-20 hr .

Scheme 33

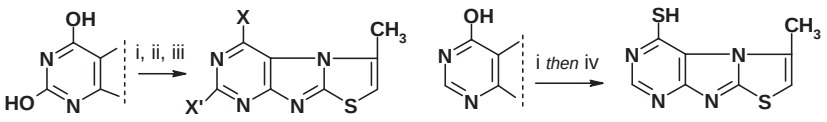


i : (*for* **121**) KNO_3, H_2SO_4, r.t. / 3 hr ; ii ; (*for* **122**) KNO_3, H_2SO_4, r.t. / 3 hr ;
iii : (*for* **121**) Br_2, $CHCl_3$ / CCl_4, 0°-r.t. / 2 hr *or* NBS, CCl_4, reflux / 3 hr .

Scheme 34

Attempts to brominate the free position 6 of compound **122** failed; so also did the attempt to nitrate **121** or **122** because the nitro group entered the most accessible position of the phenyl ring to give either 6-(4-nitrophenyl)- (**124**), or 7-(4-nitrophenyl) derivative **125**. Attempts to acylate, formylate, hydroxymethylate, chloromethylate of aminomethylate 6- or 7-substituted thiazolo[2,3-*f*]purinediones **121** and **122** also resulted in failure. The bromo group of 7-bromo derivative **123** did not react with either ammonia or amines (81KGS1267) (Scheme 34). The alkylation at $N_{(3)}$ with halogenoacetate is illustrated in Scheme 30.

Displacement of the enolic hydroxyls by chloride and further nucleophilic displacement with ammonia, amines or thiourea followed by hydrolysis of the



126 **127**, **X**, **X'** = **Cl**
128, **X** = **NH$_2$**, **X'** = **Cl**
129, **X**, **X'** = **morpholino**

130 **131**

i : $POCl_3$, reflux, 3 hr ; ii : CH_3Cl, EtOH, NH_3(g), r.t. / 5 day; iii : morpholine, reflux / 1 hr ; iv : 1. $(NH_2)_2C=S$, EtOH, heat ; 2. NaOH-H_2O.

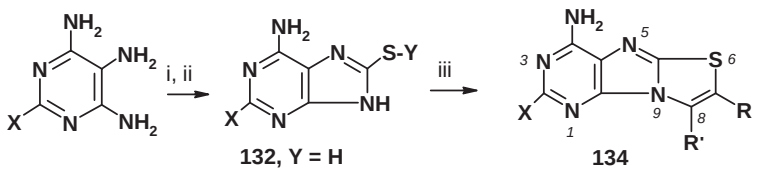
Scheme 35

isothiuronium salt, constituted an access to further derivatives as illustrated in Scheme 35 (73CPB256). Reaction of the activated methylene group in the thiazole moiety with an aromatic aldehyde and coupling with diazonium salts is presented in Scheme 33.

The IR spectra of [2,3-*f*]-derivatives were reported in Ref. 87KGS1534; the mass-spectrometric fragmentations of these heterocycles were given in Ref. 81KGS1267 and 87KGS1534.

4. *4-Amino-thiazolo[3,2-e]purines*

The synthesis of this heterocycle was based on cyclization of 8-[(acylalkyl)-thio]adenine derivatives **133** by heating with hydrogen chloride or with poly-phosphoric acid producing 4-amino-2-X-7-R-8-R′-thiazolo-[3,2-*e*]purine derivatives **134** in a modification of the method of cyclization of 8-[(acylalkyl)-thio]purinedione derivatives **101** and **102** (cf. Scheme 27) affording, however, compounds with a thiazole moiety fused to bond "f" of the purine ring. A diversity of the 6-aminopurine derivatives was manifested by the formation of compounds with a thiazolo moiety fused to bond "e" of the purine ring system. Some similarity with this approach is observed when alkylating xanthines and hypoxanthines to 7-alkyl-6-hydroxypurines and adenines to 9-alkyl-6-aminopurines. Preparation of the crucial intermediates **133** started from 2-substituted 4,5,6-triaminopyrimidines and carbon



132, **Y** = **H**
133, **Y** = **CH(R)-CO-R'**

134

132-134, **X** = **H**, **SCH$_3$**, **Cl**; **R** =**H, Alk, tert.Alk, Aryl**; **R'** = **H**, **Me**

i : CS_2 in pyridine, 60-70° / 30 min *or* $SC(NH_2)_2$, fusion; ii : 0.4 N NaOH ; Br / Cl-CH(R)-CO-R', EtOH, r.t. / 3 hr ; iii :EtOH, HCl(g), 1 hr ; reflux / 2 hr *or* PPA, 140-150° / 3 hr .

Scheme 36

disulfide or thiourea giving 8-mercaptoadenine derivatives **132**; their alkylation with α-halogenated ketones originated **133** which cyclized to **134** (Scheme 36). The fusion site was demonstrated by desulfuration of compounds **134** (X = H and SCH_3; R = H; R′ = Me) by Raney-nickel to 9-isopropyladenine and **134** (X = Cl; R = H; R′ = Me) to 2-chloro-9-isopropyladenine, respectively (73CPB342).

5. *Thiazolo[2,3-i]purines*

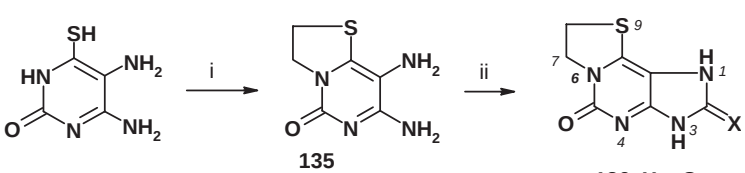
Three methods were reported to obtain the title compounds. *The first* was based on a reaction sequence starting from 5,6-diamino-4-thiouracil-sodium salt, alkylation with 1,2-dibromoethane to 7,8-diamino-2,3-dihydro-5*H*-thiazolo-[3,2-*c*]pyrimidine (**135**) and fusion with urea or thiourea under formation of a third ring to the respective 7,8-dihydrothiazolo[2,3-*i*]purine-2,5(1*H*,3*H*)-dione (**136**) and 2,3,7,8-tetrahydro-2-thioxothiazolo[2,3-*i*]purin-5(1*H*)-one (**137**) (92FES1315) (Scheme 37).

The second method started from derivatives of 6-mercaptopurines and α-halogeno-alkyl or -aryl or -heteroaryl ketones with conversion to the respective 6-[(acylalkyl)thio]- or 6-[(aroylmethyl)thio]- or 6-[(heteroaroylmethyl)thio]-purines **138** and tautomeric 7-hydroxy-7,8-dihydrothiazolo[2,3-*i*]-purines **139**. The final step of this synthesis was cyclodehydratation.

The theoretically possible formation of thiazino[2,3,4-*g*,*h*]purine **141** was not observed. The cited fusion of the thiazole ring of compound **140** (R, R′ = H) was corroborated by desulfuration with Raney-nickel to 1-ethylpurine (**142**) (96KGS 265) (Scheme 38).

Also, preparation of tautomeric **138** and **139**, having both substituents R,R′ = H was described from 6-mercaptopurine and halogenoacetaldehyde dialkyl acetals to form 6-[(2,2-dialkoxyethyl)thio]purines (77PHA558). The acid hydrolysis of the acetal groups gave 2-[(9*H*-purin-6-yl)thio]acetaldehyde. An alternate method giving this aldehyde started from 6-mercaptopurine and glycidol to 6-[(2,3-dihydroxypropyl)thio]purine and subsequent cleavage by periodic acid. 2-[(9*H*-Purin-6-yl)thio]acetaldehyde was also present in the mixture as a cyclic tautomeric form as demonstrated by its reaction with semicarbazide or dinitrophenylhydrazine backed by IR and ^{1}H-NMR (93 KGS1548) of the products.

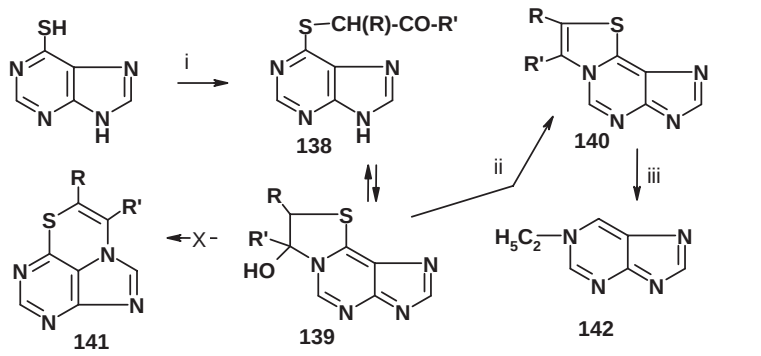
The third method is exemplified by reaction of 6-chloropurine with epichlorohydrin in the presence of alkalies giving a 1:1 mixture of 7-hydroxymethyl-7,8-dihydrothiazolo[2,3-*i*]purine (**143**) and 8-hydroxy-8,9-dihydro-7*H*-thiazino[2,3-*i*]purine



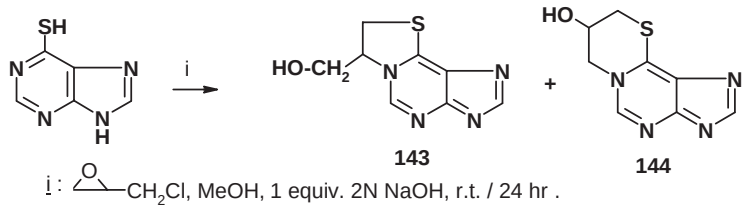
135 **136**, X = O **137**, X = S

i : 2N NaOH-PrOH, Br-CH_2CH_2-Br, r.t. / 12 hr ; 50-55° / 4 hr ;
ii : X=$C(NH_2)_2$, 220-230° .

Scheme 37



Scheme 38



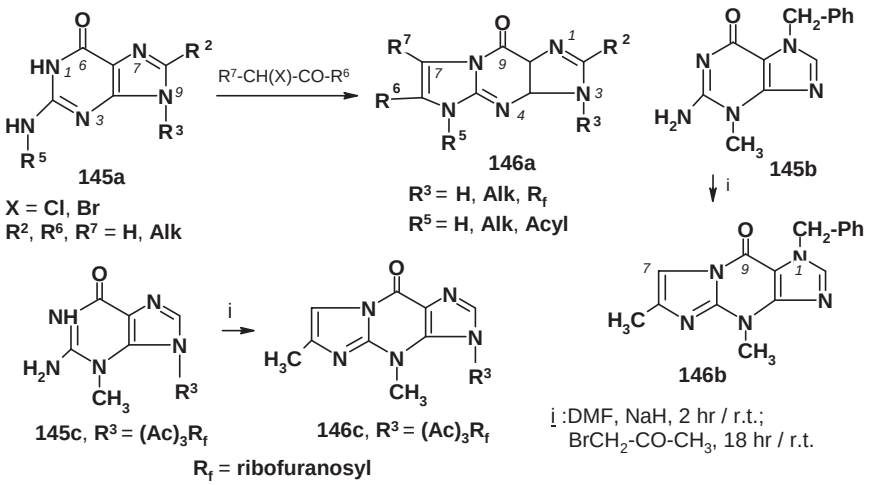
Scheme 39

(**144**). The unwanted product **144** could be separated by HPLC (72KGS996) (Scheme 39).

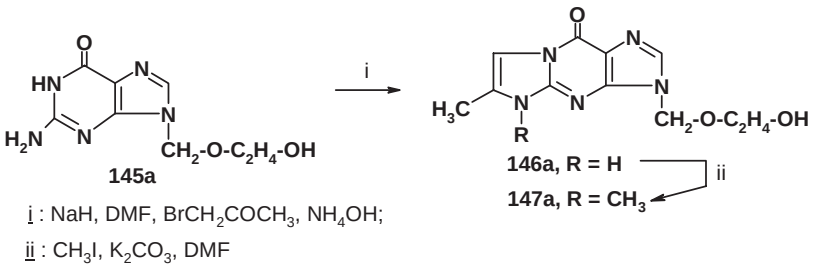
D. Imidazo-purines

1. *Imidazo[1,2-a]purin-9-ones*

To date two methods were reported to achieve this ring system: *in the first* 2-aminopurin-6-one (guanine) derivatives **145** were treated with α-halogenated carbonyl compounds to form a further ring fused to the "a" bond of the purine ring (compounds **146**) (Scheme 40). Introduction of substituents R^6, R^7 in the basic skeleton depended on the α-halogenated carbonyl compounds used. Substituents R^2 and R^3 had to be present initially in the starting guanine **145**. The 7- or 9-substituted guanines were employed advantageously when alkylation of nitrogen atom in the tricyclic derivative had no regioselective course. Thus, 7-benzyl-3-methylguanine (**145b**) afforded 1-benzyl-4,9-dihydro-4,6-dimethyl-1*H*-imidazo[1,2-*a*]purin-9-one (**146b**) (78JOC1644) and 9-(tri-*O*-acetyl-β-D-ribofuranosyl)-3-methylguanine (**145c**)



Scheme 40



Scheme 41

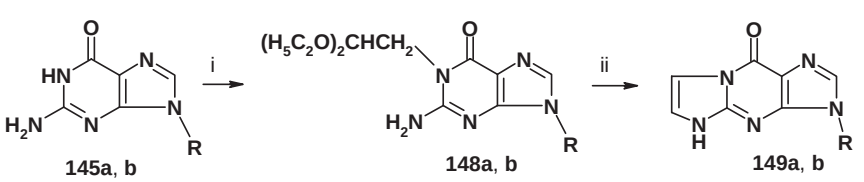
gave 3-(tri-*O*-acetyl-*β*-D-ribofuranosyl)-5,9-dihydro-4,6-dimethyl-3*H*-imidazo-[1,2-*a*]purin-9-one (**146c**) (87CPB4372). The substituent R^5 can be present either in the starting guanine or introduced into the new heterocycle by alkylation. This method was applied when preparing new potential analogues of contemporaneous virostatica—derivatives of guanine, namely 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)-methyl]-6*H*-purin-6-one = "acyclovir", 2-amino-1,9-dihydro-9-[(1,3-dihydroxy-2-propoxy)methyl]-6*H*-purin-6-one = "gancyclovir" and simpler model compounds. Thus, the 1-sodium salt of acyclovir **145a** reacted stepwise with bromoacetone and ammonia to give 5,9-dihydro-3-[(2-hydroxyethoxy)methyl]-6-methyl-3*H*-imidazo[1,2-*a*]-purin-9-one (**146a**). Subsequent methylation with methyl iodide gave the corresponding 5-methyl derivative **147a**. This substance is *effective against Herpes simplex type 1 and 2* (88JMC1351) (Scheme 41). 3-Methylguanine afforded the 4,6-dimethyl derivative with bromoacetone and with *α*-bromopropionaldehyde the isomeric 4,7-dimethylimidazo[1,2-*a*]purin-9-one. The position of methyl groups in both substances was verified by ^{1}H-NMR (71TL2725). Also water-free potassium carbonate can substitute sodium hydride. The difference in yields of the tricyclic product with both alkaline reagents was seen when reacting 7-benzyl-3-methylguanine with bromoacetone and sodium hydride (yield 41%) or potassium carbonate (81%) (89CPB284, 90CPB2656). Water-free dimethyl sulfoxide was the

alternate medium for this cyclocondensation reaction. Thus, from 9-alkyl-3-methylguanines and an excess of both bromoacetone and potassium carbonate originated 3-alkyl-3,4-dihydro-4,6-dimethyl-9*H*-imidazo[1,2-*a*]-purin-9-ones (alkyl = methyl, ethyl, benzyl) (82T1767). Yields vary depending on the above alkaline reagents. The effect of substituents in position 6 on the antiviral activity was studied with C_{3-4} ketones and also bromomethyl *tert*-butyl ketone and 4-X-phenylacyl bromides. Generally, an aryl substitution in position 6 enhanced the antiviral activity. *The most effective tricyclic analogues of gancyclovir and acyclovir were found* to be *6-phenyl- or 6-(4-methoxyphenyl)- or 7-methyl-6-phenyl*-3,9-dihydro-3-[(1,3-dihydroxy-2-propoxy)-methyl]-5*H*-imidazo[1,2-*a*]purin-9-ones and 3-[(2-hydroxyethoxyethoxy)methyl]-analogues (94JMC3187, 01JMC4284). As found later, introduction of 4-(acyloxy)phenyl-, 4-(acylamino)-phenyl- and 4-(phenoxycarbonyloxy)phenyl groupings in position 6 of the tricyclic analogues of acyclovir and gancyclovir even raised their efficacy. The 6-[4-(phenoxy-carbonyloxy)-phenyl] tricyclic analogues were pharmacologically tested as *potential antiherpetic substances* (02JMC 5052).

Chloroacetaldehyde reacted with sodium salts of acyclovir and gancyclovir to produce compounds **149a** and **149b**, respectively. Chloroacetaldehyde can be substituted by 2-bromo-1,1-diethoxyethane to give the intermediate **148** from which the final product was achieved by acid hydrolysis and cyclocondensation (91JMC2380) (Scheme 42).

A special case involved the use of glyoxal to form the third ring. For example, N^2-acetylguanine and trimeric glyoxal gave 5-acetyl-5,6,7,9-tetrahydro-9-oxo-3*H*-imidazo[1,2-*a*]purine-6,7-diol at room temperature (87ACS(B)564) and guanine with aqueous glyoxal produced 5,6,7,9-tetrahydro-9-oxo-3*H*-imidazo-[1,2-*a*]-purine-6,7-diol at elevated temperature (00JOC7697).

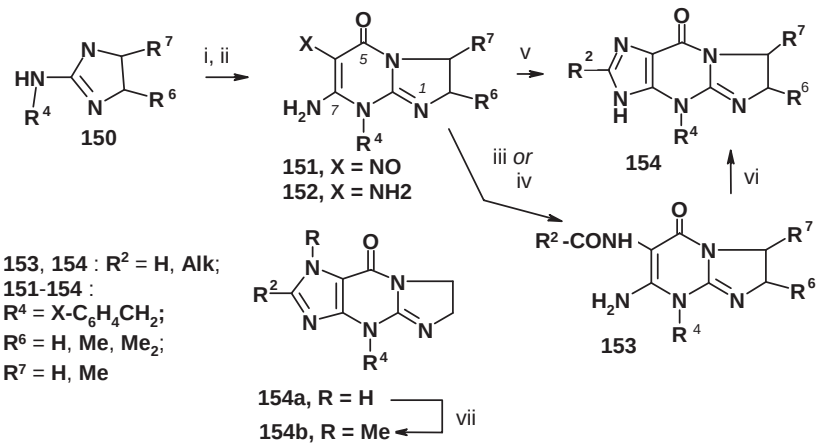
The *second method* aimed to prepare 6,7-dihydroimidazo[1,2-*a*]purin-9-ones **154** from a derivative of 2,3-dihydroimidazo[1,2-*a*]pyrimidine-5-one, the purine moiety being built up as follows: the first step involved reaction of 2-(methylthio)-imidazolinium iodide with a convenient primary amine giving 2-(substituted amino)imidazoline **150** and then with ethyl oximinocyanoacetate and alkali produced 7-amino-2,3-dihydro-6-nitroso-R^4,R^6,R^7-imidazo[1,2-*a*]pyrimidin-5(8*H*)-one **151**. Subsequent hydrogenation furnished the diamine **152**, acylation and cyclization with boiling carboxylic anhydride originated the final 6,7-dihydro-R^2,R^4,R^6,R^7-imidazo[1,2-*a*]purin-9(4*H*)-one **154**. The last two steps can be



145, **148**, **149**: **a** = CH_2-O-C_2H_4OH; **b** = CH_2-O-$CH(CH_2OH)_2$

i : Br-$CH_2CH(OC_2H_5)_2$; K_2CO, DMF; ii : 40% AcOH / reflux *or* 1.2 N HCl / r.t.

Scheme 42



i :NC-C(NOH)-CO_2Et, NaOEt, EtOH, reflux ; ii : H_2, Pd/C, EtOH ; iii : R^2 -CO_2H, H_2, Pd / C ; iv : HCO_2H, $Na_2S_2O_4$; v : $(R^2CO)_2O$, reflux ; vi : NaOH, H_2O, reflux ; vii : NaOH, EtOH - H_2O, CH_3I, r.t.

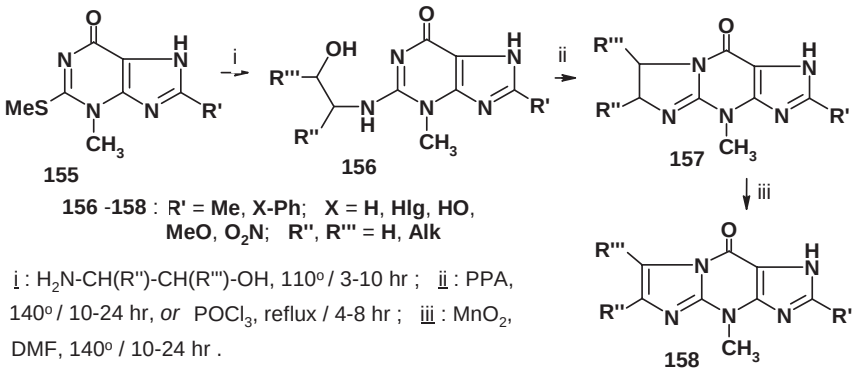
Scheme 43

substituted by reacting the nitroso group by either sodium dithionite in the presence of formic acid or hydrogenation in the presence of carboxylic acids containing more then one carbon atom to the 7-amino-6-acylamino derivative **153**. Heating with alkali closed the third imidazole ring to the final compounds **154**. Some of them exhibited enhanced *antiallergic* and *broncho-dilatation* activities, the side effects being reduced when compared with those of theophylline. Compound with the highest activity is 4-(chlorobenzyl)-6,7-dihydro-3*H*-imidazo[1,2-*a*]purin-9(4*H*)-one (80JMC1188) (Scheme 43).

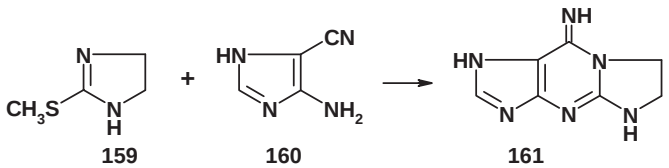
The third method was elaborated for preparation of 2-substituted tricyclic imidazo[1,2-*a*]purines **158**. Since the 8-substituted guanines are little frequent, this synthesis started from more available 3-methyl-2-methylthio-7*H*-purin-6(3*H*)-one (**155**), which on heating with aminoalcohols produced the corresponding 2-(2-hydroxyethylamino)-3-methyl-7*H*-purin-6(3*H*)-ones (**156**) and further heating in dehydrating media gave 4,6,7,9-tetrahydro-4-methyl-1*H*-imidazo[1,2-*a*]purin-9-ones (**157**). Subsequent oxidation with manganese dioxide led to 2,6- or 2,7-disubstituted-4,9-dihydro-4-methyl-1*H*-imidazo[1,2-*a*]purines **158** in good yields (95JCS(CC)2041) (Scheme 44).

The *fourth route* involved formation of the central ring of 6,7-dihydro-imidazo[1,2-*a*]purine derivatives by reaction of 4-amino-1*H*-imidazol-5-carbonitrile (**160**) with 2-methylmercapto-imidazoline (**159**) to afford the 4-imino derivative **161** under various conditions (01JHC743) (Scheme 45).

Of interest are imidazo[1,2-*a*] purine substances from the so called wye-family, isolated from phenylalanine-transfer-ribonucleic acid ($tRNA^{Phe}$) of various sorts of yeast: 4,9-dihydro-4,6-dimethyl-1*H*-imidazo[1,2-*a*]purine-9-one (“wye”, **162a**); 4,9-dihydro-4,6-dimethyl-3-*β*-D-ribofuranosyl-3*H*-imidazo[1,2-*a*]purine-9-one (“wyosine”; fluorescent Y-nucleoside from Candida albicans $tRNA^{Phe}$, **162b**); methyl

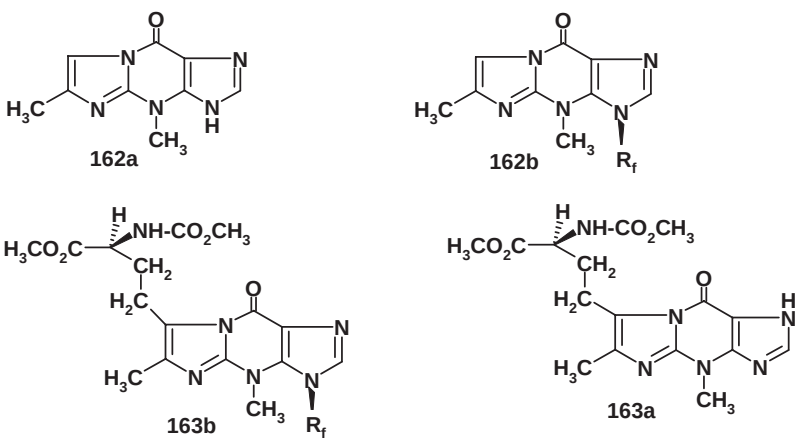


Scheme 44

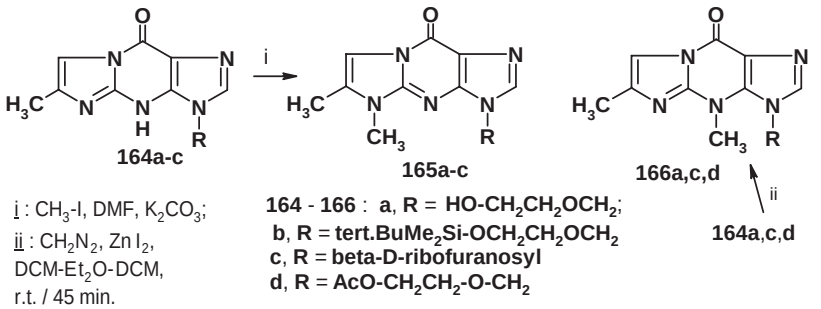


Scheme 45

4,9-dihydro-α-[(methoxycarbonyl)amino]-4,6-dimethyl-9-oxo-1*H*-imidazo[1,2-*a*]purine-7-butanoate (''wybutine''; Y-base, fluorescent minor base from yeast, **163a**); methyl 4,9-dihydro-α-[(methoxycarbonyl)amino]-4,6-dimethyl-3-β-D-ribofuranosyl-9-oxo-3*H*-imidazo[1,2-*a*]purine-7-butanoate (''wybutosine''; fluorescent nucleoside from *Saccharomyces cerevisiae* $tRNA^{Phe}$, **163b**). Owing to their interesting antiviral effects, these substances and their derivatives are subjected to intensive studies (Scheme 46). For their synthesis see paragraph on the synthesis of wybutine, wybutosine, and β-hydroxywybutine, p. 115.



Scheme 46



Scheme 47

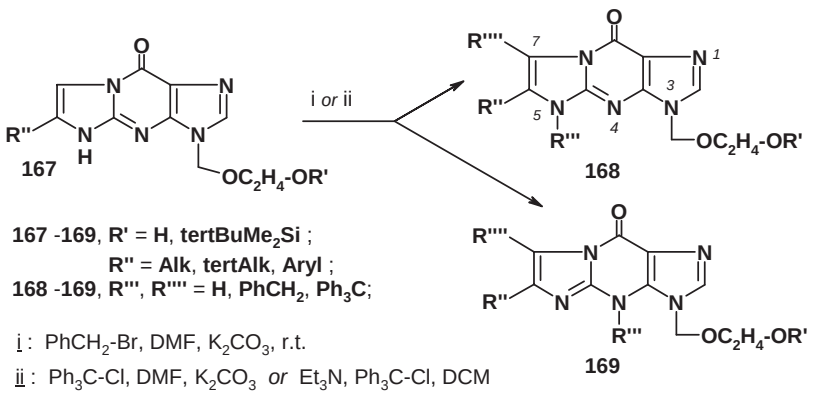
a. Reactions of the imidazo[1,2-a]purin-9-one ring system. Methylation of imidazo[1,2-*a*]purin-9-one derivatives possessing the unsubstituted N^3 and N^4 with methyl iodide took place at both these nitrogens. The methyl group entered regioselectively *position 5* of imidazo[1,2-*a*] purin-9-ones substituted in position 3, e.g., with (2-hydroxyethoxy)methyl, (2-tert-butyldimethylsilyloxyethoxy)methyl or *β*-D-ribofuranosyl groups (**164a**–**c**) under the same conditions producing compounds **165a**–**c** (83MI1). On the other hand, the diazomethane reacted with the N^4 of 3-substituted-3,4-dihydro-6-methyl-9*H*-imidazo[1,2-*a*]purin-9-ones **164a**–**c** to afford the 4,6-dimethyl derivatives **166a**,**c**,**d**.

None of the tricyclic analogues of acyclovir with a N-4 methyl group reached the antiherpetic efficacy of the parent compounds (91JCS(P1)589) (Scheme 47).

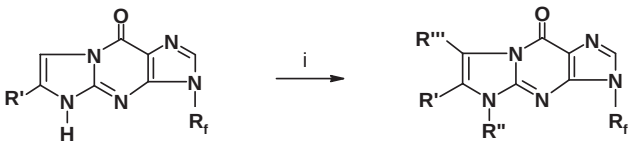
The 4-[(substituted)benzyl]-6,7-dihydro-2-substituted-imidazo[1,2-*a*]purin-9(4*H*)-ones **154a** were methylated at position N^1 with formation of compound **154b** (80JMC1188) (Scheme 43).

Benzylation and tritylation of this tricyclic system was studied in more detail (Scheme 48).

Thus, benzylation of the 3-[(2-hydroxyethoxy)methyl]-6-methyl derivative **167** gave exclusively the N-5-benzyl derivative **168**, but if the methyl group in position 6



Scheme 48



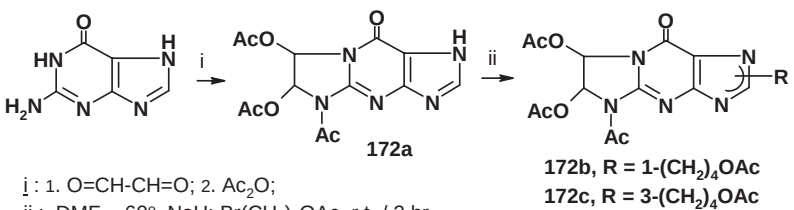
Scheme 49

was replaced by a substituted phenyl group at compound **167**, a mixture of N-5-benzyl- of **168**, N-4-benzyl- of **169** and N-5,C-7-dibenzyl derivatives of **168** was obtained. The respective components were separated chromatographically. If position 6 was occupied by a bulky tert.-butyl group in **167** then the main product was N-4-benzyl derivative of **169**. Benzylation of 6-(X-phenyl)- or 6-tert.-butyl-3-β-D-ribofuranosyl-5*H*-imidazo[1,2-*a*]purin-9-ones **170** took place in positions 5 and 7 of **171**. The mixture of isomers was separated chromatographically (Scheme 49).

Tritylation of 3-[tert.-butyldimethylsilyloxyethoxy)methyl]-3,9-dihydro-6-methyl- and 3,9-dihydro-3-[(2-hydroxyethoxy)methyl]-6-methyl-5*H*-imidazo-[1,2-*a*]purin-9-ones (**167**) did not take place at N-5, but at C-7 to form 7-trityl derivatives and a small amount of 7-(4-benzhydryl)-phenyl derivatives of **168**. Starting compounds having in position 6 of **167** only hydrogen afforded a mixture of 5-trityl and 5,7-dityrityl derivatives **168** and a small amount of 4-trityl derivatives **169**. The presence of benzhydrylphenyl derivatives **168** indicated a probable radical reaction course (98T2941, 00HCA373) (Scheme 48).

5-Acetyl-6,7-bis-(acetoxy)-5,6,7,9-tetrahydro-3*H*-imidazo[1,2-*a*]purin-9-one (**172a**) obtained by acetylation of the condensation product of guanine with glyoxal underwent alkylation with acetoxybutyl bromide in the presence of a base to give a mixture of 1- and 3-acetoxybutyl derivatives **172b**,**c**. With 1,4-dimethylpiperazine, 20% of the 1-alkyl isomer **172b** and 10% of the 3-alkyl isomer **172c** were obtained after chromatographic separation; with sodium hydride at a very low temperature, the 3-sodium salt afforded regioselectively the 1-acetoxybutyl derivative **172b** (86JHC625) (Scheme 50).

b. Electrophilic displacements. Generally, all reactions of this type took place at position 7 of the heterocycle. Reactions of 1-benzyl-4,9-dihydro-4,6-dimethyl-1*H*-imidazo[1,2-*a*]purin-9-one (**173**) were studied in more detail (99CPB1464). The

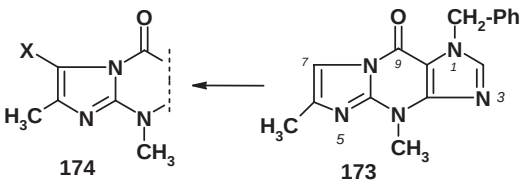


Scheme 50

chloro derivative **174c** can be prepared with N-chloro-succinimide in acetic acid. The another route the same substrate was chlorinated with N-chlorosuccinimide after previous treatment with *n*-butyllithium at −78° gave the 2-chloro derivative (29% yield). Monobromination of the starting compound **173** did not proceed regio-selectively. Only bromination of the 2-chloro derivative afforded the 7-bromo-2-chloro-1-benzyl-4,9-dihydro-4,6-dimethyl-1*H*-imidazo[1,2-*a*]purin-9-one (75%). Iodination with elemental iodine (89CPB284) in the presence of sodium hydrogen carbonate produced the anticipated 7-iodo derivative **174a**. Nitration with a nitric acid−acetic anhydride gave the 7-nitro derivative **174b**. Application of the Vilsmeier-Haack reaction formed the 7-formyl derivative **174d**, important for further syntheses. Its reduction with sodium borohydride afforded the 7-hydroxymethyl derivative **174e**. Treatment of compound **173** with phosgene resulted in 4,9-dihydro-4,6-dimethyl-9-oxo-1*H*-imidazo[1,2-*a*]purine-7-carbonyl chloride (**174f**). This intermediate was hydrolyzed to the corresponding acid **174g**, ammonolyzed to the amide **174h** and methanolyzed to the ester **174i**. Acylation of the starting **173** with oxalyl chloride gave (4,9-dihydro-4,6-dimethyl-9-oxo-1*H*-imidazo[1,2-*a*]purin-7-yl-2-oxoethanoic chloride and subsequent esterification formed the corresponding methyl ester **174j** (99CPB1464) (Scheme 51).

3-Substituted-4,9-dihydro-4,6-dimethyl-1*H*-imidazo[1,2-*a*]purin-9-ones, wyosine triacetate **175** (88T1273), gave with phosphorus oxychloride exclusively 2′,3′,5′-tri-*O*-acetyl-7-formylwyosine **176**, with bromodimethyl-phosphonium bromide the 7-bromo derivative of **176** and with iodine the iodo derivative of **176**. Over one-day, the action of anhydrous aluminium chloride resulted in a migration of the saccharide moiety from position 3 to position 1 to gave the 4,9-dihydro-4,6-dimethyl-1-(2′,3′,5′-tri-*O*-acetyl-*β*-D-ribofuranosyl)-1*H*-imidazo[1,2-*a*]purin-9-one (**177**). The position of the ribofuranosyl substituent was given by ^{15}N-NMR (Scheme 52).

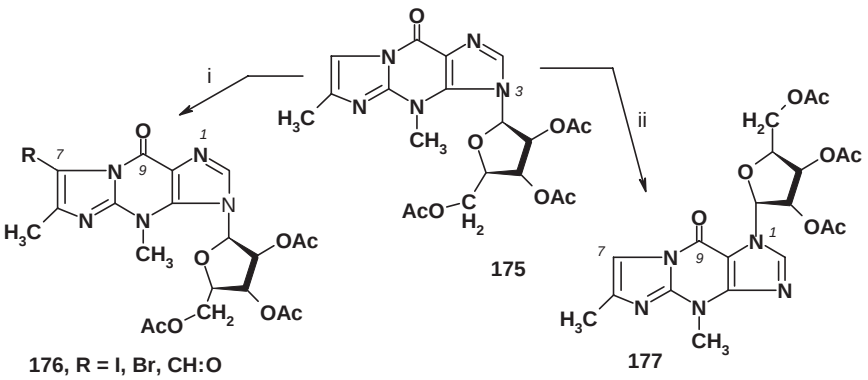
c. Rearrangements. 1-Benzyl-4,9-dihydro-4,6-dimethyl-7-substituted-1*H*-imidazo-[1,2-*a*]-purin-9-ones (**178**), where alkyl, 2-alkenyl, hydroxymethyl, methoxymethyl or



174a, X = I
174b, X = NO_2
174c, X = Cl
174d, X = CH:O
174e, X = CH_2-OH
174f, X = CO-Cl
174g, X = CO_2H
174h, X = CO-NH_2
174i, X = CO_2Me
174j, X = C0-CO_2Me

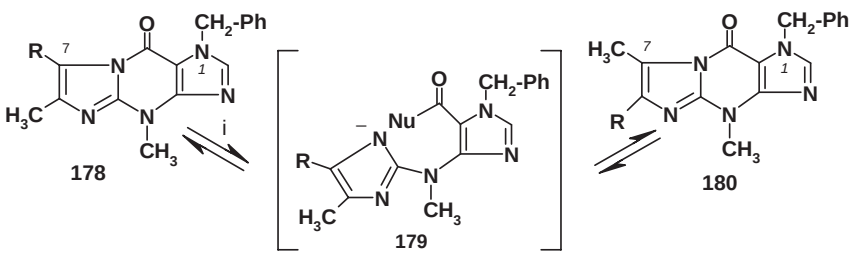
a : (for **174a**) I_2, DCM-H_2O, $NaHCO_3$; b : (for **174b**) HNO_3-Ac_2O, 0° / 9 hr; c : (for **174c**) NCS, AcOH, r.t. / 80 min; dark / 3 hr; d : (for **174d**) $POCl_3$, DMF, 0° / r.t.; e : (for **174e** from **174d**)$NaBH_4$, MeOH, r.t. / 30 min; f : (for **174f**) $COCl_2$, toluene, THF, pyridine, 0°; r.t. /30 hr ; g : (for **174f**) H_2O; h : (for **174h** from **174f**) NH_3, DCM; i : (for **174i**) MeOH, r.t. / 2 d; j : (for **174j**) 1. $(COCl)_2$, Et_3N, THF, 0°;r.t. / 5 hr; 2. MeOH, r.t. / 15 min.

Scheme 51



i : Electrophylic substitution ii : DCM,$AlCl_3$, 0°; r.t. / 24 hr

Scheme 52



178 - 180: **a**, R = $CH_2CH_2CH(CH_3)_2$; **b**, R = (E)-CH=CH-$CH(CH_3)_2$; **c**, R = CH_2-OH; **d**, R = CH_2-OCH_3, **e**, R = CHO, **f**, R = CO_2Me, **g**, R = Cl, **h**, R = Br, **i**, R = I

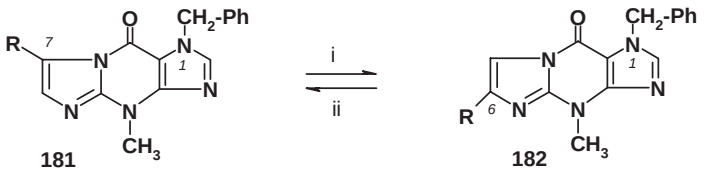
i : NaOMe-MeOH, r.t. - reflux / 6-8 hr .

Scheme 53

formyl were the substituents, isomerized in the presence of a nucleophilic (Nu^-) reagent to an equilibrium mixture with 6-substituted derivatives (position isomers) **180a**–**e**. The nucleophilic reagent can be sodium methoxide. The rearrangement involved a cleavage of the N^8–C^9 bond with a transient binding of the nucleophile to C^9 and recyclization of the N^5–C^9 bond (Scheme 53).

After neutralization of the nucleophilic reagent the position isomers of both series were separated chromatographically. Yields of compounds **180** varied within 16–89%, those of compounds **182** within 37–98% (99CPB1464) (Scheme 54).

An analogous rearrangement was observed with the preparation of 1-benzyl-4,9-dihydro-4,6-dimethyl-7-(3-methyl-1-butenyl)-1*H*-imidazo[1,2-*a*]purin-9-one (**185a**) by a three-step synthesis from 1-benzyl-4,9-dihydro-4,6-dimethyl-7-(hydroxymethyl)-1*H*-imidazo[1,2-*a*]purin-9-one (**183**), which reacted with phosphorus tribromide to the corresponding 7-bromomethyl derivative **184a** and with triphenylphosphine to the triphenylphosphonium bromide **184b**. The latter reacted



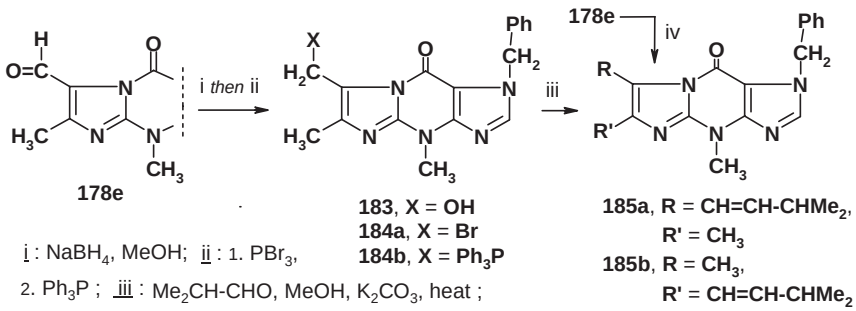
181, **182** : **a**, **R** = **Me**, **b**, **R** = **COO**$^-$, **c**,**R** = **CH$_2$OH**, **d**, **R** = **CONH$_2$**, **e**, **R** = **CO$_2$Me**, **f**, **R** = **CO-CO$_2$Me**, **g**, **R** = **CHO**, **h**, **R** = **I**, **i**, **R** = **NO$_2$**

i : 0,5 M MeONa-MeOH, r.t. / 1 hr ; ii : 10% H_3PO_4.

Scheme 54

with isobutyraldehyde in sense of the Wittig reaction to a mixture of olefins in which the main product was the *rearranged* 1-benzyl-4,9-dihydro-4,7-dimethyl-6-(3-methyl-1-butenyl)-1*H*-imidazo[1,2-*a*]purin-9-one (**185b**) in 74% yield and not the anticipated 7-(3-methyl-1-butenyl) derivative **185a**. Carrying out the Wittig reaction in the presence of *n*-butyllithium at a very low temperature afforded a mixture of (*E*)- and (*Z*)-isomers of the anticipated 7-(3-methyl-1-butenyl) derivative **185a** in a 7:2 ratio. Compound **185a** can be prepared alternatively by the Wittig reaction from 1-benzyl-4,9-dihydro-4,6-dimethyl-9-oxo-1*H*-imidazo[1,2-*a*]purine-7-carbaldehyde (**178e**) and (2-methylpropyl)-triphenyl-phosphonium iodide with butyllithium as a base at a very low temperature as an equimolar mixture of geometric isomers **185a** in a 50% yield. When this reaction was performed in the presence of two equivalents of dimsyl anion ($NaCH_2$–SO–CH_3) at room temperature, (*E*)-**185b** was isolated in 74% yield. Application of only one equivalent of the dimsyl anion resulted in formation of (*E*)-**185a** in 26% yield. The mechanism of this rearrangement is given at the beginning of this paragraph (89CPB1221) (Scheme 55).

The synthesis of wybutine, wybutosine, and β-hydroxywybutine employed 4,9-dihydro-4,6-dimethyl-9-oxo-3-[2,3,5-tris-*O*-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]-3*H*-imidazo[1,2-*a*]purine-7-carbaldehyde (**186**), which enabled the introduction of the (α-aminobuten-3-yl)-carboxylic grouping into position 7 of the heterocyclic ring by a Wittig reaction with phosphorane derived from the inner salt of



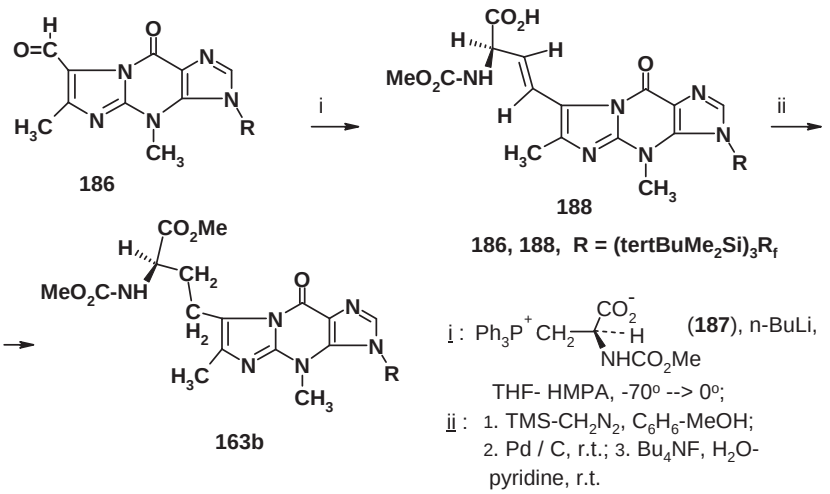
178e

183, **X** = **OH**
184a, **X** = **Br**
184b, **X** = **Ph$_3$P**

185a, **R** = **CH=CH-CHMe$_2$**, **R'** = **CH$_3$**
185b, **R** = **CH$_3$**, **R'** = **CH=CH-CHMe$_2$**

i : $NaBH_4$, MeOH; ii : 1. PBr_3, 2. Ph_3P ; iii : Me_2CH-CHO, MeOH, K_2CO_3, heat ;
iv : $Ph_3P^+CH_2CH_2Me_2I^-$, THF, n-BuLi, -78°, N_2; < 0° / 1 hr .

Scheme 55



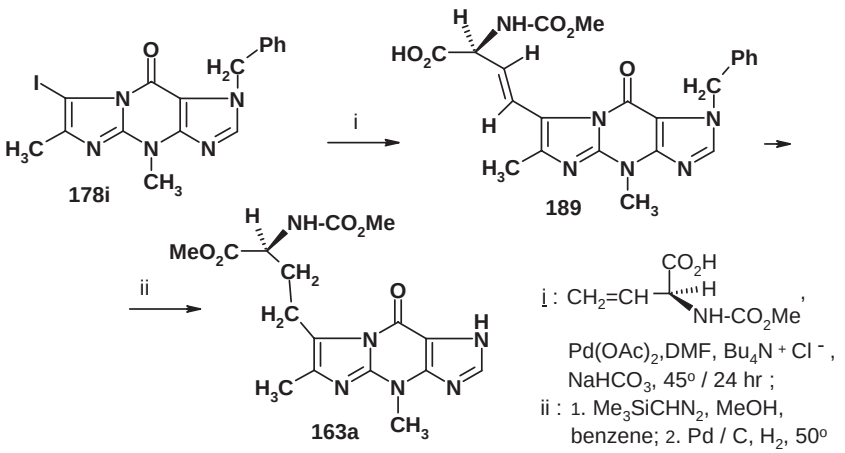
Scheme 56

(R)-2-[(methoxycarbonyl)amino]-3-triphenylphosphonio propanoate (**187**) to give the intermediate **188**. Its methylation with trimethyl-silyldiazomethane, consecutive hydrogenation of the dimethyl ester and deprotection afforded the tricyclic derivative with a saturated side chain similar to wybutosine **163b** identical with the product isolated from natural material (02CPB530) (Scheme 56).

An alternate strategy for introducing the (α-aminobuten-3-yl)-carboxylic group in position 7 of the heterocycle is offered by the Heck reaction of 7-iodo-1-benzyl-4,9-dihydro-4,6-dimethyl-1*H*-imidazo[1,2-*a*]purine-9-one (**178i**) with (S)-N-(methoxycarbonyl)- or (S)-N-(benzyloxycarbonyl)-vinylglycine, catalyzed by palladium acetate (88TL4129, 98CPB1094). Wybutine **163a** was obtained by a stepwise methylation of the carboxyl in the side chain with trimethylsilyldiazomethane, hydrogenative debenzylation and reduction of the double bond in the side chain.

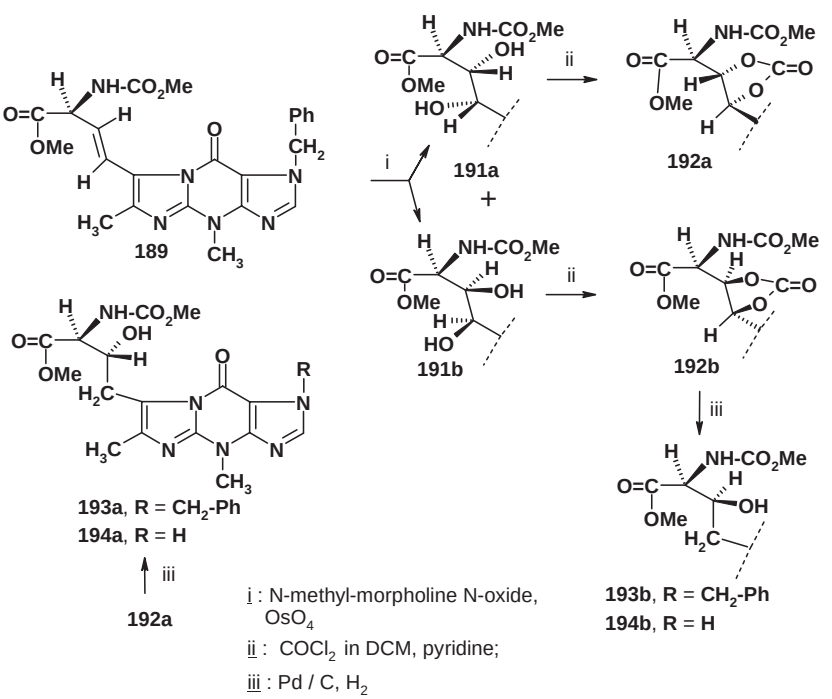
Wybutosine **163b** was prepared by a similar reaction sequence from 7-iodo-1-benzyl-4,9-dihydro-4,6-dimethyl-3-β-D-ribofuranosyl-1*H*-imidazo[1,2-*a*]-purine-9-one (Scheme 57).

The tricyclic intermediate with (α-aminobuten-3-yl)-carboxylic group **189** was utilized for the synthesis of β-hydroxywybutine. The first step was the cis-hydroxylation of the side-chain double bond by osmium tetroxide and N-methyl-morpholine-N-oxide to a mixture of vicinal glycol isomers **191a** (yield after isolation 69%) and **191b** (yield 24%). Their relative configuration was established by X-ray analysis. Triphosgene in pyridine or phosgene in dichlormethane converted the vicinal glycols into the cyclic carbamates **192a** and **192b**. Oxalyl chloride when used in place of phosgene gave the cyclic oxalates decarboxylating easily to the five-membered cyclic carbonates. The final step of this synthesis was the hydrogenation of both the isolated cyclic carbonates under elimination of carbon dioxide to α-amino-β-hydroxy-carboxylate **193a**,**b** and hydrogenolysis of the benzyl group from position 1 to a mixture of diastereomers of β-hydroxywybutine **194a** (yield 48%) and **194b** (yield 20%). *The transformation of vicinal glycols* **191a**,**b** into cyclic carbonates

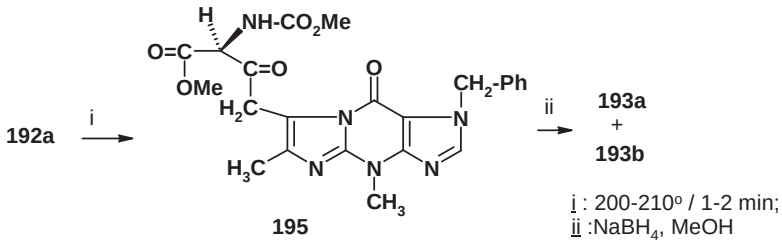


Scheme 57

192a,**b** and hydrogenolysis through elimination of carbon dioxide cleaving the $C_{(\gamma)}OCO$ bond *to β-monohydroxy derivatives* **193a**,**b** may be understood as a *regioselective dehydroxylation of the original vicinal glycols* (86TL4043, 97TL1979, 98CPB1220). The hydrogenolysis by-product was the tricyclic derivative with a saturated side chain without any hydroxyl group **163a** (Scheme 58). An analogous



Scheme 58

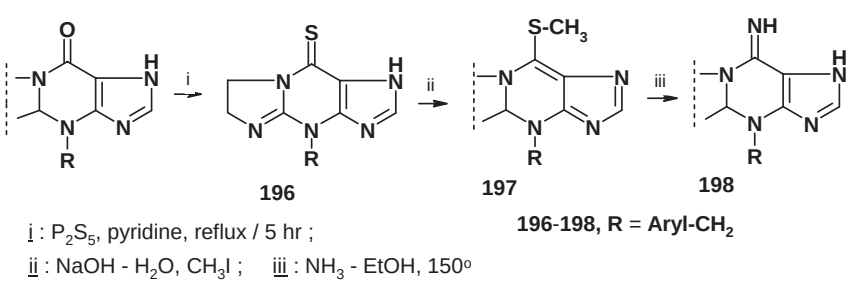


Scheme 59

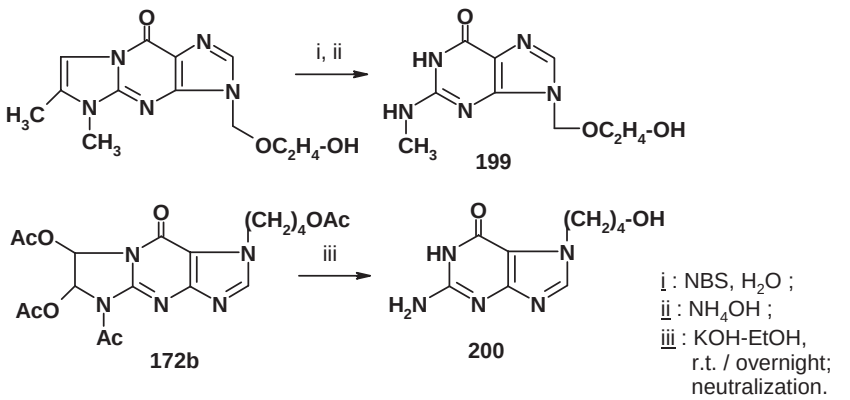
reaction sequence was applied to prepare β-hydroxy-3-(β-D-ribofuranosyl)wybutines as follows: methyl 4,9-dihydro-4,6-dimethyl-9-oxo-3-[2,3,5-tris-*O*-(tert.-butyldimethylsilyl)-β-D-ribofuranosyl]-3*H*-imidazo[1,2-*a*]purin-7-yl-(α-methoxycarbonylamino)-butenoate (**188**) was cis-hydroxylated with OsO_4 and N-methylmorpholine-N-oxide to the corresponding mixture of vicinal glycols, then transformed into cyclic carbonates (triphosgene-pyridine), which were subsequently hydrogenolyzed (elimination of carbon dioxide), and the protecting trialkylsilyl groups removed from the ribofuranosyl part of the molecule (Bu_4NF, H_2O-pyridine) (97TL1979). Short thermal decomposition of cyclic carbonates **192** formed a tricyclic α-amino-β-oxocarboxylate **195** under elimination of carbon dioxide and then reduction by sodium borohydride affording the mixture **193a**,**b** an alternate method to regioselective dehydroxylation. Compounds **193a**,**b** can be separated by HPLC using a chiral packing (yields 23 and 51%, respectively) (98CPB1220) (Scheme 59).

d. Modification of the 9-carbonyl group. 4-[(4-Chlorophenyl)methyl]-4,6,7,9-tetrahydro-1*H*-imidazo[1,2-*a*]purin-9-one can be converted into the corresponding 9-thione **196** by phosphorus pentasulfide, then, the resulting sodium salt of the thione can be methylated with methyl iodide to the 9-methylthio derivative **197** and finally treated with ammonia to give 4-[(4-chlorophenyl)-methyl]-4,6,7,9-tetrahydro-1*H*-imidazo[1,2-*a*]purin-9-imine **198** (80JMC1188) (Scheme 60).

e. Cleavage of the newly formed imidazole ring. The reaction of 3-[(hydroxyethoxy)methyl]-5,6-dimethylimidazo[1,2-*a*]purin-9(5*H*)-one (**147a**) with N-bromosuccinimide and subsequent hydrolysis led to the third N-ring cleavage affording the



Scheme 60



Scheme 61

N^2-methylguanine derivative **199** (88JMC1351). Similarly 5-acetyl-6,7-bis-(acetoxy)-1-(4-acetoxybutyl)-5,6,7,9-tetrahydro-1*H*-imidazo[1,2-*a*]purin-9-one (**172b**) produced 7-(4-hydroxybutyl)guanine (**200**) in 90% yield after hydrolysis (86JHC625) (Scheme 61).

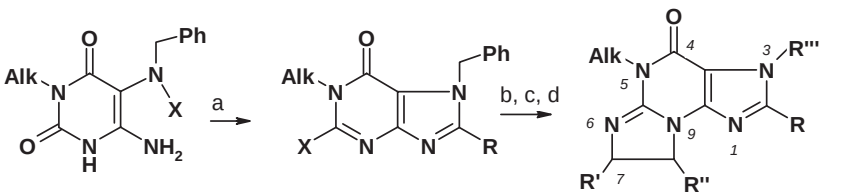
2. *Imidazo[2,1-b]purines*

Formation of the third ring proceded by reaction of 2-chloropurine derivative **203** with a trans-aminocyclopentanol giving the intermediate **204**.The third ring was closed by activation with thionyl chloride to give **205**. Catalytic debenzylation led to **206**. The starting **203** was obtained by acylation of 6-amino-5-(benzylamino)-3-alkylpyrimidine **201** to the 5-acylderivative **202**. The carboxylic acid was responsible for the substituent at position 2 of the final compound. An alternate method for less accessible carboxylic acids made use of the iodination of **205** (R = H) to the 2-iodo-derivative **205** (**R = I**) by a mixture of lithium diisopropyl amide and 1-chloro-2-iodoethane followed by a palladium-catalyzed coupling with alkylacetylene and cuprous iodide as a co-catalyst to give **205** (**R = alkyn-1-yl**). The triple bond on the side-chain was hydrogenated and simultaneously debenzylated over $Pd(OH)_2$ to **206** (**R = saturated alkyl**). The most effective *selective inhibitor of cyclic GMP-phosphodiesterase* of the 2-alkyl-derivatives was **206** (**R = $[CH_2]_3CH[CH_3]_2$**) (99BMC7) (Scheme 62).

O^6-Ethyl or O^6-benzylguanosine reacted with bromoacetaldehyde at pH 4.5 producing imidazo[2,1-*b*]purines **207** in contrast with guanosine which gave imidazo[*a*]purines with halogenoaldehydes. Catalytic debenzylation of **207b** afforded **209** with retained the ribofuranosyl residue (87JOC2374) (Scheme 63).

3. *Imidazo[2,1-i]purines*

These can be synthesized by five methods. The *first* one was based on a reaction of chloroacetaldehyde with substituted isoguanine **210** providing the tricyclic derivatives **211** (97JMC3248). Replacing the isoguanine by an adenine derivative



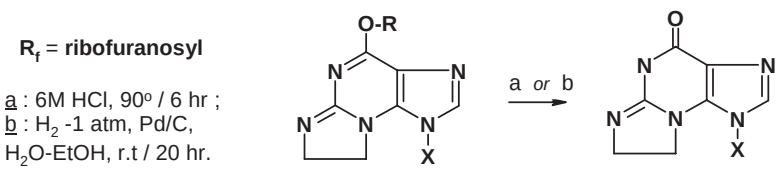
201, X = H
202, X = CO-R

203, X = Cl
204, X = NH-CH(R')-CH(R'')OH

205, R''' = CH_2-Ph
206, R''' = H ,
R', R''=Alk *or* R'-R''

a : excess $POCl_3$; b : H_2N-CH(R')-CH(R'')OH, DCM, $iPrNEt_2$, NMP; c : $SOCl_2$, DCM; d : $Pd(OH)_2$, MeOH, HCO_2NH_4, heat

Scheme 62



R_f = ribofuranosyl

a : 6M HCl, 90° / 6 hr ;
b : H_2 -1 atm, Pd/C,
H_2O-EtOH, r.t / 20 hr.

207a, R = C_2H_5
207b, R = CH_2Ph
} X = H, R_f

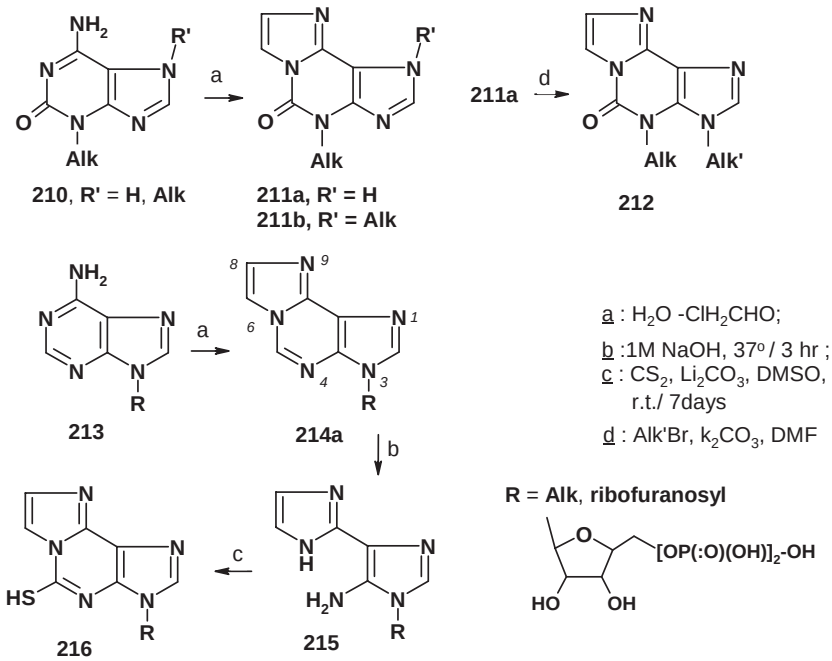
208, X = H
209, X = R_f

Scheme 63

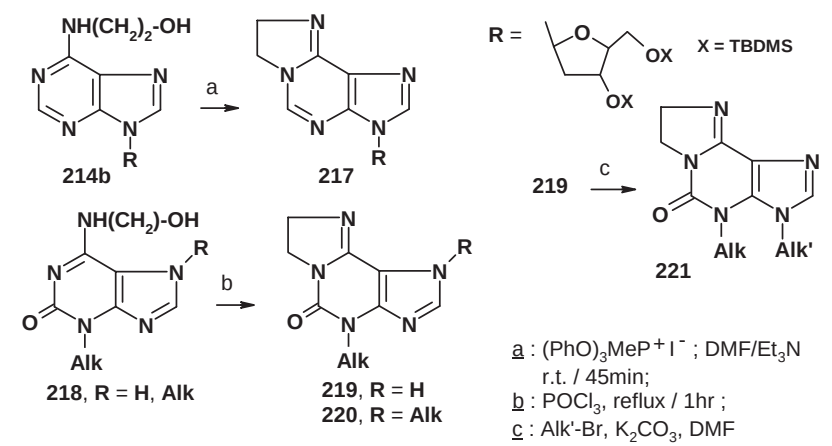
213 afforded **214a** (72B3499). The *second* method involved cyclization of 5-amino-4-(imidazol-2-yl)-1-R-imidazole **215** with carbon disulfide giving the 5-mercapto-tricyclic **214a** (87JMC2013). The third ring can also be obtained by cyclization of **215** with diethoxymethyl acetate under formation of **214a** (70JCS(C)2206) (Scheme 64).

Two other methods led to 7,8-dihydroderivates **217**. Thus, the *third* one starting from a 6-chloro-2′-deoxyriboside derivatized with tert.-butyl-dimethylsilyl-chloride and ethanolamine gave **216**. Following iodination with methyl-(triphenoxy)phosphonium iodide gave the expected N^6-(2-iodoethyl)-derivative, which, then cyclized to the tricyclic **217**. Similarly, the 7,8-dihydroderivatives **219** and **220** were prepared from the isoguanine **218** by heating in phosphorus oxychloride (98JOC4385) (Scheme 65). The *fourth* method was based on thermal cyclization of 1-(2-aminoethyl)purinedione **223** obtained from **222** to the tricyclic **224**. Derivative **223** was the by-product of an alkaline cyclization of the imidazo[1,2-*a*]pyrimidine derivative **222** (Scheme 66). The *fifth* method was based on acylation of the substituted adenine by chloroacetic anhydride to N^6-chloroacetic derivate **225** and cyclization to the 8-oxo derivative **226**. The another route offered the cyclization of 1-carboxymethyladenine derivative **227** by *N*,*N*′-dicyclohexylcarbodiimide (69JOC3492) (Scheme 67).

Compound **227** was obtained by alkylation of a substituted adenine with iodoacetic acid. Alkylation of the NH group of compound **211a** or of its 7,8-dihydro-derivative **219** with alkyl bromide gave the 3-alkyl- **212** or 3-alkyl-7,8-dihydro-derivatives **221**, respectively (97JMC3248) (see Scheme 64). The 8-oxo-compound **226** underwent a hydrolytic cleavage to **227** (69JOC3492).

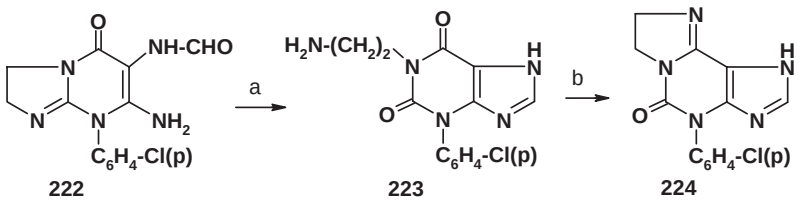


Scheme 64

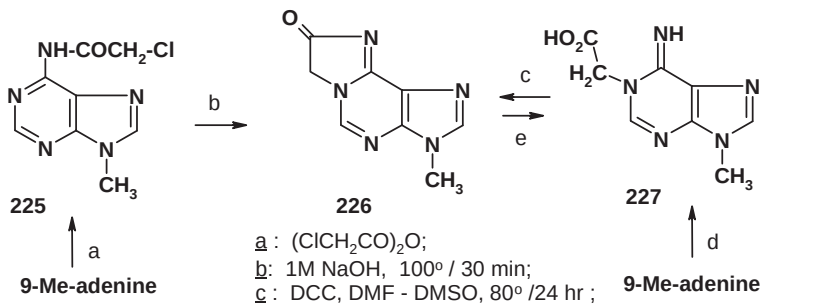


Scheme 65

Derivatives of imidazo[2,1-*i*]purines showed interesting pharmacological properties; thus, compounds **212** are effective *antagonists of A_{2A} and A_3 adenosine receptors* (02JMC3440); 2-cyclopentenyl-4-cyclopropylmethyl-8-pyridin-4-yl) derivative of **212** is a *insulin-secretion enhancer* (01MIP1); 4-phenyl derivatives of **212** exhibit a strong and *selective vasodilatation effect* (01CPB188); 4-chlorophenyl derivatives of **224** reveal a *bronchodilatation effect* (80JMC1188); 3,4-di-n-propylderivatives of **212** are



Scheme 66



Scheme 67

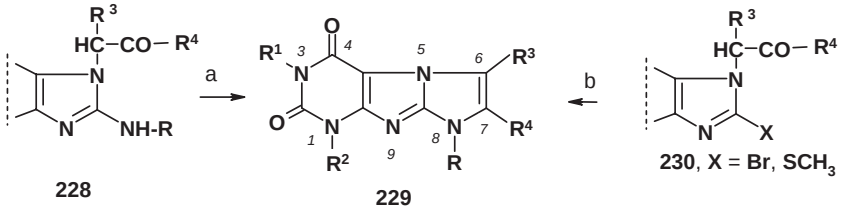
inhibitors of the cyclic AMP-phosphodiesterase (97JMC3248); 3-(5-*O*-phosphono-*β*-D-ribofuranosyl derivatives of **214a** exhibit an *inhibitory effect against priones formation* (02USP1) and the 3-(2-deoxy-5-*O*-phosphono-*β*-D-*erythro*-pentafuranosyl derivative of **214b** discloses a *competitive inhibition of HIV-1 reverse transcriptase* (02MI1).

The crystallographical structure of compound **226** was studied by an X-ray analysis (70JA6604).

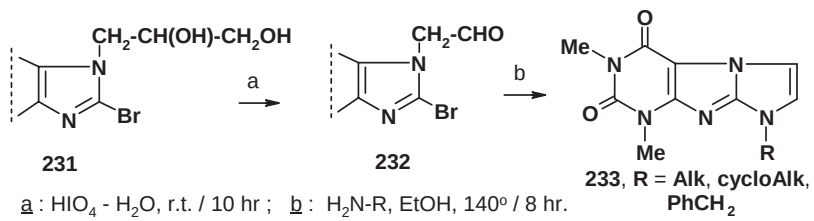
4. *Imidazo[2,1-f]purines*

The *first* of four methods leading to this heterocycle was the cyclization of 8-(subst. amino)-7-acylmethyl-purinedione **228** to 1*H*- and 3*H*-imidazo[2,1-*f*]purine-2,4-dione **229**. The starting compound **228** was obtained by an alkylation of potassium 8-(subst. amino)purinedione with either *α*-acyl-methyl halogenide, or *α*-halogenoaldehyde (71KGS682, 71KGS686, 85FZK(2)54, 87KGS1105). Also, alkylation of potassium 8-halogeno- or 8-methylmercapto-purinedione with the above mentioned acylmethyl halogenide to 8-halogeno- or 8-methylmercapto-7-acylmethyl-purinedione **230** followed by a reaction with a primary amine under closure of the imidazole ring to **229** was reported (71KFZ(2)22, 83KFZ160, 85FZK(2)54, 87KFZ566, 87KGS1105 (Scheme 68).

A modification of the first method was represented by a pyridine-catalyzed alkylation of 8-bromopurinedione to 8-bromo-7-(2,3-dihydroxypropyl) compound



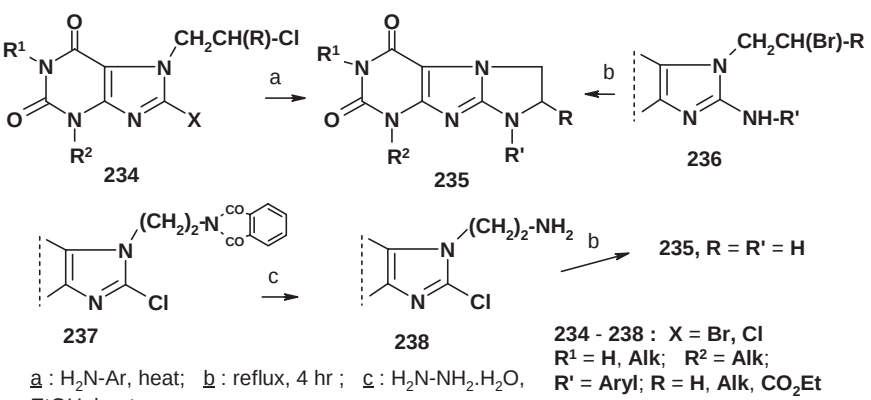
Scheme 68



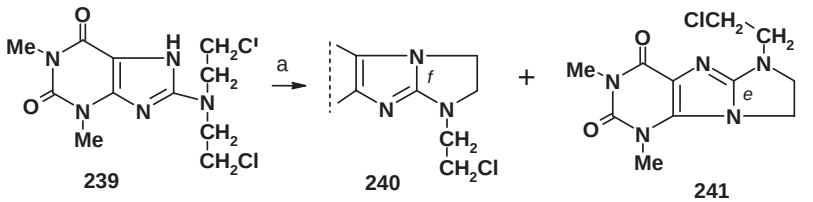
Scheme 69

231; the dihydroxypropyl grouping was then cleaved by periodic acid to 8-bromo-7-acetaldehyde derivative **232** and condensed with a primary amine to **233** (87KFZ566) (Scheme 69).

The *second* method served for preparation of 6,7-dihydro derivatives. The third imidazole ring was formed from 8-halogeno-7-(halogenoalkyl)-purinedione **234** and arylamine giving **235** (70KFZ(12)14, 62MI2, 80KPS623) or by cyclization of 8-(subst. amino)-7-(2-halogenoalkyl) derivative **236** to **235** (97PHA279, 98JHC135) (Scheme 70). The starting **234** and **236** were obtained from 8-halogeno- or 8-(subst. amino)purinediones by alkylation.



Scheme 70



a : 1 equiv. aq.NaOH, 40-50° / 10 min

Scheme 71

The *third* synthesis involves cyclization of 8-chloro-7-(2-aminoethyl)purine-dione **238** to **235** (**R**,**R′** = **H**). The intermediate **238** was prepared by hydrazinolysis of the 7-(2-phthalimidoethyl) derivative **237** (79S581). A special case of the third ring annulation constitutes a treatment of 8-bis(2-chloroethyl)amino-purinedione **239** with alkali producing a 50:26% mixture of [2,1-*f*] **240** and [1,2-*e*] **241**, respectively (85JHC105) (Scheme 71).

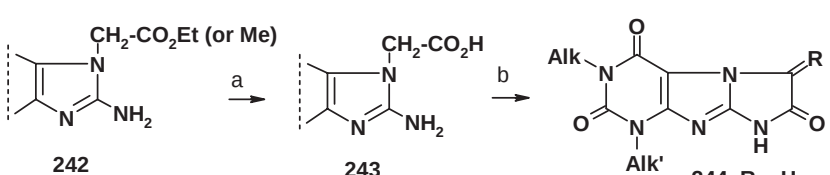
Application of the *fourth* method made it possible to obtain tricyclic derivatives with a 7-oxo group at the newly formed ring. Thus, potassium 8- aminopurinedione was alkylated with a chloroacetate to **242** and then hydrolyzed to 8-amino-7-carboxymethyl compound **243**. The ring of **243** was closed by diphenylphosphoryl azide to **244**. The methylene group in position 6 of **244** was reacted with aromatic aldehydes to give the corresponding arylmethylene compounds **245** (86KFZ1319) (Scheme 72).

Position 6 of imidazo[2,1-*f*]purinediones is the site of an electrophilic attack.

The respective nitration, bromination, Mannich reaction, Vilsmeier formylation, acetylation and hydroxymethylation of **246** yielded compounds **247a**, **247b**, **247c**, **247d**, **247e** and **247f**. The last one can be obtained by reduction of **247d** (79KGS1404, 83KFZ160, 85FZK(2)54, 84KFZ307) (Scheme 73). Alkylation of the 1,6,7,8-tetrasubstituted **248** took place at $N_{(3)}$ of the heterocycle, alkylhalogenides, benzylchloride, halogeno-acetates and phenacyl-bromide being the alkylation agents. The 1,2-epoxy-alkanes and acrylonitrile reacted similarly (83KFZ160, 88UKZ1312) (Scheme 74).

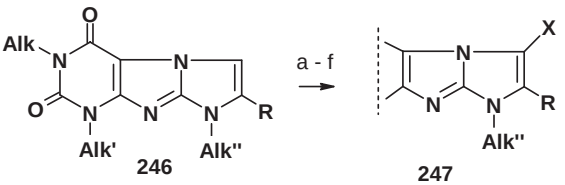
Treatment of the enol form of **248** with phosphorus oxychloride resulted in substitution of the hydroxyl group by chlorine yielding **250** (X = Cl).

Application of a stronger chlorination agent such as $POCl_3$ with PCl_5 afforded 2,4-dichloro compound **251** (**X = Cl**), the methyl group at $N_{(3)}$ being eliminated as



a : conc.HCl, 90° / 1 hr ; b : $(PhO)_2P(O)N_3$, DMF, TEA, r.t. / 12 hr.

Scheme 72

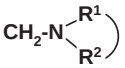


246, **247** R = Alk, Aryl

247a, X = NO_2

247b, X = Br

247c, X = CH_2-NR^1R^2,



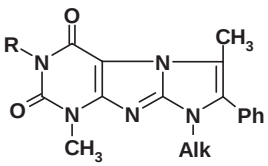
247d, X = CH:O

247e, X = $COCH_3$

247f, X = CH_2-OH

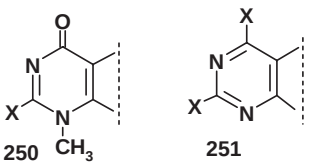
a : (for **247a**) HNO_3, AcOH, 20° / 5 hr ; b : (for **247b**) Br_2, $CHCl_3$, r.t. / 2 hr ; c : (for **247c**) HNAlkAlk' or piperidine / morpholine / piperazine, CH_2O, reflux /4 hr ; d : (for **247d**) $POCl_3$ - DMF,80° / 4 hr ; e : (for **247e**) Ac_2O, cat. H_2SO_4 or $HClO_4$, 100° / 2 hr ; f : (for **247f**) excess CH_2O, AcOH, reflux / 5 hr.

Scheme 73



248, R = H

249, R = Alk, CH_2CO_2Me, CH_2-CO-Ph, CH_2-CH(OH)-Alk, $(CH_2)_2CN$

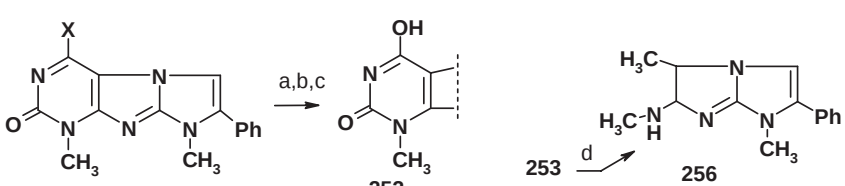


250 - **251**, X = Cl, NHAlk, NAlkAlk', 

Scheme 74

methyl chloride. The chlorine atoms of both compounds can be displaced by primary or secondary aminogroups. Chlorine at $C_{(2)}$ can be substituted at milder conditions, whilest substitution of both chlorine groups required higher temperatures (84KGS407) (Scheme 74). The enol form of **252** reacted with phosphorus pentasulfide to give 4-mercapto compound **253**, subsequent methylation gave the 4-methylthio derivative **254** and the reaction with ethanolamine the 4-(2-hydroxyethylamino) compound **255**. Compound **253** underwent cleavage of the pyrimidine ring on treatment with Raney-nickel to form 5,6-dihydroimidazo-[1,2-*a*]imidazole **256** (83KPS32) (Scheme 75).

A mass spectral fragmentation of 1,8-dialkyl-7-phenyl derivatives of **229** appeared in Ref. 87KGS1105.



253, X = SH ; **254**, X = SCH_3

255, X = NH-CH_2CH_2-OH

a : P_2S_5 ; b : CH_3I, aq.NaOH;
c : $H_2NCH_2CH_2OH$; d : Raney - Ni

Scheme 75

The N(8)-(phenylpiperazinopropyl) derivatives **235** showed a significant *anti-serotonin*, long-lasting *hypothermic* effects and *anticonvulsant* properties (99EJM1085), the 6-piperidinomethyl-, morpholinomethyl- and N-methyl-piperazinomethyl-derivatives **247c** *diuretic* and *neuroleptic effects on the heart* (85FZK(2)54). The N(8)-allyl- and hydroxyethyl derivatives of **235** displayed a *positive inotropic effect on heart* tissue (70KFZ(12)14).

5. *Imidazo[1,2-e]purines*

Tricyclic compounds **241** originated as a by-product on reaction of alkali with 8-[2-bis(chloroethyl)amino]purine **239** in 26% yield (85JHC105) (Scheme 71).

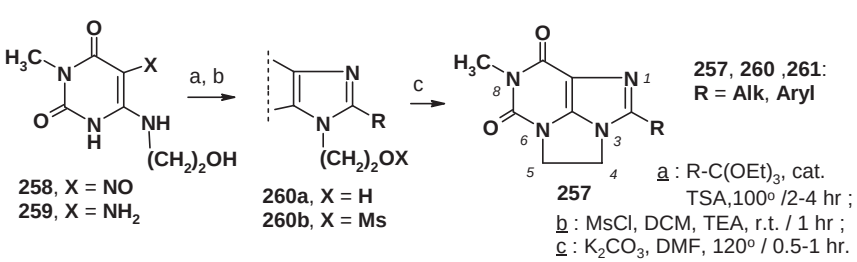
6. *Imidazo[1,2,3-c,d]purines*

Compounds with a peri-fused imidazole ring to the purine ring **257** were only little studied. Their synthesis involved an intramolecular alkylation of 8-alkyl- or 8-aryl-9-(2-mesyloxyethyl)-1-methyl-purinediones **260b**. The necessary intermediates **260b** were achieved by hydrogenation of the 6-[2-(hydroxyethyl)-amino]-3-methyl-5-nitroso-pyrimidinedione **258** to 5-amino-6-[2-(hydroxyethyl)amino] compound **259**; further reactions with the respective ortho-carboxylates and mesyl chloride gave 8-alkyl- or 8-aryl-9-(2-hydroxyethyl)-purinediones **260** or **261** (98CCC407) (Scheme 76).

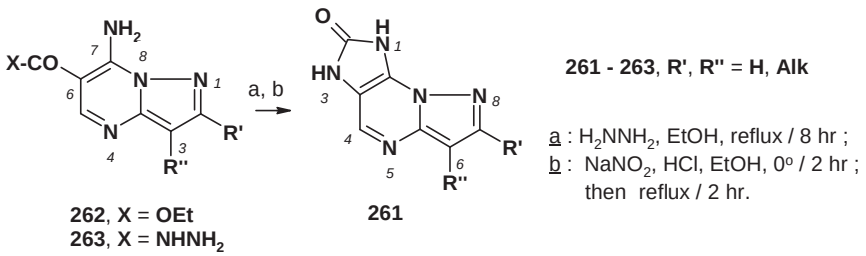
E. Pyrazolo-purines

The synthesis of pyrazolo[5,1-*b*]purin-2-ones **261** started from ethyl 7-amino-pyrazolo[1,5-*a*]pyrimidine-6-carboxylates **262**, following hydrazinolysis and reaction with HNO_2 gave the corresponding azide and the modified Curtius reaction closed the third pyrazole ring of **261**. The final tricyclic **261** can be hydrolyzed to 6,7-diamino-pyrazolo[1,5-*a*]purines (68CPB2195) (Scheme 77).

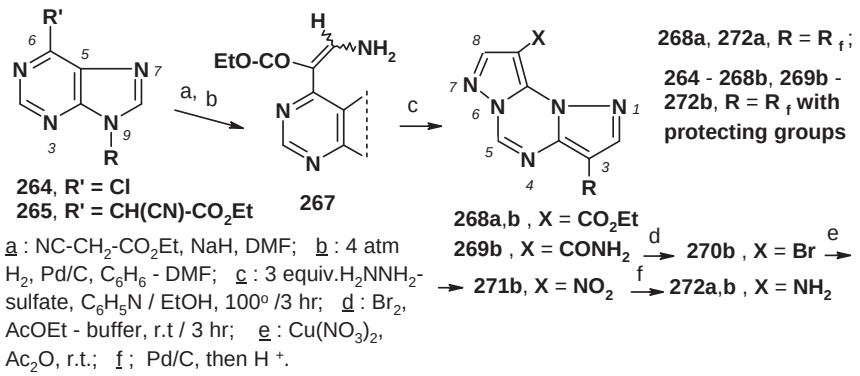
Ethyl 3-β-D-ribofuranosylpyrazolo[3,2-*i*]purine-9-carboxylate **268a**, was prepared from the 6-chloro-9-ribofuranosylpurine derivative **264** protected by tetrahydro-pyran and isopropylidene groups through 6-cyanoacetyl derivative **265**, which gave an α-aminomethylene derivative **267** by partial hydrogenation. The third pyrazole ring of **268b** was closed with hydrazine or its salts. Deprotection of the saccharide



Scheme 76



Scheme 77



Scheme 78

moiety by trifluoroacetic acid afforded the 3-β-D-ribofuranosyl derivative **268a**. Compound **268b** with ammonia gave the corresponding amide **269b** and subsequent bromination the 9-bromo-derivative **270b**; its nitrodebromination reaction [$Cu(NO_3)_2 \cdot 3H_2O$, Ac_2O] afforded 9-nitro compound **271b** and hydrogenation together with elimination of protecting groups produced **272a**. The tricyclic compounds **270b**–**72b** showed *antileukemic activity* (91TL7415, 92CPB2585) (Scheme 78).

F. Triazolo-purines

The most studied compounds of this group were purines with a triazole ring annulated to bond "*i*".

1. *[1,2,4]Triazolo[3,4-i and 5,1-i]purines*

The synthesis of [**3,4-*i***]-annulated compounds started from 6-hydrazinopurine derivatives **273**. The *first* method involved reaction with aliphatic or aromatic ortho esters closing the third triazole ring and giving **274** (**R′ = Alk**, **Aryl**). Use of carbon disulfide instead of the ortho esters produced the 3-mercapto-tricyclic **274** (**R′ = SH**).

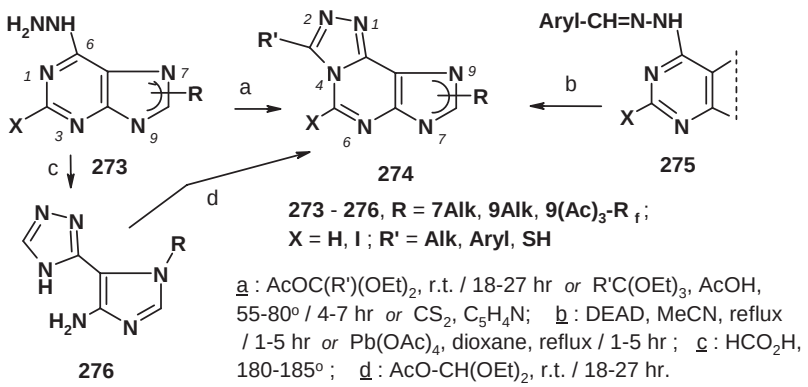
The 6-hydrazinopurine derivative was also starting material for the *second* method. Treatment with an aromatic aldehyde gave the corresponding 6-aldehydohydrazone **275** and its reaction with azodicarboxylate (DEAD) the tricyclic **274**. An alternate process was the "one-pot" access from the hydrazine derivative **273** without isolation of the *in situ* formed aldehydohydrazone **275**. Another route to form the triazolo ring involved heating **275** with lead tetraacetate.

Iodine of the 5-iodotricyclic **274** was capable of nucleophilic displacement by methoxy-, hydroxyl-, amino-, and mercapto groups. The rearrangement of [3,4-*i*]-derivatives by refluxing in formamide to [5,1-*i*]-analogues is seen in Scheme 81.

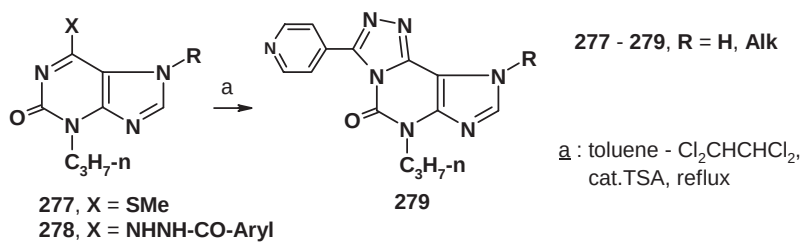
The 3-aryl-5-iodo-7-(triacetyl-*O*-ribofuranosyl) compounds **274** represent a new class of *xanthinoxidase inhibitors* (65JOC3601, 67JOC2241, 99S655) (Scheme 79).

The *third* approach was based on cyclodehydratation of 6-aroylhydrazido-purine derivative **278** under catalysis by p-toluenesulfonic acid giving rise to tricyclic **279**. The necessary intermediate **278** was accessible easily by transformation of the 6-methylthio derivative **277** by, e.g., isonicotinoyl hydrazide. Compounds **279** are stable in acid in contrast to parent triazolopurines **274** (**X = H**). Notable is their *bronchodilatation effect*, up to 100 × greater than that of theophylline (92TL3151) (Scheme 80).

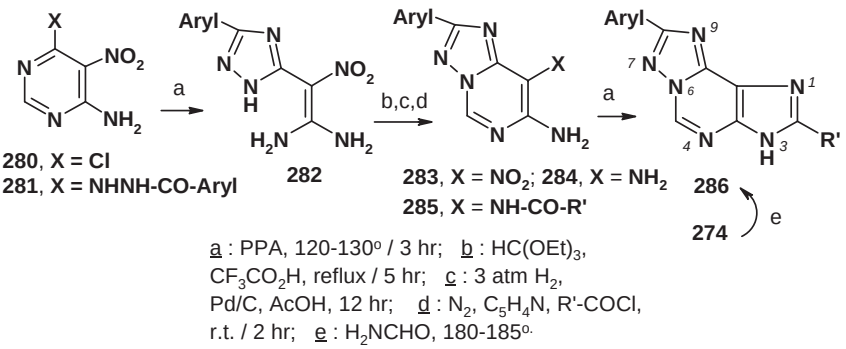
The *first* access to triazolo[**5**,**1**-*i*]purines is the rearrangement of their [3,4-*i*]-analogues **274**. The *second* method involving the alkaline cyclization of 4-amino-5-acylamino-triazolo[2,3-*c*]pyrimidine (**285**) produced the third imidazole ring of **286**.



Scheme 79



Scheme 80

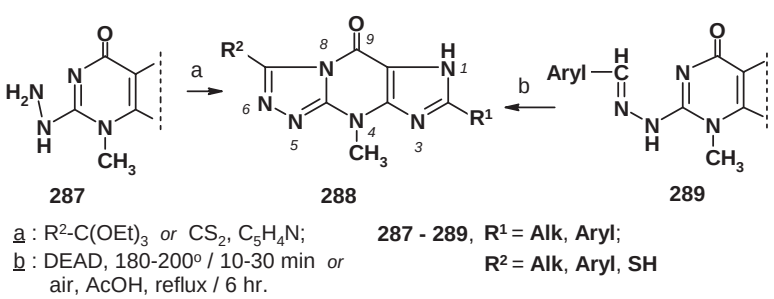


Scheme 81

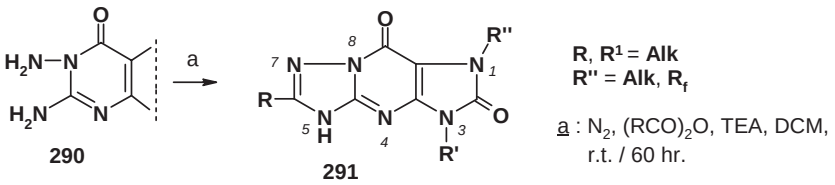
The synthesis started from 4-amino-6-aroyl-hydrazido-5-nitropyrimidine **281** which, on heating in PPA, formed the triazole segment, but at the same time cleavage of the pyrimidine moiety took place producing the 2-(triazol-3-yl)-1,1-diaminoethylene **282**. Employment of triethyl formate restored the pyrimidine portion giving the 4-amino-5-nitro-derivative **283**. The subsequent reduction of the nitro group and acylation of the 5-amino group resulted in **285** (65JOC3601, 88JOC382, 94JHC1171). A similar method starting from 4-amino-imidazol-5-carbonitrile is published in (02JMC3703). Triazolo[5,1-*i*]purines **286** are *antagonists of adenosine-A_2 receptors*, the highest efficacy was showen by a 3-(fluorobenzyl)-5-amino-8-(2-furyl)-derivative (93EJM569) (Scheme 81).

2. *[1,2,4]Triazolo[4,3-a and 1,5-a]purines*

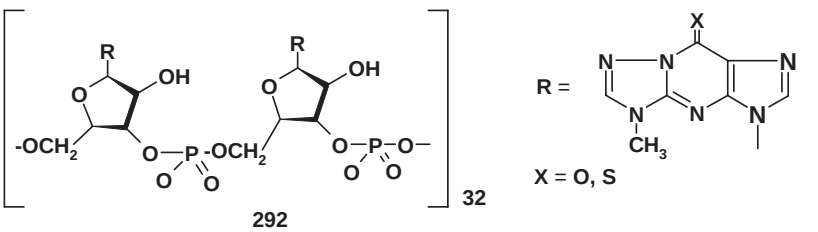
Their preparations copied those of their [*i*]-analogues. The *first* method started from 2-hydrazinopurines **287** and suitable ortho esters yielding [1,2,4]triazolo-[**4,3-*a***]purin-9-ones **288** (**R^2 = Alk, Aryl**). Substitution of ortho esters by carbon disulfide led to 7-mercapto-derivative **288** (**R^2 = SH**). The 7-aryl-derivatives were better accessible by the *second* method—the oxidative cyclization of 2-arylidenehydrazino)-derivatives **289**, such as heating with diethyl azodicarboxylate, or oxidation with aerial oxygen (85CPB3113) (Scheme 82).



Scheme 82



Scheme 83



Scheme 84

Isomeric [**1,5-***a*]-analogues of **291** can also be obtained by treatment of 1,2-diamino-7,8-disubstituted purine-6,8-diones **290** with carboxylic anhydrides. Compounds of this type are potential *B-cell-selective activators* and the 6-methyl-1-(2-piperidinoethyl)-3-*β*-D-ribofuranosyl-derivate of **291** was shown to be an example (94JMC3561) (Scheme 83).

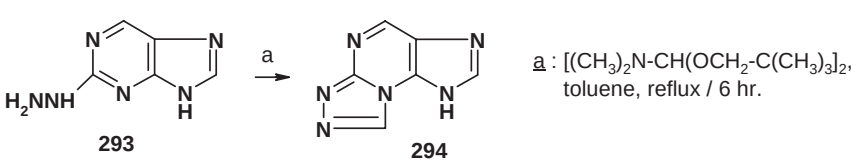
Polyribonucleotides with a triazolo[2,3-*a*]purine as a heterocyclic component **292** were also interesting from a pharmacological point of view. Several amphipatic (hydrophobic base, hydrophilic backbone) polyribonucleotides showed moderate to potent *antiviral activity against HIV* and a greater one *against human cytomegalovirus* than the already known gancyclovir (98JMC4958) (Scheme 84).

3. *[1,2,4] and [1,2,3] Triazolo[3,4-b and 5,1-b]purines*

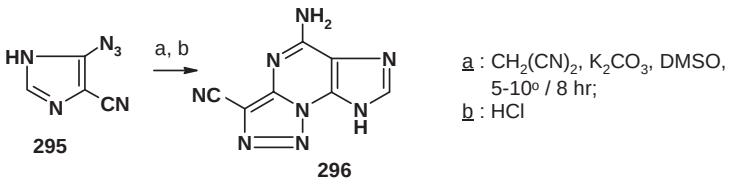
Reaction of 2-hydrazinopurine **293** with diethoxymethylacetate or preferentially with *N*,*N*-dimethylformamide dineopentyl acetal produced [1,2,4]-triazolo[**3,4-*b***]purine **294**. This compound is a strong UV-fluorescence agent (82H(17)405) (Scheme 85).

The 5-azido-4-cyanoimidazole (**295**) and malononitrile reacted to give [1,2,3]triazolo[**5,1-*b***]purine-3-carbonitrile **296** (95JHC457) (Scheme 86).

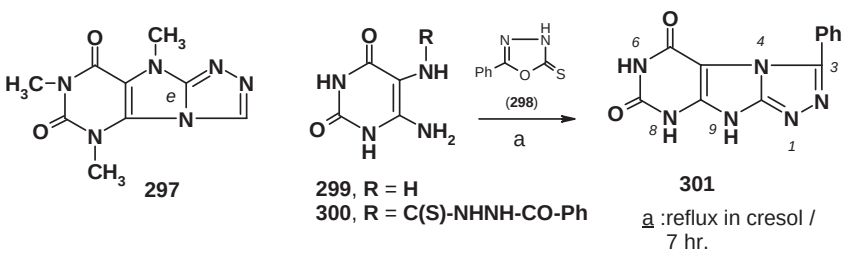
Heating 8-hydrazino-7-methylpurine-2,4-dione in formamide gave [1,2,4]triazolo[4,3-*e*]-purindione **297**. Occupation of position 7 of the starting material



Scheme 85



Scheme 86

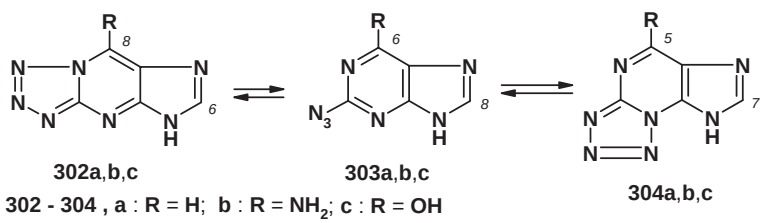


Scheme 87

prevented other than the "*e*" annulation (59ZOB3742). Action of [1,3,4]-oxazole-2-thione **298** on 4,5-diaminouracil **299** furnished [1,3,4]-triazolo[3,4-*f*]purine-5,7-dione **301**. Formation of the second and third five-membered rings proceeded through 5-thiosemicarbazidouracil **300** (93PHA109) (Scheme 87).

G. Tetrazolo-purines

The tetrazolo-purines exist in solution as a tautomeric equilibrium mixture of the cyclic form and the corresponding azidopurines (open form). The equilibrium position depended both on the solvent and the structure. The tetrazolotautomer is stabilized by the electrondonating groups and the azido-tautomer by the electronwithdrawing ones. The 2-azidopurine **303a**, 2-azidoadenine **303b** and 2-azidohypoxanthine **303c** exhibited other additional tautomers—tetrazolo-[1,5-*a*]-purine **302a**, -[1,5-*a*]adenine **302b** and -[1,5-*a*]hypoxanthine **302c** and their tetrazolo[5,1-*b*]purine analogs **304a**, **304b**, and **304c**, respectively. The tautomeric ratio was estimated from intensities of their ^{1}H-NMR spectra using the respective 6H–8H and 5H–7H signals in DMS or in trifluoroacetic acid. The azide tautomer was confirmed by its IR spectrum (Scheme 88).



Scheme 88

The azide to [1,5-*a*]-tautomeric ratio for **303a** : **302a** = 0.44; for **303b** : **302b** = 2.7; for **303c** : **302c** = 0.1.

The azide to [1,5-*b*]-tautomeric ratio for **303a** : **304a** = 3.5; for **303b** : **304b** = 1.1; for **303c** : **304c** = 0.5 (66JOC2210).

The most studied compounds are derivatives with a tetrazole ring annulated to the "*i*" of the purine ring system.

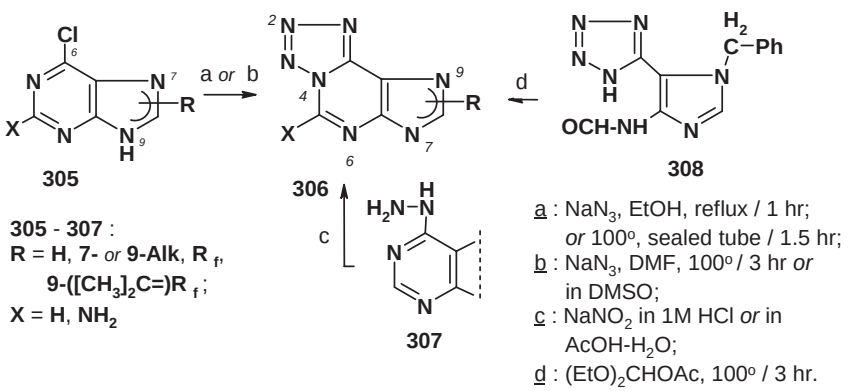
1. *Tetrazolo[5,1-i]purines*

The general preparation method was based on reaction of 6-chloropurine **305** with sodium azide or 6-hydrazinopurine **307** with nitrous acid or 1-alkyl-4-formamido-5-tetrazol-5-yl)imidazole **308** with dimethoxymethylacetate. The *first* one afforded the required tetrazolopurine **306** in low yield. The *second* one involving **307** was more advantageous (ca. 70% yield). The *third* one employing the tetrazolylderivative was only little used. The final **306** was primarily formulated as an "open" azide, but IR studies and X-ray diffraction analysis indicated the cyclic-tetrazole structure (66JOC2210, 70JHC75, 97JMC3248, 68AX(B)359).

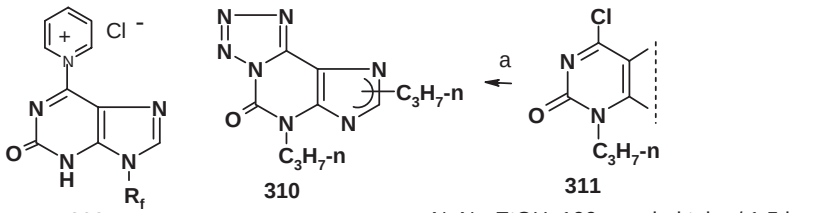
The N-(purin-6-yl)pyridinium chloride **309** was more reactive on substitution with a weak azide nucleophile (yield 87%) then the 6-chloro-analogue (yield 25%) at the same reaction conditions (96JCS(P1)15) (Scheme 89 and 90).

The equilibrium was also studied between the 6-azido- and the tetrazolo[5,1-*i*]-tautomers in relation to solvent applied. The ^{1}H-NMR spectrum in $CDCl_3$ showed a 2:3 ratio of the azido to tetrazolo species. The IR spectrum of a chloroform solution exhibited a very weak band at 2359 cm^{-1} for an N_3-group, while no absorption was found in a nujol mull (97T1595).

Compounds **310** obtained from 6-chloro-3,7-di-*n*-propyl-purinone **311** and sodium azide (Scheme 90) are more effective *inhibitors of cyclic AMP-specific phosphodiesterase* (PDE-IV) then theophylline and in addition do not display unwanted positive chronotropic action on heart—a common side effect of alkylxanthines (97JMC3248).



Scheme 89



Scheme 90

2. *Tetrazolo[1,5-a]purines*

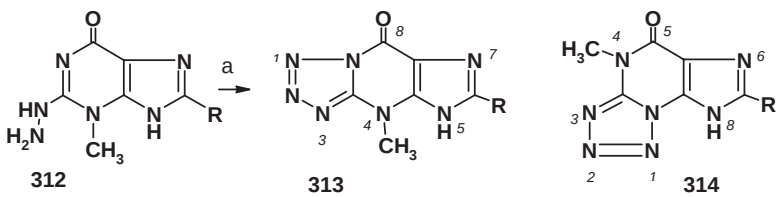
The simplest title compounds were synthetized from 2-hydrazino-3-methyl-8-R-purines **312** and nitrous acid under formation of cyclic 4-methyl-tetrazolo[1,5-*a*]-purin-9-one (**313**, **R = H**, **alkyl**, **aryl**) and not 2-azido-3-purine. The cyclic structure was corroborated by IR and ^{1}H-NMR spectra. The IR spectrum did not show the band of an azido group. With respect to the presence of the $N_{(3)}$-methyl in the starting compound, the annulation had to take place at bond "*a*" of the purine skeleton (85CPB3113) (Scheme 91).

3. *Tetrazolo[5,1-b]purines*

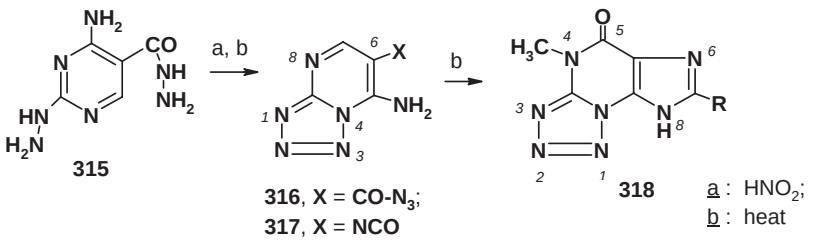
A similar method was applied when preparing exclusively the [5,1-*b*]-isomer from 2-hydrazino-1-methylpurinone. A useful access involved the treatment of nitrous acid and 4-amino-2-hydrazinopyrimidine-5-carbohydrazide (**315**) giving 5-amino-6-azidocarbonyltetrazolo[1,5-*a*]pyrimidine **316**. Subsequent heating and cyclization converted it to the corresponding isocyanate **317** and tetrazolo[5,1-*a*]purin-7-one **318**, respectively (86H1899) (Scheme 92).

4. *Tetrazolo[1,5-e]purines*

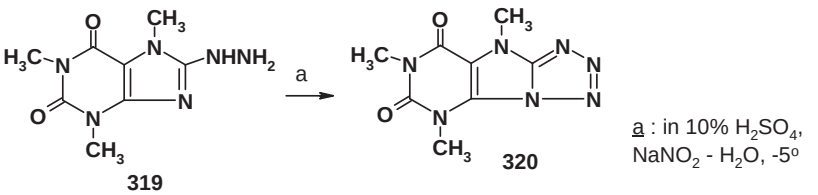
These compounds were prepared from derivatives of 8-hydrazinocaffeine (**319**) and nitrous acid producing 5,7,9-trimethyltetrazolo[1,5-*e*]purine-6,8-dione (**320**). Presence of the methyl group at $C_{(7)}$ of the original skeleton directed annulation to position "*e*" exclusively. Compound **320** exploded at about 180 °C on rapid heating (59ZOB3742) (Scheme 93).



Scheme 91



Scheme 92



Scheme 93

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Pyrazol-3-ones. Part II: Reactions of the Ring Atoms

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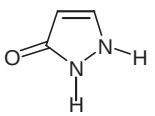
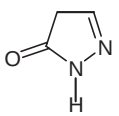
I. Introduction

The present chapter is Part II of a three part series. In Part I (01AHC(80)73) the synthesis and applications of pyrazol-3-ones **I** and **II** are described. We now present a comprehensive review of the reactions of the ring atoms (i.e., carbon and nitrogen) of pyrazol-3-ones **I** and **II**, since January 1964. The literature covered has been searched up to August 2003. As in Part I, the present work is a follow up of the major work on pyrazolones published by Wiley and Wiley in the ''Chemistry of Heterocyclic Compounds'' series of monographs (64MI1). In Part III of this series the reactivity of ring substituents of pyrazol-3-ones **I** and **II** together with syntheses since 1999, will be presented.



(I)

1,2-dihydro-3*H*-pyrazol-3-one



(II)

2,4-dihydro-3*H*-pyrazol-3-one

Following the trend of Part I, throughout Part II all pyrazolones have been named according to the IUPAC recommendations as pyrazol-3-ones and not as pyrazol-5-ones. The IUPAC nomenclature numbers the ring clockwise whereas most organic chemists are used to an anti-clockwise numbering.

Pyrazol-3-ones are known to be ambient compounds and depending on the solvent in which they are dissolved can exist in several tautomeric forms. Usually is less polar solvents such as chloroform pyrazol-3-one tautomers are dominant, whereas in more polar solvents such as dimethylsulfoxide 3-hydroxypyrazole tautomers are dominant. The most recent review article on this topic has been presented by Katritzky and co-workers (00AHC(76)157).

II. Acidity

Pyrazol-3-ones are in general weak acids and can be titrated with strong bases. 2,4-Dihydro-3*H*-pyrazol-3-ones are stronger acids than 1,2-dihydro-3*H*-pyrazol-3-ones, which are very weak. Titrating several pyrazole-3-ones with perchloric acid in acetic acid derived the most extensive data on basicity. The pK_a values range from 1.7 to 3.7, except for 4,4-disubstituted and 4-halogen substituted 2,4-dihydro-3*H*-pyrazol-3-ones. The 4,4-disubstituted 2,4-dihydro-3*H*-pyrazol-3-ones are so weak that they are essentially neutral, while the halogenated compounds have pK_a values of about 0.8 (64MI1).

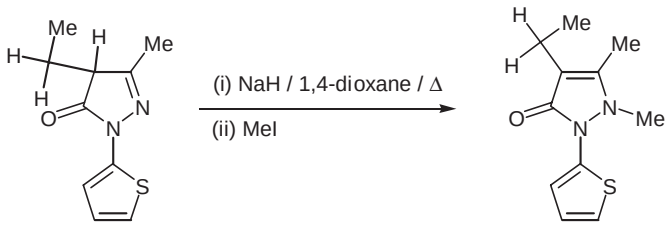
More recently, the acidity constants of several pyrazolones have been investigated both in the gas phase and aqueous solution by the AM1 method. The AM1/COSMO solvation method was employed in the case of aqueous solution calculations (99JMS(T)125).

III. Alkylation

Pyrazol-3-ones are known to be ambident compounds that upon alkylation can give N-alkylated or O- and N-alkylated products, depending on the substrate, the alkylating agent and the reaction conditions.

A. By Reaction with Alkyl Halides

By reaction with alkyl halides, esters of sulfonic and carbonic acids, trimethyloxonium tetrafluoroborate, diazo compounds, Mannich or Mitsunobu conditions or miscellaneous reagents. Methyl iodide is a versatile and effective methylating reagent that can be used at room temperature, at moderate temperatures in a tightly closed vessel or at high temperatures in an autoclave. 2,4-Dihydropyrazol-3-one **1** was methylated at N1 with sodium hydride in boiling 1,4-dioxane followed by methyl iodide at room temperature. 1,2-Dihydropyrazol-3-one **2** was obtained in 59% yield (79AP853) (Scheme 1).



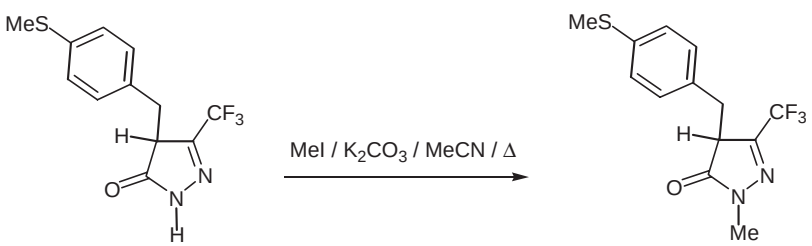
(1) (2)

Scheme 1

Methylation of N2 of pyrazol-3-one **3** required a weaker base but higher temperature. Thus **3** was heated under reflux in acetonitrile containing potassium carbonate and methyl iodide to give 2-methylpyrazol-3-one **4** in 30% yield (96JMC3920) (Scheme 2).

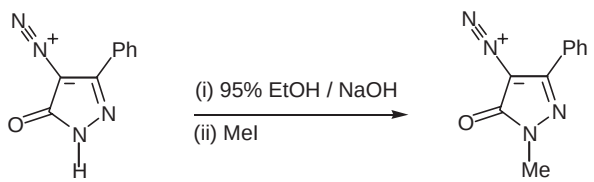
Padwa and co-workers (83JOC1069) (Scheme 3) found that 4-diazopyrazol-3-one **5** was stable when methylated by methyl iodide in 95% ethanol containing sodium hydroxide to give 2-methyl-4-diazopyrazol-3-ones **6**.

Attempted methylation of 2-aminopyrazol-3-ones **7a**,**b** with methyl iodide at room temperature proceeded slowly and it was necessary to operate at higher temperatures, which led to partial deamination of starting material. Thus at 100 °C in a sealed tube the reaction gave a mixture of pyrazol-3-ones **8a**,**b**, **9a**,**b** and **10a**,**b**, respectively (81JHC957) (Scheme 4).



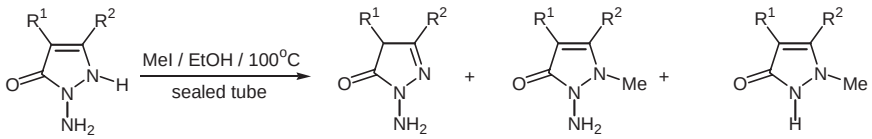
(3) (4)

Scheme 2



(5) (6)

Scheme 3



(7) **(8)** **(9)** **(10)**

(a) R^1 = Ph, R^2 = Me, **(b)** R^1 = Me, R^2 = Ph

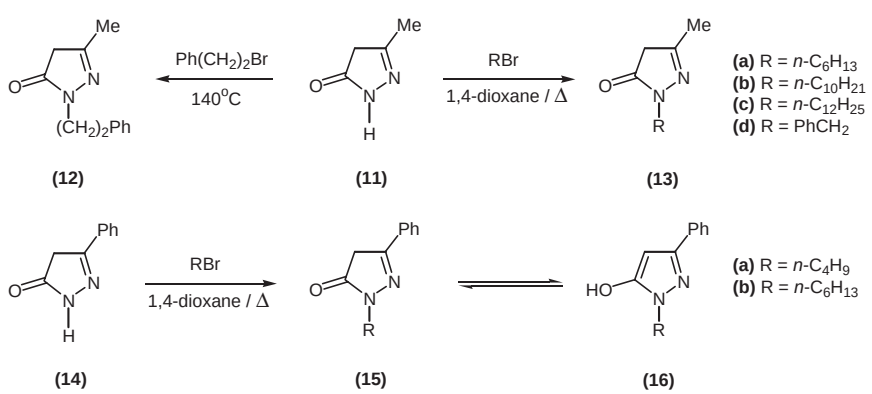
Scheme 4

Pyrazol-3-one **11** was alkylated with (2-bromoethyl)benzene at 140 °C or with *n*-hexyl, *n*-decyl, *n*-dodecyl, or benzyl bromides (01BSCQ459) in refluxing 1,4-dioxane to afford the corresponding 2-alkylpyrazol-3-ones **12** and **13a**–**d** in yields of 45–75% (65ZOR133) (Scheme 5). The structure of compounds **13a**–**d** in $CDCl_3$ was confirmed by NMR spectroscopy. In particular a signal around 172 ppm in the ^{13}C NMR spectra is assigned to the carbonyl carbon, while DEPT 145 spectra and ^{13}C–^{1}H correlation spectra further confirm the C4 methylene entity. Alkylation at N2 of pyrazol-3-one **14** with *n*-butyl- or *n*-hexyl bromide took place also by heating in 1,4-dioxane to give 2-alkylpyrazol-3-ones **15a**,**b**, respectively. It was confirmed by NMR studies that, in $CDCl_3$ the pyrazol-3-one **15a**,**b** tautomers are dominant, whereas in DMSO-d_6 the pyrazol-5-ol **16a**,**b** tautomers are dominant (99BSCQ367) (Scheme 5).

Benzylation of 1,2-dihydropyrazol-3-ones **17a**,**b** with benzyl bromide in refluxing tetrahydrofuran followed by treatment with aqueous sodium hydroxide afforded 1-benzylpyrazol-3-ones **18a**,**b** (81JHC957) (Scheme 6).

But when Begtrup (88BSB573) (Scheme 7) treated the pyrazol-3-one **19**/pyrazole **20** tautomeric mixture with 4-methoxybenzyl chloride he obtained 5% of *O*-alkylated pyrazole derivative **21** and 70% of 1-(4-methoxybenzyl)pyrazol-3-one **22**.

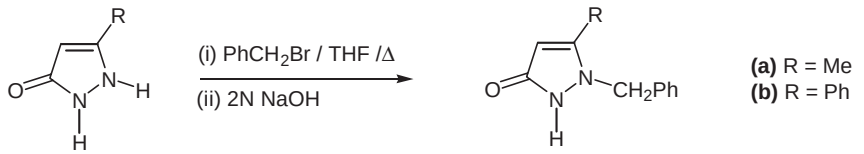
An indirect way of introducing a substituted aminohydroxypropyl group at position 1 of 1,2-dihydropyrazol-3-ones was devised by Holzer, Ecker and co-workers (98JMC4001) (Scheme 8). The method consists of reacting the sodium salt of 4-acylpyrazol-3-ones **23a**–**l** with excess epichlorohydrin and successively



(12) **(11)** **(13)**

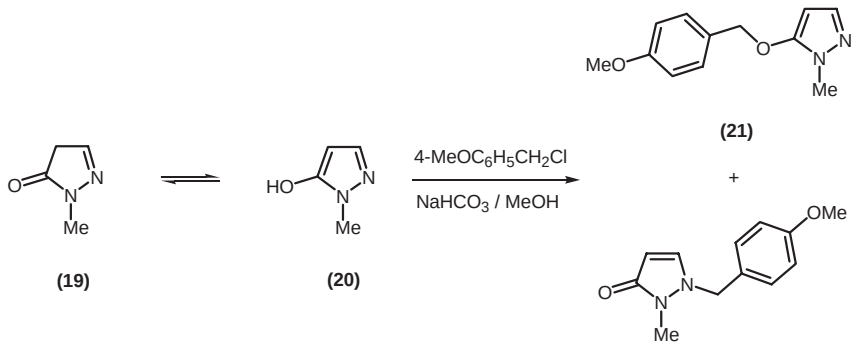
(14) **(15)** **(16)**

Scheme 5



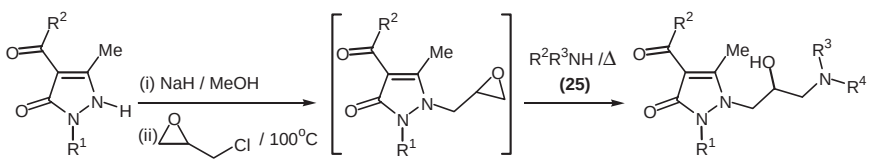
(17) (18)

Scheme 6



(19) (20) (21) (22)

Scheme 7



(23) (24) (26)

(a) R^1= Me, R^2= Ph, R^3= R^4 = *i*-Pr, **(b)** R^1= R^2= Ph, R^3= H, R^4= *n*-Pr, **(c)** R^1= R^2= Ph, R^3= H, R^4= *i*-Pr, **(d)** R^1= R^2= Ph, R^3= R^4 = *i*-Pr, **(e)** R^1= R^2= Ph, R^3= H, R^4= *t*-Bu, **(f)** R^1= Ph, R^2= 2-thienyl, R^3= H, R^4= *n*-Pr, **(g)** R^1= Ph, R^2= 2-thienyl, R^3= H, R^4= *i*-Pr, **(h)** R^1= Ph, R^2= 2-thienyl, R^3= H, R^4= *t*-Pr, **(i)** R^1= Ph, R^2= $(CH_2)_2$Ph, R^3= H, R^4= *n*-Pr, **(j)** R^1= Ph, R^2= $(CH_2)_2$Ph, R^3= H, R^4= *i*-Pr, **(k)** R^1= Ph, R^2= $(CH_2)_2$Ph, R^3= H, R^4= *n*-Bu or **(l)** R^1= Ph, R^2= $(CH_2)_2$Ph, R^3= H, R^4= *t*-Bu,

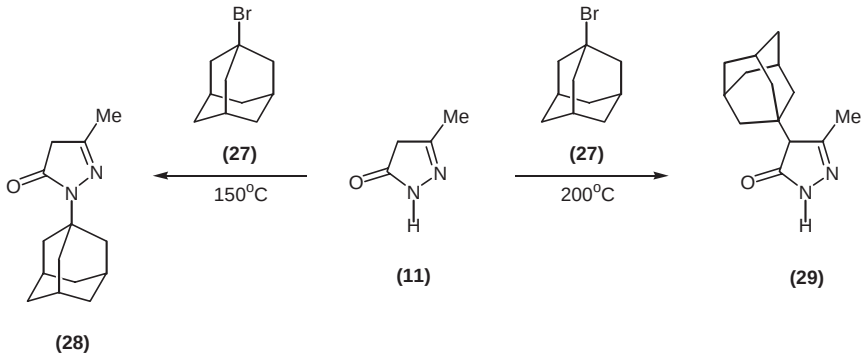
Scheme 8

treating the intermediate epoxides **24a–l** with excess appropriate amines **25a–l**. The 1-substituted 4-acylpyrazol-3-ones **26a–l** were obtained in 14–52% yield.

Heating 5-methylpyrazol-3-one **11** with 1-adamantyl bromide **27** at 150 °C afforded 2-adamantylpyrazol-3-one **28**, whereas at 200 °C 4-adamantylpyrazol-3-one **29** was obtained (99BSB735) (Scheme 9).

B. Esters of Sulfonic and Carbonic Acids

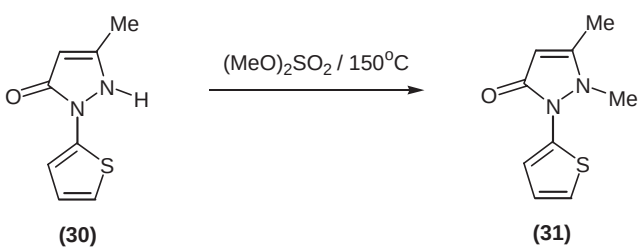
A most frequently used method for the methylation of pyrazol-3-ones is stirring at room temperature or heating in an alkaline solution with dimethyl sulfate. Usually a



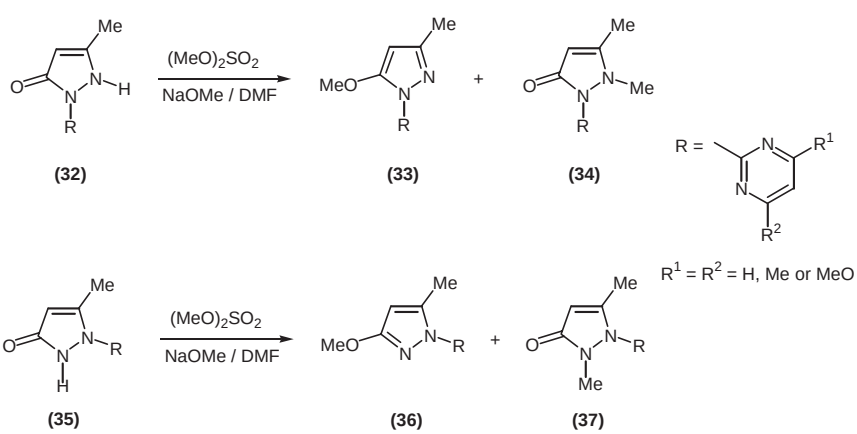
Scheme 9

10% aqueous solution of sodium hydroxide is used. Less frequent is the use of neat dimethyl sulfate at relatively high temperatures. 2-(2-Thienyl)pyrazol-3-one **30** was heated at 150 °C in dimethyl sulfate to give the 1-methyl derivative **31** in 60% yield (79AP853) (Scheme 10).

Pyrazol-3-ones **32** and **35** were treated with dimethyl sulfate in DMF containing sodium methoxide to afford a mixture of 3-methoxypyrazole **33** and 1-methylpyrazol-3-one **34**, or 3-methoxypyrazole **36** and 2-methylpyrazol-3-one **37**, respectively (69CPB1467) (Scheme 11).



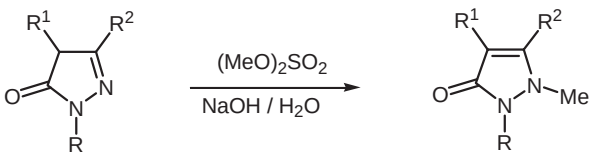
Scheme 10



Scheme 11

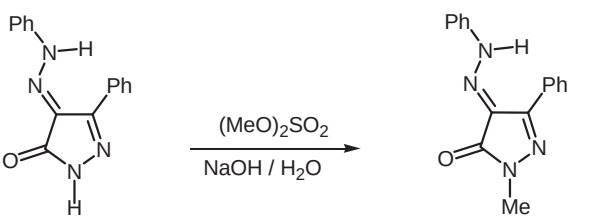
The alkylation of 2-arylpyrazol-3-ones **38a–d** or **40** required heating in 10% aqueous sodium hydroxide containing dimethyl sulfate to afford 1-methyl derivatives **39a–d** or 1-methyl derivative **41** in excellent yields (75CJC3637, 85JIC54, 89AP351) (Scheme 12).

Dimethyl carbonate proved to be an effective methylating agent when pyrazol-3-one **42** was heated at 180 °C in neat reagent to give pyrazol-3-one **43** in 73% yield and 3-methoxypyrazole **44** in 21% yield. The products were separated by fractional distillation (87CZ83) (Scheme 13).



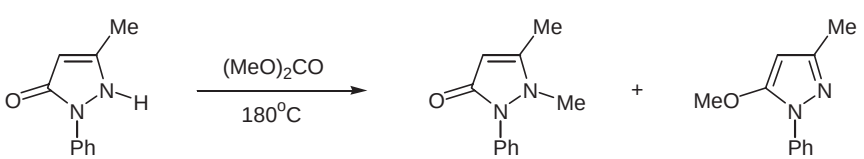
(38) **(39)**

(a) R = Ph, R^1 = 2-aminobenzyl, R^2 = Me
(b) R = Ph, R^1 = 2-aminobenzyl, R^2 = Ph
(c) R = Ph, R^1 = H, R^2 = Me,
(d) R = 4-$MeOC_4H_6$, R^1 = H, R^2 = Me



(40) **(41)**

Scheme 12

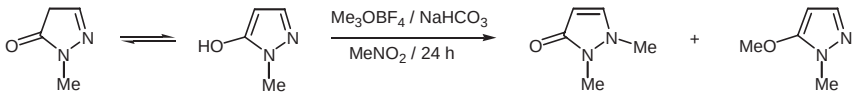


(42) **(43)** **(44)**

Scheme 13

C. With Trimethyloxonium Tetrafluoroborate

Begtrup (88BSB573) (Scheme 14) methylated the pyrazol-3-one **19**/pyrazole **20** tautomeric mixture with trimethyloxonium tetrafluoroborate and obtained almost



(19) (20) (45) (46)

Scheme 14

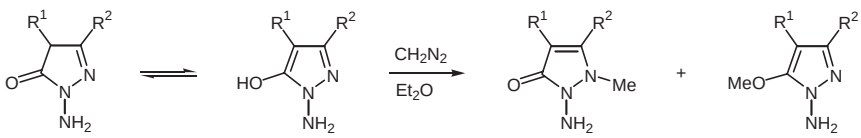
exclusively the 1-methylpyrazol-3-one **45** in 71% yield and only a trace of isomeric 3-methoxypyrazole **46**.

D. With Diazomethane or Trimethylsilylazomethane

Adembri et al. (72JHC1219) (Scheme 15) demonstrated the existence of a tautomeric mixture of 2-aminopyrazol-3-ones **47a**–**c**/2-aminopyrazoles **48a**–**c** in diethyl ether by methylation with diazomethane. The products were 2-amino-1-methylpyrazol-3-one **49a**–**c** and 2-amino-3-methoxypyrazole **50a**–**c**, respectively.

Several years later other workers used the same method to confirm that pyrazol-3,5-diones **51a**,**b**/5-hydroxypyrazol-3-ones **52a**,**b** exist as tautomeric mixtures in solution. The reactions with diazomethane took place in a mixture of diethyl ether and methanol and afforded a mixture of the respective pyrazol-3,5-diones **53a**,**b** and 5-methoxypyrazol-3-ones **54a**,**b**. The suitability of these structurally fixed methyl derivatives as model compounds in the study of the tautomeric structures by NMR spectroscopy was investigated (80CB3910) (Scheme 16).

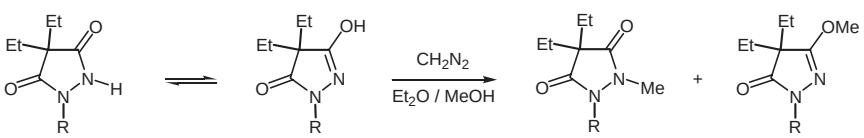
Diazomethane reacted nucleophilically at the α,β-unsaturated carbonyl entity of 5,5′-dimethyl-2,2′-diphenyl-4,4′-bipyrazole-3,3′(2*H*,2′*H*)-dione **55** to give, via intermediate **56**, the unstable spiro-cyclopropyldipyrazolone derivative **57** in 47% yield. Upon heating in ethanol **57** isomerized to the 4-[(pyrazol-5-yl)methylene]pyrazol-3-one **58**. The structure of **58** was assigned unambiguously by X-ray crystallography (89JPR584) (Scheme 17).



(47) (48) (49) (50)

(a) R^1 = H, R^2 = Ph, **(b)** R^1 = Me, R^2 = Ph, **(c)** R^1 = Ph, R^2 = Me

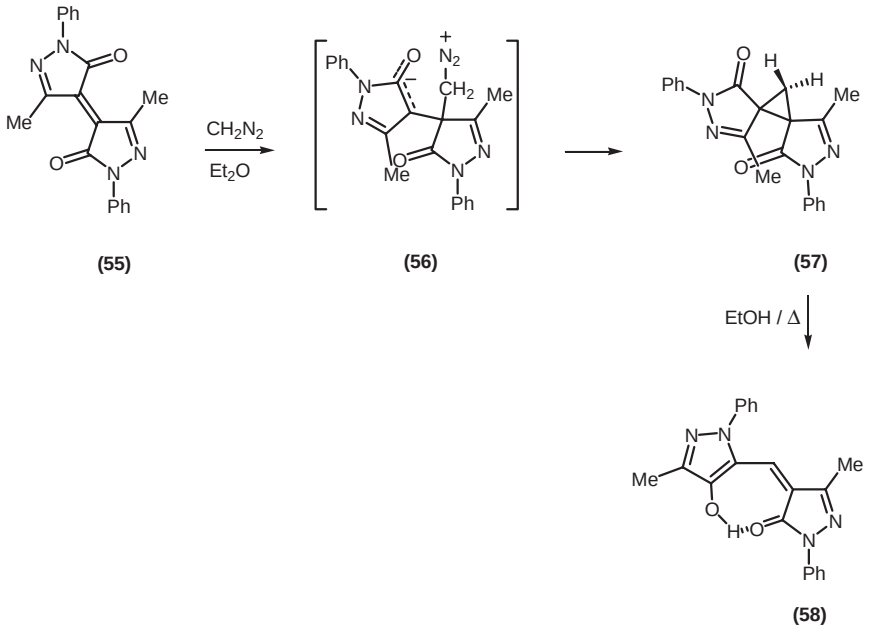
Scheme 15



(51) (52) (53) (54)

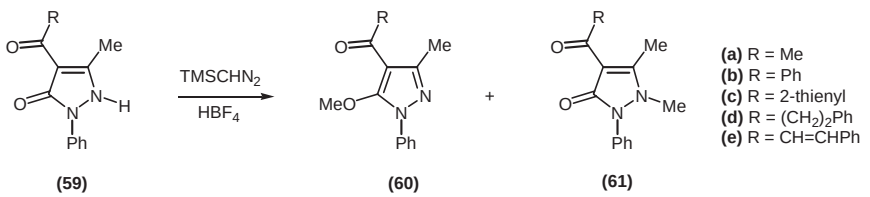
(a) R = H, **(b)** R = Me

Scheme 16



(55) (56) (57) (58)

Scheme 17



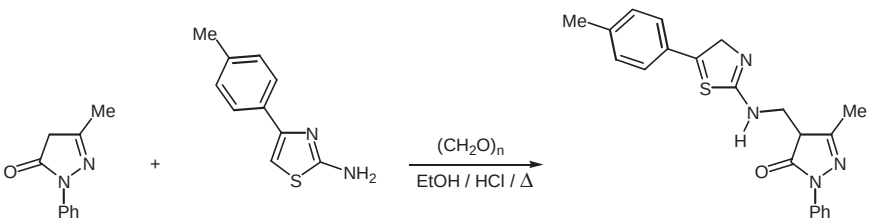
(59) (60) (61)

Scheme 18

In an effort to obtain selectively 2-methylpyrazoles by methylating 1-arylpyrazol-3-ones, Holzer and Plagens (96SP455) (Scheme 18) investigated the use of (trimethylsilyl)diazomethane. Thus pyrazol-3-ones **59a–e** were reacted with (trimethylsilyl)diazomethane and 10% aqueous tetrafluoroboric acid in dichloromethane to afford mixtures containing 5-methoxypyrazoles **60a–e** and 5-methylpyrazol-3-ones **61a–e**, in yields ranging from 8 to 58% and 11 to 45%, respectively.

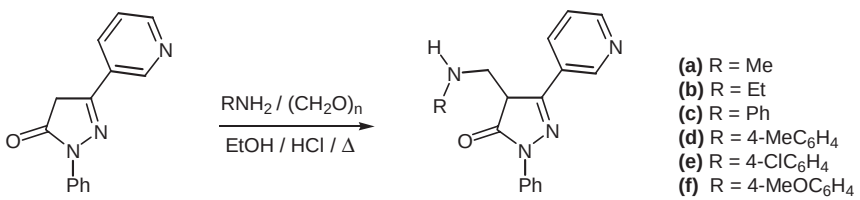
E. By the Mannich Reaction

Bhargava et al. (65BCJ912) (Scheme 19) prepared 1-[4-*p*-tolylthiazol-2-ylaminomethyl]pyrazol-3-one **64** by heating a mixture of pyrazol-3-one **62**, 4-*p*-tolylthiazol-2-ylamine **63** and paraformaldehyde in ethanolic hydrogen chloride and then adding ammonia to liberate the free base.



(62) (63) (64)

Scheme 19



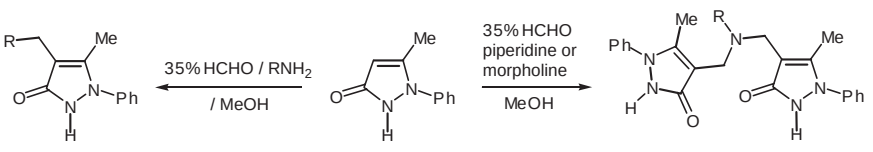
(65) (66)

Scheme 20

Sammour (72JPR612) (Scheme 20) reported that the Mannich reaction of 5-pyridin-3-ylpyrazol-3-one **65** with primary amines such as the methylamine, ethylamine, aniline, 4-toluidine, 4-chloroaniline or 4-methoxyaniline and paraformaldehyde, gave the corresponding 4-[(alkyl or arylamino)methyl]-5-pyridin-3-ylpyrazol-3-one **66** in moderate yields.

Mustafa et al. (64T531) (Scheme 21) found that pyrazol-3-one **67** condensed readily with formaldehyde in the presence of piperidine or morpholine to give the corresponding Mannich bases **68a**,**b**. However, when primary amines, namely ethylamine, aniline, 2- or 4-toluidine were used instead, 4-({[(3-oxopyrazol-4-yl)-methyl]amino}methyl)-pyrazol-3-ones **69a**–**d** were obtained.

More recently formaldehyde or paraformaldehyde in the classical Mannich reaction has been replaced by methylene chloride. Reaction of pyrazol-3-one (antipyrine) **70** with dimethylamine or piperidine in methylenene chloride at 40 °C or with morpholine in a 1:1 v/v methylene chloride/acetonitrile mixture at 50 °C,

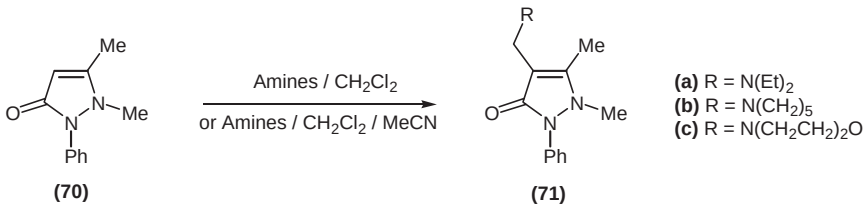


(68) (67) (69)

(a) R = $N(CH_2)_5$, **(b)** R = $N(CH_2CH_2)_2O$

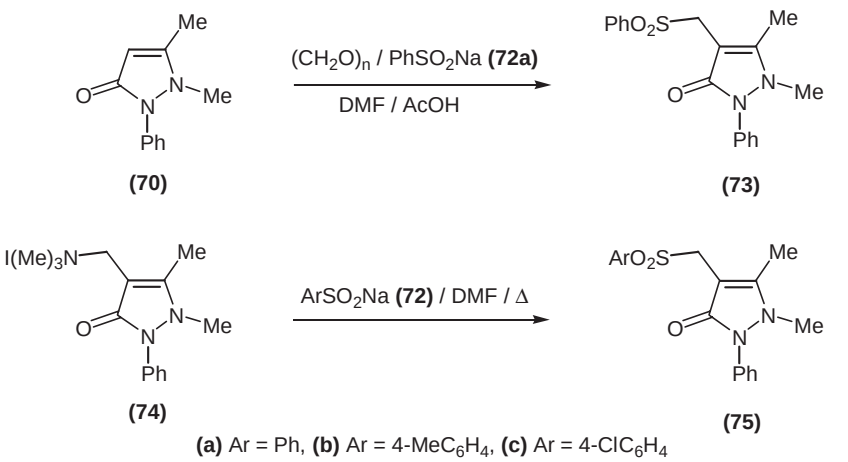
(a) R = Et, **(b)** R = Ph, **(c)** R = 2-MeC_6H_4
(d) R = 4-MeC_6H_4

Scheme 21



(70) (71)

Scheme 22



(70) (73) (74) (75)

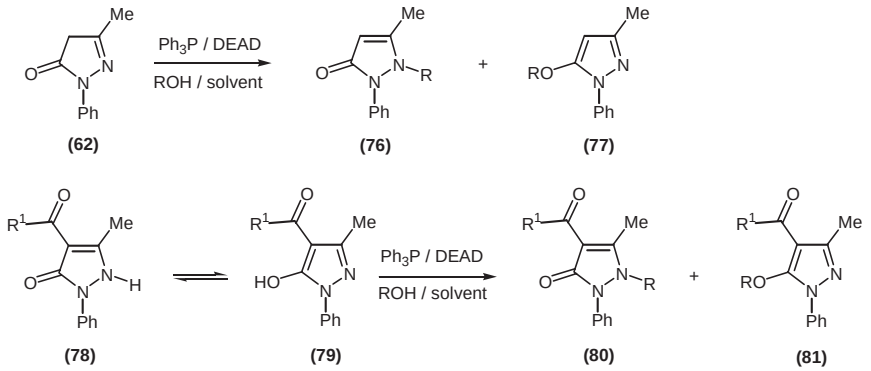
Scheme 23

afforded the corresponding *N*,*N*-dialkylaminomethyl derivatives **71a**–**c** in 78, 90 and 63% yield, respectively (93SC817) (Scheme 22).

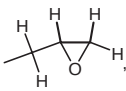
4-(Arylsulfonyl)pyrazol-3-ones can be synthesized directly from pyrazol-3-ones or indirectly via iodomethane salts of 4-(dimethylamino)methylpyrazol-3-ones. Hellmann and Müller (65CB638) (Scheme 23) synthesized 4-(phenylsulfonyl)methylpyrazol-3-one **73** by treating pyrazol-3-one **70** with paraformaldehyde and sodium benzenesulfinate **72a** in DMF with a catalytic amount of acetic acid. Eight years later Messinger (73AP603) reported that the reaction of *N*,*N*,*N*-trimethyl(3-oxopyrazol-3-yl)methanaminium iodide **74** with sodium sulfinates **72a**–**c** in DMF afforded the corresponding 4-(arylsulfonyl)methylpyrazol-3-ones **75a**–**c** in 82, 67 and 74% yield, respectively.

F. By the Mitsunobu Reaction

Holzer and Plagens (97H309) (Scheme 24) studied the alkylation of pyrazol-3-ones **62** and of the tautomeric pyrazol-3-one **78a**–**d**/pyrazol-5-ol **79a**–**d** mixtures by applying the Mitsunobu reaction [triphenylphosphine, diethyl azodicarboxylate (DEAD), alcohol, solvent]. The reactions were performed in various solvents. Using methanol as the alkylating agent the reaction of **62** in dichloromethane or THF,



(a) R = Me, R^1 = Ph, **(b)** R = Me, R^1 = 2-thienyl, **(c)** R = Me, R^1 = Bz, **(d)** R = Me, R^1 = Ph, **(e)** R = Me_2CH, R^1 = Ph

(f) R = Bz, R^1 = Ph, **(g)** R =  , R^1 = Ph

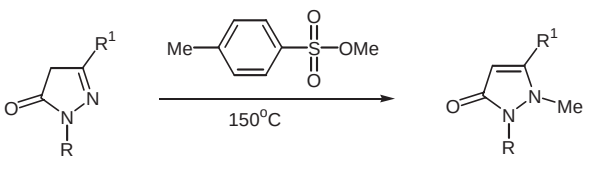
Scheme 24

78a/**79a** in acetonitrile, chloroform, dichloromethane or THF, **78b**/**79b** in dichloromethane or THF and **78c**/**79c** in benzene, dichloromethane or THF, gave mixtures of the corresponding pyrazol-3-one **76a**/pyrazole **77a** and pyrazol-3-ones **80a**–**c**/pyrazoles **81a**–**c**, in ratios ranging from 1:1.7 to 1:10.6, respectively. On the other hand the reaction under Mitsunobu conditions of pyrazol-3-one **62** with methanol in benzene, of **62** with propan-2-ol in benzene or THF, **78a**/**79a** with propan-2-ol, benzyl alcohol or 2,3-epoxypropanol in THF or **78b**/**79b** with methanol in benzene, afforded the corresponding *O*-alkylated pyrazoles **77a**, **77e** and **81e**, **f**, **g**, and **b** as single products.

G. By Miscellaneous Reagents

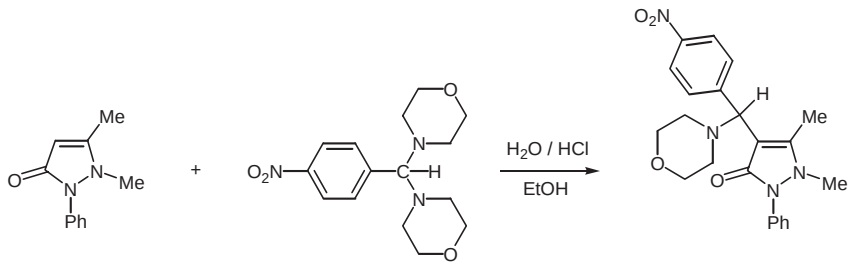
Methylation of pyrazol-3-ones **82a**–**d** with methyl *p*-toluene sulfonate was possible at 150 °C and gave 1-methylpyrazol-3-ones **83a**–**d** in excellent yields (01JHC1065) (Scheme 25).

Alkylation of pyrazol-3-one **70** with 4-[morpholin-4-yl-(4-nitrophenyl)methyl]-morpholine **84** was performed at room temperature since at higher temperatures polymerization occurred. However the reaction was extremely slow. It took



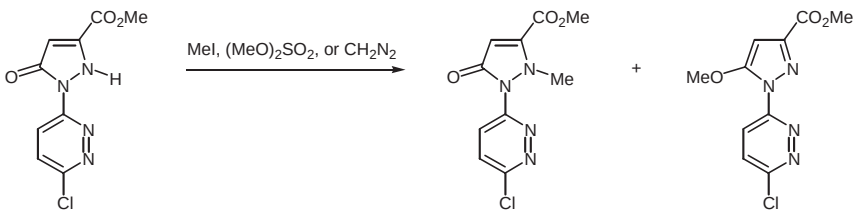
(a) R = R^1 = Ph
(b) R = Ph, R^1 = 4-ClC_6H_4
(c) R = Ph, R^1 = 4-$NO_2C_6H_4$
(d) R = 4-$NO_2C_6H_4$, R^1 = Ph

Scheme 25



(70) (84) (85)

Scheme 26



(86) (87) (88)

Scheme 27

6 months for an ethanolic solution of **70** and **84** containing aqueous hydrochloric acid to give 4-[morpholin-4-yl-(4-nitrophenyl)methyl]pyrazol-3-one **85** in 25% yield (64JPR216) (Scheme 26).

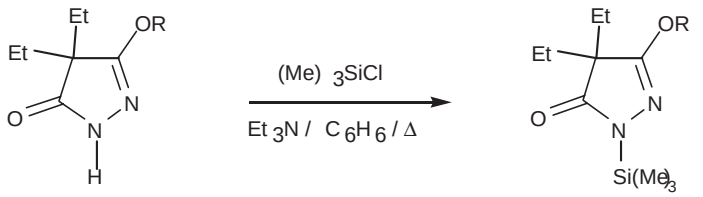
Szilagyi et al. (83H765) (Scheme 27) compared the methylation of pyrazol-3-one **86** both on N1 and the carbonyl oxygen of the ring using methyl iodide, dimethyl sulfate, or diazomethane. Thus with methyl iodide or dimethyl sulfate the results were similar, 1-methylpyrazol-3-one **87** and methyl 5-methoxypyrazole-3-carboxylate **88** were obtained in a ratio of about 1:5, whereas with diazomethane, compounds **87** and **88** were obtained in a ratio of 5:1.

Abarbi et al. (00JOC4618) reacted 3-bromopropene and 2-bromomethylacrylic acid ethyl ester with the Grignard reagent derived from 1,5-dimethyl-3*H*-5-iodo-2-phenylpyrazol-3-one and diisopropyl magnesium, and obtained the corresponding 4-allyl-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-one and 2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylmethyl)acrylic acid ethyl ester, respectively.

IV. Silylation

A. With Trimethylsilyl Chloride

Trimethylsilylation of 5-methoxypyrazol-3-one **89a** or 5-trimethyl-silyloxypyrazol-3-one **89b** with trimethylsilylchloride in benzene containing triethylamine afforded 5-methoxy-2-trimethylsilyloxypyrazol-3-one **90a** and 2,5-di(trimethylsilyloxy)-pyrazol-3-one **90b**, respectively (80CB3915) (Scheme 28).



(89) **(90)**

(a) R = Me , **(b)** R = Si (Me)$_3$

Scheme 28

The lactam-lactim structure of these compounds was established not only by conventional ^{1}H and ^{13}C NMR spectroscopy but also by ^{29}Si NMR spectroscopy.

V. Acylation

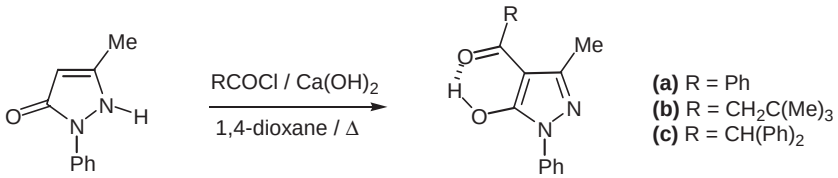
4-Acylpyrazol-3-ones are the focus of research on potential antifungal agrochemicals and their metal extracting properties.

A. With Acid Chlorides

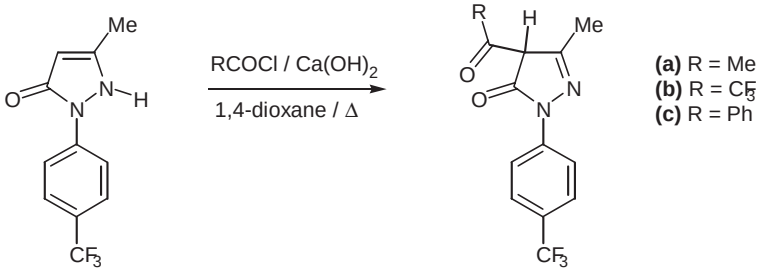
The outcome of acylation of the ring atoms of pyrazol-3-ones with acid chlorides depends on the type of substitution on the pyrazol-3-one ring. Both C- and N-acylation are possible. With 2-aryl-4-(or 5)-substituted pyrazol-3-ones **91a–c** and **93a–c** reaction with acid chlorides occurs in 1,4-dioxane with calcium hydroxide. Although C4-acylation occurs in both reactions, the former gives the more stable intramolecularly hydrogen bonded pyrazoles **92a–c** when reacted with benzoyl chloride, *t*-butylacetyl chloride or diphenylacetyl chloride (99POL3041), while the latter gives 4-acylpyrazol-3-ones **94a–c**, when reacted with acetyl chloride, trifluoroacetyl chloride or benzoyl chloride (99JOM344) (Scheme 29).

Acylation at C4 of a 1,2-dihydropyrazol-3-one was also achieved using a 4-iodo-1,2,5-trisubstituted derivative on reaction with Grignard reagents. Thus, 4-iodopyrazol-3-one **95** underwent a smooth iodine-magnesium exchange by reaction with diisopropyl magnesium in dichloromethane at $-25\,^{\circ}C$. The resulting 4-diisopropylmagnesium pyrazol-3-one was trapped by transmetallation with copper(I) cyanide lithium chloride complex, leading presumably to the corresponding copper species, followed by treatment with benzoyl chloride to afford the 4-benzoylderivatives **96** (00JOC4618) (Scheme 30).

Three examples of N1 acylation of a 1,2-dihydropyrazol-3-one have been reported. Benzoylation of 2-phthalazin-1-ylpyrazol-3-one **97a** was accomplished by heating in pyridine containing benzoyl chloride to give 1-benzoylpyrazol-3-one **98a** in 55% yield (81PHA471). On the other hand acetylation of pyrazol-3-ones **97b**,**c** occurred by heating in acetic anhydride to afford 1-acetylpyrazol-3-ones **98b**,**c** in excellent yields (91JCS(CC)314, 96T1579) (Scheme 31).

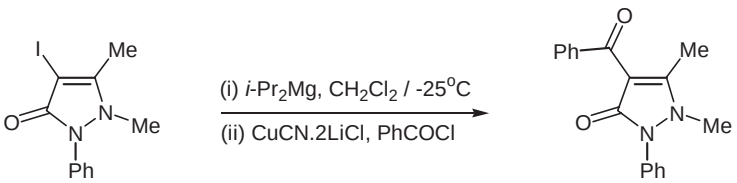


(91) (92)



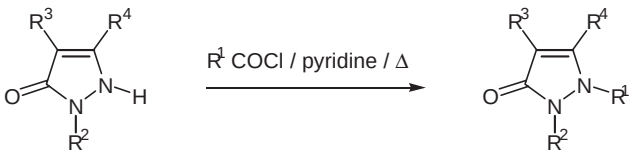
(93) (94)

Scheme 29



(95) (96)

Scheme 30

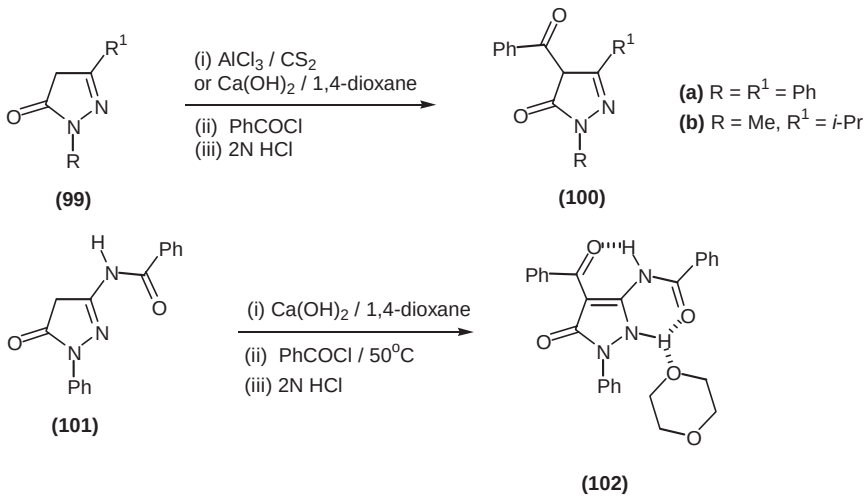


(97) (98)

(a) R^1 = PhCO, R^2 = phthalazin-1-yl, R^3 = Ph, R^4 = H **(b)** R^1 = MeCO, R^2 = 4-$NO_2C_6H_5$ R^3 = $CH_2C(H)(NHR)CO_2Bn$, R^4 = Me, **(c)** R^1 = R^2 = MeCO, R^3 = PhCOS, R^4 = H

Scheme 31

Benzoylation of 2,4-dihydro-2,5-disubstituted pyrazol-3-ones at C4 has been performed in the presence of a Lewis acid or a base. Pyrazol-3-one **99a** was treated with anhydrous aluminium chloride in carbon disulfide and pyrazol-3-one **99b** was treated with calcium hydroxide in 1,4-dioxane. Addition of benzoyl chloride followed by dilute hydrochloric acid afforded the corresponding 4-benzoylpyrazol-3-ones

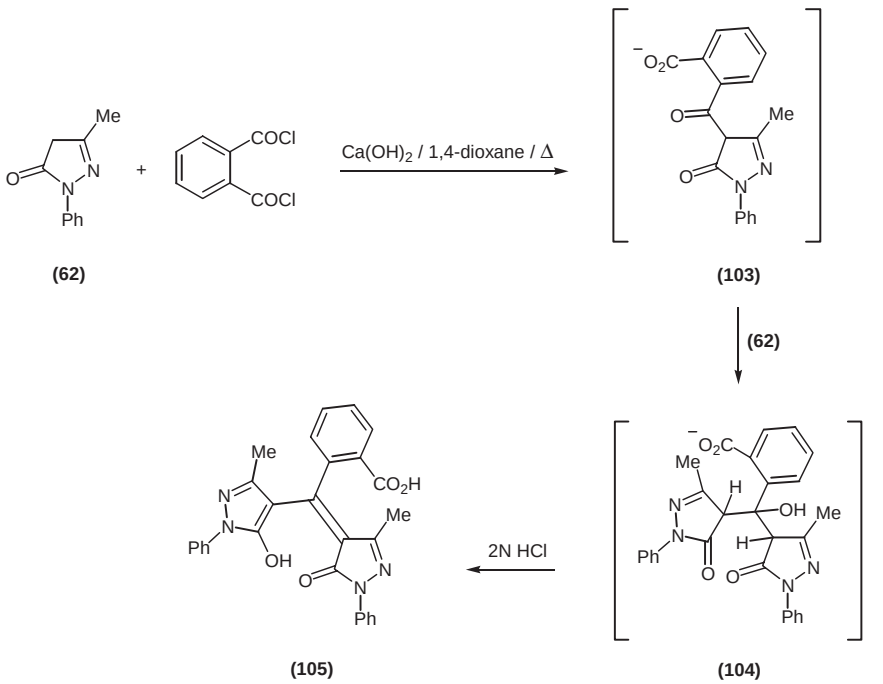


Scheme 32

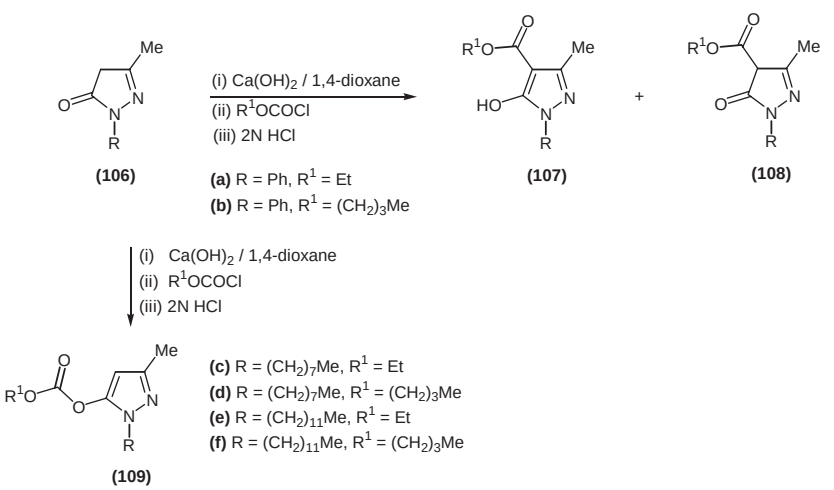
100a,**b** in 60 and 63% yield, respectively (73IJC1, 91JHC1837) (Scheme 32). Similarly, benzoylation of 2,4-dihydropyrazol-3-one **101** in the presence of calcium hydroxide gave 1,2-dihydro-4-benzoyl-5-benzoylaminopyrazol-3-one **102**. An X-ray crystal diffraction study of this compound shows that it forms two intramolecular bonds, between the NH of the benzoylamino group and the carbonyl oxygen of the benzoyl group, and between the carbonyl oxygen of the benzoylamino group and the ring NH. Compound **102** is also stabilized by an intramolecular hydrogen bond between the ring NH and the oxygen of a 1,4-dioxane solvent molecule (02JMS175) (Scheme 32).

The reaction of pyrazol-3-one **62** and phthaloyl chloride in the presence of calcium hydroxide did not give a product of acyl substitution by two pyrazol-3-one **62** molecules on one phthaloyl chloride molecule. Instead, the reaction proceeded most probably to give the 2-[(5-oxopyrazol-4-yl)-carbonyl]benzoate intermediate **103**. Nucleophilic addition of a second molecule of **62** gave the alcohol **104**. Addition of dilute hydrochloric acid causes neutralization, tautomerism and dehydration to afford [(pyrazol-4-yl)(5-oxopyrazol-4-ylidene)methyl]benzoic acid **105**, in 90% yield (01JCS(D)1790) (Scheme 33). Compound **105** was used as a polydentate ligand and reacted with cyanotin(IV) acceptors to give metal complexes. Organotin(IV) compounds such as these have previously been used in organic synthesis and catalysis (synthesis of polyesters, polyurethanes, cross-linking of silicones, esterification, polymerization etc.) and also as PVC heat stabilizers, as a component of aquatic antifouling paints, wood preservatives and biocides.

The acylation of pyrazol-3-ones **106a**,**b** with ethyl chloroformate or *n*-butyl chloroformate in the presence of calcium hydroxide gave the more stable ethyl or *n*-butyl-5-hydroxypyrazole-4-carboxylates **107a**,**b** and not the expected pyrazol-3-one tautomers **108a**,**b**. On the other hand, pyrazol-3-ones **106c**–**f**, containing an *n*-octyl or *n*-dodecyl side chain on N2 of the pyrazol-3-one, reacted with ethyl chloroformate and *n*-butyl chloroformate under similar conditions to afford surprisingly, ethyl or *n*-butylpyrazol-5-ylcarbonates **109c**–**f** in moderate yields (95JHC1377) (Scheme 34).



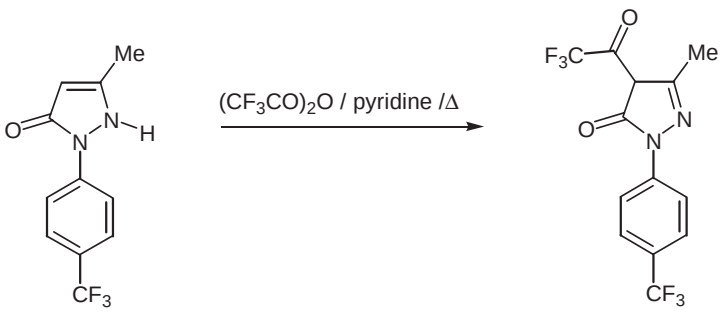
Scheme 33



Scheme 34

B. With Acid Anhydrides

1,2-Dihydropyrazol-3-one **110** was trifluoroacetylated at C4 and converted into 2,4-dihydropyrazol-3-one **111** by heating in pyridine containing trifluoroacetic anhydride (99JOM344) (Scheme 35).

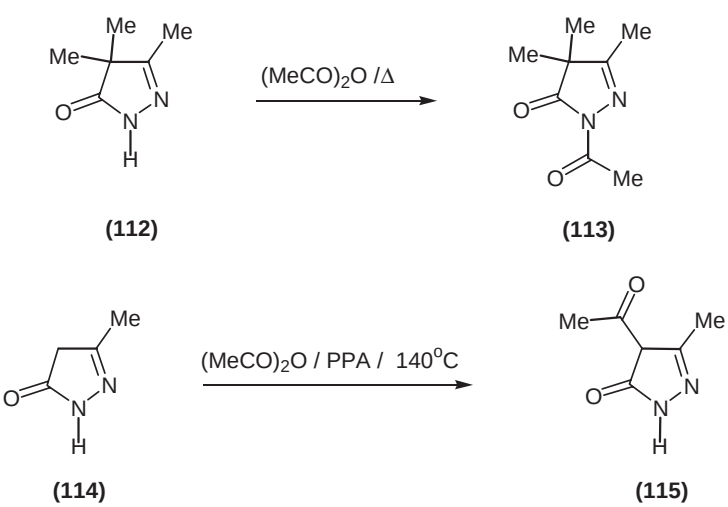


(110) **(111)**

Scheme 35

Depending on the substitution of a 2,4-dihydropyrazol-3-one, acylation with acetic anhydride can occur at N2 or C4 (Scheme 36). When 4,4,5-trimethylpyrazol-3-one **112** was heated with acetic anhydride under reflux the 2-acetyl derivative **113** was obtained in 87% yield (69JOC1717). Surprisingly no acetylation occurred on N2 of 5-methylpyrazol-3-one **114** when heated with acetic anhydride in PPA at 140 °C. Instead, acetylation occurred at C4 to give the 4-acetyl derivative **115** in only 35% yield (74CPB207) (Scheme 36).

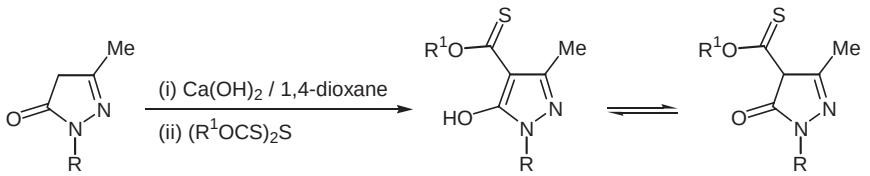
Pyrazol-3-ones **116a–d** are converted into the more stable *O*-alkyl-5-hydroxypyrazole-4-carbothioates **117a–d** instead of their tautomeric pyrazol-3-ones **118a–d** by treatment with calcium hydroxide and then with *O*,*O*-diethyl- or *O*,*O*-di-*n*-butyltrithiotricarbonate in 1,4-dioxane. The yield of the products is 38, 22, 20 and 16% respectively (95JHC1377) (Scheme 37).



(112) **(113)**

(114) **(115)**

Scheme 36



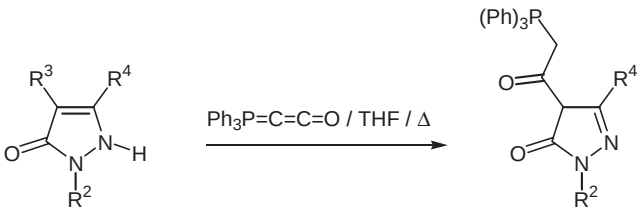
(116) **(117)** **(118)**

(a) R = Ph, R^1 = Et, **(b)** R = Ph, R^1 = $(CH_2)_3Me$, **(c)** R = $(CH_2)_7Me$, R^1 = Et, **(d)** R = $(CH_2)_9Me$, R^1 = $(CH_2)_3Me$

Scheme 37

C. By Ketenylidenetriphenylphosphorane

Pyrazol-3-ones **97a** were heated in tetrahydrofuran with ketenylidenetriphenylphosphorane to afford the corresponding pyrazole-3-one phosphonium salts **119b–f** in 44–87% yield. An X-ray single crystal analysis of **119f** is presented (00JCS(P1)1723) (Scheme 38).



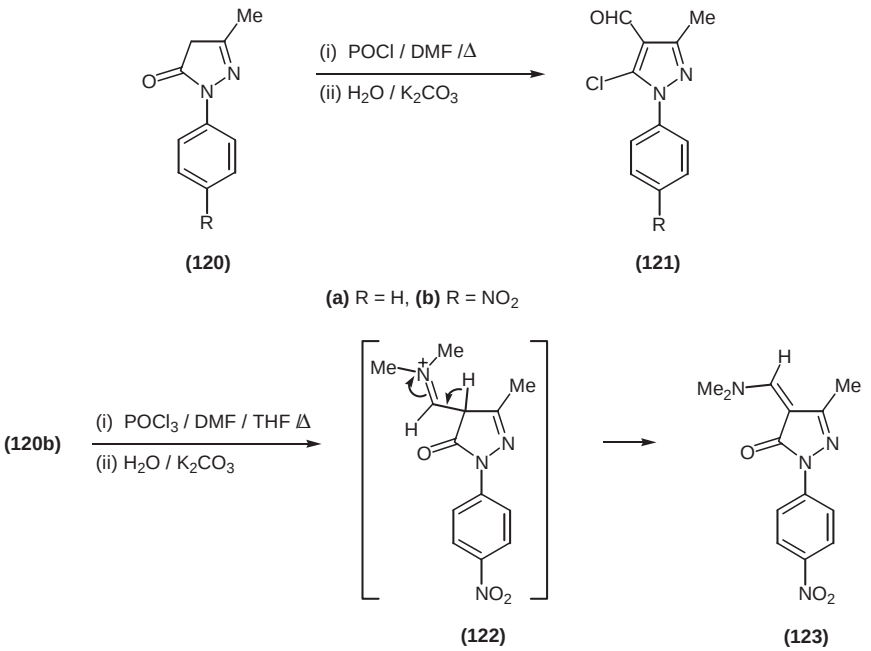
(97) **(119)**

(a) R^3 = H, R^2 = R^4 = Me , R^2 = H, R^4 = Ph, R^2 = Me, R^4 = Ph, R^2 = R^4 = Ph or R^2 = Me, R^4 = CH_2CO_2Me, **(b)** R^2 = R^4 = Me, **(c)** R^2 = H, R^4 = Ph, **(d)** R^2 = Me, R^4 = Ph, **(e)** R^2 = R^4 = Ph, **(f)** R^2 = Me, R^4 = CH_2CO_2Me

Scheme 38

D. By the Vilsmeier Formylation

Seshardi and co-workers (69IJC1006) (Scheme 39) reacted pyrazol-3-ones **120a**,**b** under Vilsmeier conditions in order to study the reactivity of the 5-methyl group, the lactam moiety and the methylene function. It turned out that heating pyrazole-3-ones **120a**,**b** with the Vilsmeier complex using DMF as solvent afforded 3-chloropyrazole-4-carbaldehydes **121a**,**b**. When pyrazole-3-ones **120b** was submitted to the Vilsmeier complex using THF as solvent and the reaction mixture was heated at reflux, the 4-dimethylaminoformylidenepyrazol-3-one **123** was obtained in excellent yield. Faster neutralization of the imino nitrogen atom after loss of a proton from intermediate **122** explains why hydrolysis of the iminium ion to aldehyde did not occur.



Scheme 39

Six years later Wrzeciono and Szostak-Rzepiak (75PHA582) (Scheme 40) repeated the Vilsmeier formylation of compound **120a** but neutralized the reaction mixture with a solution of ammonium hydroxide instead of potassium carbonate. They obtained a mixture of products consisting of pyrazole-3-ones **124**, **125**, **126** and **127**/**128** in 48, 2, 4 and 5% yield, respectively.

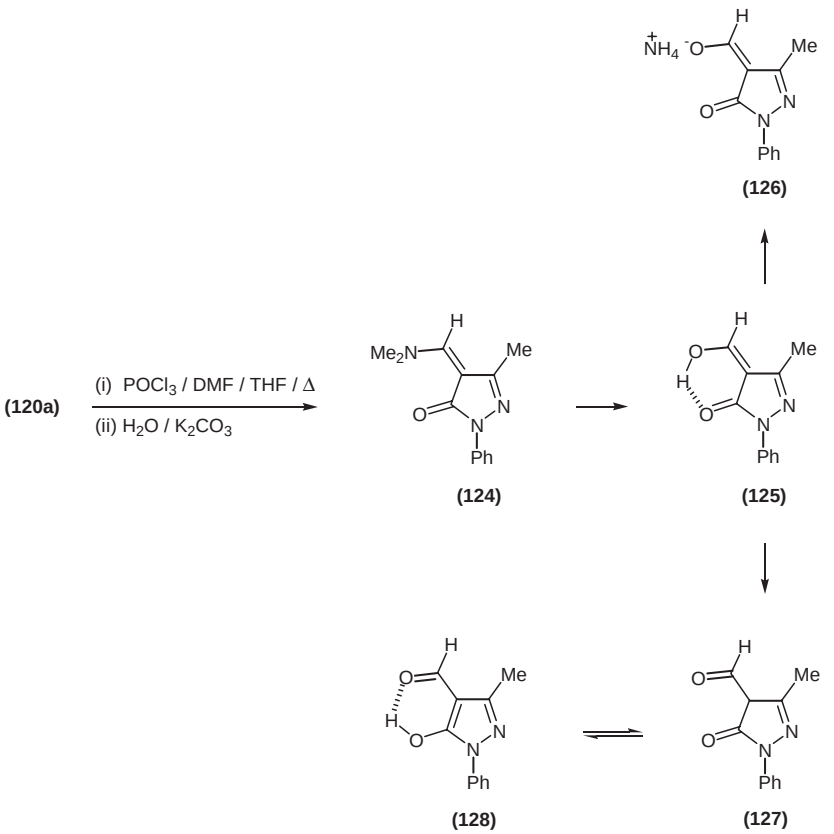
Rockley and Summers (81AJC1117) (Scheme 41) presented the only example of a 1,2-dihydropyrazol-3-one that underwent the Vilsmeier reaction. Thus treating pyrazole-3-one **129** with phosphoryl chloride and DMF in chloroform and toluene and heating at 60–65 °C afforded 4-formylpyrazol-3-one **130**.

VI. Halogenation

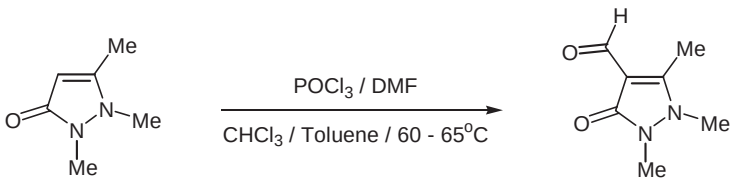
By far the most frequently encountered reactions of pyrazol-3-ones with halogens are chlorination and bromination. Only one reference refers to the introduction of a fluorine atom whereas two references describe iodinated products.

A. Fluorination

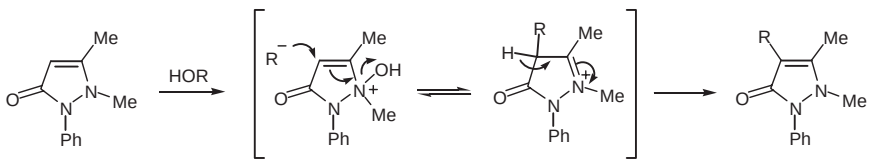
Diksic and DiRaddo (84TL4885) (Scheme 42) described the preparation of 4-fluoropyrazol-3-one **131a** and ^{18}F-labeled 4-fluoropyrazol-3-one **131b** by carrying



Scheme 40



Scheme 41



(a) R = F, **(b)** R = ^{18}F

Scheme 42

out the reaction of pyrazol-3-one **70** with hypofluorous acid and ^{18}F-labeled hypofluorous acid at pH 13. Although the yields of the fluoro derivatives were low, 36% for the chemical reaction and 15% for the radiochemical reaction, no detectable side reactions were involved. Even though an ionic mechanism was proposed, the authors cannot exclude a radical mechanism by analogy to the one observed earlier for CF_3OF.

Difluorination at C4 of compound **70** with concomitant loss of the methyl group at position 1 was observed on reaction with *N*-fluoro bis[(trifluoromethyl)-sulfonyl]imide in chloroform. The product 4,4-difluoro-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one was obtained in 38% yield. A mechanism was proposed (00JFC135).

B. Chlorination

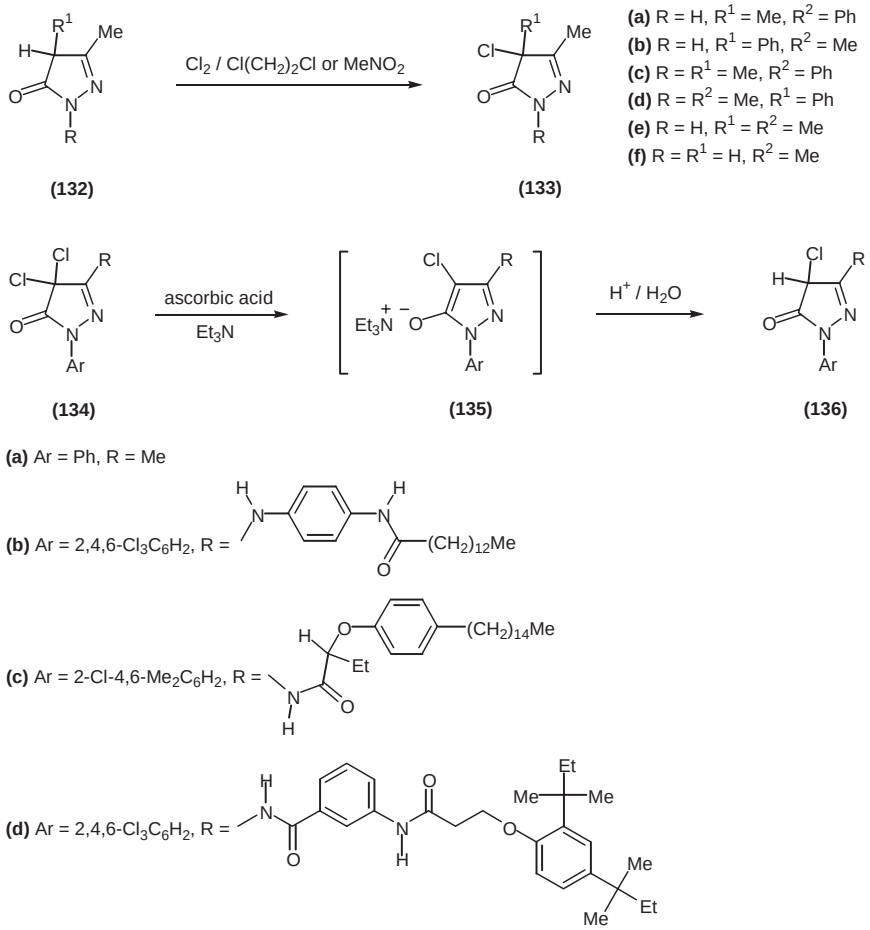
Monochlorination of 2,4-dihydropyrazol-3-ones by chlorine occurs at position 4 of the ring when this position is unsubstituted or monosubstituted (Scheme 43). The solvent in these reactions can be 1,2-dichloromethane, used for the chlorination of pyrazol-3-ones **132a–e** into 4-chloropyrazol-3-ones **133a–e** (72JHC1219, 80JA4983), or nitromethane, for the chlorination of 5-methylpyrazol-3-one **132f** into 4-chloro-5-methylpyrazol-3-one **133f** (93BSB735). Because the synthesis of 4-halopyrazol-3-ones directly is complicated by the fact that the product is very often the 4,4-dihaloderivative, Spitulnik (85S299) developed a method whereby 4,4-dichloro- or 4,4-dibromopyrazol-3-ones are selectively reduced to the monohalo derivatives. By this method 4,4-dichloropyrazol-3-ones **134a–d** were reacted with ascorbic acid and excess triethylamine in methanol to give the intermediate 4-chloropyrazole salts **135a–d** that were then acidified to yield the 4-chloropyrazol-3-ones **136a–d** in yields of 88–95%.

Dichlorination, as mentioned above, occurs readily if position 4 of the pyrazol-3-one ring is unsubstituted. Two methods have been reported (Scheme 44). Compounds **137a–c** were chlorinated with chlorine, either in dichloromethane at room temperature or in nitromethane at reflux temperature. The 4-dichloropyrazol-3-ones **138a–c** were obtained in good yields (82JOC214, 93BSB735). 1,3-Dichloro-5,5-dimethylhydantoin **140** in acetic acid was used to prepared 4,4-dichloropyrazol-3-ones (**141a–d**) (for **a–d** see Scheme 43) from pyrazol-3-ones **139a–d** (for **a–d** see Scheme 43) (85S299).

Treatment of 2,4-dihydropyrazol-3-ones with phosphoryl oxychloride above 100 °C gives 4-chloropyrazoles. Thus pyrazol-3-ones **142a–g** were converted into 4-chloropyrazoles **143a–g** in yields of above 80% (68BSF5019, 79JPR127, 91JHC1837) (Scheme 45).

When 4,4′-bipyrazol-3,3′-dione **144** was treated with phosphoryl oxychloride in chloroform at 10–30 °C only one of the two rings was chlorinated to give 4-(5-chloropyrazol-4-yl)-pyrazol-3-one **145** in 85% yield (92BCJ1652) (Scheme 46).

On heating 5-methylpyrazol-3-one **146** with phosphoryl oxychloride at 200 °C a mixture was obtained consisting of 3-chloro-5-methylpyrazole **147** and trimeric compound **148** (94CHE540) (Scheme 47).

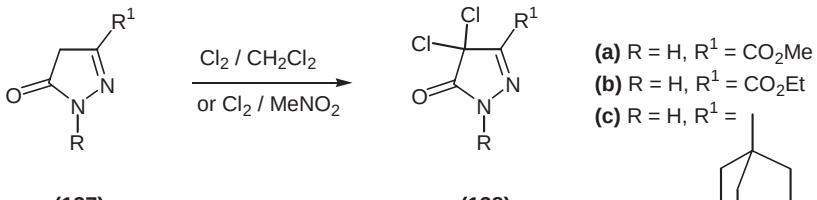


Scheme 43

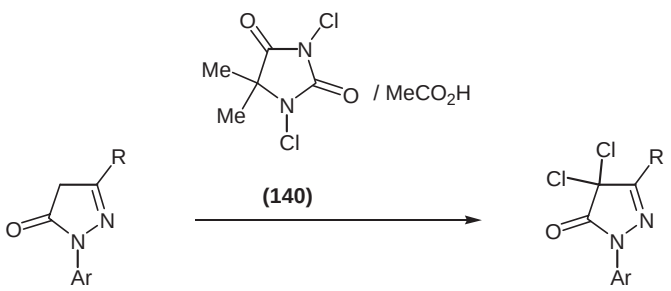
C. Bromination

Bromination of 2,4-dihydropyrazol-3-ones unsubstituted or mono substituted at position 4 occurs easily with bromine in solvents such as chloroform, 1,2-dichloroethane or acetic acid at room temperature (Scheme 48). Therefore pyrazol-3-ones **149a**–**d** react with bromine in chloroform (72JHC1219, 84ZN(B)86), **149e** in glacial acetic acid (80JPR679) and **149f** in perchloric acid (68BSF5019) to give 4-bromopyrazol-3-ones **150a**–**f** in moderate yields.

It was interesting that treatment of 4,4′-pyrazol-3,3′-dione **151** with bromine in glacial acetic acid afforded 4-bromopyrazol-3-one **152**, albeit in only 45% yield (94JPR70) (Scheme 49). Addition of bromine occurred readily at the exocyclic alkenyl group of arylmethylene pyrazol-3-ones **153a** to give 4-bromo-4-[bromo(2-aryl)methyl]-pyrazol-3-ones **154a** in yields ranging from 70 to 96% (80JIC212) (Scheme 49).



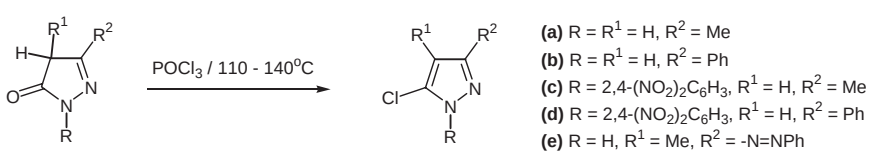
(137) (138)



(140)

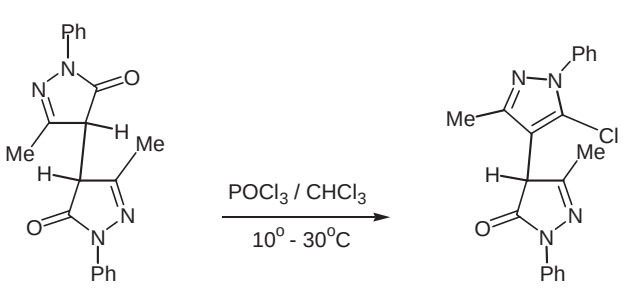
(139) (141)

Scheme 44



(142) (143)

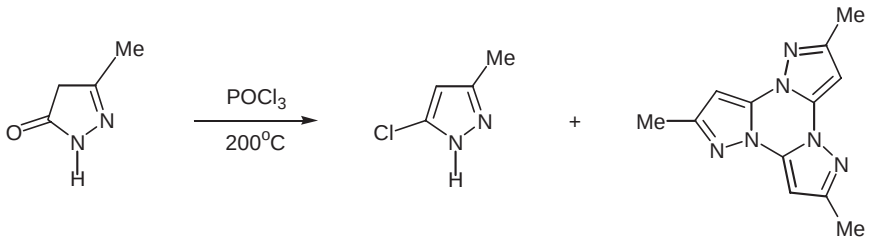
Scheme 45



(144) (145)

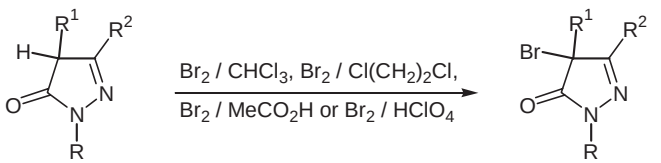
Scheme 46

4-Bromopyrazol-3-ones **157a**–**d** (for **a**–**d** see Scheme 43) have been prepared by Spitulnik (85S299) from 4,4-dibromopyrazol-3-ones **155a**–**d** (for **a**–**d** see Scheme 43) in two steps. First reduction with ascorbic acid to give monobromopyrazole salts **156a**–**d** (for **a**–**d** see Scheme 43) followed by acidification (Scheme 50).



(146) **(147)** **(148)**

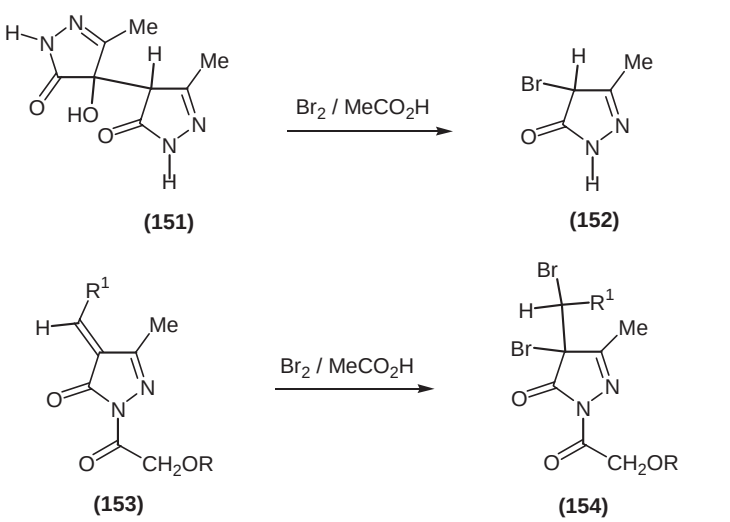
Scheme 47



(149) **(150)**

(a) R = H, R^1 = Me, R^2 = Ph, **(b)** R = H, R^1 = Ph, R^2 = Me
(c) R = R^1 = Me, R^2 = Ph, **(d)** R = R^2 = Me, R^1 = Ph
(e) R = 2,4-$(NO_2)C_6H_3$, R^1 = H, R^2 = Me, **(f)** R = Ph, R^1 = H, R^2 = Me

Scheme 48

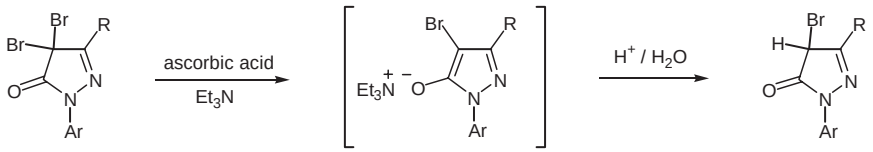


(151) **(152)**

(153) **(154)**

(a) R = 2,6-$(Me)_2C_6H_3$ or 3-Me, 4-*i*-PrC_6H_4, R^1 = 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2-HOC_6H_4, 3-HOC_6H_4, 4-HOC_6H_4, 4-$Me_2NC_6H_4$ or 4-$MeOC_6H_4$

Scheme 49



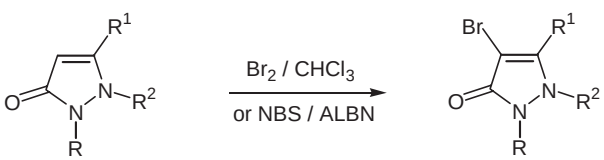
(155) **(156)** **(157)**

Scheme 50

Bromination of 4-unsubstituted 1,2-dihydropyrazol-3-ones is more rare. The reaction takes place with bromine or NBS and ALBN in chloroform. Thus pyrazol-3-ones **158a**,**b** were treated with bromine to afford 4-bromopyrazol-3-ones **159a**,**b** in 76 and 77% yield, respectively (89AP351). On the other hand treatment of pyrazol-3-one **158c** with NBS and AIBN (a,á-azoisobutyronitrile) gave 4-bromopyrazol-3-one **159c** in 73% yield (94SC2133) (Scheme 51).

Dibromination of 2,4-dihydropyrazol-3-ones with bromine occurs readily both in water or acetic acid (Scheme 52). Bromination of pyrazol-3-ones **160a–c** in water gave 4,4-dibromopyrazol-3-ones **161a–c** in high yield (67BSF328, 84S972). In acetic acid pyrazol-3-ones **160a**,**d**,**f** were also brominated in high yield to give 4,4-dibromo derivatives **161a**,**e**,**f** where compound **161e** is brominated also on the benzene ring (81S72, 93BSB735).

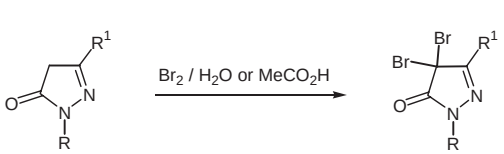
4,4-Dibromopyrazol-3-ones **164a–d** (for **a–d** see Scheme 43) were prepared in high yields by reacting the corresponding pyrazol-3-ones **162a–d** (for **a–d** see Scheme 43) with 1,3-dibromo-5,5-dimethylhydantoin **163** in acetic acid (85S299) (Scheme 53).



(158) **(159)**

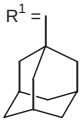
(a) R = Ph, $R^1 = R^2$ = Me, **(b)** R = 4-$MeOC_6H_4$, $R^1 = R^2$ = Me,
(c) R = H, R^1 = Me, R^2 = H

Scheme 51

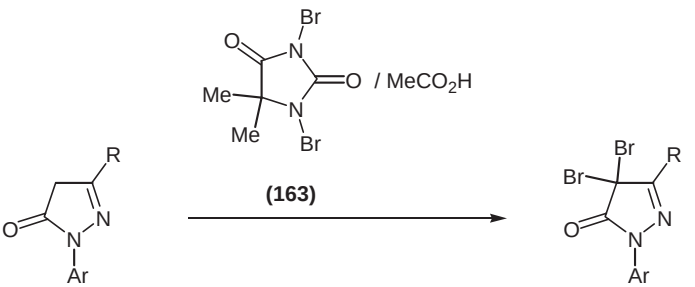


(160) **(161)**

(a) R = H, R^1 = Me
(b) R = Ph, R^1 = Me
(c) R = 2,4-$(NO_2)_2C_6H_3$, R^1 = Me
(d) R = H, R^1 = 4-$MeOC_6H_4$
(e) R = H, R^1 = 3-Br, 4-$MeOC_6H_4$
(f) R = H, R^1 =



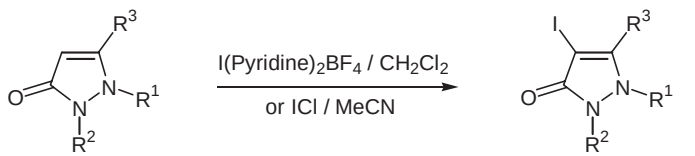
Scheme 52



Scheme 53

D. Iodination

Iodination of pyrazol-3-ones has only been reported for 1,2-dihydro derivatives (Scheme 54). Rodriguez and co-workers (97TL8397) reacted pyrazol-3-one **165a** with di(pyridine)iodonium(I) tetrafluoroborate in dichloromethane and obtained 4-iodopyrazol-3-one **166a** in almost quantitative yield. Varvounis and colleagues (01JHC1065) treated pyrazol-3-ones **165b–d** with iodine monochloride in acetonitrile and obtained 4-iodopyrazol-3-ones **166b–d** in 70, 55 and 75% yield, respectively.



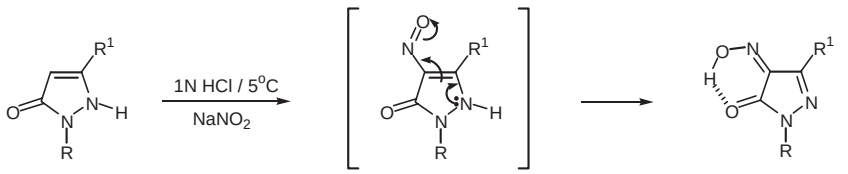
(a) $R^1 = R^3 = Me$, $R^2 = Ph$, **(b)** $R^1 = Me$, $R^2 = R^3 = Ph$
(c) $R^1 = Me$, $R^2 = Ph$, $R^3 = 4\text{-}NO_2C_6H_4$, **(d)** $R^1 = R^2 = Ph$, $R^3 = Me$

Scheme 54

VII. Nitrosation

A. Of 1,2-Dihydro-3*H*-Pyrazol-3-ones

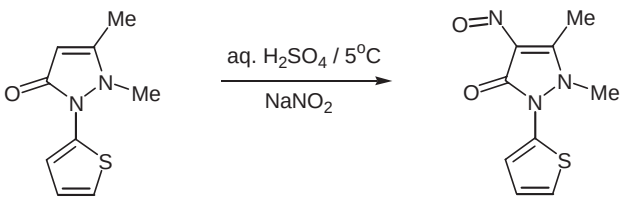
Nitrosation of 1-unsubstituted pyrazol-3-ones **167a–j** in aqueous hydrochloric acid at 5 °C with sodium nitrite afforded the corresponding pyrazol-3-one 4-oximes **169a–j** in good yields (65ZOR133) (Scheme 55). The reaction most likely takes place via the intermediate nitroso compound **168** that tautomerises to the product because of the available proton at N1.



(167) **(168)** **(169)**

(a) R = C_6H_{11}, R^1 = Me, **(b)** R = C_6H_{13}, R^1 = Me, **(c)** R = Ph, R^1 = Me, **(d)** R = 2-MeC_6H_4, R^1 = Me, **(e)** R = 4-MeC_6H_4, R^1 = Me, **(f)** R = 2-$MeOC_6H_4$, R^1 = Me, **(g)** R = $PhCH_2$, R^1 = Me, **(h)** R = $Ph(CH_2)_2$, R^1 = Me, **(i)** R = H, R^1 = Ph, **(j)** R = Me, R^1 = Ph

Scheme 55



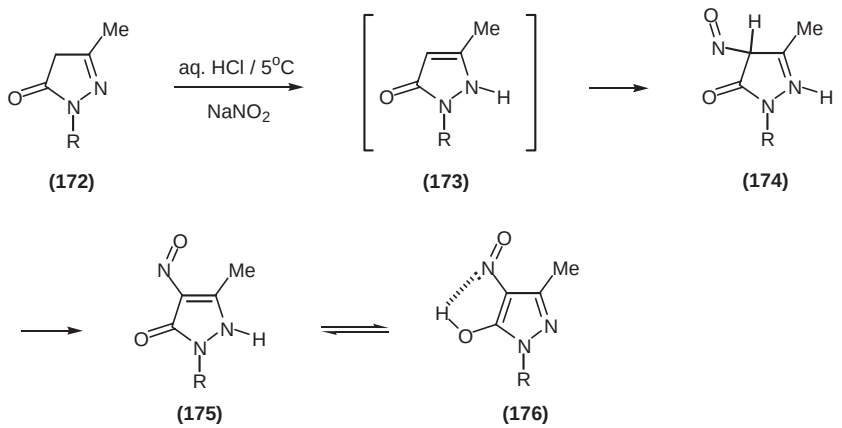
(170) **(171)**

Scheme 56

On the other hand, nitrosation of methylpyrazol-3-one **170** in aqueous sulfuric acid at 5 °C containing sodium nitrite afforded 4-nitrosopyrazol-3-one **171** in 88% yield (79AP853) (Scheme 56).

B. Of 2,4-Dihydro-3*H*-Pyrazol-3-ones

The prototropic tautomerism between 4-nitrosopyrazol-3-ones **175a–c** and 4-nitrosopyrazol-5-ols **176a–c**, derived from pyrazol-3-ones **172a–c** after nitrosation with sodium nitrite in aqueous hydrochloric acid at 5 °C, was studied by IR and by ^{1}H, ^{13}C and ^{15}N NMR spectroscopy (94JHC561) (Scheme 57). It is proposed that reaction occurs via protonation of pyrazol-3-one **172** to give intermediate 1,2-dihydropyrazol-3-one **173**, which is then nitrosated to **174**. The latter tautomerises to the more stable products. From available data it was concluded that in the solid state the equilibrium is shifted towards the NH tautomers **175a–c** whereas in the liquid state the OH tautomers **176a–c** predominate. The NMR measurements were taken in deuteriochloroform, deuteriopyridine or deuterioacetic acid. The more polar the solvent, the higher the proportion of the NH tautomers **175a–c**. To assign the ^{13}C NMR signal sequence in each tautomer, the multiplicity, the approximate coupling constant obtained from the off-resonance spectra, the chemical shifts and the electronic distribution were considered.



(a) R = *n*-C_2H_5, **(b)** R = *n*-C_6H_4, **(c)** R = *n*-C_8H_{17}

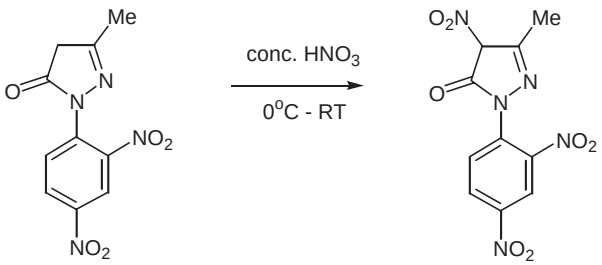
Scheme 57

VIII. Nitration

The nitration of both 1,2-dihydro- and 2,4-dihydropyrazol-3-ones has been reported. The reaction conditions vary from the relatively mild 50% aqueous nitric acid to mixtures of fuming nitric acid and concentrated sulfuric acid. The reactions are performed from 0 °C to room temperature.

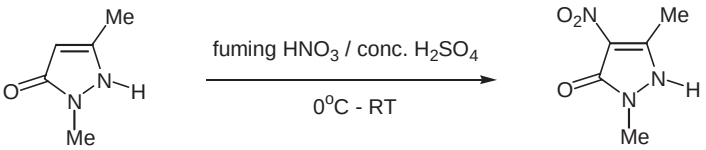
Kovar et al. (81AP532) treated 1,2-dihydro-4-isopropyl-5-methyl-2-phenyl-3*H*-pyrazol-3-one with fuming nitric acid at room temperature that resulted in at least 27 products of which eight main nitro products were isolated. One of the eight products identified was 2,4-dihydro-4-isopropyl-5-methyl-4-nitro-2-(2,4-dinitrophenyl)-3*H*-pyrazol-3-one.

Elguero et al. (68BSF5019) (Scheme 58) used concentrated nitric acid for the nitration of pyrazol-3-one **177a** and obtained 4-nitropyrazol-3-one **178b** in 50%



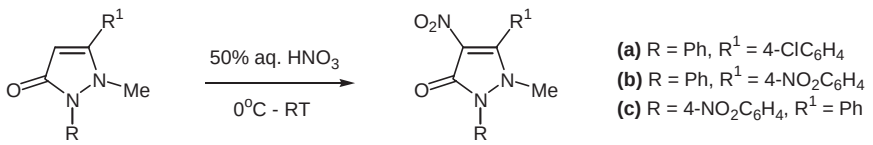
(a) R = H, R^1 = NO_2, **(b)** R = H, R^1 = NO_2,
(c) R = R^1 = H, **(c)** R = NO_2, R^1 = H

Scheme 58



(179) **(180)**

Scheme 59



(181) **(182)**

Scheme 60

yield. Using the same conditions but extended reaction time, Bergman et al. (99T10447) converted pyrazole-3-one **177c** into 4-dinitropyrazol-3-one **178d**.

Pyrazol-3-one **179** was nitrated by Hirota et al. (82JCS(P1)277) (Scheme 59) in a mixture of fuming nitric acid and concentrated sulfuric acid to give 4-nitropyrazol-3-one **180** in 43% yield.

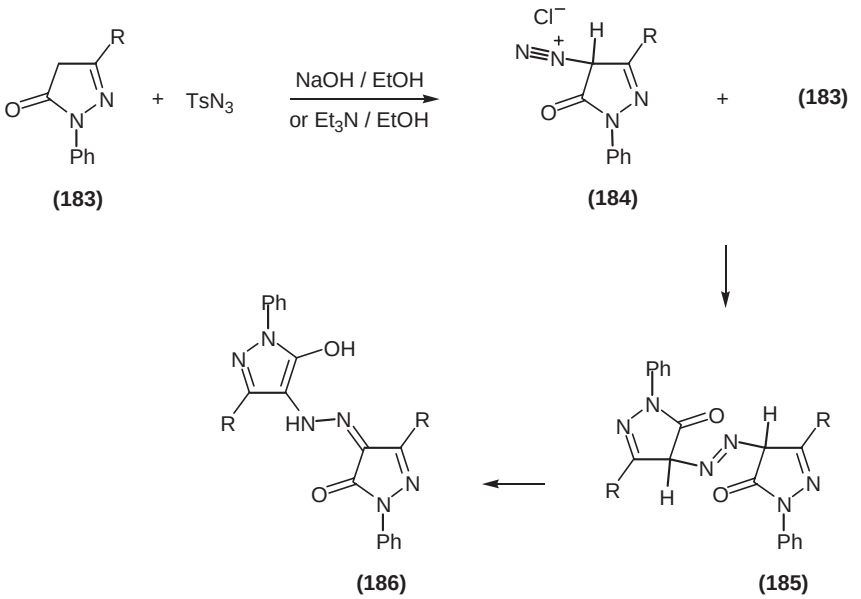
Varvounis and co-workers (01JHC1065) (Scheme 60) used 50% aqueous nitric acid for the nitration of pyrazol-3-ones **181a–c**. The 4-nitro derivatives **182a–c** were obtained in 80, 78 and 70% yield, respectively.

IX. Diazonium Salt Coupling

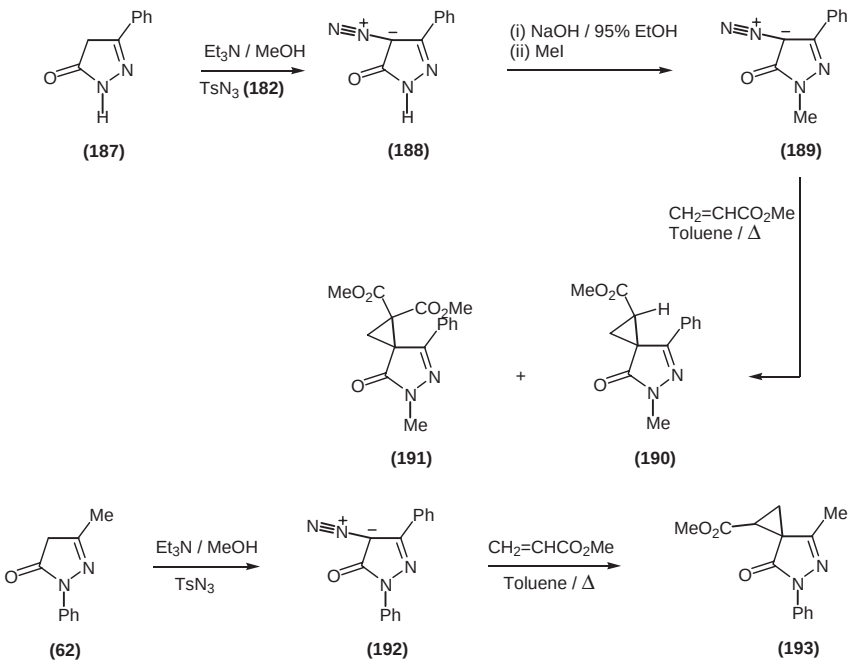
A. Diazopyrazol-3-one Formation, Coupling and Substitution

4-Toluenesulfonylazide reacted with two equivalents of each pyrazol-3-one **183a**,**b** in ethanolic sodium hydroxide or triethylamine to afford pyrazol-4,5-dione-4-*N*-(pyrazol-4-yl)hydrazones **186a**,**b**. The reaction occurs via initial formation of diazonium salts **184a**,**b** that couple with a second molecule of the respective pyrazol-3-one **181a**,**b** leading to the corresponding azo intermediates **185a**,**b**. Tautomerisation of the latter afforded the stable products **186a**,**b** (73G179) (Scheme 61).

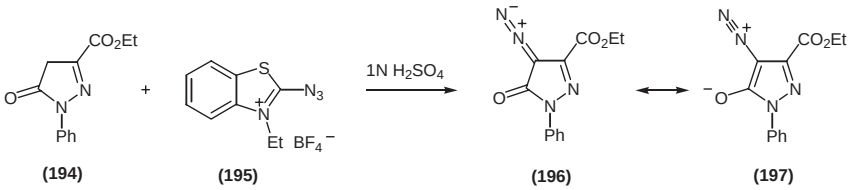
4-Diazopyrazol-3-ones **188** and **192** have been prepared in 69 and 50% yield from the corresponding pyrazol-3-ones **187** and **62** each with one equivalent of 4-toluenesulfonylazide and two equivalents of triethylamine. Diazo compound **188** was then methylated by methyl iodide to afford 4-diazo-2-methylpyrazol-3-one **189** in 95% yield (83JOC1069) (Scheme 62). Reaction of 4-diazopyrazol-3-one **189** with methyl acrylate in refluxing toluene gave a mixture containing 50% and 32% of the respective spiro(cyclopropanepyrazol-3-ones) **190** and **191**. However, similar



Scheme 61



Scheme 62



Scheme 63

reaction of 4-diazopyrazol-3-one **192** with methyl acrylate was more selective and gave a single product **193** of intermediate stereochemistry (83JOC1069) (Scheme 62).

Diazo group transfer onto pyrazole-3-one **194** by aziridinium salt **195** in dilute sulfuric acid gave mesomeric **196**/**197**. This compound exists in quite a high proportion as the diazonium enolate **197**. Compound **197** is resistant to acids and thermal stress that agrees with its structure (78H199) (Scheme 63).

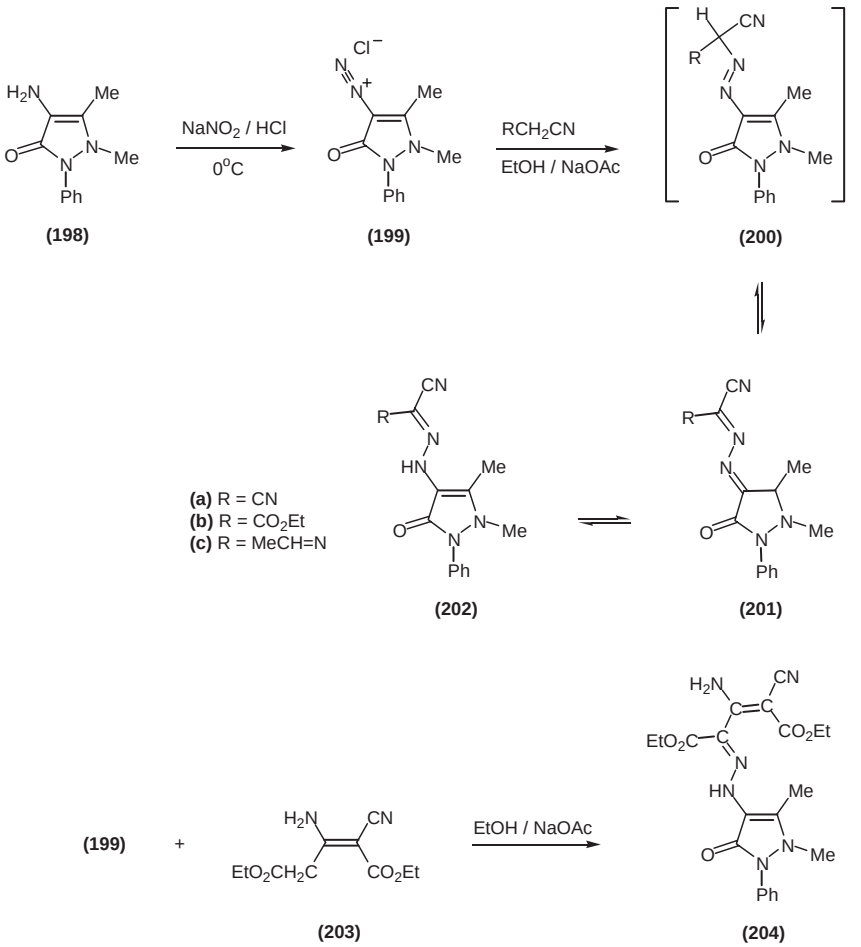
Diazotization of 4-aminopyrazol-3-one **198** followed by coupling with carbon nucleophiles has been reported by several researchers as a means of synthesizing both acyclic and cyclic 4-substituted derivatives. In all cases diazotization occurs at 0 °C with sodium nitrite in concentrated hydrochloric acid. First Elnagdi et al. (82JCS(P1)989) (Scheme 64) showed that diazotized pyrazol-3-one **198** undergoes coupling reactions with malononitrile, ethyl cyanoacetate or 3-aminocrotonitrile in ethanol containing sodium acetate to give hydrazones **202a**–**c**. Although these products could be formulated as the azo-derivatives **200a**–**c** or the azine derivatives **201a**–**c**, these structures were excluded on the basis of both infra-red and ^{1}H NMR spectroscopy. 3-Oxopyrazole-4-diazonium chloride **199** was also coupled with ethyl cyanoacetate dimer **203** to yield the hydrazonodiacetate derivative **204** (82JCS(P1)989) (Scheme 64).

Ishizuki et al. (88ACA253) (Scheme 65) prepared for analytical purposes, propane-2-one derivative **205** by coupling 3-oxopyrazole-4-diazonium chloride **199** with two equivalents of acetylacetone, and pentane-2,4-dione derivative **206** by coupling diazonium chloride **199** with one equivalent of acetylacetone. Both reactions were performed at 0 °C and in the presence of sodium hydroxide.

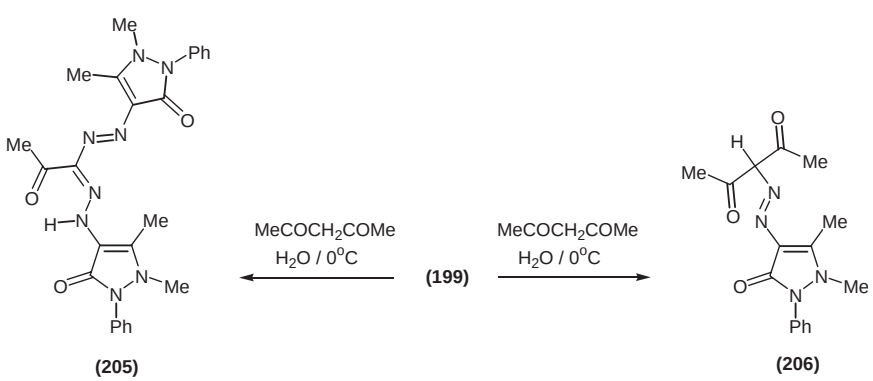
Slouka and Hejsek (91AP467) (Scheme 66) coupled diazonium salt **199** with ethyl cyanoacetylcarbamate **207** at 0 °C in the presence of sodium acetate and obtained the hydrazonocarbamate derivative **208**, in 95% yield.

B. Coupling of Pyrazol-3-ones with Aryl Diazonium Salts

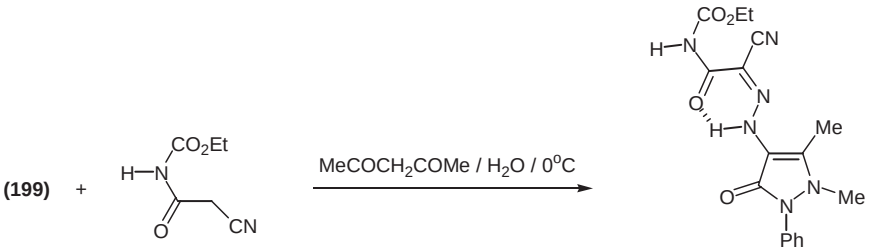
This category of coupling reactions involves only 2,4-dihydro-3*H*-pyrazol-3-ones and the majority of diazonium salts used were diazonium chlorides. Thus pyrazo-3-ones **209a**–**k** were coupled with a variety of aryl diazonium chlorides **210a**–**k** at 0 °C in aqueous solution containing in certain cases a co-solvent such as methanol, ethanol or pyridine to afford 4-arylazopyrazol-3-ones **211a**–**k** in good to excellent yields (Scheme 67) (72JPR612, 78IJC876, 86IJP40, 87JPS40, 00PJC239, 01JCS (D)1239). In one report (81CCC987) 4-diethylaminobenzenediazonium hydrogen sulfate was used to prepare 4-arylazopyrazol-3-one **211l**.



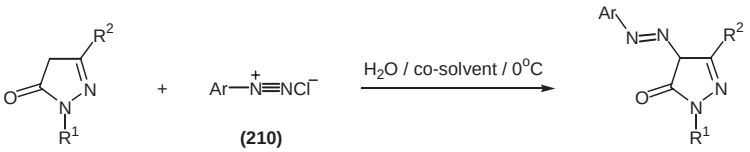
Scheme 64



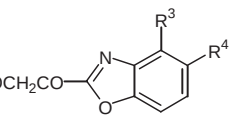
Scheme 65



Scheme 66



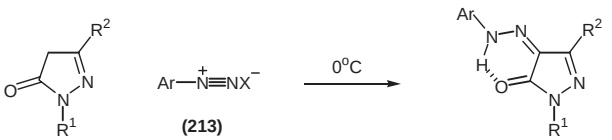
(a) R^1 = 4-ClC_6H_4, R^2 = Me, Ar = 4-ClC_6H_4
(b) R^1 = 4-ClC_6H_4, R^2 = Me, Ar = 4-MeC_6H_4
(c) R^1 = 4-$NO_2C_6H_4$, R^2 = Me, Ar = 4-ClC_6H_4
(d) R^1 = 4-$NO_2C_6H_4$, R^2 = Me, Ar = 4-MeC_6H_4
(e) R^1 = Ph, R^2 = 3-pyridyl, Ar = Ph, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$ or 4-HOC_6H_4

(f) R^1 = 

R^3 = R^4 = H, R^2 = Me, Ar = 2-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-CO_2HC_6H, 4-$CO_2HC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2,4-$(NO_2)_2C_6H_4$, or 4-$H_2NSO_2C_6H_4$.
R^3 = NO_2, R^4 = H, R^2 = Me, Ar = 2-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, or 4-$H_2NSO_2C_6H_4$.
R^3 = H, R^4 = H or NO_2, R = H or NO_2, R^2 = Me, Ar = 4-ClC_6H_4, 4-BrC_6H_4, 2-MeC_6H_4, 4-MeC_6H_4, 3-$CO_2HC_6H_4$, 4-$CO_2HC_6H_4$, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2,4-$(NO_2)_2C_6H_4$, 4-$MeOC_6H_4$ or 4-$H_2NSO_2C_6H_4$.
(g) R^1 = Ph, R^2 = Me, Ar = 4-$MeCOC_6H_4$
(h) R^1 = Ph, R^2 = Me, Ar = Ph or 4-*t*-BuC_6H_4
(i) R^1 = H, R^2 = Ph, Ar = 4-*t*-BuC_6H_4
(j) R^1 = R^2 = Me, Ar = 4-*t*-BuC_6H_4
(k) R^1 = 4-*t*-BuC_6H_4, R^2 = Me, Ar = *s*-Bu, *t*-Bu or nonyl
(l) R^1 = Ph, R^2 = Me, Ar = 4-$Et_2NC_6H_4$

Scheme 67

Coupling pyrazol-3-ones **212a**–**g** with aryl diazonium salts **213a**–**g** gave 4-arylhydrazonopyrazol-3-ones **214a**–**g** in moderate to good yields. These compounds are stabilized by intramolecular hydrogen bonding between the hydrazono NH and the oxygen atom of the pyrazol-3-one ring. Diazonium chlorides, tetrafluoroborates

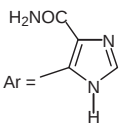


(212) X = Cl, BF_4 or HSO_4 **(213)** **(214)**

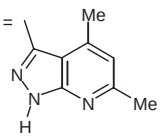
(a) R^1 = H, Ph or 2,4-$(NO_2)_2C_6H_4$, R^2 = $CH_2CONHAr'$, Ar' = Ph, 4-ClC_6H_4, or 4-MeC_6H_4, Ar = Ph, 4-ClC_6H_4, or 4-BrC_6H_4,

(b) R^1 = 4-$SO_3NaC_6H_4$, R^2 = Me, Ar = Ph

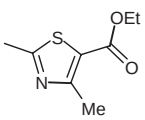
(c) R^1 = H or Ph, R^2 = Me or Ph, Ar =



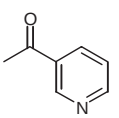
(d) R^1 = H or Ph, R^2 = Me, Ar =



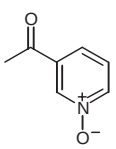
(e) R^1 = H or Ph, R^2 = Me, Ar =



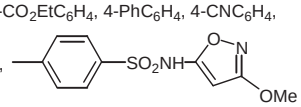
(f) R^1 =



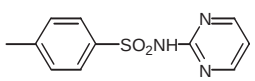
or



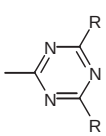
R^2 = *n*-C_3H_7, Ar = Ph, 4-$CO_2EtC_6H_4$, 4-PhC_6H_4, 4-CNC_6H_4, 4-MeC_6H_4, 4-$EtOC_6H_4$,



or



(f) R^1 = Ph or

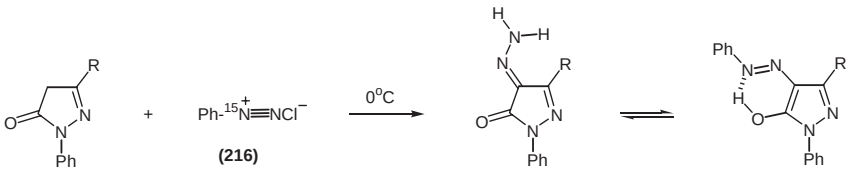


, R = morpholino, R^2 = Me, Ar = 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2,4-$(NO_2)_2C_6H_4$, or 4-$MeOC_6H_4$,

Scheme 68

and hydrogen sulfates have been used for these coupling reactions (Scheme 68) (79JPR1047, 82JPR955, 82JCS(P1)1811, 91IJC(B)878, 91PS119, 92AF1350, 96JSD176).

Diazotisation of ^{15}N-aniline followed by coupling of diazonium salt **216** with pyrazol-3-ones **215a**,**b** gave 4-phenylhydrazono derivatives **217a**,**b**. Through the use of ^{15}N labeling and NMR spectroscopy it was shown that pyrazol-3-ones **217a**,**b** exist entirely in the hydrazone form in deuterated chloroform. In hexadeuterated

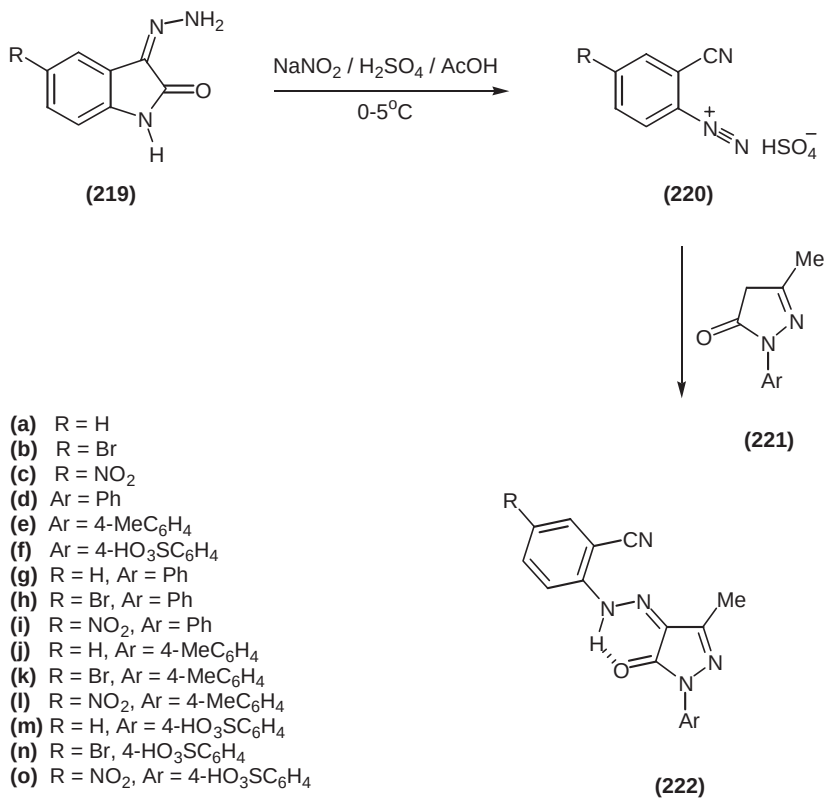


(a) R = Me, **(b)** R = NHPh

Scheme 69

dimethyl sulfoxide and pyridine compounds **217a**,**b** exist as a mixture with 4-phenyldiazopyrazol-5-ols **218a**,**b** (69JOC1685) (Scheme 69).

Recent work on the coupling of pyrazol-3-ones by Shvekhgeimer and Moreva (00CHE491) (Scheme 70) describe the *in situ* formation of aryl diazonium salts **220a**–**c** by the reaction of 1*H*-indole-2,3-dione-3-hydrazone **219a**–**c** with nitrosylsulfuric acid, followed by coupling with pyrazol-3-ones **221d**–**f** to give high yields of 4-arylhydrazonopyrazol-3-ones **222g**–**o**.

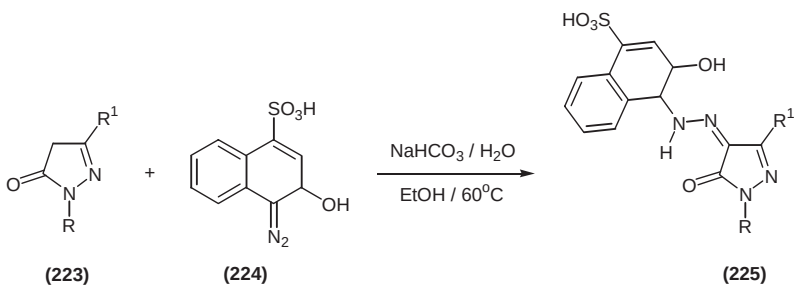


(a) R = H
(b) R = Br
(c) R = NO_2
(d) Ar = Ph
(e) Ar = 4-MeC_6H_4
(f) Ar = 4-$HO_3SC_6H_4$
(g) R = H, Ar = Ph
(h) R = Br, Ar = Ph
(i) R = NO_2, Ar = Ph
(j) R = H, Ar = 4-MeC_6H_4
(k) R = Br, Ar = 4-MeC_6H_4
(l) R = NO_2, Ar = 4-MeC_6H_4
(m) R = H, Ar = 4-$HO_3SC_6H_4$
(n) R = Br, 4-$HO_3SC_6H_4$
(o) R = NO_2, Ar = 4-$HO_3SC_6H_4$

Scheme 70

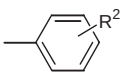
C. Coupling of Pyrazol-3-ones with 4-Diazo-3-oxo-3, 4-Dihydronaphthalene-1-Sulfonic Acid

Coupling of pyrazole-3-ones **223a–d** with 4-diazo-3-oxo-3,4-dihydronaphthalene-1-sulfonic acid **224** in aqueous ethanol with sodium hydrogen carbonate afforded the requisite 4-dihydronaphthalenehydrazonopyrazol-3-ones **225a–d** in excellent yield and purity in the majority of cases (01JMC3730) (Scheme 71).



(223) **(224)** **(225)**

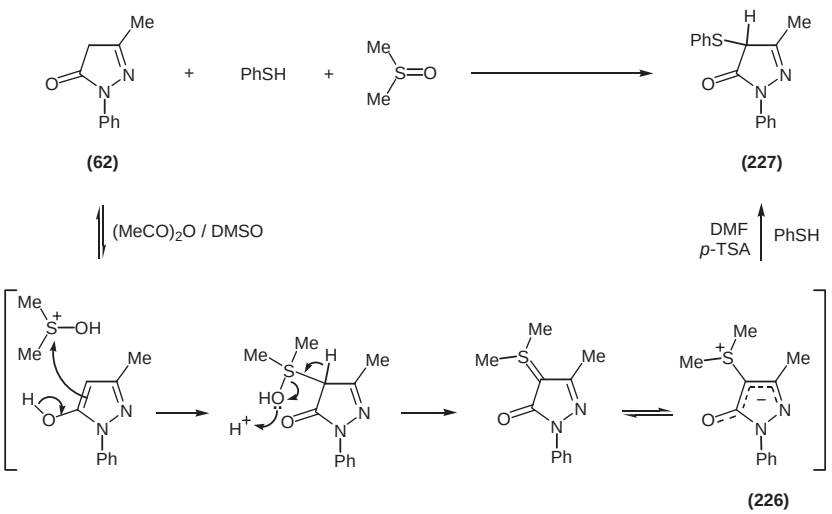
(a) R^1 = H, R = H, Me, *t*-Bu, Ph, Bz, $(CH_2)_2OH$ or 2-pyridyl

(b) R^1 = Me, R =  R^2 = H, 2-Cl, 3-Cl, 4-Cl, 2-NO_2, 3-NO_2, 4-NO_2,

2-Me, 3-Me, 4-Me, 3-CF_3, 4-CF_3, 4-F, 4-I, 4-OCH_2Ph, 3,4-$(Cl)_2$, 3,4-$(Me)_2$, 4-$CH(Me)_2$, 3-*t*-Bu, 4-*t*-Bu, 4-SO_2Me, 3-SO_2NHEt, 4-CO_2H, 4-SO_3H, (3-SO_3H, 6-Cl), (4-SO_3H, 2,5-$(Cl)_2$ or 4-OH

(c) R = 3,4-$(Me)_2C_6H_3$, R^1 = H, t-Bu, Ph, or OEt

(d) R = 4-*t*-BuC_6H_5, R^1 = CO_2Et, CO_2t-Bu, CO_2H or NH_2



(62) **(227)** **(226)**

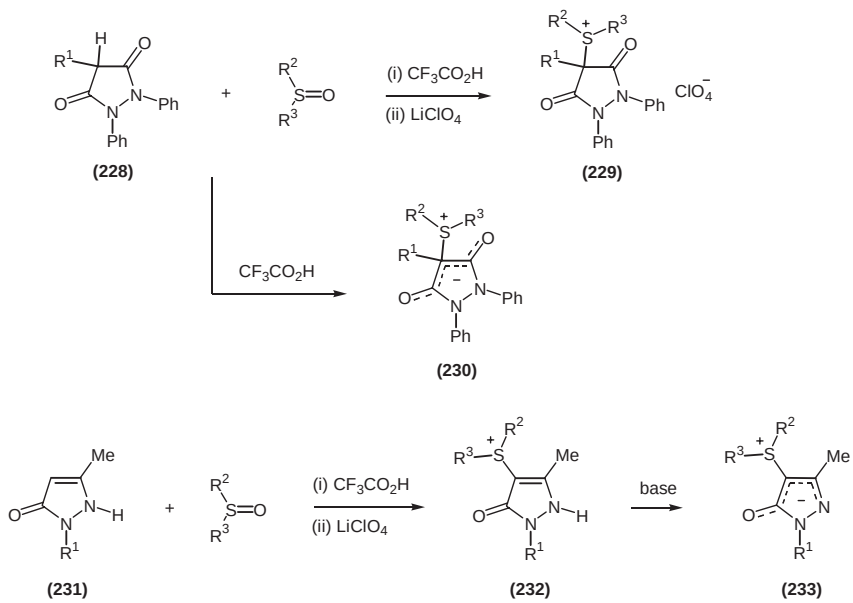
Scheme 71

X. Thiation

Otto reported (71AP505) (Scheme 72) that pyrazol-3-one **62** reacts at ambient temperature with thiophenol in dimethylsulfoxide to afford 4-phenylthiopyrazol-3-one **227** in 81% yield. It is interesting that sulfonium ylid **226** was the proposed intermediate since it could be formed by reacting pyrazol-3-one **62** with acetic anhydride in dimethylsulfoxide and could then be converted into product **226** by reacting with thiophenol in *N*,*N*-dimethylformamide and a catalytic amount of 4-toluenesulfonic acid.

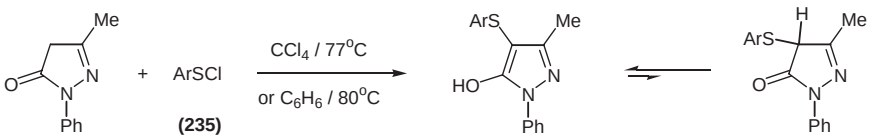
Wendebourg and Hartke (89AP473) (Scheme 72) reacted pyrazol-3-ones **228a**,**b** with dimethylsulfoxide or tetrahydrothiophene 1-oxide in the presence of trifluoroacetic acid followed by the addition of lithium perchlorate and obtained sulfonium salts **229c–e**. Under similar conditions 1,2-dihydropyrazol-3-ones **231f–i** yielded the sulfonium salts **232f–i**, which were deprotonated by base to the sulfonium ylides **233f–i**. When pyrazol-3-one **228a** was reacted with dimethylsulfoxide or tetrahydrothiophene-1-oxide in the presence of trifluoroacetic acid without addition of lithium perchlorate, sulfonium ylides **230c**,**d** were obtained.

Shermolovich et al. (99RJOC281) (Scheme 73) described the reaction of pyrazol-3-one **234** with arylsulfenyl chlorides **235a–c** that gave the corresponding 4-arylthiopyrazoles **236a–c** as major tautomers and 4-arylthiopyrazol-3-ones **237a–c** as minor tautomers. The reaction with phenylsulfenyl chloride required



(a) R^1 = H, **(b)** R^1 = *n*-C_4H_9, **(c)** R^1 = H, R^2 = R^3 = Me, **(d)** R^1 = H, R^2 = R^3 = $(CH_2)_4$, **(e)** R^1 = *n*-C_4H_9, R^2 = R^3 = Me, **(f)** R^1 = R^2 = R^3 = Me, **(g)** R^1 = Me, R^2 = R^3 = $(CH_2)_4$, **(h)** R^1 = Ph, R^2 = R^3 = Me, **(i)** R^1 = Ph, R^2 = R^3 = $(CH_2)_4$

Scheme 72



(234) (233) (237)

(a) Ar = Ph, **(b)** Ar = 2-$NO_2C_6H_4$, **(c)** Ar = 4-$NO_2C_6H_4$

Scheme 73

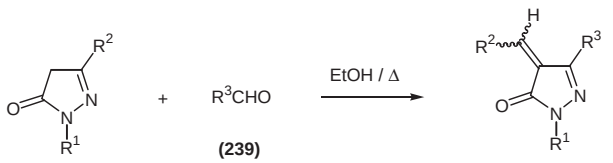
heating in carbon tetrachloride at 77 °C whereas reactions with 2- and 4-nitrophenylsulfenyl chlorides were performed in benzene at 80 °C.

XI. Condensation

These condensations involve position 4 of pyrazol-3-ones and aldehydes, ketones, α,β-unsaturated carbonyl compounds, doubly activated methylene compounds containing carbonyl functionalities or nitroso compounds.

A. With Aryl Aldehydes

Since 1964 a large number of reports describe the condensation of 2,4-dihydropyrazol-3-ones with aryl aldehydes. In contrast condensation of 1,2-dihydropyrazol-3-ones with aryl aldehydes have been reported on only three occasions. Most 4-arylmethylidenepyrazol-3-ones were isolated as (*E*/*Z*)-isomer mixtures. The simplest reaction conditions use heating under reflux in ethanol. Zimaity et al. (78IJC876), Ege et al. (83JCS(P1)325) and Ibrahim and Youssef (84CJC2841) have used this method to condense 2,4-dihydropyrazol-3-one **238a–c** with a variety of aryl aldehydes **239a–c** to give (*E*/*Z*)-4-arylmethylidine derivatives **240a–c** in over 70% yield (Scheme 74). The electronic spectra of pyrazol-3-ones **240c** were recorded on ethanolic solutions and the effect of structure on the electronic spectra were



(238) (240)

(a) R^1 = 4-ClC_6H_4, R^3 = Me or NO_2, R^2 = 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-$N(Me)_2C_6H_4$ or thien-2-yl,

(b) R = R^1 = Ph, R^2 = Me, R^3 = Ph, 4-ClC_6H_4, 4-$NO_2C_6H_4$, or naphth-2-yl, R^1 = 4-$MeOC_6H_4$ or 4-$NO_2C_6H_4$, R^2 = Me, R^3 = Ph, R^1 = R^2 = Ph, R^3 = naphth-2-yl,

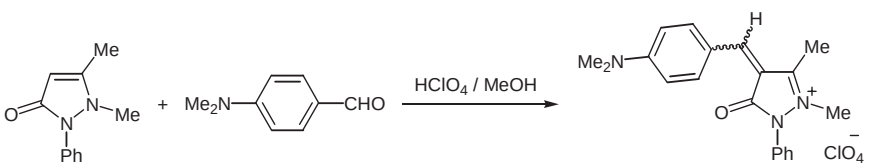
(c) R^1 = 2,4-$(NO_2)_2C_6H_3$, R^3 = Me, R^2 = Ph, 2-HOC_6H_4, 4-HOC_6H_4, 4-$NO_2C_6H_4$, 4-ClC_6H_4 or thien-2-yl

Scheme 74

discussed. The electronic absorption spectra of **240c** were also recorded using cyclohexane, diethyl ether, DMF and DMSO and their solvatochromic behavior studied. The longer wavelength band displayed by the 4-hydroxy derivative was assigned to an intramolecular CT transition. The solvated H-bond complexes formed between ethanol or DMF and this compound were investigated. Transition moment (μ_{CTL}), ΔG and K_f values for these complexes have been determined.

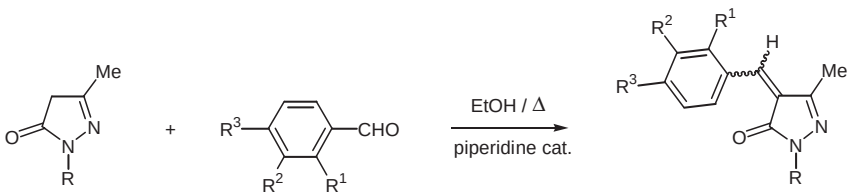
In one report the stable (*E*/*Z*)-4-[4-(dimethylaminobenzylidene)pyrazol-3-one] perchlorate **242** was isolated after reaction of pyrazol-3-one **241** with 4-dimethylaminobenzaldehyde in methanol containing perchloric acid (83M219) (Scheme 75). The condensation occurs by addition of the pyrazol-3-one to the protonated aldehyde followed by the elimination of water.

El-Shahawy et al. (88IJC(A)94) prepared (*E*/*Z*)-4-(4-dimethylamino)benzylidene-pyrazol-3-one **245a** by refluxing equimolar ratios of pyrazol-3-one **243a** and 4-dimethylaminobenzaldehyde **244a** in ethanol containing piperidine as catalyst (Scheme 76). The electronic absorption spectra λ_{max} and ε_{max} of **245a** in different solvents and mixed solvents, polar and non-polar have been measured. HMO and PPP calculations have been undertaken and also the electron densities at various positions of the compound have been found by SCF calculations. Singh and



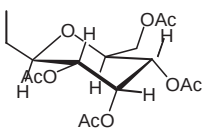
(241) (242)

Scheme 75



(243) (244) (245)

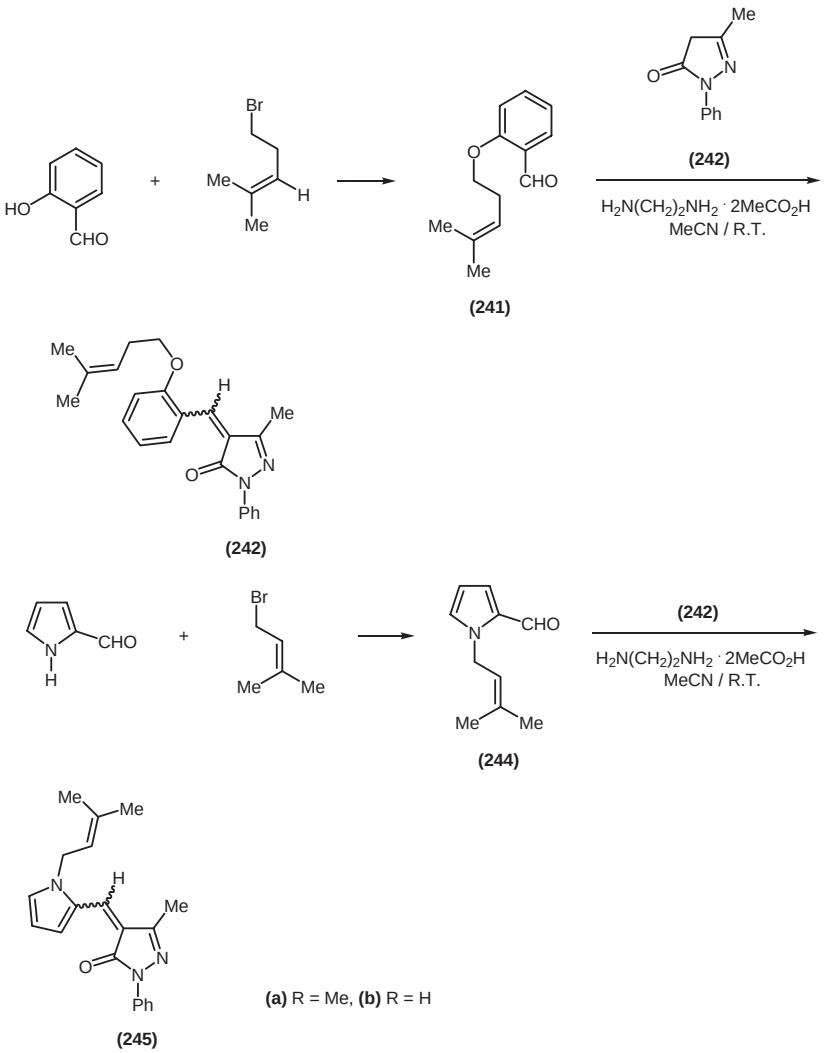
(a) R = Ph, $R^1 = R^2$ = H, $R^3 = N(Me)_2$, **(b)** R = Ph, R^1 = H, R^2 = MeO, $R^3 = OR^4$,
(c) R = Ph, R^1 = H, $R^2 = OR^4$, R^3 = MeO, **(d)** R = Ph, R^1 = H, R^2 = EtO, $R^3 = OR^4$,
(e) R = Ph, $R^1 = R^2$ = H, $R^3 = OR^4$, **(f)** R = Ph, R^1 = H, $R^2 = NO_2$, $R^3 = OR^4$,
(g) R = Ph, $R^1 = OR^4$, R^2 = EtO, R^3 = H, **(h)** R = Ph, $R^1 = R^3$ = H, $R^2 = OR^4$,
(i) R = Ph, $R^1 = OR^4$, $R^2 = R^3$ = H, R^4 =



Scheme 76

co-workers (88IJC(B)1019) prepared glucosidated (*E*/*Z*)-4-arylidenepyrazol-3-ones **245b–i** by condensation of pyrazol-3-one **243b–i** 2,3,4,6-tetra-*O*-acetyl-*β*-D-gluco-pyranosidebenzaldehydes **244b–i** using the same reaction conditions (Scheme 76).

Tietze et al. (88LA9) (Scheme 77) alkylated 2-hydroxybenzaldehyde with 5-bromo-2-methylpent-2-ene and 1*H*-pyrrole-2-carbaldehyde with 1-bromo-3-methyl-but-2-ene and obtained the corresponding aryl aldehydes **246** and **248**. Condensation of the latter with pyrazol-3-one **262** in acetonitrile containing ethylenediamine diacetate as a catalyst provided (*E*/*Z*)-4-{2-[(4-methylpent-3-enyl)oxy]benzylidine}-pyrazol-3-one **247** and (*E*/*Z*)-4-{[1-(3-methylbut-2-enyl)-1*H*-pyrrol-2-yl]methylene}-pyrazol-3-one **249**, in 67 and 99% yield, respectively.



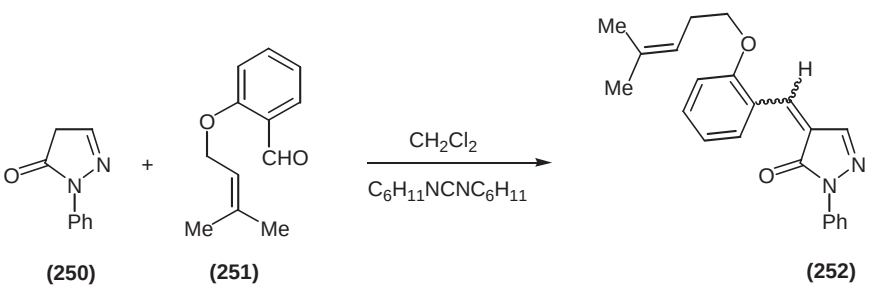
Scheme 77

A year later Tacconi and co-workers (89T775) (Scheme 78) reported that the condensation of pyrazol-3-one **250** with 2-[(3-methylbut-2-enyl)oxy]benzaldehyde **251** in dichloromethane containing *N*,*N*′-dicyclohexylcarbodiimide as catalyst, afforded (*E*/*Z*)-4-{2-[3-methyl(but-2-enyl)oxy]benzylidine}-pyrazol-3-one **252**, in only 35% yield. Compounds **247**, **249** and **252** underwent intramolecular hetero-Diels–Alder reaction at relatively low temperature.

When position 2 of a 2,4-dihydropyrazol-3-one is occupied by an electron withdrawing substituent condensation with aryl aldehydes requires heating with glacial acetic acid. Thus pyrazol-3-ones **252a**,**b** (92IJP165, 92PS253) (Scheme 79) were heated at reflux in glacial acetic acid with aryl aldehydes **254a**,**b** to afford the respective (*E*/*Z*)-4-arylidenepyrazol-3-ones **255a**,**b** in very good yield.

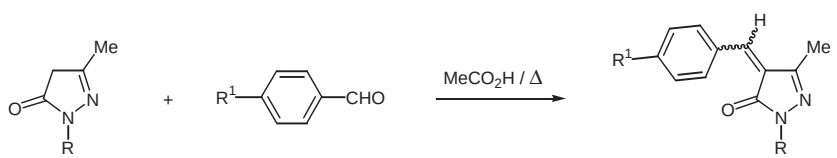
Suman and Bahel (80JIC212) (Scheme 80) reported that reaction of 1-acylpyrazol-3-ones **256a** with arylaldehydes **257a** in boiling glacial acetic acid gave (*E*/*Z*)-4-arylidenepyrazol-3-ones **258a** along with bispyrazol-3-one derivatives **259a**. Several pyrazol-3-ones **258a** were screened and found to possess significant antifungal activity.

The condensation of pyrazole-3-one **260** with substituted benzaldehydes **261a–d** was carried out in the solid state, in the molten state and in chloroform solution at 50 °C. Two products, 4-arylidenebispyrazol-3-ones **262** and 4,4′-arylmethylenebis-pyrazoles **263**, were obtained, in varying amounts according to the experimental method used (01CHJC398) (Table 1) (Scheme 81).



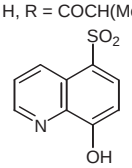
(250) **(251)** **(252)**

Scheme 78



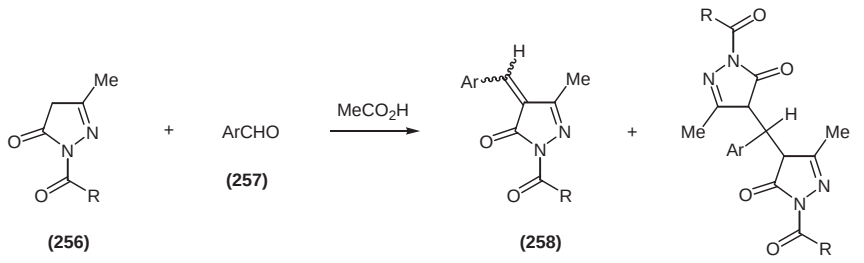
(253) **(254)** **(255)**

(a) R^1 = H, R = COCH(Me)O-3,4-(Me)(Cl)C_6H_3, COCH(Me)O-2,4-$(Me)_2C_6H_3$ or COCH(Me)O-4-(*t*-Bu)C_6H_4,

(b) R = 

, R^1 = H, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4 or 4-$NO_2C_6H_4$

Scheme 79

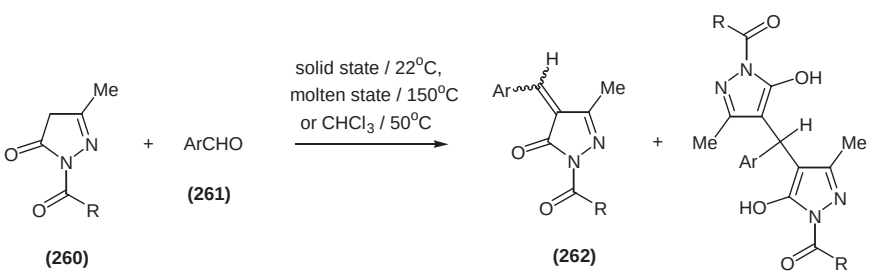


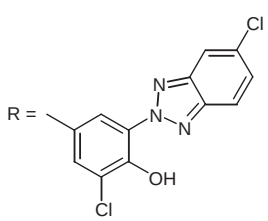
(a) R = $CH_2OC_6H_3(Me)_2$-2,6 or $CH_2OC_6H_3Me$-3-*i*-Pr-4, Ar = 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2-HOC_6H_4, 3-HOC_6H_4, 4-HOC_6H_4, 4-$(Me_2N)C_6H_4$, 4-$MeOC_6H_4$ or PhCH=CH,

Scheme 80

Table 1. REACTIONS OF (**260**) AND (**261**) IN THE SOLID AND MOLTEN STATE AND IN $CHCl_3$

	Solid state at RT		Molten state at 150 °C		In $CHCl_3$ at 50 °C	
Compounds	**262**	**263**	**262**	**263**	**262**	**263**
(a)	4%	80%	94%	0%	46%	33%
(b)	0%	87%	84%	5%	32%	52%
(c)	3%	70%	89%	0%	28%	49%
(d)	0%	92%	79%	8%	61%	21%



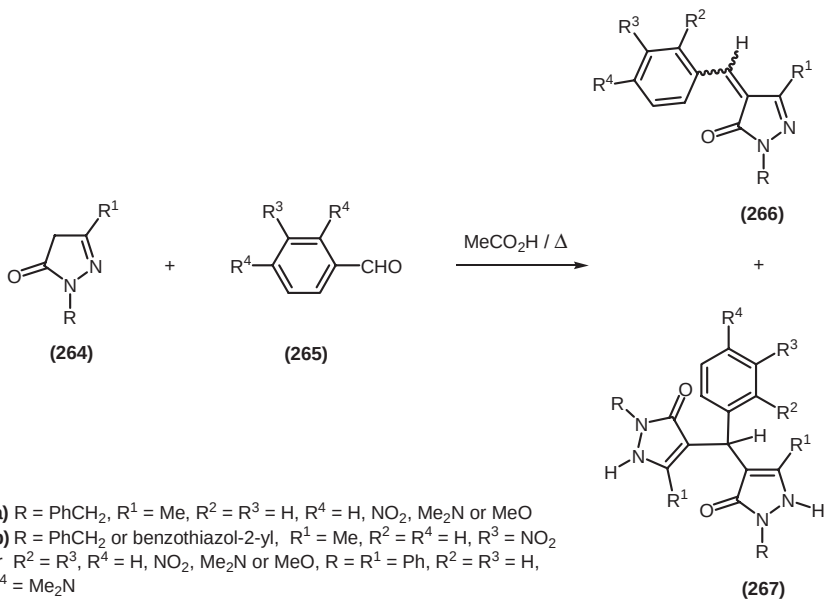


(a) Ar = 2-HO, 5-BrC_6H_3, **(b)** Ar = 2-HO, 3-$MeOC_6H_3$
(c) Ar = 2-HO, 3-MeO, 5-$NO_2C_6H_2$, **(d)** Ar = 2-Cl, 5-$NO_2C_6H_3$

Scheme 81

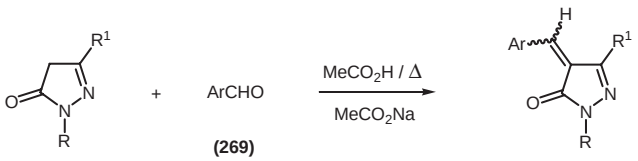
Singh and Singh (84JCED355, 91JIC165) (Scheme 82) on the other hand reported that condensation of pyrazol-3-ones **264a**,**b** with aryl aldehydes **265a**,**b**, under the same conditions, yielded (*E*/*Z*)-4-arylidenepyrazol-3-ones **266a**,**b** and 4-[(3-oxopyrazol-4-yl) (aryl)methyl]pyrazol-3-ones **267a**,**b**. It is noteworthy that the pyrazol-3-one ring of compounds **259** are represented by Suman and Bahel (80JIC212) (Scheme 80) as 1,2-dihydro tautomers whereas the corresponding pyrazol-3-one rings of compounds **267a**,**b** are 2,4-dihydro tautomers.

Several workers have found it more convenient to use sodium acetate together with glacial acetic acid. Thus Pathak and Bahel (80JIC1108), Hogal and Pawar (89JIC135), Dwivedi et al. (91JIC515), Zohdi and co-workers (92JCR(S)396) and Zohdi et al. (92JCR(M)3015) (Scheme 83), heated pyrazol-3-ones **268a**–**e** with aryl



(a) R = $PhCH_2$, R^1 = Me, R^2 = R^3 = H, R^4 = H, NO_2, Me_2N or MeO
(b) R = $PhCH_2$ or benzothiazol-2-yl, R^1 = Me, R^2 = R^4 = H, R^3 = NO_2 or R^2 = R^3, R^4 = H, NO_2, Me_2N or MeO, R = R^1 = Ph, R^2 = R^3 = H, R^4 = Me_2N

Scheme 82



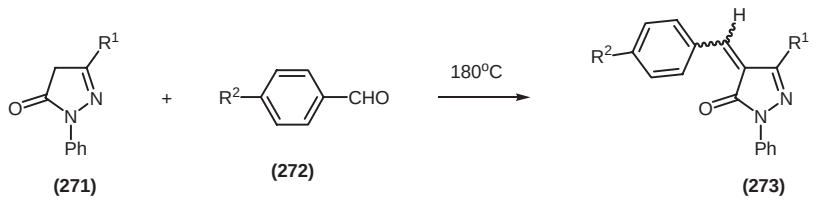
(a) R = ArCO, Ar = Ph, $PhOCH_2$, 4-$MeC_6H_4OCH_2$, 4-$ClC_6H_4OCH_2$, 4-ClC_6H_4, 4-$(Me)_2NC_6H_4$, 2-HOC_6H_4 or 4-HOC_6H_4
(b) R = ArCO, Ar = $PhCH_2$, C_6H_5CH=CH, 2-ClC_6H_4, 4-$NO_2C_6H_4$, 3,5-$(NO_2)_2C_6H_3$, 2-HOC_6H_4, $C_6H_5OCH_2$, 2-$ClC_6H_4OCH_2$ or 4-$ClC_6H_4OCH_2$, R^1 = Me Ar = Ph, 4-$(Me)_2NC_6H_4$, 2-HOC_6H_4, 3-HOC_6H_4, 4-HOC_6H_4 or 4-$MeOC_6H_4$
(c) R = Ph or ArCO, Ar = Ph, 2-ClC_6H_4, 4-ClC_6H_4, 2,4-$(Cl)_2C_6H_3$ or 4-$Me_2NC_6H_4$, R^1 = Ar = 4-ClC_6H_4, 4-$MeOC_6H_4$ or CF_3

Scheme 83

aldehydes **269a**–**e** in glacial acetic acid containing sodium acetate and obtained (*E*/*Z*)-4-arylidenepyrazol-3-ones **270a**–**e** in variable yields.

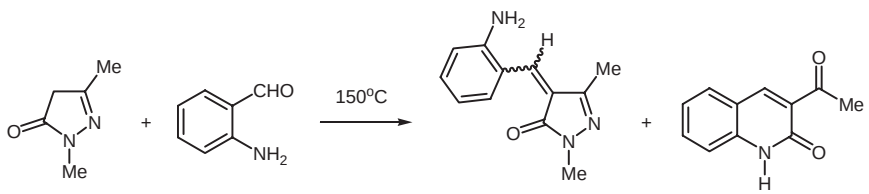
Tacconi and co-workers (72G491) and Sammour (72JPR612) (Scheme 84) prepared (*E*/*Z*)-2-phenyl-4-arylidenepyrazol-3-ones **273a**,**b** by heating pyrazol-3-ones **271a**,**b** with aryl aldehydes **272a**,**b** at 180 °C. When Abramovitch and co-workers (83JHC1539) condensed pyrazol-3-one **274** with 2-aminobenzaldehyde at 150 °C they obtained (*E*/*Z*)-4-(2-aminobenzylidene)pyrazol-3-one **275** in 70% yield and 3-acetylquinolinone **276** in 8% yield (Scheme 84).

Twelve years later Danel and Tomasik (95PJC1013) (Scheme 85) reported that upon heating pyrazol-3-ones **277a**–**d** with 2-nitrobenzaldehyde at 150 °C afforded (*E*/*Z*)-4-(2-nitrobenzylidene)pyrazol-3-ones **278a**–**d** and 4-[(5-oxopyrazol-4-yl) (2-nitrophenyl)methyl]pyrazol-3-ones **279a**–**d**. It is curious that when pyrazol-3-one **277e** was used in this reaction, the only product obtained, and in 70% yield, was (*E*/*Z*)-4-(2-nitrobenzylidine)pyrazol-3-one **278e**.



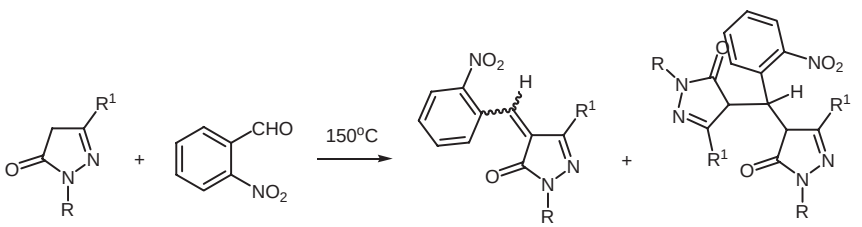
(271) **(272)** **(273)**

(a) R^1 = H, Me or Ph, R^2 = H, Me, F, Cl, Br, CO_2Me, Me_2N, NO_2 or MeO
(b) R^1 = pyridin-3-yl, R^2 = Ph, 2-ClC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$



(274) **(275)** **(276)**

Scheme 84



(277) **(278)** **(279)**

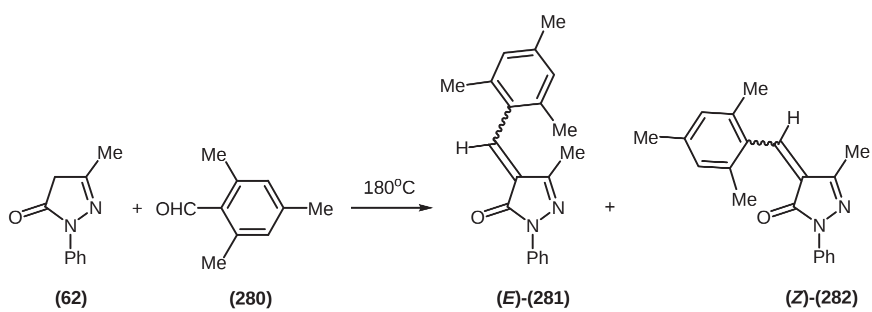
(a) R = Ph, R^1 = Me, **(b)** R = R^1 = Ph, **(c)** R = Me, R^1 = Ph,
(d) R = R^1 = Me, **(e)** R = H, R^1 = Me,

Scheme 85

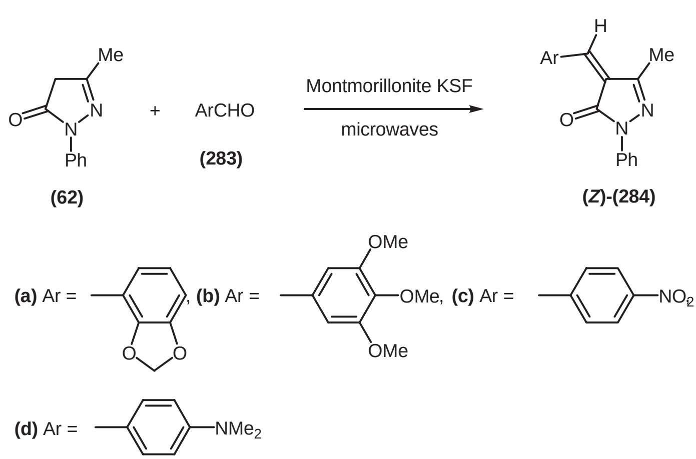
The condensation of pyrazol-3-one **62** with 2,4,6-trimethylbenzaldehyde **280** as described by Tacconi and co-workers (72G491) gave a mixture of 4-mesitylmethylidenepyrazol-3-ones (*E*)-**281** and (*Z*)-**282** (Scheme 86). These isomers were separated by fractional crystallization and their configuration assigned by NMR spectroscopy. It was established that in the (*E*)-configuration the methyl group in position 5 lies in the shielding cone of the mesityl ring and therefore occurs further upfield that the corresponding methyl group in the (*Z*)-configuration. On the other hand the vinylic proton in the (*E*)-configuration is deshielded by the carbonyl group and appears further downfield than the vinylic proton in the (*Z*)-configuration.

Villemin and Labiad (90SC3213) (Scheme 87) describe the dry condensation of pyrazol-3-one **62** with aromatic aldehydes **283a–d** by adsorption on acidic Montmorillonite KSF clay under microwave irradiation (280W) to afford (*Z*)-**284a–d** and (*E*)-4-arylmethylidenepyrazol-3-ones **285a–d** in 85 (70/30), 77 (68/32), 68 (70/30), 71 (70/30), and 92% (*Z*/*E* ratio 54/41), yield and *Z*/*E* ratios, respectively.

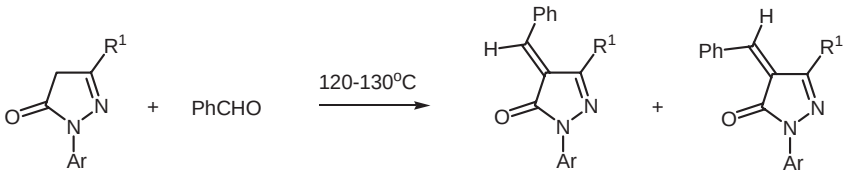
Kirschke et al. (94LA159) (Scheme 88) found that condensation of pyrazol-3-ones **286a–c** with benzaldehyde at 120–130 °C afforded mixtures of (*E*/*Z*)-4-phenylmethylidenepyrazol-3-ones that were separated by chromatography into isomers (*E*)-**287a–c** and (*Z*)-**288a**–c, respectively, in excellent yields.



Scheme 86



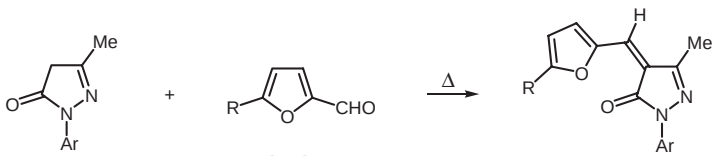
Scheme 87



(286) **(*E*)-(287)** **(*Z*)-(288)**

(a) Ar = Ph, R^1 = EtO, **(b)** Ar = 4-$NO_2C_6H_4$, R^1 = EtO, **(c)** Ar = 4-$NO_2C_6H_4$, R^1 = pyrrolidino

Scheme 88



(289) **(290)** **(291)**

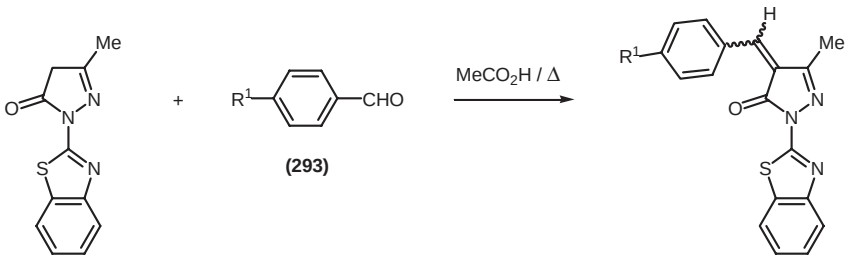
(a) Ar = 2-ClC_6H_4, **(b)** Ar = 3-ClC_6H_4, **(c)** Ar = 4-ClC_6H_4, **(d)** R = H, **(e)** R = NO_2, **(f)** R = H or NO_2, Ar = 2-ClC_6H_4, 3-ClC_6H_4 or 4-ClC_6H_4

Scheme 89

Wrzeciono et al. (78PHA264) (Scheme 89) presented the only example of condensation between an aromatic heterocyclic aldehyde and a 2,4-dihydropyrazol-3-one. Thus reaction of pyrazol-3-ones **289a–c** with furan-2-carbaldehydes **290d**,**e** afforded the furfurylidene derivatives **291f**,**g**.

Six years later Singh and Singh (84JCED355) (Scheme 90) condensed 2-(benzothiazol-2-yl)pyrazol-3-one **292** with aryl aldehydes **293a–d** in boiling acetic acid and obtained (*E*/*Z*)-4-arylmethylidenepyrazol-3-ones **294a–d** in 65, 58, 83 and 69% yield, respectively.

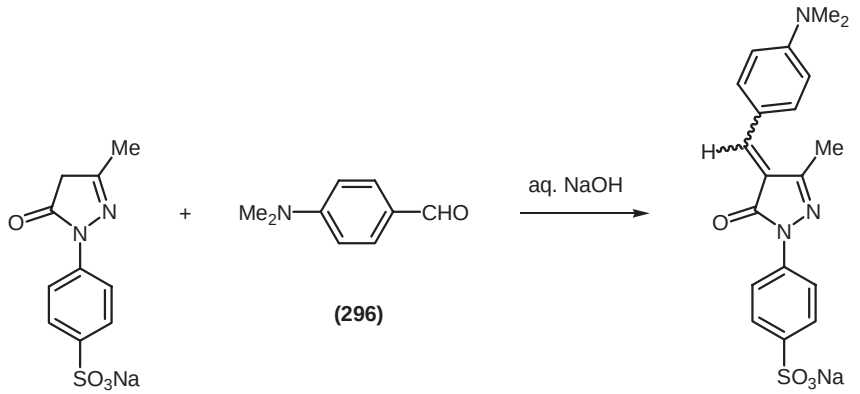
The condensation of pyrazole-3-one **295** with aldehyde **296** was found by Timple et al. (82JPR955) (Scheme 91) to work efficiently in aqueous sodium hydroxide at room temperature to give (*E*/*Z*)-4-(arylmethylidene)pyrazole-3-one **297**.



(292) **(293)** **(294)**

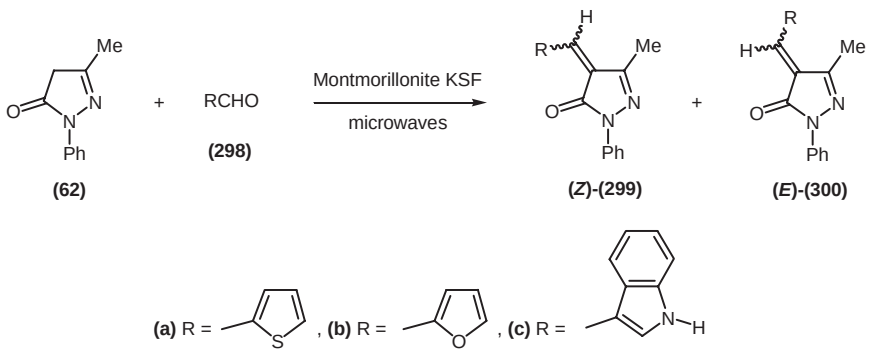
(a) R^1 = H, **(b)** R^1 = NO_2, **(c)** R^1 = Me_2N, **(d)** R^1 = MeO

Scheme 90



Scheme 91

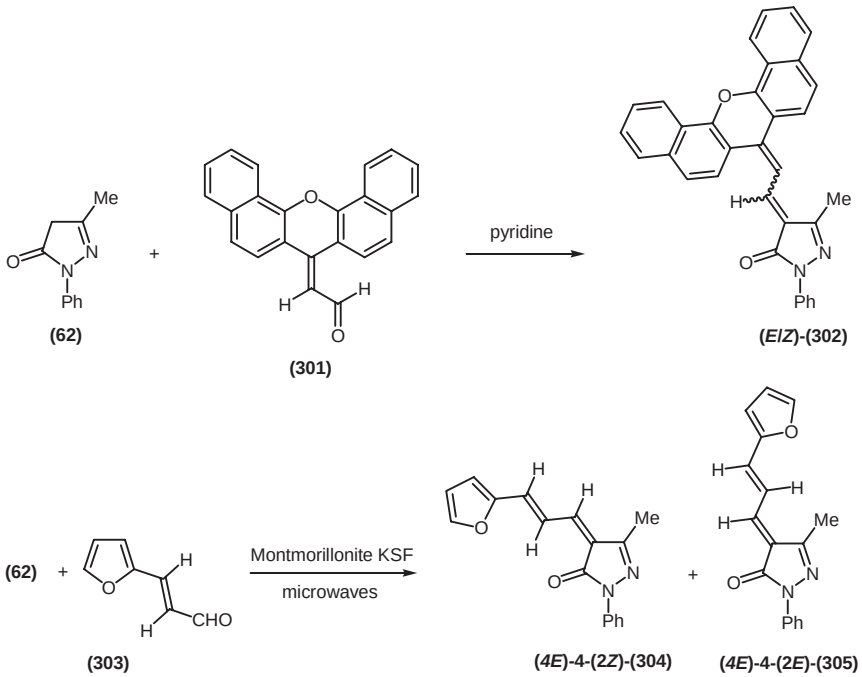
Microwave irradiation in the presence of Montmorillonite KSF clay as catalyst has also proved effective in condensations between pyrazol-3-one **62** and various heterocyclic aldehydes. Thus, thiophene-2-carboxaldehyde **298a**, 2-furaldehyde **298b** and indole-3-carboxaldehyde **298c** reacted smoothly under these conditions to give (*Z*)-**299a–c** and (*E*)-2-heteroarylpyrazol-3-ones **300a–c** in 89 (80/20), 86 (71/29) and 75% (*Z*/*E* ratio 33/67) yield and *Z*/*E*-ratios, respectively (90SC3213) (Scheme 92).



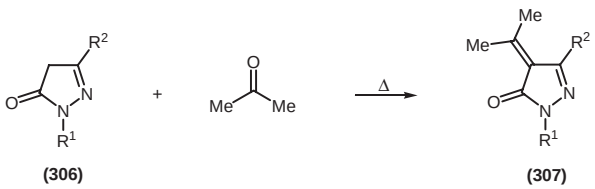
Scheme 92

B. With Non-Typical α,β-Unsaturated Aldehydes

This type of condensation works in competition with the Michael addition but addition occurs preferably at the aldehyde group since the alkene group is connected to an aryl or heteroaryl ring. The first of the two reports of this kind of condensation were given by Kamel and Shoeb (64T483) (Scheme 94). The reaction described was between pyrazol-3-one **62** and dibenzo[*c*,*h*]xanthen-7-ylideneacetaldehyde **301** in pyridine at room temperature which gave (*E*/*Z*)-dibenzo[*c*,*h*]xanthen-7-ylideneethylidenepyrazol-3-one **302**. In the second report Villemin and Labiad (90SC3213)



Scheme 93



(a) R^1 = Ph, R^2 = H, **(b)** R^1 = Ph, R^2 = Me or Ph, R^1 = 4-MeC_6H_4, R^2 = Me, **(c)** R^2 = Ph, R^1 = Ph, 2-MeC_6H_4, 4-MeC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4 or 4-BrC_6H_4, **(d)** R^2 = Me, R^1 = Ph, 3-ClC_6H_4, 4-ClC_6H_4, 3-$NO_2C_6H_4$ or 4-$NO_2C_6H_4$, **(e)** R^2 = Ph, R^1 = Ph, 4-ClC_6H_4 or 4-BrC_6H_4, **(f)** R^2 = Me, R^1 = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 4-MeC_6H_4 or 4-$MeOC_6H_4$,

Scheme 94

(Scheme 93) condensed pyrazol-3-one **62** with 3-(2-furyl)acrolein **303** by adsorption on acidic Montmorillonite KSF clay under microwave irradiation and obtained (*4E*)-4-[(2*Z*)-**304** and (4*E*)-4-[(2*E*)-3-(2-furyl)prop-2-enylidene]pyrazol-3-one **305** in 92% yield and 54/41 *Z*/*E* ratio.

C. With Ketones

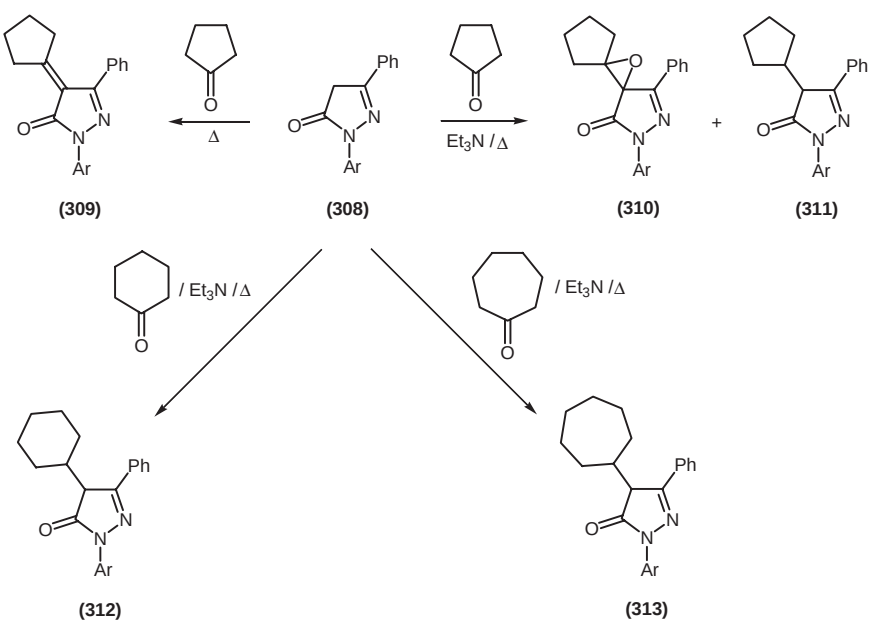
All recorded condensations with ketones have taken place at C4 of 2,4-dihydropyrazol-3-ones. Reaction even with the simplest ketone, acetone, requires heating at the boiling point. Therefore under these conditions pyrazol-3-ones **306a**–**f**

gave 4-(1-methylethylidene)pyrazol-3-ones **307a–f** in near quantitative yields (73BSF2482, 83JCS(P1)325, 83S428, 84BSB1073, 84CPB2146, 86JHC1159) (Scheme 94).

Matsugo et al. (85CPB3623) (Schemes 96–98) studied the condensation of pyrazol-3-ones **308a–c** with cyclopentanone, cyclohexanone or cycloheptanone at reflux with or without triethylamine and obtained both predictable and unpredictable results. Thus the reaction of pyrazol-3-ones **308a–c** in boiling cyclopentanone afforded 4-cyclopentylidenepyrazol-3-ones **309a–c** in high yield. However in the presence of triethylamine the above reaction gave completely different results. Two products were isolated 11-oxa-2,4-diazaspiro-[4.0.4.1]undec-3-en-1-ones **310a–c** and 4-cyclopentylpyrazol-3-ones **311a–c**. In contrast, the reaction of pyrazol-3-ones **308a–c** with cyclohexanone or cycloheptanone in the presence of triethylamine at reflux afforded the corresponding 4-cyclohexylpyrazol-3-ones **312a–c** and 4-cycloheptylpyrazol-3-ones **313a–c**. The absence of epoxides is explained by the presence of triethylamine oxide as byproduct.

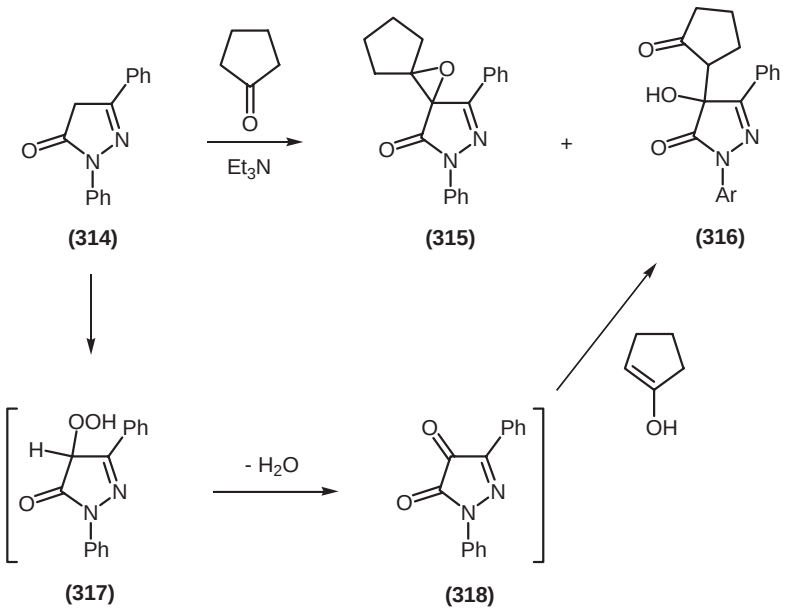
An interesting result was obtained when pyrazol-3-one **314** was reacted with cyclopentanone in the presence of triethylamine at room temperature (Scheme 97). Epoxide **315** and 4-hydroxy-4-(2-oxocyclopentyl)pyrazol-3-one **316** were obtained in 43 and 23% yield, respectively. This reaction may involve initial formation of hydroperoxide **317**, dehydration to diketone **318**, followed by addition of enolized cyclopentanone to the latter, finally leading to pyrazol-3-one **316**.

The reaction of pyrazol-3-ones **308a–c** and cyclopentanone catalyzed by triethylamine was further investigated. When the reaction was repeated in the



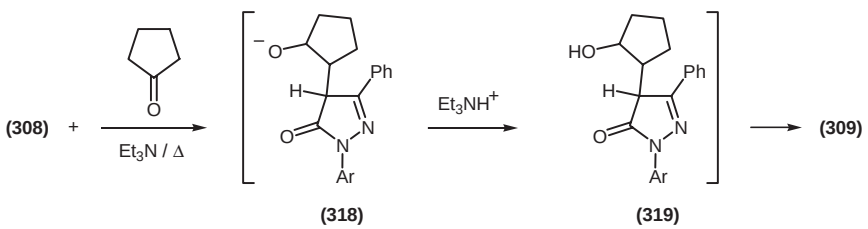
(a) Ar = Ph, **(b)** Ar = 4-ClC_6H_4, **(c)** Ar = 4-BrC_6H_4

Scheme 95



(a) Ar = Ph, **(b)** Ar = 4-ClC_6H_4, **(c)** Ar = 4-BrC_6H_4

Scheme 96

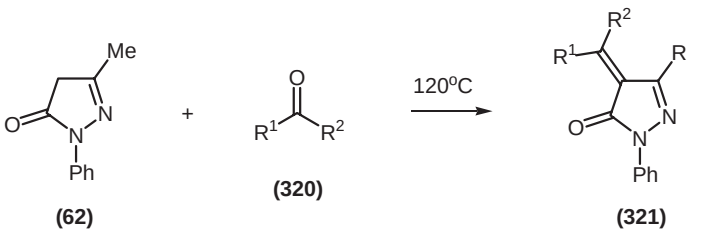


(a) Ar = Ph, **(b)** Ar = 4-ClC_6H_4, **(c)** Ar = 4-BrC_6H_4

Scheme 97

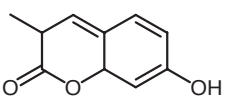
presence of 2,4,6-trimethylphenol as a radical scavenger or under an inert atmosphere using very dry conditions, the outcome of the reaction was unchanged. These and other observations derived from deuterium and O^{18} labeled NMR experiments lead to a reasonable mechanism for this reaction (Scheme 97). Thus initial formation of adduct **318**, protonation to **319** followed by dehydration may give pyrazol-3-ones **309**. No satisfactory explanation has been given for the formation of compounds **310** and **311** (Scheme 95).

Due et al. (95CHJC520) (Scheme 98) reacted pyrazol-3-one **62** with aromatic ketones **320a**–**i** in the solid state by heating at 120 °C to give 4-(diphenylmethylene)-**321a**, (*E*/*Z*)-4-[phenyl(pyridin-4-yl)methylene]—**321b**, (*E*/*Z*)-4-[1-(aryl, naphthyl or heteroaryl)ethylidene]—**321c**–**h** or (*E*/*Z*)-4-[1-(4-{[(*E*/*Z*)-1-(4-aminophenyl)ethylidene]amino}phenyl)ethylidene]pyrazol-3-one **321i**, in yields ranging from 35 to 78%.

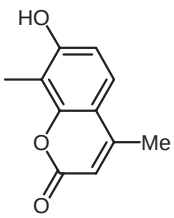


(a) $R^1 = R^2 = Ph$, **(b)** $R^1 = Ph$, R^2 = pyridin-4-yl, **(c)** $R^1 = Me$, $R^2 = 4\text{-}NO_2C_6H_4$, **(d)** $R^1 = Me$, $R^2 = 4\text{-}NH_2C_6H_4$, **(e)** $R^1 = Me$, R^2 = naphthal-2-yl,

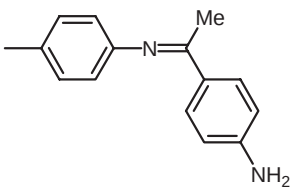
(f) $R^1 = Me$, R^2 = indol-2-yl, **(g)** $R^1 = Me$, R^2 =



(h) $R^1 = Me$, R^2 =

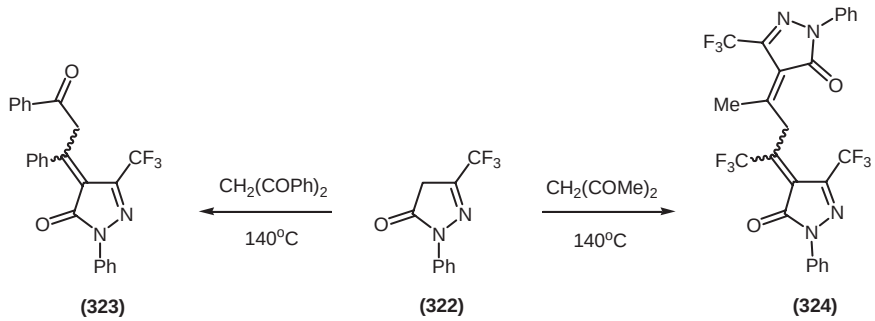


(i) $R^1 = Me$, R^2 =

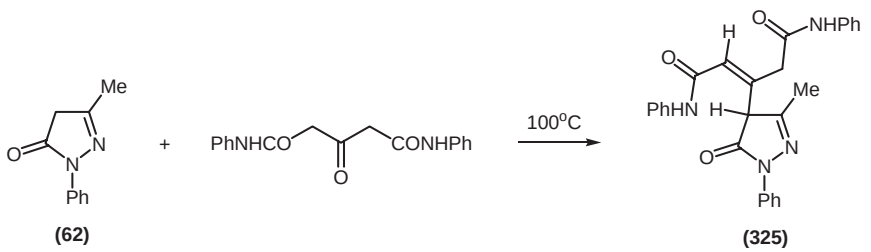


Scheme 98

In view of the considerable interest given to heterocyclic compounds containing a trifluoromethyl group on account of their excellent pharmacological activity, Zohdi et al. (92JCR(S)396, 92JCR(M)3015) (Scheme 99) synthesized, among other compounds, (*E*/*Z*)-4-(3-oxo-1,3-diphenylpropylidene)-5-trifluoro-methylpyrazol-3-one **323** and (*E*/*Z*)-[(5-oxopyrazol-4-ylidene)butylidene]pyrazol-3-one **324**, required for a medicinal chemistry program. Compounds **323** and **324** were prepared by treating 5-trifluoromethylpyrazol-3-one **322** with 1,3-diphenylpropane-1,3-dione and pentane-2,4-dione, respectively, at 140 °C. It seems that the steric hindrance in **323** caused by the two phenyl groups prevents further reaction with another molecule of **322**.



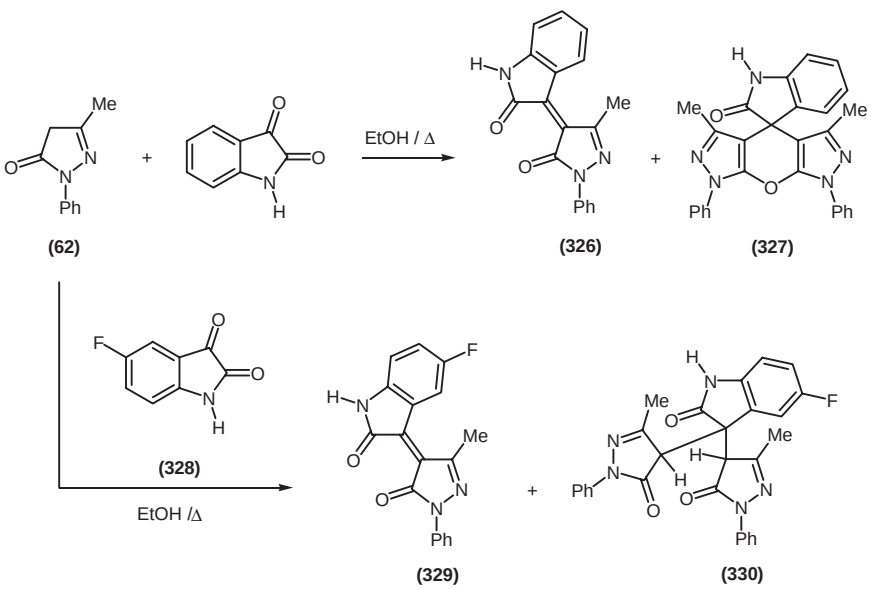
Scheme 99



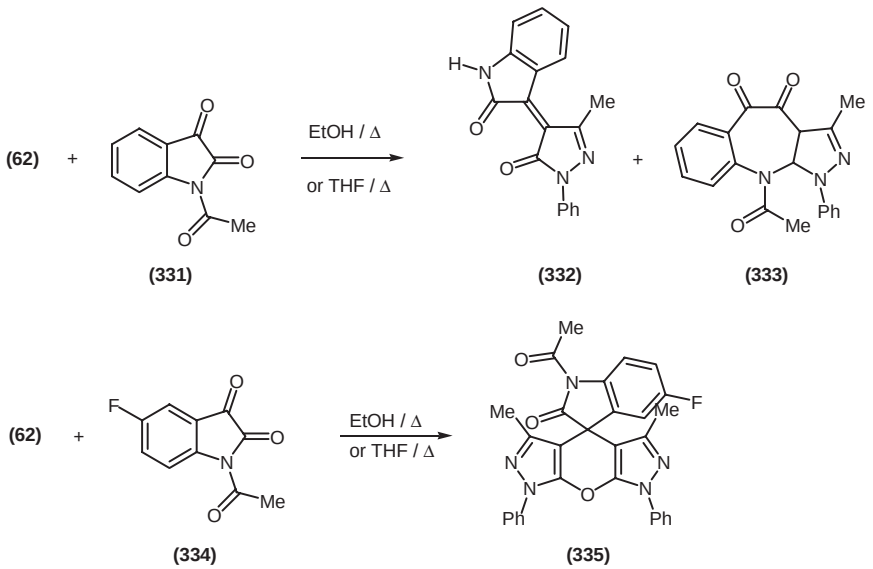
Scheme 100

In one report 3-oxo-*N*,*N*′-diphenylpentanediamide was found to condense with pyrazol-3-one **62** at 100 °C to give (*E*/*Z*)-3-(5-oxopyrazol-4-yl)-*N*,*N*′-diphenylpent-2-enediamide **325** (79JPR1047) (Scheme 100).

Joshi et al. (91H1491, 94IJC(B)483) (Scheme 101 to 104) have reported the condensation of pyrazol-3-one **62** with indone-2,3-dione derivatives or 5-fluoro derivative **328** under both thermal and photochemical conditions. Under thermal conditions **62** reacts with indone-2,3-dione in a ratio of 2:1 in boiling ethanol, to give (3*E*/*Z*)-3-(5-oxopyrazol-4-ylidene)indol-2-one **326** and spiro(pyrazolopyrazopyrazolo)indolone **327** in 12 and 80% yield, respectively. Under the same reaction conditions 5-fluoroindone-2,3-dione **328** reacted with **62** to give the expected condensation product **329** together with derivative **330**. The latter originates from addition of a further molecule of pyrazol-3-one **62** to **329**. The analogue of **330** was not isolated in the reaction between **62** and indone-2,3-dione because it intramolecularly cyclized to **327**.



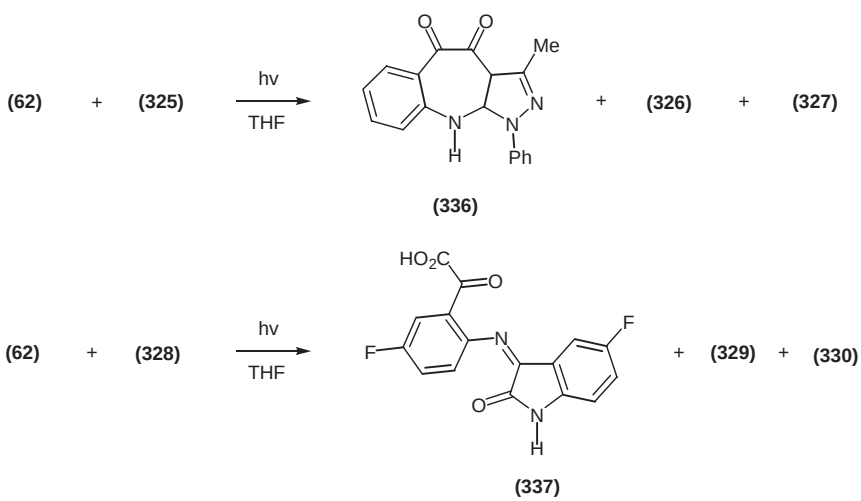
Scheme 101



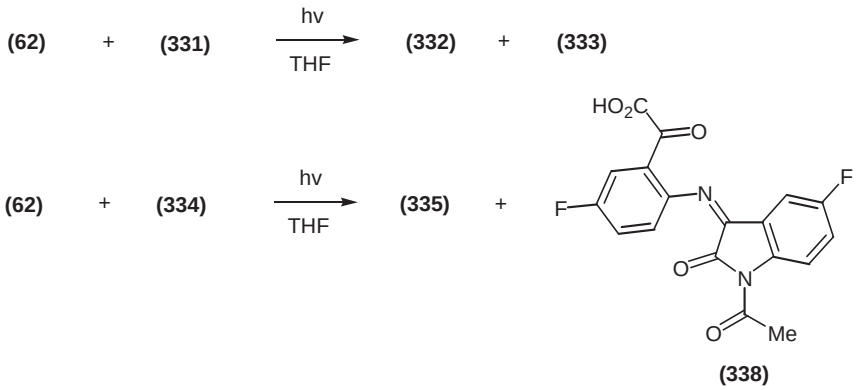
Scheme 102

The use of 1-acetyl-2,3-dione **331** as the electrophile in a reaction with **62** gave 45% of condensation product **332** and 17% of pyrazolobenzazepine **333** (Scheme 102). The electronic effect of the acetyl group of **331** has driven the nucleophile to attack C2 of the molecule causing ring opening by cleavage at the amide followed by ring closure and dehydration to **333**. The reaction of pyrazol-3-one **62** with 1-acetyl-5-fluoroindone-2,3-dione **334** gave curiously only compound **335** in 80% yield.

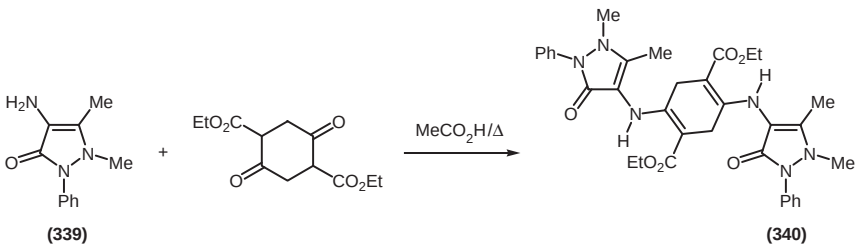
Under photochemical conditions, ultraviolet light in THF solution and under nitrogen, similar products were obtained (Scheme 103). Thus the reaction of **62** and



Scheme 103



Scheme 104



Scheme 105

325 gave **326**, **327** and pyrazolobenzazepine **336**, **62** and **328** gave **329**, **330** and 2-[(indol-3-ylideneamino)phenyl]oxoacetic acid **337**.

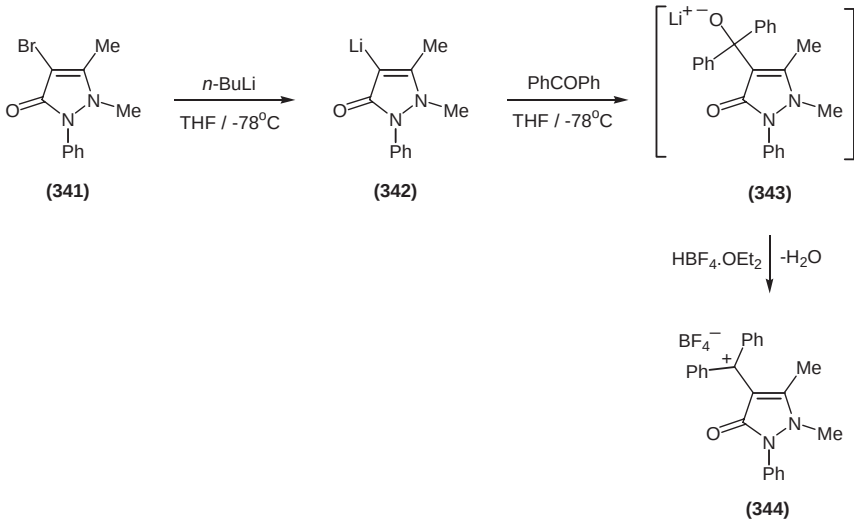
Furthermore reaction of **62** with **331** and ultraviolet light gave the same products **332** and **333** but in 17 and 40% yield, respectively (Scheme 104). On the other hand, reaction of **62** and **334** gave also the same product **335**, in 14% yield together with [indol-3-ylideneamino)-5-fluorophenyl]oxoacetic acid **338** in 37% yield.

Metwally and Afsah (84PHA95) (Scheme 105) heated 4-aminopyrazol-3-one **339** with diethyl 2,5-dioxocyclohexane-1,4-dicarboxylate in glacial acetic acid and obtained the diethyl 2,5-di(5-oxopyrazol-4-yl)amino derivative **340**.

Nucleophilic addition to a ketone by a pyrazole-3-one can also take place via a pyrazolon-4-yl anion generated from a halogen-metal exchange reaction. Akgün and Pindur (84M197) (Scheme 106) reported one such example, namely the addition of pyrazole-3-one lithium salt **342**, obtained by treating 4-bromopyrazol-3-one **341** with n-BuLi in THF at −78 °C, to benzophenone. The addition product **343** was quenched with tetrafluoroboric acid-diethyl ether complex to afford, after loss of water, (3-oxopyrazol-4-yl) (diphenyl)methylium tetrafluoroborate **344**.

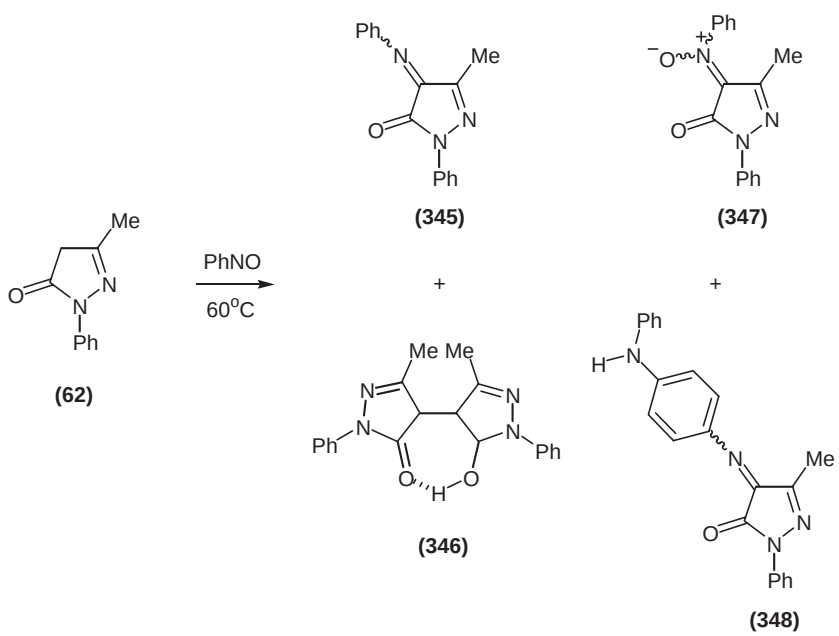
D. With Nitroso Compounds

4-Aryliminopyrazol-3-ones are widely employed as color couplers in photography. In an attempt to synthesize (*E*/*Z*)-4-phenyliminopyrazol-3-one **345** by heating



(341) (342) (343) (344)

Scheme 106



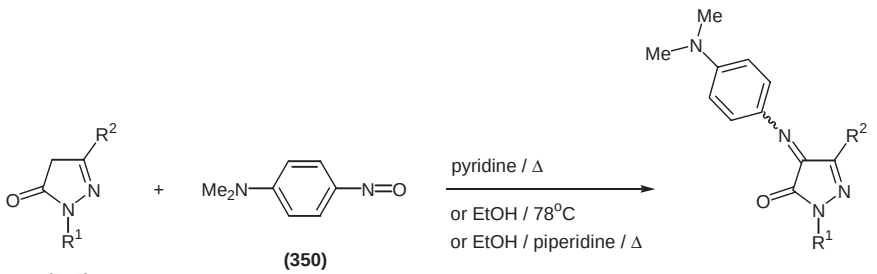
(62) (345) (347) (346) (348)

Scheme 107

pyrazol-3-one and nitrosobenzene in the solid state at 60 °C, Tacconi et al. (80JPR674) (Scheme 107) obtained a mixture containing together with (*E*/*Z*)-**345**, 4-(pyrazol-4-yl)pyrazol-3-one **346**, (*E*/*Z*)-(5-oxopyrazol-4-ylidene)-(phenyl)ammoniumolate **347** and (*E*/*Z*)-4-[(4-anilinophenyl)imino]pyrazol-3-one **348**. The yield of these products was 27, 10, 3 and 2%, respectively. Although the yield of (*E*/*Z*)-**345**

was only 27% this yield was much higher than other methods and the chromatographic separation of the compound was much easier.

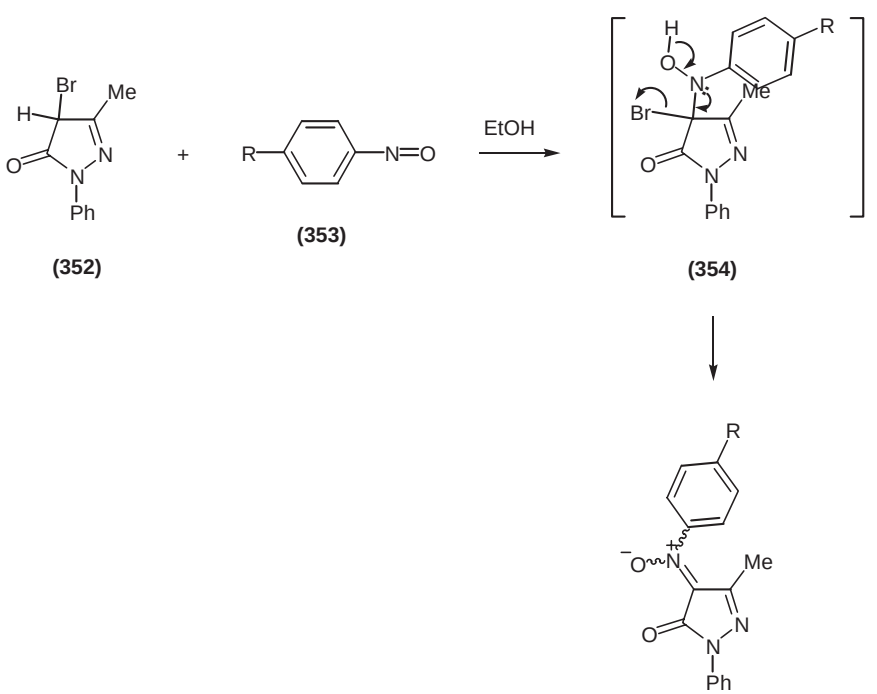
Heinisch (88JPR57) and Grigg and co-workers (94T895) and El-Shahawy et al. (88IJC(A)94) (Scheme 109) avoided the side products obtained by Tacconi et al. (80JPR674) (Scheme 108) during the reaction of pyrazol-3-ones **349a–g** with



(349) **(350)** **(351)**

(a) R^1 = H, R^2 = Me, **(b)** R^1 = H, R^2 = Ph, **(c)** R^1 = Me, R^2 = Ph, **(d)** R^1 = Ph, R^2 = Me, **(e)** R^1 = R^2 = Ph, **(f)** R^1 = 4-$MeOC_6H_4$, R^2 = Ph, **(g)** R^1 = 4-$NO_2C_6H_4$, R^2 = Ph

Scheme 108



(352) **(353)** **(354)** **(355)**

(a) R = H, **(b)** R = Me_2N, **(c)** R = PhNH, **(d)** R = Cl

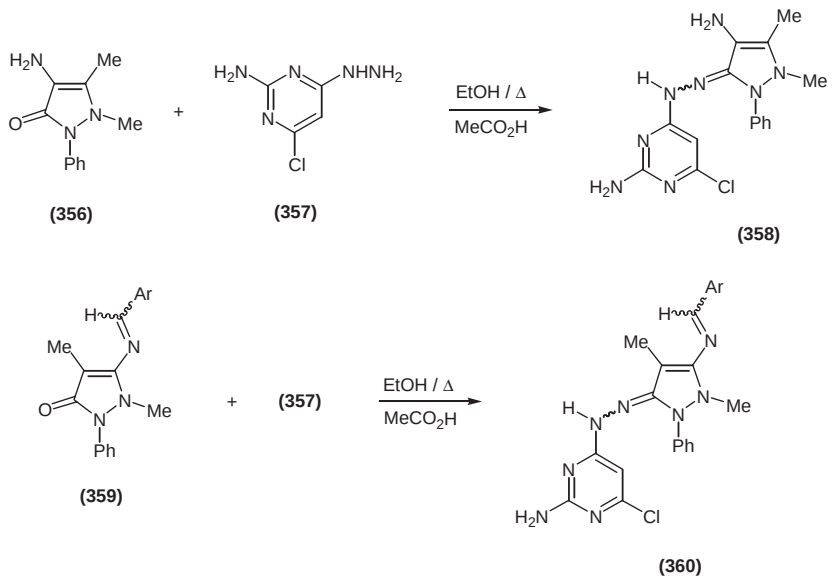
Scheme 109

N,*N*-dimethyl-4-nitrosoaniline **350**. Heinisch condensed compounds **349a–e** with **350** by heating in dry pyridine and obtained (*E*/*Z*)-4-(4-dimethylamino-phenylimino)-pyrazol-3-ones **351a–e** in good yields. Grigg found that pyrazol-3-ones **349f,g** required heating with **350** in absolute ethanol at 78 °C to give excellent yields of pyrazol-3-ones **351f,g** whereas El-Shahawy who prepared **351d**, from **349d** and **350**, used instead of pyridine as solvent, ethanol with a catalytic amount of piperidine.

When 4-bromopyrazo-3-ones condense with arylnitroso compounds the reaction takes a different course and gives nitrones. Tacconi et al. (80JPR679) (Scheme 109) demonstrated this by reacting 4-bromopyrazol-3-one **352** with aryl nitroso derivatives **353a–d** in ethanol at room temperature to yield nitrones **355a–d**, in yields ranging from 55 to 80%. The reaction proceeds via adduct **354**, which then loses hydrogen bromide.

E. With Aryl Hydrazines

Condensations by nucleophiles onto the carbonyl group of the pyrazol-3-one ring are rare. The condensation of 1,2-dihydropyrazol-3-one **356** with 2-amino-4-chloro-6-hydrazinopyrimidine **357** in ethanol under reflux in the presence of a catalytic amount of glacial acetic acid afforded hydrazone **358** in 30% yield. The (*E*/*Z*)-5-ethylideneaminopyrazol-3-one Schiff bases **359a–c** required heating in glacial acetic acid with sodium acetate and **357** in order to give the corresponding hydrazones **360a–c** that were obtained in 65, 70 and 60% yield, respectively (92JIC882), (Scheme 110).



(a) Ar = 4-ClC$_6$H$_4$, **(b)** Ar = 4-ClC$_6$H$_4$, **(c)** Ar = 4-NO$_2$C$_6$H$_4$

Scheme 110

F. By Conjugate Addition-Elimination

This type of condensation occurs readily at C4 of 2,4-dihydropyrazol-3-ones. It takes place in two steps: addition of pyrazol-3-one C4 onto an electrophile and then elimination of a neutral molecule to form a double bond. A second elimination of a neutral molecule may occur to form an exocyclic alkene at C4 of the pyrazol-3-one.

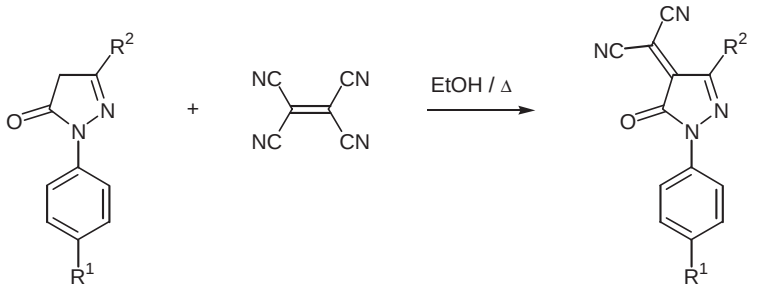
Tetracyanoethylene has been used as an electrophile by two different groups of researchers, Junek et al. (88M993) and Elnagdi and co-workers (89LA1037) (Scheme 111). Reaction with pyrazol-3-ones **361a–c** was conducted in refluxing ethanol and the products 2-(3-oxopyrazol-4-ylidene)malononitriles **362a–c**, usually deeply coloured, were obtained in over 80% yield. These compounds were further reacted with aliphatic, aromatic and heterocyclic amines.

Maquestian et al. (84BSB1073) (Scheme 112) describe the reaction of pyrazol-3-ones **363a–e** with ethyl 3-aminobut-2-enoate **364** as taking place in two steps, possibly because intermediate **365** is relatively stable. After initial conjugate addition, elimination of ammonia from **365** yields (*E*/*Z*) ethyl 3-(5-oxopyrazol-4-ylidene)butanoates **366a–e**.

Čiernik and Mistr (66CCC4669) (Scheme 113) studied the addition of bispyrazol-3-one derivatives **367a** onto salts of heterocyclic quaternary bases **368a** and determined that the elimination of ethanediol, *N*-phenylacetamide or aniline provided bispyrazol-3-ones **369a**. The reactions were performed in refluxing ethanol containing triethylamine. The yield was moderate.

Two years later Kiša and Hadráček (68M2365) (Scheme 114) used the same principle to react 2-(triazin-3-yl)pyrazol-3-one **370** with salts of heterocyclic bases **371a–c** to obtain pyrazol-3-one derivatives **372a–c**, that have been used as merocyanin dyes.

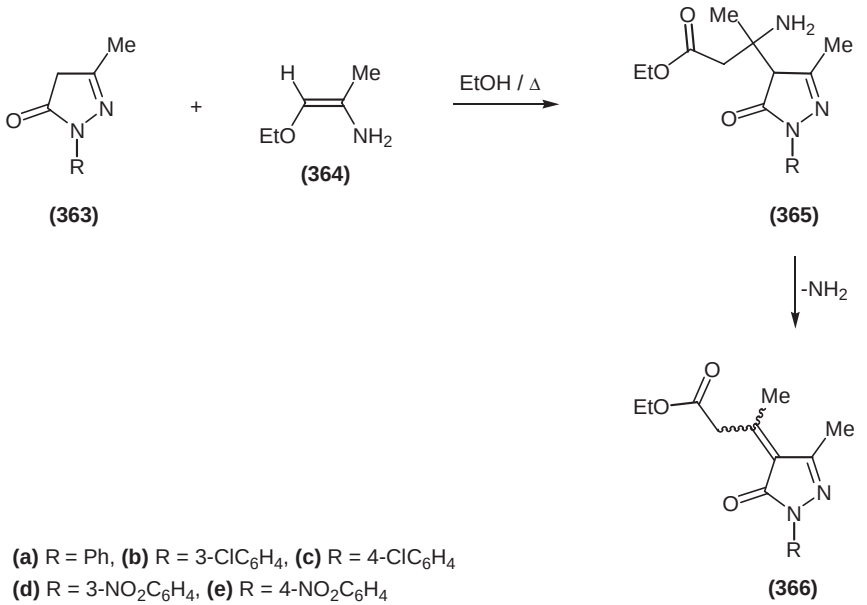
Abdel-Latif (91IJC(B)363) (Scheme 115) demonstrated that the reaction of 4-bromopyrazol-3-one **373** with ethyl 2-cyano-3-thien-2-ylacrylate **374** in refluxing ethanol containing a catalytic amount of piperidine gave pyrazol-3-one **377** in 50% yield. The first step is postulated to give the intermediate **375** followed by elimination



(361) **(362)**

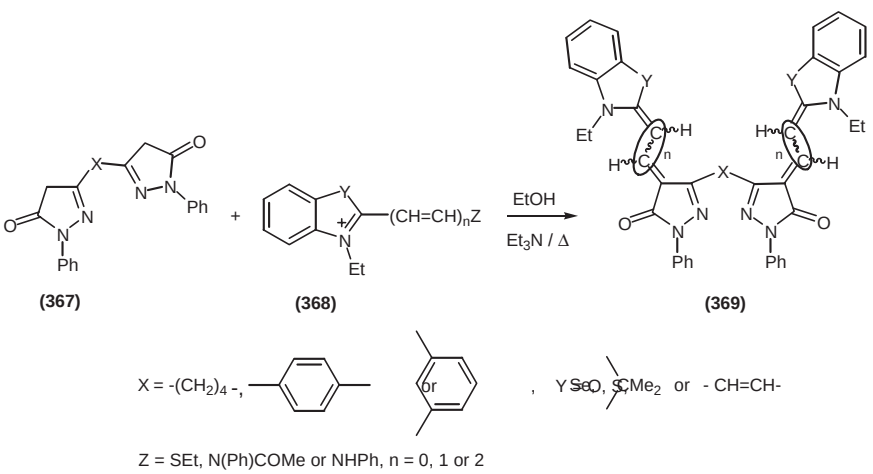
(a) $R^1 = R^2 = Me$, **(b)** $R^1 = H$, $R^2 = n\text{-Pr}$, **(c)** $R^1 = H$, $R^2 = Ph$, **(d)** $R^1 = H$, $R^2 = NH_2$

Scheme 111



(a) R = Ph, **(b)** R = 3-ClC_6H_4, **(c)** R = 4-ClC_6H_4
(d) R = 3-$NO_2C_6H_4$, **(e)** R = 4-$NO_2C_6H_4$

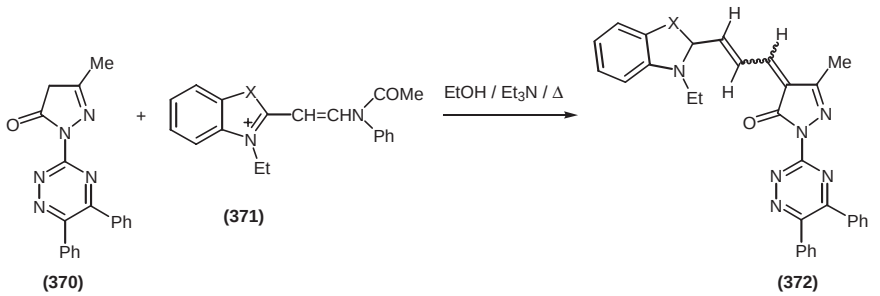
Scheme 112



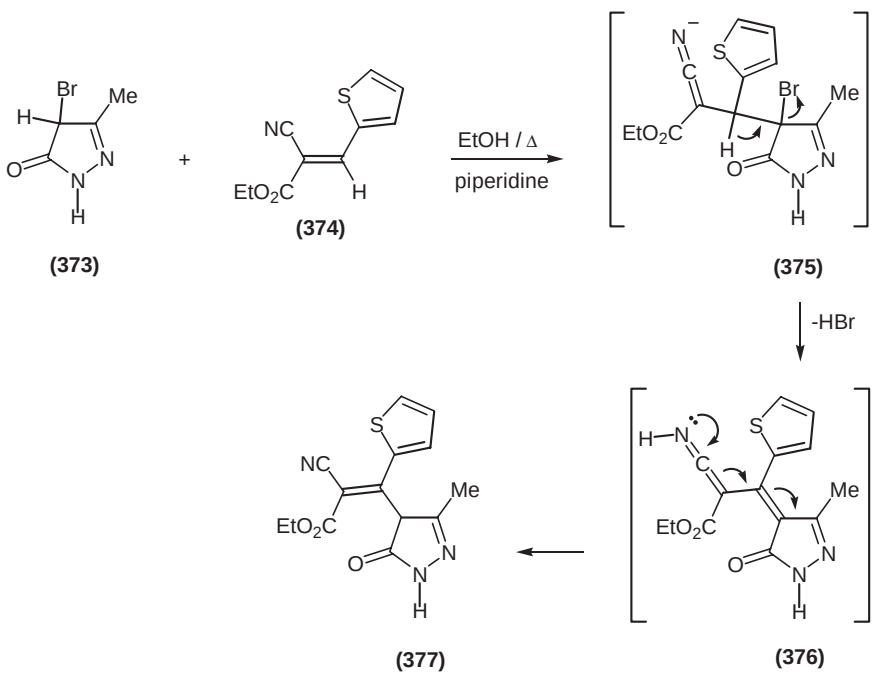
Scheme 113

of hydrogen bromide to **376**, which tautomerises to ethyl (3-oxopyrazol-4-yl)prop-2-enoate **377**.

Wilde et al. (79JPR495) (Scheme 116) reacted pyrazol-3-ones **378a** with diethyl (4-iminocyclohexa-2,5-dienylidene)ammonium salts **379** to afford the addition products **380a** that were then oxidized to 4-(4-diethylaminophenylimino)-pyrazol-3-one **381**.



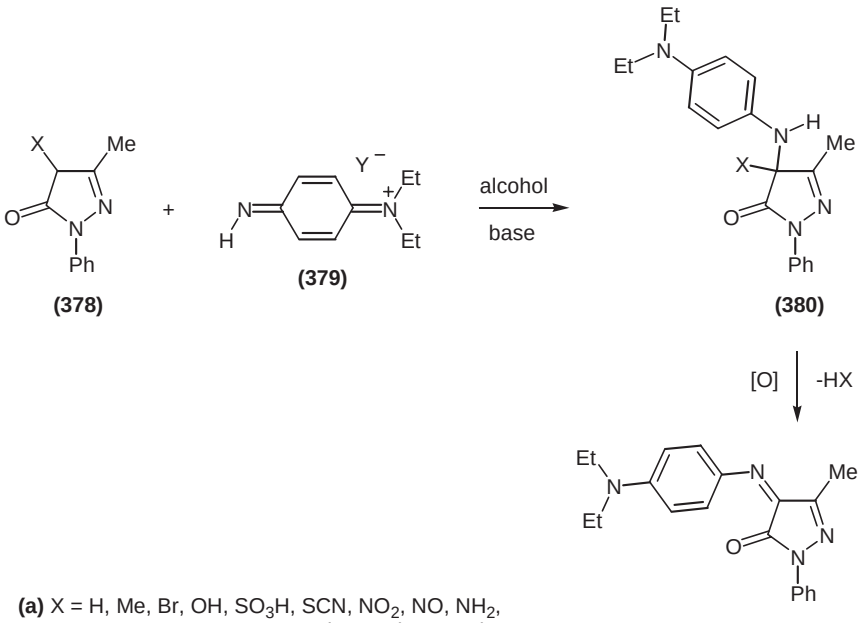
Scheme 114



Scheme 115

G. By Addition-Elimination of Pyrazol-3-ones to Activated Double Bonds

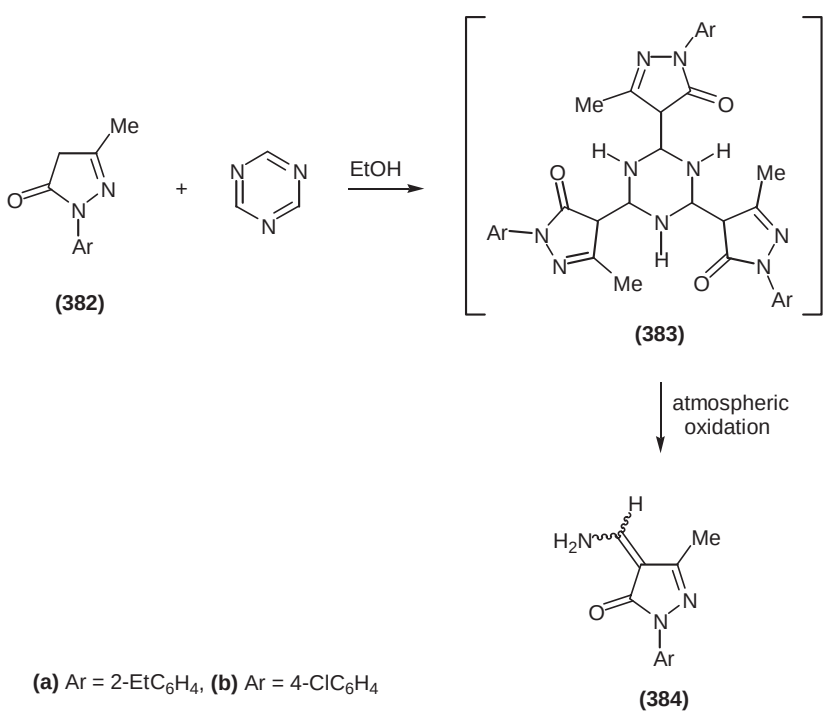
The introduction of an aminomethylene group into position 4 of 2,4-dihydropyrazol-3-ones has been studied by Kreutzberger and Kolter (85AP89, 86AP865) (Scheme 117). The method involves the reaction of electron-deficient 1,3,5-triazine with three equivalents of pyrazol-3-ones **382a**,**b** in ethanol at ambient temperature to give the intermediate tripyrazol-3-one addition products **383a**,**b**. The latter are very unstable and undergo atmospheric oxidative ring cleavage to the (*E*/*Z*)-4-aminomethylenepyrazol-3-ones **384a**,**b**.



(378) **(379)** **(380)** **(381)**

(a) X = H, Me, Br, OH, SO_3H, SCN, NO_2, NO, NH_2, NHCOMe, $NHCSNH_2$, $NHCOCCl_3$, or $N(CH_2CH_2)_2O$

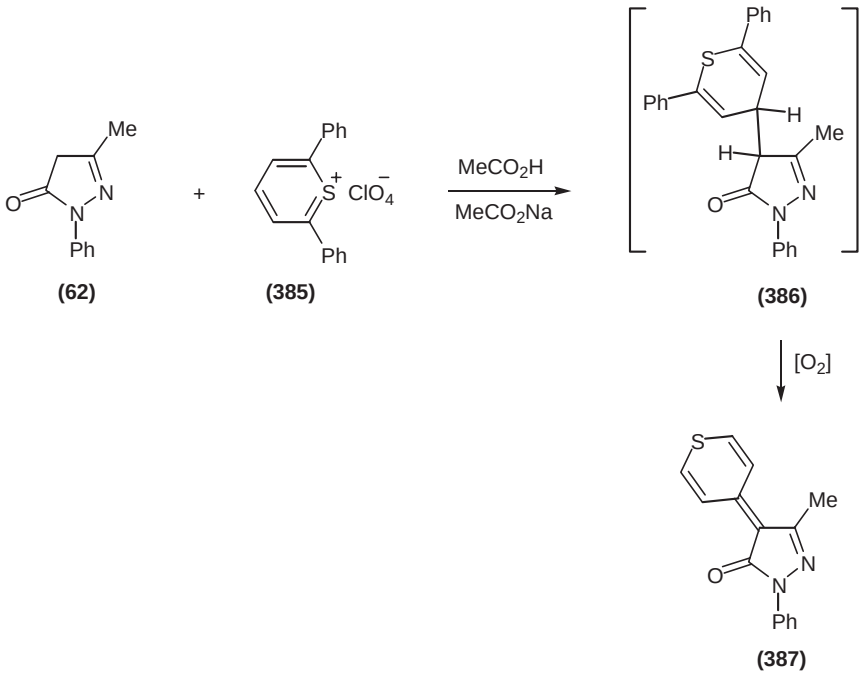
Scheme 116



(382) **(383)** **(384)**

(a) Ar = 2-EtC_6H_4, **(b)** Ar = 4-ClC_6H_4

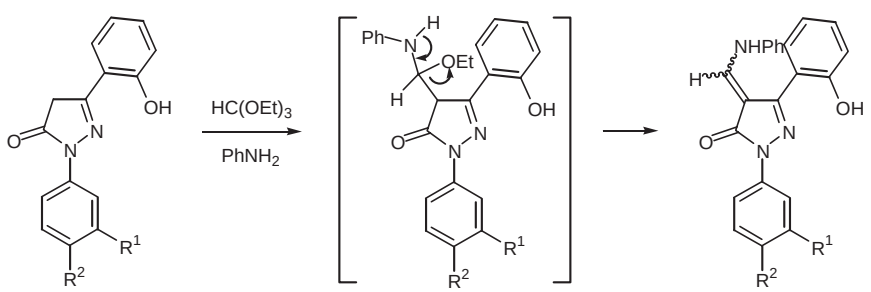
Scheme 117



Scheme 118

Wizinger and Angliker (66HCA2046) (Scheme 118) reported the only example of oxidative coupling between a 1,2-dihydropyrazol-3-one and a thiopyranylium salt. The reaction involved heating pyrazol-3-one **62** with 2,6-diphenylthiopyranylium perchlorate **385** in acetic acid and in the presence of sodium acetate to give, after atmospheric oxidation of intermediate **386**, 4-(2,6-diphenylthiopyran-4-ylidene)pyrazol-3-one **387**.

In one report (87TL5165, 89JPS239) (Scheme 119), *N*-phenylformimidic acid ethyl ester, generated *in situ* by heating under reflux triethyl orthoformate and aniline in

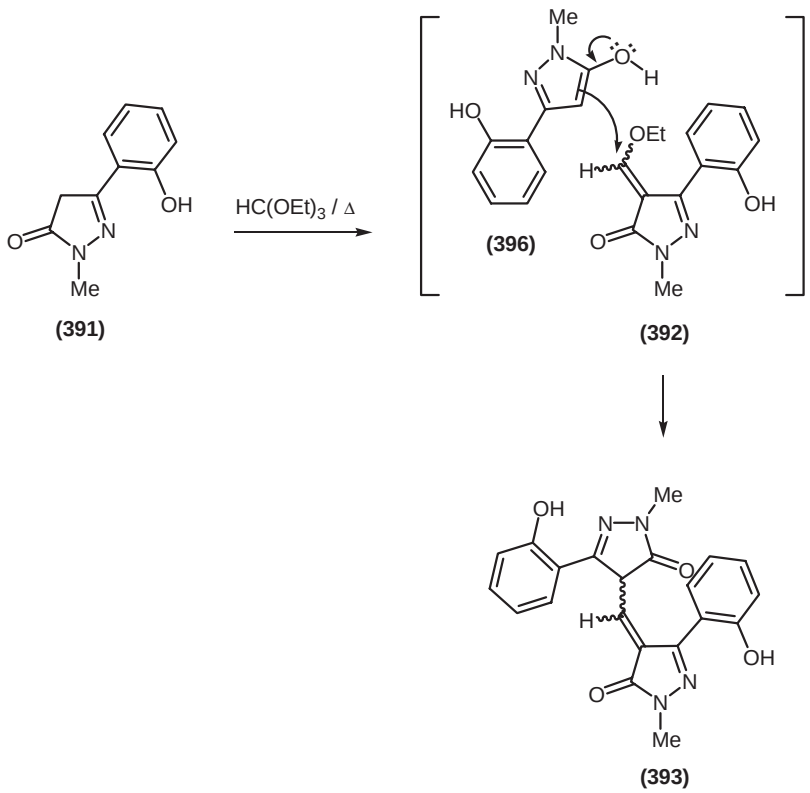


(a) $R^1 = R^2 = H$, **(b)** $R^1 = Me$, $R^2 = H$, **(c)** $R^1 = R^2 = H$, **(d)** $R^1 = Me$, $R^2 = H$, **(e)** $R^1 = H$, $R^2 = Cl$, **(f)** $R^1 = H$, $R^2 = Me$

Scheme 119

dry ethanol or toluene, was described to react with pyrazol-3-ones **388a–f** to give, via intermediate addition product **389** that loses ethanol, (*E*/*Z*)-4-phenylamino-methylenepyrazol-3-ones **390a–f**, in good to average yield.

When the condensation of two equivalents of pyrazol-3-one **391** was conducted in refluxing triethyl orthoformate without any amino compound, the reaction led to 4-[(pyrazol-4-yl)methylene]pyrazol-3-one **393** (85S548) (Scheme 120). The reaction can be envisaged initially to give (*E*/*Z*)-4-ethoxymethylene-pyrazol-3-one **392** followed by conjugate addition of **391** to the exocyclic double bond of **392** and by elimination of ethoxide ion to give product finally.

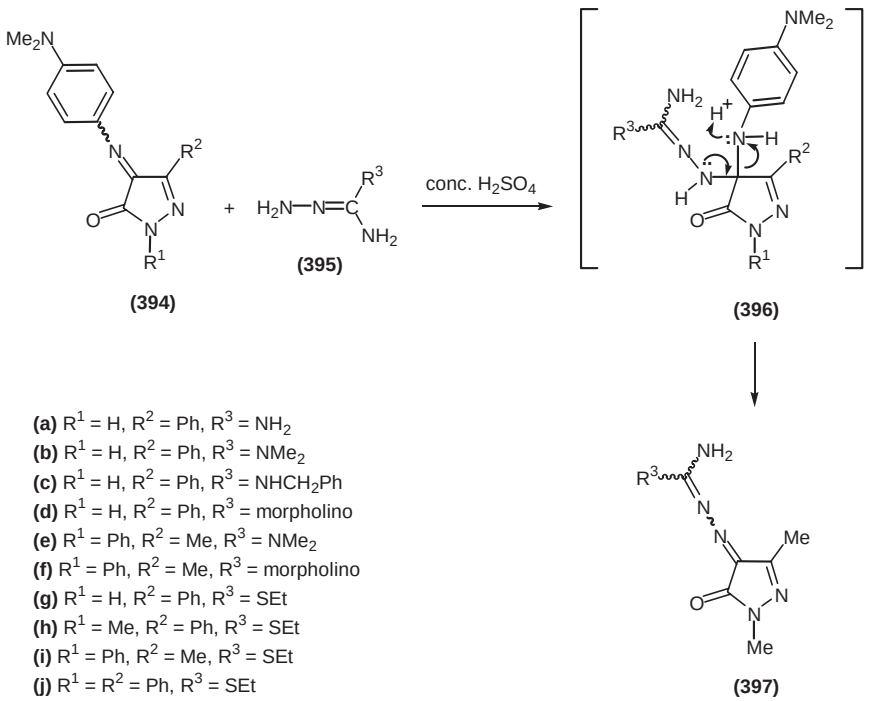


(391) (396) (392) (393)

Scheme 120

H. By Nucleophiles onto 4-(Substituted Methylene) Pyrazol-3-ones

Hydrazones and malononitrile can attack the imine carbon of 4-(arylimino)-pyrazol-3-ones resulting in an overall addition–elimination product. Heinisch (88JPR57) (Scheme 121) described the use of several hydrazone derivatives **395a–d**,**f** in their reaction with (*Z*/*E*)-4-(arylimino)pyrazol-3-ones **394a-j** in concentrated



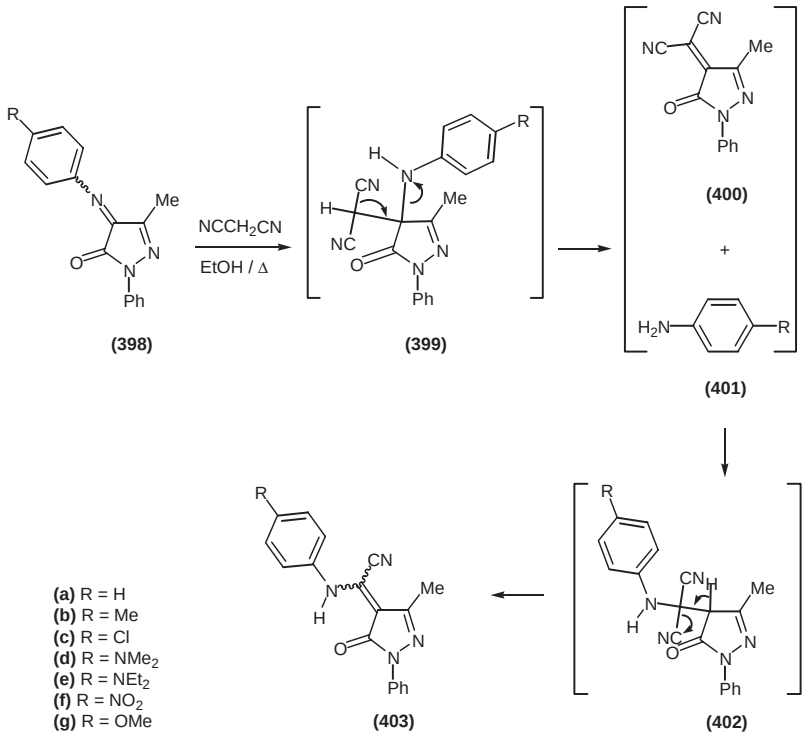
Scheme 121

sulfuric acid. It was postulated that in the first step hydrazones **395a**–**d**,**f** add to C4 of pyrazol-3-ones **394a-j** to give intermediate addition products **396a**–**j** that lose 4-dimethylaminoaniline to afford 4-{(*Z*/*E*)-2-[(*Z*/*E*)-amino(subsituted)methylidene]-hydrazono}-5-oxopyrazoles **397a**–**j**.

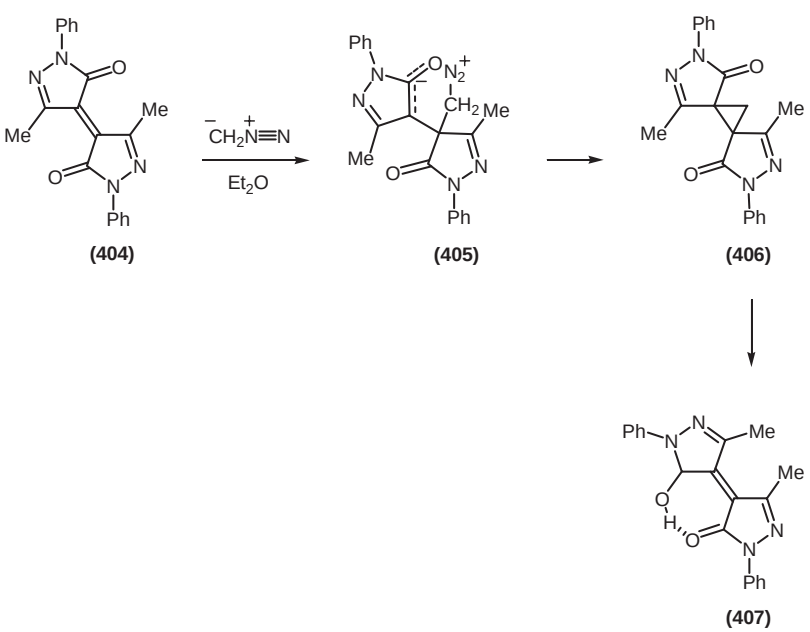
Hennig et al. (93JPR368) (Scheme 122) described the preparation of deeply colored 4-arylaminocyanomethylenepyrazol-3-ones **403a**–**g** by the reaction of malononitrile with 4-aryliminopyrazol-3-one **398a**–**g** in refluxing ethanol. Initially the reaction is postulated to give intermediate **398** that decomposes to dicyanomethylenepyrazol-3-one **400** together with eliminated anilines **401a**–**g**. Addition of the latter to the exocyclic double bond of intermediate **400** gives **402** that loses hydrogen cyanide to afford the products **403a**–**g**.

The reaction of 4,4′-bipyrazolylidene-3,3′-dione **404** with diazomethane was investigated by Hennig et al. (89JPR584) (Scheme 123). The mechanism proposed involves initial attack by diazomethane onto position 4 or 4′ of compound **404** to give intermediate inner salt **405**. Intramolecular cyclisation of the latter gave dispiroundeca-3,9-diene-1,7-dione **406** in 47% yield. This compound was found to be unstable upon standing at room temperature. When heated in ethanol it quickly isomerized into 4-(pyrazol-4-ylmethylene)pyrazol-3-one **407**, whose structure was unambiguously assigned by X-ray crystallography.

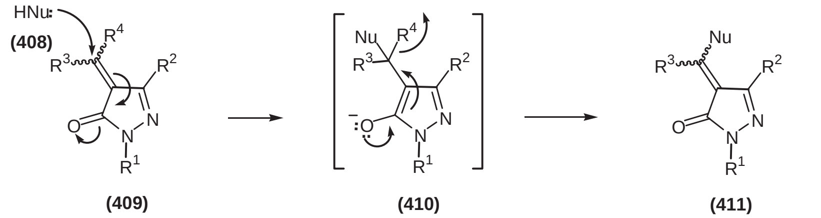
These reactions are characterized by a two step process in which conjugate addition of nitrogen or carbon nucleophiles **408a**–**e** to 4-(substituted methylene)-pyrazol-3-ones **409a**–**e**, is followed by the elimination of a small molecule from

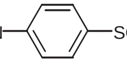


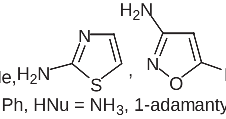
Scheme 122



Scheme 123



(a) R^1 = Ph, R^2 = Me, R^3 = H, R^4 = Me_2N, HNu = H_2N–  –SO_2R^5

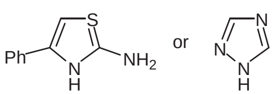
where R^5 = NH_2, N=C$(NH_2)_2$, H_2NCOMe,  Me or $H_2NC_6H_4OCH(Me)_2$

(b) R^1 = Ph, R^2 = Me, R^3 = H, R^4 = NHPh, HNu = NH_3, 1-adamantyl or piperidine

(c) R^1 = 4-ClC_6H_4, R^2 = Me, R^3 = H, R^4 = NH_2, HNu = piperidine, morpholine or 4-$FC_6H_4NH_2$

(d) R^1 = Ph, R^2 = Me, R^3 = R^4 = CN, HNu = 2-isopropyl$C_6H_4NH_2$, 3-$ClC_6H_4NH_2$,
R^1 = Ph, R^2 = n-C_3H_7, R^3 = R^4 = CN, HNu = $PhNH_2$, 2-$MeC_6H_4NH_2$, 3-$MeC_6H_4NH_2$, 2,4-$Me_2C_6H_3NH_2$, 2-$MeOC_6H_4NH_2$, 4-$MeOC_6H_4NH_2$, 2-isopropyl$C_6H_4NH_2$, 3-$ClC_6H_4NH_2$, 3,5-$(Cl)_2C_6H_3NH_2$, 4-$NO_2C_6H_4NH_2$,
R^1 = R^2 = Ph, R^3 = R^4 = CN, HNu = 3-$ClC_6H_4NH_2$,
R^1 = Ph, R^2 = NH_2, R^3 = R^4 = CN, HNu = $PhNH_2$, 3-$ClC_6H_4NH_2$, 3-$MeC_6H_4NH_2$, 2-$MeOC_6H_4NH_2$ or 4-$MeOC_6H_4NH_2$,

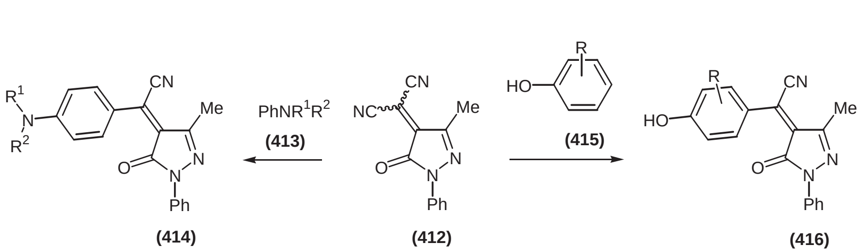
(e) R^1 = Ph, R^2 = Me, R^3 = R^4 = CN, HNu = $PhNH_2$, 2-$MeC_6H_4NH_2$, 4-$MeC_6H_4NH_2$, 2-$MeOC_6H_4NH_2$, 4-$MeOC_6H_4NH_2$, 2-$OHC_6H_4NH_2$, 4-$OHC_6H_4NH_2$, 4-$NH_2C_6H_4NH_2$, 4-$NO_2C_6H_4NH_2$, 2-$ClC_6H_4NH_2$, 4-$ClC_6H_4NH_2$, 3-$BrC_6H_4NH_2$, 4-$CO_2C_6H_4NH_2$, 2-$NH_2C_6H_4NH_2$, 2-$SHC_6H_4NH_2$, 1- or 2-naphthyl, $H_2NC_4H_9$, $H_2NC(Me)_3$, H_2NCH_2Ph, piperidine, 2- or 3-aminopyridine,



Scheme 124

intermediates **410a**–**e**, to give pyrazol-3-ones **411a**–**e** (75PHA582, 81M369, 86AP865, 88M993, 89LA1037) (Scheme 124).

Secondary and tertiary aromatic amines **413a**–**c** and activated phenols **415a**,**b** condense with 4-(dicyanomethylene)pyrazol-3-one **412** followed by hydrogen cyanide elimination to yield compounds **414a**–**c** and **416a**–**b**, respectively (89LA1037) (Scheme 125).



(a) R^1 = R^2 = Me, **(b)** R^1 = R^2 = Et, **(c)** R^1 = H, R^2 = Et **(a)** R = 2-Me, **(b)** R = 3-HO

Scheme 125

XII. Nucleophilic Addition

The reactions described in this section refer to addition of C4 of pyrazol-3-ones onto different types of electrophiles to form σ-bonds. Addition to α,β-unsaturated compounds may involve the elimination of small molecules from the electrophile. A rare case would involve a double nucleophilic reaction by the pyrazol-3-one to form a spiro compound.

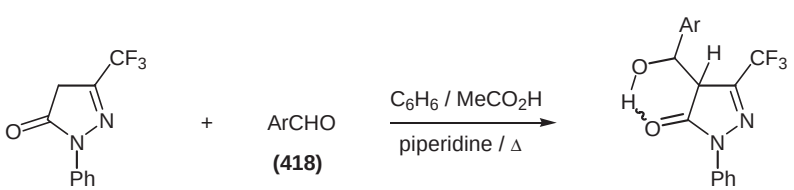
A. Of Pyrazol-3-ones to Aromatic Aldehydes

Zohdi and co-workers (92JCR(S)396, 92JCR(M)3015) (Scheme 126) have reported that reaction of pyrazol-3-one **417** with aldehydes **418a–d** in benzene containing acetic acid and piperidine gives the aldol- type products **419a–d** in good yields. In the I.R. spectra of the latter the presence of a broad absorption in the region 3400–2400 cm^{-1} and also the absenceof the typical pyrazol-3-one carbonyl absorption at around 1670 cm^{-1} suggests strong intramolecular hydrogen bonding.

Nucleophilic addition by a 1,2-dihydropyrazol-3-ones such as Grignard reagent **420** to benzaldehyde gave 4-(hydroxyphenylmethyl)pyrazol-3-one **421** (00JOC4618) (Scheme 127).

B. Of Pyrazol-3-ones to Imines and Iminium Salts

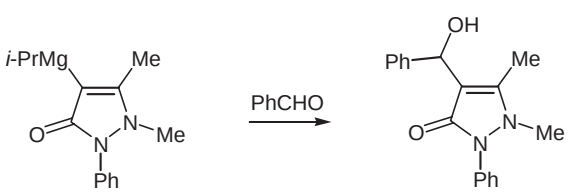
The hetero-Michael addition of 2,4-dihydropyrazol-3-one **422a–h** to trichloro-acetaldimine derivatives **423a–h** takes place best in apolar aprotic solvents and the



(417) **(419)**

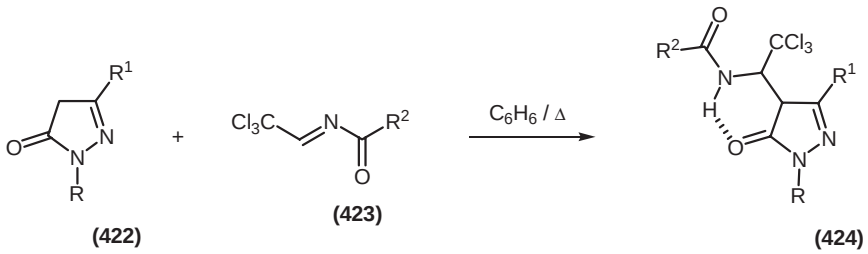
(a) Ar = Ph, **(b)** Ar = 4-MeC_6H_4, **(c)** Ar = 4-$MeOC_6H_4$, **(d)** Ar = 4-ClC_6H_4

Scheme 126



(420) **(421)**

Scheme 127



(a) R = Ph, $R^1 = R^2$ = Me, **(b)** R = R^2 = Ph, R^1 = Me, **(c)** R = Ph, R^1 = Me, R^2 = EtO,
(d) R = Ph, R^1 = Et, R^2 = Me, **(e)** R = Ph, R^1 = *t*-Bu, R^2 = Me, **(f)** R = R^1 = Ph, R^2 = Me,
(g) R = R^1 = R^2 = Ph, **(h)** R = 2,4,6-$Cl_3C_6H_2$, R^1 = R^2 = Me,

Scheme 128

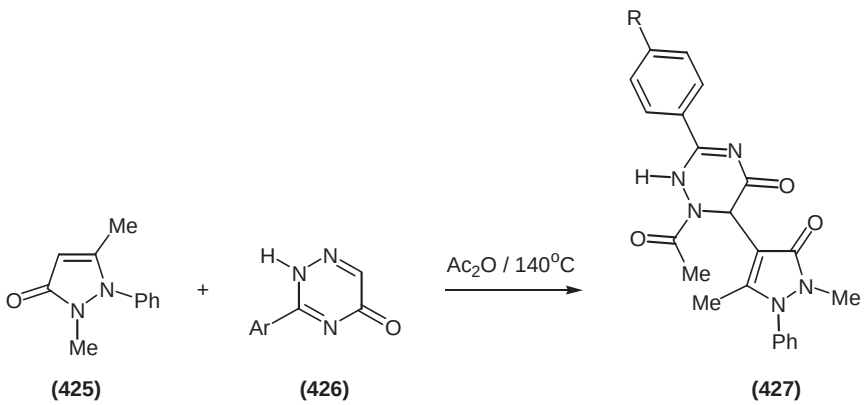
2,4,5-trisubstitutedpyrazol-3-ones **424a**–**h** are obtained in 50–90 yields (87S493) (Scheme 128).

The addition of 1,2-dihydropyrazol-3-one **425** onto 3-aryltriazin-5(2*H*)-ones **426a**,**b** required heating at 140 °C in acetic anhydride. In the products **427a**,**b** thus obtained, spectroscopic methods showed that addition occurred between C4 of the pyrazolone and C6 of the 1,2,4-triazinone, activated by acetylation at N1 (97JHC1013) (Scheme 129).

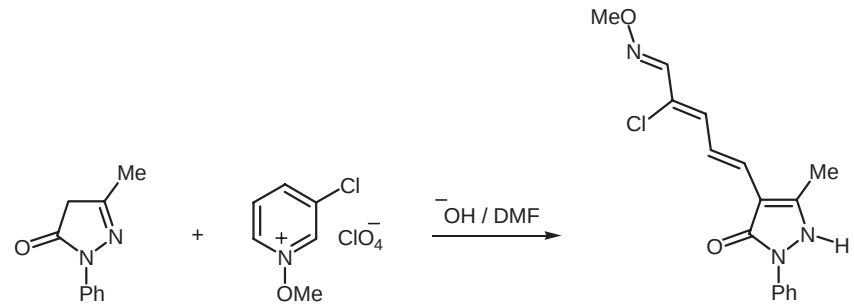
The reaction of the carbanion of pyrazol-3-one **62** generated by hydroxide ion adds to C-5 of 3-chloro-1-methoxypyridinium perchlorate **428** in DMF and then undergoes base induced ring cleavage to yield the 1,2-dihydropyrazol-3-one **429** in only 33% yield (82AP817) (Scheme 130).

The absence of strong base in the reaction between 1,2-dihydropyrazol-3-one **70** and *N*-methoxy-4-cyanoquinolinium perchlorate **430** in DMF afforded the simple addition product **431** in 70% yield (88AP897) (Scheme 131).

The addition of Grignard reagent **420** to imine **432** gave pyrazol-3-one **433** (00JOC4618) (Scheme 132).

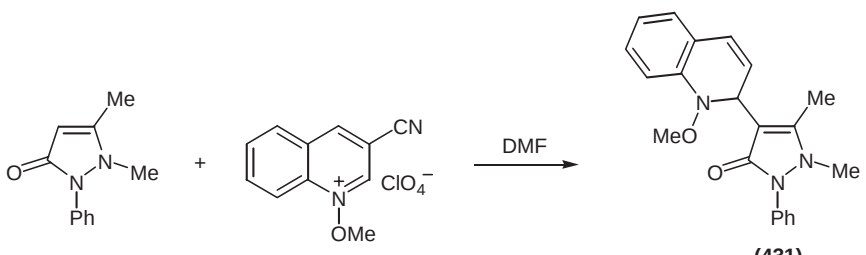


Scheme 129



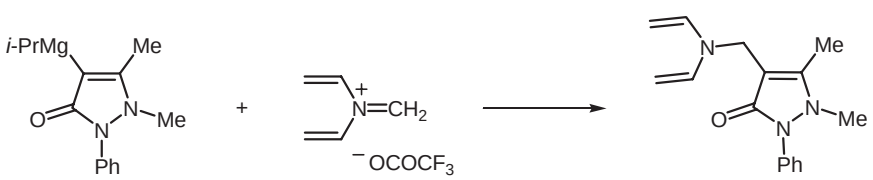
(62) (428) (429)

Scheme 130



(70) (430) (431)

Scheme 131

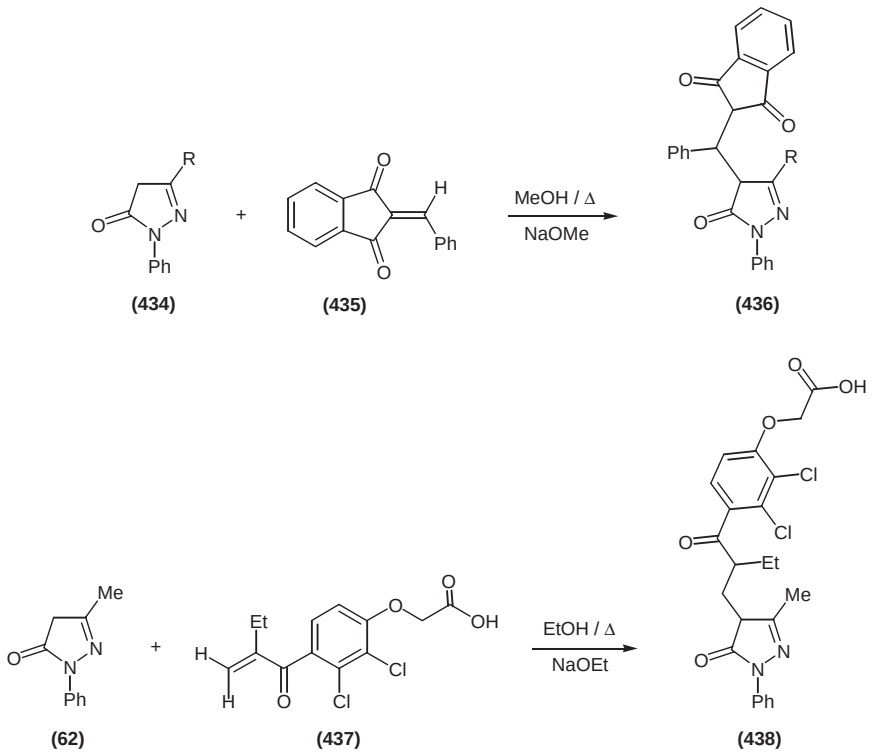


(420) (432) (433)

Scheme 132

C. Michael Addition of Pyrazol-3-ones to α,β-Unsaturated Compounds

In this category of compounds 2,4-dihydropyrazol-3-ones are the active methylene compounds that react nucleophilically at C4. A characteristic reaction is the addition of pyrazol-3-ones **434a**,**b** to 2-benzylideneindan-1,3-dione **435** in boiling methanol containing sodium methoxide to give the indan-1,3-dione derivatives **436a**,**b** in 65 and 77% yield, respectively (90PHA255) (Scheme 133). Under analogous conditions pyrazol-3-one **62** and α,β-unsaturated ketone **437** gave only 31% of 1,2-dihydropyrazol-3-one addition product **438** (97PHA32).

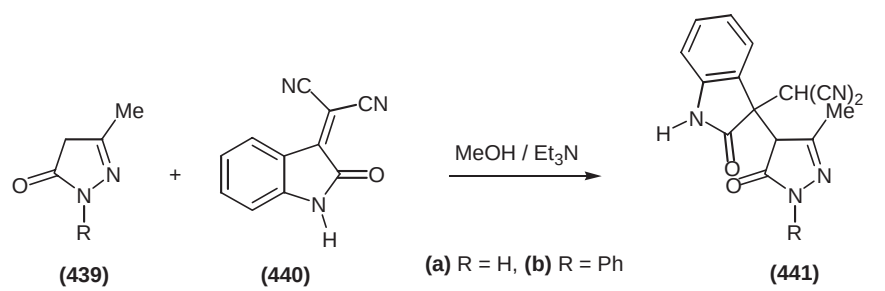


Scheme 133

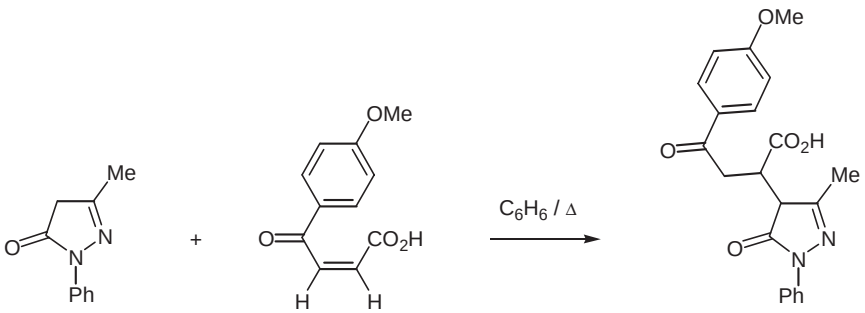
Addition of pyrazol-3-ones **439a**,**b** to 2-(2-oxoindol-3-ylidene)malononitrile **440** gave adduct **441** (82CL1123) (Scheme 134).

Ghani (91BCJ2032) (Scheme 135) prepared the 4-oxo-4-(4-methoxyphenyl)butyric acid derivative **443** by heating in benzene pyrazol-3-one **60** with 4-(4-methoxyphenyl)-4-oxobut-2-enoic acid **442**.

Another example of a Michael addition of a pyrazol-3-one onto α,β-unsaturated derivatives is the reaction of compound **444** with arylidenemalononitriles **445a** that gave pyrazol-3-one adducts **446a**, carried out in boiling methanol containing a catalytic amount of morpholine (83JOU2291) (Scheme 136).

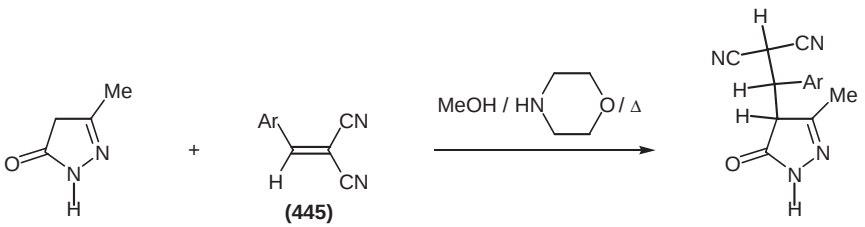


Scheme 134



(60) (442) (443)

Scheme 135



(444) (445) (446)

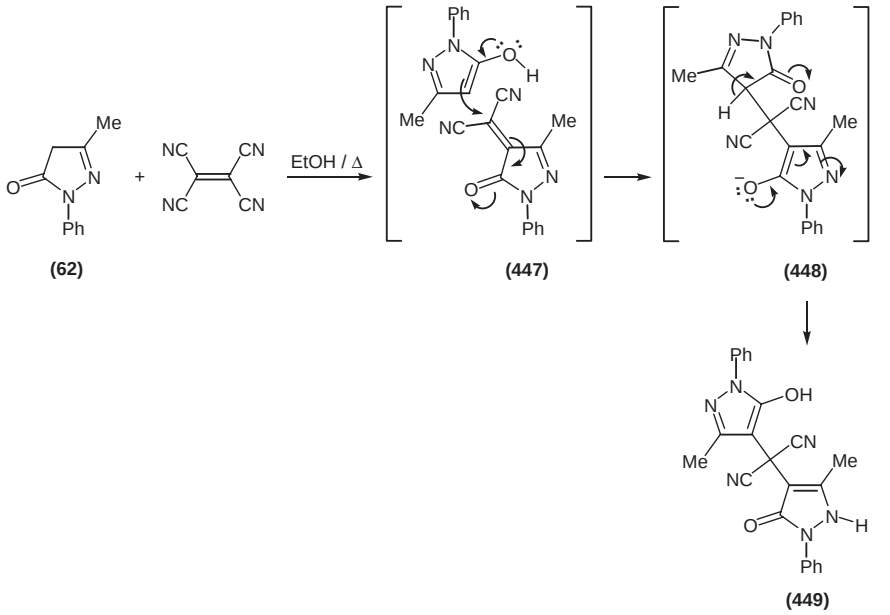
(a) Ar = 2-MeC_6H_4, 4-MeC_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 3-HOC_6H_4, 4-HOC_6H_4, 4-$(Me)_2NC_6H_4$, 4-$(Et)_2NC_6H_3$, 2,4-$(MeO)_2C_6H_3$ or 3-HO-4-$MeOC_6H_3$

Scheme 136

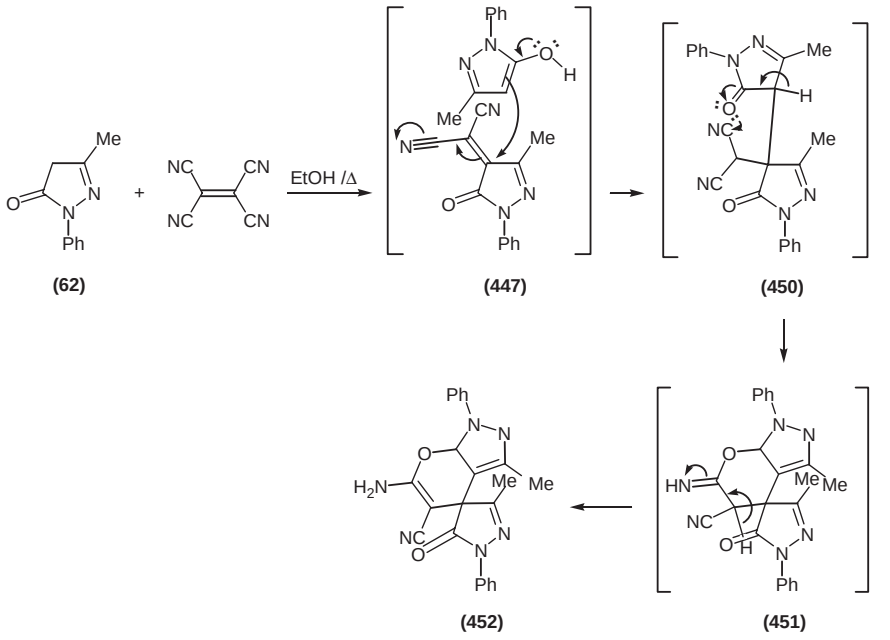
D. By Addition-Elimination to α,β-Unsaturated Compounds

Abdel-Galil et al. (88BSF658) (Scheme 137) reported that heating pyrazol-3-one **62** with tetracyanoethylene in ethanol gave 2-(3-oxopyrazol-4-yl)-2-(pyrazol-4-yl)-malononitrile **449**. The reaction initially gives intermediate **447** followed by conjugative addition of a second molecule of pyrazol-3-one **62** to the exocyclic alkene bond of **447** that leads to addition product **448**, which then tautomerises to stable product **449**.

Twelve years later Guard and Steel (01ARK732) (Scheme 138) proved that the reaction of tetracyanoethylene with pyrazol-3-one **62** in boiling ethanol affords spiro{pyrano[2,3-*c*]pyrazole-4,4′-pyrazo}-3′-one **452** and not malononitrile **447** (Scheme 138) as reported by Abdel-Galil et al. (88BSF658). The structure of **452** was unambiguously assigned by an X-ray crystal structure. Compound **452** was independently proposed by Metwally et al. (91LA961) as the product of the reaction between **447** and **62**. For the formation of **452** it was proposed that initially reaction of **62** and tetracyanoethylene gives intermediate **447**, as previously, followed by the addition of a second molecule of **62** to C4 of **447**. Addition of a carbonyl oxygen to a



Scheme 137



Scheme 138

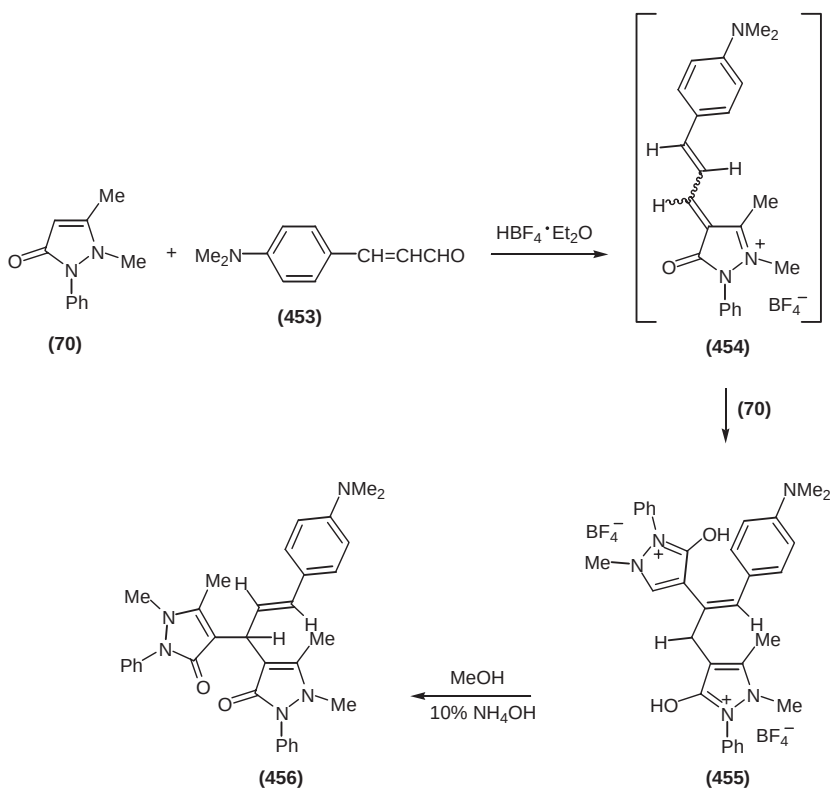
nitrile group in **450** leads to cyclized intermediate **451**, which then tautomerizes to spiropyrazolone **452**.

This type of addition also works for 1,2-dihydropyrazolones as demonstrated by Akgün and Pindur (84M197) (Scheme 139). They described that two equivalents of pyrazol-3-one **70** react with one equivalent of 3-[4-(dimethylamino)phenyl]acrylaldehyde **453** in the presence of tetrafluoroboronic acid–diethyl ether complex to afford, via the methylidene intermediate **454** the salt **455**. Addition of methanol containing 10% ammonia gave the 4-[1-(3-oxopyrazol-4-yl)-3-phenylprop-2-enyl]-pyrazol-3-one **456**.

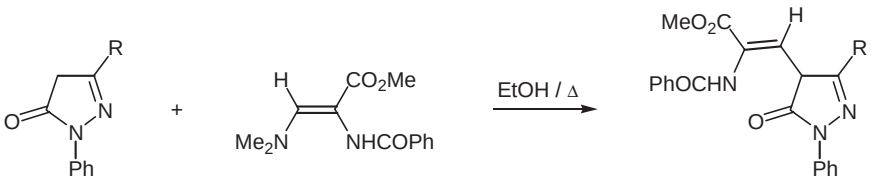
The addition-elimination reaction between pyrazol-3-one **457** and (2*Z*)-2-(benzoylamino)-3-(dimethylamino)acrylate **458** gave pyrazol-3-one **459**, with loss of dimethylamine (89JHC1273, 91JHC1961, 00SL1077) (Scheme 140).

Abarbi et al. (00JOC4618) (Scheme 141) prepared Grignard reagent **420** by treatment of the appropriate 4-iodopyrazol-3-one with diisoropyl magnesium. It then reacted with aliphatic aldehydes **460a–d** or cyclopentanone to afford the corresponding 4-(alk-1-enyl)pyrazol-3-ones **461a–d** and 4-(cyclopent-1-enyl)pyrazol-3-one **462**.

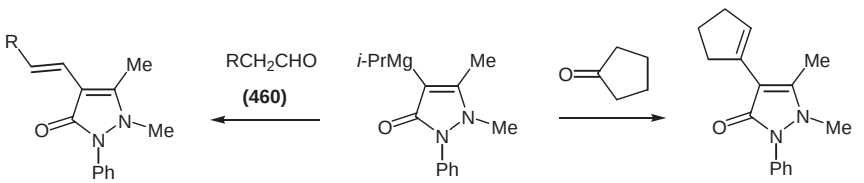
Orlova and Linerva (66JOU1103) and Pavlova and Samartseva (66JOU1686) (Scheme 142), working independently, heated pyrazol-3-one **62** with diaryl ketones



Scheme 139

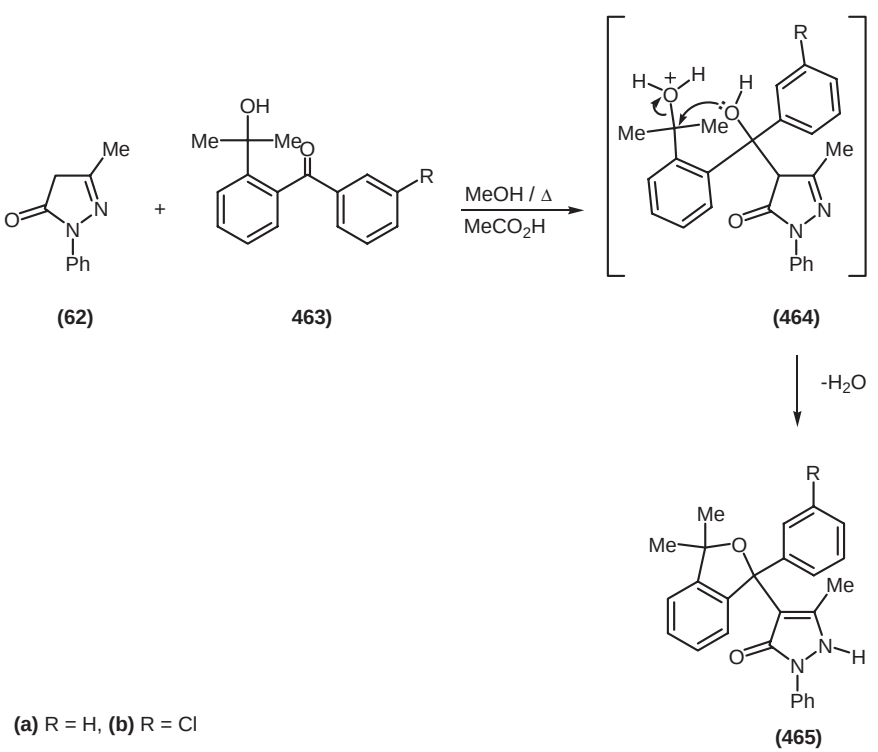


Scheme 140



(a) R = Et, **(b)** R = *n*-Pr, **(c)** R = Octyl, **(d)** R = (*E*)-2'-Octenyl

Scheme 141



(a) R = H, **(b)** R = Cl

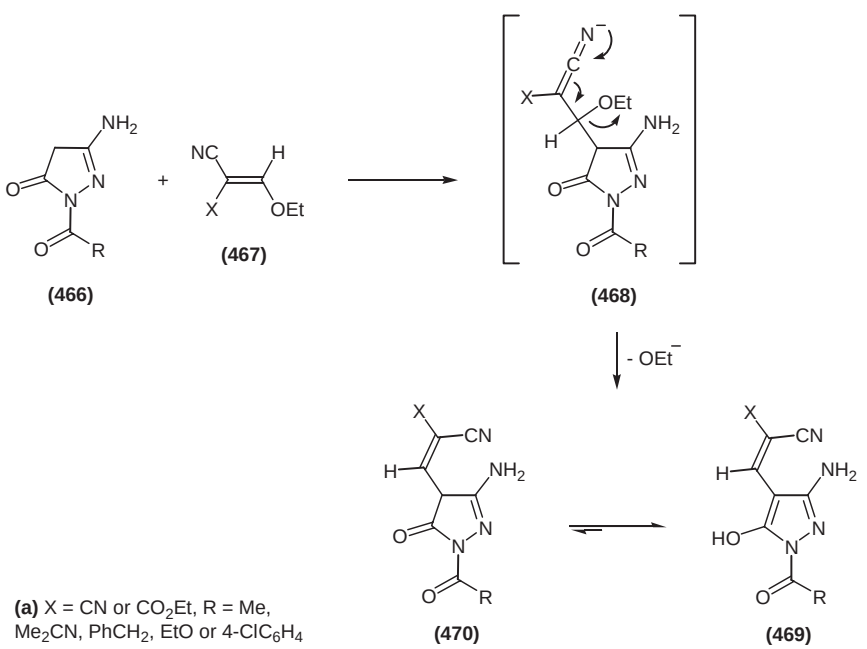
Scheme 142

463a,**b** in methanol containing acetic acid and obtained the 4-(2-benzofuran-1-yl)-1,2-dihydropyrazol-3-ones **464a**,**b**. The reaction proceeds by addition of the pyrazol-3-one onto the ketone to give intermediate addition products **465** which condensed intramolecularly.

In the reaction of 1-acyl-3-aminopyrazol-3-one **466a** with ethyl ethoxymethylene-cyanoacetate **467a** (X = CN) or ethoxymethylenemalononitrile **467a** (X = CO_2Et) initial addition gives intermediate **468** which then loses ethoxide anion to furnish a tautomeric mixture of pyrazole **469a**/pyrazol-3-one **470a**. Spectroscopic studies have shown that the pyrazole tautomer predominates almost exclusively (94JHC925) (Scheme 143).

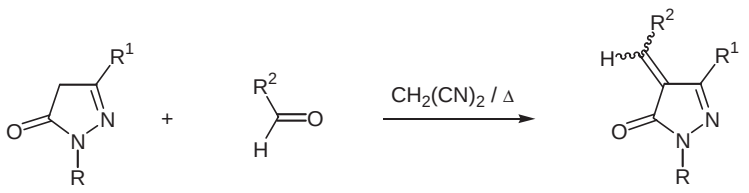
Nucleophilic addition to α,β-unsaturated compounds by pyrazol-3-ones can occur in an indirect manner. This category of reactions involves first condensation of a pyrazol-3-one to an aldehyde or addition–elimination of a pyrazol-3-one to an appropriate α,β-unsaturated compound to give an intermediate 4-methylidenepyrazol-3-one derivative, followed by nucleophilic addition of a second molecule of pyrazol-3-one to the latter, to afford methylene or substituted methylenebipyrazol-3-ones. Thus reaction of pyrazol-3-ones **471a**,**b** with formaldehyde in the presence of malononitrile can be explained by the formation first of methylidene intermediate **472** followed by the addition of a second molecule of **471** to **472** to afford the bipyrazol-3-one adducts **473a**,**b** (83JOU2291, 91JCR(M)1019) (Scheme 144).

The reaction of tetracyanoethylene with pyrazol-3-ones **474a**,**b** in ethanol at 40 °C is another example of this overall addition reaction and affords the bis(3-oxopyrazol-4-yl) (isocyano)acetonitriles **476a**,**b**, via the intermediated condensation adduct **475** (73CB914) (Scheme 145).



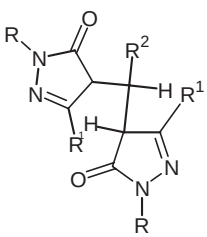
(a) X = CN or CO_2Et, R = Me, Me_2CN, $PhCH_2$, EtO or 4-ClC_6H_4

Scheme 143



(471) **(472)**

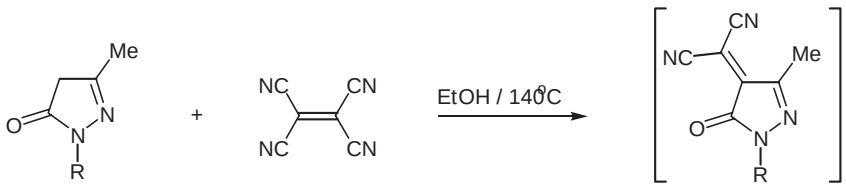
(471)



(a) R = H, R^1 = Me, R^2 = Ph, 2-MeC_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 3-$NO_2C_6H_4$,
(b) R = Ph, R^1 = Me, R^2 = H

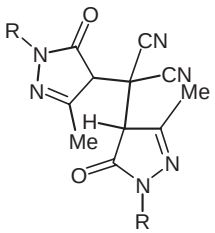
(473)

Scheme 144



(474) **(475)**

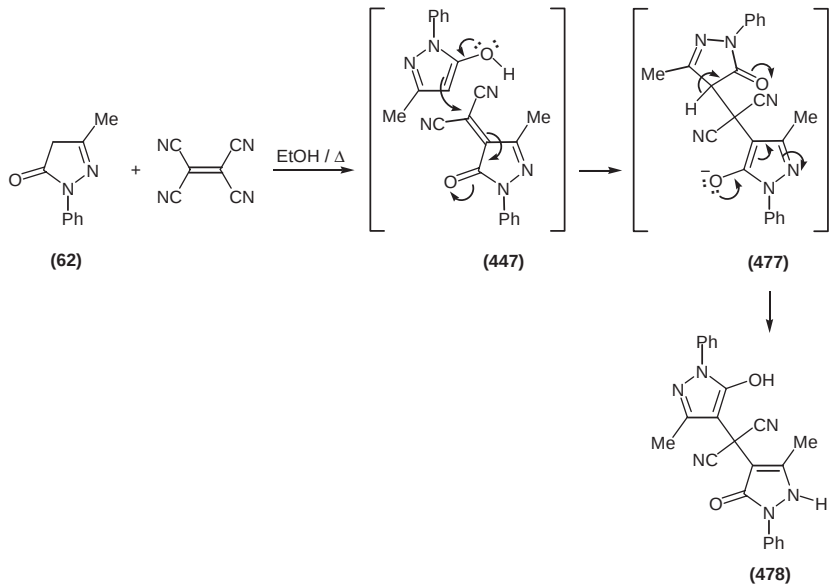
(474)



(a) R = Ph, **(b)** R = 4-MeC_6H_4

(476)

Scheme 145



Scheme 146

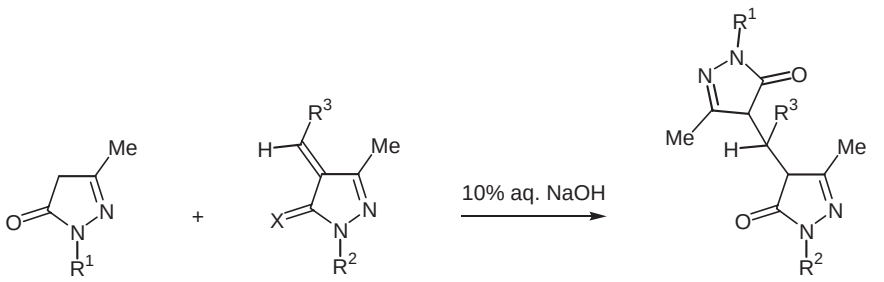
Fifteen years later, Abdel-Galil et al. (88BSF658) (Scheme 146) reported that heating pyrazol-3-one **62** with tetracyanoethylene in ethanol gave 2-(3-oxopyrazol-4-yl)-2-(pyrazol-4-yl)malononitrile **478**. The reaction initially gives intermediate **447** followed by conjugative addition of a second molecule of pyrazol-3-one **62** to the exocyclic alkene bond of **447** that leads to addition product **477**, which then tautomerizes to stable product **478**.

Reactions of this type also involve 4-arylidenepyrazol-3-ones (or thiones) that have been isolated instead of being formed *in situ*. Thus pyrazol-3-ones **479a**,**b** were treated with 4-arylidenepyrazol-3-ones **480a** in 10% aqueous sodium hydroxide and 4-arylidenepyrazol-3- thiones **480b** in boiling ethanol, respectively, to afford in good yield 4,4′-benzylidenebipyrazol-3-ones **481a** (69JIC893) and 4,4′-benzylidenebi-pyrazol-3-thiones **481b** (84JIC640) (Scheme 147).

The isolation of pyrazolylpyrazol-3-one/bis(pyrazolyl)methane perchlorates **483a** was made possible by reaction of the stable benzylidenepyrazol-3-one perchlorate **482a** with pyrazol-3-one **70** (83M219) (Scheme 148). Compound **482a** was obtained by the reaction of **70** with 4-dimethylaminobenzaldehyde **484a** in methanol containing perchloric acid. When this reaction was performed with benzaldehyde **484b** or with arylaldehydes **484c**,**d** with less cation stabilizing groups, the result was direct isolation of methane perchlorates **483b**–**d**, respectively.

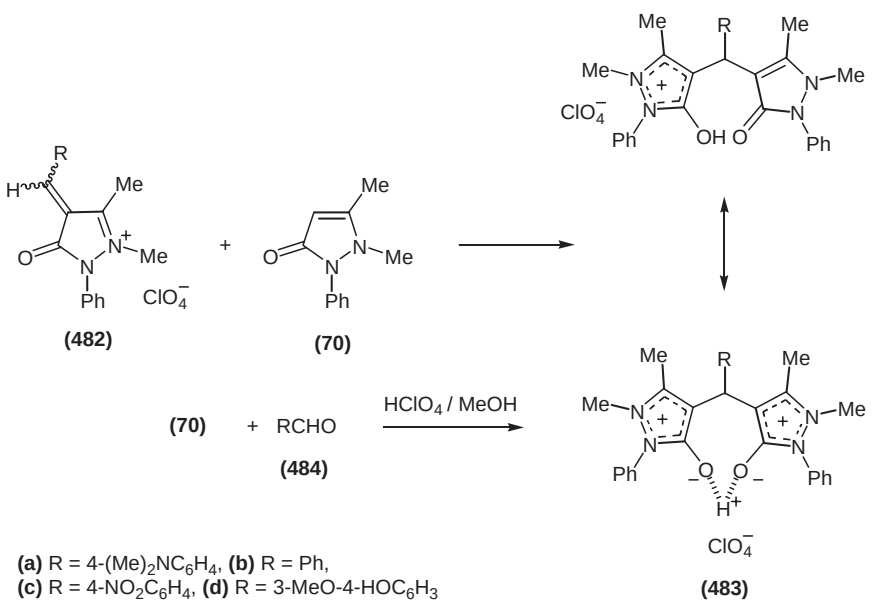
E. Inter- and Intramolecular Addition of Nucleophiles to c-4 of Pyrazol-3-ones

The addition of chloroacetyl chloride to 4-(4-dimethylamino-phenylimino) pyrazol-3-one **484a**,**b** in dry 1,4-dioxane in the presence of triethylamine was



(a) X = O, $R^1 = R^2$ = Ph, R^3 = Ph, 4-ClC_6H_4 or 3-$NO_2C_6H_4$,
(b) X = S, R^1 = H, R^2 = Ph or $R^1 = R^2$ = Ph, R^3 = Ph, 2-HOC_6H_4
or 3-HOC_6H_4, 4-HOC_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$ or $OCH_2C_6H_4$

Scheme 147

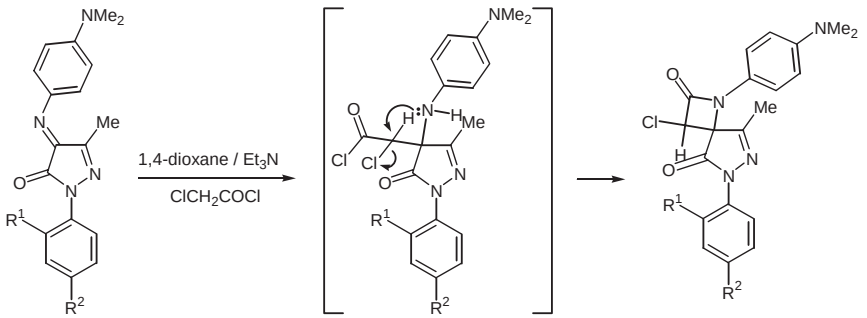


(a) R = 4-$(Me)_2NC_6H_4$, **(b)** R = Ph,
(c) R = 4-$NO_2C_6H_4$, **(d)** R = 3-MeO-4-HOC_6H_3

Scheme 148

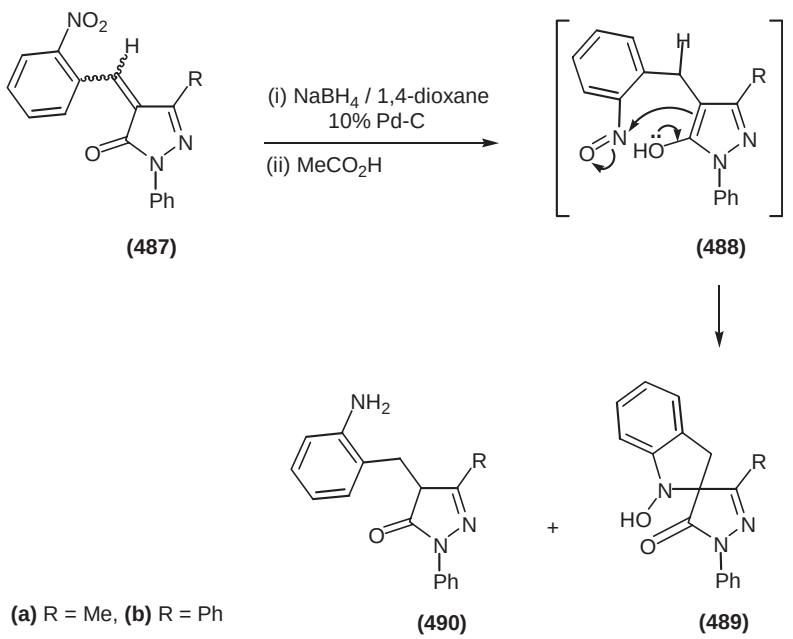
postulated to give adducts **485a**,**b** that cyclized by intramolecular acyl substitution to the spiroazetidinonepyrazol-3-ones **486a**,**b** in 35 and 40% yield, respectively (79JPR870) (Scheme 149)

The reduction of 4-[(2-nitrophenyl)methylidene]pyrazol-3-ones **487a**,**b** by sodium borohydride and 10% palladium-on-charcoal in 1,4-dioxane followed by acetic acid treatment, afforded mixtures containing spiroindolepyrazol-3-ones **489a**,**b** and 4-(2-aminobenzyl)pyrazol-3-ones **490a**,**b** (75CJC3645) (Scheme 150). A plausible explanation for the formation of derivatives **489** is concomitant reduction of the



(a) $R^1 = R^2 = H$, **(b)** $R^1 = R^2 = NO_2$

Scheme 149



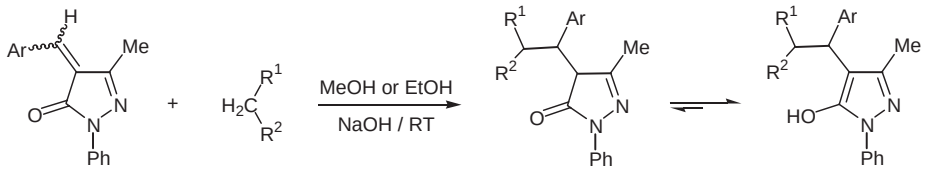
(a) R = Me, **(b)** R = Ph

Scheme 150

exocyclic double bond, considered as part of an α,β-unsaturated system, and reduction of the nitro to a nitroso group and then addition of C4 of the pyrazole as an enol to the nitroso group.

F. Michael Additions to Pyrazol-3-ones

Conjugate addition readily occurs onto 4-substituted methylenepyrazol-3-ones since the exocyclic double bond and the carbonyl group of these compounds act as a



(491) (492)

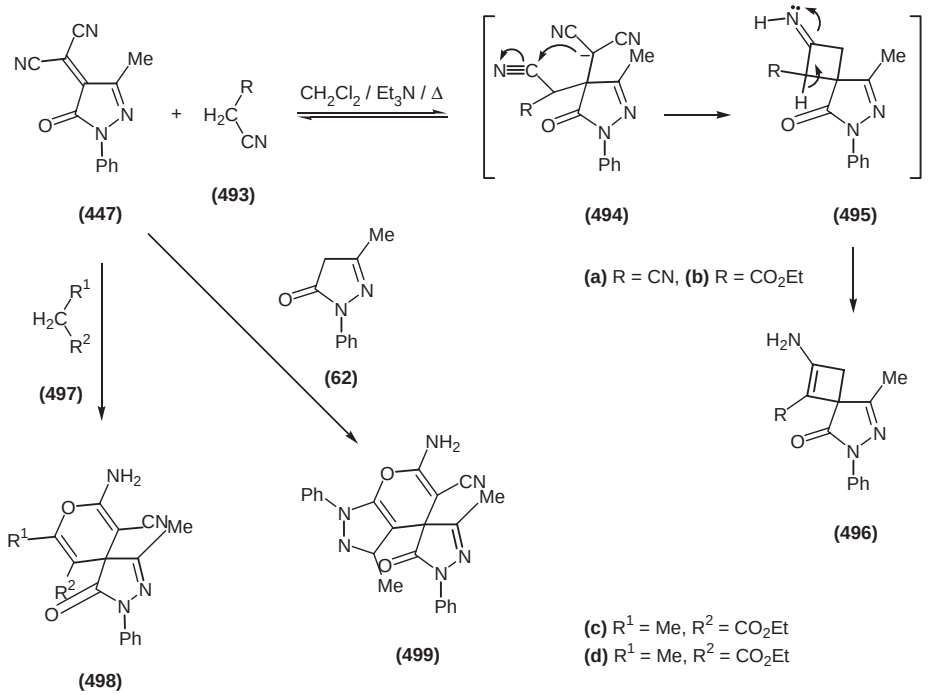
(a) Ar = 4-MeC_6H_4, R^1 = R^2 = CN, **(b)** Ar = 4-$MeOC_6H_4$, R^1 = R^2 = CN, **(c)** Ar = 4-MeC_6H_4, R^1 = R^2 = CO_2Me, **(d)** Ar = 4-$MeOC_6H_4$, R^1 = R^2 = CO_2Me, **(e)** Ar = 4-MeC_6H_4, R^1 = R^2 = CO_2Et, **(f)** Ar = Ph, R^1 = CN, R^2 = $CONH_2$, **(g)** Ar = 4-MeC_6H_4, R^1 = CN, R^2 = $CONH_2$, **(h)** Ar = 4-$MeOC_6H_4$, R^1 = CN, R^2 = $CONH_2$, **(i)** Ar = Ph, R^1 = CN R^2 = CO_2Et, **(j)** Ar = 4-MeC_6H_4, R^1 = CN, R^2 = COEt

Scheme 151

typical α,β-unsaturated group. Initial addition by a nucleophile may be followed by an intramolecular addition or substitution to give a spiropyrazol-3-one.

The reaction of (*E*/*Z*)-4-arylidenepyrazol-3-ones **491a–c** with reactive methylene compounds such as diethyl or dimethyl malonate, ethyl cyanoacetate or cyanoacetamide in alcoholic solution containing sodium hydroxide afforded the corresponding addition products **492c–j**. These adducts were found to be almost exclusively enol tautomers (79AP478) (Scheme 151).

Metwally et al. (91LA961) (Scheme 152) reacted 4-(dicyanomethylene)pyrazol-3-one **447** with malononitrile **493a** or ethyl cyanoacetate **493b** in dichloromethane



(447) (493) (494) (495)

(a) R = CN, **(b)** R = CO_2Et

(497) (62) (496)

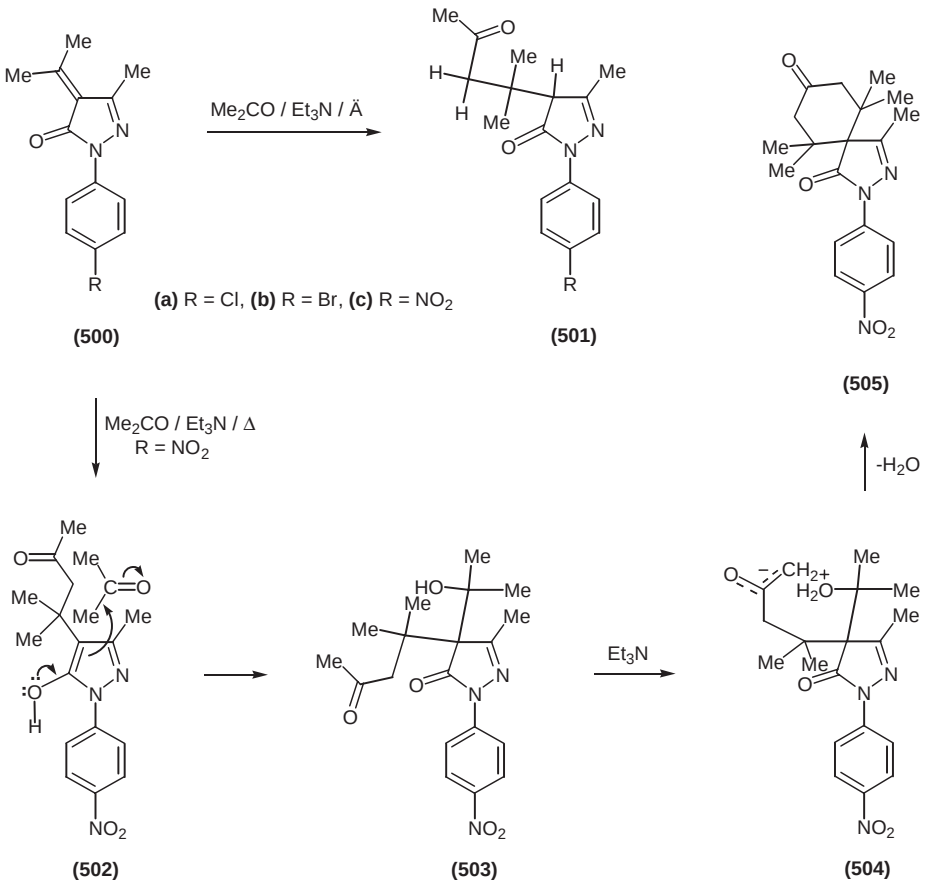
(498) (499)

(c) R^1 = Me, R^2 = CO_2Et
(d) R^1 = Me, R^2 = CO_2Et

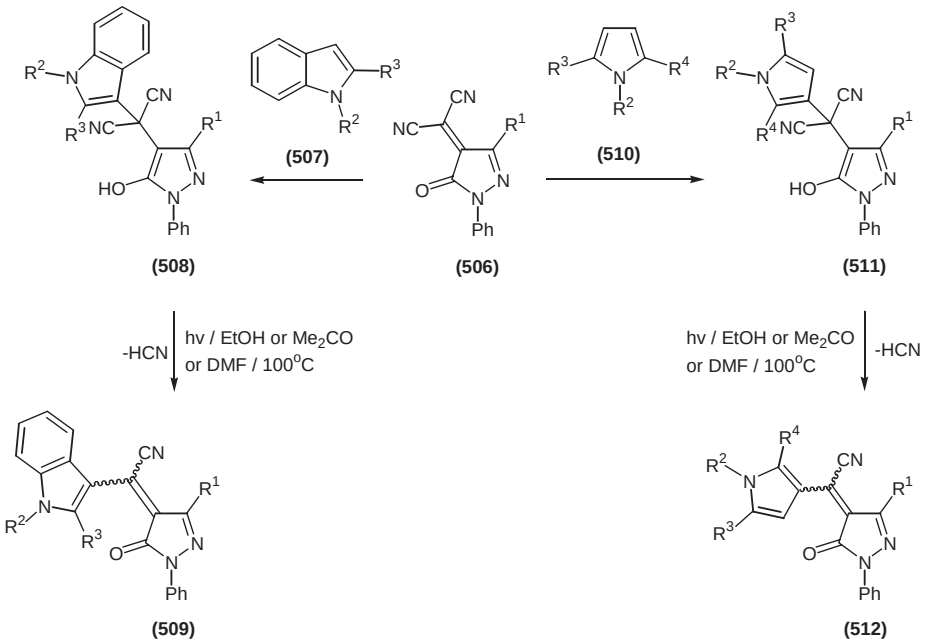
Scheme 152

containing triethylamine and obtained stable spiropyrazol-3-ones **496a**,**b**. The formation of these adducts was explained by a 1,2-addition pathway where initial addition of the carbanionic compound on the exocyclic double bond gives intermediate **494** which cyclises to **495** and then tautomerises. In the case of active methylene derivatives capable of enolization, such as ethyl acetoacetate **497c** ($R^1 = MeCO$, $R^2 = CO_2Et$), acetylacetone **497d** ($R^1 = R^2 = MeCO$) and pyrazol-3-one **62**, reaction with **447** afforded, as sole products, the spiro-pyrazol-3-ones **498c**,**d** and **499**, respectively.

Matsugo and Takamizawa (86JHC1159) (Scheme 153) treated 4-(1-methylethylidene)pyrazol-3-ones **500a**,**b** with acetone in refluxing triethylamine and obtained the addition products **501a**,**b** in 80 and 77% yield respectively. However pyrazol-3-one **500c** under the same conditions gave the spiropyrazol-3-one derivative **505** in 63% yield. The formation of **505** can be explained by the initial addition of acetone carbanion to the exocyclic double bond to give 3-hydroxypyrazol **502**, nucleophilic addition of C4 of the latter to a second molecule of acetone leading to **503**, enolisation of **503** to **504** and intramolecular condensation to **505**.



Scheme 153



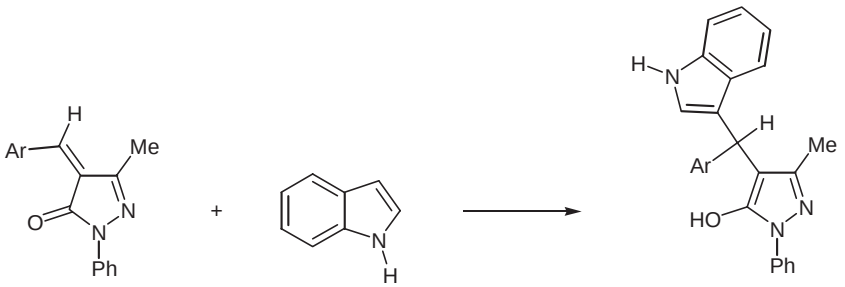
(a) R^1 = Me, **(b)** R^1 = Ph, **(c)** R^1 = Me, $R^2 = R^3$ = H, **(d)** $R^1 = R^2$ = Me, R^3 = H,
(e) $R^1 = R^3$ = Me, R^2 = H, **(f)** $R^1 = R^2 = R^3$ = Me, **(g)** R^1 = Ph, $R^2 = R^3$ = Me,
(h) R^1 = Me, $R^2 = R^3 = R^4$ H, **(i)** $R^1 = R^2$ = Me, $R^3 = R^4$ = H,
(j) R^1 = Me, R^2 = H, $R^3 = R^4$ = Me, **(k)** $R^1 = R^2 = R^3 = R^4$ = Me,
(l) R^1 = Ph, R^2 = Me, $R^3 = R^4$ H

Scheme 153 (Continued)

The addition of indoles **507c–h** and pyrroles **510i–m** to 4-(dicyanomethylene) pyrazol-3-ones **506a,b** gives (pyrazol-4-yl)(indolyl or pyrrol-3-yl)malononitriles **509c–h** and **511i–m**, respectively. Malononitriles **508c–h** and **511i–m** were subjected to either photolysis in ethanol or acetone, or thermolysis in DMF at 100 °C to yield, after elimination of hydrocyanic acid, (*E*/*Z*)-4-methylenepyrazol-3-ones **509c–h** and **512i–m**, respectively. An NMR study of compounds **509d** and **512i,j** showed that they exist as *E*/*Z* isomer mixtures. The ratio of *E*/*Z* isomers was found to be about 70/30. UV–VIS data of several compounds are discussed by means of AM1 and INDO/S-CI calculations. An X-ray crystallographic analysis of compounds **509a** is presented (92LA7) (Scheme 154).

In another example of the use of indole as the nucleophile, solid reactions between 4-arylidenepyrazol-3-ones **513a–k** and excess indole were carried out by grinding the reactants and allowing the reaction to proceed at room temperature. The 1-(3-indolyl)-1-(pyrazole-4-yl)methanes **514a–k** were obtained in 41–67% yield (99JHC697) (Scheme 154).

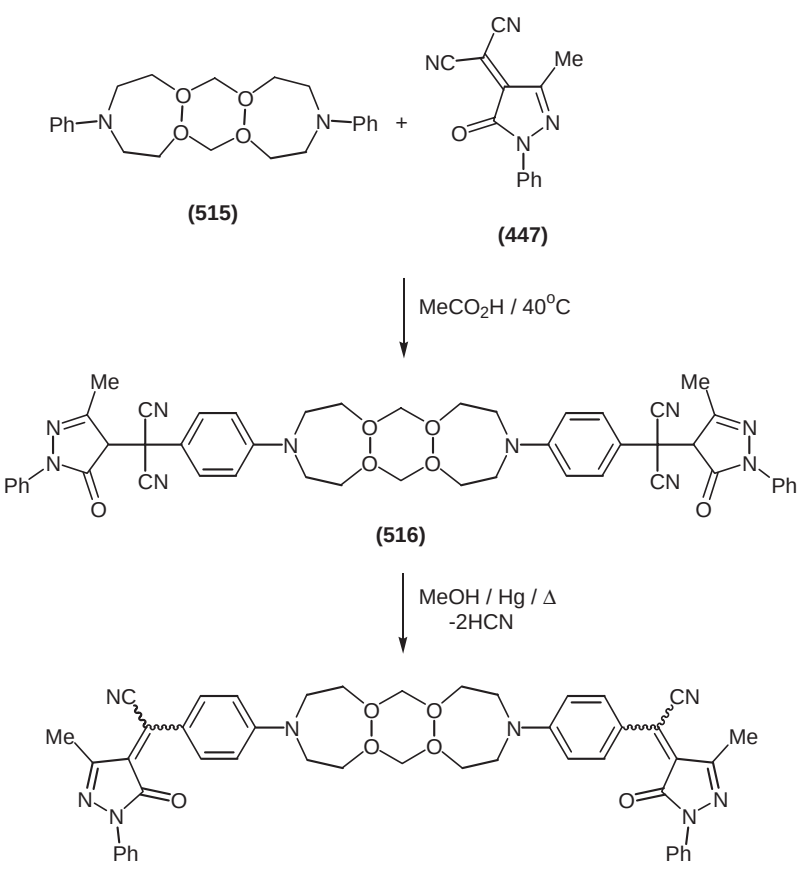
Junek et al. (92M581) (Scheme 155) demonstrated that the reaction of *N*,*N*′-diphenyldiaza-18-crown-6 **515** with pyrazol-3-one **447** in acetic acid at 40 °C afforded addition product **515** which could be converted into the



(513) **(514)**

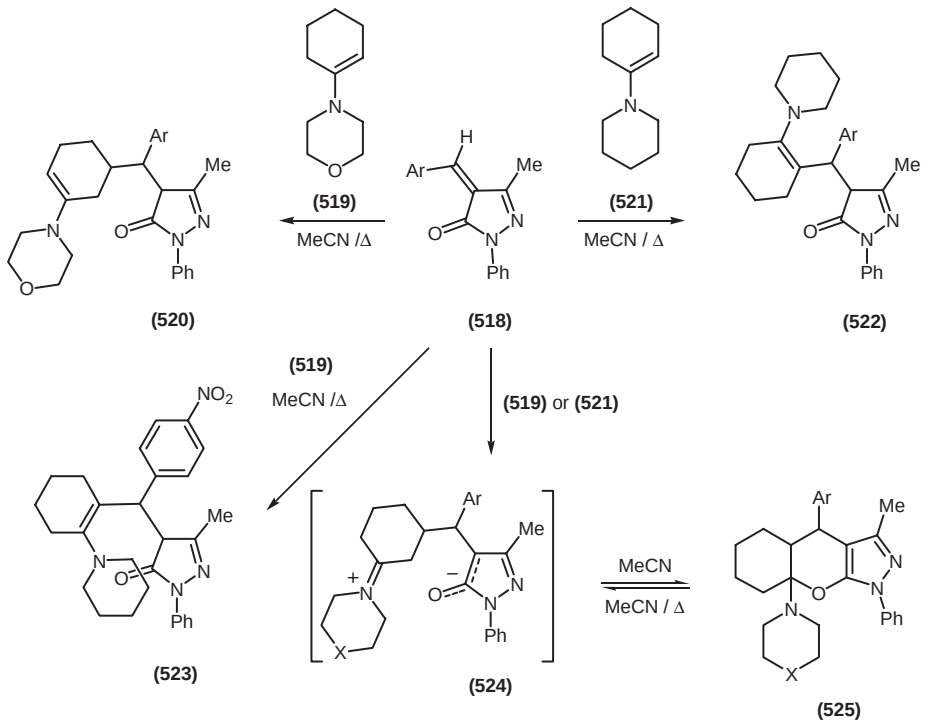
(a) Ar = Ph, **(b)** Ar = 4-FC_6H_4, **(c)** Ar = 4-ClC_6H_4, **(d)** Ar = 4-BrC_6H_4, **(e)** Ar = 4-IC_6H_4, **(f)** Ar = 4-$BzOC_6H_4$, **(g)** Ar = 4-MeC_6H_4, **(h)** Ar = 4-$MeOC_6H_4$, **(i)** Ar = 4-$NO_2C_6H_4$, **(j)**Ar = 4-$NO_2C_6H_4$, **(k)** 4-HO, 3-$MeOC_6H_3$

Scheme 154



(515) **(447)** **(516)** **(517)**

Scheme 155

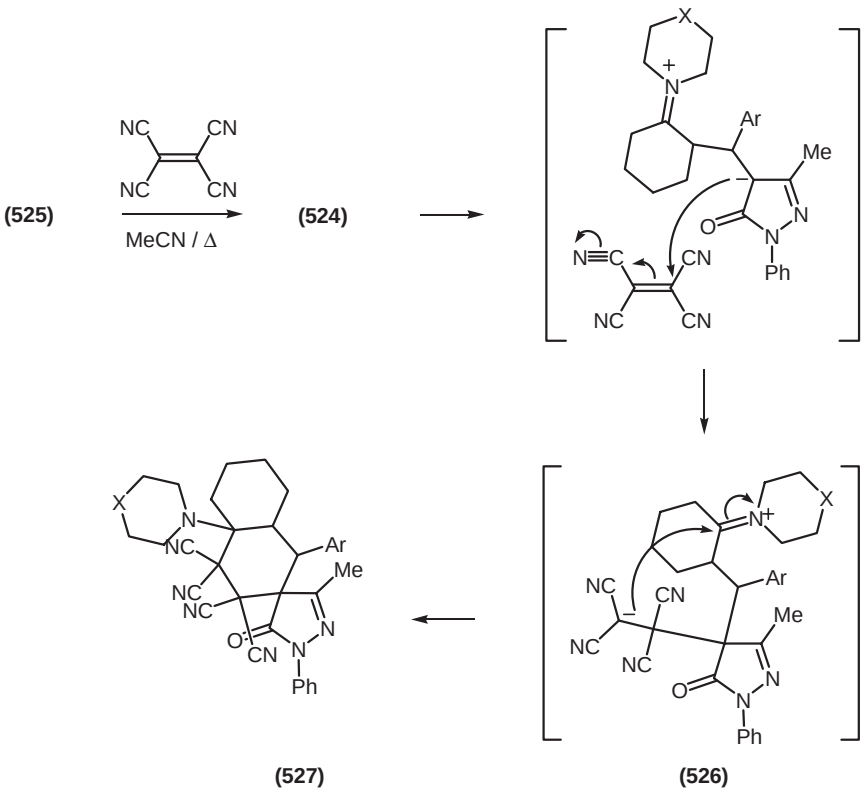


Scheme 156

(*E*/*Z*)-diphenyldiaza-18-crown-6-bispyrazolideneacetonitrile **517** by heating in methanol containing mercury.

Abdel-Rahman and Abdel-Ghany published two papers (89SC1987, 91SC1281) concerning the reaction of (*E*/*Z*)-arylmethylidenepyrazol-3-ones with enamines (Scheme 156). In the first paper, reaction of pyrazol-3-ones **518a**,**b**,**d** with 1-morpholinocyclohexene **519** in refluxing acetonitrile was described to give the less substituted alkylated enamines **520a**,**b**,**d**. On the other hand, the more substituted alkylated enamines **522a–d** and **523** were formed when pyrazol-3-ones **518a–d** reacted under the same conditions with 1-piperidinocyclohexene **521** or when **518c** was reacted with **519**. In the second paper, the reaction of pyrazol-3-ones **518a–d** with enamines **519** and **521** in acetonitrile at room temperature afforded the Diels–Alder type dihydropyran adducts **525e**,**f**. Upon heating in acetonitrile, **518e**,**f** gave the Michael-type adducts **520a–d** and **522a–d**, respectively. It was therefore proposed that the reaction of **518** with either **519** or **521** in refluxing acetonitrile proceeds via zwitterionic intermediate **524** that leads to products **525a–d**.

Further evidence of an intermediate **524** was obtained by the reaction of adducts **525e**,**f** with tetracyanoethylene in refluxing acetonitrile (Scheme 157, for **e**,**f** see Scheme 156). It was proposed that products **527e**,**f** are derived from ring opening of **525** to **524**, nucleophilic addition of the carbanionic form of **524** to tetracyanoethylene and intramolecular cyclization of intermediate **526** to afford pyrazol-3-one derivatives **527e**,**f**.



Scheme 157

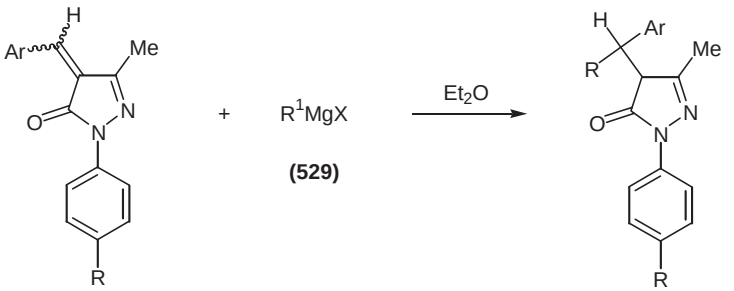
G. By Grignard Reagents

The addition of aliphatic and aromatic Grignard reagents **529a** to (*E*/*Z*)-4-arylidenepyrazol-3-ones **528b** was reported by Afsah and co-workers (78IJC876) (Scheme 158) to afford 4-diaryl(or arylalkyl)methylpyrazol-3-ones **530c**–**k** in yields ranging from 64–73%.

H. By Secondary Amines or Thiophenols

The additive behavior of the exocyclic double bond in position 4 of (*E*/*Z*)-4-arylidenepyrazol-3-ones **532a**–**c** was investigated with secondary amines and thiophenols. Thus reaction with piperidine, morpholine, thiophenol or 4-methylthiophenol gave the corresponding addition products **533d**–**f**, in good yields (72JPR612, 78IJC876) (Scheme 159).

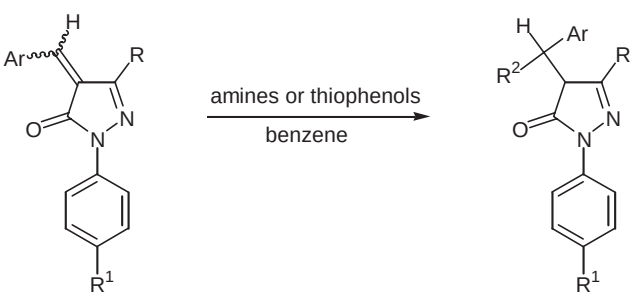
1,5-Diphenyl- or 1,5-difuran-2-yl-penta-1,4-dien-3-one **463a**,**b** furnished the spiropyrazol-3-ones **464a**,**b** by Michael addition with pyrazol-3-one **62** (99JCEN61) (Scheme 160).



(528) **(530)**

(a) R^1 = Me, Ph or cyclopentyl**, (b)** R = Cl, Ar = 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-$Me_2NC_6H_4$, benzo[1,3]dioxol-5-yl or thien-2-yl**, (c)** R = Cl, R^1 = Me, Ar = 4-$MeOC_6H_4$
(d) R = Cl, R^1 = Me, Ar = 4-$NO_2C_6H_4$**, (e)** R = Cl, R^1 = Me, Ar = 4-$Me_2NC_6H_4$
(f) R = Me, Ar = thien-2-yl**, (g)** R = Cl, R^1 = Ph, Ar = 4-$MeOC_6H_4$
(h) R = Cl, R^1 = Ph, Ar = 4-NO_2C_6**, (i)** R = Cl, R^1 = Ph, Ar = benzo[1,3]dioxol-5-yl
(j) R = Cl, R^1 = Ph, Ar = 4-$Me_2NC_6H_4$**, (k)** R = Cl, R^1 = cyclopentyl, Ar = 4-$MeOC_6H_4$

Scheme 158



(532) **(533)**

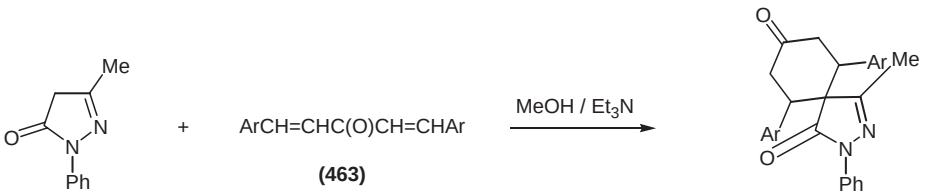
(a) R = Me, R^1 = Cl, Ar = 4-$MeOC_6H_4$, **(b)** R = Me, R^1 = Cl, Ar = 4-$NO_2C_6H_4$,
(c) R = pyrid-3-yl, R^1 = H, Ar = 4-$MeOC_6H_4$, **(d)** R = Me, R^1 = Cl, R^2 = piperidino,
(e) R = Me, R^1 = NO_2, R^2 = morpholino, Ar = 4-$MeOC_6H_4$,
(f) R = pyrid-3-yl, R^1 = H, Ar = 4-$MeOC_6H_4$, R^2 = piperidino, morpholino, thiophenol or 4-methylthiophenol

Scheme 159

XIII. Nucleophilic Substitution

A. By Pyrazol-3-ones

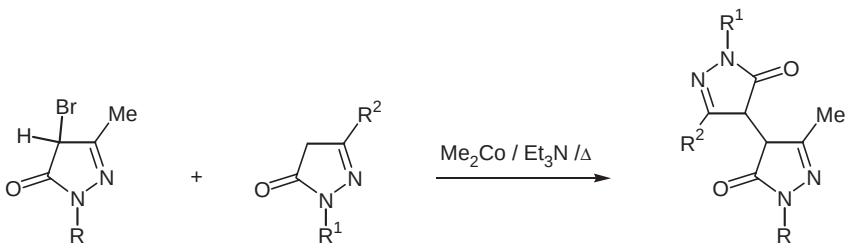
Under appropriate conditions 1,2-unsubstituted 1,2-dihydro- and 2,4-unsubstituted 2,4-dihydropyrazol-3-ones take part in nucleophilic substitutions at N2. In 2,4-dihydropyrazol-3-ones substituted at N1 nucleophilic substitution occurs at C4 as



(60) **(463)** **(464)**

(a) R = Ph, **(b)** R = 2-Furyl

Scheme 160



(535) **(536)** **(537)**

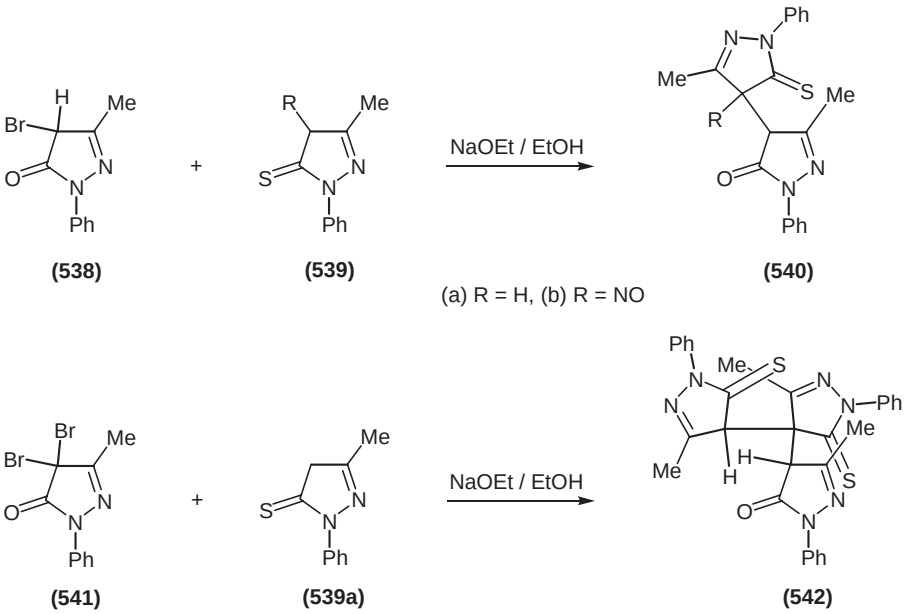
(a) R = R^1 = Ph, R^2 = Me, **(b)** R = Ph, R^1 = H, R^2 = Me, **(c)** R = R^2 = Ph, R^1 = 4-$NO_2C_6H_4$,
(d) R = R^2 = Ph, R^1 = H, **(e)** R = R^2 = Ph, R^1 = 2,4-$(NO_2)_2C_6H_3$,
(f) R = Ph, R^2 = Me, R^1 = 2,4-$(NO_2)_2C_6H_3$, **(g)** R = Ph, R^2 = Me, R^1 = $CONH_2$,
(h) R = Ph, R^2 = Me, R^1 = 2,4-$(NH_2)_2C_6H_3$, **(i)** R = R^1 = H, R^2 = Me,
(j) R = H, R^1 = Ph, R^2 = Me, **(k)** R = H, R^1 = 4-$NO_2C_6H_4$, R^2 = Ph, **(l)** R = R^1 = H, R^2 = Ph,
(m) R = H, R^1 = 2,4-$(NO_2)_2C_6H_3$, R^2 = Ph, **(n)** R = H, R^1 = 2,4-$(NO_2)_2C_6H_3$, R^2 = Me,
(o) R = H, R^1 = $CONH_2$, R^2 = Me, **(p)** R = H, R^1 = 2,4-$(NH_2)_2C_6H_3$, R^2 = Me

Scheme 161

long as there is at least one hydrogen atom in that position. Nayak and Mittra (80JIC643) (Scheme 161) prepared 4,4′-bipyrazole-3,3′-diones **537a**–**p** by reacting 4-bromopyrazol-3-ones **535a**–**p** with pyrazol-3-ones **536a**–**p** in refluxing ethanol containing triethylamine. All these compounds were screened against the the rice blast pathogen *Pyricularia oryzae* and the brown leaf spot pathogen *Helminthosporin oryzae* to find that most exhibit significant fungicidal activity comparable to standard fungicides.

Reaction of the carbanion of pyrazol-3-thione **539** with 4-bromopyrazol-3-one **538** in ethanolic sodium ethoxide afforded 5-thioxo-4,4′-bipyrazol-3′-one **540** (83JIC679) (Scheme 162). On the other hand reaction of one equivalent of 4,4′-dibromopyrazol-3-one **541** with two equivalents of **539** under the same reaction conditions yielded 5,5″-dithioxo-4,4′,4′,4″-terpyrazol-3′-one **542**.

Nucleophilic aromatic substitution of activated aryl halides has been reported for both 1,2-dihydro and 2,4-dihydropyrazol-3-ones. With 2-fluorobenzonitrile **544** pyrazol-3-one **543** required heating at 100 °C for 16 h in dimethyl sulfoxide in the



(538) (539) (540) (541) (539a) (542)

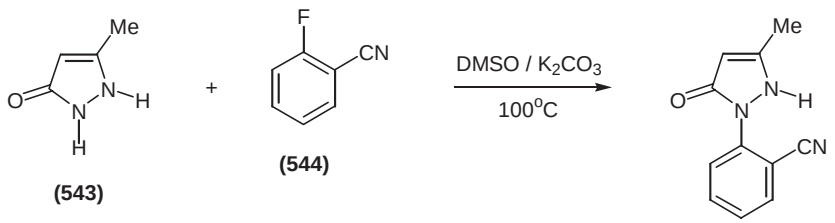
Scheme 162

presence of powered potassium carbonate to give 2-(benzo-2-nitrile)pyrazol-3-one **545** in only 47% yield (94SC123) (Scheme 163).

1-Fluoro-2,4-dinitrobenzene **547** reacted similarly with pyrazol-3-ones **546a–g** to give substitution products **548a–g** (68BSF5019) (Scheme 164).

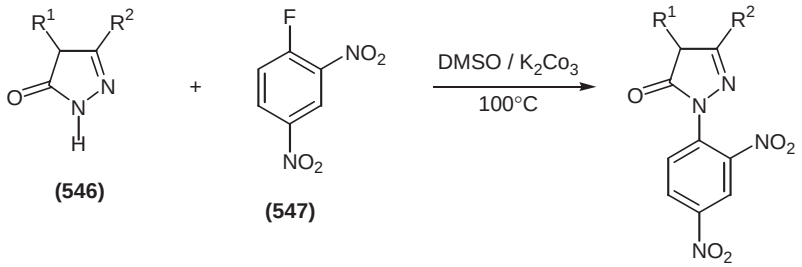
Both 1,2-dihydro- and 2,4-dihydropyrazol-3-ones are known to substitute the chlorine atom of aliphatic and heterocyclic chloro imines and aliphatic trihalogenomethylimines. Nucleophilic substitution of 2-chlorobenzo[1,3]thiazole **550** by C-2 of 1,2-dihydropyrazol-3-one **549** requires heating at 120 °C in DMF with a strong base such as sodium hydride. The product **551** was obtained in only 22% yield (88JHC543) (Scheme 165).

The reaction of 2-unsubstituted pyrazol-3-one **552** with 1-chloropropane-1,2-dione 1-(*N*-phenylhydrazone) **553** requires heating in ethanol containing triethylamine to give pyrazol-3-one **554** (84BCJ1650). Under similar conditions



(543) (544) (545)

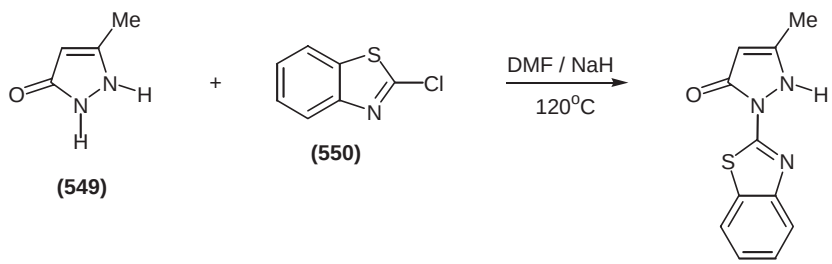
Scheme 163



(546) **(547)** **(548)**

(a) $R^1 = R^2 = H$, **(b)** $R^1 = H$, $R^2 = Me$, **(c)** $R^1 = Me$, $R^2 = H$, **(d)** $R^1 = R^2 = Me$, **(e)** $R^1 = H$, $R^2 = Ph$, **(f)** $R^1 = NO_2$, $R^2 = Me$, **(g)** $R^1 = Br$, $R^2 = Me$

Scheme 164



(549) **(550)** **(551)**

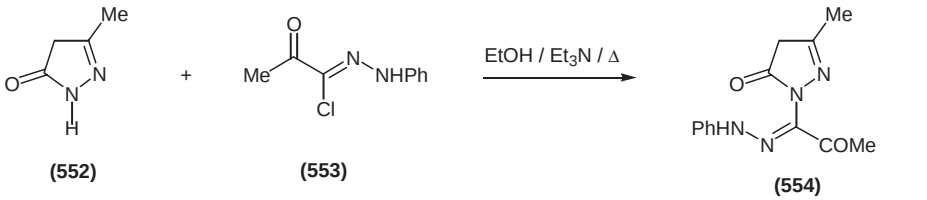
Scheme 165

pyrazol-3-one **62** displaced the trifluoromethyl group of 3,3,3-trifluoro-2-[(2,2,2-trifluoroacetyl)imino]propanoate **555** to give the 4-substituted methyl trifluoroacetyliminoacetate derivative **556** (89IZV2131) (Scheme 166).

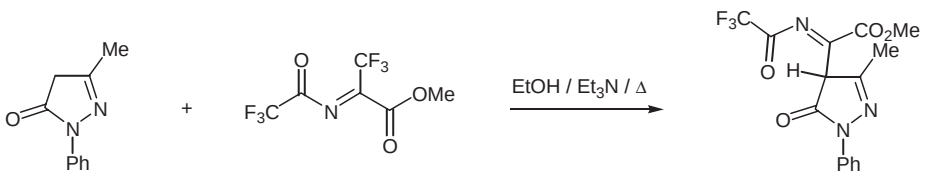
Under acidic conditions the hydroxyl group of 2-(*t*-butyl)-5,5-dimethyl-4-(4-methylphenyl)-2,5-dihydrofuran-2-ol **557**, 9*H*-xanthen-9-ol **559a**, 9*H*-thioxanthen-9-ol **559b** was displaced by C4 of pyrazol-3-one **62** in refluxing methanol or ethanol to give the corresponding pyrazol-3-one derivatives **558** and **560a**,**b** in 70, 91, and 76% yield, respectively (66JGU215, 80JHC1339, 82JHC437). The reaction worked equally well with 4-aminopyrazol-3-one **561** and either **559a** or **559b** to give 4-substituted pyrazol-3-ones **562a**,**b** in 84 and 61% yield, respectively (80JHC1339, 82JHC437) (Scheme 167).

One year later Okabayashi and co workers (83CPB3718) (Scheme 168) obtain an X-ray crystal structure of **560b** and established that it was a different tautomeric form than that previously assigned in the liquid state. In the solid state **560b** was found to be in the "N–H" tautomeric form **563** where the molecules are linked by an intermolecular hydrogen bond between N–H and C=O groups.

Tetraglucose **565** was derivatised with pyrazol-3-one **564** by dissolving it in methanol containing sodium hydroxide and heating in a sealed tube at 70 °C.

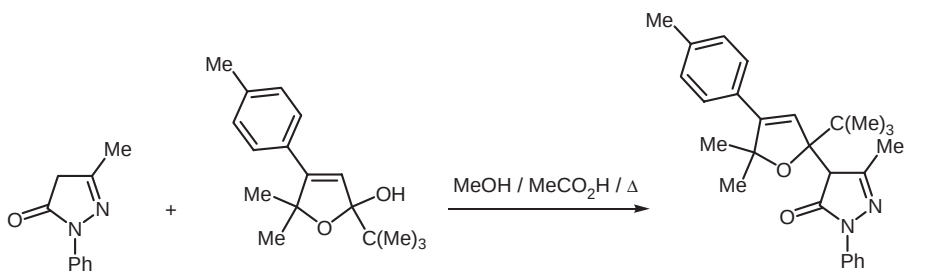


(552) **(553)** **(554)**

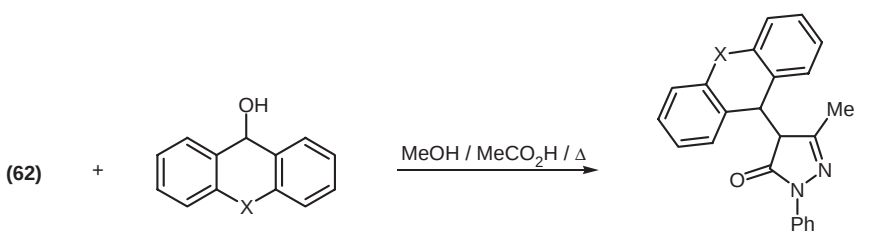


(62) **(555)** **(556)**

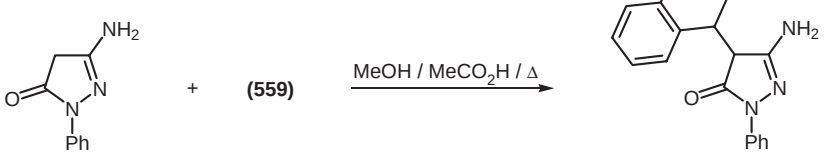
Scheme 166



(62) **(557)** **(558)**



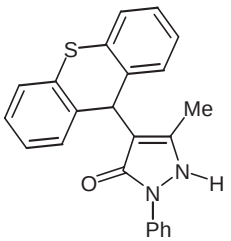
(559) **(560)**



(561) **(562)**

(a) X = O, **(b)** X = S

Scheme 167

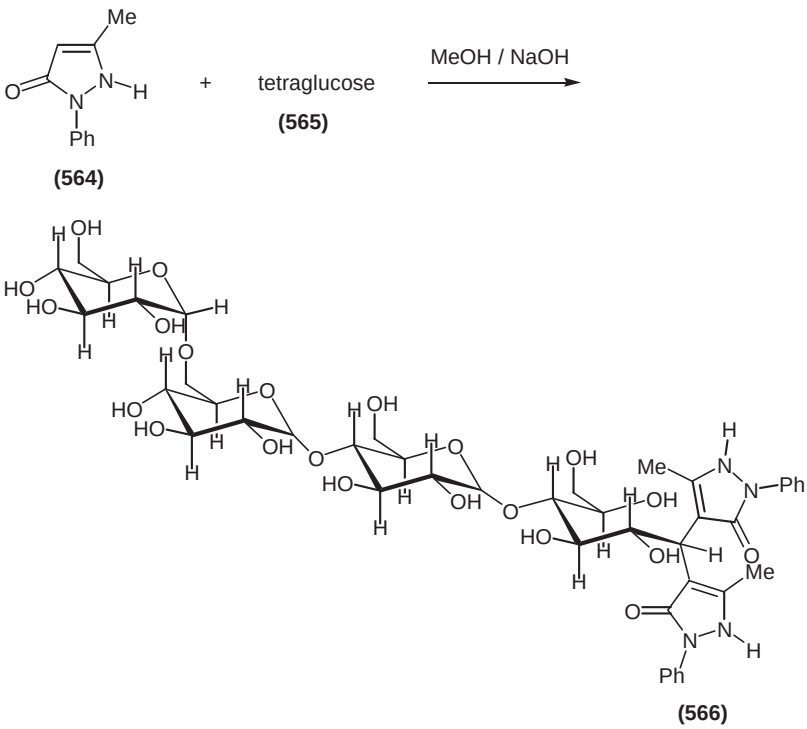


(563)

Scheme 168

The pyrazol-3-one labeled sugar derivative **566** was obtained in quantitative yield (99JMAS502) (Scheme 169). A mass spectrometric study of this product using ESI-MS and ESI-MS/MS revealed that in comparison with tetraglucose, the labeling process increases the positive mode ESI sensitivity by a factor of 10. This derivatisation also made the fragmentation pattern easier to interpret than for tetraglucose itself, owing to the dominant reducing end-containing fragment ions.

2,4-Dihydropyrazol-3-ones bearing a hydroxyethyl side-chain at C4 can undergo intramolecular substitution of the hydroxyl group at the same position to give a spiropyrazol-3-one. On the other hand, the hydroxyethyl group of 1,2-dihydropyrazol-3-ones was converted into a bromoethyl group before cyclization.

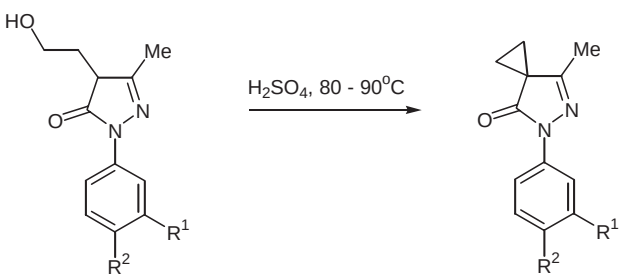


Scheme 169

Thus heating 4-(2-hydroxyethyl)pyrazol-3-ones **567a–d** in concentrated sulfuric acid at 80–90 °C gave the corresponding spiropyrazol-3-ones **568a–d** (84CZ285). 4-(2-Hydroxyethyl)pyrazol-3-ones **569a**,**b** were converted into the corresponding 4-(2-bromoethyl) derivatives **570a**,**b** by heating at 80 °C with 62% hydrobromic acid. Addition of **570a**,**b** to DMSO containing potassium carbonate at room temperature afforded the respective spiro compounds **571a**,**b**. This experiment was also done directly in an NMR tube with hexadeuterated DMSO and base (99EJMC967) (Scheme 170).

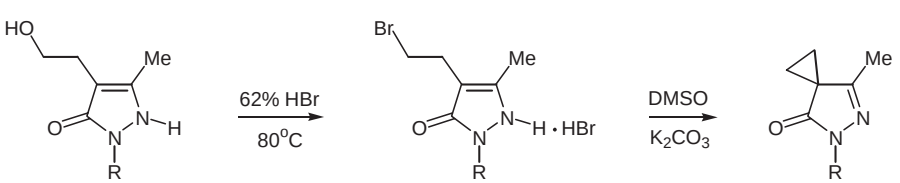
A noteworthy reaction is the overall substitution of the aldehyde group of C4 of pyrazole-3-one **572** by C4 of a second molecule of **573**. The reaction took place in a methanolic solution of sodium borohydride and led to pyrazol-4-ylmethylenepyrazol-3-one **575** (75LA2293) (Scheme 171). The mechanism proposed by the authors consists of deprotonation of **433** and addition to a neutral molecule of the same compound to give intermediate **573** after loss of hydroxide ion. Further loss of formaldehyde results in the allene **574**, which is reduced to pyrazol-4-ylmethylenepyrazol-3-one **575**.

An interesting reaction between pyrazol-3-one **62** and *N*,*N*′-diphenylformamidine **576** has appeared in a patent (69GEP1800581) (Scheme 172). The reaction took place by heating these compounds in a mixture of acetaldehyde and triethylamine and gave, in excellent yield, (*E*/*Z*)-4-[3-(pyrazol-4-yl)prop-2-enylidene]pyrazol-3-one **581**. The proposed mechanism suggests initial substitution and loss of aniline, addition of acetaldehyde to the α,β-moiety of pyrazol-3-one, loss of aniline from **578** to a 3-(5-oxo-pyrazol-4-ylidene)propionaldehyde **579c**, addition of a second molecule of **62** to



(567) **(568)**

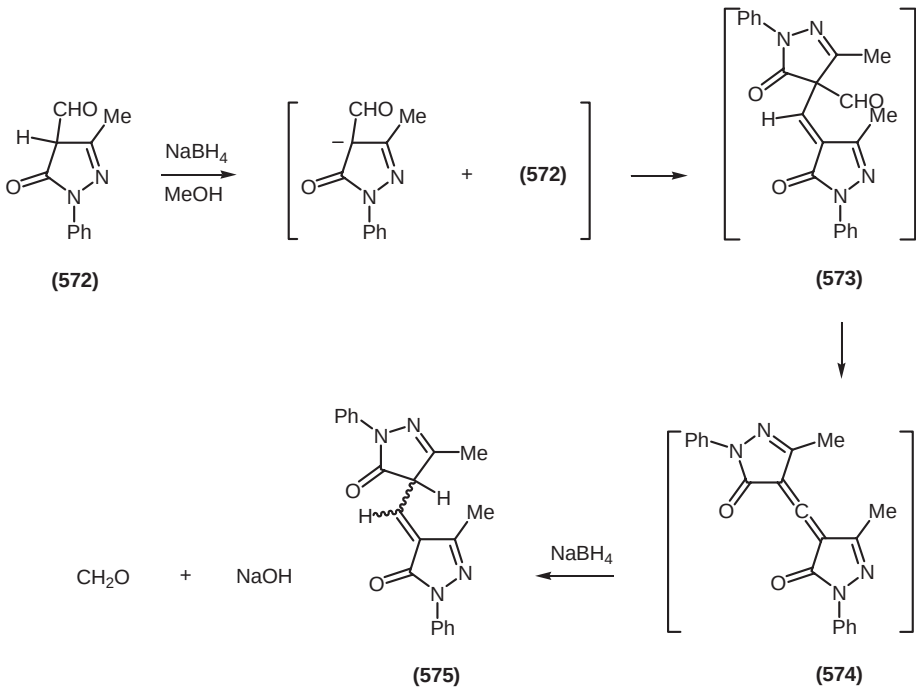
(a) R^1 = H, R^2 = Cl, **(b)** R^1 = R^2 = Cl, **(c)** R^1 = H, R^2 = NO_2, **(d)** R^1 = H, R^2 = Me



(569) **(570)** **(571)**

(a) R = H, **(b)** R = Me

Scheme 170



Scheme 171

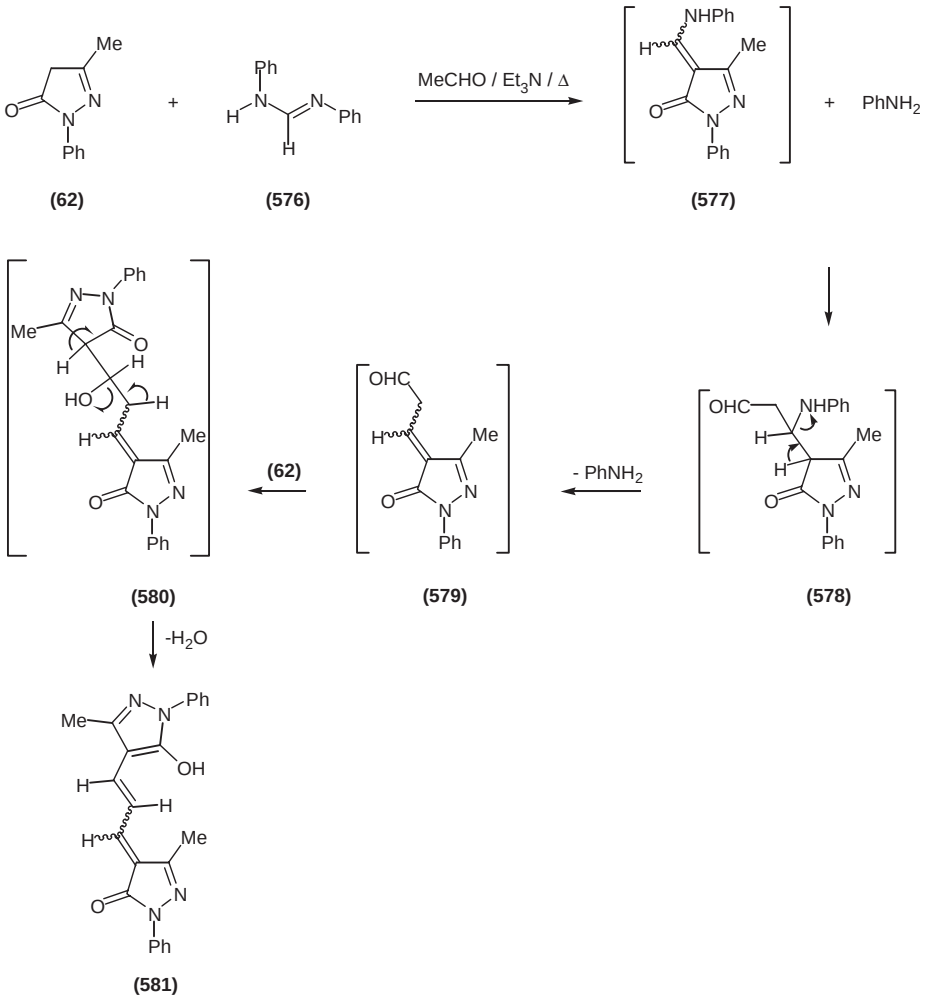
the aldehyde group of the latter, and elimination of water followed by tautomerism to afford **581**. Compounds such as **581** have found application as photographic sensitizers and as dyes for polyamide fibers.

Twelve years later Rockley and Summers(81AJC1117) (Scheme 173) limited the above reaction to the substitution and isolated several 4-(arylmethylidene)pyrazol-3-ones **584** by heating pyrazol-3-ones **582** and *N*,*N*′-diarylformamidines **583** at 170–180 °C.

Pyrazol-3-one **62** is also known to attack C4 of 4-aryliminopyrazol-3-one **585**. Compounds such as **585** known as azomethine dyes react with pyrazol-3-one **62** and lose 4-dimethylaminoaniline to give the proposed intermediate **586**. Addition of a second molecule of **62** yields the 4,4′-bis(5-hydroxy-1*H*-pyrazol-4-yl)pyrazol-3-one **587**. The reaction takes place in refluxing methanol but upon heating **587** at 140 °C, loss of a pyrazole molecule and tautomerism leads to compound **588** (88JPR435) (Scheme 174).

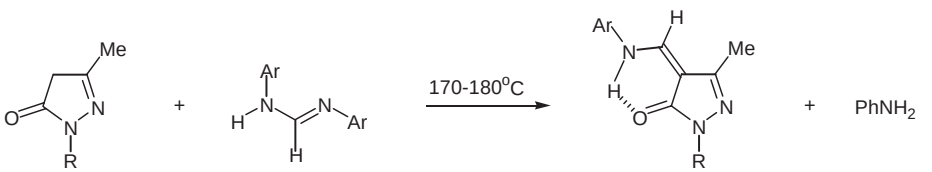
Nucleophilic attack by N2 of pyrazol-3-ones **589a–e** on chloramines displaced chloride anion to give 2-aminopyrazol-3-ones **590a–e** in good yields (81JHC957) (Scheme 175).

Several reports describe the reaction of pyrazol-3-ones with amidines and iminium salts where the group displaced is an amine. Nucleophilic substitution of ammonia by 2,5-dimethylpyrazol-3-one **591** attack on benzamidine hydrochloride **592** requires 220 °C to give via addition intermediate **593** 4-[imino(phenyl)methyl]pyrazol-3-one



(62) (576) (577) (578) (579) (580) (581)

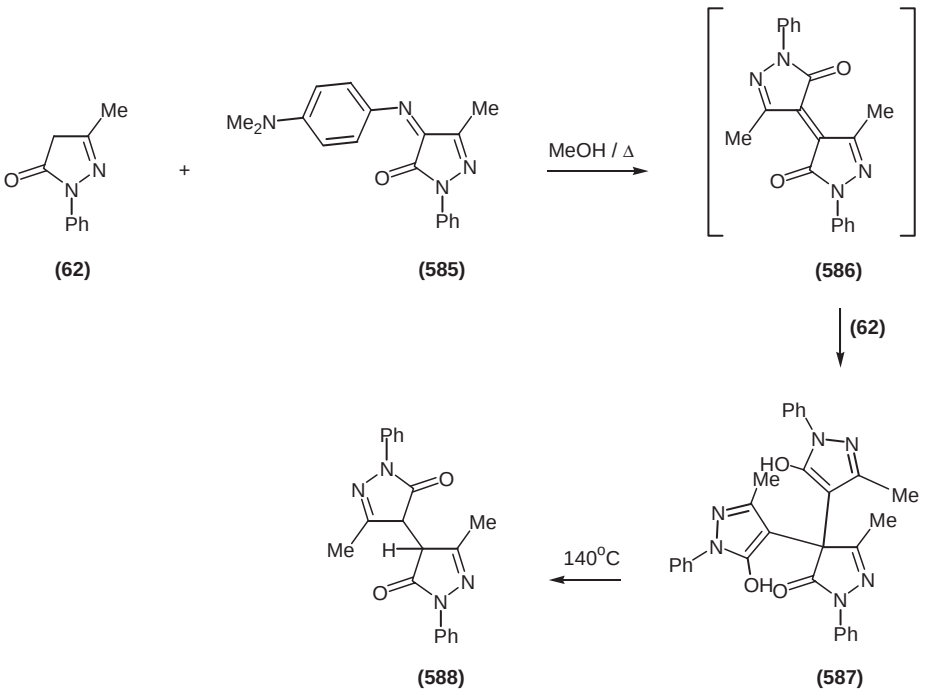
Scheme 172



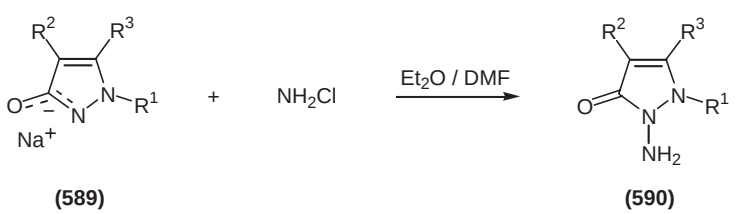
(582) (583) (584)

(a) R = H, Ar = Ph, **(b)** R = Me, Ar = Ph, **(c)** R = H, Ar = 2-ClC_6H_4, **(d)** R = Me, Ar = 2-ClC_6H_4, **(e)** R = H, Ar = 3-ClC_6H_4, **(f)** R = Me, Ar = 3-ClC_6H_4, **(g)** R = H, Ar = 4-ClC_6H_4, **(h)** R = Me, Ar = 4-ClC_6H_4

Scheme 173



Scheme 174

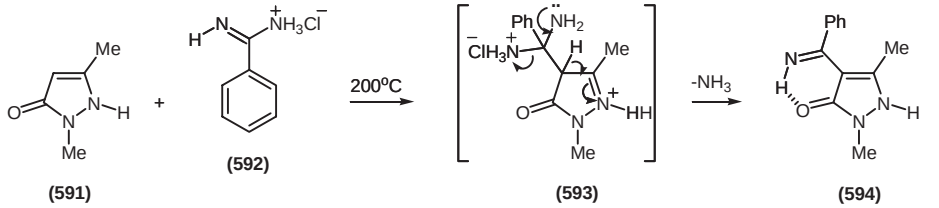


(a) $R^1 = R^3 = Me$, $R^2 = Ph$, **(b)** $R^1 = R^2 = Me$, $R^3 = Ph$ **(c)** $R^1 = Me$, $R^2 = R^3 = Me$, **(d)** $R^1 = Bz$, $R^2 = Ph$, $R^3 = Me$, **(e)** $R^1 = Bz$, $R^2 = Me$, $R^3 = Ph$

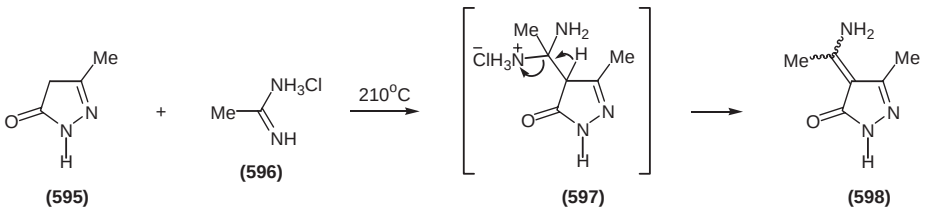
Scheme 175

594 in 60% yield. The compound is stabilized by intramolecular hydrogen bonding (73CB332) (Scheme 176).

On the other hand 2,4-dihydropyrazol-3-one **595** under similar reaction conditions attacks acetamidine hydrochloride **596** to give (*E*/*Z*)-4-(1-aminoethylidene)pyrazol-3-one **598** in 63% yield (74CPB207) (Scheme 177). The adduct **597**, formed initially in this reaction, must be losing ammonia via an elimination process involving H4. On the other hand, in the analogous adduct **593** (Scheme 176), proton loss from C4 follows neutralisation of the positive change on N1, whereas loss of ammonia is triggered by lone-pair conjugation from the neutral amino group.



Scheme 176



Scheme 177

The reaction of pyrazol-3-one **62** with iminium salts is similar to the above addition–elimination process involving pyrazol-3-one C4/H4. In the first example, two equivalents of pyrazol-3-one **62** react with iminium perchlorate **599** in tetrahydrofuran containing sodium hydride to afford the (*E*/*Z*)-bipyrazol-3-one derivative **600** in only 32% yield (82AG559). Without the use of basic conditions one equivalent of **62** reacted with iminium chloride **601** in acetonitrile to give (*Z*)-4-(3,3-dichloroprop-2-enylidene)pyrazol-3-one **602** in 84% yield (97S573) (Scheme 178).

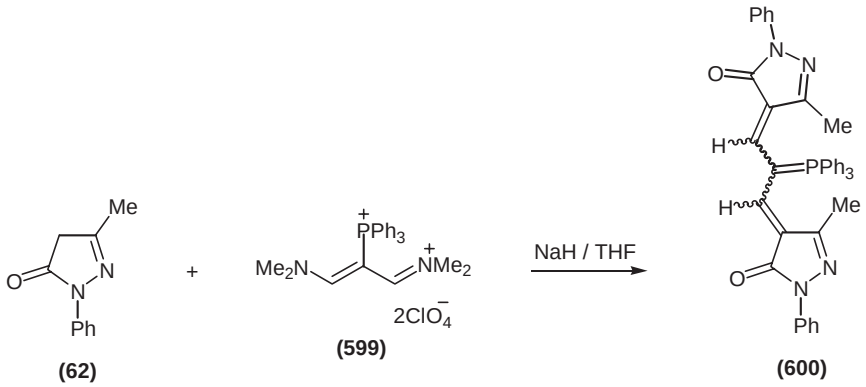
In the reaction of pyrazol-3-ones with imines, alkoxide groups have also been displaced from heterocyclic derivatives. Thus the reaction of 10-thia-8-azabenzo[*a*]-azulene **603** with pyrazol-3-one **62** in refluxing ethanol afforded pyrazol-3-one derivative **604** in 42% yield (73AP531). When the electrophile used was 2-*n*-butoxyazepine **605** reaction with **62** took a different path in the elimination step. Loss of *n*-butanol from adduct **606** gave 4-(azepin-2-ylidene)pyrazol-3-one **607** in 62% yield (88T3309) (Scheme 179).

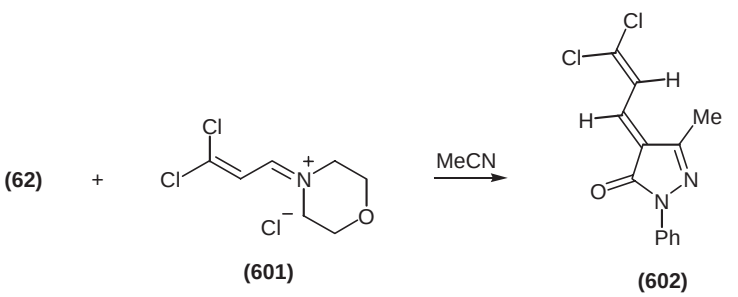
Reaction of **62** with dithiobenzoic acid **608** in 50% methanol containing sodium hydroxide gave **609** by a manner analogous to the reaction leading to compound **607** in Scheme 179. The yield of **613** was very low (18%) (81JCS(P1)2948) (Scheme 180).

The reaction of 5-hydroxypyrazol-3-ones **610a**,**b** with diaryldisulfides **611a**,**b** in DMF with potassium carbonate and bubbling air afforded the corresponding 4-phenylthiopyrazol-3-ones **612a**–**c** in moderate yields (00JHC911) (Scheme 181). The arylthiolate anions were recovered as starting disulfides after air oxidation.

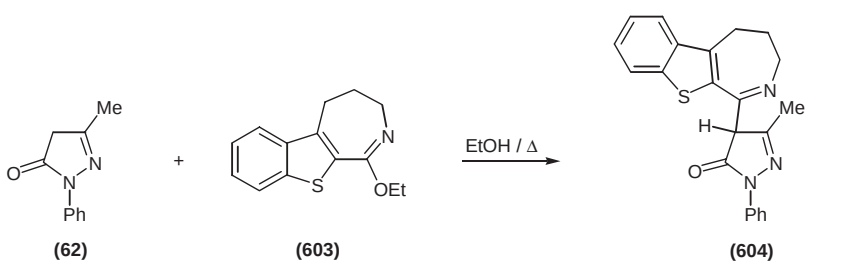
B. On Mono- or Dihalogenopyrazol-3-ones

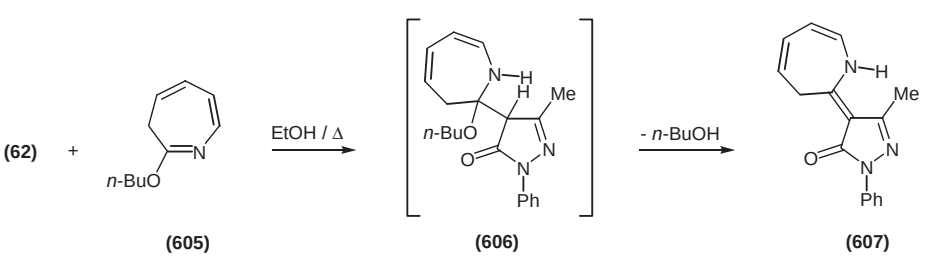
Halogens at positions 4 of pyrazol-3-ones can be displaced by both aliphatic and heterocyclic carbon and nitrogen nucleophiles and can be oxidized by lead(II)



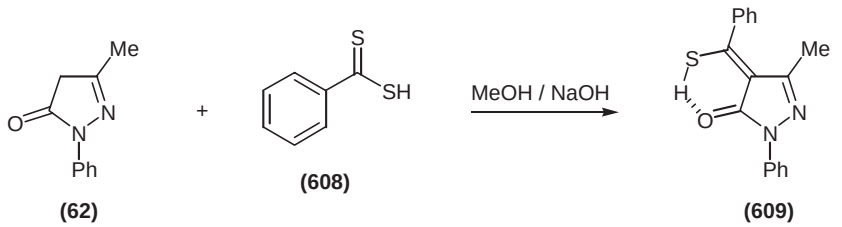


Scheme 178

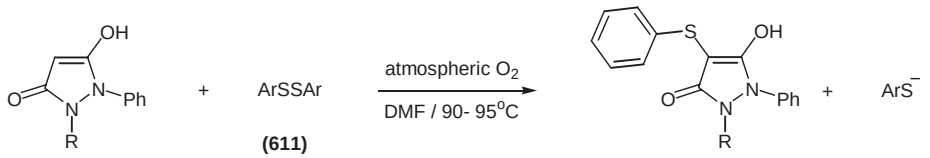




Scheme 179



Scheme 180



(a) R = H, Ar = Ph, **(b)** R = Ar = Ph, **(c)** R = Ph, Ar = 4-ClC_6H_4

Scheme 181

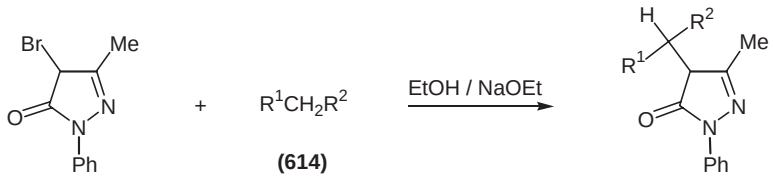
acetate. 4-Bromopyrazol-3-one **613** was treated with acetylacetone **614a**, diethyl malonate **614b** or ethyl acetoacetate **614c** in an ethanolic solution of sodium ethoxide to afford in good yield the corresponding 4-substituted derivatives **615a–c** (84ZN(B)86). When the reaction was repeated between **613** and pyrazol-3-thione **616a**,**b**, **617a**,**b** was obtained. The same reaction conditions allowed 4,4′-dibromopyrazol-3-one **618** and two equivalents of **616** to react and give **619** (83JIC679) (Scheme 182).

The reaction with nitrogen nucleophiles such as sodium azide works very well with 4,4-dichloro-3-one **620** and 4,4-dibromopyrazol-3-ones **622** in boiling ethanol and give high yields (91%) of 4,4-diazopyrazol-3-ones **621a**,**b** (76TL2513, 80ZC437). Heterocyclic amines **624a** required refluxing in ethanolic sodium hydroxide in order to displace bromide ion from 4-bromopyrazol-3-ones **623a** and give 4-thiazolidine derivatives **625a**. Some of these derivatives exhibited significant antifungal activity against the pathogens *P. oryzae* and *H. oryzae* (84JIC77) (Scheme 183).

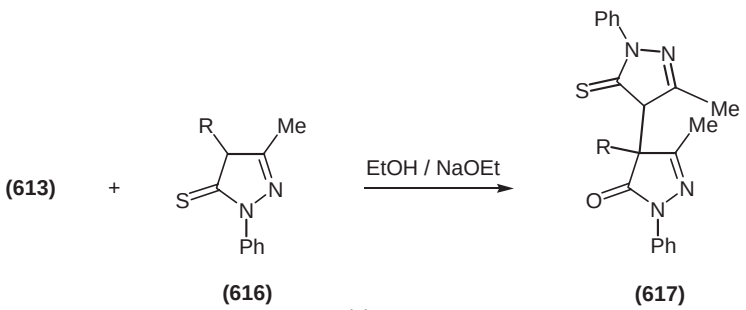
4,4-Dibromopyrazol-3-ones **626a**,**b** were treated with lead(II) acetate in acetic acid to afford pyrazol-3,4-diones **628a**,**b**. The reaction is believed to occur through initial nucleophilic substitution of both bromine atoms by acetate ion to give an intermediate 4,4-diacetoxypyrazol-3-one **627a**, which is unstable and loses acetic anhydride (84S972) (Scheme 184).

XIV. Oxidation

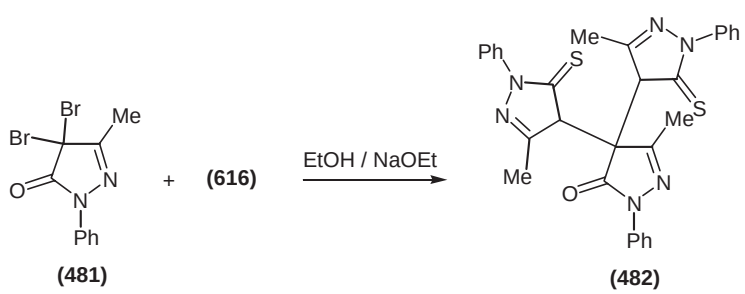
Depending on the substitution of the pyrazol-3-one ring, oxidation can lead to pyrazol-3-one radicals, carbonyl group formation on the ring or oxidative coupling.



(a) $R^1 = R^2 = MeCO$, **(b)** $R^1 = R^2 = CO_2Et$, **(c)** $R^1 = MeCO$, $R^2 = CO_2Et$



(a) R = H, R = N=O

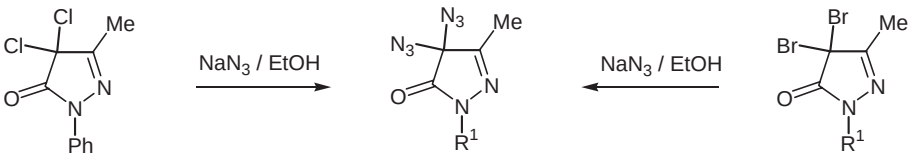


Scheme 182

Furthermore, pyrazol-3-ones have been oxidized by a variety of oxidizing agents such as ozone in oxygen, hydrogen peroxide solution, 3-chloroperbenzoic acid, aqueous sodium periodate, lead(IV) acetate with boron trifluoride etherate, or atmospheric oxidation. The reactions lead mainly to epoxidation of an alkene or imine functionality and cleavage of the pyrazol-3-one ring.

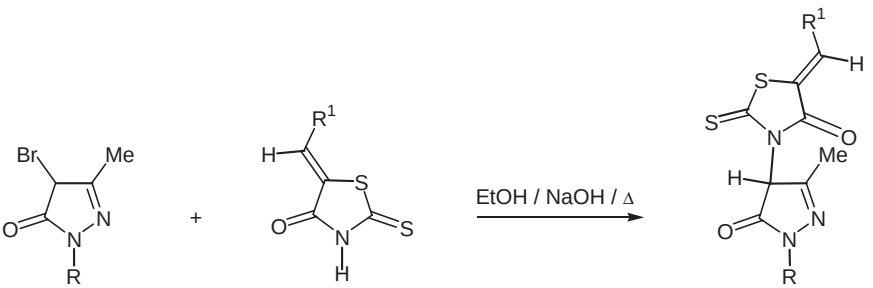
A. Nitroxide Formation via Pyrazol-3-one Radicals

Omelka et al. (93JPR435) (Scheme 185) oxidized pyrazol-3-ones **629a–k** with lead(IV) oxide in benzene, 4-nitrobenzenoic acid in benzene or Co(II)-acetylacetone *t*-butylhydroperoxide mixture. The resulting pyrazol-3-one radicals **630a–k** were detected by ERS spectroscopy directly, or after trapping with nitrosobenzene as phenyl nitroxides. Thus oxidation of pyrazol-3-ones **629b–e,j** with lead(IV) oxide in



(620) **(621)** **(622)**

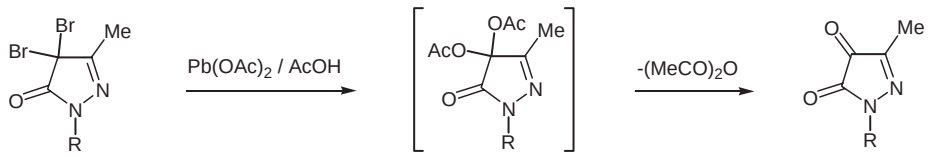
(a) R^1 = Ph or 4-BrC_6H_4, R^2 = Me, Ph 4-$NO_2C_6H_4$ or NH_2, **(b)** R^1 = Ph, R^2 = Me



(623) **(624)** **(625)**

(a) R = H or Ph, R^1 = Ph, 4-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-HOC_6H_4, 3-HOC_6H_4, 4-HOC_6H_4, 2-HO-4-$MeOC_6H_3$, OC_6H_4, 4-CH_2=CHC_6H_4 or 4-$(Me)_2NC_6H_4$

Scheme 183



(626) **(627)** **(628)**

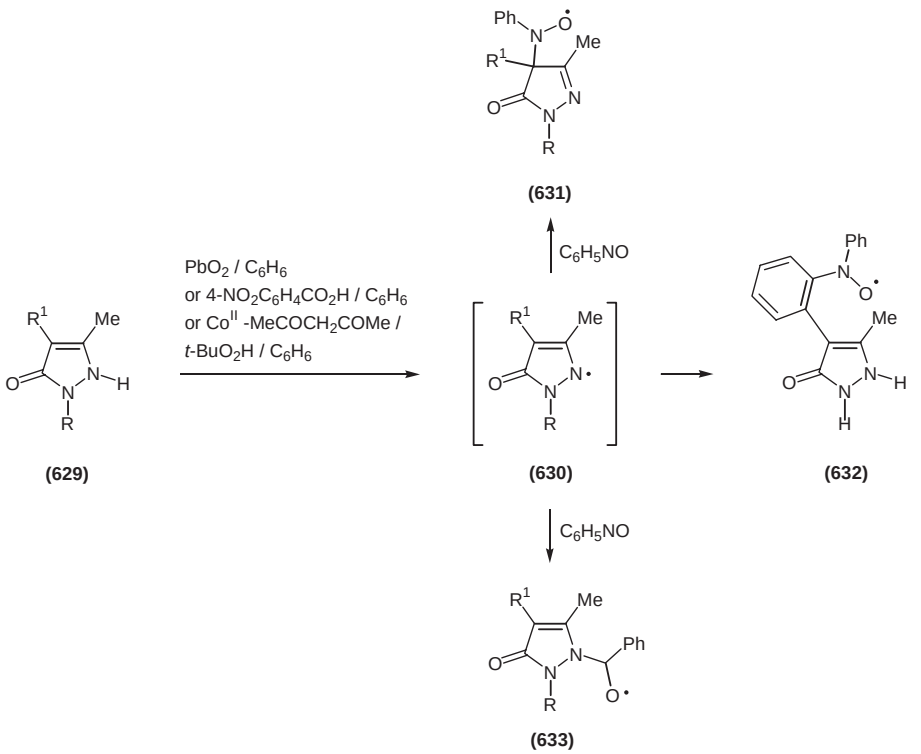
(a) R = H, **(b)** R = Ph

Scheme 184

the presence of nitrobenzene afforded phenyl nitroxides **631b–e**,**j**. Under the same reaction conditions pyrazol-3-one **629h** gave nitroxide **632** and pyrazol-3-ones **629f**,**g**,**h** gave nitroxides **633f**,**g**,**k**.

B. Oxidation of Ring Carbon Atoms Followed by Addition

The oxidation of pyrazol-3-ones **634a–c** with 30% hydrogen peroxide in glacial acetic acid led to the 4,4′-bipyrazolyl-3,3′-dione **636a–c** in 66, 38, and 96% yield respectively. The reaction occurs via oxidation to pyrazol-3,4-diones **635a–c**



(a) R = Ph, R^1 = H, **(b)** R = Ph, R^1 = Me, **(c)** R = Ph, R^1 = Et, **(d)** R = Ph, R^1 = *n*-Pr, **(e)** R = Ph, R^1 = *i*-Pr, **(f)** R = R^1 = Ph, **(g)** R = H, R^1 = Me, **(h)** R = H, R^1 = Ph, **(i)** R = R^1 = H, **(j)** R = *o*-tolyl, R^1 = Me, **(k)** R = *o*-tolyl, R^1 = Ph,

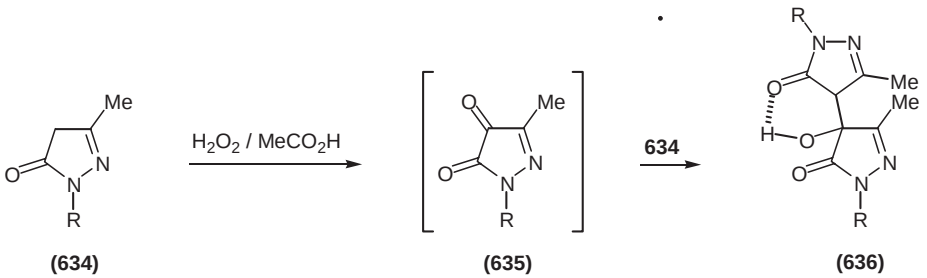
Scheme 185

followed by addition of the corresponding pyrazol-3-one **634** to the appropriate intermediate **635** (94JPR70) (Scheme 186).

C. Oxidative Coupling

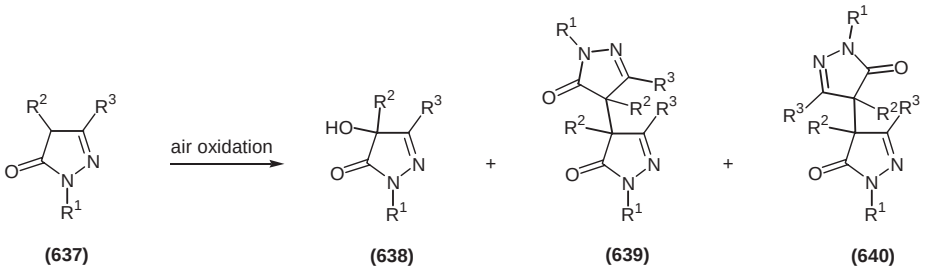
Slow air oxidation of 4,5-dialkylpyrazol-3-ones **637a–f** gave a mixture consisting of 4-hydroxypyrazol-3-ones **638a–f** resulting from the oxidation of H4 and chiral forms **639a–f** and **640a–f** resulting from oxidative coupling of the starting material at C4 (72ACS3685) (Scheme 187).

Mittra and Rout (69JIC893) and Mittra and co-workers (83JIC679) have oxidized 4,4′-benzylidenebipyrazol-3-ones **641a–c** and **643** by reaction with iodine and potassium iodide in 20% aqueous sodium hydroxide (Scheme 188). The corresponding oxidation products bipyrazolonecyclopropanes **642a–c** and dipyrazolonepyrazolthionecyclopropane **644** were isolated in good yields. Furthermore Mittra and co-workers (83JIC679) used the same reaction conditions to oxidize 5′-thioxo-4,4′-bipyrazolyl-3-one into 5′-thioxo-4,4′-bipyrazolyliden-3-one (Scheme 188).



(a) R = H, **(b)** R = Ph, **(c)** R = $CONH_2$

Scheme 186



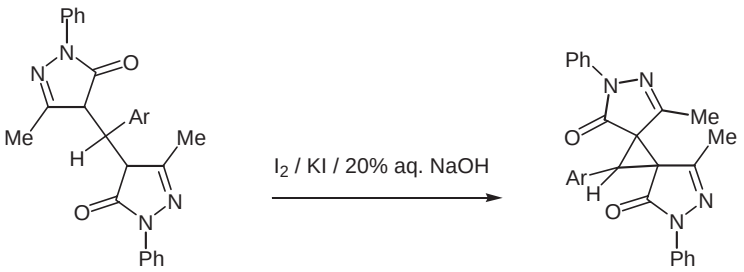
(a) R^1 = H, R^2 = Bz, R^3 = Me, **(b)** R^1 = Me, R^2 = Bz, R^3 = Me, **(c)** R^1 = R^3 = Ph, R^2 = Me, **(d)** R^1 = Ph, R^2 = R^3 = Me, **(e)** R^1 = Ph, R^2 = *n*-Bu, R^3 = Me, **(f)** R^1 = Ph, R^2 = Bz, R^3 = Me

Scheme 187

Pfeiffer et al. (92JPR365) (Scheme 189) demonstrated that oxidative coupling of pyrazol-3-one **62** with (3*H*-thiazol-2-ylidene)hydrazine **648a**–**f** gave 4-[(3*H*-thiazol-2-ylidene)hydrazono]pyrazol-3-one **649a**–**f** by two methods. In the first method potassium hexacyanoferrate was used as oxidant with hydrazones **648a**–**f** as free bases. In the second method peroxidase and 30% aqueous hydrogen peroxide were used as oxidants with hydrochloric salts of hydrazones **648a**–**f**. Aqueous DMF was the solvent in both cases. The yields of **649a**–**f** by both methods were nearly quantitative.

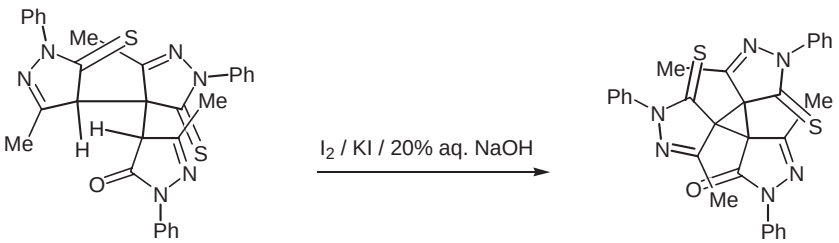
D. With Ozone

Harnish et al. (69JOC1687) (Scheme 190) introduced a dilute stream of ozone and oxygen into a methylene chloride solution of pyrazol-3-one azomethine **650** and obtained major reaction products **651a**–**d**, and minor reaction products **652e**,**f** and **653g**,**h**.

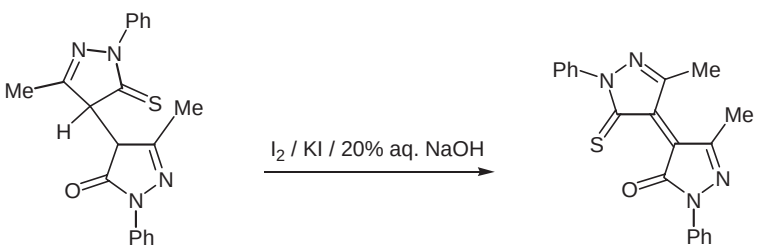


(641) **(642)**

(a) Ar = Ph, **(b)** Ar = 4-ClC_6H_4, **(c)** Ar = 3-$NO_2C_6H_4$

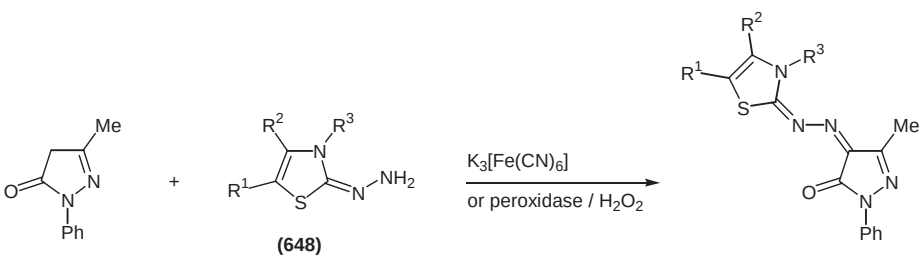


(643) **(644)**



(645) **(646)**

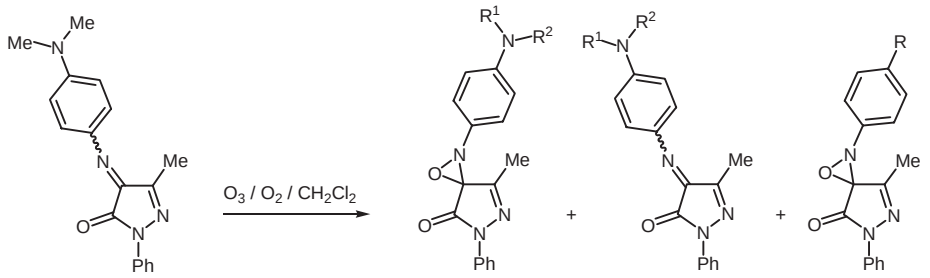
Scheme 188



(62) **(648)** **(649)**

(a) $R^1 = R^3 = Me$, $R^2 = Ph$, **(b)** $R^1 = Me$, $R^2 = R^3 = Ph$, **(c)** $R^1 = R^2 = Ph$, $R^3 = Me$,
(d) $R^1 = R^2 = R^3 = Ph$, **(e)** $R^1 = R^2 = Ph$, $R^3 = i$-Pr, **(f)** $R^2 = R^3 = Me$, $R^1 = CO_2Et$

Scheme 189

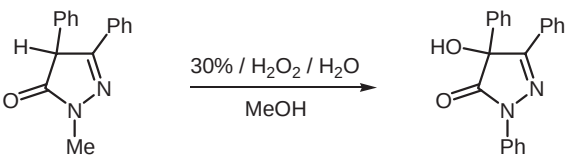


(a) $R^1 = R^2 = Me$, **(b)** $R^1 = H$, $R^2 = Me$, **(c)** $R^1 = H$, $R^2 = CHO$, **(d)** $R^1 = Me$, $R^2 = CHO$, **(e)** $R^1 = H$, $R^2 = Me$, **(f)** $R^1 = Me$, $R^2 = CHO$, **(g)** $R = NO_2$, **(h)** $R = NH_2$

Scheme 190

E. With Hydrogen Peroxide

Nye and Tany (73CJC338) (Scheme 191) oxidized 2,4-dihydropyrazol-3-one **654** with 30% hydrogen peroxide in methanol at C4 to give 4-hydroxypyrazol-3-one **655**, in 76% yield.

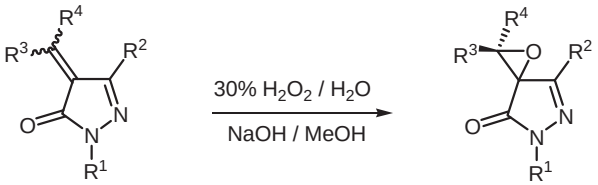


Scheme 191

Oxidation of 4-(substituted methylene)pyrazol-3-ones **656a**–**n** with 30% hydrogen peroxide in methanolic sodium hydroxide afforded the 1-oxa-5,6-diazaspiro[2,4]-hept-6-ene-4-ones **657a**–**n** in good yields The conformation of **657m** was determined by X-ray crystallography and found to have the (2R, 3R) configuration. Similar geometry was assigned to compound **657l**, however the configuration of **657n** was assigned (2S,3R) (83JCS(P1)325) (Scheme 192).

F. With 4-Chlorobenzoic Acid

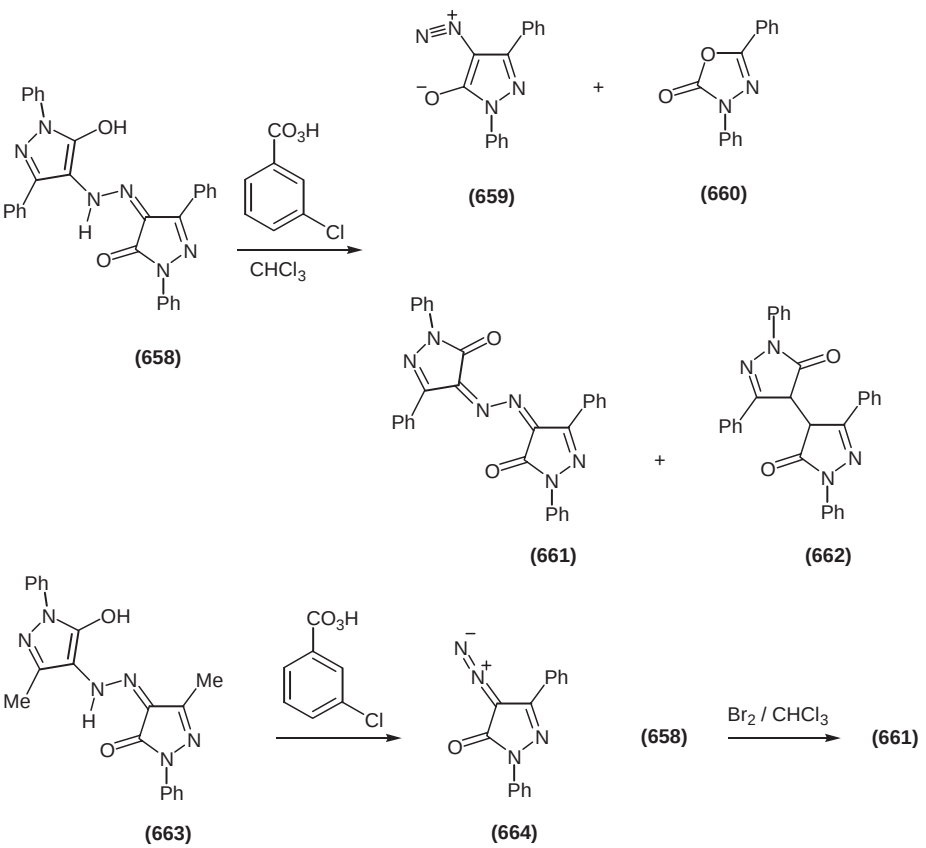
Oxidative cleavage of pyrazol-4,5-dione-4-[*N*-(pyrazol-4-yl)]hydrazone **658** occurred when this compound was oxidized with 4-chloroperbenzoic acid (73G179) (Scheme 193) to give pyrazole diazonium salt **659** in 72% yield, oxadiazol-5-one **660** in 0,5% yield, hydrazone derivative **661** in 10% yield and the bispyrazole **662** in 17% yield. Oxidation of hydrazone **663** under similar conditions



(656) **(657)**

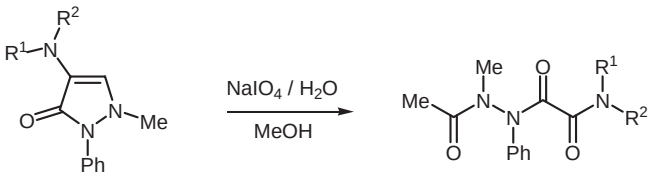
(a) R^1 = Ph, R^2 = R^3 = R^4 = Me, **(b)** R^1 = R^2 = Ph, R^3 = R^4 = Me, **(c)** R^1 = 4-$MeOC_6H_4$, R^2 = R^3 = R^4 = Me, **(d)** R^1 = R^4 = Ph, R^2 = Me,R^3 = H, **(e)** R^1 = R^2 = R^4 = Ph, R^3 = H, **(f)** R^1 = 4-$MeOC_6H_4$, R^2 = Me, R^3 = H, R^4 = Ph, **(g)** R^1 = 4-$NO_2C_6H_4$, R^2 = Me, R^3 = H, R^4 = Ph, **(h)** R^1 = Ph, R^2 = Me, R^3 = H, R^4 = 4-$Cl_2C_6H_4$, **(i)** R^1 = Ph, R^2 = Me, R^3 = H, R^4 = 4-$NO_2C_6H_4$, **(j)** R^1 = Ph, R^2 = Me, R^3 = H, R^4 = 2-naphthyl, **(k)** R^1 = R^2 = Ph, R^3 = H, R^4 = 2-naphthyl**,** **(l)** R^1 = R^3 = Ph, R^2 = EtO, R^4 = H, **(m)** R^1 = 4-$NO_2C_6H_4$, R^2 = EtO, R^3 = Ph, R^4 = H, **(n)** R^1 = 4-$NO_2C_6H_4$, R^2 = pyrrolidino, R^3 = Ph, R^4 = H

Scheme 192



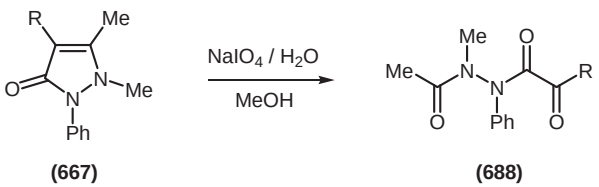
(658) **(659)** **(660)** **(661)** **(662)** **(663)** **(664)**

Scheme 193



(665) **(666)**

(a) $R^1 = R^2 = H$, **(b)** $R^1 = H$, $R^2 = Me$, **(c)** $R^1 = R^2 = Me$, **(d)** $R^1 = H$, $R^2 = i\text{-Pr}$,



(667) **(688)**

R = H, Me, Et, *i*-Pr or OH

Scheme 194

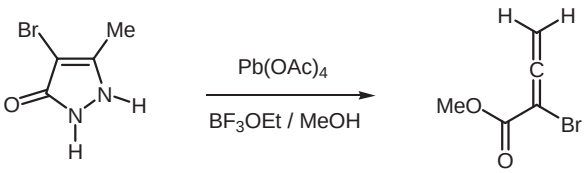
gave pyrazol-3-one diazonium salt **664** in 63% yield. The other components of this reaction were not identified. A more selective oxidation of hydrazone **658** took place when bromine in chloroform was used. Hydrazone derivatives **661** was obtained in about 90% yield (Scheme 193).

G. With Sodium Metaperiodate

Sodium metaperiodate in aqueous methanolic solution oxidatively cleaved pyrazol-3-ones **665a–d** into **666a–d** in 64–98% yield. Under the same conditions pyrazol-3-ones **667a–e** were cleaved to give the respective **668a–e** in 49–94% yield (88AP551) (Scheme 194).

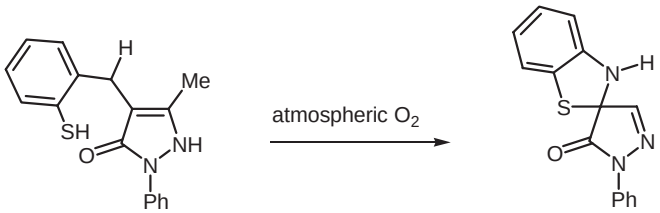
H. With Lead(IV) Acetate

Gillman et al. (94SC2133) (Scheme 195) found a convenient method to prepare methyl 2-bromo-2,3-butadienoate **670** via oxidative ring cleavage of



(669) **(670)**

Scheme 195



(671) **(672)**

Scheme 196

4-bromopyrazol-3-one **669** using lead(IV) acetate and boron trifluoride etherate in 59% yield. Compounds such as **670** are valuable building blocks for the synthesis of 2-aryl and 2-alkenyl substituted alka-2,3-dienoates via palladium-catalysed cross-coupling reactions.

I. By Atmospheric Oxidation

Coutts et al. (76CJC993) (Scheme 196) managed to convert pyrazol-3-one **671** into spiro compound **672** by subjecting an ethanolic solution of **671** to atmospheric oxidation for 48 h. Compound **672** was obtained in 33% yield.

XV. Reduction

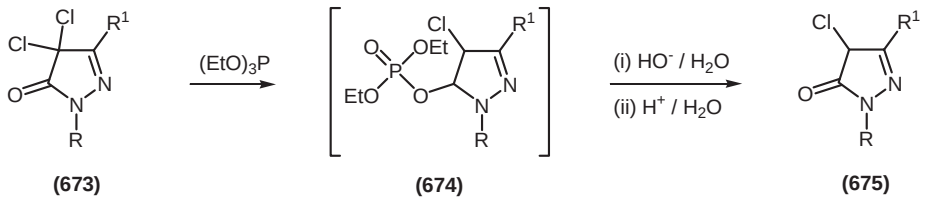
Reductions affecting the ring atoms of a pyrazol-3-one are of two types. Selective reductions of a dichloromethyl group into a chloromethyl group and the reduction of the lactam carbonyl into either a methylene group or a secondary alcohol. Exocyclic double bonds at C4 of pyrazol-3-ones such as imino groups of oximes and various alkenyl derivatives are prone to reduction under relatively mild conditions.

A. Of 4,4-Dichloropyrazol-3-ones

Selective reduction of 4,4-dichloropyrazol-3-ones **673** has been accomplished in a two-step process involving first reaction with triethyl phosphite followed by alkaline hydrolysis of the intermediate phosphate ester **674**. 4-chloropyrazol-3-ones **675** were obtained in yields ranging from 60–80% (77USP4021445) (Scheme 197).

B. Of the Carbonyl Group Of Pyrazol-3-ones

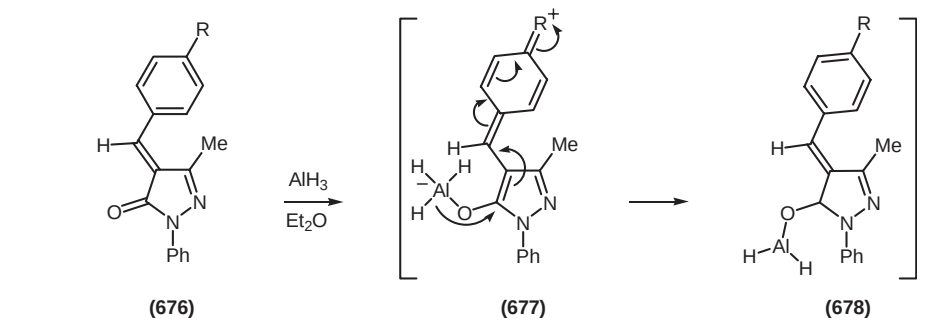
Abdel-Hamid and co-workers (91BCJ3713, 91BSF884) (Scheme 198) studied the kinetics of the chemical and electrochemical reduction of 4-(arylmethylene)-pyrazol-3-ones **676a**,**b** and 4,4-dimethylpyrazol-3-one **681**. The study was conducted in



(673) (674) (675)

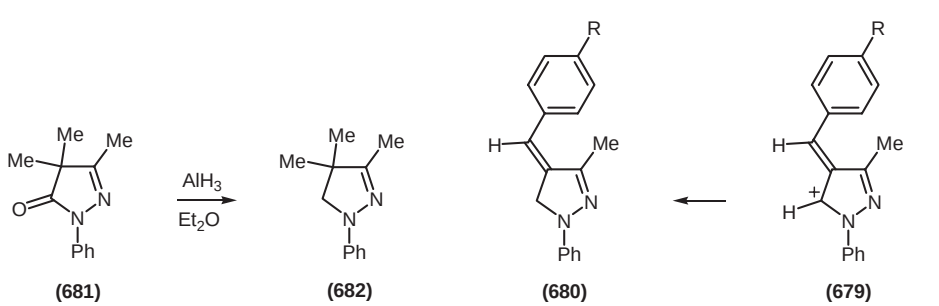
R = CH_2CF_3, Ph or 2,4,6-$(Cl)_3C_6H_2$, R^1 = NH_2, Me or 4-ClC_6H_4NH

Scheme 197



(676) (677) (678)

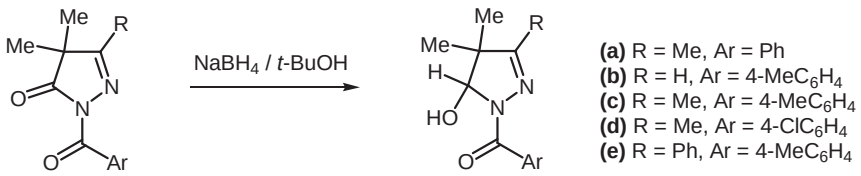
(a) R = OMe,
(b) R = Br



(681) (682) (680) (679)

Scheme 198

tetraethylammonium perchlorate and DMF solution using a hanging dropping mercury electrode. The products exhibited two diffusion-controlled irreversible mono electronic CV waves. Both waves follow $E_{rev}C_{irr}$ kinetics and are attributed to pyrazoles **680a**,**b** and **682**, where reduction of the carbonyl group selectively occurred. Chemical reduction of pyrazol-3-ones **676a**,**b** and **681** was carried out by aluminium hydride in diethyl ether. Selective reduction of the carbonyl group also occurred to give pyrazoles **680a**,**b** and **682** in 50, 80 and 22% yield, respectively. In the proposed mechanism for this reduction, coordination is first assumed to occur between the carbonyl oxygen and the aluminium followed by intramolecular hydride



(683) (684)

(a) R = Me, Ar = Ph
(b) R = H, Ar = 4-MeC_6H_4
(c) R = Me, Ar = 4-MeC_6H_4
(d) R = Me, Ar = 4-ClC_6H_4
(e) R = Ph, Ar = 4-MeC_6H_4

Scheme 199

transfer in **677** and hydrolysis of **678**, and finally hydride addition to cation **679** to give **680**. Intermediate **677** must play an important stabilizing role facilitating the reduction.

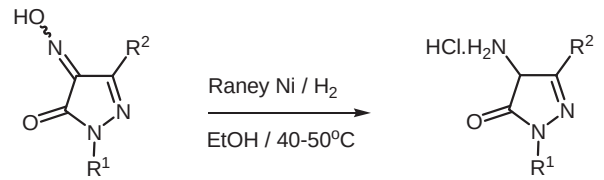
Mitikidou and Stephanidou-Stephanatou (91JHC49) (Scheme 199) managed to reduce the ring carbonyl group of 1-acylpyrazol-3-ones **683a–e** into the corresponding alcohols **684a–e** by reaction with sodium borohydride in *t*-butanol.

C. Reduction of Exocyclic Double Bonds

Khaikin et al. (65ZOR133) (Scheme 200) reduced thirteen (*E*/*Z*)-pyrazol-3-one-4-oximes **685a**,**b** by catalytic hydrogenation in ethanol at 40–50 °C using Raney nickel catalyst, and obtain fairly good yields of the corresponding 4-aminopyrazol-3-one hydrochlorides **686a**,**b**.

Coutts et al. (75CJC3637) and Wrzeciono et al. (78PHA264) (Scheme 201) reduced the respective 4-[(2-nitrophenyl)methylidene]pyrazol-3-ones **687a–c** and 4-[(2-furfuryl)methylidene]pyrazol-3-ones **687d–i** with sodium borohydride in 1,4-dioxane and obtained the corresponding pyrazol-3-ones **688a–i** in moderate to good yields. Compounds **688d–i** exhibited significant antibacterial action against *Escherichia coli* K12.J5, *Salmonella panama* Nr. 73 and *Staphylococcus aureus* 209P strains.

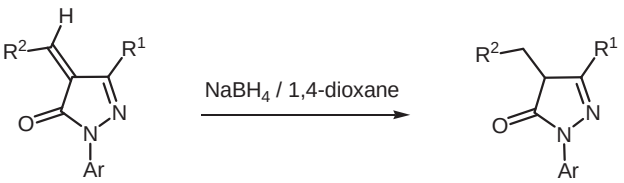
In an attempt to synthesize 4-phenylmethylidene-3-phenyliminopyrazoles **691** Tomasik and co-workers (01ARK63) (Scheme 202), condensed 4-phenylmethylidenepyrazol-3-ones **689** (R = Me or MeO) with anilines **690a–p** under various



(685) (686)

(a) R^2 = Me, R = C_6H_{11}, C_6H_{13}, $PhCH_2$, $Ph(CH_2)_2$, Ph, 2-MeC_6H_4, 4-MeC_6H_4 or 2-$MeOC_6H_4$, **(b)** R^2 = Ph, R^1 = H or Me

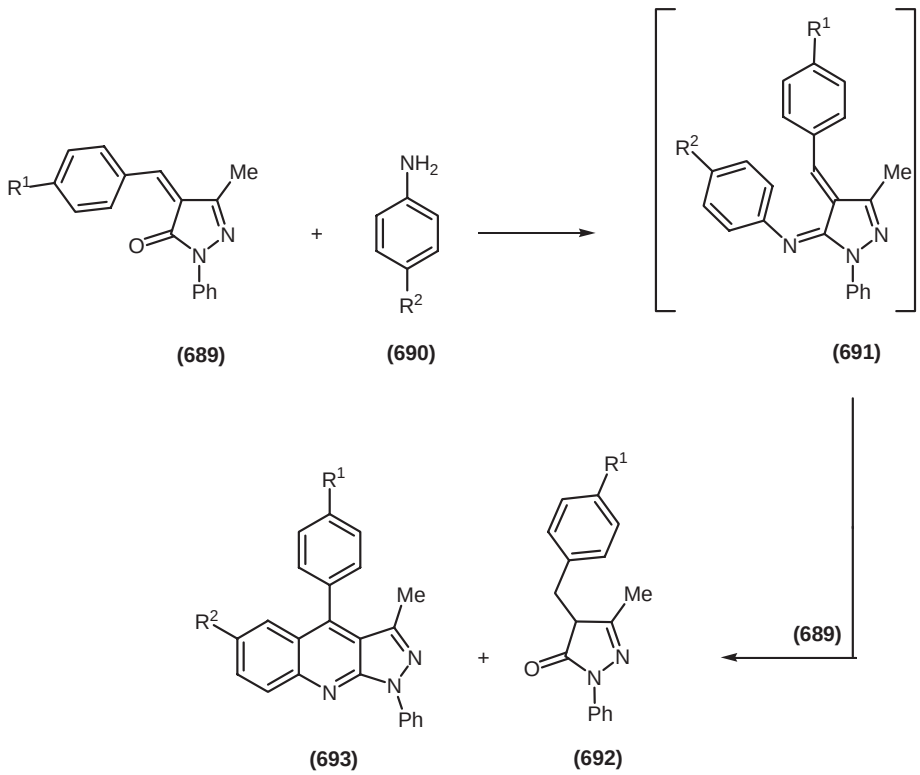
Scheme 200



(687) **(688)**

(a) R^1 = Me, R^2 = 2-$NO_2C_6H_4$, Ar = Ph, **(b)** R^1 = Ar = Ph, R^2 = 2-$NO_2C_6H_4$,
(c) R^1 = Me, R^2 = 2-NO_2-5-ClC_6H_3, **(d)** R^1 = Me, R^2 = furfur-2-yl, Ar = 2-ClC_6H_4,
(e) R^1 = Me, R^2 = furfur-2-yl, Ar = 3-ClC_6H_4, **(f)** R^1 = Me, R^2 = furfur-2-yl, Ar = 4-ClC_6H_4, **(g)** R^1 = Me, R^2 = 5-NO_2furfur-2-yl, Ar = 2-ClC_6H_4,
(h) R^1 = Me, R^2 = 5-NO_2furfur-2-yl, Ar = 3-ClC_6H_4,
(i) R^1 = Me, R^2 = 5-NO_2furfur-2-yl, Ar = 4-ClC_6H_4,

Scheme 201



(a) R^1 = R^2 = MeO, **(b)** R^1 = MeO, R^2 = H, **(c)** R^1 = MeO, R^2 = Me, **(d)** R^1 = MeO, R^2 = *t*-Bu, **(e)** R^1 = MeO, R^2 = F, **(f)** R^1 = MeO, R^2 = Cl, **(g)** R^1 = MeO, R^2 = Br, **(h)** R^1 = Me, R^2 = H, **(i)** R^1 = R^2 = Me, **(j)** R^1 = Me, R^2 = Et, **(k)** R^1 = Me, R^2 = *n*-Bu, **(l)** R^1 = Me, R^2 = F, **(m)** R^1 = Me, R^2 = Cl, **(n)** R^1 = Me, R^2 = Br, **(o)** R^1 = Me, R^2 = MeO, **(p)** R^1 = Me, R^2 = PhO

Scheme 202

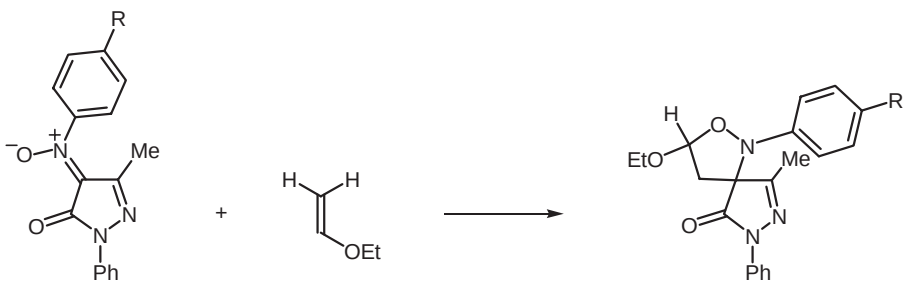
conditions such as heating in the presence of anhydrous zinc chloride, with phosphorus pentoxide in xylene or in ethylene glycol. The resulting products were 4-benzylpyrazol-3-one **692** (R^1 = Me or MeO) and pyrazolo[3,4-*b*]quinolines **693a–p** in a ratio of 1:1. It was suggested that pyrazol-3-ones **689** acted as oxidants on the initially formed pyrazoles **691** that led to products **692**.

XVI. Cycloaddition

Pyrazol-3-one derivatives have taken part in both 1,3-dipolar cycloaddition and Diels–Alder reactions. The 1,3-dipolar cycloaddition between (*Z*)-pyrazol-3-ones **694a–g** with an excess of ethyl vinyl ether gave the pyrazol-3-one-4-spiro-3-isoxazolidines **695a–g**, in nearly quantitative yield (82G483) (Scheme 203). The kinetics of this reaction was studied by quantitative spectroscopic analysis. The rate of reaction increases with the electron-withdrawing character of the substituent on the aromatic ring and a linear relationship is obtained between $\log k$ and σp constants. The LUMO nitrone–HOMO vinyl ether is taken as the dominant interaction.

Tacconi and co-workers (79JCS(P1)856) (Scheme 204) describe the [4 + 2] and [2 + 2] cycloaddition of 4-arylidenepyrazol-3-ones **696a–d** and **697e–m** with *N*,*N*′-diethylaminomethylacetylene. Pyrazol-3-ones **696a–d** have an (*E*)-configuration and pyrazol-3-ones **697e–k** have a (*Z*)-configuration. The reaction was performed in cooled benzene and gave a mixture of two products, pyrano[2,3-*c*]pyrazoles **698a–k** via a [4 + 2] cycloaddition and (4*Z*,2′*E*)-4-(1-diethylamino-2-methyl-3-arylpropenylidene)pyrazol-3-ones **670a–k** via a [2 + 2] cycloaddition to give intermediate spirocyclobutenepyrazol-3-ones **699**, followed by electrocyclic ring opening. Both products were obtained in almost quantitative yield and could be separated by fractional crystallization or column chromatography.

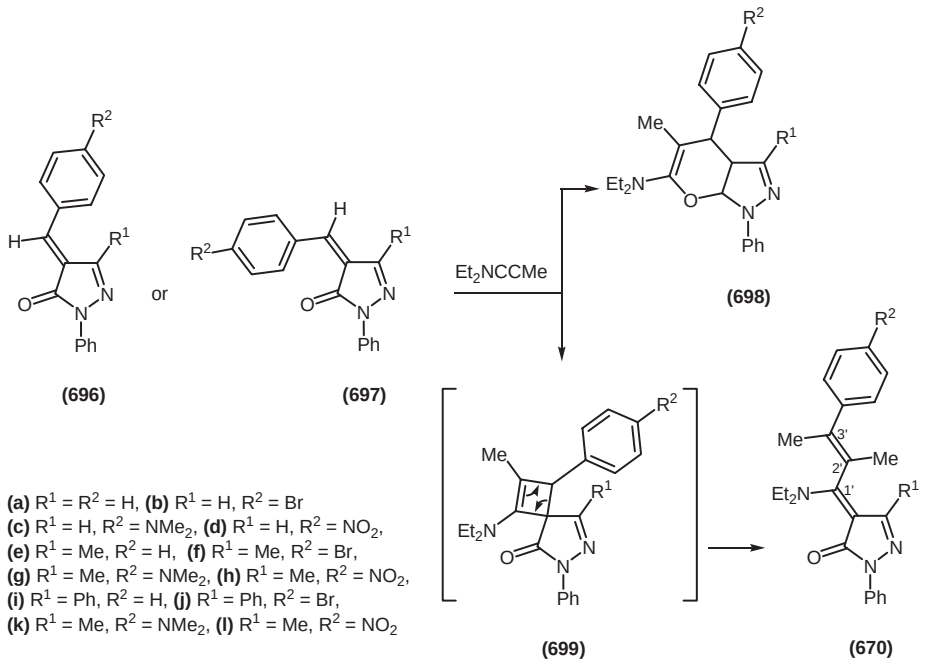
Righetti and co-workers (85TL3137, 88T5229) (Scheme 205) studied the thermal reaction between 4-arylidenepyrazol-3-ones and 2,3-dimethylbutadiene with the purpose of evaluating the electronic and configurational factors that affect the



(694) **(695)**

(a) R = H, **(b)** R = Me **(c)** R = Cl, **(d)** R = Br, **(e)** R = I, **(f)** R = NO_2, **(g)** R = CO_2Me

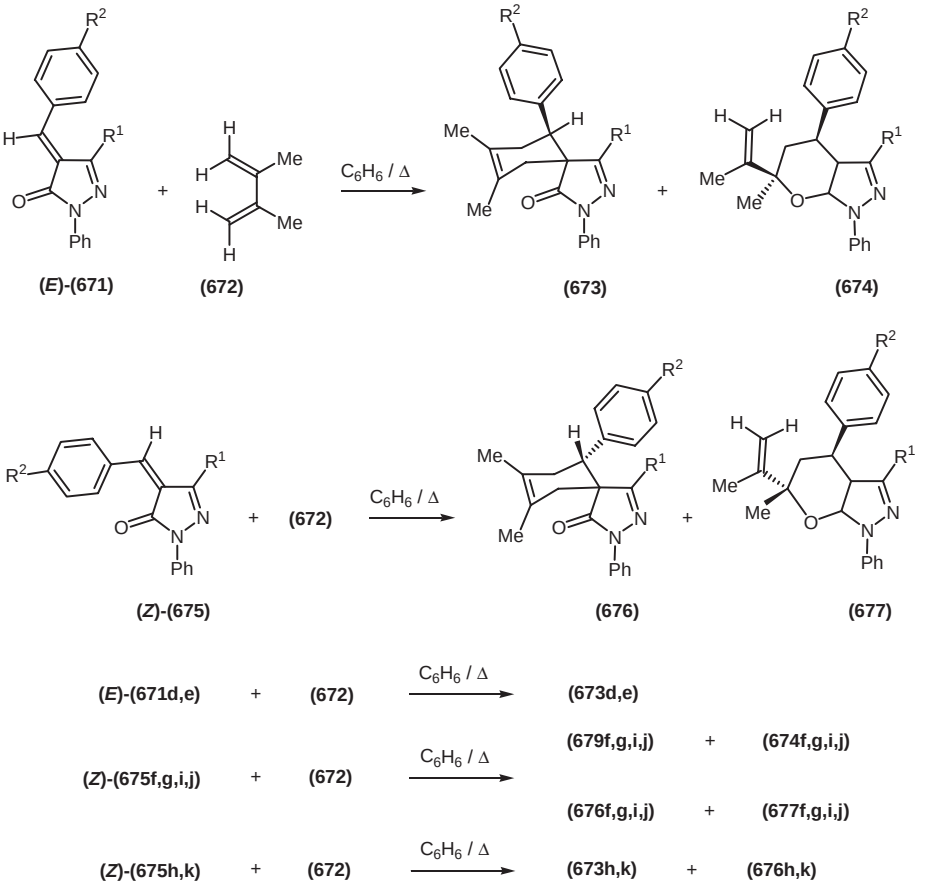
Scheme 203



Scheme 204

reactivity, as well as the influence of various catalysts on both reactivity and selectivity. The solvent for the thermal reactions was benzene and the temperature 80 or 120 °C. Thermal reaction of (*E*)-4-arylidenepyrazol-3-ones **671a**–**c**, with $R^2 =$ H or an electron-withdrawing group on the arylidene substituent and 2,3-dimethylbutadiene **672** at 80 °C gave a mixture of Diels–Alder adducts **673a**–**c** in 90% yield and heterodiene adducts **674a**–**c** in 10% yield. (*E*)-4-Arylidenepyrazol-3-ones **671d**,**e** with electron-releasing groups on the arylidene substituent react with **672** at 120 °C to give Diels–Alder adducts **673d**,**e** as single products in 90 and 97% yield, respectively. The reaction of (*Z*)-4-arylidenepyrazol-3-ones **675f**,**g**,**i**,**j** with **672** at 80 °C gave both Diels–Alder adducts **673f**,**g**,**i**,**j** and **676f**,**g**,**i**,**j** and heterodiene adducts **674f**,**g**,**i**,**j** and **677f**,**g**,**i**,**j**. The yield of adducts **673f**,**g**,**i**,**j** are 73,48, 40 and 40%, of adducts **674f**,**g**,**i**,**j** 8, 6, 20 and 20%, of adducts **676f**,**g**,**i**,**j** 14, 40, 25 and 25% and of adducts **677f**,**g**,**i**,**j** 2, 4, 10 and 10%, respectively. Interestingly, (*Z*)-4-arylidenepyrazol-3-ones **675h**,**k** and **672** at 120 °C gave a mixture of Diels–Alder adducts **673h**,**k** in 85 and 52% yield and **676h**,**k** in 9 and 43% yield, without any trace of heterodiene adducts.

The reasoning given by the authors for the outcome of these reactions is the following. Electron-releasing substituted pyrazol-3-ones (*E*)-**671d**,**e**, and (*Z*)-**675h**,**k**, (Scheme 205) did not yield dihydropyran derivatives because at 120 °C they underwent [3.3] sigmatropic rearrangement to become spirocyclohexene derivatives. The reactions of (*E*)-pyrazol-3-ones **671a**–**c** were stereospecific as explained by the Diels–Alder reactions occurring with retention of configuration of the dieniphile, and the heterodiene reactions occurring through a stabilized endo transition state.



(a) $R^1 = R^2 = H$, **(b)** $R^1 = H$, $R^2 = NO_2$ **(c)** $R^1 = H$, $R^2 = CN$, **(d)** $R^1 = H$, $R^2 = OMe$, **(e)** $R^1 = H$, $R^2 = NMe_2$, **(f)** $R^1 = Me$, $R^2 = H$, **(g)** $R^1 = Me$, $R^2 = NO_2$, **(h)** $R^1 = Me$, $R^2 = NMe_2$, **(i)** $R^1 = Ph$, $R^2 = H$, **(j)** $R^1 = Ph$, $R^2 = NO_2$, **(k)** $R^1 = Ph$, $R^2 = NMe_2$

Scheme 205

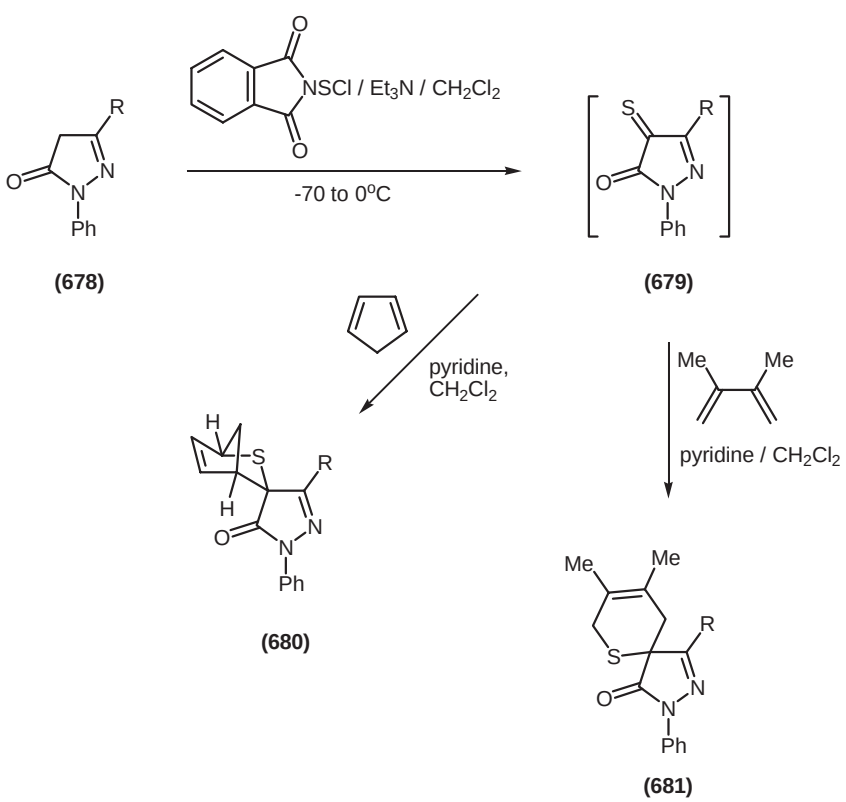
The reactions of (*Z*)-pyrazol-3-ones **675f–k** were not stereospecific since both diastereoisomers **673** and **676** and **674** and **677** were obtained.

The thermal reaction of both (*E*)- and (*Z*)-4-arylidenepyrazol-3-ones **671** and **675** with **672** was influenced dramatically in the presence of acids. For example, in the reaction **671a** with **672a** not only the rate was found to increase dramatically in the presence of $AlCl_3$ or $TiCl_4$ (4 h at room temperature) but also the chemoselectivity was changed since the diene adduct **673a** was the only product, in 95 and 90% yield, respectively. The same occurred with (*E*)-4-arylidenepyrazol-3-ones **671b–d** and **672**, $AlCl_3$ acting more efficiently than other catalysts ($TiCl_4$ or CF_3CO_2H) since single products **673b–d** were obtained in about 95% yield. With (*Z*)-arylidenepyrazol-3-ones **675** the reaction with **672** in the presence of various acids catalysts was not as chemoselective. The reaction with the highest chemoselectivity was between

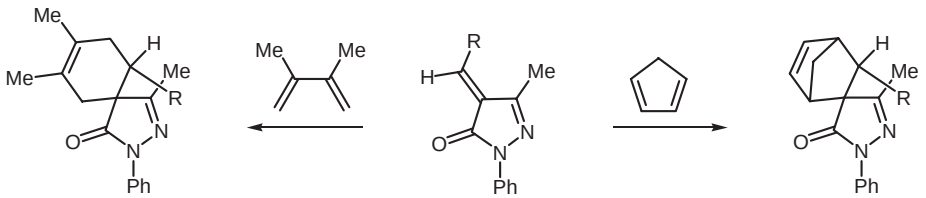
(*Z*)-benzylidenepyrazol-3-one **675f** and **672** in the presence of $AlCl_3$ that gave a mixture containing 92% of **673** and 3% of **676**.

Diels–Alder adducts of pyrazol-3-ones **678a**,**b** were obtained by reaction with *N*-chlorosulfenylphthalimide in chloroform at −70 °C. The predicted intermediate **679** was then treated with either cyclopenta-1,3-diene or 2,3-dimethylbuta-1,3-diene in a mixture of pyridine and dichloromethane at room temperature. The corresponding spiropyrazol-3-ones **680a**,**b** and **681a**,**b** were obtained in good yields (00CHE152) (Scheme 206).

The products of Diels–Alder reactions of polyfluoroalkylidenepyrazol-3-ones **682a**,**b** with 2,3-dimethylbutadiene and cyclopentadiene at room temperature and in the absence of catalysts are spiropyrazol-3-ones **683a**,**b** and **684**, respectively (00JFC111) (Scheme 207). The presence of a polyfluoroalkyl substituent at the exocyclic carbon bond of compounds **682a**,**b** increases its activity in reactions with dienes. The presence of four chiral carbon atoms in **684** caused complication in the ^1H and ^{19}F NMR spectra. Comparison of integrated intensities of the signals led the authors to conclude that one of the six possible pairs of diastereomers exists in more than 80%. The formation of only one pair of diastereomers has been observed in the case of compounds **683a**,**b**.



Scheme 206



(683) **(682)** **(684)**

(a) R = CF_3, **(b)** R = $(CF_2)_4H$, **(c)** R = CF_3, **(d)** R = $(CF_2)_4H$, **(e)** R = $(CF_2)_4H$

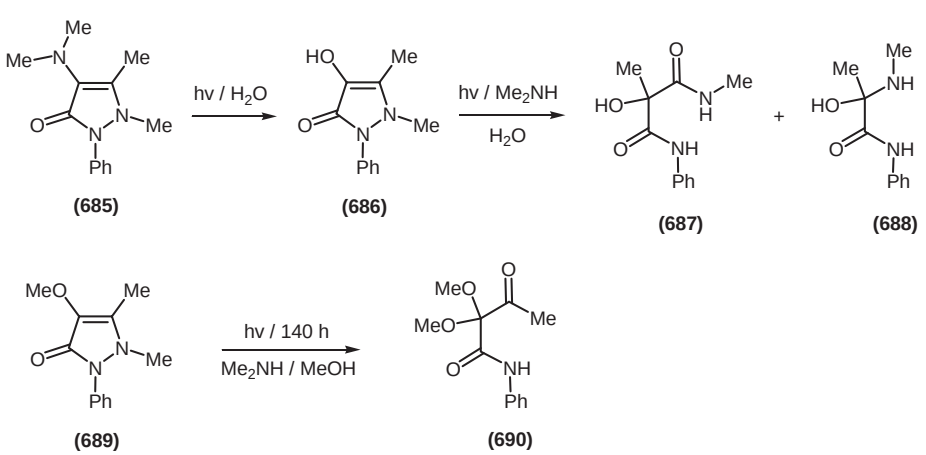
Scheme 207

XVII. Photolysis

The photo transformation of pyrazol-3-ones proceeds through one or more of a variety of pathways involving rearrangement, ring cleavage, fragmentation, oxidation, and solvolysis, and depends on the experimental conditions employed. A common feature in nearly all of these reactions was the fission of the ring N–N bond of the pyrazol-3-one ring. In some cases polymeric material was obtained.

One of the first reports on the photolysis of pyrazol-3-ones was in 1969 by Reisch and Fitzek (69TL271) (Scheme 208). Pyrazol-3-one **685** was photolysed in water to give 4-hydroxypyrazol-3-one **686**. Irradiation of the latter in the presence of an equimolar amount of aqueous dimethylamine led to the formation of 2-hydroxy-N^1, 2-dimethyl-N^3-phenylmalonamide **687** and 2-(methylamino)propanoyl-(phenyl)-carbamic acid **688**. Pyrazol-3-one **689** was irradiated for 140 h in methanol by light from a high pressure immersion Hg lamp to give 2,2-dimethoxy-3-oxo-*N*-phenylbutanamide **690** in 50% yield.

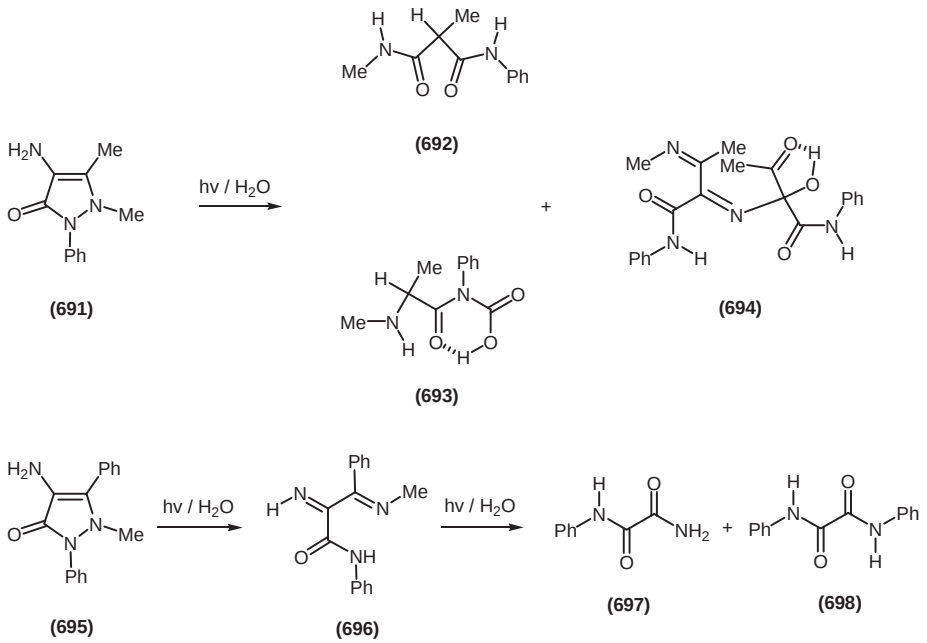
Five years later Reisch and Fitzek (74AP211) (Scheme 209) published another report on the photolysis of pyrazol-3-ones. Irradiation of 4-aminopyrazol-3-one **691**



(685) **(686)** **(687)** **(688)**

(689) **(690)**

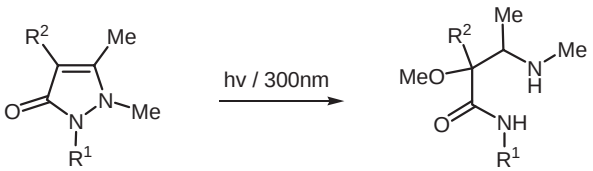
Scheme 208



Scheme 209

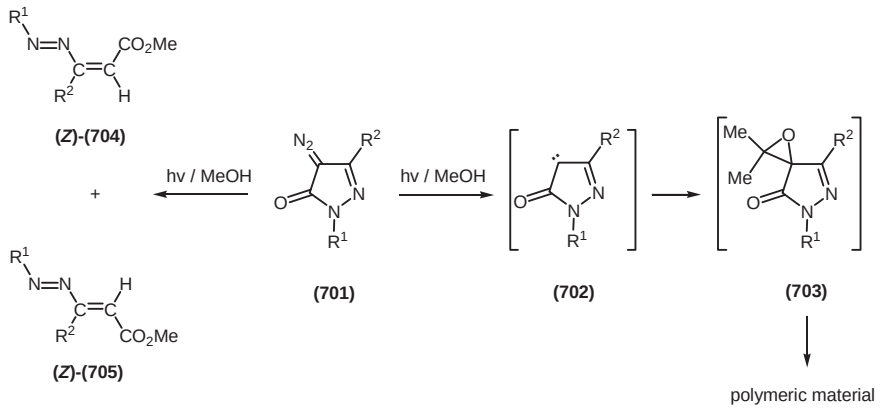
in aqueous solution gave **694** in addition to **692** and **693**, the characteristic photolysis products of pyrazol-3-ones. Intermediate **696** was isolated after irradiating 4-aminopyrazol-3-one **695** in water. Compound **696** upon further irradiation fragments into *N*-phenylethanediamide **697** and *N*,*N*′-diphenylethanediamide **698**.

When Cardy and Poquet (81T2279) (Scheme 210) irradiated at 300nm pyrazol-3-ones **699a**–**c** in methanol, cleavage occurred between the two nitrogen atoms to give the corresponding 2-methoxy-*N*-methyl(or phenyl)-3-methyliminobutanamides **700a**–**c**. When the substituent at position 4 is an electronegative group, the product is stabilised. The STO/3G *ab initio* calculations were used to study the photo cleavage and the influence of the C4 substituent, giving evidence of a mechanism which involves triplet excited states of the π,σ^* type.



(a) R^1 = Me, R^2 = H, **(b)** R^1 = R^2 = Me
(c) R^1 = Ph, R^2 = H, NH_2, NMe_2, OH or OMe

Scheme 210

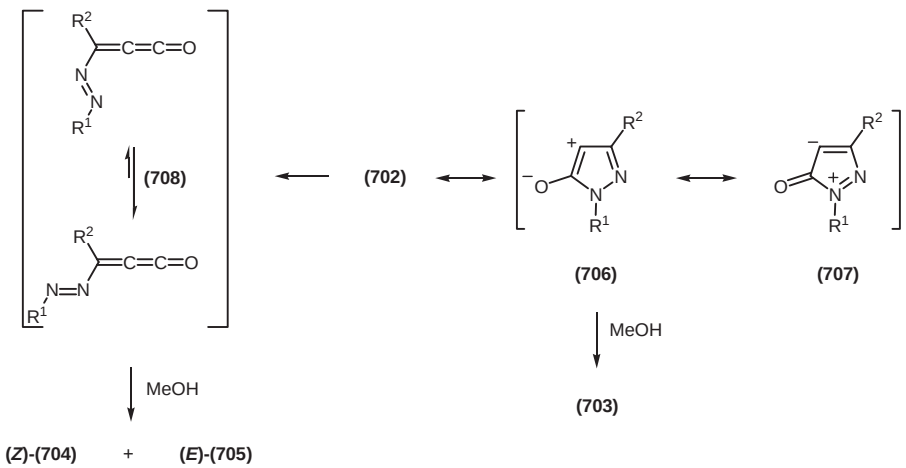


(a) R^1 = Ph, R^2 = Me, **(b)** R^1 = R^2 = Ph, **(c)** R^1 = Me, R^2 = Ph, **(d)** R^1 = 4-$MeOC_6H_4$, R^2 = Me

Scheme 211

Photolysis of 4-diazopyrazol-3-one **701a** in acetone was attempted by Griffin and co-workers (84CJC2456) (Scheme 211, 212) in order to see whether carbene **702**, a postulated intermediate, may be intercepted by acetone to give oxirane **703a**. However no isolable products and no chromatographic evidence for the formation of **703a** was obtained, apart from polymeric material. On the other hand photolysis of 4-diazopyrazol-3-ones **701a**,**b**,**e** in methanol gave a mixture of stereoisomeric (*Z*)- and (*E*)-arylazoalkenoic acids esters **704a**,**b**,**e** and **705a**,**b**,**e**, as well as polymeric material. The photolysis of 4-diazopyrazol-3-one **701c** in methanol gave methyl (*Z*)-3-methylazo-3-phenylpropenoate.

Two proposed mechanisms account for the formation of open-chain azoesters **704** and **705**. The initially formed carbene **702** has zwitterionic character, as depicted by resonance forms **706** and **707** (Scheme 212). Concerted or non-concerted



Scheme 212

nucleophilic attack and protonation of **702** in methanol results in the formation of (*Z*)-azoester **704** but fails to account for the presence of (*E*)-isomer **705**, unless it is assumed that rotation of the carbonyl function about the C4-C5 axis is possible in the transition state. In an alternative mechanism carbene **702** undergoes ring opening to ketene **708**, which subsequently is intercepted by methanol to give (*Z*)-**704** and (*E*)-**705**. The formation of (*Z*)-azoester **704c** exclusively by irradiating 4-diazopyrazol-3-one **701c** points to a direct attack of the nucleophilic solvent on carbene **702**. A study of the absorption spectra of the species generated upon steady-state photolyses in glasses at 77K, in solution at 296K and by laser and lamp flash photolysis experiments, suggests that a long-lived heterocyclic intermediate such as a carbene or its valence isomer, as well as a ketene generated by ring opening, are precursors to the esters.

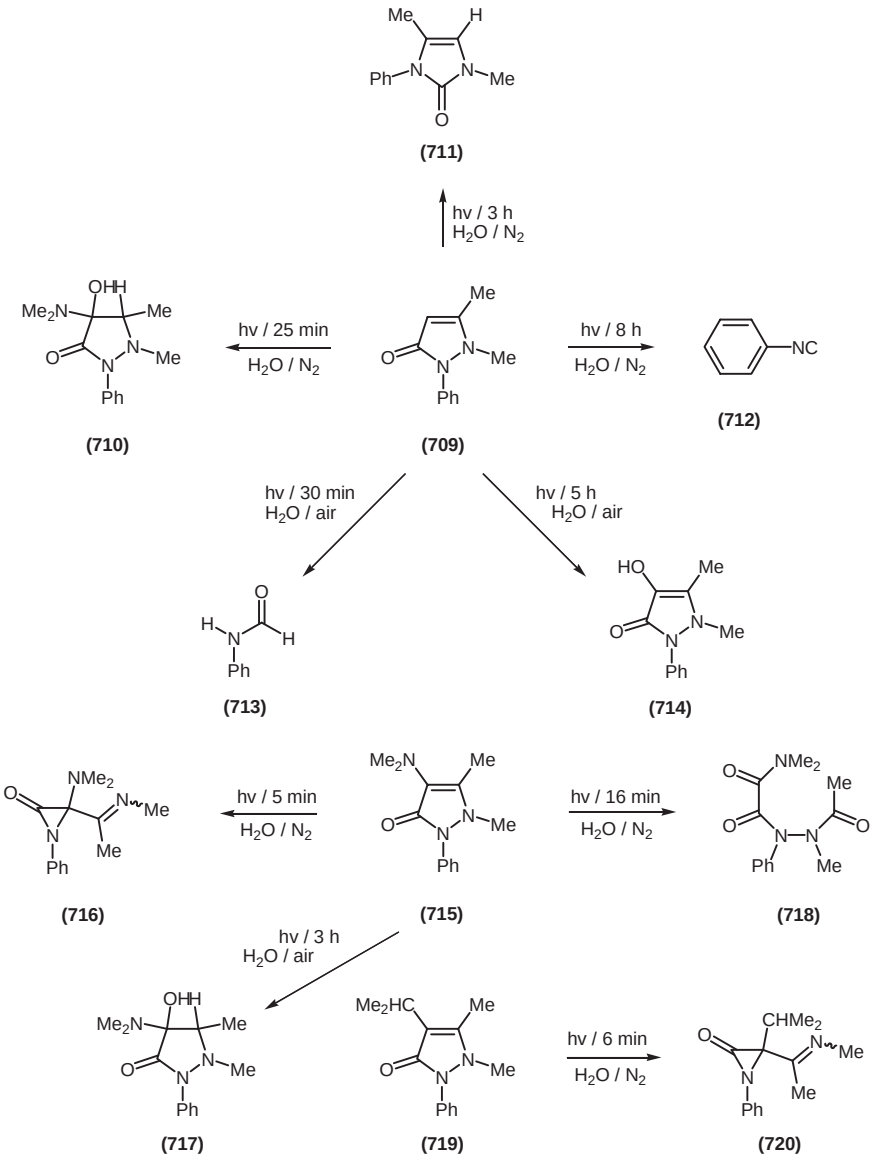
Marciniec (85PHA30) (Scheme 213) studied the photostability of eight pyrazol-3-ones that are important pharmaceuticals. These compounds are phenazone **709** aminophenazone **715**, propylphenazone **719**, nifenazone, morazone, noramidopyrine, 4-aminophenazone and isopropylaminophenazone. The reactions were done in a photoreactor with U.V. irradiation at 254 nm in an atmosphere of nitrogen or air. A total of 24 decomposition products were isolated by thin-layer chromatography and identified by u.v. and i.r. spectroscopy, mass spectrometry, and elemental analysis. The products of photochemical decomposition were compounds derived from the fission of the N–N pyrazol-3-one bond and then rearrangement, formation of a smaller ring of further fission, as well as compounds where oxidation had occurred and the pyrazol-3-one ring had remained intact. A representative number of reactions for three of the eight pyrazo-3-ones is shown in Scheme 213.

Ram and co-workers (81TL2213) (Scheme 214) studied the photo transformations of 2-benzylpyrazol-3-ones **721a**–**e** and found that benzyl migrations had occurred onto the intact pyrazol-3-one ring. The irradiation of **721a**–**e** was done at 254 nm in a nitrogen atmosphere with methanol solvent. The photoproducts were isolated by thick-layer chromatography and identified by u.v., i.r. and ^{1}H n.m.r. spectroscopy. The identified products were benzyloxypyrazoles **722a**–**e** in 18–25% yield obtained by N2 to O-benzyl migration, the betaines **723b**,**c** by N2 to C4 benzyl migration or the hydroxypyrazoles **724a**,**d**,**e** in 18–25% yield by N2 to C4 benzyl migration followed by phototropic shift, and the hydroxypyrazoles **725a**–**e** in 16–32% yield by the fragmentation followed by hydrogen abstraction, along with dibenzyl **726** in every case except **721d**. The authors propose a free radical mechanism involving the homolysis of the N–CH_2Ph bond and subsequent reactions of the radicals thus produced.

XVIII. Miscellaneous Reactions

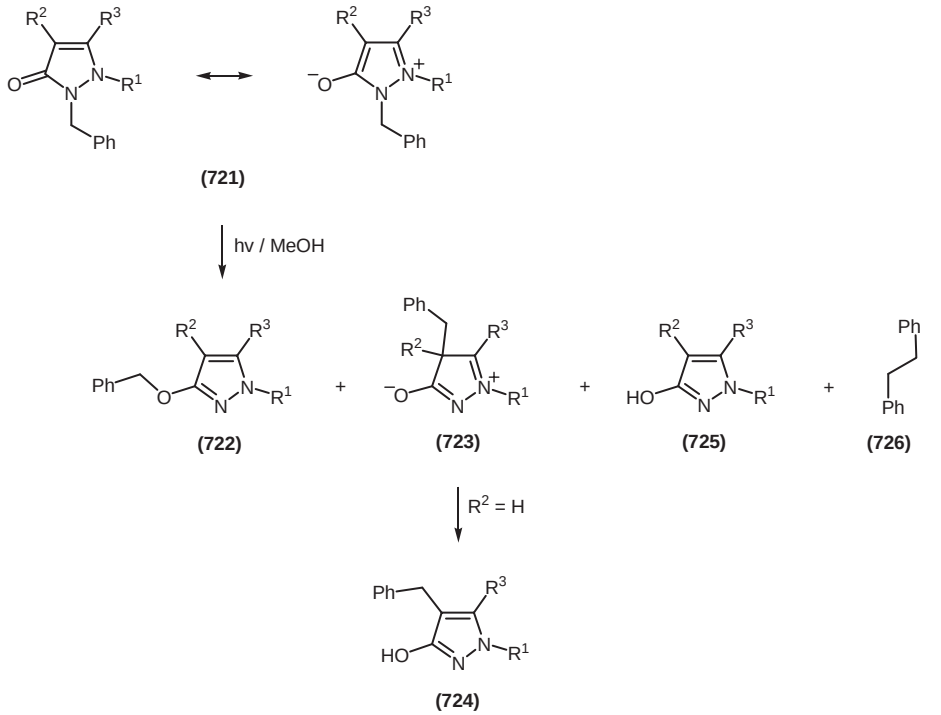
A. Radical Addition

This type of reaction was exemplified (96T1443) (Scheme 215) by treatment of 4-arylidenepyrazol-3-ones **728a**–**j** with equimolar amounts of 1,2-phenylenediamine



Scheme 213

and 1.5 molar excess of the appropriate arylaldehyde **727a**–**j**. The reaction took place in refluxing ethanol and gave reduced 4-substituted pyrazol-3-ones **729a**,**b**,**e**,**g** and/or 4,4′-linked bipyrazol-3-ones **730a**–**d**,**f**–**j** in moderate to good yields. A radical mechanism was proposed where the initiation process occurs via a single electron transfer, with the formation of an anion radical, which undergoes a proton transfer from the benzimidazoline ion radical, rapidly evolving reaction products.

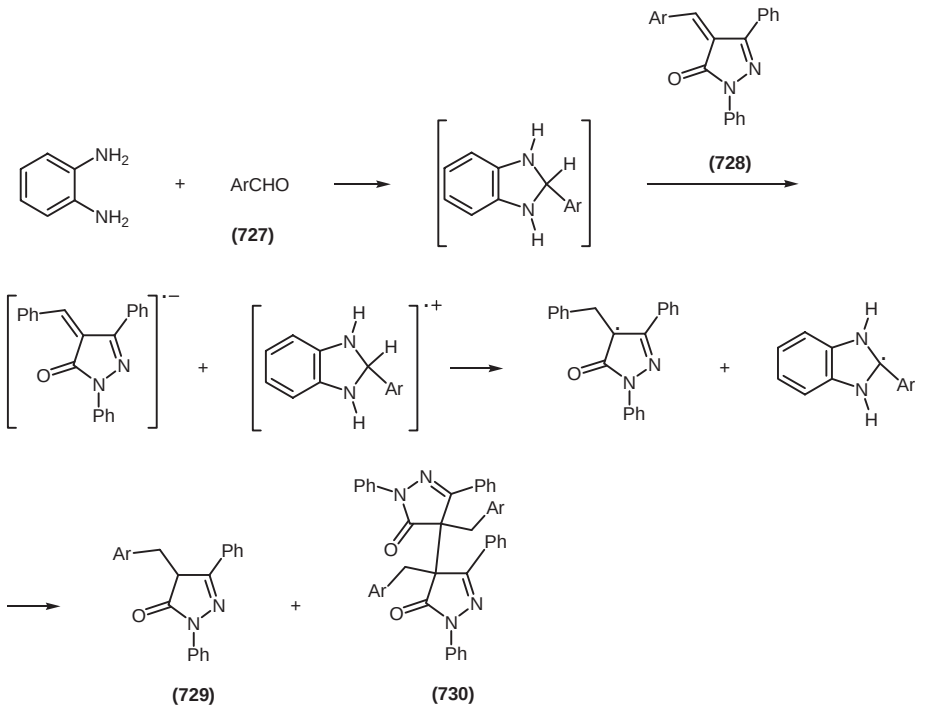


Scheme 214

B. Ring Cleavage Reactions

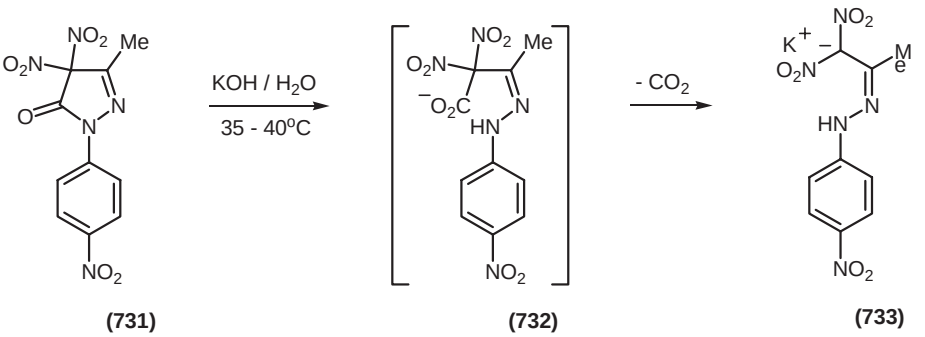
The pyrazol-3-one ring in these reactions is attacked by nucleophilic species at the carbonyl group or electrophilic species at a ring carbon. Subsequent ring opening by amide bond fracture may give stable compounds, or, ring closure may follow leading to a different ring structure. Thus addition of pyrazol-3-one **731** to aqueous potassium hydroxide at 35–40 °C afforded the decarboxylated 1,1-dinitroacetone potassium salt **733**. The mechanism is believed to proceed via nucleophilic attack of hydroxide ion on the amide carbonyl, cleavage of the amide bond, followed by decarboxylation of the intermediate carboxylate **732** (99T10447) (Scheme 216).

Phenyliodonium diacetate or iodosobenzene react electrophilically with 5-substituted pyrazol-3-ones **734a–h** in methanol at −23 °C to yield, after fragmentative loss of molecular dinitrogen, methyl 2-alkynoates **740a–h** (89T1605) (Scheme 217). However, 5-methyl-4-unsubstituted pyrazol-3-ones **740a–d** under similar conditions yielded methyl-2,3-allenic esters **744a–d** (Scheme 218). The yields from these two reactions range between 57 and 66%. The proposed mechanism for the synthesis of methyl 2-alkynoates **739a–h** involves generation of the tricoordinate a species (dimethoxyiodo)benzene, electrophilic addition of (dimethoxyiodo)benzene to give **735**, loss of methanol to form an intermediate ylide **736**, ligand transfer of a second molecule of (dimethoxyiodo)benzene to give **737** and then reductive elimination of iodobenzene to form intermediate **738**, and finally, oxidative



(a) R = Ph, **(b)** R = 3-MeC_6H_4, **(c)** R = 4-MeC_6H_4, **(d)** R = 2-$MeOC_6H_4$, **(e)** R = 3-$MeOC_6H_4$, **(f)** R =4-$MeOC_6H_4$, **(g)** R = 2-$EtOC_6H_4$, **(h)** R = 3-ClC_6H_4, **(i)** R = 4-ClC_6H_4, **(j)** R = 2,4,6-$(Me)_3C_6H_2$

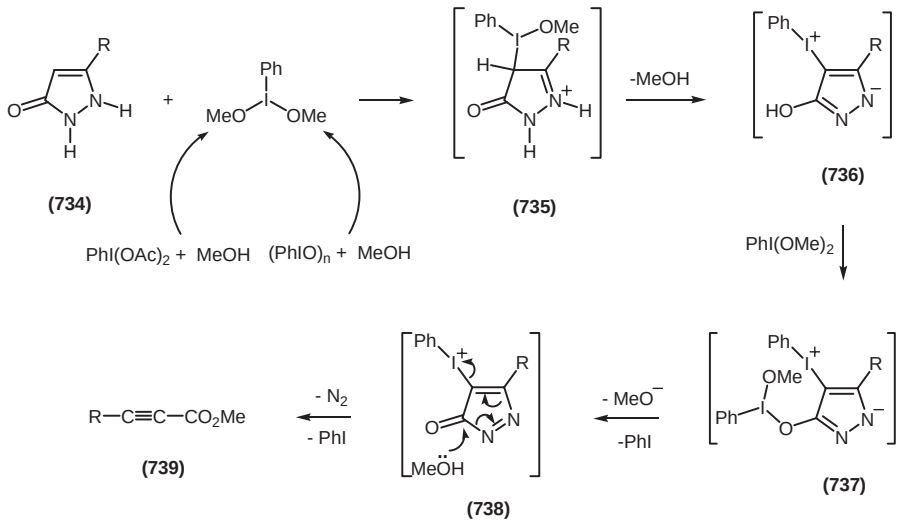
Scheme 215



Scheme 216

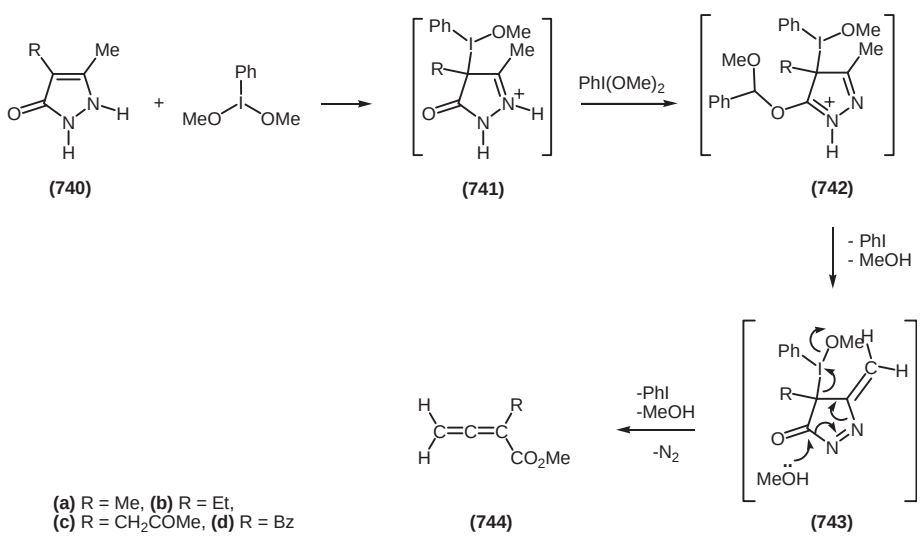
nucleophilic addition of methanol to carbonyl carbon of **738** followed by reductive elimination of molecular dinitrogen to yield methyl alkynoate **739**.

The reaction of 5-methyl-4-substituted pyrazol-3-ones **740a**–**d** under similar conditions may be explained by an analogous mechanism (Scheme 218). After formation of intermediate **741**, which due to C4 substitution of the pyrazol-3-one



(a) R = Me, **(b)** R = Et, **(c)** R = CO_2Me, **(d)** R = CH_2CO_2Me, **(e)** R = Ph, **(f)** R = 4-ClC_6H_4, **(g)** R = 4-MeC_6H_4, **(d)** R = 4-$MeOC_6H_4$

Scheme 217



(a) R = Me, **(b)** R = Et,
(c) R = CH_2COMe, **(d)** R = Bz

Scheme 218

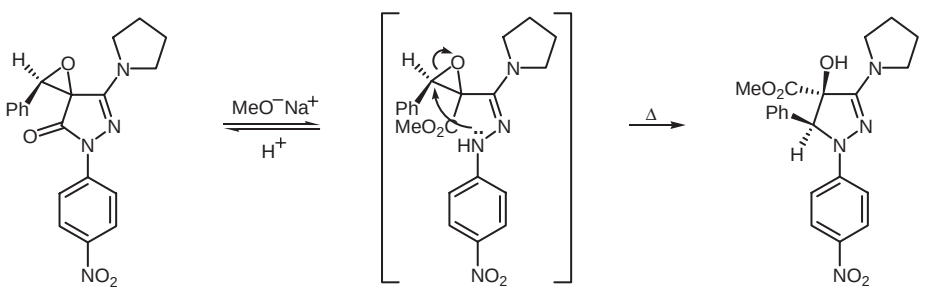
ring cannot form an ylide, a second molecule of (dimethoxyiodo)benzene adds to intermediate **741** to give **742**, which then undergoes reductive elimination of iodobenzene through the loss of a proton from the methyl or methylene group at C5, leading to intermediate **743**. Addition of methanol to the latter yields methyl 2,3-alkadienoates **744a**–**d**.

C. Ring Opening/Ring Closure

Ring opening of pyrazol-3-one ring followed by ring closure has been achieved (97LA159) (Scheme 219) by heating at reflux a solution of spiropyrazol-3-one **745** in methanolic sodium methoxide. The reaction afforded methyl (4S,5S)-4-hydroxypyrazol-4-carboxylate **747**, whose structure was determined by X-ray crystallography. The proposed mechanism involves initial attack of methoxide ion on the carbonyl carbon of **745** causing ring opening to give intermediate hydrazono-ester **746**, followed by ring closure as depicted, to give pyrazole **747**.

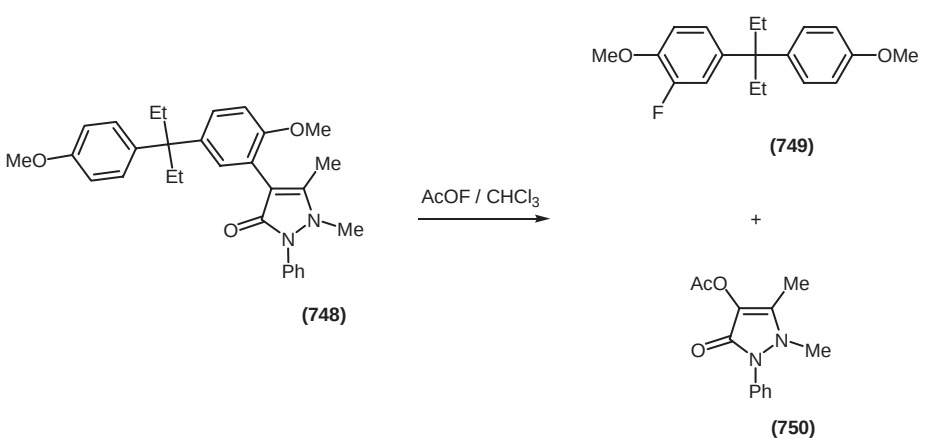
D. In ^{18}F Isotope Incorporation

Pyrazol-3-one **748** was fluorinated with acetyl hypofluorite in chloroform to give *meso*-hexestrol dimethyl ether **749** and pyrazole-3-one **750** (86BSF861) (Scheme 220). *Meso*-hexestrol in an important estrogenic hormone therapy agent.



(745) (746) (747)

Scheme 219



(748) (749) (750)

Scheme 220

With this method a fluorine atom can be attached to an activated aromatic ring, effectively by displacement of the pyrazol-3-one moiety **M750**. This method is suitable for incorporation of the important ^{18}F isotope into biologically interesting compounds, for position emitting tomography (PET) studies.

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Fluorine-Containing Heterocycles. Part II. Synthesis of Perfluoroalkyl Heterocycles from Carbonyl Compounds

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This chapter is a continuation from Part I of this review of fluorine-containing heterocycles recently published (03AHC(86)129). Part II deals with the synthesis of fluorine-containing heterocycles by condensations of two or more precursors. Major attention is paid to the use of mono- and 1,3-dicarbonyl substrates, and their nitrogen analogs.

I. Introduction

Condensation of two or more molecules with specific functional groups is a key method for the synthesis of heterocyclic compounds in general. This approach is also widely practiced for the synthesis of heterocycles with perfluoroalkyl groups (88M1, 93M2, 95CEN39, 97UK1985, 00H1411, 81UK325), one of the most important areas of fluoroorganic chemistry. Heterocyclic compounds containing perfluoroalkyl substituents have attracted much attention due to their remarkable biological activity, specific chemical reactivity, and physical properties. In particular, perfluoroalkylated six-membered heterocycles have important applications in medicinal (87T3123, 89T1409, 88JCS(P1)1837), agricultural (93PCTWO11112, 90JOC2872, 90JOC2964, 90EurP353187), host–guest chemistry (95H521), and in the chemistry of laser dyes (95IJPAP431, 87T3123).

Among nitrogen-containing heterocycles, azoles and pyrimidines play a major role because of their biological activity. Many azoles are useful in the preparation of

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drugs and agrochemicals. Trifluoromethyl-containing azoles and pyrimidines are of great interest from the viewpoint of their potential biological activity induced by the introduction of fluorine atoms; these compounds have recently been extensively studied (98ZOR411, 01CGS1232, 01ZOR915). Fluorinated azoles often exhibit increased biological activity, leading to the development of effective synthetic procedures for such heterocycles (87GERP3632291). For example, it has been found that addition of a polyfluorinated benzene ring to an azole increases the biological activity of the azole. This has stimulated syntheses and production of herbicides, plant growth regulators, and defoliants. Fluoroalkyl derivatives of pyrazole have also generated intense interest. They exhibit antibacterial, antiviral, fungicidal, herbicidal, insecticidal, pain-relieving, and other useful properties (92JFC(56)141, 91EUP418845, 98JOC2550, 94JCS(P1)2161, 90JAP(K)02129171, 87GEP3713744, 88EUP295117, 82CanP1130808). Also, they play an important part in the creation of pesticides and pharmaceuticals with a broad spectrum of applications (85JFC333). Perfluorinated heterocyclic compounds are used in medicine as effective oxygen carriers and artificial blood components.

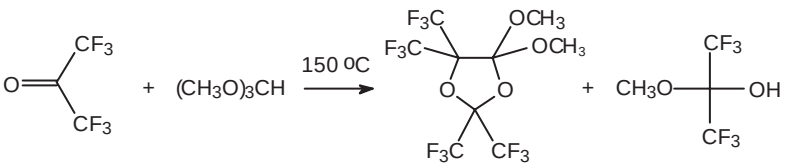
Pyrimidines, a widespread class of natural bases, are pharmaceuticals with pronounced antiviral (88JMC144), gastroantisecretory (89H985), diuretic (90AF1349), antimalarial (88CL819), and anti-HIV-1 activities (89JMC2507, 92JMC337). As is known, the presence of fluorine in the molecule enhances the physiological activity of compounds relative to their nonfluorinated analogs (87T3123). The interest in the syntheses of new fluorinated heterocyclic compounds is therefore not surprising.

A wide variety of unusual gem-(trifluoromethyl)-substituted five- and six-membered heterocyclic compounds are readily obtained by condensation of hexafluoroacetone with nitriles, isonitriles, and orthoformates, or by condensation of fluorine-containing 1,3-dicarbonyl compounds with alkylenediamines and polyethylenepolyamines (79M3, 83ZN769, 82CB2494, 97ZOR1418). This methodology leads to the synthesis of heterocyclic compounds with trifluoromethyl groups from readily available hexafluoroacetone and its derivatives Scheme 1).

However, this technique is not always effective. Substrates with perfluoroalkyl groups may not be readily available, or they may be toxic and inconvenient to handle. Therefore, for the syntheses of heterocyclic compounds, it is recommended to choose simple accessible substrates.

β-Diketones and β-ketoesters have recently become accessible substances that hold much promise as substrates in such processes.

Lithium salts of β-diketones and regioisomeric β-aminovinylketones, β-aminovinylthiones, α,β-enones, and their halogen derivatives are being actively



Scheme 1

applied (00H1411, 84ZOR1964, 89M4, 96IZV2278, 86IZV123, 93IZV2134, 99ZOR106, 99IZV1279, 96IZV1493, 97RusP2100345, 96BCZ93). α,β-Unsaturated trifluoromethylketones are also becoming increasingly important as materials for the syntheses of heterocycles with a trifluoromethyl group (99UK483).

II. From Hexafluoroacetone

Hexafluoroacetones, an accessible starting material, has found practical application in the syntheses of cyclic and heterocyclic systems due to the high reactivity of its C=O group (Scheme 2).

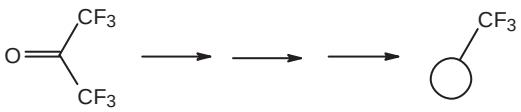
The utility of this compound in organic synthesis considerably expanded the possibility of synthesizing derivatives with two trifluoromethyl groups. The general Scheme 3 is as follows.

At first, hexafluoroacetone is converted into an intermediate (generally, a 1,3-dipole), which then undergoes cycloaddition under the action of binucleophilic reagents. This approach opens up new synthetic possibilities and offers a new methodology for the syntheses of five-membered heterocyclic compounds.

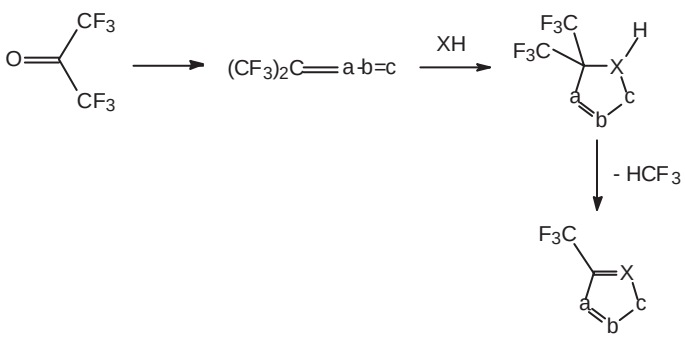
The Scheme 4 illustrates the general synthetic potentialities in reactions with α-amino azines.

As described in the following sections, condensations of hexafluoroacetone with various amines frequently give hetero-1,3-dienes as intermediates, used in the syntheses of heterocycles.

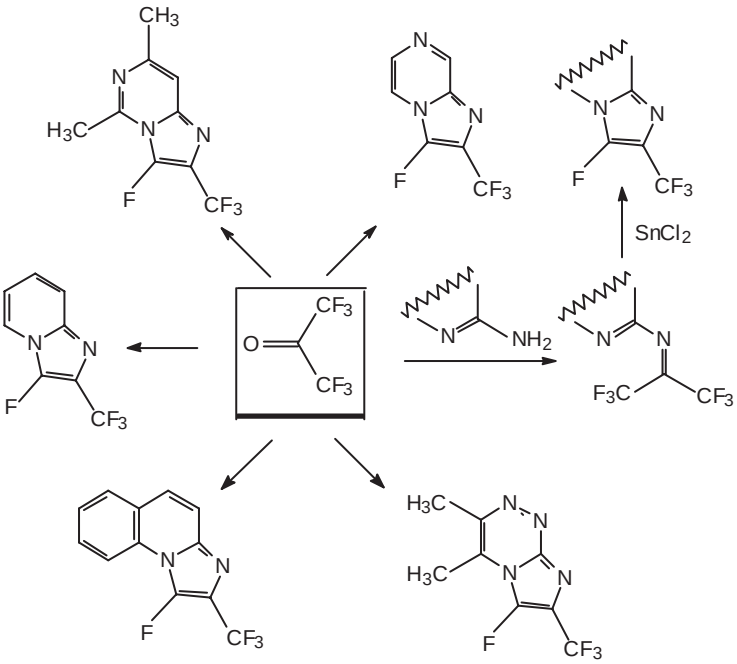
Treatment of hexafluoroacetone with 4,4-dibromobut-2-ene oxide and propargyl alcohol (91JFC(52)159) or ethylbromohydrin catalyzed by Bu_4NBr yields fluorinated 1,3-dioxolanes (Scheme 5) (93JOC972).



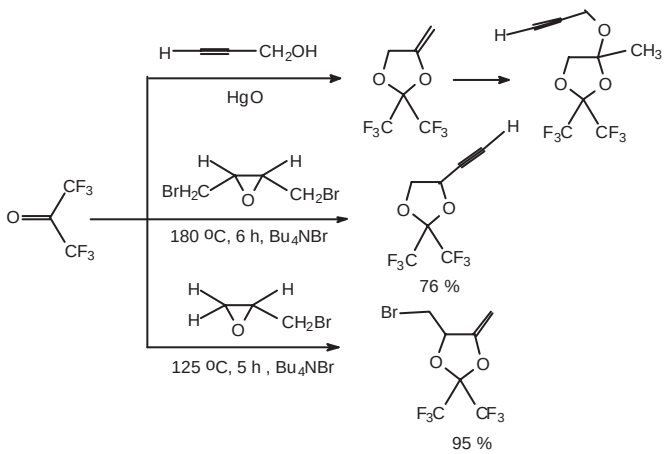
Scheme 2



Scheme 3



Scheme 4



Scheme 5

Cyanoformamidines, exhibiting nucleophilic and electrophilic properties in the 1,3-positions, react with hexafluoroacetone forming five-membered heterocycles (86CB2127). This ability to form five-membered heterocycles is the major characteristic of hexafluoroacetone, which is also inherent in some perfluorinated and partially fluorinated ketones, aldehydes, and imines in their reactions with α-functional derivatives of carboxylic acids, as well as α-amino, α-N-alkylamino,

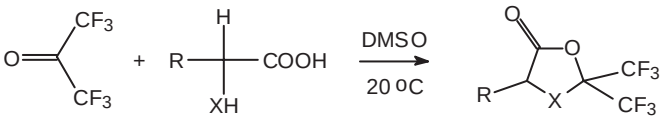
α-N-arylamino (60JA2288, 66CB1461), α-hydroxy (66CB2880), and α-mercapto (87JFC(35)87) derivatives of acids (Scheme 6).

Applying this strategy to ω-carboxy-α-amino acids, a preparatively simple regioselective carboxyl group activation is possible (91CZ77). The efficiency of this method was demonstrated by a two-step synthesis of aspartame (Scheme 7) (90CZ249). Protection of the α-amino group and activation of the α-carboxylic group is accomplished in only one step. Deprotection of the α-amino group occurs during aminolysis.

1,3,4-Oxadiazoles are obtained from diaryl and arylmethyl diazomethanes when hexa- or pentafluoroacetone is added at −20 °C (Scheme 8) (78JA4260).

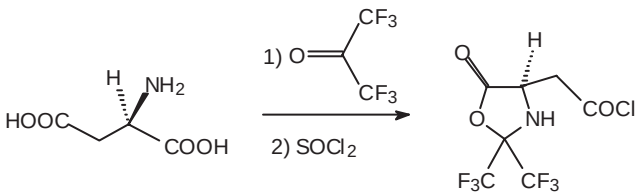
The reactions of hexafluoroacetone with trimethylsilyl ethers of enols form 4,4-bis(trifluoromethyl)-1-oxabuta-1,3-dienes (92JPC311). When heated in the presence of tin(II) chloride, the latter are transformed into 4,4-difluoro-3-trifluoromethylbut-3-en-1-one. Subsequent treatment with sodium hydride leads to 2-fluoro-3-trifluoromethylfuran, while with phosphorus pentasulfide the product is 2-fluoro-3-trifluoromethylthiophene (92JCS(CC)348). Partially fluorinated 1-oxopenta-1,4-diene, derived from hexafluoroacetone, is employed as an intermediate in the syntheses of fluorinated furans (92JCS(CC)349) and thiophenes (92JFC(58)380) (Scheme 9).

Interaction between hexafluoroacetone and various trivalent phosphorus derivatives forms five-membered ring **1** (Scheme 10); the reaction involves two

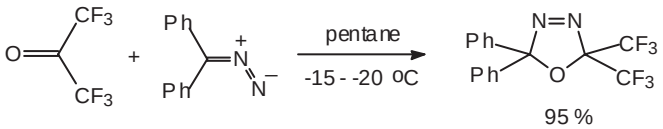


X = NH, NMe, O, S

Scheme 6

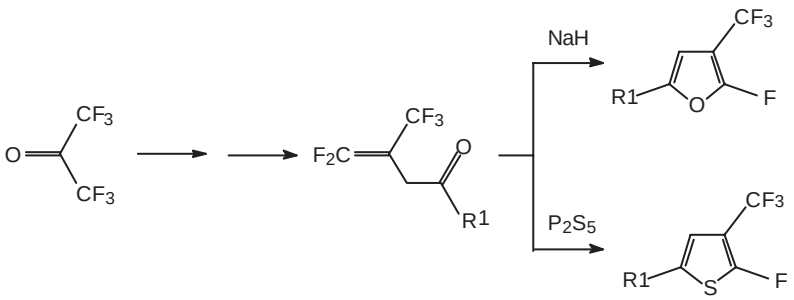


Scheme 7

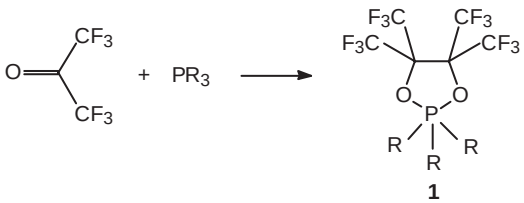


95 %

Scheme 8



Scheme 9



1

Scheme 10

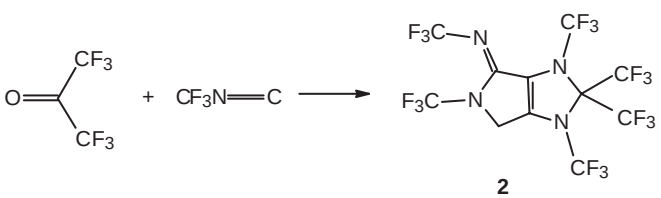
hexa-fluoroacetone molecules ([2 + 2 + 1] cycloaddition) (78CB890, 78CB2077, 79CB2380, 81IZV1592, 83CJC2264, 87ZOB1910, 88ZN(D)196, 89CB1465, 90JFC(48)99).

Hexafluoroacetone and trifluoromethyl isocyanate react to give a system of bicyclic five-membered heterocycles 2 (87AGF921, 81AHC1) (Scheme 11).

From isothiocyanatodialkylphosphites and hexafluoroacetone one btains a 1 : 1 adduct-bicyclic phosphorane **3** (87AGE921) (Scheme 12).

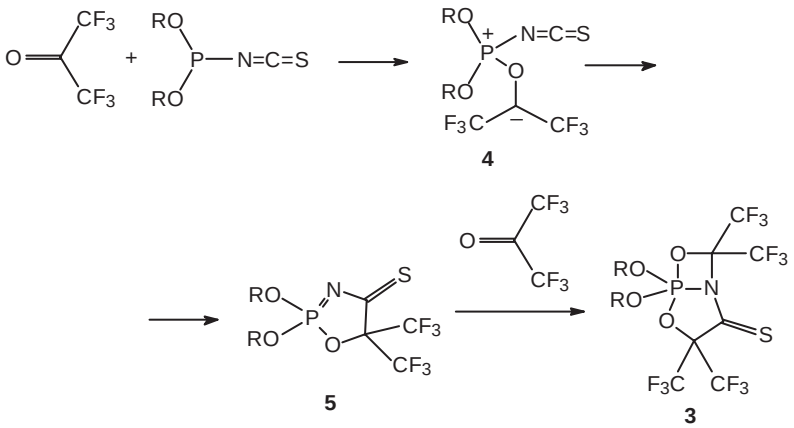
At the first stage, the reaction forms betaine **4**, cyclizing into imide **5**. The latter experiences an electrophilic attack by another hexafluoroacetone molecule, forming bicyclic phosphorane **3**. It is believed (87AGE921) that the strain in the trigonal bipyramid of the phosphorane is minimal when the two rings are axial equatorial and have an equatorial nitrogen. The activating effect of the CF_3 group in hexafluoroacetone imines makes it possible to prepare fluorinated oxazoles, thiazoles, and imidazoles using tin(II) chloride as a catalyst (82CB2494) (Scheme 13).

The first stage of the reaction is a [4 + 1] cycloaddition of $SnCl_2$ at room temperature, forming hetero-1,3-diene **6** in a quantitative yield. In solution,

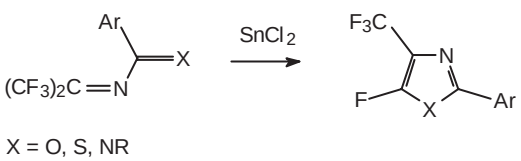


2

Scheme 11

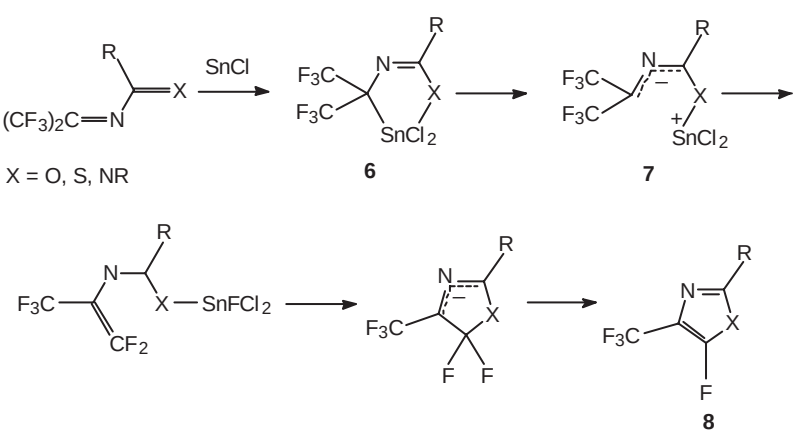


Scheme 12



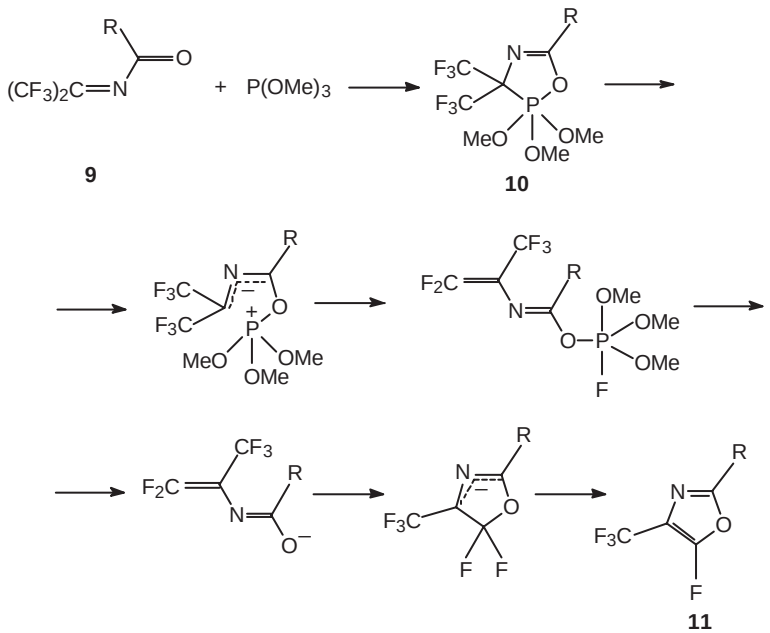
Scheme 13

cycloadduct **6** is only stable at 20 °C; above this temperature, ring cleavage into 1,X-dipolar compound **7** takes place. If trifluoromethyl substituents are present, the allyl anion eliminates the fluoride ion to form a four-coordination center on tin. Elimination of $SnFCl_2^+$ creates conditions for the generation of a heteropentadienyl anion, which undergoes electrocyclization, eliminating the fluoride ion to form heterocycle **8** (Scheme 14).



Scheme 14

In this reaction, tin is oxidized to the tetravalent state ($Sn^{+2} \rightarrow Sn^{+4}$).



Scheme 15

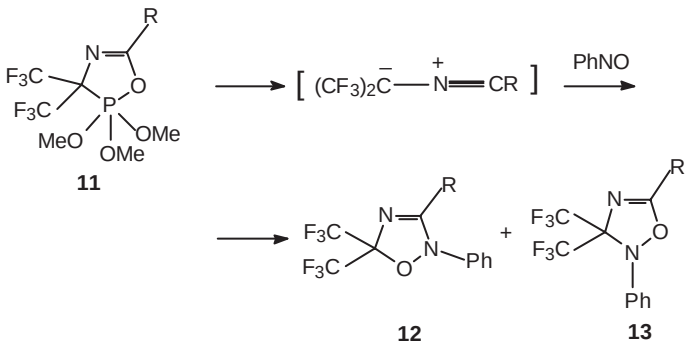
Transition metal compounds can be replaced by other substances, for example, by phosphites. Thus, 2-substituted 4-trifluoromethyl-5-fluoro-1,3-oxazole-2,4-dienes **9** were obtained by the reaction of 4,4-bis(trifluoromethyl)-N-acylimine **10** with trimethylphosphite (71CB1826, 74CB1448). The reaction occurs via the intermediate formation of 5-substituted 3,3-bis(trifluoromethyl)-2,2-dihydro-1,4,2-oxazaphospharol-4-ene **11** (Scheme 15).

A. Elimination of Triethyl Phosphate Occurs on Heating or Photolysis

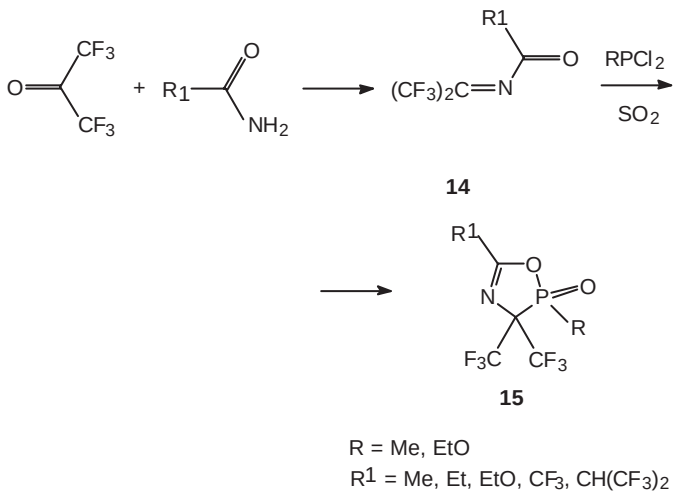
In the presence of nitrobenzene, a [3 + 2] cycloaddition takes place, forming stereoisomers: 5,5-bis(trifluoromethyl)-2,3-diaryl-1,2,4-oxadiazol-3-in **12** and 3,3-bis(trifluoromethyl)-1,5-diaryl-1,2,4-oxadiazol-4-in **13** (77CB605) (Scheme 16).

At the same time, stable oxazaphospholenes **15** are formed by reactions of hexafluoroacetone N-acylimines **14** with chlorine-containing compounds of trivalent phosphorus (92JFC(58)345, 91DOK619, 92JFC(58)375, 95IZV1809, 89IZV1213, 91IZV239) (Scheme 17).

Under the action of tin(II) chloride, the initial products, hetero-1,3-dienes, undergo an amidine skeletal rearrangement into a terminal olefin, giving a heterocycle (82JFC(20)813, 84ZN(B)1442).



Scheme 16



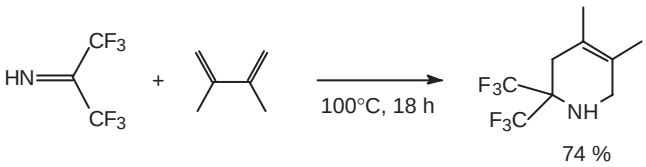
Scheme 17

A Diels–Alder reaction between hexafluoropropane-2-imine and 2,3-dimethylbutadiene at 100 °C gives an adduct in excellent yield (65JOC1398) (Scheme 18).

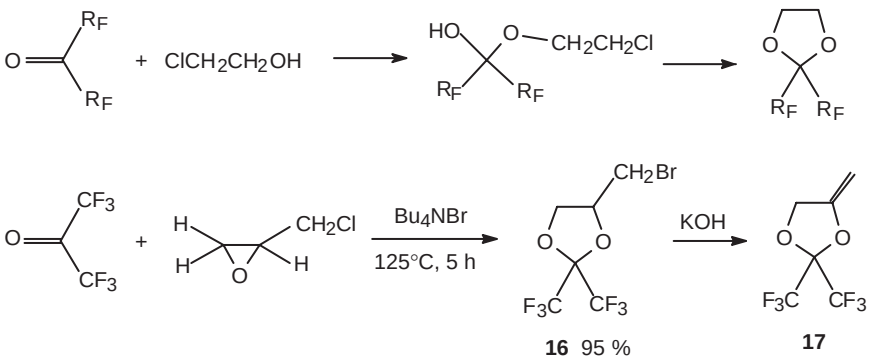
The reaction of epichlorohydrin with hexafluoroacetone in the presence of catalytic amounts of Bu_4NBr affords 2,2-bis(trifluoromethyl)-4(bromomethyl)-1,3-dioxolane **16**, which on further treatment with KOH yields 2,2-bis(trifluoromethyl)-4-methylene-1,3-dioxolane **17** (92JPK311) (Scheme 19).

The [4 + 1] cycloaddition of 4,4-bis(trifluoromethyl)-1,3-diazabuta-1,3-diene **18**, obtained by a reaction of hexafluoroacetone with an amidine in the presence of a dehydrating agent, to an isonitrile gives 5-(butylimino)-1-(2,6-dimethyl-phenyl)-2-phenyl-4,4-bis(trifluoromethyl)-2-imidazoline **19** in the form of *Z* and *E* isomers (92JFC(58)345) (Scheme 20).

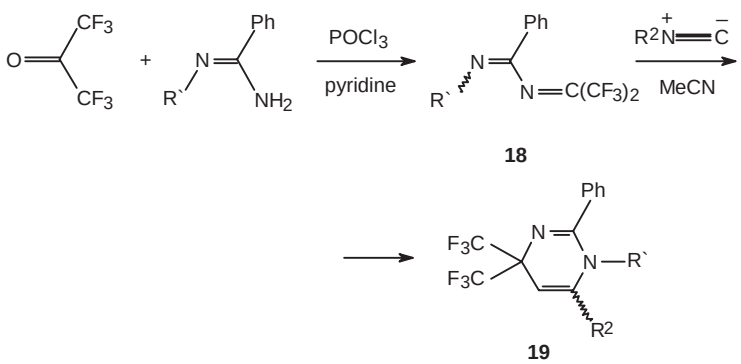
Heating with hydrazines leads to bis(trifluoromethyl)-substituted 1,2,4-triazolines **20a** and **20b**, which undergo heteroaromatization into 5-trifluoromethyl-1,2,4-thiazole **21** in the presence of azobisisobutyronitrile (AIBN) (88CZ109) (Scheme 21).



Scheme 18

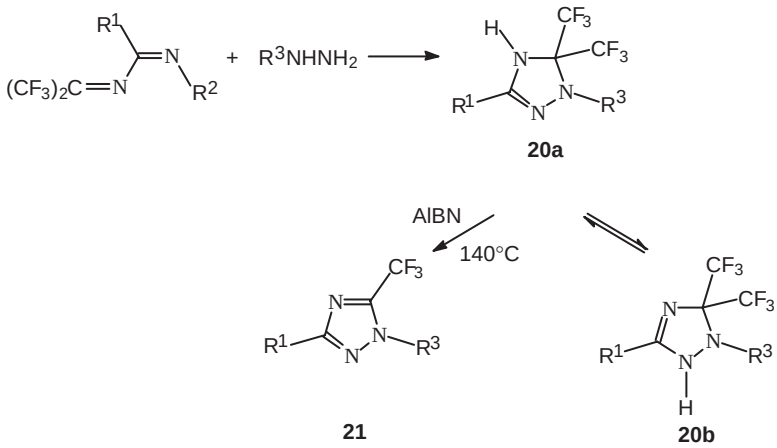


Scheme 19



R^1	R^2	Yield, %	
2,6-$(CH_3)_2C_6H_3$	t-Bu	79	
2,4,6-$(CH_3)_3C_6H_2$	t-Bu	77	
2,6-$(CH_3)_2C_6H_3$	2,6-$(CH_3)_2C_6H_3$	98	
2,4,6-$(CH_3)_3C_6H_2$	2,4,6-$(CH_3)_3C_6H_2$	93	
Ph	Bu	92	65:35
Ph	$C_6H_5CH_2$	93	74:26
Ph	c-C_6H_{11}	87	55:45

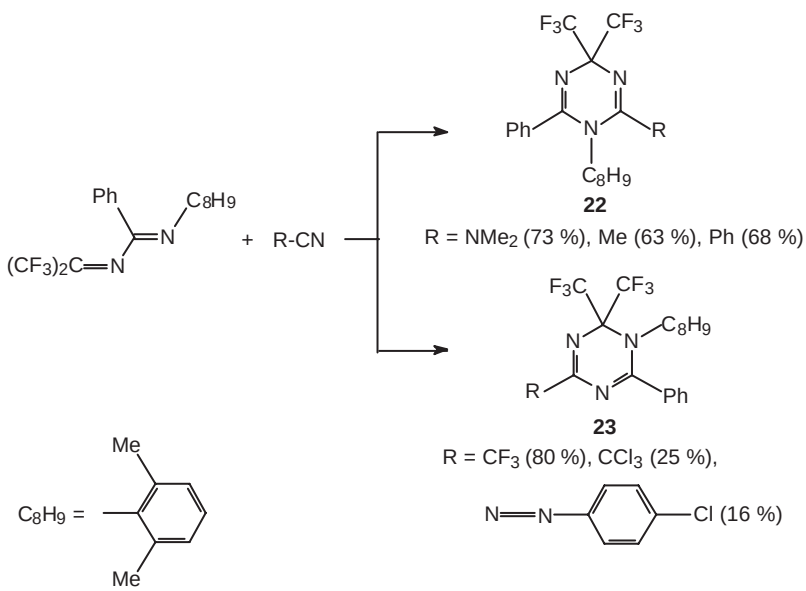
Scheme 20



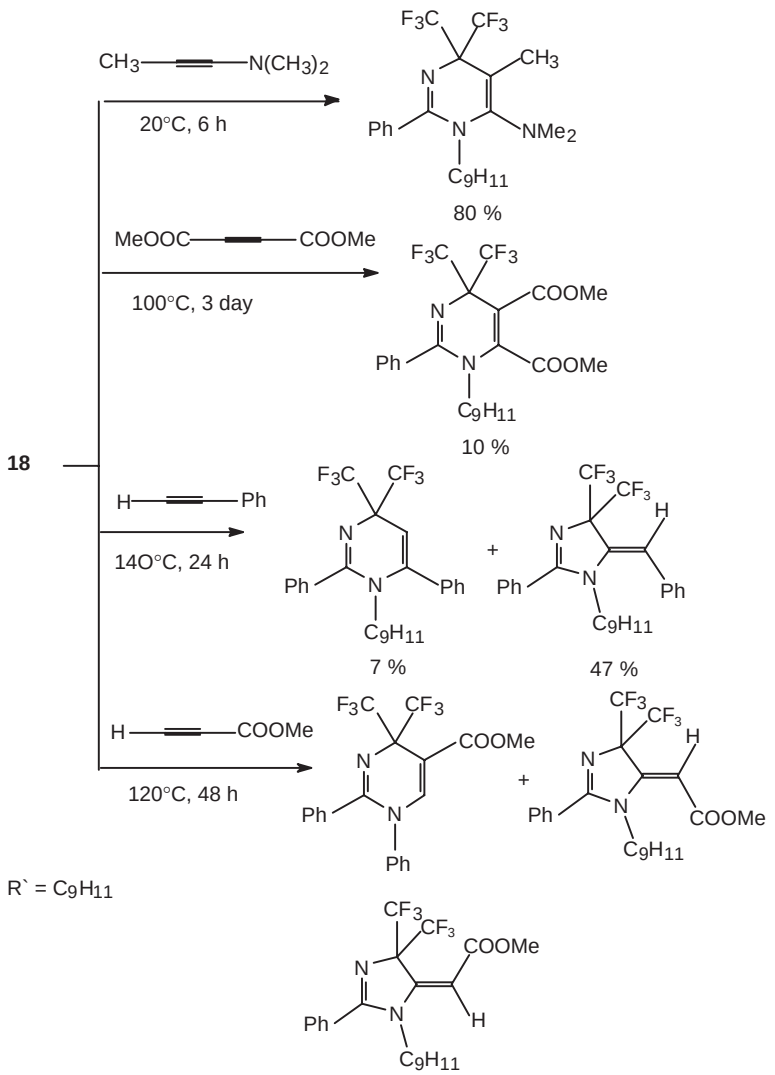
Scheme 21

4,4-Bis(trifluoromethyl)-1,3-diazabuta-1,3-diene **18** reacts with cyanamide, acetonitrile, and benzonitrile to give [4 + 2] cycloadducts, 1,4-dihydro-1,3,5-triazines **22** (84CZ205). With electron-deficient nitriles (trifluoroacetonitrile, trichloroacetonitrile, and 4-chlorophenylaza-nitrile) the six-membered heterocycle undergoes a skeletal rearrangement forming **23** (Scheme 22).

The reactions of 4,4-bis(trifluoromethyl)-substituted 1,3-diazabuta-1,3-diene with acetylene and its derivatives yield [4 + 2] cycloadducts, 4,4-bis-(trifluoromethyl)-1,4-dihydropyrimidine derivatives (83CZ271) (Scheme 23). In the reaction



Scheme 22

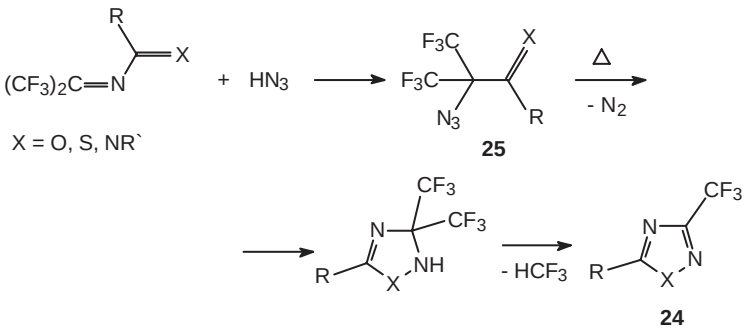


Scheme 23

of phenylacetylene and methyl acetylenecarboxylic ester, the product is (*Z*)-5-benzylidene-1-(2,6-dimethylphenyl)-2-phenyl-4,4-bis(trifluoromethyl)-2-imidazoline, whose structure is confirmed by X-ray analysis (83CZ274).

The [2 + 4] cycloadditions of α,β-unsaturated carbonyl compounds and nitriles to 4,4-bis(trifluoromethyl)-substituted hetero-1,3-dienes give heterocyclic compounds. The [4 + 2] cycloaddition of hetero-1,3-diene to methylvinylketone is highly selective when the process is conducted in the presence of equimolar amounts of 4-dimethylaminopyridine.

3-Trifluoromethyl-1,2,4-triazoles **24** were obtained in good yields by the interaction of hexafluoroacetone imines **25** with HN_3 (Scheme 24).

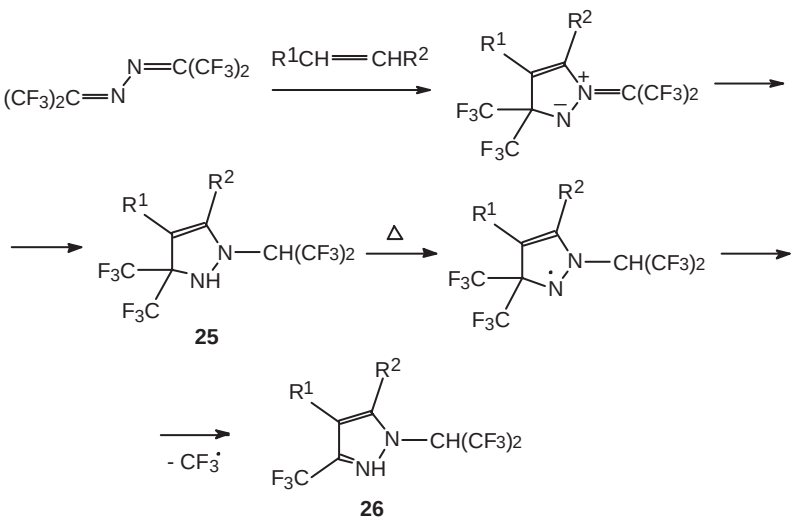


Scheme 24

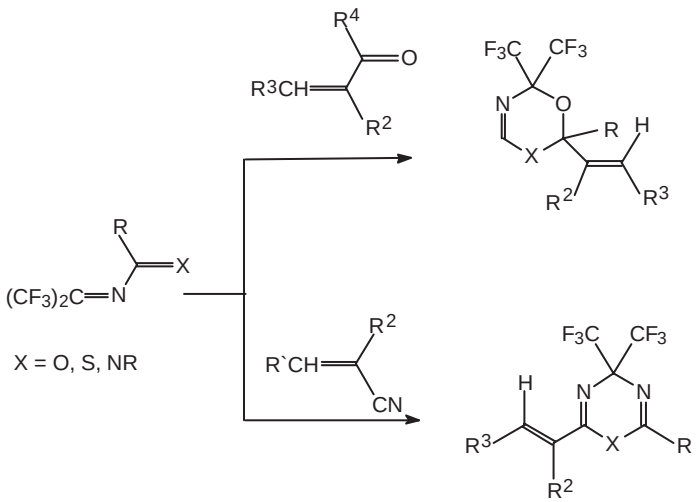
Using hexafluoroacetone azine in reactions with olefins affords 5,5-bis(trifluoromethyl)-1*H*-3-pyrazolines **25**, whose thermolysis yields 3-trifluoro-methylpyrazoles **26** (82JFC(19)437) (Scheme 25).

Trifluoromethyl derivatives of azomethine imines are effective 1,3-dipoles in reactions with unsaturated compounds. Thus, RCH = CHR type olefins and azinehexafluoroacetone react to form azomethineimine, transformed into 1*H*-3-pyrazoline (75JCS(P1)538, 79T389) (Scheme 26). Heating the latter with AIBN leads to trifluoromethyl derivatives of pyrazole (82JFC(19)437) (Scheme 26).

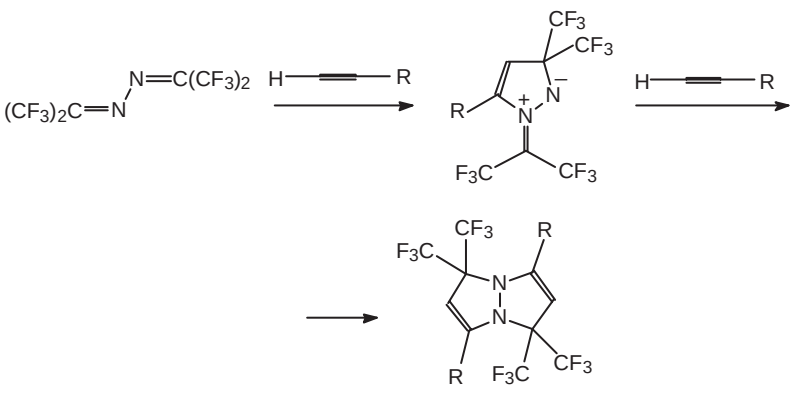
Hexafluoroacetone azine reacts with two equivalents of terminal olefins (71JCS(C)2404) and with acetylene derivatives (75TL1125), forming 1,5-diazabicyclo[3.3.0]octenes and 1,5-diazabicyclo[3.3.0]octa-2,6-dienes **27**, respectively (Scheme 27). The cycloaddition involves two [3 + 2] processes. The structure of azamethineimine is confirmed by X-ray analysis data (74AGE475).



Scheme 25



Scheme 26

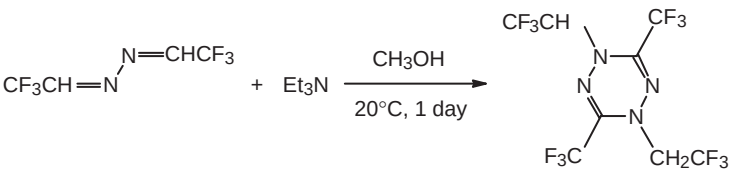


27

Scheme 27

Similar reactions were reported to take place between this intermediate and ethylene (71JCS(C)2404), acetylene (75TL1125), terminal alkenes with alkyl, aryl, and geminal dialkyl groups (74AGE475, 75CB1460, 75JCS(P1)1902, 82JFC(19)589), dienes (75JCS(P1)1411), cyclic alkenes (79T389), vinyl ethers (82LA853), alkoxyacetylenes (79LA133), and acrylonitrile (82LA845).

Trifluoroacetaldehyde azine, prepared from trifluoroacetaldehyde hydrate and hydrazine monohydrate, reacts with triethylamine in methanol to give the 1,4-dihydro-1,2,4,5-tetrazine derivatives **28**, whose structure is confirmed by X-ray analysis (95BCJ2085) (Scheme 28).



28 14.2 %

Scheme 28

The low yield of the product is the result of polymerization of the substrate (formation of a trimer and longer cyclic systems).

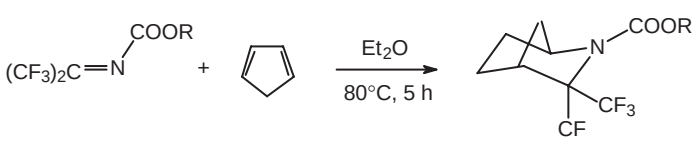
Hexafluoroacetone alkoxycarbonylimines **29**, exhibiting biphilic properties, act as 1,3-heterodienes or as dienophiles in [2 + 4] cycloadditions. With cyclopentadiene they react as dienophiles forming [2 + 4] cycloadducts, for example, 2-alkoxycarbonyl-3,3-bis(trifluormethyl)-2-azabicyclo[2.2.1]hept-5-ene **30** (95IZV1809) (Scheme 29).

With cyanoguanidines and cyanamides compound **29** behaves as a 1,3-heterodiene forming heterocyclic compounds. These reactions lead to the formation of a [2 + 4] cycloadduct as the sole product. The [2 + 4] cycloaddition (formation of a compound of type **31**) is only possible for dienophiles possessing sufficiently strong donor properties, as illustrated by reactions with various compounds containing a nitrile group (Scheme 30).

The reaction of hexafluoroacetone alkoxycarbonylimine with diethyl cyanamide is exothermic with N-cyanomorpholine at 20 °C. It takes 5–7 h, and with chloroacetonitrile or acetonitrile no reaction occurred over 3 days at 130–140 °C.

Condensation of 2-acetyloxiranes with ethyl perfluoroalkanoates gives 2,3-dihydro-3-hydroxy-6-perfluoroalkyl-4*H*-pyran-4-ones, which on dehydration form 5-substituted 2-perfluoroalkyl-4*H*-pyran-4-ones (98T2819) (Scheme 31). The dehydration of hydroxy dihydropyranones intermediates was performed by the action of a slight excess of thionyl chloride in dry pyridine.

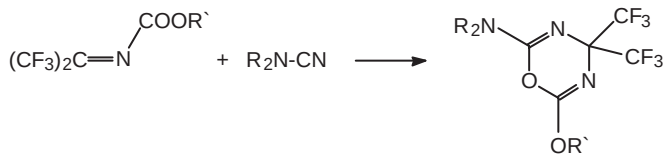
The above reactions are easy to perform and have wide synthetic potential. These advantages, along with the accessibility of substrates, make them very useful.



30

R = Me (70 %), Et (68 %), Pr^n (63.8 %),
Pr^i (53.1 %), $^iC_5H_{11}$ (41.1 %),
$PhCH_2$ (64.3 %)

Scheme 29



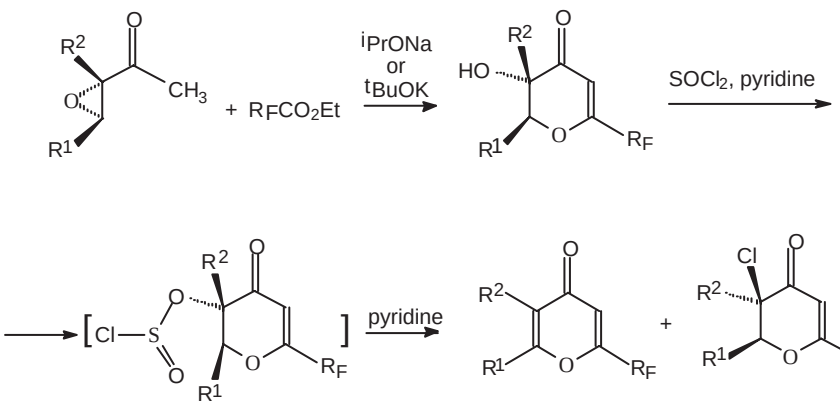
31

R_2N =  , R` = Me (83.6 %), Et (85,7 %), ^{i}Pr (78.4 %), $^{i}C_5H_{11}$ (70.4 %)

$R_2N = Et_2N$, R` = Et (73.3 %), iPr (84.2 %)

R_2N =  , R` = Et (78.0 %), ^{i}Pr (74.5 %)

Scheme 30



$R_F = CF_3, C_3F_7$

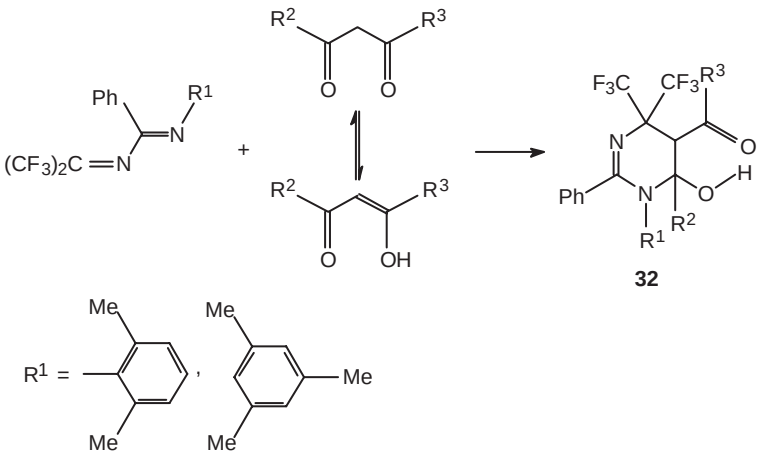
R^1 = H, R^2 = Me; R^1 = H, R^2 = Ph;

$R^1 = R^2$ = Me

Scheme 31

III. From Perfluoroalkyl-Containing β-Diketones

The strong electron-withdrawing character of the polyfluoroalkyl substituent causes increased activity of the carbonyl group of the ketone towards nucleophilic reagents. The interaction of fluorinated 1,3-diketones with polynucleophilic reagents is of great theoretical interest (reactivity studies) and from a synthetic viewpoint. 1,3-Dicarbonyl compounds react in their enol form giving [4 + 2] cycloadducts (85CZ185). For example, acetylacetone, acetoacetic ester, and chloroacetoacetic ester react with 4,4-bis(trifluoromethyl)-1,3-diazabuta-1,3-diene giving 6-hydro-4,4-bis(trifluoromethyl)-1,4,5,6-tetrahydropyrimidine derivatives **32** (Scheme 32).



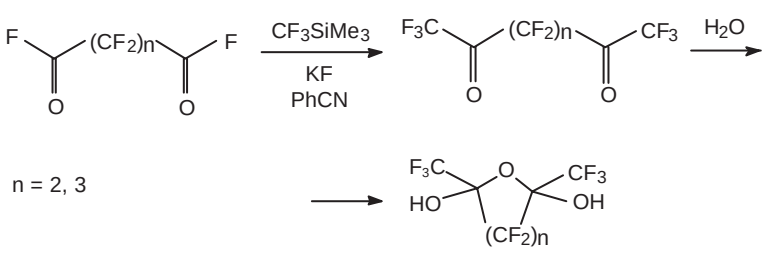
Scheme 32

Perfluorocarbonyl compounds, obtained by the interaction of (trifluoromethyl)-trimethylsilane with diacetyl fluorides $FC(O)(CF_2)_nC(O)F$ ($n = 2, 3$) in the presence of KF, exhibit high reactivity with nucleophiles, for example, with water, giving cyclic diols **33** due to intramolecular cyclization (93IC5079) (Scheme 33).

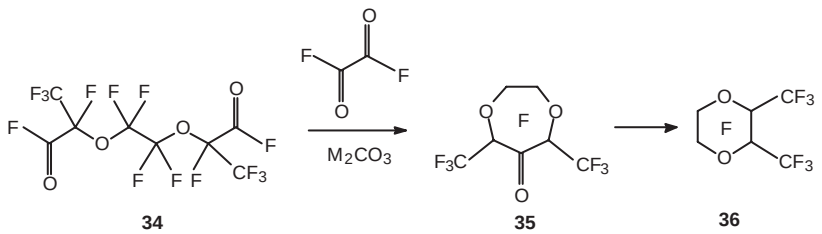
The structure of *cis* ($n = 3$) and *trans* ($n = 2$) diols **33** was confirmed by X-ray analysis.

In the presence of metal carbonates, for example Na_2CO_3 in diglyme at 80 °C over 1 h, perfluoro-2,7-dimethyl-3,6-dioxasuberic difluoride **34** (83CZ274) affords perfluoro-2,7-dimethyl-3,6-dioxacycloheptanone **35** (92JPP04,316576) which then was irradiated with UV light at −70 °C for 190 h to give 81% of perfluoro-2,3-dimethyl-1,4-dioxane **36** (92JPP04, 316577) (Scheme 34). These compounds are useful as solvents, heating media and insulating liquids.

In contrast, cyclic 1,3-diketones such as cyclohexane-1,3-dione having no stable OH···O intramolecular hydrogen bonds in the enol form, react with 4,4-bis-(trifluoromethyl)-1,3-diazabuta-1,3-diene forming a mixture of 4,4-bis(tri-fluoro-methyl)-1,4-dihydropyrimidine **37** and 4,4-bis(trifluoromethyl)-4*H*-1,3-oxazine **38** (85CZ185) (Scheme 35).

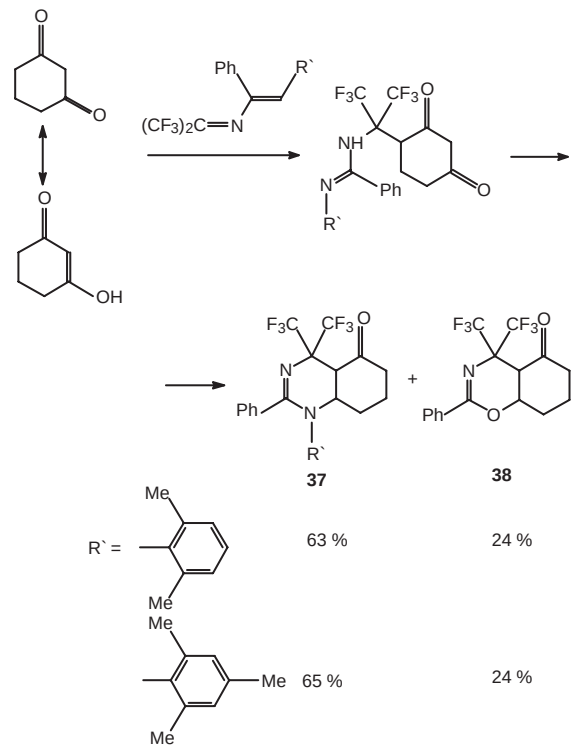


Scheme 33



34 35 36

Scheme 34

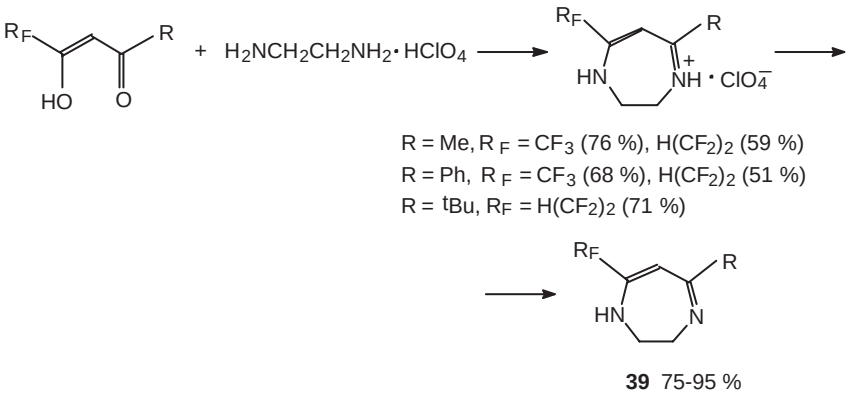


37 **38**

Scheme 35

However, fluoroalkyl-containing 1,3-diketones interact with ethylene diamine to give only *N*,*N*′-ethylenebis(aminovinylketones) (75AJC1517, 70JINC1895, 81ZVKO105, 78AJC765).

It was shown (91JFC(56)325, 91JFC(56)297, 91IZV890) that with fluorine atoms introduced into the alkyl fragments of the 1,3-diketone, the latter reacts with ethylenediamine monohydroperchlorate, producing 2,3-dihydro-1*H*-1,4-diazepine monohydroperchlorates. Neutralization with an alkali gives free bases, for example, 2,3-dihydro-5,7-bis(trifluoromethyl)-1,4-diazepine **39** (Scheme 36).



Scheme 36

The nature of the substituents in the 1,3-diketone determines the identity of the final products. In the case of $R_F = CF_3$, acidic salts were not isolable; the reaction gave only free bases due to the lowered basicity of 1,4-diazepines products having CF_3 electron-acceptor substituents and their greater thermodynamic stability than their corresponding conjugate acids. Protonated salts are isolated from more basic nonfluorinated products.

In the reactions of α,β-unsaturated ketones with ethylene-diamine perchlorate 1,4-diazepine salts are by-products of tetra-azamacrocycle formation. But for 1,3-diketones the formation of 1,4-diazepines is the main reaction route irrespective of the nature of the dicarbonyl fragment.

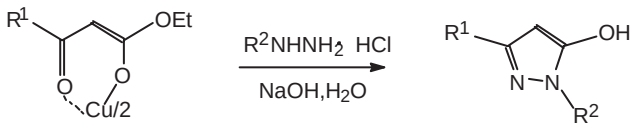
Interaction of acetylacetone with ethylenediamine leads to macrocyclic complexes (97T5847, 97JFC(86)127), whereas hexafluoroacetylacetone gives unstable *N*,*N*′-ethylenebis(aminovinyl)-ketones, which can be transformed into the corresponding 1,4-diazepines (98KGS634).

While nonfluorinated 1,3-diketones on Cu^{+2} and Ni^{+2} matrices form *N*,*N*′-ethylenebis-(aminovinylketone) chelates in their reactions with ethylenediamine, fluorinated 1,3-diketones give 2,3-dihydro-1*H*-1,4-diazepines **39** via the intermediate formation of metal chelates.

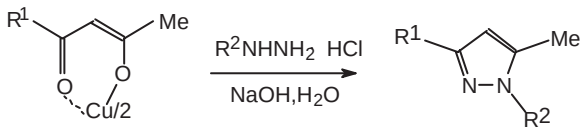
The reactions of the copper salts of β-ketoesters and β-diketones with hydrazine hydrate and phenylhydrazine lead to the corresponding pyrazoles in moderate yields that may be increased by performing the reactions in the presence of bases (Scheme 37). The structure of the product ($R_F = CF_3$, R = Ph) is confirmed by X-ray analysis (90IZV640).

The thionation of perfluoroalkyl β-diketones $RCOCH_2COMe$ [$R = CHF_2$, C_4F_9, $(CF_2)_nH$, $n = 2, 4$] or their Cu^{+2} chelates by the SPS_2^- anion formed *in situ* from P_4S_{10} and K_2CO_3 gave perfluoroalkylthiopyrans (92SL195).

The reactions between 2-polyfluoroacylcyclohexanones **40** and methylhydrazine or phenylhydrazine exclusively yields 3-CF_3 pyrazoles (01CJC183). When the chain length of the polyfluorinated substituent in the R_FCO group increases, 5-R_F-pyrazoles are isolated. The reaction of 2-(trifluoroacetyl)cyclohexanone with hydrazinopyridine gives 5-hydroxypyrazoline, an intermediate in the formation of



$R^1 = HCF_2$, $R^2 = H$; $R^1 = CF_3$, $R^2 = H$;
$R^1 = CF_3$, $R^2 = Ph$; $R^1 = C_4F_9$, $R^2 = H$;
$R^1 = C_4F_9$, $R^2 = Ph$



$R^1 = CF_3$, $R^2 = H$; $R^1 = CF_3$, $R^2 = Ph$;
$R^1 = C_6F_{13}$, $R^2 = H$

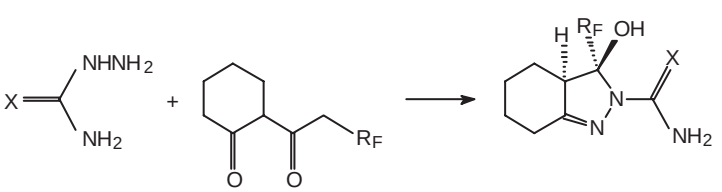
Scheme 37

5-CF_3-pyrazoles. The regiochemistry of the condensation is probably controlled by the nucleophilicity of the terminal nitrogen in the monosubstituted hydrazines and by the steric requirements of the R_F group in the 1,3-diketones (01CJC183).

Compounds **40** react with guanidine, urea, thiourea, methylisothiourea, guanylthiourea by Lewis-acid catalysis (00S1738) and with thiosemicarbazide, semicarbazide (99IZV361) in the presence of triethylamine to form the corresponding 5,6-oligomethylenepyrimidines and 3-hydroxy-2(thio)-carbamoyl-3-polyfluoroalkyl-3,3a,4,5,6,7-hexahydro-2*H*-indazoles **41**, respectively (Scheme 38). The structure of **41** (thio) is confirmed by X-ray analysis.

Similarly, asymmetrical perfluoroalkyl-containing 1,3-diketones with semi- and thiosemicarbazydes give 5-hydroxy-5-polyfluoroakyl-2-pyrazolines (00ZOR1180) (Scheme 39).

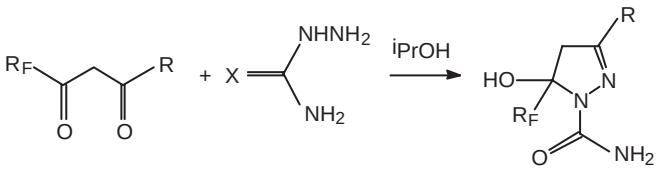
Hexafluoroacetylacetone reacts with ethylenediamine to give an unstable *N*,*N*′-ethylene-bis(aminovinyl ketone), which can be converted to the corresponding



40 **41**

R_F	CHF_2	CF_3	$H(CF_2)_2$	C_4F_9	C_6F_{13}	C_8F_{17}	CF_3	C_6F_{13}	C_8F_{17}
X	S	S	S	S	S	S	O	O	O
Yield, %	51	50	68	75	76	54	40	44	30

Scheme 38



R_F = HCF_2, CF_3, $(CF_2)_2H$, C_3F_7, C_4F_9, C_8F_{17}

R = Me, Et, ^{t}Bu, Ph, $(CF_2)_2H$

X = O, S

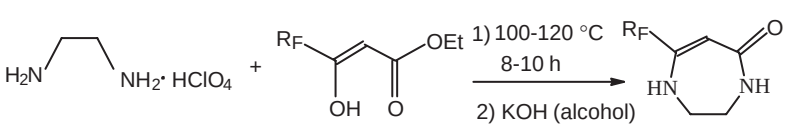
Scheme 39

1,4-diazepine (70JINC1895). In contrast, fluoroalkylated 1,3-diketones react with ethylenediamine monohydroperchlorate (100–120 °C, 8–10 h) to form 2,3-dihydro-7-fluoroalkyl-1*H*-1,4-diazepines monohydroperchlorates, intermediates which then with concentrated alcoholic KOH (pH 10–11) prepare 2,3-dihydro-7-fluoroalkyl-1*H*-1,4-diazepines **42** (81ZVKO105, 91JFC(56)325, 91IZV2088) (Scheme 40).

Lithium salts of fluorinated *β*-diketones are new fluorine-containing synthons. They are used in the syntheses of fluorinated pyrazoles, 5-hydroxy-Δ^2-isoxazolines, 2-aminopyrimidines, and 1,5-benzo- and 1,5-naphthodiazepines (98ZOR411). Thus, in reactions of lithium salts of fluorinated 1,3-diketones with hydrazine (86DAN1133), guanidine, and thiourea (87GEP3603291) hydrochlorides, and 3-aminopyrazoles (02IZV332) the products are hydroxypyrazolines or mixtures of regioisomeric pyrazoles, pyrimidines, and (7-poly-fluoroalkyl)pyrazolo[1,5-*a*] pyrimidines **43**, **44**, and **45** respectively (Scheme 41). The structure of 3-bromo-2-methyl-5-phenyl-7-trifluoromethylpyrazo-lo[1,5-*a*]pyrimidines was established by X-ray diffaction (02IZV332).

Interaction between the alkaline salts of fluorinated *β*-diketones and *ortho*-phenylenediamine and *ortho*-diaminonaphthalene forms the corresponding 2-difluoromethyl-4-phenyl-3*H*-benzo[*b*]-1,4-diazepines and 2-difluoro-methyl-4-phenyl-3*H*-naphtho[2,3-*b*]-1,4-diazepines (87GEP3603291) (Scheme 42).

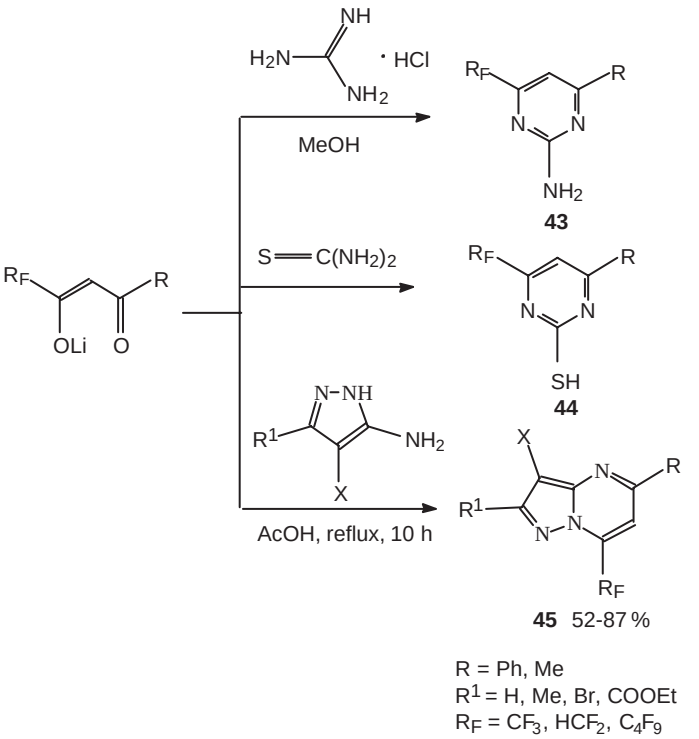
The synthesis of some fluorine-containing polycyclic compounds involves intramolecular cyclization. Thus, heating quinoxalone, obtained by the reaction of the copper chelate of ethyl pentafluorobenzoylpyruvate with *ortho*-aminophenol in dimethylsulfoxide or DMSO–NEt_3 leads to the product of intramolecular



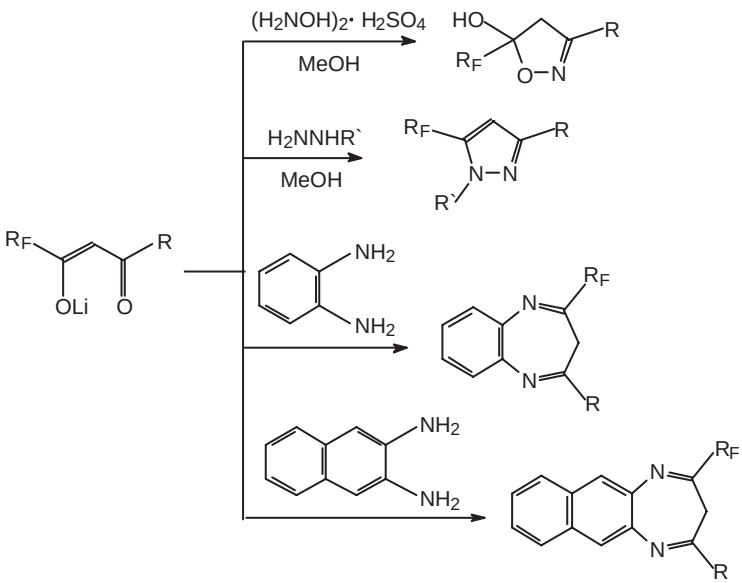
R_F = CF_3 (58 %), $H(CF_2)_4$ (78 %)

42

Scheme 40



Scheme 41



Scheme 42

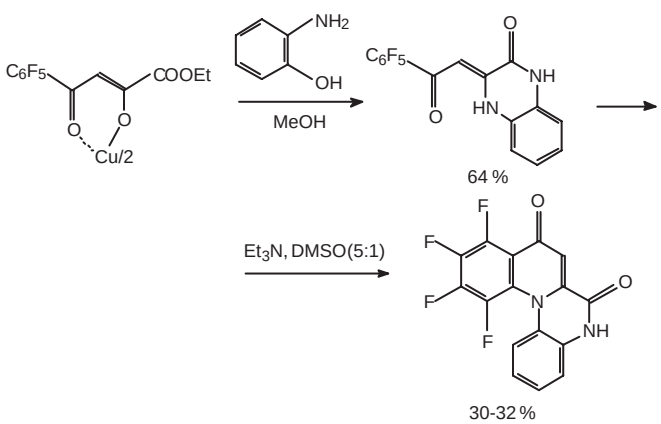
cyclization, 1,2,3,4-tetrafluoro-7,8-dihydro-5*H*-1,4-dihydroquinolino-[1,2-*a*] quinoxaline-5,7-dione (97ZOR1418) (Scheme 43). It was assumed that the final reaction proceeds by the S_NAr mechanism.

2-Perfluoroalkylbenzothiazoles are obtained by the reaction of 2-aminothiophenol with fluorinated β-diketones or β-chloro-α-(trifluoromethyl)-acrolein (91TL643). With hydroxylamine, the products are 5-hydroxy-Δ^2-isoxazolines (87GEP3603291).

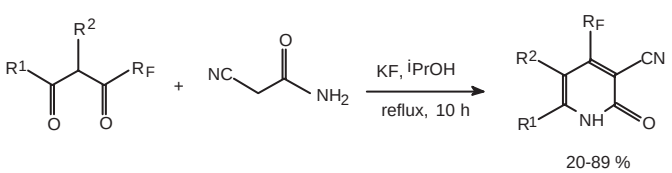
Asymmetric fluorine-containing β-diketones (01IZV643, 94JFC(67)87) on interaction with 2-cyanoacetamide in the presence KF give 3-cyano-2-pyridones in useful yields only with short polyfluoroalkyl chains (CF_2H, CF_3); the yield of the tetrafluoroethyl derivative was only 20%, and the octafluorobutyl −4% (Scheme 44).

The reactions of β-diketones with β-aminocrotonitrile in boiling ethanol gives 3-cyano-2,6-dimethyl-4-trifluoromethylpyridine (yield 66%) (97S1321) (Scheme 45).

1-Benzylsulfonyl-hexafluoropentan-2-one reacts with phthalimidosulfenyl chloride at room temperature in chloroform giving a stable phthalimidothio derivative (Scheme 46). Decomposition of these compound in the presence of 1,3-dienes as trapping reagents for the unstable α-thioxoketone has allowed a number of



Scheme 43

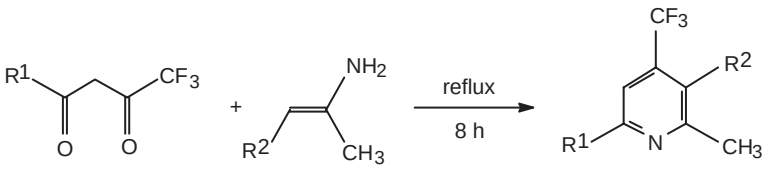


R_F = CF_2H, CF_3, $(CF_2)_2H$, $(CF_2)_4$

R^1 = Ph, 4-FC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-ClC_6H_4, 2-thienyl

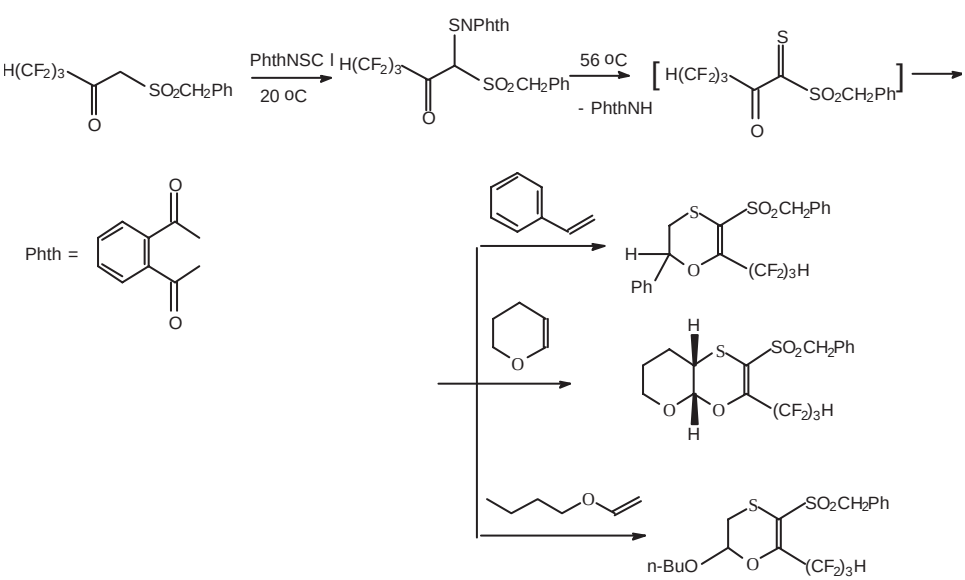
R^2 = H, $R^1 + R^2 = -(CH_2)_3-$, $-(CH_2)_4-$

Scheme 44



Solvent	R^1	R^2	Yield, %
EtOH	Ph	CN	80
	Me	CN	66
	4-$CH_3C_6H_4$	CN	80
	4-$CH_3OC_6H_4$	CN	79
	4-ClC_6H_4	CN	82
	2-Furyl	CN	74
	2-Pyridyl	CN	82
MeCN	Me	COOEt	70
	Ph	COOEt	72
	2-Furyl	COOEt	73
	2-Pyridyl	COOEt	78
	cyclohexyl	COOEt	80

Scheme 45



Scheme 46

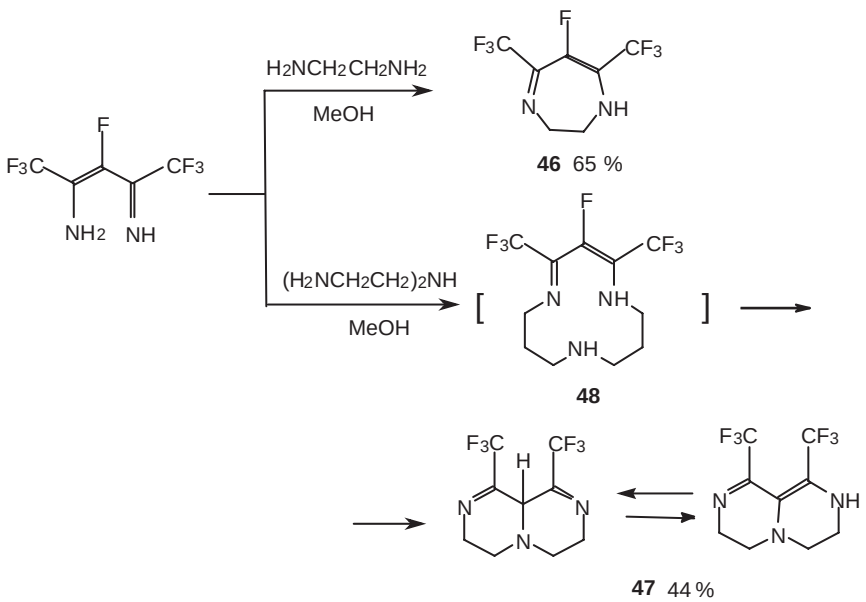
new polyfluoroalkyl ketones to be obtained they contain the thiin moiety in the α position (02JFC(115)175). Reactions proceed with regioselectivity and diastereoselectivity. Thus, in the case of cyclopenta-1,3-diene the product consists of two diastereomers in the ratio 2.4 : 1.

1,3-Amino vinylimine, for example 2-amino-4-iminoperfluoropent-2-ene obtained from perfluoropent-2-ene and ammonia, is an azo analogue of heptafluoroacetylacetone. These compounds react with ethylenediamine in alcohol to give 2,3-dihydro-6-fluoro-5,7-bis(trifluoromethyl)-1*H*-1,4-diazepine **46** (Scheme 47). The reaction with diethylenetriamine gives a nontrivial product—1,9-bis(trifluoromethyl)-3,4,6,7-tetrahydro-2*H*-pyrazino-[1,2-*a*]pyrazine **47** (93IZV1773, 94JFC(69)25), identified by X-ray analysis (94JFC(69)25). In the latter case, the reaction occurs via intermediate macrocycle **48**, which undergoes intramolecular nucleophilic substitution of fluorine by the amino group of the ethylenediamine fragment, showing the synthetic utility of analogous fluoroalkyl-containing 1,3-aminovinylketones.

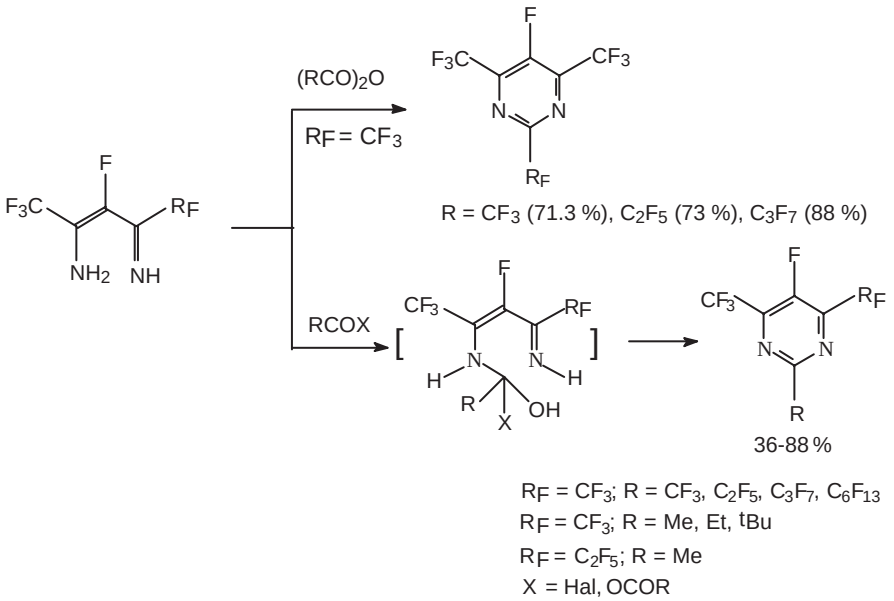
The reactions of polyfluorinated imidoylamidines with anhydrides (99IZV2195) and perfluorocarboxylic acid halides (85M6) are general processes forming pyrimidenes (Scheme 48). 2-Amino-4-iminoperfluoropent-2-ene, analogous in structure to the above imidoylamidines, interacts with anhydrides and perfluorocarboxylic acid chlorides forming 2,4,6-tris(perfluoroalkyl)-5-fluoropyrimidines (99IZV2195).

It is thought that pyrimidine formation is a two-step process including acylation of the imino enamine and further dehydration of this intermediate acyl derivative leading to ring closure.

Pyrazoles are obtained by [3 + 2] condensation of β-diketones with hydrazine and its derivatives (96M7). The same applies to the synthesis of fluorinated pyrazoles and



Scheme 47



Scheme 48

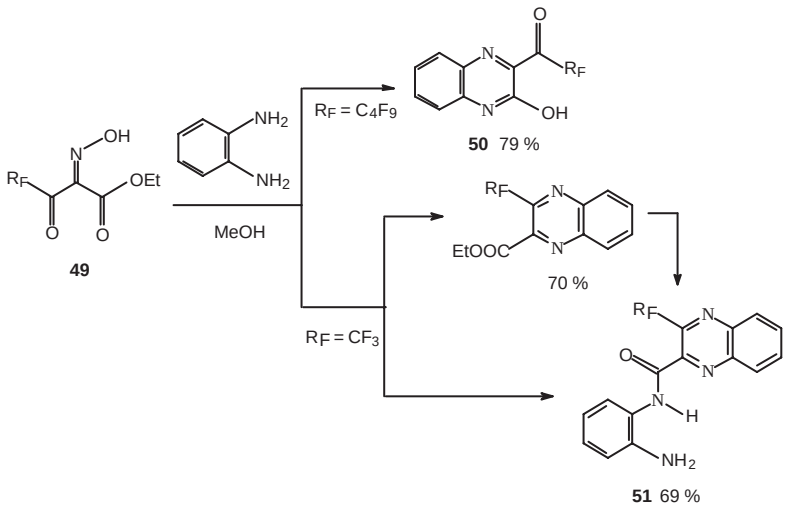
pyrimidines. Here, 1,3-bifunctional fluorinated synthetic units are employed; they are introduced in [3 + 2] and [3 + 3] cyclizations between the 1,3-bifunctional compounds and the binucleophilic reagents representing hydrazines and amidines, respectively (85M6). 1,3-Bifunctional compounds include fluoro-1,3-diketones (98JOC2550), fluorinated acetylacetylenes (89TL2049, 90JFC(48)123), and *β*-trifluoroacetyllactams (93TL5075). Thus, 2-fluoro-1,3-diketones RC(O)CHFC(O)R′ (R, R′ = Ph, CF_3; Ph, Ph; Me, Me; Me, 4-$NO_2C_6H_4$) react with phenylhydrazine forming high yields of pyrazoles (94JFC(69)25, 92JFC(56)141).

Fluorine-containing 2-oximino-1,3-oxo ethers **49** react with *ortho*-phenylenediamine in methanol, benzene, or toluene, giving substituted quinoxalines **50** and **51** rather than the expected 1,5-benzodiazepinones or benzimidazoles (98ZOR405) (Scheme 49).

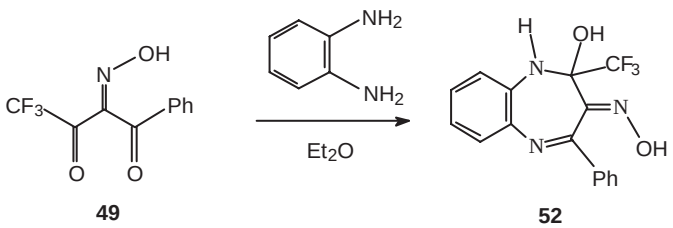
Although both **50** and **51** have a quinoxaline structure, they are formed by diamine condensation at different carbonyl groups of the starting 1,3-dicarbonyl compound, which depends on the size of the fluoroalkyl substituent. The nucleophilic reagent attacks the sterically less hindered carbon atom of the carbonyl group.

The reaction of 1,1,1-trifluoro-3-hydroxyimino-4-phenyl-2,4-butanedione in diethyl ether gives rise to 2-hydroxy-3-hydroximino-4-phenyl-2-trifluoromethyl-2,3-dihydro-1*H*-1,5-benzodiazepine **52** (yield 75%) (Scheme 50). In methanol there results a cleavage of the latter and the formation of 3-trifluoromethyl quinoxalin-2-one (98ZOR405). When heated in a vacuum or boiled in toluene, compound **52** is stable against dehydration and does not lose a water molecule.

Compound **49** containing a trifluoromethyl group ($R_F = CF_3$) and hydrazine hydrate give 3-hydroxy-2-hydroximino-4,4,4 hydrazide-trifluorobutanoyl hydrazide



Scheme 49

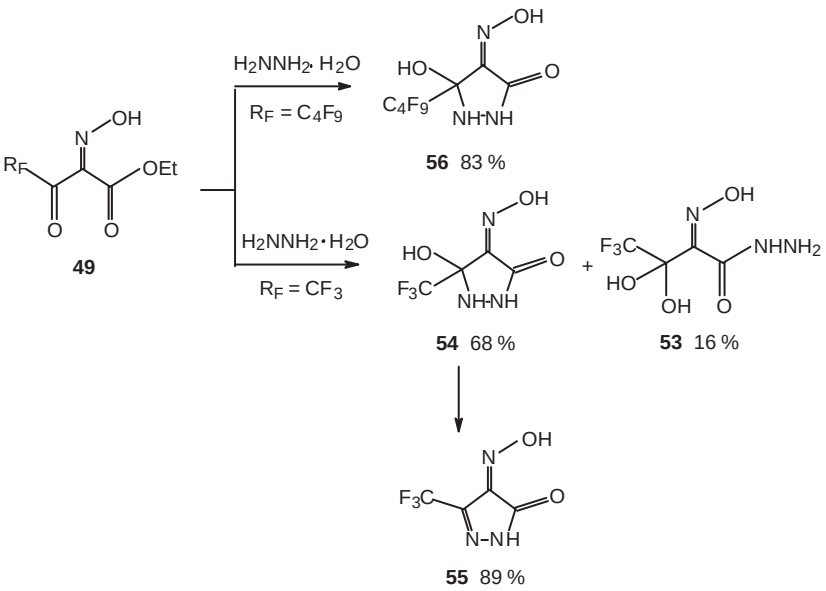


Scheme 50

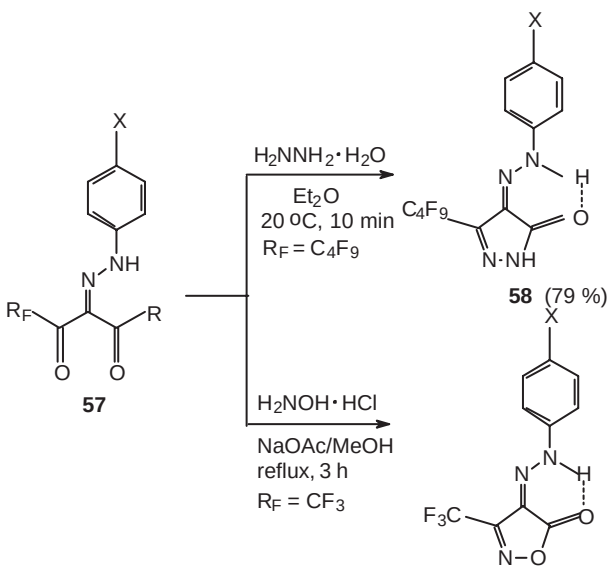
53 and 3-hydroxy-4-hydroximino-3-trifluoromethylpyrazolidin-5-one **54** (97ZOR442, 97JFC(84)107) (Scheme 51). Compound **54** is easily dehydrated on heating to 70 °C, forming pyrazolinone **55**. In the case of $R_F = C_4F_9$, heterocycle **56** is formed as the sole product.

It has been shown (98JFC(92)101) that the reaction of hydrazine in Et_2O and hydroxylamine hydrochlorides in CH_3OH in the presence of NaOAc with ethyl-2-(*para*-methoxyphenyl)-hydrazone-4,4,4-trifluoro-2,3-dioxobutanoate **57**, obtained by reactions of 1,3-ketoesters with aryldiazonium chloride, gives 3-nonafluorobutyl-4(*para*-methoxyphenyl)hydrazonepyrazolin-5-one **58** and 3-fluoromethyl-4(*para*-methoxyphenyl)hydrazonepyrazolin-5-one **59**, respectively (98JFC(92)101) (Scheme 52).

Fluorine-containing 2-arylhydrazone-1,2,3-diketo esters, 2-arylhydrazones of 1,2,3-triketones and 3-arylhydrazone-1,2,3,4-triketo esters may serve as key precursors to a variety of novel heterocycles and react with binucleophiles (85UK1997, 81UK325, 94ZOR1225). Thus, the 1,2,3-triketones arylhydrazones react with hydrazine hydrate, phenylhydrazine, thiosemicarbazide, and hydroxylamine hydrochloride to form the substituted pyrazoles and isoxazoline (98JFC(92)101, 98IZV673) (Scheme 53).

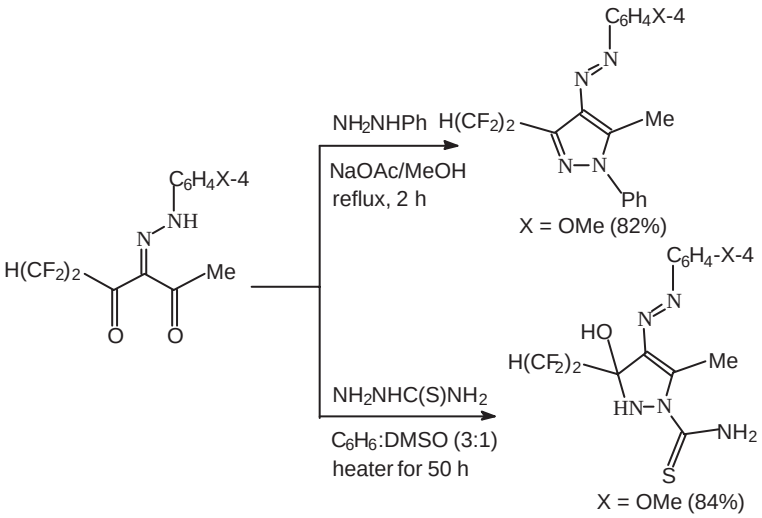


Scheme 51



$R_F = CF_3$, X = OMe, R = OEt;
$R_F = C_4F_9$, X = OMe, R = OMe

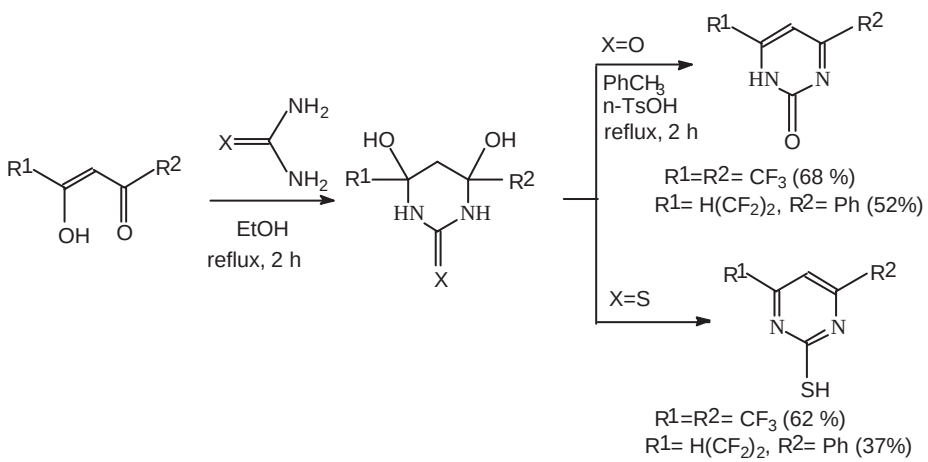
Scheme 52



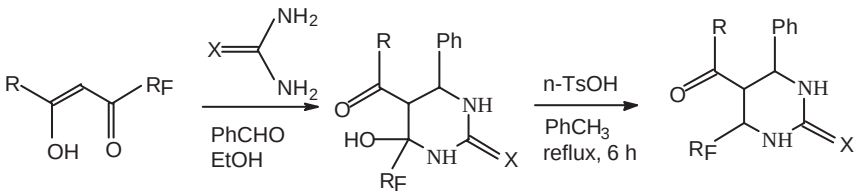
Scheme 53

Hexafluoroacetylacetone reacts with urea and thiourea to yield 4,6-bis(hydroxy)-4,6-bis(trifluoromethyl)hexahydropyrimidine-2-one and -2-thione (01ZOR915, 00JFC(103)17), respectively (Scheme 54). The dehydration of the products and also the reaction of unsymmetric fluoroalkylcontaining 1,3-diketones with urea and thiourea afford substituted pyrimidines.

The condensation of fluorinated 3-oxoesters or 1,3-diketones with benzaldehyde and urea or thiourea result in the diastereoselective formation of 4-fluoroalkyl-4-hydroxy-2-oxo(thioxo)-6-phenylhexahydropyrimidine-5-carboxylates from which by dehydration under acetic conditions the corresponding 6-fluoroalkyl-2-oxo(thioxo)-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylates were obtained (01ZOR915, 00JFC(103)17) (Scheme 55).



Scheme 54



R_F	HCF_2	$H(CF_2)_2$	C_3F_7	C_4F_9	CF_3	$H(CF_2)_2$	$H(CF_2)_2$	CF_3	CF_3
R	OEt	OMe	OMe	OEt	OEt	Ph	Me	Me	Ph
X	O	O	O,S	O,S	S	O,S	O	O	O,S

Scheme 55

Addition of a reactive group to the 2 position of the 1,3-dicarbonyl compound expands the traditional synthetic utility of these substances since their reactions with binucleophilic reagents form both the expected (benzodiazepine heterocycles) and the unexpected (quinoxalines) products.

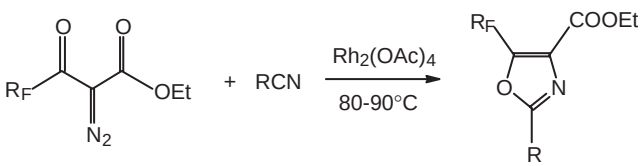
Thus, in the presence of $Rh_2(OAc)_4$, ethyl-2-diazofluoroacetoacetate, obtained by the reaction of ethylfluoroalkylacetoacetate with perfluoroalkane-sulfonylazide, reacts with nitriles giving 5-fluoroalkyl-substituted 1,3-oxazoles (00JFC(103)139) (Scheme 56).

The reactions of pentafluorobenzoylpyruvic acid with N-nucleophiles primarily involve the α-carbonyl group; however, intramolecular cyclization replacing the *ortho*-fluorine atom in the aromatic ring is also possible, giving new types of heterocycles. This kind of cyclization is not characteristic of the nonfluorinated hydrocarbon analogs.

Pentafluorobenzoylpyruvic acid is transformed by amines into the corresponding enamines, whose subsequent cyclization forms N-substituted 4-quinolone-2-carboxylic acids. Thus, treatment of pentafluorobenzoylpyruvate with gaseous or aqueous ammonia affords chromone (yield 64%) (94JFC(69)119, 94IZV299) (Scheme 57).

Pentafluorobenzoylpyruvic acid reacts at the C3 center with various binucleophiles, this reaction being the basic method for the synthesis of fluorinated chromones, quinolones, cynolones, and pyrazines.

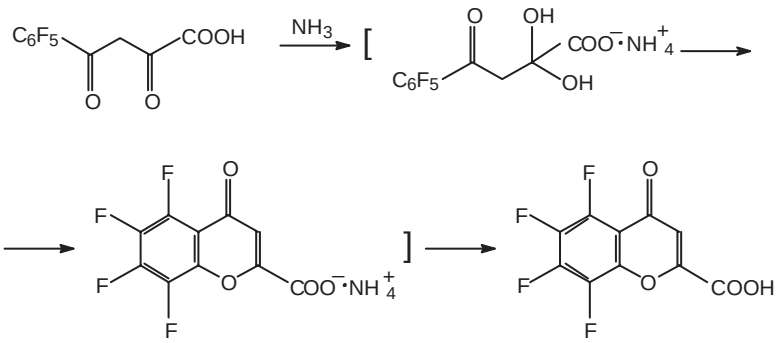
It was shown (95ZOR266, 99JFC(96)87) that copper chelates of pentafluorobenzoylpyruvic esters react with dinucleophiles (hydrazine hydrochloride,



R_F = CF_3, ClC_3F_6, C_5F_{11}

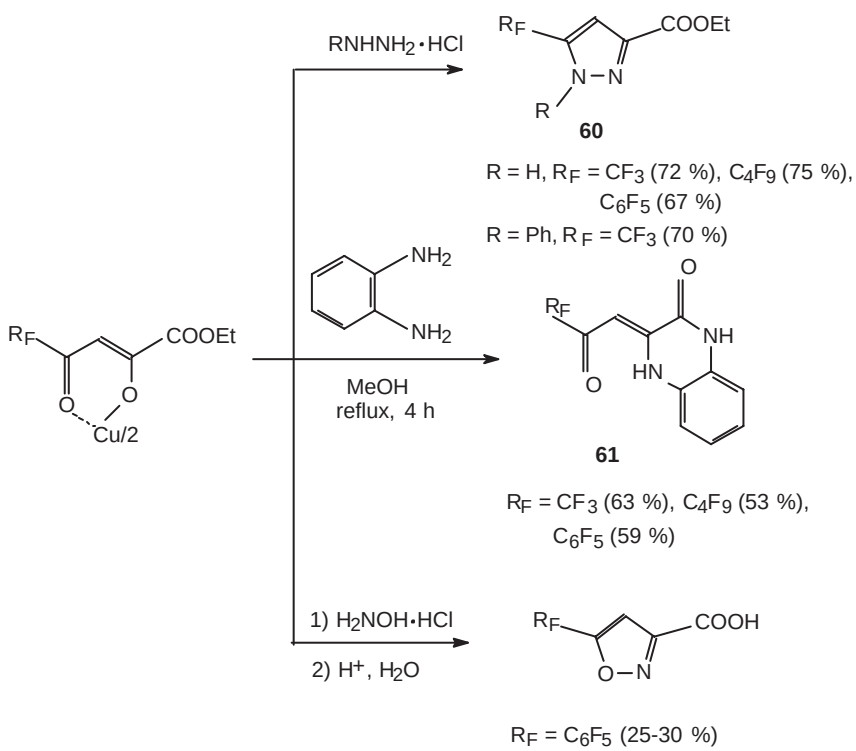
R = Ph, 3-MeC_6H_4, CH_2Ph, $ClCH_2$, $CH{=}CHCH_3$

Scheme 56



Scheme 57

phenylhydrazine, hydroxylamine hydrochloride, 1,2-ethylenedi-amine, 1,2-phenylenediamine, 2-aminophenol) to form heterocyclic compounds (Scheme 58). The reaction occurs at the β-diketone fragment and forms 5-fluoro-3-ethoxycarbonylalkylpyrazoles **60**. The reactions with *ortho*-phenylenediamine give pyrimidines **61**. Formation of these products instead of the expected 5-hydroxypyrazolines seems to be caused by the presence of the copper cation, not only orienting the reagent molecules, but also facilitating water elimination



Scheme 58

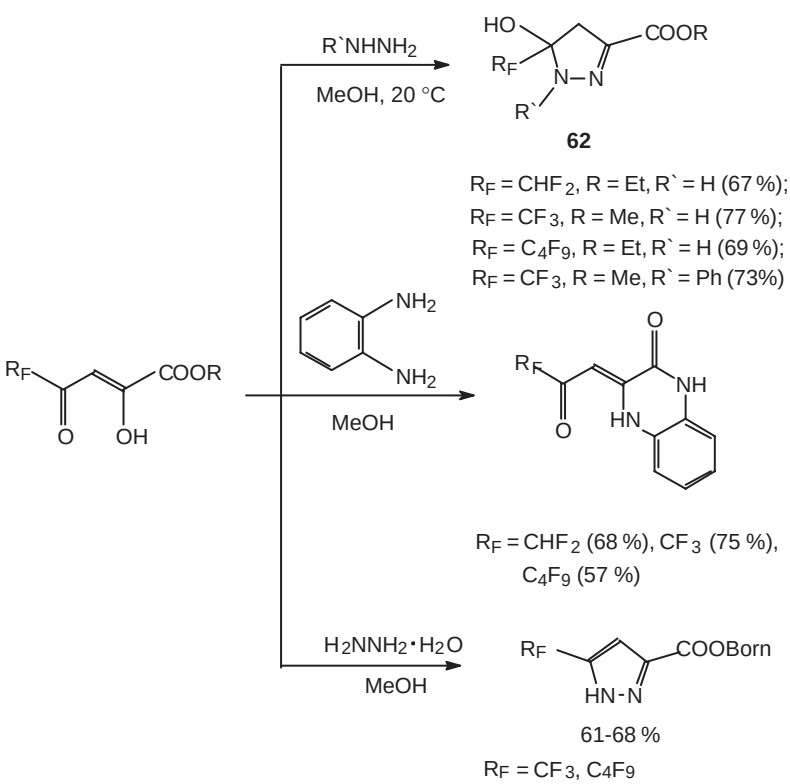
(by means of coordination) from the intermediates. In the case of hydroxylamine hydrochloride, the product is 5-pentafluorophenyl-isoxazole-3-carboxylic acid (99JFC(96)87).

At the same time, polyfluoroacylpyruvic acid itself reacts with hydrazine hydrate and phenylhydrazine at the β-dicarbonyl fragment and forms stable 5-hydroxy-3-alkoxycarbonyl-5-polyfluoroalkylpyrazolines **62** (92ZOR1380) (Scheme 59). Bornyl polyfluoroacylpyruvate and hydrazine hydrate give 3-bornyloxycarbonyl-5-fluoroalkylpyrazoles.

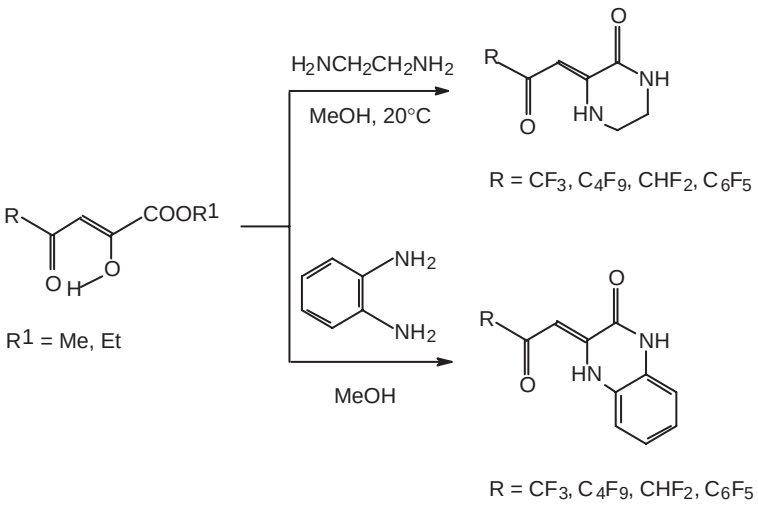
Treatment of aryl(aroyl)pyruvic acid ester metal chelates with *ortho*-phenylenediamine and ethylenediamine is accompanied by an attack at the α-ketoester fragment, forming quinoxalones and piperazinones, respectively (95ZOR266, 99JFC(96)87) (Scheme 60).

In the case of α-aminoalcohols, five-membered heterocycles are formed (Scheme 61).

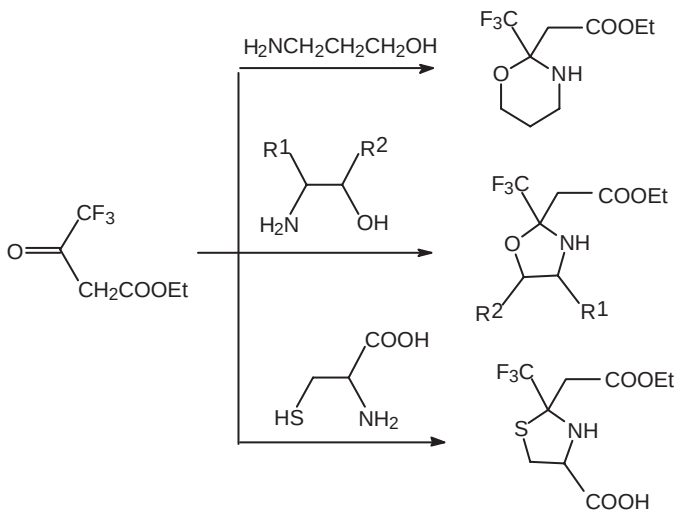
The reaction of the pentafluorobenzoylpyruvic acid with primary amines (aniline, isopropylamine, cyclohexylamine) yields addition-elimination products at the C(2) center, 2-alkylamino(anilino)-2-pentafluorobenzoylacrylic acids. In an alkaline medium, these compound undergo cyclisation and nucleophilic replacement of the



Scheme 59



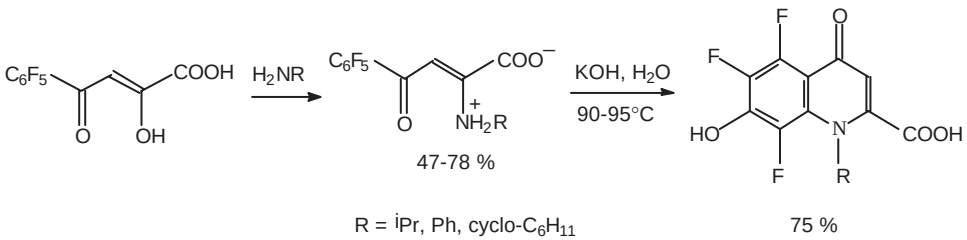
Scheme 60



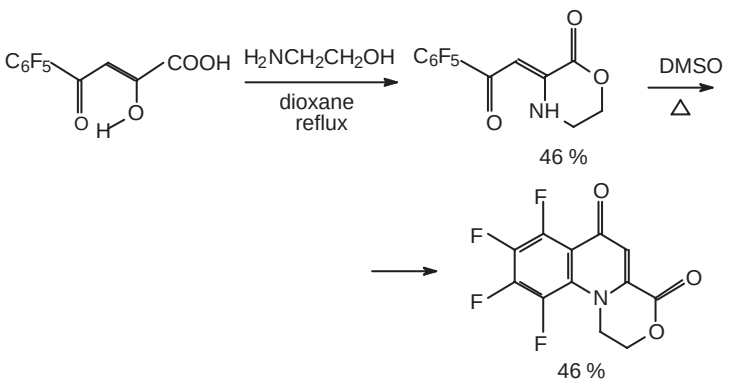
Scheme 61

fluorine atom at the C(7) atom by the hydroxy group to form 5,6,8-trifluoro-7-hydroxy-1-R-4-quinolone-2-carboxylic acids (94IZV299, 94JFC(69)119) (Scheme 62).

The reaction of pentafluorobenzoylpyruvic acid (as well as the reaction of aroylpyruvic acid) with ethanolamine in dioxane yields 3-pentafluorobenzoylmethylenemorpholin-2-one. Due to the presence of *ortho*-fluorine in the aromatic ring, the latter is capable of further cyclization forming 4-oxo-7,8,9,10-tetrafluoro-1,2,4,5-tetrahydro[1,4]oxazino[4,3-*a*]-4-quinolone (94JFC(69)119, 94IZV279) (Scheme 63).



Scheme 62

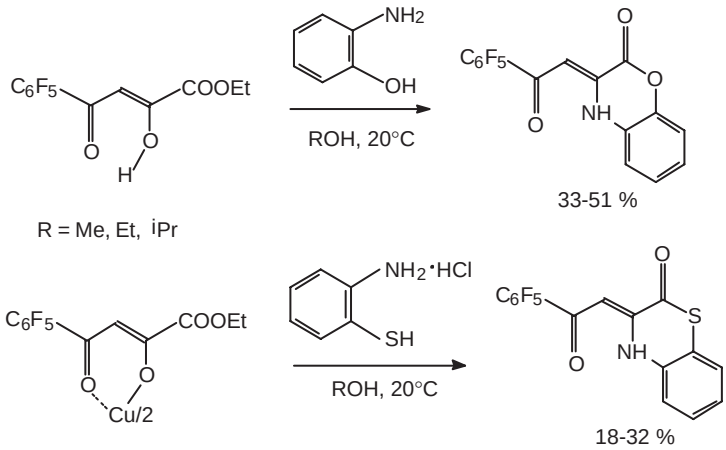


Scheme 63

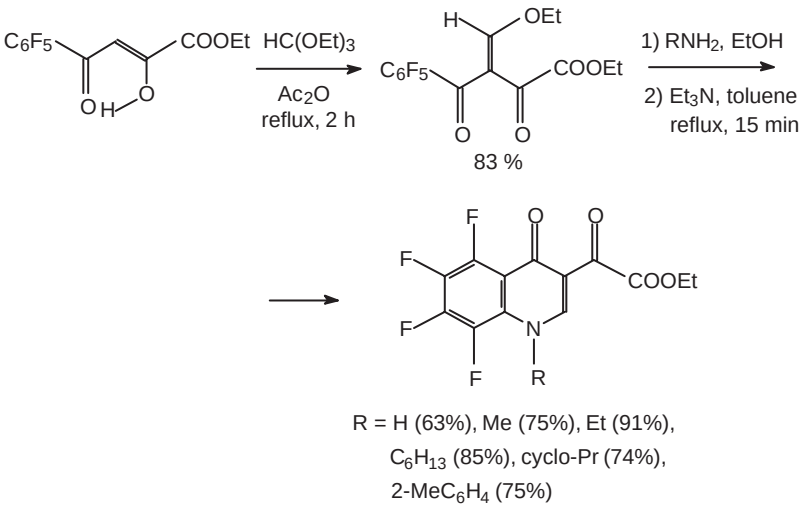
Alkaline hydrolysis opens the lactone ring to form 1-(2-hydroxyethyl)-5,6,7,8-tetrafluoro-4-quinolone-2-carboxylic acid.

Interaction between ethyl pentafluorobenzoylpyruvate and *ortho*-aminophenol (or its hydrochloride) in alcohol gives 3-pentafluorobenzoylmethylidene-2*H*-1,4-benzooxazin-2-one (99JFC(96)87, 96ZOR1386); in the reaction with *ortho*-aminothiophenol hydrochloride, the product is 3-pentafluoro-benzoyl-methylidene-2*H*-1,4-benzothiazin-4-one (00ZOR700) (Scheme 64).

Ethyl pentafluorobenzoylpyruvate was used as the starting compound for the synthesis of derivatives of fluoroquinolone (01JFC(108)187) (Scheme 65). Thus, the copper chelate of these compound was treated with triethylorthoformate in the presence of acetic anhydride to form α-ethoxymethylene-substituted ethyl pentafluorobenzoylpyruvate, which reacts with various amines (ammonia, methylamine, ethylamine, cyclopropylamine, *n*-hexylamine, and *o*-toluidine) to form acyclic precursors of quinolones—ethyl-4-alkylamino-2-oxo-3-pentafluorobenzoylbut-3-enoates (91ZVKO447, 01IZV689, 00IZV1234). These compounds in the presence of triethylamine upon heating in a dry aprotic solvent (toluene, chloroform) undergo intramolecular cyclization to form the corresponding 3-ethoxalyl-5,6,7,8-tetrafluoroquinolones. The cyclization proceeds through intramolecular substitution of the *ortho*-fluorine atom in the pentafluorophenyl substituent by the amino group.



Scheme 64

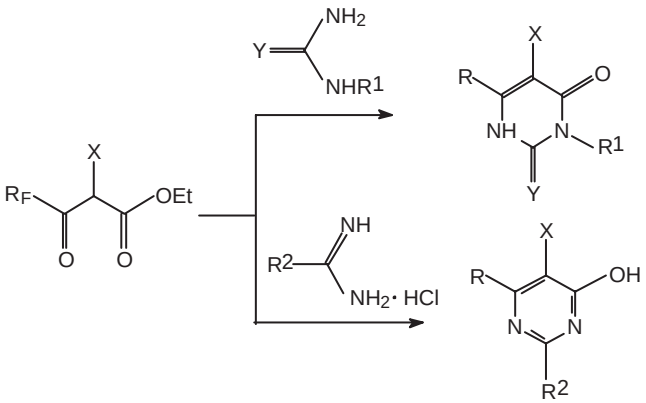


Scheme 65

Thus, aryl(aroyl)pyruvic esters can interact with N-dinucleophiles not only at the β-diketone but also at the α-ketoester fragments (93IZV858, 90IZV561, 58CCI189, 78KGS407, 64LA136).

The reactions of fluorinated β-diketones with urea (59JOC113, 69SWP293341, 71USP3580913, 53JA4091) in basic (59JOC113) or acid (53JA4091) solvents or with thiourea in the presence of sodium methoxide, or with guanidine carbonate (53JA4091) and carboxylic acid amidines lead to uracils, thiouracils, isocytosines, and 2-substituted hydroxypyrimidines, respectively (Scheme 66).

Trifluoroacetoacetic ester reacts with hydrazine hydrate to form 3-hydroxy-5(3)-fluoroalkylpyrazoles **63** (68JCS(C)1507, 81JOC1532, 85IZV144). With



R = CF_3, X = H, R^1 = H, Y = O (20 %) [59JOC113];

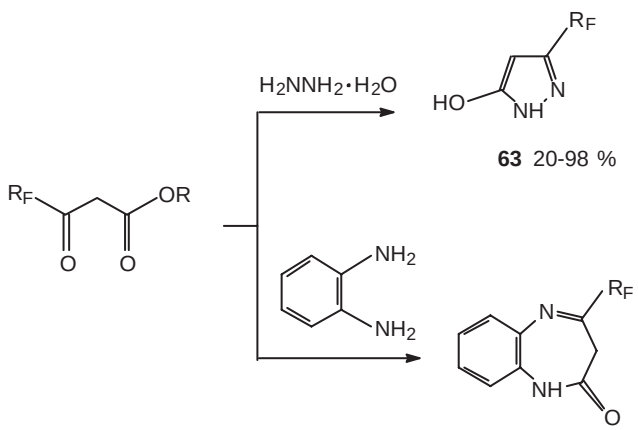
R = CH_2F, X = H, R^1 = H, Y = O (73 %) или S (67 %) [53JA4091];

R = CH_3, X = F, R^1 = Ar, Y = O [69SWP293341,71USP3580913]

Scheme 66

2-imino-thiazolidine, the products are thiazolinopyrimidines; and with amino alcohols it gives 2-trifluoromethyl-2 carbethoxymethylperhydrooxazine or the corresponding oxazoline. Finally, with cysteine, the product is 4-carboxy-2-trifluoromethyl-2-carbethoxymethylthiazolidine (Scheme 67).

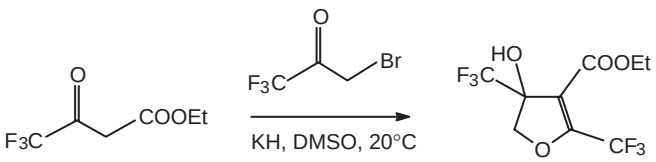
Ethyl 4,4,4-trifluoroacetoacetate and 3-bromo-1,1,1-trifluoroacetone react in the presence of KH in dimethyl sulfoxide at room temperature to form ethyl 2,4-bis(trifluoromethyl)4-hydroxydihydro-3-furanate (97JFC(81)123) (Scheme 68).



63 20-98 %

R_F = CF_3, C_3F_7, C_4F_9, $H(CF_2)n$ (n = 1, 2, 4)

Scheme 67

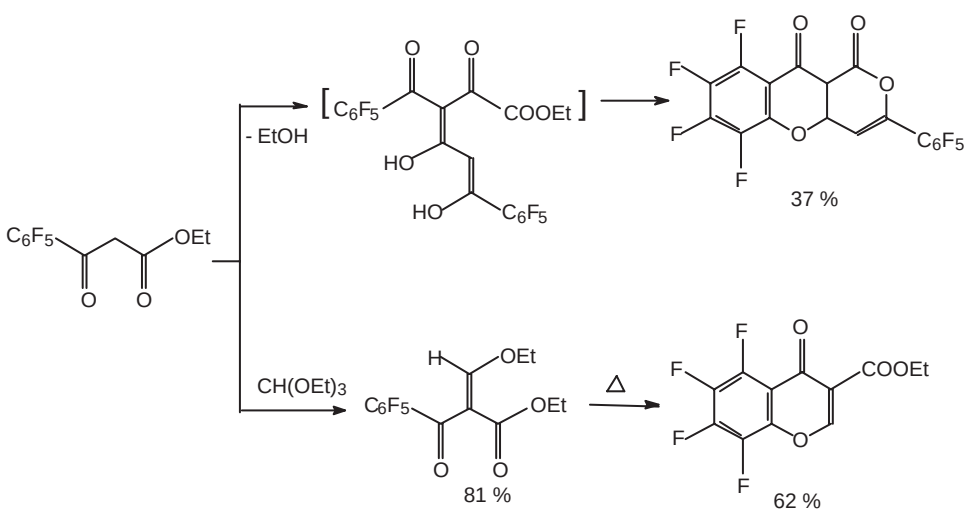


Scheme 68

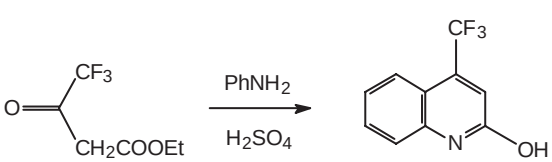
Ethyl pentafluorobenzoylacetic ester undergoes cyclization into 1-oxo-3-pentafluorophenyl-1*H*-pyrano[4,3-*b*]6,7,8,9-tetrafluorochromone (92IZV2186) (Scheme 69).

The reaction with ethyl orthoformate affords ethyl 2-ethoxymethylidene-pentafluorobenzoylacetate, which on heating undergoes cyclization into 3-ethoxycarbonyl-5,6,7,8-tetrafluorochromone (93JFC(65)37, 93IZV362).

The reactions of trifluoroacetoacetate with anilines in the presence of sulfuric or polyphosphoric acid lead to the formation of a six-membered heterocycle, oxyquinoline **64** (73JMC319, 68JMC267, 76USP3953453, 73JMC337, 80USP4202981, 77JHC1109) (Scheme 70).



Scheme 69



64

Scheme 70

These reactions indicate that the O-, N-, and S-nucleophiles attack the C(1) carbonyl carbon, although in the case of N-nucleophiles the attack may be preceded by formation of a salt with fluorine-containing β-ketoesters.

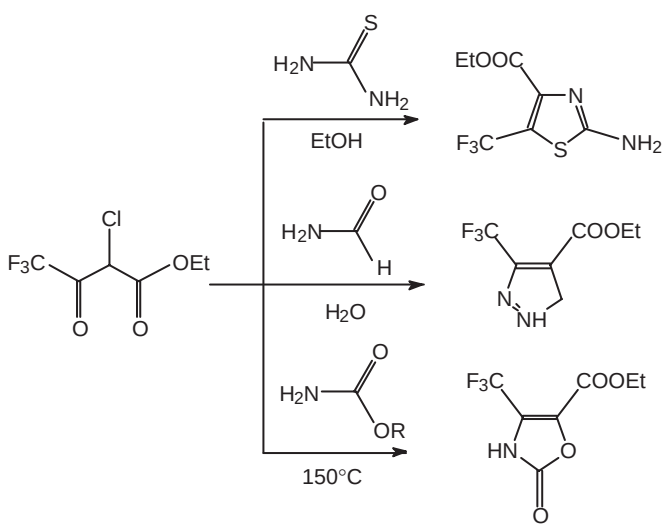
If the α-position is occupied by a chlorine atom, possessing higher leaving ability compared to fluorine, the reaction follows alternate routes, forming ethyl 2-amino-4-trifluoromethyl-thiazolecarboxylic ester in the case of thiourea (72BrP290841, 81USP4308391) and five-membered heterocyclic compounds in the case of formamidine and urethane (76USP3950353, 91USP4303439) (Scheme 71).

Bis-β-diketones **65** containing perfluoroalkyl groups are obtained by condensation of acetonylacetone with perfluorocarboxylic esters in the presence of lithium methoxide (95IZV2289, 98ZOR371) (Scheme 72).

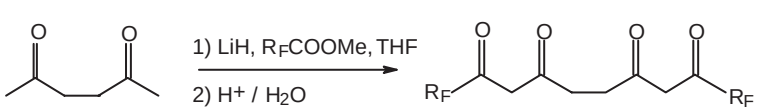
Reaction of compound **65** with binucleophiles such as hydrazine, phenylhydrazine, or hydroxylamine, leads to bis-heterocyclic compounds **66** and **67** (95IZV762) (Scheme 73).

Dehydration of bis(5-hydroxy-Δ^2-isoxazolines) occurs readily and forms isoxazoles **68**.

The reaction of 2-amino-4-phenyl-1,1,1-trifluoromethylbut-2-en-4-one **69** with acetophenone forms 2,4-diphenyl-6-(trifluoromethyl)-pyridine **70** (yield 24%) (96IZV2278) (Scheme 74).



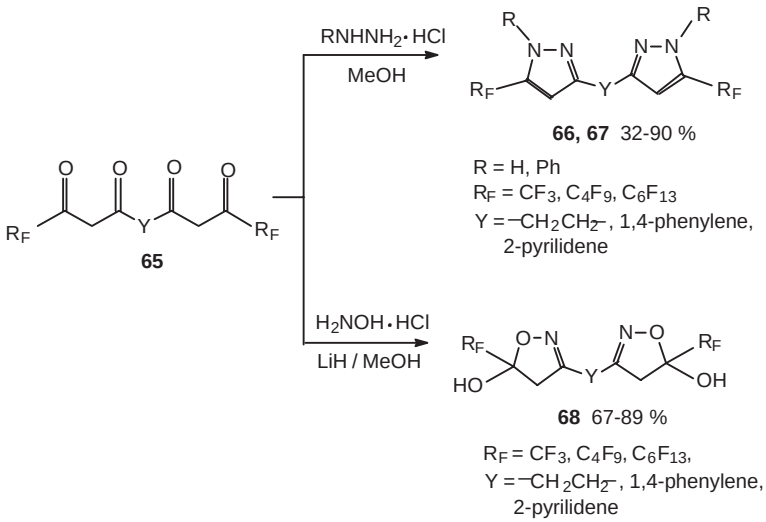
Scheme 71



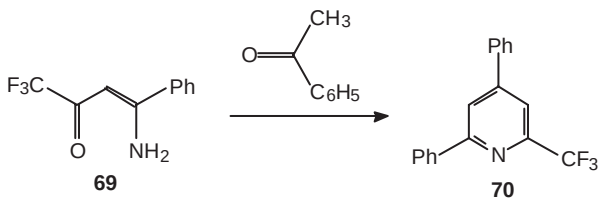
65

$R_F = C_4F_9, C_6F_{13}$

Scheme 72



Scheme 73



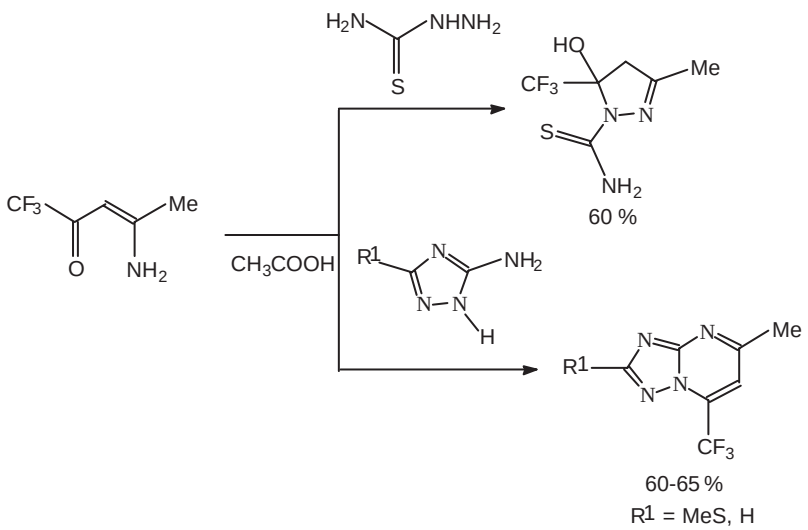
Scheme 74

The reaction of 2-amino-4-methyl-1,1,1-trifluoromethyl-2-butene-4-one with thiosemicarbazide forms 5-hydroxy-5-trifluoromethyl-2-pyrazoline, and with derivatives 3-amine-1,2,4-triazoles forms derivatives triazolo[1,5-*a*]pyrimidine (02IZV332) (Scheme 75).

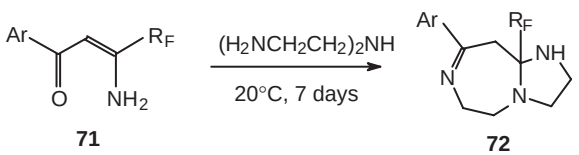
The derivatives of a new condensed triazabicyclo-[5.3.0]dec-4-ene system with a nodal nitrogen atom (7-trifluoromethyl-5-phenyl-1,4,8-triazabicyclo[5.3.0]dec-4-ene **72**) are obtained in reactions of aminoenones **71** with diethylenetriamine (room temperature, no solvent, 4–7 days) (yield 64–74% for the trifluoromethyl substituent and 23–33% for tetrafluoroethyl) (99IZV1410) (Scheme 76).

In this case, diethylenetriamine acts as a trinucleophile; its interaction with amino enone **71** involves double nucleophilic addition at the β-carbon, forming ammonia, and an attack at the carbonyl group, liberating water. The reaction takes place when the compound contains a polyfluoroalkyl substituent, not only enhancing the electrophilicity of the β-carbon atom, but also stabilizing the imidazolidine ring.

The interaction of regioisomeric β-aminovinylthiones **73** with Lawessons reagent forms $\Delta^{3,5}$-2-thioxo-1,3,2-thiazaphosphorine and $\Delta^{3,5}$-2-thioxo-1,3,2-oxazaphosphorine **74** (88SL107) (Scheme 77).



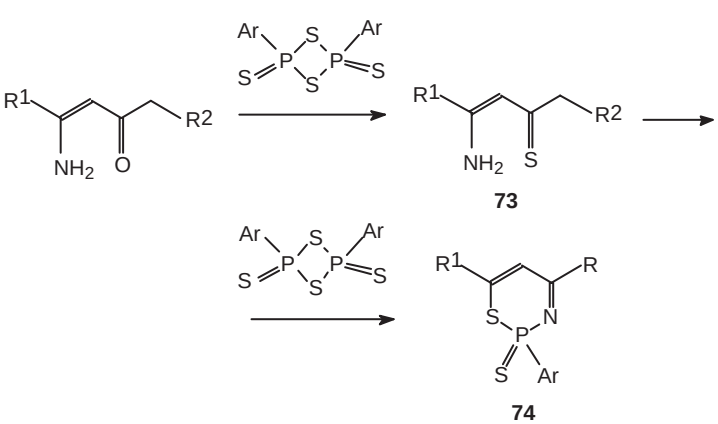
Scheme 75



71 **72**

Ar	Ph	Ph	2-C_4H_3S	2-C_4H_3
R_F	CF_3	HCF_2CF_2	CF_3	HCF_2CF
Yield, %	74	33	64	25

Scheme 76



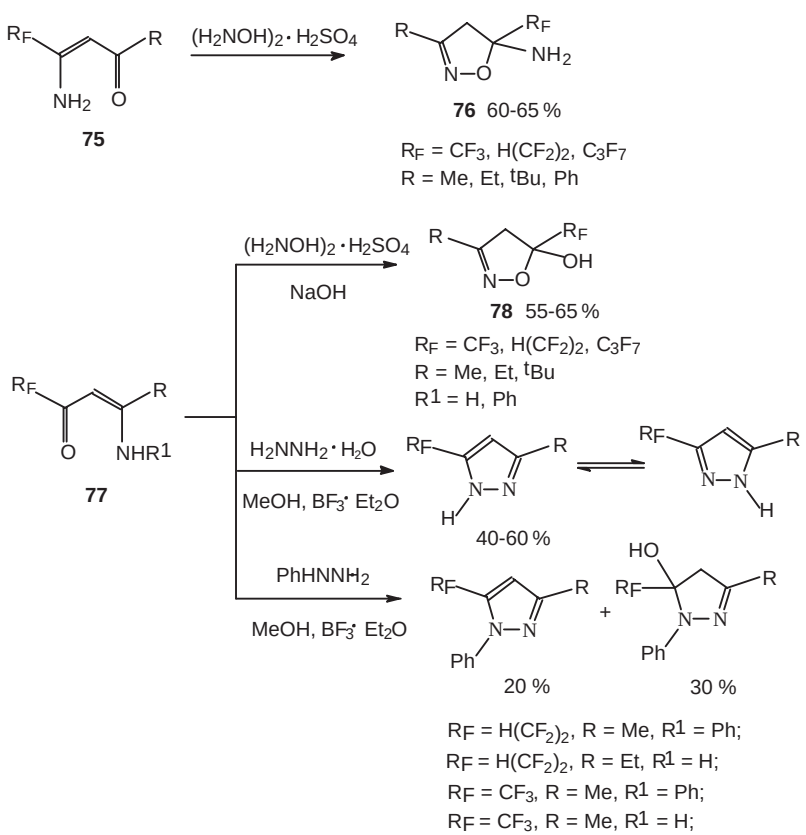
73 **74**

Scheme 77

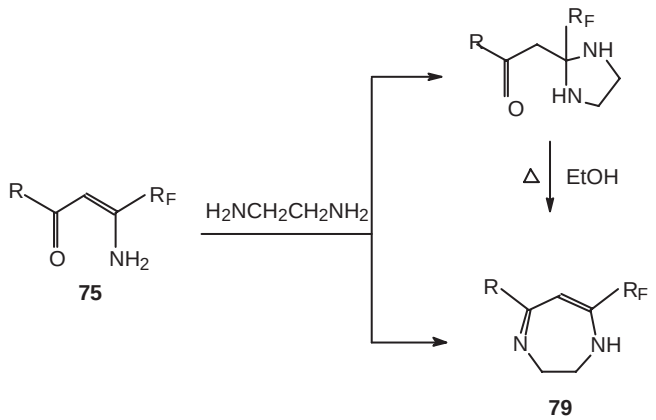
When treated with hydroxylamine, β-aminovinylketones **75** give 5-amino-5-fluoroalkyl-^{2}-isoxazoline **76**, while β-aminovinylketones **77** yield 3-hydroxy-5-fluoroalkyl-Δ^2-isoxazoline **78**; treatment of **77** with hydrazine hydrate and phenylhydrazine leads to pyrazole and mixture pyrazole and 5-hydroxy-Δ^2-pyrazoline corresponding (96IZV1306) (Scheme 78).

Condensation between ethylene diamine and β-amino-β-polyfluoroalkyl-vinyl-ketones **75** containing at two electrophilic centers, an amino group and a fluoroalkyl substituent, follows two routes (Scheme 79). Either 2,3-dihydro-1*H*-1,4-diazepines **79**, existing in its imino enamine form and generated by two nucleophilic attacks at the β-carbon and the carbonyl group, or 2,2-substituted imidazolines (81IZV455, 98KGS847, 99IZV546) are formed. The latter are only formed under kinetic control conditions and are converted into the more stable dihydrodiazepines on boiling in ethanol for 3–6 h.

The reaction of 3-amino-1-phenyl- and 3-amino-1(thien-2-yl)-4,4,4-tri-fluorobut-2-en-1-ones with 1,2-diaminopropane and 1,2-diamino-3,3,3-trifluoropropane under kinetic control conditions (room temperature, 20 h) forms a mixture of *cis* and *trans* isomers of imidazolines, one of which prevails (isomer ratio 9 : 1) (99IZV2135,

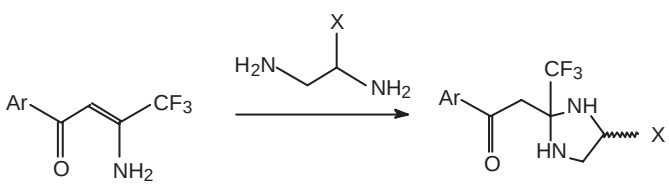


Scheme 78



R = C_4H_3S, R_F = CF_3; R = C_4H_3S, R_F = $H(CF_2)_2$;
R = Ph, R_F = CF_3; R = Ph, R_F = $H(CF_2)_2$

Scheme 79



Ar = Ph, 2-C_4H_3S
X = Me, CF_3

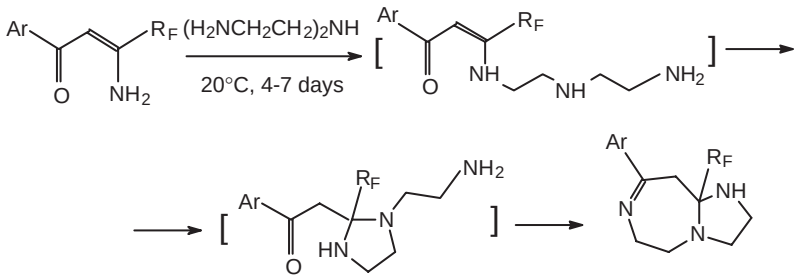
Scheme 80

99IZV2234) (Scheme 80). The available data, however, do not permit an unambiguous conclusion about the configuration of the major and minor isomers.

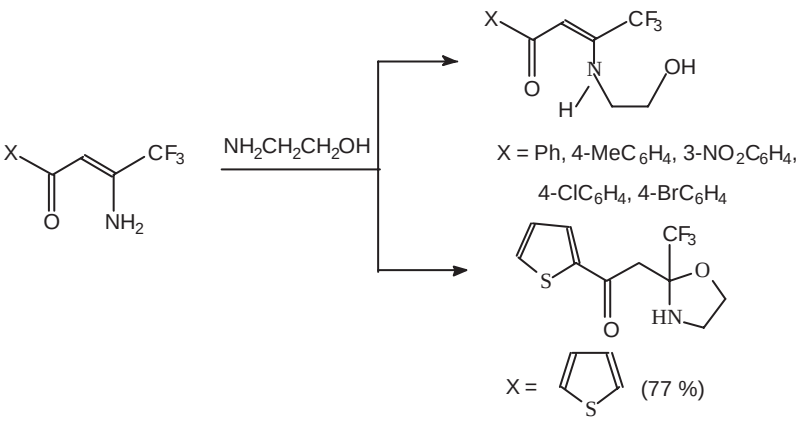
It was shown (00IZV1432) that the reactions of aminoenones with diethylenetriamine lead to a condensed system, triazabicyclo[5.3.0]dec-4-ene, with a nodal nitrogen atom (Scheme 81).

Diethylentriamine acts as a trinucleophile. Its interaction with amino enones includes double nucleophilic addition on atom Cβ with elimination of ammonia and attack on the carbonyl group accompanying by loss of a molecule of water. Successful reaction is promoted by the presence of polufluoroalkyl substituents that not only increase the electrophility of atom Cβ, but also stabilizes the imidazoline ring.

3-Amino-1-aryl-4,4,4-trifluoro-2-buten-1-ones react with 2-aminoethanol at room temperature in the absence of solvent over 2–3 days to give only aminoenones in 46–75% yield (98MC83) (Scheme 82). It is surprising that the thiophene analogue of aminoenones (3-amino-1(2-thienyl)-4,4,4-trifluoro-2-buten-1-one) reacts with 2-aminoethanol to form 2(2-thenoyl-methyl)-2-trifluoromethyloxazolidine.



Scheme 81



Scheme 82

The reactions of fluorine-containing β-aminocrotonic ethers **80** and isocyanates lead to fluorinated uracils **81** (72JHC513, 76TL243, 76BrP1427945, 76ZOR949, 81BCJ3221, 80JHC1413, 77FrP2335566, 99IZV2195) (Scheme 83).

These examples demonstrate the efficiency of using labile multiple bonds in functional groups for constructing heterocyclic rings. An important factor governing this process is the fluorine effect on the properties of such groups.

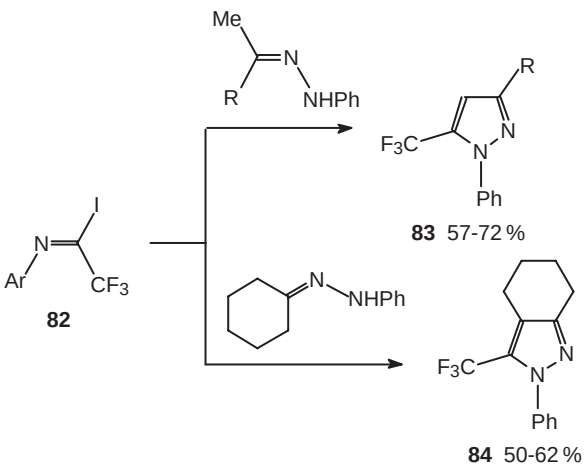
R = Ph, 4-ClC6H4, C5H11, 3,4-dichlorobiphenyl

Scheme 83

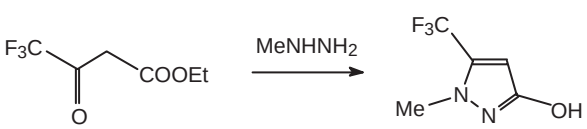
When a methyl ketone or cyclohexanone phenylhydrazone is treated with trifluoroacetimidoyl iodide **82** in the presence of excess sodium hydride, [1 + 4] cyclization into 5-trifluoromethylpyrazoles **83** and **84**, respectively, takes place (97SL679) (Scheme 84).

β-Ketoesters react with methylhydrazine with formation of five-membered heterocycles (93JHC49) (Scheme 85).

Oxidation of bis-hydrazones of aliphatic polyfluorinated *α*-dicarbonyl compounds with SO_2Cl_2 or bromine forms isomeric 1-amino-1,2,3-triazoles, one of which was identified by X-ray analysis (96JFC(79)45) (Scheme 86). Oxidation of polyfluoroalkyl-substituted glyoxal dihydrazones gives only one isomer.



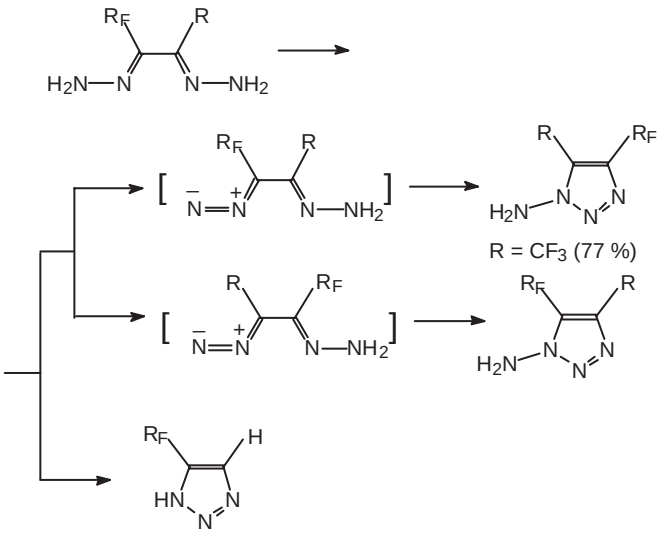
Scheme 84



Scheme 85

IV. From Other Carbonyl-Containing Compounds with Perfluoroalkyl Groups

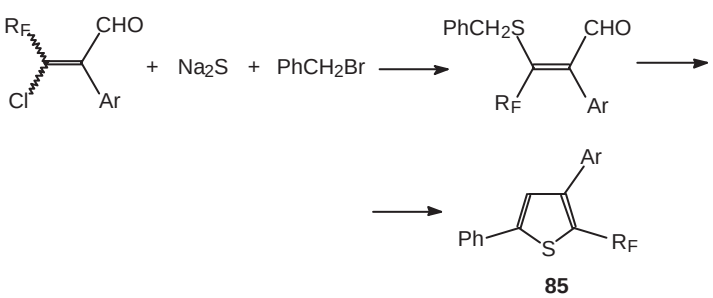
Compounds with a carbonyl group conjugated to the double bond are conventionally called Michael acceptors. The Michael reaction is a route to a carbon–carbon bond. A nucleophile adds to a Michael acceptor. Together with nucleophilic addition at the carbonyl group, this is the first step of Robinson's cyclization, which is an excellent method for the preparation of medium-sized (and especially six-membered) rings.



Scheme 86

In a fluorocarbon chain containing multiple bonds, the carbonyl group possesses high reactivity and is involved in the formation of heterocyclic systems induced by binucleophilic reagents. The mutual arrangement of the C = O group and the double bond may differ between molecules, which leads to diversity of heterocyclic compounds.

Below we consider some examples of such substrates. The C = O group is directly bonded at the multiple bond. Some compounds, for example, α-chloro-β-perfluorovinylaldehydes are effective building blocks for the synthesis of heterocycles with a perfluoroalkyl group. Thus, thiophenes **85** are formed by reaction of α-chloro-β-perfluorovinylaldehyde **86** with Na_2S and benzyl bromide (99JFC(94)91, 95JFC(70)121) (Scheme 87).



85

Scheme 87

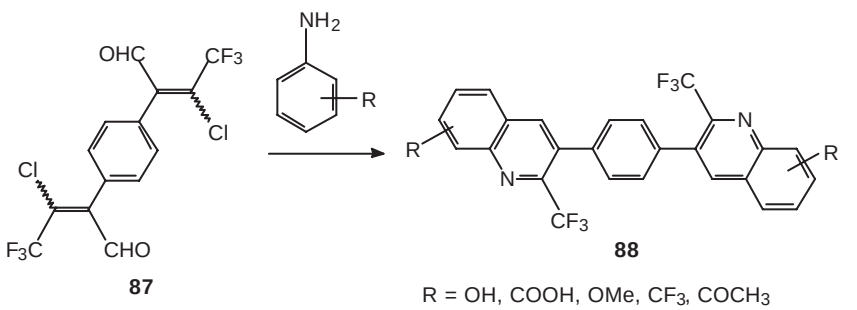
In the case of the reactions of compound **87** with anilines, the products are quinolines **88** (95JPR34) (Scheme 88).

The reaction with *para*-phenylenediamine produces 2,6-bis(perfluoroalkyl)-1,5-diazaanthracene **89**, while with *ortho*-phenylenediamine the initial product is benzodiazepine salt **90**, stable at −35 °C. At elevated temperatures the salt is transformed into benzimidazole perchlorate **91** (Scheme 89).

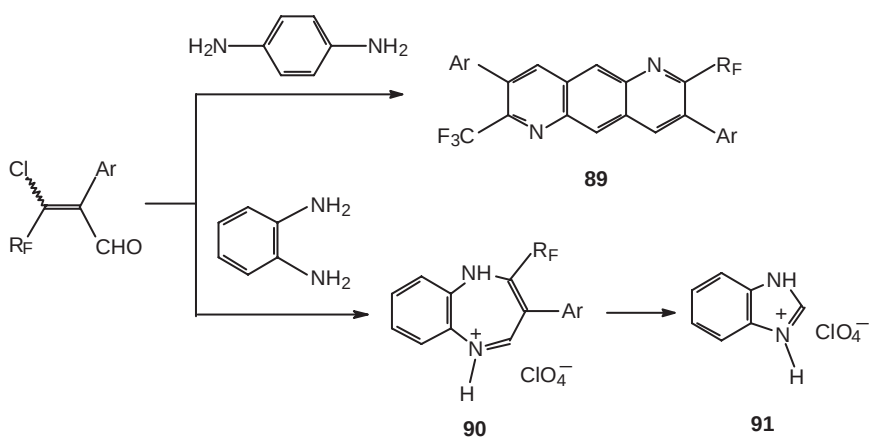
The reaction of compound **86** with phenylhydrazine in the presence of triethylamine, guanidine, and ammonium thiocyanate forms heterocyclic compounds with two heteroatoms (99JFC(94)91) (Scheme 90).

Reaction conditions play an important role. For example, when performed in diethyl ether in the presence of triethylamine, the reaction of *β*-chloro-*β*-trifluoromethylenone **92** with phenylhydrazine yields substituted pyrazole **93**; in acetic acid, the product is the isomeric pyrazole **94** (97JFC(84)145) (Scheme 91).

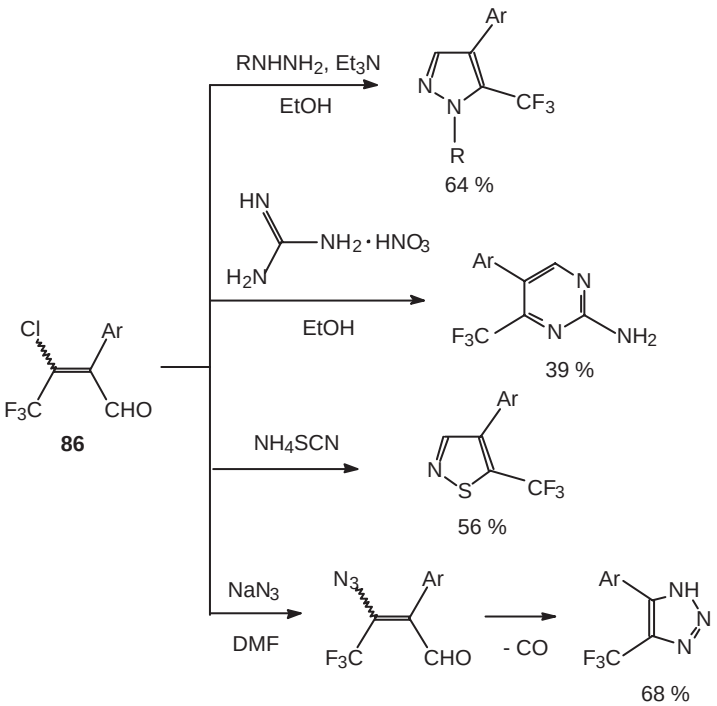
5,5,5-Trifluoro-4-trifluoromethylpent-3-en-2-one is versatile and highly reactive and provides new substances with interesting properties. Thus, it reacts with p-toluenesulfonylhydrazine and 2,4,6-triisopropylbenzenesulfonylhydrazine in



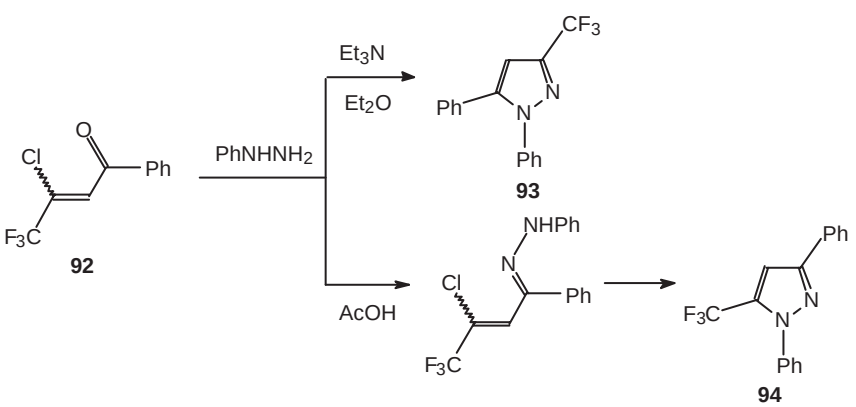
Scheme 88



Scheme 89

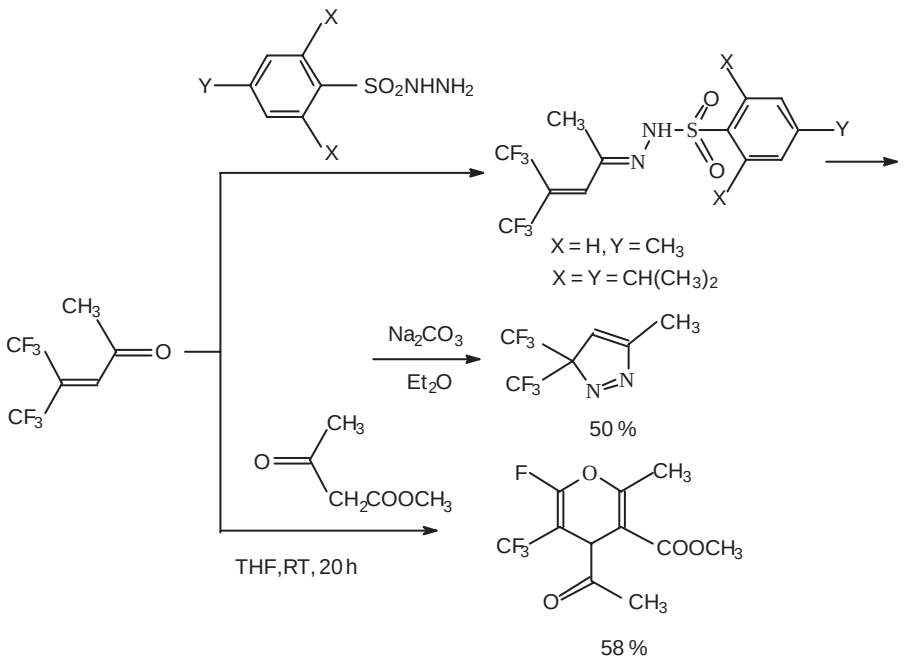


Scheme 90



Scheme 91

acetonitrile under acidic conditions to give the corresponding 1,1,1-trifluoro-2(trifluoromethyl)-4(p-poluenesulfonylhydrazone)pent-2-ene and 1,1,1-trifluoro-2(trifluoro-methyl)-4-(2′,4′,6′-triisopropylbenzene sulfonylhydrazone)-pent-2-ene in almost quantitative yields (99JFC(97)115) (Scheme 92). X-ray structures of these compound are provided. Treatment of the compound with sodium hydroxide in a two phase system gives 5-methyl-3,3-bis(trifluoromethyl)-3*H*-pyrazole.

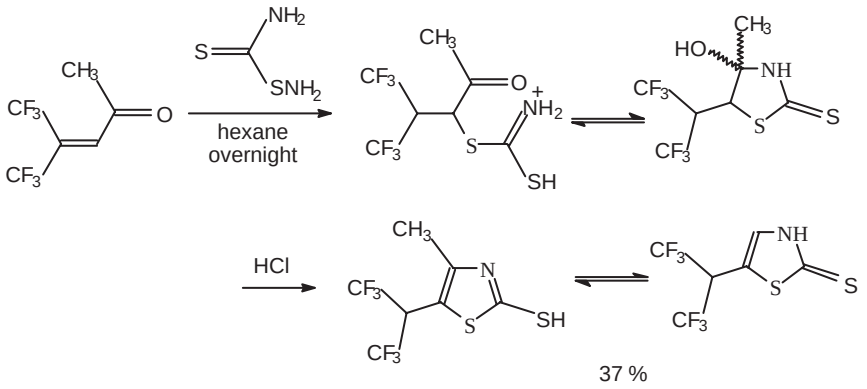


Scheme 92

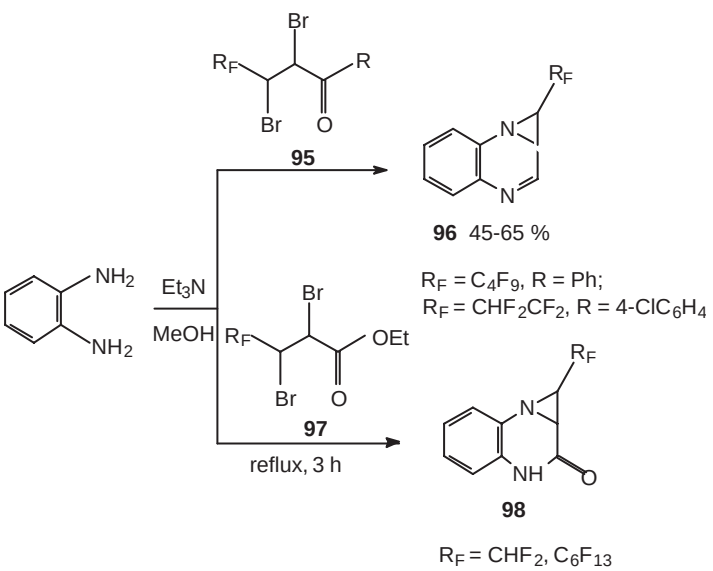
The conversion of 5,5,5-trifluoro-4-trifluoromethylpent-3-en-2-one with methyl acetoacetate in the presence of sodium hydride opens a new reaction pathway for the preparation of molecules which might show some biological and medical activities. The first step of this reaction is the anti-Michael addition of the nucleophile (α-metallated ester) to the 3-position of 5,5,5-trifluoro-4-trifluoromethylpent-3-en-2-one. In the next step metallation in the γ-position yields the enolate which attacks nucleophilically the olefinic CF_2-carbon forming 4-acetyl-2-fluoro-6-methyl-5-methoxy-carbonyl-3-trifluoromethylpyran by fluoride elimination.

The nucleophilic addition of ammonium dithiocarbamate to 5,5,5-trifluoro-4-trifluoromethyl-pent-3-en-2-one follows a Michael analog addition. The presence of two gemminal highly electronegative CF_3 groups dominates the regioselectivity. This 1,3-anti-Michael addition results in the synthesis of the new 2-mercapto-4-methyl-5(2,2,2-trifluoro-1-trifluoro-methylethyl)-1,3-thiazole derivatives (02JFC(117)185) (Scheme 93). These compounds exhibits thiol-thione tautomerism; thus, 2-mercapto-1,3-thiadiazoles exist predominately in the thione form (2-thione-4-methyl-5(2,2,2-trifluoro-1-trifluoromethyl-ethyl)-1,3-thiazoline. The dominance of the thione over the thiol form depends on a combination of different factors, among them the difference in π-electron energy. X-ray structures of these compound are provided.

When *ortho*-phenylenediamine reacts with fluoroalkyl-containing α,β-dibromoketones **95**, dihydroazirinoquinoxalinones **96** (96ZOR320) result. The reaction with ethyl α,β-dibromo-α-fluoroalkylcarboxylic esters **97** yields 2-oxo-1-polyfluoroalkyl-1,1a,2,3-tetrahydroazirino[1,2-*a*]-quinoxalines **98** (96IZV3026) (Scheme 94).



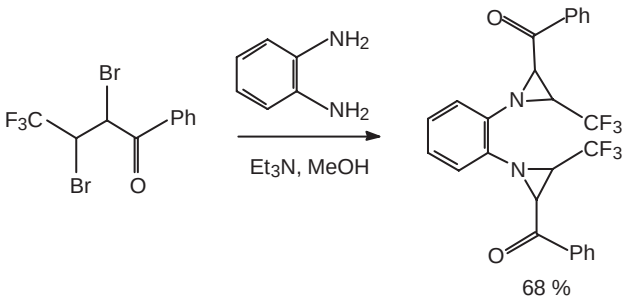
Scheme 93



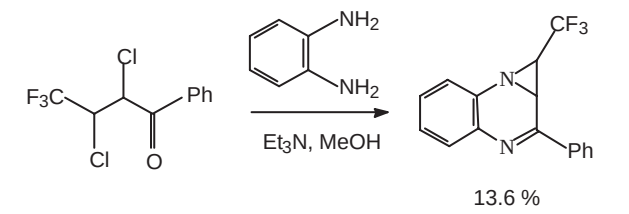
Scheme 94

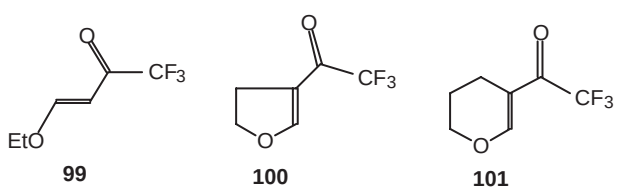
When the substrate contains a trifluoromethyl substituent, the reaction is anomalous and forms a bis-aziridinylketone. This is probably explained by factors other than steric effects. For example, the electron-accepting influence of the CF_3 group sharply accelerates dehydrobromination relative to dehydration and leads to a three-membered ring (96IZV3026, 95IZV1599, 96IZV2795) (Scheme 95).

On the other hand, dihydroazirinoquinoxalines are also prepared from a substrate with a trifluoromethyl group by using a β-fluoroalkyl-α,β-dichloropropionic ester. Thus, the reaction of *ortho*-phenylenediamine with an α,β-dichloroketone produces 1-trifluoromethyl-2-phenyl-1,1*a*-dihydroazirino[1,2-*a*] quinoxaline (99ZOR106, 96IZV3026, 99ZOR100) (Scheme 96).



Scheme 95





Scheme 96

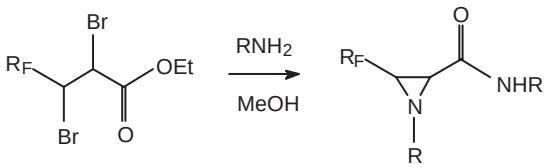
Many publications are devoted to the use of compounds with one trifluoromethyl group in the syntheses of heterocycles: 4-ethoxy-1,1,1-trifluoro-3-buten-2-one **99** and β-alkoxy enones **100** (95JHC739, 95JHC731, 96JHC1223, 96JHC1, 95S1491, 93JHC1159, 91JBCS118, 95JHC735, 97JHC509, 98JHC451, 99JHC45, 96TL9155, 99JFC(99)177).

The use of β-alkyl-β-methoxyvinyltrifluoromethylketones affords various heterocycles with a CF_3 group (95JHC739). Thus, cyclocondensation has been performed with hydroxylamine, semicarbazide, thiosemicarbazide, phenylhydrazine, and urea.

In the case of a reaction with amines only the 3-membered heterocyclic aziridine (96IZV2795) is produced (Scheme 97).

The presence of a trifluoromethyl group can lead to the formation of dihydroazirineqinoxalines with *ortho*-diamines. Thus, *ortho*-phenylendiamine with an α,β-dichloroketone gives 1-trifluoromethyl-2-phenyl-1,1*a*-dihydroazirino [1,2-*a*]quinoxaline (99ZOR106, 95IZV1599, 96IZV2795) (Scheme 98).

A significant number of studies are devoted to the synthesis of compounds with one trifluoromethyl group such as 4-ethoxy-1,1,1-trifluoro-3-buten-2-one **99** and β-alkoxy-substituted enones **100** (95JHC739, 99JFC(99)177).

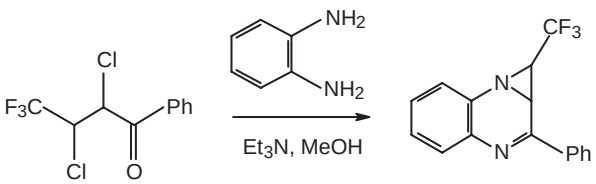


65.1-73.2 %

$R_F = CF_3$, $H(CF_2)_2$

R = Me, C_6H_{13}, $PhCH_2$

Scheme 97



13.6 %

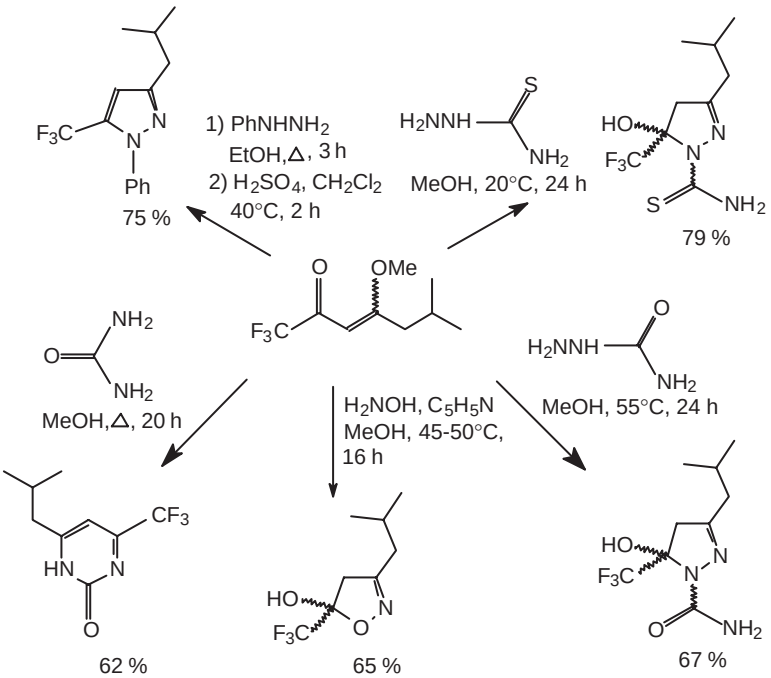
Scheme 98

Using β-alkyl-β-methoxyvinyl trifluoromethyl ketones allows the preparation of various heterocyclic compounds with a CF_3-group (95JHC739, 99JFC(99)177). Often carried out by cyclocondensation with hydroxylamine, semicarbazide, thiosemicarbazide, phenylhydrazine, and urea (Scheme 99).

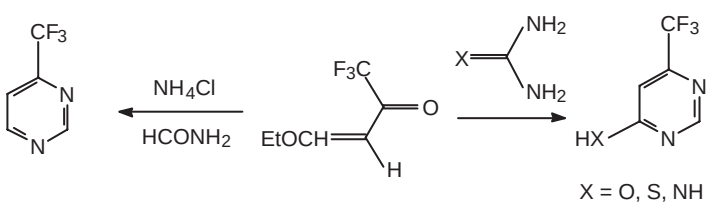
β-Alkoxyvinyl halomethyl ketones, diethylaminomethylene hexafluoromethylacetone [$Et_2NCH=C(COCF_3)_2$] and β-diketones are intermediates in the syntheses of five-, six-, and seven-membered heterocycles (for example, a series of CF_3-substituted pyridines, pyrazoles, and quinolines) (95JHC739). α,β-Unsaturated ketones with a CF_3 group are of interest as reagents in the syntheses of various heterocyclic compounds (99JFC(99)177, 01JFC(107)107, 00SC677, 01JFC(108)51. 00T7267, 00PCTWO6382). These mainly include 1,1,1-trifluoro-4-ethoxy-3-butene-2-one, 3-trifluoroacetyl-3,4-dihydro-2*H*-pyran, and 3-trifluoroacetyl-2,3-dihydrofuran.

Thus, it has been shown (01JFC(107)107, 00SC677, 01JFC(108)51, 00T7267) that 4-ethoxy-1,1,1-trifluoro-3-butene-2-one is a convenient reagent for synthesis of pyrimidines with a CF_3 group (Scheme 100).

4-Ethoxy-1,1,1-trifluoro-3-butene-2-one and 3-trifluoroacetyl-3,4-dihydro-2*H*-pyran react with phenylhydrazine in ethanol, forming the corresponding trifluoromethyl derivatives of pyrazole (01JFC(107)107). Under the same reaction condition treatment these compound with pentafluorophenyl hydrazine or tetrafluorophenyl hydrazine did not give the expected N-fluorinated phenyl pyrazole, it give undehydrated products—5-hydroxy-1-pentafluorophenyl-5-trifluoromethyl-4,5-dihydropyrazole (the molecular structure was identified by X-ray analysis) (01JFC(107)107) (Scheme 101).



Scheme 99



Scheme 100

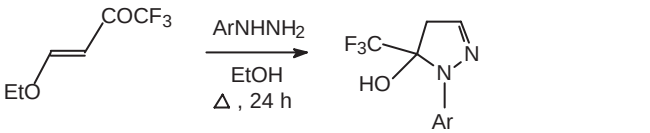
Cyclocondensation of (3 + 2) compounds of type **99** with hydrazine and methylhydrazine leads to pyrazoles (93JHC1159) (Scheme 102).

The interaction of compound **102** with hydroxylamine forms isoxazolines **103** (70JINC1895, 93JHC389, 90ZOR1877, 99JHC837, 91S483), which are dehydrated by P_2O_5 or concentrated sulfuric acid to give isoxazoles **104** (99KGS395, 97JCS(P1)1581) (Scheme 103).

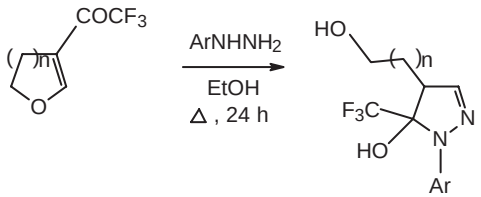
In reactions with N-methylhydroxylamine hydrochloride, the product is a 3-isoxazoline derivative (99JHC837) (Scheme 104).

In essentially neutral solvents (in the presence of sodium acetate), the reaction forms a mixture of oxime and isoxazoline. In basic solvents, isoxazoline derivatives are obtained as the sole products.

Reactions of compound **99** with aldehyde *tert*-butylhydrazones lead to 4-trifluoroacetyl-pyrazoles **105** (87POL2169). Trifluoromethylpyrimidines are

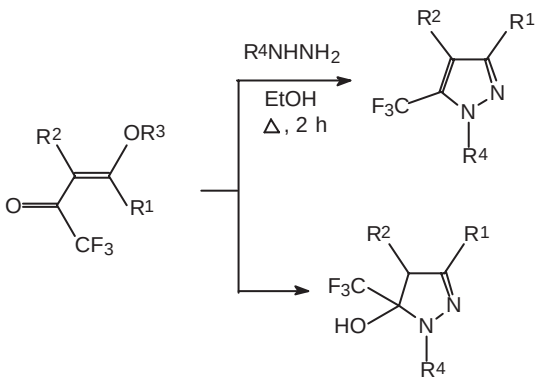


Ar = C_6F_5 (80 %), 4-HC_6F_4 (72 %)



n = 1, Ar = C_6F_5 (71 %); 4-HC_6F_4 (70 %);
n = 2, Ar = C_6F_5 (46 %); 4-HC_6F_4 (55 %)

Scheme 101

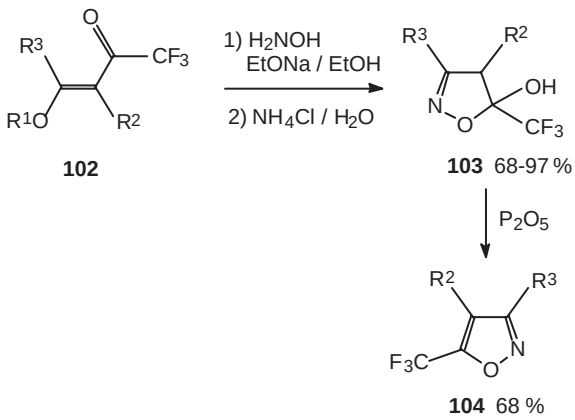


R^1	R^2	R^3	R^4
H	H	Et	H
H	Me	Et	Me
Me	H	Me	Ph

Scheme 102

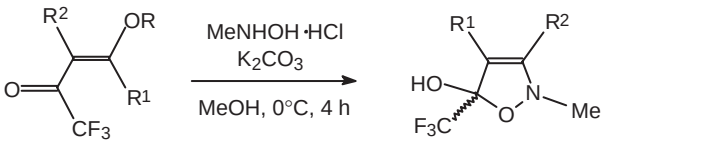
obtained when **99** is allowed to react with formamide in the presence of NH_4Cl, with urea compounds (91CGS502), and with isothiuronium salts (95JHC735) (Scheme 105).

Reactions with aromatic binucleophiles form fused ring heterocycles (00T7267). Thus, when the reaction is performed with 2-aminothiophenol, compound **99** is converted into 2-trifluoroacetyl-4*H*-1,4-benzothiazine (identified by X-ray crystallography) (Scheme 106). In the case of thioethanolamine hydrochloride, the product is 2-trifluoroacetyl-4*H*-1,4-thiazine.



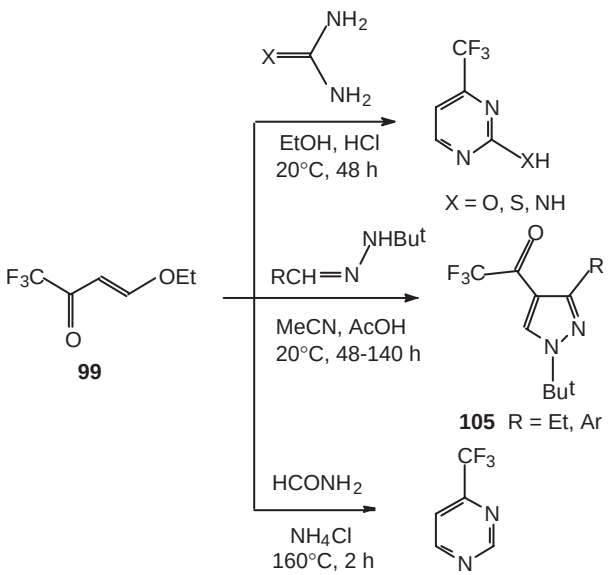
102 **103** 68-97 % **104** 68 %

Scheme 103



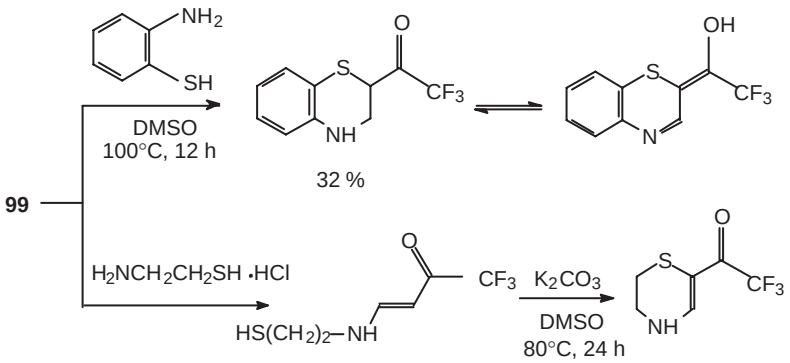
R = Me, R1R2 = —(CH2)4— (85 %)
R = Me, R1 = Ph, R2 = Me (87 %)

Scheme 104



99 **105** R = Et, Ar

Scheme 105



Scheme 106

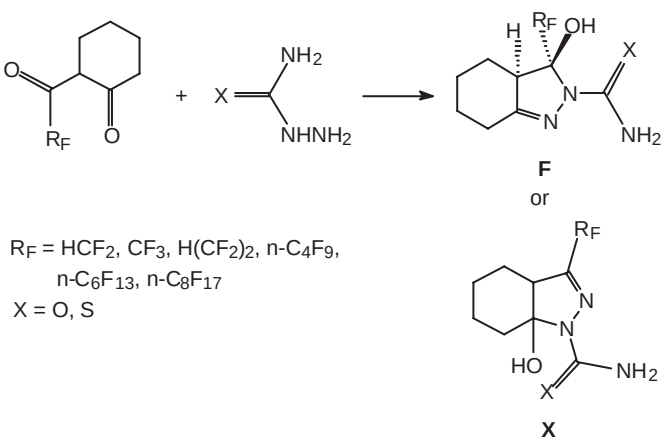
With 2-aminophenol, no reaction takes place even at 120 °C in dimethylsulfoxide.

The reaction with guanidine hydrochloride in *tert*-butanol in the presence of $KOCMe_3$ forms 6-trifluoromethyl-2-amino-4-hydroxypyrimidine (yield 49%) (00PCTWO6382).

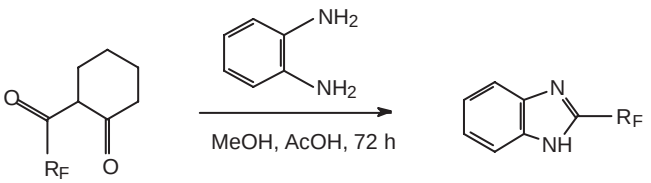
Semicarbazide and its derivatives including thiosemicarbazide react with 2-polyfluoroacyl-cyclohexanones, giving exclusively hydroxy-pyrazolines (99IZV361) (Scheme 107). The choice between the two isomeric possible forms, **F** and **X**, was made based on an X-ray investigation (for the derivative with the *n*-C_6F_{13} substituent).

The reactions of polyfluoroalkylcyclohexanones with *ortho*-phenylene diamine form 2-polyfluoroalkylbenzimidazoles (99IZV562) (Scheme 108).

Compounds **100** and **101** also react with 2-aminothiophenol, forming 3-(2,2,3-2*H*-benzothiazolyl)-2-(trifluoromethyl)tetrahydrofuran-2-ol and 3-(2,2,3-2*H*-benzothiazolyl)-2-(trifluoromethyl)tetrahydro-2*H*-pyran-2-ol, respectively (Scheme 109). The structure of the latter is confirmed by X-ray analysis (00T7267).

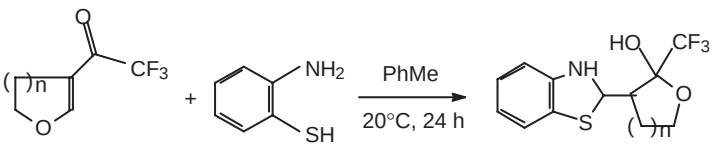


Scheme 107



R_F = CF_3, $H(CF_2)_2$, HCF_2, n-C_6F_{13}

Scheme 108

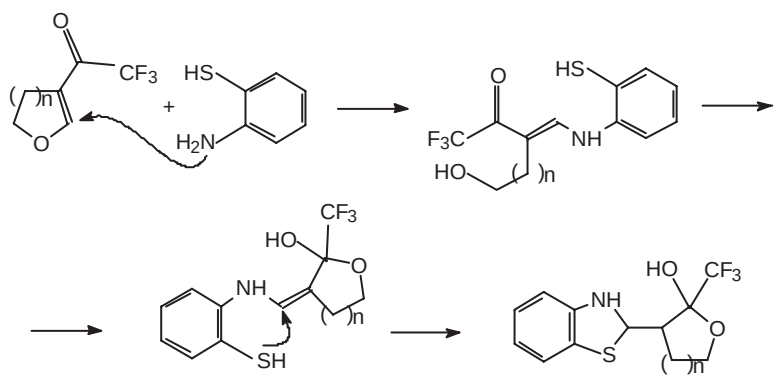


n = 2 (**100**)
n = 3 (**101**)

n = 2 (74 %)
n = 3 (70 %)

Scheme 109

The reaction scheme may be represented as follows (Scheme 110):



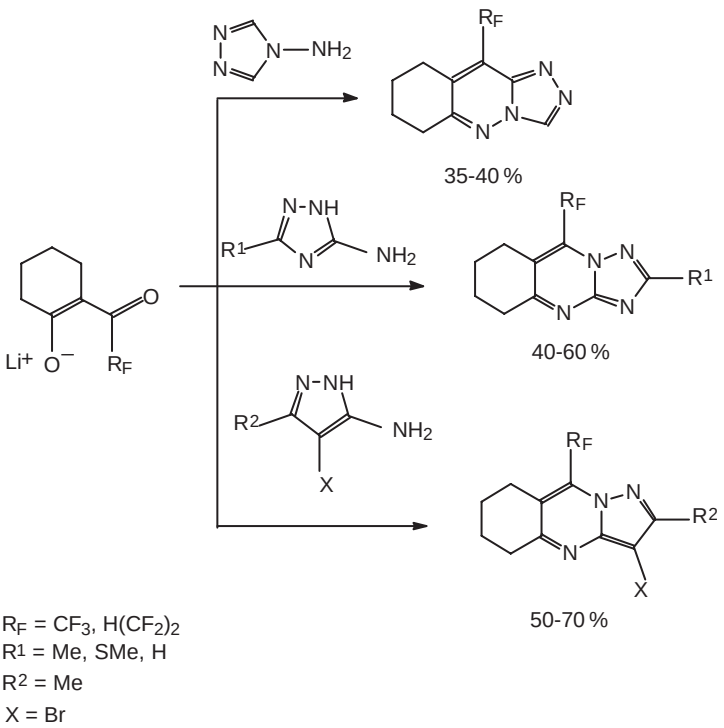
Scheme 110

The reactions between 4-amino-1,2,4-triazoles and 2-polyfluoroacylcycloalkanone lithium salt form polycyclic nitrogen-containing heterocycles with polyfluoroalkyl substituents (99IZV562) (Scheme 111).

Five-membered nitrogen-containing heterocycles may be synthesized from *N*,*N*-diethylaminomethylene-1,1,1,5,5,5-hexafluoro-acetylacetone (93TL7737) (Scheme 112).

N,*N*-Diethylaminomethylene-1,1,1,5,5,5-hexafluoroacetylacetone reacts with ureas to form pyrimidine derivatives (93TL7737) (Scheme 113).

4-Alkyl(aryl)-1,1,1-trifluoro-4-methoxyalk-3-en-2-one reacts with aminoguanidine bicarbonate, giving 6-alkyl(aryl)-2[3-alkyl(aryl)-5-trifluoro-methyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl]-4-trifluoromethylpyrimidine. The latter is converted into



Scheme 111

6-alkyl(aryl)-2[3-alkyl(aryl)-5-trifluoro-methyl-1*H*-pyrazol-1-yl]-4-trifluoromethyl-pyrimidine by reaction with concentrated sulfuric acid in methylene chloride (93TL7737).

Heating compound **101** with diethylamine yields a mixture of two products, one of which is a pyrone derivative (99MC671) (Scheme 114).

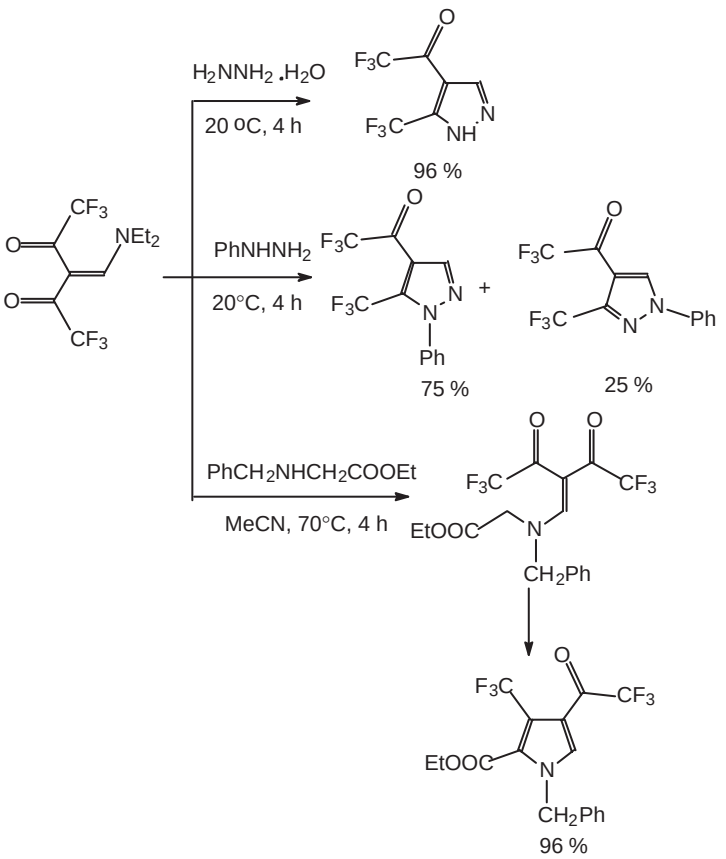
If a compound contains an arylamino group at the multiple bond, heating this compound with $TiCl_4$ leads to six-membered heterocyclic compounds (93TL7737).

β-Ethoxyvinyl trifluoromethyl ketone reacts with cyclohexyl isocyanide, forming 2,5-dihydrofuran derivative **106**, whereas *β*,*β*-diethoxyvinyltrifluoromethylketone **107** under the same conditions isomerizes into ester **108** (77IZV2061) (Scheme 115).

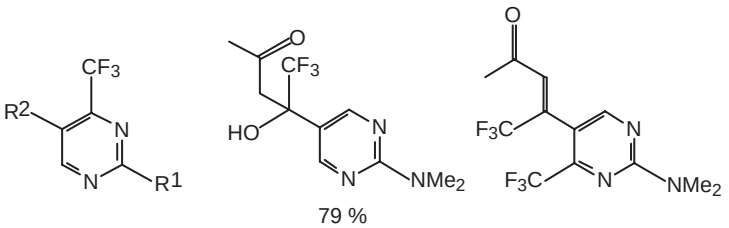
Reactions with thioacetate and 2-thiolethyleneamine give thiazole **109** and thiazepine **110**, respectively (92JFC(58)134) (Scheme 116).

The reactions of butoxy(trifluoromethyl)enone **111** with 1,2-diamines (*ortho*-phenylene diamine and 1,2-ethylenediamine) lead to 1,5-diazepines **112** and **113**; with *ortho*-aminophenol or *ortho*-aminothiophenol, the products are 1,5-oxazepines or 1,5-thiazepines 114, respectively (98KGS634, 96TL2845) (Scheme 117). Good results were obtained by using microwave (W) radiation. At the same time, in boiling xylene, the condensation leads to a mixture of products.

β-Alkoxyvinyl trifluoromethyl ketones and *β*-aryl-*β*-methoxyvinyl trifluoromethyl ketones, prepared from the respective acetophenone dimethyl-acetals by reaction with trifluoroacetic anhydride, undergo cyclocondensation with thiosemicarbazide

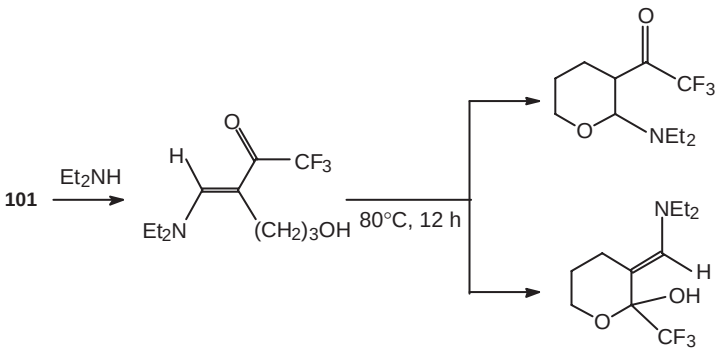


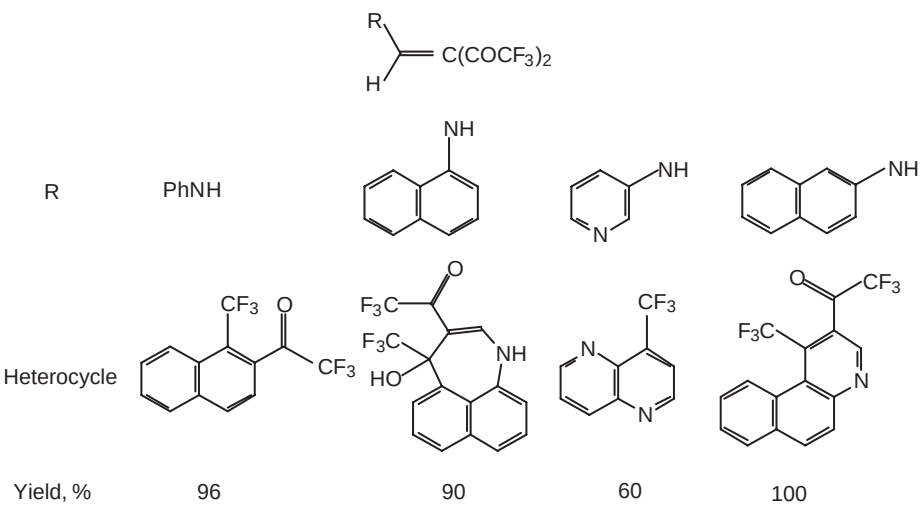
Scheme 112



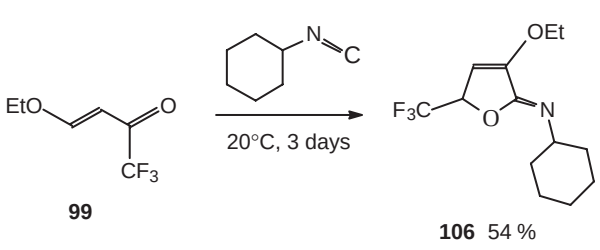
R^1	R^2	Yield, %
NMe_2	$COCF_3$	85
NMe_2	COOH	
NMe_2	COOMe	85
NMe_2	$COCF_3$	
OMe	$COCF_3$	65

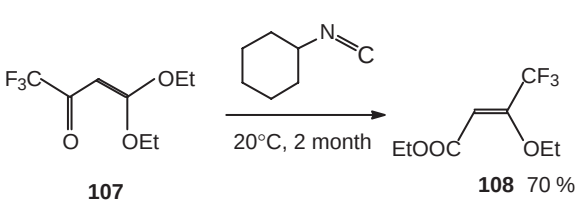
Scheme 113



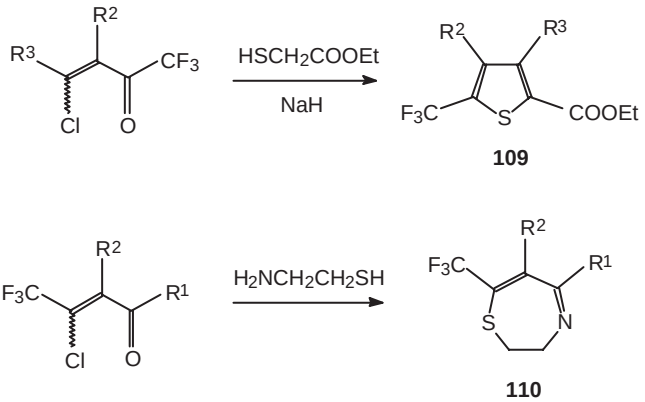


Scheme 114

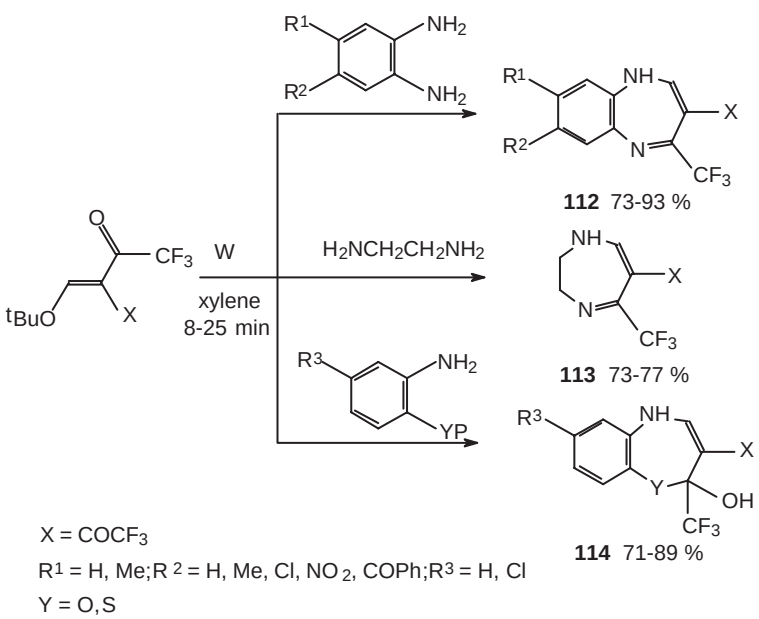




Scheme 115



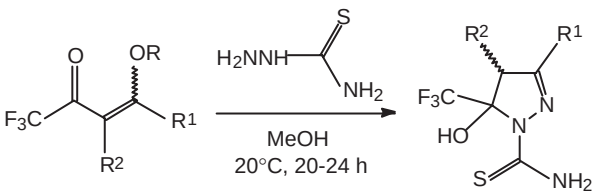
Scheme 116



Scheme 117

and semicarbazide, giving new 5-(1-thiosemicarba-zido)-2-pyrazoline-1-thiocarboxamide and 2-pyrazoline-1-carboxamide, respectively (99IZV361) (Scheme 118). Boiling with sulfuric acid gave 3-aryl(alkyl)-5-trifluoromethyl-1*H*-pyrazoles (98JFC(92)23).

Isoxazolines and isoxazoles were obtained in good yields by the interaction of acetylenic ketones **114** with hydroxylamine; the regioselectivity of the reaction depends on reaction conditions. Thus, when treated with hydroxylamine in alkaline



57-76 %

R	Et	Me	Me	Me	Me	Me	Me
R^1	H	Me	H	Ph	4-MeC_6H_4	4-BrC_6H_4	4-$NO_2C_6H_4$
R^2	H	H	Me	H	H	H	H

Scheme 118

media, ketone **114** is converted into isoxazoline **115**, whose dehydration on heating in benzene gives the corresponding isoxazole **116** (99KGS395) (Scheme 119). In acid solvents, the initial product is an oxime, whose cyclization on boiling in benzene leads to an isomer of isoxazole **116**. It seems that the possibility of aromatization has a critical effect on the reaction route. If aromatization is impossible, oxime formation seems to be preferable.

β-Ethoxy(phenoxy)substituted enones **117** are effective heterodienes; in the reverse Diels–Alder reaction, they react with vinyl ethers, giving 3,4-dihydro-2*H*-pyranes **118**, while with dihydrofuran they give derivative **119** (89S215) (Scheme 120).

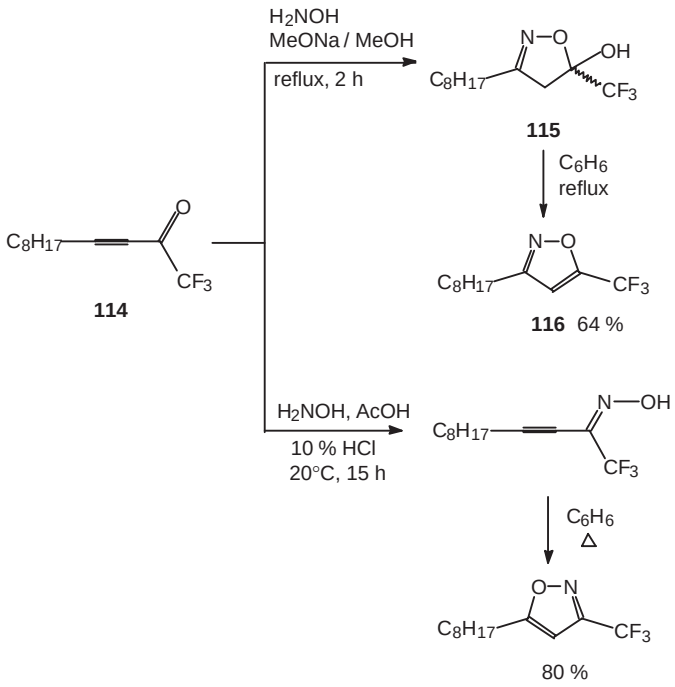
The interaction of *β*-alkoxy enones **120** with enaminonitriles leads to pyridines with CF_3 groups **121** (95JHC543) (Scheme 121).

The reaction of 2,2-diaminohexafluoropropane with an equimolar amount of glyoxal forms *cis*-2,4,6,8-tetraazabicyclo[3.3.0]-octane **122**; with an excess of glyoxal, imidazolidine **123** is formed (87JOC1113) (Scheme 122).

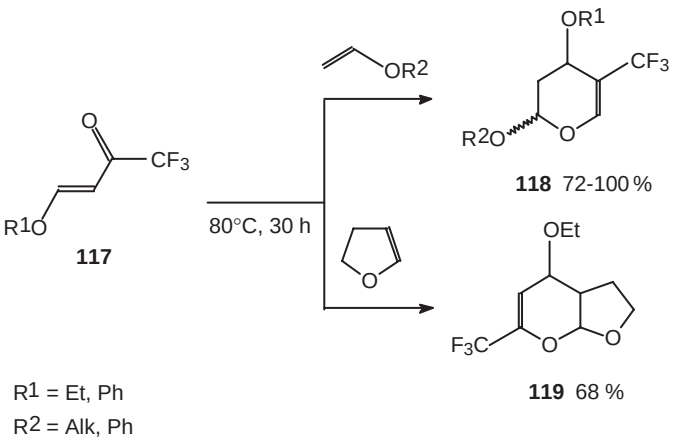
α,*β*-Dibromoketones **124** react with hydrazines in the presence of triethylamine in methanol, forming fluorine-containing pyrazoles **125** (96ZOR320, 94IZV282, 96RusP2054416, 96IZV3026) (Scheme 123).

Khomutov et al. developed effective universal methods for the syntheses of 3-fluoroalkyl-2-aziridinylketones from fluorine-containing *α*,*β*-enones (94IZV282) (Scheme 124).

The reaction of *α*-bromo-*α*,*β*-enones with ammonia or amines proved to be a more universal synthetic method, permitting a wide variation of substituents at the nitrogen atom of the aziridine ring (94IZV282).



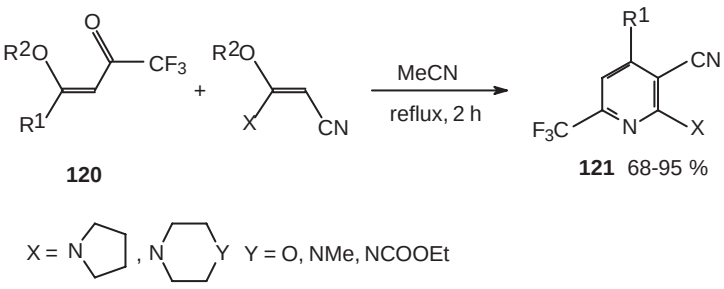
Scheme 119



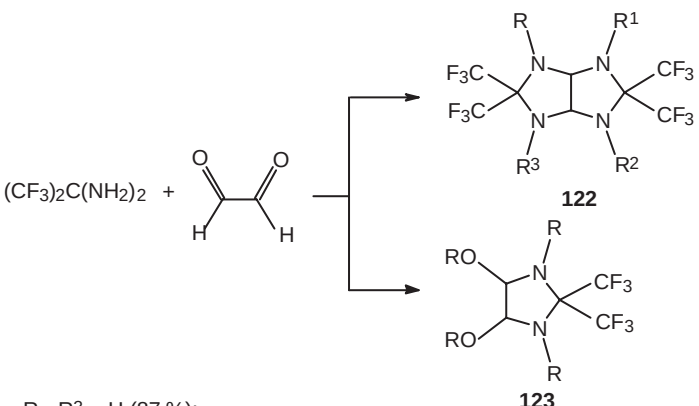
Scheme 120

V. The Synthesis of Oxygen-Containing Heterocycles by Intramolecular Cyclizations in Antimony Pentafluoride

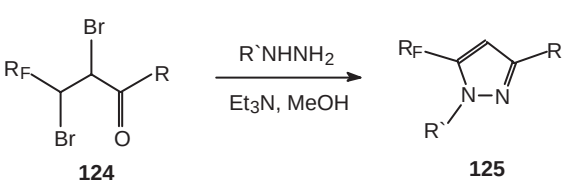
In the series of unsaturated perfluorinated compounds, the C–F bond is extremely stable. At the same time, German et al. found that the CF_3 group of the



Scheme 121

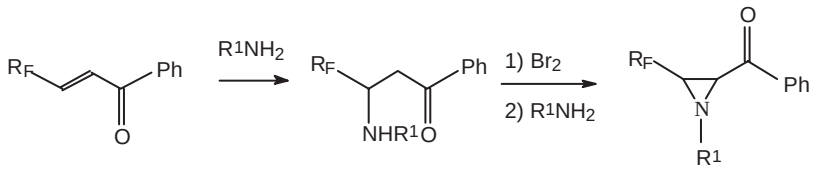


Scheme 122



Scheme 123

unsaturated fluorocarbon chain of perfluoroaliphatic compounds is involved in the formation of new chemical bonds (83IZV2765). They showed that if the molecule contains fragments capable of generating secondary carbenium ions and if the reaction is catalyzed by a powerful electrophilic acid such as SbF_5, the CF_3 group in the skeleton of a saturated perfluoroaliphatic compound can act as a functional



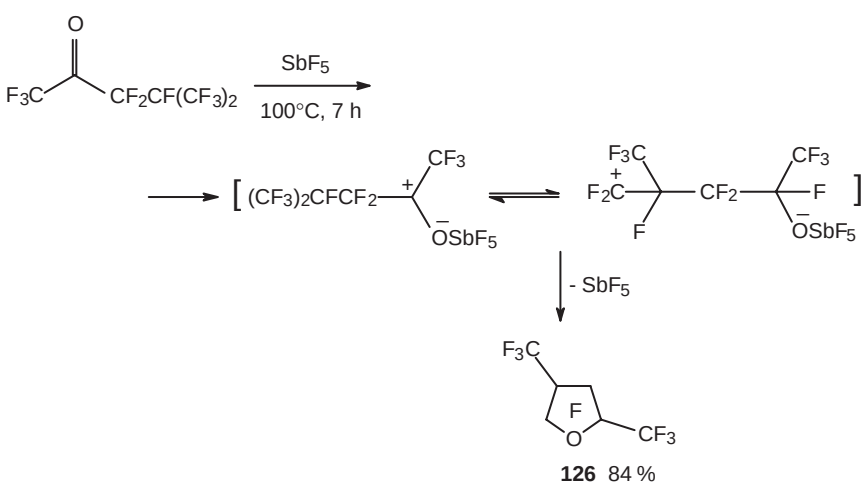
R_F = CF_3, C_6F_{13}, C_8F_{17}, $H(CF_2)_4$, $H(CF_2)_6$

R^1 = n-C_6H_{13}, $(CH_2)_2OH$, C_4H_9, H, Me

Scheme 124

group that can be involved in electrophilic perfluoroalkylation reactions. This peculiarity was employed in the design of methods for the syntheses of perfluorinated oxygen-containing heterocyclic compounds from ketones, β-diketones, and olefin α-oxides. These reactions involve the terminal CF_3 group and the oxygen atom of the carbonyl group at the opposite end of the molecule when the ring-forming chain contains five carbon atoms (91JFC(54)77). Thus, on heating perfluoro-4-methylpentan-2-one in SbF_5, one obtains perfluoro-2,4-dimethyltetrahydrofuran **126** in a high yield (Scheme 125).

The proposed reaction scheme involves coordination of SbF_5 (or perfluorobenzyl cation) at the carbonyl oxygen and isomerization of the initially generated secondary carbenium ion into the primary ion as a result of fluoride migration with subsequent reaction of the carbocationic center with the nucleophilic fragment of the molecule. The during force of the isomerization is presumably a transition from the secondary carbocation, destabilized by two electron-accepting fluoroalkyl groups, to the more stable primary carbenium ion due to the interaction of the vacant p orbital of the carbon atom with lone electron pairs of the geminal fluorine atoms.

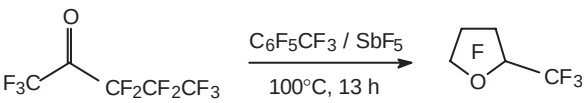


Scheme 125

The nature of the catalyst also plays an important role in these processes. Thus, cyclization of perfluoropentan-2-one in SbF_5 leads to perfluoro-2-methyloxolane **127** with a yield of 2–3%, whereas using a SbF_5–$C_6F_5CF_3$ system increases the yield of the target product to 76% (Scheme 126). Note that the reaction does not occur when the structure of the starting ketone precludes formation of an oxolane ring. Thus, heating perfluoro-2-methylpentan-3-one, perfluoro-2,6,6-trimethylheptan-3-one, and perfluorooctan-2-one in SbF_5 (150–170 °C, 20–30 h) did not end with the formation of a heterocycle.

Nevertheless, in the series of saturated perfluorinated oxygen-containing compounds, cyclizations of this kind induced by strong Lewis acids, such as carbocations or SbF_5, are general reactions. Electrophilic cyclizations of perfluoroketones possibly form either perfluorooxetanes or perfluorooxolanes. In fact, oxolanes are the sole products of this reaction. It was concluded (91JFC(54)77) that electrophilic cyclizations of saturated perfluoroaliphatic ketones under these conditions involve the CF_3 group in only those instances that lead to formation of five-membered rings.

The tendency toward formation of five-membered rings is especially conspicuous in the case of intramolecular electrophilic cyclizations of perfluoro-α-diketones in the presence of SbF_5. Thus, when heated in SbF_5, perfluorinated α-diketones $R_FC(O)C(O)CF_3$ give substituted perfluorooxolan-3-ones or 2-trifluoromethylacetylperfluorooxolane ($R_F = C_3F_7$) (Scheme 127). The structures of the starting α-diketones suggests the possibility of forming rings with different numbers of atoms (four-, five-, or six-membered). However, there is a clear-cut tendency toward formation of a five-membered ring with the carbonyl oxygen atom and a group with a required number of linear carbon atoms involving a terminal CF_3 group. Depending on the structure of the perfluoroalkyl radical, the carbonyl group not



127 76 %

Scheme 126

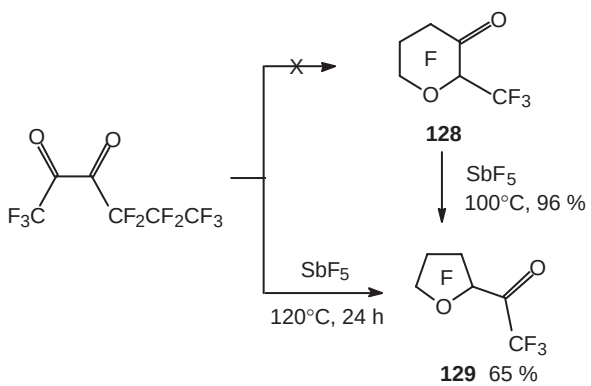
R	R`	Condition	Yield, (%)
C_2F_5	F_2	150°C, 8 h	83
$CF(CF_3)_2$	FCF_3	70°C, 6 h	81
$C(CF_3)_3$	$(CF_3)_2$	100°C, 9 h	80

Scheme 127

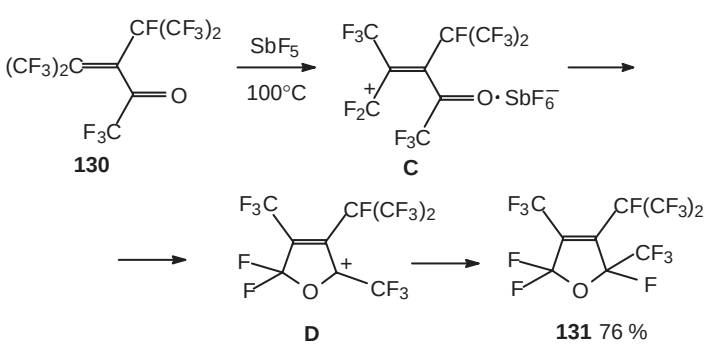
involved in the cyclization enters the ring (oxolanes) or stays outside (acyloxolanes). If this rule is violated, no cyclization takes place. For example, under comparable conditions (150 °C, 16 h), perfluoroocta-2,3-dione fails to undergo cyclization, whereas under more stringent conditions, pronounced decomposition takes place.

Isomerization of perfluoro-2-methyloxan-3-one **128** (the hypothetical product of cyclization of perfluorohexa-2,3-dione) into perfluoro-2-acyloxolane **129** is a further illustration of the high thermodynamic stability of oxolanes (Scheme 128).

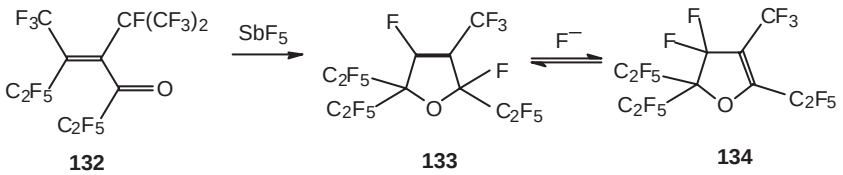
If a compound contains a carbonyl group at a double bond, the reaction with SbF_5 forms a five-membered heterocycle. Thus, heating perfluoro-3-isopropyl-4-methylbut-3-en-2-one **130** (according to ^{19}F NMR data, the conformer ratio is 1:6 at −20 °C) in SbF_5 at 100 °C is accompanied by electrophilic cyclization forming perfluoro-3-isopropyl-2,4-dimethyl-2,5-dihydrofuran **131** (91JFC(54)77, 90IZV2183) (Scheme 129). An essential condition for this reaction is the presence of a trifluoromethyl group in the β-position with respect to the carbonyl group of the vinylketone. The reaction starts with fluoride anion elimination, and the generated **C** cation attacks the carbonyl oxygen, forming a cyclic cation **D**, captured by the



Scheme 128



Scheme 129

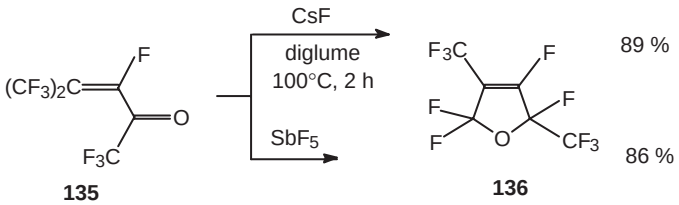


132 **133** **134**

Scheme 130

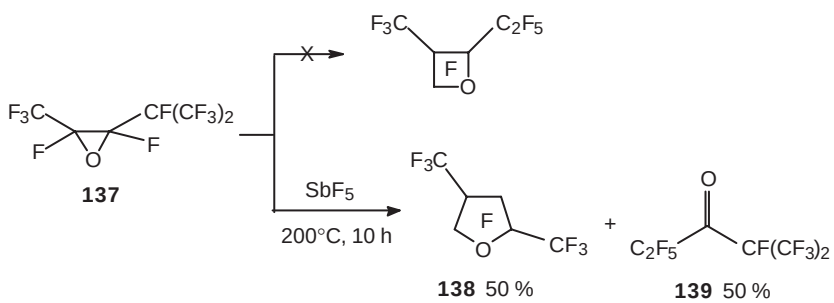
fluoride ion to give compound **131**. Likewise, heating perfluoro-4,6-dimethylhept-4-en-3-one **132** in SbF_5 yields perfluoro-2,2,4-trimethyl-5-ethyl-2,5-dihydrofuran **133**, which is subsequently transformed into thermodynamically more stable perfluoro-2-ethyl-3,5,5-trimethyl-4,5-dihydrofuran **134** (Scheme 130).

Under the action of cesium fluoride, perfluoro-4-methylpent-3-en-2-one, which does not form stable enolates, cyclizes into perfluoro-2,4-dimethyl-2,5-dihydrofuran **136**. Analogously, when treated with SbF_5, **136** cyclizes into 2,5-dihydrofuran (83IZV2765) (Scheme 131). The opening of the epoxide ring under the action of SbF_5 and HF–SbF_5 leads to perfluorinated tertiary alcohols or perfluoroketones, depending on the structure of α-oxides and the electrophile used. Therefore, α-oxides can be converted into the corresponding perfluorinated oxolane **137** (90IZV2183, 91IZV2611). For example, heating perfluoro-2-methylpent-3-ene oxide in SbF_5 affords a (1:1) mixture of perfluoro-2,4-dimethyloxolane **138** and perfluoroethylisopropylketone **139** (Scheme 132).



135 **136**

Scheme 131



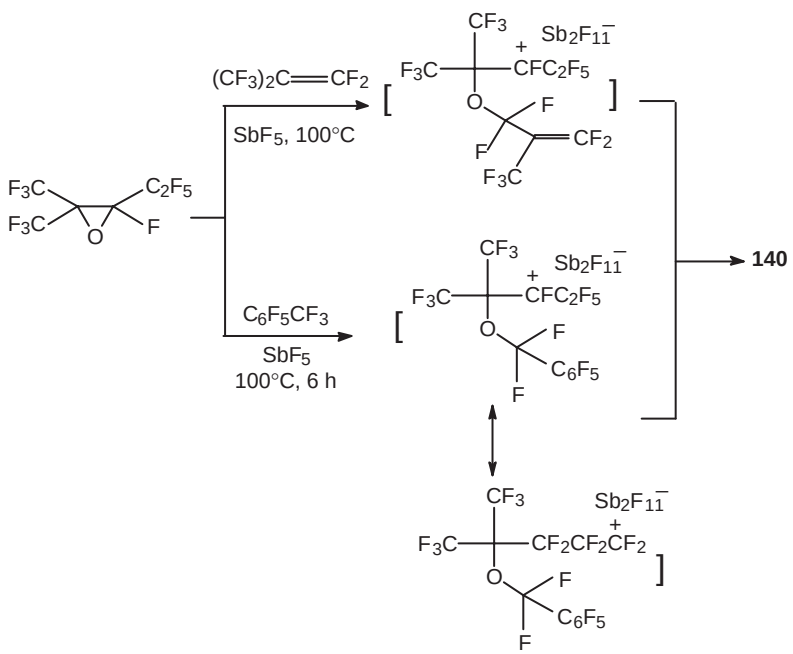
137 **138** 50 % **139** 50 %

Scheme 132

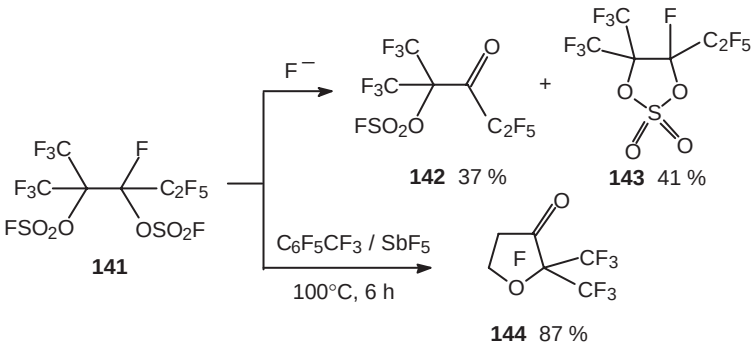
Isomerization of α-oxides can give either an oxetane or an oxolane. It appears, however, that the reaction follows the route leading to substituted perfluoro-oxolanes. Other perfluoroepoxides also undergo this reaction. Thus, the reaction of perfluoro-2-methyl-2-pentene oxide with octafluoroisobutylene in the presence of SbF_5 gives perfluoro-2,2-dimethyloxolane **140** (yield 15%) (Scheme 133). A similar result was obtained when this oxide was heated with a catalytic amount of octafluorotoluene in the presence of SbF_5 (yield 85%). In the absence of octafluorotoluene or octafluoroisobutylene oxide, even heating to 300 °C did not give compound **140**.

Other oxygen-containing derivatives can also undergo this reaction. For example, vicinal bis(fluorosulfato)perfluoroalkanes **141** undergo partial scission under the action of the fluoride ion (from SbF_5), giving α-fluorosulfatoperfluoroketone **142** and isomeric cyclic perfluoroalkene sulfate **143** as major reaction products (90IZV2048, 90IZV2057) (Scheme 134). Prolonged heating of the compound with SbF_5 leads to α-diketones (90IZV2063). At the same time, in the presence of the perfluorobenzyl cation, the product is the corresponding oxolane **144**.

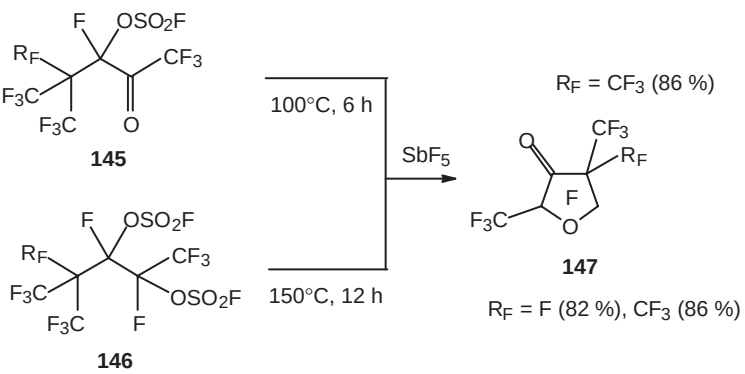
It has been shown (90IZV2063) that severad bis(fluorosulfato)perfluoro-alkanes **145** and ketofluorosulfatoperfluoroalkanes **146** heated in SbF_5 give the corresponding perfluorooxolanones **147** with high yields (Scheme 135). Cyclization occurs by cleavage of the C–F bond at the end of the saturated fluorocarbon chain. Burger et al. (83JFC(27)327) showed that the reaction of SbF_5 with perfluorotrimethylamine



Scheme 133

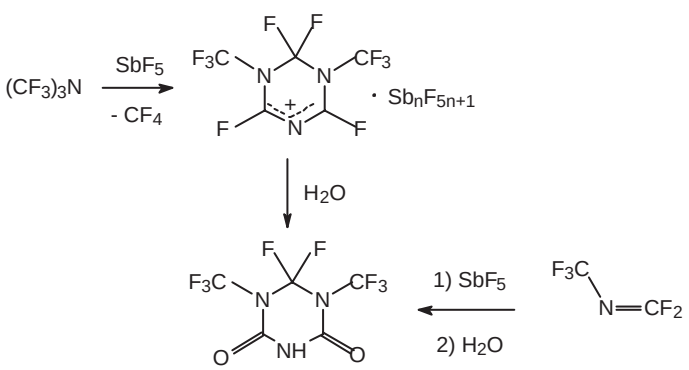


Scheme 134

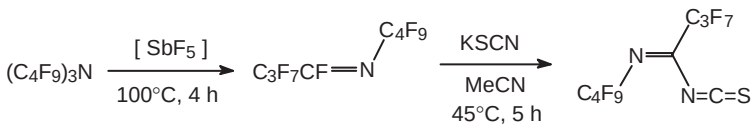


Scheme 135

forms tetrafluoromethane and a salt of fluorinated s-triazine, whose hydrolysis yields 6,6-difluoro-1,5-bis(trifluoromethyl)-[1,3,5]triazine-2,4-dione (Scheme 136). The same compound is prepared by electrophilic trimerization of perfluoro-2-azapropene induced by SbF_5 and a subsequent reaction with water (83IZV476).



Scheme 136



Scheme 137

The first reaction occurs by dealkylation, which forms perfluoro-2-azapropene, subsequently trimerized by SbF_5.

In linear and cyclic perfluorotrialkylamines, SbF_5 promotes splitting at the C–N bond, which forms the corresponding perfluoroazaalkenes (Scheme 137). Because the fluorine atom at the C=N bond is extremely labile, the latter are effective intermediates for the syntheses of various derivatives, leading to various heterocyclic compounds in reactions with binucleophilic agents. Another approach uses derivatives, in particular, those containing N=C=S groups, which are readily obtained by reaction of sodium thiocyanate with this compound. Several examples of using heterocyclic compounds are given in Chapter 3. Thus, new intramolecular cyclization reactions of perfluorinated mono- and dicarbonyl compounds induced by strong electrophiles have demonstrated the possibility of processes involving nonactivated CF_3 groups in unsaturated fluoroaliphatic chains. These reactions have no analogs in fluoroorganic chemistry. Development of this approach will hopefully lead to new data on the synthesis of heterocyclic compounds and to nontrivial synthetic procedures.

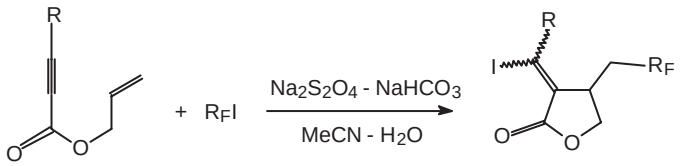
VI. New Strategy of Heterocyclic Design

Free-radical reactions have begun to find increasingly wide application in synthetic chemistry. Because of their high stereoselectivity, some of them are very appealing. At the same time, many such processes have serious limitations since they use iodine-containing systems as substrates. Nevertheless, radical cyclization has become a known technique of both cyclic and heterocyclic system design.

For most reactions involving radical intermediates, it is required that the radical precursor and the carbon site of radical cyclization be present in the same substrate. Using a radical generated separately, however, seems to be more efficient. In its reaction with a substrate, this radical gives a new radical center, which is responsible for further cyclization. This is the essence of the new strategy of heterocyclic design.

Based on this approach, the synthesis of fluorine-containing heterocyclic compounds can use one of two possibilities. The first is the introduction of a perfluoroalkyl group together with a radical site into the substrate. The second is the use of a substrate with the above radical and generation of a new radical by addition at an unsaturated group. Some examples of such reactions are given below.

In one example, accessible perfluoroalkyl iodides were employed as sources of perfluoroalkyl radicals. Irradiation, thermal treatment, or the use of a catalyst lead



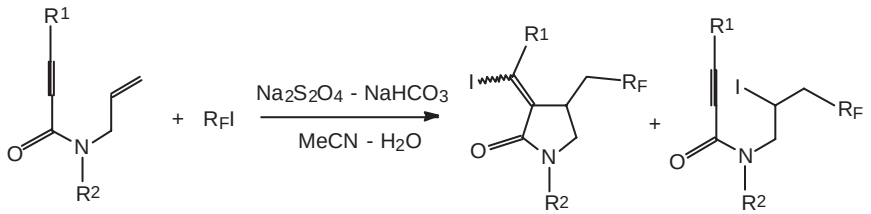
148

R	R_F	Yield,%	*E*:*Z*
H	CF_3	44	32:68
H	$Cl(CF_2)_2$	47	60:40
H	$Cl(CF_2)_4$	50	52:48
Me	CF_3	80	95:5
Me	$Cl(CF_2)_2$	83	>97:3
Me	$Cl(CF_2)_4$	82	>97:3
n-C_8H_{17}	$Cl(CF_2)_2$	92	>97:3

Scheme 138

to homolytic splitting of the C–I bond. If a molecule contains multiple bonds, a new radical center is generated by the action of the perfluoroalkyl radical. If there are two multiple bonds, R_F and I fragments add at the olefinic bond, and a five-membered heterocycle **148** is formed (this process is highly regioselective) (95T2639) (Scheme 138). In this case, the strategy is generation of a radical center with initial C–I bond cleavage and further cyclization involving this center and the multiple bond as a donor. For example, polyfluoroalkylated 3-iodoalkyliden-2-(3*H*)-dihydrofuranone is obtained by generation of a perfluoroalkyl radical initiated by reaction of R_FI with $Na_2S_2O_4$ with subsequent formation of a five-membered heterocycle. This reaction is highly regioselective (95T2639). Analogously, perfluoroalkylation of N-allyl-2-propynamide and N-allyl-2-butynamide under the action of perfluoroalkyl iodides in the presence of $Na_2S_2O_4$–$NaHCO_3$ forms perfluoroalkyl derivatives of 3-alkylidene-2(3*H*)-pyrrolidone **149** and the product of addition at a double bond **150** (95T2639, 94TL613) (Scheme 139). Cyclization by the intermediate radical is effectively used for the formation of cyclic systems (91CRV1237).

Due to the presence of a C–I bond in the substrate molecule, cyclization can occur by generation of a radical center by C–I bond cleavage. Thus, the trifluoroacetimidoyl radical, generated photochemically or thermochemically from iodine and tellurium derivatives, reacts with a multiple bond by the action of Bu_3SnH–AIBN, forming indoles **151** or quinolines **152** (93TL7933) (Scheme 141). If the CF_3 group lies at a multiple bond (compound **153**), heterocycle-forming cyclization also takes place (Scheme 142).



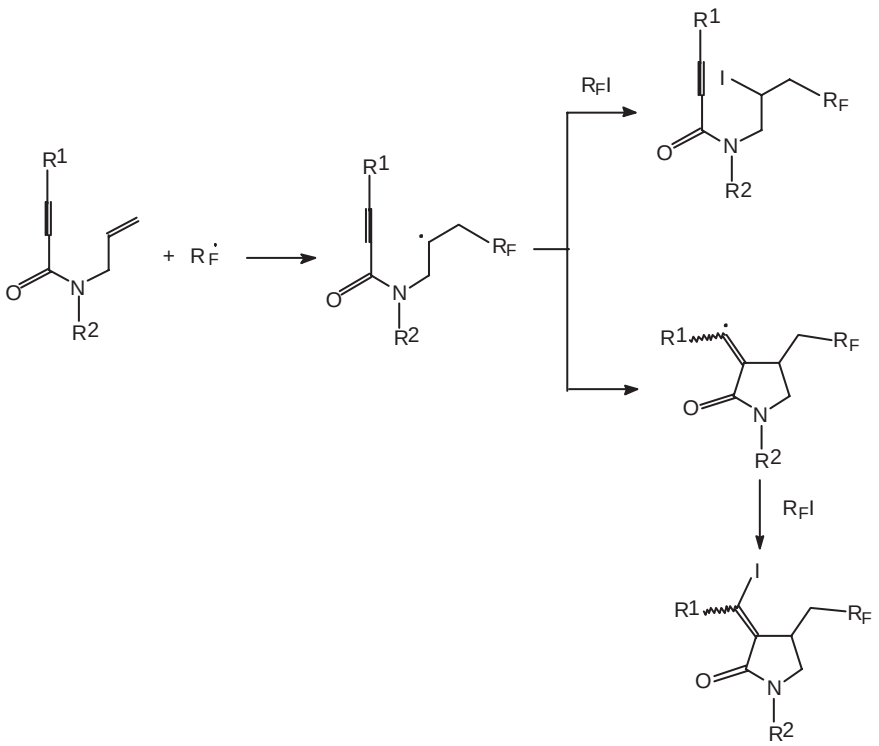
R^1	R^2	R_F	Yield, %		*E:Z*
			149	**150**	
Me	Me	$Cl(CF_2)_2$	53	19	>97:3
Me	Bn	$Cl(CF_2)_2$	50	35	>97:3
Me	Bn	$Cl(CF_2)_4$	49	29	>97:3
Pr^n	Bn	$Cl(CF_2)_2$	41	23	>97:3
Pr^n	Bn	$Cl(CF_2)4$	43	27	>97:3
H	MeCO	$Cl(CF_2)_2$	46	0	52:48
Me	PhCO	$Cl(CF_2)_2$	70	0	>97:3
Me	PhCO	$Cl(CF_2)_4$	60	0	>97:3
Me	OTs	CF_3	72	0	>97:3
CH_3	OTs	$Cl(CF_2)_4$	83	0	>97:3

Scheme 139

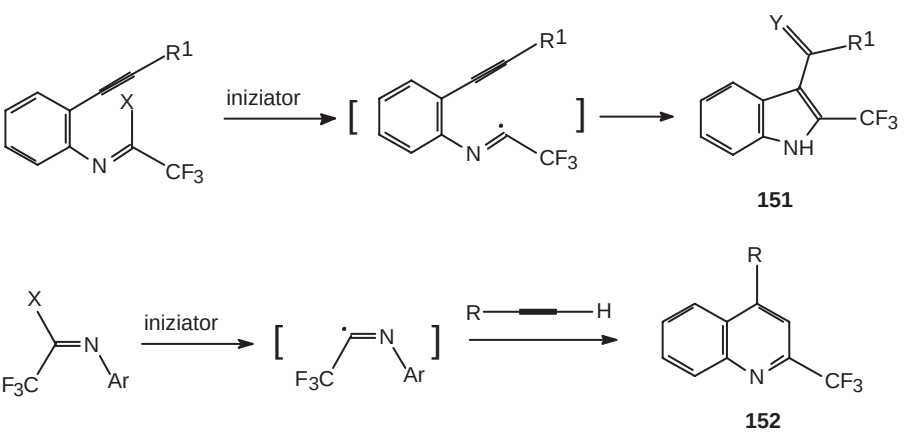
VII. Intramolecular Nucleophilic Cyclizations with Annulated Fluorinated Heterocyclic Rings

Intramolecular cyclizations involving the fluorine atoms of the benzene ring and the multiple bonds of perfluoroolefins as induced by heteronucleophiles, as well as by condensations involving several molecules with suitable functional groups, are key methods for the synthesis of various heterocyclic compounds. While condensation as a method of synthesis of fluorinated heterocycles is well known and well characterized, intramolecular nucleophilic cyclization is a new technique, permitting one to obtain perfluoroalkyl derivatives of heterocyclic compounds. Due to the presence of fluorine atoms in the starting benzene molecules, cyclizations occur by elimination of *ortho*-fluorine atoms (74FCR115).

In view of their high electronegativity, fluorine atoms accumulated in the benzene ring substantially increase the electrophilicity of the carbon atoms. This creates conditions for high mobility of the fluorine atoms of polyfluorinated aromatic compounds in nucleophilic substitution reactions and hence for intramolecular nucleophilic cyclizations by the elimination of the fluorine atom ortho to the



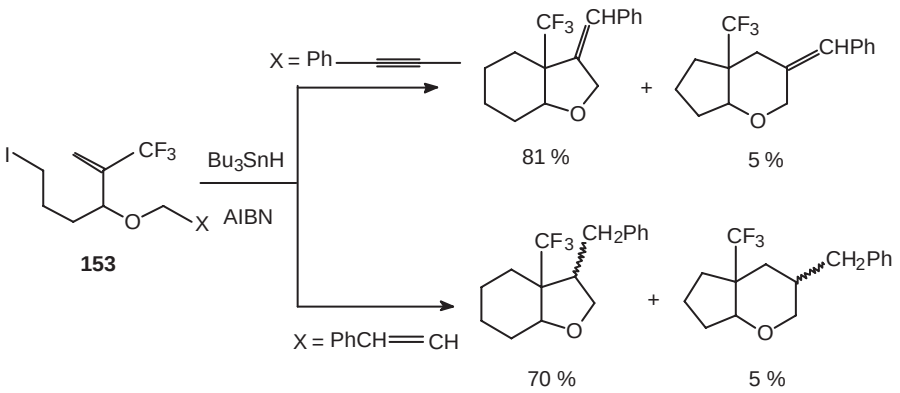
Scheme 140



X = I, TeAr, N ═ NCPh$_3$

Y = H$_2$, O

Scheme 141



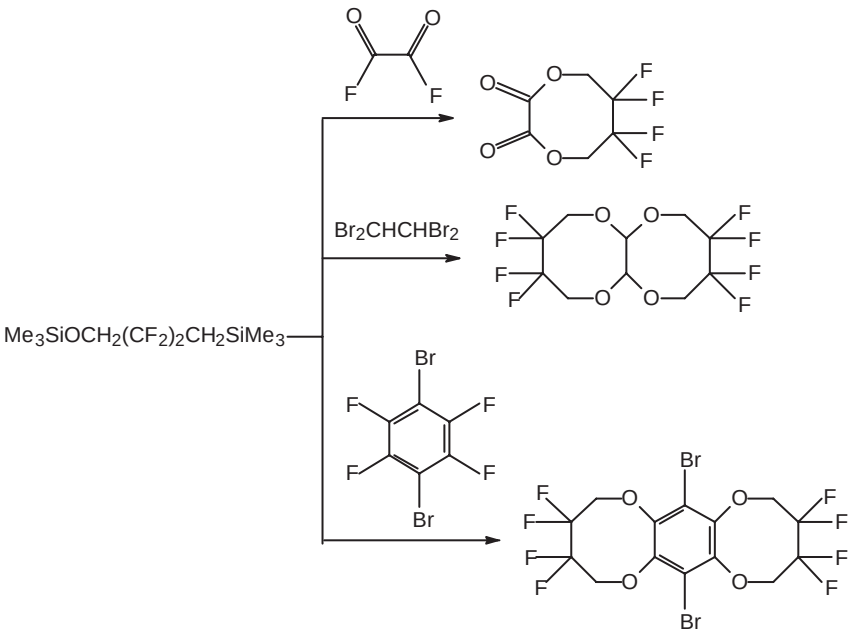
Scheme 142

functional group having a nucleophilic center. There are many examples of these reactions, which formed the basis of one of the most important and general methods for the synthesis of fluorine-containing condensed heterocyclic compounds. In these reactions, fluorinated derivatives of benzene and binucleophilic reagents serve as substrates. Work is still in progress to synthesize heterocyclic compounds by this procedure, especially in connection with drug synthesis. We cite only a few such examples.

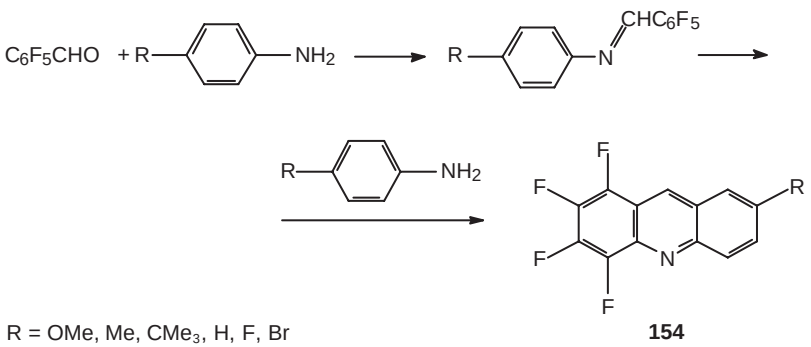
It was reported (94IC415) that the reactions of 2,2,3,3 tetrafluorobutyleneglycol triethylsilyl ether with 1,4-dibromotetrafluorobenzene, tetrabromoethane, and oxalyl fluoride form oxygen-containing heterocycles (Scheme 143). Adamson et al. (92JFC(58)300) showed that 1,2,3,4-tetrafluoroacridines **154** are formed in quantitative yields in reactions of pentafluorobenzaldehyde with substituted anilines at room temperature (Scheme 144). 2,3-Diphenyl-4,5,6,7-tetrafluorobenzofuran is formed in a reaction of hexafluorobenzene with phenyl benzyl ketone in the presence of sodium hydride (79BCJ2657) (Scheme 145). The reaction involves intramolecular nucleophilic cyclization of the generated O-nucleophile due to tautomerization of the intermediate ketone.

The reaction of iodobenzene with pentafluoroaniline in the presence of 3% $PdCl_2$-$(PPh_3)_2$ and 1.2 equivalent of 1,8-diazabicyclo[5.4.0]undec-7-ene in *N*,*N*-dimethylacetamide in the presence of carbonmonoxide forms 2-aryl-4,5,6,7-tetrafluorobenzoxazole (92JOC6351) (Scheme 146). The reaction probably occurs via the intermediate formation of a palladium complex and N-pentafluoro-phenylbenzamide.

Weak nucleophiles, generated from the corresponding derivatives of acetic and hydroxamic acids under the action of bases (KF, K_2CO_3), replace the *ortho*-fluorine atoms of the benzene ring by the intramolecular nucleophilic cyclization mechanism. This yields the corresponding heterocyclic compounds (**155** and **156**) (81BCJ3447, 93ZOR2416) (Scheme 147). It has been shown (81BCJ3447, 93ZOR2416) that 5,8-bis(vinylthio)-6,7-difluoro-2,3-dihydro-1,4-benzoxazine is formed by the reaction of 3,6-bis(vinylthio)-1,2,4,5-tetrafluorobenzene with aminoethanol in dimethylformamide in the presence of NaOH at 50 °C.

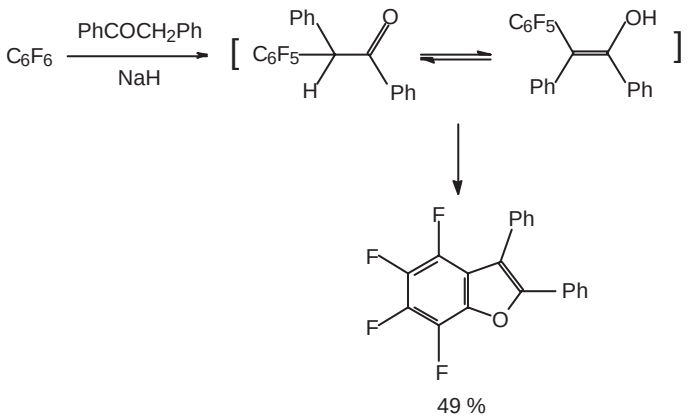


Scheme 143

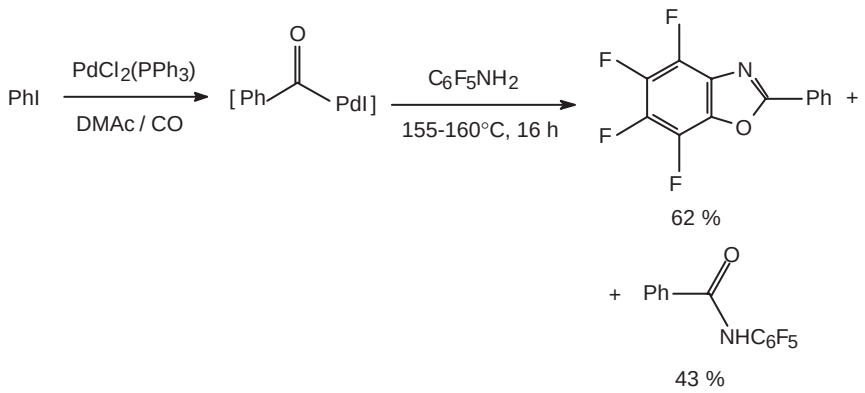


Scheme 144

In 1967, two reactions that proceeded by the intramolecular cyclization mechanism and led to fluorinated benzo[*b*]thiophenes were carried out. The first is based on the reaction of the lithium salt of pentafluorothiophenol and diethyl acetylenedicarboxylic ether (67JCS(C)1225) (Scheme 148). Here the intermediate species is a carbanion. In the second process, the starting compound is a benzylidene rhodanine derivative, giving benzo[*b*]thiophene carboxylic acid **157** in alkaline media. This reaction occurs via the intermediate S-nucleophile (Scheme 149).

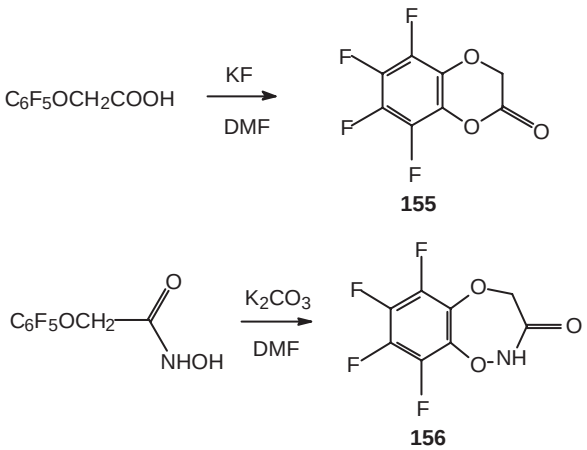


Scheme 145

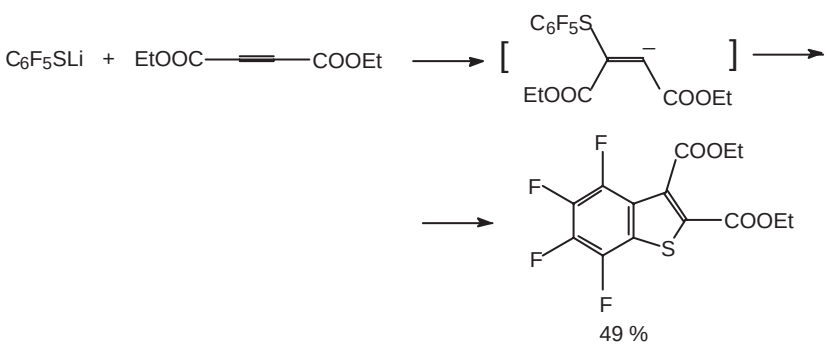


Scheme 146

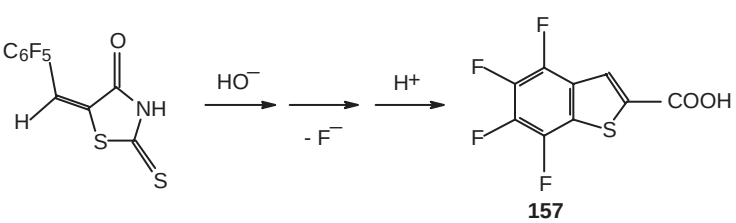
Subsequently, these processes were extended to polyfluoronaphthalene derivatives. Thus, the reaction of lithium 1,3,4,5,6,7,8-heptafluoro-2-naphthalene thiolate with dimethyl acetylenedicarboxylic ester yields isomeric dimethyl hexafluoronaphtho[*b*]thiophenedicarboxylic esters **158** and **159** (in a ratio of 8 : 92) (89JFC(43)393, 90JFC(50)229) (Scheme 150). The fluorinated derivative of 2-naphthoryl thiocyanate, obtained by condensation of 1,3,4,5,6,7,8-heptafluoronapthalene-2-aldehyde with rhodanine, is converted by alkali into a mixture of isomeric methyl hexafluoronaphtho-[*b*]thiophenecarboxylic acids **160** and **161** (in a ratio of 22 : 78) (90JFC(50)229, 91JFC(53)339) (Scheme 151). In a similar process, 1,3,4,5,7,8-hexafluoro-6-isoquinolinethiol and 2,3,5,6,7,8-hexafluoro-4-quinolinethiol gave dimethyl 4,5,6,8,9-pentafluoro-thieno[3,2-*f*]isoquinoline-1,2-dicarboxylic ester and dimethyl 4,5,6,8,9-pentafluorothieno[2,3-*g*]isoquinoline-1,2-dicarboxylic ester, respectively (94JFC(67)143).



Scheme 147

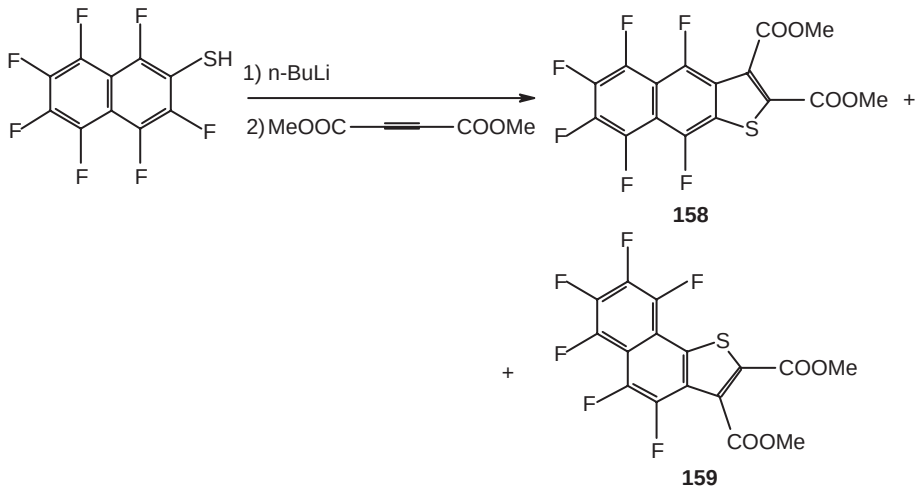


Scheme 148

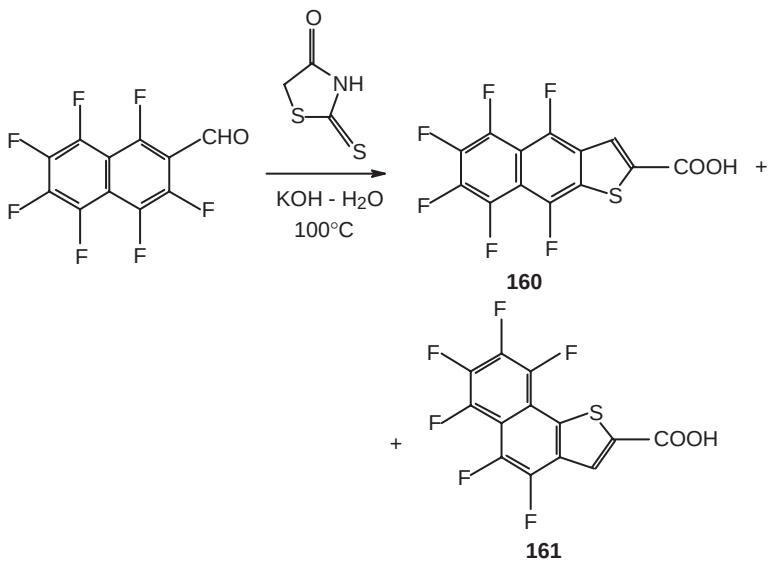


Scheme 149

(Pentafluorobenzyl)benzylketone reacts with sodium hydride in dimethylformamide to form 2-benzyl-4,5,6,7-tetrafluorobenzo[*b*]furan **162** via the O-nucleophile (81JCS(P1)1417) (Scheme 152). The interaction between hexafluorobenzene and vinylthiol in alkalies leads to the formation of tetrathio- derivative **163** (82JFC(20)173) (Scheme 153).



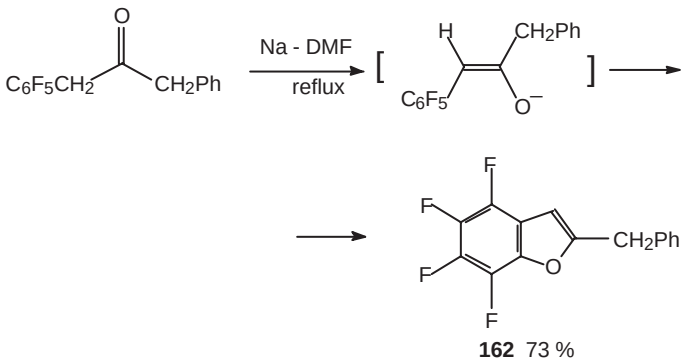
Scheme 150



Scheme 151

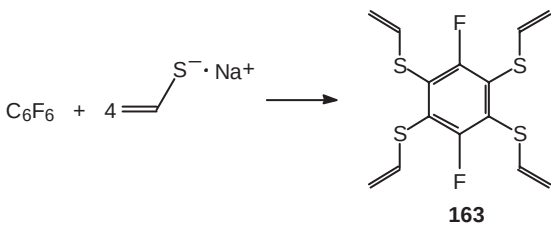
The reagent ratio 1 : 2 leads to a disubstituted product, which reacts with aminoethanol in an alkaline solvent to give 5,8-bis(vinylthio)-6,7-difluoro-2,3-dihydro-1,4-benzoxazine **164** along with other products (92ZOR1463) (Scheme 154). The formation of compound **165** is possibly explained by a Smiles type rearrangement.

When heated at 100 °C in dimethylformamide, N-(2,3,4,5,6-pentafluorobenzylidene)-2′-hydroxyaniline is converted into 1,2,3,4-tetrafluorodibenz-[*b*,*f*][1,4]-oxazepine **166**, formed in a quantitative yield (87JFC(36)93) (Scheme 155).



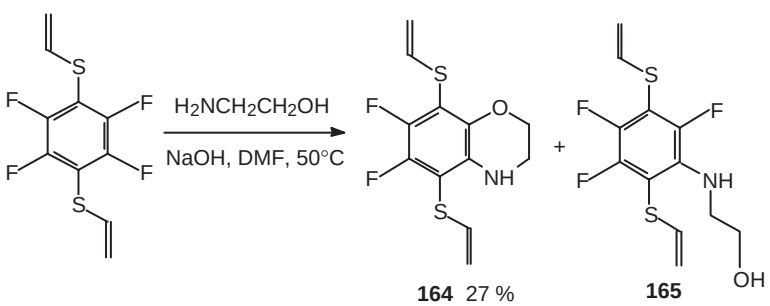
162 73 %

Scheme 152



163

Scheme 153

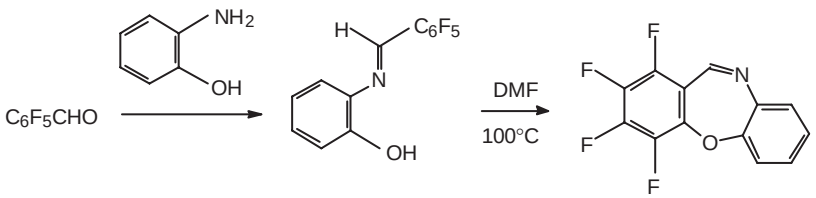


164 27 % **165**

Scheme 154

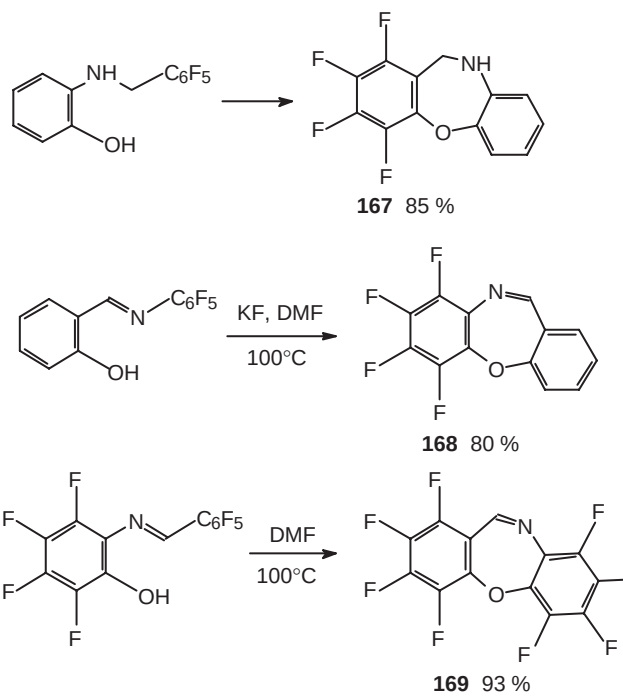
A similar procedure gave 1,2,3,4-tetrafluoro-10,11-dihydrobenz[*b*,*f*][1,4]-oxazepine **168**, and octafluorodibenzoxazepine **169** (Scheme 156).

Although the nitrogen of the N=S=N group has low nucleophilicity, an intramolecular cyclization can occur in the presence of a catalyst (fluoride ion). Thus, heating of 1-pentafluorophenyl-3-trimethylsilyl-1,3-diaza-2-thiaallene **170** in acetonitrile in the presence of cesium fluoride leads to 4,5,6,7-tetrafluoro-2,1,3-thiadiazole **171** (90JFC(50)359) (Scheme 157). It is assumed that **171** is formed via the intermediate pentacoordinated silicon anion, which is further transformed into the N-nucleophile with elimination of trimethylfluorosilane.



90 % **166** 99 %

Scheme 155



167 85 %

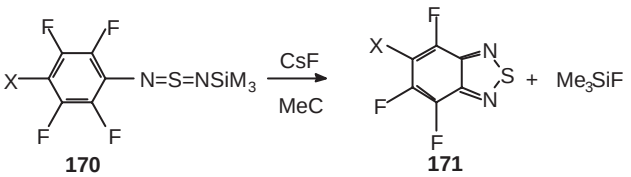
168 80 %

169 93 %

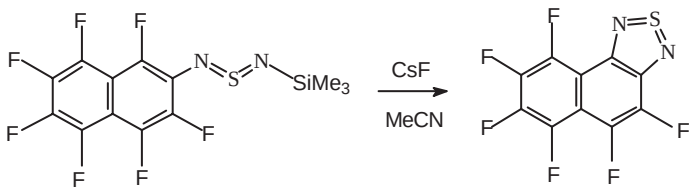
Scheme 156

The regioselective effect of the fluoride ion on intramolecular nucleophilic cyclization has also been demonstrated for heptafluoronaphthylsulfur diimide (94HAC561, 92POL1137). The reaction of the latter leads to a mixture of 4,5,6,7,8,9-hexafluoronaphtho[1,2-*c*][1,2,5]thiadiazole, whose structure was established from X-ray diffraction, and 4,5,6,7,8,9-hexafluoronaphtho-[2,3-*c*][1,2,5]thiadiazole (in the ratio 94 : 6) (94HAC561) (Scheme 158).

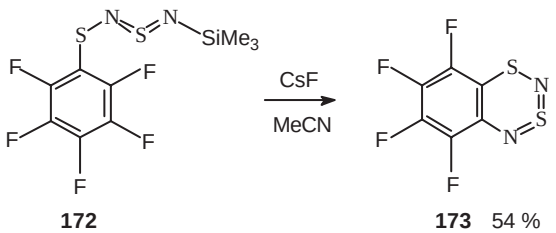
A similar reaction of 1-pentafluorophenyl-4-trimethylsilyl-2,4-diaza-1,3-dithia-2,3-butadiene **172** afforded 5,6,7,8-tetrafluoro-1,3,2,4-benzo-dithiadiazole **173**



Scheme 157



Scheme 158

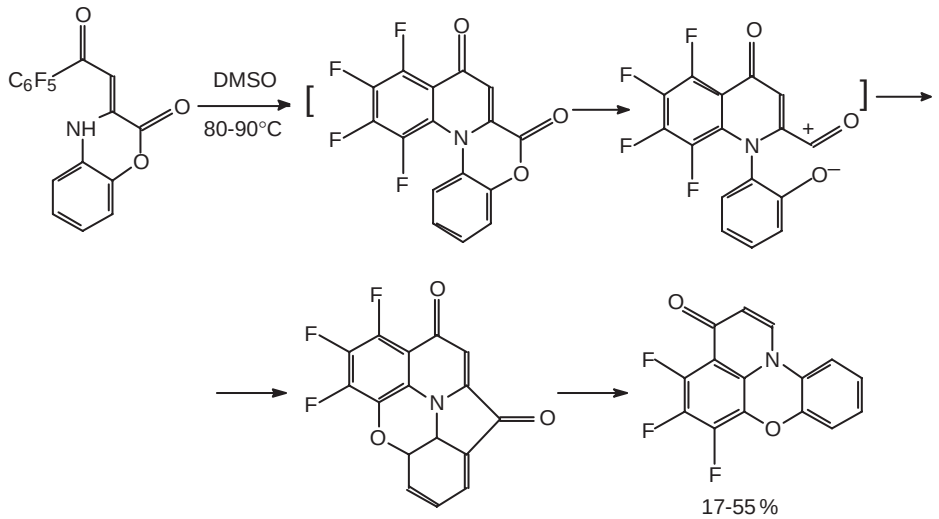


Scheme 159

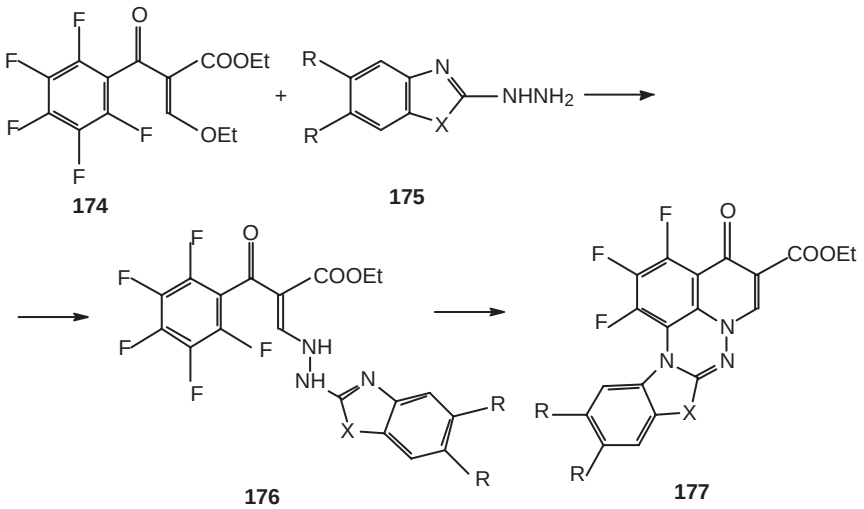
(92POL1137) (Scheme 159). The stereochemistry of this compound is confirmed by X-ray diffraction analysis and ^{19}F NMR spectroscopy.

Heating benzoxazinone under the same conditions leads to 4,5,6-tetrafluoro-3*H*-pyrido[3,2,1-*k*]phenoxazin-3-one (97ZOR1418) (Scheme 160).

To construct [*i*,*j*]-annelated quinolonecarboxylic acids, Nosova et al. (97ZOR1556, 96MC15, 97MC109, 98ZOR436, 98MC131, 99ZOR1447, 99ZOR1729, 01ZOR604) developed a method based on intramolecular cyclizations of the 3-hydrazido derivatives of 2-polyfluorobenzoylacrylic acids. In these tricyclic systems, the quinolone skeleton is annulated to the six-membered oxadiazine or thiadiazine ring. They may be regarded as analogs of ophloxacin and marbophloxacin known antibacterial agents with antitumour activity (00PCJ19). The objective of the study was to determinate the antitumour activity of new [*ij*]annelated fluoroquinolones and derivatives of a new heterocyclic system of

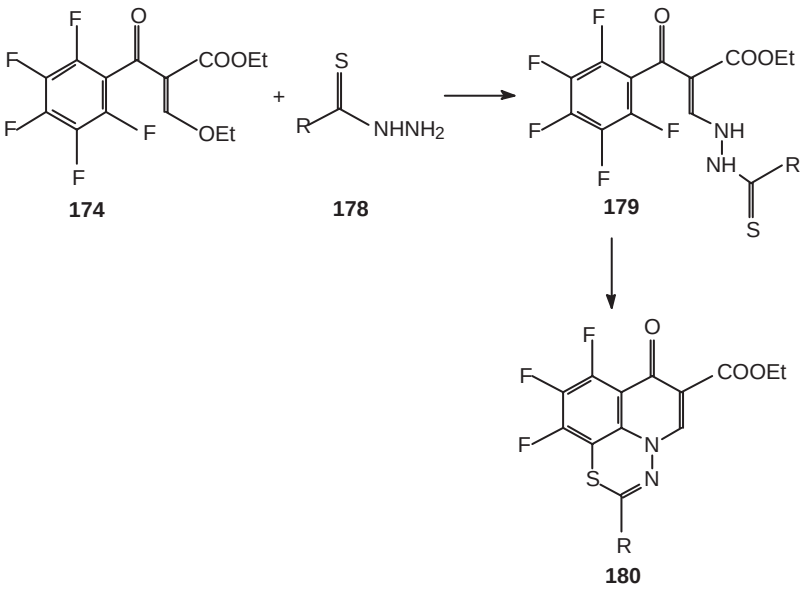


Scheme 160



Scheme 161

benzimidazo[1,2-*a*]-pyrazolo[1,5-*c*]quinazoline (00PCJ19). A number of ethyl 3-(benzazol-2-yl)hydrazino-2-polyfluoro-benzoylacrylic esters **176** were synthesized by the interaction of acrylates **174** with 2-hydrazino-benzazoles **175** in toluene (97ZOR1556) (Scheme 161). The ability of these compounds to undergo amine-imine tautomerization led to cyclizations with [*i*,*j*]-annulation of quinolines by the



Scheme 162

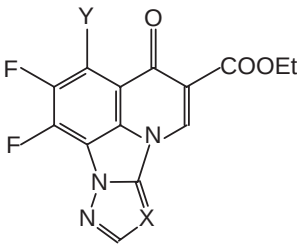
triazine ring (96MC15, 97MC109). The reaction was performed in acetonitrile in the presence of HF scavengers such as diazobicycloundec-7-ene (DBU), KF, and triethylbenzylammonium chloride (TEBA). Condensed quinolones **177** were obtained from acrylates **176** only in the presence of DBU (yield 10–70%) (98ZOR436).

The acrylates synthesized from acrylate **174** and semicarbazide **178** are boiled in benzene or toluene for 1–2 h; this gives 2R-9, 10-difluoro-7-oxo-7*H*-1,3,4-thiadiazino[6.5.4-*i*,*j*]quinoline-6-carboxylic esters **180** (yields 40–60%) (98MC131, 99ZOR1447, 99ZOR1729, 01ZOR604) (Scheme 162).

Cyclization of benzoyl acrylates **174** to condensed fluoroquinolones **180** takes place via intermediates **179**, which are not always isolated because of the fast closure of the thiadiazine ring. The structure of tricyclic fluoroquinoline **180** (R = thiomorpholin-1-yl) was established by X-ray analysis.

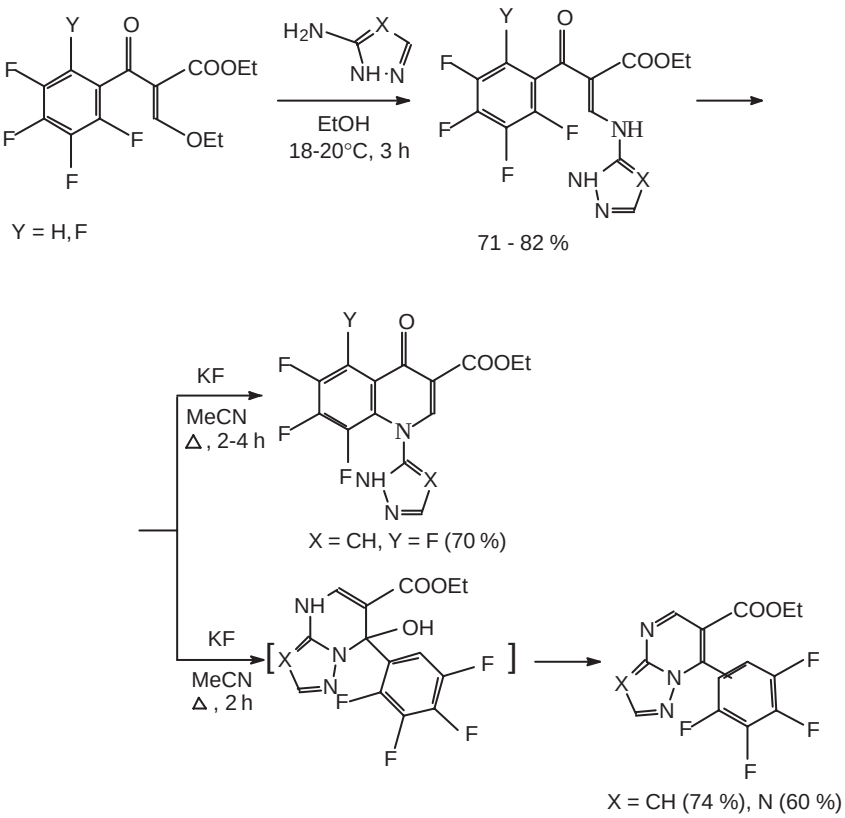
The reactions of 2-aminoazoles with ethyl 2-polyfluorobenzoyl-3-ethoxyacrylates in ethanol lead to 3-azolylamino-2-polyfluorobenzoyl-acrylates. Further cyclization of acrylates in boiling acetonitrile in the presence of potassium fluoride depends on the nature of the X and Y groups (01ZOR604).

Cyclization of ethyl 2-pentafluorobenzoyl-3(pyrazol-3-yl)aminoacrylate (X = N, Y = F) gives ethyl 4-oxo-1-(pyrazol-3-yl)-5,6,7,8-tetrafluoro-1,4-dihydroquinoline-3-carboxylic ester, whereas cyclization of the tetrafluoro-benzoyl analog (X = CH, Y = H; X = N, Y = H) with 3-aminopyrazole yields 7-tetrafluorophenyl-6-ethoxy-carbonylpyrazolo[1,5-*a*]pyrimidine; in the case of 3-amino-1,2,4-triazole, the product is 7-tetrafluorophenyl-6-ethoxycarbonyl-1,2,4-triazolo[1,5-*a*]pyrimidine (01ZOR604).

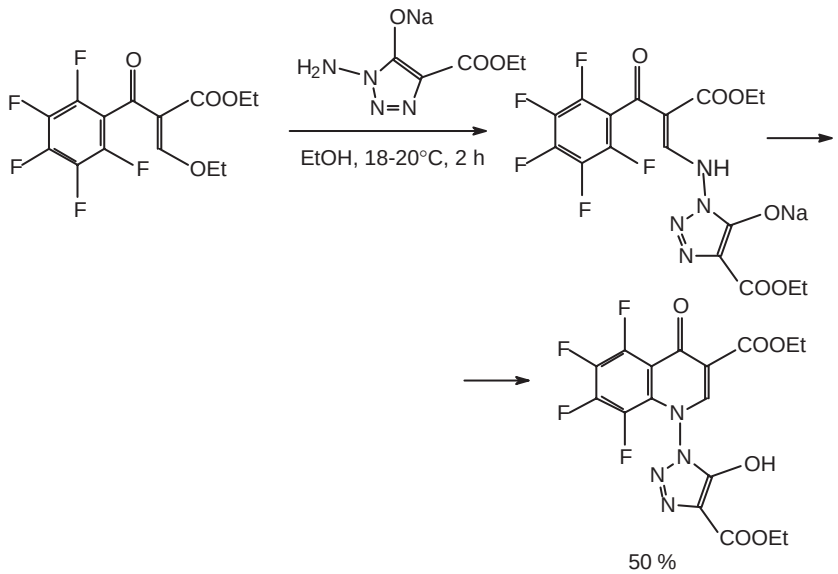


An attempt to perform further cyclization of 1-substituted quinolone using a stronger binding agent for HF (DBU) did not lead to the desired result. Lipunova et al. (01ZOR604) explained the difficulty of this cyclization by the high strain of the condensed system (Scheme 163).

The reaction of the acrylate (Y = H) with a derivative of 1-amino-1,2,3-triazole in ethanol gives a mixture of 3-(1,2,3-triazol-1-yl)-aminoacrylate and ethyl 1-(5-hydroxy-4-ethoxycarbonyl-1,2,3-triazol-1-yl)-4-oxo-6,7,8-trifluoro-1,4-dihydroquinoline-3-carboxylic ester, whereas heating this mixture in benzene leads to quinolone as the sole product (01ZOR604) (Scheme 164).



Scheme 163



Scheme 164

Cyclization of benzoyl acrylates **179** into condensed fluoroqinolones **180** proceeds through intermediates **179** which were not always possible to isolate because of rapid cyclization to the thiadiazine. The structure of the tricyclic fluoroquinolone **180** (R = thiomorpholin-1-yl) was established on the X-ray data.

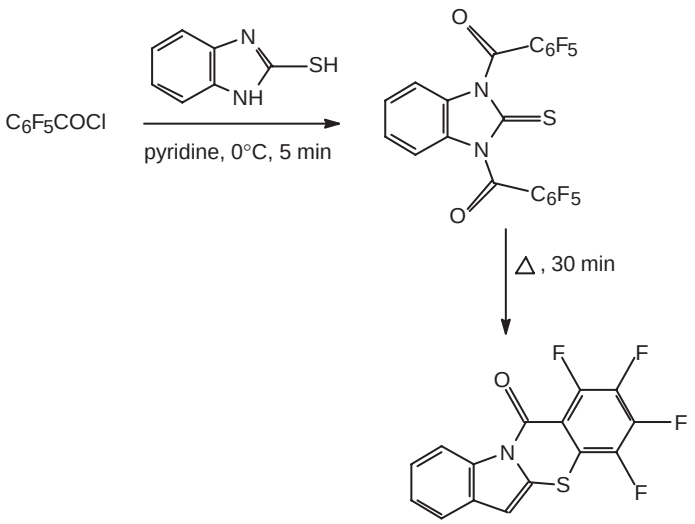
The reaction of 2-mercaptobenzimidazole with pentafluorobenzoyl chloride forms 1,2,3,4-tetrafluoro-12*H*-benzimidazo[2,1-*b*][1,3]benzo-thiazin-1,2-one (yield 50%), whose structure was confirmed by X-ray data (94JOC7688) (Scheme 165).

The formation of a heterocyclic system by intramolecular elimination of the *ortho*-fluorine atom of an aromatic ring was demonstrated by the reaction of pentafluorobenzoyl chloride with 2-imidazolidinethione or 2-mercaptoimidazole, forming 6,7,8,9-tetrafluoro-2,3-dihydro-5*H*-imidazo-[2,1-*b*][1,3]-benzothiazin-5-one (yield 54%) and 6,7,8,9-tetrafluoro-5*H*-imidazo[2,1-*b*][1,3]benzothiazin-5-one (yield 48%) (94JOC7688) (Scheme 166).

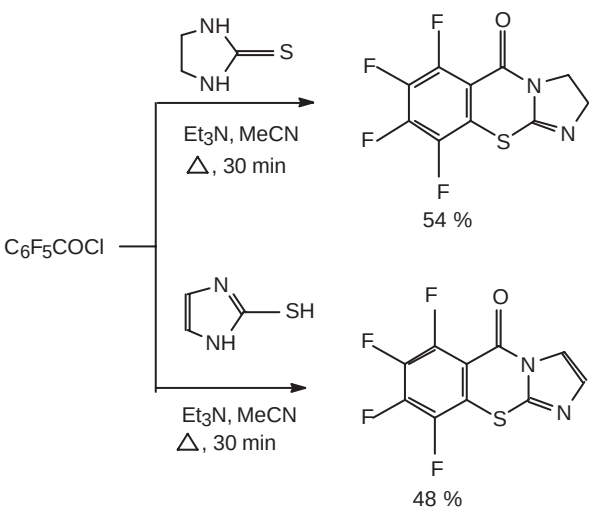
If the starting nucleophilic agent has an S = C–N triad, the cyclization involves the nucleophilic centers on sulfur and nitrogen atoms. Thus, the interaction between pentafluorobenzoyl chloride and pyrimidine-2-thione **181** forms tetrafluorobenzo-thiazinopyrimidinone **182** (94JOC7688) (Scheme 167).

Ethyl acetoacetate was acylated with 3,4,5-trifluoro-2,6-dimethoxybenzoyl chloride to give ethyl 3-oxo-2(3,4,5-trifluoro-2,6-dimethoxybenzoyl)butyrate (01IZV1090), preparated as in (01MC76). The compound was used for the synthesis of 6,7,8-trifluoro-5-hydroxy-2-methylchromone (Scheme 168).

The reaction of 2,3,4,5,6-pentafluorobenzyl bromide and 2-mercaptobenz-imidazole initially forms the product of substitution of the bromine atom by the sulfur atom to give [2(pentafluorophenyl)methyl]thio)-1*H*-benzimidazole **183**, yield 87%. The latter is cyclized by NaH in tetrahydrofuran to give tetrafluoro-benzimidazobenzothiazine **184** (yield 95%) (94JOC7688) (Scheme 169).



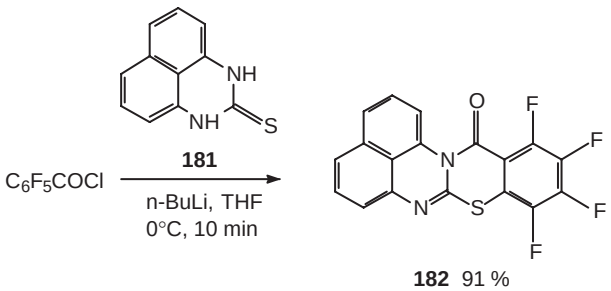
Scheme 165



Scheme 166

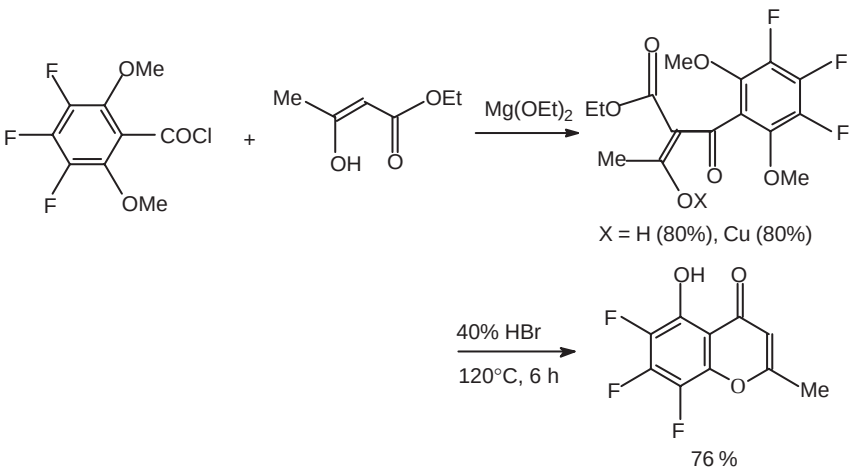
Thus, numerous examples suggest a general concept for the synthesis of polyfluorinated five- to seven-membered benzoheterocycles using intramolecular cyclization that occurs by elimination of an *ortho*-fluorine atom of the benzene ring under the action of a heteronucleophile.

The reactions may occur by nucleophilic attack of the second nucleophilic center of the binucleophile at the *ortho*-fluorine atom of the aromatic ring as in the usual S_NAr mechanism. However, an alternative mechanism is an attack of the ipso-carbon atom at the second nucleophilic center, generating an intermediate



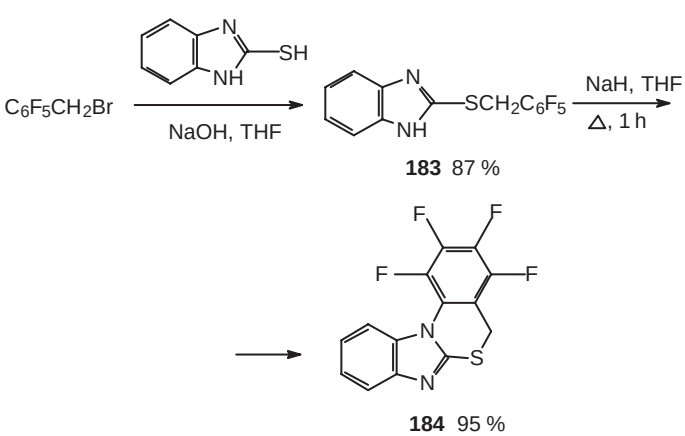
182 91 %

Scheme 167



76 %

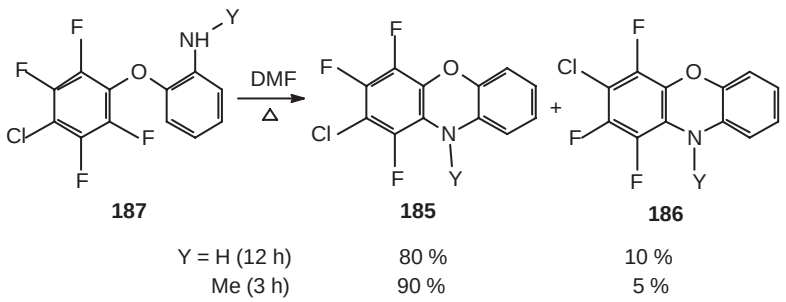
Scheme 168



183 87 %

184 95 %

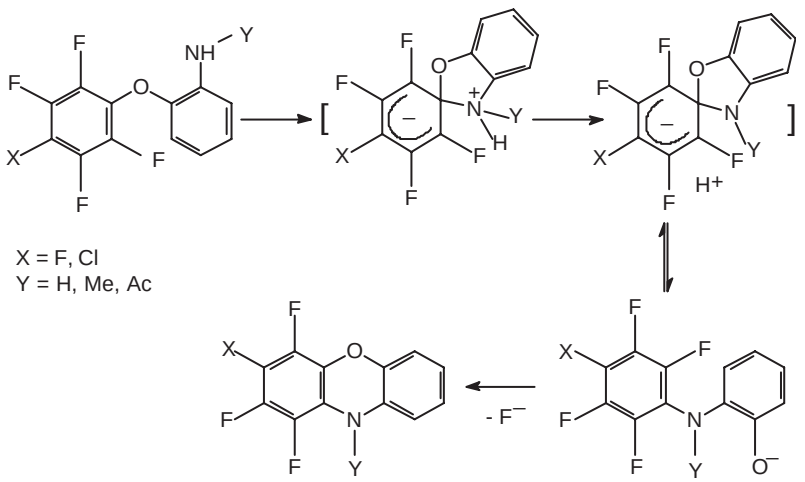
Scheme 169



Scheme 170

benzenonium anion as in an intermediate Meisenheimer complex (79ZOR1107). Further transformation of the anion leads to a cyclization product. With hexafluorobenzene as a substrate, no other mechanisms can be found because of the high symmetry of the product. Thus, the reaction of hexafluorobenzene with *ortho*-aminophenol in the presence of alkali, leading to 1,2,3,4-tetrafluorophenoxazine, was studied by several authors (67ZOB1285, 84IZVS113). Gerasimova et al. (94JFC(66)69) tried to determine the mechanism of this reaction using pentafluorochlorobenzene as a substrate. It was found that the reaction of pentafluorochlorobenzene with *ortho*-aminophenol and *ortho*-N-methyl-aminophenol leads to two isomeric phenoxazines, **185** and **186**, via the intermediate **187** of monosubstitution of the fluorine atom in the substrate (Scheme 170).

The ratio between the isomeric phenoxazine products suggests that the main route of cyclization is a direct attack of the second nucleophilic center at the *ortho*-carbon atom of the aromatic ring; an alternative route is a Smiles type rearrangement (70M9). Therefore, the following route of cyclization was proposed (Scheme 171).



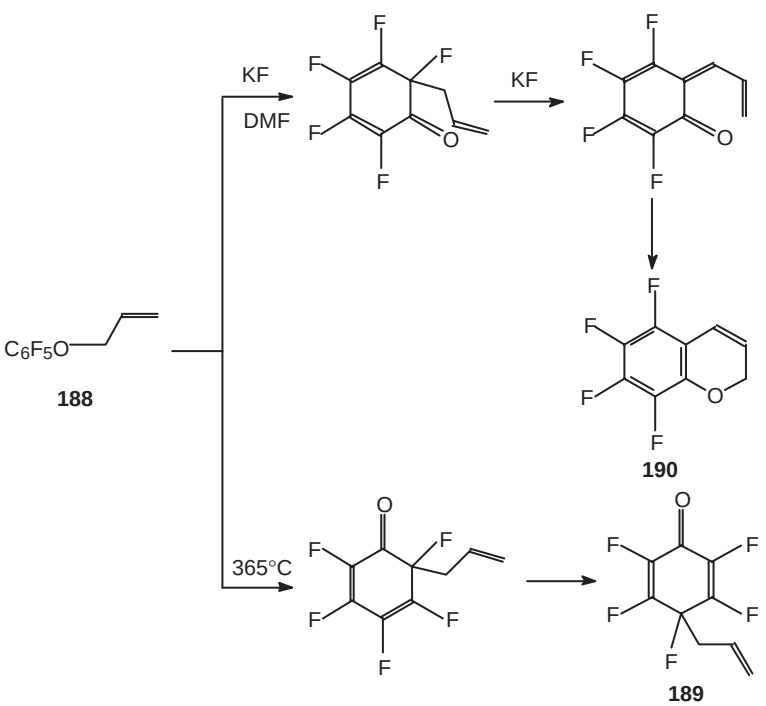
Scheme 171

The mechanism of intramolecular cyclizations cannot yet be interpreted unambiguously, more experimental data is needed for an unambiguous conclusion.

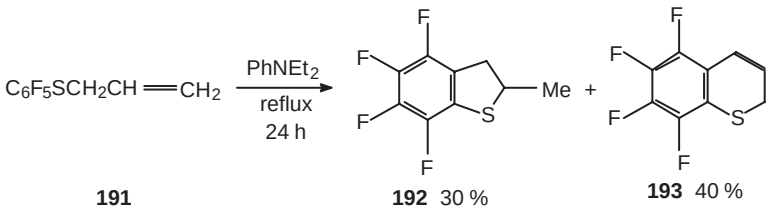
VIII. Innovations in the Use of Rearrangements in Heterocyclic Syntheses

For a number of rearrangements, the presence of fluorine atoms in a benzene ring makes it possible to obtain heterocyclic compounds. These processes occur by the mechanism of intramolecular cyclization that involves *ortho*-fluorine atoms. Thus, thermolysis (365 °C) of pentafluorophenylallyl ether **188** (71TL2377) leads to a Claisen rearrangement forming 2,5-dienone **189**. However, when boiled in dimethylformamide in the presence of potassium fluoride, this ether is converted into 5,6,7,8-tetrafluorochromane **190** (Scheme 172).

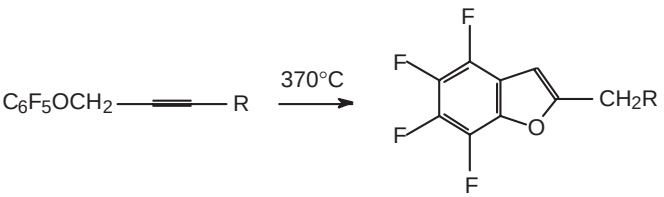
This specific behavior of some polyfluorinated benzenes underlies the new methodology for the synthesis of heterocycles with a condensed polyfluorinated benzene ring. An important role is played by the fluoride ion. As follows from the data (83JFC(22)483), the reaction initially forms the product of a Claisen rearrangement. The reaction of the latter with potassium fluoride in dimethylformamide gives an O-nucleophilic reagent, which undergoes intramolecular cyclization into 5,6,7,8-tetrafluorochromane (81JCS(P1)1417). In the case of the sulfur



Scheme 172



Scheme 173



Scheme 174

derivative, 2,3,4,5,6-pentafluorophenylprop-2-enyl sulfide **191**, the *ortho*-fluorine of the benzene ring is eliminated to form a mixture of 4,5,6,7-tetrafluoro-2,3-dihydro-2-methyl-1-benzothiophene **192** and 5,6,7,8-tetrafluorothiochromane **193** (81JCS(P1)1659) (Scheme 173).

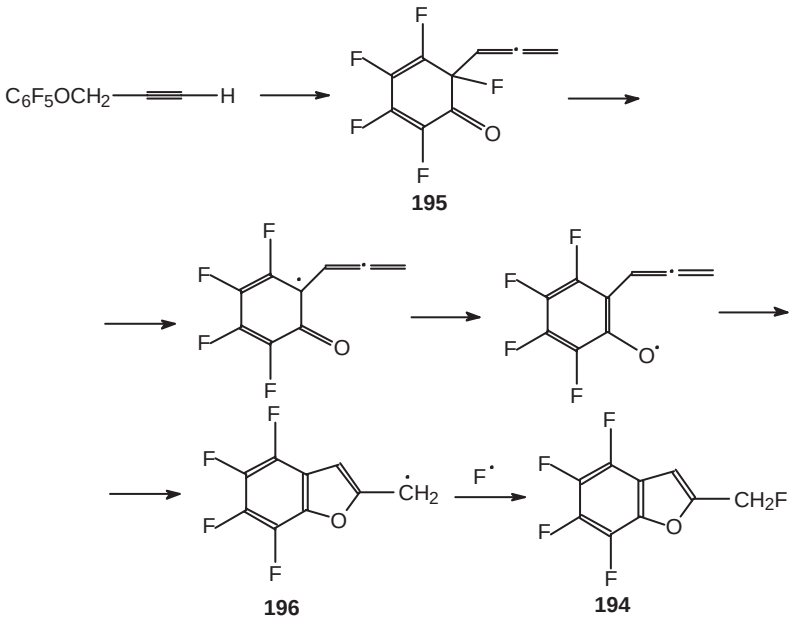
If the substrate contains a triple bond (pentafluorophenylprop-2-ynyl ether), the reaction under the same conditions forms exclusively a five-membered ring (2-fluoromethyl-4,5,6,7-tetrafluorobenz[*b*]furan **194** (yield 8%) (81JCS(P1)1417)) (Scheme 174). The yield of the target product is slightly increased by conducting the reaction in *para*-xylene.

The radical scheme is suggested (Scheme 175).

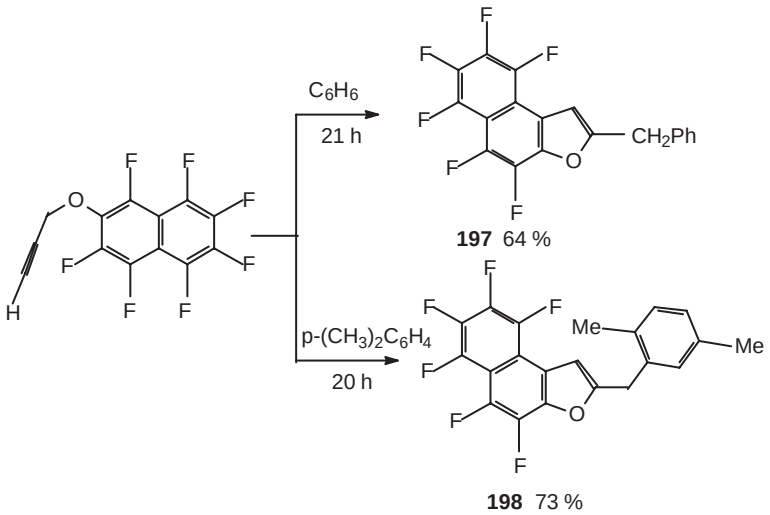
Intermediate **195** of the Claisen rearrangement undergoes homolytic fission at the aliphatic C–F bond and gives a radical center at the oxygen atom. Then radical cyclization takes place, and cyclic product **196** reacts with a fluorine atom, giving compound **194**.

1,3,4,5,6,7,8-Heptafluoro-2-naphthylprop-2-ynyl ether and its thio analog exhibit a similar behavior (85JCS(P1)2643). Benzene, *para*-xylene, and freon-113 were used as solvents. This method was employed to synthesize 2-benzyl-4,5,6,7,8,9-hexafluoronaphtho[2,1-*b*]furan **197**, 2-(2,5-dimethyl-benzyl)-4,5,6,7,8,9-hexafluoronaphtho[2,1-*b*]furan **198** (81JCS(P1)1417), 4,5,6,7-tetrafluoro-2-fluoromethylbenzo[*b*]thiophene **199** (85JCS(P1)2643), and 4,5,6,7,8,9-hexafluoro-2-fluoromethylnaphtho[2,1-*b*]thiophene **200** (85JCS(P1)2643) (Scheme 176).

Other derivatives behave in a different way. Thus, pyrolysis of pentafluorophenylpropionate in vacuum (quartz tube, 640 °C/0.01 torr) gives 4,5,6,7,8-pentafluorocyclohepta[*b*]furan-2-one 201 in 8% yield (91JFC(53)339) (Scheme 177).



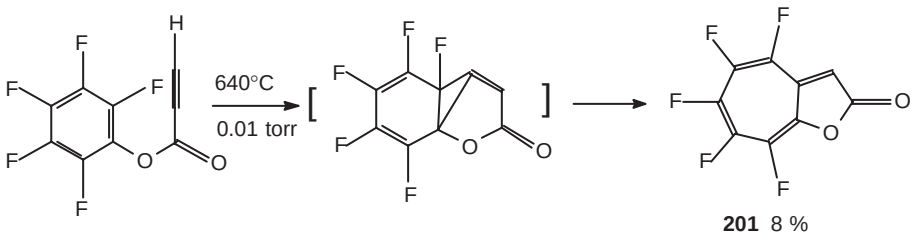
Scheme 175



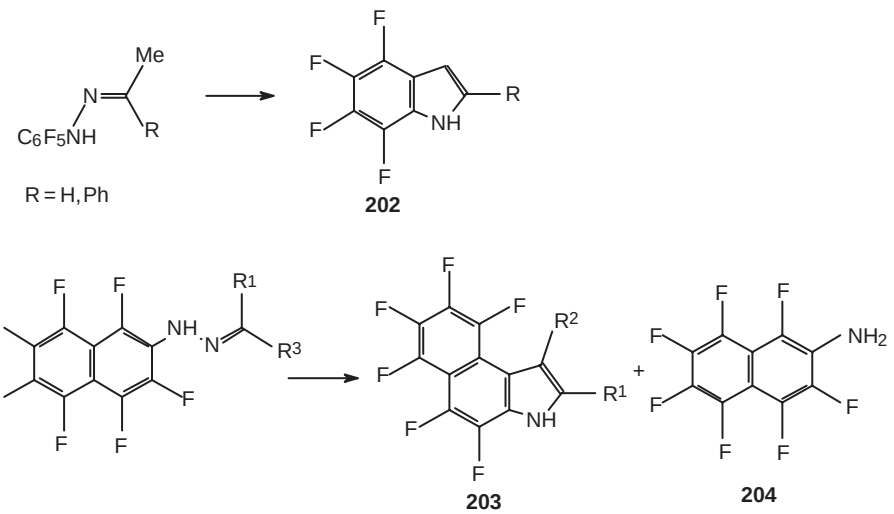
Scheme 176

The mechanism of this reaction involves carbene formation by an acetylene-methylene rearrangement.

Boiling pentafluorophenyl- and 1,3,4,5,6,7,8-heptafluoro-2-naphthylhydra-zones of some ketones in tetralin leads to the derivatives of 4,5,6,7-tetra-fluoroindole **202** and 4,5,6,7,8,9-hexafluorobenz[*e*]indole **203**, respectively (83JCS(P1)821,



Scheme 177



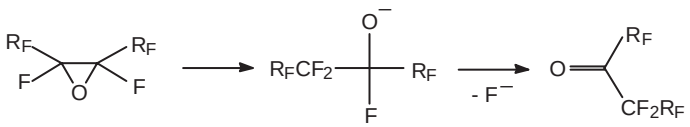
R^1 = Ph, R^2 = H, R^3 = Me (37, 21 %)
R^1 = 4-MeC_6H_4, R^2 = H, R^3 = Me (41, 12 %)
R^1 = Ph, R^2 = Me, R^3 = Et (34, 19 %)
R^1 = Ph, R^2 = Ph, R^3 = CH_2Ph (42, 0 %)
R^1 = Ph, R^2 = H, R^3 = Me (20, 17 %)
R^1 = H, R^2 = Ph, R^3 = CH_2Ph (24, 8 %)

Scheme 178

84JFC(26)77) (Scheme 178). These compounds are typically formed in Fischer's indole-forming reactions, which occur by an *ortho*-benzidine rearrangement.

IX. Polyfluoro-2,3-epoxyalkanes in the Synthesis of Heterocyclic Compounds

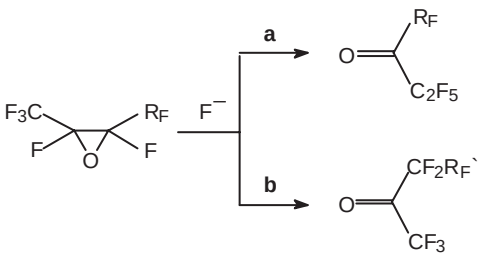
Polyfluoro-2,3-epoxyalkanes easily react with fluoride-ion, to give a convenient method of synthesis of perfluorinated ketones. Internal fluorooxiranes are known to react with nucleophilic reagents ($LiAlH_4$, NH_3, NEt_3, F^-) resulting in the formation of regioisomeric ring-opened products (Scheme 179).



R_F = CF_3, C_2F_5, -$(CF_2)_3$-, -$(CF_2)_4$-

Scheme 179

Steric factors seems to control the regiochemistry (Scheme 180).

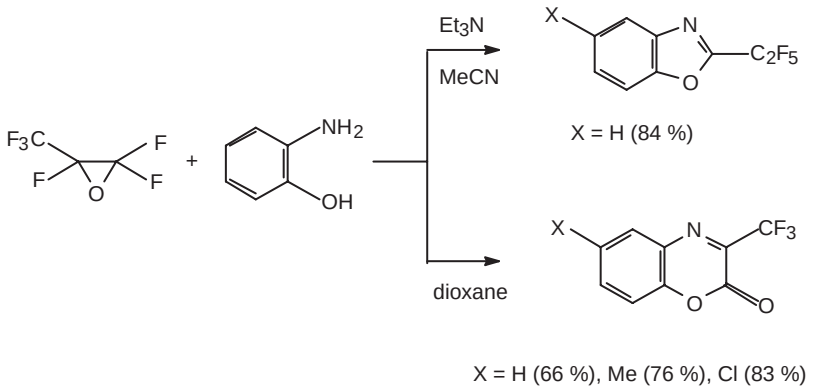


R_F	route **a**	route **b**	Yield, %
CF_3	-	-	92.5
C_2F_5	55	45	91.6
C_3F_7	74	26	89.4
C_5F_{11}	77	23	93.4
i-C_3F_7	100	0	92.0

Scheme 180

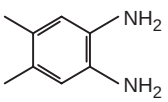
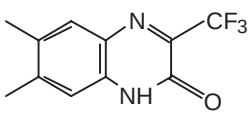
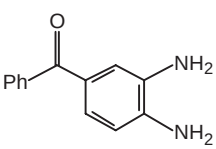
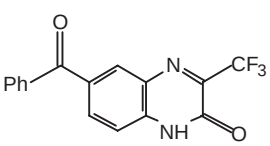
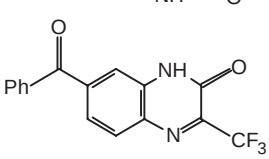
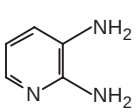
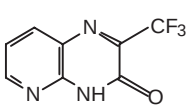
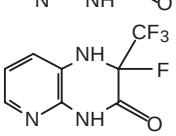
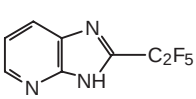
Polyfluoro-2,3-epoxyalkanes are a convenient building block for the construction of heterocyclic systems. Nucleophilic attack on the central carbon of the epoxide ring of polyfluoro-2,3-epoxyalkanes gives rise to amides or ethers of the corresponding acids. Further reaction of a second nucleophile with the C = O may follow. So, *ortho*-aminophenole and polyfluoro-2,3-epoxypropane in the presence triethylamine give 2-(pentafluoroethyl)benzoxazole (90IZV2338) (Scheme 181).

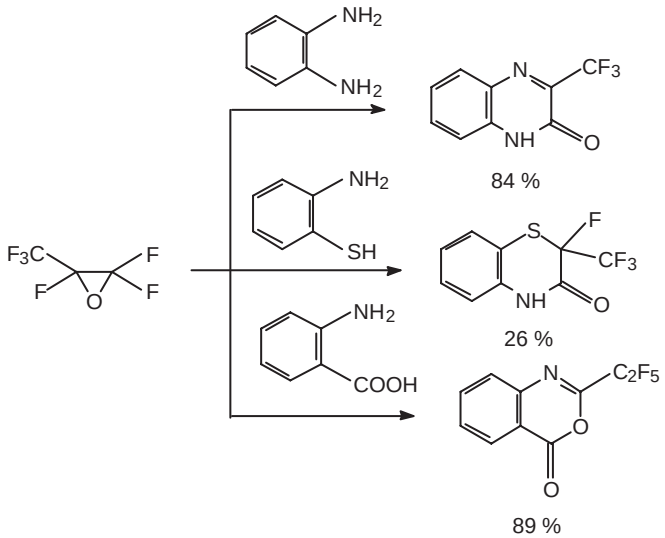
The intermediate pentafluoropropenyl fluoride reacts with *ortho*-aminophenol, giving a five-membered heterocycle. In the absence of base, for example in dioxane, a six-membered heterocycle-3(trifluoromethyl)-2*H*-1,4-benzoxazin-2-one forms (90IZV2338). Here the initial attack of the nitrogen nucleophile occurs on the central carbon atom followed by cyclization under the action of the oxygen nucleophilic center. A similar picture emerges in the reaction of polyfluoro-2,3-epoxypropane with *ortho*-phenylenediamine, *ortho*-aminothiophenole and anthranilic acid with the formation of 3-(trifluoromethyl)-2(1*H*)-qinoxalinone, 2-fluoro-2(trifluoromethyl)-2,3-dihydro-1,4-benzothiazin-3-one and 2-(pentafluoroethyl)-4*H*-3,1-benzoxazin-4-one accordingly (90IZV2338). Results for other *ortho*-diamines are in Table 1 (92JOC5630) (Scheme 182).



Scheme 181

Table 1. Products of the reactions of hexafluoro-2,3-epoxypropane with *ortho*-diamines (92JOC5630)

Reagent	Solvent (time, h; temperature, °C	Product	Yield, %
	CH_2Cl_2 (12, 23)		96
	Et_2O (12, 23)		71
			13
	CH_2Cl_2 (12, 23)		3
			31
			6

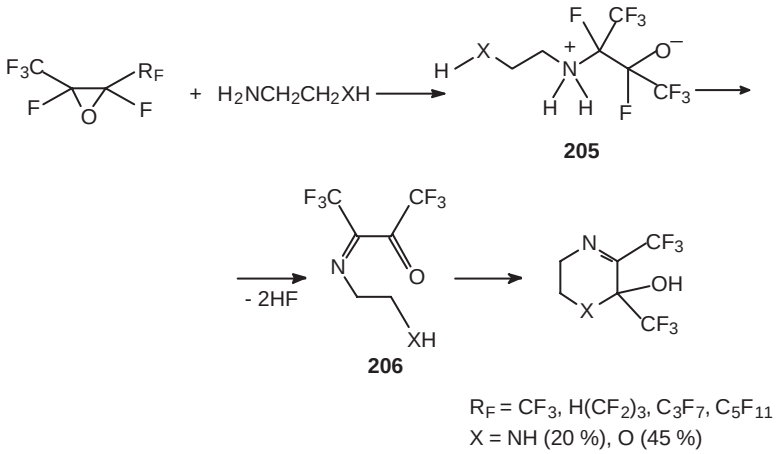


Scheme 182

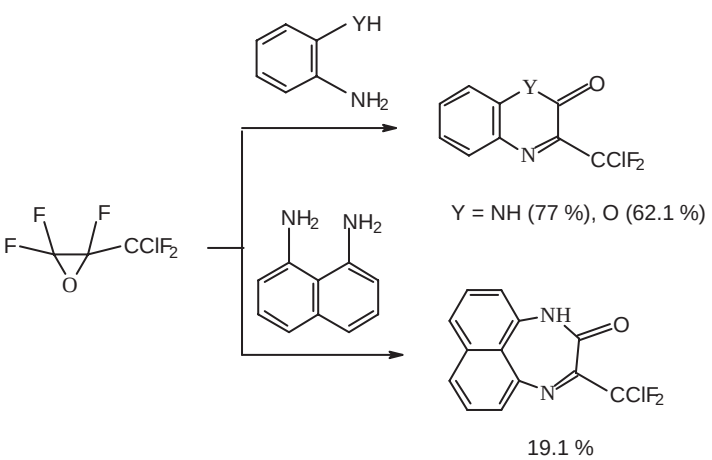
Terminal fluorooxiranes have a strongly pronounced polarization that promotes their reactions with nucleophilic reagents. So, polyfluoro-2,3-epoxyalkanes in reaction with bifunctional nucleophilic reagents (ethylenediamine, 2-aminoethanol) as opposed to hexafluoro-2,3-epoxypropene form 2,3-bis(trifluoromethyl)-1,5,6-trihydro-1,4-diazin-2-ol and 2,3-bis(trifluoromethyl)-5,6-dihydro-1,4-oxazin-2-ol, respectively (97ZOR299, 98JFC(87)49). The initial attack is by an amino group on the epoxide with the formation of adduct **205**. Then elimination of two molecules of *HF* gives 3-imino-2-butanones **206** which cyclizes (Scheme 183). In the case of unsymmertic polyfluoro-2,3-epoxyalkanes, mixtures regioisomeric heterocyclic compounds have been obtained.

2,3-Benzosubstituted 1,4-hetero-cyclic compounds (01JFC(108)1) result from the interaction of 3-chloropentafluoro-2,3-epoxypropane and benzene-1,2-diamine, 2-aminophenol, naphthalene-1,8-diamine. They give 3-(chlorodifluoromethyl)-quinazolin-2(1*H*)-one, 3-(chlorodifluoromethyl)-benzoxazin-2(1*H*)-one and 3-(chlorodifluoromethyl)-1,4-naphtho [1,8*a*, 8-*e*, *f*] diazepin-2 (1*H*)-one accordingly (01JFC(108)1) (Scheme 184).

The interaction of polyfluoro-2,3-epoxyalkanes with thiourea results in 2-amino-5-fluoro-4-hydroxy-4,5-di(polyfluoroalkyl)1,3-thiazolines (99MC231, 00JFC(104)155, 00ZOR887). It is established, that octafluoro-2,3-epoxybutane, dodecafluoro-2,3-epoxyhexane and 6-hydroundeca-fluoro-2,3-epoxyhexane do not react with thiourea under conditions described for the terminal fluorooxiranes (00JFC(104)155), probably for steric reasons. Reactions could be carried out only at increased temperature (70–90 °C, sealed tube in the case of oxiranes) using as solvent MeOH, DMSO, or DMF. As a result, heterocyclic compounds, 2-amino-5-fluoro-4-hydroxy-4,5-bis(polyfluoroalkyl)-1,3-thiazolines **207a**,**b**; **208a**,**b**, were obtained (99MC231, 00JFC(104)155, 00ZOR887) (Scheme 185). The molecular structure of the *E*-isomers of 2-amino-5-fluoro-4-hydroxy-4,5-bis(trifluoromethyl)-1,3-thiazoline and of



Scheme 183



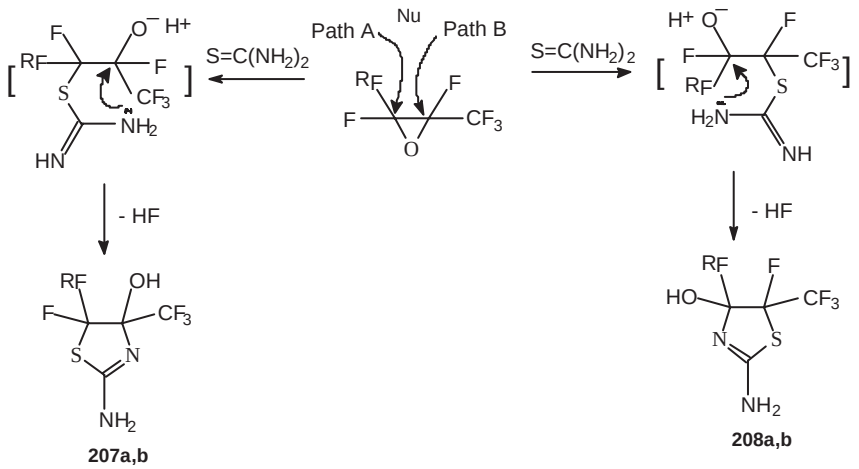
Scheme 184

2-amino-5-fluoro-5-heptafluoropropyl-4-hydroxy-4-trifluoromethyl-1,3-thiazoline has been established by X-ray crystallography (00JFC(104)155).

Symmetrical octafluoro-2,3-epoxybutane ($E:Z = 90:10$) reacting with thiourea gave one regioisomer, namely 2-amino-5-fluoro-4-hydroxy-4,5-bis(trifluoromethyl)-1,3-thiazoline **209** (Scheme 186).

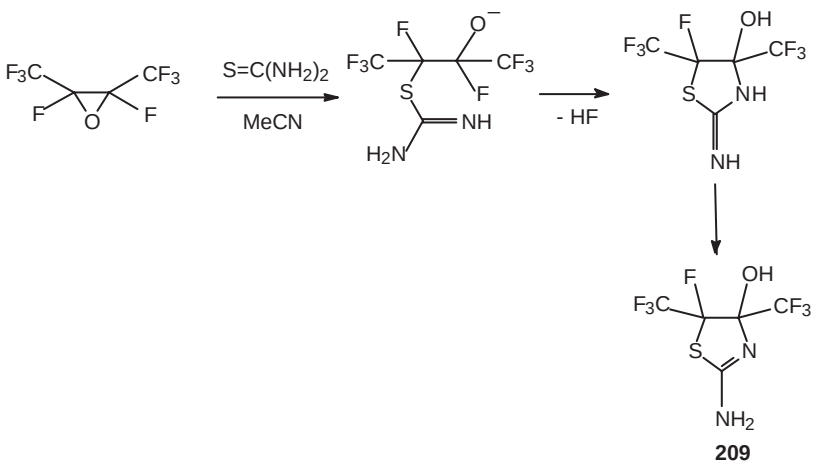
A similar reaction of asymmetrical polyfluoro-2,3-epoxyalkanes gave mixtures of regioisomers **207a**, and **208a**, which apparently arose from the initial nucleophilic attack on the carbon atoms C-3 (Path A) and C-2 (Path B) of the epoxide ring (99MC231, 00JFC(104)155, 00ZOR887).

The interaction of thiosemicarbazide with symmetrical oxirane (octafluoro-2, 3-epoxybutane, $E:Z = 90:10$) was carried out in DMSO at elevated temperatures



R_F = C_3F_7 **a**, $H(CF_2)_3$ **b**

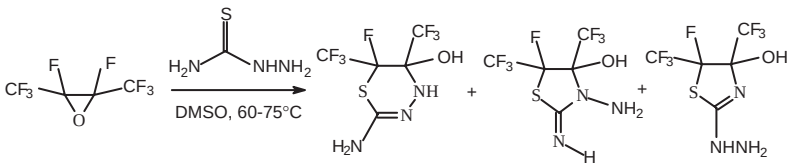
Scheme 185



Scheme 186

(60–75 °C) produce 2-amino-1,3,4-thiadiazines **210a** and products of their rearrangement—3-amino-2-iminothiazolidines, 2-hydrazinothiazolines or even pyrazole derivatives (00JFC(104)155) (Scheme 187).

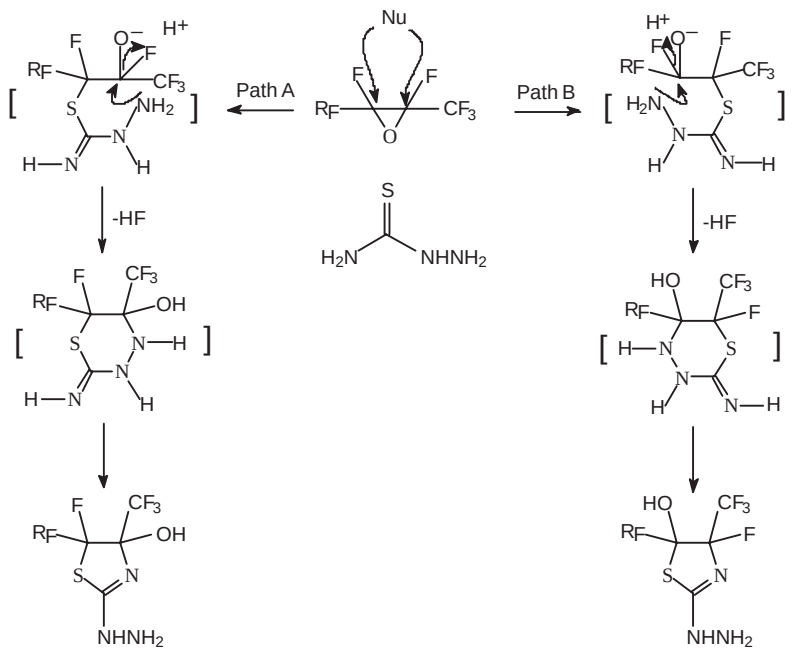
The interaction of thiosemicarbazide with dodecafluoro-2,3-epoxy-hexane (*E*: *Z* = 90 : 10) and 6-hydroundecafluoro-2,3-epoxyhexane (*E* : *Z* = 85 : 15) was carried out in DMSO at elevated temperatures (60–75 °C) gave compex mixture containing



Scheme 187

regioisomers **210b,c** and **212b,c** in *E*-forms as major products, those in *Z*-form as minor products (00JFC(104)155, 00ZOR887) [formation of end-products occurs, apparently, in result hydrolytic splittings of connection N4–C5 intermediate thiadiazines and the subsequent short circuit in thizoline cycles at participation imines nitrogen] (Scheme 188).

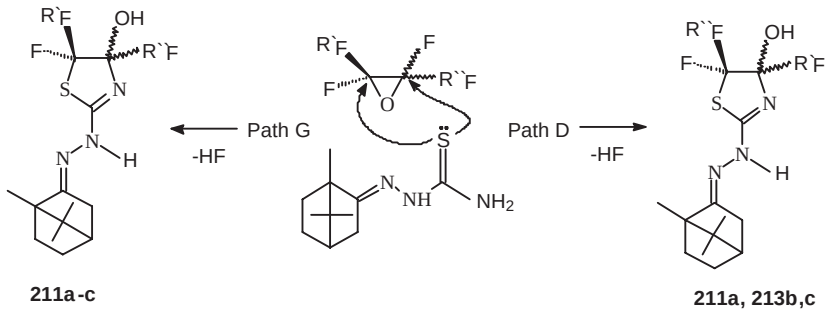
The reaction of (1S,4S)- and racemic camphor thiosemicarbazone [(1S,4S)- and rac-CTSC] leads to the formation of *trans*- and *cis*-isomers of (1S,4S)- or racemic camphor 5′-fluoro-4′-hydroxy-4′,5′-di(perfluoroalkyl)-1′,3′-thiazolinyl-2′-hydrazones **211a–c** and **213b,c** (Scheme 189). The molecular structure of the two diastereomers (1S,4S,4′R,5′R)- and (1S,4S,4′S,5′S)- of **211a** has been established by X-ray crystallography (03JFC(120)41). This result can be explained by a considerable contribution of the S_N2 type of nucleophilic substitution both to the epoxide ring



210a-c **210a, 212b,c**

R_F = CF_3 (**210a**), C_3F_7 (**210b, 212b**), $H(CF_2)_3$ (**210c,212b,c**)

Scheme 188



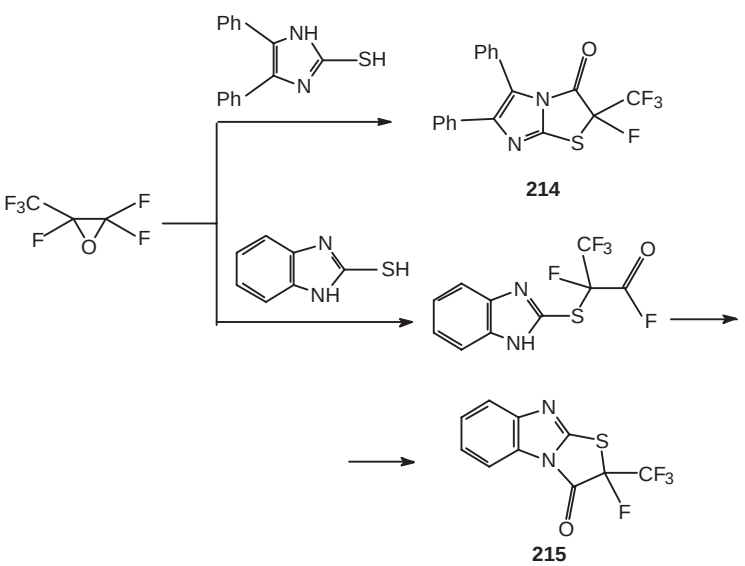
$R`_F = CF_3$; $R``_F = CF_3$ **211a**
$R`_F = C_2F_5$; $R``_F = C_2F_5$ **211b, 213b**
$R`_F = CF_3$; $R``_F = CF_3CF_2CF_2$ **211c, 213c**

Scheme 189

opening and to the thiazoline cyclization states, that cause configuration inversion at both the epoxide carbon atoms (03JFC(120)41). As a result, the starting oxirane and the resulting thiazoline have the same (*trans*- or *cis*-) configuration.

The ring opening of unsymmetrical dodecafluoro-2,3-epoxyhexane with (1S,4S)-CTSC under the same conditions occurred in both possible directions (paths G and D) to give regioisomeric (1S,4S)-camphor thiazolinylhdrazones **211c**, **213c** (44:56) consisting of mixtures of *trans*- and *cis*-isomers.

Similarly, the interaction of hexafluoro-2,3-epoxypropane with benzimidazolin-2-thione and 4,5-diphenylimidazolin-2-thione result in imidazolones **214** and **215** which are of pharmacologic (80BCSJ1694) interest (Scheme 190).



Scheme 190

Thus, Chupakhin et al. have developed an approach to synthesis of functionalised 1,3-thiazolines with two fluoroalkyl substituents, which are of interest as biologically active compounds and new convenient building blocks for complex heterocyclic systems.

X. Conclusions

The foregoing treatment evidences extensive interest in the development of new methods and approaches to the synthesis of fluorine-containing heterocyclic compounds and the application of specific features of perfluorinated organic compounds, especially perfluoroolefins and polyfluoroaromatic compounds. Significantly, these approaches use accessible and inexpensive starting materials. Recent developments of fluoroorganic chemistry have led to the discovery of new fluorine-containing heterocyclic compounds with unique structures, many of which exhibit specific biological activity and efficacy in medicinal and pesticide applications. One of the problems of fluoroorganic synthesis is the high cost of fluorine incorporation into organic molecules. But in view of the unique properties of fluoroorganic compounds imparted by fluorine, progress in fluoroorganic chemistry and technology must lower the cost of fluorine introduction into organic compounds and expand fluorine applications.

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Contents

Fluorine-Containing Heterocycles. Part II. Synthesis of Perfluoroalkyl Heterocycles from Carbonyl Compounds

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Preface

Volume 87 consists of four chapters. L. I. Belen'kii and V. N. Gramenitskaya (Moscow, Russia) have provided Part VIII of our series on the literature of heterocyclic chemistry, which covers reviews dealing with the subject, appearing during the period 1999 through 2001.

A. Rybar (Bratislava, Slovakia) has contributed the first of a two-part series dealing with annulated heterocyclo-purines. The present chapter deals with fused five-membered heterocyclo-purinediones, -purinones and -purineimines, many of which are of significant biological interest.

The third chapter is the Part II of the survey by Varvounis, Fiamegos, and Pilidis (Ioannina, Greece) on the pyrazol-3-ones. This second part is concerned with reactions taking place at the ring atoms of these important compounds.

Finally, G.G. Furin (Novosibirsk, Russia) deals with the synthesis of perfluoroalkyl heterocycles from carbonyl compounds. This is the second part of Professor Furin's survey of flourine-containing heterocycles.

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