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Volume 82

Alan R. Katritzky

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Preface

S. F. Vasilevsky and E. V. Tetryakov (Novosibirsk, Russia), together with J. Elguero (Madrid, Spain), have summarized the synthesis, chemical and spectroscopic properties, and biological activity of acetylenic derivatives of pyrazoles, a field which has shown explosive growth in the past few years.

M. Somei (Kanazawa University, Japan) has reviewed the many significant advances in indole chemistry that have recently become possible through the application of N-hydroxyindole intermediates. Much of the fundamental chemistry of this class was accomplished in Professor Somei's laboratories.

I. A. Maretina and B. A. Trofimov (Irkutsk, Russia) have contributed a chapter covering applications of diacetylenes in the preparation of heterocycles. This is another field that has grown immensely in the past decade and one which has been significantly enriched by work from these authors' laboratories.

The final chapter in this volume is authored by O. N. Chupakhin and D. N. Kozhevnikov (Ekaterinburg, Russia) and deals with 1,2,4-triazines N-oxides, an interesting compound class, which has not previously been reviewed comprehensively.

A. R. KATRITZKY
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ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 82

Synthesis and Properties of Acetylenic Derivatives of Pyrazoles

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I. Introduction

Acetylenic derivatives of pyrazole[1] have aroused great interest in recent years owing to their wide variety of biological and pharmacological properties (72IZV 2524; 93MIP1; 96BMCL797; 99BMCL979; 99USP5925769).

Moreover, acetylenyl pyrazoles are highly valuable intermediates because a triple bond is susceptible to nucleophilic, electrophilic, radical, and cycloaddition reactions, and because the terminal acetylenes display an unusually high CH acidity which can be used for both functionalizing and building up C—C bonds. In addition, compounds with a vicinal arrangement of a multiple bond and a functional group prone to intramolecular addition can be used to prepare condensed heterocyclic systems. This determines the potentialities of alkynyl pyrazoles as highly reactive synthons [83IZV688; 85IZV1367; 98HEC519; 98INP9803673; 99INP9950249; 99INP9962885; 99JCS(P1)3721].

At the same time, the results of work on the chemistry of acetylenic derivatives of pyrazole are scattered over original papers, patents, and dissertations, unavailable to a wide circle of chemists. This review is aimed at closing this gap.

[1] The review describes syntheses and properties of alkynylpyrazoles and their condensed analogs in which a triple bond is directly connected with the heterocycle.

II. Synthesis of Acetylenylpyrazoles

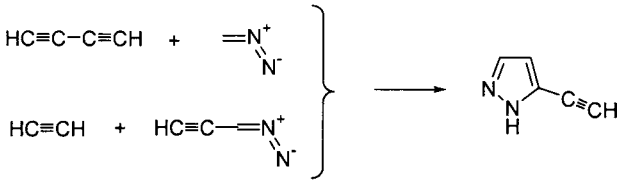
A. Cyclization Reactions

This type of reaction is represented by 1,3-dipolar cycloadditions, corresponding to one of the Huisgen categories (69MI1). The 1,3-dipolar cycloaddition corresponds to the interaction between a 1,3-dipole and a multiple system $d=e$, called the "dipolarophile," followed by a cyclic shift of electrons and completed with a five-membered ring closure (Scheme 1).

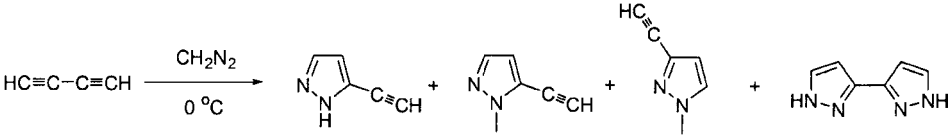
The first representative of the acetylenic derivatives, 3(5)-ethynylpyrazole, was obtained by condensation of diacetylene with diazomethane by Kuhn and Henkel (41LA279) and later by other authors (69IZV2546), and by reaction of acetylene with diazopropyne (62AG252; 68LA113) (Scheme 2).

The composition of the mixture of products of different structures depends on the diacetylene diazomethane ratio (68LA124). With a 1:1 ratio of butadiyne and diazomethane, 3(5)-ethynylpyrazole dominates (55%). The yields of isomeric 3- and 5-ethynyl-1-methylpyrazoles are 8 and 11%, respectively. The double excess of diazomethane leads mainly to a mixture of N-methylated isomers (81%), 10% of 3(5)-ethynylpyrazole, and a small amount (3%) of bipyrazole (68LA124) (Scheme 3).

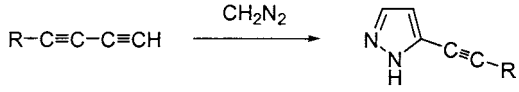
Scheme 1



Scheme 2



Scheme 3



R = Me, Et, $C(CH_3)_2OCH(Me)OBu$, $Sn(Et)_3$

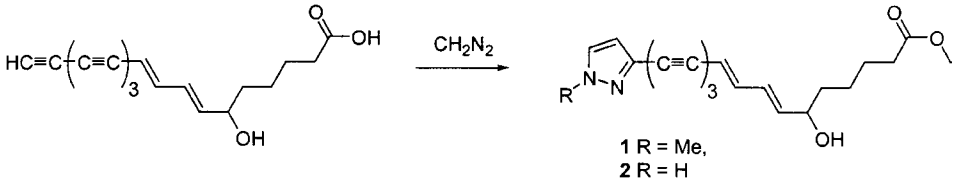
SCHEME 4

The monosubstituted diacetylenes, including the 3-triethylstannyl derivative (81%) (71ZOB2230), react with the 1,3-dipole to yield a 3(5)-alkyn-1-ylpyrazole (65ZOR610; 68KGS695) (Scheme 4).

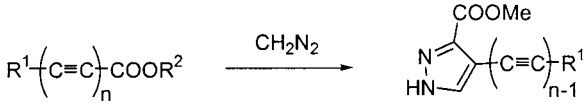
1,3-Dipolar additions of diazomethane to acetylenes under mild conditions are restricted to monosubstituted acetylenes; thus the formation of pyrazole derivatives **1** (1,3-dipolar addition, C=C isomerization, then methylation) confirms the existence of a terminal acetylene in caryoynencins (87TL3981) (Scheme 5).

While Kakisawa *et al.* (87TL3981) reported formation of *N*-methylpyrazole **1,** Yamaguchi *et al.* obtained the NH derivative **2** by reaction of caryoynencins with diazomethane in ethyl acetate at 0°C (94BSJ1717; 95JMC5015). The 1,3-dipolar addition was quite sensitive to the solvent employed, and a very low yield of pyrazole derivative **2** was obtained in ether or methanol (Scheme 5).

Compared with monosubstituted diacetylenes, the disubstituted ones add diazomethane to form 4-alkynylpyrazoles (58CB1841; 60CB1931; 68LA124). Diazomethane reacts similarly with either ethers of polyacetylenic acids (57JCS2012) or free acids (57CB124; 60CB1931; 68LA124), which is the method for synthesizing pyrazole-3-carboxylic acid esters with acetylenic substituents at position 4 of the ring (Scheme 6).

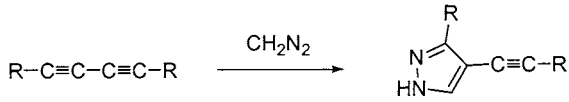


SCHEME 5



R^1 = Et, R^2 = Me, n = 2;
R^1 = Me, R^2 = H, n = 2;
R^1 = Me, R^2 = H, n = 3

SCHEME 6



R = C(O)-C_6H_5, $C(CH_3)_2OH$, CH_2O-C(O)-C_6H_5, CH_2O-C(O)-*p*-Br-C_6H_4, CH_2O-C(O)-*m*-Br-C_6H_4,

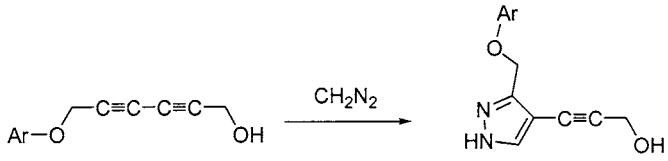
SCHEME 7

Thus, 1,4-dibenzoyl-1,3-butadiyne with diazomethane forms 3(5)-benzoylethynylpyrazole (yield 59%) (68LA124). In a similar way, the reaction of 2,7-dimethyloctadiyne-2,7-diol with diazomethane leads to 4-[3-(1-hydroxy-1-methylethyl)-1*H*-pyrazol-4-yl]-2-methylbut-3-yn-2-ol in 64% yield (58CB1841) (Scheme 7).

1,6-Dicarbaryloxy-1,6-hexadiynes react like 1,4-disubstituted butadiynes, giving rise to the corresponding 3-(aroyloxymethylene)-4-(3-aroyloxypropynyl-1)pyrazoles in an 84–89% yield (87MI1). Reaction of symmetric diacetylene esters of aromatic acids with diazomethane give 3-(benzoyloxymethyl)-4-(benzoyloxypropyn-1-yl-1)pyrazoles [Scheme 7 with R = $CH_2OC(O)C_6H_4$—Y; Y = H, Br-2, Br-4, NO_2-2, NO_2-4, $(NO_2)_2$-3,5, OMe-2, OMe-3, OMe-4 (87MI2); R = -3-Py, -4-Py (84MI1), and with R = $CH_2OC(O)C_6H_4$—Y; Y = Cl-4, Cl-2, Cl_2-2,4, I-2, 3-I (86MI2)].

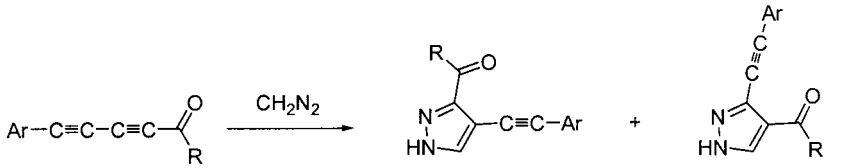
Note that 1,4-substituted butadiynes with diazomethane can form two isomers. Kuznetsov and co-workers have considered this problem in detail and established that diphenyldiacetylene with diazomethane forms, in standard conditions (ether, 0°C, 9 days), only one of the two possible regioisomers: 4-phenyl-3(5)-phenylethynylpyrazole (yield 86%) (93ZOB1107). The cyclization of derivatives of phenoxy-2,4-hexadiyn-6-oles with diazomethane leads to only one isomer of alkynylpyrazole (76MI1; 77MI1) (Scheme 8).

According to publications (68LA113; 71CAS1731; 72BSF4781), disubstituted diacetylenes react with diazomethane to form both 3- and 4-acetylenyl-substituted



Ar = *o*-Br-C_6H_4, *p*-Br-C_6H_4, 2,4-Br_2-C_6H_3, *o*-NO_2-C_6H_4, *m*-NO_2-C_6H_4, *p*-NO_2-C_6H_4

SCHEME 8



major product minor product

Ar = C_6H_5, *p*-Br-C_6H_4, *p*-Cl-C_6H_4, *p*-CH_3-C_6H_4; R = CH_3
Ar = C_6H_5, R = C_6H_5;
Ar = C_6H_5, R = OCH_3

SCHEME 9

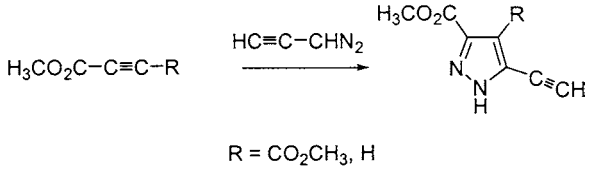
pyrazoles. In this case, the former is obtained in trace amounts (Scheme 9). The following butadiyne derivatives when treated with diazomethane at −20°C gave a mixture of two alkynylpyrazoles corresponding to a 1,3-dipolar addition of CH_2N_2 to the conjugated triple bond contiguous with the carbonyl group (86PM458).

As follows from Table I (see Section VII: Index of Tables), the yields in 4-acetylenyl compounds depend both on the reaction time and on the structure of the aromatic and acyclic components (molecular polarity). If more than one equivalent of diazomethane is used, N-methylation of pyrazole occurs.

The standard technique for obtaining alkynylpyrazoles consists of mixing up the ether solutions of diazoalkane and diacetylene or its derivatives (or diazopropyne and acetylene) and keeping the reaction mixture either for several hours or for three weeks within a narrow temperature range (0–20°C) (Tables II and III).

According to the literature data, the degree of interaction selectivity between diazoalkanes and diacetylenes is high enough. The main products can be represented by both of the regioisomeric ethynylpyrazoles. However, the reaction course substantially depends on the structures of both diazoalkane and diacetylene (91ZOB2286). Thus, the addition of diazomethane to the activated C≡C bond in arylacyldiacetylenes leads, according to the Auwers rule (29LA284), mainly or exclusively to 4-arylethynyl-3(5)-acylpyrazoles (68LA124; 71CAS1731). The interaction between diazomethane and diacetylene, its mono- and disubstituted derivatives (in both the aliphatic and aromatic series) (91ZOB2286; 93ZOB1107), gives 3-alkynylpyrazoles which can also react regioselectively with a second diazoalkane molecule to form symmetric bipyrazoles.

In the case of the reaction between 2-diazopropane and diphenyldiacetylene, the reverse (as compared with other diynes) orientation of addition of the first molecule of the diazo compound with a predominant formation of 4-phenylethynylpyrazole is observed. Therefore, it is noteworthy that whereas the regioselectivity of the addition of diazoalkanes to alkenes is well studied and its products have, as a rule, the structure been predicted with respect to electron effects, the problem of orientation



SCHEME 10

of 1,3-dipoles in reactions with a carbon–carbon triple bond is not solved. Some authors (91ZOB2286; 93ZOB1107) consider not the electronic (Auwers rule) but steric factors as the most likely to determine the courses of both of the reactions with 2-diazopropane. Indeed, in each case, the adducts formed are those in which the bulky group $C(CH_3)_2$ adds to the triple-bond carbon atom containing the less sterically bulky substituent (H < C≡CR < Ph < pyrazolyl). It is not surprising that the main product in the reaction between 2-diazopropane and diphenyldiacetylene is 4-phenylethynylpyrazole. At the same time the interaction between diacetylene and diazomethane leads to the corresponding 5-ethynylpyrazole. Kuznetsov and co-workers (91ZOB2286; 93ZOB1107) attribute this to a spatial effect.

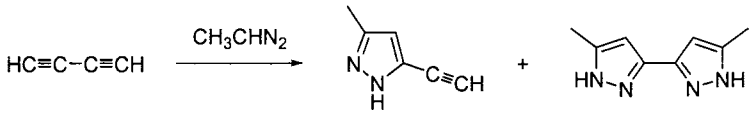
Diazopropyne reacts similarly with a monosubstituted acetylene to form 3(5)-alkynylpyrazoles (68LA113). Thus, the reaction of diazopropyne with acetylenecarboxylic acid methyl ether results in 5-ethynyl-1*H*-pyrazole-3-carboxylic acid methyl ether in 48 h in 62% yield. 5-Ethynyl-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester was prepared by reaction of diazopropyne with acetylenedicarboxylic acid methyl ether (Scheme 10).

Under similar conditions, the interaction between diacetylene and diazoethane (68CB3700) gives rise to 5-ethynyl-3-methyl-1*H*-pyrazole in 34% yield (Scheme 11).

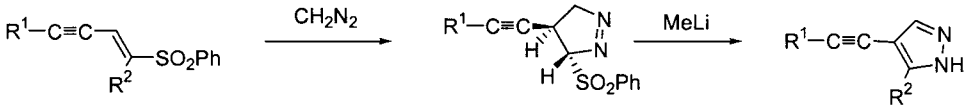
Ethyl diazoacetate adds *endo* to $Me_3Si(C{\equiv}C)_2SiMe_3$ to give 3-ethoxycarbonyl-4-trimethylsilylethynyl-5-trimethylsilylpyrazole (88JOM247).

It is interesting that when one molecule contains triple and double bonds, diazomethane adds exclusively (or mostly) to the C=C bond [68LA124; 91GEP-4001600; 97JCS(P1)695]. The addition of diazomethane to enyne sulfones occurs stereo- and regioselectively and gives pyrazolenines (50–85%) that undergo dehydrosulfonation under the action of methyllithium in THF at −78°C, resulting in 4-alkynyl-1*H*-pyrazoles (Scheme 12; Table IV) [97JCS(P1)695].

4,5-Bis(alkynyl)-1*H*-pyrazoles are also obtained by the same procedure. The reaction of (*Z*)-enediyne sulfones with diazomethane gives bis(alkynyl)-3*H*-

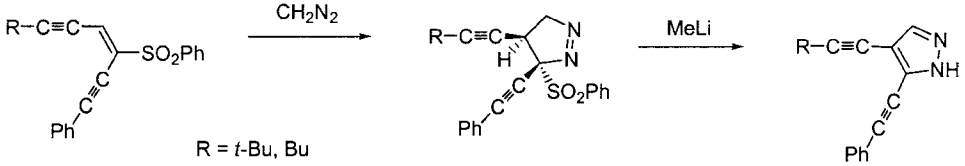


SCHEME 11



R^1 = *t*-Bu, R^2 = H; R^1 = Ph, R^2 = H; R^1 = *t*-Bu, R^2 = $(CH_2)_2Ph$;
R^1 = *t*-Bu, R^2 = SO_2Ph; R^1 = Bu, R^2 = SO_2Ph; R^1 = Ph, R^2 = SO_2Ph

SCHEME 12

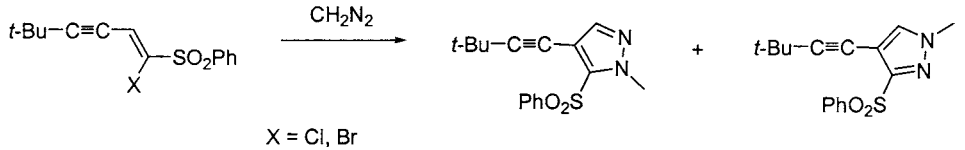


SCHEME 13

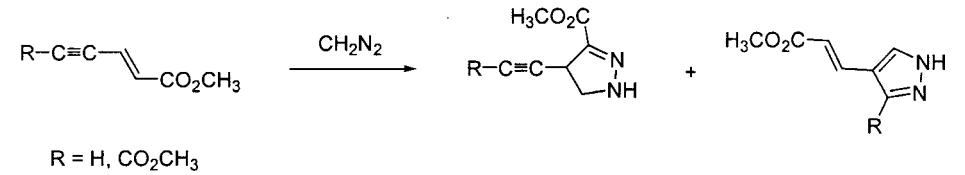
pyrazoles, accompanied by formation of the 1*H*-bis(alkynyl)pyrazole. Dehydrosulfonylation of the adducts yields 4,5-bis(alkynyl)pyrazoles (Scheme 13).

Using chloro- or bromoenines, one can immediately obtain 4-ethynylpyrazoles (omitting the stage of pyrazolenine isolation) which is accompanied by methylation and the formation of the mixture of 3- and 5-sulfonyl-1-methyl-4-acetylenylpyrazoles in about 1:2 ratio (total yield 37%) (Scheme 14).

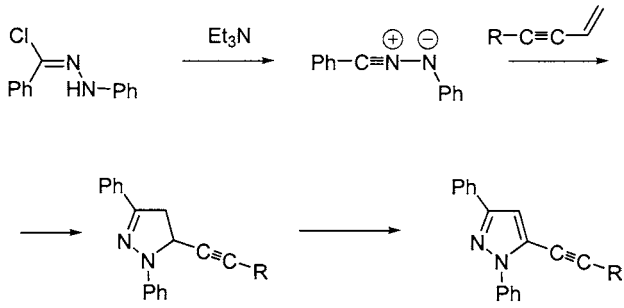
Diazomethane adds both to the double and triple bonds (the latter predominating) of the dipolarophile activated by a carbomethoxy group (68LA124) (Scheme 15).



SCHEME 14



SCHEME 15



R = H, Me, Et, Pr, *t*-Bu, CH_2-CH=CH_2, $C(Me)_2OH$, C(O)OMe, SMe, SEt, SCH_2-$CH(Me)_2$, SeMe, SeEt, TeMe, TeEt

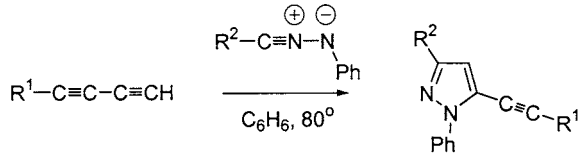
SCHEME 16

Other 1,3-dipoles, in particular, 1,3-diphenylnitrilimine (DPNI), can be used to synthesize acetylenic derivatives of pyrazole. Petrov and colleagues devoted a series of papers to 1,3-dipolar addition reactions to unsaturated compounds giving acetylenylpyrazoles (63ZOB3558; 65ZOR51; 66ZOR615). A study has been made of the cycloaddition of DPNI to vinyl-, vinylmethyl-, vinylpropyl-, vinyl-*tert*-butyl-, and vinylallylacetylenes, dimethylvinylacetylenylcarbonyl, and methyl ether of vinylpropiolic acid. It has been shown that in all cases, addition occurs to the double bond, giving rise to pyrazolines, which can be easily dehydrated with chloranil to the corresponding 5-acetylenylpyrazoles (Scheme 16).

The direction of addition, verified by acetylene oxidation into a known acid, proves that the nitrilimine carbon atom adds to the terminal atom of the enyne system, which is inconsistent with the assumed polarization of the unsaturated compound $H_2C{=}CH{-}C{\equiv}C{-}R$ from the vinyl group toward R. The authors explain this by a possible transfer of the reaction center in nitrilimine as a particle with a nucleophilic center on a carbon: $Ph{-}C{\equiv}N^{+}{-}N^{-}{-}Ph \leftrightarrow Ph{-}C^{-}{=}N^{+}{=}N{-}Ph$ (63ZOB3558).

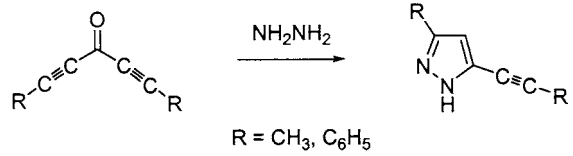
The ease with which the dipolarophile interacts with vinylacetylenes depends mainly on a spatial factor. The study of the reactions of alkylthiobuten-3-ynones-1 and their selenic and telluric analogs with DPNI shows that, in this case, nitrilimine also acts as a nucleophilic agent with a nucleophilic center on the carbon atom of the 1,3-dipole and always adds to the terminal carbon of the enyne system to form 1,3-diphenyl-5-*R*-2-pyrazolenines. The oxidation of the latter with chloranil leads to alkynylpyrazoles (65ZOR51).

The use of diacetylenic rather than vinylacetylenic compounds as dipolarophiles gives directly the aromatic heterocycle by going through the stage of aromatization. Thus, the addition of $H_5C_2OOC{-}C{\equiv}N^{+}{-}N^{-}{-}C_6H_5$ to $H_3C{-}C{\equiv}C{-}C{\equiv}CH$ yields 1-phenyl-5-prop-1-ynyl-1*H*-pyrazole-3-carboxylic acid ethyl ester (66ZOR615).



R^1 = COOEt, R^2 = Me; R^1 = COOEt, R^2 = Et; R^1 = Ph, R^2 = Et

SCHEME 17



R = CH_3, C_6H_5

SCHEME 18

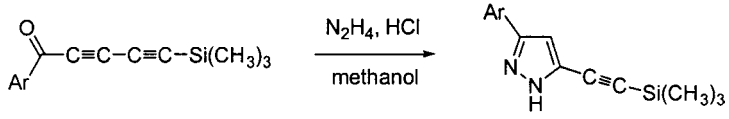
The authors reported the synthesis of 5-but-1-ynyl-1- phenyl-1*H*-pyrazole-3-carboxylic acid ethyl ester and 5-but-1-ynyl-1,3-diphenyl-1*H*-pyrazole, but they were not able to purify the compounds (Scheme 17).

Thus, the reaction of diazoalkanes and nitrilimines with diacetylenic derivatives can be used as a method for synthesizing acetylenylpyrazoles.

Another type of cyclization leading to acetylenylpyrazoles is the interaction between α-acetylenic and -diacetylenic ketones and nitrogen-containing binucleophiles.

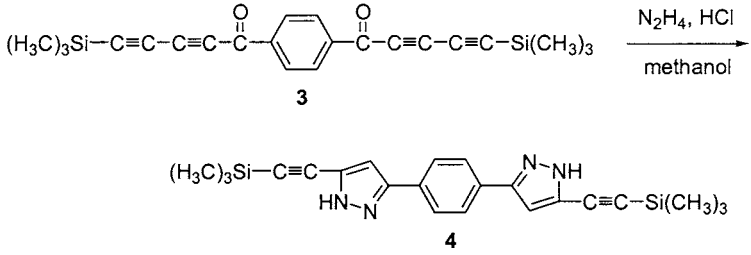
The reaction between hydrazine (usually at 0°C or room temperature in methanol or water–alcohol solution) with both α-butadiynylketones (73S47) and geminal diacetylenylketones (68LA113; 69LA117; 74JOC843) always results in 5(3)-substituted 3(5)-alkynylpyrazoles (Table V). The isomeric 1,5-diphenyl-3-pentadione with hydrazine in ethanol solution gives 3(5)-phenyl-5(3)-phenylethynylpyrazole (69LA117; 73UK511) in 79% yield (Scheme 18).

Aryl trimethylsilylbutadiynyl ketones, upon treatment with hydrazine hydrate in acidified methanol, give 3(5)-aryl-5(3)-trimethylsilylethynylpyrazoles in moderate to good yields (73S47) (Scheme 19).

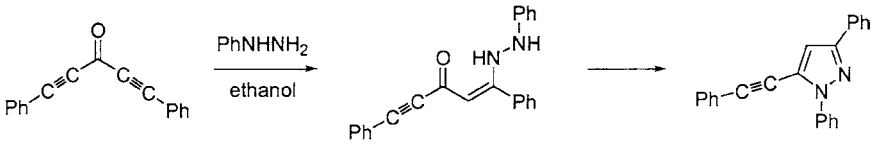


Ar = C_6H_5, *p*-Cl-C_6H_4, *p*-H_3CO-C_6H_4, *p*-NO_2-C_6H_4, 2-thienyl, 2-furanyl

SCHEME 19



SCHEME 20



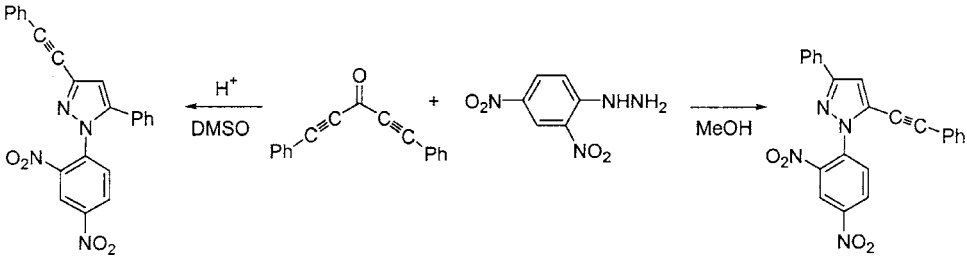
SCHEME 21

Diketone **3** is converted into dipyrazole **4** (73S47) (Scheme 20).

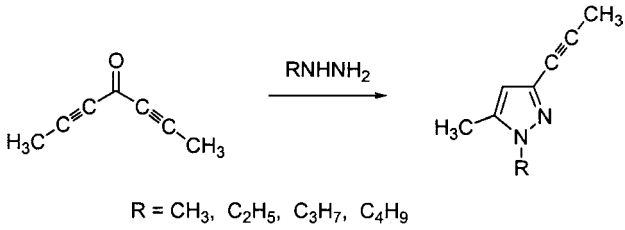
The use of substituted hydrazines, phenylhydrazine, and 2,4-dinitrophenylhydrazine (68T4285; 74JOC843) can give both 5- and 3-acetylenylpyrazole (Table VI). In this case, the direction of cyclization depends both on the hydrazine structure and the experimental conditions.

The interaction between 1,5-diphenylpentadiyn-2,4-one-1 and its aliphatic analog, 1,5-dimethylpentadiyn-2,4-one, with substituted hydrazines gives rise to a linear adduct, vinylacetylenylketone, which then cyclizes into 5-phenylethynylpyrazoles and 5-methyl-3-propynylpyrazoles in 70–90% yields, respectively (73S47) (Scheme 21).

Phenylhydrazine adds to 1,5-diphenylketone at 0°C in ethanol to give both 1,3-diphenyl-5-phenylethynyl- and 1,5-diphenyl-5-phenylethynylpyrazole, while 2,4-dinitrophenylhydrazine yields the 1,3-diaryl-5-arylethynyl derivative. In acid solution, 2,4-dinitrophenylhydrazine gives the corresponding hydrazone, which is rearranged to 3-arylethynyl isomer at high temperature (68T4285) (Scheme 22).



SCHEME 22



R = CH_3, C_2H_5, C_3H_7, C_4H_9

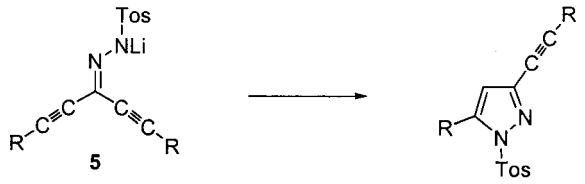
SCHEME 23

It is interesting that the cyclization of the 2,4-dinitrophenylhydrazone of the aliphatic analog, 1,5-dimethylpentadione-3, can also be performed in alkaline conditions. Heating hydrazine in boiling methanol in the presence of sodium methoxide results in 1-(2,4-dinitrophenyl)-3-propynyl-5-methylpyrazole (84%) (74JOC843).

Similarly, dipropynylketone behaves as an aliphatic analog which forms the corresponding 5-methyl-3-(1-propynyl)pyrazoles (70–90% yield) with hydrazine or monosubstituted hydrazines in methyl alcohol at room temperature (74ZOR136) (Scheme 23).

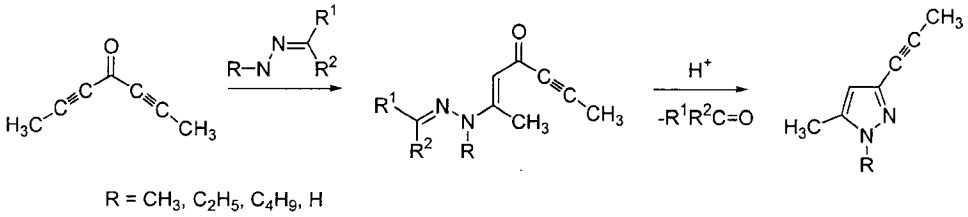
The same type of reaction occurs in the work of Hauptman (76T1293), who, studying the chemistry of diethynylcarbenes, found that the pyrolysis of the lithium salts of diethynylketone tosylhydrazones **5** (140–150°C) in the presence of olefins leads to cyclopropanes. This process results in the formation of the corresponding 3-ethynylpyrazoles. The formation of 1-*p*-tolylsulfonyl-3-alkynylpyrazoles from hydrazone runs in milder conditions (50°C, 14 h) (Scheme 24).

Although the addition of hydrazine and its derivatives to acetylenic ketones has been studied in considerable detail, their interaction with hydrazones and monoalkylhydrazones is less well known. Yandovskii and Klindukhova (74ZOR730) have studied the reaction between hydrazones and alkylhydrazones of aliphatic ketones with dipropynylketones and showed that hydrazones of acetone, methylethylketone, and cyclohexane easily add to one of the triple bonds of dipropynylketone to form 4-methyl-1,1,3-trialkyl-2,3-diaza-1,4-nonadien-7-yn-6-ones (yields

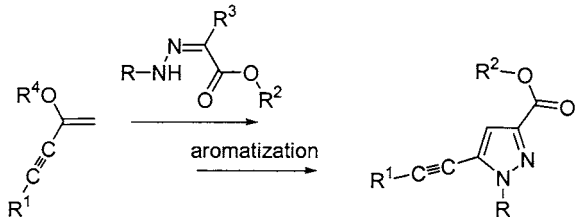


R = CH_3, $C(CH_3)_3$, $Si(CH_3)_3$, C_6H_5

SCHEME 24



SCHEME 25



SCHEME 26

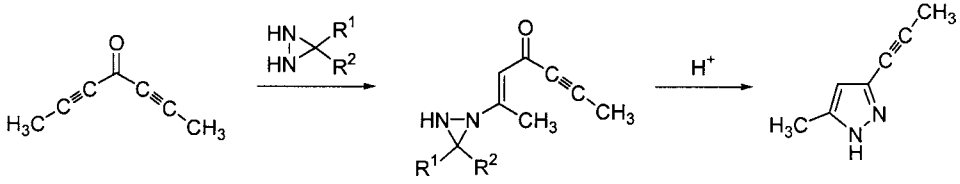
50–80%). Boiled in a water–dioxane solution in the presence of acids, these compounds turn into 1-alkyl-3-propynyl-5-methylpyrazoles (Scheme 25).

The transformation of pyrazoles causes the splitting of the C=N bond followed by cyclization of the intermediate hydrazine.

An example of the reaction of hydrazones with enynes is reported in a German patent (91GEP4001600). The alkynylpyrazoles were prepared by treating of $RNHN{=}CR^3CO_2R^2$ with $CH_2{=}CR^1OR^4$ ($R^3 = Cl$, Br; $R^4 =$ alkyl) followed by aromatization with acid (Scheme 26).

Ethynyl derivatives of 2-aryl-4,5,6,7-tetrahydroindazole were prepared from the *p*-chlorophenyl hydrazone of cyclohexanone. The hydrazone was treated with two equivalents of *n*-butyllithium at -78°C to generate the dianion, which was then quenched with the appropriate substituted ethyl ester (94MI29).

Yandovskii and Klindukhova (74ZOR1510) introduced another type of dinucleophile, 3,3-dialkyldiaziridine, to the reaction with dipropynylketone. Condensation was performed by mixing dipropynylketone with an equimolar amount of aziridine in absolute methanol at 0°C (16 h). The resulting vinylacylaziridines (50%) can lead, depending on the experimental conditions, to a linear hydrazone and cyclic alkyliden-*N*-aminopyridone and 3(5)-propynyl-5(3)-methylpyrazole (Scheme 27).



SCHEME 27

B. Elimination Reactions

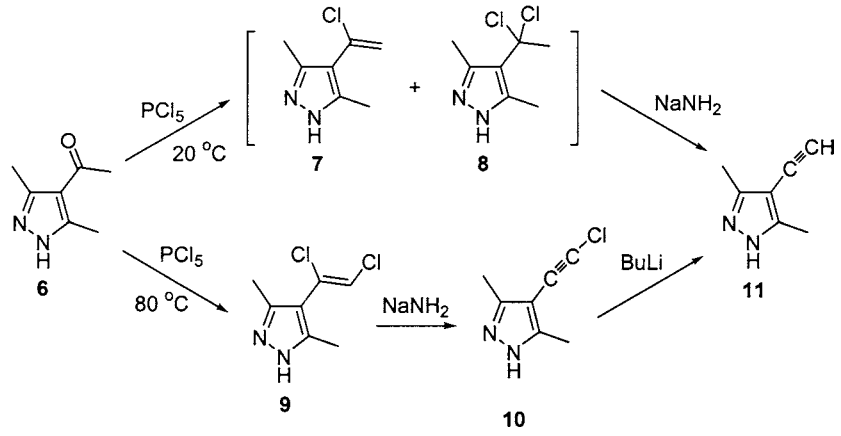
The dehydrochlorination of saturated dihalides or monohalide olefins is the usual method of elimination applied to synthesize alkyl- and arylacetylenes. The starting compounds commonly used to produce halide derivatives are, as a rule, the corresponding olefins whose interaction with halides causes the formation of *vic*-dihalides. The other ones are ketones that, during reaction with PCl_5, give a mixture of *gem*-dihalides and chlorovinyl derivatives. The preparation of acetylenic derivatives of nitrogen five- and six-membered rings by this method involves complications and the yields of desired products substantially depend on the ring structure. Thus, an attempt to dehydrobrominate pyrroledibromoacrylate under the action of sodium ethylate in alcohol failed (30LA113). The yields of all possible isomers of ethynylpyridine and ethynylquinoline obtained by the dehydrohalogenation varied from 0.1 to 33% (60CB593).

A detailed study of the transformations of methylpyrazolylketones into acetylenes under the action of PCl_5 and then a base indicates the sensitivity of these reactions to experimental conditions, the structure of the starting ketones, and the nature of the base (69IZV927; 69KGS1055; 76IZV2288).

Kotlyarevsky *et al.* (69IZV927) showed that ketones that are not substituted on the nitrogen of the ring lead to certain complications. Thus, under normal conditions (60CB593), 4-acetyl-3,5-dimethylpyrazole (**6**) gave a product containing significant quantities of the respective acetylene derivative **11** and an unexpected chloroacetylene **10.**

Variations in the reaction temperature and in the proportions of the ketone and PCl_5 were appreciably reflected in the ratio of the amounts of compound **9** obtained in the first stage to the total content of **7** and **8** and then proportionally in the composition of the final products. In the interaction of the ketones with PCl_5, an excess of the latter and high temperature make the anomalous reactions more significant. 4-(1,2-Dichlorovinyl)-3,5-dimethyl-1*H*-pyrazole (**9**) was obtained individually by the action of more than a twofold excess of PCl_5 on the acetylpyrazole **6** at 80°C in 50% yield. Under the influence of $NaNH_2$ in liquid NH_3, dichloroethylene **9** was converted into chloroacetylene **10** by loss of a molecule of HCl (yield 77%) (Scheme 28).

The elimination of hydrogen halides from dichloroethylenes as a method for the synthesis of halogenoacetylenes has not been sufficiently used owing to secondary reactions between the halogenoacetylene and bases. The exception is sodium (or lithium) chloroacetylide, which is formed almost quantitatively in the reaction of 1,2- or 1,1-dichloroethylene with sodium amide (or lithium amide) in ammonia or phenyllithium (or methyllithium) in ether (59CB1270; 59CB1950). The absence of halogen exchange side reactions in the case of 4-β-chloroethynyl-3,5-dimethylpyrazole is probably explained by the fact that the sodium salt, in the form it is obtained, is insufficiently soluble with ammonia and is similar in this respect to the chloroacetylide.



SCHEME 28

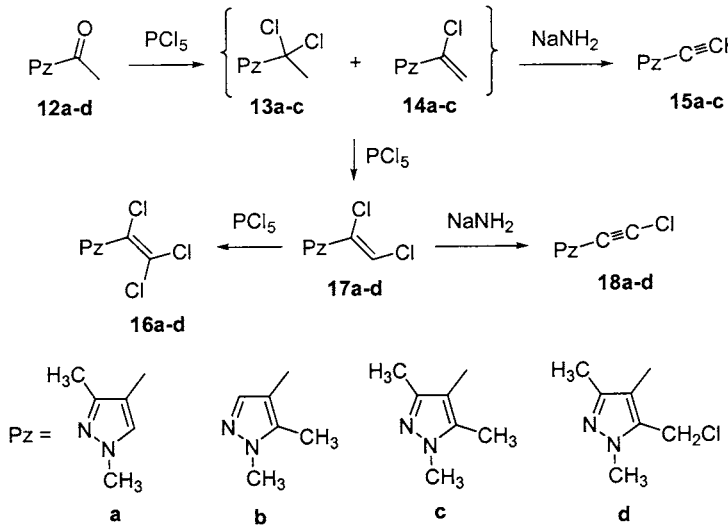
After having determined the nature of the side reaction it became clear that in order to obtain the desired ethynylpyrazole **11** the reaction between the ketone and PCl_5 would have to be performed at low temperature. Indeed, the reaction was carried out in CH_2Cl_2 at room temperature and a mixture of chlorides **7** and **8** was obtained. Dehydrochlorination of this mixture gave 66% of 3,5-dimethyl-4-ethynylpyrazole (**11**). Thus, by varying the conditions it is possible to carry out the reaction of the ketone with phosphorus pentachloride selectively in any of the above-mentioned directions.

During the investigation of the effect of the structure of the starting compound on its behavior in this reaction, it was found that N-methylated pyrazolyl ketones **12a–d** can also be converted either into the "normal" products **13a–c, 14a–c** via substitution of the carbonyl oxygen by chlorine or into the corresponding α,β-dichloroethylenes **17a–d** in 50–90% yields (76IZV2288) (Scheme 29).

The formation of the dichlorides is aided by increased temperature (60–80°C) and by an excess of PCl_5 (2–2.3 moles/mole of 4-acetylpyrazole). With a larger excess of PCl_5, further chlorination of the compounds occurs. With 3 moles of phosphorus pentachloride at 80°C in benzene, ketones **12a–d** gave pyrazolyltrichloroethylenes **16a–d** in 75% yield. Then dichlorides **17a–d** were converted quantitatively into pyrazolyltrichloroethylenes **16a–d** in 1 h under the same conditions.

Chlorination at the β position of the side chain is probably the result of phosphorylation of the intermediate vinyl chlorides followed by degradation of the phosphorus-containing products (72ZOB802).

Following the data in publications (54IZV803; 72ZOB802; 74KGS310), which indicate that the vinyl compounds are phosphorylated more readily in benzene than in $POC1_3$, the reaction was carried out in this last solvent. Accordingly, only chlorides **13a, 14a** were formed from 4-acetyl-l,3-dimethylpyrazole (**12a**) in



SCHEME 29

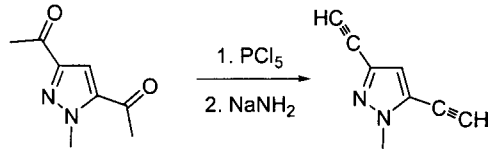
$POCl_3$, in spite of the 35% excess of PCl_5; however, it is not possible to avoid the formation of the vicinal dichloride completely in benzene, even with an equimolar amount of PCl_5.

In addition, it was clear that the presented scheme does not exhaust all the possible paths of "anomalous" chlorination. Thus, 4-acetyl-l,3,5-trimethylpyrazole with 4–5 moles of phosphorus pentachloride gave mainly 4-α,β-dichlorovinyl-5-chloromethyl-l,3-dimethylpyrazole, and its precursor (according to GLC data) was the dichloride. It could be possible that in the case of 4-chlorovinyl derivatives of pyrazole the chlorination at the β position is facilitated by the electron-donating characteristics of the 4-pyrazolyl radical (86TH1).

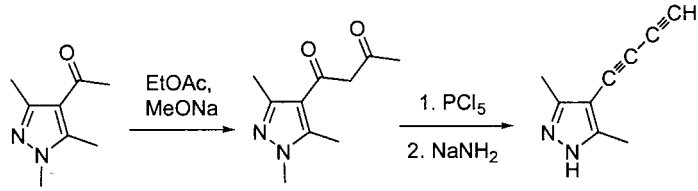
By using sodium amide in ammonia, ethynyl-*N*-methylpyrazoles **15a–c** were synthesized by dehydrohalogenation of dichlorides **13a–c, 14a–c** in 60–85% yields, calculated on acetylpyrazoles **12a–c** (Table VII).

It is known that cloroethynylpyrazoles can enter different conversions with sodium amide (see Section III.C). Vasilevsky and co-workers (76IZV2288) supposed that the rate of dehydrochlorination of vicinal dichlorides by sodium amide is higher than the rates of the subsequent processes. Indeed, by using a stoichiometric amount of the base, chloroacetylenes **18a–d** were obtained from dichlorides **17a–d** in 80–90% yields (Table VIII).

Thus, depending on the conditions, the reaction of methylpyrazolylketones with phosphorus pentachloride leads to products from substitution of the carbonyl oxygen by chlorine, α,β-dichlorovinylpyrazoles, that can be dehydrohalogenated with sodium amide to ethynylpyrazoles or to α,β-dichloroethylenes. The



SCHEME 30



SCHEME 31

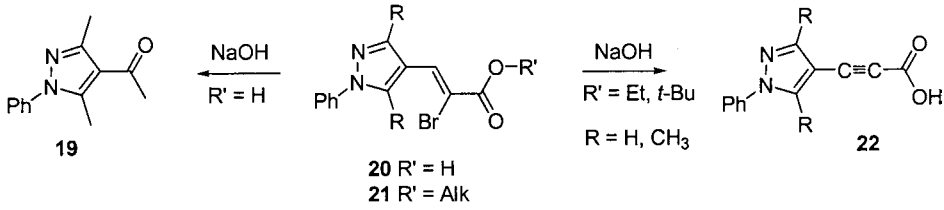
last compounds, by elimination of a molecule of hydrogen chloride under the influence of an equimolar amount of sodium amide in ammonia, give high yields of the respective 1-chloroacetylenes (Scheme 29).

The above method can also be used to simultaneously transform two acetyl groups into acetylenic ones in positions 3 and 5 of the pyrazole ring. This is demonstrated by the synthesis of 3,5-diethynyl-1-methylpyrazole (yield 62%) from 3,5-diacetyl-1-methylpyrazole (Scheme 30).

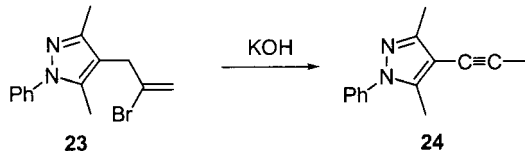
Moreover, the authors have managed to apply this synthetic Scheme to the labile and otherwise difficult-to-obtain butadiynylpyrazole, which can be prepared from 4-acetoacetyl-1,3,5-trimethylpyrazole in 36% yield (Scheme 31).

The reaction of bromine with (pyrazol-4-yl)acrylic acid and its esters and the subsequent dehydrobromination of the products have been investigated by Finar and Okoh [73JCS(P1)2008]. Attempts to dehydrobrominate bromoacrylic acids (**20**) to 3-(1-phenylpyrazol-4-yl)propiolic acids **22** failed, but were successful when bromoesters **21** were used (Scheme 32).

Popov *et al.* (75KGS1678) have described similar transformations for β-(1-methyl-3-indazolyl)-α-bromoacrylic and β-(2-methyl-3-indazolyl)-α-bromoacrylic acids (Table IX). The treatment of the bromoacrylic acids with alcohol



SCHEME 32



SCHEME 33

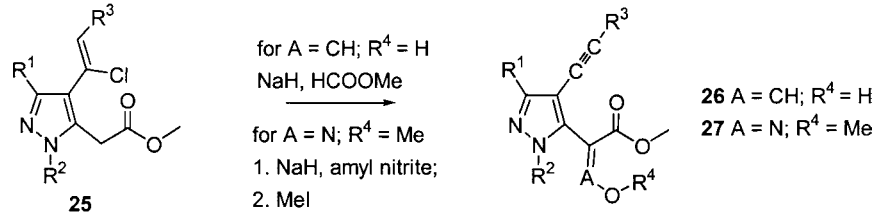
potassium hydroxide at 60°C for 2 h results in 1-methyl- and 2-methyl-3-indazolylpropynoic acids in 75% and 78% yields, respectively.

It has been shown (87KGS787) that the dehydrobromination of (2-bromopropen-3-yl)pyrazole **23** by KOH in triethyleneglycol (150°C, 0.5 h) gives the intermediate allene which is transformed into 3,5-dimethyl-1-phenyl-4-prop-1-ynyl-1*H*-pyrazole (**24**) (Scheme 33).

Eberle and Schaub (93EUP571326) describe the synthesis of a large series of 3-hydroxy-2-(2-methyl-4-prop-1-ynyl-2*H*-pyrazol-3-yl)acrylic acid methyl esters **26** and methoxyimino-(2-methyl-4-prop-1-ynyl-2*H*-pyrazol-3-yl)acetic acid methyl esters **27** by dehydrohalogenation of the corresponding chloroolefins **25** under the action of bases. In this case, the functional groups in position 5 of the pyrazole ring undergo dehydrobromination (Scheme 34).

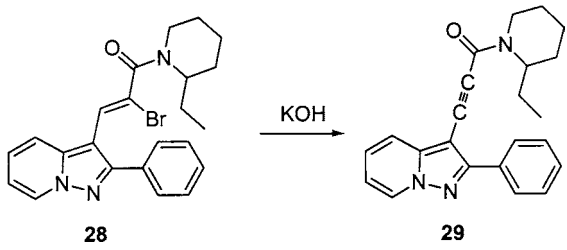
Refluxing 2-bromo-1-(2-ethylpiperidin-1-yl)-3-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)propenone (**28**) in ethanol (1.5 h) in the presence of potassium hydroxide gives disubstituted propynone **29** (Scheme 35). A number of conversions like this are described in patents (89EUP299209; 92USP5102869).

Examples of dehydrobromination leading to bromoethynylpyrazoles as illustrated by Scheme 36 are described in a patent (99USP5925769). Treatment of 1,1-dibromoolefins with tetrabutylammonium fluoride in THF at room temperature for about 24 h under N_2 gives the 1-bromo-2-(pyrazol-3-yl)acetylenes where R^1, R^2, R^3, and R^4 are independently selected from H and alkyl, alkoxy,



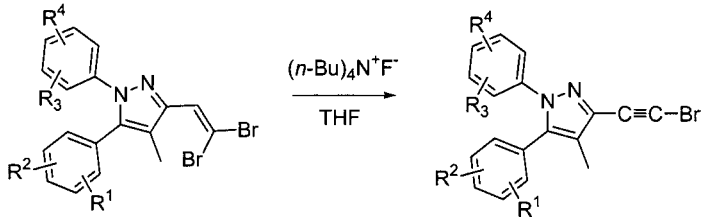
R^1 = H, alkyl, substituted aryl, CF_3; R^2 = alkyl, substituted aryl;
R^3 = substituted hydrocarbyl or heteroaryl

SCHEME 34



28 **29**

SCHEME 35

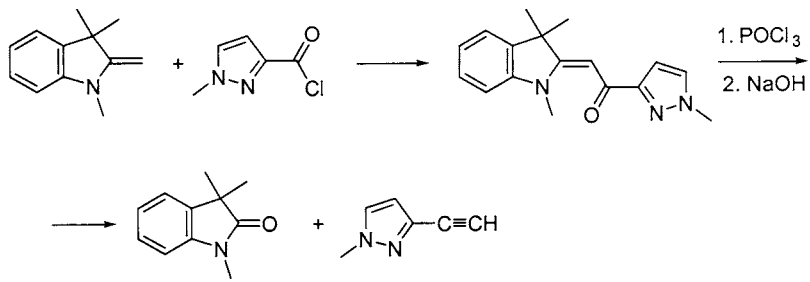


SCHEME 36

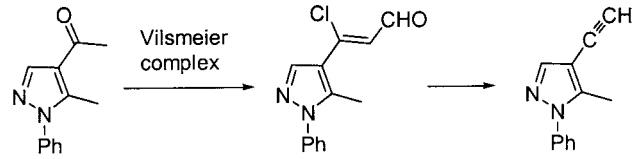
phenyl, halo, hydroxy, alkylsulfonyl, alkylthio, trihaloalkyl, amino, nitro, and 2-quinolinylmethoxy groups.

In 1987 Przhiyalgovskaya proposed an original method for producing aryl- and hetarylacetylenes by fragmentation of Fisher's acyl derivative bases (87KGS915). The enaminoketones of the indole series (Fisher bases) are readily obtained by acylation of 1,3,3-trimethyl-2-methylenindoline. Heating Fisher bases with $POC1_3$ in dioxane with subsequent action of aqueous alkali solution gives rise to oxindole and 3-ethynyl-1-methylpyrazole in 77% yield (Scheme 37).

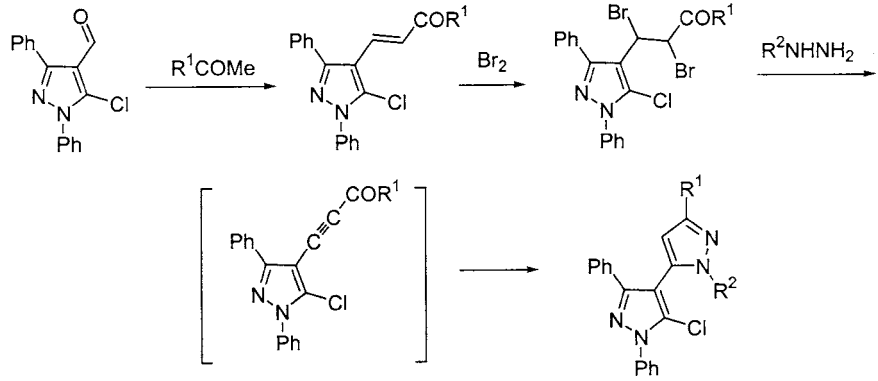
Another type of elimination reaction is the reaction of 1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone with a Vilsmeier complex to give 3-chloro-3-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)propenal, which in turn undergoes dichloroformylation



SCHEME 37



SCHEME 38



R^1 = Ph, *p*-MeC_6H_4; R^2 = Ac, Ph

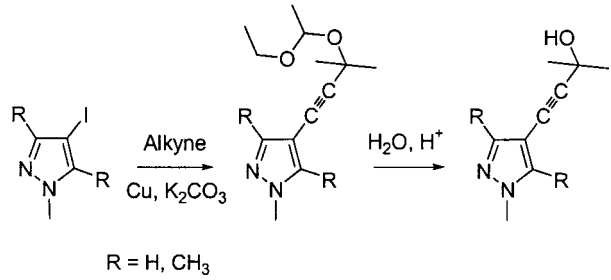
SCHEME 39

to form 4-ethynyl-5-methyl-1-phenyl-1*H*-pyrazole (Scheme 38) (77AMC135). (Polymerization of the alkyne with $PdCl_2$ afforded an oligomer which did not give an EPR signal at room temperature. Treatment of the polymer with chloranil gave a charge-transfer complex with EPR spectra.)

El-Shekeil *et al.* (88PPA25) as well as Shiokawa *et al.* (90EUP379979) reported the synthesis of alkynylpyrazoles via addition of bromine to alkene and subsequent dehydrobromination. The pyrazolylpropenones prepared by condensation of 5-chloro-1,3-dimethylpyrazole-4-carboxaldehyde with RCOMe were brominated to give the dibromides. The dibromides were treated with nucleophiles (KOH, $HONH_2$, NH_2NH_2), all of them producing the dehydrobromination, and, in the case of the two last nucleophiles, a cyclization such as that represented in Scheme 39 occurs (88PPA25).

C. Cross-Coupling of Halogenopyrazoles with Terminal Acetylenes and Their Copper(I) Salts (Tables X to XV)

In 1963 Sladkov (63IZV2213) and Castro (63JOC3313) discovered the reaction between copper acetylides and aromatic halogen derivatives. This method was of



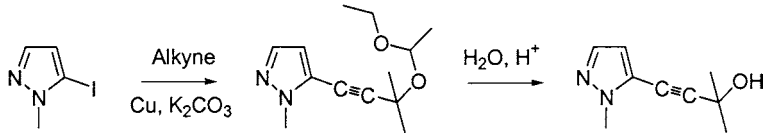
SCHEME 40

limited utility owing to the necessity of preparing explosive copper acetylides. Nevertheless, the possibility of substituting a halogen atom in pyrazoles has been shown using 3-, 5-, and even the less active 4-iodopyrazoles containing substituents of both acceptor and donor character in the ring (77IZV2306; 83IZV688; 86MI1; 90IZV2089). The cross-coupling of iodopyrazoles with copper salts of terminal acetylenes is carried out in boiling pyridine or dimethylformamide. The reaction takes 9–18 h, the product yields amount to 70–90%. For the activated 1-methyl-3-nitro-4-iodopyrazole the time of condensation with copper phenylacetylide is 1.5 h and the product yield is 94% (86MI1).

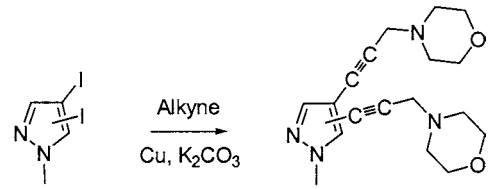
In 1971, two publications reported new experimental conditions for the synthesis of acetylenic derivatives of pyrazole (71IZV1764; 72IZV2524), which are based on the catalytic replacement of halogen in aromatic rings by acetylenic moieties (69MIP1). 1-Prop-2-ynylpiperidine and 3-(1-ethoxyethoxy)-3-methylbut-1-yne (acetal of 2-methylbut-3-yn-2-ol) were used as the starting terminal acetylenes (71IZV1764; 72IZV2524).

It should be noted that these were the first examples of the Cu-catalyzed cross-coupling of arylhalides with terminal acetylenes. The authors (71IZV1764) carried out the acetylenic condensation with unreactive 4-iodo-l,3,5-trimethylpyrazole, a compound in which the halogen atom is not only found in a position more unfavorable for replacement, but is also further deactivated by the introduction of electron-donor methyl groups (Scheme 40).

For comparison, the cross-coupling of the presumably more active 5-iodo-1-methylpyrazole with alk-1-ynes was carried out (Scheme 41).



SCHEME 41



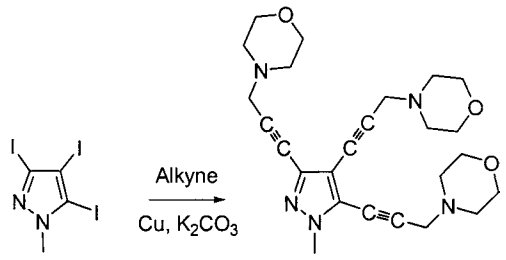
SCHEME 42

The cross-coupling was run in refluxing pyridine, under argon atmosphere, in the presence of K_2CO_3 and copper. The 5-iodopyrazole proved to be much more reactive than the 4-iodopyrazole. The latter reacted with the acetal alkyne to the extent of only 55% for 23 h, while the reaction of 5-iodo-1-methylpyrazole under the same conditions was completed in 9 h. It is noteworthy that no tarring of the reaction mixture was observed despite the long heating, and the yield of the alkynylpyrazoles reached 90%.

To ascertain the possibility of inserting more than one acetylenic moiety into the pyrazole ring, the replacement of two and three iodine atoms in the appropriate halides by different alk-1-ynes was carried out. To increase the total rate, the cross-coupling of diiodopyrazoles and triiodopyrazole was performed with higher initial concentrations of the reactants than for the monoiodides. The reaction of diiodopyrazoles with the acetal was completed for the most part in 40 h, and in 64 h in the case of triiodopyrazole. The yields of the di- and triacetals reached 70–90% (Table XIII).

A number of di- and tri-(3-*N*-morpholinopropyn-1-yl)-1-methylpyrazoles were prepared by the condensation of corresponding iodopyrazoles with 4-prop-2-ynylmorpholine in presence of Cu(0), K_2CO_3 in boiling pyridine, but without palladium catalyst. Despite the low activity of this catalytic system and the long condensation time (75–95 h) the yield of 3,4-di-, 4,5-di-, and 3,4,5-tri-(3-*N*-morpholinopropyn-1-yl)-1-methylpyrazoles reached 70–80% (Schemes 42 and 43).

The main disadvantage of the method is the prolonged heating of the mixture at high temperature.



SCHEME 43

New experimental conditions for the catalyzed cross-coupling reaction were proposed in 1975 by Heck [catalyst $PdCl_2(PPh_3)_2$], Cassar [catalyst $Ni(PPh_3)_3$ or $PdCl_2(PPh_3)_2$] (75JOM253,75JOM259), and Japanese investigators (75TL4467), who suggested the new effective catalytic system $PdCl_2(PPh_3)_2$/CuI for introducing an acetylenic moiety into arenes and hetarenes. From the various articles dealing with Pd/Cu-catalyzed cross-couplings of acetylenes with sp^2-halides, it may be concluded that this reaction has a very broad scope (98MI1).

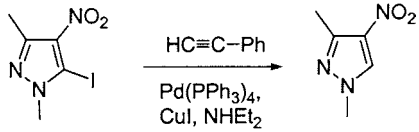
Beginning with the discovery of these methods, the cross-coupling of arylhalides with monosubstituted acetylenes or their copper salts remains the main method for producing aryl- or hetarylacetylenes. The catalytic variant of Sonogashira–Heck is most effective (75TL4467; 82ACS(B)101; 98MI2). Indeed, this method was used for preparing different acetylenylpyrazoles. This reaction needs no preparation of explosive copper acetylides and often occurs at room temperature.

The reactivity of arylhalides in the acetylenic condensation sharply decreases in the series Ar—I, Ar—Br, Ar—Cl. The rate of reaction of phenylacetylene with iodo derivatives is 800 times higher than that of the reaction with bromo derivatives and is 10^5 higher than that of the reaction with corresponding chlorides (75JOM253). Taking into account the very low activity of halogenopyrazoles (66AHC347), the catalytic variant of acetylenic condensation mainly involves the most active iodo derivatives.

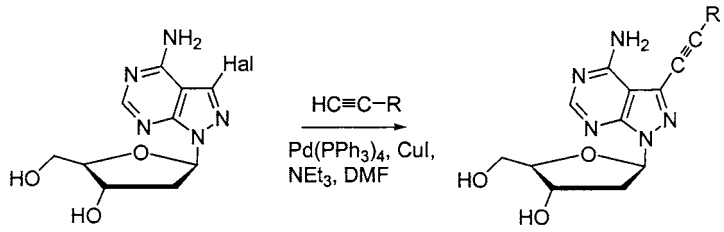
Similarly, the limitations and peculiarities of the cross-coupling of pyrazolylhalides with terminal acetylenes have been fully and systematically studied by Russian chemists (86TH1; 97TH1).

As expected, the 5-halogen derivatives are more active (83IZV688; 85MI1; 90IZV2089; 92IZV507) than are 3- or 4-iodopyrazoles. The influence of the nature of the substituent in position 4 of the ring conjugated with the halogen atom in position 5 on the rate of the cross-coupling reaction has been investigated. As halide component, these authors have chosen 5-iodo-1,3-dimethylpyrazole and its derivatives with a substituent in position 4 of both acceptor (NO_2, Cl, Br, $CONH_2$) and donor character (NHAc, NH_2). Terminal alkynes HC≡CR where R = alkyl, aryl, including bifunctional *p*-diethynylbenzene were used as the acetylenic component. Electron-withdrawing substituents increase the rate of cross-coupling (Table X).

It is noteworthy that the only deiodinated product (4-nitro-1,3-dimethylpyrazole) was isolated in a 70% yield (86TH1) by cross-coupling phenylacetylene with 5-iodo-4-nitro-1,3-dimethylpyrazole (Scheme 44).



SCHEME 44



30 Hal = Br,
31 Hal = I

SCHEME 45

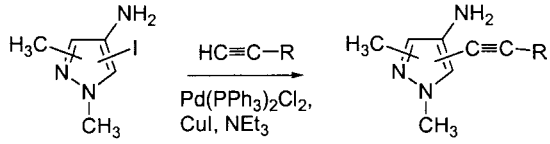
A similar phenomenon was observed for 3-amino- and 5-amino-4-iodopyrazoles. The anomalous reaction in which the products of oxidative coupling of terminal acetylenes (up to 90%) are present along with the products of deiodination (up to 90%) has been described for the first time [99JCS(P1)3713] and will be considered below in the part related to cross-coupling of 4-iodopyrazoles.

The next group of halogeno derivatives consists of 3-iodopyrazoles whose activity is close to that of 5-halogen derivatives (90IZV2089). Vicinal 3-iodopyrazoles containing carboxyl, carbamine, *N*-acetylamino, and amino groups were introduced for cross-coupling under standard conditions (75TL4467). The reaction time was varied within small limits (5–13 h) and was actually dependent on the structure of the terminal acetylenes. The yields of 3-acetylenylpyrazoles were 55–75% (Table XI).

Fusion of the pyrazole ring with a π-electron-deficient diazine ring leads to an increase in the reactivity of halogenopyrazoles [97INP9723480; 97NN821; 98JCS(P1)3233; 98USP5760028; 99HCA1640; 99JCS(P1)479; 2000HCA910]. A large series of oligonucleotides containing acetylenylpyrazolo[3,4-*d*]pyrimidines were synthesized by cross-coupling reaction by Seela *et al.* [97NN821; 98JCS(P1)3233; 99HCA1640; 99JCS(P1)479; 2000HCA910]. The iodo derivatives **31** were shown to be much more active than their bromo analogs **30** (Scheme 45). In the first case, the reaction runs for 4–7 h at room temperature. In the second case, it needs heating (45°C, 48 h or 70°C, 6 h). Note that in both cases, the tenfold excess of terminal acetylenes was used instead of the usual 20–30% (Table XV).

Special attention has been given in the literature to the preparation of alkynylpyrazoles with electron-donating substituents connected with the pyrazole ring [99JCS(P1)3713]. Both 3- (**32**) and 5-iodo derivatives (**33**) underwent successful coupling with either *p*-nitrophenyl- or phenylacetylene using $Pd(PPh_3)_2Cl_2$/CuI as catalyst in hot triethylamine under argon atmosphere. The reactions were completed within 0.5–4 h at 80°C, depending on the acetylene reactivity, and gave the alkynylaminopyrazoles in moderate to good yields (Scheme 46).

However, attempts to carry out similar couplings between iodoaminopyrazoles **32** and **33** with more electron-rich alk-1-ynes, specifically *p*-methoxyphenylacetylene and oct-1-yne under the same conditions but for 40 h, were unsuccessful; up to



32 3-I,
33 5-I

R = 4-O_2N-C_6H_4, C_6H_4

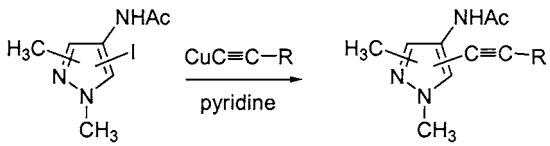
SCHEME 46

76% of the starting iodopyrazoles was recovered. Some authors [99JCS(P1)3713] tried to avoid these difficulties by applying the alternative Stephens–Castro reaction (63JOC3313) of preformed copper *p*-methoxyphenylacetylide and oct-1-ynide to obtain alkynylaminopyrazoles. However, reactions between iodopyrazoles **32** and **33** and the copper acetylides in refluxing pyridine (63JOC3313) gave a large number of products and a more intractable polymer. These complications were avoided by protection of the aminopyrazoles as the corresponding *N*-acetyl derivatives. The resulting (*N*-acetylamino)iodopyrazoles **34** and **35** coupled smoothly with the copper acetylides in pyridine at 110–115°C. The reactions required 4–10 h for completion; a similar coupling of iodobenzene with copper phenylacetylide required 10 h at 115°C (63JOC3313) (Scheme 47).

Note that iodopyrazoles **34** and **35** did not react with *p*-methoxyphenylacetylene and oct-1-yn in the presence of $Pd(PPh_3)_2Cl_2$ and CuI in boiling triethylamine. Only by using the more reactive *p*-nitrophenyl- or phenylacetylene, were the desired alkynylpyrazoles obtained in these conditions.

Thus, the rate of Pd-catalyzed couplings between 4-aminoiodopyrazoles and alk-1-ynes depends upon the electronic character of the acetylenic substituent, and an approximate criterion for choosing the method of coupling is the acidity of the alk-1-yne component (84IZV923). It can be concluded that terminal alkynes with $pK_a < 29$ (CH acidity of phenylacetylene) are able to undergo Heck–Sonogashira couplings using the $Pd(PPh_3)_2Cl_2$/CuI/Et_3N system with derivatives of 3- and 5-aminoiodopyrazoles. The synthesis of the same iodopyrazoles with less acidic alkynes ($pK_a > 29$), however, requires the use of the copper acetylide method and, for maximized yields, acetylation of the amino group.

The largest group of acetylene derivatives consists of 4-alkynylpyrazoles owing to the accessibility of the starting 4-iodo derivatives. On the other hand, because



34 3-I,
35 5-I

R = 4-MeO-C_6H_4, *n*-C_6H_{13}

SCHEME 47

of the high electron density in position 4 of the ring, the substitution of halogen atoms is more difficult. Therefore, the starting 4-halogeno derivatives often contain electron-withdrawing groups in the pyrazole ring and the duration of their reaction with terminal acetylenes is almost the same as that for 3- and 5-iodo derivatives.

Thus, Coilla described (96BMCL1279; 96MCR293) the synthesis of 1-(3,4-bisbenzoyloxy-5-benzoyloxymethyltetrahydrofuran-2-yl)-4-trimethylsilanylethynyl-1*H*-pyrazole-3-carboxylic acid methyl ester by a coupling reaction between the corresponding 4-iodo derivatives with trimethylsilylacetylene with a catalytic amount of bis(triphenylphosphine) palladium dichloride and CuI in triethylamine at 80°C for 2 h (yield 91%).

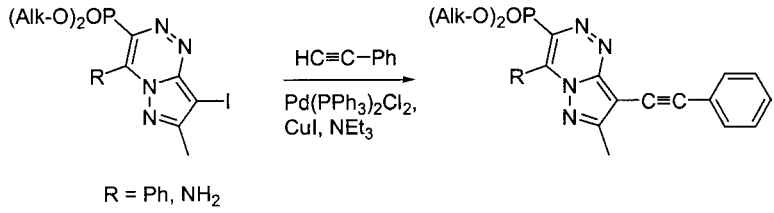
The reaction time between 4-iodopyrazoles and 1-alkynes varies from 5 to 25 h and the yield of products is 55–95%. It is noteworthy that the nature of the terminal acetylene has a greater effect on the rate of halogen atom substitution for low-reactive 4-iodopyrazoles. Thus, the reaction time for ethynylarenes is 5–6 h, and for less acidic aliphatic 1-alkynes is 10–25 h (Table XII).

Similarly, fusion of the pyrazole ring with a π-electron-deficient diazine ring leads to an increase of the reactivity of the halogenopyrazole. Thus, Neidlein showed (99H513) that (7-methyl-8-phenylethynylpyrazolo[5,1-*c*][1,2,4]triazin-3-yl)phosphonic acid dialkyl ester could be prepared by the Heck–Sonogashira reaction with corresponding 8-iodo derivatives in the presence of $Pd(PPh_3)_2Cl_2$ and CuI in $(i\text{-Pr})_2NH$ at 70–84°C (Scheme 48).

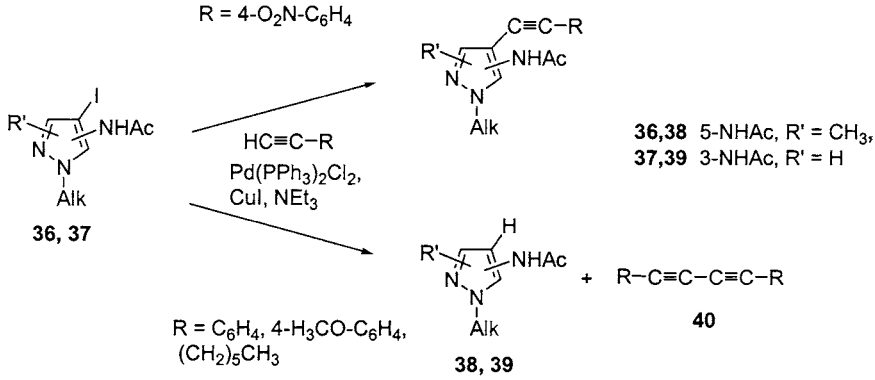
Amino-4-iodopyrazoles demonstrate the lower reactivity of the iodine atom in halogenopyrazoles. Iodopyrazoles **36** and **37** were coupled with *p*-nitrophenylacetylene in Et_3N in the presence of $Pd(PPh_3)_2Cl_2$ and CuI at 80°C to give good yields of the *N*-acetyl 4-alkynylpyrazoles (Scheme 49).

However, attempts to couple (*N*-acetyl)-4-iodopyrazole **36** under the same conditions with phenylacetylene, *p*-methoxyphenylacetylene, and oct-1-yne, once again, were unsuccessful, instead, reductive deiodination to give 5-(*N*-acetylamino)-3-methyl-1-ethylpyrazole and homo-coupling of alk-1-yne occurred (Scheme 49). The isomeric 3-(*N*-acetylamino)pyrazole **37** was somewhat less inclined to deiodination.

Similarly, the cross-coupling of N-protected 4-ethynylpyrazole with 1-(1-ethoxyethyl)-4-iodo-1*H*-pyrazole leads only to disubstituted butadiyne (2001UP1) (Scheme 50).



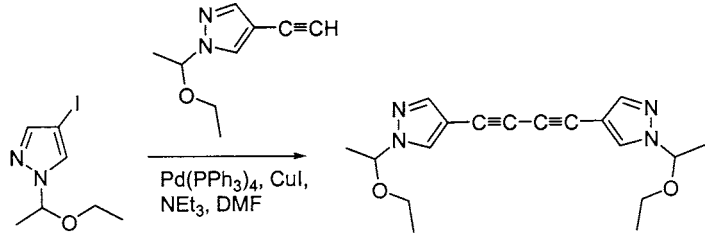
SCHEME 48



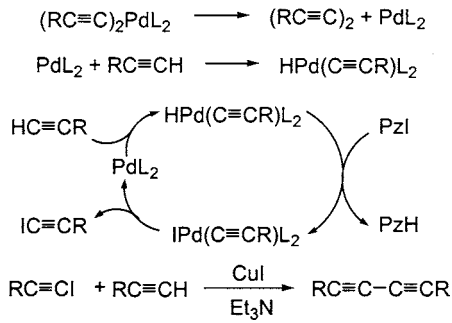
SCHEME 49

Therefore, the Pd/Cu-catalyzed cross-coupling of acetylenes with 3- and 5-(*N*-acetylamino)-4-iodopyrazoles is complicated by reductive deiodination. According to the generally accepted mechanism, this catalytic cross-coupling involves initial reaction of the precatalyst and copper acetylide with the formation of bis(triphenylphosphine) dialkynylpalladium(II), which decomposes to give bis(triphenylphosphine)palladium(0) and the "dimeric" acetylene (98MI1). In such reactions, the homo-coupled product is formed in amounts corresponding to the quantity of the precatalyst used.

It was found [99JCS(P1)3713] that, in all cases, the formation of the deiodinated products **38** and **39** was accompanied by formation of the diynes **40** which were isolated in 60–90% yield. The authors believed that the mechanism of deiodination may be represented as an interaction ofbis(triphenylphosphine)phenylethynylpalladium(II) hydride with the 4-iodopyrazole, giving rise to the bis(triphenylphosphine)phenylethynyl palladium(II) iodide complex which, due to the reductive elimination of 1-iodoalkyne and subsequent addition of alk-1-yne, converts into the initial palladium complex. Furthermore, the interaction of 1-iodoalkynes with the initial alkyne in the presence of CuI and Et_3N (the Cadiot–Chodkiewicz reaction) results in the formation of the observed disubstituted butadiynes **40** (Scheme 51).



SCHEME 50

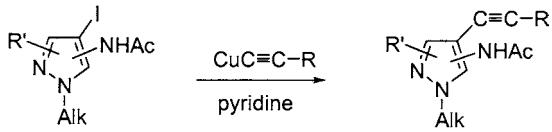


SCHEME 51

Taking into account the differences in the mechanisms of the Cu- and Pd-catalyzed coupling reactions, some authors [99JCS(P1)3713] suggested that the foregoing difficulties might again be overcome by resorting to the Stephens–Castro copper acetylide method (63JOC3313) to access the 3- and 5-(*N*-acetylamino)-4-alkynylpyrazoles. Thus, iodides **36** and **37** were treated with copper acetylides in pyridine at 110–115°C. Under these conditions, both iodopyrazoles were again relatively unreactive: couplings with copper acetylides required 14–18 h. However, generally good yields of the coupled products were secured (Scheme 52 and Table XIV).

Thus, cross-coupling of 3- and 5-(*N*-acetylamino)-4-iodopyrazoles using the Pd(0) complex occurred only with relatively high CH-acidic acetylenes, and the more vigorous copper acetylide method for halide substitution by an acetylene group is evidently more general. However, condensation of aryl halides with a functional group in the vicinal position can often be followed by cyclization of the primary reaction products (see Section III.D). The foregoing syntheses of *vic*-aminoalkynylpyrazoles were possible owing to their low reactivity in such cyclizations, probably due to the strain inherent in a condensed system consisting of two five-membered heterocycles. However, cross-coupling of iodopyrazole **36** with copper *p*-phenylbenzoylacetylide **41** gave pyrrolo[2,3-*c*]pyrazole **42** directly; presumably, cyclization is aided by the ketone group (Scheme 53).

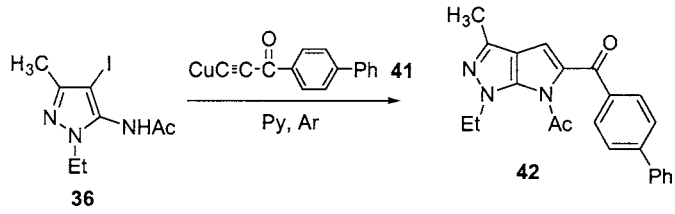
Production of nitrogen-unsubstituted acetylenyl compounds is a special case in the reactions of cross-coupling in the pyrazole series.



36, 37

R = C_6H_4, 4-H_3CO-C_6H_4, $(CH_2)_5CH_3$

SCHEME 52



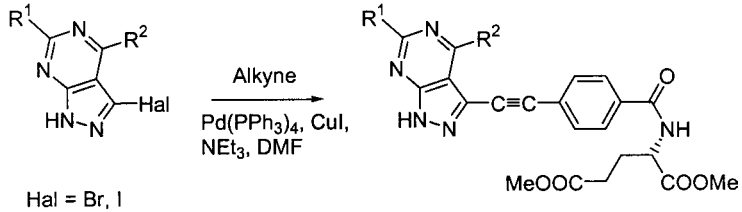
SCHEME 53

The cross-coupling of nitrogen-unsubstituted activated halogenopyrazoles with alk-1-ynes proceeds without complication. Thus, a series of ethynylated 7*H*-pyrazolo[3,4-*d*]pyrimidines was prepared (92T8089) by palladium-catalyzed C—C coupling of dimethyl *N*-(4-ethynylbenzoyl)-L-glutamate with the corresponding 5-bromo- or 5-iodo-4(3*H*)-oxo-7*H*-pyrazolo[3,4-*d*]pyrimidines in the presence of tetrakis(triphenylphosphine)palladium(0), CuI, and triethylamine in DMF (Scheme 54). It should be noted that bromo derivatives require more vigorous reaction conditions (3–18 h at 105–110°C, yields 45–60%) than iodopyrazole (3.5 h, at 85°C, yield 75%).

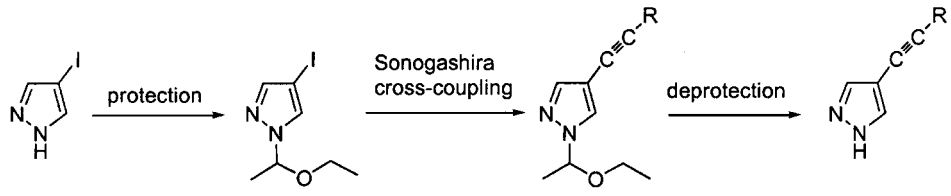
4-Bromo- and 4-iodopyrazoles do not react with terminal acetylenes under the standard conditions of the Heck–Sonogashira reaction in the presence of organic bases and solvents [82ACS(B)101]. But when the nitrogen atom is substituted, C-alkynylation can occur. If the N substituent can be later removed, it serves as a protecting group for the pyrazole N—H. From the synthetic point of view, the value of a protecting group should be judged by its availability and by its ease of introduction and removal under mild conditions that do not damage other sensitive functionalities.

In the course of the investigation of methodologies for the protection of iodopyrazoles during acetylenic cross-coupling, different authors have been seeking protecting groups that satisfy the criterion that both protection and deprotection occur efficiently under mild conditions.

An interesting example is given in article (96BMCL797). The 4-iodo-(1-*t*-Boc)pyrazole and 4-iodo-(1-MEM)pyrazole were introduced into a cross-coupling



SCHEME 54



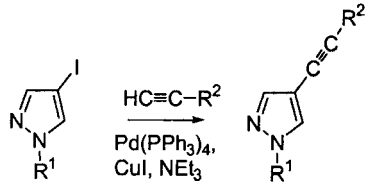
R = C_6H_5, 4-CHO-C_6H_4, $(CH_3)_2OH$

SCHEME 55

reaction with bis-alkynylcyclic urea in the presence of tetrakis(triphenylphosphine) palladium(0)/CuI in Et_2NH. The protecting group manipulations were employed to improve isolated yields.

Some of us have found a successful methodology using ethyl vinyl ether as a protecting group for the heterocyclic NH of pyrazole in the synthesis of alkynylpyrazoles (2001UP1). The reaction sequence consists of three stages: protection, main reaction (catalytic deiodoalkynylation), and deprotection. The protecting group is readily introduced by reaction of 4-iodopyrazole with ethylvinylic ether in benzene at 20°C. The cross-coupling is carried out in benzene at 60–70°C by treatment with 1-alkynes in the presence of $Pd(PPh_3)_2Cl_2$ and CuI. Deprotection is accomplished readily by the acid-catalyzed hydrolysis of the resulting alkynylpyrazoles to give the desired N-unsubstituted alkynylpyrazoles in acceptable overall yield on 4-iodopyrazole (Scheme 55).

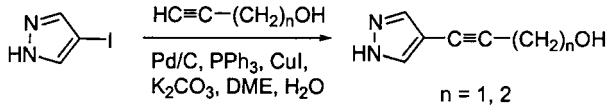
It should be noted that a considerable acceleration of the reaction for low-reactive 4-iodopyrazoles is observed for substrates in which acceptor substituents at the pyrazole nitrogen atom additionally play the role of protecting group. Thus, it has been shown (88M253) that *N*-phenacyl- and *N*-*p*-tosyl-4-iodopyrazoles interact with phenylacetylene, 2-methyl-3-butyn-2-ol, and trimethylsilylacetylene at room temperature for 3–24 h in 70–95% yields (Scheme 56).



R^1 = PhC(O), *p*-Tosyl

R^2 = Ph, $C(CH_3)_2OH$, $Si(CH_3)_3$

SCHEME 56



SCHEME 57

A similar acceleration owing to the influence of N-electron-withdrawing group was observed by other authors (87USP4663334) for *N*-acetyl-4-iodopyrazole in the reaction with alkynes [$Pd(PPh_3)_2Cl_2$, CuI, triethylamine, THF, room temperature, 1 h, 20°C].

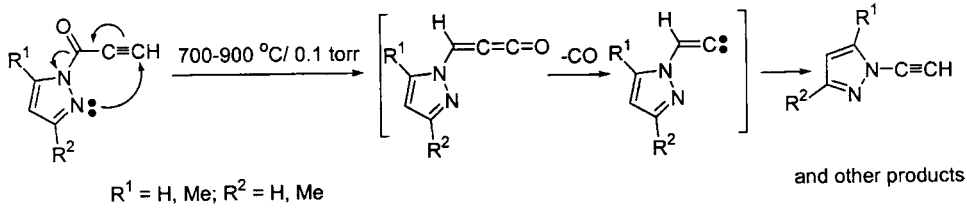
Cosford (95SL1115; 99BMCL2815) and others (98MO76) applied to 4-iodopyrazole the De la Rosa method (90SC2059) based on cross-coupling of arylhalogenides with 1-alkynes in catalytic system Pd/C, PPh_3, and CuI at a rate of 1:4:2 with 2.5 equivalents of K_2CO_3 in DME, H_2O 1:1, at 80°C. Yields of 4-(4-hydroxybutyn-1-yl)pyrazole and 4-(3-hydroxypropyn-1-yl)pyrazole were 85% and 60%, respectively. It should be emphasized that when the above-mentioned method is used with heterogeneous palladium (10% Pd/C) and 1,2-dimethoxyethane (DME) combined with aqueous potassium carbonate, the protecting group and the expensive and air-sensitive reagent $Pd(PPh_3)_2Cl_2$ can be avoided (Scheme 57).

Thus, the Castro (63JOC3313) and the Heck–Sonogashira cross-couplings (75TL4467; 91COS521) are very attractive methods for obtaining the different alkynylpyrazoles.

D. PYROLYSIS

The pyrolysis of 1-propynoylpyrazoles gives alkynylpyrazoles (85TL6373; 94AJC991). The peculiarity of these compounds is that the ethynyl group is bound to nitrogen atoms. Flash vacuum pyrolysis (FVP) of 1-propynoylpyrazole at 700–900°C/0.1 torr gives 1-ethynylpyrazole in low yield (Scheme 58).

Ring-methylated 1-ethynylpyrazoles were similarly obtained as minor products in the pyrolysis of 3,5-dimethyl- and a mixture of 3- and 5-methyl-1-propynoylpyrazoles. Pyrolysis of the 3-methyl derivative gave only pyrazolo[1,5-*a*]pyridin-5-ol



SCHEME 58

with a trace amount of an *N*-ethynylpyrazole, whereas the 5-methyl precursor gave a mixture of pyrazolo[1,5-*a*]pyridin-5-ol (4%), 3-methylpyrazole (19%), 1-ethynyl-3-methylpyrazole (11%), and 1-ethynyl-5-methylpyrazole (12%).

III. Chemical Properties of Acetylenylpyrazoles

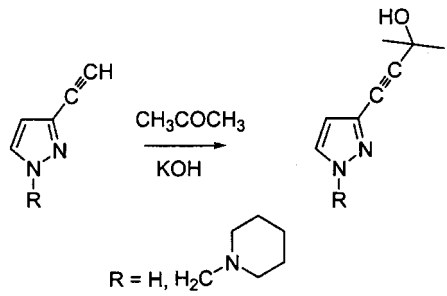
A. Reactions of Terminal Acetylenes with Participation of the C–H Bond

The high acidity of ethynylpyrazoles (pK_a 24.0–30.4; 92IZV507) determines the high reactivity of the terminal acetylenes and offers the possibility of obtaining a great number of the functionally substituted pyrazolylacetylenes.

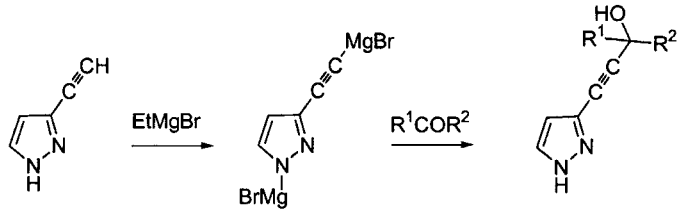
1. *The Favorsky Reaction*

The Favorsky reaction, the interaction between terminal acetylenes and carbonyl compounds in the presence of powdered dry KOH, is of limited importance for the pyrazole series, although the hydroxyacetylenic group is one of the most important protecting groups. However, most often, such an alcoholacetylenic substituent is introduced by direct alkynylation of the corresponding iodopyrazoles with 2-methyl-but-3-yn-2-ol (see Section II.C).

A typical technique of the Favorsky reaction is the interaction between terminal acetylene with a 2–3-fold excess of carbonyl compound and a 4-fold excess of dry KOH in ether at 0–20°C (Table XVI). The Favorsky reaction includes both the nitrogen-unsubstituted and -substituted ethynylpyrazoles (68KGS695; 69KGS1055). The interaction of 1-methyl-3-ethynylpyrazole and 1-(*N*-piperidino) methyl-3-ethynylpyrazole with acetone in the presence of KOH (0–20°C) results in the corresponding acetylenic alcohols in 62.5 and 68.5% yields. Under similar conditions, the nitrogen-unsubstituted 3(5)-ethynylpyrazole is obtained from acetylbenzene and the α-acetylenic alcohol in 77.5% yield (Scheme 59).

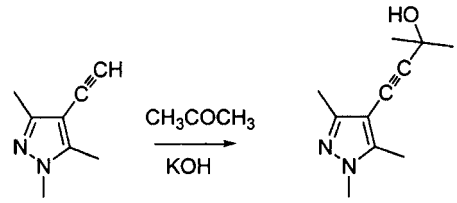


SCHEME 59



$R^1 = R^2 = CH_3$; $R^1 = CH_3$, $R^2 = Ph$;
$R^1 = CH(CH_3)_2$, $R^2 = H$

SCHEME 60



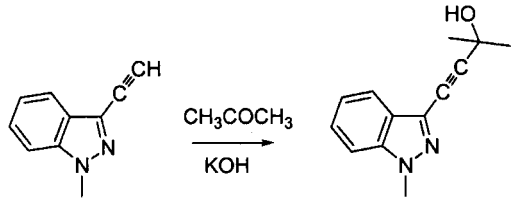
SCHEME 61

The same alcohols can be produced using the Iotzich method by boiling the Iotzich complex (ethynyl magnesium or lithium compound in ether) with a small excess of carbonyl compound. However, the yields of the alcohols obtained by this method are somewhat lower (47–53%) (68KGS695) (Scheme 60).

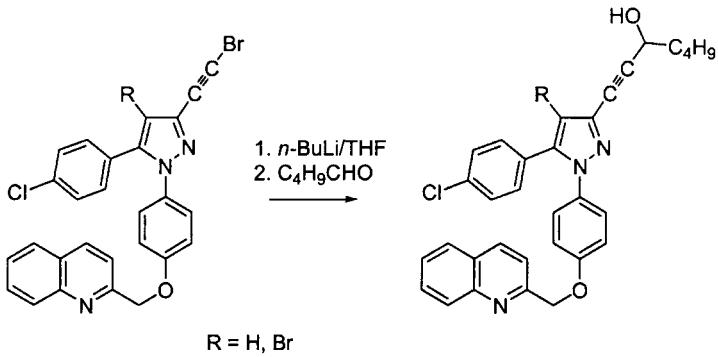
The Favorsky reaction should be considered a general method for producing pyrazolyl-α-acetylenic alcohols because even the less reactive 4-ethynyl-1,3,5-trimethylpyrazole, additionally deactivated by three donor methyl groups, reacts with acetone (Scheme 61).

Under similar conditions, 1-(1-methyl-3-indazolyl)-3-methylbutyne-1-ol-3 (78KGS1535) was synthesized in 93% yield from 1-methyl-3-ethynylindazole (Scheme 62).

Acetylenic alcohols can be obtained using another technique from bromacetylene with subsequent action of butyllithium and carbonyl compound (Scheme 63).



SCHEME 62



SCHEME 63

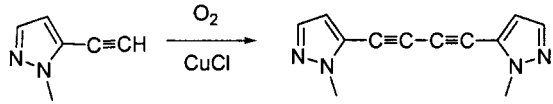
This Scheme was used to prepare a number of pyrazolylacetylenic alcohols (Table XVII).

Note that alcohol protection has lost its significance with the appearance of trimethylsilyl protection of the terminal acetylenic proton owing to the mild conditions of its removal and the high yields of the products.

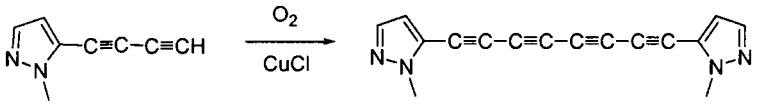
2. *Homo-Coupling*

As compared with the Chodkiewicz–Cadiot reaction, the oxidative coupling of enthynylpyrazoles by the Franke–Meister–Hay method (CuCl, pyridine–methanol, 40°C) (57USP2796442; 60JOC1275) allows synthesis of symmetric dipyrazolylbutadiynes (69IZV2546; 69KGS1055). The homo-coupling reaction has been used to prepare a number of di(pyrazolyl)butadiynes (Table XVIII). The oxidative condensation runs in high yield, and 3-ethynyl-1-methyl- and 4-ethynyl-1,3,5-dimethylpyrazole form dehydrodimers in 70% and 90% yields (69IZV2546; 69KGS1055) (Scheme 64, Table XVIII).

It has been shown that even the labile monosubstituted butadiynyl derivatives can be used as the starting terminal alkynes. Thus, the oxidative coupling of 3-butadiynyl-1-methyl-, 5-butadiynyl-1-methyl-, and 4-butadiynyl-1,3,5-dimethylpyrazole in pyridine by oxygen in the presence of CuCl at room temperature leads to conjugated octatetraynes in 75%, 83%, and 84.0% yields (69IZV2546; 69KGS1055) (Scheme 65, Table XVIII).



SCHEME 64



SCHEME 65

Moreover, it has been established that dehydrocondensation can also be applied to 3,5-diethynyl-1-methylpyrazole, which makes it possible to produce polymer (88%) with an extended system of conjugate bonds possessing semiconductor properties (2001UP2).

The presence of the aliphatic amino group complicates the course of the reaction. Thus, the oxidative coupling of 4-ethynyl-1,3-dimethyl-5-aminomethylpyrazole in mild conditions (20°C, CuCl, pyridine, O_2) leads to only 20% of butadiyne. However, acylic protection eliminates these complications, and 4-ethynyl-1,3-dimethyl-5-(acetyl)aminomethylpyrazole forms a dehydrodimer in 95% yield (Scheme 66) (86TH1).

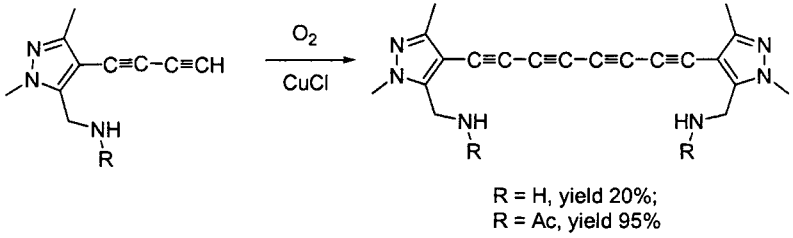
3. *Cross-Coupling*

When cross-coupling is used in the synthesis of alkyl(aryl)acetylenylpyrazoles, iodopyrazoles act most often as halide components, because the methods of their production are well developed (80IZV1071; 85MI1). The number of examples of the "reverse variant" of cross-coupling where ethynylpyrazole acts as an acetylenic component are rather scarce (96MC98; 2001UP3) (Scheme 67, Table XIX).

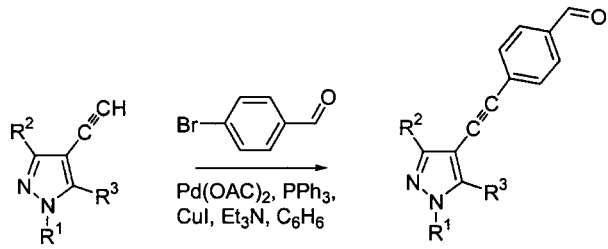
The condensation of 4-ethynyl-1,3-dimethyl-5-aminomethylpyrazole with iodobenzene in the standard conditions of the Heck–Sonogashira reaction caused no complications and the yield of disubstituted acetylene was 87% (86TH1) (Scheme 68).

Cross-coupling of 5-ethynyl-4-chloro-1,3-dimethylpyrazole with 3-iodo-4-chloronitrobenzene was carried out in the presence of $(PPh_3)_2PdCl_2$, CuI, and Et_3N (66%) (96MC98) (Scheme 69).

The same type of reactions includes the Chodkiewicz–Cadiot reaction, i.e., a coupling of terminal acetylenes with bromoacetylenes, which is performed in

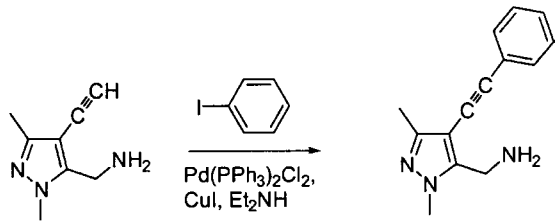


SCHEME 66



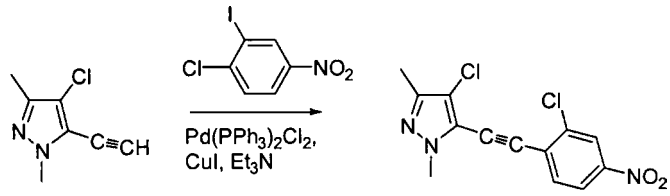
R^1 = CH_3, $CH(CH_3)OCH_2CH_3$,
R^2 = H, CH_3; R^3 = H, CH_3

SCHEME 67

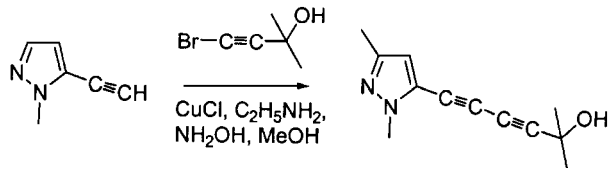


SCHEME 68

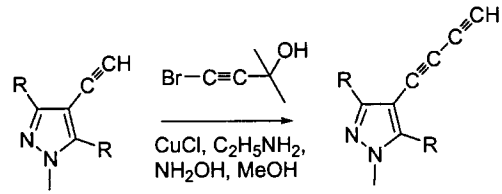
an inert atmosphere at 20–40°C in the presence of CuCl and ethylamine. Thus, 3-ethynyl-1-methyl-, 5-ethynyl-1-methyl-, and 4-ethynyl-1,3,5-trimethylpyrazole were coupled with 1-bromo-3-methylbutyne-1-ol-3 according to the Chodkiewicz–Cadiot reaction, giving the corresponding α-diacetylenic alcohols in 76%, 76%, and 75% yields (69IZV2546; 69KGS1055) (Schemes 70 and 71).



SCHEME 69



SCHEME 70



R = H, CH_3

SCHEME 71

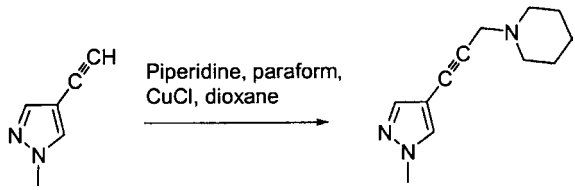
Little is known concerning the mechanism of this reaction, but most probably the intermediates are acetylides.

4. *Aminomethylation*

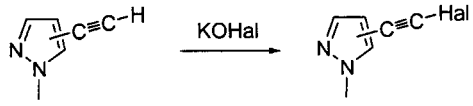
A large series of Mannich bases with secondary amines (69KGS1055; 72IZV2524; 93MIP1) was obtained using mono-, di-, and triethynylpyrazoles. Aminoalkylation of terminal acetylenes with paraformaldehyde and secondary amines was performed in argon atmosphere at 50–100°C in dioxane in the presence of CuCl, since it is known that copper salts activate ethynyl derivatives in this reaction. Diethylamine, diethanolamine, pyrrolidine, piperidine, and morpholine were used as secondary amines. The general approach depicted in Scheme 72 was used to prepare Mannich bases (Table XX).

1-(*N,N*-Diethylaminomethyl)-3-ethynylpyrazole reacts with paraformaldehyde to form a diamine in the presence of CuCl in dioxane (100°C, 3 h) in 82% yield. The aminomethylatlon of 4-ethynyl-l,3,5-trimethyl-, 4-butadiynyl-l,3,5-trimethyl-, 3,5-diethynyl-l-methyl-, 3,4-diethynyl-l-methyl-, 4,5-diethynyl-l-methylpyrazole, and 4-ethynyl-l-methylpyrazole was carried out in dioxane in the presence of CuCl (72IZV2524) under argon atmosphere. With diethylamine and piperidine the reaction was ended in 7–9 h at 35°C, whereas 2–3 h at 80°C was sufficient for its total completion with the remaining amines.

There are slight differences in the reactivity of the acetylenic groups depending on their position in the pyrazole ring. This can be followed using pyrazole diethynyl derivatives as an example. In the case of 4,5-diethynyl- and



SCHEME 72



SCHEME 73

3,5-diethynyl-l-methylpyrazole, respectively, the relative condensation rates (piperidine, 35°C) at 5-C≡CH are ~4 times higher than those at 4-C≡CH and ~1.6 times higher than those at 3-C≡CH.

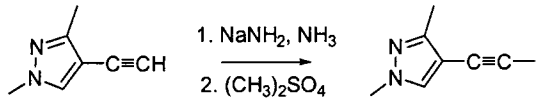
5. *Halogenation*

The interaction between terminal pyrazolylacetylenes and alkaline solutions of KOX (X = Cl, Br, I) of alkaline metals gives pyrazolylethynylhalogenides (Scheme 73; Table XXI). This method can cause complications owing to the low rate of halogenation due to the low solubility of ethynylpyrazoles in alkaline solution and the lability of both the starting ethynyl derivatives and the final products with respect to the oxidative action of KOX. To avoid possible complications, the reaction of halogenation is carried out at room temperature. To increase the reaction rate, the mixture is treated with a ~5-fold excess of KOX. For liquid ethynylpyrazoles and the resulting halogenethynylpyrazoles, these precautions gave good results and the product yields were very good (95–98%). The yields of halogenides were much lower when the crystalline monosubstituted acetylenes were used as substrates. Probably, this is due to the fact that the resulting halogenacetylene, whose solubility is worse than that of ethynyl derivatives, covered the surface of starting acetylene, thus hampering the access of the reagent. Indeed, the addition to the reaction mass of either ether or dioxane, which dissolves the substrate and the halogenoazole, causes an increase in the yields of the compounds. The action of KOBr and KOI on 4-ethynyl-1,3,5-methylpyrazole gave 4-bromethynyl- and 4-iodoethynylpyrazoles in 73% and 75% yields (76IZV2292; 77IZV2306).

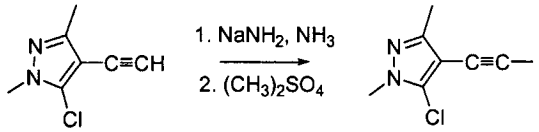
By the chlorination of 3-ethynyl-, 4-ethynyl-, and 5-ethynyl-l-methylpyrazole with KOCl the corresponding compounds were synthesized in 98%, 100%, and 94% yields. The typical procedure is as follows: To an aqueous solution of KOX (0.64 *N*) in 12.5% KOH, prepared from the corresponding halogen and potassium hydroxide in water at 5–10°C, was added the terminal acetylene, followed by stirring at room temperature until the complete disappearance of the starting material.

6. *Alkylation*

The comparatively high acidity of terminal acetylenes allows the alkylation (without isolation of an intermediate acetylide) of even the less active ethynyl



SCHEME 74



SCHEME 75

groups occupying position 4 in the pyrazole ring. Thus, methylation of 4-ethynyl-1,3-dimethylpyrazole was carried out by $(CH_3)_2SO_4$ in the presence of sodium amide in liquid NH_3 (77IZV2306). The yield of 4-(1-propynyl)-1,3-dimethylpyrazole was 71% (Scheme 74).

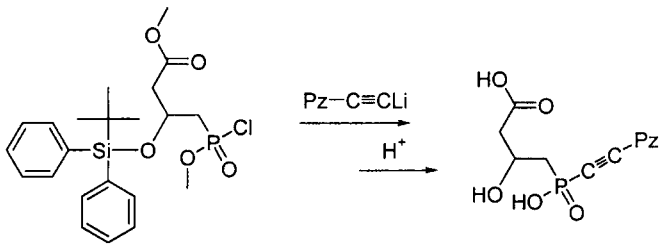
The chlorine atom does not react in these conditions, and 5-chloro-4-(1-propynyl-1,3-dimethylpyrazole was prepared similarly from the corresponding ethynyl derivative in 76% yield (Scheme 75).

7. *Metalation*

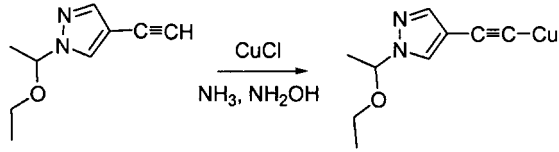
All the above-mentioned reactions are likely to result in intermediate organometal compounds and the starting terminal acetylenes can be described as the synthetic equivalents of the synthon–nucleophile $RC{\equiv}C^-$.

An example is provided by the reaction of methyl-3-([(1,1-dimethylethyl)diphenylsilyl]oxy)-4-(chloromethoxyphosphinyl)butyrate with lithium pyrazolylalkynide, which is used to prepare compounds with structure $HOP(O)(PzC{\equiv}C)CH_2CH(OH)CH_2CO_2H$ useful as 3-hydroxyl-3-methylglutaryl CoA (HMG CoA) reductase inhibitors (88GEP3817298) (Scheme 76).

Pyrazolylacetylides are rare in a free form. The only example is ethynylpyrazole copper salt obtained by means of interaction between terminal acetylene and CuCl (2001UP1) (Scheme 77).



SCHEME 76



SCHEME 77

B. REACTIONS WITH PARTICIPATION OF THE C≡C BOND

The triple bond in pyrazole derivatives gives, as do other acetylene derivatives, typical addition reactions.

1. *Halogenation*

When 4-ethynyl-3,5-dimethylpyrazole interacts with bromine, only one halogen molecule is added, probably owing to steric hindrance (71TH1) (Scheme 78).

2. *Hydrogenation*

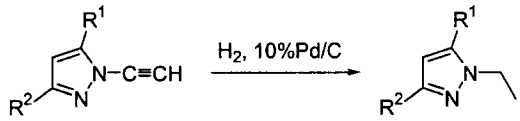
The hydrogenation of pyrazolylacetylenes shows no peculiarities. Ethynylpyrazoles are hydrogenated in high yields to the corresponding ethane derivatives on Raney nickel catalyst, platinum dioxide, or palladium catalyst at room temperature in alcohol solution.

Thus, the hydrogenation of isomeric 1-ethynyl-3-methyl- and 1-ethynyl-5-methylpyrazoles by hydrogen with 10% Pd/C in 1-ethyl-3-methyl- and 1-ethyl-5-methylpyrazoles was used to prove the structure of *N*-ethynylpyrazoles formed from pyrolysis of the corresponding *N*-propynoylazoles (94AJC991) (Scheme 79).

[4-(1,3-Bis-{6-[(bis-*tert*-butoxycarbonylmethylamino)methyl]pyridin-2-yl}-1*H*-pyrazol-4-ylethynyl)phenoxy]acetic acid methyl ester and related compounds were hydrogenated in dry methanol in the presence of 10% Pd/C for 4 h in 70% yield (97EUP770610; 99EUP967205) (Scheme 80).

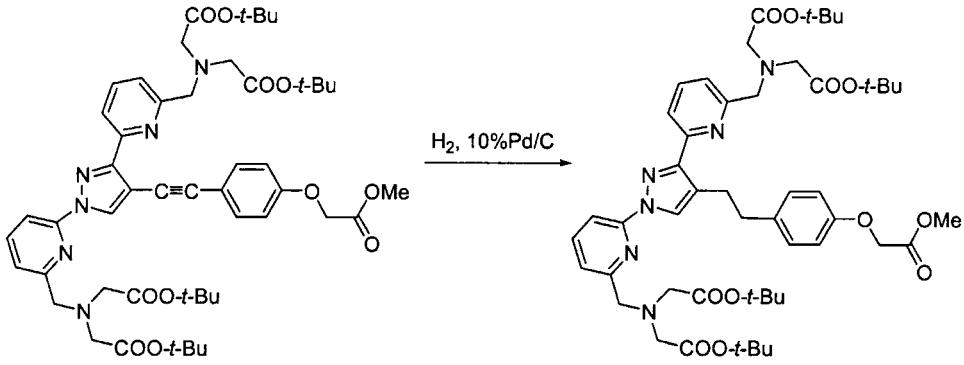
There are other examples of hydrogenation of 1-(hetaryl)-4-alkynylpyrazole derivatives to the corresponding alkanes (96EUP703234). Derivatives of 5-ethynylpyrazolo[3,4-*d*]pyrimidine in presence of 10% Pd/C were hydrogenated

SCHEME 78



R^1 = H, R^2 = Me; R^1 = Me, R^2 = H

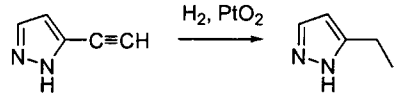
SCHEME 79



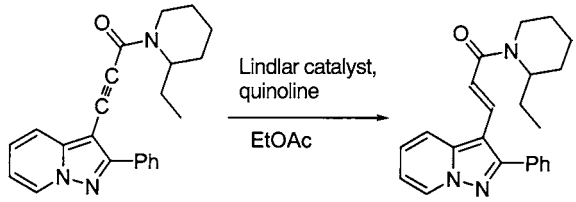
SCHEME 80

at 50 psi for 4 days in 41–78% yields (92T8089). 5-Ethynylpyrazol was hydrogenated in ether with PtO_2 at 20°C for 3 h (41LA279) (Scheme 81).

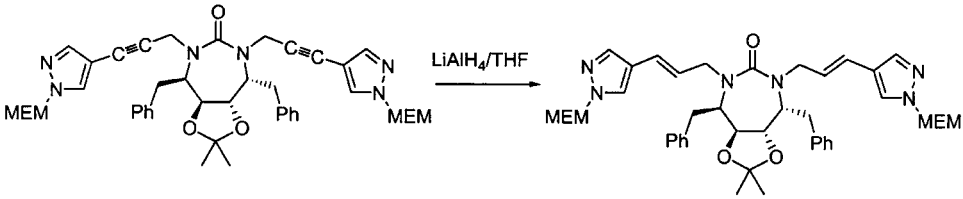
Lindlar catalyst can be used for hydrogenation of 1-[3-(2-phenylpyrazolo[1.5-*a*]pyridin-3-yl)propynoyl]-2-ethylpiperidine in ethyl acetate (38%) (Scheme 82; 89EUP299209; 92USP5102869) and 1-(hetaryl)-4-alkynylpyrazole derivatives to the corresponding alkenes (96EUP703234).



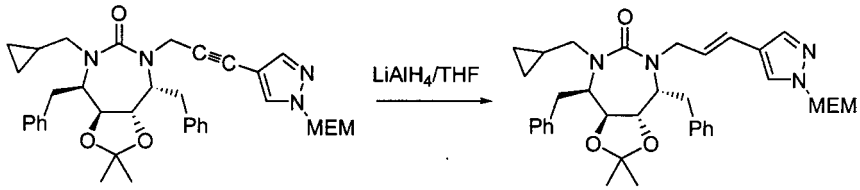
SCHEME 81



SCHEME 82



SCHEME 83



SCHEME 84

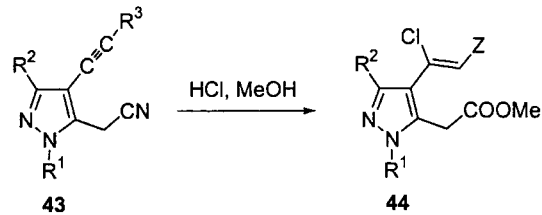
A Scheme for the preparation of a series of cyclic urea HIV protease inhibitors containing alkynyl-tethered heterocycles in the P2 region includes hydrogenation with $LiAlH_4$ in THF in 60–80% yields (96BMCL797) (Schemes 83 and 84).

3. *Hydrohalogenation*

Examples of addition of HCl to a triple bond have been reported in (93EUP 571326). Acetic acid esters of formula **44** may be obtained from alkynylpyrazoles **43** by alcoholysis with HCl in the presence of methanol (Scheme 85).

4. *Hydration*

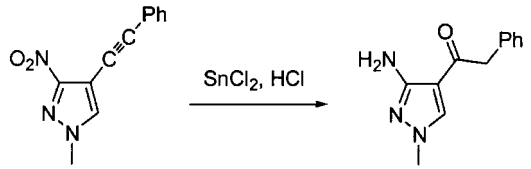
In the presence of silver oxide and BF_3–ether complex, 4-phenylethynylpyrazole forms only one isomer of the two possible ones, i.e., 2-phenyl-1-(4-pyrazolyl)ethanone in 72% yield (88M253) (Scheme 86).



SCHEME 85

R = H, Ph

SCHEME 86

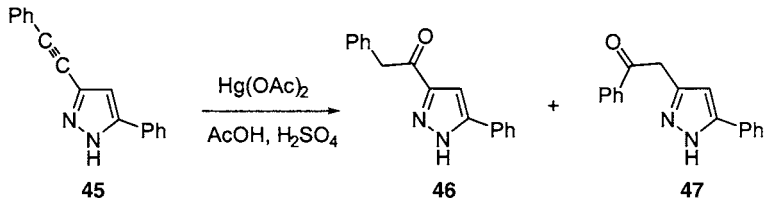


SCHEME 87

However, in the presence of the electron-withdrawing nitro group, hydration occurs already under the conditions of its reduction. In this case, the direction of addition of the water molecule is preserved. The yield of 1-methyl-4-phenylacetylpyrazole was 90% [99JCS(P1)3713] (Scheme 87).

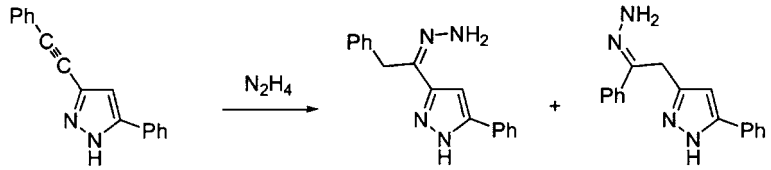
At the same time, the hydration of 3(5)-phenyl-5(3)-phenylethynylpyrazole **45** in sulfuric acid in the presence of mercury acetate leads to the formation of two isomeric ketones: **46** (yield 44%) and **47** (yield 3%) (68LA117) (Scheme 88).

The hydration of 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-ethynylpyrazole was performed with *p*-toluenesulfonic acid monohydrate in acetonitrile (2 h, room temperature) to give the corresponding 4-acetyl derivative. An alkyl substituent at the triple bond decreases the rate of hydration; the conversion of 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-(prop-1-yn-1-yl) pyrazole to the 4-propanoylpyrazole was completed after 18 h (98INP9804530; 99EUP933363).



45 **46** **47**

SCHEME 88



SCHEME 89

5. *Hydrazination*

Acetylene interacts with hydrazine in absolute ethanol to give a mixture of isomeric hydrazones in a 3:2 ratio (by NMR spectra) (68LA117) (Scheme 89).

The reaction of the propiolic derivatives with hydrazine monohydrate leads to 5-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)-2*H*-pyrazol-3-ol (Scheme 90) (90EUP379979).

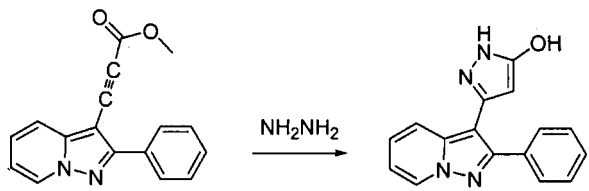
6. *Oxidation*

The presence of a triple bond allows not only mono- but also diketones to be obtained. Recently, a new reaction of acetylene oxidation to α-diketones with the $PdCl_2$–DMSO reagent has been discovered (95S1234; 95ZOR1675). Acetylenic derivatives of pyrazole bearing electron-donating substituents were oxidized with this reagent to the heterocyclic 1,2-diketones in high yield (2001UP4) (Scheme 91).

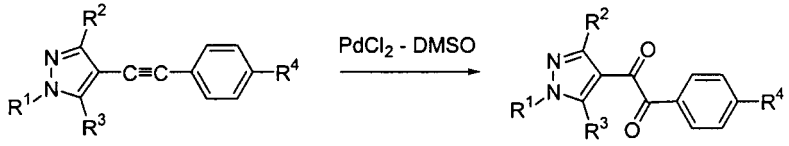
The attempted oxidation of pyrazole derivatives with electron-withdrawing substituents ($R^1 = Me$; R^2, $R^3 = COOCH_3$; $R^4 = CHO$; Scheme 91) failed (2001UP4). For the same reason the oxidation of the triple bond in 4-chloro-5-(2-chloro-5-nitrophenylethynyl)-1,3-dimethyl-1*H*-pyrazole was also unsuccessful.

C. REACTIONS WITH PARTICIPATION OF THE ≡C—X BOND

Synthetically, the most important reactions of this type are the cleavage of the ≡C—X bond and the formation of a new ≡C—H bond.

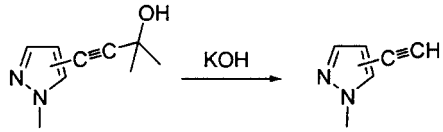


SCHEME 90



$R^1 = R^2 = R^3 = R^4 = H$; $R^1 = R^2 = R^3 = H$, $R^4 = NO_2$;
$R^1 = R^2 = R^3 = CH_3$, $R^4 = H$; $R^1 = R^3 = CH_3$, $R^2 = R^4 = H$;
$R^1 = CH_3$, $R^2 = NH_2$, $R^3 = R^4 = H$

SCHEME 91

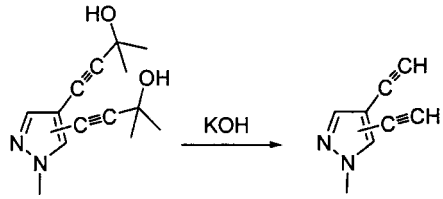


SCHEME 92

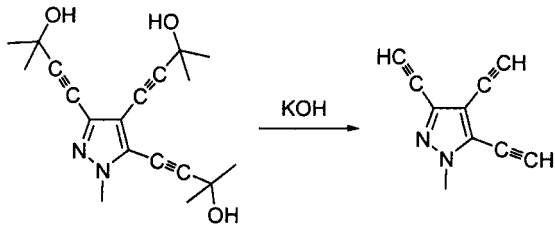
1. *Retro Favorsky Reaction*

A classical variant of the reverse Favorsky reaction implies heating of the α-acetylenic alcohol of the aromatic (heteroaromatic) series in a setup for sublimation in vacuum in the presence of 0.5–5% by weight of powdered KOH in the temperature range 120–160°C with simultaneous sublimation of the ethynyl derivative and capture of the carbonyl compound by a nitrogen trap (Table XXII). This method was used to synthesize 1-methyl-3-ethynyl- (yield 62%) (69IZV2546), 1-methyl-4-ethynyl- (84%) (72IZV2524), and 1,3,5-trimethyl-4-ethynylpyrazoles (90%) (69KGS1055) from the corresponding (1-methylpyrazolyl)-3-methylbut-1-yn-3-ols (Scheme 92).

The high stability of terminal acetylenes of the pyrazole series allows the preparation of polyethynyl derivatives like 3,4-diethynyl-, 4,5-diethynyl-, and even 3,4,5-triethynyl-1-methylpyrazole in 64%, 78%, and 41% yields, respectively, in these strong conditions (71IZV1764) (Schemes 93 and 94).



SCHEME 93



SCHEME 94

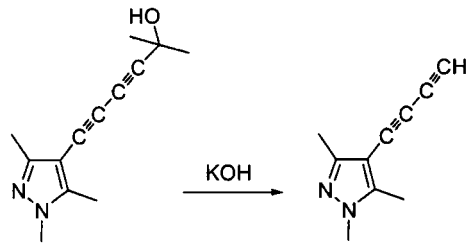
The series of 1,3-dimethyl-5-ethynylpyrazoles, including the functionally substituted ones, was obtained at lower temperature (100–105°C, 10 wt % of powdered KOH, 1.5–2 mm Hg) (86TH1).

Decreasing the temperature still further (80–90°C), the authors managed to obtain even the unstable terminal diacetylene, 1,3,5-trimethyl-4-butadiynylpyrazole (yield 45%) (69KGS1055) (Scheme 95).

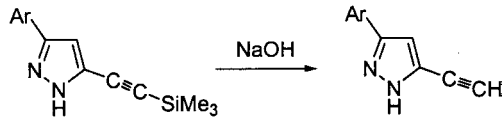
However, milder conditions are necessary for obtaining the less stable 1-methyl-3-butadiynyl- and 1-methyl-5-butadiynylpyrazole. The acetylenic alcohols were stirred with KOH at room temperature in acetylene atmosphere (to bind the isolated carbonyl compound). The product yields were 68% and 65% (69IZV2546), respectively.

In 1978, an improved technique was proposed for the cleavage of the tertiary acetylenic alcohols (78MIP1). In the setup for sublimation in vacuum, the acetylenic alcohols (0.1–2.0 g) are mixed up with KOH (2–30% by weight) and 1–5 ml of *m*-pentaphenyl ether or another high-boiling solvent to prevent local overheating. This method was used to substantially improve and stabilize the yields of mono- and polyethynylpyrazoles (78MIP1; 86TH1) as compared with the "dry method" (71IZV1764).

Later, the method of cleavage of the tertiary acetylenic alcohols in boiling benzene or toluene in the presence of NaOH or KOH was reported (88M253; 2001UP1).



SCHEME 95



Ar = Ph, 4-Cl-C_6H_4, 4-MeO-C_6H_4

SCHEME 96

2. *Desilylation*

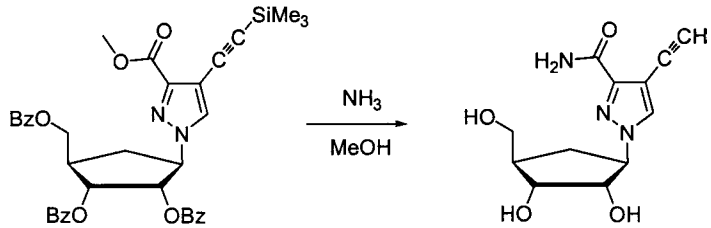
In recent years, trimethylsilyl protection has often been used for the methine proton of the acetylenic group because of the mild reaction conditions for desilylation. As a rule, the starting pyrazole trimethylsilyl derivative is mixed up, at room temperature, with a 2 *N* aqueous solution of NaOH, potash, or methanol solution in ammonia.

In (73S47) the cleavage of the trimethylsilyl protector is used to prepare the nitrogen-unsubstituted 3-aryl-5-ethynylpyrazoles (Scheme 96).

4-Ethynylpyrazole was obtained under similar conditions in 46% yield (88M253). There are other examples of the trimethylsilyl cleavage with aqueous solution of potassium hydroxide for 1-(hetaryl)-4-(trimethylsilylethynyl)pyrazole derivatives (96EUP703234).

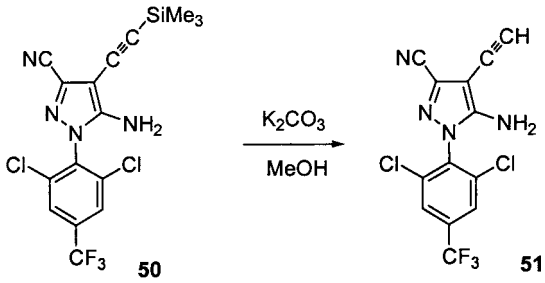
4-Ethynyl-1-β-D-ribofuranosylpyrazole-3-carboxamide was obtained in good yield by treatment of compound **48** with methanolic ammonia (96BMCL1279) (Scheme 97).

Ethynyl derivative **50** was prepared by interaction of potassium carbonate with 5-amino-3- cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trimethylsilylethynylpyrazole in methanol for 10 min (97INP9707102; 98INP9804530; 98INP9824767; 99EUP933363) (Scheme 98).



48 **49**

SCHEME 97



SCHEME 98

4-Trimethylsilylethynylpyrazole was deprotected by treatment with tetrabutylammonium fluoride (TBAF) to give monosubstituted acetylene in 90% yield. (96ADD193). The same conditions were used to cleave the trimethylsilyl group in 1-tetrahydropyranyl-3-carboxyethyl-4-[2-(trimethylsilyl)ethynyl]pyrazole (96INP 9640704).

3. *Destannylation*

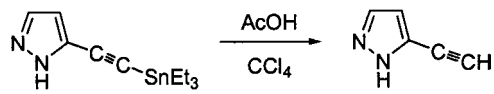
Compared with the alkaline conditions used in the above methods, the removal of the triethylstannylic group (triethyltin) occurs for 3(5)-triethylstannylethynylpyrazole at room temperature in CCl_4 solution in the presence of acetic acid (71ZOB 2230) (Scheme 99).

4. *Decarboxylation*

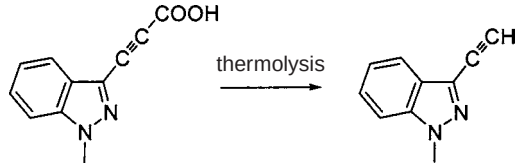
Terminal acetylenes can be obtained from the corresponding propylcarboxylic acids by thermal decomposition. Thus, 1-methyl-3-ethynyl- and 2-methyl-3-ethynylindazole were obtained by thermolysis of indazolylpropiolic acids at 150–160°C. Yields of ethynyl derivatives were 65 and 60%, respectively (75KGS1678) (Scheme 100; Table XXIII).

5. *Cineamination*

In 1973, the unexpected transformation of 4-chloroethynyl-1,3,5-trimethylpyrazole under the action of sodium amide in liquid ammonia into 5-aminomethyl-4-ethynyl-1,3-dimethylpyrazole in 85% yield was reported (73IZV2166). Within



SCHEME 99



SCHEME 100

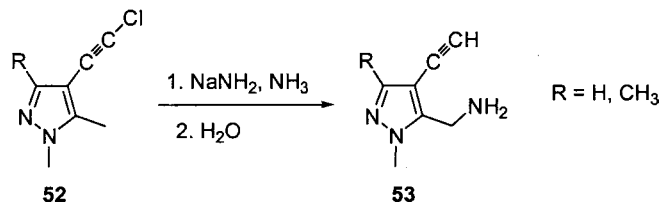
this context, the same authors investigated the reaction of $NaNH_2$ with certain chloro-, bromo-, and iodoacetylenylpyrazoles (76IZV2292) (Scheme 101).

The chemical shift of the protons of the *C*-methyl for compounds **53** changes considerably less than the shift of the protons of the methylene group in the transition from a nonpolar to an aromatic solvent. The shift induced by benzene on account of the solvent ($\delta CDCl_3$–δC_6H_6) is a quantity in the order of 0.5 ppm for 5-CH_3 in substituted pyrazoles and 0.1 ppm for 3-CH_3 (66BSF293; 66BSF3727; 66JPB1242). Thus, the aminomethyl group in the ethynylpyrazoles **53** is proved to be at position 5 of the heterocycle. The formation of the rearranged substitution product involves participation of the CH_3 group at position 5 but not position 3. Indeed, in accordance with this, 4-chloroethynyl-l,5-dimethylpyrazole is readily converted into 4-ethynyl-5-aminomethyl-l-methylpyrazole in 81% yield.

It is necessary to emphasize that the direct amination of the methyl group at position 5 of pyrazoles is impossible. Neither 1,3,5-trimethyl- nor 4-ethynyl-l,3,5-trimethylpyrazole undergoes such transformations under the reaction conditions and starting materials are recovered nearly quantitatively. Moreover, 4-bromoethynyl-l,3,5-trlmethyl- and 4-iodoethynyl-l,3,5-trimethylpyrazole with sodium amide in ammonia exchange the halogen for metal almost quantitatively and in this respect are similar to phenylchloroacetylene (Scheme 102).

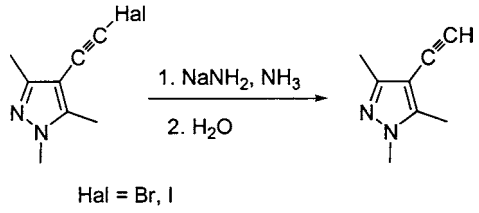
A mechanistic scheme that was proposed involves the successive or synchronous elimination of a proton and a chloride ion from the 5-methyl group and from the chloroethynyl group attached to it, followed by addition of the nucleophile (NH_3) to the intermediate bipolar carbene ion stabilized by conjugation (Scheme 103).

It should be noticed that N-unsubstituted 4-chloroethynyl-3,5-dimethylpyrazole under the action of both $NaNH_2$ and *n*-butyllithium leads only to 4-ethynyl-3,5-dimethylpyrazole (69IZV927) (Scheme 104).

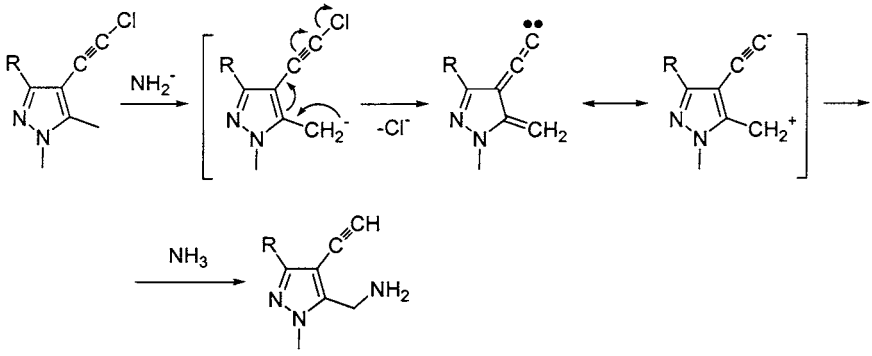


52 **53**

SCHEME 101



SCHEME 102

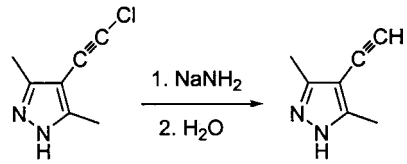


SCHEME 103

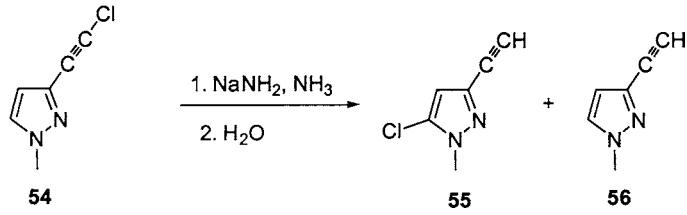
6. *Transhalogenation*

The reaction of $NaNH_2$ with pyrazolylchloroacetylenes lacking a methyl group in position 5 of the ring occurs through another pathway (Table XXIV). The 4- and the 3-chloroethynyl-1-methylpyrazoles in the absence of 5-CH_3 undergo isomerization with migration of the halogen atom to position 5 of the pyrazole ring under the action of $NaNH_2$ in liquid NH_3. Rearrangement of 3-chloroethynyl-1-methylpyrazole **54** gives 3-ethynyl-5-chloro-l-methylpyrazole **55** in 70% yield and 3-ethynyl-1-methylpyrazole **56** in 25% yield (76IZV2148) (Scheme 105).

From 4-chloroethynyl-l,3-dimethylpyrazole 80% of 4-ethynyl-5-chloro-l,3-dimethylpyrazole was obtained. There is simultaneous formation of about 10% of 4-ethynyl-l,3-dimethylpyrazole (76IZV2148; 77IZV2306) (Scheme 106).

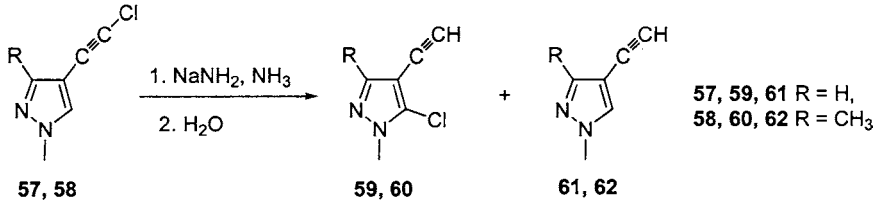


SCHEME 104



54 **55** **56**

SCHEME 105

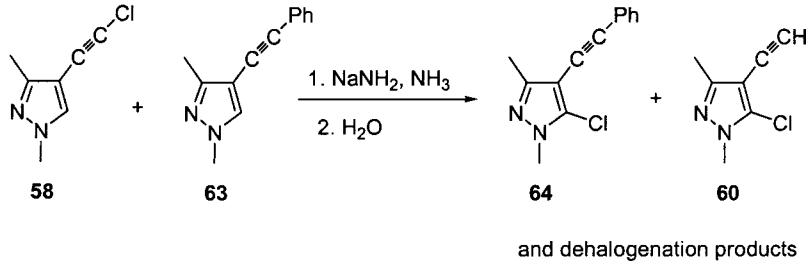


57, 58 **59, 60** **61, 62**

SCHEME 106

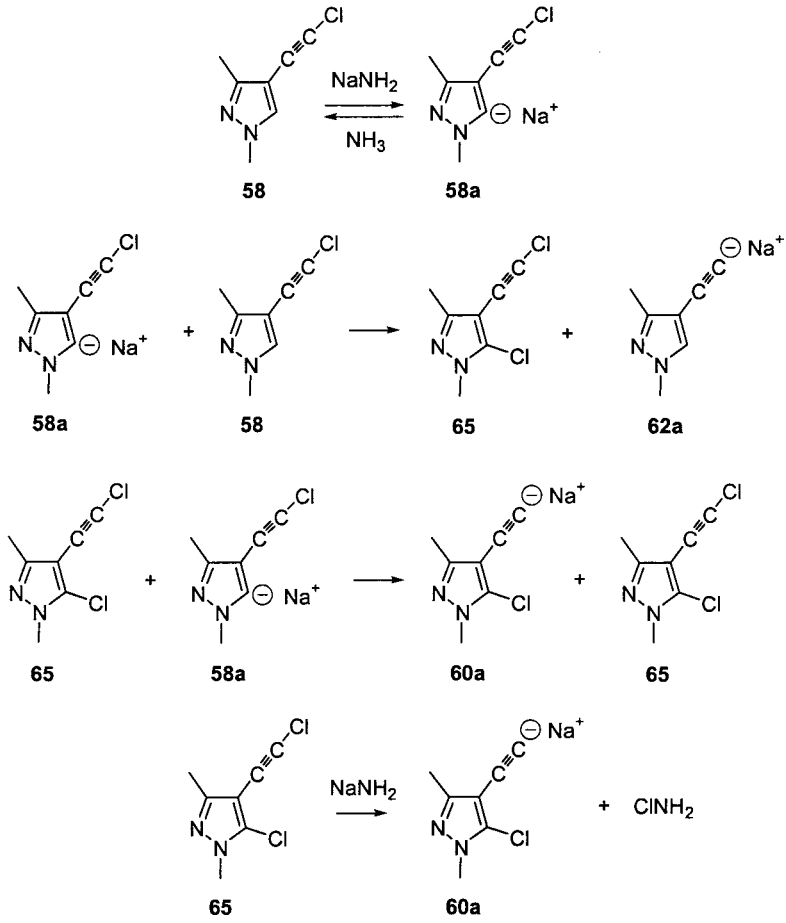
To establish the nature of the chlorine migration (intramolecular or intermolecular), rearrangement of **54** was carried out in the presence of 4-(phenylethynyl)-l,3-dimethylpyrazole **55** (molar ratio of **54**:**55** = 2). About 40% of the chlorine migrates to the 5 position of the acceptor molecule **55** (Scheme 107).

This means that this rearrangement is intermolecular, reminiscent of the base-induced halogen migration in aromatic rings known in the halobenzene series as the "halogen dance" (72ACR139; 73RTC245). The authors proposed the following mechanism (77IZV2306) (Scheme 108), with 4-(chloroethynyl)-5-chloro-1-dimethylpyrazole **65** as the key intermediate. The latter is generated by nucleophilic attack of the pyrazolyl anion **58a** on the positive halogen atom of the starting chloride **58.** Interaction between dichloride **65** and anion **58a** leads to the exchange of halogen from the side chain for metal and formation of the final reaction product as acetylide **60a.** At the same time, halogenation of **58a** regenerates **65;** therefore, the rearrangement is a chain reaction in which the reaction of **65** with **58a** represents chain propagation. The chain is interrupted by the reaction of **65** with $NaNH_2$.



58 **63** **64** **60**

SCHEME 107



SCHEME 108

The following experiment supports this mechanism. The interaction of **58** in the presence of 5-chloro-4-chloroethynylpyrazole **65** (8 mol %) containing ^{36}Cl radiolabeled in C≡CCl gives the product **60** containing 84% of ^{36}Cl. Taking into account the loss of a small amount of the ^{36}Cl in the dechlorination of **65** by $NaNH_2$, this result undoubtedly confirms that dichloride **65** is the intermediate in the rearrangement. Thus, the reaction occurs by a chain heterolytic mechanism accompanied by partial dehalogenation of the starting chloroacetylene to yield the corresponding ethynylpyrazole (77IZV2306).

The halogen migration is completely suppressed by halogen–metal exchange when the chloroethynyl group is in position 5 of the pyrazole ring. The concentrations of 3-pyrazolyl and 4-pyrazolyl anions are probably small, and they cannot compete with NH_2 anions for chlorine bonded to the acetylenic carbon.

4-Iodoethynyl- and 4-bromoethynyl-1,3-dimethylpyrazole were tested later for comparison of the migratory capacity of halogens in this transformation. This investigation showed that the tendency of these halogeno derivatives toward isomerization decreases on going from chloro to iodo compounds (77IZV2306).

D. Heterocyclizations of Vicinal Functionally Substituted Pyrazolylacetylenes

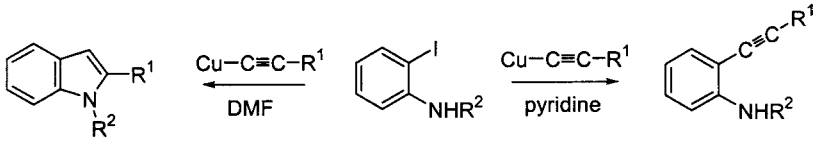
Castro *et al.* (63JOC3313) in 1963 first studied the intramolecular O—H and N—H addition via the triple bond in the aromatic series. From the 1970s through the 1990s, Russian researchers [81IZV902; 85IZV1367; 86TH1; 99JCS(P1)3721] performed the systematic study of the intramolecular heterocyclization of functionally substituted compounds using pyrazole acetylenic derivatives as an example. These studies revealed substantial differences in both the facility and direction of the isomerization in the series of benzene and pyrazole. Since this comparative study allows estimating the specificity or general features in the behavior of five- and six-membered substrates in heterocyclization reactions, we use this approach below.

1. *Aminopyrazolylacetylenes*

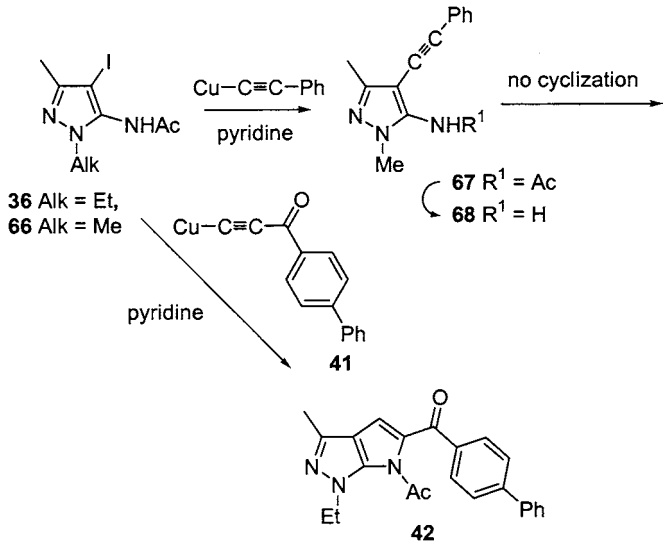
Intramolecular cyclization via addition of amino group to the triple bond in *o*-acetylenylanilines is a method for synthesizing substituted indoles. Castro and colleagues have established that the products of either substitution (acetylenylanilines) or cyclization (indoles) can be obtained from *o*-halogenanilines and copper acetylides (63JOC2163; 66JOC4071; 69JA6464) (Scheme 109).

The cyclocondensation of iodoaminopyrazole with copper acetylides and the cyclization of aminopyrazolylacetylene with different mutual arrangement in the ring of interacting groups have been studied (83IZV688).

It has been found that the fusion of the pyrazole with the pyrrole ring is difficult, probably for steric reasons. All attempts to cyclize 3-amino- and 5-amino-4-acetylenylpyrazole have failed. For example, upon prolonged heating of 5-amino-4-acetylenylpyrazole **68** in DMF in the presence of CuI and (or) CuC≡CPh, side transformations and resinification occurred. The side processes were suppressed by acylation of the amino group and substitution of DMF by inert cyclohexane. However, 80–90% of the starting compounds was recovered after heating acylamine



Scheme 109



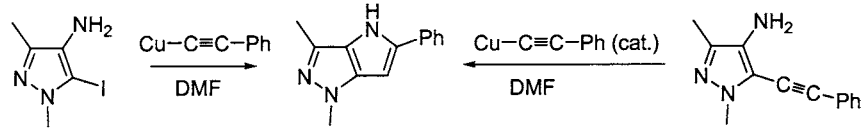
SCHEME 110

67 in the presence of CuI in DMF at 110–145°C for 15 h or amine **68** in cyclohexane at 80°C (30 h). However, cross-coupling of iodopyrazole **36** with copper *p*-phenylbenzoylacetylide **41** gave pyrrolo[2,3-*c*]pyrazole **42** directly; presumably, cyclization is aided by the ketone group (Scheme 110).

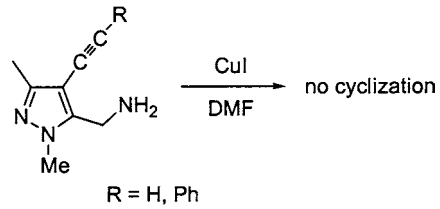
It was assumed that the failure of cyclization of 3-amino- and 5-amino-4-acetylenylpyrazole derivatives is due both to the decreased nucleophilicity of the amino groups in the acceptor positions 3 and 5 of the pyrazole ring and to the low electrophilicity of the triple bond carbons in position 4 of the ring.

As a substrate, 4-amino-5-acetylenylpyrazole **71** was chosen; in this compound the position of interacting groups is the most favorable for intramolecular cyclization. Indeed, 4-amino-1,3-dimethyl-5-phenylethynylpyrazole **71** isomerized into 1,3-dimethyl-5-phenylpyrrolo[3,2-*c*]pyrazole **70** in 65% yield under heating in DMF for 4 h in the presence of CuI (83IZV688). The authors have noticed that the cyclization of **71** is accelerated by the addition of CuC≡CPh.

Pyrrolopyrazole **70** can also be obtained by direct cyclocondensation of iodide **69** with acetylide CuC≡CPh (2 h, yield 38%) (Scheme 111).



SCHEME 111



SCHEME 112

Attempts were made to perform heterocyclization with 4-phenylethynyl- and 4-ethynyl-5-aminomethyl-1,3-dimethylpyrazole where, on the one side, a strained six-membered ring can be formed, and, on the other side, the aliphatic amino group is more nucleophilic than the aromatic (Scheme 112). However, all attempts to cyclize the ethynylpyrazole and its phenyl analog failed (86TH1).

2. *Nitroacetylenylpyrazoles*

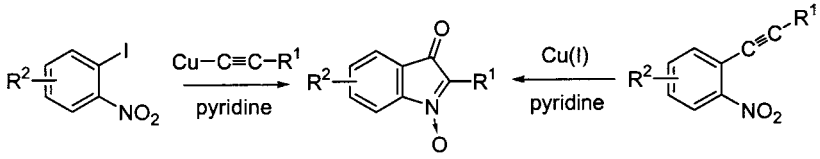
Cyclization of *o*-nitroacetylenylbenzenes and cyclocondensation of *o*-iodonitrobenzene with copper acetylides are widely used to produce isatogens [69JCS(C)2453; 69MI2; 79JHC221]. The nitro group can be either in the acetylide or in the halide components.

Iodoarenes and acetylides can bear substituents with both electron-releasing and -withdrawing character. In the case of the reaction between copper *o*-nitrophenylacetylide and aryliodide in pyridine, it has been shown that, depending on the structure of the aryl halide and the process duration, tolanes, isatogens, or their mixtures can be obtained (69MI2).

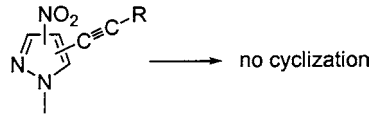
In the case of noncyclized derivatives of the aromatic series (nitrotolanes), isatogen is obtained either by a longer heating of the substrate in pyridine, or by photochemical (sun rays) or catalytic action (69MI2) (Scheme 113).

However, all attempts to isomerize *vic*-alkynylnitropyrazole into *N*-oxide in conditions of thermal, catalytic, or photochemical cyclization failed (86MI1) (Scheme 114).

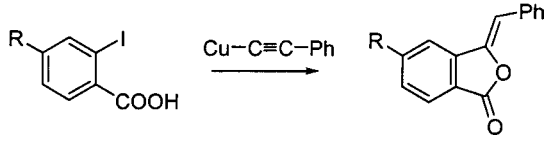
It is known that the ability of nitrotolane to cyclize depends on electronic factors (69MI2); hence 1,3-dimethyl-4-nitro-5-phenylethynylpyrazole, whose acetylene group is in the most electron-accepting position of the pyrazole ring, i.e., favorable for nucleophilic addition, was introduced into the reaction of cyclization. Thus,



SCHEME 113



SCHEME 114



SCHEME 115

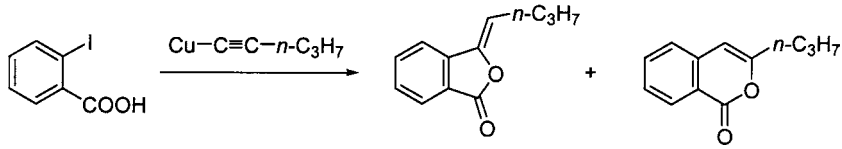
3-nitro-4-phenylethynyl- and 4-nitro-5-phenylethynylpyrazoles, like *o*-nitrophenylethynylbenzene, are incapable of photochemical, thermal, or catalytic cyclization resulting in *N*-oxides. The inability of both nitropyrazolylacetylenes and aminopyrazolylacetylenes to cyclize is attributable to the great tension of the condensed system consisting of two five-membered rings.

3. *Acetylenylpyrazolecarboxylic Acids*

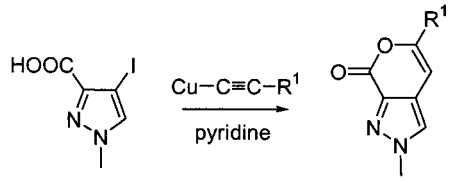
The cyclization of *o*-halogenobenzoic acids with copper acetylides mainly leads to the formation of five-membered lactones (66JOC4071; 69JA6464) (Scheme 115). Only in the case of the reaction of *o*-iodobenzoic with CuC≡C—n-C_3H_7 does the formation of a mixture of γ- and δ-lactones occur (Scheme 116).

Similar reactions in the pyrazole series occur in another way (86TH1). The iodine derivatives of pyrazolecarboxylic acids were introduced into the reaction of cyclocondensation with all possible variants of the combination of COOH group and halide and involving the acetylenic substituent. The existence of substrates with all possible variants of the arrangement of interacting groups is necessary because positions in the pyrazole ring are nonequivalent: position 4 is the most nucleophilic while 5 is the most electrophilic. This can affect the degree or even the direction of the polarization of the involved acetylene group.

Since substituents at the triple bond also determine its polarization, the copper acetylides containing both electron-releasing and electron-withdrawing groups were introduced into the reaction of cyclocondensation (78IZV1175; 81IZV902).

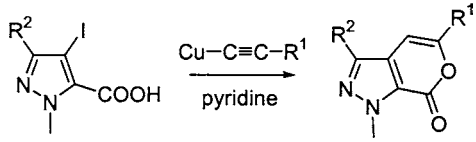


SCHEME 116



R^1 = Ph, *n*-Pr, CH_2OMe

SCHEME 117



R^1 = Ph, CH_2OMe

R^2 = H, Me

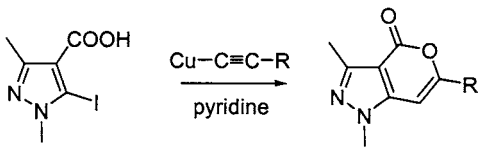
SCHEME 118

The interaction between a 4-iodopyrazole-3-carboxylic acid and copper acetylides having both donor and acceptor substituents at the triple bond generated six- rather than five-membered lactones, as in the aromatic series (Scheme 117).

The isomeric 4-iodopyrazole-5-carboxylic acid is cyclocondensed in a similar way. Introduction of the additional methyl group into the ring has no effect on the direction of cycloaddition: 4-iodo-1,3-dimethylpyrazole-5-carboxylic acid forms only δ-lactones (Scheme 118).

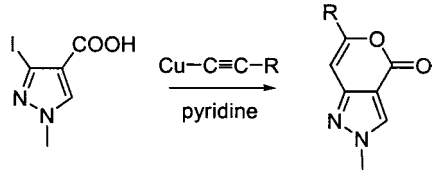
Iodopyrazoles with the "reversed" arrangement of I and CO_2H, 5-iodo-1,3-dimethylpyrazole-4-carboxylic acid, were also introduced into the reaction of condensation with copper acetylides to give the bicycles in 79% and 66% yields, respectively (Scheme 119; Table XXV).

The reaction of the isomeric 3-iodo-1-methylpyrazole-4-carboxylic acid with copper phenyl- and *p*-amylacetylide also leads to closure of the pyranopyrazole



R = Ph, *n*-Pr

SCHEME 119



R = Ph, *n*-Pr, C(=O)C_6H_4Ph

SCHEME 120

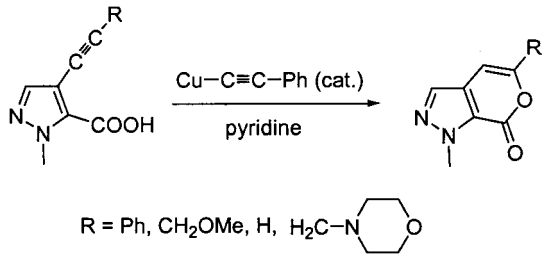
system; i.e., the direction of lactonization differs from that of cyclocondensation of *o*-halogenobenzoic acids.

To verify the generality of the cyclization of iodopyrazolecarboxylic acids, copper *p*-phenylbenzoylacetylide was used in the reaction with 3-iodo-1-methylpyrazole-4-carboxylic acid. The assumed intermediate, alkynylpyrazolylcarboxylic acid, has a distribution of the electron density which is the most favorable for closure of the five-membered cyclic ether. However, the reaction leads only to the δ-lactone (Scheme 120).

Thus, the cross-coupling of different iodo-*N*-methylpyrazolecarboxylic acids with copper acetylides leads to closure of the six-membered ring.

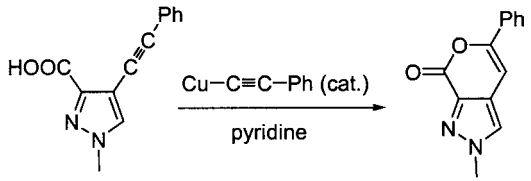
Available information on the mechanism of cyclocondensation is rather contradictory. According to one hypothesis, both the condensation of aryl halides with copper acetylides and the cyclization occur in the same copper complex (63JOC2163; 63JOC3313). An alternative two-stage reaction route has also been considered: condensation followed by cyclization (66JOC4071; 69JA6464). However, there is no clear evidence for this assumption in the literature and information on the reaction of acetylenyl-substituted acids in conditions of acetylide synthesis is absent.

For this reason, the heterocyclization of acetylenic derivatives of pyrazolecarboxylic acids with different arrangements in the ring of the interacting groups was studied (Table XXVI). The reaction is carried out in boiling pyridine in the presence of catalytic amounts of PhC≡CCu (81IZV1342). 4-Acetylenyl-1-methylpyrazole-5-carboxylic acids (Scheme 121) are fully isomerized into the pyranopyrazoles in 20 min in 62–84% yields.



R = Ph, CH_2OMe, H,

SCHEME 121



SCHEME 122

The cyclocondensation of 4-iodo-1-methylpyrazole-5-carboxylic acid with PhC≡CCu under similar conditions is over in 1.5 h. Thus, the cyclization of the 4-phenylethynyl-1-methylpyrazole-5-carboxylic acids and the cyclocondensation of the iodine acid with PhC≡CCu give the same products: pyranopyrazoles. However, the formation rate of the first reaction is much higher.

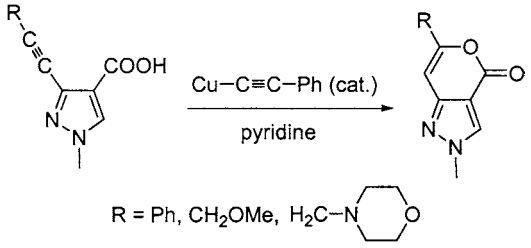
In the heterocyclization reactions of 4-acetylenyl-1-methylpyrazole-3-carboxylic acids and 4-acetylenyl-1-methylpyrazole-5-carboxylic acids the behavior is the same. Isomeric 1-methyl-4-phenylethynylpyrazole-3-carboxylic acid forms δ-lactones, 2-methyl-7-oxo-5-phenylpyrano[3,4-*c*]pyrazole, in 71% yield (20 min) (Scheme 122). The same ester is obtained by acetylenic condensation (3 h) of 4-iodo-1-methylpyrazole-3-carboxylic acid with copper phenylacetylide.

3-Acetylenyl-1,5-dimethylpyrazole-4-carboxylic acids (Scheme 123) are isomerized in a similar way. The yield of 6-substituted 2,3-dimethyl-4-oxopyrano [4,3-*c*]pyrazoles is more than 80% (0.5 h).

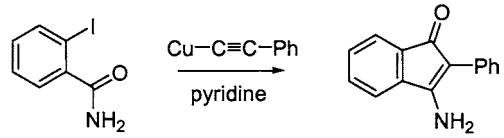
Thus, the *vic*-acetylenylpyrazolecarboxylic acids are isomerized into pyranoazoles in boiling pyridine (20–30 min) with catalytic amounts of copper acetylide. The acetylide condensation of the corresponding iodopyrazolecarboxylic acids is followed by cyclization into the same δ-lactones but with a lower rate (2–8 h).

The results obtained, i.e., agreement between the directions of cyclization and acetylenic cyclocondensation of iodazolecarboxylic acids and much shorter duration of the first reaction, confirm the assumption of the two-stage mechanism of cyclocondensation (66JOC4071; 69JA6464).

Using a suspension of silver salts in alcohol or acetonitrile for isomerization of tolane-2-carboxylic acid leads to a change in the ratio between the resulting δ- and γ-lactones to preferential formation of the five-membered cyclic ester



SCHEME 123



SCHEME 124

(65JA742). However, the heterocyclization of 4-phenylethynylpyrazole-3- and 4-phenylethynylpyrazole-5-carboxylic acid in alcohol or acetonitrile solutions in the presence of $AgNO_3$ caused, once again, the closure of the six-membered lactones.

4. *Amides of Acetylenylpyrazolecarboxylic Acids*

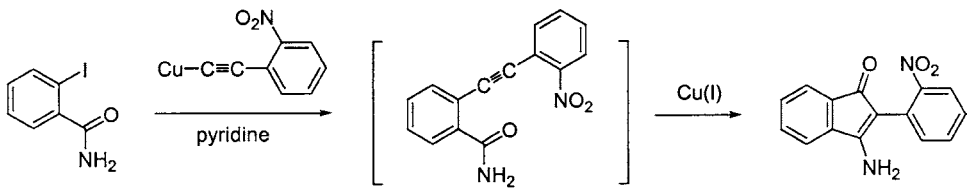
An unusual cyclization, which results in carbocycles rather than heterocycles, was described in (69JCS2453). The reaction between *o*-iodobenzamides and copper phenylacetylides in pyridine leads to indanone (74%) rather than tolane (Scheme 124).

Moreover, when carbamino and nitro groups are simultaneously in the *ortho* position to the triple bond, isomerization occurs only with participation of the amide group (Scheme 125).

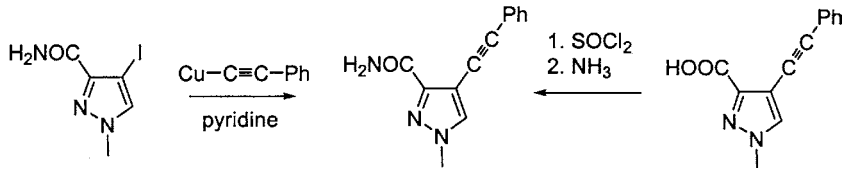
Such an easy isomerization of acetylenylbenzoic acid amides implies the formation of a five-membered nonaromatic ring condensed with the pyrazole ring. However, the pyrazole analog of *o*-iodobenzamide (amide of 4-iodo-1-methylpyrazole-3-carboxylic acid) formed under heating with CuC≡CPh in pyridine for 9 h; only the disubstituted acetylene in 71% yield is identical in all respects to the compound obtained from the corresponding acid by successive action of $SOCl_2$ and NH_3 (90IZV2089) (Scheme 126).

Interaction between CuC≡CPh and iodamide with the "reverse" arrangement of the functions (amide of 3-iodo-1,5-dimethylpyrazole-4-carboxylic acid) gave a similar result. Formation of the bicyclic compound was not observed. The yield of the acetylenylpyrazole was 62% (Scheme 127).

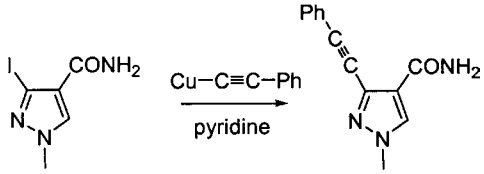
The unusual character of cyclization [69JCS(C)2453] and the results obtained by other authors (66JOC4071) for the condensation of *o*-iodobenzamide with CuC≡CPh made Vasilevsky (86TH1) reproduce this reaction. When repeating the



SCHEME 125



SCHEME 126

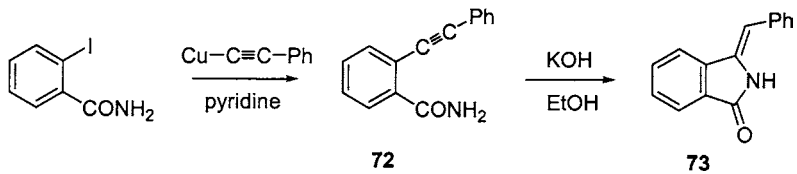


SCHEME 127

Bond–Huper [69JCS(C)2453] synthesis, no traces of the described high-melting dark red substance were found. Only tolane-2-carboxylic acid amide (yield 65%) was obtained—the white crystals with a melting temperature of 156–157°C—which coincided with the results of Castro *et al.* (66JOC4071). Thus, in conditions of acetylide synthesis, *o*-iodobenzamide forms no bicyclic product.

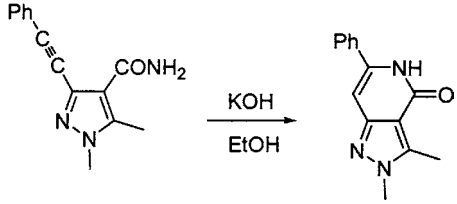
Nevertheless, the adjacent position of the amide and acetylenic groups was used in another type of heterocyclization. The nitrogen atom in the amide group is a weak nucleophile. Therefore, the N anion should be generated by potassium ethoxide. There are two possible variants of nucleophilic addition to the triple bond. Only one takes place, i.e., the formation of γ-lactam. After 7 h of heating in EtOH in the presence of KOH, amide **72** isomerized into the known isoindoline **73** in 80% yield (Scheme 128).

Intramolecular addition of the amide group to the triple bond in pyrazoles is more difficult, and results in closure of the δ-lactam rather than the γ-lactam ring. The reaction time of the 4-phenylethynylpyrazole-3-carboxylic acid amide under the same conditions is extended to 42 h (Scheme 129) (Table XXVII). The cyclization of 1-methyl-4-phenylethynyl-1*H*-pyrazole-3-carboxylic acid amide, in which the acetylene substituent is located in the π-electron-rich position of the heterocycle, is the only one complete after 107 h (Scheme 130) (90IZV2089).

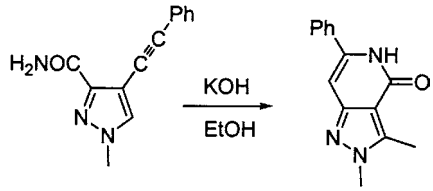


72 **73**

SCHEME 128



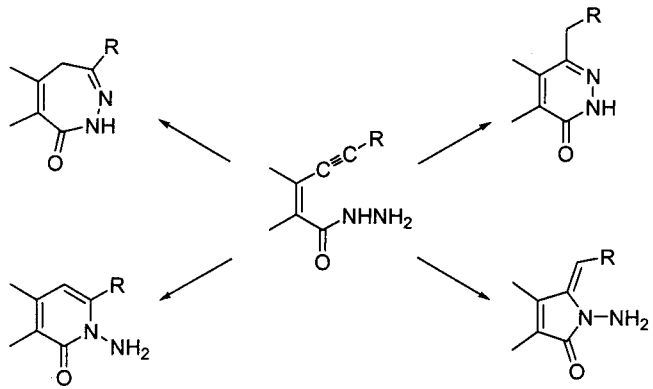
SCHEME 129



SCHEME 130

5. *Hydrazides of Acetylenylpyrazolecarboxylic Acids*

Hydrazides of vicinal acetylene-substituted derivatives of benzoic and azole carboxylic acids are important intermediate compounds because they can be used for cyclization via both α- and β-carbon atoms of a multiple bond involving both amine and amide nitrogen atoms (Scheme 131). Besides, the hydrazides of aromatic and heteroaromatic acids are convenient substrates for testing the proposed easy formation of a five-membered ring condensed with a benzene nucleus and the six-membered one condensed with five-membered azoles.



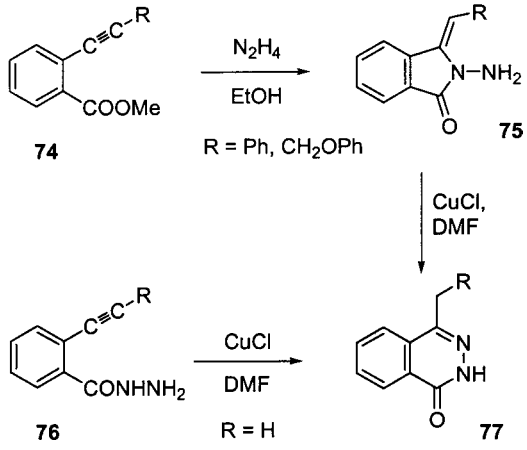
SCHEME 131

The cyclization of hydrazides of aromatic and heteroaromatic acids is likely to give four most probable products: diazepines, diazines, δ-*N*-aminolactams, and γ-*N*-aminolactams.

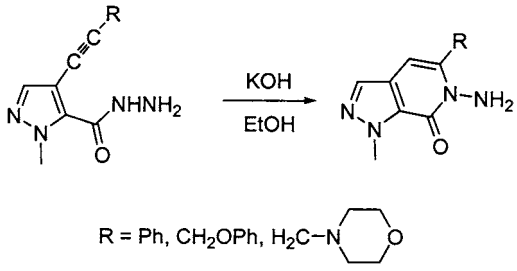
The hydrazides of acetylenylbenzoic acids can be prepared from the corresponding esters and could be heterocyclized under standard conditions (CuCl, DMF, 155°C; KOH, boiling EtOH). The hydrazide of tolane-2-carboxylic acid resulting from the boiling of ester **74** (R = Ph) with an excess $NH_2NH_2 \cdot H_2O$ in ethanol was cyclized in 70% yield into 2-amino-3-benzylidene-2,3-dihydroisoindol-1-one **75.** In the condensation of methyl benzoate **74** with hydrazine hydrate in ethyl alcohol at 20°C, γ-*N*-aminolactam was the main reaction product (yield 50%). The ease of heterocyclization and the attack of the α-C atom of C≡C by the amide nitrogen, whose nucleophilicity is smaller than that of the amine nitrogen, are probably caused by the fact that hydrazine hydrate acts as a base in this case, generating the NH_2—N^-—CO anion. Indeed, in the alcohol–KOH solution the rate increases and the isomerization direction remains the same.

Another pathway takes place upon cyclization of hydrazides of benzene carboxylic acids in the presence of CuCl in an inert atmosphere in DMF. However, only the cyclization of hydrazide **76** (R = H) in conditions of copper catalysis makes it possible to isolate compound **77** (yield 20%). Other hydrazides of acetylenylbenzoic acids react to give a complex mixture of products (Scheme 132) (85IZV1367; 85MI2).

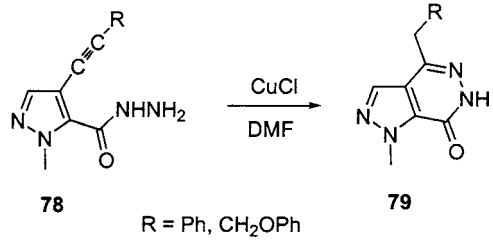
In conditions of base catalysis, the acetylenylpyrazolecarboxylic acid hydrazides, as opposed to benzene derivatives, are more difficult to cyclize compared with the benzoic acid derivatives and are isomerized only after heating in alcohol in the presence of KOH, forming not five- but six-membered lactams. The yields of pyridopyrazoles were 80–90% (Scheme 133; Table XXVIII) (85IZV1367; 85MI2).



SCHEME 132



SCHEME 133

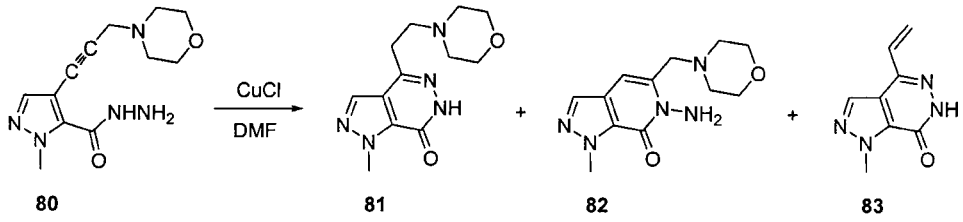


SCHEME 134

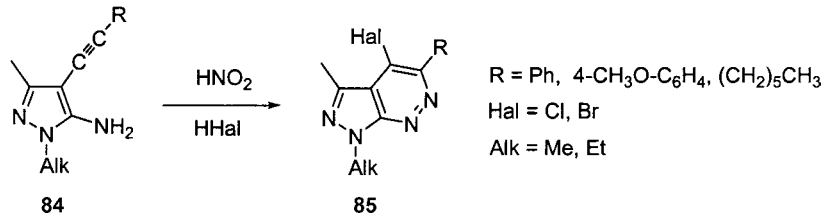
Another possibility is observed upon cyclization of hydrazides of pyrazolecarboxylic acids in the presence of CuCl in an inert atmosphere in DMF. When acetylenylcarboxylic acids are heated in the presence of CuCl in DMF, the orientation of the cycloaddition of the hydrazide group differs from that observed for cyclization in basic conditions. The cycloisomerization of hydrazides **78** in boiling DMF leads to the corresponding pyrazolopyridazines **79** in 60–71% yields (Scheme 134; Table XXIX) (85IZV1367; 85MI2).

The cycloisomerization of hydrazide **80,** catalyzed by CuCl, gives diazine **81,** *δ*-*N*-aminolactam **82,** and, unexpectedly, 6,7-dihydro-4-vinyl-1-methylpyrazolo [3,4-*d*]pyridazine-7 **83** (85MI2) (Scheme 135).

The data thus obtained allow us to make some generalizations for the heterocyclization of hydrazides of the vicinal acetylenic derivatives of pyrazolecarboxylic



SCHEME 135



84 **85**

SCHEME 136

acids. Under the action of bases, these compounds cyclize into γ- and δ-*N*-aminolactams; i.e. they always form a bicyclic system consisting of five- and six-membered rings.

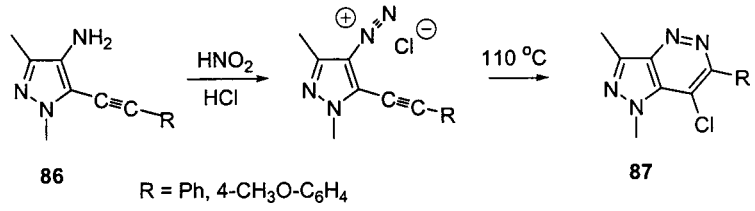
6. *Diazonium Salts of Acetylenylpyrazoles*

Some of us (94SC1733) have demonstrated that the classical Richter reaction (79MI1), the intramolecular cyclization of 2-alkynylaryldiazonium salts to give cinnolines, can be applied to the synthesis of not only 4-hydroxy- but also 4-bromo- and 4-chlorocinnolines. By attempting to extend the applicability of this reaction, it was found that the behavior of alkynylpyrazolediazonium chlorides differs from that of their benzene analogs. Thus, cyclization of 1,3-dimethyl-5-phenylethynylpyrazole-4-diazonium salts does not lead to the expected 4-hydroxydiazines (95LA775), moreover, under similar conditions, the isomeric 1,5-dimethyl-3-phenylethynylpyrazole-4-diazonium chloride does not react via a Richter mechanism (96MC190) (see Scheme 136; Table XXX).

In general, it is difficult to predict the outcome of cyclizations of alkynylpyrazole diazonium salts, even with closely related arrangements of functional groups, since reaction can occur at both the α- and β-carbon atoms of the acetylenic substituent. Moreover, it is known that the electrophilicity of the diazo group and the nucleophilicity of a triple bond markedly depend on their positions in the pyrazole ring and that this can affect both the course and ease of cyclization and even its viability (83IZV688).

In the first examples, diazotization of the 4-alkynyl-5-amino-3-methyl-l-alkylpyrazoles **84** in hydrochloric or hydrobromic acid at -15°C led to the corresponding alkynylpyrazole diazonium salts which underwent facile cyclization upon warming to 25–30°C to give fair to good yields of the 4-chloro-1-alkyl-1*H*-pyrazolo[3,4-*c*]pyridazines or the corresponding 4-bromo derivative, respectively (Scheme 136) [95LA775; 98HEC519; 99JCS(P1)3721].

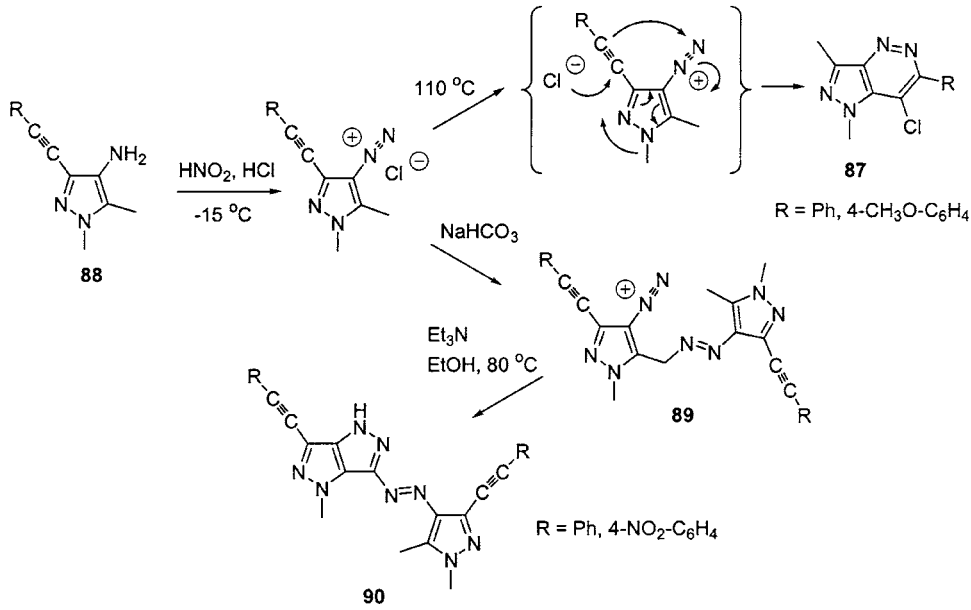
In contrast, the isomeric 5-alkynylpyrazole-4-diazonium chlorides cyclized only after heating to100–105°C for 2 h, giving good yields of the 1,3-dimethyl-7-chloro-l*H*-pyrazolo[4,3-*c*]pyridazines **87** [98HEC519; 99JCS(P1)3721] (Scheme 137).



SCHEME 137

3-Alkynylpyrazole-4-diazonium chlorides derived from the corresponding aminopyrazoles **88** underwent cyclization much more slowly than the isomeric derivatives (diazonium salt from **86**) (concentrated HCl, 100–105°C, 6 h). Surprisingly, the reaction products were identical to compounds **87** formed by cyclization of diazotized amines **86.** Thus, the cyclization of the pyrazole-4-diazonium chlorides causes methyl group migration to the neighboring nitrogen atom [98HEC519; 99JCS(P1)3721] (Scheme 138).

The behavior of aminopyrazole **88** (R = 4-NO_2—C_6H_4) under these conditions was quite different; diazotization using nitrous acid in concentrated hydrochloric acid afforded an alkynylpyrazole diazonium chloride, which did not participate in the Richter reaction, probably due to the electron-withdrawing effect of the nitro group. Instead, after neutralization of the hydrochloric acid with sodium hydrogen



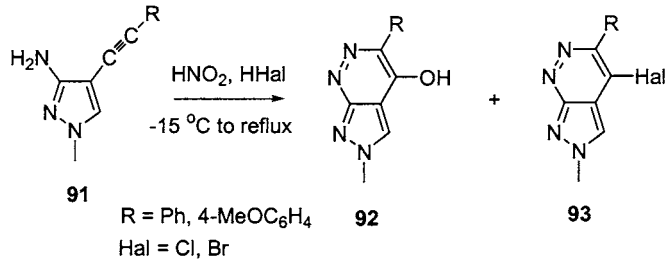
SCHEME 138

carbonate, the methyl group at position 5 of the pyrazole added to the diazonium group of a second molecule of the diazotized pyrazole. The resulting diazonium chloride **89** (R = 4-NO_2—C_6H_4) was cyclized in pyridine at 110°C to yield the pyrazolo[4,3-*c*]pyrazole **90** (R = 4-NO_2—C_6H_4) [99JCS(P1)3721].

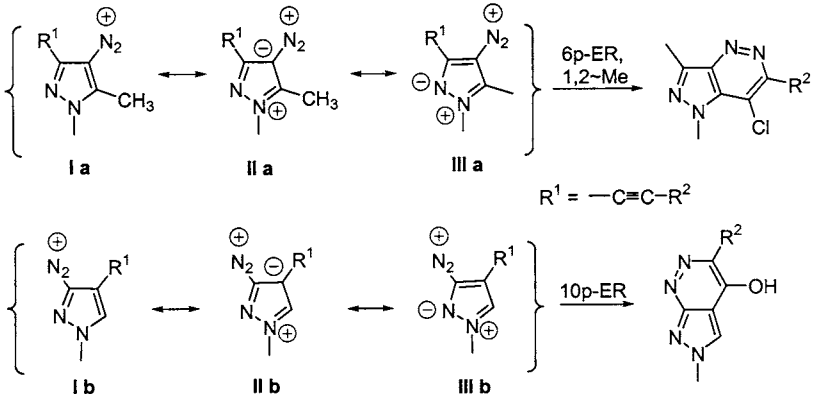
Because of the much lower reactivity of the diazonium salt with respect to the Richter cyclization, the same sequence could also be carried out starting with aminopyrazole **88** (R = Ph). The azodiazonium salt **89** (R = Ph) was thus obtained by sequential diazotization and neutralization of the resulting mixture at 5–10°C. The salt **89** (R = Ph) could be smoothly cyclized in boiling ethanol in the presence of triethylamine to afford the pyrazolo[4,3-*c*]pyrazole **90** (R = Ph) [96MC190; 99JCS(P1)3721].

To create a complete pattern of the transformations of aminoacetylenes of the pyrazole series in the Richter reaction, the cyclizations of 4-alkynylpyrazole-3-diazonium salts containing no methyl groups at position 5 of the heterocycle were studied. This excluded the possibility of intermolecular condensations between these and the diazonium functions. 4-Alkynyl-3-aminopyrazoles **91** were diazotized under standard conditions. Heating the resulting alkynylpyrazole diazonium salts in the diazotization solution at 50–60°C caused cyclization to give mainly the 5-substituted 4-hydroxy-2-methyl-2*H*-pyrazolo[3,4-*c*]pyridazines **92** together with the 4-chloro or 4-bromo derivatives **93** as minor components [99JCS(P1)3721] (Scheme 139).

The difference in behavior of 3-alkynylpyrazole-4- and 4-alkynylpyrazole-3-diazonium salts [**Ia** and **Ib,** respectively] upon Richter synthesis may be explained as follows (Scheme 140). The cyclization is assumed to be favored by the aromaticity inherent in the newly formed pyridazine ring. But in some cases, for example, upon cyclization of *vic*-alkenyldiazonium salts, the cyclic conjugated polyene is not formed at the initial stage of the reaction. In these cases, the aromaticity (75MI1) of the transition state arising from disrotatory electrocyclic cyclization may compensate for the energy losses upon the approach of the reaction centers. Obviously, these considerations may be extended to the cyclization of *vic*-alkynyl arenediazonium salts because in the disrotatory process, the overlapping of orbitals in the ring



SCHEME 139



SCHEME 140

plane is reached earlier than the π-overlapping of *p*-orbitals of both the β-nitrogen atom of the diazonium group and the β-carbon atom of the triple bond. At the same time, the electrocyclic reactions of *vic*-acetylenic derivatives of monocyclic arenediazonium salts may formally take place through a second mechanism, via the 6-electron 1,6-electrocyclic mechanism involving the entire aromatic ring system. In the former case, the energy of the transition state must be lower owing to a higher level of aromaticity. In examples of the cyclization of 3-alkynylpyrazole-4- and 4-alkynylpyrazole-3-diazonium salts **Ib,** a peculiarity of these substrates is the possibility that cyclization via a 1,6-electrocyclic reaction depends upon the degree of double bond character of the bond between carbon atoms in positions 3 and 4, which in turn is determined by the contribution of resonance structures **IIIa,b** to the true structure of the pyrazole diazonium salts. Due to the introduction of an electron-acceptor diazonium group into position 4 of the ring, the contribution of resonance structures **IIa** and **IIIa** is large when compared to the contribution of structures **IIb** and **IIIb** to the true structure of the corresponding diazonium salts. Probably, the difference lies in the fact that in the first case, the distribution of electron density favors the methyl cation migration toward the neighboring nitrogen atom.

Thus, the Richter reaction of the series of alkynylaminopyrazoles opens up a route to halo derivatives of 1*H*-pyrazolo[3,4-*c*]pyridazines, 2*H*-pyrazolo[3,4-*c*] pyridazines, and l*H*-pyrazolo[4,3-*c*]pyridazines.

The data obtained allow us to make some generalizations for the heterocyclization of the functionally substituted acetylenic derivatives of the benzene and pyrazole series. Studies of the heterocyclization of the functionally substituted acetylenic derivatives of substituted benzenes and pyrazoles reveal noticeable differences in their reactivities.

Whereas the condensation of *o*-iodonitrobenzene with copper acetylides is accompanied by cyclization into isatogens, neither 4-iodo-3-nitro- nor 5-iodo-4-nitro-1,3-dimethylpyrazole gives cyclized products in conditions of acetylide synthesis. Moreover, nitropyrazolylphenylacetylene, as compared with *o*-nitrotolane, does not undergo thermal, catalytic, or photochemical isomerization to give the fused five-membered rings.

The intramolecular nucleophilic addition of amino groups is typical for *o*-acetylenylanilines that are readily cyclized into 2-substituted indoles. In contrast, 4-acetylenyl-3-amino- and -5-aminopyrazoles cannot be cyclized. However, when amino groups are in position 4 of the pyrazole ring, where their nucleophilicity is much higher, the formation of the pyrrole ring occurs to give the condensed system of two five-membered heterocycles. The decreased tendency of the vicinal functionally substituted pyrazole acetylenic derivatives to cyclize with the closure of the five-membered ring is likely to depend on the higher strength of the annealed system of two five-membered rings as compared with the system of five- and six-membered rings.

This tendency is especially significant in compounds containing functional groups capable of addition with the formation of both five- and six-membered rings. It has been shown that for amides and hydrazides of azolecarboxylic acids, selectively, and for the acids with any arrangement of a function and triple bond, heterocyclization always leads to the closure of the six-membered ring. Similar reactions in the benzoic series mainly lead to the formation of five-membered rings.

The intramolecular cyclization of 2-alkynylaryldiazonium salts (Richter reaction) leads not only to 4-hydroxy- but also to 4-bromo- and 4-chlorocinnolines. The behavior of alkynylpyrazolediazonium chlorides differs from that of their benzene analogs. The Richter reaction of the series of alkynylaminopyrazoles gives only 4-halo derivatives of 1*H*-pyrazolo[3,4-*c*]pyridazines and l*H*-pyrazolo[4,3-*c*] pyridazines, and mainly hydroxy derivatives of 2*H*-pyrazolo[3,4-*c*]pyridazines.

Synthetically, vicinal functionally substituted aryl- and hetarylacetylenes are promising intermediates for preparing different condensed heterocyclic compounds, taking into account the fact that these polyfunctional groups can be selectively involved in cyclization processes.

IV. Structure, Spectra, and Properties of Acetylenylpyrazoles

A. Molecular Dimensions

The molecular structure has so far been determined only for 3-(pyrazol-4-yl) propargyl alcohol (98MO76) and 5-trimethylsilanyl-4-trimethylsilanylethynyl-1*H*-pyrazole-3-carboxylic acid ethyl ester (88JOM247).

The X-ray crystal structure of 3-(pyrazol-4-yl)propargyl alcohol shows that the N and O atoms are involved in chains of hydrogen bonds, running through the whole crystal, which show proton disorder in a 1:1 ratio. The bond lengths and angles in the pyrazole moiety display a quite symmetric pattern due to the proton disorder observed between both nitrogen atoms. The ring is not significantly planar and the carbon atoms of the substituent deviate progressively from its least-square plane. The C≡C bond length is slightly elongated [1.193(2) Å] compared with the triple bond in organic compounds. Selected geometric parameters (Å, deg): N(1)—N(2) 1.345(2), N(1)—C(5) 1.323(3), N(2)—C(3) 1.321(2), C(3)—C(4) 1.387(2), C(4)—C(5) 1.385(2); N(2)—N(1)—C(5) 108.6(2), N(1)—N(2)—C(3) 108.4(2), N(2)—C(3)—C(4) 109.7(1), C(3)—C(4)—C(5) 103.9(1), N(1)—C(5)—C(4) 109.5(2); C(4)—C(alkyne) 1.425(2) (98MO76).

The X-ray crystal analysis of 5-trimethylsilanyl-4-trimethylsilanylethynyl-1*H*-pyrazole-3-carboxylic acid ethyl ester was obtained only with $R = 0.17$ because the crystals of the molecule diffracted extremely weakly and only a very limited data set was available. This means that although the gross stereochemistry of the molecule has been determined, individual bond lengths are not reliable (88JOM247).

B. IR Spectra

Parameters of IR spectra (in solutions, films, or KBr) of acetylenylpyrazoles are close to those in the arylacetylene series. The values of the characteristic frequencies of the stretching vibrations of a disubstituted triple bond are in the range 2160–2260 cm^{-1}, those of the monosubstituted C≡C—H bond are in the range 2100–2160 cm^{-1}, and those of the C—H bond are in the range 3275–3325 cm^{-1} (86TH1).

For example, 3-ethynylpyrazole shows bands at 2120 cm^{-1} and 3275 cm^{-1}. 5-Ethynyl-1-methylpyrazole shows bands at 3290 cm^{-1} and 2120 cm^{-1} (68LA113).

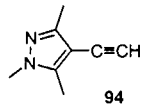
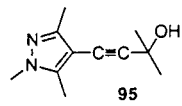
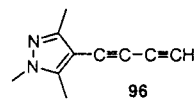
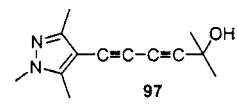
1-Ethynylpyrazole shows a sharp peak at 2170 cm^{-1} (C≡C) and 3300 cm^{-1} (≡C—H); the corresponding bands for 1-ethynyl-3,5-dimethylpyrazole appear at 2160 cm^{-1} and 3300 cm^{-1} (94AJC991).

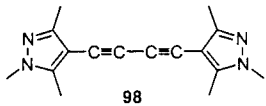
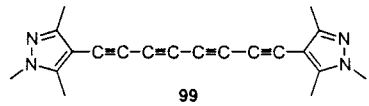
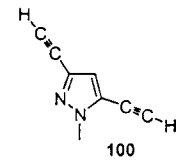
Only in one work (69KGS1055) was an attempt made to interpret the main IR spectrum parameters (in the region of stretching vibrations of triple bonds) of pyrazolylacetylenes considering a mechanical model and using the results of calculation analysis but doing no calculations. The IR spectra of all studied acetylenylpyrazoles manifest in the range 2100–2200 cm^{-1}, the stretching vibrations of the C≡C bond. Table XXXI shows the corresponding frequencies.

Using a mechanical model and a set of force constants, Popov and Lubuzh (66ZPS498) have calculated vibration frequencies for polyacetylenic groups. But these calculations are rather complex and the data on the IR spectra of acetylenic

TABLE XXXI

FREQUENCIES OF VIBRATIONS OF THE C≡C AND ≡C–H BONDS OF THE ACETYLENYLPYRAZOLES

Compound	 **94**	 **95**	 **96**	 **97**
$\nu_{C\equiv C}$	2112	2228	2212	2150, 2232
$\nu_{\equiv C-H}$	3315	—	3310	—

Compound	 **98**	 **99**	 **100**
$\nu_{C\equiv C}$	2147, 2215	2078, 2125, 2195	2122
$\nu_{\equiv C-H}$	—	—	3313

compounds are given, as a rule, at a purely descriptive level without any attempt to interpret them. At the same time, a simple qualitative method for relating the structure of such a compound to the number and arrangement of bands in its spectrum would be highly helpful.

Considering the model of a diatomic oscillator, it can be shown that an increase in the mass of X strengthens the rigidity of the C_2 atom and consequently increases the frequency of its own vibrations.

$$C_1 \cdots C_2 \cdots X$$

Indeed, in the spectrum of ethynylpyrazole **94,** the triple bond appears at 2112 cm^{-1}; and then in the spectrum of carbinol **95,** as in other disubstituted acetylenes, their frequency increases by about 100 cm^{-1}. Note that the high intensity of the 2112 cm^{-1} band of compound **94** is likely to result from the elevated electron density at position 4 of the pyrazole ring and the resulting increase in the dipole moment of the triple bond conjugate to it.

The vibrations of the diacetylenic grouping in pyrazole **96** split into symmetric and antisymmetric modes. In this case, according to the linear model of two oscillators with an elastic bond, the former must have a higher frequency owing to the rigidity of the $C_1{\equiv}C_2$ bond.

For acetylenes close in structure, the values of the characteristic frequencies of the triple bond change negligibly. Thus, 3,4-diethynyl-, 4,5-diethynyl-, and 3,4,5-triethynyl-1-methylpyrazoles have the following values for the C≡C bond frequencies: 2132, 2135, and 2138 cm^{-1}, respectively; and the band typical of the ≡C–H bond has the same value for all three polyethynylpyrazoles (3320 cm^{-1}) (71IZV1764).

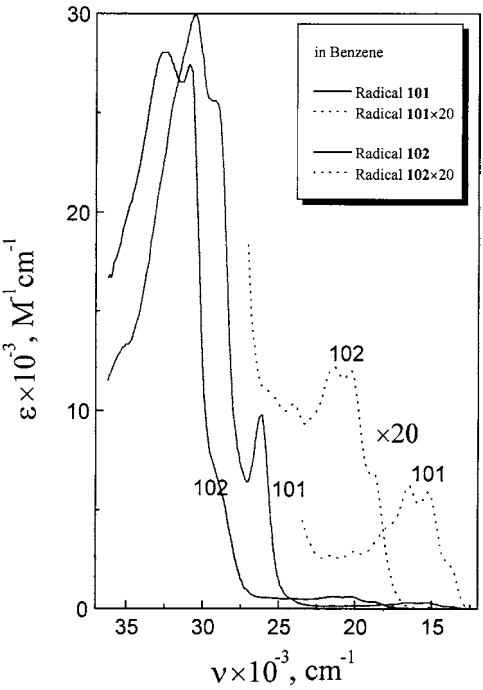
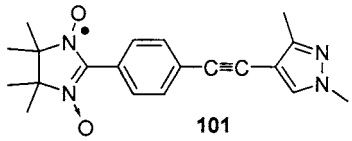


FIG. 1. Electronic absorption spectra of the nitroxyl radicals **101** and **102** in benzene.

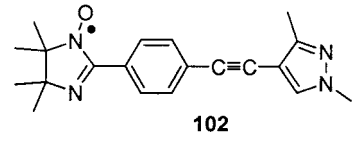
C. UV SPECTRA

The UV absorption spectra of most alkynylpyrazoles are quite similar to those of the corresponding pyrazoles. In general, they show a shift toward the visible [see (76T1293; 98JCS(P1)3233)]. The UV spectra and nonlinear optical properties have been reported for 4-(4-methoxyphenylethynyl)-1-(4-nitrophenyl)-1*H*-pyrazole and related compounds (94MI29).

The electronic spectra of radicals **101** and **102** have two sets of absorption bands in the visible and near-UV regions (Fig. 1, Table XXXII).



101



102

The splitting of both groups (visible and UV regions) is related to a vibrational structure of electron transitions (characteristic frequencies being

TABLE XXXII

DATA ON THE OPTICAL ABSORPTION SPECTRA OF RADICALS **101** AND **102**

Radical	ν, cm^{-1} (ε, M^{-1} cm^{-1})					
Visible region						
101	13900 sh[a] (120)	15200 (295)	16500 (310)	17700 sh (210)	20000 (145)	21500 (135)
102	18900 (340)	20300 (600)	21300 (610)	22800 sh (485)	24000 (515)	25500 sh (540)
Near-UV region						
101	26100 (9800)	29300 (25600)	30500 (29900)			34850 (13300)
102	29100 sh (6600)	30900 (27400)	32500 (28000)	34900 sh (20200)		

[a] sh, shoulder.

1200–1500 cm^{-1}). For radical **102,** the absorption bands are shifted toward the shortwave region, which changes the color of this radical.

7-Alkynylated 7-deazaadenine (pyrrolo[2,3-*d*]pyrimidin-4-amine) 2′-deoxyribonucleosides show strong fluorescence which is induced by the 7-alkynyl side chain. A large Stokes shift with an emission around 400 nm is observed when the compound is irradiated at 280 nm. The solvent dependence indicates the formation of a charged transition state; the fluorescence appears when the triple bond is conjugated with the heterocyclic base. Electron-donating substituents at the triple bond increase the fluorescence, while electron-withdrawing residues reduce it. In comparison, the 7-alkynylated 8-aza-7-deazaadenine (pyrrolo[3,4-*d*]pyrimidin-4-amine) 2′-deoxyribonucleosides are rather weakly fluorescent (2000HCA910).

D. ^{1}H NMR SPECTRA

The NMR parameters of the spectra of methyne protons for the simplest monoethynylpyrazoles vary even in different solvents within 1.0 ppm (from 2.7 to 3.7 ppm) and are close to those for the monosubstituted aromatic derivatives (71IZV1764; 72IZV2524; 76IZV2292). The values of the chemical shifts of acetylenic protons for 3- and 4-C≡C groups are close to one another even in different solvents, and the signal of ethynyl protons of 5-C≡CH is noticeably shifted to the weak field. Thus, ≡C—H shift in 3-ethynyl-1-methylpyrazole appears at 2.89 ppm (CCl_4); in 5-ethynyl-1-methylpyrazole, 3.49 ppm (CCl_4) (69IZV2546); and in 4-ethynyl-1-methylpyrazole, 2.88 ppm (CCl_4) (72IZV2524). Introduction of additional methyl groups moves the chemical shifts to higher fields.

For 1-ethynylpyrazole, 1-ethynyl-3,5-dimethylpyrazole, 1-ethynyl-3-methylpyrazole, and 1-ethynyl-5-methylpyrazole, the chemical shifts of the methyne protons appear in $CDC1_3$ at 3.14, 3.22, 3.05, and 3.21 ppm, respectively (94AJC991).

The same regularities are observed for polyethynylpyrazoles. Thus, for 3,5-diethynyl-1-methylpyrazole, the chemical shifts (in CCl_4) are 3-C≡CH 2.95,

5-C≡CH 3.52 ppm (69KGS1055); for 3,4-diethynyl-1-methylpyrazole (in $CC1_4$), 3-C≡CH 3.09, 4-C≡CH 3.01 ppm; for 4,5-diethynyl-1-methylpyrazole (in $CDC1_3$), 4-C≡CH 3.02, 5-C≡CH 3.62 ppm, and for 3,4,5-triethynyl-1-methylpyrazole (CD_3COCD_3), 4-C≡CH 3.64, 3-C≡CH 3.72, 5-C≡CH 4.36 ppm (71IZV1764). Note that the chemical shifts of the 5-ethynyl groups of pyrazoles are weakly dependent on the nature of substituents in the conjugate position 4 of the ring. The difference in the chemical shifts of acetylenic protons in 4-chloro-, 4-bromo-, 4-iodo-, 4-amino-, and 4-phenylethynyl-1,3-dimethyl-5-ethynylpyrazoles lies in the narrow range 3.61–3.66 ($CDCl_3$) (86TH1).

E. ^{13}C NMR Spectra

The ^{13}C NMR spectra for several alkynylpyrazoles have been measured, and selected data are presented in this section. The signals of the C≡C atoms in the ^{13}C NMR spectra resonate in the range 70–95 ppm. For 1-ethynyl-3-methylpyrazole the chemical shift of C≡CH atom appears at 58.3 ppm; the chemical shift of the **C**≡CH atom is 61.7. For 1-ethynyl-5-methylpyrazole the chemical shift of the C≡**C**H atom is 58.3 ppm, and the chemical shift of the **C**≡CH atom is 61.7 ppm (94AJC991). The direct spin–spin coupling constant of ^{13}C–^{13}C ($^1J_{C\equiv C}$) is 179.9 Hz for 5-ethynyl-1-methylpyrazole (88ZOR1595).

The chemical shifts of the C≡C carbon atoms are 83.0 and 90.4 ppm in the case of 4-phenyl-3(5)-phenylethynylpyrazole in DMSO (93ZOB1107).

For 4-phenylethynylpyrazoles the chemical shift (DMSO-d_6) of α-C is 82.09 ppm and β-C is 89.49 ppm. For 4-ethynylpyrazole these signals are shifted toward higher field, 76.06 ppm and 80.55 ppm, respectively (88MOC253).

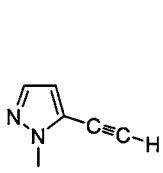
Using ^{13}C NMR spectroscopy, one can unambiguously estimate the direction and the degree of triple bond, as is demonstrated using 7-alkynyl-8-aza-7-deazaadenines [99JCS(P1)479]. The phenyl substituent at the triple bond has a weak $-I$ and $-M$ effect and causes polarization, upon which the triple bond carbon atom closest to the benzene nucleus bears a negative charge. In this case, the difference in the chemical shifts between α-C and β-C is not large and amounts to 10–13 ppm. At the same time, the butyl group having the $+I$ effect causes an opposite shift of electrons. In this case, the difference in the chemical shifts between α-C and β-C is 20–25 ppm (possibly, a push–pull system exists). The absolute values for α-C with an alkyl substituent are 71.9–73.6 ppm, and for β-C they are 93.8–96.9; for α-C with an aromatic substituent they are 91.8–93.5, and for β-C they are 80.7–82.5 ppm.

The ^{13}C NMR spectra for phenylethynyl-3*H*-pyrazoles have also been measured (91ZOB2286).

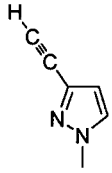
F. Thermodynamic CH Acidity of Ethynylpyrazoles

The high reactivity of monosubstituted acetylenes in many reactions (acetylenic condensation, Favorsky reaction, Mannich reaction, oxidative coupling, etc.) is determined by their acidity (71MI1; 83MI1). The literature data on the thermodynamic CH acidity of these compounds are rather scarce.

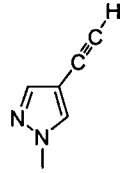
The thermodynamic CH acidity of terminal acetylenes in the series of *N*-alkylpyrazoles was studied (83IZV466). These equilibrium CH acidity measurements were performed in DMSO by the method of remetallation (75ZOB1529). It reveals some regularities concerning the influence of the ring structure, the nature of other substituents, and the position of the ethynyl group on the acidity of ethynyl pyrazoles.



p*K* = 26.9



p*K* = 29.0



p*K* = 30.4

The acidity of ethynylpyrazoles, free of other substituents, increases when the ethynyl group changes from position 4 to position 3 and then to position 5 of the pyrazole ring. The observed order of changes in equilibrium CH acidity values is in agreement with a change in the different positions of azole reactivity in reactions of electrophilic substitution (66AHC347; 67MI1).

A comparison between the values of the acidity of ethynylpyrazoles and the energies of heterocyclic cleavage of the C—H bond calculated by the CNDO-2 method (75KGS821) has revealed a correlation between these values (Fig. 2).

Experimentally obtained data confirm the order of pK_a values of the ethynyl proton 4 > 3 > 5 for pyrazoles predicted in (75KGS821) on the basis of calculations of the energy of CH bond cleavage. Of interest is also a tendency of a "pyrrole" nitrogen to increase the acidity of ethynyl-substituted compounds as compared with a "pyridine" nitrogen. The difference in the activity of "pyrrole" and "pyridine" nitrogen is about 2 log units.

The acidity of 4-ethynyl-1-methylpyrazole is lower than that of phenylacetylene (pK_a = 29.1) [75IZV2351; 79JCS(P2)726; 84IZV923]. The ethynyl group in other positions of pyrazoles has smaller pK_a values; i.e., 4-pyrazolyl radicals have a weaker electron-acceptor characteristic than the phenyl ring.

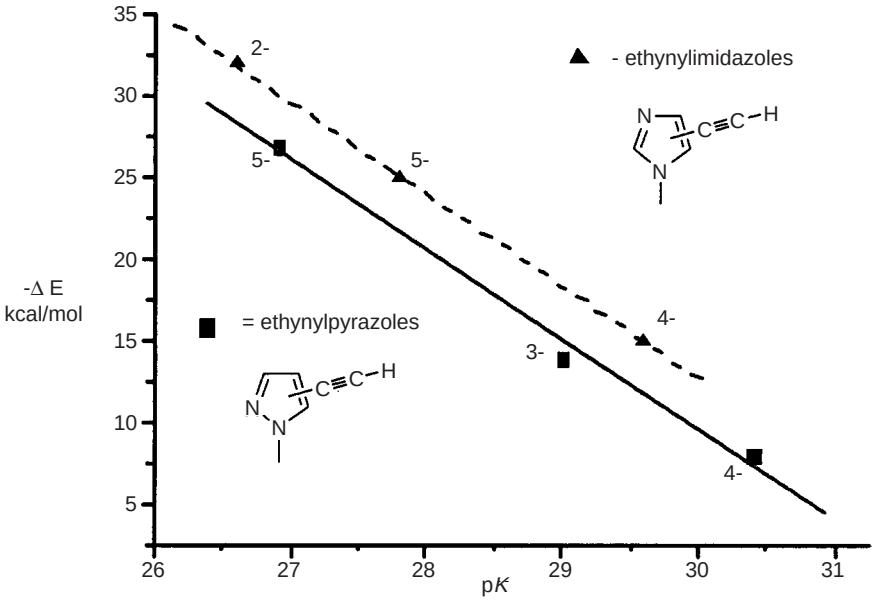
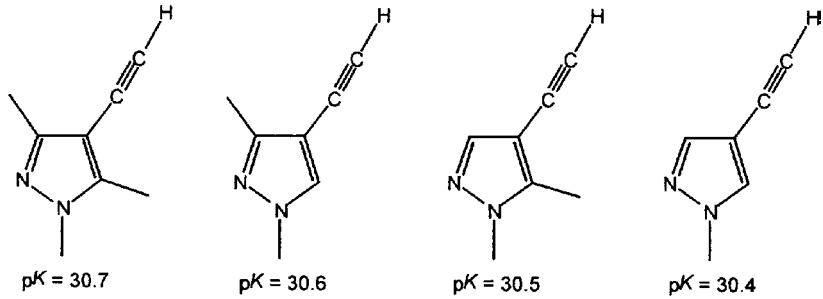
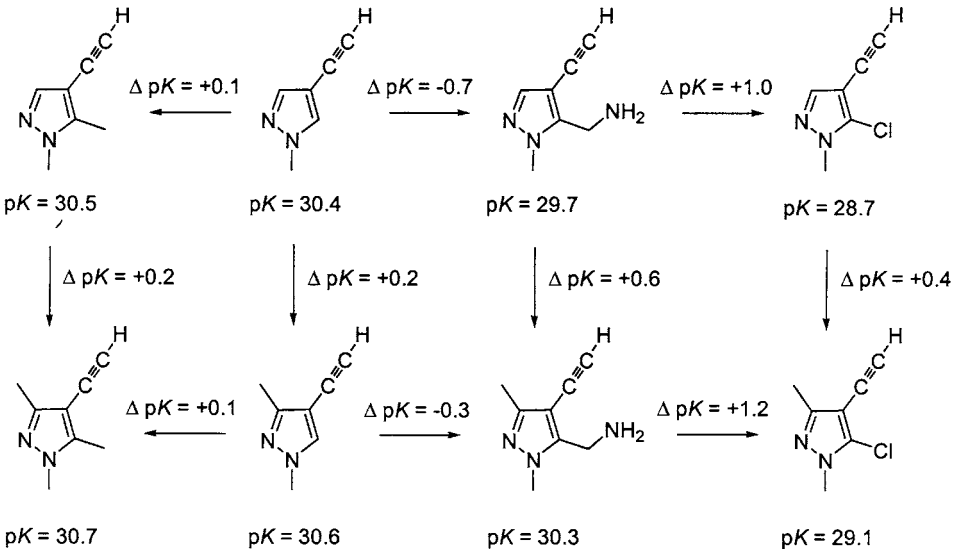


FIG. 2. Values of the acidity of ethynylpyrazoles and the energies of heterocyclic cleavage of C—H bond calculated by the CNDO-2 method (75KGS821).



4-Ethynylpyrazoles are less acidic than other CH acids in the series of both alkyl- and arylacetylenes (high pK_a values). In this case, the values of equilibrium CH acidity determined in the aprotic solvent DMSO agree with those of the "eigen" aciditiy obtained on the basis of quantum-chemical calculations on determination of deprotonation energy of terminal acetylenes (92ZOB2757). Indeed, among 27 monosubstituted acetylenes, the value of deprotonation energy (1550 kJ/mol) calculated by the MNDO/3 method for 1-methyl-4-ethynylpyrazole is second only to acetylene and methylacetylene (92ZOB2757).

The effect of substituents in the ring on the mobility of a methyne proton can be followed from the series of 5-substituted 1-methyl-4-ethynylpyrazoles and 1,3-dimethyl-4-ethynylpyrazoles. In both structural series, the acidity of compounds increases with a change in the character of substituents in the following order: $CH_3 < H < CH_2NH_2 < Cl$.

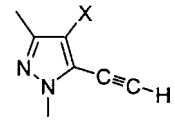


The scheme shows that the influence of substituents on CH acidity in ethynylpyrazoles is not additive as compared with benzene derivatives (84IZV923), and its value depends, for each substituent, on the nature of other groups in different positions of the azole.

The methyl group in position 5 displays weak electron-donor properties by decreasing acidity by 0.1 log unit. The methyl group in position 3 causes a slightly greater decrease in ethynyl group acidity. If there are acidifying groups in pyrazole position 5, the donor properties of 3-Me increase and ΔpK_a is 0.4 and even 0.6 unit of equilibrium CH acidity.

The acidity of 4-acetylenenylpyrazoles increases by 0.3–0.7 log units on introducing CH_2NH_2 group into position 5 of the ring. Chlorine atoms have the greatest acidifying effect. Chlorine atom in position 5 increases the acidity of 1-methyl-3-ethynylpyrazole.

In the 4-substituted 1,3-dimethylpyrazoles with ethynyl group fixed in position 5, the acidity increases with a change in the character of substituents in the series: $H = NH_2 < C{\equiv}CPh < I < Br = Cl$.



X	H	NH_2	C≡CPh	I	Br	Cl
pK_a	27.0	27.0	26.1	26.0	25.5	25.5

The increasing CH acidity in the ethynylpyrazole series points to the advantageous inductive nature of this influence. Although the data are rather scarce, some correlation is observed between the ethynyl group pK_a values and σ_I constants of substituents in heterocycles (Fig. 3).

It is known that diacetylenes (in Favorsky's reaction, for example) are 1000-fold more active than monoacetylenes. It is of interest to consider how the accumulation of triple bonds will affect the compound acidity. However, in the literature there are no data on the CH acidity of diacetylenic compounds. We were the first to estimate the pK_a of a monosubstituted diacetylene, 4-butadiynyl-1,3,5-trimethylpyrazole, to be about 24–26 log units. Unfortunately, the authors (83IZV466) have failed to determine the acidity of the diyne more accurately owing to the side processes of remetallization that complicate control over reaction.

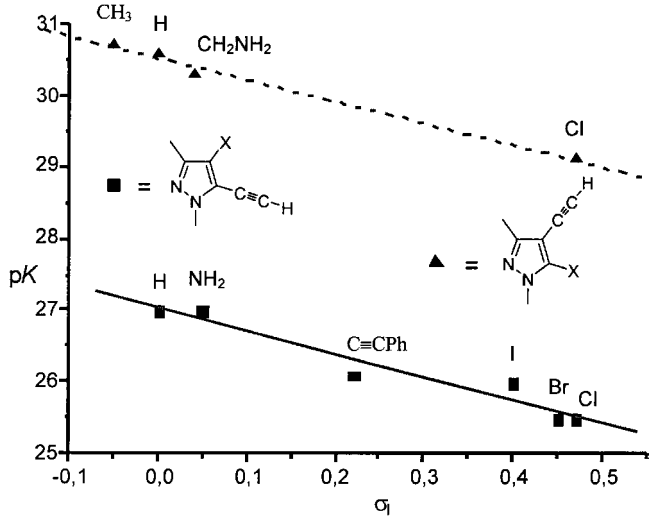
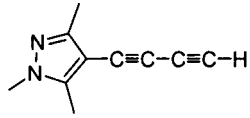
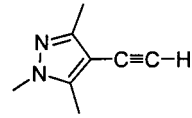


FIG. 3. The ethynyl group pK_a values and σ_I constants of substituents in ethynylpyrazoles.



pK ~ 24-26

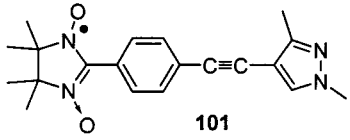


pK = 30.7

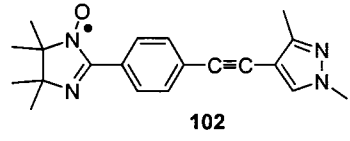
The acidity of the diacetylene is 5–6 orders of magnitude higher than that of the monoacetylenic analog.

G. Magnetic Properties of Spin-Labeled Alkynylpyrazoles

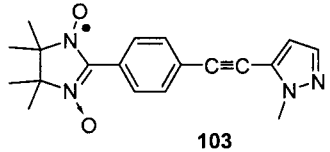
The structure of spin-labeled acetylenes includes π-electron-rich pyrazole and 4,4,5,5-tetramethylimidazoline-3-oxide-1-oxyl (nitronylnitroxyl radicals, NN) or 4,4,5,5-tetramethylimidazoline-l-oxyl (iminonitroxyl radicals, IN) fragment bound by a stable phenylacetylene bridge included in the general conjugation system of a molecule. Such compounds are rather promising for the practical solution of a problem of creation of new classes of optical and magnetic materials. The use of an acetylene fragment in a molecular structure allows a definite distance between the coordination and the paramagnetic centers that is very desirable for the design of n-dimensional molecular systems (98MC216; 99MC92).



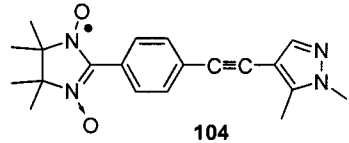
101



102



103



104

Pyrazolylethynylphenylnitroxides **101–104** are quite stable in solid state as well as in solution at ambient temperature. They have typical 2-imidazoline nitroxide EPR spectra. Figures 4 and 5 illustrate the EPR spectra of nitroxides **101** and **102.**

The spectrum of radical **101** appears as a quintet (1:2:3:2:1) caused by the hyperfine interaction (HFI) with two equivalent nitroxide nitrogen nuclei ($a_N =$ 0.74 mT), each line of the quintet being additionally split due to hyperfine

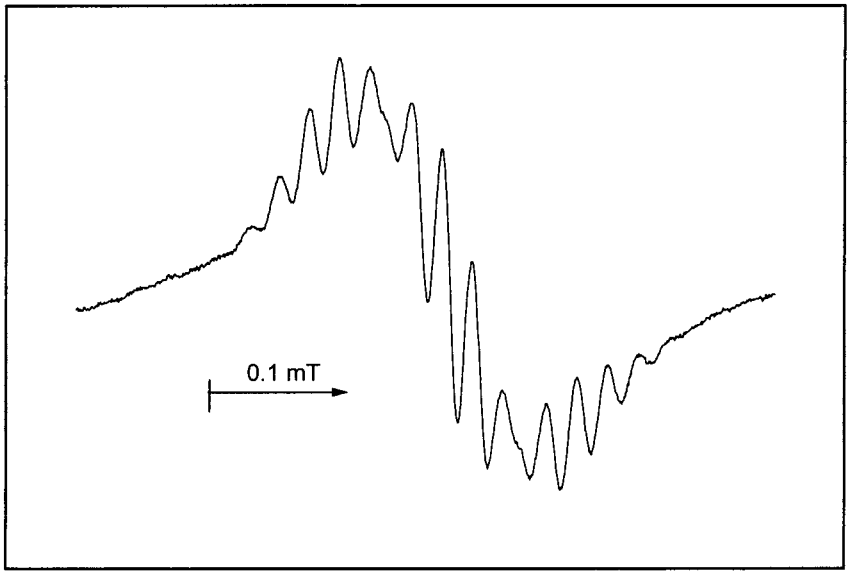


FIG. 4. The central component of the EPR spectrum of radical **101.**

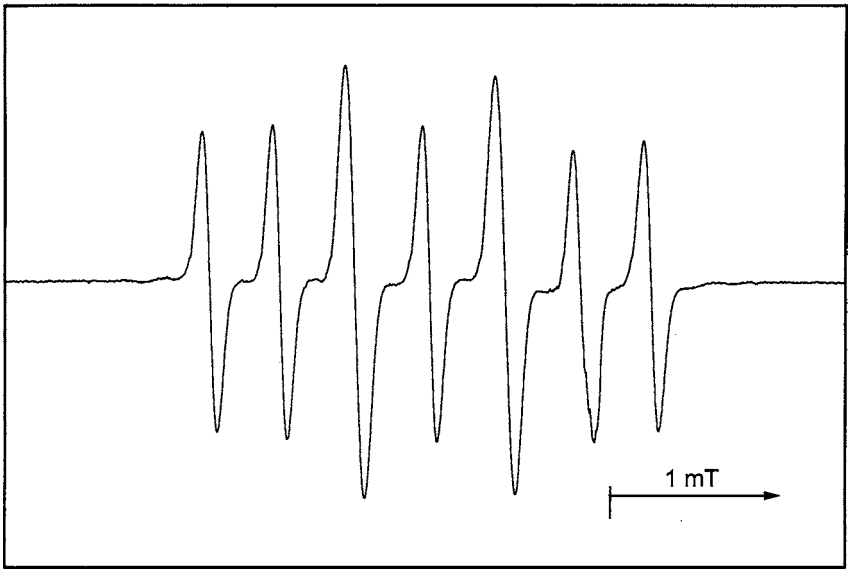


FIG. 5. The EPR spectrum of radical **102** (5×10^{-5} *M*) in an oxygen-free hexane solution at room temperature.

interaction with 12 protons of α-methyl groups [$a_H(CH_3) = 0.021$ mT] and *ortho*-protons of the benzene ring ($a_{ortho} = 0.054$ mT). Figure 4 illustrates this, depicting a central component of the quintet. The EPR spectrum of radical **102** presented in Fig. 5 is caused by HFI with two nonequivalent nitrogen of the imidazoline moiety, the hyperfine coupling constants differing about 2-fold ($a_{N1} = 0.907$ mT and $a_{N3} = 0.432$ mT).

The *g*-factors of radicals **101** and **102** are 2.0065 and 2.0059, respectively. The pyrazolylnitroxides have effective magnetic moments at room temperature corresponding to the standard values for one unpaired electron per molecule (1.71 ± 0.05 B.M.). The values of effective magnetic moments of the nitroxyls practically do not change in the temperature range 5–300K.

A fundamental parameter characterizing the EPR signals of radicals is a *g*-tensor, which depends on the electron structure of a radical, and the influence of the medium in which it is located. The conventional X-band technique (wavelength 3 cm, frequency 9.6 GHz) for determination of the *g*-tensor is ineffective in this case; this is because for most organic radicals, the anisotropy and mean values of the *g*-tensor give the spacing between the lines of different components of about several Gauss, which is comparable to a linewidth. The use of a 2-mm wave allows one to get a *g*-factor resolution of up to 10^{-5} by increasing the value of Zeeman interaction by an order of magnitude. This accuracy makes it possible to determine all *g*-tensor components, which become the individual parameters of radicals.

Figure 6 shows the EPR spectra with defined *g*-tensor and HFI components for radicals **101** and **102.**

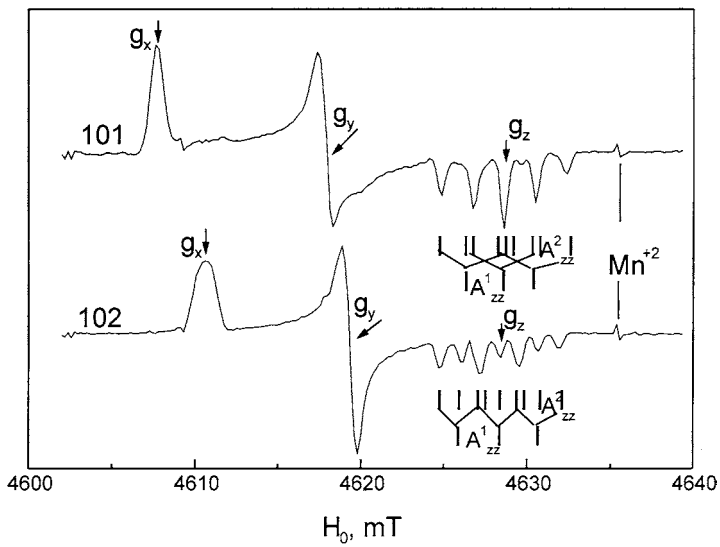


FIG. 6. EPR spectra (2-mm band) of radical **101** and **102** (5×10^{-5} *M*) in oxygen-free toluene at 130–140K.

TABLE XXXIII
THE VALUES OF *g*-FACTOR AND HFI CONSTANTS OF RADICALS **101** AND **102**

Radical	g_{xx}	g_{yy}	g_{zz}	$A_{xx}(1)$	$A_{zz}(2)$
101	2.0110	2.00660	2.00210	18.9	18.9
102	2.0098	2.00607	2.00186	23.0	12.1

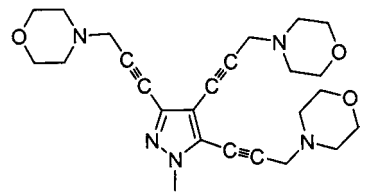
The spectra display three lines whose positions are determined by orientations of the magnetic field along each of the own axes of the *g*-tensor. The positions of the centers of three components allow one to determine the main values of the g-tensor (g_{xx}, g_{yy}, g_{zz}). Hyperfine interaction with one or two nitrogen nuclei leads to additional splitting of components. In most cases, it is possible to record the splitting of the *Z*-component into five lines upon interaction with two equivalent nitrogen nuclei (Fig. 6, radical **101**). If two nitrogen nuclei are nonequivalent, the *Z*-component splits into seven components (Fig. 6, radical **102**) owing to the overlapping of two pairs of the lines. Table XXXIII shows the magnetoresonance parameters of radicals **101** and **102** obtained by analyzing line positions in the 2-mm-band EPR spectra.

V. Biological Properties of Acetylenylpyrazoles

A. USE AGAINST HYPOXIA AND POISONING

In the last few years, interest in the use of alkynylpyrazoles in medicine and agriculture has greatly increased. Izyumov (74MI1) has studied the influence of alkynylpyrazoles (injected in rats) on different types of extreme action of an organism (hypoxia, overheating, poisoning by copper salts, etc.).

One of the most important problems in the sphere of industrial activity is that attending high ambient temperature. Therefore, the search is on for substances that can increase the resistance of organisms to dangerous overheating. Experiments on white rats show that substance **103,** called "azomopine," has a protecting effect in different temperature regimes.



103

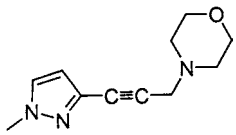
Depending on the dose and temperature regime, the screening effect azomopine is observed after intoxication by chlorophos. The survival of white rats injected with this preparation is 50% higher than that of control rats. When toxic doses of copper sulfate were injected for 7 days, 70 and 36% of the rats survived. After the simultaneous injection of azomopine, their survival increased to 100 and 70% (74MI1).

An intensive search for pharmacological means of decreasing the demand for oxygen is one of the effective methods for controlling diseases, many of which are caused by oxygen insufficiency. The influence of a number of aminoacetylenes with different numbers of morpholinopropynyl groups on the hypoxic and hypoxy tissue of animals (white rats) has been studied. Hypoxic hypoxia was induced by lifting white mice to a height of 9000 m in a pressure chamber. The survival of animals injected with azomopine was 4–6 times higher than that of the mice in the control group. In conditions of histotoxic (tissue) hypoxia caused by injection of KCN, the life of white mice in the control group was 3–4 times shorter than that of the mice injected with the azomopine (74MI1).

Among aminoacetylenes with different numbers of morpholinopropynyl groups, a substance has been found that displays antihypotoxic, thermoprotecting properties, increasing the stability of animals to intoxication by phosphor organic compounds and the salts of toxic metals. Because the efficiency of this substance exceeds that of azomopine **103** and it is nontoxic, it could be of interest to clinical medicine after additional studies.

Following the action of extraordinary stimulants (hypoxic hypoxia, hypoxia + hyperoxia, hypodynamia + hyperthermia), animals demonstrate an accumulation of malonic dialdehyde with a simultaneous fall of antiradical activity of the liver tissue. A preliminary introduction to rats of acetylene amine 3,4,5-tris(morpholinopropynyl)-1-methylpyrazole **103** and also of tocopherol antioxidant and "gutumine" antihypoxant averts activation of the lipid peroxidation processes. The inhibition of peroxidation with this agent is mediated by stabilization of lyzosomal and mitochondrial membranes. Unsaturated amines prevent destruction of the organelle membranes provoked by UV irradiation and incubation at 37°C (pH 4.7) (78MI1).

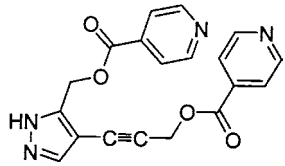
The acetylene aminopyrazole **103** was capable of inhibiting the processes of lipid peroxidation both in the enzymatic and nonenzymatic peroxidation system (76MI2). Finally, 4-[3-(1-methyl-1*H*-pyrazol-3-yl)-prop-2-ynyl]morpholine hydrochloride **104** was patented as a compound with high hypoxic activity (93MIP1).



104

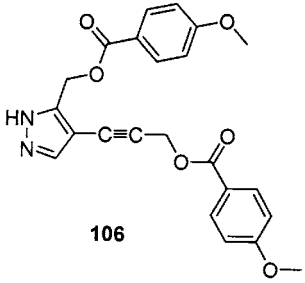
B. Use against Cardiovascular, Inflammatory, and Other Diseases

Acetylenylpyrazoles were tested on antiarrhythmia activity (84MI1). The use 5 mg/kg of compound **105** inhibited the development of aconitine arrhythmia in 50% of animals. However, it failed to prevent heart arrhythmia. A dose of 15 mg/kg prevented or substantially inhibited the break of arrhythmic activity in about 75% of white rats.

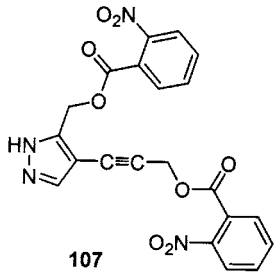


105

Compounds **106** and **107** have a pronounced antiinflammatory effect. Doses of 100 mg/kg of these compounds suppress the development of edema by 69 and 45%, respectively. Compound **108,** whose activity is 4 times higher than that of amidopyrine, has a stronger effect (87MI2).



106



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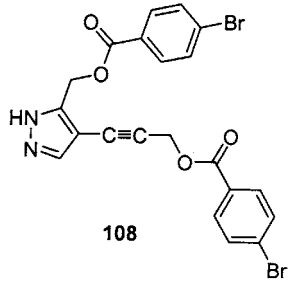
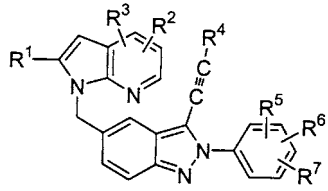


108

Tolf and colleagues prepared 4-alkynylpyrazoles and their saturated analogs and assayed them for *in vitro* inhibition of horse liver alcohol dehydrogenase (LADH). It was shown that the saturated substituents displayed increased inhibitory activity (84BAP265).

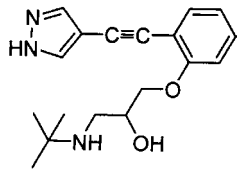
A patent (95JAP07196655) described the preparation of a 2*H*-indazole derivative of specific formula **109** useful as a therapeutic agent for a circulatory disease such as hypertension, having angiotensin II antagonism and antihypertensive action. In formula **109** R^1 = lower alkyl or alkenyl; R^2, R^3 = H, halogen, lower

alkyl, $(CH_2)_nR^9$ (R^9 = hydroxyl or alkoxy; $n = 1$–4); R^4 = aryl; $R^5 = CO_2H$ or C-bonded tetrazoline; R^6, $R^7 = H$, F, Cl, lower alkyl, etc.



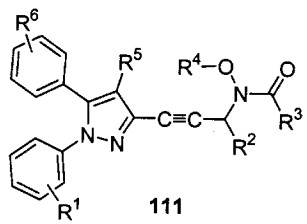
109

Different heterocyclic acetylenes including pyrazolyl derivatives **110** are useful in treating hypertension and/or angina (87USP4663334).



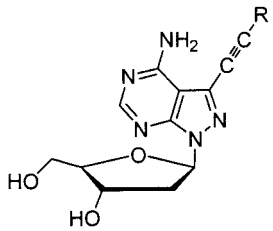
110

Compounds **111** having structural features of the dual cyclooxygenase (COX)/5-lipooxygenase (5-LO) inhibitor tepoxalin and the 5-LO inhibitor ABT-761 were prepared. Many of these hybrid compounds are potent COX and 5-LO inhibitors; two compounds (**111,** $R^1 = MeO$, $R^2 = R^4 = R^5 = H$, $R^3 = NH_2$, $R^6 = Me$; and $R^1 = MeO$, $R^2 = R^3 = Me$, $R^4 = R^5 = H$, $R^6 = Cl$) inhibited eicosanoid biosynthesis in an *ex vivo* assay, but neither improved on the main deficiency of tepoxalin, duration of 5-LO inhibitory activity (99BMCL979). Compounds **111** inhibit the production of arachidonic acid products associated with 5-lipoxygenase and cyclooxygenase and are useful in the treatment of inflammatory disorders (99USP5925769).



111

A series of Seela's papers [97NN821; 98JCS(P1)3233; 99HCA1640; 99JCS(P1) 479] described the synthesis of 7-alkynylated 8-aza-7-deazaadenine (pyrazolo [3,4-*d*]pyrimidine) 2′-deoxyribonucleosides **112** and **113.** The 7-alkynylated nucleosides show a more stable glycosylic bond than does 8-aza-7-deaza-2′-deoxyadenosine (see also 2000INP2000006771). Alkynylated 1-β-D-ribofuranosylpyrazoles were tested in different pharmacological assays (96ADD193; 96BMCL1279; 96INP9640704; 96MCR293), but they proved inactive.



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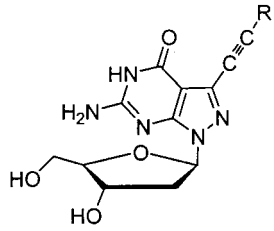
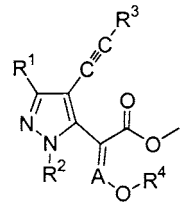


113

C. PHYTOCHEMISTRY OF ACETYLENYLPYRAZOLES

Compounds of formula **26, 27** (Section II.B) were shown to be effective against phytopathogens (93EUP571326).



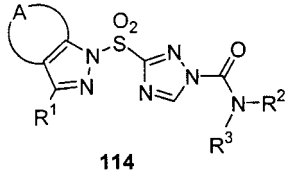
26 A = CH; R^4 = H
27 A = N; R^4 = Me

R^1 = H, alkyl, substituted aryl, CF_3; R^2 = alkyl, substituted aryl;
R^3 = substituted hydrocarbyl or heteroaryl

Their interesting fungicidal activity was established by *in vivo* tests with test concentrations from 0.5 to 500 mg a.i./l against *Uromyces appendiculatus* on pole beans, against *Puccinia triticina* on wheat, against *Sphaerotheca fuliginea* on cucumber, against *Erysiphe graminis* on wheat and barley, against *Podosphaera leucotricha* on apple, against *Uncinula necator* on grape vine, against *Leptosphaeria nodorum* on wheat, against *Phytophthora infestans* on tomato, and against *Plasmopara viticola* on grape vine. Many of the compounds of formula **26, 27**

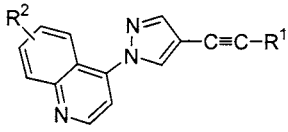
have excellent plant tolerance and systemic action. The compounds of the invention are therefore indicated for treatment of plant, seeds, and soil to combat phytopathogenic fungi, e.g., Basidiomycetes of the order Uredinales (rusts) such as *Puccinia spp., Hemileia spp., Uromyces spp.*; Ascomycetes of the order Erysiphales (powdery mildew) such as *Erysiphe ssp., Podosphaera spp., Uncinula spp., Sphaerofheca spp.,* as well as *Cochliobolus, Pyrenophora spp., Venturia spp., Mycosphaerella spp., Leptosphaeria*; Deuteromycetes such as *Pyricularia* (*Corticium*), *Botrytis*; and Comycetes such as *Phytophthora spp., Plasmopara spp.*. The compounds of formula **26, 27** are especially effective against powdery mildew and rust fungi, in particular against pathogens of monocotyledonous plants such as cereals, including wheat.

A new triazole derivative free of phytotoxicity to crops and exhibiting excellent herbicidal effect on weeds of paddy fields, especially *Echinochloa,* at a low rate of application has been described (93JAP(K)5255314). The compound of formula **en** [A is a (branched) lower alkylene or lower alkylene containing an N atom in the C chain; R^1 is a lower alkynyl; R^2 and R^3 are lower alkyls or lower alkenyl, or R^2 and R^3 are lower alkenylene groups together forming a ring]. The mechanism of action and a QSAR analysis of herbicidal 3-substituted 2-aryl-4,5,6,7-tetrahydroindazoles including ethynyl derivatives have been reported (94MI29).



114

Quinoline derivatives of formula **115** are outstandingly active as microbiocides and can be preferentially used as agricultural fungicides and bactericides for the control of undesired plant pathogens (96EUP703234).

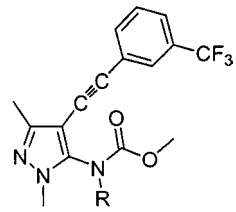


115

A number of compounds of invention (95EUP658547) include derivatives **116** which have excellent fungicidal activity. They exert excellent preventive effects on various phytopathogenic fungi, which makes them useful as an agricultural/horticultural fungicides.

116

The compounds represented by general formula **117** are useful as a insecticides, acaricides, and bactericides (99INP9946247).



117

VI. Conclusion

This review concerns compounds that have two important functionalities in the same molecule: acetylene (69MI2; 78MI3) and pyrazole (67MI1; 84MI2; 96MI1). Acetylenes occupy a central place in synthetic organic chemistry because of their availability and the great versatility of their transformations. And because of their stability, acid–base equilibria, coordination behavior, pharmaceutical properties, and easy preparation, pyrazoles are among the most used heterocycles.

The authors of this review hope to have demonstrated the versatile and frequently unexpected nature of acetylene and pyrazole reactions—a scope so broad that it cannot fail to suggest potential uses to the reader in almost any heterocyclic field.

ACKNOWLEDGMENTS

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VII. Index of Tables

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TABLE V. Alkynylpyrazoles Prepared by Cyclization of Diynones with Hydrazine [68LA113; 68T4285; 73S47; 74JOC843; 74ZOR136; 74ZOR730; 74ZOR1510].

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TABLE VIII. Halogenopyrazoles Prepared by Elimination [69IZV927; 76IZV2288; 99USP5925769].

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TABLE XI. 3-Alkynylpyrazoles Prepared by Pd/Cu-Catalyzed Couplings between Acetylenes and Pyrazolylhalides [81IZV1342; 86TH1; 99JCS(P1) 3713]

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93JHC755; 95SL1115; 96ADD193; 96BMCL1279; 96INP9640704; 96MCR293; 97EUP770610; 98EUP846686; 98JOC1109; 98MO76; 99EUP 933363; 99EUP967205; 99JCS(P1)3713; 2000JMC953].

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TABLE XXIII. Ethynyl- and Polyethynylpyrazoles Prepared by Desilylation, Destannylation, and Decarboxylation Reactions [71ZOB2230; 73S47; 75KGS1678; 88M253; 96BMCL1279; 96MCR293].

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TABLE XXVI. Pyranopyrazoles Prepared by Cyclization of Vicinal (Alkyn-1-yl)pyrazolecarboxylic Acid [81IZV1342].

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TABLE XXVIII. 6-Amino-1-methyl-1,6-dihydropyrazolo[3,4-*c*]pyridin-7-ones Prepared by Cyclization of 4-(Alkyn-1-yl)pyrazole-5-carboxylic Acid Hydrazides [85IZV1367; 85MI2].

TABLE XXIX. 1-Methyl-1,6-dihydropyrazolo[3,4-*d*]pyridazin-7-ones Prepared by Cyclization of 4-(Alkyn-1-yl)pyrazole-5-carboxylic Acid Hydrazides [85IZV1367; 85MI2].

TABLE XXX. Pyrazolopyridazines Prepared by Cyclization Followed by Diazotization of Vicinal (Alkyn-1-yl)aminopyrazoles [95LA775; 98HEC519; 99JCS(P1)3721].

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ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 82

Recent Advances in the Chemistry of 1-Hydroxyindoles, 1-Hydroxytryptophans, and 1-Hydroxytryptamines

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I. Introduction

1-Hydroxytryptophans (**1a,** Fig. 1), -tryptamines (**1b**), -indole-3-acetic acids (**1c**), -indol-1-yl glycosides (**2**), and their analogs (for example, **3**) were imaginary compounds in Somei's "1-Hydroxyindole Hypotheses," as illustrated briefly in previous papers (80MI33, 91YGK205, 91MI206, 93H1859, 95H2157, 99H1157). If their existence in living organisms and their unprecedented inter- or intramolecular nucleophilic substitution reactions on the indole nucleus with the 1-hydroxy moiety as a leaving group were assumed, the metabolism and/or biosynthesis of various indole compounds could be explained uniformly.

Based on the strong desire to verify these hypotheses, we have concentrated on developing general synthetic methods suitable for 1-hydroxyindoles. In 1989,

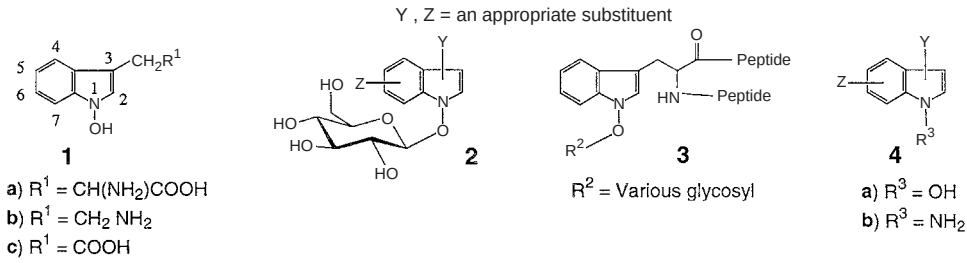
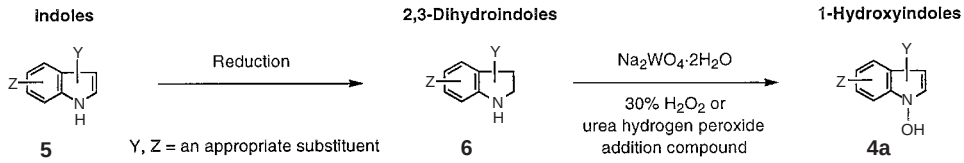


FIG. 1



SCHEME 1. Somei's method.

after nearly 25 years of elaborations, we have succeeded in discovering Somei's method, as shown in Scheme 1, consisting of initial reduction of indoles (**5**) to 2,3-dihydroindoles (**6**), followed by oxidation to 1-hydroxyindoles (**4a**) (89H1251, 91CPB1905, 91H221, 93H99, 94H273).

As a result, we could open the door to a new frontier in indole chemistry. Various 1-hydroxyindoles (**4a**), 1-hydroxytryptophans (**1a**), 1-hydroxytryptamines (**1b**), and their derivatives have been given birth for the first time. As predicted, 1-hydroxytryptophan and 1-hydroxytryptamine derivatives are found to undergo previously unknown nucleophilic substitution reactions. In addition, we have been uncovering many interesting reactivities characteristic of 1-hydroxyindole structures. From the synthetic point of view, useful building blocks for indole alkaloids, hither to inaccessible by the well-known electrophilic reactions in indole chemistry, have now become readily available. Many biologically interesting compounds have been prepared as well.

Looking back on the history, the first successful synthetic studies on 1-hydroxyindole had been reported by Acheson and co-workers [74JCS(CC)671, 78JCS(P1)1117] in 1974 using *o*-nitroaniline as a starting material. Although the applicability of this first method is narrow and confined to 1-hydroxyindole itself, their contributions in this field are important. Their efforts for derivatizations of 1-hydroxyindole are reported in their excellent reviews (79MI1, 90AHC105).

Totally independently, based on the "1-Hydroxyindole Hypotheses," we had started studies on 1-hydroxyindole chemistry in 1971 and reported the results of photoirradiation of 1-ethoxy-2-phenylindole in 1973 (73TL2451). In 1981, we discovered the second method (81H1523, 81CPB726, 81CPB3145, 85H1101, 85CPB5147, 86CPB677, 86CPB4109, 86CPB4116) applicable to the preparation of 1-hydroxyindoles; this method relied on the Leimgruber-Batcho reaction, reacting 2-nitrotoluene with *N*,*N*-dimethylformamide dimethyl acetal.

However, even this second method, including the one modified later by Acheson and co-workers [84JCR(M)1301], was ineffective in realizing our imaginary compounds (**1a-c, 2, 3,** etc.). Their birth and the start of studies on the verification of the "1-Hydroxyindole Hypotheses" had to wait until 1989 when Somei's method, the third method, was discovered.

In this review, our recent developments in the chemistry of 1-hydroxyindoles, 1-hydroxytryptophans, and 1-hydroxytryptamines, attained between the beginning of 1999 and the end of May 2001, are summarized together with results obtained

by other groups, avoiding overlap with the contents in previous reviews (79MI1, 90AHC105, 91YGK205, 99H1157), if possible.

II. Synthetic Method for 1-Hydroxyindoles, 1-Hydroxytryptophans, and 1-Hydroxytryptamines

Our idea for preparing 1-hydroxyindoles through novel 1-aminoindoles (**4b,** Fig. 1) (74TL461, 74TL3605, 75CPB2891, 78CPB2522, 78CL707) utilizing diazonium salts as an intermediate, as in phenol formation from aniline, could not be realized, although it resulted in providing the groundwork for all subsequent investigations on 1-aminoindole chemistry (95TL8099, 96JMC570, 2001SL222).

At present, three synthetic methods are reported for the 1-hydroxyindoles carrying no stabilizing functional group on the indole nucleus. Among these, judging from the standpoint of abundance of starting materials and wide applicability, our oxidation method of 2,3-dihydroindoles with $Na_2WO_4 \cdot 2H_2O$ (or $2Na_2O \cdot P_2O_5 \cdot 12WO_4 \cdot 18H_2O$) and 30% H_2O_2 (or urea–hydrogen peroxide addition compound) is the sole one generally applicable for preparing various kinds of 1-hydroxyindoles, including 1-hydroxytryptophans and 1-hydroxytryptamines (Scheme 1). Throughout the following, we abbreviate the oxidation step in this 1-hydroxyindole synthetic method as "the tungstate method."

In spite of these successful results, we continue to search for a proper reagent that can transform indole derivatives directly to the corresponding 1-hydroxyindoles.

A. Syntheses of Various 1-Hydroxytryptamine Derivatives

Table I lists some (but not all) new members of the 1-hydroxytryptamine family and related 1-hydroxyindoles (**9**) produced via the tungstate method from 1999 through 2000.

For the preparation of 2,3-dihydroindoles (**8**) from indoles (**7**), two reduction methods are known. In the column Reduction Method in the table, the one indicated **A** represents use of Et_3SiH in TFA (79JOC4809) and the other, indicated **B,** employs $NaBH_3CN$ in AcOH (77S859, 88JMC1746). Although both methods are applicable, the former is generally superior to the latter. In some cases, depending on the substrates' structures, the reverse cases are also observed. Examples are the reactions marked **B** in the column.

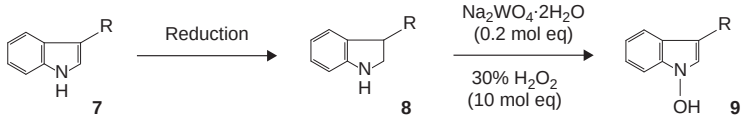
Other newly synthesized 1-hydroxyindoles appear in the following sections.

B. Synthesis of 1,2,3,4-Tetrahydro-9-hydroxy-β-carbolines

Attempts to prepare 1,2,3,4-tetrahydro-9-hydroxy-β-carboline (**11**) from 1,2,3,4,4a,9a-hexahydro-β-carboline (**10**) by the tungstate method seemed to result

TABLE I

TYPICAL EXAMPLES OF 1-HYDROXYINDOLES

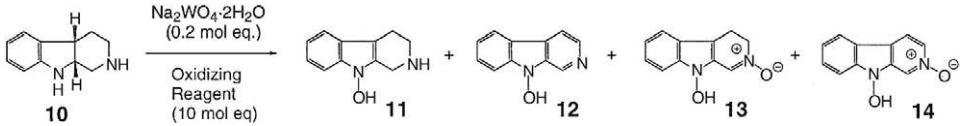


7	R	Reduction Method	Yield (%) of 8	Yield (%) of 9
a	$CH_2CONHMe$	A	86	72
b	$CH_2CH_2NHCOCH_2Me$	A	98	67
c	$CH_2CH_2NHCO(CH_2)_3Me$	A	86	60
d	$CH_2CH_2NHCO(CH_2)_5Me$	A	87	68
e	$CH_2CH_2NHCO(CH_2)_6Me$	A	96	77
f	$CH_2CH_2NHCO(CH_2)_7Me$	A	78	61
g	$CH_2CH_2NHCO(CH_2)_{20}Me$	A	91	79
h	CH_2CH_2CO—N NH	A	99	31
i	$CH_2CH_2CH_2CO$—N NH	A	99	22
j	CH_2CH_2CO—N NCOOMe	A	95	71
k	CH_2CO—N	A	99	60
l	CH_2CO—N	A	93	75
m	CH_2CO—N	A	96	69
n	CH_2CH_2—N	A	97	70
o	CH_2CH_2—N	A	93	74
p	$CH_2CH_2CH_2$—N H	A	99	62
q	$CH_2CH_2CH_2CH_2$—N H	A	97	32[a]
r	CH_2CO—N H	B	80	76
s	CH_2CH_2CO—N H	B	89	65
t	$CH_2CH_2CH_2CO$—N H	B	99	66
u	CH_2CH_2NHCO—	A	84	69
v	CH_2CH_2NHCO—	A	57	62
w	CH_2CH_2NHCO— O	A	97	64
x	CH_2CH_2NHCO—	B	83	63
y	CH_2CH_2NHCO— OH	B	85	57
z	CH_2CH_2NHCO— OH OMe	B	82	44

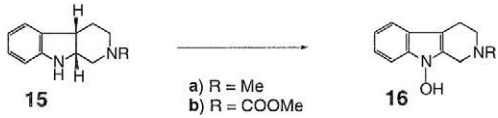
Reduction Method A: Et_3SiH in CF_3COOH (TFA). B: $NaBH_3CN$ in AcOH.

[a] Quite unstable. The yield was obtained by leading it to *N*-acetyl-1-methoxy derivative by reacting with diazomethane, followed by treatment with acetic anhydride.

TABLE II



Entry	Oxidizing Reagent	Reaction Conditions: Solvent System	Temp. (°C)	Time (min)	Yield (%) of: 11	12	13	14
1	30% H_2O_2	MeOH-H_2O (10 : 1, v/v)	19	25	0	14	21	7
2	”	MeOH-H_2O (9 : 1, v/v)	27	5	55	trace	5	5
3	98% Urea·H_2O_2	”	25.5	5	65	trace	5	2

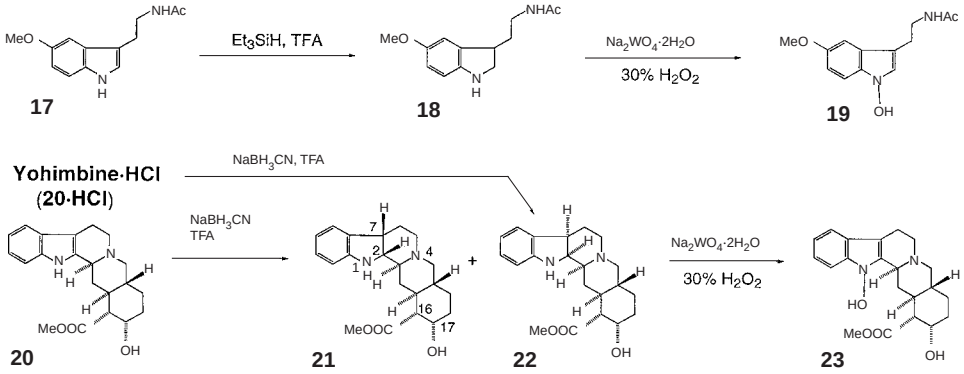


in failure. As shown in Table II (entry 1), not even a trace amount of **11** was detected in the reaction mixture when the reaction was carried out at room temperature for 25 min or longer; instead, 9-hydroxy-β-carboline (**12**), 3,4-dihydro-9-hydroxy-β-carboline *N*-oxide (**13**), and 9-hydroxy-β-carboline *N*-oxide (**14**) were produced (2000H7).

In this case, however, reaction time is found to be a dominant factor. By shortening the reaction time to 5 min (entries 2 and 3), the problem is overcome. Consequently, **11** becomes available in 55–65% yield from **10** (2000H7). As for oxidizing reagent, urea–hydrogen peroxide addition compound is a reagent of choice (92H1295). Similarly, 2-methyl- (**15a**) and 2-methoxycarbonyl-1,2,3,4,4a,9a-hexahydro-β-carboline (**15b**) afford the corresponding 2-methyl- (**16a,** 69%) and 2-methoxycarbonyl-9-hydroxy-β-carboline (**16b,** 31%), respectively (95H119).

C. Synthesis of 1-Hydroxymelatonin

Melatonin (**17**), readily available by the method described in Section V.E, is converted to *N*b-acetyl-2,3-dihydrotryptamine (**18,** 83%) by reduction with Et_3SiH in TFA (Scheme 2). Application of the tungstate method to **18** provides 1-hydroxymelatonin (**19,** 58%) as stable crystals (99H1237).



SCHEME 2

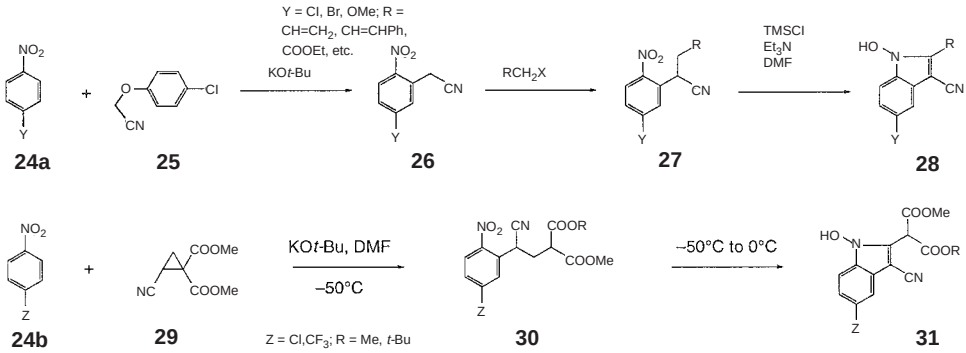
D. SYNTHESIS OF 1-HYDROXYYOHIMBINE

Formation of 2β,7β- (**21,** 9%) and 2α,7α-dihydroyohimbine (**22,** 89%) was reported upon reduction of free base of yohimbine (**20**) with $NaBH_3CN$ in TFA (Scheme 2) (74GEP2410651, 92H121). We have discovered that when yohimbine hydrochloride (**20** · HCl) is employed as a substrate, application of the same reducing reagent under the same reaction conditions results in the stereoselective and quantitative production of **22** without any detectable amount of **21** (2001H1237). Utilizing **22,** preparation of 1-hydroxyyohimbine (**23,** 86%) is attained by employing the tungstate method.

E. SYNTHESES OF 1-HYDROXYINDOLES CARRYING AN ELECTRON-WITHDRAWING GROUP

Once an electron-withdrawing group is introduced onto the indole nucleus, no matter which position it is, 1-hydroxyindoles become stable (91YGK205, 99H1157). For the preparation of such stable 1-hydroxyindoles, various reagents and conditions can be employed and many approaches have been reported, as summarized in previous reviews (79MI1, 90AHC105).

Makosza and co-workers developed a novel method as shown in Scheme 3 (93SL597, 97T5501). Utilizing their vicarious substitution of hydrogen reaction (87ACR282), nitrobenzene derivative **24a** was transformed to *o*-nitrophenylacetonitrile (**26**) by the reaction with **25.** Alkylation of **26** and subsequent base-catalyzed cyclization of the resultant *o*-nitroarylethanes (**27**) afforded 3-cyano-1-hydroxyindoles (**28**). Stalewski extends the scope of this reaction using 1-cyano-2,2-diethoxycarbonylcyclopropane (**29**) to produce 1-hydroxyindoles (**31**) in a one-pot reaction from **24b** through **30,** although yields are low (98TL9523).



SCHEME 3

III. Physical Properties of 1-Hydroxyindoles, 1-Hydroxytryptophans, and 1-Hydroxytryptamines

A. ACIDITY

The pK_a values of the 1-hydroxy moiety of (*S*)-(+)-*N*b-acetyl-1-hydroxytryptophan methyl ester (**32**), methyl 1-hydroxyindole-3-butylate (**33**), *N*b-methoxycarbonyl-1-hydroxytryptamine (**34**), 1-hydroxymelatonin (**19**), 1-hydroxy-6-nitroindole (**35**), and 1-hydroxy-5-nitroindole (**36**) are determined to be 9.8, 8.4, 8.2, 8.1, 6.9, and 6.8, respectively (Fig. 2) (2000H1881). Thus, 1-hydroxyindoles are weak acids, stronger than phenol and weaker than succinimide. Therefore,

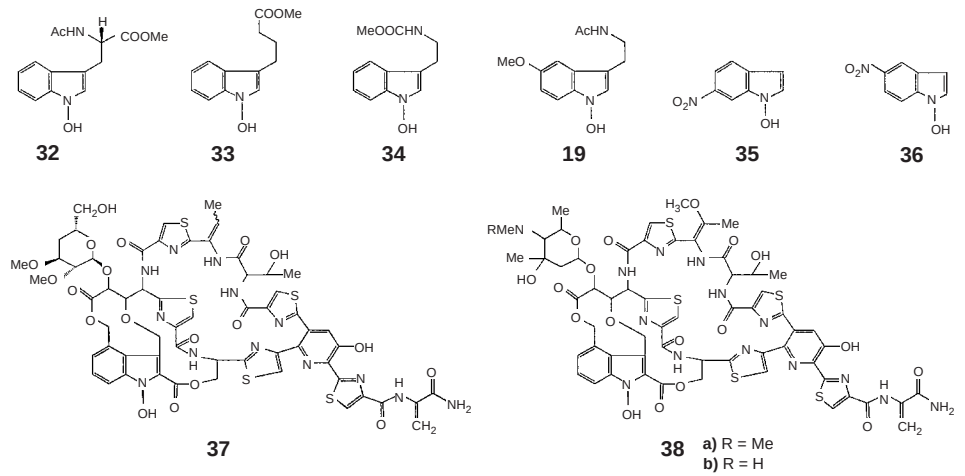


FIG. 2

in the presence of weak bases, alkylations and acylations occur smoothly (see Section IV.A for examples).

B. Stability

1-Hydroxyindoles carrying a side chain containing a free NH_2, OH, or COOH functional group are unstable. Therefore, 1-hydroxytryptophan, -tryptamine, and -indole-3-acetic acid have not been prepared yet.

However, once their carboxy or amino group is transformed to an ester or amide moiety, the corresponding 1-hydroxy compounds become sufficiently stable to be isolated and characterized. An electron-withdrawing group connected directly to the indole skeleton strongly stabilizes the 1-hydroxyindole structure. As expected, the presence of a carbonyl group at the 2 position allowed the isolation of three naturally occurring 1-hydroxyindole derivatives, **37, 38a,** and **38b** (84USP4478831, 98JAN715), although their stereochemistry remains to be determined (Fig. 2). There are further discussions about these natural products in Section VIII.

On the other hand, an electron-donating substituent destabilizes the 1-hydroxyindole structure, often to the extent that it cannot be isolated. Even in such a case, alkylation of the 1-hydroxy group greatly improves the stability. Among alkylations, methylation is the best choice. This fact explains why every isolated natural product has a 1-methoxyindole structure (91YGK205, 99H1157).

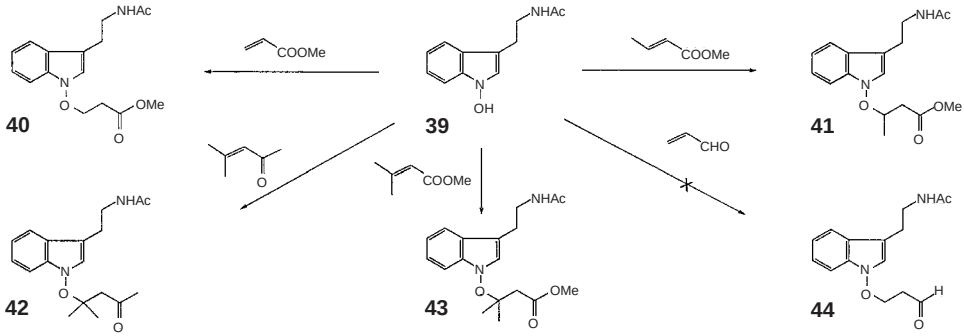
IV. Chemical Reactions of 1-Hydroxy-, 1-Alkoxy-, and 1-(α-D-Glucopyranosyl)indoles

1-Hydroxy- and 1-alkoxyindoles undergo characteristic reactions depending on their structures, reagents, and reaction conditions. At the beginning of this section, preparations of 1-alkoxyindoles and 1-(α-D-glucopyranosyl)indoles are discussed.

A. Methylation, Alkylation, Acylation, and Glucosidation

Methylation of 1-hydroxyindoles can be achieved readily by the reaction with diazomethane, MeI, or Me_2SO_4 in the presence of an appropriate base, as described in previous reviews (79MI1, 90AHC105, 91YGK205, 99H1157). Alkylation and acylation also work well with alkyl halides, acyl halides, acid anhydrides, and acids in the presence of acid activators such as DCC and so on.

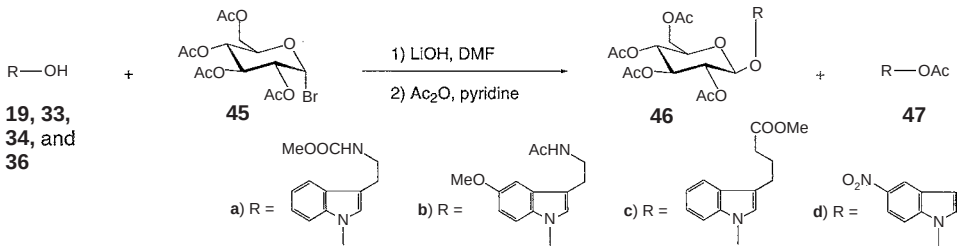
Michael addition reaction of 1-hydroxytryptamines to α,β-unsaturated carbonyl compounds is worthy of note (99H2815). Addition of *N*b-acetyl-1-hydroxytryptamine (**39**) to methyl acrylate and methyl crotonate in the presence of



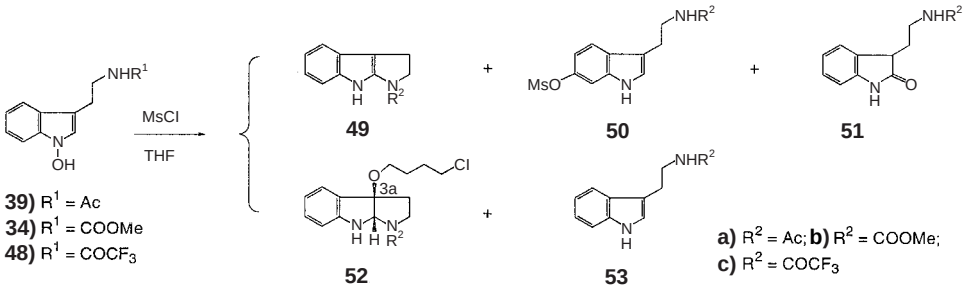
SCHEME 4

4-*N*,*N*-dimethylaminopyridine provides 1-(2-methoxycarbonyl)ethoxy- (**40,** 69%) and 1-(2-methoxycarbonyl-1-methyl)ethoxytryptamine (**41,** 72%), respectively (Scheme 4). The conjugate addition to mesityl oxide proceeds successfully as well, giving *N*b-acetyl-1-(1,1-dimethyl-3-oxo)butoxytryptamine (**42,** 49%), while the reaction with methyl 3-methylcrotonate affords **43** in a miserable yield (1.6%). Addition to acrolein results in failure, and **44** is not yet obtained.

An attempt to synthesize indol-1-yl glycosides (**2**), which were speculated to exist in living organisms (91YGK205, 99H1157), encountered much trouble. Application of known glucosidation methods (42JA691, 80AG763, 82AG184, 86AGE212, 92YGK378, 93CRV1503) to weakly acidic 1-hydroxytryptamines were completely unsuccessful. To overcome the problem, we have been able to develop a novel LiOH-promoted synthetic method (2000H1881), which works effectively upon compounds with pK_a values of 8–10 (Scheme 5). By treating 1-hydroxyindoles with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**45**) (50NAT369) in DMF in the presence of LiOH, followed by acetylation with Ac_2O and pyridine, *N*b-substituted 1-hydroxytryptamines (**19** and **34**), methyl 4-(1-hydroxyindol-3-yl)butanoate (**33**), and 1-hydroxy-5-nitroindole (**36**) are converted to the corresponding acetylated indol-1-yl glucosides (**46a–d**) in good to excellent yields together with a small amount of **47a–d.**



SCHEME 5



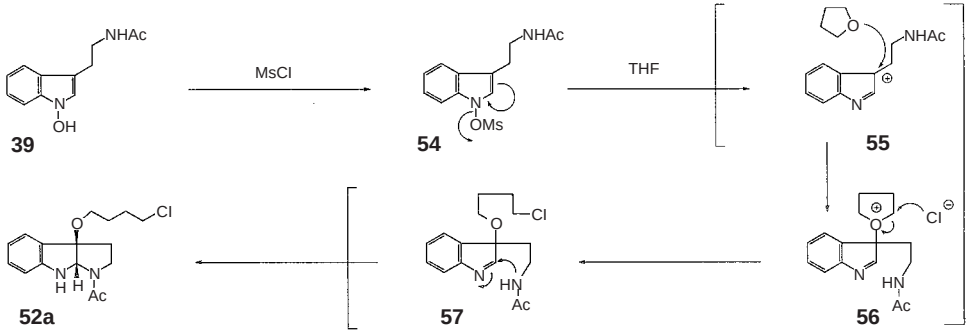
SCHEME 6

B. REACTION OF 1-HYDROXYTRYPTAMINES WITH SULFONIC CHLORIDES AND SULFONIC ACID

1. *Reaction of 1-Hydroxytryptamines with Mesyl Chloride*

The reaction of *N*b-acetyl-1-hydroxytryptamine (**39**) with mesyl chloride (MsCl) in THF in the presence of Et_3N provides 1-acetyl-1,2,3,8-tetrahydropyrrolo[2,3-*b*] indole (**49a,** 35%) (70JA343), *N*b-acetyl-6-mesyloxytryptamine (**50a,** 4%), *N*b-acetyl-2,3-dihydro-2-oxotryptamine (**51a,** 5%), 1-acetyl-3a-(4-chlorobutoxy)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**52a,** 7%), and *N*b-acetyltryptamine (**53a,** 2%) as shown in Scheme 6 (2000H483). In the same reaction with MsCl, 1-hydroxy-*N*b-methoxycarbonyltryptamine (**34**) produces **50b** (7%), **51b** (34%), and **52b** (9%), while the formation of **49b** is not observed at all. In the case of *N*b-trifluoroacetyl-1-hydroxytryptamine (**48**), **49c** (45%), **50c** (8%), **51c** (4%), and **52c** (6%) are produced. These data suggest that the yield of **49** increases, whereas the yield of **51** decreases in the order of electron-withdrawing ability of *N*b substituents (COOMe < COMe < $COCF_3$). Stability of **49** seems to govern the quantity of **51,** which is probably formed by hydrolysis of **49.**

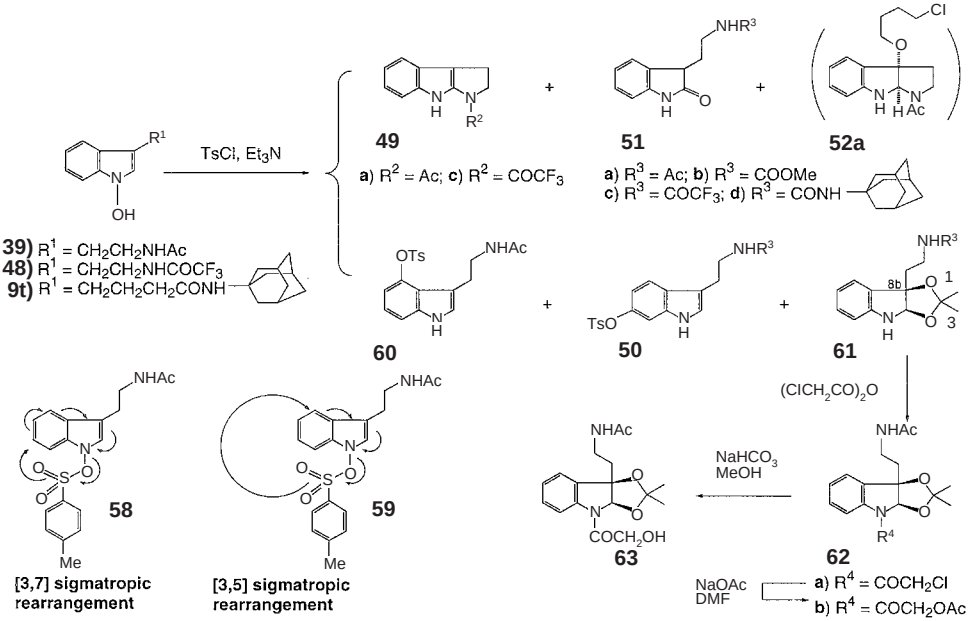
The reaction mechanism for the formations of **52a–c** can be explained as shown in Scheme 7, using **39** as a representative. Initial formation of 1-mesyloxytryptamine (**54**) from **39** with subsequent departure of the mesyloxy group generates an intermediate indol-3-yl cation **55,** which then traps THF as an oxonium ion **56.** Subsequent chloride attack on the carbon atom connected to the positive oxygen atom cleaves the ether ring to build a chlorobutoxy side chain of **57.** Final cyclization of the *N*b-nitrogen to the imine carbon atom results in the formation of pyrrolo [2,3-*b*]indole product **52a.** Formation of 6-substituted indoles **50a–c** is explained in terms of [3,7]sigmatropic rearrangement of the intermediate **54** as in the case of the corresponding tosyl intermediate **58** (Scheme 8) described in Section IV.B.2.



SCHEME 7

2. *Reaction of 1-Hydroxytryptamines with Tosyl Chloride*

The reaction of *p*-toluenesulfonyl chloride (TsCl) with 1-hydroxytryptamines was expected to follow the same reaction pathways as that of MsCl described in Section IV.B.1. In fact, it is different from the expectation (2000H2487). Thus, **39** reacts with TsCl in THF to provide **49a** (42%), **51a** (6%), **53a** (3%), **60** (0.5%), and



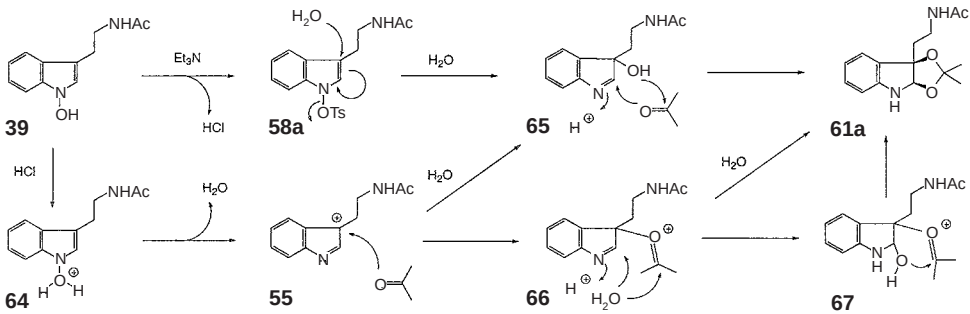
SCHEME 8

50a (5%) (Scheme 8). The complete absence of **52a** and formation of 4-substituted indole (**60**) are remarkable differences.

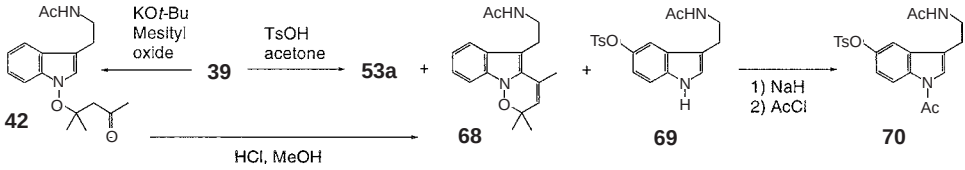
Interestingly, when the solvent is changed from THF to acetone, the reaction of **39** with TsCl generates a novel 3a,8b-dihydro-4*H*-1,3-dioxolo[4,5-*b*]indole derivative **61a** (3%) in addition to **49a** (14%), **51a** (6%), **53a** (4%), **60** (0.2%), and **50a** (3%). In the case of **48,** the yield of **61c** is raised to 11% together with **49c** (58%) and **50c** (6%). Under the same reaction conditions, **9t** produces **61d** (10%) and **51d** (49%).

Mechanisms for the formation of **60** and **50a,c** are explained by the [3,7]- and [3,5]sigmatropic rearrangements of the initially formed 1-tosyloxytryptamine as shown in formulas **58** and **59.** For the structural determination of **61a,** it is converted to 1-hydroxyacetylindole derivative **63** by a sequence of reactions: (1) reaction with chloroacetic anhydride to give **62a** (84%), (2) treatment of **62a** with sodium acetate to provide **62b** (84%), and (3) subsequent alkaline hydrolysis to **63** (85%). The structure of **63** is determined by X-ray single crystallographic analysis (2000H2487).

The proposed mechanism for the formation of **61a** is shown in Scheme 9. Initially, TsCl transforms **39** into a 1-tosyloxy derivative **58a** with concomitant formation of HCl, which serves as a proton source and alters the 1-hydroxy moiety of the second molecule **39** to a good leaving group as shown in **64.** Liberation of water from **64** leaves a resonance-stabilized indolyl cation **55** (99H1237, 2000H483). Nucleophilic addition of water to **55** produces 3-hydroxyindolenine **65,** which can also be generated by the SN2′ type addition of water onto the 3 position of **58a.** Then, a sequence of reactions—e.g., (1) protonation of the imine nitrogen, (2) nucleophilic addition of acetone to the imine carbon, and (3) addition of the 3-hydroxy group to the acetone carbonyl—converts **65** into the final product **61a.** Nucleophilic addition of acetone to **55** might take place to produce **67** through **66.** Subsequent cyclization of the aminal oxygen of **67** to the positively charged carbonyl carbon affords **61a.** The attack of water at the positively charged



SCHEME 9



SCHEME 10

carbonyl carbon on the 3 substituent of **66,** followed by cyclization of the resultant hemiketal oxygen to the imine carbon atom, is another possible pathway.

3. *Reaction of 1-Hydroxytryptamines with p-Toluenesulfonic Acid*

The results obtained by the reaction of **39** with *p*-toluenesulfonic acid (TsOH) in acetone are completely different from those observed in reactions with MsCl and with TsCl as shown in Sections IV.B.1 and IV.B.2. Although the total yield of products is not high (Scheme 10), **39** produced 2*H*-1,2-oxazino[2,3-*a*]indole (**68,** 9%), 5-tosyloxyindole (**69,** 10%), **53a** (7%), and unreacted **39** (14%) (2000H2487).

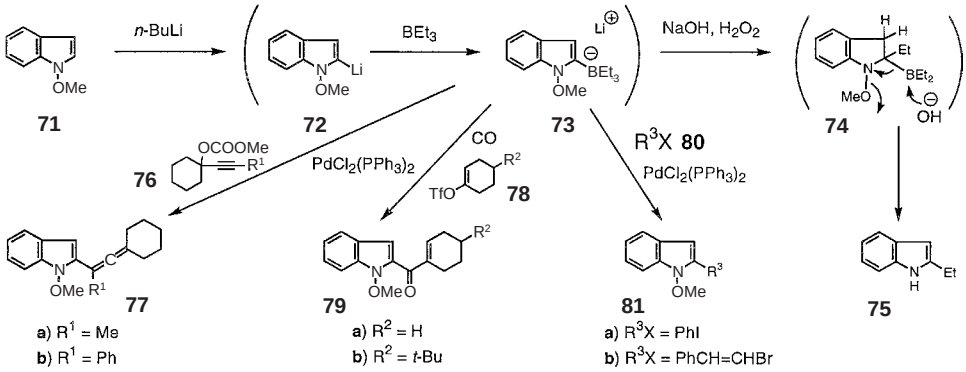
Compound **68** can also be obtained by an acid-catalyzed cyclization of **42,** which was prepared by the Michael addition reaction of **39** to mesityl oxide as shown in Section IV.A. As for the product **69,** the presence of the tosyloxy group at the 5 position instead of the 6 position is determined, utilizing the anisotropy effect of the 1-acetyl group to the C-7 proton, by comparing its ^{1}H NMR spectrum with that of **70,** obtained in 69% yield by the treatment of **69** with NaH and AcCl.

The formation of **69** suggests that even the *p*-toluenesulfonate ion can undergo the regioselective nucleophilic attack at the 5 position, as the 1-hydroxy leaving group departs from **39** upon protonation.

C. LITHIATION

Having already reported (92H1285, 92H1295, 94H31) that the 1-methoxy group facilitates regioselective lithiation at the 2 position of the indole nucleus, we then applied this novel finding to the preparation of a variety of 2-substituted indoles. This methodology has the advantage of being able to manipulate the 1 position further, making use of the readily removable nature of 1-methoxy group.

Ishikura and co-workers (95H2437) have extended the scope of this reaction, combining our results with their borate chemistry. Thus, the reaction of 2-lithio-1-methoxyindole (**72**), prepared from 1-methoxyindole (**71**) and *n*-BuLi (92H1285, 92H1295, 94H31), with triethylborane generates an indolylborate **73** *in situ* (Scheme 11). Subsequent treatment of **73** with aqueous NaOH and 30%



SCHEME 11

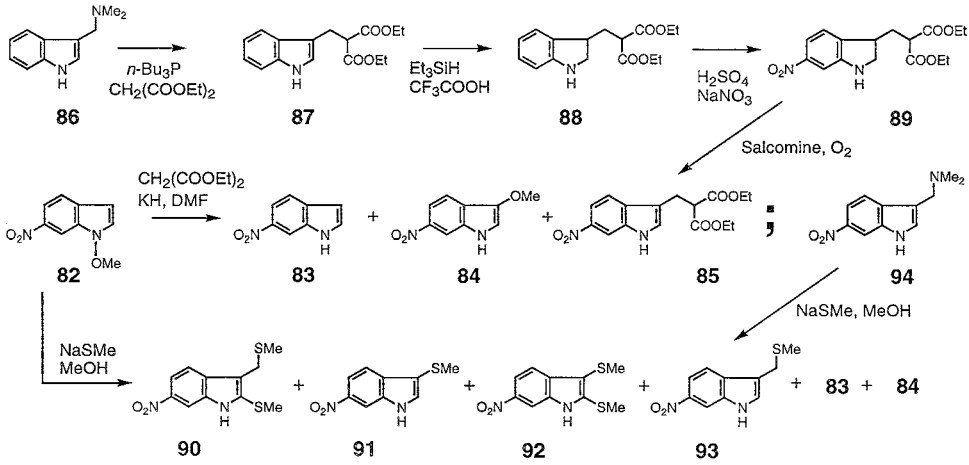
H_2O_2 is found to result in formation of 2-ethylindole (**75,** 90%). Similarly, other trialkylboranes are successfully employed for the synthesis of 2-alkylindoles. A reaction mechanism through **74** as an intermediate is proposed.

They have also developed a route to 2-allenylindole derivatives (98T13929). When prop-2-ynyl carbonates (**76**) are reacted with **73** in the presence of palladium catalyst, a cross-coupling reaction occurs to give **77a** (46%) and **77b** (45%). Under a pressurized carbon monoxide atmosphere (10 atm), the palladium-catalyzed reaction of **73** with **78** provides **79a** (60%) and **79b** (60%) (2000H2201). In a similar reaction, when the substrate is changed to aryl halides (**80**), 2-aryl-1-methoxyindoles such as **81a** (70%) and **81b** (60%) are prepared (97H2309).

D. 1-METHOXY GROUP AS A FORMALDEHYDE SYNTHON; METHYLENE HOMOLOGATION

An interesting methylene homologation reaction is found to occur at the 3 position upon reaction of 1-methoxy-6-nitroindole (**82**) with diethyl malonate in DMF at reflux using KO*t*-Bu as a base (Scheme 12). Consequently, diethyl 2-(6-nitroindol-3-yl)methylmalonate (**85,** 38%) is obtained in addition to 6-nitroindole (**83,** 47%) (2001H1151). Using KH in place of KO*t*-Bu, the yield of **85** is slightly improved to 40% together with **83** (20%) and **84** (5%). When methylsulfide ion is employed as a nucleophile for the reaction with **82,** methylene homologation is again observed. Thus, **82** provides 2-methylthio-3-methylthiomethyl-6-nitroindole (**90,** 17%), 6-nitroindole (**83,** 39%), 3-methylthio- (**91,** 4%), 2,3-dimethylthio- (**92,** 2%), 3-methylthiomethyl-6-nitroindoles (**93,** 2%), and **84** (4%).

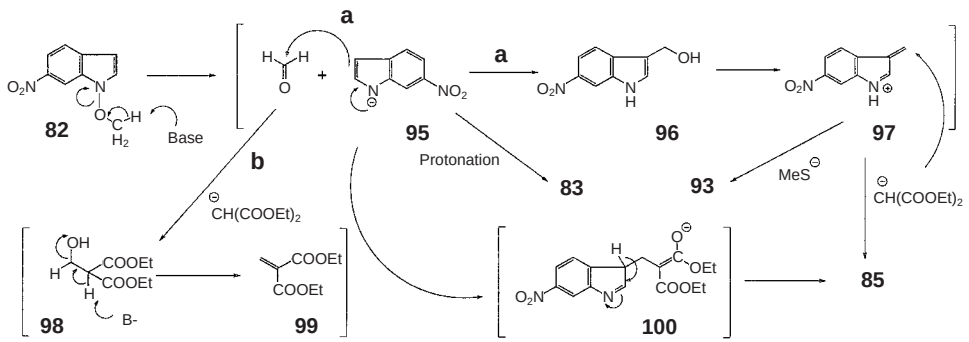
The structures of **85** and **93** are proved by comparing them with the authentic samples prepared by the following routes. Thus, gramine (**86**) is converted to diethyl 2-(indol-3-yl)methylmalonate (**87,** 83%) utilizing our reaction with



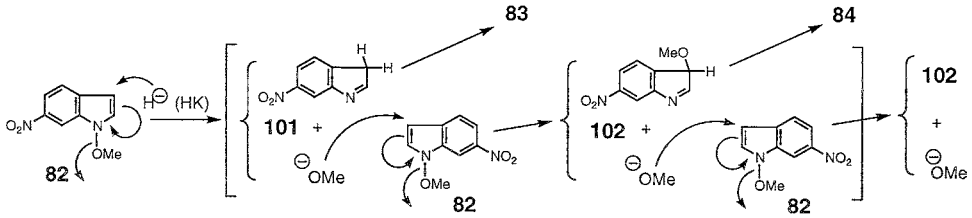
SCHEME 12

diethyl malonate and tri-*n*-butylphosphine as a catalyst (81H941). Reduction of **87** with Et_3SiH and TFA gives the corresponding 2,3-dihydroindole (**88,** 82%), and its nitration with $NaNO_3$ and H_2SO_4 provides 2,3-dihydro-6-nitroindole derivative **89** (92%). Subsequent salcomine-catalyzed oxidation (80CL1287, 85H3113, 87CPB3146) with bubbling oxygen affords **85** (56%). On the other hand, the authentic sample of **93** is prepared in 94% yield by the reaction of 6-nitrogramine (**94**) with NaSMe.

The mechanism for the formations of **83, 85,** and **93** can be explained as illustrated in Scheme 13. Initial deprotonation of the 1-methoxy group of **82** liberates formaldehyde and an indolyl anion **95,** and then protonation of **95** affords **83.** Following the reaction path **a, 95** reacts with formaldehyde to produce indole-3-methanol **96.** Unstable **96** collapses into 3-methyleneindolenine **97,** which adds



SCHEME 13

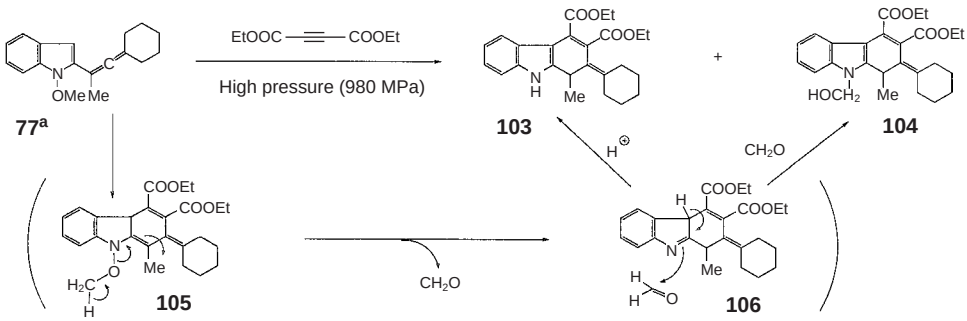


SCHEME 14

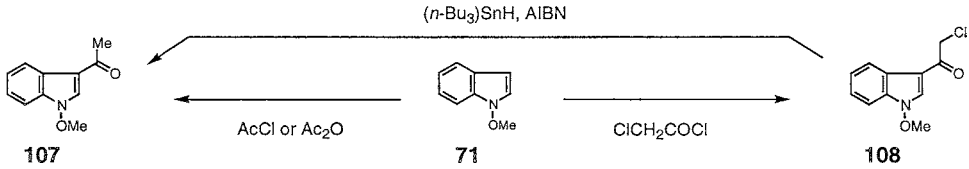
diethyl malonate to give **85** or works as a Michael acceptor of a methylsulfide ion to generate **93.** Another possibility is the reaction path **b.** Addition of diethyl malonate to formaldehyde gives an intermediate **98,** which collapses into methylenemalonate **99.** Subsequent Michael addition of **95** to **99** affords **85** through **100.**

Formation of **84** upon reaction of **82** with KH in DMF without using NaOMe is explained in terms of the initial hydride addition to **82** at the 3 position, forming **101** and a methoxide ion (Scheme 14). The newly born methoxide ion then adds to another molecule of **82** to generate **102** and another methoxide ion. The process is repeated as a chain reaction, while **101** and **102** collapse to **83** and **84,** respectively.

Another interesting example of the fact that 1-methoxy group functions as a formaldehyde synthon was found by Ishikura and co-workers (2001JHC675). 1-Methoxy-2-allenylindole (**77a**) is allowed to react with diethyl acetylenedicarboxylate under high pressure (980 MPa) to produce carbazoles **103** (50%) and **104** (36%) as shown in Scheme 15. The lack of the methoxy group in the products and formation of **104** are notable. These are explained by the splitting of the methoxy group of the Diels–Alder adduct **105** into formaldehyde and **106.** Subsequent reaction of **106** with the liberated formaldehyde generates **104.** A closely related reaction of 1-(2-oxoalkyl) oxyindole derivatives was reported by us (81CPB3145).



SCHEME 15



SCHEME 16

E. ELECTROPHILIC SUBSTITUTION REACTIONS

1. *Vilsmeier–Haack Reaction and Acylation*

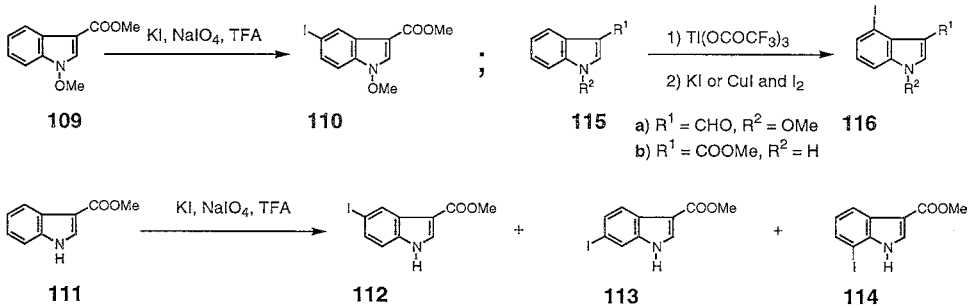
Acheson and co-workers [78JCS(P1)1117, 80AX(B)3125] reported the synthesis of 3-acetyl-1-methoxyindole (**107,** 42%) from 1-methoxyindole (**71**) by applying Vilsmeier–Haack reaction using *N*,*N*-dimethylacetamide. We repeated the reaction, but in our hands, the yield was lower (around 14%) (Scheme 16).

Our trials for attaining direct acetylation of **71** to **107** with refluxing Ac_2O or AcCl resulted in poorer yields. So, we have developed an alternative two-step approach to **107.** First, **71** is reacted with chloroacetyl chloride to give 3-chloroacetyl-1-methoxyindole (**108,** 91%) (85H1101). Subsequent chlorine–hydrogen exchange reaction of **108** with $(n\text{-Bu})_3SnH$ in the presence of AIBN affords the desired **107** (95%). In this reaction, the amount of $(n\text{-Bu})_3SnH$ and the reaction time are crucial factors for success (99H1949).

2. *Halogenations*

As for regioselectivity in the electrophilic substitution reactions, we have assumed that introducing a methoxy group to the 1 position of indole nucleus might alter its positional reactivity.

In fact, iodination of methyl 1-methoxyindole-3-carboxylate (**109**), a wasabi phytoalexin (98P1959), with KI and $NaIO_4$ (60LA84, 91JOC5903) in TFA–H_2O provides methyl 5-iodo-1-methoxyindole-3-carboxylate (**110,** 72%) predominantly



SCHEME 17

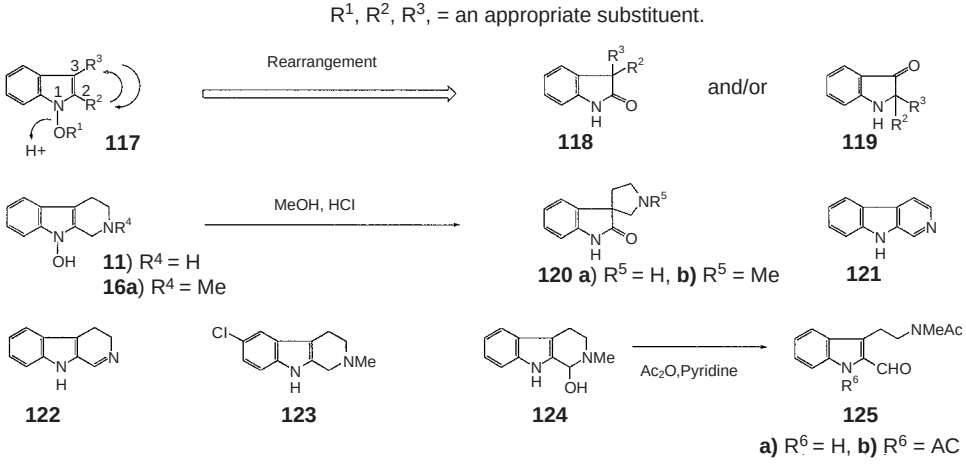
(Scheme 17). In contrast, under similar reaction conditions, methyl indole-3-carboxylate (**111**) produces 5-iodo (**112,** 58%), 6-iodo (**113,** 25%), and 7-iodo compounds (**114,** 2%) (2001H425). In both cases, iodination at the 4 position does not occur. Regioselective iodination at the 4 position of 1-methoxyindole-3-carbaldehyde (**115a**) and methyl indole-3-carboxylate (**115b**) to **116a** and **116b,** respectively, could be realized using thallium tris(trifluoroacetate) followed by treatment with KI or CuI and I_2 (79JHC993, 84H797, 87H1173).

F. Rearrangement Reactions

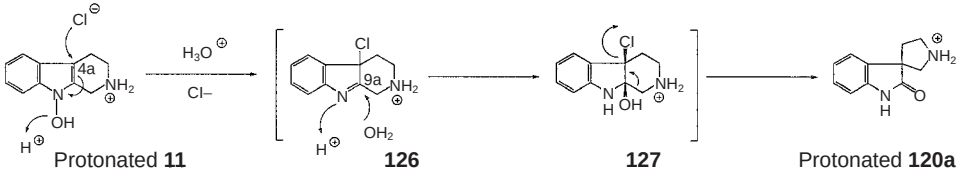
In 1991, we proposed in our "1-Hydroxyindole Hypotheses" (91YGK205) that some types of 1-hydroxyindoles (**117**) would undergo a rearrangement reaction to provide 2-oxindole **118** and/or 3-oxindole **119** as illustrated in Scheme 18. As suitable substrates for realizing the predictions, we have succeeded in finding 1,2,3,4-tetrahydro-9-hydroxy-β-carboline compounds **11** and **16a.**

When **16a** is allowed to react with HCl in refluxing MeOH, formations of (±)-**120b** (42%), **123** (9%), and **124** (46%) are observed (2000H7). Under similar reaction conditions, **11** generates (±)-**120a** (47%), **121** (2%), and **122** (36%).

The structure of (±)-**120b** is confirmed by the direct comparison with the authentic sample prepared alternatively according to the reported procedure (78JOC3705). The structure of (±)-**120a** is proved by leading it to (±)-**120b** (91%) by methylation with HCHO–AcOH–$NaBH_3CN$. The structure of **124** is determined by the fact that it provides **125a** (35%) and **125b** (39%) by treatment with Ac_2O and pyridine.



Scheme 18

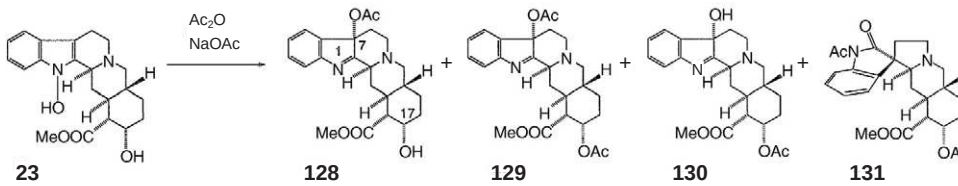


SCHEME 19

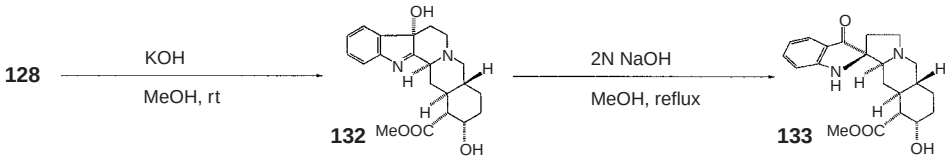
The mechanism of the rearrangement is explained as shown in Scheme 19. Protonation of the 9-hydroxy group followed by its elimination and subsequent chloride attack at the 4a-carbon generates a chloroindolenine **126.** Addition of water to the 9a-imine carbon atom of **126** gives **127.** Concerted elimination of the chloride with rearrangement of the alkyl side chain attached to the 9a carbon atom results in 3,3-disubstituted oxindole structure **120a.**

Another example is the structurally more complex yohimbine alkaloids (74GEP2410651, 92H121, 2001H1237). Thus, treatment of 1-hydroxyyohimbine (**23**) with Ac_2O in the presence of NaOAc is found to generate the desired 2-oxindole (**131**) together with 7α-acetoxy- (**128**), 7α,17α-diacetoxy- (**129**), and 17α-acetoxyyohimbines (**130**) stereoselectively (Table III) (2001H1237). The rearrangement of the 1-acetoxy group to the 7α position is best achieved in the conditions of entry 2, providing **128** (71%) and **129** (8%). As the reaction time becomes longer (entries 1–4), the yield of **128** decreases while the yield of **129** increases. Under the reaction conditions described in entries 3 and 4, the formation of 2-oxindole **131** is observed. Use of excess NaOAc makes the reaction dirty, decreasing the

TABLE III



Entry	NaOAc (mol eq)	Reaction Conditions		Yield (%) of			
		Temp. (°C)	Time (h)	**128**	**129**	**130**	**131**
1	2	63	0.5	52	12	0	0
2	”	65	1	71	8	0	0
3	”	”	6	23	41	0	9
4	”	”	40	0	40	0	15
5	20	”	6	0	0	12	12
6	—	”	48	9	44	0	16



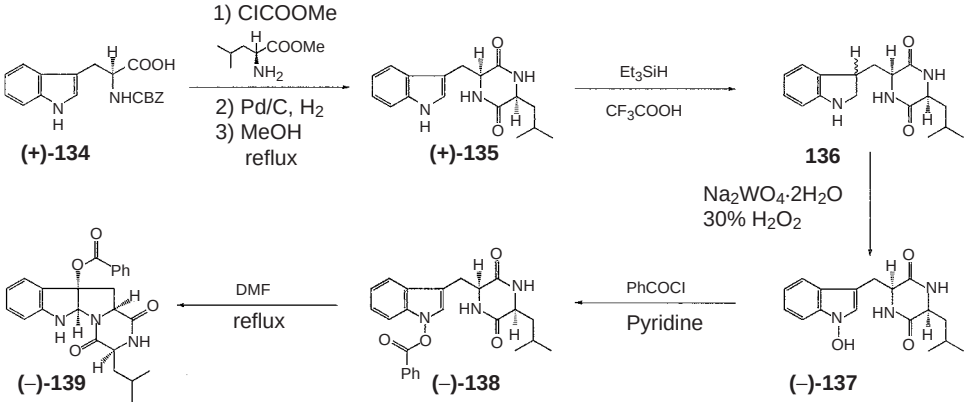
SCHEME 20

total yield of products **130** and **131** (entry 5). A slight improvement in the yield of **131** (16%) is observed by carrying out the reaction without using NaOAc (entry 6).

The structures of **129** and **131** are determined by X-ray single crystallographic analyses (2001H1237). Structures of both **128** and **130** are confirmed by chemical correlations to **129** by the reaction with Ac_2O and pyridine.

A facile rearrangement of **128** to spiroindoxyl compound (3-oxindole, **133**) was reported by Finch and co-workers (51JA2188, 63JA1520, 65JA2229, 96H87) through **132** by the hydrolysis of the 7α-acetoxy group followed by alkaline treatment (Scheme 20). These facts prove that the skeletal rearrangement of **117** into 2-oxindole **118** and 3-oxindole derivatives **119** actually occurs in accord with our prediction (91YGK205).

With the rearrangement of the 1-acetyloxy group to the 3 position now established (92H1877), we have set out to apply this methodology to a synthesis of 2*H*-pyrazino[1′,2′:1,5]pyrrolo[2,3-*b*]indole derivatives (Scheme 21). According to the reported procedures (68JOC864, 74TL509), (+)-*N*-benzyloxycarbonyl-L-tryptophan [(+)-**134**] is converted to piperazine derivative (+)-**135** (77%). Its reduction with Et_3SiH and TFA gives a 1 : 1 mixture of diastereomers **136** (83%). Application of the tungstate method to **136** provides (3*S*,6*S*)-(−)-6-(1-hydroxyindol-3-ylmethyl)-3-isobutyl-2,5-piperazinedione [(−)-**137,** 63%]. After preparing



SCHEME 21

benzoyl derivative (−)-**138** (96%) from (−)-**137,** the desired tetracyclic compound (−)-**139** (37%) is successfully produced by heating (−)-**138** in DMF at reflux (2001H2055). The structure and stereochemistry of (−)-**139** is confirmed by NOE experiment in ^{1}H NMR spectroscopy. With the success of this model experiment in hand, further efforts toward the related alkaloid synthesis are in progress.

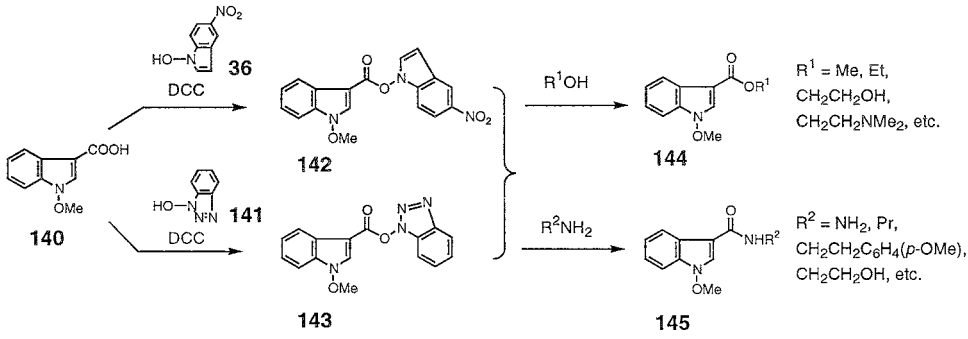
G. Functioning as Active Esters

In the previous review (91YGK205, 99H1157), we reported that 1-hydroxy-4-nitroindole forms active ester derivatives by reaction with carboxylic acids, which can be applied to acylation of various nucleophiles. To expand the scope of the reaction and obtain novel fungicidal compounds, an attempt has been made to prepare derivatives of wasabi phytoalexin **109** (98P1959).

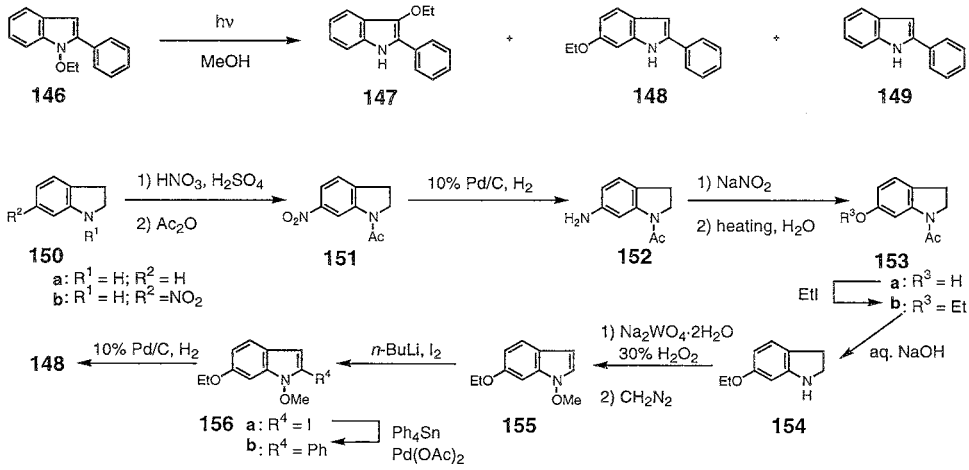
In the presence of DCC, **140** is allowed to react with both 1-hydroxy-5-nitroindole (**36**) and 1-hydroxy-1,2,3-benzotriazole (**141**). Interestingly, their corresponding active esters, **142** and **143,** are obtained in excellent yields as stable crystalline compounds. Both compounds are found to react with variety of nucleophiles, such as alcohols and amines, to produce **144** and **145** in good to excellent yields, as can be seen from the typical examples shown in Scheme 22 (2001H2361). As a result, it becomes possible to produce various kinds of derivatives of wasabi phytoalexin utilizing **142** and **143.**

H. Photorearrangement of the 1-Alkoxy Group

Based on the speculation in "1-Hydroxyindole Hypotheses" that 3-, 4-, and 6-alkoxy(or hydroxy)-substituted indole alkaloids might be the rearranged products of the corresponding 1-substituents by sunlight in plant leaves (80MI33, 91MI206, 93H1859, 95H2157), we irradiated 1-ethoxy-2-phenylindole (**146**) in



SCHEME 22



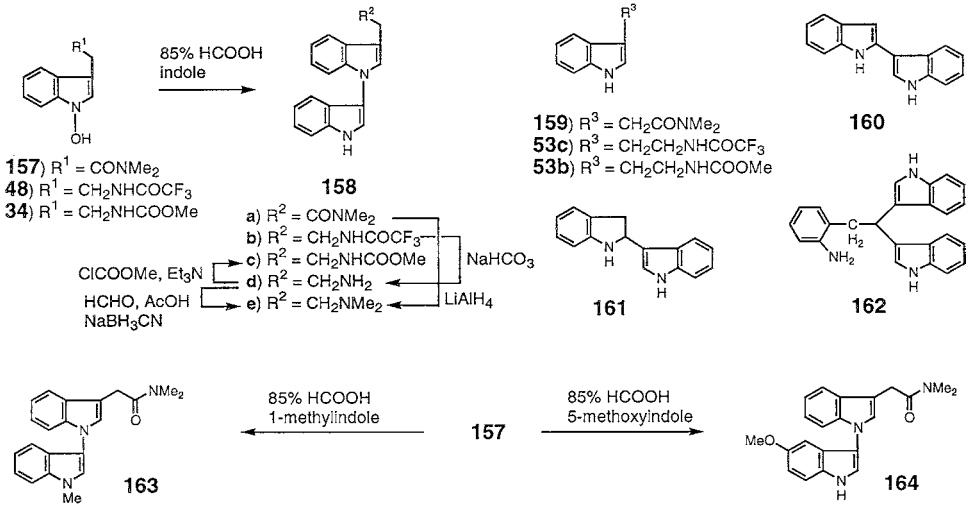
SCHEME 23

MeOH with a Hannovia UV lamp in 1973 (73TL2451). Monitoring with ^{1}H NMR spectroscopy, only two among many products appeared to contain an ethoxy group. After several separations, 3-ethoxy-2-phenylindole (**147,** 12%), 2-phenylindole (**149,** 35%), and an unknown ethoxy-containing 2-phenylindole (unknown **148,** 3%) were isolated (Scheme 23).

Its structural determination had to wait for 25 years until 1998 (98H2481), when we reached the stage where we could apply suitable characteristic reactions found in 1-hydroxyindole chemistry to the synthesis of the authentic 6-ethoxy-2-phenylindole (**148**).

Thus, 2,3-dihydroindole (**150a**) is converted to 1-acetyl-6-nitroindole (**151**) through **150b** by nitration with H_2SO_4 and HNO_3, followed by acetylation. Catalytic hydrogenation of **151** with 10% Pd/C, subsequent diazotization, and pyrolysis of the resultant 1-acetyl-6-amino-2,3-dihydroindole (**152,** 72% from **150a**) produces 6-hydroxy compound **153a** (36%). Ethylation of **153a** with EtI to **153b** (86%) with subsequent alkaline hydrolysis affords **154** (95%). Application of our tungstate method to **154,** followed by methylation with CH_2N_2, provides 6-ethoxy-1-methoxyindole (**155,** 44%). Regioselective lithiation of **155** with *n*-BuLi, followed by the reaction with I_2, results in 6-ethoxy-2-iodo-1-methoxyindole (**156a,** 55%). Stille reaction (86AGE508) of **156a** with tetraphenyltin gives 6-ethoxy-2-phenyl compound **156b** (46%). Finally, the removal of the 1-methoxy group from **156b** by catalytic hydrogenation over 10% Pd/C achieves the preparation of the authentic **148** (89%).

These data demonstrate that a photorearrangement reaction of 1-alkoxy group actually occurs. We continue to speculate that any substituents at the 1 position of indoles may migrate to 3, 4, and/or 6 positions upon photoirradiation.



SCHEME 24

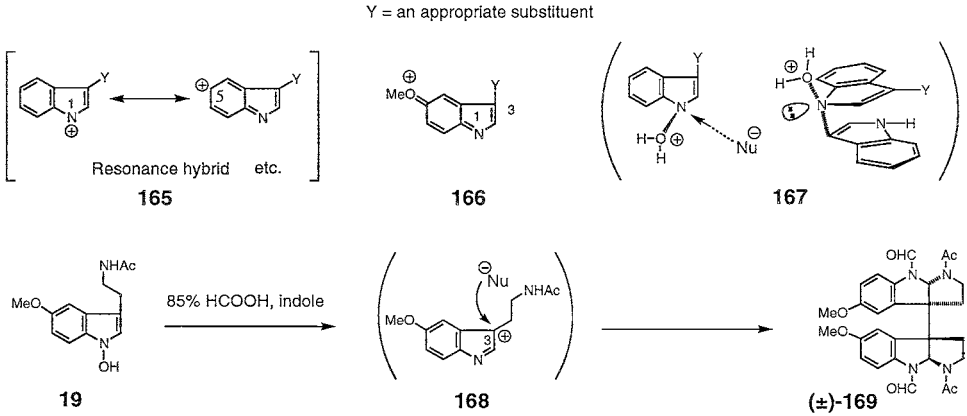
I. NUCLEOPHILIC SUBSTITUTION REACTIONS ON INDOLE NITROGEN

When we proposed the possibility of nucleophilic substitution reactions on indole nitrogen in our hypothesis, we were taken to be eccentric. Fortunately, we have been able to demonstrate examples that seem to accord with the prediction.

When 1-hydroxyindoles are treated with 85% HCOOH at room temperature in the presence of indole, a good nucleophile, 1-(indol-3-yl)indoles are produced (2001H457). As shown in Scheme 24, **157** gives **158a** (84%) and **159** (8%) together with **160, 161,** and **162,** which are the products originated from excess indole. Under similar reaction conditions, **48** provides **158b** (55%) and **53c** (9%), while **34** affords **158c** (47%) and **53b** (9%).

The structure of **158a** is determined unequivocally by X-ray single crystallographic analysis (2001H457). The structures of 1-(indol-3-yl)indoles (**158b,c**) are established by chemical correlations to **158a** as follows. Hydrolysis of **158b** with saturated aqueous $NaHCO_3$ provides tryptamine **158d** (99%). Methoxycarbonylation of **158d** with methyl chloroformate affords **158c** (99%), which is identical to the sample obtained from **34.** Dimethylation of **158d** with HCHO and $NaBH_3CN$ produces dimethyltryptamine **158e** (92%), which is identical to the sample prepared in 76% yield by the reduction of **158a** with $LiAlH_4$ in THF.

1-Methylindole and 5-methoxyindole are also found to function as nucleophiles in this unique reaction, providing **163** (65%) and **164** (50%), respectively (2002H).

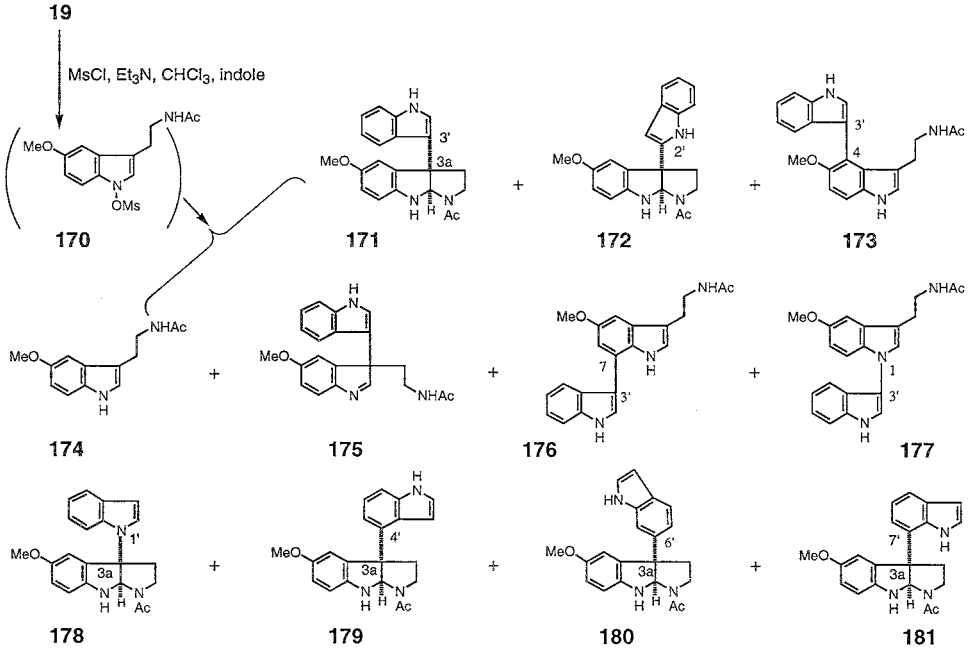


SCHEME 25

Two reaction mechanisms, such as SN1 and SN2 mechanisms, seem to be possible for explaining formations of **158a–c** (Scheme 25). The former requires a resonance-stabilized indolyl cation **165** as an intermediate, while the latter indicates the presence of a transition state like **167.** The introduction of a methoxy group into the 5 position of **165** should stabilize the corresponding cation **166,** in which nucleophilic substitution on indole nitrogen would become a predominant pathway.

However, this expectation is not realized because the reaction of 1-hydroxymelatonin (**19**) with indole in 85% HCOOH follows a different pathway, probably through cation **168,** resulting in the formation of (±)-**169** (99H1237); this is discussed in detail in Section IV.L. On the other hand, when **19** is allowed to react with MsCl in $CHCl_3$ in the presence of indole, the expected product **177** is obtained in only 7% yield through unstable intermediate **170,** together with ten other products: **171** (5%), **172** (4%), **173** (12%), **174** (7%), **175** (0.4%), **176** (7%), **178** (1%), **179** (2%), **180** (2%), and **181** (4%) (Scheme 26) (2002H).

Based on X-ray single crystallographic analysis (91CPB1905), we have already demonstrated that the 1-hydroxy oxygen on the *N*-1 of tryptophan derivative **32** lies above the plane of indole deviated by about 15° [83JCS(P2)497]. This result suggests that the indole nitrogen in 1-hydroxyindoles is no longer exactly sp^2-hybridized. Upon protonation of 1-hydroxy oxygen, the nitrogen might become more sp^3-hybridized. When water departs, a nucleophile (indole) could approach from the back side of the leaving group as shown in a transition state **167,** resulting in the formation of **158a–c, 163,** and **164.** Although such SN2 reactions on the indole nitrogen have not yet been proposed in indole chemistry, this concerted mechanism seems to be attractive (2001H457). At present, we cannot determine whether the reaction mechanism is SN1 or SN2. Further kinetic studies are needed to clarify this unprecedented reaction.



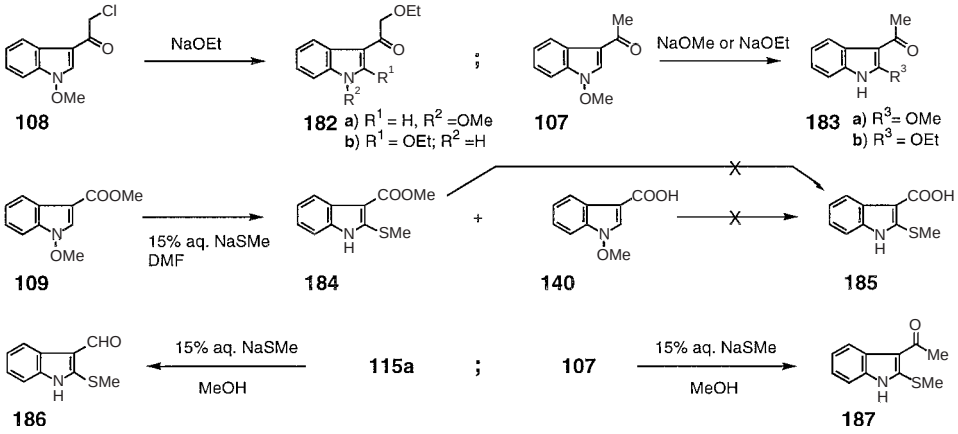
SCHEME 26

J. NUCLEOPHILIC SUBSTITUTION REACTION AT THE 2 POSITION

We have found that 1-methoxyindoles carrying a formyl group on the indole nucleus can undergo nucleophilic substitution reactions with a 1-methoxy moiety as a leaving group. When the formyl group is present at the 3 position of 1-methoxyindole, as in the case of 1-methoxyindole-3-carbaldehyde (**115a,** daikon phytoalexin), nucleophiles enter into the 2 position. When the formyl group is located at the 2 position, nucleophiles add to the 3 position (99H1157).

With an attempt to enlarge the scope of this reaction, the reactivities of 3-acetyl-1-methoxyindole (**107**) and 3-chloroacetyl-1-methoxyindole (**108**) are examined (99H1949). Interestingly, in the reaction with NaOEt in refluxing EtOH, **108** produces **182a** (17%) instead of **182b** (Scheme 27). On the other hand, **107** provides the expected 2-substituted products, **183a** (93%) and **183b** (94%), by treatment with NaOMe and NaOEt, respectively, in the corresponding refluxing alcohol (2001H425).

The reaction of wasabi phytoalexin (**109**) with excess 15% aqueous NaSMe gives methyl 2-methylthioindole-3-carboxylate (**184,** 70%) and **140** (20%). In this reaction, formation of 2-methylthioindole-3-carboxylic acid (**185**) is not observed under various reaction conditions. The fact indicates that once **140** is formed, it does not undergo nucleophilic substitution reaction. In addition, hydrolysis of the



SCHEME 27

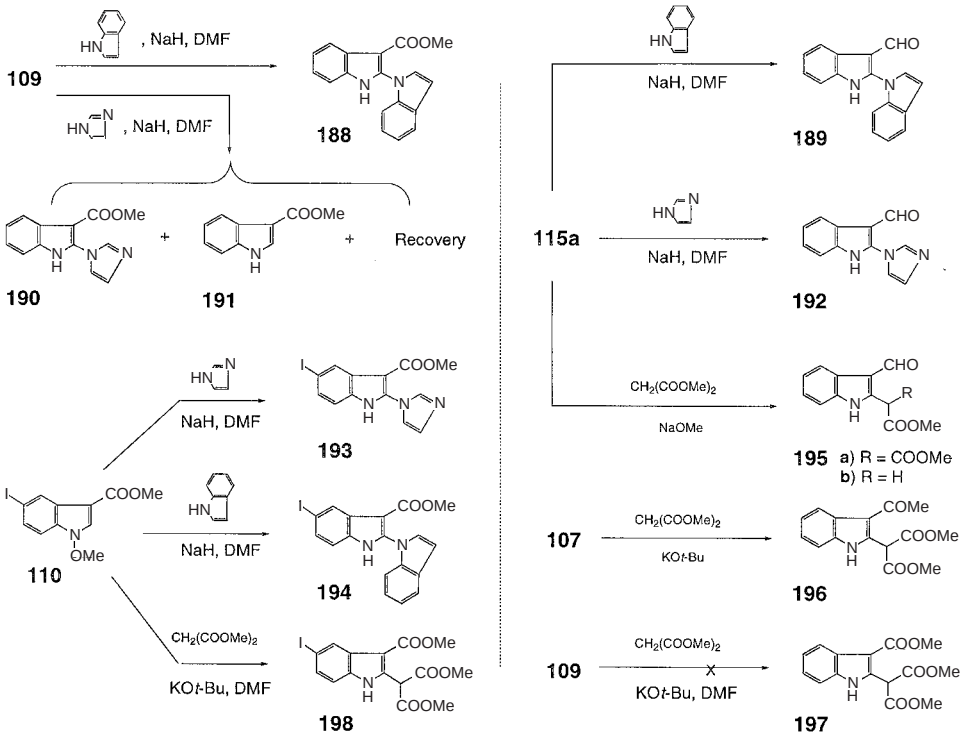
ester group of **184** to **185** does not occur because of resonance stabilization by the lone-pair electrons on the methylthio sulfur atom.

In contrast, 3-acetyl-1-methoxyindole (**107**) furnishes **187** (quantitative) in the reaction with NaSMe. Under milder conditions, daikon phytoalexin (**115a**) affords brassicanal A (**186,** quantitative) as reported previously (87MI629, 88BCJ285, 92H1877, 93MI22). From these facts, the order of relative nucleophilic substitution reactivity of 3-acyl-1-methoxyindoles is found to correlate with the electron-withdrawing ability of acyl groups (CHO > COMe > COOMe).

This trend is also observed in the reactions with nitrogen- and carbon-centered nucleophiles (2001H425). Thus, the reaction of **109** with sodium indolyl in DMF affords methyl 2-(indol-1-yl)indole-3-carboxylate (**188,** 77%). In better yield, 2-(indol-1-yl)indole-3-carbaldehyde (**189,** 95%) is formed in the corresponding reaction (99H1157) of **115a** (Scheme 28). Sodium imidazolyl reacts with **109** in DMF at 60°C to afford methyl 2-(imidazol-1-yl)indole-3-carboxylate (**190,** 28%), methyl indole-3-carboxylate (**191,** 11%), and unreacted **109** (36%). In contrast, under the same conditions, **110** and **115a** provide higher yields of methyl 2-(imidazol-1-yl)-5-iodoindole-3-carboxylate (**193,** 72%) and **192** (81%), respectively.

When highly reactive sodium indolyl is employed as a nucleophile, the difference in reactivities between **109** and **110** is not observed. Consequently, methyl 2-(indol-1-yl)-3-carboxylate (**188**) and methyl 2-(indol-1-yl)-5-iodoindole-3-carboxylate (**194**) are available in 77% yield.

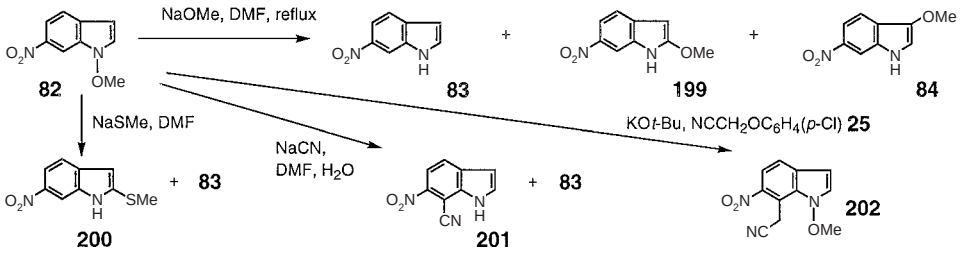
Sodium dimethyl malonate reacts with **115a,** resulting in dimethyl 2-(3-acylindol-2-yl)malonates, **195a** (53%) and **195b** (7%). Similarly, **107** affords **196** (51%), although **109** did not generate **197** at all. Interestingly, introduction of iodine into the 5 position of **109** considerably enhances the reactivity of nucleophilic substitution. Consequently, **110** results in **198** (25%) by the reaction with sodium dimethyl malonate (2001H425).



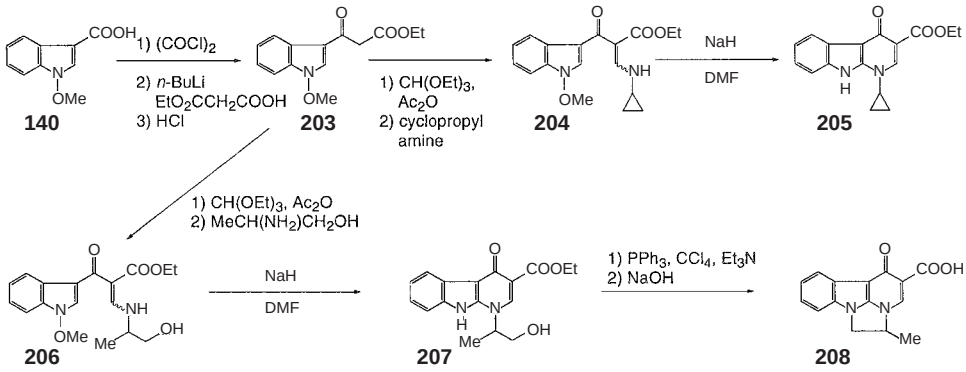
SCHEME 28

Comparison of these reactivities and antifungal activities of phytoalexin derivatives is an interesting future subject.

The effect of a nitro group at the 6 position on the nucleophilic substitution reaction has been examined using 1-methoxy-6-nitroindole (**82**) as a substrate (2001H1151). The reaction with NaOMe in refluxing DMF generates 6-nitroindole (**83,** 57%), 2-methoxy- (**199,** 22%), and 3-methoxy-6-nitroindoles (**84,** 6%) (Scheme 29). The formation of **199** and **84** can be explained by the SN2′-type nucleophilic substitution reaction at the 2 and 3 positions, respectively, with the



SCHEME 29



SCHEME 30

1-methoxy moiety as a leaving group. In the reaction with NaSMe, reductive demethoxylation of **82** becomes a major reaction, giving **83** (54%) in addition to 2-methylthio-6-nitroindole (**200,** 13%). In the above cases, introduction of nucleophiles into the benzene part of indole nucleus is not observed.

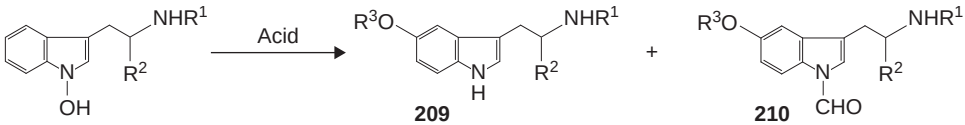
In contrast, reaction of **82** with NaCN in DMF–H_2O at reflux results in the formation of 7-cyano-6-nitroindole (**201,** 15%) and **83** (4%) as isolable products together with tar matter, and, to our surprise, 2- and/or 3-cyano-6-nitroindoles are not detected at all. When the reaction is carried out in DMSO at 150°C, only demethoxylation occurred to give **83** (62%). On the other hand, utilizing KO*t*-Bu and *p*-chlorophenoxyacetonitrile (**25**), the vicarious substitution reaction (87ACR282) of **82** proceeds smoothly to give a 7-cyanomethylated indole (**202,** 67%) (2001H1151).

An interesting application of our regioselective nucleophilic substitution reaction (94H273, 99H1157) to an intramolecular version has been demonstrated by Chung and co-workers (98H103) in their project to find a new antibacterial drugs (Scheme 30). Thus, 1-methoxyindole-3-carboxylic acid (**140**) is transformed to **204** and **206** through **203** by a sequence of reactions. Treatment of **204** and **206** with NaH in DMF produces the desired indole-fused 4-oxopyridine-3-carboxylic acids **205** (83%) and **207** (89%), respectively. Conversion of **207** to the tetracyclic derivative **208** (41%) is also reported.

K. NUCLEOPHILIC SUBSTITUTION REACTION AT THE 5 POSITION AND DIMERIZATION

Regioselective nucleophilic substitution at the 5 position is proved to occur when 1-hydroxytryptophan and -tryptamine derivatives are treated with 85% HCOOH (99H1157). Truly amazing is the fact that only substrates carrying a C—C—N structure in the side chain at the 3 position can undergo this regioselective substitution.

TABLE IV



Entry	Substrate	R^1	R^2	Acid	Product	Yield (%) of **209**	Yield (%) of **210**
1	**39**	Ac	H	20% BF_3·MeOH	**17**) $R^3 = Me$	80	0
2	**34**	COOMe	”	”	**a**) $R^3 = Me$	85	0
3	**34**	COOMe	”	85% HCOOH	**b**) $R^3 = H$	8	54
4	**32**	Ac	COOMe	H_2SO_4-MeOH	**c**) $R^3 = Me$	71	0
5	**32**	”	”	85% HCOOH	**d**) $R^3 = H$	67	12

In contrast, substrates having other structural types of side chain at the 3 position dimerize under acidic conditions, and never produce the 5-substituted products. These facts seem to support the “1-Hydroxyindole Hypotheses,” which claim the formation of serotonin from 1-hydroxytryptophan and/or -tryptamine in the acidic compartment within eukaryotic cells.

1. *Nucleophilic Substitution Reactions at the 5 Position*

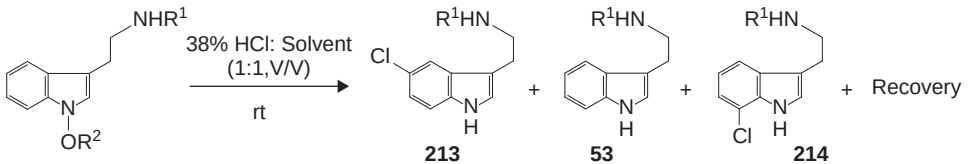
As listed in Table IV, 5-hydroxy- and 5-methoxytryptamines (**17, 209a,b,** and **210b**) and 5-hydroxy- and 5-methoxytryptophans (**209c,d** and **210d**) are now readily available utilizing acid-promoted nucleophilic substitution reactions of the corresponding 1-hydroxyindole compounds (99H1157).

Attempts to extend the reaction to the syntheses of 5-chloro and 5-bromo derivatives have led us to discover that treating 1-hydroxytryptamines simply with aqueous hydrogen halides at room temperature is sufficient to meet our end (99H2815).

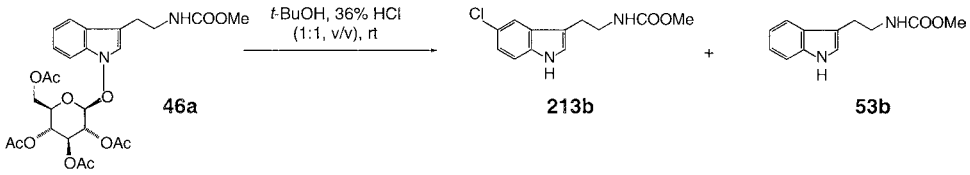
In the reaction of 1-alkoxytryptamines with aqueous HCl, 5-chlorotryptamines (**213**), 7-chlorotryptamines (**214**), and dealkoxylated tryptamines (**53**) are produced, and the results are summarized in Table V. Interestingly, the 1-substituent is an important factor in governing the yield of 5-chlorotryptamines (**213**). As the substituent changes in turn from hydroxy to methoxy, 1-(2-methoxycarbonyl)ethoxy, and 1-(2-methoxycarbonyl-1-methyl)ethoxy groups (entries 1–4), the yield of **213a** increases dramatically.

Comparison of the results in entries 1 and 6 clearly shows that the N^b substituent of the side chain at the 3 position also influences the yield of **213.** What result might we expect if we choose a methoxy group as a 1-substituent and a methoxycarbonyl group as an N^b substituent in the same molecule? Employing **212** as a starting material (entry 7), a good yield of 5-substituted product is obtained, as expected. Hence, 5-chlorotryptamine (**213b**) is now available in 80% yield.

TABLE V



				Reaction Conditions			Yield (%) of			
Entry	Substrate	R^1	R^2	Solvent	Time (h)	Product	**213**	**53**	**214**	**Recovery**
1	**39**	Ac	H	MeOH	3.5	**a**) $R^1 = Ac$	17	20	0	0
2	**211**	”	Me	”	7.5	”	55	0	4	8
3	**40**	”	CH_2CH_2COOMe	”	17	”	59	0	0	6
4	**41**	”	$CH(Me)CH_2COOMe$	”	120	”	73	0	0	6
5	**211**	”	Me	*t*-BuOH	6	”	54	0	5	10
6	**34**	COOMe	H	”	1/6	**b**) $R^1 = COOMe$	48	8	7	0
7	**212**	”	Me	”	1/6	”	80	0	0	0

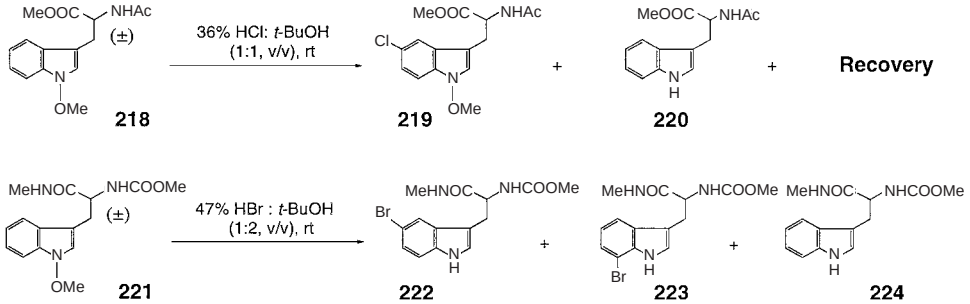


SCHEME 31

Similarly, the reaction of 1-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)oxy-*N*b-methoxycarbonyltryptamine (**46a**) with aqueous HCl proceeds smoothly, generating **213b** (55%) and deglycosylated **53b** (28%) as shown in Scheme 31 (2002UP1).

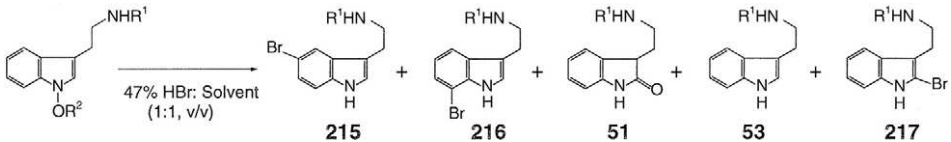
The reaction of 1-hydroxytryptamines with aqueous HBr is more complex compared with that with aqueous HCl, and many products such as **215, 216, 51, 53,** and **217** are produced as shown in Table VI (99H2815). Again, both the 1-substituent and the *N*b substituent play significant roles on the yield of 5-bromotryptamines (**215**) (entries 1–3, 6, 7, and 9). The solvent is another important factor. As its polarity (ε) increases from *t*-BuOH (11) to DMF (37), MeCN (38), $HCONH_2$ (111), and HCONHMe (182) (entries 4–8), a tendency to increase in the yield of **215b** is found, although it is not proportional. Considering the balance of these factors, **215a** and **215b** are available in 45–51% yields by choosing the reaction conditions in entries 2 and 9. Although the major product is 2-oxindole (**51b,** 35%), BBr_3 seems to promote the formation of 7-bromotryptamine (**216b,** 23%).

With 1-hydroxytryptophan derivatives, similar substituent effects are observed (99H2815). In order to realize better yields of 5-substituted tryptophans, carboxy and amino groups are transformed to ester and/or amide groups, choosing the 1-methoxy moiety as a leaving group. As a result, (±)-*N*b-acetyl-5-chlorotryptophan methyl ester (**219,** 52%) is obtained together with **220** (7%) from (±)-**218** by the reaction with aqueous HCl (Scheme 32). (±)-5-Bromo-*N*b-methoxycarbonyltryptophan methylamide (**222,** 50%) becomes readily available



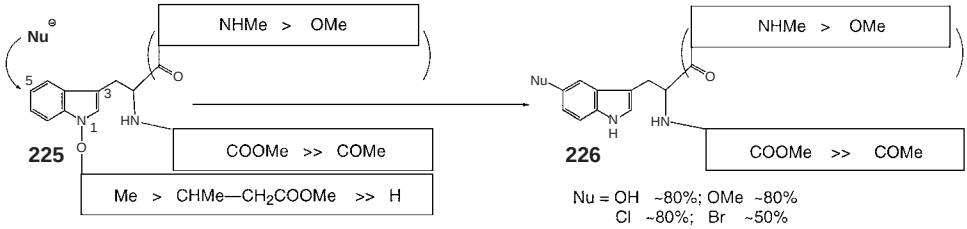
SCHEME 32

TABLE VI



Entry	Substrate	R^1	R^2	Reaction Conditions: Solvent	Temp. (°C)	Time (h)	Product	Yield (%) of: **215**	**216**	**51**	**53**	**217**
1	**39**	Ac	H	MeCN	80	3	**a**) R^1 = Ac	5	4	19	3	0
2	**40**	”	CH_2CH_2COOMe	MeOH	rt	20	”	51	8	18	11	0
3	**41**	”	$CH(Me)CH_2COOMe$	”	rt	55	”	38	8	0	10	0
4	**34**	COOMe	H	*t*-BuOH	80	1/12	**b**) R^1 = COOMe	17	8	15	6	23
5	”	”	”	DMF	80	1/12	”	27	8	13	19	0
6	”	”	”	MeCN	80	1/12	”	24	6	41	14	0
7	”	”	”	$HCONH_2$	80	1/6	”	39	6	15	10	0
8	”	”	”	HCONHMe	80	1/12	”	36	9	9	19	0
9	**212**	”	Me	$HCONH_2$	rt	1/6	”	45	8	5	9	0
10	**34**	”	H	$MeNO_2$*	rt	1	”	5	23	35	11	2

*BBr_3 (1.1 mol eq) was used as a brominating reagent.



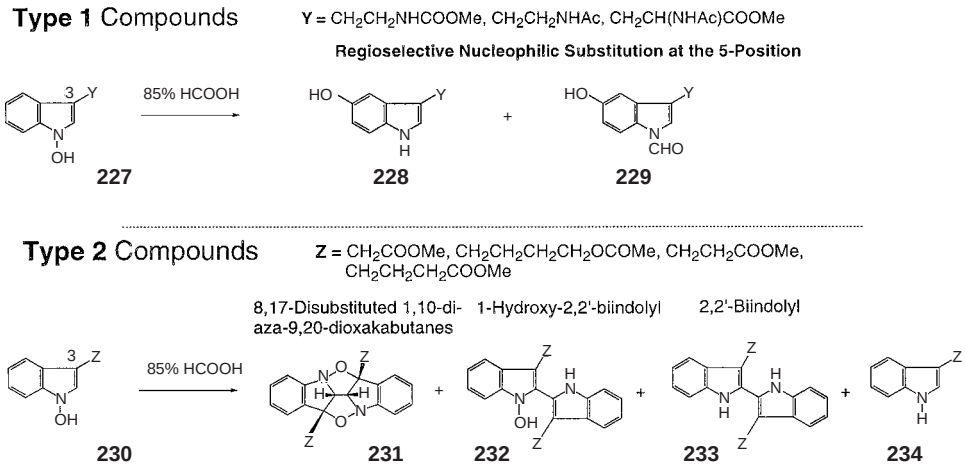
SCHEME 33

from (±)-**221** by treating it with aqueous HBr, together with formations of **223** (12%) and **224** (17%) as byproducts.

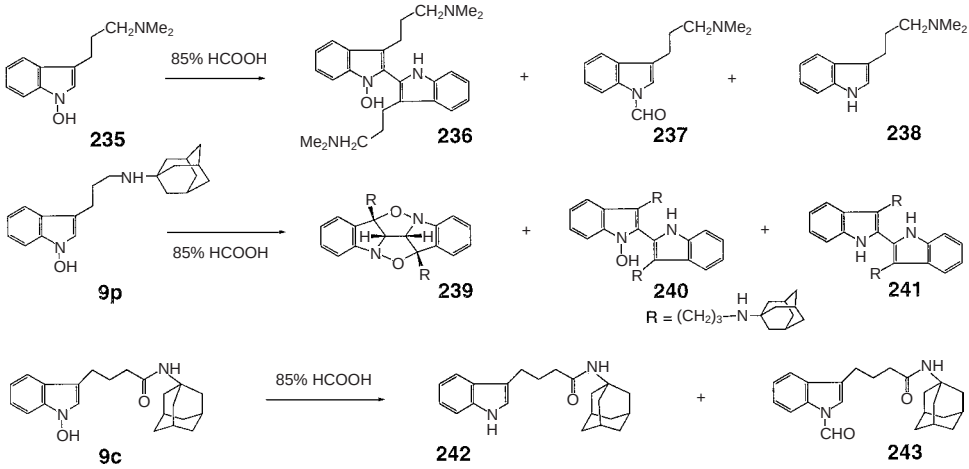
Through the above experiments, substituent effects on the acid-promoted nucleophilic substitution reactions at the 5 position are summarized as illustrated in Scheme 33. In terms of the reaction rate and product yield, the *N*b-methoxycarbonyl is superior to the *N*b-acetyl group. As a leaving group, 1-alkoxy is far better than the 1-hydroxy moiety. Among 1-alkoxy groups, 1-methoxy should be chosen in preference to others owing to its easy preparation. When tryptophan derivatives are needed, the carboxy group should be transformed in advance to an amide group rather than an ester counterpart.

2. *Effects of a Side Chain at the 3 Position on the Direction of Reaction Pathway*

As noted in the previous review (99H1157), we proposed a working hypothesis that "1-hydroxyindoles are classified into two groups from the point of reactivity characteristics toward 85% HCOOH" (Scheme 34). Thus, type 1 compounds **227**



SCHEME 34

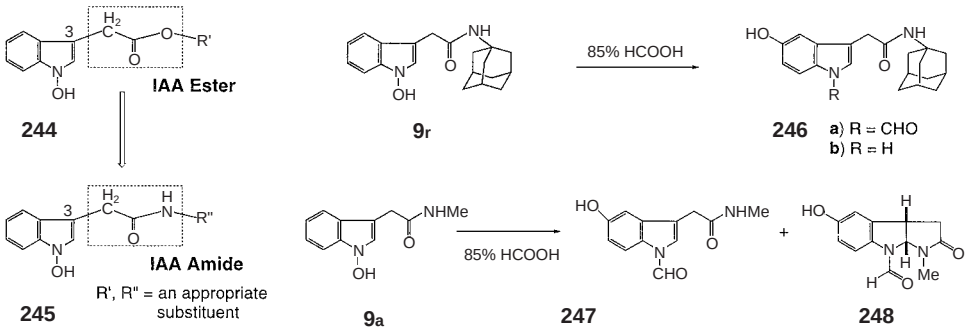


SCHEME 35

having a C—C—N structure as a side chain at the 3 position can undergo regioselective substitution reactions to produce 5-hydroxyindoles **228** and its 1-formyl derivatives **229.** In contrast, type 2 compounds **230,** which are all 1-hydroxyindoles except for **227,** provide 8,17-disubstituted 1,10-diaza-9,20-dioxakabutanes (**231**), 1-hydroxy-2,2′-biindolyls (**232**), 2,2′-biindolyls (**233**), and/or dehydroxylated products **234** without the formation of 5-hydroxy compounds **228.**

Further proofs have been obtained (2002UP1) employing the type 2 compounds, such as **235** and **9p,** which have a C—C—C—N structure as a side chain (Scheme 35). The former generates **236, 237,** and **238** upon reaction with 85% HCOOH, while the latter provides **239, 240,** and **241.** In both cases, every byproduct is thoroughly checked by ^{1}H NMR and the lack of formation of 5-hydroxy compound is confirmed. Another type 2 compound **9c** carrying a C—C—C—C—N structure as a side chain at the 3 position is also found to afford **242** and **243** instead of forming the 5-hydroxy compound. As described before (99H1157), the compounds having a C—N structure as a 3 substituent are too unstable under the reaction conditions to isolate products. They produced only tar.

Methyl 1-hydroxyindole-3-acetate (**244,** IAA ester) is a representative substrate belonging to the type 2 compounds (Scheme 36). In order to verify the working hypothesis directly, we planned to change the C—C—O side chain structure of **244** to the C—C—N structure as shown in **245** to examine whether it alters reaction pathways. Surprisingly, in accord with the hypotheses, substrates such as **9r** and **9a** undergo regioselective hydroxylation at the 5 position upon reaction with 85% HCOOH. The former produced **246a** (42%) and **246b** (18%). In the latter case, construction of 5-hydroxypyrrolo[2,3-*b*]indole skeleton (**248,** 48%) is attained in one step together with normal product **247** (20%) (2002UP1).



SCHEME 36

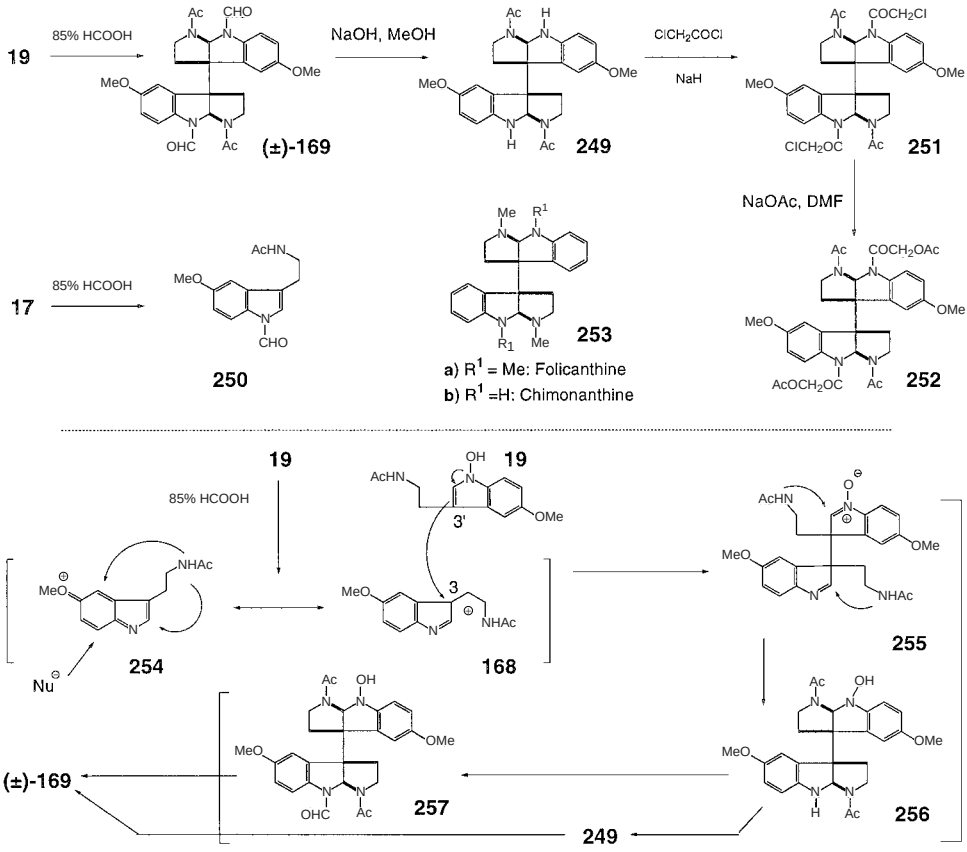
3. *Unified Mechanism for Substituent Effects*

We have proposed the following mechanism for understanding substituent effects described in Sections IV.K.1 and IV.K.2 (99H2815). The first and fast protonation occurs initially on the N^b nitrogen atom of the side chain in 85% HCOOH. The extent of its protonation depends on an attached substituent on the *N*b-nitrogen atom, both electronically and stereochemically. The protonated *N*b-nitrogen electrostatically inhibits the approach and addition of the second proton to the 3 position because of close proximity. As a result, the second protonation occurs selectively on the 1-alkoxy oxygen atom situated far from the protonated *N*b-nitrogen, culminating in the departure of the 1-alkoxy group. Protonation of the 1-alkoxy group follows the order of the electron-donating nature of the alkyl group, so that the 1-alkoxy group is more effective than the 1-hydroxy moiety. For indoles lacking the *N*b-nitrogen, a preferential proton addition occurs at the 3 position, which leads the reaction pathway toward formations of 1,10-diaza-9,20-dioxakabutanes, 1-hydroxy-2,2′-biindolyls, 2,2′-biindolyls, pyrrolo[2,3-*b*]indoles, and so on.

L. ACID-CATALYZED DIMERIZATION

When 1-hydroxymelatonin (**19**) is treated with acid, removal of its 1-hydroxy group leaves an indolyl cation (a hybrid of resonance structures **254, 168,** and so on) as shown in Scheme 37. If there is a subsequent intramolecular nucleophilic attack by the *N*b-nitrogen atom on the side chain or if an intermolecular attack by suitable nucleophiles occurs on this intermediate cation, the birth of a new type of product can be expected.

Relying on this expectation, we carried out the reaction of **19** with 85% HCOOH, and discovered the exclusive formation of (±)-**169** (44%) (99H1237), which has the same skeleton as the alkaloids folicanthine (**253a**) and chimonanthine (**253b**)



SCHEME 37

(61PCS465, 63TL1757, 64JA302, 64T565, 67T4131, 77TL2403, 81TL5323, 96JA8166). In contrast, a similar reaction of **17** with 85% HCOOH affords 1-formylmelatonin (**250,** 88%), while formation of (±)-**169** is not observed at all.

The structure of (±)-**169** is determined to have a (±)-3a,3a′-bispyrrolo[2,3-*b*] indole skeleton by carrying out X-ray single crystallographic analysis of its derivative **252** (99H1237). Compound **252** is obtained from (±)-**169** by the following sequence of reactions: (1) alkaline hydrolysis of (±)-**169** to **249** (88%), (2) conversion of **249** to **251** (71%) by treatment with NaH and chloroacetyl chloride, (3) substitution of chlorine on the chloroacetyl group for acetate **252** (93%) by the reaction with NaOAc.

The mechanism for the formation of (±)-**169** is explained in terms of an intermolecular nucleophilic dimerization. Nucleophilic addition of C-3′ of **19** to the 3 position of the initially generated cation **168** gives an imine–nitrone

intermediate **255.** Subsequent intramolecular additions of nucleophiles *N*b- and *N*b′-nitrogens to the imine and nitrone carbon atoms, respectively, form 3a,3a′-bispyrrolo[2,3-*b*]indole compound **256.** Then, formic acid functions both in the reduction of hydroxylamine to amine and in N-formylation, giving (±)-**169** through **257** and/or **249.**

V. Synthetic Studies toward Novel Heterocyclic Compounds and Natural Products

Applications of our results in 1-hydroxyindole chemistry and our tungstate method to the syntheses of novel heterocyclic compounds and biologically active natural products are summarized in this section.

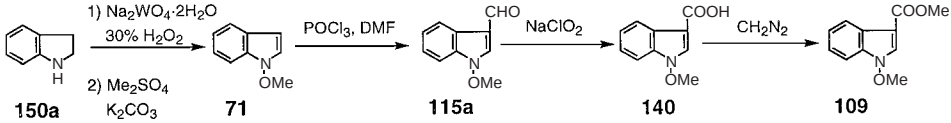
A. Wasabi Phytoalexin and Analogs

Pedras and co-workers (98P1959) isolated a phytoalexin from Wasabi (***Wasabia japonica,*** syn. ***Eutrema wasabi***) and determined its structure to be methyl 1-methoxyindole-3-carboxylate (**109**) (Scheme 38). Compound **109** had already been synthesized by Acheson and co-workers [78JCS(P1)1117] in ten steps from *o*-nitroaniline. Pedras and co-workers (98P1959) combined our tungstate method and Acheson's work, and synthesized **109** in 9% overall yield but in an impure state.

An alternative synthesis of **109** from indoline (**150a**) utilizing the tungstate method in five steps achieved a 51% overall yield (2001H425). Thus, 1-methoxyindole-3-carbaldehyde (**115a**), a phytoalexin found by Takasugi and co-workers (87MI629, 88BCJ285, 93MI22) from the plant family Cruciferae, is prepared in three steps in 54% overall yield from **150a** (92H1877). Oxidation of **115a** with $NaClO_2$ (81T2091) generates **140** (95%). Its methylation with CH_2N_2 provides a quantitative yield of **109.** By this route, pure **109** and pure **140** were produced for the first time.

B. Coerulescine

Colegate and co-workers (98P437) isolated (−)-coerulescine (**120b**) from *Phalaris coerulescens* and determined that its structure has a 3,3-disubstituted oxindole nucleus (Scheme 18). The synthesis of (±)-coerulescine (**120b**) was



Scheme 38

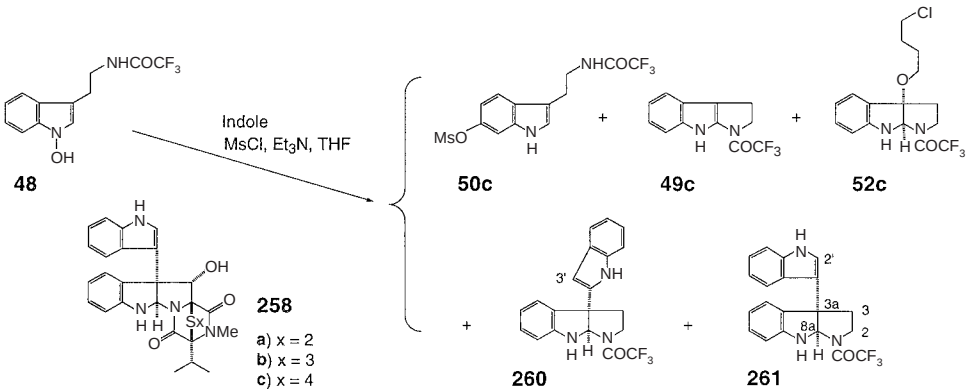
easily attained (2000H7) by utilizing the rearrangement reaction mentioned in Section IV.F. Thus, treatment of **16a** with HCl in refluxing MeOH produced (±)-**120b** (42%), **124** (46%), and 6-chloro-1,2,3,4-tetrahydro-2-methyl-β-carboline (**123,** 9%).

C. Leptosin Alkaloids

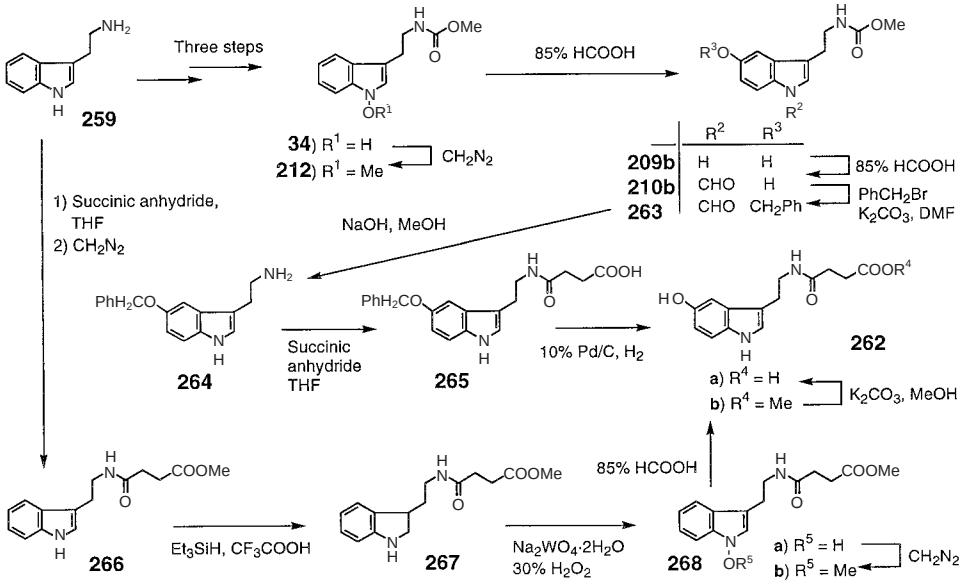
Leptosins D–F (**258a–c,** Scheme 39) [94JCS(P1)1859] were isolated by Takahashi and co-workers from the culture of a strain of *Leptosphaeria* sp. as cytotoxic substances against the P388 lymphocytic leukemia cell line comparable to that of mitomycin C. Utilizing the nucleophilic substitution reaction of 1-hydroxytryptamines, a simple methodology for the synthesis of core structures of leptosins has been developed (2000H1255).

Treatment of 1-hydroxy-*N*b-trifluoroacetyltryptamine (**48**), which is readily available in three steps from tryptamine (**259,** Scheme 40), with MsCl in THF in the presence of indole (3 mol eq) and Et_3N produces 1-trifluoroacetyl-1,2,3,8-tetrahydropyrrolo[2,3-*b*]indole (**49c,** 25%), 1-trifluoroacetyl-3a-(4-chlorobutoxy)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**52c,** 6%), *N*b-trifluoroacetyl-6-mesyloxytryptamine (**50c,** 8%), 3a-(indol-2-yl)- (**260,** 5%), and 3a-(indol-3-yl)-1-trifluoroacetyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**261,** 12%). In this reaction, solvent plays an important role. Among the tested solvents such as benzene, $CHCl_3$, 1,2-dichloroethane, THF, DMF, CH_3CN, and *N*-methylformamide, $CHCl_3$ is found to be the solvent of choice to provide a 21% yield of **261.** The use of excess indole (10 mol eq) further raises the yield to 30%.

The preferred formation of **261** over **260** is in accord with the well-known positional order 3 > 2 for reactivity of unsubstituted indole. Aiming at total synthesis of leptosin alkaloids, an application of this methodology to the 1-hydroxy-L-tryptophan derivatives seems to be promising.



Scheme 39



SCHEME 40

D. BUFOBUTANOIC ACID

In 1999, Kamano and co-workers isolated bufobutanoic acid (**262a,** Scheme 40) as a cytotoxic substance against murine P388 lymphocytic leukemia cells from Ch'an Su, and determined its structure (99H499). The first synthesis of **262a** was attained by two routes, applying regioselective nucleophilic substitution reactions of 1-hydroxytryptamines (2000H1017).

The first route utilizes 1-hydroxy-*N*b-methoxycarbonyltryptamine (**34**), prepared from **259** as a potent inhibitor of blood platelet aggregation (96H1855). It is converted to **210b** (48%) by the reaction with 85% HCOOH. Under similar reaction conditions, 1-methoxy-*N*b-methoxycarbonyltryptamine (**212**) produces predominantly 1-unsubstituted **209b** (69%). It is then converted to **210b** (70%) by prolonged reaction with 85% HCOOH at room temperature. Subsequent reaction of **210b** with benzyl bromide furnishes **263.** Alkaline hydrolysis of **263** provides 5-benzyloxytryptamine (**264**), whose amino group on the side chain is then acylated to **265** by treatment with succinic anhydride. Catalytic hydrogenation of **265** over 10% Pd/C achieves the first synthesis of **262a** in eight steps from **259** in 25% overall yield.

The second route employs acylation of tryptamine (**259**) as the first step by reacting it with succinic anhydride. After methylation with CH_2N_2, the resultant *N*b-methoxysuccinyltryptamine (**266**) is transformed to the corresponding

2,3-dihydroindole (**267**) by the reduction with Et_3SiH in TFA. Application of our tungstate method to **267** generates 1-hydroxytryptamine **268a.** Its structure is confirmed by converting it to 1-methoxytryptamine **268b** (86%) by the reaction with CH_2N_2. Then, **268a** is allowed to react with 85% HCOOH to give serotonin derivative **262b** (38%). Finally, alkaline hydrolysis of the ester part of **262b** results in the formation of **262a.** This second six-step synthesis is carried out in 13% overall yield.

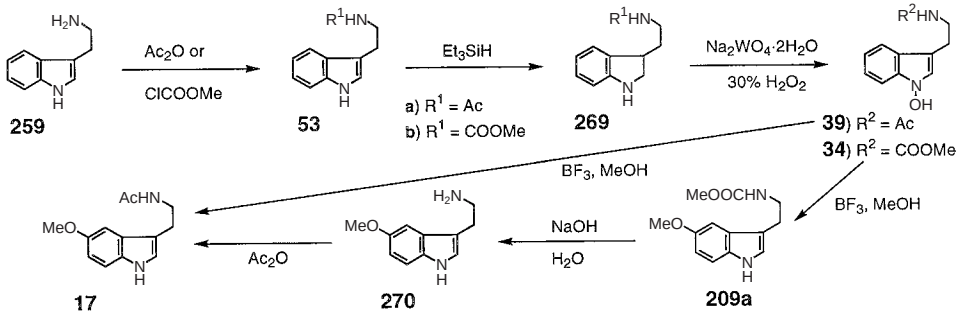
E. MELATONIN

Serotonin, *N*-methylserotonin, bufotenine, and 5-methoxy-*N*-methyltryptamine become readily available in a simple way by applying nucleophilic substitution reactions in 1-hydroxytryptamine chemistry (99H1157, 2001CPB87).

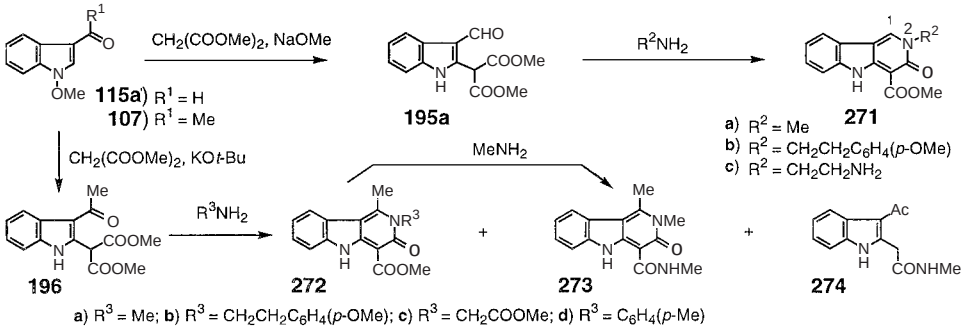
Melatonin (**17,** Scheme 41) is a hormone (58JA2587, 86MI1170, 88SCI78) secreted from the pineal gland and known to control circadian rhythms. Such biological activities as inhibition of Alzheimer β-fibrillogenesis, antiaging properties relating to radical scavenging, and antiproliferative effects on melanoma cells have also been reported (91MI99, 93E671, 93MI189, 93MI89, 96MI308, 98JBC7185).

Applying regioselective nucleophilic methoxylation of 1-hydroxytryptamines, two novel practical synthetic methods (2000H1725) for melatonin have been developed. Thus, tryptamine (**259**) is converted to *N*b-acetyl- (**53a**) and *N*b-methoxycarbonyltryptamine (**53b**) in quantitative yields by the respective reactions with either Ac_2O or methyl chloroformate. Their reduction with Et_3SiH in TFA provides 2,3-dihydrotryptamines **269a** (99%) and **269b** (97%), respectively. Application of our tungstate method to **269a** produces **39** (66%). Under similar reaction conditions, **269b** gives **34** (65%). These two compounds, **39** and **34,** are found to be promising as inhibitors of blood platelet aggregation (96H1855).

For attaining regioselective introduction of the methoxy group into the 5 position, 20% BF_3 in MeOH is found to be the reagent of choice. Utilizing these



SCHEME 41



SCHEME 42

reaction conditions, **39** and **34** are converted to **17** (80%) and **209a** (94%), respectively. Alkaline hydrolysis of **209a** gives 5-methoxytryptamine (**270,** 99%), and subsequent acetylation with Ac_2O produces **17** (92%).

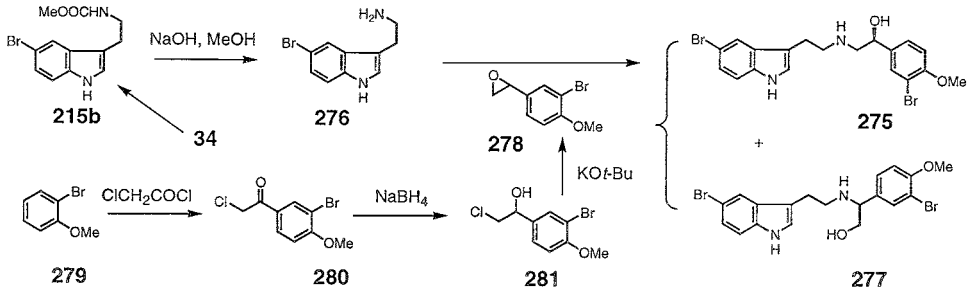
As a result, the former four-step synthesis of **17** proceeds in 52% overall yield from **259,** while the latter six-step synthesis proceeds in 55% overall yield.

F. 5*H*-PYRIDO[4,3-*b*]INDOLE (γ-CARBOLINE) DERIVATIVES

For a structure–activity relationship study on 5*H*-pyrido[4,3-*b*]indoles (γ-carbolines), we needed both 1-unsubstituted **271** and 1-substituted methyl 2,3-dihydro-3-oxo-5*H*-pyrido[4,3-*b*]indole-4-carboxylates **272** (Scheme 42).

These types of compounds are expected to be produced by utilizing nucleophilc substitution reaction at the 2 position of 1-methoxyindole-3-carbaldehyde (**115a**) and 3-acetyl-1-methoxyindole (**107**). In practice, after conversion of **115a** to **195a** (53%) as described in Section IV.J, **195a** is allowed to react with various amines. Consequently, many derivatives of **271** are obtained. Typical examples (**271a–c**) are shown in the scheme (99H1157).

On the other hand, **107** is converted to dimethyl 2-(3-acetylindol-2-yl)malonate (**196,** 51%) by the reaction with methyl malonate (99H1949). Subsequent reaction of **196** with methylamine in refluxing MeOH produces methyl 2,3-dihydro-1,2-dimethyl-3-oxo-5*H*-pyrido[4,3-*b*]indole-4-carboxylate (**272a,** 62%), *N*-methyl 2,3-dihydro-1,2-dimethyl-3-oxo-5*H*-pyrido[4,3-*b*]indole-4-carboxamide (**273,** 7%), and *N*-methyl 2-(3-acetylindol-2-yl)acetamide (**274,** 19%). *p*-Methoxyphenethylamine and glycine methyl ester react similarly with **196** to produce **272b** (64%) and methyl 2,3-dihydro-3-oxo-2-(methoxycarbonylmethyl)-1-methyl-5*H*-pyrido[4,3-*b*]indole-4-carboxylate (**272c,** 44%), respectively. *p*-Toluidine reacts very slowly and even after 48 h in refluxing MeOH, **272d** is produced in only 12% yield.



SCHEME 43

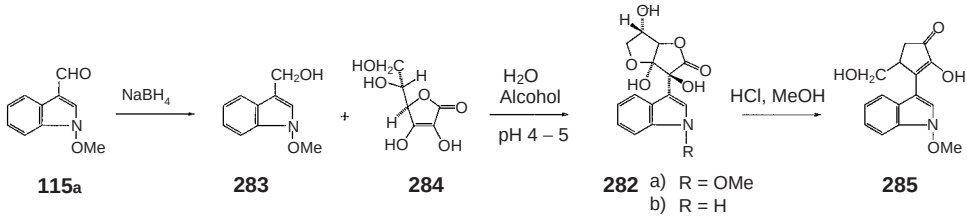
Thus, novel 2-substituted methyl 2,3-dihydro-1-methyl-3-oxo-5*H*-pyrido[4,3-*b*] indole-4-carboxylates are available. Since the methyl group at the 1 position is expected to react with various reagents, many 1-substituted derivatives could be produced.

G. BROMOCHELONIN B

Faulkner and co-workers (91JOC4403) isolated and determined bromochelonin B (**275**) as an alkaloid from marine sponge *Chelonaplysilla* sp. (Scheme 43). The alkaloid in (±)-form has been synthesized utilizing nucleophilic substitution reactions of 1-hydroxytryptamines (99H2815). Starting from 1-hydroxy-*N*b-methoxycarbonyltryptamine (**34**), it is transformed to **215b** as noted in Section IV.K.1. After alkaline hydrolysis with methanolic NaOH, the resultant 5-bromotryptamine (**276,** 88%) is converted to (±)-**275** (28%) and its (±)-isomer **277** (14%) by the reaction with 3-bromo-4-methoxystyrene oxide (**278**), which is prepared in three steps from **279** through **280** and **281.**

H. NEOASCORBIGEN

Preobrazhenskaya and co-workers (99MI265) have synthesized neoascorbigen (**282a**), which is one of the alkaloids found in the plant family Cruciferae (Scheme 44). They initially reduced 1-methoxyindole-3-carbaldehyde (**115a**) to indole-3-methanol (**283**) and allowed it to react with L-ascorbic acid (**284**) in alcohol–H_2O at room temperature at pH 4–5, resulting in the formation of **282a.** Its chemical properties are compared with those of ascorbigen (**282b**). As a result, **282a** is found to be more stable than **282b** in acidic conditions. When **282a** is heated in acidic media, it generates 3-(1-alkoxyindolyl)-2-hydroxycyclopent-2-enones (**285**) as a major product. Based on these findings, they have concluded that neoascorbigen is not a depot form of **284** in biological conditions.



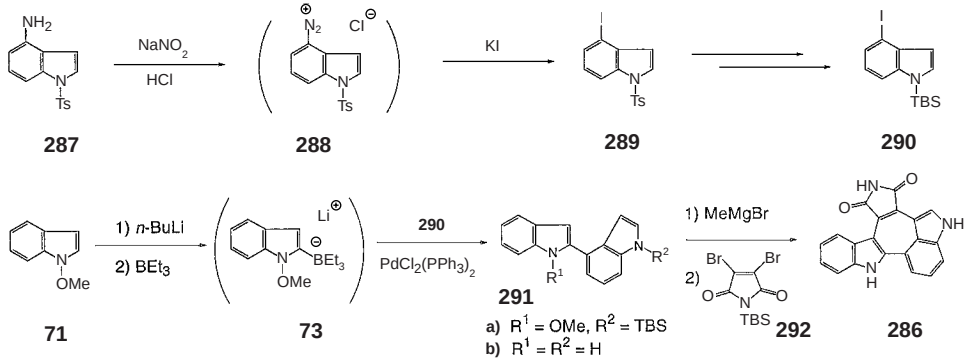
115a **283** **284** **282** **285**

SCHEME 44

Using **282a** as a standard, the neoascorbigen content in kohlrabi is determined by HPLC.

I. ARCYRIACYANIN A

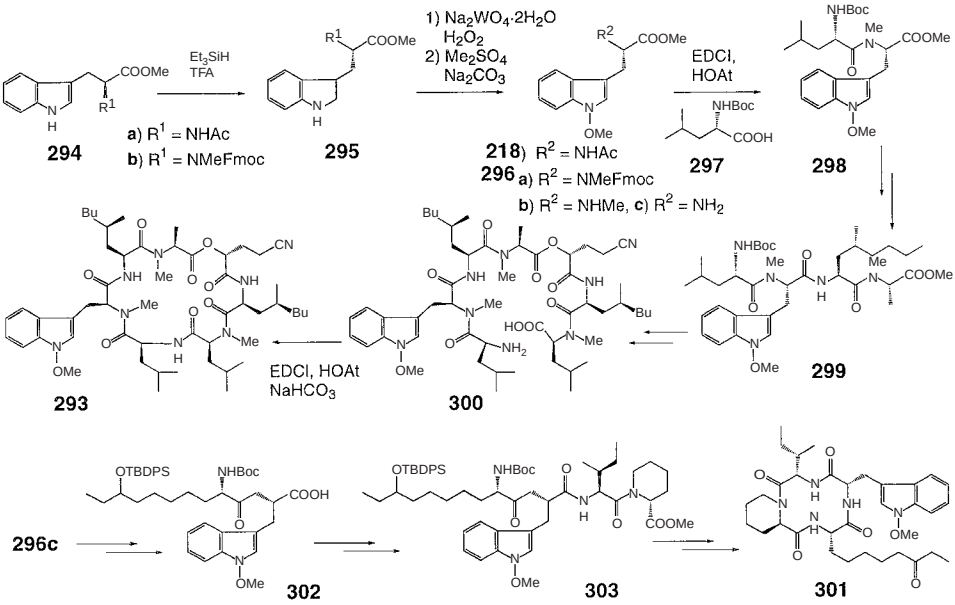
Tobinaga and co-workers (98CPB889) have successfully applied our results in indole chemistry to the synthesis of arcyriacyanin A (**286**) (Scheme 45), a pigment of the slime molds *Arcyria obvelata* Onsberg (93MI1). Employing our diazotization method (81CPB3145) using 4-aminoindoles for the preparation of 4-substituted indoles, 1-tosyl-4-iodoindole (**289**) is produced through **287** and **288** starting from 4-nitroindole. Again, our regioselective lithiation method (92H1285, 92H1295, 94H31) [extended later to borate chemistry by Ishikura and co-workers (2000H2201) as noted in Section IV.C] is applied to **71** for *in situ* formation of **73** which is then coupled utilizing a palladium catalyst with 1-*t*-butyldimethylsilyl-4-iodoindole (**290**) (derived from **289** by exchanging the protecting group at the 1 position) to provide 2,4′-biindolyl (**291a**). After removing protecting groups, the resulting **291b** is treated with a Grignard reagent, followed by the reaction with 1-(*t*-butyldimethylsilyl)-3,4-dibromo-2,5-dihydro-1*H*-pyrrol-2,5-dione (**292**), to complete the synthesis.



287 **288** **289** **290**

71 **73** **291** **292** **286**

SCHEME 45



SCHEME 46

J. HUN 7293 AND APICIDIN

Final examples of applications of our results (91CPB1905, 99H1157) in 1-hydroxytryptophan chemistry come from the work of Boger and co-workers (99JA6197) on the synthesis of HUN 7293 (**293,** Scheme 46) (96MI69) and from Kitahara and co-workers (2001H1) on the synthesis of apicidin (**301**) (96TL8077).

The former group has prepared the key intermediate, the 1-methoxytryptophan derivative **296a,** from **294b** through **295b.** These authors mistakenly claim in their report (99JA6197) that they developed the tungstate method in spite of utilizing our reaction conditions for 1-hydroxy- and 1-methoxy-*N*b-acetyltryptophan methyl ester (**218**) from **294a** through 2,3-dihydro derivative **295a** (91CPB1905, 99H1157).

After removing the protecting group of **296a,** the resulting **296b** is coupled with **297** using EDCI and HOAt to provide **298.** A subsequent sequence of reactions converts **298** to **300** through **299.** Intramolecular cyclization of **300** to **293** is accomplished by the reaction with EDCI and HOAt.

The latter group also utilizes the tungstate method for the preparation of **296c** as a key building block. It is then converted to **303** through **302** by a sequence of reactions. Subsequent ester hydrolysis, removal of the Boc group, ring closure with FDPP, removal of the TBDPS protecting group, and oxidation with TPAP and NMO complete the total synthesis of **301** (96MI69).

VI. Studies toward Biologically Active 1-Hydroxyindole Derivatives

Taking advantage of indole alkaloids and using drugs carrying the indole skeleton as substrates, we could produce many new 1-hydroxyindole analogs utilizing Somei's method. This methodology offers a quick effective approach for developing new medicines. We have already demonstrated one example, in which biologically inactive indoles are altered to potent inhibitors on blood platelet aggregation by putting the hydroxy group onto the 1 position (96H1855).

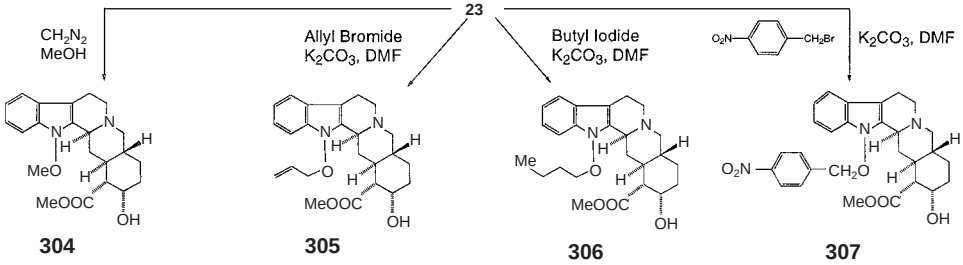
Based on these encouraging data, various attempts have been made to develop biologically active substances as follows.

A. 1-Hydroxyyohimbine and Its Derivatives

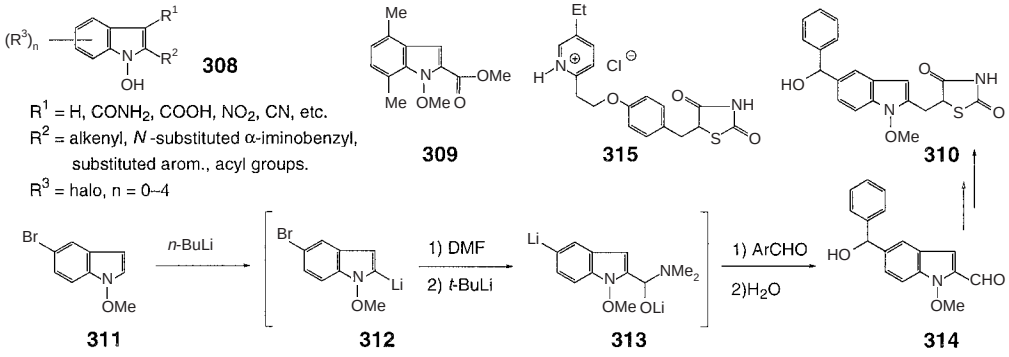
We first tried to prepare 1-hydroxyyohimbine (**23**) and its derivatives. With **23** in hand (as described in Section II.D), its methylation with CH_2N_2 is carried out to provide 1-methoxy derivative **304** (77%) (Scheme 47). Utilizing K_2CO_3 as a base in DMF, allyl bromide, butyl iodide, and *p*-nitrobenzyl bromide react successfully with **23,** resulting in the formation of **305** (93%), **306** (99%), and **307** (90%), respectively. All of these compounds, including **23** itself, are found to exhibit potent α2-blocking activity (2001H1237), and the details will be reported in due course.

B. 1-Hydroxy- and 1-Methoxyindoles Carrying an Electron-Withdrawing Group at the 2 or 3 Position

1-Hydroxyindoles carrying an electron-withdrawing group at the 2 or 3 position seem to have bactericidal activities. For example, compounds of general formula **308** (Scheme 48) have been patented as fungicides effective against *Puccinia recondita* (92EUP470665). Compound **309** is also reported to have potent inhibitory activity against drug-registant *Erysiphe graminis* and *Botrytis cinerea* [98JAP(K)10-17548].



Scheme 47



SCHEME 48

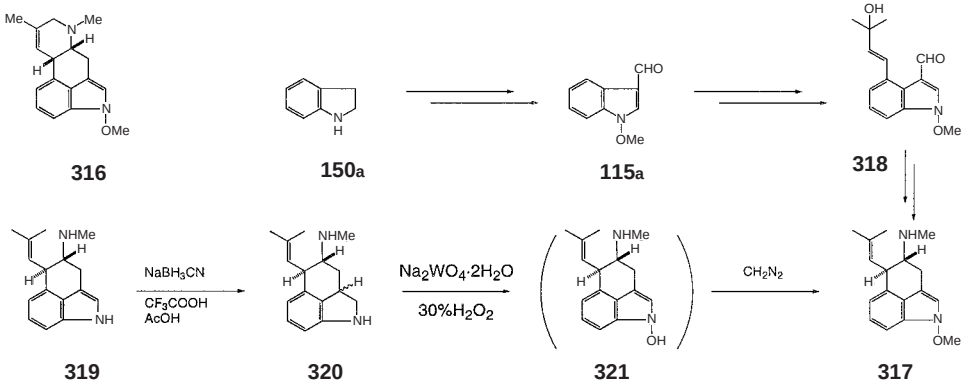
C. 1-METHOXYINDOLE DERIVATIVES

Kobayashi and co-workers (96MI274) have reported the preparation of **310** (Scheme 48), applying our regioselective lithiation at the 2 position (92H1285, 94H31) and 5-bromo-1-methoxyindole (**311**) as a starting material, which was prepared by us for the first time (91YGK205, 99H1157). Thus, 2-lithio species **312** is generated from **311** and trapped *in situ* with DMF. Subsequent lithiation with *t*-BuLi followed by addition of benzaldehyde affords a key compound **314** through **313.** A further sequence of reactions leads **314** to **310.** Since **310** has a structure similar to that of Takeda's pioglitazone hydrochloride (**315**) (81MI1045, 97MI337), it is not surprising that **310** has a potent antidiabetic activity.

D. 1-METHOXY DERIVATIVE OF ERGOT ALKALOIDS

Padmanabha and co-workers (98BMC569) isolated a novel inhibitor of the LCK tyrosine kinase from *Penicillium sp.* WC75209 and structurally characterized it as 1-methoxy-5*R*, 10*S*-agroclavine (**316,** Scheme 49). Fifteen years before this discovery, we had prepared 1-methoxy-6,7-secoagroclavine (**317**) with an expectation in our "1-Hydroxyindole Hypothesis" that someday such 1-methoxy- and 1-hydroxy derivatives of ergot alkaloids would be isolated as natural products. So, starting from indoline (**150a**), the synthesis was carried out through **115a** and **318,** applying novel reactions (86CPB677) developed in this laboratory.

After discovery of the tungstate method, we examined its applicability to the preparation of **317.** As usual, (±)-6,7-secoagroclavine (**319**) is reduced with $NaBH_3CN$ in a mixture of TFA and AcOH to the 2,3-dihydro derivative **320.** Although the products are separated to a major (72%) and a minor diastereoisomer (16%), determination of their stereochemistries is not complete. Applications of the tungstate method to each isomer afford the same product, 1-hydroxy-6,7-secoagrocalvine (**321**). However, **321** is not stable enough to characterize.



SCHEME 49

Therefore, methylation with CH_2N_2 is employed immediately after preparation of **321.** As a result, the major isomer of **320** generates **317** in 21% yield, while the minor isomer provides **317** in 27% yield (2002UP1).

Thus, our tungstate method is proved to be applicable even to ergot alkaloids. Synthesis of **316** and various 1-hydroxy derivatives of ergot alkaloids could be carried out in the near future.

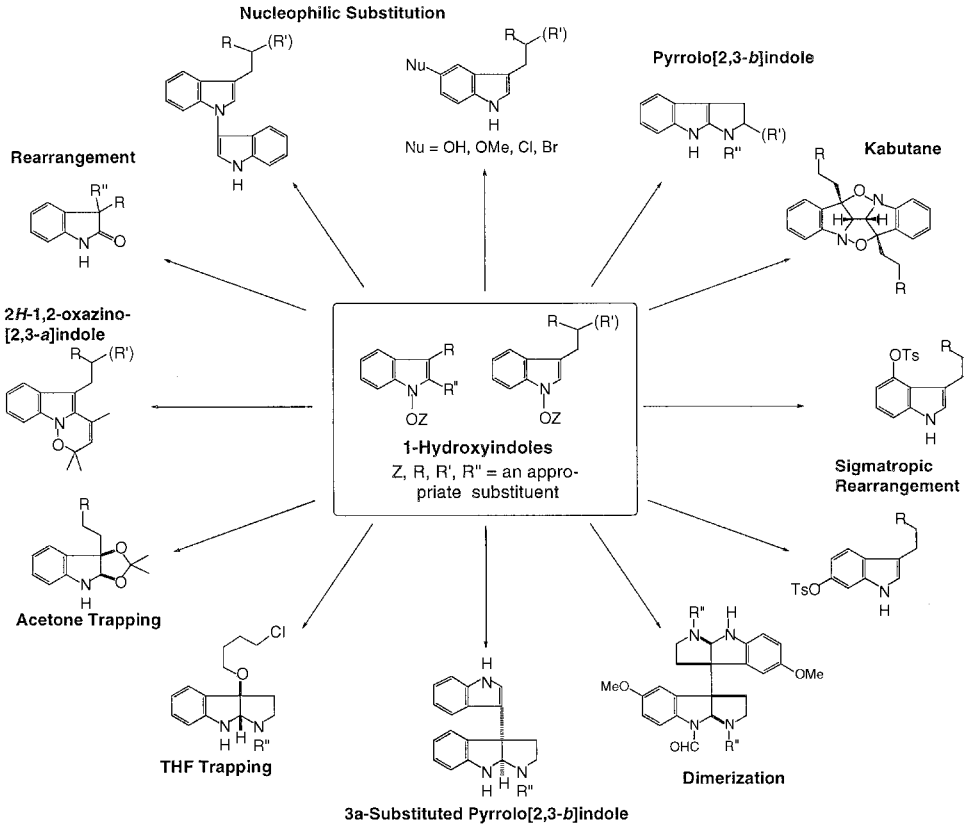
E. PHYTOALEXINS AND 1-HYDROXYMELATONIN

Daikon and wasabi phytoalexins are weak fungicidal alkaloids having a stabilized 1-methoxyindole structure. Relying on the expectation that more potent substances can be found among their derivatives, synthetic studies are in progress according to the method developed in Scheme 22 in Section IV.G.

On the other hand, multimodality of biological activities of melatonin is well known. Therefore various derivatives are needed for carrying out its structure–activity relationship study. 1-Hydoxymelatonin (**19**) would be a suitable seed for developing yet unknown results.

VII. Summary

We have thus far provided the groundwork for investigations of 1-hydroxy- and 1-alkoxyindoles and 1-hydroxytryptophans and -tryptamines, and discovered that they undergo various types of reactions depending on their structures and reaction conditions. Among these are regioselective nucleophilic substitution reaction to give 5-substituted indoles, formation of pyrrolo[2,3-*b*]indoles, formation



SCHEME 50

of 8,17-disubstituted 1,10-diaza-9,20-dioxakabutanes, dimerization to afford 2,2′-bisindole derivatives, formation of 3a,3a′-bispyrrolo[2,3-*b*]indoles, and substitution on the indole nitrogen. Typical results are shown in Scheme 50 for a quick glance.

VIII. Natural Products and Some Notes

Very little is known about the occurrence of 1-hydroxytryptamine and/or 1-hydroxytryptophan derivatives in living organisms. Many 1-methoxyindole derivatives have been isolated as natural products (87MI629, 88BCJ285, 92H1877, 93MI22) for the simple reason that they are stable under isolating processes.

As disclosed thus far, 1-methoxyindoles and particularly 1-hydroxyindoles, -tryptophans, and -tryptamines are quite sensitive to acids and other chemical

reagents, resulting in various types of compounds as summarized in Section VII. These findings suggest that the use of acids and chemicals for the isolation of indole alkaloids and peptides should be done very carefully; otherwise, 1-hydroxytryptamines and/or 1-hydroxytryptophans could not keep their genuine structures. If they did happen to exist in natural resources, they might be isolated as artifacts such as 5-substituted indole derivatives, oxindole alkaloids, and so on.

The presence of the 1-hydroxyindole-2-carboxylic acid structure in the molecule (**37,** Fig. 2), isolated from *Micromonospora globosa* cultures as an antibiotic against pathogenic Gram-positive bacteria, was reported in 1984 (84USP4478831). In 1998, structurally closely related antibiotics MJ 347-81F4-A (**38a**) and -B (**38b**) were isolated and characterized, having antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) (98JAN715). These compounds belong to the stabilized 1-hydroxyindoles with an electron-withdrawing group at the 2 position.

No 1-hydroxytryptamine or -tryptophan alkaloid that lacks a stabilizing group on the indole nucleus has been reported yet. However, isolation of **37, 38a, 38b,** HUN-7293 (**293**) (96MI69), and apicidin (**301**) (96TL8077) offers indirect evidence for the existence of 1-hydroxytryptamines and/or 1-hydroxytryptophans in living organisms. We believe their isolation will be reported in the near future.

The chemistry of 1-hydroxyindoles, especially 1-hydroxytryptamines and -tryptophans, is still in its cradle at present, yet its future development is promising. It seems to be a treasure trove whose excavation will yield many new reactions and findings.

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ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 82

Diacetylene and Its Derivatives in Heterocyclization Reactions

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I. Introduction

Acetylene compounds are often involved in reactions leading to heterocycles. Processes such as 1,3-dipolar cycloaddition, intramolecular cyclization, cyclization via twofold attack at the acetylene bond, and other reactions (69MI2; 71MI1; 78MI1; 81MI1; 85KGS1443; 91MI2; 91UK103; 00UK642) have found many applications in heterocyclic chemistry.

During the last few decades much work has been done in the systematic development of principles for enhancing the activity of nucleophilic reagents cyclizing with acetylenes by means of superbase catalytic systems consisting of a strong base and a nonhydroxylic strongly polar complex-forming solvent. Media of this kind allow the reactivity of ring-closing nucleophiles to be enhanced by some orders of magnitude with a simultaneous sharp increase of the acetylene concentration in the solution. This resulted in not only modification of many base-catalyzed reactions of acetylene but also discovery of its novel heterocyclization reactions and development of convenient methods for synthesis of basic heterocycles (81UK248; 85MI1; 86ZC41; 86ZOR1991; 95ZOR1368). An example is the reaction of acetylene with ketoximes leading to pyrroles and *N*-vinylpyrroles [80KGS1299; 84MI4; 85UK1034; 87MI1; 89UK275; 90AHC177; 92HC(48)131; 94H1193; 96ZOR1127].

An especially high potential for the synthesis of heterocycles is displayed by diacetylene formed as a side product (and flared) in acetylene manufacturing by electrocracking and oxidative or plasma pyrolysis of natural gas (96ZPK353; 00ZPK619).

In reactions with nucleophilic reagents diacetylene behaves as acetylene activated with acceptor group that is common to conjugated polyynes. Therefore, the nucleophilic addition of amines, alcohols, and thiols occurs to its terminal position and leads to the formation of the corresponding 1-heteroalk-1-en-3-ynes readily involved in diverse cyclization reactions.

The heteroenyne system is capable of further transforming to 1,3-dicarbonyl derivatives such as 4-aminobut-3-en-2-ones, 4-alkoxybut-3-en-2-ones, and 4,4-dialkoxybutan-3-en-2-ones, which also represent excellent building blocks for designing heterocycles. In modern acetylene plants, diacetylene fixation is performed (58GEP871006; 74MI3; 75MI2; 78USSRP570580; 81USSRP791713; 93USSRP1770318; 94EUP594100; 94EUP607811; 94GEP4308073; 99DIS) only with nucleophilic reagents (amines, alcohols, etc.); hence 1-heterobut-1-en-3-ynes (1,3-butenyne amines, ethers, and sulfides), being safe diacetylene equivalents, are of particular interest in preparative heterocyclic chemistry.

A considerable potential for the synthesis of heterocycles is exhibited by 4,4-dialkoxy-2-butanones (80MI1; 80MI2), which can also be produced from diacetylene on a large scale.

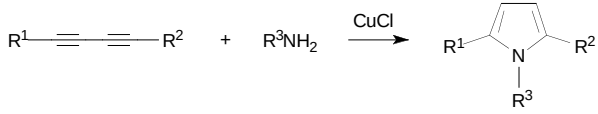
Currently, many nongeneralized and nonsystematized data on the design of heterocyclic compounds using diacetylene and its derivatives are scattered throughout the literature. The goal of this review is to fill this gap by putting all these pieces together.

First we consider diacetylene transformations leading to fundamental heterocycles (pyrroles, thiophene, selenophene, tellurophenes, pyrazoles, isoxazoles, pyridines, pyrimidines). Then cyclization reactions involving 1-heterobut-1-en-3-ynes, 4-heterobut-3-en-2-ones, and 4-heterobut-3-yn-2-ones (91UK103; 92KGS867; 00UK642) as diacetylene equivalents are discussed.

II. Reactions of Diacetylene

A. Reactions with Ammonia and Amines

If the reaction of diacetylene and its substituted derivatives with ammonia or primary amines is carried out in the presence of a copper(I) salt, the main reaction product formed in an autoclave after brief heating to 150°C turns out to be pyrrole or pyrrole derivatives **1** (65CB98; 71MI1).



R_1, R_2 = alkyl, aryl; R_3 = H, Et, *n*-Bu, Ph

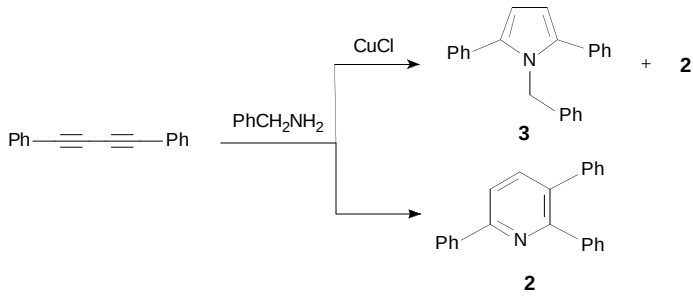
1

Because diacetylene is unstable, a stable diacetylene derivative, 1-methoxybut-1-en-3-yne (65CB98), is often employed in the synthesis of pyrroles. The reaction with ammonia proceeds under conditions of heterogeneous catalysis (a mixture of reagent vapors is passed through a catalyst-containing reactor heated to 150°C), approaching a yield of 50–70%; but with primary aromatic amines, the yield drops to 20%.

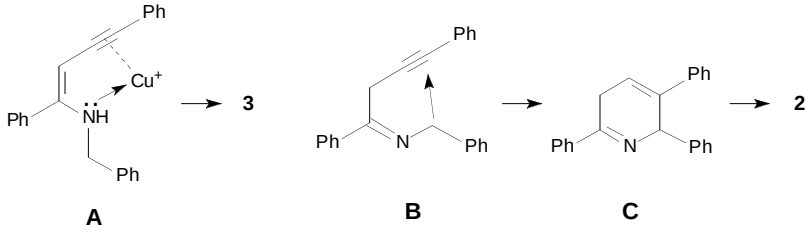
The synthesis can be conducted both in solution and without solvents. The reaction in solvent (e.g., methanol, ethanol, dioxane, dimethylformamide) is recommended for volatile 1,3-diynes and amines; in this case the pyrroles are purer and the yield is higher. With disubstituted diacetylenes, ammonia and primary alkyl- and arylamines produce 1,2,3-trisubstituted pyrroles under the same conditions (65CB98; 71MI1). Since disubstituted diacetylenes are readily obtained by oxidative coupling of acetylenes (98MI2), this reaction provides a preparative route to a wide range of pyrroles.

According to Shostakovskii and Bogdanova (71MI1), the role of catalyst is the formation of a nonpolar π-complex one of whose triple bonds has a uniform electron density distribution on both carbon atoms, thereby facilitating the interaction between the nucleophilic nitrogen atom and the fourth carbon atom in the conjugated diyne system.

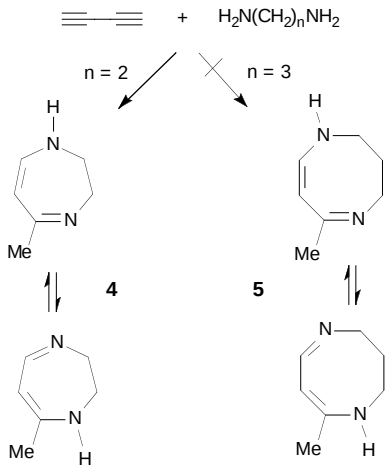
A noncatalytic reaction of diphenylbutadiyne with benzylamine leads to 2,3,6-triphenylpyridine (**2**) in 50–70% yield (72TL3487). Interestingly, in the presence of CuCl the pyrrole pathway dominates, leading to 1-benzyl-2,5-diphenylpyrrole (**3**) in 87% yield.



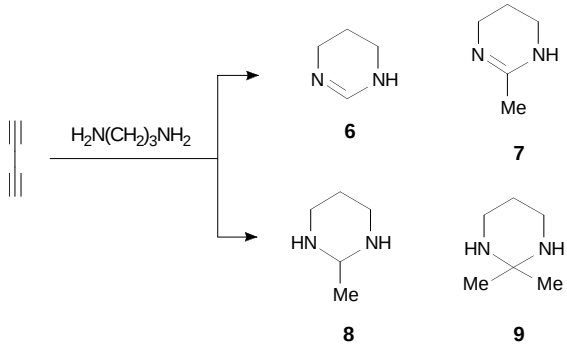
Apparently, aminobutenyne **A,** the intermediate of the pyrrole synthesis, is fixed in an advantageous configuration by coordination to the Cu^+ cation, whereas the absence of catalyst may result in the formation of imine **B** having an active methylene group which attacks the acetylene bond to form dihydropyridine **C** and then pyridine **2** (by dehydrogenation).



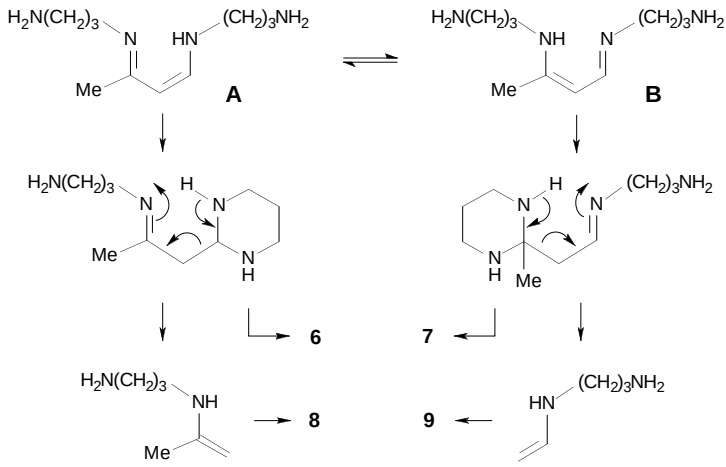
1,2-Diaminoethane reacts with diacetylene (0–25°C, 4 h) to form a mixture of tautomers of 5-methyl-2,3-dihydro-1,4-diazepine (**4**) isolated by sublimation (yield not reported) (69JOC999; 77ZC216).



With 1,3-diaminopropane (20°C, 6 h) (77ZC216), the formation of 1,2,3,4-tetrahydro-1,5-diazocyne (**5**) was expected. However, in fact, a mixture of Δ^1-tetrahydropyrimidine (**6**), 2-methyl-Δ^1-tetrahydropyrimidine (**7**), 2-methyl-(**8**), and 2,2-dimethylhexahydropyrimidines (**9**) is formed.

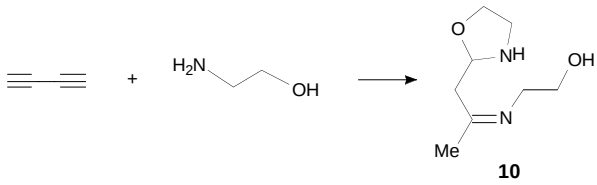


These results are explained by addition of two moles of diamine to one mole of diacetylene with the formation of the two adducts **A** and **B** which further undergo cyclization with fragmentation.



These transformations are analogous to those observed in the reaction of acetylacetone with 1,3-diaminopropane (77ZC216) and formally fit decomposition of the corresponding β-diketone derivatives.

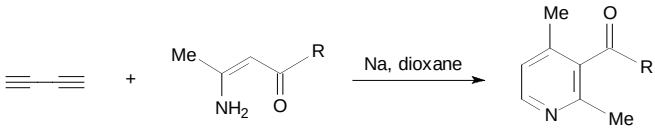
When diacetylene was passed through a benzene solution of 2-hydroxyethylamine at 0°C, crystalline 2-[2-(2-hydroxyethyl)iminopropyl]-1,3-oxazolidine (**10**) was isolated in 89% yield (00UK642).



10

A process for the preparation of functionalized pyridines from diacetylene and the ethyl ester of β-aminocrotonic acid and acetylacetonimine (72ZOR1328; 75DIS) has been described. Owing to the lower nucleophilicity of nitrogen in the initial enamine esters and enamine ketone, the reaction with diacetylene occurs in the presence of sodium metal (80°C, dioxane, 3 h, yield of up to 20%).

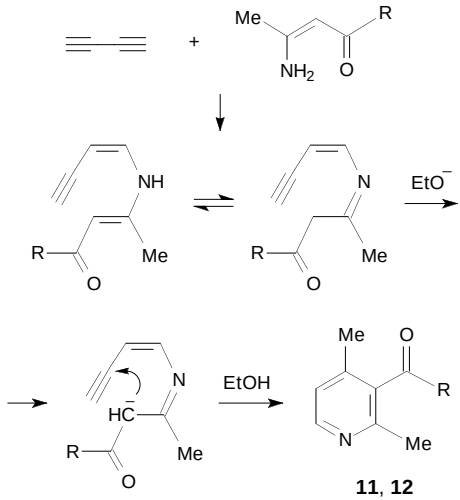
The reaction products are 2,4-dimethyl-3-acetylpyridine (**11**) and ethyl ester of 2,4-dimethyl-3-nicotinic acid (**12**).



R = Me (**11**), OEt (**12**)

11, **12**

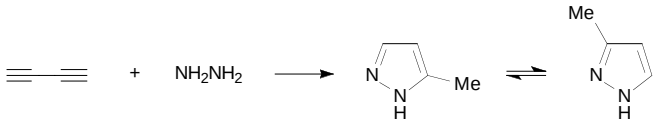
The ring closure seems to involve intramolecular attack of the deprotonated methylene group of primary adduct at the second acetylene bond (75DIS).



11, **12**

B. Reactions with Hydrazines and Hydroxylamine

In 1967 Matsoyan discovered the reaction of diacetylene with hydrazine hydrate leading to 3(5)-methylpyrazoles (**13**) (68AKZ998; 70AKZ640; 71AKZ743; 72MI1).

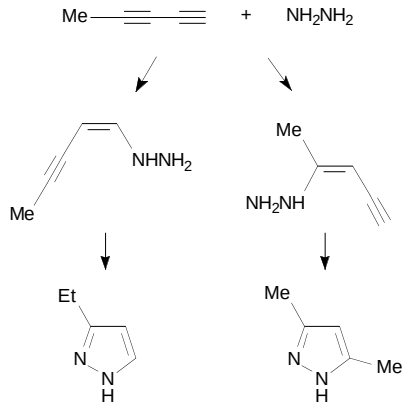


13

Diacetylene vigorously enters the reaction at room temperature. When diacetylene is passed through hydrazine hydrate at such a rate that the temperature of the exothermic reaction exceeds 50–60°C, the pyrazoles **13** are obtained in practically quantitative yield (90–95%); in a methanol solution the yield is ~60% (68AKZ998; 70AKZ640). In the tautomeric mixture, 3-methylpyrazole is the prevailing tautomer (^{1}H NMR). The reaction was proposed for removing diacetylene from acetylene manufactured by hydrocarbon pyrolysis (71ZPK1921).

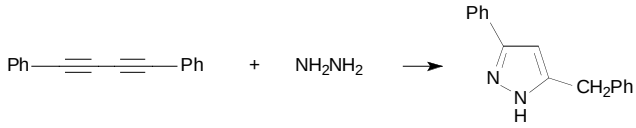
Almost simultaneously, Schroth reported that diacetylene reacts with a hydrazine hydrate solution at 80°C for 4 h to form methylpyrazoles (**13**) in 80% yield (69ZC108; 69ZC110). In the same year, other data concerning the reaction of hydrazine with diacetylene (65°C, EtOH, yield 65%), hexa-2,4-diyne, and 1,4-diphenylbuta-1,3-diyne were reported (69JOC999). Later, BASF (93GEP4137011) proposed to carry out the process at 100°C in a polar solvent with a diacetylene concentration of 14–18% in an inert gas. The yield of methypyrazoles was 90% (post-rectification purity 99%).

In the reaction of methyldiacetylene with hydrazine hydrate, both 3-ethylpyrazole (**14**) and 3,5-dimethylpyrazole (**15**) were formed in a 4:1 ratio (73DIS). Both pyrazoles were preparatively isolated (3,5-dimethylpyrazole is crystalline and ethylpyrazole is a liquid) and identified by comparison with authentic samples. These data show that primary attack of monosubstituted 1,3-diynes by hydrazine is mainly directed toward the terminal acetylenic bond.



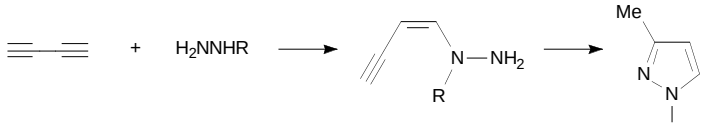
14 **15**

Diphenyldiacetylene reacts with hydrazine hydrate when boiling in ethanol to form 3-phenyl-5-benzylpyrazole (**16**) in 91% yield (68AKZ998; 70AKZ640).



16

In the reactions of nucleophilic addition to diacetylene, monoalkylhydrazines behave in two ways (71AKZ743). In an anhydrous medium at 40–50°C, the reaction with methyl- and ethylhydrazines proceeds in such a way that a more nucleophilic disubstituted nitrogen atom attacks the terminal carbon atom of diacetylene to form 1-alkyl-3-methylpyrazoles (**17**), the content of isomeric 1-alkyl-5-methylpyrazoles being 15% according to GLC (71AKZ743; 73DIS; 77AKZ332).

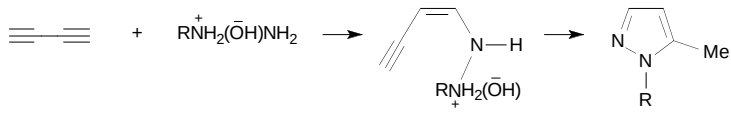


R = Me, Et

R	Me	Et
yield, %	65	60

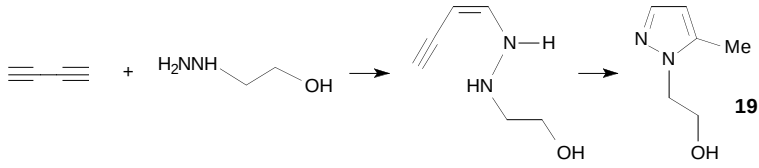
17

In aqueous solutions, the prevailing process is the primary attack of the unsubstituted nitrogen atom of alkylhydrazines at the terminal carbon atom of diacetylene with predominant formation of 1-alkyl-5-methylpyrazoles (**18**) (73DIS). The content of isomeric 1-alkyl-3-methylpyrazoles is less than 10% (GLC). In the authors' opinion, this different direction of the attack at diacetylene in aqueous media is related to the hydration of alkylhydrazines and the formation of ammonium base $RN^+H_2(OH)^-NH_2$, in which the primary amino group becomes the major nucleophilic center.

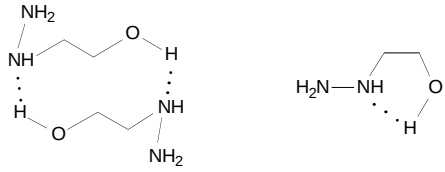


18

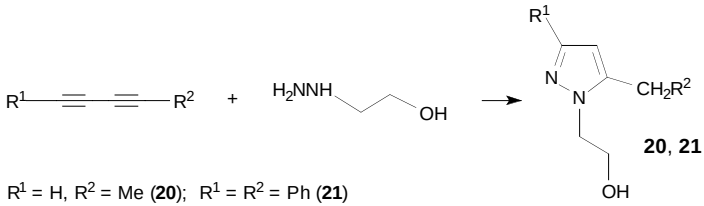
At the same time, the reaction of diacetylene with anhydrous 2-hydroxyethylhydrazine leads to 1-(2-hydroxyethyl)-5-methylpyrazole (**19**) only (71AKZ743).



This reaction pathway is explained (71AKZ743) by intermolecular and intramolecular H-bonding with predominant participation of the more basic secondary amino group.

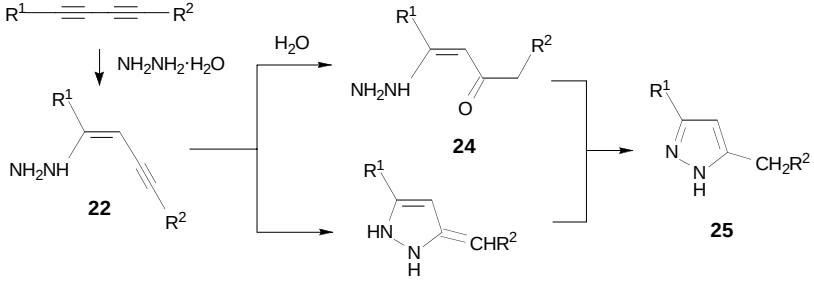


The reaction direction remains the same for methyldiacetylene and diphenyldiacetylene (120°C, 20 h, yield 85.8%) (71AKZ743), the cyclization products being 1,3,5-trisubstituted pyrazoles **20** and **21.**

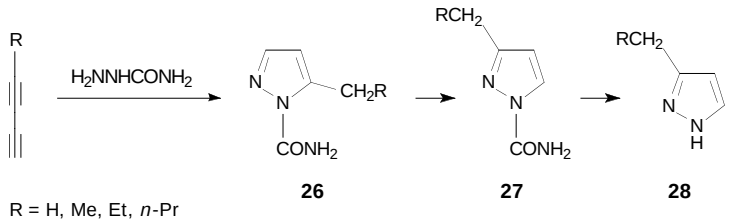


The reaction of disubstituted diacetylenes with hydrazine hydrate was reported by Darbinyan *et al.* (70AKZ640). In the first stage the addition of hydrazine to the terminal carbon atom of the diacetylene system is analogous to that of primary amines to diacetylene (69ZC108; 69ZC110). With monosubstituted diacetylenes ($R^1 = H$), hydrazine adds to the terminal triple bond. This leads to the formation of vinylacetylenic hydrazine **22** which cyclizes to dihydropyrazole **23** subjected to further isomerization to the pyrazole **25.** It is possible that hydrazine **22** undergoes hydration to the ketone **24** which can easily be cyclized to the pyrazole **25**

(70AKZ640). Although some data (00UK642) support a ready hydration of the activated triple bond in a weakly basic medium, the latter route seems less probable, since the cyclization of hydrazine **22** is a monomolecular process (70AKZ640) and the hydrazine group is much more nucleophilic than water.

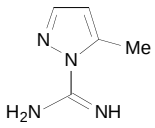


The reaction of diacetylene and its asymmetric homologs (penta-1,3-diyne, hexa-1,3-diyne) with semicarbazide (72ZOR2605) affords the amides of 3-methylpyrazole-1-carboxylic acid (**27**) (80°C, EtONa, EtOH, 40 h). Amide **26** undergoes irreversible rearrangement to amide **27** at 80°C (EtONa, EtOH).



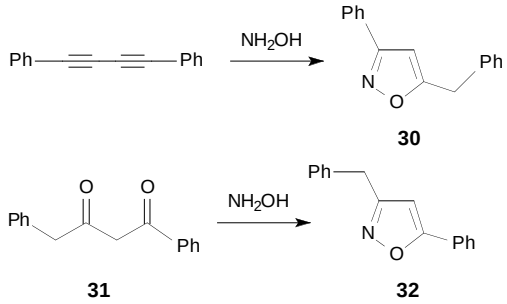
Acid hydrolysis of the adduct is followed by decarboxylation and formation of the pyrazole **28.**

Synthesis of 1-guanyl-3-methylpyrazole (**29**) (86% yield) from pyrazole **13** and aqueous cyanamide has been claimed (94GEP4237687).



29

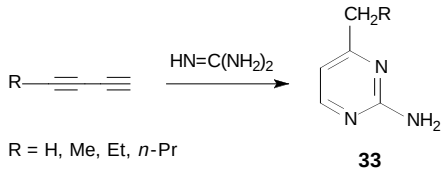
With hydroxylamine, diphenylbuta-1,3-diyne gives the isoxazole **30,** isomeric to the isoxazole **32** obtained from dicarbonyl compound **31** and hydroxylamine (69JOC999).



The structure of the two oxazoles **30** and **32** was proved by mass spectrometry (69JOC999).

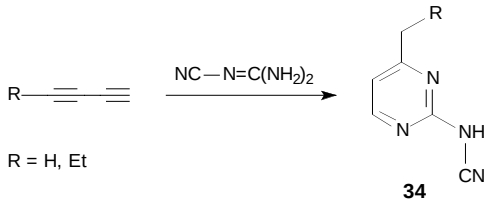
C. Reactions with Guanidine and Dicyanodiamide

The reaction of diacetylene or its monosubstituted homologs with guanidine in the presence of an equimolar amount of sodium ethylate (80°C, EtOH, 14 h) leads to 2-amino-4-alkylpyrimidines (**33**) (70ZOR1347; 71ZOR14). Their structures were proved by comparison of their properties (as well as those of their picrates) with those of authentic samples obtained by independent synthesis.



R	H	Me	Et	*n*-Pr
yield, %	25	27	24	26

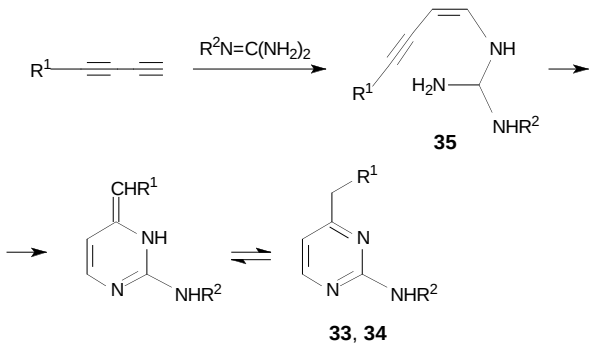
The products of the diacetylene and ethyldiacetylene cyclization with dicyanodiamide are 2-cyanamino-4-alkylpyrimidines (**34**) (80°C, EtONa, EtOH, 14 h, yield 39%) (71ZOR14).



A general process for the preparation of pyrimidines from diacetylene and carbamide derivatives $RC(X)NH_2$ (X = NH, O, S; R = Ph, OH, NH_2) with fixation and subsequent cyclization of primary products has been patented (94GEP4308073).

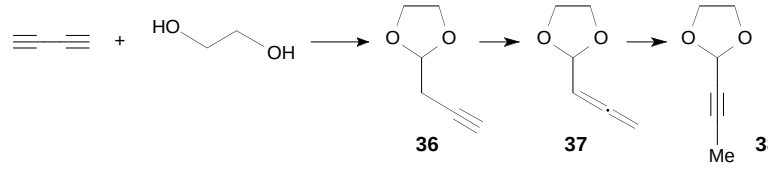
Usually, the addition of mononucleophiles to 1,3-diynes occurs in the 1,2-position to the carbon atom least substituted or least shielded by the substituent.

The formation of the pyrimidine ring is due to the addition of carbamide derivatives to the 1,3-positions of the diacetylene system, and according to Maretina *et al.* (81UK1252), the primary adducts **35** can be isolated in certain cases.

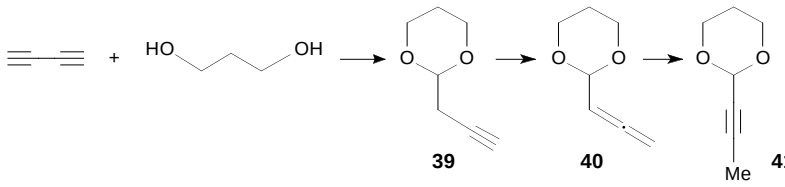


D. Reactions with Diols

Diacetylene reacts with ethyleneglycol in the presence of alkalis at 75–140°C to form a mixture of 2-(prop-2-ynyl)-1,3-dioxolane (**36**), 2-(propa-1,2-dienyl)-1,3-dioxolane (**37**), and 2-(prop-1-ynyl)-1,3-dioxolane (**38**) (1–5 h, yield 66%), the ratio of which depends on the experimental conditions (74ZOR953).

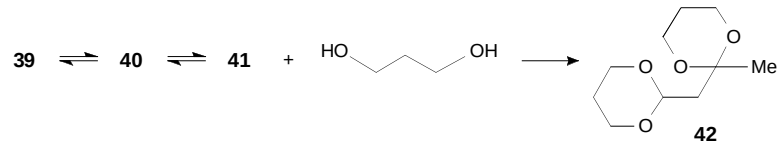


The reaction of diacetylene with propane-1,3-diol gives 2-(prop-2-ynyl)-1,3-dioxane (**39**), 2-(propa-1,2-dienyl)-1,3-dioxane (**40**), and 2-(prop-1-ynyl)-1,3-dioxane (**41**) (74ZOR953).



As in the reaction of diacetylene with alcohols (00UK642), the addition of glycols seems to start with attack at the terminal carbon atom of diacetylene, but no intermediate hydroxyl-containing enyne ether was isolated.

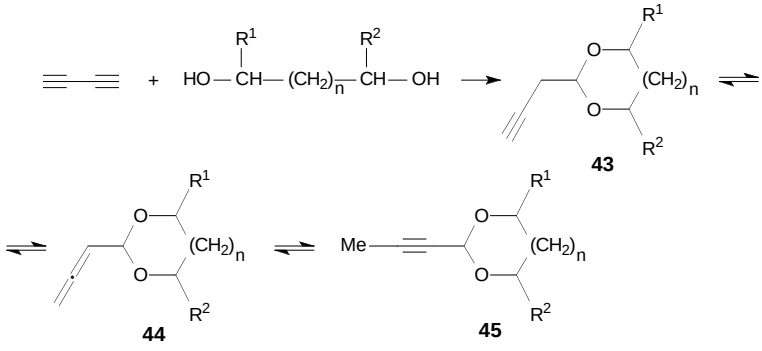
Unsaturated substituents of dioxolanes **36–38** and dioxanes **39–41** are prone to prototropic isomerization under the reaction conditions. According to IR spectroscopy, the isomer ratio in the reaction mixture depends on the temperature and duration of the experiment. However, in all cases, isomers with terminal acetylenic (**36, 39**) or allenic (**37, 40**) groups prevail. An attempt to displace the equilibrium toward the formation of disubstituted acetylene **41** by carrying out the reaction at a higher temperature (140°C) was unsuccessful: From the reaction mixture, the diacetal of acetoacetaldehyde **42,** formed via addition of propane-1,3-diol to unsaturated substituents of 1,3-dioxanes **39–41,** was isolated (74ZOR953).



The isomerization of 1,3-dioxacyclanes **43** and **44** in alcohol alkali at 170°C leads to an equilibrium mixture of isomers **43–45,** in which the content of isomer

45 does not exceed 30%. Individual products **43–45** were isolated by preparative GLC and characterized (74ZOR953).

The reaction was also extended to propane-1,2-diol, butane-2,3-diol, and butane-1,3-diols (74ZOR953).



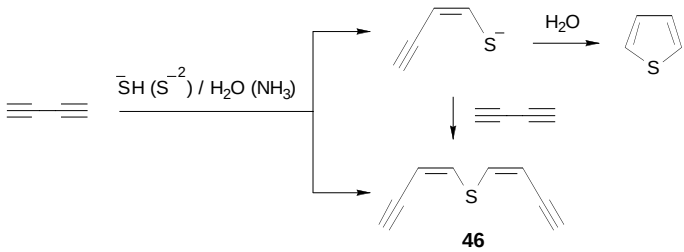
n = 0: R^1 = H, R^2 = Me; n = 1: R^1 = H, R^2 = Me; R^1 = R^2 = Me

In all cases, a general regularity is observed: Major products are represented by 1,3-dioxolanes and 1,3-dioxanes with propargyl and allenyl substituents.

E. Reactions with Sulfur, Selenium, Tellurium, Phosphorus, and Arsenic Derivatives

Systematic studies of the reactions of acetylene and substituted acetylenes with hydrogen sulfide and sulfide ions (81UK248; 83MI2; 84MI3; 86ZC41; 93MI3; 94H1193; 94MI2; 94MI3; 94PS145; 95ZOR1368) have been extended to diacetylenes (79ZOR1554; 83MI3).

Depending on the conditions, the reaction of diacetylene with sulfide ions leads either to di(2-ethynylvinyl)sulfide (**46**) (79ZOR1554) or thiophene (76DIS; 80GEP2818580; 81KGS1694), the product of cyclization of ethynylvinylthio anion or of the corresponding thiol.



The synthesis of thiophene from diacetylene was first performed by Schulte (62CB1943), who used sodium sulfide in aqueous alcohol (pH 8–10), the yield being no more than 20%.

When the reaction of diacetylene with hydrated sodium sulfide is conducted in the KOH/DMSO system, it is possible to obtain thiophene in high yield (above 90%) with practically 100% selectivity (80GEP2818580; 83MI3). Sulfide **46** does not form at all under these conditions. The reaction proceeds at 20–100°C. Excess sodium sulfide with respect to diacetylene is used. The process takes place without KOH as well (NaOH forms during the reaction, progressively increasing the basicity); however, the yield of thiophene in this case does not exceed 55%. In the presence of equimolar (with respect to sodium sulfide) amounts of KOH, the yield of thiophene approaches a quantitative value (94%). In general, the addition of KOH is needed only for triggering the synthesis, since further reaction is progressively accelerated by forming NaOH. The high selectivity of the process is worth special attention as the purity of thiophene without extra distillation approaches 99.9% (83MI3).

The reaction represents a nucleophilic addition of sulfide ions to diacetylene with subsequent cyclization of the intermediate (83MI3); hence the reaction rate is higher in nonhydroxylic highly polar solvents because they do not decrease the activity of anions by their solvation. Having high dielectric permittivity, solvents of this kind strengthen the electrolytic dissociation of alkali metal sulfides, thus creating a high concentration of weakly solvated sulfide ions. Apart from DMSO, *N*-methylpyrrolidone was also used as a solvent. The reaction was carried out under the same conditions (55°C, equimolar amount of KOH relative to sodium sulfide). The yield of thiophene was 52.5% (83M13).

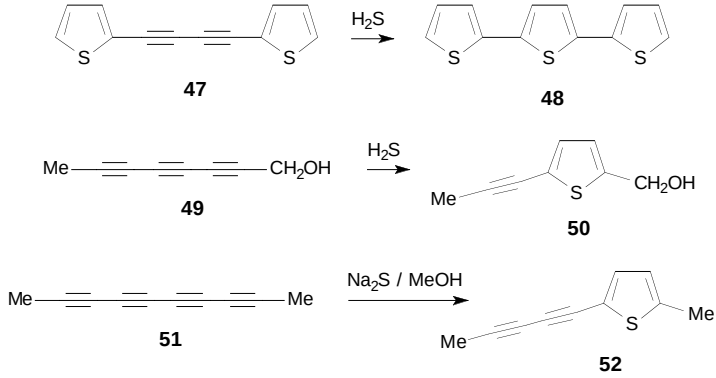
Conditions under which the reaction is directed solely toward the formation of the sulfide **46** (yield of up to 89.5%) have been reported (79ZOR1554): Liquid ammonia is used as a solvent, whereas sulfide ions are generated by ammonium sulfide formed directly in the reaction mixture from ammonia and hydrogen sulfide. The sulfide **46** possesses the *Z,Z*-configuration, providing evidence for a high *trans* stereoselectivity of the reaction (79ZOR1554).

Among reactions of sulfur-containing compounds with diacetylene, the synthesis of thiophene is of most practical interest. That is why a process for the preparation of thiophene from diacetylene and sodium sulfide by a continuous scheme was elaborated (83MI3). This resulted in a pilot process in an aqueous–alkaline medium with a constant thiophene output. The reaction was carried out at 70°C, and the yield of thiophene (99% purity) exceeded 70%, i.e., was higher than in the batchwise process. The results were stable and well reproducible. It is noteworthy that in this medium the diacetylene polymer accompanying the synthesis is not explosive. Still, the DMSO version of the synthesis remains more effective because it straightly gives pure thiophene (99.9%) in nearly quantitative yield (80GEP2818580).

The merits of this method are as follows: technological feasibility, no-waste technology, one-pot process, high yield, and purity of thiophene. Probably, for

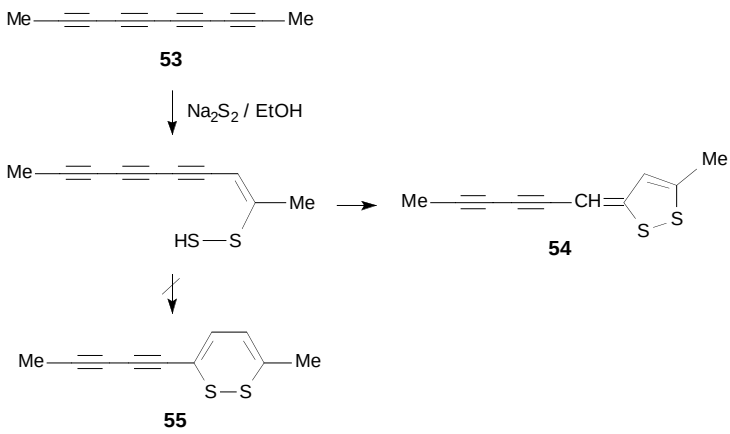
large-scale implementation of this method it would be reasonable to use diacetylene-containing industrial acetylene flows without separation of the components, as the reactivity of accompanying methylacetylene, allene, and vinylacetylene in the reaction with sulfide ions is much lower (83MI3).

Di- and tetraynes with hydrogen sulfide in an alkaline medium at 20–80°C form systems containing linked thiophene cycles. Thus, 1,4-dithienylbuta-1,3-diyne (**47**) forms 2,5-di(2-thienyl)thiophene (**48**) in 78% yield, whereas octa-2,4,6-triyn-1-ol (**49**) under the same conditions gives 5-hydroxymethyl-2-prop-1-ynylthiophene (**50**) in 50% yield (77HOU947).

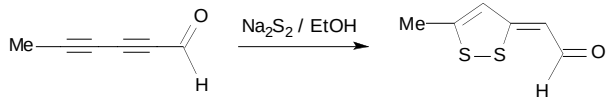


With sodium sulfide in methanol (pH = 9), deca-2,4,6,8-tetrayne (**51**) forms 5-methyl-(2-penta-2,4-diynyl)thiophene (**52**) in 60% yield (77HOU947).

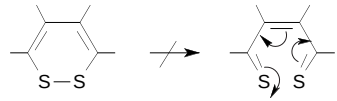
When treated with sodium disulfide in ethanol, deca-2,4,6,8-tetrayne (**53**) gives dithiafulvene **54** rather than 1,2-dithiins **55** (67CB107).



The addition of disulfide ions to a polarized 1,3-diyne system occurs in the same manner (77HOU947).



The possibility of electrocyclic valent tautomerism of the dithiins **55** with the product of their ring opening, but-2-ene-1,4-dithione (**56**), has been considered (85KGS1443; 96T12677). However, all the experimental data provide evidence for the dithiyne form **55** (85KGS1443; 96T12677).

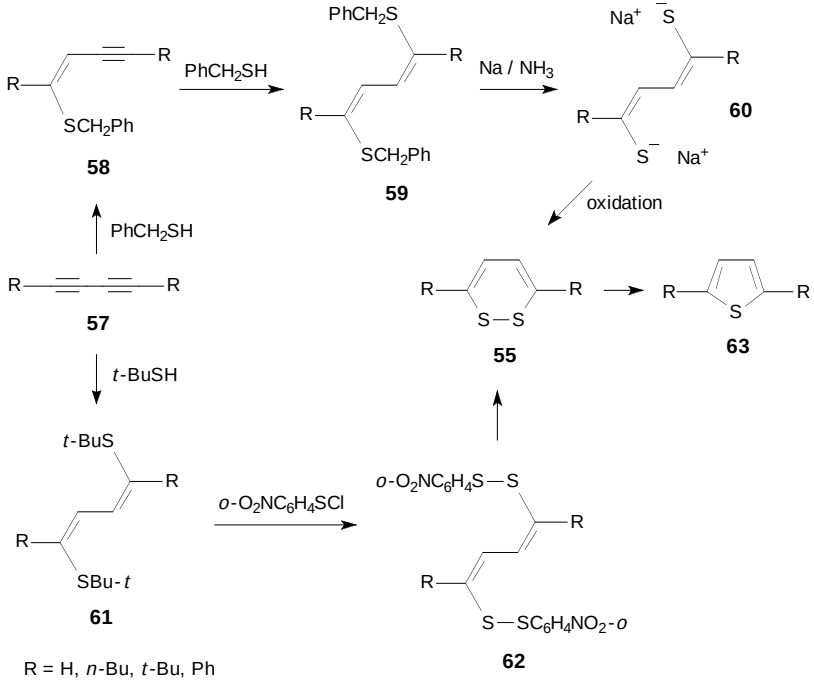


55 **56**

The addition of benzyl and *t*-butylmercaptans to diacetylene and its symmetric disubstituted homologs **57** affords 1,4-di(benzylthio)- (**59**) or 1,4-di(*t*-butylthio)-buta-1,3-dienes **(61**), respectively, from which 1,2-dithiins **55** are formed (65ZC352; 67AG685; 85KGS1443; 96T12677; 96USP5453500).

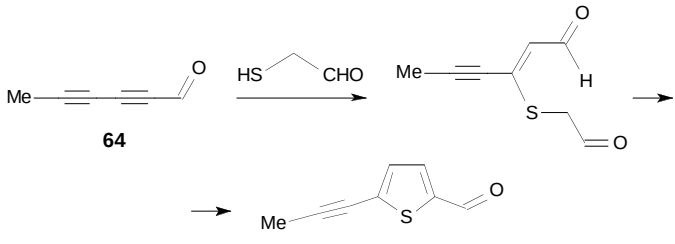
Benzylmercaptan reacts with diacetylenes **57** under base-catalyzed conditions in a regio- and stereoselective fashion to form diadducts Z,Z-1,4-di(benzylthio)buta-1,3-dienes (**59**). In this case, monoadducts **58** can be isolated (96T12677). The reaction with *t*-butylmercaptans gives good results for diacetylenes with aromatic substituents.

Dibenzylthiobutadienes **59** undergo reductive debenzylation under the action of sodium metal in liquid ammonia at -70°C with the formation of sodium dithiolate (**60**) which is instantly oxidized either with air oxygen or with special oxidants (iodine, iron chloride) to 1,2-dithiines **55.** 1,4-Di(*t*-butylthio)buta-1,3-dienes (**61**) afford 1,2-dithiins **55** by treatment with (*o*-nitrophenyl)sulfenylchloride via disulfide **62.** 1,2-Dithiins **55** can be transformed to the corresponding thiophenes **63** [see also (92MI1)]. The formation of **63** is also observed upon the fragmentation of compounds **55** in the mass spectra (principal peak) (96T12677).



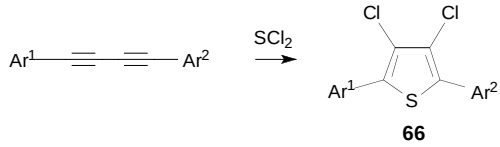
58 59 60 55 63 57 61 62

The reaction of hexa-2,4-diyn-1-al (**64**) with mercaptoacetaldehyde leads to 2-formyl-5-(prop-1-ynyl)thiophene (**65**). The addition direction is governed by the aldehyde group via intramolecular aldol condensation in the intermediate (77HOU947).



64 65

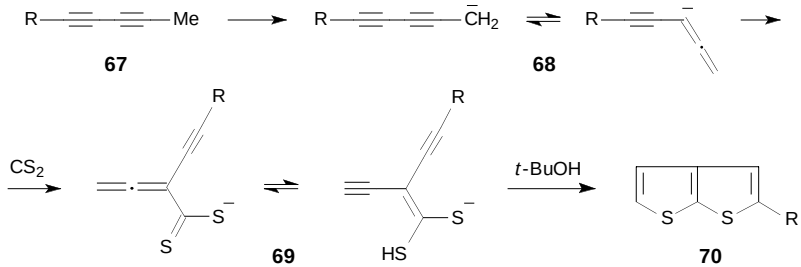
Diaryldiacetylenes react with sulfur dichloride to form 3,4-dichloro-2,5-diphenylthiophene (**66**) in a yield from 16 to 80% (67TL4819; 77HOU947).



66

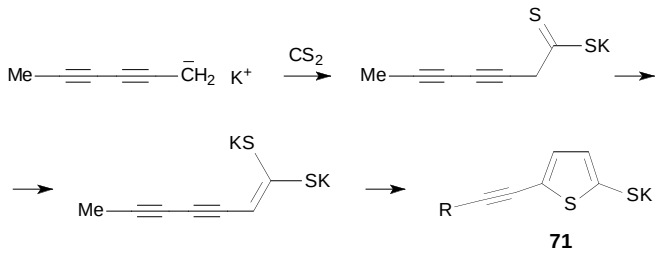
Ar^1 = Ph, *p*-MeC_6H_4, *p*-ClC_6H_4; Ar^2 = Ph, *p*-MeC_6H_4

Carbanions of substituted diacetylenes **68** generated under the action of complex superbase *n*-BuLi/*t*-BuOK/THF/hexane add to carbon disulfide to afford the intermediates **69** which further transform to thieno[2,3-*b*]thiophenes (**70**) (90DIS; 91SC145).

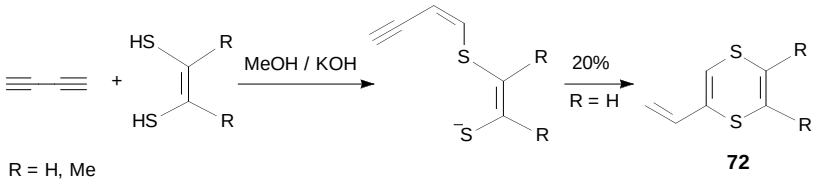


R = H, Me, Et, *t*-Bu, SMe, NMe_2, NEt_2, CH_2NEt_2, C(Me)=CH_2, C≡CMe, 2-C_4H_3S

The investigation of deprotonated hexa-2,4-diyne [$KCH_2C{\equiv}CC{\equiv}CCH_3 \rightleftharpoons H_2C{=}C{=}C(K)C{\equiv}CCH_3$] has shown (90DIS) that both carbanions are formed. In some cases CS_2 reacts with the diyne carbanion to afford 2,5-disubstituted thiophenes **71** (90DIS).

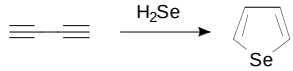


The cyclization involving *Z*-1,2-dimercaptoethenes, as with their benzo analogs, leads to 2-vinyl-1,4-dithiins **72** (69ZC184) rather than dithiacins.



72

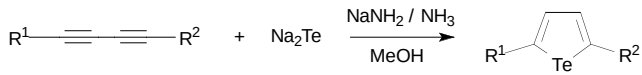
Hydrogen selenide adds to diacetylene to form selenophene **73** (yield 58%, purity 95%) (76JHC1319; 82AHC127).



73

In the KOH/DMSO/$N_2H_4 \cdot H_2O$/H_2O system or in methanol, Na_2Se reacts with diacetylene to form selenophene in 40–44% yield (90MI1).

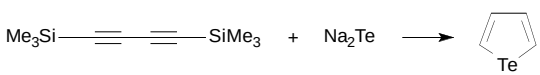
The reaction of Na_2Te with diacetylene affords tellurophene [66AG940; 72JCS(P1)199; 77AHC144; 90MI1]. Diacetylene was passed into methanol solution of Na_2Te_2 cooled to 0°C; when this reaction mixture was allowed to reach room temperature and to stand for 2 h, the yield of tellurophene was 47% (66AG940; 77AHC144). The same reaction in liquid ammonia is another version of the synthesis of tellurophene and 2,5-substituted tellurophenes **74** (83MI1).



R^1 = H, Ph, CH_2OH; R^2 = H, $C(OH)Me_2$

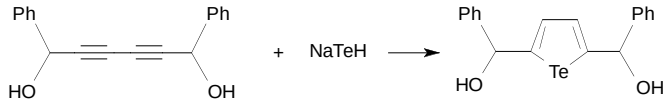
74

A modification of this method is known: When a sodium telluride solution in ethanol at 30°C is treated with 1,4-di(trimethylsilyl)buta-1,3-diyne for 3 h, the result is tellurophene in 84% yield (78CB3745).



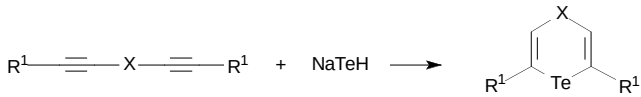
Selenophene and tellurophene were obtained in 15–20% yield by the reaction of selenium and tellurium with diacetylene in the KOH/DMSO/$N_2H_4 \cdot H_2O$/H_2O system at 0–20°C (90MI1).

Sodium hydrotelluride adds to diacetylene diol **75** to form the corresponding tellurophene **76** in 52% yield (78TL1885).



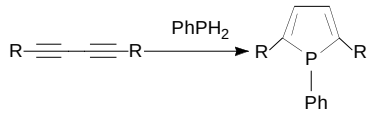
75 **76**

By the reaction of diacetylenes RC≡C−X−C≡CR with sodium hydrotelluride (X = S: −70°C, Li, NH_3, 0.6 h; X = SO_2: 40°C, DMF/MeOH; X = P(O)R^2: 20°C, CH_2Cl_2, 12 h) heterocycles **77** were prepared in 80–90% yields (73RTC1326; 75RTC92; 78RTC244).



R = Me, Et; X = S, SO_2, P(O)R^2 **77**

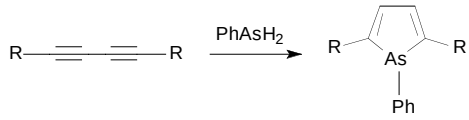
Phospholes **78** were obtained (67AG58) from diacetylene and phenylphosphine in pyridine (yield up to 29%) and with butyllithium in benzene at room temperature (yield up to 90%).



78

R = Me, Ph, *p*-C_6H_4Me, p-C_6H_4Br, β-naphthyl

Phenylarsine with symmetric disubstituted diacetylenes (*n*-LiBu, benzene) forms arsoles **79** in 33–83% yield (68TL3257).



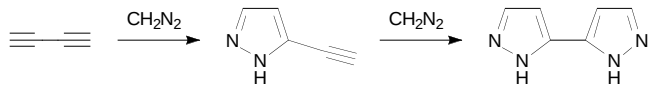
79

R	Me	Ph	*p*-C_6H_4Me	*p*-C_6H_4Cl
yield, %	33	83	58	83

F. 1,3-Dipolar Cycloaddition

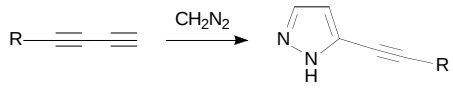
The addition of 1,3-dipoles to alka-1,3-diynes has been studied in less detail than that to conjugated alkadienes and alkenynes (80UK1801). Conjugated diynes get involved in [2+3]cycloaddition at the unsubstituted acetylene bond.

Diacetylene reacts with diazomethane in an ether solution at 0°C to form 5-ethynylpyrazole (**80**) (65ZOR610). The second diazomethane molecule adds to the remaining triple bond much more slowly. The bis adduct, 5,5′-dipyrazole (**81**), was isolated in 35% at a 1:2 diacetylene:diazomethane molar ratio.



80 **81**

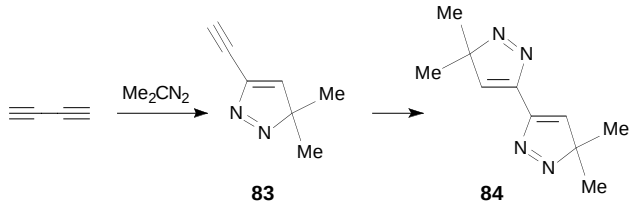
Diacetylene homologs are involved in this reaction by terminal acetylene bond to form monoadducts 5-alkynylpyrazoles **82** (65ZOR610).



R = Me, Et

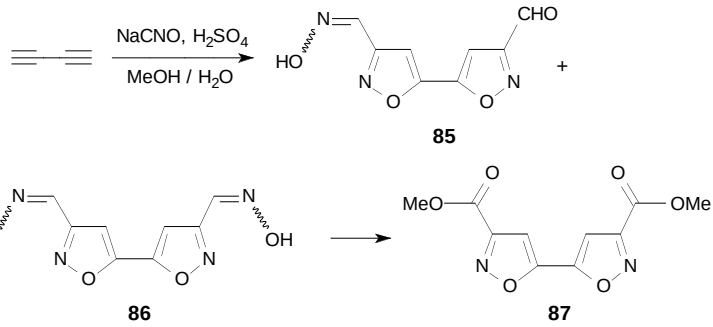
82

1,3-Dipolar addition of 2-diazopropane to diacetylene in Et_2O at −25°C to give 3,3-dimethyl-5-ethynylpyrazole (**83**) (42% yield) and at 0°C to give dipyrazole **84** (60% yield) has been described (83TL1775).



83 **84**

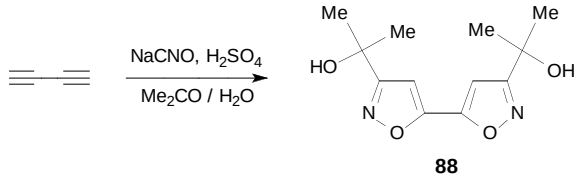
The reaction of diacetylene with cyanic acid (HCNO) proceeds at room temperature in the presence of sulfuric acid in aqueous methanol to give 3-formyl-5,5′-diisoxazol-3′-aldoxime (**85**) and 3,3′-diformyl-5,5′-diisoxazoldioxime (**86**), whose oxidation with potassium permanganate followed by esterification results in 3,3′-dicarbomethoxy-5,5′-diisoxazoles (**87**) (59G598).



85

86 **87**

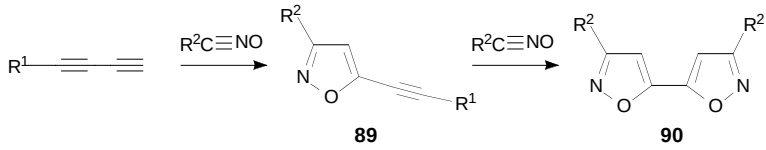
If acetone is used instead of methanol, the diol **88** is formed.



88

Diacetylene and its homologs react with alkene- and arenecarbonitrile *N*-oxides (25–30°C, Et_2O, 3 h) (59G598; 66ZOR615). The reaction proceeds stepwise to

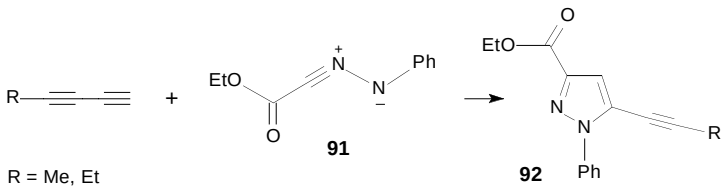
afford 3-substituted 5-alkynylisoxazoles **89** and 3,3′-disubstituted 5,5′-diisoxazoles **90** (yields 55–88%) (66ZOR615).



R^1 = H, Me, Et, Ph; R^2 = Me, Ph, *m*-$C_6H_4NO_2$

The isoxazoles **89** and **90** have been studied in detail by IR and ^{1}H NMR spectroscopy. The structure of isoxazoles **89** was also confirmed by their oxidation with potassium permanganate in acetone to 3-alkyl(aryl)-5-isoxazolecarboxylic acids.

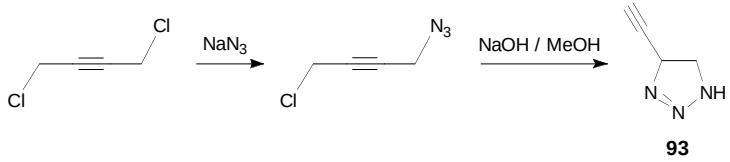
Diacetylene homologs smoothly react with *C*-carboethoxy-*N*-phenylnitrilimine (**91**) (89°C, benzene, 4 h) to form 1-phenyl-3-carboethoxy-5-(1-alkynyl)pyrazoles (**92**) in yields of 70–80% (66ZOR615).



R = Me, Et

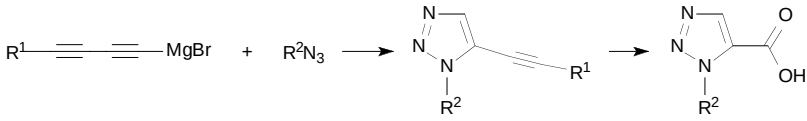
The above reactions provide convenient methods for the preparation of poorly understood acetylene derivatives of pyrazole and isoxazole.

A reaction of sodium azide with 1,4-dichlorobut-2-yne (diacetylene equivalent) has been described (89CB1175). When the monosubstitution product is treated with sodium hydroxide in methanol, 4-ethynyl-1*H*-1,2,3-triazole (**93**) is formed.



Diacetylenic Iotsitch reagents with azides (THF, 15–18°C, 20 h) afford 1-alkyl(aryl)-5-ethynyl-1,2,3-triazoles (**94**) in 48–70% yield (67ZOR2241). These

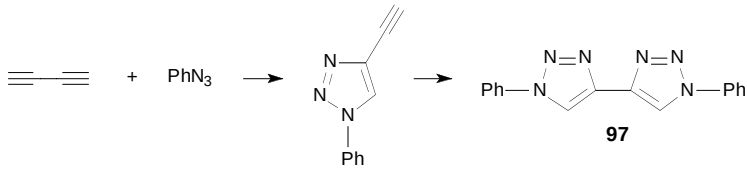
organometallics turned out to be significantly more active toward the azides than the corresponding monoacetylene derivatives.



R^1 = H, Et; R^2 = Me, Ph, *p*-$C_6H_4NO_2$, *p*-C_6H_4Br **94** **95**

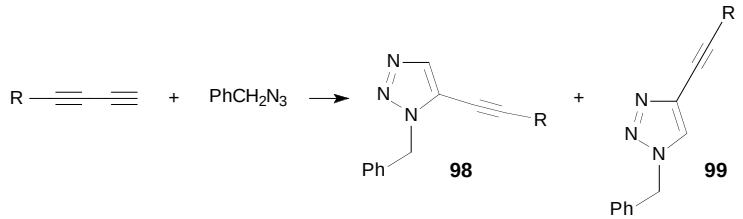
Alkynyltriazoles **94** are readily oxidized with potassium permanganate in acetone to the corresponding 1,2,3-triazole-5-carboxylic acids (**95**).

The addition of phenyl azide to diacetylene in benzene at 20–70°C has been performed (79KGS849). Depending on the amount of phenyl azide, 1-phenyl-4(5)-ethynyl-1,2,3-triazoles (**96**) and 4,4′-di(1-phenyl-1,2,3-triazoles) (**97**) were obtained in 64 and 55.5% yield, respectively.



96 **97**

The addition of benzyl azide to monosubstituted diacetylenes initially proceeds at the terminal acetylene bond to form two regioisomeric 4- and 5-ethynyl-1,2,3-triazoles **98** and **99** along with minor amounts of the corresponding diadducts (81ZOR741; 82ZOR1619).



98 **99**

R = $Me_2C(OH)$, $Me_2C(OMe)$, *n*-C_6H_{13}, Et_2NCH_2

Disubstituted diacetylenes react with benzyl azide upon long heating in toluene (12–16 h, yield 67–70%) (82ZOR1619). Comparison of the reactivity and

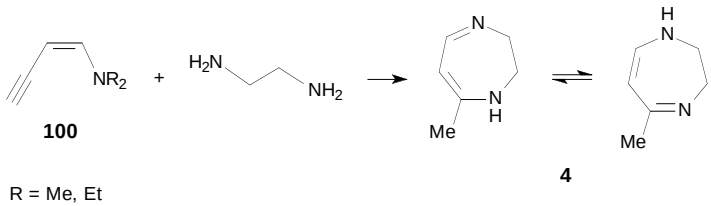
regioselectivity patterns of conjugated dienes, enynes, and diynes in the reactions of 1,3-dipolar addition indicates (80UK1801) that the addition order is mostly determined by intramolecular associations of the reactants.

III. Reactions of 1-Heterobut-1-en-3-ynes

As mentioned in the introduction, 1-heterobut-1-en-3-ynes, RXCH=CHC≡CH (X = RN, O, S; R = organic radical), are the nearest and most important diacetylene derivatives readily formed by nucleophilic addition of amines, alcohols, and thiols to diacetylene. In many heterocyclization reactions (especially those leading to fundamental heterocycles) 1-heterobut-1-en-3-ynes behave as diacetylene synthetic equivalents, but unlike diacetylene, they are nonhazardous. Therefore, the syntheses of heterocycles therefrom are often more attractive in preparative aspect.

A. Reactions with Diamines, Dithiols, and Aminothiols

The reaction of 1-dialkylaminobut-1-en-3-ynes **100** with 1,2-diaminoethane (80°C, H^+, 2 h) leads to a mixture of 5-methyl-2,3-dihydro-1,4-diazepine tautomers (**4**) (the most stable tautomers are shown) (83ZOR1541).



100

R = Me, Et

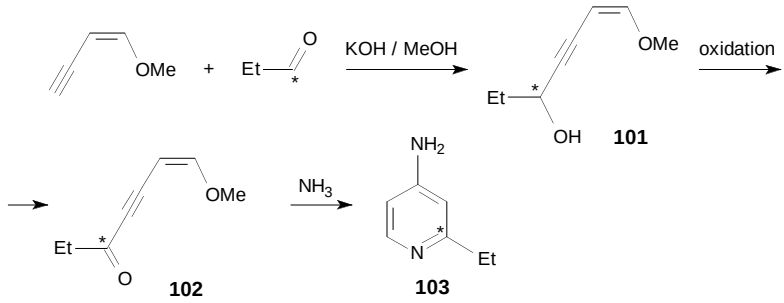
4

Cyclization takes place under acid-catalyzed conditions (sulfuric acid in dry dioxane), the yield being 76%.

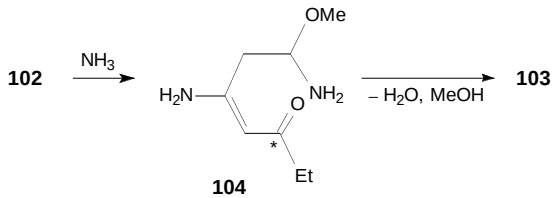
Unlike 1,2-diaminoethane, 1,2-phenylenediamine does not add to 1-dialkylaminobut-1-en-3-ynes in the presence of sulfuric acid (84DIS). An attempt to carry out the reaction in an aqueous medium under the conditions of hydroxylamine addition resulted in the isolation of 4-dialkylaminobut-3-en-2-one (84DIS).

In a sense, the synthesis of 2-[^{14}C]-4-amino-2-ethylpyridine (**103**) from 5-[^{14}C]-1-methoxyhept-1-en-3-yn-5-one (**102**) and ammonia can be attributed to

the cyclization of 1-heterobut-1-en-3-ynes with diamines (98MI1), since functional diamines are the reaction intermediates. The ketone **102** was prepared by oxidation of methoxybutenynic alcohol (**101**) obtained from methoxybutenyne and labeled propionic aldehyde by the Favorsky reaction (98MI1).

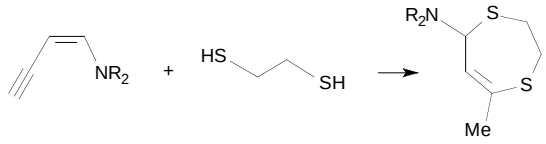


The reaction seems to involve double addition of ammonia to the ketone **102** (at the methoxyethenyl group and the triple bond) to form the diamine **104** which further undergoes cyclization to aminopyridine **103** by elimination of water and methanol.



The labeled aminopyridine **103** was further used for the synthesis of *N*-(2-ethyl-3-chloro-4-pyridin-2-yl-[^{14}C]-4-(4-chlorophenoxy)phenylacetamide-[^{14}C]-1) (98MI1).

The reaction of dialkylaminobutenynes with 1,2- and 1,3-dimercaptoalkanes also involves the formation of adducts of 1,3-orientation (85USSRP1109401; 88ZOR88), but with retention of the initial butenyne dialkylamino group, in contrast to the reaction with 1,2-diaminoethane. Thus, with 1,2-dimercaptoethane, 1-dialkylaminobut-1-en-3-ynes form 7-dialkylamino-5-methyl-7*H*-2,3-dihydro-1,4-dithiepins (**105**) in 90–96% yield (85USSRP1109401; 88ZOR88).

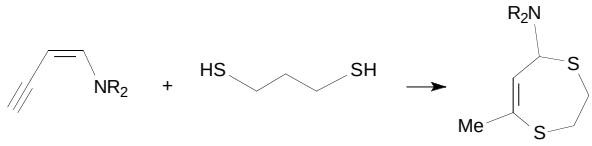


R = Me, Et; R_2N = $O(CH_2)_2N$

105

R	Me	Et	$O(CH_2)_2N$
yield, %	96	90	90

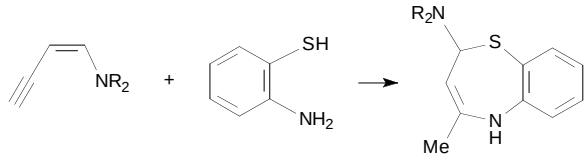
The reaction proceeds easily (0°C, 30 min) after mixing of the reagents. Under analogous conditions, from 1,3-dimercaptopropane 2-dialkylamino-4-methyl-8*H*-6,7-dihydro-1,5-dithiocins (**106**) were obtained in yields of 67 and 52% (88ZOR88).



R = Me, Et

106

The cyclization of 1-dialkylaminobut-1-en-3-ynes with 1-amino-2-mercaptobenzene occurs with the same ease (0°C, Et_2O, 20 min), the yield of 2-dialkylamino-4-methyl-5*H*-1,5-dihydro-1,5-benzothiazepines (**107**) reaching 87 and 91% (85USSRP1130565; 88ZOR88).



R = Me, Et

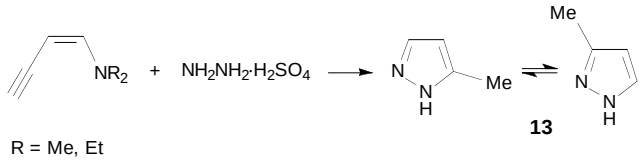
107

The high yields of the end products and the absence of other reliable synthetic routes to 1,5-benzothiazepine, 1,4-dithiepin, and 1,5-dithiocin derivatives of the above structures (85KGS1443) make these cyclizations attractive from the preparative point of view.

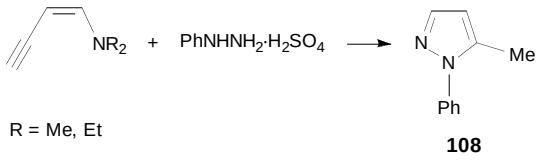
B. Reactions with Hydrazine and Hydroxylamine

The preparation of pyrazoles from heterobut-1-en-3-ynes and hydrazine provides the main pathway to the synthesis of these fundamental heterocycles [67HC (22)284; 74MI2].

A process for the preparation of 3(5)-methylpyrazole (**13**) from enynamines and hydrazine sulfate (80°C, H^+, EtOH/H_2O, 2 h, yield 72%) has been described (69ZOR1179).

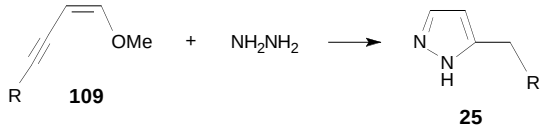


To obtain information about the cyclization pathway, an analogous reaction was carried out with phenylhydrazine (in this case, positions 3 and 5 of the forming pyrazole are nonequivalent) (69ZOR1179). The only reaction product (yield 65%) appeared to be 1-phenyl-5-methylpyrrazole (**108**).



The cyclization of 1-alkoxybut-1-en-3-ynes with hydrazine was first achieved by Franke and Kraft (55AG395). By heating 1-methoxybut-1-en-3-yne with hydrazine sulfate in an aqueous alcohol medium they obtained 3(5)-methylpyrazole (**13**) in high yield. Winter (63HCA1754) used the cyclization of 1-methoxybut-1-en-3-yne with hydrazine hydrate and phenylhydrazine to establish the structure of the initial enyne ether [in this case a mixture of 1-phenyl-3(5)-propylpyrazoles was obtained]. The reaction with hydrazine sulfate gives only one product, 3(5)-propylpyrazole.

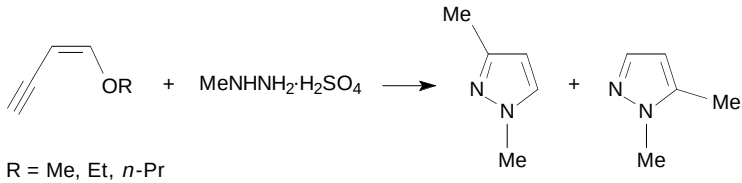
From methoxybutenyne homologs **109** and protonated hydrazine a series of 3(5)-alkylpyrazoles **25** was obtained (60–70°C, H^+, H_2O, 2 h) (70ZOR1532).



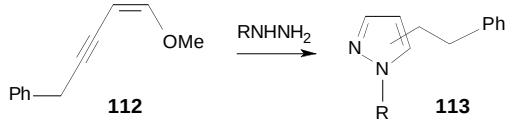
R = Me, Et, *n*-Pr, *t*-Bu

R	Me	Et	*n*-Pr	*t*-Bu
yield, %	40	42	52	59

To shed light on the reaction pathway, a cyclization with methylhydrazine was carried out (70ZOR439; 73ZOR832), since pyrazoles with nonequivalent positions 3 and 5 are obtained in this case. From 1-methoxybut-1-en-3-yne and methylhydrazine sulfate a 4:5 mixture of 1,3- (**110**) and 1,5-dimethylpyrazoles (**111**) was formed (GLC) (70ZOR439). In the reaction of methoxybutenyne homologs (R = Et, *n*-Pr) with methylhydrazine (72°C, H^+, H_2O, 2 h), lengthening of the alkyl radical leads to an increase in the content of 1,5-isomer (**111**), with yields of 50–60%. Thus, when R = Et, the ratio is 2:3 (73ZOR832).

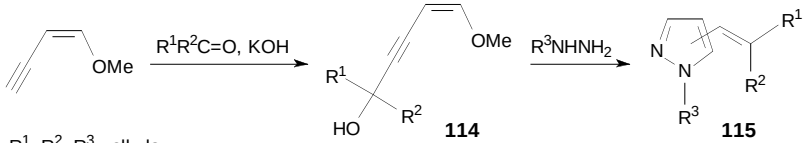


Since 1-heterobut-1-en-3-ynes are readily alkylated and functionalized at the terminal acetylenic carbon atom, their reaction with hydrazines makes it possible to introduce diverse (including functional) substituents into the pyrazole ring. For instance, from benzylated methoxybutenyne **112,** isomeric 2-phenylethylpyrazoles **113** were obtained in 74% yield (81H146).



112 **113**

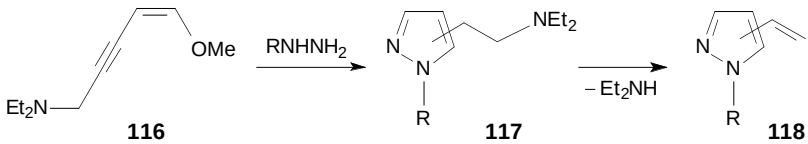
Tertiary alkoxyenyne alcohols **114,** easily prepared from alkoxyenynes and ketones by the Favorsky reaction (74ZOR1835), give, with hydrazine and alkylhydrazines in an acidic medium, 3(5)-substituted dialkylvinylpyrazoles **115** in 80% yield (81H146).



R^1, R^2, R^3 - alkyls

114 **115**

Another example of the preparation of functionalized pyrazoles is the reaction of aminomethylated methoxyenynes **116** with hydrazine and alkylhydrazines, which leads to aminoethylpyrazoles **117** (80% yield) and vinylpyrazoles **118** via Et_2NH elimination.

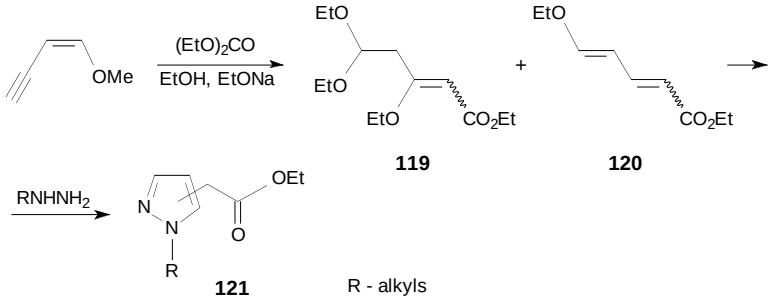


116 **117** **118**

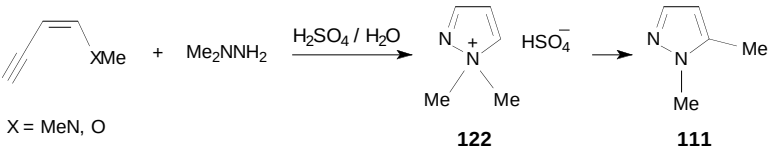
R - alkyls

The reaction of methoxybutenyne with diethylcarbonate gives a mixture of substituted acrylates **119** and **120** (yield about 50%), which quantitatively form, with

hydrazine, the ethyl esters of 3(5)-pyrazolecarboxylic acids **121.** In the presence of bases this reaction affords only 3-substituted pyrazoles (81H146).



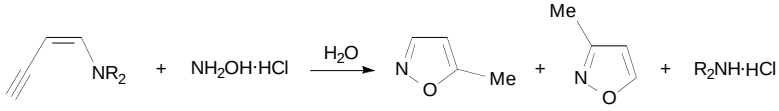
The reaction of 1-heterobut-1-en-3-ynes with nonsymmetric dimethylhydrazine furnished 1,5-dimethylpyrazole (**111**) (72ZOR651).



The reaction is assumed to involve the formation of the pyrazolium salt **122,** which undergoes Hofmann cleavage during the isolation of the end product in an alkaline medium (66MI1). The low yield of this pyrazole is likely due to aminonitrile rearrangement upon alkaline treatment. Rearrangement of this kind is common to all the compounds having a CH=N—NH aldohydrazonium system, whether the system is in an open chain or in a pyrazolium or tetrahydropyrazolium system (66MI1).

The reaction of 1-heterobut-1-en-3-ynes (X = RN, S) with hydroxylamine hydrochloride gives isoxazoles (69ZOR1179; 70ZOR2371). For instance, from 1-dimethylamino- and 1-diethylaminobut-1-en-3-ynes (60–70°C, H^+, 2 h),

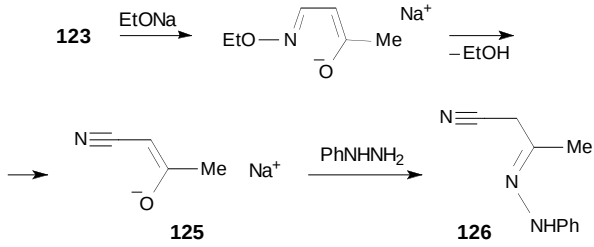
5-methylisoxazole (**123**) is produced in 56% yield. The content of the second isomer, 3-methylisoxazole (**124**), does not exceed 5% (TLC) (69ZOR1179).



R = Me, Et

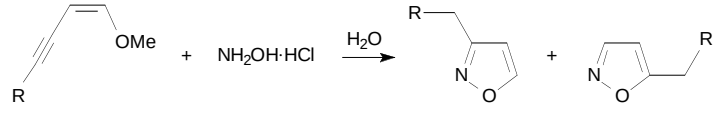
123 **124**

The methyl group position was fixed both by cleavage of the isoxazole ring with sodium ethylate and by isolation of the cyanacetone sodium salt **125.** The reaction of this salt with phenylhydrazine resulted in the phenylhydrazone of cyanacetone (**126**) (69ZOR1179).



125 **126**

The interaction of methoxybutenyne and its homologs with hydroxylamine (60–70°C, H^+, 2 h) gives a mixture of 3- (**127**) and 5-alkylisoxazoles (**128**) (70ZOR2371).



R = H, Me, Et, *n*-Pr, *n*-Bu

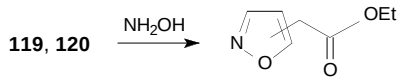
127 **128**

R	H	Me	Et	*n*-Pr	*n*-Bu
yield, %	60	51	42	41	38

For methoxybutenyne the **127**:**128** ratio is 1:2.6 (GLC). With lengthening of the alkyl radical at the acetylene bond the ratio of isomers is changed in favor of

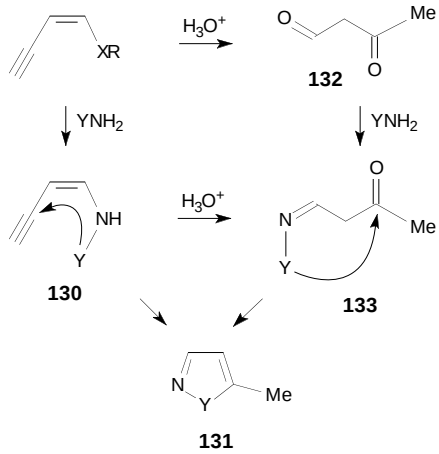
5-alkylisoxazoles. With R = Me, Et, or *n*-Pr, the mixture contains ~90% of the isomer **128,** whereas with R = *n*-Bu only this isomer retained (70ZOR2371).

A mixture of unsaturated ethers **119** and **120** obtained from methoxybutenyne and diethylcarbonate, when reacted with hydroxylamine in an acidic medium, quantitatively forms the ethyl esters of isoxazolecarboxylic acids **129** (81H146).



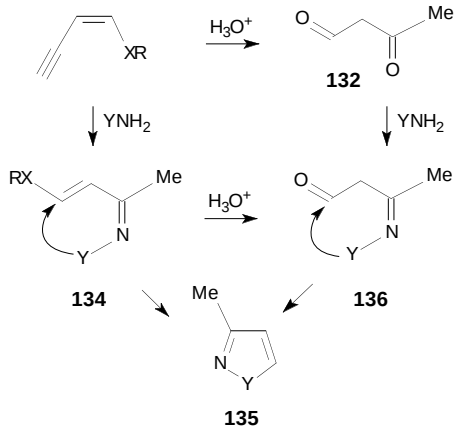
129

In the heterocyclization of 1-heterobut-1-en-3-ynes and their homologs with hydrazines or hydroxylamine, the formation of 5-substituted pyrazoles or isoxazoles **131** occurs (81UK1252; 91UK103): The primary amino group attacks the heteroenyne C-1 atom to eliminate amine, alcohol, or thiol (evidently, as an addition–elimination process). The intermediate **130** undergoes ring closure as a result of the nucleophilic attack by the second electron-donating function directed at the C-3 atom or at the carbonyl group (intermediates **132** and **133**), which is often formed due to the presence of water in the reaction mixture (81UK1252; 91UK103).



Y = OH, NHMe, NHPh; X = RN, O, S; R = Me, Et

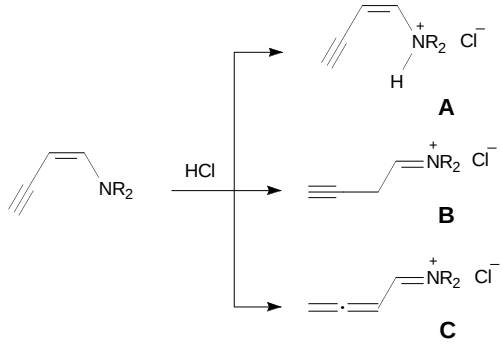
In an alternative reaction course, the primary amino group reacts with C-3, while the intermediate **134** undergoes cyclization either via nucleophilic attack by a Y function at the C-1 atom followed by elimination of HXR (also formed due to possible hydrolysis of the initial products and intermediates) or with involvement of one of the carbonyl groups (intermediates **132** and **136**) (81UK1252; 91UK103).



The synthesis of pyrazoles and isoxazoles from 1-heterobut-1-en-3-ynes is performed, as a rule, in an aqueous acid medium, i.e., under conditions favoring the hydrolysis and hydration of the initial enyne. This circumstance impedes rationalization of the experimental results. Therefore, it is reasonable to consider in brief the protonation and behavior of 1-heterobut-1-en-3-ynes under the conditions of acid-catalyzed hydrolysis.

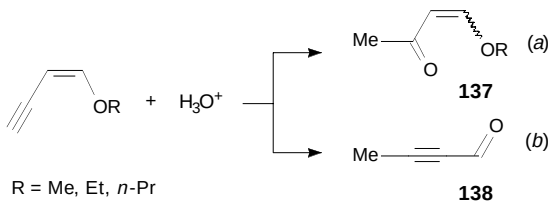
The protonation of 1-dialkylaminobut-1-en-3-ynes was studied using UV and IR spectroscopy (69MI1; 74DIS; 81UK1252). Their interaction with dry gaseous HCl (argon, acetonitrile, $-80°C$) leads to the formation of white crystalline salts which resinify on isolation. In the IR spectrum of the protonation product an intense band of the N—H stretching vibrations (structure **A**) was observed in the 2700 cm^{-1} region. Gradually, the band intensity decreases, which is accompanied by the appearance of a new band in the 1670 cm^{-1} region, corresponding to the C=N bond stretching (structure **B**) (74DIS).

In the UV spectrum of the protonation products there is a hypsochromic shift of the absorption maximum of enyne system compared to the bases (74DIS); this agrees with the data of the protonation of simple enamines and dienic amines (69MI1).

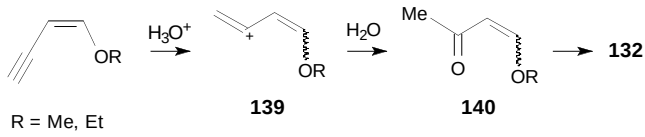


Unstable chlorides were converted to stable $SnCl_4$ complexes. In their IR spectra there is an intense absorption band in the 1900 cm^{-1} region, which is consistent with the band of allenic system (structure **C**). Unlike unstable chlorides **A** and **B,** the $SnCl_4$ complexes are stable and, when kept in an inert atmosphere, remain intact for several days. The allenic structure of the immonium salt was confirmed by studying the mercuration of the same aminobutenynes (74DIS).

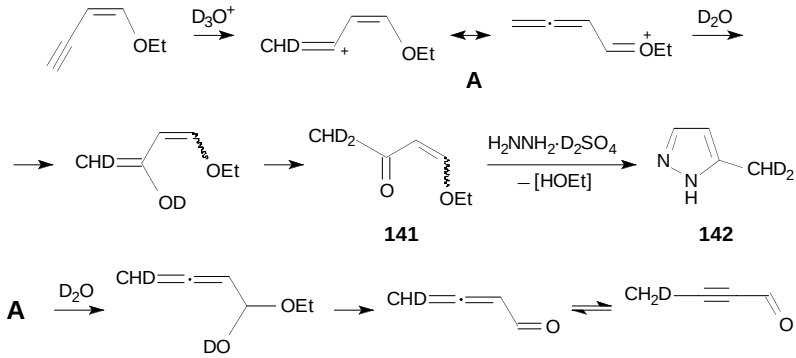
The hydrolysis of 1-alkoxybut-1-en-3-ynes in the presence of acids can follow two directions: (*a*) hydration of the triple bond and (*b*) hydrolysis of the vinyl ether structural element to form propiolic aldehyde **138** (55CB361).



The first reports concerning this reaction were contradictory (52CB475; 61BSF2393). Later, an investigation of the hydrolysis kinetics of 1-alkoxybut-1-en-3-ynes showed (73MI1; 76ZOR1384) that at a constant acid concentration the process is described by the kinetic equation of the first order. A mechanism according to which the complete hydrolysis is preceded by triple bond hydration with subsequent cleavage to acetoacetic aldehyde (**132**) has been proposed.



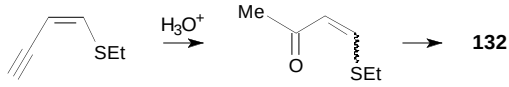
The hydration kinetics of 1-alkoxybut-1-en-3-ynes was examined using GLC at 60–75°C in the presence of sulfuric acid (73ZOR655; 74ZOR447; 74ZOR929). The results suggested that protonation of the initial enyne molecule occurs in the stage determining the hydration rate. The protonation direction was established by studying the hydration of 1-ethoxybut-1-en-3-yne in D_2O in the presence of D_2SO_4. The reaction product turned out to be 4,4-dideutero-1-ethoxybut-1-en-3-one, $D_2HCCOCH{=}CHOC_2H_5$ (**141**) (74DIS; 74ZOR929). On cyclization in the presence of $D_2SO_4$with hydrazine sulfate, **141** gave 3,3-dideutero-5(3)-methylpyrazole (**142**) containing deuterium atoms in the side chain rather than in the ring (74DIS; 74ZOR929). The absence of possible isotopic exchange under these conditions has been proved experimentally.



A direct irreversible proton transfer in limiting stage of 1-ethoxybut-1-en-3-yne hydration is confirmed by the value of kinetic isotopic effect $k_H/k_D = 2.9$. For fast reversible proton transitions this value is less than 1.

A conclusion was drawn (81UK1252) that the protonation of 1-alkoxyalk-1-en-3-ynes at C-4 to form conjugated carboxonium ion **A** is the obligatory general stage for proton-catalyzed hydration and hydrolysis. This does not contradict the possible parallel hydrolysis of the vinyl ether structural element to propiolic aldehyde or its homologs (direction *b* leading to **138**) (64CR1539; 68BSF200).

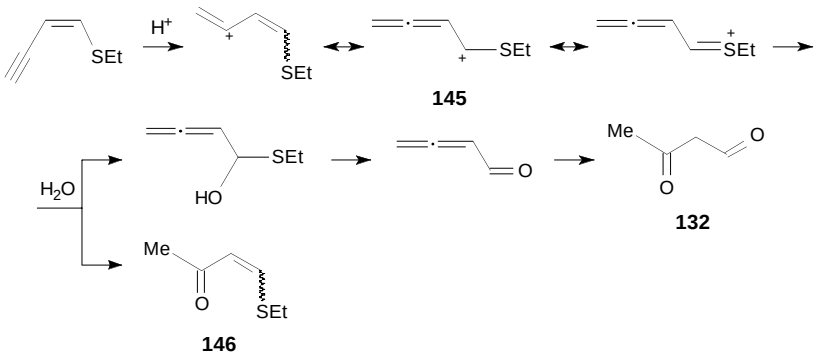
Acid hydrolysis of 1-ethylthiobut-1-en-3-yne (**143**) (10% sulfuric acid, 60–95°C) mainly involves hydration of the triple bond (evidently due to the greater hydrolytic stability of the vinyl sulfide moiety of the molecule), which results in the formation of 1-ethylthiobut-1-en-3-one (**144**). The latter is further hydrolyzed to acetoacetic aldehyde (**132**) (75IZV1975; 78IZV153).



143 **144**

The reaction kinetics studied using UV spectroscopy is formally identical to that of acid-catalyzed hydrolysis of 1-alkoxybut-1-en-3-ynes (a first-order reaction with respect to the substrate and acid) (75IZV1975; 78IZV153). At a constant acid concentration the reaction proceeds as a pseudo-monomolecular process.

The observed rate constant of 1-ethylthiobut-1-en-3-yne consumption is much higher than that of **132** accumulation. This means that the primary cation **145** undergoes further transformation in two directions.



R = H, Me, Et, *n*-Pr

One of those leads to acetoacetic aldehyde (**132**), while the other gives 1-ethylthiobut-1-en-3-one (**146**). The latter fails to hydrolyze to the aldehyde **132** under the reaction conditions (75IZV1975).

The differences in behavior of the cation **145** and its oxygen analog **139** are caused by differences in the degree of stabilization of the charge in the C-1

position. The sulfur atom is a weaker partner in the p,π-conjugation compared to the oxygen atom (75IZV1975). Therefore, in the cation **145,** the C-1 atom should experience a stronger attack from the water molecule than in the oxygen analog. The process rate is greatly dependent on the configuration of the initial compounds (78IZV153). The most prominent effect on the reactivity of 1-heteroalk-1-en-3-ynes, RXCH=CHC≡CH, is produced by the nature of heteroatom of the substituent X. When X is nitrogen, oxygen, or sulfur, the reactivity is correlated with the positive mesomeric effect of the corresponding hetero group and drops in the series $R_2N > RO > RS$ (69ZOR1179; 73ZOR832).

Since in an aqueous medium the cyclization-completing stage involves the reaction of a cationoid intermediate with a binucleophile Y such as YNH_2 (81UK1252), the end product structure is largely determined by the relative activity of C-1 and C-3 electrophilic centers in this intermediate.

With X = RN the C-1 electrophilic center is most active, and five-membered heterocycles **131** are generated (69ZOR1179). With X = O there is a competition between C-1 and C-3 electrophilic centers, the role of the latter increasing on going to sulfur analogs (X = S) in accord with a decrease in the +M effect in this series (81UK1252).

The effect of the nature of the substituent at the acetylene bond is not so noticeable. Substitution reduces the C-3 activity due to polarization effects and steric factors. As a result, in the cyclization with hydrazines and hydroxylamines an increase in the content of 5-substituted pyrazoles and isoxazoles is observed (81UK1252). As mentioned above, nonsymmetric nitrogen-containing binucleophiles H_2N—YH (Y = O, NMe, NPh) react with 1-heteroalk-1-en-3-ynes in two alternative pathways: by functions H_2N and YH.

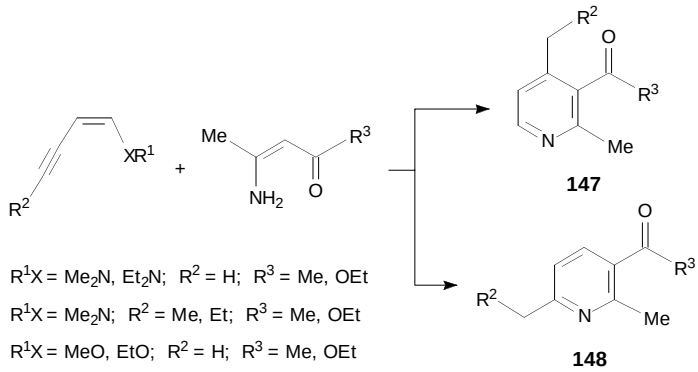
In the case of NH_2OH with a sharp difference in the nucleophilicity of the two functions, the primary amino group reacts with the carbocation C-1 center. For example, the reaction of 1-alkylaminoalk-1-en-3-ynes with hydroxylamine leads to selective synthesis of alkylisoxazoles (69ZOR1179). A preparative value of this method is evident because the use of dicarbonyl compounds as starting materials for the synthesis of alkylisoxazoles results in a mixture of isomers.

A comparative evaluation of the reactivity of nonsymmetric hydrazines with 1-heteroalk-1-en-3-ynes has been performed (81UK1252). Methylhydrazine reacts with these compounds mainly via the unsubstituted amino group (69ZOR1179). The same is observed for dialkylhydrazines (with $X = R_2N$, RO, RS) (81UK1252).

Nonsymmetric dialkylhydrazines react with enyne ethers, amines, and sulfides via the unsubstituted amino group (72ZOR651). The cause of this seems to be steric effects. The cyclization leads to quaternary pyrazolium salts, which, under the effect of alkali, undergo both Hofmann cleavage (to form 1,5-dialkylpyrazoles) and aminonitrile rearrangement, the latter greatly reducing the yield of the pyrazoles (81UK1252).

C. Reactions with Enaminocarbonyl Compounds and Cyanacetamide

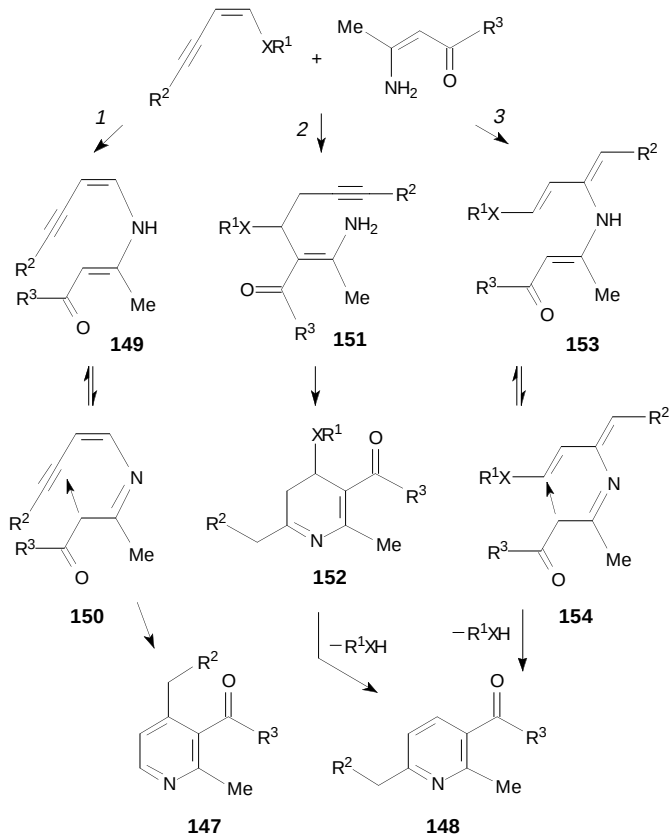
Reactions of 1-dialkylaminoalk-1-en-3-ynes and 1-alkoxyalk-1-en-3-ynes with the ethyl ester of β-aminocrotonic acid and acetylacetonimine in the presence of ammonium acetate and acetic acid (50°C, 5 h) (72ZOR1575) and without catalyst (100°C, 60 h) (75ZOR708) lead to functional isomeric pyridines **147** and **148.** Separation of the isomers by distillation is difficult owing to close boiling points. The ratio of isomeric ethyl esters of 2-methyl-4-alkyl-3-nicotinic acid (**147**) and 2-methyl-6-alkyl-3-nicotinic acid (**148**) was established using chromatography and ^{1}H NMR spectroscopy (72ZOR1575; 75ZOR708).



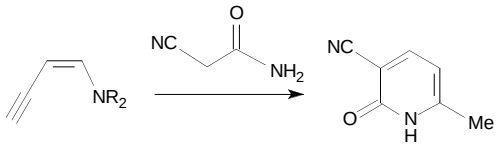
The yields of ethyl ester of 2,4-dimethyl-3-nicotinic acid (**147**) (R^2 = H, R^3 = OEt) are 45 and 43%, respectively, in the reactions of the ethyl ester of β-aminocrotonic acid with 1-dimethylaminobut-1-en-3-yne and 1-methoxybut-1-en-3-yne (75ZOR708). Isomeric 2,4-dimethyl-3-acetyl- and 2,6-dimethyl-3-acetylpyridines (R^2 = H, R^3 = Me) (**147**) and (**148**) failed to be separated by GLC (75ZOR708). Their presence was fixed by TLC (Silufol, methyl ethyl ketone:water = 95:5), the ratio being determined by ^{1}H NMR (75ZOR708). Enyne amines with acetylacetonimine form practically one isomer **147** (72ZOR1575; 75ZOR708). The formation of two isomers in the reaction of 1-heteroalk-1-en-3-ynes with the ethyl ester of β-aminocrotonic acid and acetylacetonimine is explained by competition between the two electrophilic centers of the initial enyne and the two nucleophilic centers of the addend (amine or the imine group and the α-methylene group of the imine tautomer). The reaction can follow three pathways (81UK1252):

1. Substitution of the hetero group (XR^1) at C-1 by the amino group (intermediate **149**) and cyclization of its tautomer (**150**) with the participation of the methylene group (formation of 2,4-isomer **147**).
2. Michael addition of the enamine to the 1,3-enyne double bond (intermediate **151**) and subsequent intramolecular attack of the triple bond by the amino group (intermediate **152**) with the R^1XH elimination (formation of 2,6-isomer **148**).
3. Nucleophilic attack of the C-3 atom of the 1,3-enyne by the primary amino group (intermediate **153**) and cyclization of its tautomer (**154**) via the Michael-like attack at C-1 with the R^1XH elimination (formation of 2,6-isomer **148**).

Evidently, pathway 1 is a major one for the enyne amines (90%) and prevailing one for the enyne ethers (70%).



The cyclization of the 1,3-enyne amines with cyanacetamide in the presence of bases (55°C, H_2O, 2 h) leads to 3-cyano-6-methyl-2-pyridones (**155**), yield 77% (69ZOR1179).

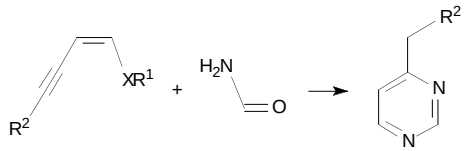


R = Me, Et **155**

Obviously, pathway 2 prevails in this case, owing to the high activity of the CH_2 group. It is also possible that the reaction involves the formation of aminobutenone [60HC(14)272; 81UK1252].

D. Reactions with Formamide, Guanidine, and Thiocarbamide

1-Heteroalk-1-en-3-ynes react with formamide (180°C, H_2O, 7 h) to furnish 4-alkylpyrimidines **156** in 30–70% yield (68ZOR1138; 70ZOR1528; 70ZOR2374).



156

R^1X = Me_2N, Et_2N; R^2 = H, Me, Et, *n*-Bu

R^1X = MeO; R^2 = H, Me, Et, *n*-Pr

R^1X = EtS; R^2 = H

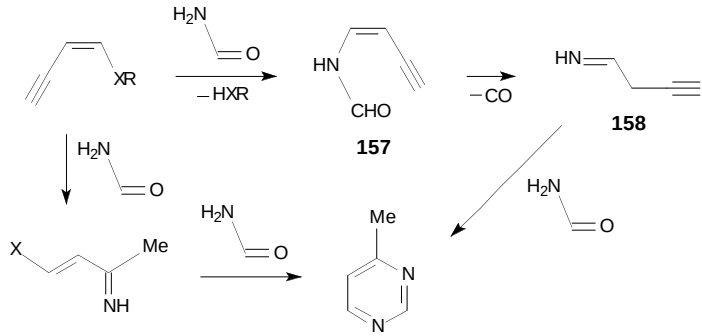
R^1X	Me_2N	MeO	EtS
yield, %	69	70	30

In the case of 1-dimethylaminobut-1-en-3-yne no 4-methylpyrimidine was isolated because its boiling point is close to that of a side product, dimethylformamide. The latter results from transamination of formamide by dimethylamine in the course of cyclization. The pyrimidines **156** were isolated and characterized as picrates (70ZOR1528). For easier isolation of pure 4-methylpyrimidine

in the cyclization with formamide, use was made of 1-pyrrolidino-, 1-piperidino-, and 1-morpholinobut-1-en-3-ynes (68ZOR1138; 70ZOR2374). In the case of 1-piperidinobut-1-en-3-ynes, apart from 4-methylpyrimidine, piperidinoformamide was isolated, i.e., the transamination of formamide during this reaction represents a general side process.

4-Alkylpyrimidines were obtained in 59–70% yield from higher 1-dimethylamino- and 1-methoxyalk-1-en-3-ynes ($R^2 =$ Me, Et, *n*-Pr) by their reaction with formamide (70ZOR2374). The exception was 1-methoxy-5,5-dimethylhex-1-en-3-yne, from which the pyrimidine was obtained in 45% yield only, which is related to steric hindrance for the attack at the acetylene bond.

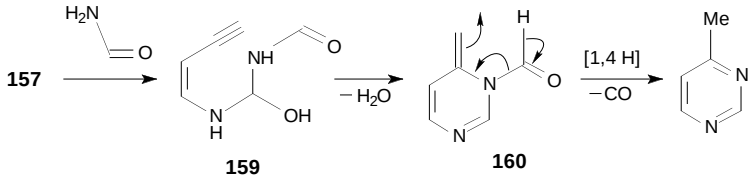
The cyclization pathway proposed (81UK1252) involves nucleophilic substitution of the hetero group (XR) by the formamide amino group to form either enyne formamide **157** or imine **158.**



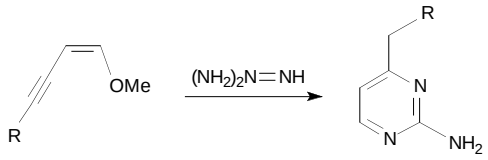
In the authors' opinion (81UK1252), the evidence for such a scheme is the isolation of formamide transamination products, dialkylformamides (in case of 1-dialkylaminoalk-1-en-3-ynes). Examples of formamide transamination, e.g., by *β*-amino-substituted carbonyl compounds, are known [58CB2832; 60CB1402; 60HC(14)272].

The cyclization of the imine **158** is believed (81UK1252) to involve the addition of the second formamide molecule to C-3 (at least primary amines readily add in a similar manner to such systems).

A likely pathway is also that in which the key stage is the addition of the second formamide molecule to the carbonyl group of the intermediate **157** to form the amide **159.** The latter, with loss of water, closes the dihydropyrimidine ring **160,** which undergoes aromatization to 4-metylpyrimidine via 1,4-hydrogen shift and decarbonylation.

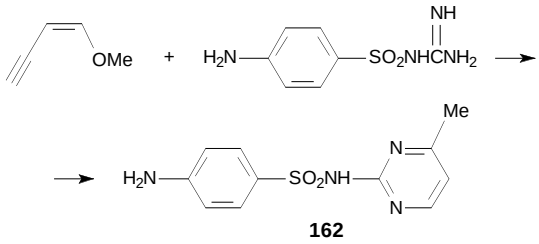


A synthesis of pyrimidine thiols in a yield of up to 60% from methoxybutenyne and thiourea has been described for the first time in (59JCS525). Later, a series of 2-amino-4-alkylpyrimidines (**161**) has been obtained in 25–27% yield from 1-methoxyalk-1-en-3-ynes and guanidine (80°C, H^+, H_2O, 2 h) (70ZOR2369).



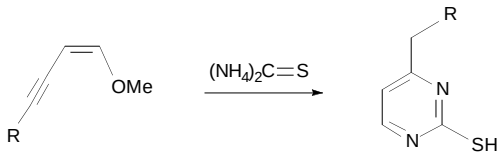
1-Alkylthioalk-1-en-3-ynes with guanidine in an acidic medium (75–85°C, 10% H_2SO_4, H_2O, 1 h) form 2-amino-4-alkylpyrimidines in a yield of about 20%, whereas enyne amines give triacetylbenzene under the same conditions (70ZOR2369).

A sulfanilamide drug of prolonged action, 2-*p*-aminobenzenesulfamido-4-methylpyrimidine (sulfomerazine **162**), first prepared by Japanese chemists from acetacetic aldehyde in 82% yield (49JPJ447), ranks among practically valuable 2-amino-4-methylpyrimidine derivatives. Later, a synthesis of this product directly from 1-methoxybut-1-en-3-yne (100°C, AcONa, AcOH, 3 h) in 64% yield has been developed (76MI1).



1-Dialkylaminobut-1-en-3-ynes with thiourea in acidic media give only triacetylbenzene, whereas in the presence of bases from the same reactants, 2-mercapto-4-methylpyrimidine is formed in 45% yield (74DIS).

The reaction of methoxyalkenynes with thiourea in aqueous HCl affords 2-mercapto-4-alkylpyrimidines (**163**) in 72–95% yield (70ZOR2369; 71KGS843).

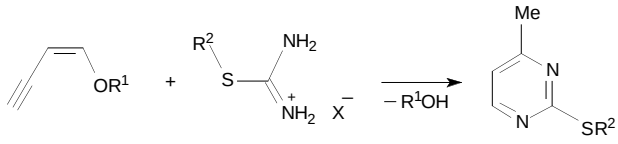


163

R = H, Me, Et, *n*-Pr

R	H	Me	Et	*n*-Pr
yield, %	95	94	80	72

1-*n*-Butoxy- and 1-*n*-amyloxybut-1-en-3-ynes do not undergo cyclization with thiourea under the same conditions, while 1-ethylthiobut-1-en-3-yne forms 2-mercapto-4-methylpyrimidine in 32% yield (74DIS). However, the reaction of 1-alkoxybut-1-en-3-ynes with *S*-alkylisothiuronium halides in an aqueous alcohol acidic medium at 60°C leads to 4-methyl-2-alkylthiopyrimidines in a yield of up to 37% (76ZOR2063).



R^1 = Me, Et; R^2 = Me, Et, *n*-Bu, $CH_2CH{=}CH_2$; X = Cl, Br, I

A prospective method for the utilization of diacetylene by its conversion to 2-mercapto-4-methylpyridine via the reaction of 1-methoxybut-1-en-3-yne with thiourea has been brought about at an industrial level (78USSRP570580; 81USSRP791713; 84MI2; 00ZPK619). Kinetic data for this reaction and optimal synthetic parameters for the end product have been reported (84ZPK1801).

Summing up the data on cyclizations of 1-heterobut-1-en-3-ynes with nucleophiles, the following features of inter- and intramolecular nucleophilic attack in these reactions should be noted.

The direction of primary intermolecular nucleophilic attack at heterosubstituted acetylenes of type HC≡C−X, where X = R_2N, RO, RS, is governed by the nature of heteroatom and can be different.

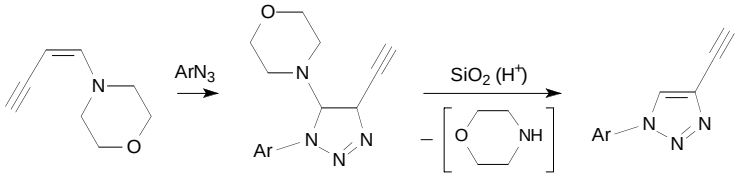
In the cyclizations of 1-heterobut-1-en-3-ynes the orientation of bidentate nucleophiles is the same for heteroenynes of all the three types (C-1 and C-3).

Compounds of the type HC≡C—CH=CHXR are not involved in a primary reaction with weak nucleophiles such as CH acids; meanwhile, a final (secondary) cyclization with participation of active methylene groups happens to be feasible. Evidently, in most cases the energy gain in the heteroaromatic system realization is the decisive factor (81UK1252).

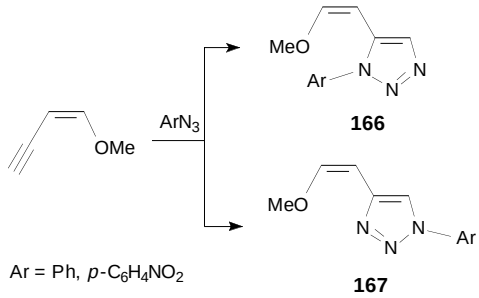
E. Reactions with 1,3-Dipoles and Other Cycloadditions

Alkylvinylacetylenes react with 1,3-dipoles exclusively across the terminal unsubstituted bond, whether it is a double or triple bond (80UK1801). 1-Heteroalk-1-en-3-ynes behave quite differently in these reactions. Orientation is largely determined by the nature of heteroatom.

The reaction of 1-morpholylbut-1-en-3-yne with aromatic azides gives 1-aryl-4-ethynyl-5-*N*-morpholino-Δ^2-triazolines (**164**), which readily eliminate morpholine to form 1-aryl-4-ethynyltriazole (**165**) during chromatographic purification (83DIS).

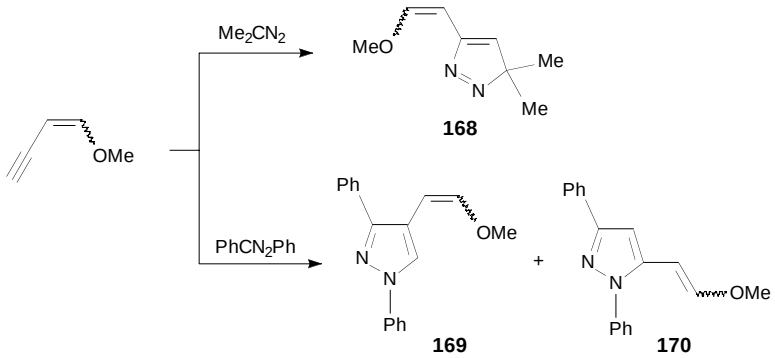


The interaction of 1-methoxybut-1-en-3-yne with aromatic azides proceeds at the unsubstituted acetylenic bond to furnish two structural isomeric triazoles, **166** and **167** (4:1 ratio), due to the different 1,3-dipole orientations (83DIS).



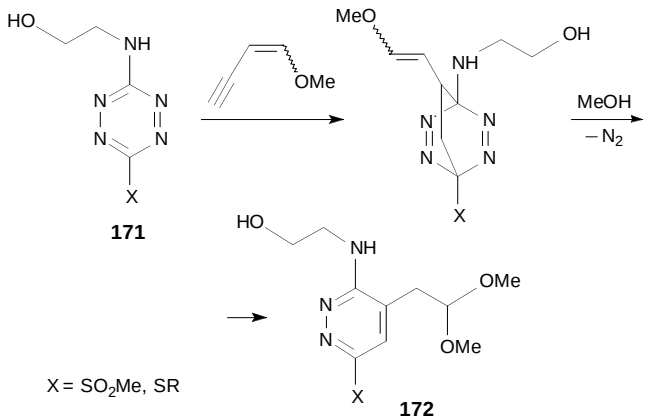
Z-Configuration of the initial compounds does not change in the reaction course, as indicated by the coupling constants of the methoxyethenyl group vinyl protons of the triazoles **166** and **167.** Adducts of *E*-configuration are present only as admixtures (83DIS).

1,3-Dipolar cycloaddition of 2-diazopropane and 1,3-diphenyldinitrilimine to *E*- and *Z*-methoxybutenynes occurs at the triple bond to form 3,3-dimethyl-5-(2-methoxyvinyl)pyrazole (**168**) and a mixture of *E,Z*-1,3-diphenyl-4- (**169**) and -5-(2-methoxyvinyl)pyrazole (**170**) [70CR(C)80].

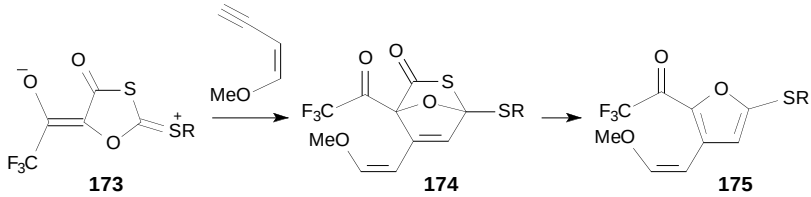


Thus, unlike enyne amines, 1-alkoxy-1,3-enynes react with 1,3-dipoles by their acetylenic bond.

1-Heterobut-1-en-3-ynes undergo other cycloaddition reactions. A synthesis of 1,2-diazines **172** via the Diels–Alder reaction of substituted 1,2,4,5-tetrazines **171** with electron-rich dienophiles, including 1-methoxybut-1-en-3-yne, has been described (96T8151; 98WO16508).

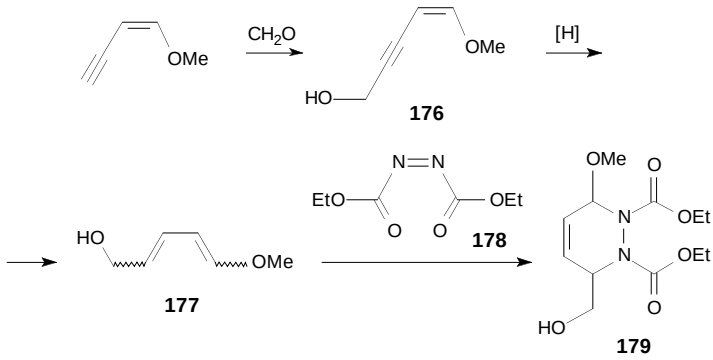


Cyclic carbonylylides **173** react with *Z*-methoxybutenyne according to the [2+3]-cycloaddition scheme to form the furan derivatives **175** via nonisolable intermediate **174** (85CB785).



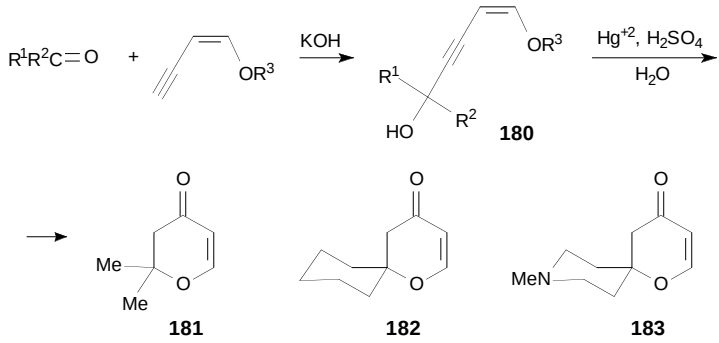
R = Me, Et, CH_2=$CHCH_2$

The Diels–Alder reaction between methoxydienic alcohol **177** [obtained by reduction of 1-methoxy-1-buten-3-yn-5-ol (**176**), the product of the 1-methoxybut-1-en-3-yne Favorsky condensation with formaldehyde] and **178** leads to the pyridazine **179** [84JCS(P1)1981].



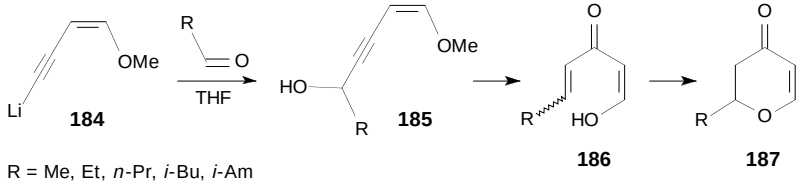
F. Cyclizations of 1-Heterobut-1-en-3-yn-5-ols

Cyclohydration of alkoxylvinylacetylenic alcohols **180** (prepared from methoxybutenyne by the Favorsky reaction) leads to dihydropyran-4-ones **181–183** under conditions of the Kucherov reaction (75MI1; 88MI1; 93MI2).



R^1 = Me; R^2 = Me, *n*-Bu; R_1–R_2 = $(CH_2)_5$, $MeN(CH_2)_4$; R_3 = Me, Et, *n*-C_6H_{13}

A synthesis of 2-alkyl-2,3-dihydro-γ-pyrones (**187**) from methoxybutenyne and aldehydes has been described (83TL4551). The condensation of lithiomethoxybutenyne (**184**) with aldehydes at −78°C leads to the secondary alcohols **185,** which form the dihydropyrones **187** via hydration of the acetylenic bond and hydrolysis of the methoxyethenyl group to the ketoenol **186** (0°C, *p*-TSA, THF, H_2O or 30% $HClO_4$, 20 min) folowed by intramolecular cycloaddition.

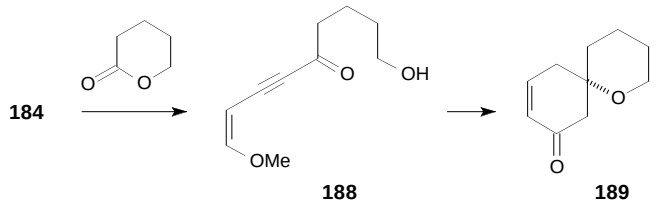


R = Me, Et, *n*-Pr, *i*-Bu, *i*-Am

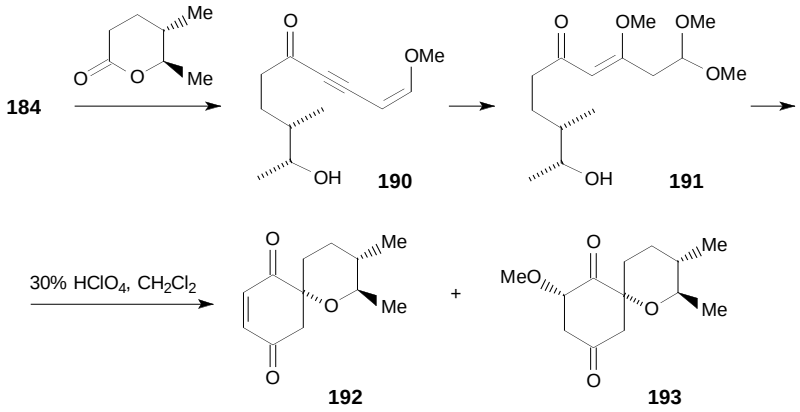
The yield of the dihydropyrones **187** is higher for larger radicals (R); for R = Me it is 40%, whereas for R = *i*-Am it reaches 80% (83TL5303). These pyrones have been patented as fungicides (80JPP80102504).

General synthetic routes to spiroketals **189** from lactones and lithiomethoxybutenyne **184** have been described (83TL5303; 88JOC652; 89JOC1157; 90JOC5894). Three synthetic schemes have been realized.

The addition of lithium acetylene **184** (obtained from *Z*-methoxybut-1-en-3-yne) to δ-valerolactones at −78°C in THF gives the ketoalcohol **188** (83TL5303; 90JOC5894). The conversion of the latter to spiroketal **189** is accomplished under the action of 30% perchloric acid in methylene chloride, yield 58% (90JOC5894).

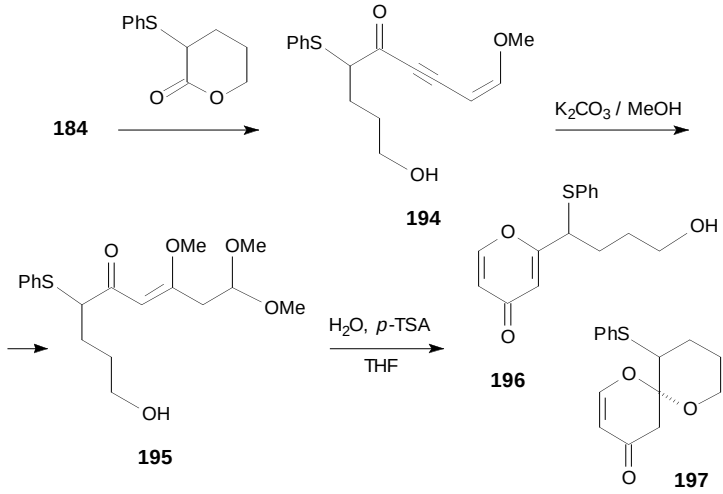


For substituted lactones this method gave a low yield of the spiroketal **189** (<5%). For 5,6-dimethylvalerolactone a second scheme has been suggested involving treatment of ketoalcohol **190** with potassium carbonate in methanol to form enole ether acetal **191** in quantitative yield (90JOC5894).

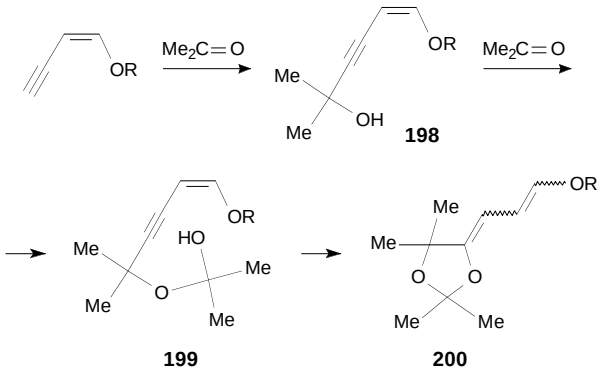


In the case of acid hydrolysis of the acetal **191** the yield of spiroketals **192** and **193** approaches 85% (under sonification).

The third synthetic scheme is employed when the phenylthio substituent is in the α-position of the lactone function, which interferes with the cyclization (90JOC5894). Acetylenic ketone **194** (95% yield) is readily transformed to the acetal **195** (with potassium carbonate in methanol); however, under the above conditions neither its hydrolysis nor cyclization to the spiroketal occurs. The spirocyclic pyrone **197** is formed in quantitative yield on treatment of **195** with *p*-toluenesulfonic acid in a 4:1 THF–H_2O mixture at reflux for 12 h.



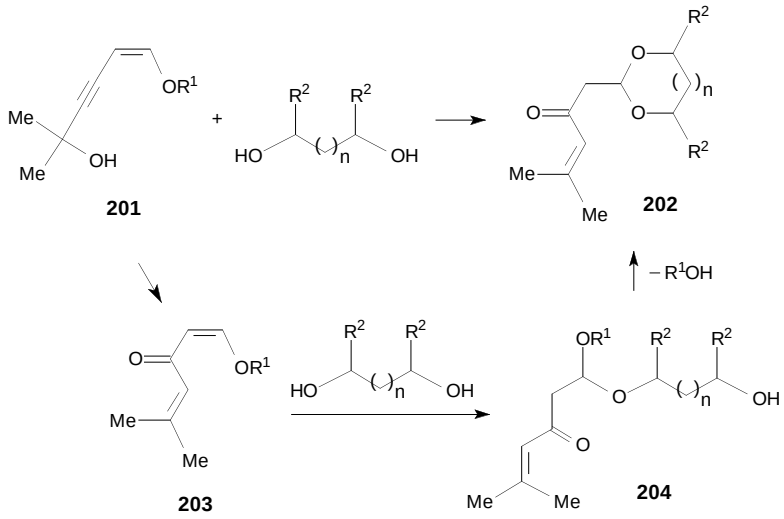
The reaction of the carbinol **198** with acetone leads to dienic 1,3-dioxolanes **200** as a result of the intramolecular addition of the hydroxyl group of the intermediate hemiacetal **199** to its triple bond (73ZOR1594).



R = Me, Et, *n*-Bu

The reaction of alkoxyenyne alcohols **201** with diols in the presence of a catalytic pair HgO/BF_3 (35°C, 1 h) gives 2-(4-methyl-2-oxo-3-pentenyl)-1,3-dioxacyclanes (**202**) in a yield of up to 64% (75ZOR516). Apparently, the reaction starts with isomerization of alkoxyenyne alcohol to alkoxydivinylketone (**203**) which adds a diol

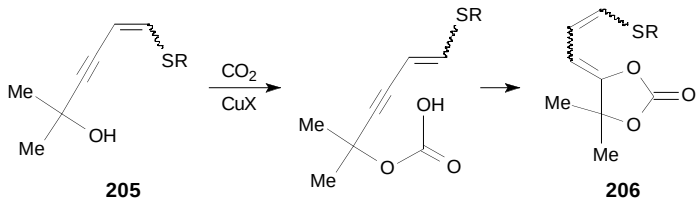
molecule at the alkoxyethenyl group to form nonsymmetric hydroxyl-containing acetal **204,** which further loses its alcohol molecule and undergoes cyclization to a 1,3-dioxolane or a 1,3-dioxane **202** (75ZOR516).



R^1 = Me, Et, *n*-Pr, *n*-Bu; R^2, R^3 = H, Me; n = 0, 1

A moderate neuroactivity of 1,3-dioxacyclanes **200** and **202** has been revealed (78KFZ61).

The reaction of tertiary alkylthioenyne alcohols (**205**) with carbon dioxide [70–73 atm, 70–75°C, Cu(I) salts, triethylamine] leads to 4,4-dimethyl-5-(alkylthioethenylmethylene)-1,3-dioxolan-2-ones (**206**) (79KGS1617; 79ZOR1319).



R = Et, *n*-Pr, *n*-Bu, *i*-Bu; X = Cl, AcO

R	Et	*n*-Pr	*n*-Bu	*i*-Bu
yield, %	88	90	77	90

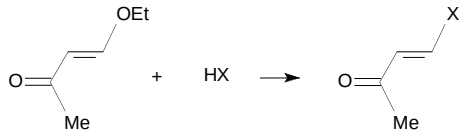
IV. Reactions of 4-Heterobut-3-en-2-ones

Enaminocarbonyl compounds and their analogs play an essential role in building heterocycles (69UK961; 74MI1).

4-Dialkylaminobut-3-en-2-ones are obtained either by hydration of 1-dialkylaminobut-1-en-3-ynes (100°C, H_2O, 5 h, yield 60–70%) (60ZOB3179; 68ZOR1138; 69ZC108; 69ZC110; 77ZC286) or by direct synthesis from diacetylene and secondary amines in an aqueous medium (80°C, yield up to 88%) (94GEP4308080). However, in the presence of 3–5% KOH at 50–70°C, 3-dialkylaminobut-2-enals $R_2NC(Me)=CH-CH=O$ (R = Me, Et, *n*-Pr, *n*-Bu) are formed in amounts of up to 46% (93USSRP1770318). Investigation of the oxygen analogs has been undertaken in an attempt to solve the diacetylene problem in industry (80MI1; 80MI2; 96ZPK353; 00ZPK619).

4-Methoxybut-3-en-2-one is formed on heating 4,4-dimethoxybut-2-one (160°C, 1 h, yield 90%) in the presence of sodium hydrocarbonate or by hydration of methoxybutenyne at 50°C in the presence of mercury sulfate (1 h, yield 60−70%) (53CB793; 60MI1; 80MI1).

The alkoxy group of 4-alkoxyalk-3-en-2-ones is readily substituted by amino and thio groups (80MI1; 84ZOR962). The reaction with ammonia as well as primary and secondary amines of the aliphatic, aromatic, and heterocyclic series proceeds either exothermally (in the case of highly basic amines) or on heating with sodium acetate (80MI1; 84ZOR962). In studying the transamination of 4-ethoxybut-3-en-2-one by primary and secondary amines (60°C, H^+, 2 h), 4-alkylamino- and 4-dialkylaminobut-3-en-2-ones were obtained (80MI1; 84ZOR962).



X = MeNH, *i*-PrNH, *t*-BuNH, PhNH, Me_2N, Et_2N, $(CH_2)_5N$, $O(CH_2CH_2)_2N$

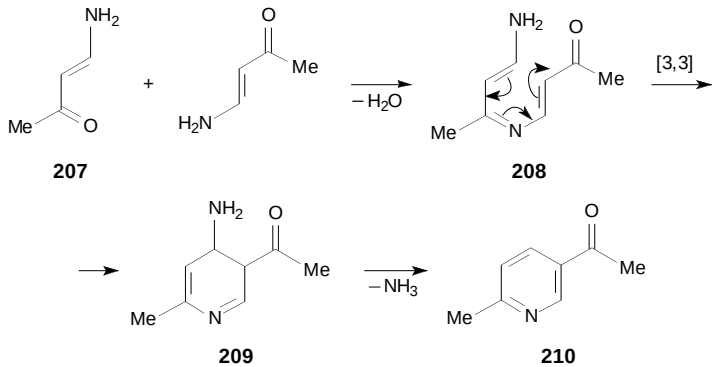
X	MeNH	PhNH	Me_2NH	Et_2NH	$O(CH_2CH_2)_2N$
yield, %	89	82	84	85	90

The kinetics of nucleophilic substitution of the methoxy group in methoxybutenone by the diethylamino group has been studied (91MI1). Thus, the reactions of 4-heterobut-3-en-2-ones with amines presented below often involve the transamination step.

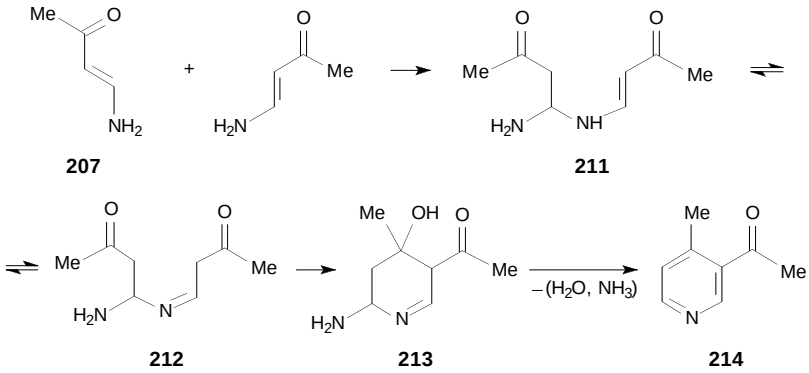
A. Reaction with Ammonia and Amines

The formation of 5-acetyl-2-methylpyridine (**210**) (yield 88%) was fixed along with an admixture of 3-acetyl-4-methylpyridine (**214**) (yield 12%) in the preparation of 4-aminobut-3-en-2-one **207** from *E*-4-ethoxybut-3-en-2-one and gaseous ammonia (−30°C, EtOH or without solvent, yield 70–75%) (80MI1; 84ZOR962; 85USSRP1122652). Pyridine **210** was also synthesized by autocondensation of aminobutenone **207** upon heating (77HOU2481; 85USSRP1122652).

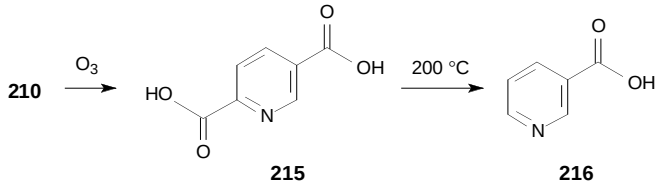
The formation of pyridine **210** appears to start with dimerization of aminobutenone **207** due to carbonyl–amino group interaction. Then the intermediate **208** undergoes [3,3]-sigmatropic rearrangement, whereupon dihydropyridine **209** eliminates ammonia.



The Michael dimerization (activated double bond–amino group interaction) affords the intermediate **211** whose tautomeric form **212** closes the tetrahydropyridine cycle **213** which undergoes aromatization with elimination of water and ammonia to isomeric pyridine **214.**

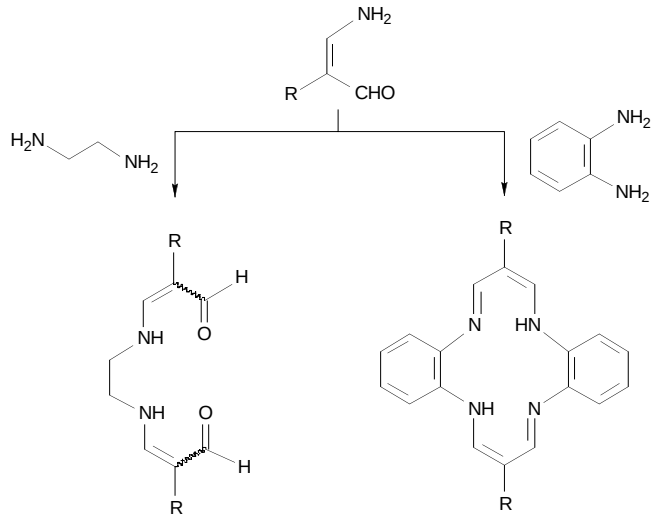


Pyridine **210** is oxidized by 20% nitric acid at the acetyl group to 2-methyl-5-pyridinecarboxylic acid, while its ozonation gives cinchomeronic acid [pyridine-2,5-dicarboxylic acid (**215**)] (75DIS) which is decarboxylated (200°C, 2 h) to nicotinic acid **216** in 97% yield (75DIS).



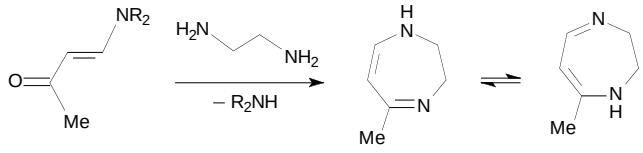
215 **216**

β-Aminoacroleins enter the transamination reaction with 1,2-diaminoethane to furnish bis adduct **217,** whereas with 1,2-diaminobenzene they yield the 2:2 macrocyclic adduct **218** (77CZ161).

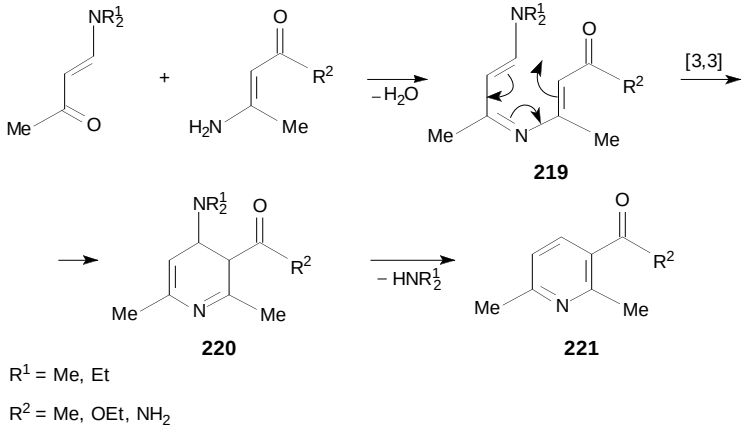


217 **218**

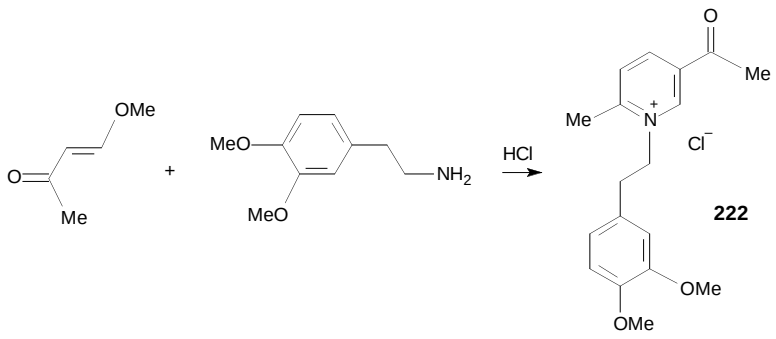
Under acid-catalyzed conditions (80°C, 10% H_2SO_4, H_2O, 3 h) dialkylamino-butenones afford a mixture of 5-methyl-2,3-dihydro-1,4-diazepine tautomers **4** in 42% yield (84DIS).



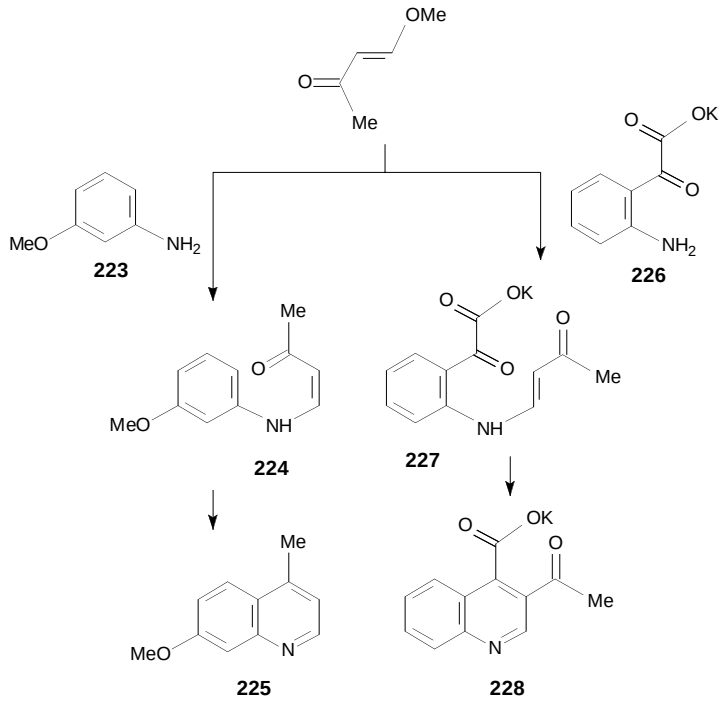
4-Dialkylaminobut-3-en-2-ones with acetylacetonimine and its analogs form only 2,6-dimethyl-3-substituted pyridines **221** (40−50°C, AcONa, AcOH, 5 h, 55%) (75DIS), seemingly via the intermediate **219** and its subsequent [3,3]-sigmatropic rearrangement to dihydropyridine **220.**



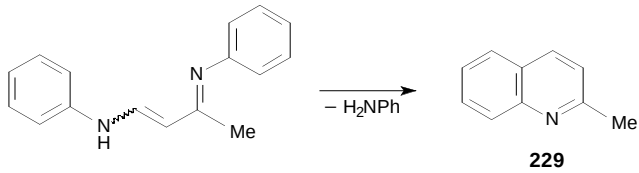
4-Methoxybut-3-en-2-one with primary amines and acids gives the pyridinium salts, e.g., **222.** In this case two molecules of methoxybutenone per one molecule of the amine enter the reaction (62M586).



In the reaction of 4-methoxybut-3-en-2-one with amines **223** and **226,** the products of methoxy group substitution **224** and **227** were isolated. Under subsequent intramolecular dehydration these products give quinoline derivatives **225** (50°C, H_2SO_4, 15 min, yield 25%) (61GEP1017613) and **228** (0°C, 35% KOH, 10 min, yield 88.7%) [65NEP6401199; 80MI2].

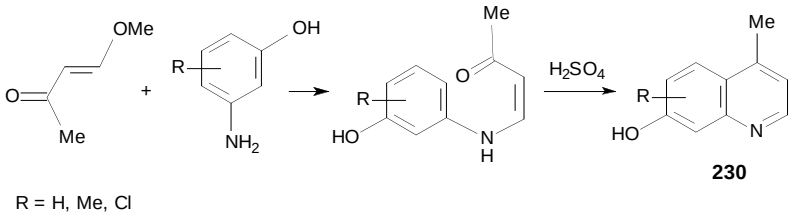


At a methoxybutenone–aniline ratio of 1:2, dianyl is formed and further undergoes cyclization with elimination of the aniline to give 2-methylquinoline (**229**) in 20% yield (60MI1).



The reactions of 4-alkoxybut-3-en-2-ones with primary aromatic amines and diamines of the aromatic and heteroaromatic series follow analogous schemes.

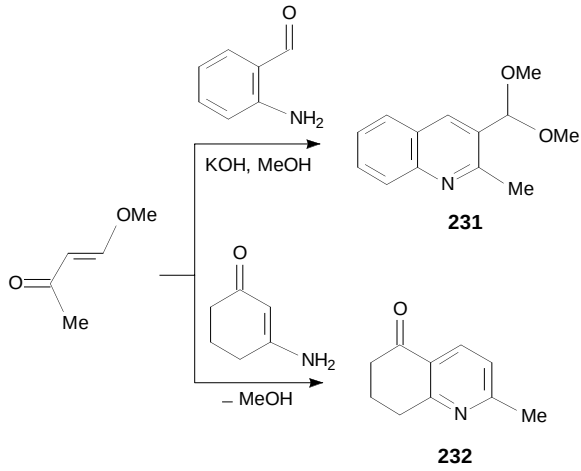
Functional amines, e.g., *m*-aminophenol, 2-methyl-2-chloro-3-aminophenol, and 4-chloro-3-aminophenol, react with 4-methoxybut-3-en-2-one to yield functional lepidine derivatives **230** (62AG161).



230

R = H, Me, Cl

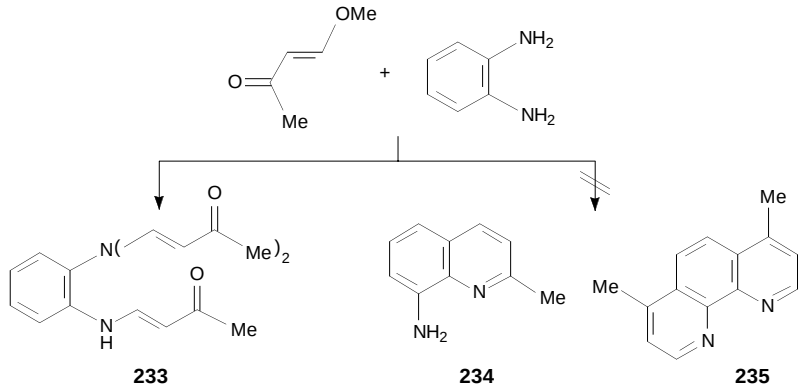
The same pathway is traced in the reaction of *o*-aminobenzaldehyde, which with 4-methoxybut-3-en-2-one forms 2-methylquinoline-3-carbaldehyde dimethylacetal (**231**) (80MI1). With 3-aminocyclohex-2-enone it gives tetrahydroquinolinone **232** in 72% yield (76BRP1432579).



231

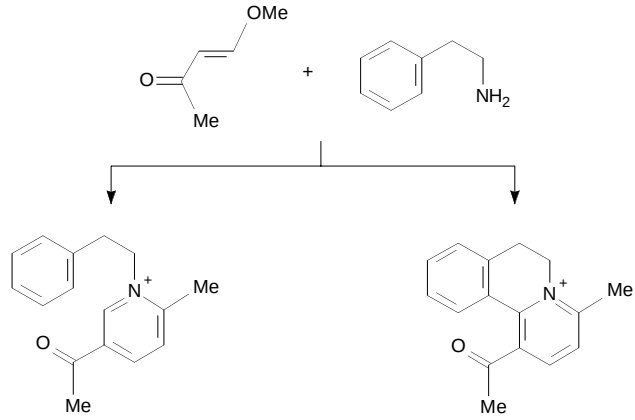
232

Surprisingly, 1,2-diaminobenzene with three molecules of 4-methoxybut-3-en-2-one forms the substitution product **233** (25°C, EtOH, 24 h, yield 90%) instead of the expected (80MI2) aminomethylquinoline (**234**) or dimethylpyridoquinoline (**235**) (80MI1; 85ZC28).



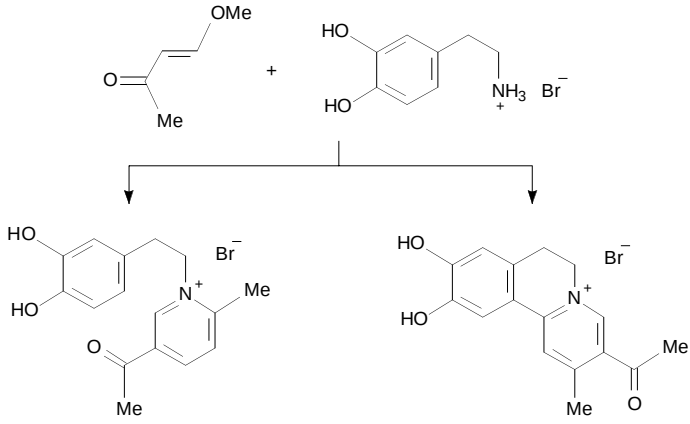
233 **234** **235**

2-Phenylethylamine and its substituted derivatives with methoxybutenone in glacial acetic acid afford the salts of the type **236,** which, when oxidized with potassium permanganate, decompose to α-pyridone, whereas in an aqueous medium the compound **237** is formed (80MI1; 62AG161).



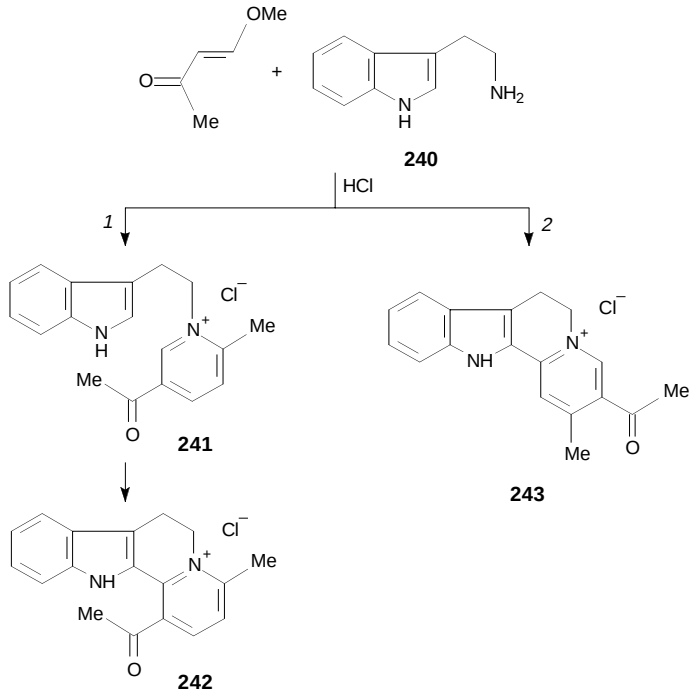
236 **237**

Analogously, 2-(3,4-dihydroxyphenyl)ethylamine hydrobromide (dopamine) with 4-methoxybut-3-en-2-one (warm acetic acid) forms pyridinium salt **238** (yield 31%) and quinolinium salt **239** (yield 40%) (64AG534; 65AG224; 80MI2). In aqueous solution at 20°C, only **239** is obtained (yield 13%).



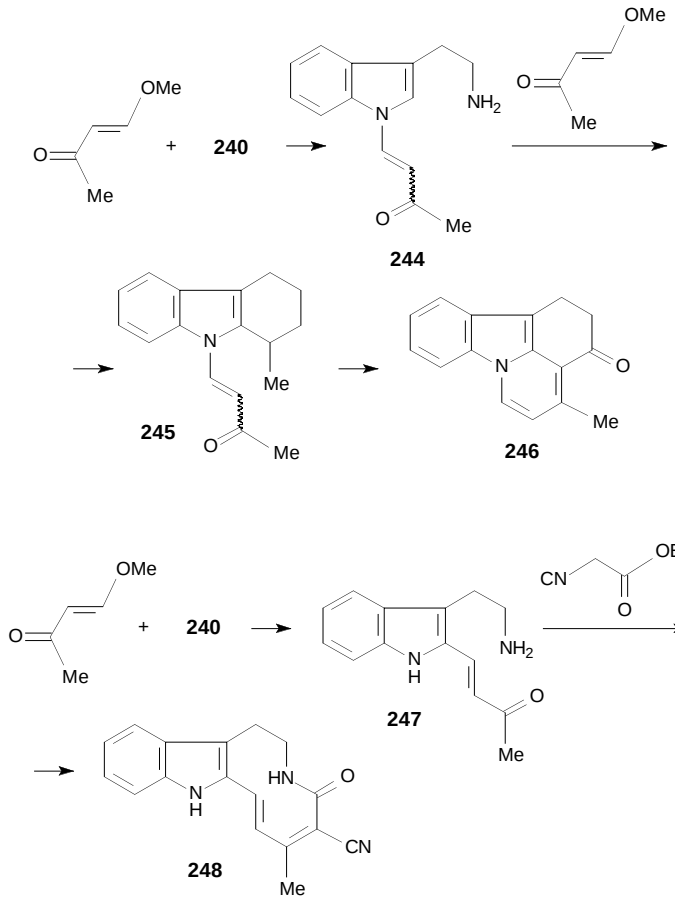
238 **239**

The reaction of methoxybutenone with 3-(2-aminoethyl)indole (tryptamine) (**240**) proceeds at both the aminoethyl group and the ring NH function (64AG534; 64CB557; 65AG224). At a 2:1 ketone–**240** ratio, the amino group reacts with the methoxyethene group and the ketone functions of the two methoxybutenone



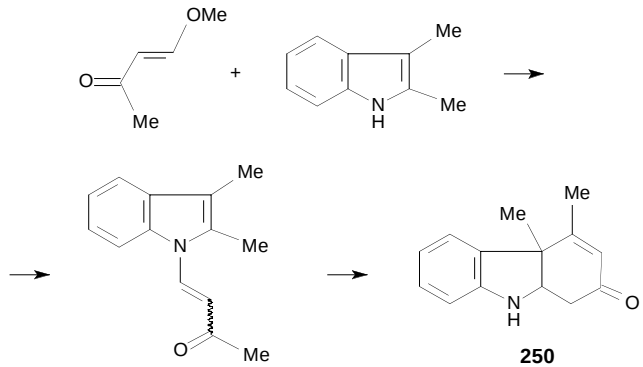
molecules to give the salt **241** (pathway 1). In the other direction, the amino group reacts only with two methoxyethene groups of the two methoxybutenone molecules to afford the salt **243** (pathway 2) (64AG534; 65AG224). Cyclization to the product **242** is effected via oxidation of the salt **241** by potassium permanganate. The salts **241** and **243** are used in syntheses of isoquinoline alkaloids. Pyridinocarbazole **243** is of interest for the synthesis of yohimbine and related compounds (62AG161).

Ketovinylation of the indole **240** NH function in concentrated hydrochloric acid results in another route of cyclization. The *N*-ketovinylindole **244** is cyclized to the tetrahydrocarbazole derivative **245** in 90% yield and further to oxobenzocarbazole **246** (62AG161).

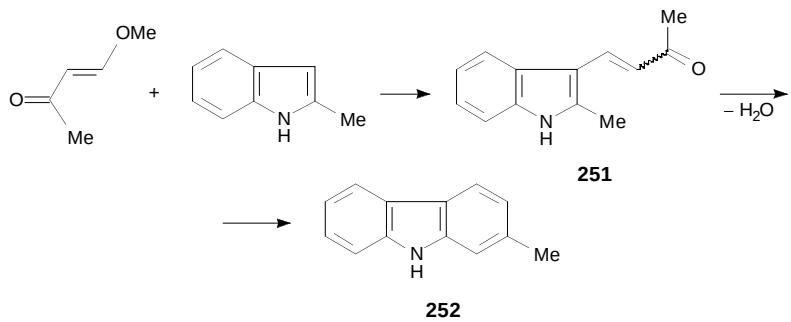


In a basic medium, it is possible to direct the ketovinylation at the α-position of the indole ring **240** to arrive at the 2-ketovinyl derivative **247** which furnishes the macrocycle **248** by condensation with cyanoacetic ester (94CZ452).

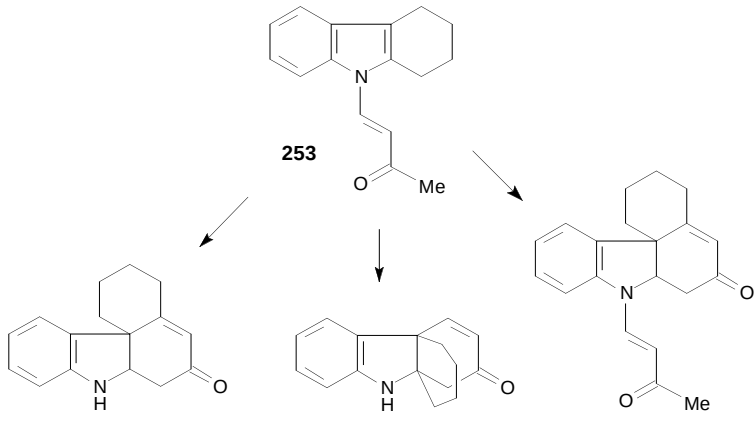
The *N*-ketovinylation of 2,3-dimethylindole and subsequent cyclization of the *N*-ketovinyl derivative **249** yield 2-keto-4,5-dimethyltetrahydrocarbazole (**250**) (65TL1703).



Interestingly, in the reaction of 2-methylindole with methoxybutenone, it is the indole β-position, rather than the NH function, that is the reaction site to form 2-methyl-3-acetoxyvinylindole (**251**), the subsequent intramolecular cyclization of which leads to 2-methoxycarbazole **252** (62TL589).

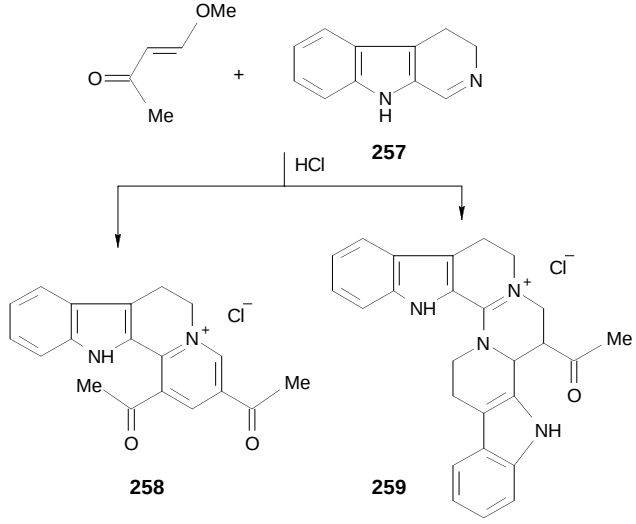


In (65TL1703; 78TL3089) there are examples of the heterocyclization of *N*-(3-oxobuten-1-yl)-1,2,3,4-tetrahydrocarbazole (**253**) obtained from methoxybutenone.



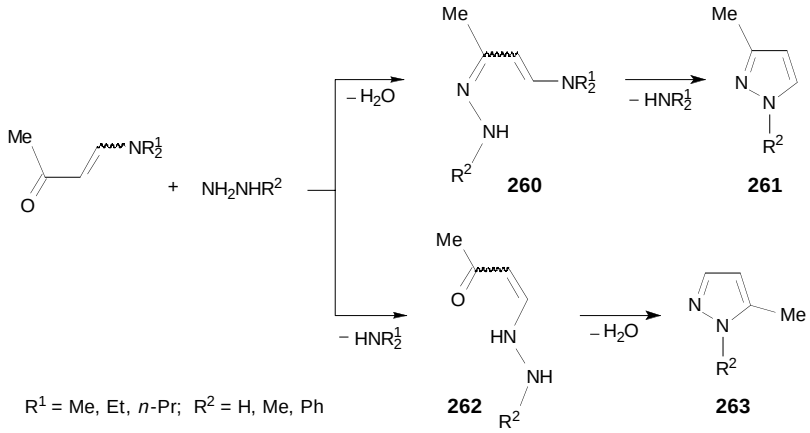
In methanol with hydrochloric acid, 78% of the major product **254** and 10–15% of its isomer **255** with a 3% *N*-oxobutenyl derivative **256** are formed.

Methoxybutenone with heterocyclic amines, e.g. **257,** condenses in either a 2:1 ratio (adduct **258**) or a 1:2 ratio (adduct **259**) (67CB1680).



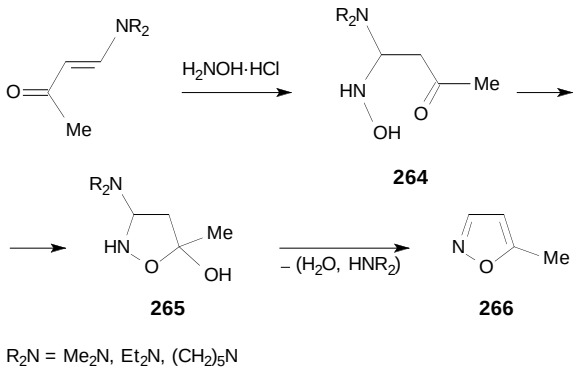
B. Reactions with Hydrazines and Hydroxylamine

The reaction of 4-diethylaminobut-3-en-2-one with monosubstituted hydrazines (95°C, H^+, MeOH, H_2O, 10 h) leads to pyrazoles **261** and **263** (yield 54%) at a ratio depending on the acidity of the medium. In an acidic medium the isomers **263** are predominantly obtained (76ZOR2063). Aminobutenones with hydrazine give only 5-methylpyrazoles (**263**) (69ZOR223). Enhydrazones **260** and **262** appear to be the synthesis intermediates.

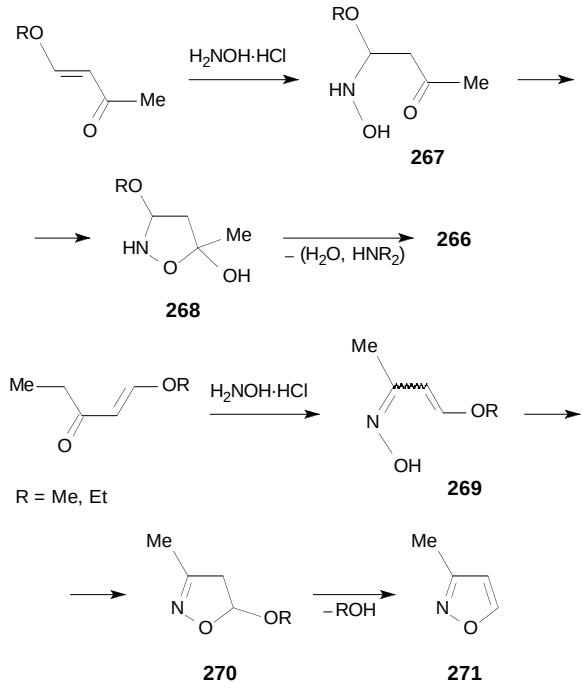


A synthesis of pyrazolopyrimidines from methoxybutenone has been patented (99WO54333).

With hydroxylamine, aminobutenones yield exclusively 5-methylisoxazole (**266**), evidently via the intermediates **264** and **265** (69ZOR223).



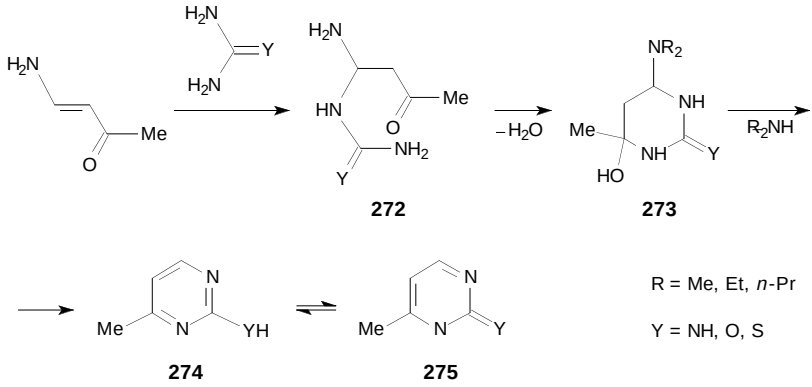
Alkoxybutenones in the same reaction give the two isomeric isoxazoles **266** and **271;** i.e., along with the intermediates **267** and **268,** the formation of intermediates **269** and **270** takes place (70ZOR2371).



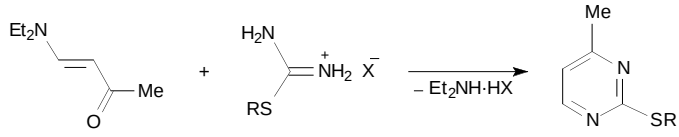
C. Reactions with Amides and Nitriles

Guanidine, carbamide, and thiocarbamide react with aminobutenones to afford tautomeric pyrimidines **274** and **275** (60ZOB1258; 65CB1081; 74MI1; 85KGS1443). The pyrimidine ring formation is thought to involve transamination (intermediate **272**) and subsequent condensation of a free amino group with the carbonyl function (intermediate **273**) (60ZOB1258).

The reaction is carried out in both acidic and basic media. Thus, for example, the interaction of 4-diethylaminobut-3-en-2-one with thiocarbamide is performed at 75°C for 30 h (EtOK, EtOH) to result in 54% yield of the major product. The existence of two tautomers **274** and **275** was proved for 2-mercapto-4-methylpyrimidine (Y = S) by IR and ^{1}H NMR spectroscopy (76ZOR2063).



The condensation of 4-diethylaminobut-3-en-2-one with 5-alkylisothiuronim salts proceeds in the presence of catalytic amounts of acids (60−90°C, 1 h) to afford high yields of 2-alkylthio-4-methylpyrimidines (**276**) (76ZOR2063).



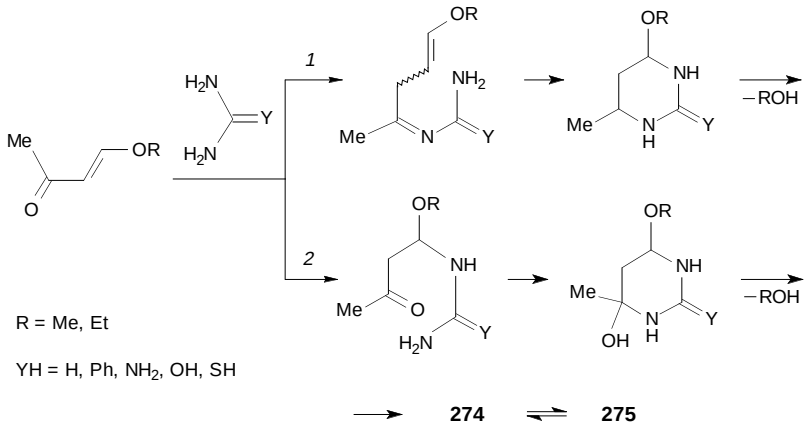
R = Me, Et, *i*-Bu, CH_2=$CHCH_2$

X = Cl, Br, I

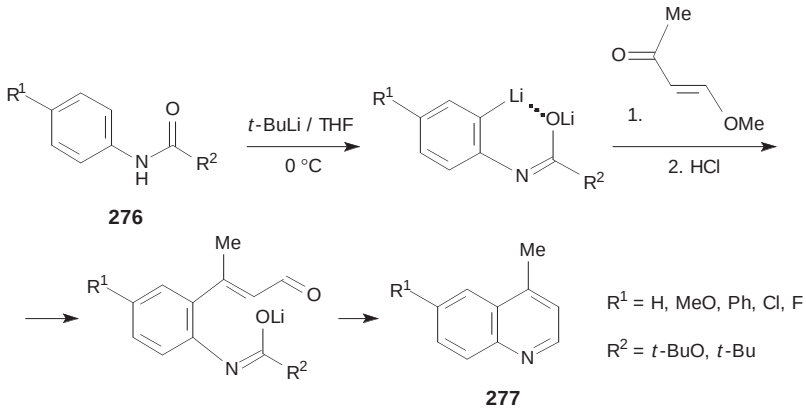
R	Me	Et	*i*-Bu	CH_2=$CHCH_2$
yield, %	60	70	67	85

More pyrimidines were obtained from methoxybutenone than from enaminoketones (60MI1; 60ZOB1258; 65CB1081; 80MI1; 80MI2). The syntheses are preferably carried out in an alkaline medium (100–200°C, Na, EtOH, 15 h). 4-Methylpyrimidine was obtained (60MI1) from 4-ethoxybut-3-en-2-one and formamide (180°C, NH_4Cl, 5 h, yield 70%). 2-Amino-4-methylpyrimidine was prepared from 4-ethoxybut-3-en-2-one and guanidine in 51% yield, whereas from 4,4-dimethoxybutan-2-one the yield amounted to 95% (60MI1). 2-Phenyl-4-methylpyrimidine was synthesized from 4-ethoxybut-3-en-2-one and benzamidine in 53% yield (60MI1).

In an alkaline medium the condensation of carbonyl and amino groups of the reactants seems to be more probable (pathway 1), although pathway 2, which is identical to the reactions of enaminoketones, is also possible.

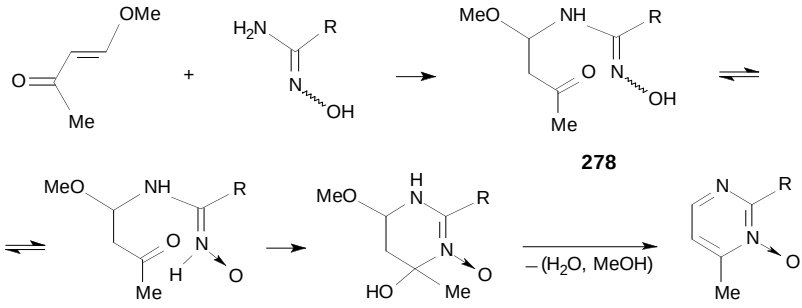


A synthesis of 4-methylquinolines **277** by the modified Friedlander reaction from *ortho*-lithiated anilides **276** and 4-methoxybut-3-en-2-one (−20°C, THF, pentane, 2 h) in 14–17% yields (in the cyclization stage) has been described (91JOC7288).



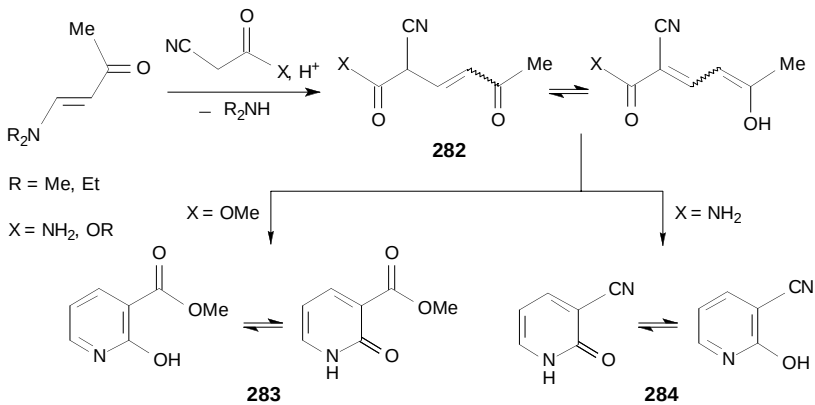
A process for the preparation of pyrimidine *N*-oxides from carboxamide oximes has been developed (98T4387). Direct oxidation of pyrimidines is inconvenient for the preparation of nonsymmetric substituted pyrimidines because it gives a mixture of oxidation products (1-*N*- and 3-*N*-oxides). Methoxybutenone with carboxamide oximes regioselectively forms *N*-oxides of pyrimidines **281,** which indicates

primary attack of the methoxyethene moiety of the molecule by the amino group (intermediate **278**) rather than by the oxime function. The reaction is completed by intramolecular addition of the nitrone function **279** (tautomeric form of the oxime **278**) to the carbonyl group with subsequent aromatization of the *N*-oxide of tetrahydropyrimidine **280** by elimination of water and methanol (98T4387). The yield of pyrimidine *N*-oxides **281** (*i*-PrOH, CF_3CO_2H, reflux, 2–17 h) is within 45–60%.



R = $ClCH_2$, 4-$F_3CC_6H_4$, 2-$MeOC_6H_4CH_2$

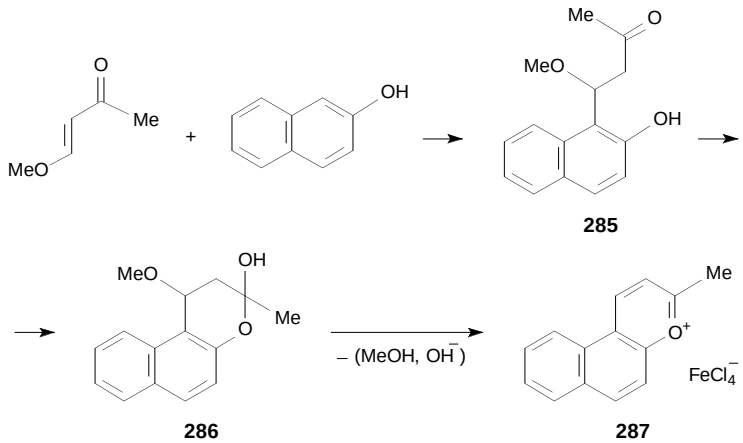
The reaction of aminobutenone with cyanoacetic ester (73IZV2543) and cyanoacetamide affords pyridine derivatives **283** and **284** in 65–76% yield (54IZV47; 72JPR353).



It is believed (54IZV47; 72JPR353) that in the first stage the intermediate **282** is formed due to the addition of the CH acid to the enamine moiety with subsequent elimination of amine. The enol form of the intermediate **282** undergoes cyclization in two fashions, depending on the nature of substituent X. In the case of the ester (X = OMe) the attack is directed to the cyano group to form substituted 3-methoxycarbonyl-1*H*-pyridin-2-one (**283**) or its tautomer (2-hydroxy-3-methoxycarbonylpyridine). With the amide (X = NH_2) intramolecular condensation leads to 3-cyano-1*H*-pyridin-2-one and its hydroxy tautomer (**284**).

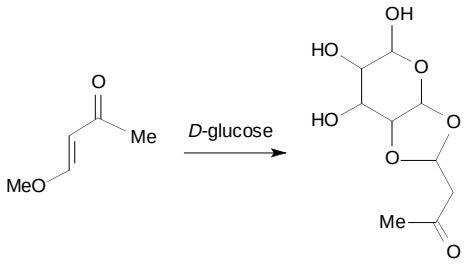
D. Reactions with Oxygen- and Sulfur-Containing Functions

The reaction of methoxybutenone with 2-naphthole ($FeCl_3$/HCl) involves the addition of the latter to the double bond (adduct **285**), cyclocondensation to give hemiacetal **286,** and the formation of 2-methyl-5,6-naphtho-(1,2)-pyrylium ferrochlorate (**287**) (60MI1).



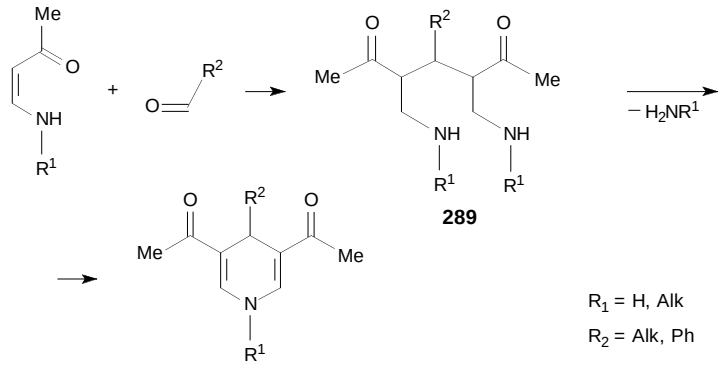
1,3-Dioxolane derivatives, which are obtained from methoxybutenone and glycols and used as antifungicides, and squalene synthetase inhibitors have been described (94MI1). The reactions of mono- and oligosaccharides with

methoxybutenone and its analogs lead to the corresponding acetylmethyldioxolanes, e.g., **288** (from D-glucose) (93MI1).



288

Aminobutenones of *Z*-configuration having at least one hydrogen atom attached to the amino group (80MI1) condense with aldehydes (EtOH, piperidine acetate, 25°C, 12 h) in 2:1 ratio to form 1,4-dihydropyridine derivatives **290** (50NKZ1061).

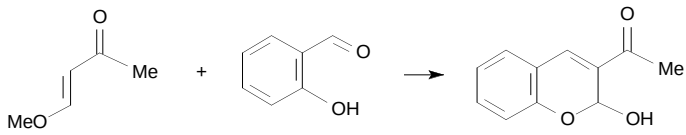


289

290

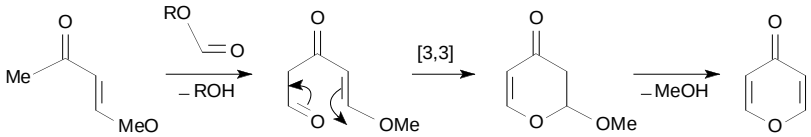
Evidently, the reaction proceeds via the formation of bis-adduct **289** which undergoes cyclization to dihydropyridine **290.** A similar reaction with methoxybutenone, but in the presence of ammonia, which is likely to involve replacement of methoxy group, has been described (80MI2).

The reaction of methoxybutenone with salicylic aldehyde (20°C, MeOK, toluene, MeOH, 15 h) affords 3-acetyl-2-methoxy-chromo-3-ene (**291**) in 14% yield (80MI1).



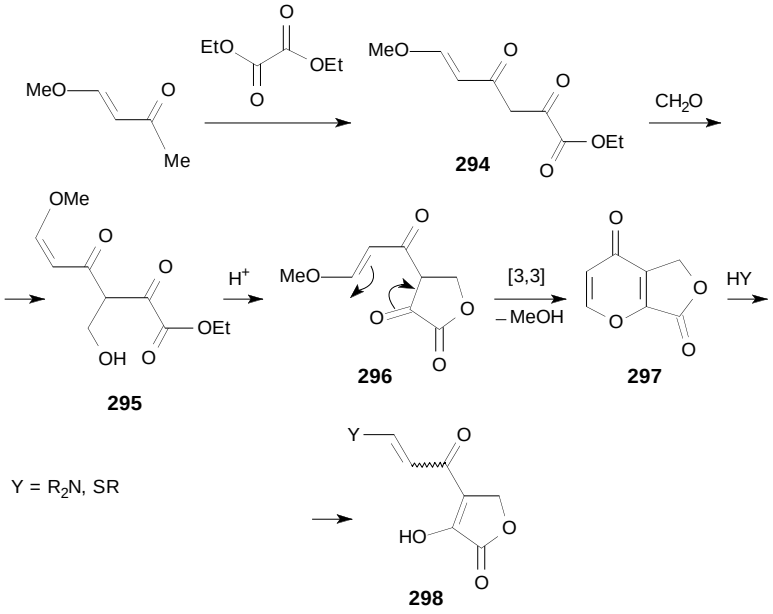
291

Preparation of γ-pyrone by the reaction of methoxybutenone with formic acid esters (10°C, MeONa, C_6H_6, 1.5 h) has been reported (73JPP7229512; 80MI2). The intermediate **292** undergoes [3,3]-sigmatropic rearrangement to form methoxydihydropyrone **293** which further eliminates methanol, thus transforming to γ-pyrone.

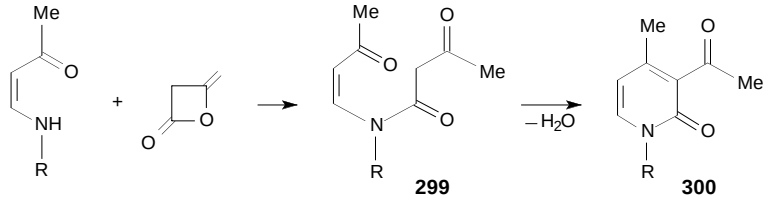


292 **293**

The condensation of alkoxybutenones with esters has been employed for the synthesis of other oxygen-containing heterocycles. Thus, methoxybutenone with oxalic acid esters gives adduct **294** (68BSF2015; 80MI2). The latter undergoes aldole condensation with formaldehyde to furnish alcohol **295** which in an acidic medium is cyclized to furanodione **296** and further to furanopyridone **297.** The ring opening of **297** by amines or mercaptans gives dihydrofuranone derivatives **298** [71CR(C)107].



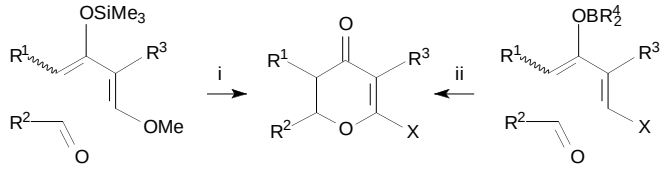
From monoalkylaminobutenones and diketene at −5°C in benzene 3-acetyl-4-methyl-2(1*H*)-pyridones **300** are formed via the intermediate amides **299** (80MI1).



R = H, Me, Et, *i*-Pr, *n*-Bu

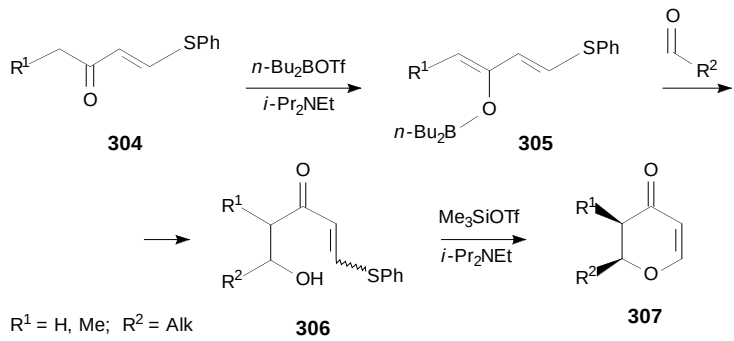
R	H	Me	Et	*i*-Pr	*n*-Bu
yield, %	53	46	38	80	61

Dihydropyrones **302** are used as intermediates in the syntheses of tetrahydropyrane. There are two approaches (i, ii) to their preparation [74JA7807; 84AG991; 85JA1246; 86JA7060; 86MI1; 87AG(E)15].



One (i) is the diastereoselective synthesis developed by the Danishevsky group, which is based on the reaction of trimethylsiloxydienes prepared from methoxybutenones and aldehydes (from fragments **301**) (−78°C, 4 h) with Lewis acids as catalysts, including Eu(fod)$_3$ [tris-(6,6,7,7,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato]europium(III)] (85JA1246; 86JA7060). Another (ii) is the asymmetric synthesis of **302** from aldehydes and dienole borinates (from fragments **303**) (90TL2213).

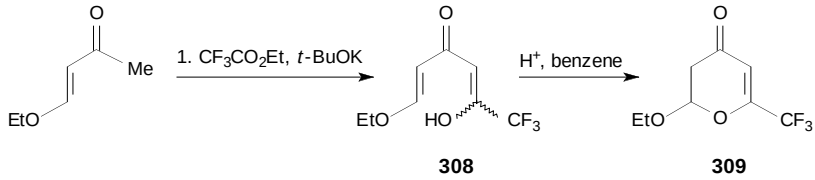
The aldol condensation of phenylthiobutenone **304** with aldehydes in CH_2Cl_2 via dienodibutylborinates **305** leads to the adduct **306** in 61% yield (diastereoselectivity >97%) (90TL2213).



The cyclization of **306** promoted by trimethylsilyl triflate and diisopropylethylamine gives *cis*-dihydropyrones **307.** Under these conditions methoxybutenone fails to form the aldol condensation product **305** (90TL2213).

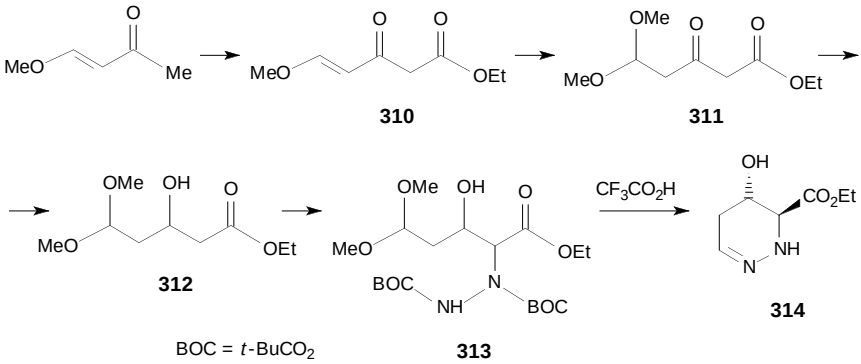
A synthetic procedure to insert the perfluoroalkyl group into the dihydropyrone cycle via ethoxybutenone has been elaborated (98T2819). 6-Ethoxy-2-trifluoromethyl-4*H*-pyran-4-one (**309**) was synthesized by the condensation of ethyl

trifluoroacetate with ethoxybutenone via the intermediate **308.** The yield in the final stage is 87% (98T2819).



308 **309**

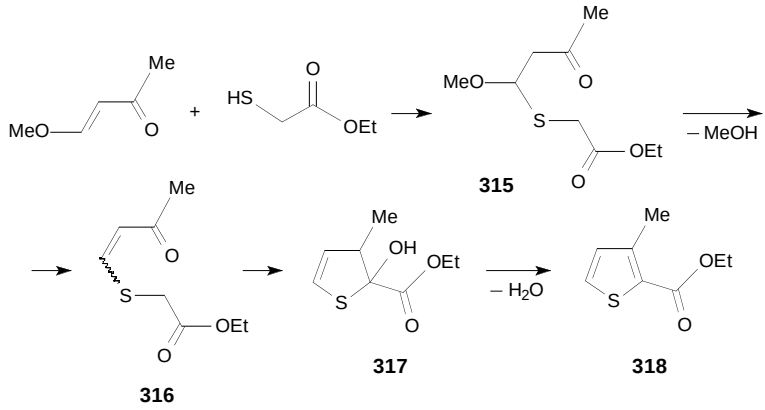
A five-step synthesis of ethyl ester of cyclic hydrazonic acid **314** used in the synthesis of natural products has been described [94JCA(CC)1867]. The condensation of methoxybutenone with $EtCO_2CN$ (*t*-BuOK, THF, −78°C) is completed with the formation of ketoester **310** in 72% yield. The addition of methanol to the latter (Triton B, MeOH, room temperature, 88%) and the reduction with $NaBH_4$ (EtOH, −78°C) leads to the alcohol **312,** yield 90%. The dianion of **312** (LDA, THF, −78°C) reacts with *t*-butylazodicarboxylate (*t*-BuO_2C─N═N─CO_2Bu-*t*) to form adduct **313,** the treatment of which with trifluoroacetic acid affords the ester **314** in 55% yield [94JCA(CC)1867].



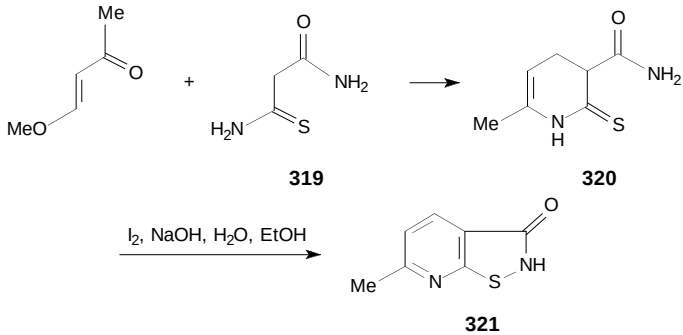
310 **311** **312** **313** **314**

BOC = *t*-$BuCO_2$

Substitution of the methoxy group in methoxybutenone with mercaptoacetic acid ester results in 4-(ethoxycarbonylmethylthio)-4-methoxybutan-2-one (**315**) which further eliminates methanol to give butenone **316.** The latter forms 2-ethoxycarbonyl-3-methylthiophene (**318**) via dehydration of the intermediate **317** (80MI1).



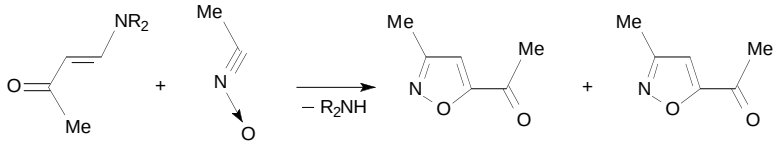
The synthesis of 2,3-dihydro-5-oxaisothiazole[5,4-*b*]pyridine **321** was performed from monothiomalonamide (**319**) and methoxybutenone (85S861). 2-Thioxo-1,2-dihydropyridine-3-carboxamide **320** forming in the first stage (piperidine–acetate, EtOH, 10 h, yield 87%) was further oxidized to isothiazolopyridine **321,** yield 95%.



E. Reactions with 1,3-Dipoles

From amino- and alkoxybutenones and benzonitrile *N*-oxide as well as from acetyl- and ethoxycarbonyl-*N*-phenylnitrilamines and *p*-methoxyphenyl azide, the corresponding functional isoxazoles, pyrazoles, and triazoles were obtained (83DIS; 83ZOR2281; 92SC2902).

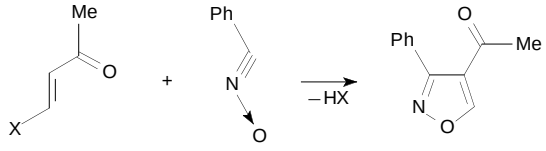
Acetonitrile oxide regioselectively reacts with dialkylaminobutenones to form 5-acetyl-3-methylisoxazole (**322**) and a small amount of 4-acetyl-3-methylisoxazole (**323**) (92SC2902).



322 **323**

R = Me, Et

The reaction of 4-dialkylamino(alkoxy)but-3-en-2-one with benzonitrile *N*-oxide (35°C, Et_2O, 8 h) follows a scheme of 1,3-dipolar cycloaddition with elimination of ammonia, the corresponding amine, or alcohol to form 3-phenyl-4-acetylisoxazole **324** in 60–67% yield (83ZOR2281).



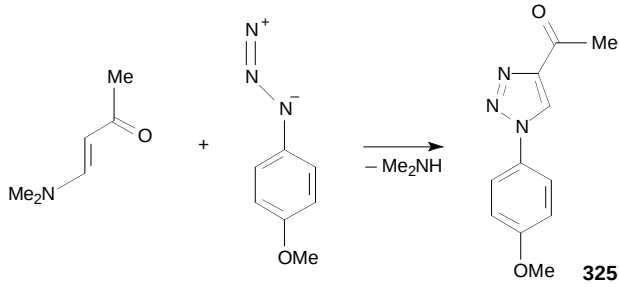
324

X = NH_2, Me_2N, Et_2N, $(CH_2)_5N$, EtO

X	H_2N	Et_2N	EtO
yield, %	67	66	60

The reaction of amino- or alkoxybutenones with acetyl- and ethoxycarbonyl-*N*-phenylnitrilamines (35°C, Et_2O, 10 h) leads to 4-acetylpyrazoles in 54–90% yield (83ZOR2281).

4-Dimethylaminobut-3-en-2-one reacts with *p*-methoxyphenyl azide (80°C, benzene, 15 h) in accordance with the electron density distribution in the initial compounds to form 1-(*p*-methoxyphenyl)-4-acetyltriazole (**325**) in 96% yield (83ZOR2281).

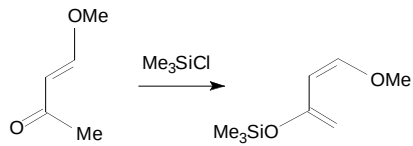


325

Thus, 4-amino- and 4-alkoxybut-3-en-2-ones react with 1,3-dipoles involving only the carbon–carbon double bond, the negative part of the 1,3-dipole adding to position 4 of the butenone. The heterocyclizations are accompanied by elimination of the 4-hetero group.

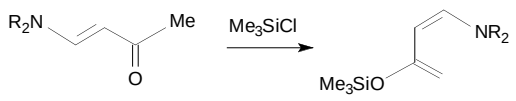
F. Other Cycloaddition Reactions

From methoxybutenone and chlorotrimethylsilane, 1-methoxy-3-trimethylsiloxybuta-1,3-diene (the Danishevsky diene) (**326**), a synthon in the Diels–Alder reactions, is obtained (Et_3N, 20 h, yield 76%) (79JPP7948765; 86MI1).



326

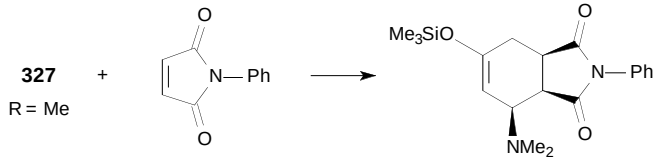
Highly reactive 1-amino-3-trimethylsiloxybuta-1,3-dienes (**327**) prepared from aminobutenones are also used for this purpose (99JOC3039).



327

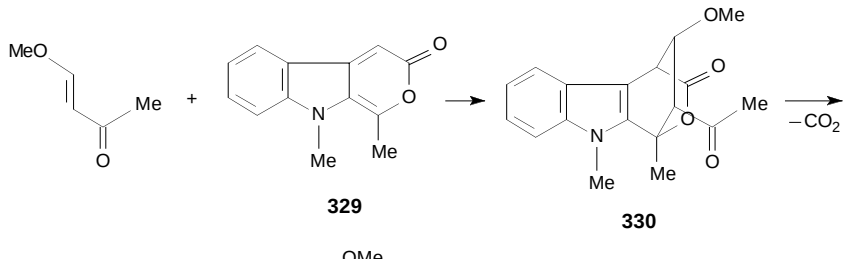
R_2N	Me_2N	Et_2N	i-Pr_2N	N
yield, %	92	95	85	89

For instance, in the reaction of a diene **327** with *N*-phenylmaleimide, which proceeds by the [4+2]-cycloaddition route at −70°C in toluene, the endo-adduct **328** is formed in 96% yield (99JOC3039).

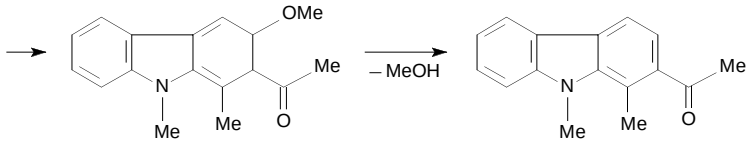


328

Pyrano[3,4-*b*]indol-3-one (**329**) enters the Diels–Alder reaction with methoxybutenone as an electron-rich olefin [92JCS(P1)415]. After decarboxylation of the primary adduct **330**, 2-acetyl-3-methoxy-1,9-dimethyl-2,3-dihydrocarbazole (**331**) eliminates methanol to form 2-acetyl-1,9-dimethylcarbazole (**332**) [92JCS (P1)415].

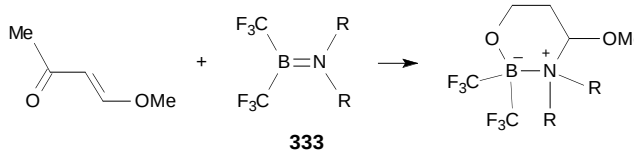


329 **330**



331 **332**

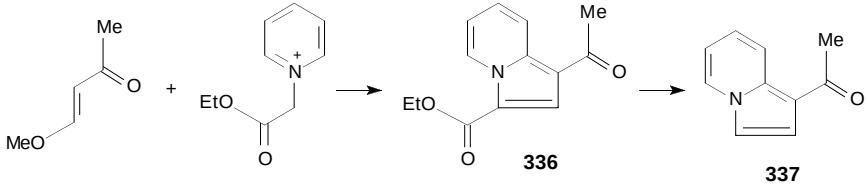
The [2+4] cycloaddition of dialkylaminobis(trifluoromethyl)boranes (**333**) to methoxybutenone (0°C, pentane, 1 h) leads to nitrogen–boron–oxygen six-membered heterocycles **334** in 60% yield (90JOM253).



R - alkyls

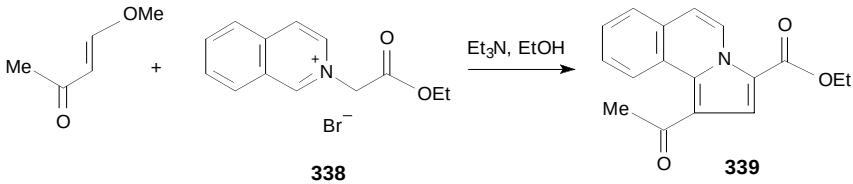
333 **334**

The pyridinium salt **335** with methoxybutenone (30°C, Et_3N, EtOH, 9 h) gives 1-acetylindolizino-3-carboxylate (**336**) in 46% yield, which further transforms to 1-acetylindolizine (**337**) [(1) NaOH, MeOH; (2) polyphosphorous acid] in 67% yield (90JHC263).



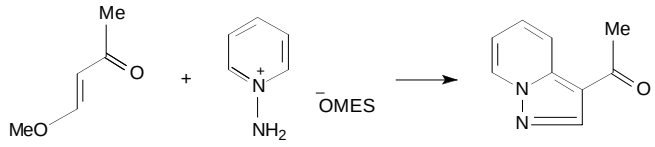
335 **336** **337**

The same reaction with the isoquinolinium salt **338** (under the same conditions) furnishes 1-acetyl-3-ethoxycarbonylpyrrolo[2,1-*a*]isoquinoline (**339**) in 72% yield.



338 **339**

1-Acetylpyrazolo[1,5-*a*]pyridine (**341**) was synthesized by a similar reaction of 1-aminopyridinium salt **340** with methoxybutenone (25°C, Et_3N, EtOH, 5 h) in 37% yield (90JHC263).

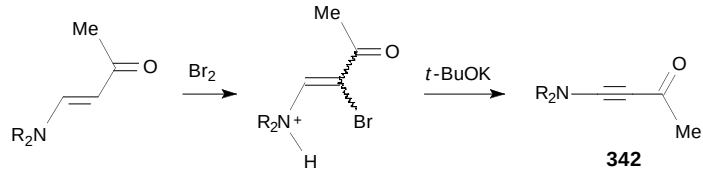


340 **341**

OMES = mesitylenesulfonate

V. Reactions of 4-Aminobut-3-yn-2-ones

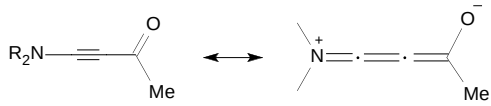
4-Dialkylaminobut-3-yn-2-ones (**342**) can be prepared from 4-dialkylaminobut-3-en-2-ones by the bromination–dehydrobromination procedure (69HCA2641; 87ZOR1635).



342

R = Me, Et; R_2 = $O(CH_2)_4$

It is known (89ZOR698) that in the case of en- and ynaminocarbonyl compounds there is a significant deviation toward decreasing the ^{13}C–^{13}C J_{CC} coupling constants from the values calculated by the additive scheme. This phenomenon is caused by leveling off the bond multiplicity due to direct polar conjugation of the lone electron pair of the nitrogen atom and the π-system of the carbonyl group through the triple bond (91UK103), thus distinguishing this class of compounds from simple ynamines (69MI2).



The contribution of the dipolar resonance form is about 30% for enaminocarbonyl compounds and exceeds 59% for the acetylene analogs (89ZOR698).

Analysis of the ^{13}C NMR chemical shifts of the triple bond carbon atoms of the substituted ynamines and comparison of these data with the corresponding values for compounds of the ethylene series suggest the presence of counterpolarization

of the orthogonal π-system of the triple bond in ynamines containing electron-withdrawing groups. This effect is expressed by an anomalously low contribution from the dialkylamino group to the shielding of the triple bond carbon nearest to the nitrogen atom (89ZOR698).

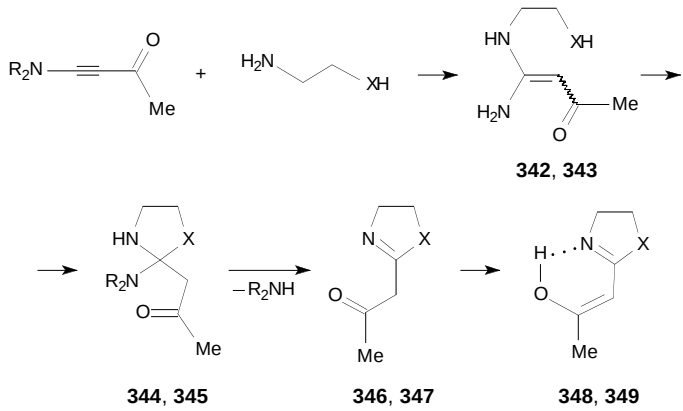
The data on the structure of conjugated ynaminoketones indicate that the electron density distribution, and consequently the reactivity, of these compounds is greatly influenced by the conjugation of electron-donating and electron-withdrawing groups through the triple bond. This influence is responsible for the specific properties of dialkylaminobutynones and accounts for their differences from ynamines (91UK103; 92KGS867) or acetylenic ketones.

This section deals with the reactions of 4-dialkylaminobut-3-yn-2-ones representing diacetylene derivatives (69HCA2641; 87ZOR1635; 91UK103; 92KGS867; 00UK642).

A. Reactions with Nitrogen-, Oxygen-, and Sulfur-Containing Dinucleophiles

1. *Aliphatic Dinucleophiles*

The aminobutynones **342** contain a push–pull system with a strongly electron-withdrawing carbonyl group; therefore, they show electrophilic properties. Cyclizations with their participation proceed differently from those with ynamines (91UK103; 00UK642) and acetylenic ketones (73UK511).



X = NH (**342**, **344**, **346**, **348**); O (**343**, **345**, **347**, **349**)

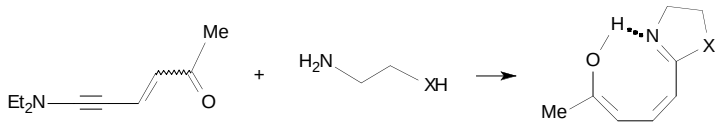
With 1,2-diaminoethane or 1-amino-2-hydroxyethane, for example, 4-dialkylaminobut-3-yn-2-ones react in THF solution at 65–70°C without catalyst (2 h) to form the corresponding 2-(acetylmethyl)-1,3-imidazolines (**346**) (70% yield) and 2-(acetylmethyl)-1,3-oxazolines (**347**) (61% yield), respectively (88USSRP1330133; 88ZOR1165).

Apparently, cyclization involves the formation of open-chain intermediates **342, 343,** further closing up to imidazolidines **344** and oxazolidines **345** which eliminate the secondary amine, thus leading to imidazolines **346** and oxazolines **347.** The latter exist in the solution exclusively in the enolic forms **348, 349** which are stabilized by conjugation and intramolecular hydrogen bonds.

In the ^{1}H NMR spectra of compounds **348, 349,** the methyl group is a singlet lying at 1.84−1.90 ppm, the olefin proton signal lies at 4.67−4.75 ppm, and the hydroxyl proton gives rise to a broadened signal in low field at 9.09−9.79 ppm. The imidazoline **348** CH_2 protons cause a multiplet signal at 3.55 ppm. In the oxazoline **349,** the CH_2O methylene group triplet is lower field shifted (4.38 ppm) compared to the CH_2N proton signal (3.70 ppm). The proton at the ring nitrogen atom gives rise to a broadened signal at 5.66 ppm.

The imidazolines containing a completely enolyzed acetyl group have also been described in [84JCS(P1)2599]. These enoles are too stable to allow recognition of the ketone form, even by varying the solvent [84JCS(P1)2599].

Aminoenyne ketones **350** (90ZOR2508) react with 1,2-diaminoethane and 1-amino-2-hydroxyethane analogously as a twofold nucleophilic attack at the triple bond followed by elimination of diethylamine to afford imidazolines **351** and oxazolines **352,** which also contain a strong hydrogen bond and a completely enolyzed vinylacetyl group (92KGS1409; 94ZOR51).



350 **351**, **352**

X = NH (**351**); O (**352**)

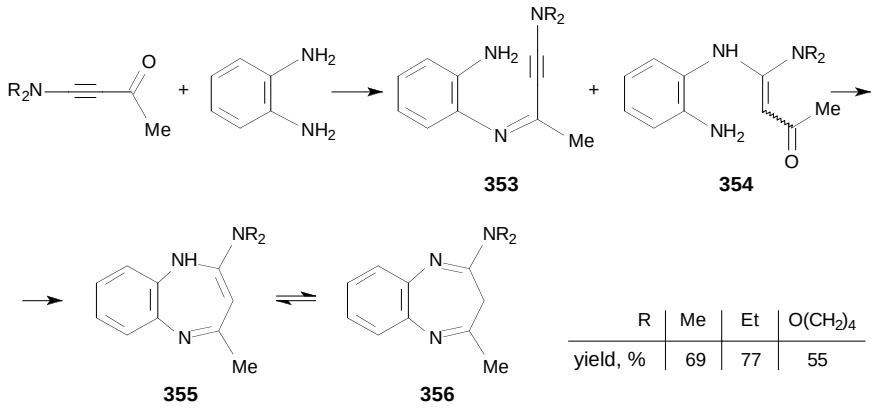
The reaction was carried out in THF at 65–70°C (3 h). In the ^{1}H NMR spectrum of imidazoline **351** the methyl protons appear as a singlet at 2 ppm. The vinyl protons are represented by doublets in the region of 5 (J = 7 Hz), 6 (J = 9 Hz), and 7 ppm. The imidazoline ring methylene protons give rise to a singlet at 4 ppm. The IR spectrum of this imidazoline shows absorption bands that confirm the

enol structure: 1600–1620 cm^{-1} (conjugated double bonds) and 3400–3600 cm^{-1} (a broad band corresponding to the associated hydroxyl group).

In these reactions, the formation of imidazoline and oxazoline rings corresponds to the reagent orientation previously observed for ynamines (84ZOR1648) and alkenylynamines (83ZOR926), as well as in their reactions with mononucleophiles such as amines (79ZOR1824; 81ZOR1807) and alcohols (80ZOR1141).

2. *Aromatic Dinucleophiles*

With aromatic dinucleophiles, ynaminoketones react in a principally different manner. Weakening of the nucleophilic properties of the reagent containing vicinal amino groups in going from 1,2-diaminoethane to 1,2-diaminobenzene leads to a change in the reaction character: Instead of imidazolines, seven-membered heterocycles, 7(8)-*R*-2-dialkylamino-4-methyl-3*H*-1,5-benzodiazepines (**356**) are formed (60–70°C, THF, 3–7 h) in 55–77% yield (88USSRP1330133; 88USSRP1362732; 88ZOR1165).



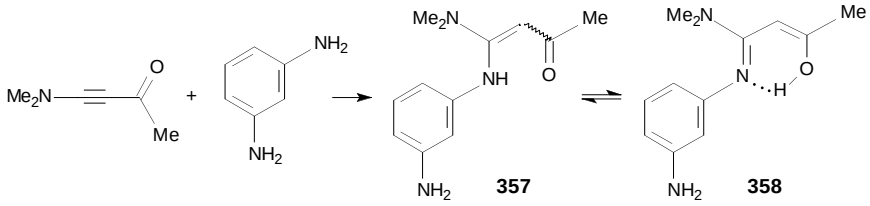
R	Me	Et	$O(CH_2)_4$
yield, %	69	77	55

R = Me, Et; $R_2 = O(CH_2)_4$

It is likely that initially the open-chain adducts **353** and **354** are formed by the addition of an amino group either to the carbonyl function or to the triple bond, whereupon these intermediates close up to the azepines **355** and their bis-imine tautomers **356**. In the ^1H NMR spectra, the methylene protons of **356** are at 2.85–2.97 ppm, whereas the methyl protons are fixed at 2.20–2.27 ppm. The IR spectra show absorption bands corresponding to the aromatic ring (1600 cm^{-1}) and to the diazepine cycle C=N double bonds (1580 cm^{-1}). However, there are no bands of

the NH function. This indicates that the diazepines exist in the bis-imine form as the most advantageous for such systems (79MI1).

To determine the site of the aromatic diamine primary attack at the ynaminoketones, the reaction of 4-dimethylaminobut-3-yn-2-one with *m*-phenylenediamine was examined in an ^{1}H NMR spectrometer ampoule (91UK103; 92KGS867). It turned out that in a $CDCl_3$ solution at 60°C *m*-phenylynediamine slowly adds to the triple bond to form tautomers **357** and **358,** the latter predominating (91UK103; 92KGS867).

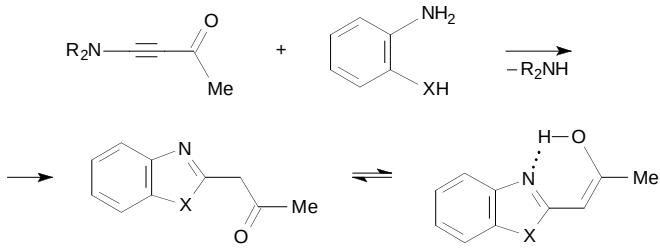


In the ^{1}H NMR spectrum of the adduct **358,** the hydroxyl proton gives a broadened signal in low field (11.7 ppm). This is not the signal of the nitrogen atom proton of the **357** form, since in aromatic amines these signals lie in higher field. For example, the protons at the *m*-phenylenediamine nitrogen atom are observed at 3.54 ppm, and those of **357** are located within the 3.6–3.7 ppm range. The ethylenic proton appears as a singlet at 4.7 ppm and the methyl proton signal is higher field displaced (1.95–2.00 ppm) compared to the signal of the initial ketone (2.13 ppm). The dimethylamino protons give a signal at 2.7 ppm, the aromatic ring protons being fixed in the 5.9–6.3 ppm region.

The formation of a stable imino–enole tautomer **358** is due to the conjugation of the C=C and C=N double bonds with the aromatic ring and hydroxyl group. The enaminoketone tautomer **357** is present in a negligible amount.

Thus, ynaminoketones with 1,2-diaminobenzene form benzodiazepines with retention of the dialkylamino group. The reaction occurs as a nucleophilic addition in the absence of catalysts. With α,β-acetylenic ketones 1,2-diaminobenzene reacts in the same manner, but under proton-catalyzed conditions (72LA24). At the same time, ynamines and enynamines furnish with 1,2-diaminobenzene substituted benzimidazoles as a result of double attack at the acetylene bond (83ZOR926; 84ZOR1648).

o-Aminophenol and *o*-aminothiophenol with 4-dialkylaminobut-3-yn-2-ones (65−70°C, THF, 20−40 min) give 2-acetylmethyl-1,3-benzoxazole (**359, 361**) and 2-acetylmethyl-1,3-benzothiazole (**360, 362**) (88ZOR1165), the reaction proceeding more easily than that with *o*-phenylenediamine.



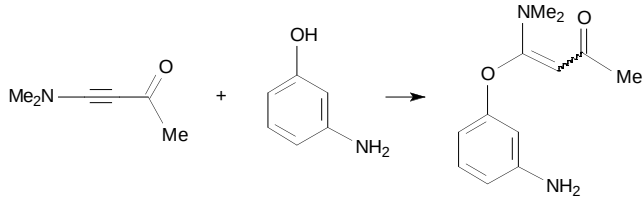
359, **360** **361**, **362**

X = O (**359**, **361**); S (**360**, **362**)

Unlike the products of condensation of 1,2-diaminoethane and 1-amino-2-hydroxyethane with aminobutynones, which exist almost exclusively in the enole form, benzoxazoles **359, 361** and benzothiazoles **360, 362** are present in the solution as a tautomeric mixture of the ketone (**359, 360**) and enole (**361, 362**) forms. This seems to be related to weakening of the imine nitrogen basicity due to adjacent oxygen and sulfur atoms.

The mass spectrum of thiazole compound **359, 362** shows intense peaks of the molecular ion and fragments [M − Me], [M − Ac]. The benzothiazole ring fragmentation produces the maximum [M − RCN] (9%) corresponding to heterocycle decomposition at the nitrogen–carbon and sulfur–carbon bonds with the charge localization on the sulfur-containing fragment (86MI2).

To determine the direction of primary attack at aminobutynones in the presence of competing hydroxyl and amino groups in the benzene ring, the reaction of 4-dimethylaminobut-3-yn-2-one with *m*-aminophenol has been examined (65–70°C, THF, 20 min). It was found that the hydroxyl group reacts first to form *O,N*-ketenacetal of 4-dimethylamino-4-(*m*-aminophenoxy)-but-3-en-2-one (**363**) (88ZOR1165).



363

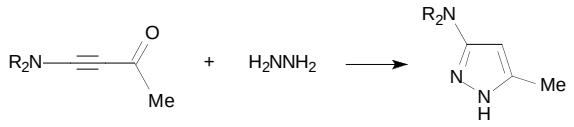
In the ^{1}H NMR spectrum of the adduct **363,** the acetyl is presented by a singlet in the 2.00 ppm region, while the ethene moiety appears at 4.75–4.99 ppm. The amino group gives a broadened signal in the 3.65 ppm region.

Thus, the reaction of 4-dialkylaminobut-3-yn-2-ones with various bifunctional reagents makes it possible to carry out a targeted synthesis of five- and six-membered nitrogen-, oxygen-, and sulfur-containing heterocycles having two heteroatoms.

B. Reactions with Hydrazines

The cyclization of ynaminoketones with hydrazine and its alkyl- and phenyl-substituted derivatives has been covered in a number of publications (69HCA2641; 76H1921; 87ZOR1635).

Unsubstituted hydrazine reacts with 4-dialkylaminobut-3-yn-2-ones in dry THF and methylene chloride (50°C, 3 h) to form 3(5)-dialkylamino-5(3)-methylpyrazoles (**364**) in 56–63% yield (87ZOR1635).

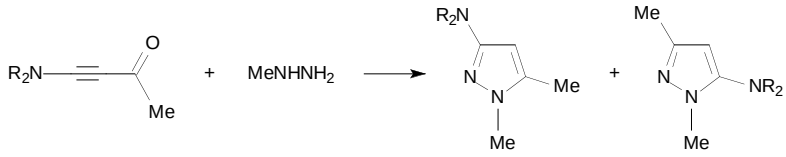


R = Me, Et; R_2 = $O(CH_2)_4$

364

R	Me	Et	$O(CH_2)_4$
yield, %	63	60	56

The reaction of 4-dialkylaminobut-3-yn-2-ones with monosubstituted alkylhydrazines, e.g., methylhydrazine, leads to a mixture of isomeric pyrazoles **365, 366** and **367, 368.**



R = Me (**365**, **367**), Et (**366**, **368**)

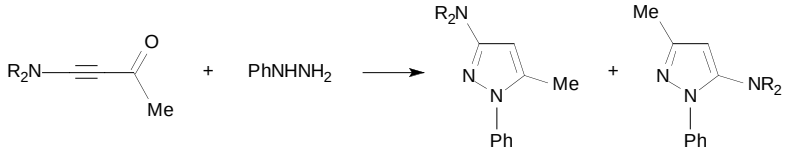
365, **366**

367, **368**

The isomer ratio for **365**:**367** and **366**:**368** was 3:4 (GLC, ^{1}H NMR). The assignment of isomers was done relative to the pyrazole ring proton. For 5-dialkylamino-3-methylpyrazoles **367, 368** the signal of this proton is at lower field (5.38–5.48 ppm)

compared to that of 3-dialkylamino-5-methylpyrazoles **365, 366** (5.07−5.18 ppm) (87ZOR1635).

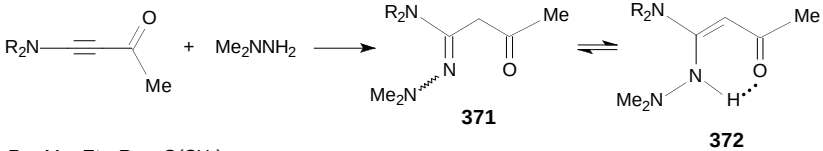
Likewise, the ynaminoketones with phenylhydrazine give a similar mixture of isomeric 1-phenyl-3-dialkylamino-5-methylpyrazoles **(369**) and 1-phenyl-5-dialkylamino-3-methylpyrazoles (**370**) in the same 3:4 ratio (87ZOR1635).



R = Me, Et; $R_2 = O(CH_2)_4$ **369** **370**

The mass spectra of the pyrazoles **365–370** display peaks of molecular ions with intensity of 52–100% compared to that of the maximum peak. All the pyrazoles are characterized by a fragment [M − 15] that corresponds to elimination of a methyl group from molecular ion, and the peaks originated from NR_2 group elimination (73HCA944). Further, the pyrazole ring fragmentation proceeds at the N—N bond, in agreement with (86MI2).

The nonsymmetric dimethylhydrazine adds exclusively to the triple bond of the ynaminoketones (70–75°C, THF, CH_2Cl_2, 3 h) to form *N,N*-dialkylamides of 3-oxobutanohydrazonic acid, which exist in solution as a tautomeric mixture of the hydrazonic (**371**) and enhydrazinic (**372**) forms, yields 49–54% (87ZOR1635).



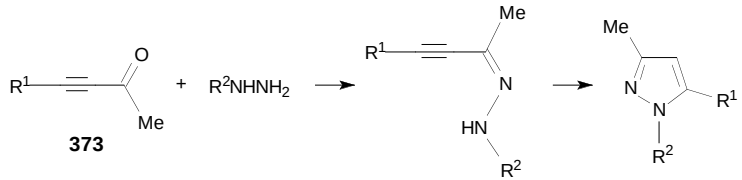
R = Me, Et; $R_2 = O(CH_2)_4$

R	Me	Et	$O(CH_2)_4$
yield, %	54	53	49

No formation of hydrazones with participation of the carbonyl function has been observed. In the ^{1}H NMR spectra, the hydrazone form **371** is represented by the methylene singlet at 3.40 ppm. The acetyl group of **371** has a signal in a lower field (2.10–2.15 ppm) compared to that of **372** (1.85–2.03 ppm), consistent with the chemical shift of the enaminoketone methyl group. The ethylenic proton of the enhydrazine form (**372**) gives a signal at 5.05–5.5 ppm. A broadened signal corresponding to the proton at the nitrogen atom of **372** appears at 7.21–7.96 ppm (87ZOR1635).

In the IR spectra, the hydrazone form (**371**) is distinguished by an absorption band of the nonconjugated carbonyl group at 1710–1730 cm^{-1} and absorption of the C=N bond in the 1450−1485 cm^{-1} region. The enhydrazine tautomers (**372**) are stabilized (apart from the conjugation) by a strong intramolecular hydrogen bond. In the high-frequency range of their IR spectra there is a wide band at 3400−3420 cm^{-1} caused by stretching vibrations of the N−H bond involved in the N−H · · · O hydrogen bonding.

It is noteworthy that, in contrast to ynaminеketones, α,β-acetylenic ketones (**373**) react with hydrazine first via the carbonyl group to form only one of two possible pyrazoles (**374**) (73UK511).

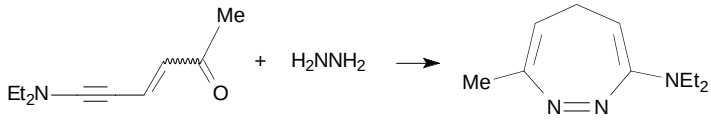


373

R^1 = H, Alk, Ar; R^2 = Me, Et, Ph

374

Cyclization of 6-diethylaminohex-3-en-5-yn-2-one (**375**), an ynaminoketone vinylog, with hydrazine yields 3-diethylamino-7-methyl-5*H*-1,2-diazepine (**375**) (97DIS).



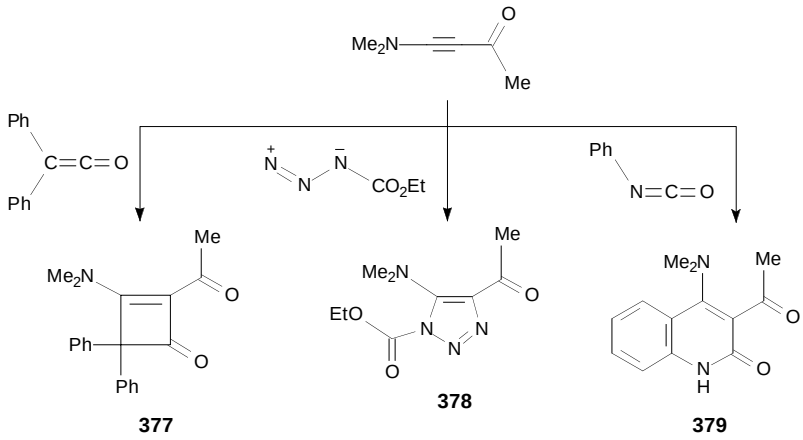
375

376

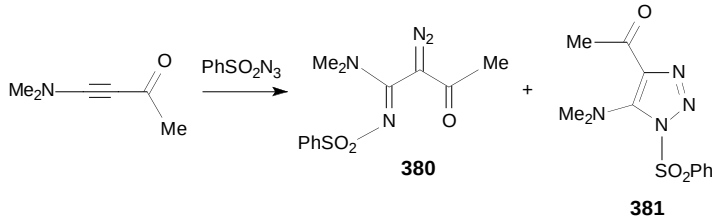
Preparative procedures for 1*H*-, 3*H*-, and 4*H*-isomers of the 1,2-diazepines (**376**) have been elaborated (84MI1). Of the four possible tautomeric diazepines, the 1*H*- and 4*H*-tautomers possessing the C=C and C=N conjugated bonds are more stable (84MI1). According to ^{1}H NMR spectra (72JA2770), the 5*H*-tautomers mainly exist in the bicyclic diazanorcaradiene form. Unlike the 5*H*-tautomers and in spite of the presence of the destabilizing the N=N moiety, the 3*H*-tautomers exist in a monocyclic diazepine form [75JCA(CC)613]. The 3*H*-tautomers of the 1,2-diazepines are also prepared from tosylhydrazones of conjugated dienic ketones [79JCS(P1)2209]. The N−C≡C−C=C systems do not form the heterocycles with hydrazines (80ZOR1149).

C. Reactions with 1,3-Dipoles and Other Cycloadditions

Analogously to ynamines and α,β-acetylenic ketones, 4-aminobut-3-yn-2-ones react with 1,3-dipoles (68HCA443; 73HCA2427; 92KGS867). The reaction of 4-dimethylaminobut-3-yn-2-one with diphenylketene follows a route of [2+2]-cycloaddition (30°C, THF, 1 h) to give 2-acetyl-3-dimethylamino-4,4-diphenylcyclobut-2-en-1-one (**377**) in 75% yield. With ethyl azidoformate (30°C, THF, 3 h), the triazole **378** is formed in 82% yield, whereas with phenyl isocyanate, the quinoline **379** is the product (by a [2+4] scheme) in 70% yield (68HCA443).

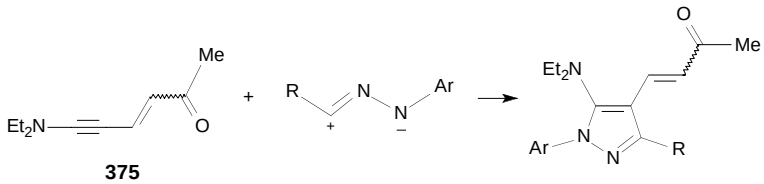


Arylsulfenyl azides in this reaction mainly give the product of the triazole ring opening **380,** which is isomeric to the expected triazole **381** detected only in negligible quantities (72S571).



The ynaminoketone vinylogs react with 1,3-dipoles (C,N-disubstituted nitrilimines, benzonitrile *N*-oxide) in a regio- and stereospecific fashion at the triple

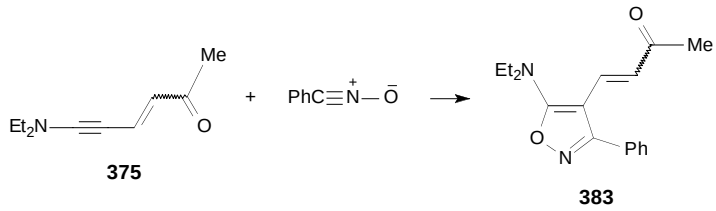
bond (93ZOR1237; 94ZOR46). For instance, 6-diethylamino-3-hexen-5-yn-2-one (**375**) with C,N-disubstituted nitrilimines (40°C, Et_2O, 18–30 h) affords substituted pyrazoles **382** in 33–48% yields.



R = MeC(O), Ar = Ph; R = Ph, Ar = *p*-BrC_6H_4

The structure of the pyrazoles **382** is determined by the X-ray analysis carried out for 3-acetyl-4-(3-oxo-1-buten-1-yl)-1-phenyl-5-diethylaminopyrazole (94ZOR46): The pyrazole ring is practically planar (mean deviation from the plane is 0.007 Å); bond lengths and valence angles are normal; the angle between the planes of the heterocycle and acetyl group in position 3 is ∼3° (indicating conjugation); the benzene ring is 127° out of the pyrazole plane; the butenone group (*E*-configuration) is turned 20° relative to the pyrazole ring.

The cyclization of the ketone **375** with benzonitrile *N*-oxide (40°C, Et_2O, 24 h) occurs in a similar manner to produce 4-(3-oxobut-1-en-1-yl)-3-phenyl-5-diethylaminoisoxazole (**383**) in 27% yield (94ZOR46).



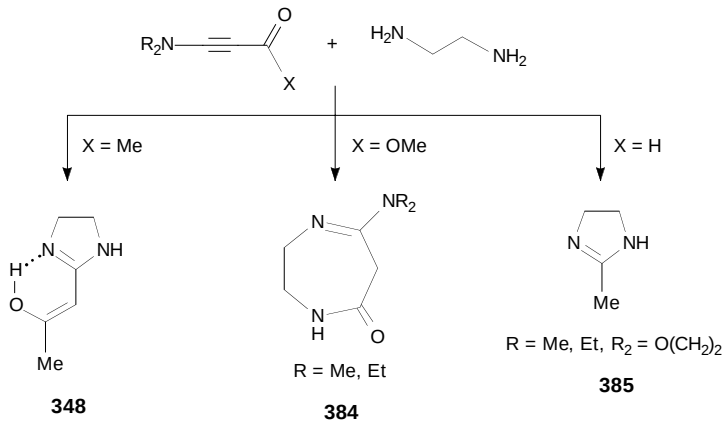
Thus, the amino group conjugated with the acetylene bond of the 1,3-enyne ketones significantly activates this bond relative to 1,3-dipoles. Enynaminoketones react with 1,3-dipoles only by the triple bond, the negatively charged 1,3-dipole atom adding to the carbon atom bound to nitrogen. The formation of the heterocycle does not involve elimination of the dialkylamino group.

D. General Remarks

Comparison of the reactivity of conjugated ynaminocarbonyl compounds (N—C≡C—C=O), their vinylacetylene analogs (N—C≡C—C=C—C=O), and acetylenic ketones (C≡C—C=O) in the heterocyclization reactions provides evidence for the highest activity of the former (92KGS867).

All these compounds possess a highly electrophilic triple bond. In a number of cases the nucleophilic addition occurs at this bond only, whereas the carbonyl function acts as a negative charge acceptor.

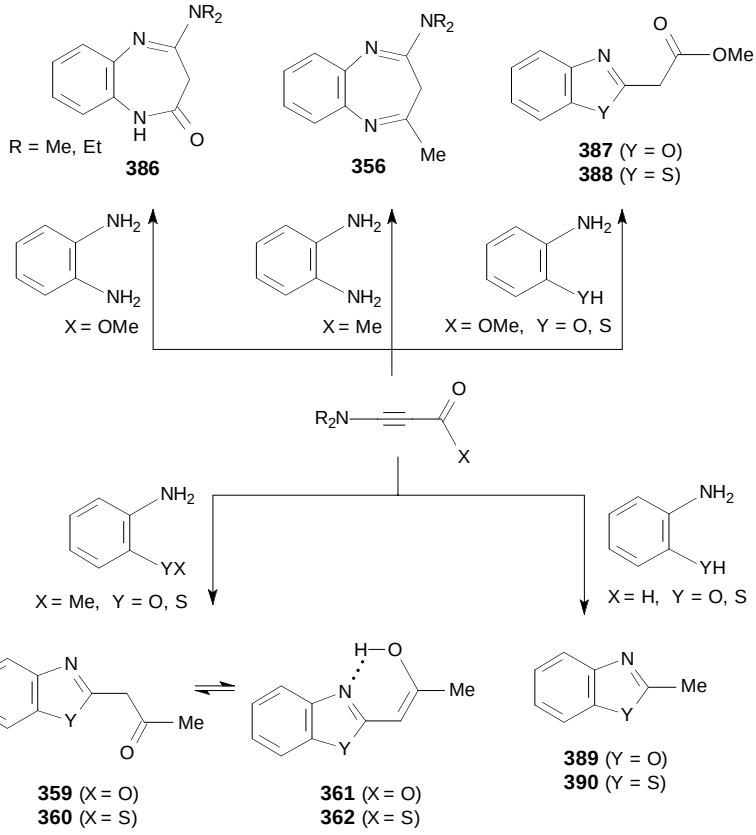
In reactions of this type, the character of cyclization is determined by the ynamine moiety. The features of the heterocyclization of diverse ynaminocarbonyl compounds are generalized by the formation of the compounds **348, 384,** and **385** (92KGS867; 00UK642).



The ynaminoketones (X = Me) obtained from diacetylene react with 1,2-diaminoethane as simple ynamines by double attack at the triple bond to form imidazoline derivatives **348.**

The ability of the ynaminocarboxylate methoxy group (X = OMe) for nucleophilic substitution results in the attack of the two electrophilic centers by 1,2-diaminoethane and the formation of diakylamino-2,3-dihydro-1,4-diazepin-7-ones (**384**) (88ZOR2321; 92KGS867; 00UK642). The high activity of the carbonyl function in the ynaminoaldehydes (X = H) is responsible for the addition of two moles of 1,2-diaminoethane at the two reactive centers, the diadduct decomposing with the carbon–carbon bond cleavage to form 2-methylimidazoline (**385**).

A decrease in the basic properties of the reagent in going from 1,2-diaminoethane to 1,2-diaminobenzene leads, in the case of ynaminoketones (X = Me), to the 1,3-orientation of binucleophile and the formation of the benzodiazepines **356,** suggesting that the carbonyl group is also involved in the heterocyclization.



Ynaminocarboxylates (X = OMe) react with 1,2-diaminobenzene in the same way to form benzodiazepine **386** (88ZOR2321).

Strengthening of the acidic properties of the reagent (1-amino-2-hydroxybenzene and 1-amino-2-mercaptobenzene) changes the route of cyclization with ynaminoketones (X = Me): The reaction proceeds exclusively via the ynamine moiety to yield benzoxazoles **359** and benzothiazoles **360** (92KGS867; 00UK642). Ynaminocarboxylates (X = OMe) with the same binucleophiles behave in a similar way; i.e., they react only via the ynamine part of the molecule to form 2-methoxycarbonylmethylbenzoxazole (**387**) and 2-methoxycarbonylmethylbenzothiazole (**388**) (no keto–enol tautomerism is observed) (88ZOR2321; 92KGS867; 00UK642). Ynaminoaldehydes give diaddition products whose fragmentation results in 2-methylbenzoxazole (**389**) and 2-methylbenzothiazole (**390**).

The above examples show that structural variation of the initial ynaminocarbonyl compounds, including those obtained from diacetylene, and the nature of

bifunctional reagents allow a targeted synthesis of five- and seven-membered heterocycles having two heteroatoms to be realized.

VI. Conclusion

The experimental data and their interpretation presented in this review suggest that the chemistry of diacetylene and its derivatives should remain a promising area for R&D activity in heterocyclic chemistry.

Historically, by the time acetylene itself found industrial application, its practical value was already obvious (00ZPK619; 00UK642). In acetylene production by electrocracking, oxidative pyrolysis of hydrocarbons, or plasma processes, the amount of diacetylene is potentially 5% of the acetylene output. Meanwhile, the problem of application of diacetylene has still not been solved, and it is currently burned in the flare (00ZPK619; 00UK642).

Acetylene production processes based on the pyrolysis of hydrocarbon feedstock remain multitonnage sources of diacetylene. Therefore, its utilization is a challenge to every creative chemist because it is senseless to burn a hydrocarbon of such a great synthetic potential. The situation resembles the use of naphtha for heating in the beginning of the 20th century, which was strongly criticized by Mendeleev: "It is like heating by burning currency bills" (49MI1).

At present, it is evident that diacetylene can be used for the creation of profitable pilot-scale facilities to produce simple and functionalized thiophenes, pyrroles, pyrazoles, pyrimidines, pyridines, and other heterocycles, as well as vitamins A and PP, geraniole, phytole derivatives, and many other high-priced specialty chemicals.

With the development of new technologies and industrial fine synthesis, the importance of products from diacetylene as unique building blocks, synthons, and monomers will increase. And it is the small-scale production of diacetylene-based heterocyclic reagents that may become the first step in the proper industrial utilization of diacetylene. This will provide a base for launching new methods for the synthesis of a large number of valuable heterocyclic compounds that are still inaccessible from cheap industrial feedstock (00UK642).

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ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 82

1,2,4-Triazine *N*-Oxides

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I. Introduction

This review deals with methods for the synthesis of 1,2,4-triazine mono-*N*-oxides and their reactivity. The interest in 1,2,4-triazines is due to their incorporation in many natural and artificial compounds, their biological activity, and other useful properties.

The presence of the *N*-oxide group in the azine ring makes it more subject to electrophilic and nucleophilic attack and substantially expands the synthetic approaches for modification of nitrogen-containing heterocycles (67MI). That is the reason for increasing interest in the chemistry of heterocyclic *N*-oxides. Several reviews on the chemistry of pyridine *N*-oxides (90H923), pyrimidine *N*-oxides (92H3), and quinoxaline *N*-oxides (95JHC1085) were published in the

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1990s. A monograph [78MI) and several reviews [84CHEC(3)385, 89AHC(46)73, 96CHEC(6)507, 97MI] on 1,2,4-triazines include some data on the chemistry of their *N*-oxides. However, data on the methods for the synthesis and chemical properties of 1,2,4-triazine *N*-oxides have never been systematized. The goal of this review is to close this gap.

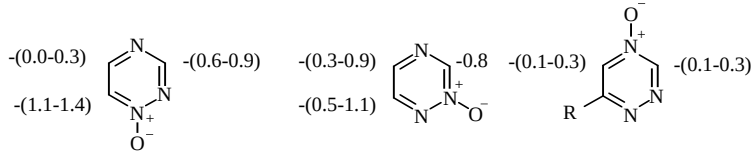
II. Molecular Spectra

It is useful to compare the spectroscopic data of 1,2,4-triazine mono-*N*-oxides with the data for the corresponding 1,2,4-triazines. Introduction of an *N*-oxide group in the 1,2,4-triazine ring changes its physicochemical properties dramatically, and the analysis of these changes allows one to determine which of three nitrogens is oxidized. The most useful method in this case is NMR spectroscopy, including ^{1}H, ^{13}C, and ^{15}N NMR.

Thus, both the upfield shifts in the ^{1}H NMR spectra of the signals of protons at positions 3 and 6 of the heterocyclic ring by 0.6–0.7 and 1.1–1.2 ppm, respectively, in comparison with those of the parent 1,2,4-triazines and the almost unchanged chemical shift of the H(5) proton are typical for 1,2,4-triazine 1-oxides (70JHC767, 71JOC787, 77JOC546).

In the ^{1}H NMR spectra of 1,2,4-triazine 2-oxides the signals of the H(3) and H(6) were found to be shifted upfield by about 0.8 ppm in comparison with the parent 1,2,4-triazines, while signals of the H(5) proton are shifted upfield by 0.3 ppm.

Analysis of the ^{1}H NMR spectra of 1,2,4-triazine 4-oxides shows upfield shifts of the H(3) and H(5) signals by 0.1–0.3 ppm. However, this rule does not apply in 5-amino-1,2,4-triazine 4-oxides. In this case the introduction of the *N*-oxide group leads to a downfield shift of the H(3) signals in comparison with the corresponding 5-amino-1,2,4-triazines by 0.3–07 ppm (00MI). It should be noted that signals of 1,2,4-triazine 4-oxide protons depend significantly on the solvent; thus, changing the solvent from $CDCl_3$ to DMSO-d_6 leads to a downfield shift of the H(3) and H(5) signals by 0.6 ppm (Table I) (71LA12).



In ^{13}C NMR spectra, signals for the 1,2,4-triazine *N*-oxide carbons in the α and γ position to the *N*-oxide group are observed in higher field [$\Delta\delta = -(18–20)$ ppm for the 1-oxides, $-(9–18)$ ppm for the 2-oxides, and $-(10–15)$ ppm for the 4-oxides) in comparison with those for the parent 1,2,4-triazines, while the signals of the

TABLE I

CHEMICAL SHIFTS δ OF THE CYCLIC PROTONS IN THE ^{1}H NMR SPECTRA OF 1,2,4-TRIAZINES AND THEIR *N*-OXIDES IN $CDCl_3$ (A) OR DMSO-d_6 (B) IN COMPARISON ($\Delta\delta$) WITH THOSE OF THE PARENT 1,2,4-TRIAZINES

Compound	Solvent	δ ($\Delta\delta$), ppm			References
		H(3)	H(5)	H(6)	
1,2,4-Triazine	A	9.63	8.53	9.24	77JOC546
1-oxide	A	9.00	8.57	8.04	77JOC546
		(−0.63)	(0.04)	(−1.20)	66JOC3917
2-oxide	A	8.82	8.00	8.42	77JOC546
		(−0.81)	(−0.53)	(−0.82)	
3-Methoxy-1,2,4-triazine	A	—	8.56	9.16	70JHC767
1-oxide	A	—	8.37	7.83	66JOC3917
			(−0.19)	(−1.33)	
2-oxide	A	—	7.70	8.12	77JOC546
			(−0.86)	(−1.04)	
3-Amino-1,2,4-triazine	B	—	8.53	8.88	77JOC546
2-oxide	B	—	8.19	8.23	77JOC546
			(−0.34)	(−0.65)	
3-(*N*,*N*-Dimethylamino)-1,2,4-triazine	A	—	8.14	8.15	77JOC546
1-oxide	A	—	7.76	7.86	77JOC546
			(−0.38)	(−0.65)	
3-Morpholino-1,2,4-triazine	A	—	8.14	8.54	86KGS1535
2-oxide	A	—	7.81	8.54	77JOC546
			(−0.33)	(−0.52)	
3-Pyrrolidino-6-phenyl-1,2,4-triazine	B	—	8.86	—	71JHC689
4-oxide	B	—	8.55	—	00MI
			(−0.31)		
6-Methyl-1,2,4-triazine	A	9.55	8.55	—	71LA12
4-oxide	A	9.28	8.22	—	71LA12
		(−0.27)	(−0.33)		
6-Phenyl-1,2,4-triazine	A	9.52	8.91	—	71LA12
4-oxide	A	9.31	8.60	—	71LA12
		(−0.21)	(−0.31)		
5-Pyrrolidino-6-phenyl-1,2,4-triazine	B	8.73	—	—	00MI
4-oxide	B	9.01	—	—	00MI
		(+0.28)			
5-Morpholino-6-phenyl-1,2,4-triazine	B	8.75	—	—	00MI
4-oxide	B	9.10	—	—	00MI
		(+0.35)			
5-Amino-6-phenyl-1,2,4-triazine	B	8.56	—	—	00MI
4-oxide	B	9.25	—	—	00MI
		(+0.69)			
5-Diethylamino-6-phenyl-1,2,4-triazine	B	8.64	—	—	00MI
4-oxide	B	9.18	—	—	00MI
		(+0.54)			

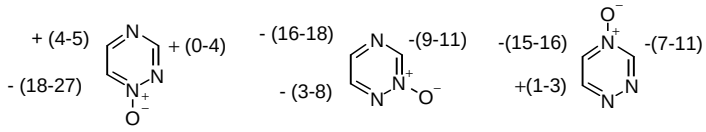
TABLE II

CHEMICAL SHIFTS δ OF THE CARBONS IN THE ^{13}C NMR SPECTRA OF 1,2,4-TRIAZINE *N*-OXIDES IN DMSO-d_6 IN COMPARISON ($\Delta\delta$) WITH THOSE OF THE PARENT 1,2,4-TRIAZINES

Compounds	δ ($\Delta\delta$), ppm			References
	C(3)	C(5)	C(6)	
1,2,4-Triazine 1-oxide*	158.5 (−0.4)	152.7 (3.1)	129.7 (−21.1)	86H951
1,2,4-Triazine 2-oxide*	143.5 (−14.6)	132.5 (−17.1)	146.0 (−4.8)	86H951
3-Methoxy-1,2,4-triazine 1-oxide*	166.5 (2.5)	154.0 (4.0)	124.5 (−18.5)	77JOC546
3-Methoxy-1,2,4-triazine 2-oxide*	152.5 (−11.5)	130.0 (−20.0)	135.5 (−7.5)	77JOC546
3-Amino-1,2,4-triazine 1-oxide	165.0 (1.7)	155.9 (6.1)	120.7 (−19.9)	86H951
3-Amino-1,2,4-triazine 2-oxide	151.6 (−11.7)	132.4 (−17.4)	134.9 (−5.7)	86H951
3-(*N*,*N*-Dimethylamino)-1,2,4-triazine 1-oxide*	161 (1)	152 (4)	120 (−18)	77JOC546
3-(*N*,*N*-Dimethylamino)-1,2,4-triazine 2-oxide*	151 (−9)	132 (−16)	133 (−5)	77JOC546
3-Amino-5,6-dimethyl-1,2,4-triazine 1-oxide	166.0 (3.9)	164.3 (5.4)	119.4 (−27.7)	86H951
3-Amino-5,6-dimethyl-1,2,4-triazine 2-oxide	148.9 (−13.2)	140.2 (−18.7)	144.2 (−2.9)	86H951
3-Amino-5,6-dimethyl-1,2,4-triazine 4-oxide	154.4 (−7.7)	143.0 (−15.9)	148.7 (1.6)	86H951
5-Methyl-1,2,4-triazine 1-oxide*	158.7 (1.7)	166.1 (5.6)	129.1 (−21.8)	86H951
6-Phenyl-1,2,4-triazine 4-oxide	149.9	132.0	157.5	86H951
3-Methyl-6-phenyl-1,2,4-triazine 4-oxide	159.4	131.4	156.4	86H951
3,6-Diphenyl-1,2,4-triazine 4-oxide	156.2	132.8	155.6	86H951
6-Phenyl-3-ethyl-1,2,4-triazine 4-oxide	161.9	131.4	156.3	86H951
5-(Indol-3-yl)-6-phenyl-5-ethyl-1,2,4-triazine 4-oxide	161.0	135.5	156.7	98ZOR429
5-(1-Methylindol-3-yl)-6-phenyl-1,2,4-triazine 4-oxide	149.0	139.4	157.3	98ZOR429
5-(1-Methylindol-3-yl)-6-phenyl-3-ethyl-1,2,4-triazine 4-oxide	160.8	136.0	135.8	98ZOR429
5-(1-Methylindol-3-yl)-3,6-diphenyl-1,2,4-triazine 4-oxide	156.1	136.1	156.0	98ZOR429
5-(2-Methylindol-3-yl)-6-phenyl-1,2,4-triazine 4-oxide	149.9	142.8	160.9	98ZOR429
3-methyl-5-(2-Methylindol-3-yl)-6-phenyl-1,2,4-triazine 4-oxide	157.9	140.2	158.9	98ZOR429

*In $CDCl_3$.

carbon in the β position are almost unchanged (Table II) (70JA7107, 77JOC546, 79JHC1389, 86H951, 86H1969, 96MI).



In ^{15}N NMR spectra, the 1-oxide signals of N(1) were shifted upfield [$\Delta\delta = -(83–87)$ ppm] in comparison with those for the corresponding 1,2,4-triazines; at the same time, the signals of N(2) and N(4) undergo a lesser upfield shift [$\Delta\delta = -(39–46)$ ppm and $-(22–24)$ ppm, respectively]. By contrast, in 1,2,4-triazine 2-oxides the signals of N(1) and N(2) are shifted upfield by almost the same value [$\Delta\delta = -(70–75)$ ppm], while the signal of the nitrogen at position 4 is hardly shifted [$\Delta\delta = -(13–23)$ ppm] (Table III) [69T1021, 80OMR305, 84SA(A)637].

In the mass spectra of 1,2,4-triazine *N*-oxides, molecular ion peaks and $[M - 16]^+$ or $[M - 17]^+$ peaks were observed. The fragmentation pattern for the 1,2,4-triazine *N*-oxides does not allow determination of the position of the *N*-oxide group (71JHC317, 71LA12, 78JOC2514, 98ZOR423, 98ZOR429).

TABLE III

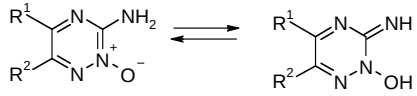
SIGNALS OF THE CYCLIC NITROGENS IN THE ^{15}N NMR SPECTRA OF 1,2,4-TRIAZINES IN DMSO-d_6 ($MeNO_2$ AS THE STANDARD) IN COMPARISON ($\Delta\delta$) WITH THOSE OF THE PARENT 1,2,4-TRIAZINES [84SA(A)637]

Compounds	δ ($\Delta\delta$)*, ppm			References
	N(1)	N(2)	N(4)	
1,2,4-Triazine	40.0	2.0	−62.0	84SA(A)637
1-oxide	−43.0	—	—	84SA(A)637
	(−83)			
3-Methoxy-1,2,4-triazine	36.0	−58.0	−124.4	84SA(A)637
1-oxide	−50.0	−97.1	−148.0	84SA(A)637
	(−86.0)	(−38.9)	(−23.6)	
3-Amino-1,2,4-triazine	35.7	−61.0	−130.0	84SA(A)637
1-oxide	−51.1	−107.0	−152.0	84SA(A)637
	(−86.8)	(−46.0)	(−22.0)	
2-oxide	−39.0	−137.0	−153.0	84SA(A)637
	(−74.7)	(−76.0)	(−23.0)	
6-Phenyl-1,2,4-triazine 4-oxide	−15.5	−11.0	−81.5	98MI

III. Chemical Properties

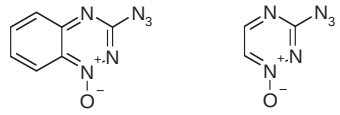
A. TAUTOMERISM

The amino–imino tautomerism in 3-amino-1,2,4-triazine 2-oxides **1** was suggested as the reason for the oxidation of 3-amino-1,2,4-triazines **2,** predominantly at N(2) (77JOC546).



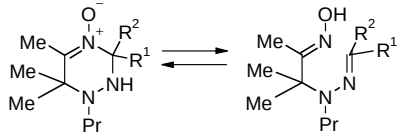
1a **1b**

Studies of presumed azido–tetrazole tautomerism for 3-azido-1,2,4-benzotriazine 1-oxides **3** show that compounds **3** exist only in the form of azides, both in the crystalline state and in solution. Similar results were obtained in the studies of 3-azido-1,2,4-triazine 1-oxides **4,** which have never been detected in the tetrazole form (69CB3818, 77JHC1221, 82JOC3886).



3 **4**

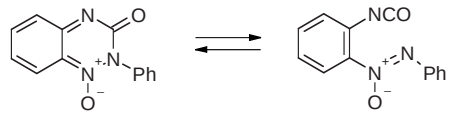
Ring–chain tautomerism was observed in a series of 1,2,3,6-tetrahydro-1,2,4-triazine 4-oxides **5** in nonpolar solvents (e.g., CCl_4) by NMR spectroscopy. Depending on the nature of substituents R^1 and R^2, the ratios of the cyclic form of 1,2,4-triazine **5a** to the open-chain form of hydrazone **5b** were found to be up to 45 : 55 (77ZOR2617).



5a **5b**

		Ratio of the cyclic **5a** to open-chain **5b** forms in CCl_4 (%)	
R^1	R^2	**5a**	**5b**
Me	Me	25	75
H	H	45	55
Me	H	40	60
i-Pr	H	10	90
p-ClC_6H_4	H	0	100

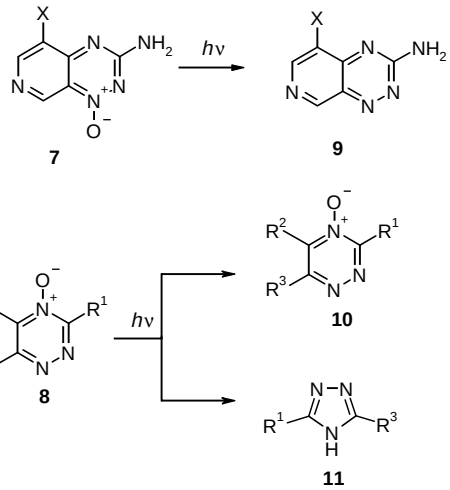
2-Phenyl-1,2,4-benzotriazin-3(2*H*)-one 1-oxide **6** exists in the cyclic form **6a** in the crystalstate, but undergoes 1,2,4-triazine ring opening in solution, resulting in 2-isocyanatoazoxybenzene **6b** [85JCS(P1)1471].



6a **6b**

B. THERMAL AND PHOTOCHEMICAL REACTIONS

UV irradiation of 3-aminopyrido[4,3-*e*]-1,2,4-triazine 1-oxides **7** or 1,2,4-triazine 4-oxides **8** leads to deoxygenation, i.e., loss of the *N*-oxide function resulting in the corresponding 3-aminopyrido[4,3-e]-1,2,4-triazines **9** and 1,2,4-triazines **10** (76ACH327, 76LA153). At the same time, UV irradiation of the 1,2,4-triazine 4-oxides unsubstituted at the 5 position proceeds as a ring contraction to form triazoles **11** (76LA153).

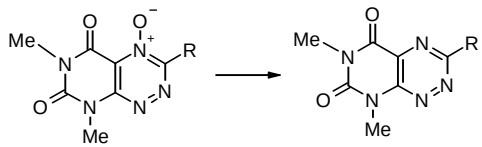


7 **9**

8 **10**

11

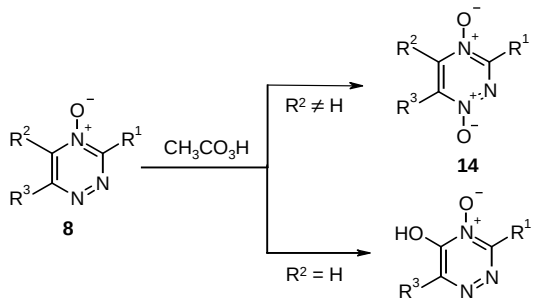
Thermal deoxygenation of fervenulin 4-oxides **12** takes place after refluxing in DMF, giving fervenulin **13** (78JOC469).



12 **13**

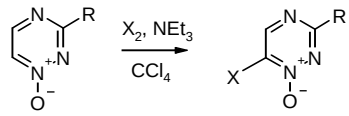
C. Reaction with Electrophiles Directed to Atoms of the 1,2,4-Triazine Ring

The reaction of 1,2,4-triazine 4-oxides **8** bearing substituents at the 3, 5, and 6 positions with peroxyacetic acid proceeds as an N-oxidation process exclusively at the 1 position, resulting in 1,2,4-triazine 1,4-dioxides **14.** Oxidation of 1,2,4-triazine 4-oxides **8** unsubstituted at the 5 position leads to 5-hydroxy-1,2,4-triazine 4-oxides **15** (76LA153).



8 **14** **15**

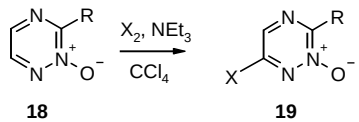
The presence of an *N*-oxide group activates the 1,2,4-triazine ring toward electrophilic attack, for instance, in halogenation reactions. Thus, 3-methoxy- and 3-amino(alkylamino)-1,2,4-triazine 1-oxides **16** react easily with chlorine or bromine to form the corresponding 6-halo-1,2,4-triazine 1-oxides **17** (77JOC3498, 78JOC2514).



16 **17**

X = Cl, Br, R = OMe, NH_2, NHMe, NMe_2

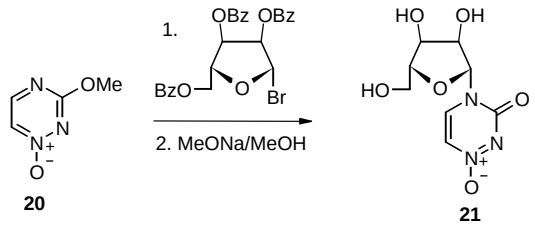
The halogenation of 3-methoxy- or 3-methyl(dimethyl)amino-1,2,4-triazine 2-oxides **18** was found to proceed in a similar manner, resulting in 6-halo-1,2,4-triazine 2-oxides **19** (77JOC3498, 78JOC2514).



18 **19**

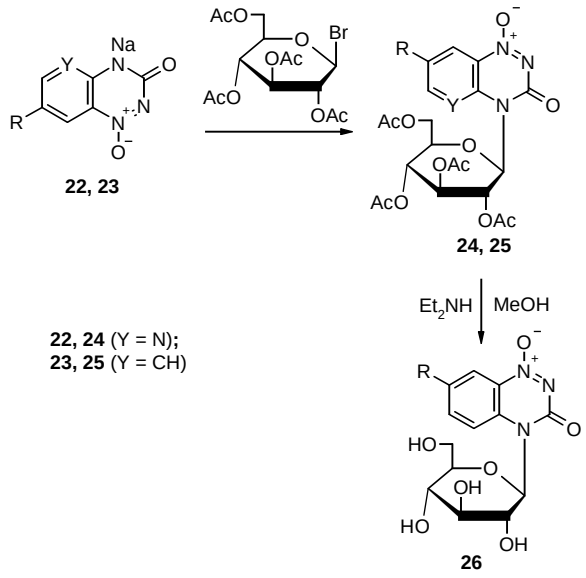
X = Cl, Br, R = OCH_3, NHMe, NMe_2

Derivatives of 3-oxo-1,2,4-triazine 1-oxide undergo alkylation with various alkylating agents. Thus the reaction of 3-methoxy-1,2,4-triazine 1-oxide **20** with 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl bromide, followed by the removal of the benzoyl protection with sodium methoxide, leads to an abnormal nucleoside: 4-(β-D-ribofuranosyl)-1,2,4-triazin-3(4*H*)-one 1-oxide **21** (73JOC3277).



20 **21**

The reaction of the sodium salts of pyrido[2,3-*e*]-1,2,4-triazin-3(4*H*)-one 1-oxide **22** (Y = N) or 1,2,4-benzotriazin-3(4*H*)-one 1-oxide **23** with acetobromoglucose results in tetra-*O*-acetyl derivatives of β-D-glucopyranosides **24, 25;** deacetylation of **25** gives nucleosides **26** (82JHC497).



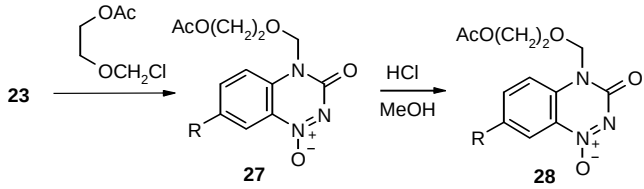
22, 23

24, 25

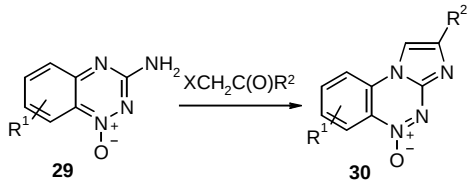
22, 24 (Y = N);
23, 25 (Y = CH)

26

Reactions of compounds **23** with 2-chloromethoxyethyl acetate lead to *N*-alkylation products **27,** which are hydrolyzed to form 4-(2-hydroxyethoxymethyl)-1,2,4-benzotriazine **28** (82JHC497).

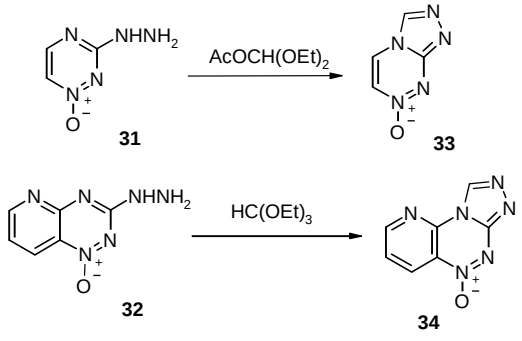


The condensation of 3-amino-1,2,4-benzotriazine 1-oxides **29** with α-halocarbonyl compounds results in imidazo[2,1-*c*]-1,2,4-benzotriazine 1-oxides **30** (82JHC61, 86MI).



X = Cl, Br; R^1 = H, Alk, AlkO, Hal; R^2 = H, COOAlk

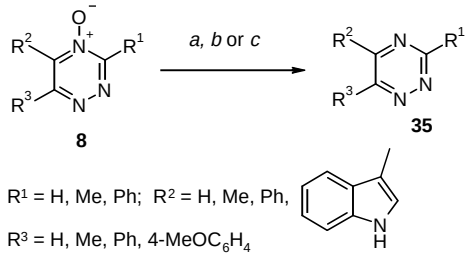
Reactions of 3-hydrazino-1,2,4-triazine 1-oxide **31** or 3-hydrazinopyrido [2,3-*c*]-1,2,4-triazine 1-oxide **32** with diethoxymethyl acetate or triethyl orthoformate proceed as cyclization reactions at the N(4) atom and the amino group to form the corresponding pyrazolo[3,4-*c*]-1,2,4-triazine 6-oxides **33** and **34** (74MI, 80JOC5421, 80MI).



D. Reactions with Nucleophiles and Reducing Agents

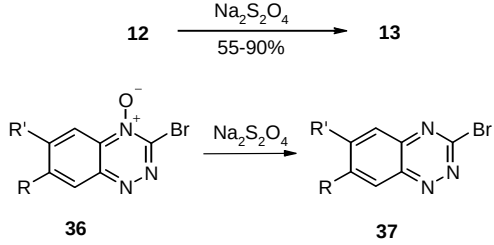
1. *Deoxygenation*

Treatment of the 1,2,4-triazine 4-oxides **8** with reducing agents is a regular procedure for their deoxygenation. Thus the reaction of 1,2,4-triazine 4-oxides **8** with triethylphosphine or PCl_3 leads to the corresponding 1,2,4-triazines **35** (in 65–95% yields), which are impossible to obtain by other methods (71LA12, 73TL1429, 98ZOR429).

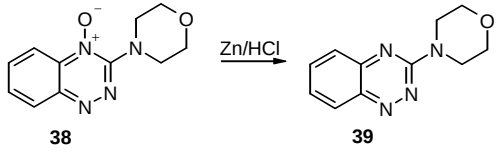


(a) $POEt_3$; (b) PCl_3; (c) H_2–Pd/C

Other reducing agents successfully deoxygenate 1,2,4-triazine *N*-oxides. Thus 1,2,4-triazine 4-oxides **8** were reduced with hydrogen in the presence of palladium on carbon, giving the corresponding 1,2,4-triazines **35** (87KGS257). The reaction of fervenulin 4-oxides **12** and 3-bromo-1,2,4-benzotriazine 4-oxides **36** with $Na_2S_2O_4$ results in fervenulins **13** and 3-bromo-1,2,4-benzotriazine **37** (77H273, 82JOC3886).



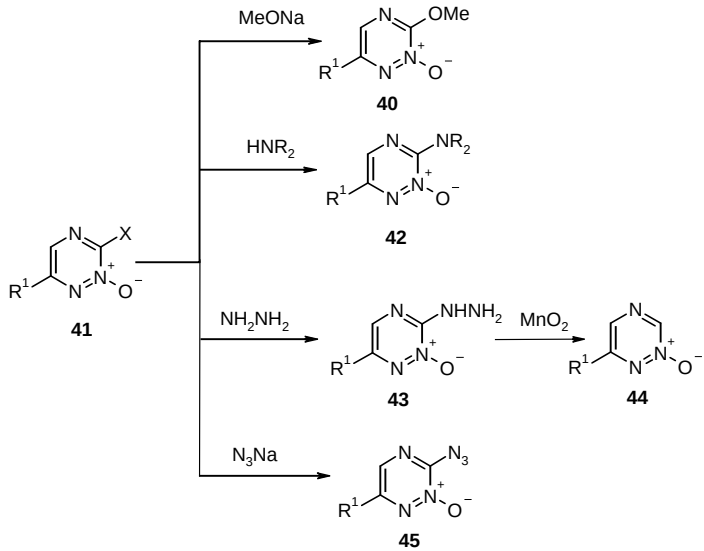
The reaction of 3-morpholino-1,2,4-benzotriazine 4-oxide **38** with zinc in hydrochloric acid afforded 3-morpholino-1,2,4-benzotriazine **39** (78USP4091098).



A very interesting feature of the 1,2,4-triazine *N*-oxides is their high reactivity toward nucleophiles in nucleophilic aromatic substitutions of good leaving groups and hydrogen, and in ring transformations initiated by nucleophilic attack. The first step of any such reaction is the addition of a nucleophile at the carbon of the 1,2,4-triazine ring, resulting in an intermediate σ-adduct. There are two possible types of these intermediates: σ^X or σ^H. In the case of σ^X-adducts, the nucleophilic addition proceeds at the carbon bearing a substituent X, followed by the elimination of the leaving group X; i.e., nucleophilic ipso-substitution takes place. Formation of the σ^H-adducts, when the nucleophilic attack is directed at the unsubstituted carbon of the heterocycle, can be followed (1) by the aromatization step to form products of the nucleophilic substitution of hydrogen or (2) by a ring transformation.

2. *Reactions of Nucleophilic Substitution of Good Leaving Groups*

Substitution of nucleofuges, such as halogens, alkoxy groups, or alkylthio groups, is a good method for the modification of 1,2,4-triazine *N*-oxides. Thus halogen atoms can be replaced in reactions with different nucleophiles. 3-Methoxy-1,2,4-triazine 2-oxide **40** was obtained in the reaction of 3-bromo-1,2,4-triazine 2-oxides **41** with sodium methoxide. When ammonia or alkylamines are used as nucleophiles, 3-amino-1,2,4-triazine 2-oxides **42** are formed. According to this

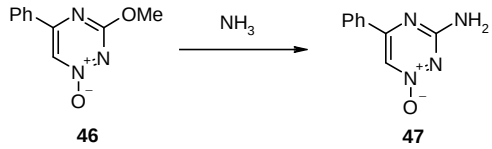


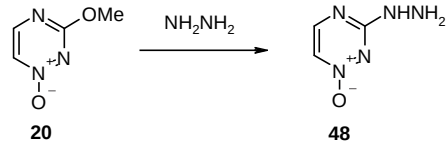
X = Cl, Br; R^1 = H, Me

HNR_2 = NH_3, $HNMe_2$, piperidine, morpholine

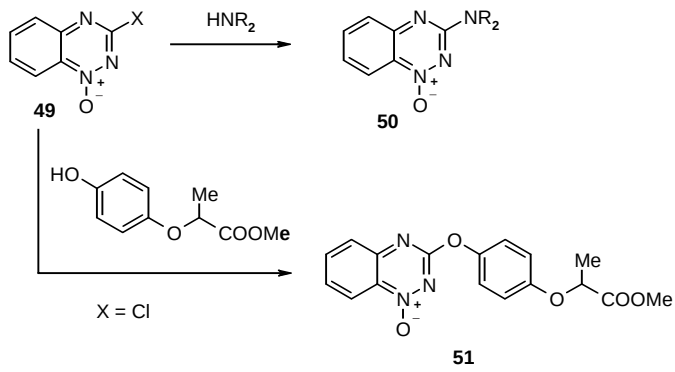
methodology, 3-hydrazino-1,2,4-triazine 2-oxide **43** was obtained starting from 3-bromo-1,2,4-triazine 2-oxide **41** and hydrazine hydrate. The treatment of **43** with an oxidant (MnO_2) leads to 1,2,4-triazine 2-oxide **44** (77JOC546). The reaction of **41** with sodium azide gave 3-azido-1,2,4-triazine 2-oxide **45** (77JHC1221).

The methoxy group is replaced in the reaction of 3-methoxy-5-phenyl-1,2,4-triazine 1-oxide **46** with ammonia, resulting in 3-amino-5-phenyl-1,2,4-triazine 1-oxide **47.** The treatment of 3-methoxy-1,2,4-triazine 1-oxide **20** with hydrazine leads to 3-hydrazino-1,2,4-triazine 1-oxide **48** (71JOC787).

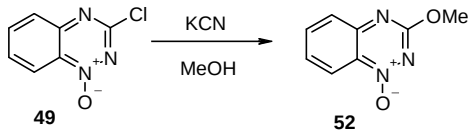




The reaction of 3-chloro- or 3-methylthio-1,2,4-benzotriazine 1-oxides **49** with amines affords 3-amino derivatives of 1,2,4-triazine 1-oxides **50** (78USP4091098, 79GEP2802488, 89MI). Displacement of the halogen in the reaction of 3-chloro-1,2,4-benzotriazine 1-oxide **49** with methyl 2-(4-hydroxyphenoxy)propionate proceeds in a similar way, resulting in **51** [81EUP24932, 82JAP(K)82102874, 82USP4368068].



Substitution of chlorine in 3-chloro-1,2,4-benzotriazine 1-oxide **49** by treatment with NaCN in methanol affords 3-methoxy-1,2,4-benzotriazine 1-oxide **52** (77GEP2538179).

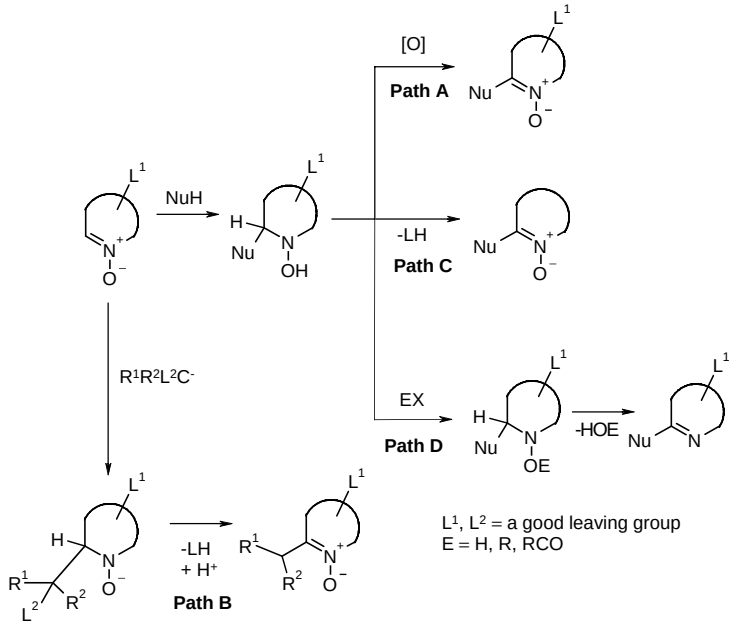


49 **52**

3. *Nucleophilic Aromatic Substitution of Hydrogen*

It is common knowledge that the S_N^H reaction is a two-step process, which includes the addition of a nucleophile at an unsubstituted carbon of an arene or hetarene followed by the aromatization of the intermediate σ^H-adduct (94MI). Elimination of the hydride ion seems to be an improbable step compared to the elimination of a nucleofuge X^- from such σ^X-adducts. Thus the aromatization of a σ^H-adduct is the key step for the whole reaction, and it can proceed by several general paths, as shown in Scheme 1.

The first possibility for aromatization of the σ^H-adducts of azine *N*-oxides is their oxidation with oxidizing agents, resulting in the corresponding substituted azine *N*-oxides with the retention of the *N*-oxide group (Scheme 1, pathway A). When σ^H-adducts contain an auxiliary leaving group, autoaromatization takes

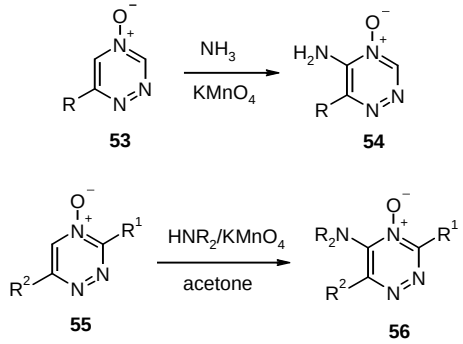


SCHEME 1

place facilitated by the elimination of the auxiliary group as anion; i.e., external oxidants are not needed. The auxiliary group can be a part of a nucleophile, whose reaction involves vicarious nucleophilic substitution of hydrogen (VNS^H) (Scheme 1, pathway B) (87ACR282). The aromatization of the σ^H-adducts can proceed via elimination of the nucleofugal group L from the substrate fragment, in which case the reaction will be cine- or telesubstitution (Scheme 1, pathway C). The presence of the *N*-oxide group in the substrate opens another way for the autoaromatization, when the hydrogen leaves the σ^H-adducts together with the oxygen-containing fragment OE as alcohol (after O-alkylation), carboxylic acid (after O-acylation), or water. In this case deoxygenative aromatization takes place (Scheme 1, path D).

All of the general classes of σ^H-adduct aromatization were found to occur in the reactions of 1,2,4-triazine *N*-oxides with various nucleophiles. From this point of view, the 1,2,4-triazine *N*-oxides are a very convenient substrate for the S_N^H reaction studies.

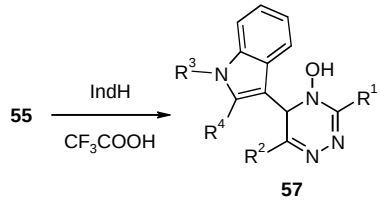
Oxidative amination is a widely used method for introducing an amino group into a heterocyclic ring. The 1,2,4-triazine 4-oxides are very susceptible substrates for such reactions. The treatment of 6-phenyl-1,2,4-triazine 4-oxide **53** with liquid ammonia in the presence of $KMnO_4$ affords 5-amino-6-phenyl-1,2,4-triazine 4-oxide **54** (85S884). The high reactivity of the 1,2,4-triazine 4-oxides **55** toward nucleophiles allows this methodology to be significantly extended. Thus, the 1,2,4-triazine 4-oxides **55** react with equimolar amounts of different aliphatic amines in acetone in the presence of $KMnO_4$, resulting in the corresponding 5-amino-1,2,4-triazine 4-oxides **56** (00MI).



53 **54** **55** **56**

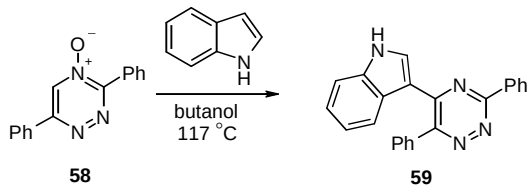
HNR_2 = $HNMe_2$, $HMEt_2$, pyrrolidine, piperidine, morpholine

1,2,4-Triazine 4-oxides **55** react with indoles in the presence of trifluoroacetic acid, giving more or less stable σ^H-adducts, 5-indolyl-4-hydroxy-4,5-dihydro-1,2,4-triazines **57,** which were isolated from the reaction mixture (98ZOR429). In this case the acid activates the substrate, and the protonated 1,2,4-triazinium cation is more active toward nucleophilic attack.

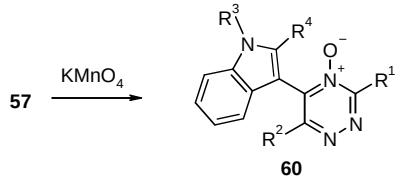


R^1 = H, Me, Et, Ph; R^2 = Ph, 4-ClC_6H_4; R^3, R^4 = H, Me

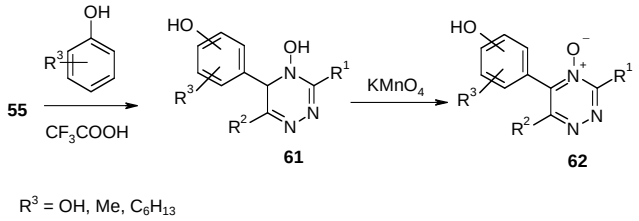
Unusually for reactions of azine *N*-oxides with nucleophiles, the stability of the intermediates **57** allows detailed study of their structure and properties using NMR spectroscopy, mass spectrometry, and X-ray diffraction (00ZOR1081). Analysis of the geometry of **57** shows that the torsion angle of OH—N(4)—C(5)—H fragment is 18°; the *syn*-conformation of the hydrogen and the N—OH group renders the autoaromatization of the σ^H-adducts, with elimination of water, difficult. Only long reflux of 3,6-diphenyl-1,2,4-triazine 4-oxide **58** with indole in butanol gave 5-(indol-3-yl)-3,6-diphenyl 4-oxide **59** in low yield (96MC116).



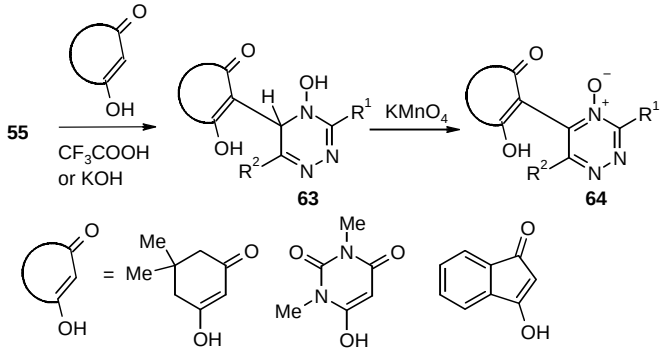
The isolated σ^H-adducts **57** undergo oxidation with $KMnO_4$ easily, resulting in the corresponding 5-indolyl-1,2,4-triazine 4-oxides **60** (98ZOR429). Separating the nucleophilic addition step from the oxidative aromatization of the intermediate σ^H-adducts allows the use of such oxidant-sensitive nucleophiles as indoles.



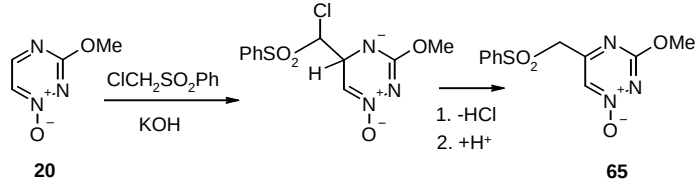
1,2,4-Triazine 4-oxides **55** react with phenols (phenol, 2,6-dimethylphenol, resorcinol, 4-hexylresorcinol) in trifluoroacetic acid in a similar way, yielding intermediate σ^H-adducts 5-hydroxyphenyl-4-hydroxy-4,5-dihydro-1,2,4-triazines **61.** Subsequent oxidation leads to the corresponding 5-hydroxyphenyl-1,2,4-triazine 4-oxides **62** (97MC116).



The reaction of 1,2,4-triazine 4-oxides **55** with CH-active 1,3-diketones (dimedone, indanedione, *N,N′*-dimethylbarbituric acid) in the presence of trifluoroacetic acid (substrate activation by protonation) or KOH (activation of the nucleophile) leads to stable σ^H-adducts **63,** whose oxidative aromatization by the action of $KMnO_4$ results in 5-substituted 1,2,4-triazine 4-oxides **64** (98MI).

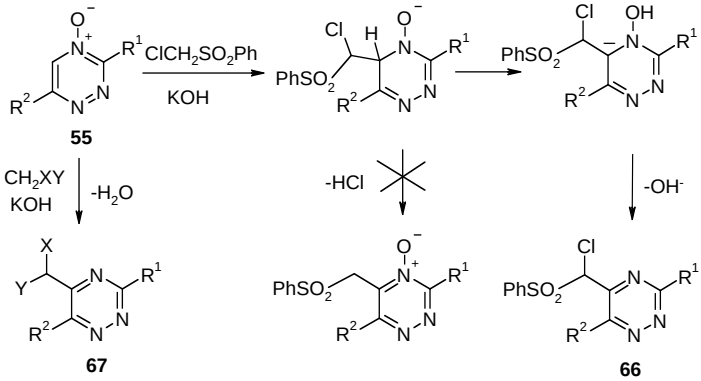


The reaction of 3-methoxy-1,2,4-triazine 1-oxide **20** with the carbanion generated from chloromethyl phenyl sulfone proceeds as the vicarious nucleophilic substitution (VNS) of hydrogen (Scheme 1, path B) via addition of the carbanion at position 5 of the heterocycle. Following base-induced elimination of HCl and protonation, 3-methoxy-5-phenylsulfonyl-1,2,4-triazine 4-oxides **65** result (88LA627).

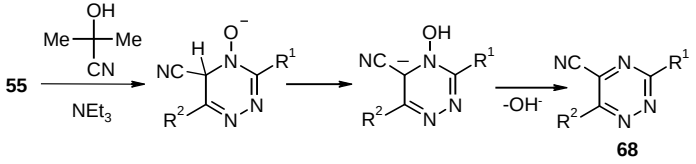


At the same time, the reaction of 1,2,4-triazine 4-oxides **55** with the anion of chloromethyl phenyl sulfone affords 5-(1-chloro-1-phenylmethyl)-1,2,4-triazines **66.** In this case, autoaromatization of the σ^H-adducts proceeds by the deoxygenative

path with the elimination of water (Scheme 1, path D) rather than the VNS scheme with elimination of HCl. It seems that the E1cb mechanism of the elimination of water takes place because of the high acidity of the H(5) proton, yielding products **66.** Similarly, the 1,2,4-triazine 4-oxides **55** react with other carbanions generated from arylacetonitriles, malononitrile, and acetophenones, giving the corresponding 5-substituted 1,2,4-triazine **67** (00MC227).

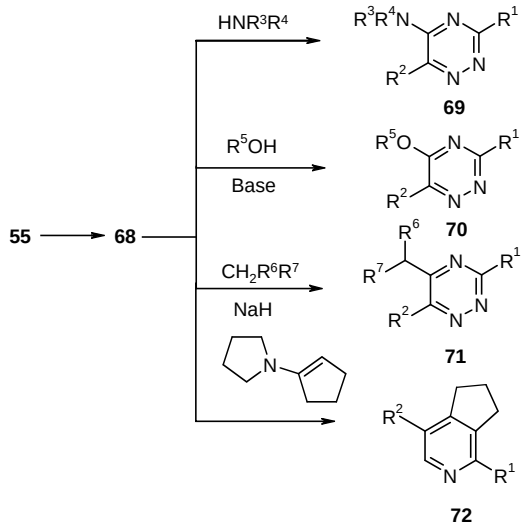


The suggested mechanism of autoaromatization of σ^H-adducts is facilitated by the use of a nucleophile that serves, at the same time, as an electron-withdrawing group, such as a cyanide anion. The direct cyanation of the 1,2,4-triazine 4-oxides **55** with acetone cyanohydrin in the presence of triethylamine (generation of the cyanide anion *in situ*) actually proceeds this way, resulting in the corresponding 5-cyano-1,2,4-triazines **68** in high yield. In this case, the addition of cyanide anion at position 5 of the 1,2,4-triazine ring is followed by the aromatization of the σ^H-adduct by the E1cb elimination of water (97MC66).

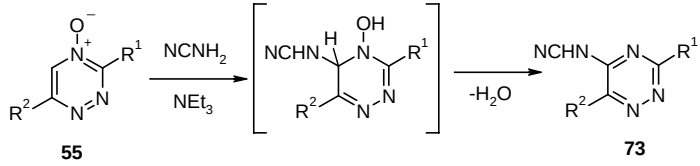


The cyano group in 5-cyano-1,2,4-triazines **68** was found to be a good leaving group in the reaction of nucleophilic substitution with water, carbanions, aliphatic alcohols, and amines, yielding various 5-amino-, 5-alkoxy-, or 5-alkyl-1,2,4-triazines (**69, 70, 71**) (87H3259, 91CPB486, 96JHC1567, 97MC66). Thus the methodology of the consecutive cyanation of the 1,2,4-triazine 4-oxides **55** and displacement of the cyano group allows ready functionalization of the 1,2,4-triazine ring. At the same time, the cyano group activates the 1,2,4-triazine ring toward

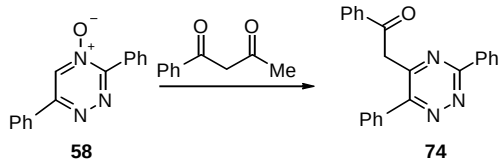
the cycloaddition reaction with enamines, resulting in the corresponding pyridines **72** (01UP1).



It was found that 1,2,4-triazine 4-oxides **55** are active enough to react with cyanamide under basic conditions according to the deoxygenative S_N^H mechanism to form 5-cyanamino-1,2,4-triazines **73** (00IZV1128). This reaction seems to be facilitated by the easy aromatization of σ^H-adducts by the E1cb elimination of water.

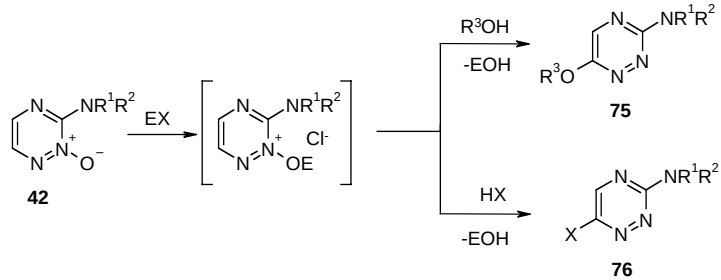


The reaction of 3,6-diphenyl-1,2,4-triazine 4-oxide **58** with benzoylacetone under basic conditions affords substituted 1,2,4-triazine **74** in low yield (96MC116).



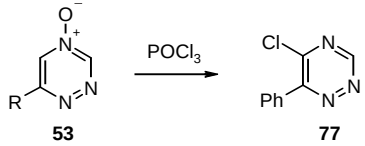
Deoxygenative autoaromatization was reported to occur in the reaction of 3-amino-1,2,4-triazine 2-oxides **42** with alcohols in the presence of HCl or acetyl chloride. In this case the intermediate σ^H-adducts undergo elimination of water or acetic acid, resulting in 6-alkoxy-3-amino-1,2,4-triazines **75** (77JOC3498). 1,2,4-Triazine 1-oxides do not react with alcohols under these conditions (77JOC3498).

6-Chloro(bromo)-3-amino-1,2,4-triazines **76** were obtained by the reaction of the 3-amino-1,2,4-triazine 2-oxides **42** with HCl or HBr (78JOC2514).

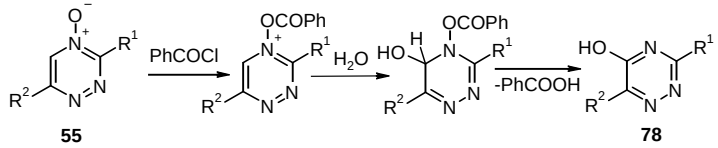


NR^1R^2 = NH_2, NHMe, NMe_2, piperidino *etc*; E = H, Ac; X = Cl, Br; R^3 = Me, Et, Pr

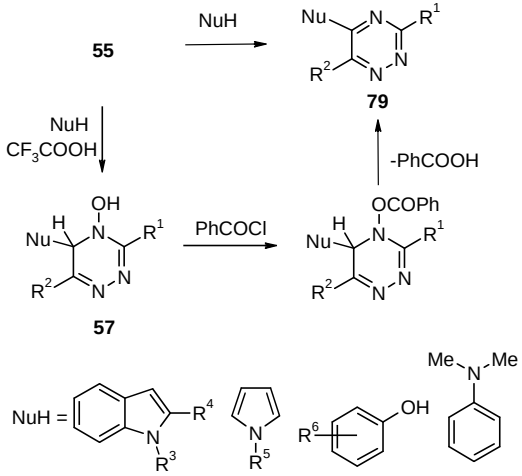
In general, deoxygenative aromatization of the σ^H-adducts by the action of an acylating agent (Scheme 1, path D) allows the introduction of different nucleophiles to the 1,2,4-triazine ring. Thus the treatment of 6-phenyl-1,2,4-triazine 4-oxide **53** with $POCl_3$ leads to the chlorination of the heterocycle in accordance with the S_N^H mechanism, resulting in 5-chloro-6-phenyl-1,2,4-triazine **77** (93MI).



The reaction of 1,2,4-triazine 4-oxides **55** with water in the presence of benzoyl chloride affords 3-hydroxy-1,2,4-triazines **78.** The mechanism suggested for this reaction includes acylation of the substrate at the oxygen of the *N*-oxide group, followed by the addition of water to the 1,2,4-triazinium cation and the autoaromatization of the σ^H-adducts with the elimination of benzoic acid.

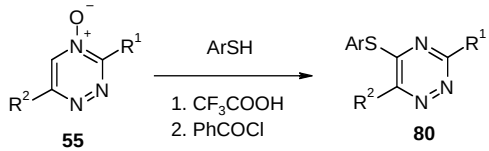


1,2,4-Triazine 4-oxides **55** react with aromatic (phenols, anilines) and heteroaromatic (indoles, pyrroles) C-nucleophiles in the presence of benzoyl chloride and trifluoroacetic acid, giving the corresponding 5-substituted 1,2,4-triazines **79.** The first step of this reaction was suggested to be the protonation of the 1,2,4-triazine 4-oxide **55,** followed by the addition of the nucleophile to the triazinium salt, resulting in σ^H-adducts **57.** The latter, after O-acylation, undergo autoaromatization with the elimination of benzoic acid. The mechanism was proved by the treatment of σ^H-adducts **57,** obtained from 1,2,4-triazine 4-oxides **55** and indoles or phenols as described above, with benzoyl chloride, yielding the same substituted 1,2,4-triazines **79** (00ZOR1081).



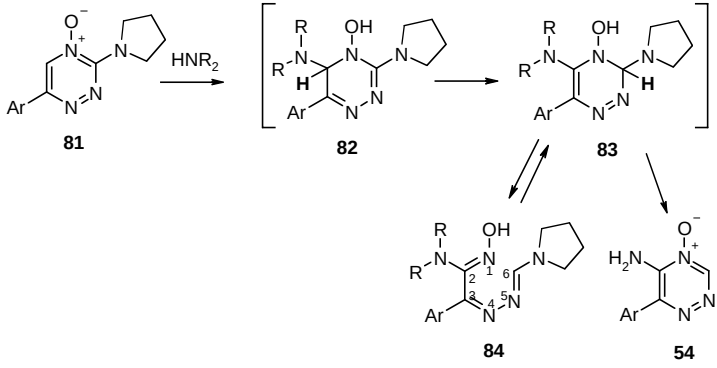
R^3, R^4, R^5 = H, Me; R^6 = OH, Me, C_6H_{13}

The reaction of 1,2,4-triazine 4-oxides **55** with thiophenols proceeds in the same manner, resulting in the corresponding 5-arylmercapto-1,2,4-triazines **80** in high yields. Thiophenols in this case react as S-nucleophiles, in spite of the relative phenols—the C-nucleophiles (01RCB1068).

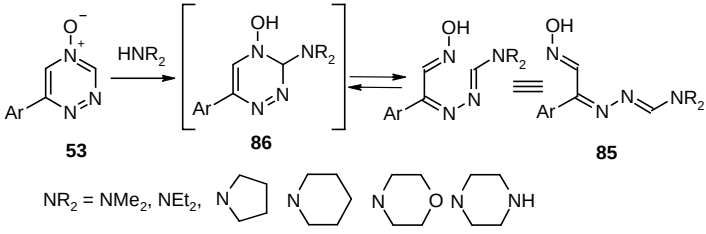


Ar = Ph, 4-Cl-C_6H_4, 4-OH-C_6H_4, 3-OMe-C_6H_4

Another pathway for the aromatization of the σ^H-adducts was found in the reactions of 3-pyrrolidino-1,2,4-triazine 4-oxide **81** with amines. Thus the treatment of 1,2,4-triazine 4-oxide **81** with ammonia leads to 5-amino-1,2,4-triazine 4-oxides **54**—products of the telesubstitution reaction. In this case the σ^H-adduct **82** formed by the addition of ammonia at position 5 of the heterocycle undergoes a [1,5]sigmatropic shift resulting in 3,4-dihydro-1,2,4-triazine **83,** which loses a molecule of pyrrolidine to yield the product **54.** This mechanism was supported by the isolation of the key intermediates for the first time in such reactions—the products of the sigmatropic shift in the open-chain tautomeric form of triazahexatriene **84.** The structure of the latter was established by NMR spectroscopy and X-ray analysis. In spite of its open-chain character, **84** can be easily aromatized by refluxing in ethanol to form the same product **54** (99TL6099).

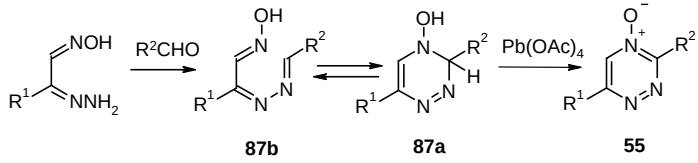


Similarly, ring opening was found in reactions of 6-aryl-1,2,4-triazine 4-oxides **53** with aliphatic amines, yielding open-chain 6-amino-1-hydroxy-1,4,5-triazahexatrienes **85.** In this case, however, the nucleophile adds to the 3 position of the heterocycle, resulting in σ^H-adducts **86,** which undergo reversible ring opening (98ZOR418).



The ring–chain isomerism was studied in a series of 4-hydroxy-3,4-dihydro-1,2,4-triazines **87,** which are models for σ^H-adducts at the 3 position of the

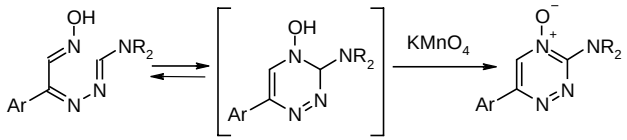
1,2,4-triazine 4-oxides. Compounds **87** were obtained by condensation of isonitrosoacetophenone hydrazones with aldehydes. It was found by NMR spectroscopy that the cyclic form of the 3,4-dihydro-1,2,4-triazines **87a** exists in the solution in equilibrium with the open-chain form of 1-hydroxy-1,4,5-triazahexatrienes **87b.** The ratio of the isomers strongly depends on the nature of the substituent R. Thus the aliphatic substituents shift the equilibrium to the cyclic form **87a,** while the aromatic or heteroaromatic ones shift the equilibrium to the open-chain form **87b.** But in spite of the isomer ratio, treatment of compounds **87** with an oxidizing agent, lead(IV) acetate, affords products of their aromatization—the corresponding 3-substituted 1,2,4-triazine 4-oxides **55** (97MC238, 98ZOR423).



Ar = Ph, 4-Tol, 4-Cl-C_6H_4, *etc.*

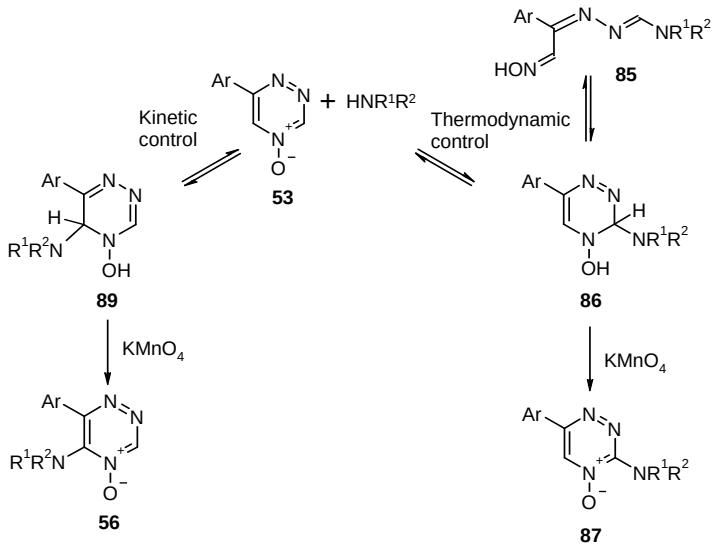
R = Me, Et, Pr^i, C_6H_{13}, C_7H_{15}, Ph, 4-$NO_2C_6H_4$, 4-$NMe_2C_6H_4$, 4-OH-C_6H_4, furyl, indolyl-3 *etc.*

Open-chain tautomerism is a general feature of 4-hydroxy-3,4-dihydro-1,2,4-triazines, including σ^H-adducts at position 3 of the 1,2,4-triazine 4-oxides. Thus triazahexatrienes **85** are the open-chain form of σ^H-adducts **86** and can be aromatized by oxidation with $KMnO_4$, yielding 3-amino-1,2,4-triazine 4-oxides **88** (98ZOR418).



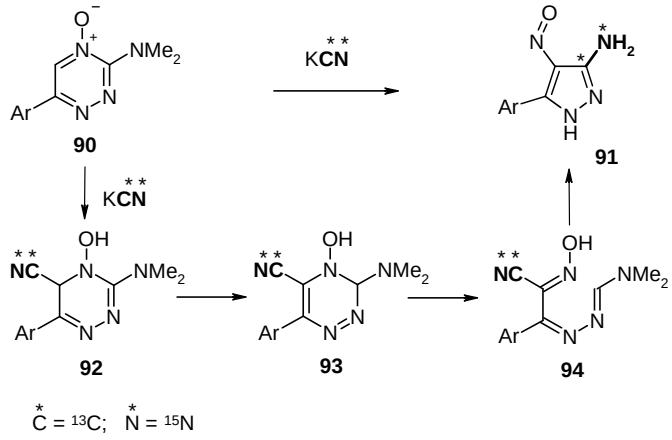
It was clearly shown by NMR spectroscopy that the addition of ammonia or primary or secondary alkylamines at position 5 of the 1,2,4-triazine 4-oxides to give the adducts **89** is a kinetically controlled process, while addition at position 3 to form the ring-opening products **85** is a thermodynamically controlled process.

The increase in thermodynamic stability of **85** is achieved by easy ring opening (01H127). This knowledge allows one to control the regioselectivity of the oxidative amination of the 6-aryl-1,2,4-triazine 4-oxides **53,** obtaining either (i) the 5-amino-1,2,4-triazine 4-oxides **56** in the reaction of **53** with amines at low temperature in the presence of the oxidant or (ii) the 3-amino-1,2,4-triazine 4-oxides **88,** provided the reaction is carried out in two steps (addition and oxidation) at room temperature or higher.

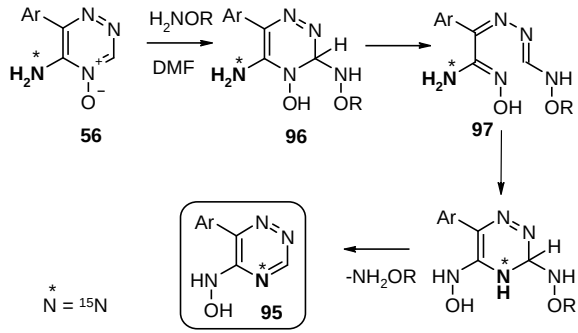


4. *Ring Transformation Reactions Initiated by Nucleophilic Attack*

There are further examples of ring transformations of 1,2,4-triazine 4-oxides. The reaction of 3-dimethylamino-1,2,4-triazine 4-oxides **90** with KCN leads to a ring contraction resulting in 3-amino-4-nitrosopyrazoles **91.** The reaction proceeds according to the ANRORC [addition of nucleophile, ring opening, ring closure] mechanism as follows. The addition of the nucleophile to the 5 position of the heterocycle results in σ^H-adducts **92,** which undergo a [1,5]sigmatropic shift of the hydrogen to form 4-hydroxy-3,4-dihydro-1,2,4-triazine **93.** The ring opening of intermediate **93** with cleavage of the C(3)—N(4) bond and subsequent recyclization gives product **91.** This mechanism was proved by reaction of **90** with the isotope-labeled KCN containing 80% excess ^{15}N and 60% excess ^{13}C; this resulted in aminopyrazoles **91*** with the same excess of isotopes, where the ^{15}N label was found to be at the amino group with ^{13}C enrichment at position 3 of the pyrazole ring (99KGS532).

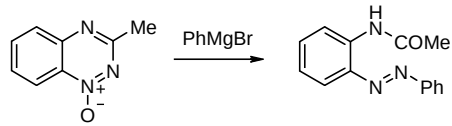


Amidine ring transformation was found to proceed in the reaction of 5-amino-1,2,4-triazine 4-oxides **56** with hydroxylamine or *O*-methylhydroxylamine to give 5-hydroxylamino-1,2,4-triazines **95.** The reaction is initiated by the addition of the nucleophile at the 3 position of the 1,2,4-triazine ring. Following the ring opening of the σ^H-adducts **96** with cleavage of the C(3)—N(4) bond, recyclization of the open-chain intermediate **97** gives the 5-hydroxylaminotriazine **95.** The products' structure and the suggested mechanism were proved by the reaction of ^{15}N-labeled 1,2,4-triazine 4-oxides **56*** containing 84% enrichment of ^{15}N at the amino group. This resulted in the hydroxylamino-1,2,4-triazine **95*** containing the same 84% excess of ^{15}N. NMR studies of the products **84*** and their hydrolytic deamination show that the nitrogen of the amino group in the starting 1,2,4-triazine 4-oxides **56** becames incorporated in the 1,2,4-triazine ring of **95** as the N(4) atom (00TL7379).

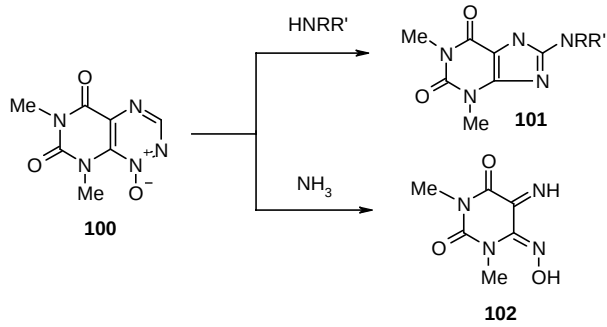


In both these ring transformation reactions, the ANRORC "troika" process takes place [99AHC(74)8]. Usually, however, the action of a nucleophile on 1,2,4-

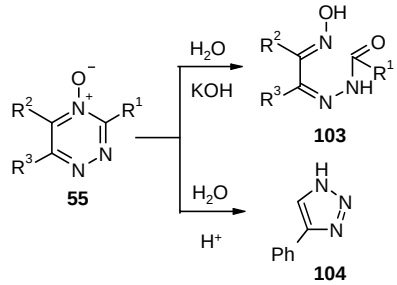
triazine *N*-oxides leads only to products of ring cleavage. Thus the reaction of 3-methyl-1,2,4-benzotriazine 1-oxide **98** with phenylmagnesium bromide results in the open-chain product 2-phenylazoacetanilide **99** [73JCS(CC)622].



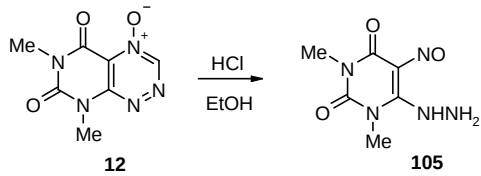
The reaction of the fervenulin 1-oxides **100** with secondary amines results in contraction of the 1,2,4-triazine ring to form 2-amino-5,7-dimethylimidazo[4,5-*e*] pyrimidine-4,6(5*H,*7*H*)-diones **101.** The reaction of the same fervenulin 1-oxides **100** with ammonia leads to the 1,2,4-triazine ring cleavage product, 1,3-dimethyl-5-imino-6-isonitrosouracil **102** (94KGS1253).



1,2,4-Triazine 4-oxides **55** undergo hydrolytic cleavage of the ring under both acidic and basic conditions. For instance, the treatment of 1,2,4-triazine 4-oxides **55** with 2 *M* KOH leads to ring opening, with formation of *N*′-(2-hydroxylimino-ethylidene) hydrazides of carboxylic acids **103.** At the same time the hydrolysis of 1,2,4-triazine 4-oxides under acidic conditions results in ring contraction to 1,2,3-triazoles **104** (76LA153).

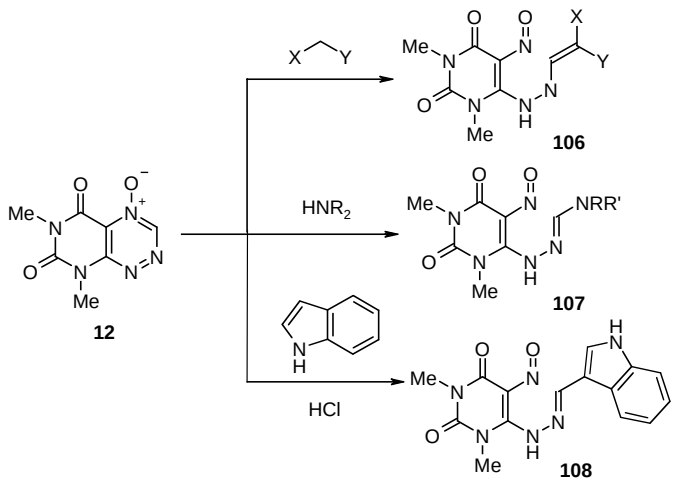


Reaction of the fervenulin 4-oxides **12** with HCl in ethanolic solution results in ring opening, yielding 1,3-dimethyl-5-nitroso-6-hydrazinouracil **105** (78JOC469, 86KFZ1228).



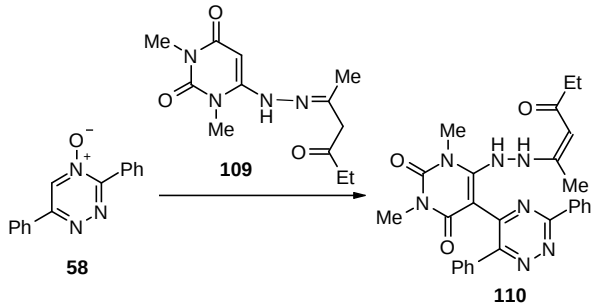
12 **105**

Fervenulin 4-oxide **12** undergoes 1,2,4-triazine ring opening after addition of different nucleophiles at the 3 position of the heterocycle. Thus, the reaction of fervenulin 4-oxide **12** with CH-active compounds leads to 1,3-dimethyl-5-nitroso-6-(ethen-1-ylhydrazino)uracils **106** (87KFZ1446). Fervenulin 4-oxide **12** reacts with amines or indoles in the same manner, resulting in 6-amino- and 6-indol-3-yl-methylenehydrazino-5-nitrosouracil **107, 108** (85KGS998, 91MC46, 97KFZ49).



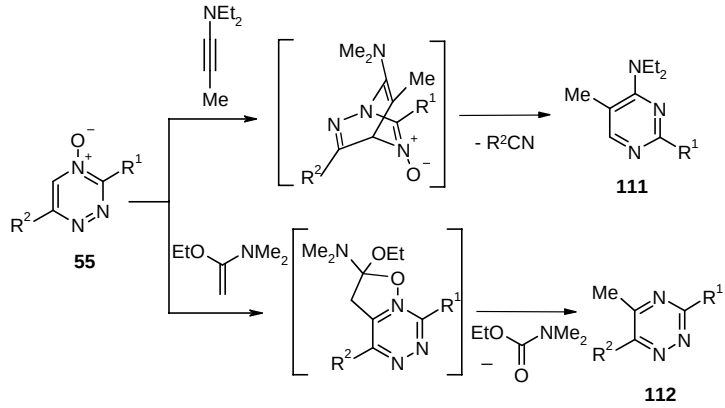
12 **106** **107** **108**

The 1,3-dimethyluracil derivative **109** with two reactive centers reacts with 1,2,4-triazine 4-oxide **58** only at the uracil fragment to afford compound **110** (96MC116).



5. *Cycloaddition Reactions*

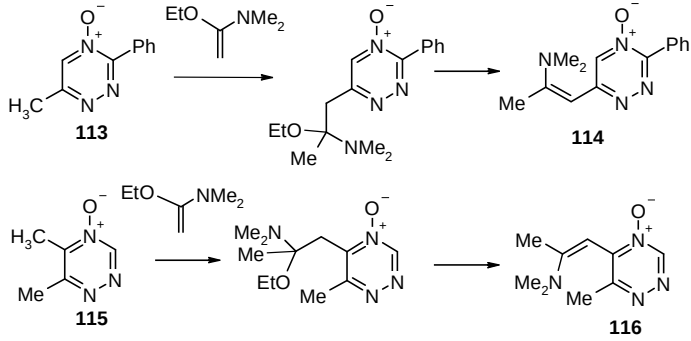
The cycloaddition reaction of 1,2,4-triazines *N*-oxides proceeds differently from the reaction of the corresponding 1,2,4-triazines. Thus the 1,2,4-triazine 4-oxide **55** acts only as a diene in the reaction with 1-diethylaminopropyne to afford 2-methyl-4-(dimethylamino)pyrimidines **111.** At the same time the 1,2,4-triazine 4-oxides **55** react with 1-(dimethylamino)-1-ethoxyethylene by 1,3-dipolar cycloaddition to give 5-methyl-1,2,4-triazines **112** (78CB240).



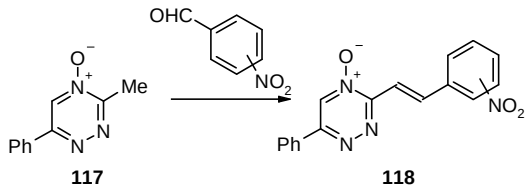
E. Reactivity of Substituents

The highly π-deficient character of the 1,2,4-triazine ring increases the nucleophilicity of the methyl group in methyl-1,2,4-triazine *N*-oxides in reactions with electrophilic alkenes and aldehydes. Thus treatment of the 6-methyl-3-phenyl-1,2,4-triazine 4-oxide **113** with 1-(dimethylamino)-1-ethoxyethylene leads to the

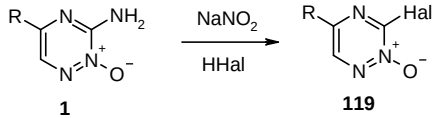
addition of the olefin to the methyl group followed by elimination of ethanol, resulting in 6-[(2-dimethylamino)-1-propenyl]-3-phenyl-1,2,4-triazine 4-oxide **114.** The reaction of this olefin with 5,6-dimethyl-1,2,4-triazine 4-oxide **115** proceeds in a similar manner, but the electrophilic attack is directed to the methyl group nearest to the *N*-oxide group at position 5 of the heterocycle, giving 5-[(2-dimethylamino)-1-propenyl]-6-methyl-1,2,4-triazine 4-oxide **116** (78CB240).



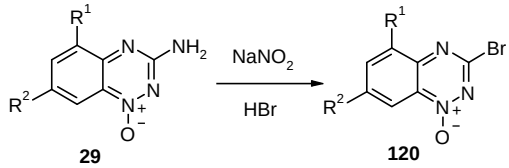
The reaction of 3-methyl-6-phenyl-1,2,4-triazine 4-oxides **117** with nitrobenzaldehyde leads to the condensation product, 3-(nitrophenylvinyl)-1,2,4-triazine 4-oxides **118.**



The treatment of 3-amino-1,2,4-triazine 2-oxides **1** or 3-amino-1,2,4-benzotriazine 1-oxides **29** with nitrous acid proceeds as a diazotization reaction, but the diazo compounds have never been isolated owing to the easy displacement of the diazo group with nucleophiles. Thus the reaction of 3-amino-1,2,4-triazine 2-oxides **1** with sodium nitrite in hydrochloric or hydrobromic acids leads to the corresponding 3-halogen-1,2,4-triazine 2-oxides **119** or 3-bromo-1,2,4-benzotriazine 1-oxides **120** (77JOC546, 82JOC3886).

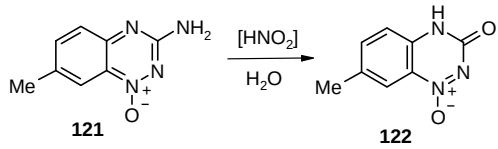


Hal = Cl, Br

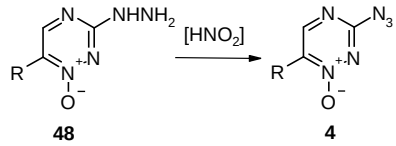


R^1, R^2 = H, Me

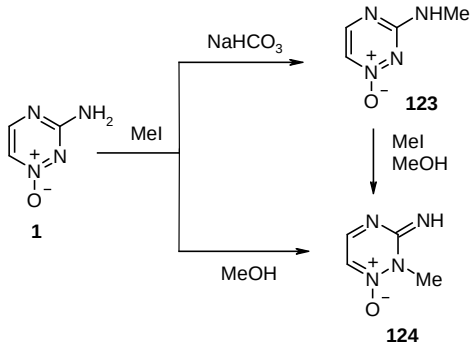
7-Methyl-1,2,4-benzotriazin-3(4*H*)-one 1-oxide **122** can be obtained in good yield by the diazotization of **121** to give 3-diazo-7-methyl-1,2,4-benzotriazine 1-oxide followed by the substitution of the diazo group with water (82JHC497).



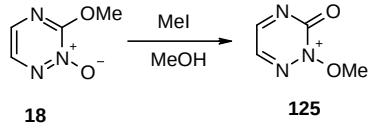
The diazotization of 3-hydrazino-1,2,4-triazine 1-oxides **48** results, as expected, in 3-azido-1,2,4-triazine 1-oxides **4** (77JHC1221, 77JOC3498).



The reaction of 3-amino-1,2,4-triazine 1-oxide **1** with methyl iodide in the presence of sodium bicarbonate leads to the methylation of the amino group to afford 3-methylamino-1,2,4-triazine 1-oxide **123.** This *N*-oxide **123,** under neutral conditions in the presence of MeI, undergoes methyl group migration to the N(2) atom of the 1,2,4-triazine ring, yielding 3-imino-2-methyl-1,2,4-triazine 1-oxide **124.** The same product **124** was obtained by direct methylation of compound **1** under neutral conditions (84TL1677).



A similar migration of the methyl group was found in 3-methoxy-1,2,4-triazine 2-oxides **18** under the same conditions to afford the 2-methoxy-1,2,4-triazin-3(2*H*)-one **125** (84TL1677).

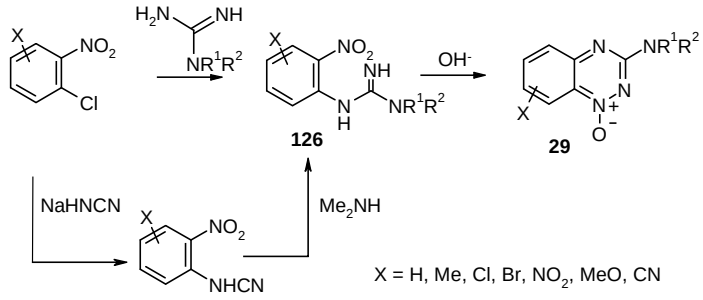


IV. Methods for the Synthesis of 1,2,4-Triazine *N*-Oxides

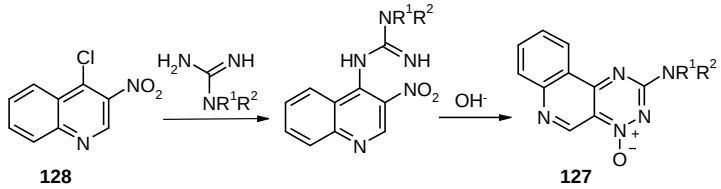
1,2,4-Triazine *N*-oxides can be obtained by two general methods: by direct oxidation of the parent 1,2,4-triazines with organic peracids, and by the formation of the *N*-oxide group of the 1,2,4-triazine ring by cyclization involving nitro, nitroso (isonitroso), or hydroxylamino groups.

A. Synthesis of Annelated 1,2,4-Triazine 1-Oxides Involving a Nitro Group

Aromatic and heteroaromatic nitro compounds containing a guanidine fragment at the *ortho* position to a nitro group readily cyclize under strong basic or acidic conditions, resulting in the corresponding benzo- or heteroannelated 1,2,4-triazine 1-oxides. This approach was used for the synthesis of a number of 3-amino-1,2,4-benzotriazine 1-oxides **29** by treatment of 2-nitrophenylguanidine **126** with an alkali (79GEP2740887, 88MI1, 88MI2, 89MI, 90MI, 94GEP4244069). The open-chain precursors **126** of the benzotriazine 1-oxides can be obtained starting with the reaction of 2-nitrochlorobenzene with guanidine or sodium cyanamide and dimethylamine (in the latter case, 3-dimethylamino-1,2,4-benzotriazine 1-oxides **29** are formed).

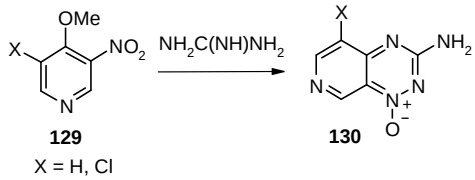


In a similar way, 3-amino-1,2,4-triazino[6,5-*c*]quinoline 4-oxides **127** were synthesized by the reaction of 4-chloro-3-nitroquinoline **128** with guanidine, followed by the cyclization of intermediate arylguanidines under basic conditions (81JHC1537).

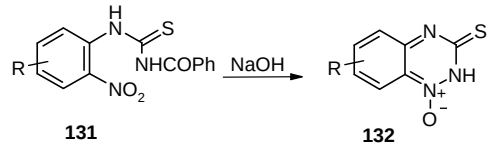


R = H, Me; R′ = H, Me, Et, *n*-Bu, *n*-$C_{10}H_{21}$, CH_2Ph, $CH_2CH_2NEt_2$

The reaction of 4-methoxy-3-nitropyridines **129** with guanidine under similar conditions results in 3-aminopyrido[3,4-*e*]-1,2,4-triazine 1-oxides **130** (76MI).



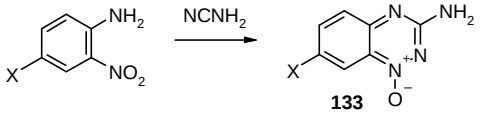
The cyclization of *N*-(2-nitrophenyl)-*N*′-benzoylthiourea **131** and its derivatives under basic conditions affords the corresponding 1,2,4-benzotriazin-3(2*H*)-thione 1-oxides **132** (80ACH123).



131 **132**

R = H, Cl, OMe, Me, SH

The reaction of 2-nitroanilines with cyanamide gives 3-amino-1,2,4-benzotriazine 1-oides **133** (88MI1, 94GEP4244009).



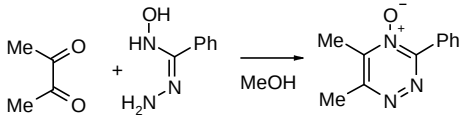
133

X = H, Me, OMe, Br, Cl, OPh, CN, NO_2

B. Synthesis of 1,2,4-Triazine 4-Oxides by Cyclization Involving Nitroso (Isonitroso) or Hydroxylamino Groups

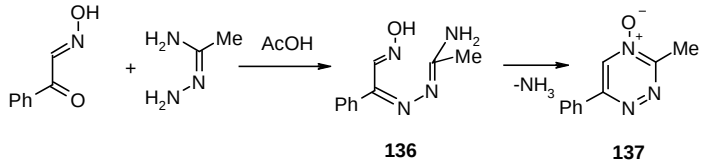
It is known that 1,2,4-triazine 4-oxides, in contrast to 1,2,4-triazine 1- and 2-oxides, cannot be obtained by oxidation. Therefore, the only way to obtain 1,2,4-triazine containing the *N*-oxide group at position 4 of the heterocycle is to form the triazine ring by cyclization, starting from compounds bearing nitroso (isonitroso) or hydroxylamino groups. There are several ways to carry out such cyclizations.

The reaction of hydroxyamidrazone **134** with dimethylglyoxal in methanol leads to 5,6-dimethyl-3-phenyl-1,2,4-triazine 4-oxide **135** (71LA12).



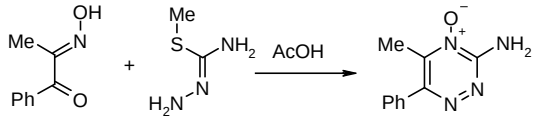
134 **135**

The condensation of amidrazone with isonitrosoacetophenone occurs via formation of the hydrazone **136.** The elimination of the ammonia molecule from intermediate **136** yields 3-methyl-6-phenyl-1,2,4-triazine 4-oxide **137** (71LA12).



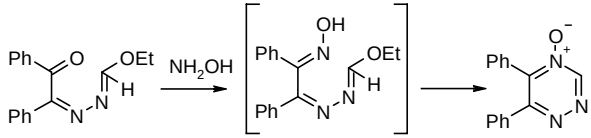
136 **137**

When *S*-methylthiosemicarbazide is used instead of amidrazone, 3-amino-1,2,4-triazine 4-oxides can be obtained. In this way 3-amino-5-methyl-6-phenyl-1,2,4-triazine 4-oxide **138** was synthesized from isonitrosopropiophenone [52CIL907, 89IJC(B)556].



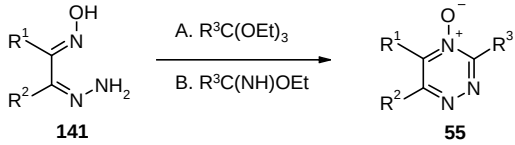
138

5,6-Diphenyl-1,2,4-triazine 4-oxide **139** was obtained by reaction of diphenylglyoxal mono-2-ethoxymethylenehydrazone **140** with hydroxylamine. The reaction proceeds via formation of an isonitroso intermediate, followed by cyclization to the 1,2,4-triazine 4-oxide **139** (71LA12).



140 **139**

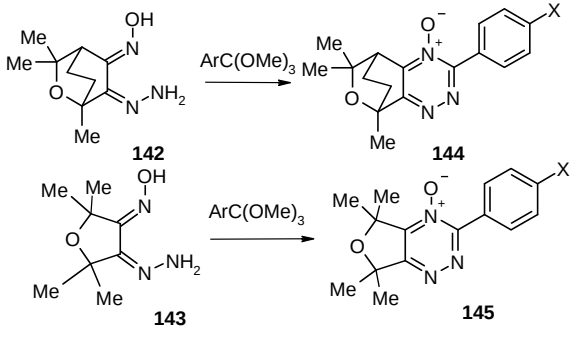
A more useful method for the synthesis of 1,2,4-triazine 4-oxides is the cyclization of α-hydrazonooximes **141** with orthocarboxylates or iminoesters. A variety of 1,2,4-triazine 4-oxides **55** were obtained by this methodology (71LA12, 73TL1429, 77LA1713, 78JMC623, 86JHC721, 87KGS257).



141 **55**

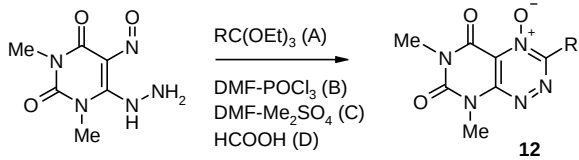
R^1 = H, Me, Ph; R^2, R^3 = H, Me, *t*-Bu, Ph, 4-$NO_2C_6H_4$, 4-MeO-C_6H_4

In the same manner, the reactions of 5-isonitroso-1,3,3-trimethyl-2-oxabicyclo-[2.3.3]octan-6-one hydrazone **142** and 4-isonitroso-2,2,5,5-tetramethyltetrahydrofuran-3-one hydrazones **143** with the corresponding orthobenzoates result in 3-aryl-5,8-dihydro-6,6,8-trimethyl-5,8-ethanopyrano[4,3-*e*]-1,2,4-triazine 4-oxides **144** and 3-aryl-5,7-dihydro-5,5,7,7-tetramethylfurano[3,4-*e*]-1,2,4-triazine 4-oxides **145** (79JHC1389).



142 **144** **143** **145**

Heteroannelated 1,2,4-triazine 4-oxides—fervenulin 4-oxides **12**—were obtained starting from 6-hydrazino-1,3-dimethyl-5-nitrosouracil. Orthocarboxylates, formic acid, dimethyl sulfate, or DMF in the presence of $POCl_3$ were used as cyclization agents (77H273, 78JOC175, 78JOC469).

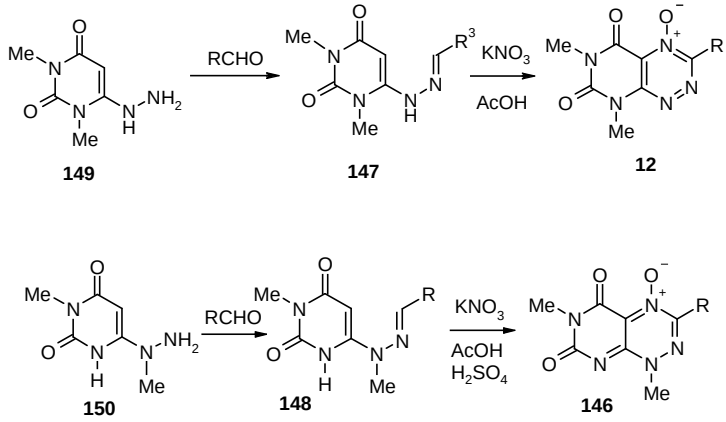


12

The method for the synthesis of 1,2,4-triazine 4-oxides **55** involving the condensation of isonitrosoacetophenone hydrazones with aldehydes followed by the oxidation of the intermediates **87** with lead(IV) acetate was reported above (97MC238, 98ZOR423).

To prepare fervenulin 4-oxides **12** or toxoflavine 4-oxides **146,** it is convenient to use the reaction of 1,3-dimethyl-2,4-dioxopyrimidin-6-yl hydrazone **147** or *N*-(3-methyl-2,4-dioxopyrimidin-6-yl) *N*-methylhydrazone **148** with potassium nitrate in acetic acid [75CPB1885, 76CPB338, 76JCS(CC)658, 82JHC1309, 93CPB362]. Diethyl azodicarboxylate can be used instead of potassium nitrate [76JCS(P1)713].

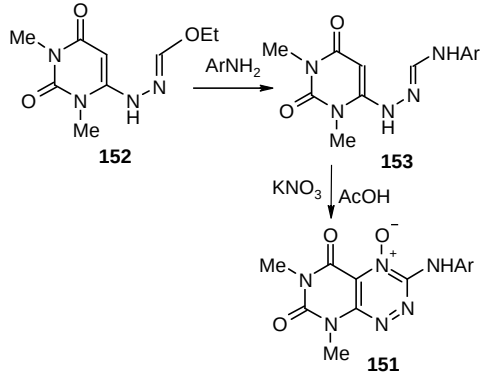
The reaction seems to proceed via formation of the NO group followed by oxidative cyclization. Compounds **147** and **148** were synthesized from the corresponding hydrazines **149** and **150** and aldehydes.



149 **147** **12**

150 **148** **146**

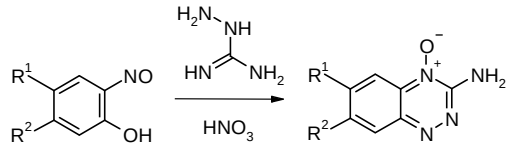
3-Anilinofervenulin 4-oxides **151** were synthesized by the reaction of 6-hydrazino-1,3-dimethyluracil with triethyl orthoformate, followed by the treatment of the hydrazide **152** with aniline and further cylization of **153** in the presence of potassium nitrate in acetic acid (82JHC1309).



152 **153** **151**

Ar = Ph, 4-ClC_6H_4, Br-ClC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4

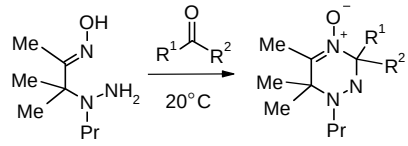
The reaction of 2-nitrosophenols with aminoguanidine nitrate in the presence of nitric acid yields 3-amino-1,2,4-benzotriazine 4-oxides **154** (75KGS1571).



154

R^1 = H, Me; R^2 = Cl, Br, Me

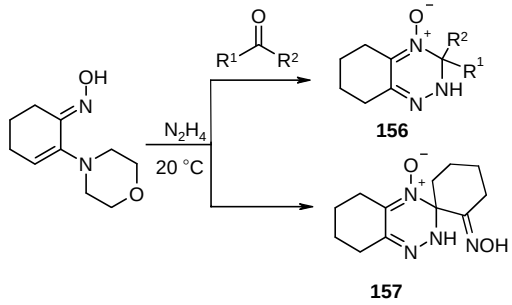
3-Hydrazino-3-methylbutan-2-one oxime reacts with aldehydes and ketones, resulting in 1,3,4,6-tetrahydro-1,2,4-triazine 4-oxides **155** (77ZOR2617).



155

R^1 = H, Me, Pr^i; R^2 = H, M

Treatment of 1-morpholino-6-iminocyclohexene with hydrazine hydrate in the presence of ketones leads to 2,3,5,6,7,8-hexahydro-1,2,4-benzotriazine 4-oxides **156.** In the absence of carbonyl compounds, this reaction affords the spirobicyclo compound **157** (75S794).

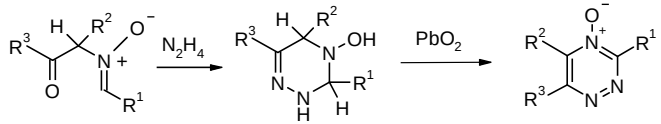


156

157

R^1, R^2 = Me, CH_2Ph, -$(CH_2)_5$-, -$(CH_2)_6$-

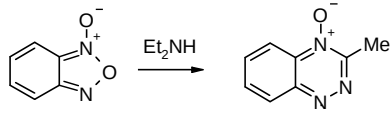
The 1,2,4-triazine 4-oxides **55** were synthesized by the reaction of nitrones **158** (generated from α-hydroxylamino ketones and aldehydes) with an excess of hydrazine, followed by the oxidation of the intermediate 4-hydroxy-2,3,4,5-tetrahydro-1,2,4-triazines **159** with lead(IV) oxide (73KGS134).



158 **159** **55**

R^1, R^2, R^3 = Me, Et, Ph

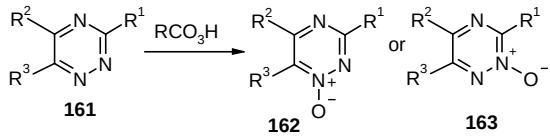
The reaction of benzofurazan *N*-oxide with diethylamine affords 3-methyl-1,2,4-benzotriazine 4-oxide **160** (79T681, 82T1793).



160

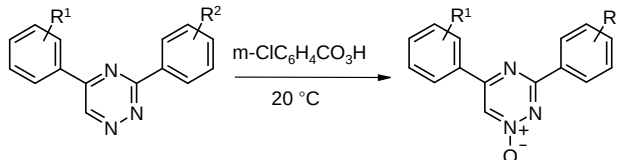
C. Synthesis of 1,2,4-Triazine 1- and 2-Oxides by Direct Oxidation of Parent 1,2,4-Triazines

The N-oxidation of 1,2,4-triazines with organic peracids or hydrogen peroxide in the presence of carboxylic acid proceeds at the N(1) or N(2) atom of the heterocycle. The direction of the reaction strongly depends on the substituents in the 1,2,4-triazine ring (Table IV). For instance, the oxidation of 3-amino-1,2,4-triazines **161** ($R^1 = NH_2$) gives mainly 2-oxides **162.** It seems that amino–imino tautomerism in 3-amino-1,2,4-triazine 2-oxides **162** is the reason for obtaining the products of the oxidation only at the N(2) atom of the heterocycle. At the same time, treatment of 3-alkoxy-1,2,4-triazines **161** ($R^1 = OAlk$) with organic peracids leads to 3-alkoxy-1,2,4-triazine 1-oxides **163** (64CPB1329, 66JOC3917, 71JOC787, 73JOC3277).



161 **162** **163**

Oxidation of 3,5-diaryl-1,2,4-triazines **164** with *m*-chloroperbenzoic acid results in 1,2,4-triazine 1-oxides **165** in 75–98% yield (95MI).



164 **165**

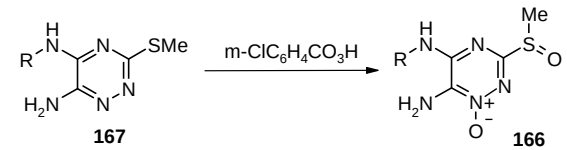
R^1, R^2 = H, 2-Me, 3-Me, 4-Me, 2-Cl, 3-Cl, 4-Cl, 3-CF_3, 4-Br, 2-F, 3-F, 4-F, 4-CF_3

TABLE IV

SELECTIVITY OF THE N-OXIDATION OF THE 1,2,4-TRIAZINES DEPENDING ON SUBSTITUENTS

R^1	R^2	R^3	Oxidizing agent	Yield (%) **162**	Yield (%) **163**	References
NH_2	H	H	*m*-$ClC_6H_4CO_3H$	80	0	77JOC546
NH_2	Me	H	*m*-$ClC_6H_4CO_3H$	80	0	77JOC546
$NH(CH_2)_2Cl$	H	H	*m*-$ClC_6H_4CO_3H$	51	0	77JOC546
$NH(CH_2)_2Cl$	Me	H	*m*-$ClC_6H_4CO_3H$	77	0	77JOC546
$NH(CH_2)_2Cl$	Ph	H	*m*-$ClC_6H_4CO_3H$	35	0	77JOC546
NH_2	Me	Me	H_2O_2/AcOH	30	0	73JOC3277
NH_2	Ph	H	H_2O_2/AcOH	37	0	66JOC3917
NHCOMe	Ph	H	H_2O_2/AcOH	45	0	66JOC3917
NHCOEt	Ph	H	H_2O_2/AcOH	41	0	66JOC3917
H	Me	Me	$PhCO_3H$	0	30	66JOC3917
H	Ph	Ph	$PhCO_3H$	0	17	66JOC3917
H	Ph	H	$PhCO_3H$	0	26	66JOC3917
OMe	H	H	*m*-$ClC_6H_4CO_3H$	0	15	66JOC3917
				0	30	71JOC787
OMe	Ph	Ph	$PhCO_3H$	0	23	66JOC3917
OMe	Me	H	$PhCO_3H$	0	26	66JOC3917
OMe	Ph	H	$PhCO_3H$	0	39	66JOC3917

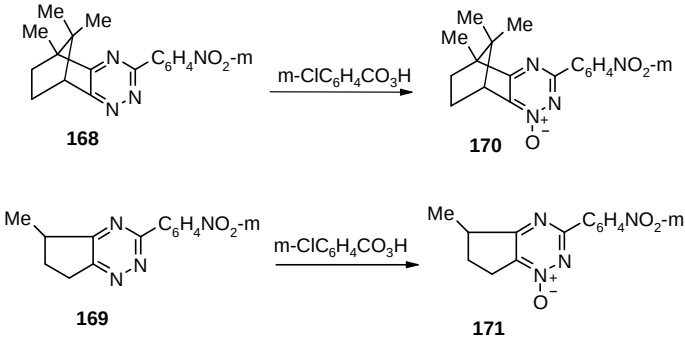
5,6-Diamino-3-methylsulfinyl-1,2,4-triazine 1-oxides **166** were synthesized using the same procedure starting from 5,6-diamino-3-methylthio-1,2,4-triazines **167** [96JCS(P1)2253].



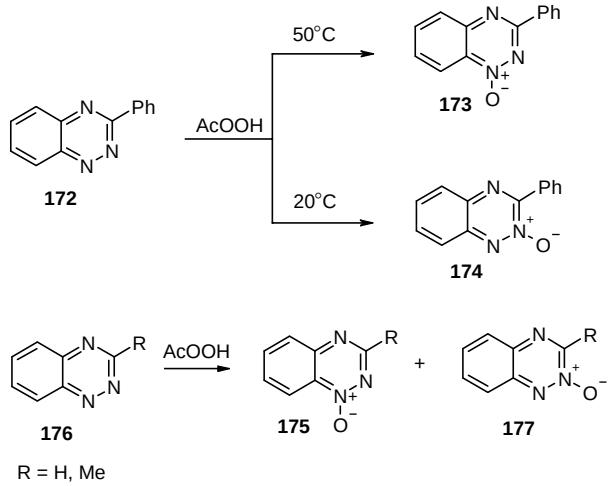
167 **166**

R = H, CH_2Ph

The treatment of 1,2,4-triazines containing the camphor (**168**) or methylcyclopentane fragment (**169**) with *m*-chloroperbenzoic acid gives annelated 1,2,4-triazine 1-oxides **170** and **171,** respectively (82JHC1201).



In some cases, the position of the N-oxidation depends on the temperature. The reaction of 3-phenyl-1,2,4-benzotriazine **172** with peracetic acid affords 3-phenyl-1,2,4-benzotriazine 1-oxide **173** at 50°C and 2-oxide **174** at room temperature (57JCS3186). Only the 1-oxide **175** was obtained by the oxidation of 3-unsubstituted 1,2,4-benzotriazine **176.** The oxidation of 3-methyl-1,2,4-benzotriazine **176** (R = Me) under the same conditions results in a mixture of 3-methyl-1,2,4-benzotriazine 1-oxide **175** and 2-oxide **177** in 25 and 10% yields, respectively.



V. Conclusion

1,2,4-Triazine 4-oxides are readily available compounds that can be used successfully for the functionalization of the 1,2,4-triazine ring. The possibilities for the

transformation of 1,2,4-triazine *N*-oxides, both to other novel 1,2,4-triazines and to other heterocyclic systems, only increases the value of these compounds. The high reactivity of the 1,2,4-triazine *N*-oxides toward nucleophiles allows studies of the nucleophilic substitution of hydrogen, which proceeds in this field by almost all known paths, and opens up possibilities for finding new reactions.

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