Oxidative Amino-Dehydrogenation of Azines

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Dedicated to the late Professor Marian Wozniak, who contributed greatly to the development of oxidative amination reactions

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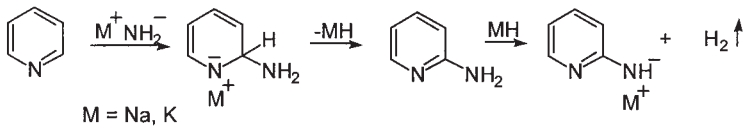
I. Introduction

Many bioactive azaheterocycles are characterized by the presence of an amino group (thiamine, cytosine, adenine, cytokinines, riboflavine, viagra, etc.). Moreover, aminoazines are valuable intermediates in organic synthesis and have found application in the development of pharmaceutically and agriculturally useful products. The extent of the interest is indicated by an overwhelming number of papers concerning the preparation of aminoazines. Methods which are frequently used are: (a) ring closure reactions of substituted non-cyclic moieties; (b) nucleophilic displacements of leaving groups (alk(aryl)oxy, silyloxy, halogen, O-sulfonate, O-phosphoroamidate, thioalkyl(aryl), sulfoxide, sulfone, cyano, nitro) by ammonia, amine, amidates) (90AHC(49)117); (c) nucleophilic replacements of aromatic hydrogens, (S_NH substitutions) (88T1, 94MI1), in particular by the well-developed *vicarious* substitution reactions (99PJC151, 98JPOC341); (d) in more specific cases by reduction of a nitro or nitroso group or by ring transformation reactions (02THS1).

This review deals with oxidative amino-dehydrogenation reactions. It concerns reactions in which a substrate reacts with an aminating agent *in the presence of an oxidant*. This amination methodology has been found to be very useful to replace ring hydrogens in highly electron-deficient azaheterocycles by an amino, alkylamino, dialkylamino, or imino group.

Aminations of azines were usually carried out by heating a π-deficient heterocycle with the metal salt of the conjugated base of an amine or (substituted) amine in an inert, apolar solvent. Several excellent review articles on this amination methodology have appeared in the literature (71MI1, 78RCR1042, 42OR91, 88AHC(44)1, 90AHC(49)117).

One of the first amino-dehydrogenation reaction described in the literature is the Chichibabin amination. Treatment of pyridine with sodium amide in an inert aprotic solvent (toluene, xylene, tetraline, decaline, or *N*,*N*-dimethylaniline) at elevated temperatures yields 2-aminopyridine in reasonable yield (24MI1, 20ZRO553). During the reaction, evolution of hydrogen takes place (42OR91). The regiospecific attack at the position, adjacent to the ring nitrogen, in an inert aprotic solvent is a general phenomenon in the Chichibabin amination of azines. That the addition mainly occurs at the C-2 position is due to the fact that the alkali metal amide, being a strongly bound ion-pair in the aprotic solvent, is added to the polarized C=N bond in the pyridine ring, forming the metal salt of σ-adduct 2-amino-1,2-dihydropyridinide. It has been suggested that a radical anion might be the precursor in the formation of the adduct (24MI1, 42JPS315, 54CR449, 77CHC210). This adduct is quite unstable due to the poor solvating power of the solvent, and aromatizes into 2-aminopyridine by loss



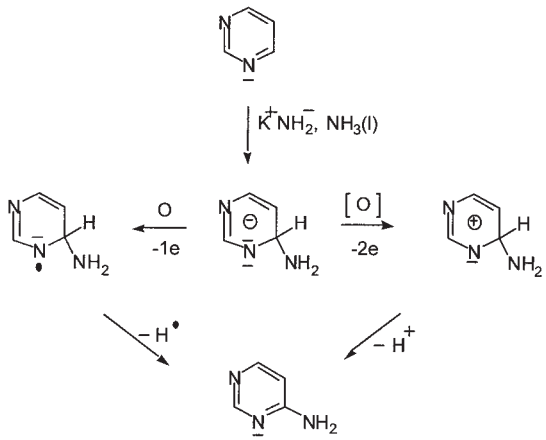
Scheme 1

of metal hydride. The metal hydride deprotonates the amino group with evolution of hydrogen (64TL3445, 70CRV667) (Scheme 1). Therefore, the S_NH reaction can formally be described to occur according to an Addition–Elimination [S_N(AE)] process, the potassium (sodium) hydride being the leaving molecule. Another suggestion, based on the experimental fact that dihydroheteroaromatics have been found as side-products in the amination of quinoline (65JHC330, 67CPB1910) as well as phenanthridine (73IJC825), is that the formation of the amino compound may take place in a Canizzaro-type disproportionation. The ring C=N bond in the starting material behaves as "aldehyde carbonyl" and receives the hydride ion by transfer from the adduct.

Sodium amide in the protic solvent liquid ammonia at the boiling point of −33 °C or even at lower temperatures, has also been used as the aminating system. The advantage of the liquid ammonia solution is its homogeneity and the use of low temperatures, avoiding side reactions. It has been used in the amination of pyridines, quinolines (38JOC424) and naphthyridines (83AHC(33)95, 83AHC(33)147). Addition of potassium nitrate improves the yield of the amination (34JA1748, 38JOC424, 72MI1). In the amination of naphthyridines sometimes potassium permanganate was used as oxidant, but its effect on the yield of the reaction was reported to be small (83AHC(33)95, 83AHC(33)147).

Liquid ammonia at low temperature together with potassium permanganate as oxidant is found to be a very useful methodology to introduce an amino group in highly electron-deficient heterocycles, such as nitropyridines, nitroquinolines, nitronaphthyridines, diazines, triazines, tetrazines, etc. (83AHC(33)95, 85T237, 87KGS1011, 88AHC(44)1, 88T1, 90AHC(49)117, 93ACS95, 94MI1). This aminating system at low temperature has the great advantage to be inactive with leaving groups, such as halogens, alkoxy or alkylthio groups.

The oxidative amination procedure is simple, but varies depending on the structure of the substrate. The substrate is dissolved in liquid ammonia, containing the potassium amide, reacted for a short time, after which the potassium permanganate is added. The reaction is completed by adding ammonium chloride to decompose the amide ion. The ammonia



Scheme 2

is evaporated off and the residue extracted with solvent. With highly electron-deficient substrates the use of potassium amide is not necessary; just dissolving the substrate in the liquid ammonia is sufficient. Thus, liquid ammonia acts as solvent as well as reagent. For a more detailed description of the procedure, one is referred to the original literature.

Amination under these homogeneous conditions is an important breakthrough in oxidative amination–dehydrogenation procedures. It has been predicted that "If these new oxidative aminations can be performed on a larger scale without any explosion hazard, they might be very useful preparatively" (90AHC(49)117).

The mechanistic role of the oxidant can be understood as follows. After addition of the amide ion to the azine (for example pyrimidine in Scheme 2) an anionic σ-adduct is formed, which is quite stable in this polar medium, as shown by NMR spectroscopy (see Section IV.A).

Since the hydride is a very poor leaving group, the role of the oxidant is to provide, in a redox-type reaction, two electrons to convert this anionic adduct into a cationic species, which aromatizes into the amino product by proton elimination (Scheme 2). It cannot be excluded that under these conditions a one-electron process occurs, yielding a pyrimidyl radical, that aromatizes by loss of a hydrogen atom.

This methodology has also been successfully applied to introduce alkylamino and dialkylamino groups into π-deficient azines, using an alkylamine or dialkylamine as solvent and reagent and potassium permanganate as oxidant. Moreover, this methodology has been applied to replace a ring hydrogen in quaternized azinium salts by an imino group.

In Section II the oxidative amino-dehydrogenation of monoazines, quinolines, naphthyridines, diazines, quinazolines, quinoxalines, triazines, tetrazines, and their bicyclic analogs is extensively discussed. Section III deals with the oxidative imino-dehydrogenation of quaternised azinium salts and Section IV with NMR data of the covalent σ-adducts and their kinetic and thermodynamic stabilities.

II. Oxidative Amino-Dehydrogenations

A. Pyridines, Quinolines, Isoquinolines, and Naphthyridines

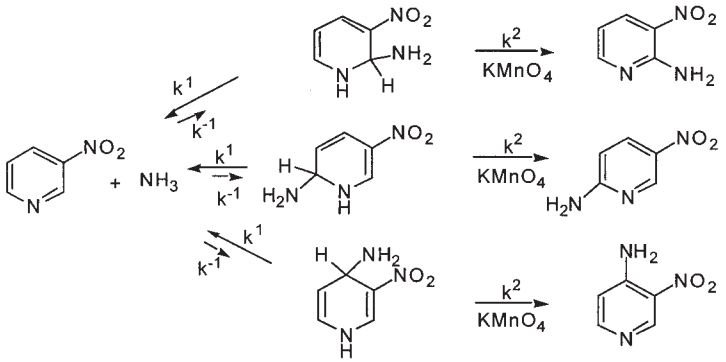
1. *Pyridines*

To prepare 2-aminopyridine by treatment of pyridine with potassium amide in liquid ammonia at $-33\,^{\circ}C$ and using permanganate as oxidant was not successful. No reaction takes place under these conditions. The aromaticity of the pyridine ring is too high to allow nucleophilic amide addition. It was surprisingly observed that treatment of a solution of 3-nitropyridine in liquid ammonia (thus without the presence of potassium amide) with potassium permanganate, gave after work-up a mixture of 2-amino-3-nitro- (33%), 4-amino-3-nitro- (24%), and 6-amino-3-nitropyridine (19%) (91LAC875). Due to the presence of the nitro group the π-deficiency is sufficiently high to allow the use of just liquid ammonia as aminating agent. The regioselectivity is however quite low; addition at position 2 is favored over addition at position 4 (ratio $\alpha/\gamma = 52/24$).

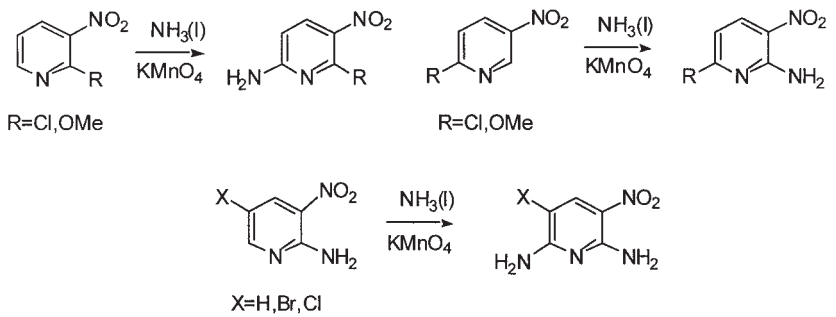
In general solutions of azines in liquid ammonia are homogeneous, making it possible to detect by ^{1}H- and ^{13}C-NMR spectroscopy the occurrence of intermediary compounds (see Section IV). In case of 3-nitropyridine the NMR spectrum in liquid ammonia did not feature any indication for intermediary covalent σ-adducts.

This result justifies the conclusion that the equilibrium between 3-nitropyridine and the possible adducts at C-2, C-4, and C-6 lies far to the left and that these adducts are only present in a small steady-state concentration (Scheme 3).

On addition of potassium permanganate the equilibrium shifts to the right, when the adducts are irreversibly oxidized into their respective amino-3-nitropyridines. Since the oxidation is assumed to be fast, the product composition probably reflects the kinetic composition of the three isomeric intermediates.



Scheme 3



Scheme 4

Site specificity was found to be considerably higher in oxidative amino-dehydrogenation reactions with derivatives of 3-nitropyridine. 2-R-3-nitropyridine (R = Cl, OMe) when treated with liquid ammonia and permanganate gives a reasonable yield of 6-amino-2-R-3-nitropyridine (R = Cl, OMe); 6-R-3-nitropyridine yields 2-amino-6-R-3-nitropyridine (R = Cl, OMe) (Scheme 4) (91LAC875). The corresponding 4-amino compounds are only obtained in small amounts. A similar observation was made on the low temperature oxidative amination of 2-amino-5-R-3-nitropyridines (R = H, Cl, Br).

All these amination reactions show exclusive S_NH substitution. There is hardly any indication for the formation of 3-nitropyridines, in which the chloro or methoxy group was replaced by an amino group, even when these leaving groups are present at the reactive α-position of the pyridine ring. It seems to be a characteristic feature of the oxidative amination

methodology that under the conditions of the reaction hardly any reaction involving substitution of leaving groups such as halogens, alkoxy, and thioalkyl groups occurs.

Oxidative amino-dehydrogenation of 2-, 4-, and 6-hydroxy-3-nitropyridines and of 4-amino- and 6-amino-3-nitropyridines met little success.

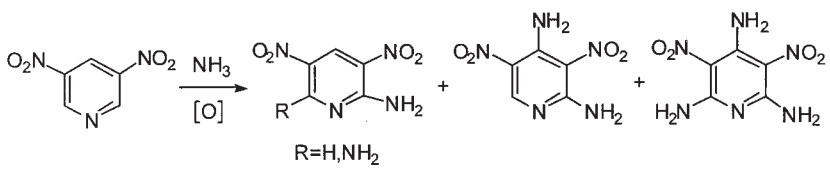
High selectivity combined with high yield was found when 3-nitropyridine reacts with a solution of DMSO/water (75/25), ammonia, and potassium permanganate at 22 °C. 6-Amino-3-nitropyridine was obtained in 90% yield; only a small amount of 4-amino-3-nitropyridine was formed (01TL4393, 01JCS(P1)376).

Due to its enhanced π-deficiency 3,5-dinitropyridine has a lower site selectivity and it can be expected that oxidative amino-dehydrogenations will take place at all three positions 2, 4, and 6. This has indeed been found. 3,5-Dinitropyridine gives a complex mixture of 2-amino-, 2,6-diamino-, 2,4-diamino-, and 2,4,6-triamino-3,5-dinitropyridines (Scheme 5) (85JOC484, 93ACS95). Mixtures of diamino- and triamino-3,5-dinitropyridines have also been found in the oxidative amination of 2-R-3,5-dinitropyridines ($R = NH_2$, OH, Cl, OMe) and 4-R-3,5-dinitropyridines ($R = NH_2$, Cl).

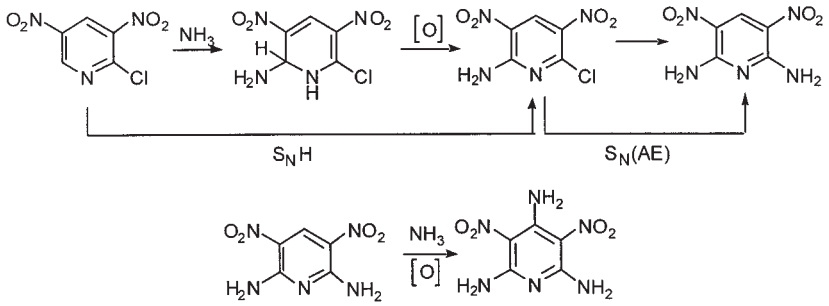
Amination of 2-chloro-3,5-dinitropyridine in liquid ammonia at −40 °C and potassium permanganate gave 2,6-diamino-3,5-dinitropyridine. Its formation indicates that besides S_NH at C-6, a S_N(AE) amino-dechlorination occurs at C-2 (Scheme 6).

NMR studies on σ-adduct formation between 2-chloro-3,5-dinitropyridine and liquid ammonia show that the site of covalent addition is temperature dependent: at −60 °C the C-4 adduct is formed, at −40 °C the C-6 adduct is obtained (85JOC484). Apparently, at −60 °C the C-4 adduct is the kinetically favored one, and at −40 °C the thermodynamically more stable C-6 adduct is obtained. The results are in agreement with those of the amination at −40 °C (Scheme 6).

Along these lines 3,5-dinitro-2,4,6-triaminopyridine has been obtained by oxidative amination of 2,6-diamino-3,5-dinitropyridine (96JHC895) (Scheme 6).



Scheme 5



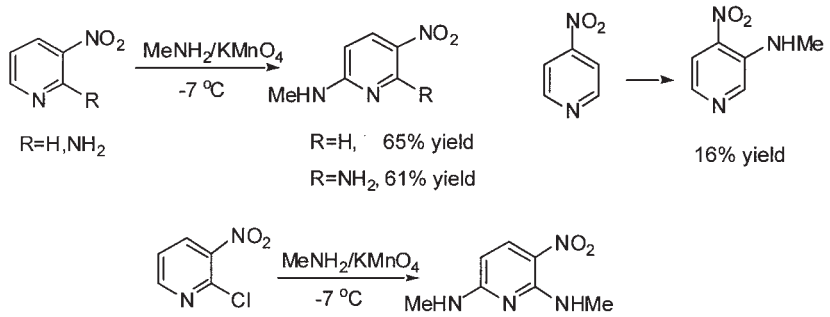
Scheme 6

Extensive investigations have been reported on the oxidative methylamination of 2-, 3-, and 4-nitropyridines (99JPC341). There is great interest in methylamino derivatives of nitroaza-aromatics due to a range of applications in medicine (90MI1). Treatment of a solution of 3-nitropyridine in boiling liquid methylamine (−7 °C) with potassium permanganate gives a reaction mixture from which 6-methylamino-3-nitropyridine could be isolated and a small yield of 2,6-bis(methylamino)-3-nitropyridine. It is evident that the site selectivity in the methylamination is higher than that found in the oxidative amination at −33 °C. Probably, due to the somewhat higher temperature of the boiling liquid methylamine (compared to that of the boiling liquid ammonia (−33 °C)), the equilibrium between the three possible isomeric adducts (Scheme 3), is shifted to the thermodynamically more stable *para* isomer. In these methylamination reactions no NMR investigation was mentioned about the occurrence of σ-adducts. It seems very reasonable to assume that the intermediates in these reactions are the 6-methylamino-1,6-dihydro-3-nitropyridines.

Methylamination of 2-amino-3-nitropyridine gives in good yield 2-amino-6-methylamino-3-nitropyridine, while methylamination of 6-amino-3-nitropyridine only gives (in a small yield) 6-amino-2-methylamino-3-nitropyridine (Scheme 7). The activating influence of the 3-nitro group on the C-6 *para* position explains this difference in reactivity.

2-Chloro-3-nitropyridine undergoes S_NH methylamination at C-6 as well as amino-dechlorination at C-2, 2,6-bis(methylamino)-3-nitropyridine being obtained (Scheme 7).

4-Nitropyridine does not give methylamination at position 2 but unexpectedly 3-methylamino-4-nitropyridine, although in low yield (Scheme 7) (99JPC341). The activating power of the nitro group on the *ortho* position is stronger than that of the ring nitrogen on the α position, ($k_{nitro}/k_{aza} > 1$), as has been observed before (65AHC145).

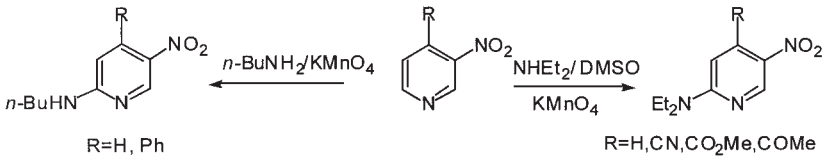


Scheme 7

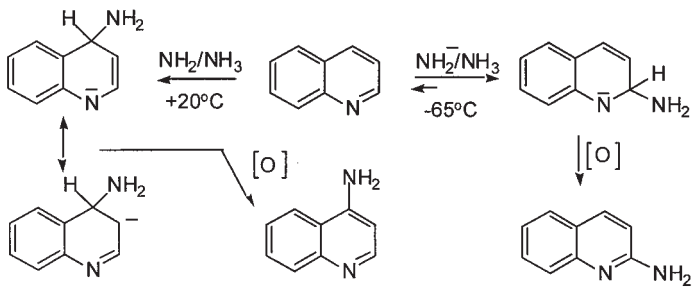
This method of alkylamination with potassium permanganate was also successfully applied to introduce a *n*-butylamino- and a diethylamino group in the para position of the nitro group in 4-R-3-nitropyridine (R = H, CN, CO_2Me, COMe) (01TL4393, 01JCS(P1)376). So 3-nitropyridine, after treatment with *n*-butylamine and potassium permanganate, is converted in excellent yield into 6-*n*-butylamino-3-nitropyridine (together with small yields of 2-*n*-butylamino-3-nitropyridine and 4-*n*-butylamino-3-nitropyridine). Diethylamination with high regiospecificity was also successfully achieved by treatment of 3-nitropyridine with a 25/75 mixture of diethylamine/DMSO and potassium permanganate. In a very reasonable yield S_NH substitution took place at the position *para* to the nitro group, 6-diethylamino-3-nitropyridine being obtained (Scheme 8). The presence of the solvent DMSO is essential since treatment of 3-nitropyridine with diethylamine and potassium permanganate or with a 25/75 mixture of diethylamine/water and potassium permanganate did not result in the formation of any product.

2. *Quinolines*

In the oxidative amination of quinoline, using potassium amide in liquid ammonia and permanganate as oxidant, it was found that the site of amination is strongly depending on temperature. When the amination is carried out at −65 °C 2-aminoquinoline is isolated (52%); 4-aminoquinoline is formed (with some 2-aminoquinoline) when the amination is performed at room temperature. By NMR spectroscopy it was unequivocally observed that at −65 °C addition of the amide ion occurs at position 2 of the quinoline ring, yielding the σ-adduct 2-amino-1,2-dihydroquinolinide, which under the conditions of the reaction remained stable. When warming up the solution this C-2 adduct irreversibly converts into the



Scheme 8



Scheme 9

4-amino-1,4-dihydroquinolinide. It is apparent that the C-2-amino adduct is the kinetically favored adduct, while at higher temperatures the thermodynamically C-4-amino isomer is formed. That the C-4 adduct is more stable than the C-2 isomer may be due to the aza-allylic stabilization in the C-4 adduct (Scheme 9) (73JOC1947). Addition of potassium permanganate gave 4-aminoquinoline. This concept of kinetic and thermodynamic control plays an important role in determining the product composition and several examples of the temperature dependency of the site of attack of the amide or ammonia will be mentioned in the text and summarized in Section IV. Oxidative amination of 3-, 4-, 5-, 6-, and 7-nitroquinolines and of 5,7-dinitro- and 6,8-dinitroquinolines, using liquid ammonia/potassium permanganate, easily leads to the formation of their respective aminonitroquinolines (85JHC353, 87JOC5643, 91PJC323). The yields vary depending on the structure of the substrate. The amino group is always introduced in the *ortho* position of the nitro group (Table I). When this position is occupied by a substituent no amination takes place. For example, whereas 5-nitroquinoline is aminated at position 6, 5-nitro-6-(chloro, bromo, methyl)quinoline does not give any S_NH products (91PJC323).

2-Nitro- and 8-nitroquinoline as well as 4-nitroquinoline *N*-oxide are unreactive.

Table I. PRODUCTS AND YIELDS OBTAINED IN THE AMINATION OF NITRO- AND DINITROQUINOLINES WITH LIQUID AMMONIA (−33 °C)/POTASSIUM PERMANGANATE

x-Nitroquinoline	*y*-Amino-*x*-nitroquinoline
$x=3$	$y=4,\ x=3$ (65%)
$x=4$	$y=3,\ x=4$ (86%)
$x=5$	$y=6,\ x=5$ (33%)
$x=6$	$y=5,\ x=6$ (10%)
$x=7$	$y=8,\ x=7$ (7%)
$x=5, 7$	$y=8,\ x=5, 7$ (40%)
$x=6, 8$	$y=5,\ x=6, 8$ (43%)

An interesting question in these amination studies is whether the addition of the amide ion is controlled by charge densities or controlled by HOMO–LUMO interactions between the incoming nucleophile and the nitroquinoline. In a charge-controlled reaction the positions with the lowest electron densities are the most susceptible ones for a nucleophilic attack. Electron densities on all C–H positions of the parent *x*-nitroquinolines ($x=3,4,5,6,7,8$) were calculated and compared with the experimental results. Also FMO calculations of the values of the stabilization energy (DE) on each C–H position were carried out (87JOC5643), using the simplified perturbation equation (76MI1):

$$\Delta E \sim 2\left[\frac{C_s^2(\mathrm{LUMO})}{E^{\mathrm{N}}_{\mathrm{HOMO}} - E^{\mathrm{A}}_{\mathrm{LUMO}}} + \frac{C_s^2(\mathrm{LUMO}+1)}{E^{\mathrm{N}}_{\mathrm{HOMO}} - E^{\mathrm{A}}_{\mathrm{LUMO+1}}}\right].$$

The results of these calculations are summarized in Table II. Formal charges predict that all nitroquinolines should have their highest reactivity at C-2. This is not confirmed by the experimental results. By comparing the experimental results with the FMO calculations it became evident that the order of reactivity of the ammonia addition is in good agreement. Thus, the addition reaction is orbital-controlled (87JOC5643).

Oxidative methylamination of 2-, 3-, 4-, 5-, 6-, 7-, and 8-nitroquinolines at −7 °C leads, as could be expected, to similar results as obtained in the oxidative amination (93LAC823). In general, the methylamination differs from the oxidative amination in several aspects: (a) the reaction occurs faster than the amination, due to the higher temperature at which the reaction is carried out, (b) gives higher yields, (c) the site specificity is less than observed in the amination, as it appears by the sometimes occurring formation of mixtures of (methylamino)nitroquinolines, and even in the case of 5-nitroquinoline formation of bis(methylamino)-5-nitroquinolines (Table III).

Table II. The Reactivity Order of Nitroquinolines with Ammonia, Calculated on Formal Charges and Orbital Control

x-Nitroquinoline	Orbial control	Formal charges	Experimental results
$x=3$	C-4 > C-2 > C-6	C-2 > C-4	C-4
$x=4$	C-3 > C-4 > C-2	C-2 > C-4	C-3
$x=5$	C-6 > C-8 > C-5	C-2 > C-6 > C-8	C-6
$x=6$	C-5 > C-7 > C-3	C-2 > C-5 > C-4	C-5
$x=7$	C-8 > C-6 > C-2	C-2 > C-8 > C-4	C-8
$x=8$[a]	C-7 > C-5 > C-2	C-2 > C-7 > C-5	C-7 > C-5

[a] This compound is only reactive in the oxidative methylamination (see Table III).

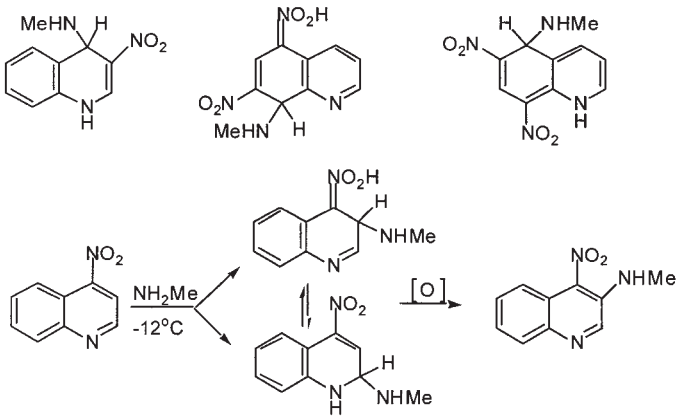
Table III. Products and Yields Obtained in the Methylamination of Nitro- and Dinitroquinolines by Methylamine (−7 °C)/Potassium Permanganate

x-Nitroquinoline	*y*-Methylamino-*x*-nitroquinoline
$x=3$	$y=4$, $x=3$ (77%)
$x=4$	$y=3$, $x=4$ (28%)
x = 5	$y=6$, $x=5$ (25%) +
	$y=8$, $x=5$ (21%) +
	$y=6,8$-bis, $x=5$ (29%)
$x=6$	$y=5$, $x=6$ (61%)
$x=7$	$y=8$, $x=7$ (54%)
$x=8$	$y=5$, $x=8$ (14%) +
	$y=7$, $x=8$ (31%)
$x=5, 7$	$y=8$, $x=5, 7$ (8%) +
	$y=6,8$-bis, $x=5, 7$ (52%)
$x=6, 8$	$y=7$, $x=6, 8$ (7%) +
	$y=5$, $x=6, 8$ (18%) +
	$y=5,7$-bis, $x=6, 8$ (32%)

In all methylaminations of the isomeric nitroquinolines, the methylamino group was never introduced at the α-position of the pyridine ring, but always *ortho* to the nitro group, again showing that the aza activation is less powerful than the nitro activation at the *ortho* position. In case of 5-nitro- and 8-nitroquinoline besides *ortho* methylamination also *para* methylamination was found.

Methylamination of 5,7-dinitroquinoline and 6,8-dinitroquinoline gave similar results. However, besides methylamination *ortho* of the nitro group, as main products were obtained the bis(methylamino)dinitroquinolines (Table III).

^{1}H-NMR spectroscopy of a solution of 3-nitropyridine in liquid methylamine shows an upfield shift of 5.33 ppm for H-4, clearly showing



Scheme 10

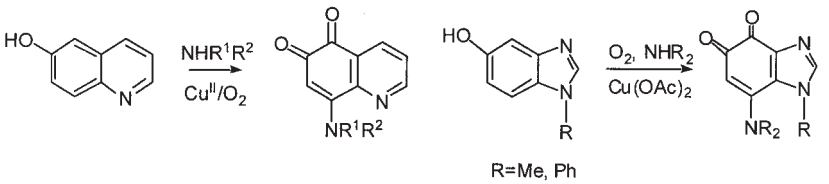
the formation of the covalent adduct 1,4-dihydro-4-methylamino-3-nitropyridine (Scheme 10) (93LAC823). For 5,8-dinitroquinoline an upfield shift was recorded for H-8 (3.78 ppm), proving the existence of the 8-methylamino σ-adduct. For 6,8-dinitroquinoline H-5 showed an upfield shift of 3.66 ppm, indicating the formation of the 5-methylamino-σ-adduct (Scheme 10).

Interestingly, ^{1}H-NMR spectroscopy of a solution of 4-nitroquinoline in liquid methylamine ($-12\,^\circ$C) convincingly showed the presence of two σ-adducts, i.e., the 3-methylamino σ-adduct (upfield shift H-3 is 3.42 ppm) and the 2-methylamino σ-adduct (upfield shift H-2 is 5.17 ppm) (98KGS967). Since after oxidation with permanganate 3-methylamino-4-nitroquinoline is the sole product, it is has been suggested that the 2-methylamino σ-adduct is kinetically favored, but converts to the thermodynamically more stable 3-methylamino σ-adduct on oxidation (Scheme 10).

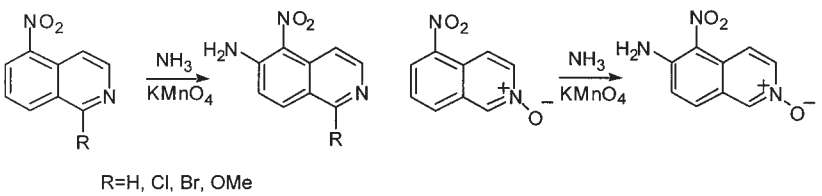
Oxidative amination, using a Cu^{II}-catalyst was reported to take place on treatment of 6-hydroxyquinoline with secondary amines in a methanol solution, 8-R_2N-quinoline-5,6-dione being obtained. So besides a S_NH (amino) reaction at C-8, a S_NH(oxo) reaction occurs at C-5 (Scheme 11) (90CPB2841). A similar reaction was found earlier with 5-hydroxybenzimidazoles (Scheme 11) (78KGS1680)

3. *Isoquinolines*

Oxidative amination of 5- and 8-nitroisoquinolines follows the same reaction pattern as observed with the mononitroquinolines. Amination takes place *ortho* to the nitro group and not *ortho* to the ring nitrogen.



Scheme 11

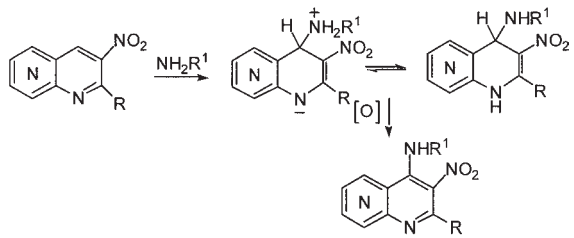


Scheme 12

1-R-5-nitro-isoquinoline (R = H, Cl, Br, OMe) is converted in reasonable-to-good yield into the corresponding 6-amino-5-nitro-1-R-isoquinolines (Scheme 12) (90LAC653). No replacement of the leaving groups at position 1 was observed, again showing the preference of the reagent for S_NH substitution rather than nucleophilic displacements. Treatment of 5-nitroquinoline *N*-oxide with liquid ammonia/permanganate gives the corresponding 6-amino-5-nitroquinoline *N*-oxide (90LAC653). FMO calculations support the concept that the amination is orbital-controlled.

4. *Naphthyridines*

There is extensive literature concerning the oxidative amination of 3-nitro-1,5-, 3-nitro-1,6-, and 3-nitro-1,8-naphthyridines. All these compounds are successfully aminated on treatment with liquid ammonia/potassium permanganate into 4-amino-3-nitro-1,*x*-naphthyridines ($x = 5$, 6, 8, Scheme 13) (83JHC9, 83RTC359, 83RTC511). No indication of the formation of 2-amino-3-nitro-1,*x*-naphthyridines was observed. The intermediary covalent 4-amino σ-adducts have been detected by NMR spectroscopy (83JHC9, 83RTC359, 83RTC511). For an extensive description of the NMR data of σ-amino adduct formation in 3-nitro-1,*x*-naphthyridines ($x = 5$, 6, 8) the reader is referred to reference (00AHC(77)285). When in these 3-nitro compounds a nucleophugal group is present at position 2, such as Cl or OEt, no replacement by an amino group occurs.



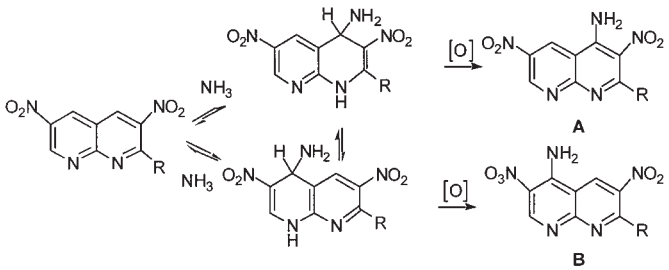
2-R-1,5-naphthyridine (R=H, Cl, OH, OEt, NH_2)	R^1= H
2-R-1,5-naphthyridine (R=H, NH_2, OH, OEt)	R^1= Me
2-R-1,6-naphthyridine (R=H, Cl, OEt, NH_2)	R^1= H
2-R-1,8-naphthyridine (R=H, Cl, OEt, NH_2)	R^1= H
2-R-1,8-naphthyridine (R=H, OMe, NH_2, NHMe, NHPh)	R^1= Me
2-R-1,8-naphthyridine (R=Cl)	R^1= Me, R = NHMe

Scheme 13

This methodology was also successfully used to introduce a methylamino group at position 4 in 3-nitro-1,8-naphthyridine and its 2-amino-, 2-methoxy-, 2-methylamino-, and 2-anilino derivatives (Scheme 13) (86JHC473, 93LAC471). In contrast to the amination, methylamination of 2-chloro-3-nitro-1,8-naphthyridine gives 2,4-bis(methylamino)-3-nitro-1,8-naphthyridine showing the higher reactivity of methylamine compared to ammonia. Very recently the methylamination of 2-R-3-nitro-1,5-naphthyridines (R = H, NH_2, OH, OEt) was reported, 2-R-3-nitro-4-methylamino-1,5-naphthyridines being obtained (03MI1).

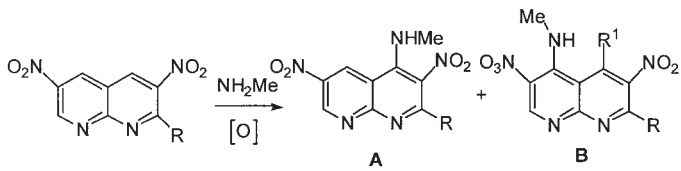
Oxidative amination of the easily accessible 2-R-3,5-dinitro-1,8-naphthyridines only takes place at C-4. With R = H, 4-amino-3,5-dinitro-1,8-naphthyridine was formed and with R = NH_2 2,4-diamino-3,5-dinitro-1,8-naphthyridine (Scheme 14) (86JHC473). For R = OEt and for R = Cl S_NH amination at C-4 as well as at C-5 was found, leading to complex reaction mixtures (Scheme 14).

A solution of 2-chloro- and 2-amino-3,5-dinitro-1,8-naphthyridine in liquid ammonia shows the presence of a covalent adduct at C-4, as proved by NMR spectroscopy (83RTC359, 83RTC511, 83JHC9, 85JHC761, 93LAC 471, 00AHC(77)285). The NMR spectrum of a solution of 2-ethoxy-3,5-dinitro-1,8-naphthyridine and 2-chloro-3,5-dinitro-1,8-naphthyridine in liquid ammonia features the presence of two covalent adducts: one at C-4 as well as one at C-5. The C-4/C-5 adduct ratio is found to be temperature dependent. For the 2-chloro compound the adduct ratio C-4/C-5 is 60/40 at −45 °C, but changes to 40/60 at room temperature. This temperature dependency for the 2-ethoxy compound is more pronounced: the C-4/C-5 adduct ratio is 50/50 at −45 °C and 85/15 at room temperature.



R = H — **A**, R = H
R = NH_2 — **A**, R = NH_2
R = OEt — **A** (R = OEt) + **B** (R = OEt)
R = Cl — **A** (R = NH_2) + **B** (R = Cl)+ **B** (R = NH_2)

Scheme 14



R = H — **A** (R = NHMe) + **B** (R = H, R^1 = NHMe)
R = NH_2 — **A** (R = NH_2)
R = NHMe — **A** (R = NHMe)
R = NHPh — **A** (R = NHPh)
R = OH — **A** (R = OH) + **B** (R = OH, R^1 = H)
R = Cl — **A** (R = NHMe)
R = OMe — **A** (R = NHMe) + **B** (R = OMe, R^1 = NHMe)

Scheme 15

The oxidative methylamination of 2-R-3,5-dinitro-1,8-naphthyridine using the liquid ammonia/permanganate at $-7\,^{\circ}C$ gave for R = H, 2,4-bis(methylamino)-3,5-dinitro-1,8-naphthyridine as main product, in addition some 2,4-bis(methylamino)-3,5-dinitro-1,8-naphthyridine (Scheme 15) (96KGS1652, 97LAR2601). This result shows that the methylamination is less specific than observed in the oxidative amination, in which 4-amino-3,5-dinitro-1,8-naphthyridine is obtained as sole product. Methylamination of 2-R-3,5-dinitro-1,8-naphthyridine (R = NH_2, NHMe, OH) gave as main products the corresponding 4-methylamino-3,5-dinitro-1,8-naphthyridines.

For R = Cl, OMe besides S_NH replacement at C-4, an addition–elimination process of the chloro atom or methoxy group by the

methylamino group occurs, leading to the formation of 2,4-bis(methylamino)-3,5-dinitro-1,8-naphthyridine. NMR spectroscopy proves the intermediary existence of the 4-methylamino σ-adduct.

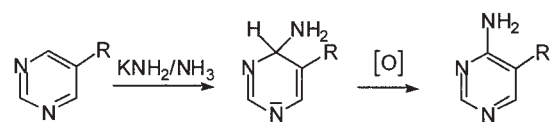
B. Pyrimidines and Quinazolines

1. *Pyrimidines*

The parent system pyrimidine when dissolved in liquid ammonia containing potassium amide at $-33\,^{\circ}C$ to which solid permanganate is added gave, after work-up, 4-aminopyrimidine. GLC of the reaction mixture demonstrated the presence of a small amount of 2-aminopyrimidine. Similar amino-dehydrogenations have also been reported for 5-bromo- and 5-phenylpyrimidine (82JHC1285). The reaction involves the anionic intermediate 4-aminodihydropyrimidinide, as proved by NMR spectroscopy (Scheme 16).

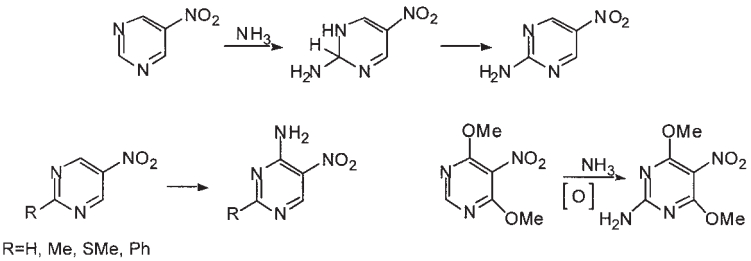
Attempts to aminate 5-nitropyrimidine by potassium amide/liquid ammonia /potassium permanganate were not successful since the compound decomposes in the presence of potassium amide. However, the high π-electron deficiency of 5-nitropyrimidine allows the use of the less nucleophilic liquid ammonia as aminating agent. Oxidative amination at $-40\,^{\circ}C$ gives 2-amino-5-nitropyrimidine (Scheme 17) (83JOC1354). ^{1}H- and ^{13}C-NMR spectroscopy at $-40\,^{\circ}C$ provided clear evidence for the intermediacy of the covalent σ-adduct 2-amino-5-nitrodihydropyrimidine. However, the addition pattern is temperature dependent as at room temperature addition occurs at C-4. Amination at position 2 has also been observed with 4,6-dimethoxy-5-nitropyrimidine, yielding 2-amino-4,6-dimethoxy-5-nitropyrimidine. No replacement of the nucleophugal methoxy group by the amino group was observed, showing again the unique feature of this aminating methodology.

When position 2 in 5-nitropyrimidine is occupied by the presence of a substituent the S_NH amination takes place at position 4. 2-Methyl-,

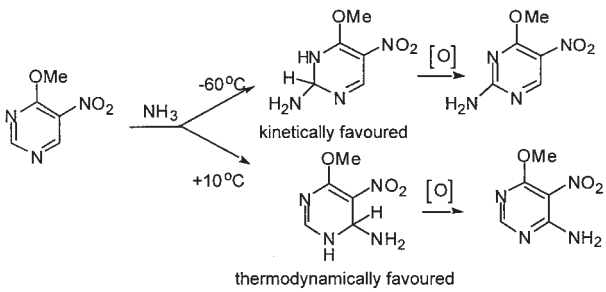


R=H, Br, Ph

Scheme 16



Scheme 17



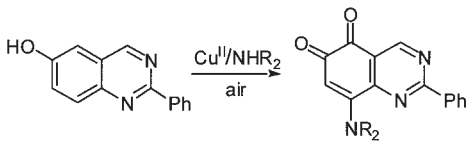
Scheme 18

2-methylthio-, and 2-phenyl-5-nitropyrimidine give in reasonable yields the corresponding 2-R-4-amino-5-nitropyrimidines (Scheme 17) (83JOC1354).

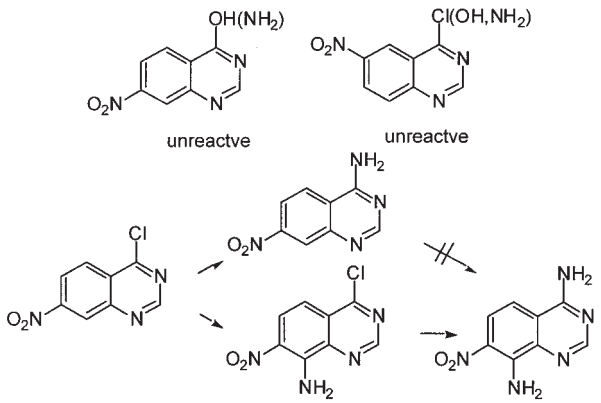
The delicate balance between adduct formation at position 2 or at position 4 is shown in the amino-dehydrogenation of 4-methoxy-5-nitropyrimidine. The course of the amination is found to temperature dependent. Treatment with liquid ammonia/permanganate at $-60°$ to $-70\,°C$ gave 2-amino-4-methoxy-5-nitropyrimidine, while at $+20\,°C$ 6-amino-4-methoxy-5-nitropyrimidine is obtained (Scheme 18) (83JOC1354). This result indicates that at low temperature the C-2 adduct is the kinetically favored one and at room temperature the C-4 adduct is thermodynamically favored.

2. *Quinazolines*

One of the first reports concerning the oxidative amination in quinazolines is the Cu^{II}-catalyzed amination of 6-hydroxy-2-phenylquinazoline with piperidine and air. It provides 8-piperidino-2-phenylquinazoline 5,6-quinone (Scheme 19) (71KGS283, 71KGS1698).



Scheme 19



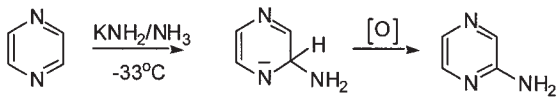
Scheme 20

Amino-dehydrogenation studies were also reported with 4-R-6-nitro- and 4-R-7-nitroquinazolines (=Cl, OH, NH_2) (93MI1). Nearly all compounds were found to be non-reactive, with exception of 4-chloro-7-nitroquinazoline, which gave besides amino-dechlorination at C-4, yielding 4-amino-7-nitroquinazoline, a small yield of 4,8-diamino-7-nitroquinazoline. The formation of the last mentioned compound was explained by an initial formation of 8-amino-4-chloro-7-nitroquinazoline, which reacts further into the 4,8-diamino compound (Scheme 20) (93ACS95). It is also evident that in nitroquinazolines S_NH substitution does not occur on the carbon adjacent to the ring nitrogen but takes place *ortho* to the nitro group.

C. Pyrazines and Quinoxalines

1. *Pyrazines*

There is one report describing the oxidative amination of pyrazine, using potassium amide as nucleophile, liquid ammonia at $-35\,^{\circ}C$ as solvent and



Scheme 21

potassium permanganate as oxidant. Aminopyrazine is obtained in good yield (Scheme 21) (82JHC1285).

2. *Quinoxalines*

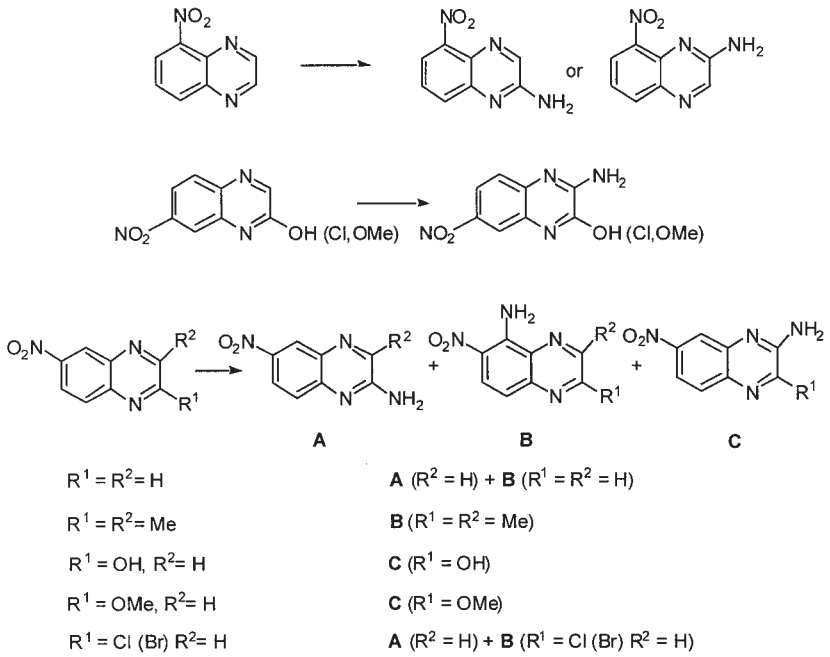
Aminonitroquinoxalines are obtained, usually in low yield, when nitroquinoxalines, containing the nitro group in the benzene ring, are treated with liquid ammonia and potassium permanganate at −33 °C (92LAC899).

Thus, 5-nitroquinoxaline on amination under the above-mentioned conditions gives substitution on position 2 (or 3). It is remarkable that no S_NH substitution took place at the position 6, *ortho* to the nitro group, as was usually observed in the amination of the nitroquinolines and nitronaphthyridines. Even when position 2 and 3 are occupied by a methyl group, no amination at position 6 was observed: 2,3-dimethyl-5-nitroquinoxaline did not give any amino product (Scheme 22).

S_NH amination of 2-R-7-nitroquinoxalines (R = Cl, OH, OMe) provides the corresponding 3-amino-2-R-7-nitroquinoxalines. No replacement of the chloro or methoxy group at position 2 takes place (Scheme 22).

A confusing picture was shown by the oxidative amination of 6-nitroquinoxalines. S_NH substitution at C-2 and C-3 was found, depending on the character of the substituent at position 2 and/or 3. 6-Nitroquinoxaline yields a mixture of 2-amino- and 5-amino-6-nitroquinoxaline in high yield. That the S_NH substitution took place on the carbon adjacent to the ring nitrogen, which in other heterocycles is hardly observed, may be explained by activation of both the nitro group and ring nitrogen at C-2. 2,3-Dimethyl-6-nitroquinoxaline gives 5-amino-2,3-dimethyl-6-nitroquinoxaline as a sole product. However, exclusive S_NH substitution in the pyrazine ring was found with 2-R-6-nitroquinoxaline (R = OH, OMe), leading to the formation of the 2-R-3-amino-6-nitroquinoxaline (R = OH, OMe). In case of R = Br, Cl the oxidative amination gives S_NH substitution at C-5 and amino dehalogenation at C-2, leading to a mixture of 5-amino-2-R-6-nitroquinoxaline (R = Br, Cl) and 2-amino-6-nitroquinoxaline (Scheme 22).

In order to understand the nature of the regioselectivity of the amination reaction MNDO calculations of the ground state of some nitroquinoxalines

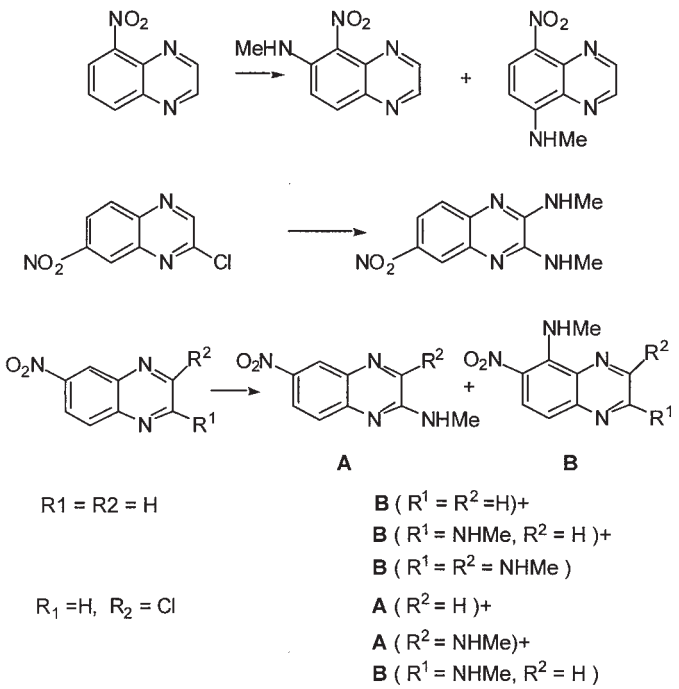


Scheme 22

were carried out, reactivity indices, such as superdelocalizability, and charge distribution on the carbons were determined. Comparing the results of these calculations with the experimental results, no correlation could be found with the preferable positions of the NH_3 attack. It has been argued that not the readiness to form σ-adducts, but susceptibility to oxidation determines the regiospecificity of the overall process.

Extension of this work by studying the oxidative methylamination of 5-, 6-, and 7-nitroquinoxalines, using liquid methylamine at room temperature and permanganate as oxidant, gives, as could be expected, similar results to those obtained in the oxidative amination (Scheme 23) (94IJHC75).

The methylamination is less selective. This lower selectivity is due to the stronger nucleophilicity of methylamine as also shown by the methylamino-dehalogenation occurring with 2-chloro-5-nitroquinoxaline and 2-chloro-7-nitroquinoxaline into 2-amino-5-nitroquinoxaline and 2-amino-7-nitroquinoxaline, respectively. Amino-dehydrogenations with these compounds were not observed (see Scheme 22). It is important to note that 5-nitroquinoxaline gives methylamination at position *ortho* and *para*

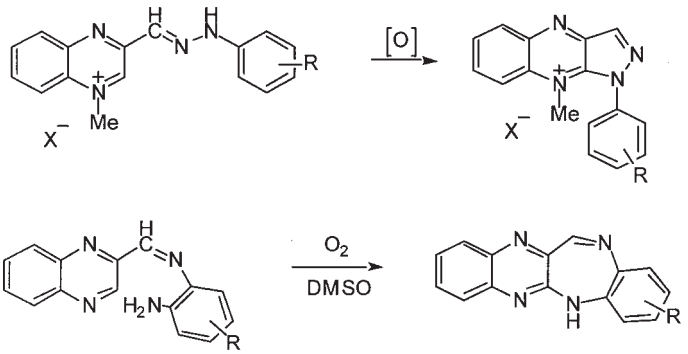


Scheme 23

to the nitro group whereas oxidative amination gives substitution in the pyrazine ring.

FMO calculations predict that the C-6 position in 5-nitroquinoxaline and the C-5 position in 6-nitroquinoxalines are the preferential positions for nucleophilic attack (94IJHC75). These calculations are in good agreement with the experimental results. Calculations of formal electron charges on carbon atoms of these ring system show no correlation with the experimental results, excluding a charged controlled methylamination reaction.

Interesting examples of intramolecular oxidative amination have recently been reported. Permanganate oxidation of the arylhydrazones of 3-formyl-1-methylquinoxalinium salts leads to pyrazoloquinoxalinium salts (Scheme 24) (02MC68). The reactive α-position in the quinoxalium ring makes the addition of the hydrazone nitrogen easily possible. Oxidation of a DMSO solution of the condensation product of 2-formylquinoxaline with *ortho*-phenylene diamine



Scheme 24

by oxygen at 80 °C yields a benz[1,4]diazepinoquinoxaline derivative (Scheme 24) (03TL).

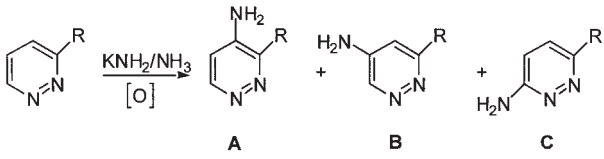
D. Pyridazines

A review on nucleophilic substitution of hydrogen atoms in the pyridazine series has been published (01KGS1611). Oxidative amination of pyridazine, using potassium amide in liquid ammonia at −35 °C and potassium permanganate as oxidant gave 4-aminopyridazine in high yield (82JHC1285). In a very similar way 4-cyano-3-phenylpyridazine and 3,6-di(2-pyridyl)-4-cyanopyridazine could be converted into the corresponding 5-aminopyridazines (Scheme 25) (88JHC831).

Oxidative amination of 4-nitropyridazine does not require the use of potassium amide. With liquid ammonia/potassium permanganate at −45 °C 5-amino-4-nitropyridazine is obtained, although, in a rather low yield (88JHC831). The 3-aryl- and 3,6-diaryl-4-nitropyridazines are however aminated in very high yield into the corresponding 5-amino compounds (Scheme 26).

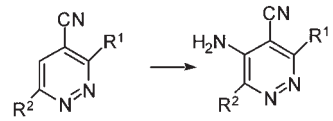
There is convincing NMR spectroscopic evidence for the intermediate 5-amino-4-nitro-2-5-dihydropyridazine.

Oxidative amination of 4-nitropyridazine *N*-oxide and some methoxy- and chloro-derivatives using liquid ammonia and potassium permanganate exclusively gave the corresponding 5-aminopyridazine *N*-oxides in reasonable yields (86JHC621). No replacement of the methoxy group and/or chloro atom by the amino group was observed (Scheme 26).



R = H — A (R = H)

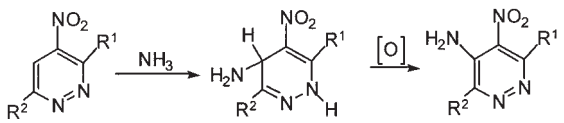
R = Ph — A (R = Ph) + B (R = Ph) + C (R = Ph)



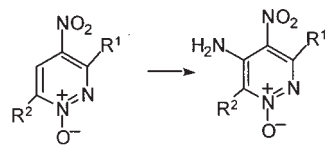
R^1 = Ph; R^2 = H

R^1 = R^2 = α-pyridyl

Scheme 25



R^1=R^2=H; R^1=R^2=2-pyridyl; R^1=H, R^2=Ph; R^1=H, R^2=*p*-OMeC6H4



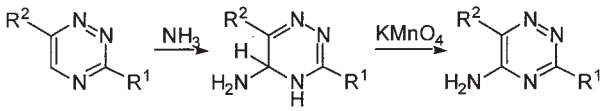
R^1=R^2=H; R^1=R^2=OMe; R^1=OMe, R^2=Cl

Scheme 26

E. Triazines

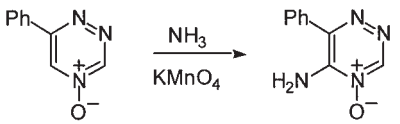
1. *1,2,4-Triazines*

1,2,4-Triazine with its high electron-deficiency is converted with high yield into 5-amino-1,2,4-triazine on treatment with liquid ammonia and potassium permanganate (85S884, 86MI1). Similar reactions were reported for 3- and 6-substituted 1,2,4-triazines and 6-phenyl-1,2,4-triazine-1-oxide (Scheme 27). Even 1,2,4-triazines containing easily replaceable groups, such as chloro, methoxy, and thiomethyl, undergo exclusively S_NH



R^1 =H, Me, Ph, Cl, OMe, SMe, NH_2

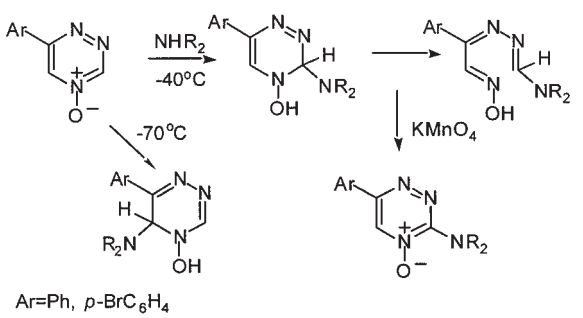
R^2=H, Ph, Br



Scheme 27

substitution. Also 3-amino-1,2,4-triazine is converted under these mild conditions into 3,5-diamino-1,2,4-triazine, although in modest yields (Scheme 27). No adduct could be detected by NMR spectroscopy, leading to the conclusion that the intermediary 3,5-diamino-4,5-dihydro-1,2,4-triazine is only present in a low steady-state concentration. On oxidation the equilibrium between the 3-amino compound and the adduct shifts to the adduct side, converting into the 3,5-diamino product. In agreement with the proposed mechanism, introduction of bulky substituents at position 5 prevents the amination.

Interesting results were obtained in the S_NH oxidative dialkylaminations of 6-aryl-1,2,4-triazine-4-oxides (98ZOK423), When these compounds are subjected to a reaction with a series of dialkylamines at −40 °C in the presence of potassium permanganate, they are converted into 3-dialkylamino-1,2,4-triazine-4-oxides (Scheme 28).



Ar=Ph, *p*-BrC_6H_4

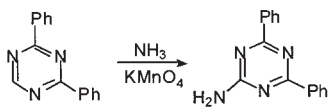
NR_2=NMe_2, NEt_2, pyrrolidino, morpholino, piperidino, *N*-methylpiperidino, piperazino

Scheme 28

It has been successful to isolate intermediates and to identify them by NMR spectroscopy as 3-aryl-6-dialkylamino-1-hydroxy-1,4,5-triaza-1,3,5-hexatriene. Treatment with potassium permanganate of these open-chain structures gave ring closure into 3-dialkylamino-1,2,4-triazine-4-oxides. Also, in these reactions it was observed that the regiospecificity of the addition is temperature dependent. Whereas at $-40\,^{\circ}C$ the addition occurs at C-3, at $-70\,^{\circ}C$ the addition takes place at C-5 (01H127). Whether on oxidation at $-70\,^{\circ}C$ the 5-dialkylamino-6-phenyl-1-2-4-triazine-4-oxide is formed is unknown.

2. *1,3,5-Triazines*

In the 1,3,5-triazine series the oxidative amination of diphenyl-1,3,5-triazine into aminodiphenyl-1,3,5-triazine has been reported (Scheme 29) (82JHC1285).

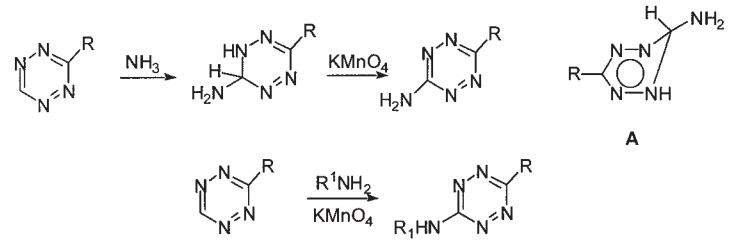


Scheme 29

F. 1,2,4,5-Tetrazines

Oxidation of a solution of 3-alkyl(aryl)-1,2,4,5-tetrazines in liquid ammonia with permanganate proved to be an excellent route for preparing 6-amino-1,2,4,5-tetrazines (Scheme 30) (81JHC123). The covalent σ-adduct, i.e., amino-dihydro-1,2,4,5-tetrazine, is intermediate, as proved by NMR spectroscopy. Based on model studies of 3-phenyl-1,6-dihydro-1,2,4,5-tetrazine, this non-isolable amino-dihydro-1,2,4,5-tetrazine has been characterized as having a homotetrazole structure **A** (Scheme 30) (81JOC3805).

A great variety of 3-alkyl- and 3-aryl-1,2,4,5-tetrazines can also easily be alkylaminated when treated with appropriate primary alkylamines in the presence of potassium permanganate (Scheme 30). The yields vary depending on the size of the alkyl group in the amine. Attempts to introduce an arylamino group were unsuccessful.



R=Me, *t*-Bu, Ph

R=Ph; R^1=Et, *n*-Bu, *n*-Oct, *i*-Prop

R=*t*-Bu; R^1=Et, *n*-Bu, *n*-Oct, *i*-Prop

R=Me; R^1=Et, *n*-Bu, *n*-Oct

Scheme 30

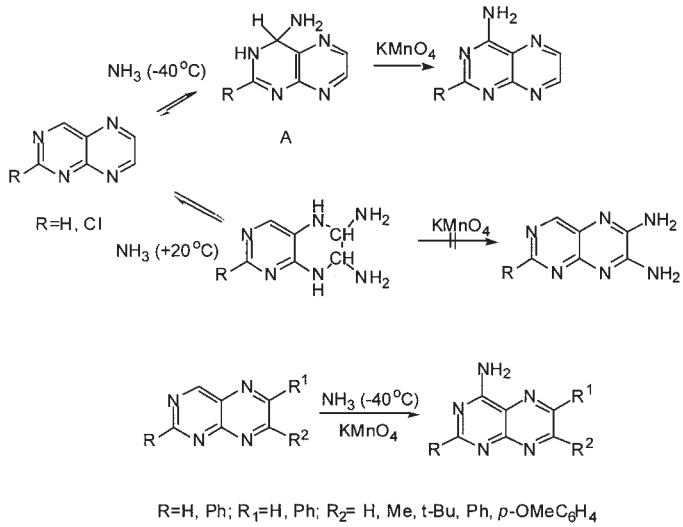
G. Pyrimidopyrazines (Pteridines) and Pyrimidopyridazines

1. *Pteridines*

Pteridine and 2-chloropteridine were aminated by liquid ammonia (−40 °C) and potassium permanganate into the corresponding 4-aminopteridines (86JHC473). Under these conditions no amino-dechlorination at C-2 was found. The regiospecificity of adduct formation is temperature dependent. At −33 °C the C-4 adducts, i.e., the 4-amino-3,4-dihydro-2-R-pteridines (R = H, Cl), were formed as identified by NMR spectroscopy (Scheme 31). However, at temperatures up to 25 °C addition of ammonia takes place at positions C-6 and C-7, yielding the 2:1 σ-adducts 6,7-diamino-5,6,7,8-tetrahydropteridines. Attempts to oxidize the C-6/C-7 diadduct into a 6,7-diaminopteridine were not successful (Scheme 31).

Interestingly, 2-phenylpteridine behaves differently. At −40 °C the 1:1 adduct is formed, while at −60 °C two adducts are present in the solution. One is the C-4 monoadduct, the other one is the 2:1 C-6/C-7 diadduct, as is proven by NMR spectroscopy. Oxidation of the mixture of the two adducts only gave 4-amino-2-phenylpteridine. Apparently the oxidation rate of the 1:1 adduct at C-4 is faster than the oxidation of the 2:1 diadduct, shifting the equilibrium between both adducts to the C-4 adduct. So the rate of the oxidation determines the ratio of the products obtained.

The 7-aryl (alkyl)pteridines (R = R^1 = H, R^2 = Ph, *p*-OMe–C_6H_4, Me, *t*-Bu), and the 6,7-diaryl(alkyl)-pteridines (R = H, R^1 = R^2 = Ph, Me) are



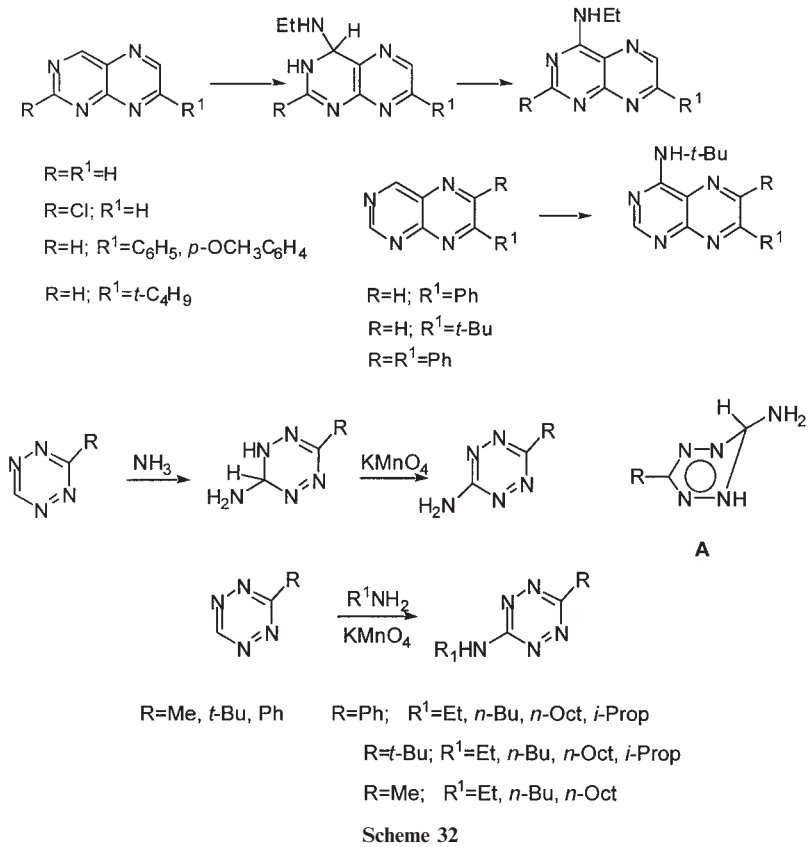
Scheme 31

also converted by treatment with liquid ammonia/permanganate at −40 °C into their respective 4-aminopteridines in good yield (Scheme 31). NMR spectroscopy shows that the regiospecificity of the ammonia addition at C-4 for the 7-monosubstituted as well as to the 6,7-disubstituted pteridines is independent of the temperature.

Oxidative alkylamination of pteridine and its 2-chloro, 7-aryl, or 7-*t*-Bu derivative, using an alkylamine (Alkyl = Et or *t*-Bu) and potassium permanganate as oxidant, gave the corresponding 4-alkylamino pteridines (Scheme 32) (82JHC1527, 86JHC843).

2. *Pyrimidopyridazines*

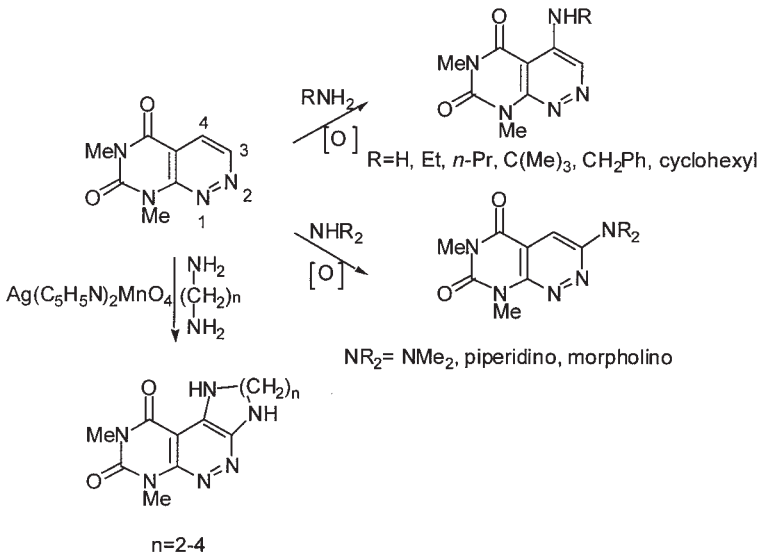
Interesting amination chemistry has been found with 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione. When this compound reacts with primary amines in the presence of an oxidant the corresponding 4-alkylamino derivatives are obtained. The observation was made that with secondary amines the corresponding 3-dialkylamino compounds are formed, although in moderate yields (99RCB1150). Treatment with an α,ω-diaminoalkane in the presence of silver permanganate pyridine complex leads to a tandem S_NH–S_NH substitution at position 3 as well as at position 4, leading to annelation at position 3,4 of the pyridazine ring with a



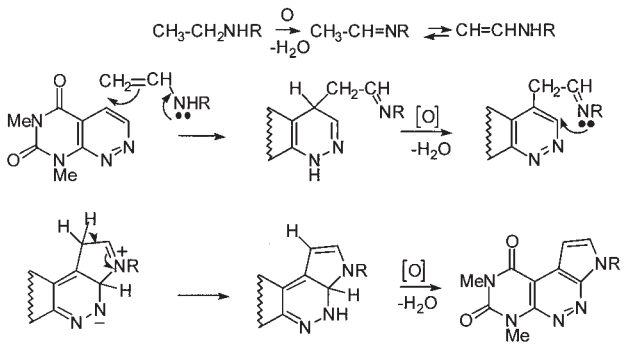
Scheme 32

six-membered ring ($n = 2$), seven-membered ring ($n = 3$), or eight-membered ring ($n = 4$) (Scheme 33) (00MC150).

Another interesting example of a tandem S_NH–S_NH substitution was found when 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione reacts with diethylamine in the presence of the oxidant silver permanganate pyridine complex. Unexpectedly pyrrole ring annelation to the pyridazine nucleus was observed, yielding 6,8-dimethyl-3-ethylpyrrolo[2′,3′;3,4]pyridazino[6,5-*d*]pyrimidine-7,9(6*H*,8*H*)-dione (Scheme 34) (01TL5981). The annelation reaction can be described as a reaction of an enamine (formed by oxidation of the amine with the permanganate (84TL2577)), involving first addition of the electron-rich carbon to the electron-deficient C-4 position and subsequently an intramolecular addition of the nitrogen to C-3. In both steps the oxidant is required to achieve the aromatization step. A similar pyrrole annelation reaction has also been performed with



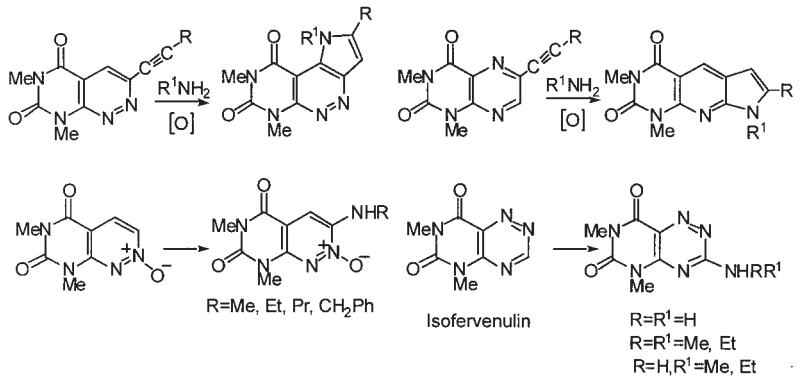
Scheme 33



Scheme 34

di-*n*-propylamine, di-*n*-butylamine, methyl-*n*-propylamine, and ethyl-*n*-propylamine.

A useful expansion of the pyrrole-ring annelation methodology was found when 3-alkynyl-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione reacts with an amine and silver permanganate pyridine complex. It was postulated that first amination at the C4-position takes place, followed by an intramolecular cyclization into the pyrrolopyridazinopyrimidine derivative (Scheme 35). A similar reaction was reported with 6-alkynyl-1,3-dimethylpyrimido[4,5-*b*]pyrazinedione (03MI3).



Scheme 35

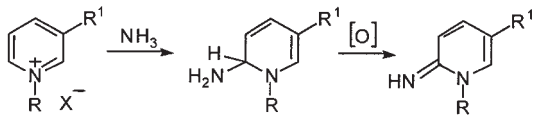
6,8-Dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione *N*(2)-oxide gives oxidative alkylamination at position 3 (Scheme 35) (88KGS1696) and isofervenulin gives, with ammonia or an alkylamine in the presence of an oxidant, (alkyl)amination at C-3 (Scheme 35) (88KGS1696, 00KGS1403). This C-3 substitution of isofervenuline is claimed to be the first example of amination in the triazine ring at position 3.

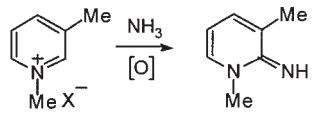
III. Oxidative Imination

A. Pyridines, Quinolines, and Naphthyridines

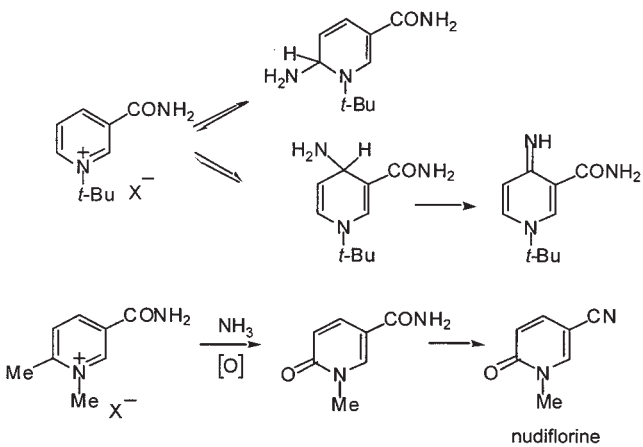
1. *Pyridines*

Liquid ammonia and potassium permanganate can also effectively be applied to introduce an imino group in the highly electron-deficient *N*-alkylazinium salts. Adding *N*-methylpyridinium iodide to a solution of potassium permanganate in liquid ammonia at $-33\,^{\circ}C$ gave a reaction mixture, from which a high yield of 1,2-dihydro-2-imino-1-methylpyridine could be isolated (Scheme 36) (86JHC1015). Studying the regiospecificity of the imination of some 3-substituted pyridinium salts, it was found that imination of the 1-methyl-3-R^1-pyridinium salts ($R^1 = CONH_2$, Ph) takes place at position 6, thus *para* to the substituent at position 3. No trace of the isomeric 2-imino compound could be detected (Scheme 36) (84TL3763). Surprisingly, 1,3-dimethylpyridinium iodide ($R^1 = Me$) shows imination at position 2. No explanation was offered for this difference in regiospecificity between the methyl group, aminocarbonyl and the phenyl group, but steric effects at position 3 certainly contribute to this effect (86JHC1015).





Scheme 36

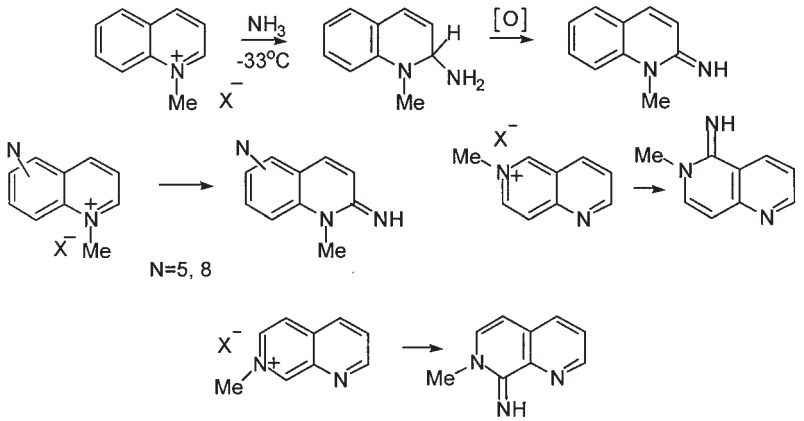


Scheme 37

When the bulky *t*-butyl group is present at the ring nitrogen of 3-aminocarbonylpyridine, oxidative amination occurs at C-4, yielding 3-aminocarbonyl-1-*t*-butyl-4-imino-1,4-dihydropyridine (Scheme 37). No imination was observed at C-6, although NMR spectroscopy of a solution of 3-aminocarbonyl-1-*t*-butylpyridinium iodide clearly shows the presence of two adducts, one adduct at C-4, the other one at C-6 (ratio: 4:6).

After oxidation the 4-imino product is exclusively obtained, indicating that the rate of oxidation at C-4 is faster than at C-2, which is certainly due to the sterically hindered environment around C-6, making that position less easy to reach for the oxidant (Scheme 37).

As expected 3-aminocarbonyl-1,6-dimethylpyridinium iodide does not undergo imination in liquid ammonia/potassium permanganate, as position 6 is blocked for addition. Surprisingly, however, an oxo-demethylation



Scheme 38

reaction occurs at C-6, yielding 3-aminocarbonyl-1-methylpyridone-6. Dehydration of the aminocarbonyl group with phosphorous oxychloride provided a new entry to the well-known alkaloid nudiflorine (Scheme 37) (86JHC1015).

2. *Quinolines and Naphthyridines*

N-Methylquinolinium salts and *N*-methylnaphthyridinium salts, when treated with liquid ammonia/potassium permanganate, are iminated at the position adjacent to the quaternized nitrogen.

N-Methylquinolinium iodide gives 1-methyl-2-imino-1,2-dihydroquinoline. The intermediacy of the covalent adduct is recorded by NMR spectroscopy (Scheme 38) (84TL3763). *N*-Methyl-1,5- and *N*-methyl-1,8-naphthyridinium salt also yield the corresponding 2-imino compounds. The 6-methyl-1,6-naphthyridinium salt gives imination at C-4 and the 7-methyl-1,7-naphthyridinium salt gives imination at C-8 (Scheme 38) (85JOC3435). In all these reactions the intermediary covalent σ-addducts are observed by NMR spectroscopy.

IV. Covalent σ-Adducts

A. NMR Spectroscopy

In this review the important role of NMR spectroscopy as a diagnostic tool in detecting the occurrence of intermediary covalent σ-adducts has

been mentioned. In this section a short summary of the several adducts observed by NMR technique is discussed.

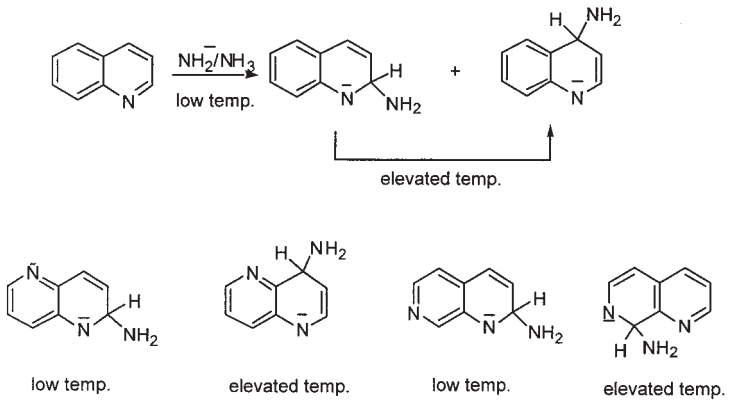
A solution of a substrate in liquid ammonia (or alkylamine) has the attractive feature that it is homogeneous, making it easily possible to detect, by using ^{1}H- and ^{13}C-NMR spectroscopy, the covalent σ-adducts formed between the substrate and the aminating agent. Due to the change of rehybridisation of the carbon to which the aminating agent is added (sp^2–sp^3) both the carbon and the attached hydrogen show a substantial upfield shift in the NMR spectrum (^{1}H-upfield shifts of 3–5 ppm, ^{13}C-upfield shifts of 60–80 ppm). Numerous investigations on σ-adduct formation at low temperature give overwhelming evidence for the intermediary existence of these σ-adducts in the amination reaction (94MI1, 00AHC(77)285). This means that the equilibrium between the substrate and the covalent σ-adduct is usually on the adduct side. In the presence of an oxidant the adduct aromatizes into the amino product. In cases when more than one adduct is formed and after oxidation only one product is formed (see for example in Section III.A.1 on the imination of 3-aminocarbonyl-1-*t*-butylpyridinium salt), the conclusion seems justified that the oxidation rate is the determining factor for establishing which product is formed.

NMR-proven σ-adduct formation between the amide ion and an azine system was found for quinolines (73JOC1947, 85JHC353), isoquinolines (73JOC1947, 74RTC273), 1,*x*-naphthyridines ($x = 5$, 6, 7, 8) and 2,*x*-naphthyridines ($x = 6$, 7) (78JOC1673, 81JOC2134), pyrimidine, pyrazine and pyridazine (72JA682, 75OMR86), purine (79JOC3140, 80RTC267), and pteridines (86JHC473).

Much NMR work has been carried out on adduct formation between more π-deficient azines and liquid ammonia. Examples are 5-nitropyrimidines (83JOC1354), 4-nitropyridazine *N*-oxide (75RTC233, 76RTC21), 3,5-dinitropyridines (85JOC484), 3- and 4-nitroquinolines and the 5,7- and 6,8-dinitroquinolines (87JOC5643, 85JHC353), 5- and 8-nitroisoquinolines (90LAC653) 3-nitro-1,*x*-naphthyridines ($x = 5$, 6, 8) (83RTC359, 83JHC9, 83RTC511, 93LAC471, 00AHC(77)285), 3,6-dinitro-1,8-naphthyridines (85JHC761), 1,2,4-triazines (01H127), pyrimido[5,4-*e*]1,2,4-triazine (87JHC1657) *N*-alkylquinolinium (84TL3763) and *N*-methylnaphthyridinium salts (85JOC3435).

B. Kinetic vs. Thermodynamic Stabilities

An important aspect of the liquid ammonia (amide) amination is the temperature dependency of the site where the amination takes place. So, it



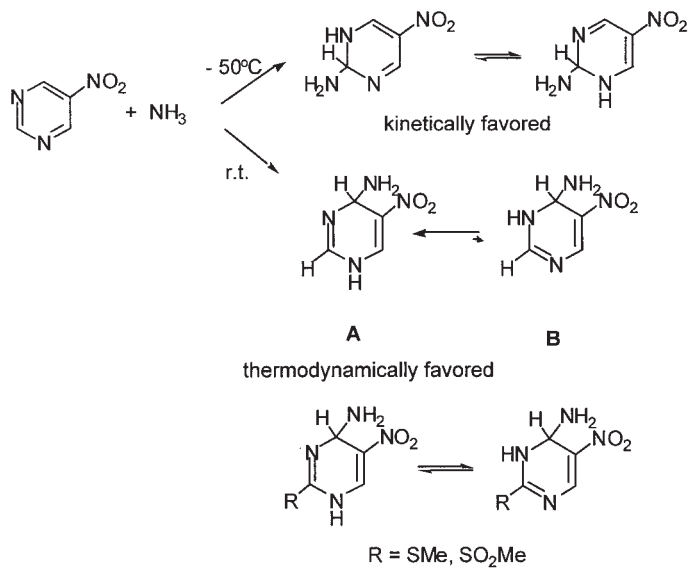
Scheme 39

has been observed that treatment of quinoline with potassium amide in liquid ammonia at −45 °C leads to addition of the amide ion at position 2 of the quinoline ring system and at position 4. When warming up the solution, the 2-amino-1,2-dihydroquinolinide irreversibly converts into the 4-amino-1,4-dihydroquinolinide. It is apparent that the C-2-amino adduct is the kinetically determined adduct, while at higher temperatures the thermodynamically C-4-amino isomer is formed. That the C-4 adduct is more stable than the C-2 isomer may be due to the allylic stabilization in the C-4 adduct (Scheme 39) (73JOC1947). Addition of permanganate gives a good yield of 4-aminoquinoline (85JHC353).

A similar temperature dependency was also observed with the 1,*x*-naphthyridines (*x* = 5, 7). Dissolving 1,5-naphthyridine in liquid ammonia/potassium amide at −40 °C, a very rapid formation of the C-2 adduct was observed (78JOC1673, 83AHC(33)95). At +10 °C the NMR spectrum was drastically changed and clearly showed the presence of the thermodynamically more stable C-4 adduct. This concept of kinetically vs. thermodynamically favored formation explains the controversial results in the amide-induced amination of 1,5-naphthyridine (68JOC1384, 70JHC593).

The NMR spectrum of 1,7-naphthyridine in liquid ammonia/potassium amide at −40 °C showed the presence of the C-2 and the C-8 σ-adducts. Increasing the temperature of this mixture from −40 °C to +10 °C the mixture irreversibly converts into the C-8 adduct. Addition of potassium permanganate gives 8-amino-17-naphthyridine. The allylic contribution in the C8-adduct accounts for its higher stability.

Temperature dependency was also found in the adduct formation between 5-nitropyrimidine and liquid ammonia (83JOC1354). In the



Scheme 40

temperature range between −60 °C and −33 °C two different adducts can be formed, i.e., the C-2 adduct and the C-4 adduct. By allowing to stand for 1 h at −40 °C or for 5 min at room temperature only the C-4 adduct is formed, which is clear evidence that the C-2 adduct is kinetically favored, and the C-4 adduct the thermodynamically more favored one (Scheme 40).

^{15}N-NMR investigations were carried out to establish the tautomeric structures of the covalent σ-adducts formed between 5-nitropyrimidine and liquid ammonia (86JOC1147). The proton-coupled ^{15}N-NMR spectrum of the C-4 adduct obtained from 5-nitropyrimidine and liquid ammonia at room temperature (83JOC1354) exhibits a singlet at 124 ppm, a doublet at 288 ppm, a singlet at 333 ppm (NO_2), and a singlet at 45 ppm (NH_2). The doublet at 288 ppm shows the occurrence of nitrogen in a N=C–H fragment and has been ascribed to N-3, being coupled to H-2, present in 4-amino-1,4-dihydro-5-nitropyrimidine (**A**). The singlet at 124 ppm is ascribed to N-1 in the 1,4-dihydro compound. The tautomeric 4-amino-3,4-dihydro-5-nitropyrimidine (**B**) is not present since a doublet or doublets of N-1 cannot be detected. The 1,4-dihydro tautomer **A** is the correct tautomeric structure (Scheme 40).

The^{15}N-NMR spectrum of the C-2 adduct, observed at low temperature, when 5-nitropyrimidine is dissolved in liquid ammonia at −50 °C, shows

besides the nitrogen of the nitro group and the amino group, one doublet at 282 ppm, indicating that the C-2 adduct exists as a mixture of 2-amino-1,2-dihydro- as 2-amino-2,3-dihydro-5-nitropyrimidine, being in equilibrium by a rapid proton transfer (on the NMR time-scale) (Scheme 40).

^{15}N-NMR spectroscopy of a solution of 2-methylthio- or 2-methylsulfonyl-5-nitropyrimidine in liquid ammonia showed that the C-4 adduct is a mixture of the 4-amino-3,4-dihydro- and 4-amino-1,4-dihydro-5-nitropyrimidine (Scheme 40).

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Conformational Analysis of Saturated Heterocyclic Six-Membered Rings

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I. Introduction

Saturated six-membered heterocyclic rings can be found in various fields of chemistry, e.g., natural products, drugs and polymers. Representative molecules are cyclohexane derivatives in which ring methylenes are either substituted by alkyl or other functional groups or replaced by one or more heteroatoms (mainly nitrogen, oxygen, and sulfur).

These cyclohexane-like rings are characterized by the presence of various non-planar conformations: *chair*, *boat*, and *twist conformations*. The starting point when dealing with the stereochemistry of these six-membered rings is therefore conformational analysis. The method of choice is NMR spectroscopy; as a result the preferred conformer(s) and the *axial*/*equatorial* position of attached substituents at the preferred conformer(s) are obtained.

In addition, the six-membered rings are both conformationally and configurationally mobile. In almost all cases at ambient temperature, the ring interconversion proves to be fast on the NMR time scale. So, in order to analyze the conformational equilibrium, this dynamic process has to be slowed down. Often the rate of ring interconversion can be obtained employing the theory of dynamic NMR spectroscopy, i.e., line shape analysis.

This review covers the relevant literature from 1995 to 2002. The conformational analysis of cyclohexanes and the corresponding O- and S-heterocyclic analogues up to 1994 has been reviewed by Bushweller (95MI25) and Kleinpeter (95MI201), and in the *Advances in Heterocyclic Chemistry* by Kleinpeter (98AHC217), respectively. Crabb and Katritzky (84AHC3) and Delpuech (92MI169) have dealt with the conformational equilibria of N-heterocyclic six-membered rings. Therefore, in the case of saturated O-heterocycles the literature was covered from 1997 and for the six-membered N-heterocycles it was reviewed from 1990.

A lot of fresh material, *especially* the quantum mechanical study of conformational equilibria made good progress and improved enormously our insight into the steric and electronic factors affecting various conformers. Many conformational equilibria have to be reevaluated.

II. New Methodologies for the Investigation of Conformations and Conformational Equilibria

The methodologies for studying both the conformers at equilibrium and their rates of interconversion are mainly based on NMR spectroscopy. Variable temperature measurements are of great help to "freeze" the conformational equilibria. Also, quantitative determinations of ring interconversion and N-inversion barriers rely exclusively on dynamic NMR methods. In addition to the *state of the art*, already reviewed previously (*vide supra*), only a very few methods and applications were added.

The conformational equilibria in six methylcyclohexanes were investigated using the temperature dependence of the ^{13}C chemical shifts at temperatures above the coalescence point (01JCS(P2)302). Using conformationally homogeneous reference compounds, the temperature dependence was analysed for the conformational enthalpy differences: ΔH^0_{ax-equ} of methylcyclohexane 1.92 kcal/mol, of 2- and 3-methylcyclohexanone 1.58 and 1.35 kcal/mol, of 3-methyloxane 1.50 kcal/mol and of 2- and 4-methylpiperidine >2.6 and 2.30 kcal/mol, in very good agreement with previous literature values and theoretical *ab initio* calculations. Also, *vicinal* isotope effects on $^{13}C,^{2}H$ or $^{13}C,^{1}H$ coupling constants were used for the estimation of the position of conformational equilibria in deuterated cyclohexanes (94JCS(P2)2375).

The ground state conformations of ethyl and isopropyl groups in some heteracyclohexanes (94IJC(B)971), and of the methoxy group in methoxycyclohexane with adjacent methyl group substitution (94JCS(P2)1965) were studied by *vicinal* H,H and H,C coupling constants, respectively, and by molecular mechanics calculations.

It is known that the preferred conformation of the nitro group in nitrocyclohexane is *equatorial* (95MI25); the ^{15}N shielding in the *axial*/*equatorial* conformers is not informative because of insignificant shielding difference (98MRCS85). In 1-Me-1-NO_2-cyclohexane, however, the ^{15}N chemical shift in the two conformers is strongly different, showing that the nitro group is predominantly *axial* (98MRCS85). ^{15}N NMR spectroscopy was also suitable to monitor quantitatively the *cis*/*trans* isomers (20% : 80%) of 1-methyl-2-hydroxymethyl-piperidine at ambient temperature (92MI1311).

The $n \rightarrow 3s$ RYDBERG spectra of cyclohexane and a series of oxygen-containing ring systems are extremely sensitive to subtle changes in molecular conformation; both the magnitude and the sign of the shifts were examined (97JPC(A)8970). By rapid cooling in a molecular beam, higher energy conformers could be frozen out and investigated individually.

III. Conformational Analysis and Stereodynamics of Six-Membered Rings and Conformation of Substituents at the Six-Membered Ring

A. Cyclohexanes

The conformational equilibria of monosubstituted cyclohexanes are of continuous interest. The conformational enthalpy (ΔH°), entropy (ΔS°) and free energy ($-\Delta G^\circ$) of methyl-, ethyl-, and *iso*-propyl-cyclohexane were reinvestigated both experimentally (^{13}C enriched signals at different temperatures were evaluated to give values for K) and computationally (cf. Table I). The computed structural data indicated that an *axial* alkyl substituent leads to local flattening of the cyclohexane ring but there was no evidence of a 1,3-*syn-axial* interaction with the *axial* hydrogens. A variable temperature NMR study allowed the determination of the same thermodynamic parameters for the following substituents: benzyl, *tert*-butyl, SMe, SOMe, SO_2Me, SPh, SOPh, and SO_2Ph (cf. Table I). The structures and relative energies of the conformers of phenylcyclohexane **1** (00JOC1181) and dimethylphosphinoylcyclohexane **2** (01JOC2925) were calculated at high theoretical levels. The latter gave thermodynamic parameters that were in excellent agreement with the experimental data (**1**: $\Delta G^\circ = 2.87 \pm 0.09$ kcal/mol; **2**: $\Delta H^\circ = -1.96$ kcal/mol).

In addition, the conformational energies of some new substituents on cyclohexane were determined (cf. Table II); the conformational analysis of cycl-OR (95CJC566) (R = CH_2–CH_2–Me—**3**, = CH_2–CH_2–OEt—**4**, = CH_2–CH_2–O–*i*-Pr—**5**) was published [$-\Delta G^\circ$: **3**: 1.3 ± 0.05 kcal/mol, **4**: 1.46 ± 0.05 kcal/mol, **5**: 1.46 ± 0.05 kcal/mol (all values estimated for methylene chloride solutions)]. These OR substituents are all substantially larger than that for the OMe function ($-\Delta G^\circ = 0.74$ kcal/mol) (74TL579) and, therefore, prefer the *equatorial* position to a larger degree. Kleinpeter et al. (02JMS(T)223, 03CEJ1360) experimentally studied and calculated *ab initio* the conformational equilibria of a large variety of cyclohexanol esters. It was assessed that hyperconjugative interactions $\sigma_{C-C}/\sigma_{C-H} \rightarrow \sigma^*_{C-O}$ together with a steric effect—destabilization of the *equatorial* conformers with increasing bulk of the substituent—were the determinant factors affecting the position of the conformational equilibria (cf. Table II). Thus, because hyperconjugation, found here, is responsible for the stabilization of the *axial* conformer in the case of 2-substituted six-membered saturated heterocyclic compounds (i.e., the *anomeric* effect), the question therefore arises: Can the *anomeric* effect really be construed as anomalous or rather is it a general physical organic phenomenon?

Table I. EXPERIMENTAL CONFORMATIONAL ENTHALPIES (ΔH°), ENTROPIES (ΔS°) AND FREE ENERGIES (ΔG°) FOR MONOSUBSTITUTED CYCLOHEXANES IN SOLUTION

Substituent	$-\Delta H^\circ$/kcal/mol	ΔS°/eu	$-\Delta G^\circ$/kcal/mol	Reference
–Me	1.76 ± 0.10	0.2 ± 0.2	1.80 ± 0.02	99JOC2089
–Et	1.54 ± 0.12	1.3 ± 0.8	1.75 ± 0.02	99JOC2089
–*i*Pr	1.40 ± 0.15	3.5 ± 0.9	1.96 ± 0.02	99JOC2089
–Benzyl	1.52	0.81	1.76	91JOC4802
–*t*Bu	5.00	−0.44	4.87	96JOC6465
–SMe	1.05 ± 0.09	0.48 ± 0.31	1.14	00JOC969
–S(O)Me	1.08 ± 0.06	1.55 ± 0.30	1.36	00JOC969
–SO_2Me	2.66 ± 0.09	-0.26 ± 0.30	2.61	00JOC969
–SPh	1.04 ± 0.11	0.32 ± 0.38	1.10	00JOC969
–S(O)Ph	1.22 ± 0.06	1.82 ± 0.15	1.54	00JOC969
–SO_2Ph	2.44 ± 0.1	1.66 ± 0.26	2.74	00JOC969

Table II. CONFORMATIONAL EQUILIBRIA OF MONOSUBSTITUTED CYCLOHEXANES IN SOLUTION

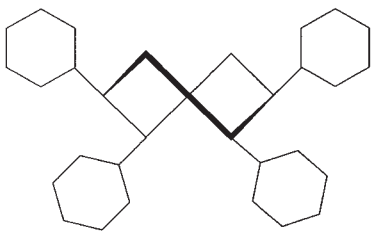
Conformation	Substituent	Conformat. equil.[a]	Reference
Chair	–TlPh	0.9	91MRC248
Chair	–Tl(X)$_2$Ph (X = F, Cl)	*equ.*	94MRC303
Chair	–Tl–Tl-cyclohexyl	1.0	94MRC303
Chair	–OCH_2CH_2Me	1.29 ± 0.05	95CJC566
Chair	–OCH_2CH_2OEt	1.46 ± 0.05	95CJC566
Chair	–OCH_2CH_2O*i*Pr	1.46 ± 0.05	95CJC566
Chair	–OCOMe	0.678	03CEJ1360
Chair	–OCOEt	0.864	03CEJ1360
Chair	–OCO*i*Pr	0.696	03CEJ1360
Chair	–OCO*t*Bu	0.409	03CEJ1360
Chair	–$OCOCF_3$	0.639	03CEJ1360
Chair	–$OCOCH_2Cl$	0.698	03CEJ1360
Chair	–$OCOCHCl_2$	0.549	03CEJ1360
Chair	–$OCOCCl_3$	0.384	03CEJ1360
Chair	–$OCOCH_2Br$	0.686	03CEJ1360
Chair	–$OCOCHBr_2$	0.513	03CEJ1360
Chair	–$OCOCBr_3$	0.327	03CEJ1360
Chair	–NHCOMe	1.6 (CD_2Cl_2)	90CHR11

[a] $\Delta G^\circ = -RT \ln K$ ($K = [a]/[e]$).

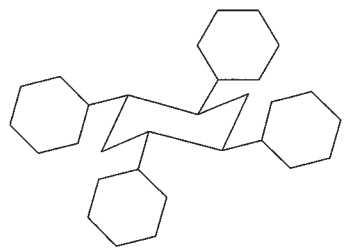
In opposition to a central principle of alicyclic conformational analysis, Kang and Yin reported that a complex O-cyclohexyl nitronate and the corresponding O-cyclohexyloxime constitute the first stable *axial* conformer of monosubstituted cyclohexanes at ambient temperature (97JA8562). Snyder and co-workers (99JA11864) reevaluated the corresponding

conformational equilibria (and studied in addition seven analogs of O-cyclohexyl nitronate) and found the O-*equatorial* conformation to be predominate (*equ*:*ax* = 3:1) in full agreement with other O-cyclohexyl derivatives. Also, the conformational equilibrium of cyclohexyl-*N*,*N*-dimethylcarbamate (R = $OCONMe_2$) was studied (01JBCS215); as expected the *equatorial* conformer is predominating 61–88% depending on the solvent and the parameter used for the estimations.

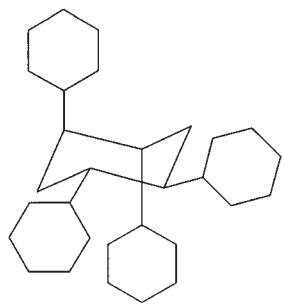
The energy difference between the *chair* and *twist–boat* conformations in cyclohexane is 6.1 kcal/mol (98JPC(A)3756). It was shown experimentally that four cyclohexyl groups in a *cis*,*syn*,*cis*-1,2,4,5 pattern render the *twist–boat* conformation the lowest energy conformation of the central ring (99JOC6505) (cf. Scheme 1). In the corresponding *trans*,*syn*,*trans* and *trans*,*anti*,*trans* forms, all rings (as also the peripheral rings in the *cis*,*syn*,*cis* form) all adopt *chair* conformations; the peripheral rings in the *trans*,*syn*,*trans* form are all located at *equatorial* positions of the central ring, whereas in the *trans*,*anti*,*trans* form a pair of *vicinal* cyclohexyl



cis,syn,cis form



trans,syn,trans form



trans,anti,trans form

Scheme 1

substituents are located at *axial* and a pair at *equatorial* positions (cf. Scheme 1) (99JOC6505).

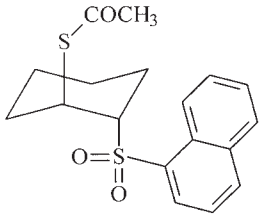
On the other hand, in penta- and hexa(spirotetrahydrofuranyl)cyclohexyl systems the chair conformation of the central cyclohexane ring is still preserved (96JA4504). The boat conformation of the cyclohexane ring can be stabilized also by careful substitution. A series of hopanoid hydrocarbons, the D cyclohexane ring prefers the boat conformation by 1.3–2.5 kcal/mol (95JA6532).

The slightly distorted di-*axial* chair conformation of *trans*-1,2-bis(trimethylsilyl)cyclohexane is more stable than the di-*equatorial* analog as concluded from both low temperature ^{13}C NMR spectroscopy (1.50–1.70 kcal/mol) and molecular mechanics calculations MM3 (1.26 kcal/mol) (97JCS(P2)1365). The distortion of the chair conformation, as the MM3 calculations suggested, was supported by NOE and $^{3}J_{H,H}$ measurements. The ring inversion of the corresponding *cis* isomer coalesces at 236 K; a value of $\Delta G^{\#} = 12.0$ kcal/mol could be calculated for the ring reversal, somewhat higher than that for cyclohexane (10.3 kcal/mol) (95MI25).

In the two *cis*/*trans* isomers of 4-chlorocyclohexane carboxylic acid the conformers with *axial* chloro atoms have conformational energies ca. 30% below those with *equatorial* chloro atoms (99MI7); in this connection the proportion of the *trans*-di-*axial* conformer is greater than expected.

In a detailed ^{1}H NMR study (employing also $Pr(NO_3)_3$ and $Eu(fod)_3$ as shift reagents), Palaima et al. (97MI74) estimated the stereoconfigurations and conformational equilibria of the *cis*/*trans* isomers of 3- and 4-aminocyclohexane carboxylic acid; the *cis*/*trans* ratios of the isomeric mixtures were determined.

Corey et al. (99TL7745) on synthesizing *trans*-1,2-dithiacyclohexane derivatives found that sulfone **6** prefers both in solution and in the solid state the di-*axial* conformer. X-ray analysis of the crystalline phenyl sulfide **7** also demonstrated the 1,2-di-*axial* conformer in the solid state; however, the ^{1}H NMR spectrum of this compound in CD_2Cl_2 at 193 K revealed both 1*e*,1*e* and 1*a*,2*a* forms in a ratio of 2.6:1 (cf. Scheme 2). The *chair* structures of the 1*a*,2*a* conformer of these two compounds are somewhat distorted to relieve 1,3-di-*axial* steric repulsions between the sulfur appendeges and the nearby hydrogens. The preferred di-*axial* conformer of **6** and **7** also in solution was derived from the $^{3}J_{H\text{-}1,H\text{-}2}$ ca. 5.2 Hz. The large preference in stability also in solution for the di-*axial* relative to the di-*equatorial* conformation is the consequence of substantial steric repulsion between the *vicinal* substituents in the di-*equatorial* form. The cyclohexane thiol **8** and the corresponding cyclohexanol **9**, on the other hand, clearly exist as the 1,2-di-*equatorial* conformers in chloroform solution since in each case $^{3}J_{H\text{-}1,H\text{-}2} = 10.0$ Hz (99TL7745) (cf. Scheme 2).



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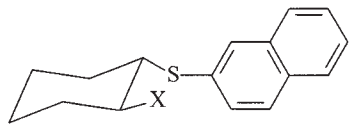
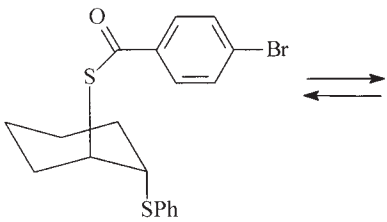
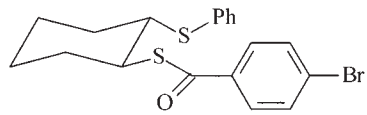


X= SH **8** X= OH **9**





7 aa **7 ee**

Scheme 2

Wiberg (99JOC6387) calculated the conformational energies of *axial*/*equatorial* fluoro-, chloro-, bromocyclohexane, the di-*axial*, *axial*/*equatorial*, and di-*equatorial* conformers of 1,2- 1,3-, and 1,4-dihalocyclohexanes using hybrid density function methods; the effect of solvent was taken into account employing the SCI-PCM method. The agreement with experimental data was sufficient. The following results were most interesting: (i) *axial*-halogen flattens the cyclohexane ring but no evidence of 1,3-di-*axial* interactions of halogen and *axial* ring hydrogen was found and (ii) in the cases of 1,2 and 1,4-dihalocyclohexanes the preference of the di-*axial* forms increases due to the well-known *gauche* effect in the former but due to electrostatic effects in the 1,4-dihalocyclohexanes. From the electron diffraction pattern of gaseous *trans*-1,4-dichlorocyclohexane at 380 K the conformational equilibrium was obtained ($\Delta G^\circ = -0.09$ kcal/mol); the MP2/6-311G* calculation gave the best agreement with the experimental value of ΔG° (99JPC(A)7709).

Williams et al. (96JOC1927), by semiempirical AM1 calculations, studied the 1,3-di-*axial* conformation of *cis*-1,3-diarylcyclohexane in order to investigate in detail arene–arene π-stacking. Consistent with the experimental results, arene–arene π-stacking is controlled primarily by electrostatic rather than charge transfer interactions.

Table III. CONFORMATIONAL EQUILIBRIA OF POLYSUBSTITUTED CYCLOHEXANES IN SOLUTION

Conformation	Conformational equilibria compound	Reference
Chair	1*e*2*e*⇌1*a*,2*a*(−1.50 to 1.70 kcal/mol)[a]	97JCS(P2)1365
Chair	1*e*-SH,2*e*-S(2′-naphthyl)	99TL7745
Chair	1*e*-OH,2*e*-S(2′-naphthyl)	99TL7745
Chair	1*a*-$SCOCH_3$,2*a*-SO_2(2′-naphthyl)	99TL7745
Chair	1*a*-SCOCH=CHPh,2*a*-SO_2(2′-naphthyl)	99TL7745
Chair	1*a*-SCOPh(*p*)Br,2*a*-SPh⇌1*e*,2*e*	99TL7745
Chair	1*a*-Cl,4*a*-Cl⇌1*e*-Cl,4*e*-Cl (−0.09 kcal/mol)	99JPC(A)7709
Chair	1*e*-NHCOMe,2*e*-NHCOMe	96ACSA938
Chair	1*e*-NHCSMe,2*e*-NHCOMe	96ACSA938
Chair	1*e*-NHCSMe,2*e*-NHCSMe	96ACSA938
Chair	1*e*-NMeCOMe,2*e*-NHCOMe	96ACSA938
Chair	1*e*-NMeCSMe,2*e*-NHCOMe	96ACSA938
Chair	1*e*-NMeCSMe,2*e*-NHCSMe	96ACSA938
Chair	1*a*-OH,2*e*-COX,3*e*-NR_2,5*e*-Me	02CEJ2585
Chair	1*a*-OH,2*e*-COX,3*e*-SPh,5*e*-Ph	02CEJ2585
Chair	1*a*-OH,2*e*-COX,3*e*-*n*Bu,5*e*-Ph	02CEJ2585

[a] $\Delta G^\circ = -RT \ln K$ ($K = [aa]/[ee]$).

Sandström and co-workers (96ACSA938) studied both the configurational and the conformational behavior of the *cis*/*trans* isomers of 1,2-di(thio)acetamido-cyclohexanes (cf. Table III) by ^1H and ^{13}C NMR spectroscopy as well as by molecular modeling and found that the *trans* isomers strongly prefer the *ee*-conformation in the *Z*,*Z* configuration. This was clearly shown to be the case by the values of the *vicinal* coupling constants of H-1 and H-2 (10.8–11.0 Hz and ca. 3.5 Hz); the same coupling constants indicate the stronger preference of the NHCSMe group for the *equatorial* orientation in the *cis* analogs dominated by the *Z*,*Z* configuration. When the corresponding NMeCO(S)Me substituents are attached to cyclohexane in the 1,2-positions, both the configurational and conformational behavior gets more complex; in addition to the *Z*,*Z* isomer, the *Z*,*E* and *E*,*E* isomers were observed but the 1*e*,2*e* conformation predominated in the *trans* compounds with no significant amount of the *a*,*a* invertomer (96ACSA938).

The positions of the equilibria between the di-*equatorial* and di-*axial* conformers of *trans*-1,2-dimethoxycyclohexane and *trans*-2-methoxy-cyclohexanol were determined accurately by ^{13}C NMR spectroscopy at $-80\,^\circ C$ using a number of solvents ranging from non-polar pentane to the strongly polar methanol (cf. Table IV) (96AJC379). The di-*equatorial* conformer is preferred under all conditions but the extent increases

Table IV. Conformational Equilibria for *trans*-1,2-Dimethoxycyclohexane and *trans*-2-Methoxycyclohexanol in Different Solvents

	trans-1,2-Dimethoxycyclohexane		*trans*-2-Methoxycyclohexanol	
Solvent	Percentage 1*e*2*e*	ΔG°/kcal/mol	Percentage 1*e*2*e*	ΔG°/kcal/mol
Pentane	57.2 (±1.0)	0.12 (±0.02)	98.8	0.84 (±0.05)
Toluene-d_8	72.0 (±1.0)	0.36 (±0.02)	95.2	1.15 (±0.05)
CS_2	65.6 (±1.0)	0.25 (±0.02)	96.5	1.27 (±0.1)
THF-d_8	67.2 (±1.0)	0.27 (±0.02)	93.9	1.05 (±0.09)
CD_2Cl_2	95.0 (±1.0)	1.12 (±0.09)	> 99	> 1.7
Acetone-d_6	80.0 (±1.0)	0.53 (±0.02)	97.1	1.34 (±0.15)
Methanol-d_4	90.2 (±1.0)	0.72 (±0.05)	97.3	1.39 (±0.15)

[a] $\Delta G^\circ = -\mathrm{RT} \ln K$ ($K = [1a2a]/[1e2e]$).

with solvent polarity, being greater in the latter case. These values have been used, in conjunction with theoretical and other experimental data, to determine new OCCO torsional parameters for the MM3 force field (96AJC379).

Similarly, Abraham et al. (93JCS(P2)1061) studied the conformational equilibria of *cis*-cyclohexane-1,3-diol but employed 14 solvents at ambient temperature; the $-\Delta G^\circ$ values were directly calculated from the *vicinal* H-1,H-2 coupling constants [$J(1,2)_{trans}$] and alternatively from the observed peak width of the H-1/H-3 signal (***d***) (cf. Table V). The free energy differences range from 0.1 kcal/mol in CCl_4 to 2.7 kcal/mol in aqueous solution, generally favoring the di-*equatorial* conformation. In inert solvents, e.g., CCl_4 and $CHCl_3$, the conformational equilibria proved strongly concentration dependent. From this solvent dependence, the authors concluded that in the strongly polar solvents water, alcohols, acetone, and DMSO-d_6 there is no intramolecular hydrogen bonding; in this case, the conformational equilibria can be attributed to both the solvent polarity and to preferential solvation of the di-*equatorial* conformer. In CCl_4, however, an intramolecular hydrogen bond in the di-*axial* conformer of ca. 1.6 kcal/mol is formed, which also may be present in the polar solvents but much less noticeable.

The solvent dependence of the conformational equilibria of *trans*-1,4-dimethoxycyclohexane and *trans*,*cis*-1-Me-3,5-dimethoxycyclohexane was studied by low temperature ^{1}H NMR spectroscopy (90JCR(S)152) (cf. Table VI). The conformational equilibria of *trans*-1-acceptor–2-donor-substituted cyclohexanes **10ee**⇌**10aa** were studied with respect to intramolecular charge-transfer (donor–acceptor) complexes (CT) in the di-*equatorial* conformation (02JOC6938); the CT absorptions and the

Table V. CONFORMATIONAL EQUILIBRIA FOR *cis*-1,3-DIHYDROXYCYCLOHEXANE IN DIFFERENT SOLVENTS

Solvent	Percentage 1*e*3*e* from $J(1,2)_{trans}$	Percentage 1*e*3*e* from *d*	ΔG°/kcal/mol[a]
D_2O	96.5	98.9	0.64
DMSO-d_6	89.6	91.1	0.39
CD_3CN	84.6	87.1	0.27
CD_3NO_2	80.6	83.3	0.23
Methanol-d_1	94.5	96.7	0.45
Ethanol-d_1	–	91.4	0.33
Acetone	81.6	86.5	0.26
Pyridine	89.1	91.6	0.34
CH_2ClCH_2Cl	65.2	65.1	0.09
CD_2Cl_2	–	64.8	0.09
Piperidine	87.1	90.4	0.32
$CDCl_3$	61.7	61.2	0.06
Benzene	60.2	59.6	0.055
CCl_4	55.2	55.4	0.03

[a] $\Delta G^\circ = -RT \ln K$ ($K = [1a3a]/[1e3e]$).

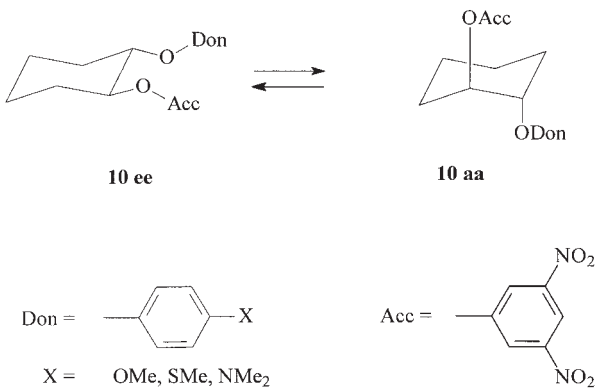
Table VI. CONFORMATIONAL EQUILIBRIA FOR *trans*-1,4-DIMETHOXYCYCLOHEXANE AND *trans*,*cis*-1-METHYL-3,5-DIMETHOXYCYCLOHEXANE IN DIFFERENT SOLVENTS (90JCR(S)152)

Solvent	*trans*-1,4-Dimethoxycyclohexane		*trans*,*cis*-1-Methyl-3,5-dimethoxycyclohexane	
	Temp./K	ΔG°/kcal/mol	Temp./K	ΔG°/kcal/mol
n-Pentane	173	0.11 ± 0.04[a]	173	0.44 ± 0.06[b]
CS_2	180	0.28 ± 0.05	173	0.47 ± 0.06
$(CD_3)_2O$	173	0.55 ± 0.06	173	0.65 ± 0.06
$CHFCl_2$	173	1.4 ± 0.1	173	0.25 ± 0.10
Acetone-d_6	172	0.71 ± 0.06	173	0.65 ± 0.10

[a] $\Delta G^\circ = -RT \ln K$ ($K = [1a4a]/[1e4e]$).
[b] $\Delta G^\circ = -RT \ln K$ ($K = [1e3a5a]/[1a3e5e]$).

equilibrium constants were determined by UV–VIS spectroscopy at 298 K and NMR spectroscopy at 298 K, respectively; the donor–acceptor interactions range between 0 and −1 kcal/mol as confirmed by an X-ray structure (cf. Scheme 3).

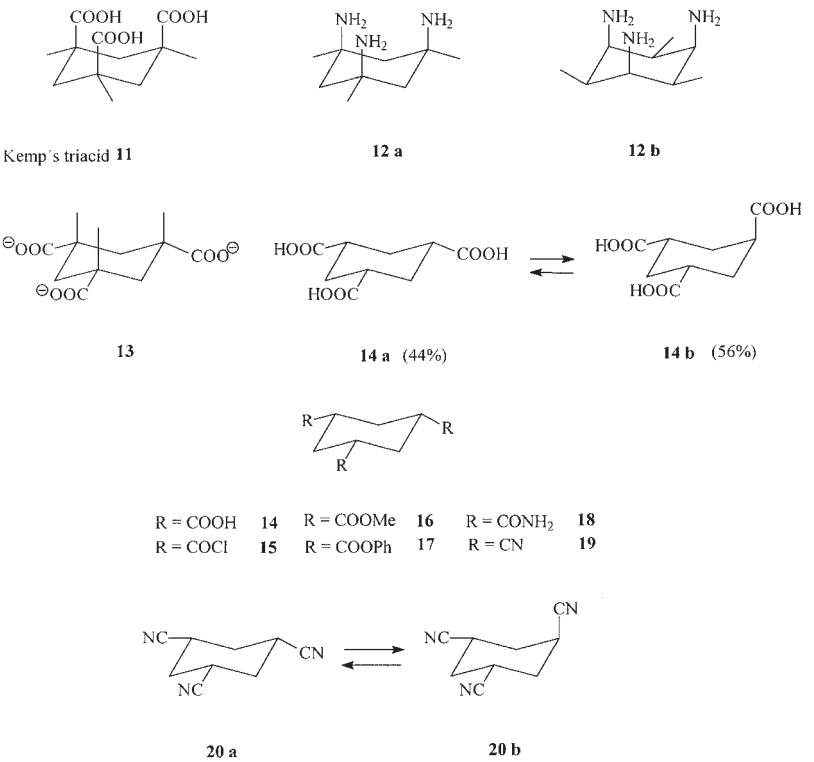
The spatial structures of a number of mono- and disubstituted 1,1-dimethoxycyclohexanes were studied by ^{13}C NMR spectroscopy



Scheme 3

(98STC411). In the monosubstituted compounds (Me, Et, *i*Pr, and OMe on C-2), the substituents are *axially* oriented contrary to their normal *equatorial* orientation on C-3 and C-4. The disubstituted compounds (1,X-dialkyl—X = 3, 4, 5, 6) exist as *cis*/*trans* isomers. In the more stable isomeric form the 2-substituent is *axial* and the other is *equatorial* and in the less stable isomer, both substituents are *equatorial*, excluding the *cis*-2,6-dimethyl derviative where the ^{13}C NMR shift data point to a predominance of the di-*axial* form.

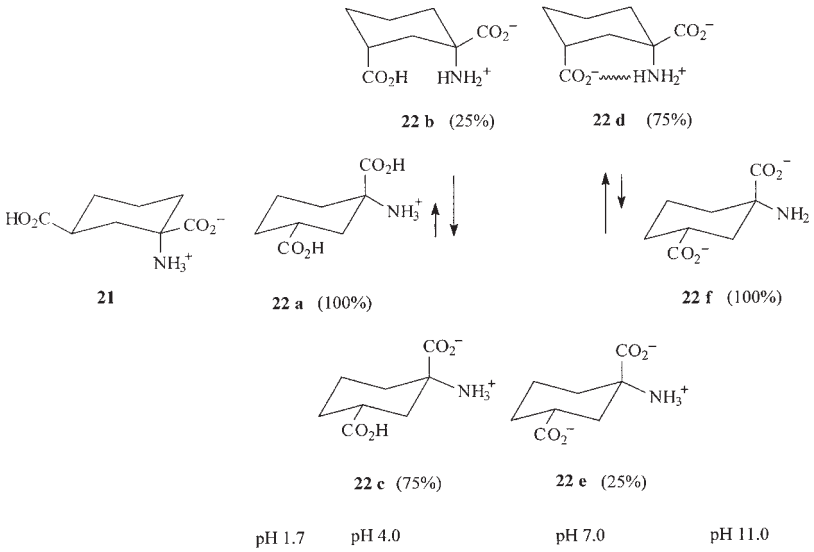
Kemp's triacid **11** (cf. Scheme 4), a cyclohexane derivative in which 1,3,5-*cis* methyl groups force three *cis*-1,3,5-carboxyl groups into the all-*axial* conformation (81JOC5140), has served in the last two decades as a useful framework for the design of enzyme models (98JA105), (96JA10928). Both the *cis*,*cis*-1,3,5-triaminocyclohexane analog **12a** (02AG2693) and the isomer **12b** (97JCS(P2)1445) were found in the same preferred conformation. The *axial* position of the nitrogen atoms with respect to the methyl substituents is controlled by hydrogen bonding among the amino groups and the smaller size of the amino groups and a supporting $\sigma_{C-H} \rightarrow \sigma^*_{C-N}$ interaction. Protonation (**12a** · 1HCl, **12b** · 1HCl) established in each case the preference for three *axial* nitrogen atoms; only **12a** · 3HCl, **12b** · 3HCl adopt conformations, no doubt due to electrostatic repulsion, with three *equatorial* cationic ammonium groups. When Kemp's triacid is treated with NaOH solution, the conformation changes to the invertomer **13** (cf. Scheme 4) (97CL1253) also due to electrostatic repulsion. In this preferred conformation *cis*,*cis*-cyclohexane-1,3,5-tricarboxylic acid **14a** also was found (01JCCS193); the steric effect due to the three *axial* carboxylic groups overrides the effect of intramolecular hydrogen bonding in the tris-*axial* conformer. Chemical



Scheme 4

functionalization of the triacid **14** gives the triacid chloride **15** and various other derivatives **16**–**19**; all the derivatives were shown by NMR analysis to have the symmetrical tris-*equatorial* conformation (01JCCS193), no *cis*,*trans* isomers were found. Heating triacid **14** and trinitrile **19** at 240 °C causes isomerization (01JCCS193) to reach an equilibrium between **14a** : **14b** = 44% : 56% and **20a** : **20b** = 30% : 70%. In the *cis*,*trans*-isomers **14b** and **20b** two substituents were found in an *equatorial* and one in an *axial* position, corroborated of the X-ray structure of **20b**.

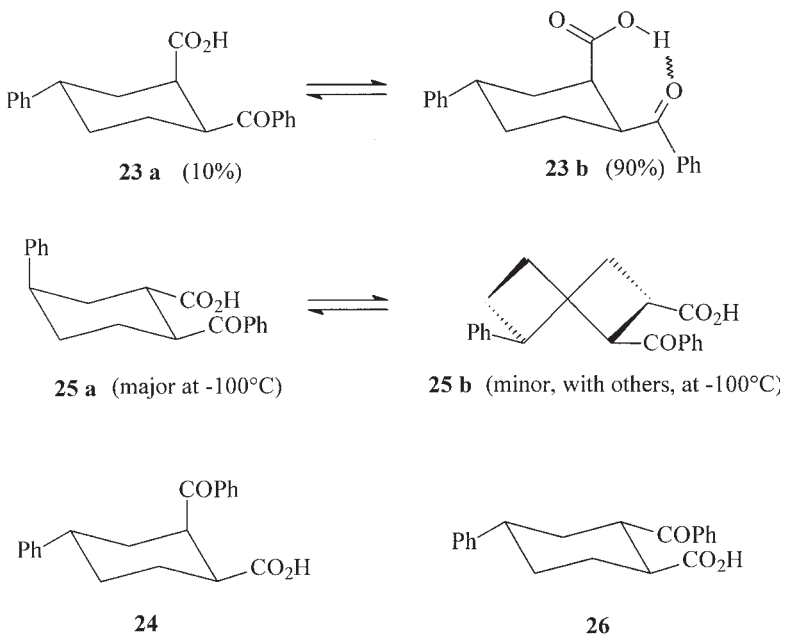
In the case of a number of 1,1,3- and 1,2,4-tris-substituted cyclohexanes very interesting conformational equilibria were detected, depending on intramolecular hydrogen bonding and the pH value of the medium. In aqueous solution, two glutamic acid analogs containing a cyclohexane ring substituted in position 1 by an amino and a carboxyl group, and in position 3 by another carboxyl group exclusively exhibit chair conformations (cf. Scheme 5) (93JCS(P2)525). When the two carboxyl



Scheme 5

groups are *cis* they are *equatorial* and the amino group is *axial* (**21**) at all pH values. In the corresponding *trans*-isomer, however, the conformational equilibria are strongly pH dependent: at pH 1.7 **22a** and at pH 11.0 **22f** exclusively, but at pH 4 equilibria **22b/22c** and at pH 7 **22d/22e** were detected (cf. Scheme 5) (93JCS(P2)525).

The conformational preference of *trans*-5-phenyl-*cis*-2-benzoyl-1-cyclohexane-carboxylic acid **23**, its 4-*trans* phenyl positional isomer **24** and both their 2-*trans* benzoyl epimers **25** and **26**, respectively, were elucidated by means of NMR spectroscopy (cf. Scheme 6) (00JCS(P2)687). Compounds **24** and **26** showed no exchange broadening on lowering the temperature down to −60 °C; also using DMSO-d_6 as solvent, disrupting the intramolecular hydrogen bonding between the carboxyl proton and the phenoxy carbonyl group did not significantly change the conformations; epimers **24** and **26** exist as preferred conformers (cf. Scheme 6). The NMR spectra at −60 °C revealed that *trans*-5-phenyl-*cis*-2-benzoyl-1-cyclohexanecarboxylic acid **23** exists in an equilibrium between two conformers with the same chair conformation—one with (**23b**) and the other without (**23a**) intramolecular hydrogen bonding. One (**25**) of the epimers, on the other hand, only decoalesced at −100 °C in acetone-d_6 into two conformers, the major conformer was clearly identifiable as a *chair* conformer (**25a**), the signals of the minor conformer were not really



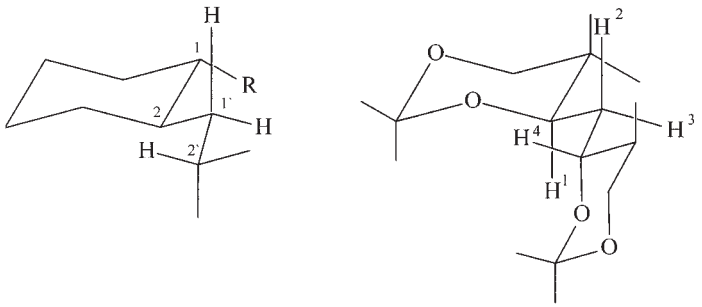
Scheme 6

recognizable and represent an equilibrium of still rapidly interconverting *twist–boat* conformers (**25b**) (00JCS(P2)687).

Using a highly efficient and stereoselective synthesis, three functionalized 1,2,3,5-tetra-substituted cyclohexanes were obtained as single stereoisomers (cf. Table III) (02CEJ2585).

An isopropyl group in the *equatorial* 2-position of 1-*equatorially* substituted cyclohexane adopts a preferred conformation (cf. Scheme 7); the vicinal coupling constants between the diastereotopic protons at C-1′ and the tertiary protons at C-2 and C-2′ provide evidence for the predominant conformer (01EJOC1857). The same preferred conformation was observed in the 2-position of the 3-*equatorially* substituted tetrahydropyrane ring, in bis(1,3-dioxanyl)methanes (96TL4479) and the corresponding oligo-1,3-dioxanylmethanes up to the pentakis(1,3-dioxanyl) methane (02CEJ1292, 02EJOC2613). Nature uses this type of conformational preorganization of side chains to hold the pharmacophor in a distinct shape (01EJOC1857).

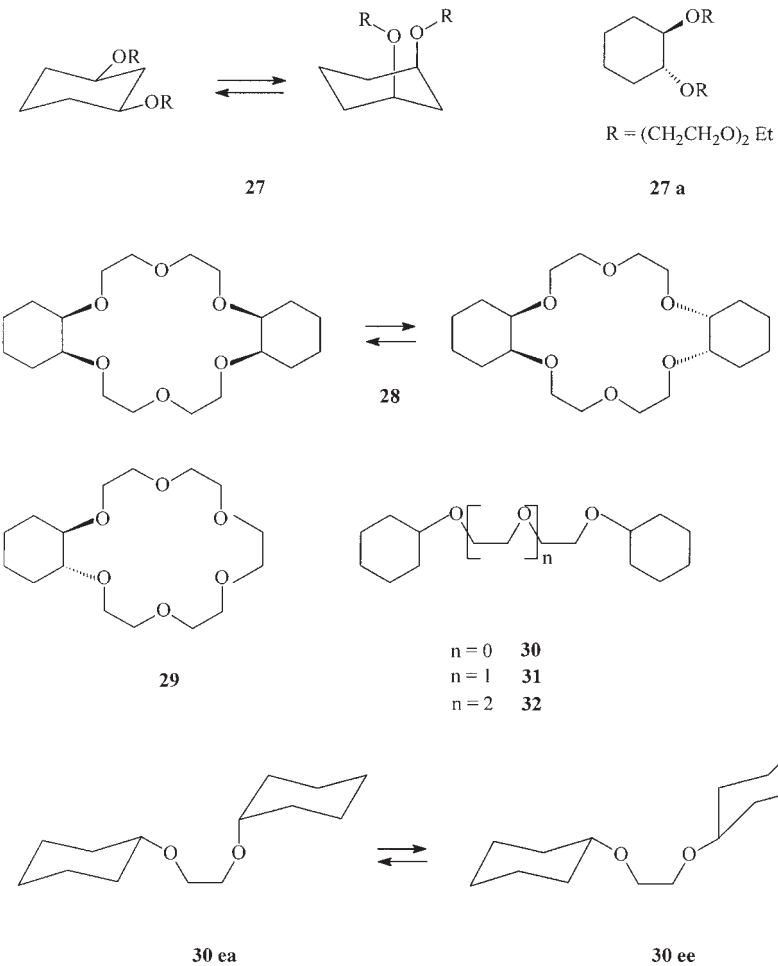
Actually, the conformational equilibrium of cyclohexane-based 1,3-dipodands **27** changes from a conformational mixture biased towards the



Scheme 7

di-*equatorial* (*ee*) conformer by ring inversion to an *aa* conformation upon Na^+ complexation (89JCS(CC)236) (cf. Scheme 8). Also, the *trans*-1,2-di-podand **27a**, the corresponding di-*cis*-cyclohexyl-18-crown-6 **28** and *trans*-cyclohexyl-18-crown-6 **29** were studied (02T6729); the podand and the macrocyclic compound derived from cyclohexane with a *trans* stereochemistry form complexes to several alkaline and alkaline-earth cations with a lower complexation constant than those observed with the *cis* stereochemistry. The conformational free energy differences between *cis-syn-cis*- and *cis-anti-cis*-dicyclohexano-12-crown-4 ethers as well as their 18-crown-6 **28** and 24-crown-8 analogs are small (< 0.36 kcal/mol) due to the *cis*-1,2-disposition of the oxygenated substituents (89CJC449, 84TL3963, 85CJC2847, 92CJC1688). In the corresponding *trans*-cyclohexanomonothiacrown ethers (97PS181) the di-*equatorial* orientation of C–S and C–O bonds was found to be predominant.

For dicyclohexanoethyleneglycol **30** and the diethylene and triethyleneglycol congeners **31** and **32**, the conformational equilibria **30ea**⇌**30ee** are strongly shifted to **30ee** ($\Delta G^\circ = 1.12 \pm 0.1$ kcal/mol). Within the error limits, the same values were found for **31** and **32** (95CJC566). The corresponding *aa* conformer was not identified due to its low abundance. The similar conformational behavior was reported for the corresponding ditellurides **33** (94MRC303) (cf. Scheme 9). The voluminous $PhTeX_2$ substituents act like steric anchors and are fixed in the *equatorial* position while the PhTe group in the monosubstituted cyclohexane prefers the *equatorial* conformation ($\Delta G^\circ = 0.9$ kcal/mol) (91MRC248). The dicyclohexano ditelluride **36** still favors the *equatorial* orientation; the signal intensity ratio of **36ee** : **36ea** is ca. 9 : 1 indicating a slightly higher equatorial preference for cyclohexyl-Te–Te ($\Delta G^\circ = 1.0$ kcal/mol) than for PhTe. Again, the third conceivable conformer **36aa** could not be identified due to its very low abundance.

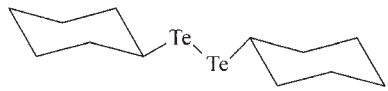


Scheme 8

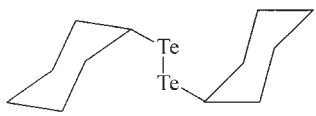
The 1-methyl-1-cyclohexyl cation **37** has previously (87JA7811) been proposed to exist in superacid solution as a rapidly equilibrating pair of ***hyperconjomers***, one isomer involving *equatorial CC hyperconjugation*, and the other one with *axial C–H hyperconjugation* (cf. Scheme 10). Using a combination of three independent experimental methods (comparison of experimental and theoretical ^{13}C chemical shifts in the hyperconjomers, d_4-deuteration at C2–C6, and nucleophilic substitution reactions) together with the corresponding theoretical data, von Schleyer et al. have now obtained virtual proof for this concept (01JCS(P2)869) even when the **37CC⇌37CH**

33 e **33 a**

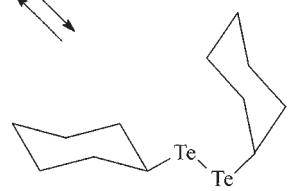
X = Cl **34**
X = F **35**



36 ee

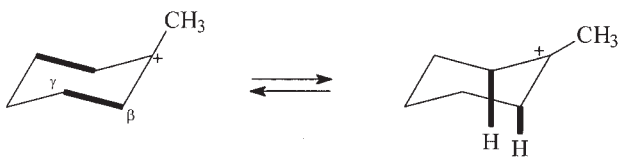


36 aa



36 ea

Scheme 9



37 (CC) **37** (CH)

Scheme 10

equilibrium could not be "frozen out". Both the experimental and theoretical results clearly show **37CH** to be the dominant isomer in solution.

Only one special paper concerning the ring interconversion in solution of cyclohexane derivatives was published. The ring inversion of *cis*-1,2-bis(trimethylsilyl)cyclohexane coalesces at 236 K, a values of $\Delta G^{\#} = 12.0$ kcal/mol was calculated for this dynamic process, somewhat higher than that for cyclohexane (10.3 kcal/mol) (95MI25).

Steiner and Saenger (98JCS(P2)371) studied the occurrence and properties of *axial* substituents in crystalline cyclohexane by a CSD database

analysis (97MI) and found (by considering the inclination angle α of the X–C(1)-bond of the *axial* substituent and the C(1)–C(3)–C(5) plane—$\alpha = 90°$ in cyclohexane) that the **steric strain** of the *axial* conformation increases for bulkier substituents: X = O ($\alpha = 94.2°$) = N(94.1°) < S(96.5°) = CN (96.4°) < Br (99.7°) < Csp^3 (101.0°) < Csp^2 (102.5°) < SO_2Ph (104.6°) < P=S$(Ph)_2$ (109.8°), **without**, even in the latter two cases, forcing the cyclohexane ring to adopt the *boat* conformation. This was explained by the well-known intramolecular interactions between the *axial* substituent with the *axial* H-atoms in the 3,5-positions. The interpretation of these contacts as **hydrogen bonds** proved to be inadequate.

Both the conformational equilibria and the barrier to ring inversion of monohalocyclohexanes were studied in a liquid crystalline solution ($-\Delta G° = 0.5$ kcal/mol; $\Delta G^{\#} = 13.88 \pm 0.2$, and 9.70 ± 0.55 kcal/mol for chloro- and iodo-cyclohexane (00LC1171)) and in the solid inclusion compound that fluorocyclohexane forms with thiourea (99MRC15) (nearly equal *axial* and *equatorial* populations; $\Delta H^{\#} = 9.41 \pm 0.62$ kcal/mol and $\Delta S^{\#} = -3 \pm 3$ cal/mol K; $\Delta G^{\#}$ (263 K) $= 10.15 \pm 1.3$ kcal/mol (97JCS(CC)961)). In another paper, Müller studied the thiourea inclusion compounds with substituted cyclohexanes bearing polar or non-polar substituents by dynamic ^{13}C MAS NMR spectroscopy (95MRC113). A dramatic increase in the population of the *axial* conformer in thiourea is found for all the cyclohexanes bearing polar substituents, while those for non-polar substituents show almost identical values in solution and in the inclusion compound. With more efficient packing, polar host–guest interactions provide a major contribution to the stabilization of the *axial* conformer. The barriers to ring inversion are equivocal compared with the values obtained in solution, but the ring inversion (due to sufficient population of the *axial* conformer) could be determined for the first time in $C_6H_{11}OH$ ($\Delta H^{\#} = 13.49 \pm 0.5$ kcal/mol; $\Delta S^{\#} = 13.2 \pm 2$ cal/mol K), $C_6H_{11}SH$ ($\Delta H^{\#} = 15.3 \pm 0.5$ kcal/mol; $\Delta S^{\#} = 18.5 \pm 2.0$ cal/mol K) and $C_6H_{11}CH_3$ ($\Delta H^{\#} = 12.3 \pm 0.5$ kcal/mol; $\Delta S^{\#} = 10.1 \pm 2.0$ cal/mol K) (95MRC113).

The ring inversion of cyclohexane-d_{11} was studied also in capsules. Encapsulation into a "Jelly Doughnut" increases the barrier: $\Delta G^{\#}$ (248 ± 0.5K) $= 10.55 \pm 0.05$ kcal/mol by ground state stabilization (97JA11701) and for free cyclohexane-d_{11} $\Delta G^{\#}$ (233 ± 0.5K) $= 10.25 \pm 0.05$ kcal/mol. Encapsulation into calix[4]arene, which dimerizes via hydrogen bonding, has no effect (97JA11701). On the other hand, the rate of chair-to-chair interconversion of cyclohexane-d_{12} was determined in its neat plastic crystalline phase ($\Delta G^{\#}$ (222 ± 3 K) $= 10.8 \pm 0.1$ kcal/mol) because the plastic phase provides a more motionally restricted environment (93JPC2497).

Table VII. SOLID STATE STRUCTURES OF SUBSTITUTED CYCLOHEXANES

Conformation	Position and conformation of substituents	Reference
Chair	1*e*(*R*),2*e*(*R*)-N=CH–C_6H_5	02AX640
Chair	spiro-5,5-hydantoin · H_2O	97AX(C)1659
Chair	spiro-5,5-hydantoin,2*e*(3′-indolyl) · H_2O	97AX(C)1659
Chair	1*e*-Me-1*a*-benzoyl-4*e*-*t*-Bu	97AX(C)1255
Chair	1*e*-Me-1*a*-thiobenzoyl-4*e*-*t*-Bu	97AX(C)1255
Chair	*β*-Cyclodextrin-1*a*,4*a*-diol · $5H_2O$	98JCS(P2)371
Chair	1*a*,4*a*-diol	98JCS(P2)371
Chair	1*e*,4*e*-diol	98JCS(P2)371
Chair	1*e*-OCOPh,4e-OCOPh	82AX(B)211
Chair	1*e*-OH,2*e*-OPh(*o*-Br,*p*-Me)	01AX(E)1211
Chair	1*e*,4*e*-di-CN	95AX(C)1020
Chair	1*a*-$SCOCH_3$,2*a*-SO_2(2′-naphthyl)	99TL7745
Chair	1*a*-SCOPh(*p*)Br,2*a*-SPh	99TL7745
Chair	1*e*-O-Ph(SMe)(*p*),2*e*-OCOPh(3,5-diNO_2)	02JOC6938
Chair	1*e*-CN,3*e*-CN,5*a*-CN	01JCCS193
Chair	1*e*-COOMe,1*a*-Br,4*e*-COOMe,4*a*-Br	00MI35
Chair	1*a*-COOEt,2*a*-COOEt,4*e*5*e*-16-crown-8	02T6729
Boat	*cis*-1-*t*-Bu,4-C$(Me)_2CH_2$–OCOPh–Br(*p*)	84HCA669
Chair	1*a*,2*a*,3*e*,4e,5*e*,6*e*-hexa-Br	94AJC1395
Chair	1,2,3,4,5,6-all-*a*-*i*Pr	90JA893
Chair	1*e*-COOH,1*a*-NH_3^+,3*e*-COOH	93JCS(P2)525

The X-ray structures of a large number of cyclohexane derivatives were published; the conformation of the cyclohexane ring and the conformations of substituents on the saturated six-membered ring are given in Table VII.

Both LIS data (99JCS(P2)99) and ^{13}C NMR spectra of cyclohexene oxide (98JA1485) proves that the compound exists in enantiomeric *half-chair* conformations with C-4 and C-5 displaced from the ring plane. At −187.7 °C the exchange between these two half-chair conformers is slow on the NMR time scale; for the free energy of activation of the interconversion, 4.3 ± 0.2 kcal/mol (at −178.2 °C) was determined for the solution ($CHClF_2$: $CHCl_2F$: CHF_3 = 5 : 1 : 1) but 9.1 kcal/mol (at −81 °C) for the solid state (00JOC3207).

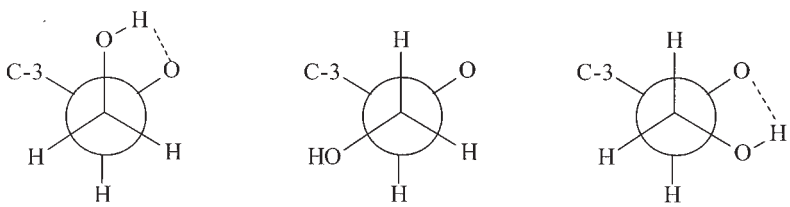
B. OXANES (TETRAHYDROPYRANES)

Recently, only the conformational analysis of 4-hydroxy-tetrahydropyran **38** and of 2-(hydroxymethyl)-tetrahydropyran **39** was published (98JCS(P2)1751). The low temperature ^1H NMR study of **38** gave 8.5%

to the *axial* conformer, which is $\Delta G^{\circ}(equ\text{–}ax) = 1.02$ kcal/mol. This is almost identical to the ΔG° value of the hydroxyl group in cyclohexane (98AHC217), showing clearly there is no OH $\cdots$ O interaction. For **39**, a useful model for $CH_2OH \cdots O$ interactions in D-glucose and derivatives, at 288 K in $CDCl_3$ the following populations were determined: $gg = 31\%$, $gt = 66\%$, and $tg = 3\%$ (cf. Scheme 11). Compared with D-glucosides, in both cases, the *tg* conformer populations with no possiblity to hydrogen bond are very small, obviously a general phenomenon. In sugars this fact had been attributed to destabilization due to syn-*axial* C-6-OR $\cdots$ O-4-OR oxygen–oxygen interactions.

Anselmi et al. (02JCS(P2)1525), very recently published the conformational analysis and dynamics of *cis*/*trans*-4-methylcyclohexyl tetrahydropyranyl ethers (cf. Scheme 12) and compared their structures with the floral odors of the compounds. The *cis* isomer **40**(cis), endowed with a main white flower note, has an bent, oval molecular shape. The *trans* derivatives **40**(trans) and **41**, exhibit different odors, possess an extended structure of cylindrical molecular shape. Brenna et al. (02CJC714) reexamined the configuration/conformation of rose oxide analogues. However, the conformational analysis provided poorer results than published previously (78JPC303) without even citing the previous paper.

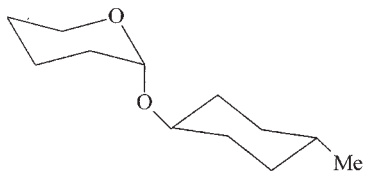
Finally, Freeman et al. (99JMS(T)87, 01JMS(T)19, 01JPC(A)10123), employing both the *ab initio* theory and density function theory, calculated (i) the energies of *chair*, *half-chair*, *sofa*, *twist*, and *boat* conformers of tetrahydropyran, (ii) the conformational enthalpies (ΔH°), entropies (ΔS°) and free energies (ΔG°) of 2-methyl, 3-methyl, and 4-methyltetrahydropyran, and (iii) the same parameters for a larger variety of 3-alkyl-tetrahydropyran, and, last but not least, of 3-(trimethylsilyl)tetrahydropyran. When including electron correlation, MP2 calculations gave ΔG° values in good agreement with experimental results (98AHC217).



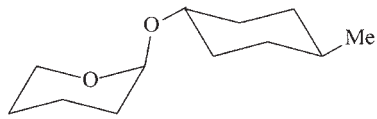
gauche, gauche *trans, gauche* *gauche, trans*

39

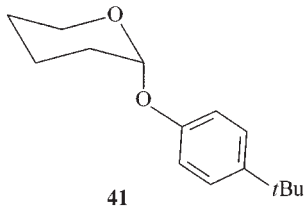
Scheme 11



40 (*cis*)

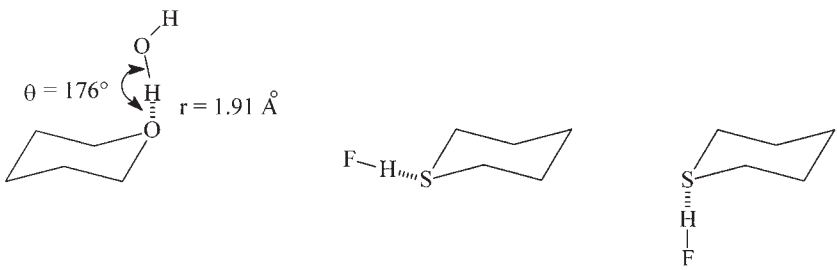


40 (*trans*)



41

Scheme 12



Scheme 13

The tetrahydropyran–water system was investigated by molecular beam FT microwave and free jet millimeter wave spectroscopies (98CEJ1974) as well as by *ab initio* calculations. In the complex, the water lies in the plane of symmetry of tetrahydropyran and the water proton is involved in the hydrogen bond *axial* with respect to the ring (cf. Scheme 13); the O(ring)···H bond distance is about 1.91 Å and the free water proton is in an *E* geometry. Using the same methods, the thiane-hydrogen fluoride system was studied (02CEJ1603); the *axial* form was found to be more stable.

In 2-benzoyl-oxane (also in 2-benzoyl-thiane, -1,3-dithiane, 1,3-oxa-thiane) the benzoyl substituent adopts the *equatorial* conformation in the solid state (99IJC617).

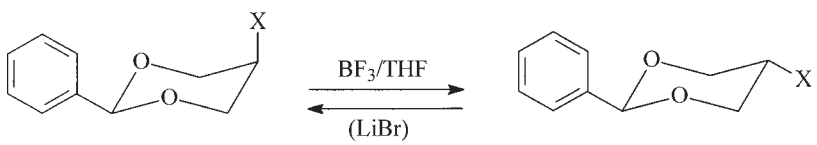
C. 1,3-Dioxanes (1,3-Dioxacyclohexanes)

The amount of conformational results obtained for 1,3-dioxanes is much larger. The position of the equilibria of the diastereomeric *cis*/*trans*-5-substituted 2-phenyl-1,3-dioxanes after equilibration by means of BF_3 (in the absence and presence of LiBr) was determined (cf. Scheme 14 and Table VIII) (97JOC4029). The salt effect on the equilibria was critically evaluated. In **42**–**45** the *axial* conformer is more preferred when the LiBr salt is present (general salt effect); in **46**–**49** no significant salt effect was observed and in **50** the preference of the NHCOMe substituent for the *equatorial* position increases with the LiBr concentration (due to interruption of the intramolecular hydrogen bond of the NH proton to the ring oxygen atoms). The lithiated 1,3-dioxanes converged to structures with ditopic coordination (01JPOC488).

2-Ethinyl-1,3-dioxanes and the 2-ethinyl-5,5-dimethyl and 2-phenylethinyl-5,5-dimethyl analogs were studied in several solvents by low temperature ^1H and ^{13}C NMR spectroscopy; the two substituents –C≡CH and –C≡CPh prefer in $CDCl_3/CS_2$ the *equatorial* chair conformer. The enthalpy difference (ΔH°) of 2-phenylethinyl-5,5-dimethyl-1,3-dioxane was also estimated in various solvents: in toluene-d_8 −0.69 kcal/mol, in $CDCl_3/CS_2$ (2:1) −1.44 kcal/mol and in acetone-d_6 −1.39 kcal/mol (98RJGC130). The ethinyl substituent in 2-ethinyl-2,4,4-trimethyl-1,3-dioxane (98CHE141) and in 2-silylethinyl-2,4,4,6-tetramethyl-1,3-dioxane (98CHE431) adopts the *axial* position while the 1,3-dioxane ring was found in a nearly ideal *chair* conformation both in solution and in the solid state.

The conformational equilibrium of 2-methoxy-1,3-dioxane was studied again both in the gas state (97JMS335) and in acidic/basic solutions (97JA585).

Uehara et al. (99JOC1436) studied in solution and in the solid state the conformational equilibria of 2,2-diaryl-1,3-dioxanes with aryl substituents



X = COOH **42**
= COOMe **43**
= CONHMe **44**
= CH_2OH **45**

X = OH **46**
= OCOMe **47**
= $OCOCH_2OAr$ **48**
= NO_2 **49**

X = NHCOMe **50**

Scheme 14

Table VIII. CONFORMATIONAL EQUILIBRIA OF 5-SUBSTITUTED 2-PHENYL-1,3-DIOXANES DEPENDENT ON THE PRESENCE OF LiBr AT 25 °C IN THF

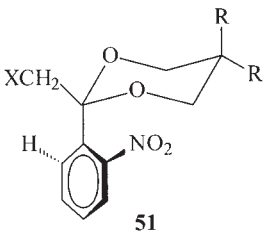
		ΔG°/kcal/mol	
Compound	Substituent	Pure	Comp.: LiBr (1:1)
42	COOH	-0.77 ± 0.03	-0.41 ± 0.03
43	$COOCH_3$	-0.50 ± 0.02	-0.15 ± 0.03
44	$CONHCH_3$	-0.76 ± 0.05	-0.67 ± 0.04
45	CH_2OH	-0.20 ± 0.01	-0.04 ± 0.02
46	OH	-0.38 ± 0.04	-0.35 ± 0.03
47	$OCOCH_3$	0.47 ± 0.01	0.45 ± 0.02
48	$OCOCH_2OPh(2\text{-}Me)$	0.56 ± 0.02	0.89 ± 0.03
49	NO_2	0.73 ± 0.02	0.52 ± 0.03
50	$NHCOCH_3$	0.94 ± 0.03	0.44 ± 0.03

of different electronic properties and found that these compounds exist in the *chair* conformation in which the electron-withdrawing aryl groups were always *axial* and the electron-donating aryl groups were always *equatorial*. Both the solution NMR data and the X-ray crystallographic data on the conformational preferences and bond lengths at the anomeric carbon clearly indicate the anomeric effect $\sigma_{n\text{-}O} \rightarrow \sigma^*_{C\text{-}aryl}$ to be responsible for the preferences observed. The aromatic substituent in 2-aryl-1,3-dioxanes prefers the *axial* conformation and, in addition, the *orthogonal* rotamer **51** (cf. Scheme 15), a new class of atropisomers (98T2905).

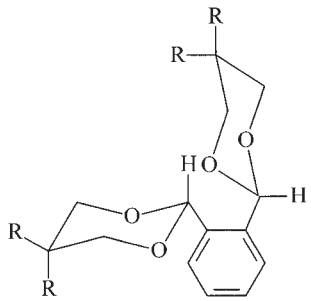
From French cider the *cis*/*trans*-isomeric 2-methyl-4-pentyl- (**52a**, **53a**) and 2-methyl-4-(2′)(*Z*)-pentenyl-1,3-dioxanes (**52b**, **53b**) were identified by NMR, NOE, H,H-decoupling and various chromatographic techniques (cf. Scheme 16); as the compounds exhibit a weak ''green note'' they may contribute to the flavor of cider (97JAFC3178).

The *erythro*/*threo* diastereomers of a larger variety of 4,5-disubstituted 1,3-dioxanes (chiral conformationally restricted arachidonic acid analogs **54**–**59**) proved to be of enantiomerically pure stereochemistry (cf. Scheme 17) (99TA139); the epimers were clearly identified by the coupling patterns of the protons in positions 4, 5, and 6, reflecting the *ax*,*equ* (*threo*) and *equ*,*equ* (*erythro*) relationships of the two substituents.

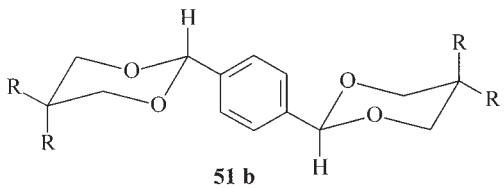
(4*S*,5*S*)-5-Amino-4-phenyl-2,2-dimethyl-1,3-dioxane and (4*R*,5*R*)-5-amino-(4′-biphenyl)-2,2-dimethyl-1,3-dioxane were synthesized and employed as chiral solvating agents for the *ee* determination of compounds bearing an acidic proton by means of ^{1}H NMR spectroscopy (99TA323). Based on the rigid conformation of the two amines, they are



51

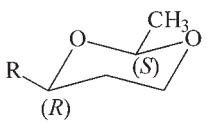


51 a

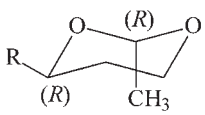


51 b

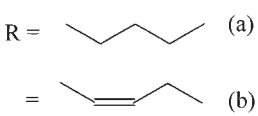
Scheme 15



52 a,b



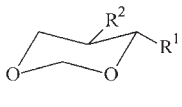
53 a,b



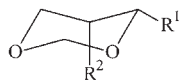
Scheme 16

also very suitable as chiral derivatizing agents in order to determine absolute configurations.

Grosu et al. synthesized and studied in detail the stereochemistry of two 1,3-dioxane ring systems linked via *ortho*-, **51a** (98MI53), and *para*-phenylene groups, **51b**, respectively (98ACSA366). Both the *ortho*- and *para*-phenylene groups show an *equatorial* orientation with respect to both heterocycles (cf. Scheme 15).



54 - 59 (*erythro*)



54 - 59 (*threo*)

$R^1 = CH_2OH$	CH_2OAc	CHO	$CH{=}CH(CH_2)_4CH_3$ (*cis*)
$R^2 = OCH_2OMe$	OH	OCH_2OAc	OCH_2OMe
$R^1 = CH{=}CH(CH_2)_4CH_3$ (*cis*)		$CH{=}CH(CH_2)_4CH_3$ (*cis*)	
$R^2 = OH$		$OCH_2COOAlk$	

Scheme 17

Grosu et al. also synthesized a variety of new 5,5-disubstituted (96MI71) and 2,2,5,5-tetrasubstituted 1,3-dioxanes (98M723); the compounds exhibit anancomeric structures with the bulkier substituents in an *equatorial* conformation. The same authors also studied the stereochemistry of trispiro- (98M59), dispiro- (96T12783), and spiro-1,3-dioxanes (97T6215), when the substituents are close to the spiro carbon atoms, they induce anancomericity of the heterocycle, and when they are further away, the 1,3-dioxanes proved to be flexible.

Ganguly and Fuchs studied negatively and positively (protonated) charged 1,3-dioxanes at the MP2/6-31+G* level of theory (97JOC8901) and proved that the preferred site of protonation of 1,3-dioxane is *axial* because the *equatorial* lone pair was hyperconjugatively stabilized.

The X-ray structures of two anthraquinone derivates of 1,3-dioxane were published. In both 1-methoxy-4-(2-methylprop-2-enyloxy)-2-[(2*R*,6*R*)-4,4,6-trimethyl-1,3-dioxan-2-yl]-anthraquinone and 4-hydroxy-3-(2-methyl prop-2-enyloxy)-2-[(2*R*,6*R*)-4,4,6-trimethyl-1,3-dioxan-2-yl]anthraquinone the 1,3-dioxane ring adopts the chair conformation and the substituents in positions 2 and 6 are in *equatorial* conformations (99AX(C)436). Finally, Freeman et al. (02JMS(T)43), employing both *ab initio* theory and density function theory, calculated the energies of *chair*, *half-chair*, *sofa*, *twist*, and *boat* conformers of 1,3-dioxane.

D. 1,4-Dioxanes (1,4-Dioxacyclohexanes)

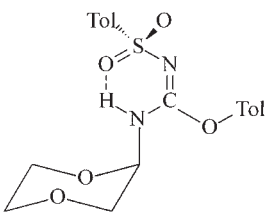
Chapman and Hester studied the ring inversion of 1,4-dioxane by using both *ab initio* theory and density function theory (97JPC(A)3382). In addition to the most stable chair conformer two twist–boats were also

identified and a half-chair structure as the transition state for the ring interconversion. The value obtained for the free energy of activation was in good agreement with the experimental one.

Both the *vicinal* H,H (whether the substituent was *axial* or *equatorial*) and the long range "W" H,H coupling constants (whether the substituent is adjacent to the ring oxygen atom or not) in the 1,4-dioxane skeleton were used to identify several structural isomers of 2,5- and 2,6-disubstituted 1,4-dioxanes (97CMR359). All the possible isomers were identified, including the separated frozen isomers from the equilibrating ones, and the separated 2,5- from the 2,6-disubstituted ones.

The conformational/configurational behavior of an isourea derivative of 1,4-dioxane **60** was studied using X-ray crystallographic analysis (02T2621). The dioxane ring adopts the chair conformation (cf. Scheme 18), the imidoyl amino group the *axial* position. The tosyl and tolyl groups about the C=N bond retain the *E* configuration.

X-ray analysis and NMR solution studies of a number of 2,5-diethoxy-2,5-bis(CH_2OX)-1,4-dioxanes **61** indicated the *trans* isomer to adopt the chair but the *cis* isomer the twist–boat conformation (cf. Scheme 18) (99T2193). In the case of the hydroxymethyl derivative (X = H), due to the twist–boat conformation, the *cis* isomer has the four oxygen atoms suitably located for coordination of the calcium ion (cf. Scheme 18).



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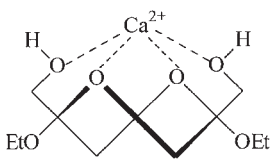
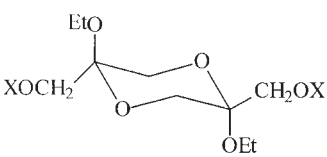
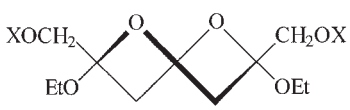




61 (*trans*)



61 (*cis*)

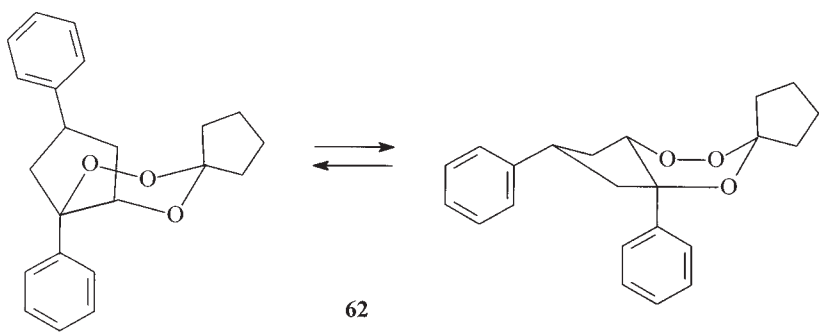
Scheme 18

E. Trioxanes and Tetraoxanes (Tri- and Tetraoxacyclohexanes)

Recently, semiempirical MO methods were employed to calculate the structure of some halogeno-1,2,4-trioxanes (00JMS(T)137). In agreement with experimental results (98AHC217) the chair conformation is the preferred one, although there exist molecules adopting twist conformations. The same result was obtained using DFT calculations of 1,2,4-trioxane and of the powerful anti-malarial drug artemisinin, containing the 1,2,4-trioxane ring system (99JMS(T)103). The conformation of *trans*-3,6-dimethoxy-1,2,4-trioxane was calculated by *ab initio* MO (02MI223); stereoelectronic effects force the compound to adopt exclusively the di-*axial* substituted chair conformer. Finally, Jubert et al. (00JMS(T)165) calculated and studied experimentally using UV spectroscopy the highly pharmacologically active compound AJ30 (**62**) and found that the electronic spectrum, in agreement with the theoretical results, corresponds to a mixture of boat and chair conformations (cf. Scheme 19).

Müller and co-workers (02JPC(B)7781) investigated the molecular behavior of perdeuterated 1,3,5-trioxane in a cyclophosphazene inclusion compound by dynamic ^{2}D NMR spectroscopy. The experimental data revealed a relatively complex motional behavior (rotational motion around the C_3 axis of the molecule and around the channel long axis) in the phosphazene host channels; the ring inversion process was almost uneffected by the host lattice and activation barriers, as reported from solution NMR studies (90JPC8845), were derived.

Jubert et al. also studied the conformational structure of 3,3,6,6-tetramethyl-1,2,4,5-tetraoxane both by DFT calculations and experimentally by vibrational spectroscopy (00JMS(T)85, 99JRS479); the chair



62

Scheme 19

and twist conformations (the latter ca. 3 kcal/mol less stable; no boat conformer) were identified. In *trans*-3,6-diphenyl-1,2,4,5-tetraoxane (99JMS(T)29) and *trans*-3,6-dimethoxy-1,2,4,5-tetraoxane (98JMS(T)311) the conformation with two substituents located in the *axial* positions of the chair conformer was found to be the most stable. Also a number of steroidal dispiro-1,2,4,5-tetraoxane (96ST688) and cyclohexano-dispiro-1,2,4,5-tetraoxanes (00JMC1246, 01JHC463) proved to exist in an *all-chair* conformation.

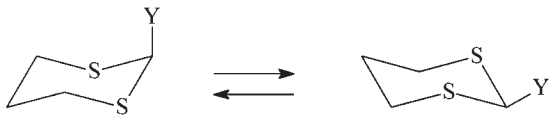
F. Thianes (Thiacyclohexanes), 1,3-Dithianes, and 1,4-Dithianes (1,3- and 1,4-Dithiacyclohexanes)

The conformational preference of the $-P(=O)Ph_2$ group at position 2 of the thiane ring was estimated at low temperature ($\Delta G^\circ = -0.46 \pm 0.11$ kcal/mol, $\Delta H^\circ = -1.29 \pm 0.12$ kcal/mol and $\Delta S^\circ = 4.8 \pm 0.7$ cal/mol.K) (98T1375). The substantial predominance of the *axial* conformer (in contrast to the *equatorial* cyclohexane analog (98AHC217) was interpreted to strongly manifest the anomeric effect in S–C–P segments. The *axial* preference of the same substituent at position 2 of 1,3-dithiane is even larger ($\Delta G^\circ = -1.0$ kcal/mol) (98AHC217). From high level DFT calculations Cuevas (00JA692) concluded that there are attractive interactions of the type $C–H^{axial}\cdots{}^{-}O–P^{+}Ph_2$; this conclusion is supported by dipole moment measurements (96ZOB1122).

Thiane (00JMS(T)225), 2-, 3-, 4-alkyl substituted thianes (98JPOC831, 99JPOC176), thiane-1-oxide and a number of 3-substituted thiane-1-oxides (01JMS(T)287, 01JMS(T)203) were calculated with HF and DFT theories employing extended basis sets, and the results were compared with experimentally determined conformational equilibria. The conformational free energies (ΔG°) of conformers and rotamers are discussed in terms of repulsive non-bonded interactions in the *axial*/*equatorial* conformers.

The conformational equilibria of 2-substituted 1,3-dithianes **63** were determined by application of variable temperature ^{13}C NMR spectroscopy (cf. Scheme 20) (99T359). The thermodynamic data, given in Table IX, provide strong evidence that the predominance of the *axial* conformer in **63** is enthalpic in origin; more polar solvents stabilize the more polar *equatorial* conformation. Both *ab initio* and DFT calculations reproduce the experimental results (99T359).

The conformational behavior of the dimethylamino group in the 2-position of 1,3-dithiane was studied by means of *ab initio* quantum



63 (*axial*) **63** (*equatorial*)

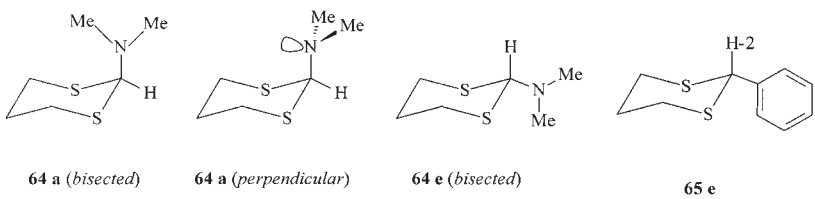
63 a Y = SC_6H_5 **63 b** Y = COOEt **63 c** Y = COC_6H_5

Scheme 20

Table IX. Experimental Conformational Enthalpies (ΔH°) and Entropies (ΔS°) of 2-Substituted 1,3-Dithianes in Solution

Compound	Substituent	Solvent	ΔH°/kcal/mol[a]	ΔS°/cal/mol K[b]
63a	S–Ph	toluene-d_8	-1.51 ± 0.4	3.23 ± 0.8
63a	S–Ph	CD_2Cl_2	-1.35 ± 0.5	2.94 ± 0.8
63b	COOEt	toluene-d_8	-2.13 ± 0.4	3.99 ± 0.8
63b	COOEt	CD_2Cl_2	-1.03 ± 0.4	1.32 ± 0.6
63b	COOEt	CD_3OD	-1.68 ± 0.3	4.25 ± 1.0
63c	COPh	toluene-d_8	-1.67 ± 0.4	1.92 ± 0.6
63c	COPh	CD_2Cl_2	-0.63 ± 0.3	1.01 ± 0.6

[a]Negative values indicate enthalpically preferred *axial* conformer.
[b]Positive values indicate entropically preferred *equatorial* conformer.



64 a (*bisected*) **64 a** (*perpendicular*) **64 e** (*bisected*) **65 e**

Scheme 21

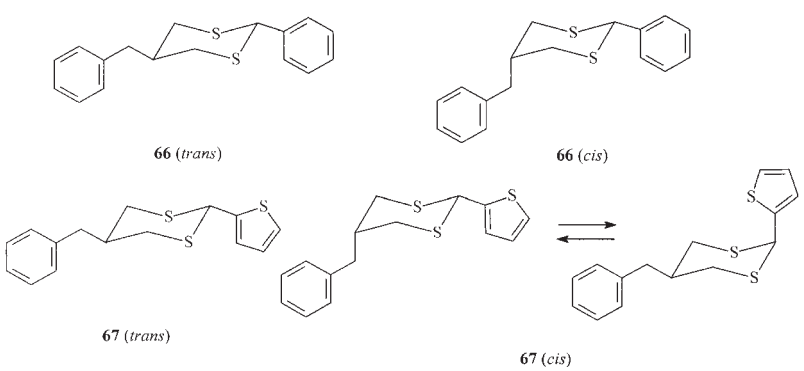
chemical calculations including electron correlation (97JCS(P2)1835). Three ground state conformers, two *axial* and one *equatorial* (cf. Scheme 21), were found; **63e** was preferred both in the gas state and in solution. Conclusions are in full agreement with experimental data (98AHC217). On the MP2 level of theory, the *perpendicular axial* conformer was more stable by 1.75 kcal/mol, explained by the smaller steric interference of the dimethylamino group with the *axial* protons in 4,6-positions. The identical conformational behavior was obseved for the 2-phenyl substituent in

1,3-dithiane (94CJC1722); the long range $^{6}J_{\text{H-2,H-}p}$ coupling constant indicated that the bisected conformer (phenyl plane *perpendicular* to the pseudo plane of the dithiane ring) is the most stable and that the apparent two-fold barrier to rotation about the C_{sp^2}–C_{sp^3} bond is 2.29 kcal/mol as obtained by a hindered rotor model (94CJC1722). The corresponding *axial* conformer is at least 2 kcal/mol less stable than the *equatorial* conformer **65e**, but was calculated to prefer (as the dimethylamino group) the *perpendicular* orientation instead of the bisected orientation in the *equatorial* conformer.

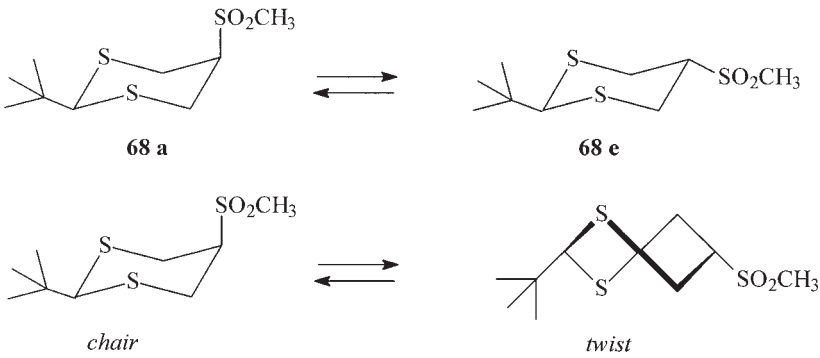
The conformation of –SeH and –Se-Aryl in the same 2-position of 1,3-dithiane was carefully investigated by Senyurt and Aviyente (98JCS(P2)1463) by semiempirical and *ab initio* quantum chemical calculations. The preference for the *axial* conformers was confirmed with electron withdrawing groups at aryl (Aryl = *p*-NH_2, *p*-NMe_2, *p*-OMe and *p*-Me, and *p*-NO_2) enhancing this trend, serving as another proof for hyperconjugation stabilizing the *axial* conformer with increasing electron withdrawal of the substituent (03CEJ1360).

Apaydin et al. (97JMS(T)113) also calculated the conformational equilibria of some 5-substituted 1,3-dithianes by the PM3 method in the gas phase and in solution, displaying a resonable agreement with available experimental data. The chair conformation of the six-membered ring was confirmed; the *equatorial* position of the substituents in position 5 (alkyl, OMe, SMe) are the most stable in all media and the effect of the solvent on the equilibrium is only minor.

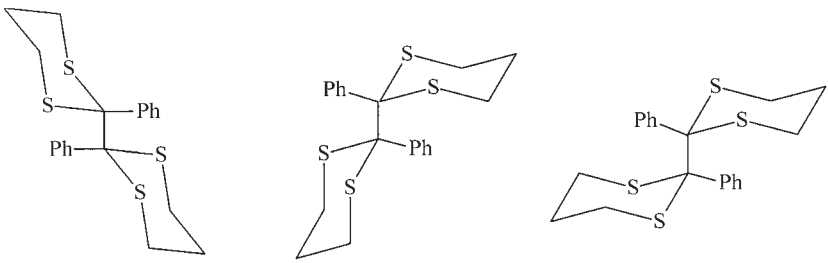
Purposely, as models for copolymers, the *cis*/*trans*-isomers of 2,5-disubstituted 1,3-dithianes (cf. Scheme 22) were synthesized and conformationally studied (02CEJ1546). The conformational equilibrium in the *trans* isomers always arranges the benzyl and the thienyl groups in the



Scheme 22



Scheme 23



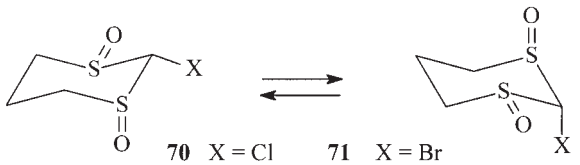
Scheme 24

equatorial position. The *cis* isomer **66-cis** is *anancomeric* (the benzyl substituent in an *axial* position) while the 2-thienyl analog **67-cis** was still undergoing a conformational equilibrium which was not frozen out.

Configurational and conformational assignment of *cis*/*trans*-2-*t*Bu-5-Me-sulfonyl-1,3-dithiane, based on ^{1}H NMR analysis (*esp.* $^{3}J_{\text{H-5,H-4,6}} = 6.0$ Hz), revealed that the *trans* isomer adopts the chair, and the *cis* isomer a twist–boat conformation in order to minimize steric and electrostatic repulsive interactions of the *axial* SO_2Me group (cf. Scheme 23) (02TL 9369). Chemical equilibration shows the *trans* isomer to be more stable by $\Delta G^{\circ}_{323\text{K}} = -1.50 \pm 0.04$ kcal/mol.

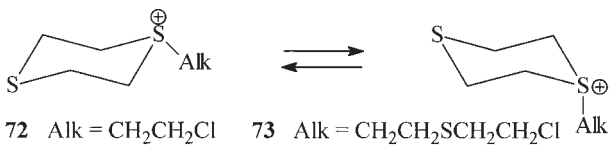
2,2′-Diphenyl-*bis*-1,3-dithianyl **69** exists in an *equatorial*,*equatorial* conformation in the solid state (cf. Scheme 24) (00JCS(P2)2090). In solution there is a rotameric mixture with a predominantly high population (> 85%) of the same conformer, as concluded from dipole moment measurements and molecular orbital calculations.

Frozen ^{1}H and ^{13}C NMR solution spectra of 1,3-dithiane monooxide showed the conformational equilibrium to be dominated by the equatorial



70 X = Cl **71** X = Br

Scheme 25



72 Alk = CH_2CH_2Cl **73** Alk = $CH_2CH_2SCH_2CH_2Cl$

Scheme 26

S=O group (90%) (99RJGC5). X-ray analysis of the crystalline 2-chloro-1,3-dithiane *trans*-1,3-dioxide **70** showed that the chlorine atom adopts the *axial* conformation, while the analogous 2-bromo compound **71** crystallises in the alternative conformation with the bromo atom in an *equatorial* position (97JCS(P2)21). However, variable temperature NMR experiments (cf. Scheme 25) revealed that both halogen substituents exhibit a pronounced *axial* preference in CD_2Cl_2 solution: **70** ($\Delta G^\circ = -0.94$ kcal/mol) and **71** ($\Delta G^\circ = -1.07$ kcal/mol).

Very recently, the HF, MP2, and DFT calculated conformational equilibria of 4-X substituted thiane-1,1-dioxides (X = Me, CH_2OH, $COCH_3$, COC_2H_5, CN, F, Cl, Br, and $OCOCH_3$) were published (02STC115).

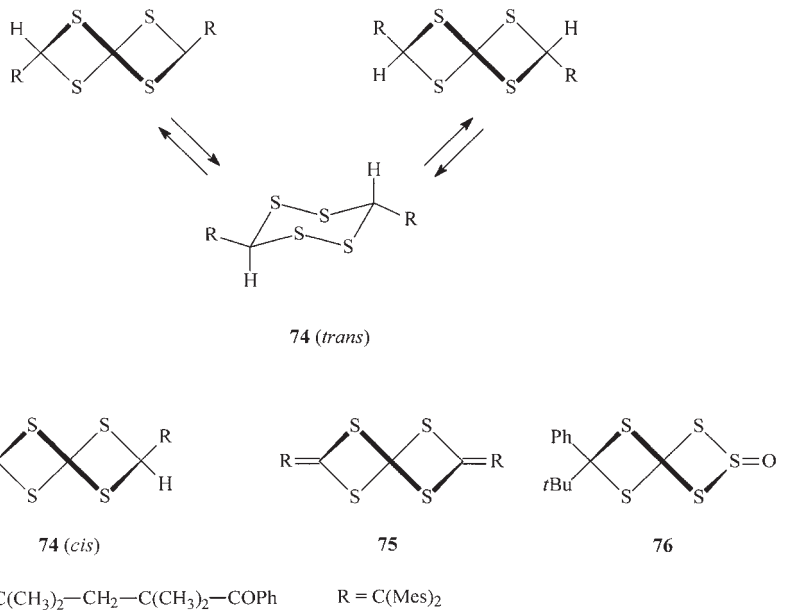
For the 1,4-dithiane skeleton, two S-alkyl-1,4-dithianium salts **72** and **73** were studied by variable temperature NMR spectroscopy in the solid state (^{13}C CP-MAS) (99JMS93); line shape variations were attributed to the conformational motion of the six-membered ring (cf. Scheme 26). Also, the vibrational frequencies of the 1,4-dithiane derivative were analysed in detail; it was corroborated that the molecule exists in the C_{2h} configuration similar to the *chair* form of cyclohexane (99SA(A)121).

G. Trithianes, Tetrathianes, and Pentathianes (Tri-, Tetra-, and Pentathiacyclohexanes)

Standard *ab initio* molecular orbital calculations of 1,3,5-trithiane confirm the *chair* conformation to be the most stable conformer, next to the *twist–boat* conformation, being 3 kcal/mol higher in energy than the *chair*

conformer (01JOC5343). In addition, the enthalpy of formation for this compound in the solid state (-2.1 ± 0.6 kcal/mol) and in the gas phase (-20.2 ± 0.6 kcal/mol), and its enthalpy of sublimation (22.3 ± 0.05 kcal/mol) were determined.

The conformational equilibria of the *cis*/*trans*-isomers of 3,6-*bis*(1,1,3,3-tetramethyl-4-oxo-4-phenylbutyl)-1,2,4,5-tetrathiane were studied in detail by Ishii et al. (00BCJ729). In the case of the *trans* isomer, the NMR lines split into two signals each upon lowering the temperature (intensity ratio 2.4 :1); the major conformer was assigned to the *twist* form, the minor one to the *chair* conformer (cf. Scheme 27). The free energy of activation of interconversion between the two conformers was estimated to be 13.3 and 12.8 kcal/mol, respectively. In the solid state only the *chair* conformer was observed. The *cis* isomer, both in solution and in the solid state, exists exclusively as the *twist* conformer (cf. Scheme 27). 1,2,4,5-Tetrathiane structures with 3,6-exomethylene moieties (**75**) also exist as a twisted conformer; however, it is not a perfect twist conformation since the two C=C bonds are at an angle of 166°, rather than 180° (96JOC7326). The tetrathiane ring interconversion of the twist conformer involves a planar central ring as an intermediate or transition state (cf. Scheme 27).



Scheme 27

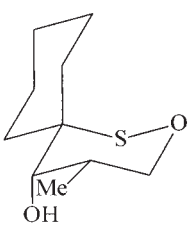
Finally, the S-oxide of 6-*t*Bu-6-phenylpentathiane **76** takes the *twist* conformation both in the crystalline state and in solution (01TL3117) (cf. Scheme 27).

H. Oxathianes

The HF, MP2, and DFT theories were used to calculate the optimized geometries and relative energies of the *chair*, *half-chair*, *sofa*, *twist*, and *boat* conformers of 1,2-oxathiane (02STC149). As the most stable conformation, in agreement with experimental results, the *chair* conformer was identified to be at least 4.6 kcal/mol more stable than the next conformer, the 3,6-*twist* conformation. As a comparison, the chair conformation of 1,2-oxathiane was found to be 9.6 and 10.0 kcal/mol less stable than the chair conformers of 1,3-oxathiane and 1,4-oxathiane, respectively (02STC149).

The stereochemistry of a few substituted 1,2-oxathianes **77**–**79**, freshly synthesized (98TL1251), was studied (cf. Scheme 28); the conformation of the substituents at the six-membered ring is in agreement with NOE enhancements and the characteristic *ax*/*ax* vs. *ax*/*equ* and *equ*/*equ vicinal* H,H coupling constants.

The stereochemistry, physical and chemical properties and some transformations of 1,3-oxathianes, especially alkyl substituent effects on the preferred conformers, were reviewed (99MI73, 00MI17). Also 1,3-oxathiane and its 2-substituted homologs were theoretically calculated using the semiempirical AM1 and PM3 methods (98MI14); the experimental parameters are adequately reproduced. In the case of 5-alkyl substituted 1,3-oxathianes the semiempirical calculations are in general in agreement with the experimental ΔG° values (01RJGC1571), but the proportion of



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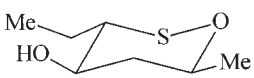

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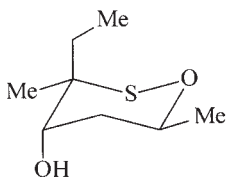


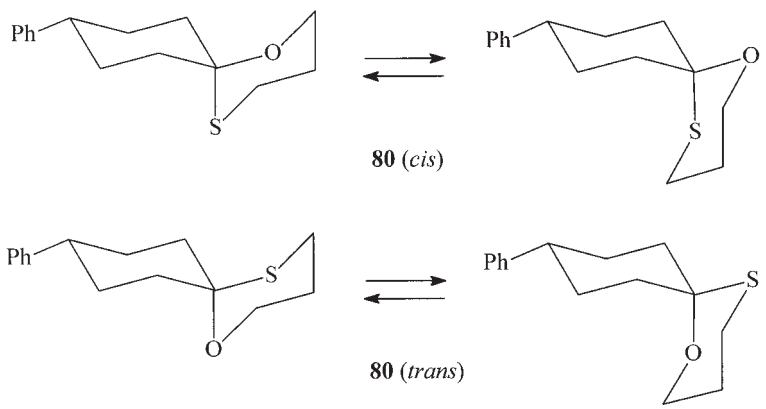
79

Scheme 28

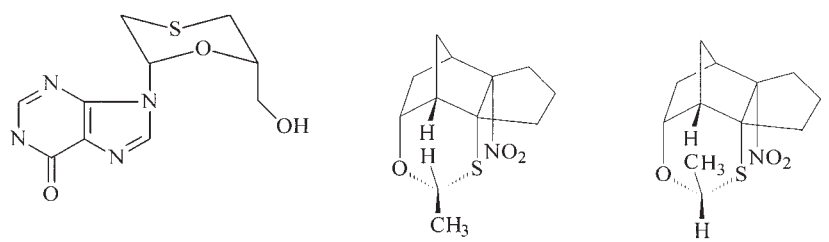
the *equatorial* conformer was twice as large as that given in the literature (95MI201).

Mager et al. studied the stereochemistry of the *cis*/*trans*-isomeric spiro-1,3-oxathiane **80** (00TL1976). The cyclohexane ring with the *equatorial* phenyl substituent is *anancomeric*, whereas the 1,3-oxathiane ring is flipping (cf. Scheme 29); the equilibrium ratio between the *trans* and *cis* isomers of ca. 60 : 40 is in agreement with the ratio of the conformational energies of MeO/MeS groups on the cyclohexane ring.

The optically active 1,3-oxathiane derivative **81**, synthesized as a chiral auxiliary (cf. Scheme 30), has been reported. The isomers were assignend by X-ray diffraction in the solid state (*trans*) and by NOE experiments in solution (*cis*) (97CPB778). Rules for the specification of the absolute configuration of the enantiomers (*R* or *S*) for 1,3-oxathianes and other heterocycles with at least two hetero atoms were proposed and proved



Scheme 29



82 **81** (*cis*) **81** (*trans*)

Scheme 30

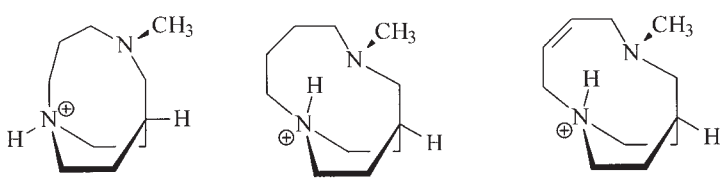
useful for the explanation of the stereoisomerism of monocyclic compounds and also spiranes (96CI311).

In addition, the X-ray crystal structures of two 1,4-oxathiane derivatives were published (00AX1510, 01AX560); the di-*axial* conformation of the hydroxymethyl group in position 3 and of the 1,9-dihydro-6*H*-purin-6-one group in position 6 in compound **82** is surprising (01AX560) (cf. Scheme 30). The X-ray structures of the sulfones of the isomeric 2,6-di-OEt-3-OMe-1,4-oxathianes were published (00CEJ1858): the 4,4-dioxa-1,4-oxathiane ring was found as a chair conformer with all three substituents in the *equatorial* positions (*trans*) and the *cis* isomer with 2*a*3*a*6*e* conformations. A detailed analysis of the IR spectrum of 1,4-oxathiane proved the molecule to exist a C_s configuration similar to the chair form of cyclohexane (01SA2417).

I. Piperidines and Piperidinium Salts

Three "aza-belted" piperidines (five- and six-atom belt) were synthesized and the NMR spectra recorded to provide information about the conformations (90JOC3825). Compound **83**, having a five-atom belt, exists with a *boat* piperidine ring having an outward pyrimidalised nitrogen (cf. Scheme 31), a conclusion based on a comparison of observed ^{1}H NMR *vicinal* coupling constants with those calculated using MM2 geometries. MM2 predicts this conformation is favored over other conformers by at least 2.6 kcal/mol. ^{13}C NMR chemical shifts suggest a gross conformational change between **83** and the six-atom belt compounds **84** and **85**. The piperidine ring is still in a *boat* conformation but having inward paramidalised nitrogens (cf. Scheme 31).

Otherwise, the piperidine ring system was considered to be in the stable *chair* conformation. The two different experimental barriers to ring inversion and N-inversion of N-methylpiperidine were reconsidered. An accurate line shape analysis of the dynamic NMR spectra in the gas phase

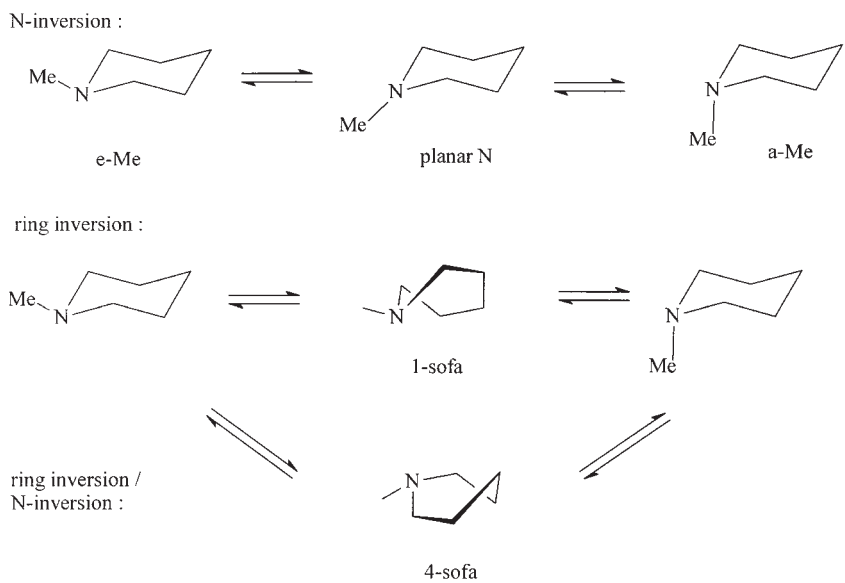


83 **84** **85**

Scheme 31

was performed to determine the higher barrier ($\Delta G^{\#} = 12.0$ kcal/mol, 92JPC10201). This barrier was assigned to the ring inversion process (cf. Scheme 32). The 1,4-*half-chair* transition state with a planar amino fragment, similar to that of cyclohexane derivatives, was assumed to be the rate determining transition state. However, a careful MM3 study of N-methylpiperidine proved the stereodynamics to be different from cyclohexane. The highest points on the reaction pathway corresponds to the 1-*sofa* conformer (along the ring inversion process) and the 4-*sofa* conformer (along a combined ring inversion/N-inversion process), the energy difference between the two transition states was too small to decide between the two pathways (98JMS(T)265). The lower barrier is 8.7 kcal/mol; ultrasonic technique (92MI169) was used for the N-inversion process (cf. Scheme 32).

The X-ray structure of 1-piperidino-2,4-dinitrobenzene was published (95MI801). The piperidine ring exhibits a slightly distorted chair conformation; the N-atom is almost in a plane due to the partial C,N double bond, and the aromatic ring shows a slight boat deformation with the *o*/*p*-nitro groups twisted out of plane. UV and NMR data indicate that the molecule in solution presents a conformation similar to that in the solid state. In the crystalline anhydrous N-methylpiperidine betaine **86** (cf. Scheme 33) the piperidine ring adopts the usual chair conformation



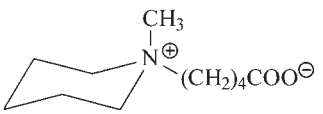
Scheme 32

with the methyl group in the *axial* and the $(CH_2)_nCOO^-$ group in the *equatorial* position (99JMS125); the torsional barrier about the N–C-1′ bond of the acetic acid analog **87** was calculated (PM3) to be 6.6 kcal/mol due to Coulombic interactions between the charged groups (01JMS251).

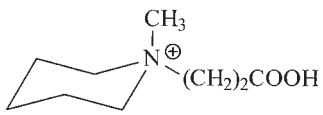
5-(Piperidino)valeric acid **88** adopts the chair conformation with the substituent in an *equatorial* conformation (99JMS125) as does 1-[1-(1-phenylethyl)cyclohexyl]piperidine **89** (91AX(C)223) but occupying the *axial* site of the cyclohexane ring (cf. Scheme 34).

Examination of the properties of N-borane adducts, e.g., **90**, of piperidine, substituted piperidines and various other N-containing six-membered ring heterocycles constitutes an alternative approach to variable temperature NMR spectroscopy in that borane can be used as a locking agent for the observation of preferred conformers (cf. Scheme 35). In addition, the adducts can be very helpful for the assignment of the chemical shifts of the other substituents in the molecule as well as to acertain the configuration at the substituted positions (91T6903).

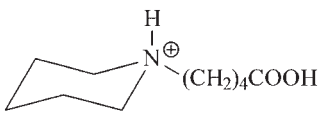
Many overlapping ^{1}H NMR signals of *n*-(γ-aminopropyl)piperidine, which prevent conformational assignments, were converted to well resolved



86

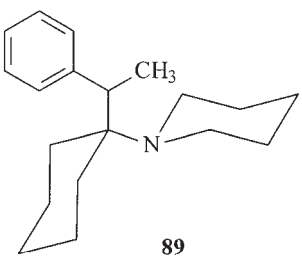


87



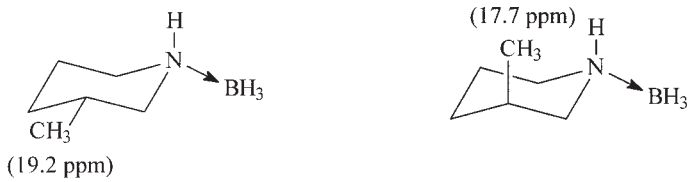
88

Scheme 33



89

Scheme 34



90

86 % 14 %

Scheme 35

first order multiplets by the addition of a Eu(II) monophthalocyanine complex as a new shift reagent selective for primary aliphatic amines (93MI377).

AM1 and PM3 calculations of *axial*/*equatorial* N-alkylpiperidine predicted the *axial* conformer to be more stable than the *equatorial* conformer; thus, these methods are not recommended at least for the conformational analysis of molecules containing amine functionalities (93AJC547). The conformational equilibria of aliphatic amines, obtained by MM3 calculations, on the other hand, generally fit to within experimental error, including dipole moments (90JA8307). HF calculations using a polarized basis set of medium size [6–31G* (95JOC986) and 6–31G** 98JCC961] proved adequate enough for the prediction of the *axial*/*equatorial* equilibria of substituted piperidines. It was generally indicated that *ab initio* methods, which include larger basis sets, give better agreement with experimental data and also give more reliable predictions in cases where no experimental data exist (96JMS(T)21).

Both the COOMe and the C≡N groups in position 2 of piperidine prefer the *equatorial* conformer (2-R=COOMe, at 221 K, $\Delta G^\circ = 0.66$ kcal/mol; 2-R = C≡N, at 227 K, $\Delta G^\circ = -0.97$ kcal/mol); the strongly increased amount of *axial* conformer in case of C≡N was explained by the anomeric effect (92T6161); steric effects were ignored.

The conformational analysis of substituted piperidines has been well documented (92MI169). There is a large effect on the conformational equilibrium of 4-substituted piperidines when protonating the ring nitrogen atom (91MI205). For polar substituents (Br, F in **91/92a**,**b**) the conformational preference was reversed on protonation (no change in conformational energy for 4-methyl (cf. Table X and Scheme 36). ΔG° changes from 0.4 to −0.4 and 0.2 to −0.8 kcal/mol for 4-bromo- and 4-fluoro-piperidine and this was quantitatively explained by the electrostatic interaction of the substituent and the protonated ring nitrogen atom. Also, 3-fluoro- and *cis*-3,5-difluoropiperidine were studied (93JA3356, 00JA544). The free base

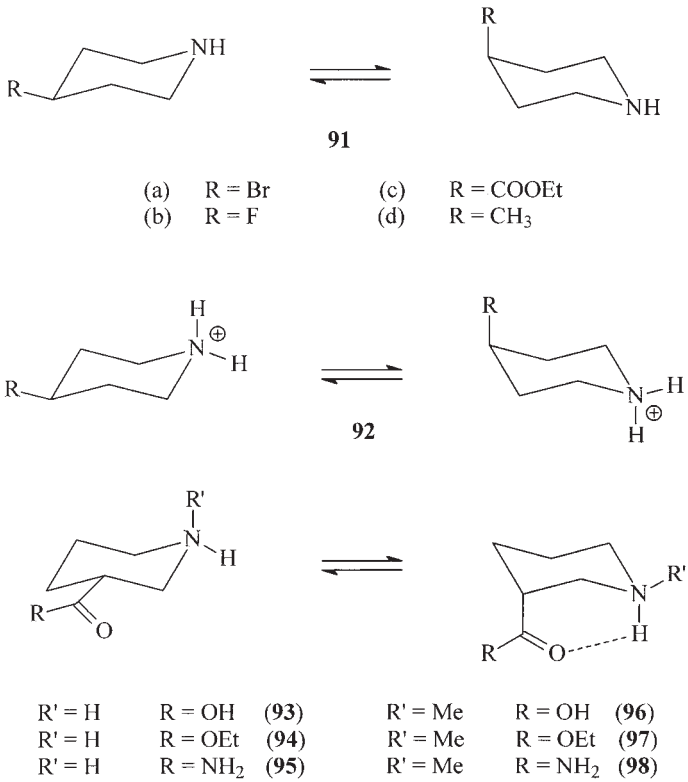
Table X. CONFORMATIONAL EQUILIBRIA (ΔG°/kcal mol^{-1}) OF 3- AND 4-SUBSTITUTED PIPERIDINE DERIVATIVES AND THE INTRAMOLECULAR HYDROGEN BONDING ENERGY (ΔG_{HB}/kcal mol^{-1}) OF NIPECOTIC ACID AND DERIVATIVES AT 22 °C

		Free base		Cation	
Compound	Solvent	ΔG°	ΔG_{HB}	ΔG°	ΔG_{HB}
91a	$CDCl_3$	0.4 ± 0.1	–	-0.4 ± 0.1	–
91b	$CDCl_3$	0.2 ± 0.1	–	-0.8 ± 0.1	–
91c	$CDCl_3$	1.3 ± 0.1	–	0.6 ± 0.1	–
91d	$CDCl_3$	1.9 ± 0.1	–	0.9 ± 0.1	–
93	MeOD	0.0 ± 0.1[a]	-2.0 ± 0.1[a]	0.48 ± 0.1	-0.90 ± 0.1
	D_2O[b]	–	–	-1.46 ± 0.1[b]	-1.0 ± 0.1[b]
94	MeOD	0.77 ± 0.1	-0.62 ± 0.1	–	–
	D_2O/DCl	–	–	0.37 ± 0.1	-1.03 ± 0.1
95	MeOD	1.06 ± 0.1	-0.8 ± 0.1	–	–
	D_2O/DCl	–	–	-2.4 ± 0.1	-1.4 ± 0.1
97	MeOD	1.0 ± 0.1	-1.4 ± 0.1	–	–
	D_2O/DCl	–	–	-0.08 ± 0.1	0.49 ± 0.1
98	MeOD	1.3 ± 0.1	-0.6 ± 0.1	–	–
	D_2O/DCl	–	–	-0.47 ± 0.1	-1.4 ± 0.1
[c]	CD_2Cl_2	0.15 (at 220 K)			
[d]	CD_2Cl_2	−0.35 (at 220 K)			

[a] For the corresponding zwitterion.
[b] For the corresponding anion.
[c] 1-Me-3-OAc from Ref. 90CHR11.
[d] 1-Me-3-NHAc from Ref. 90CHR11.

of 3-fluoropiperidine exists as the *equatorial* conformer but in the hydrochloride the fluorine atom adopts the *axial* position. In *cis*-3,5-difluoropiperidine, the di-*axial* conformer is preferred in aqueous solution, explained by attractive charge-dipole interactions between N^+–H and C–F bonds.

Abraham et al. (00JCS(P2)2382) studied the conformational equilibria of piperidine-3-carboxylic acid (nipecotic acid—**93**), of the corresponding ester (**94**) and amide (**95**) and of some of their N-methyl derivatives (**96**–**98**—cf. Scheme 36) as neutral compound, cations, and anions and if possible also as zwitterions in neutral, acidic, and basic media by "frozen" low temperature NMR or at room temperature by the *vicinal* H,H coupling constant method, depending on the melting point of the solvents. The conformer populations (free energy differences) and the hydrogen bond energies in the *axial* conformers are shown in Table X. These data provide a quantitative measure of both the hydrogen bonding interaction in these systems and the effect of solvation. Two major conclusions could



Scheme 36

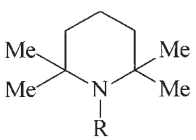
be drawn: (i) The cation (C=O···H–N^+ and anion (COO^-···HN) hydrogen bond energies in nipecotic acid and the ethyl ester are roughly comparable (ca. 1 kcal/mol) and are solvent independent; in contrast (ii) the hydrogen bonding between neutral donor and acceptor groups (NH···N) is largely solvent dependent.

The conformational equilibria of some more substituted piperidines were studied in solution or in the solid state; the position of the conformational equilibria or the preferred conformers are given in Table XI.

The stereodynamics of N-substituted 2,2,6,6-tetramethylpiperidines **99** (cf. Scheme 37a) were studied by Abraham and Lunazzi et al. (93JCS(P2)1299). The temperature dependence of the NMR spectra showed that a conformational interconversion takes place; this could be ring inversion, N-inversion, rotation about the exocyclic bond or a complex combination of these processes. Barriers to this process are shown in Table XII. The rate-determining process changes as the nitrogen

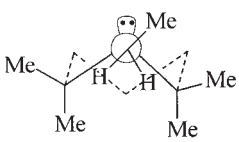
Table XI. CONFORMATIONAL EQUILIBRIA OF POLYSUBSTITUTED PIPERIDINES IN SOLUTION AND/OR IN THE SOLID STATE

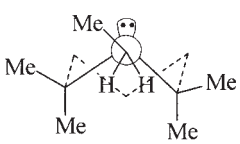
Conformation of piperidine	Conformational equilibria or preferred conformer	State	Reference
Chair	1*e*-$CH_2C_6H_5$-4*e*CH_2-purine	in $CDCl_3$	02MRC549
Chair	3*a*-NHAc (ca. 50%)	in CD_2Cl_2	90MI11
Chair	1*e*-Me-3*a*-NHAc (ca. 50%)	in CD_2Cl_2	90MI11
Chair	3*a*-OAc (ca. 50%)	in CD_2Cl_2	90MI11
Chair	1*e*-Me-3*a*-NHAc (34%)	in CD_2Cl_2	90MI11
Chair	1*a*-Me-2*e*-CH(Ph)COOMe · HCl	Solid	98JOC1785
Chair	1*a*-Me-2-*e*-(1′)adamanyl	$CHCl_2F$/ $CHClF_2$ (1:1)	01JOC4989
Chair	1*a*-Me-2-*e*-(2′)adamanyl	$CHCl_2F$/ $CHClF_2$ (1:1)	01JOC4989
Chair	1*a*-3′α-OH-5′α-androstanyl-17′-one	in $CDCl_3$	99JCS(P1)3311
Chair	1*e*-Me-3*e*-CH_2OH-4*e*-C_6H_4-F(*p*)	in CCl_4	02JOC161



99a R = OH
99b R = OMe
99c R = OCH_2Ph
99d R = O*i*Pr
99e R = O*t*Bu
99f R = H
99g R = Me

99h R = Et
99i R = Pr
99j R = $CH_2CH(OH)Me$
99k R = $CH_2CH(OH)Ph$
99l R = CH_2tBu
99m R = $CH_2C(OH)Me_2$
99n R = $CH_2C(OH)MePh$
99o R = *n*Bu





99h

Scheme 37

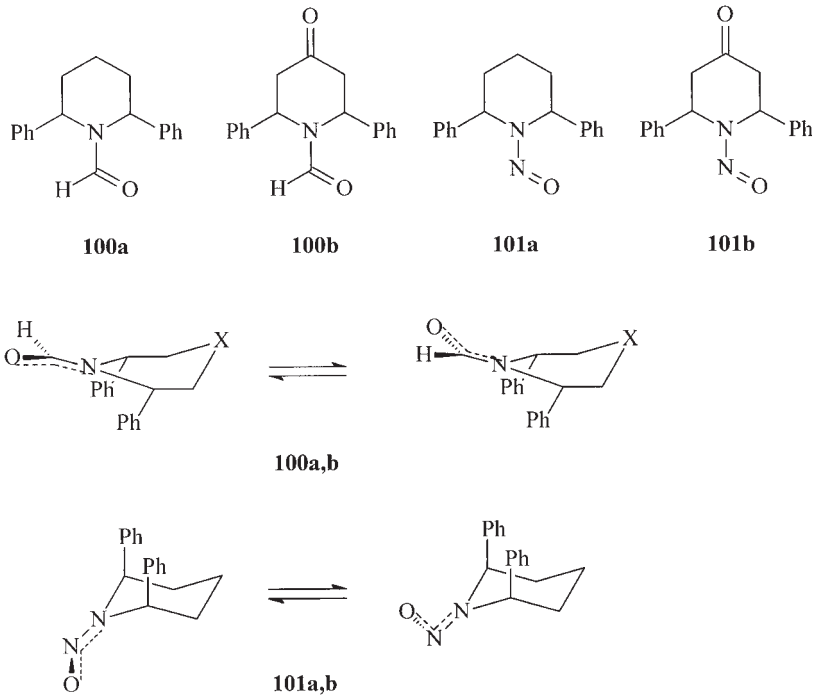
Table XII. BARRIERS ($\Delta G^{\#}$/kcal mol^{-1}) TO THE INTERCONVERSION PROCESS IN N-SUBSTITUTED 2,2,6,6-TETRAMETHYLPIPERIDINES **99**

Compound	Substituent	Solvent	Coalecence temperature (T_c/°C)	Barrier to interconversion $\Delta G^{\#}$/kcal mol^{-1}
99a	OH	THF-d_8	−42	11.5
99b	OMe	CCl_4	40 to 80[a]	17.0
99c	OCH_2Ph	$CDCl_3$	56	16.4
99d	$OCH(CH_3)_2$	$CDCl_3$	13	13.9
99e	DMSO-d_6	$CDCl_3$	> 189	> 24.9
99f	H	CD_2Cl_2	−100	7.7 (8.0)[b]
99g	Me	CD_2Cl_2	−98	8.2
99h	Et	CD_2Cl_2	−52	10.3
99i	*n*Pr	CD_2Cl_2	−52	10.5
99j	*i*Pr	C_6D_5Br	at −37.6	12.2 ± 0.2[c]
99k	$CH_2CH(OH)Ph$	CD_3OD	0–20[a]	12.9
99l	CH_2tBu	–	–	15.6[d]
99m	$CH_2C(O)Me_2$	C_6D_5Br	at 61.4	18.5 ± 0.2[c]
99n	$CH_2C(O)MePh$	C_6D_5Br	at 92.2	19.3 ± 0.1[c]

[a]Complete line shape analysis over this temperature range.
[b]In $CDCl_3$.
[c]From complete line shape analysis (02CEJ3016).
[d]Calculated by molecular mechanics.

substitutuent changes: in **99f** (R = H: 7.7–8.0 kcal/mol) ring inversion, in **99a** (R = OH: 11.5 kcal/mol) N-inversion, and in the other N-Alk and N-OAlk derivatives **99b–e** and **99g–l** rotation about the exocyclic bond proved to be the rate-deterimining step of the overall conformational interconversion.

The same authors, in a different paper (93JA3494), have shown that the N–R substituent prefers to be *equatorial* and that the conformation about the exocyclic N–R bond is due to a rapid equilibrium between two nearly *eclipsed* conformations (cf. Scheme 37b). The second ground state of the dynamic process, the *anti*-conformation (after 180° of rotation), could not be detected experimentally but was calculated by molecular dynamics to be less stable by 5.5 kcal/mol than the preferred *syn*-conformers, e.g., **99h** (cf. Scheme 37). The transition state in **99b–e** and **99g–l** occurs when the exocyclic substituent has its maximum interaction with an *equatorial* methyl group about 120° on either side of the ground state. The dynamic behavior of **99h,i** and **99o** (R = *n*Bu) was also studied by the MM3 force field (99CEJ449); the authors concluded that the experimental barriers of **99h,i** and **99o** belong to a complex combination of ring inversion, N-inversion and rotation about the exocyclic bond.



Scheme 38

Table XIII. BARRIERS ($\Delta G^{\#}$/kcal mol^{-1}) TO RESTRICTED ROTATION ABOUT THE EXOCYCLIC N–R BOND IN N-SUBSTITUTED *cis*-2,6-DIPHENYLPIPERIDINES **100**–**101**

Compound	Substituent	Solvent	Coalecence temperature (T_c/°C)	Barrier to interconversion $\Delta G^{\#}$/kcal mol^{-1}
100a	N=O	$CDCl_3$	–	15.7
100b	N=O	$CDCl_3$	–	17.3
101a	CH=O	DMSO-d_6	80	18.1
101b	CH=O	DMSO-d_6	123	19.3

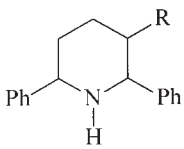
The restricted rotation about the exocyclic N–R bond in N-nitroso and N-formyl-*cis*-2,6-diphenylpiperidines was studied (cf. Scheme 38 and Table XIII) (91JOC4833, 99IJC(B)325). Flattened boat conformers with the phenyl substituents in quasi-*axial* positions (**100a**,**b**) (99IJC(B)325) and flattened chair conformers with *axial* phenyl substituents (**101a**,**b**) (95JOC7411) were observed as preferred conformations. The energy minima

are at 0° and 180° of the torsional angle O=CH–N–C(2) and O=N–N–C(2), respectively, and the hybridization of the ring nitrogen atom is very close to sp^2. The higher barriers to rotation in the N-nitroso derivatives are due to more effective ground state stabilization.

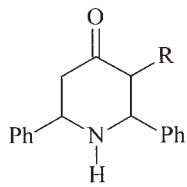
In *trans*,*trans*,*cis*-2,6-diphenyl-3-alkyl substituted piperidines **102** and the corresponding 4-ones (**103**) (cf. Scheme 39) all the substituents adopt the stable *equatorial* positions on the chair conformer (92IJC(B)677), and in differently methyl substituted N-acetyl-2,6-diphenyl-4-acetoxypiperidines the saturated six-membered ring, in order to avoid steric hindrance, no longer adopts the chair conformation (97MRC372). Boat conformers with the acetoxyl group in the flagpole position (**103f**) were observed (cf. Scheme 39).

Adamantane forces the N-methyl group in N-methylspiro[piperidine-2,2′-adamantane) **104** and in the corresponding morpholine derivative (cf. Scheme 40) to adopt the *axial* conformation (98JCS(P2)1701). The steric interaction between the N-methyl and adamantane hydrogens proved to be so strong that compounds **104** undergo an enantiomerization, slow on the NMR time scale, which could be studied by dynamic NMR spectroscopy. The free energies of activation at the coalescence temperature are 15.2 kcal/mol (**104a**) and 14.3 kcal/mol (**104b**), respectively.

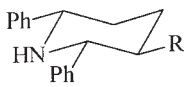
Brouwer and Krijnen (95JOC32), by *ab initio* and semi-empirical quantum chemical calculations of piperidine, N-methylpiperidine and a number of derivatives incorporating π-electron acceptors at the 4-position



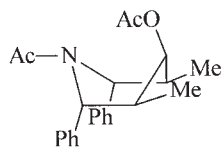
R = H **102a**
= Me **102b**
= Et **102c**
= *i*Pr **102d**
= 3,5-di-Me **102e**



103a
103b
103c
103d
103e

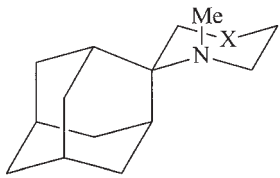


102



103f

Scheme 39



104

(a) $X = CH_2$
(b) $X = O$

Scheme 40

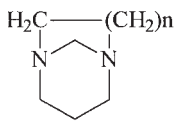
of the saturated six-membered ring (C^4H_2, $C^4{=}O$, $C^4{=}C(CN)_2$, $C^4{=}NH_2^+$, and CH^+) studied the efficiency of through-bond interactions between the nitrogen donor and the electron acceptor group. Along the N-inversion pathway, the transition state of the *axial* conformer is stabilized, whereas the *equatorial* conformation is less influenced.

J. 1,2-Diazacyclohexanes (Hexahydropyridazines and Tetrahydropyridazines)

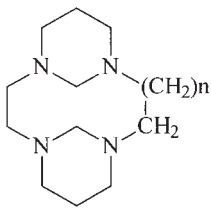
Only two tetrahydropyridazine derivatives were studied by X-ray diffraction and NMR spectroscopic methods (91JCS(P1)273, 99JCR(S) 186). The conformational properties of the tetrahydropyridazine ring are controlled by steric interactions exhibiting a *boat*-like geometry. Khanamiryam et al. (93MI539) synthesized a series of 1,2,4-*tris*-substituted hexahydropyridazines but studied only the structure of the 4-oxime of 2-methyl-1(2-phenylethyl)-hexahydropyridazines in the solid state; the hexahydropyridazine ring adopts the chair conformer, having substituents (in position 1) in an *equatorial* conformation and (in position 2) in an *axial* orientation.

K. 1,3-Diazacyclohexanes (Hexahydropyrimidines)

The stereostructures of the N,N-bridged 1,3-diazacyclohexanes **105**–**110** (cf. Scheme 41) were studied both in the gas phase and in solution (93JA6580). The borderline for change over from the *axial*,*axial*-bridged conformer to the *axial*,*equatorial*-bridged conformer was defined for $n = 4$

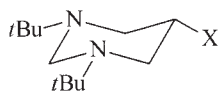


n = 1 **105**
n = 2 **106**
n = 3 **107**
n = 4 **108**
n = 5 **109**
n = 6 **110**

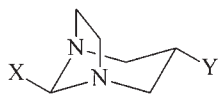


n = 1 **111**
n = 2 **112**

Scheme 41



X = H **113**
X = Me **114**



X = H Y = H **115**
X = Me Y = H **116**
X = Me Y = Me **117**
X = C_6H_4-NO_2(*p*) Y = Me **118**

Scheme 42

in the gas phase but for $n = 5$ in $CDCl_3$ solution; the solvent effect is reasonably attributed to better solvation of *equatorial* lone pairs. The tricyclic bisaminals **111** and **112** were also studied having 10- and 12-membered rings; they adopt conformations each having an *axial*,*equatorial*-bridged 1,3-diazacyclohexane ring.

The ring interconversion of the 2-*axial*/*equatorial*-substituted *chair* conformers of 1,3-dimethyl-2-methoxy-1,3-diazacyclohexane was studied by low temperature ^1H and ^{13}C NMR spectroscopy (94JA715) and found to be 8.6–9.1 kcal/mol well above the barrier for the N-inversion (< 6.7 kcal/mol), still fast on the NMR time scale.

The anancomeric 1,3-di-*t*Bu-1,3-diazacyclohexanes **113**, **114** and the 1,5-diaza-bicyclo[3.2.1]octanes **115**–**118** (cf. Scheme 42) were investigated to

find evidence regarding the anomeric effect as a stereoelectronic interaction (97JCS(P2)2633). Both the chemical shift and the $^1J_{CH}$ variations support the existence of a strong $\sigma_{n\text{-}N} \rightarrow \sigma^*_{C-H}$ hyperconjugative interaction.

The solid state structures published for a number of different azacyclohexanes are collected in Table XIV; the preferred conformer and the preferred conformations of the substituents on the saturated six-membered rings are also given.

L. 1,4-Diazacyclohexanes (Piperazines)

With respect to a new C-substituent, only 2-(trifluoromethyl)piperazine was synthesized and studied by ^{1}H NMR spectroscopy (95RTC97). The six-membered ring exists in the chair conformation and the CF_3 group occupies exclusively the *equatorial* position.

The possible conformers of N,N-disubstituted piperazines and their interconversions by ring and nitrogen inversion were described by Cross et al. (94MRC509) and involve ring inversion and many N-inversions to return the N-substituents to their original position. It was also assumed that the conformations with *equatorial* N-substituents have the lowest energy. This dynamic process was studied for a number of N,N-disubstituted piperazines (cf. Scheme 43 and Table XV). The solvent does not have a large effect on the $\Delta G^{\#}$ value (99ACSA7), but in the protonated species (in DMSO) the inversion is considerably hindered (96JMS195). Bulky substituents increase the ring inversion barrier (94MRC509).

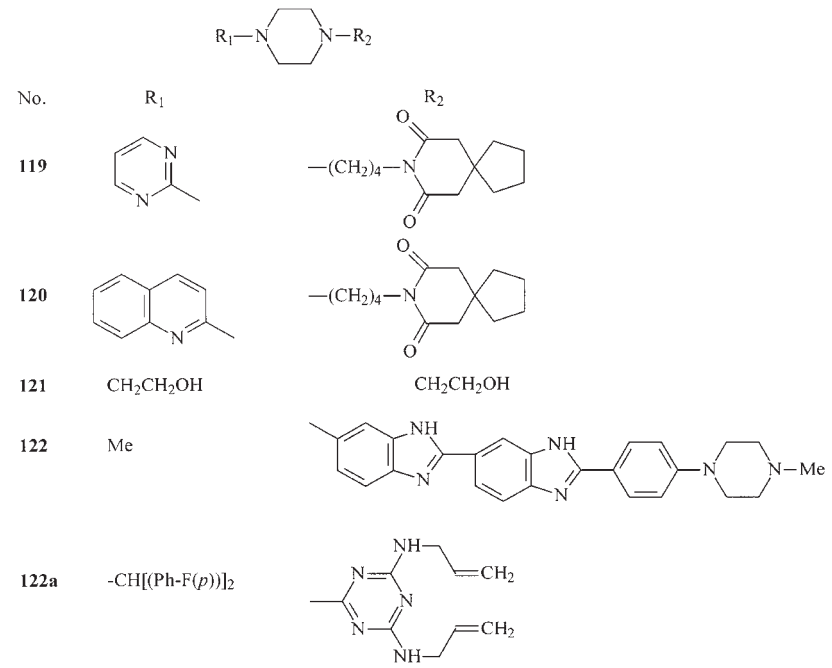
A careful ^{1}H NMR study, together with the results of the accompanying molecular modeling calculations, predicted the most stable conformation of piperazine-1,4-bis(N-methylaceto-hydroxamic acid) **123** (cf. Scheme 44) (97JCS(P2)1977); the hydroxamate moities of the side chains interact with the nearby amino function via hydrogen bonded six-membered ring structures, tilted ''upward'' and ''downward''.

A new *para*-cyclophane (with two 1,4-bridged piperazine rings) **124** and its intermediate **125** (cf. Scheme 45) have been studied by dynamic NMR spectroscopy (96JCS(D)239); the activation enthalpy of 14.6 kcal/mol and 15.0 kcal/mol, respectively, was determined for the *chair–chair* interconversion of the piperazine ring. The *para*-cyclophane topology proved to be of no influence on the ring interconversion, but protonation facilitated this dynamic process. The palladium(II) complexes of **124a**, **125a** are highly rigid and force the piperazine rings to adopt the *boat* conformation (cf. Scheme 45). The same boat conformation was observed in the Ni(II), Cu(II), and Pd(II) complexes of 1,4-bis(*o*-aminobenzyl)1,4-piperazine **126a** (96JCS(D)1659) (cf. Scheme 45), and in the Pt(II) complex

Table XIV. SOLID STATE STRUCTURES OF SUBSTITUTED AZACYCLOHEXANES

Conformation	Heterocycle	Position and conformation of substituents	Reference
Chair	1,3-Diaza-CH	1*a*-NO_2-3*a*-NO_2-5*a*-ONO_2	00JOC1200
Chair	1,3-Diaza-CH	1,3*aa*-$COCH_2CH_3$-5,5-di-OH	01AX(E)1183
Chair	1,4-Diaza-CH	1*e*-1-C_6H_4Cl(*p*)-4*e*-X[a]	97RJGC141
Chair	1,4-Diaza-CH	1*e*-C_6H_4OMe(*o*)	97AX(B)976
Chair	1,4-Diaza-CH	1*e*-C_6H_4OMe(*m*)	97AX(B)976
Chair	1,4-Diaza-CH	1*e*-$C_6H_4CF_3$(*m*)-2*e*-Me	97AX(B)976
Boat	1,4-Diaza-CH	1pseudo*e*-1,4-pseudo*a*-Pt-X[b]	97AX(C)1580
Chair	1,4-Diaza-CH	1*e*-Me-4*e*-$CH_2C_6H_2$,OH(*o*),CN(*m*),X(*m*)[c]	97AX1116
Chair	1,4-Diaza-CH	1,4*ee*CH_2Ph-1,4*aa*-$InMe_3$	97AX278
Chair	1,4-Diaza-CH	1*e*-CH_2CH_2OH,1*a*-H-4*e*-$CH_2CH_2SO_3^-$	96AX1687
Chair	1,4-Diaza-CH	1*e*-$CH_2C_6H_2$-*tris*-OMe(*o*,*m*,*p*)-4*e*-X[d]	96MI761
Chair	1,4-Diaza-CH	1,4*a*-O-1,4*e*-CH_2CONHCH(R)COOMe[e]	98JCS(CC)2511
Chair	1,4-Diaza-CH	1,4*ee*-$CH_2C_6H_2OH$(*o*)CHO(*m*)Br(*m*)[f]	98AX780
Chair	1-Aza-3,5-dithia-CH	1*a*-CH_3	93PS111
Chair	1-Aza-3,5-dithia-CH	1*a*-*t*Bu[g]	93PS111

[a] X = 4-(N-naphthylimindo)butyl.
[b] *trans*-bis(N-methylpiperazine-*N*,*N*′)platin(II) dichloride tetrahydrate.
[c] X = 1*e*-Me-4*e*-CH_2-piperazyl.
[d] X = bis(4-fluoropenyl)methyl.
[e] R = H, Me, *i*Pr, *i*Bu, Ph, benzyl.
[f] Same structure with differently substituted aryl substituent (98AX644, 98AX365).
[g] Instead of 1*a*CH_3—1*a*CH_2SCH_2-1*a*-aza-3,5-dithia-CH and bridging analogs of different chain length.

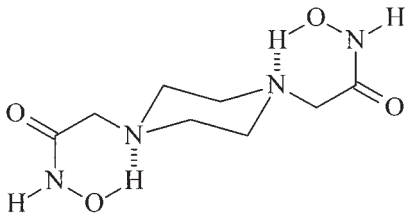


Scheme 43

Table XV. BARRIERS ($\Delta G^{\#}$/kcal mol^{-1}) TO THE INTERCONVERSION PROCESS IN N,N-DI-SUBSTITUTED PIPERAZINES

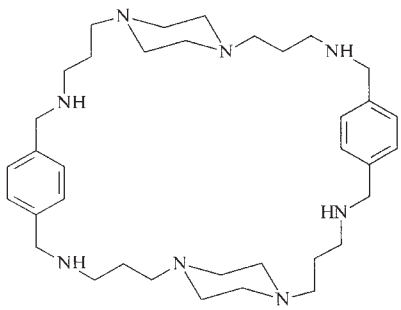
Compound	Substituents	Solvent	Barrier to interconversion $\Delta G^{\#}$/kcal mol^{-1}	Reference
119	cf. Scheme 43	CD_2Cl_2	9.29 ± 0.1	96JMS195
		DMSO-d_6	17.6 ± 0.1	96JMS195
120	cf. Scheme 43	DMSO-d_6	17.9 ± 0.1	96JMS195
121	1,4-CH_2CH_2OH	Acetone-d_6/ CD_3OD (1:1)	12.4 ± 0.02	99ACSA7
122	cf. Scheme 43	D_2O	16.6 ± 0.1	94MRC509
122a	cf. Scheme 43	CD_3OD	14.2 ± 0.2	01MRC77

of N-methylpiperazine **127a** (97AX1580); in one case, the piperazine ring was also observed in a *twist–boat* conformation (in the neutral complex *trans*-NiL$(NCS)_2$ **126b**). The piperazine subunits in a number of macrocyclic Cu(I) complexes (96ICA119, 98IC941), of Pt(II) N-methylpiperazinium complexes (98ICA419, 98ICA410, 98AX27) and of the Co(II) complex

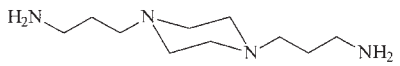


123

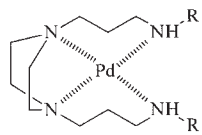
Scheme 44



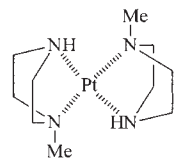
124



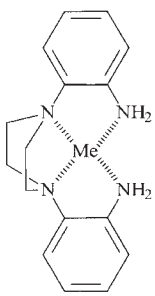
125



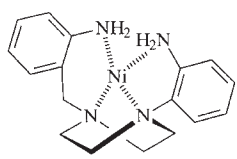
124a, 125a



127a



126a

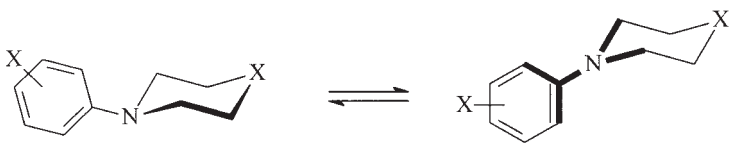


126b

Scheme 45

of an open-chain piperazine-pyridine ligand (98ICA55) adopt chair conformations with the N-substituents in an *equatorial* position.

Dijkstra (93RTC151) studied the conformation of 4-arylpiperidine using molecular mechanics and semiempirical calculations and found that mainly electronic effects of the arene ring determine the conformational behavior; steric effects play a minor role. Electron-withdrawing substituents increase conjugation and force the aryl substituent and the ring nitrogen atom



$X = CH_2$, NH

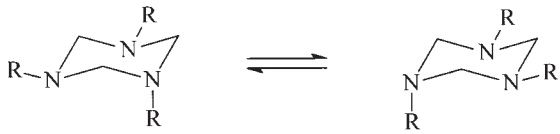
Scheme 46

towards the same plane; electron releasing substituents have the opposite effect. The energy difference between the *coplanar* and *perpendicular* conformations is reduced. 4-Arylpiperidines prefer the *perpendicular* conformation. There are a number of X-ray structures of the two different N–Ph conformations where *coplanarity* due to conjugation implies a near sp^2 hybrid orbital of the ring nitrogen atom (97PJC1005, 96AX607, 98AX992) and *perpendicularity* indicates steric hindrance (96AX391, 98AX1127, 98MI461) (cf. Scheme 46).

A large number of X-ray structures of substituted 1,4-diazacyclohexanes was published (cf. Table XIV).

M. Triazacyclohexanes (Hexahydrotriazines) and Other 1,3,5-Triheterocyclohexanes

The stereodynamics of 1,3,5-trialkyl-1,3,5-triazacyclohexanes **128**–**131** (cf. Scheme 47) were studied by low temperature ^1H and ^{13}C NMR spectroscopy (00JA308). Two dynamic processes were detected. The signals decoalesce over the temperature range from 330 down to 190 K due to slowing of the chair-to-chair interconversion and the corresponding barrier to ring inversion decreases with increasing bulk of the alkyl substituents. At even lower temperatures, below 190 K, the ^1H and ^{13}C NMR spectra show a second decoalescence due to slow N-inversion. Finally, under slow exchange conditions the spectra show a strong preference for the *eea* conformation, no other conformations were detected, but in case of R = neopentyl, at 147 K, also ca. 10% of the *eee* conformer was observed (95JA3054); this is a rare, unequivocally documented example of an *axial tert-butyl group on the chair conformation of a saturated six-membered ring*.



R = Me **128** R = *i*Pr **130**
R = Et **129** R = *t*Bu **131**

Scheme 47

Table XVI. BARRIERS ($\Delta G^{\#}$/kcal mol^{-1}) TO RING INTERCONVERSION AND N-INVERSION IN 1,3,5-TRIALKYL-1,3,5-TRIAZACYCLOHEXANES

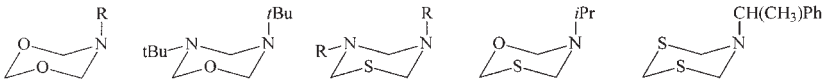
Compound	Substituents	Solvent	Conformational interconversion ($\Delta G^{\#}$/kcal mol^{-1}) ring interconversion N-inversion (*eae* to *aee*)
128	1,3,5-tri-Me	toluene-d_8	12.9 ± 0.1 (at 280 K), 7.8 ± 0.2 (at 170 K)[a]
129	1,3,5-tri-Et	toluene-d_8	12.4 ± 0.1 (at 260 K), 6.9 ± 0.2 (at 147 K)[a]
130	1,3,5-tri-*i*Pr	toluene-d_8	11.2 ± 0.1 (at 240 K), 6.7 ± 0.2 (at 137 K)[a]
131	1,3,5-tri-*t*Bu	toluene-d_8	10.3 ± 0.1 (at 225 K), 5.7 ± 0.2 (at 117 K)[a]

[a]In 50% CF_2Cl_2/50% CHF_2Cl.

The free energies of activation for interconversion among *eea* conformations via sequential N-inversion decrease with increasing bulk of the alkyl substituents (cf. Table XVI).

The barriers to chair-to-chair interconversion of 1,3,5-tri-alkyl-1,3,5-triazacyclohexanes were compared with the corresponding barriers in a number of 1,3,5-trialkyl-1,3,5-triheterocyclohexanes, including 1,3-dioxa-5-azacyclohexane **132**, 1-oxa-3,5-diaza-cyclohexanes **133**, 1-thia-3-oxa-5-azacyclohexanes **134**, 1-oxa-3-thia-5-azacyclohexane **135** (cf. Scheme 48) (99H2085), and 1,3-dithia-5-azacyclohexanes **135a** (94TA633). The free energies of activation ($\Delta G^{\#}$) show that the 1,3,5-triazacyclohexanes have the highest energy barriers because they have two N-alkyl groups in *equatorial* positions to stabilize the chair conformer (cf. Table XVII). Heterocycles **132**–**135** have similar $\Delta G^{\#}$ values; the nature of the heteroatom is not relevant to the dynamic interconversion process.

The 1,3,5-triheterocyclohexanes **128**–**135** and borane or chloroborane form stable adducts which have frozen conformations as shown by the geminal coupling pattern of the CH_2 groups (95TA1585, 99EJOC2063, 99EJIC2069). The configuration of the nitrogen atoms in the borane and chloroborane adducts is determined by the size of the N-substituents. Bulky *iso*-propyl groups direct the borane moieties into



R = *i*Pr **132a** = *t*Bu **132b** [R] = -α-methylbenzyl **132c**

133

R = *i*Pr **134a** = Me **134b** [R] = -α-methylbenzyl **134c**

135

135a

Scheme 48

Table XVII. BARRIERS ($\Delta G^{\#}$/kcal mol^{-1}) TO RING INTERCONVERSION IN 1,3,5-TRIALKYL-1,3,5-TRIHETEROCYCLOHEXANES (99H2085)

Compound	Substituents	Solvent	Ring interconversion ($\Delta G^{\#}$/kcal mol^{-1})
132a	*i*-Pr	C_4D_8O	10.7
132b	*t*-Bu	C_4D_8O	11.0
132a	*R*-CH(Me)Ph	C_4D_8O	11.7
133	*t*-Bu	C_4D_8O	10.3
134a	*i*-Pr	C_4D_8O	10.3
134b	Me	C_4D_8O	11.3
134a	*R*-CH(Me)Ph	C_4D_8O	11.2
135	*i*-Pr	C_4D_8O	10.7
135a	*R*-CH(Me)Ph	C_4D_8O	11.5 ± 0.2[a]

[a]From Ref. 94TA633.

axial positions, while methyl groups direct them to *equatorial* positions. The formation of stable cationic zinc(II) alkyl complexes of N-alkylated 1,3,5-triazacyclohexanes was reported and analyzed by X-ray diffraction (96JOM121).

A theoretical MP2 study of **132d** (R = Me) and **133a** (N–R = Me) prove the *axial* preference of the H_3C–N–C–O unit is due to hyperconjugation, being more important than steric effects (97JOC6144).

From the pK_a values of the conjugated acids of a large series of hydroxylated piperidines and hexahydropyridazines, a consistent difference in basicity was found between stereoisomers having an *axial* or *equatorial* OH group in a position β or γ to the amine function because an *equatorial* OH group is more strongly electron-withdrawing than an *axial* OH group (02CEJ1218). This difference in electron withdrawing power is explained by the difference in charge/dipole interactions in the two systems. This stereoelectronic effect affects the basicity of the piperidines and hexahydropyridazines and can cause the amines to change the conformation upon protonation.

N. 1,3-Oxazinanes (Perhydro-1,3-oxazines)

The stereochemistry of the preferred conformers of several 3-acyloxy-1,3-oxazinanes **136** were established by ^{1}H and ^{13}C NMR spectroscopy (99JCS(P2)877). A strong anomeric effect dictates the selection of the preferred conformers (cf. Scheme 49). By variable temperature NMR spectroscopy the rate-limiting process in the conformational equilibria was studied; in Table XVIII both the composition of the conformers (cf. also Scheme 49) and the energy barriers $\Delta G^{\#}$ for the rate limiting process in the conformational equilibria of **136a–f** are given. A decrease in the energy barrier with an increase in steric crowding in the molecules indicated N-inversion to be the rate limiting process in the interconversion of the compounds. The preferred conformers of **136f** in solution was proven by X-ray diffraction to be the same as in the solid state.

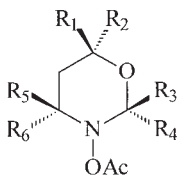
The same authors studied the stereodynamics of some 6-substituted 3-hydroxy-1,3-oxazinanes **137** (cf. Scheme 50) (99SA(A)1445); the composition of the conformational equilibria and the barriers to N-inversion are shown in Table XVIII. Again the conformer with an *axially* disposed hydroxyl substituent was found to be preferred (cf. Scheme 50), the minor conformer was the di-*equatorial* invertomer after N-inversion. The *axial* preferences of the R–N–C–O units are due to hyperconjugation (97JOC6144).

Further, the stereochemistry of substituted 1,3-oxazinanes was studied in the solid state, [2-$C_6H_4NO_2$(*p*)-5-Ph (93T2115), 2-$C_6H_4NO_2$(*p*)-3-*i*Pr (91AX(C)1994)] and also in solution [2-(2′-pyrrolyl)-4-COOMe-5-H and 2-(2′-pyrrolyl)-4-COOMe-5-$CH_2CH(CH_3)(CH_2)_4CH_3$ (99P1731)]. All substituents were found to be in the *equatorial* position as the 1,3-oxazinane *chair* conformer.

O. 1,4-Oxazinanes (Morpholines)

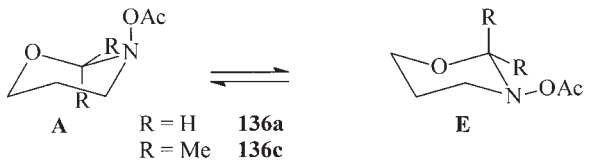
The stereodynamics of a number of N-substituted morpholines was studied (cf. Table XIX). When the N-substituent is capable of conjugative interactions with the morpholino nitrogen atom, a substantially lower barrier to ring inversion was observed. The barrier to ring interconversion was solvent independent (91T7465). The sterically restricted rotation about the exocyclic N–C bond was strongly dependent on the bulkiness of the aryl ring (01JCR(S)265).

A number of solid state structures of N-substituted morpholines show (cf. Table XX) the substituents prefer exclusively the *equatorial* position on the *chair* conformer of the saturated 6-membered ring, as in a number of 2,2-spiro compounds (02JMC11).

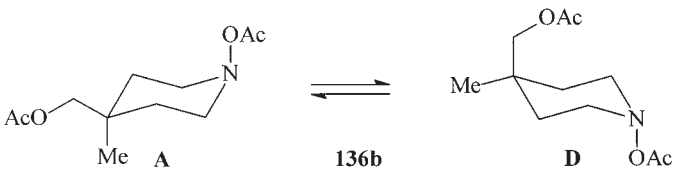


136

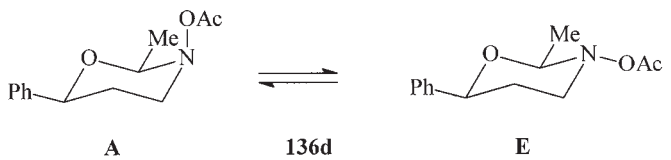
136a R^1 - R^6 = H
136b $R^1 = CH_2OAc$, R^2 = Me, R^3 - R^6 = H
136c R^1 = H, $R^3 = R^4$ = Me, $R^2 = R^5 = R^6$ = H
136d R^1 = Ph, R^3 = Me, $R^2 = R^4 = R^5 = R^6$ = H
136e R^1 = Ph, R^2 - R^5 = H, R^6 = Et
136f R^1 = Ph, R^3 = Me, R^5 = Et, $R^2 = R^4 = R^6$ = E



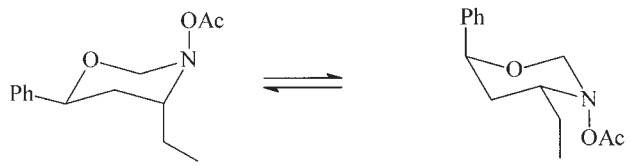
A R = H **136a** **E**
R = Me **136c**



A **136b** **D**



A **136d** **E**



A **136e** **D**

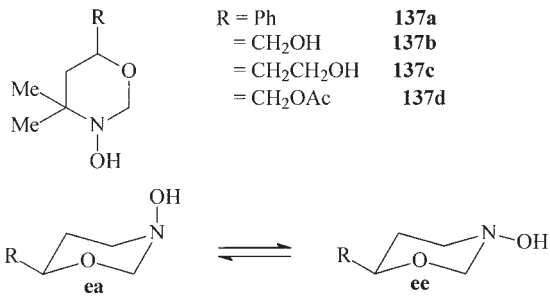
A **136f** **E**

Scheme 49

Table XVIII. Barriers ($\Delta G^{\#}$/kcal mol^{-1}) to the Interconversion Process in N-Acyloxy-1,3-oxazines and Participation of Conformers in the Conformational Equilibria

Compound	Composition of conformers/%[a]	$\Delta G^{\#}$/kcal mol^{-1}	Reference
136a	100% **A**	15.1	99JCS(P2)877
136b	75% **A**, 25% **D**	15.4 (14.7)	99JCS(P2)877
136c	100% **A**	14.5	99JCS(P2)877
136d	92% **A**, 8% **E**	16.1 (14.6)	99JCS(P2)877
136e	75% **A**, 25% **D**	14.5 (13.8)	99JCS(P2)877
136f	93% **A**, 7% **E**	17.0 (15.4)	99JCS(P2)877
137a	83% *ea*, 17% *ee*	14.9	99SA(A)1445
137b	90% *ea*, 10% *ee*	15.4	99SA(A)1445
137c	82% *ea*, 18% *ee*	15.1	99SA(A)1445
137d	85% *ea*, 15% *ee*	15.2	99SA(A)1445

[a]Structure of the compounds and conformers, cf. Scheme 49.



Scheme 50

P. 1,2-Thiazinanes (Perhydro-1,2-thiazines)

The X-ray structures of two derivatives of 3,6-dihydro-1,2-thiazine 1-oxide **137** indicate (cf. Scheme 51) (02AX165, 02AX198) the six-membered ring to be a *half-chair* conformer with the S=O bond in an *quasi-axial* position.

Q. 1,4-Thiazinanes (Perhydro-1,4-thiazines)

Eliel and co-workers (93JOC3905) measured the position of the conformational equilibria in 3- and 4-methyl-1,4-thiazinanes, *cis*- and *trans*-2,3-dimethyl-1,4-thiazinanes, their N-methyl derivatives and several sulfoxides and sulfones **138**–**164** (cf. Scheme 52). The free energy differences, ΔG°, were calculated from low temperature ^{13}C NMR spectra

Table XIX. BARRIERS ($\Delta G^{\#}$/kcal mol^{-1}) TO RING INTERCONVERSION AND C,N RESTRICTED ROTATION IN N-SUBSTITUTED MORPHOLINES

Substituent	Solvent	Ring interconversion $\Delta G^{\#}$/kcal mol^{-1}	Restricted rotation $\Delta G^{\#}$/kcal mol^{-1}	Reference
H	CD_2Cl_2	10.1	–	91T7465
Me	CS_2	11.1	–	91T7465
CHO	C_2D_5OD	7.5	22.1	93MI745
Cyclohexyl	$CD_2Cl_2/CHClF_2$ (1:1)	10.6	–	91T7465
1-Cyclohexenyl	$CD_2Cl_2/CHClF_2$ (1:1)	9.1	–	91T7465
Ph	$CF_2Cl_2/CHClF_2$ (1:1)	7.2	–	91T7465
Ph-NH_2(*p*)	$CF_2Cl_2/CHClF_2$ (1:1)	8.0	–	91T7465
Ph-NO_2(*p*)	$CHClF_2$	10.6	–	91T7465
$PhNO_2$(*o*)tetra-Cl	–	–	15.8	01JCR(S)265
$PhNO_2$(*o*)tri-Cl (*o*,*m*,*p*)	–	–	15.0	01JCR(S)265

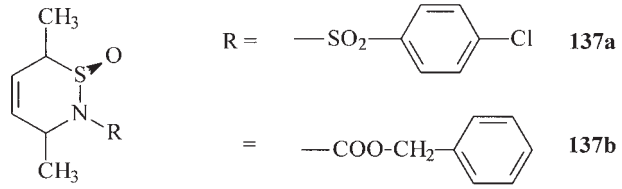
Table XX. PREFERRED CONFORMERS OF SUBSTITUTED MORPHOLINES IN THE SOLID STATE

Conformation of morpholine	Preferred conformer	Reference
Chair	1*e*-$(CH_2)_2$NHCOEt	02JMS105
Chair	1*e*-C(*t*Bu)=CH–CH(Et)CH_2COO*t*Bu	92ZN869
Chair	1*e*-C(Ph)=CH–CH(Et)CH_2COO*t*Bu	92ZN869
Chair	1*e*-C(Ph)=C(Ph)NO_2	90AX1659
Chair	1*e*-[2′-(3′-Ph-4′, 5′-di-COOEt)]	98MI133
Chair	1*e*-[P(O)-1,3-dioxyl]	98HAC271
Chair	1*e*-$SiMe_3$-1*a*BH_3	98AX(C)1645
Chair	1*e*-$(CH_2)_n$COOH[a]	01JMS261

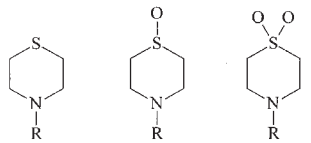
[a] $n = 2$, 3, 4, and 5.

(cf. Scheme 53 and Table XXI). Comparing the conformational energies of the various substituents, a number of interactions between the substituents could be defined:

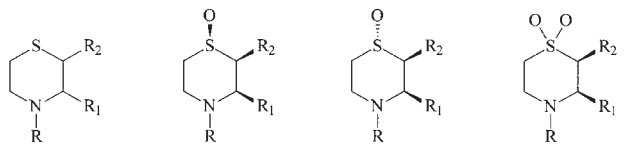
(i) The Me/OSO(*gauche*) interaction in sulfones (0.31 kcal/mol),
(ii) the SO/Me(*syn-axial*) interaction in sulfoxides (ca. 2.1 kcal/mol),
(iii) the SO/H(*axial*) interaction in sulfoxides (−0.42 kcal/mol), and
(iv) the OSO/H(*axial*) interaction in sulfones (ca. 0.7 kcal/mol).



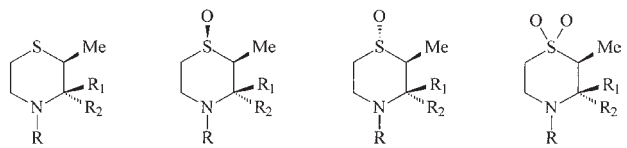
Scheme 51



R	Compd.	Compd.	Compd.
H	**138**	**140**	**142**
Me	**139**	**141**	**143**



R	R_1	R_2	Compd.	Compd.	Compd.	Compd.
H	Me	H	**144**	**148c**	**148t**	**150**
Me	Me	H	**145**			
H	H	Me	**146**	**149c**	**149t**	**151**
Me	H	Me	**147**			**152**

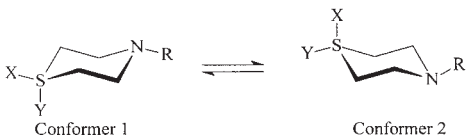


R	R_1	R_2	Compd.	Compd.	Compd.	Compd.
H	Me	H	**153**	**157c**	**157t**	**161**
Me	Me	H	**154**	**158c**	**158t**	**162**
H	H	Me	**155**	**159c**	**159t**	**163**
Me	H	Me	**156**	**160c**	**160t**	**164**

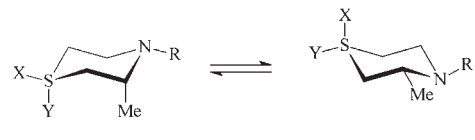
Scheme 52

Finally, the effect of solvents on the position of the conformational equilibria was rather small suggesting that polar interactions are only minor.

The stereochemistry of the sulfoxides of the 1,4-thiazinane-3,5-dicarboxylates (02JCS(P2)1066) in solution and in the solid state (cf. Scheme 55) indicates the *axial* position of the sulfoxide oxygen

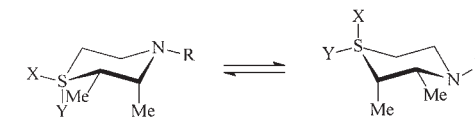


Compd.	R	X	Y
140	H	:	O
141	Me	:	O
142[a]	H	O	O
143[a]	Me	O	O

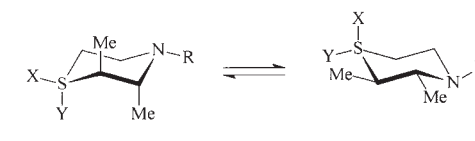


Compd.	R	X	Y
144[b]	H	:	:
145	Me	:	:
148c[b]	H	:	O
148t[b]	H	O	:
150[b]	H	O	O

Compd.	R	X	Y
146	H	:	:
147	Me	:	:
149c[b]	H	O	:
149t[b]	H	:	O
151	H	O	O
152	Me	O	O



Compd.	R	X	Y
153	H	:	:
154	Me	:	:
157c[b]	H	:	O
157t[b]	H	O	:
158c	Me	:	O
158t	Me	O	:
161[b]	H	O	O
162	Me	O	O



Compd.	R	X	Y
155	H	:	:
156	Me	:	:
159c[b]	H	O	:
159t[b]	H	:	O
160c[b]	Me	O	:
160t[b]	Me	:	O
163[b]	H	O	O
164[b]	Me	O	O

[a]Degenerated equilibrium
[b]Only conformer 2 was observed

Scheme 53

is 1.9 kcal/mol more stable than the *equatorial* arrangement and that the thiazinane S-oxides with *syn*-3-carbonyl substituents are stabilized by electrostatic interactions between the S=O and the C=O carbon.

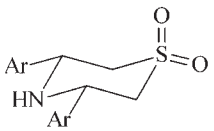
The *vicinal* H,H coupling constants in the ^{1}H NMR spectra of a number of *cis*/*trans*-isomeric 3,5-diaryl-1,4-thiazinane-1,1-dioxides **165**

Table XXI. Conformational Equilibria of Thiazananes (93JOC3905)

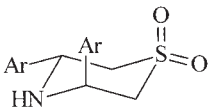
Entry	Compound	Solvent	T/K	N[a]	K = [**2**]/[**1**][b]	ΔG° /kcal mol^{-1}
1	**140**	CD_2Cl_2	183	2	0.52 ± 0.03	−0.23 ± 0.02
2	**141**	CD_2Cl_2	183	2	0.10 ± 0.00	−0.84 ± 0.01
3	**146**	CD_2Cl_2	193	3	40.17 ± 7.25	1.41 ± 0.07
4	**147**	CD_2Cl_2	183	5	45.37 ± 14.17	1.37 ± 0.12
5	**149*t***	CD_2Cl_2	193	4	12.01 ± 1.56	0.95 ± 0.05
6	**151**	CD_2Cl_2	183	3	20.23 ± 2.76	1.09 ± 0.05
7	**152**	CD_2Cl_2	193	5	16.76 ± 3.63	1.07 ± 0.08
8	**145**	CD_2Cl_2	173	2	13.71 ± 1.06	0.90 ± 0.03
9	**153**	CD_2Cl_2	183	5	11.03 ± 1.19	0.87 ± 0.04
10		acetone-d_6	183	5	9.32 ± 2.52	0.77 ± 0.07
11		CD_3OD	183	6	3.46 ± 0.79	0.45 ± 0.08
12	**154**	CD_2Cl_2	183	6	0.14 ± 0.02	−0.72 ± 0.01
13		acetone-d_6	203	5	0.17 ± 0.03	−0.72 ± 0.01
14		CD_3OD	183	6	0.06 ± 0.01	−1.03 ± 0.06
15	**156**	CD_2Cl_2	163	5	3.56 ± 0.76	0.40 ± 0.07
16		acetone-d_6	173	3	1.56 ± 0.19	0.15 ± 0.04
17		CD_3OD	173	3	22.90 ± 1.36	1.08 ± 0.02
18	**158*c***	CD_2Cl_2	193	3	3.40 ± 0.44	0.47 ± 0.05
19		acetone-d_6	193	4	5.42 ± 0.67	0.65 ± 0.05
20		CD_3OD	193	3	1.97 ± 0.05	0.26 ± 0.01
21	**158*t***	CD_2Cl_2	193	3	5.66 ± 0.43	0.66 ± 0.03
22		acetone-d_6	193	4	7.41 ± 0.89	0.77 ± 0.05
23		CD_3OD	193	4	5.04 ± 0.73	0.62 ± 0.06
24	**162**	CD_2Cl_2	203	5	3.34 ± 0.67	0.48 ± 0.08
25		acetone-d_6	203	5	4.12 ± 1.03	0.56 ± 0.10
26		CD_3OD	203	4	2.36 ± 0.39	0.34 ± 0.07

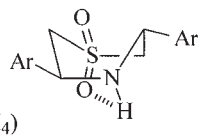
[a]Number of pairs of signals integrated to compute K.
[b]See Scheme 53 for conformations **1** and **2**.

and **166** (cf. Scheme 54) (93IJC(A)535) suggest that the *cis* isomers **165** exist in *chair* conformations with the aryl groups in an *equatorial* position (cf. Scheme 54). For the *trans* isomers *boat* conformers make significant contributions to prevent the 1,3-di-*axial* interactions between the aryl groups and sulfonyl oxygen in the *chair* conformation, an intramolecular hydrogen bonding in the *boat* conformation provides stabilization. If the 3,5-diaryl-1,4-thiazinane-1,1-dioxides are substituted further in positions 2 and 6 (**167**–**170**—cf. Scheme 54) (94IJC(B)1134, 95IJC(B)816, 99IJC(B)926, 99PS167, 02PS431), these molecules largely exist in *chair* conformations with *equatorial* orientations of all the substituents.

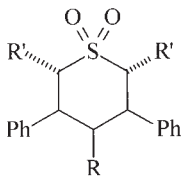


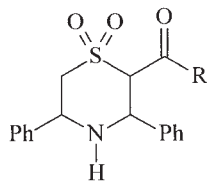
Ar = Ph **165a**
p-Cl-C_6H_4 **165b**
p-OMe-C_6H_4 **165c**
o-Cl-C_6H_4 **165d**





166 (Ar = *o*-Cl-C_6H_4)





R' = H R = H **167a**
R = Me **168a**
R' = COOMe R = H **167b**
R = Me **168b**
R' = COOEt R = H **167c**
R = Me **168c**
R' = COPh R = H **167d**

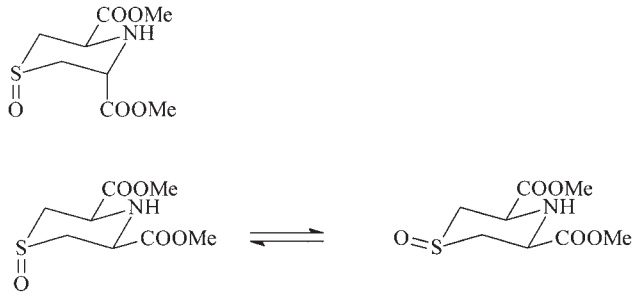
R = C_6H_5 **169a**
= *p*-Me-C_6H_4 **169b**
= *p*-Cl-C_6H_4 **169c**
R = OMe **170a**
= OEt **170b**

Scheme 54

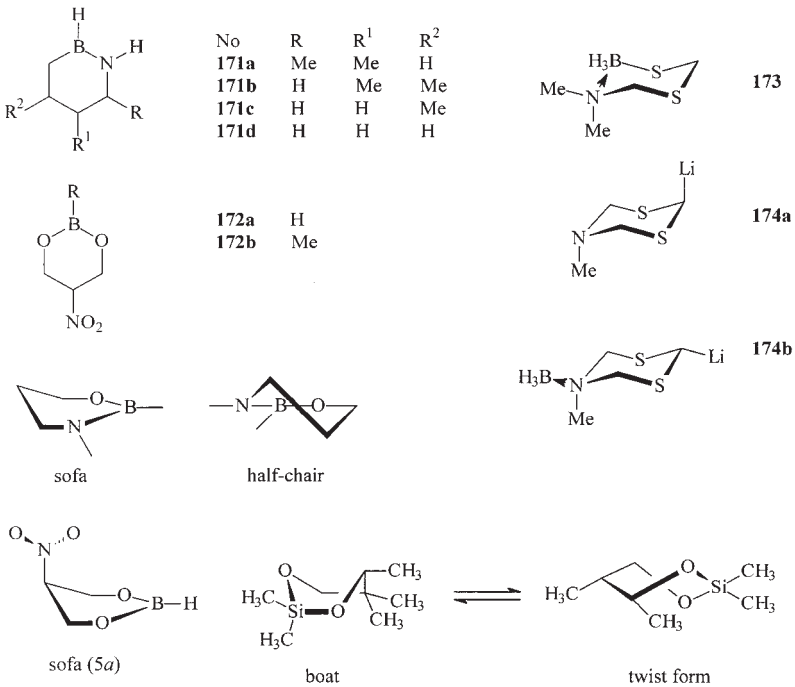
R. 1,3,2-Oxazaborinanes

Kuznetsov (96CH106, 99CH935, 99CH1033) synthesized and investigated the stereochemistry of a number of substituted 1,3,2-oxazaborinanes **171**–**172**. From the experimental NMR and a comparison of experimental and calculated H,H coupling constants and accompanying empirical (MM2) and semi-empirical (AM1) quantum chemical calculations, he concluded that the cyclic boron esters adopt several conformers (*sofa* and *half-chair*—cf. Scheme 56) in the ground state but the N–H bond generally in an *equatorial* orientation. On the other hand, the *cis*/*trans*-isomers of 2,2,4,5-tetramethyl-1,3-dioxa-2-silacyclohexane prefer *boat* (*cis*) and *twist* forms (*trans*) as the most stable conformers (cf. Scheme 56) (98RJGC578). The 5-nitro compound adopts the *sofa* conformation with an *axial* nitro group *perpendicular* to the plane of molecular symmetry.

Flores-Parra et al. (93CB863) studied the reactivity of dithiazinanes towards BH_3, BD_3, and BF_3 and obtained from the reaction mixture the



Scheme 55



Scheme 56

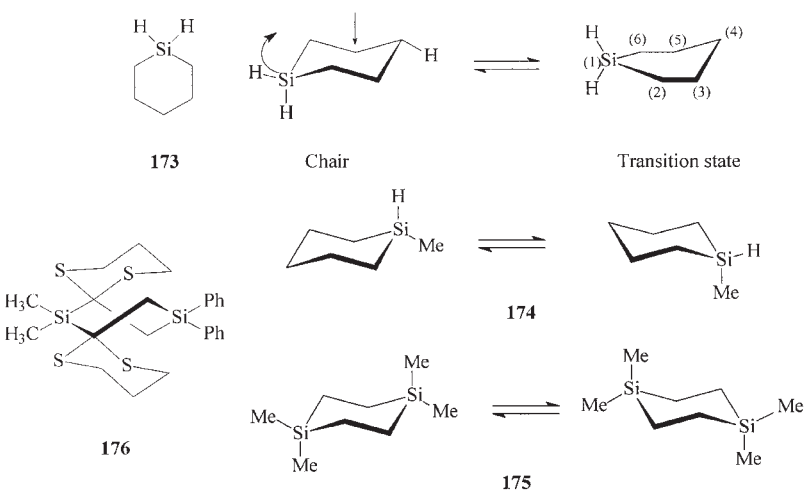
clean boradithiazinan **173**. By variable temperature NMR spectroscopy, the activation energy of the ring interconversion was determined ($\Delta G^{\#} = 12.3 \pm 0.1$ kcal/mol; for the corresponding BD_2 analog: $\Delta G^{\#} = 12.2 \pm 0.2$ kcal/mol). The same authors reported the synthesis of some structurally analogous lithium organic compounds **174a**,**b** (97CB813) that

show preferred *chair* conformations with two different configurations at the carbanion centre having the lithium ion in *axial* or *equatorial* positions (cf. Scheme 56).

S. SILACYCLOHEXANES

The structures and relative energies for the basic conformations of silacyclohexane **173** were calculated using HF, MP2, RI-DFT and MM3 methods (00ZAAC853). All predict the *chair* form to be the dominant conformation (boat and twist forms, also found, are less stable); the transition state for the chair-to-chair interconversion consists of a *sofa-like half-chair* conformation (cf. Scheme 57). The steric energy of the transition state is 6.57 kcal/mol higher than that of the chair conformation.

The molecular structure and the conformational equilibrium of 1-methyl-1-silacyclohexane **174** were determined by gas electron diffraction, in solution by low temperature NMR spectroscopy and by *ab initio* quantum-chemical calculations (02JOC3827, 03JPC243). The *equatorial* methyl conformation is preferred and the ring interconversion barrier is less than 6 kcal/mol (cf. Table XXII). A similar barrier to ring interconversion was found for 1,1,4,4-tetramethyl-1,4-disilacyclohexane **175** (98T13181) (cf. Scheme 57 and Table XXII).



Scheme 57

Table XXII. CONFORMATIONAL EQUILIBRIA (ΔG°) AND BARRIERS ($\Delta G^\#$/kcal mol^{-1}) TO CHAIR–CHAIR INTERCONVERSION IN SILACYCLOHEXANES

Compound	Method	ΔG°/kcal mol^{-1}	$\Delta G^\#$/kcal mol^{-1}	Reference
174	gas state	0.45(68% *e*Me)	–	02JOC3827
	NMR[a]	0.23(74% *e*Me)	5.81 (5.56)	02JOC3827
	MO calc.	0.46–0.6(68–73% *e*Me)	5.92 (5.84)[b]	02JOC3827
175	NMR[a]	–	6.0 ± 0.15	98T13181
177a	NMR[c]	55% 1*e*-Me	–	98ZAAC65
177b	NMR[c]	65% 1*e*-Et	–	98ZAAC65
177c	NMR[c]	76% 1*e*-*i*Pr	–	98ZAAC65
177c	NMR[c]	93% 1*e*-*t*Bu	–	98ZAAC65
180	NMR[a]	–	4.7 ± 0.2	98JOC9125

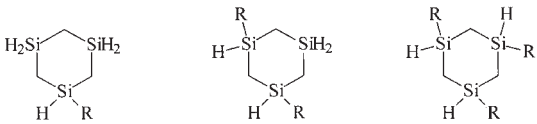
[a]At 110 °C; solvent: CD_2Cl_2, $CHFCl_2$, CHF_2Cl (1:1:3).
[b]Result of the DFT calculation (B3LYP).
[c]Obtained from weighted averages of $^3J_{H1aH2a}$ and $^3J_{H1e,H2e}$ coupling constants; references: $^3J_{H1aH2a} = 8.8$ Hz and $^3J_{H1e,H2e} = 1.1$ Hz.

A number of 1,3-dithianyl-substituted 1,4-disilacyclohexanes were synthesized (98TL3197) and one molecular structure (**176**) was studied by X-ray diffraction (cf. Scheme 57). The two 1,3-dithianyl rings adopt strain-free *chair* conformations, whereas the conformation of the 1,4-disilacyclohexane ring was a *twist–boat*. The *twist* form was attributed to steric repulsion between the *exo*-cyclic C–S bonds; the interaction between the silicon and the two sulfur atoms was also considered.

The gas-phase structure of 1,3,5-trisilacyclohexane was determined by gas electron diffraction (01JMS245) and compared with the results of quantum chemical calculations (98JMS(T)91). The *chair* conformation, the strongly preferred conformer, is more flattened than cyclohexane due to the intrinsically large Si–C–Si bond angles. By the quantum chemical calculations also the *twist* and *boat* conformers were identified to be much less stable than the *chair* conformation. The *chair-to-chair* interconversion barrier is 5.5 kcal/mol; the transition state was identified as a *sofa* conformation with an approximately C_s symmetry, similar to the transition state in **173** (cf. Scheme 57).

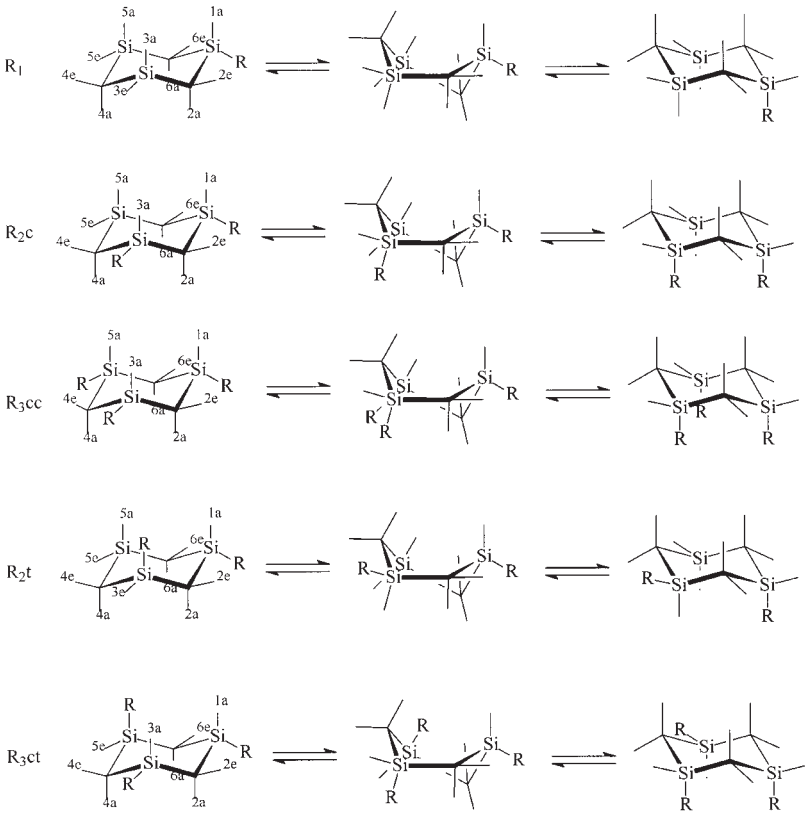
1,3-Disilacyclohexane (02MI) and 1,4-disilacyclohexane (03MI) were synthesized and the ring interconversion studied by *ab initio* quantum chemical calculations; the lowest energy path for the ring inversion consists of a *half-chair* transition state and a flat region consisting of a *boat* and two *twist* forms of nearly equal energy.

Si-Alkyl substituted 1,3,5-trisilacylohexanes **177–179** were prepared and their ^{1}H (98ZAAC65), ^{13}C (98ZAAC1973), and ^{29}Si NMR spectra (99JAAC97) were analyzed with respect to their conformational preferences



177 **178** **179**

R = Me (**a**), Et (**b**), *i*Pr (**c**), *t*Bu (**d**)



R = Me (**a**), Et (**b**), *i*Pr (**c**), *t*Bu (**d**)

Scheme 58

(cf. Scheme 58). In addition, the relative energies of the basis conformations were calculated by the quantum chemical methods HF and DFT (01JMS(T)61). At room temperature, the conformational equilibria were not frozen and the position could be only estimated by *vicinal* H,H coupling constants (98ZAAC65) and the theoretical

calculations (01JMS(T)61). From these results the following conclusions were drawn:

(i) For the monosubstituted compounds $\mathbf{R_1}$, the following conformational equilibria were estimated: 55% 1*e*-Me, 65% 1*e*Et, 76% 1*e*-*i*Pr and 93% 1*e*-*t*Bu.
(ii) For $\mathbf{R_3ct}$ as the most stable conformer, the *twist–boat* conformation has all the large substituents in *pseudo-equatorial* positions.
(iii) The quantum chemical calculations predict in all cases the *equatorial chair* conformation to be of the lowest energy. In the most cases the inverted *chair* (cf. Scheme 58) is the next lowest in energy. Except for $t\mathrm{Bu}_1$, $t\mathrm{Bu}_2c$, $i\mathrm{Pr}cc$, and $t\mathrm{Bu}_3cc$ the *twist–boat* conformations are calculated to be lower in energy than the inverted *chair*(*axial*) conformers.

From 1,3,5-trisilacyclohexane a number of titanium complexes Cp′Ti $(\mu\text{-O})_3[\mathrm{Si}(t\mathrm{Bu})\text{-}\mathrm{CH}_2]_3$ were analyzed by ^{1}H, ^{13}C, and ^{29}Si NMR spectroscopy in solution and by X-ray structural analysis in the solid state (02MI).

Finally, the ring interconversion of dodecamethylcyclohexasilane **180** was studied at very low temperatures by complete line shape analysis (98JOC9125); the free energy of activation is 4.7 kcal/mol and the interconversion was suggested to be the same as that of cyclohexane-like derivatives. The higher flexibility of **180** was also found in the solid state.

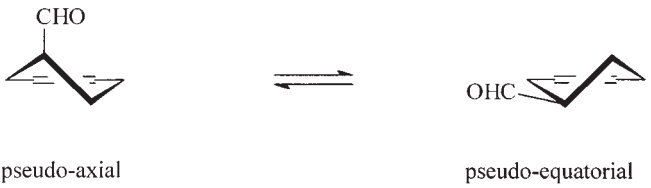
T. Miscellaneous Six-Membered Rings with One *Endo*- or *Exo*-Cyclic Double Bond

1. *Formylcyclohexene*

The ^{1}H and ^{13}C NMR spectra of 4-formylcyclohexene at very low temperatures (98JPOC84) indicate two preferred conformers, the *equatorial half-chair* and *axial half-chair*. (The rotation of the formyl group was not yet frozen at the lowest temperature.) The free energy of activation is 5.6 kcal/mol. The conformational preferences proved to be solvent dependent (cf. Scheme 59, e.g., in $\mathrm{CF_2Cl_2}$ 89%*e* : 11%*a* at 108 K).

2. *2-Halocyclohexanones*

The conformational equilibria of 2-F-, 2-Cl-, 2-Br, and 2-I-cyclohexanone were determined in the gas state and in various solvents by measuring the H,H coupling constants between the protons in positions 2 and 3 at room



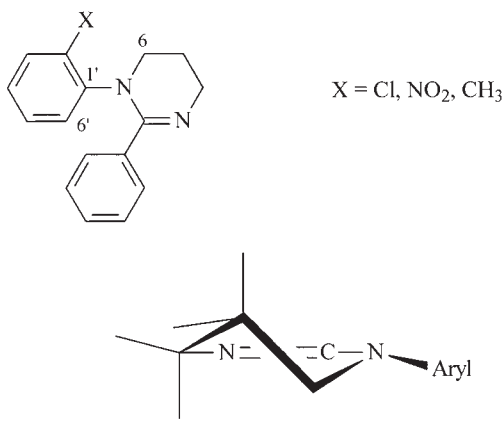
Scheme 59

temperature (02JCS(P2)1494). In 2-fluorocyclohexanone the *axial* conformation is the most stable in the gas phase ($\Delta G^\circ = -0.45$ kcal/mol); in solvents, the *equatorial* conformer predominates.

The other halocyclohexanones show similar behavior but the free energy differences in the gas state are larger [$\Delta G^\circ(\mathrm{Cl}) = -1.05$ kcal/mol, $\Delta G^\circ(\mathrm{Br}) = -1.5$ kcal/mol and $\Delta G^\circ(\mathrm{I}) = -1.9$ kcal/mol)] and the *axial* conformer is still the predominating conformer in solution. The experimental results are corroborated by DFT calculations. For the fluoro and the chloro compounds, there is a clear attractive *gauche effect* between the halogen and oxygen atoms in the *equatorial* conformer.

3. *N-Aryl-2-phenyl-tetrahydropyrimidine*

Three different dynamic processes were detected in N-aryl-2-phenyl-tetrahydro-pyrimidine (cf. Scheme 60) by dynamic NMR spectroscopy: enantiomerization of stereolabile atropisomers, restricted rotation about the Ph–C bond and, presumably, ring inversion of the tetrahydropyrimidine

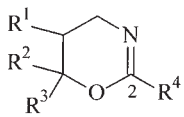


Scheme 60

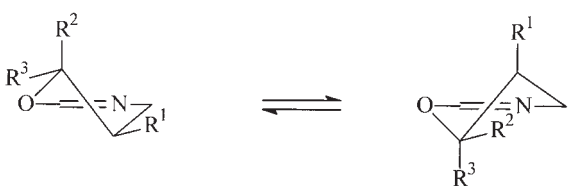
ring (01JOC6679). Single crystal X-ray diffraction yielded a molecular structure (half chair with *equatorial* aryl substituent—dihedral angle C6–N–C1′–C6′ = 72°) in good agreement with the results obtained by *ab initio* calculations.

4. *5,6-Dihydro-4H-1,3-oxazines*

The stereostructures of a number of dihydrooxazines **181a–i** were established on the basis of proton chemical shifts and H,H coupling constants to be two rapidly equilibrating *half-chair* conformations (cf. Scheme 61) (93MRC615). This ^{1}H NMR study indicated a preferred *half-chair* conformation for the heterocycle at room temperature with the bulkier substituents in an *equatorial* position. The arrangement of the substituents at positions 5 and 6 slightly influences the conformation of the heterocycle in order to prevent *eclipsed* configurations.



R^1	R^2	R^3	R^4	No.
H	H	$(CH_2)_5Me$	Ph	**181 a**
H	H	$(CH_2)_5Me$	$CH{=}CH_2$	**181 b**
H	Me	CH_2-*t*Bu	Ph	**181 c**
H	Me	CH_2-*t*Bu	$CH{=}CH_2$	**181 d**
*t*Bu	Me	Me	$CH{=}CH_2$	**181 e**
$(CH_2)_3Me$	Me	H	Ph	**181 f**
Me	$(CH_2)_3Me$	H	Ph	**181 g**
$(CH_2)_3Me$	Me	H	$CH{=}CH_2$	**181 h**
Me	$(CH_2)_3Me$	H	$CH{=}CH_2$	**181 i**



Scheme 61

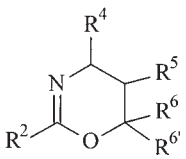
Novel polysubstituted 5,6-dihydro-4*H*-1,3-oxazines **182a–k** were synthesized and the configurations/conformations of the compounds deduced from detailed NMR investigations (01JCS(P2)530). The compounds studied are shown in Scheme 62. The conformational equilibria/preferred conformers are given in Scheme 63 together with the driving force for the position of the conformational equilibria. Beside destabilizing steric *axial*/*axial* repulsions, hyperconjugative interactions (*the anomeric effect*) between the ring oxygen and an sp^2 carbon atom attached to position 6 was found to play a major role as a driving force.

5. *Tetrahydroisoquinolines, Isoquinoline-fused Perhydro-1,3-oxazine-4-one, and Norbornane-fused Perhydro-1,3-oxazines*

Bernath (92MI107) reviewed the synthesis and conformational analysis of these condensed-skeleton saturated heterocycles.

6. *Tetrahydro-1,3-thiazin-2-thiones*

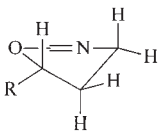
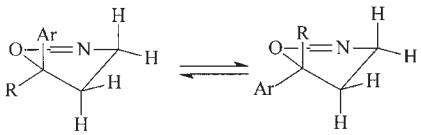
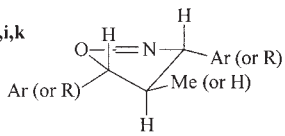
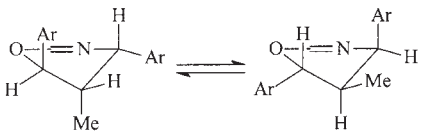
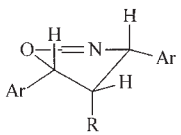
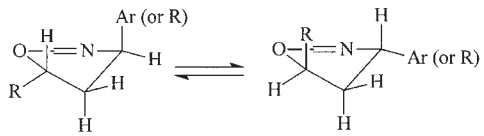
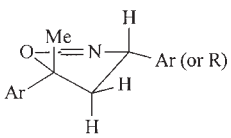
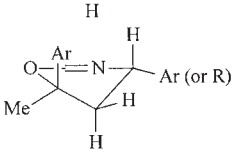
The conformational distribution of all possible diastereomeric thiazine-thiones **183a** and their N-alkyl derivatives **183b–e** (cf. Scheme 64) was



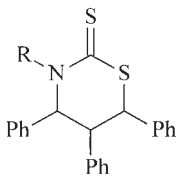
Compd.	R^2	R^4	R^5	R^6	$R^{6'}$
182 a	Ph	H	H	Ph	CH_3
182 b	Ph	H	H	H	$(CH_2)_{17}CH_3$
182 c	Ph	*p*-CH_3-C_6H_4	H	CH_3	Ph
182 d	Ph	*p*-$CH_3C_6H_4$	H	H	$(CH_2)_{17}CH_3$
182 e	*p*-CH_3O-C_6H_4	*p*-Br-C_6H_4	H	CH_3	Ph
182 f	*p*-CH_3O-C_6H_4	*p*-Br-C_6H_4	H	H	$(CH_2)_5CH_3$
182 g	*p*-CH_3-C_6H_4	*p*-NO_2-C_6H_4	CH_3	H	Ph
182 h	Ph	CH_2CH_2Ph	H	CH_3	Ph
182 i	*p*-CH_3-C_6H_4	CH_2CH_2Ph	H	H	*n*-C_4H_9
182 k	Ph	*p*-CN-C_6H_4	CH_3	H	Ph

Scheme 62

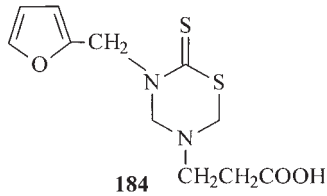
Conformational equilibria of 5,6-dihydro-4*H*-1,3-oxazine

Compd.	Conformation	Driving force in the conformational equilibriu
182b		Axial-axial repulsion
182a		Steric interaction
182g,i,k		Axial-axial repulsion
182g,k		Anomeric effect
182k		Axial-axial repulsion
182d,f,i		Axial-axial repulsion
182c,e,h		Axial-axial repulsion
182e,h		Axial-axial repulsion

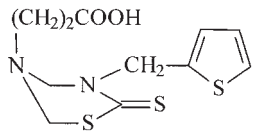
Scheme 63



R = H **183a**
R = Me **183b**
R = Et **183c**
R = *i*Pr **183d**
R = allyl **183e**



184



184a

Scheme 64

determined on basis of H,H coupling constants (00PS239). The diastereomers adopt the *sofa* conformations shown in Scheme 65. The *allylic strain* induced by the N-substituents leads to strong preference for either *aae*- or *aee*-conformations depending on the *trans*,*cis*- and *cis*,*trans*-configuration which shows the balancing role of the third *cis* phenyl group. The analogous N,N-disubstituted tetrahydro-2*H*-1,3,5-thiadiazine-2-thione derivative **184** (cf. Scheme 64) adopts a favorable envelope conformation **184a** in which the N-5 atom lies out of the main plane (01T7361).

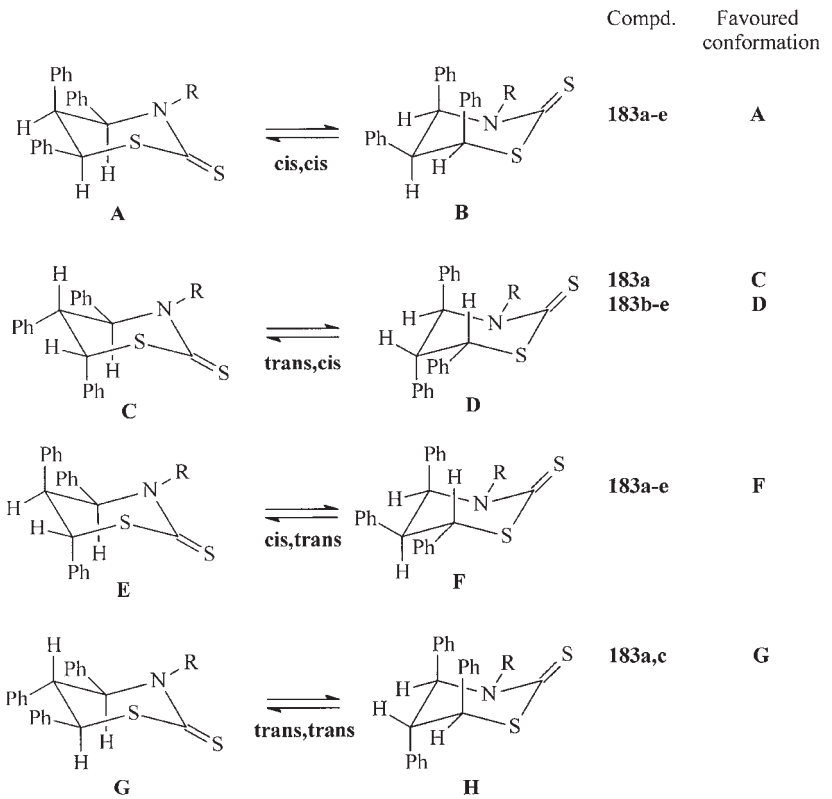
7. *Solid State Structures*

In Table XXIII, the X-ray structures of some really interesting compounds with one *endo*- or *exo*-cyclic double bond are shown.

8. *Theoretical Conformational Analysis*

The conformational preferences in alkyl- and phenyl-substituted 3-piperideines (1,2,3,6-tetrahydropyridines) were theoretically calculated by *ab initio* and molecular mechanics calculations (01CEJ4715). A set of rules for the estimation of the position of conformational equilibria were derived that are very reliable as indicated by comparing the results with previous stereochemical assignments.

Freeman et al. (00JMS(T)145, 98JCC1064) studied by *ab initio* quantum chemical calculations the geometry and conformational equilibria of all isomeric dihydrodioxines (**185**) and dihydrodithiines (**186**) (cf. Scheme 66).

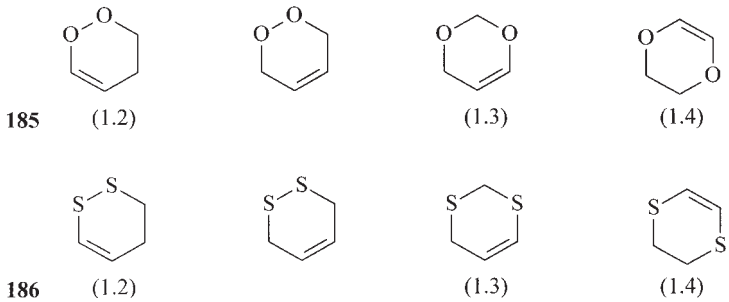


Scheme 65

Table XXIII. PREFERRED CONFORMERS OF SIX-MEMBERED RINGS WITH ONE *EXO*- OR *ENDO*-DOUBLE BOND IN THE SOLID STATE

Conformation	Six-membered ring	Preferred conformer	Reference
Half-chair	2,4-dioxa-CH-1-one	2*a*-CH(Me)Et-2*e*-NHCOC$_6$H$_5$	97MI51
Chair	piperidin-4-one	2,6*ee*(2′-thienyl)-3*e*Me-5*e*-Me	95MI177
Boat	piperidin-4-one	1-CHO-2*a*-Ph-3*e*-Me-5*a*-Me-6*e*-Ph	99MI769
Boat	piperidin-4-one	1-NO-2*e*-Ph-3*a*-Me-5*e*-Me-6*a*-Ph	99MI769
Half-chair	5,6-dihydro-2*H*-1,4-oxazine	2*a*-OH-3*e*-Me-4-Me-5*e*-Me-6*e*-Ph[a]	95TA2715
Half-chair	5,6-dihydro-2*H*-1,4-oxazine	2*a*-OH-3*e*-Me-4-Me-6*e*-Ph[a]	00SC2721

[a]Three more compound were published (3*e*-*n*Pr, 3*e*-Et, and 3*e*-Ph instead of 3*e*-Me).



Scheme 66

They found that the compounds exist in *half-chair* conformations and that their *boat* conformers are the transition states for ring interconversion.

The methods of synthesis, the configurational and conformational aspects of the stereochemistry and the main spectral properties and reactions of 1,3-oxathiane derivatives were reviewed after submitting the manuscript (2003H1477).

Acknowledgments

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Fluorine-Containing Heterocycles. Part I. Synthesis by Intramolecular Cyclization

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I. Introduction

A. Intramolecular Cyclization: A Route to Heterocycles with Fluorine-Containing Fragments

The development of methods of obtaining organic compounds with a certain structure is one of the central problems of organic chemistry. The properties of a relatively new class of fluorine-containing organic compounds, such as heterocyclic ones, are substantially determined by the peculiar influence of fluorine atoms as substituents.

Recent results show the new, unique properties of fluorine-containing compounds and areas of their practical applications (84M1, 82M2, 94M3, 92M4, 91M5, 94M6, 90M7). As to heterocyclic compounds, many of them

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are known to be useful as biologically active substances. The introduction of fluorine atoms can lead to substantial increases of biological activity, making wide investigations in the field of fluorine-containing heterocyclic compounds necessary (82M, 93M8, 87M9, 87M10). Thus, the high pharmacological activity of fluorine-containing steroids (anti-inflammatory action) and 5-fluorouracyl (cancerolytic action) can be mentioned. The introduction of a trifluoromethyl group in the molecule can increase lipophilicity, facilitating biological activity and their migration through membranes. In some cases the introduction of perfluoroalkyl groups leads not only to enhanced pharmacological action, but also to the substantial diminishing of undesirable side-effects. Hence the use of compounds containing perfluoroalkyl groups as drugs and pesticides.

Regioselective substitution of hydrogen by fluorine or by perfluoroalkyl groups in heterocyclic systems has significant effects on the biological and physical properties of molecules (90YGKKS16, 95OPP33). In recent years, therefore, synthetic strategies have been actively developed in the chemistry of fluorinated heterocycles. These use the methodology of heterocycle formation at the expense of the double bond of the perfluoroolefin and the binucleophilic reagent.

Recent investigations focus on the introduction of fluorine atoms and perfluoroalkyl groups into molecules of known bioactive compounds to improve their properties. The modification of biological activity in this way can be connected with the following factors:

(a) The presence of a vinyl fluorine atom allows for its substitution by the nucleophilic centers of the natural substrates. Their electrophilic centers (e.g., metal ions) can coordinate with heteroatoms (e.g., thiazoline and its substituent in position 2). The biological activity of vinyl fluoride, based on the irreversible inhibition of fermentative reactions, has been established.
(b) The presence of superlipophilic perfluorinated groups substantially facilitates the permeability of biologically active substances by two mechanisms: a decrease in melting point of the compound because of a lesser stability of the crystalline lattice, leading to an increase in solubility and an increase in affinity both to lipophilic and to aqueous phases, leading to an increase in permeability.

Fluoroolefins are key compounds playing a fundamental role in synthetic fluoroorganic chemistry. Modification of the properties of the double bond by the introduction of fluorine atoms permits the development of reaction routes that are missing in the hydrocarbon series. This creates excellent opportunities for the syntheses of definite structures,

including heterocyclic ones, which may be of interest for the syntheses of biologically active compounds having pharmaceutical and agricultural applications.

Heterocyclic compounds are known to form a substantial number of pesticides and drugs, stimulating synthetic activity (94AHC1, 95ZOR1704). The main purpose of these investigations is the modeling, synthesis, separation from the natural sources and identification of compounds, acting as selective agonists or antagonists of ligands *in vivo*.

Progress in pharmaceutical science is, in turn, directly connected with the discovery of new reactions, suitable for the purposeful synthesis of compounds of a certain structure, forming a basis for the development of new kinds of drugs possessing the necessary biological activity. The effect of fluorine in that case reveals itself both in the modification of the properties of the organic substrate and the physiological action of the molecule as a whole.

As to the practical side of the problem, the methods of synthesis of new heterocyclic compounds with necessary properties have to fulfil some important requirements: the simplicity of the process both in reagents and conditions, satisfactory reproducibility, regioselectivity, and high yields. According to these, the development of convenient approaches and methods of direct perfluoroalkylation can be considered as one of the serious problems of synthetic organic chemistry.

The development of synthetic methods for obtaining the heterocyclic compounds containing perfluoroalkyl groups, has been reviewed (95M11, 96M12, 99UK483, 97M13, 01M14, 88M15, 95M16, 96CR1, 81AHC1, 95CEN39, 92T189). A substantial number of publications in that field is devoted to the modification of natural compounds by the introduction of fluorine atoms or perfluoroalkyl groups. The investigations have provided substantial progress in the design of new reagents and synthetic methods.

Moreover, the attachment of fluorine-containing substituents to an azole ring generally considerably increases its biological activity. For example, the introduction of a polyfluorinated benzene ring onto a pyrazole results in a sharp increase in biological activity and these compounds have been applied to the synthesis of herbicides and plant growth regulators (87GerDE3603291).

Fluorine-containing heterocyclic compounds play an important role in drug and pesticide design. The key methods of synthesis of these compounds are based on condensation and intramolecular cyclization processes induced by heteronucleophiles. They may affect the fluorine atoms of a benzene ring and the multiple bond of perfluoroolefins. Intramolecular cyclizations are characteristic of unsaturated polyfluorinated compounds. Therefore,

systematic studies of these processes have been carried out. Two nucleophilic centers are effective for heterocyclic system design. Such reactions occur by nucleophilic addition at the multiple bond with subsequent stabilization of the intermediate carbanion, generating a new multiple bond. The latter may be isomerized by the bases in the system, forming heterocycles varying in size. Therefore, it is important to study the role and effects of fluorine atoms on multiple bond reactivity.

Recent years are marked by an increase in interest in the synthesis of new ligands, based on fluorine-containing heterocyclic compounds. These ligands can be used for extraction and separation of metal ions, catalysis of interphase transfer, the creation of materials with anti-corrosive properties etc. Fluorine-containing heterocyclic compounds can be applied also for practical purposes, such as liquid dielectrics, high-temperature lubricants, complexones, and extragents. The possibility of creating a new class of high-temperature amorphous fluoroplastics on the basis of number of heterocycles, including perfluoro-4-methyl-1,3-dioxolane. Nitrogen-containing heterocycles with N–F fragments, e.g., some derivatives of N-fluoropiperidines, have been found to be effective, mild, and selective fluorinating reagents (99JFC(97)79).

The ability of fluoroolefins to undergo nucleophilic reactions, not inherent in their hydrocarbon analogs, is especially pronounced in perfluoroolefins, whose chemistry is being actively developed owing to their wide industrial production. Perfluoroolefins approach activated olefins such as α,β-unsaturated carbonyl compounds or polycyanoolefins in reactivity. At the same time, the diversity of perfluoroolefin reactions is a consequence of the lability of the CF_2 group of fluoroolefins and the possibility of further tranformations of adducts associated, in particular, with the high CH-acidity of the $(CF_3)_2CH$ group. All these characteristics of perfluoroolefins, along with their accessibility, lead to wide applicability of these compounds in fluoroorganic synthesis.

The high electrophilicity of perfluoroolefins is the result of the profound electron-accepting effect of fluorine atoms and CF_3 groups combined with the capability of vinyl fluorine atoms to be effectively conjugated with the C=C bond. The reactivity of perfluoroolefins does not depend so strongly on the statistical distribution of electron density (or on the induced positive charge on the C=C carbon atoms in perfluoroolefins) as it does on the dynamic properties of this distribution.

As is known, the greater the number of fluorine atoms in the organic molecule, the higher the positive charge on carbon atoms; this is due to the difference in electronegativity between C and F. This effect, in turn, enhances the reactivity of fluorine atoms attached at the C=C or C–F bond in an aromatic ring. As a result, intramolecular nucleophilic cyclizations

at the multiple bond of perfluoroolefins and at the *ortho*-fluorine atom of the perfluorinated benzene ring make it possible to obtain heterocyclic systems. These processes are well-known (95OPP33, 94AHC1, 62AHC1, 85JFC(28)361, 78IJC80, 96CR1, 01M11, 01M12, 98HS355). The above reactions underlie one of the most important and general methods for the synthesis of fluorine-containing benzoheterocycles. Nucleophilic reagents with two nucleophilic centers are used along with heteronucleophiles, whose reactions with unsaturated perfluorinated compounds generate a new nucleophilic center involved in intramolecular nucleophilic cyclizations. This methodology offers tremendous opportunities for the preparation of new cyclic systems and for the design of new approaches. Wide prospects are envisaged for both the syntheses of biologically active compounds and theoretical rationalization of the nature of the carbon–fluorine bond. In the case of internal perfluoroolefins, the presence of a CF_2 fragment gives rise to a new possibility to form a heterocyclic ring. Thus the intermediate carbanion generated by the interaction between the nucleophile and the double bond of the fluoroolefin may be stabilized, forming either the primary multiple bond or a new one. If the nucleophilic part contains another nucleophilic center, or if the latter is generated under the reaction conditions, then the intramolecular nucleophilic cyclization may involve both multiple bonds, affording heterocycles differing in size and structure.

The nature of the heteroatom in the binucleophilic reagent is a critical factor in these processes, since the heteroatom is involved in the formation and stabilization of the intermediate carbanion, determining the site of attack of the second nucleophilic center at the carbon atom of either the primary or secondary multiple bond. The direction of these processes is the result of the combined action of several factors, permitting selective control over the formation of the heterocyclic system. These processes, therefore, are most interesting and important for perfluorinated compounds because they are impossible for olefins from the hydrocarbon series and offer an opportunity to vary the properties of functional groups due to the introduction of fluorine atoms. It should be emphasized that the nucleophilic reactions of perfluoroolefins do not merely form a heterocyclic ring; they also lead to heterocyclic rings with perfluoroalkyl groups.

Syntheses of heterocyclic compounds with perfluorinated side chains are mainly performed by substitutional fluorinations of the available fragments or by the introduction of a perfluoroalkyl group in the heterocycle. The development of convenient approaches and direct perfluoroalkylation methods is a current challenge.

This approach to perfluoroolefins and their derivatives permits one to obtain various heterocyclic compounds including biologically active ones. Moreover, it is also important for theoretical studies on the nature

of the C–F bond based on experimental data. The analysis of the available experimental data seems to be inadequate (94ZOR1704). Development of a new effective synthetic methodology for the selective introduction of the perfluoroalkyl group in organic molecules is associated with the search for new compounds possessing biological activity for the creation of pharmaceuticals and agrochemicals as well as technical materials.

This methodology has enormous potential in the syntheses of new cyclic systems, as is evident from the material presented below. Also, new approaches using other polyfunctional model compounds may appear. Naturally, this offers wide prospects for the syntheses of new biologically active compounds and for enhancing the biological activity in known compounds due to the introduction of perfluoroalkyl groups. Accumulation of new information will be helpful in theoretical treatments of the nature of the C–F bond and investigations of the fluorine effect on the reactivity of organic systems with fluorine atoms. For perfluoroolefins, this methodology has become an important approach employed for the syntheses of various perfluoroalkyl derivatives of heterocyclic compounds. The main purpose of this review consists in the analysis of the main tendencies in the development of synthetic methods in the field of heterocyclic compounds containing perfluoroalkyl groups as substituents in order to reveal the new approaches towards the formation of heterocyclic systems, including systems with one or more heteroatoms (N, O, S, P, etc.). Substantial attention is paid to the possibilities of applying perfluorinated olefines and their derivatives as synthons to obtain new heterocyclic compounds and convenient routes to new fluorine-containing substances for pharmacological investigations.

In the syntheses of heterocyclic compounds with perfluoroalkyl groups, the key methods are based on two types of chemical transformations. The first type involves the introduction of the perfluoroalkyl group on the heterocyclic system, namely, substitutional fluorination of fragments already available in the system or direct introduction of the perfluoroalkyl group onto the heterocycle.

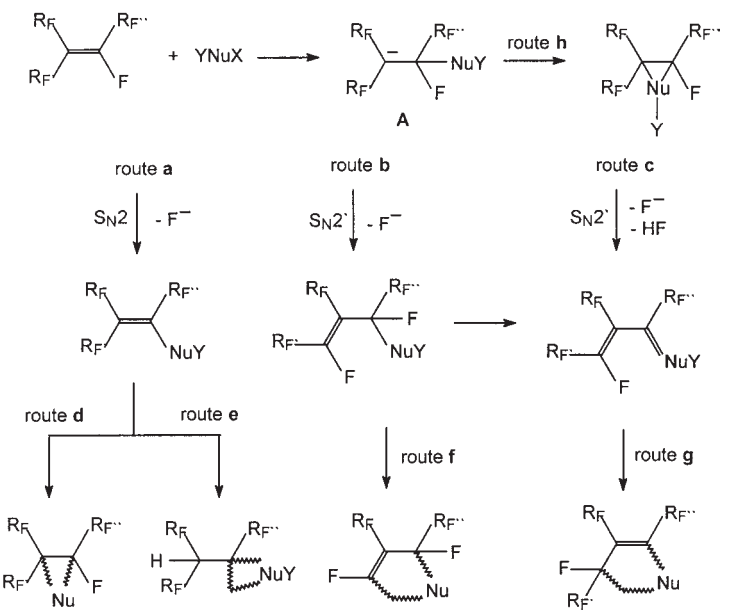
The second type is the construction of a heterocyclic system from units containing perfluoroalkyl groups or their fragments. Each type has its own advantages and weaknesses. Thus, reactive species used in processes of the first type are perfluoroalkyl radicals and carbocations, and the processes are conducted by elaborate methods (thermolysis, photolysis, electrolysis, one-electron oxidation, etc.), whereas reactions of the second type use condensation of molecules with suitable groups and nucleophilic reactions of perfluoroolefins.

Another interesting and important technique uses reactions of perfluoroolefins with nucleophilic reagents. The peculiar chemical behavior

of perfluoroolefins lies in the initial addition at the multiple bond and further elimination.

The nucleophile initially adds at the multiple bond, forming carbanion **A**. Further transformations of **A** occur in line with electronic and steric effects, depending on the reaction conditions and on the use of nucleophilic catalysis. Several routes are possible, leading to different reaction products. Note that the use of nucleophilic catalysis is a general technique in the chemistry of compounds with electrophilic multiple bonds; in particular, it is widely employed for dimerization and trimerization of activated olefins, keteneimines, etc.

The study of the factors governing the intramolecular nucleophilic cyclization and ring formation from systems with double bonds bearing a mobile fluorine atom is illustrated by reference to the reactions of internal perfluoroolefins and perfluoroazaalkenes with nitrogen containing binucleophiles. This leads to a wide range of possible structural types of heterocyclic compound. Heterocycles having one or more heteroatoms along with perfluoroalkyl substituents are prepared by intramolecular nucleophilic cyclizations of intermediates containing the double bond and a potential nucleophilic center on the substituent at the double bond. Reactions of perfluoroolefins with 1,3-bidentate nucleophiles in the presence of bases lead to various heterocycles with five-, six-, seven-, and eight-membered rings; they have been actively studied in recent years.



If the charge on carbon in carbanion **A** is stabilized by redistribution on the neighboring perfluoroalkyl groups and if the nucleophilic reagent is large, then double bond formation is sterically favorable. When the α-carbon bears a fluorine atom, elimination of fluoride ion occurs, generating a double bond between the α- and β-carbon atoms (route **a**). If the fluorine atom is lacking or the route is energetically unfavorable, a multiple bond between the β- and γ-carbon atoms is generated (route **b**). When the α-position of the nucleophile has a mobile hydrogen atom, hydrogen fluoride is eliminated and a butadiene derivative is formed (route **c**). If a bidentate nucleophilic reagent is used, intramolecular nucleophilic cyclization follows several routes leading to the formation of a heterocyclic system. Indeed, five- or six-membered (routes **d** and **e**), or seven to nine-membered (routes **f** and **g**) heterocyclic compounds with perfluoroalkyl substituents are obtained depending on the nature and structure of the nucleophilic reagent and the electronic and steric effects of the intermediate carbanions and the effect of fluorine-containing groups.

When the functional group having a nucleophilic center is situated at the multiple bond and possesses electron-donor properties, the attack of the nucleophilic center occurs at the α-atom, generally forming five-membered heterocycles (route **e**). However, if the group is an electron-acceptor, then the attack takes place at the β-carbon atom of the multiple bond (route **h**). In the case of aromatic *ortho*-binucleophiles, the attack is at the β-carbon atom for steric reasons, irrespective of the character of the functional substituent at the multiple bond. When the added functional fragment has a mobile hydrogen atom at the α-position, elimination of hydrogen fluoride under the action of bases will occur along with the formation of a multiple bond between the α-carbon atom of the initial multiple bond and the α-atom of the given functional fragment (route **c**). The carbanion at the β-carbon atom is stabilized by elimination of the fluoride ion at the γ-carbon (route **g**). If, however, there is no mobile hydrogen atom in the α-position of the functional fragment, then only route **f** is realized, also leading to seven- or higher-membered heterocycles if the functional fragment contains another nucleophilic center. Examples are given below.

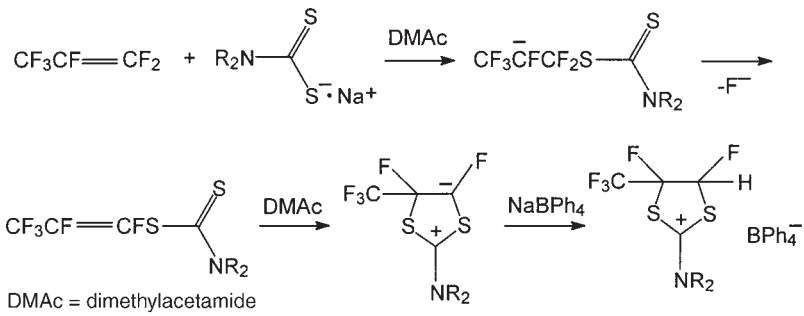
Thus the synthesis of heterocyclic compounds with one or more heteroatoms along with perfluoroalkyl groups is possible if the fluorinated molecule has a multiple bond and if an anionic center may be generated at the heteroatom or carbon atom of the functional group in intramolecular nucleophilic cyclization reactions. These new approaches point to the specific effect of fluorine atoms and to the important role of the electronic effects in

the hydrocarbon skeleton of the molecule in determining the direction of attack of the nucleophilic center; they also permit one to reveal new reactions not inherent in hydrocarbon analogs, providing new methods. The importance of such reactions is dictated by the accessibility of perfluoroolefins, and the results of investigations make them a powerful tool of modern organic synthesis.

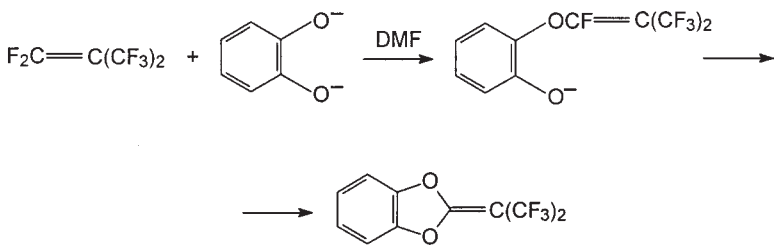
Systemization of experimental data on the syntheses of heterocyclic compounds with perfluoroalkyl groups from perfluoroolefins is based on reactions with various 1,1-, 1,2-, 1,3-, and 1,4-binucleophilic reagents. While the main features of nucleophilic reactions are preserved, further transformations of the primary products (or adducts, or the products of substitution of the functional groups at the internal multiple bond) occur under the influence of the added functional group containing a heteroatom. Here one can expect dramatic differences in the effect of the nature of the nucleophilic reagent between cyclizations by new nucleophilic centers and centers already available in the molecule. Another important aspect is isomerization of the primary internal olefin into the terminal olefin or internal olefin with a different structure under the action of the nucleophilic agent. This may be critical to the structure of the heterocycle formed.

II. Reactions of Binucleophilic Reagents with Terminal Perfluoroolefins

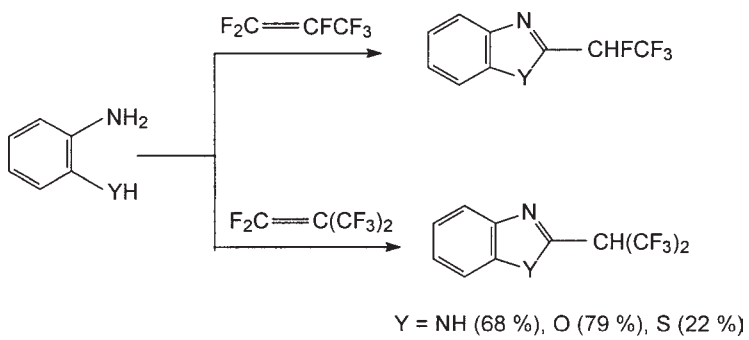
Terminal perfluoroolefins have two fluorine atoms at the double bond. The carbon atoms of the latter bear a significant positive charge, and the nucleophilic agents easily replace the fluorine atoms at the multiple bond. The reactions of binucleophilic reagents with terminal perfluoroolefins form heterocyclic systems. The first step of the reaction involves a nucleophilic attack at the carbon atom of the double bond, generating a carbanion. The latter is stabilized by elimination of the fluoride ion and formation of a new double bond. Subsequent cyclization by the intramolecular attack of the nucleophilic center at the double bond leads to the formation of a heterocyclic system. For example, when a reaction mixture of hexafluoropropylene and sodium dialkylaminodithiocarbamate in dimethylacetamide is heated with aqueous sodium tetraphenylborate, one obtains the tetraphenylborate salt of 2-dialkylamino-4-trifluoromethyl-4,5-difluoro-1,3-dithiolan-2-yl (78JFC(12)193). This compound is formed by intramolecular cyclization of the S-nucleophilic center.



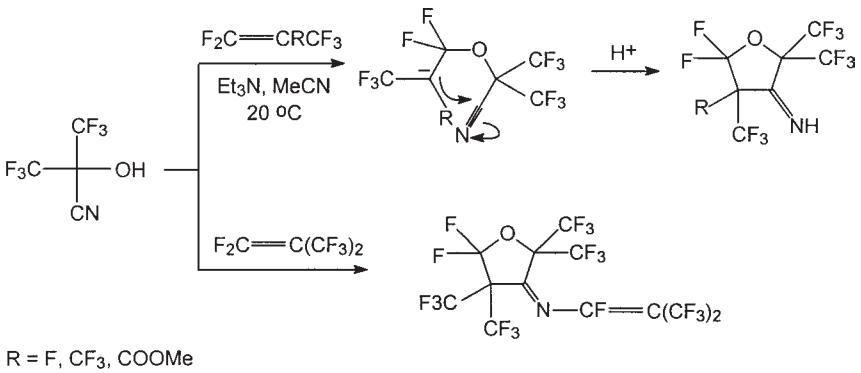
The reaction of perfluoroisobutylene with the disodium salt of pyrocatechol in dimethylformamide yields 2-[2,2,2-trifluoro-1-(trifluoromethyl)-ethylidene]-1,3-benzo[*d*] dioxolane (78JFC(12)211, 73NKK563).



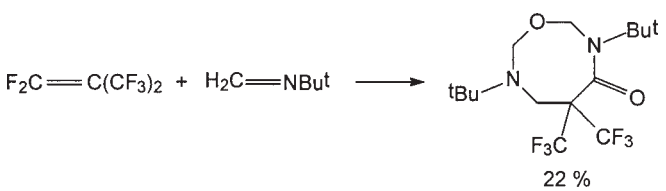
In the case of nucleophiles with an NH_2 group, however, an enamine is the primary product. The second nucleophilic center subsequently attacks the N=C carbon atom linked to the active fluorine atom, forming a five-membered benzoheterocycle. The reaction of hexafluoropropylene and perfluoroisobutylene with *ortho*-phenylenediamine, 2-aminophenol, and 2-aminothiophenol occurs analogously and leads to the derivatives of benzimidazole, benzoxazole, and benzthiazole, respectively.



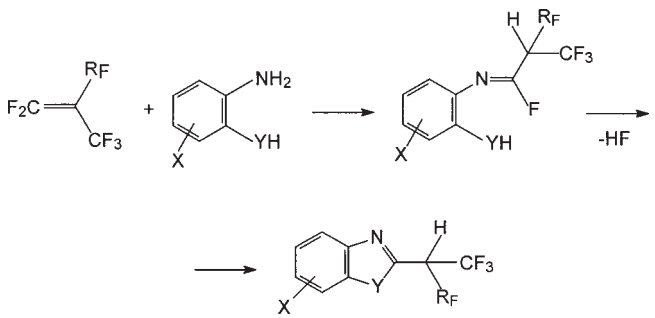
The reactions of perfluoroolefins with hexafluoroacetone cyanohydrin under conditions of nucleophilic catalysis yield 3-iminotetrahydrofuran. The latter evidently forms via the intermediate carbanion involved in the intramolecular nucleophilic cyclization (91JFC(54)401). This is an example of synthesis following route **f**.



The reaction of perfluoropropylene with pyridine methylide affords pyrrolo[1,2-*a*]-pyridine (85JC(RS)33). Azomethineimides, *N*-iminopyridinium, and iminoquinolinium ylides are transformed by perfluoropropylene, 2*H*-pentafluoropropene, and perfluorobut-2-ene into the corresponding pyrazoles (80JFC(15)179). The reaction of octafluoroisobutylene with N-methylene-*tert*-butylamine leads to a mixture of products, among which is 3,7-di-*tert*-butyl-5,5(trifluoromethyl)-1-oxa-3,7-diazacyclooctan-4-one (96ZOB344).



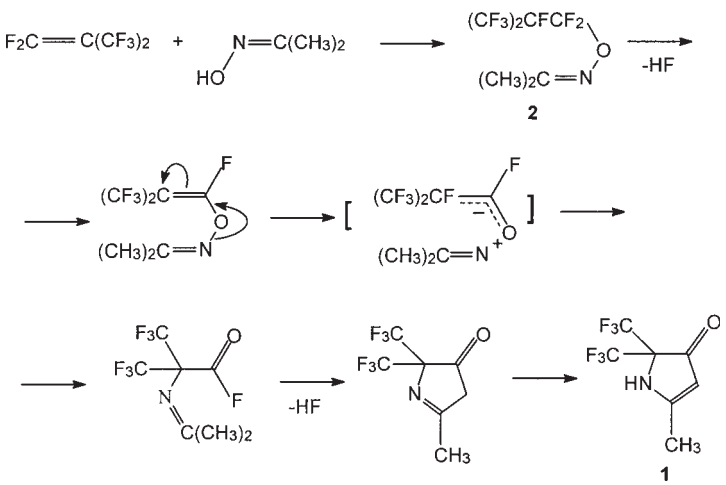
The reactions of terminal perfluoroolefins with *ortho*-bifunctional benzenes used as nucleophilic reagents result in the five-, seven-, and nine-membered benzoheterocycles. In this case, aprotic dipolar solvents are generally employed, and the base is triethylamine. Thus the products of the reactions of *ortho*-substituted anilines with terminal perfluoroolefins are five-membered benzoheterocyclic compounds.



$R_F = CF_3$, Y = O, X = H (79 %); X = 5-Cl (86 %)
X = 5-Me (95 %); X = 7-Me (87 %)
Y = NH, X = H (68 %); X = 5-Cl (83 %)

1,2-Phenylenediamine and 2-aminophenol initially give N-arylimidoyl fluoride. Elimination of hydrogen fluoride from the product and further intramolecular nucleophilic cyclization lead to perfluoroalkyl derivatives of benzimidazole and benzoxazole, respectively. In the case of 2-aminothiophenol, the reaction occurs at the sulfur atom and forms a carbanion. If R_F is fluorine, then the carbanion is destabilized by the interaction of the lone electron pairs of fluorine with the center, and the stabilization reactions occur with participation of the proton. If, however, R_F is the trifluoromethyl group, the negative charge is stabilized by it. The fluoride ion is eliminated with further intramolecular nucleophilic cyclization.

Octafluoroisobutylene reacts with acetone oxime to give pyrrolone derivative **1** via the intermediate formation of compound **2**.



III. Internal Perfluoroolefins as Intermediates in the Syntheses of Heterocyclic Compounds

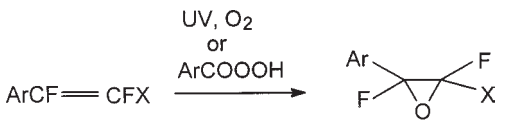
A. Synthesis of Three-Membered Heterocycles, Containing Nitrogen, Sulfur, and Oxygen Atoms

Small heterocycles are of interest in view of their high reactivity and role in biosynthesis. Moreover, for the three-membered ring with an oxygen atom, the ease of ring cleavage creates conditions for polycondensations and heterocyclizations. The former give perfluorinated polyethers with a broad spectrum of practical applications, and the latter affords various heterocyclic compounds.

Hexafluoropropylene oxide is an important intermediate in fluoroorganic synthesis. It is useful in the production of surfactants, perfluoropolyether oils, solvents, perfluorinated alkylvinyl ethers, and other materials.

Oxidation of perfluoroolefins is one of the routes to compounds containing a three-membered ring with an oxygen atom. Various oxidants are used for this purpose, but the yield of the target products is not always satisfactory. The first report of a general method uses alkaline hydrogen peroxide at low temperature (67USP3321515, 80JFC(15)339, 94TL6721).

For example, oxidation of fluorine-containing stilbenes by oxygen on exposure to UV radiation and in the presence of chlorine or perbenzoic acid leads to epoxidation products.

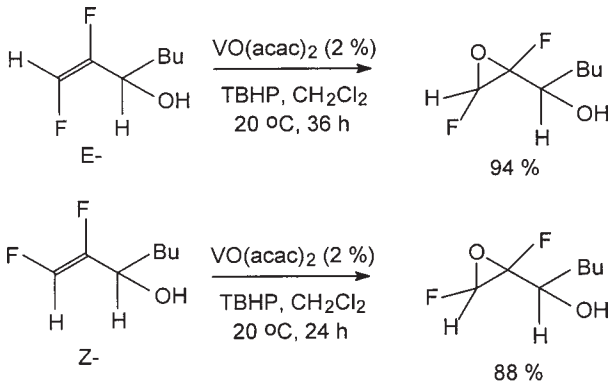


X = Cl, F, CF_3, Ar, CF═CFAr

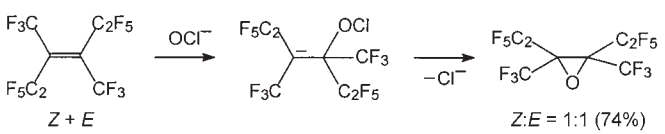
One of the industrial methods for the production of hexafluoropropylene oxide is oxidation of hexafluoropropylene by oxygen in an inert solvent at a temperature of ~150 °C and pressure 40 atm. Conversion of hexafluoropropylene is 70%, and the yield of hexafluoropropylene oxide is 70% based on the converted olefin. The low degree of conversion on oxidation of hexafluoropropylene leads to considerable losses of the target product because of the close boiling points of these substances. When the reaction is conducted in 1,1,2-trifluorotrichloroethane (freon 113), conversion reaches 95%, and the yield of the target oxide is 85%.

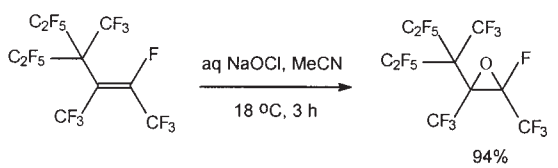
Oxidation of the corresponding olefins by oxygen in the presence of initiators in an inert solvent at elevated temperatures leads to the formation of perfluorinated epoxides (00RP2157805). The initiators are either halogens, trifluoromethylhypofluorite, and tetrafluoroethylene in amounts of 1.0–15.0 v/o% or free-radical producers (94ZOR309).

The *Z* and *E* α,β-difluoroallyl alcohols are epoxidized by $VO(acac)_2$ in the presence of *tert*-butylhypoperoxide (TBHP), the process being diastereoselective for the *Z*-isomer (yield 83%) (93JFC(63)157). For epoxidation by $VO(acac)_2$ and $Ti(OPr^i)_4$, hypoperoxides are used (90JOM173).

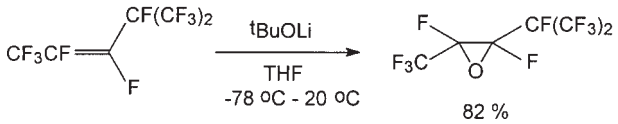


Oxidation of internal perfluoroolefins by alkaline solutions of hydrogen peroxide and alkaline and alkaline-earth hypohalides leads to the formation of olefin oxides, the yield of the target product being 40–50%. The reaction with sodium hypochlorite in an alkali in the presence of acetonitrile is an example of epoxidation performed by the nucleophilic attack of the OCl^- anion of the multiple bond with further elimination of the chloride anion by the intermediate carbanion (79IZV2509, 79IZV2812, 79RP666176, 89ZOR265, 83JFC(23)103, 82JFC(20)243, 90JFC(49)21, 82IZV1586).



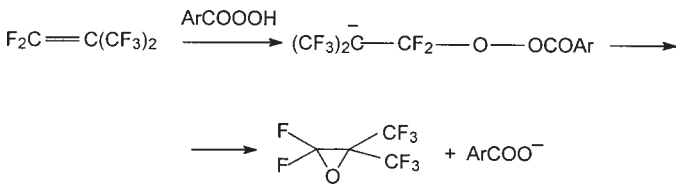


Analogous properties are inherent in lithium *tert*-butyl peroxide used for epoxidation of electron-unsaturated olefins (86JCS(CC)1378, 88JCS(P1)2663).

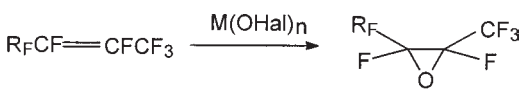


Using this methodology for systems with fluorine atoms considerably enriches our knowledge of the properties of olefinic systems. The reagent also plays an important role. Thus calcium hypochlorite is occasionally ineffective in epoxidations of fluoroolefins, whereas lithium *tert*-butyl peroxide is extremely effective (95JCS(CC)629, 96RCI703).

Alkaline epoxidation of perfluoroolefins has become widely practised in organic synthesis (66KGS873, 70JOC2054, 77USP4010212). It should be noted that aromatic peracids are also effective reagents acting as nucleophiles. Thus octafluoroisobutylene gives an epoxide by the action of aromatic peracids (82IZV2344).

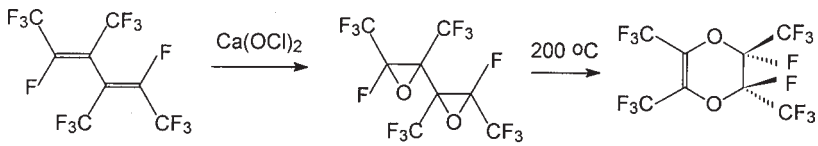


Epoxidation of terminal and internal perfluoroolefins by aqueous solutions of alkaline and alkaline-earth hypohalides in alkaline media is conducted in the presence of aprotic solvents (79IZV2509, 79RP666176).

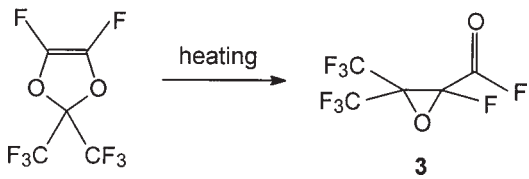


Hal = Cl, Br
n = 1, 2
M = Na, K, Ba, Ca
R_F = CF_3 (80 %), C_2F_5 (72 %), C_3F_7 (94 %)

The reaction of perfluoro-3,4-dimethylhexa-2,4-diene with calcium hypochlorite leads to the formation of a diepoxide, rearranging at 200 °C into the corresponding derivative of 1,4-dioxane (96RCI703).

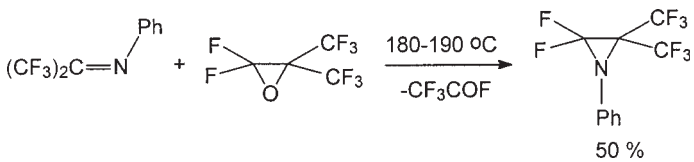


Another technique uses thermal rearrangement of fluorinated dioxolanes. For example, thermolysis of 2,2-bis(trifluoromethyl)-4,5-difluoro-1,3-dioxolane gives the corresponding epoxide **3** (90JA9671).

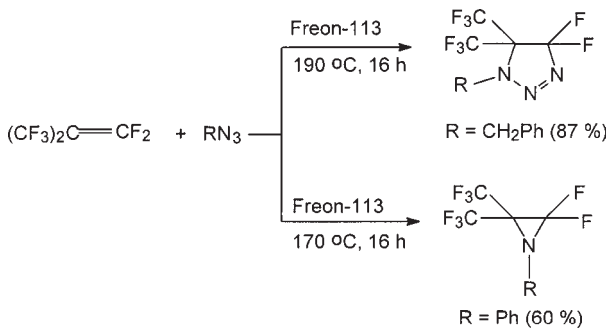


3

Cycloaddition of halocarbenes to azomethines is a general method for the synthesis of halogen-containing aziridines (78JOC1346). The derivatives of three-membered heterocycles with perfluoroalkyl groups are obtained by this technique. As a source of difluorocarbene one uses hexafluoropropylene oxide, which is readily available. Thus the interaction of hexafluoroacetone anil with difluorocarbene, generated by thermolysis of hexafluoropropylene oxide at 180–190 °C, leads to a 1,4-cycloadduct and the corresponding 1-phenyl-2,2-difluoro-3,3-bis(trifluoromethyl)aziridine (86IZV248).

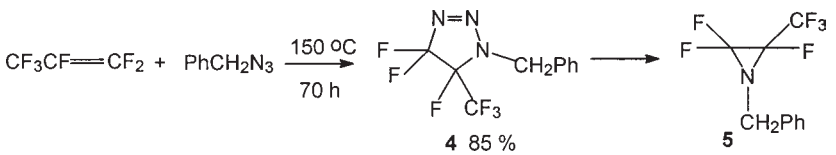


Reactions of perfluorinated olefins with sodium azide give other products whose structure depends on the original olefin. For instance, the interaction of octafluoroisobutylene (66JOC789) or perfluorobut-2-ene (86JOC332) with benzylazide leads to stable 1-benzyl-4,4-difluoro-5,5-bis (trifluoro-methyl)-1,2,3-triazole and 1-benzyl-4,5-difluoro-4,5-bis(trifluoromethyl)-1,2,3-triazoline, respectively. With phenylazide, however, octafluoroisobutylene gives 1-phenyl-2,2-difluoro-3,3-bis(trifluoromethyl)-aziridine. The nature of the substituent at nitrogen, therefore, plays an important role in stabilization of the five-membered ring.



The high-temperature reaction occurs via elimination of molecular nitrogen on nitrene generation (78JOC1346).

This is also characteristic of other perfluoroolefins. Thus cycloaddition of benzylazide to hexafluoropropylene at 150 °C leads to triazoline **4**; pyrolysis of the latter gives aziridine **5**, liberating nitrogen (66JOC789).

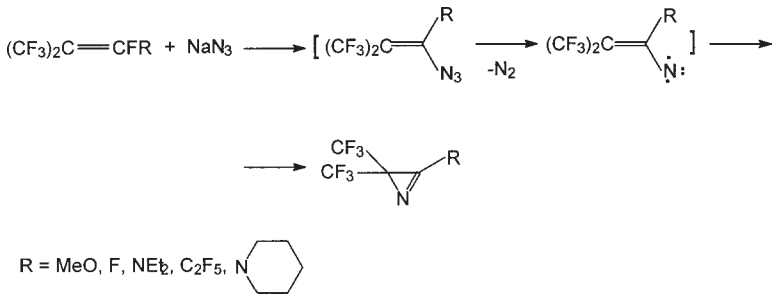


Another approach uses the interaction of perfluoroolefins with bifunctional nucleophiles, for example, with the derivatives of hydrazoic acid, in particular, with sodium azide.

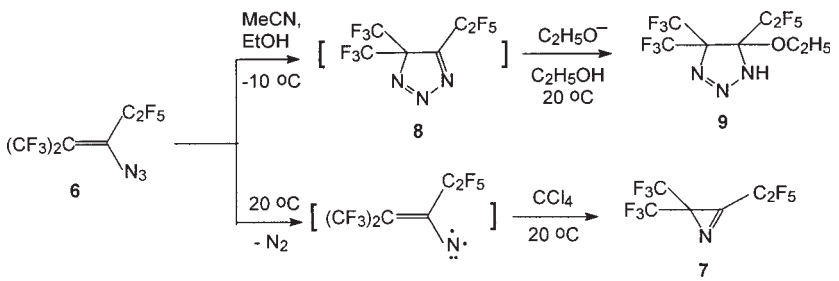
Methoxyaziridine was synthesized from methylperfluoroisobutenyl ether (or dimethylamino- and N-piperidinoperfluoroisobutenyl ethers) and sodium azide; the intermediate unsaturated azide was not isolated (86JOC332, 75IZV2732). The reaction of perfluoropropylene with hydrazoic acid salts gave unstable perfluoropropenyl azide, whose spontaneous decomposition leads to 2,3-difluoro-2-trifluoromethylazirine. The analogous reaction does not lead to 2,2-bis(trifluoromethyl)-3-fluoroazirine from perfluoroisobutylene (97ZOR772). The reaction of perfluoro-2-methylpent-2-ene with sodium azide at −10 °C gives the derivative of this perfluoroolefin **6**, which is stable at that temperature. Storage in carbon tetrachloride at room temperature or UV irradiation of compound **6** leads to azirine derivative **7** (97ZOR772). In an acetonitrile–ethanol mixture, however, the reaction yields stable 5-ethoxyperfluoro-4,4-dimethyl-5-ethyl-1,2,3-triazole **8**.

Perfluorinated olefins containing an azido group at the double bond undergo transformations in at least two ways. First, under UV irradiation

such derivatives split off nitrogen to give an intermediate singlet perfluoroalkenylnitrene resulting in the formation of perfluoroalkyl azirines.



Second, intramolecular cyclization involving the azido group and the double bond could yield 1,2,3-triazoline derivatives; these may be thermally unstable and may undergo nitrogen elimination to afford azirine derivatives. The reaction of perfluoro-2-methylpent-2-ene with NaN_3 in a 1:2 acetonitrile–ethanol mixture at $-10\,^{\circ}C$ (2 h) yielded stable 5-ethoxy-5-pentafluoroethyl-4,4-bis(trifluoromethyl)-4,5-dihydro-1*H*-1,2,3-triazole **9**, whose structure was confirmed by X-ray analysis, Fig. 1 (01JFC(110)21, 97ZOR772).



The route of formation of azirines is not yet clear. It is assumed that the reaction follows two routes. The first route involves the intermediate formation of a nitrene generated from the corresponding unstable azide, which undergoes intramolecular radical cyclization. The second route starts with the formation of a triazoline ring, which is thermally unstable and gives the corresponding azirine, eliminating nitrogen.

Substituted perfluoroolefins react with phenylazide, forming a five-membered heterocycle. Thus the interaction between phenyl azide and methyl 5,5,5-trifluoro-2-oxo-4-trifluoromethylpenten-3-ate gives methyl 3-phenyl-5,5-bis(trifluoromethyl)-4,5-dihydro-3*H*[1.2.3]triazolecarboxylate in high yield (76T1995).

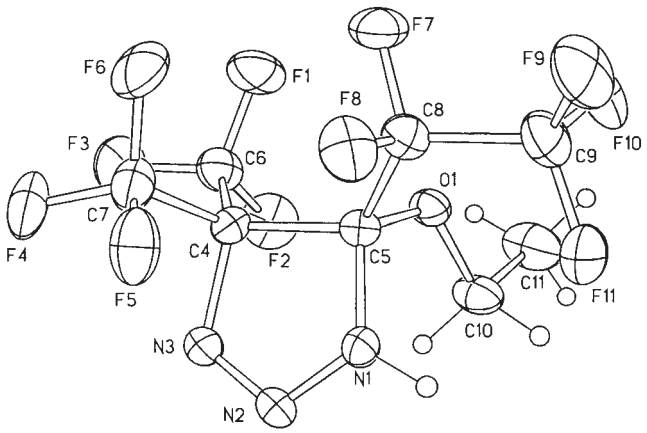
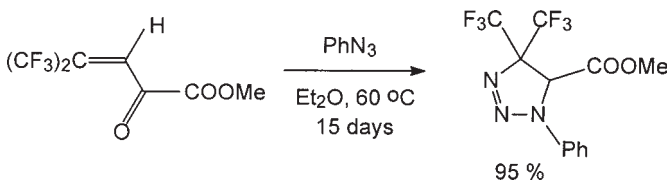
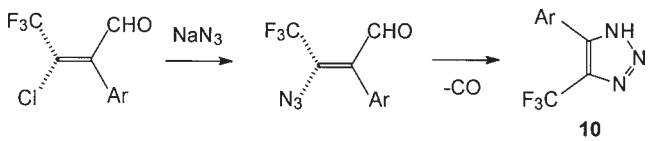


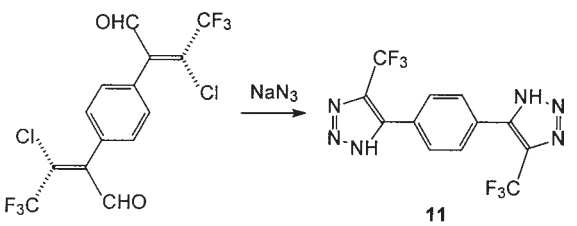
Fig. 1. Crystal structure of compound **9** (X-ray analysis) (01JFC(110)21).



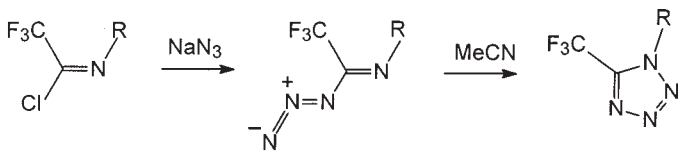
In the case of β-chloro-β-perfluoroalkylvinylacetaldehydes, the reaction with sodium azide affords 4-perfluoroalkyl-substituted triazoles **10** and **11**.



Ar	Ph	4-$CF_3C_6H_4$	4-Ph	3-$CF_3C_6H_4$
Yield,%	68	54	79	32



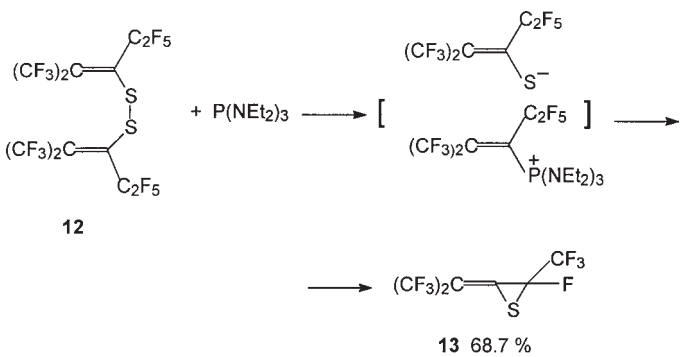
N-Substituted trifluoroacetimidoyl chlorides react with sodium azide to give 1-substituted 5-trifluoromethyltetrazoles (76T1995).



R	Yield, %
Ph	80
4-MeC_6H_4	91
3,4-$(Me)_2C_6H_3$	68
4-ClC_6H_4	53
2-$NO_2C_6H_4$	53
4-BrC_6H_4	55

Imidoyl chlorides are important building units for the construction of various heterocyclic systems with CF_3 and perfluoroalkyl groups (99JFC(99)83, 95JSOC43, 97JSOC1081, 99JFC(97)11).

The new approach to the synthesis of heterocyclic compounds, namely, the nucleophilic substitution of the fluorine atom in a CF_2 or CF fragment in the α-position to the multiple bond is characteristic of unsaturated perfluorinated compounds. Some examples of this process forming heterocycles differing in size and various nucleophilic centers are known. Thus the possibility of the nucleophilic substitution of the fluorine atom in the CF_2 group at the multiple bond was shown (97CJC278, 89IZV116) using as an example the reaction of di(perfluoroalkenyl)disulfides **12** with $P(NEt_2)_3$, forming 2-trifluoromethyl-2-fluoro-3-hexafluoroisopropylidenethiirane **13**.

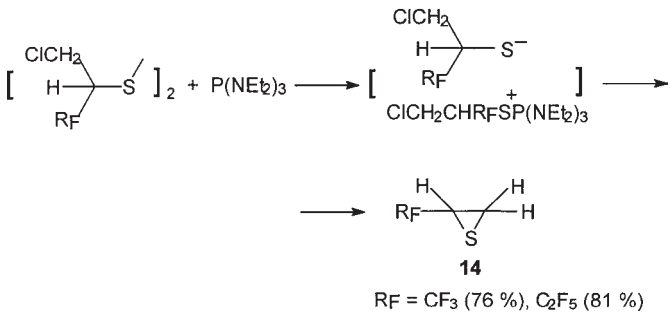


12

13 68.7 %

As is known, symmetrically substituted dialkyl sulfides with a halogen atom in the β-position relative to the sulfur atom react with $P(NEt_2)_3$ with the

formation of an S-nucleophile in the intermediates, nucleophilically substituting the halogen to give thiirane **14**.



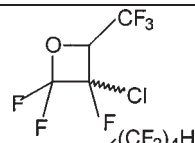
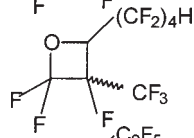
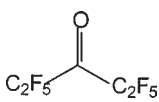
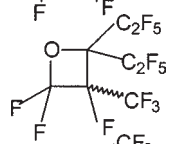
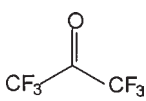
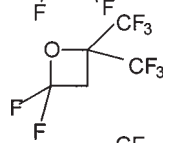
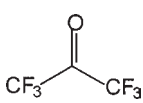
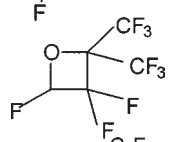
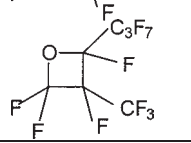
The primary reaction seems to be the nucleophilic attack of phosphorus at the sulfur atom of polyfluoroalkyl or polyfluoroalkenyl disulfides, forming an intermediate. The anion of the intermediate undergoes intramolecular nucleophilic cyclization leading to thiirane derivatives.

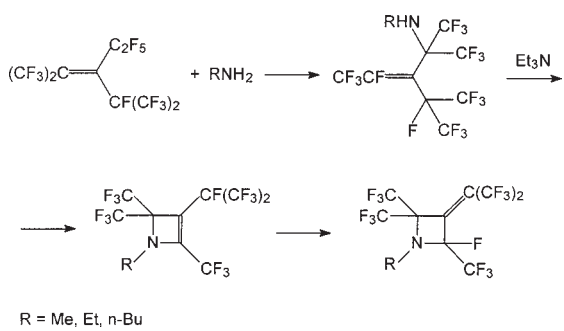
B. Four-Membered Heterocyclic Compounds with Atoms of V–VI Group Elements

While three-membered heterocycles with an oxygen atom are obtained by oxidation of perfluoroolefins, four-membered ones are generally formed by photoinitiated cycloaddition of olefins to carbonyl-containing compounds. This approach was used to obtain oxetanes with perfluoroalkyl groups (62JA1553, 88JFC(40)201). One can also employ Lewis acids or aluminum fluoride/chloride (95JOC3419, 92USP5162594, 92USP5157171), or hydrogen fluoride (61JA386). Table I gives some examples of fluorooxetanes obtained by [2 + 2] cycloaddition.

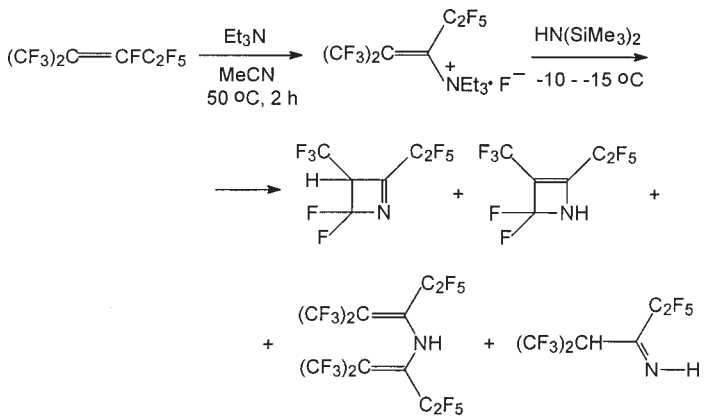
Intramolecular nucleophilic cyclization also leads to four-membered heterocycles. Primary alkylamines can act as binucleophiles; in reactions with unsaturated compounds, they can utilize both NH_2 hydrogen atoms. Heating 4-alkylaminoperfluoro-4-methyl-3-isopropyl-pent-2-ene, obtained by the reaction of primary alkylamines with perfluoroolefins at 100 °C in the presence of triethylamine leads to intramolecular nucleophilic cyclization forming N-alkylperfluoro-2,4,4-trimethyl-3-isopropyl-2-azetine. The latter is readily transformed into N-alkylperfluoro-2,4,4-trimethyl-3-isopropylazetidine by reaction with Et_3N or anhydrous CsF in acetonitrile (96JFC(79)97).

Table I. FLUORINE-CONTAINING OXETANES

Fluoroalkene	Carbonyl compound	Promoter	Product	Yield (%)	References
CF_2=CFCl	CF_3CHO	UV		14	62JA1553
CF_2=$CFCF_3$	$H(CF_2)_4CHO$	UV		59	62JA1553
CF_2=$CFCF_3$		UV		46	62JA1553
CH_2=CF_2		$AlCl_xF_y$		80	95JOC3419
CHF=CF_2		$AlCl_xF_y$		98	95JOC3419
CF_2=$CFCF_3$	C_3F_7COF	UV		73	62JA1553

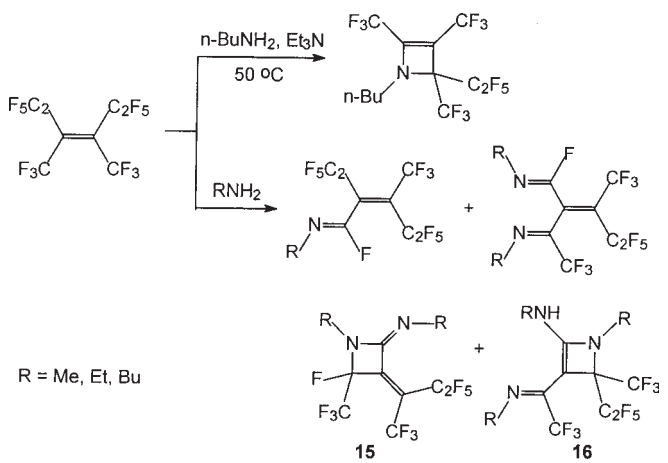


The reaction of hexamethyldisilazane with the adduct of perfluoro-2-methylpent-2-ene and triethylamine yields perfluoro-3-methyl-4-ethylazete and perfluoro-2-methyl-3-ethylazetine, the former being predominant (98ZOR42).

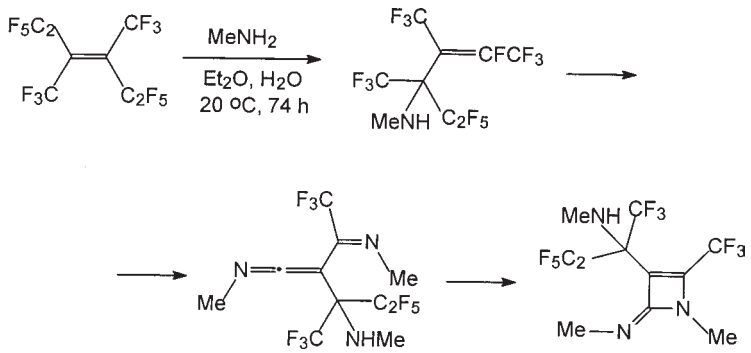


The formation of these compounds may be explained by the following transformations. The weakly nucleophilic hexamethyldisilazane initially reacts at the carbon atom of the multiple bond, and fluoride ion elimination takes place in the new zwitterion, forming a terminal double bond. Further catalysis by the fluoride ion generates an active N-nucleophile; intramolecular cyclization involving the latter leads to a four-membered heterocycle.

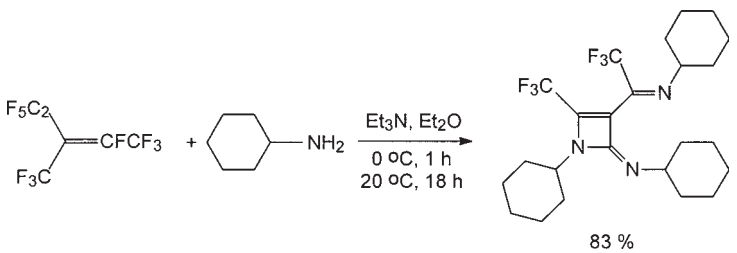
Intramolecular nucleophilic cyclization is used for the synthesis of four-membered heterocycles. This is a general route for reactions of many perfluoroolefins with primary amines. Thus the interaction between perfluoro-3,4-dimethylhex-3-ene and butylamine in the presence of triethylamine forms N-butyl-perfluoro-2,3,4-trimethyl-2-ethyl-1,2-dihydroazete (87ASCC31). In the absence of triethylamine, a mixture of products is obtained, among which are the derivatives of azetidine **15** and azete **16**.



In the case of the reaction with methylamine, the product is 3-(1-methylamino)-1-(trifluoromethylperfluoropropyl)-4-methylimino-4-methyl-2-trifluoromethyl-2-azete (00ZOR109).



The reaction of the tetrafluoroethylene trimer with seven equivalents of dry triethylamine and three equivalents of cyclohexylamine in dry ether gave 1-cyclohexyl-2-trifluoromethyl-3-(2,2,2-trifluoroethylidene)cyclohexylimino-4-N-cyclohexylimino-2-azete (80JCS(P1)1551).



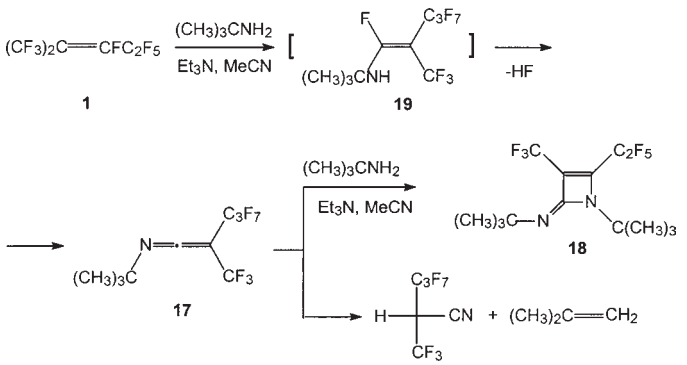
In reactions of primary alkylamines with internal perfluoroolefins, intramolecular nucleophilic cyclization gives a heterocyclic compound with a perfluoroalkyl group. As mentioned above, primary alkylamines can be binucleophilic reagents with nucleophilic centers on the nitrogen atom. Such compounds having an NH_2 group form four-membered heterocycles and many polycyclic heterocycles with one nitrogen atom.

Since primary alkylamines are binucleophilic reagents, both amino hydrogen atoms are lost in reactions with unsaturated compounds. However, it should be realized that these are rather strong bases catalyzing isomerization of perfluoroolefins.

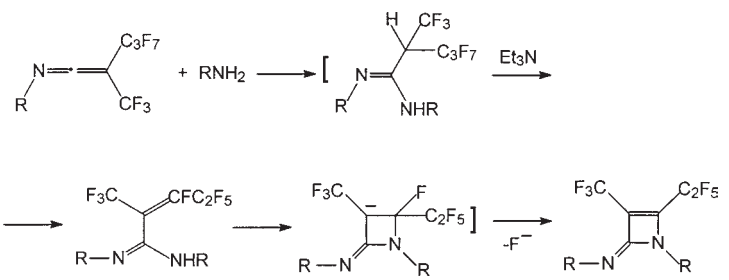
Thus isomerization of perfluoro-2-methylpent-2-ene can give perfluoro-2-methyl-1-pent-1-ene. The terminal multiple bond of the latter is rather labile with respect to the nucleophilic reagents. This can change the reaction

route, leading to many polycyclic heterocycles with one nitrogen atom. Indeed, the reaction between perfluoro-2-methylpent-2-ene and *tert*-butylamine leads to the formation of *tert*-butyl(pentafluoroethyl)-2-trifluoromethyl-1-ethylideneamine **17**. This compound reacts with excess *tert*-butylamine in the presence of Et_3N in acetonitrile with intramolecular cyclization forming *tert*-butyl[1-*tert*-butyl-4-pentafluoroethyl-3-trifluoromethyl-1*H*-azet-2-ylidene]amine **18** (00ZOR109, 00ZOR33).

Compound **17** is probably produced by intermediate formation of *tert*-butyl(octafluoro-2-trifluoromethylpent-1-enyl)amine **19** with further elimination of HF and generation of the C=C=N group. Compound **17** reacts with *tert*-butylamine at the carbon atom of the C=C=N group; the intramolecular cyclization of this compound leads to compound **18** (00ZOR109, 00ZOR33).

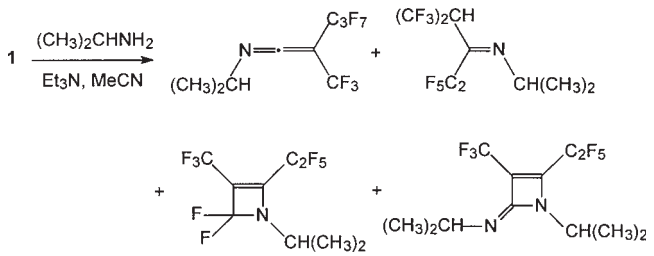


The scheme of transformations may be represented as follows.



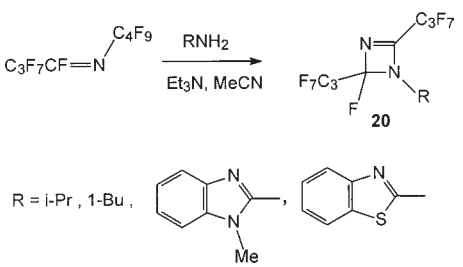
Perfluoro-2-methyl-2-pentene behaves analogously with other sterically hindered amines, for example, isopropylamine. The formation of a four-membered heterocycle in this case may be interpreted by addition at the C=C bond, dehydrofluorination, and replacement of the fluorine atom in the isomerized perfluoro-2-methyl-1-pentene. Subsequent intramolecular

cyclization of compound **17** gives isopropyl[1-isopropyl-4-pentafluoro-ethyl-3-trifluoromethyl-1*H*-azet-2-ylidene]amine (00ZOR109).



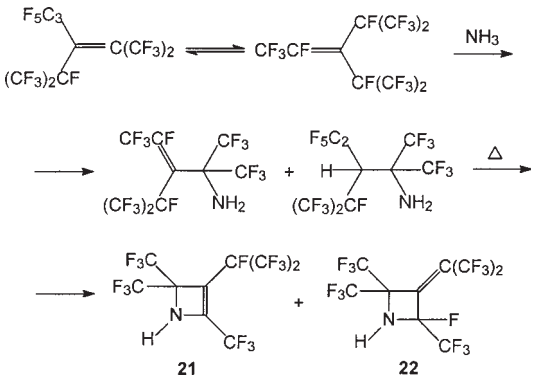
In this case, however, 1-isopropyl-4,4-difluoro-2-hexafluoroethyl-3-trifluoromethyl-1*H*-azetine is formed, which points to a direct reaction of olefin **1** with isopropylamine. This suggests that steric factors play a definite role in this reaction. Indeed, the interaction between olefin **1** and ethylamine is the second route of this reaction. If, however, no isomerization of perfluorolefin takes place under the action of the starting alkylamine, or if a symmetrically substituted structure is formed, then only one heterocyclic compound is obtained. This is realized for perfluoro-5-azanon-4-ene. Irrespective of the character of the nucleophilic reagent, diazete derivative **20** is produced.

The reactions of two equivalents of the 2-amino derivatives of N-methylbenzimidazole and benzothiazole with perfluoro-5-azanon-4-ene give perfluoropropyl derivatives of diazete **20**. The reactions of isopropylamine and *tert*-butylamine with this perfluoroazaalkene probably follow the same route, forming a diazetine ring. These compounds are probably formed by intramolecular nucleophilic cyclization, replacing the fluorine atom at the internal double bond and forming a heterocyclic ring (00ZOR120).

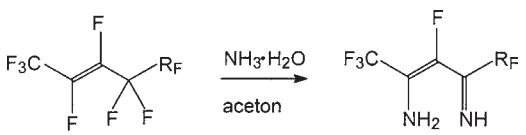


This is a general reaction for primary amines acting as binucleophiles. A special catalyst is not needed, since its role is played by the alkylamine itself. These reactions unambiguously point to a dependence on the reagent and its structure.

Intramolecular cyclization can afford four-membered heterocycles using reactions of perfluoroolefins with ammonia (81IZV2641). Thus in the reaction of a mixture of isomeric trimers of hexafluoropropylene with ammonia, the fluorine atoms at the double bond are substituted in both isomers. The reaction initially gives a mixture of 2-amino-perfluoro-2-methyl-3-isopropyl-3-hydroxypropane and 4-aminoperfluoro-4-methyl-3-isopropyl-pent-2-ene. Subsequent intramolecular cyclization forms 3-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)-2,2,4-tris(trifluoromethyl)-1,2-dihydroazete **21** and 2-fluoro-2,4,4-tris(trifluoromethyl)-3(2,2,2-trifluoro-1-trifluoromethylethylidene)azetine **22**(96JFC(79)97).

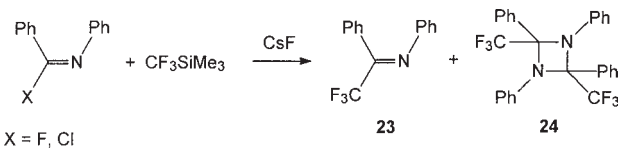


At the same time, linear internal perfluoroolefins react with ammonia, forming exclusively fluorine-containing β-diamines (98UP1).



R_F = CF_3, C_2F_5, C_3F_7, C_4F_9

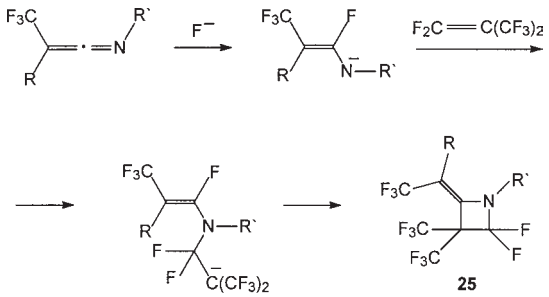
The interaction between (trifluoromethyl)trimethylsilane and *N*-(phenyl)-benzimidoyl chloride (or fluoride) in the presence of a source of the fluoride ion gives *N*-(phenyl)iminotrifluoroacetophenone **23** along with 2,4-di(trifuoromethyl)-2,4-diphenyl-1,3-diazetidine **24** (94UP1).



X = F, Cl

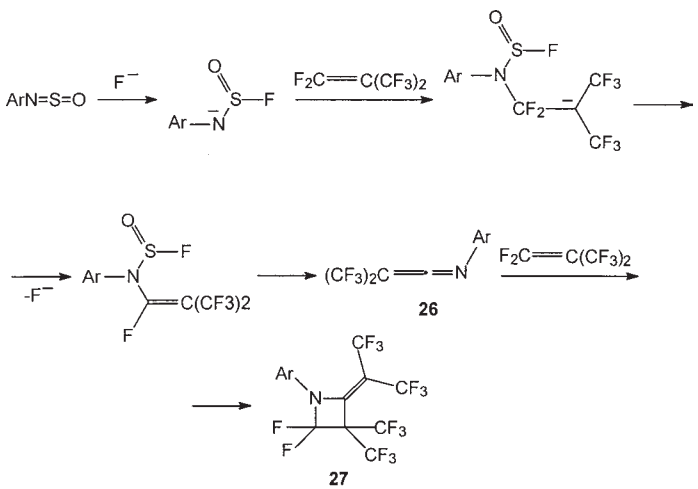
23 24

In the presence of alkaline metal fluorides or tertiary amines, perfluoroolefins react with fluorine-containing keteneimines to form azetidines **25** in mild conditions (76IZV1813). The role of the catalyst seems to be the transformation of the electrophilic keteneimine into the nucleophilic mesomeric anion capable of adding at the multiple bond of the perfluoroolefin. The addition is accompanied by cyclization generating a catalyst.



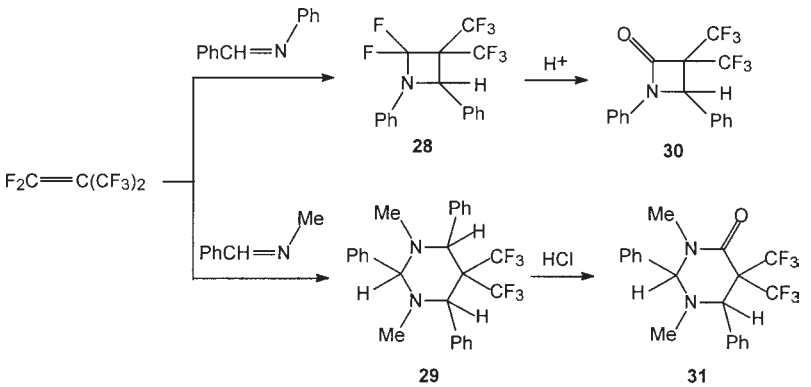
R = CF_3, COOEt

Azetidines are also formed in the reaction of octafluoroisobutylene with N-sulfinyl-amines in the presence of CsF (79IZV396). The initial reaction is vinyl substitution and β-elimination of SOF_2 rather than cycloaddition. The forming keteneimine **26** adds one more octafluoroisobutylene molecules, generating azetidine **27**.

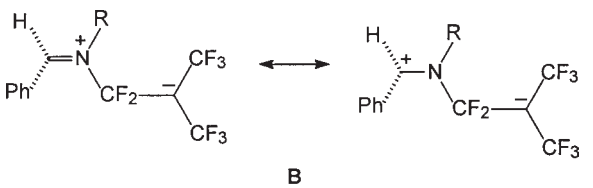


Perfluoroisobutylene reacts with benzalaniline and benzalmethylamine, giving 1,4-diphenyl-2,2-difluoro-3,3-bis(trifluoromethyl)azetidine **28** and

1,3-dimethyl-2,4-diphenyl-5,5-bis(trifluoromethyl)-6,6-difluorohexahydro-1,3-diazine **29**, respectively. In acid media, saponification of the CF_2 group forming compounds **30** and **31**, respectively, takes place.

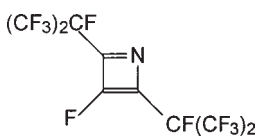


Cycloaddition may be represented in terms of the formation of a dipolar ion B, whose stabilization depends on steric factors and on the character of substituent R. When R = Ph, formation of **B** with cyclization takes place under stringent conditions (200 °C). When R = Me, the nucleophilicity of the nitrogen atom in the compound is much higher, and the reaction occurs without heating, with **B** attacking the second azomethine molecule to form the more favorable six-membered ring.

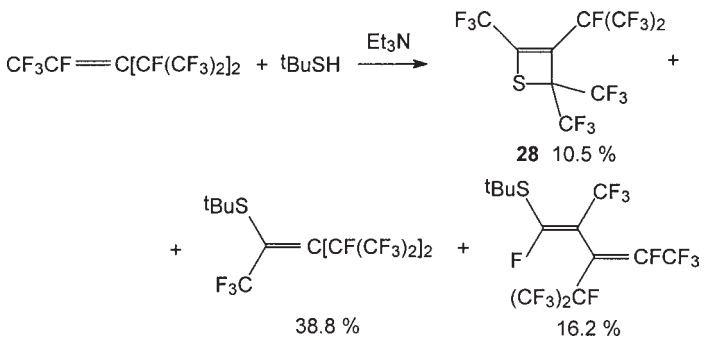


These results clearly demonstrate the importance of steric factors in reactions of perfluoro-2-methylpent-2-ene with primary alkylamines.

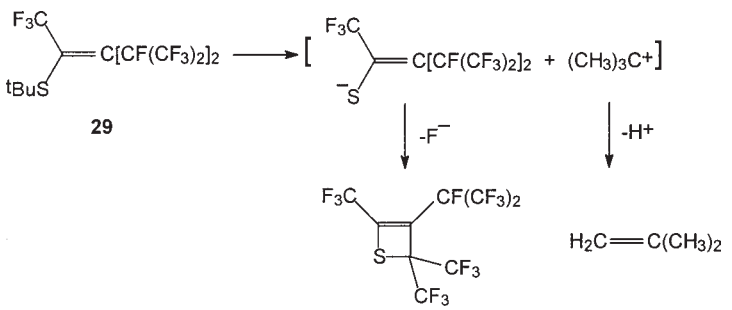
Photolysis of perfluoro(4,6-diisopropyl)-1,2,3-triazine at 77 K gives perfluoro-2,4-diisopropylpyrazete (90JCS(P1)983, 87JCS(CC)1699).



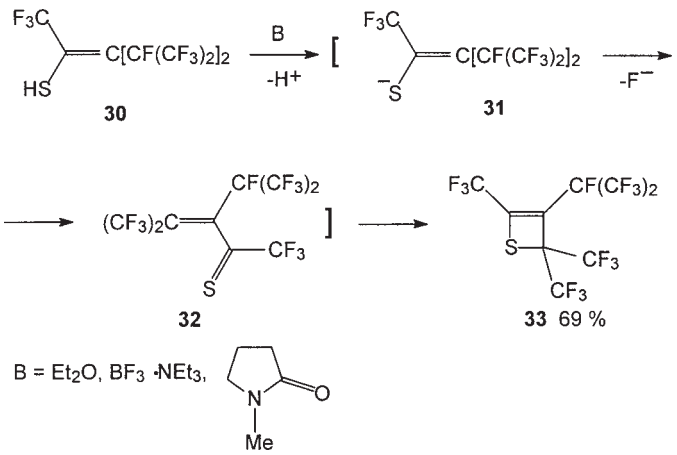
It was assumed (90JFC(48)133, 87IZV957) that perfluoro-2,4,4-trimethyl-3-isopropyl-2-thiete **28** is produced by the reaction of isomeric perfluoro-3-isopropyl-2-methyl-2-pentene with *tert*-butylmercaptan in the presence of triethylamine, which takes place by intramolecular cyclization of the S-nucleophile at the carbon atom of the CF fragment.



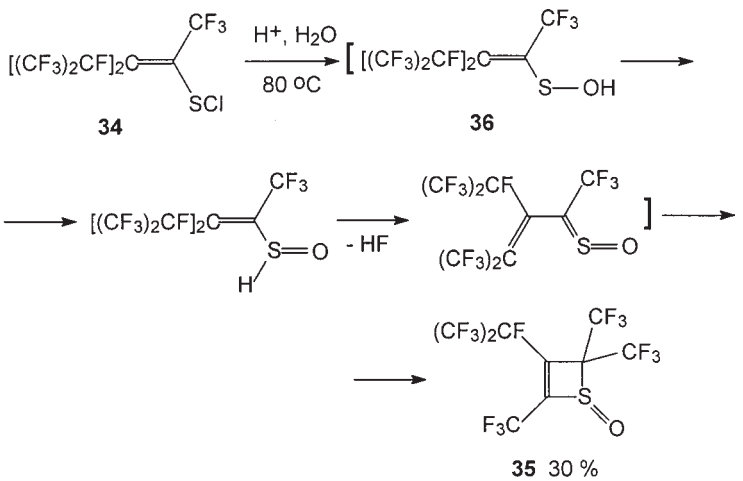
The *tert*-butyl cation generated as a result of C–S bond cleavage in compound **29** gives isobutylene under the reaction conditions.



Perfluoro-3-isopropyl-4-methyl-2-thiolpent-2-ene **30** is deprotonated by bases (Et_2O, BF_3NEt_3, NEt_3), giving the intermediate anion **31**. The latter may be stabilized by elimination of the fluoride ion from the γ-position, giving hetero-1,3-diene **32**, which is probably more thermodynamically stable than the four-membered isomer. Compound **32** gives perfluoro-3-isopropyl-2,4,4-trimethylthiete **33** as a reaction product (yield 69%) (89IZV1380).



Hydrolysis of perfluoro-3-isopropyl-4-methylpentenyl-2-sulfenyl chloride **34** having a mobile allyl fluorine atom ends with the formation of perfluoro-2,4,4-trimethyl-3-isopropylthiete **35** (yield 30%) (89IZV1380). The reaction occurs via the intermediate formation of the derivative of sulfenic acid **36** due to the high mobility of the allylic fluorine atom.



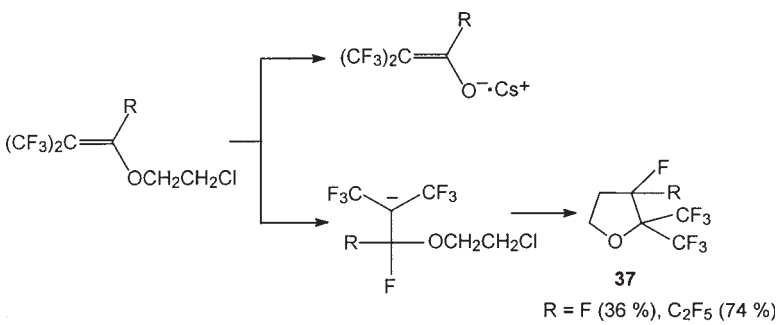
These examples demonstrate the efficiency of the activated double bonds with functional groups for the syntheses of various heterocyclic compounds with perfluoroalkyl groups when binucleophilic regents are

used. In this case, the effect of fluorine on the properties of functional groups is of critical importance.

C. Methods for the Synthesis of Five-Membered Heterocyclic Compounds

Alkylperfluoroalkenyl ethers are easily cleaved at the oxygen–carbon bond by various nucleophilic agents, including the fluoride ion, forming the corresponding enolates (81IZV2641). The competing reaction leads to fluorine-containing tetrahydrofurans. For example, 2-trifluromethyl-1-β-chloroethoxy-1,3,3,3-tetrafluoroprop-1-ene is converted by cesium fluoride into 1,1-difluoro-2,2-bis(trifluoromethyl)tetrahydrofuran. The addition of the fluoride ion at the double bond of the vinyl ether probably generates the carbanion, which participates in an intramolecular nucleophilic cyclization involving the CH_2Cl group.

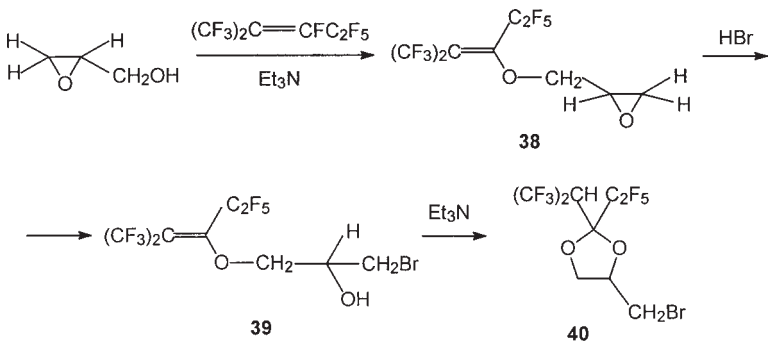
In the case of the reaction of perfluoro-2-methylpent-2-ene with epichlorohydrin in the presence of CsF or triethylamine in an aprotic dipolar solvent (diglyme, acetonitrile), tetrahydrofuran derivative **37** is formed (81IZV1085). Here the fluoride ion adds to the multiple bond, forming a C-nucleophile, which then reacts with epichlorohydrin, replacing chlorine and cleaving the epoxide ring at the O–CH bond. The intermediate O-nucleophile undergoes intramolecular nucleophilic cyclization, replacing the fluorine atom of the CF_2 fragment.



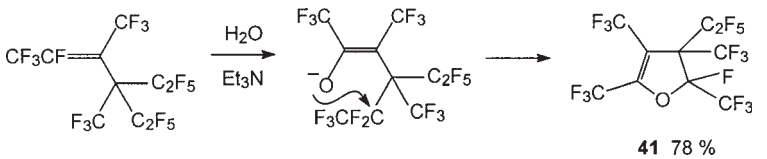
37

R = F (36 %), C_2F_5 (74 %)

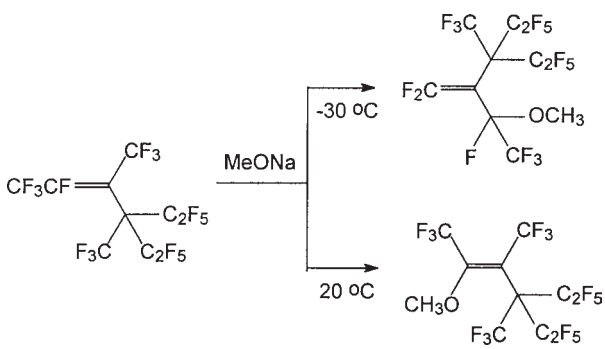
When perfluoro-2-methylpent-2-ene reacts with glycidol, the initially formed product is vinyl ether **38**, whose epoxide ring opens under the action of mineral acids (8% HBr, 33% HCl). Alcohol **39** formed in the course of ring cleavage is readily cyclized into 1,3-dioxolane **40** in the presence of catalytic amounts of NEt_3.



The tetrafluoroethylene pentamer reacts with aqueous triethylamine, giving dihydrofuran derivative **41** (79JCS(P1)214).



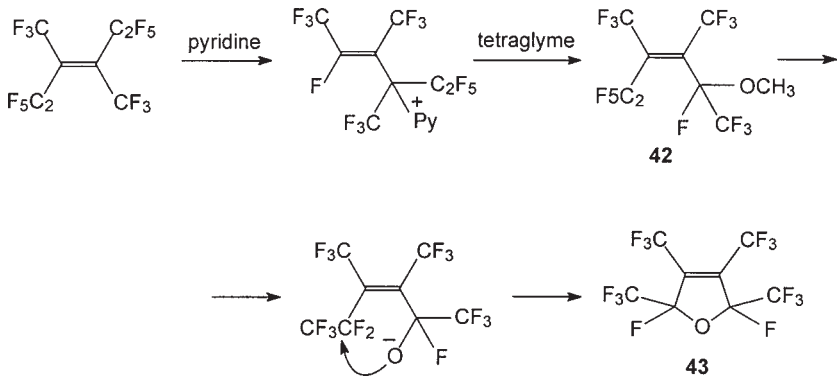
Note that the reaction of the tetrafluoroethylene pentamer with the alkoxide anion at low temperatures (−30 to −40 °C) yields the kinetically controlled product, whereas the thermodynamically controlled product is obtained at 20 °C (94JFC(67)95, 88CJC446).



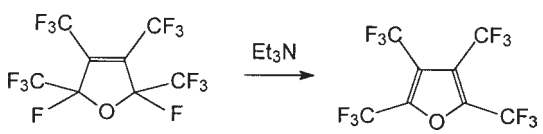
In the case of the reactions with amines, the corresponding heterocycle is produced (94JFC(67)95, 88CJC446).

The reaction of *trans*-perfluoro-3,4-dimethylhex-3-ene with methanol in tetraglyme in the presence of CsF starts with a nucleophilic attack at the

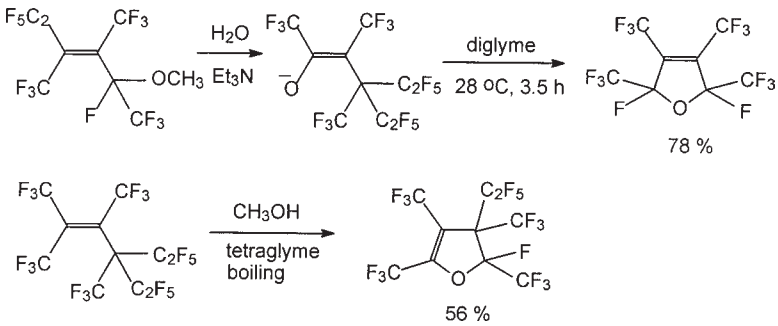
multiple bond, forming 2-methoxy-4-dimethylhex-3-ene **42**. The O–C bond is split with generation of an O-nucleophilic center involved in the intramolecular cyclization forming *trans*-perfluoro-2,5-hydro-2,3,4,5-tetramethylfuran **43** (yield 34–43%) (79JCS(P1)214).



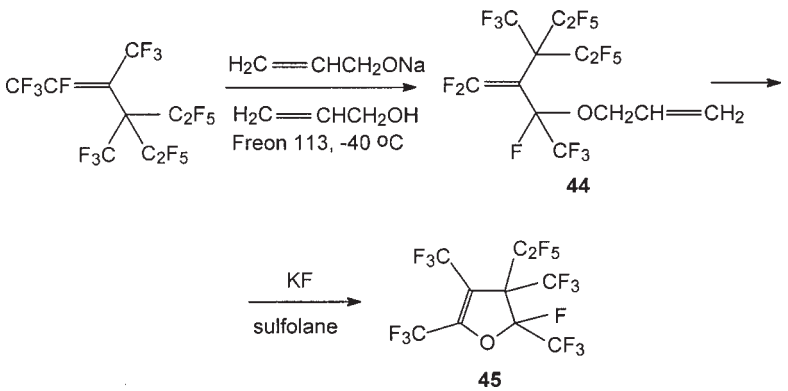
The process probably involves the intermediate O-anion of the nucleophile generated by C–O bond cleavage in ether **42**, reacting further at the carbon atom of the CF_2 group. This cyclization is promoted by triethylamine, leading to the formation of perfluorotetramethylfuran (yield 41%), not readily accessible by conventional methods (79JCS(P1)214).



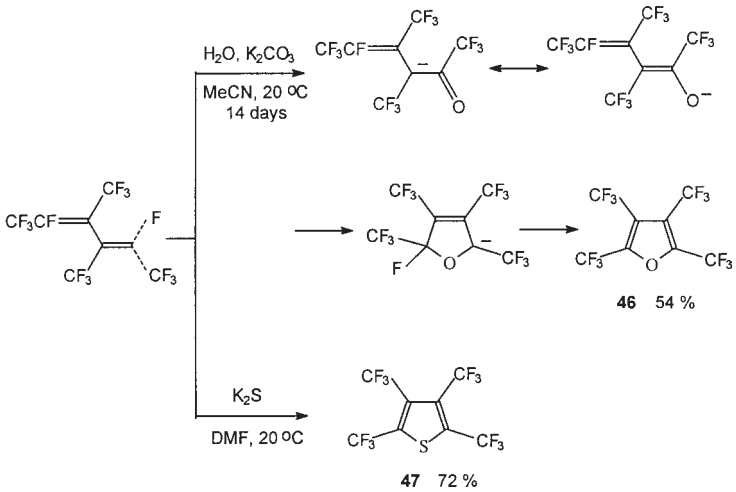
In another example, 2-methoxyperfluoro-3,4-dimethyl-4-ethylhex-2-ene reacts with pyridine or CsF, or with water in the presence of triethylamine, forming perfluoro-2,5-dihydro-2,3,4,5-tetramethylfurans (79USP983009). The reaction occurs via the intermediate formation of the O-anion, involved in intramolecular nucleophilic attack of the O-nucleophilic center at the difluoromethylene group. Perfluoro-3,4-dimethylhex-2-ene behaves analogously with methanol in the presence of pyridine (or triethylamine, or trimethylamine).



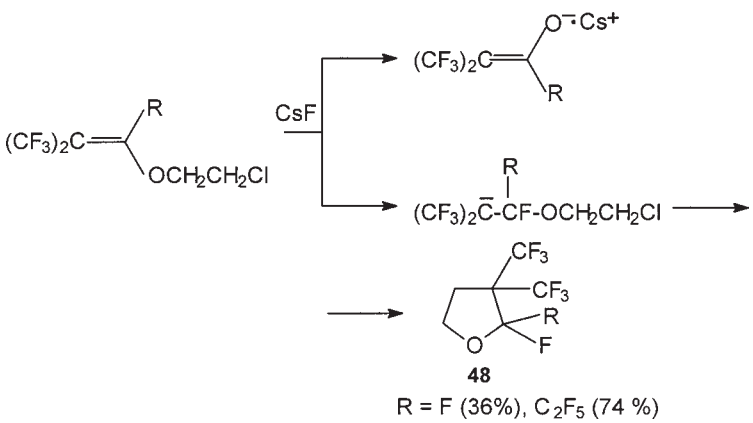
In this case, a mixture of *cis*- and *trans*-perfluoro-4,5-dihydro-2,3,4,5-tetramethyl-4-ethylfurans is obtained. This is a general reaction, which also works with other perfluoroolefins and alcohols. For example, when the tetrafluoroethylene pentamer reacts with allyl alcohol in the presence of bases, the initial reaction is nucleophilic addition at the multiple bond, forming olefin **44**, followed by the formation of perfluoro-4-ethyl-2,3,4,5-tetramethyl-4,5-dihydrofuran **45** in the presence of KF (87ASCC31).



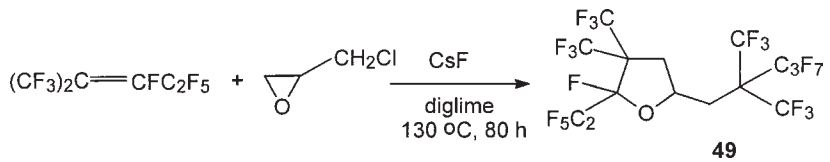
Hydrolysis is probably a more complex process, since 3,4-bis(trifluoromethyl)perfluorohexa-2,4-diene gives a cyclic product—perfluorotetramethylfuran **46** (94JCS(P1)3119, 90JCS(CC)1127). The reaction involves vinyl substitution of fluorine with subsequent fast electrocyclization of the intermediate carbanion accompanied by fluoride ion elimination. An analogous reaction of 3,4-bis(trifluoromethyl)perfluorohexa-2,4-diene with sodium sulfide or thiourea forms perfluorotetramethylthiophene **47** (90JCS(CC)1127).



If a molecule has a multiple bond and a nucleophilically mobile chlorine atom, then the fluoride ion attacks the double bond, generating a carbanion stabilized by two trifluoromethyl groups, and intramolecular nucleophilic cyclization forming a five-membered heterocycle **48** is possible.

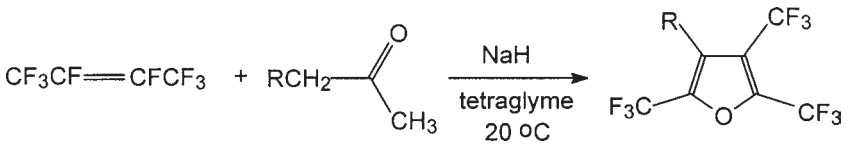


The interaction of perfluoro-2-methylpent-2-ene and epichlorohydrin in the presence of CsF or triethylamine in aprotic solvents forms tetrahydrofuran **49**. The reaction occurs by cleavage of the epoxide ring under the action of the fluoride ion generating an O-nucleophilic center, which reacts at the multiple bond of the perfluoroolefin. Further cyclization the new terminal double bond gives the final reaction product.



49

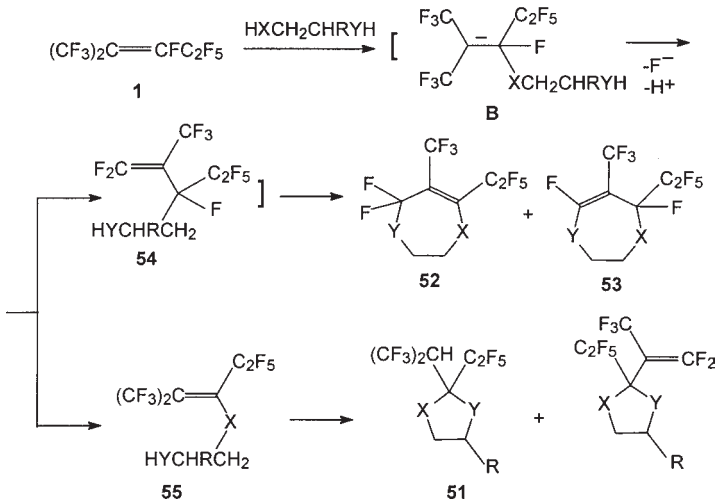
The nucleophile may be alkylacetoacetal, which reacts with perfluorobut-2-ene in the presence of sodium hydride at room temperature, forming 2,3-bis(trifluoromethyl)-4-methylfuran **50** (83JCS(P1)1239).



50

The authors explained the formation of these compounds as follows. The O-nucleophile initially attacks the C=C bond of the perfluoroolefin, forming a carbanion. The latter may be stabilized by elimination of the fluoride ion from the γ-position of the CF_2 fragment, giving a multiple bond. The olefin has a mobile fluorine atom in the allyl position, leading to intramolecular nucleophilic cyclization induced by the O- or N-nucleophiles. This process may be regarded as an example of the important role of the intermediate from the highly active perfluoroolefin, determining the direction of the subsequent attack of the O- and N-nucleophiles.

The interaction of perfluoro-2-methylpent-2-ene with ethyleneglycol under conditions of nucleophilic catalysis by bases (CsF, NEt_3, NaOH) leads to the formation of intermediate carbanion **B**, stabilized by fluoride ion elimination, forming compound **51**, the product of formal substitution of the fluorine atom at the multiple bond of olefin **1**. The multiple bond in **51** bears a substituent possessing electron-donor properties. Further intramolecular nucleophilic cyclization affects the α-carbon atom of this multiple bond, leading to the formation of a five-membered heterocycle—2-pentafluoroethyl-2-hexafluoroisopropyl-1,3-dioxolane **51**—as the major reaction product (85IZV2066, 96ZOB1995). In addition, the reaction gives 5-pentafluoroethyl-5-perfluoro-(2′-methyl) ethinyl-1,3-dioxolane.



X = Y = O, R = H, Me; X = S, Y = O, R = H; X = Y = S, R = H

Elimination of the fluoride ion from the CF_3 group of carbanion **B** leads to the formation of olefin **54** with a terminal multiple bond. Intramolecular cyclization of olefin **54** gives a minor amount (5%) of seven-membered heterocycles: 5-pentafluoroethyl-6-trifluoromethyl-5,7-difluoro-1,4-dioxacycloheptene-6 **52** and 5-pentafluoroethyl-6-trifluoromethyl-7,7-difluoro-1,4-dioxacycloheptene-5 **53**.

The same situation is observed for binucleophiles with O- and S-atoms (2-mercaptoethanol, dithioglycol, glycidol, 1,2-propyleneglycol). The interaction of perfluoroolefins with bifunctional nucleophiles leads to 1,3-dioxolane and 1,4-dioxepin (85NKK1974). Generation of aromatic structures using this methodology has not been fully covered in the literature (73USP3749793). The initial act of the reaction is the addition of the O-nucleophilic center (or the S- or N-nucleophile $HXCH_2CH_2RYH$) of ethyleneglycol at the double bond forming carbanion **B**; the latter may be stabilized by fluoride ion elimination from the α-CF or α-CF_3 group. The product is compound **54** in the former case and **55** in the latter. Then the intramolecular interaction of the HO group or the alkoxy anion with the electrophilic center of the molecule leads to the five- and seven-membered heterocycles. The ratio between these heterocycles depends heavily on the nature of the solvent used and the nucleophilic reagent. The higher the nucleophilicity of the nucleophile, the higher the yield of the compound (Tables II and III).

The formation of the perfluoroalkyl derivatives of 1,3-dioxolane in reactions of perfluoroolefins with ethyleneglycol is a general process. It was

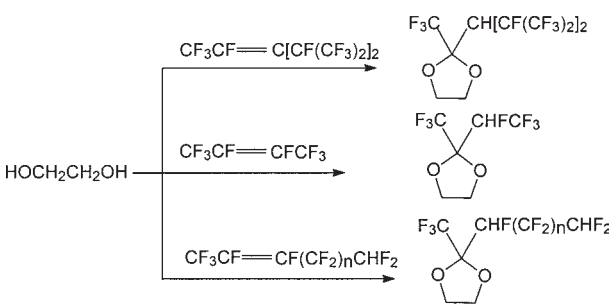
Table II. Dependence of the Ratio of the Products of the Reaction between Perfluoro-2-methylpent-2-ene and Ethylene Glycol in the Presence of NEt_3 in Various Solvents (85IZV2066)

	Ratio of products (%)	
Solvent	**51**	**52 + 53**
Dimethylformamide	81	19
Hexamethylphosphoramide	77	23
Dimethylsulfoxide	74	26
Ethyl acetate	53	47
Diglyme	52	48
CH_3CN	72	28
Diethyl ether	40	60
Dioxan	39	61

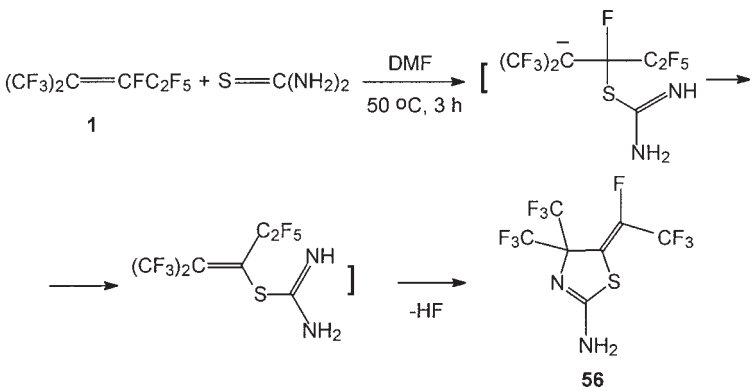
Table III. Dependence of the Ratio of the Products of Nucleophilic Reactions of Perfluoro-2-methylpent-2-ene on the Type of Nucleophile (in Diethyl ether) (85IZV2066)

	Ratio of products (%)	
Nucleophile	**51**	**52 + 53**
$HOCH_2CH_2OH$	40	60
$HOCH_2CH(CH_3)OH$	48	52
$HOCH_2CH_2SH$	83	17
$HSCH_2CH_2SH$	86	14

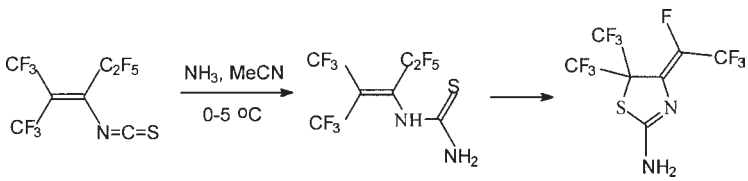
performed with the hexafluoropropylene trimer, ω-hydroperfluorooct-2-ene, ω-hydroperfluorononon-2-ene (96ZOB1995), and perfluorobut-2-ene (73USP3749793).



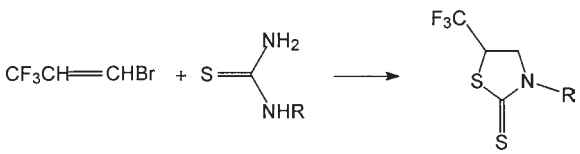
The reactions of perfluoroolefins with ambidentate nucleophiles leads to substitution of the fluorine atom at the double bond. As mentioned above, stabilization of carbanion **A** may occur via the olefin (route **b**) produced by fluorine elimination from the CF fragment. If the entering functional fragment is an electron-accepting substituent with respect to the olefin moiety, it creates a significant positive charge on the β-carbon atom. Then the presence of another nucleophilic center in this functional fragment will lead to intramolecular nucleophilic cyclization involving the β-carbon atom of the multiple bond and to the formation of a five-membered heterocycle (route **d**). Thus, the interaction between perfluoro-2-methylpent-2-ene and thiourea in dimethylformamide (MeCN, DMSO, sulfolane) at 50 °C gives an intermediate olefin having a group with weak electron-accepting properties at the multiple bond. Therefore, intramolecular cyclization occurs by an attack of the free amino group at the β-carbon atom of the multiple bond, giving 2-aminoperfluoro-4,4-dimethyl-4,5-dihydro-5-ethylidene-1,3-thiazole **56** in the *E*-configuration. The structure was confirmed by X-ray analysis (93KGS253, 92JFC(58)179, 93JPP05-04979, 92HAC101).



Note that for the synthesis of heterocyclic compounds one need not have an **a**–**b**–**c** triad in the substrate; it is essential that the triad be formed in the course of the reaction with perfluoroolefins. This is natural since substituted thioureas must exhibit the same properties as thiourea itself. This was verified by reference to the reaction of perfluoro-2-methyl-3-isothiocyanatepent-2-ene with ammonia. When ammonia attacks the carbon atom of the N=C=S group, a derivative of thiourea having an **a**–**b**–**c** triad is formed; subsequent intermolecular cyclization can occur via an attack of the S-nucleophilic centers at the multiple bond, forming isomeric compound **56** (03UP1).



It was shown (78JFC(12)193) that the product of the reaction of perfluoro-2-methylpent-2-ene with potassium ethyldithiocarbamate in dimethylformamide is 5,5-bis(trifluoromethyl)-5-(tetrafluoroethylidene)-2-fluoro-2-ethoxy-1,3-dithiolane. Analogously, the reaction of 1,1,1-trifluoro-methyl-2-bromoprop-2-ene with thiourea and its N-substituted derivatives yields 5-trifluoromethyl-2-thione-thiazolidines **57** (92JFC(58)365).



57

These examples demonstrate the efficiency of using the C=C double bond for heterocycle formation. In this case, the intramolecular nucleophilic cyclization involves the nucleophilic center of the nucleophile at the double bond of the functional fragment together with the heteronucleophile generated in the course of the reaction under conditions of nucleophilic catalysis by the fluoride ion.

1-N-Aryl derivatives of azoles containing perfluoroalkyl groups are of interest as intermediates in the syntheses of potentially bioactive substances useful for the creation of pharmaceuticals and agrochemicals (00JFC(104)263, 98HS355, 95CEN39). They are generally synthesized by introducing perfluoroalkyl groups on the heterocycle by using various techniques (92M10, 96T8619, 93M8). In recent years, a new approach has been developed, which is based on reactions of accessible and commercially available perfluoroolefins with binucleophilic reagents (85JCO3640, 88JAP(K)63 162663, 80CL583, 87RP1456418, 89RP1456419, 93M8, 89JAP(K)01 22855, 90IZV2583, 99JFC(98)29, 94IZV2039, 94IZV 1838, 91IZV1463, 89IZV116, 01UP1). It was shown (99JFC(98)29) that reactions between perfluoro-2-methylpent-2-ene and arylhydrazines in the presence of triethylamine give 1-aryl derivatives of pyrazole. The key step of this process is the intermediate formation of a conjugated system of bonds C=C–C=N. The intramolecular nucleophilic cyclization, which occurs in this intermediate, leads to the formation of a five-membered heterocycle.

1-H-Pyrazoles and their derivatives with a few CF_3 groups possess increased biological activity and are used in medicine and in agrochemical production (77M12, 75JOC810, 96EJP341, 97JMC547, 92LAC947, 97JMC547, 91JFC(55)199, 94JMC2411, 90JAP(K)02 129171, 90EP295117). Regioselective substitution of hydrogen by a perfluoroalkyl group or fluorine in a heterocyclic system produces a substantial effect on the biological and physical properties of the molecule (84JSOC775, 84JSOC809). As a result, more publications have recently appeared dealing with syntheses of fluorine-containing heterocyclic compounds using binucleophilic reagents and the double bond of perfluoroolefins. Thus the reactions perfluoro-2-methylpent-2-ene react with 2-mercaptobenzimidazole, 2-mercaptobenzimidazole, 1,4,5,6-tetrahydropyrimidine-2-thione, 1,2,4-triazole-3-thione, form novel five-membered heterocycles containing perfluoroalkyl groups (Table IV).

In the thione–thiol equilibrium for these reagents, the thiol form is more reactive; it attacks the carbon atom of the multiple bond, and the stabilized carbanion generates a multiple bond. Subsequent intramolecular cyclization involving the nitrogen atom of the binucleophile leads to the product.

Perfluoro-2-methylpent-2-ene reacts with hydrazones in the presence of sodium carbonate in tetrahydrofuran at 0 °C, giving an azine in a yield of 35% (85JCO3640, 88JAP(K)63 162663, 80CL583). These azines are transformed into pyrazoles on heating with a mixture of sodium carbonate and cesium fluoride in dioxane at 100 °C. Cyclization to pyrazoles may be understood in terms of fluoride ion attack at the intermediate containing a system of conjugated multiple bonds (route **a**). When heated in the presence of sodium carbonate without cesium fluoride, azines reacted slowly and led to methanes with pyrazole rings (route **c**).

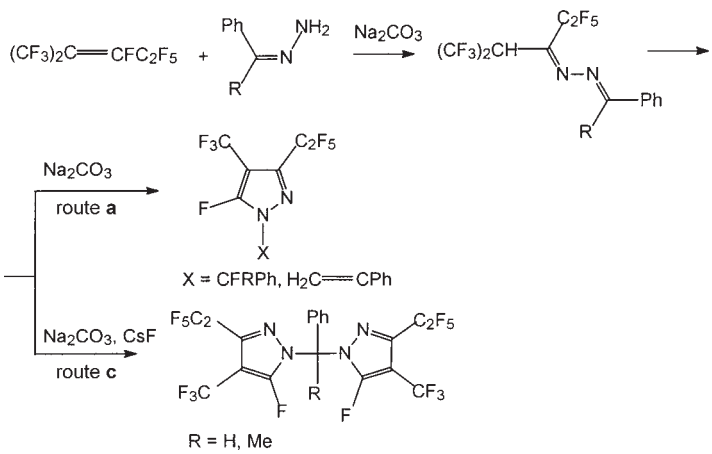
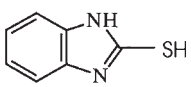
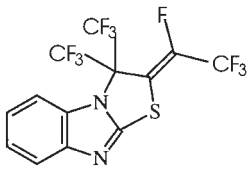
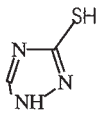
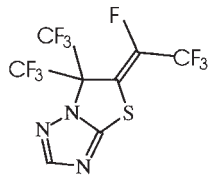
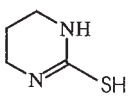
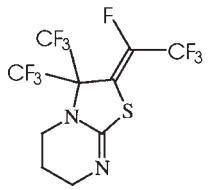
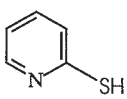
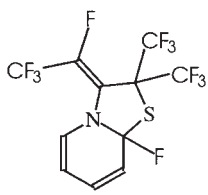
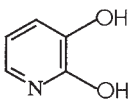
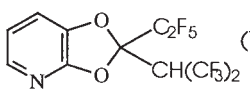
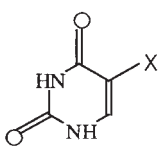
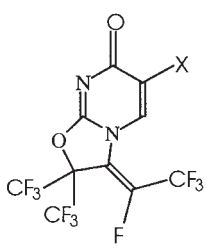


Table IV. PRODUCTS OF THE REACTION OF PERFLUORO-2-METHYLPENT-2-ENE WITH BINUCLEOPHILES

Nucleophile	Product (Isolated yield, %)	References
	 (80)*	02BKCS1017
	 (50)	03ZOB00
	 (57)	03ZOB00
	 (51)	03ZOB00
	 (70)	03ZPC00
 X = H X = F	 (64) (53)	03IZV00

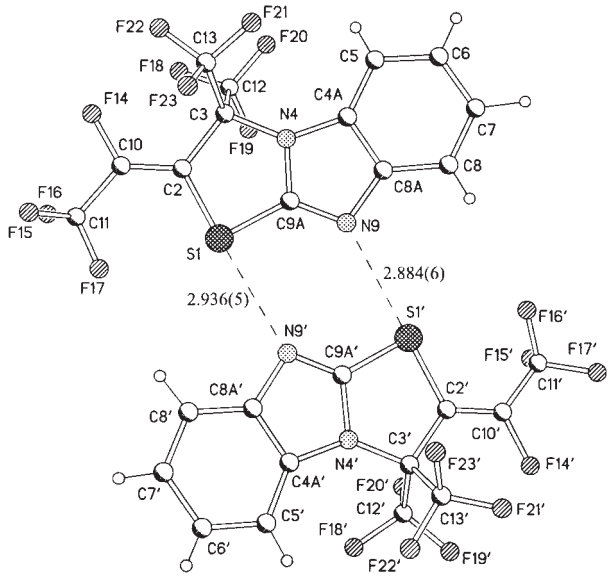
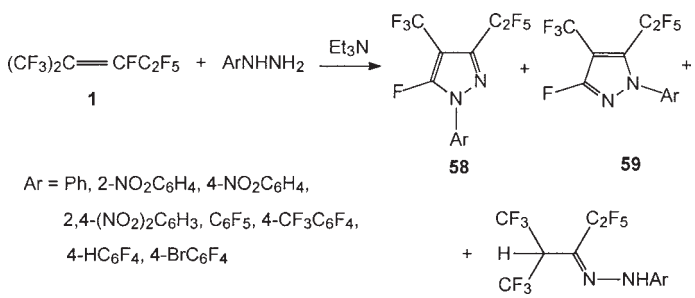


Fig. 2. Crystal structure 2-tetrafluoroethylidene-3,3-bis(trifluoromethyl)-2,3-dihydrobenzo-[4,5]imidazo[2,1-*b*]thiazole according to X-ray analysis (01 1ZV457), cf. also (02BKCS1017).

Based on the assumptions about the reaction mechanism, one can predict that this technique will be applicable to other binucleophiles for the synthesis of perfluoroalkylated heterocyclic compounds. For example, the reaction of arylhydrazine with perfluoro-2-methylpent-2-ene in the presence of triethylamine led to N-arylperfluoro-3-ethyl-4-methylpyrazole **58** and N-arylperfluoro-4-methyl-5-ethylpyrazole **59** in different ratios depending on the reaction conditions (89RP1456419, 87RP1456418, 90IZV2583; 89JAP(K)01 22855; 99JFC(98)29). *Syn*- and *anti*-aminoimines are intermediates in syntheses of pyrazoles; they were isolated individually. On heating in the presence of triethylamine they are transformed into mixtures of **58** and **59**.



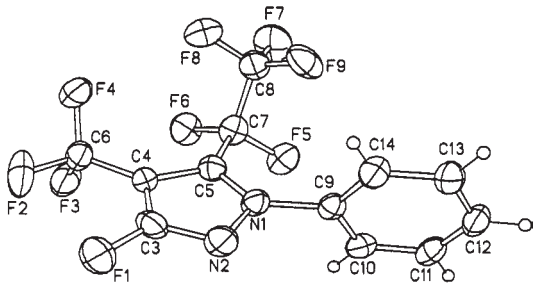
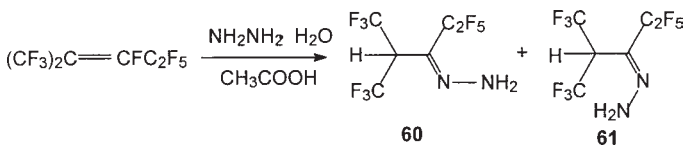


Fig. 3. Crystal structure of N-phenylperfluoro-4-methyl-5-ethylpyrazole **59** according to X-ray analysis (99JFC(98)29).

The structure of N-phenylperfluoro-4-methyl-5-ethylpyrazole **59** was confirmed by X-ray analysis (Fig. 3) (99JFC(98)29).

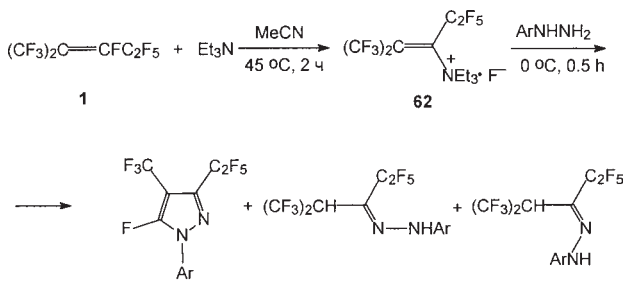
Polyfluorinated arylhydrazines proved to be sufficiently active nucleophilic reagents in reactions with perfluoro-2-methylpent-2-ene, giving fluorine-containing pyrazoles.

At the same time, the interaction between perfluoro-2-methylpent-2-ene and hydrazine hydrate under the same conditions leads to the formation of the imine of the corresponding ketones **60** and **61**.



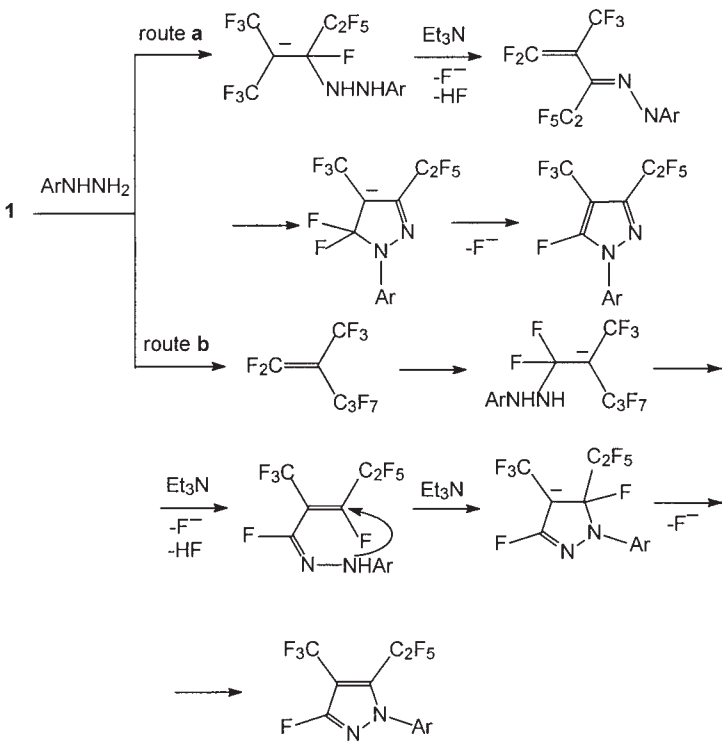
60 **61**

The reaction rate decreases dramatically when the benzene ring contains nitro groups. The reaction is accelerated by using the prior formation of perfluoroalkenyltriethylammonium salt **62**, which is much more electrophilic than the starting perfluoroolefin.

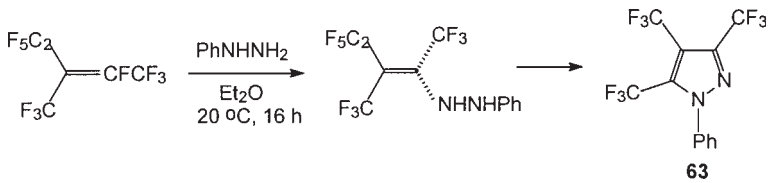


Ar = 2,4-$(NO_2)_2C_6H_3$, 4-$NO_2C_6H_4$, C_6F_5,
4-$CF_3C_6F_4$, 2-$NO_2C_6H_4$

It is believed that the reactions of perfluoro-2-methylpent-2-ene with arylhydrazines proceeds according to the following scheme (89RP1456419). The reaction initially forms the product of vinyl substitution, which further undergoes prototropic isomerization (enamine is converted into keteneimine), dehydrofluorination (formation of a terminal double bond), and cyclization (formation of a pyrazole ring). According to this scheme, triethylamine affects all three stages. At the first stage, it promotes the initial attack at the activated C=C bond (forming the triethylammonium salt); at the stage of dehydration, HF is eliminated and two equivalents of HF formed in the course of the process are neutralized.

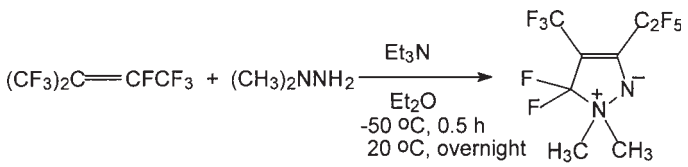


The reaction of the tetrafluoroethylene trimer with phenylhydrazine in the presence of three equivalents of triethylamine leads to the formation of *E* and *Z* octafluoro-3-trifluoromethyl-4-(N-phenylhydrazino)pent-3-enes, which further undergo intramolecular cyclization into 3,4,5-tris(trifluoromethyl)-1-phenylpyrazole **63** (98JFC(88)169).



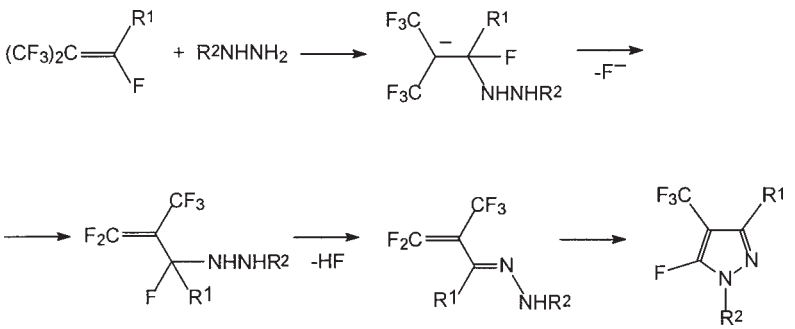
63

In the case of the reaction of perfluoro-2-methylpent-2-ene with 1,1-dimethylhydrazine in the presence of triethylamine as the dehydrofluorinating agent and Et_2O as a solvent at −50 to 0 °C, the product is 5,5-difluoro-1,1-dimethyl-3-pentafluoroethyl-4-trifluoromethyl-1-pyrazolin-2-yl **64** (87RP1456418, 90IZV2583).



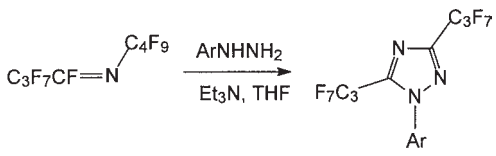
64

The reactions of 1,1-bis(trifluoromethyl)-2-fluoroethylene with compounds having two nucleophilic centers leads to the formation of five-membered heterocycles (90IZV2583, 88S194).



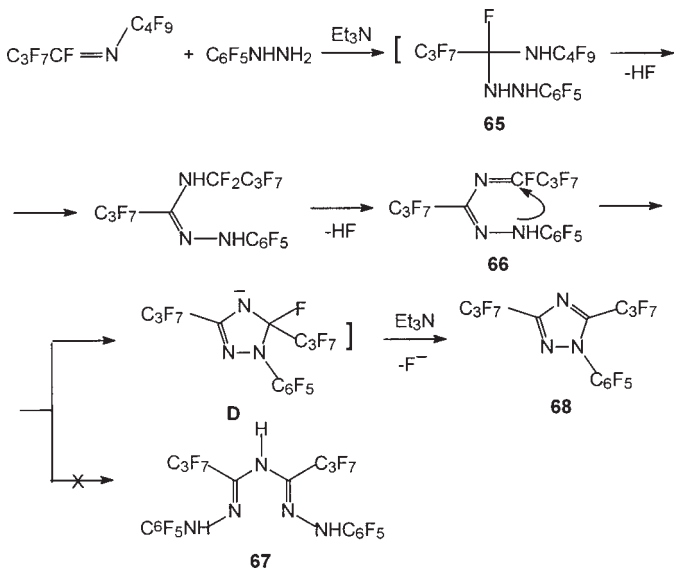
In this case, another multiple bond is generated in the course of the reaction, and the compound acts as some kind of a 1,3-dielectrophile.

The interaction between perfluoro-5-azanon-4-ene and arylhydrazines in the presence of triethylamine in tetrahydrofuran under very mild conditions forms 1-aryl-3,5-bis(heptafluoropropyl)-1*H*-[1.2.4]triazoles (01ZOR1693, 01IZV457).



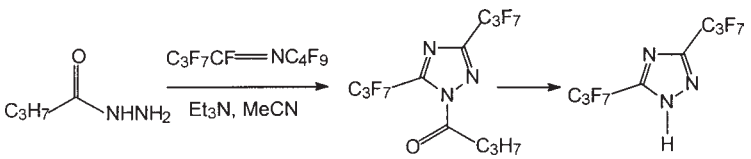
Ar = Ph, 2-$NO_2C_6H_4$, 2,4-$(NO_2)_2C_6H_3$, C_6F_5,
4-HC_6F_4, 4-BrC_6F_4, 4-$CF_3C_6F_4$, 4,4`-$H_2C_{12}F_8$

The [1.2.4]triazoles are possibly formed according to the following scheme. Pentafluorophenylhydrazine attacks by its N-nucleophilic center located on the NH_2 fragment of the hydrazine group, forming compound **65**. In the presence of triethylamine, the hydrogen fluoride molecule may be eliminated to form compound **66**. Further transformation is either by fluorine substitution at the C=N bond by the hydrazine group and transformation of this compound into dihydrazone **67**, or by intramolecular nucleophilic cyclization forming compound **68**.

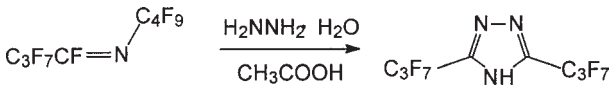


The nature of aryl ring is immaterial to the process under these conditions. In the case of 4,4′-dihydrazinooctafluorodiphenyl, triazole rings are formed from two hydrazine groups.

Butanoic acid hydrazide reacts with perfluoro-5-azanon-4-ene in the presence of triethylamine in acetonitrile, forming bis(heptafluoropropyl)-1*H*-[1.2.4]triazole.

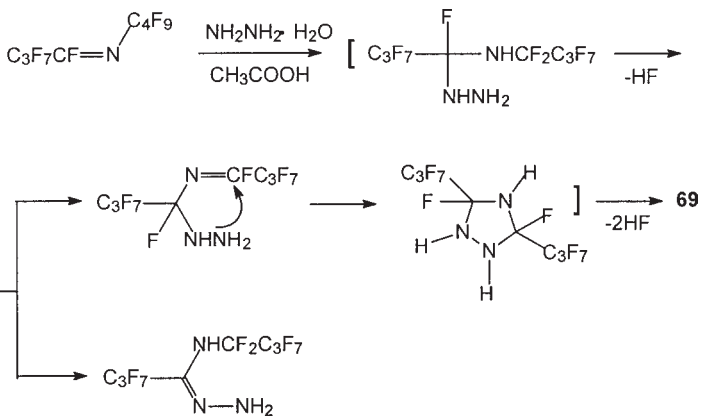


When hydrazine hydrate reacts with perfluoro-5-azanon-4-ene in acetic acid, the product of cyclization is triazole[1.3.4] **69** (yield 42%) (01ZOR1693). For thermodynamic reasons, the formation of the triazole ring is preferable to the formation of the [1.2.4]triazole derivative.

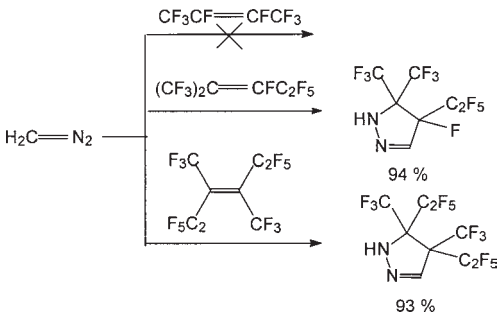


69

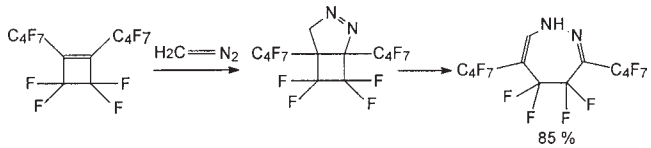
The reaction scheme is as follows:



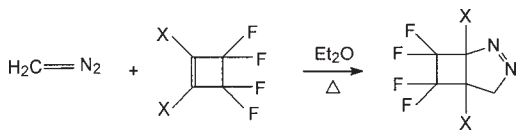
Unsaturated electron-deficient compounds are excellent dipolarophiles. This is especially true for fluorinated alkenes, in which the perfluoroalkyl group lies at the multiple bond. They react with diazomethane, forming heterocyclic compounds. The nature of the perfluoroalkyl group, however, plays an important role. Thus perfluorobut-2-ene is unreactive with diazomethane, whereas perfluoroolefins with sterically hindered perfluoroalkyl groups give cycloaddition products in high yields (83JCS(CC)5).



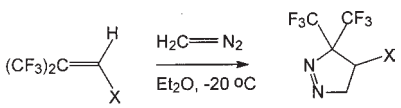
A seven-membered heterocycle is formed from the bicyclic heterocycle initially produced by the reaction of fluorine-containing cyclobutene with diazomethane due to a rearrangement leading to a high yield of the product (83JCS(CC)5).



It should be noted that the nature of the substituent other than fluorine at the multiple bond has a considerable effect on the rate of the reaction between the substituted polyfluorocyclobutene and diazomethane. Thus when X = H, the reaction time is 5 min (yield 71%) (83TL4047, 89T39); when X = F, the reaction rate is drastically decelerated, and a comparable yield (55%) is observed after the reaction mixture has been kept for 14 days (84JCS(P1)509).

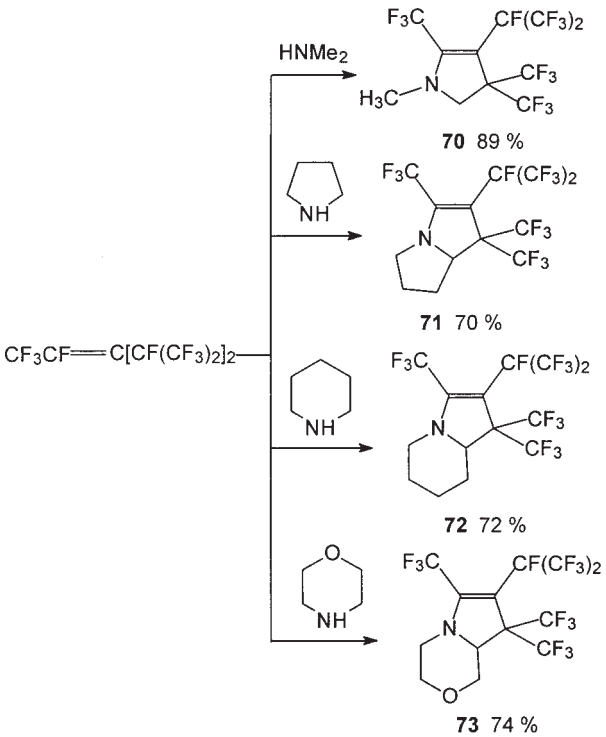


Fluorinated α,β-unsaturated carbonyl compounds acting as dipolarophiles react with diazomethane, giving 1,3-dipolar cycloaddition products with high regioselectivity (76T1995, 00IZV1770).



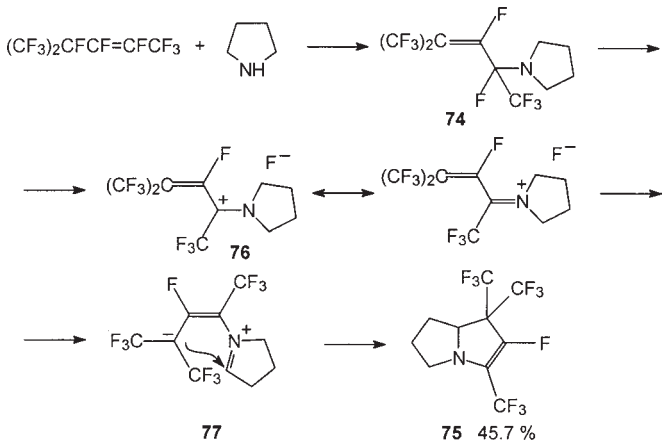
X = COOMe (100 %), COPh (100 %), CN (70 %)

An interesting approach to the synthesis of nitrogen-containing heterocycles with two rings and steric hindrance at the nitrogen atom was developed (90IZV1685, 91JFC(54)221, 83IZV2561, 89JFC(45)152). Thus the reaction between perfluoro-3-isopropyl-4-methylpent-2-ene and secondary amines (dimethylamine, pyrrolidine, etc.) gives the following heterocyclic compounds:1-methyl-4(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)-3,3,5-tris (trifluoro-methyl)-2,3-dihydro-1*H*-pyrrole **70**, 6(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)-5,7,7-tris(trifluoromethyl)-2,3,7,7a-tetrahydro-1*H*-pyrrolizine **71**, 2-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-1,1,3-tris(trifluoromethyl)-1,5,6,7,8,8a-hexahydroindolizine **72**, and 7-(1,1,2,2-tetrafluoro-1-trifluoro-methylethyl)-6,8,8-tris(trifluoromethyl)-3,4,8,8a-tetrafluoro-1*H*-pyrrolo-[2.1-*c*]oxazine **73**.



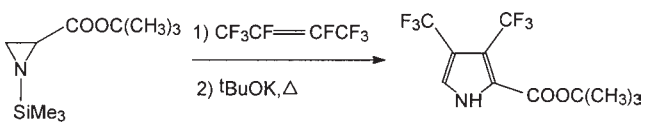
It was found (91JFC(54)221) that the product of interaction between perfluoro-4-methylpent-2-ene and pyrrolidine is 4-pyrrolidineperfluoro-2-methylpent-2-ene **74**. On storage in the absence of bases it is converted into 2,4,4-*tris*-(trifluoromethyl)-3-fluoro-1-azabicyclo-[3.3.0]oct-2-ene **75**. The formation of compound **75** may be explained as follows. The mobile

fluorine atom at the carbon bonded to the nitrogen atom is eliminated in the form of an anion, giving salt **76**. Cation **76** is stabilized by proton elimination from the α-carbon atom of the pyrrolidine ring under the action of the fluoride ion, leading to zwitterion **77**, whose intramolecular nucleophilic cyclization leads to reaction product **75**.

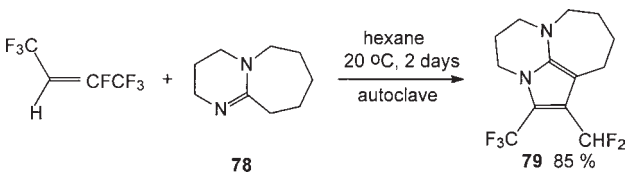


Thus an essential condition for such reactions is the secondary formation of a multiple bond, which is not necessarily a terminal process.

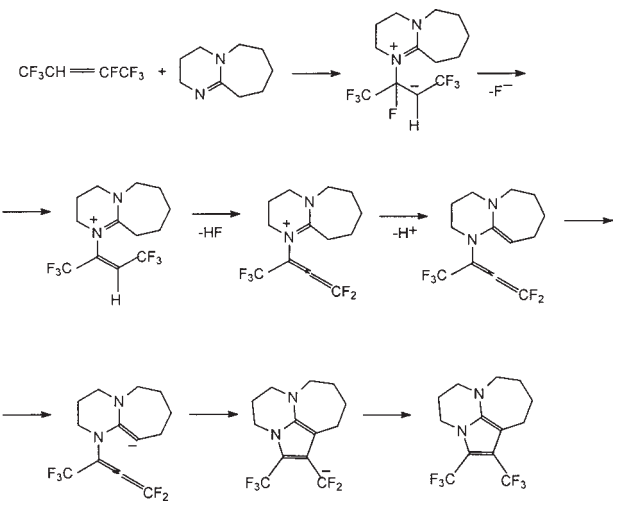
This methodology yields various heterocyclic compounds in reactions using internal perfluoroolefins or systems with conjugated multiple bonds as precursors. Hopefully, this approach will find wide use and new information will permit more profound generalizations. On thermolysis or photolysis aziridines are converted into azomethine ylides, reacting with perfluoroolefins (for example, hexafluoropropylene and perfluorobut-2-ene) to give pyrrole derivatives (autoclave, 160 °C) (76CJC218).



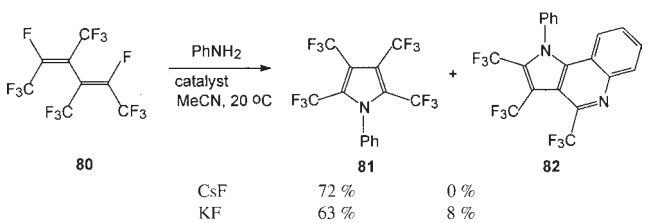
The reaction of 2*H*-heptafluorobut-2-ane with 1,8-diazabicyclo[5.4.0]-undecan-7-ene **78** (reagent ratio 1:4) leads to tricyclic pyrrole—1,9-diaza-bicyclo[5.4.0]undecano-[*a*,*b*-2]-difluoromethyl-3-trifluoromethylpyrrole **79** (96JFC(79)121).



The reaction route seems to be as follows:



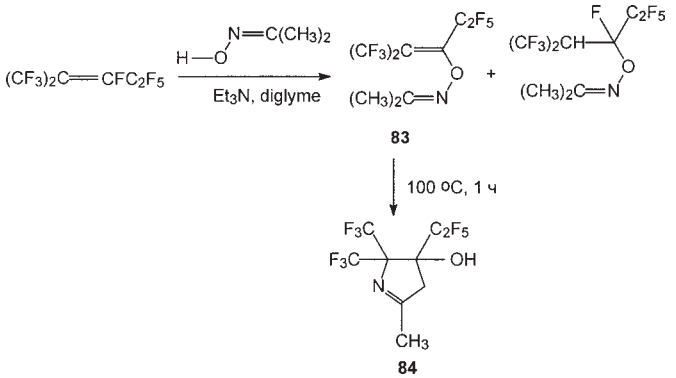
In the case of perfluorodiene **80**, the reaction with aniline in the presence of CsF forms pyrrole **81**; in the presence of KF, small amounts of pyrroloquinoline **82** with a combination of five- and six-membered rings is obtained (94JCS(P1)3119, 97JCS(P1)1457).



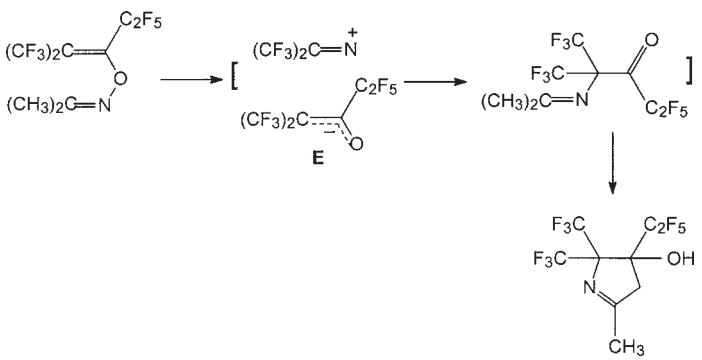
The ratio between **81** and **82** depends on the alkaline metal fluoride used. Thus if cesium fluoride is employed, the product is **81** alone, whereas in the case of potassium fluoride, **81** and **82** are formed, the ratio between these compounds depending on the nature of substituent in the benzene ring C_6H_5X: for KF, 20 °C, MeCN (the values in parentheses are yields of **81** and

82) MeCN: X = H (62; 27%), 4-Me_2N (81; –%), 4-MeO (73; 21%), 2-MeO (37; 37%), 3-MeO (50; 19%), 4-F (45; 52%), 4-Cl (18; –%), NO_2 (79; –%).

Another interesting process was found (94IZV1068, 94IZV1073, 94IZV1449). Investigation of the reaction of perfluoro-2-methylpent-2-ene with acetone oxime showed that the acetone oxime ether 3-perfluoro-2-methylpent-2-en-2-yl **83** formed initially reacts at 100 °C for 1 h, giving 4-hydroxy-3-methyl-5,5-bis(trifluoromethyl)-4-pentafluoroethylpyrrolone-1 **84** in quantitative yield; the structure of this product was confirmed by X-ray analysis.

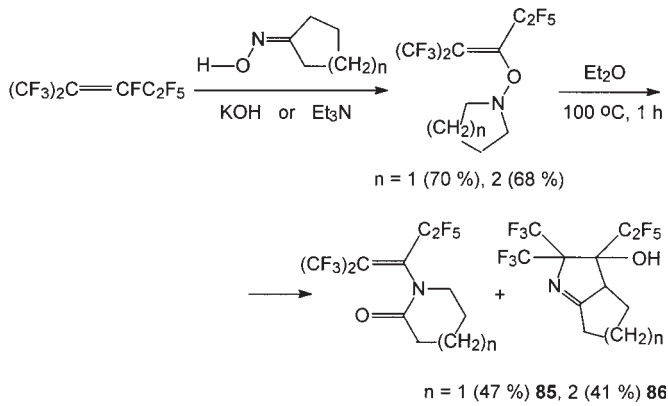


It was assumed (94IZV1068, 94IZV1073, 94IZV1449) that, after heterolytic cleavage of the N–O bond, the cationoid species migrates (without any structural changes) from the oxygen atom to the carbon of the mesomeric anion **E**. This tight ion pair is stabilized by C–N bond formation.



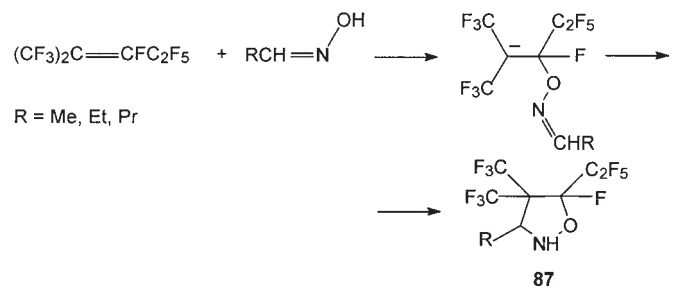
This reaction is probably of general character. Thus the reaction of cyclopentanone and cyclohexanone oximes with perfluoro-2-methylpent-2-ene forms perfluoroalkenyl ethers. Thermolysis of the latter leads to

compounds of two types: 4-hydroxy-5,5-bis-(trifluoromethyl)-4-pentafluoroethyl-2,3-trimethylenepyrrolidine-1 **85** (yield 47%) and 4-hydroxy-5,5-bis(trifluoromethyl)-4-pentafluoroethyl-2,3-tetramethylenepyrroline **86** (yield 41%) (94IZV1068).



The driving force of the thermolysis may be the high reactivity of the N–O group and its tendency towards possible heterolytic cleavage. The electron-deficient nitrogen atom migrates from oxygen to carbon in the transition state, and stabilization is achieved by C–N bond formation during the subsequent cyclization involving the carbanion center generated in the γ-position relative to the N=C multiple bond.

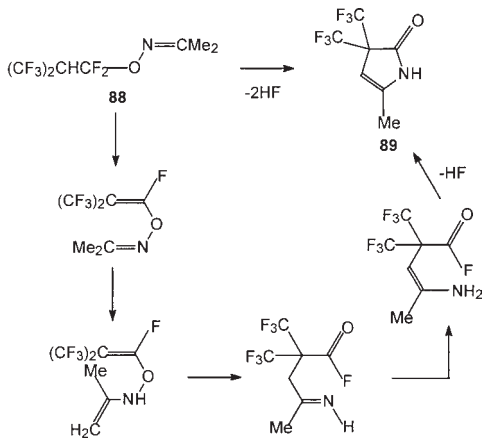
Reactions of perfluoroolefins with aliphatic aldehyde oximes lead to cyclization product **87** without a rearrangement of the carbon skeleton.



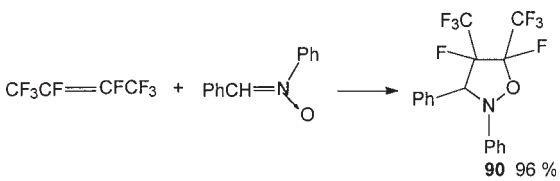
87

Dehydrofluorination of *O*-(β-hydroperfluoroisobutyl)-acetoneoxime **88** affords a heterocyclic compound initially identified as 3,3-bis(trifluoromethyl)-5-methyl-Δ^4-pyrrolinon-2-one (89IZV204). More recently (94IZV951), the compound was identified from X-ray analysis data as

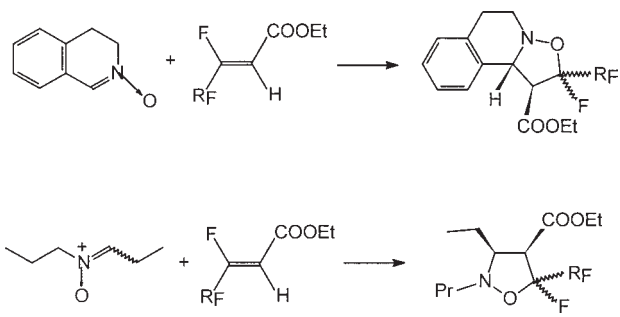
2,2-bis(trifluoromethyl)-5-methyl-Δ^4-pyrrolinone-3 **89**. The following route was suggested for this reaction:



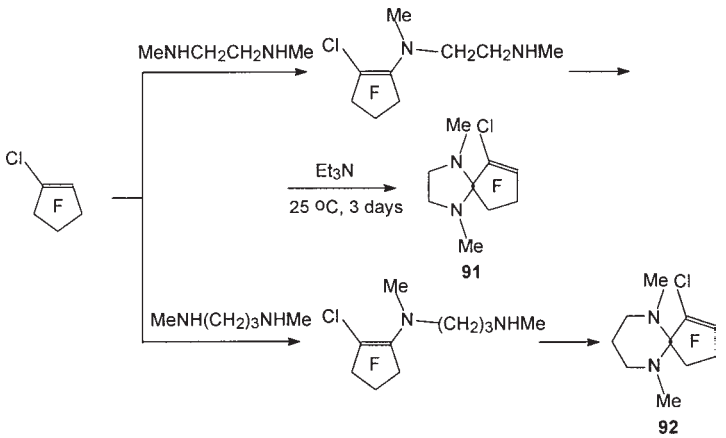
The reaction of C,N-diphenylnitrone with octafluorobut-2-ene at room temperature led to 4,5-difluoro-2,3-diphenyl-4,5-bis(trifluoromethyl)-isoxazolidine **90** (92JFC(58)101).



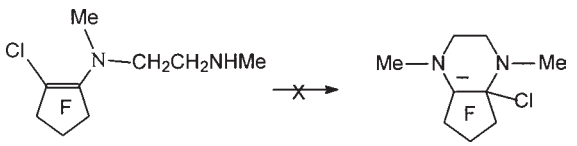
Nitrones interact with substituted perfluoroolefins by the 1,3-cycloaddition mechanism. For example, with ethyl 2-hydroxypolyfluoroalk-2-enoate they give 5-fluoroalkylisoxazolidine in the form of a mixture of two *cis* and *trans* epimers.



The reaction of *N*,*N*′-dimethylethylidenediamine with 1-chloroperfluorocyclopentene forms a five-membered heterocycle (6-chloro-7,8,8,9,9-penta-fluoro-1,4-dimethyl-1,4-diazaspiro[4,4]non-6-ene) **91**, whereas *N*,*N*′-dimethyl-1,3-propylidenediamine gives a six-membered ring (2-chloro-2,3,3,4,4-pentafluoro-6,10-diazaspiro[4,5]-dec-1-ene) **92** (94JOC173). The intramolecular nucleophilic cyclization affects the α-carbon atom of the multiple bond.

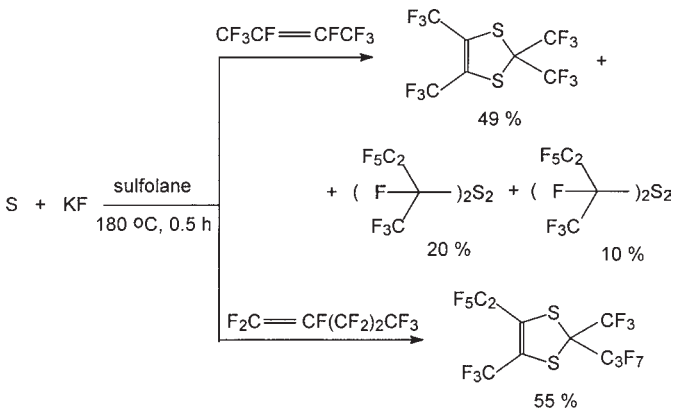


This result may be explained by carbanion destabilization by the nitrogen preventing the alternative nucleophilic attack at the β-carbon atom of the multiple bond as shown below for the case of the six-membered heterocycle.

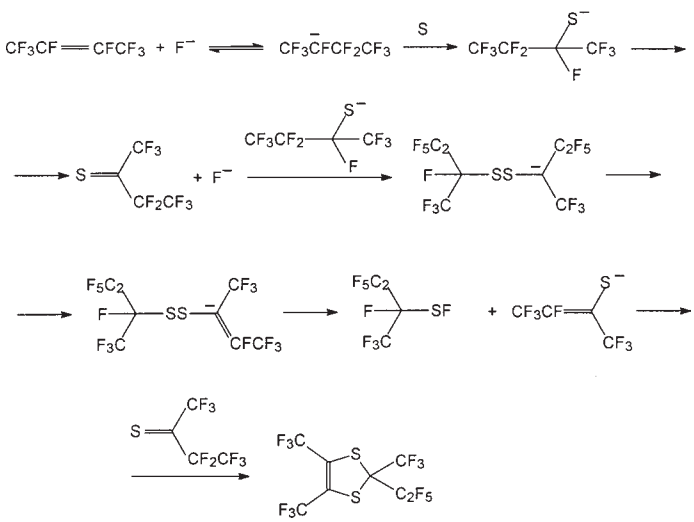


These examples demonstrate the utility of bifunctional nucleophiles in reactions of perfluoroolefins with an internal multiple bond leading to various heterocyclic compounds with perfluoroalkyl substituents.

The reactions of some internal perfluoroolefins (perfluorobut-2-ene, perfluoropent-1-ene, and perfluoropent-2-ene) with an S–KF–sulfolane system lead to a five-membered heterocycle-[1,3]-dithiol derivative (82CL201). Thus the reaction with perfluorobut-2-ene gives perfluoro-2-ethyl-2,4,5-tris(trifluoromethyl)-[1,3]dithiol.



The reaction scheme suggested in Ref. 82CL201 involves the following key steps: carbanion generation under the action of the fluoride ion on the perfluoroolefin and intermediate formation of perfluorodialkylthioketone:

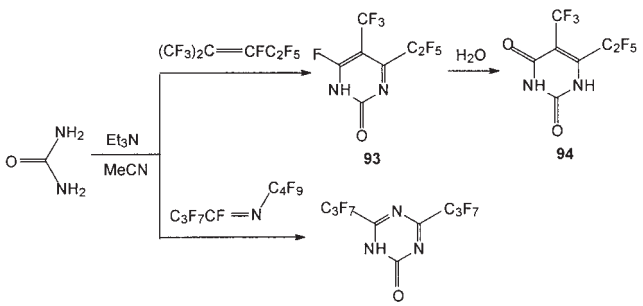


The reactants in the presence of 2,3-dimethyl-1,3-butadiene forms the Diels–Alder adduct—4,5-dimethyl-2-pentafluoroethyl-2-trifluoromethyl-3,6-dihydro-2*H*-thiopyran (82CL201).

D. Six-Membered Heterocycles with One or More Heteroatoms

The factors governing intramolecular nucleophilic cyclizations and ring formation from double bonded systems bearing a mobile fluorine atom are illustrated by reference to reactions of internal perfluoroolefins and perfluoroazaalkenes with nitrogen-containing binucleophiles. These reactions give a wide range of structural types of heterocyclic compounds. Heterocycles with one or more heteroatoms bearing perfluoroalkyl substituents are prepared by intramolecular nucleophilic cyclization of intermediates having a double bond and a potential nucleophilic center on the substituent at the double bond. Reactions of perfluoroolefins with 1,2-, 1,3-, or 1,4-bidentate nucleophiles in the presence of bases form various heterocycles with five-, six-, seven-, and eight-membered rings. In recent years, these reactions have been studied extensively.

Thus reactions of perfluoro-2-methylpent-2-ene and perfluoro-5-azanon-4-ene with urea in the presence of triethylamine in dipolar aprotic solvents (MeCN, DMF) form 6-fluoro-4-pentafluoroethyl-5-trifluoro-methyl-1*H*-pyrimidin-2-one **93** and an s-triazine derivative, respectively (00JFC(103)105, 80/82JAP(K)85377).

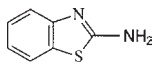
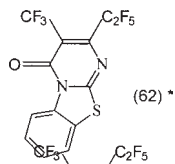
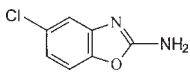
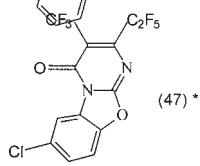
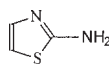
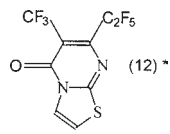
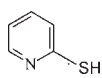
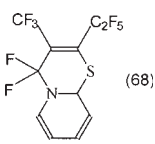
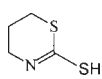
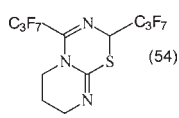
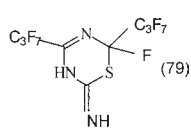
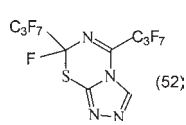
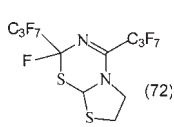


Due to the high mobility of the fluorine atom in the 5 position in compound **93**, the reactants also form 6-pentafluoroethyl-5-trifluoro-methyl-1*H*-pyrimidine-2,4-dione **94**.

If the *N*,*S*- or *N*,*N*-binucleophile has an **a**–**b**–**c** triad, the character of the heterocyclic product depends on the nature of the nucleophile initiating the reaction with perfluoroolefins and perfluoroazaalkens (Table V) (03PU1).

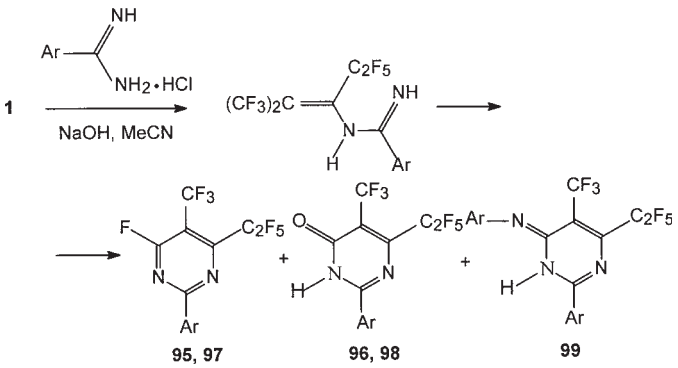
The reaction of perfluoro-2-methylpent-2-ene with benzamidines in the presence of sodium hydroxide affords 4-fluoro-2-phenyl-6-pentafluoro-ethyl-5-trifluoromethylpyrimidine **95** (00JFC(103)105). In compound **95**, the fluorine atom in the 5 position possesses high mobility; in a

Table V. SYNTHESIS OF SIX-MEMBERED HETEROCYCLES CONTAINING PERFLUOROALKYL GROUPS

Olefin	Nucleophile	Product (Isolated yield, %)	References
$(CF_3)_2C{=}CFC_2F_5$		 (62) *	02JFC(23)1017
		 (47) *	02JFC(23)1017
		 (12) *	02JFC(23)1017
		 (68)	2003UP1
$C_3F_7CF{=}NC_4F_9$		 (54)	2003UP1
	$(H_2N)_2C{=}S$	 (79)	2003UP1
		 (52)	2003UP1
		 (72)	2003UP1

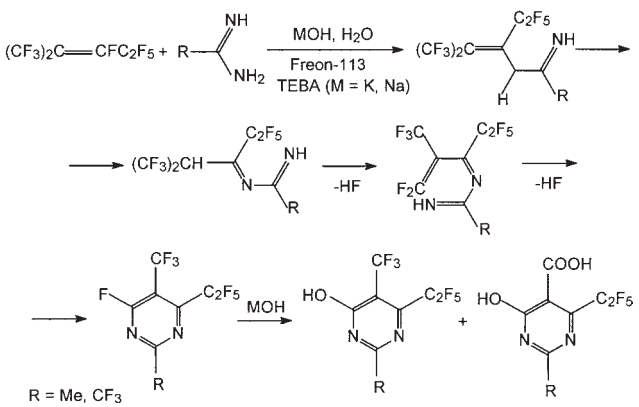
*Structure was confirmed by X-ray analysis (02BKCS1017).

humid atmosphere the compound is converted into 6-pentafluoroethyl-2-phenyl-5-trifluoromethyl-3*H*-pyrimidin-4-one **96**. In the reaction of perfluoro-2-methylpent-2-ene with 4-nitrobenzamidine in the presence of an alkali, compound **99** is obtained along with the expected compounds **97** and **98** (00JFC(103)105).

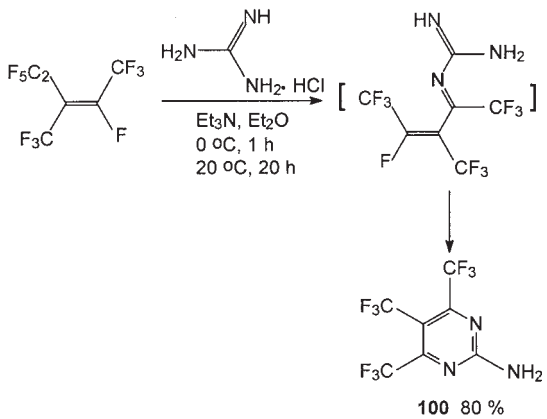


Ar = Ph **95, 96**, 4-$NO_2C_6H_4$ **97, 98, 99**

When perfluoro-2-methylpent-2-ene reacts with amidine, the products may be vinylamidine, fluoropyrimidine, or hydroxypyrimidine depending on the reactivity of the amidine and on the presence of a catalyst as well as reaction time. In moderately polar media such as diethyl ether, the initial product is vinylamidine, promoting subsequent cyclization and dehydrofluorination; the products of these transformations may be isolated and characterized. Meanwhile, other transformations occur with comparable rates. Therefore, the reaction in diethyl ether may not be used for the synthesis of fluoropyrimidines. However, hydroxypyrimidine may be obtained under these conditions with a yield of up to 60%. Analogous results were obtained when the reaction was conducted in Freon-113 (97IZV2024).



The reaction of the tetrafluoroethylene trimer with guanidine hydrochloride in dry ether forms light-sensitive 2-amino-4,5,6-tris(trifluoromethyl)pyrimidine **100** in a high yield (98JFC(88)169).



It was established (01IZV457) that the products of the reaction of perfluoro-2-methylpent-2-ene and perfluoro-5-azanon-4-ene with guanidine hydrochloride in the presence of triethylamine are 4-fluoro-6-pentafluoroethyl-5-trifluoromethyl-pyrimidin-2-ylamine **101**, whose structure was confirmed by X-ray analysis (Fig. 4) and compound **102**, respectively.

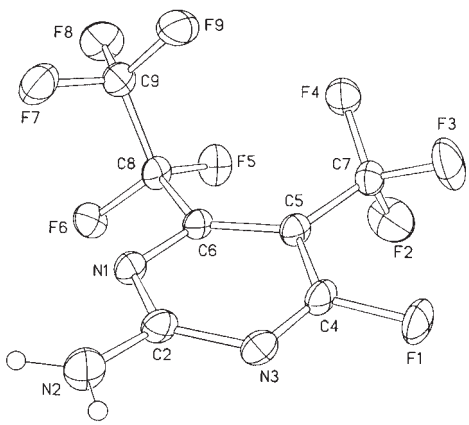
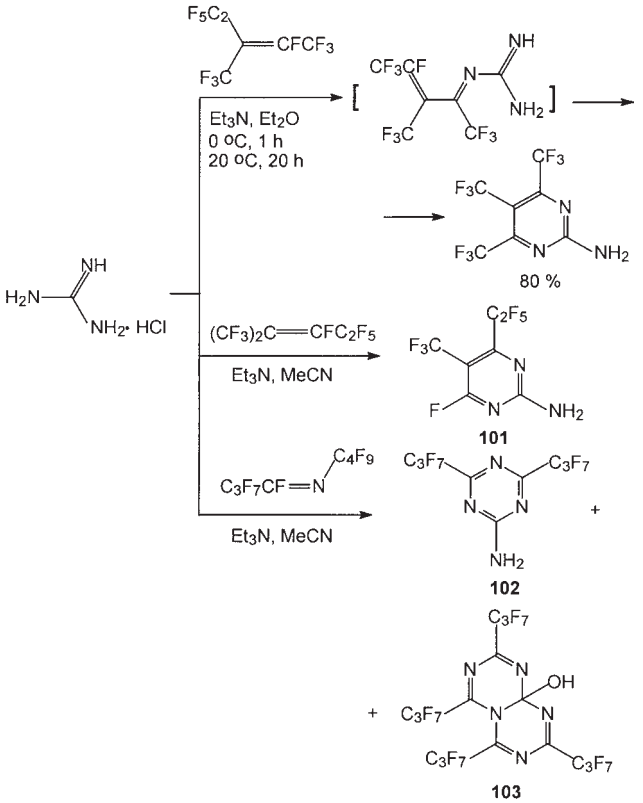
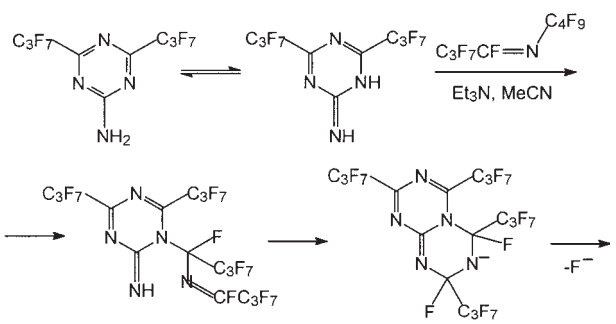
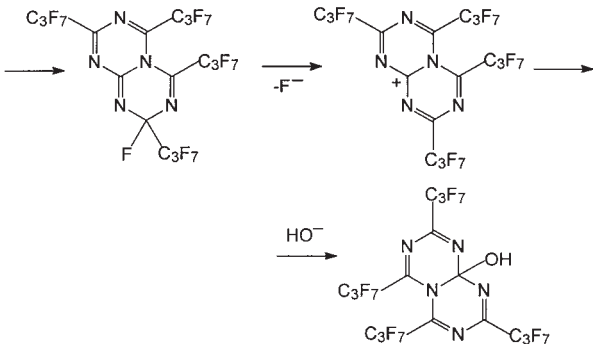


Fig. 4. Crystal structure of 4-fluoro-6-pentafluoroethyl-5-trifluoro-methylpyrimidin-2-ylamine **101** according to X-ray structural analysis (01IZV457).



Note that in the case of the reaction of guanidine hydrochloride with perfluoro-5-azanon-4-ene one obtains a mixture of products **102** and **103**. Compound **103** is the product of further reaction of perfluoro-5-azanon-4-ene with **102**. It may be assumed that **103** is formed according to the following scheme:

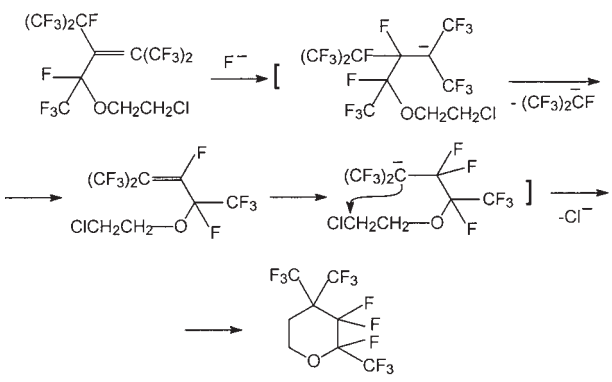




The reaction seems to start with an attack of the ring nitrogen atom of the s-triazine at the carbon atom of the multiple bond of another perfluoro-5-azanon-4-ene molecule. The product of this reaction undergoes intramolecular cyclization involving the C=N bond and the NH fragment to give the N-anion. Base-induced elimination of the fluoride-anion from the CFC_3F_7 group leads to a compound, which also undergoes fluoride anion elimination, giving product **103**.

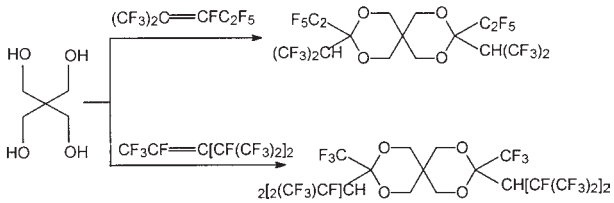
Thus conditions are provided for further interactions between active perfluoroazaalkene and the reaction product whose structure involves an N–C–NH triad. This opens up an opportunity to construct bicyclic nitrogen-containing heterocycles with perfluoroalkyl groups.

β-Chloroethyl ether also undergoes two competing reactions: alkylation of the fluoride ion and a reaction leading to a substituted tetrahydropyran. In this case, the carbanion is stabilized by elimination of the perfluoroisopropyl anion and formation of a multiple bond, whereupon the unsaturated ether reacts with the fluoride ion to give a C-nucleophile. The latter replaces chlorine in the molecule, giving 2,2,2-trifluoro-1,3,3-tris(trifluoromethyl)tetrahydropyran **104**.

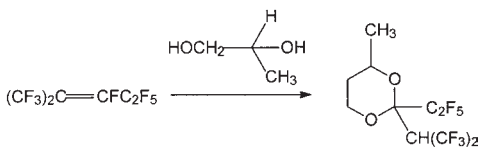


104

Using pentaerythritol and 1,3-butanediol as nucleophilic agents under conditions of base catalysis in reactions with perfluoroolefins leads to six-membered heterocycles (in particular, to spiro derivatives of 1,3-dioxane) (96ZOB1995).

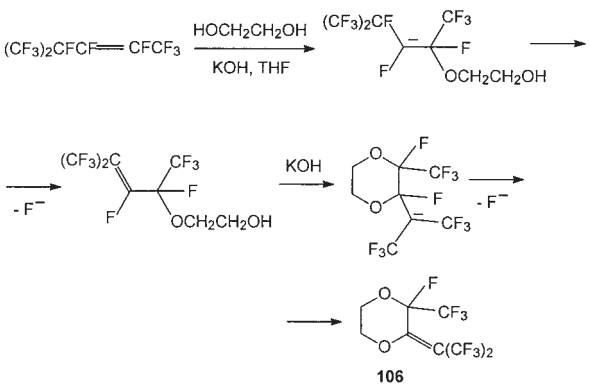


The reaction with 1,3-butanediol yields 4-methyl-2-pentafluoroethyl-2-(2,2,2-trifluoro-1-trifluoromethyl-ethyl)-[1,3]dioxane **105** (93JP60-259206).



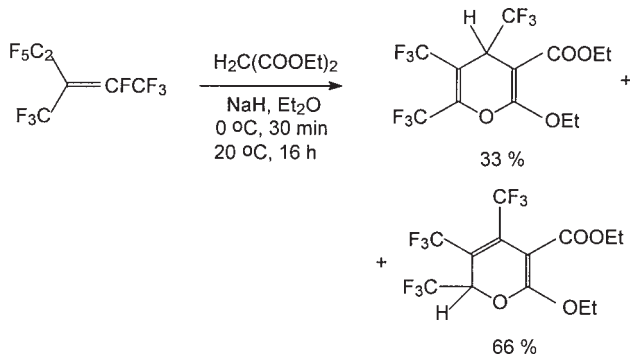
105

The reaction of perfluoro-4-methyl-2-pentene with ethylene glycol also leads to 2-fluoro-2-trifluoromethyl-3-(2,2,2-trifluoro-1-trifluoromethylethylidene)-1,4-dioxane **106** (96ZOB1995). The formation of the six-membered heterocycle occurs via generation of the intermediate carbanion and fluoride ion elimination from the γ-position. Subsequent intramolecular nucleophilic cyclization involving the O-nucleophilic center and the internal double bond leads to a 1,4-dioxane derivative (route **e**).

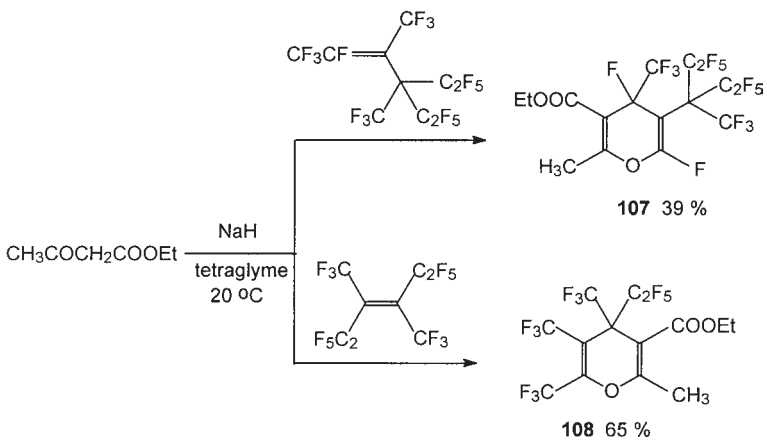


106

The reaction of the tetrafluoroethylene trimer with one equivalent of diethylmalonate and two equivalents of sodium hydride in dry ether gives a mixture of 5-carboethoxy-6-ethoxy-2,3,4-tris(trifluoromethyl)-2-pyran and 5-carboethoxy-6-ethoxy-2,3,4-tris(trifluoromethyl)-4-pyran in a 2.1:1 ratio with a total yield of 71% (98JFC(88)169).

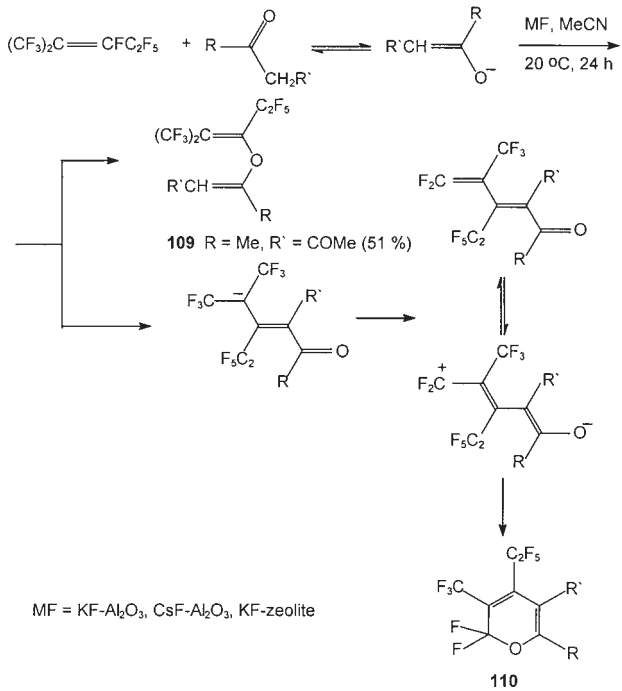


The reaction of the tetrafluoroethylene tetramer and pentamer with ethylacetoacetate gives pyran derivatives **107** and **108**, respectively (83JCS(P1)1239, 83JCS(P1)1235).



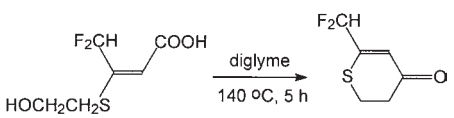
Another nucleophilic center can also appear due to tautomerization of the unsaturated bonds induced by bases such as the fluoride ion. Thus the reaction of perfluoro-2-methylpent-2-ene with active methylene compounds, for example, acetylacetone, ethylacetoacetate, benzoylacetonitrile, and benzoylmethylperfluoroalkylketones in the presence of KF gives not only the products of nucleophilic substitution of fluorine

at the multiple bond (compound **109**) but also the 5-derivatives of 4-(pentafluoroethyl)-2,2-difluoro-3-(trifluoromethyl)-6-methyl-2*H*-pyran **110** (81JFC(18)213).



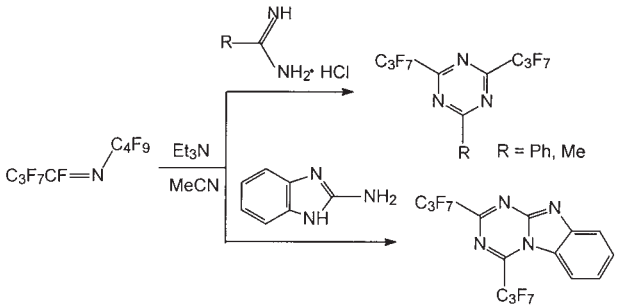
110

Another route for cyclization involves participation in the intramolecular attack of the O-nucleophilic center reacting at a C=O group at high temperatures (140 °C). Thus on heating the *Z*-isomer of 4,4,5,5,6,6-hexafluoro-3-(3-mercaptopropyloxy)-hex-2-enic acid **111** in diglyme gives 6-difluoromethyl-2,3-dihydrothiopyran-4-one **112**. The *E*-isomer is unreactive in this case.

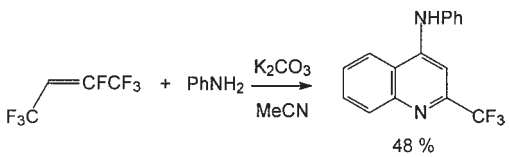


111 **112**

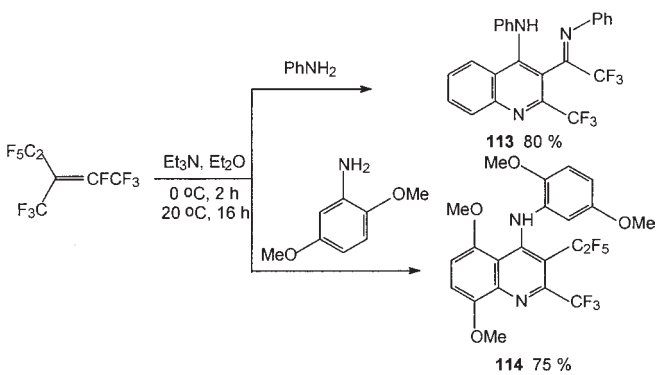
The interaction of perfluoro-5-azanon-4-ene with amidines and 2-aminobenzimidazole occurs with formation of a six-membered heterocycle, giving 2,4-bis(heptafluoropropyl)-6-phenyl-[1,3,5]triazine, 2,4-bis(heptafluoropropyl)-6-methyl-[1,3,5]triazine, and a tricyclic compound—2,4-bis(heptafluoropropyl)benz-[4,5]imidazo[1,2-*a*][1,3,5]triazine (01IZV457).



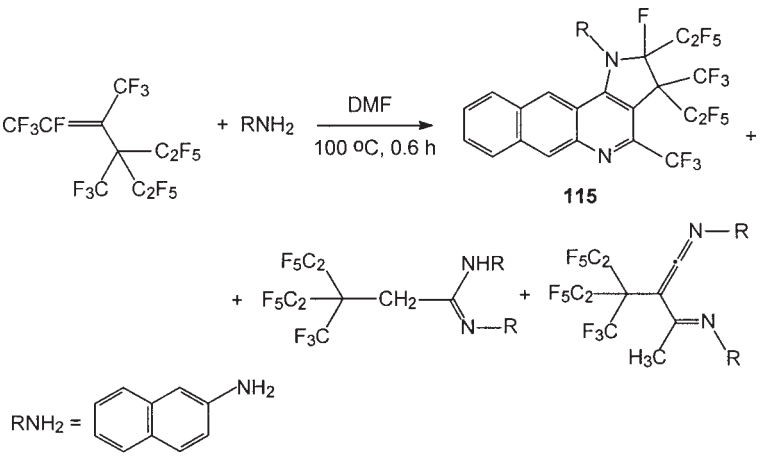
Aromatic primary amines are not only binucleophiles at the amino group, but they also exhibit the properties of C,N-binucleophiles. Their reactions with internal perfluoroolefins lead to quinoline derivatives (98JFC(88)169, 94JCS(CC)134, 98T4949). Thus the reaction of aniline with 2*H*-heptafluorobut-2-ene yields phenyl(2-trifluoromethylquinolin-4-yl) amine (00ZOR109); when the reaction is carried out with the tetrafluoroethylene trimer, it leads to 2-trifluoromethyl-3-(1-N-phenylimino-2,2,2-trifluoroethyl)-4-(N-phenylamino)quinoline (98JFC(88)169).



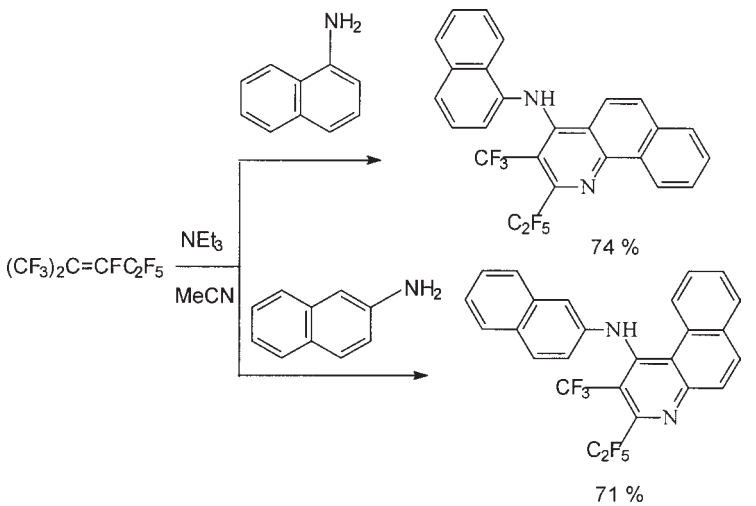
The reaction of the tetrafluoroethylene trimer with aniline or 2,5-dimethoxyaniline forms 2-trifluoromethyl-3-(1-N-phenylimino-2,2,2-trifluoroethyl)-4-(N-phenylamino)quinoline **113** (whose structure was confirmed by X-ray analysis) and 2-trifluoromethyl-3-pentafluoroethyl-4-(N-2,5-dimethoxyphenyl)-amino-5,8-dimethoxyquinoline **114** with yields 80 and 75%, respectively (98JFC(88)169).



Interaction of the tetrafluoroethylene pentamer and β-naphthylamine leads to compound **115**.



In the reaction of perfluoro-2-methylpent-2-ene with 2-methoxy-5-aminopyridine it is converted to a derivative of [1,5]naphthyridine (94JCS(CC)134). It is interesting to note that the carbon atom next to the amino group in the 1,3(N,C)-binucleophilic reagents acts as the second nucleophilic center to form a heterocycle. Two equivalents of α- and β-aminonaphthalene react with one equivalent of perfluoro-2-methylpent-2-ene to yield the final product (02BKCS1017).



It was assumed that for aromatic amines the electron-donor substituents on the benzene ring promote the formation of quinolines. Indeed, it was established that the reaction of perfluoro-2-methylpent-2-ene with 2,4-dimethoxyaniline gives 4(2,4-dimethoxyanilino)-6,8-dimethoxy-2-pentafluoroethyl-3-trifluoromethylquinoline (94JCS(CC)134).

The product of the reaction of perfluoro-2-methylpent-2-ene with aniline in the absence of bases or in the presence of triethylamine is [2-pentafluoroethyl-3-trifluoromethylquinolin-4-yl]phenylamine **116**, whose structure was confirmed by X-ray structural analysis (Fig. 5) (00JFC(104)263).

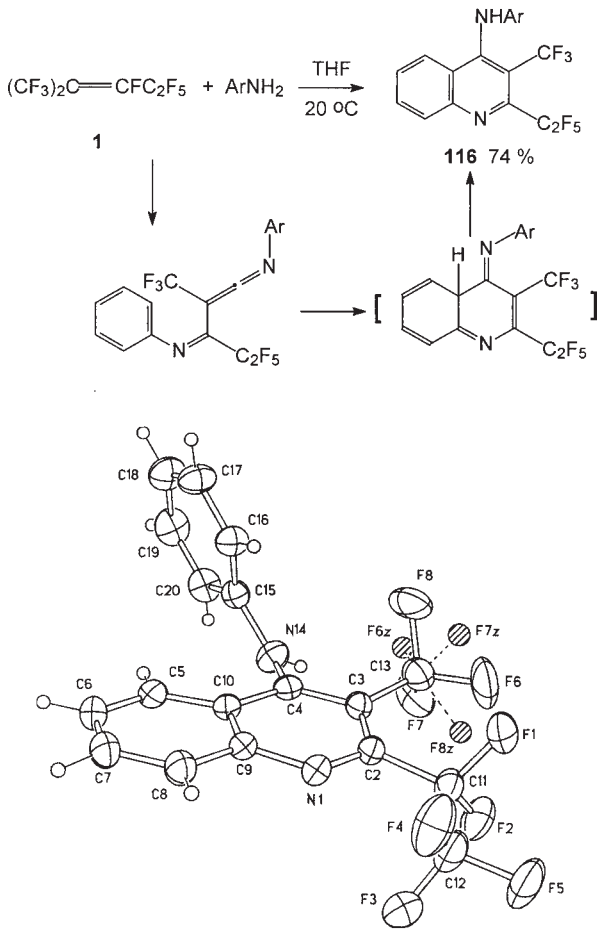
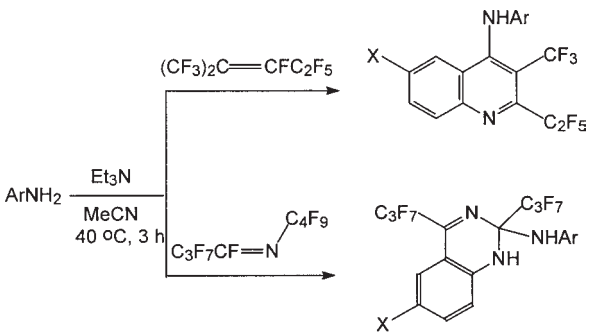


Fig. 5. Crystal structure of (2-pentafluoroethyl-3-trifluoromethylquinolin-4-yl)phenylamine **116** by X-ray analysis (99IZV1578).

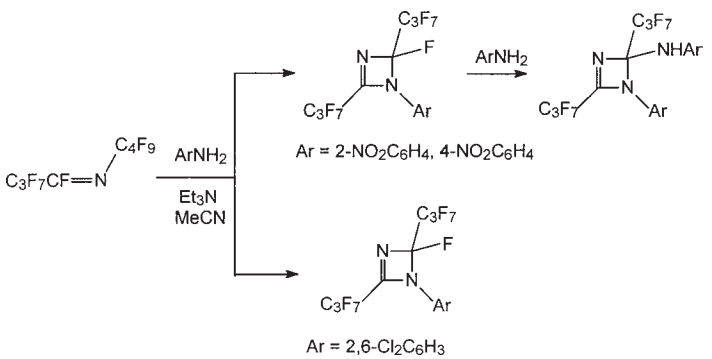
However, there is some controversy. For example, the reaction of octafluoro-3,4-bis(trifluoromethyl)-hexa-2,4-diene with aniline yields 1-phenyltetrakis-(trifluoromethyl)-1*H*-pyrrole (94JCS(P1)3119) but not the expected 2,3,4,5-tetrakis-(trifluoromethyl)-1*H*-benzo[*b*]azetin.

It was shown (00JFC(104)263) that perfluoro-2-methylpent-2-ene and perfluoro-5-azanon-4-ene smoothly react with two moles of aniline, 4-fluoroaniline, and 4-methoxyaniline in the presence of three moles of Et_3N in acetonitrile, forming derivatives of quinoline and quinazoline.



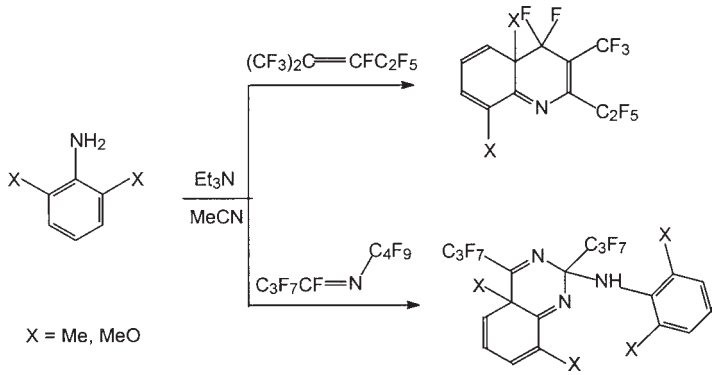
XAr = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$

The introduction of the nitro group and fluorine atoms in the benzene ring considerably decreases the nucleophilic properties of the C-anion center compared to the N-anion, forming diazetine derivatives (00JFC(104)263).



In the reaction of perfluoro-5-azanon-4-ene with 2,6-dimethylaniline, the attack at the carbon atom of the new N=C bond forms a six-membered heterocycle derived from dihydroquinazoline (00JFC(104)263). If the 2,6-positions of the benzene ring of aniline contain electron-donor substituents

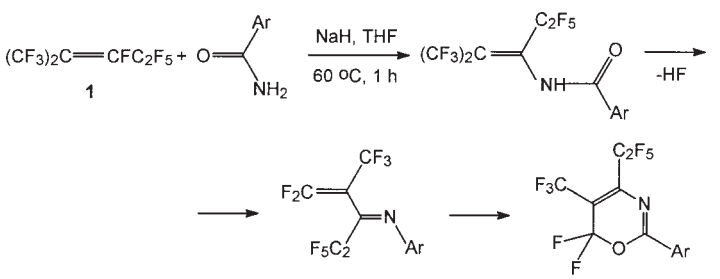
(Me, MeO), then cyclization by the C-anion center is possible. Thus the reactions of perfluoro-2-methylpent-2-ene and perfluro-5-azanon-4-ene with 2,6-dimethylaniline form dihydroquinoline and dihydroquinazoline derivatives, respectively.



Thus with electron-donor substituents in the benzene ring anilines lead to quinazolines, whereas four-membered heterocycles are formed in the case of electron acceptors or halides in the *ortho*-positions.

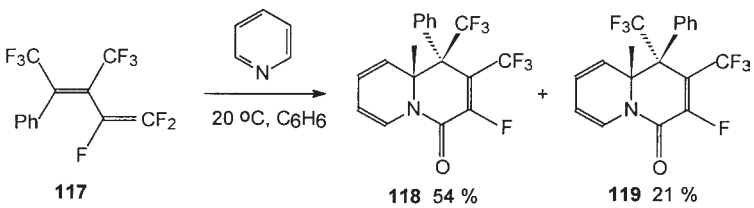
It seems that suitable reaction conditions leading to the formation of a specific compound may be found by using various nucleophiles. These reactions are potentially useful routes to fluorinated heterocyclic compounds.

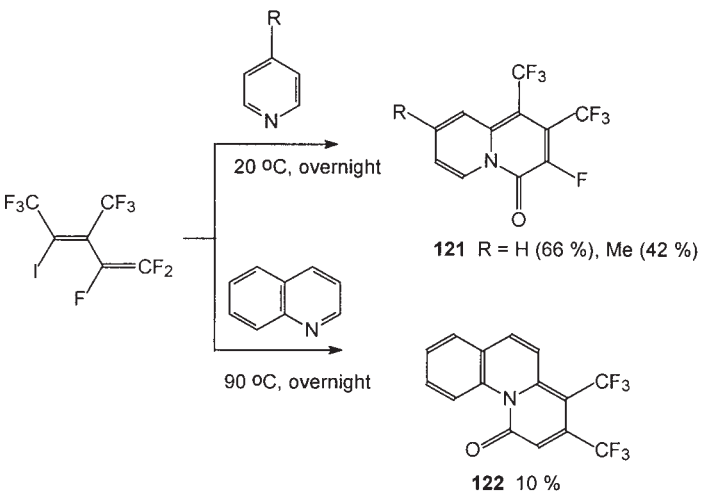
In the presence of sodium hydride in tetrahydrofuran, amides of benzoic acid derivatives are effective N-nucleophiles. With a bidentate nucleophile such as sodium salt of benzoic acid amide, perfluoro-2-methylpent-2-ene forms 6,6-difluoro-4-pentafluoroethyl-2-aryl-5-trifluoromethyl-6*H*-[1,3]-oxazine in a moderate yield (98JOC569).



Ar = Ph (66 %), 4-$NO_2C_6H_4$ (37 %),
4-$MeOC_6H_4$ (30 %), MeC_6H_4 (21 %)

Pyridine and its derivatives react with 1,3-pentadienes forming cyclic products. This type of cyclization was observed by the authors of 95JFC(72)49. They showed that in the reaction of (*Z*)-1,1,2,5,5,5-hexafluoro-4-phenyl-3-trifluoromethyl-1,3-pentadiene **117** with pyridine the products are [1*S*,9*aR*]- and [1*S*,9*aS*]-3-fluoro-9*a*-hydro-1,2-bis(trifluoromethyl)-1-phenyl-4*H*-quinolizin-4-ones **118** and **119** with 54 and 21% yields, respectively. The structure of the compounds was confirmed by X-ray analysis. Similarly, the reaction of (*Z*)-1,1,2,5,5,5-hexafluoro-4-iodo-3-trifluoromethyl-1,3-pentadiene **120** with 4-substituted pyridines gives the derivative of 4*H*-quinolizin-4-one **121**; with quinoline, the product is derivative **122**.





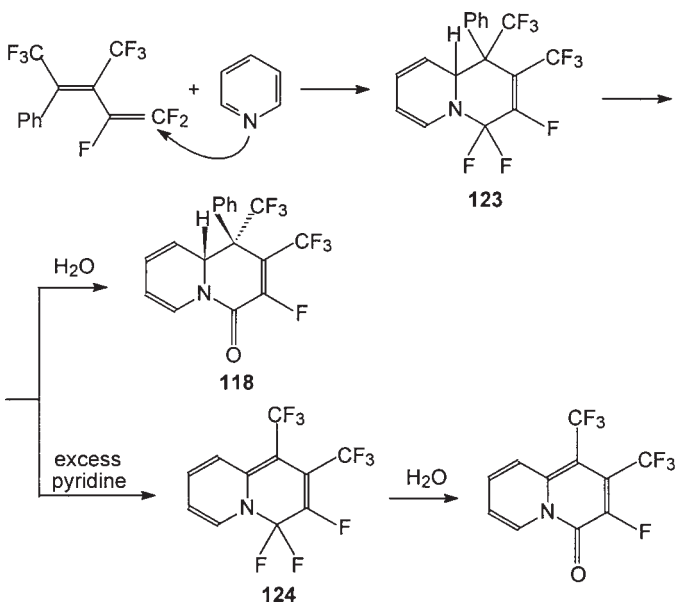
The mechanism of the process seems to be as follows. At first, the carbon atom of the terminal multiple bond is attacked by the N-nucleophile to form an internal salt stabilized by fluoride anion elimination from the α-CF_2 fragment. This leads to compound **123**, whose hydrolysis

yields compounds **118** and **119**. With an excess of pyridine, benzene is eliminated to form compound **124**, and hydrolysis of the latter leads to compound **121**.

This approach affords various heterocyclic compounds obtained from internal perfluoroolefins or conjugated double bond used as precursors. Hopefully, practical applications of this approach will increase in number and new information will permit more profound generalizations.

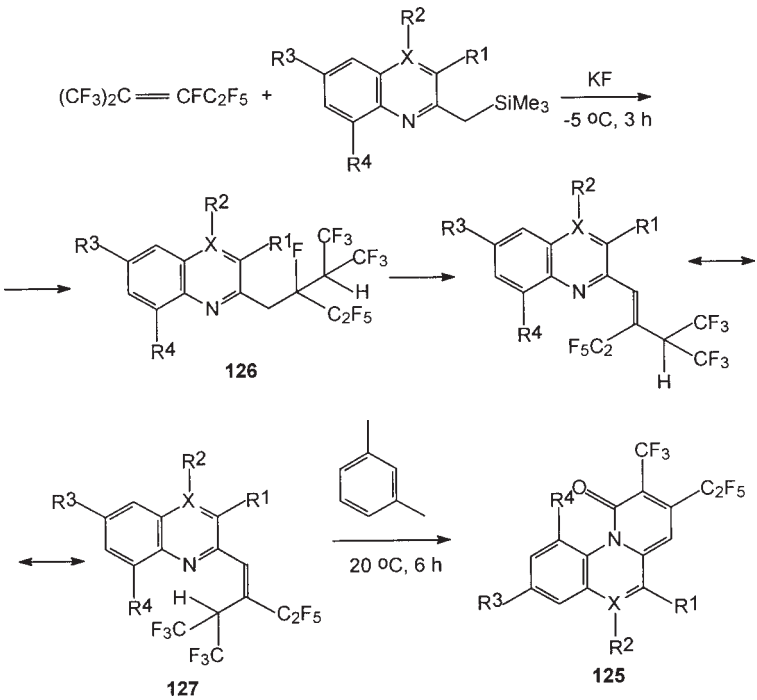
When perfluoro-2-methylpent-2-ene interacts with the 2-quinoline-2-methyl anion generated from 2-(trimethylsilylmethyl)quinoline in the presence of catalytic amounts of tetrabutylammonium fluoride or KF, the product is 3-pentafluoroethyl-2-trifluoromethyl-pyrido[1,2-*a*]quinolin-1-one **125** in 36% (93%) yield (92NKK1455).

The reaction occurs via the formation of the intermediate adduct **126** and a mixture of *E*/*Z*-isomeric alkenes **127** (for $R^1 = R^2 = R^3 = R^4 = H$, the yield is 29 and 11%, respectively). The reaction product is formed by intramolecular cyclization of olefins initiated by bases (water, Na_2CO_3, NaOH) in tetrahydrofuran (xylene). The authors did not give any interpretation of the reaction route. One can assume that the reaction proceeds by the following scheme. Under the action of bases, olefins undergo elimination of hydrogen fluoride and the formation of compound **128** containing a terminal double bond.

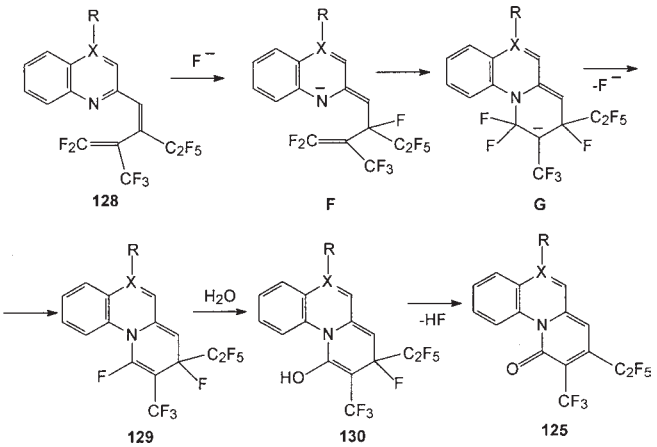


Further addition of the fluoride anion at the internal multiple bond generates hetero-anion **F**, which is involved in the intramolecular cyclization affecting the active terminal double bond. Stabilization of carbanion **G** occurs by fluoride ion elimination and formation of compound **129** having a multiple bond with a mobile fluoride atom.

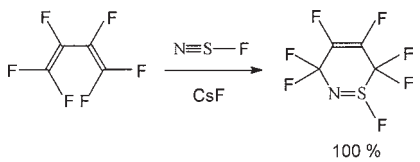
When water reacts with compound **129**, this fluorine atom is substituted to form compound **130**. When boiled in xylene, the latter liberates hydrogen fluoride to give the final compound **125**.



X	R^1	R^2	R^3	R^4	Yield, %
C	H	H	H	H	93
C	H	Me	H	H	92
C	H	H	Me	H	83
C	H	H	Cl	H	90
C	H	H	H	Cl	86
N	Me	–	H	H	35

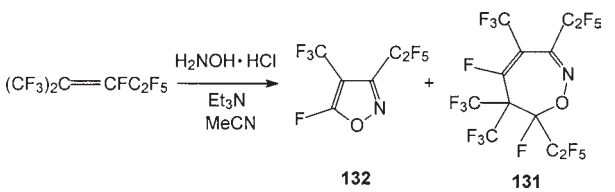


[4 + 2]Cyclizations can be employed to build new rings. Perfluorobuta-1,3-diene reacts with thiazyl fluoride quantitatively to provide the heterocycle (79JCS(CC)35).

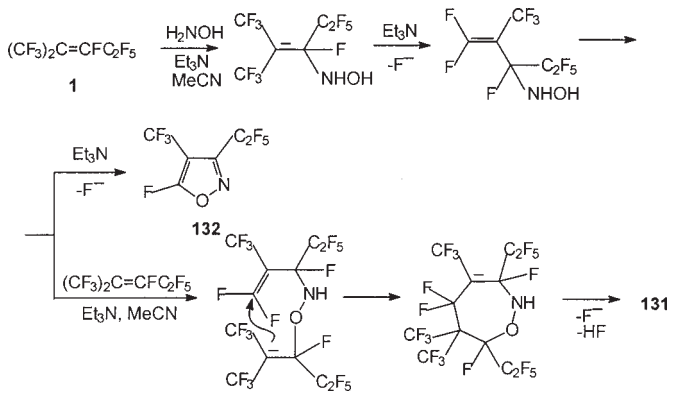


E. Seven-Membered Cycles with Many Heteroatoms Obtained from Internal Perfluoroolefins

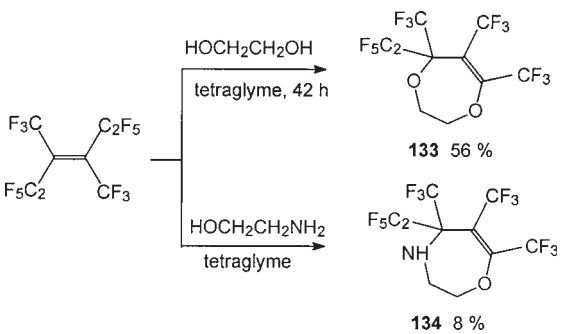
Syntheses include nucleophilic addition or substitution of a binucleophilic reagent to perfluoroolefins followed by an intramolecular nucleophilic cyclization to afford seven-membered heterocycles. Thus, with the reaction of perfluoro-2-methylpent-2-ene with hydroxylamine, the major product is compound **131**, whereas the expected compound **132** is obtained in a low yield (01JFC(110)11).



This may be explained by the participation of the two nucleophilic centers of hydroxylamine.

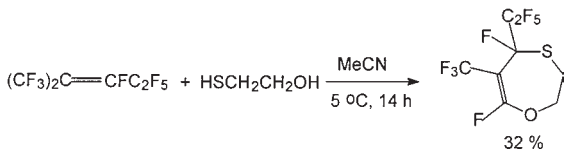


The above examples demonstrate the possibilities for syntheses of various heterocyclic compounds with perfluoroalkyl groups using bifunctional nucleophiles in reactions of perfluoroolefins involving their double bonds. Chambers et al. (79JCS(P1)214) found that the reaction of perfluoro-3,4-dimethylhex-3-ene with ethylene glycol in tetraglyme forms a seven-membered heterocycle, 5-pentafluoroethyl-5,6,7-tris-(trifluoromethyl)-1,4-dioxacyclohept-6-ene **133**, while with ethanolamine the product is 5-pentafluoroethyl-5,6,7-tris-(trifluoromethyl)-1-oxa-4-azacyclohept-6-ene **134**.



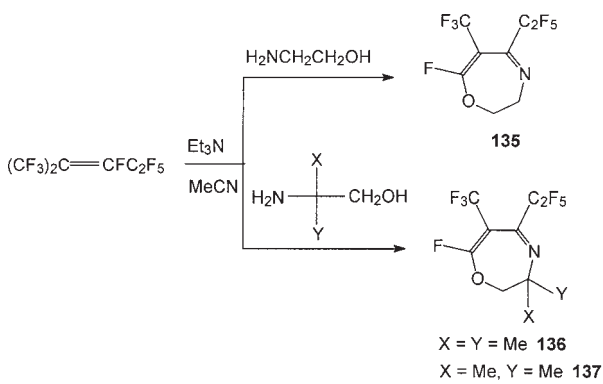
The case is similar for other perfluoroolefins. Thus treatment of perfluoro-2-methylpent-2-ene with 2-mercaptoethanol in acetonitrile in the presence of potash led to 5,7-difluoro-5-pentafluoroethyl-6-trifluoromethyl-3,5-dihydro-2*H*-[1,4]-oxathiepin (94IZV1073, 89JAP(K)01 265087) but not to its isomer 5,5-difluoro-6-trifluoromethyl-6-(pentafluoroethyl)-1,4-oxathiepin-6

(85IZV2066). This is probably associated with the fact that during the attack of the S-nucleophile the anion is mainly stabilized by elimination of the vinyl fluorine atom, since the intermediate anion formed in this process is energetically preferable to the isomeric anion due to conjugation between the lone electron pair of the sulfur atom and the double bond. The product is of interest in syntheses of pharmaceuticals and agrochemicals.



A similar picture is observed for other bifunctional O- and S-nucleophiles (2-mercaptoethanol, dithioglycol, glycidol, 1,2-propyleneglycol).

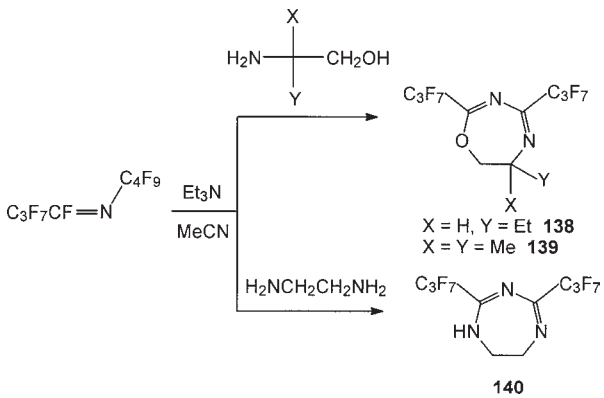
Monoethanolamine reacts with perfluoro-2-methylpent-2-ene in the presence of triethylamine, forming 7-fluoro-5-pentafluoroethyl-6-trifluoromethyl-2,3-dihydro[1,4]oxazepin **135** (01JFC(110)11). If the compound has bulky substituents in the β-position relative to the amino group, attack at the internal double bond is sterically hindered, and the internal olefin isomerizes in the presence of the base to the terminal olefin. The attack of the N-nucleophilic center of monoethanolamine occurs at the carbon atom of the terminal double bond, giving 5-fluoro-3,3-dimethyl-7-pentafluoroethyl-6-trifluoromethyl-2,3-dihydro[1,4]-oxazepin **136** or **137** as the major product.



The formation of these compounds is explained as follows. The initial addition of the O-nucleophile at the double bond generates the carbanion. The latter is stabilized by fluoride ion elimination from the γ-position of the CF_2 fragment, forming an olefin with a multiple bond in the allyl position relative to the initial center of the nucleophilic addition.

Subsequent intramolecular nucleophilic attack by the second O- or N-nucleophilic center affecting the carbon atom of this multiple bond leads to a cyclization product. This demonstrates the role of the intermediate (and rather reactive) terminal perfluoroolefin, directing the subsequent O- and N-nucleophilic attack.

Seven-membered heterocycles **138**–**140** are formed when perfluoro-5-azanon-4-ene reacts with monoethanol derivatives and ethylenediamine.



Thus the reaction of 5-perfluoro-5-azanon-4-ene with ethylenediamine in the presence of triethylamine leads to compound **140**, whose structure was confirmed by X-ray analysis (Fig. 6) (01JFC(110)11).

The situation is more complicated when the reaction is performed with ethyleneglycol. In this case, a mixture of five- **142** and seven-membered **141** heterocycles is formed.

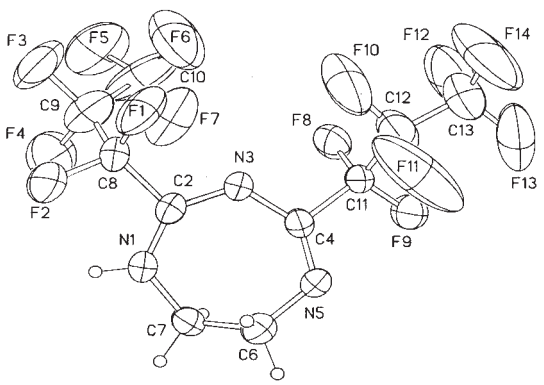
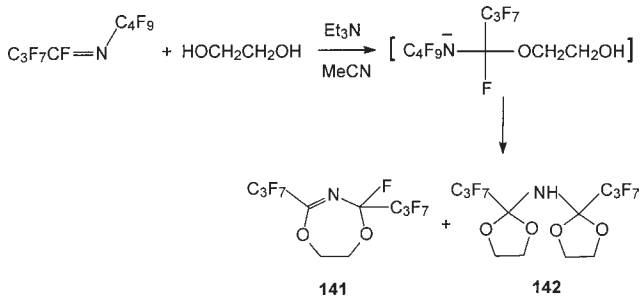
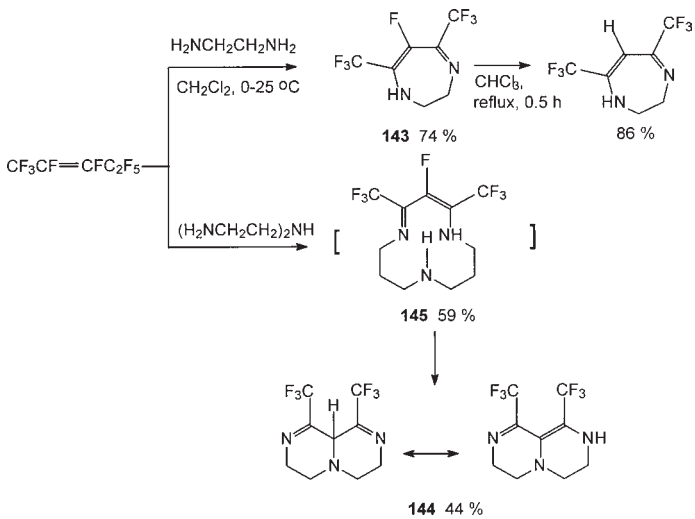


Fig. 6. Crystal structure of 2,4-bis(heptafluoropropyl)-6,7-dihydro-1*H*[1.3.5]thiazepin **140** according to X-ray analysis (01JFC(110)11).

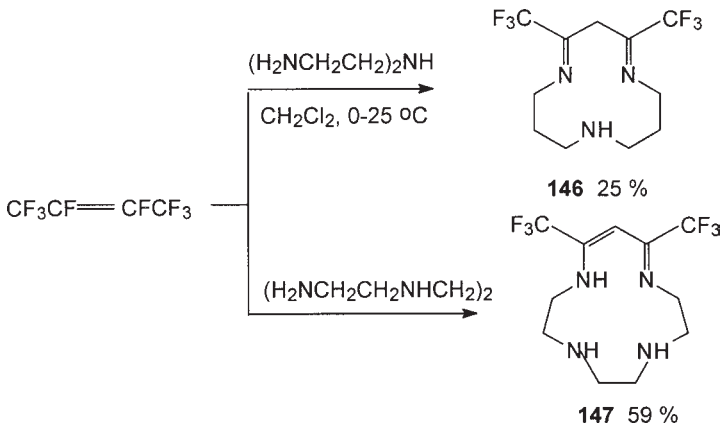


141 **142**

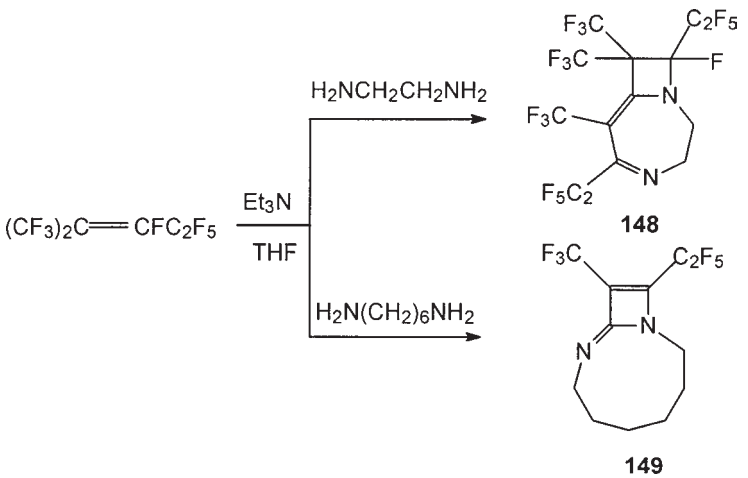
Reaction of perfluoro-2-pentene with ethylenediamine, diethylenetriamine, and triethylenetetramine leads to the formation of novel fluoro-containing azaheterocycles (**143**, **144**, **146**, **147**) in 25–74% yields (94JFC(69)25, 92IZV2170). These structures may result from the intramolecular nucleophilic substitution of the labile fluorine atom (for example, the macrocyclic compound **145**). Interaction of perfluoropent-2-ene with ethylendiamine leads to 5,7-bis(trifluoromethyl)-6-fluoro-2,3-dihydro-1*H*-1,4-diazepine **143** (91JFC(54)297), and with diethylenetriamine unexpectedly gives 1,9-bis(trifluoromethyl)-3,4,6,7-tetrahydro-2*H*-pyrazino [1,2-*a*]pyrazine **144**, whose structure was confirmed by X-ray analysis (94JFC(69)25). The transamination reaction of 2-amino-4-iminoperfluoro-pent-2-ene with ethylenediamine gives compound **143**, and with diethylene-triamine the transamination is accompanied by intramolecular nucleophilic substitution of the α-fluorine atom giving compound **146** (93IZV1773). Heating compound **143** with diethylenetriamine but gave the 1,4-diazepine.



Under certain conditions, the reaction of perfluoropent-2-ene with diethylenetriamine and triethylenetetraamine yields polyazaheterocycles: 2,4-trifluoromethyl[10]-1,4-diene **146** and 11,13-trifluoromethyl-[13]-11,13-diene **147**, respectively (92IZV2170, 93IZV1773).



The interaction between perfluoro-2-methylpent-2-ene and ethylenediamine in the presence of triethylamine forms 5,9-bis(pentafluoroethyl)-6,8,8-tris(trifluoromethyl)-9-fluoro-1,4-diazabicyclo[5.2.0]nona-4,6-diene **148**. With hexane-1,6-diamine, the product is 11-(pentafluoroethyl)-10-trifluoromethyl-1,8-diazabicyclo[7.2.0]undeca-8,10-diene **149** (99IZV1578). The structure of **148** was confirmed by X-ray analysis (Fig. 7) (99IZV1578).



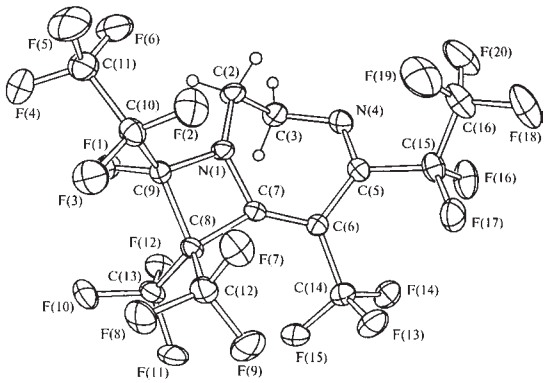
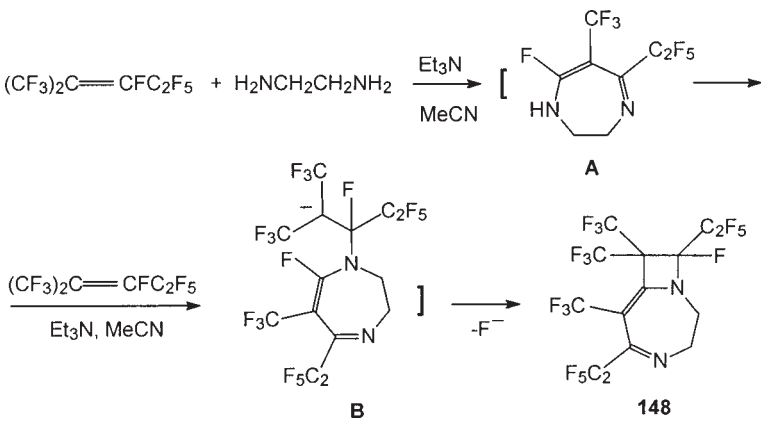


Fig. 7. Crystal structure of 9-fluoro-5,9-bis(pentafluoroethyl)-6,8,8-tris(trifluoromethyl)-1,4-diazabicyclo[5.2.0]nona-4,6-diene **148** acording to X-ray diffraction data (99IZV1578).

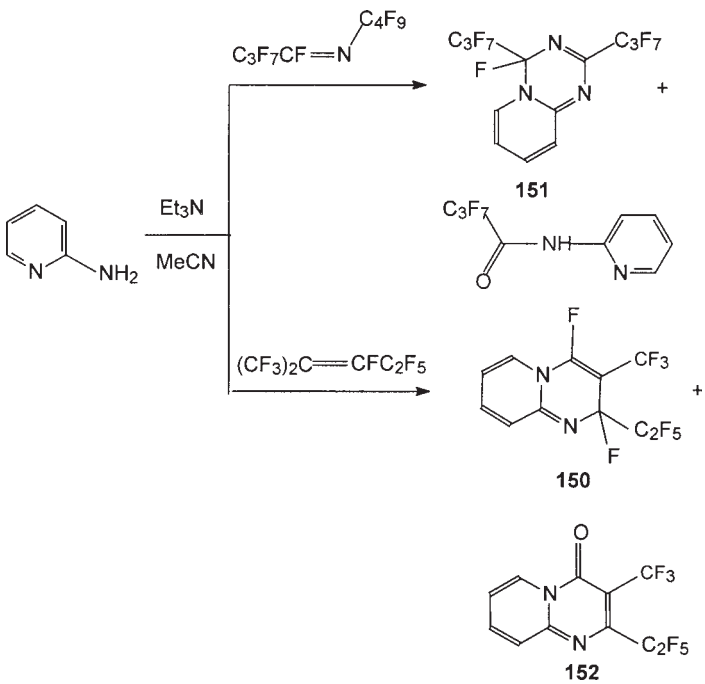
The formation of compound **148** may be represented by the following scheme:



Apparently, ethylenediamine initially attacks the carbon atom of the double bond to give an anion. Elimination of the fluoride ion from the CF_3 group and elimination of HF affords *N*(2-(trifluoromethyl)-perfluoropent-1-en-3-ylidene)ethylene-1,2-diamine. Subsequent transformations of this compound can follow different pathways. For instance, one pathway includes intramolecular nucleophilic cyclization, resulting in compound **A**. This product can react with perfluoro-2-methylpent-2-ene

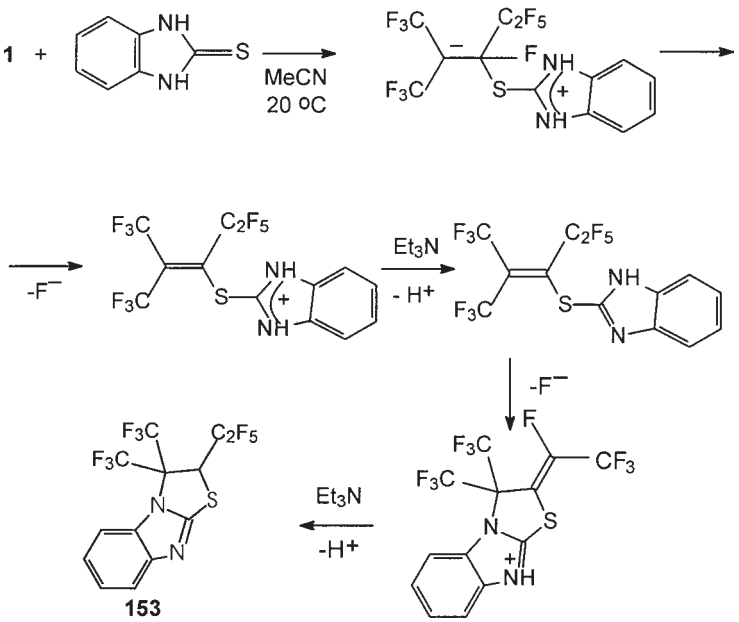
to give anion **B**. Intramolecular cyclization of the anion gives compound **148** (99IZV1578).

To construct a pyridopyrimidine ring, one generally uses condensations based on the amidine-type fragment of 2-aminopyridine and its derivatives with various acylating and alkylating agents. Reactions between 2-aminopyridine and perfluoro-2-methylpent-2-ene as well as perfluoro-5-azanon-4-ene in the presence of triethylamine lead to 2,4-difluoro-2-pentafluoroethyl-3-trifluoromethyl-2*H*-pyrido[1.2-*a*]pyrimidine **150** and 2-fluoro-2,4-bis-(heptafluoropropyl)-2*H*-pyrido[1,2-*a*][1.3.5]triazine **151**, respectively. In compound **150**, the fluorine atom in the 4 position is easily replaced by an hydroxy group when the compound is allowed to stay in a humid atmosphere; the reaction forms 2-pentafluoroethyl-3-trifluoromethyl-pyrido[1.2-*a*]pyrimidin-4-one **152**, whose structure was confirmed by X-ray analysis (2001UP1).



The reaction between perfluoro-2-methylpent-2-ene **1** and benzimidazoline-2-thione in the presence of triethylamine forms (2*E*)-2-(1,2,2,2-tetra fluoroethylidene)-3,3-bis(trifluoromethyl)-2,3-dihydro-[1,3]thiazolo-[3,2-*a*]-benzoimidazole **153** (Table IV), whose structure was confirmed by X-ray

analysis (01IZV1027, 02BKCS1017). The following reaction scheme is suggested:

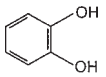
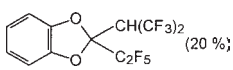
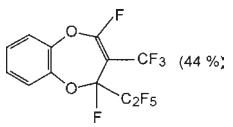
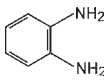
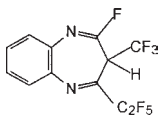
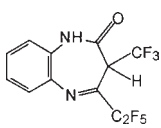
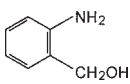
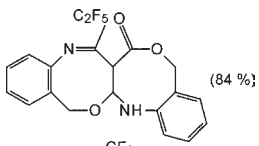
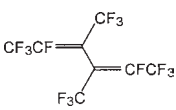
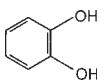
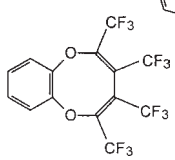
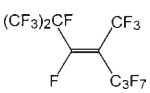
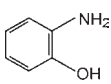
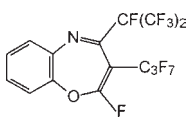
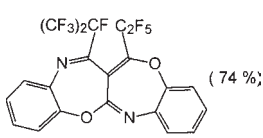
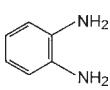
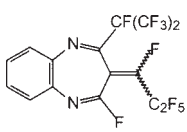
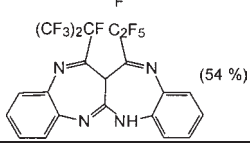


It is assumed that at the initial stage, after benzimidazoline-2-thione has been added to compound **1**, the resultant anion formed, then is deprotonated by triethylamine added to the resulting suspension. The ensuing intermediate undergoes intramolecular heterocyclization into compound **153**. Using acetonitrile as a solvent is also essential because of its low ability to undergo proton transfer and the low solubility of benzimidazoline-2-thione in it. This combination of properties initially yields the kinetic product and then leads to activation of the second nucleophilic center.

Interaction of internal perfluoroolefins with nucleophilic reagents such as *ortho*-difunctional benzenes forms new types of five-, seven-, and nine-membered benzoheterocycles (Table VI).

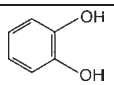
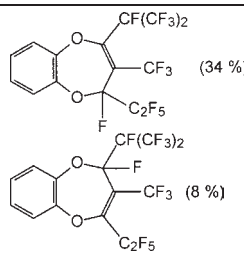
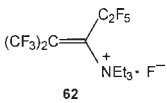
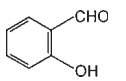
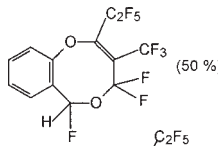
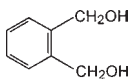
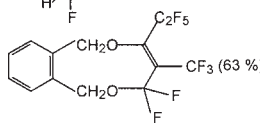
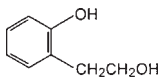
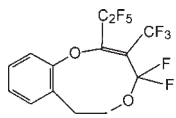
In this case, aprotic bipolar solvents and triethylamine are employed. Thus, interaction of perfluoro-2-methylpent-2-ene with 2-aminophenol in the presence of triethylamine in diethyl ether affords 4-fluoro-2-(pentafluoroethyl)-3-(trifluoromethyl)-1,5-benzoazepine **154** (80JFC(16)75).

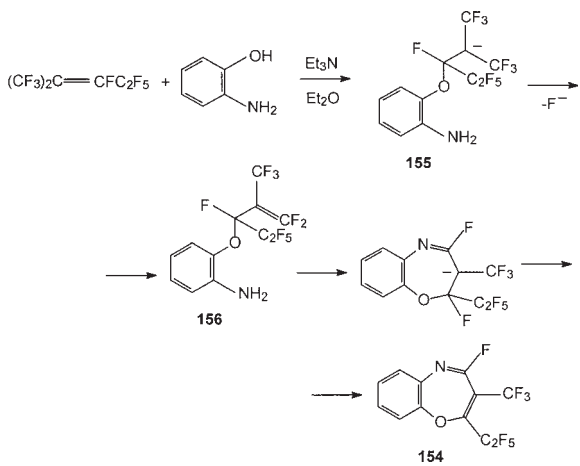
Table VI. REACTIONS OF PERFLUOROOLEFINS WITH *ortho*-BIFUNCTIONAL BENZENES

Perfluoroolefin	Nucleophile	Product (Yield, %)	References
$(CF_3)_2C{=}CFC_2F_5$		 (20 %);  (44 %);	80JFC(16)75
		 	80JFC(16)75
		 (84 %);	93JOC6671
			97JCS(P1)1457
		  (74 %);	80JFC(16)75
		 (30 %);  (54 %)	80JFC(16)75

(*Continued*)

Table VI. Continued

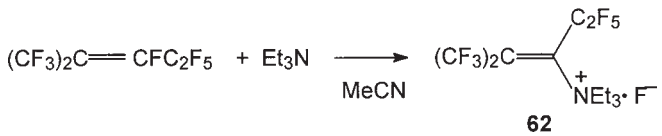
Perfluoroolefin	Nucleophile	Product (Yield, %)	References
			80JFC(16)75
 **62**			81JFC(18)447
			81JFC(18)447
			81JFC(18)447



The authors suggested the following scheme. At the first stage, the O-nucleophilic attack at the carbon atom of the internal multiple bond generates carbanion **155**, stabilized by elimination of the fluoride anion

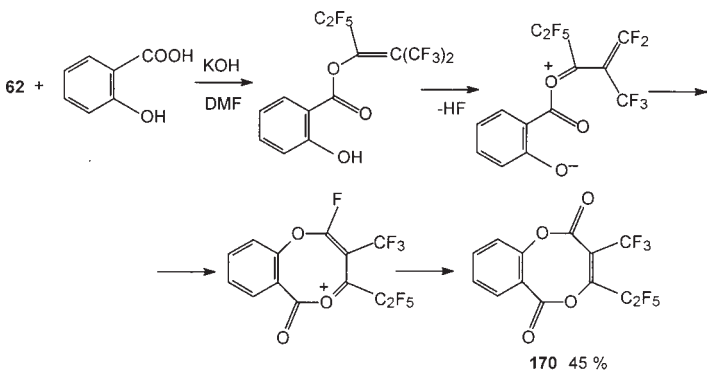
from the CF_3 group, forming olefin **156**. Intramolecular nucleophilic cyclization by N-nucleophilic attack at the carbon atom of the terminal multiple bond leads to the final reaction product **154**.

Salicylic acid and salicylaldehyde possess low nucleophilicity and are capable of reacting only with very strong electrophiles. In reactions with perfluoroolefins, these compounds are used as nucleophiles after preliminary activation of the starting olefin. For example, the olefin is converted into a salt of the perfluoroalkenyltrialkyl-ammonium ion by using trialkylamines **62** (81JFC(18)447). This salt has a positively charged nitrogen center thereby increasing the positive charge on the α-carbon atom and the efficiency of nucleophilic attack at this carbon atom.



62

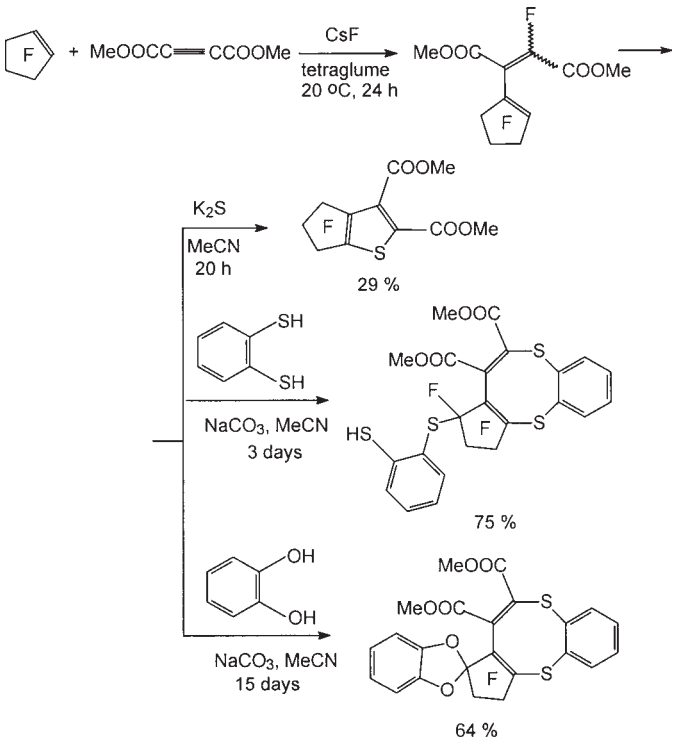
In the reaction of salicylic acid and salicylaldehyde with salt **62**, the products are 4-(pentafluoroethyl)-3-(trifluoromethyl)-2*H*,6*H*-1,5-benzodioxosine-2,6-dione and 2-(pentafluoroethyl)-4,4,6-trifluoro-3-(trifluoromethyl)-4*H*,6*H*-1,5-benzodioxosane, respectively (81JFC(18)447). The following reaction route was suggested. The O-nucleophile initially interacts with the salt to give a compound with a terminal double bond and carboxy multiple bond with a positively charged oxygen atom. Intramolecular cyclization then leads to a product in which a fluorine atom is replaced by an hydroxy group with subsequent formation of the reaction product on tautomerization.



170 45 %

The mixture of the *E* and *Z* isomers of methyl 2-fluoro-3-(heptafluorocyclopent-1-enyl)-4-methoxypenta-2,4-dienoate obtained by the reaction of

pentafluorocyclopentene with dimethyl acetylenedicarboxylic ether in the presence of cesium fluoride in tetraglyme (yield 40%) reacts with K_2S, pyrocatechol, and 1,2-benzodithiol, forming heterocyclic compounds (01JFC(107)171).



IV. Conclusions

These results demonstrate the possibility of synthesizing new types of heterocyclic system. Reactions of perfluoroolefins with bidentate nucleophiles in the presence of bases lead to various heterocycles with five-, six-, seven-, and eight-membered rings containing perfluoroalkyl groups; they have been actively studied. The approach enhancing the electrophilicity of the starting perfluoroolefin by transforming it into a salt by the action of trialkylamines enables one to perform reactions with low-nucleophilic reagents due to the increased positive charge on the carbon atoms of the double bond thereby accelerating a reaction with a nucleophile. This

methodology can be used as an efficient way to synthesize various heterocycles with perfluorinated alkyl substituents. Thus syntheses of condensed polycyclic heterocycles using perfluoro-2-methylpent-2-ene and ambidentate nucleophiles is one useful approach yielding new types of heterocycles on varying the structure of the perfluoroolefin. Systematic studies of the reactivity of perfluoroolefins towards nucleophiles is attractive, since it extends the possible syntheses of fluorinated heterocyclic compounds. Reactions of internal perfluoroolefins with nucleophiles are especially interesting because different reagents and reaction conditions can lead to various organofluoro products.

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The Synthesis of Heterocyclic Compounds with Hypervalent Organoiodine Reagents

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I. Introduction

The impressive development of hypervalent organoiodine chemistry during the past three decades and incorporation of organoiodine(III) and organoiodine(V) reagents into the synthetic arsenal are thoroughly summarized in three monographs (92MI1, 97MI1, 03MI1) and numerous reviews (81CSR377, 83MI1, 83MI2, 83YGK251, 84CHEC563, 84S709,

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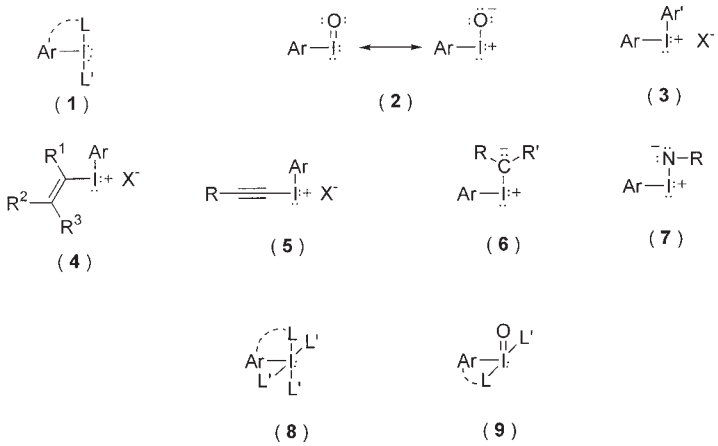
86ACR244, 86YGK660, 87RCR826, 89RCR544, 89RHA92, 90S431, 90SL365, 92ACR529, 92AGE274, 92MI2, 93MI1, 94H409, 94MI1, 94SL221, 95MI1, 95MI2, 95MI3, 95YGK893, 96CRV1123, 96CRV1757, 96PAC881, 97RHA133, 97OPP409, 97RHA213, 97T1179, 98AHC1, 98SL221, 98T10927, 99MI1, 99MI2, 99OR273, 99S1271, 00JOM494, 00MI1, 00RCR105, 00CSR315, 01MI1, 01OR327, 02ACR12, 02CRV2523, 02MI1). The current popularity of polyvalent iodine reagents can be attributed, in part, to their relatively benign nature, in comparison with toxic heavy-metal oxidants such as Tl(III) and Pb(IV) that exhibit similar reactivity patterns with organic substrates. However, this consideration alone fails to convey the uniqueness and versatility of the hypervalent iodine manifold. In this review, the utility of hypervalent organoiodine reagents for the synthesis of heterocyclic compounds, ranging from classical ring structures to natural products, is surveyed. The information is organized by reagent and reaction types. For example, heterocyclic syntheses with aryl-λ^3-iodanes are divided among α-carbon oxidations, cyclodehydrogenations, biaryl couplings, phenolic oxidations, radical cyclizations and oxidative rearrangements; although it is recognized that many reactions fit more than one category. The structures, equations, and schemes represent **selected** transformations and may not include exhaustive tabulations of all reported R-groups and structural types, especially when they cannot be economically summarized.

Several reviews devoted to heterocyclic synthesis with polyvalent iodine reagents have been published (94H409, 94MI1, 94SL221, 98AHC1, 00MI1). Two of these are centered on specific reagents, while a third is focused on nitrogen heterocycles. This review is meant to provide continuity with the earlier comprehensive treatment of this subject by Moriarty and Prakash in *Advances in Heterocyclic Chemistry* (98AHC1). Literature coverage is primarily for the 6-year period, 1997–2002, but earlier publications are often cited for the sake of completeness.

II. Hypervalent Organoiodine Reagents

The hypervalent iodine reagents discussed in this article are derived from iodoarenes and, for clarity of treatment, are separated into standard structural categories; namely, the aryl-λ^3-iodanes, **1** and **2**, the iodonium salts, **3**–**5**, the iodonium ylides, **6** and **7**, and the aryl-λ^5-iodanes, **8** and **9**.



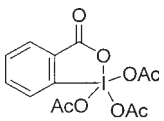
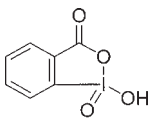
Some specific reagents of importance to this review are shown in Table I and are identified with names commonly used in the literature; selected acronyms are also given. The reader is alerted, however, that while some acronyms (HTIB, IBX, DMP) appear to have gained general acceptance, others depend on the nomenclature preferences of individual authors. For example, $PhI(OAc)_2$ is variously designated in the literature as DAIB, DIB, BAIB, IBD, PID, PIA, and PIDA. Acronyms for $PhI(OCOCF_3)_2$ include BTIB, BTI, IBTA, and most commonly PIFA [i.e., for phenyliodosyl- or phenyiodine(III) bis(trifluoroacetate)].

Single crystal X-ray structures of most of the compounds in Table I have been reported: **10** (77AX(B)1620, 79JCS(D)854), **11** (84AX(C)877, 84JCS(D)1709), **12** (76JOC3609), **15** (95IC3210), and **17** (81CSC489, 97JCS(P2)589). In addition, the structure of iodosylbenzene (**13**), an amorphous solid, has been ascertained by EXAFS and X-ray powder diffraction methods (94JCS(CC)2367). Some of the reagents (DAIB, BTIB, HTIB, and DMP) are also commercially available. Finally, it is noted that the phenyl-λ^3-iodanes and their ring-substituted analogs serve as important progenitors of iodonium reagents.

A. Aryl-λ^3-Iodanes

Aryl-λ^3-iodanes of type **1** are stabilized by the presence of electronegative heteroatom ligands (L and L′). They are essentially T-shaped at iodine and are generally regarded as pseudo trigonal–bipyramidal systems, at least from the standpoint of primary bonding. According to a commonly accepted MO-model, the L–I–L′ triad in **1** is held together by a three center-four

Table I. SELECTED HYPERVALENT ORGANOIODINE REAGENTS

Reagent	Name	Acronym
$PhI(OAc)_2$ (**10**)	(Diacetoxyiodo)benzene, Iodobenzene Diacetate	DAIB
$PhI(OCOCF_3)_2$ (**11**)	[*Bis*(trifluoroacetoxy)iodo]benzene	BTIB
PhI(OH)OTs (**12**)	[Hydroxy(tosyloxy)iodo]benzene, Koser's Reagent	HTIB
PhI=O (**13**)	Iodosylbenzene, Iodosobenzene	–
PhI(CN)OTf (**14**)	Cyano(phenyl)iodonium Triflate	–
PhI=NTs (**15**)	[(Tosylimino)iodo]benzene, ((*N*-*p*-Toluenesufonyl) imino)phenyliodinane	–
 (**16**)	1,1,1-*Tris*(acetoxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one, Dess-Martin Periodinane	DMP
 (**17**)	*o*-Iodoxybenzoic Acid	IBX

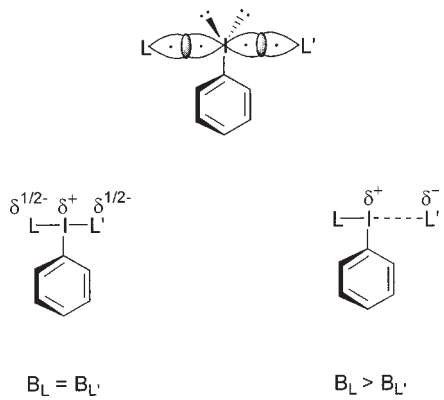
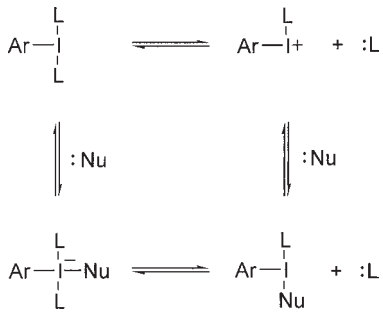
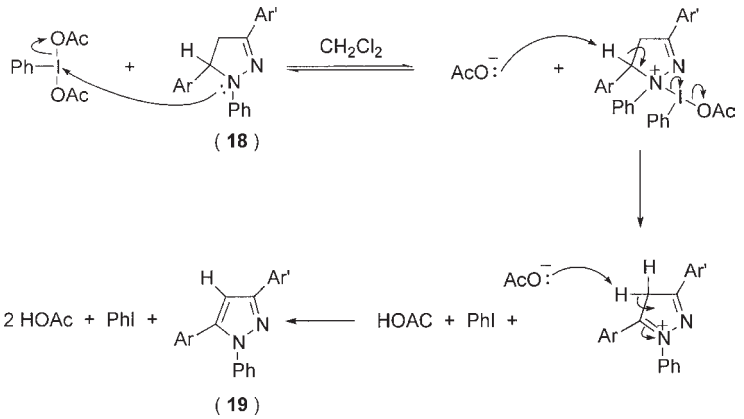


Fig. 1. Schematic representation of the [3c-4e] bond in phenyl-λ^3-iodanes.

electron [3c-4e] bond and is inherently polarized; either symmetrically, when $L = L'$, or unsymmetrically, when $L \neq L'$ and the ligands differ in basicity, B (Fig. 1) (69AGE54, 83MI1, 83SCI509). When ΔB is large, the structure of **1** approaches the iodonium limit, $ArI^+L\ L'^-$. Thus, in addition to being oxidants, the aryl-λ^3-iodanes **1** are electrophilic at iodine and undergo ligand exchange with nucleophiles via the associative and dissociative



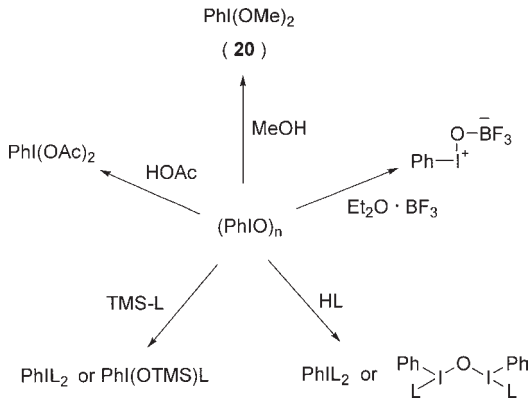
Scheme 1



Scheme 2

pathways depicted in Scheme 1 (03MI1); this includes the nucleophilic sites of organic functional groups.

Many reactions of aryl-λ^3-iodanes **1** with organic substrates are initiated by ligand exchange and can be rationalized with heterolytic mechanisms. In some cases, stable iodonium compounds are obtained (i.e., aryliodination), but more generally, the substrates are oxidized, and the aryliodanes are reduced to iodoarenes. The modes of oxidation are diverse and sometimes depend on the specific aryliodane and conditions under which it is employed. The polar mechanism shown in Scheme 2 for oxidation of the pyrazolines **18** to the pyrazoles **19** with (diacetoxyiodo)benzene in dichloromethane serves to illustrate some of these points (97SC2683, 01MI2). It is emphasized, however, that organic reactions of aryl-λ^3-iodanes can also follow electron-transfer and radical pathways (97RHA213), and that heterolytic mechanisms found in the



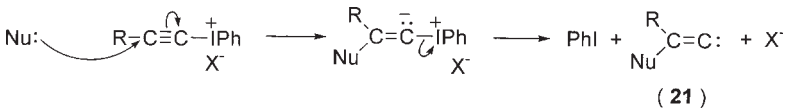
Scheme 3

literature may sometimes be based more on intuition than incontrovertible evidence.

Among the iodosylarenes **2**, iodosylbenzene (**13**) is the most well-investigated (97MI1), and might equally be grouped with the iodonium ylides, **6** and **7**. Because of its zwitterionic character, iodosylbenzene is polymeric in the solid-state [$(PhIO)_n$] and insoluble in common organic solvents. However, it can be "depolymerized" (and activated) with Lewis acids such as $Et_2O \cdot BF_3$ and so employed in various solvents (85TL4501, 89RHA92). Iodosylbenzene dissolves solvolytically in methanol (83IC1563, 86ACR244) and acetic acid to give (dimethoxyiodo)benzene (**20**) and DAIB, respectively, and reacts with various Brönsted acids and trimethylsilyl reagents (90JOU1633, 90TL4821, 91TL733) to give aryl-λ^3-iodanes of type **1**, or, in some cases, their μ-oxo analogs (Scheme 3).

B. Iodonium Salts

Whether the iodonium salts are truly iodonium salts, and not highly-polarized, unsymmetrical λ^3-iodanes, has recently been questioned by Ochiai on the basis of X-ray evidence (03MI1). For example, diphenyliodonium chloride, or "chloro(diphenyl)-λ^3-iodane" [$Ph_2I^+Cl^-$ or $Ph_2\overset{\delta+}{I}\ -\overset{\delta-}{Cl}$], exists in the solid-state as a centrosymmetric dimer comprising two ψ-TBP units and exhibits a C–I–C angle of 92.3°, far from the expected tetrahedral angle of an onium salt (77JCS(D)217). In either case, organoiodine(III) compounds of types **3**–**5**, with two unsaturated carbon ligands, although electrophilic, are less electrophilic at iodine than **1**, and they are weaker chemical oxidants. For example, while aryl-λ^3-iodanes **1**



(**21**)

Scheme 4

are readily reduced by the iodide ion and can be assayed iodometrically, diaryliodonium ions can be isolated as stable iodide salts, $Ar_2I^+I^-$ (56MI1).

From a synthetic standpoint, diaryliodonium salts are premier reagents for the arylation of nucleophilic substrates, with and without transition metal catalysis, and are useful components for palladium-catalyzed coupling and carbonylation reactions (83MI2, 84S709, 92MI1, 96CRV1123, 97MI1, 99S1271, 02CRV2523, 03MI1). Appropriately substituted diaryliodonium salts serve as convenient benzyne precursors (97OPP409).

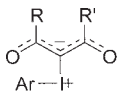
Alkenyl(aryl)iodonium salts **4** are similarly efficacious for the alkenylation of nucleophiles. Such reactions proceed by various mechanisms, including addition–elimination, α-elimination, vinylic S_n1 and S_n2, and ligand-coupling (LC) pathways (89RHA92, 95MI3, 00JOM494, 00RCR105, 02ACR12).

Alkynyl(aryl)iodonium salts, **5**, react with various nucleophiles by a Michael-addition/α-elimination sequence leading to alkylidenecarbenes **21** (Scheme 4) (89RHA92, 92AGE274, 95MI2, 95MI3, 98T10927, 99MI2). This important pattern of reactivity was first elucidated by Ochiai and his co-workers in the mid-1980s (86JA8281). Whether the carbenes rearrange to alkynes (i.e., the alkynylation pathway), or undergo intra- or intermolecular insertion or addition reactions depends, to some extent, on the choice of nucleophile, the structure of R, and composition of the reaction medium. Alkynyliodonium salts also find application in Diels–Alder and [3 + 2] dipolar cycloaddition reactions, cyclocondensations with ambident nucleophiles, and transition metal-catalyzed coupling and carbonylation reactions.

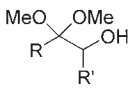
C. Iodonium Ylides

Iodonium ylides of type **6** cannot be isolated, unless the "carbanion" center is substantially stabilized (83MI1, 92MI1, 97MI1, 02MI1). For example, although iodonium enolates **22** can be prepared by base-catalyzed condensations of DAIB or iodosylbenzene with β-dicarbonyl compounds, they are not similarly available from unactivated ketones and esters. Indeed, cyclic and acyclic mono-ketones are converted to α-hydroxy dimethylketals **23** with DAIB (or **13)** in KOH/MeOH (86ACR244, 99OR273). Other

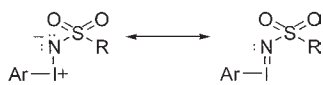
electron-withdrawing groups, such as NO_2, SO_2Ph, and $^{+}PPh_3$, can be employed to stabilize the ylidic structures, and iodine(III)–carbon ylides derived from nitrogen heterocycles (e.g., indole, pyrazole, dicyanoimidazole) are also known. The iodine(III)–nitrogen ylides **7** require similar stabilization for isolation, the most prominent examples being the *N*-sulfonyliminoiodanes **24**. It is emphasized, however, that unstable iodonium ylides can sometimes be employed *in situ* for synthetic purposes. In the area of heterocyclic synthesis, iodonium ylides serve as "1,3-dipoles" in cyclocondensation reactions, carbenoid precursors, and nitrene-transfer reagents (83MI1, 92MI1, 97MI1, 02MI1).



(**22**)



(**23**)



(**24**)

D. Aryl-λ^5-Iodanes

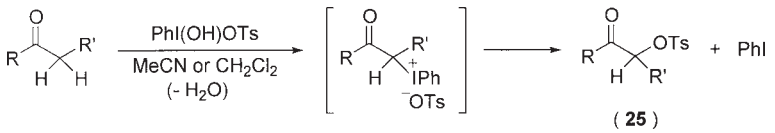
Except for the Dess-Martin periodane, which has been widely employed as a selective oxidant in various synthetic protocols (97MI1, 02CRV2523), organoiodine(V) compounds have received much less attention than their iodine(III) counterparts for organic synthesis. However, recent publications in this area indicate that this is likely to change.

III. Synthesis of Heterocyclic Compounds

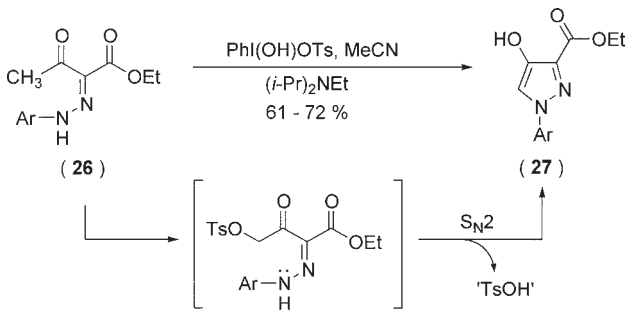
A. Synthesis with Aryl-λ^3-Iodanes

1. *Oxidations at α-Carbon*

The treatment of ketones and β-dicarbonyl compounds with [hydroxy(tosyloxy)iodo]benzene (HTIB) provides ready access to α-tosyloxy ketones **25** (Scheme 5) (82JOC2487, 90SL365, 92TL7647, 01MI1). The tosyloxy ketones (α-TK) are excellent non-lachyramatory alternatives to α-halogeno ketones for the synthesis of five- and six-membered heterocyclic compounds, especially the azoles and related systems (94H409, 98AHC1). For example, the keto arylhydrazones **26** react with HTIB to give the *N*-arylpyrazoles **27**, presumably through α-TK intermediates (Scheme 6) (91SC1583).



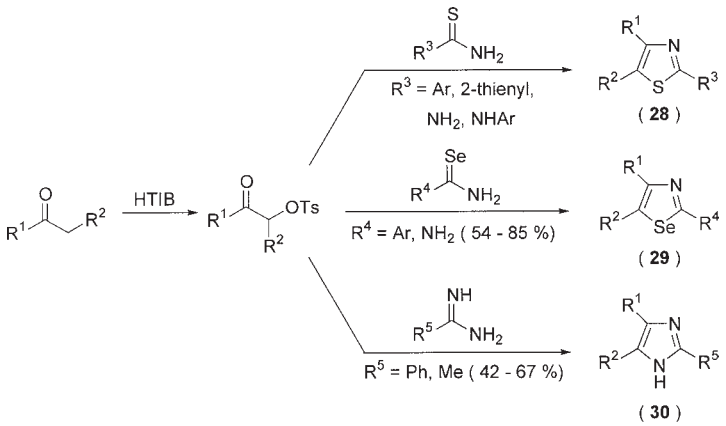
Scheme 5



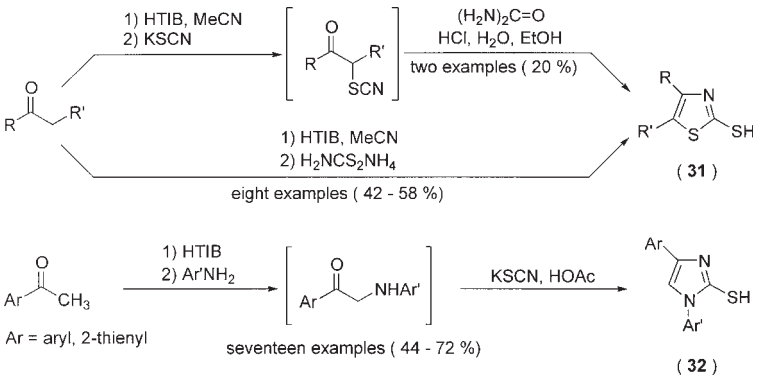
Scheme 6

Intramolecular cyclizations of the type shown in Scheme 6 have been employed for the synthesis of acyloxylactones (90TL2001) and 2-aroylbenzofuran-3(2*H*)-ones (92S629) from appropriate ketonic precursors; lactonizations of 4-aroylbutyric acids with 4-poly[hydroxy(tosyloxy)iodo]-styrene have also been demonstrated (01JCR(S)480). However, most applications of HTIB in heterocyclic synthesis are based on the biphilic reactivity of α-TK with multidentate nucleophiles. For example, the sequential treatment of ketones with HTIB and thioamides (or thioureas) leads to the corresponding thiazoles **28**, and represents the α-tosyloxy ketone version of the classical Hantzsch-thiazole synthesis (Scheme 7) (92MI3, 92S845, 95IJC(B)660). Similar preparations of the selenazoles **29** (92S845, 00S1219) and 1*H*-imidazoles **30** (01S2075) have been reported (Scheme 7). At a practical level, transformations of this type can be effected by initial isolation of the α-TK, or by a one-pot procedure in which the α-TK are employed *in situ*, sometimes after a change in solvent.

Two approaches to the mercaptothiazoles **31** by the HTIB-method have been described; one in which the α-TK are initially converted to α-thiocyanato ketones, and a more direct route involving treatment of the α-TK with ammonium dithiocarbamate (Scheme 8) (93SC1455, 01SC415). The mercaptoimidazoles **32** can be prepared by a one-pot sequence in which α-anilino ketones are generated from α-TK intermediates and cyclized with potassium thiocyanate (Scheme 8) (94IJC(B)116).



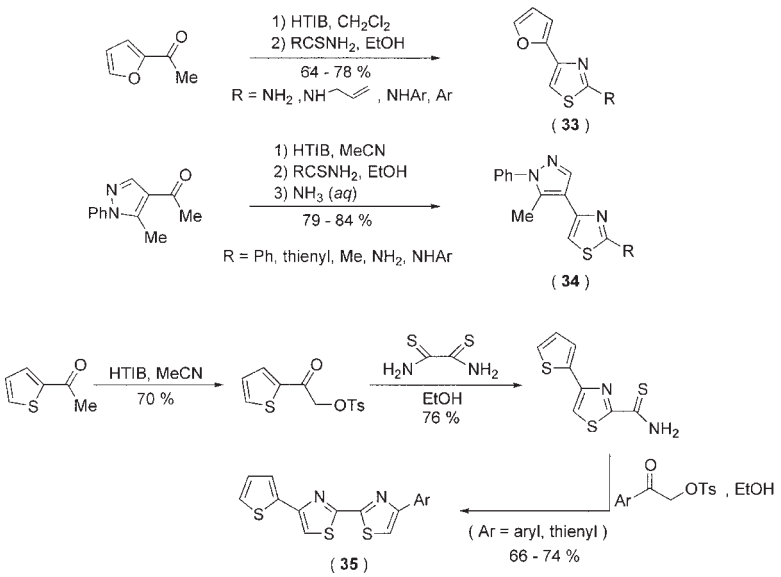
Scheme 7



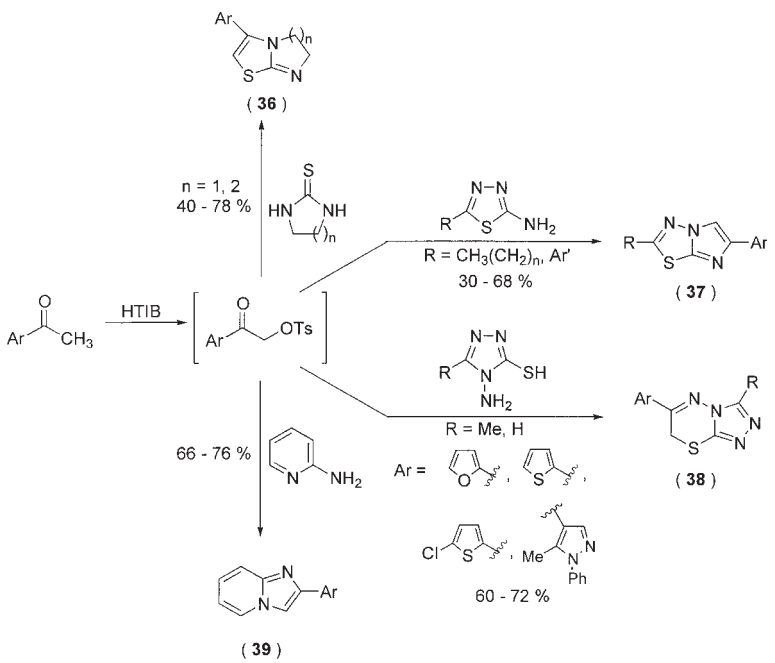
Scheme 8

A notable advantage of the HTIB-method is the ready availability of α-tosyloxy derivatives of heteroaryl methyl ketones, thus enabling convenient syntheses of bi-, ter-, and quaterheterocycles. In addition to representatives already cited, examples of such compounds include the (furyl)thiazoles **33** (98SC2371), (pyrazolyl)thiazoles **34** (97JIC940), and the aryl(thienyl)- and bis(thienyl)bithiazoles **35** (01SC3747) shown in Scheme 9.

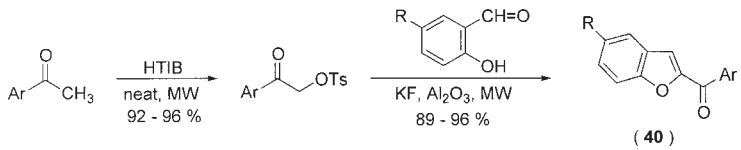
One-pot, HTIB-mediated syntheses of various bridgehead heterocycles, **36**–**39**, have also been reported (Scheme 10). In this case, the α-TK are exposed to multidentate nucleophiles which possess heterocyclic structures; more specifically, cyclic thioureas (92JCS(P1)707, 92SC1293), 2-amino-1,3, 4-thiadiazoles (94JCR(S)38, 94MI2, 94IJC(B)686), 4-amino-5-mercapto-1, 2,4-triazoles (98SC3133) and 2-aminopyridine (98JIC770) have been utilized



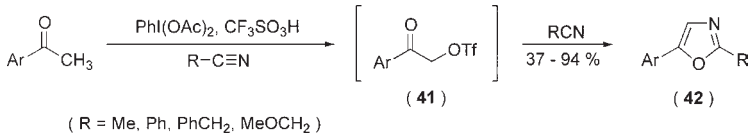
Scheme 9



Scheme 10



Scheme 11



Scheme 12

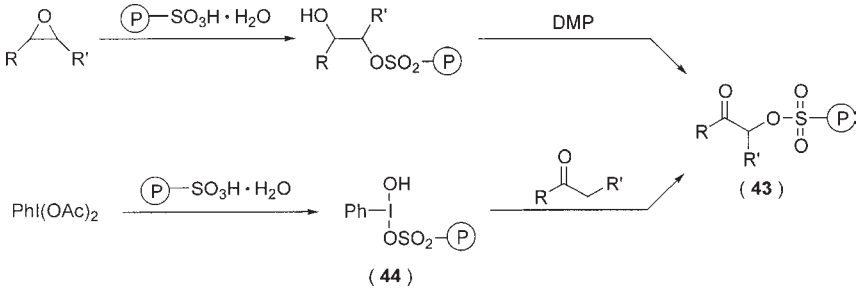
for this purpose. Reaction times for preparation of the imidazopyridines **39** are reduced significantly when the ionic liquid, butylpyridinium tetrafluoroborate, is the mediating solvent (02S1505).

The synthesis of oxygen-heterocycles by intermolecular reactions of α-TK with nucleophiles has received only limited attention. However, α-tosyloxy derivatives of several acetophenones have been prepared by brief exposure of neat HTIB/ketone mixtures to microwave (MW) radiation, and employed on mineral oxide surfaces for microwave-assisted syntheses of thiazoles and 2-aroylbenzofurans **40** (Scheme 11) (98JCS(P1)4093, 99JHC1565).

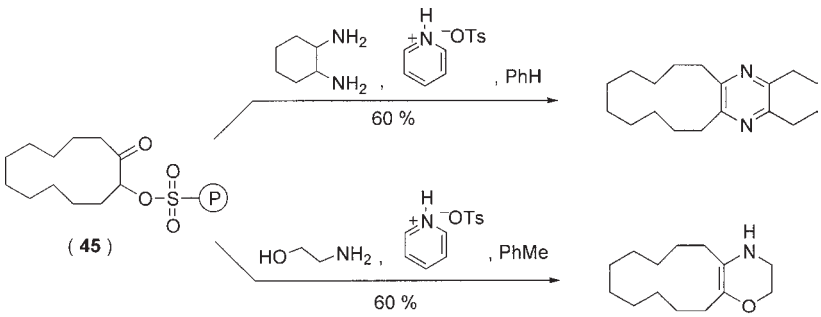
The treatment of acetophenones with DAIB/triflic acid in nitrile solvents leads to the oxazoles **42** (Scheme 12) (98JHC1533). Such reactions presumably involve the intermediate formation of ketol triflates **41** (89TL667) and do not occur with HTIB.

The potential of polystyrene analogs **43** of α-TK for the elaboration of "privileged" heterocycle libraries has been demonstrated (00JA10246, 02JA5718). The synthesis of **43** (22 examples) was accomplished by ring-opening of epoxides with a polystyrene sulfonic acid resin and oxidation of the resulting alcohols with the Dess-Martin periodane; or by the oxysulfonylation of ketones with the polystyrenesulfonate analog **44** of HTIB (Scheme 13). Treatment of the polymer-linked cyclododecanone derivative **45** with bidentate nucleophiles (O, N, and S) in the presence of pyridinium tosylate was investigated in detail and results in the release of ring-fused heterocycles from the solid support; specific examples are shown in Scheme 14.

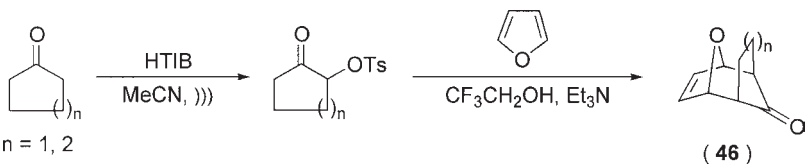
Finally, α-TK, prepared from ketones and HTIB by the sonication technique (92TL7647), have been utilized as precursors to oxallyl



Scheme 13



Scheme 14

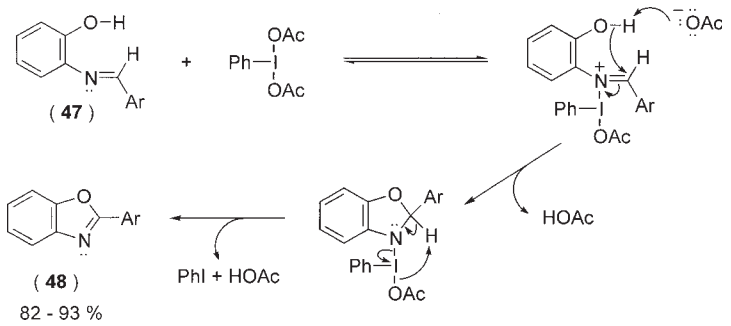


Scheme 15

cations and employed with furan in [4 + 3] cycloaddition reactions for preparations of the oxygen-bridged bi- and tricyclic alkanones **46** (Scheme 15) (02SL489).

2. *Cyclodehydrogenations and Related Oxidations*

(Diacetoxyiodo)benzene (DAIB) is well-suited for the synthesis of azoles from bifunctional substrates via cyclodehydrogenation pathways. Such oxidations occur with C-heteroatom or heteroatom–heteroatom bond



Scheme 16

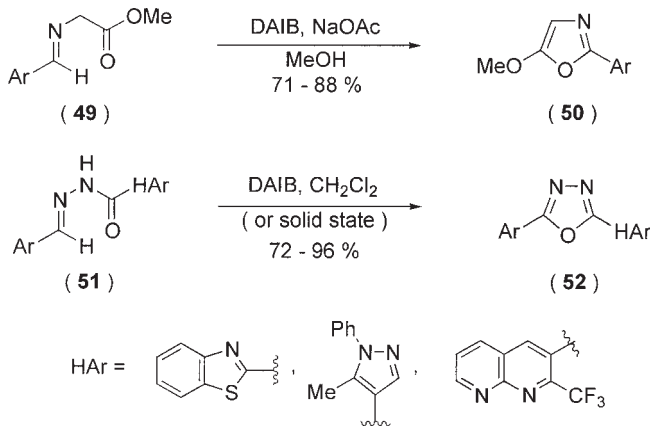
formation and can usually be accounted for by a three-stage "mechanism" featuring (1) ligand-exchange at iodine, (2) cyclization–deprotonation of the resulting iodine(III) intermediate, and (3) deprotonation of the final intermediate with the reductive loss of iodobenzene. This mnemonic is illustrated in Scheme 16 with DAIB-oxidations (MeCN or MeOH) of the *ortho*-phenolic arylaldimines **47** to the benzoxazoles **48** (97TL2621). Similar oxidations of the 3-pyridyl analogs of **47** (Ar = 3-pyridyl) have been reported, the aldimines having been generated *in situ* (99JHC429).

The proximity effect of the functional groups in **47** is instructive. Thus, *N*-aryl aldimines of the type, ArCH=NAr′, are reported to give azoarenes [Ar′N=NAr′] and aldehydes [ArCH=O] with DAIB (77IJC(B)376), while phenols are oxidized to quinones, quinol ethers, or quinone acetals, depending on the nature of the reaction medium (92MI2, 01OR327).

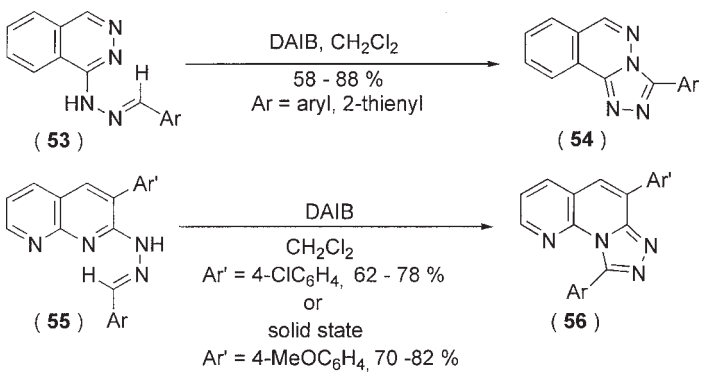
The oxygen atom of the carbonyl group can also participate in C–O bond formation. This has been demonstrated with DAIB-oxidations of the *N*-glycyl imines **49** to the 5-methoxyoxazoles **50**, catalyzed by sodium acetate (00JCR(S)382), and of the acylhydrazones **51** to the 1,3,4-oxadiazoles **52** (98IJC(B)797, 01IJC(B)619) (Scheme 17). Synthesis of the naphthyridine analogs of **52** was effected by grinding solid mixtures of the hydrazones and DAIB with mortar and pestle.

Treatment of the *N*-3-phthalazinyl hydrazones **53** with DAIB results in C–N bond formation and affords the 1,2,4-triazolophthalazines **54** (98IJC(B)583); similar oxidations of the *N*-2-naphthyridinyl hydrazones **55** lead to the 1,2,4-triazolonaphthyiridines **56** (02IJC(B)1894, 02SC2377) (Scheme 18).

Whereas the foregoing oxidations involve the formal loss of two hydrogen atoms from different locations in the substrate, others proceed by dehydrogenation of a single atomic site. For example, admixture of the

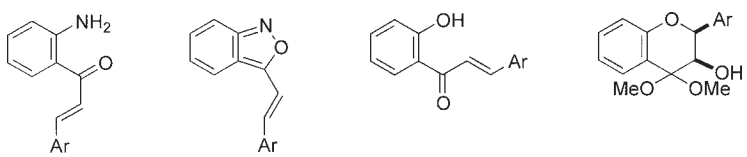


Scheme 17

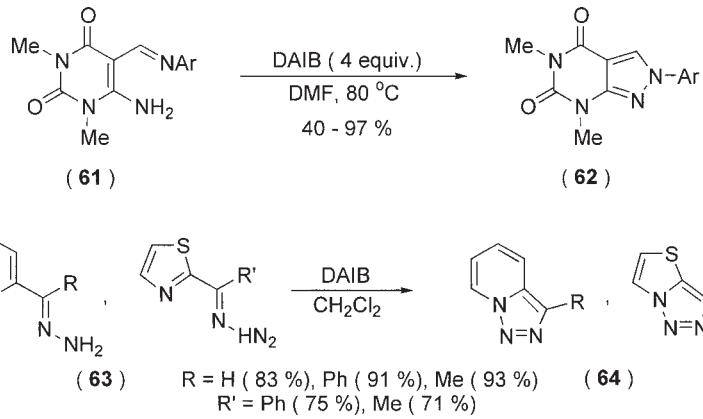


Scheme 18

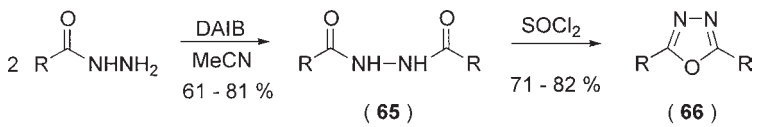
o-aminochalcones **57** with DAIB in methanolic potassium hydroxide [i.e., *in situ* formation of $PhI(OMe)_2$ (94MI1, 99OR273)] provides access to the (*β*-styryl)benzisoxazoles **58** (97TL3147). This transformation (O–N bond formation) was unexpected, since *o*-hydroxychalcones **59** afford flavanone dimethylketals **60** under these conditions (94MI1).



(57) (58) (59) (60)



Scheme 19

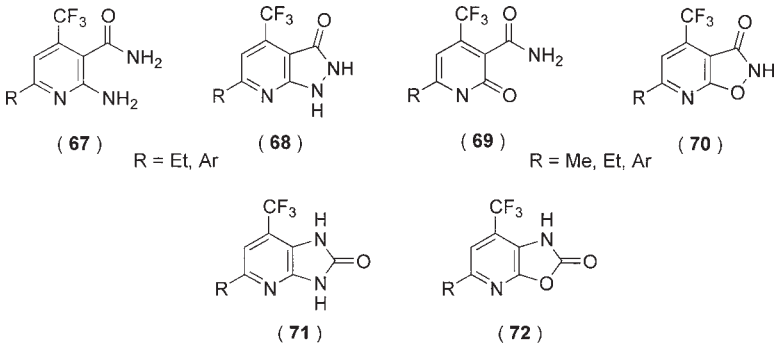


Scheme 20

DAIB-oxidations of the *N*-arylimines **61**, derived from 2-amino-5-formyluracil, lead through N–N bond formation to the pyrazolopyrimidines **62** (Scheme 19) (97SL1409). Oxidative N–N coupling also occurs when the pyridyl- and thiazolyl hydrazones **63** are exposed to DAIB leading, in this case, to the ring-fused 1,2,3-triazolo heterocycles **64** (Scheme 19) (00SC417).

An example of the use of DAIB for intermolecular N–N bond formation is provided by the synthesis of 1,3,4-oxadiazoles **66** from acylhydrazides by the two-step sequence shown in Scheme 20 (97JCR(S)468). The intermediate diacylhydrazides **65** can be isolated or simply generated *in situ* prior to treatment with thionyl chloride.

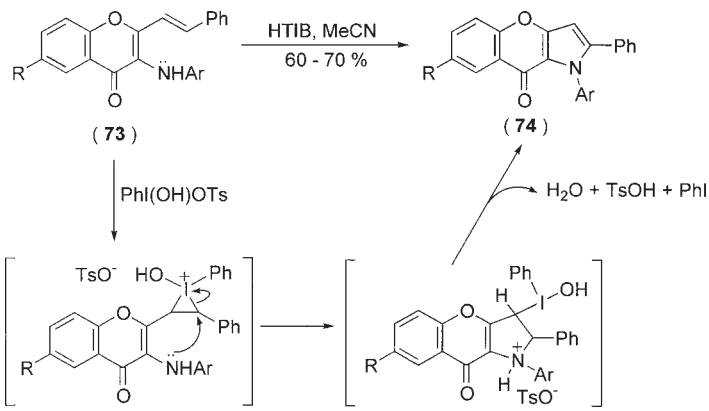
The 2-aminonicotinamides **67** react with [*bis*(trifluoroacetoxy)iodo]benzene (BTIB) in aqueous DMF to give the pyrazolopyridines **68**; under the same conditions, the amidopyridones **69** are converted to the isoxazolopyridines **70** (97SC2217). These results are somewhat suprising, since BTIB, DAIB, and HTIB are useful reagents for the Hofmann rearrangement (Section III.A.6), and the formation of **71** and **72** from isocyanate intermediates might have been expected.



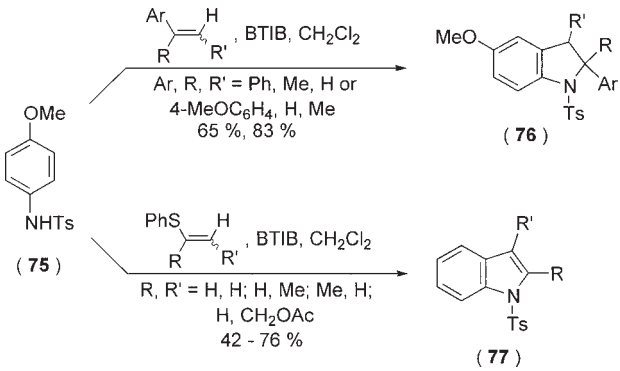
The styryl-enaminone derivatives of flavone, **73**, undergo cyclization to the benzopyranopyrrole-9-ones **74** with HTIB in acetonitrile (Scheme 21) (97IJC(B)536). In view of the known reactivity of HTIB with olefinic substrates (90SL365), this transformation is probably directed by hyperiodination of the *β*-styrene moiety in **73**.

The treatment of *N*-tosyl-*p*-anisidine (**75**) and several of its derivatives with BTIB in the presence of "activated" alkenes provides an interesting example of an intermolecular cyclodehydrogenation sequence (99H1785). Arylpropenes are converted to *N*-tosylindolines **76** under these conditions, while alkenyl sulfides lead to the *N*-tosylindoles **77** (Scheme 22). The intermediate formation of *N*-tosylnitrenium ions in these reactions was suggested.

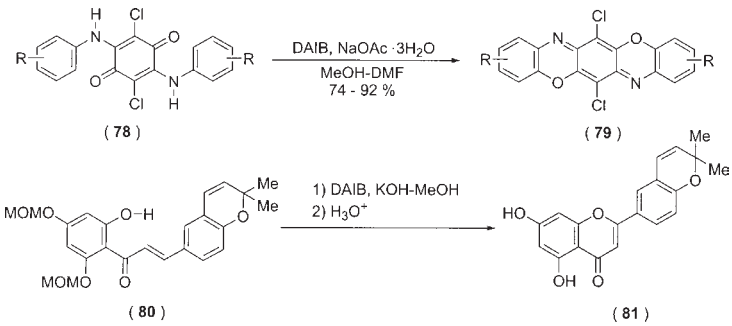
Recent applications of aryliodanes for the preparation of six-membered heterocycles include DAIB-oxidations of the *bis*(arylamino)benzoquinones **78** to the triaryldioxazines **79** (Scheme 23) (99JCR(S)618), and the synthesis



Scheme 21



Scheme 22

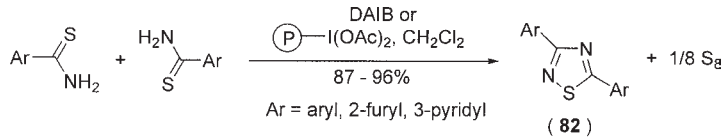


Scheme 23

of several naturally-occurring prenylated flavones from 2′-hydroxychalcones with DAIB in methanolic KOH (98T13867). An example of the latter transformation is the synthesis of yinyanghuo-C (**81**) from the protected chalcone **80** (Scheme 23).

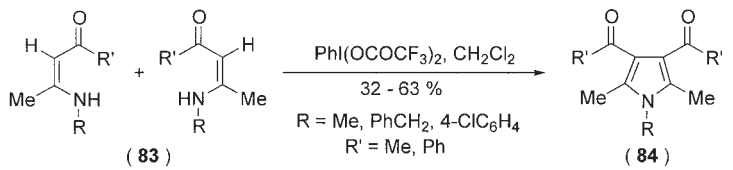
The synthesis of heterocyclic compounds with aryl-λ^3-iodanes extends to oxidative-condensation reactions. This approach has recently been employed for the synthesis of 1,2,4-thiadiazoles **82** by the treatment of thioamides with DAIB or its polystyrene variant (Scheme 24) (02SC2155). The production of **82** in these reactions is accompanied by the formation of elemental sulfur.

Exposure of the enaminones **83** and enamine esters **85** to BTIB affords the highly-substituted pyrroles **84** and **86**, respectively (Scheme 25) (01JCR(S)150, 01SC1619). DAIB is less effective in this context, giving lower yields of **86** from the enamine esters, and leading to replacement of the vinylic hydrogen in enaminone **83** ($R = PhCH_2$, $R' = Ph$) with the acetoxy group, instead of pyrrole formation.

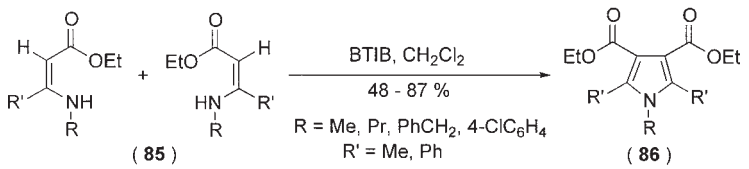


(**82**)

Scheme 24

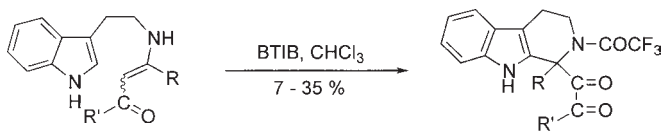


(**83**) (**84**)



(**85**) (**86**)

Scheme 25



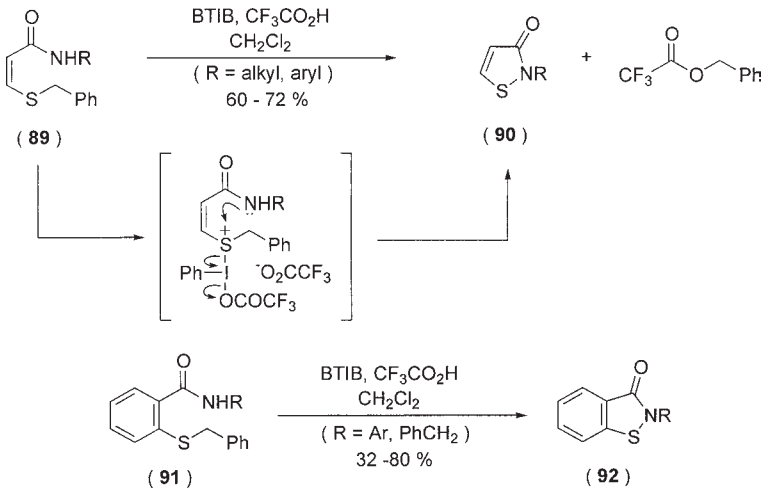
(**87**) (**88**)

R, R' = Me, OEt; Me, Me; Ph, Me; Pr, OEt

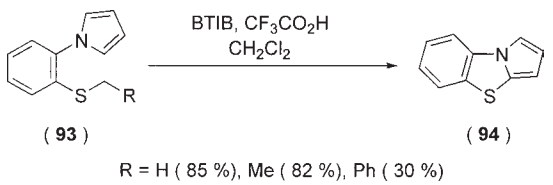
Scheme 26

The enaminones **87**, derived from tryptamine, undergo Pictet-Spengler cyclization to the tetrahydro-β-carbolines **88** with BTIB (Scheme 26) (98TL2865). Admixture of **87** (R = Me, R′ = OEt) with DAIB or HTIB did not result in cyclization of the substrate.

BTIB can be utilized in conjunction with trifluoroacetic acid(TFA) for "interrupted Pummerer reactions" leading to heterocyclic products. This is illustrated in Scheme 27 with BTIB-induced conversions of the benzylsulfanylalkenamides and -benzamides **89** and **91** to the isothiazolones **90** and **92** via N–S bond formation (01MI3, 01H1231). Similar treatment of the 1-(2-alkylthiophenyl)pyrroles **93** affords the pyrrolo[2,1-*b*]benzothiazoles **94**, in this case by C–S bond formation (Scheme 28) (99H1437).



Scheme 27

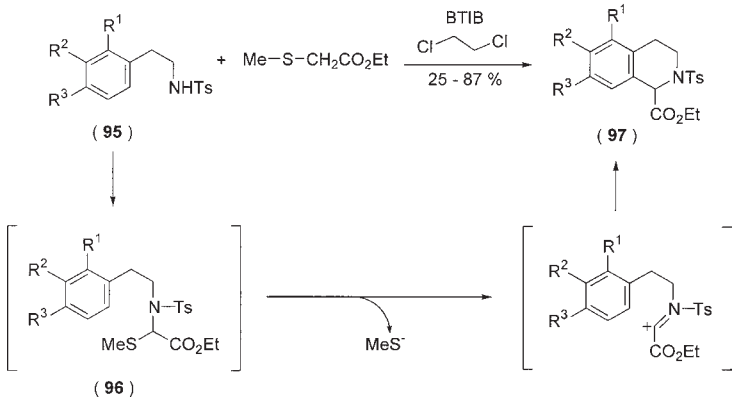


Scheme 28

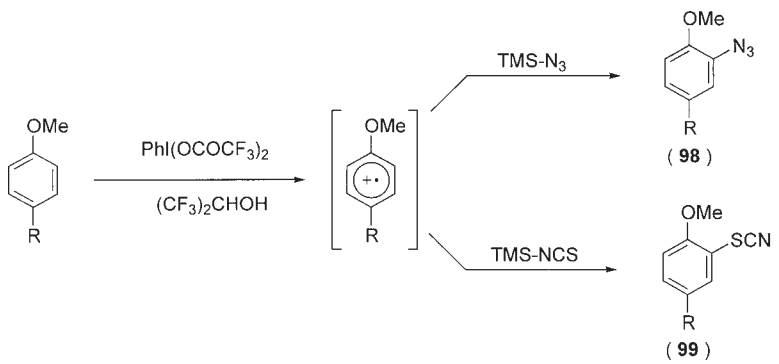
The *N*-tosyl-*β*-phenethylamines **95** react with ethyl (methylthio)acetate in the presence of BTIB to give the *N*-tosyl tetrahydroisoquinoline derivatives **97**, probably through the normal Pummerer product **96** (Scheme 29) (02H1). Pictet-Spengler cyclization of **96**, with the loss of methanethiol, would lead to **97**.

3. *SET Reactions and Biaryl Couplings*

The exposure of aromatic ethers to BTIB in $(CF_3)_2CHOH$ or CF_3CH_2OH (TFE) leads to arene cation-radical intermediates and permits the introduction of nucleophiles (N_3^-, AcO^-, NCS^-, ArS^-) into the alkoxyarene nucleus (94JA3684, 95JOC7144). For example, the treatment of *para*-substituted anisoles with BTIB in the presence of trimethylsilyl azide or -isothiocyanate affords the 2-anisyl azides **98** or 2-anisyl thiocyanates **99**, respectively (Scheme 30).



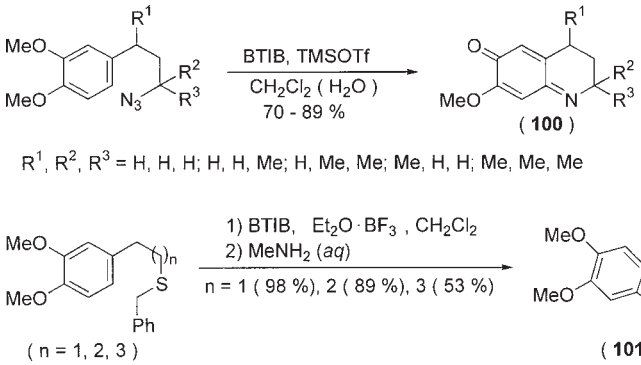
Scheme 29



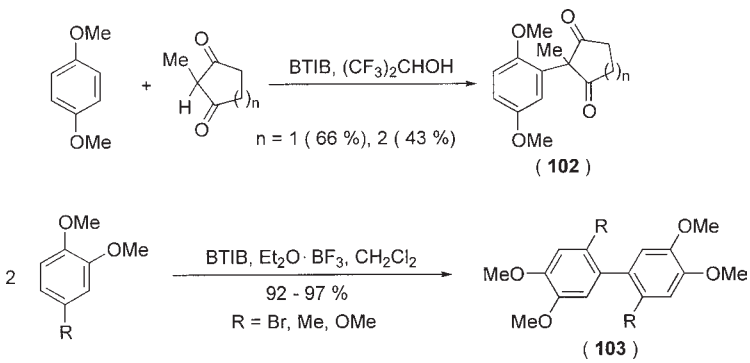
Scheme 30

Intramolecular reactions of this type have been utilized for syntheses of the heterocyclic quinonimines **100** and sulfides **101** from veratroles and anisoles possessing azidoalkyl and benzylsulfanylalkyl side-chains (Scheme 31) (96CC1491, 96CC2225, 99CPB241); and for construction of the pyrroloiminoquinone ring-system found in certain marine alkaloids (98JCS(P1)635, 99CC143). The use of BTIB in combination with trimethylsilyl triflate or $Et_2O \cdot BF_3$ extends the solvent repertoire for such oxidations to dichloromethane and, in the case of sulfide substrates, prevents sulfoxide formation.

BTIB-oxidations of aromatic ethers can also be directed to C,C-bond formation. Intermolecular examples include oxidative heterocouplings of 1,4-dimethoxybenzene with β-dicarbonyl compounds, presumably via their enol tautomers, to the arylated β-dicarbonyl derivatives **102**



Scheme 31

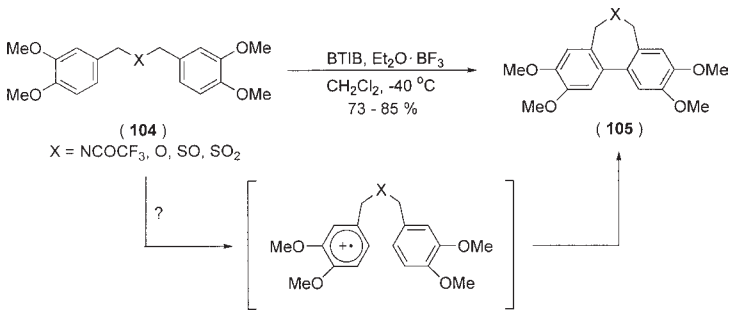


Scheme 32

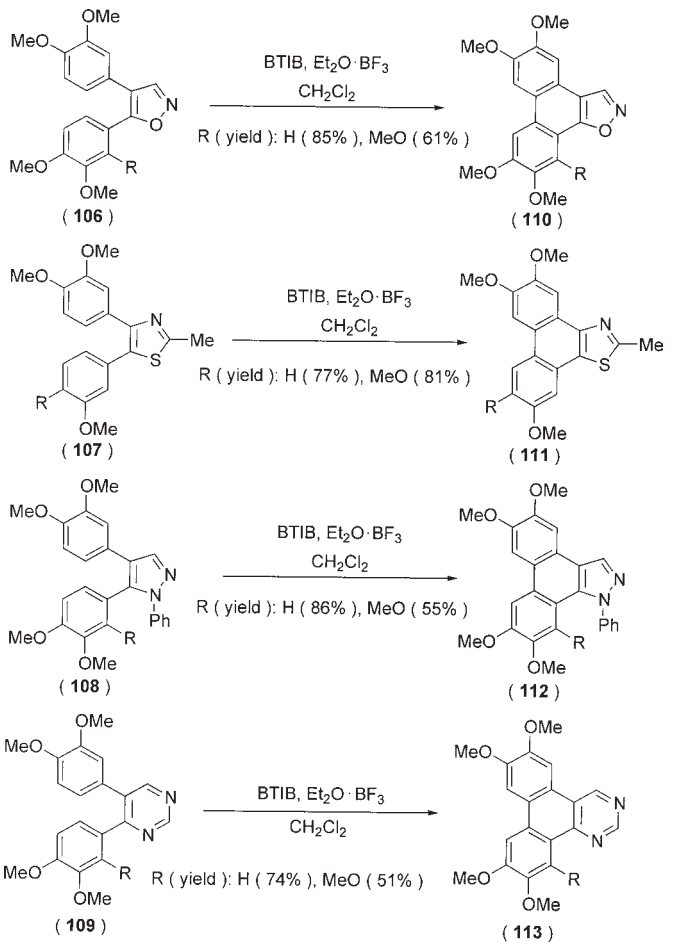
(94JA3684), and homocouplings of methoxybenzenes and methoxynaphthalenes to biaryls **103** (01T345) (Scheme 32).

When the methoxyarene rings are tethered by carbon-heteroatom chains, as in **104**, such oxidations proceed in intramolecular fashion and afford the benzo-annulated seven-membered heterocycles **105** (Scheme 33) (96CC1481, 98JOC7698, 01T345). Selected coupling reactions of the types shown in Schemes 32 and 33 have also been demonstrated with the polystyrene analogs of BTIB and DAIB (01T345).

During the past several years, the BTIB/$Et_2O \cdot BF_3$ combination has been utilized for conversions of the diaryl azoles and pyrimidines, **106**–**109**, to the phenanthro-fused isoxazoles **110** (99TL3479), thiazoles **111** (99TL5067, 01SL1161, 02EJO2126), pyrazoles **112** (00JOC7010), and pyrimidines **113** (99TL3479) (Scheme 34). The presence of methoxy groups in at least one



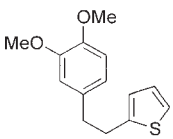
Scheme 33



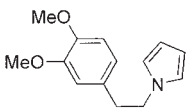
Scheme 34

arene ring is vital for the success of these reactions, the yields of products ranging from 0 to 23% when the diphenyl analogs of **106–109** were employed.

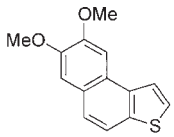
Oxidations of several 1-(3,4-dimethoxyphenyl)-2-(heteroaryl)ethanes with BTIB/$Et_2O \cdot BF_3$ have also been investigated (01SL1161). The 2-thienyl and *N*-pyrrolyl analogs **114** and **115** gave the naphthothiophene and pyrroloisoquinoline derivatives **116** (52%) and **117** (48%), respectively. However, the 2-furyl, *N*-methyl-2-pyrrolyl, and 6-methoxy-2-pyridyl congeners failed to give phenanthroid heterocycles under these conditions.



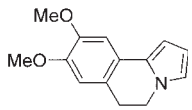
(**114**)



(**115**)

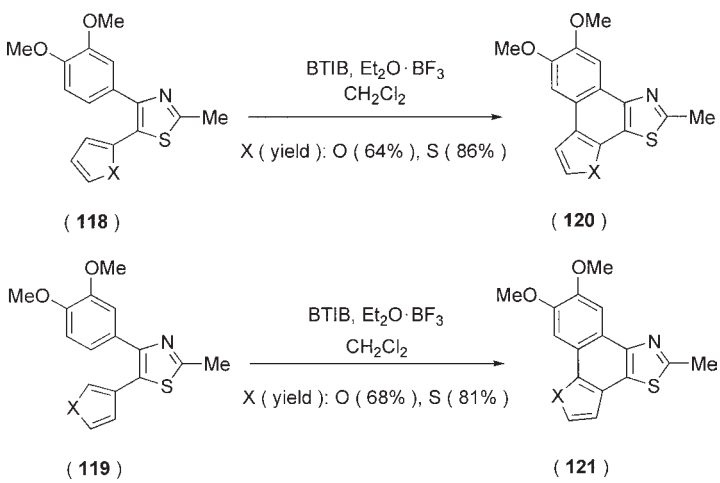


(**116**)



(**117**)

On the other hand, phenanthroid-fused thiazoles possessing thiophene, furan, and methoxypyridine rings are readily available by the treatment of 2-methyl-4-(3, 4-dimethoxyphenyl)-5-heteroarylthiazoles with BF_3-activated BTIB (02EJO2126). This is illustrated in Scheme 35 with oxidations of the 2- and 3-furyl and -thienyl analogs **118** and **119** to the regioisomeric thiazolo tetracycles **120** and **121**. The 6-methoxy-2- and -3-pyridyl analogs of **118** provide similar access to thiazolobenzoquinoline derivatives.

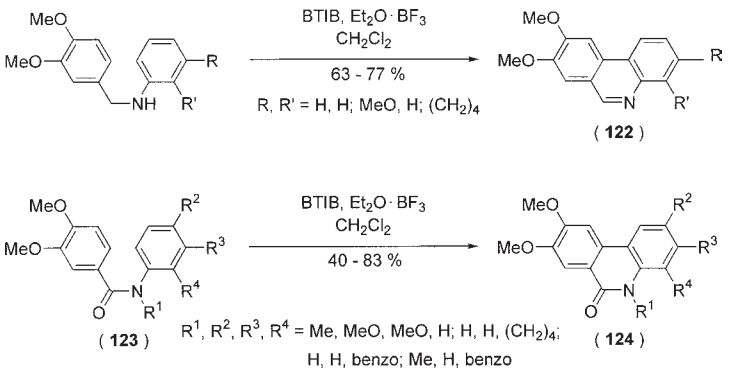


Scheme 35

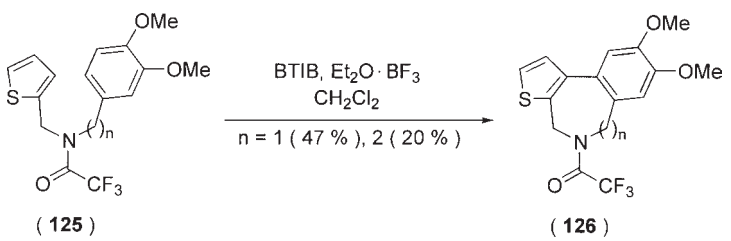
The BTIB/$Et_2O \cdot BF_3$ (CH_2Cl_2) system is also useful for conversions of methoxy-substituted aryl benzyl amines to the phenanthridines **122**, and of methoxy-substituted *N*-arylbenzamides **123** to the phenanthridones **124** (Scheme 36) (01T5403). In the case of the amide cyclizations, a methyl group was installed at nitrogen, or a higher reaction temperature was employed, to generate the proper amide configuration for intramolecular coupling.

Related oxidations of the trifluoroacetamides **125**, possessing nitrogen-tethered dimethoxyphenyl and α-thienyl rings, lead to the tricyclic azepine ($n = 1$) and azocene ($n = 2$) derivatives **126** (Scheme 37) (02T8581). Formation of the expected thienoquinoline analog ($n = 0$) was not observed under these conditions.

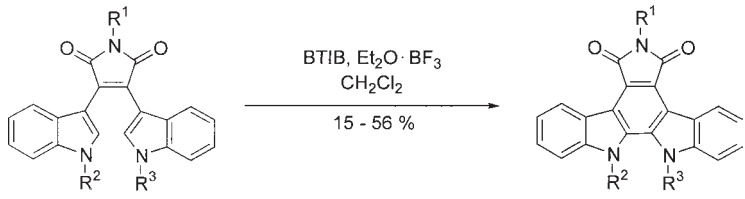
Treatment of the *bis*(indolyl)maleimides **127** with activated BTIB results in heteroaryl–heteroaryl coupling and affords modest yields of the indolo[2,3-*a*]carbazoles **128** (Scheme 38) (01TL3271). The parent member of the imide series (i.e., R^1, R^2, $R^3 = H$) and maleimides possessing one *N*-methylindolyl group and one *p*-anisyl or α-naphthyl group did not give carbazoles with BTIB.



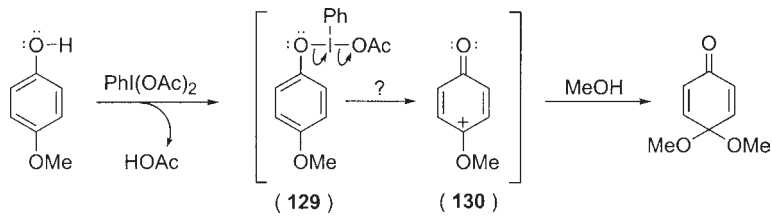
Scheme 36



Scheme 37



Scheme 38



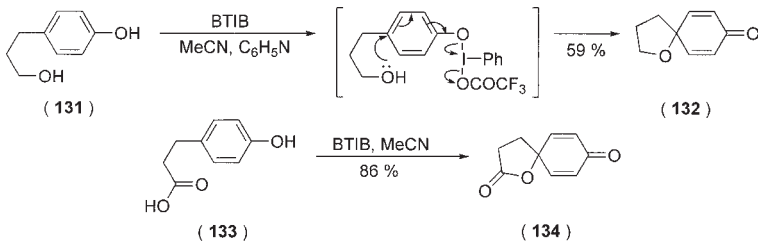
Scheme 39

4. *Phenolic Oxidations*

DAIB and BTIB oxidations of phenols proceed through aryloxyiodane **129** and/or aryloxenium ion **130** intermediates and are quite useful for the preparation of quinones, quinol ethers, and quinone acetals (e.g., Scheme 39) (88TL677, 92MI2, 93JCS(P1)1891, 01OR327). When phenols bearing nucleophilic side chains are used as substrates, such oxidations provide fertile ground for the assembly of heterocyclic structures. This can be accomplished by oxidative-cyclization reactions of different types.

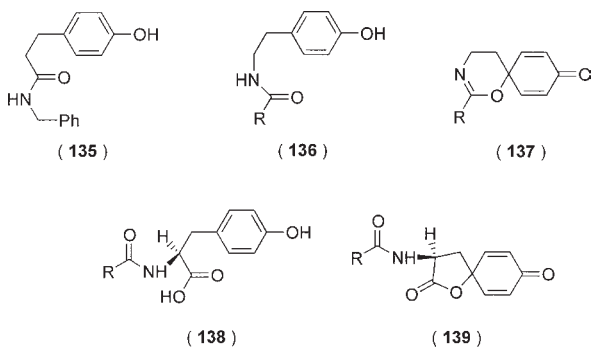
a. Spirocyclizations. The aryliodane-induced spirocyclization pathway was first demonstrated with BTIB-oxidations of uncluttered *para*-substituted phenols and is exemplified in Scheme 40 with conversions of 3-(4-hydroxyphenyl)propanol (**131**) and 3-(4-hydroxyphenyl)propanoic acid (**133**) to the heterocyclic spirodienones **132** and **134**, respectively (87JOC3927).

The treatment of phenolic amides with BTIB also results in C–O bond formation. Thus, *N*-benzyl-3-(4-hydroxyphenyl)propanamide (**135**) affords the spirolactone **134** (87JOC3927), while the *N*-acytyramines **136** are converted in CF_3CH_2OH to the spiroannulated oxazines **137** (91JOC435). Oxidations of protected tyrosines **138** with DAIB or



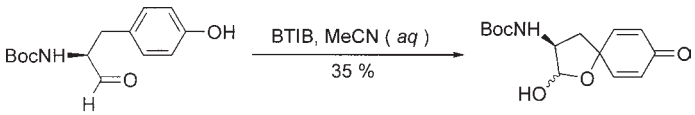
Scheme 40

BTIB likewise lead to the spirolactones **139** (91TL6613, 93JOC7195, 96JCS(P1)1385).



The conversion of *N*-Boc tyrosinal **140** to the spirolactol **141** with BTIB in aqueous acetonitrile is a useful variant of the tyrosine oxidation (Scheme 41) (96JCS(P1)1385). Similar cyclizations of appropriate *N*-acyltyrosinals were incorporated into concise total syntheses of the antibiotic, aranorosin, and its 6′-epimeric analog.

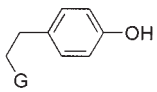
In an effort to harness phenolic oxidations for the preparation of azaspirocycles, the phenolic amine, iminoether, and imidazoline derivatives **142** were screened with DAIB in trifluoroethanol; in no case was the desired azaspirodienone obtained (00JOC4397). This was finally achieved with oxazoline derivatives of tyrosine. More specifically, DAIB-oxidations of **143** afford moderate yields of the spirolactams **144**, presumably via hydrolysis of spirooxazolinium intermediates (Scheme 42) (98TL4667, 00JOC4397). In order to avoid Michael-addition of the hydroxyl group in **144** to the dienone ring, the alcohols were promptly acetylated. Spirolactamization of **143** (R = NHTs, R′ = 4-$MeOC_6H_4CH_2$) with DAIB was a key step in a recent total synthesis of the immunosuppressant FR901483 (01OL765). An alternate synthesis of



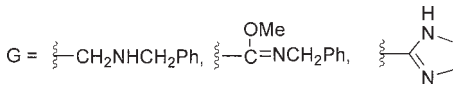
(**140**) (**141**)

Scheme 41

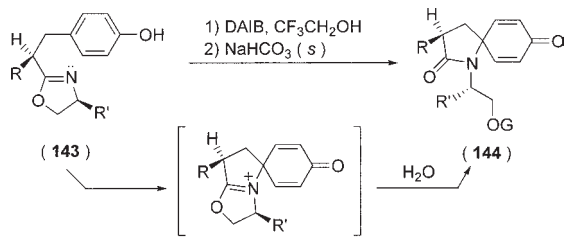
FR901483 features a unique example of azaspirodienone formation by DAIB-oxidation of a phenolic 2°-amine (00AGE4593).



(**142**)



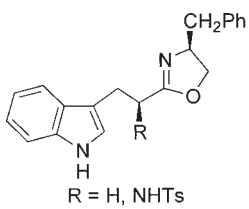
The indolic oxazolines **145** appear to behave similarly with DAIB in TFE, but in this case, the putative spirolactam intermediates **146** are converted spontaneously to diastereomeric mixtures of the tetracyclic structures **147** (99TL4985, 00JOC4397).



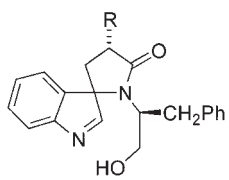
(**143**) (**144**)

R, R' = NHBoc, $PhCH_2$; NHTs, $PhCH_2$; H, H: G = H, Ac
yields of **144**, G = Ac (22 - 42 %)

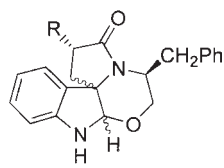
Scheme 42



(**145**)



(**146**)

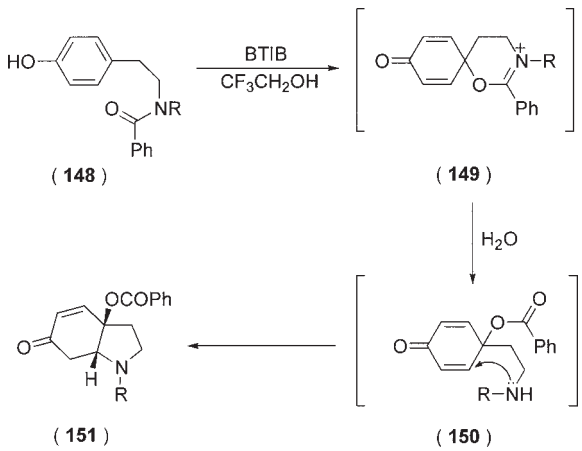


(**147**)

b. Oxidation–Michael Addition Sequences. Hypervalent iodine oxidations of phenols to quinoid intermediates, and Michael-additions of ring-tethered nucleophiles to the quinoid nucleus is a useful approach to ring-fused heterocycles. For example, whereas the acyltyramines **136** react with BTIB (in TFE or K_2CO_3/CH_2Cl_2) to give the spirooxazines **137**, the *N*-alkyl acyltyramines **148** lead to the hexahydroindolones **151**; presumably via hydrolysis of spirocyclic intermediates **149** to the benzoyloxydienones **150**, and Michael closure of the latter to **151** (Scheme 43) (91JOC435).

A more deliberate application of this approach entails DAIB-oxidation of the protected phenolic alcohols **152** to the *ortho*-quinol acetates **153**, and conversion of **153** to the bicyclic phenolic ethers **154** with tetrabutylammonium fluoride, TBAF (Scheme 44) (98JOC9597).

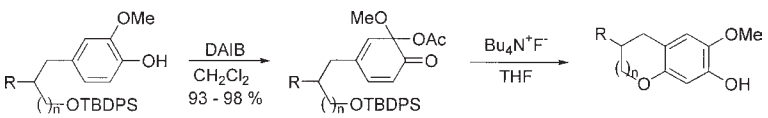
A similar two-step sequence, beginning with the protected *o*-methoxy phenolic amines **155**, provides access to the indoline and tetrahydroquinoline derivatives **156**, while oxidation of the amides **157** with DAIB and



(**148**) (**149**) (**151**) (**150**)

R = Me (54 %), Et (48 %)

Scheme 43

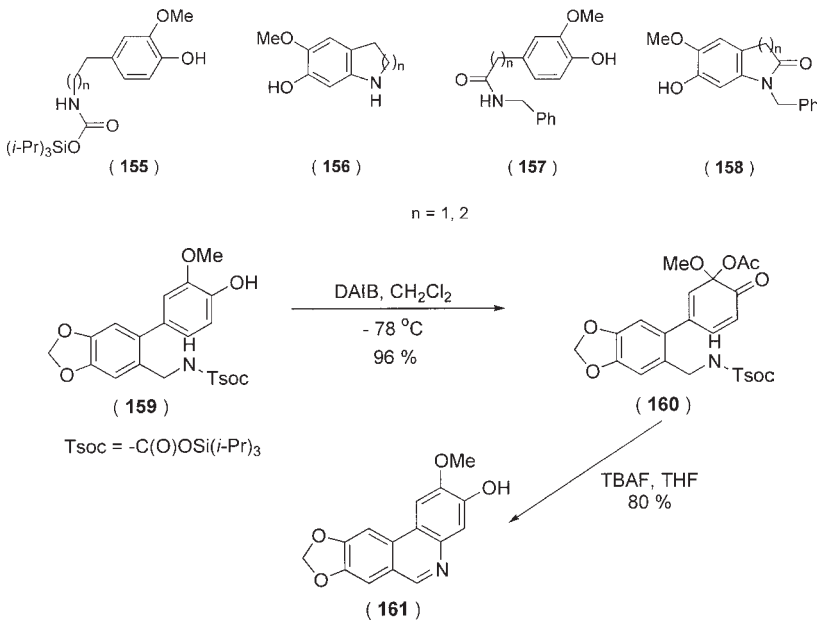


(**152**) (**153**) (**154**)

R, n (yields of **154** from **153**) : Me, 0 (57 %); H, 1 (89 %); Me, 2 (20 %)

Scheme 44

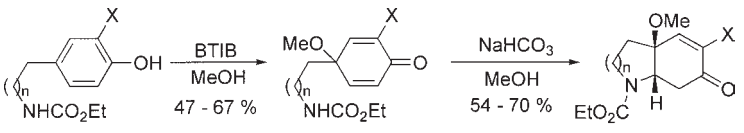
treatment of the resulting quinol acetates with a base leads to the oxoindole and quinoline derivatives **158** (01TL7393, 02JOC3425). Extension of this procedure to the phenolic amine **159** leads through quinol **160** to the oxygenated phenanthridine **161**, a potential precursor of lycoricidine (Scheme 45) (02JOC3425).



Scheme 45

BTIB-oxidations of the phenolic carbamates **162** have been employed, as shown in Scheme 46, for syntheses of the hydroindolenones and hydroquinolenones **163** (99TL4183). The treatment of **162** (X = H, $n = 1$) with BTIB–$C_6H_5N \cdot (HF)_n$ in CH_2Cl_2 leads directly to the corresponding fluoro hydroindolenone.

Studies directed toward the synthesis of amaryllidaceae alkaloids provide instructive examples of the combined use of spirocylization and Michael addition pathways in phenolic oxidations (03MI1). For example, treatment of the norbelladine derivative **164** with BTIB leads, by way of C,C-bond formation, to the spiroannulated azepine **165** (Scheme 47) (96JOC5857, 98JOC6625). Hydrolysis of the amide moiety in **165** results in Michael addition of the nitrogen center to the dienone ring and affords (±)-oxomaritidine (**166**). BTIB-oxidation of the appropriate

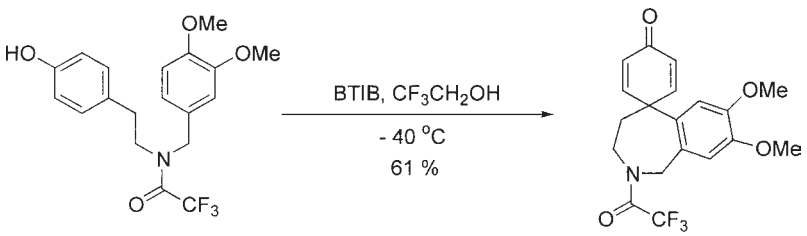


(**162**)

n = 1, X = H, Cl, Br
n = 2, X = H

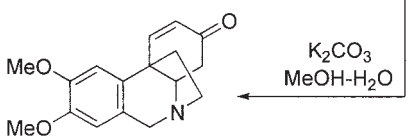
(**163**)

Scheme 46



(**164**)

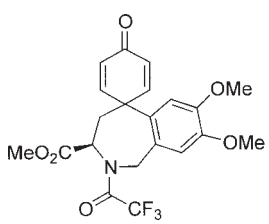
(**165**)



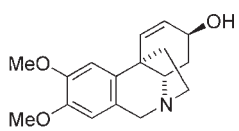
(**166**)

Scheme 47

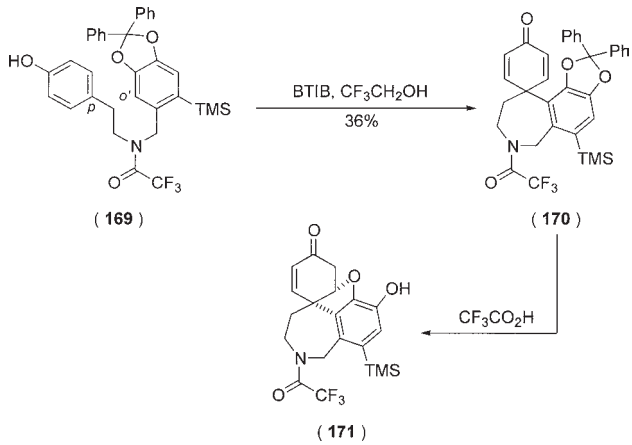
chiral norbelladine gives the spiroazepine **167**, a pivotal intermediate in a reported synthesis of (+)-maritidine (**168**) (77CPB2681). In one six-step synthesis of (±)-epimaritidine, beginning with 3,4-dimethoxybenzyl alcohol, polymer-supported reagents were used throughout, including the polystyryl analog of BTIB for the spirocyclization step (99JCS(P1)1251).



(**167**)



(**168**)



(**169**) (**170**) (**171**)

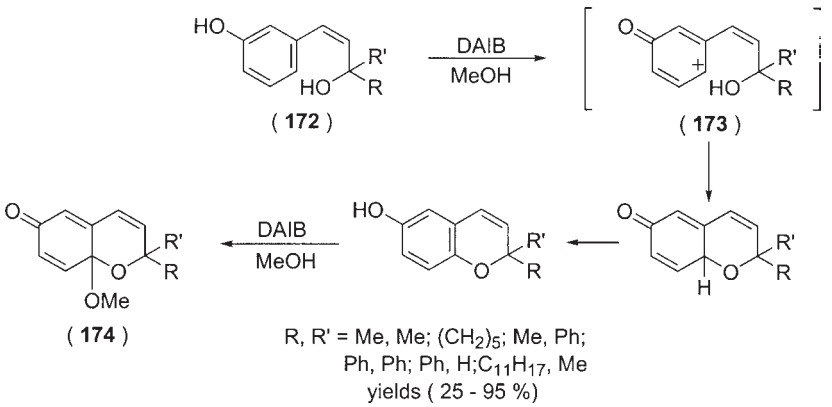
Scheme 48

BTIB-oxidation of the norbelladine derivative **169** furnishes the spiroazepine **170** (Scheme 48) (98JOC6625). Exposure of **170** to trifluoroacetic acid initiates a deprotection-cyclization sequence leading quantitatively to the tetracyclic enone **171** (isolated as the methyl ether). The function of the trimethylsilyl group in **169** is to direct the regiochemistry of the spirocyclization step to *p*–*o*′ coupling. Compound **171** features the basic ring system of the galanthamine-type alkaloids and was deftly employed by Kita and co-workers for synthesis of five members of this family, including the first total synthesis of (+)-sanguinine (98JOC6625).

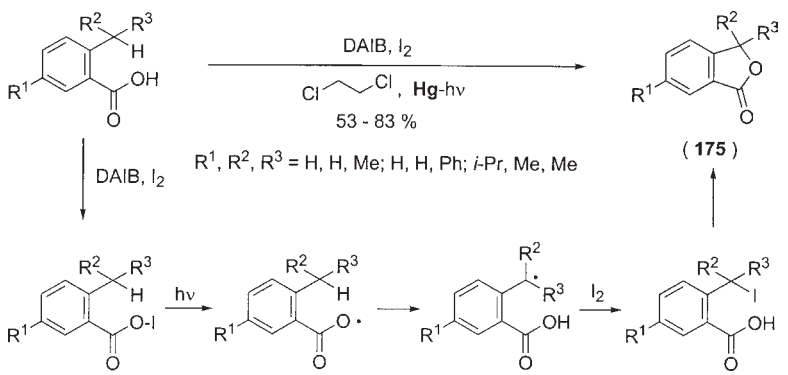
c. Cycloannulation. Oxidations of phenols containing nucleophilic *meta*-side chains provide an alternate route to ring-fused heterocycles. This approach has been utilized for conversions of the unsaturated phenolic alcohols **172** to the methoxy-substituted dihydrochromenones **174** with DAIB in methanol (Scheme 49) (97T3879). The formation of **174** presumably involves the direct capture of phenoxenium intermediates **173** (or their aryloxyiodane equivalents) by the alcohol side-chain, the methoxy group being introduced in a subsequent oxidation step. Similar conversions of epoxy derivatives of **172** to epoxy analogs of **174** were demonstrated.

5. *Radical Pathways*

The generation of oxygen-centered radicals from carboxylic acids and alcohols with the tandem reagent, $PhI(OAc)_2$–I_2, is an established practice



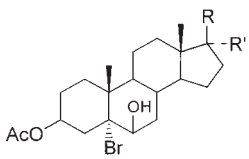
Scheme 49



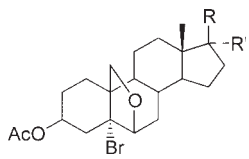
Scheme 50

(i.e., the Suárez system) and offers several routes to heterocyclic structures (97RHA213). The conversion of *o*-alkylbenzoic acids to the γ-lactones **175** with DAIB–I_2, under the influence of light, is an example of the 1,5-hydrogen abstraction pathway (Scheme 50) (99JCS(P1)1713). A mechanism for these reactions involving benzylic iodination of the starting acids prior to lactone formation was suggested, the iodination sequence being mediated by the generation of carboxyl radicals. The efficacy of various iodanes for this transformation has also been evaluated (97JCS(P1)787, 99JCS(P1)1713).

Sonication of the steroidal bromohyrins **176** in the presence of DAIB–I_2 enables remote oxidation of the C-19 methyl group leading, via alkoxy radicals, to the 6β, C-19 furan derivatives **177** (99TL8711).



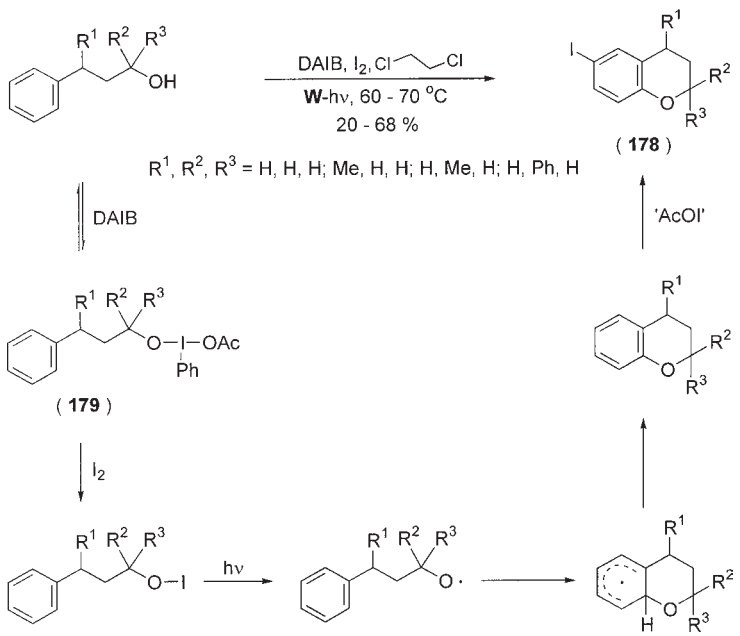
(**176**)



(**177**)

R, R' = O; Ac, H; $COCH_2OAc$, H; C_8H_{17}, H

Light-induced reactions of 3-phenylpropanols with DAIB–I_2 follow the radical-cyclization pathway depicted in Scheme 51 and eventuate in the 6-iodochromans **178** (97JCS(P1)787). An NMR study of a solution of 3-phenylpropanol and DAIB in $CDCl_3$ indicates that alkoxy radical formation is preceeded by ligand-exchange between the alcohols and DAIB, leading to the monoalkoxyiodanes **179**. The conversion of **179** to the corresponding alkyl hypoiodites, and photolytic homolysis of the hypoiodites to alkoxy radicals appear to be ultimately responsible for construction of the chroman ring-system (97JCS(P1)787). The 6-iodo substituent in **178** is thought to be introduced via electrophilic iodination of the aromatic nucleus after cyclization has occurred.

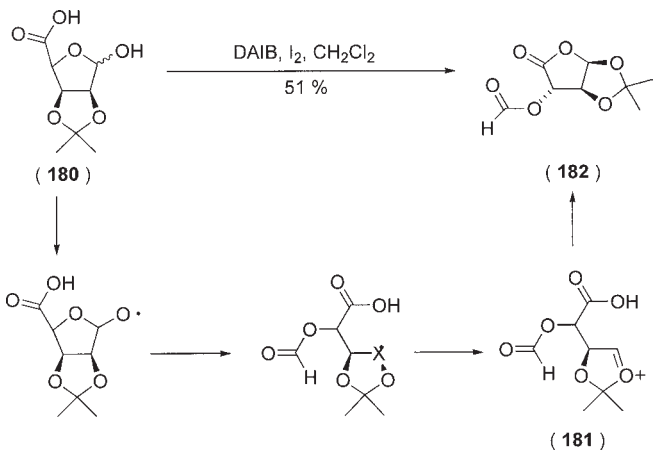


Scheme 51

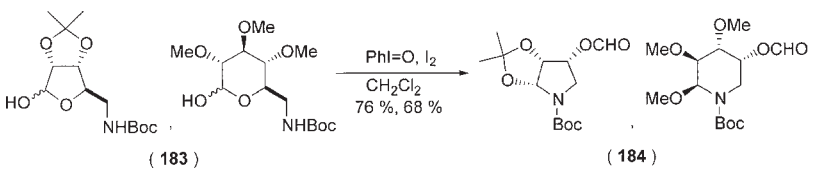
Treatment of the alduronic acid **180** with DAIB–I_2 furnishes the formyloxylactone **182** (Scheme 52) (98JOC2099). This and related reactions proceed by a radical fragmentation–oxidation sequence, culminating in the formation and intramolecular capture of oxycarbenium ion intermediates (e.g., **181**).

Oxidations of this type, promoted by PhIO–I_2, have been exploited for syntheses of densely functionalized pyrrolidines and piperidines, e.g., **184**, from *N*-protected amino sugars, e.g., **183** (Scheme 53) (97TA1971, 01JOC1861). The advantage of iodosylbenzene over DAIB in this context is presumably to circumvent capture of the oxycarbenium ion intermediates by the acetate ion (92AGE772).

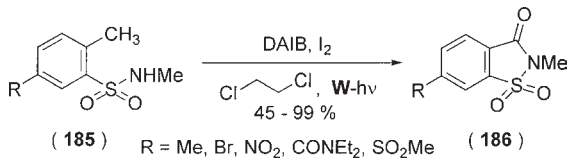
The Suárez system is also useful for the production of nitrogen-centered radicals (97RHA213). Thus, exposure of mixtures of the *N*-methyl-*o*-toluenesulfonamides **185**, DAIB (3 equiv), and I_2 (1 equiv) to a tungsten light-source results in formation of the saccharin derivatives **186** (Scheme 54) (98SL131, 99T14885). These reactions are thought to proceed by exhaustive iodination of the *o*-methyl group in **185**, mediated by sulfonamido radicals such as **187** (i.e., the 1,5-hydrogen abstraction



Scheme 52

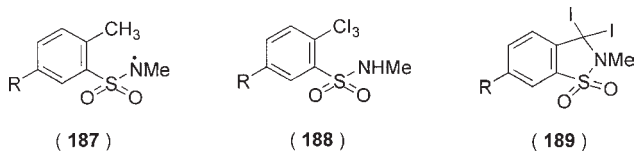


Scheme 53



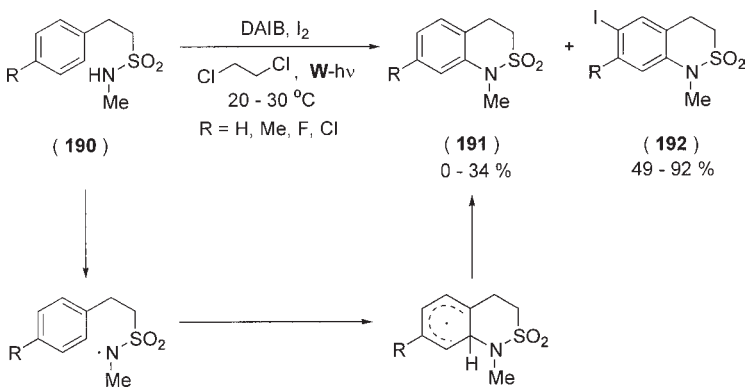
Scheme 54

pathway). Hydrolysis of the C–I bonds, perhaps after cyclization of **188** to **189**, would give **186** (99T14885).



The use of a mercury lamp instead of a tungsten source for DAIB–I_2 oxidations of *N*-alkyl-*o*-toluenesulfonamides affords mixtures of saccharins and their sulfoxamide analogs (99TL14885). The efficiency of sulfoxamide formation depends on the nature of the *N*-alkyl group and was demonstrated primarily with *N*-ethyl analogs of **185**.

Irradiation of the *β*-(aryl)ethanesulfonamides **190** in the presence of DAIB–I_2 provides access to the dihydrobenzothiazine dioxides **191** and **192** (Scheme 55) (00JOC926). In these reactions, formation of the thiazine ring by the radical cyclization pathway to give **191** is followed by electrophilic iodination of the arene nucleus to give **192**.



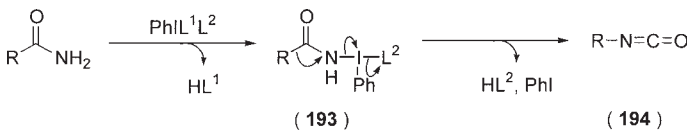
Scheme 55

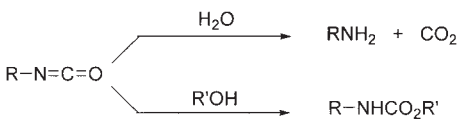
6. *Oxidative Rearrangements*

Aryl-λ^3-iodanes (BTIB, HTIB, and DAIB) are excellent reagents for the Hofmann rearrangement of carboxamides (84JOC4272, 86JOC2669, 90SL365, 93JOC2478, 97T1179, 02CRV2523). Such reactions proceed through N–I(III) intermediates **193** to isocyanates **194**, which are ultimately converted to carbamates or amines (Scheme 56).

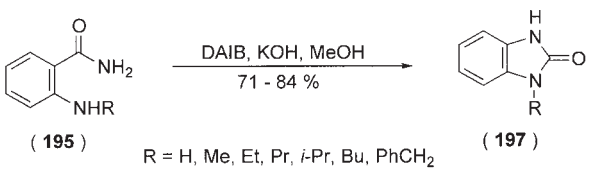
DAIB-induced conversions of the anthranilamides **195** and salicylamides **196** to the benzimidazolones **197** and benzoxazolones **198**, respectively, and similar rearrangements of two representative pyridinecarboxamides, are recent examples of direct heterocyclic ring-construction by the iodine(III)–Hofmann pathway (Scheme 57) (01S541). These reactions may be contrasted with BTIB-oxidations of the 2-aminonicotinamides **67** and amidopyridones **69** in aqueous DMF (Section II.A.2) which lead, without rearrangement, to N–N and N–O bond formation (97SC2217).

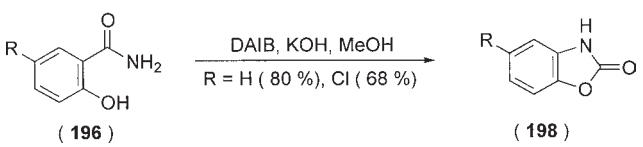
Iodine (III)–Hofmann reactions have also been used for the preparation of key intermediates in synthetic protocols directed to heterocyclic targets. Thus, rearrangement of the cyclobutenamide **199** to the cyclic





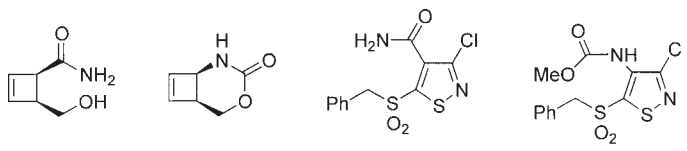
Scheme 56



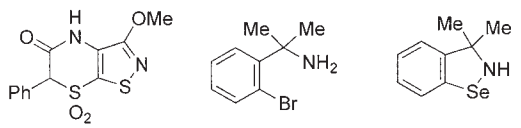


Scheme 57

carbamate **200** with DAIB in KOH–MeOH was a key step in recent syntheses of two cyclobutene nucleosides (97JOC2166), while conversion of the isothiazolyl amide **201** to the carbamate **202** with DAIB in methanol enabled synthesis of the novel isothiazolothiazine derivative **203** (02MI2). The 3°-amine **204**, prepared from the corresponding amide with BTIB in aqueous acetonitrile, was converted directly to the benzoisoselenazoline **205** with KSeCN and CuI (20 mol%) in DMF (00JOC8152).

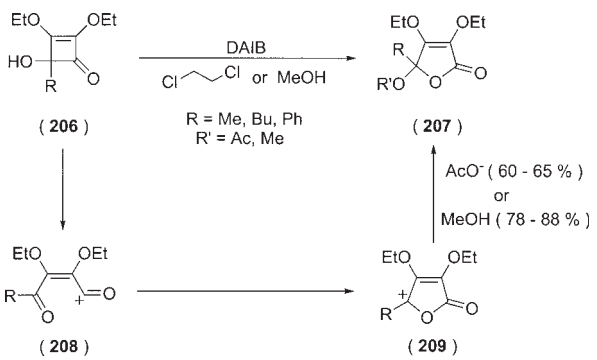


(**199**) (**200**) (**201**) (**202**)



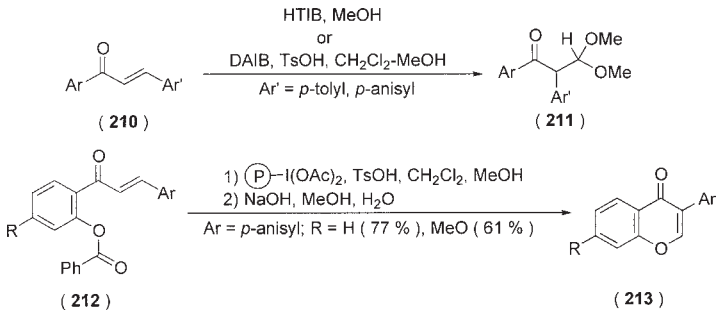
(**203**) (**204**) (**205**)

The 4-hydroxycyclobutenones **206** react with DAIB in dichloroethane to give the 5-acetoxy-2(5*H*)-furanones **207** (R′ = Ac); when methanol is the solvent, methoxyfuranones **207** (R′ = Me) are obtained, and in higher yields (Scheme 58) (99JOC8995). A polar mechanism involving formation of the ring-opened acyl cations **208** and their recyclization to the furanonyl cations **209** was proposed to account for ring-expansion and introduction of the nucleophile. Further evidence for furanonyl



(**206**) (**207**) (**208**) (**209**)

Scheme 58



Scheme 59

cation intermediates was provided by the isolation of ethylidenefuranone isomers of **207** when **206** (R = vinyl) was the substrate.

The treatment of various chalcones **210** with HTIB or DAIB–TSOH in a methanolic medium leads to the β-keto dimethylacetals **211** (Scheme 59) (02S2490). This rearrangement can also be effected with poly[4-(diacetoxy)-iodo]styrene and has been developed into a one-pot synthesis of isoflavones (e.g., **213**) from benzoyl-protected 2′-hydroxychalcones (e.g., **212**), via base-catalyzed cyclization of the acetal intermediates.

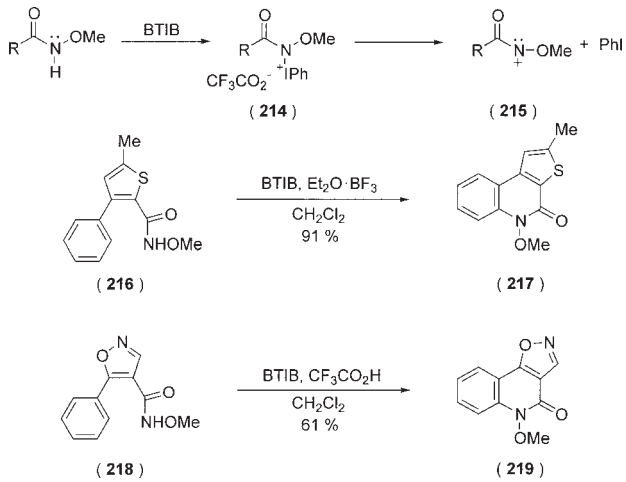
7. *Oxidation of N-Methoxyamides*

Whereas the *N*–I(III) intermediates generated from 1°-amides and BTIB rearrange to isocyanates with the loss of iodobenzene (84JOC4277), similar derivatives, **214**, of *N*-methoxyamides serve as progenitors of acylnitrenium ions, **215** (Scheme 60) (90CL581). This mode of reactivity has been exploited for syntheses of heterocycle-fused quinolinones (02T8581). Treatment of the phenyl-substituted *N*-methoxyamides **216** and **218** with activated BTIB delivers high yields of the thieno- and isoxazoloquinolinones **217** and **219**, respectively (Scheme 60). Similar reactions of appropriate *N*-methoxyamides with BTIB enable preparations of thiazolo- and pyrazoloquinolinone analogs of **217** and **219**.

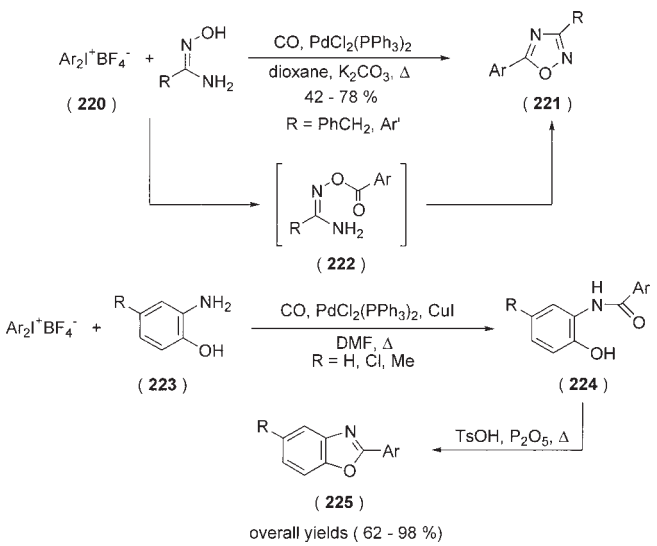
B. Synthesis with Iodonium Salts

1. *Diaryliodonium Salts*

Diaryliodonium salts are viable alternatives to aryl halides for palladium-catalyzed cross-coupling reactions (02CRV2523). In the area of heterocyclic synthesis, Pd(II)-catalyzed carbonylation of diaryliodonium



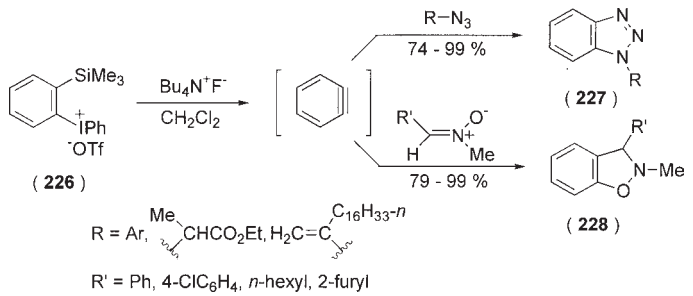
Scheme 60



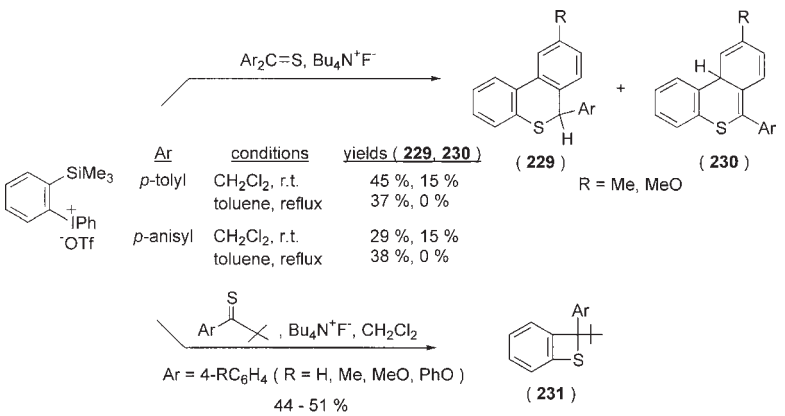
Scheme 61

tetrafluoroborates **220** in the presence of amidoximes has been employed for preparation of the oxadiazoles **221** (Scheme 61) (02SC887); the formation and dehydration of *O*-acylamidoxime intermediates **222** presumably occurs in these reactions.

Similar carbonylations of **220** in the presence of *o*-aminophenols **223**, facilitated with a Cu(I) co-catalyst, afford the benzanilide derivatives **224**,



Scheme 62



Scheme 63

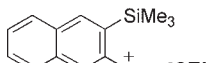
which can be dehydrated without isolation to the arylbenzoxazoles **225** (Scheme 61) (01JCR(S)235).

Phenyl[2-(trimethylsilyl)phenyl]iodonium triflate (**226**) has emerged as a superior benzyne precursor; i.e., admixture of **226** with *tetra-n*-butylammonium fluoride (TBAF) enables the generation of benzyne in dichloromethane at room temperature (95JCS(CC)983). When organo azides or -nitrones are available in the reaction medium, high yields of the benzotriazoles **227** or benzisoxazolines **228** are obtained (Scheme 62) (98HC205).

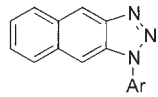
The treatment of **226** with TBAF in the presence of thiobenzophenones results in a novel [4 + 2] cycloaddition reaction leading to the dibenzothiapyrans **229** and low yields of the olefinic regioisomers **230**; as expected, the presence of **230** in the product mixtures is suppressed at higher reaction temperatures (Scheme 63) (96TL8883, 00BCJ155). Reactions of **226** and

TBAF with thiopivalophenones, on the other hand, afford the [2 + 2] cycloadducts **231** (00BCJ155).

Phenyl[3-(trimethylsilyl)naphthyl]iodonium triflate (**232**) has also been described and utilized with aryl azides for synthesis of two naphthotriazoles **233** (98JOC8579).



(**232**)

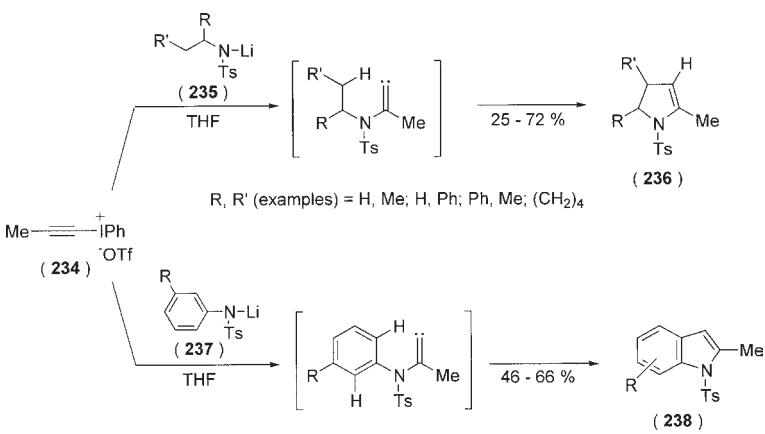


(**233**)

2. *Alkynyl(phenyl)iodonium Salts*

a. Alkylidenecarbene Insertions. The generation of alkylidenecarbenes **21** by exposure of alkynyl(aryl)iodonium salts **5** to nucleophiles (Scheme 4; Section II.B) is an exceptionally useful starting point for the assembly of heterocyclic structures. This is generally accomplished by intramolecular insertion and addition reactions of the alkylidenecarbenes.

Intramolecular insertions of alkylidenecarbenes **21** into C–H bonds favor the formation of five-membered rings. For example, the lithium tosylamidates **235** react with phenyl(propynyl)iodonium triflate (**234**), via carbene intermediates, to give the *N*-tosyldihydropyrroles **236** (Scheme 64) (95JOC7722, 96JOC5440). The *N*-tosylanilide salts **237**, on the other hand, are predisposed for [1,5]-insertion into the *ortho*-CH bonds of the aromatic ring, and afford mixtures of the regioisomeric *N*-tosylindoles **238** with **234**.



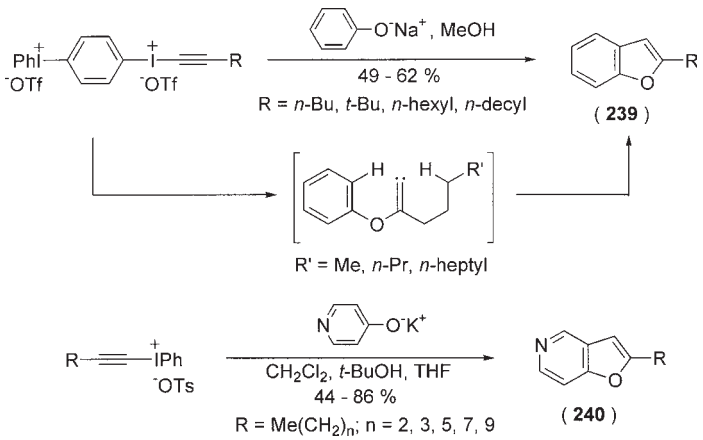
Scheme 64

Carbenic insertions are similarly useful for syntheses of the benzofurans **239** and furopyridines **240** depicted in Scheme 65 (97JCS(P2)1511, 98TL5375). It is noteworthy that the carbene intermediates in the benzofuran pathway show preference for aromatic over aliphatic CH-bond insertion.

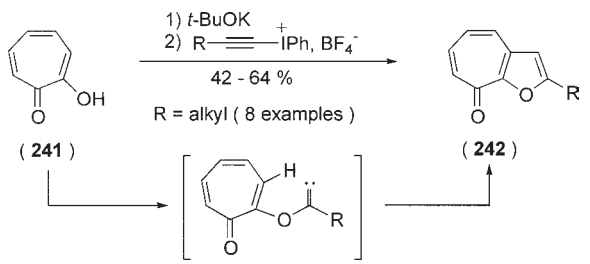
The sequential treatment of tropolone (**241**) with potassium *tert*-butoxide and alkynyliodonium fluoroborates furnishes the furotropones **242**, and is an example of carbenic insertion into a vinylic CH-bond (Scheme 66) (96TL5539).

The butynyl(phenyl)iodonium triflates **243**, possessing an ether or acetal linkage at C-4, react with sodium *p*-toluenesulfinate to give the 3-tosyldihydrofurans **244** (00OL2603, 00JOC8659). These formal carbenic C–O bond insertions are thought to occur through vinyloxonium ylide intermediates (Scheme 67).

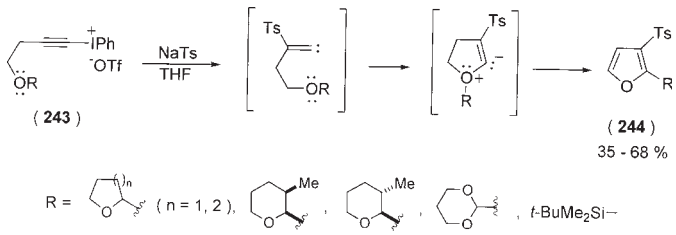
In recent years, Feldman and co-workers have employed alkynyliodonium triflates for the synthesis of relatively complex heterocyclic structures.



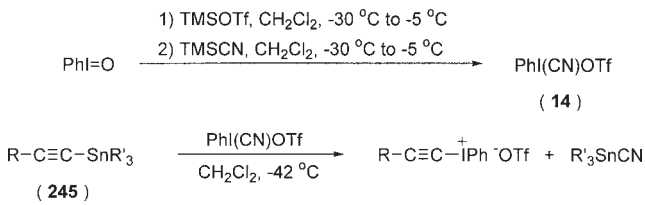
Scheme 65



Scheme 66



Scheme 67



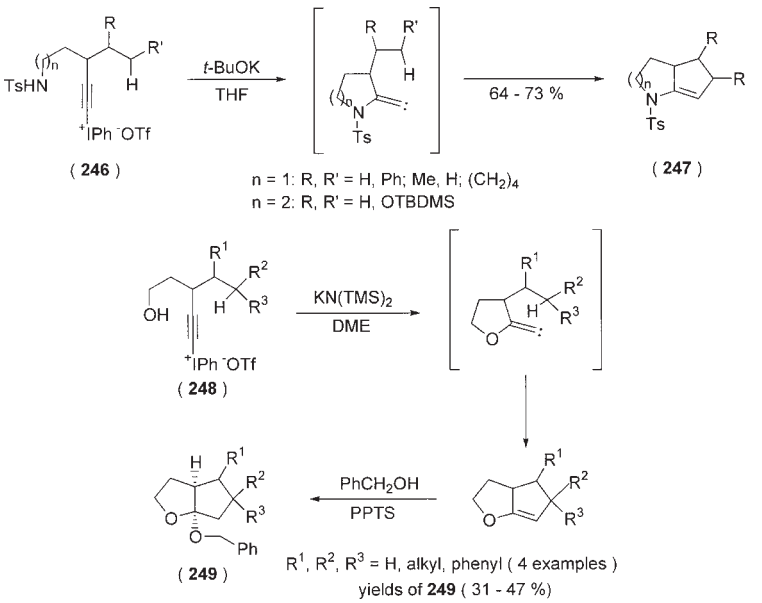
Scheme 68

In such protocols, it is expedient to generate the iodonium intermediates by the treatment of alkynylstannanes **245** with cyano(phenyl)iodonium triflate (**14**); i.e., Stang's reagent (Scheme 68) (90TL4821, 93JA2590, 94JA93). For example, the branched *N*-tosylamino alkynyliodonium triflates **246**, prepared from the corresponding tributyl(alkynyl)stannanes, were converted with potassium *tert*-butoxide to the tosylenamides **247** (Scheme 69) (95JA7544, 96JOC5440). Similar bicyclizations of the alkynyliodonium triflate **248** provide access to the ring-fused tetrahydrofurans **249** (Scheme 69) (98TL2911).

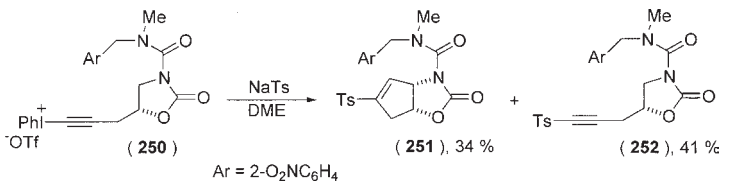
The carbene-insertion pathway has recently been applied in total asymmetric syntheses of the anti-leukemic alkaloid, (−)-agelastatin A, and the dibromo analog, (−)-agelastatin B (02JA9060, 02JOC7096). Treatment of the (oxazolidinonyl)propynyliodonium triflate **250** with sodium *p*-toluenesulfinate leads to a mixture of the bicyclic oxazolidinone **251** and the carbenic rearrangement product **252** (Scheme 70); compound **251** is a key intermediate in the agelastatin synthesis.

Similar treatment of the iodonium triflate **253** affords the CH-insertion product **254** and the 3-tosyldihydrofuran **255**; the furan derivative probably originates from an oxonium ylide intermediate (Scheme 71).

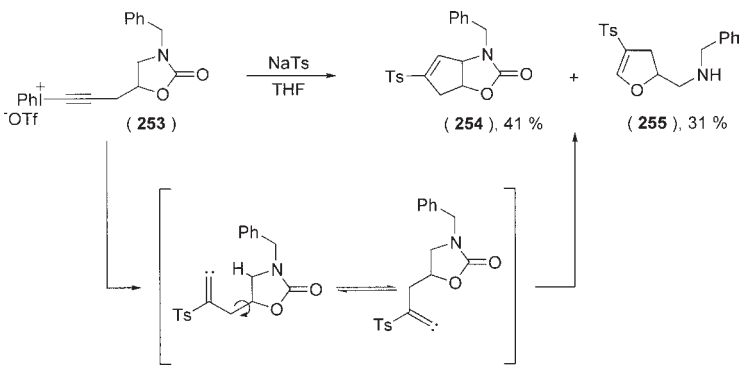
Conversion of the alkynyliodonium triflate **256** to the bicyclic dihydropyrrole **257** appears to be an example of alkylidenecarbene capture by a carbamate nitrogen atom (Scheme 72) (99H1283). Competitive insertion of the carbenic center into a CH-bond of the oxazolidine ring was not observed.



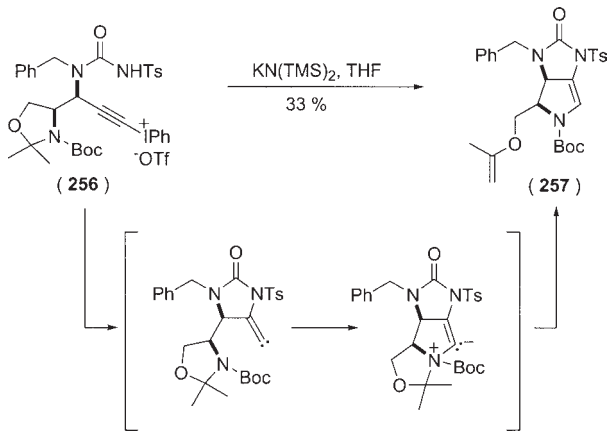
Scheme 69



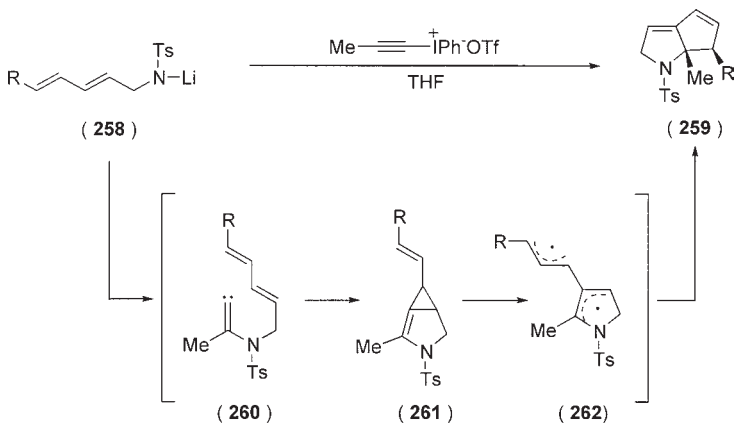
Scheme 70



Scheme 71



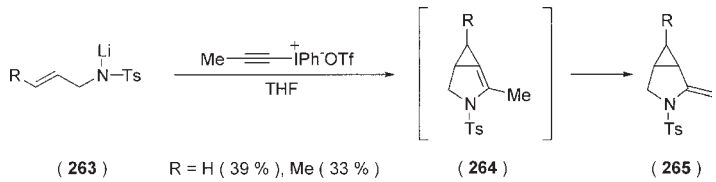
Scheme 72



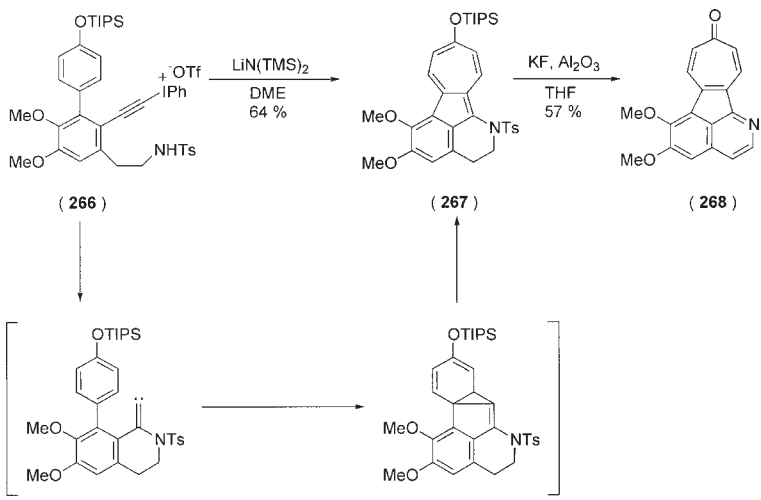
R (yield of **259**) : Me (24%), TMS (27 %), Ph (58 %), 4-$MeOC_6H_4$ (51 %)
4-$O_2NC_6H_4$ (12 %), (*E*)-PhCH=CH (35 %), CO_2Me (0 %)

Scheme 73

b. Alkylidenecarbene Additions. Reactions of the lithium (*E*,*E*)-alkadienyltosylamidates **258** with phenyl(propynyl)iodonium triflate (**234**) proceed stereoselectively to the azabicyclo[3.3.0]octadienes **259** (98JA4027, 99JOC5650). A mechanism for these reactions featuring intramolecular addition of alkylidenecarbenes **260** to the proximate double bond of the diene chain was proposed (Scheme 73). Rearrangement of the strained bicyclic adducts **261**, through the diyl radical species **262**, accounts for the formation of **259**.



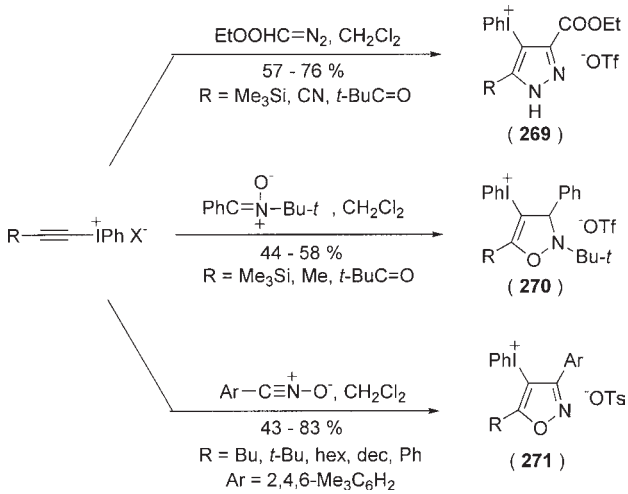
Scheme 74



Scheme 75

Admixture of **234** with the allylic tosylamidate salts **263** delivers the isolable (methylene)azabicyclohexanes **265** (98TL4781, 99JOC5650). Evidence that initially-formed carbene "adducts", **264**, isomerize to **265** by a deprotonation–reprotonation sequence (Scheme 74) was discussed. Various analogs of **265**, generated *in situ*, have been employed with HCl for the synthesis of stereodefined 1-acetyl-2-(tosylamino)methylcyclopropanes (01SL1656).

An intramolecular alkylidenecarbene addition is featured in a recent total synthesis of the tropoloisoquinoline alkaloid, pareitropone (02JA11600, 02JOC8528). More specifically, the pareitropone skeleton was assembled by base-catalyzed "bicyclization" of the alkynyl(biaryl)-iodonium triflate **266** to the tetracyclic compound **267**, one step away from the target structure **268**. The conversion of **266** to **267** is thought to occur via the carbene addition—norcaradiene isomerization sequence depicted in Scheme 75. Similar bicyclization of the methoxy analog of **266** (i.e., OMe vs. OTIPS) was also demonstrated.

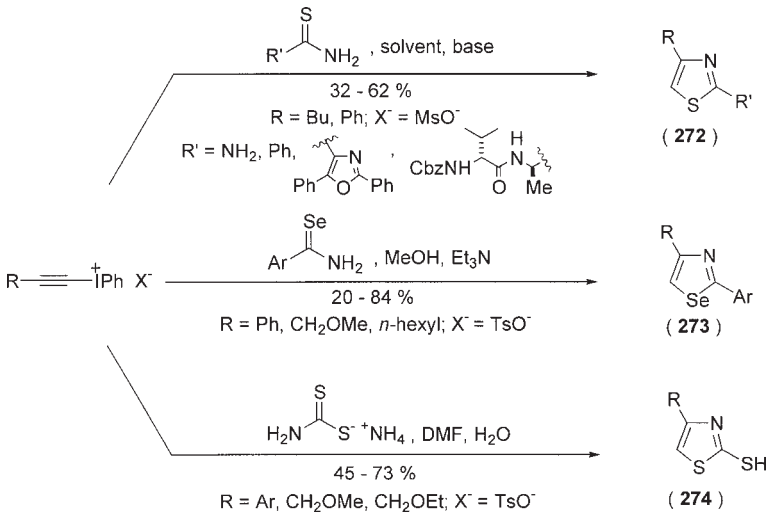


Scheme 76

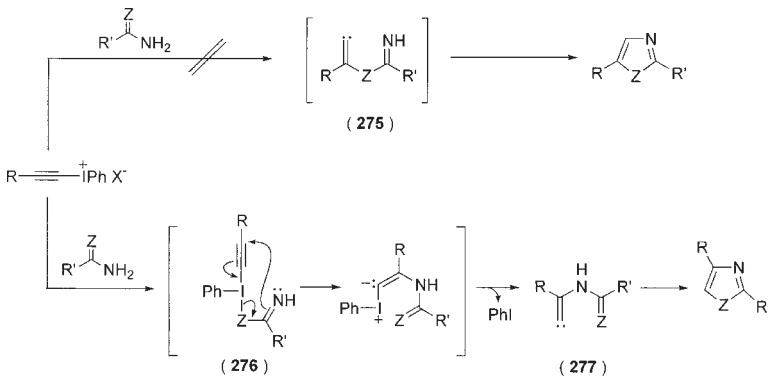
c. Cycloadditions. Alkynyl(phenyl)iodonium salts undergo [3 + 2] cycloadditions with dipolar compounds to give heteroaryl(phenyl)iodonium salts (89JCS(P1)827, 92T3527, 97TL8793, 02JOM(646)196). Recent demonstrations of such reactions include preparations of the pyrazolyl-, dihydroisoxazolyl-, and isoxazolyliodonium salts **269**–**271** shown in Scheme 76 (97TL8793, 02JOM(646)196). In each of these examples, the regiochemistry of cycloaddition appears to be consistent with attachment of the nucleophilic atom of the dipolar component to the β-carbon atom of the alkynyliodonio moiety. That this is not always the case is indicated in the earlier reports.

d. Cyclocondensations. The treatment of alkynyl(phenyl)iodonium salts with thioamides and selenoamides in the presence of base affords the 2,4-disubstituted thiazoles **272** and selenazoles **273**, respectively; when ammonium dithiocarbamate is the nucleophile, the 4-substituted 2-mercaptothiazoles **274** are obtained (Scheme 77) (96JOC8004, 01JHC503, 01S358).

A surprising feature of these reactions is their apparent departure from the Michael-addition/α-elimination sequence, which is expected to lead, via alkylidenecarbenes **275**, to a 2,5-disubstitution pattern in the products. This has been attributed to the initial formation of iodine(III)–sulfur(selenium) adducts **276** and their collapse by a "hetero-Claisen rearrangement" to the isomeric alkylidenecarbenes **277** (Scheme 78). In view



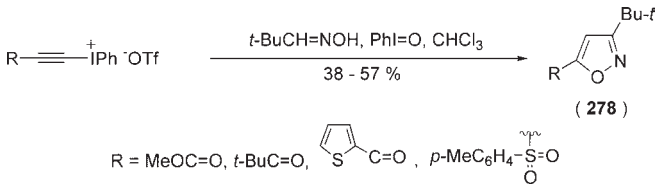
Scheme 77



Scheme 78

of the T-shaped structures of aryl-λ^3-iodanes, such a process would presumably require pseudorotation at iodine in **276** (90JA5677).

Alkynyl(phenyl)iodonium triflates react with pivaldehyde oxime in the presence of iodosylbenzene to give the isoxazoles **278** (Scheme 79) (97TL8793). Although the purpose of iodosylbenzene was to oxidize the oxime to the corresponding nitrile oxide, thus providing access to isoxazolyliodonium salts, its overall influence on the outcome of these reactions has not been firmly established.



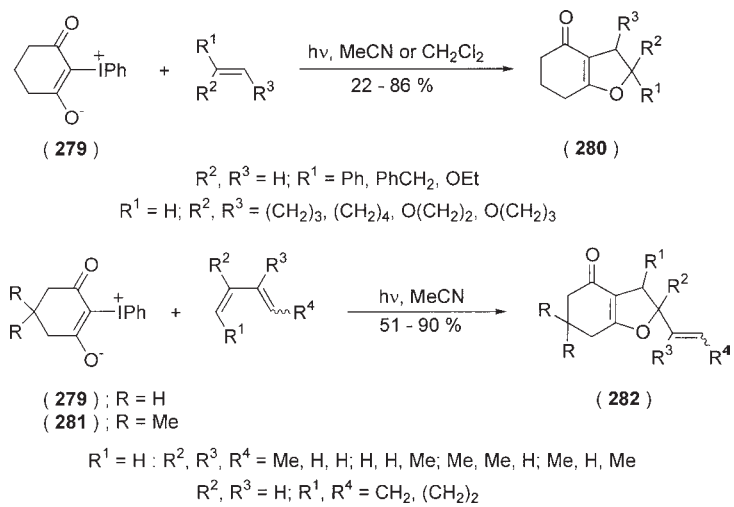
Scheme 79

C. Synthesis with Iodonium Ylides

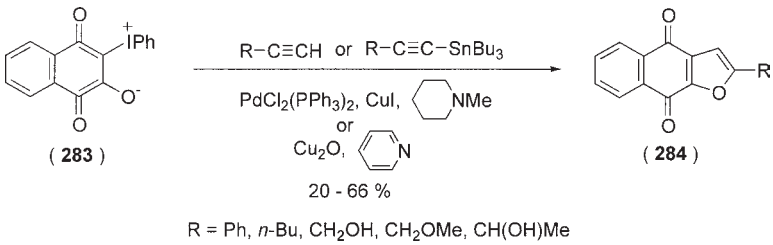
1. *Iodine(III)–Carbon Ylides*

Iodonium ylides derived from cyclic β-dicarbonyl compounds serve as 1,3-dipolar equivalents in thermal and photochemical reactions with heterocumulenes, acetonitrile, alkenes, and alkynes (02MI1). Recent examples include light-induced reactions of 2-phenyliodonio-1,3-cyclohexanedionate (**279**) with alkenes and enol ethers to give ketonic bicyclic dihyrofurans **280**, compounds of interest in connection with the paniculides (Scheme 80) (98TL9073). Similar photochemical [3 + 2] "cycloadditions" of **279** and the dimedonate ylide **281** with conjugated dienes afford the related dihydrofurans **282** (Scheme 80) (99SL1925).

Pd(II)/Cu(I)-promoted reactions of the 2-hydroxynaphthoquinone ylide **283** with terminal alkynes or their tributylstannane derivatives afford moderate yields of furonaphthoquinones **284** (Scheme 81) (97TL837). It was



Scheme 80

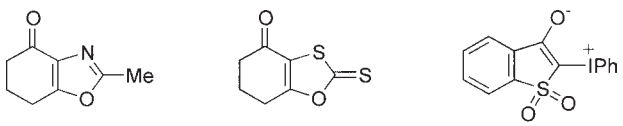


(**283**) (**284**)

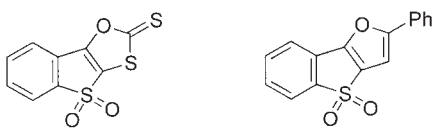
Scheme 81

suggested that the formation of **284** is preceeded by Cu(I)-reduction of **283** to the corresponding iodoquinone, although the authentic iodoquinone gave a much lower yield (20% vs. 66%) of **284** (R = Ph) with phenylacetylene under Pd(II)/Cu(I)-catalysis.

Thermal reactions of the iodonium enolate **279** with acetonitrile and carbon disulfide in the presence of $Cu(acac)_2$ lead to the heterobicyclic ketones **285** and **286**, respectively (98TL9073), while similar treatment of the hybrid sulfonyl–carbonyl ylide **287** with CS_2 or phenylacetylene affords the tricyclic sulfones **288** and **289** (97T9365).



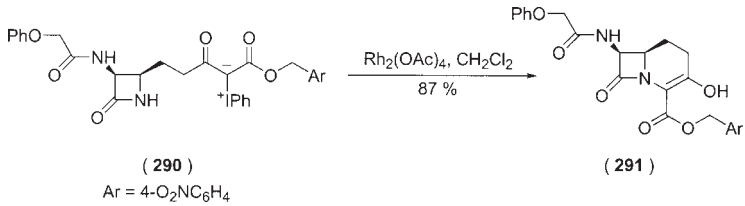
(**285**) (**286**) (**287**)



(**288**) (**289**)

The azetidinonyl iodonium ylide **290** is a safe and convenient alternative to the related diazo compound for synthesis of the carbacephalosporin precursor **291** (Scheme 82) (97TL6981). The ylide was prepared in 88% yield from the corresponding β-ketoester and was cyclized to **291** with a Rh(II)-catalyst, presumably via a Rh-carbenoid intermediate.

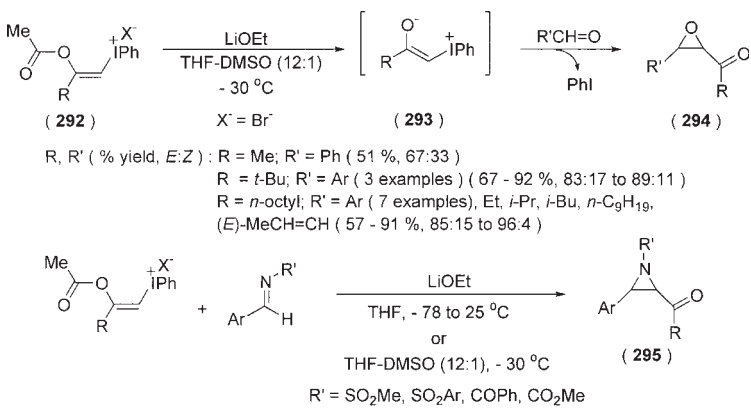
Iodonium enolates **293**, formally derived from unactivated monoketones, can be generated *in situ* by the action of lithium ethoxide on (*Z*)-β-acetoxyvinyliodonium salts **292** (97JA11598, 98TL5569, 99JOC3181). When aliphatic or aromatic aldehydes are present in the reaction



(**290**)
Ar = 4-$O_2NC_6H_4$

(**291**)

Scheme 82



(**292**) $X^- = Br^-$ (**293**) (**294**)

R, R' (% yield, *E*:*Z*) : R = Me; R' = Ph (51 %, 67:33)
R = *t*-Bu; R' = Ar (3 examples) (67 - 92 %, 83:17 to 89:11)
R = *n*-octyl; R' = Ar (7 examples), Et, *i*-Pr, *i*-Bu, *n*-C_9H_{19},
(*E*)-MeCH=CH (57 - 91 %, 85:15 to 96:4)

(**295**)

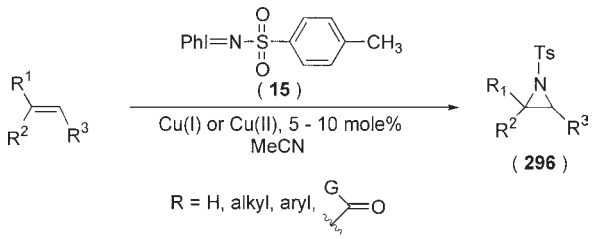
R' = SO_2Me, SO_2Ar, COPh, CO_2Me

Scheme 83

medium, α, β-epoxyketones **294** are obtained, with high preference for the (*E*)-stereoisomers (Scheme 83). *N*-Sulfonyl- and *N*-carbonylimines of aromatic aldehydes behave similarly with **293** and afford the aziridine derivatives **295**, but in this case, the stereochemical outcomes are more complex.

2. *Iodine(III)–Nitrogen Ylides*

The sulfonyliminoiodanes **24** (Section II.C) can be readily prepared by base-catalyzed condensations of sulfonamides with DAIB (92MI1). When employed with transition metal catalysts, they serve as nitrene-transfer agents and are useful for nitrene addition and insertion reactions (92MI1, 02CRV2523, 03MI1). [(Tosylimino)iodo]benzene(**15**) is the most prominent member of the iminoiodane family and is commonly utilized in the Evans aziridination reaction (Scheme 84) (91JOC6744, 94JA2742). In the Evans procedure, sulfonyliminoiodanes are mixed with olefinic substrates in the presence of a Cu(I) or Cu(II)-catalyst, leading



Scheme 84

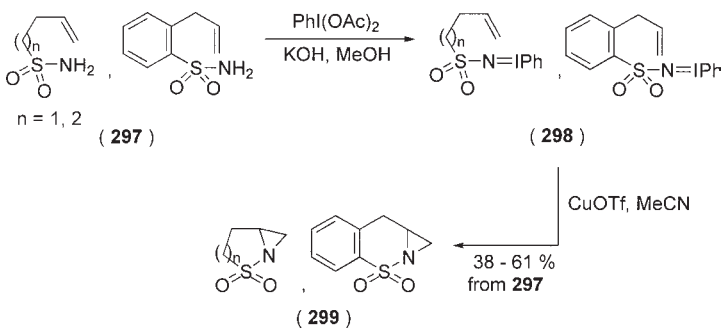
thereby to *N*-sulfonylaziridines **296**; alkyl, aryl, and electron-withdrawing (e.g., CO_2R, COR) groups can be so incorporated into the aziridine ring.

Synthetic developments in this area, including applications of the nosyl (97TL6897, 97TA3563) and β-(trimethylsilyl)ethanesulfonyl (99JOC5304) analogs of **15**, and asymmetric aziridination reactions have been reviewed (02CRV2523, 03MI1). Furthermore, because aziridinations of this type appear to be mediated by copper-nitrenoids, "$L_nCu{=}NSO_2R$" (95JA5889), substantial attention has been given to ligand and catalyst development (93JA5326, 93JA5328, 95JA5889, 96TL6189, 98T15731, 99JCS(P2)1043, 99OM5435, 99TA3833, 00IC4913, 00JA7132, 01CC785, 01IC5060, 01OL1423).

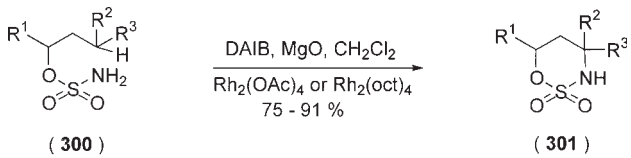
Intramolecular aziridinations of the olefinic sulfonamides **297**, by means of the iminoiodane derivatives **298**, have recently been demonstrated (Scheme 85) (00OL2327). Ring-opening reactions of the bi- and tricyclic sultams **299**, thus obtained, with selected nucleophiles were explored and provide access to functionalized cyclic sulfonamides.

Treatment of the sulfamate esters **300** with DAIB in the presence of a Rh(II)-catalyst (and MgO) leads directly to the oxathiazines **301** (Scheme 86) (01JA6935). Although a detailed mechanism for γ-CH bond insertion in **300** was not presented, it is tempting to conclude that rhodium nitrenoids, generated from initially formed iminoiodanes, are ultimately responsible for oxathiazine production. The formal insertion of "nosylnitrene" into allylic and benzylic CH bonds in Rh(II)-catalyzed reactions of PhI=Ns with cyclohexene, indan, (*R*)-2-phenylbutane, and a series of ethylbenzenes has been reported and lends credence to such a process (96T1543, 98CJC738, 98JPO597). Regardless of the mechanism, DAIB-cyclizations of sulfamate esters possessing a prochiral γ-methylene group proceed with high *syn*-distereoselectivity. In the case of the sulfamate ester derived from (*S*)-3-methyl-1-pentanol, formation of the oxathiazine ring occurs enantiospecifically.

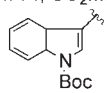
Rh(II)-catalyzed reactions of the alkyl carbamates **302** with DAIB lead similarly to the oxazolidinones **303** (Scheme 87) (01AGE598). Depending



Scheme 85

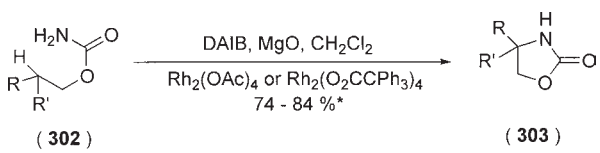


R^1, R^2, R^3 = CO_2Et, H, Ph; CO_2CH_2Ph, H, *n*-Pr; CO_2Me, Me, Me; *n*-Pr, Me, Me; H, Me, Et (chiral); H, H,



and examples of the formation of bicyclic oxathiazines

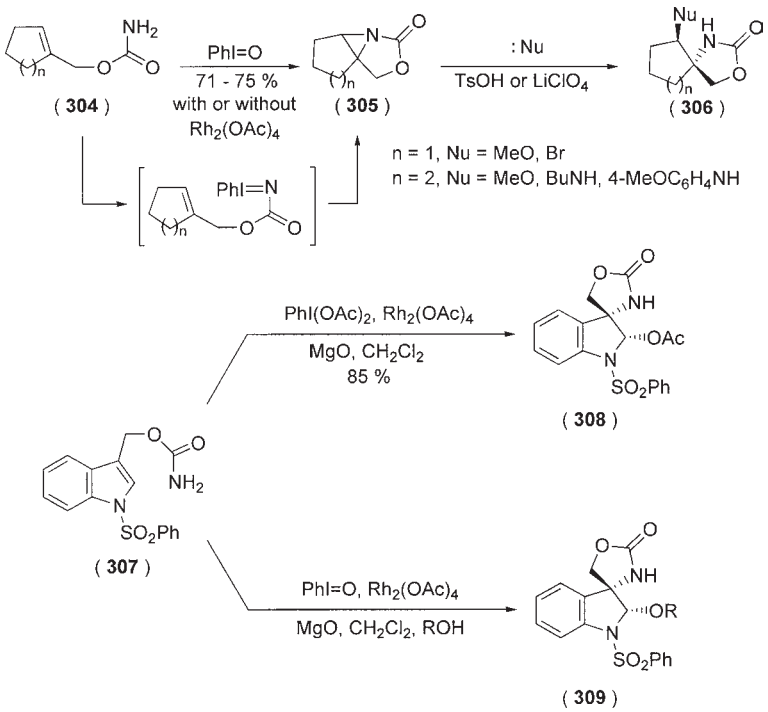
Scheme 86



R, R' = H, Ph; H, Et; Me, Me; $(CH_2)_5$; $O(CH_2)_4$
and examples of the formation of bicyclic oxazolidinones
*R, R' = H, Et (44 %)

Scheme 87

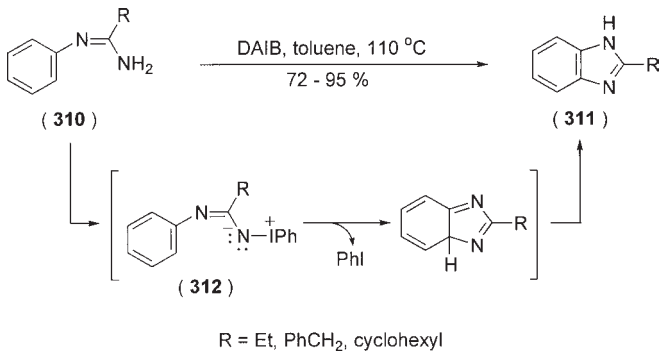
on the structure of **302**, monocyclic, bicyclic, and spirocyclic oxazolidinones are available by this approach. The stereospecific nature of β-CH bond insertion in such cyclizations was nicely demonstrated by the synthesis of enantiomerically pure (*R*)-4-ethyl-4-methyloxazolidinone from the carbamate derivative of (*S*)-2-methyl-2-butanol. In control studies with a representative carbamate, it was shown that oxazolidinone formation



Scheme 88

does not occur without the rhodium catalyst and is greatly facilitated with magnesium oxide.

Exposure of the (cycloalkenyl)methyl carbamates **304** to iodosylbenzene in the presence or absence of $Rh_2(OAc)_4$ gives the tricyclic aziridines **305** (Scheme 88) (02OL2137). Reactions of **305** with nucleophiles, facilitated with tosic acid or lithium perchlorate, proceed with cleavage of the C–N edge bond and afford the *anti*-spirooxazolidinones **306**. Intramolecular "aziridination" of the indolyl carbamate **307** with DAIB, on the other hand, requires Rh(II)-catalysis and leads directly to the acetoxy-substituted *syn*-spirooxazolidinone **308** (Scheme 88) (02OL2137). When iodosylbenzene is used instead of DAIB and alcohols are available in the reaction medium, alkoxy-substituted *syn*-spirooxazolidinones **309** are obtained. Whereas the conversion of **304** to **305** appears to proceed by direct cyclization of intermediate iminoiodanes, the production of **308** from **307** was attributed to the intervention of a rhodium nitrene, which collapses to **308** through zwitterionic intermediates (02OL2137).



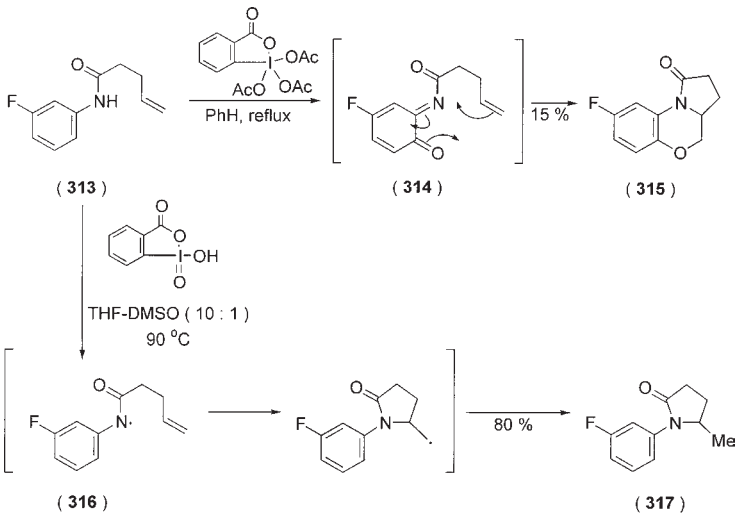
Scheme 89

The *C*-alkyl-*N*-phenylamidines **310** react with DAIB to give the benzimidazoles **311** (Scheme 89) (97JCS(P1)2319). A mechanism for this transformation involving the generation and cyclo-α-elimination of iodine(III)–nitrogen ylides **312** has been proposed. It is noteworthy that *C*,*N*-dialkyl- and *C*,*N*-diarylamidines are converted to ureas, acetylureas, and/or carbamoylamidines under these conditions, presumably via Hofmann rearrangement of intermediate ylides of type **312** to the corresponding carbodiimides (97JCS(P1)2319, 01JCS(P1)680).

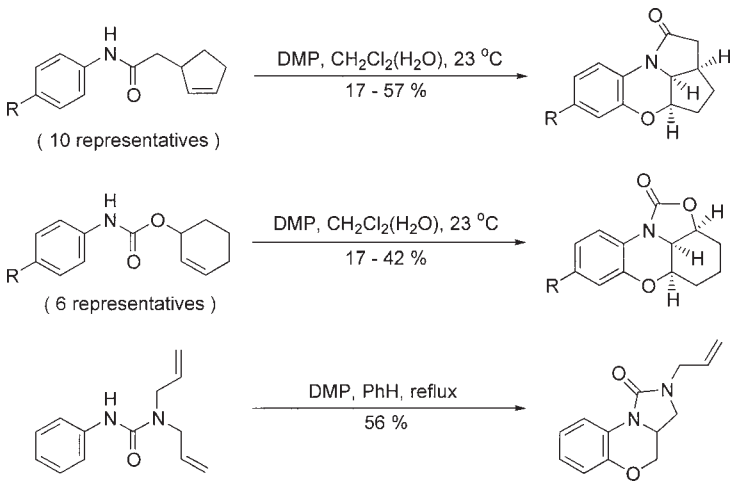
D. Synthesis with Aryl-λ^5-Iodanes

In recent years, Nicolaou and co-workers have employed the Dess-Martin periodane (DMP) and *o*-iodoxybenzoic acid (IBX) with *N*-arylalkenamides in two fundamentally different heterocyclization pathways; these are illustrated with a representative substrate in Scheme 90 (00AGE622, 00AGE625, 00AGE2525, 01AGE202, 02JA2212, 02JA2233). Treatment of the *N*-arylpentamide **313** with DMP initiates an oxidation–cyclization sequence eventuating in the tricyclic oxazine derivative **315.** This transformation is thought to involve initial oxidation of **313** to the *o*-iminobenzoquinone **314**, and its conversion to **315** by an intramolecular [4 + 2] cycloaddition reaction. Exposure of the amide to IBX, on the other hand, affords the *N*-arylpyrrolidinone **317**, most probably through the nitrogen-centered radical **316**.

Although product yields are generally in the low to moderate range, a variety of DMP "cascade-cyclizations" have been demonstrated and extended to urethane-based analogs of the *N*-arylalkenamides. Selected reactions of this type are presented in Scheme 91 (00AGE622, 01AGE202, 02JA2212).



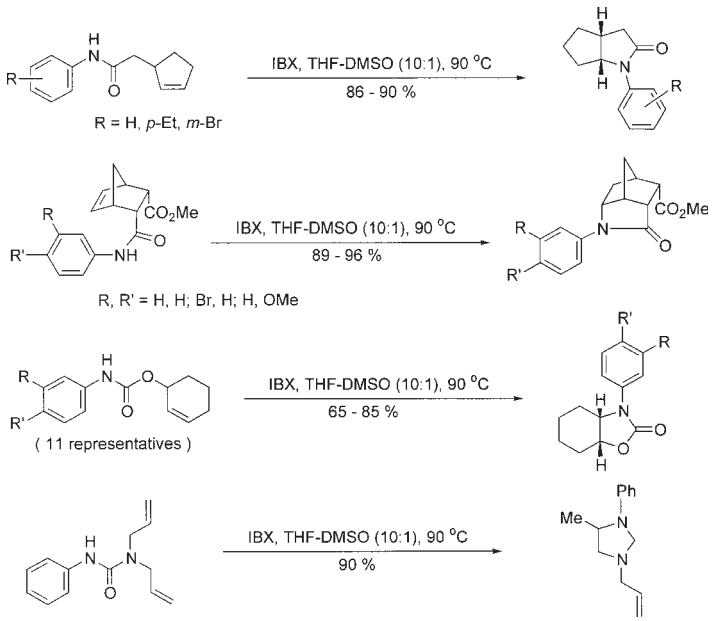
Scheme 90



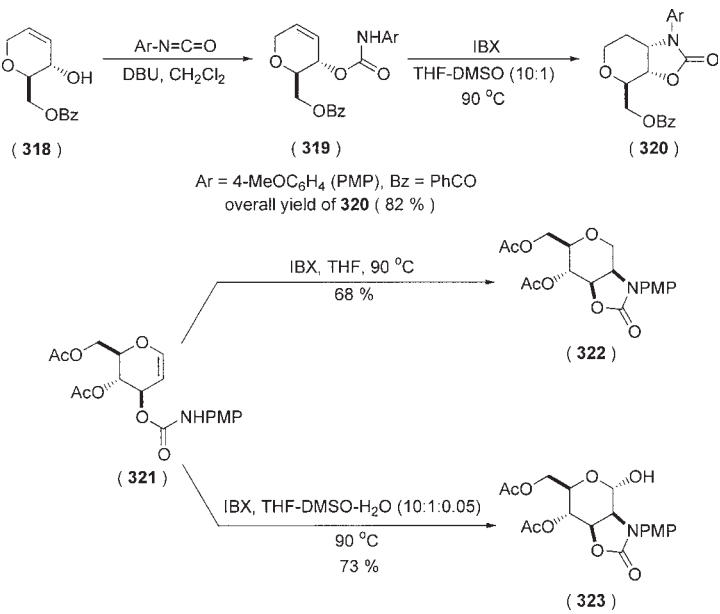
Scheme 91

IBX-oxidations of unsaturated *N*-aryl amides and urethanes proceed more efficiently and provide access to a substantial variety of pyrrolidinones and oxazolidinones, examples of which are shown in Scheme 92 (00AGE625, 01AGE202, 02JA2233).

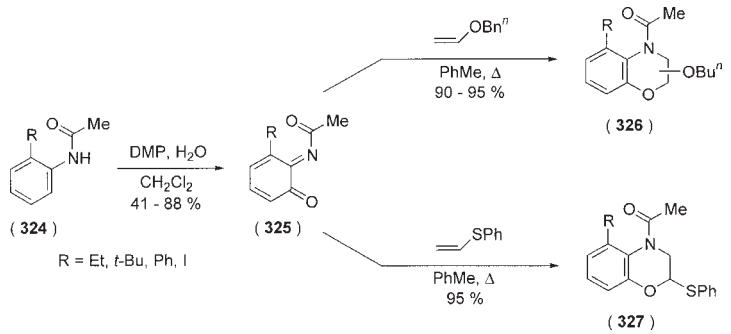
The IBX approach to oxazolidinones is readily adaptable to the synthesis of amino sugars (Scheme 93) (00AGE2525, 02JA2233). For example, conversion of the dihydropyranyl alcohol **318** to the carbamate derivative



Scheme 92



Scheme 93



Scheme 94

319 with *p*-methoxyphenyl (PMP) isocyanate, and oxidation of the latter with IBX furnishes the protected amino sugar **320**. IBX-oxidation of the glucal carbamate **321**, under anhydrous conditions, leads to the 1-deoxy amino sugar derivative **322**, but when water is present in the reaction medium, the amino sugar **323** is obtained instead.

Oxidation of the *ortho*-substituted acetanilides **324** with DMP leads to the isolable *o*-iminobenzoquinones **325** (Scheme 94) (02JA2221). The iminoquinones undergo "inverse electron demand" Diels–Alder reactions with the vinyl ether and vinyl sulfide shown in Scheme 94, thus providing access to the benzoxazine derivatives **326** and **327**.

Acknowledgments

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Organometallic Complexes of Pyridines and Benzannulated Pyridines

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Abbreviations

acac	acetylacetonate
AN	acetonitrile
Bu	butyl
cod	cyclooctadiene
COE	cyclooctene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
dcpe	dicyclohexylphosphinoethane
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppb	diphenylphosphinobutane
dppf	$Fe(Ph_2PC_5H_4)_2$

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dppm	diphenylphoshinomethane
dppp	diphenylphosphinopropane
Et	ethyl
Fc	ferrocenyl
hfacac	hexafluoroacetylacetonate
Me	methyl
nbd	norbornadiene
OTf	triflate
Ph	phenyl
pip	piperidine
Pr	propyl
py	pyridine
tfb	tetrafluorobenzobarrelene
THF	tetrahydrofuran
THT	tetrahydrothiophene
Tol	tolyl

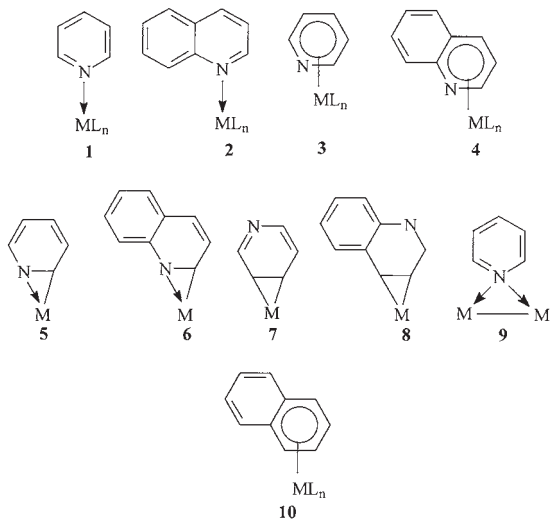
I. Pyridines and Benzannulated Pyridines

A. Introduction

Following analysis of the general trends in coordination modes of the five-membered heterocycles (99AHC(72)1, 01AHC(78)1, 01AHC(79)115, 01AHC(80)157, 01AHC(81)167, 02AHC(83)117, 03AHC(84)191, 03AHC(85)1), we turn our attention to the six-membered derivatives, being illustrative of the π-deficient ligands.

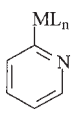
Trends in coordination chemistry of variously substituted pyridines follow from the analysis of the modes of their protonation and molecular-complex formation (69JA2590, 76JA318, 76JA854, 77JA3617, 77JA5729, 79JA6520, 79JA7141, 79JA7146, 80JA5191, 81JA1344, 83H1717, 84JA6552, 89JA4178, 91JA1770, 97JPC(A)4409), the nature of pyridyl and quinolyl molecules, ions, and radicals (68JCS(A)2696, 72JA720, 74MI1, 75JA1548, 75JCS(P2)841, 75JCS(P2)1581, 98JPC(A)6697), and those for acridine (97JPC(A)3554). The most typical situation for pyridine, quinoline, and their derivatives is the η^1(N)-coordination **1** and **2** (85CHC1, 85MI1, 87MI1). This constitutes the most common mode. Pyridine and quinoline manifest the $\eta^6(\pi)$-donor function **3** and **4** predominantly in case of restriction of access to the lone pair by bulky substituents in the α-position (78JHC1057, 83JCS(CC)909, 02OM2800). Bulky 2,4,6-*tert*-butyl groups not only enhance the tendency for the $\eta^6(\pi)$-complexation (89P1641) but also for the cyclometallation reaction followed by the

η^2(N,C)-coordination of a derivative of pyridine. The latter, **5** and **6**, attracts major attention (90JA2814, 95P3315, 95P3335) and subsequent chapter will be devoted to the analysis of this mode only. The η^2(C,C)-coordination **7** and **8** is rare (87JA8101, 89JA2896). There are also references to the μ-η^1(N) mode **9** (82JCS(CC)238, 83JCS(D)649). For the benzannulated pyridines modes of type **10** are quite frequent (88OM2250, 89OM1375, 91OM770).

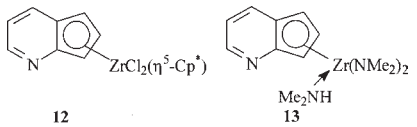


B. Complexes of Pyridines with Non-Transition and Early Transition Elements

4-Methyl- and 4-*tert*-butylpyridine as solvents in the reaction mixture of *n*-butyl lithium and aniline give rise to the η^1(N)-coordinated species $[\{PhN(H)Li\}_x(4\text{-}R\text{-}C_5H_4N)]$ ($x=1$, R = Me; $x=4$, R = *t*-Bu) (00JCS(D)1225). The adduct $[Pb(Br)C_6H_3\text{-}2,6\text{-}(C_6H_2\text{-}2,4,6\text{-}i\text{-}Pr_3)_2]\cdot py$ contains the η^1(N)-coordinated pyridine (00OM2874). However complexes of non-transition and late transition metals are often η^1(C)-coordinated, e.g., **11** (97TL7087).

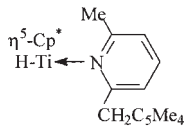


Lithium salt of cyclopenta[*b*]pyridinyl with [(η^5-Cp*)$ZrCl_2$] gives the η^5-complex **12** (02JCS(D)2995). Cyclopenta[*b*]pyridine with [$Zr(NMe_2)_4$] gives **13** in the presence of dimethylamine.



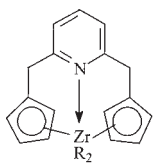
12 **13**

2-Methylpyridine with [(η^5-Cp*)(η^1-$C_5Me_4CH_2$)Ti] gives the product of hydrogen transfer from position 6 of 2-methylpyridine to the titanium site along with the C–C bond formation between pyridine and CH_2-group, **14** (87AGE330).



14

The ligand 2,6-$(CH_2C_5H_4)_2C_5H_3N$ (L) forms [$LUCl_2$] (91JOM(412)327) and [$LLnCl]_2$ (94JOM(471)97), where the geometry is trigonal-pyramidal and the ligand is coordinated via the nitrogen heteroatom and the π-systems of cyclopentadienyl-containing substituents. The same situation is observed for [$LZrCl_2$] (93JCS(D)3341) and [$LZr(Cl)(H_2O)]_2[ZrCl_6]$ (95ZAAC1106). Complex [$LZrCl_2$] follows from the disodium salt of L and zirconium(IV) chloride. Further reaction with RMgCl or RLi in a molar ratio 1:2 allows to afford [$LZrR_2$] (R = *n*-Bu, Me, CH_2SiMe_3) (97OM5312) having a structural pattern **15**. If the molar ratio is maintained as 1:1, [LZrRCl] (R = *n*-Bu, Me, CH_2SiMe_3) follow. Lithium salt of 3-(2-pyridyl)indene with [$Zr(NR_2)_4$] (R = Me, Et) gives **16** (R = Me, Et) and with [(η^5-Cp)$ZrCl_3$] gives **17** (01JOM(621)197). 2,4,6-Tri-*tert*-butylpyridine with titanium vapors gives **18** (97JOM(528)77).



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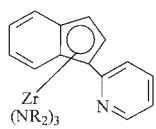
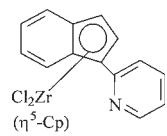
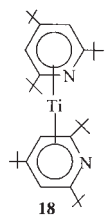


16

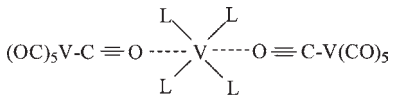


17



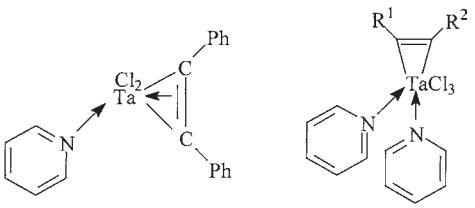
18

Pyridinium and acridinium salts (LH) with $[V(CO)_6]^-$ form $[LH]^+[V(CO)_6]^-$ (86JOM(303)111). $V(CO)_6$ with pyridine forms $[V(py)_6][V(CO)_6]_2$ through the intermediate stage of **19** (83JCS(CC)650).



19

The organometallic derivative $[C_5H_5NH][TaCl_4(PhC{\equiv}CPh)(py)]$ contains an η^1(N)-coordinated pyridine (80IC2352, 81JCS(D)2373). Reaction of $[TaCl_2(SC_4H_8)_3]$ with tolane and further with pyridine gives **20** (79JA5094, 80IC2352). Interaction of $[TaCl_3(R^1C{\equiv}CR^2)(DME)]$ ($R^1 = R^2 =$ Et, n-C_5H_{11}, Ph; $R^1 =$ Ph, $R^2 =$ Me) with pyridine gives **21** ($R^1 = R^2 =$ Et, n-C_5H_{11}, Ph; $R^1 =$ Ph, $R^2 =$ Me) (03OM464).



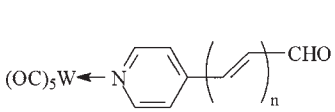
20 **21**

C. Complexes of Pyridines with Chromium Group Derivatives

1. *Common Coordination Modes*

Classical organometallic compounds with the chromium–carbon bond include $[Cr(OH_2)_5(CH_2Hpy)]^{3+}$ (Hpy is a 3- or 4-substituted pyridinium cation) (65JCS7029, 71JCS(B)1841). Compounds of the same type, $[M(\eta^5\text{-}Cp)(CH_2R)(CO)_3]^+$ (R = 3-Hpy^+, 4-Hpy^+; M = Mo, W) can be reduced to yield $[M(\eta^5\text{-}Cp)(CH_2R)(CO)_3]^{2+}$ (75JCS(CC)163). The latter can easily be converted to $[M(Cl)(CH_2R)(CO)_3]^+$. Reaction of $[Cr(CO)_5]^{2-}$ with pyridine in the presence of water gives $[Cr(CO)_5(py)]$ along with H_2 and OH^- (57ZAAC151). An older bibliography of chromium, molybdenum, and tungsten carbonyl complexes of pyridine includes (57ZAAC314, 58CI(M)1003, 59TL13, 59ZN(B)600, 60CB2087, 60ZN(B)413, 60ZN(B)621, 60ZN(B)813, 61CB398, 61ZPC(27)439, 61ZPC(28)268, 62CB1767, 63CB2220,

63CB2859, 63ZN(B)769, 65JCS5346, 73JCS(D)1743). $[W(CO)_5(py)]$ can be prepared from $(Et_4N)[W(CO)_5Cl]$ and pyridine (73MP179, 79JOM(179)253, 81JOM(219)53, 84IC132, 91JPP(A)289, 97CCR(159)211, 97IC4620) or $[W(CO)_6]$ and pyridine in photochemical conditions (91IC567). This organometallic species was also studied in the adsorbed state (85IC2565). It gives rise to $[W(CO)_3(py)(PPh_3)_2]$ (89IC4285). Species $[W(CO)_5L]$ (L is a variety of differently substituted pyridines) contain the η^1(N)-coordinated heterocyclic ligands (61CB2031, 62ZPC(34)393, 72IC1967, 74IC905, 80JA6874, 86JA5830, 94CRV195, 94JA10089, 95AGE21, 98ADOC98, 98ICA(279)243, 98JOM(562)197, 00EJIC229, 01CSR355). Pyridine ligands with $[W(CO)_5(THF)]$ enter photolysis reaction and generate **22** (n = 0–2) and **23** (X = Y = COOMe; X = CN, Y = COOMe, N_2O; X = Y = CN) with interesting non-linear optical properties (72APP545, 86BSCB211, 89JMEC10, 89T4103, 02JOM(656)102).



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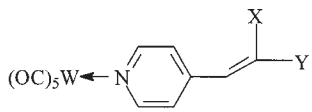
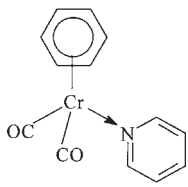


23

Interaction of various pyridines (L = pyridine, 3-benzyl-, 4-ethyl-, 4-phenyl-, 4-benzyl-, 4-cyano-, 4-formyl-, 3,4-dimethyl-, 3,5-dichloro-, and 3,5-dibromopyridine) with $[W(CO)_6]$ in photochemical conditions gives *cis*-$[W(CO)_4L_2]$ through the stage of $[W(CO)_5L]$ (78IC3385). 4-Cyanopyridine, however, is capable of a bridging function, when coordination takes place via the nitrogen heteroatom and nitrile nitrogen in $[(OC)_5W(\mu\text{-}NC_5H_4CN)W(CO)_5]$ (89JOM(363)335) and $[(OC)_4(n\text{-}Bu_3P)W(\mu\text{-}NC_5H_4CN)W(PBu_3\text{-}n)(CO)_4]$ (87JOM(321)215). Another route to the final products lies through the reaction of excess ligand with *cis*-$[W(CO)_4(pip)_2]$. These synthetic schemes are general and allowed to prepare other pyridine complexes of composition *cis*-$[W(CO)_4L_2]$ (68BCSJ359, 68BCSJ863, 74JA998, 75JOM(97)405, 76JA3931).

Species **24** is a representative of the family of the η^1(N)-coordinated complexes of pyridine (64CB1877). It can be prepared by irradiation of a solution containing pyridine and $[(\eta^6\text{-}C_6H_6)Cr(CO)_3]$ in toluene in an argon atmosphere (92JA5693). Photochemical reaction of pyridine with $[(\eta^5\text{-}MeC_5H_4)_2Mo_2(CO)_6]$ gives $[(\eta^5\text{-}MeC_5H_4)Mo(CO)_3]$ and *fac*-$[Mo(CO)_3(py)_3]$ (85JOM(282)201, 89IC4414, 92IC4885), and *cis*-$[Mo(CO)_4(py)_2]$ (69JA4963, 84IC4315, 88CJC397, 89IC4414). Other illustrative examples are $[(\eta^5\text{-}Cp^*)CrMe_2(py)]$ (89JA9127) and $[(\eta^5\text{-}MeC_5H_4)Mo(CO)_3(py)][BPh_4]$ (79JOM(181)117).



24

Known η^1(N)-coordinated complexes of 4-substituted pyridines include $[W(CO)_5$(4-R-pyridine)] (R = H, CN, HCO, MeCO, PhCO) (76JA4105, 77IC3154, 79MI1, 80JA6874, 82JA3804, 87CRV711, 89CRV549, 89IC2205, 89IC3663, 90IC3866, 91IC3543, 93IC3822), as well as $[M(CO)_5$(4-R-pyridine)] (M = Cr, Mo; R = CN, HCO, MeCO) (69CB3608, 74CRV401, 82JA2038, 85JA5807, 86OM450). Photolysis of 4-acetylpyridine with $[W(CO)_5(THF)]$ gives $[W(CO)_5$(4-acetylpyridine)] (93IC4226). Photochemical and redox properties of the complexes $[M(CO)_5L]$ (M = Cr, Mo, W; L = pyridine, 4-cyano- and 4-acetylpyridine) synthesized from $[M(CO)_5(THF)]$ under photochemical conditions, were studied extensively (76JA4105, 81IC2778, 81ICA(53)L151, 82AGE700, 82CB910, 82JA2038, 82JA3804, 84IC504). Thus, species with 4-cyanopyridine on electrochemical or chemical reduction produce paramagnetic radical-anions (84IC504). Complex $[Mo(CO)_5(py)]$ (59JCS2323, 62JCS4712, 63IC533, 69AICR135) in combination with $Me_3Al_2Cl_3$ and tetraalkylammonium chlorides is applied in catalysis of the metathesis of olefins (76JCS(CC)930, 77IC2545). 4-Methylpyridine with $[Mo(CO)_6]$ gives $[(\eta^1$-4-Mepy$)_3Mo(CO)_3]$ (96JCC235). Ultraviolet photolysis of $[W(CO)_5L]$ (L = py, 3-Brpy) (67IC1731) leads to $[W(CO)_5]$ and L (75JCS(CC)696, 79JCS(D)184).

Among the η^1(N)-coordinated pyridine complexes of molybdenum and tungsten are those formed between $[M_2(OR)_6]$ (M = Mo, W; R = Me, Et, Ph) and pyridine in an atmosphere of carbon monoxide leading to $[M_2(OR)_6(py)_2(\mu$-CO)] (82JA7030). Interaction of pyridine with $[M(\equiv CR)(COOCF_3)(CO)_4]$ [M=Cr, Mo, W; R = Alk, Ar, C≡CBu-*t*, $SiPh_3$, $C_5H_4Mn(CO)_3$, $\frac{1}{2}(C_5H_4)_2Fe$] gives the η^1(N)-coordinated substitution products $[M(\equiv CR)(COOCF_3)(CO)_2(py)_2]$ (85OM608, 89JCS(D)2261, 89P2265, 91JA5057, 93MI1).

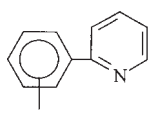
The η^1(N)-coordinated species $[Mo(CO)_3(py)_3]$ prepared from $[Mo(CO)_6]$ and pyridine is useful for the synthesis of various π-allyl molybdenum compounds (68JOM(13)P1, 97OM5365). The η^3-allyl complexes $[(\eta^3$-allyl$)Mo(CO)_2Br(py)_2]$ form $[(\eta^3$-allyl$)Mo(CO)_2$(S,S)(py)] with the anionic S,S-donors, dithiocarbamates and xanthates of sodium and potassium, M′(S,S) (81JOM(218)185). $[(\eta^3$-$C_3H_5)Mo(CO)_2(py)_2Br]$ (68JOM(14)375) with thallium hexafluorophosphate in acetonitrile gives

$[(\eta^3\text{-}C_3H_5)Mo(CO)_2(py)(AN)_2](PF_6)$ (01JOM(632)197). Reaction of $[(\eta^6\text{-arene})_2Mo](PF_6)$ (arene = C_6H_6, PhMe) with pyridine gives $[(\eta^6\text{-arene})Mo(py)_3](PF_6)$ (79IC1835). The last product undergoes a substitution reaction with 1-methylimidazole giving rise to $[(\eta^6\text{-arene})Mo(1\text{-methylimidazole})_3](PF_6)$. With carbon monoxide, $[Mo(CO)_2(py)_4](PF_6)$ is formed.

Species $[Mo(CO)_5(py)]$ and $[Mo(CO)_4(py)_2]$ are described in detail (63IC533, 66AICR1). Species $[M(CO)_3(py)_3]$ (M = Mo, W) react with mercury(II) chloride and give $[M(CO)_3(py)_2]HgCl_2 \cdot \frac{1}{2}HgCl_2$ containing the metal–mercury bond (83JOM(254)325). $[M(CO)_4(2\text{-Mepy})_2]$ and $[M(CO)_3(py)_3]$ (M = Mo, W) react with mercury(II) cyanide to yield $2[M(CO)_3(2\text{-Mepy})]HgCN \cdot nHgCN$ (M = Mo, $n = 3$; M = W, $n = 4$) and $2[M(CO)_3(py)] \cdot HgCN \cdot \frac{1}{2}Hg(CN)_2$ (M = Mo, W), respectively. Mercury(II) thiocyanate gives the tricarbonyl derivatives $[M(CO)_3(2\text{-Mepy})]Hg(SCN)_2 \cdot \frac{1}{2}Hg(SCN)_2$ and $[M(CO)_3(py)]Hg(SCN)_2$ (M = Mo, W).

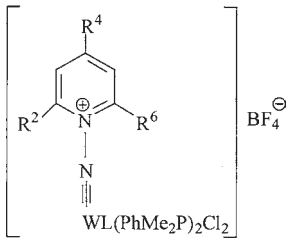
Pyridine and its derivatives react with $[MI_2(CO)_3(AN)_2]$ to yield either mononuclear complexes $[WI_2(CO)_3(AN)L]$ (L = 3-Clpy, 3-Brpy, 4-Clpy, 4-Brpy) and/or dimeric species $[M(\mu\text{-}I)I(CO)_3L]_2$ [M = W, L = py, 2-Mepy; M = Mo, W, L = 4-Mepy, 3,5-Me_2py, 2-Clpy, 2-Brpy, 3-Clpy, 3-Brpy, 4-Clpy, 4-Brpy) (87JOM(329)209). Pyridine, 3-chloropyridine, and 3,5-dimethylpyridine (L) react with $[WI_2(CO)(AN)(\eta^2\text{-}RC_2R)_2]$ (R = Me, Ph) to yield $[WI_2(CO)L(\eta^2\text{-}RC_2R)_2]$ (L = py, 3-Clpy, 3,5-Me_2py; R = Me, Ph) (88IC2287).

2-Alkenylpyridines on reaction with $[Mo(CO)_4(nbd)]$ undergo isomerization. Thus, $2\text{-}CRMe{=}CR'C_5H_4N$ gives $[M(CO)_4(2\text{-}CH_2{=}CRCHR'C_5R_4N)]$ (R = R′ = H, M = Mo, W; R = H, R′ = Me, M = W; R = Me, R′ = H, M = W); $2\text{-}CH_2{=}CRCH_2CH_2C_5H_4N$ gives $[M(CO)_4(2\text{-}CRMe{=}CHCH_2C_5H_4N)]$ (R = H, M = Cr, Mo, W; R = Me, M = Mo, W), and $2\text{-}CH_2{=}CH(CH_2)_3C_5H_4N$ with $[W(CO)_4(nbd)]$ yields $[W(CO)_4(2\text{-}CHEt{=}CHCH_2)C_5H_4N]$ (74JOM(66)C46, 79JCS(D)1078). Complexes $[(OC)_5W(\mu\text{-L})W(CO)_5]$ (L = *trans*-1,2-bis(4-pyridyl)ethylene and 1,2-bis(4-pyridyl) ethane) are known (89IC85). Reaction of $[(\eta^6\text{-phenyl lithium})Cr(CO)_3]$ with pyridine gives **25** (78JOM(153)59).



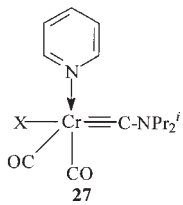
25

Hydrazido-complexes $[WCl_2(NNH_2)(L)(PMe_2Ph)_2]$ (L = CO, C_2H_4) react with 2,4,6-trisubstituted pyrilium tetrafluoroborate salts to form (1-pyridinio)imido-complexes **26** (L = CO, C_2H_4, $R^2 = R^4 = R^6 = Me$; L = CO, C_2H_4, $R^2 = R^6 = COOEt$, $R^4 = Ph$) (96IC5118).



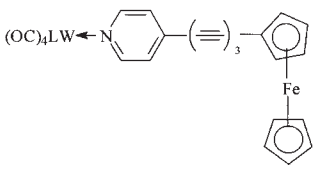
26

A group of pyridine-substituted carbyne complexes (85JA7775, 85OM608, 86OM1504, 87OM925, 88JOM(339)309, 88JOM(347)127, 88JOM(349)367, 89JCS(D)2261, 89ZN(B)1023, 90JOM(382)143, 90JOM(383)179, 95JOM(491)47, 95JOM(498)91, 95OM2987), e.g., species **27** (X = Cl, Br) (93JOM(461)99) contain labile η^1(N)-coordinated pyridine ligands, which leads to an interesting chain of further transformations of these species (97JOM(532)207).



27

Complexes **28** (L = CO, PPh_3) and **29** contain the η^1(N)-coordinated ferrocenylpyridines (96JOM(517)217, 96OM5028, 02IC132).



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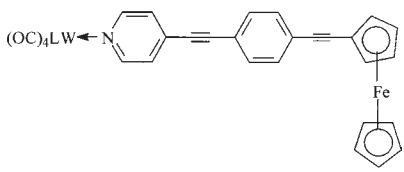
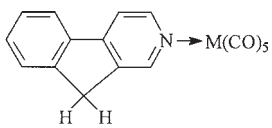


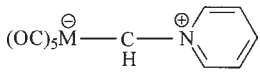
29

2-Azafluorene with $[M(CO)_6]$ (M = Cr, Mo) forms the η^1(N)-coordinated species **30** (M = Cr, Mo) (82JOM(231)5).



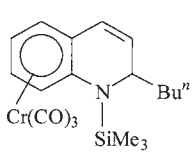
30

Fischer carbene complexes [$(OC)_5M{=}CR(OEt)$] (M = Cr, W; R = *cyclo*-Pr, Ph, CH_2Ph, $(CH_2)_3Me$, $(CH_2)_3Ph$) react with dihydropyridines to yield pyridinium ylides **31** (M = Cr, W) (96JA12045, 98OM361, 00T5001, 01JOM(617)571).



31

Quinoline on reaction with *n*-butyl lithium/trimethylchlorosilane and further with chromium hexacarbonyl does not give the η^6-coordinated species of quinoline via the carbocycle but rather forms hydrogenated quinolines, **32** and **33** (00ICA(310)147). Quinoline does not give clear products on reaction with [(η^5-N-methylpyrrole)$Cr(CO)_3$] but quinaldine forms a η^6-complex (94JOM(470)C4). Thermolysis of quinaldine with [$Cr(CO)_6$] gives the η^1(N)-complex **34** similar to [$Cr(CO)_5$(py)] (63IC533, 81IC4090). The same product follows from photolysis of [$(THF)_3Cr(CO)_3$] (99JOM(575)141). On the other hand, thermolysis of quinaldine with [$(AN)_3Cr(CO)_3$] gives species **35** with the $\eta^6(\pi)$-coordination via the carbocyclic ring.



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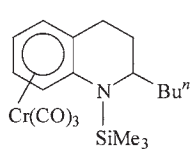

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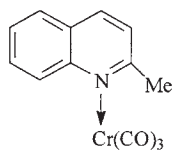

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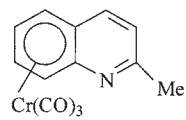
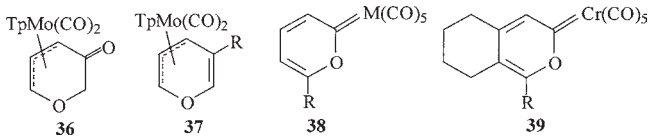
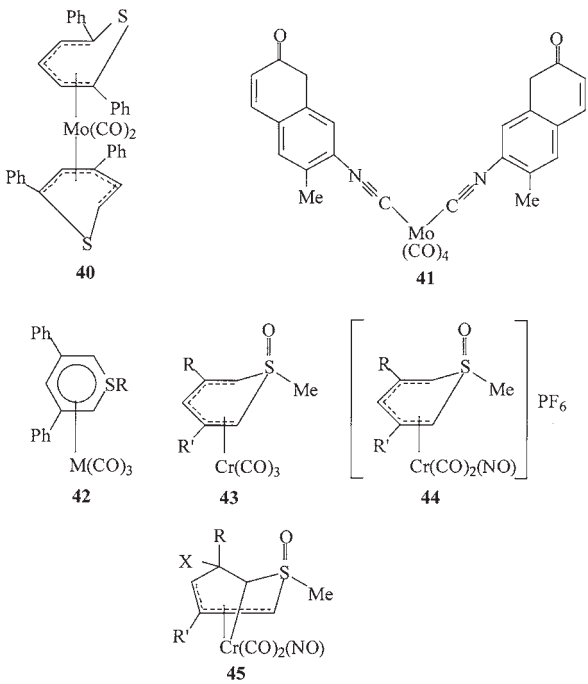


35

3-Oxopyranyl species **36** are derived from 6-acetoxydihydropyran-3-one (99JA5811). On the addition of Grignard reagents RMgBr (R = Me, Ph) to **36**, with subsequent quench using trifluoroacetic anhydride/triethylamine, the $\eta^3(\pi)$-coordinated species **37** (R = Me, Ph) are formed (00JA10458). Interaction of [$M(CO)_5L$] (M = Mo, W; L = THF, NEt_3) with β-ethynyl-α,β-unsaturated esters or amides gives 2-pyranylidene complexes **38** (M = Mo, W; R = OH, OMe, NH_2, NMe_2) (95JA8045, 96AGE1823, 96JA11319, 98JA1928, 98OM2942, 99JOC1344, 00OM5525). In the same way, β-ethynyl-α,β-unsaturated ester and chromium hexacarbonyl give carbene **39** (R = OMe) (02JOM(645)228). Species **39** (R = Ph) are produced from [$Cr(CO)_5$(THF)] in the presence of triethylamine.



2,4,6-Triphenylthiopyrilium perchlorate on thermolysis with $[Mo(CO)_6]$ yields sandwich **40** with the η^5-coordination mode (99JOM(584)171). Reflux of $[Mo(CO)_4(pip)]$ with 7-isocyanocoumarin gives **41** (02JOM(642)97). Thiabenzene salts when treated with $[L_3M(CO)_3]$ (L = AN, cycloheptatriene; M = Cr, Mo, W) give complexes **42** (R = Me, Et; M = Cr, Mo, W) (83JOM(257)275). Complexes **43** (R = R′ = Ph; R = Me, R′ = Me, Ph; R = *t*-Bu, R′ = Ph) (78CB1710, 81CB1, 83AGE498, 83CB1327, 83CB2022) react with $NOPF_6$ to yield the cationic species **44** with the same set of substituents. Compound **44** with $LiBHEt_3$ yields the imido-complexes **45** (85CB1545).

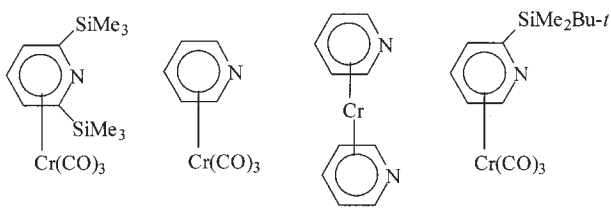


2. η^6-(π)-*Coordination Mode*

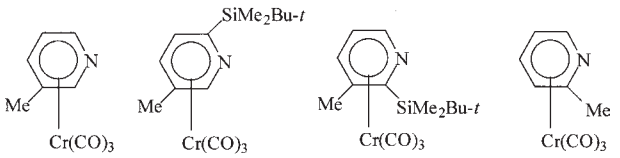
A η^6-coordinated pyridine was first suspected as the product of the reaction of N-methylpyridinium iodide with chromium hexacarbonyl

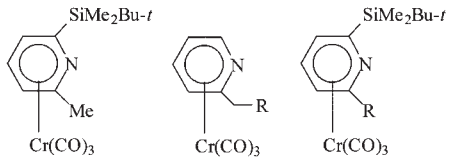
(59PCS61). In fact the product is $(N\text{-Mepy})^{+}[Cr(CO)_5I]^{-}$ and not $[(N\text{-Mepy})Cr(CO)_3]I$ (59ZN(B)736). Pyrolysis of a related salt could give small amount of $[(2\text{-Mepy})Cr(CO)_3]$ (60CB1156). Pyridine on thermolysis with $[Cr(CO)_6]$ gives $[(py)_3Cr(CO)_3]$ with a η^1(N)-coordination mode (66CB1732). The η^6-coordination via the six-membered heteroring becomes possible when the 2- and 6-positions are substituted with methyl or bulkier ethyl groups (75AGE273, 75AGE639, 76ZN(B)321, 83JOM(243)39, 84ZN(B)207). In some examples (59ZN(B)736, 60CB1156) the structural proof is ambiguous. The hypothesis was that on thermolysis of the complex $[Cr(CO)_5(2\text{-Mepy})I]$, the products are $[(\eta^6\text{-2-Mepy})Cr(CO)_3]$, 2-methylpyridinium iodide, and chromium hexacarbonyl. Co-condensation of chromium atoms with a mixture of pyridine and trifluorophosphine gives a mixture of two volatile products, $[(\eta^1\text{-py})Cr(PF_3)_5]$ and $[(\eta^6\text{-py})Cr(PF_3)_3]$ (75AGE273). Thermolysis of pentamethylpyridine and 2,4,6-trimethylpyridine with $[Cr(CO)_6]$ gives the η^6-coordinated tricarbonylchromium complexes (75AGE639).

Since the 2- and 6-positions of the pyridine ring are main reactivity sites (84MI1), an attractive goal is to devise a synthetic route to η^6-complexes of pyridine when the 2- and/or 6-positions are vacant. One of the routes includes preliminary complexation of 2,6-bis(trimethylsilyl) pyridine by its thermolysis with $[Cr(CO)_6]$, which yields **46**, with subsequent desilylation using tetra-*n*-butylammonium fluoride and water to yield **47** (89JCS(CC)995, 91JCS(P1)501, 94AX(C)1669). Complex **48** was prepared using a similar procedure (88CB1983). The other synthetic pattern is based on 2-*tert*-butyldimethylsilylpyridine containing one very bulky substituent in the heteroring (91JCS(P1)501). Thermolysis with $[Cr(CO)_6]$ gives **49** and desilylation with tetra-*n*-butylammonium fluoride and water gives **47**. The same route was applied to the $(\eta^6$-3-methylpyridine)tricarbonyl chromium complex **50**, which can be prepared in two ways—via **51** and **52**. Finally, the η^6-2-methylpyridine analogue **53** follows from the same steps via species **54**. Another achievement is the pair **55** (R = Me, $CH_2CH{=}CH_2$) and **56** (R = Me, $CH_2CH{=}CH_2$).

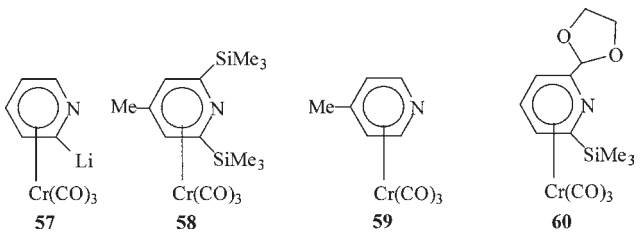


46 **47** **48** **49**



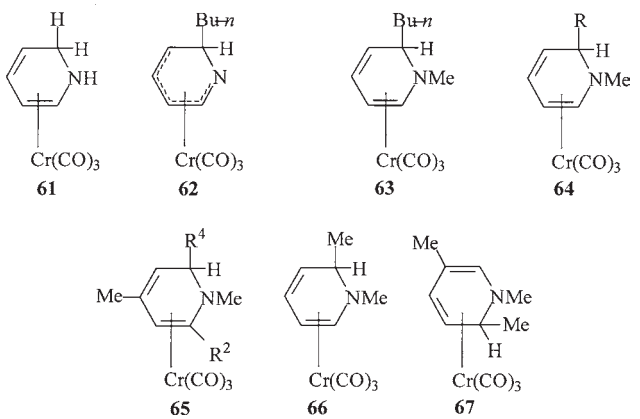


Complex **47** can be lithiated to position 2 with di-*iso*-propylamide lithium to yield **57** and then methylated with methyl iodide to produce **53**. The sequence of lithiation and methylation applied to complex **46** gives **58** and further desilylation as above allows to prepare **59**. Another η^6-complex, **60**, is prepared by thermolysis.

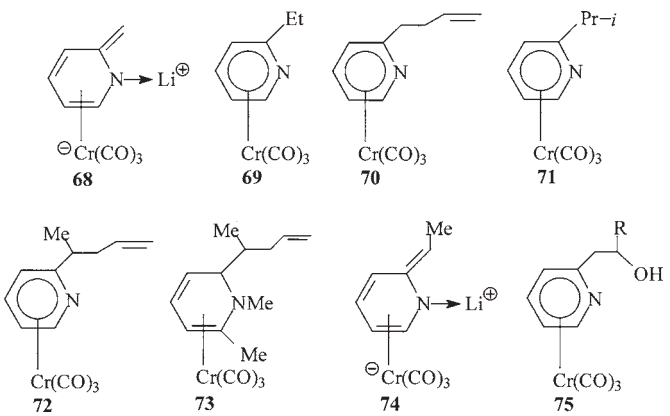


Treatment of complex **47** with di-*iso*-butylaluminum hydride followed by methanol produced the 1,2-dihydro complex **61** (91JCS(P1)757). With *n*-butyl lithium, the same complex gives **62**, which has not been isolated. However, on further treatment with methyl iodide, species **62** is the product. If the combination of reactants acting on **47** is RLi (R = Me, *t*-Bu, Ph) and methyl iodide, then a series of complexes **64** (R = Me, *t*-Bu, Ph) can be obtained. This kind of behavior is in contrast to the uncomplexed pyridine, for which the major products are 2-methyl-5-R-pyridines (71JCS(CC)1420). The reactivity pattern for the η^6-complexes of substituted pyridines, **49**, **53**, and **59**, remains the same, a variety of the products being generalized in scheme **65** (R^4 = H, R^2-*t*-BuMe_2Si, R^6 = Me, *n*-Bu, *t*-Bu, Ph; R^4 = H, R^2 = Me, R^6 = Me, *n*-Bu, *t*-Bu, Ph; R^4 = Me, R^2 = H, R^6 = Me, *n*-Bu, *t*-Bu, Ph) (91JCS(D)757). This contrasts with the behavior of uncomplexed substituted pyridines (69CRV693). Treatment of **50** with methyl lithium and then methyl iodide gives a mixture of products, **66** and **67**, and hence,

is peculiar (91JCS(P1)757). Product **66** also follows from **53** and product **67** follows from **52**, but after the MeLi/MeI action, desilylation with tetra-*n*-butylammonium fluoride follows.

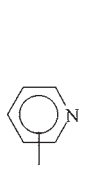


Treatment of complex **53** with di-*iso*-propylamide lithium leads to the intermediate **68**, which on quenching using methyl iodide gives species **69**, and using allyl bromide gives species **70** (91JCS(P1)1009, 91SL25). Combination of di-*iso*-propylamide lithium and methyl iodide applied to complex **69** gives **71**, and applied to complex **70**, species **72** is obtained. The latter with methyl lithium and then methyl iodide gives **73**. Species **69** with lithium di-*iso*-propylamide yields **74**. Complex **53** also undergoes the chain of nucleophilic addition/electrophilic quench with lithium di-*iso*-propylamide/benzaldehyde or pivaldehyde (aldol reaction) to produce **75** (R = Ph, *t*-Bu).



Photolysis of $[(\eta^6\text{-}2,6\text{-}R_2C_5H_3N)Cr(CO)_3]$ (R = H, Me, Me_3Si) in the presence of carbon monoxide gives $[(\eta^1\text{-}(N)\text{-}2,6\text{-}R_2C_5H_3N)Cr(CO)_5]$ (R = H, Me) or the product of loss of carbon monoxide ($R = SiMe_3$) (96OM3679).

Co-condensation of chromium vapor with pyridine and PF_3 gives the $\eta^6(\pi)$-complex **76** (75AGE273). Similarly, with 2,6-dimethylpyridine chromium vapor produces sandwich **77** (R = Me) (76IC2735, 76JA1044). Starting with 2,6-bis(trimethylsilyl)pyridine and followed by desilylation, complex **77** (R = H) results (88CB1983). The chain of transformations includes interaction of 2,6-bis(trimethylsilyl)pyridine with chromium vapor giving first $[\{\eta^6\text{-}2,6\text{-}(Me_3Si)_2C_5H_3N\}_2Cr]$, then in water–methanol medium—$[(\eta^6\text{-py})_2Cr]^+$, and finally with $S_2O_4^{2-}$ in an alkaline medium—the complex **77** (R = H). The following chain also exists: chromium vapor with benzene and pyridine form the mixed sandwich $[(\eta^6\text{-}C_6H_6)Cr(\eta^6\text{-py})]$. The gas-phase synthesis appears most efficient for the $\eta^6(\pi)$-complexes of this nature (59ZN(B)736, 72JOM(44)353, 95RCR201).



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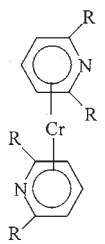
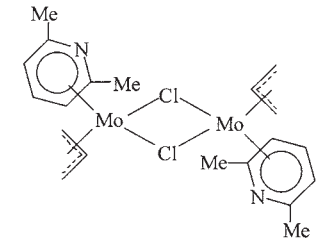


77

Complex $[Mo(\eta^6\text{-}2,6\text{-}Me_2py)_2]$ can be prepared using the metal-vapor synthesis (87OM1691, 87OM1696). Reaction of this species with allyl chloride gives the dimeric $[(\eta^3\text{-}C_3H_5)Mo(\eta^6\text{-}2,6\text{-}Me_2py)Cl]_2$ (93JOM(459)125). Dimer **78** with sodium acetate or pivalate gives the carboxylato species **79** (R = Me, *t*-Bu) (96JOM(513)247) and with methyl magnesium chloride gives species **80**. Treatment of **81** with neat trimethylphosphine gives species **82** ($L = PMe_3$) (98JOM(550)63). Protonation of **82** ($L = PMe_3$) by $HBF_4 \cdot Et_2O$ gives **83** ($L = PMe_3$). A similar set of reactions takes place when **81** is reacted with diphenylphosphine or dimethylphenylphosphine. The products are **82** ($L = PPh_2H$, $PPhMe_2$). The products of protonation by $HBF_4 \cdot Et_2O$ are **83** ($L = PPh_2H$, $PPhMe_2$). A couple of complexes **82** ($L = PPh_2H$, $PPhMe_2$) forms a couple of borane adducts **84** ($L = PPh_2H$, $PPhMe_2$) with $BH_3 \cdot THF$ in ether. Starting species **81** also reacts with tridentate phosphine ligand $t\text{-}Bu(CH_2PH_2)_3$ to yield the Mo–L derivative of similar nature that can be protonated in the same manner.



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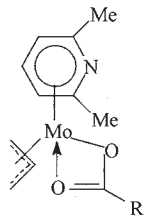

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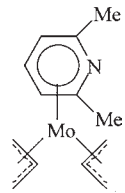

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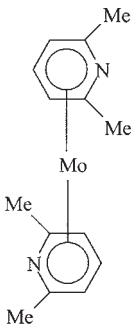

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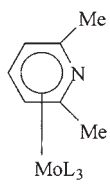

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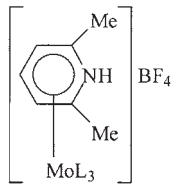

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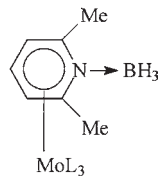


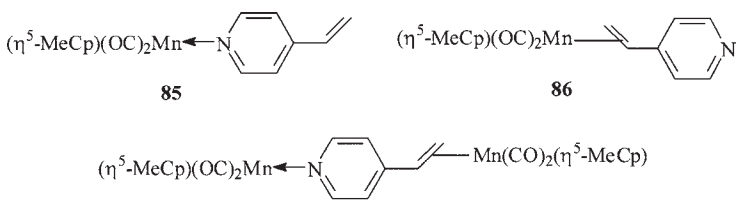
84

D. Complexes of Pyridines with Manganese Group Derivatives

The known η^1(N)-coordinated complexes of pyridine and its derivatives in the manganese group are $[Mn(Br)(CO)_3L_2]$ (L = py, 3-Brpy, 4-Mepy) (59JCS1501, 66JINC2627, 69AICR53, 90IS156) and $[Re(Cl)(CO)_3L_2]$ (L = pyridine, 4-cyanopyridine, 4-phenylpyridine, isoquinoline) (67IC1246, 67ICA(1)172, 92JPC257, 92JPC3059), $[(\eta^5\text{-Cp})M(CO)_2L]$ (M = Mn, Re; L is a substituted pyridine ligand) (77IC160), as well as $[(\eta^5\text{-}C_5H_4Me)Mn(CO)_2(3\text{-}CNC_5H_4N)]$ (87JOM(333)347) and $[(\eta^5\text{-Cp})Mn(CO)_2(py)]$ (60ZN(B)675). Species $[(\eta^5\text{-Cp})Re(CO)_2L]$ (L = py, 4-Phpy) (88JA6243) are obtained by the photochemical reaction of the pyridine ligand with $[(\eta^5\text{-Cp})Re(CO)_2(THF)]$ (89JA6602). Another illustration of the η^1(N)-coordination is the series $[XRe(CO)_3L]$ (X = Cl, Br, I; L = py or a substituted py) (78JA2257, 79JA2888, 79JA7415). Interaction of the radical species $[Re(CO)_4L]^{\bullet}$ [L = PMe_3, $P(O\text{–}i\text{-}Pr)_3$] with the pyridinium salts P^+ containing substituents 3,4-$(CN)_2$, 2,4-$(CN)_2$–, 2-Cl–3NO_2–, 2-CN, 2-Cl–3-CN–, 4-CN, 4-COPh, 2-COPh–, 2-COMe, 4-COMe, 3,4,5-Cl_3–, 2-(2′-NMe(py)), 3-CN–, 3-COPh–,

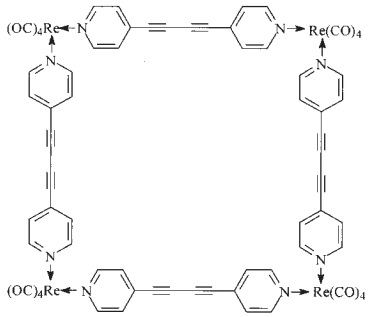
4-$CONH_2$, 3-COMe, and 3-COOMe leads to $[P]^+[Re(CO)_4L]^\bullet$ (89JA5185). Similar behavior is observed in the process of oxidation of $[Mn(CO)_5]^\bullet$ (87JA3632). Photolysis of $[Mn_2(CO)_9]$ in pyridine gives $[Mn_2(CO)_9(py)]$ and $[Mn(CO)_3(py)]^+[Mn(CO)_5]^-$ (81IC3528). Pyridine with the anionic cluster $[H_4Re_3(CO)_9]^-$ gives the η^1(N)-coordinated complex $[H_4Re_3(CO)_9(py)]^-$ (96OM2543). Other examples of η^1(N)-coordination in the rhenium chemistry involve carbonyl species of the pyridyl ligands incorporating an alkyne moiety (95IC2323, 96JOM(517)217). $[(\eta^5\text{-Cp})Mn(CO)_2(THF)]$ and 4-acetylpyridine (L) give a simple η^1(N)-coordinated ligand-substitution product $[(\eta^5\text{-Cp})Mn(CO)_2(L)]$ (99JOM(572)65). Ligands FcCH=CH–*p*-C_5H_4N, FcCH=CHC(Me)=CHCH=CHCH=C(Me)CH=CH–*p*-C_5H_4N, 1′,1′-Fc(–CH=CH–*p*-$C_5H_4N)_2$, *p*-$Me_2NC_6H_4CH$=CHCH=CH–*p*-C_5H_4N, and *p*-$Me_2NC_6H_4CH$=CHCH(Me)=CHCH=CHCH=C(Me)CH=CH–*p*-C_5H_4N (L) with $[Re(CO)_5Br]$ give the η^1(N)-coordinated species *fac*-$[BrRe(CO)_3L_2]$ and *cis*-$[BrRe(CO)_4L]$ as potential non-linear optical materials (99EJIC483). Compound $[Mn(CO)_3(CH_2Hpy)]^+$ with a 3- or 4-substituted pyridinium ion contains the manganese–carbon bond (71JCS(A)910). $[Re(CO)_2Cl(2\text{-styrylpyridine})_2]$ experiences *trans–cis* isomerization of the η^1(N)-coordinated ligands in conditions of the photochemically induced electrolysis (83JA7241).

4-Vinylpyridine with $[(\eta^5\text{-}MeC_5H_4)Mn(CO)_2(EtOH)]$ gives a mixture of products—η^1(N)-coordinated, **85**, η^2-coordinated via the vinyl framework, **86**, and $\eta^1(N):\eta^2$-coordinated dinuclear species **87** (82JOM(231)C9).

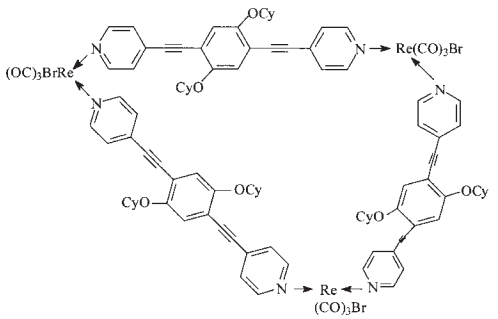


85 **86** **87**

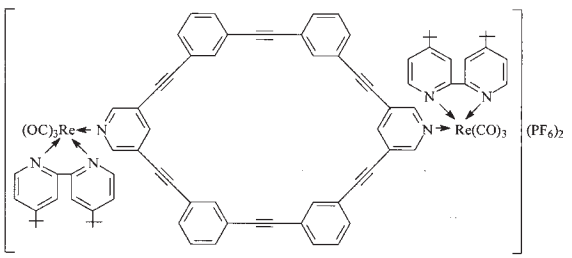
1,4-Dipyridylbutadiyne with $[ClRe(CO)_5]$ gives complex **88**, and 1,4-bis(4′-pyridylethynyl)-2,5-dihexylbenzene with $[BrRe(CO)_5]$ gives **89** (99IC4181). The cyclic pyridine-containing phenylacetylene ligands with $[(t\text{-}Bu_2bpy)Re(CO)_3(AN)](PF_6)$ give dinuclear complexes **90** and **91** with attractive photophysical properties (01OM2353). Fluorene- and carbazole-based oligopyridines on thermolysis with $[Re(CO)_5X]$ (X = Cl, Br) produce complexes **92** (X = –CH=CH–, –C≡C–) and **93** (Y = $–CH_2C{\equiv}CCH_2C_6H_4–$ = –, $–CH_2C{\equiv}CCH_2C_6H_4CH_2C{\equiv}CCH_2–$, $–CH_2C(H)=C(H)–CH_2–$, R = Cy, X = Br; Y = $–CH_2CH=CHCH_2–$, R = Ph, X = Cl) (01OM2262).


(OC)4Re
Re(CO)4
(OC)4Re
Re(CO)4

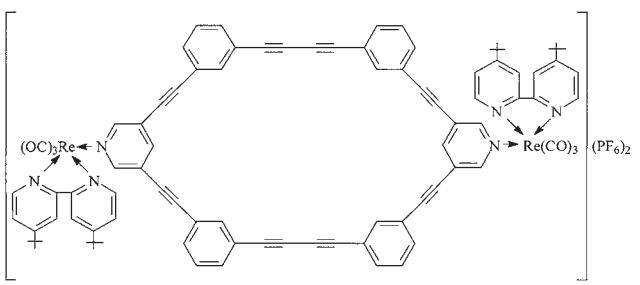
88


OCy
(OC)3BrRe
Re(CO)3Br
CyO
CyO
OCy
CyO
OCy
Re
(CO)3Br

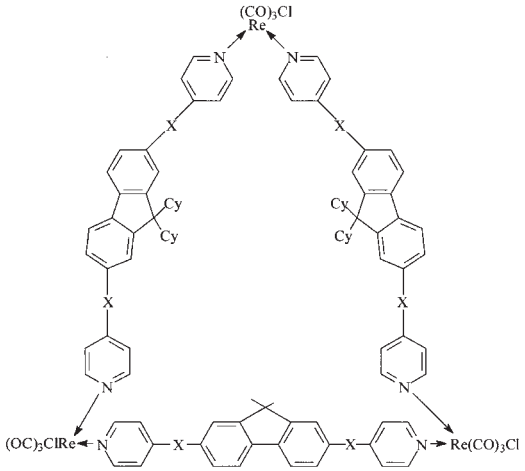
89


(OC)3Re
Re(CO)3
(PF6)2

90


(OC)3Re
Re(CO)3
(PF6)2

91



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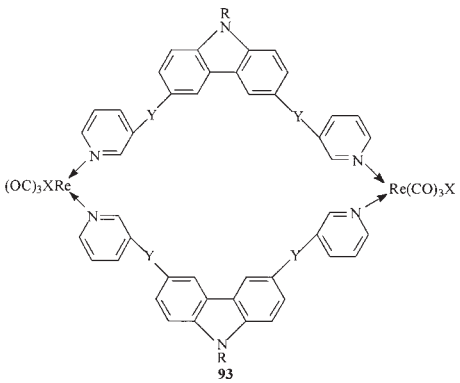
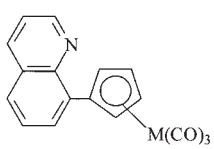
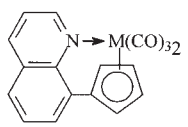


93

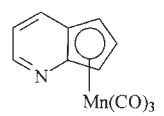
Interaction of $[(\eta^5\text{-ClZnC}_5\text{H}_4)\text{M(CO)}_3]$ (M = Mn, Re) with 8-bromoquinoline in the presence of $[\text{Pd(PPh}_3)_2]$ as a catalyst gives species **94** (M = Mn, Re), which on photolysis experience decarbonylation and form **95** (01JOM(622)66). Complex **96** follows from the corresponding ligand, $[\text{Mn(CO)}_5]$, and potassium (85JOM(296)83).



94

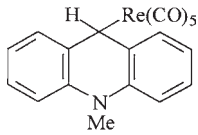


95



96

N-Methylacridinium salts react with $[Re(CO)_5]^-$ by nucleophilic addition to yield adduct **97** (97JPOC542).

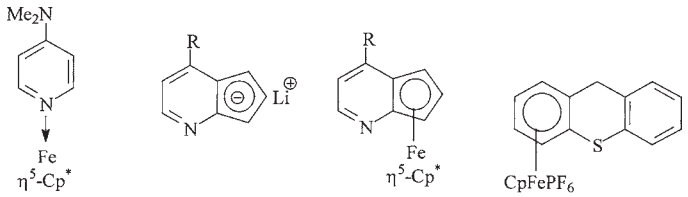


97

E. Complexes of Pyridines with Iron Group Derivatives

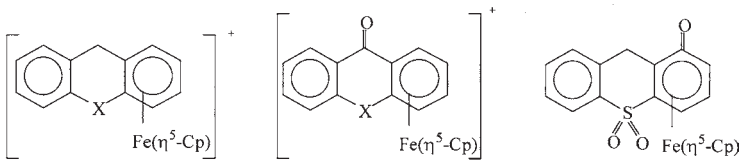
Pyridine and $[Fe_2(CO)_9]$ give η^1(N)-coordinated $[Fe(py)(CO)_4]$ (74JA3438). The same product follows from $[Fe(CO)_5]$ and excess pyridine in the presence of $Me_3NO \cdot 3H_2O$ (80IC392). Pyridine with [(THF)(Et)GaFe $(CO)_4$] gives the η^1(N)-coordinated $[(py)_2(Et)GaFe(CO)_4]$ (80IC2381). Similar species are $[(py)_2MeGaFe(CO)_4]$ (73JA679) and $[(py)_3ZnFe(CO)_4]$ (78IC1477). The structure of [(η^4-EtOOC–CH=CH–CH=CH–COOEt) $Fe(CO)_2\{\eta^1$(N)-L$\}$] (L = pyridine, quinoline) is square-bipyramidal (81JOM(216)79, 87JOM(320)91). Organometallic species [(η^5-Cp)$Fe(CO)_2$ $(CH_2Hpy)]^+$ incorporating 3- or 4-substituted pyridinium ion contain the iron–carbon bond (71JCS(B)662). Reaction of [(η^6-toluene)$Fe(H)_2(SiCl_3)_2$] with pyridine gives [(η^6-toluene)$FeH(SiCl_3)$(py)] but the product is readily converted to $[FeCl_2(py)_4]$ (97IC2119). 4-(Dimethylamino)pyridine forms the η^1(N)-coordinated complex **98** with the (η^5-Cp*)Fe framework (00ACR412). Ligands **99** (R = H, NMe_2, C_4H_8N) on interaction with iron(II) chloride and lithium cyclopentadienyl give sandwiches **100** (R = H, NMe_2, C_4H_8N–pyrrolidino) (96JOC7230). Species similar to **100**, where along with the η^5-Cp* framework there can be η^5-C_5Ph_5 and R = Me_2N or pyrrolidino (98JA7479, 98JA11532, 98JOC3154, 99JA2637) are efficient acylation catalysts (01AGE234). Among species of the type **100** (R = Me_2N, pyrrolidino) and pentaphenylcyclopentadienyl along with pentamethylcyclopentadienyl, the one with R = pyrrolidino appears to be an efficient catalyst of the enantioselective synthesis of β-lactam (02JA1578). The result of interaction of iron(II) chloride with lithium pentamethylcyclopentadienyl and further with 2-chloro-4-methyl-7-cyclopenta[*b*]pyridinyl lithium is sandwich similar to **100** with R = Me but containing the chloro-substituent in position 2 of the heteroring (00JCS(CC)377, 02AGE3892). The latter reacts with methylmagnesium bromide to yield analogue of **100** with 2- and 4-methyl substituents in the heteroring. Subsequent combination of nucleophilic addition of *n*-butyl lithium and electrophilic quench by $ClPPh_2$

gives an efficient catalyst of hydrosilylation of ketones formulated as **100** (R = Me and substituent in position 2 is CH_2PPh_2). A complex of similar nature but containing the sulfur heteroatom is **101** (92ICA(194)207).



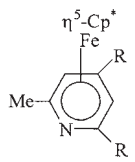
98 **99** **100** **101**

η^6-Xanthene and η^6-thiaxanthene complexes of iron, **102** (X = O, S) are prepared by the ligand exchange reaction between the heterocycle and ferrocene (86JOM(305)199). Chemical oxidation using potassium permanganate leads to the ketones **103** (X = O, S). In the case of X = S, sulfone **104** is also obtained.



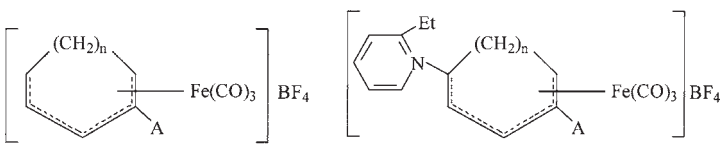
102 **103** **104**

Reaction of $[(\eta^5\text{-Cp*})Fe(AN)_3]^+$ with HC≡CR (R = COOEt, CH_2NMe_2) appears to be a unique oxidative coupling process leading to the $\eta^6(\pi)$-complexes of iron **105** (R = COOEt, CH_2NMe_2) (02OM2578).



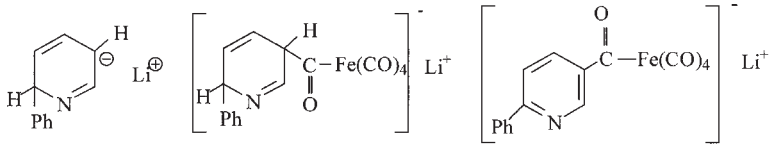
105

Reaction of 2-ethylpyridine with complexes **106** ($n = 1$, A = H, MeO; $n = 2$, A = H) yields **107** ($n = 1$, A = H, MeO; $n = 2$, A = H) (86JCS(D)2707).



106 **107**

Pyridine with phenyl lithium gives **108**, which reacts with iron pentacarbonyl to yield **109** (77JA3166), which can lose molecular hydrogen and form **110**. Substances **109** and **110** were not isolated but used for the synthesis of formyl- and acetylpyridines.

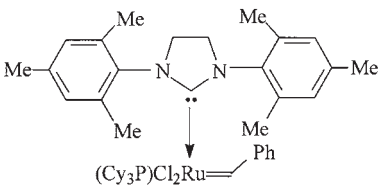


108 **109** **110**

Complexes $[(\eta^4\text{-cod})Ru(Cl)H(amine)_2]$ exchange amine ligands with pyridine, 4-methylpyridine, 4-dimethylaminopyridine (L) to yield $[(\eta^4\text{-cod})Ru(Cl)HL_2]$ (81JOM(219)115). The η^1(N)-coordinated case occurs in $[RuCl_2(CO)(py)_2]$ (66JCS(A)300). Pyridine with $[(\eta^5\text{-Cp*})RuBr_3]_n$ in ethanolic medium forms the η^1(N)-coordinated $[(\eta^5\text{-Cp*})RuBr_2(py)]$ (86JOM(314)C46). Electrooxidation of $[OsH_3(CO)(PPh_3)_3](PF_6)$ in the presence of pyridine yields the η^1(N)-coordinated $[OsH(CO)(PPh_3)_2(py)_2](PF_6)$ (96P1937). The latter with 4-*tert*-butylpyridine undergoes the ligand-exchange reaction to give $[OsH(CO)(PPh_3)_2(py)(4\text{-}t\text{-Bupy})](PF_6)$. Complex $[OsH(CO)(PPh_3)_3(S)](PF_6)$ ($S = CH_2Cl_2$) gives first $[OsH(CO)(PPh_3)_3(py)](PF_6)$ and then $[OsH(CO)(PPh_3)_2(py)_2](PF_6)$. Species $[RuCl_2(CO)(L)(PPh_3)_2]$ (L = py, 3-CNpy, 4-CNpy, 2-Mepy, 3-Mepy, 4-NH_2py, 4-Me_2Npy) are prepared by the ligand-exchange reaction starting from $[RuCl_2(CO)_2(PPh_3)_2]$ or $[RuCl_2(CO)(DMF)(PPh_3)_2]$ (98P203). The η^1(N)-coordination is observed in $[Ru_3(\mu_3\text{-O})(\mu\text{-MeCOO})_6(py)(CO)(H_2O)]$ (96CL745). The η^1(N)-illustrations include ruthenium complex with pyridine and 4-cyanopyridine containing an oxygen tripod ligand (99IC136). 4-Cyanopyridine with $[\{(\eta^6\text{-arene})RuCl_2\}_2]$ (arene is benzene, *p*-cymene, or hexamethylbenzene) forms monomeric, $[(\eta^6\text{-arene})RuCl_2(4\text{-CNpy})]$, and dimeric, $[\{(\eta^6\text{-arene})RuCl\}_2(\mu\text{-4-CNpy})]$ species (74JCS(D)233, 96IJC(A)434, 98IJC(A)165, 98JOM(568)13, 99IJC(A)190). $[(\eta^6\text{-arene})RuCl_2(PR_3)]$ ($R_3 = Ph_3$, Et_3, $MePr^i_2$) in the presence of ammonium hexafluorophosphate give $[(\eta^6\text{-arene})RuCl(PR_3)(4\text{-CNpy})](PF_6)$ (00JOM(605)74). Reaction of the Ru(IV) dimeric bis-allyl $[\{(\eta^3:\eta^3\text{-}C_{10}H_6)RuCl(\mu\text{-Cl})\}_2]$ with 4-cyanopyridine gives the mononuclear product $[(\eta^3:\eta^3\text{-}C_{10}H_6)RuCl_2(4\text{-CNpy})]$ (65TL4187, 74JOM(76)394, 90IC1360, 91JCS(D)1563, 00JOM(613)250). Along with this product, a dinuclear species $[\{(\eta^3:\eta^3\text{-}C_{10}H_6)RuCl_2\}_2(\mu\text{-4-CNpy})]$ is formed (00JOM(613)250), where coordination of the heteroaromatic ligand is via the pyridine and nitrile nitrogen atoms. $[(\eta^3:\eta^3\text{-}C_{10}H_6)RuCl_2(4\text{-CNpy})]$ with $[\{Ru(\eta^6\text{-arene})(\mu\text{-Cl})Cl\}_2]$ (arene = C_6H_6,

$C_{10}H_{14}$, C_6Me_6) and $[\{(\eta^5\text{-Cp*})Rh(\mu\text{-Cl})Cl\}_2]$ forms the Ru(IV)–Ru(II) and Ru(IV)–Rh(III) dinuclear complexes with the same pattern of the bridging 4-cyanopyridine ligand. $[(\eta^6\text{-}p\text{-}NeC_6H_4CHMe_2)Ru\{\eta^2\text{-}Ph_2PCH(Me)Ph_2PO\}](SbF_6)$ with pyridine 3,5-dimethylpyridine, and isoquinoline (L) forms the η^1(N)-coordinated adducts $[(\eta^6\text{-}p\text{-}NeC_6H_4CHMe_2)Ru\{\eta^2\text{-}Ph_2PCH(Me)Ph_2PO\}L](SbF_6)$ (00OM5174). Complex **111** with excess pyridine forms species **112** (01OM5314).

$[OsX_2(py)_2(CO)_4]$ (X = Cl, Br) where the X ligands are mutually *trans* on thermolysis isomerizes to the species where pyridine ligands are mutually *trans* (81JOM(218)211). Pyridine with *trans*-$[OsX_4(CO)_2]^-$ or $[OsX_5(CO)]^{2-}$ gives *trans*-$[OsX_4(py)(CO)]$ (X = Cl, Br) (81JOM(220)201). *trans*-$[OsX_4(CO)_2]^-$ also give rise to $[OsX_2(py)_3(CO)]$ (X = Cl, Br), where X_2 ligands are disposed in a mutual *trans* manner (81JOM(220)210). Using the oxidative ligand exchange, the mixed ligand complexes $[Os(XY)(py)_3(CO)]$ ($X \neq Y = Cl$, Br, I; X and Y are mutually *trans*) were prepared. Benzo[*h*]quinoline and $[M_3(CO)_{12}]$ (M = Ru, Os) form only the mononuclear complexes $[M(CO)_2L_2]$ (HL = benzo[*h*]quinoline; M = Ru, Os) (83JCS(D)2121). Pyridine and its numerous derivatives form strong complexes with [(tetraphenylporphyrin)Ru(CO)] (82IC3618, 82IC4248). Pyridine, however, does not react with $[Ru(\eta^4\text{-cod})(\eta^6\text{-COT})]$ (03OM2378).



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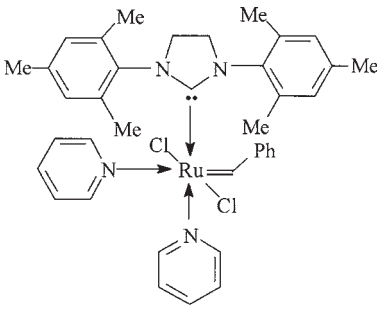


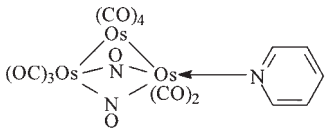
112

In $[(\eta^5\text{-Cp})Ru(\eta^6\text{-aminocoumarin})]^+$, ruthenium is η^6-coordinated to the arene counterpart (89IC2285, 91IC2221).

$[RuCl_2(CH_2CH_2C_5H_4N)Ru(CO)(PPh_3)_2]$ (85JCS(D)873) with $[MS_4]$ (M = Mo, W) gives $[RuCl_2(CH_2CH_2C_5H_4N)Ru(CO)(PPh_3)]_2(\mu\text{-}MS_4)$ (M = Mo, W) (92IC26). Photolysis of $[(PhNCHS)Ru(CO)(PPh_3)]_2MS_4$ (M = Mo, W) with pyridine gives $[(PhNCHS)Ru(py)_2]_2(\mu\text{-}MS_4)$ (M = Mo, W). Reaction of $[(PhNCHS)Ru(PPh_3)](\mu\text{-}MoS_4)[(Ph_3P)(OC)Ru(PhNCHS)]$ with pyridine yields $[(PhNCHS)Ru(py)_2](\mu\text{-}MoS_4)[(Ph_3P)(OC)Ru(PhNCHS)]$.

Pyridine and $[Os_3(CO)_9(NO)_2]$ give the η^1(N)-coordinated species **113** (79JCS(D)557). Excess pyridine with $[Os_6(CO)_{18}]$ gives the pentanuclear

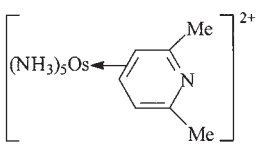
dianion $[Os_5(CO)_{15}]^{2-}$ as the main product (84JCS(CC)1089) but not $[Os_6(CO)_{19}]^{2-}$ as previously considered (79JOM(179)143). A neutral product of this reaction is $[Os_6(CO)_{17}(py)_2]$ (84JCS(CC)1089) containing the $\mu_3(CO)_2$-framework.



113

Pyridine with $[RuH_2(\eta^2\text{-}H_2)_2(PCy_3)_2]$ gives the η^1(N) coordinated complex of composition $[RuH_2(\eta^2\text{-}H_2)_2(py)(PCy_3)_2]$ (03OM1630). In contrast, acridine in this type of reaction gives the product $[RuH_2(\eta^4\text{-}C_{13}H_9N)(PCy_3)_2]$, where the acridine ligand is η^4-coordinated via two double bonds of one of the carbocyclic rings. Further treatment of product by hydrogen causes decomplexation of the ligand and its hydrogenation via the ring that has been coordinated. This study has a practical implication with regards to the problem of catalytic hydrodenitrogenation of fuels.

2,6-Dimethylpyridine on reaction with $[(NH_3)_5Os(TMB)]^{2+}$ gives the η^2-coordinated species **114** (87JA8101). Protonation gives $[(NH_3)_5Os(\eta^2\text{-}2,6\text{-}Me_2pyH)]^{3+}$. Oxidation of **114** in electrochemical or chemical conditions gives the η^1(N)-coordinated species **115**, the process being reversible.



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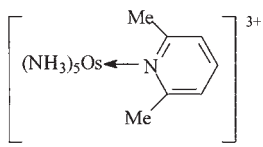
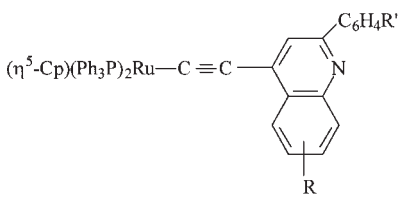


115

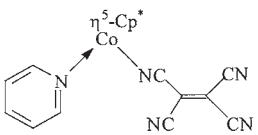
N-Benzylideneanilines cycloadd $[(\eta^5\text{-Cp})Ru(C{=}C{=}C{=}CH_2)(PPh_3)_2]$ to give the 4-ethynyl quinoline complexes **116** (R = H, 4-Me, 4-OMe; R′ = H, 3-NO_2, 4-NO_2) (97JCS(CC)715).



116

F. Complexes of Pyridines with Cobalt Group Derivatives

Compounds $[Co(CN)_5(CH_2Hpy)]^{2-}$, where HPy is a 3- or 4-substituted pyridinium, contain a cobalt–carbon bond (70JCS(A)523). Pyridine reacts with $[Co_2(CO)_8]$ by the radical-chain route to yield $[Co(\eta^1\text{-py})_6][Co(CO)_4]_2$ (87JOM(330)201). Cobalt(III) complexes $[(\eta^5\text{-Cp*})Co(py)Cl_2]$ and $[(\eta^5\text{-Cp})Co(py)Cl_2]$ contain the η^1(N)-coordinated pyridine ligand (84CB743, 86OM980, 87JOM(320)391). The structure of the Co(I) complex **117** is tentative and could be interpreted as the Co(III) species **118** (86JOM(310)249). Pyridine with $[(\eta^5\text{-Cp*})Co(\eta^2\text{-}CH_2SiMe_3)_2]$ gives the cobalt(I) species **119** (00OM1247). Reduction of $[(\eta^5\text{-Cp*})Co^{II}(acac)]$ by potassium in neat pyridine gives species **120** (95CB321). $[(\eta^5\text{-Cp*})Co(\mu\text{-Cl})]_2$ with pyridine experiences cleavage of the chloride bridge and formation of the mononuclear species $[(\eta^5\text{-Cp*})Co(Cl)(py)]$ (85JOM(279)C29). Pyridine influences the $[Co_2(CO)_8]$-catalyzed hydroesterification reaction. The catalytically active species is $[H_2Co_3(CO)_{10}(py)_5]$ which reacts with 2-vinylpyridine to yield the cyclometallated species (65BCSJ710, 67BCSJ135, 68BCSJ1876, 69BCSJ571, 69BCSJ2590, 73BCSJ524, 77CL115).



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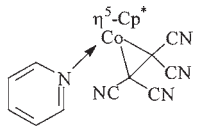

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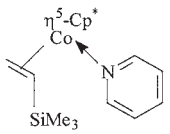
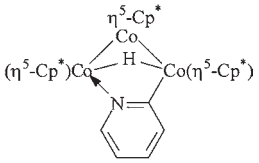


119



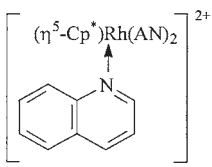
120

2-Bromo-6-ethynylpyridines 2-Br-(6-C≡CR)C_5H_3N (R = H, Me_3Si, Fc) with $[Co_2(CO)_6(dppm)]$ and 2,6-diethynylpyridines containing the same set of substituents with $[Co_3(CO)_8]$ and $[Co_2(CO)_6(dppm)]$ form η^2(C=C) coordinated cluster species, where the $Co_2(CO)_6$ and $Co_2(CO)_4(dppm)$ frameworks perform the coordinating function (02JOM(648)251).

Species $[(\eta^4\text{-cod})IrCl(2\text{-methylpyridine}]$ is a representative of the η^1(N)-coordination situation (57JCS4735, 78ICA(27)21, 80IC7). Pyridine reacts with $[P(CH_2Ph)Ph_3]_2[\{Rh(\mu\text{-Cl})(C_6F_5)_3\}_2]$ to yield the η^1(N)-coordinated mononuclear species $[P(CH_2Ph)Ph_3][RhCl(C_6F_5)_3(py)]$ (90JCS(D)1503).

$[Rh(C_6F_5)_3(Et_2O)_x]$ ($x = 2$, 3) with the same ligand gives $[Rh(C_6F_5)_3(py)_2]$. $[Rh(CO)_n(py)_{4-n}]$ ($n = 2$, 3) and $[Rh_5(CO)_{13}(py)_2]$ are efficient catalysts for the water gas shift reaction (80JMC227, 94IC1719). Pyridine with $[Rh_2(\mu\text{-}Cl)_2(CO)_4]$ gives *cis*-$[Rh(CO)_2Cl(py)]$ (57CB2425). Further addition of pyridine gives not $[Rh_2(\mu\text{-}Cl)_2(CO)_4(py)_4]$ as stated in (57CB2425) and not $[Rh(CO)_2(py)_2]$ as stated in (65JCS1900) but $[Rh_2(\mu\text{-}CO)_3Cl_2(py)_4]$ (98JCS(D)1403). Progressive addition of pyridine to *trans*-$[Rh_2(\mu\text{-}Cl)_2(CO)_2(C_xH_y)_2]$ ($C_xH_y = C_2H_4$, C_8H_{14}) (75JOM(94)241) gives $[Rh_2(\mu\text{-}Cl)_2(CO)_2(C_xH_y)_2(py)_2]$ ($C_xH_y = C_2H_4$, C_8H_{14}). Other examples include $[Rh(CO)_3(py)]^+$ (93JOM(460)C34) and *cis*-$[Ir(CO)_2Cl(py)]$ (93IC3287). $[(\eta^4\text{-cod})Rh(py)_2](ClO_4)$, $[(\eta^4\text{-cod})Rh(PPh_3)(py)](PF_6)$, $[(\eta^4\text{-cod})Rh(PPh_3)(4\text{-Mepy})](PF_6)$ are illustrative of η^1(N)-coordinated species (72JOM(35)389, 76JOM(105)365, 99EJIC27). $[(\eta^5\text{-Cp*})Rh(AN)_3]^{2+}$ forms the η^1(N)-complexes with 2-methylpyridine, quinoline, 2-methylquinoline, 5,6- and 7,8-benzoquinolines as well as acridine (L) of composition $[(\eta^5\text{-Cp*})RhL(AN)_2]^{2+}$ (82JA5234, 84JOC4500, 85OM1743, 88OM2250, 91OM54, 91OM1965, 92JA5187). Pyridine and 4-*tert*-butylpyridine (L) with $[Rh_2(C_8H_{14})_4(\mu\text{-}Cl)_2]$ in CH_2Cl_2, $CHCl_3$, and $PhCH_2Cl$ give the products of oxidative addition $[RhL_3Cl_2(CH_2Cl)]$, $[RhL_3Cl_2(CHCl_2)]$, and $[RhL_3Cl_2(CH_2Ph)]$ (99JCS(D)1109).

The reaction of quinoline with $[(\eta^5\text{-Cp*})Rh(AN)_3]^{2+}$ gives the η^1(N)-coordinated complex **121** (88OM2250). If this reaction occurs in acetone or acetonitrile containing traces of water, the product is $[(\eta^5\text{-Cp*})Rh(quinoline)(\mu\text{-}OH)]_2(BF_4)_2$. The reaction of isoquinoline with $[(\eta^5\text{-Cp*})Rh(AN)_3]^{2+}$ or $[(\eta^5\text{-Cp*})Rh(p\text{-xylene})]^{2+}$ gives complex **122**. 2-Methyl quinoline gives a mixture of products **123** and **124**. In **124** coordination is fulfilled via the benzene ring.



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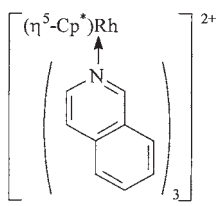

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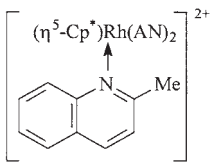

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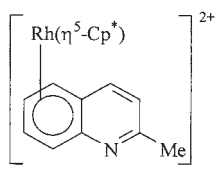


124

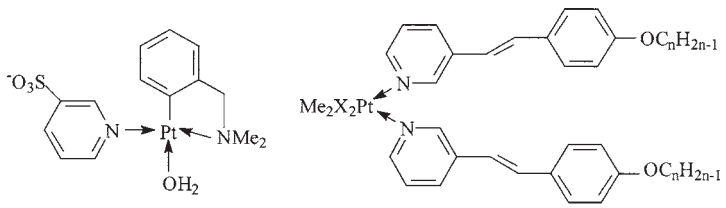
Species *cis*-[$Rh(CO)_2L_2$] (L = 4-Mepy, 2-Mepy, 2,6-Me_2py) (73JOM(63)423) catalyze the water gas shift reaction (89JMC247) and selective reduction of nitrobenzene to aniline (98CATL183, 00P487). The list of the η^1(N)-coordinated rhodium species also includes [$Rh(CO)(py)_3$](PF_6), [$Rh_5(CO)_{13}(py)_2$]$^-$ (93JOM(460)C34, 94IC1719), and [$Rh_6(CO)_{15}$(4-Vinpy) (93RCB937, 01JCS(D)2015). Complexes *cis*-[$M(CO)_2Cl$(4-X-py)] (M = Rh, Ir; X = NMe_2, *t*-Bu, H, CN, *trans*-CH=CHC_6H_4–4-NMe_2) as well as [(η^4-cod)RhCl(4-X-py)] and *cis*-[(η^2-COE)$_2$IrCl(4-X-py)] (X = *trans*- or *trans*, *trans*-$(CH{=}CH)_nC_6H_4$–4-NMe_2; $n = 1$, 2) are prepared from the corresponding pyridine and appropriate organometallic dimeric species of rhodium or iridium (00OM1775). The reaction of pyridine with [$Rh(C_6Cl_5)_3$] gives [$Rh(C_6Cl_5)_3$(py)] (00ICA(308)51). Reaction of [(η^5-Cp)(Me)Rh(μ-CH_2)]$_2$ containing rhodium–rhodium bond with pyridine and 2-methyl pyridine (L) in the presence of HPF_6 leads to the product of substitution of one of the methyl groups, [(η^5-Cp)(Me)Rh(μ-CH_2)$_2$Rh(L)(η^5-Cp)]$_2$ (83JCS(CC)971).

Pyridine, 2-methyl-, 3-methyl-, 4-ethyl-, 4-*n*-propyl-, 4-benzyl-, and 2-methoxypyridines (L) with [{(η^5-Cp*)Rh}$_2$(μ-OH)$_3$](ClO_4) in the presence of perchloric acid form the η^1(N)-coordinated complexes [{(η^5-Cp*)RhL}$_2$(μ-OH)$_2$](ClO_4)$_2$ (86JOM(316)221). The iridium complex [{(η^5-Cp*)Ir}$_2$(μ-OH)$_3$](BF_4) with pyridine and HBF_4 forms [{(η^5-Cp*)Ir(py)}$_2$(μ-OH)$_2$](BF_4)$_2$. Variously substituted pyridines (L) react with [(η^4-diolefin)$_2$Rh](ClO_4) yield a series of complexes η^1(N)-coordinated via the heteroatom, [(η^4-diolefin)RhL_2](ClO_4) (diolefin = tfb, L = 4-NH_2py, 2-NH_2py, 4-CNpy, 2-CNpy; diolefin = cod, L = 4-NH_2py, 2-NH_2py, 4-NMe_2py, 4-CNpy, 2-CNpy; diolefin = nbd, L = 4-NH_2py, 2-NH_2py, 4-CNpy) (81JOM(220)103). 4-Amino- and 4-cyanopyridine (L) also react with [$RhCl(CO)(PPh_3)$($Me_2CO)_x$](ClO_4) and produce [$Rh(CO)L_2(PPh_3)$](ClO_4). Interaction of [(η^4-cod)Rh(4-CNpy)](ClO_4) with [(η^4-cod)$_2$Rh](ClO_4) gives a dinuclear product [(η^4-cod)$_2$Rh(4-CNpy)$_2$](ClO_4)$_2$. A series of ligands (L) with the dimer [(η^4-diolefin)Rh]$_2$ gives the neutral species [(η^4-diolefin)Rh(L)] (diolefin = tfb, L = 4-NH_2py, 2-NH_2py; diolefin = cod, L = 4-NH_2py, 4-NMe_2py). 4-Aminopyridine with [$RhCl(CO)_2]_2$ yields [$RhCl(CO)_2$(4-NH_2py)].

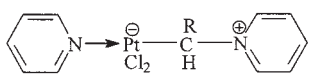
G. Complexes of Pyridines with Nickel Group Derivatives

The η^1(N)-coordinated cases in the organoplatinum chemistry include [$PtMe_2X_2$(py)$_2$] (X = Br, I) (74JOM(72)305). Pyridine ligands (L) with *trans*-[$Pt(DMSO)_2Cl(Me)$] give the substitution products [Pt(DMSO)(L)Cl(Me)]

(L = py, 2-Mepy, 3-Mepy, 4-Mepy, 2,4-Me_2py, 2,6-Me_2py, 3,5-Me_2py, 2-Phpy, 4-NMe_2py, 2-Clpy, 4-Clpy, 4-CNpy, 2-Acpy, quinoline, 2-methylquinoline, 5-aminoquinoline) (96IC7691, 02ICA(330)189). $[Pt(DMSO)(py)_2Me]^+$ supplements this list (96IC5087). Pyridine with the η^3-but-3-enyl complexes $[Pd(X)\{CH(COOMe)CR^1{=}CHR^2)\}]$ (X = Cl, hfacac; R^1 = Cl, H; R^2 = H, OMe, OEt, OPr^i) give the thermally stable η^1(N)-coordinated adducts $[Pd(X)(py)_2\{CH(COOMe)CR^1{=}CHR^2)\}]$ (76JCS(D)1890). *Para*-substituted styryl(pyridyl)platinum(II) species $[(p\text{-}R\text{–}C_6H_4CH{=}CH_2)PtCl_2(NC_5H_4X)]$ (R = NMe_2, X = 4-Me; R = H, X = 4-Me; R = NO_2, X = 4-Cl, 4-Me) contain the η^1(N)-coordinated pyridine ligand (73JCS(CC)449, 76JCS(D)1865). *Trans*-[Pt(Me)(XC_5H_4N)(dppe)] (X = 4-NMe_2, 4-Me, H, 4-COOMe, 4-COMe, 4-CN) contain the η^1(N)-monodentately coordinated pyridine ligands (79CJC958). Among the η^1(C)-coordinated complexes are the 4-pyridyl cationic species $[(Ph_2PCH_2CH_2PPh_2)Pt(\eta^1\text{-4-py})(CNC_6H_{11})]^+$ and 2-pyridyl derivatives $[Pd(CNR)(2\text{-py})(dppe)]^+$ (R = Me, Ph) (94JCS(D)407, 97JOM(535)29). Another illustration of the η^1(N)-coordinated complexes is **125** (96JCS(D)1471, 96JCS(D)1472, 97MI2). Various 4-alkoxy-4′-stibazole ligands with $[PtMe_2X_2]$ (X = I, Br) give the η^1(N)-coordinated complexes **126** (*n* = 3–10, 12, X = I; *n* = 10, X = Br), some of which reveal liquid-crystalline properties (02JOM(645)206). Interaction of $[(\eta^2\text{-}C_2H_4)PtCl_2(py)]$ with diazo compounds and pyridine gives the pyridine ylide species **127** (66JCS(CC)396, 87OM28). Complexes $[PhPtIL_2]$ (L = PPh_3, $PMePh_2$, PEt_3) react first with silver triflate and then the carboxylic derivatives of pyridine containing 2-, 3-, and 4-COOH substituents (py) to yield a range of the η^1(N) species $[PhPt(py)L_2](OTf)$ (03IC1057).



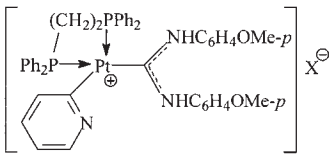
125 **126**



127

The 2-pyridyl complex $[PtCl(C_5H_4N\text{-}2)(dppe)]$ (89JOM(361)155, 90ICA(176)5, 92JCR(S)296, 92JOM(438)253) and 4-methoxyphenyl isocyanide gives **128** (X = Cl), which can be converted to **128** ($X = ClO_4$) using

sodium perchlorate (94JCS(D)407). The chloride complex reacts with zinc chloride in the presence of triethylamine to give the heterodinuclear species **129**. The same starting complex with 4-methoxyphenyl isocyanide and then ethanol gives **130**. Further interaction with $ZnCl_2/NEt_3$ gives **131**.



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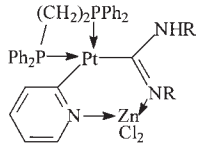

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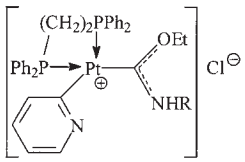

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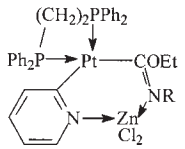
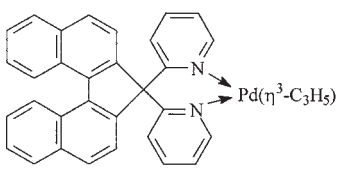


131

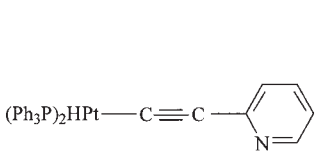
7,8-Benzo[*h*]quinoline and 8-methylquinoline (L) react with $(N^nBu_4)_2[Pt_2(\mu\text{-}C_6F_5)_2(C_6F_5)_4]$ to cleave the bridge and form the η^1(N)-coordinated anionic species $(N^nBu_4)[Pt(C_6F_5)_3L]$ (96IC6009). Similar chemistry can be noted for 2-methyl-4-R-pyridine ligands (87OM517). Interaction of $(n\text{-}Bu_4N)[Pt_2(\mu\text{-}C_6F_5)_2(C_6F_5)_4]$ with diphenyl-2-pyridylmethane, 2-benzyl pyridine, and 2-hydroxymethylpyridine (L) give simple η^1(N)-coordinated products $(n\text{-}Bu_4N)[Pt(C_6F_5)_3L]$ (97JCS(D)1559). Similar products contain the platinum–nitrogen bonds (87IC503, 87IC508, 90IC1812, 96IC6009). 2,2′-Bis(pyridyl)-1,1′-binaphthalene with $[Pd(AN)_2(\eta^3\text{-}C_3H_5)](OTf)$ gives **132** with the η^1(N)-coordination mode (00JCS(D)1723).



132

2-Ethynylpyridine and *trans*-$[PtHCl(PPh_3)_2]$ in the presence of diethylamine and copper(I) iodide gives **133** (99OM1653). Reaction of the product with *cis*-$[Pt(C_6F_5)_2(THF)_2]$ gives **134**, where the coordination of the entering platinum site is via the nitrogen heteroatom and triple bond of the exocyclic substituent. On standing in solution, species **134** produces a mixture of

135 and **136**. The zwitter-ionic product **137** is also formed in the reaction of **134** with triphenylphosphine.



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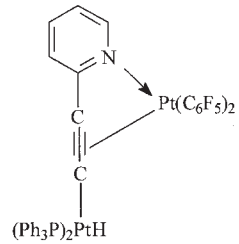

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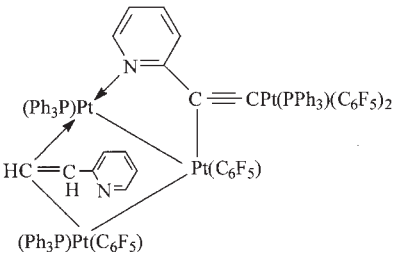

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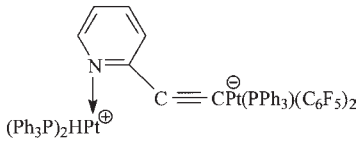

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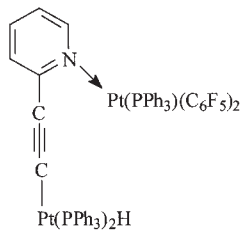
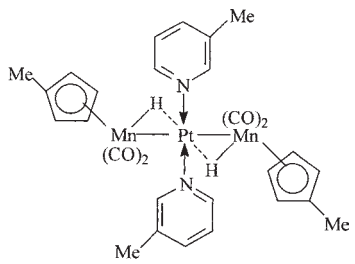


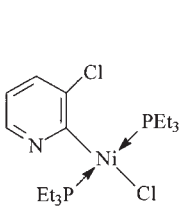
137

$[(3\text{-Mepy})_2PtCl_2]$ reacts with $Na[(\eta^5\text{-}C_5H_4Me)(CO)_2Mn(SiMe_3)]$ to give the heteronuclear hydrido-complex **138** (87JOM(320)C11).



138

2,3-Dichloropyridine with [Ni(η^4-cod)$_2$] in the presence of triethylphosphine gives the η^1(C)-coordinated species **139** (95P2637). With [Ni(η^2-C_2H_4)$_2$(dcpe)], the η^1(C)-product **140** follows. With [$NiCl_2(PPh_3)_2$], the chelate combining the η^1(N) and η^1(C)-modes, is the result, **141**, precedent known for the product of the reaction of 2-chloropyridine with [$Ni(PPh_3)_4$] (80BCSJ139, 87JOM(323)123) as well as some palladium (83JOM(255)385, 86JOM(303)283) and platinum (83JOM(255)385, 89JOM(361)155) analogues, including the structural report for [$PdBr(C_5H_4N$-2)$(PPh_3)_2]_2$ (80CL913, 81H1603) and [$PdX(2$-$C_5H_4N)L_2$] (X = Cl, Br; L = PEt_3, PMe_2Ph) (80JA2475, 83JOM(251)393). 3,4-Dibromopyridine with [$NiBr_2(PPh_3)_2$] gives a mixture of **142** and **143**, which on further interaction with dcpe give **144** and **145** (95P2637). Reduction of complex **140** with sodium amalgam gives the 2,3-pyridine complex **146**, which is, however, unstable. Formation of the 2-pyridyl nickel structures takes place during the low temperature adsorption of pyridine on Ni(100) (82JA2034).



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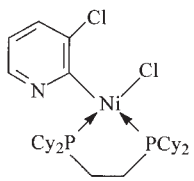

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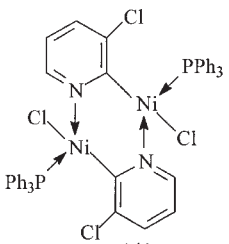

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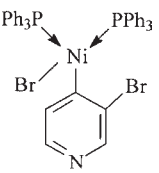

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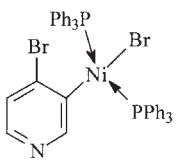

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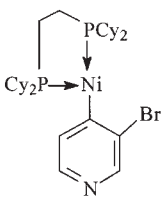

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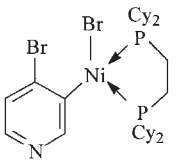

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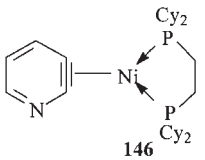
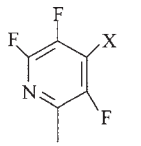


146

Reaction of [(η^4-cod)$_2$Ni] first with trimethylphosphine and then C_5F_4XN (X = H, F) gives the η^1(C)-coordinated 2-pyridyl products **147** (X = H, F) as predominant isomers (97OM4920). This process is thus an oxidative addition and involves C–F bond activation. 2,4,6-Trifluoro-3,5-dichloropyridine, in contrast, forms the 4-pyridyl species **148**, if similar conditions are applied, and the C–Cl bond is activated. Species **147** (X = F) reacts with trimethylsilyl triflate to yield *trans*-[Ni(OTf)(2-C_5F_4N)$(PEt_3)_2$] (99OM1710). Metathesis of the latter with NaOPh yields *trans*-[Ni(OPh)(2-C_5F_4N)$(PEt_3)_2$] along with the adduct *trans*-[Ni(OPh)(2-C_5F_4N)$(PEt_3)_2$]·HOPh.

trans-[NiF(2-C_5F_4N)(PEt_3)$_2$] with phenyl lithium and then methanol gives *trans*-[NiPh(2-C_5F_4N)(PEt_3)$_2$]. *trans*-[Ni(OTf)(2-C_5F_4N)(PEt_3)$_2$] with methyl lithium gives *trans*-[NiMe(2-C_5F_4N)(PEt_3)$_2$].



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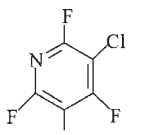
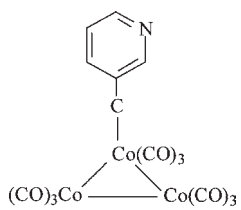


148

3- and 4-Bromopyridine oxidatively add to [Pd(PPh_3)$_4$] to give the η^1(C)-coordinated *trans*-[PdBr(C_5H_4N)(PPh_3)$_2$] containing 3- and 4-pyridyl moieties, respectively (80CL913, 80JA2475). The products easily enter metathesis with small anions (81H1603). 2-Bromopyridine forms the dinuclear species *trans*-[Pd_2Br_2(PPh_3)$_2$(μ-C_5H_4N)] with the η^2(N,C)-mode of the 2-pyridyl framework (81H1603), which could be converted to the mononuclear species (81ICA(54)L69). Similarly, 2-bromopyridine with [Pd_2(dppm)$_2$] gives the dinuclear complex [Pd_2(μ-C_5H_4N)(μ-dppm)$_2$]Br_2 (98JCS(D)3777), again with the η^2(N,C)-coordinated 2-pyridyl. However, with [Pd(dppp)$_2$], the product is different and can be formulated as [Pd_2(η^1-dppp)$_2$(μ-C_5H_4N)(μ-dppp)]Br_2. Apart from the bridging 2-pyridyl and diphenylphosphinopropane groups, there are two η^1(P)-coordinated dppp ligands. In turn, [Pd(dppb)$_2$] forms oligomeric *trans*-[{PdBr(C_5H_4N)(μ-dppb)}$_n$] with the η^1(C)-coordinated 2-pyridyl at room temperature but dinuclear *trans*-[Pd_2Br_2(μ-C_5H_4N)(μ-dppb)] on reflux. 2-Bromopyridine and [Pd(dppf)$_2$] give the mononuclear η^1(C) 2-pyridyl species *cis*-[PdBr(C_5H_4NH)(η^2-dppf)]Br, where the phosphine ligand is chelated. Protonation of 2-pyridyl is referred to some HBr present in the starting 2-bromopyridine. Finally, 2-chloroquinoline and [Pd(dppb)$_2$] give *trans*-[Pd_2Cl_2(μ-C_9H_6N)$_2$ (μ-dppb)], where the 2-quinolyl moiety is η^2(C,N)-coordinated.

3-Chloromethylpyridine with [$Co_2(CO)_8$] gives the product **149** (98JOM(570)113), which with *trans*-[$PdCl_2$($NCPh_2$)] gives [$PdCl_2${NC_5H_4-3-$CCo_3(CO)_9$}$_2$].

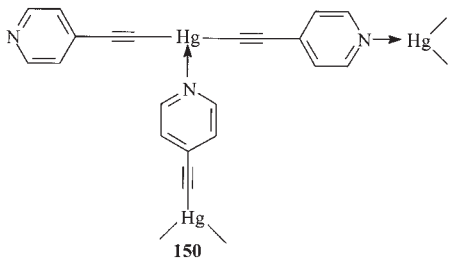


149

H. Complexes of Pyridines with Late Transition and Rare Earth Metal Derivatives

Organometallic compounds $[(\eta^5\text{-Cp})Fe(CO)_2(CH_2Hpy)]^+$, $[(OC)_3Mn(CH_2Hpy)]^+$, $[Cr(OH_2)_5(CH_2Hpy)]^{3+}$ $[Co(CN)_5(CH_2Hpy)]^{2-}$ on reaction with mercury(II) salts give $[Hg(CH_2Hpy)]^+$ and thallium(III) salts gives $[Tl(CH_2R)]^{2+}$ with mercury–carbon and thallium–carbon bonds, respectively, where Hpy stands for a 3- or 4-substituted pyridinium cation (67JCS(B)633, 68JCS(A)2297, 69JCS(B)107, 70JCS(A)523, 71JCS(A)910, 71JCS(B)662, 71JCS(B)1841, 76JCS(D)2456).

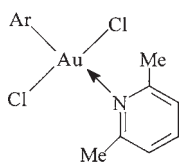
4-Ethynylpyridine with mercuric acetate forms a polymeric species, **150**, whose unit, illustrates the coordination situation around the mercury site (96JOM(515)259). Similar situation is observed in (pyrid-2-yl)phenyl mercuric chloride (89JCS(CC)570).



150

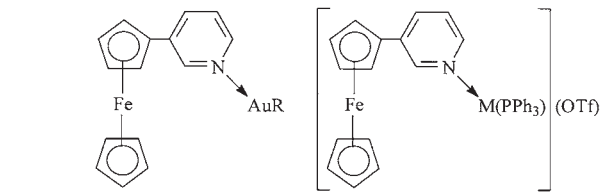
Reaction of $[(\eta^5\text{-Cp*})NdI_2(THF)_3]$ with excess pyridine gives $[(\eta^5\text{-Cp*})NdI_2(py)_3]$ (99P1389). The product with $KC_5H_4SiMe_3$ yields $[(\eta^5\text{-Cp*})(\eta^5\text{-}C_5H_4SiMe_3)NdI(py)]$. Other illustrations of the η^1(N)-coordinated species in the rare earth metal chemistry are $[(\eta^5\text{-}C_5H_4SiMe_3)_2NdI(py)_2]$ (97AX(C)850) and $[(\eta^5\text{-Cp})_3Nd(py)]$ (87AJC907).

Cases of the η^1(N)-coordination of gold include $[(Ar)AuCl_2(py)]$ (72JCS(CC)26, 76JOM(105)399). Complexes $[ArClAu(\mu\text{-Cl})_2AuClAr]$ with 2,6-dimethylpyridine give **151** (Ar = Ph, 4-tolyl, 3,4-xylyl, 2,4-xylyl, 2,5-xylyl, mesityl, 4-cumenyl, 4-methoxyphenyl, 4-chlorophenyl) (01JCS(D)2330). One more example is *trans*-$[AuCl_2(C_3H_2N_2Ph)(3,5\text{-}Me_2C_5H_3N)]$ (98JOM(568)225).

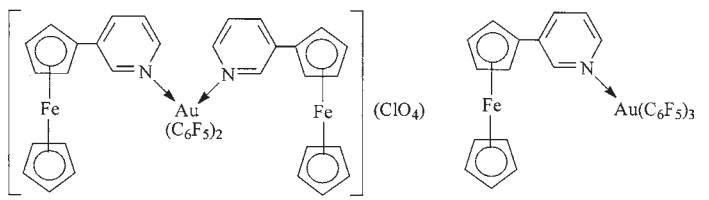


151

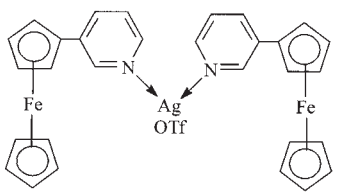
3- and 4-Ferrocenylpyridines are relatively new ligands (89IC2347, 92IC765). 3-Ferrocenylpyridine with [AuCl(THT)] or [Au(C_6F_5)(THT)] gives the η^1(N)-coordinated species **152** (R = Cl, C_6F_5) (99JOM(592)258). [Au(OTf)(PPh_3)] or [Ag(OTf)(PPh_3)] give the cationic species **153** (M = Au, Ag). The gold(III) species emerge from 3-ferrocenylpyridine and [Au(C_6F_5)$_2$(OEt_2)$_2$](ClO_4) giving **154** or [Au(C_6F_5)$_3$(OEt_2)] when the product is **155**. Finally, 3-ferrocenylpyridine reacts with silver triflate to yield **156**. The ferrocenyl-based ligand (η^5-Cp)Fe(η^5-C_5H_3(–C≡C–C_5H_4N)$_2$ with [Cu(OTf)$_2$] also gives the η^1(N) complex of composition CuL_2 (03JOM (671)43).



152 **153**



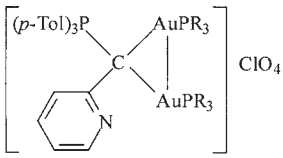
154 **155**



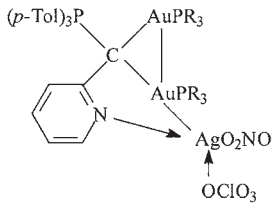
156

Reaction of [Au(acac)(PR_3)] (R = Ph, Cy, Me) with [(*p*-Tol)$_3$$PCH_2$(2-$C_5H_4$N)]$ClO_4$ gives **157** (R = Me, Cy, Ph) (93IC3748, 97IC4938). Further interaction of the products with silver nitrate and [Au(PR_3)(acetone)]$^+$ gives the trinuclear species **158** and **159**, respectively, where R = Me, Cy, Ph. Pyridine with [(η^1-Cp)$_2$Cd] gives [(η^1-Cp)$_2$Cd{η^1(N)-py)$_2$}] (87JOM(322) C37). 4-Ethynylpyridine and similar ligand with –C≡C–C_6H_4–C≡CH in the 4 position react with [Ph_4P][Au(acac)$_2$] to yield complexes of the type **160**

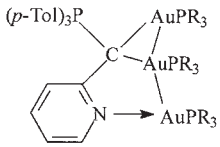
[03JOM(678)82]. Further interaction of the products with methyl iodide gives products of the type **161**.



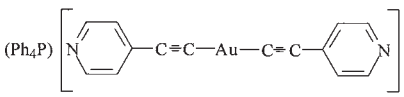
157



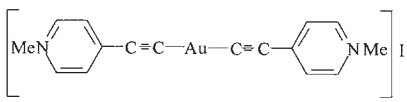
158



159



160



161

II. Conclusions

1. In complexes of pyridine derivatives with non-transition and early transition elements along with the η^1(N) and $\eta^6(\pi)$ modes, η^1(C) and mixed coordination modes, e.g., $\eta^1(N):\eta^5(\pi):\eta^5(\pi)$, are observed.
2. Chemical and photochemical properties of the η^1(N)-coordinated and variously substituted Group VI and VII carbonyl derivatives as well as their analogues have been extensively studied. Some pyridinium salt and pyridinium ylide C-coordinated complexes occur. Quinoline and quinaldine form the $\eta^6(\pi)$ coordinated complexes via the carbocyclic ring, the unsubstituted derivative being hydrogenated via the pyridine ring. Pyrylium and thiopyrylium complexes present a variety of modes but are scarce. A series of acetylenic 1,4-dipyridyl ligands form cyclic complexes with attractive photophysical properties.
3. The $\eta^6(\pi)$ coordinated complexes via the heteroring attracted special attention in the organometallic chemistry of the chromium group. The optimal way for their synthesis is to start with the pyridine ligands containing bulky alkyl or silyl substituents in the *ortho* positions of the heteroring. To remove these substituents on further transformations often appears possible, but also it is interesting to derivatize the ring substituents, obtain corresponding species with the partially saturated heteroring, and insert substituents at the heteroatom or quaternize it.

Many developments in this field are achieved using metal vapor synthetic approach.

4. Organoiron pyridine complexes contain the ligand coordinated in η^1(N) and $\eta^6(\pi)$ fashion. Besides in the complexes containing the fused cyclopentadienyl or phenyl ring, the coordination is fulfilled via the latter and these complexes possess valuable catalytic properties. Ruthenium and osmium compounds present a variety of the η^1(N)-coordinated structures, although in osmium chemistry, the η^2(C,C) coordination is also possible.
5. Organometallic chemistry in the cobalt group is almost entirely a list of various η^1(N) coordinated species. In contrast, the organonickel group offers more frequent cases of the η^1(C) complexes containing 2-, 3-, and 4-pyridyl species, sometimes in isomeric mixtures.

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Subject Index

Preface

Volume 86 of Advances in Heterocyclic Chemistry consists of five chapters.

The oxidative amino-dehydrogenation of azines is treated by Henk van der Plas (Wageningen University, the Netherlands) who has played a major role in exploiting this interesting field emphasizing developments that occurred since the review of related work by McGill and Rappa in Advances in Heterocyclic Chemistry, Volume 44, which appeared in 1988.

Recent advances in the conformational analysis of heterocyclic six-membered rings are covered by Erich Kleinpeter (Potsdam University, Germany). The present chapter covers the relevant literature from 1995 to 2002 and gives references to earlier reviews, which treat the earlier literature.

The first part of a projected short series of the synthesis of fluorine-containing heterocycles has been written by Georgii Furin (Novosibirsk Institute of Organic Chemistry, Russian Academy of Sciences). This emphasizes the important effects on chemical–biological and physical properties of the substitution of hydrogen by fluorine, which is of significance for the whole range of organic chemistry.

Applications to the synthesis of heterocyclic compounds of hypervalent organoiodine reagents are covered by Gerald Koser (University of Akron, Ohio) who is well known for his own book in the field. The present review provides continuity with the earlier comprehensive treatment of the subject by Moriarty and Prakmash in Volume 69 of Advances in Heterocyclic Chemistry, which covered the field up through 1996.

Finally, Alexander Sadimenko (University of Fort Hare, South Africa) has provided another fine contribution in his comprehensive coverage of organometallic complexes of heterocycles; this one deals with pyridines and benzpyridines.

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