5.01
Pyridines and their Benzo Derivatives: Structure

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5.01.1 INTRODUCTION: PERSPECTIVES

In the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨84CHEC-I(2)99⟩, the standard theoretical and experimental methods for evaluation of the structure of pyridine and its derivatives were stressed, which represented the main thrust of the fundamental work in this area during the years surveyed. It was seen that such methodologies as molecular orbital calculations, spectroscopic and diffraction techniques, and so on, yielded fundamental theoretical and experimental information on the basic structural characteristics of these systems.

This updated article will attempt to focus, to a large extent, on these bread-and-butter matters. Investigations of tautomerism, conformation, aromaticity and like phenomena, in the gas phase, or in association with simple organic solvents, continue legitimately to occupy the pyridine and piperidine structural litany. There are still all too many important problems in these areas to be solved, as will be shown.

Since 1984, however, much more attention has been concentrated on the nature of solvation, particularly in the presence of water or aqueous solvents, and of occlusion effects, and on the way in which the pyridine and related structures interact with the surrounding media and the way in which these structures are thereby influenced. Most experimental measurements on the ostensibly static pyridine structure reflect the nature of such structural variations, and these can therefore afford great insight into the electronic character of the pyridine structures, and the structural modifications induced by the media in which the measurements are taken. Often such modifications reflect the biochemical importance of such structures, which may thus be considered to fall into the biomimetic category, and plainly this gives enormously increased relevance to such investigations.

To give an example, accounts of investigations of tautomerism in these systems are almost invariably prefaced and impregnated with references to their biological importance, as for example in mutagenesis. Many such systems are also of pharmaceutical potential, or bear similarities to compounds that are. Thus, in general, the manner in which a structure may be constrained from its normal conformation by interaction with an enzyme surface becomes highly relevant.

These considerations are paralleled by the study of the incorporation of the pyridine structure as a vital unit in the design of large-scale molecules. Such studies are of intense interest in 1995. In some cases, the pyridine nucleus acts merely as an essentially inert "spacer", but more usually the active character of the ring, sponsored particularly by the nitrogen atom, makes incorporation of the pyridine ring in such constructs of greater significance.

This significance is fuelled by the fact that such structures—supramolecules—represent valuable additions either to materials science, with their importance to applied chemistry, or to the gamut of biomimetic structures, with importance in research on the organic–biological interface. These multidisciplinary global approaches give broad insight into the most important vistas of chemistry, and thus represent the most profitable way forward. The author therefore has strived to reflect and describe the importance of these matters within this section.

5.01.2 MOLECULAR CHARACTERISTICS

5.01.2.1 Theoretical Methods: Molecular Orbital Calculations

The concept of aromaticity is dominant in pyridine structural considerations. This concept is probably the most contentious in the theoretical roster, and thus it poses a very real challenge to quantitative conceptualization ⟨91H(32)127⟩. Resonance or stabilization energy arising from the delocalization of the π-electrons within the cyclic delocalized system requires calculation by molecular orbital (MO) methods, using parametrizations which may be controversial. In turn, such calculations may be supported or authenticated by a variety of different experimental criteria considered to reflect aromaticity that display considerable errors. Moreover, the concept itself is a nebulous one: estimates of aromaticity may vary according to the criteria selected to delineate it, particularly if trying to put a quantitative estimate on it ⟨89JA7⟩.

The particular question of the relative difference between the aromaticity of benzene on the one hand and that of pyridine on the other has received much discussion ⟨93AHC(56)303⟩. It might be contended that pyridine should be less aromatic than benzene because the nitrogen atom in a heteroaromatic six-membered ring attracts electrons from the π-system, but generally calculations reveal that the aromaticities of the two rings are more or less similar, depending on the criterion of aromaticity considered and the mode of calculation employed.

In the latest of such calculations (for a resumé of previous methods, see the previous edition ⟨84CHEC-I(2)99⟩), electron–electron repulsion is treated as the repulsion between a single electron and the approximated electronic distribution of all other electrons; this is the self-consistent field (SCF) method. Applications of the Hartree–Fock equations to the Schrödinger equation without the use of arbitrary parameters are known as *ab initio* calculations. The basis set of molecular MO functions is formed by a linear combination of one-electron functions describing the atomic orbitals (AOs) of each constituent atom. Basis sets developed by Hehre et al. ⟨B-86MI 501-01⟩ have been implemented in the Gaussian 82–90 programs, and these, as we shall indicate as appropriate, are widely used.

As well as different levels of MO approximation, the calculations can be directed at different modes of structural analyses. Thus, isodesmic bond separation involves the processes of Equations (1) and (2), which yield experimental ΔH° (298 K) values of 64.1 (267.9), and 65.5 (273.8) kcal mol^{-1} (kJ mol^{-1}) for benzene and for pyridine, respectively. These values can be matched rather precisely by calculations using the Gaussian 82 *ab initio* program and the 6-31G* (5D) basis set, to give 58.2 (243.3) and 60.7 (253.7) kcal mol^{-1} (kJ mol^{-1}), respectively ⟨85TL5667⟩: however, the assumption of equal numbers of formal single and double bonds between carbon atoms and nitrogen atoms in reactants and products can be criticized, as the authors point out.

$$+ \; 6\,CH_4 \quad = \quad 3\,C_2H_6 \; + \; 3\,H_2C{=}CH_2 \qquad (1)$$

$$+ \ 5\,CH_4 + NH_3 = 2\,C_6H_6 + MeNH_2 + 2\,H_2C{=}CH_2 + 2\,H_2C{=}NH \quad (2)$$

Nevertheless, although absolute magnitudes are changed when using the homodesmotic group separations of Equations (3) and (4), supposedly more accurate, the calculated values of 24.8 (103.7) and 25.8 (107.8) kcal mol^{-1} (kJ mol^{-1}) for benzene and pyridine, respectively, and the experimental value of 21.6 (90.3) kcal mol^{-1} (kJ mol^{-1}) for benzene, do not alter the picture of the relative stabilities. This is also confirmed by the superhomodesmotic reaction scheme, which directly measures the effect of cyclizing an already delocalized structure, and gives values of 25.99 (108.64) and 25.78 (107.76) kcal mol^{-1} (kJ mol^{-1}) for benzene and pyridine, respectively ⟨88JA4204⟩.

$$+ \ 3\,H_2C{=}CH_2 = 3\ \textit{trans}\text{-}\,H_2C{=}CH{-}CH{=}CH_2 \quad (3)$$

$$+ \ 3\,H_2C{=}CH_2 = 2\ \textit{trans}\text{-}\,H_2C{=}CH{-}CH{=}CH_2 + \textit{trans}\text{-}\,H_2C{=}CH{-}N{=}CH_2 \quad (4)$$

Resonance energy calculations afford a similar story and, indeed, reveal that the aromaticities of quinoline and isoquinoline are also on a par with the original pair of benzene and pyridine (Table 1) ⟨93AHC(56)303⟩.

Table 1 Resonance energies.

Compound	*DRE* (eV)[a]	*HSRE(β)*[b]	*TRE(β)*[c]
Benzene	0.145	0.065	0.046
Pyridine	0.167	0.058	0.038
Quinoline	0.148	0.052	0.036
Isoquinoline	0.148	0.051	0.033

[a]Dewar resonance energy (electron volts). [b]Hess and Schaad resonance energy. [c]Topological resonance energy.

Bond orders may well also form the basis of a criterion of aromaticity ⟨81JOM(215)315, 85KGS867⟩. The latest and probably most effective is the parameter I_6 (Equation (5)). This equation is based on a statistical treatment of the deviations in skeleton bond orders from standard values arising from bond length measurements ⟨85T1409⟩. Values of interest here for I_6 are benzene, 100; pyridine, 85.7; pyridinium methiodide, 66.7; pyridine *N*-oxide, 74.4; pyridinium dicyanomethylide, 70.1; and pyridinium *N*-nitroimine, 76.0 ⟨86T89⟩. The values indicate that, even within these electron-deficient nuclei, the aromaticity remains high, although decreasing with increasing electron-withdrawing power of the substituent attached to the positive nitrogen atom of the ring.

$$I_6 = 100\,(1 - V/V_k)\ (\%) \quad (5)$$

where

$$V = \frac{100}{N_o}\sqrt{\frac{\Sigma(N-N_o)^2}{n}}$$

and

$V_k = 33.3$ for pyridine and derivatives,
N = bond order,
n = number of bonds in the ring,
$N_o = \Sigma_n N/_n$.

A critical analysis using principal component analysis ⟨89JA7⟩ discerns that Bird's I_6 and the DRE are the best measures of "classical" aromaticity in heterocycles in general, while magnetic aromaticity, discussed in Section 5.01.2.2, provides a second criterion which is orthogonal to the first.

Dimensions for benzene and pyridine calculated from an SCF standpoint with a 3–21 basis set are given in Figure 1 ⟨88JA4204⟩. The geometries of 4-methylpyridine and *N*-protonated pyridine

(the dimensions of these structures are also given in Figure 1) have been computed as well, in the former case at the Hartree–Fock level using a 4–21 basis set of Gaussian orbitals ⟨83JA7037, 86T1265⟩, and in the latter case using a 4–31 set ⟨89CPL(158)193⟩, enabling the calculation of the details of the IR vibrational bands for both molecules. This method depends on the transferability of scale factors between related molecules. Thus the harmonic force field of pyridine can be calculated by *ab initio* methods, and standardized with the benzene scale factors ⟨84JA2765⟩.

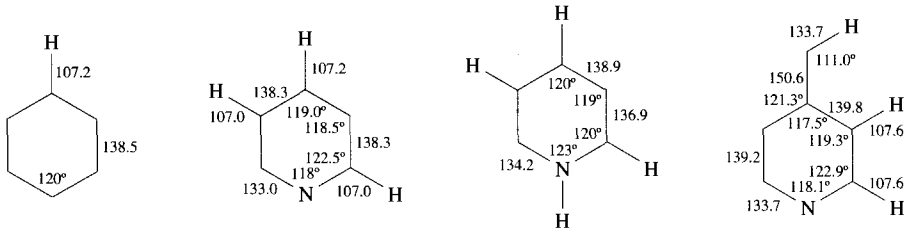


Figure 1 Dimensions (pm) of benzene, pyridine, and the pyridinium ion from SCF/3-21G* calculations.

Vibrational spectra may also be calculated using molecular mechanics, although not with such accuracy as in the above case. Allinger and coworkers have used his MM3 force field program for such a calculation for pyridine and related compounds ⟨93JA11906⟩, and have also shown that structures and heats of formation (and dipole moments) may be estimated with much greater accuracy. Testimony of this is provided in Table 2, which well illustrates the excellent agreement, with the exception of the benzoquinolines, for which in consequence it is suggested that it may be the experimental values that are faulty. Resonance energies may also be estimated, as follows in kcal mol^{-1} (kJ mol^{-1}): benzene, 17.79 (74.36); pyridine, 17.02 (71.14); naphthalene, 26.30 (109.90); quinoline, 25.53 (106.71); isoquinoline, 25.68 (107.34); acridine, 30.09 (125.78); 3,4-benzoquinoline, 37.57 (157.04); 5,6-benzoquinoline, 37.06 (154.91); 7,8-benzoquinoline, 37.06 (154.91). Each value should be divided by the number of aromatic rings in the compound to provide direct comparison with previous discussion, e.g. Table 1.

Table 2 Heats of formation[a] for pyridine and analogues.

Compound	*Heat of Formation* (kcal mol^{-1})	
	Calculated	*Experimental*[a]
Pyridine	33.60	33.55
2-Me	23.91	23.71
3-Me	25.47	25.43
4-Me	24.77	24.88
2,3-DiMe	16.13	16.32
2,4-DiMe	15.07	15.27
2,5-DiMe	15.77	15.89
2,6-DiMe	14.20	14.03
3,4-DiMe	17.06	16.75
3,5-DiMe	17.34	17.40
Quinoline	49.24	51.8
Isoquinoline	49.94	48.2
Acridine	68.96	69.90
3,4-Benzoquinoline	64.04	58.20
5,6-Benzoquinoline	64.04	55.90
7,8-Benzoquinoline	63.93	55.19

[a]⟨81MI 501-01, B-86MI 501-02⟩.

In a very interesting study ⟨88JA6337⟩, MNDO calculations have been carried out on 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP (**1**) and 1-methyl-4-phenylpyridinium ion, MPP^+ (**2**), together with the intermediate structures lying between the two as potential metabolites in their interconversion. This scheme is important in view of the formation of MPTP (**1**) as a by-product in the illicit production of "reversed meperidine" (**3**), which leads to the the proposed sequence of neurotoxins involved in an irreversible Parkinsonian syndrome in humans. In particular, the greater calculated stability of the dihydropyridine derivative $MPDP^+$-2,3 (**4**) by 4.7 kcal mol^{-1} (19.6 kJ mol^{-1}) over the corresponding 2,5-dihydrocompound (**5**) rationalizes the occurrence of the former

but not the latter in tissue preparations, and indicates the biological relevance of the route shown in Figure 2.

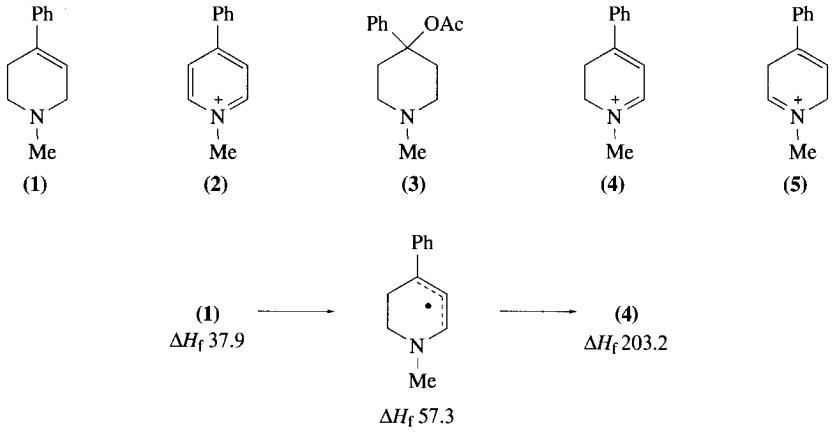


Figure 2 Heats of formation (kcal mol^{-1}; 1 kcal $mol^{-1} = 4.186$ kJ mol^{-1}).

A theoretical study has been made of the charge distribution in pyridine and the aminopyridines using *ab initio* calculations involving an STO-3G minimal basis set of orbitals ⟨83JCS(P2)1735⟩. The calculations give the ring nitrogen atom as the basic site for these compounds, foreshadowing the work of Scorrano given in the tautomerism section (5.01.2.3.3) ⟨93JCS(P2)283⟩. They also reveal that observed chemical shifts in the ^{15}N NMR patterns correlate with the calculated nitrogen charge densities, paralleling the correspondence between ^{13}C chemical shifts and charge distribution for carbon atoms of similar hybridization and substitution pattern, a conclusion which has been echoed in subsequent work on 4-substituted pyridines ⟨85CJC3226⟩. Comean *et al.* note that as for the charge density on aromatic and ethylenic carbon, and carbonyl and dialkyl ether oxygen atoms, the gain in π-electron density gives an upfield shift prevailing over the σ-electron loss, which on its own produces downfield shifts. These points are illustrated in Table 3 for these substituted pyridines, and similar effects have been found to be at work on the ^{15}N NMR chemical shifts investigated for pyridine and the aminopyridines ⟨92JA8634⟩. Here the charge densities and the charge densities induced by deprotonation to yield the corresponding nitranions (including for the aminopyridine anions the *syn* and *anti* forms) have been calculated at the RHF/6-31G+ level using the Gaussian 88 package. Resulting calculated geometries invariably indicated planarity, enabling σ/π charge separability.

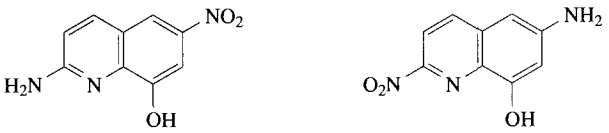
Table 3 Calculated nitrogen charges q and ^{15}N NMR resonance shifts for 4-substituted pyridines.

4-Substituent	q_σ[a]	q_π[a]	q_{tot}[a]	Δ[b]
OH[c]	−175.5	−95.3	−270.8	−138
NH_2	−176.2	−96.6	−272.8	−42
OMe	−189.0	−69.9	−258.9	−27
Me	−190.6	−69.7	−260.3	−11
H	−195.5	−59.6	−255.1	0
COMe	−199.0	−51.2	−250.2	25
CHO	−199.4	−49.3	−248.7	29
CN	−200.5	−39.7	−240.2	9
NO_2	−204.4	−28.8	−233.1	28

[a]Mulliken net average charge analysis caried out by means of STO-3G SCF calculations, using the Gaussian 76 program set. [b]Parts per million (ppm) from pyridine, neat for 4-COMe, 4-CHO and pyridine; all others in acetone. [c]In pyridone form.

Coupled perturbed Hartree–Fock *ab initio* calculations using the Gaussian 80 program on variously substituted 8-hydroxyquinolines have enabled the prediction of the dipole moments (μ) and first- (α) and second-order (β_{vec}) polarizabilities for these molecules ⟨92JA6475⟩. Figure 3 shows the calculated values for two such molecules with opposite charge transfer routes in the excited states. For 2-amino-8-hydroxy-6-nitroquinoline the acceptor character of the pyridine ring and the donor character of the benzene ring are opposed by the positioning of the electron-donating group (EDG)

and the electron-withdrawing group (EWG), whereas for 6-amino-8-hydroxy-2-nitroquinoline both tendencies reinforce one another. These influences hold potential for the design of such molecules for nonlinear optical applications (see Section 5.01.3).



μ	6.63 D (2.21 x 10^{-29} C m)	11.28 D (3.76 x 10^{-29} C m)
α	17.550 x 10^{6} pm^3	17.517 x 10^{6} pm^3
β_{vec}	5.4702 x 10^{-50} $C^3m^3J^{-2}$	5.2839 x 10^{-50} $C^3m^3J^{-2}$

Figure 3 Parameters μ, α, and β_{vec} for substituted 8-hydroxquinolines.

Perturbational molecular orbital theory (PMO) is sufficiently powerful to explain the influence of the nitrogen atom in the pyridine, quinoline, and isoquinoline rings, interpreted as a perturbation in the benzene and naphthalene hydrocarbon systems, on their magnetic circular dichroism (MCD) spectra ⟨84T3845⟩. The Pariser–Parr–Pople (PPP) approximation may be used to predict that the MCD sign will gradually change as the π-donor power of 4-substituents in the pyridinium ring is increased, and this is shown in the spectra of Figure 4. PPP calculations, with configuration interaction, may also be used to predict the absorption maxima of the UV/visible spectra of *N*-arylpyridinium hemicyanine dyes (**6**), where there is an extensive range of substituents of all types. In these compounds, the *N*-phenyl ring is already twisted to the extent of 35–55° from the plane of the substituted phenyl ring, so the introduction of a nitro substituent into the 2-position does not significantly alter the UV spectrum.

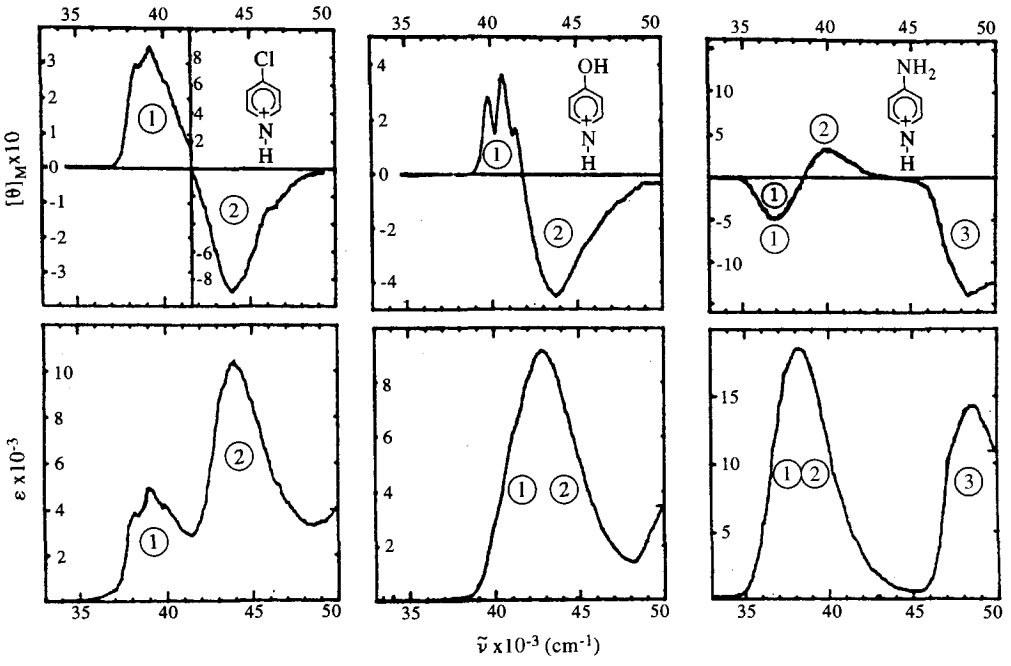
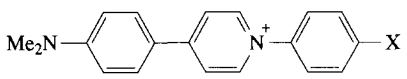


Figure 4 MCD (top) and UV (bottom) absorption curves for protonated pyridinium ions with 4-substituents increasing in π-donor strength from left to right. (Reproduced with permission from ⟨78JA6828⟩).



(**6**)

5.01.2.2 Experimental Structural Methods; Molecular Dimensions; Spectroscopy and Diffraction Methods

New and refined spectroscopic techniques give further information about the pyridine structure and its interaction with electromagnetic radiation. High-resolution NMR spectroscopy ⟨87JA56⟩ on pyridine and 2,6-dimethylpyridine, using large sample volumes, for example, allows the resolution of all possible ^{13}C–^{15}N couplings in the ^{13}C spectrum at natural isotopic abundance within narrow resonances. The relevant absolute values of the coupling constants, together with those for the one-bond and long-range ^{13}C–^{13}C scalar coupling constants, are given in Table 4.

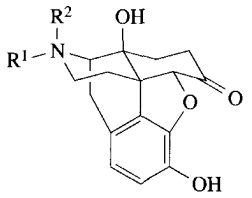
Table 4 Carbon-13–nitrogen-15 and carbon-13–carbon-13 coupling constants (Hz) in pyridine and 2,6-dimethylaminopyridine.

Compound	*Coupled nucleus*	*C-2*	*C-3*	*C-4*	*Me(2)*
Pyridine	N	0.729	2.515	3.802	
	C-2		54.21	2.867	
	C-3	54.200		53.657	
	C-4	2.868	53.66		
	C-5	13.942			
	C-6		13.943		
2,6-Dimethylpyridine	N	1.018	2.596	2.401	9.776
	C-2		56.598	1.858	51.27
	C-3	56.597		54.733	7.53
	C-4	1.859	54.731		a
	C-5	11.815			
	C-6		11.813		5.63
	Me(2)	51.258	7.514	3.108	
	Me(6)	5.669	a		

[a] Unresolved satellites.

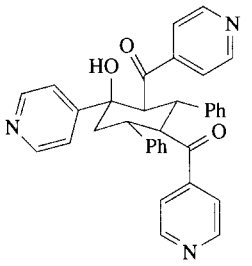
The spectrum of pyridine may also be measured in liquid crystal solution by employing *p*-ethoxybenzylidene-*p*-(*n*-butyl)aniline or ZLI 1167 as solvents, which enables the determination of chemical shift tensors of every carbon atom in natural abundance ⟨85JA7304⟩. The isotropic chemical shift is irregular (150, 124, and 136 for C-2, C-3, and C-4, respectively), but the tensor component perpendicular to the ring varies in proportion to the inductive influence of the nitrogen (36, 7.5, and 4.4). The solvent 4,4′-di-*n*-heptylazoxybenzene, together with Merck systems IV and ZLI 1167, have also been used as solvents for the study of the ^1H NMR of (^{14}N)- and (^{15}N)pyridine in a partially oriented nematic phase, in the case of phase IV in the presence of amounts of iodine ranging from 0 to 60 mol% ⟨83JCS(P2)171⟩. These measurements reveal that the complexation by iodine removes pyridine from solvent exchange processes, which is the main source of the large geometrical distortion found in the absence of the halogen. These distortions in the nematic phase mean that there is generally little correspondence between molecular dimensions of pyridine in this phase and dimensions as revealed by gas-phase microwave spectroscopy, although distortions are least in nematic phase ZLI and here there is some consistency with dimensions obtained by microwave.

Experimental structural methods permit the assignment of configuration. Proton NMR together with ^{13}C NMR involving 360 MHz COSY-45 N-type selection allows complete stereochemical designation of the three quaternary salts of the opiate antagonists naloxane and oxymorphone ⟨86JCS(P2)735⟩. The stereochemistry thus obtained is shown in structures (**7**), the configurations at the nitrogen atom being confirmed by nuclear Overhauser difference spectra.



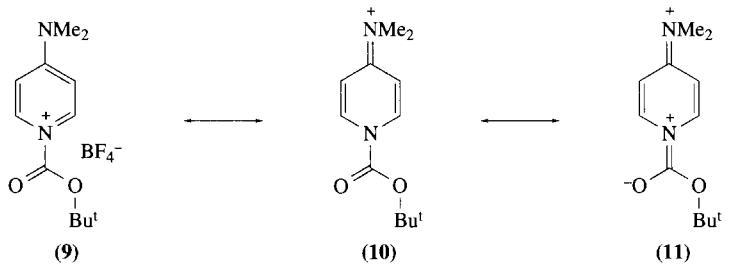
(**7**)
$R^1 = H_2C{-}CH{=}CH_2$, R^2 = Me
R^1 = Me, $R^2 = H_2C{-}CH{=}CH_2$
$R^1 = R^2 = H_2C{-}CH{=}CH_2$

2D NMR also reveals the stereochemistry of the product of the rather unusual reaction between 4-acetylpyridine and benzaldehyde, which yields an analogue of the Kostanecki triketone, which is obtained by the reaction of benzaldehyde with acetophenone ⟨91LA(12)1337⟩. In particular, the 4-pyridyl group at C-1 is shown to be equatorial in (**8**), and this is confirmed by x-ray analysis of the compound.

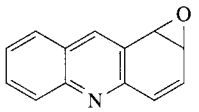


(**8**)

X-ray analysis has also been useful in structural investigation of intermediates arising in other important reactions. For example, the catalytic effect of pyridines in acylation reactions is supposed to arise from *N*-acylpyridinium formation. Thus, the tetrafluoroborate structure (**9**) is involved in the transfer of Boc groups (Boc = *t*-butoxycarbonyl). X-ray crystallography shows that the carbonyl, pyridyl, and amino groups are virtually planar, explained by the through conjugation shown in structures (**10**), (**11**), and (**12**), while bond lengths show this to be much enhanced over 4-dimethylaminopyridine ⟨91AG(E)1656⟩. The positioning of the anion over the carbonyl carbon atom in (**9**) indicates the trajectory of nucleophilic approach, furnishing a further example of crystal structure as a guide to reaction trajectories ⟨83ACR153⟩.



(**9**) (**10**) (**11**)

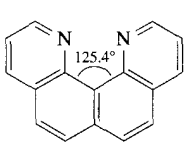


(**12**)

A second example is provided by the study of the crystal structure of acridine 1,2-oxide (**12**) ⟨94JOC984⟩. Such arene oxides are implicated as intermediates on the pathway to the ultimate carcinogens, bay-region diol epoxides. The crystalline compound (**12**) is found to exist in two independent molecular forms, in which the epoxide ring angle has an average value of 82° to the carbon system.

Quino[7,8-*h*]quinoline (**13**) and benzo[1,2-*h*:4,3-*h'*]diquinoline (**14**) are both active proton sponges, and again noteworthy structural features are revealed by x-ray crystallography ⟨89AG(E)84, 89AG(E)86⟩. The former molecule turns out to be, surprisingly, almost planar, with the central external angle of the naphthalene unit being distorted as shown by 5.4°, resulting in an increased N–N distance of 272.8 pm. Structure (**14**), on the other hand, is helical, so here the N–N distance is almost as great as in structure (**13**), 270.5 pm. The monocation obtained by reaction of this latter compound with perchloric acid shows the expected downfield shifts in the ^{1}H NMR, the acidic hydrogen down to $\delta = 24$, a uniquely large shift for such proton sponges, presumably due to the anisotropy effect of the helical aromatic system.

Azaaromatic molecules may be studied in metastable triplet states by laser flash/electron spin echo (ESE) spectroscopy ⟨87ARP141⟩, and the elusive lowest triplet (T_0) state of pyridine has now been examined by this technique ⟨85CPL(117)203⟩ with deuterated pyridine as a 0.1% guest in a



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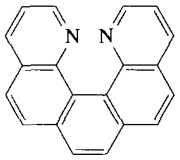
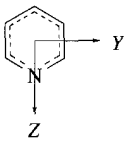


(14)

deuterated benzene host single crystal at 1.2 K. Zero-field splittings indicate that the T_0 state involves considerable $^3n\pi^*$ character, and this is supported by the fact that the electron paramagnetic lines have three components due to hyperfine ^{14}N interaction. The applied magnetic field may be imposed at variable orientations to the pyridine axes (**15**). This discloses that there are two different sites for all four magnetically nonequivalent pyridine molecules in the benzene host unit cell, so that with the magnetic field parallel to the *x*-axis, splitting of the signal is observed from the vibronic coupling between the two sites, which are energetically similar T_0 states of distorted pyridine. A minor third component is indicated by additional weak bands in the ESE signal of the triplet state of the two major sites, which comprises pyridine molecules that have their twofold axes rotated by $\pi/3$ in the plane of the molecule.



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5.01.2.3 Thermodynamic Aspects

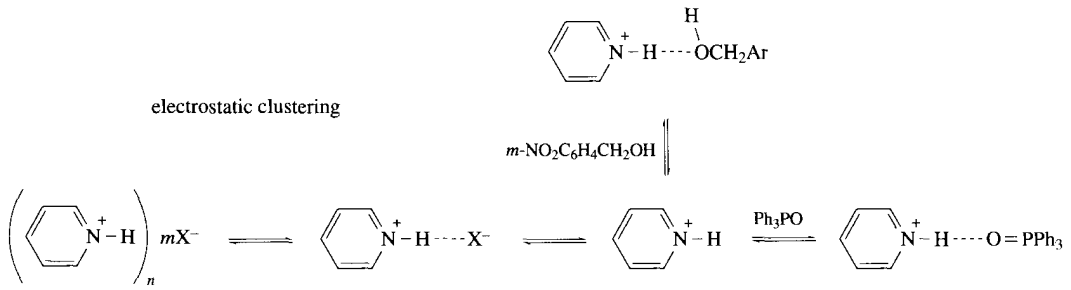
5.01.2.3.1 Solvation and solvent and associative effects

The roles of calorimetric and spectroscopic measurements continue in harmony in the elucidation of solvent–solute and solute–solute interactions. For example, the molar enthalpies of complexation of pyridine with iodine are -36 kJ mol^{-1} (CCl_4) and -34 kJ mol^{-1} (C_6H_{12}) by calorimetry, with corresponding values of -33.1 and -34.6, respectively, using the UV absorbance of the pyridine/iodine complex ⟨84JCS(P2)731⟩. For 2,6-dimethylpyridine the complex formation constant is reduced considerably from that for pyridine itself (from 106 to 46 in cyclohexane), but the enthalpy of formation remains sensibly constant, and thus independent of steric considerations. The discrepancies which do occur between the two methods are considered to arise from the formation of contact charge transfer complexes, which can be detected by spectroscopic means but go undetected in calorimetry. A further calorimetric study ⟨87JCS(P2)1713⟩ of the influence of weakly polar solvents—cyclohexane, benzene, chlorobenzene and the like—on the complexation constants K_c of methylpyridines with iodine contrasts the values for the 4-methylpyridines with those for the 2-methyl derivatives, which clearly shows the influence of the steric effect in the latter case.

The calorimetric technique also enables the evaluation of the enthalpy of transfer of substituted pyridines from the gas phase to various hydrocarbon and chlorinated hydrocarbon solvents ⟨89JCS(P2)1845⟩. Here dispersion forces of unspecified nature appear to dominate the solvation process: polarization and polarizability effects and specific interactions at N appear to play only a minor part, as evidenced by the lack of correlation of $\Delta H_{tr(g\text{-}s)}$ with pK_a, foreshadowing the difficulty of correlating aqueous solubilities of this class of compound, as discussed later in this section.

UV spectroscopy has been used for study of the self-association of pyridine monocarboxylic acids and esters in aqueous solution ⟨92JST(274)105⟩, and of the influence of traces of water on the protolytic equilibria of pyridine *N*-oxides in aprotic solvents ⟨90MI 501-01⟩. Spin saturation transfer NMR experiments, applicable to the investigation of rapid chemical exchange processes at room temperature, provide data on the hydration of pyridine-4-carbaldehyde with D_2O ⟨86M841⟩. Here the signal of the aldehyde proton (9.9 ppm.) and of the proton of the protonated aldehyde (5.8 ppm.) are well separated and show no line broadening. 4-Channel Raman spectroscopy yields information on the pyridine–methanol system using dependence of frequencies, line widths, and integrated intensities on concentrations ⟨93MI 501-01⟩.

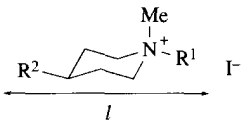
Fast-ion bombardment mass spectrometry (FABMS) can be used to study hydrogen bonding in pyridinium systems, which also gives good accord with other more conventional spectroscopic techniques ⟨87JCS(P2)1129⟩. The pyridinium salts with Cl^-, Br^-, and I^- were prepared as matrix complexes with a variety of hydrogen-bond acceptors, of which *m*-nitrobenzyl alcohol and triphenylphosphine oxide were the most successful. The resultant interactions are shown in Scheme 1, as analyzed by the effect of concentration, nature of the anion, and potential hydrogen-bond strength on the intensity of the relevant peaks, which, for example, in the pyridinium bromide–triphenylphosphine oxide system occurred at *m/z* 80 (pyridinium ion), *m/z* 279 (triphenylphosphine oxide ion), and *m/z* 358 (the hydrogen-bonded complex).



Scheme 1

Variation in dielectric constant has been used to measure the association of variously substituted dimethylphenols with pyridine in benzene and cyclohexane ⟨86JCS(P2)573⟩. The greater polarizability of the former solvent gives rise to generally greater dipole moments than in C_6H_{12}, the calculations for which involve the assumptions that the hydrogen bond follows the line of the nitrogen lone pair orbital, that the COH angle is 115°, and that there is free rotation around the OH—N axis.

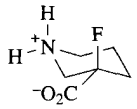
Solvent polarizability also plays a part in the elucidation of the association constants determined by ^1H spin lattice relaxation times of *N*-methyl quaternary piperidinium iodides (**16**) ⟨85JCS(P2)83⟩, where the association arises as ion pair formation, the degree of association increasing as we descend the series of decreasingly polar solvents CD_3OD, $(CD_3)_2CO$, CD_2Cl_2. There is a good degree of correspondence between the relaxation times T_1 and the overall length *l* of the piperidinium ion, as estimated from Drieding models, and this is taken to suggest that T_1 measures the overall rotational motion rather than the internal rotation of the methyl group.



(16)
R^1 = Me, Et, Pr^i, Bu^n, Bu^i
R^2 = H, Bu^t

Aqueous solvation is of particular importance and complexity. Study of protonated 3-fluoropiperidines ⟨93JA3356⟩, via 1-D and 2-D NMR involving particularly H–H and H–F coupling constants and chemical shifts, reveals that the fluoro substituent has a strong tendency to take up the axial conformation when in the 3-position of the piperidinium ring, both in the gas phase and in aqueous solution. Carboxylate has a corresponding tendency in the gas phase, the effects arising as a result of NH^+–F attraction and NH^+–CO_2^- attraction, respectively. In aqueous solution, however, while free energy of solvation is not sufficient to reverse the effect for fluoro, it does so for carboxylate, so that, for example, salt (**17**) exists in the form shown. The dominance of the fluoro-effect is noted in structure (**18**), where both groups are found to take up the axial position, although under basic conditions the all-equatorial form (**19**) is favored. This sensitive measure of differential aqueous solvent effects constitutes a good testing ground for parametric, force field, and quantum mechanical treatments for aqueous solvation. Indeed, the treatment of pyridine derivatives themselves constitutes a major challenge to theories of aqueous solvation, for Taft and his coworkers have found little success in the correlation of aqueous solubilities or solvent/water partition coefficients for such compounds with solvatochromic parameters, stressing the importance of polarization, polarizability, and hydrogen bonding influences, which have been successful with most other cat-

egories of solute, both aliphatic and aromatic ⟨87JPC1996, 88JPC5244⟩. The standard linear solvation energy relationships are, however, useful in the interpretation of the influence of a wide range of solvents, including many alcohols and other hydrogen bond donors and acceptors, on the charge transfer band of *N*-alkylpyridinium iodides ⟨92JCS(P2)343⟩, although water is not included in the list.



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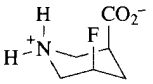

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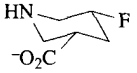


(19)

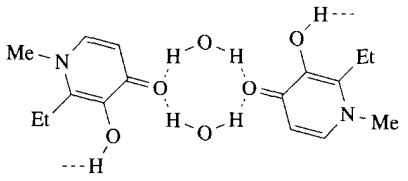
Water (or D_2O) is, however, included in the list of solvents in which the ^{13}C spin relaxation times of piperidine and *N*-methylpiperidine have been measured ⟨89JCS(P2)523⟩, using the technique described for the *N*-methylpiperidinium salts above ⟨85JCS(P2)83⟩. Using this data, calculations can be made estimating the solvent effect on the anisotropy of the molecular motion with ellipsoid tumbling about two different axes. The solvents may thus be grouped into three classes:

(i) those in which the molecules rotate with no interaction (C_6H_{12}, $C_6H_5NO_2$, $(CD_3)_2SO$);

(ii) those where the rotation is effected by hydrogen (deuteron) bonding between the nitrogen lone pair and the solvent ($CDCl_3$, CH_3OD, D_2O), which increases the effective molecular size in the direction of the lone pair, and thus provides confirmation of the conformational preferences of the lone pair—equatorial for piperidine, axial for *N*-methylpiperidine (see further discussion in Section 5.01.2.3.4.1; and

(iii) $(CD_3)_2CO$, which interacts with piperidine by acting as a hydrogen bond acceptor.

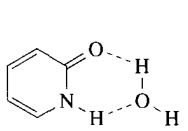
Crystal structure determinations of 2-ethyl-3-hydroxy-1-methyl-4-pyridone are of interest because these types of compound are potentially effective chelators for treatment of iron or aluminum overload, or for the administration of isotopes. X-ray measurements ⟨93JCR(S)50⟩ show that in the hydrated molecule the water molecules bridge pairs of ligands, as shown in structure (**20**). Small-order changes in formal structure may drastically alter hydration: in 1,2-diethyl-3-hydroxy-4-pyridone there is no intermolecular hydrogen bonding and the molecule is anhydrous.



(20)

Hydrogen bonding in 2-pyridone–H_2O and in 2-pyridone–$2H_2O$ has been investigated by rotationally resolved fluorescence excitation spectra in both the S_0 and S_1 electronic states ⟨93JA9708⟩, using hydrogen- and oxygen-labelled species to enable interpretation. The monohydrate shows an increase in zwitterionic form over the anhydrous species, although this contribution to the resonance hybrid decreases on excitation. It contains two nonlinear hydrogen bonds with the amine hydrogen and the carbonyl oxygen (**21**), which increase in length and thus decrease in strength on excitation. The dihydrated species (**22**) shows stronger hydrogen bonding, because the hydrogen bonds are not so bent as in the monohydrate (**21**), and the water–water hydrogen bond is nonlinear and out of plane with the rest of the molecule, which gives rise to two conformational isomers with different fluorescence excitation spectra. The pyridone–NH_3 complex is found by the same experimental methodology ⟨93JA9718⟩ to provide the first example of a single gas-phase ammonia molecule acting both as hydrogen bond donor and acceptor ((**23**), (**24**)), evidence for the two separate hydrogen bonding roles arising particularly from the correlation between hydrogen bond distances and the barriers to rotation in both the S_0 and S_1 states. In the 2-pyridone–$2(NH_3)_2$ complex (**25**) the heavy atoms are planar, but again the bridging hydrogen bond between the two solvating ammonia molecules leads to the observation of different spectra in the two states, indicative of conformational isomerism.

The interconversion of 2-pyridones with their dimers in solution is too fast to measure by ^1H or ^{13}C NMR, even at low temperatures. However, if the pyridone carries a 6-dimethylamino substituent, the interconversion rate is slowed down and the two forms of NMR analysis in TFH-d_8 at $-118\,°C$ reveal the presence of the two distinct species ⟨91JA721⟩. Consideration of structure (**26**; R = Et)



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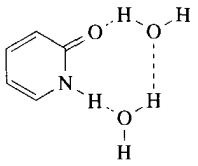

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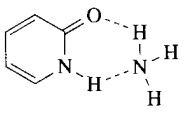

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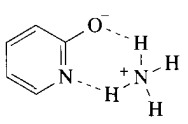

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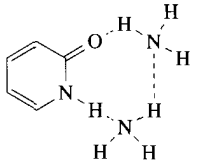
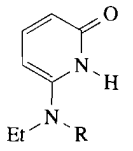


(25)

shows this to be due to steric hindrance by comparison with structure (**26**; R = H), where only averaged signals are found under the same conditions for NMR measurement and electronic factors are ruled out because 2-pyridone and structure (**26**; R = Et) have similar association constants. Spectral characteristics suggest that the monomer is present in the hydroxypyridine form, and that this tautomerizes to the pyridone structure in the dimer (**27**) since this gives a large ^{13}C chemical shift between C-3 ($\delta = 101.3$) and C-5 ($\delta = 86.4$) diagnostic of the -one form.



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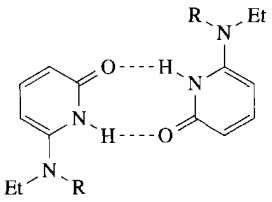

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5.01.2.3.2 Substituent effects

Interrelationships between substituent effects on spectral characteristics of various kinds, and in turn on pK_a of pyridine derivatives, have invited much investigation. The pyridine *N*-oxide nucleus has been particularly popular in this regard.

In a typical investigation ⟨83JCS(P2)345, 84JCS(P2)223⟩, the IR spectra of substituted pyridine *N*-oxide trifluoro- and trichloracetates have been measured in chloroform as well as dichloromethane, and the characteristics of the broad OH absorption band between 3000 and 400 cm^{-1} have been described separated from the superimposed skeletal absorptions. The center of gravity of this band has been found to vary between limits of 2050 cm^{-1} (for 4-NO_2) and 1527 cm^{-1} (for 4-NMe_2) for the trifluoroacetates, with virtually the same limits for the trichloroacetates. Indeed, the overall values for the two are very similar and may be treated together, as may the data for the chemical shift of the hydrogen-bonded proton in the ^1H NMR spectra. These coincidences are illustrated in Table 5, and give rise to Equation (6). The correlation of both spectral quantities with pK_a gives biphasic plots with intersecting straight lines of opposing slopes as the data of Table 5 imply, but the reason for this is not clear-cut. The broad OH band for these compounds displays five overlapping absorption bands A–E, which are found to vary in intensity and position with solvent, and which are strongly dependent on the proton acceptor properties of the N—O function and thus on the substituent effect ⟨84JCS(P2)1997⟩.

Nuclear-quadrupole resonance ⟨85MRC315⟩, ^{13}C ⟨88MRC303, 91JCS(P2)1161⟩, and ^{17}O NMR spectroscopy ⟨85MRC276⟩ shed further light on these interactions in the substituted pyridine *N*-oxides. For the *N*-oxides complexed with $CHCl_2COOH$ in dichloromethane and acetonitrile, a curved correlation has been found between the integrated intensities of the broad OH band and the frequency at its center of gravity ⟨87SA(A)1553⟩, while diagnosis of the second derivative of the carbonyl absorption measured by FTIR reveals that the hydrogen bonding in these complexes is better described by a strongly asymmetric single minimum potential than a double potential energy well ⟨91SA(A)125⟩.

Table 5 Spectral characteristics of hydrogen-bonded complexes of substituted pyridine *N*-oxides (XC_5H_4NO) and CF_3COOH (A) and CCl_3COOH (B).

X	pK_a	ν (cm^{-1})	δ (ppm)
4-NO_2	−1.70	2050 (A)	14.60
		2073 (B)	14.40
4-Cl	0.36	1506	17.12
		1512	16.85
H	0.79	1346	17.98
		1366	17.72
4-OMe	2.05	1199	18.78
		1178	18.71
4-NMe_2	3.88	1527	17.22
		1509	17.12

$$\delta\ (\pm 0.12\ \text{ppm}) = 24.298 - 4.7222 \times 10^{-3}\ \nu_H \quad (r = 0.997) \tag{6}$$

Interpretation of the ^{13}C NMR chemical shifts of substituted pyridine *N*-oxides in $CDCl_3$, D_2O, $HClO_4$ (60% in D_2O), and $Cl_2CHCOOH$ (60% in $CDCl_3$), and of the *O*-methylated derivatives in $(CD_3)_2SO$ and D_2O ⟨91JCS(P2)1161⟩ involves distinction between substituent effects and hydrogen bonding. The hydrogen bonding effect is taken as $\Delta_1 = \Delta(D_2O) - \Delta(CDCl_3)$, and the protonation effect as $\Delta_2 = \Delta(HClO_4) - \Delta(D_2O)$, while $\Delta_3 = \Delta(HClO_4) - \Delta(CDCl_3)$ and $\Delta_4 = \Delta(Cl_2CH\text{-}COOH) - \Delta(CDCl_3)$ are taken to reflect increasing hydrogen bonding strength in the complexes. Thus the chemical shift differences ($\Delta_3 - \Delta_4/\Delta_4$) afford good correlations with the chemical shifts of the hydrogen-bonded protons and with the center-of-gravity frequency for the OH IR band, and are uninfluenced by the substituent effect, as shown by lack of correlation of this quantity with pK_a. In turn, the chemical shifts themselves are difficult to correlate and show nonadditive substituent effects, although a limited dual-substituent parameter correlation is afforded by the C-6 chemical shift for the 3-substituted pyridine *N*-oxides, for which ρ_I is 4.08 and ρ_R is 21.99.

3-Substituents in pyridine *N*-oxides also give a σ_I correlation (Equation (7)) for ^{17}O NMR spectroscopy (measured at natural abundance) in DMSO at 80 °C ⟨86TL5649⟩. The familiar push–pull or amphoteric nature of the pyridine *N*-oxides makes itself felt in the correlation for 4-substituted derivatives (Equation (8)), in which both σ_R^+ and σ_R^- figure equally ⟨86TL3013⟩. The correlation of shifts for both 3- and 4-substituents with pK_a is only poor, but this is not a feature arising from the dipolar aprotic solvent, because the shifts correlate precisely with the concomitant data in acetonitrile ⟨85MRC276⟩.

$$\Delta\delta\ ^{17}O_{DMSO} = 35.5\sigma_I - 2.1 \quad (r = 0.983,\ s = \pm 1.9,\ n = 12) \tag{7}$$

$$\Delta\delta\ ^{17}O_{DMSO} = 53\ (\sigma^o + 0.8\Delta\sigma_R^+ + 0.8\Delta\sigma_R^-) \quad (r = 0.994,\ s = \pm 3.8,\ n = 10) \tag{8}$$

Complexation of pyridines with further (Lewis) acid systems has been realized in an extensive study in which a series of alkyl-substituted pyridines have been complexed with a wide variety of boron Lewis acids, BF_3, BH_3, $B(OH)_3$, and BX_3, where X is a selection of alkyl, aryl, hydroxy, alkoxy, and aryloxy groups ⟨87JCS(P2)771⟩. The differences in chemical shifts between the ^{13}C NMR shift of the 4-proton in the *N*-oxide in the free form and for the complex with BF_3 measured in $CDCl_3$, and the enthalpy of formation of the complexes ΔH_c, show a rough correlation, thus providing a measure of strength of the N—B bond. No such correlation exists, however, with ^{11}B NMR. Study of the more bulky boron Lewis acids provides evidence for the expected steric hindrance with 2-substituted alkyls.

Complexes of a wide variety of substituted pyridines have been studied by low-temperature (−40 °C) ^{13}C and ^{19}F NMR in dichloromethane ⟨83JCS(P2)475⟩, which enables distinction between

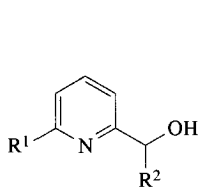
the ^{13}C signals for the free bulk pyridines and their complexed partners (see Table 6). In this case there is a correlation between the ^{19}F chemical shift and the enthalpy of formation of the complex for the alkylpyridines. There is also a reasonable correlation between the BF_3 ^{19}F and the C-2 ^{13}C chemical shifts, which suggests the latter also reflect complexation strength. Other effects also appear to be at work: a polarizability influence of the BF_3 on the C-3, C-4, and C-5 sites of the pyridine molecule, together with a paramagnetic effect, accounting for the low-field C-2 and C-6 carbon resonances, arising from the interaction of low-lying energy levels in the nitrogen atom.

Table 6 Chemical shifts for complexation of BF_3 with substituted pyridines XC_5H_4N at $-40°C$ in dichloromethane.

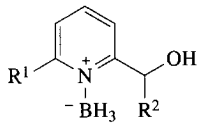
X	$\delta^{19}F$ (ppm)[a]	$\delta^{13}C$ (ppm)[b]					
		2-C	*3-C*	*4-C*	*5-C*	*6-C*	
H	11.1	150.2 (−6.6)	124.4 (+2.5)	136.9 (+7.6)	124.4 (+2.5)	150.2 (−6.6)	
2-Me	14.7	158.7 (−1.4)	124.0 (+5.4)	137.2 (+6.7)	121.5 (+2.2)	149.1 (−4.9)	24.4[c] (−3.1)
2-Cl[d]	15.1	151.2 (−2.8)	125.3 (+4.8)	139.5 (+6.6)	123.1 (+1.6)	150.5 (−3.6)	
3-Cl	11.2	148.9 (−5.7)	132.9 (−3.1)	136.6 (+7.6)	125.2 (+2.7)	148.0 (−5.7)	
4-Me	11.0	140.9 (−4.3)	126.2 (+1.2)	151.9 (+5.8)	126.2 (+1.2)	146.9 (−4.3)	21.5[c] (+0.4)

[a]With respect to internal C_6F_6. [b]With respect to internal $SiMe_4$. Values in parentheses are chemical shift differences between the complexed and free pyridine signals, a positive sign indicating a shift to lower field in the complex. [c]Me. [d]At $-20°C$.

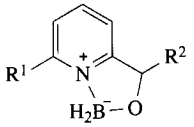
Boron-11 NMR has also been used to study the formation of five-membered N–B-containing rings whose structure is modulated by substitution both on the heteroaromatic nucleus and on the boron atom (although these important studies involve not so much systematic substituent change as systematic structural changes, but for convenience are best grouped in this section). Reaction of pyridylmethanols (**28**) with $BH_3 \cdot Me_2S$ gives the sequence of compounds (**29**)–(**31**) ⟨88JCS(P2)1787⟩. For the unsubstituted compounds (**29**)–(**31**) ($R^1 = R^2 = H$) the ^{11}B NMR signals were as follows: (**29**) −14.0 ppm, $J = 96$ Hz (quartet); (**30**) 3.7 ppm, $J = 110$ Hz (triplet); (**31**) 9.6 ppm, singlet; −14.0, $J = 110$ Hz (quartet).



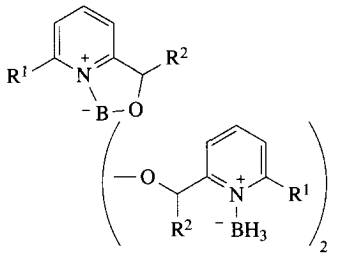
(**28**)



(**29**)

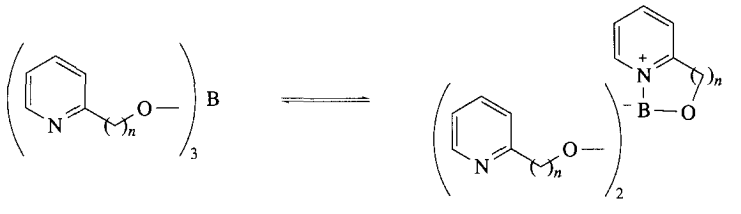


(**30**)



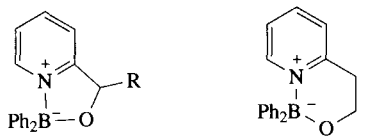
(**31**)

Investigation of the systems (**32**) and (**33**) (Equation (9)) by variable-temperature ^{11}B NMR measurements enabled determination of equilibrium constants for the two processes and thus the relative stability of the five- and six-membered ring forms ⟨88JCS(P2)1787⟩.



(**32**) $n = 1,2$ (**33**) (9)

Further measurements ⟨92JCS(P2)527⟩ have been made on the related systems (**34**) and (**35**), and in all cases the five-membered ring system is found to be more stable than the six-membered form by ≈28 kJ mol^{-1}, in support of which crystallography shows the N—B distance to be 164.2 pm in (**34**) and 168.5 pm in (**35**). Molecular mechanics calculations suggest that this is not a steric effect, and indeed indicate the opposite order of stability from that predicted by steric considerations. The deduction is therefore made that the effect comes about through σ-bond assistance to five-membered ring formation via through-bond interactions, an effect which is known to disfavour six-membered ring formation, but which does not appear to be incorporated in the molecular mechanics MMX program.



(**34**)
R = H, Me, Ph

(**35**)

5.01.2.3.3 Tautomerism

It was noted initially that NMR longitudinal relaxation times can be used for determination of the site of protonation in polyfunctional acids and bases ⟨93JCS(P2)283⟩. Thus, the ^{14}N NMR spectrum of 4-aminopyridine shows clearly from the sharpening of the signal for the ring nitrogen that protonation has occurred here (Figure 5). This type of procedure promises to be an important innovation in elucidation of heterocyclic tautomeric structures, even for cases of fast exchange.

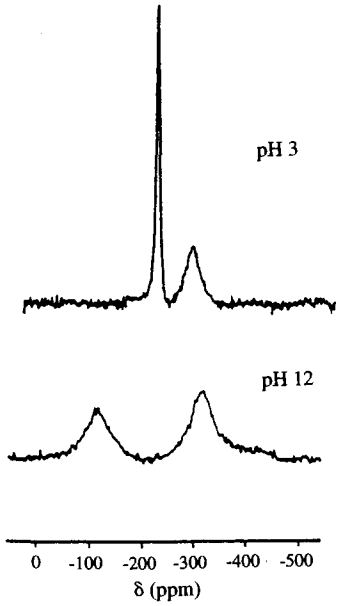
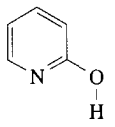


Figure 5 Nitrogen-14 NMR spectrum of 4-aminopyridine. The downfield peak is the ring nitrogen atom; its sharpening at pH 3 reveals this to be the site of protonation. (Reproduced with permission from ⟨93JCS(P2)283⟩).

New light is also shed on an old problem in the case of the tautomerism 2-pyridone⇌2-hydroxypyridine and substituted analogues, which continues to attract much attention owing to its chemical, biological, and theoretical importance. Here both tautomers often occur in significant proportions (see ⟨84CHEC-I(2)99⟩ Table 15), and thus the influence of media can be readily investigated and modelled ⟨83JA3568, 84CPL(170)330, 87JA6283, 90CPL(171)475, 91H(32)329, 92JA1645⟩, with *ab initio* MO calculations proving particularly useful in these studies. These calculations may include both geometric optimization and electron correlation at the highest level of *ab initio* theory (as

detailed in Section 5.01.2.1), as well as molecular dynamics simulations. In a typical investigation directed at 6-chloro-2-pyridone ⟨91JCS(P2)799⟩, for example, calculations at the 6-31G** level confirm that gas phase and nonpolar phase favor the hydroxy form, an effect enhanced over the parent molecule by the electronegative substituent in the 6-position. In more polar media, and in aqueous solution, the oxo tautomer predominates (see ⟨84CHEC-I(2)99⟩ Table 15), the estimated solvation energy differences ⟨91JCS(P2)799⟩ being accurate to within 1.5 and 0.2 kcal mol^{-1} (6.3 and 0.8 kJ mol^{-1}) for aqueous and carbon tetrachloride solutions, respectively.

Experimental assessments of the concentration of the minor hydroxy tautomer of 2-pyridone and substituted derivatives in cyclohexane and acetonitrile solution may be carried out by the use of fluorescence spectroscopy ⟨85JCS(P2)1423⟩. For the parent compound, the pyridinol component in cyclohexane is found to be 4.08% and in acetonitrile 1.22%; this preference for the hydroxy form in the former over the latter solvent is maintained over a fair range of variously substituted pyridones. *Ab initio* calculations ⟨85JA7569⟩ on 4-hydroxypyridine, the minor tautomer in aqueous solution, include 92 water molecules in the estimations, and thus give a very detailed picture of the solvated molecule, while the experimental technique of microwave spectroscopy not only gives an accurate estimation of the 2-hydroxypyridine/2-pyridone ratio of 3 : 1 in the gas phase but also reveals that the former isomer is predominantly in the (*Z*)-form (**36**) and that both isomers are planar ⟨93JPC46⟩.



(**36**)

Interestingly enough, because the additive properties of partition terms are still of much importance within overall quantitative structure–activity relationships (QSARs) for drug design, calculation of the logarithmic partition coefficient log *P*, employing its additive properties, for partition between *n*-octanol and water, is sufficiently accurate to indicate that the pyridone form in both 2- and 4-isomers is predominant in either medium ⟨90CMC295⟩, although the hydroxy form might have been considered a candidate for the *n*-octanol imitation lipid phase. It seems, however, to work well. The measured log *P* for 2-pyridone is −0.58; the calculated value for this form is −0.57 and for the 2-pyridinol is 0.89.

Quantitative predictions of high quality based on the AMI MO method reveal the relative stabilities and the proton affinities of the hydroxypyridine and thiopyridine systems in the gas phase ⟨89JST179⟩. If such calculations are incorporated with a self-consistent reaction field (SCRF) to account for solvent polarity, they clearly confirm the hydrogen-bonded hydrate 2-pyridone–$2H_2O$ to be energetically more favorable than 2-hydroxypyridine–$2H_2O$ ⟨89JOC6030⟩. Using this approach, estimates can be made for log K_T values (**37**)⇌(**38**) (Equation (10)) in polar media of dielectric constant $\varepsilon = 1$ and 78.4. Table 7 shows the good agreement between the latter values and the experimental values of log K_T for water. The agreement of the gas-phase predictions with the experimental values is very poor, however, and this demonstrates that dielectric solvation is a major factor in determining the medium influence on such tautomerisms.

(**37**) (**38**) (10)

The same MO approach, allied with PM3 calculations, also predicts, in keeping with NMR and UV data on fixed-form model compounds (the time-honored and ever-reliable procedure for tautomeric investigation), that a wide variety of substituted 4-quinolone-3-carboxylic acids exist in the oxo form ⟨92T6135⟩ both in aqueous and DMSO solution, despite the intramolecular hydrogen bond stabilization available to the hydroxy form. Solid-state NMR and x-ray crystallography revealed that in general the 4-quinolone form also predominates in the crystalline state. But the situation in this system is not a simple one: thus, the same type of MO calculation on the parent 4-quinolone molecule predicts the hydroxy form to be predominant ⟨91MI 59-01⟩. Experimental techniques give conflicting views. Thus, metastable-ion mass spectrometry indicates that in the gas phase at reduced pressure 4-quinolone exists in the hydroxy form ⟨88JCS(P2)347⟩. This work also

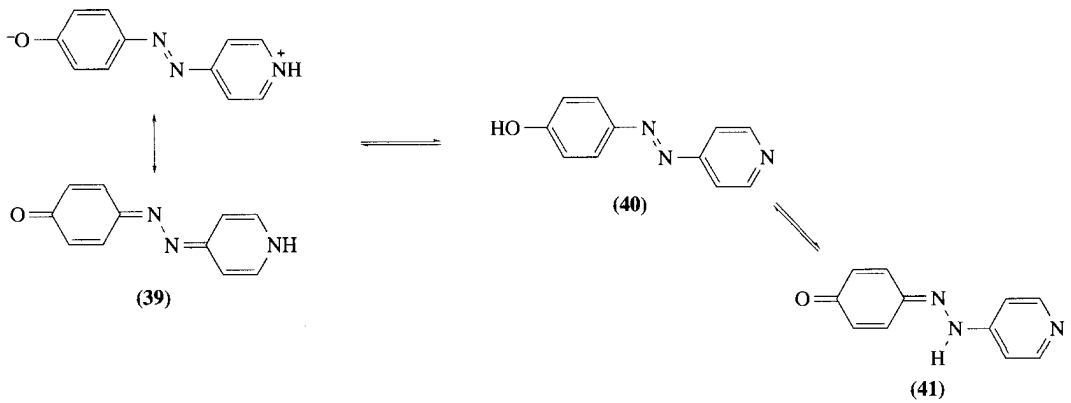
Table 7 Calculated tautomeric ratios for the tautomeric forms of substituted pyridines in water (dielectric constant 78.4).

Substituent[a]	log K_T[b]	log K_T[c]
2-O	−2.8	−3.1
2-NH	7.8	6.0
2-S	−4.7	−4.7
2-CH_2	14.8	13.3
3-O	6.7	0.1
3-NH	20.0	d
3-S	−2.4	−2.2
3-CH_2	25.7	d
4-O	−3.0	−3.3
4-NH	7.2	8.7
4-S	−7.3	−4.6
4-CH_2	14.8	13.4

[a]X in. [b]Calculated. [c]Experimental. [d]Unobservable.

indicates that both tautomers are present to a measurable extent in the 2-quinolone molecule. Even in these well-studied systems, it is evident that more research is necessary before precise quantification of the way in which the influence of the inherent stabilities of the alternative tautomers, and the effect on those stabilities of hydrogen bonding, both intra- and intermolecular, and general solvent effects, polarity and the like, can be assessed. At the same time, consideration must be given to the extent to which we regard, on the one hand, an experimental procedure as defining and quantifying a certain phenomenon and, on the other hand, a well authenticated phenomenon as being used to estimate the accuracy of a new experimental methodology.

Moreover, the preference for the pyridone form over the pyridinol in aqueous solution is not matched in systems where more extensive conjugation is possible. Thus, of the possible tautomers (**39**)⇌(**40**)⇌(**41**) of the 4-(4′-hydroxyphenylazo)pyridine system in aqueous media (Scheme 2) UV and NMR studies ⟨83T1091⟩ employing fixed model compounds show that tautomer (**41**) has a negligible presence. Tautomer (**40**) predominates more than a hundredfold over (**39**); the quinonoid canonical contribution to the latter, according to the authors, is "associated with a destabilizing effect", that is to say, involved in the resonance hybrid with a smaller mixing coefficient than would be the case if it were more stable relative to the other canonicals.

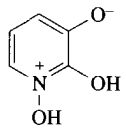


Scheme 2

Systematic work on the 3-substituted 2-hydroxypyridine *N*-oxide system (**42**)⇌(**43**) (Equation (11)) in DMSO, involving NMR analysis, shows the pyridone form to be favored ⟨90JCS(P2)1215⟩. X-ray crystallography of the unsubstituted derivative (**42**; R = H) reveals this tautomeric preference to be retained in the crystalline state, as it is for 1-hydroxy-5-methoxy-6-methyl-2-pyridone ⟨83ACR146⟩ and for 1-hydroxy-*N*,*N*-dimethyl-2-oxodihydropyridine-6-carboxamide ⟨85IC954⟩. Thus, in the crystalline state of pyridone structure (**42**; R = H) ⟨90JCS(P2)1215⟩, there is a short C–O linkage (125.2 pm) as in other pyridones (cf. the C–O length of 133 pm in the 2-hydroxypyridines).

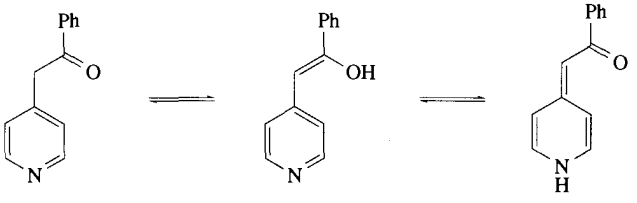
There is no evidence for any detectable zwitterionic form (**44**) in the 2,3-dihydroxy compound in its crystalline state.

(42) R = H, OMe, OH (43) (11)



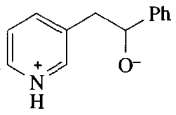
(44)

4-Phenacylpyridines can display both keto–enol (vinylogous pyridone–pyridinol tautomerism) and ketoimine–enaminone tautomerism (**45**)⇌(**46**)⇌(**47**) (Scheme 3). These tautomerisms and the related situation for the 2-isomers may be investigated in aqueous solution by classical UV methods incorporating model compounds, together with kinetic studies of rates of relaxation of the enolimine, formed by acidifying an aqueous solution of the enolate anion, to the more stable ketoimine ⟨93JCS(P2)2285⟩. Relative tautomeric stabilities fall in the order ketoimine (**45**) > enaminone (**46**) > enolimine (**47**) in aqueous solution, and the same order is found for the tautomerism of 2-phenacylpyridine; for the 3-isomer, enol > zwitterion (**48**).



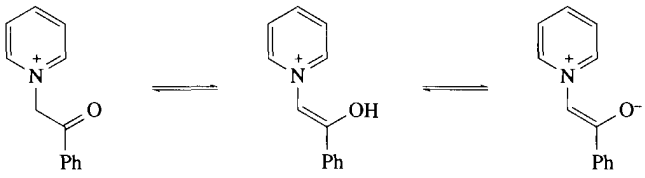
(**45**) Ketoimine (**46**) Enolimine (**47**) Enaminone

Scheme 3



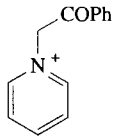
(**48**)

The keto form is also favored over the enol form in the 1-phenacylpyridinium and 4-dimethylamino-1-phenacylpyridinium ion tautomerism and ionization processes (**49**)⇌(**50**)⇌(**51**) (Scheme 4), providing a model, from the activating effect of the 1-pyridinium group, for carbanion stabilization of azomethine ylides ⟨93JCS(P2)2297⟩; compare (**52**) and (**53**). These measurements illustrate the efficacy of measuring very small equilibrium keto–enol ratios by measuring rates of enolization and ketonization in acid solutions by quenching the enolate anion.

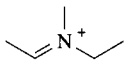


(**49**) (**50**) (**51**)

Scheme 4



(52)



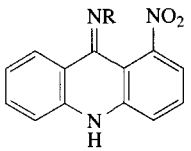
(53)

For tautomerism in 2-phenacylquinolines ⟨88T3319⟩, however, the enaminone form predominated for a wide variety of substituted derivatives, as revealed by NMR spectroscopy. This is at least partially rationalized by the fact that the measurements are carried out in $CDCl_3$, while the quinoline structure is also predicted to favor the enaminone structure more than in the pyridine examples discussed above. One exception is 1-phenyl-2-(quinol-2-yl)-propan-1-one, which NMR revealed to be in the keto form (**54**), presumably because of steric compression in the conformation of the enolimine form, required for hydrogen bonding to the ring nitrogen atom (**55**), between the methyl group and both the hydrogen atom at C-3 and phenyl (Equation (12)).

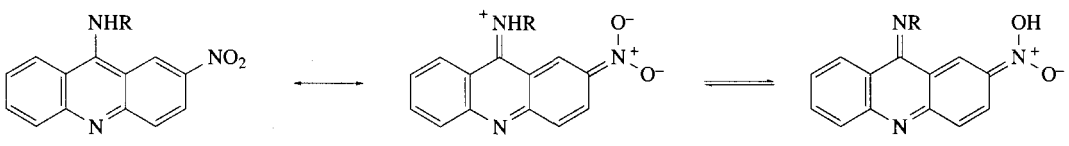
(12)

(54) (55)

The biological activity of acridine derivatives, particularly their anticancer activity, has provided the stimulus for investigations of tautomerism of the acridin-9-amines. X-ray crystallographic measurements on *N*,*N*-dimethyl-*N'*-(1-nitro-9-acridyl)propane-1,3-diamine, or nitracrine, reveal that the molecule exists as the imino tautomer (**56**), with the nitro group twisted out of the plane of the ring ⟨82MI 501-01, 85JA2067⟩. On the other hand the 2-nitro derivative is in the planar amino form ⟨90JCS(P2)1501⟩, presumably to take advantage of the stabilizing amino–nitro through-conjugation (**57**)⇔(**58**), and indeed this isomer may in consequence convert to the *aci* form (**59**), as is also the case with the 4-nitro compound (Scheme 5). UV spectra in hexane, methanol, and toluene can be correlated with semiempirical MNDO geometry optimization and PPP calculations of oscillator strengths, requiring suitable parametrization of the nitro group in its various forms (NO_2, NO_2H, NO_2^-), showing that the imino form is predominant where possible (the 2- and 4-isomers), although, as in the pyridone–pyridinol situation, this is profoundly influenced by solvent, with inert and nonpolar media favouring the amino structure. In ethanolic ethoxide the *aci* form is favored, and these variable tautomeric forms in the solution phase suggest that alternative tautomers may be favored under physiological conditions.



(56)
R = $-(CH_2)_3NMe_2$



(57) (58) (59)

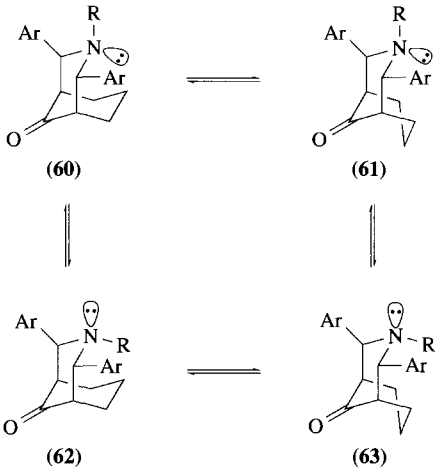
Scheme 5

5.01.2.3.4 Conformation

(i) Piperidines

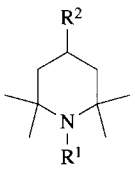
Substantial reviews have appeared dealing at length with conformational equilibria in nitrogen-containing saturated six-membered rings ⟨84AHC(36)1⟩, and more recently with all aspects of piperidine chemistry including conformation ⟨B-91MI 501-02⟩.

Interest has focused on the conformation of 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones, since they have the γ-aminobutyric acid (GABA) skeleton, but with restricted conformations so that they serve as conformationally restricted analogues giving information on the topography of the receptor site ⟨94JOC2565⟩. These available conformations are shown in structures (**60**)–(**63**) (Scheme 6). The preference is always for chair–chair conformations, and cases of R = Me are monoconformational in all media studied, with the *N*-methyl group in the equatorial position (**60**). X-ray crystallographic measurements show that in the solid state (**60**; R = H) is also the preferred form, with the formation of intermolecular hydrogen bonds, while (**62**; R = H) is the predominant form in $CDCl_3$ solution, as revealed by ^1H NMR, and in the gas phase, as predicted by AM1 quantum mechanical calculations.

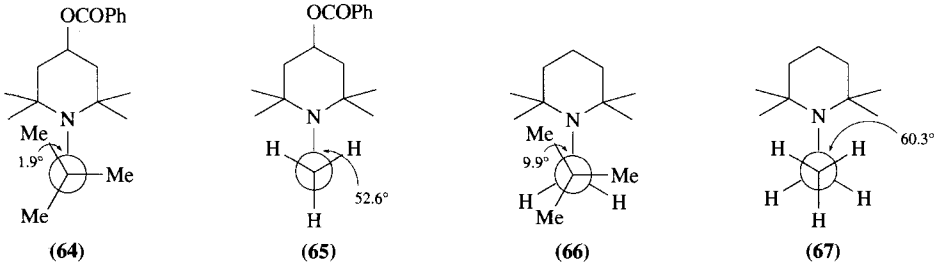


Scheme 6

Quantum mechanical MM3 calculations, together with x-ray crystallographic studies, are also useful in defining conformational preference in *N*-alkyl and alkoxy derivatives of 2,2,6,6-tetramethylpiperidines (**64**)–(**67**), in which a saturated bond has a threefold rotational potential with



(**64**) R^1 = OBu^t, R^2 = OCOPh
(**65**) R^1 = OMe, R^2 = OCOPh
(**66**) R^1 = CH_2Bu^t, R^2 = H
(**67**) R^1 = CH_2Me, R^2 = H



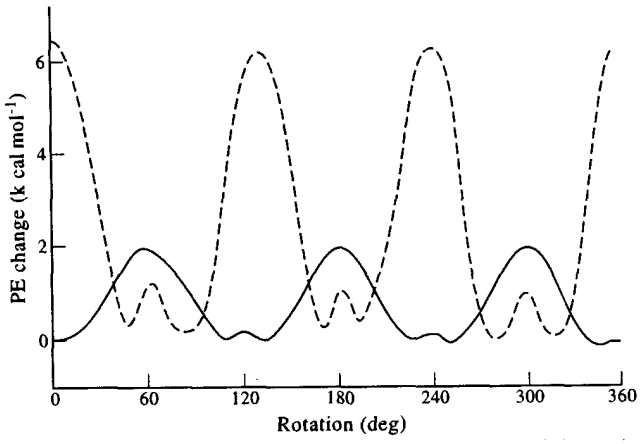
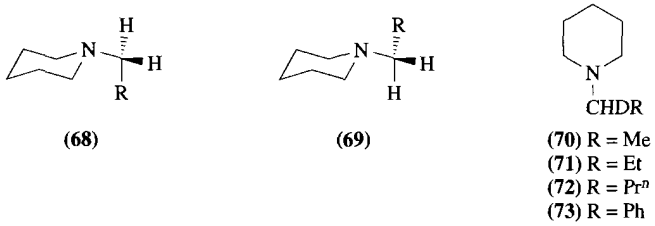


Figure 6 Potential energy changes (kcal mol^{-1}) for rotation about the CH_2—Bu^t bond in (**66**) (solid line) compared with those for rotation about the central bond in 2,2,3,3-tetramethylbutane (dashed line). (1 kcal $mol^{-1} = 4.186$ kJ mol^{-1}).

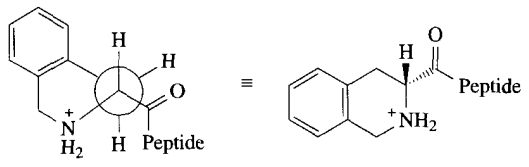
three successive eclipsed double minima, as shown for structure (**66**) (Figure 6) ⟨93JA3494⟩. As shown in the Newman projections, the *t*-butyl groups thus prefer to be almost eclipsed, while in the corresponding methyl compounds the groups are staggered. *N*-Alkylpiperidines can also have *gauche* (**68**) or *anti* (**69**) conformations, and ^{13}C NMR of isotopically substituted compounds (**70**)–(**74**) in CF_2Cl_2 enables this to be elucidated ⟨89JA4548⟩. The proportion of *gauche* isomers is found to decrease in the sequence (**70**) > (**71**) = (**72**) > (**73**), a result confirmed again by quantum mechanical (MM2) calculations.

Further information from fixed models on binding of peptide neurotransmitters and hormones to receptor sites is also obtained by ^1H NMR studies on the 1,2,3,4-tetrahydroisoquinolinecarboxylic (Tic) residue ⟨91JA2275, 94JOC1789⟩. D-Tic with a free amino group prefers the *gauche* (−) conformation (**74**), but peptide chain attachment on the amino group causes 1,2-pseudoequatorial strain and thus ring flip to the *gauche* (+) form (**75**) (Equation (13)).

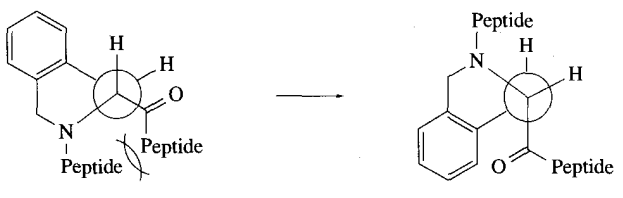


(**68**) (**69**)

(**70**) R = Me
(**71**) R = Et
(**72**) R = Pr^n
(**73**) R = Ph



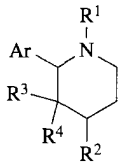
(**74**)



(**75**)

(13)

The preferred conformation of piperidines and their biological activity, this time their analgesic properties, has been the motivation for the investigation of the C—C sp^2–sp^3 rotational barriers of 3,3-dimethyl-2-(3,4,5-trimethoxy)-4-piperidones and piperidinium salts, and their ketal derivatives (**76**), for which nuclear Overhauser effects are diagnostic ⟨84JHC715⟩. The possibility of several concurrent dynamic processes as well as the restricted rotation of the aromatic group—nitrogen inversion, piperidine ring inversion, free base–conjugate acid equilibria—make the analysis a complex one. Dynamic ^1H and ^{13}C NMR studies of the 3-methyl, the 2-(3-indolyl) and the *N*-methyl and *N*-formyl derivatives (**76**) enable the elucidation of the influence of *N*- and 3-substituents on the rotational barrier to trimethoxyphenyl and to indolyl ⟨86T3957, 89H(29)2185⟩. Similarly, in the *N*-hydroxy- and *N*-acyloxy-2,2,6,6-tetramethylpiperidines (**77**), conformational processes involve ring inversion, nitrogen inversion, and rotation about the N—O bond; of these, temperature-varying dynamic NMR measurements reveal the nitrogen inversion barrier to be the major contributor to the interconversion of structures (**77**) in $CDCl_3$, being usually of the order of 12 kcal mol^{-1} (50 kJ mol^{-1}) ⟨92JCS(P2)1027⟩.

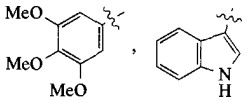


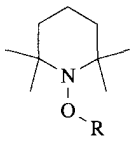
(**76**)

R^1 = H, Me, CHO

R^2 = =O,

R^3, R^4 = H, Me

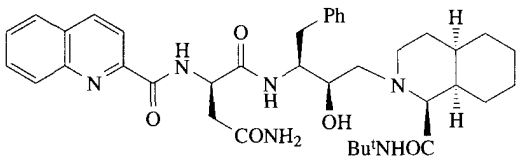
Ar = 



(**77**)

R = H, CHO, COMe, COBu^t, $COCF_3$

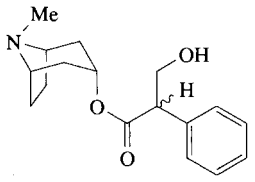
Both *N*- and 4-substituted pyridines also have pharmaceutical importance, and here again proton and ^{13}C NMR studies give insight into their conformations and thus their enzyme-binding propensities ⟨83TL1855, 89MRC964⟩. The crystal structure of the HIV proteinase inhibitor Ro 31-8959 (**78**), containing the decahydroisoquinoline nucleus, has been measured in its protein-bound conformation ⟨91JMC3340⟩. This shows similar structural features to those observed for the compound in solution, which were elucidated ⟨93JCS(P2)475⟩ by proton NMR on the two *cis*- and the two *trans*-bridged isomers of decahydroisoquinoline-3-(*S*)-carboxylic acid. The system (**78**) was shown to have the *cis* bridge with equatorial *N*-CH_2 and CONHBu^t groups, although obviously in the bound structure the proteinase active site demands deviations from the staggered geometry favored in solution.



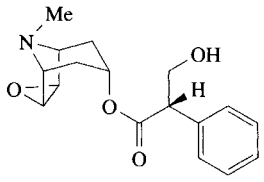
(**78**)

Among the plethora of new theories and refined experimental techniques, old favorites still appear to be alive and well, and therefore it is good to record again in this review the use of model compounds for elucidation of chemical problems. Thus, the protonation of the N atom of piperidines (counterions $MeSO_2O^-$, Cl^- or Br^-) leads to two epimers, normally only detectable, if at all, by very low-temperature NMR. However, the alkaloid structures (**79**)–(**83**), atropine, scopolamine,

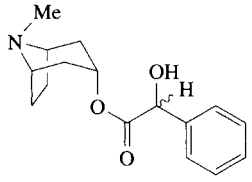
homatropine, benzotropine, and cocaine, constitute model systems for the definition of this problem, since they contain a rigid piperidine nucleus. Major and minor components were observed in the protonated forms in both ^{1}H and ^{13}C NMR through the doublet multiplicity of the ^{+}NH—Me grouping ⟨88JOC2172⟩, and the peak assignments were checked by solid-phase ^{13}C NMR. In CD_2Cl_2 the equatorial/axial ratio for the methyl group is 18.1 for all five tropane salts; in D_2O it is 7.1 for all except scopolaminium bromide (**80**), where it is 1 : 18 (i.e., predominantly axial, as it is in the crystalline state) and the salt of cocaine (**83**), where only the equatorial isomer could be observed.



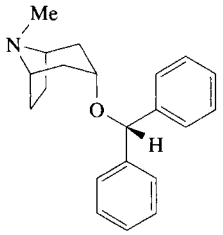
(79)



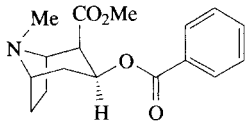
(80)



(81)



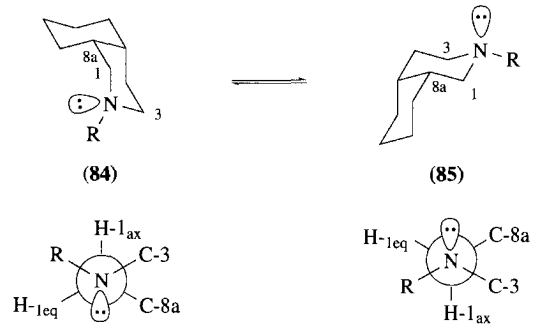
(82)



(83)

The conformational situation in piperidine and *N*-methyl- and *C*-methylpiperidines has been well summarized ⟨85JA1907⟩, and it is pointed out that the assumption that the hydrogen on nitrogen in piperidine is equivalent to that on carbon in its van der Waals characteristics is incorrect. Indeed, molecular mechanics calculations using the MM2 force field show that in fact the H/H axial and the lone pair (lp)/H axial interactions are actually attractive, at about -0.02 and -0.03 kcal mol^{-1} (0.08 and 0.12 kJ mol^{-1}), respectively. The resultant difference in energies of the two conformers is found to arise solely from torsional terms and is only 0.06 kcal mol^{-1} (0.25 kJ mol^{-1}), with virtually identical structures for the two conformers, and an overall preference for the N—H equatorial form of merely 0.30 kcal mol^{-1} (1.25 kJ mol^{-1}). The calculated energy difference for the *N*-methyl compound is 2.50 kcal mol^{-1} (10.5 kJ mol^{-1}), with the steric preference for the methyl group axial being dominated by bending and torsional terms. The calculated dipole moments for both piperidine and *N*-methylpiperidine (1.10 and 0.64 Debye respectively) are close to experimental values, and confirm the validity of the calculations. These calculations also bear out, partially at least, the observed high conformational preference for 2-methylpiperidine (2.11 kcal mol^{-1}; 8.82 kJ mol^{-1}), due to the shorter C—N bond length and ring puckering around the nitrogen atom, causing an increase in 2,6-*syn*-diaxial repulsions compared to those in methylcyclohexane.

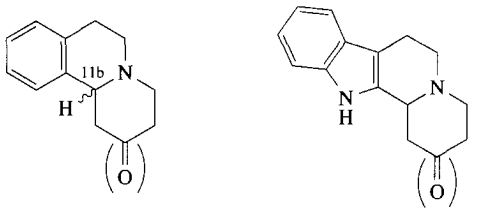
This distortion of the piperidine ring is also increased by increasing the bulk of the substituent at nitrogen ⟨82JOC3890⟩, resulting in a flattening and a greater mobility, thus suggesting that this may aid complexation ("drugs cannot act unless they bind"—Ehrlich ⟨1897MI 501-01⟩) of piperidine-containing drugs with the receptor site. On the other hand ⟨84JCS(P2)583⟩, the position of conformational equilibria in *N*-alkyl-*cis*-decahydroisoquinolines, involving conformational forms (**84**) and (**85**) (Equation (14)) is related to the inductive effect of the *N*-substituent: (**84**)/(**85**) = 0.43 for R = H; 0.61 for Me; 1.17 for Et; 1.05 for Pr^{i}; 0.48 for CH_2CF_3; 0.28 for CH_2CCl_3 at ≈220 K. In this system, ring-puckering cannot effect the results because, as the Newman projections show, the *gauche* interactions involving R are identical in both conformers (**84**) and (**85**). The important factor here must therefore be the magnitude of the *gauche* propylamine (lone pair) interactions, which do differ between structures (**84**) and (**85**), becoming more severely repulsive as a result of electron repulsion from the *N*-substituent. A further factor, intramolecular Coulombic interactions arising from the inductive effects of the C—N and C—halogen bonds, arises in explanation of the ring inversion equilibria in 4-chloro-, 4-bromo-, and 4-methoxy-1-alkylpiperidines in $CFCl_3$–$CDCl_3$ at 192 K ⟨84JCS(P2)737⟩.



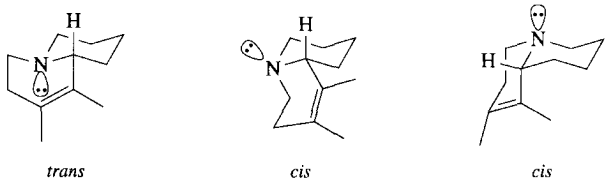
(14)

(84) (85)

Synthesis of benzo[*a*]quinolizidines ⟨88H(7)1653⟩ and -2-ones ⟨87T3021⟩ (**86**), and indolo[2,3-*a*]-quinolizidines (⟨89JOC5591⟩, but see also ⟨94T4873⟩) and -2-ones ⟨90T4443⟩ (**87**) has posed the question of the configuration of the fused ring. The ^{1}H NMR of the methine proton at C-11b, from its chemical shift and signal multiplicity, shows the rings to be *trans*-fused (Scheme 7).



(86) (87)



trans *cis* *cis*

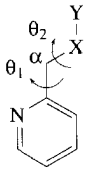
Scheme 7

(ii) Pyridines

Comparison of the preferred conformations of 2-alkylpyridines with those of the corresponding alkylbenzene in the gas phase, utilizing mass-resolved excitation spectroscopy (time-of-flight mass spectroscopy) backed up with semiempirical MOPAC 5/PM3 calculations, shows that whereas in toluene the methyl group is essentially a free rotator, the motion of the methyl group is highly hindered in both the ground (S_0) and excited states (S_1) of 2-methylpyridine ⟨92JA5269⟩. Conformations of other alkyl groups may be defined by torsional angles θ_1 and θ_2 as shown in Figure 7; here again there are significant differences between the benzenoid and pyridinoid cases. Thus, for 2-propylpyridine (propyl being a so-called Janus type group ⟨85TL4673⟩, capable of presenting either an ethyl or *t*-butyl type face towards a site of steric consideration) there are two populated conformers, one *gauche* together with the most stable *anti* conformer, in which θ_1 is about 17°, while 3-methyl-1-propylbenzene exists in three conformations, two *gauche* and one *anti*. These and other differences come about because of the attraction between the electronegative nitrogen in pyridine and the electropositive hydrogen atoms.

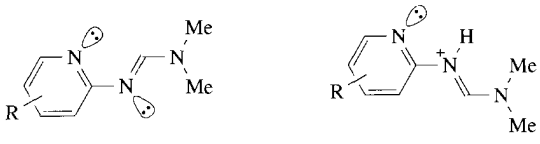
In the 2-substituted amidines, ^{1}H NMR NOE effects reveal the *anti* conformer (**88**) to be predominant in $CDCl_3$, because of repulsion between the nitrogen lone pairs in the alternative conformer ⟨92JCS(P2)331⟩. This preference is retained on protonation at the imino nitrogen with CF_3COOH in $CDCl_3$, but the *syn* form (**89**) for the conjugate acid takes over when R is electron-donating and the solvent is DMSO.

The influences of alkyl substitution have been explored for a number of polymethyl 3- and *N*-isopropylpyridine derivatives ⟨83T4209⟩. On cooling, two conformers can be observed and the



$\theta_1 = \theta$ (N–C_{ipso}–C_α–X)
$\theta_2 = \theta$ (C_{ipso}–C_α–X–Y)

Figure 7 Torsion angles for alkylpyridines.



(88) **(89)**

R = 4-Me, 5-Me, H
5-Cl, 5-Br, 5-NO_2

rotational barriers can be obtained by dynamic NMR techniques using line shape analysis. Barriers to rotation of the isopropyl group in the 3-position when flanked by methyl groups are of the order of 11.5 kcal mol^{-1} (48.1 kJ mol^{-1}) in $CHFCl_2$ solvent (see Figure 8), and several kcal more than this, in CH_3CN and C_5D_5N solvent, for the shortened C—N^+ bond, as expected (see Figure 9). These processes, in which the isopropyl groups take up the "gear-clashed" conformation shown have also been examined by molecular mechanics calculations (MMI), which confirm the gear-clashed stance of the isopropyl group in these situations.

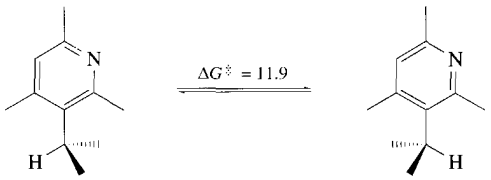


Figure 8 Barrier to rotation (kcal mol^{-1}) for the isopropyl substituent in 2,4,6-trimethyl-3-isopropylpyridine. (1 kcal mol^{-1} = 4.186 kJ mol^{-1}).

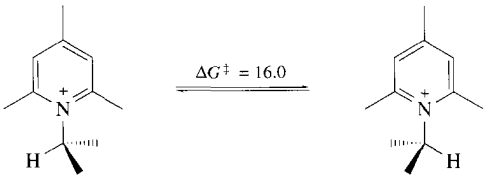
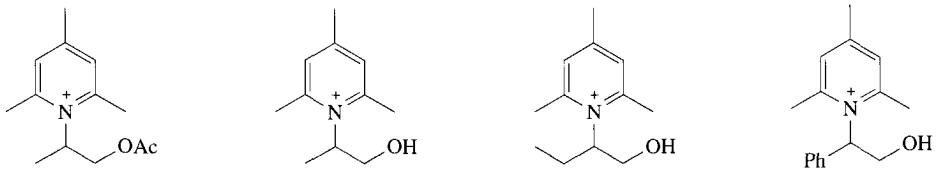


Figure 9 Barrier to rotation (kcal mol^{-1}) for the isopropyl substituent in 2,4,6-trimethyl-*N*-isopropylpyridine. (1 kcal mol^{-1} = 4.186 kJ mol^{-1}).

Further studies on hindered rotation around the C—N^+ bond ⟨84T2547⟩ employing ^1H dynamic NMR shows barriers as designated in structures (**90**)–(**93**) (Figure 10). The effect of increasing bulk and complexity of the pyridinium *N*-substituent is clearly seen, while the barriers given in structures (**94**), (**95**), and (**96**) (Figure 11) show again the influence of the reduced length of the C—N^+ compared to the C—C bond. The chemical nonequivalence of the 2,6-dimethyl groups and of the

3,5-CH groups are clearly seen in Figures 12 and 13, for structure (**92**) (^{1}H NMR) and structure (**91**) (^{13}C NMR), respectively, measured in deuterated pyridine. Indeed, the noncoalescence of the diastereotopic hydrogens in the *N*-substituent of (**92**) occurred even at 110°C, the maximum temperature possible with the solvent used, which is indicative of the high rotational barrier.



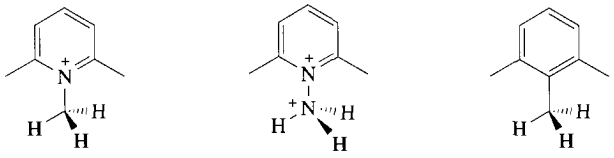
17.2 kcal mol^{-1} (71.9 kJ mol^{-1}) **(90)**

16.4 kcal mol^{-1} (68.6 kJ mol^{-1}) **(91)**

19.3 kcal mol^{-1} (80.7 kJ mol^{-1}) **(92)**

15.0 kcal mol^{-1} (62.7 kJ mol^{-1}) **(93)**

Figure 10 N—C rotational barriers in 2,4,6-collidinium salts.



16 kcal mol^{-1} (67 kJ mol^{-1}) **(94)**

16 kcal mol^{-1} (67 kJ mol^{-1}) **(95)**

13 kcal mol^{-1} (54 kJ mol^{-1}) **(96)**

Figure 11 N^+—C, N^+—N^+, and C—C rotation barriers in 2,6-dimethyl-substituted six-membered rings.

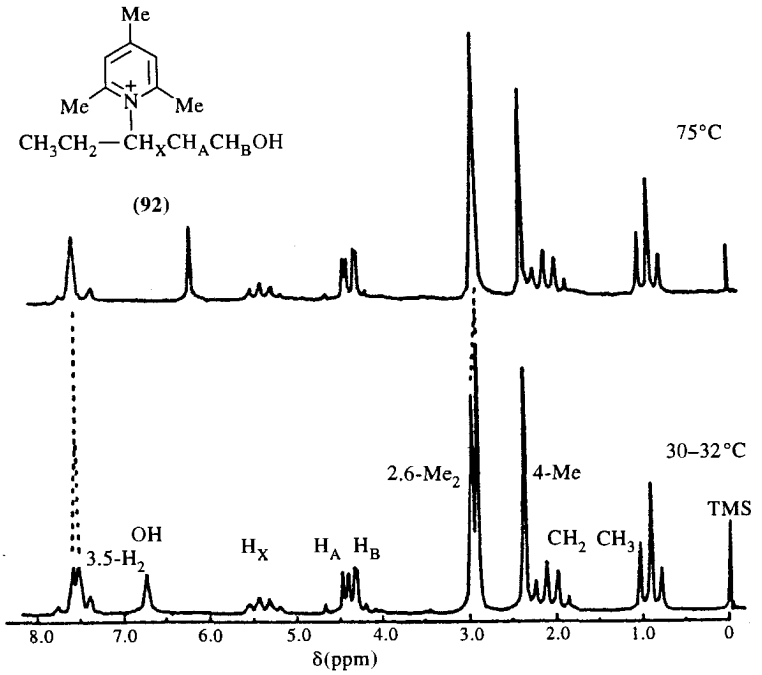


Figure 12 The chemical shift nonequivalence of the 2,6-Me_2 groups and of the 3,5 aromatic protons in the ^{1}NMR spectrum (60 MHz) of the compound (**92**) at room temperature and the coalescence of the signals at higher temperature, in solvent C_5D_5N. (Reproduced with permission from ⟨84T2547⟩).

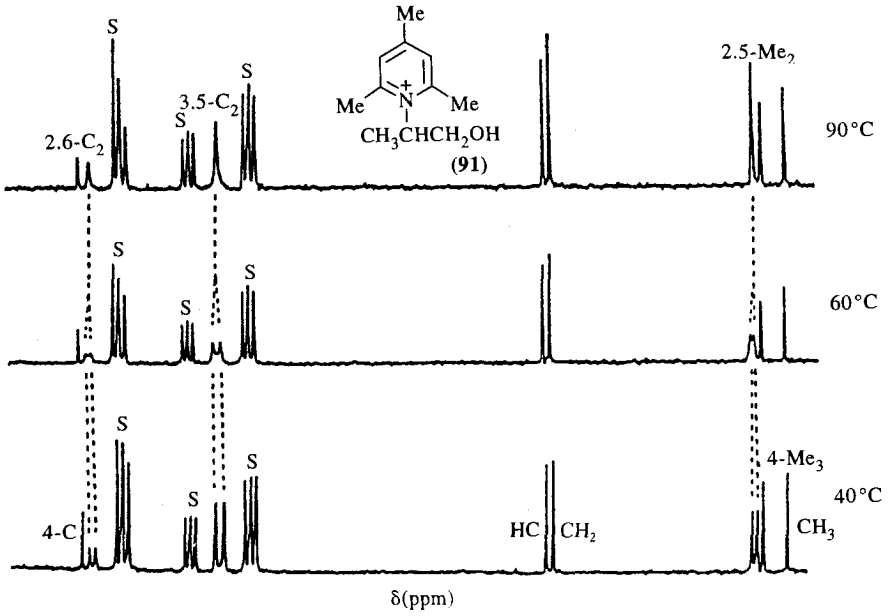
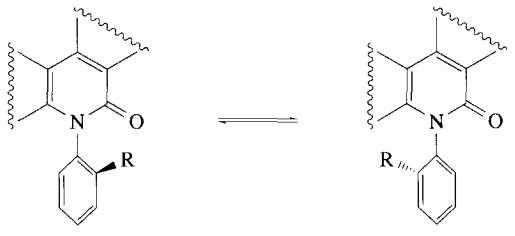
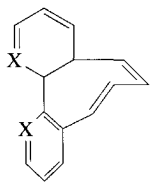


Figure 13 The chemical shift nonequivalence of the 2,6-Me_2 and the 2,6 and 3,5 aromatic carbons in the ^{13}C NMR spectrum (25.2 MHz) of the compound (**91**) at 40 °C and the coalescence temperature of the signals at higher temperature in C_5D_5N. S refers to solvent (pyridine carbon atoms). Peak assignments on the top spectrum are for signals which coalesce on heating; assignments are indicated on the lower spectrum. (Reproduced with permission from ⟨84T2547⟩).

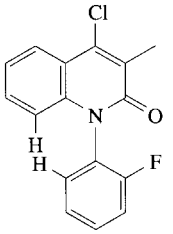
In fact, separation of enantiomers (**97**) and (**98**) (Equation (15)) may be achieved in the case of sterically hindered *N*-aryl-2(1*H*)-quinolones and *N*-aryl-6(5*H*)-phenanthridones using liquid chromatography on triacetylcellulose with aqueous ethanol as eluant; barriers to rotation may then be determined by thermal racemization. These barriers are given in Figure 14. The same separative method (with addition of a little ammonia to prevent acid-catalyzed racemization) may be used to obtain the enantiomers of cycloocta[2,1-*b*:3,4-*b*']dipyridine (**99**; X = N) ⟨92JCS(P2)1625⟩, between which there is a barrier of 25 kcal mol^{-1} (104 kJ mol^{-1}), some 0.5 kcal mol^{-1} lower than for the hydrocarbon (**99**; X = CH). The CD spectrum and CNDO/S calculations enable distinction of the (*R*)- and (*S*)-isomers. The enantiomers have a tub-shaped cyclooctatetraene ring, as represented for one in structure (**99**), and the angles between the pyridine rings, between the bridge double bonds, and between a double bond and a ring are 62.4°, 62.8°, and 65.2°, respectively.



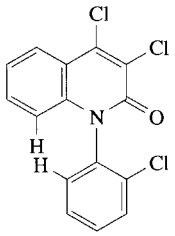
(97) (98) (15)



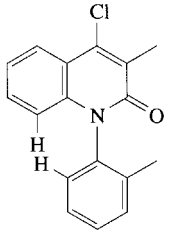
(**99**)
X = N, CH



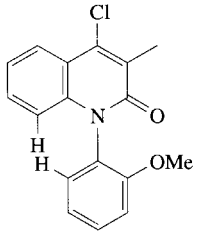
105.1 (53°)



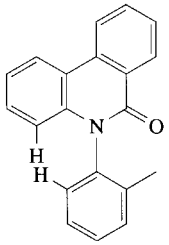
127.4 (129°)



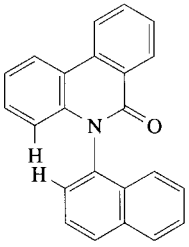
127.2 (129°)



118.8 (85.7°)



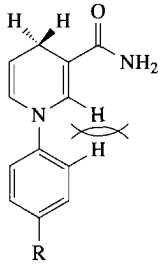
119.3 (80.5°)



126.5 (109.6°)

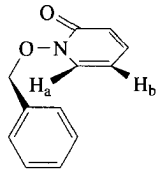
Figure 14 Barriers to rotation (kJ mol^{-1}) between enantiomers (**97**) and (**98**).

The standard of performance of MO calculations in this sort of situation has received attention in studies on the biologically important substituted 1-phenyl-1,4-dihydronicotinamides (**100**) ⟨90T319⟩. The semiempirical all-valence-electron SCF methods, MNDO and the AM1 approximations, perform somewhat differently. The AM1 method produces values of 38.7° and 33.8° for phenyl twist, representing a compromise between resonance stabilization in the planar structure (greatest for R = NO_2) and the *ortho*-hydrogen steric repulsion shown in (**100**). MNDO, however, appears to neglect the resonance effect and in this case the phenyl ring is predicted to be perpendicular to the dihydropyridine ring.

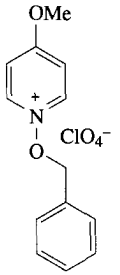


(**100**) R = H, NO_2

Rotation about the N—O bond is also hindered. In the case of cyclic hydroxamic acids the barrier is 9–10 kcal mol^{-1} (38–42 kJ mol^{-1}). In the ground state, the conformation of 1-benzyloxy-2-pyridone is as depicted in structure (**101**), as deduced from the upfield shift of H_a and H_b and downfield shift of the benzylic protons in ^1H NMR in chloroform at room temperature. Because of the high N—O rotation barrier, this may also be assumed to be the conformation in the vibrationally unrelaxed singlet excited state ⟨90JCS(P2)499⟩. The N—O bond in this type of compound is much longer than in pyridine *N*-oxides (for pyridine *N*-oxide it is 129.3 pm). Thus, x-ray crystallographic measurements reveal the N—O bond length in 1-benzyloxy-4-methoxypyridinium perchlorate (**102**) to be 140.1 pm, typical of an N—O single bond ⟨91JCS(P2)69⟩. The molecule has a *trans* conformation around the central C—O bond (although both AM1 and PM3 calculations predict the *gauche* isomer to be more stable than the *trans* isomer by about 4 kcal mol^{-1} (17 kJ mol^{-1}) in the gas phase: see comments on the relative performance of MO methods earlier in this Section), and the aromatic rings are inclined at an angle of 9.1° to one another.



(**101**)

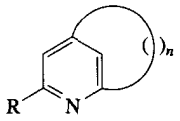


(**102**)

X-ray crystallographic ⟨83JCS(P2)1585⟩ as well as ^1H NMR measurements also give information on the complexation of lanthanide shift reagents (LSR) to alkylpyridines. As expected, these studies reveal that there can be pronounced steric interactions with alkyl groups in the 2- or 2,6-positions. In such cases, coordination may also be more effective with $Ln(fod)_3$ (fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dione) than with $Ln(dpm)_3$ (dpm = 2,2,6,6-tetramethylheptane-3,5-dione) ⟨85TL4673⟩. Conformational alterations may thus be observed on complexation, and therefore shift reagents must be used with caution in structural assessments.

Pyridinophanes (**103**; R = Ph, $n = 7$–9) show equivalence of the geminal benzylic protons in their ^1H NMR in CD_2Cl_2, indicative of rapid flipping of the methylene chains ⟨90JCS(P1)1119⟩ at room temperature. On cooling to −60 °C, (**103**; $n = 7$) shows a signal at δ −1.45 due to H_{endo} (Figure 15), and the geminal protons appear as four independent signals, from the coalescence temperature of which (20 °C) an energy barrier to ring flip of 12–13 kcal mol^{-1} (50–54 kJ mol^{-1}) can be estimated. In contrast, for the smaller ring (**103**; $n = 6$), the coalescence temperature is 150 °C, with a concomitant energy barrier of 21–22 kcal mol^{-1} (88–92 kJ mol^{-1}), while a multiplicity of methylene

signals not found for its homologues indicate that in this case there is not only flipping of the ring but also pseudorotation (Figure 16). Variable-temperature ^{13}C NMR with line shape analysis gave $\Delta G^{\ddagger}$ for this process of 9.8 kcal mol^{-1} (41.0 kJ mol^{-1}) with a coalescence temperature of -30°C.



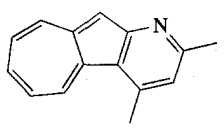
(103)

Figure 15 Ring flipping in the pyridinophane (**103**; n = 7).

Figure 16 Pseudorotation in the pyridinophane (**103**; n = 6).

The ^1H NMR of the series (**103**; $n = 7$–9) also gives evidence for steric compression between the methylene bridge and the 3-H aromatic proton, which moves downfield as the ring gets smaller. In structure (**103**; $n = 6$), however, this proton moves to higher field, which has been ascribed to a decrease in the aromaticity of the pyridine ring due to distortion. This interpretation is confirmed by UV spectroscopic characteristics and MNDO calculations.

Azuleno[2,1-*b*]pyridine (**104**) and azuleno-annulated [n](2,4)pyridinophanes (**105**; $n = 6$–9) reveal ^1H NMR aromatic patterns which can be interpreted in terms of electron withdrawal from the azuleno system by the pyridine ring. As well as this effect, those recorded above for structures (**103**) make their appearance in this series also. Thus, in the case of (**105**), steric compression between H-3 on the pyridine ring and the methylene chain, and further, where $n = 6$, a distorted pyridine ring with a reduced ring current, can be discerned by the same methodology ⟨94JOC1309⟩. In (**105**; $n = 7$–9) the geminal protons in the benzylic positions again give a single signal at room temperature, indicative of rapid ring flipping, for which low-temperature measurements permit the measurement of the separate signals and thus the coalescence temperature. For structure (**105**; $n = 7$), this temperature is -30°C, and the corresponding barrier is 10.8 kcal mol^{-1} (45.1 kJ mol^{-1}), but for the restricted situation when $n = 6$ the coalescence temperature is 90°C, with a barrier of 18.1 kcal mol^{-1} (75.7 kJ mol^{-1}).



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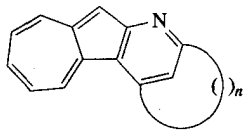


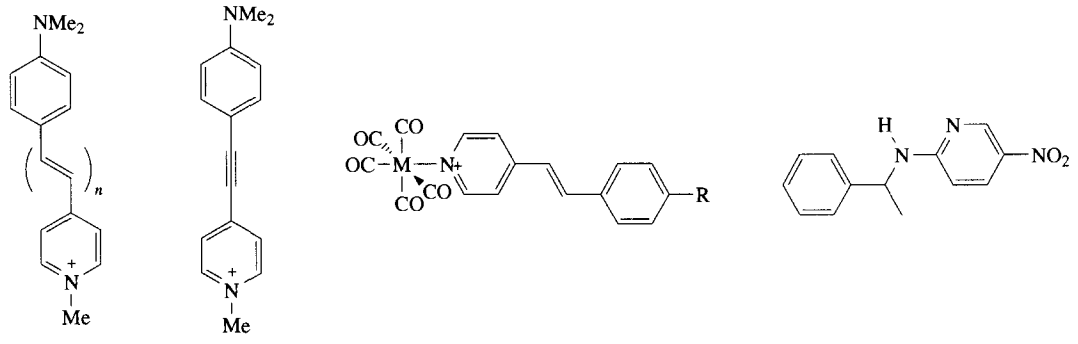
(105)

5.01.3 SUPRAMOLECULES AND SUPRAMOLECULAR ASSEMBLAGES: NEW MATERIALS, BIOMIMETIC STRUCTURES, AND HOST–GUEST COMPLEXES

The chemistry of supramolecules forms an area of ever-increasing interest and application, arising from the extreme importance of such molecules, whether viewed in an academic or an applied light. Supramolecules are molecular assemblages, aggregates, or associations and pyridine derivatives,

particularly the bipyridines ⟨84AHC281⟩ and acridine, frequently play a key role in their construction and thus in their subsequent structure and behavior.

In the realm of new materials and molecular devices, nonlinear optics (NLO) deals with the interaction of applied electromagnetic fields with chemical compounds, resulting in a change of frequency or phase. Molecules are required of the form in which an acceptor functionality is linked via a conjugate system to a donor function. An example from 1994 is the incorporation of active components (**106**) and (**107**) in self-assembled superlattices, which show a wide variation in hyperpolarizabilities with structure ⟨94CRV195⟩. ZINDO (intermediate neglect of differential overlap, parameterized for transition metal systems) MO calculations give a good account of the variation in λ_{max} (e.g. for (**105**), computed 479 nm, experimental 509 nm). This type of molecule may also be tuned by complexation, as in the complexes (**108**). Here ZINDO computations for M = Cr can predict the electronic transitions to the excited state which governs NLO properties. (+)-2-[(α-Methylbenzyl)amino]-5-nitropyridine (**109**) is a further NLO molecule, in this case added to a charge-transporting polymer ⟨94CRV127⟩.



(**106**) n = 1,2 (**107**) (**108**) R = NO_2, CHO, H, NMe_2 (**109**)

Assembling [2]rotaxanes (wheel and axle) can involve three basic processes (Figure 17). The latest of these ⟨93CC1269⟩ involves slippage, in which the axle (**110**) is linked by a 4,4′-bipyridine, and the wheel (**111**) is a bisparaphenylene-34-crown-10 ether. Heating the two components in acetonitrile at 60°C yields the rotaxane, which can be characterized by FABMS and ^{1}H and ^{13}C NMR, but extrusion of the wheel occurs at 100°C. In other developments ⟨94NAT(369)133⟩, the pyridine component may be incorporated in the wheel, as in structure (**112**), where two bipyridinium units are connected by *p*-xylyl groups, and here the rotaxane acts as molecular switch. At room temperature in acetonitrile the wheel moves at random along the axle, but favors the benzidine station at 229 K. In acid solution, the amino groups on the axle are protonated, repelling the positively charged wheel, and this is subsequently restricted to the biphenol area.

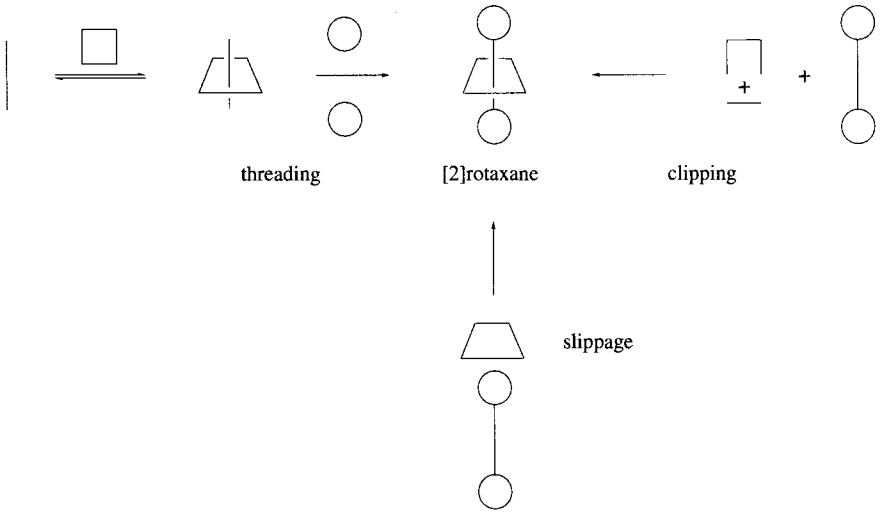
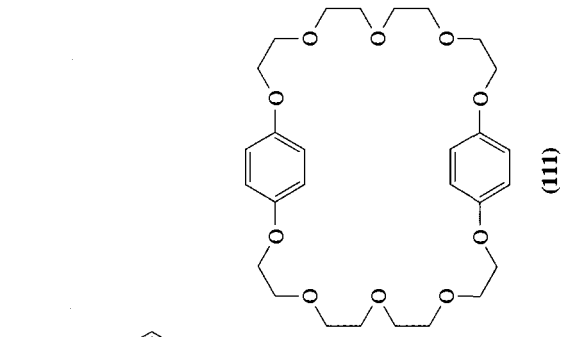


Figure 17 Assembling (2)rotaxanes.



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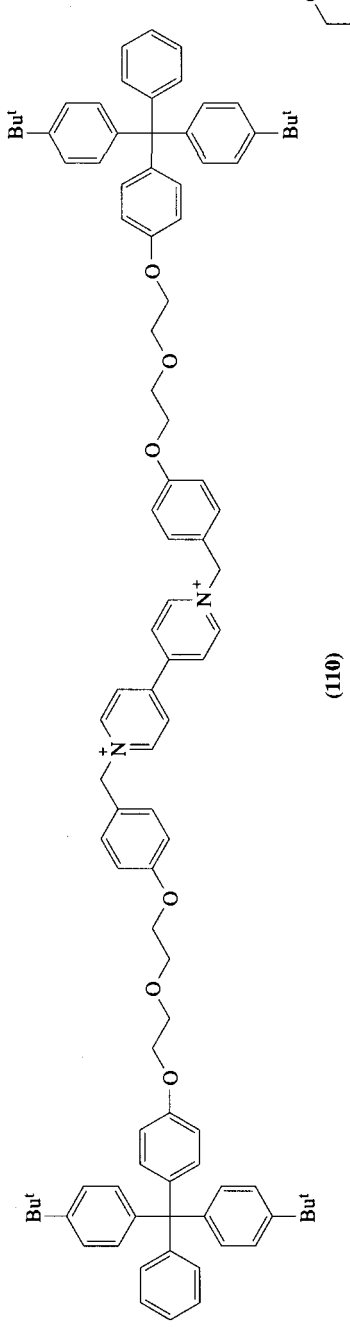

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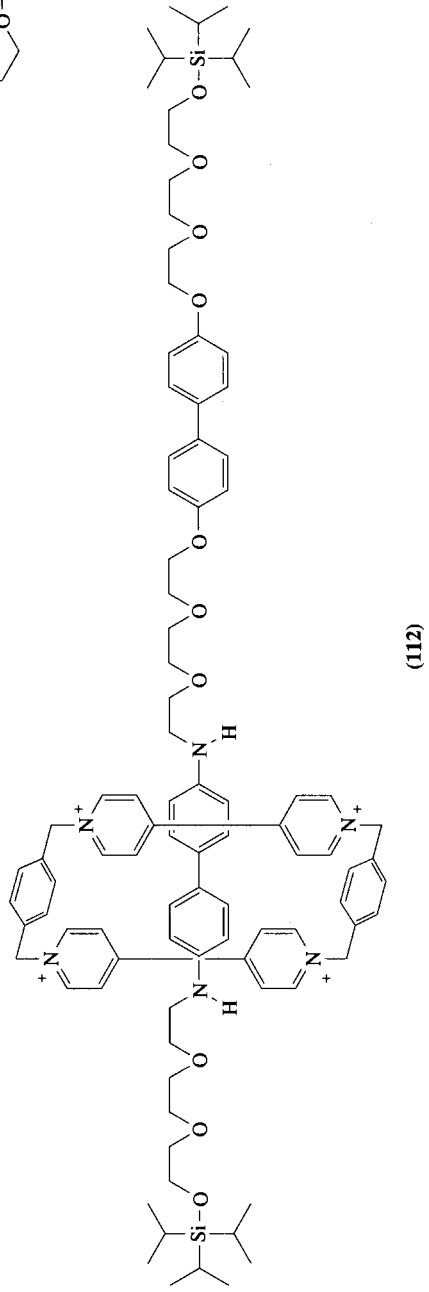
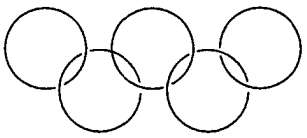


(112)

The wheel designated in structure (**112**), i.e., cyclobis(paraquat-*p*-phenylene), has also been utilized for the two terminal units of the unique [5]catenane olympiadane (**113**), these units being linked to the central unit, cyclobis(paraquat-4,4′-biphenylene), by two trisnaphthol [57]crown-15 molecules ⟨94AG(E)1286⟩.



(**113**)

1,4-Bipyridine also features in the inorganic cyclophane $[(en)M(4,4'\text{-bipyridyl})]_4$, bearing eight positive charges ⟨91TL5589⟩, where M is palladium or platinum, en is ethylenediamine, and the counterions are nitrate. This promises to be a discerning host towards its guests, in that the complexation is influenced by hydrophobic, electrostatic and charge transfer interactions as well as steric effects.

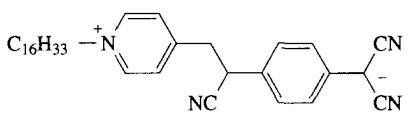
Cyclobis(paraquat-*p*-phenylene) can also function as a cyclophane ⟨93JA5298⟩, within whose cavity a large number of benzenes may be incorporated as electron donors, for which x-ray studies indicate virtually coplanar π-systems. Table 8 gives the characteristics of some of these complexes, the absorption bands of which are ascribed to charge transfer interactions within the inclusion complex, for electron-rich 1,4-disubstituted benzenes. An ultrashort laser pulse excites electron transfer to yield the radical cation of the cyclophane, the rate of decay of which is linearly related to ΔG°, the exergonicity of absorption. It may be noted in Table 8 that the maximum of the Gaussian-shaped absorption bands λ_{max} depends on the electron donor properties of the aromatic molecule, i.e., the ionization potential, while the association constant reflects the size and thus the van der Waals contact forces.

Table 8 Characteristics of charge transfer complexes formed between cyclobis(paraquat-*p*-phenylene) and aromatics in acetonitrile solution.

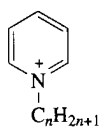
Donor	K (mol^{-1})[a]	V (cm^{-1})[b]	λ_{max} (nm)[c]
Benzene	17		290
Toluene	16		319
p-Dichlorobenzene	3		312
p-Dimethoxybenzene	18	1300	475
p-Diaminobenzene	112	1570	655
p-Dimethylaminobenzene	42	1800	820

[a]K = Association constant. [b]Degree of electronic coupling. [c]Absorption band.

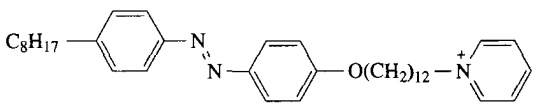
Conducting Langmuir–Blodgett films also involve deposition procedures for conducting layers involving supramolecular organization of acceptor and donor molecules. These must be amphiphilic (i.e., have a polar head and a hydrophobic body), and ones for which charge transfer interactions may occur ⟨B-93MI 501-02⟩. A number of pyridine-based structures fall into this category—(**114**), (**115**), and (**116**).



(**114**)

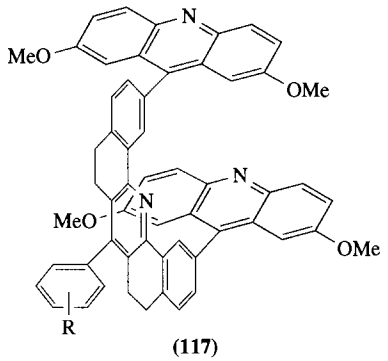


(**115**)
$n = 18, 22, 24$



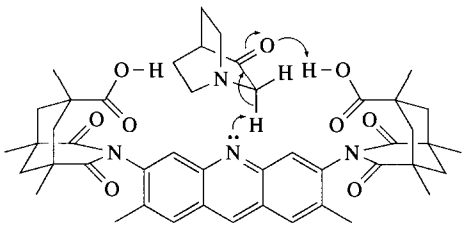
(**116**)

A new class of host has been described which contains two acridine chromophores held cofacially by a rigid dibenz(*c,h*)acridine spacer ⟨89JA8528⟩, so-called molecular tweezers. The complexing properties of these hosts towards guest molecule 2,4,5,7-tetranitrofluorenone have been examined, and in this case the sandwiching effect well outweighs charge transfer effects. Thus the association constants for (**117**) are 3400 mol^{-1} (R = 3,5-diBu^t) and 700 mol^{-1} (R = 4-Bu^t), but only about 3 mol^{-1} for the charge transfer complex with 2,7-dimethoxy-9-phenylacridine.



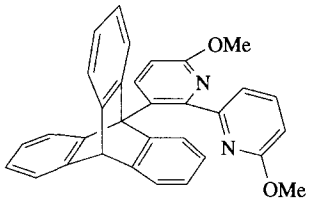
(**117**)
R = 3,5-diBu^t, 4-Bu^t

Among the best-known biomimetic hosts is that described for the acridine-derived acid (**118**) ⟨88JA923, 90ACR399, 91JA1453⟩. In this host, the acridine unit often assumes merely the role of an inert spacer but, for the enolization of quinuclidone shown, the binding of the guest and its subsequent reaction are intimately controlled by the acridine basic center.

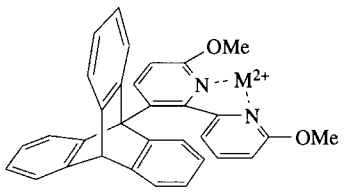


(**118**)

A further novel structure is afforded by the molecular brake (**119**)/(**120**) ⟨94JA3657⟩. With the brake disengaged, the triptycene moiety spins freely (**119**); when the brake is engaged by complexation of the bipyridyl unit with M^{2+}, for example Hg^{2+}, rotation is arrested (**120**).



(**119**)



(**120**)

5.01.4 SUMMARY

In this review, the continuing importance of measurements of the fundamental structure of simple pyridine derivatives and the nature of their interactions in solvent media, and the solvent's influence on their structure have been discussed. Some of these systems are now so well authenticated (for example, the 2- and 4-pyridone tautomerism and the solvent and media influence thereon) that roles may be reversed and the systems may often be utilized as model testing grounds for new experimental or theoretical techniques. Even so, there is still much here for more precise experimental definition,

in particular the perennial question of what is meant by aromaticity, particularly in heterocyclic systems.

Nevertheless, both for the subject under discussion and in general, the main thrust of work and expenditure of research capital comes in two areas: the chemistry–biology interface, specifically the interaction between substrates and proteins (enzyme surfaces), and the chemistry of new materials and supramolecular assemblages and devices. Both represent big group and big expenditure scenarios, and are cross- and inter-disciplinary to a very great extent, which provides them inevitably with enormous potential for profound scientific insight and innovation. Indeed, these two subject areas are not themselves mutually exclusive—the latter division contains as a vital subunit biomimetic systems, as has been noted above. And within these divisions, as the author has attempted to show, pyridine derivatives have an absolutely vital part to play; but it will certainly occupy increasingly larger attention in any future discussion of pyridine architecture.

The advances in computing and the ready availability of suitable packages means that molecular orbital calculations are now routinely carried out, and this trend is manifest in the area under survey. Nevertheless, there are still discrepancies here, as has been noted in individual cases, and once again the area may prove to be a useful testing and authenticating ground for this type of methodology.

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5.02
Pyridines and their Benzo Derivatives: Reactivity at the Ring

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5.02.1 GENERAL REACTIVITY PATTERNS

5.02.1.1 Neutral Molecules

Pyridines and their benzo derivatives contain one nitrogen atom in a six-membered aromatic ring. The electron-deficient nature of these heterocycles, as compared to the corresponding benzenoid compounds, can be attributed to the electron-withdrawing, inductive (I), and mesomeric (M) effects of the nitrogen atom. These (M) effects are more pronounced at the C-2 and C-4 positions as compared to C-3 (Figure 1).

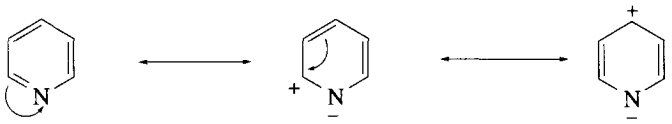


Figure 1 Mesomeric effects.

Even with this electron-deficient nature, pyridines undergo electrophilic substitution. Compared to benzene, the 3 position of pyridine is considerably less reactive towards electrophilic attack due to deactivation by the ring nitrogen. Under harsh conditions, some pyridines do undergo electrophilic substitution at C-3, as evidenced by their nitration in low yield. In benzo derivatives of pyridine, because the deactivating effects of nitrogen are attenuated in the distant ring(s), electrophilic attack occurs in the benzene ring (Figure 2).

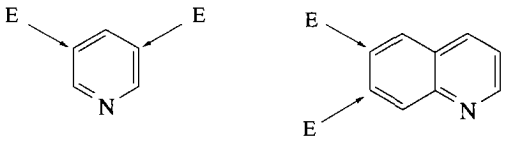


Figure 2 Regiochemistry of electrophilic substitution.

The reactivity of pyridine has been well studied theoretically, employing Hückel and extended Hückel methods ⟨59JA1935, 62JCS4881, 65CCC355, 67T2513, 68CCC3138, 90AHC(47)318⟩. The σ^+ values for pyridine as the free base were determined in the gas phase and are shown in Figure 3 ⟨62JCS4881, 71JCS(B)2382, 90AHC(47)318⟩. The π-electron densities and localization energies for pyridine have been calculated (Figure 4) and, based on these values, the electrophilic reactivity order for pyridine is $3 \gg 2 \gg 4$. By comparison, the 3-position of pyridine is as deactivated as the *meta* position of chlorobenzene, and the 2- and 4-positions are as reactive as the *ortho* and *para* positions in nitro-

benzene ⟨62JCS4881, 90AHC(47)318⟩. The deactivation at the 4-position is due to the accumulation of positive charge at C-4 in the highest occupied molecular orbital.

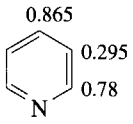


Figure 3 σ^+ Values for pyridine as free base.

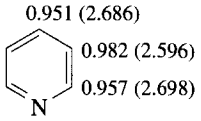


Figure 4 π-Electron densities and (localization energies) for electrophilic substitution.

In contrast, nucleophiles react mainly at the α-carbon of the pyridines. Only very strong nucleophiles (e.g., NH_2^-, RLi, H^-, $NaNH_2$ and OH^-) react readily with pyridines. The reaction of benzo derivatives of pyridine with nucleophiles is more facile than with simple pyridines, and addition can occur at both the α- and γ-position. Nucleophiles react at C-2 and C-4 of quinoline, C-1 of isoquinoline and the 9 position of acridine (Figure 5).

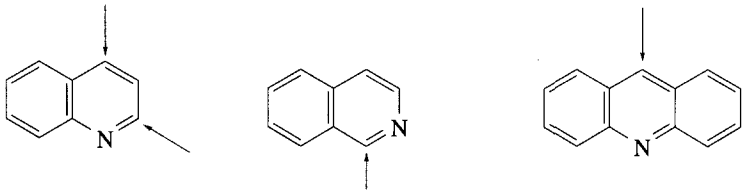


Figure 5 Regiochemistry of nucleophilic substitution.

Free radical reactions of pyridine do not show as high regioselectivity as is observed in electrophilic and nucleophilic reactions. The regioselectivity is mainly dependent upon the nature of the radical. Aryl radicals attack at all three positions, but alkyl radicals preferentially attack the α- and γ-positions, and halogen radicals attack mainly the α-position.

5.02.1.2 Pyridinium Cations

As would be anticipated, pyridinium cations exhibit low reactivity towards electrophiles. Only those pyridinium salts bearing highly activating substituents at C-2 and C-4 react with electrophiles at C-3. Calculated localization energies for the pyridinium cation are given in Figure 6 ⟨59JA1935⟩. However, auxiliary inductive parameters were not used in determining these values, nor was hydrogen bonding taken into account. Similar to neutral benzopyridines, cations of benzopyridines undergo electrophilic reaction on the benzene ring.

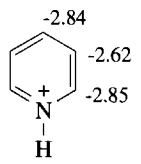


Figure 6 Calculated localization energies.

Various nucleophiles undergo reaction with these cations, for example, hydroxide, chloride, alkoxide, sulfide, cyanide, amines, carbanions, and organometallic reagents. The adducts thus formed, depending upon the reaction conditions and the substituents on the pyridine ring, can be isolated or may undergo further transformation to provide stable products. Pyridinium and benzopyridinium cations react with hard nucleophiles at the α-position (usually) and soft nucleophiles at the γ-position. Radical reactions of these pyridinium cations are also known, as are cycloaddition reactions.

5.02.1.3 Pyridones (Oxo-pyridines)

Electrophilic reactions of pyridones are pH dependent. Under acidic conditions (<pH 6), the neutral molecule is the reactive species, but above pH 6 the conjugate anion is the reactive species. Pyridones undergo electrophilic reactions at the nitrogen and oxygen, as well as in the *ortho* and *para* positions to the oxo group. Electrophilic halogenation of pyridones is quite facile, and regiospecific halogenation can be achieved in many cases. Sulfonation and nitration need highly acidic conditions and are therefore more difficult.

5.02.1.4 *N*-Oxides

N-Oxides of pyridine and their benzo derivatives react with both electrophiles and nucleophiles. Theoretical calculations of π-electron densities and experimentally determined σ^+ values show that the electrophilic reaction of pyridine *N*-oxide occurs with a positional order of 2 > benzene ≥ 4 > 3 (Figure 7) ⟨59JA1935, 75JCS(P2)277, 90AHC(47)321⟩. Calculations using CNDO/2 also suggest the same positional order ⟨71TL387⟩.

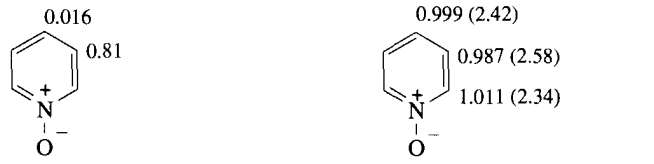


Figure 7

Strong electrophiles like NO_2^+ react at the 4-position, and soft electrophiles (e.g., mercury(II) acetate) react preferentially at C-2. In contrast, *N*-hydroxypyridinium cation undergoes electrophilic reaction at C-3. Electrophiles like alkyl or acyl halides react at oxygen to give the *N*-alkoxy or *N*-acyloxy derivatives. However, in the case of acyl halides, further reaction of the counterion occurs, making isolation of the *N*-acyloxypyridine difficult. Strong nucleophiles react at the α-carbon of the pyridine *N*-oxide, and subsequent rearomatization occurs with loss of the *N*-oxide oxygen. Nucleophiles like cyanide or halide need coordination of the *N*-oxide function with metals or phosphorus reagents before attack at the α- or γ-carbons can occur.

Stated briefly above is a general outline of the reactivity patterns of pyridines and their benzo derivatives. Detailed examination of these reaction types appears in the following sections. The literature between 1981–1994 is reviewed.

5.02.2 ELECTROPHILIC ATTACK AT NITROGEN

Under mild conditions the pyridine nitrogen reacts with electrophiles. These reactions can be categorized into the following groups.

(i) Protonation and salt formation with protonic acids.

(ii) Formation of coordination compounds with Lewis acids.
(iii) Coordinate complex formation with transition metals.
(iv) Quaternary salt formation with acyl and alkyl halides, alkenes, and alkynes.
(v) Formation of *N*-halogen salts with halonium reagents.
(vi) *N*-Oxidation.

A detailed description of most of these reactions is given in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) and only those developments after 1981 are discussed here. The main emphasis is on the reactions of acyl and alkyl halides to form pyridinium salts.

5.02.2.1 Protonation and Salt Formation

The low basicity of pyridine ($pK_a = 5.2$) compared to aliphatic amines ($pK_a \approx 10$) does not prevent the formation of salts and protonation. Several pyridinium salts have been prepared and used as organic reagents. Among them chromium salts of pyridine have become important reagents in organic synthesis because of their mild oxidizing capability ⟨79TL399, 80TL731, 82S245⟩. Pyridinium chlorochromate (Corey's reagent), pyridinium dichromate, and $(Py)_2CrO_3$ (Collins' reagent) are the most widely used. These reagents have been made on polymer support in an effort to make them more convenient to use ⟨81JOC1728⟩. Pyridinium bromide perbromide is a useful brominating agent and has been made in polymeric form ⟨48JA417⟩. Pyridinium 3-nitrobenzenesulfonate is a mild acid catalyst for the formation of ortho ester protecting groups in nucleosides ⟨83JA2044⟩. Pyridinium *p*-toluenesulfonate ⟨77JOC3772, 79S724⟩ and pyridinium trifluoroacetate are used as catalysts in the oxidation of secondary alcohols and can be prepared by treating pyridine with the corresponding acid ⟨79TL399⟩.

Protonation of pyridine is observed upon absorption in the gas phase on Ag/AgX interfaces. The absorbed water on these surfaces is responsible for the protonation ⟨84CPL(107)502⟩. Thermodynamics of both gas phase and aqueous phase protonation of 2-*t*-butylpyridine, 4-*t*-butylpyridine, 2,4-di-*t*-butylpyridine, and 2,6-di-*t*-butylpyridine have been studied ⟨84JA4341⟩. The aqueous basicity of 2,6-di-*t*-butylpyridine is anomalous compared to that of the other alkyl-substituted pyridines; this is attributed to entropy rather than enthalpy effects. The enthalpy change for the transfer of the protonated 2,6-di-*t*-butylpyridine from the gas phase to the aqueous phase is as expected; however, the corresponding entropy change is abnormal. The aqueous protonated 2,6-di-*t*-butylpyridine is hydrogen bonded to a water molecule via the *N*—H bond. The observed loss of entropy is due to the substantial restrictions in the internal rotations in the solution complex of protonated 2,6-di-*t*-butylpyridine, which is not found in other pyridinium ions in aqueous solution. Hydrogen bonding to water at the pyridine nitrogen is probable in a water solution of 2,6-di-*t*-butylpyridine. Results from the calculation of free energy of activation of proton transfer between morpholine, imidazole, 3,4-lutidine, and pyridine were found to be in agreement with experiment ⟨84IZV70⟩.

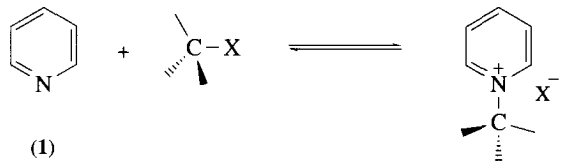
Theoretical evaluation of the difference in free energies of transfer from the gas phase to an aqueous solution of pyridine, 2-fluoropyridine and its conjugated acid has shown the major contributor to be electrostatic interactions in the aqueous phase ⟨85JPC4695⟩. The interaction of pyridine with acetic acid has been studied using viscosity, electric conductivity, and voltammetry ⟨86ZOB1482⟩. A detailed description of the thermodynamics of these salt formations has been dealt with in CHEC-I ⟨84CHEC-I(2)165⟩.

5.02.2.2 Lewis Acids

Pyridines and their benzo derivatives readily form adducts with various Lewis acids ⟨77HC(32-1), 84CHEC-I(2)165⟩, for example, various alkyl- and arylboranes and borane hydrides.

5.02.2.3 Alkyl Halides and Related Compounds

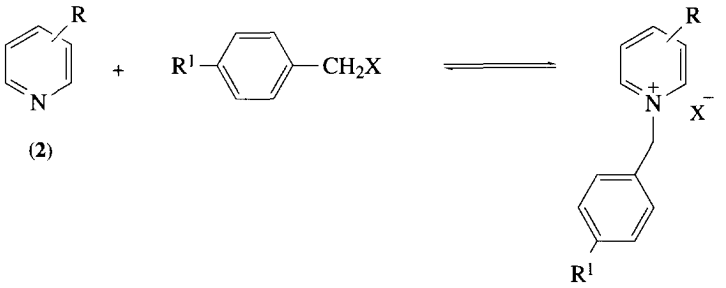
Quaternization of pyridine (**1**) with alkyl halides or related compounds is an example of the Menschutkin reaction (Equation (1)) ⟨84CHEC-I(2)165⟩, and has been the subject of numerous mechanistic studies ⟨84JCS(P2)2093, 84MI 502-01, 84ZOR1714, 85MI 502-01, 85PJC439, 86MI 502-01, 87JCS(P2)1439, 87MI 502-01, 87MI 502-02, 87MI 502-03, 87T4089, 88MI 502-01, 88MI 502-02, 88MI 502-03, 93MI 502-01⟩.



(1)

(1)

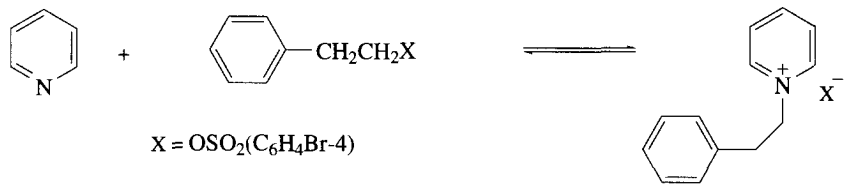
A dissociative S_N2 mechanism has been proposed based on kinetic studies of the pyridinium salt formation with *para*-substituted benzyl halides and substituted pyridines (**2**) in MeOH-MeCN mixtures (Equation (2)) ⟨88MI 502-02⟩. The quantum mechanical approach was consistent with kinetic results. Kinetic data for the reaction of benzyl chloride with pyridine in DMF under high pressure suggests a bimolecular reaction ⟨87MI 502-03, 88MI 502-01, 93MI 502-01⟩. A transition state model has been proposed for the reaction of methyl iodide with substituted pyridines which accurately correlates the rate of methylation ⟨83JOC4892⟩.



(2)

(2)

The high pressure reaction of 2-phenylethyl 4-bromobenzenesulfonate (**3**) with pyridine gives second-order rate constants at various pressures and temperatures (Equation (3)). The reaction mechanism is S_N2 and the C—N bond formation in the transition state is the rate determining step ⟨84MI 502-01⟩. In a related study on the rate constants and activation parameters for the reaction of 2-phenylethyl 3-nitrobenzenesulfonates with substituted pyridines, it was shown that electron-releasing substituents in both reactants accelerated the rate of reaction, and electron-withdrawing substituents increased C—N bond formation relative to bond breaking in the transition state ⟨87T4089⟩. The S_N2 character of the reaction increased with pressure ⟨87JCS(P2)1439⟩.



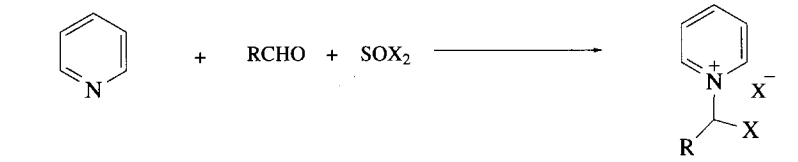
$X = OSO_2(C_6H_4Br\text{-}4)$

(3)

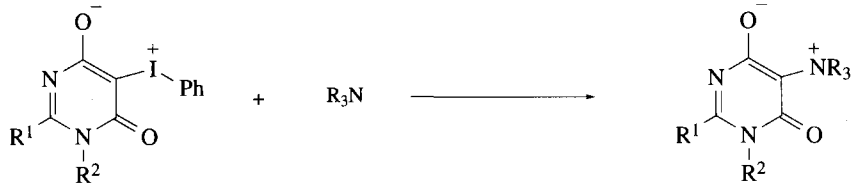
(3)

N-Methyl salts of pyridines can be obtained using trimethyl phosphate as the methylating agent, and the rates of these reactions have been measured in D_2O and in $CDCl_3$. The results show an early activated complex for all pyridines, with the most nucleophilic substrate showing the most reactant-like activated complex ⟨89JPO377⟩. Alternatively, homogeneous amine *N*-methyl transferases convert pyridines to the *N*-methylpyridinium salts ⟨88BP1673⟩. As expected, substitution at the 2-position of the pyridine hindered the *N*-methylation.

Pyridines react with aldehydes in the presence of thionyl halides to form pyridinium salts (Equation (4)) ⟨87BSB719⟩. Dithioester-stabilized pyridinium and isoquinolinium salts have been prepared and the structures determined by x-ray crystallography ⟨87JHC917⟩. Pyridyl- and isoquinolylpyrimidones (**5**) have also been synthesized by treating the corresponding heterocycle with iodonium ylides (**4**) (Equation (5)) ⟨84JHC385⟩. Stable rotamers of 9-(2-bromomethyl-6-methylphenyl)fluorene (**6**) reacted with pyridine and 2-methylpyridine to form the corresponding salts (**7**) (Equation (6)).

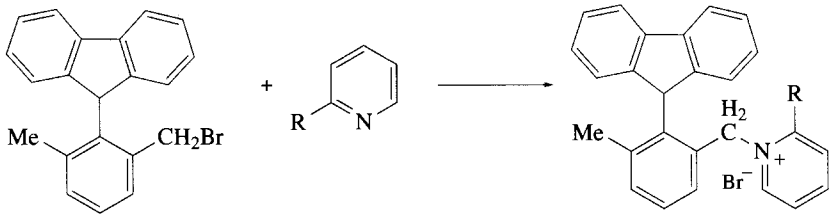


(4)



(4) NR_3 = Pyridine or Isoquinoline (5)

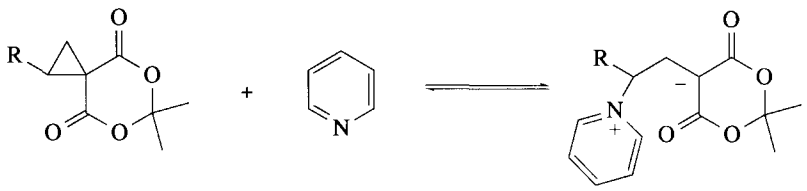
(5)



(6)

(6) (7)

From rate studies, it was concluded that the reaction is controlled by a steric effect and is not dependent on the nucleophilicity of the pyridines ⟨84BCJ525⟩. Various pyridinium, quinolinium, and isoquinolinium salts of squaric acid have been prepared by treating squaryl dichloride with the corresponding heterocycle ⟨84TL4475, 84S436, 85S1055⟩. Nucleophilic opening of spiroactivated cyclopropanes (**8**) with pyridines gives pyridinium ylides (**9**) (Equation (7)). This reaction was shown to be reversible, providing conditions for obtaining rates and equilibria data along with activation and other thermodynamic parameters ⟨84TL5477, 86JCS(P2)43⟩.



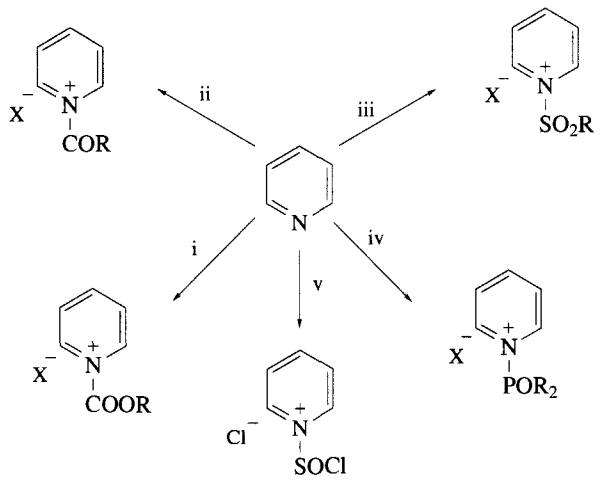
(8) (9) (7)

Long chain malonic ester pyridinium and 4,4′-bipyridinium ylides have been synthesized by treating pyridines with distearyl bromomalonates. The products were evaluated as vesiculating pH indicators because of their change in color with pH ⟨87MI 502-04⟩. Polymeric pyridinium, quinolinium, isoquinolinium, and methylquinolinium salts capable of removal of chromium(VI) from living organisms have been synthesized ⟨87MI 502-05⟩. The cyclic sulfate of dimethyl L-tartrate forms pyridinium salts ⟨93MI 502-02⟩, and an analogous salt has also been obtained with 4-dimethylaminopyridine.

Several biologically active onium salts of pyridinium carbapenems ⟨92JAN940⟩, (pyridino)methylpenems ⟨87JAN1636⟩, ketoalkylpyridinium halides ⟨91JIC99⟩, and 8-pyridinotheophyllinate ⟨88KGS1000⟩ have been prepared by treating the corresponding halides with pyridines. Reaction of pyridines with triflate derivatives of pyranosides gives pyridinium pyranosides ⟨92ZN(B)589⟩.

5.02.2.4 Acyl Halides and Related Compounds

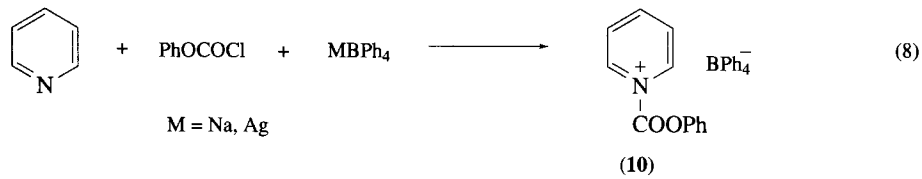
Acylation of pyridines can be achieved at temperatures as low as −78 °C. Similarly, pyridines react with sulfonyl halides and with anhydrides to give pyridinium salts ⟨73RCR642, 84CHEC-I(2)165⟩. Acyl halides and chloroformates react instantaneously with pyridines to form pyridinium salts (Scheme 1).



i, ROCOX ; ii, RCOX ; iii, RSO_2X ; iv, R_2POX ; v, $SOCl_2$

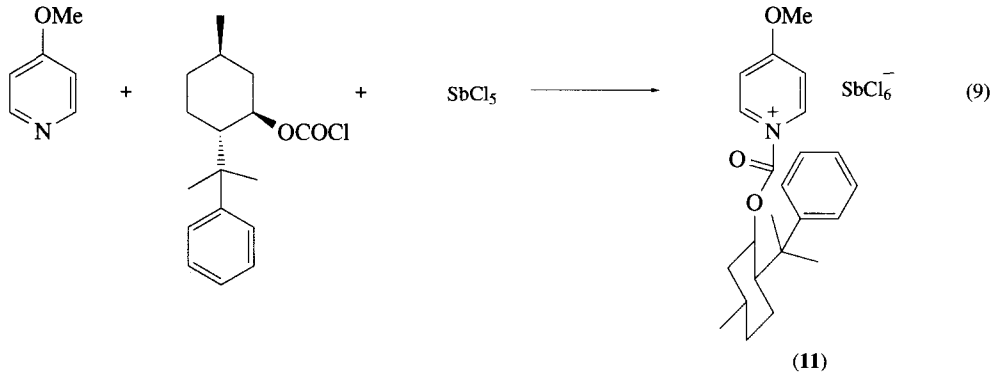
Scheme 1

Stable *N*-acylpyridinium and *N*-acylisoquinolinium salts (**10**) have been isolated and their structures determined by single crystal x-ray analysis (Equation (8)) ⟨92JOC5136, 94AX(B)25⟩. A stable chiral pyridinium salt (**11**) has also been isolated and its structure determined in the same manner (Equation (9)) ⟨94AX(B)25⟩. Kinetic studies on the salt formation of substituted benzoyl compounds with pyridines show that bond formation is advanced in the transition state ⟨85MI 502-02, 92MI 502-01⟩.



(8)

(**10**)



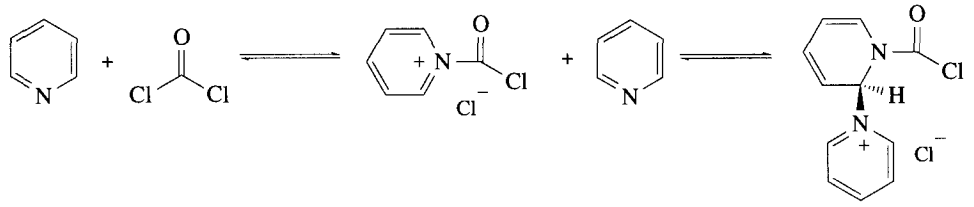
(9)

(**11**)

Similarly, kinetic data for the reactions of substituted imidoyl chlorides with pyridines have been obtained ⟨84DOK(274)1388, 87UKZ79⟩. Rate constants have been determined for the salt formation of pyridines with methyl chloroformate, and it has been found that the rate-determining step is the formation of the tetrahedral intermediate ⟨88MI 502-04⟩.

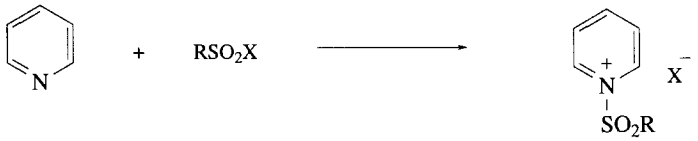
Solvent effects on the pyridinolysis of 2,4-dinitrophenyl methyl carbonate and 2,4-dinitrophenyl acetate in aqueous ethanol have been studied and Brønsted-type plots obtained. The curves are described by a semiempirical equation based on the existence of a tetrahedral intermediate ⟨86JOC5072⟩. Similarly, kinetic and mechanistic studies of the reaction of pyridine with 2,4-dinitrophenyl *p*-nitrobenzoate have been performed ⟨83JCS(P2)453⟩.

Reaction of two equivalents of pyridine with one equivalent of phosgene has been reported to give a 1,2-dihydropyridine-pyridinium salt (**12**) (Scheme 2) ⟨88JOC6145⟩. Trifluoroacetyl triflate reacts with pyridine to give the trifluoroacetylpyridinium salt ⟨87JOC4156⟩, and alkyl- and arylsulfonyl halides give the corresponding pyridinium sulfinates (**13**) (Equation (10)) ⟨82PJC533, 83MI 502-01, 86BSF881, 86ZOR222, 91IZV1934⟩.



(**12**)

Scheme 2



(**13**) (10)

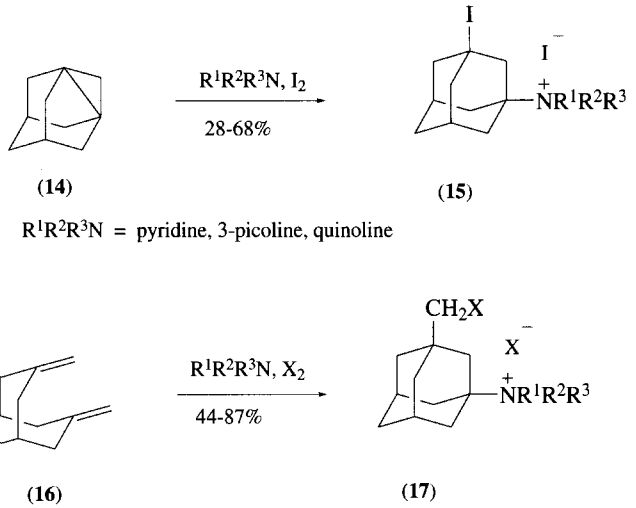
N-Phosphorylation of pyridines can be achieved by treating phosphoryl halides with pyridines ⟨84JA7591, 84JA7597⟩. Equimolar or excess pyridine reacts with $RP(X)Cl_2$ below room temperature to form pyridinium betaines, and stable crystalline betaines have been isolated when 4-dimethylaminopyridine is used as the pyridine component ⟨90PS(49)251⟩.

5.02.2.5 Activated Alkenes

Michael acceptors react with pyridines, quinolines, and isoquinolines under acid catalysis to give stable pyridinium betaines, and the reaction can be reversed by the addition of a base ⟨84CHEC-I(2)165⟩. Treatment of 1,3-dehydroadamantane (**14**) with pyridines, 3-picoline, or quinoline and iodine at $-10\,^{\circ}C$ to $0\,^{\circ}C$ gives 28–68% yields of pyridinium salts (**15**), and 3,7-dimethylenebicyclo-[3.3.1]nonane (**16**) provided 44–87% yields of the corresponding pyridinium salts (**17**) (Scheme 3) ⟨84ZOR2554⟩.

5.02.2.6 Halogens

Pyridines and their benzo derivatives react with all the halogens to give *N*-halogenopyridinium salts. The complexes of pyridine, methyl nicotinate, and methyl isonicotinate with chlorine have been well studied ⟨87JA7204⟩. The studies suggest that the pyridine/chlorine atom complex has a long three-electron σ bond between nitrogen and chlorine. Pyridine iodo compounds can be prepared by treating $TiI_3[AsF_6]$ with pyridines, from which the pyridinium salt $[C_5H_5NI]^+[AsF_6]^-$ has been isolated and characterized ⟨90ZAAC(586)93⟩. Several syntheses of *N*-fluoropyridinium salts have been reported. These compounds have received growing interest because of their use as fluorinating agents ⟨91MI 502-01⟩. *N*-Fluoropyridinium triflate can be prepared by fluorination of pyridine with F_2 in acetonitrile in the presence of CF_3SO_3Na (Equation (11)) ⟨90OS(69)129⟩. Fluorine nitrate on reaction with pyridine gives *N*-fluoropyridinium nitrate ⟨91IZV2403⟩. Among other fluorinating



Scheme 3

agents used, caesium fluoroxysulfate is less active than elemental fluorine and fluoromethyl hypofluorite, but more active than perchloryl fluoride ⟨90JA8563, 91T7447, 92TL1069, 93JOC4476, 94TL8951⟩.

A detailed study of the properties of *N*-fluoropyridinium salts has been performed. Various stable *N*-fluoropyridinium salts with different counterions, such as triflate, FSO_3^-, BF_4^-, SbF_6^-, ClO_4^-, $MeSO_3^-$, etc. with substituents on the pyridine ring have been prepared by counteranion displacement of the unstable pyridine F_2 complex or by fluorination of Lewis acid complexes of pyridines. It was found that the stability of *N*-fluoropyridinium salts depends on the nucleophilicity or basicity of the counter ions, and the electronic nature and position of ring substituents ⟨91BCJ1081⟩.

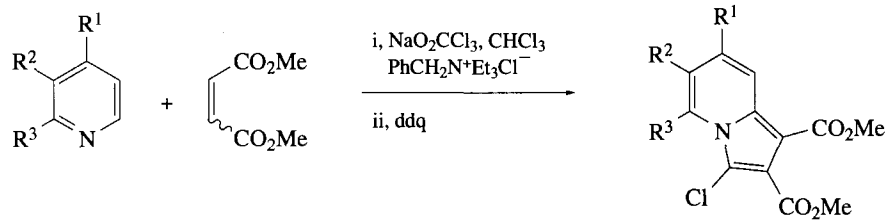
5.02.2.7 *N*-Oxidation

N-Oxidation of pyridines with peracids was first discovered by Meisenheimer in 1926 ⟨26CB1848⟩. Since then, several peracids have been used for the *N*-oxidation of pyridines and their benzo derivatives ⟨84CHEC-I(2)165⟩. A detailed kinetic study on the solvent effects of the *N*-oxidation of pyridine, 8-hydroxyquinoline, quinoline, and acridine showed that the rate of the reaction is slow in protic solvents due to hydrogen bonding effects ⟨93MI 502-03⟩. Aminopyridines have been converted into *N*-oxides by Caro's acid under neutral or basic conditions. Thus oxidation of 2-aminopyridine with potassium peroxymonosulfate gave 2-aminopyridine 1-oxide in 51% yield ⟨93JCR(S)412⟩. A comparative study of pyridine oxidations using magnesium monoperphthalate versus *m*-chloroperbenzoic acid has been reported. The study showed that magnesium monoperphthalate is stable at ambient temperatures and oxidizes pyridine under mild conditions to give pyridine *N*-oxide ⟨87S1015⟩. Other oxidation agents used for *N*-oxidations are dioxiranes ⟨92JA1346, 93AG771⟩ and organic hydrotrioxides ⟨82IZV1922⟩. *N*-Oxidation of pyridines, isoquinoline, and quinoline can be achieved at high temperature using certain six-membered heteroaromatic *N*-oxides as oxidants ⟨87KGS1075⟩. Pyridines undergo efficient autoxidation to their *N*-oxides in polar solvents like H_2O and MeOH at temperatures above 80 °C in high yields. An electron-transfer pathway is proposed for this reaction ⟨85JOC1563⟩. A similar autoxidation has been reported at high oxygen pressures ⟨88JOC1695⟩. Rate constants for the reaction of atomic oxygen with pyridine from 323 K to 473 K have been determined using chemiluminescence transitions ⟨83JPC4933⟩. Catalytic oxidation of pyridines to the *N*-oxides with oxygen is an alternative, lower temperature route for the synthesis

of pyridine *N*-oxides. The catalysts which have been used are Pt/Al_2O_3 ⟨83MI 502-02⟩, 26% Cu/Al_2O_3, 30% $CuCr_2O_4/Al_2O_3$, 5% $CuCr_2O_4/Al_2O_3$ ⟨83MI 502-03⟩, fullerene ⟨94EF810⟩, and $VO(PO_3)_2$ ⟨86KGS75⟩.

5.02.2.8 Carbenes

Carbenes react with pyridines to give nitrogen ylides. These pyridinium ylides can be trapped with appropriately activated alkenes. Thus, treating pyridines with dimethyl fumarate or dimethyl maleate followed by CCl_3CO_2Na gives dihydroindolizines (**18**) (Equation (12)) ⟨87KGS856, 90KGS355⟩.



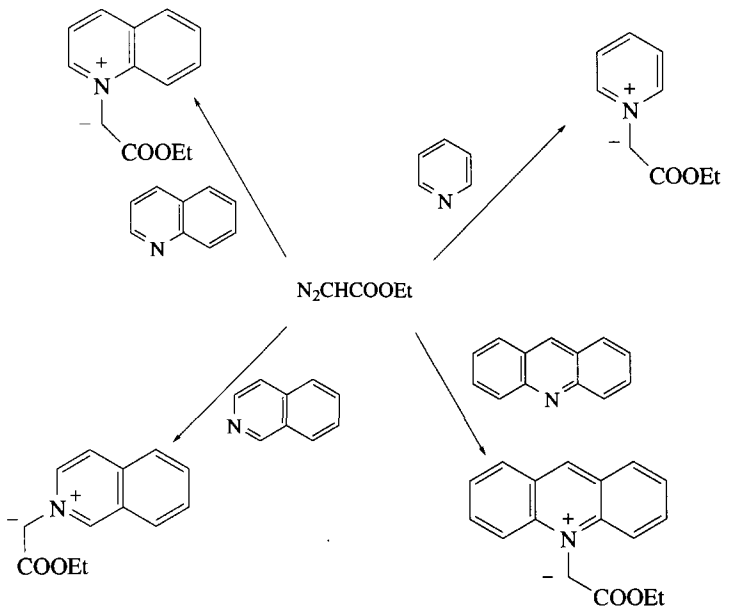
(12)

(**18**)

R^1 = H, Me, R^2 = R^3 = H;
R^1 = H, R^2 = R^3 = (CH:CH)$_2$

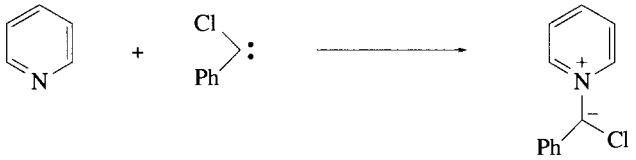
5-47 %

The relative rates of the reaction of ethoxycarbonylcarbene with pyridine, quinoline, and acridine have been studied (Scheme 4) ⟨88JOC4374⟩. The relative stability of the heterocyclic ylides was found to be acridine > quinoline > pyridine, and the reactivity order was found to be pyridine > quinoline > acridine. These conclusions were supported by kinetic data. Isoquinoline also yields a stable ylide upon reaction with ethoxycarbonylcarbene ⟨70TL941⟩.



Scheme 4

Similarly, phenylchlorocarbene reacted with pyridine to give the corresponding ylide (Equation (13)). It has been suggested that these reactions are irreversible, and activation energies have been used to support this hypothesis ⟨89TL1335⟩.



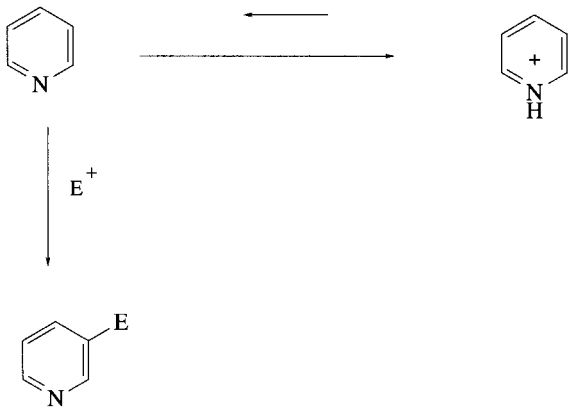
(13)

The reaction of triplet diphenylcarbene with pyridine has also been well studied, and a mechanism for this reaction has been proposed using kinetic data as supporting evidence ⟨90TL953⟩. The ylides formed from the reaction of pyridines with carbenes have been used as probes for determining the yield and dynamics of the carbene. Thus, the carbenes generated from laser flash photolysis of alkylbromo- and alkylfluorodiazirines were trapped by pyridine to form the pyridinium ylides. These ylides absorb intensely between 350 and 400 nm and are long-lived, so formation of the carbenes can easily be monitored ⟨94JPO24⟩.

5.02.3 ELECTROPHILIC ATTACK AT CARBON

5.02.3.1 General Reactivity

The electron-withdrawing effect of nitrogen in pyridine and its benzo derivatives makes these heterocycles less reactive than benzene toward electrophiles. These effects are profound at the 2- and 4-positions and diminished at the 3-position. Electrophilic substitution at carbon is further complicated in that these reactions are often carried out in highly acidic conditions, which means that the reactive species is either a small amount of free base or the less reactive conjugate acid (Scheme 5). When electrophilic attack does occur, it is generally at the 3-position.



Scheme 5

In contrast, hard electrophiles such as nitronium ions have been shown to attack the 4-position of pyridine *N*-oxide because of resonance stabilization in the reaction intermediate (Wheland intermediate ⟨84CHEC-I(2)186⟩). With soft electrophiles such as Hg^{2+}, attack occurs at C-2, and with the conjugate acid of pyridine *N*-oxide, reaction occurs at C-3.

Electron-releasing substituents on pyridine enhance its reactivity towards electrophiles. For example, 3-hydroxypyridine reacts readily with strong electrophiles at C-2 and with weak electrophiles at C-6. Both the 2- and 6-positions have to be blocked to direct reaction to C-4.

Further discussion only deals with advances in this area since 1982. (For references before 1982, see ⟨84CHEC-I(2)⟩.) For a discussion of metallation and the reactivity of metallated species towards electrophiles, see Chapter 5.03.

5.02.3.2 Halogenation

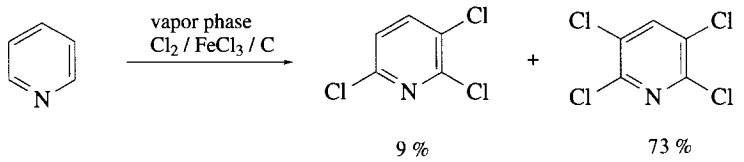
Pyridines and their benzo derivatives can be halogenated by electrophilic, nucleophilic (see Section 5.02.4.1), or radical reactions (see Section 5.02.6.1). Electrophilic halogenations of pyridines and their benzo derivatives are difficult due to the electron-deficient nature of the ring. In the benzo

derivatives of pyridines the homocyclic ring preferentially reacts with electrophilic halogenating agents. The presence of an activating group in the heterocyclic ring can enhance the reactivity in some halogenation processes. Several review articles have appeared on the halogenation of pyridines ⟨84AHC(35)281, 88AHC(44)199, 90AHC(47)303, 93AHC(58)272, 94AHC(59)286⟩. Electrophilic halogenation of pyridine at carbon follows the orientation order $3 > 4 \geqslant 2$.

5.02.3.2.1 Chlorination

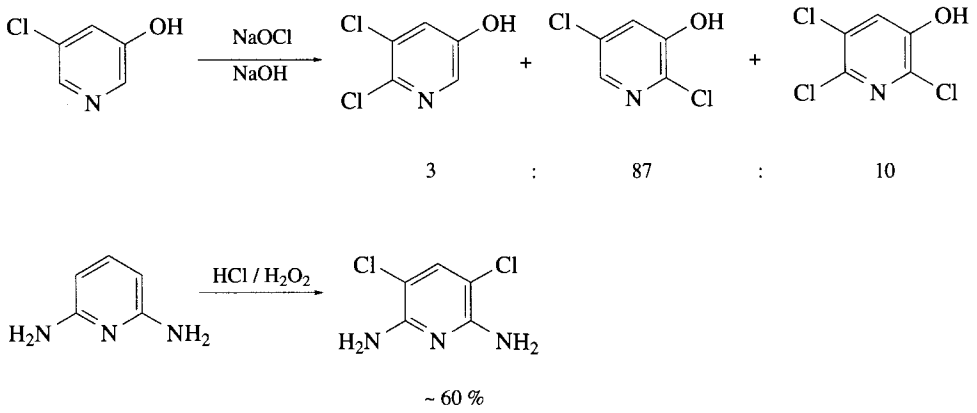
Chlorination of pyridines normally gives complex mixtures of products ⟨93AHC(58)272⟩. Under electrophilic attack 3-chlorination can be achieved. At higher temperatures homolytic chlorination at the 3-, 4-, and 2-positions may occur.

There has been a detailed kinetic study on the stepwise chlorination of pyridine to pentachloropyridine, which has helped in finding the right conditions to maximize the yields ⟨69USP3420833, 80JOU1845, 81JAP(K)120666, 81JAP(K)120667, 82FRP2477540, 83JAP(K)58206564, 84GEP3306905, 87USP4701532, 89EUP311050, 89FRP2477540, 90USP4939263, 91ZPK1297⟩. Various catalysts have been used in the vapor phase chlorination of pyridines, for example, alumina, chlorides, and fluorides of transition metals, or carbon and lead (Equation (14)). In liquid phase chlorinations the isomer ratio can be altered by the addition or removal of HCl ⟨90USP4939263⟩.

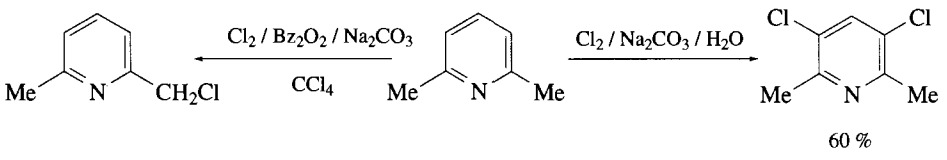


(14)

Pyridines containing electron-donating substituents can readily be chlorinated ⟨93AHC(58)275⟩, and a variety of reagents have been used for this purpose (e.g., sulfuryl chloride ⟨91URP1657495⟩, sodium hypochlorite ⟨89SC553, 89SC1505, 90S499⟩, chlorine in acetic acid ⟨90S681⟩, sulfuric acid, or with Lewis acid catalysts ⟨83EUP78410, 86USP4594422⟩, and hydrogen chloride with an oxidizing agent ⟨80CC1139, 88GEP3707361, 89SC553, 90S499⟩). Some representative examples of these chlorinations are shown in Scheme 6. Normally, chlorination occurs at the positions *ortho* and *para* to the substituents. However, by varying the reaction conditions one can obtain nuclear or side-chain chlorination of picolines (Scheme 7) ⟨80CHE89, 91GEP4016175⟩.



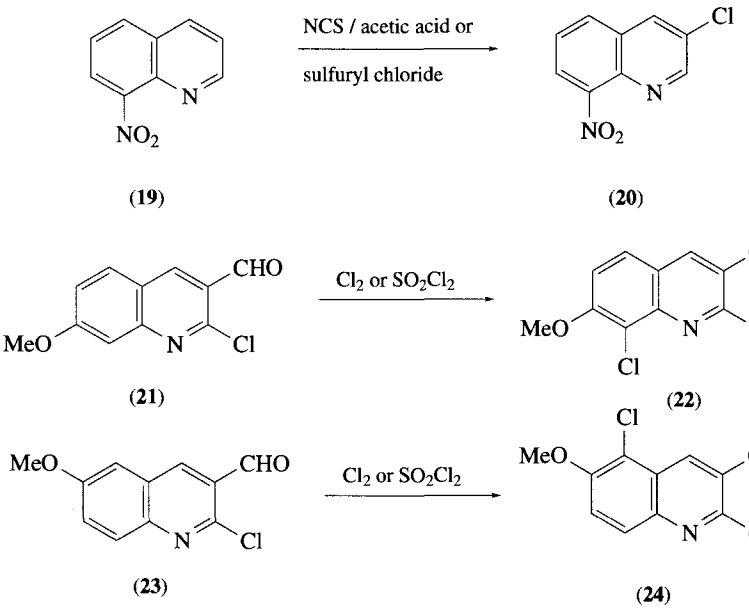
Scheme 6



Scheme 7

Electrophilic chlorination of pyridine 1-oxide is also possible. However, due to the π-electron deficiency, this reaction is more difficult than for simple pyridines. An example of this substitution reaction is chlorination of 2-acetamidopyridine 1-oxide with hydrogen chloride and hydrogen peroxide, which resulted in a mixture of 5-chloro and 3,5-dichloro derivatives. Chlorination of 3-acetamido pyridine 1-oxide gave the 2,4,6-trichloro product, and the 4-isomer underwent 3,5-dichlorination under the same conditions.

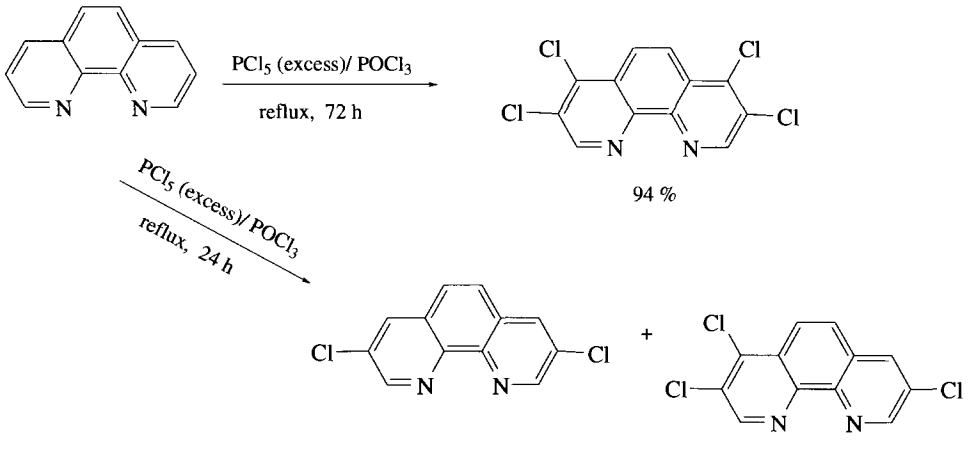
Electrophilic chlorination of quinoline under neutral conditions occurs in the orientation order $3 > 6 > 8$. Hammett σ^+ values predict an order for electrophilic substitution of $5 > 8 \approx 6 > 3$. The reactivity order can be affected by substitution of an electron-withdrawing group in the benzene ring, which directs the chlorination to the pyridine ring. Thus NCS in acetic acid or sulfuryl chloride in *o*-dichlorobenzene converts 8-nitroquinoline (**19**) into 3-chloro-8-nitroquinoline (**20**) in high yield (Equation (15)) ⟨91M935⟩. In contrast, 7-(**21**) or 6-methoxy-2-chloroquinoline-3-carbaldehyde (**23**), upon reaction with chlorine in 1,2,4-trichlorobenzene or with sulfuryl chloride gave the 2,8-(**22**) and 2,5-dichloro products (**24**) in good yields (Scheme 8) ⟨91SC1929⟩.



(15)

Scheme 8

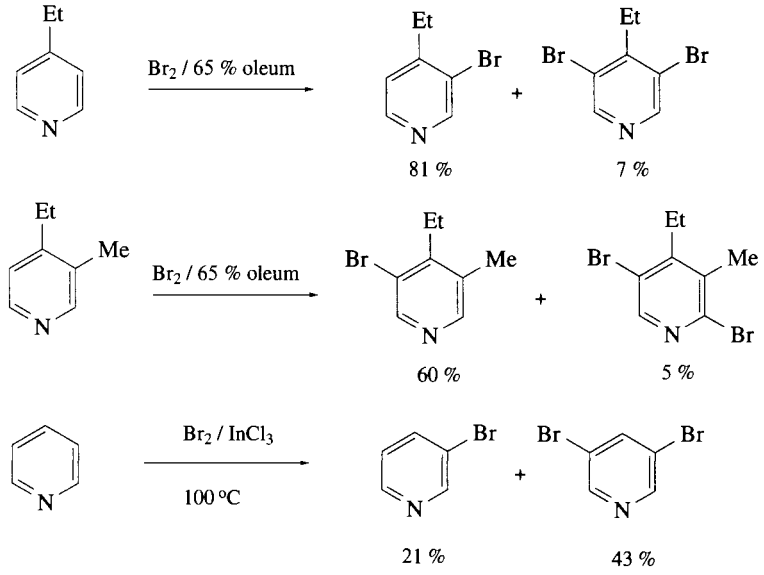
Unlike other substituted quinolines, all the possible isomers of monochloroquinolinols have been synthesized ⟨91M935⟩. Under basic conditions 8-hydroxyquinoline reacts as an anion to give 7-chloro-8-hydroxyquinoline. Excess of phosphorus pentachloride and phosphoryl chloride chlorinated 1,10-phenanthroline *meta* and *para* to the annular nitrogens (Scheme 9) ⟨92BCJ2007⟩.



Scheme 9

5.02.3.2.2 Bromination

Pyridines undergo bromination to give 3-bromo or 5-bromopyridines under a variety of conditions (bromine in aqueous solution ⟨82JA4142, 90S499⟩, in acetic acid ⟨81JAP(K)128759, 85CHE1399, 86JHC1849, 90S681⟩, in oleum ⟨62RTC864, 65RTC951, 70RZC779, 88ZC59, 89ZC287⟩, with bromine monofluoride ⟨88JOC1123, 88JOC5545⟩, with dioxane dibromide ⟨82CHE1284⟩, with bromine and Lewis acids ⟨81CHE923, 88JOC5545, 89BRP2213478⟩, with sodium hypobromite ⟨90S497, 90S499⟩, and with hypobromous acid in aqueous perchloric acid ⟨74JOC3481⟩). A few examples of these brominations are given in Scheme 10.



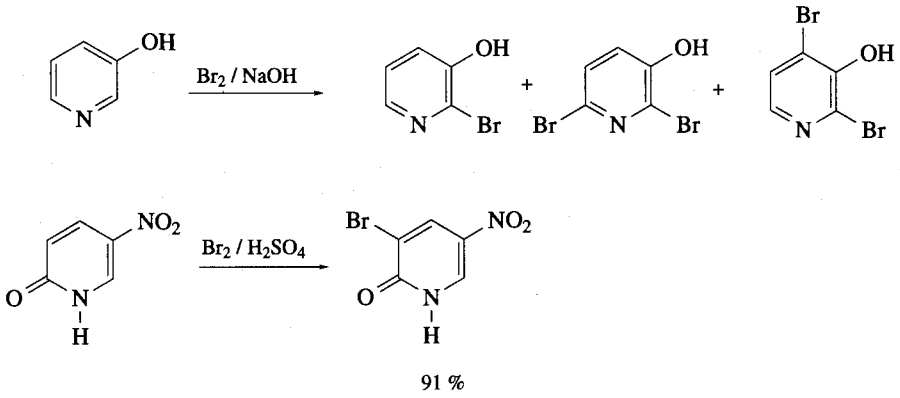
Scheme 10

Selective monobromination has been shown to be difficult on pyridines with strong activating groups. Only under forcing conditions can either pyridine or weakly activated pyridines, such as picolines, be brominated ⟨83JOC1064, 88ZC59, 89ZC287⟩. Bromination usually occurs at the 3- and 5-positions, and if these are blocked, 2- and 6-bromination can be achieved. When the pyridine is complexed or when a stronger electrophile is employed, bromination is more facile. Bromine monofluoride, prepared *in situ* by passing fluorine through a cold solution of bromine in trichlorofluoromethane, has been found to be an effective reagent for the bromination of pyridine ⟨88JOC1123, 88JOC5545⟩.

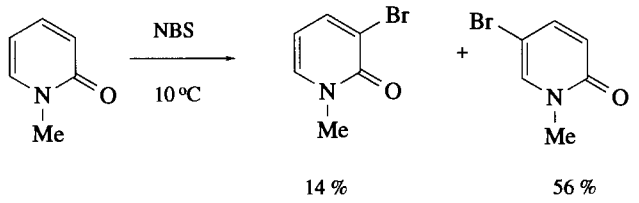
Strong activating groups on the ring, like hydroxy and amino, enhance the ease of bromination, and direct the bromination *ortho* and *para* unless these positions are blocked (Scheme 11) ⟨82CHE1284, 82JA4142, 89JPR369, 90S497, 90S499⟩. Several 3-hydroxypyridines undergo monobromination under aqueous alkaline conditions *ortho* and *para* to the hydroxy group. Increasing the proportion of bromine to substrate results in dibrominated product. Under the conditions studied, no mono 4-bromo species was observed ⟨90S497⟩.

Detailed mechanistic studies on the bromination of pyridines have been performed ⟨74JOC3481, 93AHC(58)283⟩. Bromination of 2-aminopyridines using bromine in dilute sulfuric acid has also been well studied, and the kinetic data show that the minority free base species reacts with molecular bromine, and the usual substituent effects apply on the rates of these brominations ⟨70JCS(B)117, 78APO(16)1, 93AHC(58)285⟩.

Brominations of 2- and 4-pyridones have been shown to be pH dependent. At lower pH (below 6) the neutral molecule reacts but at higher pH the conjugate anion is the reactive species. However, *N*-methyl or *N*-alkylpyridones are not particularly reactive above pH 6 because they cannot form anions ⟨82JA4142, 90AHC(47)303, 93AHC(58)285⟩. In the case of 4-pyridones, once monobromination occurs, the second bromination is much faster due to more facile anion formation ⟨83CJC2556⟩. Effective bromination of these pyridones can be achieved using NBS or dioxane dibromide (Equation (16)) ⟨82CHE1284⟩. Bromination of 2- and 4-pyridones is possible even when a strong electron-withdrawing substituent is present ⟨83JOC3297, 84EGP205895, 85CHE1399, 90S499⟩.

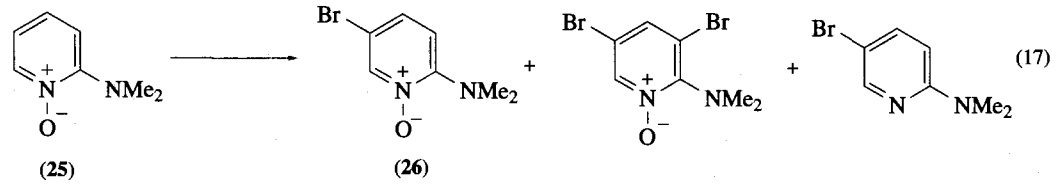


Scheme 11



(16)

The electrophilic bromination of pyridine 1-oxides is also known and has been more widely studied than the corresponding chlorination. Strong electron-releasing groups on the pyridine 1-oxide favor nuclear bromination. In the case of 4-methoxypyridine 1-oxide, bromination occurred at C-3 along with ether hydrolysis. However, bromination of 2-dimethylaminopyridine 1-oxide (**25**) gave the 5-bromo-derivative (**26**) as the major product (Equation (17)) ⟨83JOC1064⟩.

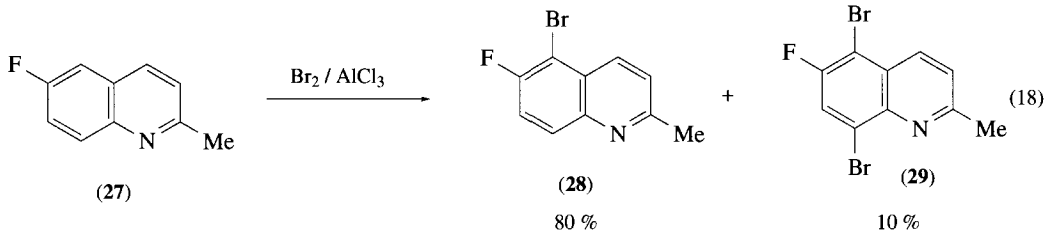


(17)

(**25**) (**26**)

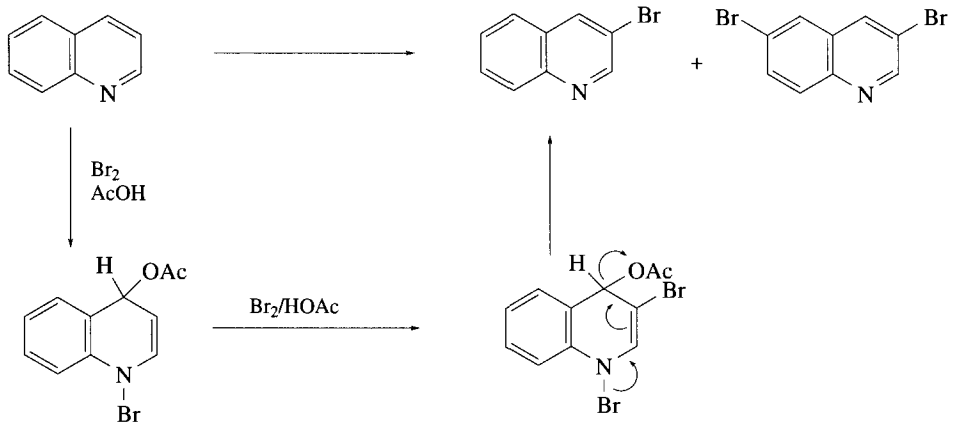
Br_2 / Et_3N / CCl_4	48	8	35
Br_2 / K_2CO_3 / CCl_4	57	9	26

Bromination of quinoline, like the pyridines, also shows a pH dependence. Unlike the pyridines, quinolines show a selectivity rather than reactivity dependence. Under neutral conditions quinoline can be brominated to provide the 3-bromo derivative along with polybrominated products ⟨59CI(L)1449, 62JCS291, 62JOC1318, 63JOC2865, 90AHC(47)385⟩. In contrast, the bromination of quinolinium species in acidic media usually results in 5- and 8-bromo products. In the presence of a Lewis acid catalyst a variety of mono-, di-, and tribromoquinolines are produced ⟨64JOC329, 85CHE458⟩. After a detailed study on the regiochemistry of quinoline bromination in the presence of a variety of Lewis acids, it was found that catalysts derived from elements with *p*-orbitals and *d*-orbitals are quite active, and the *p*-orbital elements are superior to the *d*-orbital elements in regioselective bromination. The formation of 3,6,8-tribromoquinoline by copper(II) sulfate-catalyzed bromination of quinoline is explained using back-donation from Cu^{2+} *d*-orbitals ⟨85CHE458⟩. Aluminum chloride-catalyzed bromination of 6-fluoro-2-methylquinoline (**27**) in 1,2-dichloroethane gave mainly the 5-bromo derivative (**28**) along with small amounts of 5,8-dibromo products (**29**) (Equation (18)) ⟨92JHC895⟩.

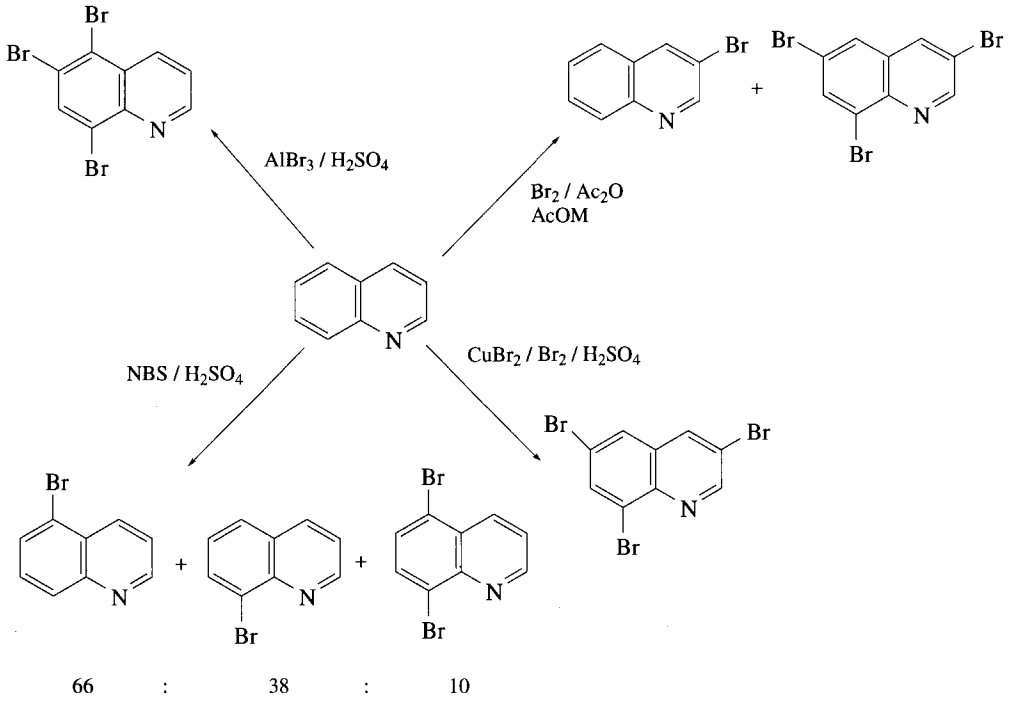


(18)

Metal acetate-catalyzed bromination of quinolines is believed to occur via 1,4-addition of bromonium acetate (Scheme 12) ⟨85CHE458⟩. At low temperatures NBS in sulfuric acid gives the same ratio of products as with bromine/sulfuric acid/silver sulfate, but at higher temperatures extensive dibromination occurred (Scheme 13) ⟨88CHE892⟩.

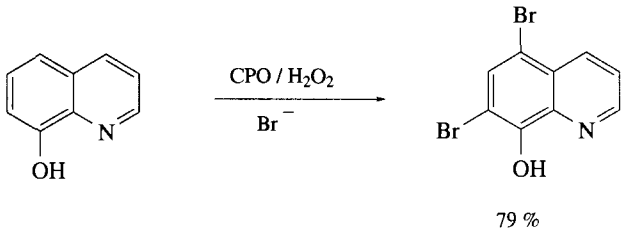


Scheme 12

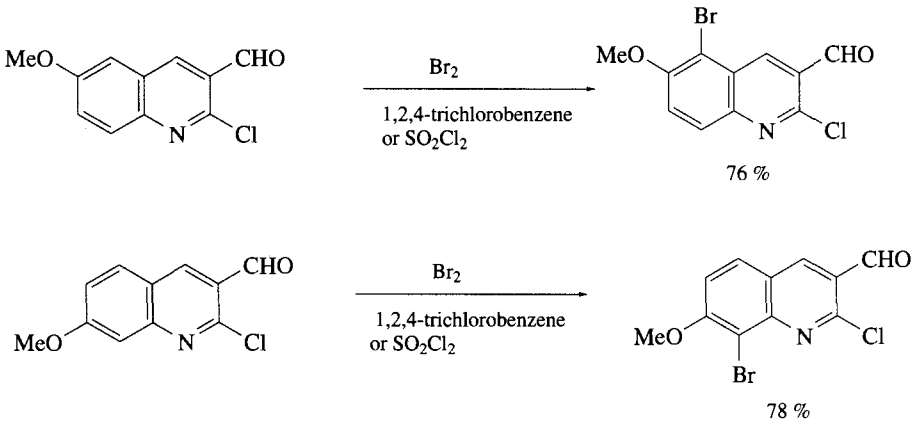


Scheme 13

As in the other related systems, hydroxy or alkoxy substituents direct the bromination to their *ortho* and *para* positions (Scheme 14) ⟨72JOC4078, 86JCR(S)122, 87JHC1313, 90LA1083, 91SC1929, 92M617⟩. For instance, treatment of 8-hydroxyquinoline with bromine in acetic acid results in a mixture of 5-bromo and 5,7-dibromo compounds. All other possible monobromo derivatives of 8-hydroxyquinoline have been prepared ⟨91M935, 94AHC(59)290⟩.



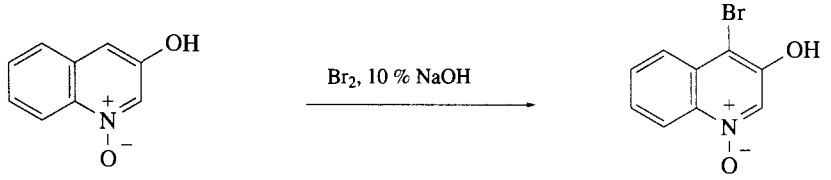
CPO = chloroperoxidase from *Caldamyces fumago*



Scheme 14

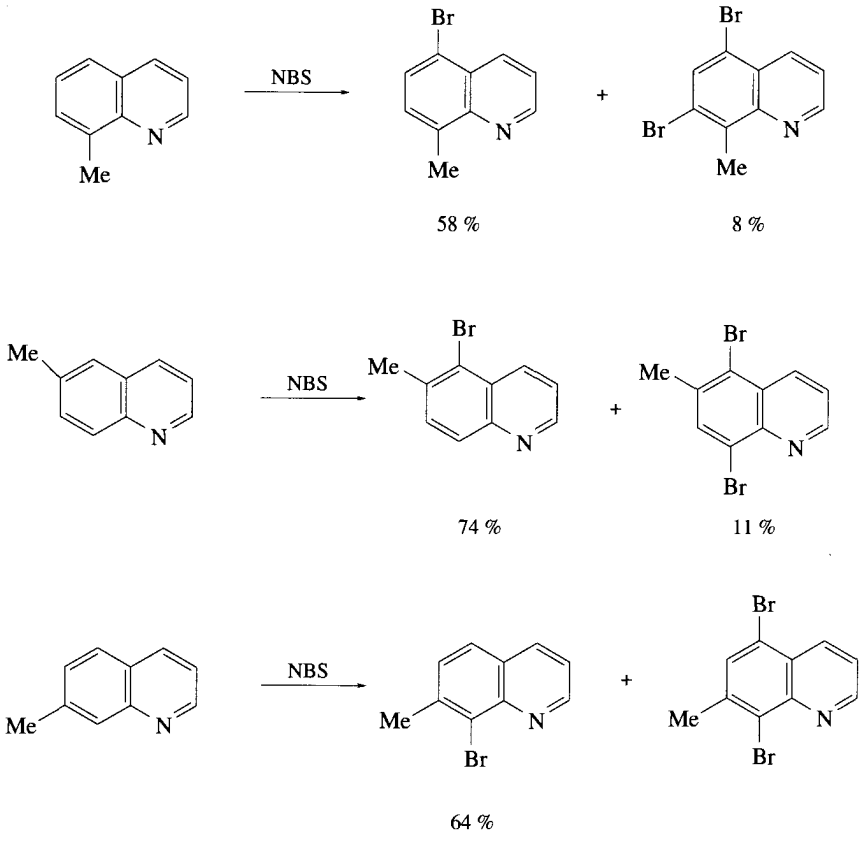
Under basic conditions, mainly *ortho*-bromination occurs in 6- and 8-methylquinolines. The bromination occurs at the 5-position due to the combined orienting effects of the substituents and the pyridine ring. Bromination of 7-methylquinoline was also shown to occur at both the 5- and 8-positions (Scheme 15) ⟨83CHE1093, 88CHE892⟩. The bromination of 2-alkyl-6-bromoquinolines with bromine sulfuric acid-silver nitrate resulted in the predominant formation of 2-alkyl-5,6-dibromoquinolines.

Quinoline 1-oxide can be converted into 3-bromoquinoline 1-oxide by reaction with bromine and acetic acid ⟨61CPB414, 65YZ62⟩. In the presence of thallium acetate the same reaction gives the 4-bromo derivative. Similarly, 2-methyl-, 2-cyano-, and 3-bromoquinoline 1-oxides gave the 4-bromo products ⟨79H(12)475⟩. A variety of brominating agents can be used to brominate C-4 of 3-hydroxyquinoline 1-oxide. The activation by both the *N*-oxide and 3-hydroxy groups make these brominations facile (Equation (19)) ⟨84BAU1522⟩.



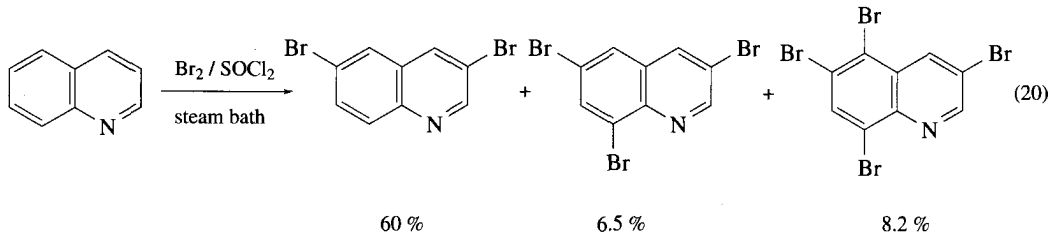
(19)

Bromination of quinolines substituted with deactivating groups requires forcing reaction conditions, and these substituents have been shown to also affect the orientation of bromination. An example is the bromination of 6-nitroquinoline with bromine in sulfuric acid to give the



Scheme 15

8-bromo derivative. Under the same conditions 8-methyl-5-nitroquinoline gave the 7-bromo product, and 7-chloroquinoline provided 5-bromo-7-chloroquinoline ⟨88CHE892⟩. Polybromination of quinoline and 9,10-phenanthroline can be achieved using bromine in thionyl chloride (Equation (20)) ⟨91JPR351⟩.

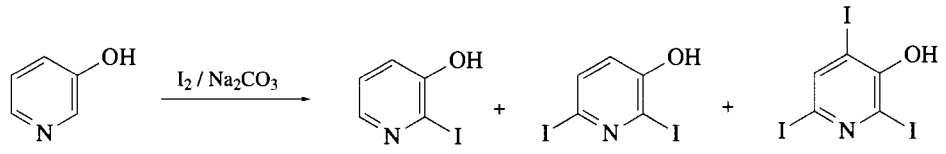


(20)

5.02.3.2.3 Iodination

Electrophilic iodinations of pyridines are not as common as brominations. Pyridine can be iodinated by iodine in oleum; however, a very low yield of the desired C-3-substituted product is obtained ⟨57JCS387⟩. Di- and trimethyl substituted pyridines under similar reaction conditions do give the 3-iodo derivatives in reasonable yield ⟨70RZC779, 93AHC(58)289⟩. Solvent effects on the interactions between aminopyridines and iodine show that solvation by aromatic solvents is stronger than that by carbon tetrachloride, and interactions with aromatic solvents are even stronger with alkylpyridines ⟨86JCS(P2)1319⟩. Calorimetric and spectroscopic measurements of the formation constant and molar enthalpy of complexation for the interaction of pyridine and 2,6-dimethylpyridine with iodine in carbon tetrachloride and in cyclohexane show that disubstitution causes a decrease in the formation constant but does not influence the molar enthalpy of complexation ⟨84JCS(P2)731⟩.

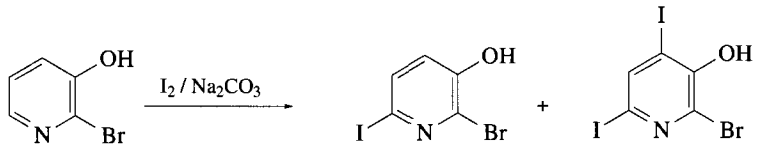
Various 3-hydroxypyridines can be regioselectively iodinated under basic conditions, and sodium carbonate is a superior base for this transformation (Equation (21)) ⟨90S497⟩. The 2-iodo derivative (**30**) is the major product, but when the 2-position is blocked, the 6-iodo compound (**31**) is formed predominantly (Equation (22)) ⟨90S497⟩. In a similar manner, treatment of 2-aminopyridine with iodine monochloride gave 2-amino-5-iodopyridine (Equation (23)) ⟨92AJC877⟩, while iodine monochloride converts 2,6-disubstituted 4-pyridones into 3-iodo and 3,5-diiodo products ⟨86JHC1849⟩.



(21)

(**30**)

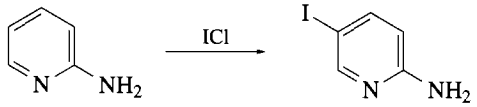
I_2 (mole)	Na_2CO_3 (mole)					
1	2	85	:	5	:	0
2	3	2	:	94	:	4



(22)

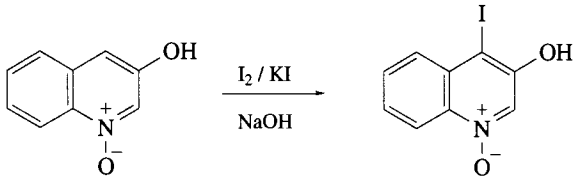
(**31**)

88 : 8



(23)

Iodination of unsubstituted quinolines is difficult and generally gives mixtures of products. However, quinolines with activating groups can be iodinated in good yield. For example, 8-methylquinoline gives 5-iodo-8-methylquinoline at room temperature under acidic conditions ⟨83CHE1093⟩. Hydroxyquinolines can be iodinated with iodine in methanol ⟨71JHC821⟩ or with NIS in acidic or neutral media ⟨72JOC4078⟩. Treatment of 3-hydroxyquinoline 1-oxide (**32**) with iodine and potassium iodide in 10% aqueous caustic soda gives 3-hydroxy-4-iodoquinoline 1-oxide (**33**) (Equation (24)) ⟨84BAU1522⟩. Iodination of pyridine and its benzo derivatives can also be achieved via metallation reactions (see Chapter 5.03).



(24)

(**32**) (**33**)

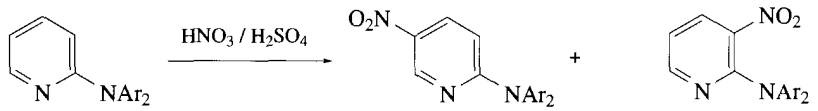
5.02.3.3 Nitration

As with other electrophilic reactions, the electron-deficient nature of pyridine makes nitration difficult. Since most of the nitration conditions include protic acids, protonation of the pyridine nitrogen occurs first, which makes the pyridine even less reactive towards the nitrating agents. Even under harsh conditions like potassium nitrate in oleum at 300 °C only 15% of 3-nitropyridine is

obtained ⟨12CB428⟩. Electron-donating substituents, for example, methyl, hydroxy, and amino groups, increase the reactivity of pyridine towards nitration and, surprisingly, some electron-withdrawing groups also increase yields of the nitrated products. The nitration rate constants of substituted pyridines (e.g. 3-OH, 3-MeO, 4-MeO, 4-Me_2N, and 2-Me_2N) were linearly correlated with localization energies ⟨83KGS639⟩.

In the nitration of pyridines, it has been shown that the reactive species can be either the conjugate acid or the free base. The state of the reaction species depends on the substituents present on the pyridine ring. Electron-withdrawing substituents favor reaction on the free base, and electron-donating substituents favor reaction on the conjugate acid. In general, pyridine derivatives with $pK_a > 1$ will nitrate as the conjugate acid, whereas those with $pK_a < 2.5$ will nitrate as the free base ⟨67AG(E)608, 90AHC(47)292⟩. Log K_2^0 values for the nitrations of 2,6-dichloro- and 2-methoxypyridine are −9.01 and −8.68, respectively ⟨83CHE514⟩. From the activation parameters for the nitration of dichloro- and dimethoxypyridines, it was inferred that the compounds with $\Delta S^{\ddagger}$ (e.u.) values of 12–16 react as the free bases. In contrast, those with values of −18 to −20 react as the conjugate acids ⟨67JCS(B)1204, 67JCS(B)1213⟩. The nitrations of 2,4- and 2,6-dimethoxypyridine occur at the 5- and 3-positions, respectively, and proceed via their conjugate acids. The second nitration of the latter compound involves a less reactive and less basic substrate which, like 2,6-dichloropyridine, is nitrated as the free base ⟨67JCS(B)1204⟩. This dependence can also affect the regioselectivity of the nitration. Although 6-nitration of 2-nitro-3,5-dimethoxypyridine takes place on the free base, 3,5-dimethoxypyridines undergo 2-nitration via the conjugate acid ⟨67JCS(B)1213⟩. To maximize the yield of 2-nitro-3,5-dimethoxypyridine, the nitration is carried out under strongly acidic conditions, generally sulfuric acid, which ensures reaction via the conjugate acid.

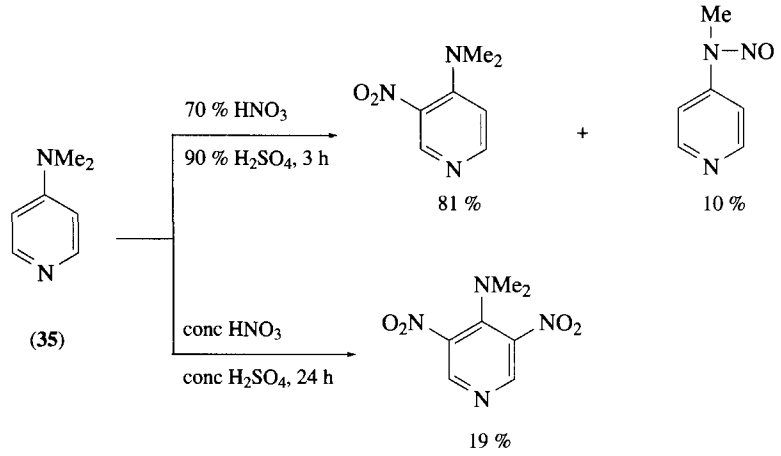
In the nitration of 2- or 4-phenyl-substituted pyridines, reaction occurs on the conjugate acid. Thus nitration occurs on the phenyl ring, due to reduced reactivity of the protonated pyridine. Based on the partial rate factors, the orientation effect of these nitrations was found to be *ortho* and *para* directive ⟨68JCS(B)862, 71JCS(B)712, 73JCS(P2)253⟩. Nitration of aminopyridines results in the formation of various products depending upon reaction conditions and the substituents on the amine group ⟨72JCS(P2)1950, 80CHE272⟩. Reaction of 2-anilinopyridines with nitric acid/sulfuric acid gave a mixture of 2′- and 4′-nitro products in poor yield. With nitric acid, the 2′,4′-dinitro derivatives were obtained in quantitative yield. However, nitration of *N*,*N*-diaryl-substituted aminopyridines in nitric acid/acetic anhydride gives pyridyl-(3- and 5-positions) and phenyl-nitrated products. From these results it was inferred that the conjugate acid was the reactive species in the former and the free base in the latter ⟨72CPB2678, 72CPB2686⟩. Nitration of 2-diarylaminopyridines (**34**) with nitric acid/sulfuric acid gave 93% of 5-substitution and 7% of 3-substitution (Equation (25)). Nitration of 4-*N*,*N*-dimethylaminopyridines (**35**) resulted in a mixture of products (Scheme 16) ⟨72JCS(P2)1940⟩.



Nitration of pyridones and hydroxypyridines has been achieved with relative ease as compared to pyridines. For example, 3-hydroxypyridine gives 74% 2- and only 1% of the 6-substitution product, and none of the 4-substitution product was observed ⟨68JOC478⟩. These results are consistent with the calculated charge densities ⟨69BAU1452⟩. Nitration of 2-substituted (methyl or chloro) 3-hydroxypyridines provided both 4- and 6-nitrated products, the former being the major isomer ⟨68JOC478, 69BAU1452⟩. The suggested mechanism involves coordination of the electrophile with the hydroxy group, thus promoting *ortho* substitution. This is supported by the decreasing ratio of 4- versus 6-substitution with increasing temperature and the complete absence of 4-substitution in the nitration of 3-methoxy-2-methylpyridine ⟨69BAU1452⟩.

Simple 2-pyridone can be nitrated in sulfuric acid at 80°C to give 100% yield of 3-nitro-2-pyridone. In contrast, nitration of 2-pyridone in 20% oleum at 0°C gave 17% 3- and 83% 5-substitution. The nitration was determined to take place on the free base both at low and high acidity ⟨68JCS(B)1477, 71TL2211, 72JCS(P2)1953⟩. Similarly, 4-pyridone reacts as the free base with nitrating agents, except at high acidity, and is less reactive than 2-pyridone ⟨68JCS(B)1477, 90AHC(47)299⟩.

Pyridine *N*-oxides are easily nitrated at the 4-position (Figure 8) ⟨51RTC581, 64CI(L)1577, 66JCS(B)870, 67JCS(B)1213⟩. Strong electron-donating groups like dimethylamino and hydroxyl substituents direct



Scheme 16

nitration *ortho* or *para* (Figure 9) ⟨67JCS(B)1213, 67JCS(B)1235, 70BAU2440, 70RCR627, 72JCS(P2)1940⟩. When an electron-donating group is present *ortho*/*para* to the nitrogen, the pK_a value increases and nitration occurs via the conjugate acid at the 3-position (Figure 10) ⟨67JCS(B)1213, 68JCS(B)862⟩. Nitration of 2,3′-bipyridine *N*-oxide occurs in the *N*-oxide containing ring, and it is suggested that the conjugate acid is involved since 5-nitration is observed. In contrast, 2,3′-bipyridine *N*′-oxide could not be nitrated ⟨75CHE352⟩.

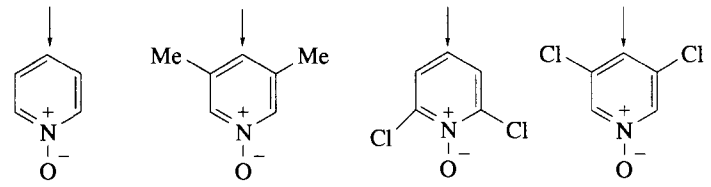


Figure 8 Regiochemistry of nitration.

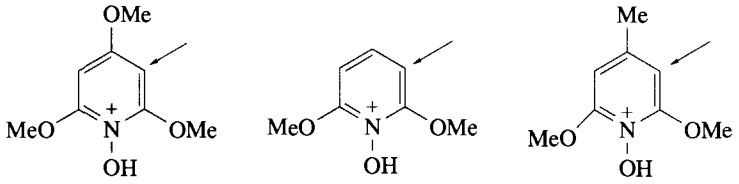


Figure 9 Regioselective nitration.

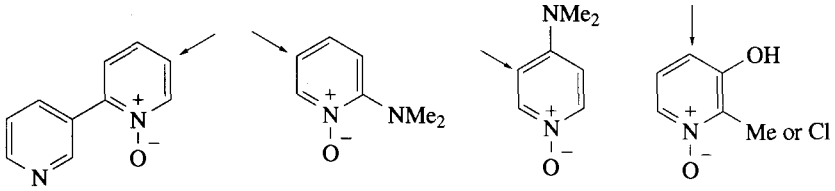


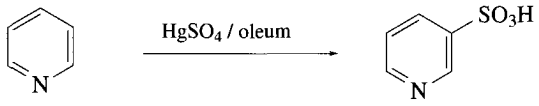
Figure 10 Substituent directed nitration.

Similar to the pyridine series, nitric acid, or metallo nitrates in acetic anhydride nitrate quinoline to give 3-nitroquinolines; however, some formation of 6- and 8-nitroquinolines is observed

⟨40JA1640, 57JCS2521⟩. Also 3-nitroquinoline can be obtained by nitration of quinoline with tetranitratotitanium(IV) ⟨74JCS(P1)1751, 40JA1640, 57JCS2521⟩. Based on rate–acidity profiles, the reacting species was proposed to be the quinolinium ion ⟨62CI(L)1057, 63CI(L)1283, 63JCS4204, 64T81⟩. Quinolines with strong activating groups at the 6-position and electron-withdrawing groups at the 4-position give good yields of 5- and 8-nitro derivatives. Nitration of substituted 4-chloro-6-methoxyquinolines provides a mixture of products depending upon the substituent ⟨69JCS(C)1369⟩. For a detailed account of nitration of pyridine and its benzo derivatives, see ⟨84CHEC-I(2)165, 90AHC(47)292, 90AHC(47)369⟩.

5.02.3.4 Sulfonation and Mercuration

Pyridine-3-sulfonic acid (**36**) can be obtained in 75% yield by treating pyridine with mercuric sulfate in oleum (Equation (26)) ⟨42CB1108, 43JA2233, 58RTC963, 90AHC(47)310⟩. Aluminum and vanadium compounds can be used as catalysts for the sulfonation of pyridines ⟨84CHEC-I(2)165⟩. The yield of the pyridine sulfonic acid is dependent on the reaction temperature and concentration of the oleum used. The methylpyridines are sulfonated at the β-position; thus, 2- and 3-methylpyridine gave the 5-sulfonic acid derivatives in 60% and 23% yield, respectively, whereas 4-methylpyridine gave the 3-sulfonic acid derivative in 40% yield ⟨43JA2233⟩. It is assumed that the low yields of products are due to the formation of the deactivated pyridine sulfur trioxide complex, and this assumption is supported by the fact that 2,4- and 2,6-dimethylpyridines failed to sulfonate due to the facile formation of the sufur trioxide complex. The more sterically hindered 2,6-di-*t*-butylpyridine is readily sulfonated at C-3 under aprotic conditions in liquid SO_2 (37% yield, 4 hr, −35°C). This result may be due to steric hindrance preventing the formation of the deactivating pyridine SO_3 complex ⟨53JA3865, 66JA986⟩. Hydroxy- and aminopyridines can also be sulfonated with some degree of regioselectivity ⟨90AHC(47)310⟩.

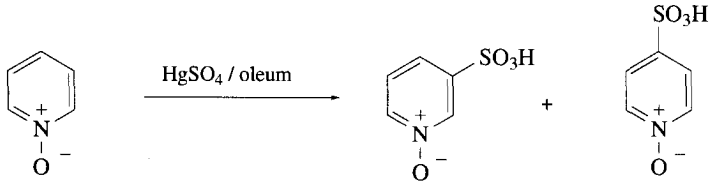


75 %

(**36**)

(26)

Pyridine *N*-oxide (**37**) is less reactive than pyridine, and only 40–45% of the pyridine-3-sulfonic acid *N*-oxide (**38**) can be obtained along with the 4-isomer (**39**) and unreacted starting material by using the same conditions that gave a 75% yield of pyridine sulfonation (Equation (27)) ⟨55JA2902, 59RTC586⟩. Quinoline and isoquinoline both undergo sulfonation in the benzene ring ⟨77HC(30)1⟩.



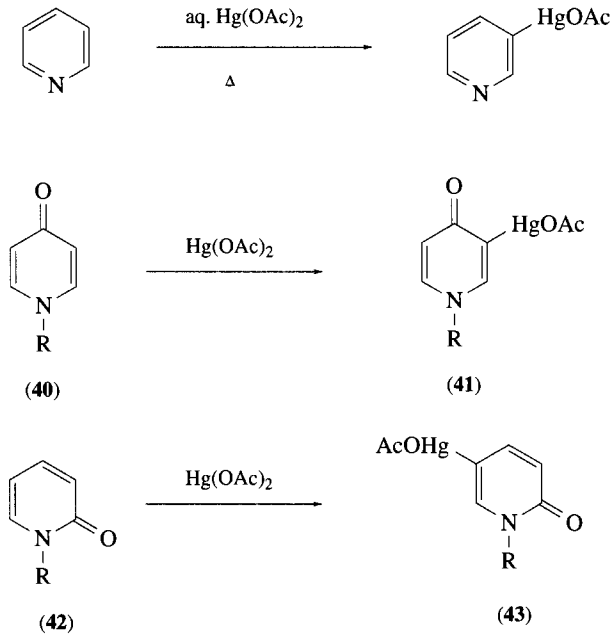
(**37**) (**38**) (**39**)

40-45 %

(27)

Analogous to sulfonation, pyridine yields 3-pyridylmercury(II) acetate by heating with aqueous mercury(II) acetate (Equation (28)) ⟨55JA4658⟩. Quinoline is mercurated on nitrogen at room temperature, but the 3- and 8-substituted derivatives are obtained at 160°C. Mercuration of 4-pyridone (**40**) with mercury(II) acetate gives the 3-mercurated product (**41**), while mercury(II) acetate-acetic acid provides the 5-mercurated product (**43**) with 2-pyridone (**42**) (Scheme 17). With 3-hydroxypyridine, mercuration occurred at C-2 ⟨74HC(14)489⟩, whereas 4-aminopyridine gave 3- and 5-mercurated products (Figure 11). Pyridine *N*-oxide is readily mercurated at C-2 under

neutral conditions but under acidic conditions there was significant mercuration at C-3 (Scheme 18) ⟨62RTC124⟩.



Scheme 17

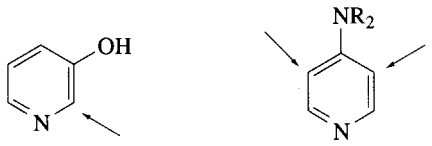
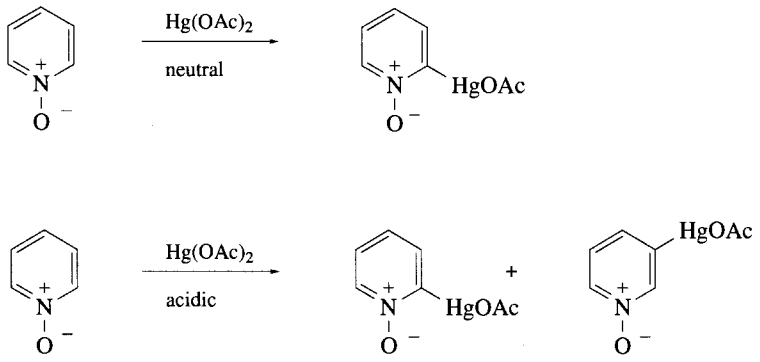


Figure 11 Electrophilic mercuration.



Scheme 18

5.02.3.5 Diazo Coupling

Pyridine is not reactive enough to undergo direct azo coupling. In contrast, hydroxypyridines do react, and 2-pyridone gives the 5-phenylazo derivative (Figure 12) ⟨75RCR823⟩. Monoamino-

pyridines do not give nuclear substitution, but 2,6-diaminopyridine does undergo azo coupling at the 3-position, and with excess diazonium salt 3,5-disubstitution occurs. Quinolin-4-one couples at C-3, with further substitution at nitrogen; likewise, 3-hydroxyquinoline has been shown to couple at the 4-position ⟨72BAU452⟩.

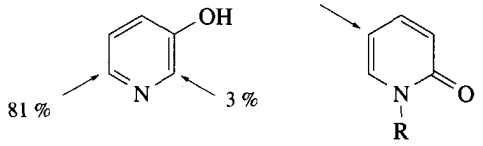


Figure 12 Diazo coupling

5.02.3.6 Nitrosation

Pyridines bearing two or more activating substituents undergo *C*-nitrosation. *N*-Nitrosation along with *C*-nitrosation has been reported to occur when monoaminopyridines are treated with nitrous acid ⟨75RCR823⟩. Nitrosation of 2,6-diaminopyridine, 6-aminopyridin-2-one, and 6-hydroxypyridin-2-one all occur at the 3-position (Figure 13) ⟨72JCS(P2)1940⟩.

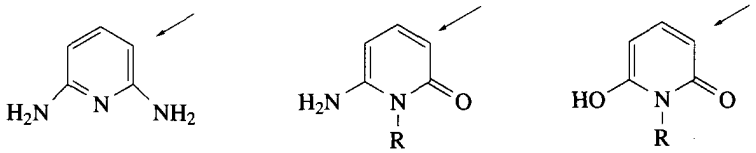


Figure 13 C-3 Nitrosation.

5.02.3.7 Acylation and Alkylation

Carbon acylation and alkylation of pyridine or pyridine *N*-oxide is extremely difficult ⟨49JA387, 66AHC(6)229, 77JOU1231, 84CHEC-I(2)165, 90AHC(47)308⟩. Carboxylation of 2-pyridone and 3-hydroxypyridine can be achieved *ortho* and *para* to the oxygen substituent under basic conditions (Figure 14) ⟨24CB1161, 90AHC(47)308⟩. Certain 2-acylpyridines can be obtained by heating chloroalkyl esters with pyridines and subsequent treatment with sodium hexamethyldisilazide (Scheme 19). Isoquinolines can also be acylated at the 1-position using the same method (Equation (29)). The mechanism of the acylation is as shown in Scheme 19 ⟨86CB279⟩.

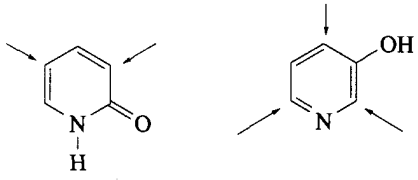
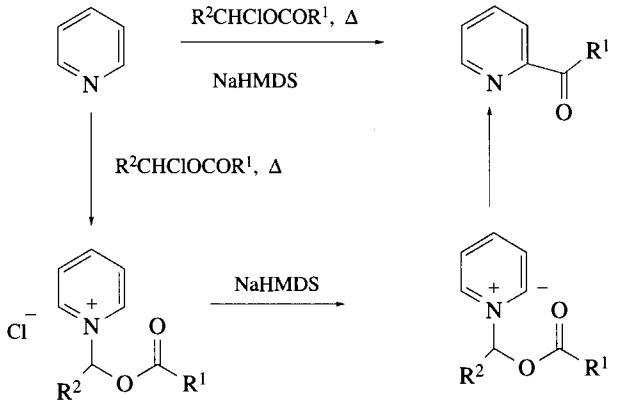
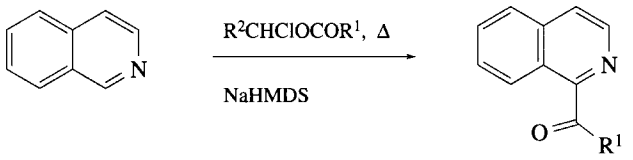


Figure 14 Regioselective carboxylation.



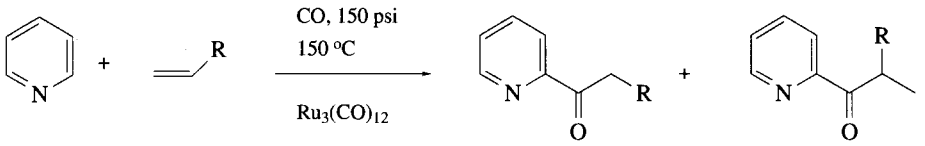
Scheme 19



(29)

57 %

Acylation of pyridines has been achieved using a $Ru_3(CO)_{12}$ catalyzed reaction (Equation (30)) ⟨92JA5888⟩. Heating an alkene and $Ru_3(CO)_{12}$ in pyridine as the solvent at 150 °C with carbon monoxide at a pressure of 150 psi provides the 2-acylated product. Conversion of 1-hexene to the acylated product is 65% after 16 h; only the 2-acylated products are observed. The proposed mechanism is the initial nucleophilic attack of pyridine on the metal center followed by pyridine coordination and *ortho* metallation to afford cluster complexes (Figure 15). Alkene coordination and insertion into the bridging hydride followed by migration of the alkyl group to the carbonyl carbon and subsequent reductive elimination gives the 2-acylated products. This mechanism is supported by kinetic data which show that the reaction is first order with respect to pyridine and $Ru_3(CO)_{12}$ and is zero order with respect to CO pressure and alkene concentration. Various alkenes react with pyridines having at least one α-hydrogen to give the expected products under these conditions. Reaction of 2,6-lutidine did not give any acylated product, which is consistent with the finding that only the α-position is activated. The less nucleophilic pyridines like 4-chloropyridine were found to be less reactive. Benzopyridines are also less reactive and reacted at a slower rate than pyridine.



(30)

R = C_4H_9 13 : 1

5.02.3.8 Oxidations

Pyridines undergo ozonolysis to give products corresponding to addition of ozone to both Kekulé forms ⟨84CHEC-I(2)165⟩. Pyridines have been converted into 2-pyridones using copper sulfate (Equation (31)) ⟨79JHC(16)1283⟩. A similar conversion using zinc sulfate heptahydrate or tricadmium sulfate octahydrate and oxygen has also been reported ⟨88CC1163⟩. The conversion was in the range of 2–15%.

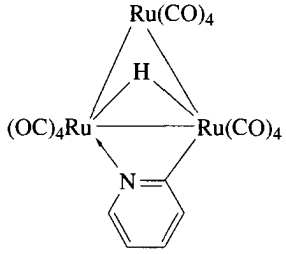
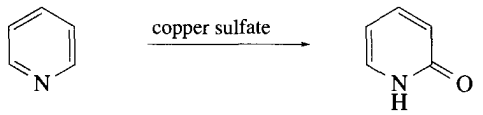


Figure 15 Pyridine cluster complex.



(31)

Quinoline can be oxidized under ozonolysis conditions to pyridine-2,3-biscarboxaldehyde. Oxidation of 2-alkyl- or 2-aryl-substituted quinolines with permanganate can, depending on conditions, give either the pyridine or the benzene ring oxidized product. Similarly, the oxidation of isoquinoline with permanganate can occur in both rings. Electron-withdrawing or -releasing substituents can direct the oxidation to either the benzene or pyridine ring. In 5-aminoisoquinoline, the oxidation occurred in the benzene ring; however, 5-nitroquinoline gave the product of pyridine ring oxidation.

5.02.4 NUCLEOPHILIC ATTACK AT CARBON

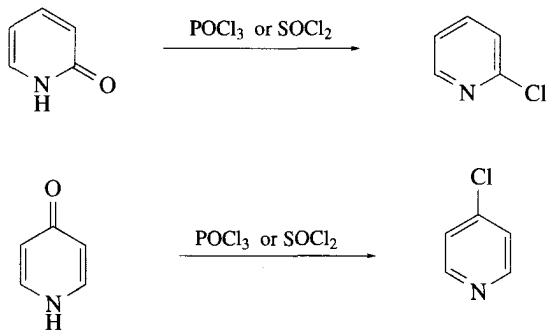
5.02.4.1 Introduction

Many nucleophiles react with halogenated pyridines effecting displacement of halogen, whereas only strong nucleophiles react with simple pyridine. In contrast, pyridine *N*-oxide and certain pyridones readily undergo nucleophilic substitution. Nucleophilic reactions of pyridinium salts are quite facile and in some cases give substituted pyridines via an addition–elimination mechanism.

5.02.4.2 Halogenation: Formation of a Carbon–Halogen Bond

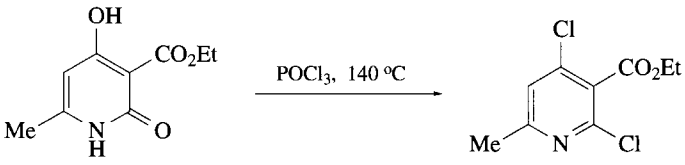
5.02.4.2.1 Chlorination

Nucleophilic chlorinations of pyridines and their benzo derivatives are quite common. Among these, introduction of the chlorine to the 2-, 4-, and 6-positions by the reaction of pyridones with phosphoryl or thionyl chloride is the most widely used method (Scheme 20) ⟨80AG(E)388, 84S743, 85CZP219406, 87CHE865, 87CI(L)694, 88ACS(B)524, 89CPB2117, 89SC553, 90S499, 90S681⟩. The other reagents used for this purpose are phosgene in *N*,*N*-dimethylformamide ⟨83EUP72777⟩ and phosphorus pentachloride ⟨88ACS(B)524⟩.

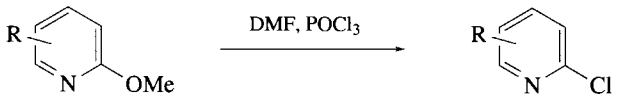


Scheme 20

For the conversion of 2- and 4-pyridones to the corresponding chloropyridines, thionyl chloride in refluxing methanesulfonic acid has been found to be the most efficient reagent ⟨87CI(L)694⟩. When ethyl 4-hydroxy-6-methyl-2-pyridone-3-carboxylate (**44**) was heated at 140°C with phosphoryl chloride, ethyl 2,4-dichloro-6-methylpyridine-3-carboxylate (**45**) was obtained in 89% yield (Equation (32)) ⟨88S479⟩. The Vilsmeier–Haack reagent is also known to convert 2-methoxypyridines (**46**) into 2-chloropyridines (**47**) in 50–71% yield (Equation (33)) ⟨90SC2971⟩. Direct nucleophilic halogen exchange can be carried out on 2- and 4-bromopyridines and/or their *N*-oxides in a polar aprotic solvent ⟨85USP4546192⟩.

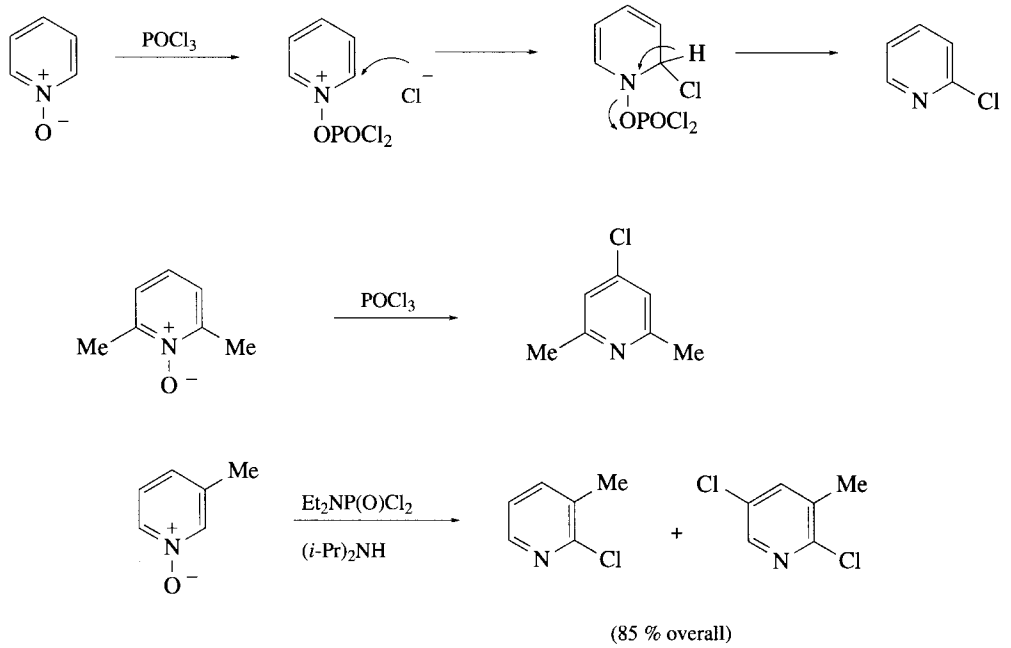


(44) (45) 89 % (32)



(46) (47) 50-71 % (33)

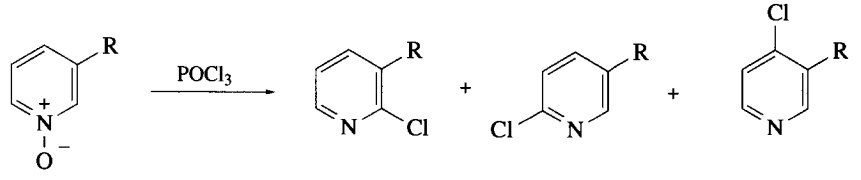
When the oxygen of the pyridine *N*-oxide is coordinated with electrophilic phosphorus reagents, chloride ions can attack the pyridine nucleus (Meisenheimer reaction) ⟨81JHC939, 83T291, 88CPB2244, 88S479, 90JHC1841, 92EUP463464, 93AHC(58)227⟩, and examples are shown in Scheme 21.



Scheme 21

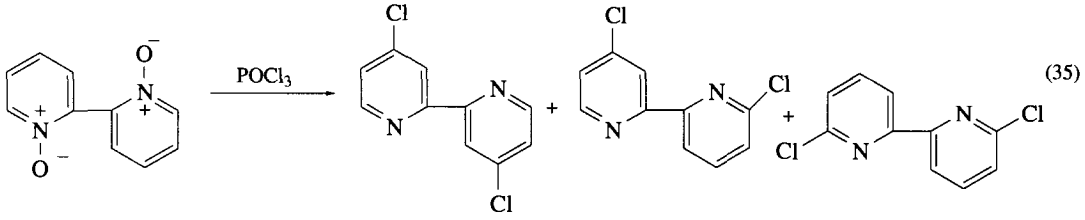
The attack of chloride ion occurs preferentially at the 2- and 6-positions rather than at the 4-position. Substitution of an electron-withdrawing group at C-3 enhances the reactivity at C-2, but an electron-releasing group appears to be quite nonspecific in its directing effects (Equation (34)) ⟨88CPB2244⟩. Reaction at C-4 can be forced if the 2- and 6-positions are blocked ⟨90JHC1841⟩. Nucleophilic chlorination of 2,2′-bipyridine di-*N*-oxide by heating with phosphoryl chloride gave a mixture of products (Equation (35)), the major of which was 4,4′-dichloro-2,2′-bipyridine. On the

other hand, 4,4′-dinitro-2,2′-bipyridine di-*N*-oxide (**48**) under similar conditions also underwent chlorodenitration (Equation (36)) ⟨83T291⟩. Similar chlorodenitration was observed when **4**-nitropyridine 1-oxide was treated with hydrogen chloride, phosphoryl chloride, and acetyl chloride ⟨86JHC177, 91T1697⟩.

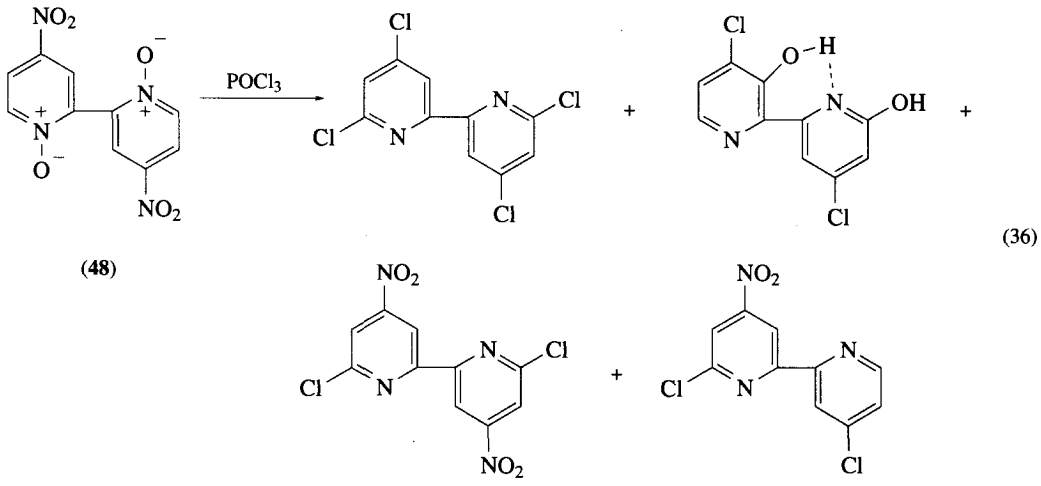


(34)

R				
H	70	:	0	: 30
Me	30	:	27	: 43
Ph	32	:	46	: 22
NMe_2	34	:	47	: 19
CN	88	:	10	: 2
NO_2	73	:	27	: 0



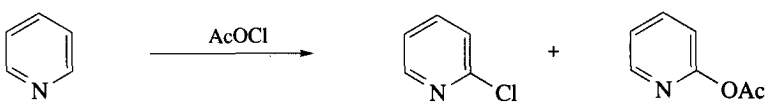
(35)



(36)

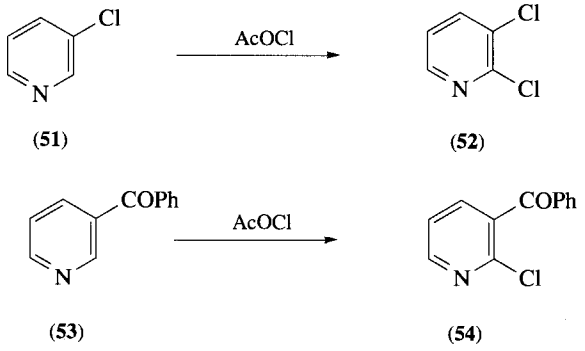
(48)

Acetyl hypochlorite in methylene chloride converts pyridine into 2-chloropyridine (**49**) as the main product and 2-acetoxypyridine (**50**) as a minor product (Equation (37)) ⟨87TL2705, 88JOC1123⟩. Similarly, 3-chloropyridine (**51**) can be converted into 2,3-dichloropyridine (**52**) with acetyl hypochlorite, and 3-benzoylpyridine (**53**) gave the 2-chloro product (**54**) in around 80% yield (Scheme 22) ⟨88JOC1123⟩.



(37)

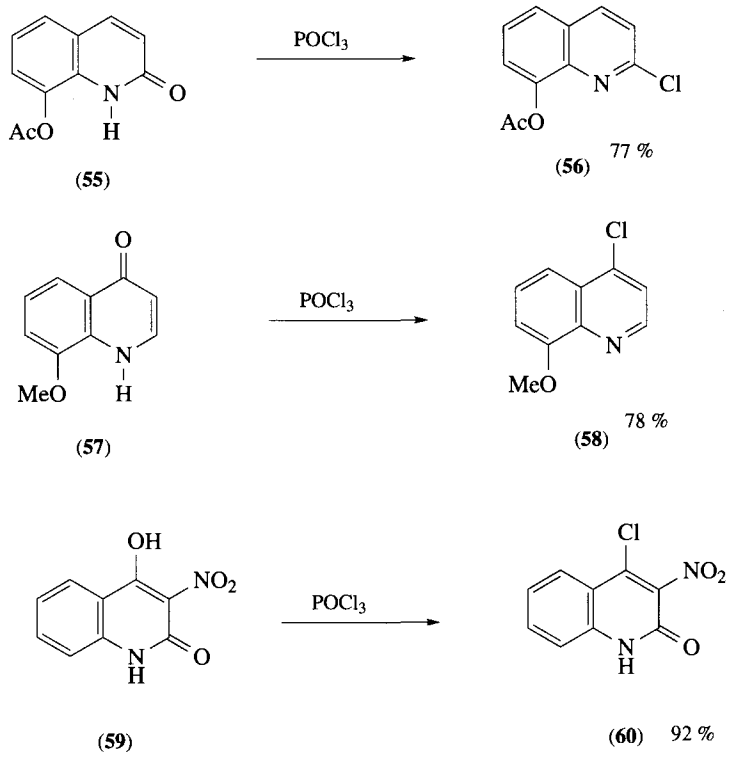
(49) (50)



Scheme 22

High yields of 3-chloropyridines can be obtained from the corresponding aminopyridines via the Sandmeyer chlorodediazoniation. Chlorodediazoniation has been used to prepare all three chloropyridines in high yields. Sandmeyer-type conditions proved to be less successful when concentrated hydrochloric acid was used ⟨92ACS157⟩.

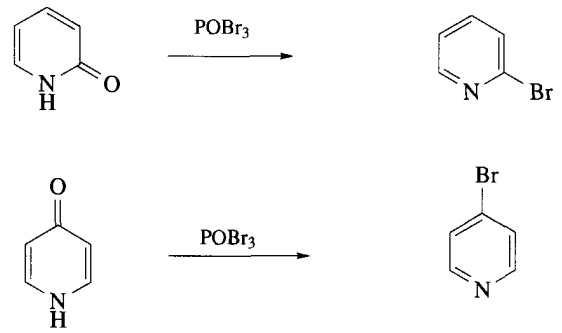
Pyridine *N*-oxides and pyridones, and hydroxyquinolines and quinolones can also be converted to the chloro derivatives using variety of reagents ⟨86M1305, 91M935, 91MIP57729, 94AHC(59)288⟩. Some examples are the conversion of 8-acetoxy-2-quinolone (**55**) and 8-methoxy-4-quinolone (**57**) into the 2-(**56**) and 4-chloro derivatives (**58**) ⟨91M935⟩, and 4-hydroxy-3-nitro-2-quinolone (**59**) to 4-chloro-3-nitroquinolone (**60**) in high yield (Scheme 23) ⟨92JHC225⟩. These reaction conditions can also be used for the preparation of chlorinated phenanthrolines ⟨88YZ1148⟩. However, chlorination of the substituents has been reported when phosphorus pentachloride, or PCl_5 in combination with phosphoryl chloride, is used as the chlorinating agent ⟨91JHC1549⟩. Similar chlorination of the substituents is likely when sulfuryl chloride and NCS are employed ⟨83KFZ1055, 86S835⟩.



Scheme 23

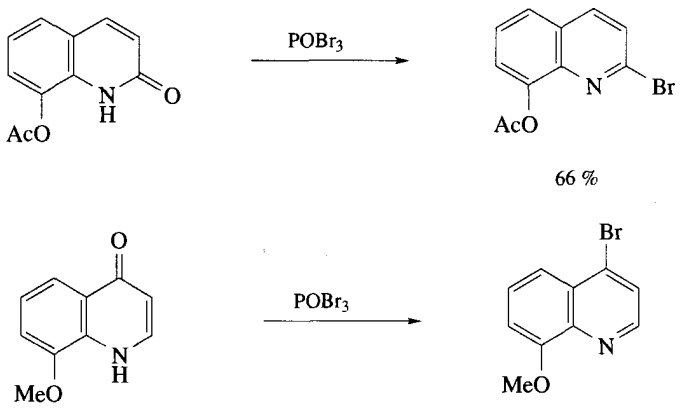
5.02.4.2.2 Bromination

Nucleophilic brominations of pyridine and their benzo derivatives are useful methods for preparing 2-, 4-, and 6-bromopyridines. The reaction of 2- and 4-pyridones with phosphoryl bromide gives 2- and 4-bromopyridines, respectively (Scheme 24) ⟨78CHE55, 83TL2973, 88ACS(B)524, 89M1095, 90S499⟩. An alternate method for preparing bromopyridines is the nucleophilic displacement of groups like nitro and chloro. This can be achieved using HBr, either on the substituted pyridine or the corresponding *N*-oxide ⟨81JAP(K)115776, 83JAP(K)5818360, 87MI 502-06⟩. An alternative nucleophilic displacement method is the reaction of alkyl bromides with *N*-fluorinated pyridines. A limitation of this procedure is that the weakly basic pyridines do not give *N*-fluoropyridines by reaction with electrophilic fluorine ⟨91JOC6298⟩. All the nucleophilic displacement procedures are known to give high yields of 2-bromopyridines ⟨88JOC1123⟩.



Scheme 24

Nucleophilic brominations on benzo derivatives of pyridines have been achieved via diazonium salts ⟨87JHC181⟩ and via syntheses based on hydroxy and oxoderivatives (Scheme 25) ⟨91M935⟩. The former process has been used to prepare 5-, 6-, 7-, and 8-bromo derivatives of quinoline. For the benzo derivatives, the use of bromine–halogen exchange reactions are not common for the preparation of bromo derivatives.

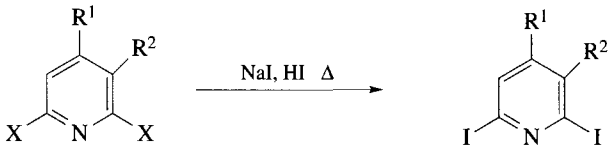


Scheme 25

5.02.4.2.3 Iodination

As with other halogenations, iodinated pyridines can be obtained in good yield using the Sandmeyer reaction ⟨87MI 502-07⟩. Halogen exchange also can be achieved; thus, treatment of 2,6-dichloropyridine with a high concentration of iodide ion gives 2,6-diiodopyridine ⟨80JOM(186)147⟩.

In a similar manner, the presence of iodide ion transformed 2,6-dichloronicotinic acid (**61**; $R^1 = H$, $R^2 = CO_2H$, $X = Cl$) into 2,6-diiodonicotinic acid (**62**; $R^1 = H$, $R^2 = CO_2H$) (Equation (38)) ⟨86JOC953⟩.



(38)

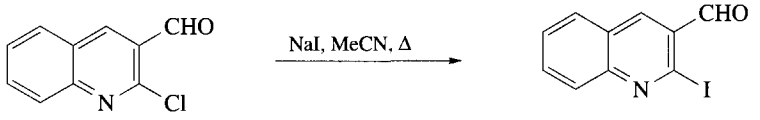
(**61**)

$R^1 = H, CF_3$
$R^2 = H, CF_3, CO_2H$
X = Cl, Br

(**62**)

37-51 %

Halogen exchange on 5-chloro-8-hydroxy-7-iodoquinoline with cross linked polystyrene-4-vinylpyridinium dichloroiodate gave the 5,7-diiodo derivative ⟨89JCS(P1)2279⟩. Similarly, sodium iodide in refluxing acetonitrile converted 2-chloroquinoline-3-carbaldehyde (**63**) into 2-iodoquinoline-3-carbaldehyde (**64**) in 90% yield (Equation (39)) ⟨81JCS(P1)2509⟩.



(39)

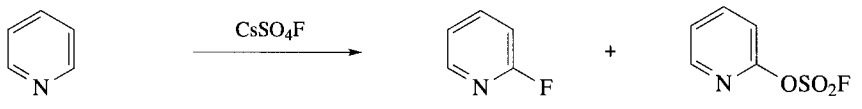
(**63**)

(**64**) 90 %

5.02.4.3 Fluorination

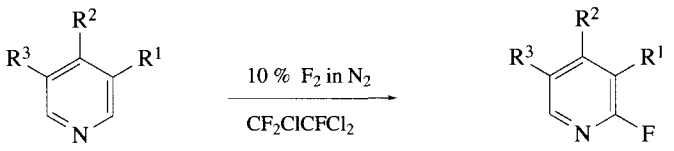
Ring fluorination of pyridine and its benzo derivatives is believed to occur through a nucleophilic process. In electron-deficient pyridines and their benzo derivatives, fluorination on the pyridine ring is kinetically competitive with annular and side chain fluorination. These fluorinations may proceed through initial formation of a pyridine fluorine complex ⟨87TL255, 91BCJ1081, 93AHC(58)291⟩.

Electrochemical fluorination of pyridine in presence of a fluoride ion source gives 2-fluoropyridine in 22% yield ⟨85MI 502-03⟩. Xenon difluoride and xenon hexafluoride have been used to fluorinate pyridine to give a mixture of 2- and 3-fluoropyridine along with 2,6-difluoropyridine ⟨76JFC(7)179⟩. Caesium fluoroxysulfate at room temperature in ether or chloroform converted pyridine to 2-fluoropyridine (**65**) in 61 and 47% yield respectively, along with 2-fluorosulfoxypyridine (**66**) (Equation (40)) ⟨90TL775⟩. There are also several reports on the preparation of 2-fluoropyridines by direct reaction of fluorine diluted in an inert gas and dissolved in a polyhalogenated solvent (Equation (41)) ⟨65ZC64, 87TL255, 88USP4786733, 91BCJ1081⟩. Base-catalyzed decomposition of *N*-fluoropyridinium salts gives 2-fluoropyridines in low yields ⟨87TL2705, 89JOC1726⟩.



(40)

Solvent	(**65**)		(**66**)
n-C_5H_{12}	56	:	44
Et_2O	61	:	39
C_6H_{12}	70	:	30
CCl_4	70	:	30
$CHCl_3$	47	:	17

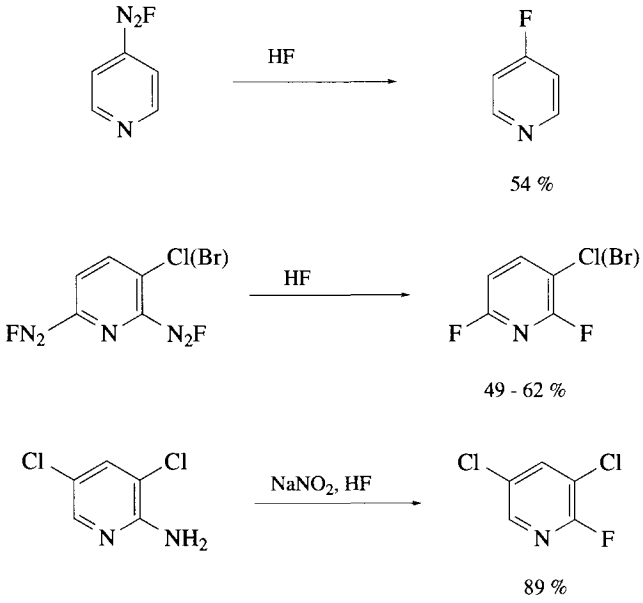


(41)

26 - 61 %

R^1 = H, Me, Cl, CO_2Me
R^2 = H, Me, Et, *i*-Pr, COMe, CO_2Me
R^3 = H, Me, Cl

Nucleophilic fluorination such as chlorine–fluorine exchange or Balz–Schiemann reactions of diazonium fluoroborates are reported to yield fluoropyridines. Fluoroborates can also be converted to fluoro compounds by ultraviolet irradiation. Synthesis of 2-fluoropyridines ⟨71JA3060, 81JOC4567⟩ and the 3- and 4-isomers ⟨80CC1139, 81JFC(18)497, 81JOC4567, 85JHC145, 87LA857, 88JFC(38)435, 89S905, 90S681⟩ has been achieved by this method. 2-Fluoropyridines can be prepared from diazonium fluorides, even with weak nucleophiles such as fluoride ion in hydrofluoric acid (Scheme 26) ⟨81JFC(18)497, 81JOC4567⟩.



Scheme 26

Halogen exchange is a somewhat more difficult process but has been used to prepare fluoropyridines. This reaction is often carried out at high temperatures and has been reported using a variety of fluoride sources (such as BrF_3, SbF_5, KF, HF) in dipolar aprotic solvents ⟨63JOC1666, 86USP4567274, 87JAP(K)6212758⟩.

Fluorination of quinolines using a caesium tetrafluorocobaltate at 350°C gives a mixture of saturated polyfluoro compounds ⟨82JFC413⟩. All the monofluoroquinolines except the 4-fluoro derivative are available from the amino precursors ⟨49JA1785⟩ via the Sandmeyer reaction. Halogen exchange has also been employed in some cases to yield the desired fluorinated compound. Various 2-fluoroquinolines are obtained in good yields by the reaction of potassium fluoride with 2-chloroquinolines ⟨62RTC1058⟩. Preparation of 2-fluoroquinoline can also be carried out, in higher yield (99%), by treating the 2-chloro derivative with tetrabutylphosphonium hydrogen difluoride or dihydrogen trifluoride under mild conditions ⟨92H(34)1507⟩. Halogen–fluorine exchange at C-3 of some 3-chloroquinoline-2,4-diones ⟨92M617⟩, and fluorine–nitro group exchange ⟨87JHC181⟩ are the other methods for the synthesis of fluoroquinolines. Gaseous fluorine diluted with argon converts 2-methylisocarbostyril in acetic acid to the 4-fluoro derivative ⟨82H(17)429⟩. Fluoroisoquinolines can also be obtained by fluoride displacement of nitro groups and/or diazonium fluoroborates ⟨87JHC181⟩.

5.02.5 CARBON NUCLEOPHILES

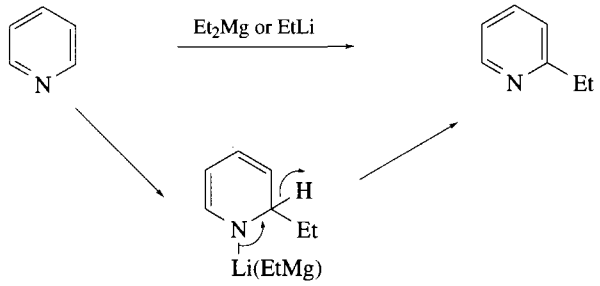
5.02.5.1 Organometallics and Enolates

5.02.5.1.1 Neutral molecules

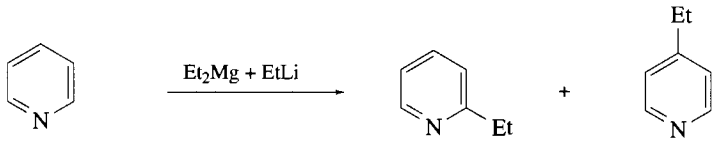
Pyridines and their benzo derivatives react with organometallic reagents both as the free bases and as pyridinium salts. Normally, the reaction occurs at the α-position, but in certain cases it can be selective at the γ-position. Selectivity depends on the organometallic reagent and the substituents on the pyridine ring. The reactivity of pyridines as the free bases is relatively low, but can be enhanced by an electron-withdrawing group ⟨84CHEC-I(2)165⟩.

On heating, Grignard reagents, with no free metals present, normally react with pyridine to give 2-substituted pyridines ⟨84CHEC-I(2)165⟩. But in the presence of free metals, mixtures of 4- and 2-substituted pyridines are obtained. By increasing the amount of free metal, exclusive formation of the 4-substituted product is observed.

Aryllithiums, like phenyllithium, arylate the 2-position of a pyridine ring. This reaction has been shown to be an addition–elimination process. As with metal free Grignards, lithium reagents generally add to the 2 position. This has been demonstrated with Et_2Mg or EtLi, which react with pyridine to give only 2-substituted products (Scheme 27) ⟨85TL275⟩. However, a mixture of Et_2Mg and EtLi reacts with pyridine to give a mixture of 2- and 4-substituted products (Equation (42)). The amount of 4-substituted products can be increased by the addition of crown ethers ⟨90OM1778⟩. Magnesiate species are thought to be responsible for these changes in regioselectivity. In the reaction of Bu^nLi with pyridine, the intermediate 2-Bu(C_6H_5N)Li was characterized, and it was shown to be a 1,2-dihydro-2-butylpyridine ⟨88POL665⟩.



Scheme 27

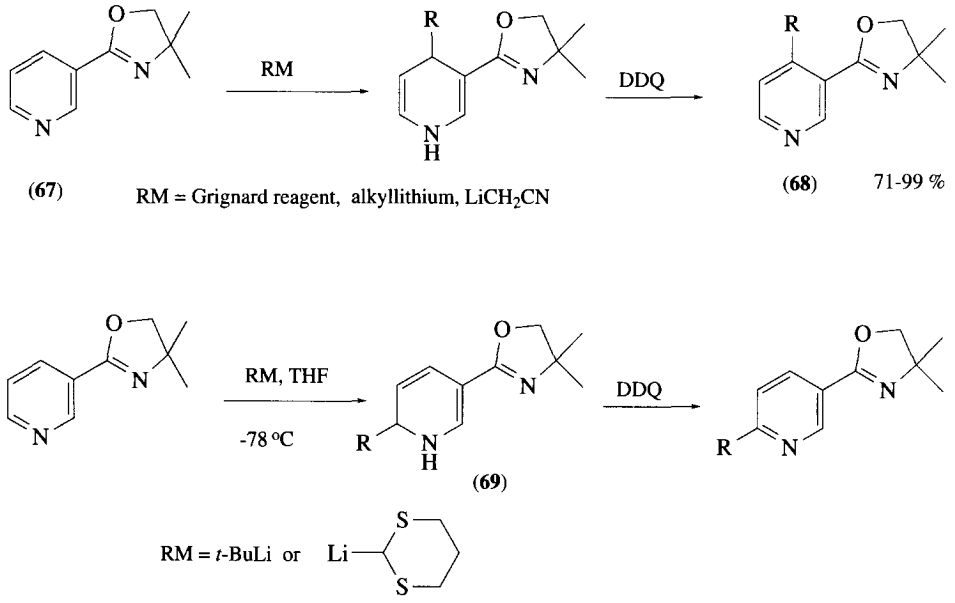


(42)

Grignard reagents, alkyllithiums, or lithiated acetonitrile react with 4,4-dimethyl-2-(3-pyridyl)-oxazoline (**67**) to give 4-substituted 1,4-dihydropyridines (**68**), but the same reaction with *t*-butyllithium or lithiodithiane results in formation of 2-substituted 1,2-dihydropyridines (**69**). These dihydropyridines can be aromatized to the corresponding pyridines using ddq (Scheme 28) ⟨82JOC2633⟩. The regioselectivity of the organolithium reaction with 3-pyridyloxazolines was found to depend on temperature and solvent ⟨84H(22)1091, 84JCS(P1)2227, 84JOC56, 86H(24)125⟩.

Methoxy-containing oxazolinylpyridines (**70**) on reaction with organolithium reagents gave the 4-substituted products (**71**), whereas hydroxy-containing oxazolinylpyridines (**72**) gave 2-substituted products (**73**) (Scheme 29) ⟨82H(18)13⟩. *N*-Phenylnicotinamides reacted with organolithiums to give 4-substituted 1,4-dihydropyridines ⟨83TL4735⟩. Methyllithium addition to nicotine (**74**) gave predominately the 2,5-disubstituted product, along with the 3,4- and 2,3-disubstituted materials ⟨83JOC4899⟩. Other alkyllithium reagents also reacted regioselectively with nicotine to provide 2,5-disubstituted nicotinoids in low optical purity (Scheme 30) ⟨82TL2519, 85T595⟩. Reaction of 2-methoxypyridine with alkyllithiums afforded a 2-substituted 1,2-dihydropyridine intermediate, which was oxidized to a 2-methoxy-6-alkylpyridine ⟨86JOC2184⟩.

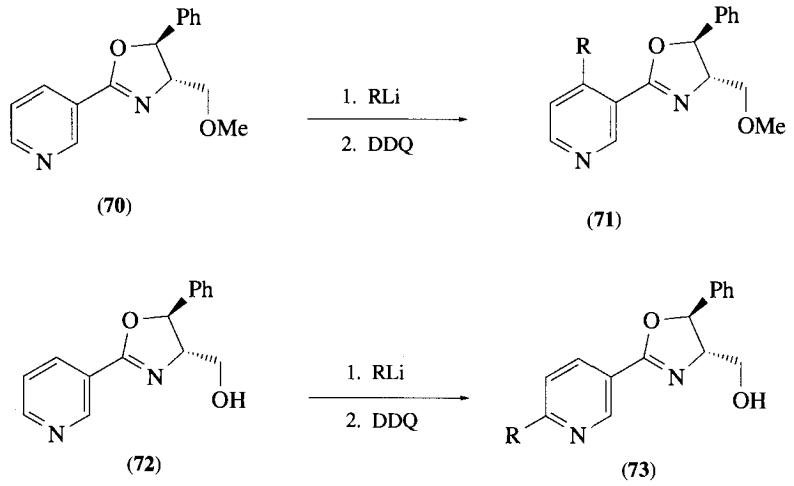
Reaction of (4-alkylphenyl)lithiums with pyridine gave 2-(4′-alkylphenyl)-1-lithio-1,2-dihydro-



(67) RM = Grignard reagent, alkyllithium, $LiCH_2CN$ (68) 71-99 %

(69)

Scheme 28



(70) (71)

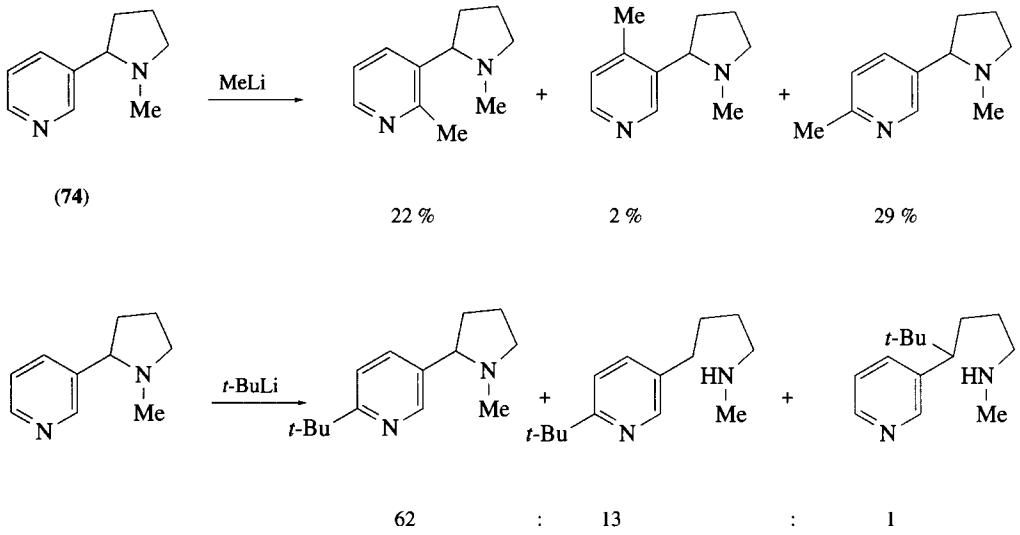
(72) (73)

Scheme 29

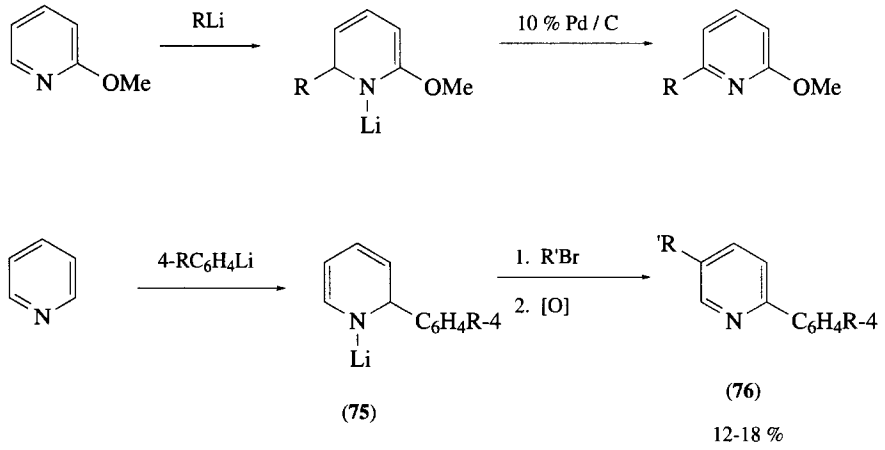
pyridines (**75**), which on further reaction with alkyl halides afforded 2-(4′-alkylphenyl)-5-alkylpyridines (**76**) (Scheme 31) ⟨85KGS1389⟩. Pyridine and its benzo derivatives reacted with perfluoroalkyllithiums in presence of boron trifluoride etherate to give the corresponding perfluoroalkyl addition or substitution products in good yields. These reactions were regioselective towards the α-position of the heterocycle ⟨88CL1165⟩.

5.02.5.1.2 Via pyridinium salts

Both *N*-alkyl and *N*-acylpyridinium salts undergo reaction with organometallic reagents more easily than with pyridine. *N*-Alkylpyridinium salts on treatment with Grignard reagents give 2-substituted-1,2-dihydropyridines ⟨84CHEC-I(2)165⟩. An asymmetric version of these reactions has been reported, and the resulting 1,2-dihydropyridines have been used as intermediates for the synthesis of normetazozine and nordextromorphan (Equation (43)) ⟨93JOC2052⟩. Reaction of

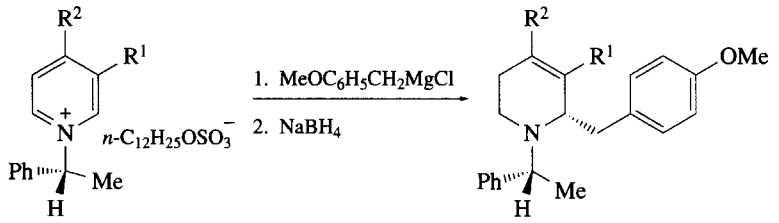


Scheme 30



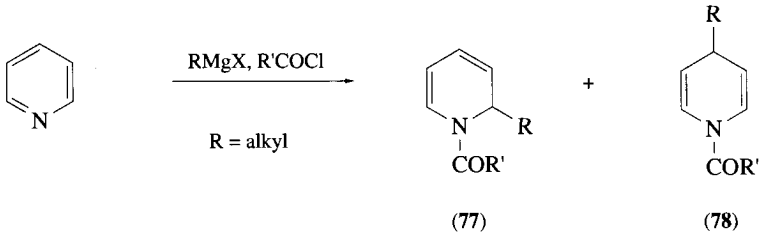
Scheme 31

N-(*t*-butyldimethylsilyl)pyridinium triflate with Grignard reagents was found to occur with high regioselectivity, resulting in 4-substituted 1,4-dihydropyridines ⟨82TL3935⟩.



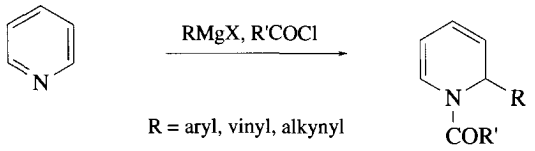
(43)

N-Acylpyridinium salts react with organometallic reagents efficiently and in many cases regioselectively ⟨88AHC(44)199⟩. With Grignard reagents, *N*-acylpyridinium salts can give 2-substituted 1,2-dihydropyridines, 4-substituted 1,4-dihydropyridines, or a mixture of the two depending upon the structure of the nucleophile and the substituents on the pyridine ring (Equation (44)) ⟨82CRV223, 88H(27)291, 88AHC(44)199⟩. It has been shown that alkyl Grignards and *N*-acylpyridinium salts give mixtures of 1,2- (**77**) and 1,4-dihydropyridines (**78**), whereas aryl, vinyl, and alkynyl Grignard reagents yield mainly the 1,2-dihydropyridine products (**79**) (Equation (45)) ⟨88AHC(44)199⟩.



(44)

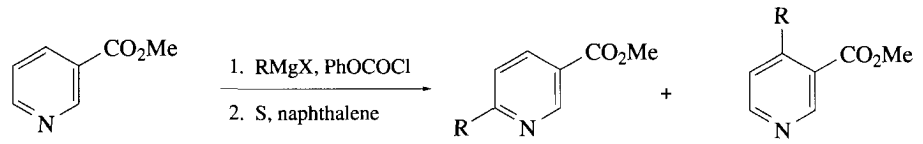
(77) (78)



(45)

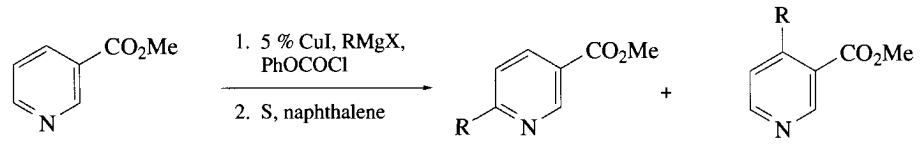
(79)

The regioselectivity of Grignard addition to *N*-acylpyridinium salts has been controlled in many ways. The addition of a catalytic amount of copper salt leads to the predominant formation of the 4-substituted 1,4-dihydropyridine ⟨82JOC4315⟩. Stoichiometric organocopper reagents (R_2CuLi, RCu, $RCu{\cdot}BF_3$) have also been shown to add regioselectively to the 4-position ⟨74CJC3563, 82TL429, 84BCJ1994⟩. Grignard reagents react with 1-phenoxycarbonyl salts of alkyl nicotinates to give both 2 and 4 addition products. Aryl Grignard reagents add to *N*-phenoxycarbonyl salts of methyl nicotinate to give the 2 and 4 adducts in a ratio of 84:16. Alkyl Grignard reagents are less regioselective (Equation (46)) ⟨84H(22)151⟩. The regioselectivity towards C-4 addition products can be enhanced by the presence of catalytic amounts of copper salts (Equation (47)). The dihydropyridines can be aromatized to pyridines using various methods ⟨88AHC(44)210⟩. A similar approach has been used to convert 3-halopyridines, 3-pyridinols, and 3-acylpyridines into 3,4-disubstituted pyridines ⟨83JHC1239, 84H(22)339, 85JHC1419, 86H(24)3199⟩.



(46)

R		
Me	40	60
n-Bu	43	57
c-C_6H_{11}	16	84
Ph	84	16

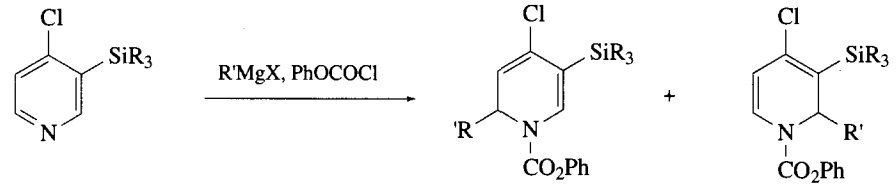


(47)

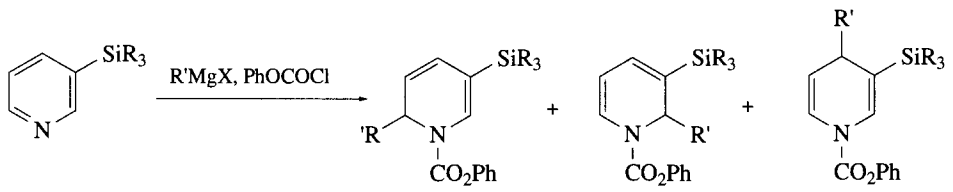
R		
Me	1	99
n-Bu	7	93
c-C_6H_{11}	4	96
Ph	5	95

For complete regiocontrol towards C-2 addition products, an easily removable block at C-3 has been used in the form of the trialkylstannane or -silane group. Thus, pyridines substituted at

C-3 with a trialkylstannane or -silane group react with Grignard reagents to give predominantly the C-6 adduct (Scheme 32) ⟨87TL759, 90JOC292⟩. Similarly, a trimethylstannyl substituent at C-4 directed the reaction to occur exclusively α to the nitrogen (Equation (48)) ⟨84TL4867⟩.

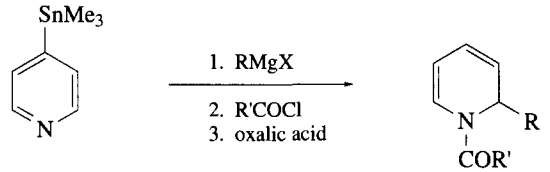


R	R'			
Me	Me	66	:	34
	n-Bu	72	:	28
Et	Me	88	:	12
	n-Bu	93	:	7
n-Pr	Me	87	:	13
	n-Bu	93	:	7
i-Pr	Me	100	:	0
	n-Bu	100	:	0



R	R'					
Et	Me	74	:	19	:	7
	n-Bu	72	:	14	:	14
	c-C_6H_{11}	71	:	8	:	21
	Ph	100	:	0	:	0
i-Pr	Me	100	:	0	:	0
	n-Bu	100	:	0	:	0
	c-C_6H_{11}	100	:	0	:	0
	Ph	100	:	0	:	0

Scheme 32

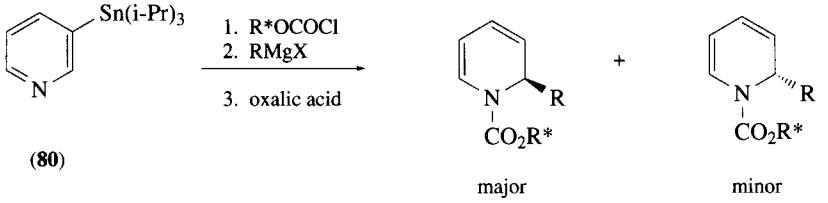


(48)

39-70 %

An asymmetric synthesis of 1,2-dihydropyridines has been achieved by the addition of Grignard reagents to the pyridinium salt generated from 3-(triisopropylstannyl)pyridine (**80**) and the chloroformate of 8-arylmenthyl based chiral auxiliaries (Equation (49)) ⟨91JOC7167⟩. The pyridinium salt generated from 4-methoxypyridine and acyl halides reacted with Grignard reagents α to the nitrogen to give 1,2-dihydropyridines, which on acidic workup provided the 2,3-dihydropyridones (Equation

(50)) ⟨86TL4549, 89TL5053⟩. This reaction has been used to prepare a variety of dihydropyridones and 4-methoxy-1,2-dihydropyridines, which have been utilized as building blocks for the synthesis of various alkaloids ⟨83TL2711, 85TL43, 86TL4549, 87TL759, 87TL1843, 88JA7445, 88TL6711, 89TL5053, 90JOC292, 91JOC2506, 91TL5697, 91TL5889, 91TL5919, 92JOC4098, 94CC2681, 95JOC711⟩. An asymmetric version of the reaction has been carried out with high diastereoselectivity and in high yields (Equation (51)) ⟨90JOC2574, 94JA4719, 94TL7343⟩. Various Grignard reagents have been used in this reaction, and the resulting enantiopure 2,3-dihydro-4-pyridones (**81**) have been used in the asymmetric synthesis of various naturally occurring alkaloids ⟨91JA6672, 92TL7635, 92JOC5807, 93JOC7732, 93CC1838, 94TL829⟩.



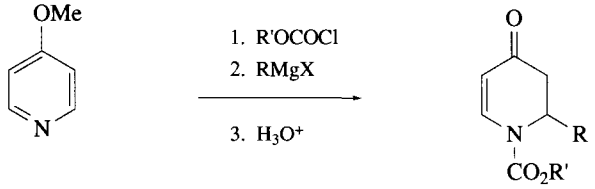
(49)

(**80**)

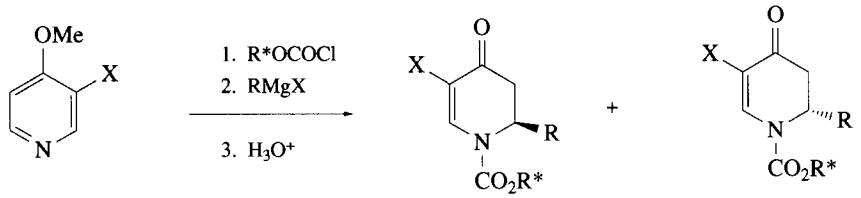
major minor

R* = (-)-8-phenylmenthyl R* = (-)-8-(4-phenoxyphenyl)menthyl

R	de	de
n-Pr	78	82
c-C_6H_{11}		91
Bn		76
vinyl		90
Ph	84	89
4-MeC_6H_4		92



(50)



(51)

(**81**)

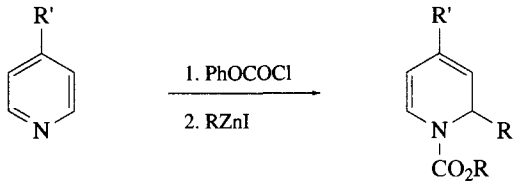
de = 18-98 %

X = H, SiR_3. SnR_3

R = aryl, alkyl

R* = (-)-menthyl, (-)-8-phenylmenthyl, (-)-8-(4-phenoxyphenyl)menthyl, (-) and (+)-trans-(α-cumyl)cyclohexyl, (-)- and (+)-2-(α-cumyl)-4-(2-propyl)cyclohexyl

Apart from Grignard reagents, other organometallic reagents such as zinc reagents and various tin reagents have been shown to add to *N*-acylpyridinium salts. Alkylzinc iodides react with *N*-acylpyridinium salts to give corresponding dihydropyridines (Equation (52)) ⟨87TL1843, 87JOM(333)139⟩. Thus, alkylzinc iodides on reaction with *N*-acylpyridinium salts, prepared from 4-phenyl- and 4-*t*-butylpyridine, gave the corresponding 2-alkyl-1,2-dihydropyridines.

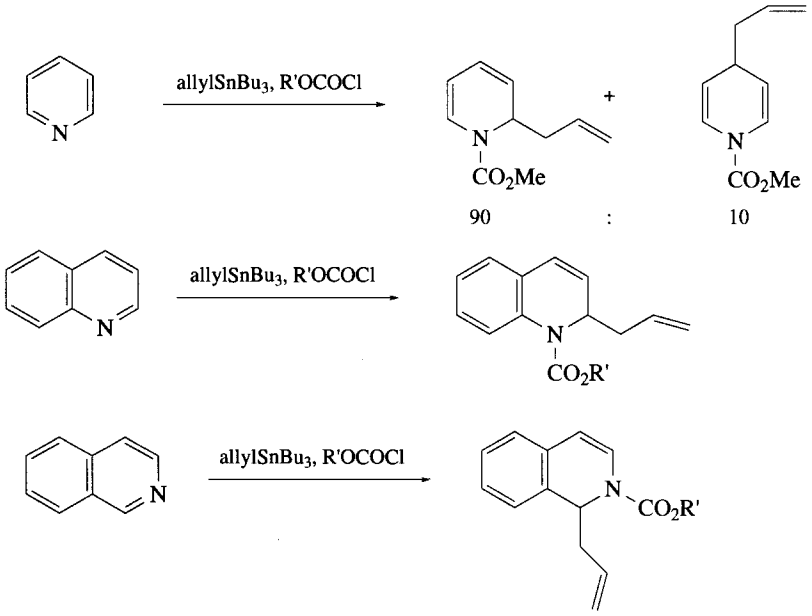


(52)

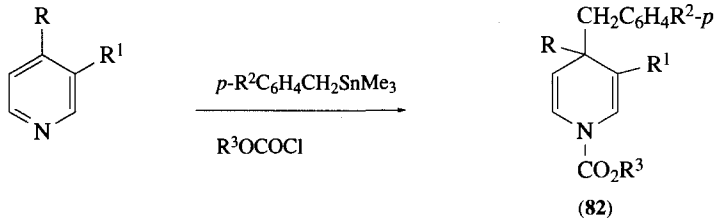
R' = Ph, *t*-Bu
R = alkyl

35-81 %

Tin reagents also react with *N*-acylpyridinium salts to give the 2- and 4-substituted dihydropyridines ⟨85JOC287, 86TL211, 88JOC3507, 94TL989⟩. Allyltin reagents add regioselectively α to the nitrogen of the pyridinium, quinolinium, and isoquinolinium salts (Scheme 33) ⟨85JOC287⟩. Substituted allyltin reagents give products with poor regioselectivity ⟨88JOC3507⟩. Benzyltin reagents add at the γ-position of *N*-acylpyridinium salts, resulting in 1,4-dihydropyridines (**82**) (Equation (53)) ⟨86TL211⟩. In contrast, ethyl (tributylstannyl)acetate preferentially reacts at the α-position of an *N*-acylpyridinium salt ⟨94TL989⟩.



Scheme 33



(53)

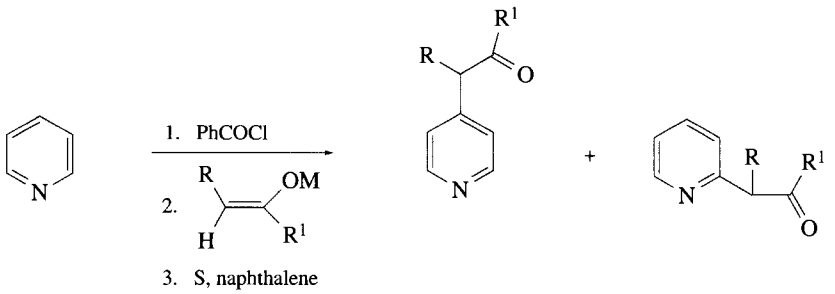
(**82**)

R = H, CN, CHO
R^1 = H, Cl, Br, CHO, CN, OAc
R^2 = H, Me, OMe
R^3 = CH_2, CH_2CCl_3

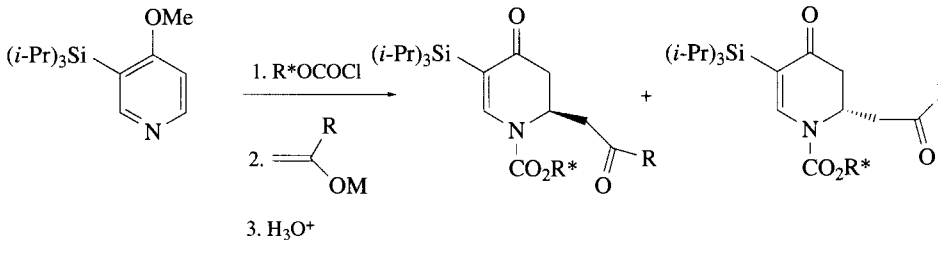
56-100 %

Titanium enolates react with *N*-acylpyridinium salts to yield 1,4-dihydropyridines, which on subsequent oxidation (aromatization) give 4-(2-oxoalkyl)pyridines (Equation (54)) ⟨84TL3297⟩. An analogous reaction of *N*-acylpyridinium salts with a zinc enolate has been used in the synthesis of (±)-epilupinine ⟨86TL2219⟩. Zinc enolates have also been shown to react with chiral *N*-acyl-

pyridinium salts with high diastereoselectivity (Equation (55)) ⟨93JOC5035⟩. Other metallo enolates gave products with lower diastereoselectivity. These reactions have been utilized to prepare substituted 2,3-dihydro-4-pyridones, which were used in the asymmetric synthesis of (−)-sedamine and (−)-porantheridine ⟨93JA8851, 93JOC5035⟩.



(54)



(55)

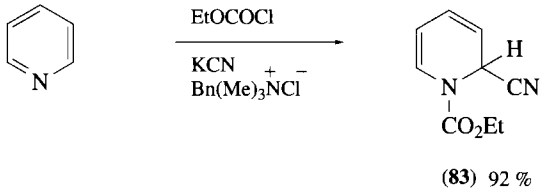
5.02.5.1.3 Cyanide

Neither pyridine nor pyridine *N*-oxide reacts with cyanide ion to form stable products, but cyanide does add to the quaternary salts of pyridine and its benzo derivatives. The first example of these reactions was reported by Reissert in 1905, who showed that quinoline reacted with benzoyl chloride in aqueous potassium cyanide ⟨05CB1603⟩. Four years later Kaufmann reported the reaction of 1-methylquinolinium salt with aqueous potassium cyanide to give the 1,4-adduct rather than the 1,2-adduct. This reaction was named the Reissert–Kaufmann reaction ⟨09CB3776⟩. Reissert compounds from the *N*-oxides were first reported by Henze ⟨36CB1566⟩, and thus named as the Reissert–Henze reaction. Quinoline *N*-oxide reacts with benzoyl chloride and potassium cyanide to give 2-cyanoquinoline in good yield by the elimination of benzoic acid from the initial adduct. Various *N*-alkoxypyridinium salts react with cyanide with immediate elimination of alcohol, to give cyanopyridines, and this reaction was named after its discoverers as the Felly–Beavers–Tani reaction ⟨59JA4004⟩. In contrast to *N*-alkoxy substituents, *N*-alkyl substituents are poor leaving groups, consequently aromatization of dihydro derivatives derived from cyanide addition to *N*-alkyl pyridinium salts is difficult. By using certain *N*–*N*-linked substituents good yields of 4-cyanopyridines have been obtained ⟨79JCS(P1)1698, 80S694⟩. *N*-Alkylnicotinic acid and its derivatives readily undergo addition of cyanide to give the 1,2-adduct under kinetic control and the 1,4-adduct under thermodynamic control.

The Reissert reaction has been very widely used, and it has been the subject of several previous reviews ⟨55CRV511, 68AHC(9)1, 79AHC(24)187, 73H(1)165, 80H(14)1033, 81BSB609, 84CHEC-I(2)165⟩.

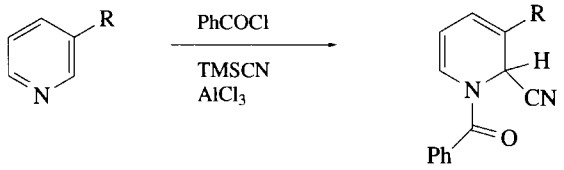
Pyridine Reissert compounds have been synthesized using different methods. Treatment of pyridine with ethyl chloroformate and potassium cyanide in aqueous methylene chloride in the presence

of benzyltrimethylammonium chloride provided a 92% yield of a pyridine Reissert compound (**83**) (Equation (56)) ⟨85OPP60⟩. In a similar manner, pyridines react with trimethylsilyl cyanide, benzoyl chloride, and aluminum chloride to yield 1-benzoyl-2-cyano-1,2-dihydropyridines (**84**). Several 3-substituted pyridines have also been shown to give Reissert compounds in high yields (Equation (57)) ⟨87CC1765⟩. However, diethylaluminum cyanide, ethyl chloroformate, and pyridine in toluene provided 4-cyano-1-ethoxycarbonyl-1,4-dihydropyridine (**85**) in 54% yield (Equation (58)) ⟨93JHC893⟩. The regioselectivity of trimethylsilyl cyanide addition has been shown to be solvent dependent, and addition can be directed 1,2 by the presence of copper(I) iodide. Thus, use of acetonitrile and toluene favored 1,2-addition, while methylene chloride gave mixtures of 1,2- and 1,4-adducts. However, in the presence of CuI, use of either methylene chloride or THF gave exclusively the 1,2-adduct.



(56)

(**83**) 92 %

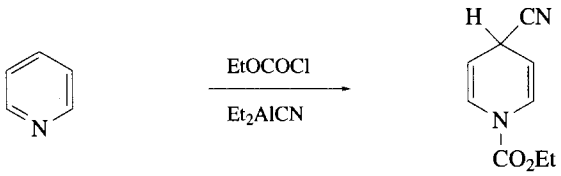


(57)

R = H, COMe, CO_2Me, CN

(**84**)

16-80%



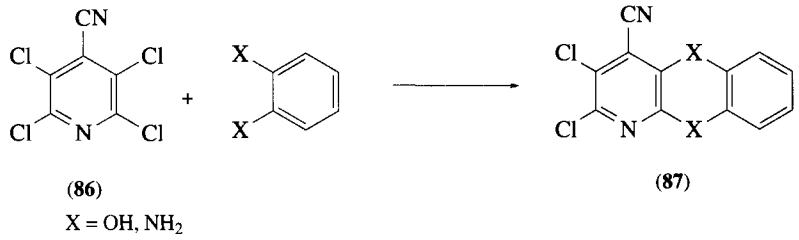
(58)

(**85**)

5.02.5.2 Heteroatom Nucleophiles

Various heteroatom nucleophiles react with pyridines and their benzo derivatives. Among them, the reactions of oxygen and nitrogen nucleophiles are the most common ⟨84CHEC-I(2)220, 90UK888⟩. Under normal conditions, pyridine does not react with oxygen nucleophiles like hydroxide ion; however, at elevated temperatures, reaction does occur. Electron-withdrawing substituents on the pyridines facilitate the reaction with oxygen nucleophiles. *N*-Alkylpyridinium salts react with hydroxide ion to form the corresponding oxygenated pyridines ⟨84CHEC-I(2)220, 90UK888⟩.

The displacement of nitro, cyano, and halogens can be achieved using oxygen nucleophiles. For example, tetrachloro-4-cyanopyridine (**86**) reacts with oxygen nucleophiles like catechol to give the pyridobenzdioxin derivatives (**87**) (Equation (59)) ⟨82JCS(P1)2897⟩. Direct oxygenation of pyridines with acetyl hypofluorite, through a proposed addition–elimination process, has provided the corresponding 2-acetoxypyridines (Scheme 34) ⟨87JA3789, 89H(28)249⟩. The reaction of 3-methylpyridine with AcOF resulted in a 1 : 1 mixture of 2- and 6-acetoxy derivatives. The same reaction with methanol as solvent provided 2-methoxypyridines in good yield ⟨91JOC6298⟩. In a similar manner, quinolines also underwent acetoxylation to give 2-acetoxyquinolines.

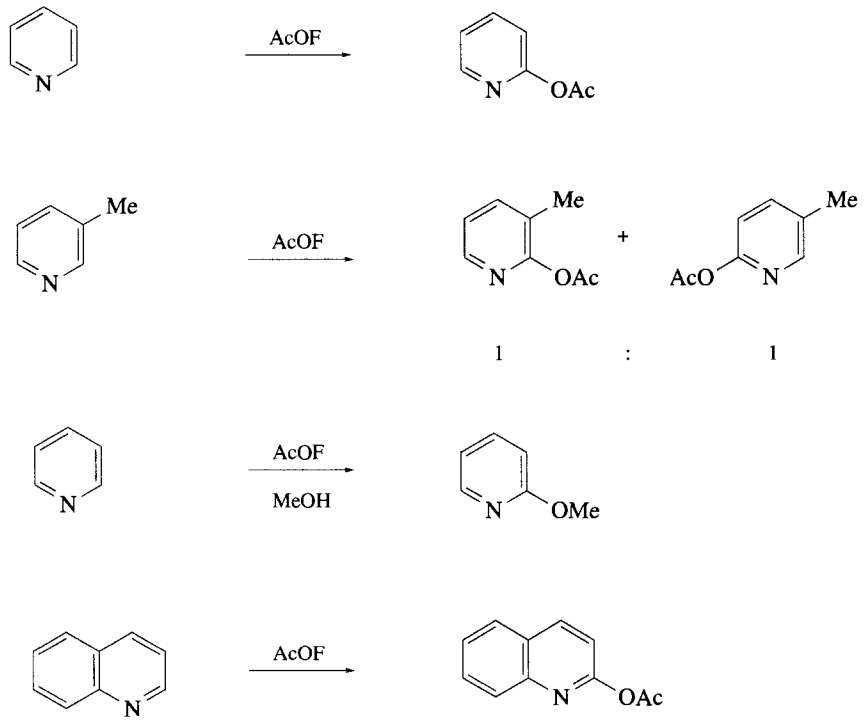


(59)

(86)

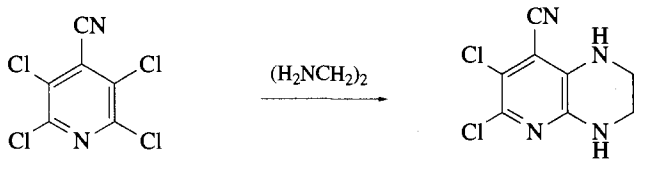
X = OH, NH_2

(87)

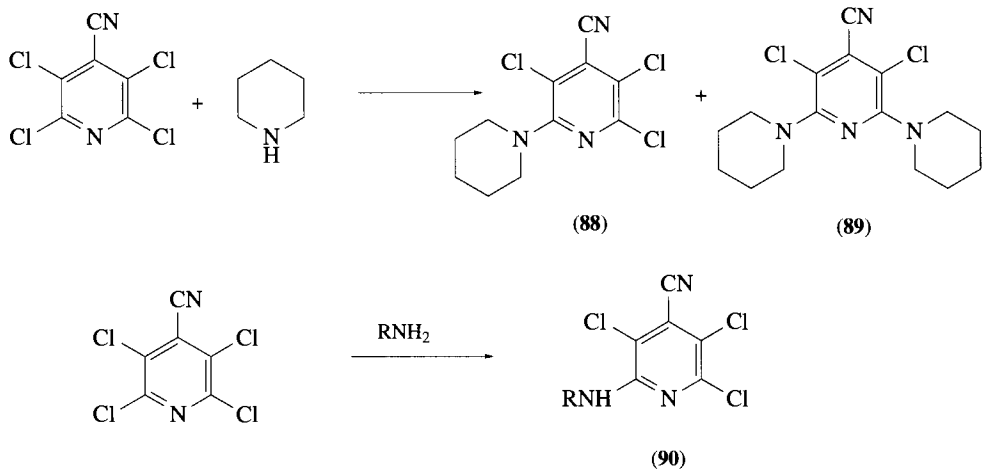


Scheme 34

Reaction of pyridines with nitrogen nucleophiles is an old process, dating back to the Chichibabin reaction ⟨14MI 502-01⟩. Pyridines and their benzo derivatives react with sodium amide to form the 2- and 4-amino derivatives. For a detailed description of these reactions, see CHEC-I. Pyridinium salts also react with nitrogen nucleophiles to form aminopyridines ⟨84CHEC-I(2)165⟩. There have been several improvements reported for the synthesis of 4-dimethylaminopyridine ⟨83MI 502-04, 90MI 502-01, 92MI 502-02, 93MI 502-04⟩. Halogen–nucleophile exchange has also been utilized for the amination of pyridines. Tetrachloro-4-cyanopyridine reacts with amine nucleophiles to give the corresponding aminopyridines by displacement of chloride ions (Equation (60)) ⟨82JCS(P1)2897⟩. Piperidines react with tetrachloro-4-cyanopyridine to give 4-cyano-6-piperidino-2,3,5-trichloro- (**88**) and 4-cyano-3,5-dichloro-2,6-dipiperidinopyridine (**89**). Similarly, anilines provide 2-anilino-3,5,6-trichloro-4-cyanopyridines (**90**) (Scheme 35).

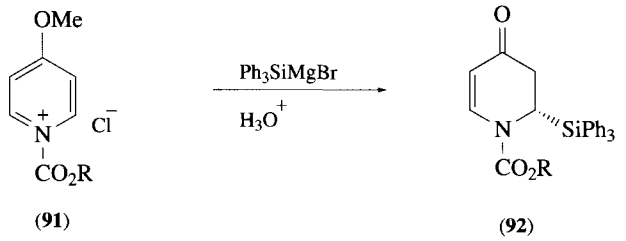


(60)



Scheme 35

Among the other heteroatom anions, silicon anions react very smoothly with pyridine and its salts. Reductive silylation of pyridines results in formation of 1,4-disilyl-1,4-dihydropyridines ⟨87BCJ1497⟩. Silicon anions, in the form of Grignard reagents, add to chiral *N*-acylpyridinium salts (**91**) to form 2-triarylsilyl-1,2-dihydropyridines (**92**) in high *de* (Equation (61)) ⟨92JA10972⟩. The use of sulfur and phosphorus nucleophiles is discussed in CHEC-I ⟨84CHEC-I(2)165, 84CHEC-I(2)244⟩.



(61)

(**91**)

(**92**)

R = (-)-8-phenylmenthyl

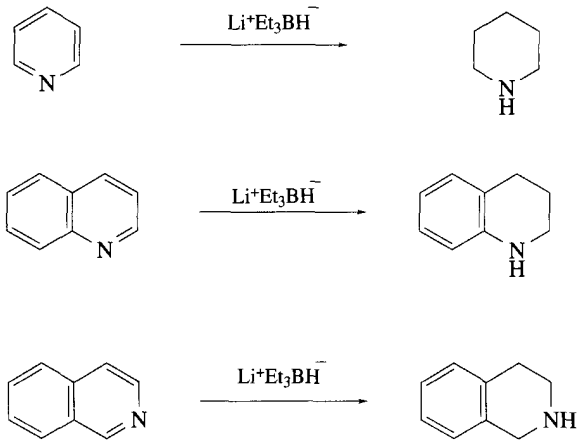
5.02.5.3 Chemical Reduction

Chemical reduction of pyridines to di-, tetra-, and hexahydropyridines can be achieved using hydrides and free electrons. Depending on the reaction conditions and the reagents used, partial or complete reduction can be achieved ⟨84CHEC-I(2)165⟩.

5.02.5.3.1 Hydride reduction

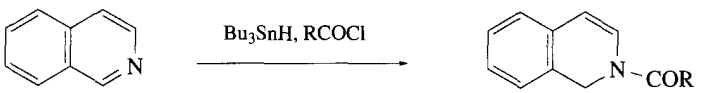
Theoretical calculations (MNDO/3MO) of the possible anions formed by addition of hydride to pyridinoid heterocyclic compounds, and experimental results, suggest that the thermodynamically most stable products are obtained with mild reducing agents. By monitoring pyridine reduction with strong reducing agents (i.e., MgH_2 and AlH_3), it was shown by ^1H NMR that, initially, a mixture of 1,2- and 1,4-dihydro-1-pyridyl anions are formed, but the final product is the 1,4-dihydro-1-pyridyl anion. The proposed mechanism for this selective reduction is a hydride exchange between reduced and unreduced substrate molecules coordinated to the same metal ion ⟨83JCS(P2)989⟩. Reduction of pyridines with diisobutylaluminum hydride ⟨85JOC2443⟩, lithium 9-boratabicyclo-[3.3.1]nonane ⟨84JOC3091⟩, 9-*sec*-amyl-9-borabicyclo[3.3.1]nonane ⟨89MI 502-01⟩, aluminum hydride-

triethylamine complex ⟨93JOC3974⟩, bis(diethylamino)aluminum hydride ⟨94MI 502-01⟩, and sodium diethyldihydroaluminate ⟨92MI 502-03⟩ have been reported to occur slowly, whereas lithium triethylborohydride (super hydride) reduces isoquinolines, quinoline, and pyridines effectively to give 1,2,3,4-tetrahydroisoquinolines, 1,2,3,4-tetrahydroquinoline, and piperidines (Scheme 36). The mechanism of this reduction has been explored using lithium triethylborodeuteride ⟨93TL7239⟩. Potassium triethylborohydride also reacts rapidly with pyridine ⟨87MI 502-08⟩.

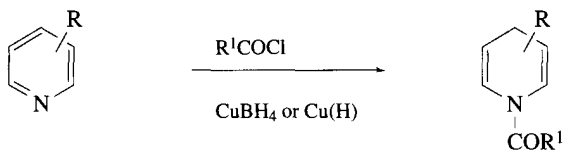


Scheme 36

Pyridine *N*-oxide is more reactive towards hydrides than pyridine. A comparison of pyridine and pyridine *N*-oxide reductions with thexylchloroborane, thexylborane, and diborane shows that none of these reagents reduce pyridine, but pyridine *N*-oxide consumes three equivalents of hydride with all three reagents ⟨86JOC5264⟩. Similarly, pyridine *N*-oxide reacts with lithium 9-boratabicyclo-[3.3.1]nonane with the uptake of three equivalents of hydride ⟨84JOC3091⟩, but only two moles of hydride uptake was observed when pyridine *N*-oxide was treated with diisobutylaluminum hydride ⟨85JOC2443⟩. Aluminum hydride–triethylamine complex reacts with picoline *N*-oxide very slowly ⟨93JOC3974⟩. However, potassium triisopropoxyborohydride and potassium triphenylborohydride do not react with pyridine *N*-oxide ⟨84JOC885, 87JOC5564⟩. Pyridines can also be reduced via their quaternary salts ⟨84CHEC-I(2)165⟩, and *N*-alkyl and *N*-acyl salts of pyridines and their benzo derivatives can be reduced with various hydride sources ⟨84CHEC-I(2)165⟩. Tributyltin hydride, for example, has been used to reduce *N*-acylisoquinolinium salts to dihydroisoquinolines (Equation (62)) ⟨88CL913⟩. Copper(I) borohydride and copper hydride have been used to reduce the 1-acyl salts of pyridine, 3-picoline, 3-ethylpyridine, 3-chloropyridine, and methyl nicotinate to the corresponding 1,4-dihydro products (Equation (63)) ⟨84JOC3392⟩.



(62)



(63)

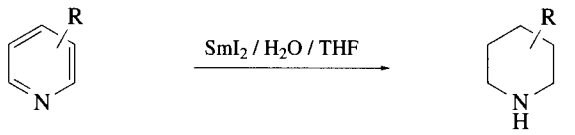
R = H, 3-Me, 3-Et, 3-Cl, 3-COOMe

R^1 = PhO, BnO, EtO, Me, *n*-Pr

20-65 %

5.02.5.3.2 With free electrons

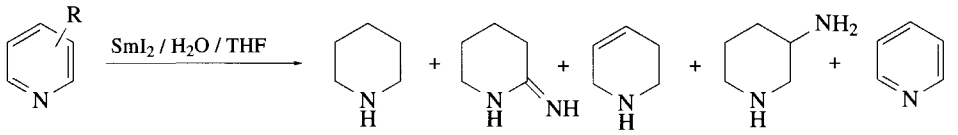
Samarium diiodide rapidly reduces pyridine to piperidine in the presence of water at room temperature in excellent yield ⟨93H(36)2383⟩, and various substituted pyridines have been reduced similarly (Equation (64)). It has been shown that six equivalents of SmI_2 are needed for complete reduction of pyridines. Alkyl and aryl substituted pyridines gave the corresponding substituted piperidines, but under similar conditions aminopyridines gave a mixture of products (Equation (65)). Chloropyridines are reported to give the corresponding unsubstituted piperidines with reductive elimination of chlorine. Cyanopyridines also underwent reductive elimination of the cyano group and were subsequently reduced to piperidines. Pyridinecarboxamides gave pyridylmethanols, methylpyridines, methyldihydropyridines, and methylpiperidines as products (Equation (66)).



89-97 %

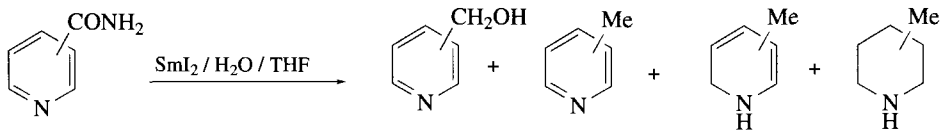
(64)

R = H, 2-Me, 3-Me, 4-Me, 2-Ph



(65)

R = 2-NH_2, 3-NH_2, 4-NH_2



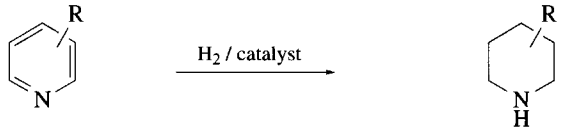
(66)

Electrochemical reduction of pyridines to piperidines can be achieved using different methods. Piperidines can be obtained in high yield by the electrochemical reduction of pyridine on a lead cathode in the presence of carbon dioxide and Pd–Ni or Cu–Ni catalysts ⟨89KFZ1120⟩. In the absence of catalyst, 4,4′-bipyridine was produced as the major product ⟨90MI 502-02⟩. A detailed investigation of the kinetics and mechanism of the electrochemical reduction of pyridine, 2,6-lutidine, and isonicotonic acid using different cathodes has shown that a nickel cathode with 3–5% of skeleton copper has the best electrocatalytic properties ⟨89KFZ866⟩. The influence of the pH of the electrolyte on these reductions is interesting. In acidic solutions with pH < 3, polymeric soluble products were formed. At higher pH the rate of the reduction decreased and was lower even at pH 7–9. At pH 13, the polymerization was minimum, and acceleration of the reduction was observed; however, 2,2′-, 2,4′-, and 4,4′-tetrahydrobipyridines were the major products, and dihydropyridine was the side product. Electrochemical reduction of pyridine and cyanomethylpyridines in acetonitrile has also been carried out with a mercury cathode ⟨83JCR(S)192⟩. Cathodic reduction of pyridine in liquid ammonia is known to give radical anions as intermediates ⟨82MI 502-01⟩.

5.02.5.4 Hydrogenation and Hydrodenitrogenation

Hydrogenation of pyridines and their benzoderivatives can be carried out with various catalysts (Equation (67)). Pyridine on treatment with unsupported ruthenium powder (< 120 mesh) in a slurry reactor under 330–930 psi H_2 at 140–240 °C gives piperidine free of any partially hydrogenated products ⟨83MI 502-06⟩. The activation energy is estimated to be approximately 44 kcal mol^{-1}. Kinetic studies showed a shift in the controlling mechanism from chemical control in the lower

temperature region to mass transfer control in the higher temperature region. Different forms of rhodium have also been shown to be useful in the hydrogenation of pyridine. Rhodium complexes $Rh(MeCOCHCOMe)[POPh_3]_2$ ⟨83JMOC193⟩, rhodium complexes with *N*-phenylanthranilic acid ⟨83MI 502-07⟩, Rh black, Rh/SiO_2, Rh/Al_2O_3, Rh/MgO ⟨87DOK(294)410⟩, Rh-polyacrylic acid, Rh-polymethacrylic acid ⟨90MI 502-03, 84KGS1032⟩, and (5-pentamethylcyclopentadienyl)rhodium tris-(acetonitrile) dication complex ⟨92JA5187⟩) can hydrogenate pyridines to piperidines.



(67)

Activation energies for the hydrogenation of pyridine to piperidine on Rh black, Rh/SiO_2, Rh/Al_2O_3, and Rh/MgO at 20 atm H_2 were found to be 37.5, 23.9, 25.2, and 45.6 KJ mol^{-1}, respectively. At 80 atm, the activation energy increased ⟨87DOK(294)410⟩. The rates of hydrogenation on Rh-polyacrylic acid and Rh-polymethacrylic acid were influenced by both steric and electronic factors ⟨90MI 502-02⟩. A similar study on the rate of hydrogenation of pyridine and 2-, 3-, and 4-picoline over Rh, Ru, Pt, and Pd black catalysts shows the influence of electronic and steric factors on the rates of hydrogenation ⟨91IZV30⟩. Under extremely mild conditions a catalytic precursor $[Cp^*Rh(CH_3CN)_3]^{2+}$ has been used for regioselective hydrogenation of the heteroaromatic ring of benzopyridines. The same catalyst also effects hydrogenation of 2-methylpyridine to 2-methylpiperidine. Again steric and electronic effects are thought to be dominating factors controlling the relative rates of hydrogenation ⟨92JA5187⟩. The substrates studied were 2-methylpyridine, quinoline, 2-methylquinoline, 5,6- and 7,8-benzoquinoline, and acridine.

Other metal catalysts have been used for the reduction of pyridines and their benzo derivatives. Hydrogenation of pyridine containing 25% H_2O over a Ni–Cr catalyst provided 97–99% yield of piperidine ⟨83ZPK1185⟩. The H_2O present supposedly prevents localized heating of the catalyst and the formation of resins. Large scale hydrogenation of pyridines with Ni/Cr catalyst trained at 170 °C for 110–125 h gave a good yield of the piperidine (88.8–92.7%) ⟨85MI 502-04⟩. Kinetic studies of the hydrogenation of alkylpyridines over Ni/Cr catalyst show that the reactivity decreases in the order pyridine > 2- > 3- > 4-methylpyridine ⟨85MI 502-05⟩. The activation energy for the hydrogenation of pyridine at 100–180 °C and 20–80 atm over Ni/Cr catalyst was found to be 89–90 KJ mol^{-1} ⟨90IZV20⟩.

Hydrogenation of pyridine over Raney nickel at 200 °C resulted in 1,5-dipiperidylpentane (73.1%), piperidine (19.8%) and pyridine (4.7%), with a 95.4% conversion ⟨85MI 502-06⟩. The 1,5-dipiperidylpentane results from the reaction of the byproduct of hydrodenitrogenation of pyridine with pyridine. The same hydrogenation has been carried out in aqueous solution ⟨85MI 502-07⟩. Effective reduction of pyridine to piperidine with Raney nickel can be effected in refluxing isopropanol ⟨85JOC394⟩.

The rate of pyridine hydrogenation over Pd-black or palladium supported on MgO or Al_2O_3 in water at 5–10 mpa at 50–150 °C and 1–10 mpa is found to be constant, and contact is necessary at the electron-deficient surface of the catalyst ⟨89IZV55⟩. Optimal pressure for hydrogenation of pyridine to piperidine over platinum is reported to be 2.0–2.5 mpa, and at 20–8.1 mpa the activation energy was 35.5–42.2 KJ mol^{-1} ⟨85ZPK322⟩. It has been noted that the catalyst gets deactivated by strong irreversible absorption of piperidine. A mixture of monoalkylated and *N*-formylated piperidines can be obtained by treating pyridine over cobalt(0) precatalysts with synthesis gas ⟨84MI 502-02⟩. Catalytic hydrogenation of 2,6-di-*t*-butylpyridine over Pt/C gives *cis*-2,6-di-*t*-butylpiperidine ⟨86JOC1889⟩.

It has been shown that hydrodenitrogenation of pyridines does occur over some metal catalysts. Hydrodenitrogenation of pyridine and benzopyridines over MoS_2 results in formation of saturated and unsaturated hydrocarbons. Pyridine under the above mentioned conditions gives a mixture of C_5 alkenes and alkanes, benzene, and toluene. In contrast, quinoline gave 75% saturated and aromatic hydrocarbons and 25% alkenes. The major products were toluene (16%), methylcyclohexane (15.2%), cyclohexane (12.8%), and ethylcyclohexane (10.9%) ⟨83MI 502-08, 83MI 502-09⟩. Hydrodenitrogenation has been studied with group 9 cluster carbonyls, Pd-black, and CoMo ⟨83ANY415⟩. The kinetics of pyridine hydrodenitrogenation over Al_2O_3 or SiO_2 supported Co, MoO_3, NiO, or WO_3 showed the reaction is first order in the total nitrogen content, and the most effective catalyst was found to be Al_2O_3 supported MoO_3 (15.6%), CoO_3 (4.0%), and SiO_2 4.8 (%) ⟨83MI 502-05⟩.

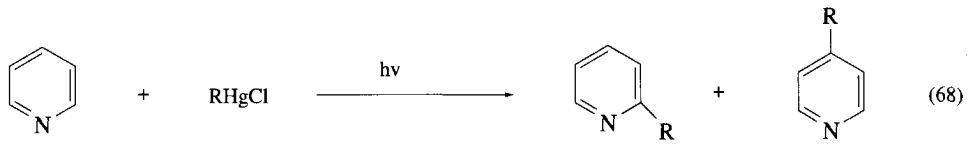
5.02.6 FREE RADICAL ATTACK AT CARBON

5.02.6.1 Halogenation

Radical chlorination of pyridine assisted by ultraviolet irradiation can be achieved in reasonably good yields ⟨80JGU354, 85CPB1009, 88JAP(K)63156774, 89JAP(K)01132564, 90USP4891108, 91JAP(K)03236374, 93AHC(58)274⟩. Regiospecific chlorination of pyridine at the α-position occurs rapidly during irradiation in the presence of chlorine dissolved in carbon tetrachloride ⟨67JHC375⟩. Nuclear and side-chain chlorination of 4-picoline is known to occur under γ-irradiation conditions ⟨80JGU354⟩. Halogenated pyridines such as 3,4,5-trichloro-2-trichloromethylpyridine can give open-chain chlorinated products under thermal (160–245 °C) and photochemical conditions. A mechanism in which a simultaneous attack of chlorine atom on the nitrogen and α-carbon has been proposed ⟨85JOU1163⟩. Vapor phase bromination of pyridine results in formation of approximately equal amounts of 2- and 3-bromopyridine. By contrast, the use of bromine chloride gives mainly 2-bromopyridine ⟨67JHC377⟩.

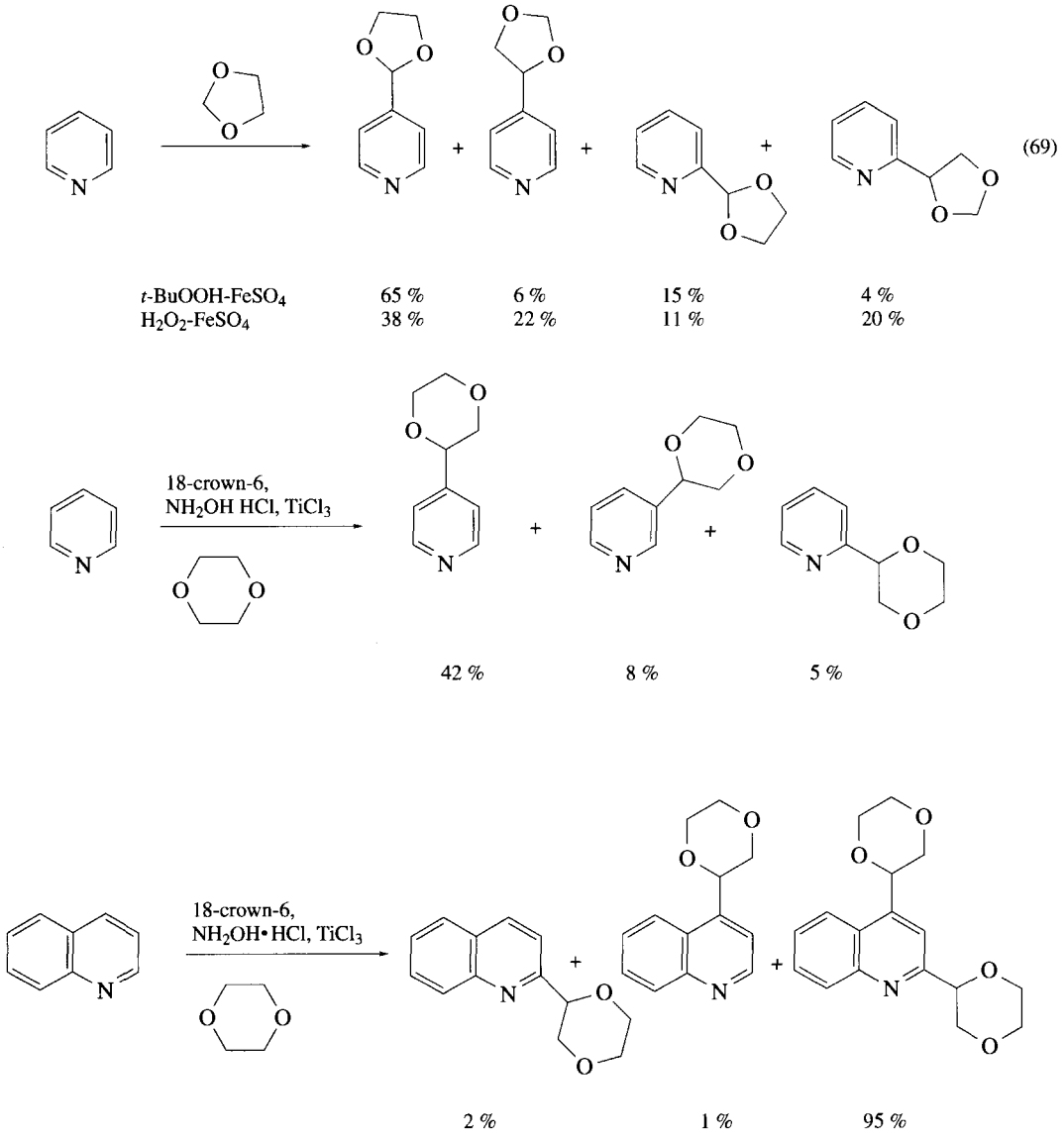
5.02.6.2 Alkylation and Arylation

Under standard conditions, radicals usually react at the 2-position of pyridines ⟨69CCC1110, 84CHEC-I(2)293⟩, and this regioselectivity is shown in the free radical reactions of alkylmercurial compounds with pyridines (Equation (68)) ⟨84MI 502-02, 85JOC3423, 89H(28)143, 93JA10596⟩. The major product formed was found to be the 2-substituted pyridine. Homolytic alkylation of pyridine by 1,3-dioxolane, initiated by Me_3COOH-$FeSO_4$, gives a mixture of products with 4-substituted pyridines predominating, but initiation with H_2O_2-$FeSO_4$ changes the ratio of products considerably (Equation (69)) ⟨85ZOK193⟩. Pyridines and quinolines, when subjected to homolytic alkylation with 1,4-dioxane and 18-crown-6 initiated by hydroxylamine hydrochloride and titanium trichloride, give mixtures of alkylated products in high yields (Scheme 37). Pyridine gives 4- (42%), 3- (8%) and 2-substituted pyridines (5%) with 99% conversion. Quinoline, under the same conditions, gives 4- (1%), 2- (2%), and 2,4-disubstituted quinoline (95%) with a 98% conversion ⟨87DOK(297)372⟩. Rates of hydrogen abstraction by trifluoromethyl radicals from pyridines in the gas phase at 295–673 K under photolytic and thermal conditions have been determined ⟨86JCS(F2)1991⟩. Homolytic perfluoropropylation of pyridines can be achieved under mild conditions with bis(heptafluoropropyl)peroxide ⟨86BCJ215⟩. Perfluoroalkylated products can be obtained by treating pyridines with perfluoroalkanesulfonyl bromide/benzoyl peroxide, perfluoroalkanesulfinate/oxidant or perfluoroalkyl iodide/sodium dithionite with tetraalkylammonium salts ⟨93MI 502-05⟩.



(68)

R	Yield (%)	2-/4-
Et	64	2.0
Bu^n	66	2.4
n-C_6H_{13}	50	
$Me_3CCH_2CH_2$	64	2.5
Me_3CCH_2	54	1.9
Pr^i	72	1.6
C_6H_{11}	69	3.1
2-norbornyl	90	4.1
Bu^t	94	1.4



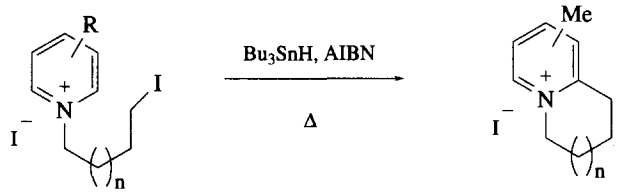
Scheme 37

Homolytic arylations of pyridines are more common than alkylations, and aryl radicals have been generated from various precursors. Photolysis of aryl or pyridyl oxime esters in pyridine provides phenylpyridines as well as bipyridyls, with the α-substituted pyridines as the major products ⟨84TL3887⟩. The rate constants for the addition of phenyl radical to protonated and unprotonated 4-substituted pyridines have been determined by studying the competition between phenyl radical addition and chlorine abstraction from carbon. The 4-arylpyridines were the major products, and no 3-substituted pyridines were observed. Among the solvents studied (MeCN, DMF, DMSO, and HMPA), MeCN gave the highest yields and selectivity ⟨91OPP438⟩.

Homolytic arylation of pyridines can also be carried out by generating the radical on the pyridine and allowing this intermediate to react with aromatic hydrocarbons and heterocycles. Thus, reaction of 4-aminopyridine *N*-oxide with amyl nitrite generates the 1-oxido-4-pyridyl radical, which reacts with aromatic compounds in acetic acid to give the arylated products. A study of the rate of the reaction found that there is a substituent dependence on the rate constants and on the degree of protonation. Based on the rate constants, phenyl radical from PhN_2X or Bz_2O_2 has been used to generate alkyl radicals (produced by iodine or H abstraction), which react with pyridines to form the alkylated substituted pyridines ⟨86JOC4411⟩. Free radical 4-nitrophenylation of pyridine gave 2-, 3-, and 4-(4-nitrophenyl)pyridines. A three-center transition state has been proposed to account for

the predominance of the 2-substituted product ⟨91JHC1153⟩. Arylation of pyridine with aryldiazonium tetrafluoroborate can give a mixture of 2-, 3-, and 4-arylpyridines when the aryl group is phenyl or 4-nitrophenyl. Reaction of 2-aminopyridine *N*-oxide provides a similar product ⟨84CPB1780⟩. Reaction of quinoxaline and quinoline in acetic anhydride containing zinc gives the quinoxaline radical, and *N*-acetyl radicals, which recombined to give *N*-acetyldihydroquinoline-1,2-dihydroquinoxaline ⟨85KGS967⟩. Isoquinoline reacts similarly.

N-Iodoalkylpyridinium salts undergo intramolecular radical cyclization upon treatment with tributyltin hydride and AIBN to give corresponding fused heterocycles in good yields (Equation (70)). Using this reaction, various [6,5], [6,6], and [6,7] fused pyridinium salts have been prepared. It has been noted that 2,6-disubstituted pyridinium salts failed to undergo the radical reaction ⟨90TL1625⟩.



(70)

R = H, Me
n = 1, 2, 4

58-79 %

5.02.6.3 Miscellaneous

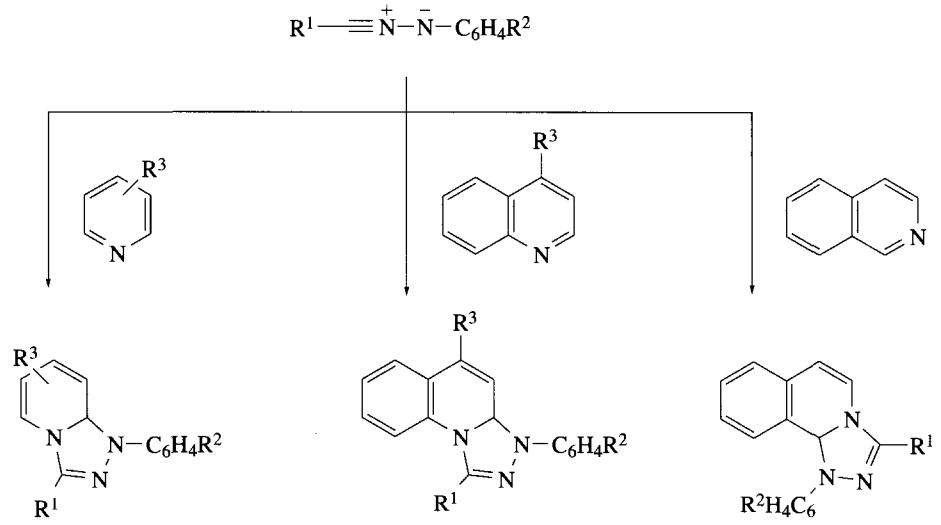
Radical cations of substituted pyridines can be generated using γ-rays at 77 K ⟨84JCS(F1)2803⟩. Relative rate constants have been determined for the radical hydroxylation of benzenes, pyridines, and furans. It is noted that the polarity of the transition state increases with decreasing conjugation energy in the aromatic system ⟨83UKZ865⟩. The radicals formed from pyridine, 3-methylpyridine, 3,5-dimethylpyridine, 2,6-dimethylpyridine, and 2,4,6-trimethylpyridine by the attack of H, HO, and O radicals in aqueous solutions were studied by pulse radiolysis. Rates of formation and decay of these radicals for the protonated and unprotonated forms have been determined ⟨93RPC825⟩. Oxoalkylation of pyridine, 4-methylpyridine, and quinoline in acetic acid with alkyloxy radicals generated from 1-methylcyclobutanol or 1-methylcyclopentanol by lead tetraacetate or manganese triacetate provides the oxoalkylated products in 52–95% yield. Application of this reaction to 4-methylpyridine gave only the 2-alkoxy derivative, but pyridine provided the 2- and 4-oxoalkylpyridines in 3 : 1 ratio. In contrast, equal amounts of 2- and 4-(oxoalkyl)quinolines resulted under the same reaction conditions ⟨92DOK(326)460⟩.

5.02.7 THERMAL AND PHOTOCHEMICAL REACTIONS AND THOSE INVOLVING CYCLIC TRANSITION STATES

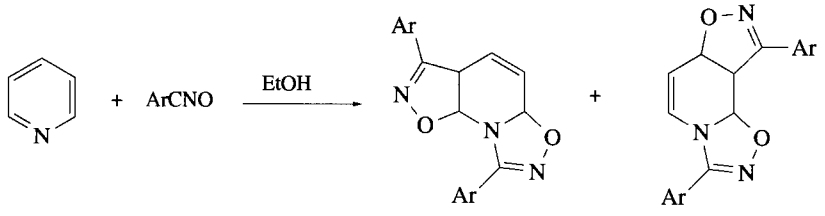
Cycloaddition reactions of pyridines and their benzo derivatives have been the subject of several reviews. Diels–Alder reactions ⟨83T2869, 86CRV781, 84CHEC-I(2)303⟩, cycloaddition reactions of mesoionic heterocycles ⟨80AHC(26)1, 84CHEC-I(2)303⟩, and cycloaddition reactions of heteroaromatic betaines ⟨76AG(E)1, B-79MI 502-01, 89CRV827⟩ have been reviewed.

Pyridines and their benzo derivatives undergo cycloaddition reactions under photolytic and thermal conditions with various dienophiles, dienes ⟨91HCA1095⟩, and 1,3-dipolarophiles ⟨89CRV827⟩. The C=N bond of pyridine, quinoline, and isoquinoline reacts with 1,3-dipolarophiles in a facile manner ⟨89DOK(8)31, 92JHC771⟩. Thus, aryl nitrileimines react with the C=N bond of pyridine, quinoline, and isoquinoline to form cycloadducts (Scheme 38) ⟨92LA885⟩. Nitrile oxides undergo facile reactions with pyridines to form biscycloadducts as well as cross-adducts (Equation (71)) ⟨89JHC757⟩. Cycloaddition of cyclopropane derivatives with pyridine has given various heterocyclic adducts ⟨83JOC2629, 86JOC4639, 89JOC3652⟩. Reaction of tetrachlorocyclopropene (**93**), with pyridine at 0°C gave unusual pyridinium salts (**94**) and (**95**) (Equation (72)) ⟨83JOC2629⟩. Treatment of pyridines with 2,3-diarylsubstituted propenones gives 2,3-diaryl-1-hydroxyindolizines

and 1,2-diaryl-3-hydroxyindolizines, depending on the substituents on the pyridine and the reaction conditions ⟨86JOC4639⟩. The same reaction, when subjected to exhaustive oxidative conditions, produced the coupled 1,1′- or 3,3′-dioxo-7,7′-bisindolizine ⟨89JOC3652⟩.

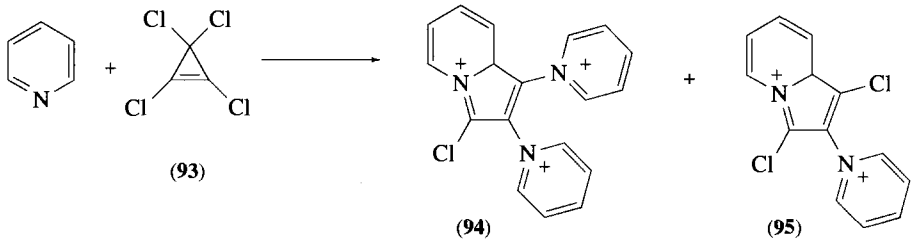


Scheme 38



Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4 22-28 % 5-9 %

(71)

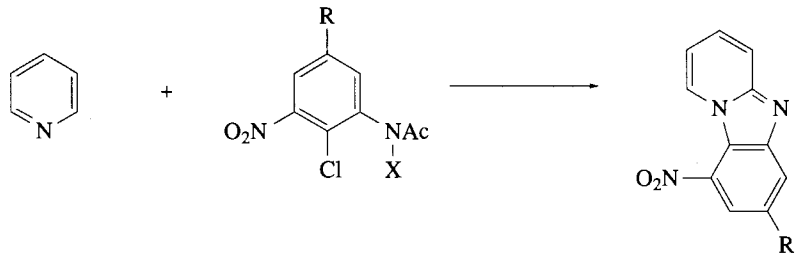


(93) (94) (95)

(72)

Treatment of pyridine and 3- and 4-methylpyridine with trifluoromethylnitrileimines produced cycloadducts ⟨87JHC1391⟩. Pyridines undergo cycloaddition with suitably substituted aromatic and heterocyclic amines and their derivatives to form polycyclic compounds (Equation (73)) ⟨86JHC1419, 86JHC1741, 86JHC1091, 91CB1237⟩. Treatment of 4-(3-trifloxypropenylidine)morpholinium triflates with two equivalents of pyridine resulted in the formation of 4-(1,9*a*-dihydro-2*H*-quinolizin-2-ylidene)-morpholinium salts in quantitative yield ⟨89S735⟩. Similar reactions of quinoline and isoquinoline

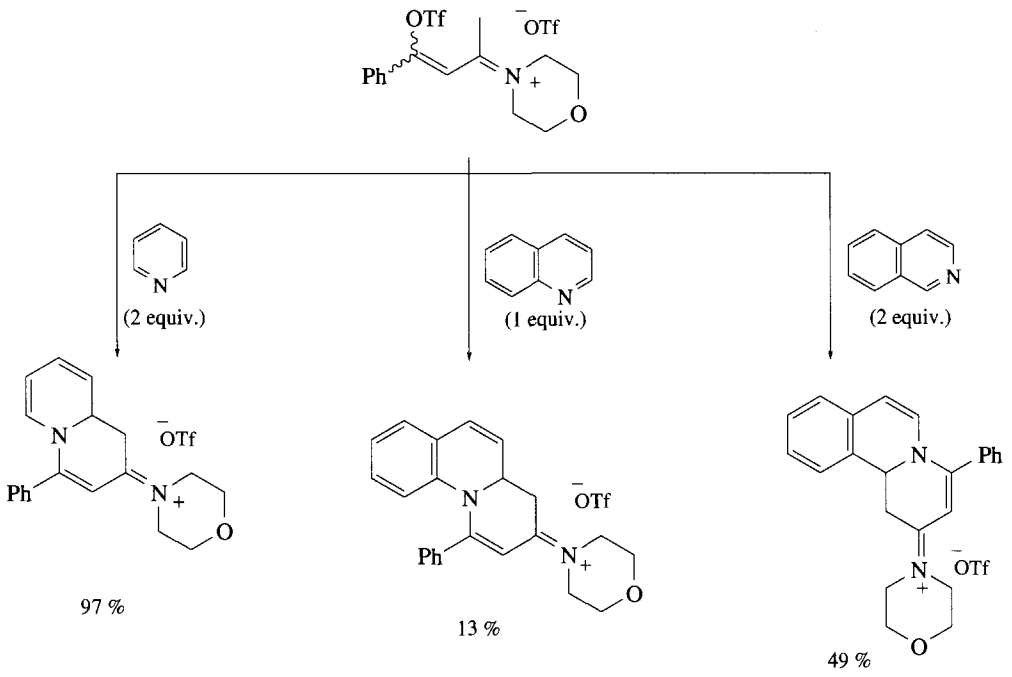
are reported to yield 13 and 53% of the cycloaddition products (Scheme 39). Refluxing a mixture of 6,7-dichloroquinoline-5,8-dione, active methylene compounds (i.e. acetylacetone, ethyl acetoacetate, ethyl cyanoacetate, and/or diethyl malonate), and pyridine in absolute ethanol or in excess pyridine gives 6-substituted indolizino[2,3-*g*]quinoline-5,12-diones ⟨91CCC695⟩.



(73)

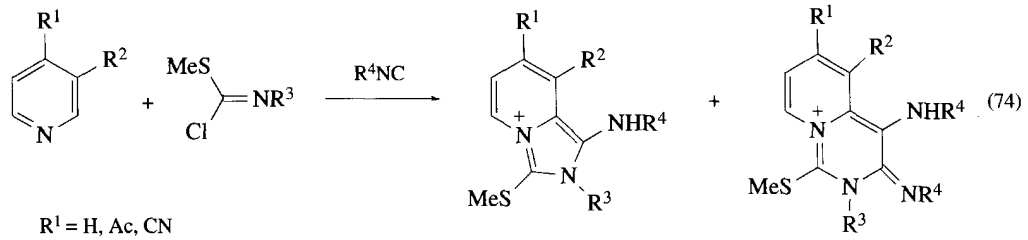
R = CN, CF_3
X = OH, OAc

51-63 %

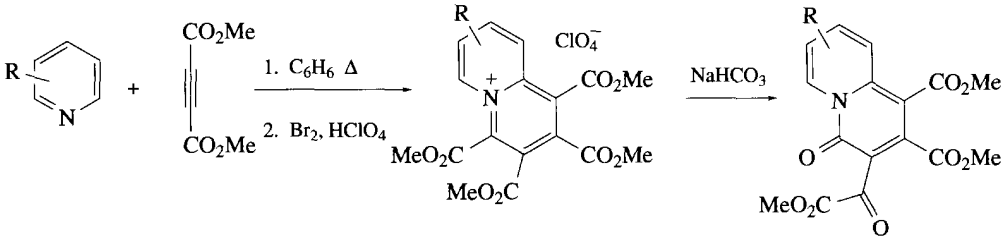


Scheme 39

Pyridines undergo sequential *N*-imidoylpyridinium formation and then cycloaddition upon treatment with methylthioimidates and isocyanides to give pyridino[1,2-*c*]dihydropyridinium salts (Equation (74)) ⟨93TL2319⟩. Pyridines react with trimethylsilylmethyl trifluoromethylsulfonate to give *N*-(trimethylsilylmethyl)pyridinium trifluoromethylsulfonates, which upon reaction with caesium fluoride and dimethyl acetylenedicarboxylate provides indolizines ⟨84CL279, 84H(22)701⟩. Dimethyl acetylenedicarboxylate undergoes cycloaddition with *C*-silylated pyridines to form the corresponding *C*-silylated tetramethyl-9*aH*-quinolizine-1,2,3,4-tetracarboxylates, which rearrange as shown in Scheme 40 ⟨83CB2564⟩. In a novel three-component reaction, 1,3-dimethyl-6-(triphenylphosphoranylideneamino)uracil reacts with pyridines and isocyanates to give new polycyclic cycloadducts ⟨91TL4473⟩.



R^1 = H, Ac, CN
R^2 = H, Br
R^3 = Et, *i*-Pr, 2,6-$Me_2C_6H_3$
R^4 = Et, *i*-Pr, *t*-Bu



R = Me_3Si, Me_3SiCH_2

Scheme 40

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5.03
Pyridines and their Benzo Derivatives: Reactivity of Substituents

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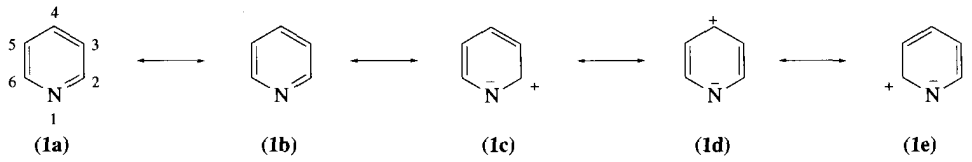
5.03.1 INTRODUCTION: THE EFFECT OF THE PYRIDINE RING ON REACTIONS OF SUBSTITUENTS

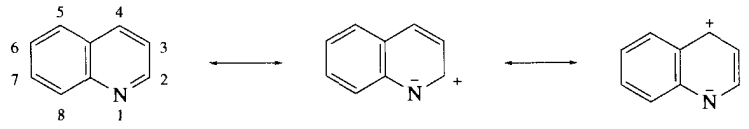
Pyridine (**1**) and its benzo analogues (**2**) and (**3**) possess an electronegative atom which exerts an uneven electronic effect on the ring atoms and hence on substituent groups. The π-electron densities in pyridine show that the atoms at positions 2, 4, and 6 are most affected by the electron withdrawal. Dipole moments indicate that the polar canonical forms (**1c**), (**1d**), and (**1e**) make a substantial contribution to the structure of pyridine. Similarly, quinoline (**2**) and isoquinoline (**3**) show significant electron withdrawal from positions 2 and 4, and 1 and 3 respectively (Schemes 1 to 3). It follows then that the reactivity of substituents at positions α and γ to the ring nitrogen can be significantly different from that of the same substituents when attached to the benzene ring. In general, substituents β to the ring nitrogen or located in a fused benzene ring exhibit the reactivity expected of such substituents in a benzenoid system.

In the case of pyridinium and related cations, the effects of electron withdrawal by the ring nitrogen are increased. Thus *N*-protonation, *N*-alkylation, or *N*-oxide formation results in more dramatic change in substituent reactivity at the α- and γ-positions.



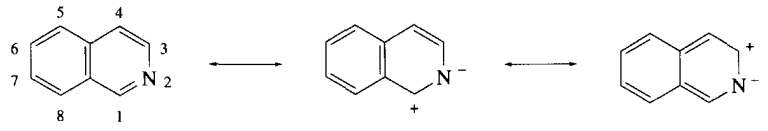
(**1a**) (**1b**) (**1c**) (**1d**) (**1e**)

Scheme 1



(**2a**) (**2b**) (**2c**)

Scheme 2



(**3a**) (**3b**) (**3c**)

Scheme 3

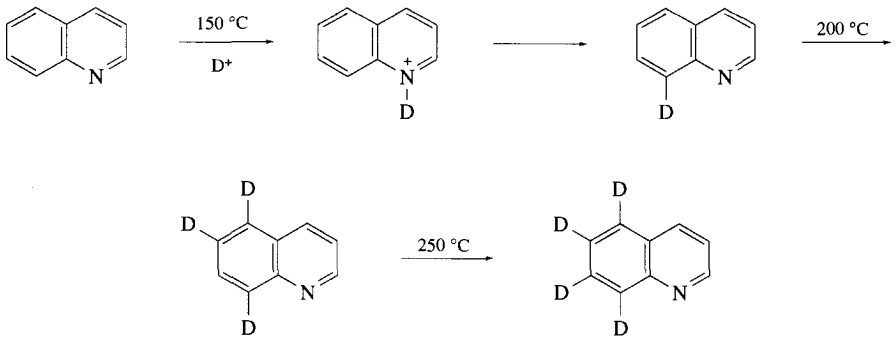
5.03.2 FUSED BENZENE RINGS

5.03.2.1 Substitution Reactions in Fused Benzene Rings

Quantitative aspects of the electrophilic substitution of heterocycles have been extensively reviewed by Katritzky and Taylor ⟨90AHC(47)277⟩.

5.03.2.1.1 Deuteration

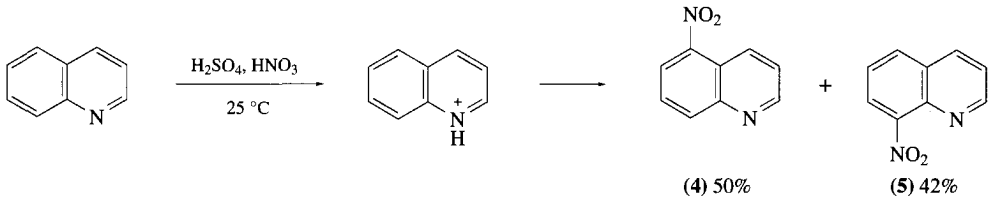
The deuteration of quinoline and quinoline *N*-oxide in deuteriosulfuric acid proceeds via the conjugate acid (Scheme 4) and the reaction occurs in the positions 8 > 5, 6 > 7 > 3, where the rates increase with increasing acid concentration and with temperature ⟨71JCS(B)4, 72IZV2092, 75TL1395⟩. In the case of isoquinoline and isoquinoline *N*-oxide, reaction occurs first in position 5 and then in position 8 ⟨71JCS(B)4⟩. For 4-hydroxyisoquinoline at 145 °C, the positional order was found to be 3 > 5 > 8 > 6.



Scheme 4

5.03.2.1.2 Nitration

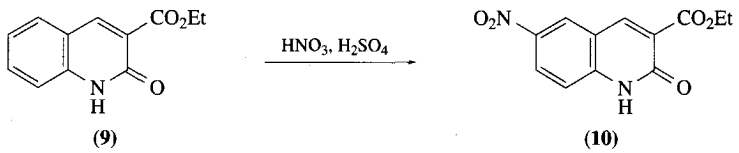
The nitration of benzopyridines in strongly acidic solution occurs very easily, and preferentially in the carbocyclic rings. The nitration of quinoline in nitric and sulfuric acids at 25 °C yields 5-nitroquinoline (**4**) and 8-nitroquinoline (**5**) (Scheme 5) ⟨57JCS944, 57JCS2521⟩. However, the nitration of quinoline in acetic anhydride (HNO_3–Ac_2O at 100 °C) as solvent yields 3-nitroquinoline in low yield (6%) via a dihydroquinoline intermediate ⟨63PMH(1)124⟩. Under more forcing conditions (fuming HNO_3, H_2SO_4, 100 °C), the nitration of quinoline leads to 5,7- and 6,8-dinitroquinoline ⟨08CB1735⟩.



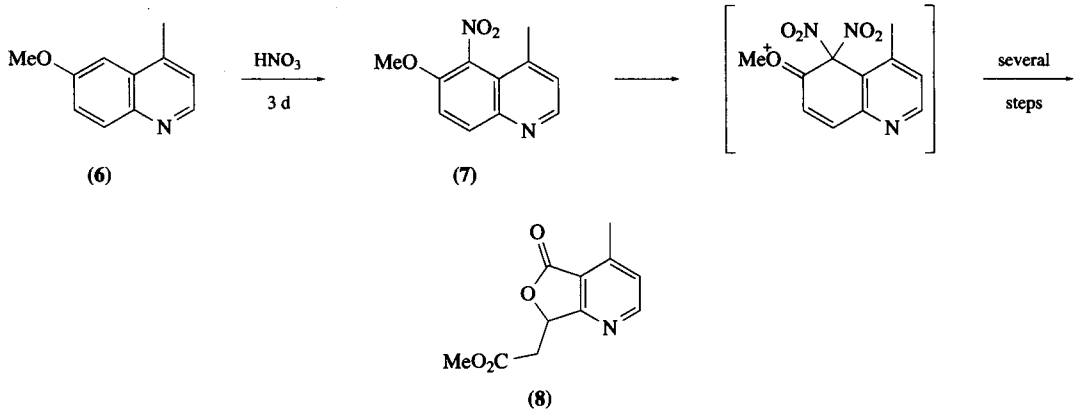
Scheme 5

7-Nitroquinoline is obtained by the action of nitrogen dioxide on quinoline and, at higher temperatures, 5,7-dinitroquinoline is formed ⟨36CB1874⟩.

The nitration of 6-methoxy-4-methylquinoline (**6**) in fuming nitric acid for 3 days initially takes place at position 5 (**7**). Subsequent *ipso*-nitration to the nitro group leads via a series of intermediates to the lactone (**8**) (Scheme 6) ⟨92JCR(S)308⟩. However, nitration of the 2-oxoquinoline-3-carboxylate (**9**) with nitric acid in sulfuric acid produces only the 6-nitro derivative (**10**), based on nuclear Overhauser effect (NOE) studies (Equation (1)) ⟨84JHC349⟩.



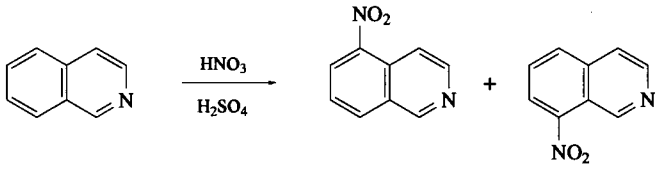
(9) (10) (1)



(6) (7) (8)

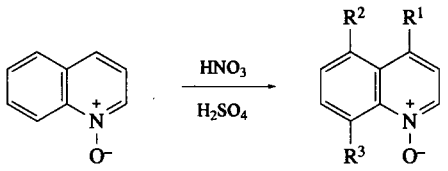
Scheme 6

The nitration of isoquinoline with nitric and sulfuric acids also occurs at positions 5 and 8, with the 5-nitro derivative predominating (Equation (2)) ⟨B-64MI 503-01⟩. However, with nitric acid in acetic anhydride, the free base is involved and the product is the 4-nitro derivative (14% yield) ⟨72OPP9⟩.



(2)

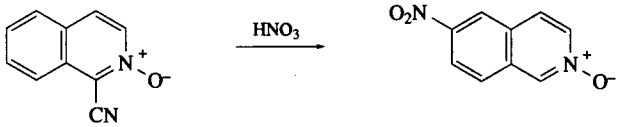
Nitration into the heterocyclic ring can compete with nitration into the fused benzene ring if the hetero ring contains an *N*-oxide. Thus, nitration of quinoline *N*-oxide (**11**) with mixed acid at 0–20 °C gives 8-nitroquinoline *N*-oxide (**12**) as the major isomer together with the 5-nitro derivative (**13**) but at 60–100 °C the major product is the 4-isomer (**14**) (Equation (3)) ⟨50JPJ22, 68JCS(B)316, B-71MI 503-01⟩. Also, 1-cyanoisoquinoline 2-oxide (**15**) gives mainly 6-nitroisoquinoline 2-oxide (**16**) on nitration with fuming nitric acid (Equation (4)) ⟨77H(8)403⟩.



(11)

(3)

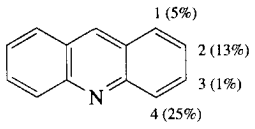
0–20 °C (**12**) $R^1 = R^2 = H$; $R^3 = NO_2$
(**13**) $R^1 = R^3 = H$; $R^2 = NO_2$
60–100 °C (**14**) $R^1 = NO_2$; $R^2 = R^3 = H$



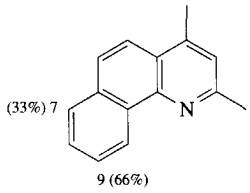
(15) (16)

(4)

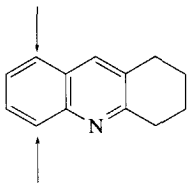
Acridine (**17**) shows a 190-fold increase in relative reactivity compared to quinoline and is nitrated to yield a mixture of 1-, 2-, 3-, and 4-nitro derivatives ⟨38CB808, 57JCS2521⟩. Nitration of 2,4-dimethylbenzo[*h*]quinoline (**18**) occurs at the 7- and 9-positions ⟨77MI 503-01⟩. Nitration of 1,2,3,4-tetrahydroacridine (**19**), 2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (**20**), and 7,8,9,10-tetrahydrophenanthrene (**21**) proceeds as expected in the benzenoid ring ⟨65JPJ645⟩.



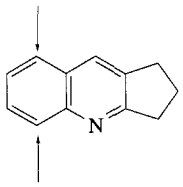
(17)



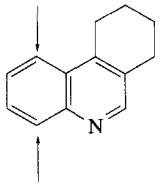
(18)



(19)



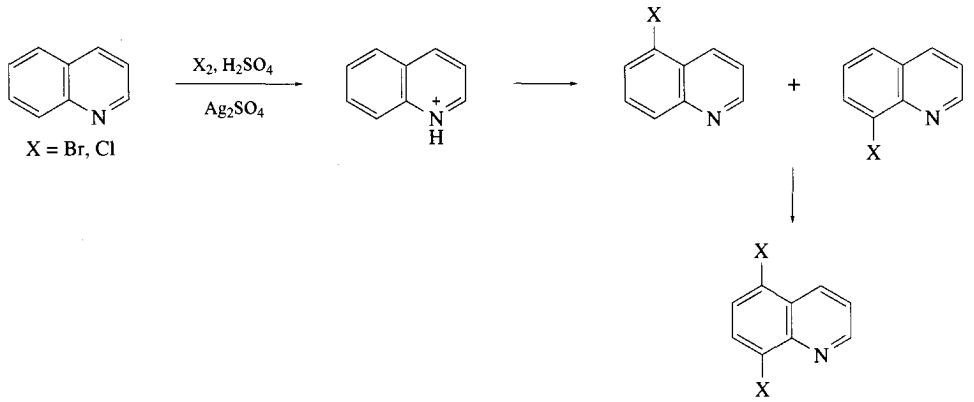
(20)



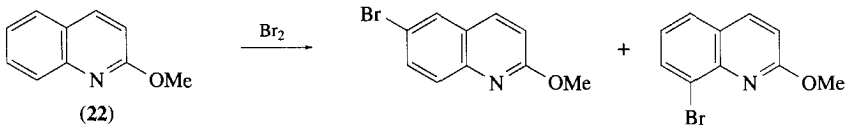
(21)

5.03.2.1.3 Halogenation

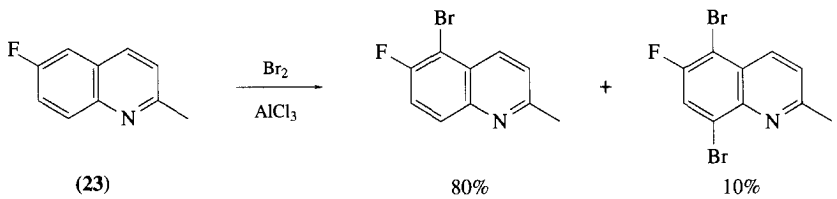
A number of reviews on the halogenation of quinolines have been published ⟨84CHEC-I(2)165, 84CHEC-I(2)315, 90AHC(47)277, 91PHC186, 94AHC(59)245⟩. The bromination and chlorination of quinoline in sulfuric acid in the presence of silver sulfate gives both 5- and 8-haloquinolines together with the 5,8-dihalo derivatives (Scheme 7) ⟨75JHC1015⟩. Bromination of 2-methoxyquinoline (**22**) occurs at the 6- and 8-positions (Equation (5)) ⟨93JCS(P1)181⟩, while bromination of the aluminum chloride complex of 2-methyl-6-fluoroquinoline (**23**) gives the 5-bromo derivative (80%) together with the 5,8-dibromo derivative (10%) (Equation (6)) ⟨92JHC895⟩.



Scheme 7

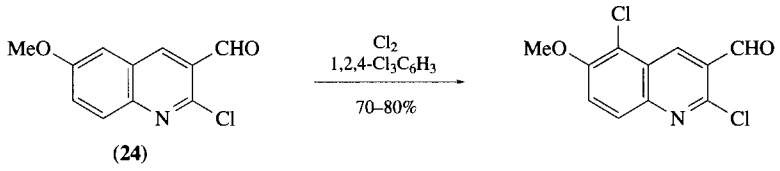


(22) (5)

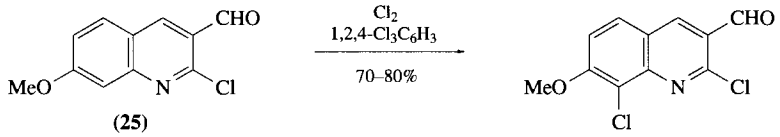


(23) 80% 10% (6)

The position of chlorination can be influenced by the substituents in the benzo ring. Thus, the chlorination of 2-chloro-6-methoxyquinoline-3-carbaldehyde (**24**) with chlorine in 1,2,4-trichlorobenzene gives the 2,5-dichloro derivative (Equation (7)) while the 7-methoxy isomer (**25**) yields the 2,8-dichloroquinoline (Equation (8)) ⟨91SC1929⟩.

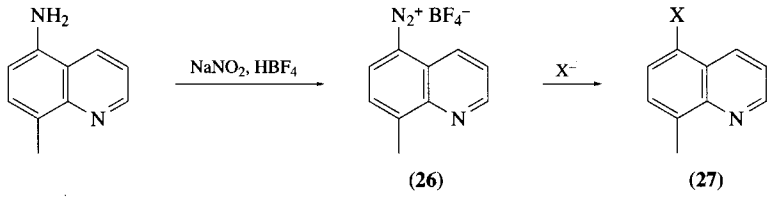


(24) (7)



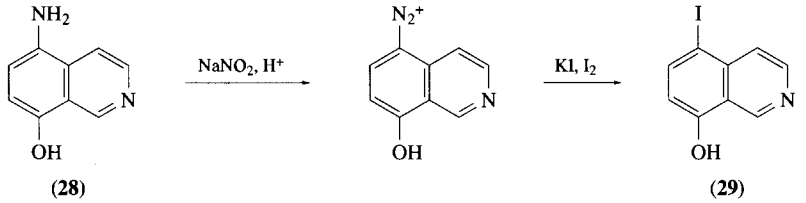
(25) (8)

The Sandmeyer reaction is frequently used to prepare 5-, 6-, 7-, and 8-halo quinolines from the corresponding amino compounds. Thus, diazotized 5-amino-8-methylquinoline tetrafluoroborate (**26**) is converted into 5-halo-8-methylquinoline (**27**) (Scheme 8) ⟨83KGS1373⟩. Similarly, aminoisoquinolines can be converted into the corresponding haloisoquinolines. 5-Amino-8-hydroxyisoquinoline (**28**), for example, is converted into the 5-iodo derivative (**29**) by treatment of the corresponding diazonium salt with potassium iodide and iodine (Scheme 9) ⟨66JMC46⟩.



(26) (27)

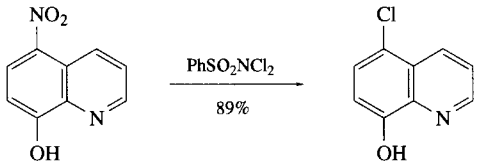
Scheme 8



(28) (29)

Scheme 9

By using aryl dichlorosulfonamides it is possible to displace the 5-nitro group of 5-nitro-8-quinolinol (**30**) with chlorine (Equation (9)) via an S_EAr mechanism ⟨83MI 503-01⟩.

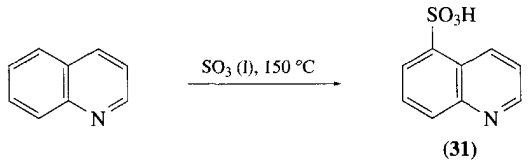


(30) (9)

5.03.2.1.4 Sulfonation

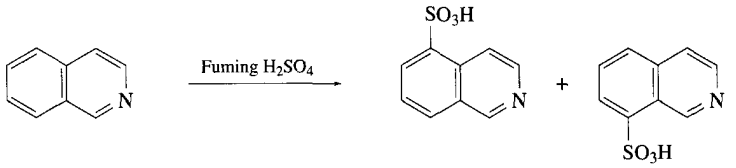
Sulfonation of quinoline (sulfuric acid–sulfur trioxide, 100–300 °C) gives mixtures of the 5-, 6-, and 8-quinolinesulfonic acids with the 8-isomer predominating at 100 °C ⟨1870LA(155)311, 1882CB683,

46JOC277〉. The amount of the 5-isomer increases to some extent with increasing temperature 〈1882CB1979, 1887CB731〉, but at higher temperatures (300 °C) the thermodynamically favoured 6-sulfonic acid is produced 〈1888JPR258〉. Liquid sulfur trioxide at 150 °C will convert quinoline into quinoline-5-sulfonic acid (**31**) (Equation (10)) 〈91JAP(K)3227973〉.



(**31**) (10)

Isoquinoline is sulfonated with fuming sulfuric acid to yield the 5- and 8-sulfonic acids, with the former predominating below 180 °C (Equation (11)) 〈1892JPR241, 1895JPR1, 35JA1840, 70T1961〉. However, sulfonation of 4-hydroxyisoquinoline with 20% oleum at 200 °C gives the 8-sulfonic acid derivative only 〈72BAU406, 72IZV457〉.



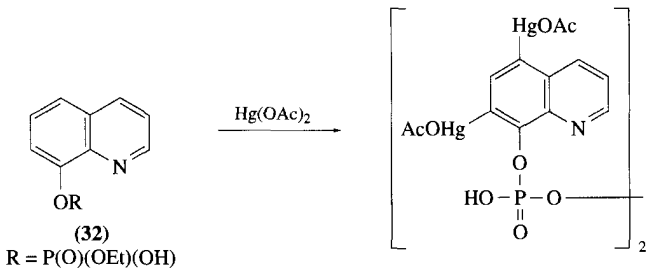
(11)

Chlorosulfonation of quinolines with chlorosulfonic acid produces 5- and 8-chlorosulfonylquinolines 〈79MI 503-01, 84URP1074869〉.

5.03.2.1.5 Mercuration

Mercuration of quinoline and isoquinoline occurs only in the pyridine ring, yielding the 3- and 4-mercuriochlorides, respectively 〈31JPJ542〉. However, when heated at 160 °C in the presence of NaCl, quinoline produces quinoline-8-mercuriochloride 〈31JPJ542〉. Chloromercuration and acetoxymercuration take place at the 8-position 〈53JPJ823〉.

The treatment of the 8-hydroxyquinoline phosphate (**32**) with mercuric acetate produces a tetramercurated dimer mercurated at positions 5 and 7 in the benzo rings (Equation (12)) 〈84MI 503-01〉.



(**32**)
R = P(O)(OEt)(OH)

(12)

5.03.2.1.6 Acylation, alkylation, and arylation

(i) Electrophilic processes

Friedel–Crafts acylation fails with quinoline and isoquinoline 〈41LA(549)238〉. However, 8-hydroxyquinoline, using acetyl chloride and benzoyl chloride in the presence of aluminum chloride, produces 5-acetyl- and 5-benzoyl-8-hydroxyquinolines in 45% and 77% yields, respectively 〈41LA(549)238〉.

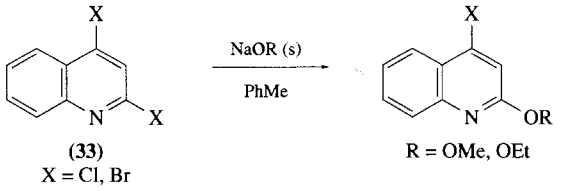
(ii) Homolytic processes

Phenylation of quinoline, using benzoyl peroxide, gives all seven phenylquinolines where the order of phenylation is 8 > 4 > 3 > 5 > 6 > 7 > 2 ⟨58AJC200, 71BSF2612⟩.

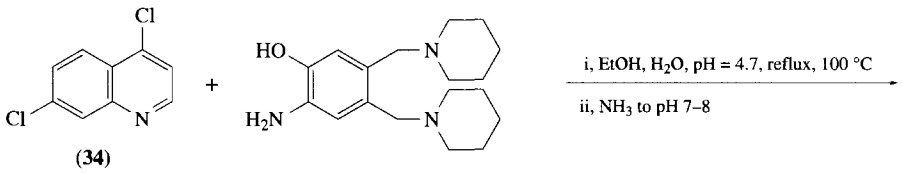
Homolytic methylation of quinoline using *t*-butyl peroxide as a methyl radical source gives a monomethyl fraction containing up to 31% 8-methyl- and 16% 5-methylquinoline ⟨69JCS(C)388, 70JCS(C)2169⟩.

5.03.2.1.7 Nucleophilic displacement

Nucleophilic substitution in quinoline normally takes place at position 2 and to a lesser extent at position 4. Thus, 2,4-dichloro- and 2,4-dibromoquinoline (**33**) react with sodium alkoxide to yield only the 2-alkoxy-4-haloquinolines (Equation (13)) ⟨93JCS(P1)181⟩. Replacement of halogen in the benzo ring occurs less readily than the replacement of halogen at positions 2 or 4. Thus, 4,7-dichloroquinoline (**34**) reacts with 2-amino-4,6-bis[(1-piperidinyl)methyl]phenol to form only the 4-substituted derivative, a potent antimalarial (Equation (14)) ⟨92AJC1651⟩. However, 4,7-dichloro-2-methylquinoline (**35**) is reported to form the 4,7-di(phenylhydrazino) derivative (56%) when heated under reflux with phenylhydrazine in ethanol and HCl (12 N) (Equation (15)) ⟨62JPC56⟩.



(13)



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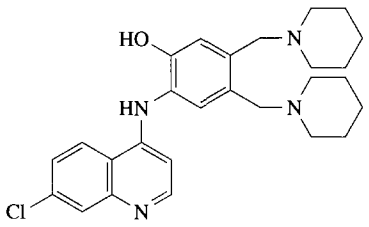
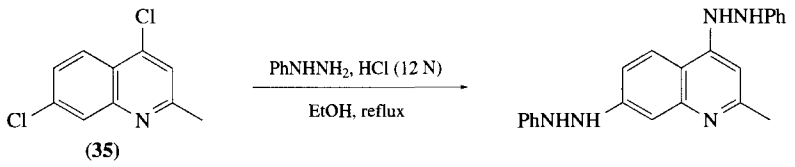
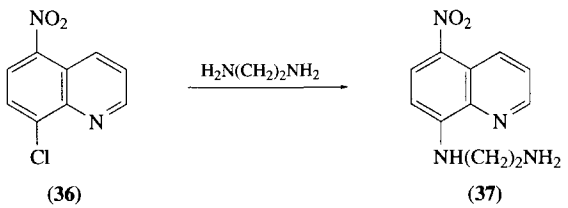




(15)

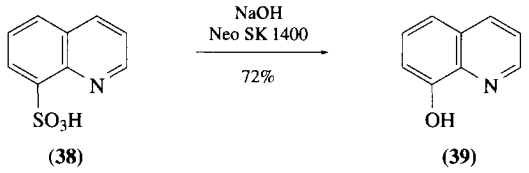
Activation of a substituent in the benzo ring can assist its displacement. Thus, when 8-chloro-5-nitroquinoline (**36**) is heated with 1,2-diaminoethane the chlorine is displaced to yield the mono-condensation product (**37**) (Equation (16)) ⟨32MI 503-01⟩.



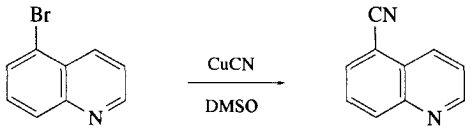
(16)

Substitution reactions of halogen in the benzo ring can occur via an aryne intermediate. The reaction of 6-bromoquinoline with lithium piperidide and piperidine in refluxing anhydrous diethyl ether, for example, gives 5- and 6-piperidinoquinoline via an elimination–addition mechanism involving a 5,6-dehydroquinoline (5,6-quinolyne) ⟨64LA(680)31⟩.

Nucleophilic substitution in the benzo ring of quinoline usually requires the replacement of an existing substituent. For instance, the treatment of molten quinoline-8-sulfonic acid (**38**) with sodium hydroxide in Neo SK 1400 (dibenzyltoluene) produces 8-hydroxyquinoline (**39**) in 72% yield (Equation (17)) ⟨93JAP(K)501036⟩. Again, 5-bromoquinoline (**40**) undergoes a normal addition–elimination process with copper cyanide in DMSO to give 5-cyanoquinoline (**41**) as the sole product (Equation (18)) ⟨74JCS(P1)1518⟩.

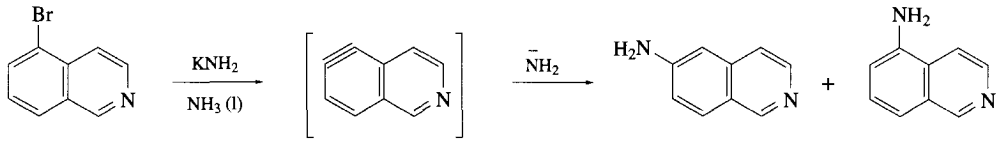


(38) (39) (17)



(40) (41) (18)

Isoquinoline readily undergoes nucleophilic attack in the hetero ring and substitution in the benzo ring requires displacement of an existing substituent. Potassium amide in liquid ammonia converts 5-bromoisoquinoline (**42**) into 5- and 6-aminoisoquinolines ((**44**) and (**45**)) via an elimination–addition mechanism involving 5,6-isoquinolyne (**43**) (Scheme 10) ⟨75S732⟩.

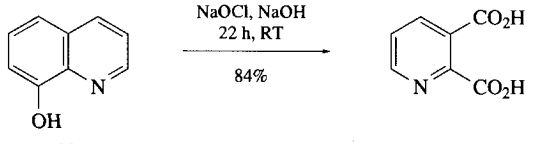


(42) (43) (44) 47% (45) 21%

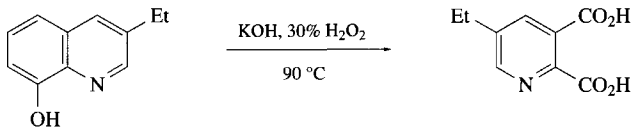
Scheme 10

5.03.2.2 Oxidation in Fused Benzene Rings

The benzo fused ring of quinoline is susceptible to oxidative ring cleavage by many reagents. Thus, oxidation with aqueous sodium hypochlorite and sodium hydroxide converts 8-hydroxyquinoline (**39**) into pyridine-2,3-dicarboxylic acid (quinolinic acid) (**46**) in 84% yield (Equation (19)) ⟨90JAP(K)283370⟩, and alkaline hydrogen peroxide at 90 °C has been used for the related oxidation of 3-ethyl-8-hydroxyquinoline (**47**) to 5-ethylpyridine-2,3-dicarboxylic acid (**48**) (Equation (20)) ⟨88EUP259687⟩.



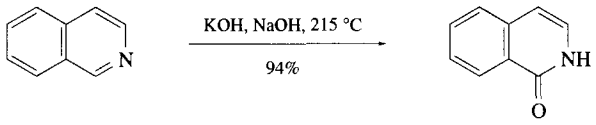
(39) (46) (19)



(47) (48) (20)

Quinolinic acids can also be prepared from quinoline and substituted quinolines in good yields by perchlorate oxidation under acidic conditions in the presence of catalysts such as ruthenium chloride ⟨91JAP(K)3287576⟩, ammonium vanadate ⟨87GEP3614756⟩, and copper sulfate ⟨87EUP232118⟩.

Oxidation of isoquinolines with ozone or permanganate usually results in attack at both rings to give both cinchomeronic and phthalic acids. However, potassium hydroxide and sodium hydroxide mixtures have been used as oxidants for isoquinoline at 215 °C to give isocarbostyril (**49**) in 94% yield (Equation (21)) ⟨89GEP3814361⟩.



(49) (21)

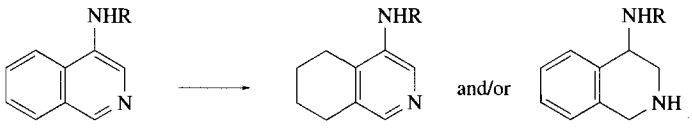
5.03.2.3 Reduction of Fused Benzene Rings

The reduction of quinolines and isoquinolines with complex metal hydrides has been reviewed by Keay ⟨86AHC(39)1⟩ and their catalytic hydrogenation has been reviewed by Freifelder ⟨63MI 503-01⟩.

The hetero ring of quinoline is more easily reduced than the carbocyclic ring and selective reduction of the benzo-fused ring is seldom possible (however, see below).

Isoquinoline can be completely reduced to *cis*- and *trans*-decahydroisoquinoline with hydrogen in acetic acid with a trace of sulfuric acid ⟨48JA2617⟩. The benzo rings of both quinoline and isoquinoline can be selectively reduced in high yield using platinum oxide in either concentrated hydrochloric acid or TFA at 50 psi, giving the 5,6,7,8-tetrahydro derivatives ⟨75JOC2729⟩. Analogous reductions have been recorded for 2-, 3-, 6- and 8-methylquinolines ⟨75JOC2729, 80JCS(P1)1933⟩.

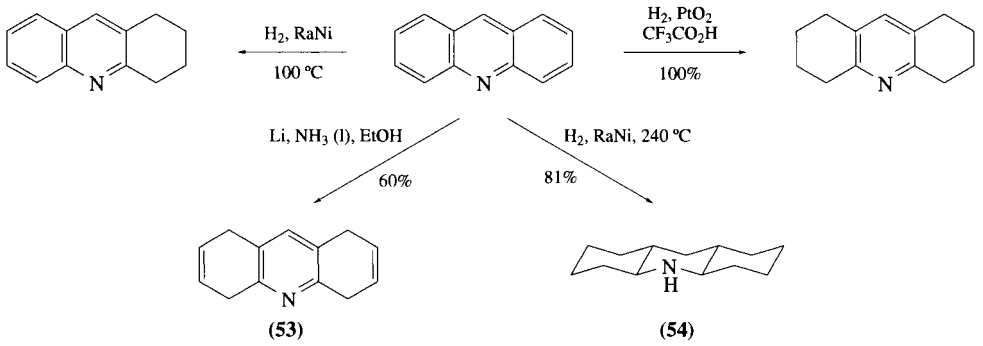
The hydrogenation of 4-acetamido- (**50**; R = COMe) and 4-benzamidoisoquinoline (**50**; R = COPh) over Adams catalyst in acetic acid–sulfuric acid gave the corresponding 5,6,7,8-tetrahydroisoquinoline (**51**), while their reduction over Adams catalyst in acetic acid or over Raney nickel in ethanol yielded the corresponding 1,2,3,4-tetrahydroisoquinoline (**52**). However, 4-aminoisoquinoline (**50**; R = H) over either Adams catalyst in sulfuric acid or Raney nickel in ethanol was reduced to the 5,6,7,8-tetrahydro derivative (**51**; R = H) (Equation (22)) ⟨67YZ547⟩.



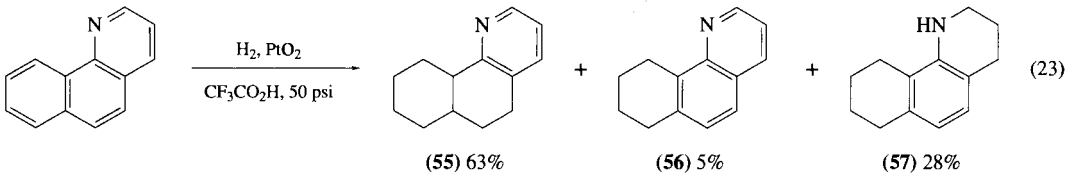
(50) R = H, COMe, COPh (51) (52) (22)

Acridine is cleanly hydrogenated in both benzene rings over platinum oxide in trifluoroacetic acid at 50 psi ⟨75JOC2729⟩. However, when the reduction is performed over Raney nickel at 100 °C, one benzene ring only is hydrogenated and 1,2,3,4-tetrahydroacridine is obtained ⟨41JA1563⟩. Partial hydrogenation of both benzene rings is possible with lithium and ethanol in liquid ammonia, producing 1,4,5,8-tetrahydroacridine (60%) (**53**) ⟨69AJC1103⟩. Complete reduction of acridine to α-perhydroacridine (**54**) is possible using Raney nickel at 240 °C (Scheme 11) ⟨68BCJ2458⟩.

Hydrogenation of benzo[*h*]quinoline over platinum oxide in trifluoroacetic acid at 50 psi gives 5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinoline (**55**) as the main product (63%) together with 7,8,9,10-tetrahydrobenzo[*h*]quinoline (**56**) (5%) and 1,2,3,4,5,6,7,8-octahydrobenzo[*h*]quinoline (**57**) (28%) (Equation (23)) ⟨75JOC2729⟩.



Scheme 11

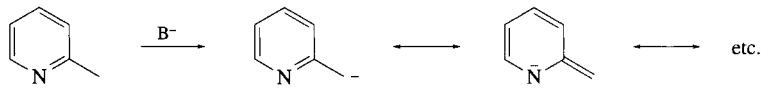


5.03.3 *C*-LINKED SUBSTITUENTS

5.03.3.1 Alkyl Groups

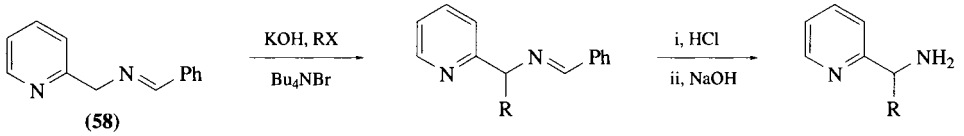
5.03.3.1.1 Alkyl substituents attached to carbon

Alkyl groups α and γ to a pyridine nitrogen are noticeably more reactive than alkyl groups attached to a benzene ring, especially in base-catalyzed reactions involving deprotonation of the alkyl substituent (Scheme 12). In the case of quaternary salts and *N*-oxides, proton removal from an α- or γ-alkyl group is even easier, and relatively mild basic catalysts often suffice ⟨58LA(613)171⟩.



Scheme 12

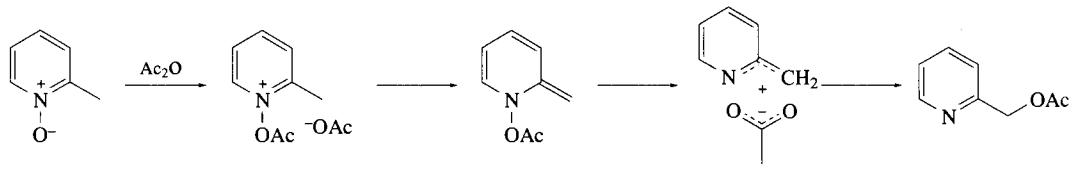
Strong bases such as sodamide in liquid ammonia or organolithiums convert 2- and 4-alkylpyridines and -quinolines completely into the corresponding anions which which can readily be alkylated, acylated, carbonylated, and nitrosated ⟨69AP(302)494⟩. Bases such as alkoxide or hydroxide ions, aliphatic amines or even an alkylpyridine or alkylquinoline can react with activated alkyl groups in azines to produce anions which react with suitable electrophiles such as aromatic and aliphatic aldehydes ⟨59JCS1641⟩, nitroso compounds ⟨63JCS4600⟩, phthalic anhydride ⟨1883CB163, 01LA(315)303⟩, selenium dioxide ⟨37JA524⟩, formaldehyde–amine mixtures ⟨31MI 503-01⟩, and halogens ⟨23JCS2882, 70MI 503-01⟩. The doubly activated methylene group of the 2-iminomethylpyridine (**58**) is readily alkylated under phase-transfer conditions (Scheme 13) ⟨92SC265⟩.



Scheme 13

Treatment of 2-methylpyridine *N*-oxide with acetic anhydride gives 2-pyridylmethyl acetate (**61**) as the main product (Scheme 14) ⟨72JA932⟩. The mechanism is said to involve the formation of the

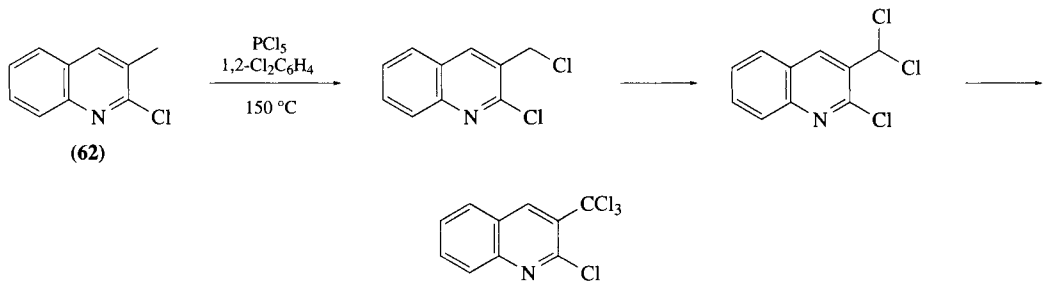
N-acetoxypyridinium salt (**59**), deprotonation of the 2-alkyl group, and the formation of an ion-pair intermediate of type (**60**) ⟨72JA932⟩. A mechanism involving a radical-pair intermediate has also been proposed ⟨62JA3359⟩, but this appears to be unlikely ⟨68JCS(C)831, 68TL257⟩. The use of acetyl chloride as a cosolvent reduces the level of by-products formed in this reaction ⟨85H(23)1697⟩. The reaction of 2-methylquinoline *N*-oxide with benzoyl chloride can also be explained by a similar mechanism ⟨64T2671, 68JOC2762⟩.



(**59**) (**60**) (**61**)

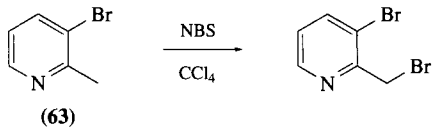
Scheme 14

Halogenoalkylpyridines and halogenoalkylquinolines can result from halogenation of alkylpyridines and alkylquinolines with phosphorus halides. 2-Chloro-3-methylquinoline (**62**) with phosphorus pentachloride in 1,2-dichlorobenzene at 150°C yields a mixture of mono-, di-, and trichloromethyl compounds (Scheme 15) ⟨91JHC1549⟩. *N*-Bromosuccinimide can be used to monobrominate the methyl groups of 3-bromopicoline (**63**) ⟨92S528⟩, 4-aryl-3,6-bis(alkoxycarbonyl)-2,5-dimethyl-1,4-dihydropyridines (**64**) (Equations (24) and (25)) and 5-halo-8-methylquinoline ⟨83KGS1373, 88TL6935, 89KGS1422, 91KGS1230⟩.

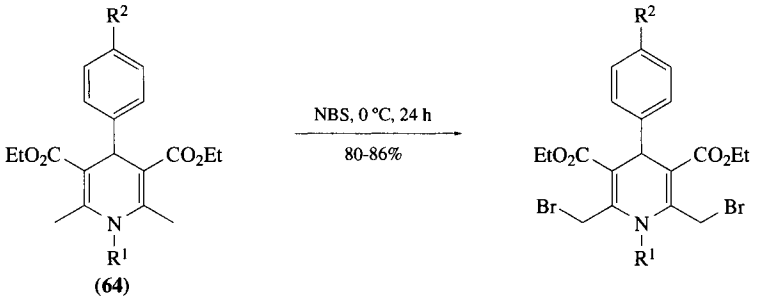


(**62**)

Scheme 15



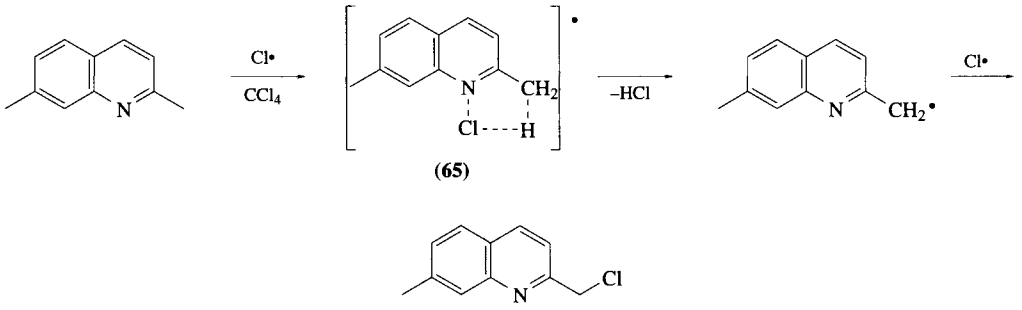
(**63**) (24)



(**64**) (25)

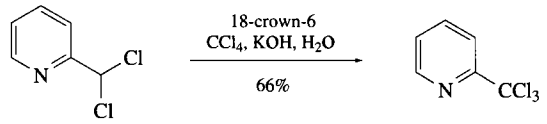
R^1	R^2
$PhCH_2$	$3\text{-}O_2NC_6H_4$
Ph	$4\text{-}BrC_6H_4$
$4\text{-}MeOC_6H_4$	H

The use of chlorine atoms to chlorinate selectively the 2-methyl groups of 2,6- and 2,7-dimethylquinoline involves an intramolecular hydrogen transfer where a loose σ^*-type complex (**65**) is formed between a chlorine atom and the pyridine ring (Scheme 16) ⟨92JA6003⟩.



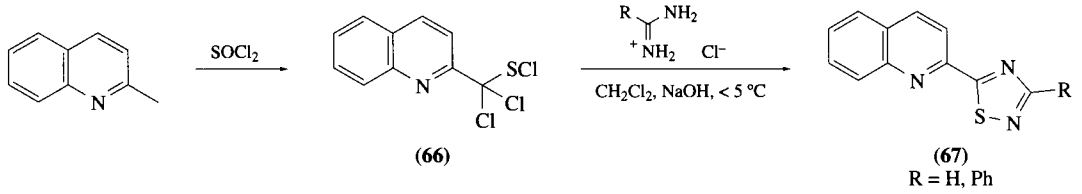
Scheme 16

Under phase-transfer catalytic conditions, chlorination of 2-and 3-dichloromethylpyridines with potassium hydroxide and 18-crown-6 in aqueous carbon tetrachloride yields the corresponding 2- and 3-trichloromethylpyridines respectively in 66% and 27% yields (Equation (26)) ⟨90KGS50⟩.



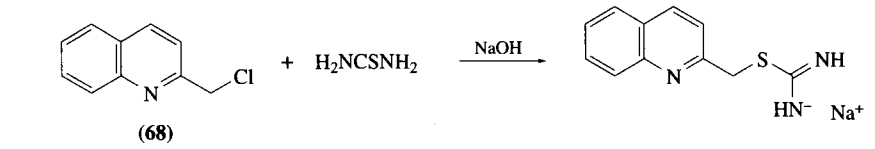
(26)

Refluxing thionyl chloride converts 2-methylquinolines into dichloro(2-quinolyl)methanesulfenyl chlorides (**66**) which can be converted into 5-(2-quinolyl)-1,2,4-thiadiazoles (**67**) with amidines (Scheme 17) ⟨88JCS(P1)3019⟩.

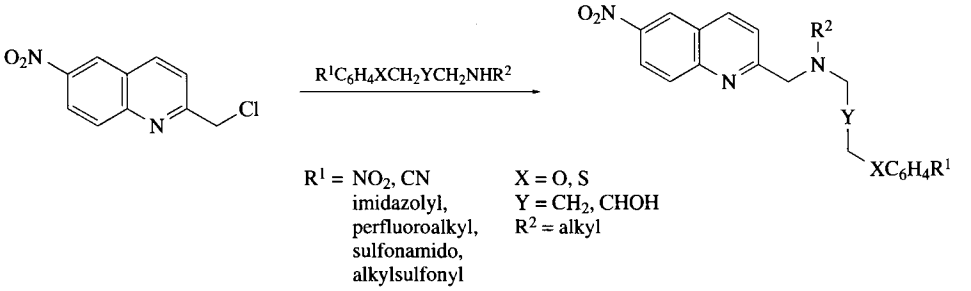


Scheme 17

The halogens of 2-chloromethylquinoline (**68**) and of 9-bromomethylacridine (**69**) are readily displaced by nucleophiles such as thiourea (Equation (27)) ⟨85MI 503-01, 89CS313⟩, aliphatic amines (Equation (28)) ⟨92USP5084463⟩, and aromatic amines (Equation (29)) ⟨92MI 503-01⟩. 3-(Trichloromethyl)pyridine is converted into the acetal (**70**) by reaction with methoxide, probably by the mechanism shown in Scheme 18 ⟨89JCS(P1)283⟩. The bromine of the 3-bromomethylpyridine derivative (**71**; X = Br) has been converted into the triphenylphosphonium bromide (**71**; X = $^{+}PPh_3Br^{-}$) for the selective Wittig reaction leading to (**72**), an intermediate precursor to HR780(1), a potent HMG-CoA reductase inhibitor (Equation (30)) ⟨90TL2545⟩.

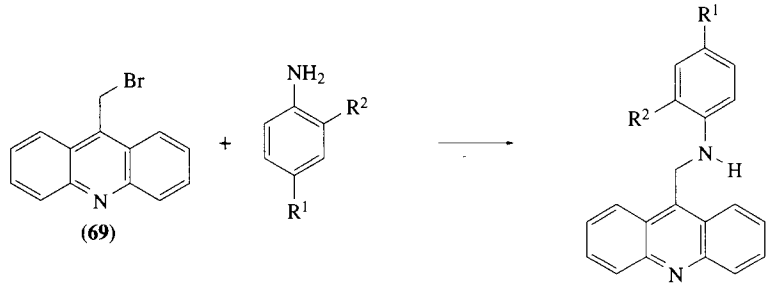


(27)



(28)

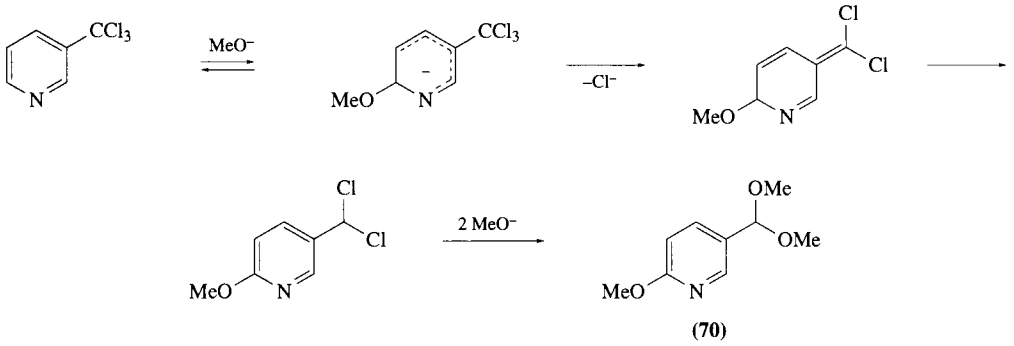
Scheme 18



(69)

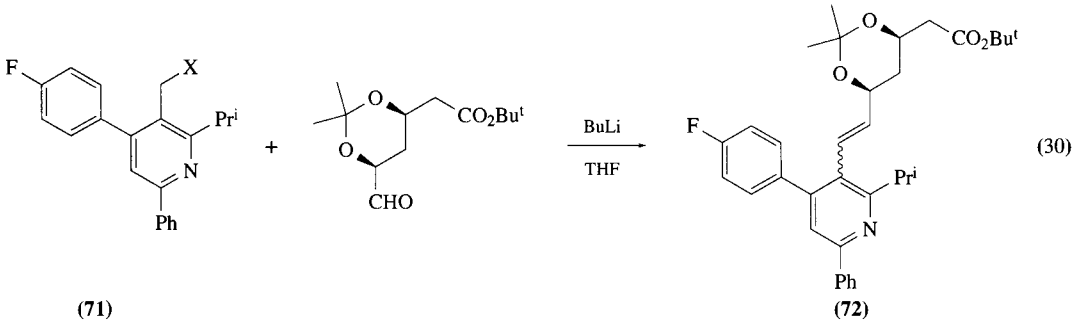
(29)

R^1 = H, OMe
R^2 = $NHSO_2Me$, $SO_2NHC(NH_2)$=NH



(70)

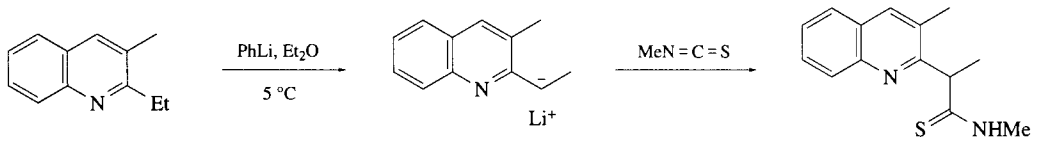
Scheme 18



(71) (72)

(30)

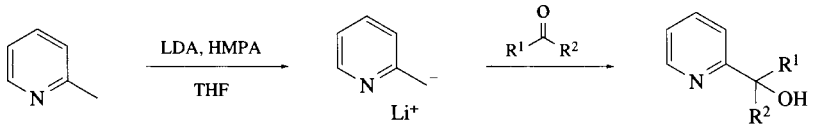
2-Alkylpyridines react in base with one or two equivalents of isothiocyanate to give thiocarboxamides and di(thiocarboxamides) ($PyCMe(CSNHMe)_2$) while 2-alkylquinolines yield only thiocarboxamides under the same conditions (Scheme 19) ⟨93PS(78)97⟩. 2- and 3-Picoline and 3-methylquinoline can be lithiated with lithium diisopropylamine complexed with HMPA, and the products condensed with numerous electrophiles (Scheme 20) ⟨75S705, 76JOC716, 93JHC707⟩.



Scheme 19

5.03.3.1.2 Alkyl substituents attached to nitrogen

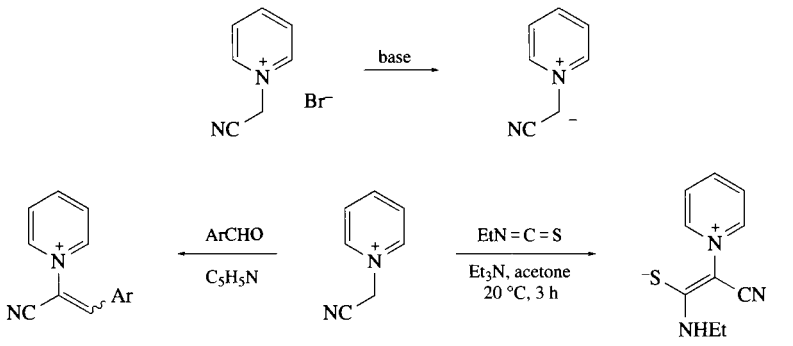
In *N*-alkylpyridinium salts, the positively charged ring nitrogen facilitates the abstraction of a proton from the adjacent *N*-alkyl carbon, and the resultant ylides condense normally with electro-



$R^1 = R^2 = Ph$; $R^1 = R^2 = 4\text{-}Me_2NC_6H_4$; $R^1 = Ph$, $R^2 = 4\text{-}ClC_6H_4$; $R^1 = Ph$, $R^2 = CH{=}CHPh$

Scheme 20

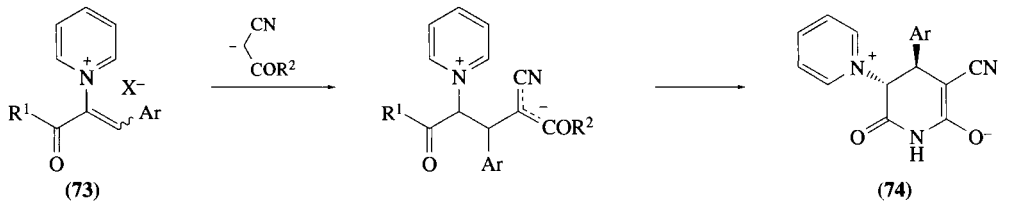
philes such as aromatic aldehydes ⟨53AG617⟩ and ethyl isothiocyanate (Equation (31) and Scheme 21) ⟨83JPR261⟩.



(31)

Scheme 21

The pyridinium salts (**73**) cyclocondense with methyl cyanoacetate and cyanoacetamide to afford pyridinolates (**74**) with *trans*-stereoselectivity (Scheme 22) ⟨90ZOR1571⟩.



(**73**)

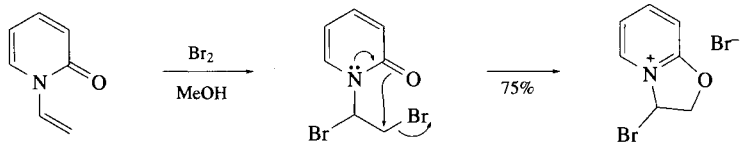
R^1 = MeO, NH_2
X = Cl, Br
Ar = Ph, 4-BrC_6H_4

R^1 = OMe, $R^2 = NH_2$
or
$R^1 = NH_2$, R^2 = OMe

(**74**)

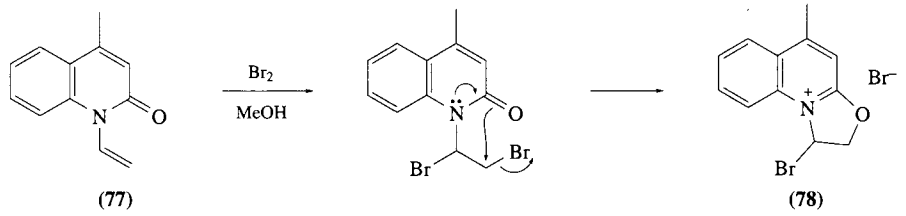
Scheme 22

Bromination of 1-vinyl-2-pyridone (**75**) with bromine in methanol, and of 4-methyl-1-vinyl-2(1*H*)-quinolone (**77**) with bromine in carbon tetrachloride gave the bicyclic salts (**76**) and (**78**) respectively, via intramolecular cyclization (Schemes 23 and 24). Iodination using iodine in ethanol yielded the corresponding iodo adducts ⟨91MI 503-01⟩. Intramolecular free-radical cyclization of the iodoalkylpyridinium salts (**79**) can be achieved with tributyltin hydride–AIBN mixtures in acetonitrile–tetrahydrofuran (Equation (32)) ⟨90TL1625, 90TL3495⟩.



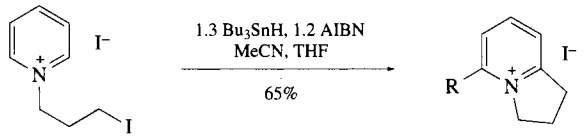
(**75**) (**76**)

Scheme 23



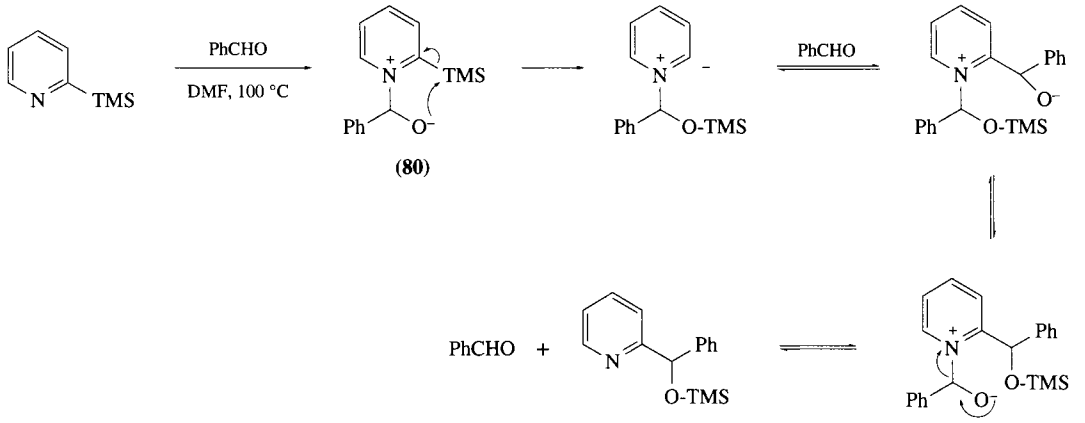
(77) (78)

Scheme 24



(79) (32)

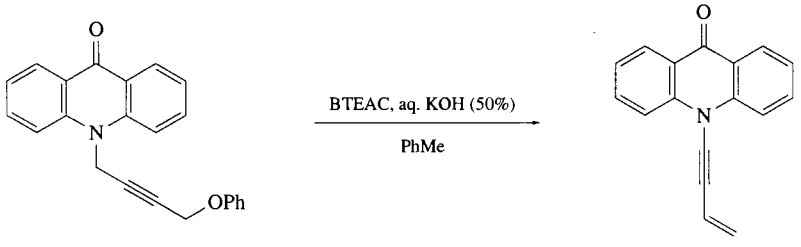
The *N*-benzylpyridinium betaines (**80**) are postulated as the intermediates in the carbodesilylation of 2-trimethylsilylpyridine with benzaldehyde, as outlined in Scheme 25 ⟨92CB1131⟩.



(80)

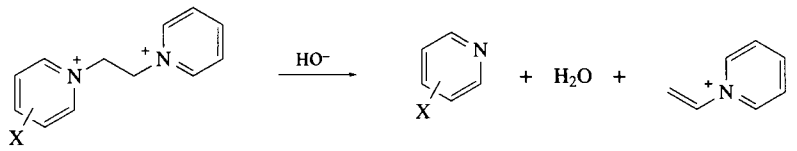
Scheme 25

N-Propargyl compounds can be rearranged to *N*-ethynyl derivatives. Thus, the phase-transfer catalyzed (benzyltriethylammonium chloride and aqueous potassium hydroxide (50%)) conversion of 10-(4-phenoxybut-2-ynyl)acridone (**81**) to the 10-ethynylacridone (**82**) in toluene occurs with loss of phenol (Equation (33)) ⟨94SC217⟩.



(81) (82) (33)

The base-promoted elimination reactions of *N*-(2-bromoethyl)pyridinium cations and *N,N'*-ethylenebispyridinium dications (**83**) proceed via an *E*1cB reaction mechanism in aqueous solution (Equation 34) ⟨91JA6950, 92CJC1195⟩.

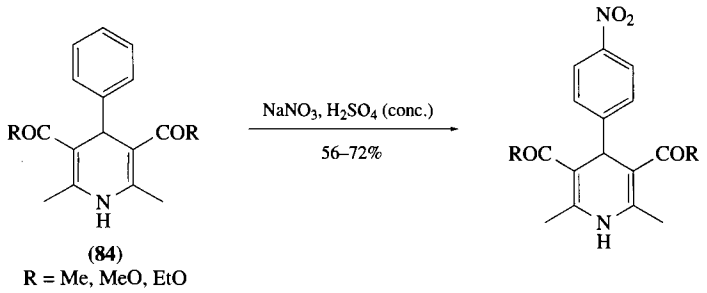


(83) (34)

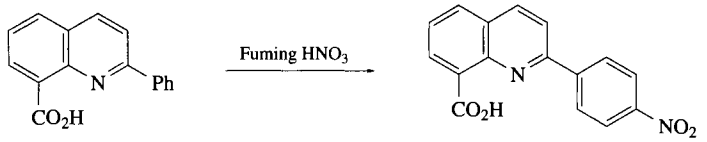
5.03.3.2 Aryl Groups

A review of the nitration of phenyl-substituted heterocycles has been published ⟨93AHC(58)215⟩.

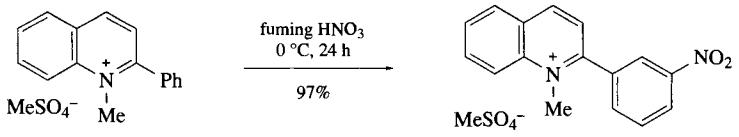
Electrophilic substitution of phenylpyridines occurs exclusively in the phenyl ring, as expected. 4-Phenylpyridine, for example, yields mononitration products in the ratio *o*:*m*:*p*, 20:33:47 ⟨68JCS(B)862, 71JCS(B)712⟩. However, the 4-phenyl-1,4-dihydropyridine (**84**) on nitration with sulfuric acid and sodium nitrate yields exclusively the 4-nitrophenyl derivative in 56–72% yield (Equation (35)) ⟨87KGS68⟩. The nitration, sulfonation, and bromination of 1-phenylpyridinium cations occurs in the *meta*-position of the 1-phenyl group ⟨86H(24)2545⟩. 2-Phenylquinoline-8-carboxylic acid (**85**) is nitrated with fuming nitric acid to produce the 2-(4-nitrophenyl) derivative, which crystallizes from solution (Equation (36)) ⟨89JMC396⟩. The charged quinolinium system exhibits a marked electron-withdrawing power, as shown by the nitration of 1-methyl-2-phenylquinolinium methosulfate (**86**) by nitric acid to yield the 1-methyl-2-(3-nitrophenyl)quinolinium salt (97%) (Equation (37)) ⟨30JCS2236⟩. The activating and *para*-directing influence of an *N*-oxide group toward electrophilic substitution does not extend to phenyl substituents; thus, 2-phenylpyridine 1-oxide (**87**) is nitrated primarily in the *meta*-position (Equation (38)) ⟨58JCS1754⟩ as is 2-phenylquinoline *N*-oxide ⟨77CPB1256⟩.



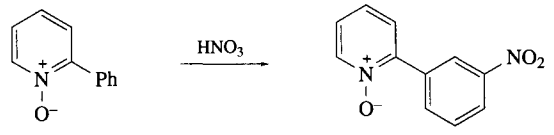
(84)
R = Me, MeO, EtO (35)



(85) (36)



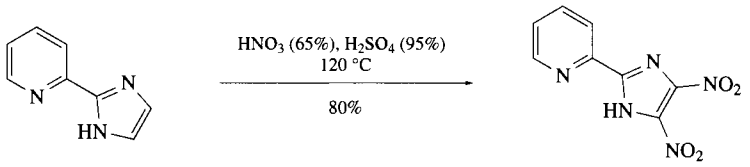
(86) (37)



(87) (38)

The nitration of 2-(2-pyridyl)imidazole (**88**) with a mixture of nitric (65%) and sulfuric (35%) acids at 120°C yields 2-(2-pyridyl)-4,5-dinitroimidazole (**89**) as the sole product with no nitration

in the pyridine ring (Equation (39)) ⟨85MI 503-02, 87S385⟩. Similarly, the bromination, iodination, and nitration of 3-(2-quinolyl)tropolone (**90**) affords the 5-substituted-3-(2-quinolyl)tropolones (**91**) with no substitution in the quinoline moiety (Equation (40)) ⟨92MI 503-02⟩.

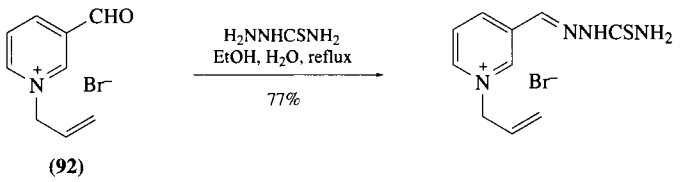


(88) (89) (39)

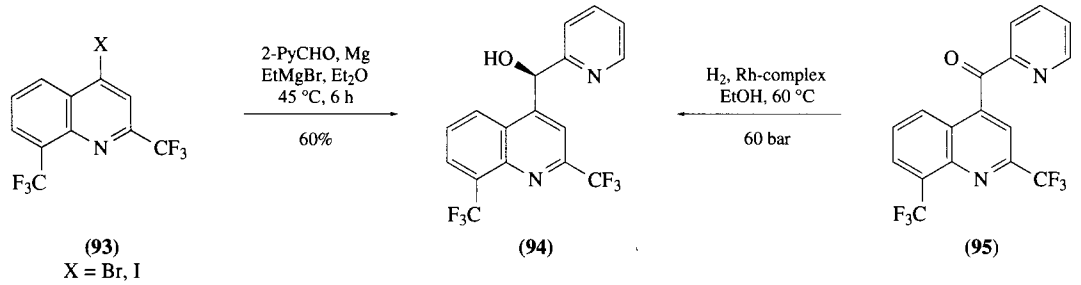
(90) (91) X = Br, I, NO_2 (40)

5.03.3.3 Acyl Groups

The chemistry of acylpyridines and their benzo derivatives resembles those of phenyl ketones and aldehydes. For instance, 1-allyl-3-formylpyridinium bromide (**92**) condenses with thiosemicarbazide in refluxing ethanol to give the corresponding thiosemicarbazone in 77% yield (Equation (41)) ⟨93KGS1088⟩. As expected, pyridine-2-carboxaldehyde undergoes the Grignard reaction with 4-bromo- and 4-iodo-2,8-bis(trifluoromethyl)quinoline (**93**) in the presence of magnesium metal and a catalytic amount of ethylmagnesium bromide in diethyl ether to afford the secondary alcohol (**94**), which is an intermediate for the antimalarial mefloquine hydrochloride (Scheme 26) ⟨92MIP170915⟩. The presence of lithium bromide significantly improves the addition of organolithium reagents to the carbonyl group of 2-pyridyl ketones ⟨85JCS(P1)213⟩.



(92) (41)

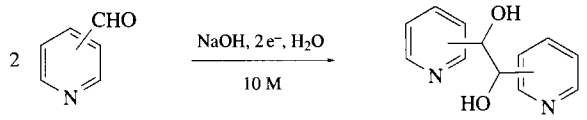


(93) X = Br, I (94) (95)

Scheme 26

Acylpyridines and their benzo derivatives are readily reduced to alcohols. Thus, asymmetric hydrogenation of the pyridyl bis(trifluoromethyl)quinolyl ketone (**95**) with hydrogen at 60 bar over rhodium diphosphine complex catalysts yields the corresponding alcohol (**94**) in 90% yield and 82% enantiomeric excess (Scheme 26) ⟨93EUP553778⟩. The reduction of 2-acetylpyridine with the alcohol dehydrogenase from *Lactobacillus kefir* in isopropanol yields the optically active (*R*)-alcohol

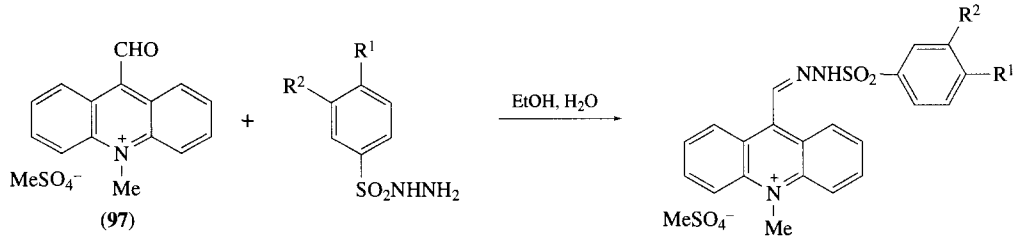
with 97% *ee* ⟨92JOC1532, 92CB1169⟩. 2-, 3-, and 4-Pyridinecarboxaldehydes are readily electroreduced to pinacols (**96**) in solutions of sodium hydroxide (< 10 M) (Equation (42)) ⟨86JEC277⟩.



(42)

(**96**)

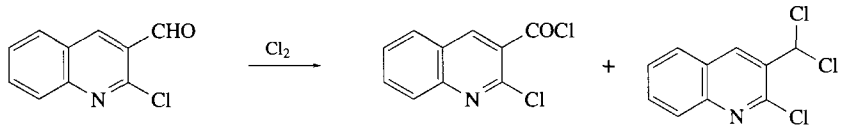
Aldehydes and ketones of π-deficient heterocycles form the usual derivatives, phenylhydrazones, semicarbazones, etc. Thus, the 9-acridinecarboxaldehyde salts (**97**) readily react with arylsulfonylhydrazines to give sulfonylhydrazones which show *in vitro* cytotoxicity against Ehrlich ascites carcinoma (Equation 43) ⟨91MI 503-02⟩. They also react with halogenating agents. For example, the chlorination of 2-chloroquinoline-3-carboxaldehyde yields 2-chloroquinoline-3-carbonyl chloride (**98**) and 2-chloro-3-dichloromethylquinoline (**99**) (Equation (44)) ⟨91SC1929⟩.



(43)

(**97**)

R^1 = H, Me, Cl, OH, AcNH; R^2 = H, CO_2H

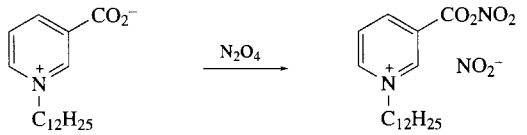


(44)

(**98**) (**99**)

5.03.3.4 Carboxylic Acids and Derivatives

In water, pyridinecarboxylic acids exist largely as zwitterions ⟨57JA2050⟩. The acids can be converted into esters with alcohols and mineral acid catalysis, and by the use of diazoalkanes. *N*-Alkylbetaines are formed when pyridinecarboxylic acids are treated with alkyl halides ⟨03M519⟩ and alkyl sulfates ⟨33ZPC(222)105⟩ in alkali. The pyridinium-3-carboxylate betaine (**100**) reacts with dinitrogen tetroxide to yield the acyl nitrate (**101**) which can be used for highly selective *ortho*-nitration of phenols (Equation (45)) ⟨85CC512⟩.

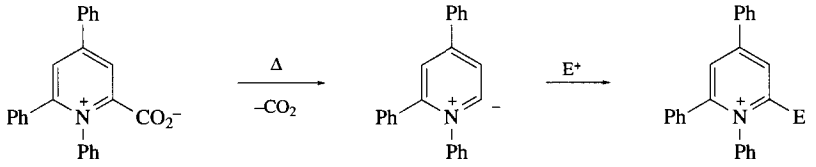


(45)

(**100**) (**101**)

Pyridinecarboxylic acids readily undergo decarboxylation on heating, the general order of reactivity being $\alpha > \gamma > \beta$. The carboxylic acids of quinoline and isoquinoline show similar behavior ⟨69JA6115, 70LA(732)43⟩. The activated pyridinium-2-carboxylate betaines (**102**) readily undergo thermal decarboxylation to yield intermediate ylides (**103**) which can be trapped with electrophiles (Scheme 27) ⟨85JCS(P1)2167⟩.

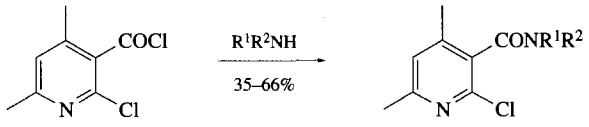
Carboxylic acid derivatives of pyridine and its benzo analogues in general show normal reactivity at the functional group ⟨62HC(14)212⟩. For example, substituted nicotinoyl chlorides react with primary and secondary amines to yield the corresponding amides (Equation (46)) ⟨93KFZ34⟩, and



(102) (103) E = CO_2H, COPh

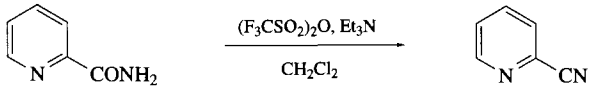
Scheme 27

primary amides can be dehydrated to nitriles (Equation (47)) ⟨93MI 503-01⟩. Oximes such as (**104**) can be dehydrated to nitriles by hydroxide ion catalysis (Equation (48)) ⟨86JPS608⟩.

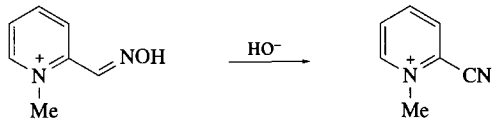


(46)

R^1 = H, R^2 = alkyl, $PhCH_2$
R^1–R^2 = morpholino, piperidino

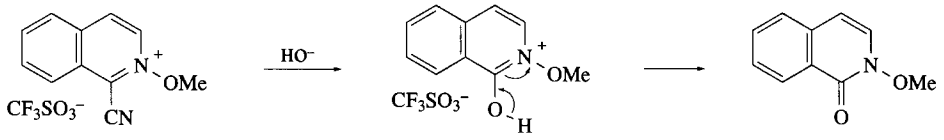


(47)



(104) (48)

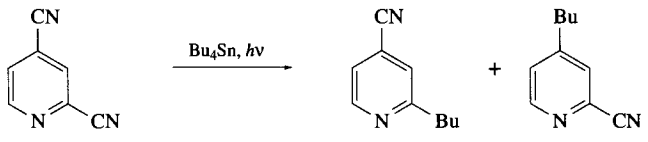
Cyano-substituted isoquinolines undergo normal attack by oxygen, carbon, and nitrogen nucleophiles in the hetero ring at positions 1 and 4. Thus, 1-cyano-*N*-methoxyisoquinolinium salts (**105**) react with aqueous hydroxide to yield *N*-methoxyisoquinolone (**106**) (Scheme 28) ⟨93AP(326)785⟩.



(105) (106)

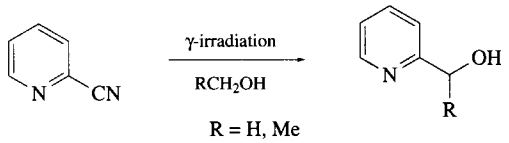
Scheme 28

The photochemical reaction of 2,4-dicyanopyridine with tetrabutyltin produces both 2-butyl-4-cyanopyridine (**107**) and 4-butyl-2-cyanopyridine (**108**) by *ipso*-substitution with strong evidence of an electron-transfer mechanism (Equation (49)) ⟨92TL3201⟩. In a further example, γ-irradiation of pyridinecarbonitriles in methanol and ethanol results in replacement of the cyano group by a hydroxyalkyl group (Equation (50)) ⟨84CL769⟩.



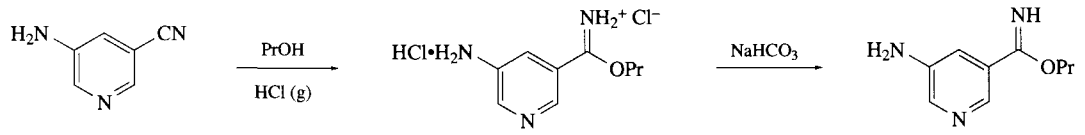
(107) 45 : 55 (108)

(49)

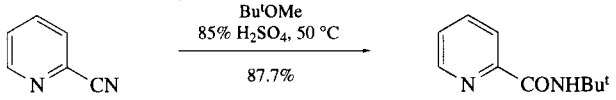


(50)

Cyanopyridines undergo alcoholysis (Pinner synthesis) in the presence of an alcohol and dry hydrogen chloride (Scheme 29) ⟨92MIP12150⟩. In the presence of 85% sulfuric acid, 2-cyanopyridine reacts with *t*-butyl methyl ether to give the corresponding herbicidal carboxamide (**109**) (Equation (51)) ⟨86GEP3537762⟩. The normal reaction of Grignard reagents with 3-cyanopyridine yields 3-acylpyridines. However, 4-benzyl-3-cyanopyridine is formed with benzylmagnesium chloride (**110**) (Equation (52)) ⟨87MI 503-01⟩.



Scheme 29



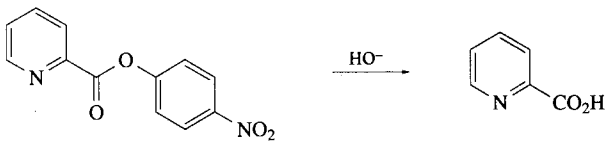
(51)

(**109**)

(52)

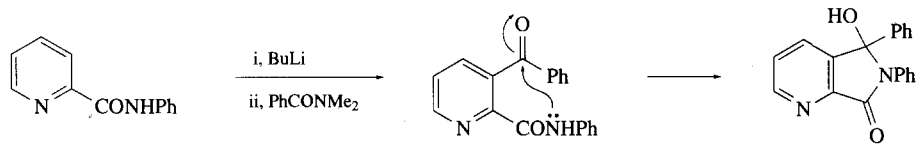
(**110**)

As expected, carboxylic acid esters and amides undergo base-catalyzed hydrolysis. 4-Nitrophenyl picolinate can be hydrolyzed in the presence of cationic micelles and lipophilic 2-hydroxymethylbenzimidazoles complexed to zinc(II) ions (Equation 53) ⟨87CL1303, 91TL193⟩. Methyl nicotinate can be hydrolyzed in aqueous dimethyl sulfoxide ⟨90JIC463⟩. The ethanolysis of 1-methoxycarbonylpyridinium ions displays a non-linear Brønsted plot (two branches) ⟨91DOK(317)893⟩. The hydrolysis of pyridine carboxamides proceeds largely by an A2 mechanism in acid, but in very strong acid a changeover to an A1 mechanism is observed ⟨92JCR(S)410⟩.



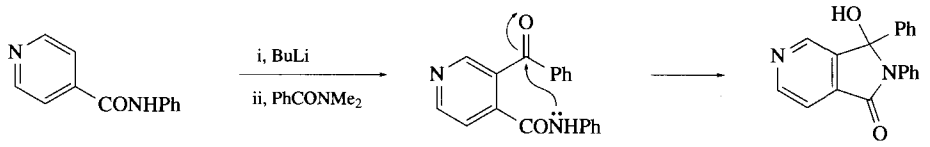
(53)

Lithiation of the pyridine carboxanilides (**111**) and (**113**) followed by treatment with *N*,*N*-dimethylbenzamide yields mainly pyrrolopyridinones (**112**) and (**114**) respectively via an intramolecular nucleophilic attack (Schemes 30 and 31) ⟨90M909⟩.



(**111**) (**112**)

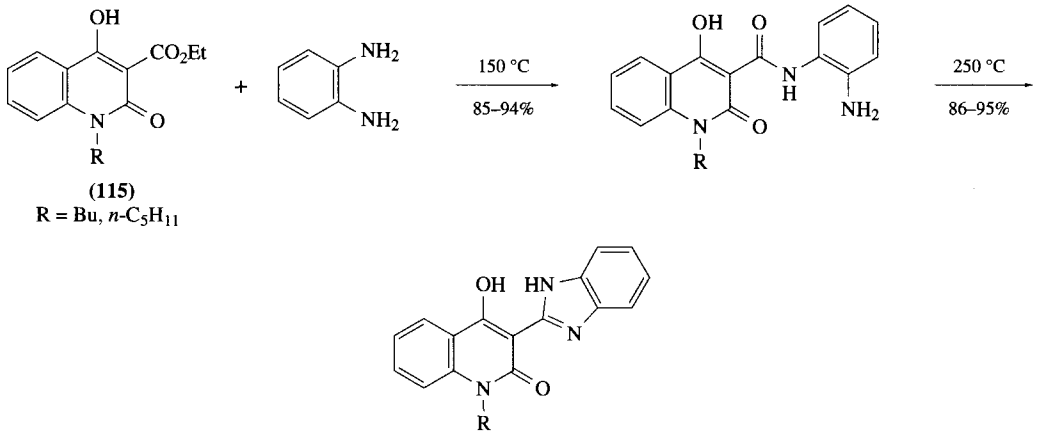
Scheme 30



(113) (114)

Scheme 31

Condensation of the 4-hydroxyquinoline-3-carboxylates (**115**) with 1,2-phenylenediamine at 150°C produces the expected anilides which cyclocondense at 250°C to form the benzimidazoles (**116**) in high yield (86–95%) (Scheme 32). These benzimidazoles (e.g. R = Bu, pentyl) possess antithyroid activity ⟨93KGS105⟩.

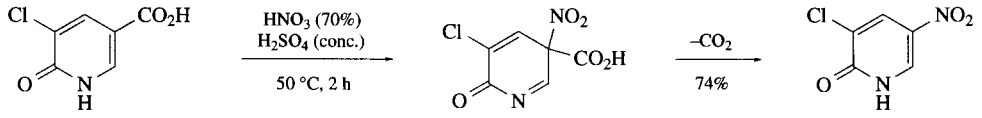


(115)
R = Bu, n-C_5H_{11}

(116)

Scheme 32

The nitration of 5-chloro-1,6-dihydro-6-oxopyridine-3-carboxylic acid (**117**) with nitric and sulfuric acids at 50°C gives 3-chloro-5-nitropyridin-2(1*H*)-one (**118**) (74%) via decarboxylation (Scheme 33) ⟨92EUP467308⟩.

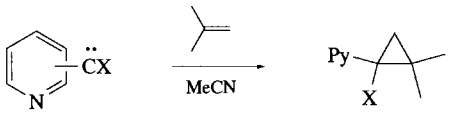


(117) (118)

Scheme 33

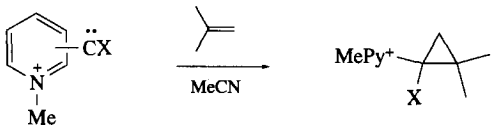
5.03.3.5 Other Substituted Alkyl Groups

The 2- and 3-pyridylhalocarbenes (**119**) and the corresponding *N*-methylpyridiniumhalocarbenes (**120**) are good electrophiles and add easily to alkenes (Equations (54) and (55)) ⟨92TL1427⟩.



(119)
X = Cl, F

(54)



(55)

(120)
X = Cl, F

5.03.4 *N*-LINKED SUBSTITUENTS

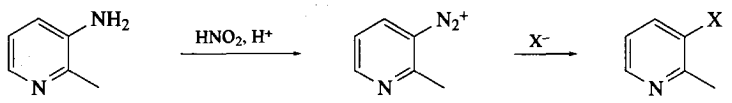
The chemistry of the *N*-linked substituents of the π-deficient heterocycles principally concerns the reactivity of amino and nitro functional groups. Other nitrogen functions are derived from either or both the amino and nitro parents and thus are discussed in Sections 5.03.4.1 and 5.03.4.2.

5.03.4.1 Amino Groups and Related Functions

5.03.4.1.1 Amino groups attached to carbon

Most aminopyridines and their benzo derivatives exist in the amino form rather than the tautomeric pyridonimine form. Likewise, α- and γ-aminopyridine *N*-oxides exist predominantly in the amino form.

β-Aminopyridines and their benzo analogues give normal diazonium salts with nitrous acids which can be converted into their corresponding β-halogeno compounds by the Sandmeyer reaction (Scheme 34) ⟨84MI 503-02⟩. However, pyridine-2- and -4-diazonium ions are unstable and immediately react with the aqueous solvent to yield pyridones.

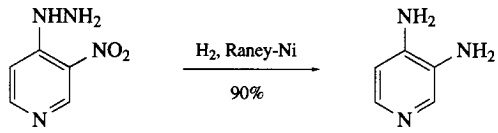


X = Cl, Br

Scheme 34

Electron-impact tandem mass spectroscopy has been used to investigate the mass spectral fragmentation pathways of phenylazopyridine *N*-oxides ⟨92CJC1028⟩.

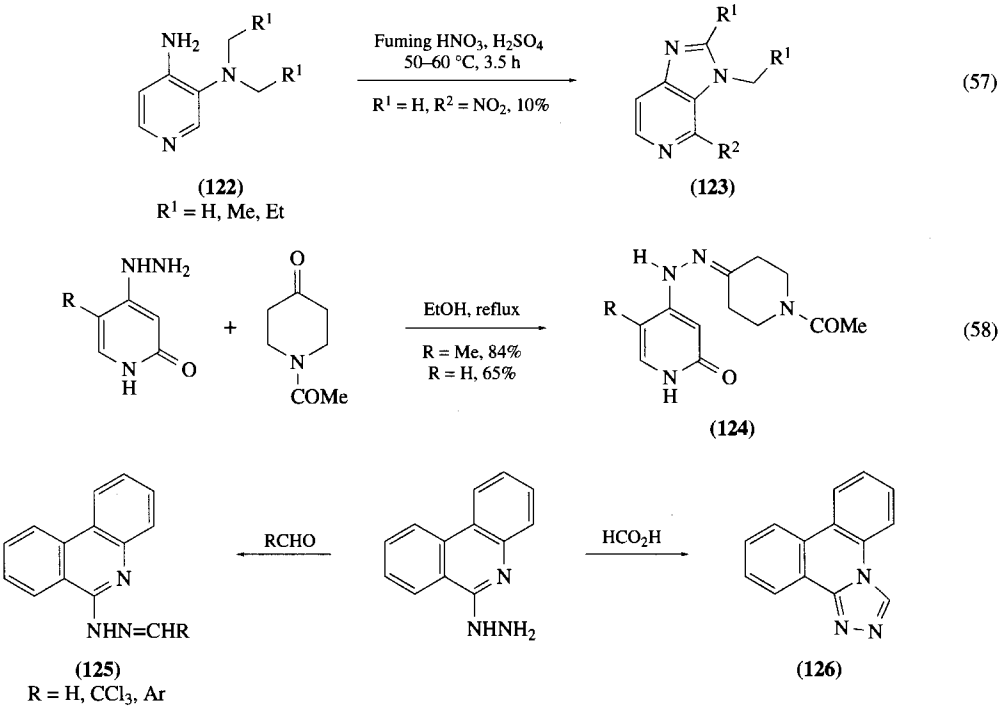
The reduction of diazonium salts gives the expected pyridylhydrazines (**121**), which on hydrogenation over Raney nickel form the corresponding diaminopyridines (Equation (56)) ⟨85EUP159112⟩.



(56)

(121)

Schiff-base formation occurs normally with 3-aminopyridine ⟨69CR(C)1319⟩ and aldehydes; imines of 2-aminopyridine, though isolable, are less stable. However, 4-amino-3-(dialkylamino)pyridines (**122**) under acidic conditions cyclize to imidazo[4,5-*c*]pyridine derivatives (**123**) via imine formation (Equation (57)) ⟨92H(34)1491⟩. 4-Hydrazino-1*H*-pyridin-2-ones react as expected with *N*-acetyl-4-piperidone to yield the corresponding hydrazones (**124**) (Equation (58)) ⟨86T2303⟩. 6-Hydrazinophenanthridine also condenses with aldehydes to give hydrazones (**125**). Condensation with formic acid, however, gives the triazolophenanthridine (**126**) (Scheme 35) ⟨92KGS531⟩.

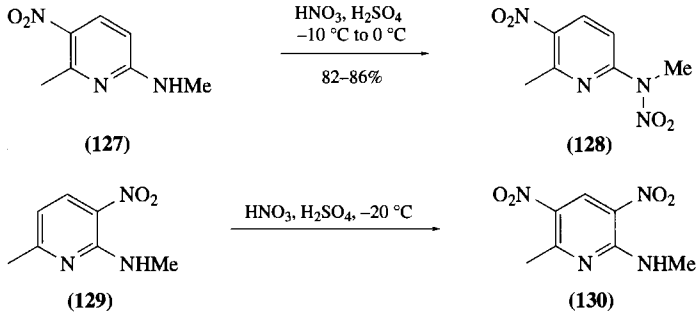


(57)

(58)

Scheme 35

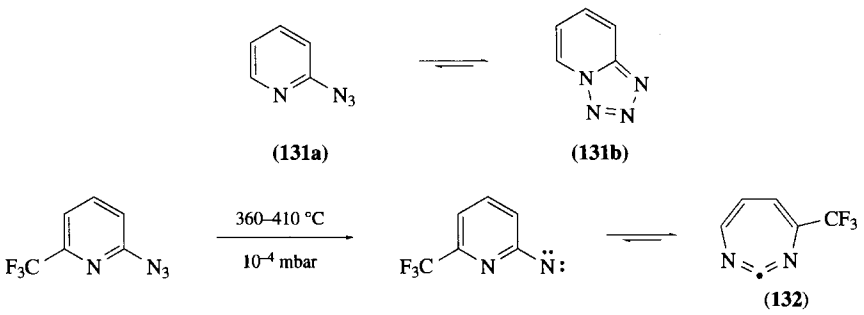
The nitration of 2-methyl-6-methylamino-3-nitropyridine (**127**) with nitric and sulfuric acids at −10 to 0°C gives the methylnitroamino derivative (**128**) (82–86%), while the isomeric 6-methyl-2-methylamino-3-nitropyridine (**129**) at −20°C gives only the 3,5-dinitro-2-methylamino derivative (**130**) (Equations (59) and (60)) ⟨85MI 503-03⟩.



(59)

(60)

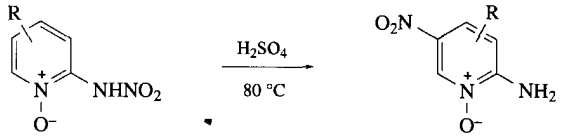
2-Azidopyridines (**131**) exist largely in the tetrazolo[1,5-*a*]pyridine form (**131b**) (Equation (61)). They undergo photolytic and thermolytic insertion and ring expansion to yield, for example, the 1,2-didehydro-1,3-diazepine (**132**), which was identified by FTIR spectroscopy (Scheme 36) ⟨92CC1062⟩.



(61)

Scheme 36

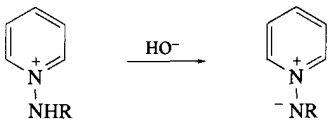
In sulfuric acid, 2-nitroaminopyridine *N*-oxides are converted into 2-amino-5-nitropyridine *N*-oxides (**133**) (Equation (62)) ⟨87MI 503-02⟩.



R = H, 3-Me, 4-Me, 6-Me (**133**) (62)

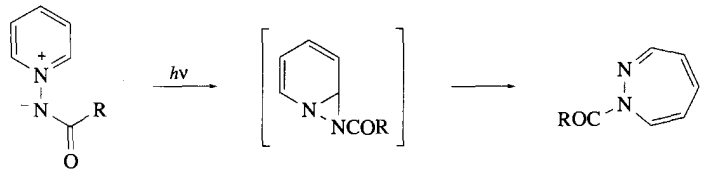
5.03.4.1.2 Amino groups attached to nitrogen

N-Aminopyridinium salts and their benzo analogues can be converted into pyridinium imines (**134**) and their benzo analogues by treatment with base (Equation (63)) ⟨62TL387, 70JOC433, 72JOC3106, 80YZ1⟩.



(**134**) (63)

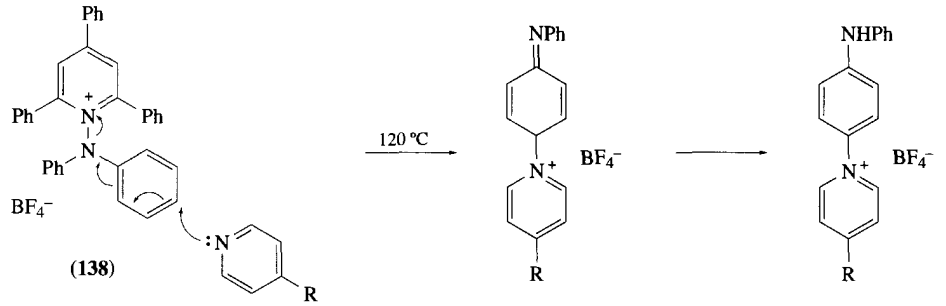
Under photochemical conditions, pyridinium imines undergo ring expansion, ring contraction, and imino group migration. For example, the photoisomerization of 1-iminopyridinium ylides (**135**) to diazepines (**137**) takes place via an electrocyclic reaction involving a 1,7-diazanorcaradiene-like intermediate (**136**) (Scheme 37) ⟨90JPC4464⟩.



(**135**) (**136**) (**137**)

Scheme 37

2,4,6-Triphenyl-1-(diphenylamino)pyridinium tetrafluoroborate (**138**) reacts with pyridines, quinoline, and isoquinoline to give substitution S_N2'-type products by nucleophilic attack at the *para*-position of one of the benzene rings of the 1-substituent (Scheme 38) ⟨85JCS(P1)2155⟩.



(**138**)

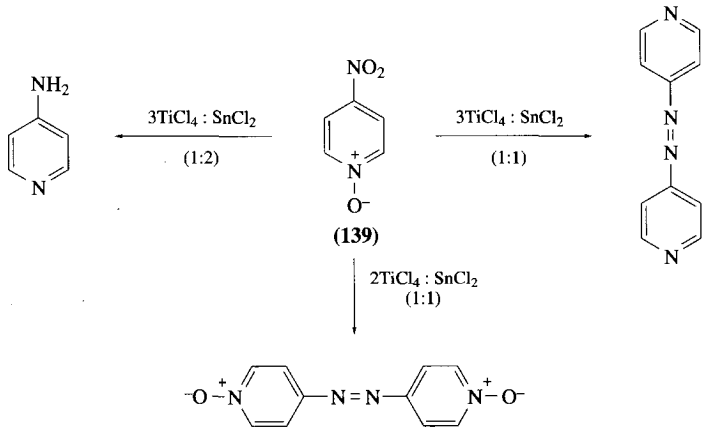
R = H, Me, NMe_2

Scheme 38

5.03.4.2 Nitro Groups

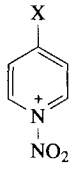
Nitroazines are susceptible to nucleophilic displacement and reduction. As expected, nitro groups situated α and γ to the ring nitrogen show increased susceptibility to nucleophilic attack and subsequent loss of the nitro group.

Nitropyridines, their benzo analogues, and their *N*-oxides can be reduced to the amino derivatives by standard methods such as catalytic hydrogenation. 2-Hydrazino-3-nitropyridine, for example, can be hydrogenated to 2,3-diaminopyridine ⟨85EUP159112⟩. The reduction of 4-nitropyridine *N*-oxide (**139**) with titanium tetrachloride and stannous chloride yields symmetrical azopyridine di-*N*-oxide, azopyridine, and 4-aminopyridine depending on the ratio of reagents used (Scheme 39) ⟨90JPR423⟩.



Scheme 39

N-Nitropyridinium cations (**140**) are used in the nitration of various aromatics and the key intermediates are charge-transfer complexes ⟨92JA1756⟩.



(140)
X = CN, CO_2Me, Cl, H, Me, OMe

5.03.4.3 *O*-Linked Substituents

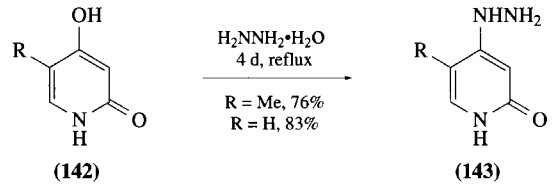
2- and 4-Pyridone and their benzo analogues exist predominantly in the oxo form (**141a**), rather than the hydroxypyridine form (**141b**) (Equation (64)) ⟨76AHCS(1)84⟩. In the case of 2-pyridone, AMI calculations show that the lactim tautomer is slightly preferred ⟨89JCR(S)56⟩. In nonaqueous solutions the keto form is thermodynamically preferred over the enol form, but in the gas phase the enol structure is known to be preferred ⟨81JA3233, 82JA612⟩. The tautomerism of 4-quinolones is a function of the substituents. The conjugate acids of the keto forms have pK_a values of ca. 1 while the NH ionization has a pK_a value of 7–10, depending on the substituents ⟨92T6135⟩. The phototautomerization of 7-hydroxyquinoline occurs via an excited-state photon-transfer process ⟨89JCS(F2)39⟩.

(64)

(141a) **(141b)**

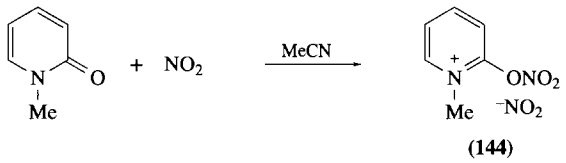
Katritzky and Lagowski have reviewed keto–enol tautomerism in 2- and 4-substituted pyridines ⟨63AHC(1)339⟩.

Pyridones behave as cyclic amides and do not normally react with nucleophilic "ketonic reagents" such as hydrazine. However, 4-hydroxy-1*H*-pyridin-2-ones (**142**) react with hydrazine hydrate to produce 4-hydrazino-1*H*-pyridin-2-ones (**143**) (Equation (65)) ⟨86T2303⟩.



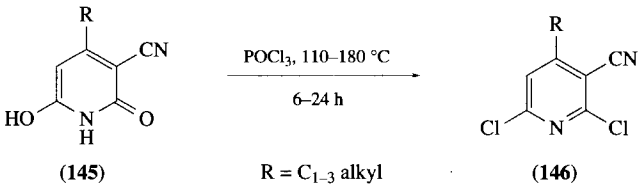
(65)

N-Alkyl derivatives of 2- and 4-pyridone are readily nitrated with nitric and sulfuric acids to form the 3- or 5-mono-, and then 3,5-dinitro derivatives. However, the milder nitration of *N*-methyl-2-pyridone with nitrogen dioxide in acetonitrile yields the nitrate ester salt (**144**) which can be used to nitrate phenols in the *o*-position selectively (Equation (66)) ⟨88T4555⟩.

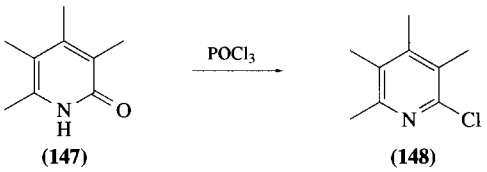


(66)

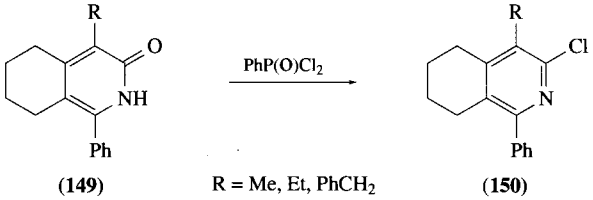
Chlorodeoxygenation of the hydroxypyridones (**145**) at 110–180°C for 6–24 h gives the 2,6-dichloro derivative (**146**) (Equation (67)) ⟨92MIP22532, 92SC2829⟩. Phosphorus oxychloride treatment of 3,4,5,6-tetramethyl-1*H*-pyridin-2-one (**147**) yields 2-chloro-3,4,5,6-tetramethylpyridine (**148**) (Equation (68)) ⟨90SC2699⟩, while phenylphosphonic dichloride treatment of the tetrahydroisoquinolones (**149**) produces the corresponding 3-chloro derivatives (**150**) (Equation (69)) ⟨90MI 503-01⟩. All the possible monochloro 8-quinolinols have been synthesized ⟨91M935⟩.



(67)



(68)

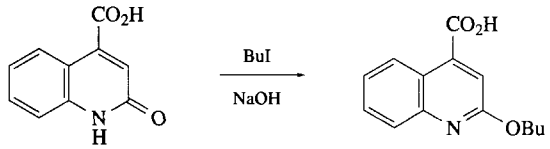


(69)

5.03.4.4 Alkylation of Hydroxypyridines, Pyridones, and their Benzo Analogues

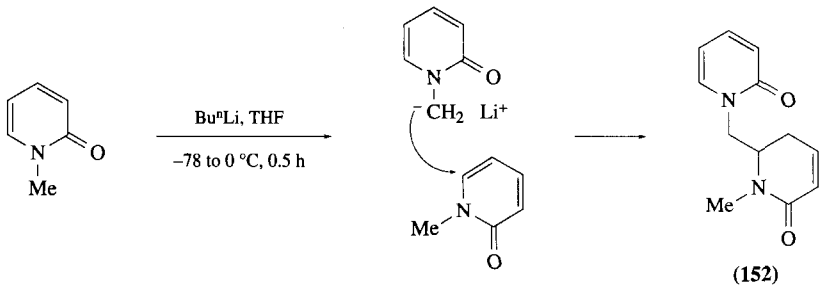
The alkylation of pyridinols and pyridones is complex, as it may occur at either the oxygen or the nitrogen atom, depending on the conditions and the reagents used. An example of exclusive

O-alkylation is shown by 2-oxo-4(1*H*)-quinolinic acid (**151**) which is *O*-butylated with butyl iodide and alkali (Equation (70)) ⟨92MIP12150⟩.



(151) (70)

In the lithiation of *N*-substituted 2- and 4-pyridones, the 4-isomer is smoothly metallated at the 2-position. However, lithiation of 1-methyl-2-pyridone takes place at the *N*-methyl group and affords the dimer (**152**) by conjugate addition to the starting material (Scheme 40) ⟨85CC1021⟩.

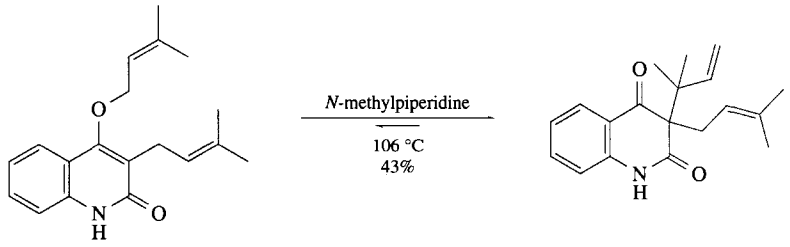


(152)

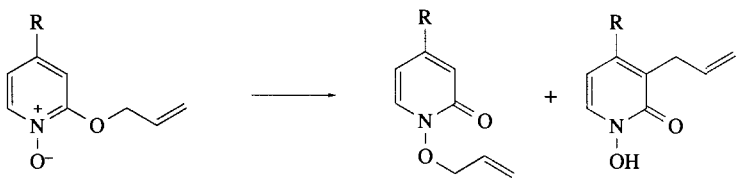
Scheme 40

5.03.4.5 Ethers

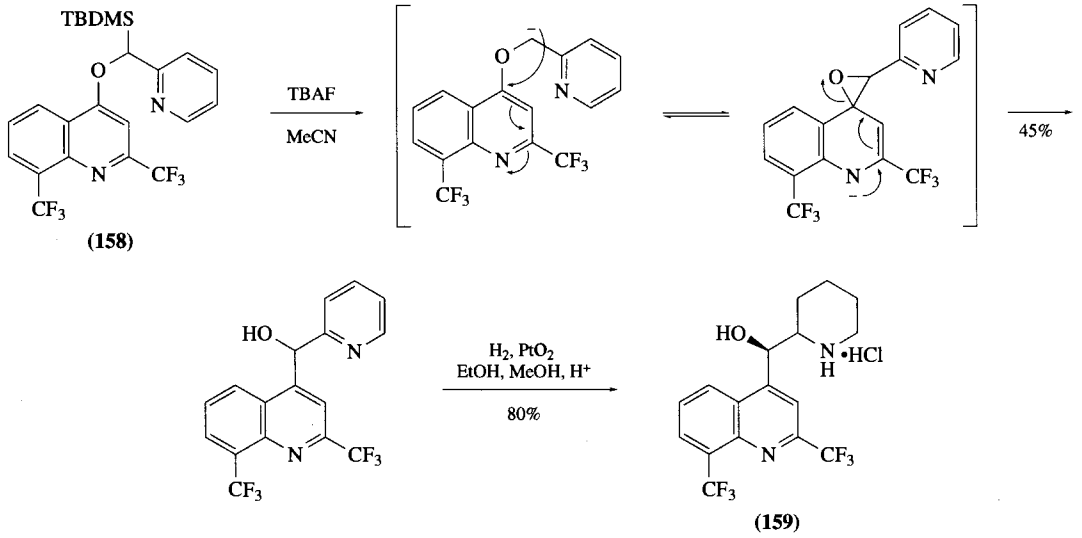
Quinoline allyl ethers on heating undergo the Claisen rearrangement to give mainly the *ortho* products ⟨66BSF586, 67JHC131⟩. For instance, on heating, the quinoline alkaloid (**153**) rearranges to the alkaloid buchapsine (**154**), although in this case the rearrangement is reversible (Equation (71)) ⟨85TL4253⟩. Likewise, 2-allyloxypyridine *N*-oxides (**155**) are converted into *N*-allyloxypyridine-2-pyridones (**156**) and 3-allyl-*N*-hydroxy-2-pyridones (**157**) (Equation (72)) ⟨90JCS(P1)1623, 90JCS(P1)1631⟩. A fluoride ion-catalyzed Wittig rearrangement of a pyridyloxyquinoline (**158**) provides a high-yielding synthesis of mefloquine (**159**), an antimalarial drug, as outlined in Scheme 41 ⟨89T1409⟩.



(153) (154) (71)

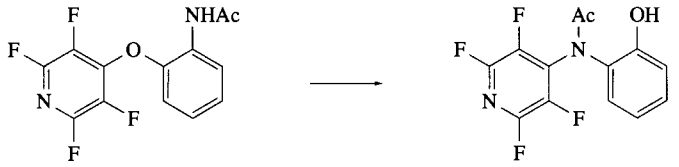


(155) R = H, OMe, NO_2 (156) (157) (72)



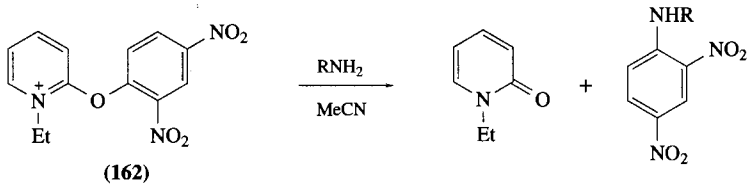
Scheme 41

The intramolecular Smiles rearrangement of the polyfluorinated 2-(acetylamino)diaryl ether (**160**) provides a convenient synthesis of the corresponding diarylamine (**161**) (Equation (73)) ⟨90IZV850⟩.



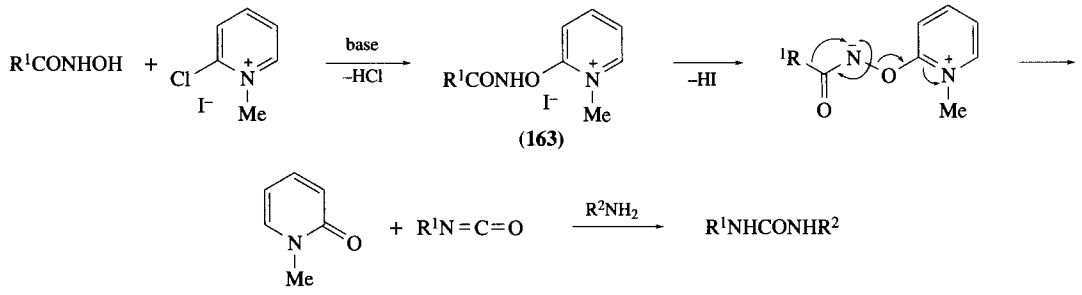
(73)

Nucleophilic attack by amines in acetonitrile on *N*-ethyl-2-(2,4-dinitrophenoxy)pyridinium cations (**162**) takes place predominantly at the benzene ring to produce 1-ethyl-1*H*-pyridin-2-one (Equation (74)) ⟨88ZOR2156, 88ZOR2161⟩.



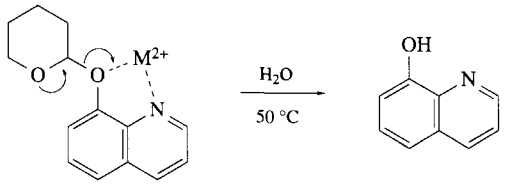
(74)

The pyridinyl ethers (**163**) derived from hydroxamic acids and 2-chloro-1-methylpyridinium iodide undergo the Lossen rearrangement to provide a convenient preparation of isocyanates and hence ureas (Scheme 42) ⟨89S61⟩.



Scheme 42

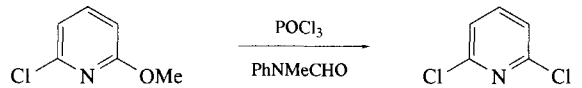
Acetals of 8-hydroxyquinoline are readily hydrolyzed in the presence of divalent ions even though metal–ion binding (e.g. (**164**)) to the acetals is weak (Equation (75)) ⟨87JCS(P2)143⟩.



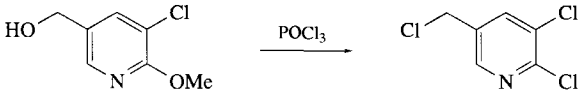
(75)

(**164**) $M^{2+} = Ni^{2+}, Co^{2+}, Zn^{2+}$

3-, 5-, and 6-Halopyridines are frequently synthesized from the corresponding 2-methoxypyridines under Vilsmeier–Haack conditions (Equation (76)) ⟨90SC2971⟩. Again, treatment of 3-chloro-5-hydroxymethyl-2-methoxypyridine (**165**) with phosgene or phosphorus oxychloride gives 2,3-dichloro-5-chloromethylpyridine (**166**) (Equation (77)) ⟨91GEP3924683⟩.



(76)



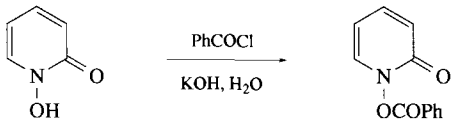
(77)

(**165**) (**166**)

5.03.4.6 Acylation of Hydroxypyridines, Pyridones, and their Benzo Analogues

Acylation reactions are complicated in that either or both *O*- and *N*-acylation may occur. Acetylation and benzoylation of 2-pyridone under normal conditions gives the *O*-acetyl and *O*-benzoyl products respectively. 3-Hydroxypyridine is acetylated and benzoylated to yield the *O*-substituted products, and carbostyril (2-quinolone) and 4-quinolone give the *O*-acetyl isomers on acetylation.

The potassium salt of 1-hydroxypyridin-2(1*H*)-one reacts with benzoyl chloride to produce 1-benzoyloxypyridin-2(1*H*)-one (**167**) (Equation (78)) ⟨64JCS4651⟩.



(78)

(**167**)

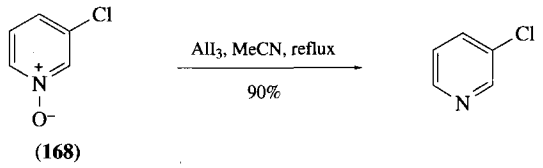
5.03.4.7 *N*-Oxides and their Derivatives

N-Oxides are readily reduced to the parent heterocycles using trivalent phosphorus compounds such as triphenylphosphine, phosphorus trihalides, and triethyl phosphite. Readily reduced substituents are not affected although nitro groups may be displaced by halogen.

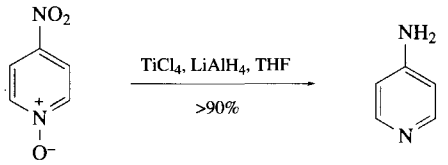
Traditional methods used to reduce heterocyclic *N*-oxides in the absence of other reducible substituents include catalytic hydrogenation, use of metals and acid, iron(II) oxalate ⟨61CJC2134⟩, sodium borohydride, and lithium aluminum hydride ⟨70CCC2802⟩.

The deoxygenation of 3-chloropyridine *N*-oxide (**168**) with aluminum triiodide in refluxing acetonitrile produced 3-chloropyridine in 80% yield (Equation (79)) ⟨90S337⟩. A titanium(0) slurry, prepared by reduction of titanium tetrachloride with lithium aluminum hydride or magnesium in diethyl ether, readily deoxygenates pyridine *N*-oxides (Equation (80)) ⟨87S1013, 88JPR154⟩. Titanium trichloride in water will also reduce pyridine *N*-oxide to pyridine in 96% yield ⟨89JOU596, 89JMC2474, 89SC897⟩. A mild method of reducing pyridine *N*-oxides involves the use of trifluoroacetic acid and

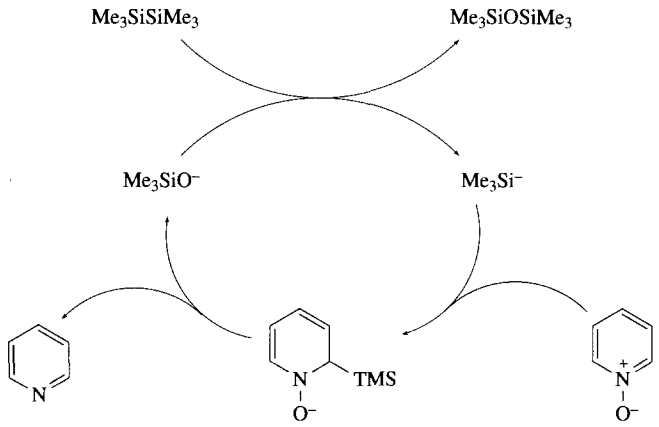
sodium iodide in acetonitrile ⟨90G67, 90G647⟩. Brief treatment (5 min) of picoline *N*-oxide with samarium iodide produces picoline in 83% yield ⟨87SC329⟩. Pyridine *N*-oxide is deoxygenated by hexamethyldisilane in the presence of trimethylsilyllithium via the mechanism outlined in Scheme 43 ⟨85JOC400⟩.



(168) (79)

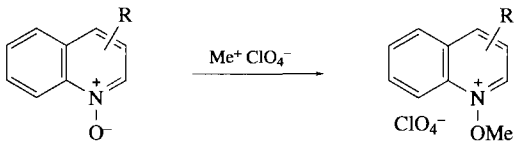


(80)



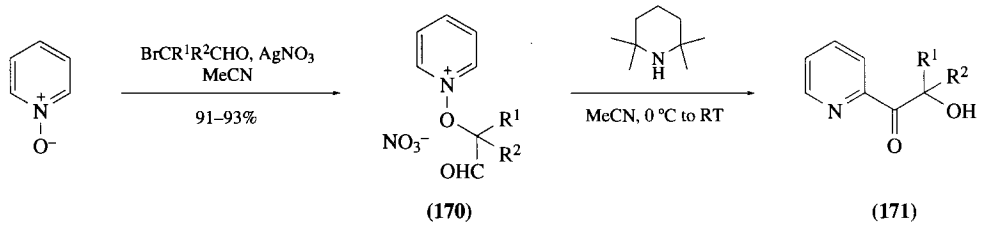
Scheme 43

N-Alkoxypyridinium salts and their benzo analogues are readily produced by reaction of the *N*-oxides with alkyl halides, dialkyl sulfates ⟨73OSC(5)269⟩, alkyl arenesulfonates, trialkyloxonium salts ⟨66CB1769⟩, and trialkyl phosphites and their thio analogues ⟨71JGU524⟩. Cardiotonic agents, *N*-methoxyquinolinium compounds (**169**) are prepared by alkylation of the corresponding *N*-oxides with methyl perchlorate (Equation 81) ⟨93AP(326)229⟩. *N*-Methoxyquinolinium salts undergo nucleophilic attack at position 2, followed by elimination of methanol ⟨88AP(321)897⟩. *N*-Alkoxypyridinium nitrates (**170**) are produced by reaction of pyridine *N*-oxide with bromoacetaldehydes. These nitrates undergo base-catalyzed rearrangement to form 2-hydroxyacylpyridines (**171**) (Scheme 44) ⟨91JHC1127⟩.



R = H, 2-Me, 3-Br, 3-CN (**169**) (81)

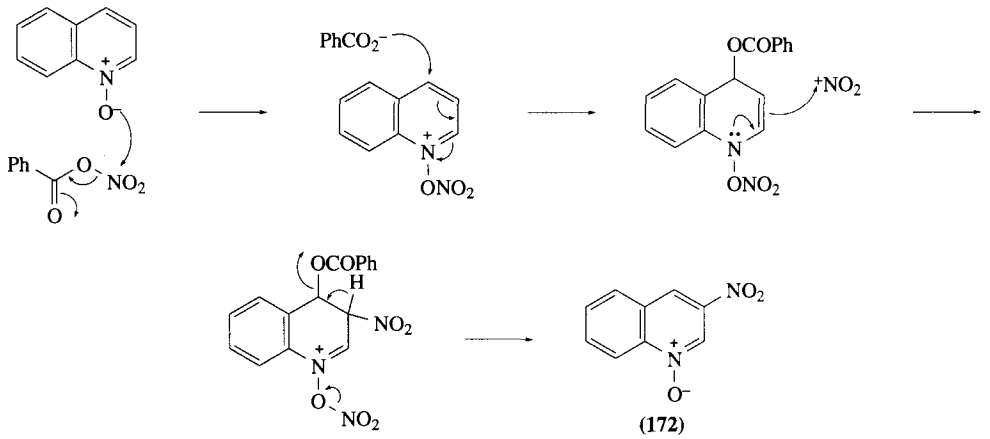
Quinoline *N*-oxide can be easily nitrated with benzoyl nitrate to give 3-nitroquinoline *N*-oxide (**172**) ⟨57CPB56⟩. The proposed mechanism is outlined in Scheme 45 and probably involves the initial reaction of benzoyl nitrate with the oxygen of the *N*-oxide. If the 3-position is blocked, nitration occurs only in the 6-position; for example, 3-bromoquinoline *N*-oxide yields 3-bromo-6-nitroquinoline *N*-oxide (**173**) (Equation (82)) ⟨59CPB195⟩.



(170) (171)

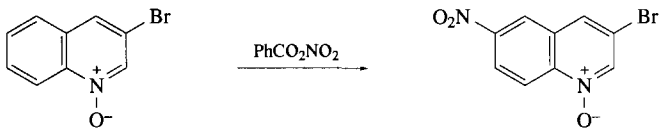
$R^1 = R^2 = Me, Ph$; $R^1 = Me$, $R^2 = Ph$

Scheme 44



(172)

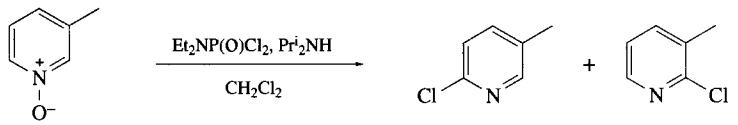
Scheme 45



(82)

(173)

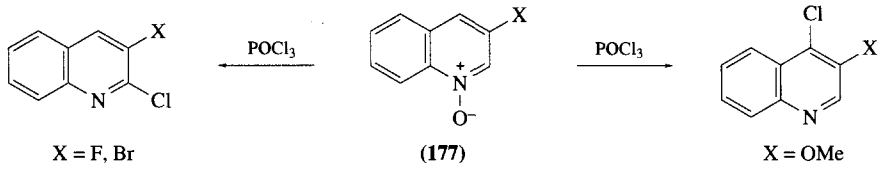
The chlorination of 3-methylpyridine *N*-oxide (**174**) with diethyl phosphoramidic dichloride and an acid acceptor such as diisopropylamine gives a mixture of 2-chloro-5-methylpyridine (**175**) (82%) and 2-chloro-3-methylpyridine (**176**) (12%) (Equation (83)) ⟨90GEP3839332⟩. Reaction of (**174**) with (dichloromethylene)dimethylimmonium chloride and triethylamine in methylene chloride also gives a mixture of (**175**) (73%) and (**176**) (18%) ⟨91GEP4020053⟩. These reactions proceed by initial bond formation between the nucleophilic oxygen of the *N*-oxide and the electrophile.



(83)

(174) (175) 82% (176) 12%

Treatment of 3-fluoro- and 3-bromo-quinoline *N*-oxide (**177**; X = F, Cl) with phosphorus oxychloride results in reductive chlorination, with the chlorine entering at position 2 (Scheme 46). However, similar treatment of 3-methoxyquinoline *N*-oxide (**166**; X = OMe) yields 4-chloro-3-methoxyquinoline (Scheme 46) ⟨91H(32)1579⟩.



X = F, Br (177) X = OMe

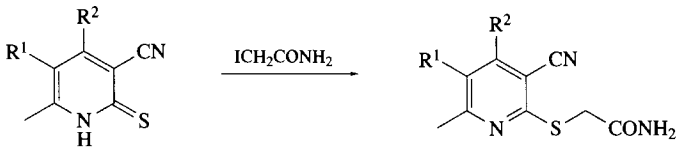
Scheme 46

5.03.4.8 S-*Linked Substitients*

5.03.4.8.1 Thiols, their tautomers, and related compounds

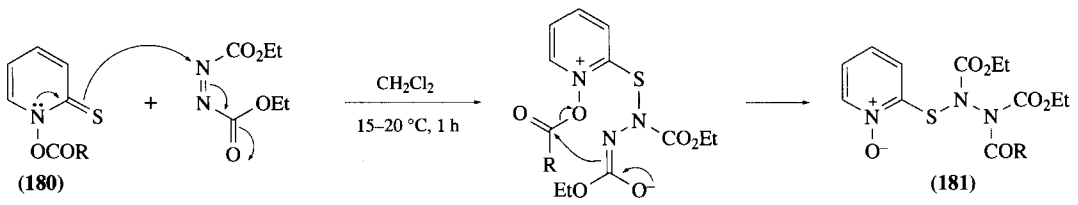
Thiol–thione tautomerism is similar to that exhibited by the oxygen analogues but the α- and γ-thiones are slightly more favored than the corresponding α- and γ-oxo compounds. Infrared spectroscopy has been used to study the tautomerism of pyridine-2(1*H*)-thione ⟨90JPC7406⟩.

Alkylation of pyridinethiols and pyridinethiones usually occurs predominantly or exclusively at the sulfur. The alkylation of the substituted pyridine-2(1*H*)-thiones (**178**) with iodoacetamide gives the (carbamoylmethyl)thioethers (**179**) (Equation (84)) ⟨91KGS1674⟩. The *N*-acyloxypyridine-2(1*H*)-thiones (**180**) react exclusively at the sulfur atom with dead to produce the *N*-oxides (**181**) (Scheme 47) ⟨88T7385⟩. The *S*-alkylation of *N*-substituted pyridine-2(1*H*)-thiones (**182**) provides a route to 2-alkylthio-substituted pyridinium salts (**183**) (Equation (85)) ⟨82S472, 83TL5805, 85TL469⟩.



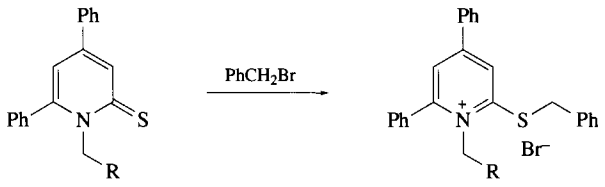
(84)

(178) R^1 = 4-C_5H_4N, R^2 = *m*-$O_2NC_6H_4$ (179)



R = $PhCH_2CH_2$, $CH{=}CH_2$, $CH_2CH{=}CH_2$, cyclohexyl, 1-adamantyl

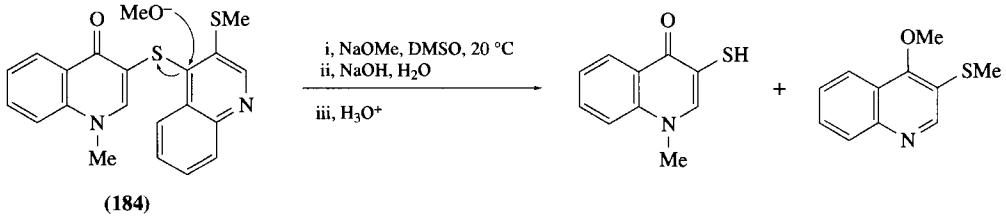
Scheme 47



(85)

(182) R = H, Ph, 4-MeC_6H_4 (183)

Displacement of thioether substituents in quinoline thioethers such as the 3,4′-diquinolinyl sulfide (**184**) can be achieved with methoxide (Equation (86)) ⟨90RTC509⟩.

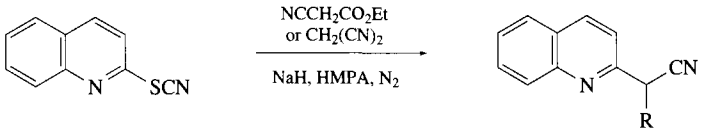


(86)

(184)

Less reactive *C*-nucleophiles such as ethyl cyanoacetate and ethyl malononitrile carbanions react with 2-quinolyl thiocyanate (**185**) to yield the corresponding *ipso*-substitution products (**186**) and (**187**) (Equation (87)) ⟨92CPB1090⟩.

A review of the chemistry of heteroaromatic sulfoxides and sulfones is available ⟨90AHC(48)1⟩.



(87)

(**185**)

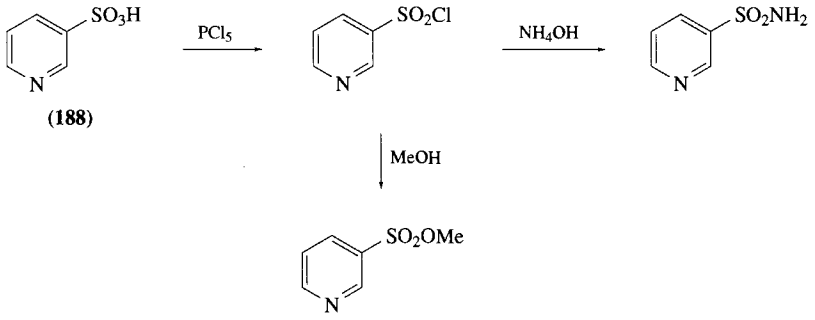
(**186**) R = CO_2Et, 52%
(**187**) R = CN, 71%

5.03.4.9 Sulfonic Acids and Related Compounds

The sulfonic acids are strong acids and tautomerize to the more weakly acidic zwitterions. The acids can be esterified with alcohols and hydrogen chloride, but pyridinesulfonic acids react with methyl iodide or dimethyl sulfate and alkali to produce *N*-methyl salts (zwitterions).

The α- and γ-sulfonates readily undergo nucleophilic displacement, by hydroxide on fusion with alkali, or by cyanide on fusion with potassium or sodium cyanide. However, these reactions do not take place with sulfonates at the β-position.

Pyridine-3-sulfonic acid (**188**) is converted into the sulfonyl chloride with phosphorus pentachloride, and the 2-isomer results from the reaction of the corresponding sodium sulfonate with benzotrichloride. As expected, the sulfonyl chlorides readily react with alcohols and amines, etc. (Scheme 48).



(**188**)

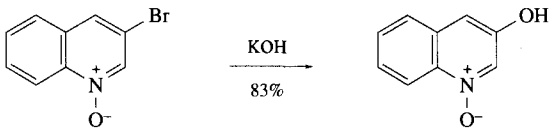
Scheme 48

5.03.5 HALOGEN SUBSTITUENTS

5.03.5.1 Nucleophilic Displacement

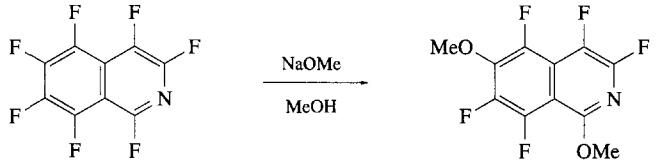
5.03.5.1.1 Oxygen and sulfur nucleophiles

Oxygen nucleophiles displace halogen from heterocycles extremely easily. Aqueous base or acid can easily hydrolyze 2- and 4-halopyridines. 2-Halogenoquinolines usually show greater reactivity than the 4-isomers. Hydrolysis of 3-bromoquinoline *N*-oxide (**189**) with potassium hydroxide produces 3-hydroxyquinoline *N*-oxide in 83% yield (Equation (88)) ⟨84IZV1660⟩. Sodium methoxide in methanol displaces fluorine from positions 1 and 6 of heptafluoroisoquinoline (**190**) to yield 1,6-dimethoxy-3,4,5,7,8-pentafluoroisoquinoline (**191**) (Equation (89)) ⟨66JCS(C)2328⟩.



(88)

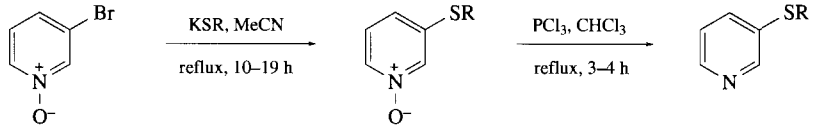
(**189**)



(89)

(190) (191)

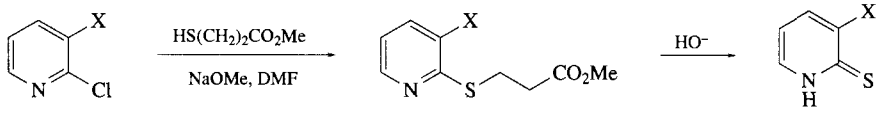
Halopyridines with electron-withdrawing groups undergo nucleophilic displacement with sulfur nucleophiles ⟨87JHC85⟩. 3-Substituted thiopyridines are not readily available by nucleophilic substitution of 3-halopyridines. However, 3-bromopyridine 1-oxide (**192**) reacts with potassium thiolates under anhydrous conditions to give good yields of the 1-oxides of 3-substituted thiopyridines (**193**) which can be reduced to the desired pyridine thioethers (Scheme 49) ⟨87JCR(S)378⟩. Also, halogenated pyridines (**194**) can be converted into pyridinethiones and -thiols using methyl 3-thiolpropionate (Scheme 50) ⟨92JPC119⟩.



(**192**) (**193**)

R = Me, Et, Ph, 4-MeC_6H_4

Scheme 49

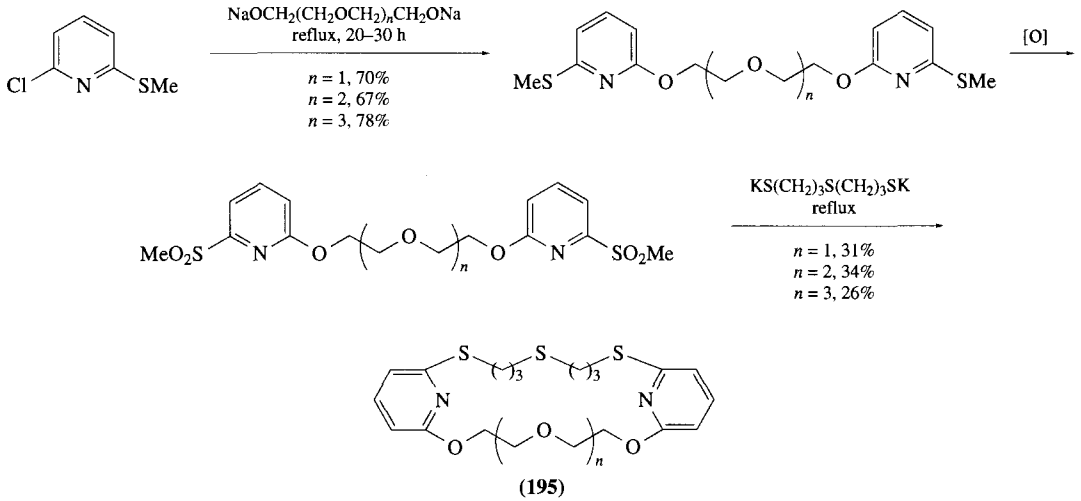


(**194**)

X = Cl, NO_2, COMe, CO_2Me

Scheme 50

ipso-Substitution of sulfinyl and sulfonyl groups at positions 2 and 6 of pyridine by alkoxide and thioalkoxide anions follows the order $RSO_2 > RSO > Br = Cl \gg RS$ and this trend has been used in the preparation of 2,6-disubstituted pyridine macrocycles (**195**) (Scheme 51) ⟨84JCS(P1)1839⟩.

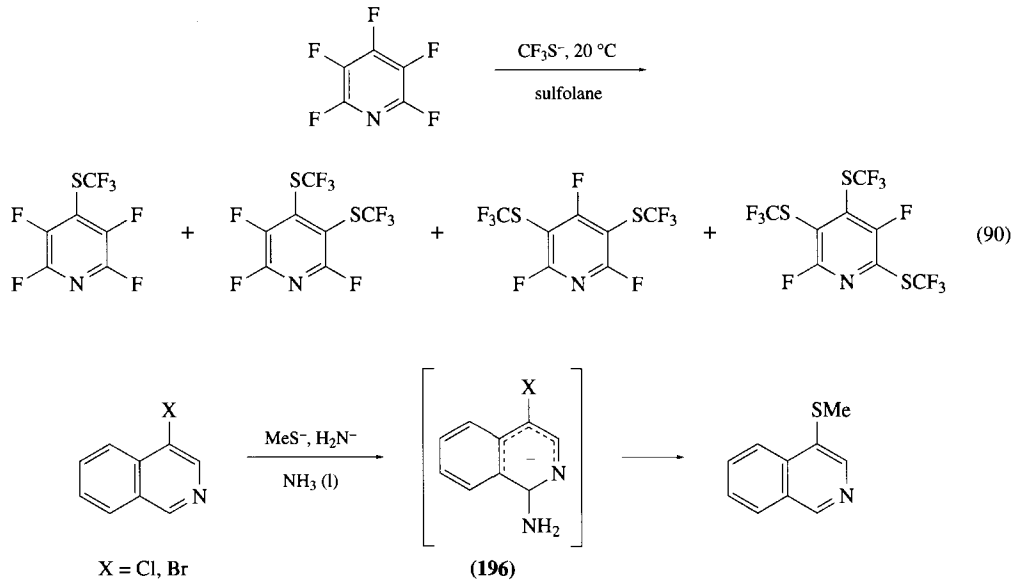


(**195**)

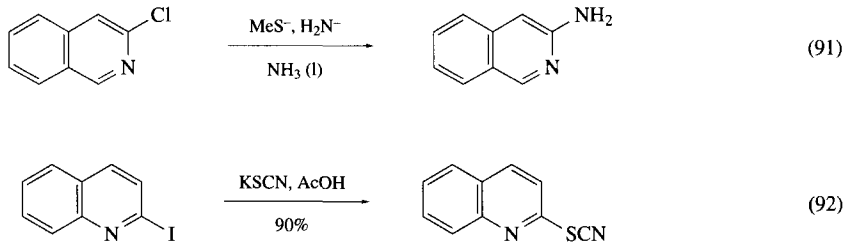
Scheme 51

Nucleophilic substitution of pentafluoropyridine by trifluoromethanethiolate ion has been shown to yield mono-, di-, and trisubstituted products (Equation (90)) ⟨87JCS(P1)2119⟩. 4-Bromo- and

4-chloroisoquinoline in refluxing ammonia containing amide and thiomethoxide ions react preferentially with thiolate to give 4-(methylthio)isoquinoline. The initial step involves Meisenheimer adduct (**196**) formation by amide attack at position 1. An $S_{RN}1$ mechanism is thought to be involved (Scheme 52) ⟨91JOC2805⟩. In contrast, 3-chloroisoquinoline gives 3-aminoisoquinoline under identical conditions (Equation (91)) ⟨91JOC2805⟩. Treatment of 2-iodoquinoline with potassium thiocyanate yields 2-quinolyl thiocyanate in 90% yield (Equation (92)) ⟨89CPB618⟩.

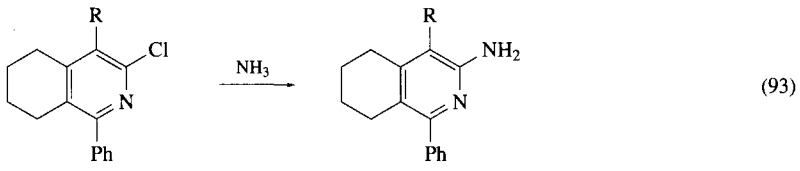


Scheme 52



5.03.5.1.2 Nitrogen nucleophiles

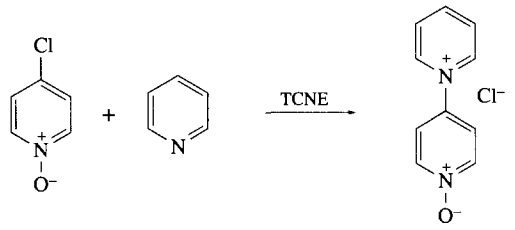
Activated halogens, such as those situated α or γ to the ring nitrogen, or *ortho* or *para* to an electron-withdrawing group, can be displaced by ammonia and amines ⟨90AHC(49)117⟩. Thus, ammonia displaces chlorine from 3-chloro-5,6,7,8-tetrahydroisoquinoline (**197**) to yield the corresponding amine (Equation (93)) ⟨90MI 503-01⟩. Nucleophilic substitution proceeds more easily with pyridinium salts and *N*-oxides ⟨60JCS4953⟩.



(**197**) R = Me, Et, CH_2Ph

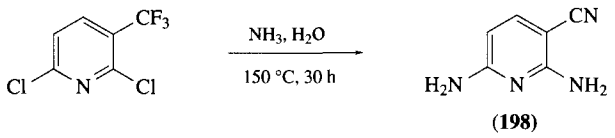
Pyridine and quinoline nucleophiles displace chlorine from 4-chloropyridine *N*-oxide and 4-chloroquinoline *N*-oxide, giving quaternary salts (Equation (94)). The reaction is facilitated by

tetracyanoethylene ⟨91ZOR955⟩. The effect of alkyl substituents on the rate constant of the displacement of halogen from 4-chloro-1-ethylpyridinium ions by substituted pyridines has been reported ⟨92JCR(S)53⟩.



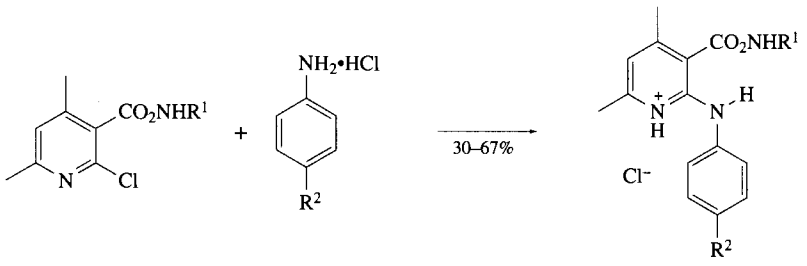
(94)

Complete halogen displacement from 2,6-dichloro-3-trifluoromethylpyridine with aqueous ammonia at 150°C forms 2,6-diamino-3-cyanopyridine (**198**) (Equation (95)) ⟨85BRP2144740⟩. 2-Chloronicotinamides (**199**) react with aniline hydrochlorides to give the expected 2-arylaminonicotinamide hydrochlorides (**200**) which possess anticonvulsant activity (Equation (96)) ⟨93KFZ34⟩. A variation of this reaction has been used in the synthesis of the potent analgesic, Flunixin (**201**), by the reaction of ethyl 2-chloronicotinate with 2-methyl-3-trifluoromethylaniline in ethylene glycol at 160°C (Equation (97)) ⟨94H(38)2243⟩.



(**198**)

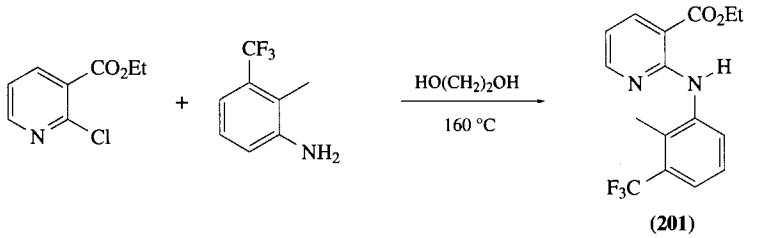
(95)



(**199**)
R^1 = H, OMe

(**200**)
R^1 = alkyl, CH_2Ph
R^2 = H, OMe

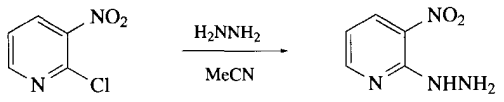
(96)



(**201**)

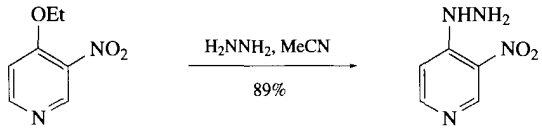
(97)

Treatment of 2-chloro-3-nitropyridine with hydrazine in acetonitrile gives 2-hydrazino-3-nitropyridine (**202**) (Equation 98) ⟨52JA3828, 85EUP159112⟩ and 3-nitro-4-ethoxypyridine gives 3-nitro-4-hydrazinopyridine (**203**) similarly in 89% yield (Equation (99)) ⟨85EUP159112⟩. Ethyl carbazate, acethydrazide, benzhydrazide, or tosylhydrazide can be used in place of hydrazine ⟨85EUP159112⟩. 2- and 4-Chloroquinolines react readily with boiling hydrazine to give the appropriate hydrazinoquinolines ⟨66JCS(C)1980⟩.



(98)

(202)

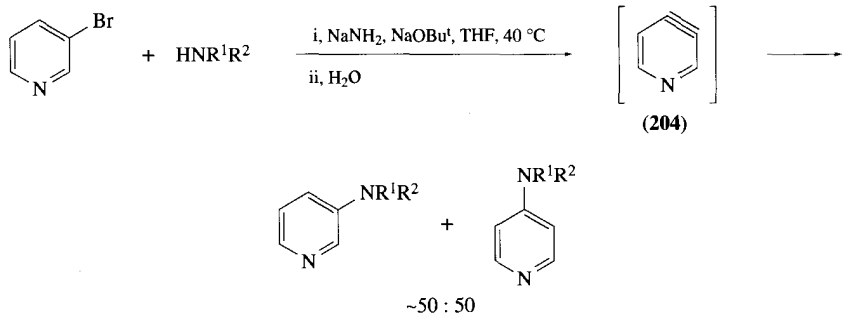


(99)

(203)

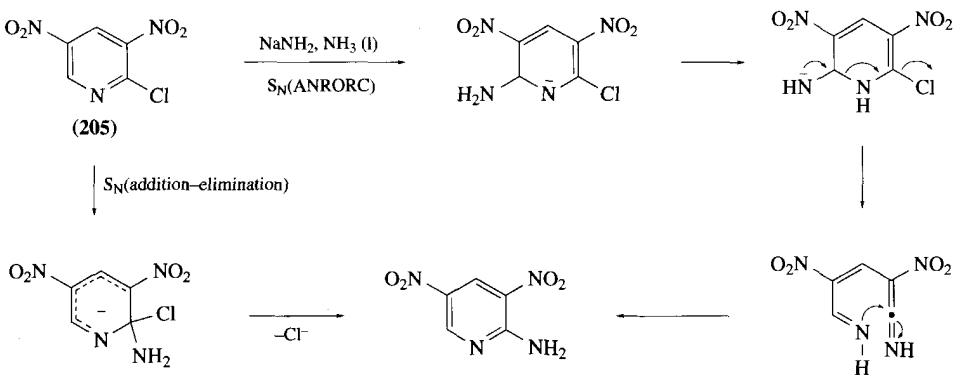
In many of the reactions of haloazines, the halogen can be displaced by an amide ion either by an addition–elimination or elimination–addition mechanism.

β-Halopyridines usually react by a pyridyne (elimination–addition) mechanism. Thus 3,4-dehydropyridine (**204**) can be generated and used for nucleophilic condensations of amines, ketones, and nitrile enolates (Scheme 53) ⟨90TL7599⟩. Reviews of heteroaryne chemistry are available ⟨B-67MI 503-01, 71AG(E)20, 82T427⟩.



Scheme 53

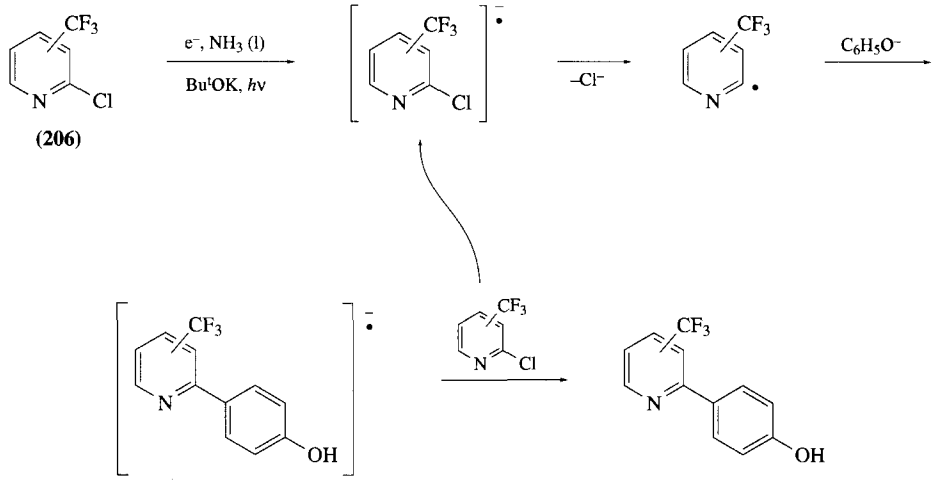
A nucleophilic displacement of halogen which involves the initial addition of a nucleophile to a ring carbon atom not carrying the halogen followed by electrocyclic ring opening is called the ANRORC (Addition of Nucleophile, Ring Opening, Ring Closure) process. Thus, the reaction of 2-chloro-3,5-dinitropyridine (**205**) with amide ion proceeds partially (7%) via an S_N (ANRORC) mechanism but mainly (93%) via the classical S_N (addition–elimination) mechanism (Scheme 54) ⟨86JOC3209⟩.



Scheme 54

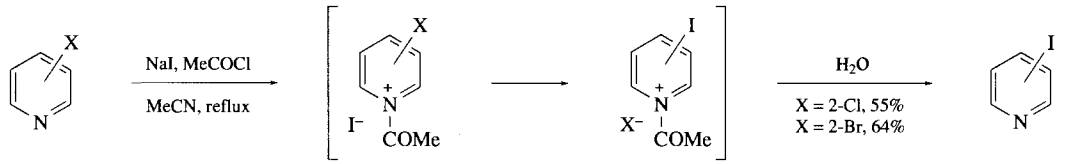
5.03.5.1.3 Other nucleophiles

Heteroaromatic halides can undergo nucleophilic substitution via electron transfer in the initial step ($S_{RN}1$ mechanism). The $S_{RN}1$ reactions are radical chain processes and are often photochemically initiated. For example, 2-chloro(trifluoromethyl)pyridines (**206**) in the presence of naphtholate and phenolate yield 2-heterobiaryl derivatives by the $S_{RN}1$ pathway (Scheme 55) ⟨91SL923, 93T7883⟩.



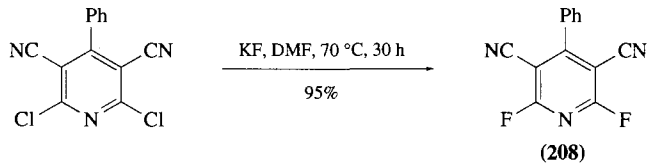
Scheme 55

Halogen exchange reactions occur readily at the α- and γ-positions, especially if the ring nitrogen carries a positive charge. Bromo- and chloropyridines are converted into the corresponding iodo derivatives by treatment with sodium iodide and acetyl chloride in acetonitrile, and the *N*-acetyl derivative (**207**) is proposed as an intermediate (Scheme 56) ⟨90TL6757⟩. Treatment of 2,6-dichloro-3,5-dicyano-4-phenylpyridine with potassium fluoride in dimethylformamide yields 2,6-difluoro-3,5-dicyano-4-phenylpyridine (**208**) (Equation 100) ⟨87GEP3528459⟩.



(207)
X = 2-Br, Cl or 4-Br, Cl

Scheme 56

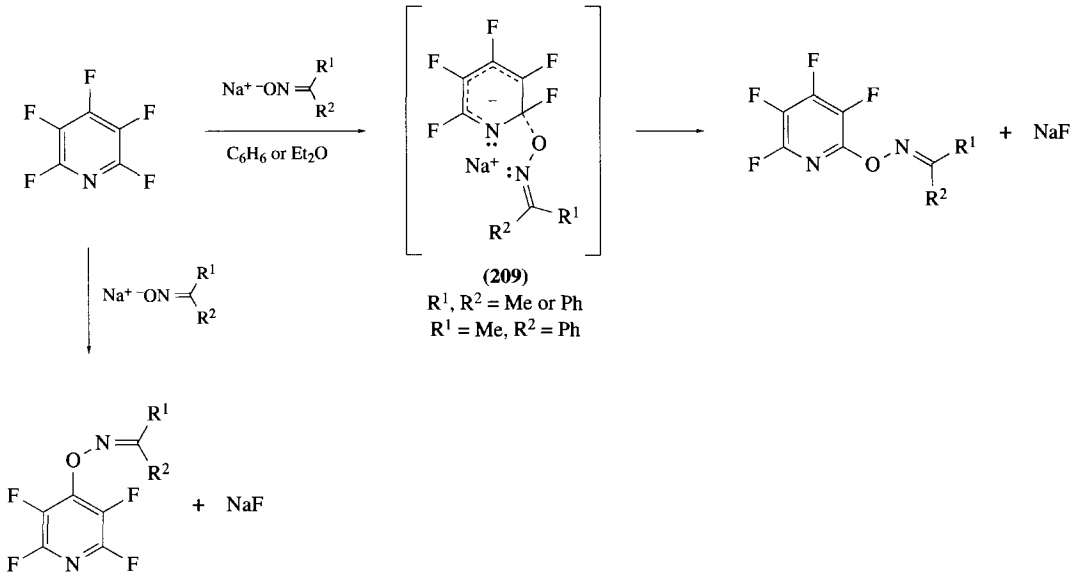


(100)

(208)

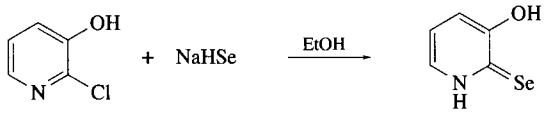
Nucleophilic substitution of pentafluoropyridine normally occurs at the 4-position, but when a sodium oximate is used a mixture of 2- and 4-substituted products is obtained. The transition state (**209**) for substitution at the 2-position is stabilized by association with the sodium ion (Scheme 57) ⟨89CC1268⟩.

Silvester has reviewed the nucleophilic and electrophilic substitution of fluoro-heterocycles ⟨94AHC(59)1⟩.



Scheme 57

2-Chloro-3-hydroxypyridine reacts with sodium hydrogen selenide to produce the corresponding selone (**210**) (Equation (101)) ⟨86JCS(P1)2075⟩.



(101)

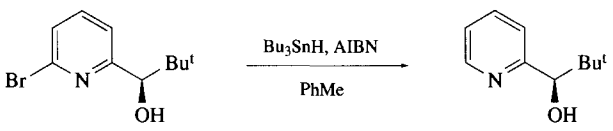
(**210**)

5.03.5.2 Reductive Dehalogenation

Halogens in the α- and γ-position of pyridine and quinoline and their derivatives are readily replaced by hydrogen in catalytic hydrogenations. Reductive removal of halogen can be achieved by palladium-catalyzed hydrogenolysis in acetic acid and alkaline acetate ⟨44RTC141, 46JA1322⟩. Halogens in α- and γ-positions to nitrogen are more reactive than those in the β-positions towards reductive dehalogenation. For instance, in the presence of lithium aluminum hydride the fluorine in the γ-position of β-chlorotetrafluoropyridine (**211**) is replaced by hydrogen in preference to the chlorine in the β-position (Equation (102)) ⟨64CI(L)835, 65JCS594⟩. Radical debromination of α-bromopyridines can be effected by tributyltin hydride–AIBN in toluene (Equation (103)) ⟨92CB1169⟩.

(102)

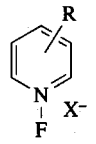
(**211**)



(103)

5.03.5.3 Halogens Attached to Nitrogen

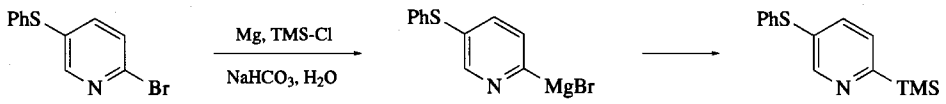
Pyridine–fluorine complexes (**212**) are unstable and can be used as fluorinating agents. Electron-withdrawing substituents increase their effectiveness but decrease the stability ⟨90JA8563, 91BCJ1081, 93JHC1361, 95AHC(62)1⟩.



(212)

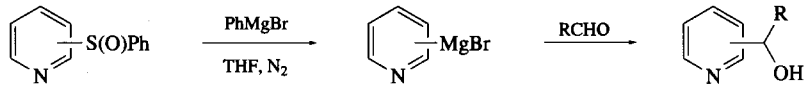
5.03.6 METALS

Under normal conditions, halopyridines do not readily form Grignard reagents. However, 2-bromo-5-phenylthiopyridine with magnesium does form the Grignard reagent (**213**) which can be silylated in the presence of trimethylsilyl chloride (Scheme 58) ⟨92CB1131⟩. Pyridyl and quinolyl sulfoxides have been reacted with Grignard reagents to form the corresponding 3- or 4-pyridyl or 3- or 4-quinolyl Grignard reagents (ligand-exchange procedure), which can be trapped with aldehydes (Scheme 59) ⟨86TL3899⟩. The 2-pyridyl Grignard reagent is not formed by this procedure; only 2,2′-bipyridyl is isolated.



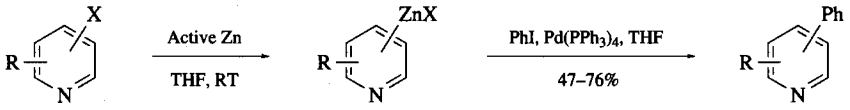
(213)

Scheme 58



Scheme 59

Halopyridines can be converted into pyridylzinc reagents (**214**) using activated zinc in tetrahydrofuran. Their treatment with iodobenzene and palladium yields phenylpyridines (Scheme 60) ⟨92JHC1245, 92TL4495, 92TL5373⟩.

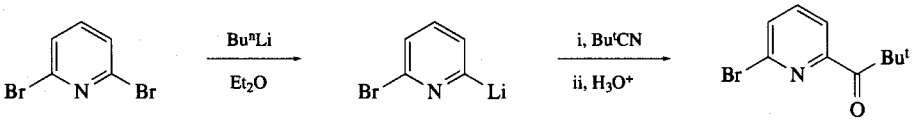


(214)

X = 2-Br, 3-I, 4-I; R = H, 2,6-Me_2

Scheme 60

Pyridyllithium reagents are not formed by interaction of halogenopyridines with lithium metals but by halogen–metal exchange with an alkyllithium, usually *n*-butyllithium. Thus, selective lithiation of 2,6-dibromopyridine with *n*-butyllithium in diethyl ether yields the 2-lithio derivative (**215**) (Scheme 61) ⟨92CB1169⟩.

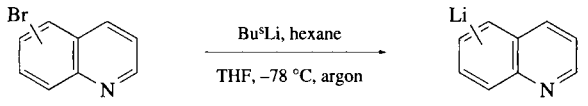


(215) (216)

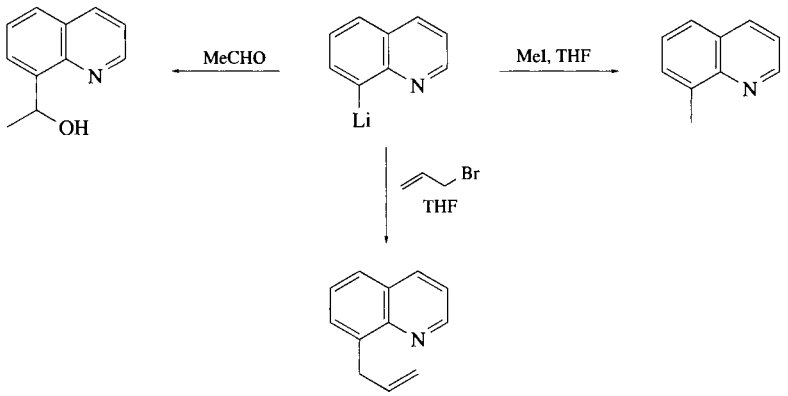
Scheme 61

Pyridyllithium compounds react with a wide range of compounds, including esters, aldehydes, ketones, nitriles, and amides. Thus, 6-bromo-2-pyridyllithium (**215**) reacts with pivalonitrile or methyl pivalate to produce the *t*-butyl pyridyl ketone (**216**) (Scheme 61) ⟨92CB1169⟩.

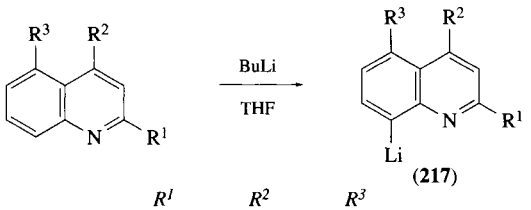
The direct metalation of the benzo ring of quinoline is not facile. Halogen–metal exchange in the carbocyclic rings of quinolines has been successfully achieved and all four possible types of lithio derivatives have been prepared from the analogous bromides (Equation (104)) ⟨69JHC243, 80JOC1514, 87JOM(336)1, 89JMC1936⟩. These quinolyllithium compounds react with alkyl halides, allyl halides, and aldehydes (e.g. Scheme 62) ⟨80JOC1514⟩. The direct lithiation of 2-phenyl-, 4-pivalamido-, and 2-butyl-5-ethoxyquinoline is reported to give the 8-lithio derivatives (**217**) presumably as the result of nitrogen complexation (Equation (105)) ⟨88JOM(354)273, 91AHC(52)187⟩. The lithiation of all carbocyclic positions in quinolines can be achieved by directed metalation ⟨91AHC(52)187⟩.



(104)



Scheme 62

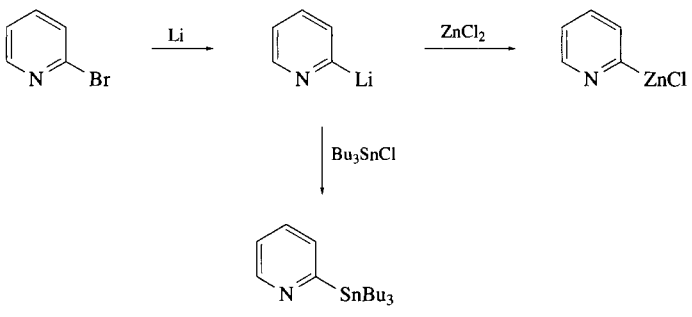


(**217**)

(105)

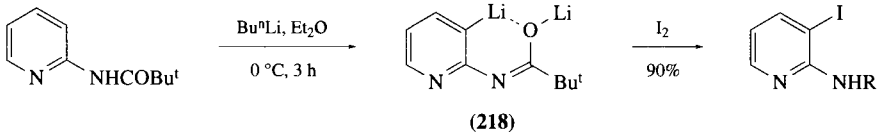
R^1	R^2	R^3
Ph	H	H
H	Bu^{t}CONLi	H
Bu	H	OEt

Pyridyllithiums and their benzo analogues can be used to introduce other metals and nonmetals, such as mercury, boron, phosphorus, tin, and arsenic. Thus, 2-bromopyridine undergoes lithium–halogen exchange followed by transmetallation with zinc chloride or tributyltin chloride (Scheme 63) ⟨68JOM(11)499, 82H(18)117, 88OS(66)67, 88S485, 90JHC2165⟩.



Scheme 63

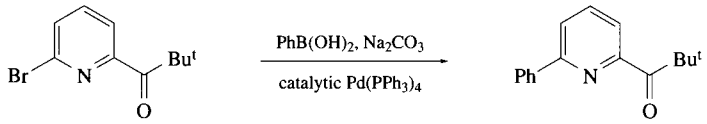
The protected 2-aminopyridine, when lithiated at position 3 (**218**) and then quenched with iodine, provides the 3-iodo derivative in 90% yield (Scheme 64) ⟨86S670⟩.



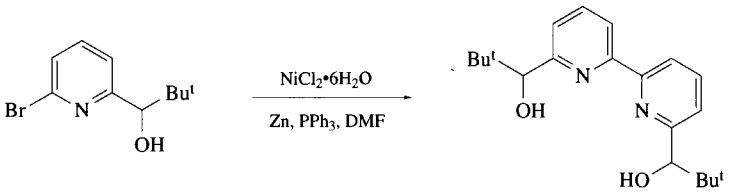
(**218**)

Scheme 64

The phenylation of substituted pyridines can be achieved by tetrakis(triphenylphosphine)-palladium(0)-catalyzed coupling of bromopyridines with phenylboronic acid via a pyridylpalladium species (Equation (106)) ⟨81SC513, 84JOC5237, 88TL2135⟩. Related nickel-mediated homocoupling of substituted bromopyridines affords 2,2′-bipyridines (**219**) (Equation (107)) ⟨92CB1169⟩.



(106)

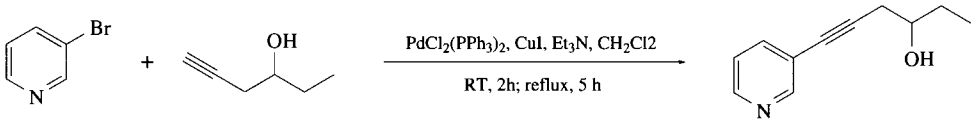


(107)

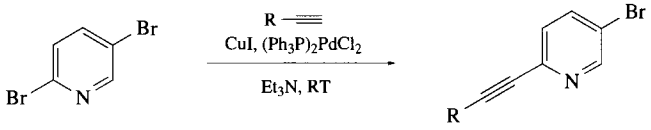
(**219**)

An extensive review outlining the use of the organometallics of lead, tin, boron, aluminum, zinc, magnesium, copper, mercury, and nickel in coupling reactions of π-deficient azaheterocycles including pyridine, quinoline, and isoquinoline is available ⟨95AHC(62)305⟩.

Alkynylation of 3-bromopyridine can be achieved by palladium catalysis in the presence of copper(I) iodide (Equation (108)) ⟨89JMC1820⟩. However, 2,5-dibromopyridine undergoes regio-selective coupling with terminal alkynes to give the corresponding 2-alkynyl-5-bromopyridines (**220**) (Equation (109)) ⟨88JOC386⟩.



(108)

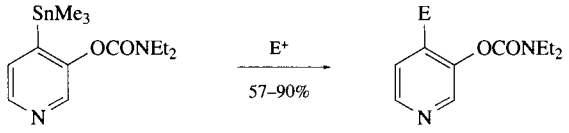


(109)

(**220**)

R = TMS, Bu, $HOCH_2$, $MeO_2C(CH_2)_3$, Ph

Trimethylstannylpyridines (**221**) and quinolines (**222**) show synthetic potential for the introduction of acyl groups into the nucleus by *ipso*-destannylation with acid chlorides (Equations (110) and (111)) ⟨82H(19)41, 85JOC5436⟩.



(110)

(**221**) E = Ac, I

(222)

(111)

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5.04
Pyridines and their Benzo Derivatives: Reactivity of Reduced Compounds

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Technical University of Helsinki, Espoo, Finland

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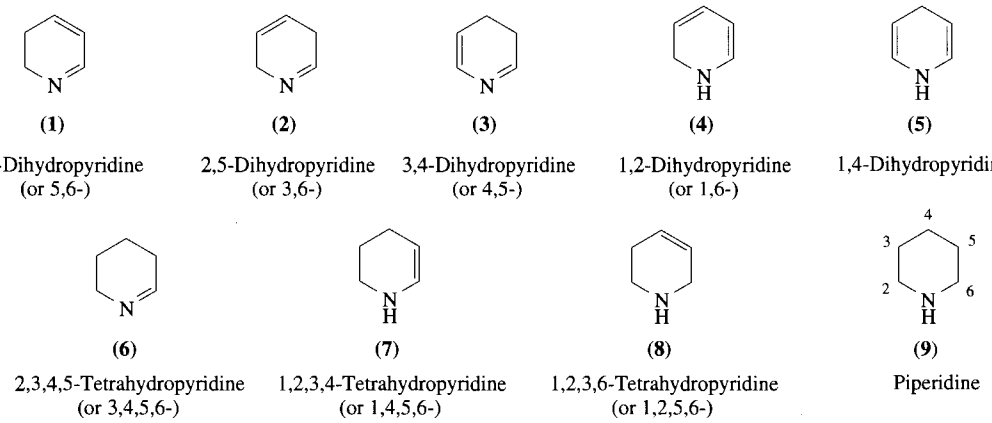
5.04.1 INTRODUCTION

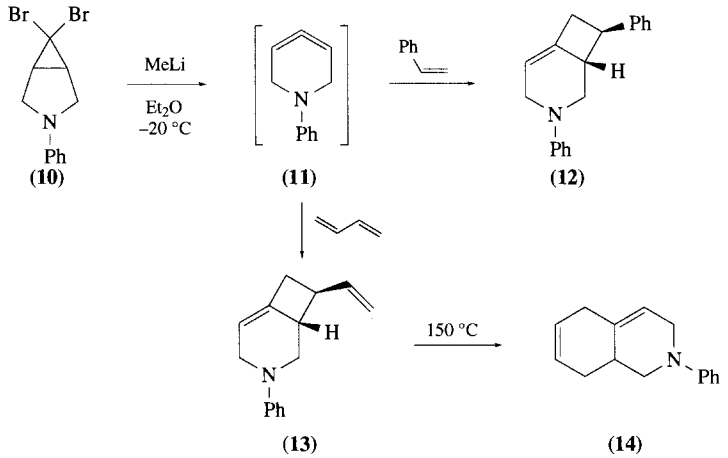
Reduced pyridines have become increasingly important both as pharmacologically active compounds and as useful intermediates in organic synthesis. The number of new methods for their preparation and for their manipulation as a means of reaching more complicated heterocyclic systems, particularly natural products, continues to grow. Likewise, new aspects of their reactivity have been recognized.

The nomenclature, and especially the numbering of reduced pyridines, are somewhat of a problem. The old Δ^n-piperideine naming system is still occasionally used. For the numbering, two systems exist: either the remaining double bond(s) or the reduced carbon atoms have the priority. The latter system, which is more widely employed, is adopted in this work. To refresh the reader the structures and names of the eight partially reduced pyridines (five dihydropyridines and three tetra-

hydropyridines), in addition to the fully reduced pyridine (hexahydropyridine or piperidine), are reproduced (Structures (**1**)–(**9**)).



Compounds (**1**)–(**9**) represent the classical reduced pyridines, the properties of which are still being studied. An illustration of some new progress in the field is a report describing a rather unusual structure, 1-phenyl-1-aza-3,4-cyclohexadiene (**11**), the first isodihydropyridine ⟨94CB1137⟩. This cyclic allene, generated from the bicyclic pyrrolidine (**10**), reacted with styrene to form the [2 + 2] cycloadduct (**12**) (Scheme 1). Reaction with 1,3-butadiene gave the bicyclic compound (**13**), which on heating rearranged to the partly reduced isoquinoline (**14**).



Scheme 1

The treatment of reduced pyridines in this chapter is divided according to their distinct structural types, in order better to indicate their individual behavior under different reaction conditions. The properties of reduced quinolines and isoquinolines are discussed in conjunction with the corresponding reduced pyridines, according to their similar reactivity with reduced pyridines, not the formal structural resemblance.

5.04.1.1 Theoretical Methods

A number of theoretical studies on the reactivity of reduced pyridines, especially those of biological significance, have been carried out in the early 1990s. The oxidative stability of 3-substituted *N*-methyl-1,4-dihydropyridines has been investigated with semiempirical molecular orbital methods (AM1) ⟨91RRC647⟩. Soft–hard acid–base theory was found inappropriate for the examination. A review dealing with the applications of semiempirical and *ab initio* methods to the study of dihydropyridine oxidation mechanisms has been published ⟨94H(37)1373⟩.

The AM1 molecular orbital method has also been used to investigate the dithionite reduction of pyridinium salts ⟨93JST(283)27⟩. As is well known, this reaction yields mainly 1,4-dihydropyridines,

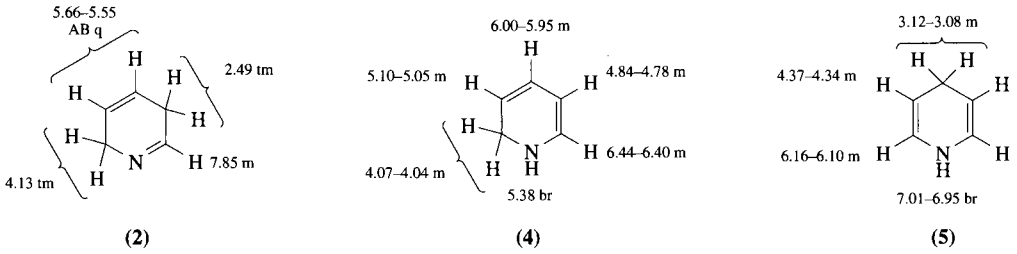
which are thermodynamically more stable than the 1,2- or 1,6-isomers. The calculated heats of formation suggest that the formation of the 1,4-isomers may be thermodynamically controlled.

The stability order of dihydropyridines has been a subject of debate, and not much new has been reported that would settle the question. An *ab initio* MO-SCF study supports the earlier theoretical conclusions ⟨82CCC2735⟩.

The relationship between the degree of flatness and the antagonist activity of some biologically important 1,4-dihydropyridines has been of interest. An *ab initio* quantum mechanical conformational analysis of 1,4-dihydropyridine (**5**) itself provided evidence for a very flat boat conformation, which could easily defold to a planar ring ⟨88MI 504-01⟩. X-ray studies mostly support the planar structure. In the solid state, crystal forces may have the major influence on the conformation. The effects of substituents, especially the common 4-phenyl group, also have to be taken into account.

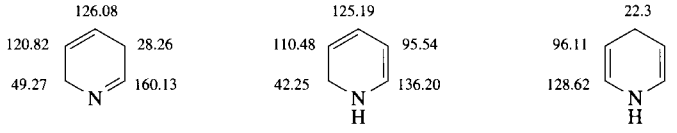
5.04.1.2 Experimental Structural Methods and Thermodynamic Aspects

An excellent account of developments since the mid-1980s in the NMR spectroscopy of piperidines and other reduced pyridines can be found in a book that deals with piperidine ⟨B-91MI 504-01⟩. Examples of two-dimensional NMR are included. A mixture of 2,5- (**2**), 1,2- (**4**), and 1,4-dihydropyridine (**5**) was formed when the reaction product of $LiAlH_4$ and pyridine was hydrolyzed. These three isomers proved to be stable in the absence of oxygen, and their ^1H and ^{13}C NMR data could be assigned from the spectra of the mixture ⟨93JOC1840⟩. The data are depicted in Figures 1 and 2.



(**2**) (**4**) (**5**)

Figure 1 ^1H NMR data of dihydropyridines (**2**), (**4**), and (**5**) (C_5D_5N).

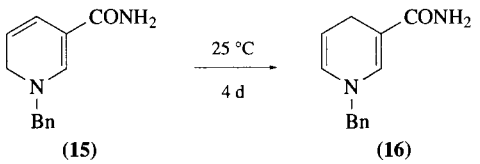


(**2**) (**4**) (**5**)

Figure 2 ^{13}C NMR data of dihydropyridines (**2**), (**4**), and (**5**) (C_5D_5N).

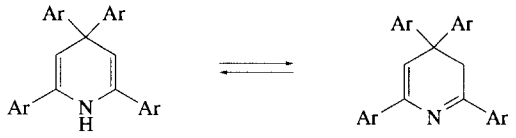
^{13}C NMR spectroscopy has been applied for stereochemical study of two special subgroups of the reduced pyridines, 2-cyanopiperidines, and 2-cyanotetrahydropyridines (α-aminonitriles) ⟨85H(23)1707⟩.

1,2-Dihydropyridines tend to isomerize to the corresponding 1,4-isomers and this generally slow process is usually faster in the solid state than in solution ⟨83G569⟩. At 25°C, in the absence of oxygen, the 1,2-dihydropyridine (**15**) is transformed into the reduced nicotinamide derivative (**16**) in about 4 days (Equation (1)). In $CDCl_3$ the isomerization, which can be regarded as a [1,3] sigmatropic shift, takes the same time to complete, whereas in CD_3OD there is no change after 30 days. The conversion is notably slower at −20°C.



(**15**) (**16**) (1)

Proton tautomerism in dihydropyridines has been little studied. Contrary to the observation ⟨84CHEC-I(2)365⟩ that the unsubstituted 1,4-dihydropyridine (**5**) does not tautomerize to 3,4-dihydropyridine (**3**), the long-known tetraaryl-substituted 1,4-dihydropyridine (**17**) has been found, under certain conditions, to be in dynamic equilibrium with its 3,4-dihydro tautomer (**18**) (Equation (2)) ⟨89CCC1854⟩. This result was obtained after a detailed NMR investigation in various solvents and at several temperatures.



(17) (18) (2)

5.04.2 REACTIVITY OF DIHYDROPYRIDINES

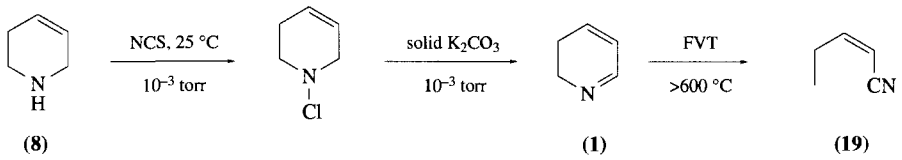
Classically, the chemistry of dihydropyridines has been focused on the most stable 1,2- and 1,4-isomers, which are the only isomers where the nitrogen lone pair is capable of interacting with the π-system of the ring double bonds. The other three types of dihydropyridines have not been studied so much but now the chemistry of their iminium ions and equivalents has opened new vistas. Perhaps the best-known property of dihydropyridines is their easy oxidation to pyridines; their use as reducing agents, especially as models of the biologically important NADH system, is continually investigated.

The latest general review covering the chemistry of dihydropyridines appeared in 1982 ⟨82CRV223⟩. The basic features of the chemistry can be found in the old but still frequently referred to review that was published in 1972 ⟨72CRV1⟩.

One of the most outstanding advances in the chemistry of reduced pyridines, and especially of the various iminium ions, has been with the Polonovski reaction, and especially its modification, the Polonovski–Potier reaction ⟨90OR85⟩. This has found numerous applications, particularly in the synthesis of alkaloids ⟨82BSB985, 84H(22)1591⟩. Some of the latest achievements are described below.

5.04.2.1 2,3-Dihydropyridines and the Corresponding Iminium Salts (Including α-Aminonitriles)

2,3-Dihydropyridine (**1**) has been prepared and characterized by NMR and infrared below −80 °C ⟨84TL3847, 88T4447⟩. At higher temperatures it polymerizes, and flash vacuum thermolysis (FVT) at ca. 600 °C gives mainly the (*Z*)-isomer of 2-pentenenitrile (**19**), which evidently confirms the intermediacy of 2,3-dihydropyridine (Scheme 2).

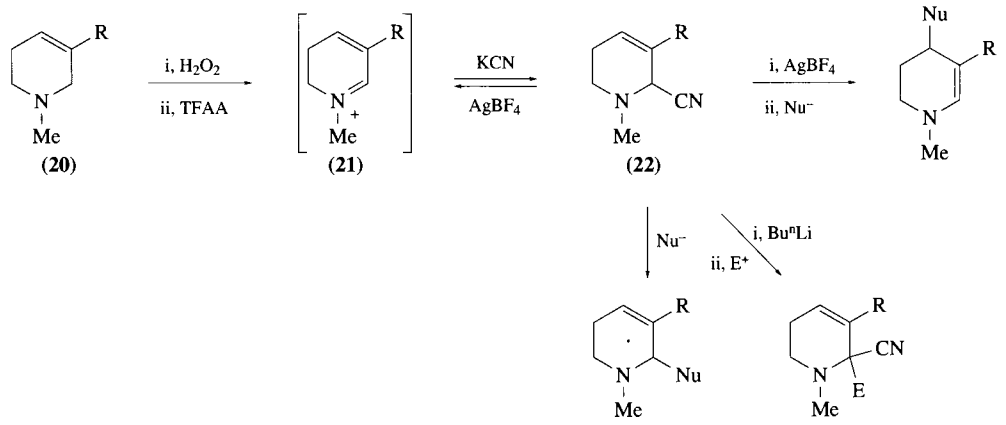


(8) (1) (19)

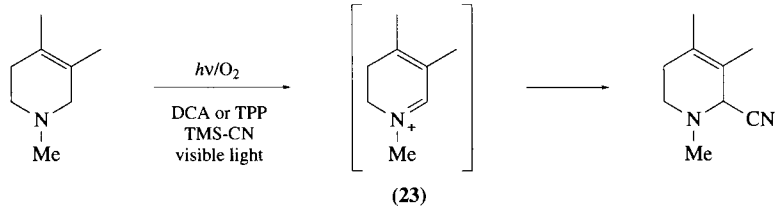
Scheme 2

Trapping of iminium intermediates such as (**21**) (formed via the Polonovski–Potier reaction) with cyanide ion, to yield α-aminonitriles such as (**22**), facilitates their use in various organic transformations (Scheme 3) ⟨82BSB985⟩. These α-aminonitriles are masked 2,3-dihydropyridinium salts, and both nucleophiles and electrophiles can be used in the functionalization of the α-carbon. Regiospecific cyano adducts are obtained, since the ring double bond of (**20**) directs the formation of the iminium ion.

In an alternative method for the preparation of α-aminonitriles such as (**22**), the iminium intermediate (**23**) is created photochemically and cyanotrimethylsilane acts as the cyanide source ⟨91SL739, 94S291⟩. The conditions are milder and the overall yield of aminonitriles is somewhat better than with the Polonovski–Potier reaction (Scheme 4).



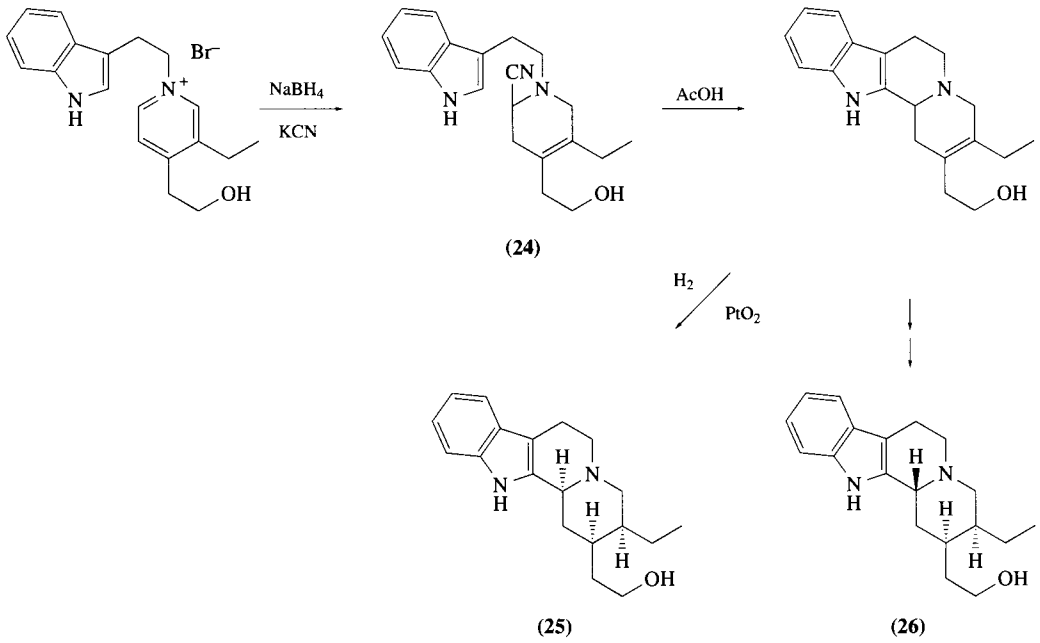
Scheme 3



Scheme 4

5.04.2.2 2,5-Dihydropyridines and the Corresponding Iminium Salts

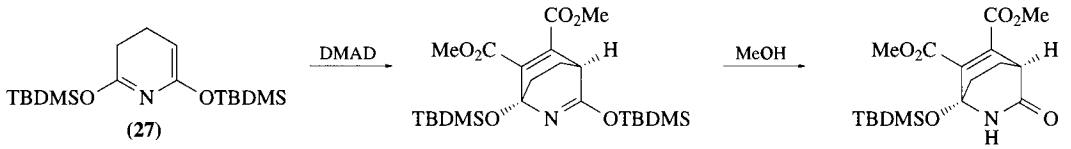
2-Cyano-1,2,3,6-tetrahydropyridines may be regarded as 2,5- or 1,2-dihydropyridine equivalents, which can be prepared by means of the Fry reductive cyanation from pyridinium salts ⟨84CHEC-I(2)365⟩. This method has been especially valuable for the synthesis of indole alkaloids. The short syntheses of (±)-corynantheidol (**25**) and its 3-epimer (**26**) via α-aminonitrile (**24**) serve as an example (Scheme 5) ⟨90H(31)1351⟩. Several other reactions of these α-aminonitriles with indoles have been presented ⟨87T391, 89TL5655, 89TL5659⟩.



Scheme 5

5.04.2.3 3,4-Dihydropyridines

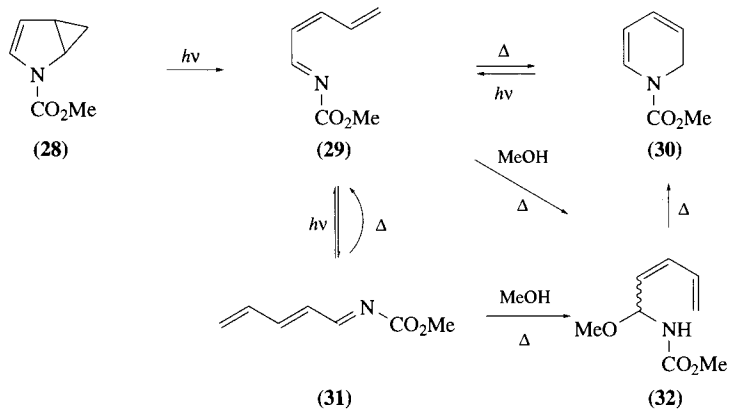
Diels–Alder reactions of a new heterodiene, 2,6-bis(*t*-butyldimethylsilyloxy)-3,4-dihydropyridine (**27**), available from glutarimide, have been examined ⟨87CB657⟩. Addition of various dienophiles, for example dimethyl acetylenedicarboxylate (DMAD) (Scheme 6), to (**27**) gives adducts in which one of the silyloxy groups can be hydrolyzed. Later, when alkenes were used as dienophiles, this reaction was found to proceed with high diastereoselectivity, mainly to *exo* adducts ⟨88TL4573⟩. In catalyzed reactions the *exo*/*endo*-selectivity was found to depend on the Lewis acid used ⟨89TL5887⟩. Moreover, some of the products could be converted to substituted cyclohexanones by treatment with tetrabutylammonium fluoride.



Scheme 6

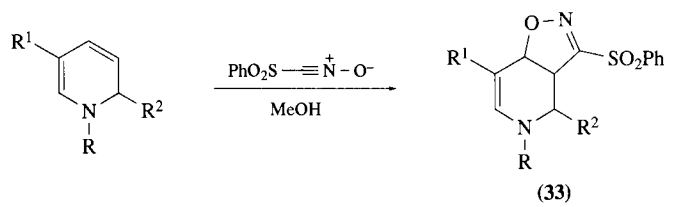
5.04.2.4 1,2-Dihydropyridines

Further studies have been done on the 2-azabicyclo[3.1.0]hex-3-ene ring system ⟨84CHEC-I(2)365⟩. *N*-Methoxycarbonyl-1,2-dihydropyridine (**30**) is obtained in as much as 85% yield when the bicyclic starting compound (**28**) is irradiated with a low-pressure mercury lamp ⟨91TL6895⟩. Evidence for the intermediacy of 1-azahexatrienes is provided by the photolysis of (**31**) in methanol, which gives a mixture of methoxy adducts (**32**), which on heating are converted into (**30**) (Scheme 7). A closely similar cyclization was reported in 1984 ⟨84JOC4025⟩. Moreover, formation of 1-azahexatrienes (**29**) and (**31**) was observed in the photolysis of (**30**) at −40 °C. At 37 °C, compound (**29**) gives dihydropyridine (**30**) in quantitative yield. Upon photolysis at low temperature, on the other hand, the ring of (**30**) opens to provide (**29**) and (**31**).



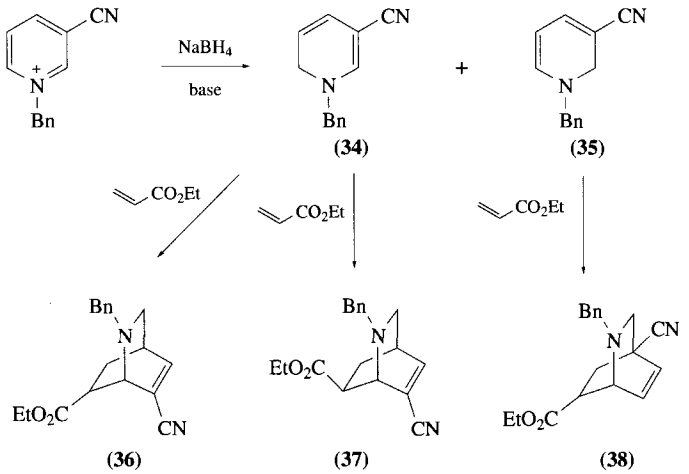
Scheme 7

The Diels–Alder reaction is the most studied cycloaddition of 1,2-dihydropyridines. A number of experiments have been carried out on this reaction, and only a few examples can be mentioned here. An example of the more rare 1,3-dipolar cycloaddition is the reaction of *N*-substituted 1,2-dihydropyridines with benzenesulfonylformonitrile oxide, which affords regiospecifically isoxazoles such as (**33**) (Equation (3)) ⟨84JOC123⟩.



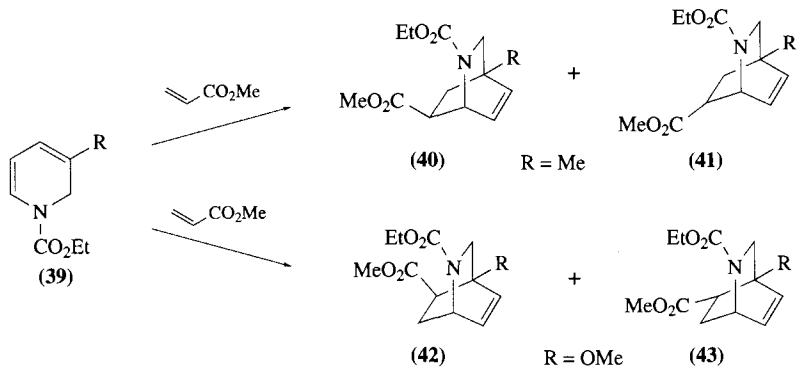
(3)

Some new aspects of the Diels–Alder reactions of 1,2-dihydropyridines have been described. In a re-examination of the original Büchi experiment ⟨84CHEC-I(2)365⟩, *N*-benzyl-1,6-dihydropyridine-3-carbonitrile (**34**) was reacted with ethyl acrylate ⟨84IJC(B)263⟩. The *endo*-adduct (**36**) was now obtained in better yield, in addition to the previously undetected *exo*-adduct (**37**). In addition, dihydropyridine (**35**), which had previously been regarded as inactive, gave the new product (**38**) (Scheme 8).



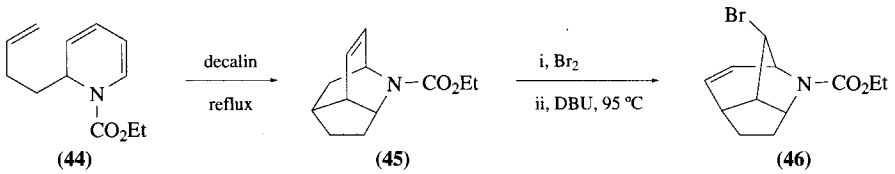
Scheme 8

The effect of substituents on the regio- and stereochemistry of the Diels–Alder reaction of 3-substituted 1,2-dihydropyridines has been studied for methyl, ethyl, methoxy, and trimethylsilyl groups ⟨86JOC3672⟩. The reaction of the 3-methyl derivative (**39**; R = Me) with methyl acrylate gives *exo*- and *endo*-adducts (**40**) and (**41**), whereas the methoxy substituent directs the cycloaddition to the two regioisomers (**42**) and (**43**) (Scheme 9). The asymmetric version of this reaction provides access to chiral isoquinuclidines ⟨88TL4423⟩.



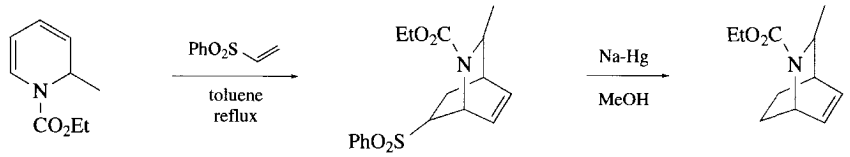
Scheme 9

An intramolecular variant of the above cycloaddition has been performed and the effects of alkyl substituents in different locations of the starting dihydropyridine have been examined in detail ⟨91T8499⟩. Without substituents on (**44**), the reaction gives adduct (**45**), which with bromine treatment rearranges to (**46**) (Scheme 10).



Scheme 10

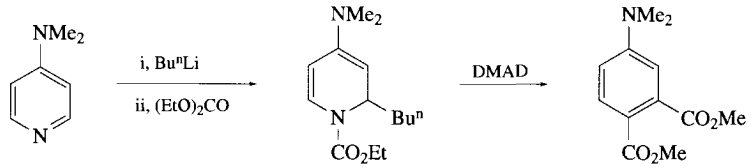
The use of phenyl vinyl sulfone as the dienophile provides regioselective access to some alkyl-substituted dehydroisoquinuclidines which are difficult to prepare by other methods ⟨90SC1949⟩. Diels–Alder reaction of dihydropyridine (**47**) with this sulfone gives intermediate (**48**), the desulfonylation of which yields the dehydroisoquinuclidine (**49**) (Scheme 11). (*E*)-Bis(phenylsulfonyl)ethylene has been used as dienophile in an analogous manner ⟨92JOC4103⟩.



(47) (48) (49)

Scheme 11

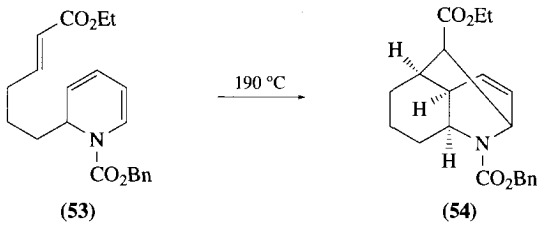
In yet another Diels–Alder study, 4-dimethylaminopyridine (DMAP) (**50**), a well-known reagent in organic synthesis, was converted into the 1,2-dihydropyridine (**51**) ⟨86T835⟩. The cycloaddition between (**51**) and dimethyl acetylenedicarboxylate (DMAD) was followed by the cycloreversion of the unstable bicyclic intermediate to give the dimethyl phthalate (**52**) (Scheme 12). Other dienophiles which have been reacted with *N*-methoxycarbonyl-1,2-dihydropyridine (**30**), include α-acetoxyacrylonitrile ⟨89JOC2893⟩ and various nitrosocarbonyl compounds ⟨85JOC2080⟩. In an asymmetric Diels–Alder study, chiral α,β-unsaturated oxazolines were used as dienophiles ⟨90JA6672⟩.



(50) (51) (52)

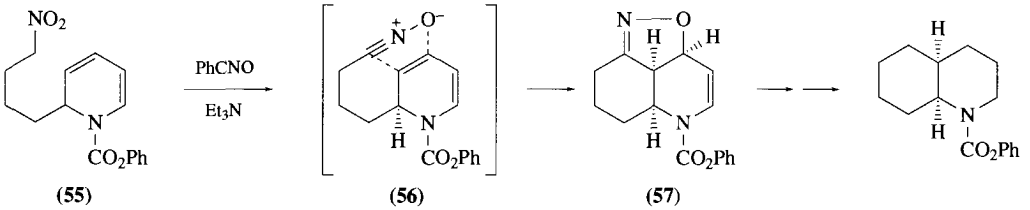
Scheme 12

The rarely encountered intramolecular Diels–Alder reaction of suitably substituted 1,2-dihydropyridines has been shown to produce new polycyclic systems ⟨83TL2711⟩. When ester (**53**) was refluxed in decalin, the bicyclic quinoline derivative (**54**) was obtained (Equation (4)). Later, a simple analogue of (**54**), possessing the same ring system, was similarly synthesized ⟨84TL4867⟩; a cranberry alkaloid derivative was earlier incorrectly proposed to have this skeleton.



(53) (54) (4)

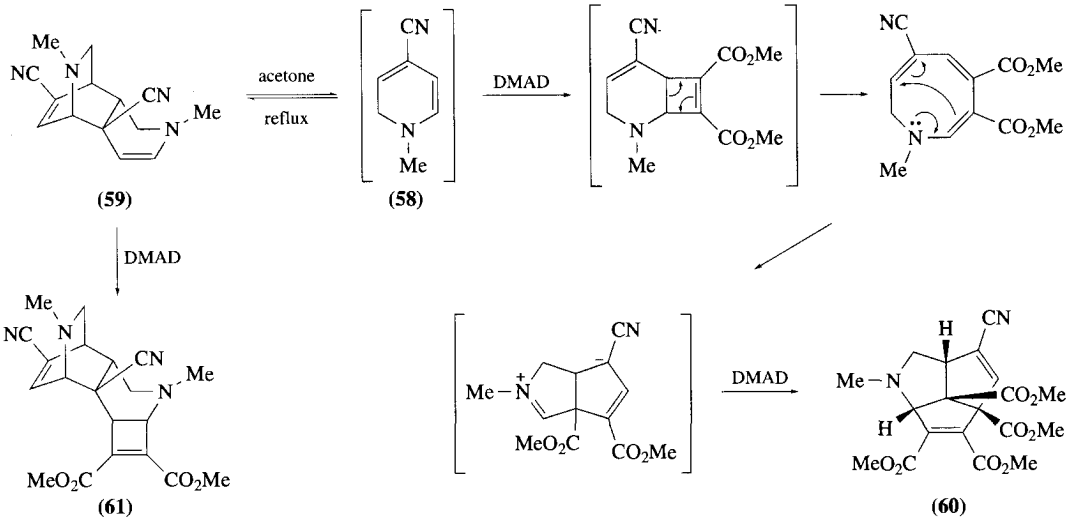
The intramolecular 1,3-dipolar cycloaddition reaction starting from dihydropyridine (**55**) and proceeding via nitrile oxide (**56**) and isoxazoline (**57**) provides access to the *cis*-decahydroquinoline ring system ⟨85TL43⟩ (Scheme 13).



(55) (56) (57)

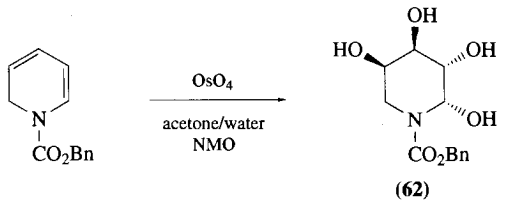
Scheme 13

The chemistry of *N*-methyl-4-cyano-1,2-dihydropyridine (**58**) has some interesting features. As known, at −45°C the compound self-condenses to form a [2 + 2] adduct, which above −20°C isomerizes to a [4 + 2] dimer ⟨92JCS(P2)1821⟩. The [4 + 2] dimer (**59**) is in equilibrium with (**58**) even in refluxing acetone. Furthermore, (**58**) reacts twice with DMAD to give finally a tricyclic product (**60**) (15%) (Scheme 14). Dimer (**59**) reacts once with DMAD to yield the main product (**61**) (50%). Structures of both adducts were confirmed by x-ray crystallography.



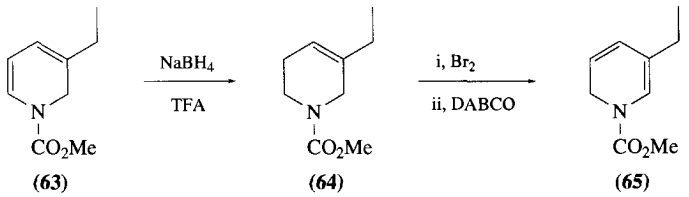
Scheme 14

A hetero-Diels–Alder reaction between nitrosobenzene and 1,2-dihydropyridines affords adducts which, after *cis*-hydroxylation and *N—O* bond hydrogenolysis, give amino sugar derivatives ⟨85HCA95⟩. 1,2-Dihydropyridines can also be directly oxidized to the corresponding tetrahydroxy derivatives by treatment with OsO_4 ⟨90TL2139, 94T1135⟩. This double glycolization is stereospecific and provides an alternative access to amino sugars, for example aminoarabinose (**62**) (Equation (5)).



(5)

The Fowler reduction has become a very useful method for the preparation of *N*-alkoxycarbonyl-1,2-dihydropyridines ⟨72JOC1321⟩. However, starting from 3-ethylpyridine, for example, this reaction gives only isomer (**63**) (Scheme 15). A simple process for the conversion of a 1,2-dihydropyridine into the 1,6-isomer has now been achieved ⟨84JOC4025⟩, where the enamine double bond of the *N*-acylated 1,2-isomer (**63**) is first reduced to obtain tetrahydropyridine (**64**). This is followed by bromine addition and subsequent base-catalyzed elimination of two HBr molecules to obtain the 1,6-isomer (**65**). A regiospecific method to obtain isomers like (**65**) has been reported ⟨86JOC5456⟩. As the key feature this involves a Vilsmeier reaction of 1,2-dihydropyridines.



Scheme 15

The α-lithiation of 2,4-disubstituted *N*-*t*-BOC-1,2-dihydropyridines followed by reaction with electrophiles offers a powerful method for the synthesis of important 2,4,6-trisubstituted dihydropyridines and, after aromatization, the corresponding pyridines ⟨88TL1751⟩.

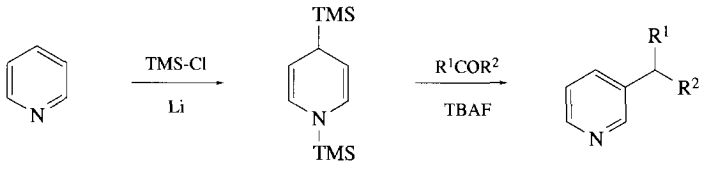
5.04.2.5 1,4-Dihydropyridines

The reactions of 1,4-dihydropyridines are summarized in two reviews covering the years 1981–1985 and 1986–1990, respectively ⟨88H(27)291, 93CHE489⟩. These reviews include an account of some of the methods for aromatization of, for example, Hantzsch-type dihydropyridines. In aromatization, one of the main side reactions is the cleavage of the 4-substituent. Cleavage dominates especially when the group is strongly electron releasing ⟨91SC2137, 93TL623⟩.

The variation in the reducing capabilities of 1,4-dihydropyridines according to their substitution pattern has been examined ⟨87MI 504-01⟩. 1-Aryl-1,4-dihydropyridines were found to be better reducing agents than the corresponding 1,4-dihydronicotinamides, the actual NADH models. Reductions of heteroaromatic cations by 1,4-dihydronicotinamides and related reducing agents have been reviewed ⟨91MI 504-02⟩.

1-Acyl-4-alkyl(aryl)-1,4-dihydropyridines, which are available from 1-acylpyridinium salts and Grignard reagents, can be converted to 2-lithiated derivatives and thereafter alkylated to yield, after aromatization, 2,4-substituted pyridines ⟨83TL2807⟩.

Direct introduction of alkyl groups to the 3-position of the pyridine ring, the electrophilic aromatic substitution of which usually is extremely difficult, has been achieved via silylated 1,4-dihydropyridines, such as (**66**) ⟨87BCJ1497⟩. Although these are readily oxidized to pyridines, they are also stable enough to be used as enamines, which in the presence of tetrabutylammonium fluoride (TBAF) react with aldehydes and ketones to form 3-alkylated pyridines, for example (**67**) (Scheme 16).



(**66**) (**67**)

Scheme 16

1-Acyl-1,4-dihydropyridines can be formylated with the Vilsmeier reagent ⟨87H(26)2159⟩. Friedel–Crafts acylation of 1-acyl-1,4-dihydropyridines occurs at the 3-position, analogously to the earlier reaction performed with vinylogous urethanes ⟨83TL3683⟩.

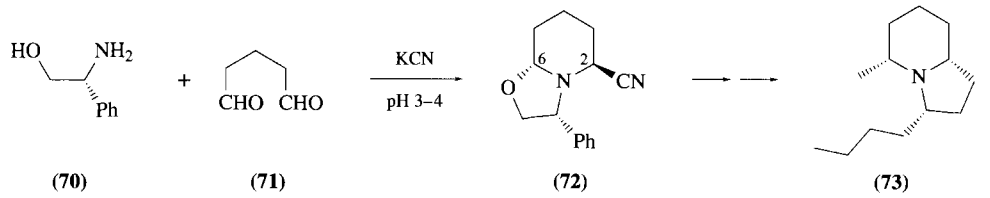
Successful preparation of stable 1,4-dihydropyridines (including chiral ones) via dithionite reduction without electron-withdrawing substituents at the 3- and/or 5-positions has been reported ⟨94TL707⟩. Hydrophobic effects evidently play an essential role in this reaction, as the long *N*-alkyl chain (at least five carbons) was found to be crucial for obtaining products stable enough for characterization. There has also been increasing interest in chiral 1,4-dihydropyridines as synthetic intermediates ⟨94JOC1877⟩.

The regioselectivity of the α-lithiation of unsymmetrical 3-substituted *N*-*t*-BOC-1,4-dihydropyridines is controlled by the nature of the 3-substituent and the base that is used ⟨88JOC4437⟩. Metalation occurred predominantly at C-6 when the substituent at C-3 was a methyl or methoxy group and the base was mesityllithium. Metalation at C-2 took place when the 3-substituent was strongly *o*-directing, for example a halogen.

Suitably substituted 1,4-dihydropyridines undergo interesting rearrangements. A [3,3]-sigmatropic rearrangement takes place when the 2-allylthio-1,4-dihydropyridine (**68**) is heated, and the product is the tetrahydropyridinethione (**69**) (Equation (6)) ⟨90DOK(314)1427⟩. Allylseleno derivatives behave similarly ⟨91IZV1888⟩.

(**68**) (**69**) (6)

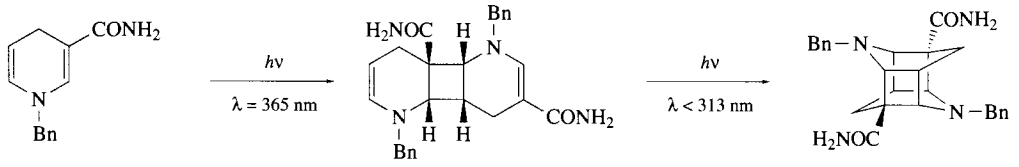
The (−)-2-cyano-6-oxazolopiperidine derivative (**72**) is a chiral 1,4-dihydropyridine equivalent, which can be prepared from (−)-phenylglycinol (**70**), glutaraldehyde (**71**), and KCN ⟨83JA7754⟩. Selective functionalization of either C-2 or C-6 of (**72**) can be achieved, and has been used for the conversion of (**72**) to the piperidine alkaloid (−)-monomorine I (**73**) (Scheme 17) ⟨85JOC670⟩. Compound (**72**) has subsequently served as starting material for numerous alkaloids. The technique has been designated as the CN(R,S) method ⟨88TL1391⟩.



(**70**) (**71**) (**72**) (**73**)

Scheme 17

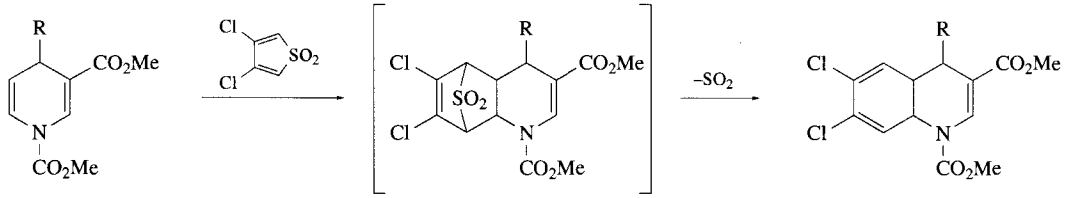
1,4-Dihydropyridines undergo photochemical dimerization to form cage compounds ⟨84CHEC-I(2)365⟩. The same dimerization was observed when *N*-benzyl-1,4-dihydronicotinamide (**16**) was irradiated in anhydrous methanol ⟨83TL5399⟩. Initial irradiation with filtered light (medium-pressure Hg lamp, $\lambda = 365$ nm) gave a [2 + 2] adduct (**74**), which, when irradiated with unfiltered light ($\lambda \leqslant 313$ nm), underwent a further cycloaddition to form cage adduct (**75**) (Scheme 18).



(**16**) (**74**) (**75**)

Scheme 18

The use of a 1,4-dihydropyridine as dienophile in the Diels–Alder reaction has been reported ⟨86JOC5328⟩. For example, the reaction of dihydropyridine (**76**) (R = Me) with 3,4-dichlorothiophene 1,1-dioxide gives the quinoline derivative (**78**) in 70% yield via adduct (**77**) (Scheme 19). With some other ring substituents (R) the major side product is methyl nicotinate.



(**76**) (**77**) (**78**)

Scheme 19

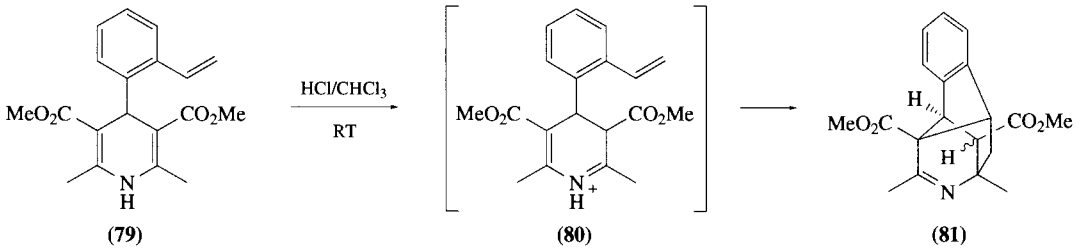
It has long been known that 4-chloromethyl-1,4-dihydropyridines react with carbanions to form ring-expanded products. In a new approach ⟨85CJC843⟩ this reaction is accompanied by the intramolecular Michael addition to furnish the 2-azabicyclo[3.2.1]oct-3-ene system.

A stereoselective reduction of Hantzsch-type 1,4-dihydropyridines conducted with triethylsilane in trifluoroacetic acid gives all-*trans*-isomers of the corresponding 1,2,3,4-tetrahydropyridines and piperidines ⟨85S210⟩. The reaction proceeds in the presence of a variety of sensitive groups.

Conformationally rigid derivatives of 1,4-dihydropyridines have been prepared by an intramolecular formal [4 + 2] cycloaddition of suitably substituted 4-aryl-1,4-dihydropyridines ⟨85JOC2427⟩. The acid-catalyzed cyclization of the vinyl derivative (**79**) proceeds via iminium ion (**80**) to afford the diastereomeric mixture (**81**) (Scheme 20). Similar treatment of a methoxy derivative of (**79**) affords different products via competing intramolecular cyclization processes ⟨86CJC556⟩.

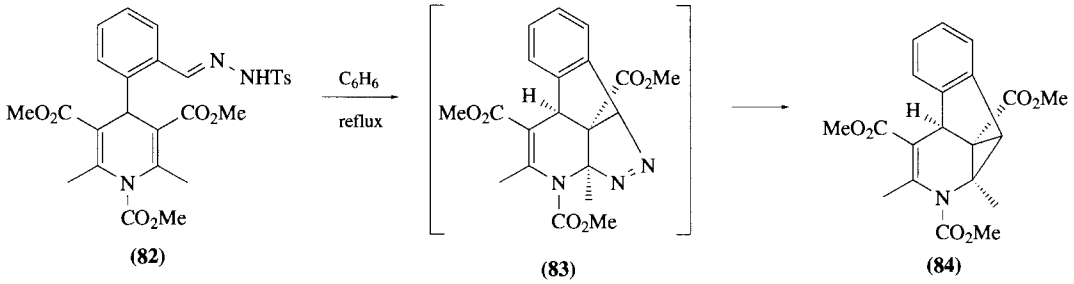
In a study of an intermolecular variant of the above reaction it was shown that iminium ions of type (**80**) are also formed under Lewis acid catalysis ⟨87JOC1136⟩. Later it was concluded that only highly reactive alkenes, such as unhindered styrenes, give synthetically useful results ⟨89JOC4134⟩.

In another cyclization of a Hantzsch-type dihydropyridine, a cyclopropane ring was formed



Scheme 20

⟨85JOC4120⟩. Refluxing the tosylhydrazone (**82**) in benzene gave directly the cyclopropane derivative (**84**), presumably via intermediate (**83**) (Scheme 21). In related investigations, some other bridged molecules were prepared analogously via intramolecular cyclization ⟨86S144, 86JHC1471⟩.



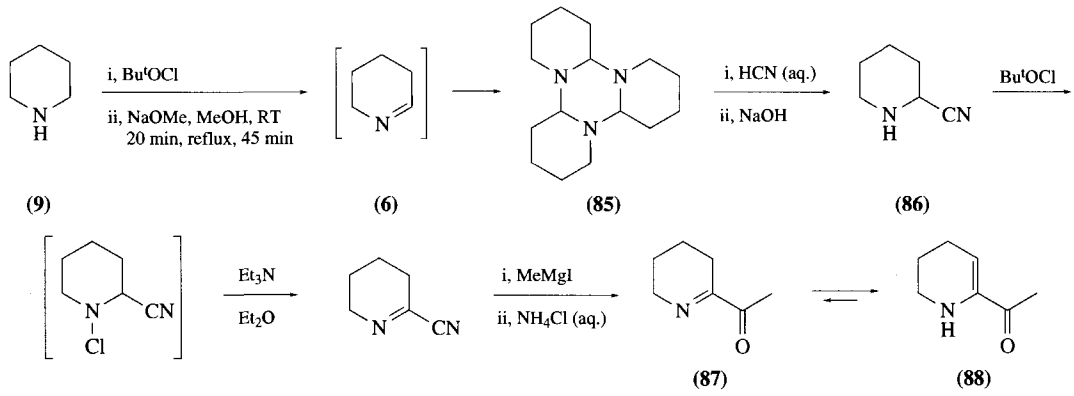
Scheme 21

5.04.3 REACTIVITY OF TETRAHYDROPYRIDINES

Of the three parent tetrahydropyridines (**6**), (**7**), and (**8**), isomers (**6**) (imine) and (**7**) (enamine) are generally interconvertible, whereas isomer (**8**) (allylic amine) mainly exhibits the properties of an alkene or secondary amine.

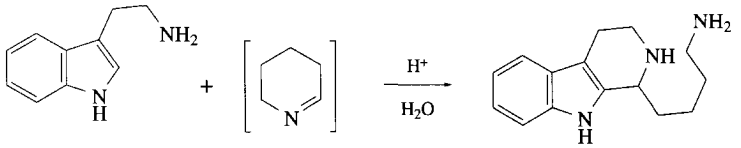
5.04.3.1 2,3,4,5-Tetrahydropyridines and the Corresponding Iminium Salts (Including α-Aminonitriles)

The parent heterocycle 2,3,4,5-tetrahydropyridine (**6**), conveniently handled as its trimer (**85**), reacts with aldehydes to form 5-alkylidene or 5-arylidene-2,3,4,5-tetrahydropyridines ⟨83BSJ3199, 87ACS(B)208⟩. Trimer (**85**) was used in a synthesis of the bread flavor compound 6-acetyl-1,2,3,4-tetrahydropyridine (**88**, existing in equilibrium with its imino tautomer **87**) ⟨93JOC2904⟩. The procedure describes an efficient modified conversion of piperidine (**9**) into 2-cyanopiperidine (**86**), which is then transformed to (**88**) (Scheme 22).



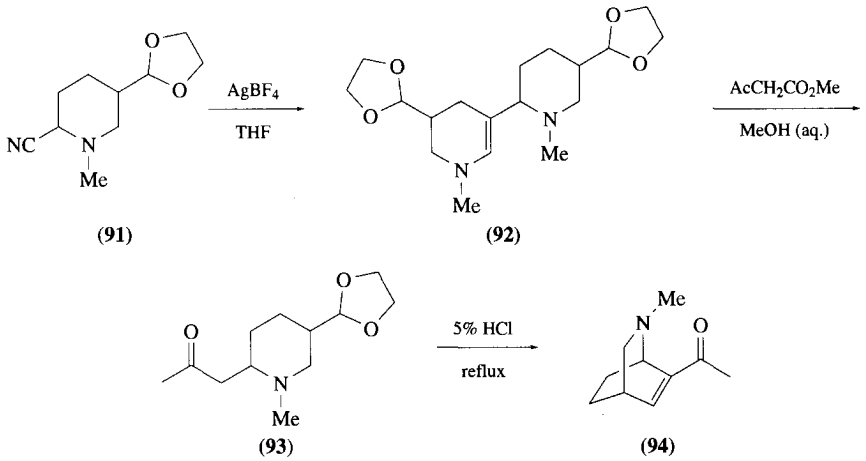
Scheme 22

Tryptamine (**89**) and tetrahydropyridine (**6**) (as its trimer (**85**)) react in a Pictet–Spengler reaction to afford the β-carboline (**90**) (Equation (7)). Structural formula (**90**) represents the revised structure for the indole alkaloid nazlinin ⟨93CC174⟩.



(89) (6) (90) (7)

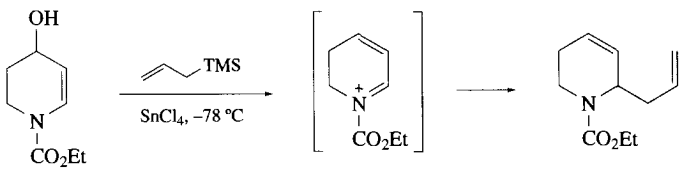
One of the applications of the Polonovski–Potier reaction has been the construction of the important isoquinuclidine ring system ⟨85H(23)1735⟩. Aminonitrile (**91**), which is a 2,3,4,5-tetrahydropyridine equivalent, dimerizes to (**92**) when treated with $AgBF_4$ (Scheme 23). Reaction of the dimer (**92**) with acetoacetic ester gives the ketone (**93**) in a higher yield than the direct reaction of the monomer (**91**). Isoquinuclidine (**94**) is obtained from (**93**) by acid treatment.



(91) (92) (93) (94)

Scheme 23

N-Ethoxycarbonyl-4-hydroxy-1,2,3,4-tetrahydropyridine (**95**) is a precursor of *N*-acyl iminium species (**96**) and reacts with nucleophiles under Lewis acid catalysis to afford mainly 2-substituted products ⟨84JOC1674⟩. Thus, this Ferrier-type process gives the 1,2,3,6-tetrahydropyridine (**97**) when (**95**) is treated with allyltrimethylsilane and stannic chloride at −78 °C (Scheme 24). Similarly, *N*-alkoxycarbonyl-6-methoxy-1,2,3,6-tetrahydropyridines, which can be generated electrochemically, serve as alternative starting compounds for the iminium intermediate (**96**) ⟨87CL639⟩. As has been shown, iminium intermediates such as (**96**) react with alkylzinc iodides to afford 6-substituted 1,2,3,6-tetrahydropyridines ⟨88TL6711, 94H(37)1121⟩.

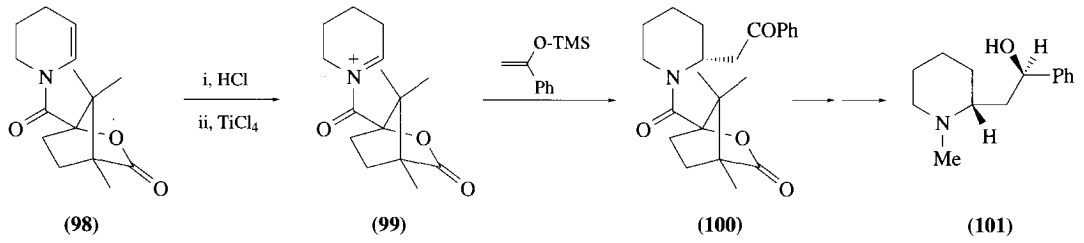


(95) (96) (97)

Scheme 24

Nucleophilic addition to chiral *N*-acyl iminium species constitutes an additional method for the preparation of chiral α-substituted piperidines (see below) ⟨87H(26)921, 87AP(320)1050⟩. When the iminium intermediate (**99**), created from the enamide (**98**) by acid treatment, was reacted with the trimethylsilyl enol ether of acetophenone, amide (**100**) was obtained together with its diastereoisomer, in this case in a 2:1 ratio (Scheme 25). Subsequent standard manipulation led to the

piperidine alkaloid (+)-sedamine (**101**). Introduction of modified chiral auxiliaries enhanced the stereoselectivity of the reaction (**98**) → (**100**) ⟨88H(27)2549, 94T3113⟩.

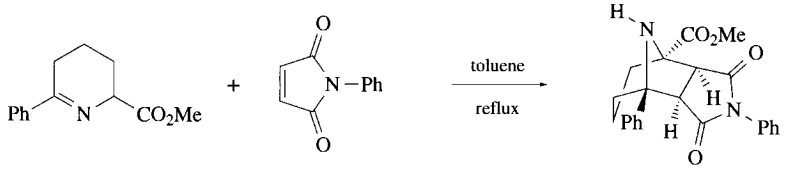


(**98**) (**99**) (**100**) (**101**)

Scheme 25

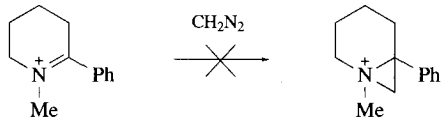
Acylated 2-methoxypiperidines are *N*-acyl iminium ion precursors and react with nucleophiles under acid catalysis ⟨85T4367⟩. α-Alkylated products are obtained with organocopper reagents ⟨90ACS707⟩. Similar results have been obtained with the corresponding formamidines ⟨90TL4723⟩. Stereochemically, the formamidine method introduces a route to piperidines with 2-axial-6-equatorial substituents ⟨92TL867⟩.

A new activated imine (**102**), synthesised from an open chain precursor, reacts with alkenes in a 1,3-dipolar sense ⟨87TL1397⟩. The adduct (**104**) from the cycloaddition reaction of (**102**) with *N*-phenylmaleimide (**103**) was found to possess *exo* stereochemistry (Equation (8)). Analogous reactions have been carried out in the isoquinoline series ⟨91CJC1156⟩.

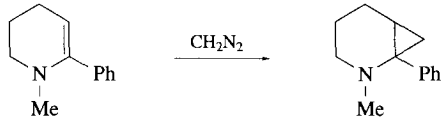


(**102**) (**103**) (**104**) (8)

Study has been made of the reaction of cyclic iminium salts with certain carbenes ⟨87AP(320)298⟩. Surprisingly, diazomethane does not react with the iminium salt (**105**) to give (**106**), but it does react with the corresponding enamine (**107**) to form the cyclopropane (**108**) (Equations (9) and (10)).



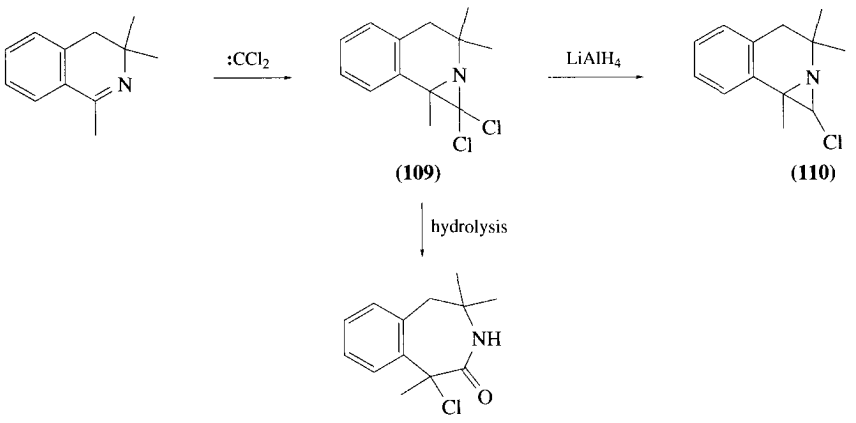
(**105**) (**106**) (9)



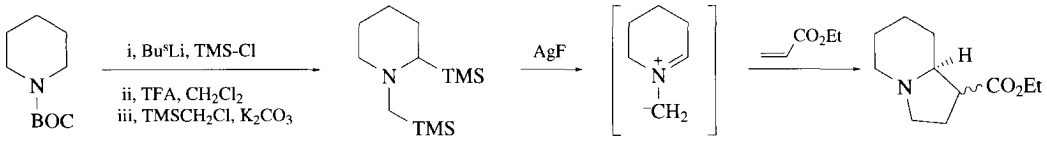
(**107**) (**108**) (10)

Dichlorocarbene reacts with substituted 3,4-dihydroisoquinolines to give aziridino adducts (**109**) ⟨90KGS1086⟩. Hydrolysis of (**109**) leads to ring expansion, and reduction with $LiAlH_4$ gives the monochloro adduct (**110**) (Scheme 26).

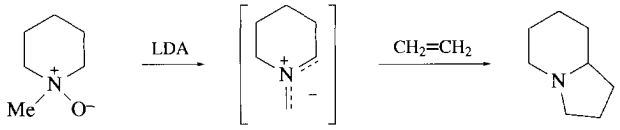
Azomethine ylide (**113**), which can be generated from the trimer of 2,3,4,5-tetrahydropyridine (**85**) via a silylation/desilylation process, reacts in low yield with alkenes or alkynes in a 1,3-dipolar cycloaddition to form the indolizidine skeleton ⟨82CPB3167⟩. Higher yields of cycloadducts such as (**114**) were obtained when the same ylide (**113**) was prepared from *N*-*t*-BOC-piperidine (**111**) via the disilylated intermediate (**112**) (Scheme 27) ⟨93TL4861⟩. Treatment of *N*-methylpiperidine *N*-oxide with LDA also produces ylide (**113**) ⟨85JOC2910⟩, reaction of which with ethylene gave indolizidine (**115**) in 63% yield (Scheme 28).



Scheme 26

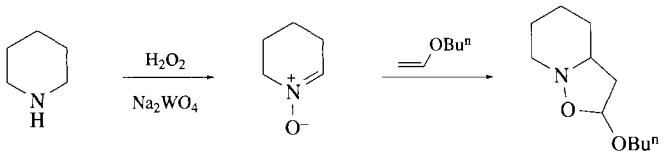


Scheme 27



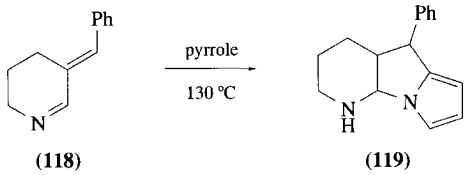
Scheme 28

Cycloaddition of azomethine *N*-oxides (nitrones) can be regarded as an analogous reaction to the above 1,3-dipolar examples. Piperidine can be oxidized, for example with H_2O_2/Na_2WO_4 ⟨84CC874, 88JCS(P1)2251, 90JOC1736⟩, to nitrone (**116**), which reacts with alkenes to form fused isoxazolidines, for example (**117**) (Scheme 29). The N—O bond in (**117**) can be cleaved, giving rise to 2-substituted piperidines. Furthermore, access is possible to both *trans*-2,6-⟨90JCS(P1)2323⟩ and *cis*-2,6-dialkylpiperidines ⟨94JCR(S)32⟩.



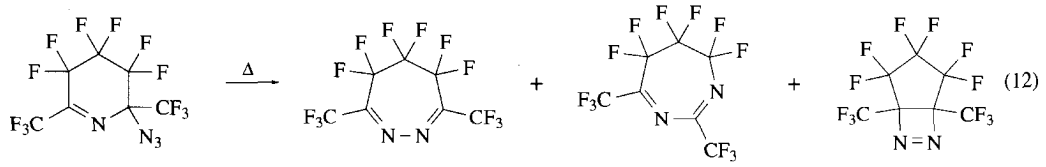
Scheme 29

Both 1,2- and 1,4-addition products can be obtained from the reaction of 5-benzylidene-2,3,4,5-tetrahydropyridine (**118**) with various nucleophiles ⟨84BCJ1271⟩. Pyrrole is notable in reacting in a 1,4-manner with (**118**), giving rise, after cyclization, to the tricyclic product (**119**) (Equation (11)).



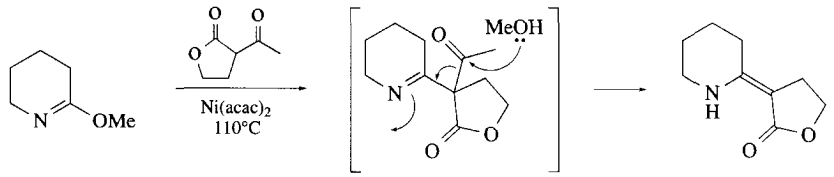
(11)

Some interesting reactions of fluorinated reduced pyridines have been presented ⟨83CC1117⟩. Perfluorinated 2-azido-2,6-dimethyl-2,3,4,5-tetrahydropyridine (**120**) gives under flow pyrolysis diazepine (**121**) and the minor products (**122**) and (**123**) (Equation (12)). The bicyclic product (**123**) is probably formed from (**121**).



(120) (121) (122) (123) (12)

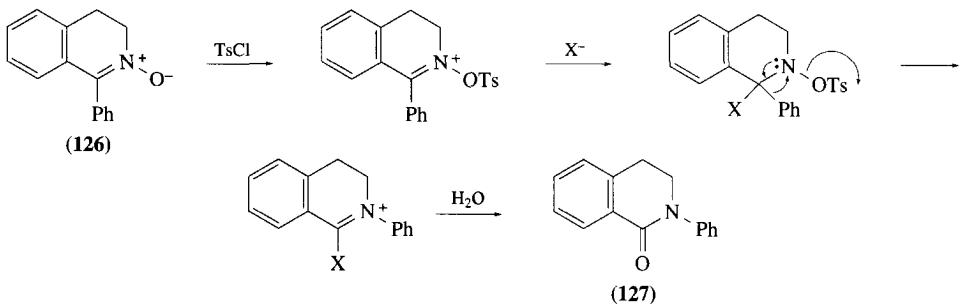
The chemistry of lactim ethers offers another method for the introduction of substituents to the α-position of piperidines (see Section 5.04.4.1). Condensation of lactim ether (**124**) with 2-acetylbutyrolactone under Ni catalysis gives the β-enamino lactone (**125**) (Scheme 30) ⟨93S69⟩.



(124) (125)

Scheme 30

The reaction of nitrones with acid chlorides furnishes some interesting rearrangement products ⟨82T3471⟩. For example, the *N*-oxide of 1-phenyl-3,4-dihydroisoquinoline (**126**) reacts with *p*-toluenesulfonyl chloride to give the dihydroisoquinolone (**127**) according to the mechanism depicted in Scheme 31. Under slightly different reaction conditions aromatization is the main competing reaction.



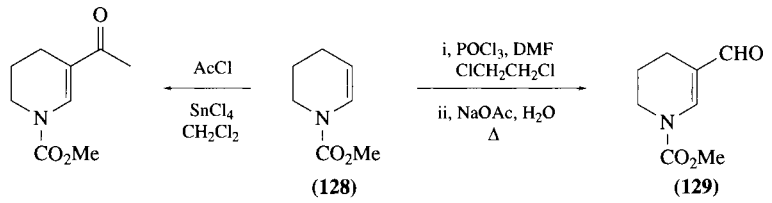
(126) (127)

Scheme 31

5.04.3.2 1,2,3,4-Tetrahydropyridines

An electrochemical method has been presented for the preparation of *N*-methoxycarbonyl- or *N*-acyl-substituted 1,2,3,4-tetrahydropyridines from the corresponding piperidines ⟨82JA6697⟩. Some reactions of these tetrahydropyridines, which are actually less reactive than normal enamines, were investigated. The Vilsmeier reaction of tetrahydropyridine (**128**) gives the formyl derivative (**129**) in high yield. The yield is significantly lower with the corresponding *N*-acylated tetrahydropyridine. The Friedel–Crafts reaction works well too, especially when reagents are used in large excess (Scheme 32). In addition, hydroboration of (**128**) leads to β-hydroxypiperidines. The stereoselectivity

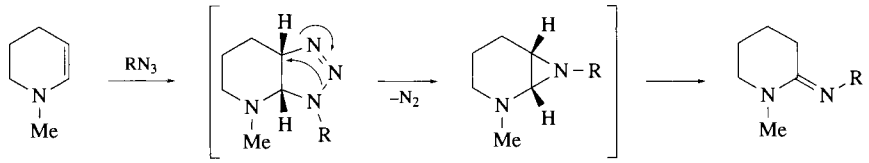
of this reaction with 2-substituted derivatives of (**128**) has been examined ⟨93TL7569⟩. The 2,5-*trans*-isomer is the major product, being formed in abundance particularly at low temperature.



(**128**) (**129**)

Scheme 32

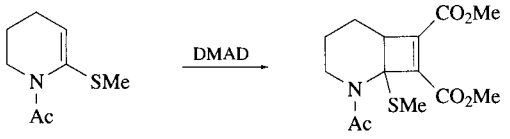
The 1,3-dipolar cycloaddition between *N*-methyl-1,2,3,4-tetrahydropyridine (**130**) and organic azides affords pharmacologically interesting 2-piperylidenesulfonamides or 2-piperylidenecyanamides ⟨82JHC1259, 87JHC1413⟩. Evidence for a bicyclic intermediate (**131**) (Scheme 33) was obtained in a similar reaction with 1,4-dihydropyridines. The reaction has also been performed with 1,2-dihydropyridines to give bicyclic aziridines ⟨85CJC2362⟩.



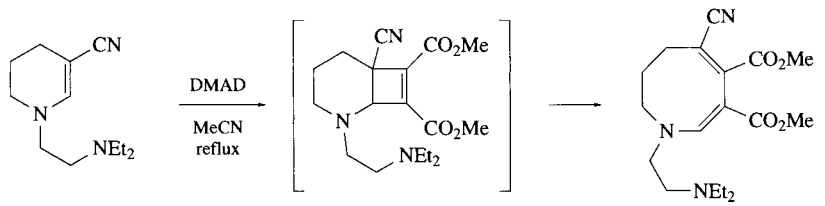
(**130**) (**131**)

Scheme 33

A [2 + 2]-type cycloaddition reaction of enamine (**132**), a ketene *S*,*N*-acetal, with dimethyl acetylenedicarboxylate gives cyclobutene derivatives, for example (**133**) (Equation (13)) ⟨82CPB3959⟩. Products with an expanded ring were obtained when an *N*-methyl derivative was used. The expected ring expansion also took place when a differently substituted tetrahydropyridine was used ⟨92JCR(S)16⟩. Compound (**136**) possessing the eight-ring azocine skeleton was obtained, via the non-isolated cycloadduct (**135**), when tetrahydropyridine (**134**) was refluxed with DMAD (Scheme 34). The reaction also works with some 1,2-dihydropyridines.



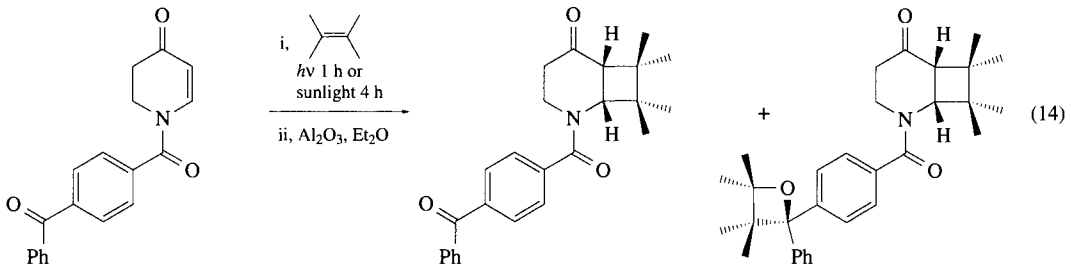
(**132**) (**133**) (13)



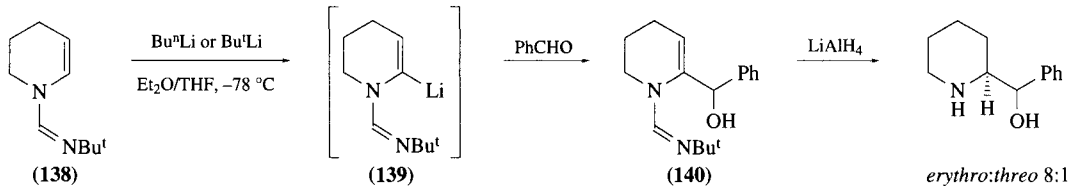
(**134**) (**135**) (**136**)

Scheme 34

2,3-Dihydro-4-pyridones undergo cycloaddition with alkenes to yield bicyclic products ⟨87C341, 89CC1727⟩. With an internal sensitizer, such as in compound (**137**), sunlight is enough to initiate the reaction ⟨91HCA163⟩. In this case, addition to the benzophenone carbonyl is a minor side reaction (Equation (14)).

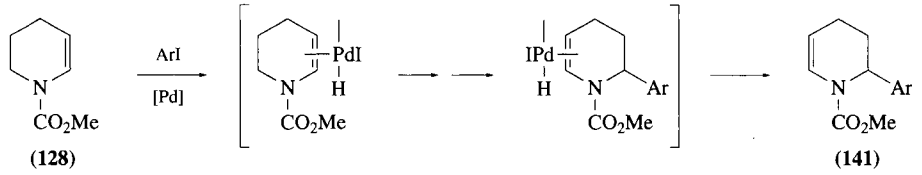


1,2,3,4-Tetrahydropyridine, as its formamidine derivative (**138**), can be converted into the α-lithiated intermediate (**139**), which reacts with electrophiles to form α-alkylated products ⟨85JOC1019⟩. Thus, formamidine (**138**) gives enaminoalcohol (**140**) when treated with benzaldehyde (Scheme 35). The procedure is described in more detail in the piperidine section (see Scheme 49 below).



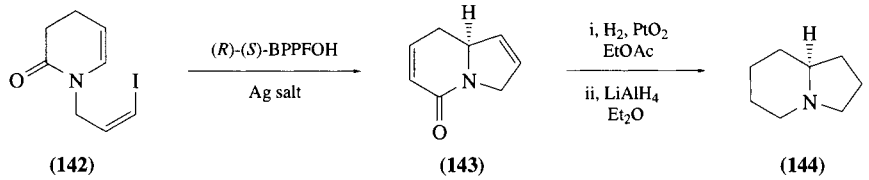
Scheme 35

Palladium-catalyzed α-arylation of cyclic enamides has been reported to proceed with double-bond migration ⟨90JOC2464⟩. Thus, treating *N*-methoxycarbonyl-1,2,3,4-tetrahydropyridine (**128**) with an aryl iodide in the presence of a palladium catalyst leads to the α-substituted product (**141**), possibly via σ-adduct intermediates (Scheme 36).



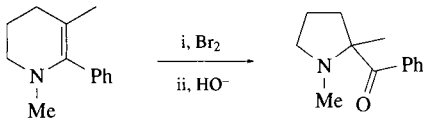
Scheme 36

The indolizidine skeleton can be constructed by means of an asymmetric intramolecular Heck reaction ⟨93TL4965, 94T371⟩. Catalyzed by a chiral Pd complex ((*R*)-(*S*)-BPPFOH) in the presence of a silver salt, iodide (**142**) cyclized to the indolizidine derivative (**143**) (Scheme 37). Catalytic hydrogenation and reduction furnished the alkaloid (+)-δ-coniceine (**144**).



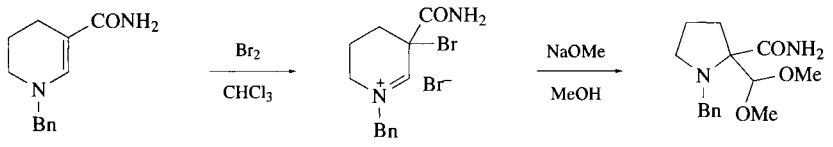
Scheme 37

When suitably substituted endocyclic enamines are reacted first with bromine and then treated with base, ring contraction takes place ⟨84CHEC-I(2)511⟩. This reaction has already been studied with acyclic enamines. Thus, tetrahydropyridine (**145**) gives pyrrolidine (**146**) in good yield (Equation (15)) ⟨84JCR(S)66⟩. Under similar reaction conditions exocyclic enamines undergo ring expansion.



(145) (146) (15)

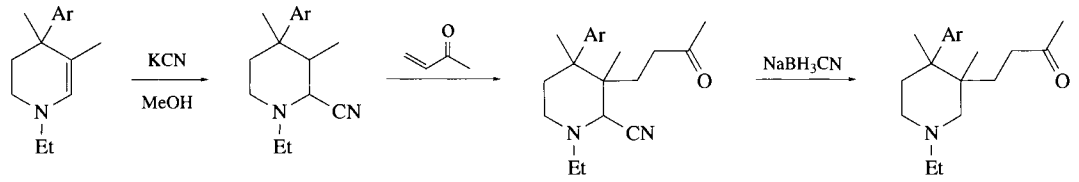
In another application, *N*-benzyl-1,4,5,6-tetrahydronicotinamide (**147**) is converted with bromine into the stable iminium salt (**148**), which reacts with various nucleophiles (e.g. MeO^- in Scheme 38) to afford ring contraction products ⟨87JHC481⟩.



(147) (148)

Scheme 38

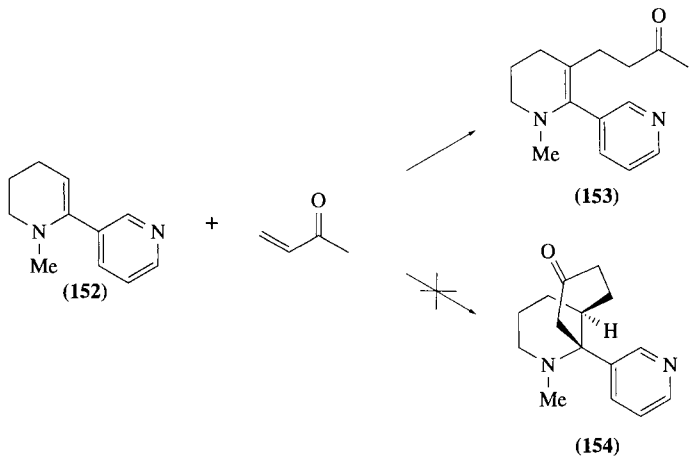
The Michael reaction of enamines lacking the β-proton can be carried out by trapping the intermediate iminium ion with cyanide ion ⟨88TL6831⟩. It turned out to be even more useful to employ aminonitrile (**149**) directly as an enamine equivalent (Scheme 39). The cyano group can easily be removed from the Michael adduct (**150**) to obtain the corresponding piperidine (**151**).



(149) (150) (151)

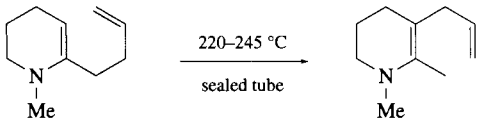
Scheme 39

Some limitations of the Robinson annelation of 1,2,3,4-tetrahydropyridines have been examined ⟨83CC1422⟩. Tetrahydropyridine (**152**) gives the Michael adduct (**153**) but fails to afford the expected annelated product (**154**) (Scheme 40). The explanation for this lies in steric and other factors.



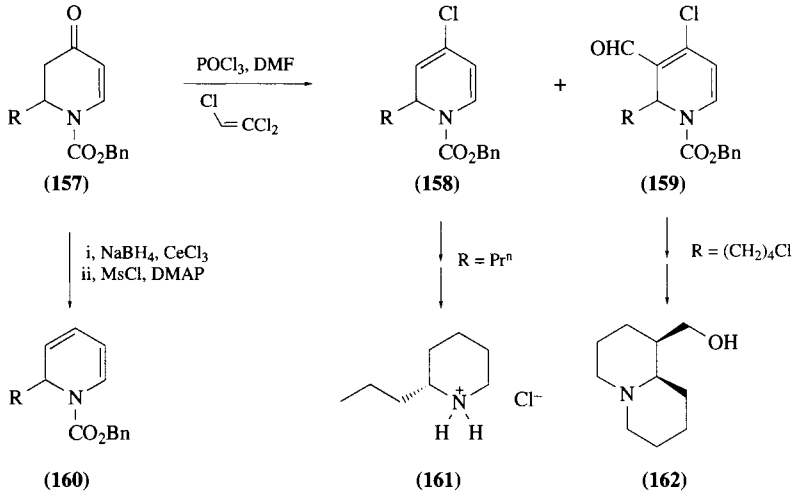
Scheme 40

Rearrangements are relatively rare in endocyclic enamines, but some sigmatropic rearrangements have been performed with suitably substituted tetrahydropyridines ⟨83CCC3407⟩. When *N*-methyl-6-(3-butenyl)-1,2,3,4-tetrahydropyridine (**155**) was heated in a sealed tube, a [3,3]-sigmatropic rearrangement took place to afford the 5,6-disubstituted tetrahydropyridine (**156**) (Equation (16)).



(155) (156) (16)

Addition of Grignard reagents to *N*-acyl-4-methoxy-3-(triisopropylsilyl)pyridines gives 2-substituted *N*-acyl-2,3-dihydro-4-pyridones, which have turned out to be valuable synthetic intermediates ⟨86TL4549⟩. With the use of chiral acyl groups, several alkaloids have been synthesized in an enantioselective manner ⟨94JA4719⟩. As these compounds possess several structural features, they can be manipulated in a variety of ways, for example by Michael addition, alkylation, 1,2-addition, and electrophilic substitution. A route to 1,2-dihydropyridines (**160**) from (**157**) is available via reduction/dehydration ⟨91JOC7197⟩ (Scheme 41). The Vilsmeier reaction of 2-substituted *N*-acyl-2,3-dihydro-4-pyridones (**157**) gives 4-chloro-1,2-dihydropyridines (**158**) in high yields ⟨92TL7635⟩. Moreover, use of a large excess of the Vilsmeier reagent results in additional formylation at C-3 to give (**159**) ⟨93JOC7732⟩. These two important findings have been exploited in the syntheses of the alkaloids (−)-coniine (**161**) and (±)-lupinine (**162**), respectively.



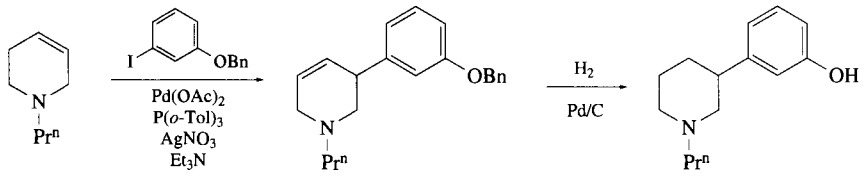
(157) (158) (159) (160) (161) (162)

Scheme 41

5.04.3.3 1,2,3,6-Tetrahydropyridines

The useful transformation of *N*-alkyl-1,2,3,6-tetrahydropyridines into enamines is usually achieved with a strong base. Rhodium(III) salts perform the same isomerization from allylamines into enamines ⟨90BSF648⟩. A facile conversion of *N*-acyl-1,2,3,6-tetrahydropyridines to *N*-acyl enamines occurs under palladium catalysis ⟨87H(26)917, 87AP(320)1050⟩.

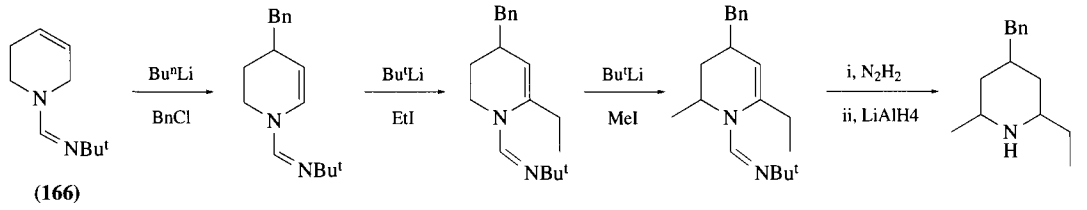
The palladium-catalyzed Heck reaction ⟨92JOC4015⟩ of tetrahydropyridine (**163**) and 3-(benzyloxy)iodobenzene gives regioselectively the arylated tetrahydropyridine (**164**) (Scheme 42). Compound (**164**) can be hydrogenated to racemic preclamol (**165**), the first example of a dopamine autoreceptor agonist.



(163) (164) (165)

Scheme 42

1,2,3,6-Tetrahydropyridines can be alkylated by using the formamidine methodology (see Schemes 35 and 49) ⟨85JOC1019⟩. Starting from tetrahydropyridine (**166**), access to 4-substituted, 2,4-disubstituted and, finally, 2,4,6-trisubstituted piperidines (or tetrahydropyridines) is possible through a series of alkylations as depicted in Scheme 43.



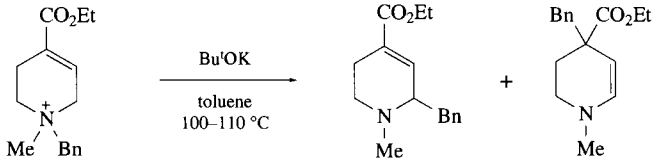
(166)

Scheme 43

Search for some pharmacologically active 4-alkoxy-4-alkyl-substituted piperidines has led to a new preparative method for these compounds. Methanol adds in Markovnikov manner to the double bond of 1,2,3,6-tetrahydropyridines in a photochemical reaction ⟨87CCC1298⟩. Acid catalysis leads only to polymerization.

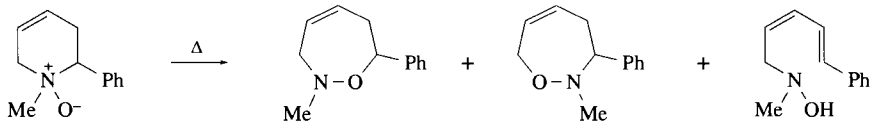
The attempted Michael addition of *N*-methyl-1,2,3,6-tetrahydropyridine-4-carbonitrile resulted in nucleophilic attack to C-2 rather than, as expected, to C-3 ⟨82TL4485⟩. The starting compound is probably rearranged to the corresponding enamine, which in turn can be protonated to an iminium salt. A comparison of this reaction with phenols and thiophenols has been published ⟨84JHC981⟩.

The Stevens rearrangement was found to take place with the tetrahydropyridinium salt (**167**), affording two products (**168**) and (**169**) (Equation (17)) ⟨81JCS(P1)1754, 87JCR(S)57⟩.



(167) (168) (169) (17)

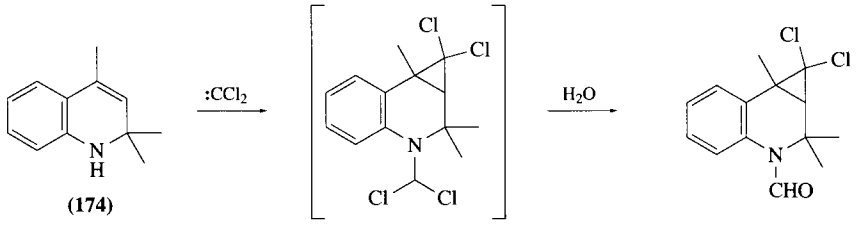
Thermal rearrangement of certain α-substituted 1,2,3,6-tetrahydropyridine *N*-oxides leads to the formation of 1,2-oxazepines ⟨84CPB4117⟩. In addition to the major Hofmann elimination product (**173**), thermolysis of *N*-methyl-2-phenyl-1,2,3,6-tetrahydropyridine *N*-oxide (**170**) gives the two 1,2-oxazepines (**171**) and (**172**) (Equation (18)). The Hofmann product (**173**) is probably formed directly from (**170**) as the oxazepine (**171**) could not be converted into (**173**) by heating.



(170) (171) (172) (173) (18)

Stevens [3,2] rearrangement of substituted 1,2,3,6-tetrahydropyridinium salts proceeds with ring contraction to give substituted pyrrolidines ⟨90TL4351⟩. The method is especially suitable for the stereoselective synthesis of some trisubstituted pyrrolidines.

Dichlorocarbene has been reported to react with 2,2,4-trimethyl-1,2-dihydroquinoline (**174**) at both the 3,4-double bond and the nitrogen atom ⟨88IZV1413⟩ (Scheme 44).



(174)

Scheme 44

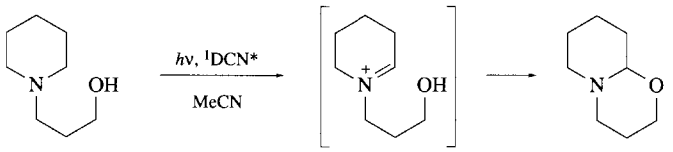
5.04.4 REACTIVITY OF PIPERIDINES

Because of their lack of double bonds, piperidines exhibit a quite different reactivity than the partially reduced pyridines. In piperidines the nitrogen atom and its α-position are the main sites for synthetic manipulation.

Piperidine chemistry has been reviewed in an excellent book ⟨B-91MI 504-01⟩. Work on the synthesis and reactions of substituted piperidines has also been evaluated ⟨92OPP585⟩. In addition to the many applications of the Polonovski–Potier reaction, another main effort during the early 1990s has been the search for new stabilizing groups for creating anions α to the nitrogen of piperidines and related quinolines.

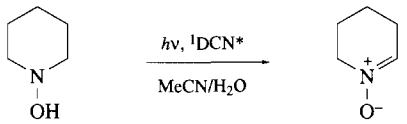
5.04.4.1 Piperidines

The Polonovski–Potier reaction is a convenient means for converting piperidines to the corresponding iminium species, which can then be trapped with cyanide ion as described above (see Scheme 3). Other new methods for preparing α-aminonitriles include substitution of 2-phenylsulfonylpiperidines ⟨91T1311⟩ (cf. Scheme 54 below) and an electro-oxidative technique ⟨94H(38)1711⟩. A photochemical oxidation method, using 1,4-dicyanonaphthalene (DCN) as the electron acceptor, is available ⟨88TL4153⟩, for example for converting (**175**) into oxazine (**176**) (Scheme 45). Previously this reaction was applied for the synthesis of nitrones (**116**) from *N*-hydroxyamines (Equation (19)) ⟨87TL2649⟩. It has been found that irradiation of (**175**) in the presence of ketones effects the same overall conversion into oxazine (**176**) ⟨94TL1715⟩.



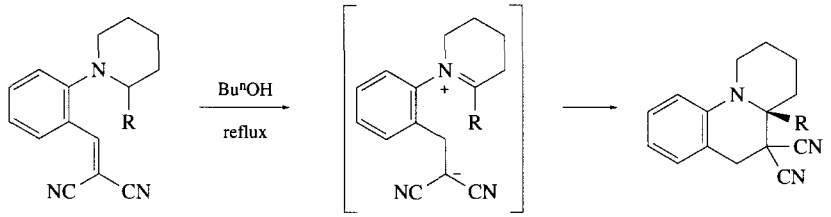
(**175**) (**176**)

Scheme 45



(**116**) (19)

An interesting formation of iminium ions proceeds through a 1,5-hydrogen transfer ⟨89JOC199⟩. In refluxing butanol the aniline derivative (**177**; R = Me) is selectively converted via the iminium intermediate (**178**) to the benzo[*c*]quinolizine (**179**) (Scheme 46). The regioselectivity is lower with a substituent (R = CH_2OCH_3) that stabilizes the iminium species less well.

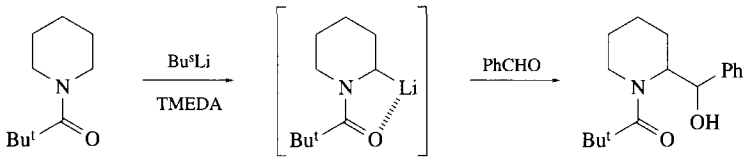


(**177**) (**178**) (**179**)

Scheme 46

Different groups at the nitrogen atom of piperidine or isoquinoline stabilize the corresponding carbanion at the 2-position of the ring. *N*-Acylpiperidines, when treated with alkyllithium reagents, form α-lithiated "dipole-stabilized" species, which react with electrophiles (Scheme 47) ⟨84JA1010⟩.

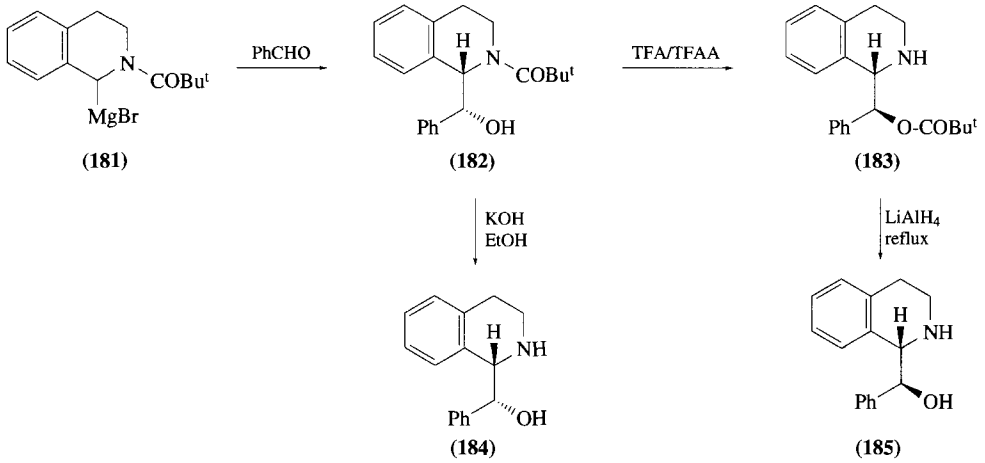
With choice of a proper acyl group, the amides, for example (**180**), can be cleaved to the corresponding secondary amines.



(**180**)

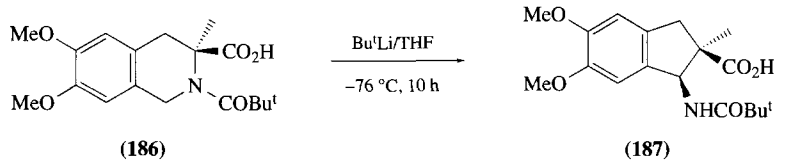
Scheme 47

Addition of magnesium bromide to lithiated 2-pivaloyl-1,2,3,4-tetrahydroisoquinoline leads to the formation of the magnesium derivative (**181**) ⟨83T1963, 84AG235, 87HCA1357⟩, the structure of which has been established by x-ray crystallography ⟨85JOM(285)1⟩. The reaction of (**181**) with aldehydes proceeds in high diastereoselectivity, for example benzaldehyde gives exclusively (**182**) (Scheme 48). The other diastereomer (**183**) can be obtained from (**182**) by heating in TFA/TFAA. This process is accompanied by *N*,*O*-acyl transfer. Reduction or saponification of the isomers gives the corresponding amino alcohols (**184**) and (**185**).



Scheme 48

An unexpected rearrangement occurred when tetrahydroisoquinoline (**186**) was lithiated and then treated with various oxidants ⟨93HCA2640⟩. Instead of the expected dimerization, lithiated tetrahydroisoquinoline (**186**) was transformed into an aminoindane (**187**) as the result of a formal 1,2-migration (Equation (20)). Finally, it was found that no oxidant was actually needed.

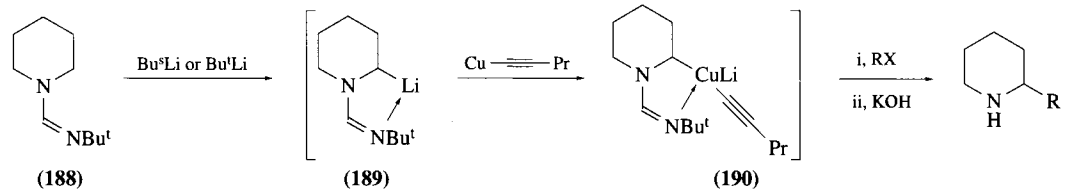


(**186**) (**187**) (20)

Use of the *t*-butoxycarbonyl moiety (*t*-BOC) appears to offer an even more convenient method for the α-lithiation of piperidines and related secondary amines ⟨89TL1197, 90JOC2578, 93JOC1109⟩ and 1,2,3,4-tetrahydroisoquinolines ⟨91JHC1769⟩. This protecting/stabilizing group is easily added and removed.

The α-metalation of piperidine and 1,2,3,4-tetrahydroquinoline as well as many other nitrogen heterocycles via the corresponding *N*-formamidines, reported for the first time in 1980 ⟨84CHEC-I(2)365⟩, has now been successfully employed in numerous applications, including asymmetric synthesis ⟨92T2589⟩. Alkylation of piperidine by this method suffered from low yields until cuprate reagents were used ⟨84JA3270⟩. Thus, formamidine (**188**) forms a lithio derivative (**189**), which

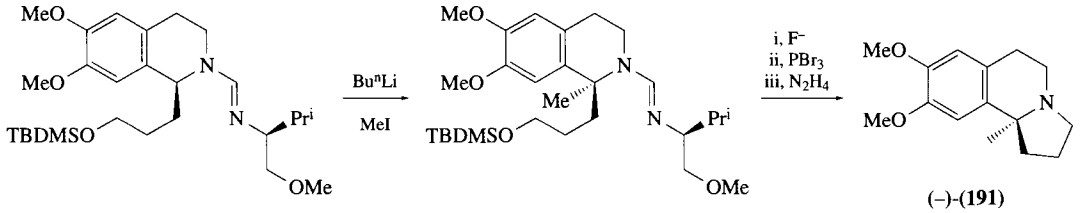
readily reacts with benzaldehyde, for example, but alkylation with alkyl halides requires initial treatment with pentynylcopper and proceeds via mixed cuprate (**190**) (Scheme 49).



(**188**) (**189**) (**190**)

Scheme 49

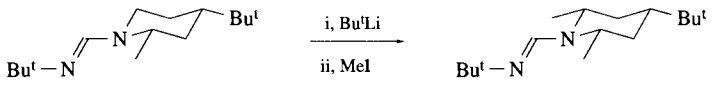
The introduction of chiral formamidines into the above process marks a notable new method of asymmetric alkylation ⟨84T1361⟩. One of the problems in this area—the asymmetric synthesis of 1,1-disubstituted tetrahydroisoquinolines—has been overcome by using a smaller-sized chiral auxiliary ⟨91TL5501⟩. An enantioselective synthesis of some medicinally important pyrroloisoquinolines, such as (−)-(**191**), serves as an example (Scheme 50).



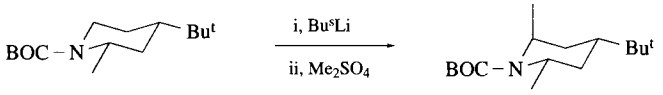
(−)-(**191**)

Scheme 50

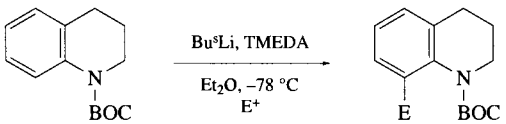
In a comparison of the formamidine (Scheme 49) and urethane methods, it was found that they produce stereochemically different products ⟨91JOC2751⟩. Thus, on alkylation, formamidine (**192**) yields the 2,6-diequatorial product (**193**), whereas the corresponding *t*-BOC-piperidine (**194**) gives (**195**), where the 6-substituent is axial (Equations (21) and (22)). The result can be explained by the different steric requirements for the two stabilizing groups. The regioselectivity of the two methods has also been studied for 1,2,3,4-tetrahydroquinolines ⟨93JOC6538⟩. The *t*-BOC-activated tetrahydroquinoline (**196**) gave exclusively the aryl ring alkylated product (**197**), while the formamidine (**198**) gave only the C-2 alkylated compound (**199**) (Equations (23) and (24)). Interestingly, when the aryl *ortho* position of (**196**) was deliberately blocked metalation at C-2 was observed.



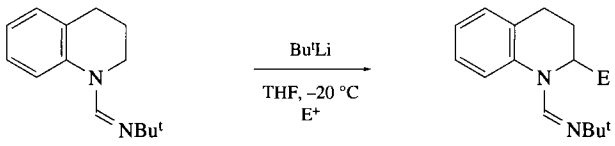
(**192**) (**193**) (21)



(**194**) (**195**) (22)

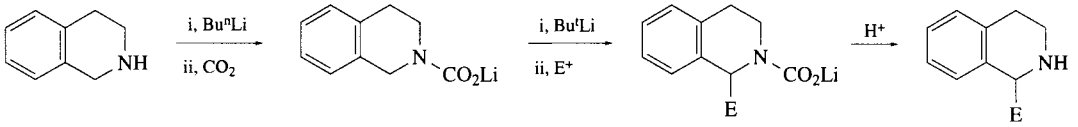


(**196**) (**197**) (23)



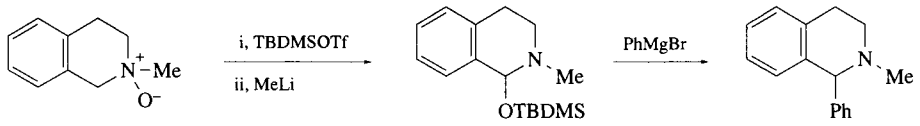
(**198**) (**199**) (24)

In one more method of α-alkylation, employed in the tetrahydroisoquinoline series, carbon dioxide is used both to create the activating group and to protect the secondary amino group ⟨86T2571⟩. A general example of this simple method is depicted in Scheme 51.



Scheme 51

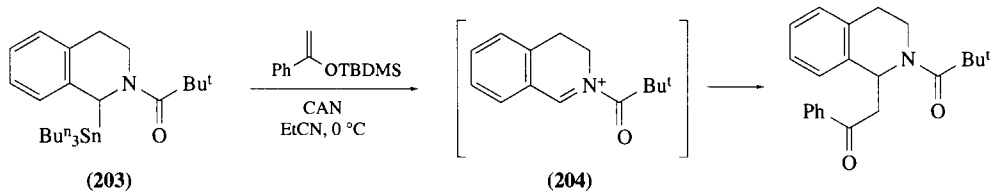
A nucleophilic method of α-alkylation, where α-silyloxyamines are reacted with Grignard reagents, gives reasonable yields in the tetrahydroisoquinoline series ⟨84TL4677⟩. Thus, the *N*-oxide of *N*-methyl-1,2,3,4-tetrahydroisoquinoline (**200**) is first treated with *t*-butyldimethylsilyl trifluoromethanesulfonate and then with methyllithium to give the α-silyloxyamine (**201**). The reaction of (**201**) with a Grignard reagent, for example phenylmagnesium bromide, gives the alkylated product (**202**) (Scheme 52). With *N*-substituted piperidine *N*-oxides alkylation takes place at the nitrogen alkyl group. Similar results are obtained when a peroxy group is used instead of the above silyloxy moiety ⟨90TL7475⟩. To obtain the peroxides, the amino group has to be acylated prior to the ruthenium-catalyzed oxidation with *t*-butyl hydroperoxide.



(**200**) (**201**) (**202**)

Scheme 52

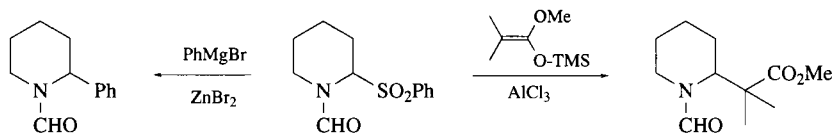
Oxidation of 2-pivaloyl-1-tributylstannyl-1,2,3,4-tetrahydroisoquinoline (**203**) with some metallic oxidants followed by treatment with nucleophiles gives 1-substituted products ⟨93CL125⟩. The reaction can be assumed to proceed via either an acyliminium species or a carbon radical, the former of which (**204**) is presumed to be the reactive intermediate in this case. The reaction of (**203**) with a silyl enol ether of acetophenone is depicted in Scheme 53.



(**203**) (**204**)

Scheme 53

Another route to α-substituted piperidines (and pyrrolidines) is the reaction of *N*-acylated 2-benzenesulfonylpiperidines with nucleophiles (e.g. organozinc reagents and silyl enol ethers) ⟨90SL48⟩. The starting piperidines, such as (**205**), are available from the corresponding 2-methoxypiperidines. Performing the substitution in dichloromethane allows the use of alkyl organometallic reagents ⟨90SL749, 91T1311⟩. Two examples of this method are shown in Scheme 54.

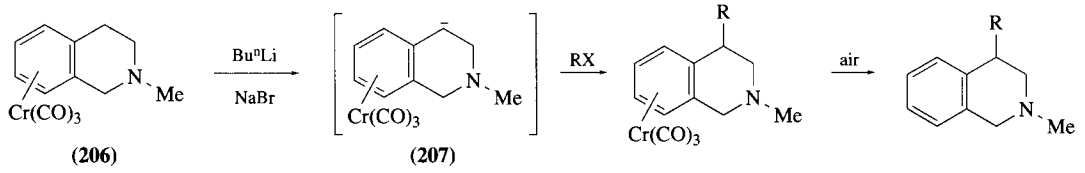


(**205**)

Scheme 54

The use of tricarbonylchromium complexes permits the substitution of 1,2,3,4-tetrahydroisoquinolines at the 4-position ⟨85CC619, 86JCS(P1)2257⟩. The method is based on the observation that this kind of complex stabilizes the benzylic carbanion. Complex (**206**), prepared from *N*-methyl-1,2,3,4-tetrahydroisoquinoline, gives anion (**207**) when treated with BunLi. This reacts with alkyl halides to form, after decomplexation, 4-substituted products in good yield and high stereoselectivity

(Scheme 55). The reaction of (**207**) with carbonyl compounds will take place, but requires special techniques.



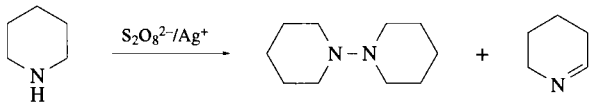
(**206**) (**207**)

Scheme 55

The first example of α-alkylation of piperidines without stabilizing groups has been reported ⟨93JA7515⟩. The approach is based on Sn–Li exchange, which had earlier met with difficulties in acyclic compounds ⟨93TL51⟩.

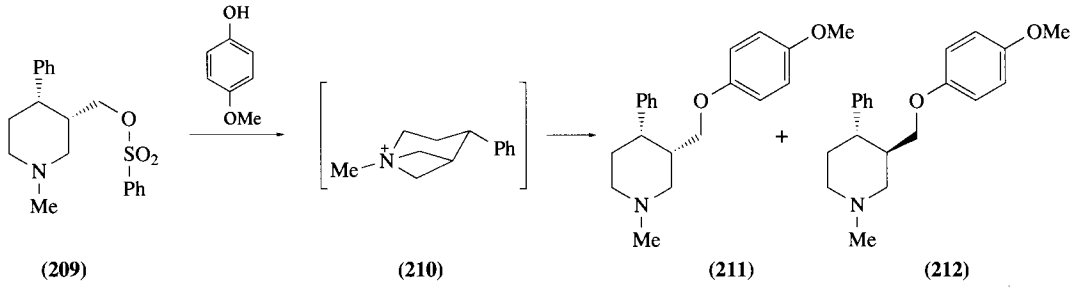
Additionally, the α-alkylation of piperidine can be achieved via piperidinooxazolines ⟨89JOC175⟩ and oxazolidines ⟨91TL1443⟩. Photo-induced electron transfer (PET) is one of the novel carbon–carbon bond-forming techniques, which has been applied in the α-allylation of tertiary amines, including *N*-alkylated piperidine and tetrahydroisoquinoline ⟨92TL5107⟩.

Silver(I)-catalyzed oxidation of unsubstituted piperidines gives the 1,1′-bipiperidine (**208**) in addition to a small amount of 2,3,4,5-tetrahydropyridine (**6**), as indicated by vapor pressure chromatography ⟨82JCS(P1)3031⟩. A methyl substituent in (**9**), especially at the 2-position, increases the amount of the imine product (Equation (25)).



(**9**) (**208**) (**6**) (25)

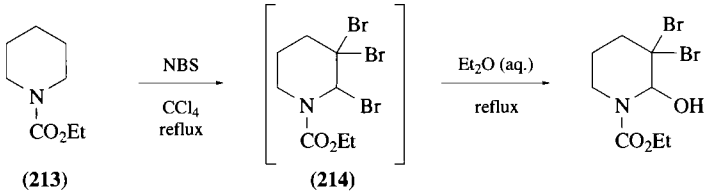
A new bicyclic system (**210**) has been reported as an intermediate when the *cis*-piperidine (**209**) is subjected to a substitution reaction ⟨83TL5151⟩. Reaction of (**209**) with *p*-methoxyphenol gives a 15:85 mixture of *cis*- and *trans*-isomers (**211**) and (**212**), whereas the pure *trans*-isomer of (**209**) gives exclusively the *trans*-compound (**212**) (Scheme 56). Evidence for intermediate (**210**) was obtained from ^{13}C-enrichment experiments. A compound of type (**210**) has been postulated to be an intermediate in essentially the same kind of substitution reaction ⟨92T9753⟩.



(**209**) (**210**) (**211**) (**212**)

Scheme 56

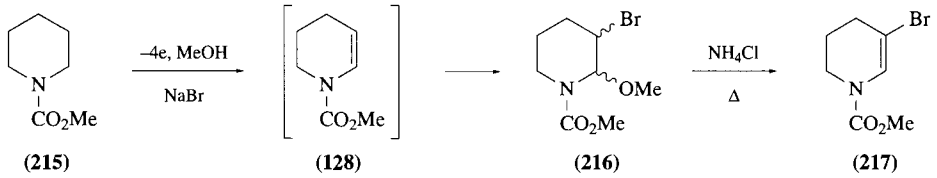
Reinvestigation of a very old observation, the reaction of *N*-ethoxycarbonylpiperidine (**213**) with *N*-bromosuccinimide (NBS), has revealed that the product is the 2,3,3-tribromo derivative (**214**) ⟨84G83⟩. The reaction probably starts with radical bromination at the 2-position, which explains the 2-hydroxy products obtained after hydrolysis (Scheme 57).



(**213**) (**214**)

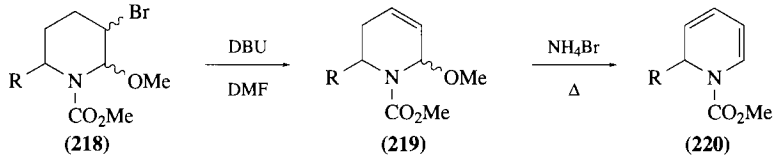
Scheme 57

Electrochemical oxidation of *N*-methoxycarbonylpiperidines offers an access to some specific 2,3-disubstituted piperidines (the method works with pyrrolidines as well) ⟨87JOC536⟩. As an example, anodic oxidation of (**215**) in methanol containing NaBr gives the disubstituted product (**216**), probably via enamine (**128**). Subsequent elimination affords 5-bromo-1,2,3,4-tetrahydropyridine (**217**) (Scheme 58).



Scheme 58

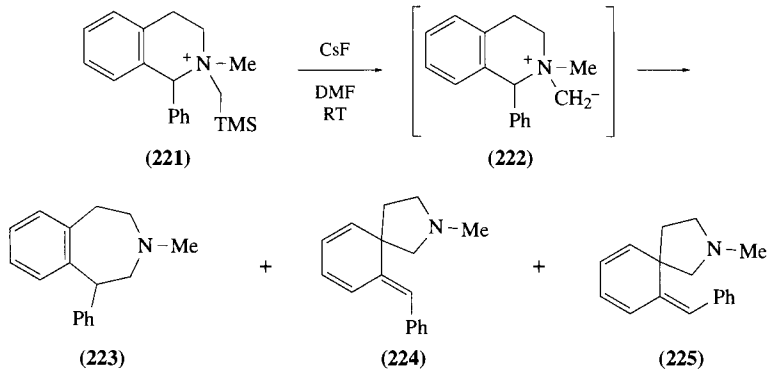
Intermediates of type (**216**) have proven to be valuable synthetic intermediates ⟨87TL4073⟩. Treatment of (**218**) with base, for example, leads to tetrahydropyridine (**219**), which after elimination of methanol gives dihydropyridine (**220**) (Scheme 59). 2-Substituted piperidines can thus be regioselectively converted into the 2-substituted 1,2-dihydropyridines. Another study of electrochemical oxidation of piperidines has presented some additional elimination reactions of compounds of type (**218**) ⟨87S242⟩. Furthermore, a method to prepare 3-acetonyl-1,2,3,4-tetrahydropyridines via compounds of type (**218**) has been achieved ⟨87CL1553⟩.



Scheme 59

The reaction of (**218**) with active methylene compounds leads first to 2-substituted piperidines, which are rearranged to 3-substituted products under base catalysis ⟨87CL1447⟩. This application has found use in the synthesis of an intermediate for the indole alkaloid eburnamonine. Furthermore, the methoxy group in compound (**218**) can be substituted with an aryl group, which by treatment with silver nitrate migrates from the α-position to the β-position ⟨93T8503⟩.

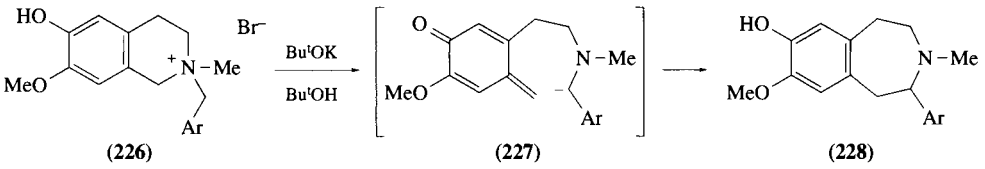
Interesting rearrangements occur with certain 1-phenylsubstituted tetrahydroisoquinolinium ylides ⟨92JOC6711⟩. When a mixture of isomers (**221**) is treated with cesium fluoride to produce the ylide (**222**), three products are obtained via a radical mechanism: benzazepine (**223**) as the major product and the two spirocyclic pyrrolidines (**223**) and (**224**) (Scheme 60).



Scheme 60

The base-catalyzed rearrangement of certain tetrahydroisoquinolinium salts leads to the formation of the pharmacologically important 3-benzazepine skeleton ⟨84JOC581⟩. Starting from the 6-hydroxy-substituted salt (**226**) the reaction proceeds via quinone methide (**227**) to yield benza-

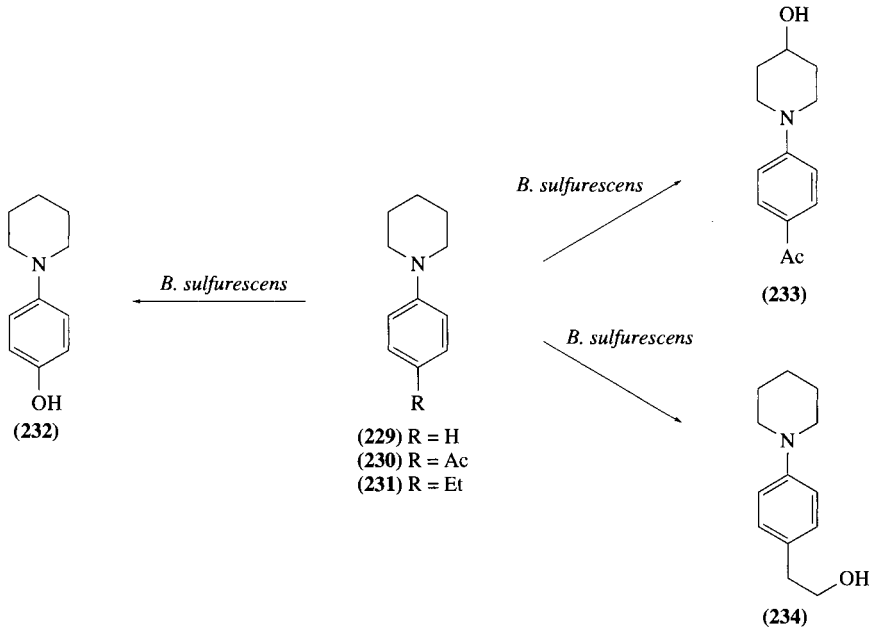
zepine (**228**) in good yield (Scheme 61). Experiments with a 6-methoxy derivative excluded a Stevens-type mechanism since different kinds of products were formed.



(226) (227) (228)

Scheme 61

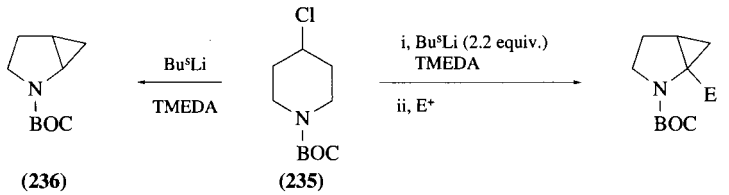
A number of biotransformations worthy of notice have been reported. Several substituted *N*-phenylpiperidines have been treated with *Beauveria sulfurescens* ATCC 7159, a common microbiological oxidant ⟨93JCS(P1)881⟩. *N*-Phenylpiperidine (**229**) is oxidized by *B. sulfurescens* to phenol (**232**), but when electron-withdrawing substituents are present at the *para* position, the products are oxidized in the heterocyclic ring, for example, (**230**) gives (**233**) in 66% yield (Scheme 62). *N*-(4-Ethylphenyl)piperidine (**231**) is converted to the primary alcohol (**234**), but the reaction is less selective when the position of the substituent is changed.



(232) (229) R = H (230) R = Ac (231) R = Et (233) (234)

Scheme 62

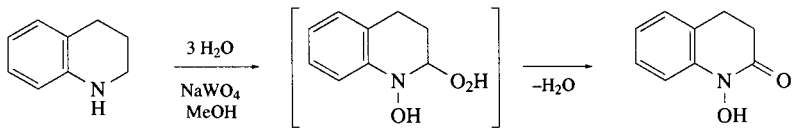
Intramolecular alkylation of *N*-*t*-BOC-4-chloropiperidine (**235**) leads to the 2-azabicyclo-[3.1.0]hexane ring system ⟨94JOC276⟩. Treating (**235**) with base yields the bicyclic product (**236**) where the cyclopropyl proton α to nitrogen can be removed and substituted with electrophiles (Scheme 63).



(236) (235)

Scheme 63

Oxidation of 1,2,3,4-tetrahydroquinolines with hydrogen peroxide and a tungsten catalyst furnishes the corresponding hydroxamic acids ⟨87CC1471⟩. This reaction is believed to proceed via the intermediacy of hydroperoxide (**237**) (Scheme 64).



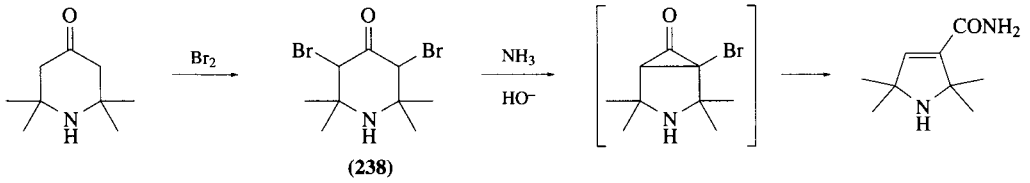
(237)

Scheme 64

5.04.4.2 Piperidones

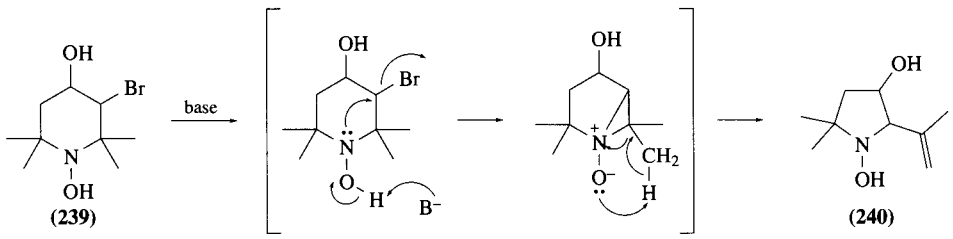
A typical application illustrating the reactivity of 2-piperidones at the lactam carbonyl is the reaction with Meldrum's acid to give β-enaminoesters ⟨83S195⟩, aminomethyleneketenes ⟨87TL885⟩, and tetrahydroindolizines ⟨88JOC5680⟩. The reaction with alkynylboranes yields alkynylpiperidines ⟨83TL1719⟩.

3,5-Dibromo-2,2,6,6-tetramethyl-4-piperidone (**238**) undergoes ring contraction by Favorskii rearrangement when treated consecutively with aqueous ammonia and NaOH ⟨83MI 504-01⟩ (Scheme 65). Treatment of the 3-bromo-1,4-dihydroxypiperidine (**239**) with alcoholic KOH or Et_3N in $CHCl_3$ results in rearrangement with ring contraction to give the pyrrolidine (**240**) ⟨87IZV1582⟩. This process probably involves nucleophilic attack of the nitrogen lone pair at C-3 to generate a 1-azabicyclo[3.1.0]hexane intermediate followed by a Cope rearrangement (Scheme 66). Intermediates of this type have even been isolated. Treatment of the 4-piperidone (**241**) with base, for example, generates the bicyclic compound (**242**) via an intramolecular nucleophilic substitution ⟨87IZV1685⟩ (Scheme 67).



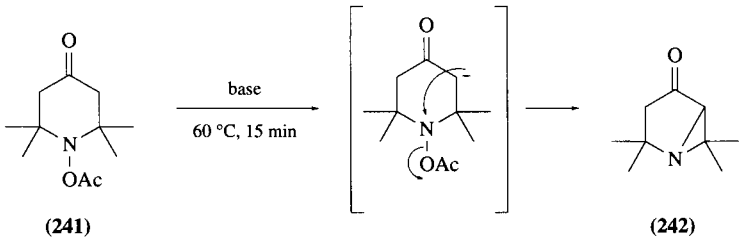
(238)

Scheme 65



(239) (240)

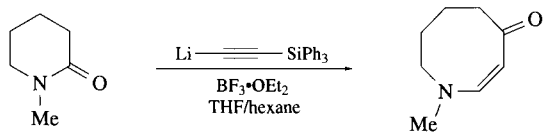
Scheme 66



(241) (242)

Scheme 67

A two-carbon ring expansion takes place when lactams are treated with lithium triphenylsilylacetylide ⟨87JOC2929⟩. Thus, the eight-ring enaminone (**244**) is formed in 42% yield from *N*-methyl-2-piperidone (**243**) (Equation (26)).



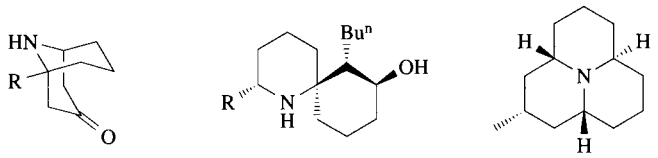
(243) (244) (26)

5.04.5 IMPORTANT COMPOUNDS AND APPLICATIONS

This section reports on a few applications of reduced pyridines since the mid-1980s. Two groups of compounds are discussed: alkaloids and other important compounds. Ways in which the reactivity of reduced pyridines can be exploited have been reviewed in publications dealing with pyridine and piperidine alkaloids ⟨B-85MI 504-01, B-85MI 504-02⟩, indolizine alkaloids ⟨B-93MI 504-01⟩, and alkaloid synthesis via iminium ions and α-aminocarbanions ⟨B-88MI 504-02⟩.

5.04.5.1 Alkaloids

Many piperidine alkaloids have significant pharmacological properties and therefore they are typical targets in the exploitation of new synthetic techniques. Of the procedures described above the CN(R,S) method (see Scheme 17) permits the preparation of several alkaloids, including (−)-euphococcinine (**245**) and (−)-adaline (**246**) ⟨92JOC4211⟩, derivatives and precursors of perhydrohistrionicotoxin (**247**) ⟨91TL2485, 93JOC6451⟩, and precoccinelline (**248**) ⟨94T3139⟩.

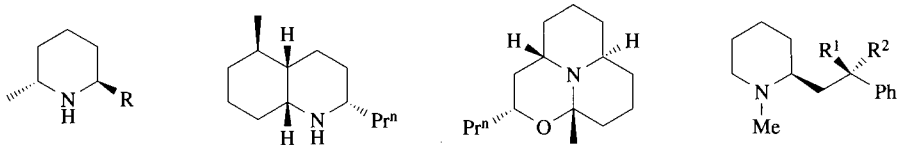


(**245**) R = Me
(**246**) R = C_5H_{11}

(**246**) R = C_5H_{11} (**248**)

The ant venom solenopsin A (**249**), possessing a challenging 2,6-*trans*-dialkylpiperidine structure, has been a favorite target for studies on the asymmetric alkylation of piperidines. It was prepared by the *N*-acyldihydro-4-pyridone methodology (see Scheme 41) ⟨94TL829⟩. Other alkaloids that have been synthesized by this method include (−)-pumiliotoxin C (**250**) ⟨93CC1838⟩, (−)-porantheridine (**251**) ⟨93JA8851⟩, and (−)-sedamine (**252**) ⟨93JOC5035⟩. The formamidine method (see Schemes 49 and 50 above) is another approach to a number of alkaloids, for example (−)-pumiliotoxin C ⟨93JA6652⟩ and isoquinoline alkaloids ⟨92T2589⟩.

Cycloaddition of chiral nitrones (see Scheme 29 above) leads to a variety of alkaloid structures, of which may be mentioned the diastereo- and enantiocontrolled synthesis of (−)-allosedamine (**253**) ⟨94HCA554⟩.



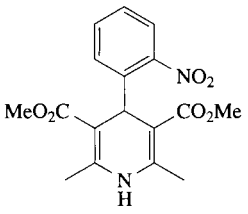
(**249**) R = $(CH_2)_{10}Me$ (**250**) (**251**)

(**252**) R^1 = H, R^2 = OH
(**253**) R^1 = OH, R^2 = H

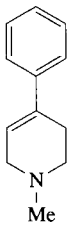
5.04.5.2 Other Important Reduced Pyridines

Several dihydropyridines are important compounds in pharmacology. Since the discovery of the calcium-channel antagonist nifedipine (**254**) in 1971, several other compounds of related 1,4-dihydropyridine structure have been prepared and investigated. An on-line search of *Chemical Abstracts* for nifedipine itself, not including its pharmacological derivatives, affords about 4000 entries which may give some idea of the extent of this research. Being dihydropyridines of Hantzsch-type, investigation of the chemical behavior and reactivity of these compounds has a long history.

One of the most studied tetrahydropyridines is *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (**255**), which is a potent Parkinsonism-inducing neurotoxin ⟨83PNA(80)4546, 84PNA(81)4591⟩.



(254)



(255)

Nor can one forget the enormous amount of work that has been—and still is being—carried out on NADH systems and models, but a detailed evaluation of this area goes beyond the scope of this work.

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5.05
Pyridines and their Benzo Derivatives: Synthesis

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5.05.1 INTRODUCTION

In the introduction to the corresponding section in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨84CHEC-I(2)395⟩ the enormous range of synthesis available for pyridines and their benzologues was reported. Reference should again be made to books which list the synthetic pathways to pyridines ⟨60HC(14-1)99, 74HC(14(Suppl. 1)224⟩, for quinolines ⟨77HC(32(1))93⟩, and for

isoquinolines ⟨81HC(38(1))139⟩. Polycycles have also been dealt with in books: acridines ⟨B-66MI 505-01, 73HC(9)141⟩, phenanthridines ⟨B-52MI 505-01⟩ benzoquinolines ⟨B-52MI 505-02⟩, and "azachrysenes" ⟨81JHC207⟩. Remarkably, there have been no new books on the synthesis of the specific heterocycles covered here; reviews on specific methods appear under the appropriate section (e.g. a review on azadienes in Section 5.05.2.2 describing synthesis with formation of two bonds). There are reviews which give syntheses of classes of compound, such as pyridines ⟨91HOU(E7a-2)286⟩, dihydropyridines ⟨82CR223, 88H(27)269, 92CHE363⟩, piperidines ⟨83CRV379, 84S895⟩, 3-nitropyridines ⟨91CHE681⟩, nitroazines ⟨85CHE113⟩, quinolines and quinoline *N*-oxides ⟨91HOU(E7a-1)290, 91HOU(E7a-1)493⟩, isoquinolines and isoquinoline *N*-oxides ⟨91HOU(E7a-1)571, 91HOU(E7a-1)741⟩, compounds containing quinoline and isoquinoline units ⟨91H(32)759⟩, acridines ⟨91HOU(E7a-2)115⟩, phenanthridines ⟨91HOU(E7a-2)157⟩, of condensed heteroaromatic compounds using palladium catalysts ⟨88H(27)2225⟩, and of various cyclizations including formation of pyridines, quinolines, and other systems ⟨90T1385, 90T3321⟩.

The emphasis in the present review is on syntheses published since the mid-1980s, with reference, where possible, to the principal classical syntheses, particularly if there have been improvements in technique or clarification of mechanisms. The syntheses are first discussed in an order related to the number of bonds made in forming the ring, starting from nonheterocyclic fragments, after which ring transformations are described.

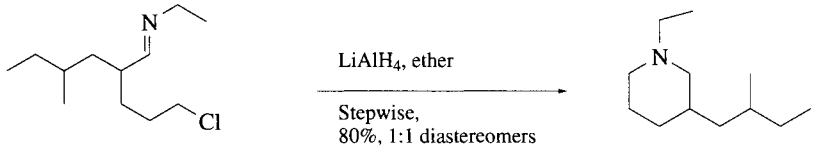
5.05.2 RING SYNTHESIS FROM NON-HETEROCYCLIC COMPOUNDS

5.05.2.1 Formation of One Bond

5.05.2.1.1 Bond formation adjacent to nitrogen

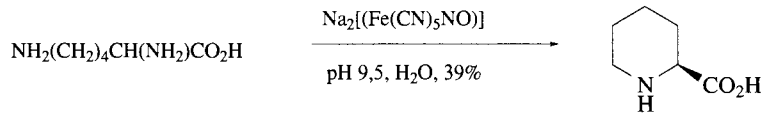
Syntheses start with those giving saturated rings and proceed through those for partially unsaturated rings to fully unsaturated. Within classes the cyclizations are grouped by mechanism. Lactams are classed as tetrahydro derivatives, exocyclic double bonds are discounted (exomethylene piperidines will be found with piperidines). The emphasis with hydrogenated derivatives will be on stereospecificity.

The oldest piperidine syntheses involved the displacement of a good leaving group by the nucleophilic nitrogen atom. Variants on this involve the use of imine reduction to generate the saturated nitrogen, as in the synthesis of stenusine (**1**) (Equation (1)) ⟨93JOC132⟩, of disodium nitrosopentacyanoferrate to cyclize lysine to L-pipecolic acid (**2**) (Equation (2)) ⟨82S163⟩, and the Mitsunobu reaction to cyclize aminoalcohols (**3**), producing *cis*/*trans* mixtures of piperidines without great stereoselectivity (Equation (3)) ⟨93TL3223⟩. Other sources of the nucleophilic nitrogen are oximes ⟨89H(28)813⟩, aziridines opened by nucleophiles ⟨89JOC5324⟩, oxazolines with catalytic camphor-10-sulfonic acid ⟨91TL4159⟩, and oxiranes (opened by benzylamine to give an *N*-benzylpiperidine) ⟨89TL6077⟩. The nucleophilicity of the nitrogen can be enhanced if the anion is used; addition of nucleophiles to imines has led to substituted piperidines (**3a**) in very good yields (Equation (4)) ⟨89T3907⟩. Anodic oxidation of a protected lysine ester gave the methoxypipecolate (**4**) with complete retention of chirality (Equation (5)) ⟨83CC1169⟩.



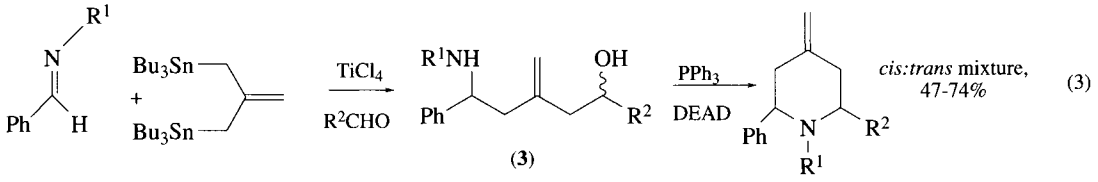
(1)

(1)



(2)

(2)



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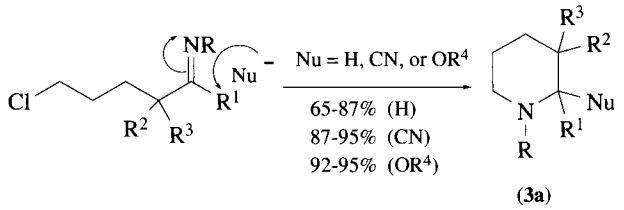
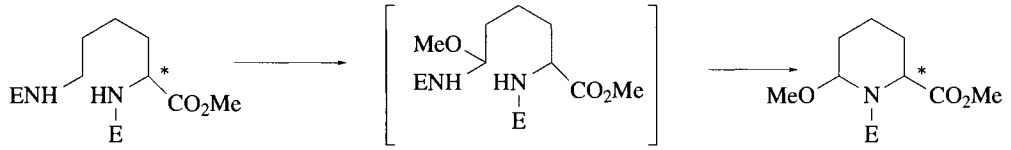


(3a)

(4)

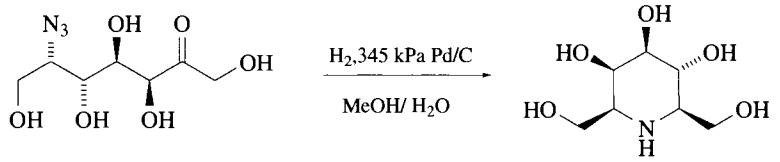


E = CO_2Me

(4) 47%, 100% *ee*

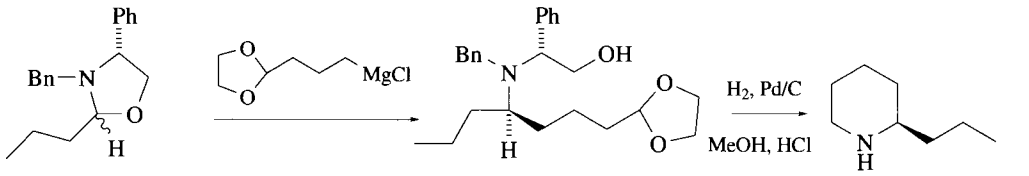
(5)

The nucleophilic nitrogen atom can also be used to attack a suitably placed carbonyl group. Aldehydes or ketones give piperidines under reducing conditions; examples of a concealed amino group (as azide), and of a protected amine and protected aldehyde are provided by the synthesis of piperidines (**5**) (Equation (6)) ⟨94TL359⟩, (*R*)-(−)-coniine (**6**) (Scheme 1) ⟨92H(33)17⟩, the sugar-derived (**7**) (Equation (7)) ⟨92T727⟩, and the use of double protection to allow the synthesis of piperidines (**8**) and (**9**) from a single precursor (Scheme 2) ⟨84JOC2948⟩.



(5) 94%, one diastereomer

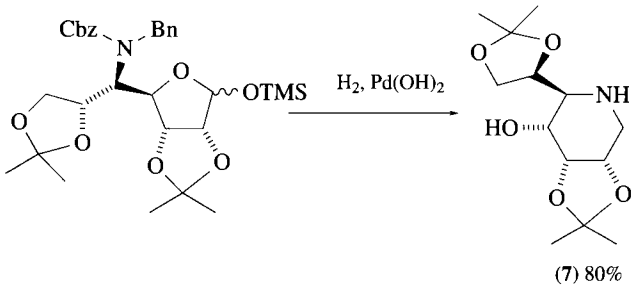
(6)



84%, one diastereomer

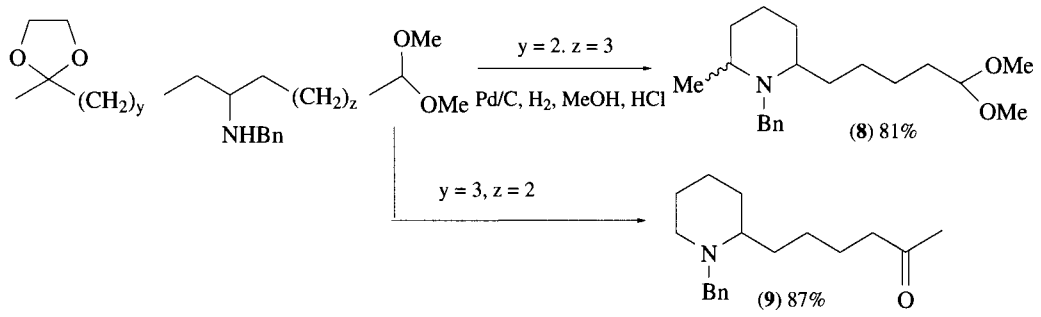
(6) (*R*)-(-) coniine, 90%

Scheme 1



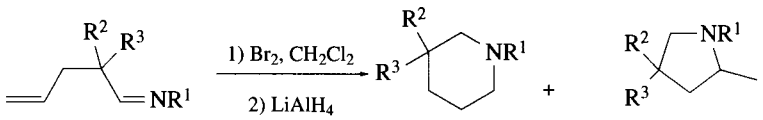
(7) 80%

(7)



Scheme 2

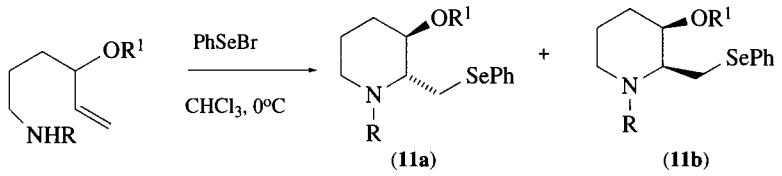
Initiation of cyclization by electrophilic attack on a double bond has been reviewed ⟨85CHE359, 86CRV857⟩ and can give useful *cis/trans* selectivity for disubstituted piperidines. Examples are shown where the initiation is by bromine to give piperidines (**10**) preferentially over pyrrolidines (Equation (8)) ⟨94TL1925⟩, by phenylselenyl bromide to give 2,3-disubstituted piperidines (**11a**) and (**11b**) (Equation (9)) ⟨94TL5065⟩, by mercuric acetate or trifluoroacetate to give piperidines (**12**) (Equation (10)) ⟨80TL75⟩ and (**13**) (Equation (11)) ⟨84JOC2838⟩, and by silver ions, where attack on suitably placed allenes produces piperidines with unsaturated side chains such as (**14**) (Equation (12)) ⟨83TL3997⟩ and (**15a**) and (**15b**) (Equation (13)) ⟨85TL729⟩. It is worth noting that the mercury substituents can be converted into alcohols or removed by reduction, while phenylselenyl residues can also be converted into alcohols.



(8)

(**10**) 74-95% 3-8%

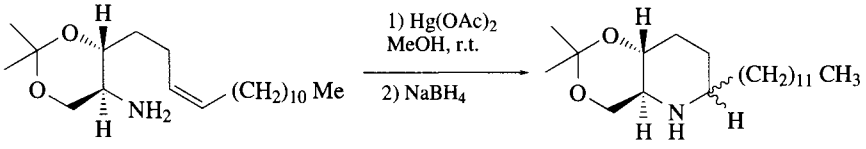
R^1, R^2, R^3 = various alkyl groups



(9)

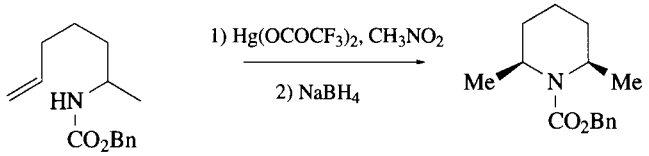
(**11a**) (**11b**)

27-68% yield; 11a / 11b ratios from 3:1 to 5:1



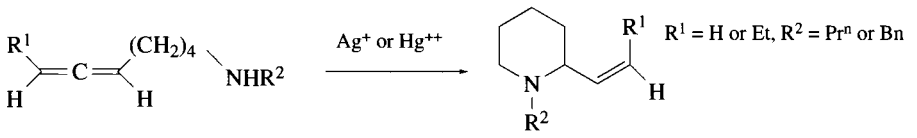
(10)

(**12**) 8αH, 4%; 8βH, 85%



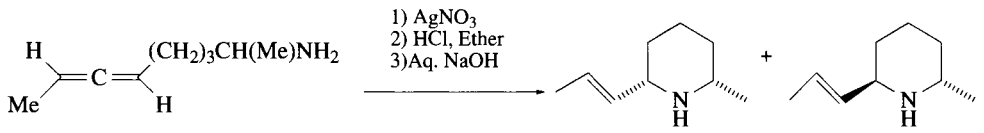
(11)

(**13**) 93% (less than 2% trans)



(12)

(**14**) 76-95% with Ag (35-55% with Hg)

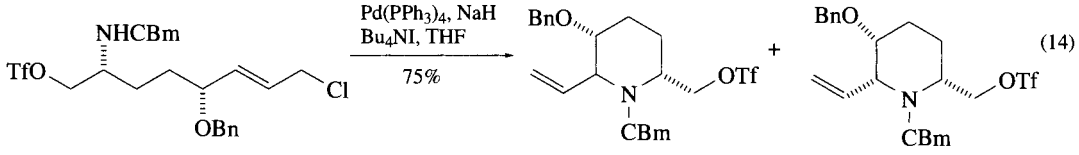


(13)

(**15a**) (**15b**)

95%, a:b = 62:38

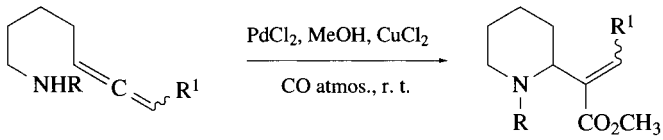
Various transition metal catalysts have also been used to initiate cyclization of an amino group on to a double bond. The yields are, on the whole, not comparable with those obtained in the above electrophile-induced cyclizations, but the three examples given (others are in the Section 5.05.2.1.3 on dihydropyridines) illustrate one case with high stereoselectivity giving piperidines (**16a**) and (**16b**) (Equation (14)) ⟨94T5681⟩ and two which involve both cyclization and functionalization in the synthesis of compounds (**17**) (Equation (15)) ⟨86TL6009⟩ and (**18**) (Equation (16)) ⟨92TL6835⟩.



(14)

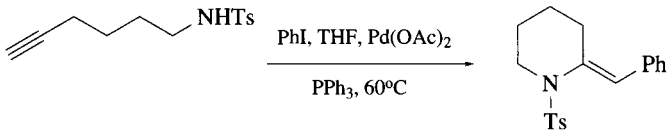
CBm = Carboxymethyl

(**16a**) (**16b**) a:b ratio = 12:1



(15)

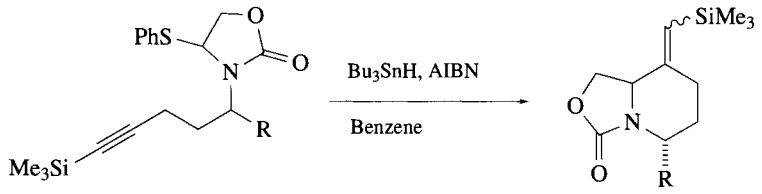
(**17**) Various R, R1 = H, Me, 20-52%



(16)

(**18**) 58%

Highly functionalized piperidines (**19**) have been synthesized by a radical route (Equation (17)) ⟨90H(30)263⟩.

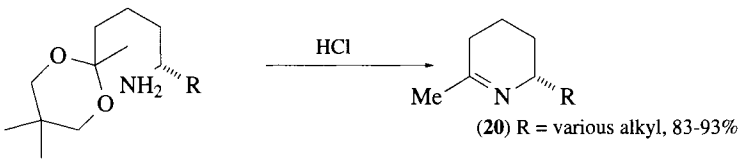


(17)

(**19**) R = Me, 72%, Prn, 70%

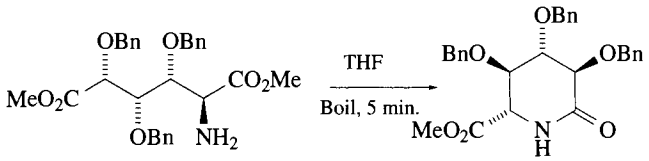
Tetrahydropyridines and tetrahydropyridones can be obtained by cyclization between an amine and aldehyde or a ketone or ester, respectively. Examples are provided by tetrahydropyridines

(**20**) (Equation (18)) ⟨87JOC4274⟩ and the tetrahydropyridone (**21**) (Equation (19)) ⟨94TL4869⟩. An intramolecular Michael addition gives mixtures of tetrahydropyridines (**22**) and (**23**) (Equation (20)) ⟨89T239⟩, while the azides (**24**) are converted, via intermediate phosphinimines, into the pyridone (**25**), or from (**24**; R = CO_2Me) into the tetrahydropyridine (**26**) Scheme 3 ⟨93JOC6097⟩.



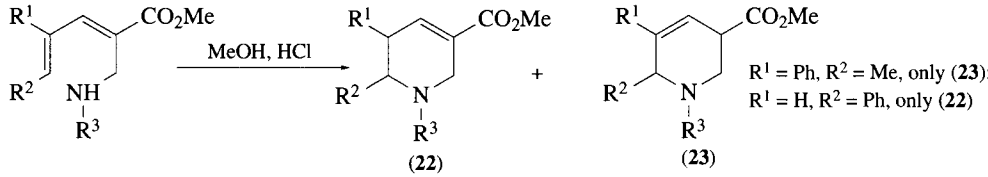
(**20**) R = various alkyl, 83-93%

(18)



(**21**) 100%

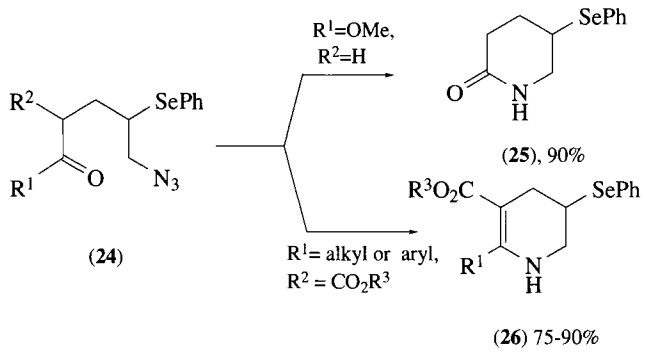
(19)



(**22**)

(**23**)

(20)



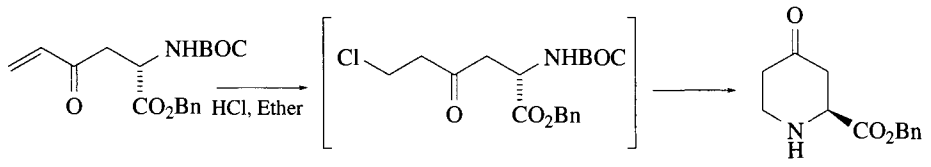
(**24**)

(**25**), 90%

(**26**) 75-90%

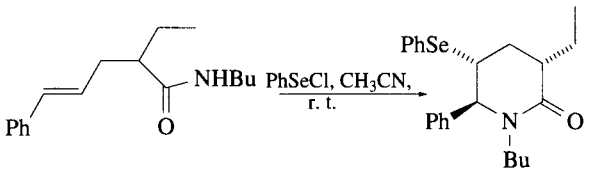
Scheme 3

The synthesis of the 4-oxopipecolate (**27**) is achieved by electrophilic addition of hydrogen chloride followed by nucleophilic displacement of chloride, with an *ee* of 100% (Equation (21)) ⟨94TL4417⟩. Phenylselenyl chloride initiates cyclization to an amide group, giving high yields of single stereoisomers, as shown for piperidinone (**28**) (Equation (22)) ⟨87JOC2018⟩. Sodium aurichloride produces quantitative yields of the exomethylene piperidines (**29**) at room temperature from aminoalkynes (Equation (23)) ⟨87H(25)297⟩, and the piperidines (**29**) are isomerized to 3,4,5,6-tetrahydropyridines at their boiling point. Mercuric acetate-induced cyclization gives a high yield of tetrahydroquinolines (**30**) from 2-(2-propen-1-yl)anilines (Equation (24)) ⟨91AJC1749⟩.



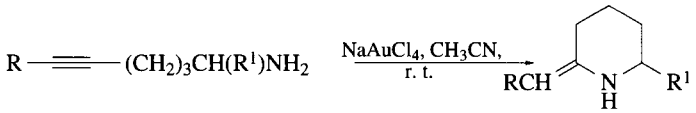
(**27**)

(21)



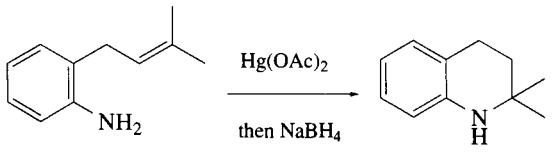
(22)

(**28**), 73%, single stereoisomer



(23)

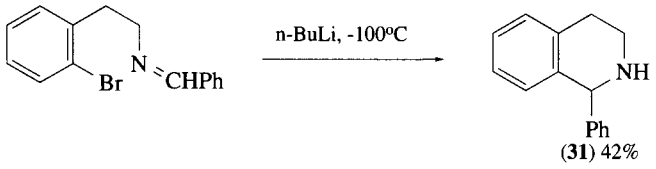
(**29**), 100%, R = n-C_6H_{13} or n-C_5H_{11}
R^1 = H or Me



(24)

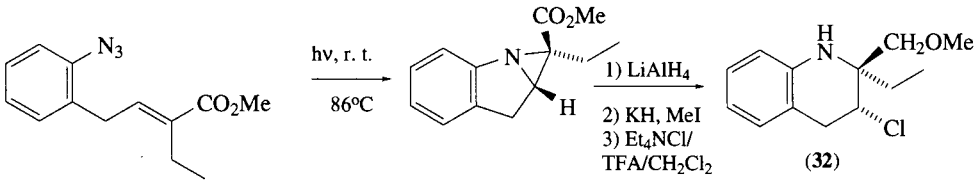
(**30**), 88%

Cyclization via halogen–metal exchange gives tetrahydroisoquinoline (**31**) (Equation (25)) ⟨81JOC327⟩, and the tetrahydroquinoline (**32**) is formed via a nitrene and an intermediate aziridine (Equation (26)) ⟨90TL6031⟩.



(25)

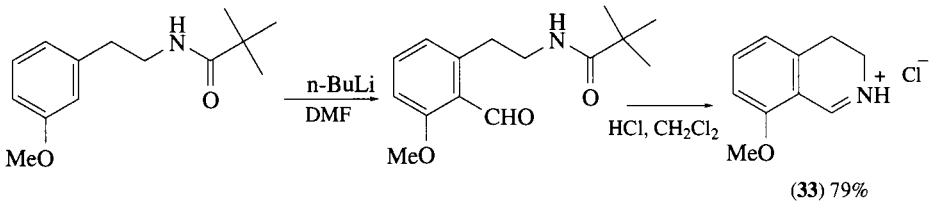
(**31**) 42%



(26)

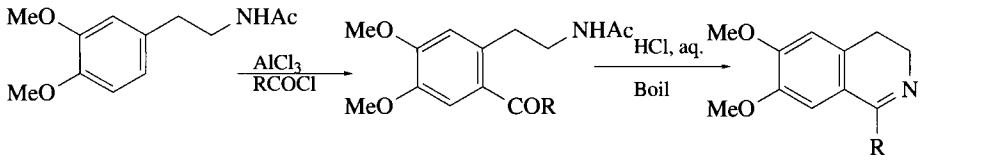
(**32**)

If dihydropyridines, -quinolines, and -isoquinolines are to be made by cyclization of amino to carbonyl groups, the second unit of unsaturation should be inert, as in a benzene ring. Two approaches to dihydroisoquinolines (**33**) (Scheme 4) ⟨91TL1965⟩ and (**34**) (Scheme 5) ⟨88H(27)2403⟩ illustrate alternative routes to introduce the carbonyl group. The use of a chiral auxiliary allows cyclization with high enantiomeric excess; examples shown are 2,3-dihydro-4-pyridones (**35**) (Equation (27)) ⟨89AG(E)1067⟩ and 1,4-dihydropyridines (**36**) (Equation (28)) ⟨88TL6437⟩. Acid- and base-catalyzed cyclizations have produced dihydro-4-quinolinones (**37**) and (**38**) from similar precursors (Scheme 6) ⟨90JOC1757⟩.



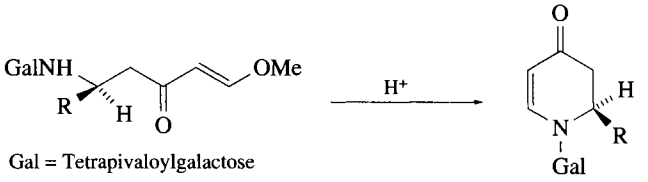
(**33**) 79%

Scheme 4



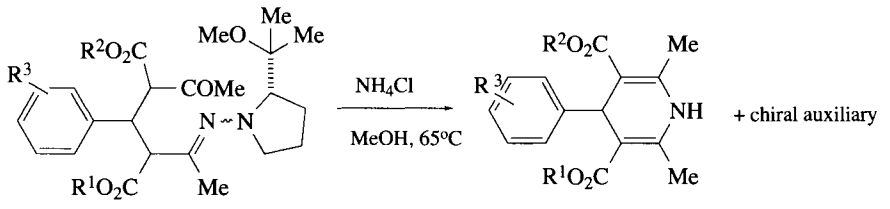
(**34**) R = alkyl, aryl;90-97%

Scheme 5

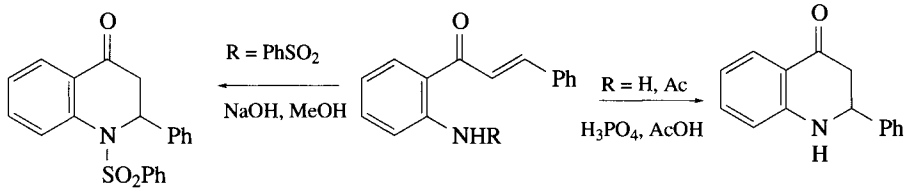


Gal = Tetrapivaloylgalactose

(**35**) R = alkyl, aryl, all [*S*]; 90-96%, 92-96%*ee* (27)



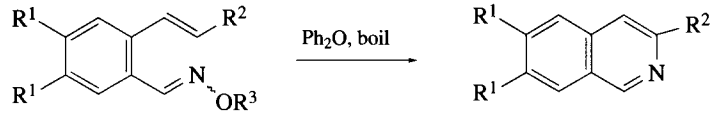
(**36**) 64-72%, 84-98%*ee* (28)



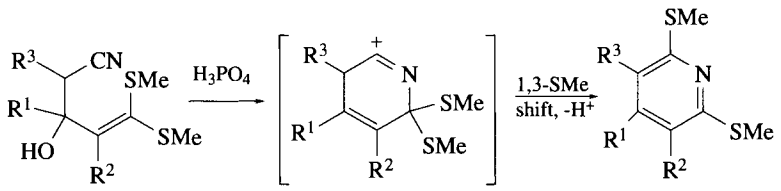
(**37**) (**38**)

Scheme 6

Concerted electrocyclic reactions can give fully aromatic pyridines if the intermediate dihydro species can eliminate H_2O or MeOH as in examples (**39**) (Equation (29)) ⟨89H(28)275⟩, (**40**) (Scheme 7) ⟨90T2561⟩, and (**41**) (Scheme 8) ⟨89T3131⟩. The cyclization of amino groups to carbonyl groups requires an unsaturated substrate or a leaving group if the final product is to be aromatic. Examples showing the synthesis of pyridine rings in polycyclic systems are provided by the compound (**42**) (Scheme 9) ⟨93S290⟩ and the benzo[*h*]quinoline (**43**) (Equation (30)) ⟨92H(33)585⟩.

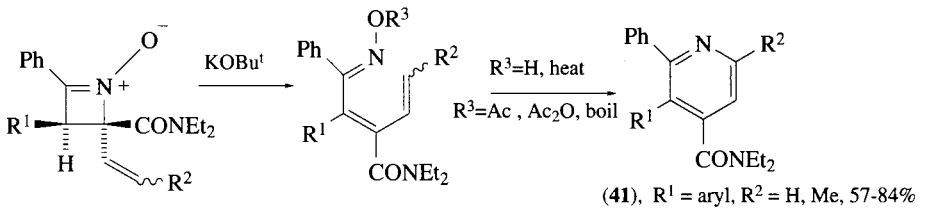


(**39**) e.g. R^1 = OMe, R^2 = H or Me, 88 and 70% (29)



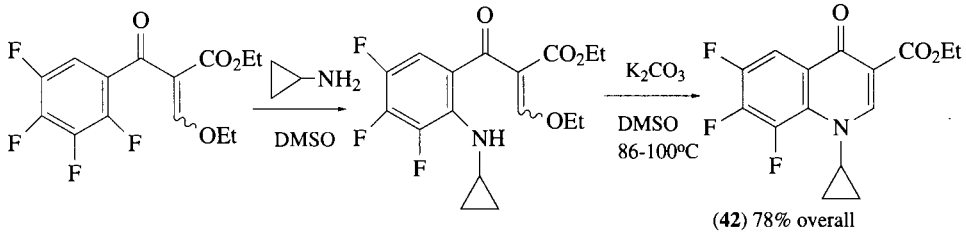
(**40**) R^1 = aryl, R^2 = R^3 = H, Me, 68-82%

Scheme 7



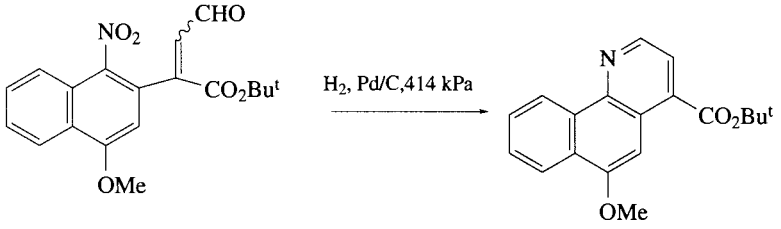
(**41**), R^1 = aryl, R^2 = H, Me, 57-84%

Scheme 8



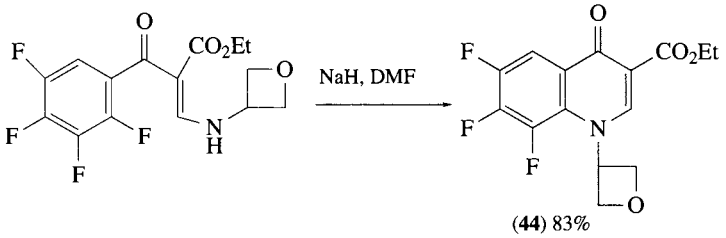
(**42**) 78% overall

Scheme 9

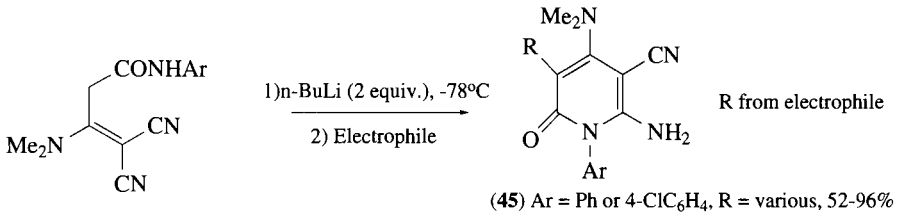


(**43**) 64% (30)

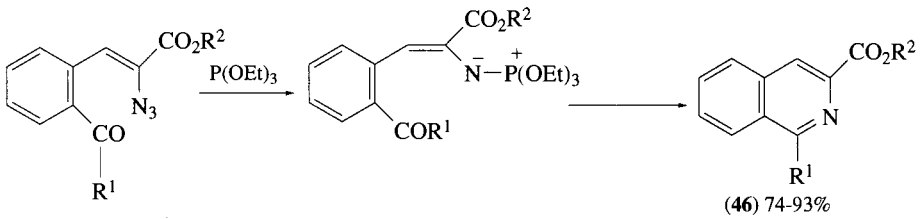
Nitrogen anions are more reactive than the corresponding amines, displacing aryl fluoride to give quinolone (**44**) (Equation (31)) ⟨91JHC1061⟩, reacting with nitriles to give aminopyridones (**45**) (Equation (32)) ⟨86S1063⟩, or, in the form of a nitrogen ylide, cyclizing to give isoquinolines (**46**) (Scheme 10) ⟨87JCS(P1)921⟩.



(**44**) 83% (31)



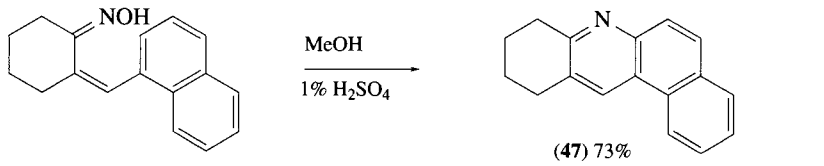
(**45**) Ar = Ph or 4-ClC_6H_4, R = various, 52-96% (32)



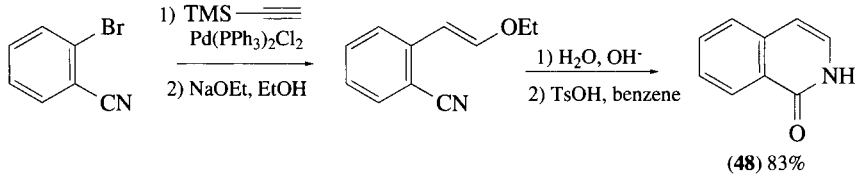
(**46**) 74-93%

Scheme 10

Electrophilic cyclization of oximes can give polycycles, such as compound (**47**) (Equation (33)) ⟨93TL5325⟩; in this case the cyclization is unambiguous. Electrophilically initiated attack on an amide gives isocarbostyril (**48**) (Scheme 11) ⟨85CPB626⟩.

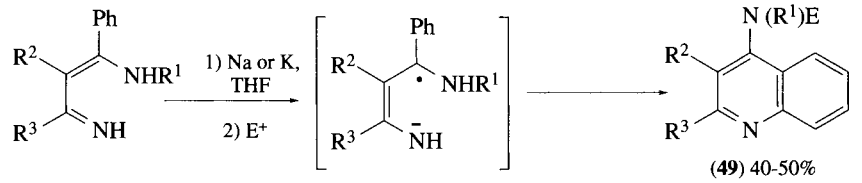


(33)

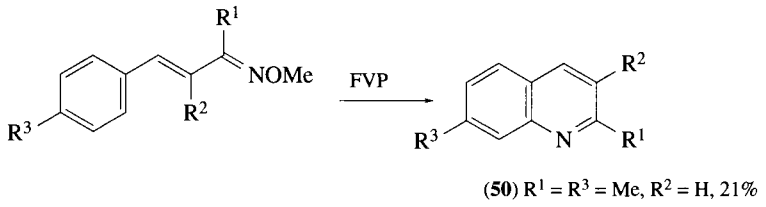


Scheme 11

There are a few radical cyclizations which lead to quinolines. A radical anion is intermediate in the cyclization of azadienes to aminoquinolines (**49**) (Equation (34)) ⟨89JOC2596⟩, and radicals are assumed to be formed during flash vacuum pyrolysis of the methoxyl ethers of cinnamaldehyde oximes ⟨84JCS(P1)1569⟩. The yields are poor, but the substituent is unambiguously at position 7 in the quinolines (**50**) (Equation (35)).



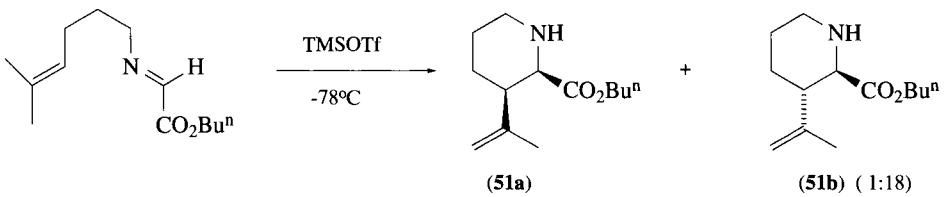
(34)



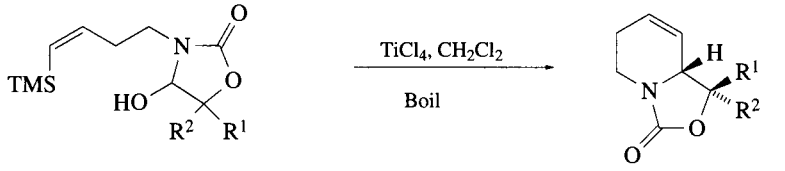
(35)

5.05.2.1.2 Bond formation between α and β carbons

To form piperidines it is usual to generate a carbocation δ to the nitrogen of an imine. The center can be generated with TMS triflate, giving high stereospecificity, as shown in the preparation of piperidines (**51a**) and (**51b**) (Equation (36)) ⟨89S439⟩, by titanium tetrachloride as in the synthesis of piperidine derivative (**52**) (Equation (37)) ⟨86H(24)621⟩, or with formic acid and participation of a suitably placed TMS group as illustrated for compounds (**53a**) and (**53b**) (Equation (38)) ⟨85TL3155⟩. A photochemical cyclization gives piperidine (**54**) (Equation (39)) ⟨93TL5239⟩, while radical cyclization gives mixtures of piperidines (**55**) and pyrrolidines (Equation (40)) ⟨92T4659⟩.

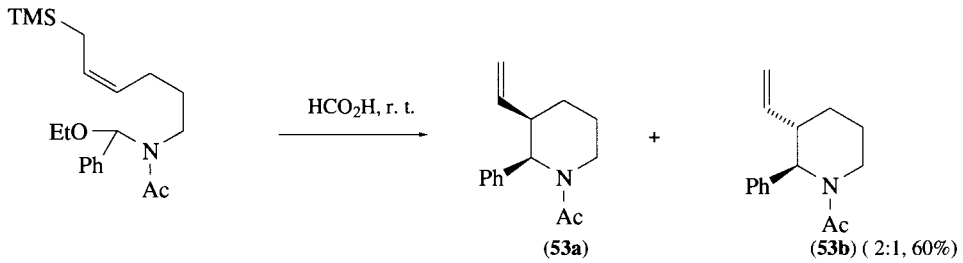


(36)



(37)

(**52**) R^1 = Me, Et, R^2 = H, 65-70%



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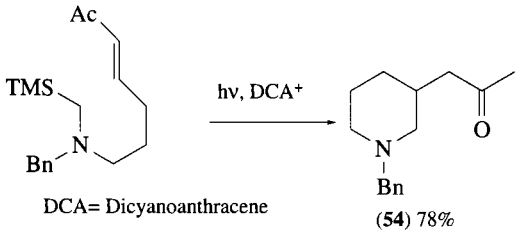

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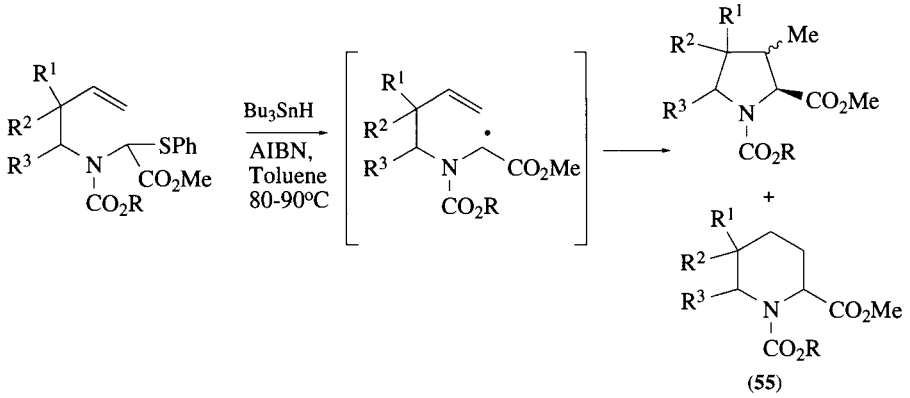
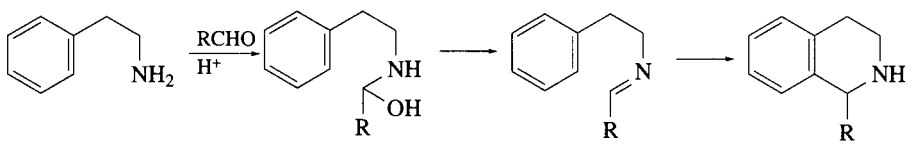
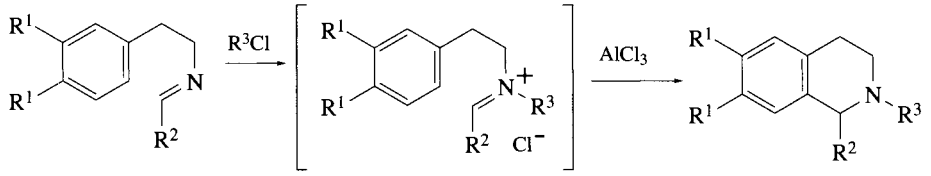


(40)

Most of the interest in this type of ring closure to produce tetrahydro derivatives centers on possible improvements to the Pictet–Spengler synthesis of tetrahydroisoquinolines ⟨81HC(38(1))170⟩ (Scheme 12). The synthesis is successful with unactivated arenes if the imine is first quaternized as shown for compounds (**56**) (Equation (41)) ⟨89S59⟩; in earlier papers Lukanov *et al.* used benzenesulfonyl derivatives for the quaternization ⟨87S204⟩. There are examples of cyclization initiated by protonic acids which can be regarded as activated Pictet–Spengler syntheses, as illustrated in the syntheses of tetrahydroisoquinolines (**57**) (Equation (42)) ⟨87S824⟩ and (**58**) (Equation (43)) ⟨92CB2571⟩, particularly the latter, where the aromatic ring need have no strongly electron donating substituents.

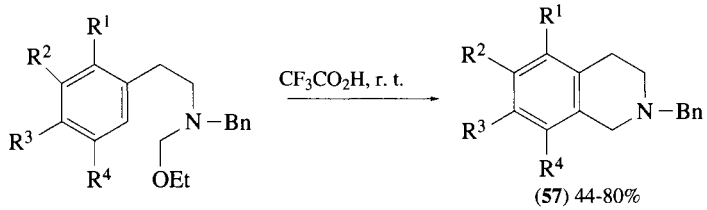


Scheme 12



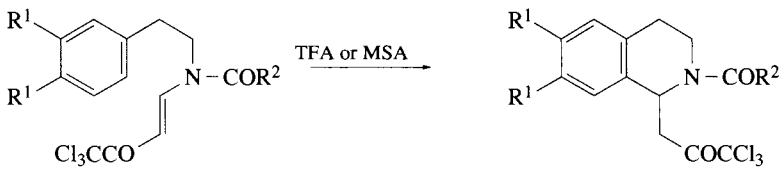
(41)

(**56**) R^1 = H, 70-80%



(42)

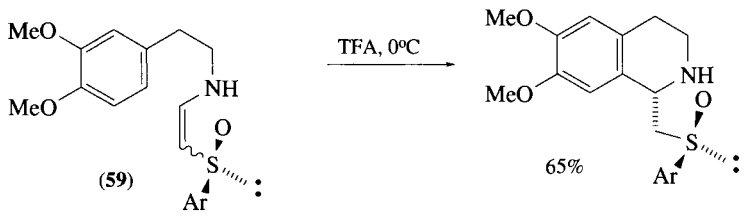
(**57**) 44-80%



(43)

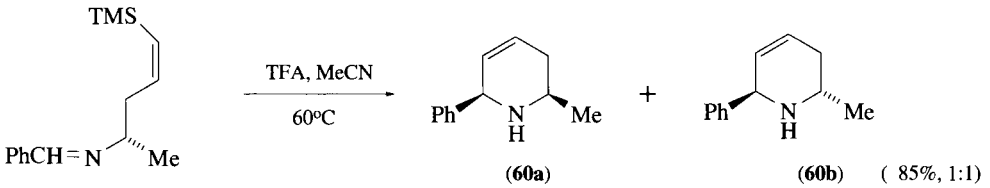
(**58**) e.g. R^1 = H, R^2 = Me, 81%

Chirality at position 1 is important for alkaloid synthesis, and cyclization of the enamine (**59**) gives only the (1*S*) form if the aryl substituent is 2-nitrophenyl (Equation (44)) ⟨91TL6861⟩. Initiation of cyclization to give 1,2,3,6-tetrahydropyridines can be by protonation, as in examples (**60a**) and (**60b**) (Equation (45)), while silver ion-assisted ionization gives only *trans*-2,6-dialkyl derivatives (**61**) (Equation (46)) ⟨88T3919⟩. An uncatalyzed cyclization gives the highly substituted tetrahydroquinoline (**62**) with a *de* >98% (Equation (47)) ⟨89JOC209⟩.



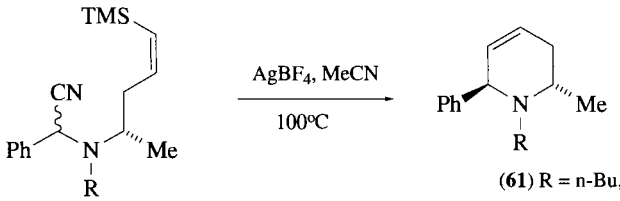
(**59**)

(44)



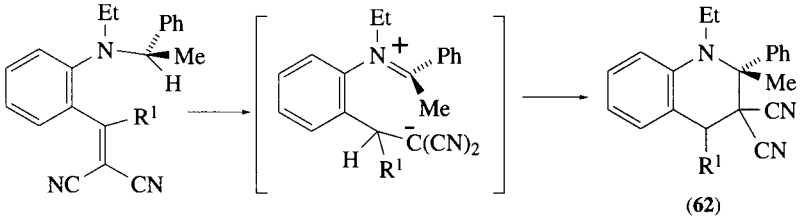
(**60a**) (**60b**) (85%, 1:1)

(45)



(46)

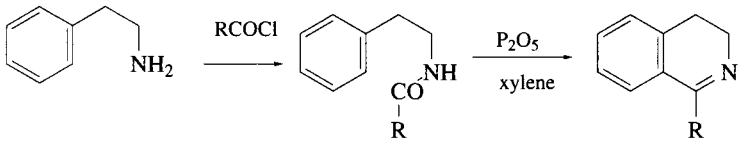
(**61**) R = n-Bu, 57%; R = Me, 51%



(47)

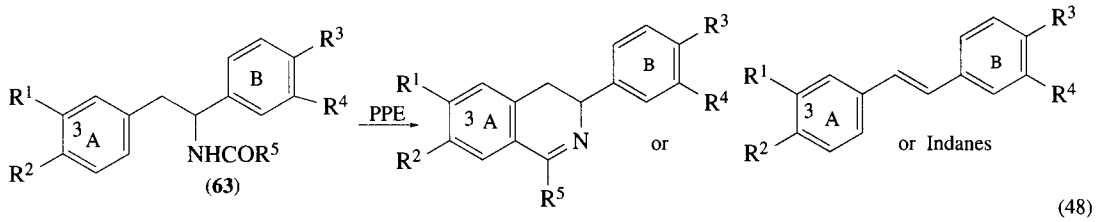
(62)

Useful syntheses of dihydropyridine rings are primarily confined to the production of dihydroisoquinolines, the most famous route being due to Bischler and Napieralski (Scheme 13) ⟨81HC(38(1))142⟩.

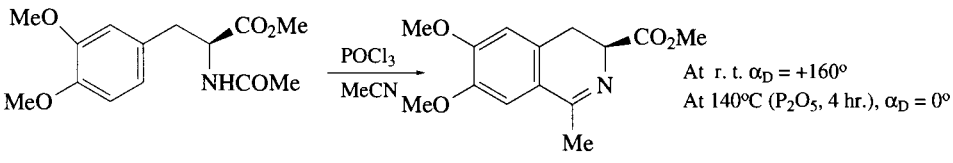


Scheme 13

Three groups have addressed the problem of the retro-Ritter reaction during attempts to synthesize 3-aryl-3,4-dihydroisoquinolines (stilbenes and indanes are formed as major products). In the earliest modification, the use of PCl_5 with RCN as the solvent (R being the same as in the amide RCONH—) gave 3-aryl derivatives in 58–81% yield ⟨83H(20)1247⟩. A second group found that Bischler–Napieralski cyclization of the generalized amide (**63**) was favored by an electron-releasing group in ring A at position 3, and an electron-withdrawing group in ring B, the nature of the acyl group having little effect (Equation (48)) ⟨89JHC25⟩. In the third modification, the retro-Ritter reaction was prevented by incorporating the intermediate imine into a ring and cyclizing with ferric chloride; in the example shown, the resulting dihydroisoquinoline (**64**) has no activating groups on the benzene ring (Scheme 14) ⟨91JOC6034⟩. The reaction was unsuccessful when R^1 = phenyl. Another interest concerns the retention of chirality in a group at position 1 or at position 3, for example in the synthesis of (*R*) and (*S*) forms of tetrahydroisoquinoline (**65**) (Scheme 15) ⟨86H(24)2099⟩. Kametani *et al.* have emphasized the importance of temperature on chirality in the synthesis of ester (**66**) (Equation (49)) ⟨82H(19)535⟩, a point which is further illustrated by the retention of stereochemistry in the synthesis of compound (**67**) (Equation (50)) ⟨94TA1567⟩.

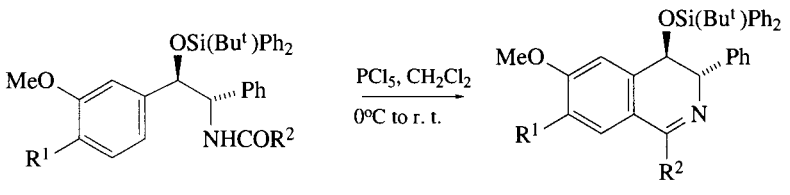


(48)



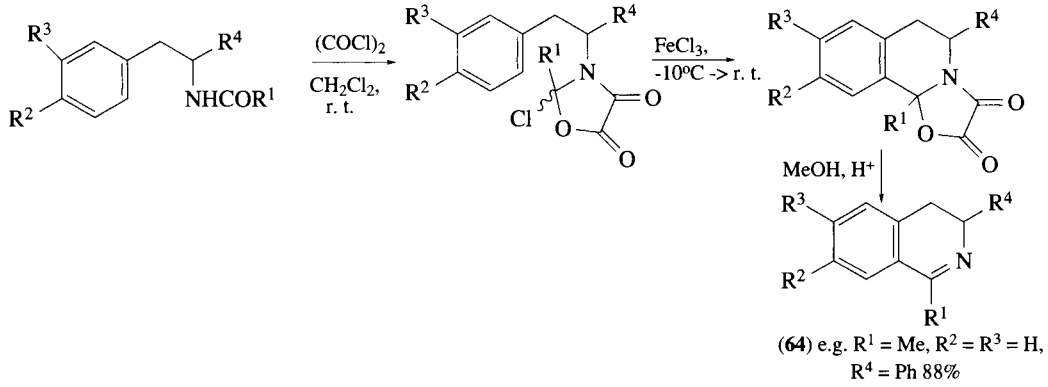
(49)

(**66**) 83%

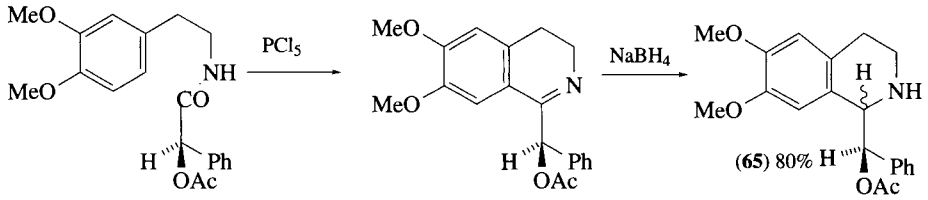


(50)

(**67**) $R^1 = R^2$ = Ph, 96%

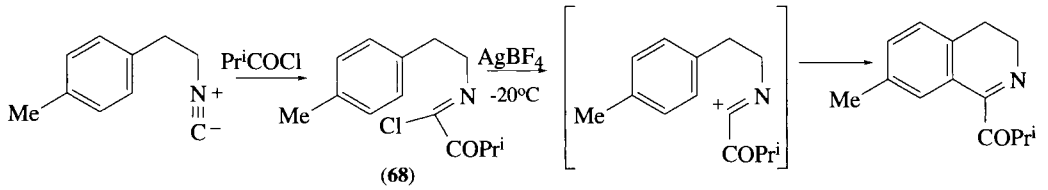


Scheme 14

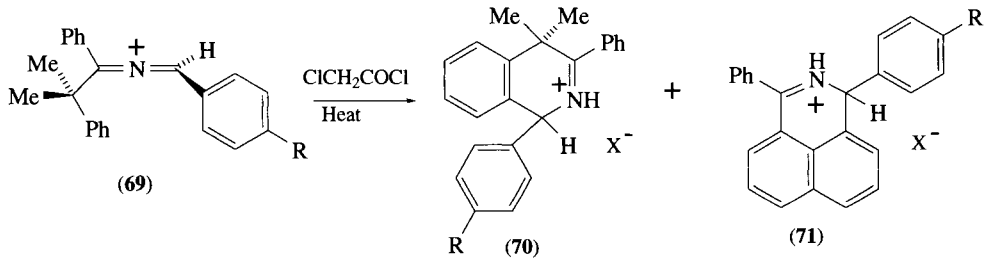


Scheme 15

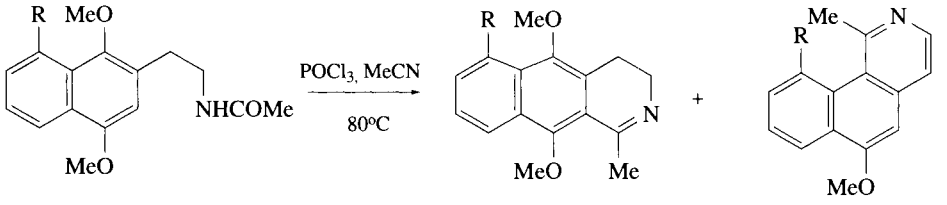
A modification in which unactivated arenes can take part starts from aryl ethyl isocyanides; the intermediates (**68**) are cyclized by silver ion-assisted ionization (Scheme 16) ⟨86JOC1159⟩. By using azoniaallenes (**69**) the unusual 1,4-dihydroisoquinolines (**70**) are formed; the 1-substituted naphthalenes give benzo[*d*,*e*]isoquinoline derivatives (**71**) (Equation (51)) ⟨89CB1711⟩. Attempted preparation of a dihydrobenz[*g*]quinoline (**72**) led also to the aromatic benz[*h*]isoquinoline (**73**) by an *ipso* substitution (Equation (52)) ⟨88JHC661⟩. A synthesis of dihydroisoquinolin-3-ones (**74**) uses the elimination of benzotriazole to generate the intermediate iminium species (Scheme 17) ⟨93JHC381⟩.



Scheme 16



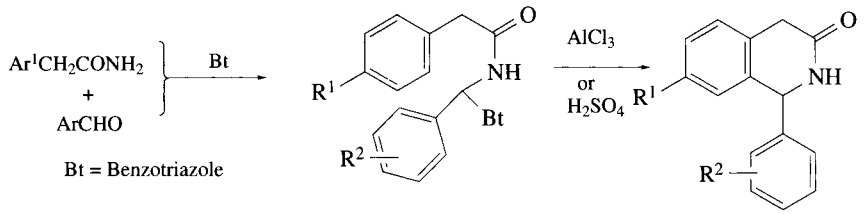
(51)



(72)

(73) R = H, 70:30 **72:73**
R = OMe, **73** only, 62%

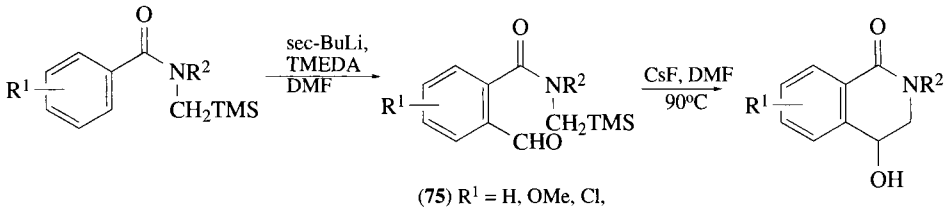
(52)



(74) R^1 = H or OMe,
R^2 = H, Me, Cl, 47-95%

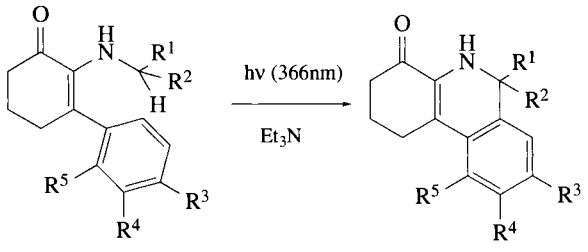
Scheme 17

Cyclizations to give dihydroisoquinolones have been achieved by caesium fluoride initiation (TMS elimination) from compound (**75**) (Scheme 18) ⟨89TL5837⟩, and a similar bond formation by a photochemical procedure gives the phenanthridone (**76**) (Equation (53)) ⟨84H(22)97⟩. A less obvious formation of the 3,4-bond is seen in the synthesis of cyclopropa[*c*]isoquinolines (**77**) (Equation (54)) ⟨84CC1531⟩. Flash vacuum pyrolysis of unsaturated acyclated hydroxamic acids gives 1,2-dihydropyridines (**78**) (Equation (55)) ⟨84JOC4025⟩.



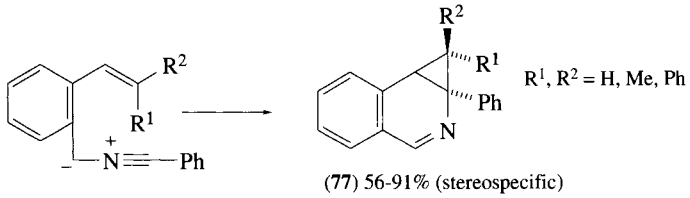
(75) R^1 = H, OMe, Cl,
R^2 = Me, Pr^i,68-84%

Scheme 18



(**76**) low conversion,
50-70% yield

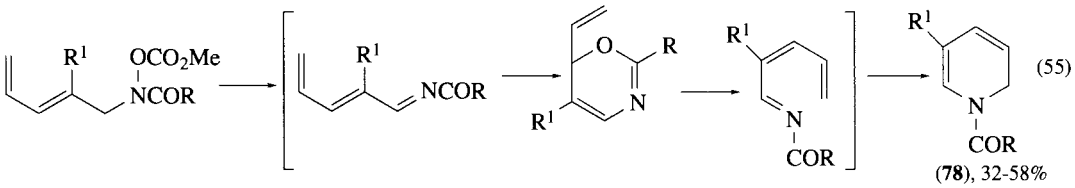
(53)



(**77**) 56-91% (stereospecific)

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

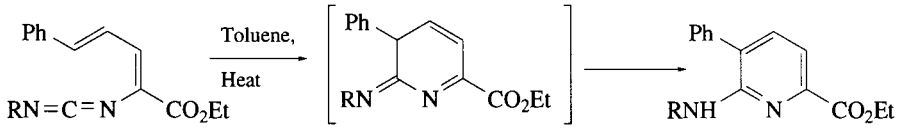
(54)



(55)

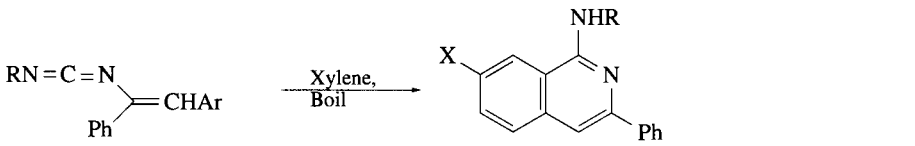
(**78**), 32-58%

Electrocyclization reactions can give fully aromatic heterocycles if the initially formed product has an exocyclic double bond which can migrate as in the formation of the aminopyridines (**79**) (Equation (56)) ⟨89CB307⟩ or if there is a group which can undergo elimination. A similar reaction gives aminoisoquinolines (**80**) (Equation (57)) ⟨86CL135⟩, while imines derived from 2-aminostyrene give a variety of quinolines (**81**) (Equation (58)) ⟨88JOC4218⟩. Pyrolysis of the cyclopropylcarboxaldehyde derivatives (**82**) gives azahexadienes, which cyclize to mixtures of pyridines (**83**) and 4-chloropyridines (**84**) (Equation (59)) ⟨89JOC4275⟩; added WO_3 improves the yields.



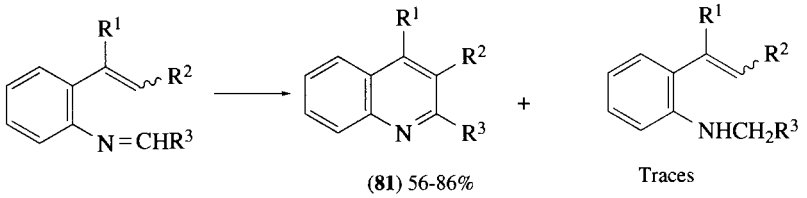
(56)

(**79**) R = Et, Aryl, 68-86%



(57)

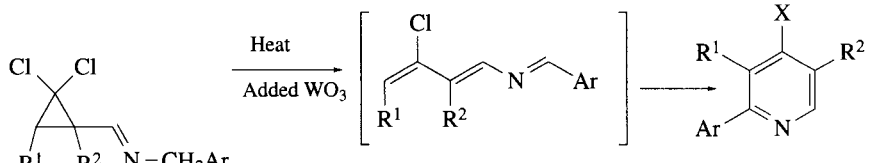
(**80**) X = Me, MeO, Cl; Ar = Ph, 4-MeC$_6$H$_4$; 12-86%



(58)

(**81**) 56-86%

Traces

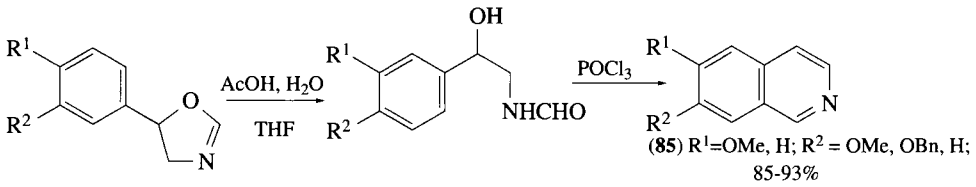


(59)

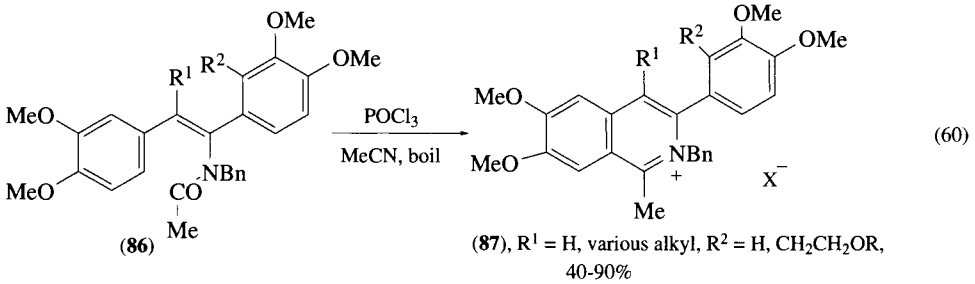
(**82**)

(**83**) X = H, 19-65%
(**84**) X = Cl, 1-22%

Electrophilic cyclizations include the important Pictet–Gams synthesis of isoquinolines from β-hydroxy-β-phenethylamides ⟨81HC(38(1))161⟩. Modifications include the use of aryloxazolines, as in the synthesis of isoquinoline (**85**) (Scheme 19) ⟨81JOC3742⟩, and the use of enamides (**86**) as starting material for quaternary salts (**87**) (Equation (60)) ⟨94T2207⟩. Electrophilic cyclization has also been used to form the 2,3-bond of quinoline from 2-acetamidostyrenes (**88**) (Equation (61)) ⟨87H(26)1883, 93S225⟩, and the reduced phenanthridines (**89**) (Scheme 20) ⟨89TL6865⟩ (also used for dibenzophenanthridines).



Scheme 19



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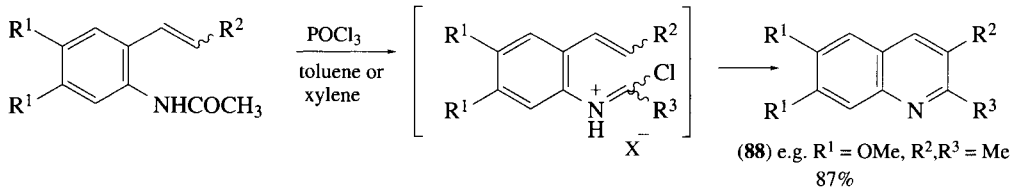

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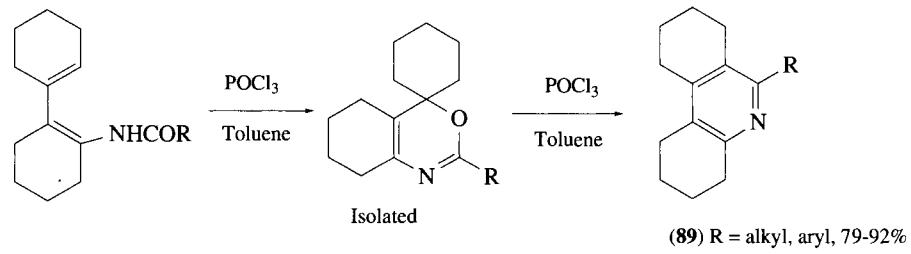
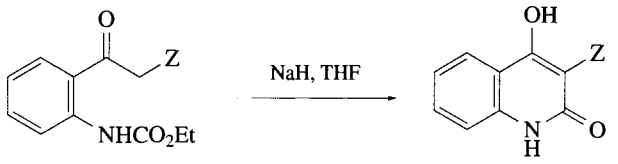


Scheme 20

Anionic cyclization can give 2,4-dihydroxyquinolines (**90**) (Equation (62)) ⟨91H(32)2151⟩ and radical cyclizations the phenanthridines (**91**) (Scheme 21) ⟨85S107⟩.



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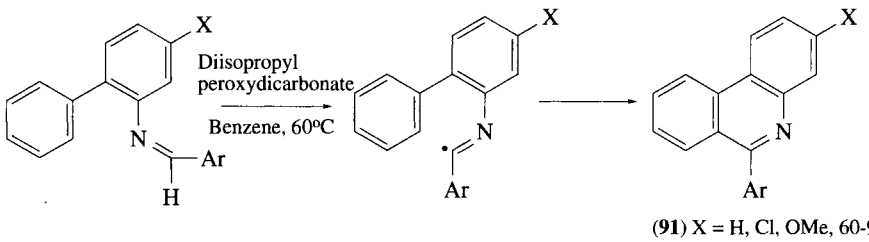
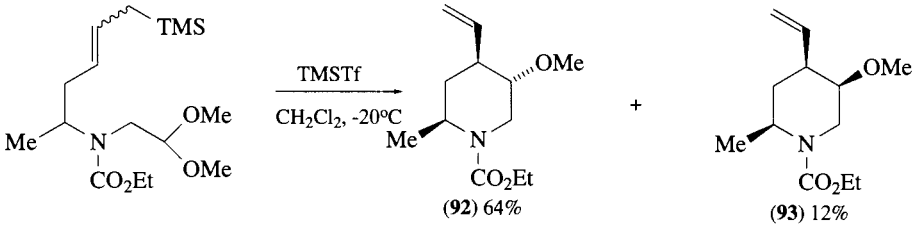


Scheme 21

5.05.2.1.3 Bond formation between β and γ carbons

Fully saturated rings can be made by electrophilic, nucleophilic, radical, or organometallic routes. In the electrophilic procedures a carbocation is generated β to nitrogen and reacts with a suitably placed double or triple bond of a second substituent chain. Examples using carbocations derived from acetals are shown, giving mixtures of piperidines (**92**) and (**93**) ⟨88TL3247⟩ with some stereoselectivity (Equation (63)), and (**94**) ⟨87H(26)2805⟩ with complete stereospecificity and 82–83% *ee* (Equation (64)). Chloramine-T converts the oxime (**95**) into the isoxazolopyridine derivative (**96**), which can easily be reduced to an aminoalcohol (Scheme 22) ⟨90H(30)817⟩. The anion derived from nitrile (**97**) can displace the chloride to give the cyanopiperidine (**98**) in good yield (Equation (65)) ⟨81HCA2203⟩. Radical cyclization on to a cyclohexadiene ring gives *cis*-octahydroisoquinolines (**99**) with good stereoselectivity (Equation (66)) ⟨89TL2611⟩.



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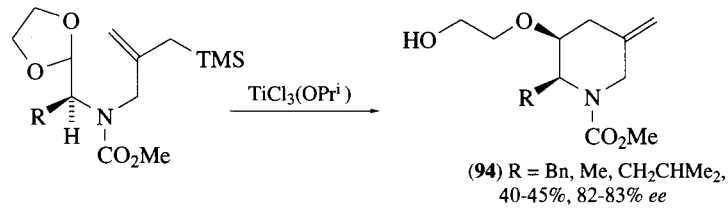

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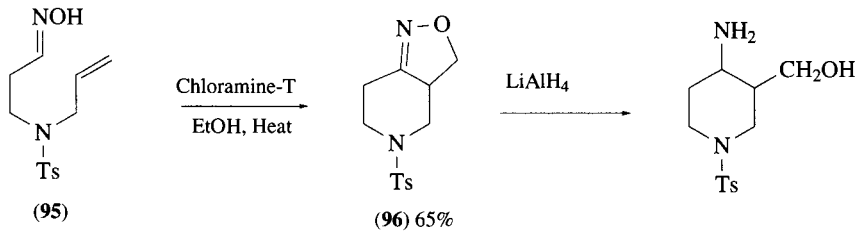
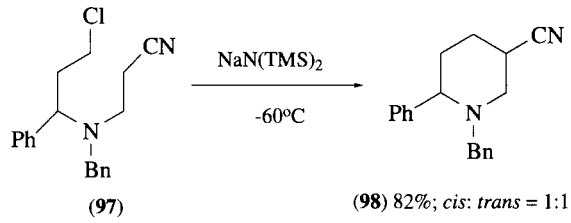
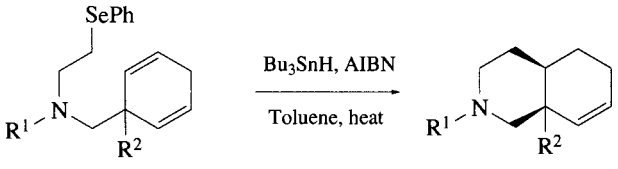


Scheme 22

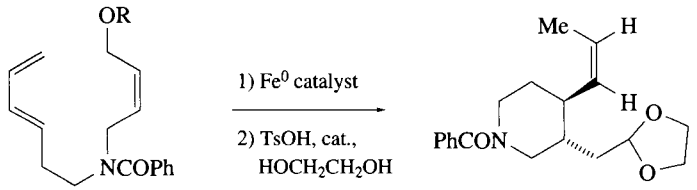


(65)



(66)

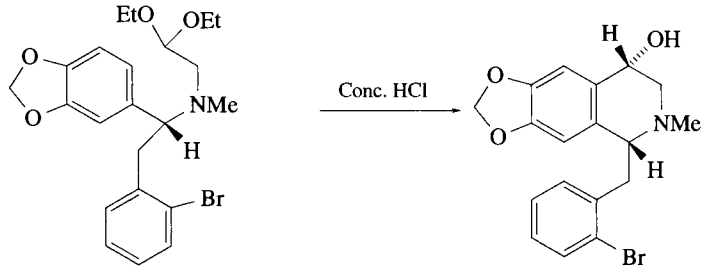
Suitable dienes or enynes have been cyclized, using zirconium ⟨94SL451⟩, chromium ⟨93H(35)679⟩, or iron(0) reagents ⟨90TL2865⟩. The iron-catalyzed cyclization, exemplified by the synthesis of compound (**100**) (Equation (67)), can give high yields and good stereoselectivity (controlled by the stereochemistry of the starting alkenes).



(**100**) 85%

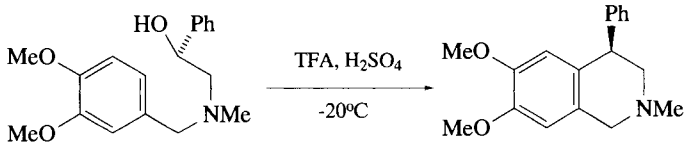
(67)

For dihydropyridine rings and pyridones the same range of reactions is available. Tetrahydroisoquinolines are obtained when a carbocation is generated β to the nitrogen. This has been achieved by protonation ⟨91CHE756⟩ or phenylselenation ⟨88JOC3615⟩ of a double bond, and from acetals ⟨90TL3125, 90TL7591⟩, in which case the products are 4-hydroxy derivatives such as (**101**) (Equation (68)). In the case of compound (**101**) a single diastereomer was formed ⟨82H(19)45⟩. An interesting difference is observed when the carbocation is derived from alcohols (**102**) (Equation (69)) and (**103**) (Equation (70)) ⟨89JCS(P1)2223⟩; in the former case the S_N1 mechanism accounts for the low enantiomeric excess. Two groups have reported the formation of 4-phenylthiotetrahydroisoquinolines via Pummerer reactions differing only in *N*-protection ⟨92T7803, 93H(35)47⟩. The yields can be high as shown for compounds (**104**) (Equation (71)), but *meta*-substituted arenes can give mixtures.



(**101**) 68%, single diastereomer

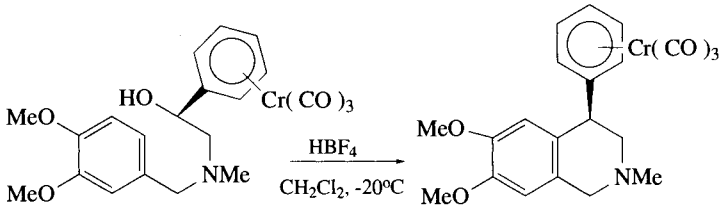
(68)



(**102**)

(-)-(*R*), 54% *ee*, 50% conversion

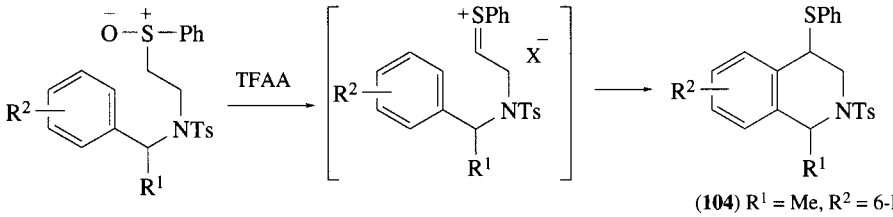
(69)



(**103**)

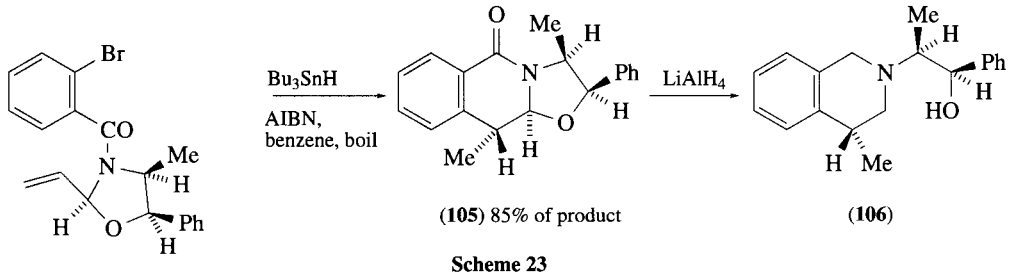
(+)-(*R*), *ee*>96%, after decomplexation

(70)



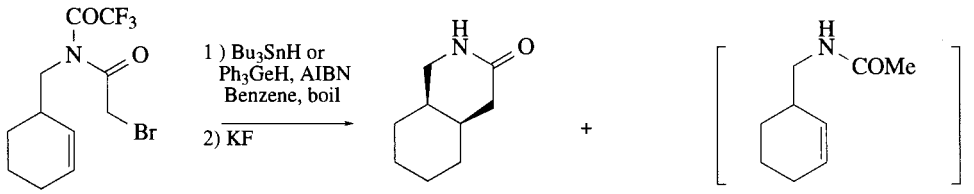
(104) R^1 = Me, R^2 = 6-Me, 88% (71)

Radical cyclizations are often based on the reactions of aryl bromides ⟨93TA273⟩ or alkyl bromides ⟨89H(28)723, 90H(31)1781⟩ with tributyltin hydride/AIBN. In the former case stereoselection has been observed in the preparation of compound (**105**), which was reduced to compound (**106**) (Scheme 23). In the production of reduced isoquinolone (**107**), the use of triphenylgermanium hydride increased the yield of cyclized product (Equation (72)).



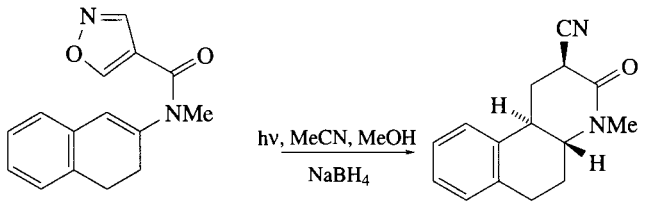
(105) 85% of product (106)

Scheme 23

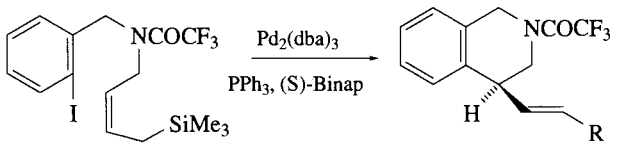


(107) Bu_3SnH, 65%; Ph_3GeH, 85% 24%; 0% (72)

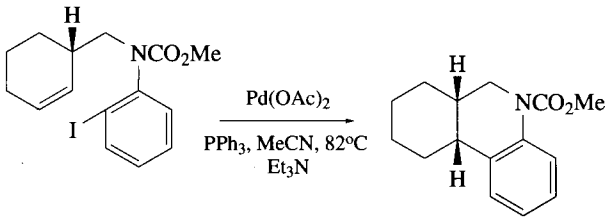
Photochemical cyclization has been well studied by Ninomiya and co-workers, particularly in the synthesis of polycycles ⟨82H(18)217, 84JCS(P1)2911, 85JCS(P1)487⟩ and piperidines ⟨91H(32)2319⟩, where yields and stereochemistry are much affected by solvents; an example is the preparation of the benz[*f*]quinoline derivative (**108**) (Equation (73)). Transition metal-mediated cyclizations of alkyl halides ⟨91TL2545⟩ or aryl halides ⟨87JOC4130, 93H(35)85, 94AG(E)1089⟩ to arenes or double bonds, respectively, have given isoquinolines (**109**) (Equation (74)) and phenanthridine derivatives such as (**110**) (Equation (75)). Metal-catalyzed decomposition of diazo compounds can give piperidinones (**111**) with moderate to good enantiomeric excess ⟨94T1665⟩ if the metal has a chiral ligand (Equation (76)).



(108) 47% (73)

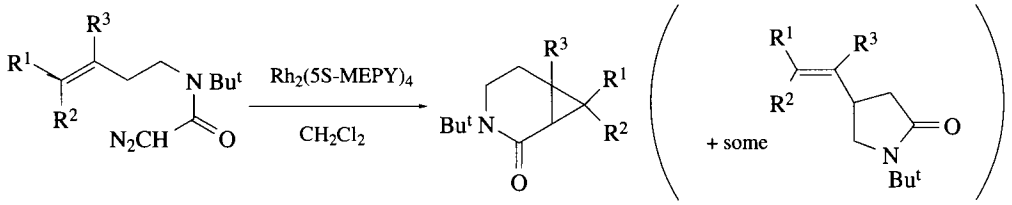


(109) 70%, 72% *ee*, largely R = H (74)



(75)

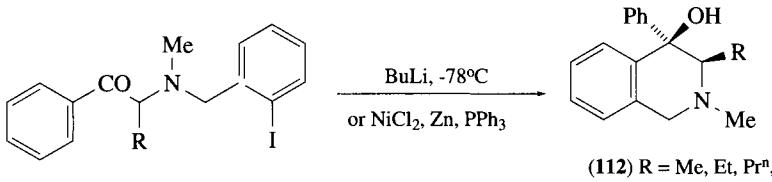
(**110**) 74%



(76)

(**111**) $R^1 = R^3 = H$, $R^2 = Et$, 94%, 90% *ee*

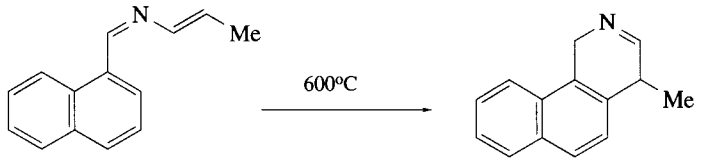
A large number of 4-hydroxytetrahydroisoquinolines have been made by intramolecular attack of an aryllithium on a suitably placed ketonic carbonyl group ⟨92T67⟩; the reaction can also be achieved, with generally lower yields, with nickel chloride, zinc, and triphenylphosphine. Similar reactions ⟨93T1017⟩ give single diastereomers (**112**) (Equation (77)).



(77)

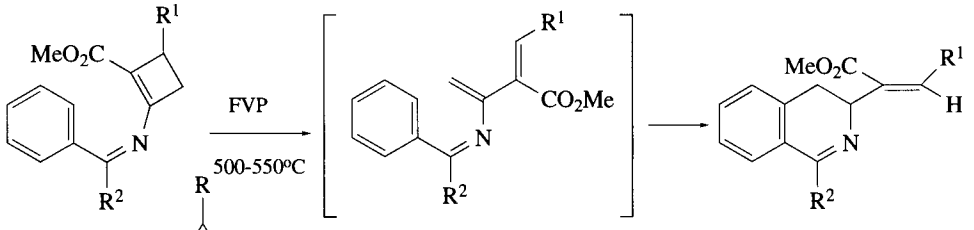
(**112**) R = Me, Et, Pr^n, Ph, 31-73%

Concerted electrocyclizations can lead to 3,4- and other dihydroisoquinolines or their benzologues, as shown for compound (**113**) (Equation (78)) ⟨83JOC5348⟩; the cyclobutene derivatives (**114**) lead to 3-alkenyl dihydroisoquinolines (Equation (79)) ⟨93JOC6442⟩. Photochemical cyclization can give good yields of 3,4-dihydroquinolin-2-ones ⟨84H(22)237⟩; the use of chiral catalysts gives products with moderate enantiomeric excess. Other photochemical syntheses (of isoquinolinones) gave mixtures ⟨82CC842, 91JOC4977⟩. A number of cyclizations with intermediate carbocations have been used to give 1,2-dihydroisoquinolines ⟨86CPB4056⟩ or isoquinolinones ⟨91S476⟩, and Friedel–Crafts cyclizations have given dihydro-3- or -4-isoquinolinones ⟨87JOC2615, 87S637⟩. An example of such a synthesis gives the 3-isoquinolinone (**115**) (Equation (80)) ⟨91JCS(P1)2499⟩.



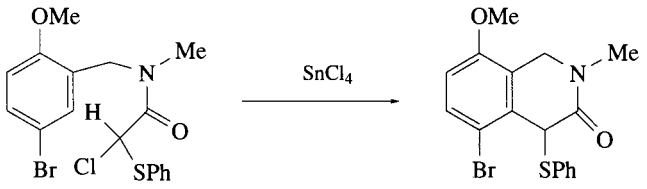
(78)

(**113**) 65%



(79)

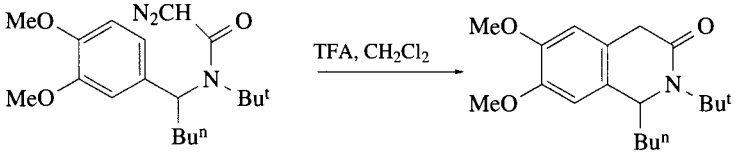
(**114**) R^1 = H, Me, R^2 = Ph, 53-68%



(115) 69%

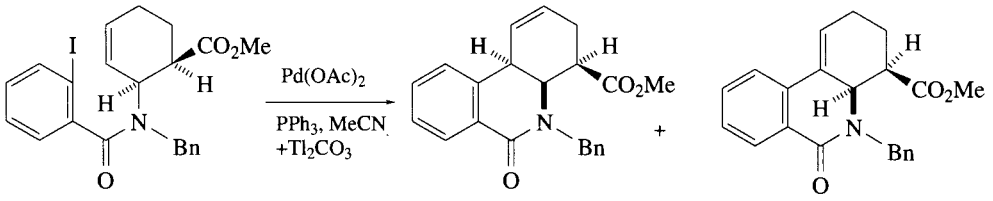
(80)

Radical cyclization can also give 3,4-dihydro-2-quinolinones from 2-halo-*N*-(3-butene-1-oxy)-anilines ⟨91TL2829⟩. Dieckmann cyclization produces good yields of 2,3-dihydro-3-methoxycarbonylquinolin-4-one ⟨91T665⟩. Carbenes generated from diazoketones insert into aromatic C—H bonds to give dihydroisoquinolin-3-ones, such as (**116**) (Equation (81)) ⟨88TL2643⟩. Palladium coupling of suitable *o*-iodobenzamides gives 4-alkylideneisoquinolin-1-ones ⟨88TL4325⟩ or reduced phenanthridinones such as (**117a**) and (**117b**) (Equation (82)); addition of thallium carbonate leads to (**117a**) only, in 78% yield ⟨91TL687⟩.



(116) 57%

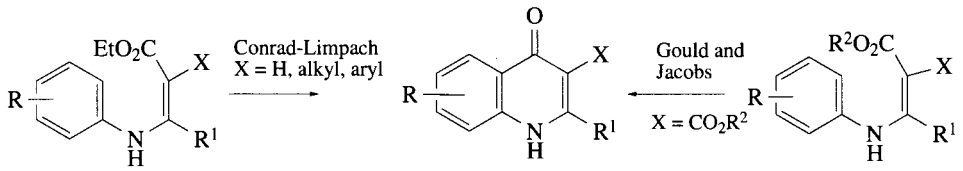
(81)



(117a) (117b)

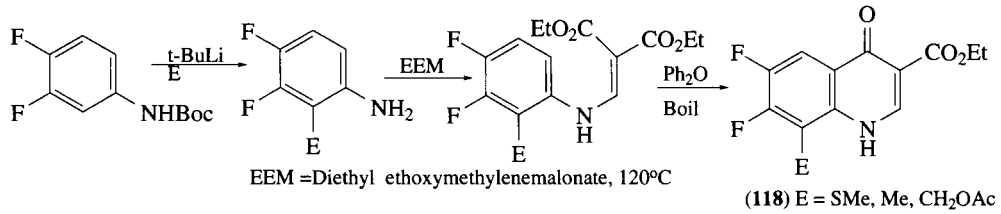
(82)

The most frequently used synthesis of 4-quinolinones is the Conrad–Limpach cyclization ⟨77HC(32(1))139, 77HC(32(1))146⟩ and its modification due to Gould and Jacobs (Scheme 24).

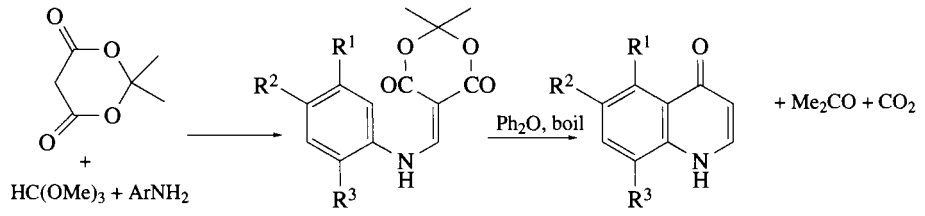


Scheme 24

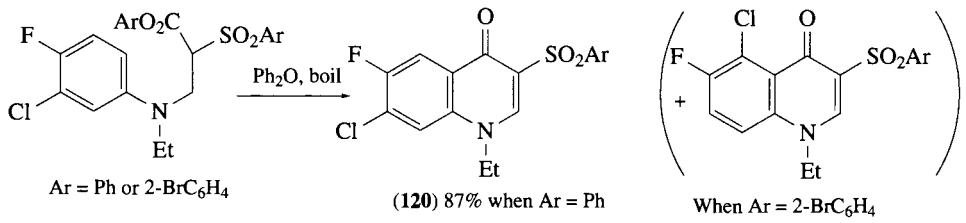
Reported here is a simple example of the Gould and Jacobs synthesis modified to give 8-substituted quinolinones (**118**) (Scheme 25) ⟨92T7373⟩, and various modifications to the group involved in the cyclization. The Meldrum's acid derivatives (**119**) allow the production of 2,3-unsubstituted quinolinones (Scheme 26) ⟨85SC125⟩, while 4-quinolinone-3-sulfonic acids (**120**) can be produced, using the 2-bromophenylsulfonyl group as a protected sulfonic acid (Equation (83)) ⟨88H(27)1119⟩. Ketene dithioacetals can react with aromatic amines to give the necessary starting materials for cyclization ⟨90JHC1217⟩ or can themselves take part in cyclization as modified malonanilides, giving 4-alkylthioquinolines (**121**) (Equation (84)) ⟨92S1291⟩. Acridin-1-one derivatives (**122**) have been produced using dithiocarboxylates (Equation (85)) ⟨91JHC1245⟩, and dithioketenimines (**123**) cyclize at lower temperatures with an interesting rearrangement to give 2-alkoxy-4-quinolinones (Equation (86)) ⟨86JHC597⟩.



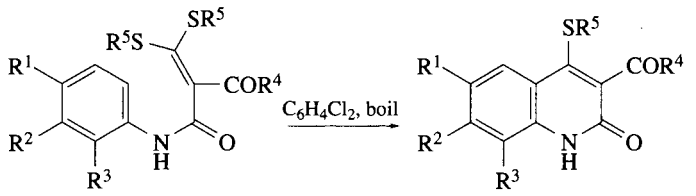
Scheme 25



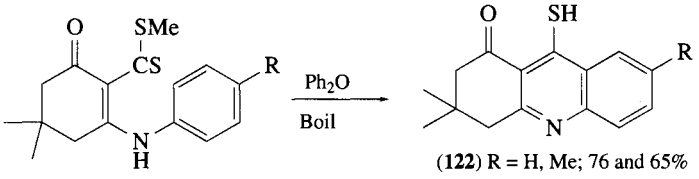
Scheme 26



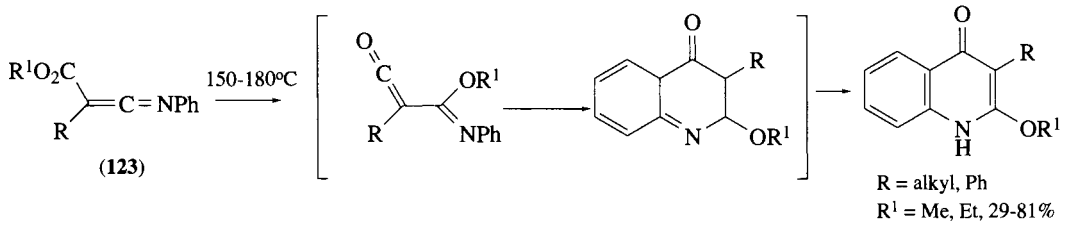
(83)



(84)



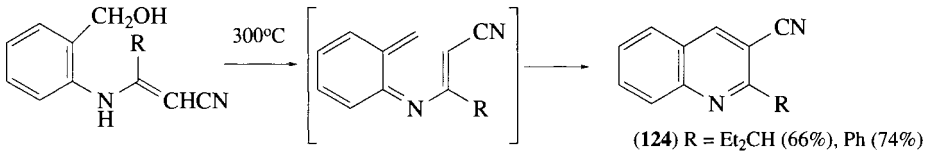
(85)



(86)

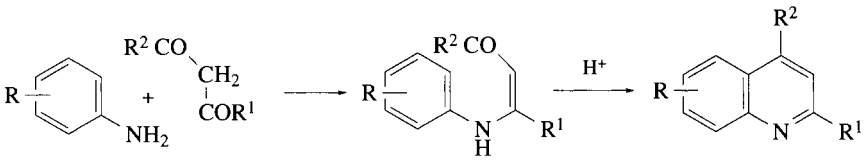
The Conrad–Limpach synthesis is regarded as a 6π electrocyclic reaction; other such reactions rely on high temperatures to generate an "azatriene" and have limited applicability ⟨88JCS(P1)277⟩, as in the synthesis of 3-cyanoquinolines (**124**) (Equation (87)). One 6π electrocyclic reaction which has mechanistic implications for the Doebner–von Miller and Skraup syntheses ⟨89JOC1269⟩ is dealt with in Section 5.05.2.2.3.ii. A large number of well-known syntheses of quinolines, isoquinolines,

and acridines rely on electrophilic cyclization. Previously reviewed in detail are the Combes synthesis of quinoline (Scheme 27), the Knorr synthesis of 2-quinolinones (Scheme 28), and the malonanilide synthesis of 4-hydroxy-2-quinolinones (Scheme 29) ⟨77HC(32(1))119, 77HC(32(1))151, 77HC(32(1))158⟩ the Pomerantz–Fritsch (Scheme 30) ⟨87H(25)601⟩ and Schlittler–von Müller (Scheme 31) syntheses of isoquinolines ⟨81HC(38(1))218, 81HC(38(1))221⟩, and the standard approach to 9-acridones ⟨39OS(19)6⟩ (Equation (88)).

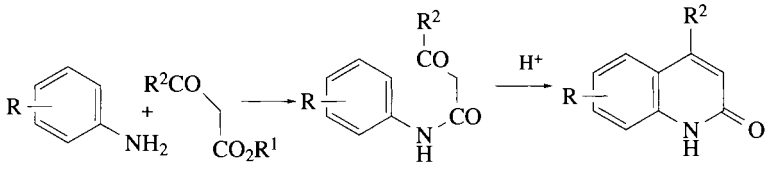


(87)

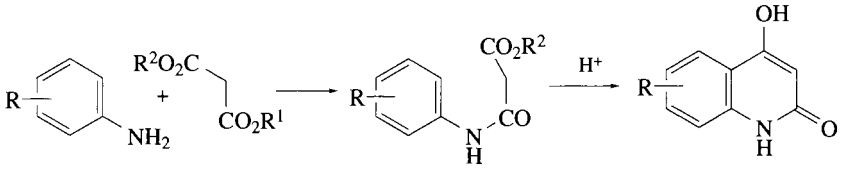
(**124**) R = Et_2CH (66%), Ph (74%)



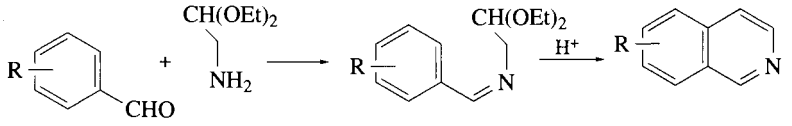
Scheme 27



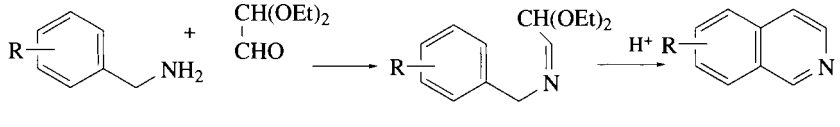
Scheme 28



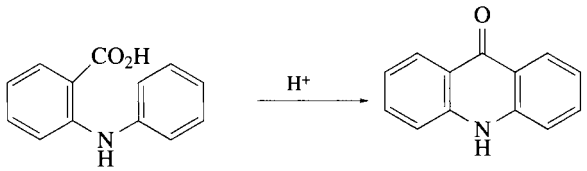
Scheme 29



Scheme 30



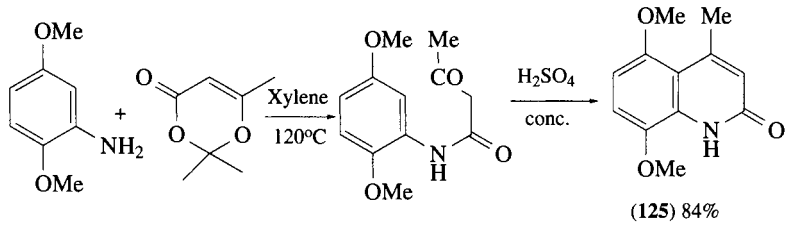
Scheme 31



(88)

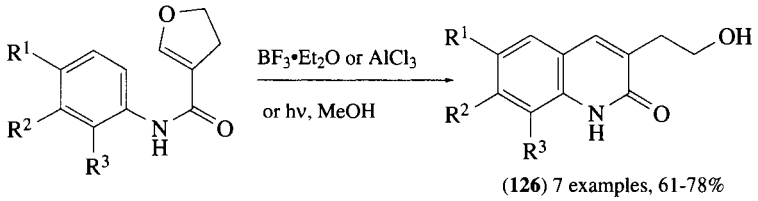
A modified route to the acetoacetanilides required for Knorr syntheses is shown in the production of 2-quinolone (**125**) (Scheme 32) ⟨91S727⟩. Enol ethers or ketals can replace the terminal carbonyl

group as in the synthesis of quinolinones (**126**) (Equation (89)) ⟨82S160⟩ and (**127**) (Equation (90)) ⟨93JOC7581⟩. Derivatives of β-naphthylamine usually give angular fused polycycles, but in the Combes synthesis both angular (**128**) and linear (**129**) derivatives are produced (Equation (91)) ⟨86JHC1207⟩. The closely related malonanilide synthesis has been improved by the use of methanesulfonic acid containing 10% P_2O_5 ⟨88JHC857⟩; in the example given, the yield of (**130**) is 95% (Equation (92)). Change of cyclization agent can have dramatic effects on yields, as illustrated for the preparation of compound (**131**) (Equation (93)) ⟨93TL7737⟩.



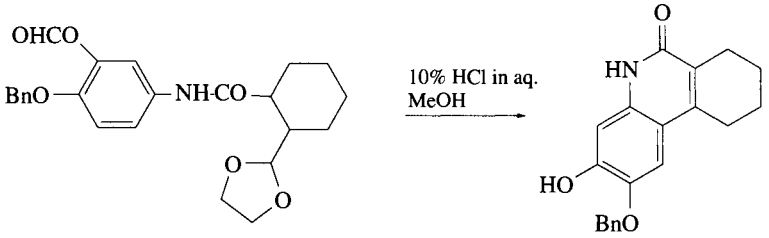
(**125**) 84%

Scheme 32



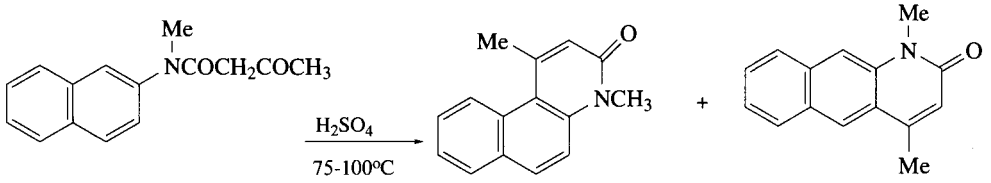
(89)

(**126**) 7 examples, 61-78%



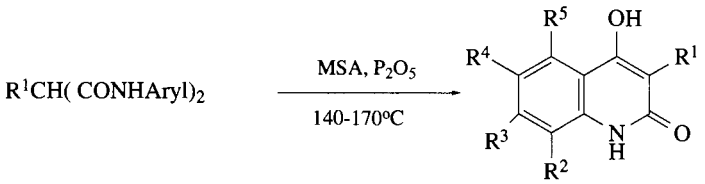
(90)

(**127**) 100%



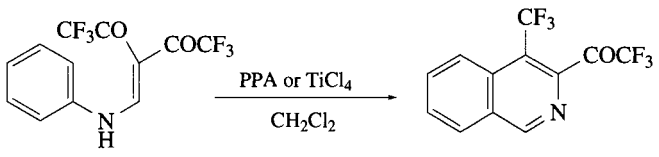
(91)

(**128**) 23% (**129**) 27%



(92)

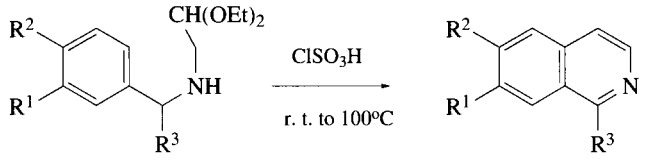
(**130**) 14 examples, R^1 = Et, R^2 = R^5 = Cl, 95%



(93)

(**131**) PPA (10%), $TiCl_4$ (96%)

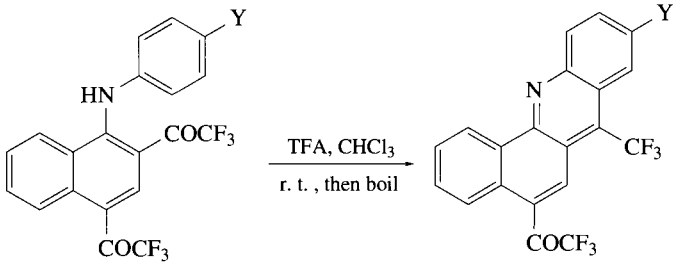
A modification of the Pomerantz–Fritsch synthesis allows amines to be used rather than imines, the initial product being dehydrogenated by the chlorosulfonic acid used in cyclization. The example product shown, (**132**), illustrates the maximum yield (Equation (94)), and when R^3 is isopropyl the synthesis fails ⟨80H(14)1151⟩.



(94)

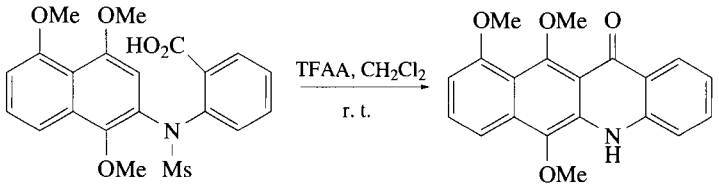
(**132**) 12 examples; $R^1 = R^2 = H$, R^3 = Et, 63%

Almost all acridine and acridone syntheses use electrophilic cyclization, of ketones or aldehydes and of carboxylic acids, respectively. Yields can be very good, and examples (**133**) (Equation (95)) ⟨90S1135⟩ and (**134**) (Equation (96)) ⟨93H(36)2109⟩ have been chosen to show the synthesis of higher polycycles. Procedures for acridone synthesis using PPA ⟨85S217⟩ and PPE ⟨85S220⟩ give yields of 75–100%.



(95)

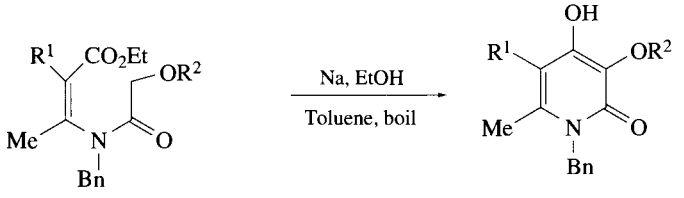
(**133**) Y = H, Me, OMe, Cl; 97-100%



(96)

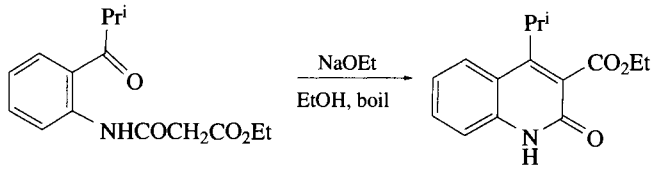
(**134**) 94%

Anionic cyclization can give good results in the synthesis of quinolinones. It is less commonly used for pyridone synthesis, although yields of compounds (**135**) are between 61% and 70% (Equation (97)) ⟨91H(32)99⟩. Condensation between an *ortho* carbonyl group and an active methylene group on an anilide side chain can give high yields as in the Camps reaction ⟨77HC(32(1))191⟩. Examples are shown where activation is provided by ester groups and the condensation is to a ketone to give 2-quinolone (**136**) (Equation (98)) ⟨91S56⟩ or to an ester to give 4-hydroxy-2-quinolinones (**137**) (Equation (99)) ⟨91CHE1237⟩. The former case is one where poor yields are obtained by the Friedländer synthesis (see Section 5.05.2.2.2). By using stronger bases, imines of type (**138**) can be cyclized, giving a variation on the von Niementowski synthesis of 4-quinolinones (Equation (100)) ⟨86TL5323⟩. Cyclization to an *ortho* cyano group gives 4-amino-2-quinolinones (**139**) (Scheme 33) ⟨91CB1237⟩. By a series of nucleophilic displacements of fluorine from the trifluoromethyl group in compounds of type (**140**), a variety of 4-substituted quinolines were obtained, the 4-substituent arising from the base used (Equation (101)) ⟨90JOC4777, 92JHC1753, 92JOC196⟩.



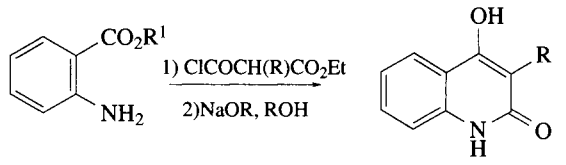
(97)

(**135**) R^1, R^2 = alkyl



(98)

(**136**) 93%

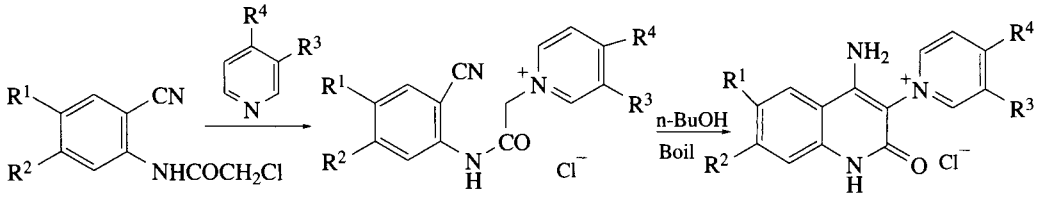


(99)

(**137**) R = Me, Pr^n, Bn; 83-95%

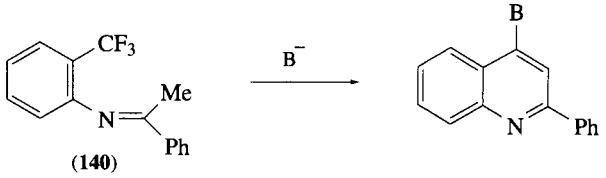
(100)

(**138**) 10 examples, 58-95%



(**139**) 9 examples,50-85%

Scheme 33

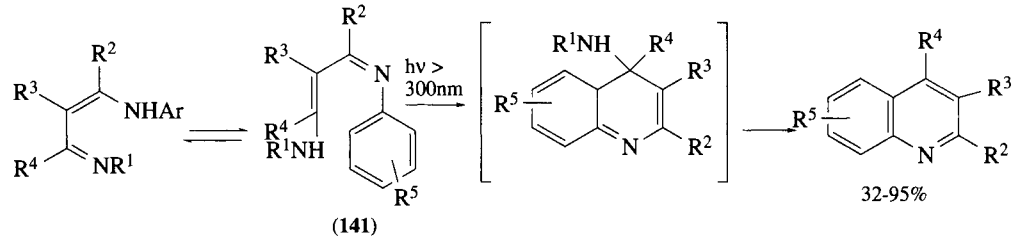


(**140**)

B: RO Bu^{t}O NPr$^i_2$
% 80-86 83 88

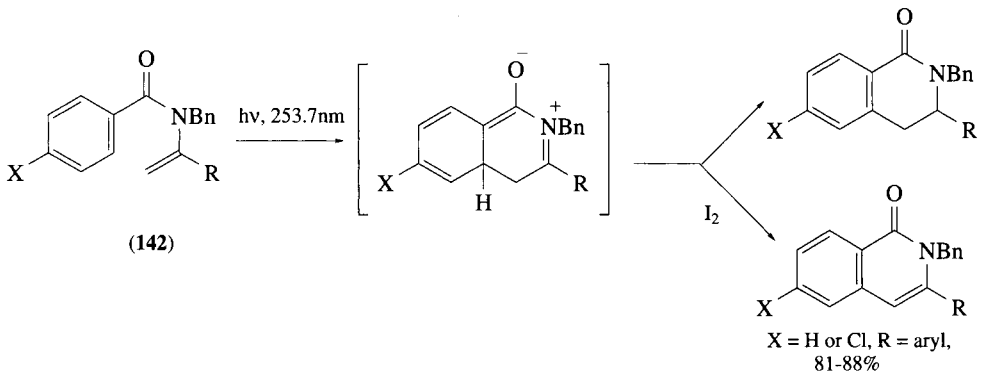
(101)

Photochemical cyclization of unsaturated imines (**141**) gives excellent yields of quinolines in many cases (Scheme 34) ⟨93TL5321⟩, while the amides (**142**) can give isoquinolin-1-ones or the dihydro derivatives, depending on the presence or absence of iodine (Scheme 35) ⟨86S576⟩. Phenanthridine production from stilbazoles (**143**) is said to be improved by the presence of BF_3 to prolong the lifetime of the intermediate (*Z*) imine (**144**) (Scheme 36) ⟨88TL5213⟩.



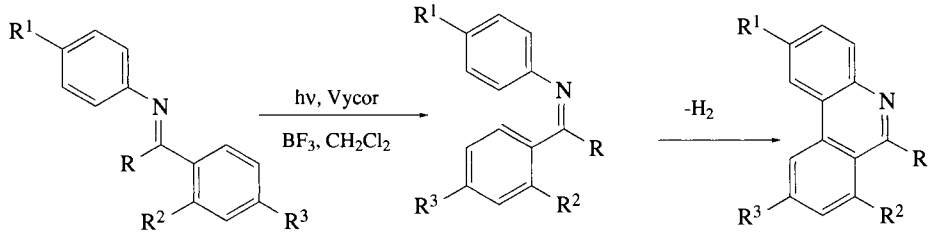
(**141**) 32-95%

Scheme 34



(142)

Scheme 35



(143) (144)

5 examples, 38-46%,
rest recovered s. m.

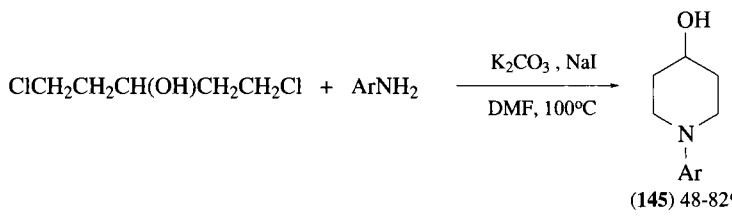
Scheme 36

5.05.2.2 Formation of Two Bonds

5.05.2.2.1 From [5 + 1] and [9 + 1] atom fragments

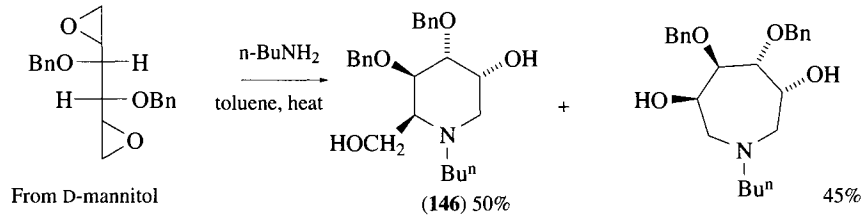
(i) From a nitrogen derivative and a five-carbon fragment

The traditional route to piperidines by reaction between a 1,5-dihalopentane and ammonia or an amine is illustrated by the synthesis of 4-hydroxypiperidines (**145**) (Equation (102)) ⟨88JCS(P1)2881⟩. A variant using bis-oxiranes derived from L-iditol and D-mannitol gives highly substituted piperidines such as (**146**) with stereochemical control (Equation (103)), although hexahydroazepines are also formed ⟨94TL3293⟩. Glutaric dialdehydes condense with amines in the presence of borohydrides to give *N*-substituted piperidines in high yield ⟨91S447⟩. In the presence of benztriazole, at room temperature, 2,6-di(benztriazol-(1-yl)piperidines are formed, again reducible by sodium borohydride to *N*-substituted piperidines ⟨90JOC3205⟩. Reaction with the optically active amine (**147**) gives an unsaturated piperidine, converted by treatment with KCN to a single chiral compound, which in turn gave coniine (Scheme 37) ⟨83JA7754⟩. Ammonium bromide, with 1,5-diketones and cyanoborohydride at room temperature, stereospecifically gives *cis*-2,6-dialkylpiperidines (**148**) (Equation (104)) ⟨84S597⟩.

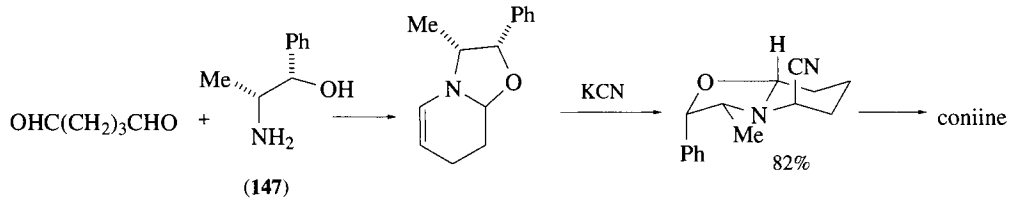


(145) 48-82%

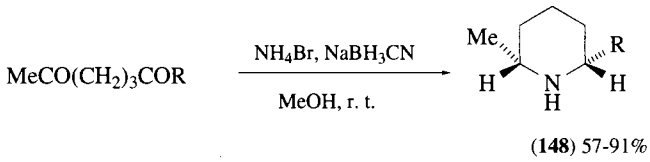
(102)



(103)



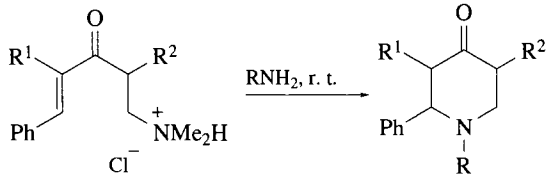
Scheme 37



(104)

(**148**) 57-91%

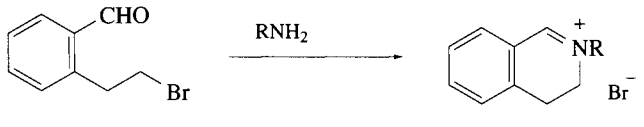
A combination of Michael addition and subsequent nucleophilic displacement gives 4-piperidinones (**149**) (Equation (105)) ⟨91CHE183⟩.



(105)

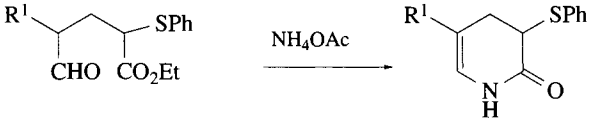
(**149**) 57-91%

Higher levels of unsaturation are illustrated in the syntheses of compounds (**150**) (Equation (106)) ⟨88S1001⟩, (**151**) (Equation (107)) ⟨90JHC311⟩, and (**152**) (Equation (108)) ⟨93JHC1003⟩; benzo[*d*,*e*]isoquinoline derivatives (**153**) and (**154**) have been reported with bromide and malonate acting as leaving groups (Scheme 38) ⟨94T7495⟩.



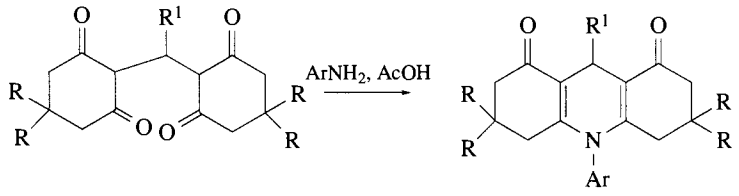
(106)

(**150**)



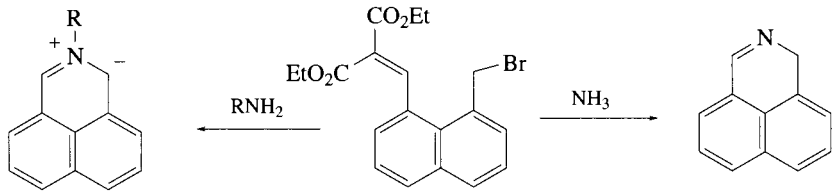
(107)

(**151**) R^1 = CH_3(Et)CH (*S*); 68%, Chirality retained



(108)

(**152**) R = H, Me; R^1 =H, various aryl, 66-76%

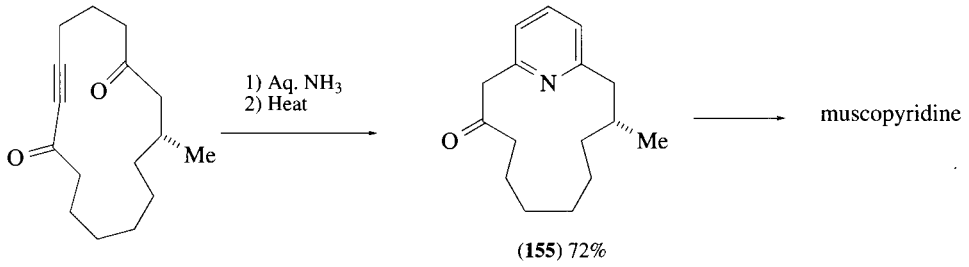


(**153**) R = Bn (72%),
Ph (62%)trapped by N-phenylmaleimide

(**154**), 31%

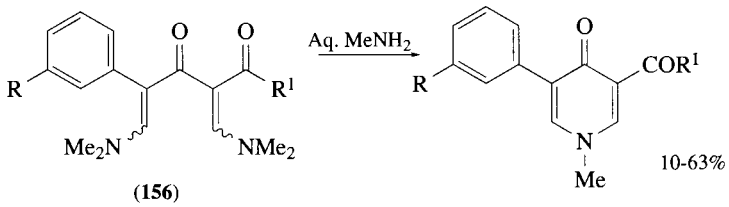
Scheme 38

Pyridines can be obtained from glutaraldehydes and hydroxylamine; the aldehydes can be partly protected as monoacetals ⟨81SC71⟩ or as 1,3-dioxolanes ⟨85SC807⟩. Pyridines can also be made by the action of ammonia or amines on ketoalkynes to give, for example, compound (**155**) (Scheme 39) ⟨82H(18)149⟩, on bis Vilsmeier adducts (**156**) (Equation (109)) ⟨83H(20)2189⟩, or ketene dithioacetals (**157**) (Equation (110)) ⟨90JOC5589⟩. Isoquinolinium imides (**158**) have been made from suitable diketones (Equation (111)) ⟨85S106⟩. 3-Substituted isoquinolines (**159**) have also been prepared by the 1,5-dicarbonyl route, the required diketones being ingeniously generated from acyloxybenzocyclobutenes by flash vacuum pyrolysis (Scheme 40) ⟨85TL3959⟩.

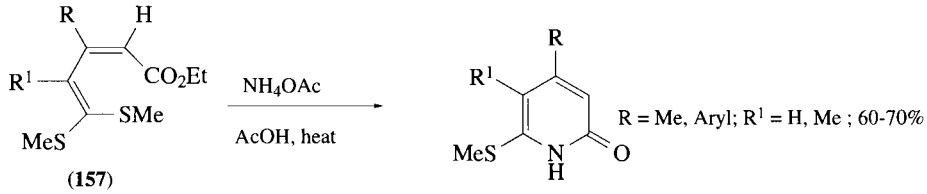


(**155**) 72%

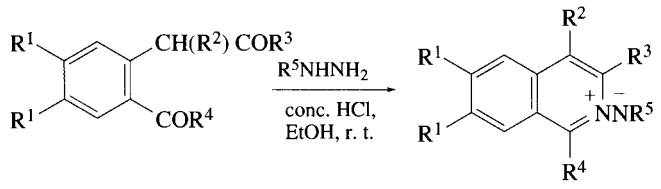
Scheme 39



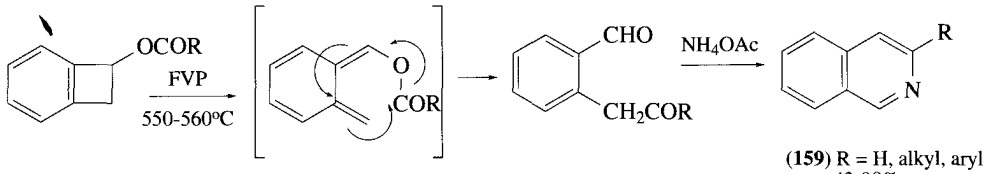
(**156**) (109)



(**157**) (110)



(**158**) 42-85% (111)

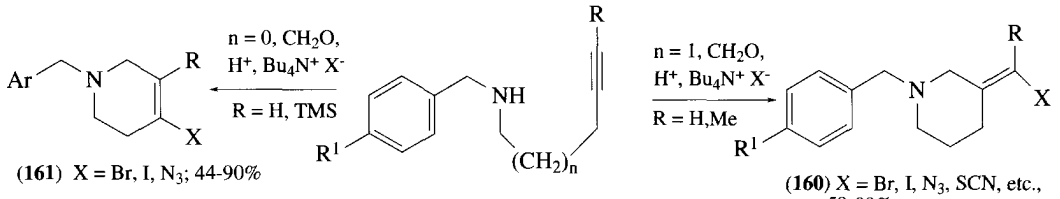


(**159**) R = H, alkyl, aryl
43-90%

Scheme 40

(ii) By insertion of the α-carbon atom

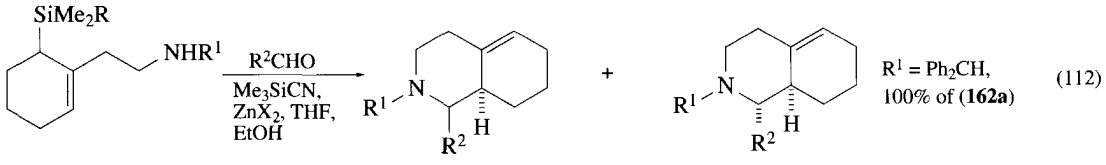
Most of the reactions of this type involve iminium ion formation with subsequent cyclization to a remote double or triple bond. Overman *et al.* have used this approach in a number of cases; in those illustrated (Scheme 41), the position and nature of the alkyne can lead to exocyclic, compound (**160**), or endocyclic, compound (**161**), double bonds ⟨88JA612⟩. In the synthesis of octahydroisoquinolines (**162a**) and (**162b**) (Equation (112)), only (**162a**) is formed when R^2 is a large group ⟨93JOC6947⟩. A double cyclization converts either diene, (**163**) or (**164**), into a decahydroisoquinoline (Scheme 42) ⟨85JOC3449⟩.



(**161**) X = Br, I, N_3; 44-90%

(**160**) X = Br, I, N_3, SCN, etc.,
59-89%

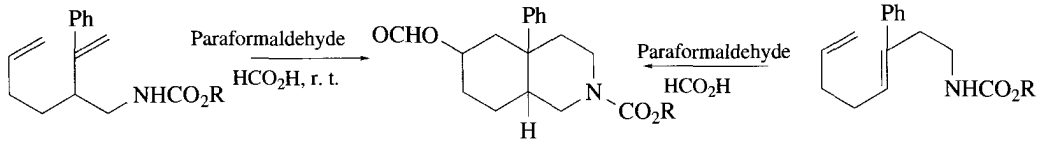
Scheme 41



(112)

(**162a**)

(**162b**) 48-88%



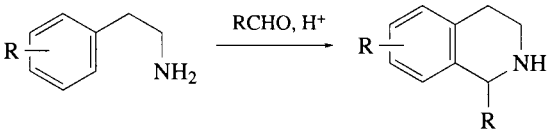
(**163**)

62-75%

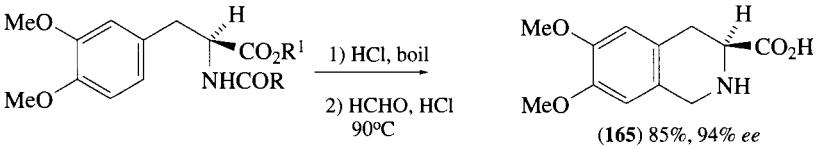
(**164**)

Scheme 42

The most important reaction giving tetrahydro derivatives is the Pictet–Spengler synthesis of tetrahydroisoquinolines (Equation (113)) ⟨81HC(38(1))170⟩. Since the mid-1980s the major interest has been in stereochemistry. Thus the carboxylic acid (**165**) was obtained in 94% *ee* (Equation (114)) ⟨90S550⟩. When aldehydes other than formaldehyde are used, it has been reported that the reaction is diastereoselective and thermodynamically controlled, a 3-aryl group being pseudo axial as in compound (**166**) (Equation (115)) ⟨87T1943, 88T203⟩. Where two cyclization positions are available, as in the phenethylamine (**167**), it has been observed that low pH favors cyclization *para* to an hydroxyl group (Equation (116)) ⟨83JOC1932⟩. Cyclization of *N*-formyl derivatives is possible; in the generalized amide (**168**) no cyclization was observed when Ar = *p*-$MeOC_6H_4$ (Equation (117)) ⟨92S1245⟩.

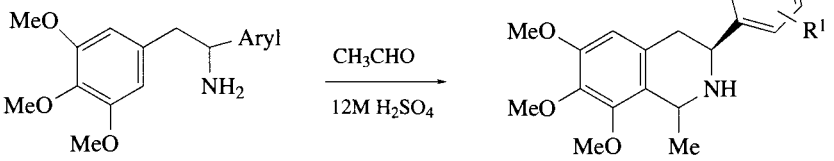


(113)



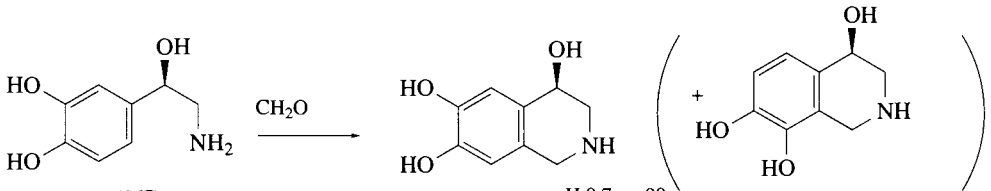
(165) 85%, 94% *ee*

(114)



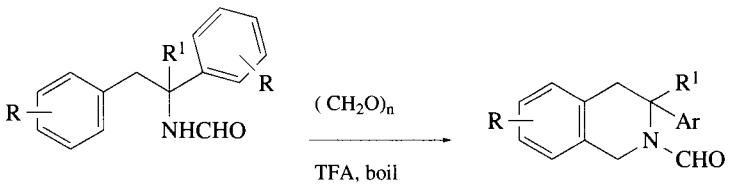
(166)

(115)



(167)

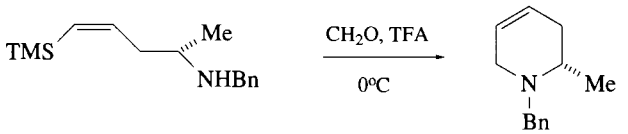
(116)



(168) 50-100%

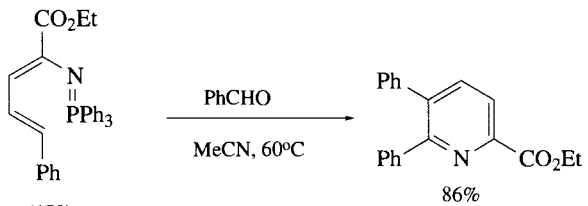
(117)

Tetrahydropyridines can be prepared with high enantiomeric excess via iminium species, as shown for compound (**169**) (Equation (118)) ⟨93TL5243⟩; a variant uses an aldehyde and KCN to provide an intermediate α-cyano species, which can be cyclized by silver fluoroborate ⟨87JA6097⟩. Phosphinimines such as compound (**170**) react with benzaldehyde to give pyridines (Equation (119)) ⟨90JCS(P1)2193⟩. Carbon monoxide can be inserted into 1-aminopent-4-enes to give 2-pyridones (**171**), using a rhodium catalyst (Equation (120)) ⟨90TL4795⟩; a similar reaction uses a bromopentene and palladium catalysis ⟨83JOC4058⟩.



(**169**) 40-45%, *ee* >99%

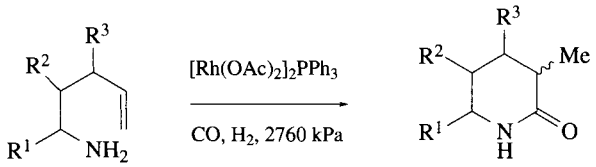
(118)



86%

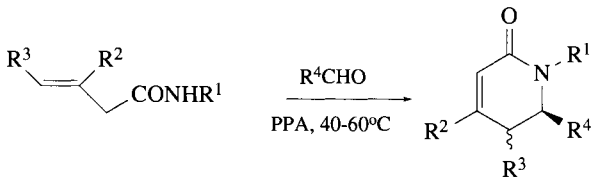
(**170**)

(119)

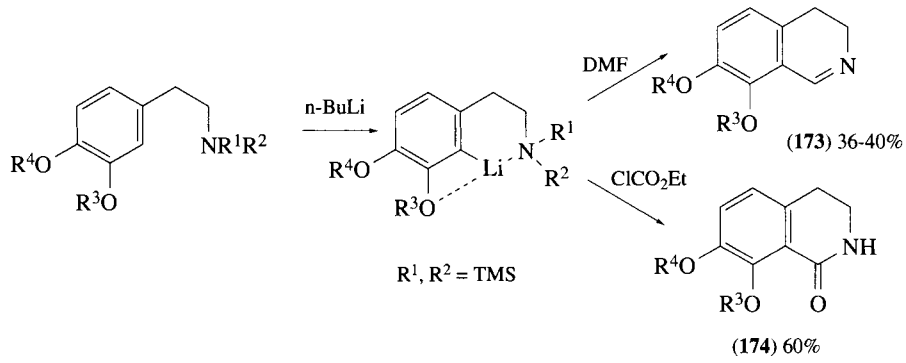


(171) 83-98% (120)

Dihydropyridones (**172**) are obtained from enamides and aldehydes under acid catalysis (Equation (121)) ⟨92JOC5045⟩. β-Phenylethylamines with a *meta* oxy function react with butyllithium to give a stable lithio complex which in turn reacts with DMF to give dihydroisoquinoline (**173**) or with ethyl chloroformate to give the dihydroisoquinolones (**174**) (Scheme 43) ⟨88TL3865⟩.

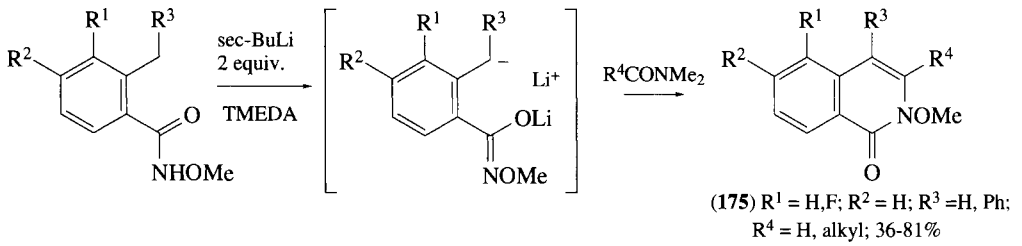


(172) $R^1 = R^2 = R^3$ = H, alkyl, R^4 = aryl, 50-95% (121)



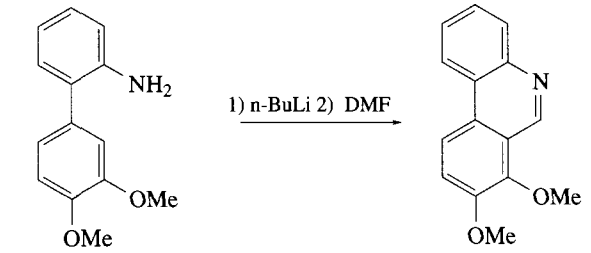
Scheme 43

For formation of fully aromatic compounds a number of groups have used lithiation of an *ortho*-placed methyl or alkyl group or directed lithiation of a benzene ring, followed by addition of DMF or a related species to provide the extra carbon atom. Examples are the *N*-methoxyisoquinolin-1-ones (**175**) (Scheme 44) ⟨93JOC3643, 92JOC2700⟩ and the phenanthridine (**176**) (Equation (122)) ⟨81T825⟩. It has been reported that use of acetonitrile as the solvent in a Bischler–Napieralski synthesis can lead to incorporation of the solvent to provide one of the ring carbons and the nitrogen in isoquinoline by-products ⟨90JHC1665⟩. Trimethyl orthoformate provided the α carbon in the synthesis of 4-pyridone (**177**) (Equation (123)) ⟨90JOC380⟩, and carbon monoxide participated in the palladium-catalyzed synthesis of quinolines (Equation (124)) (**178**) ⟨92SL513⟩.



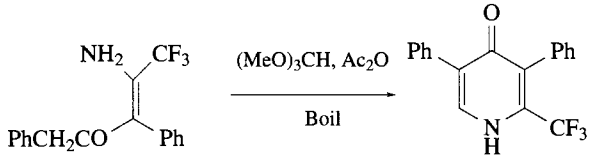
(175) R^1 = H,F; R^2 = H; R^3 =H, Ph; R^4 = H, alkyl; 36-81%

Scheme 44



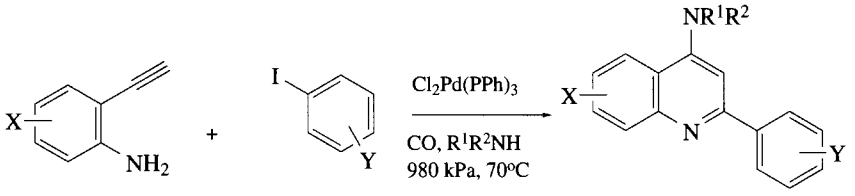
(**176**) 58%

(122)



(**177**) 45%

(123)

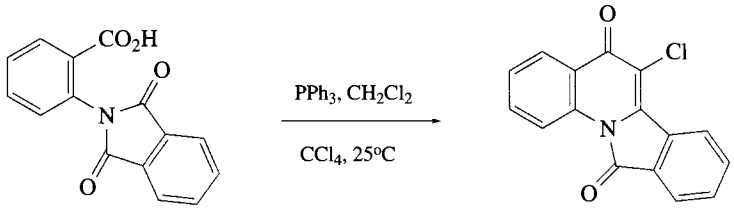


(**178**) 11 examples, 43-86%

(124)

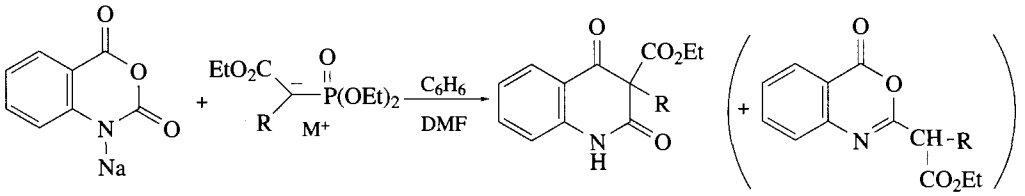
(iii) Insertion of a β-carbon atom

There are only two examples of such insertions, both involving phosphorus ylides, to give the fused quinolinone (**179**) (Equation (125)) ⟨90T3489⟩ and the quinoline-2,4-dione (**180**) (Equation (126)) ⟨82S231⟩.



(**179**) 84%

(125)



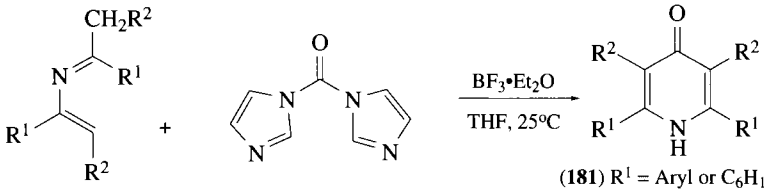
(**180**) R = alkyl, 20-69%

(126)

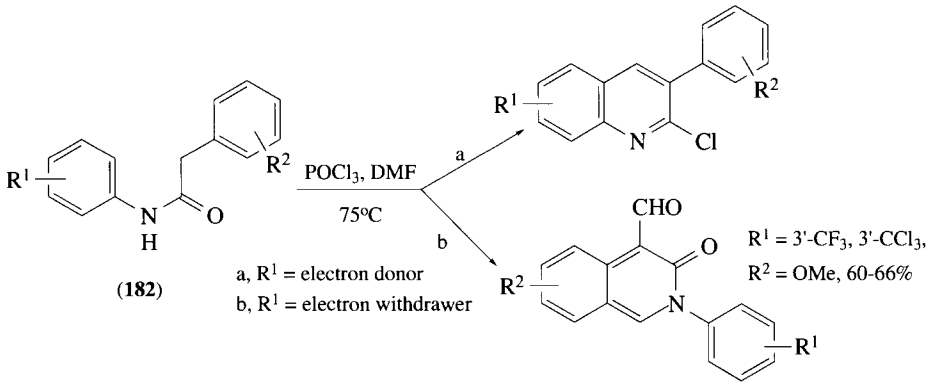
(iv) Insertion of a γ-carbon atom

Diimidazolylmethanone has been used to insert a γ-carbonyl group into an alkylazadiene to produce the 4-pyridones (**181**) (Equation (127)) ⟨91JOC6751⟩. The Vilsmeier reagent has been used

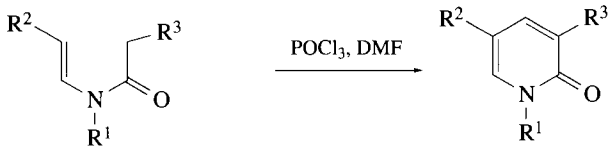
to synthesize quinolines from acetanilides; the reaction has been reviewed ⟨93H(35)539⟩. The phenylacetanilides (**182**) can give quinolines or isoquinolinones, depending on the electron density in ring A (Scheme 45) ⟨84S349⟩. Reaction of the Vilsmeier reagent with enamides gives 2-pyridones (**183**) (Equation (128)) ⟨84JCS(P1)1173⟩ and with the vinylogous enamides (**184**) gives quinolines (Equation (129)) ⟨83TL517⟩. An acridinium salt (**185**) has been synthesized by the Bernthsen reaction, from triphenylamine and a benzoic acid (Equation (130)) ⟨93TL7161⟩.



(**181**) R^1 = Aryl or C_6H_{11}, R^2 = alkyl, 75-90% (127)

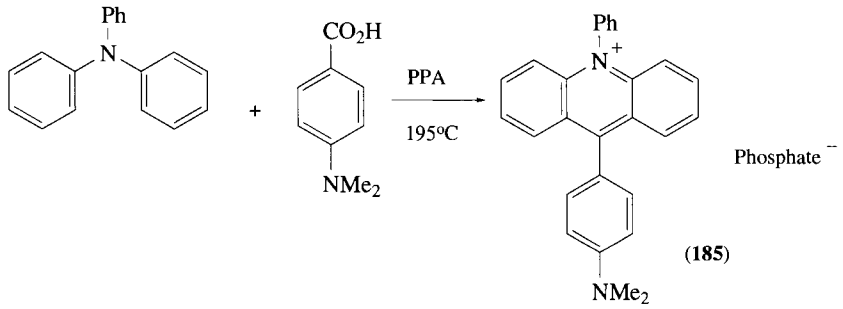


Scheme 45



(**183**) R^1, R^2 = alkyl, R^3 = Me, H, 44-69% (128)

(**184**) R = OMe or NO_2, 60-73% (129)

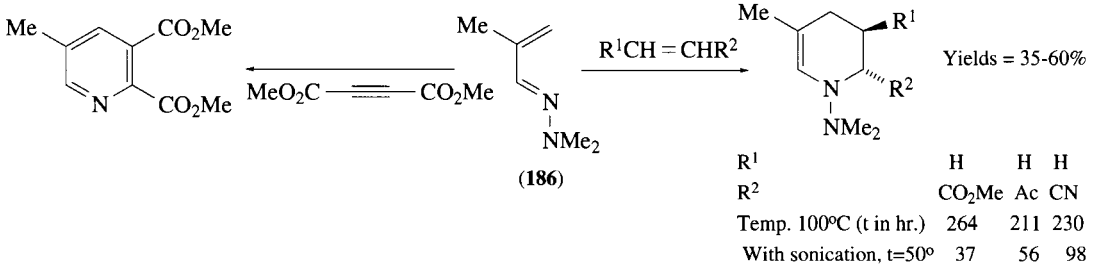


(130)

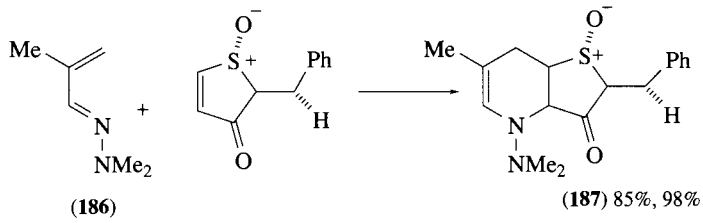
5.05.2.2.2 From [4 + 2] atom fragments

(i) Nitrogen in the four-atom fragment

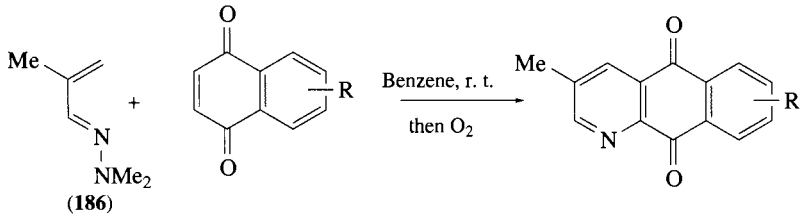
(a) Bonding to nitrogen. A number of reviews are available on ($4\pi_s + 2\pi_s$) cycloadditions, notably in books ⟨87AHC246, B-87MI 505-01, 91COS(5)470⟩. The number of such reactions has grown rapidly since the first edition of this work ⟨84CHEC-I(2)441⟩. Examples of the type of *N*-substitution are provided by the hydrazone (**186**). The first illustrates the acceleration which can be achieved by sonication (Scheme 46) ⟨94T10047⟩, the second a high diastereomeric excess of compound (**187**) (Equation (131)) ⟨89TL3061⟩, and the third the formation of a tricycle where regioselectivity can be high (Equation (132)) ⟨87JOC2285⟩.



Scheme 46

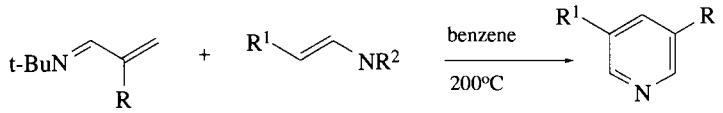


(131)



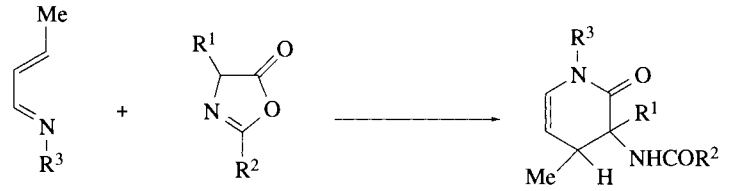
(132)

Azabutadienes with an *N*-alkyl substituent react with enamines to give a range of 3,5-disubstituted pyridines (**188**) (Equation (133)) ⟨84JOC2691⟩, and with oxazolones to give dihydropyridones (**189**) (Equation (134)) ⟨86JHC1007⟩. Mixtures of regioisomeric tetrahydropyridines are formed in reactions between *N*-aryl-1-azabutadienes and alkenes ⟨93JOC2075⟩; with phenylketene the dihydro-2-pyridone (**190**) is formed at room temperature (Scheme 47) ⟨91S1026⟩. More common are 1-azabutadienes with electron-withdrawing *N*-substituents. Boger and co-workers have reacted *N*-sulfonyl derivatives such as (**191**) with a variety of enol ethers and ketene acetals to give tetrahydropyridines and octahydroisoquinolines (Equation (135)) ⟨90JOC2999, 91JA1713⟩; *exo*/*endo* ratios can be quite high. The *N*-acetyl-1-azabutadiene (**192**) can react with unactivated alkenes to give regioisomers and stereoisomers of 1,4,5,6-tetrahydropyridine-2-carbonitriles (Equation (136)) ⟨90JOC5646⟩. An intramolecular electrocyclization produces the α-substituted pyridines (**193**) (Equation (137)) ⟨91T10053⟩.



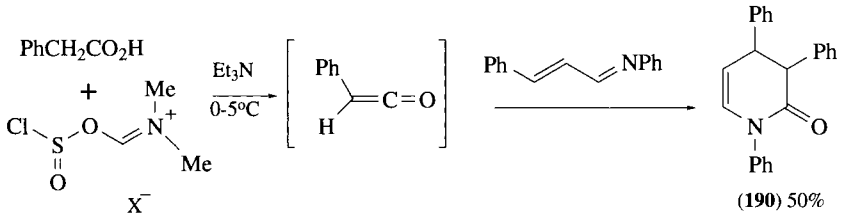
(133)

(**188**) R = Pr^i, C_6H_{11}; many R^1; 21-74%



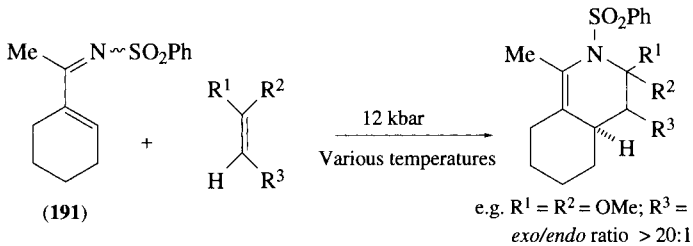
(134)

(**189**) R^1 = Me or Ph; R^2 = aryl; R^3 = Pr^i or C_6H_{11}; 65-90%



(**190**) 50%

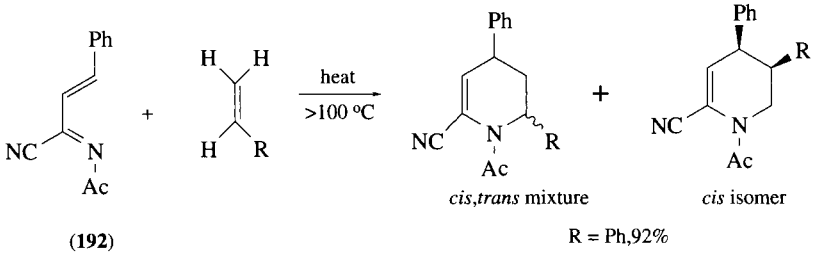
Scheme 47



(135)

(**191**)

e.g. R^1 = R^2 = OMe; R^3 = H; 63%, *exo/endo* ratio > 20:1



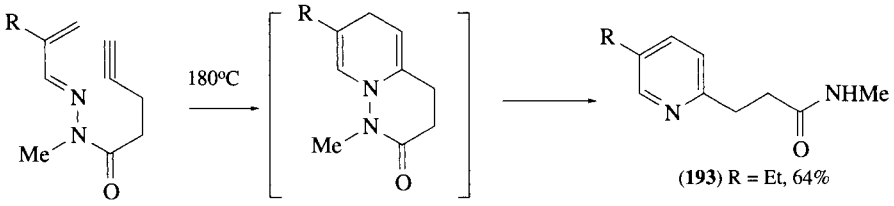
(136)

(**192**)

cis,trans mixture

cis isomer

R = Ph,92%

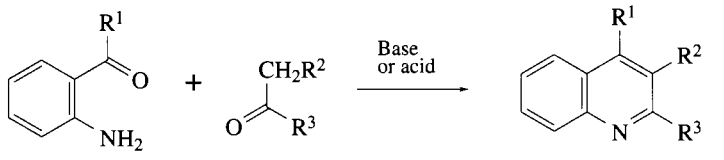


(137)

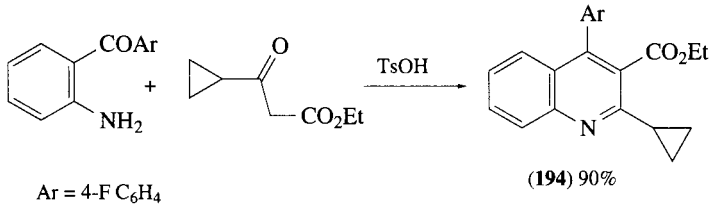
(**193**) R = Et, 64%

A versatile synthesis of quinolines is due to Friedländer, with modification by Pfitzinger and von Niementowski ⟨77HC(32-1)93⟩. The essence of the synthesis is given in (Equation (138)). When R^1 is alkyl or aryl the scheme shows the original Friedländer synthesis, when R^1 = OH (or O^-) the intermediate in the Pfitzinger synthesis, and when R^1 = OR^4 the Von Niementowski modification. Examples are chosen to show variants. A high-yield, acid-catalyzed Friedländer synthesis of quinoline (**194**) uses *p*-toluenesulfonic acid (Equation (139)) ⟨93TL8267⟩. Variants with amides or esters in place of ketones use phosphoryl chloride to give 2-diethylaminoquinolines (**195**) (Equation (140)) ⟨87S810⟩ or piperidine in ethanol to give 2-quinolinones (**196**) (Equation (141)) ⟨93H(36)1387⟩. Use of a suitable *β*-ketoamide in the Pfitzinger reaction leads to quinoline-3,4-dicarboxylic acid derivatives (**197**) (Equation (142)) ⟨88CHE531⟩. Indanones and tetralones condense with isatin to give the

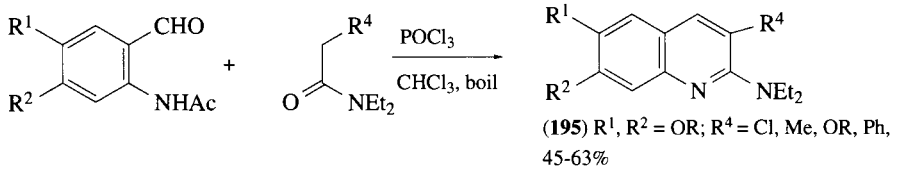
intermediates (**198**), which are reported to cyclize in very high yield under acid conditions (Scheme 48) ⟨93S993⟩; simple ketones were also used but yields are lower. Anthranilates react with benzynes to give acridones (**199**) (Equation (143)) ⟨90TL2869⟩, and 2-pyridones (**200**) are obtained in high yields from enaminoketones and β-ketoesters (Equation (144)) ⟨84H(21)91⟩. Coppola has used isatoic anhydride with a wide range of ketones and β-ketoesters and strong bases to synthesize 4-quinolinones, such as compound (**201**) (Equation (145)) ⟨88S81⟩.



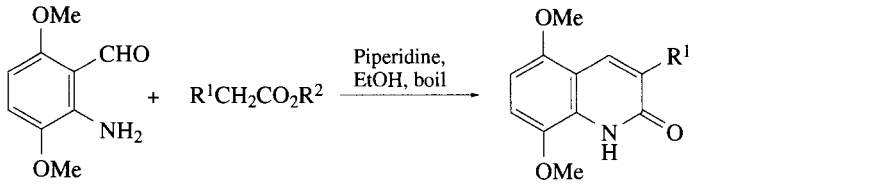
(138)



(139)



(140)



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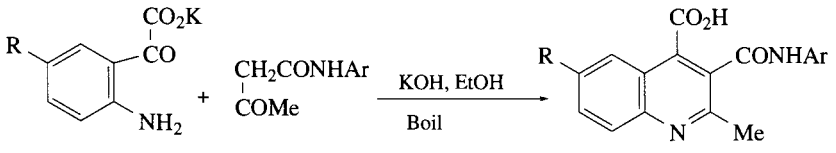
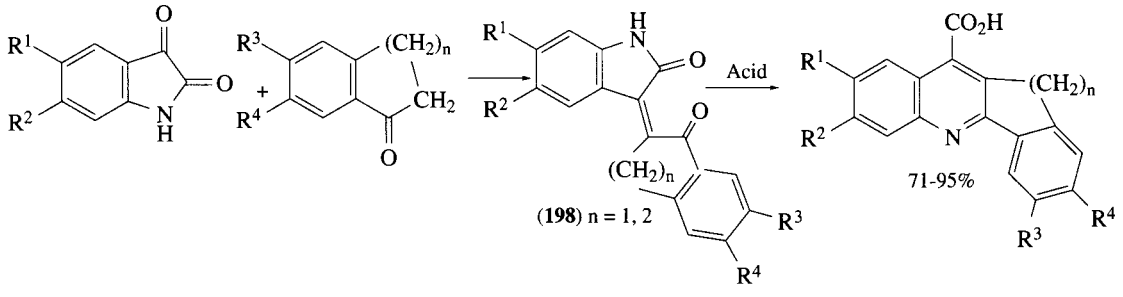
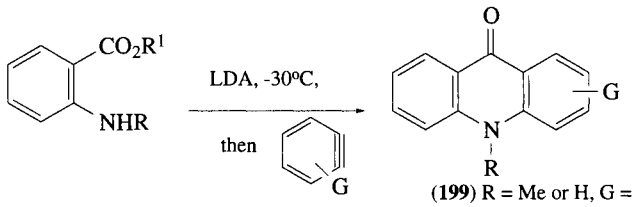


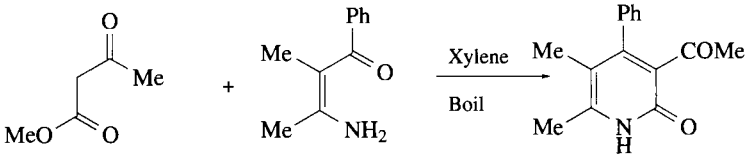
(142)



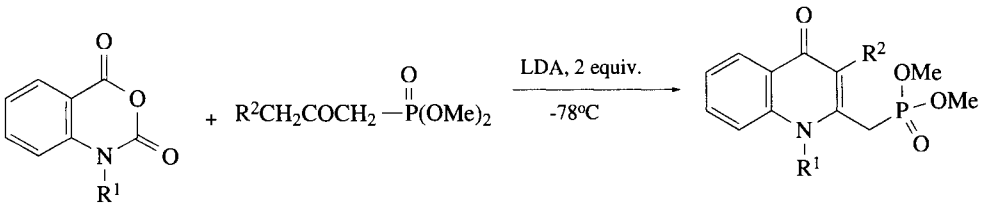
Scheme 48



(199) R = Me or H, G = H or OR, 31-71% (143)

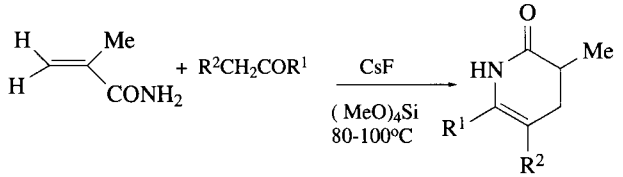


(200) 93% (144)

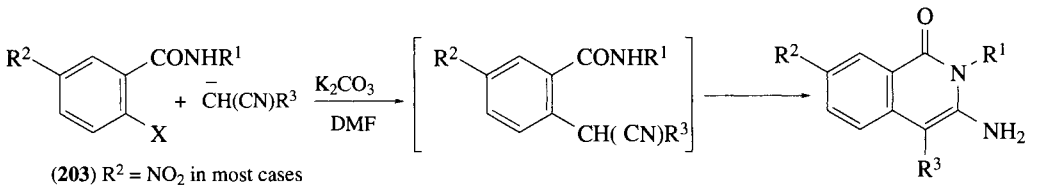


(201) R^1 = allyl, Ph; R^2 = H, alkyl, Ph; 39-61% (145)

Among the base-catalyzed routes to pyridine rings, a number start from α,β-unsaturated amides, which are condensed with ketones; thus the dihydro-2-pyridones (**202**) are obtained in moderate to good yields (Equation (146)) ⟨86T2293⟩. When the 2-haloamides (**203**) ⟨91CHE307⟩ are used, the reaction is initiated by base (Equation (147)); in less activated aryl halides photochemical activation was used, with ketones as co-reagents ⟨81S729⟩. Bis(methylthio)methylidenemalononitriles or cyanoacetamides can provide the four-atom component in condensations with active methylene compounds, as illustrated for the synthesis of 2-pyridones (**204**) (Equation (148)). Conversely, in the synthesis of quinoline *N*-oxides (**205**), the alkylidene malononitrile acts as the two-atom component (Equation (149)) ⟨85H(23)2557⟩. Quinoline *N*-oxides are also obtained by a Wittig–Horner reaction on 2-nitrobenzaldehydes (**206**) (Equation (150)) ⟨84JOC4999⟩.

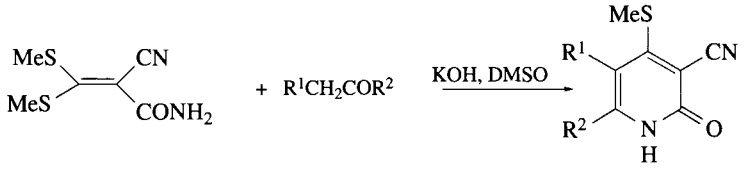


(202) e.g. $R^1 = R^2$ = Me, 76% (146)

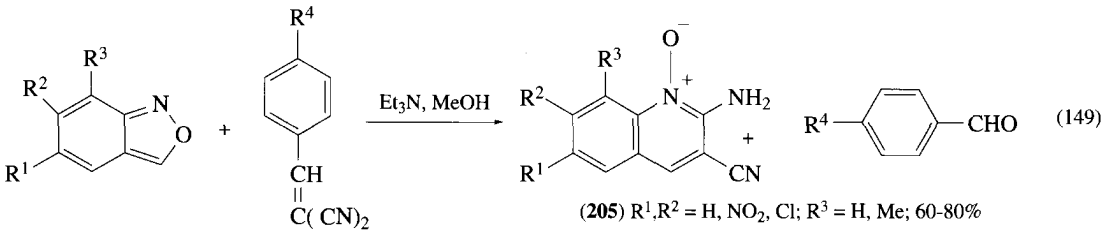


(203) $R^2 = NO_2$ in most cases

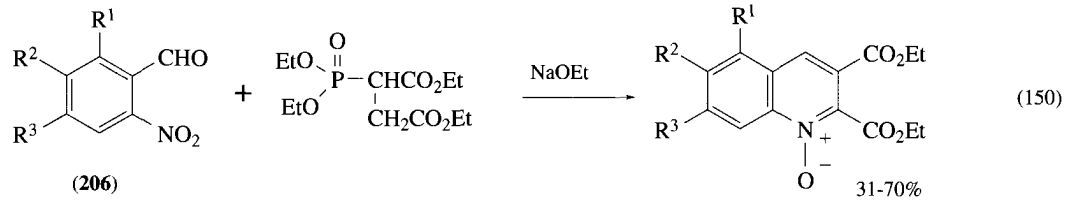
61-83% (147)



(204) R^2 = CO_2Et or COMe for yields of 63-77% (148)

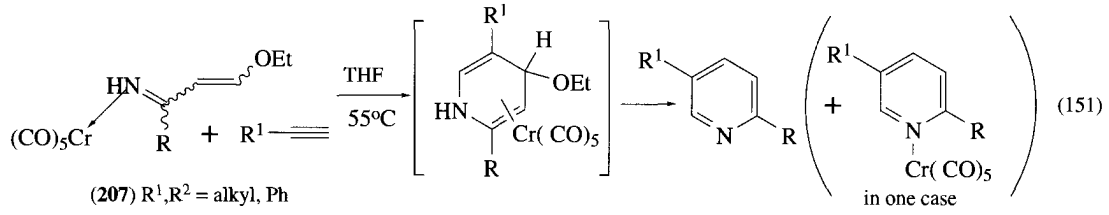


(205) R^1,R^2 = H, NO_2, Cl; R^3 = H, Me; 60-80% (149)

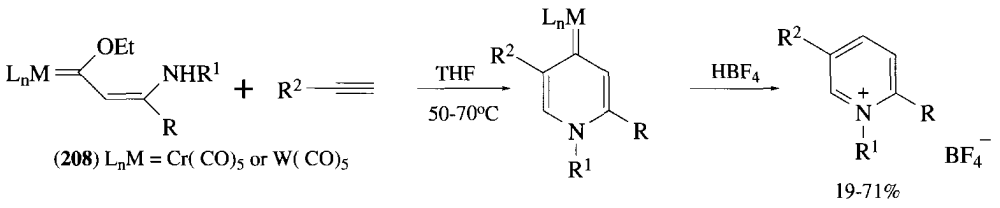


(206) (150)

A number of syntheses of pyridines and pyridones involve transition metals. The chromium or tungsten pentacarbonyl derivatives (**207**) (Equation (151)) ⟨92CB2765⟩ and (**208**) (Scheme 49) ⟨93CB2535⟩ react with alkynes to give pyridines or pyridinium derivatives, respectively. Finally in this section, two transformations postulated to go through cyclic intermediates deserve mention, namely reaction of the aminobenzaldehyde imine (**209**) with carbon suboxide (Equation (152)) ⟨84S266⟩, and the regioselective photochemical addition of the aminoacrolein (**210**) to alkenes with subsequent fission of the cyclobutane ring and recyclization (Scheme 50) ⟨86S190⟩.



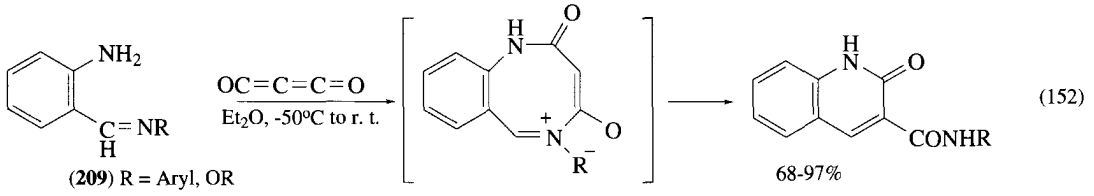
(207) R^1,R^2 = alkyl, Ph (151)



(208) L_nM = Cr(CO)5 or W(CO)5

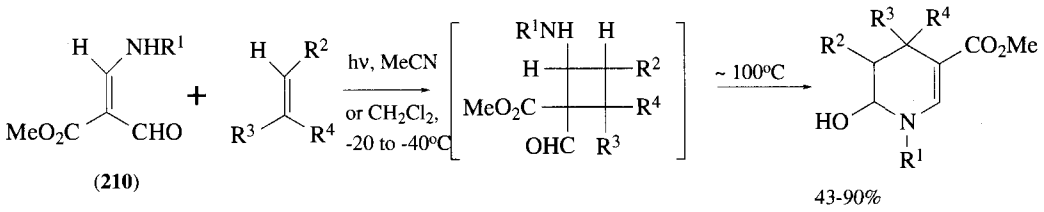
19-71%

Scheme 49



(209) R = Aryl, OR 68-97% (152)

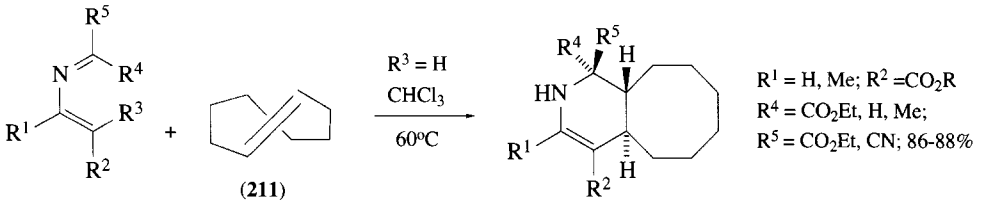
(b) Bonding to a terminal carbon atom. Popular choices for ($4\pi_s + 2\pi_s$) cycloaddition reactions are 2-azabutadienes, for which *ab initio* calculations are available ⟨92JOC3031, 92JOC6736⟩. Electron-poor azadienes can react with the simple (but reactive) alkene (**211**) (Equation (153)) ⟨93TL4377⟩, or enamines ⟨93TL4097⟩ where the yields and stereoselectivity are poor. Better results are obtained with unsaturated carbodiimides such as compound (**212**) (this may be two-stage, with a secondary 6π electrocyclization) (Equation (154)) ⟨91BCJ1325⟩. Electron-rich 2-azabutadienes react with electron-deficient alkenes such as naphthoquinones ⟨91H(32)915⟩ to give the benzoisoquinolinetriones (**213**) (Equation (155)), or with alkynes to give the pyridines (**214**) (Equation (156)) ⟨82JA1428⟩. Alkenyl



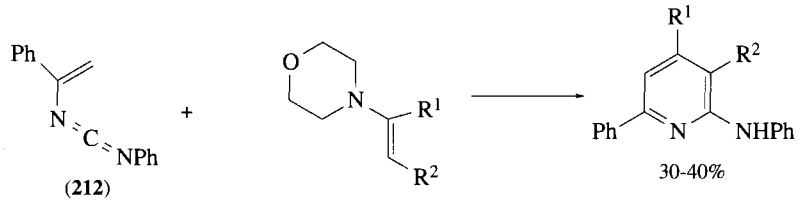
(210)

Scheme 50

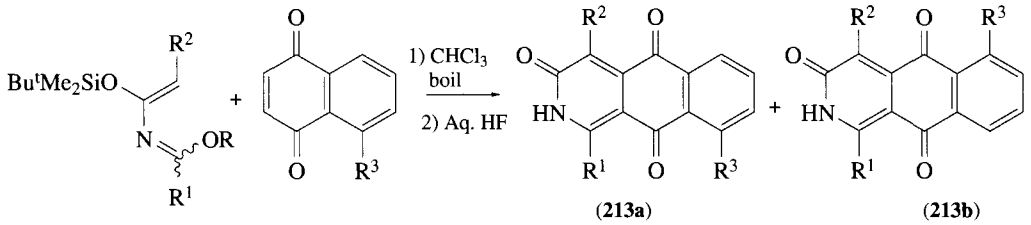
isocyanates react with benzyne to give phenanthridone derivatives (**215**) (Scheme 51) ⟨89JOC4019⟩, with enamines to give a variety of reduced isoquinoline-1-ones ⟨89JOC224⟩, and with the ketene (**216**) (Equation (157)) (alkenylisothiocyanates also react) ⟨88T543⟩. An intramolecular 2-azadiene cyclization has been thoroughly examined for the effects of temperature and time; one isomer, (**217**), predominates (Equation (158)) ⟨88TL4799⟩.



(211) (153)

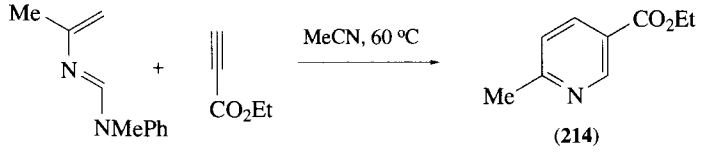


(212) (154)

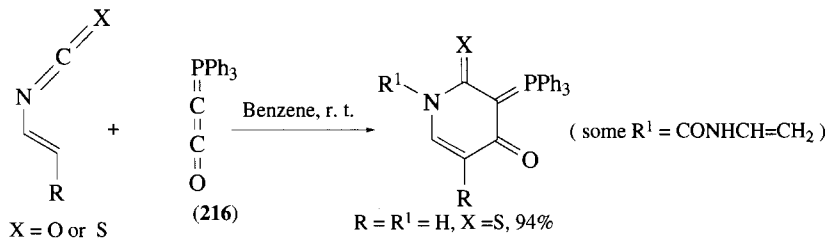


(213a) (213b) (155)

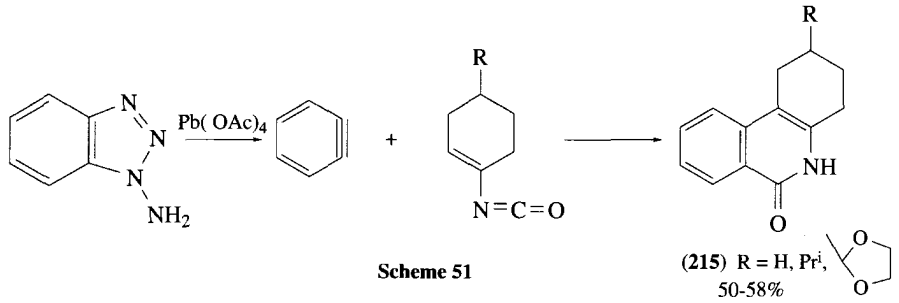
When R^3 = OH, (**213a**):(**213b**) ratio > 78:22
When R^3 = OAc, (**213a**):(**213b**) ratio 30:70 to 54:46



(214) (156)

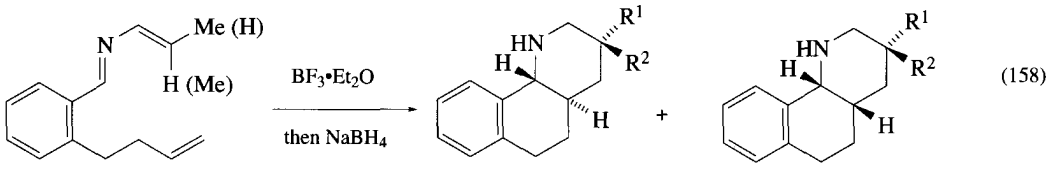


X = O or S (216) $R = R^1$ = H, X =S, 94% (157)



Scheme 51

(**215**) R = H, Pr^i, 50-58%

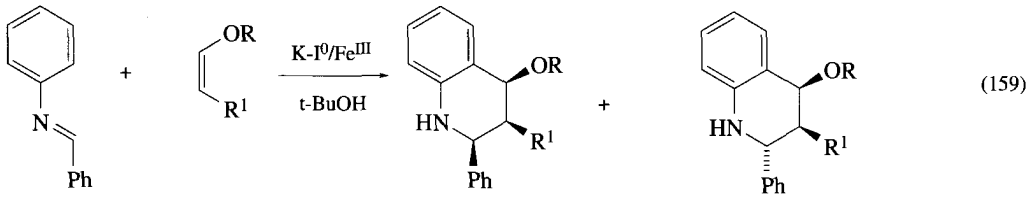


(158)

8 : 1, EE : EZ

(**217**) R^1 = H, R^2 = Me, 47%; others 13%

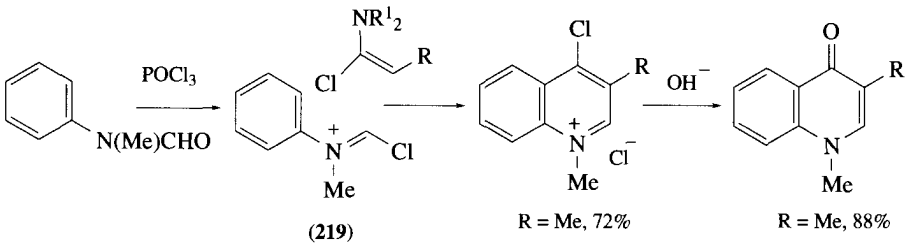
Schiff bases derived from anilines can function as 4π components. They react stereoselectively with enol ethers in the presence of BF_3 etherate or iron(III)-doped acidic montmorillonite ⟨88TL3585, 89TL7237⟩, as shown in the formation of tetrahydroquinolines (**218a**) and (**218b**) (Equation (159)). Iminium salts (**219**) give 4-chloroquinolinium salts and hence *N*-methyl-4-quinolinones (Scheme 52) ⟨93TL3629⟩, while some degree of diastereoselectivity is obtained on reaction of the enantiomerically pure iminoesters (**220**) with alkenes (Equation (160)) ⟨89JCS(P1)2245⟩. Nitrilium salts are reported to react with alkynes to give good to excellent yields of quinolinium salts (**221**) (Equation (161)) ⟨92S875⟩.



(159)

(**218a**) 63%

(**218b**) 19%

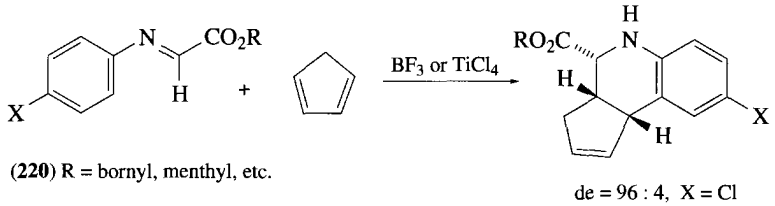


(**219**)

R = Me, 72%

R = Me, 88%

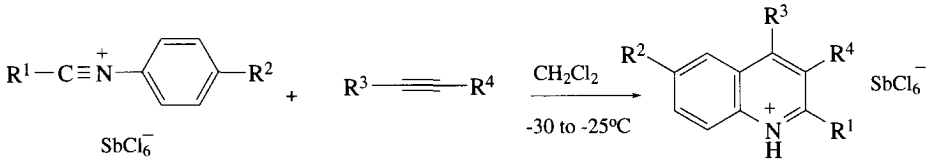
Scheme 52



(160)

(**220**) R = bornyl, menthyl, etc.

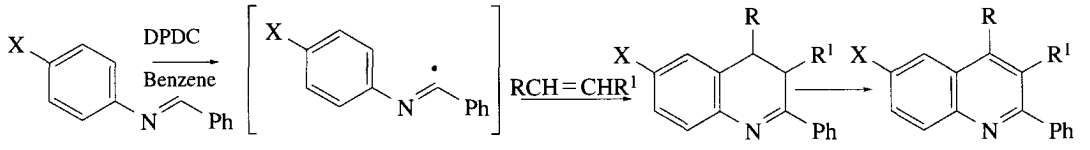
de = 96 : 4, X = Cl



(161)

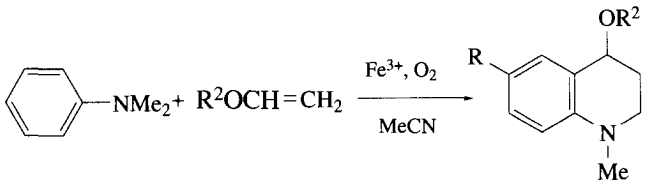
(**221**) 16 examples, 61-88%

A number of reactions apparently closely related to those above are thought to involve radical intermediates, generated by the action of DDQ or diisopropyl peroxycarbonate on Schiff bases. Alkenes or alkynes can then be added with apparently high regioselectivity; an alkene example gives quinolines (**222**) (Scheme 53) ⟨89G637, 93T10157⟩. One-electron oxidation of dimethylaniline followed by addition of enol ethers gives 4-alkoxyquinolines (**223**) (Equation (162)) ⟨89JOC4700⟩. Anodic oxidation of dimethylanilines ⟨82JA5753⟩, or oxidation with ruthenium trichloride/H_2O ⟨90H(31)415, 92TL6991⟩ in methanol, gives *N*-methoxymethyl derivatives (**224**) (Scheme 54). Treatment of these with Lewis acids produces iminium salts which react with alkenes or alkynes to give reduced quinolines in high yield.



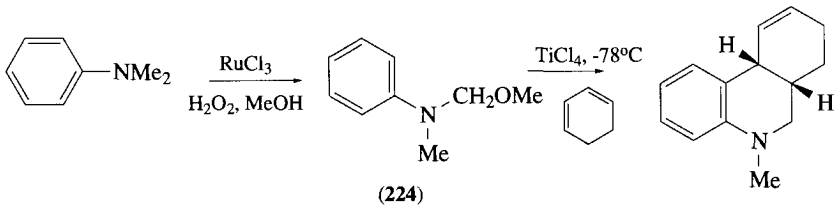
(**222**)
e. g. X = OMe, R = CN, R^1 = H, 57%

Scheme 53



(162)

(**223**) R = H, OMe; R^2 = OBu^n or OBu^i; 65-86%



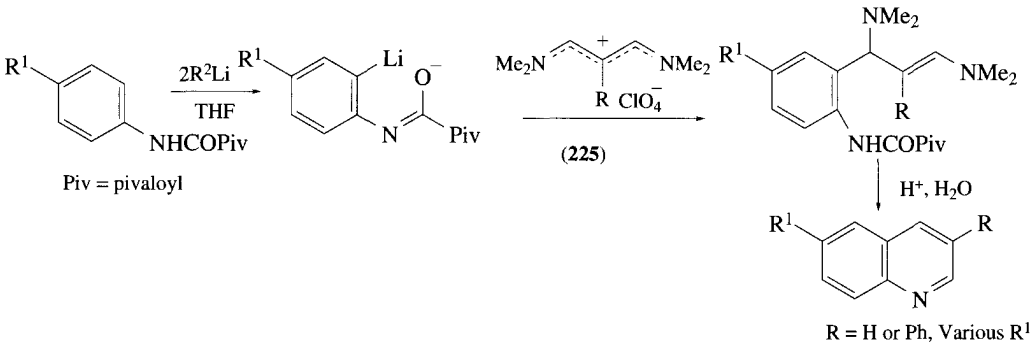
(**224**)

Scheme 54

A reaction said to be a new variant on the Friedländer synthesis uses directed lithiation on an anilide to produce an *o*-lithio species which, when treated with the Vilsmeier reagent (**225**), gives a product which is hydrolyzed to give quinolines in moderate to excellent yield (Scheme 55) ⟨91JOC7288⟩.

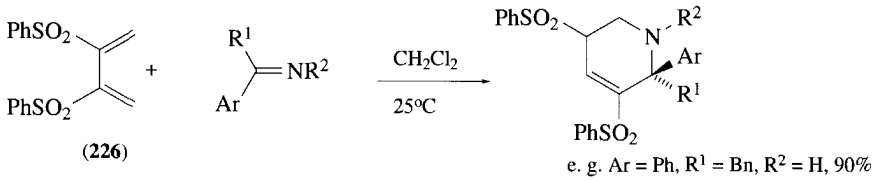
(ii) Nitrogen in the two-atom fragment

Electrocyclic ($4\pi_s + 2\pi_s$) reactions where the 2π component is an imine or iminium species have been much used for synthesis of reduced pyridines and pyridones; a good review is available ⟨B-

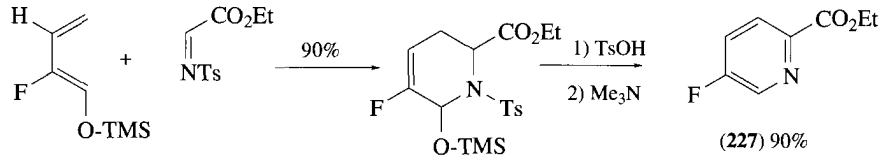


Scheme 55

87MI 505-01〉 and there is a more general review of imine cycloadditions 〈87H(26)777〉. Control of stereochemistry and enantioselectivity has been important and has been reviewed 〈94S535〉. A few examples will be given to show the potential of the reaction. The di(phenylsulfonyl)diene (**226**) gives high yields of tetrahydropyridines where one phenylsulfonyl group has migrated and the double bond has isomerized (Equation (163)) 〈91JOC2713〉. In the synthesis of the fluoropyridine (**227**), groups are present on diene and imine which can be eliminated easily to produce the aromatic product (Scheme 56) 〈93T1445〉.

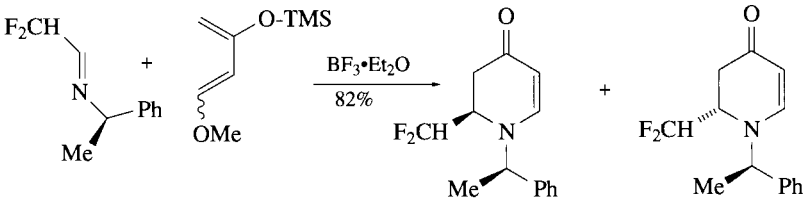


(163)



Scheme 56

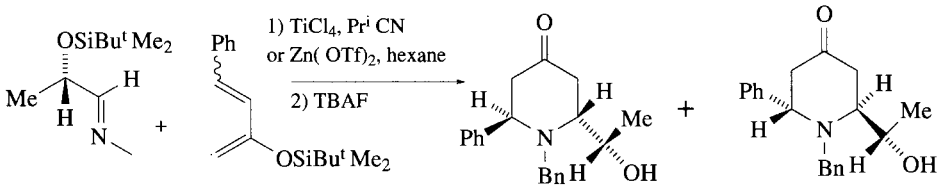
Enantioselectivity can be achieved by using a chiral directing group on the imine, on the diene (less common), or by using a chiral catalyst. One example of the use of a chiral imine (>98% *ee*) gives dihydropyridones (**228a**) and (**228b**) in a ratio of approximately 1 : 4, each being obtained with >99% *ee* (Equation (164)) 〈94TA1029〉. The chiral directing group can be attached to the carbon atom of the imine as in the synthesis of (**229a**) and (**229b**), where the use of titanium tetrachloride or zinc triflate as Lewis acids can give good yields and opposing diastereoisomeric excess (Equation (165)) 〈94SL495〉. Higher-polarity solvents with titanium tetrachloride raise the diastereoisomeric excess, as does the use of *n*-hexane with zinc triflate. In the dienes (**230**), the pyrrolidine substituent gives good enantioselectivity, and can be removed on hydrolysis of the product (Scheme 57) 〈93JA4403〉. With a chiral catalyst, such as the boron derivative (**231**), piperidinones (**232**) with acceptable to good enantiomeric excesses have been obtained (Equation (166)) 〈93T1749〉. Iminium ions react with dienes, but the reaction may be sequential rather than concerted. New methods for generating iminium ions are from aminomethylbenzotriazoles 〈93JOC4049〉 or from aldehydes and *N*-sulfonyl-*p*-toluenesulfonamide 〈89TL3037〉; the latter method is illustrated for the synthesis of tetrahydropyridines (**233**) (Scheme 58). Nitriles with electron-withdrawing substitutents can react with ethoxydienes to give pyridines (**234**) (Equation (167)) 〈89S623〉. Regioselectivity is good in this case, but in another, catalyzed, case it is poor 〈86S584〉.



(164)

(**228a**) α (*R*),6(*R*) (**228b**) α (*R*), 6(*S*)

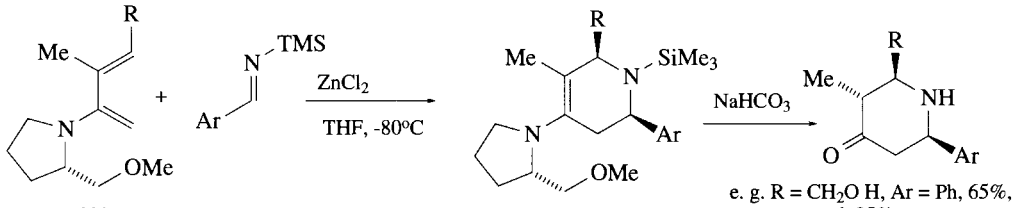
Ratio (**228a**)/(**228b**) = 19:81; both > 99% *ee*



(165)

(**229a**) (**229b**)

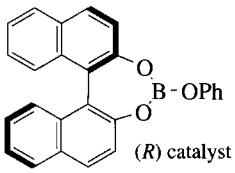
Ratio of (**229a**)/(**229b**) is 14:6 ($ZnOTf_2$) or 2:9 ($TiCl_4$)



(**230**)

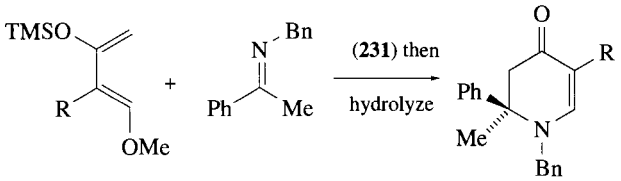
e. g. R = CH_2O H, Ar = Ph, 65%, and 95% *ee*

Scheme 57



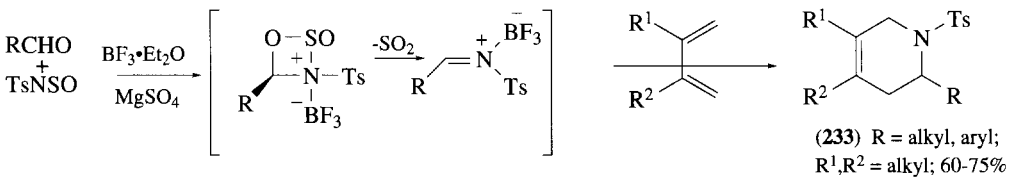
(*R*) catalyst

(**231**)



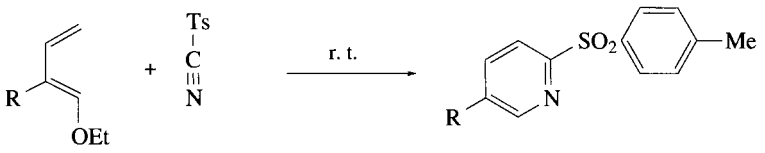
(166)

(**232**) R =H, Me, 72-75%, 82% ee



(**233**) R = alkyl, aryl; R^1,R^2 = alkyl; 60-75%

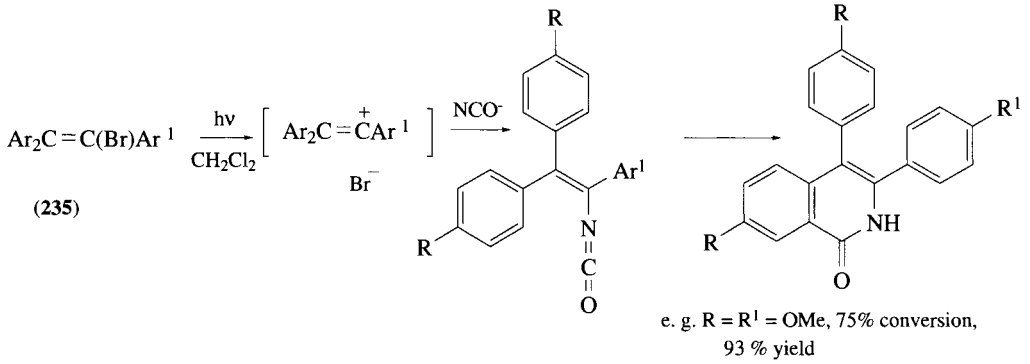
Scheme 58



(234) R = alkyl, 64-81%

(167)

In a photolytic procedure involving generation of vinyl cations, cyanate anion substitutes into the cation derived from bromoalkene (**235**) to give an intermediate unsaturated isocyanate which gives an isoquinolin-1-one (Scheme 59); thiones are produced from isothiocyanates ⟨90JOC1801⟩.

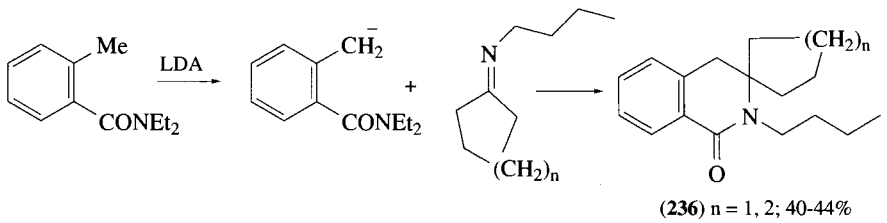


(235)

e. g. R = R^1 = OMe, 75% conversion, 93 % yield

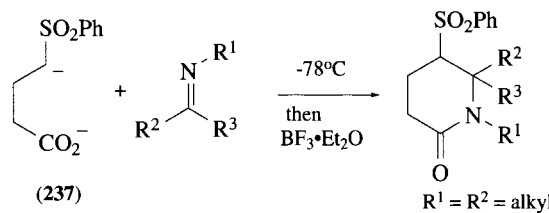
Scheme 59

There are a number of syntheses which involve anionic attack on imines. In the synthesis of 3,4-dihydroisoquinolin-1-ones (**236**), directed lithiation of a toluamide provides the anion (Scheme 60) ⟨89JOC2992⟩. In other examples the anion was formed from isobenzofuranones ⟨83JCS(P1)1453⟩ or dianions such as (**237**), which give tetrahydropyridinones (Equation (168)) ⟨88JOC5389⟩. Alkyl and aryl cyanides can react with active methylene compounds in basic media to give isoquinolinones (**238**) (Equation (169)) ⟨82JOC3787⟩, 4-pyridones (**239**) (Equation (170)) ⟨85H(23)2983⟩, 4-hydroxy-2-pyridones (**240**) (Equation (171)) ⟨90JOC2964⟩, and polysubstituted 2-aminopyridines (**241**) (Equation (172)) ⟨85CB2198⟩. The base-catalyzed reaction of primary amines with 1,2-dibenzoylbenzene gives isoquinolines (**242**), the α-methylene group (in some cases unactivated) appearing as C-3 (Equation (173)) ⟨80H(14)789⟩. Pyridine-2-thiones (**243**) are produced by base-catalyzed condensation of enediones with isothiocyanates (Scheme 61) ⟨83S1025⟩.



(236) n = 1, 2; 40-44%

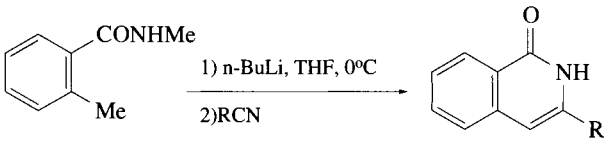
Scheme 60



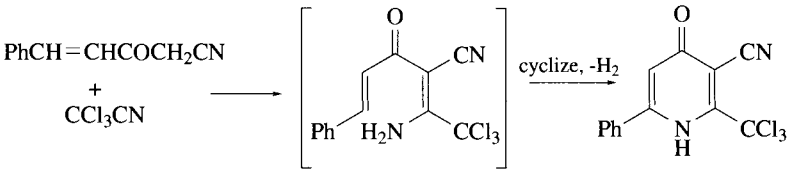
(237)

R^1 = R^2 = alkyl, R^3 = H; 66-90%

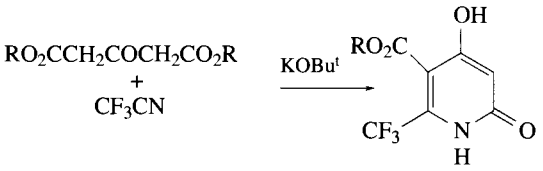
(168)



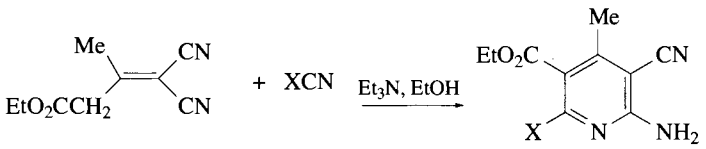
(238) 42-87% (169)



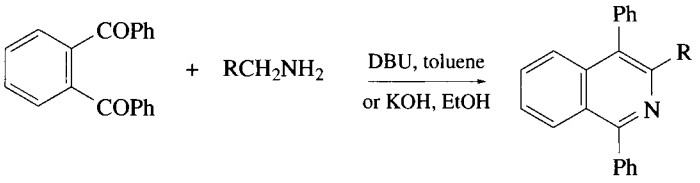
(239) 78% (170)



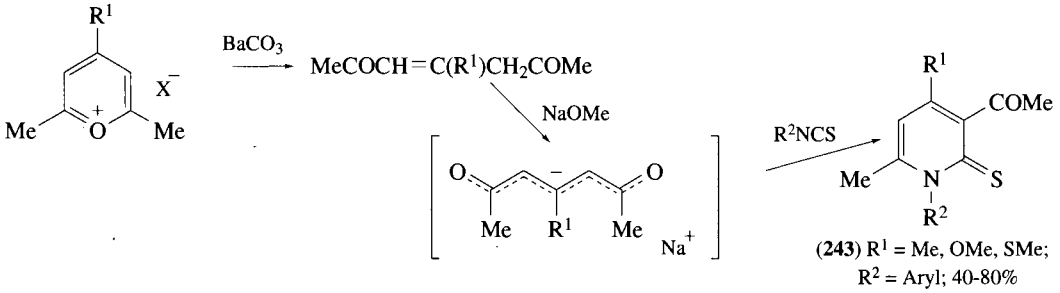
(240) R = Me (57%), Et(95%) (171)



(241) X = CCl_3, OPh, 54-65% (172)



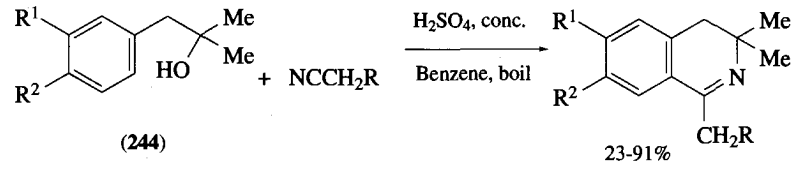
(242) R = Ph(96%), Pr^n(89%), CO_2Et(61%), CN(14%) (173)



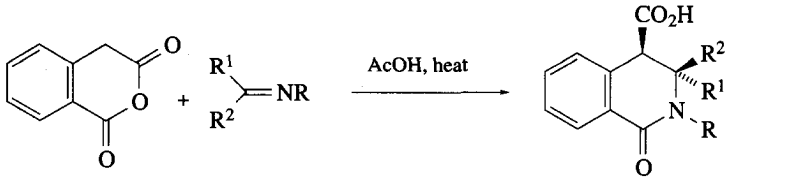
(243) R^1 = Me, OMe, SMe; R^2 = Aryl; 40-80%

Scheme 61

Nitriles can also give dihydroisoquinolines when they react with suitable electrophiles, derived for example from phenylethanols (**244**) (Equation (174)) ⟨91CHE523⟩, while homophthalic anhydride reacts with imines in boiling acetic acid to give dihydroisoquinolin-1-ones (**245**) (Equation (175)) ⟨93JHC257⟩.



(244) 23-91% (174)



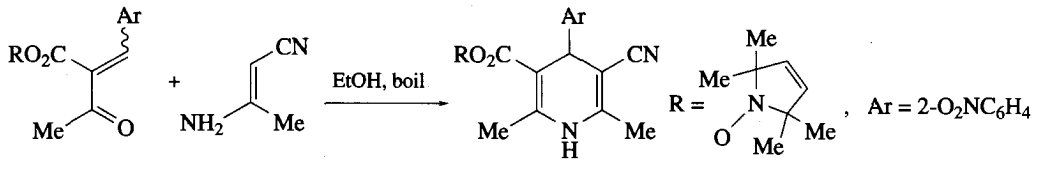
(245) 13 examples, 35-70% (175)

5.05.2.2.3 *From two three-atom fragments*

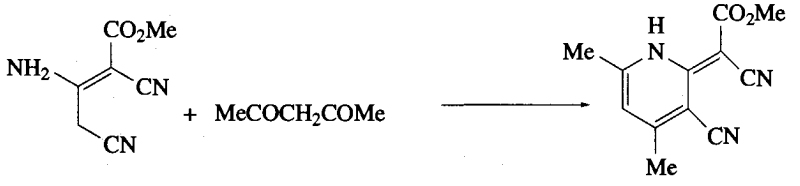
This section is divided according to the nature of the three-atom fragment. First are syntheses with two acyclic or alicyclic fragments, giving pyridines or *bz*-tetrahydroquinolines or -isoquinolines (using enamines or imines, and then cyanoacetamides, cyanoacetate, malonamides, and malononitriles). Second are syntheses from one acyclic or alicyclic and one aromatic fragment, and finally syntheses from two aromatic fragments.

(i) Two acyclic or alicyclic fragments

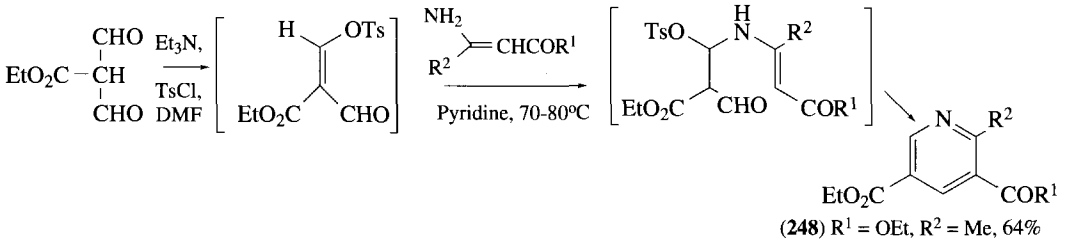
(a) Syntheses using enamines or imines. The original Hantzsch synthesis (see Section 5.05.2.4.2), still widely used, combined a β-ketoester, an aldehyde, and ammonia. It is well established that the intermediates are β-aminoacrylates and α,β-unsaturated ketones, and these are often used, particularly when unsymmetrically substituted pyridines are required. Here follow examples of the modified Hantzsch synthesis, to give dihydropyridines (**246**) where a radical center is present (Equation (176)) ⟨91S91⟩, and of a Mumm variation using a β-diketone and an aminoester, to give pyridine (**247**) (where the tautomeric form shown is preferred) (Equation (177)) ⟨83H(20)2405⟩. A new approach to the use of malonic aldehydes uses a tosyloxymethylene group as protection, giving trisubstituted pyridines (**248**) (Scheme 62) ⟨86S400⟩. In some cases hydroxytetrahydropyridines are isolated ⟨89S719⟩, and the full stereochemistry of the two isomers (**249a**) and (**249b**) has been used in a discussion of the mechanism of the Hantzsch synthesis (Equation (178)) ⟨93TL1967⟩. Note that unsymmetrical β-diketones and 2-methylene-1,3-diones frequently lead to mixtures of pyridines ⟨88JHC125⟩. Modifications to the enamine component reported are the use of phosphinimines to give pyridines (Equation (179)) (**250**) via a 6π electrocyclic reaction and dehydrogenation ⟨93TL3773⟩, the *in situ* formation of lithium β-amidoacrylonitriles, leading to pyridines (**251**) via elimination of methanethiol (Scheme 63) ⟨91S889⟩ and the use of *N*,*N*-bis(trimethylsilyl)enamines and chalcones, activated by addition of caesium fluoride ⟨90JOC2878⟩.



(246) (176)

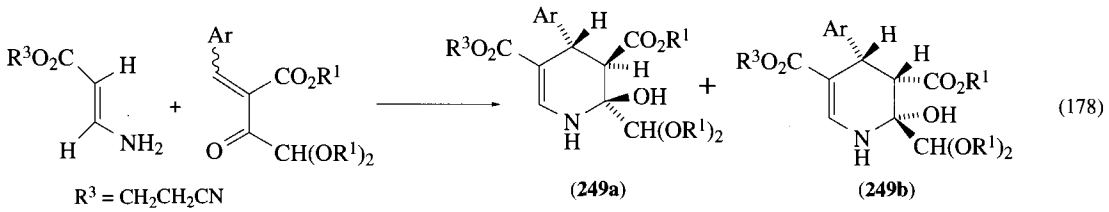


(247) 92% (177)

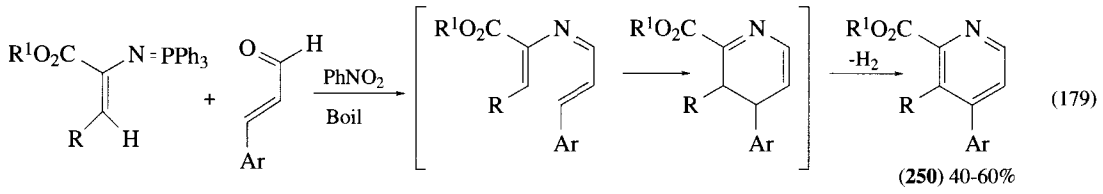


(**248**) R^1 = OEt, R^2 = Me, 64%

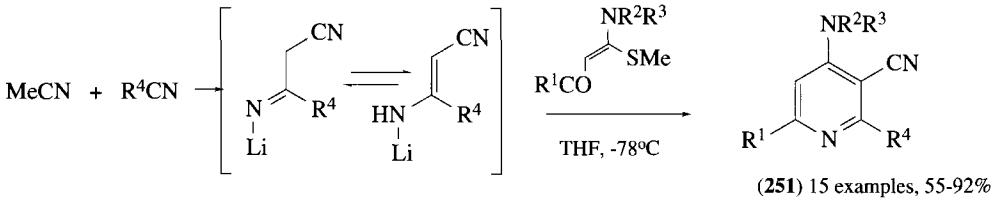
Scheme 62



(178)

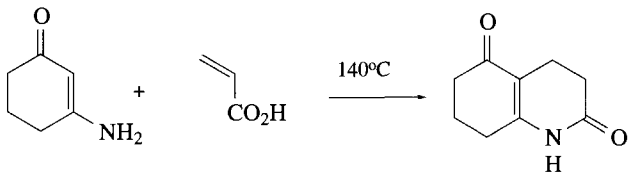


(179)



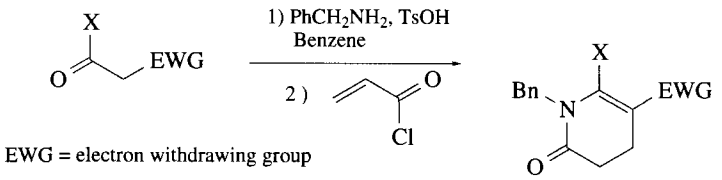
Scheme 63

Enamines and α,β-unsaturated acid derivatives give 2-pyridones. Yields can be high, as shown for the tetrahydroquinolinedione (**252**) (Equation (180)) ⟨81JOC3719⟩, and completely regiospecific, as shown for the dihydro-2-pyridones (**253**) (Equation (181)) ⟨93TL8197⟩. Ethoxymethylene- and arylidenemalonates can give high yields of 2-pyridone-3-carboxylates ⟨89JHC1859⟩; in the example given, use of a chiral substituent on nitrogen gives the bicyclic pyridone ester (**254**) (Equation (182)), and high enantiomeric excesses can be obtained ⟨87TL3795⟩. Alkynic esters can also be used ⟨87S662⟩. Enamines and carbon suboxide give 2,4-dihydroxypyridines, (**255**) (Equation (183)) ⟨92JHC237⟩; similar compounds are obtained from diaryl malonates or malonyl chloride with β-ketoamines ⟨88S87⟩. Enaminoketones react with arylidenemalononitriles to give good yields of 2-aminopyridines (**256**) (Equation (184)) ⟨89S775⟩.



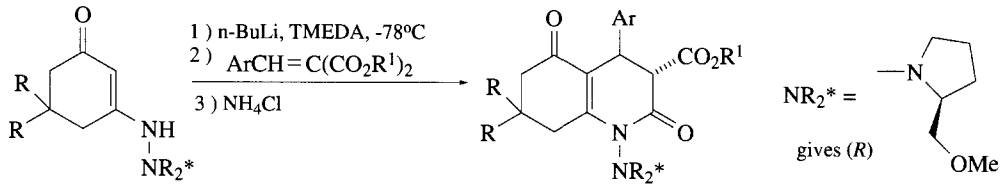
(**252**) 95%

(180)



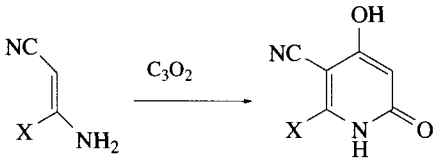
EWG = electron withdrawing group

(253) X = Me, CO_2Me, 45-96% (181)

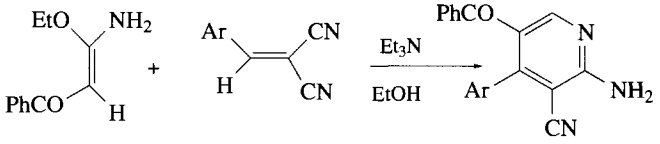


(254), 50-60%, 98% ee

Enantiomer gives (*S*) (182)

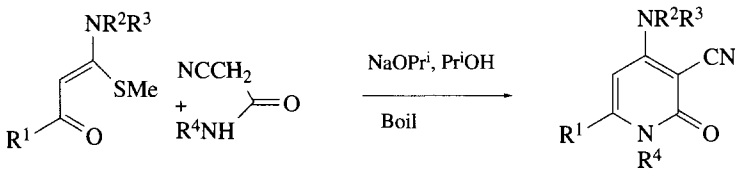


(255) X = various saturated *N*-heterocycles (183)

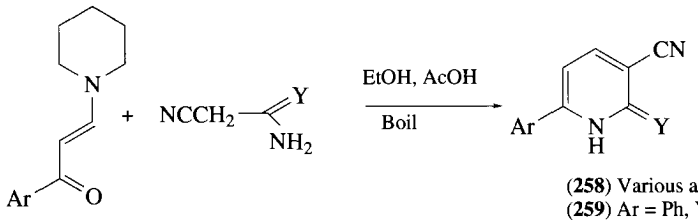


(256) 60-85% (184)

(b) Syntheses using cyanoacetic and malonic acid derivatives. A very large number of pyridines have been synthesized using cyanoacetamide (or cyanothioacetamide), malononitrile, malonamide, and closely related compounds, which provide the N–C(2)–C(3) fragment. There are reviews which include these syntheses ⟨86H(24)2023, 87H(26)205, 93CR1991⟩. Principal co-reagents are α,β-unsaturated ketones, arylidene malononitriles (there is a review ⟨83H(20)519⟩ of the use of α,β-unsaturated nitriles in the synthesis of pyridines), and β-diketones or β-ketoaldehydes. Two examples of condensation between unsaturated ketones and cyanoacetamides, cyanothioacetamides, or cyanoselenoacetamide illustrate the production of 2-pyridones (**257**) ⟨82S214⟩ by base catalysis (Equation (185)), and pyridine-2-thiones (**258**), and pyridine-2-selenones (**259**) ⟨88CHE658⟩ by acid catalysis (Equation (186)). With the β-ketoaldehyde enolate (**260**), cyanoacetamide gives a 3-cyano-2-pyridone (Equation (187)) ⟨90T7693⟩, and with β-diketones cyanothioacetamide gives 3-cyanopyridine-2-thiones (**261**) (Equation (188)) ⟨85JOU2230⟩. Malonamides with α,β-unsaturated ketones give generally high yields of 6-hydroxypiperidin-2-ones (**262**) (Equation (189)) ⟨85JCS(P1)1681⟩, while the monothioamide (**263**) (R = H) cyclizes to the normal amide with α,β-unsaturated ketones (Scheme 64) ⟨87CHE817⟩, but the substituted amide (R = alkyl or aryl) cyclizes to the thioamide with β-diketones ⟨85S861⟩. Acetoacetamides (**264**) can act as both partners in a cyclization, with the interesting difference that the anilides give 4-pyridones, while the *N*-alkylamides give 2-pyridones (Equation (190)) ⟨82JMC131⟩.

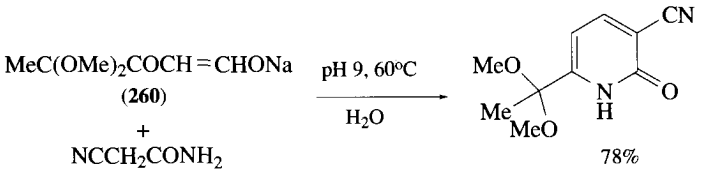


(257) 53-71% (185)



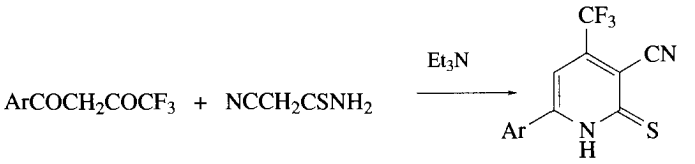
(186)

(**258**) Various aryl, Y = S, 57-79%
(**259**) Ar = Ph, Y = Se, 50%



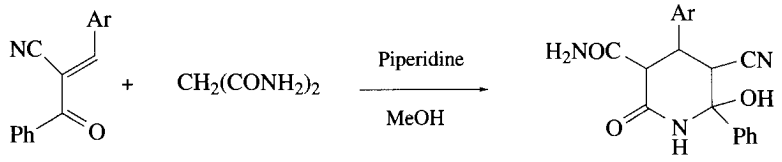
(187)

78%



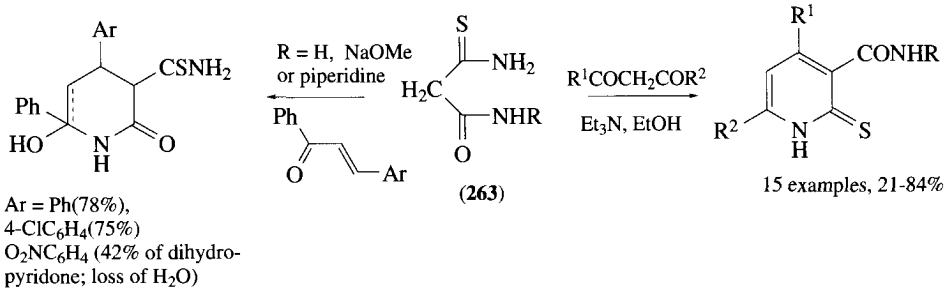
(188)

(**261**) Ar = Ph,84% , 2-thienyl, 78%



(189)

(**262**) Various aryl, 63-87%

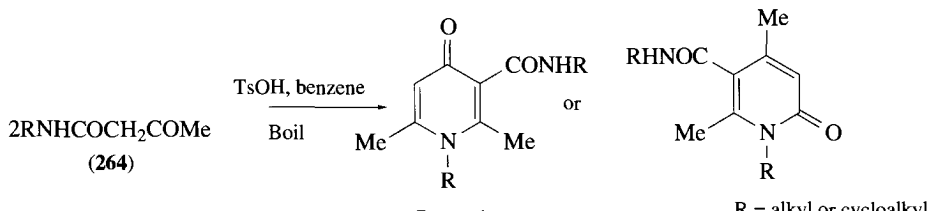


Ar = Ph(78%),
4-ClC$_6$H$_4$(75%)
O$_2$NC$_6$H$_4$ (42% of dihydropyridone; loss of H$_2$O)

(**263**)

15 examples, 21-84%

Scheme 64

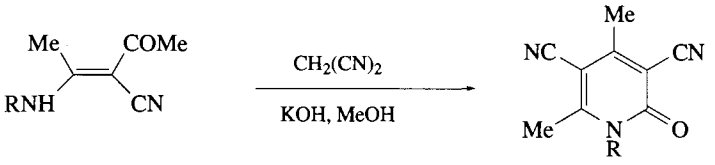


(190)

R = aryl

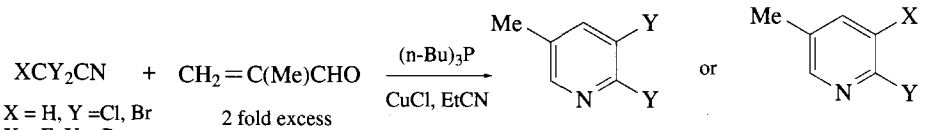
R = alkyl or cycloalkyl

Malononitriles react with α,β-unsaturated ketones to give 2-pyridones, such as (**265**) (Equation (191)) ⟨87H(25)393⟩, and haloacetonitriles have been used as three-atom components in the synthesis of dihalopyridines (**266**) and (**267**) (Equation (192)) ⟨85JOC5115⟩.



(191)

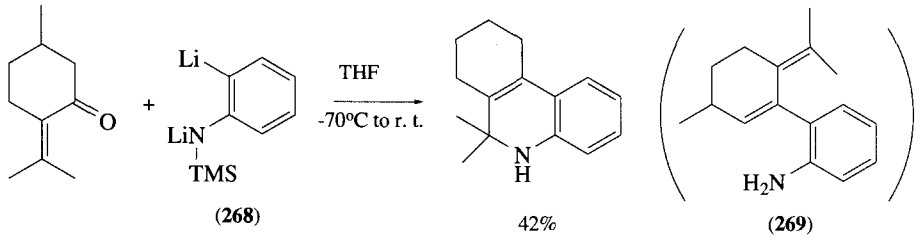
(**265**) R = Ph(65%), R = Me(35%)



(192)

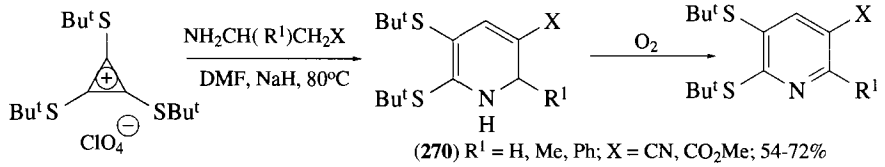
(**266**) Y = Cl, Br(40%) (**267**) X = F, Y = Br, ~30%

(c) Miscellaneous methods. Among miscellaneous syntheses in this section are two where the nitrogen is at the terminus and two with nitrogen in the center of the three-atom fragment. The dilithiated *N*-trimethylsilyaniline (**268**) reacts with pulegone as shown in Equation (193) to give a reduced phenanthridine at room temperature, but on heating the mixture gives compound (**269**) ⟨86JHC1353⟩. Cyclopropenium salts react with amino acid derivatives to give, for example, the di-*t*-butylthiodihydropyridines (**270**) (Scheme 65) ⟨89T3217⟩. The delocalized anions (**271**) react with the alkene (**272**) to give a product which can be readily cyclized by lithium iodide or TBAF (Scheme 66) ⟨88TL4819⟩, while the carbodiiminium species (**273**) reacts with alkenes (**274**) to give highly substituted pyridines via an intermediate 1,5-hydrogen shift and electrocyclization (Equation (194)) ⟨94S509⟩.



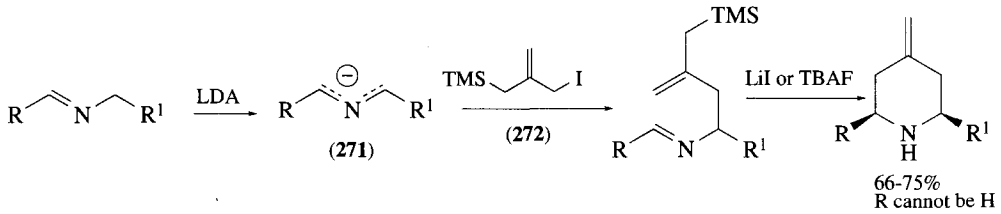
(193)

(**268**) 42% (**269**)



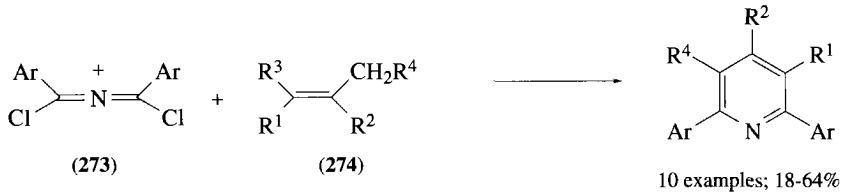
(**270**) R^1 = H, Me, Ph; X = CN, CO_2Me; 54-72%

Scheme 65



66-75%
R cannot be H

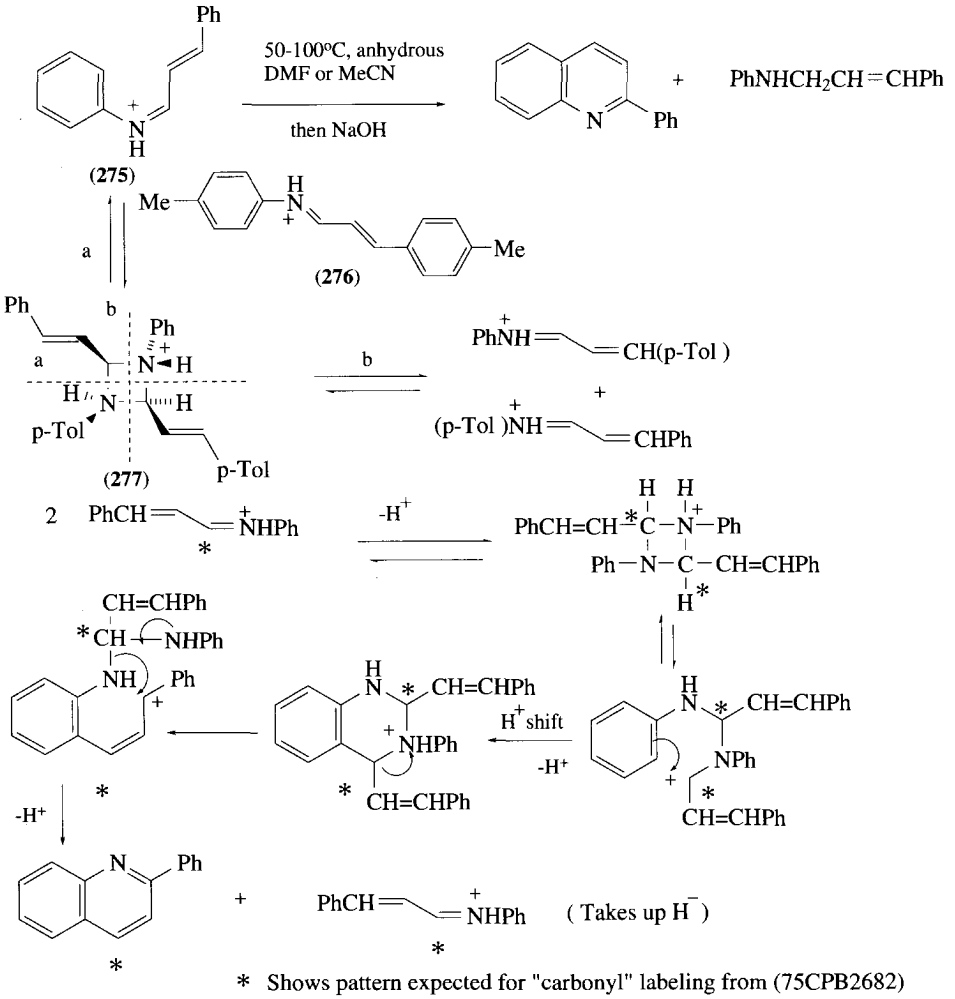
Scheme 66



(273) (274) 10 examples; 18-64% (194)

(ii) One acyclic fragment and one fragment containing an aromatic ring

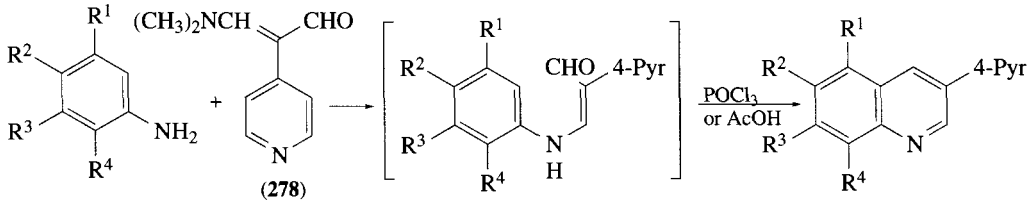
(a) Syntheses of quinolines. The most famous quinoline synthesis is due to Skraup, which can be considered as a special case of the Doebner–von Miller synthesis (nominally category [3 + 2 + 1] but dealt with here for convenience). Both have been reviewed ⟨77HC(32(1))100⟩. An important mechanistic study ⟨89JOC1269⟩ has led to a new proposal which is briefly dealt with here. The formation of 2-phenylquinoline from cinnamaldehyde and aniline has been assumed to be the result of an initial Michael addition rather than Schiff base formation. Eisch and Dluzniewski have shown that the heating of Schiff base (**275**) under strictly anhydrous conditions in DMSO or acetonitrile gives 2-phenylquinoline (although only in 35% yield) together with the reduced anil (30%). No 4-phenylquinoline was found. Further, a mixture of the Schiff bases (**275**) as hydrochloride and (**276**) at 25°C in DMSO gave in 5 minutes a mixture of all four possible Schiff bases (there was no reaction unless acid was present). Hence they suggest (Scheme 67) the formation of a diazetidine (**277**) which can cleave in either direction. A similar reaction with the presumed intermediate (**277**) in the Skraup synthesis from Schiff base (**275**) leads to the formation of the 2-phenylquinoline, and also agrees with labeling studies which indicated that the "carbonyl" carbon is found at position 4 ⟨75CPB2682⟩.



* Shows pattern expected for "carbonyl" labeling from (75CPB2682)

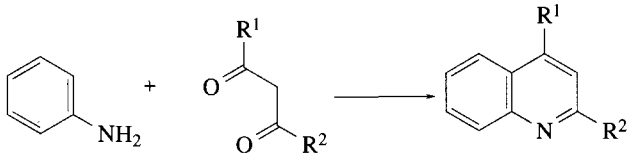
Scheme 67

A thorough study of the Utermohlen modification of the Skraup reaction (using 3-nitrobenzene-6-sulfonic acid as the acid catalyst, dehydrating agent, and oxidizing agent) was made with 3-Y–4-X-substituted anilines to study the ratio of 5,6- to 6,7-disubstituted products ⟨89H(29)2345⟩. The authors' results confirm those of Palmer ⟨62JCS3645⟩ that inductive effects exert control of product ratio, and that there are no steric effects. A further study of the ratios of 5- to 7-substituted quinolines from *meta*-substituted anilines indicates that the use of 2-butanol as the solvent and quinones as oxidants improves the ratio of 7- over 5-substituents, for example giving a ratio of 7.5 : 1 with *m*-chloroaniline ⟨93JHC17⟩. Glycerol and anilines react in boiling diglyme with ruthenium trichloride and tri-*n*-butylphosphine to give quinolines (76% yield for quinoline itself); a ratio of 9 : 1 of 7-methylquinoline over 5-methylquinoline from *m*-toluidine has been reported ⟨87JOC1673⟩. In what appears to be a two-stage Skraup reaction, the substituted aminal (**278**) reacts with anilines, with subsequent cyclization by phosphoryl chloride or acetic acid to give 3-(4-pyridyl)quinolines (Scheme 68) ⟨91JHC1453⟩. Only one isomer, the 7-substituted, is reported from *m*-chloro- and *m*-methoxy-anilines.



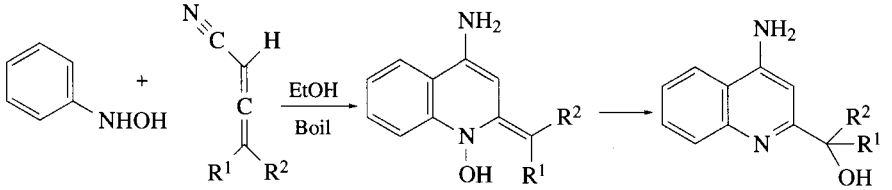
Scheme 68

The Combes synthesis (Equation (195)) has been reviewed ⟨92CHE845⟩.



(195)

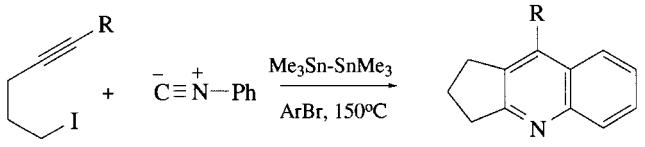
A mild synthesis of quinolines involves the boiling of an ethanolic solution of phenylhydroxylamine with the allenic nitrile (**279**) (Scheme 69) ⟨89JCS(P1)251⟩. An anionic route relying on the reaction of the dianion of the protected aniline (**280**) with an imine provides a route to unusual substitution patterns in phenanthridines (Scheme 70) ⟨94TL4899⟩. A free radical approach from phenyl isocyanide gives a range of cyclopentano[*b*]quinolines (**281**) (Equation (196)) ⟨91JA2127⟩. A palladium-catalyzed coupling of *o*-iodoanilines with a number of 1,4-dienes gives 2-alkenyl-1,2,3,4-tetrahydroquinolines (**282**) (Equation (197)) ⟨93JOC4509⟩, and amide formation from anilines and esters (**283**) gives excellent yields of 4-spirocyclohexadienyltetrahydroquinolines or the 2-substituted isomers (Equation (198)), the nucleophilicity at C-6 of the aniline, and to some extent the temperature, determining the ratio of products ⟨91TL1953⟩.



(279)

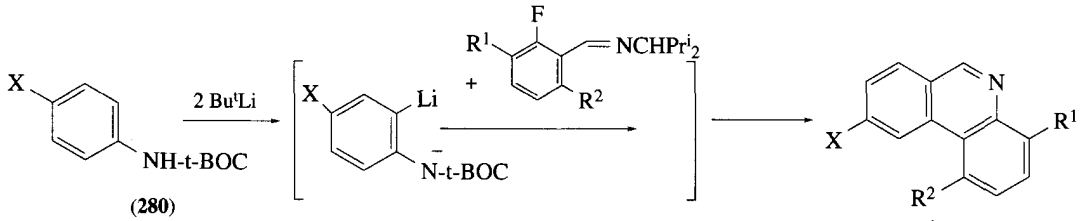
R^1, R^2 = alkyl, 83-86%

Scheme 69



(196)

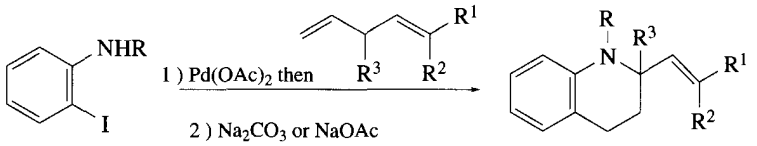
(**281**) R = Me, Bn, Ph, 36-70%



(280)

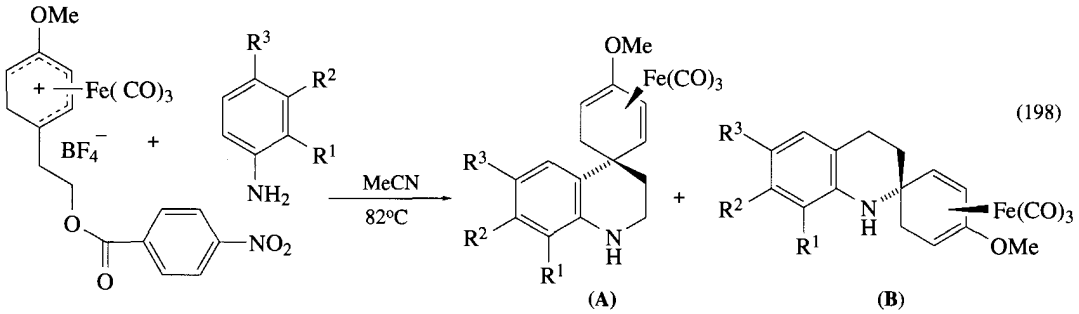
X = various,;R¹ = H, F, ;
R² = H, Cl, F; 21-74%

Scheme 70



(197)

(**282**) R = H, Ts; R¹, R², R³ = alkyl; 52-75%



(198)

(**283**)

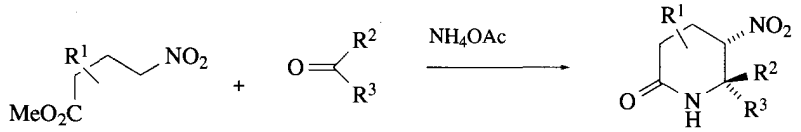
(**A**) (**B**)

70-86%, A/B ratio from 35:1 to 1:9

5.05.2.3 Formation of Three Bonds

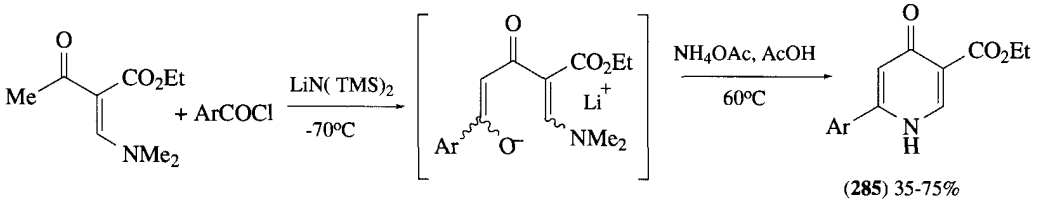
5.05.2.3.1 From a fragment containing four atoms and two one-atom fragments

Two examples of this type of synthesis use a compound with an active methylene group, a carbonyl compound, and ammonia, the first to give 2-piperidinones (**284**) (Equation (199)) ⟨93TL5831⟩, the second to give 4-pyridones (**285**) (Scheme 71) ⟨91JOC4963⟩. Yields of 4-pyridones are poor if aliphatic acid chlorides are used.



(199)

(**284**) R¹ = Me, H; R² = aryl, alkyl;
R³ = H, alkyl; 17-98%



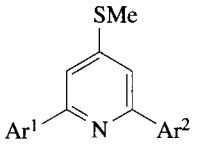
(**285**) 35-75%

Scheme 71

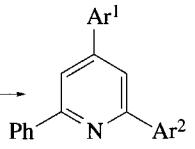
5.05.2.3.2 From fragments containing one, two, and three atoms

(i) Syntheses using ammonia or simple amines to produce pyridines

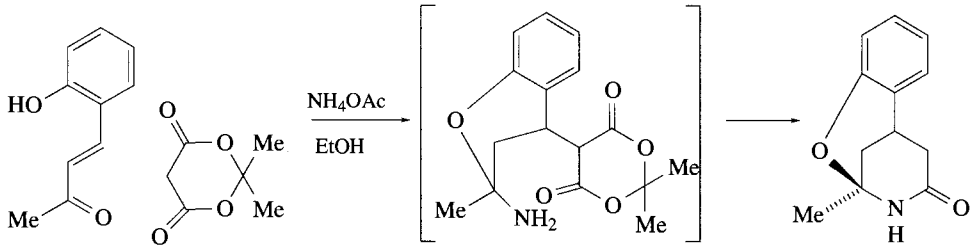
Most of the syntheses in this category are variants on the Hantzsch synthesis (see Section 5.05.2.4.2), and have been thoroughly reviewed ⟨84CHEC-I(2)470⟩. Dithioacetals of β-ketoaldehydes have been used as three-carbon components to give mainly excellent yields of 4-methylthiopyridines (**286**) (Equation (200)) ⟨82JOC3027⟩, and sulfonium groups have been used to activate the carbonyl two-carbon component in the synthesis of triarylpyridines (**287**) (Equation (201)) ⟨81S314⟩. An *ortho* hydroxyl group in the enone (**288**) can participate in a Hantzsch synthesis with Meldrum's acid to give the bridged product (**289**) (Equation (202)) ⟨90JCS(P1)1315⟩. Better yields of similar products are obtained in the (3 + 3) version of the Hantzsch synthesis.

$Ar^1COCH{=}C(SMe)_2 + Ar^2COCH_3 \xrightarrow[\text{AcOH, boil}]{NH_4OAc}$ 

(**286**) Various aryl, 48-99% (200)

$PhCOCHSMe_2 + Ar^1CH{=}CHCOAr^2 \xrightarrow[\text{AcOH, boil}]{NH_4OAc}$ 

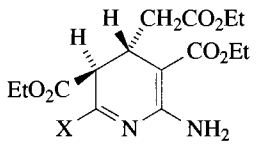
(**287**) 50-80% (201)



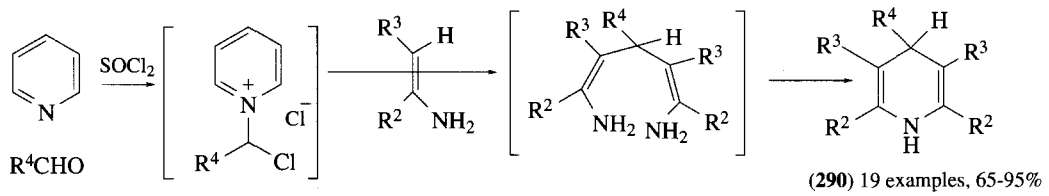
(**288**) (**289**) (202)

(ii) Syntheses using enamines as the source of nitrogen

A large number of symmetrical 1,4-dihydropyridines (**290**) have been prepared by using a single enamine as three-atom and as two-atom components, the aldehyde as a one-carbon component being activated as a pyridinium salt (Scheme 72) ⟨92T1263⟩. An alkyne provides C-4 in a synthesis of 3,4-dihydropyridines (**291**) (Equation (203)) ⟨81S227⟩.

$NH_2(X)C{=}CHCO_2Et + {\equiv}{-}CO_2Et \longrightarrow$ 

(**291**) X = OEt, 43%; X = NH_2, 64% (203)

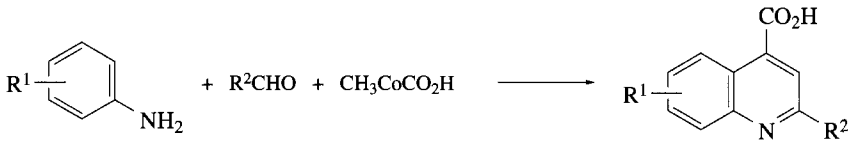


Scheme 72

(iii) Syntheses using arylamines and two acyclic fragments

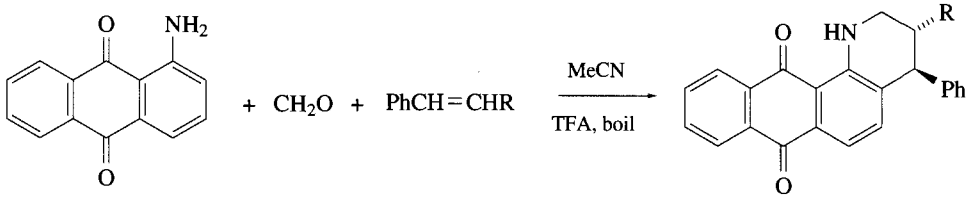
The Doebner–von Miller synthesis of quinolines has been dealt with in Section 5.05.2.2.3, although it is often performed with two molecules of an aldehyde, rather than an α,β-unsaturated aldehyde. The modifications due to Baeyer (Equation (204)) and Doebner (Equation (205)) have been reviewed ⟨77HC(32(1))115, 77HC(32(1))126⟩.

(204)



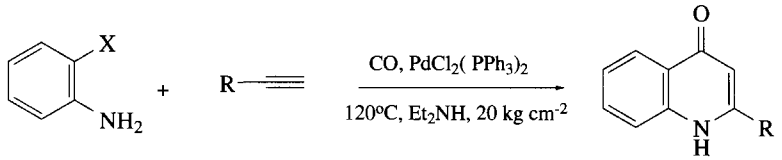
(205)

A synthesis which involves intermediate iminium species has been used to produce polycycles (**292**) (Equation (206)) ⟨91TL7103⟩; the isolation of intermediate alcohols which can be subsequently cyclized indicates that the reaction is not concerted. Transition metal-mediated syntheses using palladium ⟨91TL237⟩ or chromium ⟨90JOM(389)C1⟩ use carbon monoxide to provide the single carbon unit, giving, respectively, 4-quinolinones (**293**) (Equation (207)) and 3-hydroxypyridines (**294**) (Equation (208)). A benzyne is involved in the synthesis of the 1-aminoisoquinoline (**295**), where C-1 is derived from the cyanide of the pyridylacetonitrile (Equation (209)) ⟨92H(34)99⟩.



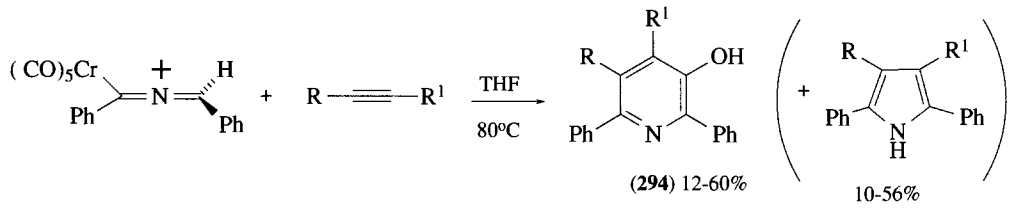
(206)

(**292**) R = H (86%), R = Me (82%)

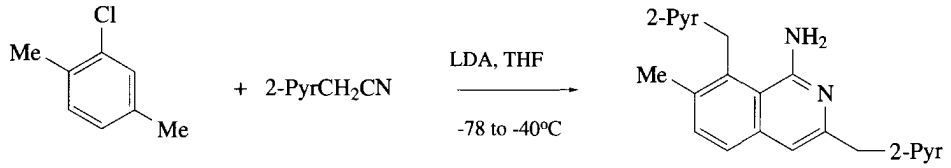


(207)

(**293**) R = alkyl or aryl, 61-95%



(208)



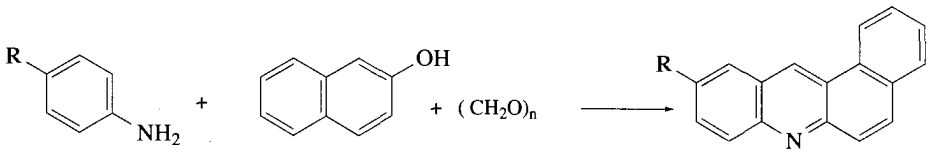
2-Pyr = 2-Pyridyl

(295) 52%

(209)

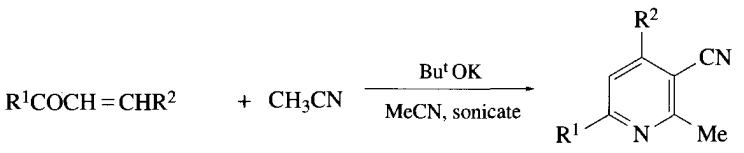
(iv) Miscellaneous syntheses

The common synthesis of acridines reviewed earlier ⟨84CHEC-I(2)476⟩ is illustrated by the synthesis of benzo[*a*]acridines (**296**) (Equation (210)) ⟨91JHC321⟩. Acetonitrile provides a two- and a one-carbon fragment for the ring in pyridines (**297**) (Equation (211)) ⟨91JHC161⟩, while cyanoacetamide serves a similar role in the synthesis of the pyridines (**298**) (Equation (212)) ⟨87CJC2717⟩.



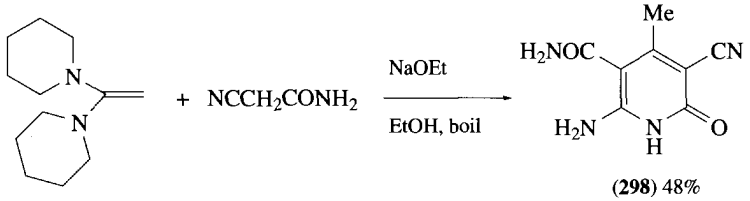
(**296**) R = $C_{12}H_{25}$, 37%

(210)



(**297**) R^1, R^2 = aryl, 36-93%

(211)



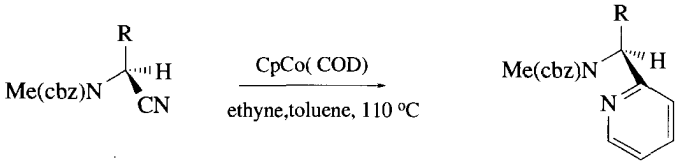
(**298**) 48%

(212)

5.05.2.3.3 From three two-atom fragments

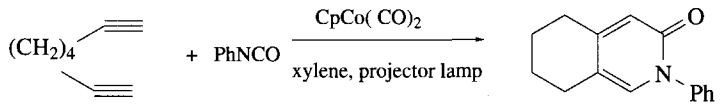
(i) Catalytic methods

Cobalt-catalyzed syntheses using ethyne and nitriles have been well reviewed ⟨85AG(E)248, 90AHC(48)177⟩. Side chain chirality can be preserved, as shown in the synthesis of pyridine (**299**) (Equation (213)) ⟨92S972⟩. Isocyanates can also be used, although yields are poor, as illustrated in the reactions with diynes to produce isoquinolin-3-ones (**300**) (Equation (214)) ⟨84JOC4786⟩. Nickel-catalyzed condensations can give excellent yields of pyridones (**301**) (Equation (215)) ⟨82S324⟩.



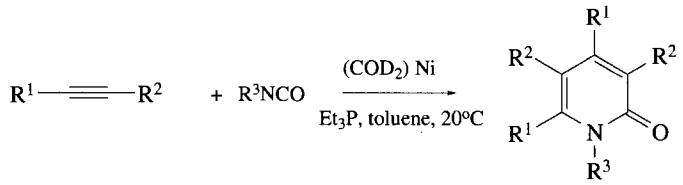
(**299**) R = alkyl, 63-70%

(213)



(214)

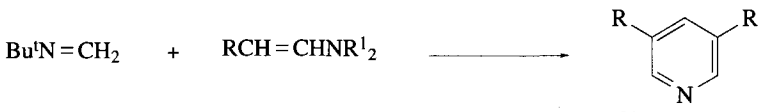
(**300**) 16%



(215)

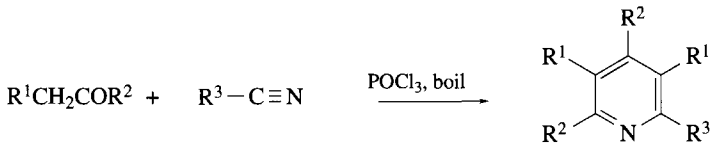
(**301**) R^1, R^2, R^3 = alkyl, aryl, 13-84%

Imines and enamines give good yields of 3,5-disubstituted pyridines (**302**) when treated with toluenesulfonic acid at high temperatures, possibly via azetes (Equation (216)) ⟨82AG(E)213⟩, while nitriles and ketones give poor yields of pyridines (**303**) when boiled with phosphoryl chloride (Equation (217)) ⟨85H(23)1639⟩.



(216)

(**302**) R = alkyl, Ph, PhS, 67-87%



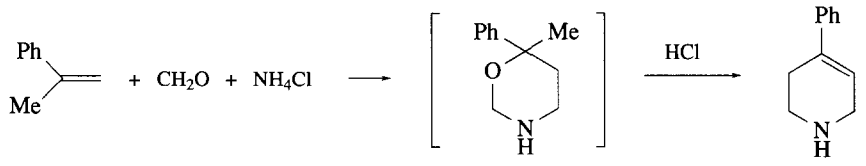
(217)

(**303**) 10-37%

5.05.2.4 Formation of Four Bonds

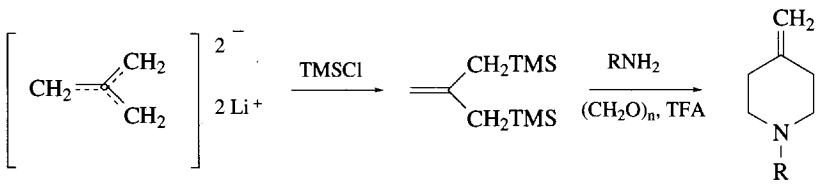
5.05.2.4.1 From a fragment containing three atoms and three one-atom fragments

Three examples are given here. The reaction between α-methylstyrene, formaldehyde and ammonia gives 1,2,5,6-tetrahydropyridine (**304**) (Equation (218)) ⟨85CB551⟩, via a reduced 1,3-oxazine, while an alkene and the trimethylenemethane dianion give good yields of 4-methylene-piperidines (**305**) (Scheme 73) ⟨91T3981⟩. The general synthesis of 4-piperidinones (**306**) from acetonedicarboxylates (Equation (219)) has been discussed in detail ⟨84CHEC-I(2)481⟩.



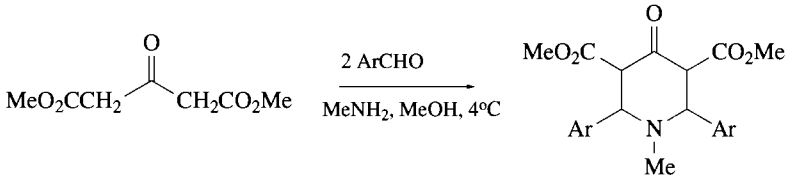
(218)

(**304**) 46-50%



(**305**) R = alkyl, 65-71%

Scheme 73



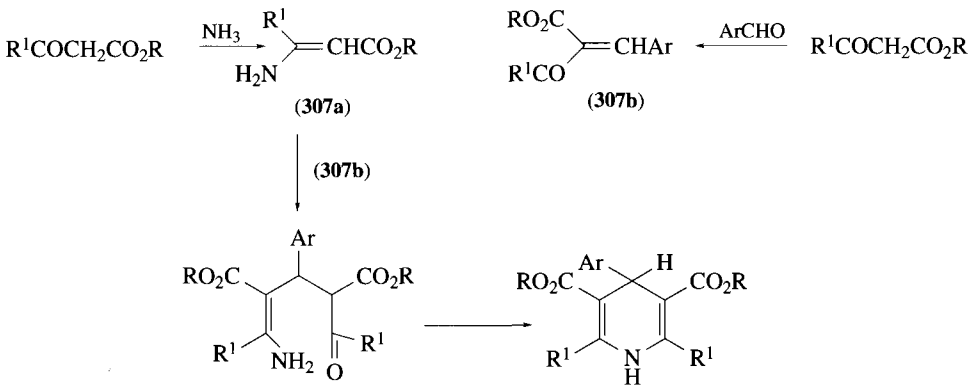
(306) 22-74%

(219)

5.05.2.4.2 *From two two-atom fragments and two one-atom fragments*

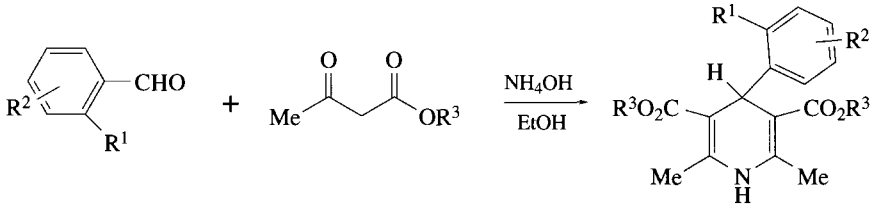
(i) Hantzsch and related syntheses

The Hantzsch synthesis has been mentioned in Section 5.05.2.2.3, although the classical route uses two molecules of a β-ketoester, with one each of an aldehyde and ammonia (Scheme 74). Reviews are available, the scope being indicated by tables ⟨60HC(14-1)510⟩; other reviews are more recent ⟨74HC(14(Suppl. 1))224, 92CHE363⟩, and there is a review on dihydropyridines which includes synthesis ⟨82CRV223⟩. The mechanism has been studied by ^{13}C and ^{15}N NMR spectroscopy, and this has confirmed (Scheme 74) that enamine (**307a**) and enone (**307b**) are intermediates, with Michael addition of compound (**307a**) to (**307b**) being the rate-determining stage. No evidence of intermediates on alternative reaction pathways was observed ⟨87T5171⟩.



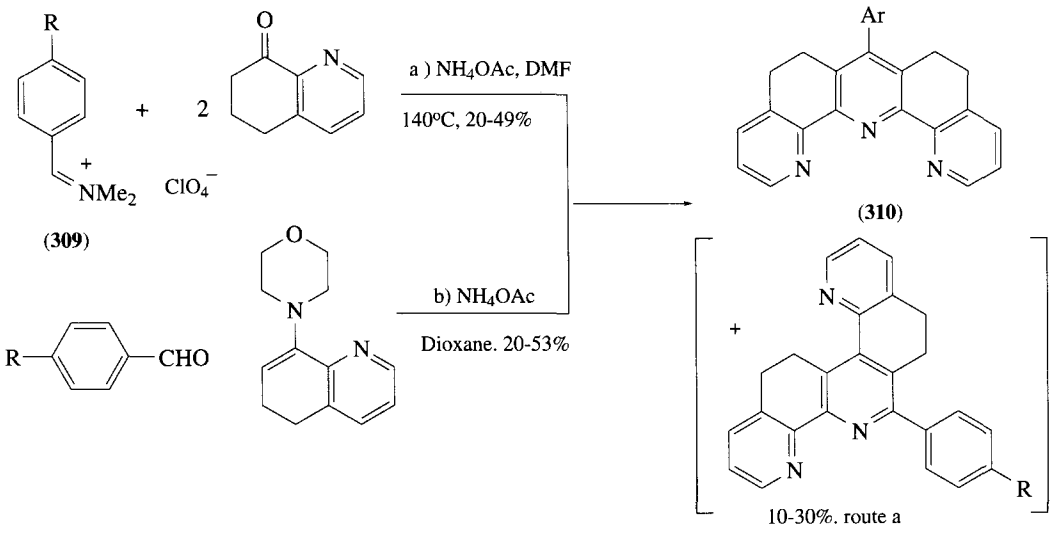
Scheme 74

Practical modifications worth mentioning are the use of microwaves (400 W) to accelerate the reaction ⟨92SL297⟩. Reactions which took up to 48 h can be completed in 3–4 min; all examples given are of hindered aldehydes, giving dihydropyridines (**308**) (Equation (220)). The second procedure uses an autoclave and claims increases of up to 30% in yield over conventional procedures ⟨83S761⟩. Modifications to reagents include the use of the Vilsmeier product (**309**) in place of an aromatic aldehyde in the synthesis of the polycycles (**310**) ⟨93TL1775⟩ and the use of the morpholine enamine to provide another route to the same heterocycles (Scheme 75) ⟨87TL4023⟩. In reactions with salicylaldehydes, dihydropyridines (**311**) and (**312**) have been isolated under Hantzsch conditions (Equation (221)) ⟨87S499⟩.



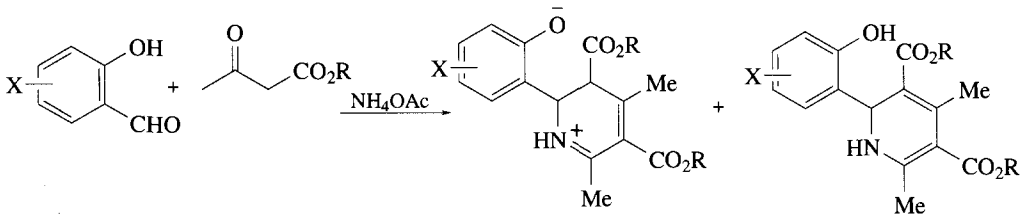
(308) e.g. R^1 = Cl, R^2 = H, R^3 = Et, 55%

(220)



(309) (310)

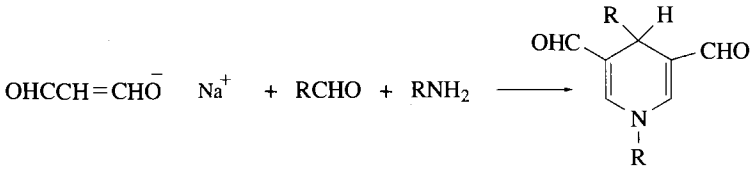
Scheme 75



(311) R = Me, Et; various X (312)

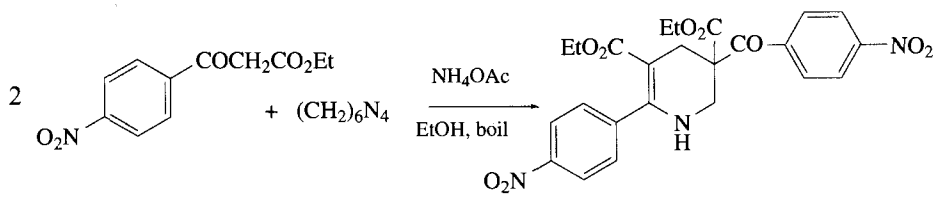
(221)

Malonaldehyde (as the sodium salt) reacts with amines or amino acids and aliphatic or aromatic aldehydes to give 1,4-dihydropyridines (**313**) (Equation (222)) ⟨88T2793⟩. In one reported Hantzsch synthesis a novel (2 + 1 + 1 + 1 + 1) synthesis of tetrahydropyridine (**314**) appears to have taken place (Equation (223)) ⟨86CHE410⟩.



(313) 22-54%

(222)



(314) 32%

(223)

5.05.3 SYNTHESES FROM OTHER RING SYSTEMS

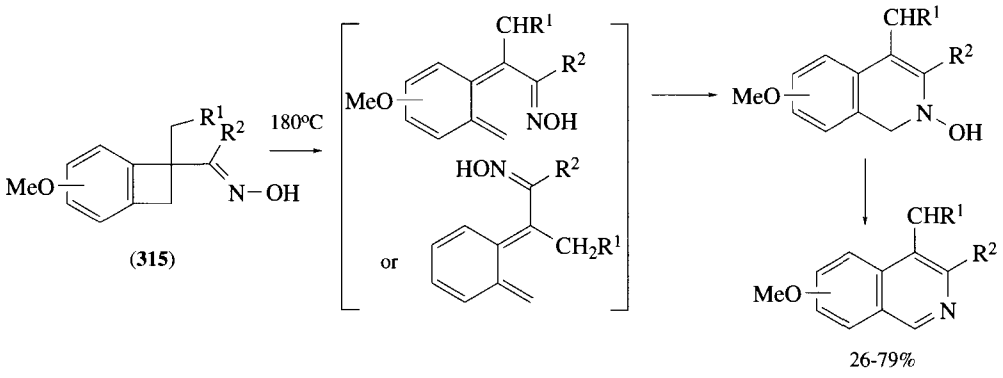
The classic reference work remains a two-volume work of van der Plas ⟨B-73MI 505-01⟩

5.05.3.1 From Three-membered Rings

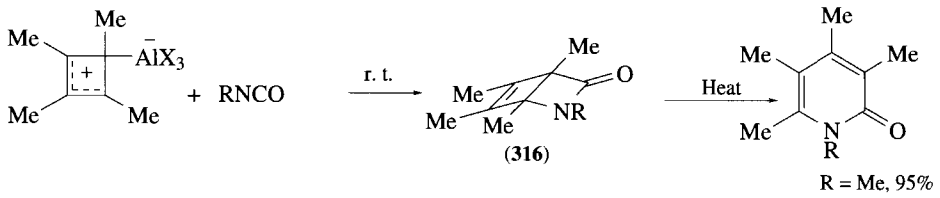
A few methods of synthesis from cyclopropanes and aziridines have been reviewed ⟨84CHEC-I(2)484⟩.

5.05.3.2 From Four-membered Rings

Two methods are described from carbocyclic rings. In the first, concerted ring opening of a benzocyclobutane (**315**) gives a 6π system which cyclizes, the resulting dihydro *N*-hydroxyisoquinoline losing water to give isoquinolines (Scheme 76) ⟨89H(28)39⟩. In the second, cyclobutenium salts react with isocyanates to give azabicyclohexanes such as (**316**), which are heated to produce 2-pyridones (Scheme 77) ⟨82JOC997⟩. The additions are regioselective.



Scheme 76



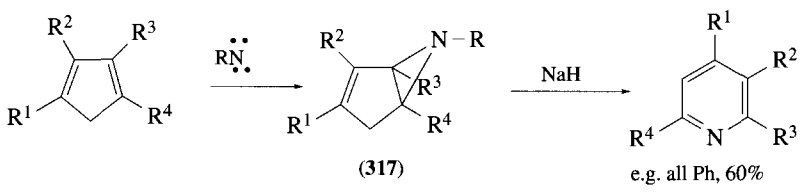
Scheme 77

5.05.3.3 From Five-membered Rings

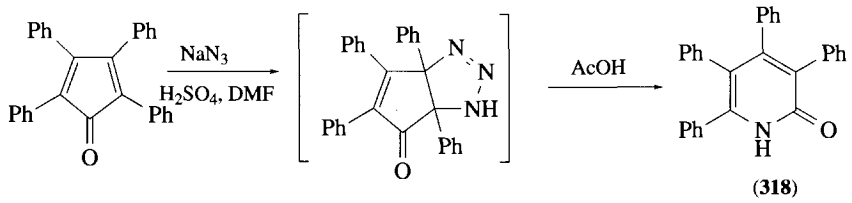
5.05.3.3.1 Carbocyclic rings

Pyridines are obtained when cyclopentadienes react with phthalimidonitrene, and the resulting bicycles (**317**) are opened by sodium hydride (Scheme 78) ⟨84H(22)1369⟩. Tetraphenylcyclopentadienone undergoes dipolar cycloaddition with the azide ion, subsequent treatment with acetic acid giving the 2-pyridone (**318**) (Scheme 79) ⟨86JOC1544⟩.

Beckmann rearrangement of cyclopentanone oximes or their derivatives gives piperidinones. The

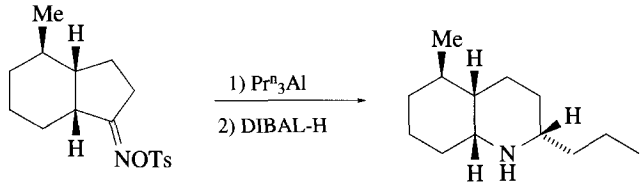


Scheme 78

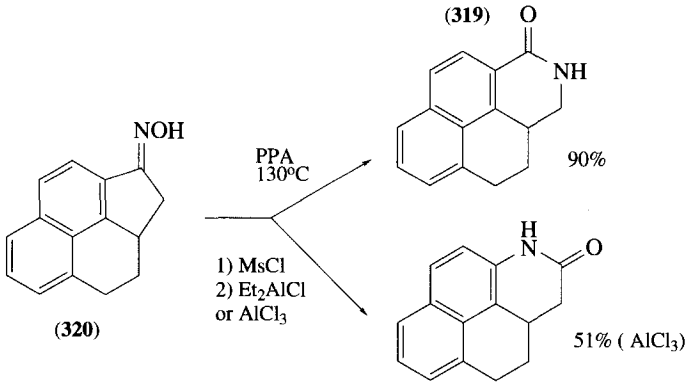


Scheme 79

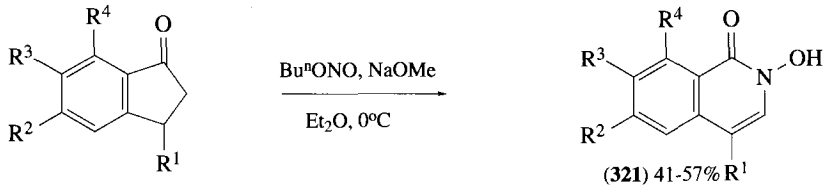
use of a trialkylaluminum followed by reduction with DIBAL-H in the synthesis of an alkaloid (**319**) is illustrated in (Equation (224)) ⟨83JA2831⟩. Indanones have been reported preferentially to give quinolinones rather than isoquinolinones, so that the polycyclic oxime (**320**) is of interest, giving rearrangement in either direction, depending on the reagent (Scheme 80) ⟨86JHC747⟩. Some indanones give *N*-hydroxyisoquinolin-1-ones (**321**) on treatment with *n*-butyl nitrite and sodium methoxide (possibly via ring opening and reclosing) (Equation (225)) ⟨81LA52⟩, while indane-1,2-dione monoximes (**322**) give good yields of 1,3-dichloroisoquinolines under Beckmann rearrangement conditions (Equation (226)) ⟨87JHC677⟩.



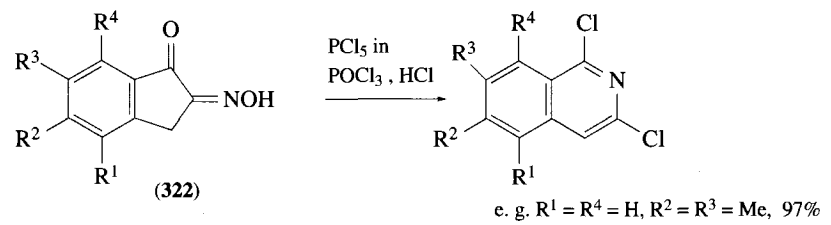
(224)



Scheme 80



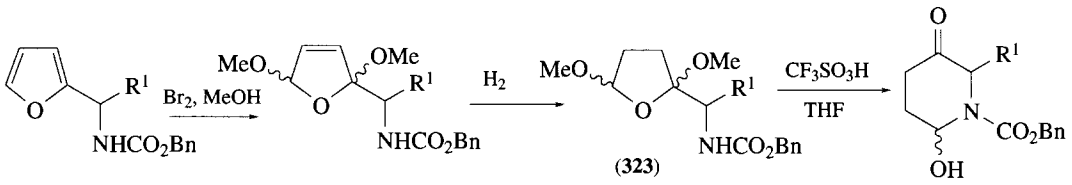
(225)



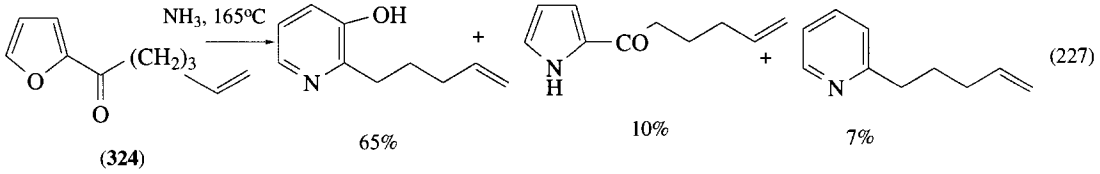
(226)

5.05.3.3.2 From furans, pyrroles, and benzologues

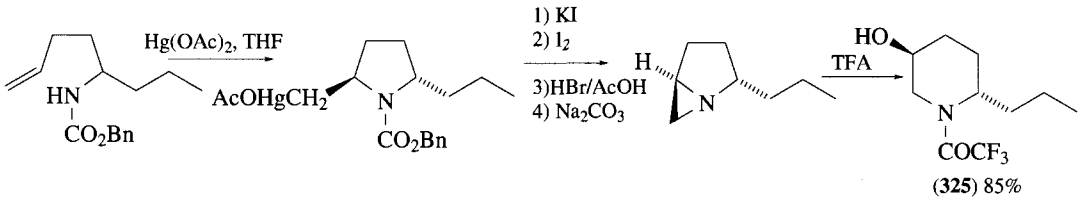
Tetrahydrofuran rings can act as protecting groups in the usual synthesis of piperidines (examples are in Section 5.05.2.1). The dimethoxytetrahydrofuran ring in compound (**323**) serves a similar purpose (Scheme 81); it is pointed out that optical activity at the α carbon can be retained ⟨86TL5085⟩. A similar use of furan itself is shown in the high-temperature reaction between ammonia and the furan (**324**) (Equation (227)) ⟨92S645⟩.



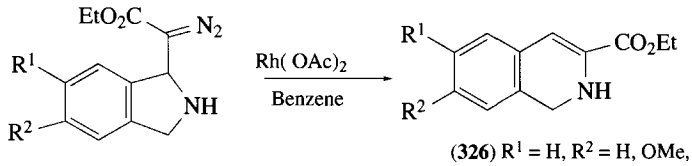
Scheme 81



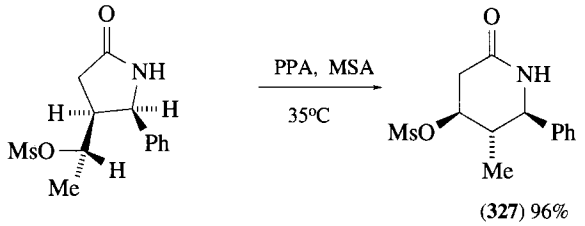
To convert pyrrolidines or dihydropyrroles into piperidines, an extra carbon atom is required; in the preparation of (**325**) the α carbon forms an aziridine, which is then treated with TFA (Scheme 82) ⟨84JOC40⟩. In the synthesis of (**326**) a carbene generated from the diazoacetate by a rhodium catalyst inserts into the pyrrolidine ring (Equation (228)) ⟨86JOC1120, 84H(22)2571⟩), and in (Equation (229)) a Wagner–Meerwein rearrangement to an exocyclic carbocation gives the piperidinone (**327**) with the stereochemistry shown ⟨91JOC2603⟩. Catalytic insertion of carbon monoxide into pyrrolidines is not regiospecific; either of the substituted 2-piperidinones (**328**) or (**329**) can be obtained (Equation (230)) ⟨92JA7018⟩. In one case the yield of compound (**328**) was more than doubled if ruthenium dodecacarbonyl was added.



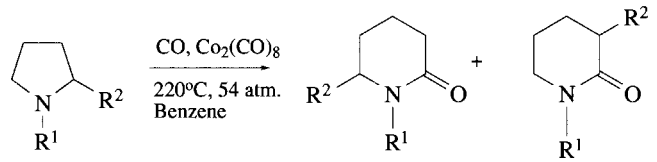
Scheme 82



(228)



(229)

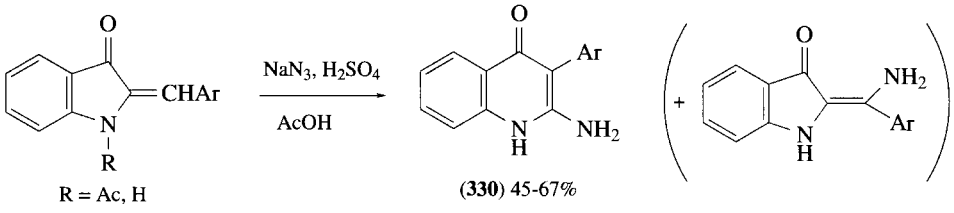


(328) (0-61%) (329) (15-64%)

R^1 = Me, $CH_2CO_2R^3$; R^2 = Ph, Bn, H, CH_2OMe, Me

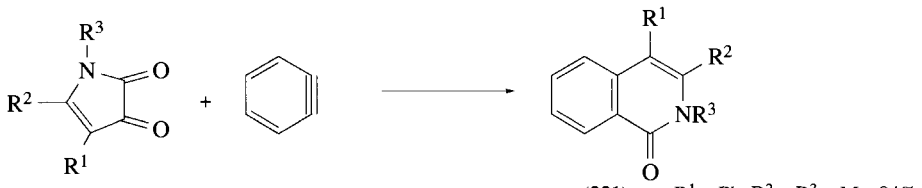
(230)

Isatins or pyrrole-2,3-diones and their derivatives can be expanded by carbenes ⟨84CHEC-I(2)492⟩, but also by hydrazoic acid, as in the preparation of (**330**) (Equation (231)) ⟨85CHE234⟩, and by arynes, as in the syntheses of (**331**) (Equation (232)) ⟨93JOC3113⟩ and (**332**) (Equation (233)) ⟨92JOC5907⟩. Phthalimides undergo insertion of carbanions derived from active methylene derivatives, giving not the expected isoquinolinediones, but quinoline-2,4-diones such as (**333**) (Scheme 83) ⟨86JCS(P1)13⟩. From aromatic pyrroles the best known route to pyridines is via carbene addition ⟨84CHEC-I(2)490⟩. Ring expansion of a cyclopropa[*b*]pyrrole by ultraviolet light gives dihydropyridines (**334**) (Scheme 84) ⟨91TL6895⟩. Insertion of an allenic carbene into a wide range of substituted pyrroles has shown that the carbene preferentially attacks the more electron-rich (more substituted) pyrrole double bond ⟨87JCS(P1)1347⟩.



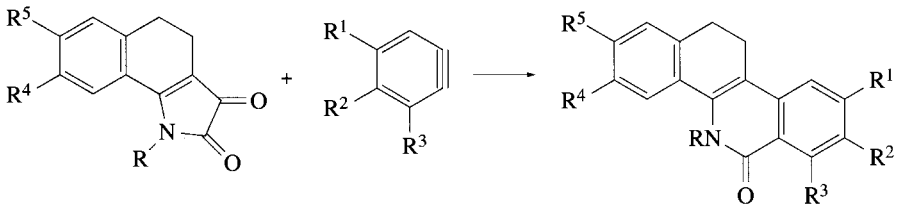
R = Ac, H (**330**) 45-67%

(231)



(**331**) e. g. R^1 = Ph, R^2 = R^3 = Me, 94%

(232)

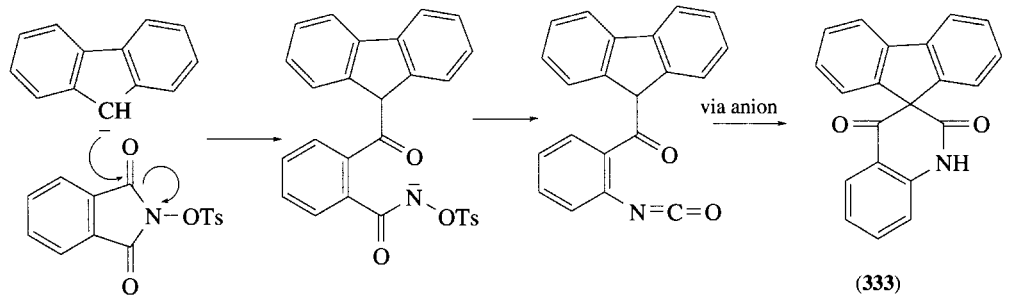


(**332**) 16-50%

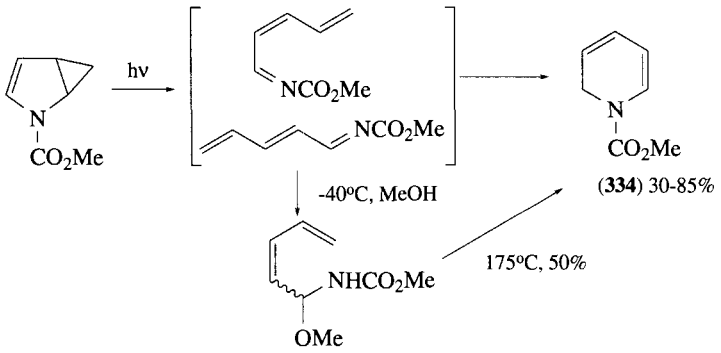
(233)

5.05.3.3.3 From oxazoles, isoxazoles, thiazoles, and their benzologues

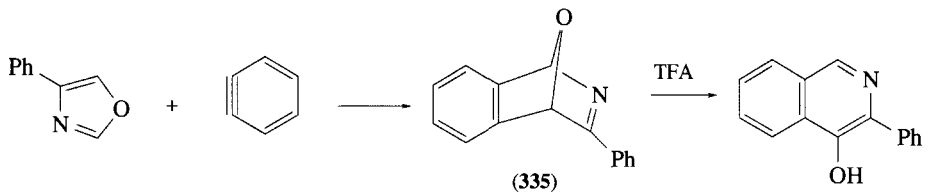
Oxazoles have been used as four-atom components in ($4\pi_s + 2\pi_s$) cycloadditions to give intermediates which can be further transformed into pyridine or its benzologues. The area has been well reviewed ⟨74AHC(17)99, 84CHEC-I(2)494⟩, and new examples only will be quoted. Benzyne reacts with 4-phenyloxazole to give the adduct (**335**) in quantitative yield, which in turn is converted by acid into a 4-hydroxyisoquinoline (Scheme 85) ⟨88JOC5595⟩. An intramolecular Diels–Alder reaction from oxazole (**336**) allows the isolation either of hydroxybenzoquinolines or the ester (**337**) (Scheme 86) ⟨84JOC4325⟩. Oxazolones or oxazolidones can lose carbon dioxide, to generate reactive species for cyclization, as in the preparation of quinolines (**338**) (Scheme 87) ⟨93TL3471⟩ and pyridines (**339**)–(**341**) (Equation (234)) ⟨82JA286⟩.



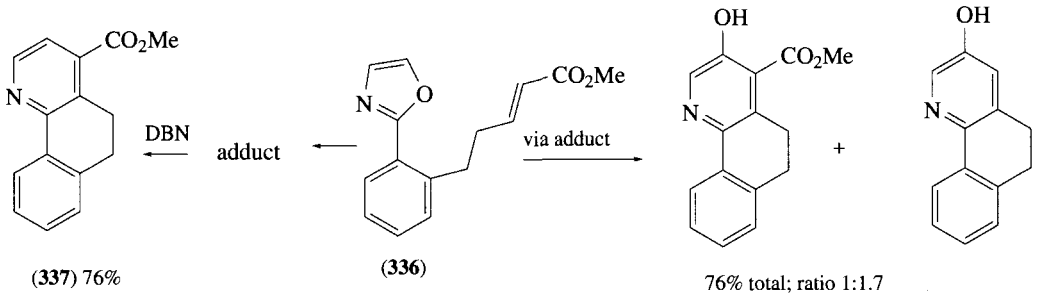
Scheme 83



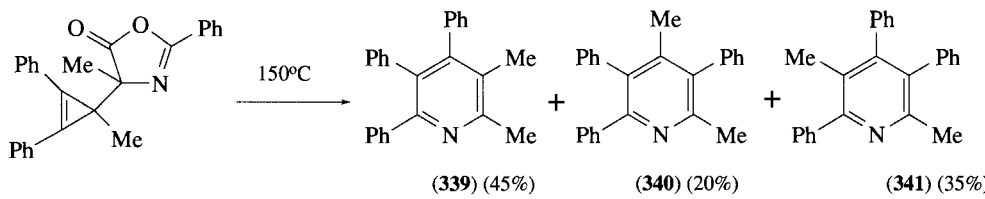
Scheme 84



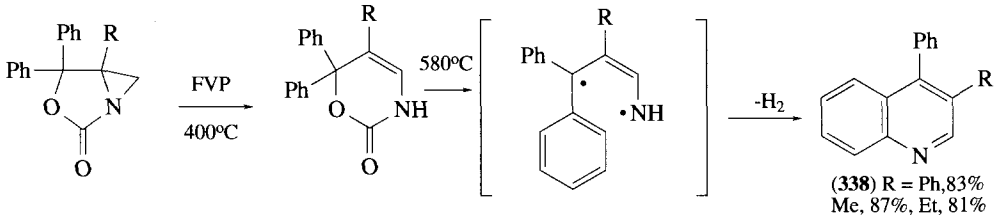
Scheme 85



Scheme 86

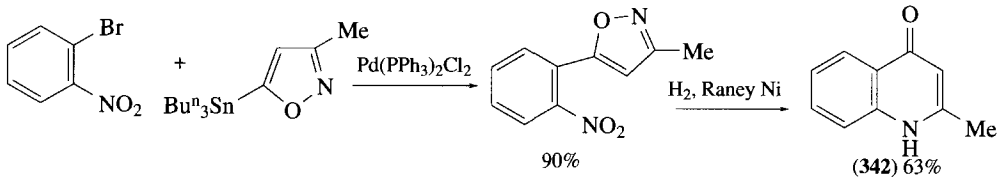


(234)

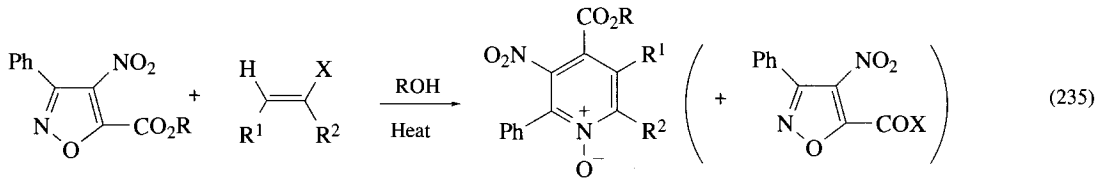


Scheme 87

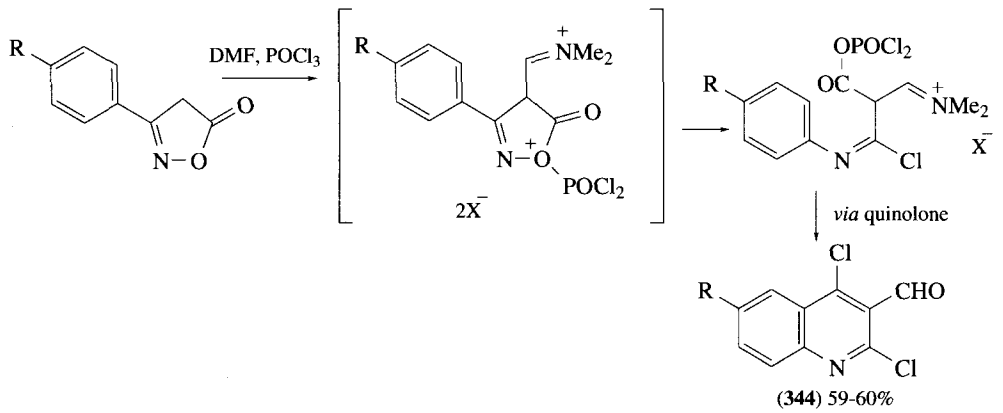
Isoxazoles can be reduced to enaminoketones, which may then cyclize; an example is provided by the preparation of the 4-quinolone (**342**) (Scheme 88) ⟨91T5111⟩. A route to pyridine *N*-oxides (**343**) involves an initial cycloaddition of an alkene (Equation (235)) ⟨92JOC3713⟩, and 3-formylquinolines (**344**) are obtained when 5-hydroxy-3-arylisoxazoles are treated with the Vilsmeier reagent (Scheme 89) ⟨93S623⟩. Simple isoxazolines can give pyridine *N*-oxides (**345**) on treatment with DBU (Equation (236)) ⟨90TL1949⟩, and 2-phenylpyridine or 3-phenylisoquinoline are obtained when the bi or tricyclic isoxazolines (**346**) are heated with diironenneacarbonyl (Equation (237)) ⟨85H(23)339⟩, while the spirocyclopropylisoxazolidine (**347**) is converted by heat or irradiation into a tetrahydro-4-pyridone (Equation (238)) ⟨92JOC5666⟩.



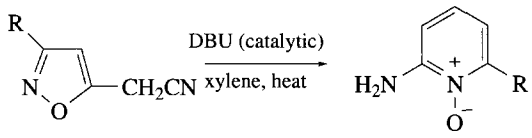
Scheme 88



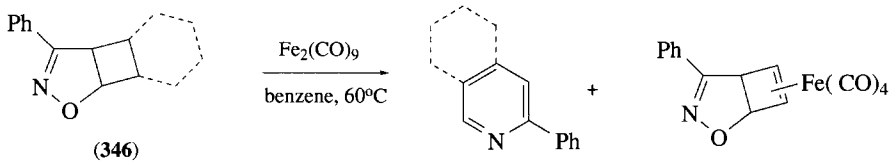
(**343**) R, R^1, R^2, = alkyl, < 20%



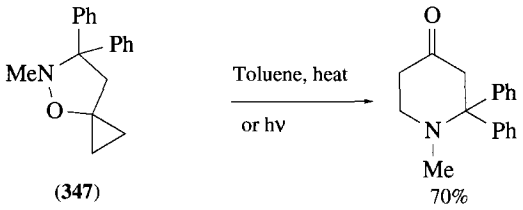
Scheme 89



(345) R = alkyl, alkenyl, aryl, 58-90% (236)

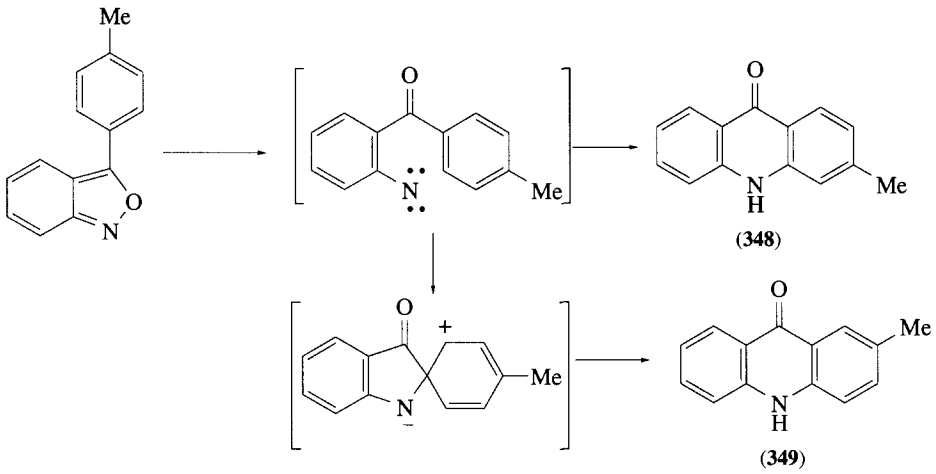


(346) (237)



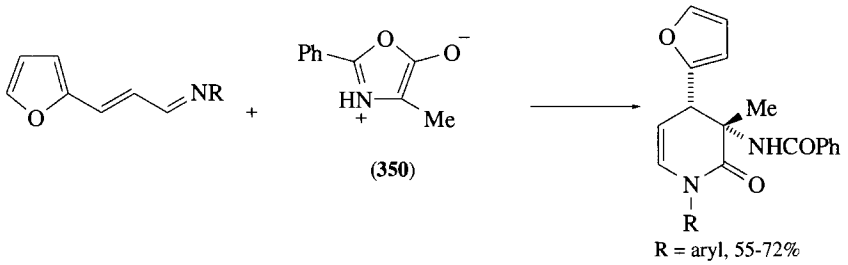
(347) (238)

Heat converts 3-*p*-tolylanthranil into the acridone (**348**) or (**349**) (Equation (239)). The mechanism of this transformation has been studied, and it has been noted that higher temperatures give more rearranged product, via a spirodiene intermediate. Iron was found to be a catalyst for the reaction ⟨83JCS(P1)2077⟩.

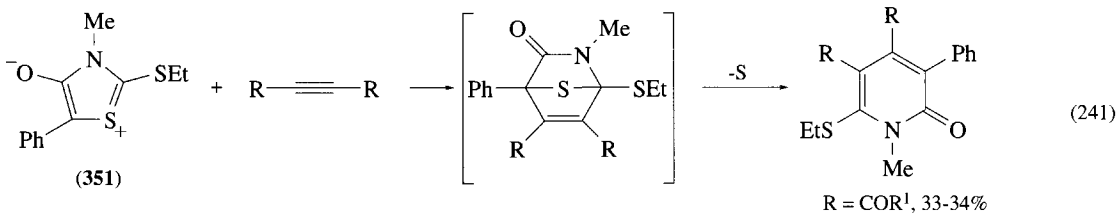


(348) (349) (239)

The mesoionic oxazole (**350**) reacts with azabutadienes to give dihydro-2-pyridones (Equation (240)) ⟨84H(22)287⟩, while the oxidothiazolium betaine (**351**) reacts with alkynes to give 6-ethylthio-2-pyridones (Equation (241)) ⟨87CB1017⟩.



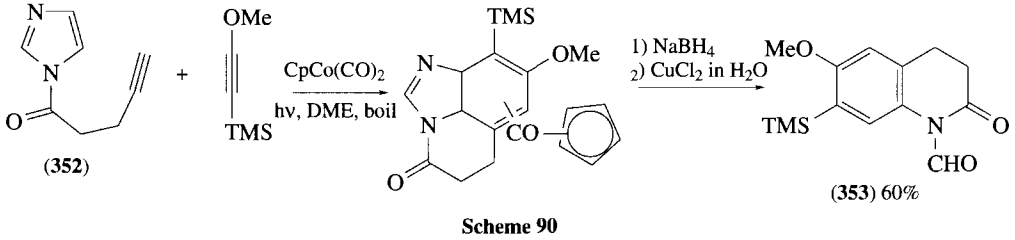
(350) R = aryl, 55-72% (240)



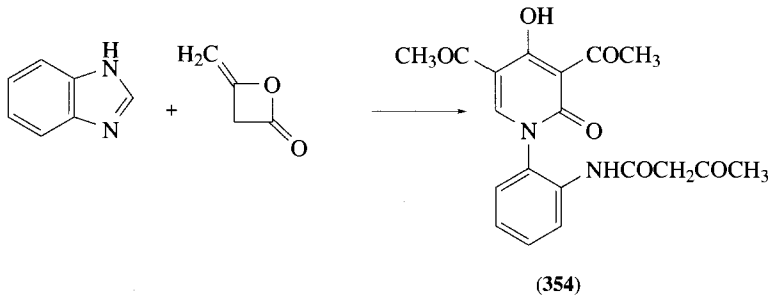
(241)

5.05.3.3.4 Other five-membered heterocyles

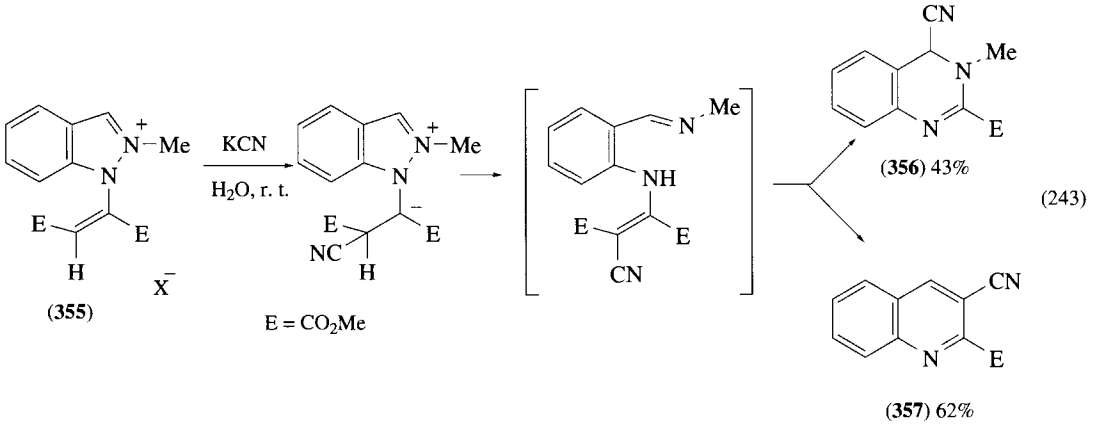
In an extraordinary reaction, N-1, C-4, and C-5 of the imidazole (**352**) become N, C-8, and C-8a in the dihydroquinolone (**353**) (Scheme 90) ⟨87AG(E)1035⟩. Benzimidazole provides the nitrogen atom for the hydroxypyridinone (**354**) (Equation (242)) ⟨86H(24)419⟩. Indazolium salts have weak N—N bonds, and treatment of (**355**) with potassium cyanide gives, after cleavage and recyclization, a mixture of the dihydroquinazoline (**356**) and the quinoline (**357**) (Equation (243)) ⟨92JOC4151⟩.



Scheme 90

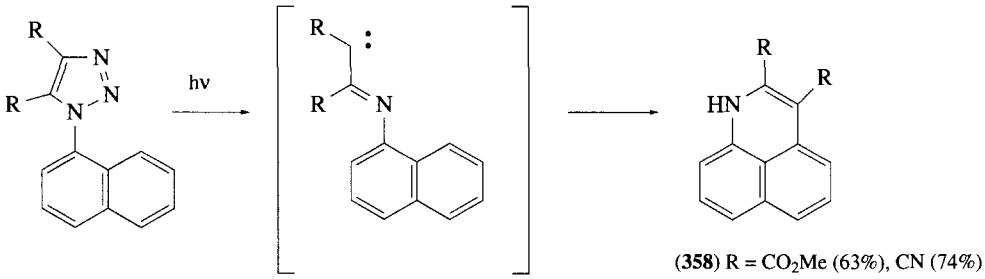


(242)



(243)

1,2,3-Triazoles can lose nitrogen thermally ⟨88TL953⟩ or photochemically ⟨87JCS(P1)413⟩, generating radicals or carbenes. In an example of the latter route, intramolecular insertion of the carbene is the basis of a high-yielding route to benzo[*d*,*e*]quinolines (**358**) (Equation (244)).



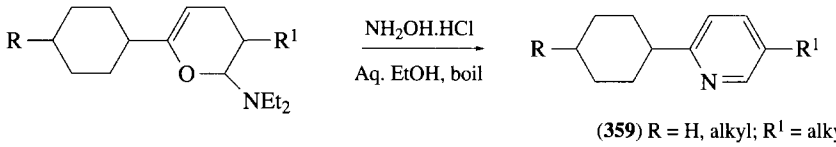
(244)

(**358**) R = CO_2Me (63%), CN (74%)

5.05.3.4 From Six-membered Rings

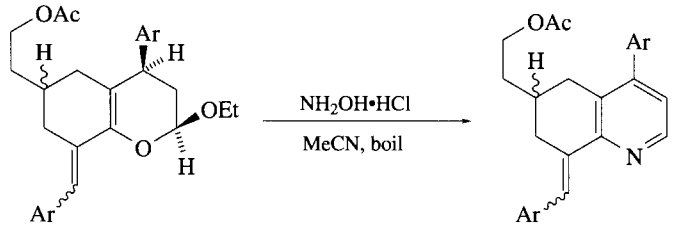
5.05.3.4.1 Pyrans, pyrones, pyrylium salts, and their benzologues

Tetrahydropyrans, heated with amines and a titania catalyst, give mainly pyrrolidines, but aniline is reported to give *N*-phenylpiperidine with 74% conversion ⟨90TL2991⟩. Introduction of unsaturation makes the reaction easier. Dihydropyrans with an amino or ether group at position 6 are cyclic derivatives of 1,5-diketones and, as such, react with hydroxylamine under mild conditions to give pyridines such as (**359**) (Equation (245)) ⟨84CHE515⟩ and (**360**) (Equation (246)) ⟨89TL5559⟩. In the latter case the reaction can be performed without decomposition of an azido group on the arene. Treatment of 4*H*-pyrans with ammonium acetate gives pyridines (**361**); similar pyrans when treated with sulfuric acid give dihydro-2-pyridones (**362**) (Scheme 91) ⟨86H(24)1675⟩.



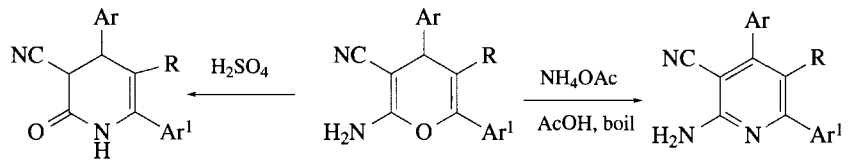
(245)

(**359**) R = H, alkyl; R^1 = alkyl, 10-46%



(246)

(**360**) 52% from cyclohexanone derivative



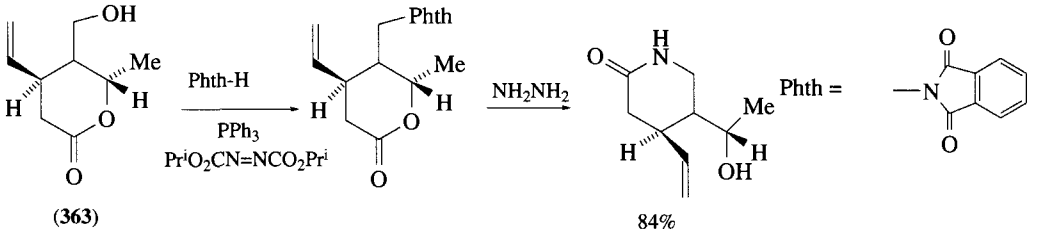
(**362**) various aryl, R = PhCO, 31-34%

e. g. (**361**) R = Ar^1 = Tolyl; Ar = Ph; 91%

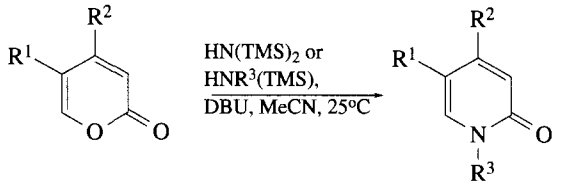
Scheme 91

The conversion of the tetrahydro-2-pyrone (**363**) into a highly substituted piperidin-2-one involves a Mitsunobu reaction followed by release of the primary amine by hydrazine (Scheme 92) ⟨90H(30)583⟩. Pyrones can give very high yields of pyridones on treatment with amines; the use of silyl-protected amines or ammonia is illustrated by the synthesis of 2-pyridones (**364**) (Equation (247)) ⟨91S883⟩ and stereochemical stability by the synthesis of the polycycle (**365**) (Equation (248)) ⟨82H(17)83⟩. The reactivity of 4-pyrones is strongly affected by substituent groups; it has been

reported that the 3-methoxy-4-pyrone (**366**) reacts with arylamines in boiling dilute aqueous acid (Equation (249)), a considerable improvement over the usual sealed-tube method ⟨86JHC5⟩. By contrast, 3-phenylthio-4-pyrones react with methanolic ammonia at room temperature, giving 94–100% yields of 4-pyridones ⟨87CB1505⟩. Glutaric anhydrides react with amines to give glutarimides. From the 2-pyrone (**367**) the product from reaction with hydrazine is a dihydro-2-pyridone (Equation (250)), not, as previously reported, a diazepine ⟨86H(24)393⟩. From the homophthalic anhydride (**368**) and an imine, a single product of fixed stereochemistry was obtained (Equation (251)) ⟨82H(19)1587⟩.

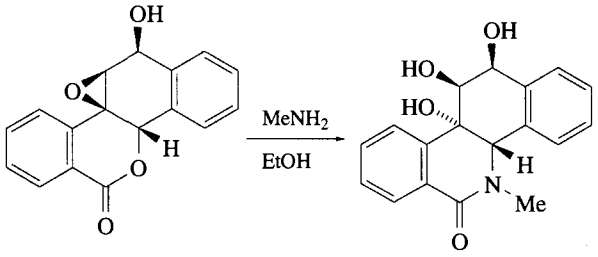


Scheme 92



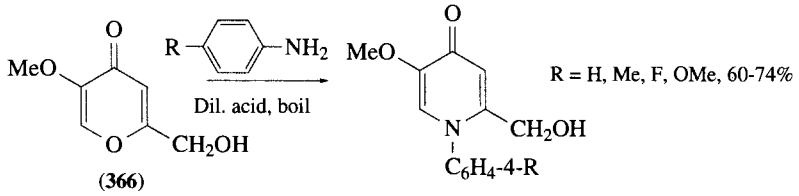
(247)

(**364**) 13 examples, 16-97%



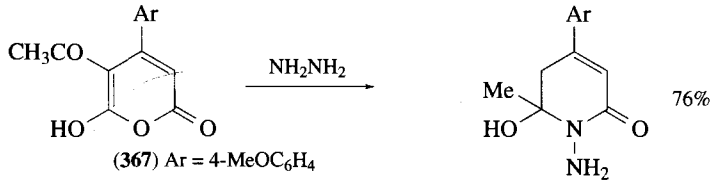
(248)

(**365**) 99% (4b (*R*), 10b (*S*), 11 (*S*), 12 (*S*))



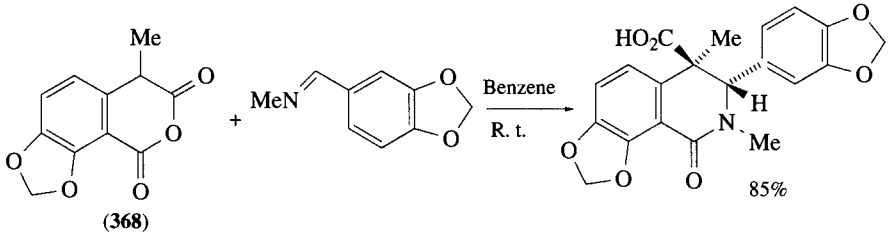
(249)

(**366**)



(250)

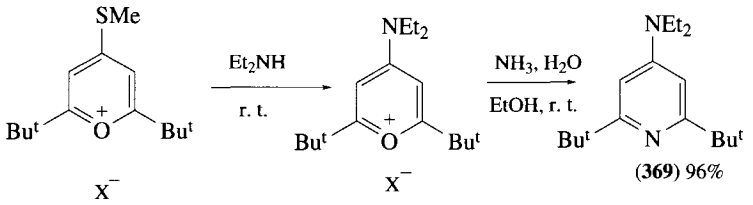
(**367**) Ar = 4-MeOC$_6$H$_4$



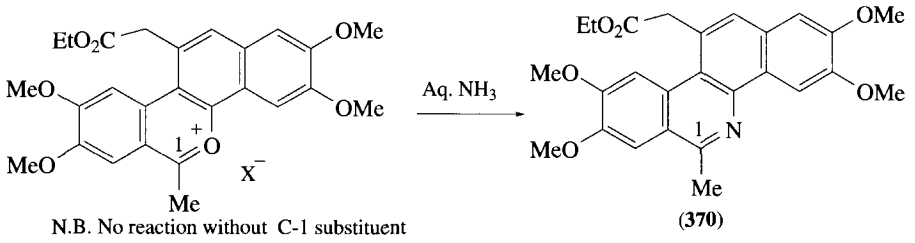
(251)

(**368**)

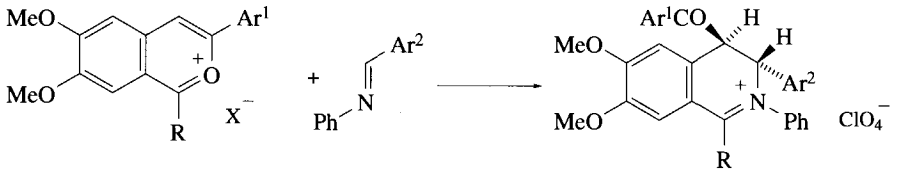
Many pyrylium salts have been converted into pyridines (using ammonia) or pyridinium salts (using amines), and the mechanism has been presented in a review ⟨80T679⟩. The use of the synthesis to produce a highly hindered pyridine (**369**) ⟨87S839⟩ and an example (**370**) which reveals a limitation ⟨89JHC1601⟩ are illustrated in Scheme 93 and Equation (252), respectively. The reaction of 2-benzopyrylium salts with Schiff bases gives 3,4-dihydroisoquinolinium salts (**371**) (Equation (253)) ⟨90CHE960⟩.



Scheme 93



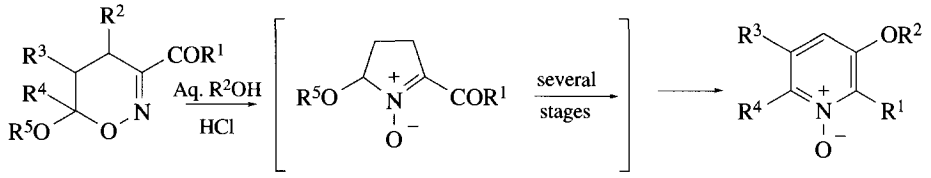
N.B. No reaction without C-1 substituent (252)



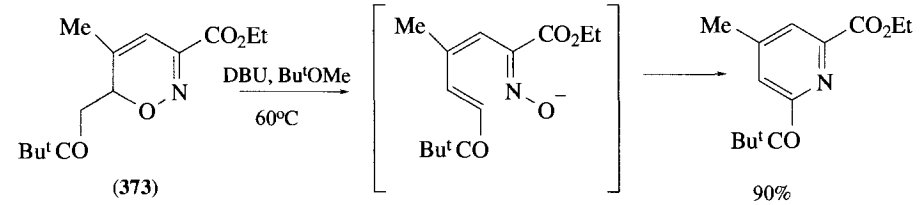
(371) Quantitative (253)

5.05.3.4.2 Oxazines, diazines, and their benzologues

The rearrangement of 4,5-dihydro-1,2-oxazines into pyridine *N*-oxides (**372**) is thought to proceed via a pyrrolenine *N*-oxide (Equation (254)) ⟨85JCS(P1)2769⟩, while the base-catalyzed rearrangement of the 6*H*-1,2-oxazine (**373**) involves an intermediate electrocyclization (Equation (255)) ⟨89S908⟩.

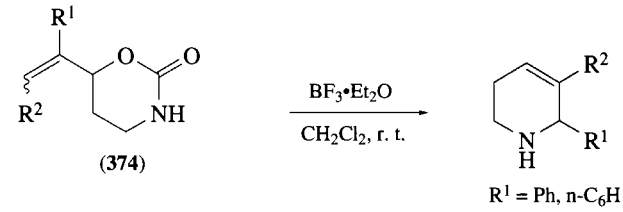


(372) 30-81% (254)



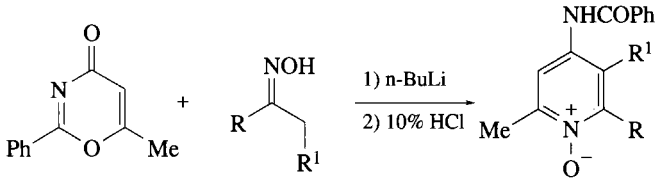
(373) 90% (255)

Reduced 1,3-oxazin-2-ones (**374**) rearrange on treatment with boron trifluoride to give tetrahydropyridines (Equation (256)) ⟨91JOC4341⟩. In the synthesis of pyridine *N*-oxides (**375**), 1,3-oxazin-4-ones, which are unstable to strong bases, act as three-atom components (Equation (257)) ⟨89H(29)1443⟩, while in the synthesis of 2-pyridones (**376**) they act as four-atom components (Scheme 94) ⟨85CPB975⟩.



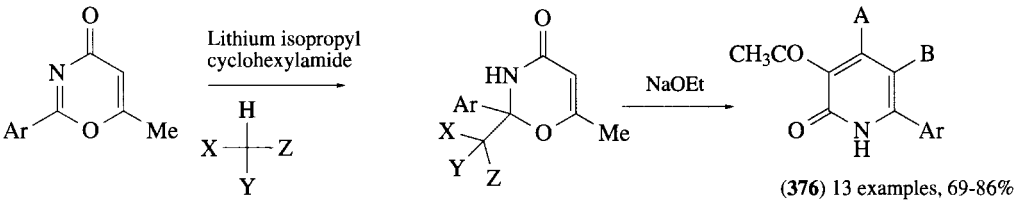
R^1 = Ph, n-C_6H_{13}; R^2 = H, TMS; 20-85%

(256)



(**375**) R = alkyl, Ph; R^1 = H, alkyl; 15-80%

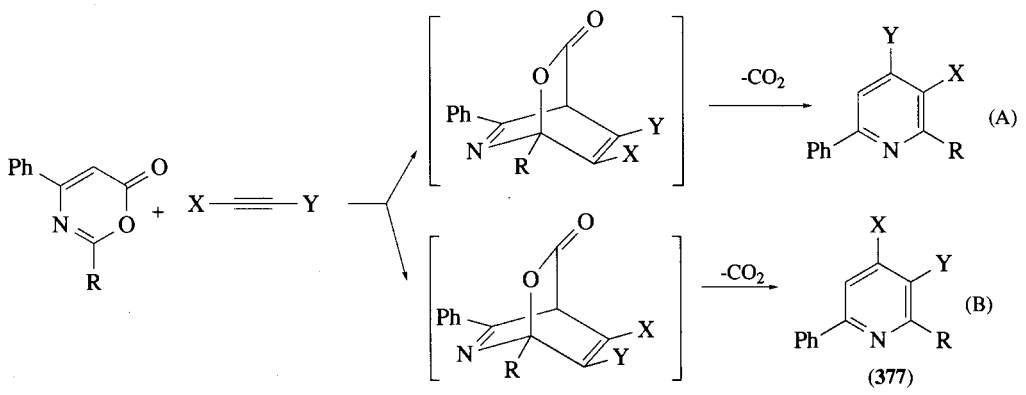
(257)



(**376**) 13 examples, 69-86%
e. g. X = H, Y = Ph, Z = CO_2Et, then
A = OH, B = Ph

Scheme 94

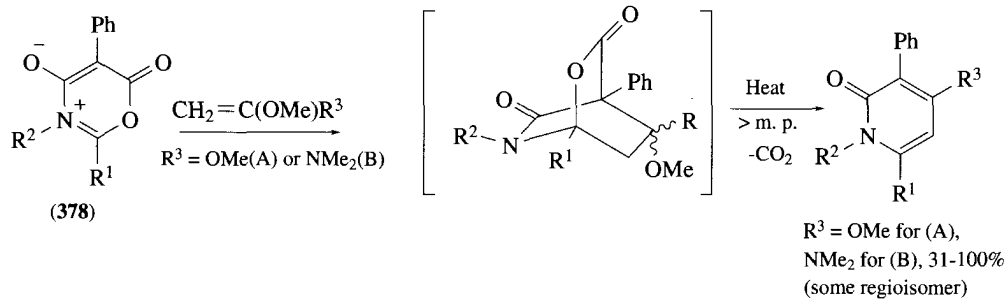
A reaction common to this group of heterocycles is the Diels–Alder addition with subsequent elimination of a bridge to give pyridine derivatives. Thus, 1,3-oxazin-6-ones react with alkynes to give pyridines (**377**) with some degree of regioselectivity (Equation (258)) ⟨90H(30)771⟩, and compounds of type (**378**) react with electron-rich alkenes to give 2-pyridones (Scheme 95) ⟨88CB951⟩. Similar Diels–Alder additions of alkynes with 1,4-oxazin-2-ones give pyridines (**379**) and (**380**) with, in some cases, high regioselectivity (Equation (259)) ⟨94T5211⟩.



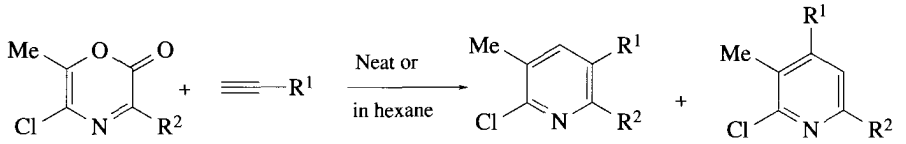
(**377**)

Total yields, 20-71%
A/B ratio = 1.35-1.8

(258)



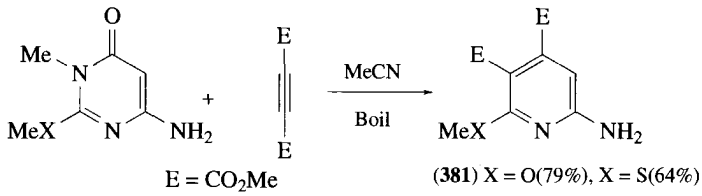
Scheme 95



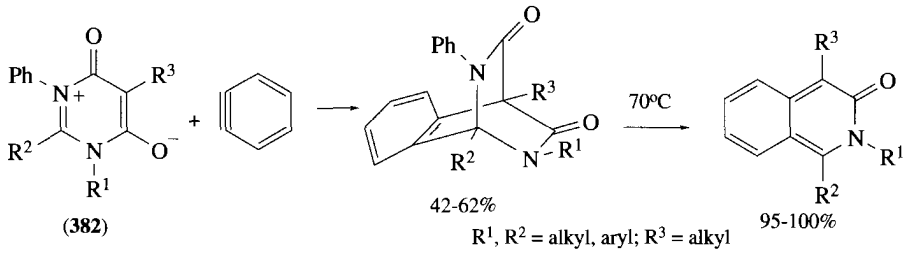
(259)

(379) (380)
73-95%; ratios 100:1 to 10:90

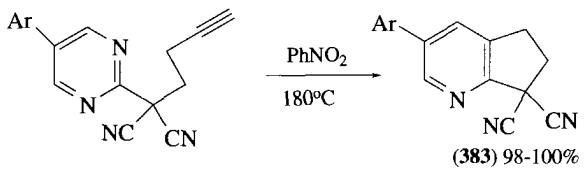
Cycloadditions using heteroaromatic dienes have been thoroughly reviewed ⟨B-87MI 505-01⟩; examples quoted here are mainly subsequent to the review. There are intermolecular examples of addition to pyrimidinones giving diesters (**381**) (Equation (260)) ⟨94T10345⟩ and to the mesomeric betaines (**382**), giving isoquinolin-3-ones (Scheme 96) ⟨83H(20)1367⟩, and intramolecular examples giving very high yields of cyclopenta[*b*]pyridines (**383**) (Equation (261)) ⟨89T6891⟩ and the tricyclic compound (**384**) (Equation (262)) ⟨89T6511⟩. A study of intermolecular addition to pyrazin-2-ones by alkynes showed the need for a hydrogen at C-6, a leaving group at C-5, and a substituent with high donor capacity ⟨92JOC2935⟩. Here, unusually, the bridge in the bicyclic intermediate is retained as a cyanide in the pyridin-2-ones (**385**) (Equation (263)). In a study of intramolecular cyclization in pyrazines it was observed that conditions were much milder when the pyrazine was quaternized (30–100 °C lower temperature), and this observation was used to accelerate the reaction of unquaternized pyrazines by performing the reaction in TFA to give compound (**386**) (Equation (264)) ⟨89T6519⟩.



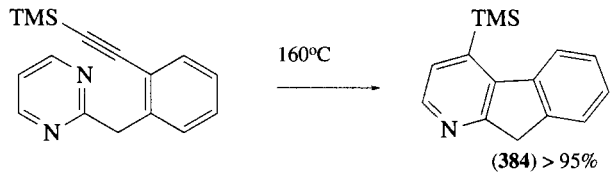
(260)



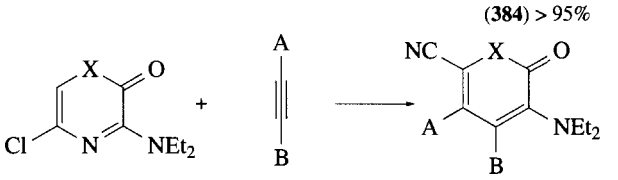
Scheme 96



(261)

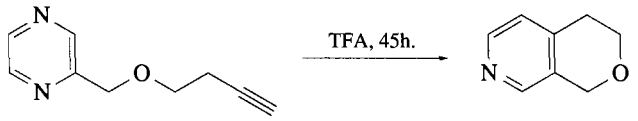


(384) > 95% (262)



(384) > 95% (263)

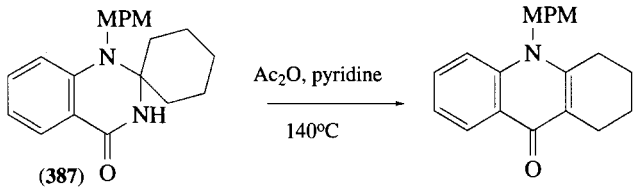
(385) e. g. A = B = CO_2Me; X = NPh(95%), NMe (95%)



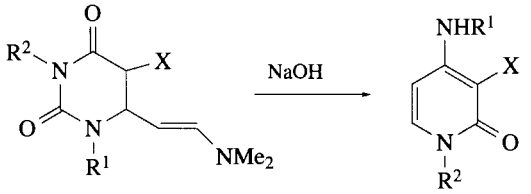
(264)

(386) unprotonated needs 195°C, 135h.

Other routes which convert pyrimidines into pyridines or benzologues involve acetic anhydride treatment of quinazolinones such as (**387**) (Equation (265)) ⟨87H(26)191⟩, basic treatment of pyrimidin-4-ones ⟨82CHE657⟩ or -2,4-diones ⟨88JHC985⟩ which have enamine side chains to give, for example, compounds (**388**) (Equation (266)), and the reaction of enolates with 2,4-dichloropyrimidine to give pyridines (**389**) (Equation (267)) ⟨85JOC3442⟩. Irradiation of pyrimidin-2-ones (**390**) gives bicyclic intermediates which, on heating, give quinolines (Scheme 97) ⟨83JCS(P1)1773⟩.

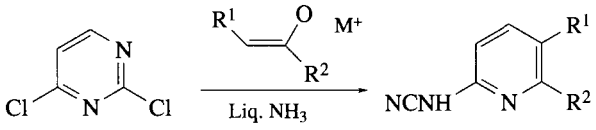


(265)



(266)

(388) 13 examples, 9-95%

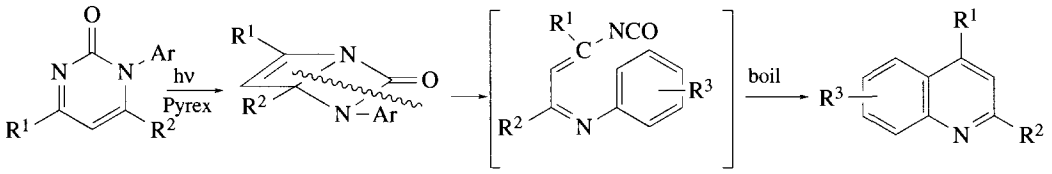


(267)

(389) R^1 = H, Me; R^2 = alkyl; 43-68%

5.05.3.4.3 Triazines and benzotriazines

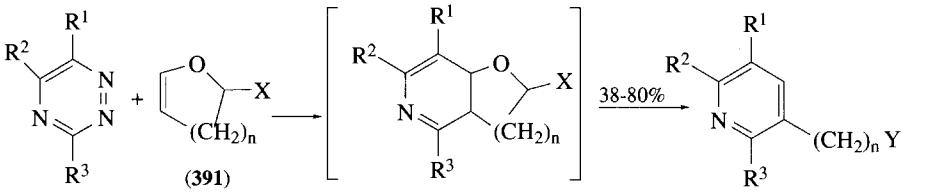
All entries in this section relate to Diels–Alder additions, and have been reviewed ⟨B-87MI 505-01, 91COS(5)491⟩. Of the two suitable triazines (the 1,2,3- and 1,2,4-triazines) only the latter have been heavily exploited. Of interest here are addition across C-3/C-6, and the factors which affect regiochemistry. For additions involving electron-rich dienophiles there is a tendency for the more



(390) R^1, R^2 = aryl

Scheme 97

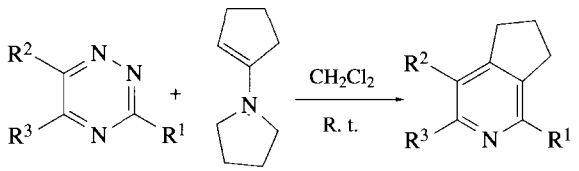
electron-rich carbon to become attached to C-3 as in the reaction of the cyclic enol ethers (**391**) (Equation (268)) ⟨93T5277⟩. Enamines can be used with relatively unactivated triazines as shown in the synthesis of cyclopenta[*c*]pyridines (**392**) (Equation (269)) ⟨93H(35)1089⟩. A lower degree of activation in the dienophile can be tolerated in intramolecular cycloadditions as in the synthesis of cyclopenta[*b*]pyridines (**393**) (Equation (270)) ⟨91JOC1807⟩ or with 1,2,4-benzotriazines, where addition of norbornadiene followed by elimination of cyclopentadiene gives the quinoline (**394**) (Equation (271)) ⟨89H(29)2253⟩. Benzyne addition provides a route to isoquinolines (**395**) (Equation (272)) ⟨92T6821⟩. Substituted benzynes give mixtures.



(391)

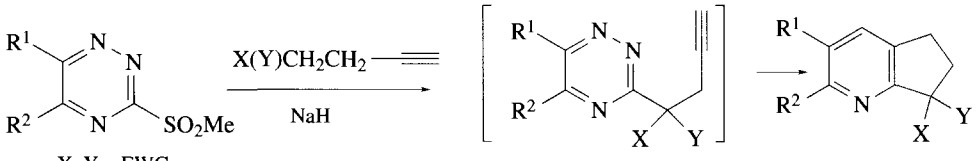
Y = CH_2OH when X = H, n = 1 or 2
Y = CHO when X = OMe or OEt, n = 2

(268)



(269)

(**392**) 16 examples, 55-88%

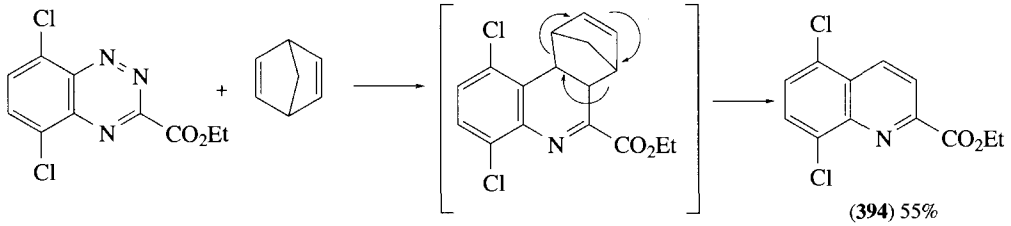


X, Y = EWG

(270)

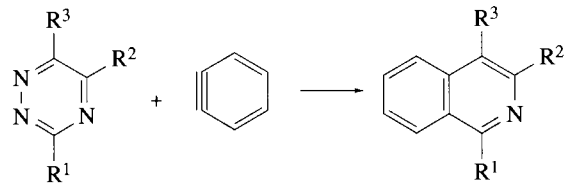
(**393**) 10-80%

393, 10-80%



(271)

(**394**) 55%



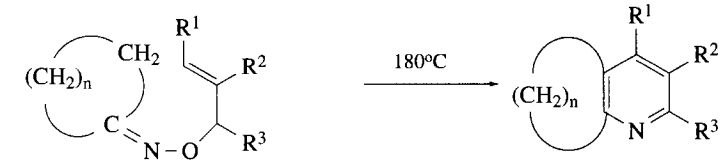
(272)

(**395**)

5.05.3.5 From Seven-membered Rings

5.05.3.5.1 From carbocyclic compounds

When heated in a sealed tube, *O*-allyloximes of cycloalkanones (**396**) are converted, via a 2,3-sigmatropic shift, into cycloalkanopyridines (Equation (273)) ⟨83CPB2601⟩.



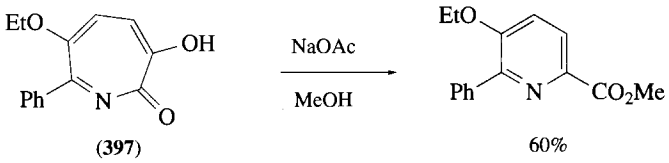
(**396**) $R^1 = R^2 = R^3$ = H or Me

n = 3-6, 10, 30-65%

(273)

5.05.3.5.2 From azepines or benzologues

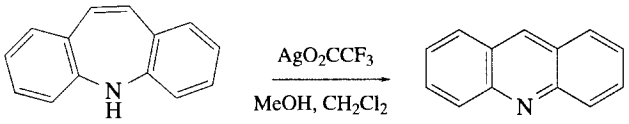
Azepinone (**397**) reacts with mild base in methanol to give a methyl picolinate (Equation (274)) ⟨85H(23)1509⟩, while dibenzazepine (**398**) gives acridine in 94% yield when treated with silver trifluoroacetate (Equation (275)) ⟨88JOC1112⟩.



(**397**)

60%

(274)



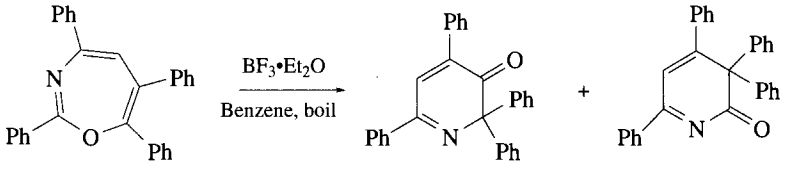
(**398**)

94%

(275)

5.05.3.5.3 From oxazepines

Oxazepine (**399**) is converted by treatment with boron trifluoride etherate in boiling benzene into a mixture of 3- and 2-pyridones (Equation (276)) ⟨85H(23)1399⟩.



(**399**)

72%

10%

(276)

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5.06
Pyridines and their Benzo Derivatives: Applications

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Reilly Industries Inc., Indianapolis, IN, USA

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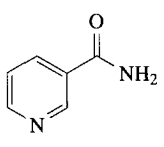
5.06.1 INTRODUCTION

Heterocyclic compounds are widely distributed in nature, and among the six-membered heterocyclic compounds the chemistry of pyridine and of its benzo derivatives, especially quinoline and

isoquinoline, is particularly well known, and many important compounds have been synthesized. Wide-ranging applications have been discovered, including their use as reagents in organic synthesis, as precursors to nonheterocycles, polymers, dyestuffs, additives, pharmaceuticals, agrochemicals, veterinary products, surfactants, and corrosion inhibitors. The applications of pyridine and its benzo derivatives have been reviewed in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) and elsewhere ⟨84CHEC-I(2)511, B-93MI 506-01⟩.

5.06.2 NATURAL PRODUCTS

Although pyridine does not occur free in nature, its derivatives are found abundantly as natural products, some of which are of fundamental importance to living systems. Naturally occurring pyridine derivatives include nicotinamide (**1**), vitamin B_6 (pyridoxol) (**2**), nicotine (**3**), and more complex systems such as nicotinamide adenine dinucleotide (NAD).



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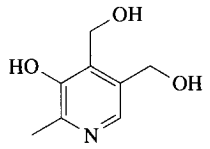

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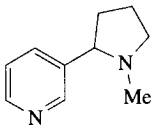

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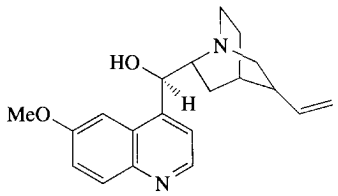
The alkaloid quinine (**4**) is a traditional antimalarial drug ⟨62JCS3526, B-79MI 506-01⟩, the skeleton of which has been used as the basis for the design of many synthetic antimalarial compounds, chloroquine (**5**) being an example. The opium alkaloid papaverine (**6**) is a nonspecific smooth muscle relaxant and vasodilator. Anabasine (**7**) ⟨35JA959⟩, nicotine ⟨B-89MI 506-01⟩ and nornicotine (**8**) ⟨78JOC3922⟩ have all been used as pesticides.



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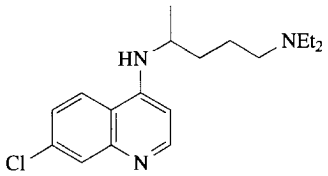

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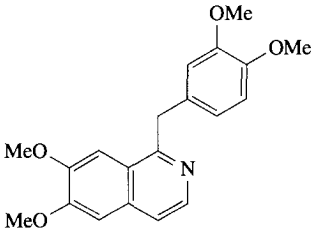

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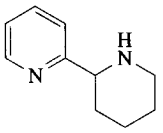

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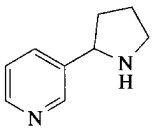
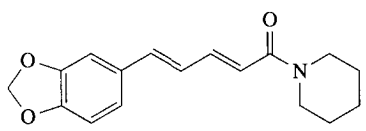


(8)

Many polycyclic alkaloids containing the piperidine moiety have been reported ⟨B-89MI 506-02⟩. Piperidine itself was first isolated from the alkaloid piperine (**9**), which occurs in black pepper (*Piper nigrum*). Pyrolysis of piperine over soda lime gives piperidine ⟨B-53MI 506-01⟩. Piplartine (**10**) ⟨68TL2395⟩ and pipermethystine (**11**) ⟨79T437⟩ are isolated from *Piper longum* and *P. methystine*, respectively, and have been shown to possess a variety of pharmacological activities including anticonvulsive, antiepileptic, fungicidal, and anesthetic properties.



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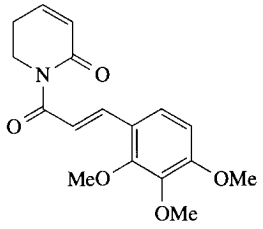

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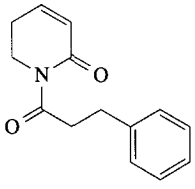
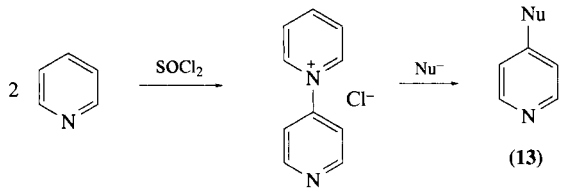


(11)

5.06.3 REAGENTS IN ORGANIC SYNTHESIS

Pyridine is weakly basic ($pK_a = 5.2$), and is widely used both as a solvent and a catalyst, particularly in condensation, dehalogenation, and acylation reactions ⟨43OSC(2)109⟩. The use of pyridine as a solvent–base forms the basis of the Doebner modification of the Knoevenagel condensation of aldehydes with malonic acid and its derivatives. 4-Picoline, 2-methyl-5-ethylpyridine (MEP), and collidine (2,4,6-trimethylpyridine) are used as solvents for resins and in dehydrohalogenation reactions.

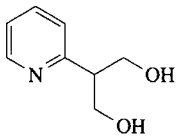
Pyridine on reaction with thionyl chloride gives *N*-(4-pyridinyl)pyridinium chloride hydrochloride (**12**), which provides access to 4-substituted pyridines (**13**) by nucleophilic displacement (Equation (1)) ⟨73OSC(5)977⟩. 2-(2-Pyridinyl)-1,3-propanediol (**14**) is used for the protection of carbonyl groups as ketals ⟨87TL1195⟩. The conversion of ketones into enol triflates has also been mediated with pyridine ⟨88OSC(6)757⟩.



(**12**)
Nu = NH_2, NMe_2, OR

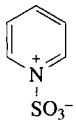
(**13**)

Scheme 1



(**14**)

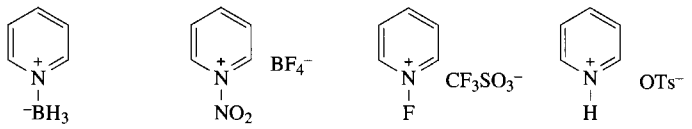
Pyridine, through its lone pair of electrons on nitrogen, reacts with a wide range of Lewis acids to give complexes, many of which are useful synthetic reagents. Pyridine hydrochloride is used as a demethylating agent for *N*-methyl cyclic ketonitrones ⟨92IJC462⟩. Pyridine *N*-oxides are mild oxidizing agents useful for the conversion of alkyl halides to aldehydes ⟨57JOC1135⟩ and α-bromo esters to carbonyl compounds ⟨65ZOR1121⟩, while pyridine-sulfur trioxide (**15**), a mild sulfonating agent, is used to prepare sulfate esters and to sulfonate sensitive substrates such as indoles ⟨B-67MI 506-01, B-74MI 506-01⟩.



(**15**)

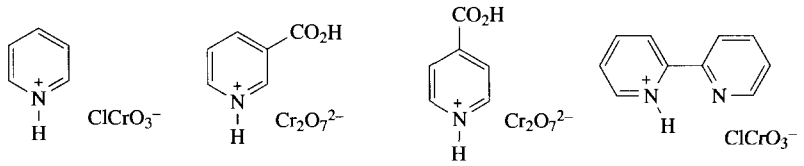
The pyridine–borane complex (**16**) finds utility as a mild and selective reducing agent ⟨B-67MI 506-02⟩, while *N*-nitropyridinium tetrafluroborate (**17**) is used as a nitrating agent ⟨68JA4742, 78S452⟩ and *N*-fluoropyridinium triflate (**18**) for fluorination ⟨90JA8563⟩. Pyridinium *p*-toluenesulfonate (PPTS) (**19**) has been found to be superior to *p*-toluenesulfonic acid in the tetrahydropyranylation of certain alcohols, especially those containing an acid-sensitive functionality, and it has also been used for the deprotection of tetrahydropyranyl ethers in ethanol ⟨77JOC3772⟩. Other applications are acetalization and transacetalization reactions where more acidic conditions are undesirable, and indeed PPTS appears to have become the reagent of choice for these conversions ⟨79S724⟩.

Pyridinium chlorochromate (PCC) (**20**) oxidizes benzylic ketones smoothly to α-diketones ⟨88SC1573⟩ and aldehydes to acyl azides in the presence of azide ⟨88SC545⟩. PCC-mediated allylic oxidations have also been reported ⟨86SC1371⟩. The development of 3-carboxypyridinium dichro-



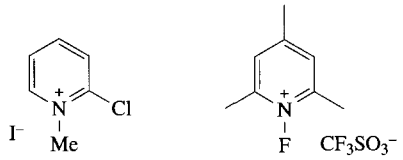
(16) (17) (18) (19)

mate (NDC) (**21**), 4-carboxypyridinium dichromate (**22**), and chromate complexes of 2,2′-bipyridine (**23**) as mild, stable oxidation agents ⟨85SC1197⟩ has enabled the smooth oxidation of primary and secondary alcohols to carbonyl compounds, especially in the case of acid-labile and complex molecules ⟨80S691, 80SC951⟩.



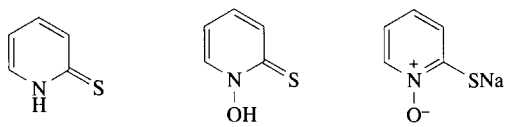
(20) (21) (22) (23)

2-Chloro-1-methylpyridinium iodide (**24**) is a reagent for the formation of carboxylate esters from acids and alcohols ⟨75CL1045⟩, carboxamides from acids and amines ⟨75CL1159⟩, lactones from ω-hydroxy acids ⟨76CL49⟩, and carbodiimides from *N*,*N*′-disubstituted thioureas ⟨77CL575⟩. *N*-Fluoro-2,4,6-trimethylpyridinium triflate (**25**) is a stable and selective electrophilic fluorinating agent ⟨92H(33)105⟩.



(24) (25)

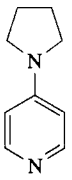
Pyridine-2-thione (**26**) and its analogues have found general synthetic utility in C—C bond-forming reactions, and are used to prepare activated thioester synthons of blocked amino acids for peptide synthesis ⟨71JCS(C)2890⟩. The 1-hydroxy analog (**27**) is used in decarboxylative iodination ⟨89TL6967, 90TL1965⟩, while homologation of acids is achieved via the carbon dioxide trapping of carbon radicals generated from the acyl derivatives of (**27**) ⟨91TL3309⟩; the hydroxyl radicals generated from (**27**) find many applications in organic synthesis ⟨92BSF145⟩. The sodium salt of 1-hydroxypyridine-2-thione (**28**) is also used for novel radical decarboxylation reactions ⟨86TL6337⟩, and this chemistry has been extended to key synthetic targets, for example the stereocontrolled synthesis of versatile carbapenem intermediates has been achieved using the Barton reaction ⟨92TL749⟩.



(26) (27) (28)

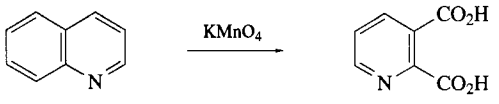
The use of *N*,*N*-dimethylaminopyridine (DMAP) (**13**), (Nu = NMe_2) as a catalyst in organic synthesis has been reviewed since its original discovery ⟨78AG(E)569, 83CSR129, 85OS(63)183⟩. DMAP is a superior catalyst to pyridine for the acylation of tertiary and sterically hindered tertiary alcohols ⟨78AG(E)569⟩. For example, 1-methylcyclohexanol, a sterically hindered alcohol, is acetylated readily in the presence of a catalytic amount of DMAP but not pyridine. DMAP is also used as a catalyst for transesterification ⟨85JOC3618, 88JOC449⟩, alkylation, halogenation, cyanation, and silylation, and

as an accelerator in the manufacture of polyurethanes. 4-Pyrrolidinopyridine (**29**) is likewise an efficient liquid catalyst for room temperature esterification of carboxylic acids ⟨78TL4475⟩.

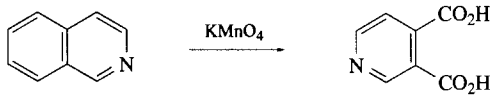


(**29**)

Quinoline and alkylquinolines are used in high-temperature reactions as solvents and catalysts, especially for decarboxylations and Rosenmund reductions ⟨63OSC(4)731⟩, and in the processing of resins and terpenes. Quinolinium acetate has been used for the cleavage of methyl or ethyl esters of hindered carboxylic acids ⟨75S330⟩, and quinolines and isoquinolines are utilized as precusors for various pyridine mono- and dicarboxylic acids, which are obtained by oxidation with potassium permanganate ⟨1885RTC285⟩ or with ozone (Equations (1) and (2)) ⟨89S880⟩. Quinine is used in chiral synthesis to resolve isomers ⟨86CCC401⟩.

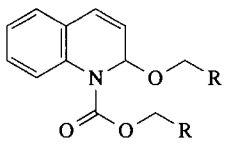


(1)



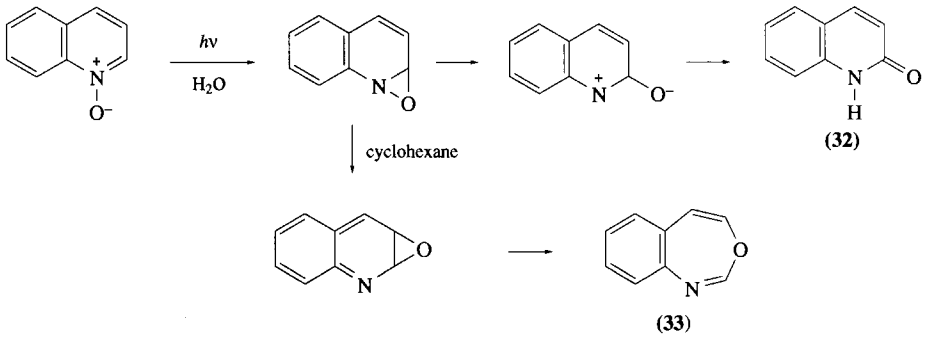
(2)

2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) (**30**) and its analogue 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (IIDQ) (**31**) are useful condensing agents for peptides as little or no racemization occurs ⟨68JA1651, 71JMC49, 72CC942⟩. EEDQ has similarly been used for the synthesis of 5(4*H*)-oxazolones ⟨88ZC439⟩.



(**30**) R = Me
(**31**) R = Pr^{i}

Like pyridine, quinoline and isoquinoline form *N*-oxides with organic peracids. Quinoline *N*-oxides ⟨B-82MI 506-01⟩ are useful synthetic intermediates, giving 2-quinolones (**32**) as the major products on photolysis in water or ethanol, but in cyclohexane the benzoxazepine (**33**) is formed from the parent *N*-oxide (Scheme 2) ⟨79TL3761⟩.



(**32**)

(**33**)

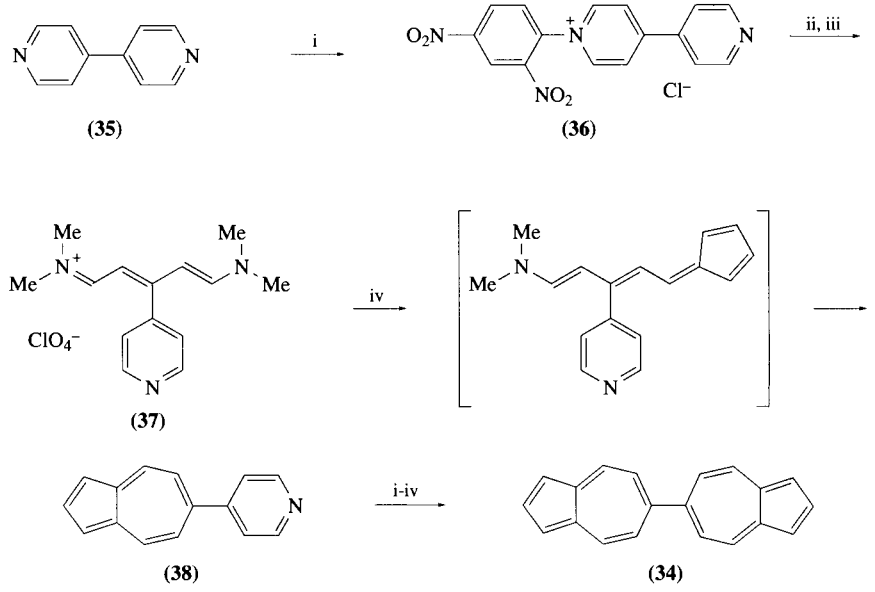
Scheme 2

5.06.4 SYNTHESIS OF NONHETEROCYCLES

Many nonheterocyclic compounds have been prepared using heterocyclic compounds. This section highlights some of the classical uses of pyridine and its derivatives in that role. Excellent review articles have appeared on this subject ⟨78H(10)349, 84CHEC-I(1)413⟩.

5.06.4.1 Biaryls

The base-induced ring opening of substituted pyridinium salts, a well-documented phenomenon, provides an entry into the 6,6′-biazulene system (**34**) (Scheme 3) ⟨80S31, 80S589⟩. Reaction of 4,4′-bipyridine (**35**) with 2,4-dinitrochlorobenzene yields the monoquaternary salt (**36**), which undergoes ring opening in aqueous dimethylamine to furnish the 2,4-pentadieniminium salt (**37**). Further reaction with cyclopentadiene and sodium methoxide in pyridine gives the azulene (**38**). Repetition of the sequence on the remaining pyridine ring affords the biazulene (**34**).

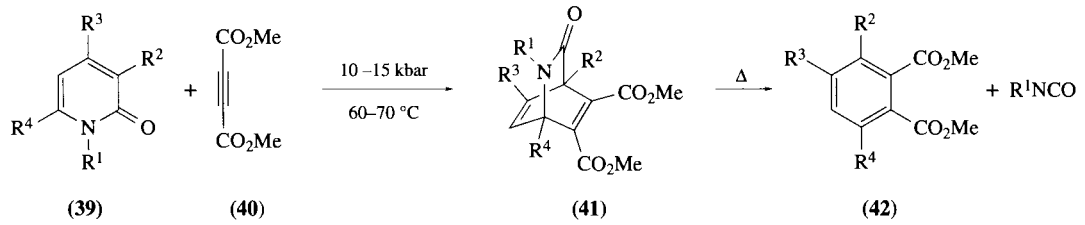


i, 2,4-$(NO_2)C_6H_3Cl$; ii, Me_2NH, EtOH, H_2O; iii, $NaClO_4$; iv, cyclopentadiene, NaOMe, py

Scheme 3

5.06.4.2 Benzene Derivatives

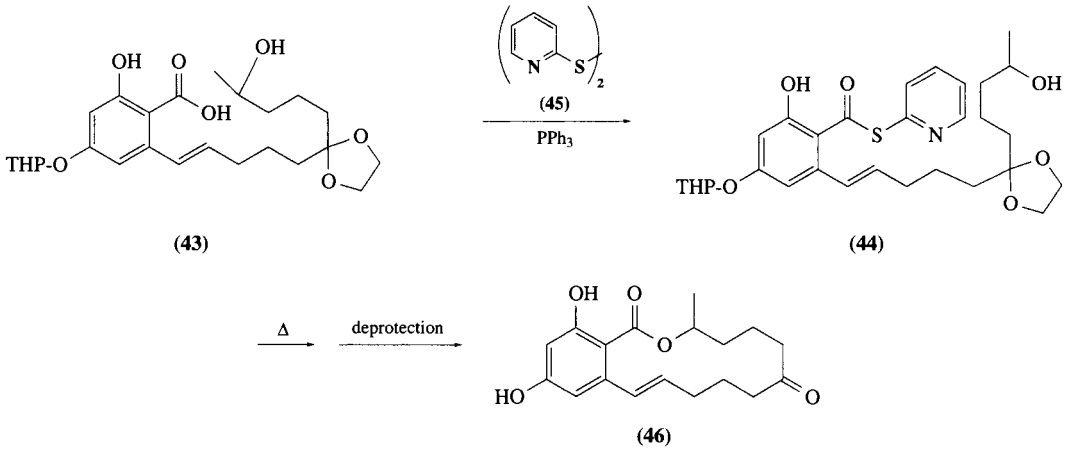
The cycloaddition chemistry of pyridones is analogous to that of α-pyrones ⟨79CC1091⟩. Pyridones (**39**) react under high pressure with acetylenedicarboxylic esters (**40**) to furnish cycloadducts (**41**) which on heating lose a molecule of an isocyanate to yield substituted aromatics (**42**) (Scheme 4).



Scheme 4

5.06.4.3 Lactones

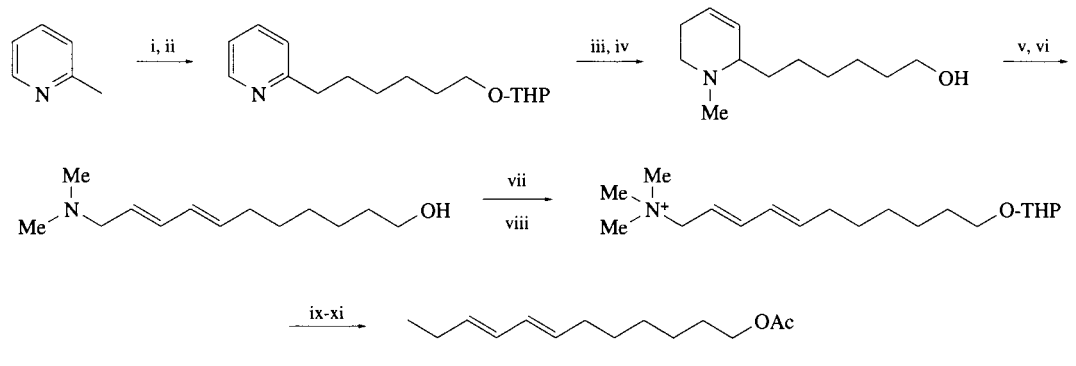
Medium- and large-ring lactones are prepared in good yields from ω-hydroxyacids, for example (**43**), via cyclization of the corresponding 2-pyridine thiolesters (**44**) ⟨75JA5614, 76TL3409, 79AG(E)308⟩, which are easily prepared by reaction of the acid with 2,2′-bipyridyl disulfide (**45**) and triphenylphosphine. (±)-Zearalenone (**46**) was prepared in this way (Scheme 5).



Scheme 5

5.06.4.4 Conjugated Dienes

The preparation of conjugated dienes from pyridines is exemplified by the transformation of 2-picoline into the sex pheromone (**47**) of *Lobesia botrana*, a major pest of vineyards ⟨80TL67⟩. Key steps are the reduction and Hofmann elimination with ring opening to give the intermediate (7*E*,9*Z*)-undecadien-1-ol (Scheme 6).



(**47**)

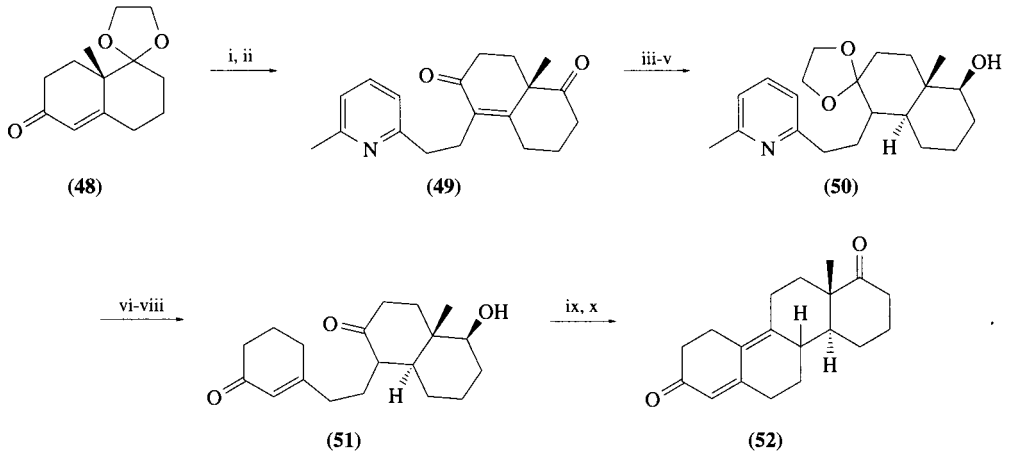
i, Bu^nLi; ii, $Cl(CH_2)_5O$-THP; iii, MeI; iv, $NaBH_4$; v, MeI; vi, KOH; vii, DHP, TsOH; vii, MeI; ix, Me_2CuLi; x, TsOH, MeOH; xi, Ac_2O, py

Scheme 6

5.06.4.5 Steroids

2-Vinylpyridines are important bis-annelating agents in steroid synthesis, the key steps of which are Michael addition to the vinyl group followed by conversion of the pyridine ring into a 1,5-diketone by a reduction–hydrolysis sequence. For example, the base-catalyzed reaction of the enone (**48**) with 6-vinyl-α-picoline followed by the reduction of the saturated ketone group of (**49**), the

hydrogenation of the double bond and acetalization affords the alcohol (**50**), which is transformed to (**51**) by three steps: (i) reduction, (ii) hydrolysis/cyclization, and (iii) deketalization. Jones oxidation of the alcohol (**51**) and cyclodehydration gives D-homoestrone (**52**) (Scheme 7) ⟨72CC373⟩.

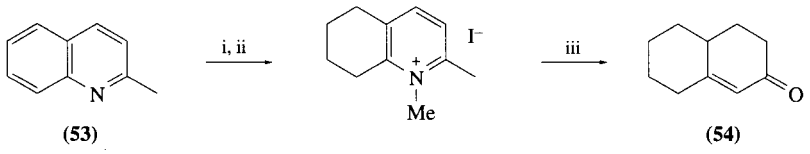


i, 6-vinyl-α-picoline, $EtCMe_2O^-K^+$; ii, H^+; iii, $NaBH_4$; iv, H_2, Pd/C; v, $HOCH_2CH_2OH$, H^+; vi, Na, NH_3, EtOH; vii, NaOH, EtOH, H_2O; viii, HCl(aq.); ix, Jones reagent; x, NaOEt, EtOH

Scheme 7

5.06.4.6 Octalones

2-Methylquinoline (**53**) and its derivatives can be used as precursors for the synthesis of 2-octalones, for example (**54**), via quaternization, ring opening, and aldol-type cyclization ⟨90JOC2237⟩ (Scheme 8).



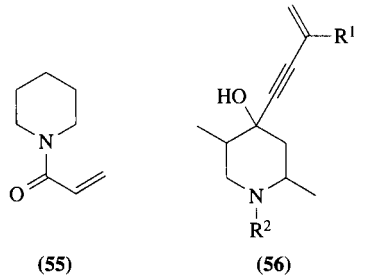
i, H_2/TFA/PtO_2; ii, MeI; iii, NaOEt

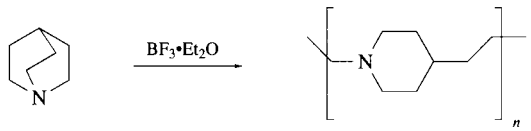
Scheme 8

5.06.5 POLYMERS

5.06.5.1 Polypiperidines

Few piperidine polymers have been reported. For example, 1-acryloylpiperidine (**55**), although a typical amide monomer, is not very reactive in polymerization reactions ⟨80MI 506-01⟩. Polymers with polyelectrolyte behavior were obtained from the piperidine monomer (**56**) via free radical polymerization of the double bond ⟨80MI 506-02⟩, and polymers containing a piperidine ring (**57**) have been prepared by cationic polymerization of quinuclidine (**58**) (Equation (3)) ⟨73MI 506-01⟩ or reduction of polyvinylpyridines.

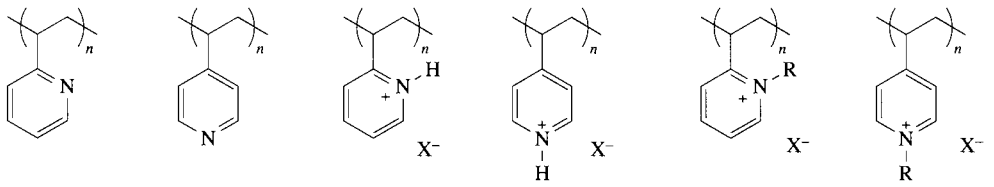




(58) (57) (3)

5.06.5.2 Polyvinylpyridines

Polyvinylpyridines are an important class of polymers with interesting properties due to the presence of the weakly basic nitrogen atom, which makes possible a similar variety of reactions in pyridine polymers (e.g., (**59**) and (**60**) as in the monomeric species, for example reaction with acids (**61**) and (**62**), quaternization (**63**) and (**64**), and complexation with metals. The most common pyridine ring polymers, derived from 2-vinyl-, 4-vinyl-, and 2-methyl-5-vinylpyridine, may be prepared either by the direct polymerization of preformed monomers or by subsequent derivatization of the polymers. The preparation and polymerization of the vinylpyridines have been reviewed extensively ⟨B-74MI 506-02⟩, and these materials are used for adhesion, as impact modifiers, antistatic agents, and ion exchange resins, for heavy metal chelation, as detergent additives, and as catalysts and catalyst supports ⟨B-66MI 506-03⟩.



(59) (60) (61) (62) (63) (64)

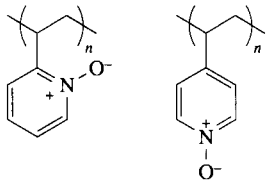
2-Vinylpyridines have practical uses as comonomers for synthetic rubbers and fibers. The homopolymer of 2-methyl-5-vinylpyridine has properties similar to those of polystyrene. 2-Vinylpyridine rubber has better flex cracking, tearing, resilience, and tensile properties than styrene–butadiene rubber ⟨61MI 506-01⟩. It was reported that the highest values for strength, elasticity, and abrasion resistance were achieved when the rubber contained butadiene (70%), styrene (25%), and 2-methyl-5-vinylpyridine (5%). Since 2-vinylpyridine has a high affinity for metal salts, zinc chloride, zinc oxide, stannous chloride, and cadmium chloride can be used as vulcanizing agents ⟨62MI 506-01, 63MI 506-01⟩. 2-Vinylpyridine monomers complexed with metal salts act as vulcanizing agents for ethylene–propylene or butadiene–styrene rubber ⟨68MI 506-01⟩. For ethylene–propylene rubber, the tensile strength is increased from 32 kg cm^{-2} to 78 kg cm^{-2} when 15 parts of 2-methyl-5-vinylpyridine–zinc chloride complex are added to the rubber together with 10 parts of zinc oxide and one part of peroxide, and the mixture then vulcanized ⟨68MI 506-02⟩.

Copolymers of 2-vinylpyridines with styrene and butadienes are used as tire cord adhesives for bonding reinforcing fibers to a rubber matrix ⟨85JP6096674⟩. Copolymers of ethylene–propylene grafted with 2-vinylpyridine have a good balance of dispersancy and thickening properties when incorporated into fuels and lubricating oils ⟨77GEP(O)2634033⟩, while copolymers of styrene and 4-vinylpyridinedicyanomethylide are photochemically active and may be photoreticulated by irradiation with a mercury source ⟨80MI 506-01, 81MI 506-04⟩.

2-Vinylpyridine rubber itself has a high adhesivity for tire cord materials such as rayon, nylon, and polyester. 2-Vinylpyridine may be used as a bonding material between glass fiber and resin in fiber-reinforced plastics, and it is an important comonomer for improving the dyeability of acrylic fiber ⟨57IEC1929⟩. Vinylpyridine copolymers are weakly basic resins that can be used for anion exchange after quaternization or as selective ion exchangers for metal ions, by complexation of the pyridine nitrogen atom. Amphoteric ion exchangers are easily obtained by copolymerization with acidic monomers ⟨67URP197946⟩. Copolymers of vinylpyridine with acrylic or methacrylic acid are soluble in water over a wide range of pH; an amphoteric coating material for pharmaceutical use can be prepared from the copolymers ⟨62JPS1061⟩.

A wide array of initiators can be used to polymerize vinylpyridines (e.g., free radical, anionic, or cationic) ⟨65MI 506-01, 84MI 506-01⟩, and the monomers are somewhat more reactive than styrene. Anionic initiators for vinylpyridine monomers include *n*-butyllithium ⟨77MI 506-01⟩, 2-ethylpyridyllithium ⟨81JA3666⟩, dibenzylmagnesium ⟨80MAC799, 80MI 506-03⟩, and cumylbarium ⟨83MI 506-01⟩.

Poly(2-vinylpyridine) *N*-oxides (**65**) may be prepared either by polymerization of the 2-vinylpyridine *N*-oxide monomer or by oxidation of the corresponding polymer by H_2O_2 ⟨62MAC244⟩. They are used in the treatment of silicosis and have been found to be effective in preventing liver damage in rats exposed to CCl_4. Reviews by Holt ⟨71MI 506-01⟩ and by Harington ⟨76MI 506-01⟩ discuss this subject in detail. 4-Polyvinylpyridine *N*-oxides (**66**) are reported to inhibit dye transfer during laundering of colored fibers ⟨94EUP579295⟩.



(**65**) (**66**)

The use of pyridine-containing polymers as supports for reagents in organic reactions has been reviewed ⟨B-90MI 506-01⟩, and offers the possibilities of enhanced selectivity and recyclability as major attractions.

Reducing agents derived from polyvinylpyridine and sodium borohydride, borane, or borane with dimethyl sulfide are milder than their precursors ⟨74MI 506-03, B-75MI 506-01, 80JOC2724⟩. Greber and Merchant have prepared a Girard reagent P with poly(4-vinylpyridine), ethyl α-chloroacetate or α-bromoacetate and hydrazine ⟨69MI 506-01⟩. This reagent is useful for the selective separation of ketonic and nonketonic materials.

Complexes of poly(4-vinylpyridine) with $Rh_4(CO)_{12}$, $Co_4(CO)_{12}$, or $Co_2(CO)_8$ catalyze the oxo reaction of alkenes such as 1-pentene or ethylene under mild conditions ⟨70GEP(O)1937225, 75JAP(K)129508, 77GEP(O)2633959⟩. Alkenes have been isomerized at 100 °C with catalysts prepared from polyvinylpyridines and ruthenium(II) or rhodium(I). The polymeric catalysts are easily recycled, and exhibit better stabilization of active intermediates and longer lifetimes than conventional catalysts ⟨77JMOC379⟩. The copper complex of poly(4-vinylpyridine) catalyzes the air oxidation of thiosalts ⟨80JMOC389, 81JMOC9⟩ and the oxidation of substituted phenols ⟨70IZV2722⟩. The reaction of formaldehyde with acetylene is catalyzed by the copper complex of poly(4-vinylpyridine) ⟨81EUP22164⟩. A similar poly(4-vinylpyridine)–copper complex catalyzes the synthesis of ketazine ⟨77JAP(K)131987⟩.

1,2,3,4-Tetrahydronaphthalen-1-one is produced by the liquid phase oxidation of tetralin using 2% chromium(III) acetate supported on cross-linked poly(4-vinylpyridine) resins ⟨83GEP(O)3229001, 88EUP269407⟩.

The hydrolysis of esters such as 4-nitrophenyl acetate, 3-nitro-4-acetoxybenzoic acid and aspirin is catalyzed by poly(1-alkylvinylpyridinium halides) ⟨70MI 506-01, 71CI(L)819, 74MI 506-04, 74MI 506-05, 75MI 506-02, 75MI 506-03, 79MAC1617⟩. The 6-nitro-1,2-benzisoxazole-3-carboxylate anion was decarboxylated using catalysts prepared by quaternizing poly(4-vinylpyridine) with a variety of alkyl halides ⟨77JOC306, 81JOC868⟩.

Homopolymers of 2- and 4-vinylpyridines (**59**) and (**60**) and their quaternary alkyl halides (**63**) and (**64**) have been used as phase transfer catalysts for the ethylation of phenylacetonitrile with ethyl bromide ⟨77MAC3165⟩.

Poly(1-alkylvinylpyridinium halides) have been shown to be good negative electron beam resists for microlithography. Doping poly(2-vinylpyridines) with iodine or an organic electron acceptor such as 7,7′,8,8′-tetracyanoquinodimethane (TCNQ) results in the formation of semiconductors with conductivities of 10^{-4} S cm^{-1} and 10^{-2} S cm^{-1}. A series of polyvinylpyridinium ions with different molecular weights, distributions, counterions, alkyl groups, and degrees of quaternization have been studied to elucidate the structural variable that influences the resist performance ⟨82MI 506-02⟩. In general, electron beam sensitivities increased with polymer molecular weight, and sensitivity was greatest when the 1-alkyl group was isopropyl or heptyl ⟨82MI 506-02⟩. Use of polymeric quaternary salts as negative resists simplifies the manufacture of microelectronic printed circuits. The natural electroconductivity of the polymer film prevents a build-up of electrostatic charge during exposure to an electron beam. Use of the polymers also makes it unnecessary to coat the substrate with a metal oxide.

Various pyridine-based homopolymers can be used in lithography and reprography. Poly(2-vinylpyridine) (**59**) can function as a key coat for dry transfer sheets and provides adhesion between the photosensitive layer and the carrier sheet. The polymer splits cleanly from the carrier sheet

during transfer and resists penetration of the adhesive ⟨74FRP2214593⟩. Polyvinylpyridines have also been used as binders to hold photosensitive materials to lithographic plates ⟨76USP3942988⟩. Electrophotographic materials prepared with polyvinylpyridines as the photoconductor have shown excellent image clarity and resolution ⟨76JAP(K)30741⟩. The dimethyl sulfate quaternary salt of poly(4-vinylpyridine) prevents contamination of lithographic printing plates ⟨77GEP(O)2701144⟩. Polyvinylpyridines have proven useful for the preparation of toners and toner carrier particles. Poly(2-vinylpyridine), in combination with polystyrene, carbon black, and iron powder, provided a positively charged toner that gave good black images with good halftone reproducibility ⟨75JAP(K)124648⟩. Durable toner carrier particles were also obtained when iron or steel particles were coated with poly(2-vinylpyridine) (**59**) and polyurethane ⟨77USP4007293⟩, silicone ⟨80JAP(K)127569⟩ or cellulose methyl ether ⟨76USP3947370⟩. A heat-sensitive color-forming agent that shows electrical conductivity was prepared with poly(4-vinylpyridine) (**60**) and poly(vinylidene halide).

Polyvinylpyridines in combination with polyvinyl alcohol form excellent dye mordant or image receiving layers. Mordant layers containing the polyvinylpyridines bind both metallized and non-metallized acidic dye developers. Solutions of polyvinylpyridines ⟨58USP2830900⟩ or their quaternary salts ⟨69USP3459580⟩ form thin films that protect the image surface of instant film prints. The unique ability of poly(2-vinylpyridine) to adhere to both hydrophilic colloid layers and hydrophobic supports makes the polymer useful as an anchor for photographic film ⟨52USP2606832⟩. Poly(4-vinylpyridine) used as a layer separation for color emulsions prevents dye diffusion and reduces the necessary silver content of the multilayer color photographic material ⟨62BEP618228, 79GEP(O)2846694⟩.

Fibers incorporating polyvinylpyridines show excellent dyeing intensity and are color-fast ⟨66URP183181, 68SAP6707236, 68USP3361843, 69GEP(O)1903368, 79MI 506-02⟩. Polyvinylpyridinium phosphate is reported to impart permanent fire retardancy to cellulose textiles ⟨61USP2992942⟩. Permanently stiffened cotton textiles have been obtained upon treatment with a poly(4-vinylpyridine) latex followed by treatment with a solution of polyacrylic acid. When cellulose is treated with the iodo complex of poly(2-methyl-5-vinylpyridine) a bacteriostatic effect is produced. Polyvinylpyridinium salts can be used as, for example, flocculants, ion exchangers, and emulsifiers. Polyvinylpyridinium chlorochromate may be used for the oxidation of benzyl alcohol to benzaldehyde ⟨78JOC2618⟩.

Treatment of bleached kraft paper with poly(2- or 4-vinylpyridine) is reported to increase TiO_2 retention in pulp slurries from 20% to 80% ⟨77MI 506-02⟩. Poly(1-methyl-4-vinylpyridinium chloride) functions as a conductive paper coating ⟨71CT304⟩.

The addition of a quaternary salt of a polyvinylpyridine to a conventional bright nickel bath at concentrations ranging from 0.05 g l^{-1} to 0.3 g l^{-1} gave a product that was more corrosion resistant after subsequent chromium plating, without the formation of micropores or microcracks ⟨68MI 506-02⟩. The polymeric quaternary salts were effective for plating steel or plastics ⟨73USP3758389⟩.

Poly(4-vinylpyridine) is a film-forming corrosion inhibitor in nonoxidizing acid solutions, including HCl, in acid concentrations up to 37%. Poly(4-vinylpyridine) prevents corrosion of metals and alloys including iron, aluminum, copper, brass, magnesium, solders, and so forth ⟨69USP3466188⟩. Derivatives of the polyvinylpyridines, including quaternary alkyl halide salts and betaines (such as those prepared from chloroacetate), also function as corrosion inhibitors ⟨70USP3505235⟩.

Acid salts ⟨55MI 506-01⟩ and quaternary alkyl halide salts ⟨68DOK(182)369, 75MI 506-04, 76MI 506-02⟩ of polyvinylpyridines are polyelectrolytes effective as emulsifying and dispersing agents. In some instances the use of polymeric salts as emulsifying agent resulted in the acceleration of the radical-catalyzed polymerization. Stable oil-in-water emulsions ranging from 1% to 20% can be broken by the addition of a poly(1-alkylvinylpyridinium) halide ⟨59USP2915476⟩.

Acid solubility and film-forming properties have made the polyvinylpyridines useful in the medical and biological fields. A skin-like bactericidal film can be formed from polyvinylpyridine and acetylpyridinium chloride. Poly(2- and 4-vinylpyridine) have both been used to prepare oxygen- and moisture-resistant tablet coatings which disintegrate in 5–20 min in the presence of artificial gastric juices ⟨60BRP888131, 71GEP(O)2021786, 81MI 506-01⟩.

Poly(4-vinylpyridine) has been used as a carrier for the antitumor drug sarcolysin. The drug-loaded polymer was less toxic and had a better tumor cure rate than sarcolysin alone ⟨74MI 506-06⟩. The fluoride salts of *N*-alkyl derivatives of polyvinylpyridines have shown promise as fluoridation compositions for human teeth. Tooth enamel treated with the polymeric fluorides have shown good fluoride uptake ⟨82MI 506-03, 82MI 506-04⟩. Polyvinylpyridine stimulates antibody formation in rats and rabbits inoculated with *Bordetella pertussis* cells. Polyvinylpyridines are reported to cause mitogenic effects in spleen cells ⟨78DOK(242)490⟩.

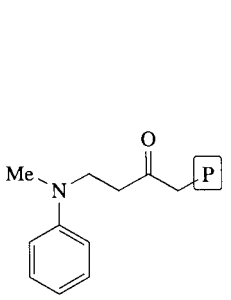
The ion exchange properties of the polyvinylpyridines have made the polymers important com-

ponents of membranes capable of a variety of separations. The adhesive and film-forming properties of the polymers facilitate membrane preparation by several techniques. Poly(4-vinylpyridine) deposited onto a polyvinyl chloride substrate gives a membrane that shows 90% chloride rejection, 99% magnesium and calcium rejection, and 99% sulfate rejection ⟨70USP3503789⟩. High-pressure reverse osmosis membranes are prepared with poly(4-vinylpyridine) and cellulose acetate that give approximately 90% salt rejection and 97% rejection of polyethylene glycol ⟨80CR(C)37, 80JAPS1969⟩. A selective membrane capable of separating two or more kinds of cations of differing electrical charge from an electrolyte during electrodialysis can be prepared by coating a cation exchange membrane with poly(4-vinylpyridine) ⟨75JAP15468⟩. Membranes that show greater permeability for oxygen than nitrogen are prepared by casting polyvinylpyridine onto chromium-plated steel. Woven hoses treated with poly(2-vinylpyridine) show salt-rejecting properties ⟨70MI 506-02⟩.

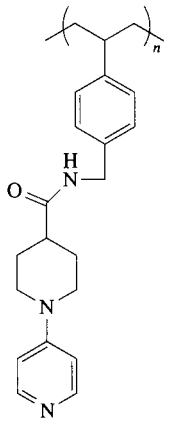
Poly(4-vinylpyridinium halides) and poly(1-methyl-4-vinylpyridinium halides) are reported to possess antiviral activity against tobacco mosaic virus, cucumber mosaic virus, and cucumber green mottling virus. The polymers prevent viral infections in tobacco, tomato, pepper, cucumber, and watermellon plants ⟨79JAP(K)157828⟩. Herbicides bound to poly(4-vinylpyridine) possess both herbicidal and growth-regulating properties ⟨76RRC937⟩.

5.06.5.3 Polymeric Alkylaminopyridines

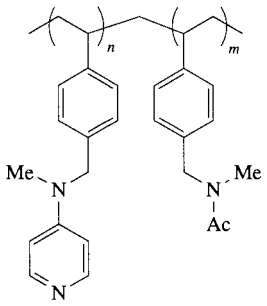
Polymeric versions of the nucleophilic catalyst DMAP have been developed, and syntheses and applications have been reviewed. In most cases the materials are as effective as DMAP and may be recycled with minimal loss in activity ⟨82CI(L)722, 84TL4521, 87MM767, 88MI 506-01⟩. Many approaches to and supports for polymeric forms of DMAP-type catalysts have been reported, (**67**)–(**70**) ⟨79JA6020, 81BCJ631, 82JA799, 84EUP106434, 84TL4521, 85JA4249, 85MI 506-01, 87CT58⟩.



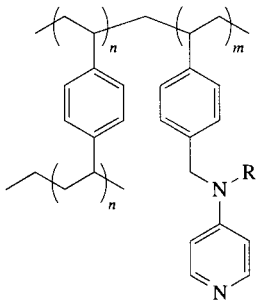
(**67**)



(**68**)



(**69**)



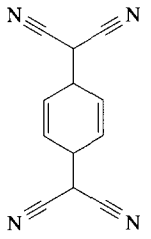
(**70**)

1,4-Dihydronicotinamides bound to a variety of insoluble supports (e.g., cross-linked polystyrene resins) are formed by the reduction of the nicotinamide salt precursor with sodium dithionite. The materials have been used for the stereospecific delivery of hydride ions to carbonyl compounds, and offer the advantage of a recylable reagent and easy workup ⟨79MI 506-03⟩.

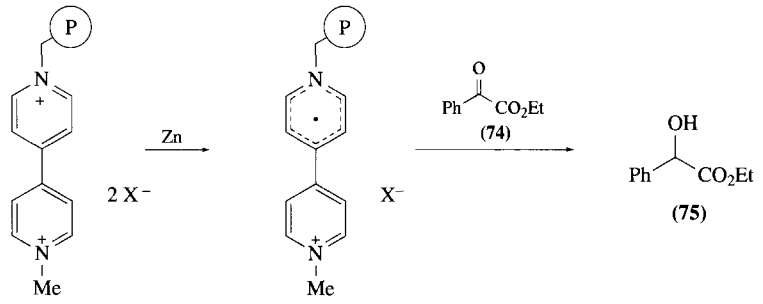
5.06.5.4 Polyviologens

These polymers, which are useful as polyelectrolyte redox polymers ⟨81CSR49⟩ and for the preparation of conductive polymers when complexed with the radical anion of TCNQ (**71**), are prepared directly from the monomer by a Menschutkin reaction. They contain pendant viologens (**72**), and a reducing agent is obtained by a pre-reduction with sodium dithionite, zinc metal, electrochemically, or by exposure to light. Utilization of the reduced poly(viologen) (**73**) as an electron transfer mediator was demonstrated by the addition of a catalytic amount of the polymer

to a mixture of zinc powder, ethyl benzoylformate (**74**), and water–acetonitrile. A quantitative yield of ethyl mandelate (**75**) was obtained after 2 d at room temperature; without the polymer no reaction was observed even after a month (Scheme 9) ⟨79MAC1⟩.



(**71**)

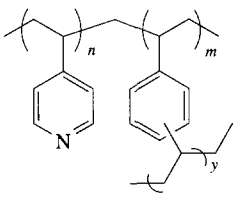


(**72**) (**73**) (**75**)

Scheme 9

5.06.5.5 Ion Exchange Resins

Cross-linked polyvinylpyridines are completely insoluble in all solvents and show high heat stability. Such polymers have been used as catalysts, supports for metals, for metal recovery, in pollution control applications, and as acid scavengers, particularly in nonaqueous media ⟨91MI 506-01⟩. The cross-linked resin (**76**) made from 4-vinylpyridine and divinylbenzene has been used to remove hexavalent chromium ions from water ⟨73JAP(K)75898⟩ by complexation. This type of resin can also be used to remove or recover phenol from waste water ⟨84JAP(K)5995228⟩.

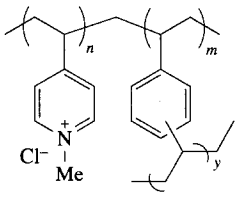


(**76**)

Cross-linked 4-vinylpyridine polymers have been found to be excellent catalysts for the Knoevenagel reaction and catalytic amounts of the resin hydrochlorides may be used for ketal and enamine formation. Similarly, polymer acid salts in bead form act as catalysts for the tetrahydropyranylation of primary, secondary, and tertiary alcohols, and phenols ⟨88S393⟩.

The macroporous anion exchange resin, Reillex HPQ (**77**), based on a copolymer of 1-methyl-4-vinylpyridinium chloride and divinylbenzene, has been utilized for plutonium separation ⟨89MI 506-03⟩. In strong acid it shows low sensitivity to pH in the range 2–4, with high sorption capacity and high selectivity for uranium in acid media in the presence of iron(III) ⟨92MI 506-01⟩. It has also been used for the selective recovery of chromate from low concentrations in aqueous solutions in the pH

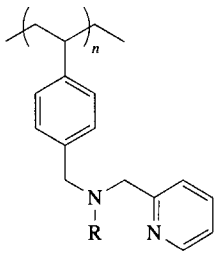
range 2–8 ⟨93MI 506-02⟩. Reillex HPQ shows superior radiolytic stability and has been used for isolating pertechnetate [TcO_4^-] from a variety of radioactive waste streams ⟨94MI 506-01⟩.



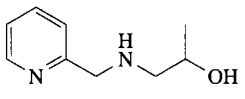
(77)

The 4-vinylpyridine–divinylbenzene gel bead copolymer Reillex 425 (**76**) complexed with 1–7% rhodium(O) is used in an improved synthesis of acetic acid from methanol ⟨68SAP6802174, 88EUP277824⟩, and has been used for the conversion of methyl formate to acetic acid ⟨85GEP3333317⟩.

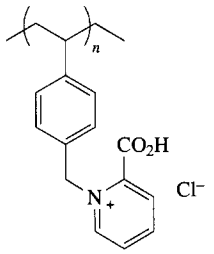
Ion exchange resins that are selective for copper and nickel have been prepared by reaction of chloromethylated polystyrene with 2-picolylamines (**78**) ⟨77USP4031038⟩. These materials are suited for the recovery of copper and nickel in hydrometallurgical operations, because of their excellent selectivity in the presence of excess iron(III) ions at low pH. Utilization of *N*-hydroxyalkylpicolylamines (**79**) results in ion exchange resins with higher capacities. Incorporation of the 2-hydroxypropyl group in the resin (R = $CH_2CHOHMe$) (**80**) led to a stronger adsorption for copper(II) ion by a factor of at least six and resulted in an ultimate capacity of 40 g l^{-1} of resin ⟨79MI 506-04, 84MI 506-02⟩.



(**78**) R = H
(**80**) R = $CH_2CH(OH)Me$



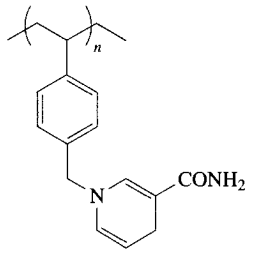
(79)



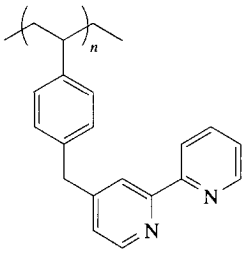
(81)

Amphoteric ion exchange resins (**81**) and (**82**) have been prepared by the reaction of pyridinecarboxylic acids derivatives, especially 2-pyridinecarboxylic acid, with chloromethylated polystyrene ⟨76IZV33⟩. The resin (**81**) exhibited pronounced selectivity for Cu^{2+} and Ni^{2+} ions and also, at low acidity, for the UO_2^{2+} ion. Resins prepared with a bipyridine unit attached to cross-linked polystyrene, (**83**), show large capacities for Fe^{3+}, Ni^{2+}, and Pd^{2+} ions ⟨77JA7733⟩.

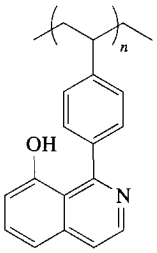
Procedures for the separation of copper from nickel and nickel from magnesium have been developed using 8-hydroxyisoquinoline functional resins (**84**) and (**85**) ⟨74MI 506-07⟩. These resins have also been used for the separation of uranyl ions from sea water, and up to 84% of the uranium was removed ⟨77CI(L)634⟩. Reissert chemistry has been employed for polymeric attachment of the isoquinoline derivatives ⟨76MM688, 76MM10⟩.



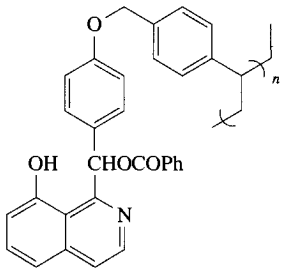
(82)



(83)



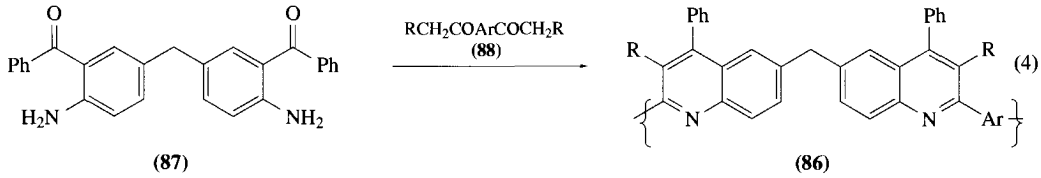
(84)



(85)

5.06.5.6 Polyquinolines

Polyquinolines are versatile, thermally stable polymers and are characterized by repeating quinoline units, which display a catenation pattern of 2,6, 2,4, or 3,6 units ⟨94KO(12)1045⟩. Polyquinolines (**86**) are formed by the step-growth polymerization of *o*-aminophenyl ketone monomers (**87**) and ketone monomers (**88**) containing α hydrogens (mostly acetophenone derivatives) (Equation (4)). Alternatively, they may be prepared by the Friedländer reaction ⟨1882CB2572⟩, which involves either an acid- or a base-catalyzed condensation of an *o*-aminoaromatic aldehyde or ketone with a ketomethylene compound ⟨76MM489, B-90MI 506-02⟩. Polyquinolines have also been obtained by a postpolymerization thermal treatment of poly(enaminonitriles) ⟨89MM1084⟩. The resulting polymers show excellent thermal stability ⟨B-75MI 506-06⟩, with initial weight losses occurring between 500 °C and 600 °C in air.



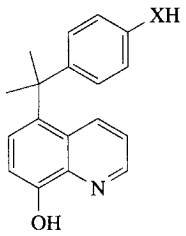
(87) (86) (4)

Most of the polyquinolines display photoresponsive ⟨85MM321⟩ and photomechanical effects as manifested by a contraction in polymer film samples upon irradiation. The coordinating ability of polyquinoline ligands for specific transition metals has allowed their use as catalysts in hydroformylation reactions ⟨83MM839⟩ and for the electrochemical oxidation of primary alcohols ⟨89CM259⟩. Rigid polyquinolines display high conductivity values, generally of the order of 8–11 S cm^{-1} ⟨87MM258⟩. Some biphenylene end-capped polyquinolines have been used to make carbon fiber-reinforced composites ⟨84MM14⟩.

5.06.5.7 Polyvinylquinolines

Polymers based on 2- and 4-vinylquinoline and 8-hydroxy-2-methyl-3-vinylquinoline have been prepared ⟨70MI 506-03⟩. Polycarbonates, polyesters, and polyamides having 8-hydroxyquinoline end groups are synthesized by carrying out the polymerization in the presence of monomers such as 5-substituted 8-hydroxyquinolines, which act as chain terminators ⟨76MAC2927⟩. The polymer chain can be extended by complexation with transition metal ions. Methacrylate derivatives of 5-sub-

stituted 8-hydroxyquinolines (**89**) have been prepared and polymerized to give ion exchange resins. Friedel–Crafts alkylation (of arylalkyl halides with 8-hydroxyquinoline derivatives) has also been used to incorporate 8-hydroxyquinoline into polymers ⟨79MAC897⟩.

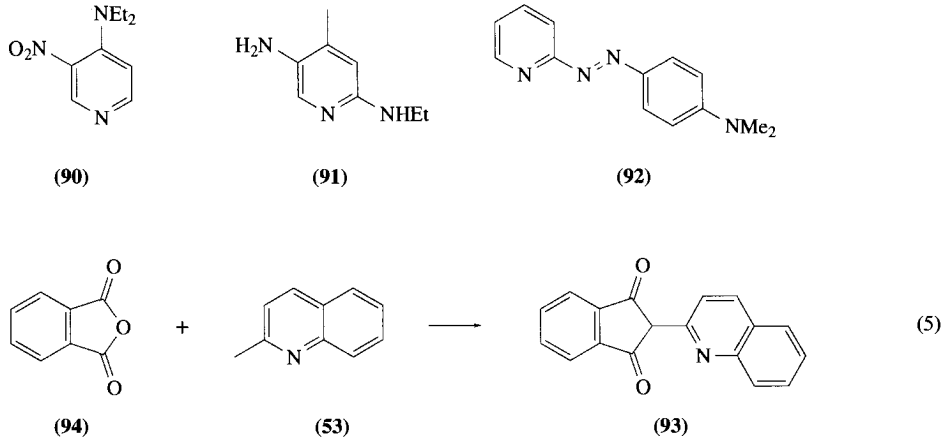


X = O, NH

(**89**)

5.06.6 DYES

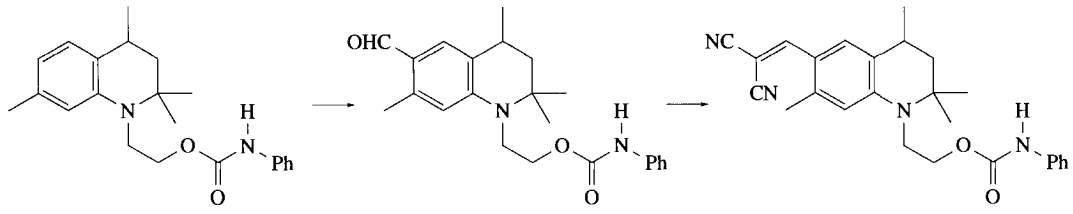
Pyridine derivatives are used as hair dyes: 4-*N*,*N*-diethylamino-3-nitropyridine (**90**) is fast yellow on white hair ⟨79JAP23631⟩ and 5-amino-2-(*N*-ethylamino)-4-methylpyridine (**91**) is fast red when used in conjunction with hydrogen peroxide ⟨79JAP28330⟩. Pyridyl azo derivatives (**92**) have been used as dyes for acrylic ⟨79GEP2851373⟩ and polyester fibers ⟨79JAP938332⟩, respectively. Quinoline yellow (quinophthalone) (**93**) is prepared by the condensation of phthalic anhydride (**94**) with quinaldine (**53**) in the presence of zinc chloride (Equation (5)) ⟨17MI 506-01⟩. The simple methine dye (**95**) can be prepared via a Vilsmeier formylation of the appropriate tetrahydroquinoline derivative (**96**) followed by Knoevenagel condensation of the product (**97**) with malononitrile (Scheme 10) ⟨66FRP14466673⟩. Compounds of this type are bright yellow dyes, usually with moderate fastness properties ⟨81BRP2077282⟩. The chemistry of dyes in general has been reviewed ⟨84CHEC-I(1)317, 93KO(8)542, 93KO(8)672⟩.



(**90**) (**91**) (**92**)

(**94**) (**53**) (**93**)

(5)

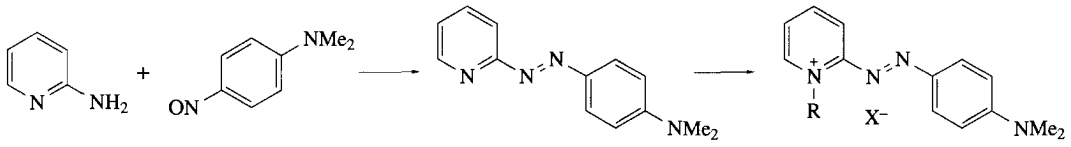


(**96**) (**97**) (**95**)

Scheme 10

5.06.6.1 Cationic Dyes

There are many heterocyclic amines which have been used in the synthesis of cationic dyes including pyridine and quinoline derivatives ⟨B-76MI 506-03, 92KO(3)821⟩. The azo dye (**98**) may be prepared by the condensation of a primary amine and a nitroso compound (**99**) ⟨58USP2864813⟩; the resultant dye is then quaternized with either dimethyl sulfate or with alkyl halides.

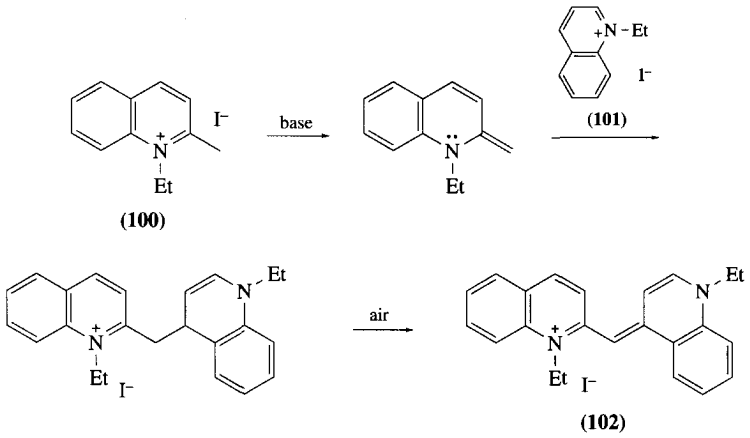


(**99**) (**92**) (**98**)

Scheme 11

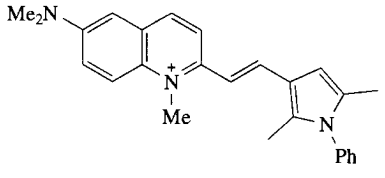
5.06.6.2 Cyanine Dyes

The chemistry of cyanine dyes has been reviewed ⟨B-77MI 506-03, 93KO(7)782⟩. These materials are used as sensitizers in photographic emulsions, and are formed by the base-catalyzed reaction of a methyl-substituted quinolinium salt (**100**) with *N*-ethylquinolinium iodide (**101**). An example of the formation of a cyanine dye, the purple compound (**102**), is shown in Scheme 12. This type of reaction can easily be extended to include other heterocyclic systems, such as (**103**).



(**100**) (**101**) (**102**)

Scheme 12

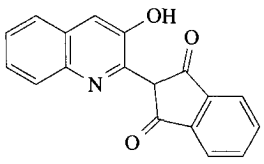


(**103**)

5.06.6.3 Quinophthalone Dyes

Quinophthalone dyes are outstanding for their color brilliance and light fastness ⟨74MI 506-08⟩, and are among the most important yellow disperse dyes. The simplest, CI disperse yellow 54 (**104**),

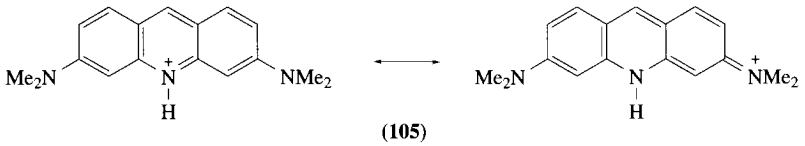
can be prepared by condensation between chloroacetone and isatin, followed by fusion of the resulting 3-hydroxy-2-methylquinoline-4-carboxylic acid with phthalic anhydride ⟨68FRP1523982, B-70MI 506-04⟩.



(104)

5.06.6.4 Acridine Dyes

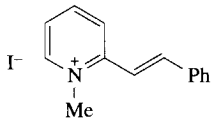
A number of synthetic dyes containing the acridine (e.g., acridine orange (**105**)) or 9-acridinone moiety have been prepared ⟨73HC(9)579⟩ which are water-soluble and display good light fastness. 9-Acridanone dyes are of interest as disperse dyes for synthetic fibers, whilst more complex quinacridones have been used as high-grade pigments ⟨73HC(9)579⟩.



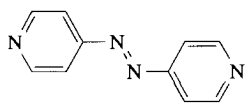
(105)

5.06.6.5 Photochromic Compounds

Compounds which exhibit photochromism are classified according to the mode of their photochemical reaction, because changes in color can arise as a result of isomerization, tautomerism, oxidation, and so forth. They are used in producing prints and proofs of limited lifetime and in areas such as halography, dosimetry data display, and microimaging. Certain azo compounds and substituted ethylenes can undergo photo-induced *cis–trans* isomerization. The *trans* isomer is invariably the thermodynamically more stable and absorbs at longer wavelengths than the *cis* isomer. One or both aromatic rings in stilbenes or azobenzenes can be replaced by heterocycles. Examples include 2-styrylpyridine methiodide (**106**) and 4,4′-azopyridine (**107**) ⟨53JCS1281⟩.



(106)

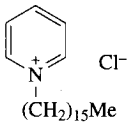


(107)

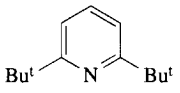
5.06.7 ADDITIVES

The subject of heterocyclic compounds as additives has been extensively studied and reviewed ⟨84CHEC-I(1)393⟩. Additives are used for various purposes: to improve processing, to modify performance or appearance, to prevent or retard aging, and to reduce cost. Higher alkylpyridinium salts are used in the textile industry as dye auxiliaries and spin bath additives (antistatic agents

and softeners). The cetylpyridinium salt (**108**) has been used as a component in toning media ⟨81NEP7907761⟩. 2,6-Di-*t*-butylpyridine (**109**), prepared by reacting Bu^tLi with 2-*t*-butylpyridine, is used as an additive for lubricating oil and gasoline ⟨53JA3865⟩.



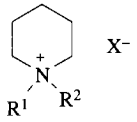
(**108**)



(**109**)

5.06.7.1 Antistatic Agents

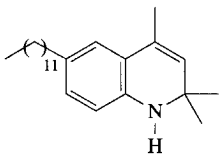
The chemistry of antistatic agents has been reviewed ⟨92KO(3)540⟩. Commercial antistatic agents include pyridinium and piperidinium salts (**110**), which act by reducing the tendency of surfaces to accumulate electrostatic charges ⟨80MI 506-01⟩. They are effective in increasing the surface conductance, most often by making use of the higher conductivity of water.



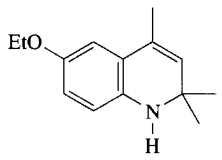
(**110**)

5.06.7.2 Antioxidants

Antioxidants are used in many applications, and the chemistry of these materials has been reviewed ⟨92KO(3)424⟩. For example, the degradation of polymers may be inhibited by the addition of antioxidants, and the most important chain transfer antioxidants are phenols and aromatic amines ⟨B-79MI 506-05, 80PAC365⟩. Two quinoline derivatives are used as antioxidants in the rubber industry. 6-Dodecyl- (**111**) and 6-ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline (**112**) are mainly used as antioxidants in animal feed, but can also be used to preserve the color of paprika and chili powder ⟨94KO(11)805⟩.



(**111**)



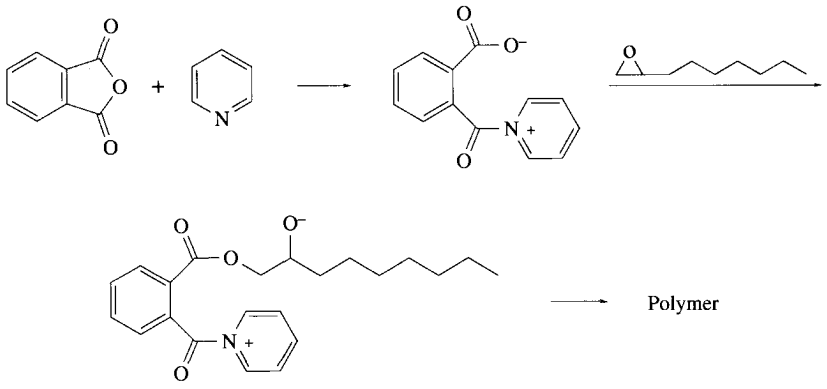
(**112**)

5.06.7.3 Curing Agents for Epoxy Resins

Certain heterocyclic compounds, including pyridines and piperidines, are used to accelerate both amine and anhydride cures of epoxy resins (Scheme 13) ⟨B-68MI 506-03⟩. In the case of anhydride cures, the use of an amine catalyst not only accelerates the cure but also improves the thermal stability of the cured resin.

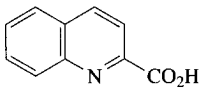
5.06.7.4 Corrosion Inhibitors

Most metals are subject to corrosion, which occurs at metal surfaces in the presence of oxygen and moisture ⟨B-63MI 506-01, B-76MI 506-04, B-78MI 506-01⟩. Certain compounds reduce or inhibit these



Scheme 13

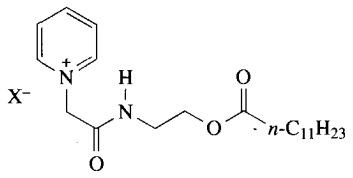
reactions by adsorption onto the metal surface. They act by forming a barrier to oxygen and moisture, by complexing with metal ions, or by removing corrodants from the surface. Good correlation has been observed between the corrosion inhibition and certain methyl-substituted pyridines ⟨65MI 506-02⟩. Quinaldic acid (**113**) and 8-hydroxyquinoline are believed to act as chelating agents that can coordinate with and stabilize metal ions and prevent the anodic dissolution of copper from occurring ⟨B-64MI 506-01, 71MI 506-02, 75MI 506-05, 77MI 506-04⟩. Oils, greases, and waxes are also used for the temporary inhibition of corrosion, acting as barriers and preventing the condensation of water on the metal surface. Inhibitors such as piperidine are often incorporated to give added protection.



(**113**)

5.06.7.5 Surfactants

Anionic and nonionic surfactants are used as wetting, spreading, emulsifying, dispersing, and foaming agents ⟨B-80MI 506-05⟩. Cationic surfactants, such as (**114**), are mainly used as biocides and softening agents, but there are few commercially important pyridine derivatives among those. Piperidinium compounds find application in hair-conditioning formulations as antistatic agents.



(**114**)

5.06.7.6 Germicides and Sanitizers

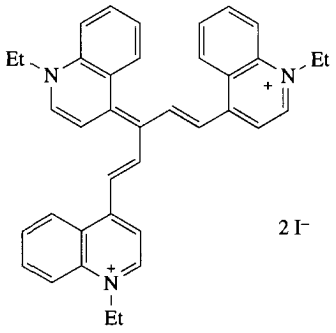
The quaternary ammonium salts of isoquinoline and pyridine are most often used as disinfectants and sanitizers for hard sufaces. Cetylpyridinium chloride (**108**) is used as a germicide and sanitizing agent. Other industrial applications are limited to slimicides for paper mills and cooling-water systems.

5.06.7.7 Preservatives

The control of bacteria, mildews, slimes, algae, and fungi has led to preservatives becoming important industrial additives. *N*-Alkylpyridinium halides (e.g., cetylpyridinium chlorides) are often used as disinfectants and sanitizers for hard surfaces ⟨B-68MI 506-05⟩ and also as preservatives in cosmetics. *N*-Alkylisoquinolinium halides are used as preservatives in water treatment.

5.06.7.8 Sensitizers

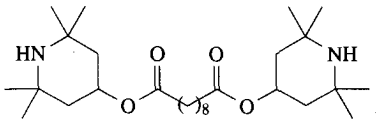
Comprehensive reviews have been published on the use of cyanine dyes as sensitizing dyes, for example (**115**) ⟨B-71MI 506-03, 77HC(30)441, B-77MI 506-05, 93KO(8)838⟩. Two or three nitrogen heterocycles linked by an odd number of conjugated double bonds are often used as sensitizers.



(115)

5.06.7.9 Light Stabilizers

Sterically hindered piperidine derivatives such as (**116**) and (**117**) are used as ultraviolet light stabilizers for a number of polymers ⟨70GEP(O)1929928, 78MI 506-02, 81MI 506-01⟩.



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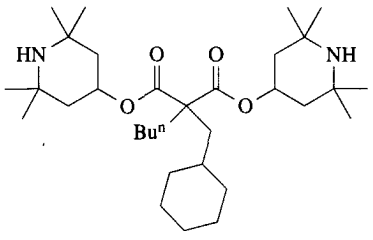
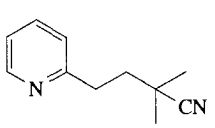


(117)

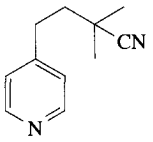
5.06.7.10 Flavors and Fragrances

2,2-Dimethyl-4-(2- or 4-pyridyl)butyronitriles (**118**) and (**119**), prepared by the addition of isobutyronitrile to 2- or 4-vinylpyridine in the presence of a base such as NaH and LDA ⟨93USP5236897⟩,

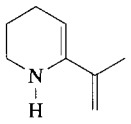
are useful for imparting herbaceous, new-mown hay, and fresh lilac aromas to bleaches, a number of cosmetic formulations and detergents and soaps. 6-Acetyl-1,2,3,4-tetrahydropyridine (**120**) is currently considered as a most significant bread flavor component ⟨93JOC2904⟩.



(**118**)



(**119**)



(**120**)

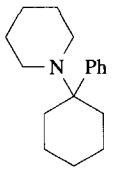
5.06.8 PHARMACEUTICALS

The applications of pyridine-containing compounds in the pharmaceutical field have been reviewed extensively ⟨84CHEC-I(1)143, B-93MI 506-01, B-94MI 506-02, 94KO(11)565⟩.

5.06.8.1 Analgesic and Anesthetic Drugs

5.06.8.1.1 Anesthetics

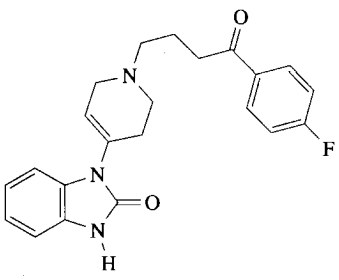
This subject has been extensively reviewed ⟨92KO(2)779, 92KO(12)778, 93RTC43, B-94MI 506-03⟩. Phencyclidine (**121**) is a piperidine derivative ⟨63USP3097136⟩ used as an anesthetic but has powerful hallucinogenic properties and has been the subject of abuse.



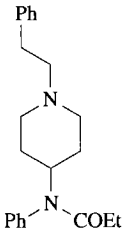
(**121**)

Anesthesia without muscular relaxation is achieved by the simultaneous use of the neuroleptic drug droperidol (**122**) and the narcotic analgesic fentanyl (**123**). 2-Piperidinecarboxylic acid is a feedstock for the synthesis of local anesthetics such as mepivacaine hydrochloride (**124**) and bupivacaine hydrochloride (**125**). Mepivacaine hydrochloride is used for peripheral nerve blocks and extradural anesthesia and has little topical activity. The analog, bupivacaine hydrochloride, one of the most potent and longest duration anesthetic reagents in clinical use, is also one of the most toxic. Other piperidine derivatives are mostly used as general anesthetics, namely droperidol and propipocaine (**126**) ⟨69MI 506-02⟩.

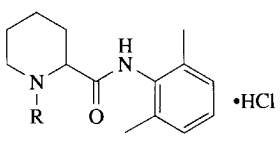
2-Methylquinoline (**53**) ⟨B-89MI 506-02⟩, its sulfate salt, and the isoquinoline derivative



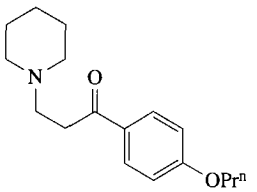
(**122**)



(**123**)

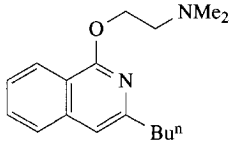


(**124**) R = Me
(**125**) R = Bu^n

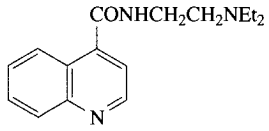


(**126**)

dimethisoquin (**127**) ⟨49JA937, 52USP2612503⟩ are also used as anesthetics. Dibucaine (**128**) is a very potent and long-acting local anesthetic, but it is toxic.



(**127**)

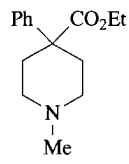


(**128**)

5.06.8.1.2 Analgesics

The subject of analgesics has been extensively reviewed ⟨80MI 506-06, 92KO(2)729, 93RTC43, B-94MI 506-03⟩. Analgesics in current use are broadly classified either as opioids, which produce their effects by stimulating opioid receptors within the central nervous system (CNS), or as nonsteroidal anti-inflammatory drugs (NSAIDs), which are thought to act in part by inhibiting prostaglandin formation.

Unlike the general anesthetics and sedatives, the potent, centrally active analgesics bind to specific receptors in the CNS. The piperidine derivative pethidine (**129**) is a strong analgesic which is a spasmolytic agent and a valuable alternative to morphine, but it is additive. Many related piperidine derivatives have since provided clinically useful analgesics. Analogs of pethidine with larger *N*-substitutents, for example the *N*-*p*-aminophenylethyl analog anilerdine (**130**), frequently have higher activities. Hydroxylation of the phenyl nucleus gives the oxypethidine (**131**) series in which some compounds, for example the (+)-3-methyl derivative, are potent narcotic antagonists. The ester function may be reversed as in alphaprodine (**132**), which has a rapid onset and short duration of action and is useful in obstetrics. The stereoisomeric betaprodine (**133**) is also a potent analgesic. Lastly, a very active compound such as fentanyl (**123**) may be obtained by interposing a nitrogen atom between the phenyl substituent and the piperidine ring.



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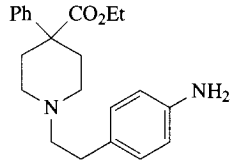

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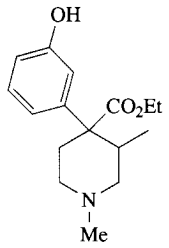

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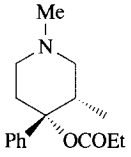
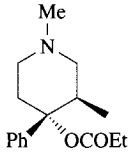


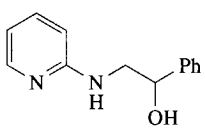
(**132**)



(**133**)

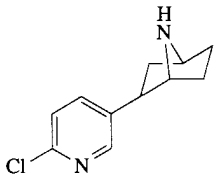
Several common structural features necessary for opioid analgesic activity have been identified from the action of the analogs. The nitrogen atom of the piperidine ring in particular appears to be essential for pharmacological activity and is believed to attach to an anionic center in the receptor. Fentanyl and alphaprodine retain the key 4-phenylpiperidine ring structure. These agents appear to interact more strongly with the κ receptor than morphine, although they are still strong μ agonists. Fentanyl is more potent than morphine, with a much shorter duration, and is used to aid the induction and maintenance of inhaled anesthesia.

Morphine and other opium alkaloids affect the activity of the bowel and have long been used in antidiarrheal medicines. Pethidine has a similar effect, and the piperidine diphenoxylate is effective in the treatment of diarrhea in doses that do not produce any CNS effects. Phenylramidol (**134**) ⟨59JA4351⟩, a codeine-like drug that is nonaddictive and is derived from 2-aminopyridine, is a skeletal muscle relaxant used in the treatment of rheumatism ⟨59JA4347⟩.



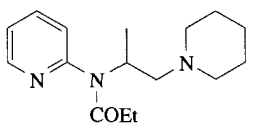
(**134**)

Epibatidine (**135**), first isolated from the skin of the Ecuadorean poison frog *Epipedobates tricolor*, has shown potent analgesic activity (200–500 times more effective than morphine) and has a nonopioid mode of action. This has lead to much interest in this compound, and several research groups have reported its total synthesis ⟨94JOC1771⟩.



(135)

The pyridine derivatives propiram (**136**) ⟨63BRP939947⟩, clonixin (**137**) ⟨B-93MI 506-01⟩, doxpicomine (**138**) ⟨81MI 506-03⟩, and isonixin (**139**) ⟨77AF1457⟩ are all used as analgesics as well as anti-inflammatories. Nifenazone (**140**) ⟨53GEP897407⟩ is a condensation product of a pyrazole derivative and nicotinamide ⟨53GEP897407, 63BEP635597⟩. Flunixin (**141**) is a potent analgesic suitable for parenteral administration as well as an anti-inflammatory analgesic used to treat horses. It is prepared by coupling 2-methyl-3-trifluoromethylaniline and 2-chloronicotinic acid ⟨94H(38)2243⟩.



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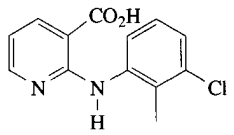

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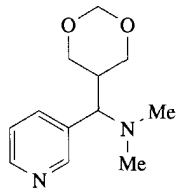

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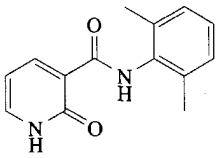

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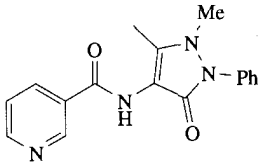

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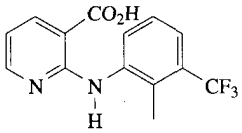


(141)

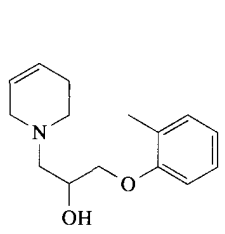
The piperidine derivatives tolpronine (**142**) ⟨62BRP889075⟩, picenadol (**143**) ⟨84MI 506-03⟩, piritramide (**144**) ⟨61BEP606850⟩, phenampromide (**145**) ⟨59JA1518, 62USP3016382⟩, and the pyridone derivative pyrithyldione (**146**) ⟨37USP2090068, 61BRP872190⟩ are all used as analgesics, as are the quinoline derivatives nicafenine (**147**) ⟨82MI 506-05⟩, glafenine (**148**) ⟨65NEP296793, 80S54⟩, and floctafenine (**149**) ⟨80S54⟩.

5.06.8.2 Psychopharmacological Drugs

5.06.8.2.1 Anxiolytic agents

Generalized anxiety disorder is a syndrome characterized by unrealistic or excessive feelings of apprehension. Panic disorder is a second type of anxiety disorder that is characterized by discrete periods of intense fear that do not occur in association with specific anxiety-provoking situations. The chemistry of anxiolytic agents has been reviewed ⟨B-94MI 506-04⟩. Alpidem (**150**) ⟨88MI 506-02⟩ is a pyridine-based and pipequaline (**151**) ⟨81LS1439⟩ a quinoline-based derivative which are used in the treatment of these disorders. Some substituted 4-hydroxypiperidine derivatives have also been used as anxiolytic agents ⟨83JMC621⟩.

Buspirone (**152**) is one of a new generation of anxiolytic drugs lacking the classical benzodiazepine unit. Studies of structure–activity relationships of buspirone and some analogs have been reported, indicating their usefulness as high-affinity 5-HT_{1A} serotonin ligands ⟨86JMC1476, 88JMC1968, 88JMC618, 90JMC633⟩.



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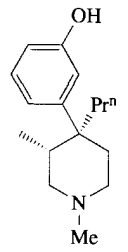

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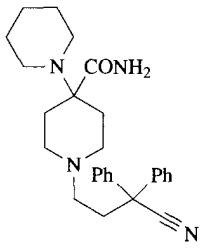

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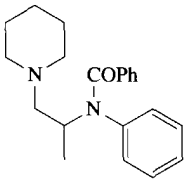

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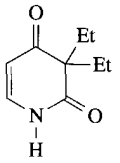

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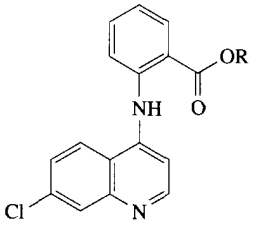

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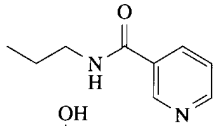

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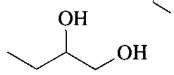

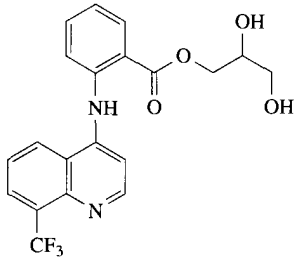

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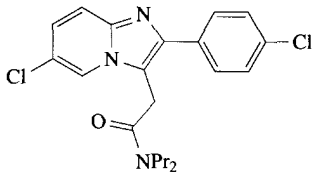

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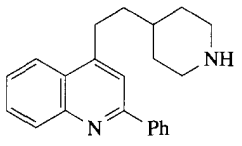

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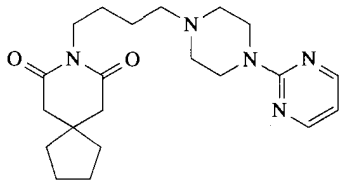

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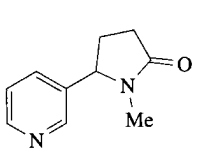
5.06.8.2.2 Antidepressants and tranquilizers

Depression is a very common illness, and three of the most prevalent types of depressive disorders are major depression, dysthymia, and bipolar disorder, formerly called manic–depressive illness. Cotinine (**153**) ⟨57JA149⟩, iproniazid (**154**) ⟨53JOC994⟩, and nialamide (**155**) ⟨62USP3040061⟩ are derivatives of nicotinic and isonicotinic acids, respectively, used as antidepressants. Piberaline (**156**) ⟨72GEP(O)2215545⟩ is derived from 2-picolinic acid while pyrisuccideanol (**157**) is derived from pyridoxol (vitamin B_6) ⟨71GEP(O)2102831⟩. Azacyclonol (**158**) can be prepared by hydrogenation of α,α-diphenyl-4-pyridinemethanol ⟨57USP2804422, 61MI 506-01⟩ and its hydrochloride salt has also been used as a tranquilizer.

Derivatives of acridine and phenanthridine are used as antidepressants and tranquilizers. Examples are clomacran (**159**), ⟨64USP3131190⟩ and fantridone (**160**) ⟨68BRP1135947⟩. Fantridone is obtained by alkylation of the anion of phenanthridone with 3-chloro-*N*,*N*-dimethylpropylamine. Quipazine (**161**) ⟨70GEP2006638, 85JMC1394⟩, a quinoline derivative, is prepared by the condensation



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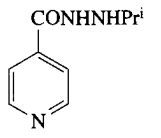

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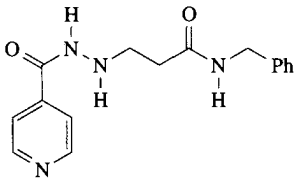

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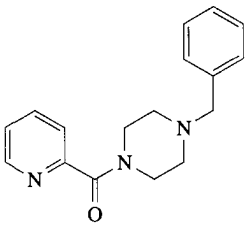

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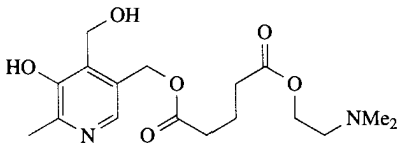

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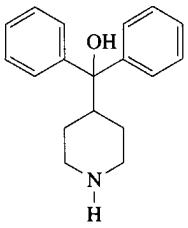
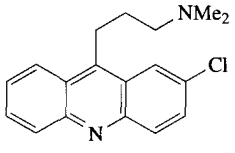


(158)

of 2-chloroquinoline with piperazine. The conformationally restricted indenopiperidine (**162**), potentially useful as an antidepressant, has been prepared from the 6-aryl-2-piperidone derivative ⟨81JHC1437, 84JMC432⟩.



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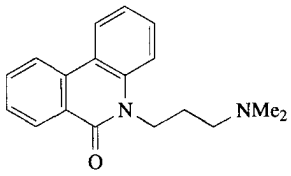

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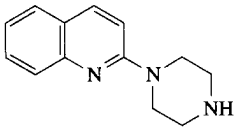

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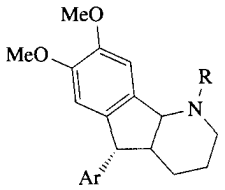
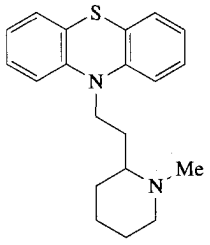


(162)

5.06.8.2.3 Psychotropic agents

Psychosis is a general term denoting mental disorders in which an individual's capability to distinguish reality and to communicate is impaired. The psychotropic agents thioridazine (**163**) and pericyazine (**164**) are derived from 2-(2-pyridyl)ethanol and 4-pyridone, respectively ⟨B-94MI 506-05⟩.



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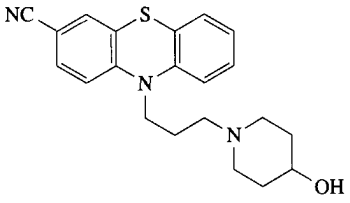
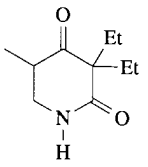


(164)

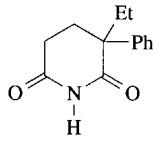
5.06.8.2.4 Sedatives and hypnotics

Sedation and hypnosis (sleep from which arousal is easy) represent lower levels of CNS depression, and increasing doses of sedative–hypnotic drugs will produce sedation, hypnosis, anesthesia, and death from respiratory depression. Dioxopiperidines analogous to the barbiturates are used for sedation and the induction of sleep ⟨B-94MI 506-06⟩. The 2,4-dioxo compound pyrithyldione (**146**)

⟨37USP2090068⟩, introduced in 1936, and its saturated analog proved to be toxic. They were replaced by methylprylone (**165**). The 2,6-dioxo compound glutethimide (**166**) ⟨B-94MI 506-01⟩ has been used but has fallen into disfavor while thalidomide was withdrawn after producing a series of fetal abnormalities on its introduction in Germany and Great Britain. Eldoral (**167**) is obtained by the condensation of 5-bromo-5-ethylbarbituric acid with piperidine ⟨33GEP589146, 43BEP449934⟩. Zolpidem tartrate (**168**) is a hypnotic medication derived from 2-amino-5-methylpyridine ⟨91MI 506-02⟩. The reaction of methyl coumalate with 1,3-diaminobenzene followed by cyclization affords amphenidone (**169**), which is used as a hypnotic ⟨60USP2947754⟩.



(**165**)



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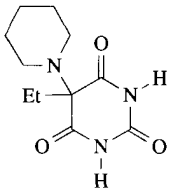

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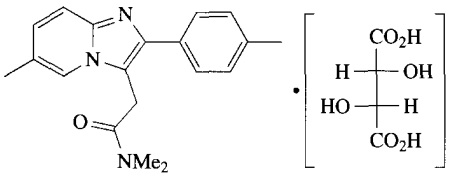

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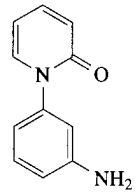
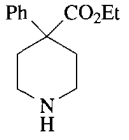


(**169**)

5.06.8.3 Antitussive Agents

The chemistry of antitussive agents has been reviewed ⟨93RTC43, 94KO(9)1061⟩. Cough suppressants currently in use include centrally acting opioids and nonopioids. Most antitussives are opioids and have the potential to cause constipation and to be abused. Meperidine (**170**) ⟨47JA2941, 52JA1844⟩ and picoperine (**171**) ⟨68FRP1511398, 70GEP(O)1935172, 70JMC704⟩ have been used to suppress or relieve coughing.



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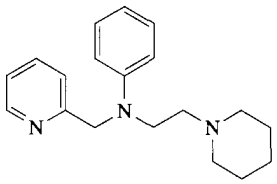
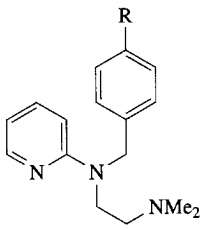


(**171**)

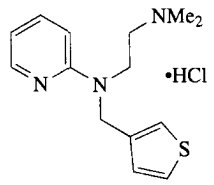
5.06.8.4 Antihistamines

There are a number of reviews on antihistamines in asthma therapy ⟨89MI 506-04, 89MI 506-05, 89MI 506-06, 89MI 506-07⟩. 2-Aminopyridine and its derivatives are used in the synthesis of a number of antihistamines including tripelennamine (**172**) ⟨46JA1999, B-59MI 506-01⟩, *p*-bromotripelennamine (**173**) ⟨51USP2572569⟩, methapyrilene hydrochloride (**174**) ⟨47JA980, 52USP2581868⟩, and pyrilamine maleate (**175**) ⟨46JA1999, 50USP2502151, 80KO(12)481⟩. 2-Chloropyridine is the feedstock for the synthesis of the antihistamines chlorpheniramine (**176**) ⟨54USP2676964, 58MI 506-01⟩, chloropheniramine maleate (**177**) ⟨B-93MI 506-01⟩, and dexbrompheniramine (**178**) ⟨62USP3061517⟩, which are obtained by the pyridylation of substituted phenylacetonitriles. Chloropheniramine shows H_1 receptor blocker activity ⟨79MI 506-06⟩. Carbinoxamine (**179**) is based on *p*-chlorophenyl-2-pyridylcarbinol

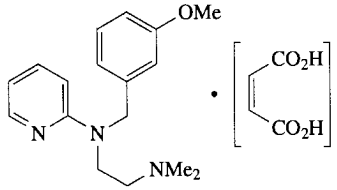
⟨83JPS1342⟩, and *N*-ethoxycarbonyl-4-piperidone is a starting material for the synthesis of loratadine (**180**) ⟨81USP4282233, 89MI 506-08⟩.



(**172**) R = H
(**173**) R = Br



(**174**)



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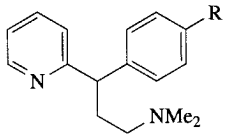
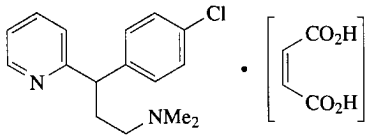
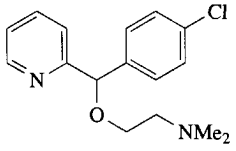


(**176**) R = Cl
(**178**) R = Br



(**177**)



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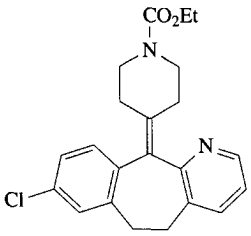
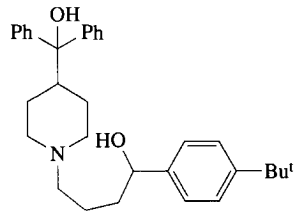


(**180**)

Terfenadine (Seldane) (**181**), a nonsedating antihistamine, is derived from azacyclonol ⟨73GEP(O)2303306⟩. Tasuldine (**182**) may be prepared by the condensation of 3-(chloromethyl)pyridine with 2-mercaptopyrimidine ⟨86MI 506-01⟩, and doxylamine (**183**) is derived from phenyl-2-pyridylmethylcarbinol and β-*N*,*N*-dimethylaminoethyl chloride in the presence of a base ⟨49JA887, 67MI 506-02⟩. Clinical investigation of the H_1 antihistamine chlorpheniramine revealed that this reagent showed a bronchodilating effect and provided some protection against exercise-induced asthma ⟨77MI 506-06⟩. Dimethindene (**184**) ⟨60JA2077, 61USP2970149⟩ is derived from a 2-substituted pyridine.



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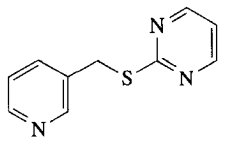

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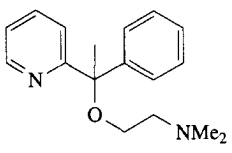
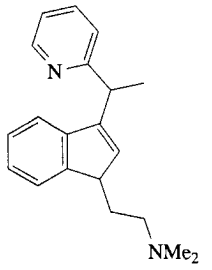


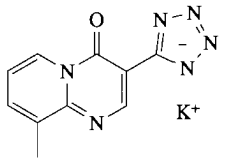
(**183**)



(**184**)

5.06.8.5 Antiallergic/Antiasthmatic Agents

The chemistry of antiasthmatic agents has been reviewed ⟨92KO(2)830⟩. Pemirolast potassium (**185**), synthesized from 2-amino-3-methylpyridine, is used for antiallergic/antiasthmatic medication. 2-Chloro-6-methylnicotinic acid is an intermediate for the synthesis of the 1,8-naphthyridone antiallergy agent (**186**) ⟨88JMC2108⟩.



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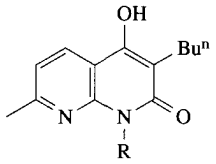
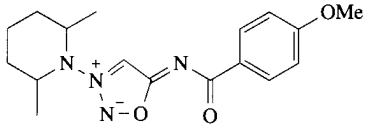


(186)

5.06.8.6 Cardiovascular Drugs

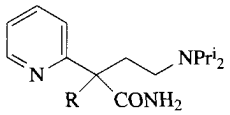
Pirsidomine (**187**) ⟨B-94MI 506-07⟩ is a cardiovascular drug derived from 2,6-dimethylpiperidine. A sydnone derivative, it is considered to be an NO donor because *in vitro* studies have shown its ability to relax isolated blood vessels through the spontaneous release of NO and the subsequent activation of guanylate cyclase.



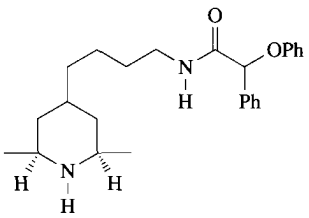
(187)

5.06.8.6.1 Antiarrhythmics

Considerable progress in cardiac electrophysiology has been achieved, and a large number of new antiarrhythmic drugs have become available for clinical use to relieve symptoms caused by arrhythmia or to prevent sustained ventricular arrhythmia, which has the potential to cause sudden death ⟨93MI 506-03⟩. Disopyramide (**188**), pentisomide (**189**), and oxiramide (**190**) are used as cardiac depressants ⟨73JMC309, 79MI 506-07, 87MI 506-01⟩. Pirmenol (**191**) is very effective in the short- and mid-term treatment of chronic premature ventricular beats, and tolerance to the drug is generally good ⟨80MI 506-02, 81MI 506-05, 91JMC12⟩.



(**188**) R = Ph
(**189**) R = Bu^t



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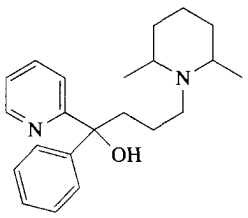
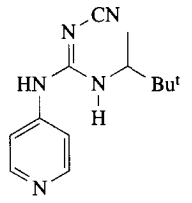


(191)

5.06.8.6.2 Antihypertensives

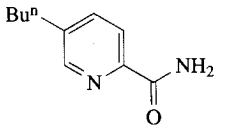
Hypertension is the most common of cardiovascular diseases. Antihypertensive agents lower blood pressure, and their modes of action have been reviewed ⟨86MI 506-02, 92MI 506-02⟩. Pinacidil (**192**) ⟨78JMC773⟩, a 4-aminopyridine derivative, is a vasoactive antihypertensive agent ⟨76GEP(O)2557438⟩. A potent vasodilator, it acts through opening potassium channels, and its fast

onset of action makes it suitable for use in hypertensive crises. Its pharmacology and mechanism of action have been reviewed ⟨86MI 506-03, 90MI 506-03⟩.



(192)

The calcium antagonists bupicomide (**193**) ⟨73MI 506-02⟩ and nitrendipine (**194**) have been used to reduce hypertension and angina ⟨72GEP(O)2117571, B-84MI 506-04⟩. 1,2,2,6,6-Pentamethylpiperidine (pempidine) (**195**) is used as an antihypertensive agent ⟨57JA5289, 58NAT1397⟩. Amlodipine (**196**) ⟨88MI 506-03⟩ represents a new Ca^{2+} antagonist within the subgroup of the dihydropyridines. The major advantage of this novel compound is its long duration of action, allowing once daily dosing. It is prepared by the Hantzsch synthesis from 4-(2-azidoethoxy)acetoacetate with methyl 3-amino-crotonate and 2-chlorobenzaldehyde.



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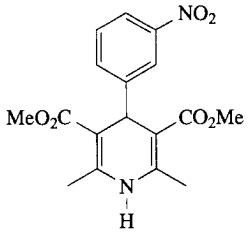

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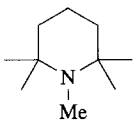

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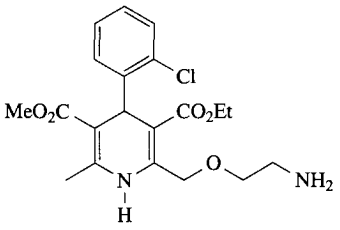
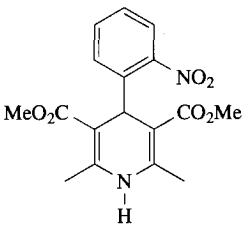


(196)

The 1,4-dihydropyridine nifedipine (**197**) is a calcium channel blocker ⟨68SAP6801482⟩, and the mechanism of action has been reviewed ⟨86GP255⟩. Nisoldipine (**198**), another dihydropyridine, is used as an antihypertensive agent ⟨77GEP(O)2549568, 86MI 506-04⟩.



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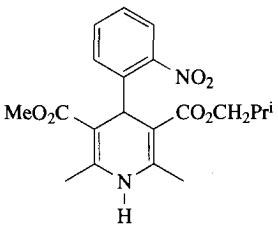
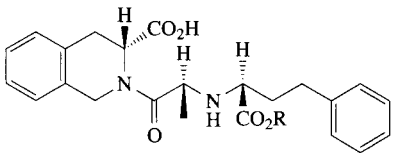
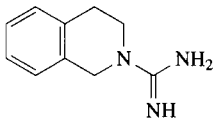


(198)

Antihypertensive agents such as quinapril (**199**) ⟨85MI 506-02⟩, quinapirilat (**200**) ⟨88MI 506-04⟩, and debrisoquine (**201**) ⟨63BEP629007, 65JMC125, 69MI 506-03⟩ are derived from 1,2,3,4-tetrahydro-isoquinoline. Debrisoquine acts by diminishing the sympathetic impulses by depleting the stores of noradrenaline in the nerve endings and blocking their release.



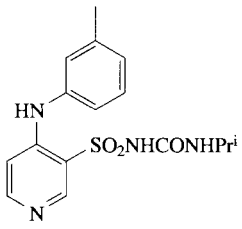
(199) R = Et
(200) R = H



(201)

5.06.8.7 Diuretics

Diuretic agents have been reviewed ⟨93KO(8)398, B-94MI 506-08⟩. Diuretics act on the renal tubes to reduce the volume of extracellular fluid, thus preventing edema, and torasemide (**202**) ⟨91MI 506-03⟩, a loop diuretic, has potential value in the treatment of mild to moderate hypertension and severe edema. It is superior as regards the duration of action and effects on potassium and calcium. Etozolin (**203**), a piperidine derivative, is a diuretic with choleretic properties ⟨63USP3072653⟩.



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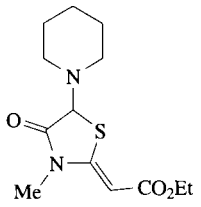


(203)

5.06.8.8 Gastrointestinal Drugs

5.06.8.8.1 Antiulcer agents

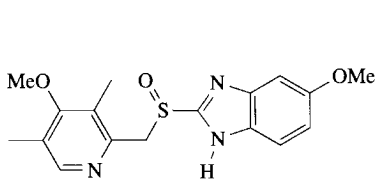
Peptic ulcers result from an imbalance between the aggressive action of acid and pepsin and the gastroduodenal mucosal defensive systems in the stomach and duodenum. The inhibition of gastric acid secretion and the enhancement of mucosal defensive systems have proved to be useful therapeutic approaches for promoting healing of peptic ulcers ⟨93RTC43⟩. Omeprazole (**204**) ⟨79EUP5129, 86MI 506-05⟩ is used as antiulcer agent and is synthesized from 2,3,5-trimethylpyridine *N*-oxide, while pirenzepine (**205**), used for antiulcerative medication, is prepared from 3-amino-2-chloropyridine. Another antiulcer agent, picartamide (**206**) ⟨82MI 506-06⟩, is pyridine based. Bis(*N*-methylpyridiniummethylthio)methane diiodide (**207**) is useful in the treatment of ulcers by the suppression of gastric acid secretion ⟨80BRP2038327⟩. Many imidazo[1,2-*a*]pyridines, such as (**208**), have been prepared and show antiulcer activity ⟨93CL1317⟩.

5.06.8.8.2 Antidiarrheal agents

The antidiarrheal agent mebiquine (**209**) is obtained from 6-methyl-8-hydroxyquinoline ⟨69GEP1811581⟩, and also shows some parasiticidal properties. Nicainoprol (**210**) ⟨84BJP79⟩ is obtained by the condensation of the 8-substituted tetrahydroquinoline derivative with nicotinoyl chloride. Diphenoxylate (**211**) ⟨59USP2898340⟩ is a piperidine-based antidiarrheal agent.

5.06.8.9 Antidiabetics

Both icotidine (**212**) ⟨85MI 506-03⟩ and midaglizoline (**213**) are pyridine-based drugs used in the treatment of diabetes ⟨B-93MI 506-01, 86MI 506-06⟩, and they stimulate insulin release via an interaction with the K^+ channel of pancreatic β cells.



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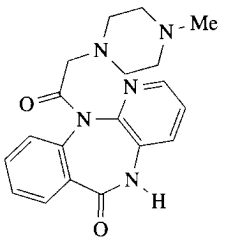

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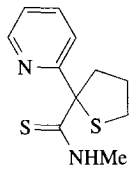

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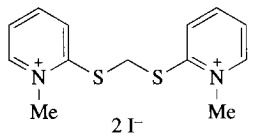

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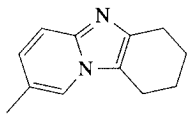

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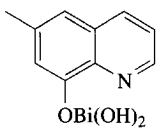

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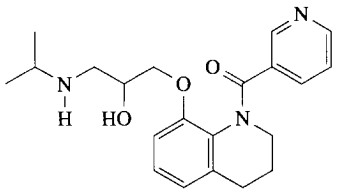

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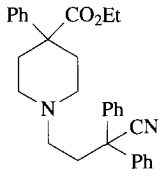

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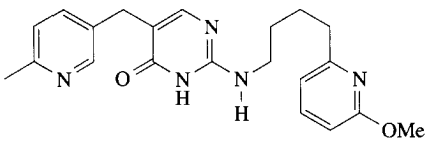

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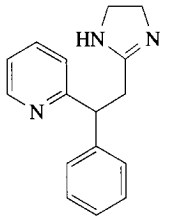


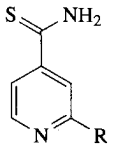
(213)

5.06.8.10 Anti-infective Therapy

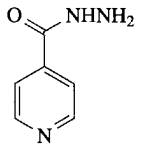
5.06.8.10.1 Antibacterials

Pyridine-based antibacterials such as protionamide (**214**) ⟨58BRP800250, 66JAP6622185⟩, ethionamide (**215**), ⟨58BRP800250⟩, isoniazid (**216**) ⟨52USP2596069, B-79MI 506-01⟩, opniazide (**217**) ⟨79MI 506-08⟩, and aconiazide (**218**) ⟨80JPS1284⟩, all derived from isonicotinamide, exhibit activity as antibacterial agents. The higher alkylpyridinium salts also exhibit antibacterial activity. The azo derivative phenazopyridine (**219**), which is prepared by the coupling of benzenediazonium chloride with 2,6-diaminopyridine, is used as a urinary tract anti-infective agent in conjunction with antibacterials ⟨43JA2241⟩.

Quinoline-based antibacterials have been reviewed ⟨92KO(2)854, 92MI 506-03, B-94MI 506-08, 94MI 506-09⟩. The most important structural features necessary for antibacterial activity of quinolones include a carbocylic acid at the 3-position and an alkyl or aryl group at the 1-position. All of the newer generation quinolones have a fluorine attached at the 6-position and a nitrogen heterocycle (pyrrolidine or piperazine) attached at the 7-position. Oxolinic acid (**220**) and AB 206 (**221**) both show antibacterial activity. Nalidixic acid (**222**) ⟨62USP3149104, 64AAC628, 87MI 506-02⟩, a 1,8-naphthyridine, is obtained via the reaction of 2-amino-6-methylpyridine with diethyl ethoxymethylenemalonate, followed by cyclization of the resulting intermediate. AB 206 (**221**) is more active than nalidixic acid ⟨80AAC203⟩. Antibacterial agents that are available today include enoxacin (**223**) ⟨80JMC1358,



(214) R = Pr^n
(215) R = Et



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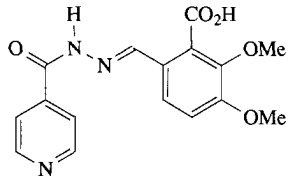

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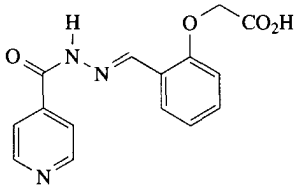

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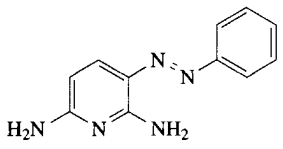
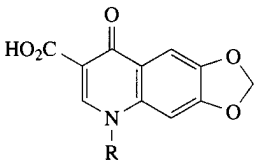


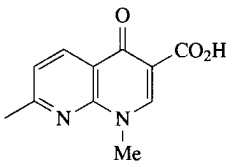
(219)

84JMC292〉, cloxyquin (**224**) 〈B-82MI 506-07〉, and rosoxacin (**225**) 〈72GEP(O)2224090〉. These are analogs of nalidixic acid and act by a similar mechanism.

Cephapirin sodium (**226**) is an antibacterial which is derived from 4-aminopyridine 〈73JMC1413〉 (see next section).



(220) R = Et
(221) R = OMe



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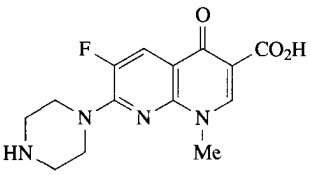

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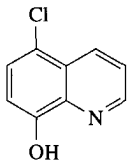

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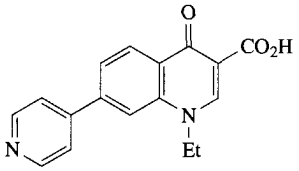

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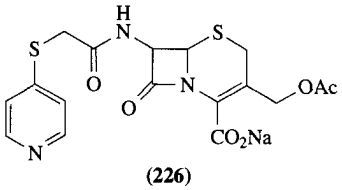
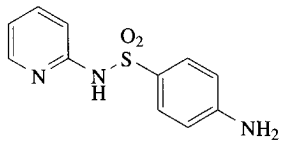


(226)

5.06.8.10.2 Antibiotics

Several reviews on antibiotics have been published 〈92KO(3)1, 92KO(2)893, B-94MI 506-10, B-94MI 506-15〉. Sulfapyridine (**227**) was one of the first synthetic antibiotics to exhibit general utility for human therapy. Introduced in 1938, sulfapyridine showed greater potency than sulfanilamide, was effective against a wider range of bacteria, and cut the death rate in pneumococcal pneumonia from 25% to about 6%. Two semisynthetic cephalosporins which contain the pyridine moiety are cephaloridine (**228**) 〈65FRP1384197〉, which contains a quaternized ring, and cephapirin sodium (**226**)

⟨71USP3578661⟩, which is based on pyridine-4-thioglycollic acid. Cepharin sodium is obtained via the reaction of 4-pyridylpyridinium chloride hydrochloride with the corresponding thioglycollic acid derivative.



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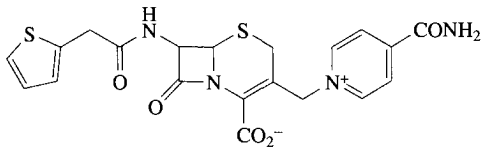
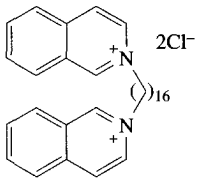


(228)

5.06.8.10.3 Antifungal agents

2,2′-Hexadecamethylenediisoquinolinium dichloride (hedaquinium dichloride) (**229**) functions as an antifungal agent and is also used as a topical antiseptic ⟨58JCS1489, 60BRP839505⟩. It is obtained by the *N*-alkylation of isoquinoline with the appropriate dihalide. Ciclopirox (**230**) ⟨70SAP6906039⟩, a substituted 2-pyridone, is a broad-spectrum antifungal agent. The antifungal agent acrisorcin (**231**) is a 1 : 1 mix of 9-aminoacridine and 4-hexylresorcinol ⟨B-89MI 506-09⟩.



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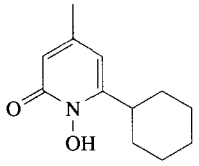

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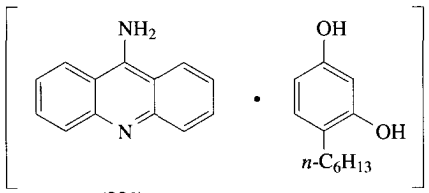


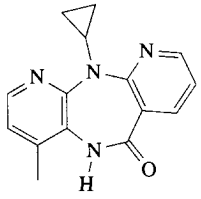
(231)

5.06.8.10.4 AIDS drugs

The acquired immunodeficiency syndrome (AIDS) is a complex disease produced by human immunodeficiency virus (HIV) infection. Since 1983, when HIV was discovered, an extensive knowledge of the molecular characteristics of the virus has been acquired. Nevertheless, effective anti-HIV therapy still remains as a major but elusive goal in the field of drug therapy. Excellent reviews have been published on this subject ⟨92KO(3)576, 92MI 506-04, B-94MI 506-11⟩.

HIV reverse transcriptase is essential for viral replication. Compounds that interfere with the virus in associated reverse transcriptase have been the most extensively studied for the chemotherapy of HIV disease. Inhibitors of reverse transcriptase can prevent the spread of viral infection to new cells, but do not interfere with the replication of HIV genomes that are integrated into the host genome. A number of pyridine-containing reverse transcriptase inhibitors are undergoing clinical evaluation, including nevirapine (**232**), atevirdine (**233**), and delavirdine mesylate (**234**) ⟨B-94MI 506-11⟩.

HIV-protease is an aspartic protease encoded by the retrovirus that cleaves specific amide bonds



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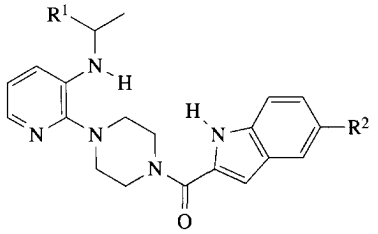
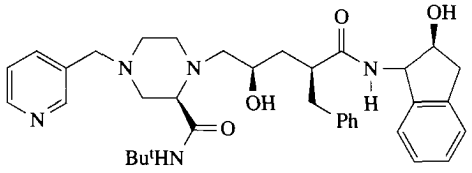


(233) R^1 = H, R^2 = OMe
(234) R^1 = Me, R^2 = $NHSO_2Me$

in polyproteins or their precursors and induces the production of infectious viral particles. Protease inhibitors have been shown to be additive or synergistic with reverse transcriptase inhibitors. Pyridyl-substituted imidazoles have been reported as capable of inhibiting cytokins and to be potentially useful for the treatment of HIV infections ⟨B-94MI 506-11⟩.

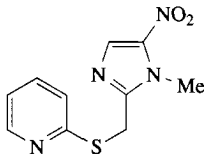
3-Amino-2-chloro-4-methylpyridine and 2-chloronicotinic acid are both used for the preparation of nevirapine, a potent inhibitor of human immunodeficiency virus-1 (HIV-1) reverse transcriptase ⟨90SCI1411, 91JMC2231⟩. The orally active HIV-1 protease inhibitor L-735524 (**235**), derived from 3-chloromethylpyridine, is a potent inhibitor of HIV replication ⟨94TL673⟩.



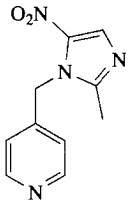
(**235**)

5.06.8.10.5 Antiprotozoals

Antiprotozoals have been reviewed, and pirinidazole (**236**) and panidazole (**237**) are pyridine-based antiprotozoals ⟨92KO(3)456, 92KO(3)489⟩.



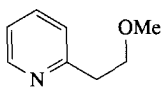
(**236**)



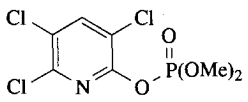
(**237**)

5.06.8.10.6 Anthelmintics

Anthelmintic drugs are used to eradicate parasitic worm infections; they act locally on worms in the gastrointestinal tract or systemically on those that have invaded various body tissues ⟨94MI 506-12⟩. The veterinary anthelmintic metyridine (**238**) is prepared by the addition of methanol to 2-vinylpyridine ⟨65BRP889748⟩. Similarly, fospirate (**239**) is derived from the reaction of 3,5,6-trichloro-2-pyridinol with phosphoryl chloride followed by treatment with methanol ⟨66MI 506-01⟩.



(**238**)

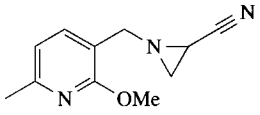


(**239**)

5.06.8.11 Stimulants

5.06.8.11.1 Immunostimulants

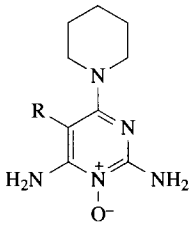
The pyridine derivative ciamexon (**240**) has been used in the treatment of adjuvant arthritis ⟨81FRP2445316⟩, and is prepared by the condensation of 2-methoxy-6-methylpyridin-3-ylmethylamine with 2-bromoacrylonitrile in the presence of triethylamine. 4-Acetamidopyridine *N*-oxide has been used as a neuromuscular stimulant ⟨80MI 506-06⟩.



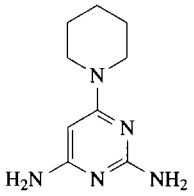
(240)

5.06.8.11.2 Hair growth stimulants

Minoxidil (**241**), fluorominoxidil (**242**), and 2,6-diamino-4-piperidinopyrimidine (**243**) have been used as hair growth stimulants ⟨92MIP9208705, 92MIP9221317, B-94MI 506-13⟩. Minoxidil is also used as an antihypertensive agent ⟨86MI 506-07⟩.



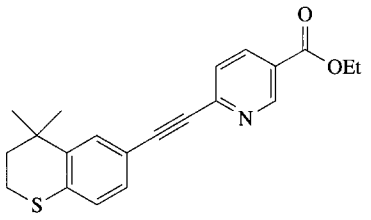
(**241**) R = H
(**242**) R = F



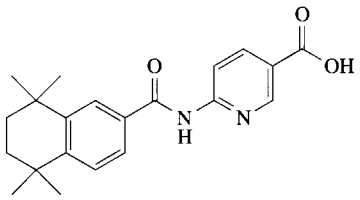
(**243**)

5.06.8.12 Antipsoriatics

Psoriasis is an inflammatory, chronic, noncontagious skin disease characterized by reddish patches and white scales on human body. Psoriasis therapy is aimed at decreasing the cell turnover, hyperkeroatosis, or vascularity of the superior dermis. Two pyridine-based topical retinoids, namely (**244**) and (**245**), have been developed for the treatment of psoriasis ⟨93MIP9316067, 93MIP9306086⟩.



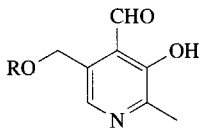
(**244**)



(**245**)

5.06.8.13 Enzymes

Many enzyme-catalyzed reactions require coenzymes (or cofactors) in addition to the enzyme and the substrate for reactions to proceed ⟨79COC(5)489, B-79MI 506-09⟩. Nicotinamide is a component of the important coenzyme nicotinamide adenine dinucleotide (NAD^+) and its phosphate ($NADP^+$). The latter coenzyme, one component of the B_2 complex of vitamins, occurs in red blood corpuscles and participates in biochemical redox reactions. Pyridoxal (**246**) occurs in yeast and wheat germ, and is an important food additive. The 5-phosphate of pyridoxal (**247**) is a coenzyme in the decarboxylation and transamination of amino acids ⟨78B1282⟩.



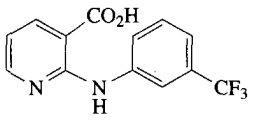
(**246**) R = H
(**247**) R = $P(O)(OH)_2$

3-Pyridinecarboxylic acid (niacin) is used extensively in the diets of both humans and animals for the prevention of pellagra-like diseases. It is an important component of vitamin premixes in animal feeds and is used as a food-enriching agent in cereal products. 3-Cyanopyridine and 2-methyl-5-ethylpyridine are the feedstocks for both niacinamide and niacin. 3-Cyanopyridine is produced by the vapor phase ammoxidation of 3-methylpyridine ⟨B-54MI 506-01, 59USP2904552, 61USP2993051, 80MI 506-07⟩.

Both pyridoxol (**2**) ⟨38JA983, 39JA1242, 62USP3024245⟩ and pyridoxol hydrochloride ⟨B-68MI 506-04⟩ are components of the vitamin B_6 complex, which is present in many foodstuffs, and especially good sources of this complex are yeast, liver, and cereals.

5.06.8.14 Anti-inflammatory Drugs

Many NSAIDs have been developed in recent years, and the subject has been extensively reviewed ⟨B-74MI 506-09, 92KO(2)729⟩. Anti-inflammatory agents such as clonixin (**137**) ⟨67NEP6603357⟩, niflumic acid (**248**) ⟨66BSF2316⟩, and pranoprofen (**249**) are derived from 2-chloropyridine-3-carboxylic acid. Esterification of 2-pyridylmethanol with ibuprofen produces ibuprofen piconol (**250**), which shows not only anti-inflammatory but also analgesic and antipyretic activity ⟨80JAP87770⟩.



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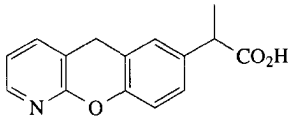

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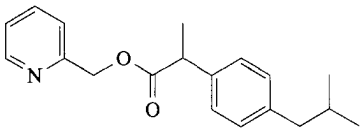
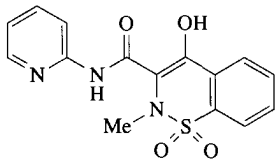


(250)

2-Amino- and 2,6-diaminopyridines are used as precursors for the synthesis of various anti-inflammatory agents. Examples are piroxicam (**251**) ⟨70GEP(O)1943265, 72JMC848, 84MI 506-05⟩, tenoxicam (**252**), and piroxicam cinnamate (**253**) ⟨87MI 506-03⟩, which are derived from 2-aminopyridine. Due to the absence of cardiovascular or CNS effects, piroxicam is used in the treatment of rheumatoid arthritis.



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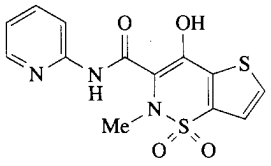

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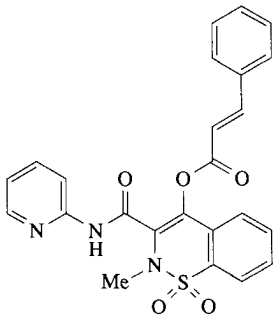
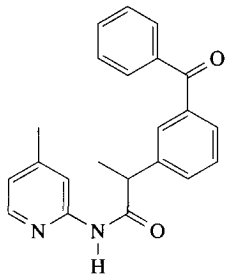


(253)

Niflumic acid derivatives (**248**) ⟨65NEP6414717, 66BSF2316, 67NEP6610738, 69GEP(O)1802777⟩ and isonixin (**139**) are also used as analgesics. Piketoprofen (**254**) ⟨70GEP(O)1943265, 76BRP1436502⟩ is derived from 2-amino-4-methylpyridine and torasemide (**202**) ⟨75GEP(O)2516025⟩ from 4-amino- or 4-chloropyridine. Pifoxime (**255**) ⟨70GEP(O)2003430⟩ is piperidine based. Nicoboxil (**256**) is derived from nicotinic acid. Both galosemide (**257**) and torasemide (**202**) are used as diuretics.

5.06.8.15 Anti-infective Agents

Cetylpyridinium halides are used both as disinfectants and preservatives ⟨44MI 506-01⟩. Quinoline- and isoquinoline-based disinfectants include 8-hydroxyquinoline ⟨B-54MI 506-02⟩, 5-chloro-8-hydroxy-7-iodoquinoline (**258**) ⟨57JOC1111⟩, and *N*-laurylisoquinolinium bromide (**259**) ⟨85MI 506-04⟩,



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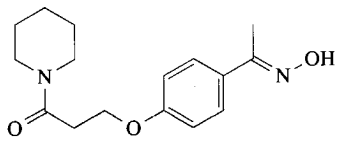

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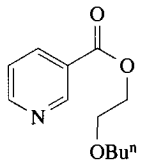

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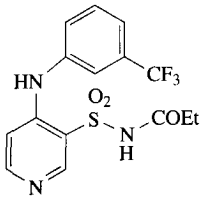
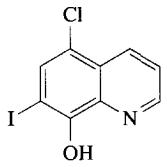


(257)

which is obtained by simple *N*-alkylation of the base heterocycle. A mixture of 3,6-diaminoacridine (**260**) and 3,6-diamino-10-methylacridinium chloride is a well established anti-infective agent, often called acriflavine.



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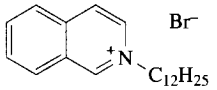

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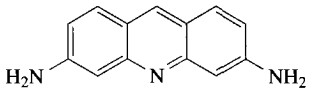
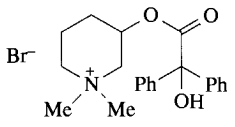


(260)

5.06.8.16 Cholinergic Agents

Compounds that are capable of improving cholinergic transmission within the CNS are called cholinergic agents. Dialkylpiperidinium bromides, such as pipenzolate bromide (**261**) ⟨52JA1485, 59USP2918406⟩ and fenpiverinium bromide (**262**) ⟨54BRP708859, 57JA4451⟩, and 3-(*N*,*N*-diethylamino-ethyl-3-phenylglutarimide (**263**) ⟨53USP2664424⟩ are used as cholinergic agents. Fenpiprane (**264**) is also used as an antiallergic and antispasmodic drug ⟨53USP2662886⟩.



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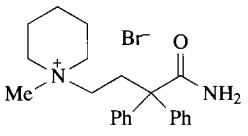

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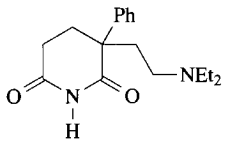

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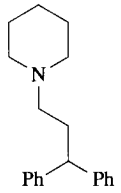
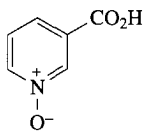


(264)

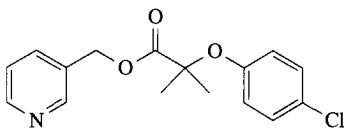
5.06.8.17 Hypolipidemic Agents

Increased levels of total low-density lipoprotein (LDL) cholesterol is identified as a risk factor for the development of coronary heart disease. Reduction of LDL cholesterol concentrations in the plasma of hypercholesterolemic patients has been shown to reduce the incidence of cardiovascular mortality. Hyperlipidemic agents are used to regulate and reduce LDL cholesterol in the circulatory system. Several drugs derived from 3-substituted pyridines have been developed, including oxiniacic

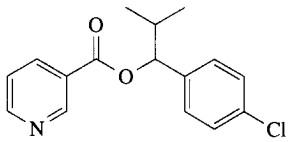
acid (**265**) ⟨62BEP618968⟩, which is obtained by *N*-oxidation of nicotinic acid, nicofibrate (**266**) ⟨67NEP6610738, 70GEP1948320⟩ from 3-pyridylmethanol, and nicoclonate (**267**) ⟨65FRP(M)3454⟩ and picafibrate (**268**), which are derived from nicotinic acid and nicotinamide, respectively.



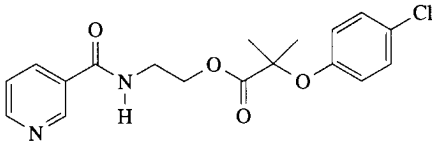
(**265**)



(**266**)



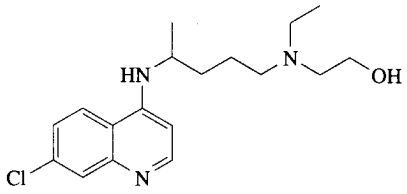
(**267**)



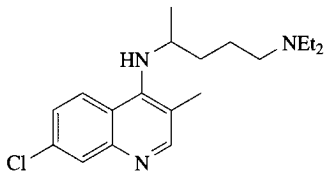
(**268**)

5.06.8.18 Antimalarials

Malaria is caused by several species of protozoan parasities known as plasmodia. Quinine (**4**), a constituent of Cinchona bark, has been used as a drug for the treatment of malaria for many centuries ⟨44JA849, B-79MI 506-01⟩. Heavy demand occurred for quinine during the World Wars, which prompted searches for synthetic substitutents. Loss of efficacy of synthetic drugs, as resistant strains of plasmodia developed, also meant continuing research. Novel antimalarials were developed starting from 4-amino-7-chloroquinolines and 8-amino-6-methoxyquinolines ⟨B-77MI 506-06⟩. The key intermediate for 4-amino-7-chloroquinoline is 4,7-dichloroquinoline, which reacts with aliphatic diamines to yield the synthetic chloroquine (**5**) ⟨46JA113⟩ and hydroxychloroquine (**269**) ⟨50JA1814, 51USP2546658, 82MI 506-08⟩. Sontoquine (**270**) is derived from the 3-methyl analog of chloroquine ⟨46JA380⟩.

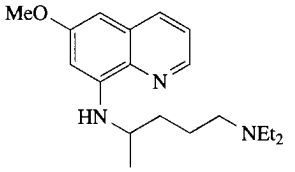


(**269**)



(**270**)

Both pamaquine (**271**), which was first developed in Germany from 8-amino-6-methoxyquinoline ⟨46JA1584⟩, and clamoxyquine (**272**), show similar antiamebic activity ⟨48JA40, 61JOC4070⟩. The tetrahydroquinoline derivative oxamniquine (**273**) is used to control blood flukes (*Schistosoma mansoni*), which are a major cause of disease in tropical regions.



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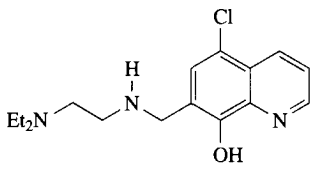

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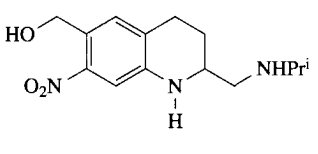
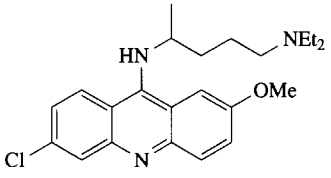


(**273**)

Almost simultaneously with quinolines, a series of acridine antimalarial compounds were developed, and quinacrine (**274**) was extensively used during the World War II under the trade

name Atabrine ⟨38USP2113357, B-75MI 506-06⟩. Dimethacrine (**275**) is a dihydroacridine derivative bearing geminal dimethyl groups, yet still exhibits antimalarial activity ⟨63BRP933875⟩.



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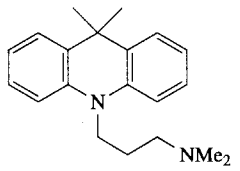
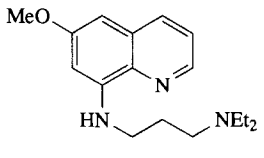


(**275**)

Quinoline derivatives such as plasmocid (**276**) ⟨45JA664⟩, cinchonine (**277**) ⟨67T3253⟩, quinocide (**278**) ⟨56MI 506-01⟩, primaquinine (**279**) ⟨55JA4816, B-75MI 506-07⟩, and mefloquine hydrochloride (**280**) ⟨79GEP2806909⟩ are widely used as antimalarial drugs. Amodiaquin (**281**) is prepared from 4,7-dichloroquinoline and 4-acetamido-2-diethylaminomethylphenol ⟨48JA1363⟩.



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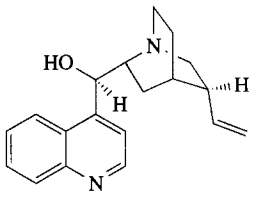
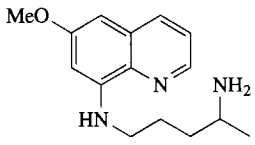


(**277**)



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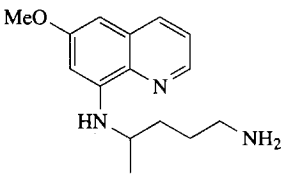

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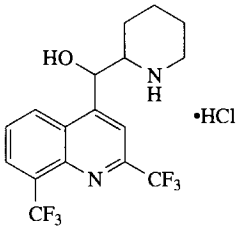

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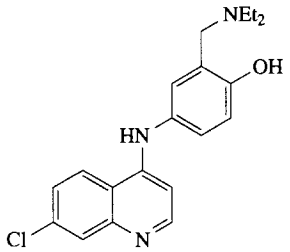
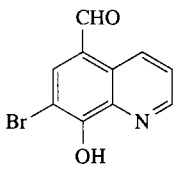


(**281**)

5.06.8.19 Antiseptics

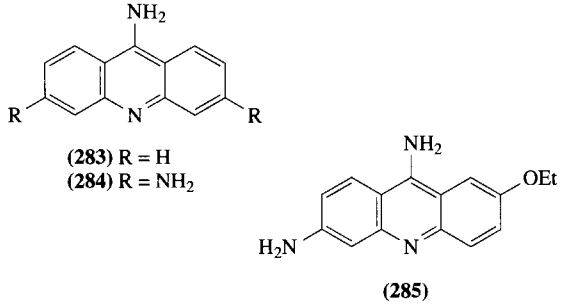
Cetylpyridinium chloride (**108**) ⟨44MI 506-01⟩, a topical anti-infective, is also used as a preservative and a veterinary disinfectant ⟨93KO(8)237⟩, and the iodine complex of (**259**) is used as an antiseptic ⟨B-93MI 506-01⟩. Broxyquinoline (**282**) is prepared by the bromination of 5-formyl-8-quinolinol, and is used as both an antiseptic and a disinfectant ⟨55JA6671⟩.



(**282**)

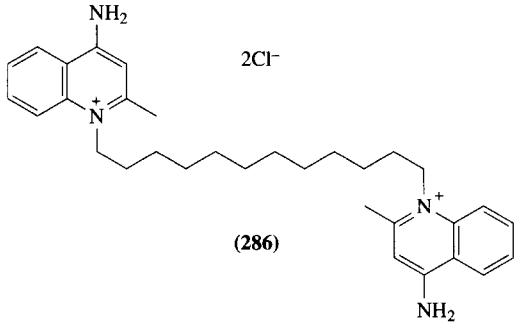
9-Aminoacridine (**283**) ⟨55OSC(3)53, B-73MI 506-03⟩, proflavine (**284**), and ethacrin (**285**) have been used as topical antiseptics ⟨B-66MI 506-02⟩. 2,2′-Hexadecamethylene-diisoquinolinium dichloride

(**229**) ⟨58JCS1489, 60BRP839505⟩ and 1,1′-decamethylene-bis[4-amino-2-methylquinolinium) chloride] (dodecyldequalinium chloride) (**286**) ⟨56BRP745956, 58JCS1489⟩ are obtained by heating isoquinoline and 2-methyl-4-aminoquinoline with the appropriate dihaloalkanes.



(**283**) R = H
(**284**) R = NH_2

(**285**)



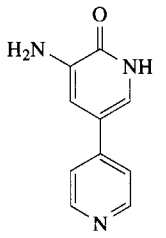
(**286**)

5.06.8.20 Antituberculosis Agents

Isoniazid (**216**) is an effective antituberculosis agent which has been used for many years. The recent resurgence of tuberculosis in Africa, Europe, and the USA has led to an increased demand for this material, which is conveniently prepared from methyl isonicotinate by reaction with hydrazine ⟨58USP2830994⟩. Extensive clinical use has shown that isoniazid possesses an additional antidepressant effect.

5.06.8.21 Cardiotonic Drugs

Amrinone (**287**), piroximone (**288**), and milrinone (**289**) are cardiotonic drugs used to reduce cardiac contractility. Amrinone is derived from 3-amino-2-pyridone ⟨77USP4004012, 78LS1139, 83JPS817⟩. Milrinone ⟨81FRP2470124, 83USP4413127, 85H(23)1479⟩ is prepared either by the reaction of 1-(4-pyridinyl)-2-propanone (**290**) with ethoxymethylenemalononitrile (**291**) or of 4-alkoxy-3-(4-pyridinyl)-3-butene-2-one (**292**) with malononitrile without the use of an external base (Scheme 14). Piroximone ⟨91AF1225⟩ is prepared by the acylation of 1,3-dihydro-4-ethyl-2*H*-imidazol-2-one with isonicotinic acid under Friedel–Crafts conditions.



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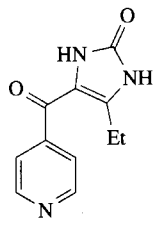
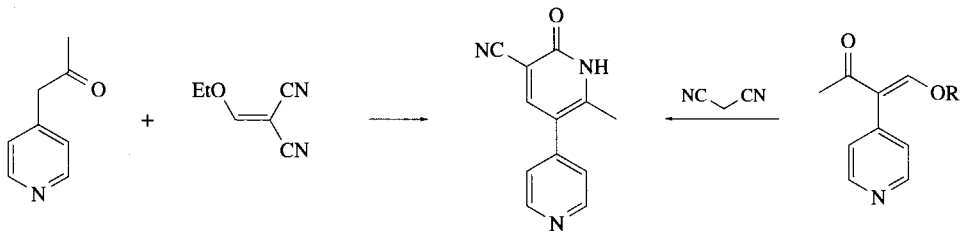


(**288**)

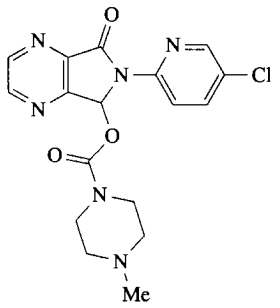


(**290**) (**291**) (**289**) (**292**)

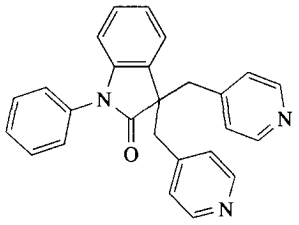
Scheme 14

5.06.8.22 CNS Stimulants

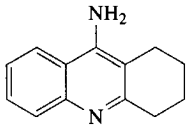
Zopiclone (**293**) ⟨73GEP(O)2300491⟩, derived from 2-amino-5-chloropyridine and used as a CNS drug ⟨90MI 506-03⟩, is the first of a family of nonbenzodiazepines which show a pharmacological profile similar to chlordiazepoxide and nitrazepam. Linopirdine (**294**), an orally active cognitive enhancer targeted to ameliorate deficiencies associated with Alzheimer's disease by stimulating CNS neurotransmitter release (such as acetylcholine, dopamine, and serotonin), is obtained by the alkylation of 1-phenyloxindole using two equivalents of 4-picolyl chloride hydrochloride under phase transfer conditions ⟨93SC1617⟩. 9-Amino-1,2,3,4-tetrahydroacridine (**295**) is used for the treatment of Alzheimer's disease and is also an acetylcholinesterase inhibitor ⟨87MI 506-04, 90MI 506-04, 91MI 506-04⟩. The piperidine derivatives methylphenidate (**296**) ⟨44HCA1748⟩ and pipradrol (**297**) are used as CNS stimulants ⟨48JA4001, 53USP2624739⟩.



(**293**)



(**294**)



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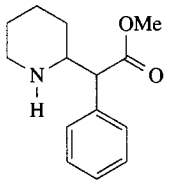

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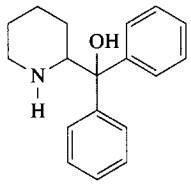
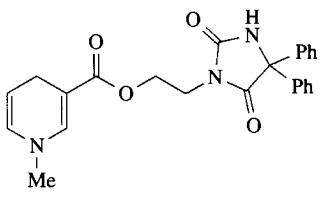


(**297**)

5.06.8.23 Antiepileptic Drugs

The dihydropyridine derivative (**298**), which was synthesized by sodium dithionite reduction of the *N*-methylpyridinium salt precursor, decreases the incidence or severity of spontaneous seizures occurring in patients with epilepsy ⟨91MI 506-05⟩.

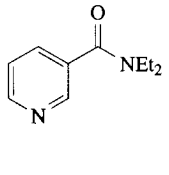


(**298**)

5.06.8.24 Central and Respiratory Stimulants

Most cough suppressants and antitussives currently in use are centrally acting opioids and nonopioids. Nikethamide (**299**), prepared from nicotinoyl chloride and diethylamine hydrochloride

⟨22USP1403117, 46JCS763⟩, is also used as a respiratory stimulant in animals. The respiratory stimulant pimeclone (**300**) is prepared by the Mannich reaction of piperidine, formaldehyde, and cyclohexanone ⟨40CB1399⟩.



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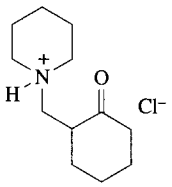
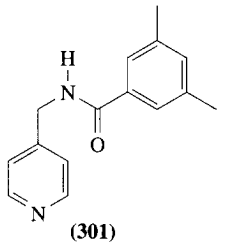


(**300**)

5.06.8.25 Neuroleptic Agents

Picobenzide (**301**) ⟨79AF1714⟩ and pyritinol (**302**) ⟨61USP3010966⟩ are used as neuroleptic agents to counter psychotic behavior.



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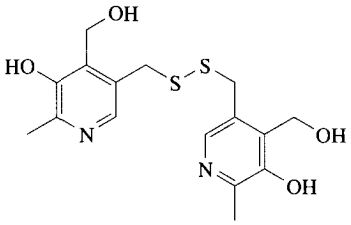
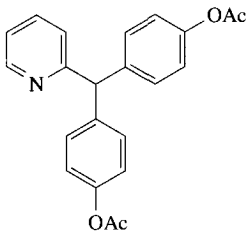


(**302**)

5.06.8.26 Laxative

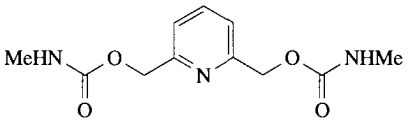
The cathartic agent bisacodyl (**303**), derived from 2-pyridinecarboxaldehyde, is used to promote evacuation of the bowel ⟨55BRP730243⟩.



(**303**)

5.06.8.27 Antiarteriosclerotic Agent

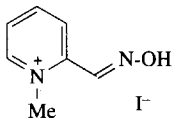
Anginin, 2,6-pyridinedimethanol bis(methylcarbamate) (**304**), is used to reduce lipid and cholesterol levels in the blood. It is prepared from 2,6-pyridyldimethanol ⟨66JAP22185⟩.



(**304**)

5.06.8.28 Antidotes

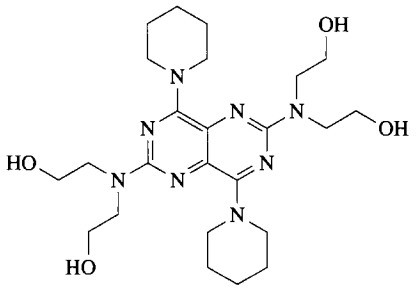
Quaternary salts of pyridinecarboxaldehyde oximes, particularly pralidoxime methiodide (**305**) ⟨B-64MI 506-02, B-88MI 506-05⟩, are used as antidotes for poisoning by organophosphate acetylcholinesterase inhibitors.



(305)

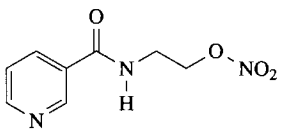
5.06.8.29 Vasodilators

Vasodilators are classified into three catagories: cerebral, coronary, and peripheral. Piperidine is used in the production of vasodilators such as dipyridamole (**306**) and minoxidil (**241**) ⟨B-93MI 506-01⟩. Minoxidil has been used as a vasodilator, but latterly it has become more popular as a hair restorer; it is obtained by the reaction of piperidine with 2,6-diamino-4-chloropyrimidine *N*-oxide.



(306)

The coronary vasodilator nicorandil, (**307**) ⟨80USP4200640⟩, is a potassium channel opener derived from nicotinamide that can lower blood pressure after a single dose with no significant changes in heart rate ⟨77GEP(O)2714713⟩. Nicotinyl alcohol (**308**), a peripheral vasodilator, is prepared by the reduction of 3-cyanopyridine in the presence of aqueous sulfuric acid, and it is also used as a stabilizer for riboflavin ⟨49USP2458430, 50USP2520037, 52USP2615896⟩. A smooth muscle relaxant, nicametate (**309**), is prepared from nicotinoyl chloride and diethylaminoethanol ⟨42JA1721⟩.



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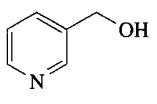

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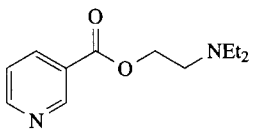
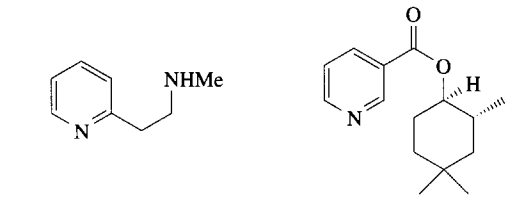


(309)

Examples of pyridine-based vasodilators include betahistine (**310**) ⟨41JA2771⟩, ciclonicate (**311**) ⟨69GEP1910481⟩, homonicotinic acid (**312**) ⟨46USP2408020⟩, gapicomine (**313**) ⟨B-93MI 506-01⟩, cicletanine (**314**) ⟨85AF1714⟩, and nicotinyl alcohol ⟨50USP2520037⟩. Dipyridamole (**306**) is a coronary vasodilator, and picodralazine (**315**) ⟨B-82MI 506-09⟩ is used as peripheral vasodilator. 2-(3-Pyridyl)tetrahydrothiopyran-2-carbothioamide derivatives (**316**) and their analogs are derived from 3-picolyl chloride, and are a novel family of potent potassium channel openers. Piperidine-based antihypertensive agents include primaperone (**317**), minoxidil, and dipyridamole ⟨B-82MI 506-10⟩. The isoquinoline derivative papaverine (**6**) ⟨62JCS3526⟩ is used as a cerebral vasodilator.



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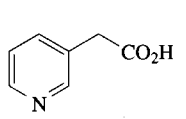
(311)



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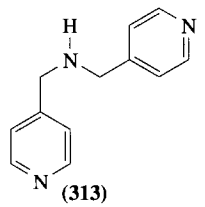

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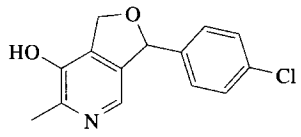

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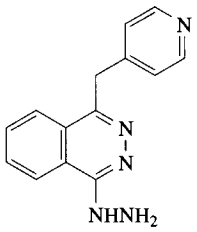

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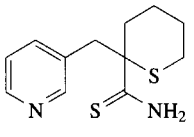

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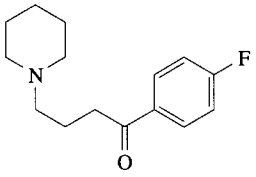
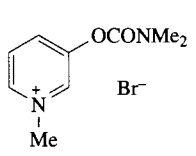


(317)

5.06.8.30 Anticholinesterases

Anticholinesterase agents act by reversibly inhibiting acetylcholinesterase, the enzyme that breaks down acetylcholine, thereby increasing the duration of action of acetylcholine. Both pyridostigmine bromide (**318**) and distigmine bromide (**319**) are currently prescribed for this purpose, and both are derived from 3-hydroxypyridine ⟨B-93MI 506-01⟩.



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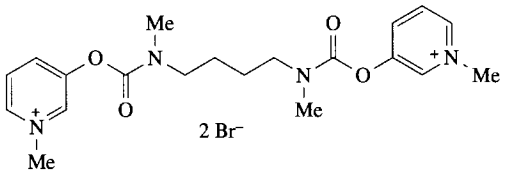
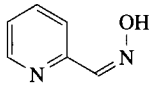


(319)

Cholinesterase inhibition, the mechanism whereby a number of insecticides and nerve gases function, may be reversed by acid salts of pyridine-2-carbaldehyde oxime (**320**). Obidoxime chloride (**321**), based on the 4-aldoxime ⟨61JPS109, 64USP3155674⟩, and the iodide and methanesulfonate salts ⟨57USP2816113⟩, all exhibit cholinesterase reactivation.



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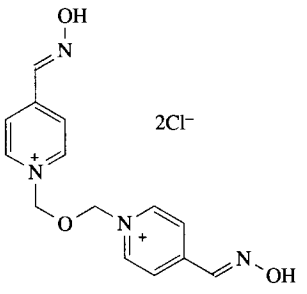
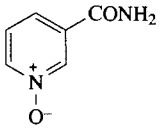


(321)

5.06.8.31 Radiosensitizers

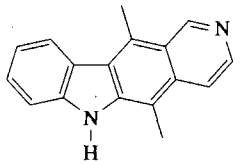
A number of radiosensitizers have been developed to suppress tumor growth ⟨B-94MI 506-14⟩. Nicotinamide *N*-oxide (**322**) is used as radiosensitizer to help promote tumor regression during radiation therapy ⟨80MI 506-07⟩.



(322)

5.06.8.32 Anticancer Agents

The subject of anticancer activity has been reviewed recently ⟨93KO(5)870⟩. Numerous synthetic routes to ellipticine (**323**), which shows anticancer activity, have been reported including three-step syntheses starting from either 3-acetylpyridine ⟨59JA4434⟩ or 2-chloro-3-ethylpyridine ⟨75CC540⟩. 2,2′-Dipyridine-6-thiocarbamide (**324**) shows anticancer activity ⟨81JMC1181⟩.



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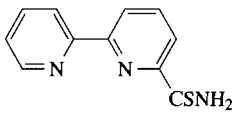
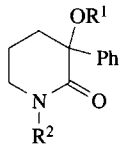


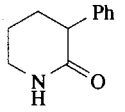
(324)

5.06.8.33 Anticonvulsants

Some piperidine derivatives (**325**) exhibit anticonvulsant activity. The most active compounds of this group include 3-phenyl-2-piperidone (**326**) ⟨84JMC202⟩. A series of 3-benzyl-2,6-piperidinediones and 1-methyl-3-benzyl-2,6-piperidinediones have been synthesized as potential anticonvulsant drugs to treat epilepsy. The most active in the series is the 4-chlorobenzylglutarimide (**327**). The synthesis of these compounds is based on the regioselective reaction of the dianion prepared from sodium glutarimide with electrophiles such as alkyl halides, aldehydes, ketones, and esters ⟨90JMC926⟩. (+)-PD-145950 (**328**) is three times more potent than the racemate and 20 times more potent than the (−) enantiomer in a test of electroshock-induced convulsions in mice ⟨93BMC39⟩.



(325) R^1 = H, Me
R^2 = H, Me, CO_2Et



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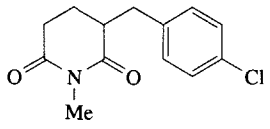

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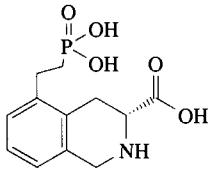


(328)

5.06.9 VETERINARY PRODUCTS

Many drugs developed for human use eventually find a place in veterinary medicine, but in this section only drugs developed solely for veterinary use are covered. The chemistry of veterinary products has been reviewed ⟨84CHEC-I(1)201, B-93MI 506-01⟩.

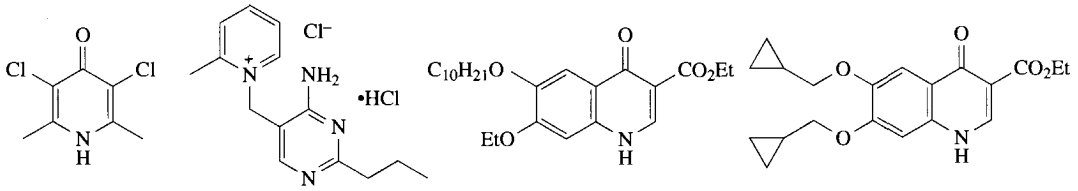
5.06.9.1 Anthelmintics

Conjugate addition of methoxide to 2-vinylpyridine offers methyridine (**238**), an antinematodal agent (anthelmintic) which has been used in domestic animals for the treatment of worm infections ⟨61NAT59, 62BRP889748⟩. In animals, roundworms are by far the greatest problem, followed by the liver fluke, lungworm, tapeworm, and heartworm. Methyridine, active at 200 mg kg^{-1} both orally

and parenterally, has a wide range of activity but is erratic against abomasal parasites. 2-Vinylpyridine itself is used as as an antinematodal agent ⟨61NAT59, 62BRP889748⟩. The trichloropyridine derivative fospirate (**239**) ⟨66MI 506-01⟩ is used as a veterinary anthelmintic, and drugs containing the quinoline or acridine moiety have been described ⟨50USP2515912, B-75MI 506-08⟩.

5.06.9.2 Antiparasitics

A number of pyridine and quinoline derivatives find use as veterinary drugs ⟨73MI 506-03, 92KO(3)456⟩, and clopidol (**329**), amprolium (**330**), and various quinolones all function as antiparasitics in the control of coccidiosis in chickens. Amprolium ⟨60JA2974, 60USP3065132⟩, a quaternary salt of 2-methylpyridine, decoquinate (**331**) ⟨68FRP1531495, 68CI(L)56⟩, cyproquinate (**332**) ⟨68SAP6705655, 70JMC870⟩, and clopidol ⟨65NEP6410223⟩ are examples of coccidiostats.



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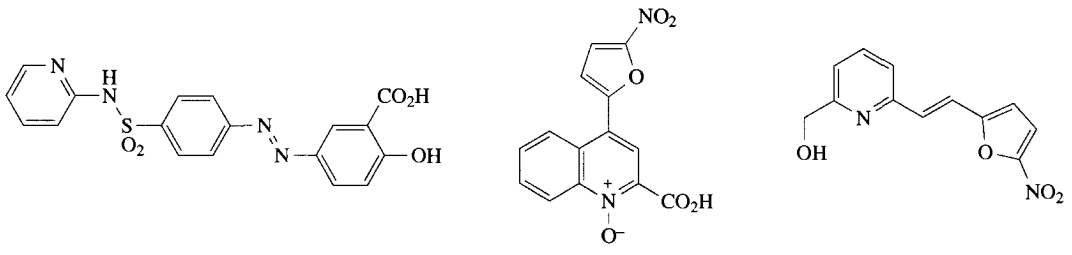
5.06.9.3 Antibacterials

Sulfasalazine (**333**) is an antibacterial used for veterinary purposes ⟨46USP2396145, B-79MI 506-10⟩. It is used in humans for the treatment of ulcerative colitis and Crohn's disease and is prepared from sulfapyridine by diazotization and coupling with salicylic acid ⟨92KO(2)876⟩. Nifuroquine (**334**), a quinoline *N*-oxide derivative, is used as a veterinary antimicrobial agent ⟨68SAP6703220⟩, and nifurpirinol (**335**) is used for certain diseases in fish ⟨67BRP1053730, 70JAP14072⟩.



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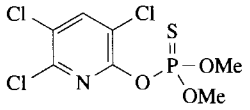
5.06.10 AGROCHEMICALS

Many pyridine derivatives exhibit considerable useful bioactivity, in terms of their use as herbicides, insecticides, and fungicides. Several books and reviews can be recommended for general reading and background information on agrochemicals ⟨B-77MI 506-07, B-78MI 506-03, B-79MI 506-11, 84CHEC-I(1)185, 87MI 506-05, 91MI 506-06, 92MI 506-05, B-93MI 506-01⟩.

5.06.10.1 Acaricides

Chlorpyrifos-methyl (**336**) is used as both an acaricide and insecticide to control insects, mites in stored grains, household pests, flies, aquatic larvae, and various foliar crop pests ⟨64FRP1360901⟩.



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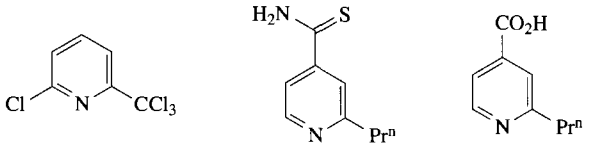
5.06.10.2 Bactericides

Chlorination of α-picoline affords 2-chloro-6-trichloromethylpyridine (nitrapyrin) (**337**) ⟨63BEP624800⟩, which is selectively active against *Nitrosomonas* bacteria, the organism responsible for the conversion or nitrification of ammonium ions to nitrite ions in soil ⟨64USP3135594⟩. This compound thus acts as a nitrification inhibitor and prolongs the beneficial effects of nitrogen fertilizers. The antibacterial protionamide (**338**) is derived from 2-propylisonicotinic acid (**339**) ⟨76KFZ96⟩. Rosoxacin (**225**) is an example of a quinoline-based bactericide ⟨72GEP(O)2224090⟩.



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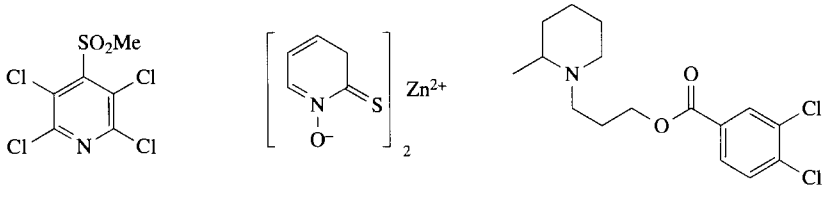
5.06.10.3 Fungicides

Paints are attacked in both the liquid and dry state by various microorganisms, particularly under damp and humid conditions. Fungicides such as 4-methylsulfonyl-2,3,5,6-tetrachloropyridine (Dowicil S-13) (**340**) are being used increasingly to prevent such attacks. Thus, addition of Dowicil S-13 to alkyd gloss and latex paint increased the mold resistance for 2 yrs in the tropics, with loss of the fungicidal activity occurring through decomposition in sunlight and leaching by water ⟨71MI 506-03⟩. Fungicides are also used in paper production and to protect plastics, wood, and textiles ⟨B-69MI 506-04⟩. Zinc pyrithione (**341**), the zinc salt of 2-pyridinethiol *N*-oxide, is a fungicide derived from 2-chloropyridine *N*-oxide. Both Dowicil S-13 and zinc pyrithione are rapidly translocated herbicides that selectively kill broad-leaved weeds. They mimic a natural auxin, indole-3-acetic acid, which is responsible for promoting cell elongation, and hence cause unrestrained growth ⟨B-75MI 506-09⟩. The piperidine derivative piperalin (**342**) is used to control powdery mildew on roses, lilacs, and zinnias ⟨B-93MI 506-04⟩.

Fluazinam (**343**), derived from 2,3-dichloro-5-trifluoromethylpyridine, has a broad range of uses



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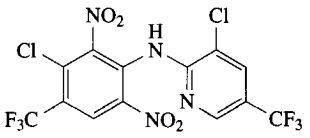
on crops such as vegetables and vines. Pyrifenox (**344**) is used for the control of scab and powdery mildew on apples, pears, vines, and bananas.



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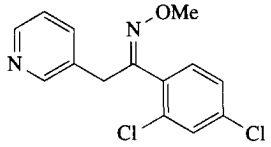

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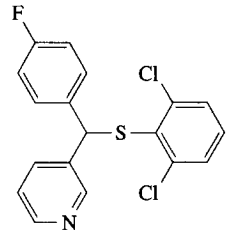
The 3-benzylpyridine derivative (**345**) is reported to show 100% activity against powdery mildew of barley ⟨94JAP(K)625168⟩, while the 3-aminopyridine derivative buthiobate (**346**) is used to control powdery mildews on apples, pears, peas, strawberries, beans, cucurbits, and capsicums ⟨73BRP1337359⟩. The pyridylpyrimidine derivative (**347**) showed fungicidal activity towards *Pir-icularia oryzae*-inoculated rice plants ⟨94GEP(O)4227811⟩.

The most significant quinoline fungicides are metal chelates of 8-hydroxyquinoline ⟨56CR217⟩. Related compounds include quinacetol sulfate (**348**) and halacrinate (**349**) ⟨B-77MI 506-08⟩.



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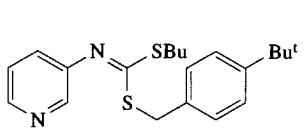

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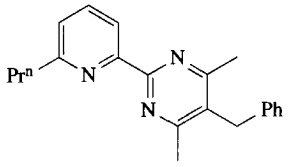

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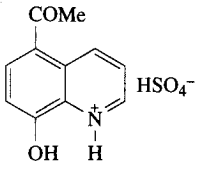

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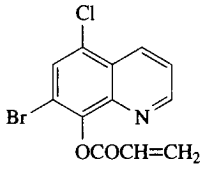

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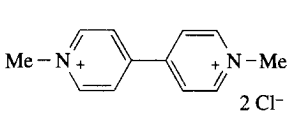
5.06.10.4 Herbicides

A major use of pyridine is in the manufacture of the herbicides paraquat (**350**) and diaquat (**351**). 2,2′-Bipyridine ⟨63AHC(2)179⟩ is synthesized by the oxidative dimerization of pyridine over hot Raney nickel, while 4,4′-bipyridine is made by the free radical coupling of the pyridine radical anion generated by sodium in liquid ammonia, followed by air oxidation. The quaternization of 4,4′-bipyridine with methyl chloride gives paraquat, and the reaction of 2,2′-bipyridine with 1,2-dibromoethane gives diquat. Paraquat and diquat are nonselective, quick-acting herbicides, active against most green plants. The herbicides are very rapidly inactivated by irreversible adsorption on contact with soil, particularly clays. Diquat is mainly used as a desiccant to aid harvesting, and for aquatic weed control. A number of reviews of all aspects of these compounds have been published ⟨68MI 506-01, B-75MI 506-09⟩.

In the early 1980s, new postemergent herbicides such as fluazifop-butyl (**352**) were developed for



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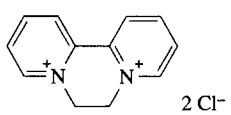

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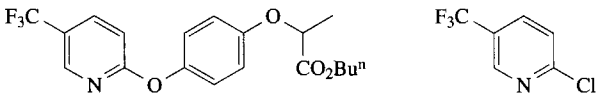
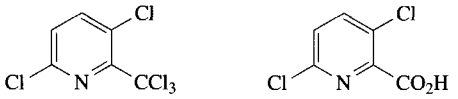
the control of annual and perennial grasses in broad-leaved crops. 2-Chloro-5-trifluoromethylpyridine (**353**) is a precursor for fluazifop-butyl ⟨78BEP865137, B-87MI 506-08⟩, which is a promising heterocyclic representative of a new group of phenoxypropionic acids that are not auxin mimics.



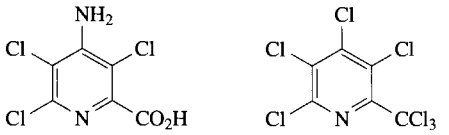
(**352**) (**353**)

Chloropyridines are widely used as herbicides, and a variety of commercial products have been introduced. Chlorination of 2-methylpyridine gives 3,6-dichloro-2-trichloromethylpyridine (**354**), which on hydrolysis gives 3,6-dichloropicolinic acid (clopyralid) (**355**) ⟨67USP3317549⟩. Clopyralid is tolerated by crops such as sugar beet and small-grain cereals but shows excellent postemergence activity against many of the weeds tolerant to phenoxyalkanecarboxylic acids ⟨76GEP2558399⟩. Compounds containing halophenoxypyridine ring systems such as fluazifop-butyl are used to eliminate grass-like weeds in broad-leaved crops.



(**354**) (**355**)

4-Amino-3,5,6-trichloro-2-picolinic acid, picloram (**356**), is manufactured from 2-methylpyridine via 2,3,4,5-tetrachloro-6-trichloromethylpyridine (**357**). It is a potent systemic herbicide which is usually formulated with other herbicides; it exhibits high activity against many broad-leaved plants and conifers, and is used in forestry to clear a variety of bush and tree species ⟨63BEP628487, 66USP3285925, B-76MI 506-05⟩.

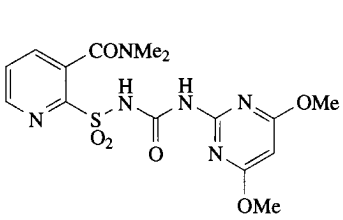


(**356**) (**357**)

Nicosulfuron (**358**) and diflufenican (**359**) are derived from 2-chloronicotinic acid and are used for the postemergent control of annual and perennial grasses in maize and to control broad-leaved weeds ⟨89EUP323881⟩. Imazethapyr (**360**), is used as a soybean broad-leaved weed herbicide ⟨B-87MI 506-06⟩. The cereal herbicide fluroxypyr (Starane) (**361**) is derived from pentachloropyridine ⟨73USP3761486, 87MI 506-07⟩, while thiazopyr (**362**), which is used on fruit crops, is synthesized by a Hantzsch-type reaction ⟨88H(27)269⟩. Octachloro-2,3′-bipyridine (**363**) ⟨72BRP1276253⟩ is used as a herbicide, and is obtained by gas phase chlorination of 2,3′-bipyridine ⟨81MI 506-02⟩.

The reaction of 2,3,5,6-tetrachloropyridine (**364**) with paraformaldehyde/potassium cyanide gives the 2-cyanomethoxy derivative precursor to 3,5,6-trichloro-2-pyridinyloxyacetic acid, triclopyr (**365**) ⟨75USP3862952⟩; (**365**) shows strong herbicidal action against broad-leaved and woody weeds, and is useful in noncrop areas. The pyridyl-imidazolinone herbicides such as imazapyr (**366**), imazethapyr ⟨B-87MI 506-06⟩, and imazaquin (**367**) are all broad-spectrum herbicides with activity on broad-leaved and grassy weeds ⟨B-87MI 506-08⟩. They are structurally based on either quinolinic acid or 5-alkylquinolinic acid. Dithiopyr is a pre-emergent and early postemergent herbicide for the control of annual grasses and broad-leaved weeds, and it is prepared by a modified Hantzsch pyridine synthesis using ethyl 4,4,4-trifluoroacetoacetate, isobutyraldehyde, and ammonia ⟨85EUP133612⟩. Imazaquin has been used in soybean crops as a pre- and postemergent herbicide ⟨81EUP41623⟩. Piperophos (**368**) is a selective herbicide active against annual grasses and sedges in seeded or flooded rice. Sulfanilide (**369**) has also been used as a herbicide ⟨79GEP2850821⟩.

Fluoridone (**370**) is a relatively new herbicide which has found application in aquatic plant management ⟨79MI 506-11, 79MI 506-12⟩ and in the treatment of cotton crops. The picolinic acid derivative (**371**) was prepared by the condensation of methyl 3-hydroxy-6-(1-pyrrolidinyl)picolinate with 4,6-dimethoxy-2-pyrimidylmethanesulfonic acid. It showed herbicidal activity against a wide variety of weed species ⟨93EUP567133, 93MIP9317015⟩.



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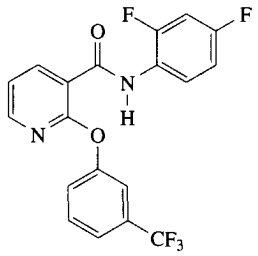

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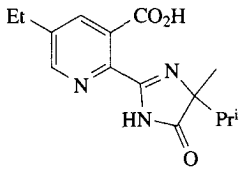

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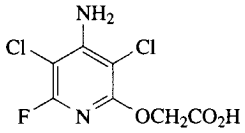

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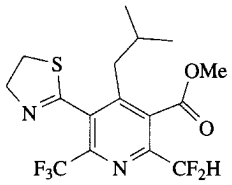

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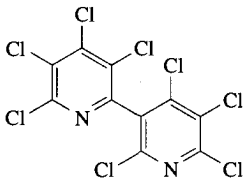

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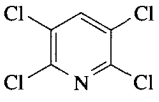

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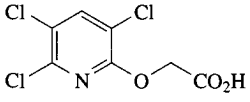

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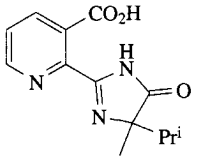

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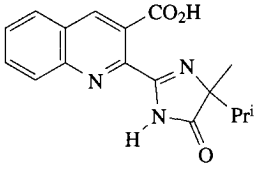

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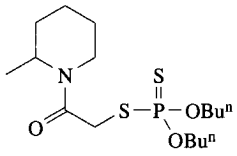

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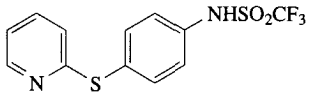

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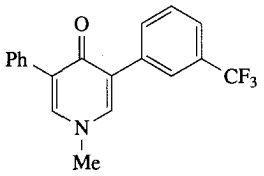

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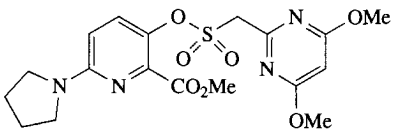

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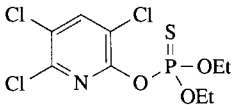
5.06.10.5 Insecticides

2,3,5,6-Tetrachloropyridine is used to produce insecticides of the chloropyrifos type. Chloropyrifos-methyl (**336**) and -ethyl (**372**) are examples of organothiophosphate insecticides which kill on ingestion or contact ⟨64FRP1360901⟩. They are used for the control of flies, household pests, mosquitoes (larvae and adults), and various crop pests in soil and on foliage ⟨B-71MI 506-04, B-71MI 506-05⟩.

Pyrethroids containing a pyridine unit are used as insecticides ⟨80JAP115869⟩. Synthetic pyridine-based pyrethroids such as (**373**) have made a significant impact in the insecticidal field, particularly in the treatment of the cotton boll-weevil ⟨80USP4228172, 80USP4221799, 80JAP115869, 81FRP2469403⟩. Simple thiosemicarbazone derivatives (**374**) of 2-acetylpyridine have demonstrated insecticidal activity.



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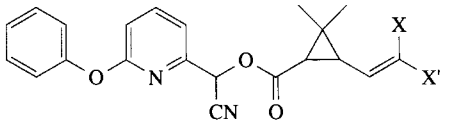

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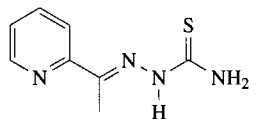
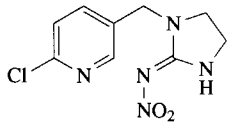


(374)

Imidaclopyrid (**375**) is derived from 2-chloro-5-methylpyridine and is used to control sucking insects, including rice hoppers, aphids, thrips, and white flies, and also in seed dressing ⟨90GEP(O)3830238⟩. 1-Diethoxymethyl-2-nitroimino-3-(2-chloro-5-methylpyridyl)imidazolidine (**376**) is an experimental insecticide ⟨91EUP455000⟩. Nitroethylene-based compounds such as (**377**), derived from 2-chloro-5-aminomethylpyridine, are used to control *Aulacophora femoralis* ⟨93JAP(K)5279208⟩. The *N*-cyano-*N*′-pyridylmethylacetamidine (**378**) is prepared from 2-chloro-5-aminomethylpyridine, and has shown some insecticidal activity ⟨93JAP(K)5178834⟩.



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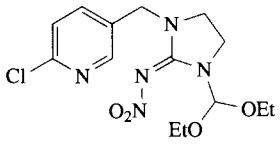

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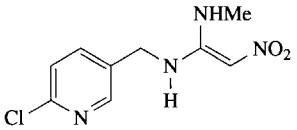

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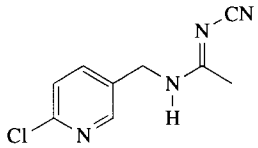
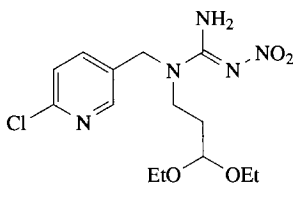


(378)

Nitroguanidine (**379**) is used to control *Phaedon cochleariae* larvae on cabbage leaves ⟨94GEP(O)4236204⟩. 2-(2,6-Dichloroisonicotinoylamino)-4,4-bis(trifluoromethyl)-5-tetrafluoroethylidene-2-thiazoline (**380**) has shown very high insecticidal activity ⟨93JAP(K)5286970⟩.



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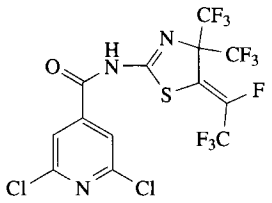
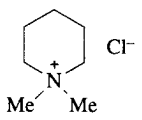


(380)

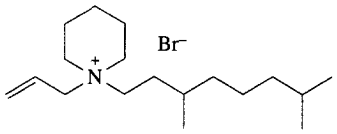
5.06.10.6 Plant Growth Regulators

Pix (mepiquat) (**381**) is a plant growth regulator derived from 1-methylpiperidine by quaternizing with MeCl. It is used on cotton at early bloom or when plants are 60 cm high to reduce vegetative growth and to increase earliness in picking with beneficial effect on the quantity or quality of fiber yield. Piproctanyl, the *N*,*N*-dialkylpiperidinium bromide (**382**), is used as a plant growth regulator

which reduces internodal elongation, thus decreasing plant height and producing stronger stems and deeper foliage ⟨76E37⟩. The chemistry of plant growth regulators has been reviewed extensively ⟨94KO(12)815⟩. The growth regulator Seritard (inabenfide) (**383**) is derived from isonicotinic acid.



(**381**)



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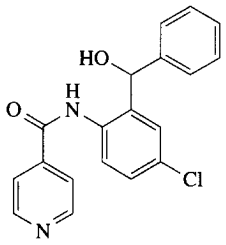
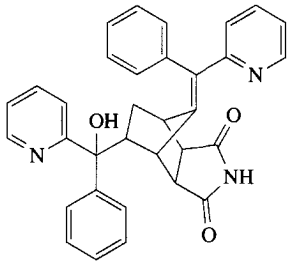


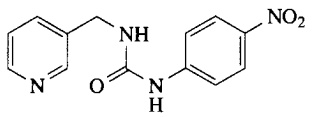
(**383**)

5.06.10.7 Rodenticides

Norbormide (**384**) is derived from 2-benzoylpyridine ⟨66JOC2141⟩. It a selective rodenticide lethal to all members of the genus *Rattus* that have been tested, but it is relatively nonlethal to other rodents. Pyriminil (**385**) is derived from 3-aminomethylpyridine and is used as rodenticide ⟨74GEP(O)2409686, 74MI 506-10, 78MI 506-04⟩.



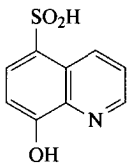
(**384**)



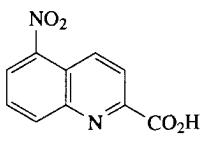
(**385**)

5.06.11 REAGENTS FOR QUALITATIVE AND QUANTITATIVE ANALYSIS

Nitrogen heterocycles are extensively used in the analysis of metals, particularly by spectral methods. 2,2′-Bipyridine is used as a reagent for the determination of iron ⟨24JA414, 60USP2962502⟩. 8-Hydroxy-5-quinolinesulfonic acid (**386**) has been used for the spectrophotometric determination of manganese, and 5-nitroquinaldic acid (**387**) to determine the presence of zinc, while 2-quinolinecarboxylic acid is used for the determination of copper, zinc, and uranium, with which it forms insoluble salts ⟨64IC1549, B-89MI 506-10⟩. The related 5-quinolinecarboxylic acid is used for the qualitative detection of cadmium, copper, iron, lead, mercury, silver, and thallium, and for the quantitative determination of copper.



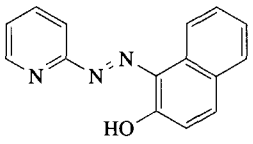
(**386**)



(**387**)

1-(2-Pyridylazo)-2-naphthol (**388**) is a reagent for the spectrophotometric determination of nickel, cobalt, vanadium, and zinc ⟨69ANC510⟩. 4-(2-Pyridylazo)resorcinol (**389**) is a highly selective and

sensitive reagent for cobalt and iron ⟨72AC1091⟩ and 2-(2-pyridylazo)benzimidazole (**390**) is used for the fluorometric determination of gallium, indium, and zinc ⟨69ACA425⟩. 4-Alkyl-2-thiolpyridines are used in flotation processes for the recovery of metal concentrates from metal-bearing ores ⟨80BRP2029274⟩.



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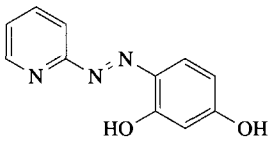

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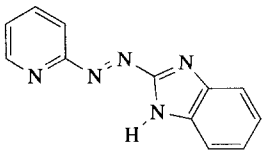
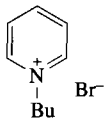


(390)

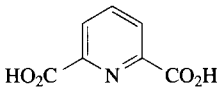
5.06.12 MISCELLANEOUS

1-Butylpyridinium bromide (**391**) and other lower 1-alkyl homologs exist as solids at ambient temperature, but admixture of these salts with aluminum chloride leads to melts that can exist as liquids below room temperature in fairly wide proportions. The utilization of these molten salts for battery electrolytes ⟨78USP4122245⟩ and electroplating baths for aluminium has been proposed ⟨87JAP(K)6270593⟩. These binary salts are reportedly excellent solvents and catalysts for Friedel–Crafts reactions ⟨86JOC480⟩ and for the formylation of toluene by carbon monoxide ⟨84USP4554383⟩.



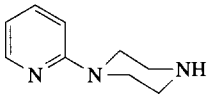
(391)

The presence of certain metal ions can have detrimental effects on photographic materials. For example, calcium ions found in hard water can form troublesome precipitates during processing. This problem can be alleviated by the use of a sequestrant such as the pyridinedicarboxylic acid (**392**), which forms an innocuous coordination complex with certain metal ions ⟨B-75MI 506-10⟩.



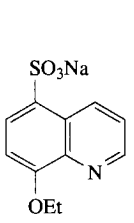
(392)

1-(2-Pyridinyl)piperazine (**393**) showed antianaphylactic activity ⟨87JMC13, 91CE775⟩. A method for suppressing the desire to smoke comprises inhaling an effective amount of a volatile smoking suppressant composition containing 2-acetylpyridine in a solvent of propylene glycol ⟨94USP5336680⟩. 4-Aminopyridine is used in the treatment of spinal cord injuries ⟨94MIP2085785⟩, and it has also been shown to be an effective bird repellent in corn fields where destructive feeding is a problem ⟨82CT710⟩.

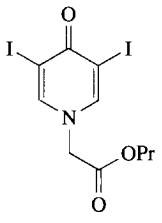


(393)

The actinoquinol sodium salt (**394**) has been used in ultraviolet screens ⟨54MI 506-03⟩. 4-Pyridone is the starting material for the synthesis of diodone and its propyl ester propyliodone (**395**). These compounds are used as x-ray contrast media ⟨73GEP2219707, 74USP3795698, B-93MI 506-01⟩.

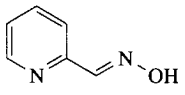


(**394**)

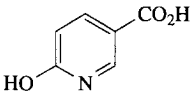


(**395**)

syn-2-Pyridinealdoxime (**396**) is a reagent for phosphotriester cleavage in oligonucleotide synthesis ⟨78TL2727⟩. 2,3-Pyridinedicarboxylic acid inhibits glucose synthesis ⟨67B2129⟩. 2,6-Pyridinedicarboxylic acid (dipicolinic acid) is a chelating agent and enzyme inhibitor which also induces sporulation. The sodium salt rapidly removes catalytically essential zinc ions from the metalloenzyme carbonic anhydrase ⟨69B2045⟩. 6-Hydroxynicotinic acid (**397**) stimulates adrenocortical secretion ⟨69MI 506-05⟩.

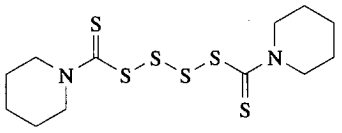


(**396**)



(**397**)

A major use of piperidine is in the production of dithiuram tetrasulfide (**398**), which is used as a vulcanization accelerator in the rubber industry. 2,2,6,6-Tetramethylpiperidinoxy (TEMPO) (**399**), a free radical, is used for the selective oxidation of primary hydroxy groups in primary and secondary diols ⟨90TL2177⟩. 4-Hydroxy-2,2,6,6-tetramethylpiperidinoxy (4-hydroxy-TEMPO) (**400**) is a spin label for biological molecules and has been used to prepare spin-labeled NADP, an inhibitor of dihydrofolate reductase ⟨79B2414⟩. It is also used for the synthesis of spin-labeled di- and tri-2-deoxyadenylates ⟨86RTC116⟩. 4-Amino-2,2,6,6-tetramethylpiperidinoxy (**401**) has been used to study intramolecular viscosity ⟨80B5593⟩ and as a spin label.



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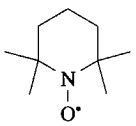

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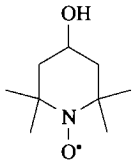
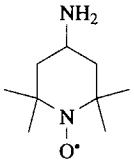


(**400**)



(**401**)

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5.07
Pyrans and their Benzo Derivatives: Structure

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University of Central Lancashire, Preston, UK

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5.07.1 INTRODUCTION

5.07.1.1 Nomenclature

Six-membered oxygen heterocycles constitute a group of compounds which occur widely throughout the plant kingdom and are of significance in marine organisms. Many of their number exhibit

biological activity; some are in use as drugs, whilst others show potential in the area of electronic organic materials. Chapter 5.10 assesses the applications and value of these heterocycles. Their syntheses are discussed in the following chapter, which includes a survey of the major literature in this area. These works sometimes contain structural aspects of oxygen heterocycles and hence reference should be made to these texts. Structural information is also scattered thinly throughout the chemical literature and hence complete coverage is impossible. Data is presented so that a broad appreciation of the structure of oxygen heterocycles can be achieved.

Since publication of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), in 1984, significant developments have occurred in the application of theoretical methods, particularly with regard to aromaticity, ring geometry and conformation, and in ^{17}O NMR spectroscopy.

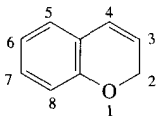
A variety of names have been used for derivatives of pyrans and their benzologs, many of which have been described in two treatises on oxygen heterocyclic compounds ⟨77HC(31), 81HC(36)⟩. The use of trivial names is still common in the literature because the systematic names are unwieldy and less familiar. The nomenclature used in this and the following two chapters is shown below, with some alternative names given in parentheses.

Six-membered oxygen heterocyclic compounds are based on three molecules: 2*H*-pyran (**1**), 4*H*-pyran (**2**), and the pyrylium cation (**3**). The benzolog (**4**) of 2*H*-pyran is known as 2*H*-1-benzopyran, chrom-3-ene and 2*H*-chromene, and a similar situation obtains for the corresponding derivative (**5**) of 4*H*-pyran. The benzolog (**6**) of pyrylium is known both as benzopyrylium and chromylium, with a preference for the former. Higher benzologs are referred to as naphthopyrans, exemplified by 2*H*-naphtho[1,2-*b*]pyran (**7**), whilst xanthene, strictly 9*H*-xanthene, and xanthylium are used for (**8**) and (**9**).

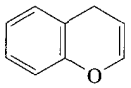
(1)
2*H*-Pyran

(2)
4*H*-Pyran

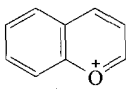
(3)
Pyrylium



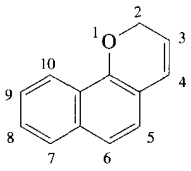
(4)
2*H*-1-Benzopyran
(2*H*-Chromene)



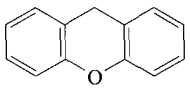
(5)
4*H*-1-Benzopyran
(4*H*-Chromene)



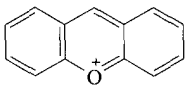
(6)
1-Benzopyrylium



(7)
2*H*-Naphtho[1,2-*b*]pyran
(Benzo[*h*]chromene)

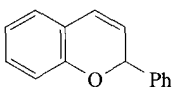


(8)
Xanthene
(9*H*-Xanthene)

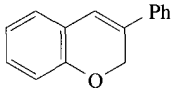


(9)
Xanthylium

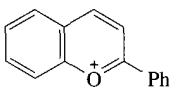
The flavonoids have such a widespread natural occurrence that a trivial nomenclature has evolved, and this approach is retained in this work. The phenyl derivatives of 2*H*-1-benzopyran and benzopyrylium are known as flavene (**10**), isoflavene (**11**), and flavylium (**12**).



(10)
Flavene
(2-phenyl-2*H*-benzopyran)



(11)
Isoflavene
(3-phenyl-2*H*-1-benzopyran)

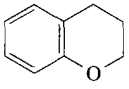


(12)
Flavylium
(2-phenyl-1-benzopyrylium)

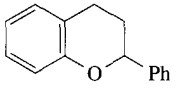
The partially reduced pyrans (**13**) and (**14**) are named from 2*H*-pyran, and the benzolog (**15**) is called chroman, whilst flavan is used for the 2-phenyl derivative (**16**).

(13)
3,4-Dihydro-2*H*-pyran

(14)
3,6-Dihydro-2*H*-pyran

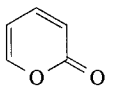


(15)
Chroman

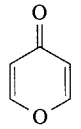


(16)
Flavan

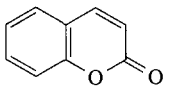
The ketones derived from the pyrans are called pyranones (**17**) and (**18**), although the name pyrone is still in common use. Trivial names rather than systematic names are generally used for the benzologs coumarin (**19**), chromone (**20**), and xanthone (**21**), and the 2-phenyl derivative of chromone is called flavone (**22**). The trivial names dihydrocoumarin, chromanone and flavanone are used for the molecules (**23**), (**24**), and (**25**), respectively, in which the heterocyclic ring is saturated.



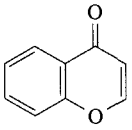
(**17**)
Pyran-2-one
(2*H*-Pyran-2-one)



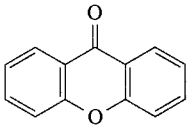
(**18**)
Pyran-4-one
(4*H*-Pyran-4-one)



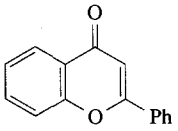
(**19**)
Coumarin
(2*H*-1-Benzopyran-2-one)



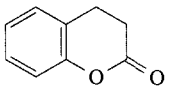
(**20**)
Chromone
(4*H*-1-Benzopyran-4-one)



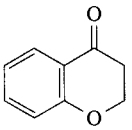
(**21**)
Xanthone
(9*H*-Xanthen-9-one)



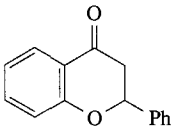
(**22**)
Flavone
(2-phenyl-4*H*-1-benzopyran-4-one)



(**23**)
Dihydrocoumarin
(3,4-dihydro-2*H*-1-benzopyran-2-one)

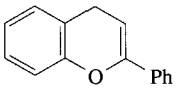


(**24**)
Chroman-4-one
(2,3-dihydro-4*H*-1-benzopyran-4-one)

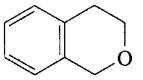


(**25**)
Flavanone
(2-phenyl-2,3-dihydro-
4*H*-1-benzopyran-4-one)

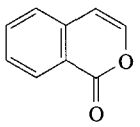
The names of some less common oxygen heterocycles (**26**)–(**28**) are shown. The above list is not intended to be comprehensive, but is designed to give the reader an awareness of nomenclature in this area.



(**26**)
4*H*-Flavene
(2-phenyl-4*H*-1-benzopyran)



(**27**)
(1*H*-2-Benzopyran)
(Isochromene,
1*H*-2-chromene)



(**28**)
Isocoumarin
(1*H*-2-benzopyran-1-one)

5.07.2 THEORETICAL METHODS

The rapid advances made in the past decade in the area of theoretical calculations have not bypassed six-membered oxygen heterocycles. Applications to pyrans and related compounds are summarized in Table 1, from which it can be seen that much attention has been focused on conformational details. Aromaticity is considered in Section 5.07.4.2 and the earlier work has been summarized ⟨84CHEC-I(3)573⟩.

Table 1 Theoretical calculations on six-membered oxygen heterocycles.

Compound type	*Method*	*Information*	*Reference*
2*H*-Pyran	3-21G, STO-3G	Stability, geometry	90CCC10, 90JMS261
4*H*-Pyran	STO-3G	Stability	90JMS261
Tetrahydropyrans	HF/6-31G*	Conformation	94JOC2138
	MM2		93JA4170
	6-31G, OPLS	Conformational energies	94JA2199
	MMX	Conformation	95IJC695
Chromans	MMP2, AM1	Conformation	91MI 507-01
Tetrahydrocannabinols	MM2, MMP2	Conformation	95T1017
Robustadials	MMP2	Conformation	88JOC3688
Pyran-2-one	PM3	Excited state geometry	92BCJ354
Pyran-4-one	CNDO/2, MINDO/3	Geometry, ionisation energies, dipole moments	85JST(133)95, 87ACH855
	MNDO	Dipole moments, geometry	93JPO489
Vinylogous pyran-4-ones	CNDO/2	Dipole moments	85LA1587
Dihydropyran-4-ones	MMX	Conformation	92BSB291
Tetrahydropyranones	MM2, 6-31G	Conformation	93JOC1367
Coumarin	AM1	Geometry	93LA609
	MP2/6-31G	Conformation	93JCS(P2)2423
Naphthocoumarins	MMP2-6-31G, AM1, PM3	Structure, isomerization barrier, Geometry	95T3149 93MI 507-xx
Dinaphthopyranone	AM1, MNDO	Enantiomerization	94LA91
Coumarin photo dimer	CNDO/S	Charge densities, CD spectra	89JA4387
Chromone	CNDO/2, MINDO/3	Geometry, PE spectra	87ACH855
	SCF-MO	Reactivity	84JCS(P2)2119
	MINDO/3, STO-3G	PE spectra	85JCS(P2)1191
	AM1	Conformation	93M539
	AM1	Geometry	94CCC1673
Flavonoids	MM2, MMP2, AM1	Conformation	91MRC569
Xanthenes	CNDO/2, AM1, PM3	Energy levels, solvato chromism	91MI 507-04, 94JCS(P2)1397
Pyranopyrandione	MNDO	Geometry	89G573
Pyrylium	STO-3G	Stability	90JMS261
Benzopyrylium	PPP-C1, QCFF PI	Structure	89M715, 90ZC26, 90ZC64
Flavylium	PPP	UV–vis spectra	94CCA163
	HMO	Aromatic stability, reactivity	91JCS(P2)891
2-Styrylbenzopyrylium	HMO, PPP	UV–vis spectra	92JCS(P2)1933
Benzoflavylium	HMO, PPP	Aromatic stability, reactivity	94G53

5.07.3 EXPERIMENTAL STRUCTURAL METHODS

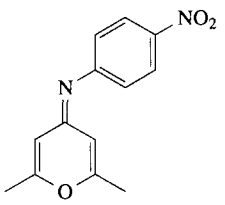
5.07.3.1 X-Ray and Electron Diffraction Determinations

A comprehensive list of molecular dimensions from x-ray investigations prior to 1970 includes a number of six-membered oxygen heterocycles ⟨72PMH(5)1⟩.

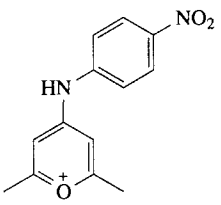
Crystal structures of 2,6-dimethyl-4-(4-nitrophenylimino)-4*H*-pyran (**29**) and its salts have been determined. The 4-aryl ring is rotated out of the plane of the pyran ring to reduce interaction between H-3 and H-2′. The increase in length of the C=N and C(2)—C(3) bonds and the decrease of the O—C(2) and C(3)—C(4) bonds along the series free base to hydrobromide to methobromide are interpreted in terms of the greater significance of the pyrylium canonical form (**30**) to the overall structure of the methobromide ⟨81JCS(P2)303⟩. Structures of a group of highly substituted 4*H*-pyrans have been determined by x-ray analysis ⟨87AX(C)1430, 87JST(162)19, 90AX(C)1727, 93T7133⟩ and several metal π-complexes of 2*H*-pyrans have also been investigated using this technique. A near-planar structure is indicated for the pyran moiety ⟨90JA9660⟩.

Molecular dimensions have been reported for the complex 2,2-dimethylchromene derivatives bromouliginosin B (**31**) ⟨68JA4723⟩ and dibromoeriostoic acid (**32**) ⟨67AX(B)120⟩. The structure of the fused 4*H*-1-benzopyran (**33**) has been established ⟨86JOC5036⟩.

Electron diffraction studies of gaseous xanthene (**8**) indicate that the C—O bonds have considerable double bond character, implying sp^2 hybridization of the heteroatom. Full molecular parameters are documented ⟨90JST(221)315⟩.



(29)



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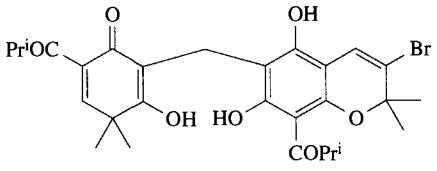

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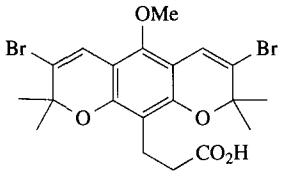

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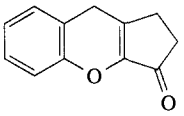
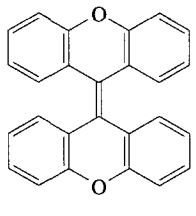


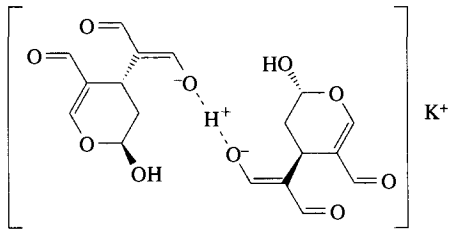
(33)

X-Ray studies of dixanthylenes (**34**) indicate that in the ground state the molecule adopts a folded geometry in which the center rings are boat shaped and the two tricyclic systems are folded in opposite directions to relieve steric interactions ⟨63JCS308⟩. However, in its colored form the two halves are considered to be planar but are twisted about the central bond ⟨73JA6177, 76JCS(P2)438⟩. ^{1}H NMR studies confirm the folded nature of 2,2′-disubstituted dixanthylenes in solution, but the low energy barrier for thermal *E,Z* isomerization is indicative of a high energy content of the folded conformation ⟨79JA665⟩.

The potassium salt of the hexameric form of malondialdehyde has been shown to be potassium hydrogen bis-[*trans*-4-(1,3-dioxopropan-2-yl)-5-formyl-2-hydroxy-3,4-dihydro-2*H*-pyran (**35**) ⟨92TL1361⟩. In the fused dihydropyran (**36**), obtained from the allyl propynyl ether, PhC≡CCH$_2$ OCH$_2$CH=CH-1-naphthyl, the phenyl, and naphthyl moieties are *cis* to each other and the configurations at the three cyclopropane carbon atoms are *RS* ⟨95JOC5567⟩.



(34)



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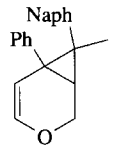


(36)

The molecular structure of gaseous tetrahydropyran has been determined by electron diffraction; the dimensions are presented in Figure 1 ⟨79ACS(A)225⟩. The molecule exists in the chair form with C_s symmetry. The torsional angles suggest that the heteroatom causes no flattening of the ring relative to that of cyclohexane.

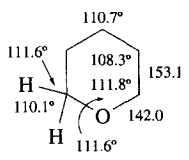
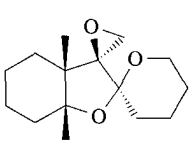


Figure 1 Bond lengths (pm) and bond angles (°) for tetrahydropyran.

The stereochemistry of the spiropyran (**37**) has been established by x-ray analysis ⟨84H(22)2449⟩, and the conformations and dimensions of the spirocyclic chromans (**38**) have been ascertained ⟨80TL4973, 81AX(B)1620, 82AX(B)1001⟩. The crystal structure and polymorphic behavior of (**39**) and related *N*-chlorinated derivatives have been investigated ⟨89JPS256, 90JHC1793⟩.



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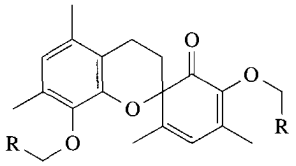

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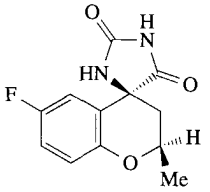
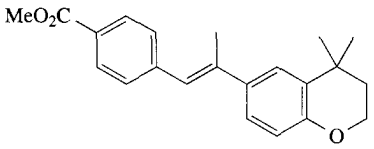


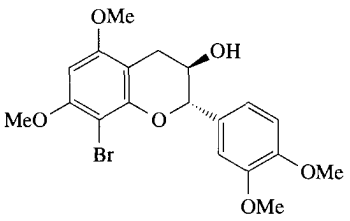
(39)

A combined crystallographic and theoretical analysis of the *E*- and *Z*-isomers of the 6-substituted chroman (**40**) shows greater steric crowding about the double bond in the latter isomer. The resulting loss of conjugation may link with the reduced pharmacological activity of the *Z*-isomer ⟨91MI 507-01⟩. Structural information on chromans derived from (+)-nopinone and (*S*)-(−)-β-pinene and on some benzocyclobutene homoisoflavans has established their absolute configurations ⟨88JA5213, 90T6565, 93JOC6163⟩.

The conformation of the heterocyclic ring in 8-bromotetra-*O*-methyl-(+)-catechin (**41**) is between a C-2, C-3 half-chair and a C-2 sofa arrangement ⟨78CC695⟩. The position of the outer flavonoid linkage in the epicatechin series of procyanidin dimers has been established by x-ray studies ⟨83MI 507-01⟩.



(40)



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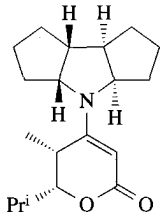
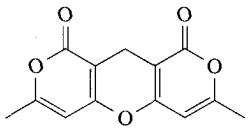


(42)

Although x-ray crystallography has not been applied to pyran-2-one itself, some simple alkyl analogs have been examined ⟨79CB423, 82AX(B)1865, 82AX(B)2163⟩. These data have been averaged to produce a "standardized ring geometry" for the parent compound. This approach is justified since the electronic influence of alkyl substituents and therefore structural variations are relatively minor. Data so obtained ⟨84T2451⟩ have been compared with that found in alternarian acid, a fungal metabolite.

Structural details of the 4-amino-substituted pyran-2-one (**42**) have been reported ⟨90AX(C)1551⟩. The short C(4)—N bond is indicative of extended conjugation. The dipyranopyrandione (**43**), formed from the base-catalyzed reaction of dehydroacetic acid with formaldehyde, is essentially planar ⟨89G573⟩.

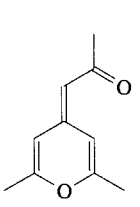


(43)

Detailed molecular dimensions for 2,6-dimethylpyran-4-one are available ⟨65ACS217⟩. The pyranone ring in 2,6-bis(diethylamino)-3,5-diphenylpyran-4-one is slightly non-planar and the substituents themselves show large deviations from coplanarity with the ring ⟨76AX(B)915⟩. The vinylogous pyran-4-one (**44**) is almost planar and possesses the *s-cis* conformation as shown ⟨85LA1587⟩. The same conformation is adopted by the related compound (**45**) ⟨83LA1807⟩.

The molecular dimensions of coumarin are given in Figure 2 ⟨74AX(B)1351, 76MI 507-01⟩. A useful compilation of the molecular geometry of the pyranone ring in a range of coumarins has been published ⟨75AX(B)1287⟩.

Crystal data is available on pyranocoumarins ⟨70AX(B)2022⟩, furocoumarins ⟨88JHC407, 90AX(C)2146⟩, and thienocoumarins ⟨92MI 507-01⟩, whilst interest in the photo-dimers of coumarins has resulted in detailed structural investigations ⟨91JCS(P2)981, 93BCJ900, 94JCS(P2)1223⟩. The chirality



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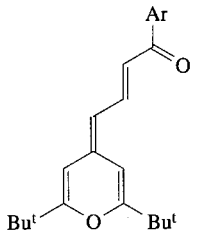

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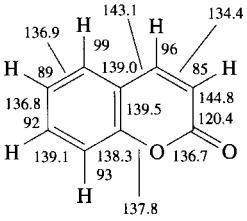


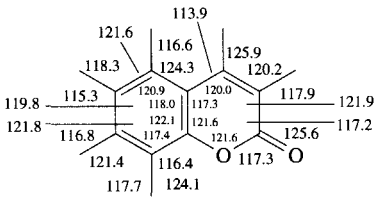
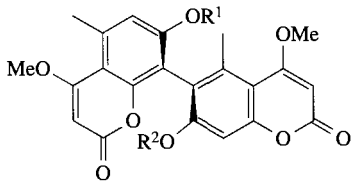


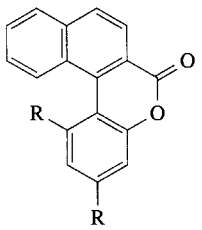
Figure 2 Bond lengths (pm) and bond angles (°) for coumarin.

of the axis between the coumarin units in the bicoumarins, the desertovins, (**46**) has been established as *R* by x-ray analysis ⟨95JCR(S)92⟩.



(46)

Benzo[*b*]naphtho[1,2-*d*]pyranones (**47**) are helically twisted molecules which occur as two chiral enantiomeric rotational isomers. X-ray analysis indicates that the pyranone ring exists in a twist-boat conformation, irrespective of the presence of sterically hindering substituents ⟨92LA225, 92ZK271, 92ZK275⟩. Crystal data for racemic 4*H*-dinaphtho[2,1-*b*:1′,2′-*d*]pyran-4-one (**48**) are available ⟨94LA91⟩.



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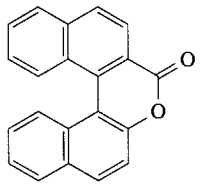


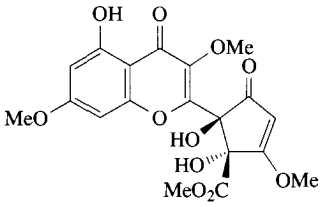
(48)

X-ray and NMR analysis have been used to confirm the structures of the adducts formed between 4-hydroxycoumarin and aliphatic aldehydes ⟨93HCA1194⟩.

The crystal structure of the naturally occurring chrysograyanone (**49**), the first chromone with a 2-cyclopentenyl group, has been determined ⟨92TL5977⟩.

The chromone unit in 3-bromoflavone is essentially coplanar, but the 2-phenyl group is twisted approximately 45° out of coplanarity with the rest of the molecule, steric interaction between C-3 and H-2′ dominating the structure. Full geometric details of this compound are given ⟨82AX(B)983⟩. Whereas benzo[*h*]flavone (**50**) is non-planar with a torsion angle of 23° between the 2-phenyl group and the rest of the molecule, the benzo[*f*]isomer (**51**) is approximately planar ⟨80MI 507-01⟩.

A similar situation obtains in flavanones. The phenyl ring is about 40° out of planarity with the benzene ring in *cis*-3-bromoflavanone. The pyranone ring adopts a sofa conformation, with the



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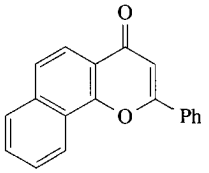

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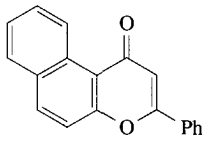
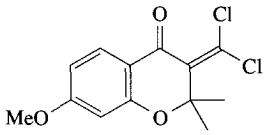


(51)

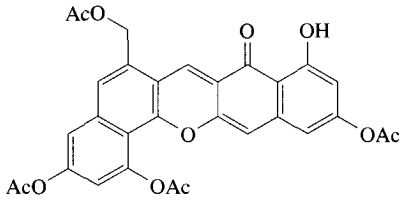
phenyl group equatorially disposed and the halogen atom axial ⟨82AX(B)981⟩, whilst the 2-substituent in 4′-bromoflavanone is almost perpendicular to the mean plane of the remainder of the molecule in which the pyranone unit is in the half-chair conformation ⟨74AX(B)154⟩. X-Ray analysis of the *cis*- and *trans*- forms of isorotenone provides some evidence for the instability of the latter *trans*-B/C ring fused isomer ⟨93JCS(P1)2605⟩.

The product from the Ag(I) assisted solvolysis of the adduct from 4-chloro-7-methoxy-2,2-dimethylchromene and dichlorocarbene has been confirmed as the 3-dichloromethylenechroman-4-one (**52**) by x-ray crystallography ⟨90JCS(P1)139⟩.

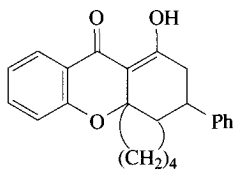


(52)

Xanthone (**21**) is a planar molecule in both the gaseous and solid phases ⟨82MI 507-01, 89JST(213)263, 90AX(C)1725⟩. The structure of the dibenzo[*b*,*h*]xanthen-8-one (**53**), a green fungal pigment, has been determined ⟨91CC1009⟩, as have those of the enamine-derived cyclohexano[*d*]xanthone (**54**) ⟨93CC159⟩, the fungal metabolite podosporin A (**55**), a benzo[*d*]xanthene ⟨88JOC4567⟩, and the benzo[*kl*]xanthene (**56**) ⟨95JHC17⟩. Complex molecules containing a xanthene moiety whose structures have been determined by x-ray analysis include beticolin 2 ⟨92JA1478⟩, cebetin B ⟨92JA5967⟩, ohioensin ⟨93JOC366⟩ and trioxacomans ⟨92JOC61⟩.



(53)



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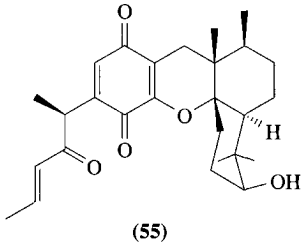

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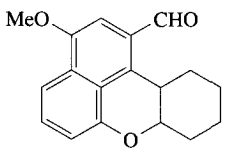
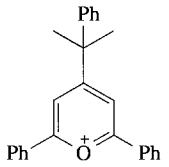


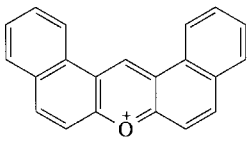
(56)

Crystallographic data on pyrylium salts confirm the planarity of 3-acetyl-2,4,6-trimethylpyrylium ⟨74CC614⟩.

In 2,6-diphenyl-4-(2-methyl-2-phenylethyl)pyrylium (**57**), the reduction in the angles O–C(2)–2–Ph and O–C(6)–6–Ph to around 112° is attributed to steric interactions between 2′-H and 3-H and 2″-H and 5-H, since the angles C(3)–C(2)–2Ph and C(5)–C(6)–6–Ph are correspondingly larger than expected. This feature may be enhanced by attractive interactions between 6′-H and 6″-H and the heteroatom ⟨89JCS(P2)613⟩.



(**57**)



(**58**)

Structural analysis by x-rays indicates that the ion pairs 2,6-di-*t*-butyl-4-arylpyrylium 2-naphthalenesulfonate are arranged in a face-to-face manner rather than the T-shape predicted by both spectroscopic and molecular mechanics calculations ⟨94JOC1119⟩.

X-ray data for the dibenzoxanthenium salt (**58**) indicate that, although each ring is planar, the molecule as a whole is distorted from coplanarity ⟨73CSC91⟩.

5.07.3.2 Microwave Spectroscopy

The ring skeleton of 3,6-dihydro-2*H*-pyran is twisted such that the heteroatom and C(2) are on opposite sides of the plane formed by the remaining carbon atoms. Structural details are given in Figure 3 ⟨74JCP(60)3987⟩. The microwave spectrum of 3,4-dihydro-2*H*-pyran also indicates that a twisted conformer is the most stable arrangement. The estimated angle of twist of 30.5° is very similar to that determined for the 3,6-dihydro-isomer (31.5°) ⟨85ZN913⟩.

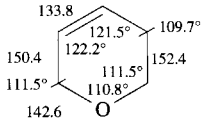
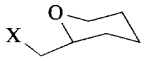


Figure 3 Bond lengths (pm) and bond angles (°) for 3,6-dihydro-2*H*-pyran.

Both 2-aminomethyltetrahydropyran (**59**; X = NH_2) and tetrahydropyran-2-ylmethanol (**59**; X = OH) exist predominantly in a chair form in which the equatorial substituent is able to form an intramolecular hydrogen bond ⟨79JA4499⟩.



(**59**)

Microwave spectra have been reported for both pyran-2-one and pyran-4-one ⟨73JA2766, 81JCS(F2)79⟩. The molecular dimensions are given in Figure 4.

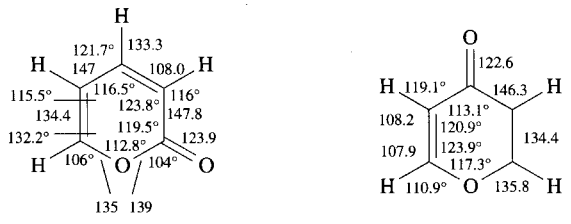


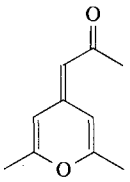
Figure 4 Bond lengths (pm) and bond angles (°) for pyran-2-one and pyran-4-one.

5.07.3.3 Dipole Moments

Whilst the measurement of dipole moments is worthwhile in its own right, it is particularly valuable for the estimation of interactions between component parts of a molecule and for the determination of the stereochemistry of compounds. Disparity between the observed moment and that calculated by vector addition of the individual group moments or by theoretical methods such as CNDO/2 may indicate that the actual structure is not truly represented by the simple molecular diagram. A compilation of dipole moments of six-membered oxygen heterocycles is available ⟨84CHEC-I(3)573⟩.

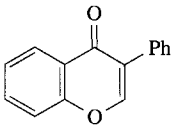
The dipole moments of pyran-4-one and the corresponding thione have been determined from Stark effects ⟨81JCS(F2)79⟩ and from dielectric measurements ⟨52AC(R)673⟩. Their magnitudes are higher than those calculated, suggesting some contribution from polar canonical forms to the actual structure of the molecule. However, better agreement is observed with the CNDO/2 calculated value for pyran-4-one and so the picture is not totally clear ⟨85JST(133)95⟩.

The CNDO/2 calculated dipole moments for the *s-cis* (**44**) and *s-trans* (**60**) conformations of 2,6-dimethyl-4-(2-oxopropylidene)-4*H*-pyran are 3.54 D and 6.35 D, respectively. The experimentally determined dipole is 3.71 D and so there is little doubt that in solution the pyran exists in the *s-cis* conformation ⟨85LA1587⟩.



(60)

Correlation of the observed and calculated dipole moments of flavone (**22**) and isoflavone (**61**) occurs when the phenyl ring is rotated out of the plane of the chromone moiety by about 30° and 50°, respectively, indicating that neither molecule is planar ⟨B-77MI 507-01⟩.



(61)

5.07.3.4 NMR Spectra

Virtually all publications relating to the synthesesis of six-membered oxygen heterocycles contain NMR data. Only a distillation of this large quantity of material is presented in this section. The early work has been reviewed ⟨B-73MI 507-01⟩.

5.07.3.4.1 Proton NMR spectra

(i) Pyrans, their benzologs and reduced derivatives

Although 2*H*-pyran has not yet been isolated, the ^{1}H spectra of a number of C-2 substituted derivatives have been studied. The data for 2,2,4,6-tetramethyl-2*H*-pyran given in Figure 5 is typical

of the 2*H*-pyran system, but other spectra are available ⟨81CCC748, 83JPR729, 84JPR657, 91CB1425, 91HCA27⟩.

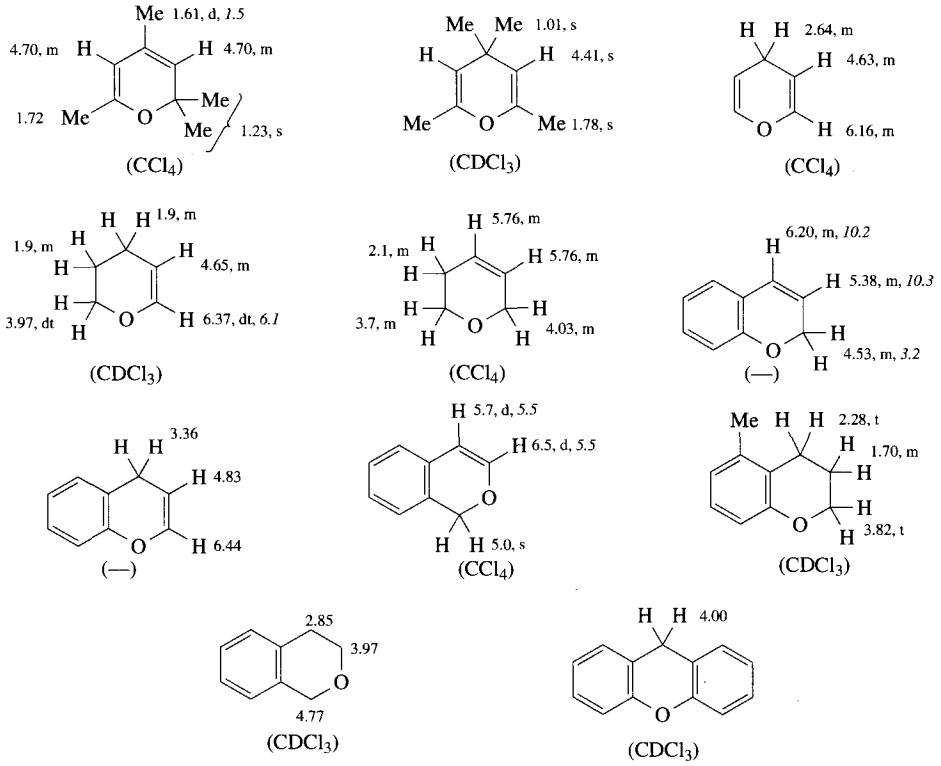


Figure 5 ^{1}H NMR spectra of representative pyrans and fused pyrans ⟨62JA2452, 64T2091, 66JOC3032, B-67MI 507-01, 68JOC2416, 69BSF1715, 69JOC3169, 71BSF1362, 72BSF707, B-74MI 507-01, 85MRC754⟩.

The valence isomerism of *cis*-dienones to 2*H*-pyrans continues to be of interest (see Section 5.07.4.4.2). The ^{1}H spectrum of the 2*H*-pyran (**62**), obtained by irradiation of *trans*-β-ionone, shows signals attributable to *cis*-β-ionone (**63**), which exists in equilibrium with the pyran (Figure 6) ⟨66JA619⟩.

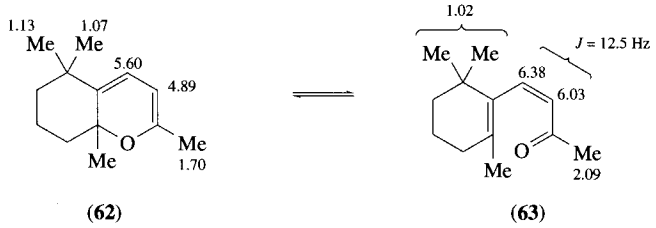
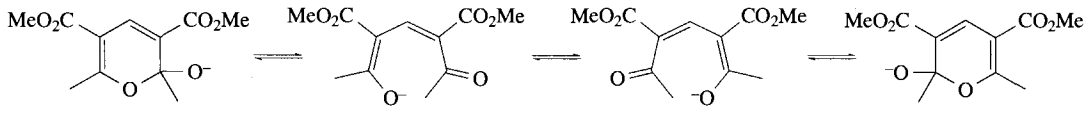


Figure 6 ^{1}H Chemical shift data (ppm) for *cis*-β-ionone (**63**) and its valence isomer (**62**).

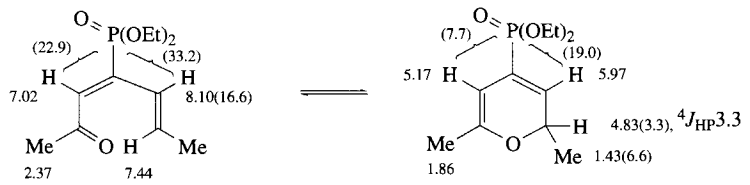
Both dimethyl 2,4-diacetylpent-2-enedioate and 1,1,3,3-tetraacetylpropene exist in the cyclic forms, which are substituted 2*H*-pyrans, but the influence of solvent, temperature, and base-catalysis on the acetyl resonances suggests an equilibrating system of cyclic and acyclic structures (Scheme 1) ⟨79JCS(P1)478⟩.

Syntheses of the 2,4-dienones (**64**) result in the isolation of their valence isomers, the dialkyl 2*H*-



Scheme 1

pyran-4-ylphosphonates (**65**); ^{1}H NMR data for the dimethyl derivative are given in Figure 7 ⟨85CB2917⟩.



(**64**) (**65**)

Figure 7 ^{1}H Chemical shift data [ppm (Hz)] for diethyl (2,6-dimethyl-2*H*-pyran-4-yl)phosphonate (**65**) ($CDCl_3$).

Full analyses of the spectra of 4*H*-pyran and a 2,4,4,6-tetraaryl derivative have been reported ⟨65MI 507-01, 92JCS(P2)1301⟩. The deshielding effect of the heteroatom is manifest in the chemical shift of H(2). Substitution in 4*H*-pyrans has little effect on the coupling constants, although allylic coupling between H(5) and a 6-Me group is clearly resolved in (**66**) when X is COMe or CO_2Me ⟨69JOC3169⟩. Chemical shift data for two 4*H*-pyrans are given in Figure 5, and other examples can be found ⟨83JOC2736, 87CCC2687⟩.

(**66**) (**67**)

On the basis of allylic and homoallylic coupling constants, it is concluded that 3,6-dihydro-2*H*-pyran adopts a half-chair conformation, as is preferred by the carbocyclic analog, cyclohexene ⟨80CHE571⟩. Variable temperature NMR studies show that *trans*-6-alkoxy-3,6-dihydro-2*H*-pyran-2-carboxylic acids exist exclusively in conformation (**67**) ⟨70OMR(2)55⟩. In the preferred structure of some 2-substituted 3,6-dihydro-2*H*-pyrans, H-2 is axial ⟨72OMR(4)537⟩, whilst a detailed NMR study of some 3,6-dimethyl-3,6-dihydro-2*H*-pyran-2,2-dicarboxylates indicates that the compounds exist in half-chair conformations ⟨72JOC3997⟩.

Chemical shift data has been reported for 2-alkoxy-, 2-phenoxy- and 6-alkoxy-3,4-dihydro-2*H*-pyrans ⟨75JOC2234, 78JOC667, 82TL603⟩. Most of the compounds which are monosubstituted at C(2) exist predominantly in the conformation in which the anomeric proton is equatorial (**68**; X = Y = H). However, 2-methoxy-4-methyl-3,4-dihydro-2*H*-pyran exists as a *cis–trans* mixture of diastereoisomers at the anomeric 2-position (**68** and **69**; R = Y = Me, X = H). One conformer is detected by NMR for the 2-methoxy-2-methyl compound, and the preferred conformation is thought to be that in which the methoxy group is axial (**68**; X = Me, Y = H).

(**68**) (**69**)

Spectral data for both 3,6-dihydropyran and the 3,4-dihydro compound are presented in Figure 5.

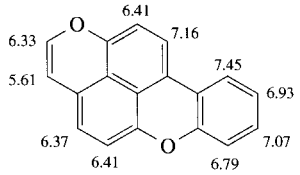
The most stable conformation for tetrahydropyran is the chair form (**70**). Detailed analyses of the spectra of the fully reduced pyran and some deuterated analogs have established the influence of the heteroatom on chemical shift differences between axial and equatorial protons at the three sites ⟨75CRV611⟩ and on the vicinal coupling constants ⟨76JOC1380⟩.

(**70**)

In addition to the aromatic multiplet, the ^{1}H spectrum of 2*H*-chromene exhibits a multiplet at δ 4.53 (2-CH_2) and peaks at δ 5.38 (3-H) and δ 6.20 (4-H) (Figure 5). Although both the shifts and multiplicities of the last peaks are influenced by substituents, H(4) always appears downfield of H(3), even in complex molecules ⟨93CPB187⟩. In the widely occurring 2,2-dimethylchromenes, the complexity of the spectra is simplified and H(3) and H(4) appear as doublets ($J_{3,4}$ *ca.* 10 Hz) and the *gem*-dimethyl groups resonate at about δ 1.5 ⟨83JCS(P1)827⟩. Substitution at the alkenic carbon atoms further simplifies the spectra; H(3) appears as a singlet around δ 6.0 in both 4-bromo-2,2-dimethylchromenes ⟨94T2507⟩ and some 4-aroyl derivatives ⟨94JCS(P1)653⟩ and H(4) at about δ 6.7 in the isomeric 3-bromo derivatives ⟨94JCS(P1)1733⟩. When a substituent is present at C(5) in 2*H*-chromenes, long-range coupling of about 0.5 Hz is observed between H(4) and H(8) ⟨94JCS(P1)1925⟩.

Spectral data for 4*H*-chromene are given in Figure 5, and data for some 4-substituted derivatives are available ⟨89S69⟩. The different chemical shifts of 4-CH_2 and of the 2-CH_2 unit in 2*H*-chromenes is noteworthy, whilst the coupling constant $J_{2,3}$ is about 6 Hz, appreciably smaller than $J_{3,4}$ in 2*H*-chromenes.

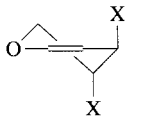
Assignments of the ^{1}H NMR signals for the pentacyclic compound, 1,6-dioxabenzo[*a*]pyrene (**71**) are given in Figure 8 ⟨95JHC17⟩. Data for the precursor 4-formyl-3-hydroxy-tetrahydrobenzo[*kl*]-xanthene and its 1-formyl isomer are also available.



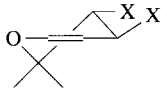
(71)

Figure 8 ^{1}H Chemical shift data (ppm) for 1,6-dioxabenzo[*a*]pyrene ($CDCl_3$).

The spectra of chromans are much more complex than those of chromenes. In many cases, signals from the three methylene units appear as triplets, implying flexibility of the half-chair heterocyclic ring (Figure 5). Substitution at C(3) or C(4) restricts the flexibility of the chroman ring, and it has been established that the 3,4-dihalogenochromans derived from the addition of halogen across the double bond of a chromene exist with the substituents in the *trans*-diaxial conformation (**72**). However, the most probable conformation for the corresponding 2,2-dimethyl compounds is considered to be *trans*-diequatorial (**73**), in which 1,3-diaxial interaction between a 2-methyl group and a 4-halogeno substituent is avoided ⟨81HC(36)169⟩.



(72)



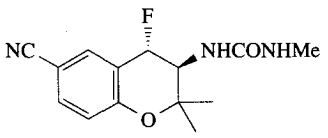
(73)

In the robustadials, in which the pyran fragment is essentially a 2,2,4-trisubstituted chroman, 3-H_{ax} resonates upfield of 3-H_{eq}, whilst 4-H is the furthest downfield ⟨89JOC1562⟩. Proton NMR data for a range of pterocarpans have been collated ⟨86H(24)2911⟩.

Axial and equatorial hydroxy groups in chroman-4-ols can be distinguished on the basis of their chemical shifts in DMSO; the pseudo-axial OH proton resonates at significantly higher field ⟨79BCJ2163⟩. In 3-aminomethylchroman-4-ols, the coupling constant for $J_{3,4}$ for the *trans*-isomer is larger (8.2 Hz) than for the *cis*-compound (4.4 Hz) ⟨88JMC2300⟩. A 5-formyl substituent appears to alter the disposition of the hydroxy group in 2,2-dimethylchroman-4-ols. Thus, in the parent compound $J_{3ax,4}$ is 8.9 Hz and $J_{3eq,4}$ 6.1 Hz, implying that coupling involves a pseudo-axial 4-H and that the OH moiety is pseudo-equatorial. For the 4-hydroxychroman-5-carbaldehyde, values of $J_{3ax,4}$ 6.0 and $J_{3eq,4}$ 4.3 Hz are observed, suggesting that the coupling proton is now pseudo-equatorial and that the 4-OH group occupies a pseudo-axial site. Confirmation is provided by the 8-formyl isomer, for which $J_{3ax,4}$ is 9.2 and $J_{3eq,4}$ 6.2 Hz. Steric interaction of the 5-*peri*-substituent renders the pseudo-axial site less hindered than the pseudo-equatorial position ⟨94JCS(P1)1925⟩.

However, care is necessary in assigning stereochemistry on the basis of coupling constants alone. For instance, the coupling constant between the *trans*-H(3) and H(4) in the 4-fluoro-3-

ureidochroman (**74**) is only 5.2 Hz, considerably smaller than expected. In the *cis*-4-amidochroman-3-ol (**75**), $J_{3,4}$ is 4 Hz ⟨90TL3649⟩.



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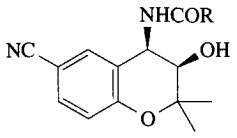
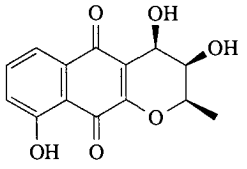


(75)

Proton and ^{13}C spectral data for (−)-cryptosporin (**76**), the enantiomer of the fungal metabolite and a naphtho[2,3-*b*]pyran, and several related compounds, have been published ⟨89HCA1649⟩.

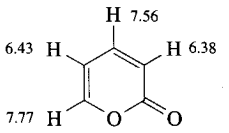


(76)

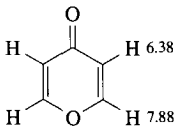
The preferred conformations of some methylisochromans have been established on the basis of the *vic* H(3), H(4) coupling constants. Data for the parent compound are given in Figure 5 ⟨85MRC754⟩. The relative stereochemistry of some 3,4-dihydro-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyrans has been established ⟨92AJC2025⟩.

(ii) Pyranones, their benzologs and reduced derivatives

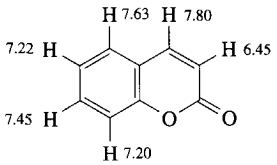
The spectrum of pyran-2-one consists of two complex multiplets centered at 6.4 ppm (H(3) and H(5)) and 7.6 ppm (H(4) and H(6)). Substituents have little effect on the coupling constants of the pyranone ring protons, and hence ^1H NMR can be useful in establishing the position of substituents ⟨69JHC1, 69JOC2239⟩. Figure 9 contains the spectral parameters for pyran-2-one, and data on substituted derivatives are available ⟨68JHC275⟩.



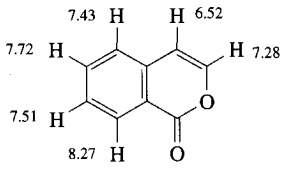
$J_{3,4}$ 9.4; $J_{4,5}$ 6.3; $J_{5,6}$ 5.0 ($CDCl_3$)



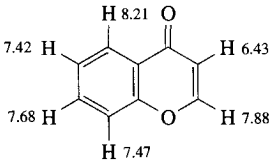
$J_{2,3}$ 5.96; $J_{3,5}$ 2.68 ($CDCl_3$)



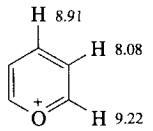
$J_{3,4}$ 9.8; $J_{5,6}$ 8.5 ($CDCl_3$)



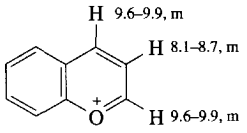
$J_{3,4}$ 5.7; $J_{5,6}$ 7.9; $J_{6,7}$ 7.3; $J_{7,8}$ 8.0 ($CDCl_3$)



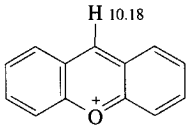
$J_{2,3}$ 6; $J_{5,6}$ 8; $J_{6,7}$ 7; $J_{7,8}$ 8.4 ($CDCl_3$)



(CF_3CO_2D)



(CF_3CO_2H)



(D_2SO_4)

Figure 9 ^1H NMR spectra of representative pyranones and pyrylium salts ⟨64AJC1305, 64SA871, 65SA1277, 69JHC1, 73OMR(5)251, 75JA5472, 81JHC1325, 85SA(A)913⟩.

In 5,6-disubstituted derivatives of 5,6-dihydropyran-2-one, long-range coupling of about 2 Hz is observed between H(4) and H(6), indicative of a *trans* diaxial configuration of the 5- and 6-substituents, which allows a near-planar arrangement of H(4), C(4), C(5), C(6) and H(6) ⟨69JHC1⟩.

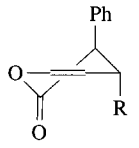
Much of the ^{1}H NMR work on pyran-4-ones has been concerned with the aromatic nature of the system, and several reports of aromatic character are based on the downfield shifts relative to those for non-aromatic dihydro analogs ⟨68T923⟩. Proton NMR data for pyran-4-one is given in Figure 9; the spectrum consists of two multiplets, with the upfield signal being associated with H(3) and H(5). All the couplings in pyran-4-one have been assigned ⟨64SA871, 67SA(A)55⟩. Spectral data for substituted pyran-4-ones can be found in ⟨84CHEC-I(3)573⟩.

The chemical shifts of H(3) and H(4) in coumarin are similar to those in pyran-2-one (Figure 9). The signal for H(3) is usually at higher field than that for H(4), so that distinction between 3- and 4-substituted derivatives is possible. Coupling between the alkenic protons $J_{3,4}$ is 9.8 Hz, and this pair of doublets is a characteristic feature of the ^{1}H NMR spectra of coumarins. The calculated electron densities for the aromatic ring correlate well with the observed chemical shifts, with H(5) and H(7) occurring downfield of H(6) and H(8). In addition to the expected aromatic proton coupling constants, long-range couplings are observed between H(4) and H(8) (*J ca.* 0.6 Hz) ⟨67JCS(C)2000⟩, and other inter-ring couplings have been identified ⟨68AJC2445⟩. Substitution in the aromatic ring exerts a small influence on the signals for H(3) and H(4). Substitution at C(5) deshields H(4), but electron-releasing substituents at C(5) and C(7) shift the signal from H(3) upfield. Substituents in the 3- and 4- positions are also affected by substitution in the aromatic ring ⟨72MI 507-01, 78T1221⟩. Rules have been devised to assist in structure elucidation of coumarins ⟨72MI 507-02⟩ and further information accrues from solvent-induced shifts ⟨66T3301, 88JIC630⟩. Lanthanide shift reagents have also proved of value in the elucidation of substitution patterns in coumarins ⟨78JCS(P2)391⟩.

Proton NMR data is available for 4-aminocoumarins ⟨94JHC1353⟩, variously annulated pyranocoumarins ⟨87MRC740, 91MRC631⟩ and for a 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one ⟨93JCS(P1)1019⟩.

In isocoumarins, H-3 resonates downfield of H(4) and both signals are influenced by substitution at the 3- and 4-positions (Figure 9) ⟨67BSF2224, 85SA(A)913⟩.

The relative configurations and conformational aspects of some 3,4-disubstituted 3,4-dihydrocoumarins have been investigated. In the case of the *cis*- and *trans*-4-alkyl-3-phenyl derivatives (**77**) and (**78**), the phenyl substituent is axially disposed in both isomers ⟨75MI 507-01⟩. For 3-substituted 2-oxo-4-chromanacetic acid esters, the *trans*-compound exists as a diaxial half-chair conformer (**79**), but the conformation of the *cis*-isomer is uncertain ⟨85MI 507-01⟩.



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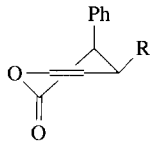
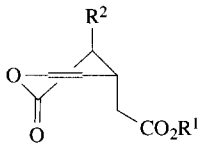
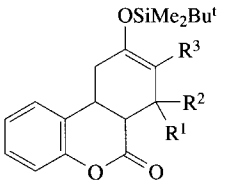


(78)



(79)

The ring junction in the cycloadducts derived from 6-methylpyran-2-one and coumarin with 2-(trialkylsilyl)oxydienes has been established as *cis*, with $J = 4.4$ to 4.8 Hz. The *trans* isomer, obtained by protonolysis of the trimethylsilyl enol ether of the *cis*-adduct, has $J \simeq 14$ Hz. Comprehensive spectral data are provided for several partially reduced dibenzo[*b*,*d*]pyran-6-ones (**80**) and 6,9-diones (**81**) ⟨91JOC5052⟩ and for some 2,3-fused chroman-4-ones ⟨91JOC2058⟩.



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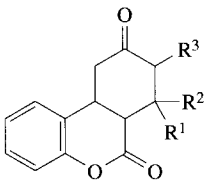


(81)

The chemical shifts of the protons of the heterocyclic ring of chromone (Figure 9) are very similar to those of coumarin and pyran-4-one. They are largely unaffected by benzannulation, implying little or no aromaticity in the hetero-ring. However, the proximity of the carbonyl group to the

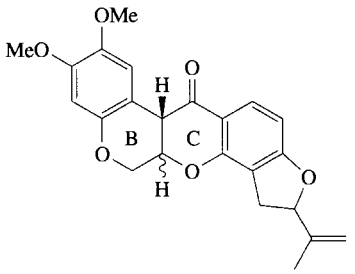
fused aromatic ring results in downfield shifts of all the aromatic protons relative to those in coumarin. This effect is greatest at C(5) and is sufficiently strong to separate the signal for H(5) from those of the other aromatic protons. A detailed study of the ^{1}H NMR spectrum of chromone has shown that the chemical shifts agree well with those predicted from electron density calculations ⟨64SA871⟩. The location of substituents in chromone can often be determined from NMR spectra, and this technique has been used in the elucidation of the structures of naturally occurring chromones ⟨92TL5977, 93JCS(P1)1153, 93TL419, 94TL4693⟩. Data for 2-methyl-2-chromen-4-thione is available ⟨83PS(14)139⟩. Derivatives of chromone for which ^{1}H NMR data are available include 2-styryl-chromones ⟨95JCR(S)58⟩ and their various Diels–Alder adducts ⟨92JCR(S)248⟩, some heterodiene adducts of 3-acylchromones ⟨94T11755⟩ and mould metabolites ⟨83JCS(P1)1365⟩.

The ^{1}H NMR spectral parameters of chroman-4-one are given in Figure 9. The methylene groups appear as triplets at δ 2.8 (3-CH_2) and δ 4.55 (2-CH_2) ⟨68JHC133⟩. The commonly encountered 2,2-dimethylchroman-4-one system possesses a much simplified spectrum, the signals for both the *gem*-dimethyl and the 3-methylene units appearing as singlets at about 1.6 ppm and 2.7 ppm respectively. In 3-substituted chroman-4-ones, a halogen atom is axial in the predominant conformation ⟨68JHC745⟩, whereas a methyl group is equatorially disposed ⟨73BCJ1839⟩. In 3,3-dichloro-2,2-dimethylchroman-4-one, the *gem*-dimethyl signal is broad at room temperature but becomes a sharp singlet at 50°C. Conversely, at −20°C two separate signals are observed corresponding to the pseudo-axial and equatorial methyl groups. It appears that the halogen atoms slow the ring inversion appreciably ⟨94T5245⟩.

Solvent-induced shifts in flavanones vary significantly with the solvent and with the basicity of the oxygen atoms in the substrate. Thus, trifluoroacetic acid induces downfield shifts, but benzene upfield shifts of acetoxy, methoxy, aromatic, and hetero-ring protons ⟨94IJC17⟩. Benzene-induced shifts can help to differentiate linear and angular chromenoflavones ⟨90MI 507-01⟩. Methods available for the determination of flavanone structures have been surveyed ⟨B-89MI 507-01⟩.

The application of ^{1}H NMR spectroscopy to flavonoids and their glycosides has been reviewed. Much information is tabulated and typical spectra are presented ⟨B-94MI 507-01⟩.

The coupling constant for the 6a, 12a protons in rotenoids (**82**) is much larger (around 12 Hz) for the *trans*-isomer than for the *cis*-B/C ring fused compound (about 4 Hz) ⟨93JCS(P1)2605⟩. The chemical shift of H(1) in 12a-hydroxyrotenoids is diagnostic for the mode of ring fusion; the *trans*-system is deshielded (δ 7.6 to 8.0) relative to the *cis*-structure (δ 6.4 to 6.8) ⟨62JCS775⟩. Complete assignments of both ^{1}H and ^{13}C resonances in rotenone (**82**) have been published ⟨88JHC351⟩.



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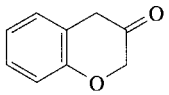


(83)

Chroman-3-one (**83**) shows singlets for 2-CH_2 (δ 4.32) and 4-CH_2 (δ 3.51) and, unlike the 4-one, the H(5) signal is no longer separated from the other aromatic protons ⟨70JHC197, 81JHC1123⟩.

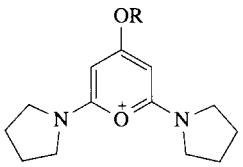
The spectrum of xanthone reveals deshielding of H(1) and H(8) by the carbonyl group ⟨65T1833⟩. A complete analysis of the spectra of xanthone and some oxygenated analogs has been carried out ⟨70JCS(B)603⟩. Both aromatic solvent-induced shifts and lanthanide shift reagents have been useful in structural elucidation of xanthones ⟨72JCS(P1)1382, 75JCS(P1)1563⟩. Xanthydrols incorporating crown ethers through 1- and 8- hydroxy functions show downfield shifts of all the ^{1}H resonances when trifluoroacetic acid is added to their solution in $CDCl_3$. The resulting solutions are considered to contain a carbocationic species ⟨95JCS(P2)697⟩.

(iii) Pyrylium salts

In the pyrylium cation, all the protons are strongly deshielded, with H(2) furthest downfield and H(3) the least deshielded ⟨73OMR(5)251⟩. Partial ^{1}H spectral parameters for pyrylium, benzopyrylium,

and xanthylium salts are shown in Figure 9. The nature of the anion has little effect on the chemical shift of the ring protons.

Strongly electron-releasing groups at the 2-, 4- and 6-positions exert a profound effect not only on the chemical shift of H(3) and H(5), which are moved upfield by 2–3 ppm, but also on the electronic structure of the pyrylium salts (**84**). It is proposed that such compounds are better described as bridged pentamethine cyanines (**85**) ⟨88MRC707⟩.



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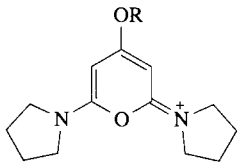


(85)

In a similar manner, the trimethine cyanine structure is dominant for 2,4-diaminopyrylium salts ⟨87MRC688⟩. The 2-amino group in 2,7-diaminobenzopyrylium salts is likewise involved in delocalization of the positive charge, with a shortening of the C(2)—N bond, and evidence for *E*- and *Z*-isomers of the iminocoumarin structure is obtained when the ^{1}H NMR spectrum is recorded at −60°C ⟨89CHE621⟩.

Proton NMR data is available for various 3,5- and 5,6-bridged pyrylium salts ⟨90RRC415, 92RRC141⟩.

5.07.3.4.2 ^{13}C NMR spectra

(i) Pyrans, their benzologs and reduced derivatives

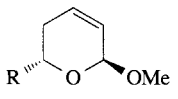
As part of an investigation into the valence isomerism between 2,4-dienones and 2*H*-pyrans, the ^{13}C spectra of several 2*H*-pyran-4-ylphosphonates (**65**) have been recorded. The sp^3 hybridized C(2) resonates at about 71 ppm and the trigonal C(6) at δ 153–159. In both cases, coupling to phosphorus, $^3J_{PC}$, is between 12 and 16 Hz. In the dienone, the carbonyl carbon atom resonates in the range δ 190–200, some 40 ppm downfield of C(6) in the pyran ⟨85CB2917⟩.

Although the assignment of the signals to C(3) and C(4) is uncertain, the chemical shifts for 2,2-di-*t*-butyl-6-methyl-2*H*-pyran are given in Figure 10. The ring carbon atoms of 2-amino-2*H*-pyrans ⟨89IZV1323⟩ are shielded relative to the corresponding 2-methoxy compounds ⟨91CB1425⟩ and in 4-phenyl-2*H*-pyrans C(1)′ is deshielded, in accord with the non-aromatic nature of these pyrans ⟨81CS(18)256⟩. Spectral parameters for a 2*H*-1-benzopyran are given in Figure 10, and other data are available ⟨92JCS(P1)573⟩.

The ^{13}C spectra of 6-methoxy-3,6-dihydro-2*H*-pyran and some 2-substituted derivatives (**86**) have been recorded ⟨74MI 507-02⟩. The carbon atoms of the double bond resonate between 126 ppm and 130 ppm, with the signal for C(5) downfield of that for C(4). The proximity of the heteroatom ensures that C(2) and C(6) appear downfield of C(3) and the methoxy group deshields C(6) still more. The signals for C(2) and C(6) of the *trans*-isomer (**86**) occur at higher field than those for the *cis*-isomer (**87**). Configurational assignments for 3,6-dihydro-2*H*-pyrans have been made from the magnitude of the geminal ^{13}C–H coupling constants ⟨73TL1037⟩ and from the sensitivity of the chemical shift to steric hindrance ⟨B-72MI 507-03⟩.

Data for 3,4-dihydro-2*H*-pyrans is given in Figure 10. The dimer (**88**) of pinocarvone, obtained from the SeO_2 oxidation of (1*S*)-(−)-β-pinene, is effectively a 3,4-dihydro-2*H*-pyran, and the chemical shifts are similar to those of the parent compound ⟨93JCS(P2)437⟩.

^{13}C Signals for some 4-aryliminopyrans (**89**) and their salts (**91**) have been assigned. The large downfield shifts of C(2), C(4), and C(6) observed in more polar solvents are indicative of an increase in the positive character of these atoms and are attributed to significant contributions from resonance structures (**90**) and (**92**) ⟨81JCS(P2)303, 81JCR(S)200⟩.



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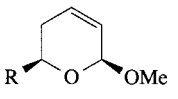

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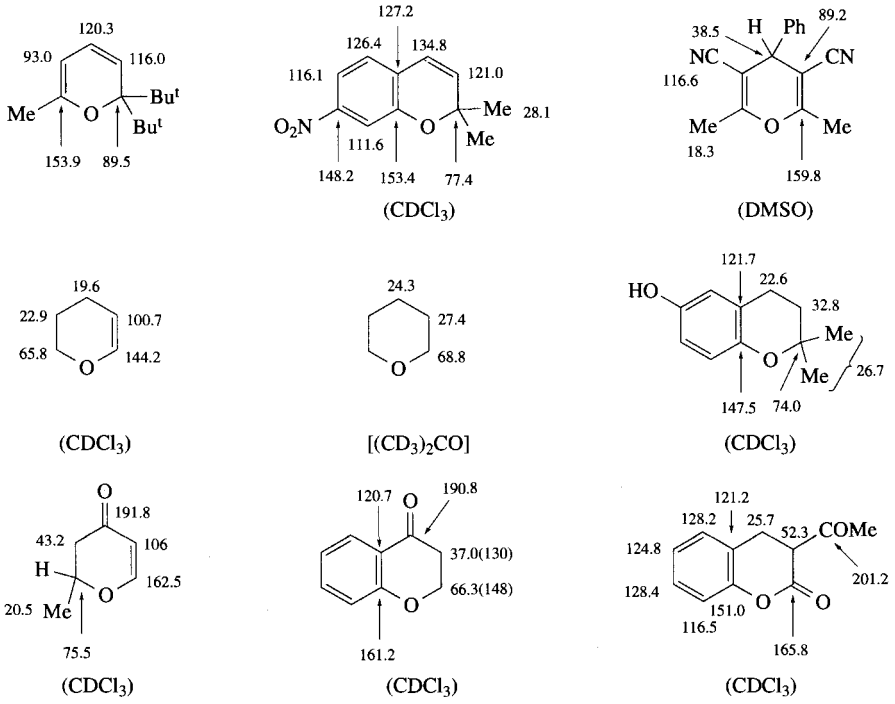
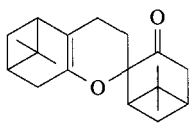


Figure 10 ^{13}C NMR spectra of representative pyrans and fused pyrans ⟨74OMR(6)233, 76T229, 78T433, 79JST(56)87, 82JOC3649, 85JST(127)127, 85MRC793, 91CB2633, 92JCS(P1)573⟩.



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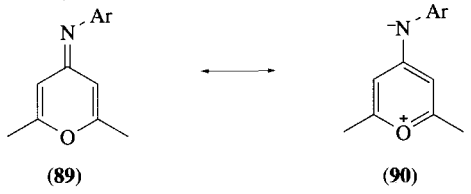
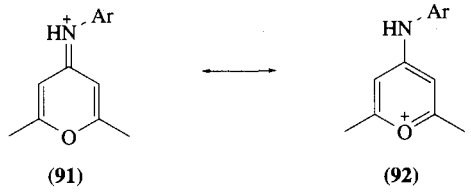


(89) **(90)**



(91) **(92)**

Spectral data for 3,5-dicyano-2,6-dimethyl-4-phenyl-4*H*-pyran are given in Figure 10, and those for a range of 2-amino-4*H*-pyrans have been recorded ⟨85MRC793⟩. The combined influence of a 3-cyano function, the 2-amino group and the heteroatom brings about an upfield shift of C(3) to 50–60 ppm, a remarkable shift for an alkenic carbon atom. Data are also available for other highly substituted 4*H*-pyrans ⟨85LA1987, 92CCC546, 92JCS(P2)1301⟩ and for some partially reduced 2-amino-3-cyano-4*H*-chromenes ⟨95JCR(S)178⟩. Figure 11 shows the ^{13}C resonances for some dioxapyrenes and 1,6-dioxabenzo[*a*]pyrene derived by the use of inverse δ^{13}C–δ^1H 2D correlations ⟨95JHC17⟩.

The influence of the heteroatom on the ^{13}C chemical shifts of tetrahydropyran (Figure 10) can be assessed by comparison with that of cyclohexane (δ 27.7), since both molecules adopt a chair

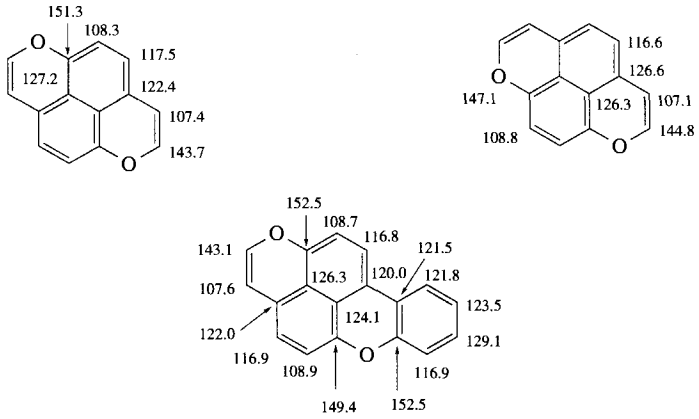
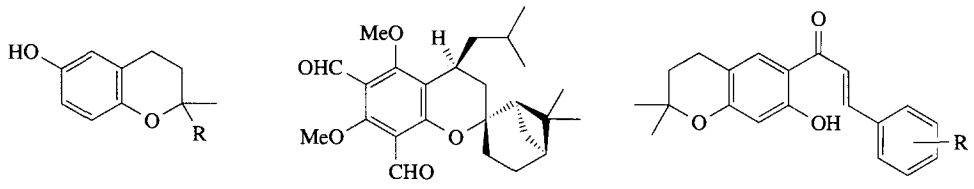


Figure 11 ^{13}C chemical shift data (ppm) for some dioxapyrenes ($CDCl_3$).

conformation. A pronounced deshielding of C(2) is observed together with a small upfield shift of C(4); C(3) is virtually unaffected ⟨74OMR(6)233⟩. Electron-withdrawing substituents at the 2-position deshield C(2) by about 30 ppm and C(3) by about 4 ppm, but cause upfield shifts of C(4), C(5), and C(6). A comparatively large shielding of C(4) indicates a preference of the 2-substituent for the axial position. ^{13}C Chemical shift differences have also been used to assign the configuration of a 4-amino substituent; an axial NH_2 group exerts a shielding of about 4–5 ppm ⟨80JOC4352⟩. Carbon-13 data for various 2- and 2,6-disubstituted derivatives of tetrahydropyran have been reported and analyzed to assist in stereochemical assignments ⟨82JA3635, 83OMR(21)94, 87T4699, 90JCS(P1)1717⟩.

The ^{13}C spectra of chromans (Figure 10) resemble those of 3,4-dihydro-2*H*-pyrans insofar as deshielding increases in the sequence C(4), C(3) and C(2), and C(8a) is downfield of C(4a). The spectra of 6-hydroxy-2,2-dimethylchroman (**93**; R = Me) have been thoroughly investigated because they serve as model compounds for the tocopherols (**93**; R = phytyl) ⟨76T229⟩. The ^{13}C spectrum of (2*R*, 4′*R*, 8′*R*)-α-tocopherol has been completely assigned ⟨89JOC560⟩.

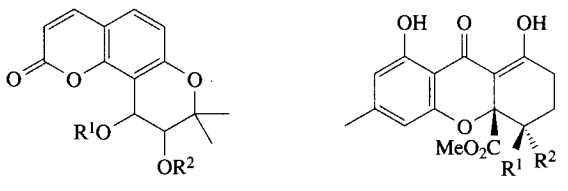
In the robustadial (**94**), the pyran ring resonances are at δ 118.8 (C(4a)), 163.5 (C(8a)), 85.7 (C(2)), 39.3 (C(3)), and 27.1 (C(4)) in $CDCl_3$ ⟨88JOC4562⟩, and similar data were obtained for a range of dihydrobenzopyran derivatives (**95**) ⟨92MRC560⟩.



(**93**) (**94**) (**95**)

A pseudo-axial orientation is indicated by ^{13}C NMR for the hydroxy group in chroman-4-ol and *trans*-2-methylchroman-4-ol. The *cis*-isomer has a pseudo-equatorial hydroxy group, and the resonances for C(2), C(3), and C(4) are at lower field than those of the *trans*-compound ⟨77JCS(P1)217⟩.

The relative configurations at the chiral centers in the chroman unit of some khellactones (**96**) have been established using ^{13}C chemical shift differences of the *gem*-dimethyl function. The $\Delta\delta(Me_2)$ is greater than 3 ppm for the *cis* isomer but smaller than 2 ppm for the *trans* compound ⟨89MRC653⟩.



(**96**) (**97**)

In isochroman, both carbon atoms adjacent to the heteroatom are shifted downfield, appearing at δ 67.9 (C(1)) and 65.3 (C(3)). The C(4) is marginally downfield (28.5 ppm) of the corresponding atom in chroman (22.6 ppm) ⟨85MRC754⟩.

(ii) Pyranones, their benzologs and reduced derivatives

Carbon-13 spectral data for a selection of pyran-2-ones and pyran-4-ones have been tabulated ⟨84CHEC-I(3)573⟩. Generally, in pyran-2-ones signals for C(4) and C(6) occur downfield of those for C(3) and C(5) in accord with the localization of positive charge at the former positions (Figure 12). An analysis of all of the C–H couplings has been reported ⟨75CJC1980⟩.

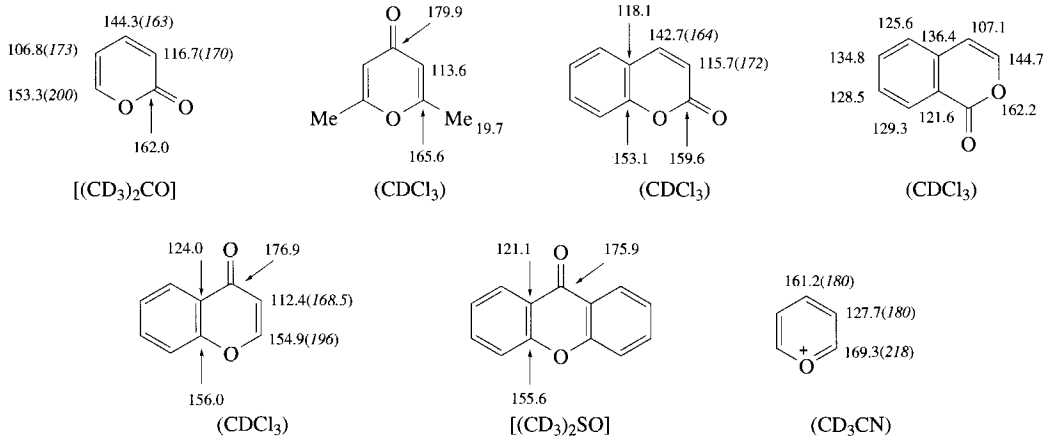


Figure 12 ^{13}C NMR spectra in ppm (Hz) of representative pyranones and pyrylium ⟨74JOC1935, 75JOC1175, 76CJC280, 76JOC2777, 77OMR(9)16, 79JST(56)87, 79T2035, 85SA(A)913⟩.

In pyran-4-ones, C(2) and C(6) resonate downfield of C(3) and C(5), whilst the signal for C(4) is furthest downfield (Figure 12). Coupling constants for pyran-4-ones are readily derived. The C(2) shows a $^1J_{CH}$ value of about 200 Hz, characteristic of a carbon atom bonded to an oxygen heteroatom, whilst the value for C(3) is smaller (around 165 Hz). Long-range couplings have also been obtained ⟨80OMR(13)244⟩.

The chemical shifts and coupling constants for coumarin are given in Figure 12, from which it can be seen that the shifts for C(2), C(3) and C(4) correspond closely to those for pyran-2-one. Good correlations have been noted between chemical shifts and charge densities ⟨75JOC1175⟩ and between δ values and Hammett constants for coumarins and 6- and 7-substituted derivatives ⟨79JCS(P2)435⟩. Carbon-13 data for many substituted coumarins have been published ⟨88MRC430, 89MRC705, 89MRC892, 89MRC1181, 90MI 507-02, 90MRC732⟩. Earlier assignments to spectral data for methoxycoumarins have been revised, the value of *peri*-proximity effects being highlighted ⟨89MRC348⟩. The ^{13}C chemical shifts of 4-arylcoumarins are solvent dependent, and the proximity of signals from quaternary carbon atoms can lead to errors in assignment, though 2D heteronuclear correlation spectroscopy (HETCOR) can resolve the problem ⟨87CPB3909, 89MRC1181⟩. The ^{13}C spectra of some 3,4-fused pyranocoumarins and furocoumarins have been recorded ⟨91MRC631, 94SA(A)161⟩.

The influence of a hydroxy or a methoxy group on the ^{13}C spectra of coumarins is to shift the signal from the substituted carbon downfield by about 30 ppm, but to cause upfield shifts for the carbon atoms *ortho* and *para* to the substituent ⟨75T2719⟩. Structure elucidation is also assisted by general observations about coupling constants. Thus, $^1J_{CH}$ for C(3) is often greater than the other $^1J_{CH}$ values. Typically, $^2J_{CH}$ values are no larger than 4 Hz, three-bond coupling constants are in the range 4–10 Hz, and $^4J_{CH}$ values are less than 2 Hz.

The ^{13}C spectra of a range of isocoumarins have been published; data for the parent compound are given in Figure 12 ⟨85SA(A)913⟩.

The similarity of the chemical shifts between the heterocyclic ring carbon atoms of chromone and pyran-4-one is apparent from Figure 12. Several general features can be recognized in the ^{13}C spectra of chromones. The lower field signal associated with the carbonyl carbon atom is essentially unaffected by substitution in the system. The signal from C(2) is always at lower field and that from

C(3) is usually at higher field than all other C–H signals, though substitution at these sites can markedly influence these resonances ⟨79JST(56)87, 94CCC1673⟩. The signals associated with the benzenoid ring carbon atoms are not influenced to any significant extent by substituents in the heterocyclic ring. Similarly, the pyranone ring carbon shifts are insensitive to substituents at C(6) and C(7). The resonances of the ring junction carbon atoms (C(4a) and C(8a)) are largely unaffected by substitution in either ring ⟨81JCS(P1)2557⟩. The values of $^{1}J_{CH}$ couplings for C(2) and C(3) correspond to those observed for pyran-4-one. Two-bond couplings for these atoms are typically 6–7 Hz, whilst $^{3}J_{CH}$ couplings of 9 Hz have been observed for C(8a) and of 4–5 Hz for C(4a) ⟨79JST(56)87⟩.

Other references to ^{13}C spectral data for chromones and related compounds are available ⟨91H(32)1563, 92TL5977, 93TL419, 94TL4693, 95JCR(S)58⟩, and a comparison of the ^{13}C resonances in coumarins, chromones and chroman-4-ones and their S, Se, and Te analogs has been published ⟨83SA(A)693⟩.

The application of ^{13}C NMR spectroscopy to flavonoid chemistry has been discussed ⟨B-89MI 507-02, 93MRC418, 93MRC518, 94H(38)1287⟩.

The spectra of xanthones are characterized by the low-field carbonyl carbon resonance (Figure 12), which is largely unaffected by substituents. However, hydrogen bonding to a 1-hydroxy group deshields the C(9) resonance still further. The carbonyl signal is at about 172 ppm and the saturated carbon atoms resonate in the region 30–45 ppm in some substituted 1,2,3,4-tetrahydroxanthones ⟨92JCR(S)248⟩. The α- and β-diversonolic esters (**97**; $R^1 = OH$, $R^2 = H$ and $R^1 = H$, $R^2 = OH$), metabolites of *Penicillium diversum*, possess the 2,3,4,4a-tetrahydroxanthene structure. Significant downfield signals are shown by C(8) (160 ppm), C(1)(*ca.* 167 ppm), and C(9)(181 ppm). Most of the ^{13}C resonances are influenced by the addition of D_2O, which facilitated the structure elucidation ⟨83JCS(P1)1365⟩. The ^{13}C NMR spectrum of the fungal pigment beticolin which contains the same heterocyclic nucleus has been analyzed ⟨93JCS(P1)145⟩.

Much of the interest in xanthone centers on the naturally occurring polysubstituted derivatives ⟨89P599, 91TL4737, 93H(36)1359, 93JOC6565, 93TL8251⟩. Studies of substituent effects on the spectra of xanthones have culminated in a set of additivity rules and a computer program to allow the identification of polyhydroxyxanthones ⟨80T3273⟩.

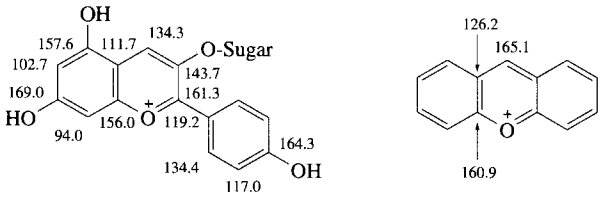
Spectral data for a 3,4-dihydrocoumarin are given in Figure 10. The resonances for C(3) and C(4) show typical aliphatic shifts ⟨85MI 507-01⟩.

The ^{13}C spectra of chroman-4-ones are similar to those of chromones, except that the shifts for C(2) and C(3) occur at much higher field as expected of methylene carbon atoms (Figure 10). The heteroatom shields the γ-carbon atom so that the signal for C(4) is upfield of that in the homocyclic analog, 1-tetralone. The $^{1}J_{CH}$ coupling for C(2) is large, in keeping with the proximity of the heteroatom ⟨79JST(56)87⟩. Rotenoids contain a chroman-4-one nucleus, and ^{13}C data on these systems are available ⟨88JHC351, 93CPB187, 93JCS(P1)2591, 93JCS(P1)2605⟩.

(iii) Pyrylium salts

The chemical shifts of C(2), C(4) and C(6) of pyrylium salts are amongst the lowest reported for six-membered rings with a single heteroatom and arise from the severe perturbation of the π-cloud brought about by the positively charged oxygen atom (Figure 12) ⟨77OMR(9)16⟩. Alkyl substituents shift the pyrylium ring carbon signals further downfield, although correlation of the shifts with calculated charge densities is lost. Aryl substituents at the 2-, 4-, and 6- positions interact with the pyrylium system and the response is a deshielding of the 2′-, 4′-, and 6′- resonances. Spectral data for a range of 2- and 2,6- tertiary amino substituted pyrylium salts has been published ⟨88MRC707⟩.

Carbon-13 data for the anthocyanidin nucleus of an anthocyanin and the xanthylium cation are shown in Figure 13.



(DMSO-d_6/HCl) (CF_3CO_2H)

Figure 13 ^{13}C chemical shift data (ppm) for benzologs of the pyrylium cation ⟨75BSF2023, 88ACS462⟩.

5.07.3.4.3 ^{17}O NMR spectra

Whilst ^{17}O NMR spectroscopy is never likely to provide the amount of structural information which ^{1}H and ^{13}C NMR offer, its application to oxygen heterocycles can yield detailed information about inter- and intramolecular influences ⟨B-91MI 507-02⟩.

The ^{17}O shift of tetrahydropyran is quoted as 5.0 ppm ⟨80T2793⟩ and 8.8 ppm for the neat liquid ⟨79TL3649⟩, a small downfield shift relative to its acyclic analog, ethoxypropane (δ 1.5). A methyl group in the 2-position exerts a deshielding effect of about 25 ppm, whilst 3- and 4-methyl substituents have negligible influence (Figure 14). A similar deshielding is noted for a 2-OCH_3 group, though the orientation of the substituent is important. An equatorially disposed methoxy function exerts a 10–14 ppm greater effect than an axial substituent (Figure 15) ⟨81JOC4948⟩.

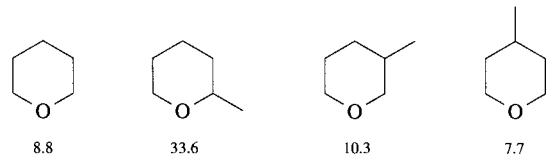


Figure 14 ^{17}O NMR spectra (ppm) for some tetrahydropyrans.

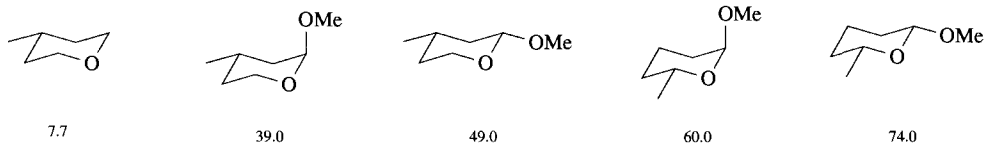


Figure 15 ^{17}O NMR spectra (ppm) for some disubstituted tetrahydropyrans.

The ring heteroatom in pyran-2-one resonates at 245.6 ppm and is little influenced by methyl, methoxy, and methoxycarbonyl substituents. The shift of the exocyclic oxygen atom (333.3 ppm) indicates appreciable single-bond character for the carbonyl group, implying interaction with the lone-pair electrons of O(1). Saturation of the pyranone ring brings about upfield shifts of the endocyclic oxygen (Figure 16) which ultimately resonates at 166.5 ppm in tetrahydropyran-2-one ⟨89H(29)301⟩. Benzannulation also causes an upfield shift of the heteroatom signal, which in coumarin absorbs at 217.6 ppm, with a further shift to 204 ppm in dihydrocoumarin. Methyl and methoxy substitution in the aromatic ring of coumarin have only a minor deshielding effect (Figure 17) ⟨87MRC489⟩.

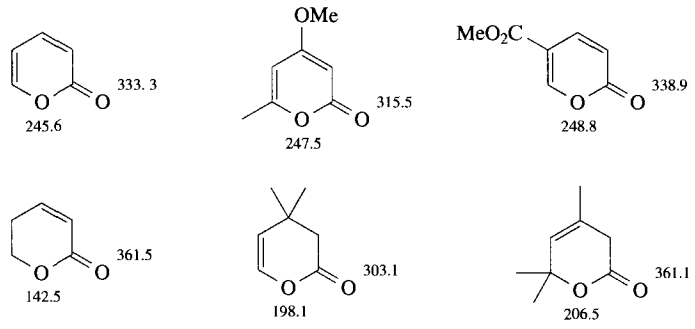


Figure 16 ^{17}O NMR spectra (ppm) for some pyran-2-ones (CH_3CN).

Related effects are seen in the pyran-4-one system. The ring heteroatom in the parent compound resonates at 174.2 ppm, considerably upfield of the 2-isomer, whilst the carbonyl resonance is downfield (463.6 ppm), indicating reduced interaction between the two oxygen atoms. Tetrahydropyran-4-one resonates at 10.3 ppm, vastly different from the 2-isomer and reflecting the insulation of the ring heteroatom from the carbonyl group. Similarly, $\delta_{C=O}$ (560.4 ppm) is not significantly different from that for cyclohexanone (557.1 ppm). The *cis*-2,6-diphenyl groups shift the heteroatom signal to 49.9 ppm, somewhat greater than the effect of *trans*-disubstitution (δ 45.9), but the influence on the carbonyl resonance is reversed (δ 563.7 and δ 568.1, respectively). The

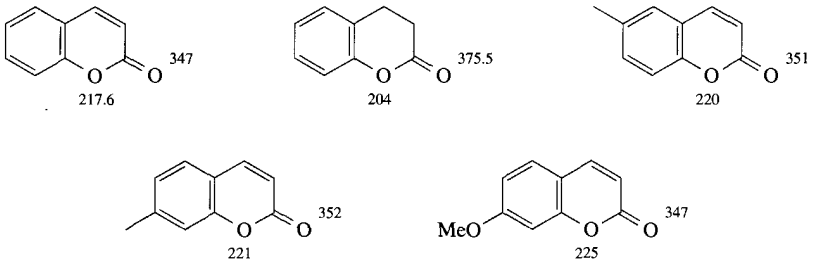


Figure 17 ^{17}O NMR spectra (ppm) for some coumarins.

response to additional methyl substitution at the 3- and 5-positions in *cis*-2,6-diaryltetrahydropyran-4-ones is a downfield shift of O(1) and an upfield shift for C=O (Figure 18) ⟨89JOC4758⟩.

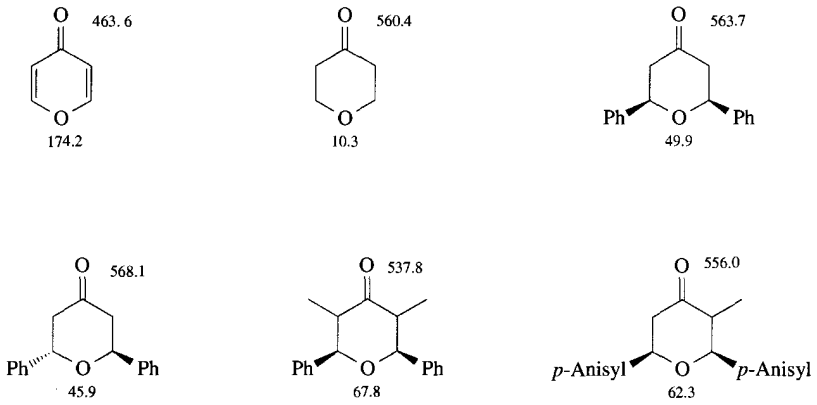


Figure 18 ^{17}O NMR spectra (ppm) for some pyran-4-ones.

Benzannulation brings about an upfield shift of about 20 ppm, and a second ring fusion causes a further 20 ppm such that the heteroatom in xanthone resonates at 137.2 ppm (Figure 19) ⟨84OMR757⟩. Significant upfield shifts are observed on saturation of the 2,3-double bond, exemplified by the data for chromone (δ 162) and chroman-4-one (δ 70) in chloroform ⟨89MRC170⟩. In general, variations in chemical shift of the order of 2–4 ppm occur on change of solvent from toluene to chloroform or acetonitrile ⟨87JHC365, 89MRC170⟩.

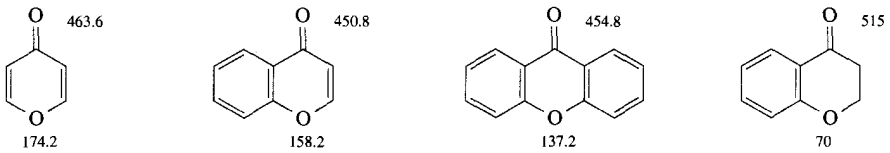


Figure 19 ^{17}O NMR spectra (ppm) for benzologs of pyran-4-one.

Introduction of a 2-phenyl group into chromone has a marginal effect, and O(1) in flavone resonates at δ 160, but it causes a downfield shift of 23 ppm in chroman-4-one. A greater shift is observed in 2,2-dimethylchroman-4-one (δ 117), the effects of the β-methyl groups being additive. Substituents in the aromatic ring of the chromanone have a minor effect on O(1) ⟨89MRC170⟩, but a 5-methyl group shifts the carbonyl resonance downfield by 25 ppm, attributed to van der Waals repulsion rather than to changes in the torsion angle (Figure 20) ⟨90JOC425⟩. The effects of methoxy substituents in the 2-phenyl ring of flavones have been addressed ⟨90MRC557⟩.

Oxygen-17 NMR spectroscopy provides a valuable means of distinguishing between coumarins and chromones, compounds which may be formed together during synthesis. Not only are the chemical shifts different for both the endo- and exocyclic oxygen atoms, but the separation of the two signals is also quite distinctive, being of the order of 130 ppm for coumarins, but about 280 ppm for chromones ⟨93CPB211⟩.

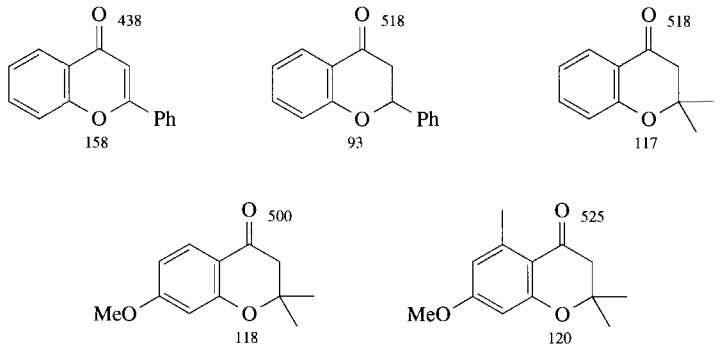
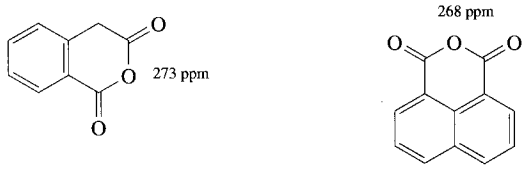


Figure 20 ^{17}O NMR spectra (ppm) for some chroman-4-ones and flavone.

The chemical shifts of the ring heteroatoms in the diones (**98**) and (**99**) are very similar to that of acetic anhydride (273 ppm), indicating interaction with the carbonyl function rather than with the ring system.



(**98**) (**99**)

The variation in chemical shift of the heteroatom in xanthene which occurs on replacement of the 4-methylene unit by a carbonyl group has been attributed to a combination of the electronic effect of the new function and the ensuing changes in the dihedral angle between the planes of the two aromatic rings. The introduction of a second heteroatom further illustrates this point (Figure 21) ⟨87JHC365⟩.

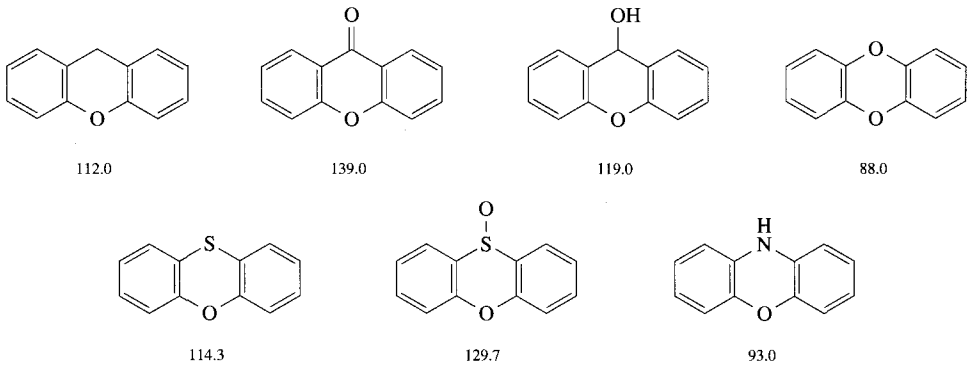


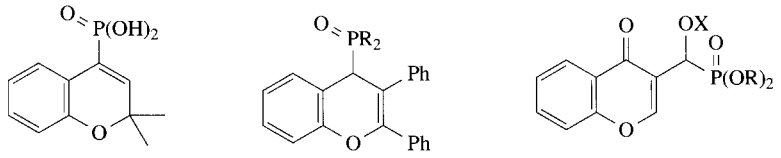
Figure 21 ^{17}O NMR spectra (ppm) for xanthene and some related compounds.

5.07.3.4.4 Other nuclei

Phosphorus-31 NMR spectra have been recorded for pyrans and benzopyrans in which a phosphorus-containing substituent is attached to the heterocycle directly through phosphorus and for those where the substituent is bonded through an intermediate carbon atom.

The 2*H*-1-benzopyran-4-phosphonic acid (**100**), isolated from the reaction of a chroman-4-one with PBr_3, exhibits a ^{31}P signal at 15.1 ppm and H(3) appears as a doublet with $^3J_{PH} = 20.2$ Hz ⟨94T2507⟩.

Both 2- and 3-phenylbenzopyrylium chlorides are attacked at the 4-position by triethyl phosphite and diphenylphosphinic acid esters to yield the *P*-substituted 4*H*-1-benzopyrans (**101**). When R = OEt, the ^{31}P signal is around 21 ppm but is shifted downfield to about 30 ppm when R = Ph. In the former compounds, $^1J_{PC}$ is 144 Hz, but is about 67 Hz in the diphenyl derivatives ⟨93PS(84)129⟩.



(100) (101) (102)

In the isomeric 2- and 4-oxobenzopyran-3-phosphonates, the ^{31}P signal is between 5.1 ppm and 21.8 ppm for the coumarin ⟨85JHC1713, 91TL5341⟩ and 14.8 to 17.3 ppm in the chromone ⟨92PS(71)67⟩. In the former compound, $^{3}J_{PH}$ is 16 Hz and about 11 Hz in the latter.

The phosphonates (**102**; X = H or R) derived from 3-formylchromone by treatment with dialkyl phosphonates and trialkyl phosphites respectively, exhibit a ^{31}P signal between 22 ppm and 28 ppm, with coupling constants of $^{1}J_{PH} = 22$ Hz, $^{3}J_{PH} = 13.5$ Hz and $^{4}J_{PH} = 4.5$ Hz ⟨91PS(61)83⟩.

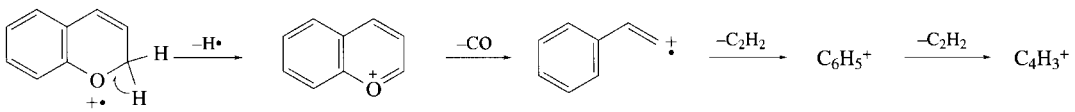
Fluorine-19 NMR spectra have been reported for 2-trifluoroprenyl analogs of vitamin E ⟨88CPB2950⟩ and for several tetrafluorochromones ⟨93JFC37⟩.

5.07.3.5 Mass Spectrometry

Several reviews provide coverage of the mass spectra of oxygen heterocycles. The most important of these ⟨B-71MI 507-01⟩ has now been revised and expanded to include all the significant work in this area up to 1981 ⟨B-85MI 507-02⟩. Specialized reviews deal with chromans ⟨B-74MI 507-02⟩ and flavonoids ⟨B75MI 507-02, B-80MI 507-02⟩. Since the publication of CHEC-I in 1984, there have been relatively few new studies in this field.

5.07.3.5.1 Pyrans, their benzologs and reduced derivatives

The small amount of work on the mass spectra of 2*H*-pyrans relates to a hexasubstituted derivative, which fragments to generate pyrylium and oxepin cations ⟨81CCC748⟩. The benzolog, 2*H*-chromene (**4**) and its derivatives have received considerable attention. Generally the fragmentation of chromenes proceeds by loss of one of the C(2) substituents from the molecular ion as shown in Scheme 2 for 2*H*-chromene itself. Initial elimination of a hydrogen radical from $[M]^{+\cdot}$ leads to the benzopyrylium ion (**4a**), which appears at *m/z* 131 as the base peak. The fragmentation of 2-methyl-2*H*-chromene involves α-cleavage of a methyl radical, leading again to the benzopyrylium ion (**4a**). In a similar fashion, 2,2-dimethylchromenes afford a 2-methylbenzopyrylium ion as the base peak ⟨84CHEC-I(3)573⟩.



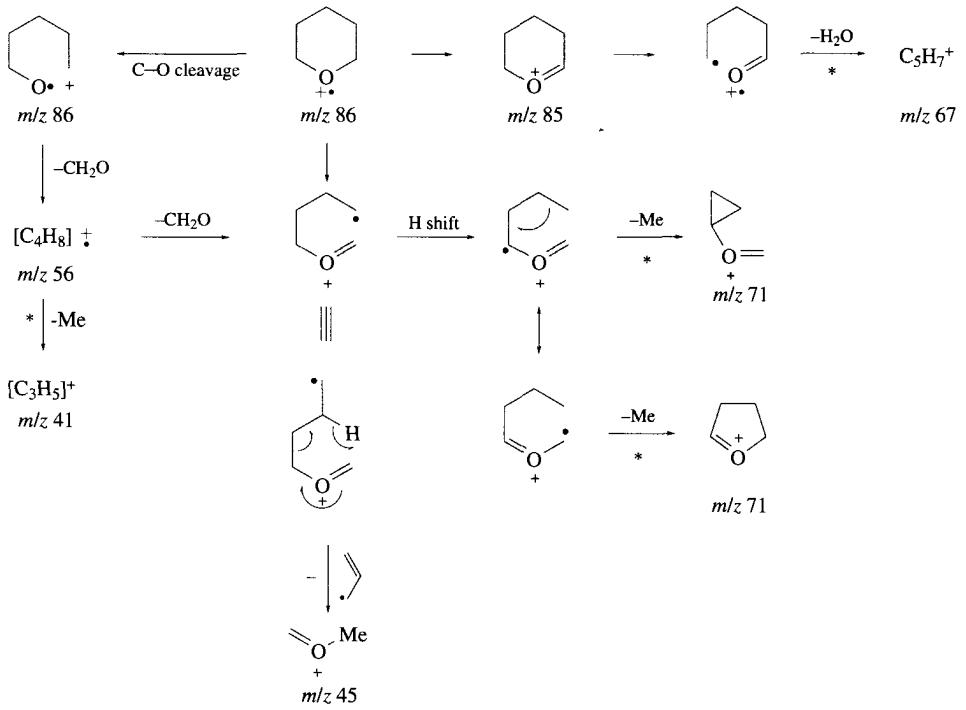
(**4**) *m/z* 132 (**4a**) *m/z* 131 (100%) *m/z* 103 (8%) *m/z* 77 *m/z* 51

Scheme 2

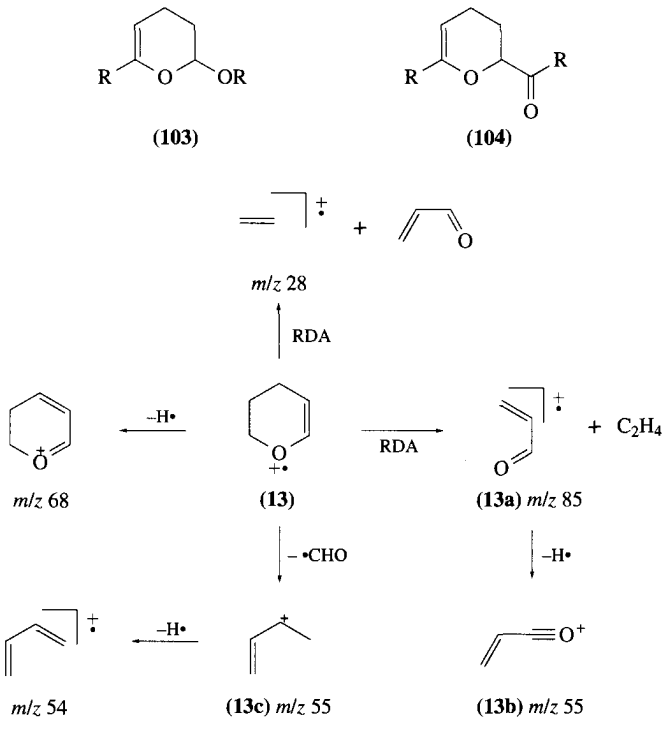
Mass spectral data of 4*H*-pyrans is sparse but suggests the facile generation of a pyrylium species ⟨83CCC3123, 87MI 507-01⟩. Similarly, the dibenzolog 9*H*-xanthene (**8**) loses a hydrogen radical from the molecular ion to give the stable xanthylium ion. Subsequent fragmentation yields a species *m/z* 152 by elimination of a CHO radical. However, a study of xanthene-9-d_2 suggested that the xanthylium structure for the $[M\text{-}1]^{+}$ fragment may be inappropriate, and a sequence involving the participation of two pyrylium ions has been proposed ⟨69OMS(2)829⟩.

The fragmentation pathways for tetrahydropyran, elucidated by deuterium labeling and measurements of metastable ion transitions, are shown in Scheme 3 ⟨68OMS(1)403⟩. Surface ionization mass spectrometry indicates that tetrahydropyran forms a stable ion, $[M\text{-}5H]^{+}$, which is presumably aromatized ⟨91MI 507-03⟩. 2-Alkyl- and 2-alkoxy-tetrahydropyrans fragment by α-cleavage of the substituent from $[M]^{+}$, leading to the base peak at *m/z* 85 ⟨68JOC2266⟩. The fragmentation of 3-hydroxytetrahydropyrans involves loss of a CH_2OH radical derived from the 3-OH and 2-methylene groups and leads to an $[M\text{-}CH_2OH]^{+}$ ion (*m/z* 71) ⟨72T1881⟩.

The EI mass spectral fragmentation of 3,4-dihydropyran (**13**) parallels that of cyclohexene, decomposition of the molecular ion proceeding by the routes shown in Scheme 4 ⟨65T1885⟩. Retro-Diels–Alder (RDA) cleavage follows two pathways, leading to the loss of either propenal or ethene.



Scheme 3

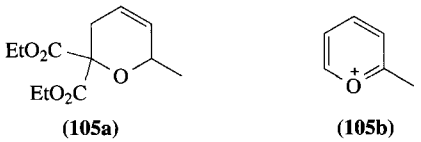


Scheme 4

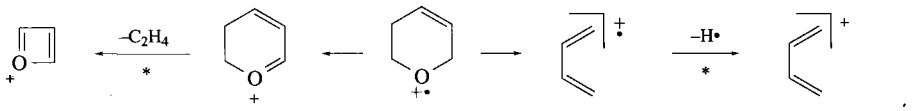
The fragmentation of 2-substituted dihydropyrans is dependent on the nature of the substituent. Thus 2-alkoxy derivatives (**103**) decompose by both α-cleavage and RDA fission, yielding an oxonium ion and a vinyl ether fragment, respectively. However, for the 2-carbonyl derivatives (**104**; R = Me, OMe, etc.), the RDA pathway is completely suppressed ⟨82OMS(17)327⟩.

3,6-Dihydro-2*H*-pyran (**14**) fragments by RDA cleavage with charge retention on the diene

fragment (**14a**). The alternative loss of H· from $[M]^{+}$· produces the oxonium ion (**14b**) which subsequently eliminates ethene to give (**14c**) (Scheme 5) ⟨70IZV1184⟩. Substituents can alter the course of fragmentation, and the *gem* diester (**105a**) affords the pyrylium species (**105b**) by sequential loss of CO_2Et, CO and ethanol ⟨72CJC1539⟩.



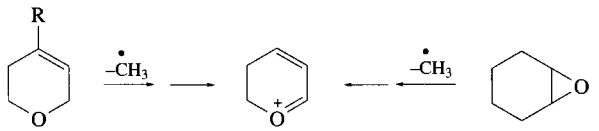
(**105a**) (**105b**)



(**14c**) *m/z* 55 (**14b**) *m/z* 83 (**14**) *m/z* 84 (**14a**) *m/z* 54

Scheme 5

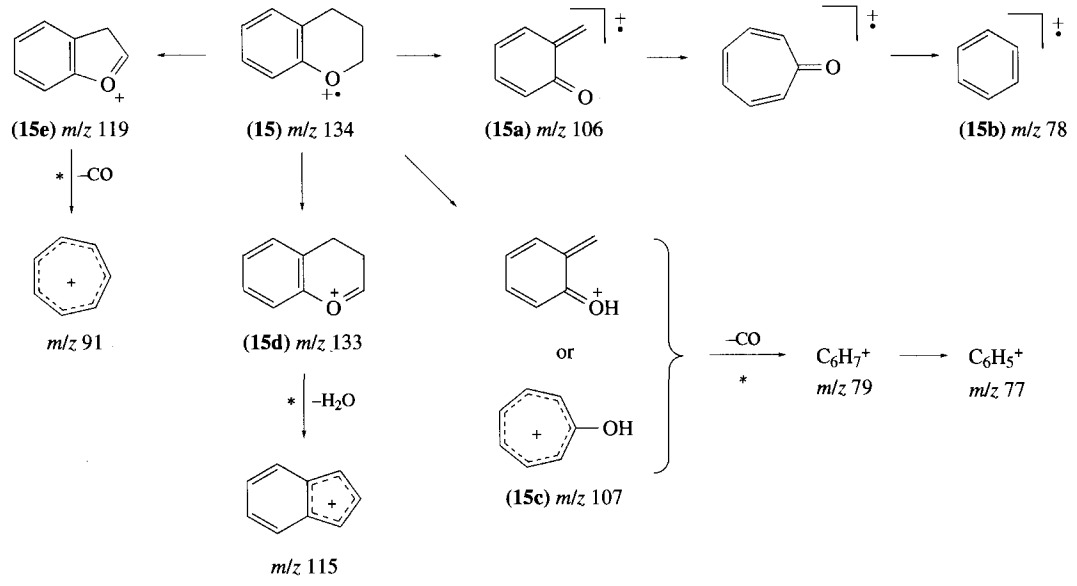
5,6-Dihydro-4-methyl-2*H*-pyran (**106**) eliminates CH_3· from the molecular ion to generate the base peak (*m/z* 83). The same ion is produced by fragmentation of cyclohexene oxide (Scheme 6) ⟨84OMS(19)506⟩.



(**106**)

Scheme 6

The mass spectrometry of chroman (**15**) has been extensively studied and reviewed ⟨B-74MI 507-03⟩. Fragmentation occurs by the pathways shown in Scheme 7. The molecular ion, which is the base peak, undergoes RDA cleavage to (**15a**). Hydrogen transfer in the RDA cleavage is also observed, leading to (**15d**) ⟨70OMS(3)409, 70OMS(3)753⟩. RDA fragmentation both with and without hydrogen transfer also features in the mass spectra of the *cis*-3-hydroxy-2-methoxy dimethylacetals (**107**) derived from chromone and flavone by hypervalent iodine oxidation in methanol ⟨85JHC583⟩.

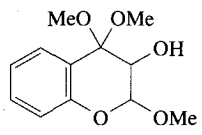


(**15e**) *m/z* 119 (**15**) *m/z* 134 (**15a**) *m/z* 106 (**15b**) *m/z* 78

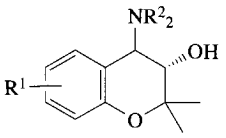
m/z 91 (**15d**) *m/z* 133 or (**15c**) *m/z* 107 $C_6H_7^+$ *m/z* 79 $C_6H_5^+$ *m/z* 77

m/z 115

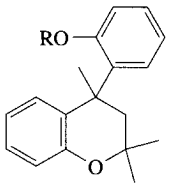
Scheme 7



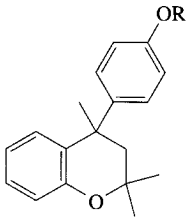
(107)



(108)



(109)



(110)

The principal ions from chroman-4-ol correspond to $[M-H]^+$, $[M-OH]^+$, and $[M-H_2O]^+$. RDA expulsion of ethene from the molecular ion is also accompanied by loss of hydrogen, giving ions at *m/z* 122 and 121 ⟨64T1185⟩. In the case of 2,2-dimethylchroman-4-ols, it is H(4) which is eliminated during formation of the $[RDA-H]^+$ ion ⟨78OMS(13)653⟩. The EI mass spectra of a range of *trans*-4-aminochroman-3-ols (**108**) show intense RDA peaks, together with ions arising from hydrogen transfer both to and from the RDA ions. Evidence indicates that transfer to the RDA fragment arises from the *gem* dimethyl group at C(2), whilst loss of hydrogen from the RDA species is dependent on the nature of the 4-amino substituent ⟨85OMS(20)440⟩.

Less information is known about chroman-3-ols, but based on the relative abundances of the $[M-OH]^+$ ions from chroman-3-ols and the 4-hydroxy isomers, the carbocationic center at C(4) is considerably more stable than that at C(3). Differences in the fragmentation patterns of these two chromanol systems have been summarized ⟨77HC(31)146⟩. A four-center skeletal rearrangement involving oxygen migration is proposed to account for the fragmentation observed in a series of 4-benzoylaminochroman-3-ols ⟨95JMS1023⟩.

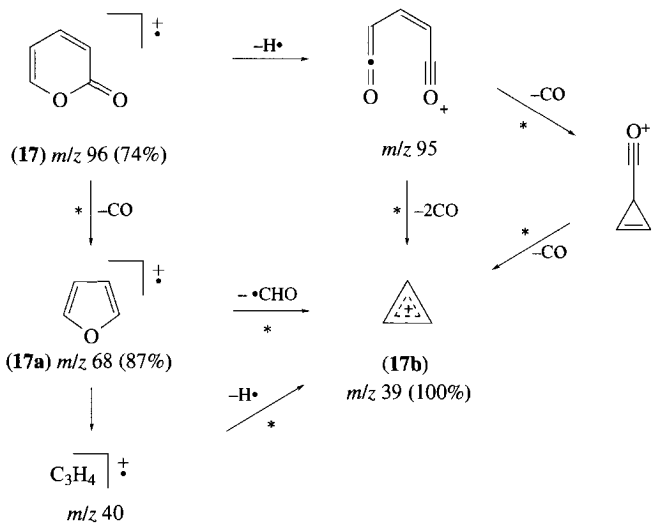
Further evidence of the influence of ortho substituents on fragmentation patterns is provided by the mass spectra of the chromans (**109**) and (**110**) ⟨94OMS(29)26⟩.

Isochroman fragments by RDA cleavage to the *o*-quinodimethane (Equation (1)) ⟨70JCS(B)1727⟩.

(1)

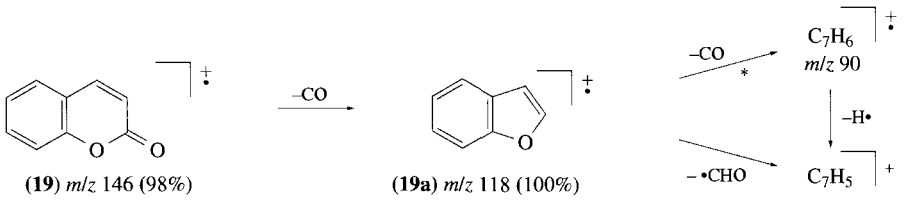
5.07.3.5.2 Pyranones, their benzologs and reduced derivatives

The mass spectrum of pyran-2-one (**17**) shows prominent peaks for the molecular ion and at *m/z* 68 (**17a**), corresponding to the loss of CO, whilst the base peak arises from the cyclopropenium ion (**17b**) ⟨65JA3022⟩. Fragmentation pathways are given in Scheme 8. Fragmentation by loss of carbon monoxide is generally important for pyran-2-ones.



Scheme 8

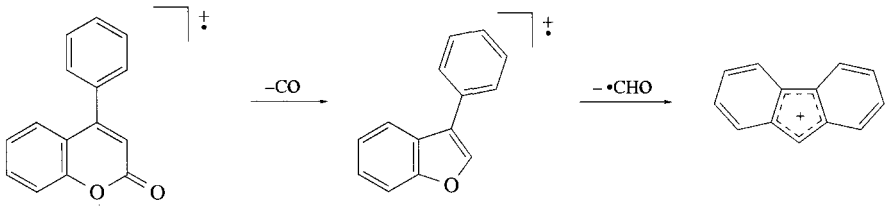
A vast amount of spectral information on coumarins has been accumulated and several reviews have been published, some of which relate to more complex and heterofused coumarins ⟨75RCR603, B-85MI 507-01⟩. As with pyran-2-one, carbon monoxide loss represents the only facile fragmentation pathway for the large majority of coumarins and normally leads to the base peak. Although the structure of the resulting species has been a matter of debate, it is considered to be a benzofuran radical cation (**19a**). The molecular ion (**19**) is usually abundant and further fragmentation often involves loss of a second CO molecule (Scheme 9) ⟨64AJC975, 92OMS(27)1220⟩.



(**19**) *m/z* 146 (98%) (**19a**) *m/z* 118 (100%)

Scheme 9

Simple alkyl coumarins fragment by extrusion of CO ⟨71OMS(5)249⟩, but for those coumarins with long alkyl side chains the dominant processes involve side chain fragmentation and cleavage. Fragmentation of 4-phenylcoumarin leads to the fluorenyl cation and is shown in Scheme 10 ⟨63TL891⟩.



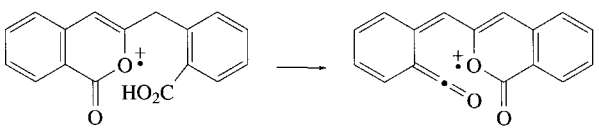
m/z 222 (100%) *m/z* 194 *m/z* 165

Scheme 10

Mass spectra of hydroxy- and alkoxycoumarins have been intensively studied. Different behavior is shown by 3- and 4-hydroxycoumarins. The decomposition sequence of the former is initiated by carbon monoxide loss from $[M]^{+\cdot}$ giving a 2-hydroxybenzofuran ion. Subsequently two major pathways operate: one leading to the benzene radical cation (*m/z* 78), the other to a phenonium ion at *m/z* 77 ⟨77IJC(B)816⟩. In 4-hydroxycoumarins, carbon monoxide expulsion from the molecular ion is virtually suppressed and the base peak results from loss of a ketene fragment by RDA cleavage. The fragmentation pathway is shown in Scheme 11 ⟨71OMS(5)249, 72JCS(P1)1924⟩. Mass spectral data on halogenocoumarins ⟨71ZOR388⟩ and aminocoumarins ⟨80ZOB940⟩ has been published.

Studies on the negative-ion chemistry of coumarin and some alkyl, hydroxy and alkoxy derivatives indicate that the most common reaction involves proton transfer from the coumarin to the reagent ion, OH^-, leading to $[M\text{-}H]^-$. Other processes involve attack by $O^{-}\cdot$ which leads to M^- and $[M-H+O]^-$ species. The $[M\text{-}H]^-$ ions undergo many fragmentations which enable isomeric coumarins to be distinguished ⟨93OMS(28)1148⟩.

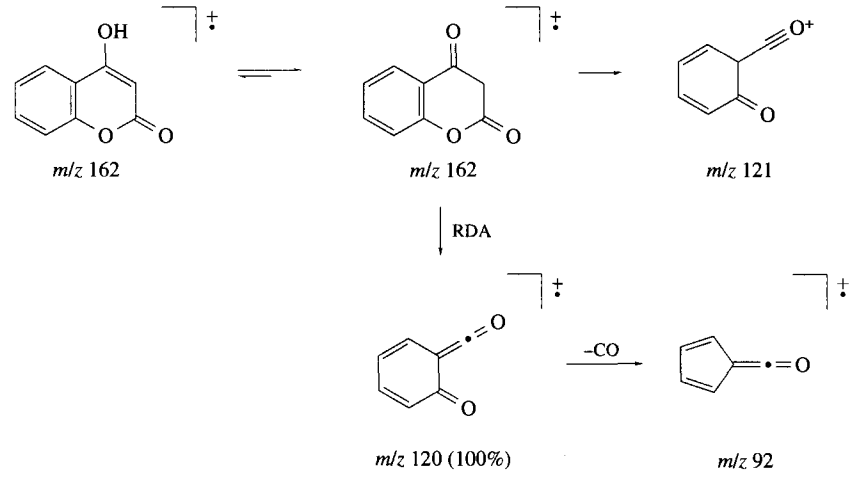
Mass spectrometry of isocoumarins has received little attention, but the isocoumarin (**111**) gives a significant peak for the $[M\text{-}H_2O]^{+}\cdot$ fragment (**111a**) (Equation (2)) ⟨65BSF3025⟩.



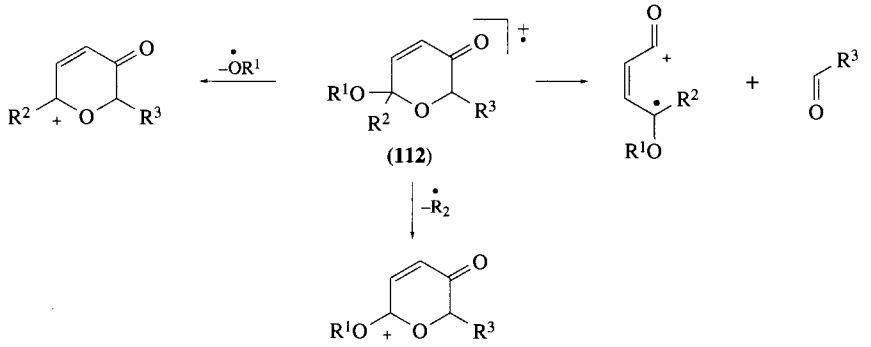
(**111**) (**111a**) (2)

The prominent fragmentations of the molecular ion of 2- and 6-substituted pyran-3-ones (**112**) are RDA ring-opening and cleavage of the substituent. The nature of the substituent plays a significant role in the relative importance of the two modes (Scheme 12) ⟨88MI 507-01⟩.

The fragmentation pathways of pyran-4-one (**18**) are presented in Scheme 13 ⟨64JA3833⟩. The

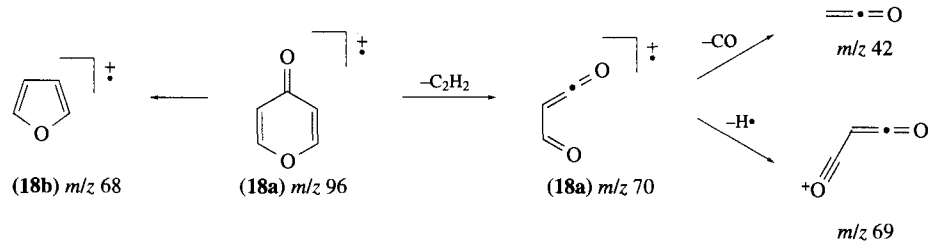


Scheme 11



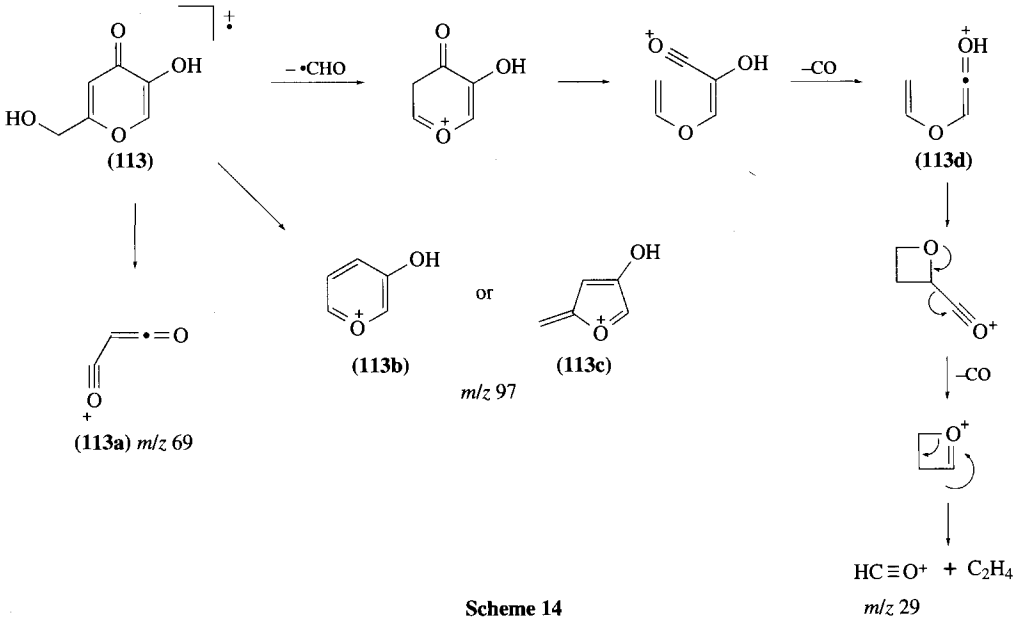
Scheme 12

molecular ion is the base peak, but RDA cleavage of $M^{\ddagger}$ leading to an $[M\text{-}C_2H_2]^{\ddagger}$ ion (**18a**) is important. In contrast to pyran-2-one, breakdown of $M^{\ddagger}$ by loss of CO to give $[M\text{-}CO]^{\ddagger}$ constitutes only a minor pathway. The structure of this ion has been established as the furan species (**18b**) ⟨79JA4973⟩, and later work has confirmed that both 4,6-dimethylpyran-2-one and 2,6-dimethylpyran-4-one fragment to a dimethylfuran cation radical by loss of CO ⟨85OMS(20)258⟩. Substituents can influence the relative significance of the two pathways ⟨64JA3833, 65T1855⟩, none more so than when an oxygen function is present in the 3-position.



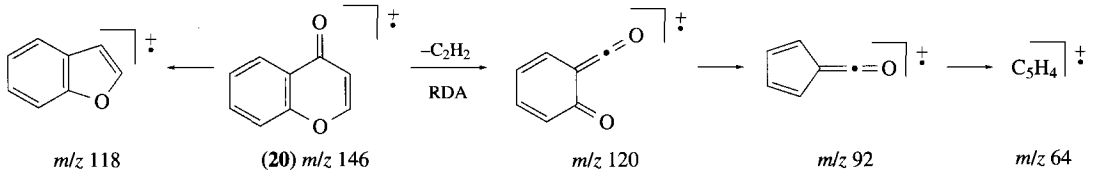
Scheme 13

Kojic acid (**113**) is a pertinent example ⟨67MI 507-02⟩. Here RDA cleavage and loss of CH_2OH radical produces ion (**113a**), *m/z* 69, whilst extrusion of CO and loss of HO· from the side chain gives the ion (**113b**) or (**113c**). Loss of a CHO radical from the hydroxymethyl substituent, followed by ring opening and loss of carbon monoxide, leads to the ion (**113d**) which ultimately breaks down to ethene and an $HC{\equiv}O^+$ fragment (Scheme 14). Fragmentation of 3-hydroxypyran-4-one and various alkyl derivatives is complex and is dependent on the nature of the substituents, but proceeds from a stable, abundant molecular ion. RDA cleavage, loss of CO, H, and alkyl radicals, and various rearrangements all play a part ⟨90ACS916⟩.



Scheme 14

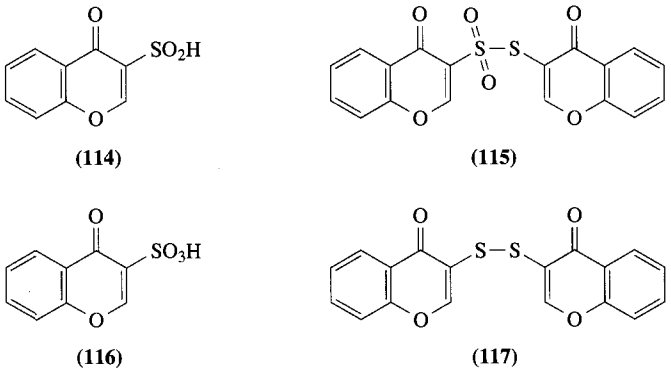
Mass spectral data for chromone (**20**) have been reported ⟨B-85MI 507-01⟩. The abundant molecular ion fragments both by expulsion of carbon monoxide, the favored route, and by ring cleavage by a retro-Diels–Alder reaction (Scheme 15). The formation of the $[M\text{-}CO]^{+}\cdot$ ion parallels the behavior shown by the isomeric system, coumarin. However, substituents may divert the course of fragmentation ⟨79OMS(14)345⟩.



Scheme 15

Following substitution at the 3-position and at the 5-, 6-, and 7- positions of 2-styrylchromones, the usual RDA fragmentations are not predominant; substituent loss is the major pathway ⟨95JCR(S)58⟩. Mass spectral data for chromone-3-carboxaldehyde ⟨74T3553⟩ and for analogs of ethyl chromone-2-carboxylate ⟨71OMS(5)857⟩ is available. The mass spectra of 3-(cycloalken-1-yl)chromones resemble those of isoflavone ⟨85TL1879⟩.

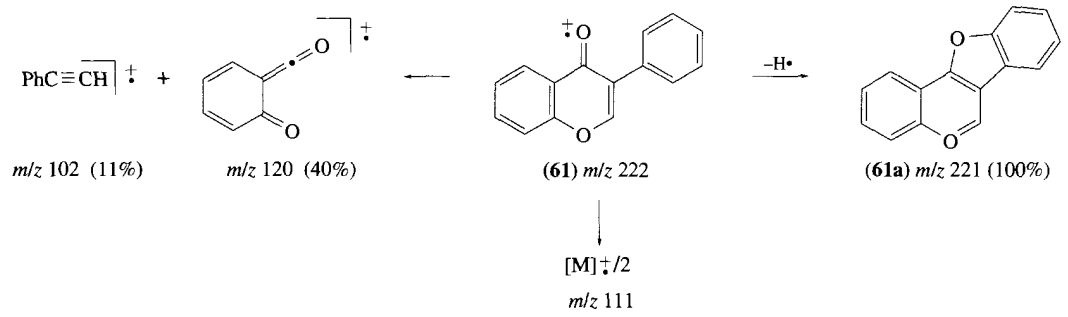
The mass spectrum of chromone-3-sulfinic acid (**114**) shows a peak at *m/z* 386 attributed to the thiosulfonate (**115**) arising from a disproportionation reaction. In addition, ions corresponding to chromone-3-sulfonic acid (**116**) (*m/z* 226) and the disulfide (**117**) (*m/z* 354) are present ⟨84AP(317)15⟩.



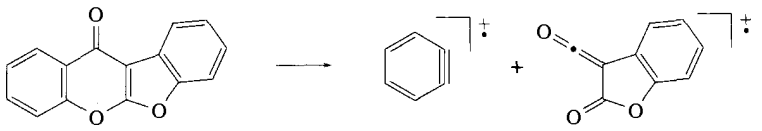
Applications of FAB mass spectrometry to anthocyanines has been reviewed ⟨89P2127⟩ and is widely used to obtain molecular weights of flavonoids. The ion spray technique has also proved useful in this area ⟨92P1593⟩. The mass spectrometry of prenylated flavanoids has been reviewed ⟨92H(33)405⟩.

The high stability of flavones is reflected by the intensity of their molecular ions, which often appear as the base peak. Flavone (**22**) itself fragments in a similar manner to chromone, giving an $[RDA]^{\ddagger}$ ion at *m/z* 120 and ionized phenylethyne, *m/z* 102; an $[RDA\text{-}CO]^{\ddagger}$ fragment at *m/z* 92 is also observed. Loss of carbon monoxide from the molecular ion gives the 2-phenylbenzofuran ion at *m/z* 194 and further breakdown leads to the benzoyl ion $PhC{\equiv}O^{+}$ ⟨64AJC975⟩.

The mass spectra of isoflavones resemble those of flavones, with cleavage by a retro-Diels–Alder pathway being prominent. The fragmentation pathways of isoflavone (**61**) are given in Scheme 16. The base peak is due to the [M-1] ion (**61a**). Fragments from the RDA pathway are observed, but $[M\text{-}CO]^{\ddagger}$ peaks are either very weak or not present at all ⟨66BSF2892⟩. However, when an oxygen atom links C(2) to C(2)′, as in (**118**), an alternative RDA cleavage generates benzofuran and benzyne fragments (Equation (3)) ⟨91H(32)1563⟩.

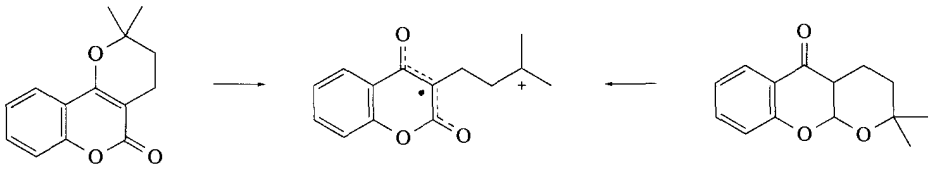


Scheme 16



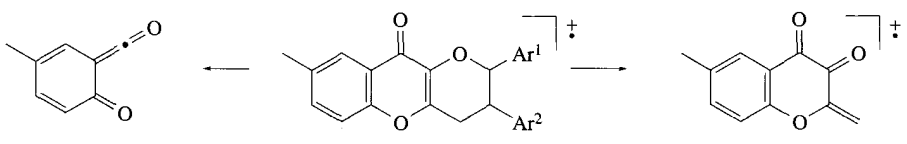
(118) (3)

The isomeric pyranocoumarins (**119**) and pyranochromones (**120**) exhibit a common fragmentation pattern, although there is variation in the relative abundances of the common ions. It is envisaged that rupture of the O(1)—C(2) bond of the pyran ring leads to a common radical cation (**121**) (Scheme 17) ⟨85OMS(20)740⟩. Two modes of RDA cleavage are proposed for the fragmentation of pyranochromones (**122**), involving rupture of the two heterocyclic rings (Scheme 18) ⟨91IJC790⟩.



(119) (121) (120)

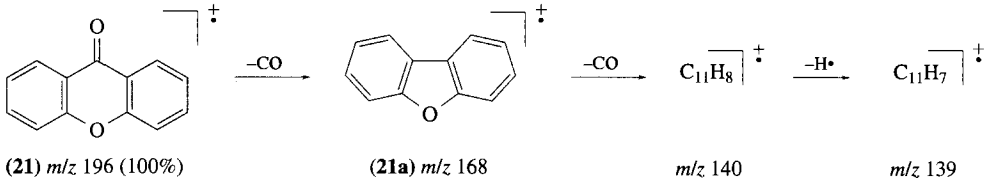
Scheme 17



(122)

Scheme 18

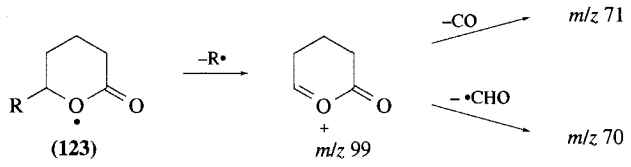
Xanthone (**21**) is extremely stable, and the molecular ion appears as the base peak. Fragmentation of $[M]^{+\cdot}$ involves extrusion of carbon monoxide, giving the dibenzofuran ion (**21a**) (Scheme 19) ⟨64AJC975⟩. Data on substituted xanthones includes methoxy ⟨73OMS(7)667⟩, hydroxy, nitro, and amino derivatives ⟨74MI 507-04⟩. The mass spectra of some naturally occurring xanthones have been briefly reviewed ⟨B-74MI 507-03⟩, and the fragmentation of a benzopyranoxanthone has been reported ⟨89P599⟩.



(**21**) *m/z* 196 (100%) (**21a**) *m/z* 168 *m/z* 140 *m/z* 139

Scheme 19

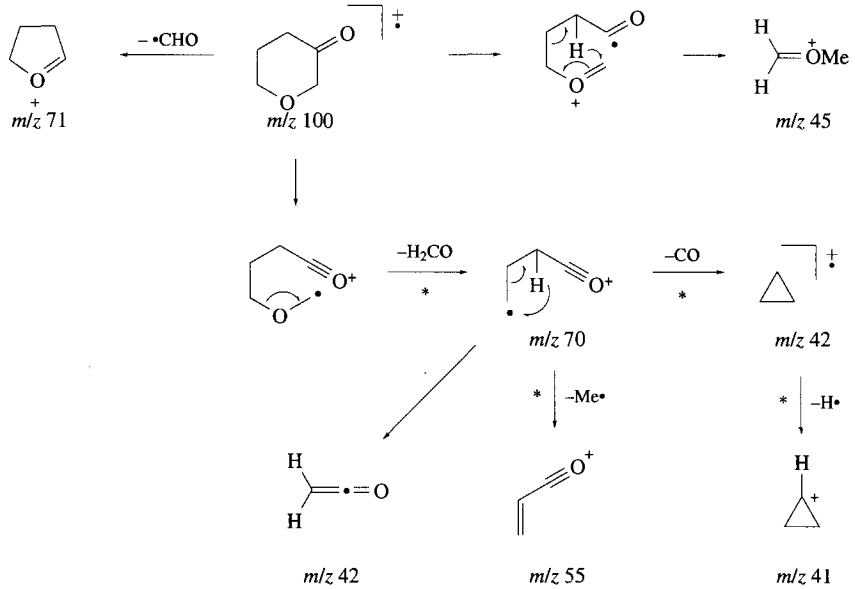
The mass spectra of tetrahydropyran-2-ones (**123**) and related lactones have been discussed ⟨B-85MI 507-01⟩. A generalized fragmentation pathway is outlined in Scheme 20. Other routes include loss of CO_2 from $[M]^{+\cdot}$ and the elimination of the heteroatom with its adjacent carbon atom and its substituent as a neutral carbonyl molecule ⟨68OMS(1)279⟩.



(**123**) *m/z* 99

Scheme 20

A detailed investigation of the fragmentation behavior of tetrahydropyran-3-one is summarized in Scheme 21 ⟨74JOC279⟩. There appears to be no detailed information on the mass spectrometry of tetrahydropyran-4-ones.

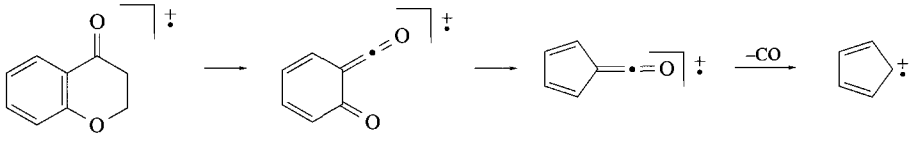


Scheme 21

There is some similarity in the mass spectra of dihydrocoumarin (**23**) and coumarin, since both decompose by two successive losses of carbon monoxide from the molecular ion. However, dihydrocoumarin also eliminates ketene, leading to an $[RDA]^{+\cdot}$ ion at *m/z* 106 ⟨64AJC975⟩.

Chroman-4-one (**24**) breaks down by a retrodiene fragmentation of $[M]^{+\cdot}$, giving an $[RDA]^{+\cdot}$ ion at *m/z* 120 as the base peak. Subsequent loss of CO generates ion (**24a**), *m/z* 92. A minor peak at

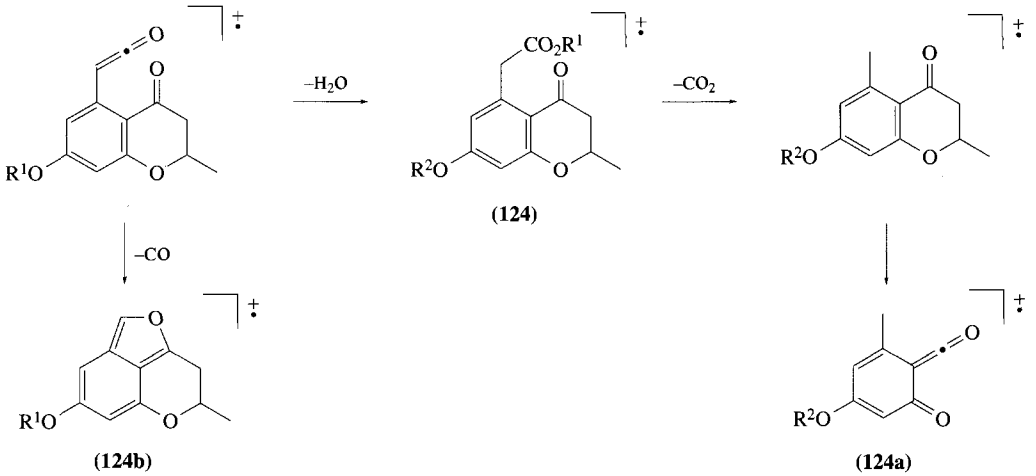
m/z 121 is attributed to an $[RDA + H]^+$ ion formed by hydrogen transfer prior to ring cleavage (Scheme 22) ⟨64T1185⟩. The abundance of the $[RDA + H]^+$ ion is markedly greater in 2,2-dimethylchroman-4-ones. Deuterium labeling studies confirm that a 2-methyl group is the source of the transferred hydrogen atom ⟨78OMS(13)653⟩. Loss of one of the 2-methyl groups to give the $[M - Me]^+$ ion is also a prominent pathway ⟨73MI 507-02⟩.



(24) *m/z* 148 *m/z* 120 **(24a)** *m/z* 92 *m/z* 64

Scheme 22

The 5-acetic acid derivatives of 2-methylchroman-4-ones (**124**) undergo an initial decarboxylation which is followed by RDA cleavage to give the base peak (**124a**). A second pathway involves loss of water prior to elimination of carbon monoxide to give (**124b**). For the derived esters, isobenzofuran ion (**124b**) is the base peak and the RDA fission appears to be unimportant. However, for both 2-methyl-4-oxochroman-5-carboxylic acid and its ester, RDA cleavage is the major fragmentation pathway and is followed by loss of the 5-substituent to give the base peak, *m/z* 120 (Scheme 23) ⟨88AJC535⟩.

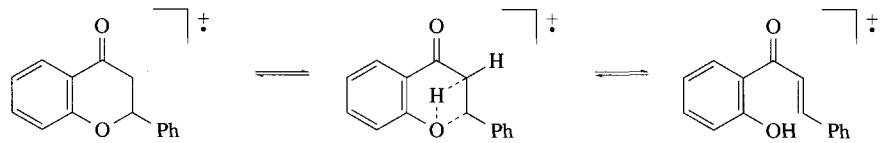


(124) **(124b)** **(124a)**

Scheme 23

The mass spectral behavior of flavanones has been widely studied and comprehensively reviewed ⟨B-75MI 507-02, B-80MI 507-02⟩. Flavanone (**25**) fragments by a retro-Diels–Alder pathway, giving an $[RDA]^+$ ion at *m/z* 120 as the base peak, together with ionized phenylethene, *m/z* 104. An intense $[M - 1]$ peak has been ascribed to the 4-hydroxyflavylium ion. The mass spectra of flavanone and 2′-hydroxychalcone (**125**) are virtually identical, and this has been attributed to a ring-chain tautomeric equilibrium between the two molecular ions (Scheme 24) ⟨92OMS(27)1299⟩. Mass spectral behavior has been used to substantiate NMR data and hence correct the proposed structure of the flavanone, falciformin ⟨90JOC1193⟩.

A characteristic feature of the mass spectrum of isoflavanone, 3-phenylchroman-4-one, is its

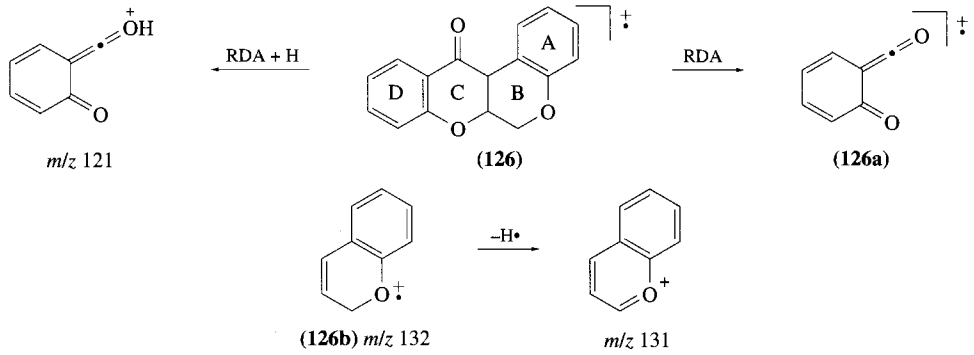


(25) **(125)**

Scheme 24

simplicity. Fragmentation of the molecular ion gives the base peak, $[RDA]^{\ddagger}$, which decomposes by loss of carbon monoxide. Hydrogen transfer occurs leading to the $[RDA + H]^+$ ion ⟨66BSF2892⟩.

The fragmentation of rotenoids, a class of natural products based on the chromanochromanone (**126**) system is typified by Scheme 25. Retro-Diels–Alder fission of the chromanone ring C leads to (**126a**) and (**126b**) on which the charge preferentially resides and which gives rise to the base peaks ⟨B-85MI 507-01⟩.

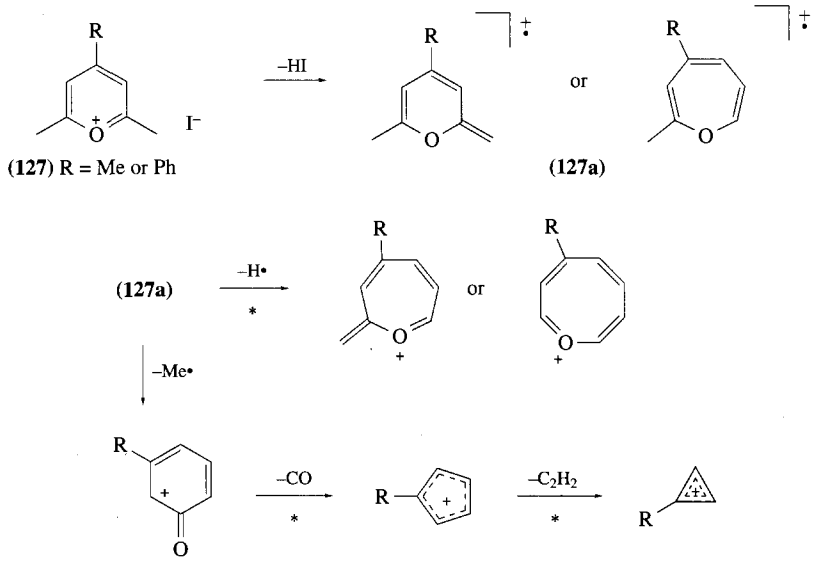


Scheme 25

5.07.3.5.3 Pyrylium salts

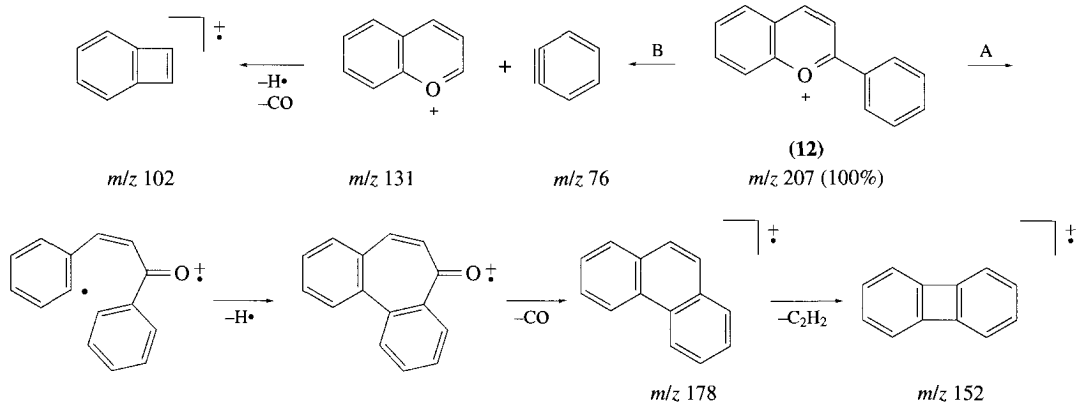
Few mass spectral studies have been carried out on pyrylium salts, which may be a consequence of their low volatility. The fragmentation pathway for (**127**; R = Me or Ph) is given in Scheme 26. The base peak arises from an $[M - HI]^{\ddagger}$ ion (**127a**); the molecular ion is not observed. It is noted that pyrylium salts which carry a methyl group adjacent to the heteroatom give a prominent peak associated with the acetyl cation $[MeCO]^+$ at *m/z* 43. Elimination of a 4-phenyl group has not been observed. Measurements of ionization potentials have shown that 2,4,6-triphenylpyrylium salts undergo thermal reduction to the corresponding free radicals in the mass spectrometer. Dimerization is precluded on steric grounds. Thermal elimination of HI from 4-methyl-2,6-diphenylpyrylium iodide gives 4-methylene-2,6-diphenyl-4*H*-pyran ⟨82AHC(S2)1⟩.

The highly stable molecular ion derived from the flavylium salt (**12**) fragments by the two



Scheme 26

pathways outlined in Scheme 27 ⟨69AK(30)393⟩. One route proceeds via the $[M-H]^+$ ion and involves cleavage of the C(4)—C(4a) bond, whilst the other arises from loss of the 2-phenyl substituent.



Scheme 27

5.07.3.6 UV Spectroscopy

Limited data on the UV spectra of oxygen heterocycles is available in the volumes dedicated to the applications of physical methods to heterocyclic chemistry ⟨63PMH(2)1, 71PMH(3)67⟩.

UV data on simple pyrans are scarce. Highly substituted 2*H*-pyrans are sufficiently stable to exist as such or at least in equilibrium with the acyclic valence isomer. 2,2,4,6-Tetramethyl-2*H*-pyran absorbs at 221 nm and 278 nm and *cis*-β-ionone (**63**) at 208 nm and 253 nm ⟨71JOC1977⟩. From the limited data available it appears that 4*H*-pyrans absorb at shorter wavelengths than the related 2*H*-isomers. Normal substituent effects operate in both systems. Thus 3-acetyl and 3-ethoxycarbonyl substituents shift λ_{max} to 284 nm and 270 nm, respectively, from about 250 nm, and a further red shift to 296 nm and 285 nm follows the introduction of a second of these substituents ⟨69JOC3169⟩.

The vacuum UV spectrum of 3,4-dihydro-2*H*-pyran (**13**) in solution shows a broad absorption centered at 195 nm, whilst that of the vapor of tetrahydropyran consists of two systems of closely spaced bands beginning at 193 nm and the higher intensity band at 184 nm ⟨63PMH(2)1⟩.

The photoelectron spectra of tetrahydropyran ⟨72JA5599⟩, 3,4-dihydro-2*H*-pyran and 4*H*-pyran have been recorded ⟨78HCA1388⟩, as have the electron transmission spectra of 4*H*-pyran and pyran-4-one ⟨86MI 507-01⟩.

2*H*-1-Benzopyran and its simple derivatives generally exhibit maxima in the ranges 220–240, 260–280 and 300–340 nm, and spectral data are available on naphthopyrans ⟨84CHEC-I(3)573⟩.

The limited data available on 4*H*-1-benzopyrans indicates absorption at 275–285 nm, similar to di- or polysubstituted phenols, with an additional peak around 210 nm. Xanthene shows maxima at 250 nm, 278 nm and 292 nm, with the last peak red-shifted in xanthydrol ⟨84CHEC-I(3)573⟩.

Chromans show several absorption bands in the 260–290 nm region, the position and intensity being relatively independent of substituents other than those containing non-bonding electrons ⟨81HC(36), 84CHEC-I(3)573⟩. The UV photoelectron spectra of chromans show differences from those of other cyclic and acyclic ethers which have been attributed to decreased conjugation of the oxygen and hyperconjugative effects of the 4-methylene unit ⟨76T167⟩.

Pyran-2-one shows end absorption at 216 nm and a maximum at 289 nm. On the other hand, pyran-4-one absorbs at 246 and 260 nm and it is therefore possible to distinguish the two pyranones provided both isomers are available; the one with the longer wavelength absorption is the pyran-2-one. Indeed, 4-methoxy-6-methylpyran-2-one (λ_{max} 280 nm) and 2-methoxy-6-methylpyran-4-one (λ_{max} 240 nm) have been identified in this manner ⟨84CHEC-I(3)573⟩.

A detailed study of the electronic absorption and emission spectra of pyran-4-ones has been carried out ⟨75JCS(F2)1812⟩. The strong bands between 200 nm and 300 nm are red-shifted in ethanol, which, coupled to their intensity, indicates that these are $\pi \rightarrow \pi^*$ transitions. Weaker, longer wavelength absorptions which blue shift in ethanol are assigned to $n \rightarrow \pi^*$ transitions. Pyran-4-ones

exhibit weak fluorescence with λ_{max} 360–395 nm in ethanol and have been observed to phosphoresce in rigid media at 77 K.

A list of the UV spectra of a wide range of coumarins is available ⟨71PMH(3)190⟩ from which it can be seen that these compounds show maxima at about 275 and 315 nm. The exact positions vary with solvent and also show a dependency on both the nature and position of substituents ⟨74MI 507-05, 77H(7)933, 78T1221⟩. Significant shifts to the red follow the introduction of electron-donating groups at the 7-position, and additional red shifts result when an acceptor group is present at C(3). Thus, 7-diethylamino-4-methylcoumarin absorbs at 370 nm in ethanol and its 3-heptafluoropropyl derivative at 400 nm ⟨92CB467⟩. The 7-hydroxycoumarins respond to various electron-withdrawing groups at C(3) in a similar manner ⟨85BCJ731⟩. Interestingly, an additional 4-cyano group brings about a further red shift of about 30–40 nm, and these compounds are orange-red.

Coumarins are of value as fluorescent brightening agents, tunable dye lasers, and in various biological applications (see Chapter 5.10), uses which are based on the emission of light of longer wavelength than that used to effect excitation. Coumarins with a 7-amino or 7-hydroxy substituent fluoresce strongly, and this is intensified by an electron-withdrawing function at C(3). Certain substituents can also improve the photochemical stability of coumarins ⟨92CB467⟩.

The UV spectrum of isocoumarin shows maxima at 228, 239, 253, 261, and 318 nm in ethanol ⟨60NKZ654⟩.

Chromone and many of its derivatives exhibit four bands centered on 205, 225, 240, and 300 nm. The main absorption peaks at 240 nm and 300 nm are generally of shorter wavelength than the corresponding bands in coumarins. The higher-wavelength bands are shifted to the red as solvent polarity increases, and these absorptions are assigned to $\pi \rightarrow \pi^*$ transitions ⟨72SA(A)707⟩. Electron-withdrawing substituents at the 2-position cause red shifts of the $\pi \rightarrow \pi^*$ bands, whilst a 2-methyl group brings about a small hypsochromic shift. Donor groups in the aromatic ring increase the intensity and red shift of these absorptions ⟨76JHC211⟩.

Photoelectron spectra of various chromones ⟨85JCS(P2)1191⟩, naphtho[1,2-*b*]pyran-4-one and its [2,1-*b*] and [3,2-*b*] isomers and xanthone have been obtained ⟨91MI 507-04⟩.

UV Spectral data for some chromanones has been collated ⟨77HC(31)⟩. Chroman-4-one itself shows maxima at about 260 nm and 330 nm in ethanol. The long-wavelength band is influenced by substituents in the aromatic ring, but is essentially unaffected by substituents at C(2). The phosphorescence spectra of chroman-4-one at 4.2 K have been studied ⟨92MI 507-02⟩. Absorption at 274.5 nm is noted for chroman-3-one.

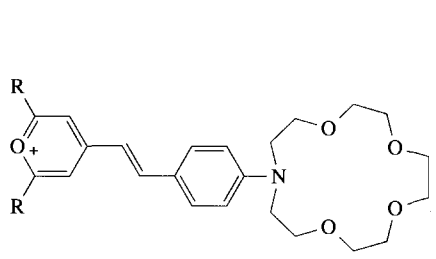
The UV spectra of most simple xanthones consist of three or four strong bands between 230 nm and 340 nm. Many naturally occurring xanthones are yellow as a result of a red shift of the longest-wavelength band arising from the presence of several hydroxy or related functions. Careful analysis of the spectra at different pH allows the oxygenation pattern to be established ⟨84CHEC(3)573⟩. Phosphorescence spectra of xanthone have been measured ⟨91MI 507-05⟩.

The UV spectra of pyrylium salts have been reviewed ⟨82AHC(S2)1⟩. The parent perchlorate absorbs at 270 nm, and the 2,4,6-trimethyl derivative shows maxima at 230 nm and 285 nm. Introduction of phenyl groups shifts the absorption towards the visible region, and pyrylium perchlorates containing two or three such groups are yellow, e.g. 2,4,6-triphenylpyrylium perchlorate, λ_{max} 408 nm in ethanol ⟨86MI 507-02⟩. The nature of the anion influences the color of the compounds, the iodides being much deeper in color, a feature attributed to a charge transfer band ⟨64T119⟩. The effect of a 3-methyl substituent is to bring about a hypsochromic shift of the long-wavelength band in 2,4,6-triphenylpyrylium salts, whilst *p*-substituents in the 2- and 6-phenyl rings bring about a bathochromic shift proportional to their electron-donating ability ⟨85JPR151⟩.

Both the 4-styryl-pyrylium (**128**) and -bispyrylium (**129**) salts show only one absorption band in the 320–450 nm region because of overlapping bands consequent upon the γ-styryl system. However, 2,6-bisstyryl-3,5-nonamethylenepyrylium salts (**130**) show two distinct bands. All of these compounds are highly colored ⟨92RRC141⟩. 2-(4-Chlorobutadienyl)pyrylium salts (**131**) absorb between 478 and 570 nm, although incorporation of a 4-dimethylaminophenyl substituent at the 4-position of the butadienyl side chain shifts the absorption to around 700 nm ⟨88ZC286⟩. The pyrylium salt (**132**) absorbs at 593 nm as a consequence of the extended conjugation ⟨90JA3845⟩.

The response to *p*-substitution in the phenyl rings is variable. Substitution in the 4-phenyl ring causes a small shift of the $\pi \rightarrow \pi^*$ transition to the red. Electron-withdrawing groups in either the 4- or 6-phenyl rings induces a blue shift, whereas donating groups bring about a bathochromic shift. Restricting the rotation of 2- and 6-phenyl rings as in (**133**) causes a more significant red shift (around 30–45 nm). Restricted rotation of the 4-phenyl group (**134**), which is not considered to be oriented along the polarization axis, has little effect ⟨86MI 507-03⟩.

Benzopyrylium perchlorate exhibits maxima at 241 nm, 326 nm, and 349 nm ⟨81JHC1325⟩.



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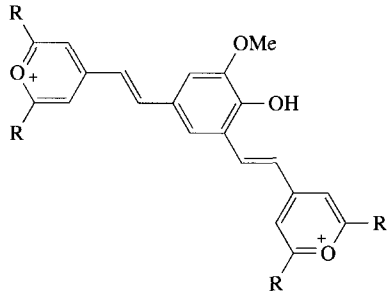

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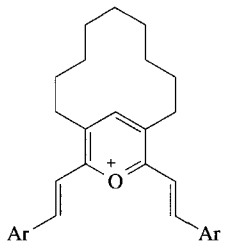

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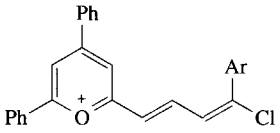

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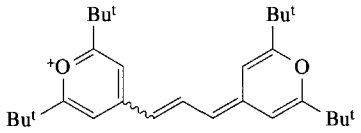

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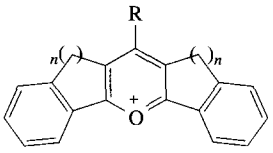
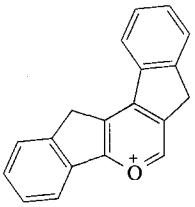


(133)

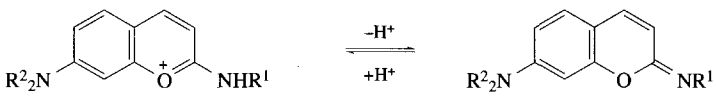
n =2, R = Ph, λ_{max} 446 nm



(134)

λ_{max} 395 nm

Introduction of amino functions at the 2- and 7-positions leads to pronounced red shifts (430–475 nm), and the compounds are yellow to red according to the nature of the amine substituent. The influence of a 4-methyl substituent is hypsochromic, whilst incorporation of the 7-nitrogen atom into a ring brings about a red shift of 20–30 nm of the long-wavelength band ⟨89CHE621⟩. The spectra of those salts containing a secondary amino function at C(2) show a marked dependence on pH, indicating an acid–base equilibrium between the pyrylium species and a 2-iminocoumarin (Equation (4)).



(4)

5.07.3.7 Infrared and Raman Spectroscopy

There are few papers devoted exclusively to IR and Raman studies of oxygen heterocycles, but such information is frequently incorporated into work describing the synthesis and reactions of these compounds. The early work has been summarized ⟨63PMH(2)242, 71PMH(4)339⟩, and specialized texts cover some areas in greater detail.

Information on the IR spectra of 2*H*-pyrans is limited. The major absorptions relate to the stretching vibrations of C=C, which occur at about 1650 cm^{-1} and 1610–1600 cm^{-1}, and the C—O bond between 1080 cm^{-1} and 1070 cm^{-1} ⟨84JPR657, 91CB2633⟩.

More data is available on 4*H*-pyrans, including the IR and Raman spectra of 4*H*-pyran itself ⟨62JA2452, 93JA8396⟩. Generally, the stretching vibrations are at a higher frequency than for the 2*H*-pyrans, occurring about 1680 cm^{-1} and 1630 cm^{-1} for the C=C and 1260 cm^{-1} for the C—O bonds ⟨87CJC704, 87MI 507-01, 87JST(162)19, 92JCS(P2)1301⟩.

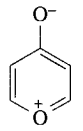
Benzannulation has only marginal effects on the C=C and C—O absorptions, as do shifting the

heteroatom and partial saturation of the pyran ring. Data relating to these and other similar molecules have been collated ⟨84CHEC-I(3)573⟩.

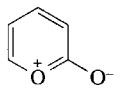
Detailed analysis of the IR and Raman spectra of tetrahydropyran and of various tetrahydropyranols have been reported ⟨50JA4397, 60JCS4565, 70JCP(53)376⟩.

Chroman-3-ols and 4-ols show the expected OH absorption band between 3625 and 3200 cm^{-1} ⟨70BSF1139, 70JOC2282⟩, as do the 3,4-diols ⟨68BSF4203⟩. Deductions about the conformations of chromanols have been made from this absorption ⟨74BCJ509, 81JCS(P2)944⟩ and information on the influence of substituents in chromanols is available ⟨77HC(31), 81HC(36)⟩.

The infrared spectra of pyranones are characterized by the absorption associated with the carbonyl group. Pyran-4-ones are more basic than the 2-isomers, a feature attributed to a greater contribution from the aromatic structure (**135**) to the hybrid structure of pyran-4-one than from (**136**) to the structure of the 2-one ⟨B-77MI 507-02⟩. This feature is reflected in the different C=O stretching frequencies: about 1660 cm^{-1} for pyran-4-ones and about 1725 cm^{-1} for pyran-2-ones. Both isomers also show C=C absorptions. In the case of pyran-2-ones, two bands separated by about 80 cm^{-1} occur in the region 1667–1540 cm^{-1}. However, one C=C absorption band in pyran-4-ones is found at higher frequencies than the C=O stretching band ⟨84CHEC-I(3)573⟩.



(135)

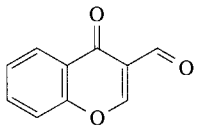


(136)

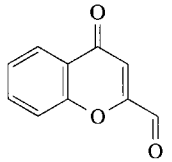
The carbonyl group absorption in coumarins is influenced by substituents but normally occurs within the range 1740–1670 cm^{-1} ⟨90JOC4349⟩. The frequency varies with the solvent used, probably as a consequence of the basicity of the carbonyl group together with steric factors in both solute and solvent. The carbonyl absorption frequently shows as a doublet which is attributed to Fermi resonance of $\nu_{C=O}$ with an overtone of a lower lying fundamental ⟨90MI 507-03⟩. Other absorptions at about 1600 cm^{-1}, 1270–1210 cm^{-1} and 1145–1065 cm^{-1} are attributed to C=C and C—O vibrations ⟨76RRC1207⟩. A full analysis of the solution IR and Raman spectra of 6*H*-benzo[*b*]-naphtho[1,2-*d*]pyran-6-one has been reported ⟨93MI 507-01⟩.

The carbonyl absorption band in chromones is also influenced by substituents and solvents; it occurs at about 1650 cm^{-1}; much information is available ⟨77HC(31)⟩.

The influence of a 2- and a 3-formyl substituent on the frequency of the C=O (ring) stretch in chromones has been used to make structural assignments. Thus, 3-formylchromone adopts an *s-cis* conformation (**137**) involving a weak hydrogen bond between H(2) and CHO rather than between the two carbonyl functions. On the other hand, the 2-formyl derivative adopts an *s-trans* array (**138**) ⟨93M539⟩. The ring carbonyl absorption is at about 1650–1685 cm^{-1} and the formyl C=O stretch between 1700 cm^{-1} and 1730 cm^{-1} in all the formyl compounds studied.



(137)



(138)

Dihydrocoumarins and chroman-4-ones exhibit $\nu_{C=O}$ at 1775–1720 cm^{-1} and about 1680 cm^{-1}, respectively ⟨74JCS(P1)569, 77HC(31)215⟩, typical of lactones and aromatic acyclic ketones.

The carbonyl stretch in xanthone occurs at about 1660 cm^{-1} ⟨58JCS294⟩, and a full analysis of the vibrational spectrum of this tricyclic compound has been reported ⟨85SA(A)537⟩.

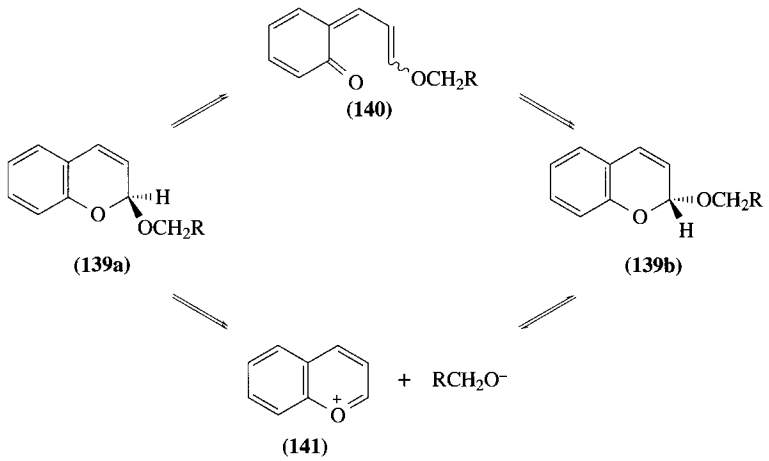
Tabulated IR data on systems containing a pyranone nucleus are available ⟨84CHEC-I(3)573⟩.

5.07.4 THERMODYNAMIC ASPECTS

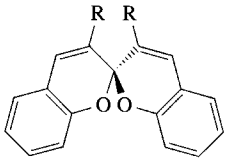
5.07.4.1 Chromatography

The enantiomers of the chiral chromenes (**139a** and **b**; R = Me or Ph) have been separated by liquid chromatography on triacetyl- and tribenzoyl-cellulose. The barriers to the interconversion of

the enantiomers, which may proceed via ring opening to the dienone (**140**) or by way of a chromylium cation (**141**), have been determined by thermal racemization (Scheme 28). The conversion of the bulkier *O*-benzyl derivative is energetically more demanding ⟨93CCA209⟩. A similar approach has been used to investigate 2,2′-spirobichromenes (**142**) ⟨90C336⟩, and the enantiomers of some 3-aminochromans ⟨95MI 507-01⟩, chroman-2-carboxylic acid derivatives ⟨92LA543⟩, and all eight stereoisomers of α-tocopherol ⟨90HCA782⟩ have been separated using various chromatographic techniques.

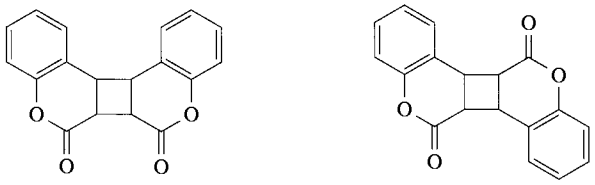


Scheme 28



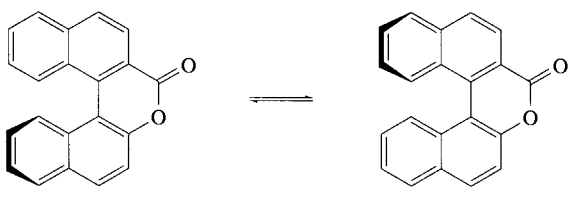
(**142**)

Two photodimers of coumarin, (**143**) and (**144**), have been resolved by liquid chromatography. The experimental CD spectra of the enantiomers have been compared with spectra calculated by a semi-empirical matrix technique using transition moments and charge densities and geometries obtained by x-ray crystallography in order to establish the absolute configuration ⟨89JA4387⟩.



(**143**) (**144**)

Both chromatographic resolution of the lactone-bridged biaryl (**145a** and **b**) and chemical generation of the (*M*)-enantiomer have been achieved. The lactone has a lower racemization barrier than similar carbocyclic helicenes ⟨94LA91⟩.



(**145a**) (**145b**)

The optical resolution of a variety of rotenoids has been accomplished by chiral phase HPLC. In many instances the absolute stereochemistry at the *cis*-B/C ring junction influences the elution order, with the 6aα,12aα-enantiomers being more strongly retained by the chiral stationary phase ⟨87JHC845⟩.

The relationship between HPLC retention time calculated in terms of topological indices and the structure of some anthocyanins has been investigated ⟨93JC(A)115⟩.

5.07.4.2 Aromaticity

The various methods available for assessing aromaticity have been reviewed ⟨B-75MI 507-03⟩. Those techniques which have been applied to heteroaromatic compounds are the subject of a review ⟨74AHC(17)255⟩ which includes a discussion of the evidence for aromaticity in pyrylium salts and 2- and 4-pyranones. This latter survey has now been updated to include an excellent critique of the characteristics associated with aromaticity and the methods attempting to quantify them ⟨93AHC(56)303⟩. Since the publication of CHEC-I in 1984, several indices have been refined or introduced in an attempt to obtain a more quantitative picture of heteroaromaticity. Although there are many pitfalls associated with such a task, the question of aromaticity of the pyranones and pyrylium salts has perhaps been defined most clearly by indices based on the extent of bond length alternation in the ring. Thus, the Harmonic Oscillator Model of Aromatic Stability (HOMA) ⟨72TL3839⟩ and Bird's (I_6) Aromaticity Index ⟨85T1409⟩ (Table 2) provide sensible measures of the aromatic character of these systems, which correlate well with their reactivity patterns. It should be stated at the outset that all the available evidence indicates that the systems considered here have, at best, weakly aromatic characteristics.

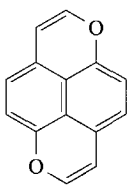
Table 2 HOMO and Bird's I_6 indices for some aromatic compounds.

Compound	*HOMA*	I_6
Benzene	various[a,b]	100[c]
Pyridine	0.995[b]	85.7[c]
Pyran-2-one	−0.341[b]	32.9[c]
Pyran-4-one	−0.146[b]	37.2[c]
Pyran-4-thione	0.326[b]	47.9[c]
Pyrylium cation		65.8[c]
2,4,6-Triphenylpyrylium	0.481[b]	50.5[b]
2,6-Diphenyl-4-(2-phenylpropan-2-yl)pyrylium	0.605[b]	53.6[b]

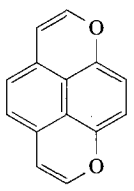
[a] Dependent on source of bond lengths, 0.996 (x-ray), 0.979 (electron diffraction), 0.969 (microwave spectroscopy). [b] ⟨89JCS(P2)613⟩. [c] ⟨86T89⟩.

5.07.4.2.1 Pyrans

Proton chemical shift data indicates that extended delocalization of the π-cloud electrons is disrupted by the heteroatoms in the dioxapyrenes (**146**) and (**147**) and in the dioxabenzo[*a*]pyrene (**71**) ⟨92JHC1149, 93JHC739, 95JHC17⟩.



(**146**)



(**147**)

5.07.4.2.2 Pyranones

There have been numerous theoretical studies on pyranones. The MO delocalization energy (DE) of pyran-2-one has been calculated by a number of techniques of varying sophistication. An early MO-LCAO treatment indicated considerable aromaticity for both 2- and 4-pyranone; the calculated DE values were 2.896β and 2.868β, respectively (*cf.* benzene 2β) ⟨62CCC1242⟩. However, since different parameters were used in each case, comparison of the absolute values cannot be made. Indeed, the orders of DE for the pyranones calculated by the HMO method are parameter-dependent ⟨64T831⟩. Calculation of DE by an iterative procedure (ω,β) gave lower values which were considered to be more realistic than those calculated by the Wheland–Pauling method ⟨69CR(C)(269)298⟩ and which suggested that 2- and 4-pyranones are equally aromatic. Later work based on the additivity of π-bond energies in non-aromatic model compounds concludes that neither pyranone is aromatic ⟨76JA2750⟩. However, the aromaticity indices (A_1), which are unity for benzene and pyridine, indicate considerable aromatic character for both pyranones ⟨67MI 507-03⟩ (Table 3).

Table 3 Specific delocalization energies (β), aromaticity indices (A_1), and topological resonance energies per electron (TRE(PE)) for pyranones and their benzologs.

Compound	DE_{sp} (β)[a]	A_1[b]	*TRE(PE)*[c]
Pyran-2-one	0.464	0.79	
Pyran-4-one	0.428	0.72	
Coumarin	0.421		44.68
Isocoumarin	0.656		42.23
Chromone	0.401		46.90
3*H*-2-Benzopyran-3-one			15.56
Xanthone	0.750		

[a] ⟨78BSF545⟩. [b] ⟨67MI 507-03⟩. [c] ⟨82JHC625⟩. The TRE(PE) values are expressed as a percentage of the value for benzene.

Determination of Specific Delocalization Energy (DE_{sp}) values for 2- and 4-pyranones and a number of benzologs has been performed by a simple HMO method, the more sophisticated HMO $\omega'\omega''\beta$ method and by one of Pople's semi-empirical MO methods ⟨74BSF538⟩. The results from the two latter methods are in general agreement and give a relative order of aromaticity: tricyclic pyranones > 2- and 4-pyranones > bicyclic pyranones ⟨74BSF545⟩. It is surprising that the simple benzologs appear to be less aromatic than the pyranones themselves.

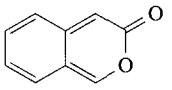
(i) Pyran-2-ones and coumarins

Spectral studies appear to indicate little aromatic character for pyran-2-ones. Thus, the UV spectra are consistent with an enol lactone structure ⟨71PMH(3)67⟩, whilst the carbonyl stretching frequencies in the IR spectra are in the typical lactone range 1720–1740 cm^{-1} ⟨63PMH(2)252⟩. Calculations employing extended Hückel Theory (EHT) indicate a high bond order for the carbonyl group in pyran-2-one and some coumarins. Carbonyl bond stretching frequencies calculated using MO-derived bond orders are in good agreement with the experimental values ⟨78IJC(A)64⟩. It seems that pyran-2-ones possess little or no betaine character, an essential requirement for the system to develop aromaticity.

There is no evidence for a significant diamagnetic ring current in the ^1H NMR spectrum of pyran-2-one ⟨69JHC1⟩. Coupling constant data suggests some bond localization in pyran-2-ones, and this is supported by ^{13}C chemical shifts ⟨74JOC1935⟩. Molecular magnetic susceptibility anisotropies for 2- and 4-pyranones show no non-local contributions, indicating little or no π-electron delocalization, and hence the pyranones are classed as non-aromatic ⟨73JA2766⟩. The HOMA and I_6 indices calculated from experimentally determined bond lengths are in good agreement (Table 2) and are indicative of low aromaticity in these systems ⟨86T89, 89JCS(P2)613⟩.

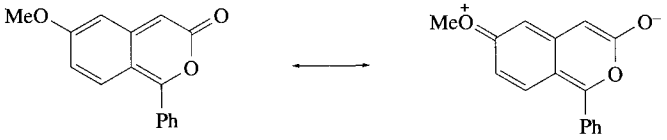
Chemical evidence also points to pyran-2-ones being non-aromatic. The ring is readily cleaved by nucleophiles, typical behavior of a lactone ⟨62CI(L)1829⟩, whilst electrophilic substitution requires forcing conditions. The facile bromination proceeds via addition to the double bond and subsequent elimination of HBr ⟨69JOC2239⟩. The diene-like nature of pyran-2-one is apparent from the ease with which it undergoes Diels–Alder reactions with, for example, maleic anhydride. The cycloaddition chemistry of pyran-2-ones has been reviewed ⟨92T9111, 93C3⟩.

Complete aromaticity in coumarin (**19**), isocoumarin (**28**) and 3*H*-2-benzopyran-3-one (**148**) can only be realized if the O—CO function contributes two electrons to form a 10 π-electron system, implying a betaine structure. The available evidence suggests that the heterocyclic ring in these compounds is not markedly aromatic but that the molecules are simply benzo-fused enol lactones. The specific delocalization energies for coumarin, isocoumarin and chromone are given in Table 3 ⟨74BSF545⟩.



(148)

The topological resonance energies per electron (TRE(PE)) of coumarin and some isomers, expressed as percentages of the value for benzene, are given in Table 3 ⟨82JHC625⟩. This approach suggests low aromaticities for coumarin, isocourmarin and chromone, whilst (**148**) is non-aromatic in keeping with its *o*-quinonoid structure ⟨70JCS(C)536⟩. Although 3*H*-2-benzopyran-3-one is not isolable, substituents in the heterocyclic ring impart some stability. For example, the 1,4-diphenyl compound has been obtained, though it is readily attacked by nucleophiles ⟨70JCS(C)530⟩. Subsequent work has shown that the 1-aryl-6-alkoxy analogs of (**148**) are of high stability, ascribed to a donor–acceptor interaction between the pyranone carbonyl group and the alkoxy function. In the 7-alkoxy isomers, where no such interaction is possible, the compounds are not isolable, being readily attacked by nucleophiles ⟨91JCS(P1)169⟩.



Physical data is also consistent with a low aromaticities in these systems. For instance, the IR spectra of coumarin and isocoumarin show carbonyl frequencies characteristic of lactones, and EHT MO calculations show high π-bond orders for their carbonyl groups ⟨78IJC(A)64⟩.

The chemical behavior of coumarin resembles that of pyran-2-one to a large extent. Electrophilic substitution occurs preferentially in the benzenoid ring at C(6), though substitution can occur at C(3) under more forcing conditions. Coumarin is readily attacked by nucleophiles to give ring-opened products.

(i) Pyran-4-ones and chromones

Early work on the aromaticity of pyran-4-one has been reviewed ⟨68T923⟩.

Values of DE_{sp} and Julg (A_1) aromaticity indices for pyran-4-one and chromone are given in Table 3. The various data indicate appreciable aromaticity for pyran-4-one, but this contrasts greatly with the HOMA and I_6 indices, which suggest that these systems are only marginally aromatic (Table 2).

The carbonyl stretching frequency in pyran-4-one occurs in the region 1660–1678 cm^{-1} and for chromone at 1650–1665 cm^{-1}, considerably different from pyran-2-ones (1725 cm^{-1}). However, MO calculations indicate high carbonyl group π-bond orders and give satisfactory agreement between calculated and experimental carbonyl group frequencies ⟨74BSF545⟩.

Evidence for aromatic character in pyran-4-ones from NMR studies is somewhat contradictory. Thus, whereas chemical shift data suggests a ring current for 2,6-dimethylpyran-4-one comparable in magnitude to that of benzene ⟨68T923⟩, the almost identical coupling constants $J_{2,3}$ for the pyranone and 2,3-dihydro-2,2-dimethylpyran-4-one indicate a lack of aromaticity. Carbon-13 NMR data is supportive of both an α,β-unsaturated ketonic system and a heteroaromatic molecule.

Dipole moment studies on some 2,6-bis(dialkylamino) derivatives of pyran-4-one and the corresponding thione indicate a significant mesomeric interaction, implying a contribution from dipolar species, though not necessarily confirming aromaticity ⟨93JPO489⟩.

Full structural data for pyran-4-one determined by microwave spectroscopy gives evidence for a

small degree of delocalization. Further shortening of the C(3)—C(4) bond and lengthening of the C(2)—C(3) linkage is observed in pyran-4-thione, suggesting enhanced aromaticity which is supported by both the HOMA and I_6 indices (Table 2) ⟨81JCS(F2)79⟩.

5.07.4.2.3 Pyrylium salts

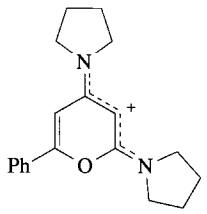
The planar pyrylium cation (**3**) possesses 6π electrons and may therefore be expected to be aromatic in character. The positively charged oxygen atom is a destabilizing influence, and the pyrylium ion can be regarded as a cyclic oxonium salt. However, its enhanced stability relative to aliphatic and alicyclic oxonium salts is doubtless due to some aromatic character.

Spectral studies lend support for the aromatic character of pyrylium salts. The similarity in the UV spectra of pyrylium and pyridinium salts is clear. These species are iso-π-electronic, show the same C_{2v} symmetry, and the energies of their respective molecular orbitals are comparable ⟨71PMH(3)67⟩. The ^{1}H NMR spectrum for pyrylium perchlorate shows low-field resonances (δ 8.02 to 9.22), indicating a substantial diamagnetic ring current ⟨73OMR(5)251⟩.

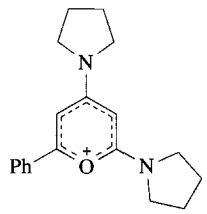
Calculations of the π-electon density using the HMO method reveal considerable delocalization of the positive charge. The electron density decreases in the order C(3) > C(4) > C(2), and the correlation of proton chemical shifts and π-electron densities is good ⟨66RRC1193⟩. Total charge densities for the pyrylium ion calculated by the INDO MO method show an increase of positive charge at the 2-, 4-, and 6-positions, and a linear relationship with the ^{13}C chemical shifts exists ⟨77OMR(9)16⟩.

Both aromaticity indices, HOMA and I_6, are different from those of truly aromatic systems, indicating that the pyrylium ion is intermediate between aromatic and non-aromatic systems ⟨89JCS(P2)613⟩. It should be noted, however, that it is more aromatic than the pyranones. Comparative data is given in Table 2.

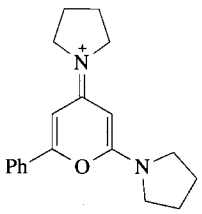
The x-ray structure of 6-phenyl-2,4-dipyrrolidinopyrylium fluoroborate suggests that a vinamidine structure (**149**) is more appropriate than a delocalized pyrylium salt (**150**) ⟨90T2935⟩. In solution, (**151**) is significant ⟨88TL4695⟩.



(**149**)

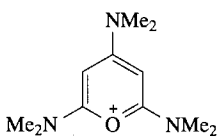


(**150**)

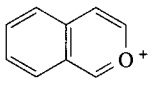


(**151**)

From a chemical reactivity point of view, also, pyrylium salts are not typically aromatic. Attack by nucleophiles occurs readily, especially at C(2), and further reactions, usually involving ring opening, lead to a variety of products. As expected in view of the overall electron deficiency of the system, electrophilic substitution does not occur; the successful dinitration of 2,4,6-tris(dimethylamino)pyrylium (**152**) is attributed to the delocalization of charge onto the substituents and hence a much reduced contribution by the pyrylium cation ⟨88MRC707⟩.



(**152**)



(**153**)

Both 1- and 2-benzopyrylium salts (**6**) and (**153**) are 10π-electron systems and so are potentially aromatic. Calculations of charge densities by CNDO/2 indicates delocalization of the positive charge over the whole system, with C(2) and C(4) being particularly electron deficient and therefore the sites for nucleophilic attack in 1-benzopyrylium salts ⟨70ACS2745⟩. High stability and low reactivity are predicted for flavylium salts ⟨91JCS(P2)891⟩, the 5,6-benzoflavylium cation ⟨94G53⟩

and 2-styrylbenzopyrylium salts ⟨92JCS(P2)1933⟩, especially when electron-releasing substituents are present in the benzopyrylium unit and the 2-styryl substituent.

The ^{1}H NMR spectrum of (**6**) indicates the presence of a ring current and shows resonances in the region 9.60–9.90 ppm ⟨81JHC1325⟩. Carbon-13 NMR data for the 2-benzopyrylium system indicate a high degree of charge density in both heterocyclic and carbocyclic rings, supporting evidence for the aromaticity of this ring system ⟨76OMR(8)324⟩.

The xanthylium ion (**9**) has a different chemistry from that of pyrylium and its mono-benzologs. Nucleophilic attack occurs exclusively at C(9), indicating the importance of the carbocation (**9a**) to the resonance hybrid. The properties of the xanthyliums resemble those of the carbocations derived from di- and tri-phenylmethanes rather than simple pyrylium salts. However, comparison of the ^{13}C chemical shifts of C(9)(165.1 ppm) with those for the central carbon of the diphenylmethyl cation (202.2 ppm) and the analogous triphenyl species (212.7 ppm) suggests appreciable charge delocalization in the xanthylium ion. CNDO/2 calculations support this view ⟨75BSF2023, 75JA5472⟩.

(**9**) (**9a**)

5.07.4.3 Conformations

Several texts include reviews on the conformation of six-membered oxygen heterocycles ⟨B-71MI 507-02, B-77MI 507-03, B-80MI 507-03⟩.

5.07.4.3.1 Reduced pyrans and their benzologs

The chair conformation has been established as the prevalent structure for tetrahydropyran by microwave spectroscopy ⟨69CJC1289⟩ and electron diffraction measurements on the gaseous molecule ⟨79ACS(A)225⟩. This structure is supported by NMR ⟨67JCS(B)1203⟩ and IR studies ⟨67SA(A)391, 75SA(A)339⟩.

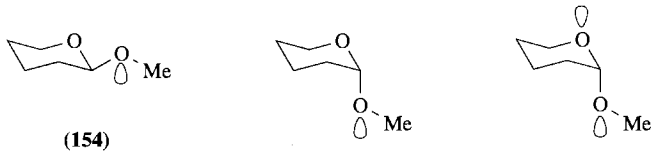
The free energy of activation for ring inversion in tetrahydropyran (Figure 22) is 43.0 kJ mol^{-1} at 212 K by the coalescence temperature method ⟨73JA4634⟩. This value is almost identical with that for cyclohexane (42.3 kJ mol^{-1}) and it thus appears that the introduction of the heteroatom has little effect on the conformational mobility of cyclohexane.

Figure 22

Substituents in the 3- and 4-positions are subject to the normal interactions encountered in cyclohexanes, although 1,3-interactions now involve a lone pair of electrons on the heteroatom. However, a substituent adjacent to the heteroatom may exhibit a preference for axial stereochemistry, providing a manifestation of the anomeric effect, the origin of which is attributed to the stabilizing overlap of the heteroatom lone pair with the antibonding orbital of an anticoplanar carbon–heteroatom bond ⟨B-83MI 507-02⟩.

Both conformers of 2-methoxytetrahydropyrans and related compounds are stabilized by anomeric effects. In the equatorial conformer (**154**), stabilization results from the *exo*-anomeric effect, but in the axial conformer the *exo*- and *endo*-anomeric effects are in opposition (Figure 23). In view of the preference for the axial conformer, the *endo*-effect is more significant and indeed is sufficient to overcome the steric repulsions associated with this conformation ⟨92T6151⟩. Whilst a similar situation obtains with the 2-cyanotetrahydropyrans, the increased bulk of a methoxycarbonyl group

outweighs the *endo*-anomeric effect, and 2-methoxycarbonyltetrahydropyran exists preferentially in the equatorial conformation ⟨92T6161⟩.



(154)

Figure 23 Anomeric effects in 2-methoxytetrahydropyran.

The determination of thermodynamic parameters ΔH° and ΔS° for the conformational equilibrium in a range of 2-alkoxytetrahydropyrans indicates that the axial preference is a consequence of the higher entropy of the axial conformations. This study stresses the importance of recording conformational equilibrium over a wide temperature range ⟨90T2097⟩. Solvation can influence a conformational equilibrium, and calculations indicate that the equatorial conformer of 2-methoxytetrahydropyran is stabilized by hydration by about 8 kJ mol^{-1} over the axial anomer ⟨94JA2199⟩.

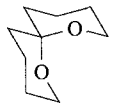
A detailed investigation of three-bond coupling constants in the NMR spectra of some 2-methoxy- and 2-methylamino-tetrahydropyrans indicated that in solution there is a strong preference for the rotamers in which an exocyclic heteroatom lone pair is antiperiplanar to the endocyclic O—C2 bond, i.e. as (**154**) ⟨90T1625⟩.

The preferred conformation in the 3,4,4,5-tetrasubstituted tetrahydropyrans is determined by the size of the 4-substituents since this influences the competition between the destabilizing steric and stabilizing *gauche* effects. Thus, when both R^1 and R^2 are bulky (e.g. Ac, CO_2Et), conformation (**155**) is preferred, but when $R^1 = CN$, the acetoxy groups adopt equatorial dispositions (**156**) ⟨92T6839⟩.

(155) (156)

Various model compounds have been studied in order to understand better the conformations of *C*- and *O*-glycosides. The different conformational preferences of 2-ethyltetrahydropyrans and 3-methyltetrahydropyran arise from differing stabilities of the *gauche* and *anti* O–C–C–C conformers of the equatorial forms ⟨93JA4170⟩.

The conformation (**157**) is sterically or stereoelectronically the most stable and the only form of 1,7-dioxaspiro[5.5]undecane which exists at room temperature. It is suggested that the minimum value for the *endo* and *exo* anomeric effect is about 25 kJ mol^{-1}. On the other hand, the spiro ether, 1-oxaspiro[5.5]undecane, is conformationally mobile, with (**158**), in which the heteroatom is axially oriented with respect to the carbocyclic ring, being the more stable ⟨90CJC597⟩. The *trans*-1-oxadecalin (**159**) is the thermodynamically favored conformer ⟨74JOC2040⟩.

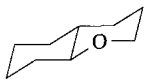


(157)

(158)

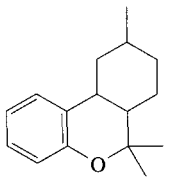
The most stable form of 3,4-dihydro- and 5,6-dihydro-2*H*-pyrans is the half-chair arrangement ⟨84CHEC-I(3)573⟩. The absolute configuration of (+)-2-methoxy-3,4-dihydro-2*H*-pyran has been established as *S* ⟨85G23⟩.

Studies of the conformations of 3,4-dihalogenochromans and 3-halogenochroman-4-ols and their



(159)

2,2-dimethyl derivatives have been summarized ⟨81HC(36)⟩. The pyran ring in the hexahydrocannabinol derivative (**160**) adopts a half-chair conformation according to detailed NMR studies ⟨88T2329⟩, and a combined NMR and molecular mechanics investigation has resulted in a complete stereostructural characterization of the four diastereoisomers of 3,4-dihydro-4-(2-methylpropyl)-spiro[2*H*-benzopyran-2,2′-bicyclo[2.2.1]heptane (**161**) ⟨88JOC3688⟩. Both NMR and theoretical calculations have established the preferred conformations of some dihydroxy derivatives of 1-aminomethylisochromans (**162**), semi-rigid analogs of catecholamines ⟨93JMC3077⟩.



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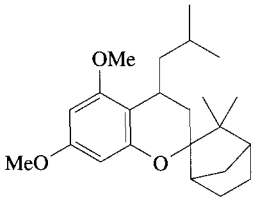

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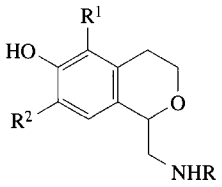
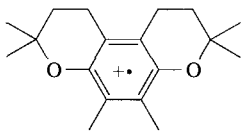


(162)

R^1 = H, R^2 = OH
R^1 = OH, R^2 = H

A study of the ESR and ENDOR spectra of the cation radicals derived from the benzodipyrans (**163**) and (**164**) has established the activation energy for the conformational interconversion of the heterocyclic ring. Comparison of the results with data derived by x-ray analysis of the 6-hydroxychroman (**165**) ⟨83JA6505⟩ suggests that different conformations for the pyran ring prevail in solution and in the solid state ⟨85BCJ1928⟩.



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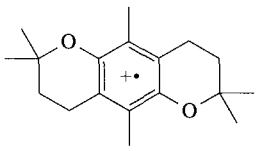

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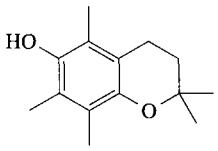
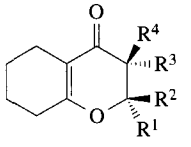


(165)

5.07.4.3.2 Reduced pyranones and their benzologs

Half-chair conformations have been established for *cis*- and *trans*-tetrahydropyran-2-ones ⟨74JOC3890⟩. Studies of the conformational effects in tetrahydropyran-3-ones have indicated the importance of an anomeric effect ⟨77NJC79, 79MI 507-01⟩, and theoretical calculations have shown the presence of this effect in tetrahydropyran-4-ones ⟨93JOC1367⟩. The more stable conformations for the hexahydro-4*H*-benzopyran-4-ones (**166**) have a half-chair cyclohexene ring and a sofa conformation for the pyranone unit ⟨92BSB291⟩.



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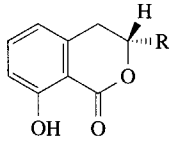

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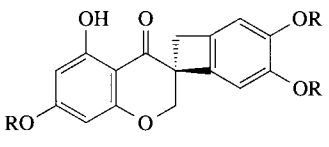


(168)

The size of the acyl group in 3-acyl-3,4-dihydrocoumarins influences not only the conformation of the pyranone ring but also the position of the keto–enol equilibrium. Thus, as R increases in size, the equatorial preference of the acyl group increases. Concomitantly, the mobility of H(3) decreases

as it is forced to take up an axial disposition ⟨85JST(127)127⟩. The absolute configuration of some naturally occurring 3-substituted 3,4-dihydroisocoumarins (**167**) has been established by their synthesis from optically active epichlorohydrins ⟨94TL3949⟩.

Conformational preferences of substituents in chromones have been discussed ⟨85MRC90, 91JCS(P2)927, 91MRC569⟩. The *R* configuration at C(3) has been established for some 3-benzylchroman-4-ones by exciton coupling ⟨88T4981⟩, and a full structural analysis for related benzocyclobutene homoisoflavanones (**168**) using ^{1}H NMR, CD, and x-ray techniques indicated the *R* configuration at the chiral centre ⟨90T6565⟩.

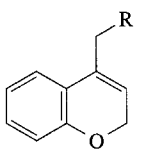
5.07.4.4 Tautomerism

A treatise on tautomerism in heterocycles reviews the work in this area on pyrans and fused pyrans ⟨76AHC(S1)1⟩.

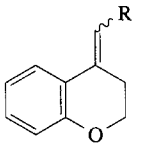
5.07.4.4.1 Prototropy

(i) Potential methyl groups

A thermodynamic equilibrium between 4-alkyl-2*H*-chromenes (**169**) and the corresponding methylenechromans (**170**) has been revealed by IR and NMR studies ⟨68BSF4203⟩.

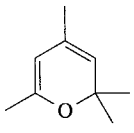


(**169**)

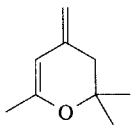


(**170**)

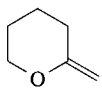
Proton NMR spectra show that both pyrans (**171**) and (**172**) exist as such in solution and do not interconvert ⟨64BSF1492⟩. The isomerization of (**173**) to (**174**) in solution favors the latter; ΔG° is -21.8 kJ mol^{-1} ⟨74ACS(B)1234⟩.



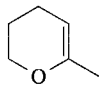
(**171**)



(**172**)



(**173**)



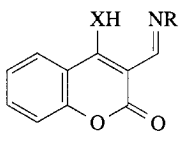
(**174**)

(ii) Potential hydroxy groups

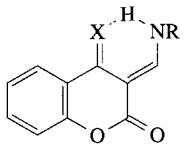
Tautomerism in hydroxypyranones has been extensively studied and the major investigations have been reviewed ⟨63AHC(1)339, 76AHC(S1)116, 84CHEC-I(3)573⟩. The tautomeric behavior of 4-hydroxycoumarins has been extensively studied. This appears to be the preferred form in solution, although the 2-hydroxychromone tautomer is present in the solid state ⟨82JHC385⟩. In contrast, 3-hydroxychromone exists as such. There does not appear to be any evidence which supports the existence of chroman-3,4-diones ⟨71MI 507-03⟩.

Schiff bases derived from 3-formyl-4-hydroxycoumarin (**175**; X = O) and the related sulfur and selenium compounds (**175**; X = S or Se) exist in the tautomeric keto amino forms. Calculations for the model compounds 3-methylimino-4-X-pyran-2-one indicate that the hydroxy imino tautomer is destabilized by about 24, 49, and 48 kJ mol^{-1}, showing increased stability of the keto amine structure for X = S and Se. Proton NMR data shows a marked preference for the *Z*-rotamer (**176**), in keeping

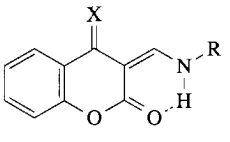
with the greater strength of a hydrogen bond between NH and a keto structure compared with NH and an ester function (**177**) ⟨93JCS(P2)2423⟩.



(**175**)



(**176**)



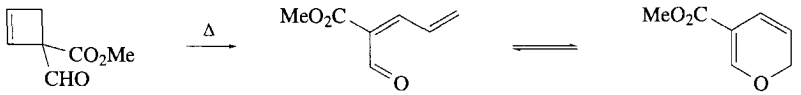
(**177**)

The size of the acyl group in 3-acyldihydrocoumarins influences the keto–enol equilibrium, a feature attributed to the change in conformation of the pyranone ring. The larger acyl groups COPh and COBu^t force the tautomeric proton to adopt an axial disposition, and the keto form is present exclusively in acetone-d_6 solution and in vast excess in $CDCl_3$. However, the enolic tautomer is present in significant amounts in the acetyl derivative ⟨85JST(127)127⟩.

5.07.4.4.2 Ring-chain tautomerism

There is much interest in the valence isomerization of the 2*H*-pyran system, not least because of the commercially valuable photochromic properties exhibited by the benzologs.

Thermolysis of a cyclobutene yielded a mixture of methyl 2-formylpenta-2,4-dienoate (**178**) and 5-methoxycarbonyl-2*H*-pyran (**179**) (Scheme 29) ⟨92TL883⟩.

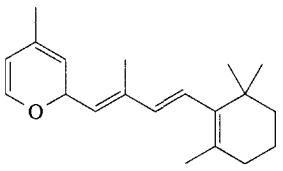


(**178**) (**179**)

Scheme 29

Whilst the penta-substituted 2*H*-pyran (**180**; R = Me) contains only traces of its acyclic tautomer (**181**; R = Me), ^{13}C NMR indicates that 5-acetyl-2,2,6-trimethyl-2*H*-pyran (**180**; R = H) contains about 35% of the valence isomer (**181**; R = H) at 30 °C. It appears that the 3-methyl group sterically destabilizes the dienone ⟨80IZV1011⟩. The terpenoid 2*H*-pyran (**182**) exists as such, but can be converted into its stable acyclic tautomer under suitable conditions ⟨91TL4499⟩.

(**180**) (**181**)



(**182**)

The equilibria between the fused 2*H*-pyrans (**183**) and their dienone tautomers (**184**) are strongly dependent on both the solvent and temperature. In tetrachloroethene (TCE), only 9% of the open-chain form is present at about 30 °C, but this rises to 40% at 113 °C ⟨81T1571⟩. The nature of R also plays a significant role ⟨85HCA192⟩.

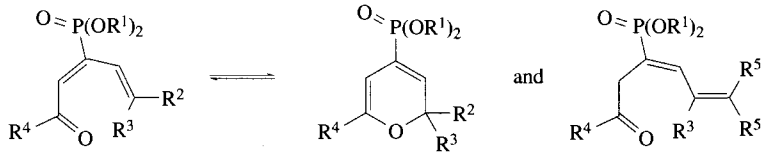
(183) **(184)**

Solvent effects play a major role in the tautomerism of 2-dimethylamino-2*H*-pyrans (**185**). The ring-opened form is favored by polar and protic solvents, being present to the extent of about 15% in TCE but rising to about 30% in $CDCl_3$ and to 100% in D_2O for (**186**; R = Cl) ⟨85IZV1075⟩. Similar observations were made with the related 5,6,7,8-tetrahydro-2*H*-1-benzopyran and its [1,2-*b*] benzolog ⟨891ZV1323⟩.

(185) **(186)**

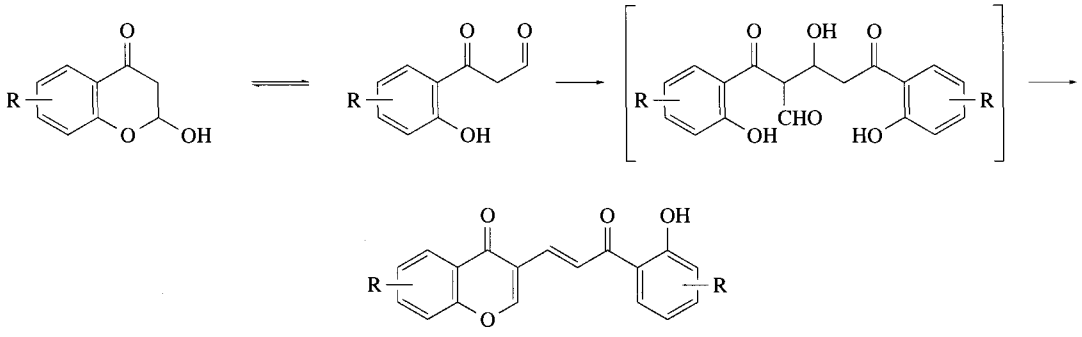
Conversion of simple 2*H*-1-benzopyrans into the open-chain tautomer can be observed on UV irradiation at low temperature. Stabilization of the dienone species can be achieved by extending the conjugation through fusion of a benzene ring at the 5,6- and 7,8-positions and by introducing aryl substituents at C(2). The ring-opened forms are yellow to orange, those derived from the 7,8-isomer surviving better than those from naphtho[2,1-*b*]pyran. Photochromism is lost when a 1-substituent is present in the latter system. Ring closure is a complex process, involving changes in the geometry of the dienone.

The reaction between dialkyl (1-oxo-2-alkenyl)phosphonates and (2-oxoalkylidene)triphenylphosphoranes yields the conjugated dienones (**187**). The nature of the substituents at C(5) influences the structure of the isolated product. Only when a 5-phenyl substituent is present is the dienone isolated. When the substituents are H or Me, the valence isomer, the 2*H*-pyran-4-ylphosphonate (**188**), is obtained either alone or admixed with the non-conjugated dienone (**189**), a product of a 1,5-H shift ⟨85CB2917⟩.



(187) **(188)** **(189)**

Ethyl 4-(2-hydroxyphenyl)-2,4-dioxobutanoate, prepared from 2-hydroxyacetophenone and diethyl oxalate, exists as the 2-hydroxychroman-4-one ⟨77LA1707⟩. This feature appears common to 1,3-diketones of this type ⟨75JCS(P1)1706, 77IJC331⟩. However, on melting, 2-hydroxychroman-4-ones are dimerized to the yellow 1-(2-hydroxybenzoyl)-2-(4-oxo-4*H*-1-benzopyran-3-yl)ethenes, presumably through interaction of the tautomeric forms of the substrate (Scheme 30) ⟨88IJC811⟩. 4-Amino-5-formylpentanoic acid, glutamate semialdehyde, exists in the cyclic form 5-amino-6-hydroxy tetrahydropyran-2-one ⟨93TL1177⟩.



Scheme 30

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5.08
Pyrans and their Benzo Derivatives: Synthesis

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University of Central Lancashire, Preston, UK.

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5.08.1 INTRODUCTION

Six-membered oxygen heterocyclic compounds occupy an important slot in natural product chemistry, featuring in plant life, most notably as the flavonoids, and in the marine environment ⟨95CRV2041⟩ where they form a part of the wide range of macrocyclic molecules. The presence of oxacyclic units in polyether and macrolide antibiotics, for example, the avermectins ⟨89JA2967, 91JCS(P1)667, 94OPP617⟩, brevetoxins ⟨89JA6666, 89JA6676, 89JA6682, 95JA10227, 95JA10239, 95JA10252⟩, swinholides ⟨95T9393, 95T9413, 95T9437, 95T9467⟩, and milbemycins ⟨89T7161, 94OPP617⟩, has stimulated intense synthetic activity in pyran chemistry because of the significant pharmacological activity shown by these systems. The old, established synthetic routes to pyrans and their benzologues are still of value and in active use, but these have been supplemented by preparations based on newer methodologies.

The literature covering oxygen heterocycles is extensive. The earlier work is comprehensively covered by the major compilations and their updated editions such as Elderfield ⟨B-50MI 508-01, B-51MI 508-01, B-61MI 508-01⟩, and Rodd's "Chemistry of Carbon Compounds" ⟨B-77MI 508-01, B-90MI 508-01⟩. Annual reviews in "Progress in Heterocyclic Chemistry" cover the significant advances and some aspects of oxygen heterocycles are covered at intervals in "Contemporary Organic Synthesis" ⟨95COS133, 95COS189⟩. More specialized texts cover the benzologues of 2*H*-pyran and oxidized derivatives ⟨77HC(31), 81HC(36), 87HC(47-1), 92HC(47-2)⟩, and the flavonoids ⟨B-62MI 508-01, B-75MI 508-01, B-82MI 508-01, B-85MI 508-01, B-94MI 508-01⟩. Reviews on the use of palladium-catalysts ⟨88H(27)2225, 92H(33)1079⟩ and α-oxoketenes ⟨94SI219⟩ in synthesis contain material relevant to this chapter. Accounts of naturally occurring oxygen heterocycles include ⟨B-63MI 508-01, B-73MI 508-01, B-82MI 508-02⟩ and ⟨86MI 508-01⟩.

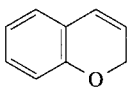
This chapter should be read in conjunction with the corresponding section in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I).

5.08.2 PYRANS AND FUSED PYRANS: 2*H*-PYRANS

Simple pyrans are unstable compounds, a characteristic of a dienolic ether system. 2*H*-Pyran (**1**) has not yet been synthesized although it features as a ligand in a number of metal complexes. 4*H*-Pyran (**2**), first synthesized in 1962, is now well studied. Stabilization follows the incorporation of unsaturated groups and from the fusion of aromatic rings. Thus, 2*H*-1-benzopyrans (**3**) have an extensive chemistry and are widespread in nature. Two other benzologues are considered, 4*H*-1-benzopyran (**4**) and 1*H*-2-benzopyran (**5**). The chemistry of pyrans has been reviewed ⟨83AHC(34)145, 95AHC(62)19⟩.

(1)

(2)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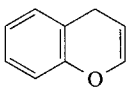
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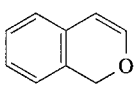

(5)

The overall instability of this system is reflected in the relative paucity of literature on derivatives of 2*H*-pyran. The system undergoes a facile electrocyclic ring opening to the dienone (**6**) (Equation (1)) although both species may be present in equilibrium under normal conditions (see Chapter 5.07). Substitution, especially at C-2, is essential for the existence of the pyran.

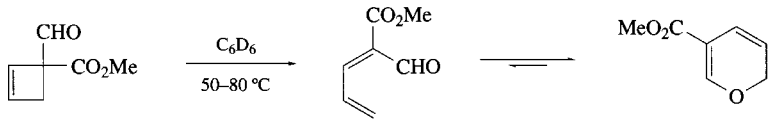
(6) (1)

5.08.2.1 Formation of one bond

(i) Adjacent to the heteroatom

Several syntheses of 2*H*-pyrans are based on the preparation of the acyclic precursors (**6**) in the hope that the dienone⇌2*H*-pyran equilibrium will favor the heterocycle. It should be emphasized that often the product will contain a mixture of both valence isomers.

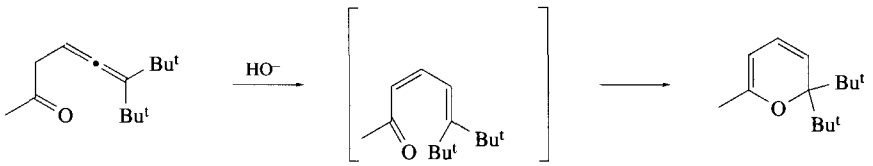
Thermal conrotatory ring opening of the cyclobutene (**7**) involves inward rotation of the formyl group leading to the dienal (**8**), which spontaneously cyclizes to methyl 2*H*-pyran-5-carboxylate (**9**). Although (**9**) could not be isolated in a pure state, it has been trapped as the Diels–Alder adduct with tetracyanoethylene (Scheme 1) ⟨92TL883⟩.



(7) (8) (9)

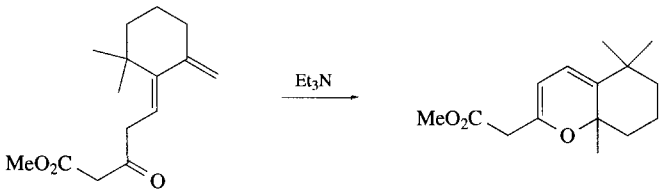
Scheme 1

The reaction of base with the allene (**10**) leads to the 2,2-di-*t*-butylpyran (**11**) by way of the dienone (Scheme 2) ⟨91CB2633⟩ and the dienone (**12**) similarly forms a 2*H*-pyran (**13**) ⟨85JOC1939⟩.



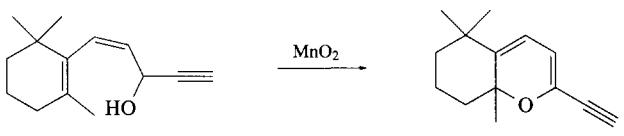
(10) (11)

Scheme 2

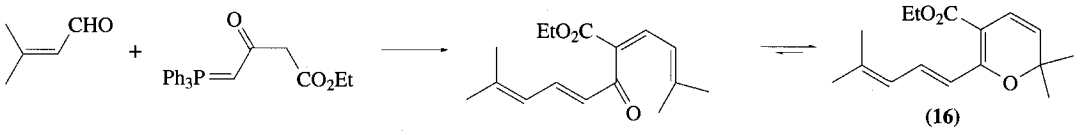


(12) (13)

Oxidation of the dienol (**14**) leads to the 6-ethynyl-2*H*-pyran (**15**) ⟨85JA1034⟩, whilst a Wittig reaction is used to produce the pentadienyl derivative (**16**) (Scheme 3) ⟨87TL4721⟩.

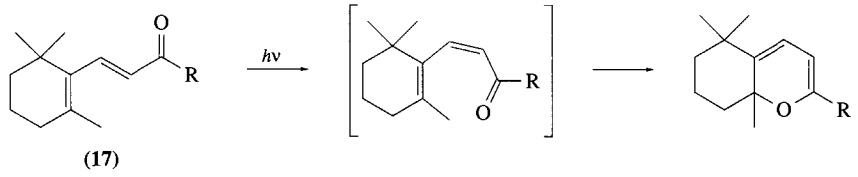


(14) (15)



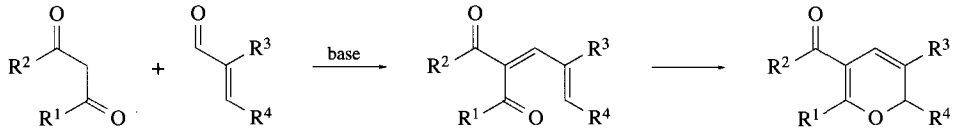
Scheme 3

The 2*H*-pyran system is also formed when β-ionone (**17**; R = Me) and its derivatives are irradiated, yielding fused 2*H*-pyrans with a variety of substituents at the 6-position (Scheme 4) ⟨83CL651, 83RTC355, 85HCA192, 85JOC1939, 89SC1759⟩.



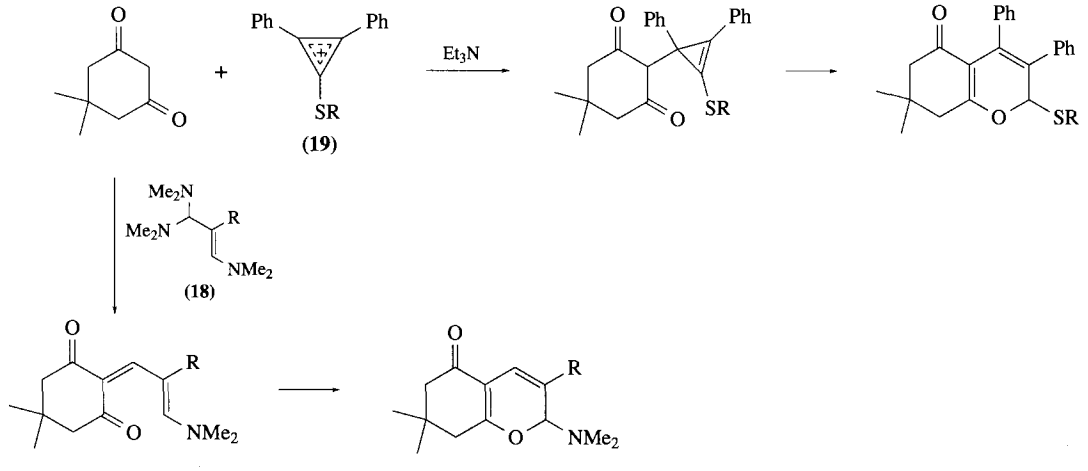
Scheme 4

The dienone precursors can also be obtained using Knoevenagel methodology, utilizing the condensation of anions derived from 1,3-dicarbonyl compounds with α,β-unsaturated aldehydes (Scheme 5). Thus, simple 1,3-diketones yield the 2*H*-pyran directly ⟨88IZV1815⟩ and cyclohexan-1,3-diones afford fused pyrans ⟨82S683, 84JHC913, 87JOC1972⟩.



Scheme 5

Alternative substrates to the α,β-unsaturated compound include (**18**), which yields 2-dimethylamino-2*H*-pyrans ⟨88KGS1325⟩, and the cyclopropenium salt (**19**) which affords a 2-alkylsulfanylpyran (Scheme 6) ⟨84BCJ734⟩.

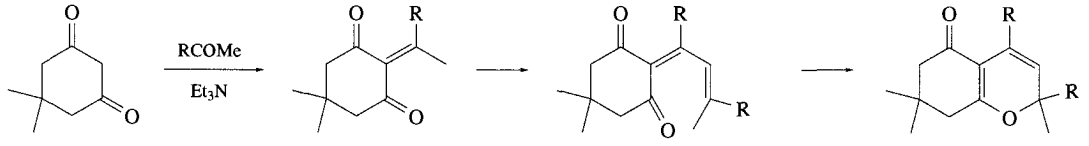


Scheme 6

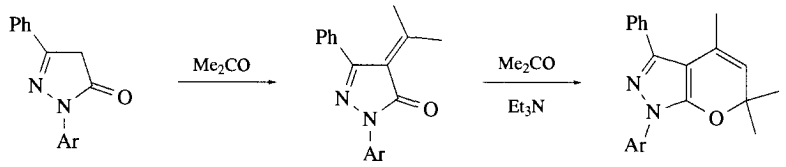
The anions of 1,3-dicarbonyl compounds also react with perfluoroalkenes, though there is some dispute about the nature of the products ⟨83JCS(P1)2451⟩.

Using the same methodology, dimedone reacts with ketones to form the 2-alkylidene derivatives which undergo a second condensation with the ketone to give dienones and hence 2*H*-pyrans

(Scheme 7) ⟨89IJC81⟩. In a similar manner, acetone reacts with 2-aryl-3,4-dihydro-3-oxo-5-phenyl-2*H*-pyrazoles to form pyrano[2,3-*c*]pyrazoles (Scheme 8) ⟨83S482⟩.

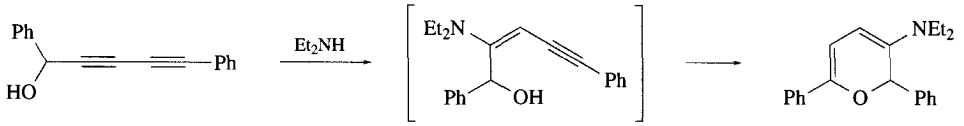


Scheme 7



Scheme 8

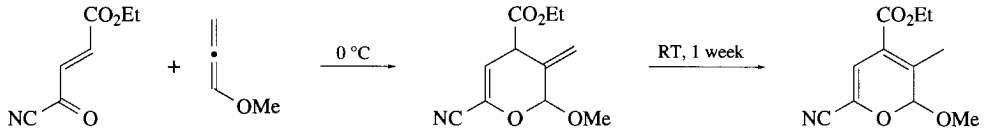
The function of the dienone can be served by a pent-2-en-4-yn-1-ol, which can be formed *in situ* by the addition of a secondary amine to a penta-2,4-diyn-1-ol (Scheme 9) ⟨82CZ296⟩, and by a 5-hydroxy-5-methoxypent-2-en-1-one ⟨83AP(316)454⟩. Acid chlorides react with but-3-enynes in the presence of $AlCl_3$ to form 2*H*-pyrans via addition to the triple bond ⟨90ZOR965⟩.



Scheme 9

5.08.2.2 Formation of two bonds

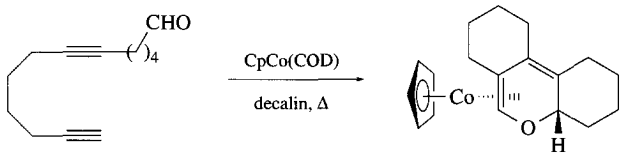
Although hetero-Diels–Alder reactions with α,β-unsaturated carbonyl compounds usually lead to 4*H*-pyrans, when the dienophile is an allene, a 2*H*-pyran results (Scheme 10) ⟨91CB1425⟩.



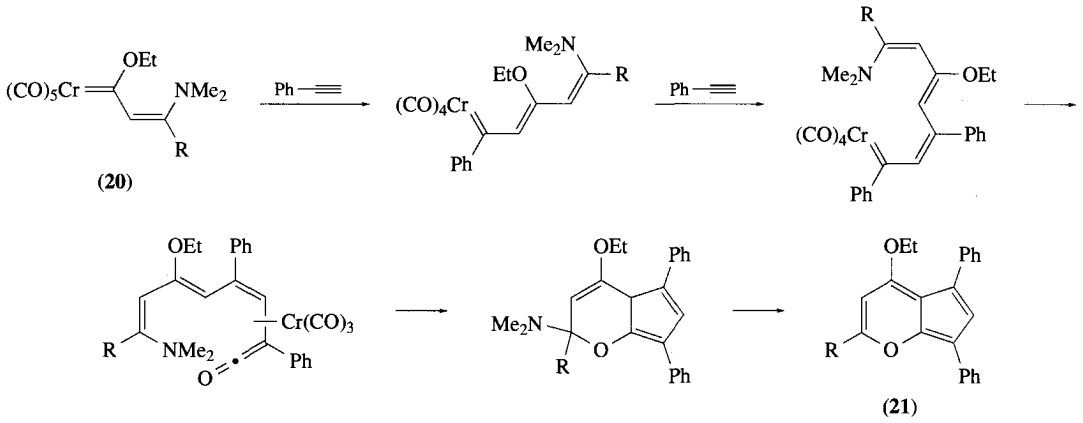
Scheme 10

The chromium complex (**20**), obtained from $Cr(CO)_5$ and a terminal alkyne, reacts with phenylacetylene to form cyclopenta[*b*]pyrans (**21**), which are red solids isoelectronic with azulene. A proposed mechanism suggests that the bicyclic species results from an intramolecular [4 + 2] cycloaddition (Scheme 11) ⟨91AGE1658⟩.

Metal assisted [2 + 2 + 2] cycloadditions involving a carbonyl function can lead to 2*H*-pyrans. Thus, dimerization of 5-cyclodecynone effected by a cobalt cyclopentadienyl complex yields a fused 2*H*-pyran, but rather more impressive is the intramolecular version outlined in Equation (2) ⟨89TL2893⟩. The 2*H*-pyrans can be liberated from these complexes ⟨89SL15⟩.

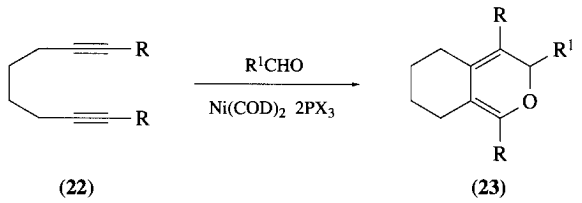


(2)



Scheme 11

In a similar fashion, the dialkyne (**22**) reacts with aldehydes in the presence of Ni(0) complexes to form the bicyclic pyrans (**23**) (Equation (3)) ⟨88JA8570⟩.



(3)

(**22**) (**23**)

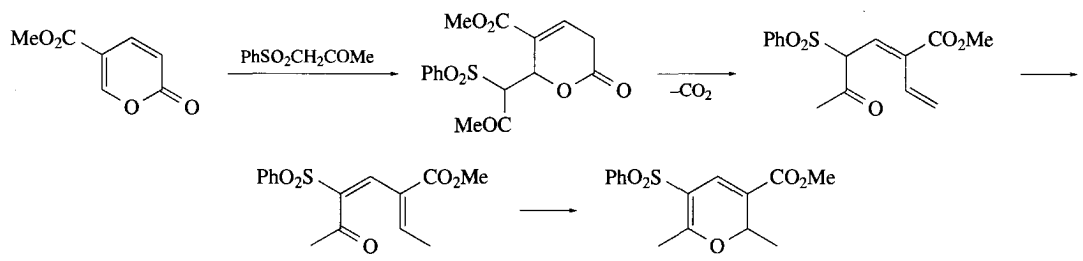
5.08.2.3 From a preformed heterocyclic ring

(i) From reduced pyrans

Various hydroxy derivatives of dihydropyrans have been dehydrated to the 2*H*-pyran ⟨87JCS(P1)2125, 91TL4499⟩.

(ii) From pyranones

Methyl 2-oxopyran-5-carboxylate is decarboxylated on treatment with $PhSO_2CH_2COMe$ under basic conditions. Initial addition of the carbanion is followed by ring opening, decarboxylation and ring closure, which culminates in the formation of the 2*H*-pyran (Scheme 12) ⟨84JA7143⟩.



Scheme 12

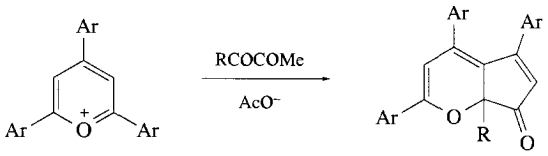
Reaction of pyran-2-ones with Grignard reagents gives 2,2-disubstituted 2*H*-pyrans ⟨87JCS(P1)2125⟩ and oxalyl chloride in DMF converts 2,3-dihydro-2,2-dimethyl-6-phenylpyran-4-one into the corresponding 4-chloro-2*H*-pyran ⟨92HCA27⟩.

(iii) From pyrylium salts

Nucleophilic attack at C-2 of pyrylium salts can lead to 2*H*-pyrans, but competitive attack at the 4-position is often favored and hence 4*H*-pyrans are preferentially formed. Additionally, ring opening can occur, further frustrating attempts to produce 2*H*-pyrans. Clearly, the substituents present in the pyrylium salt play a significant role in determining the nature of the final product and the choice of nucleophilic reagent and reaction conditions also has a major effect. Thus, whilst Me_2CuLi affords the 4*H*-pyran on reaction with 2,4,6-trisubstituted pyrylium salts in THF, it yields the 2*H*-pyran in diethyl ether ⟨89JOC1931⟩.

2-Acetoxy-2*H*-pyrans are formed when acetate ion reacts with 2,4,6-triphenylpyrylium ⟨83JCS(P1)497⟩ and the reaction of water ⟨84JCS(P2)867⟩, methoxide ions ⟨89JCS(P2)1393⟩, and amines ⟨85JCS(P2)171⟩ have been studied in detail.

The reaction of acetate ions in the presence of 1,3-diketones results in a sequence of ring opening and ring closures which lead to fused 2*H*-pyrans (Equation (4)) ⟨89JPR306⟩.



(4)

Only highly substituted pyrylium salts yield stable 2*H*-pyrans on reaction with 1,3-diketones ⟨86JPR359⟩ and primary ⟨84JCS(P2)49⟩ and secondary ⟨84JPR657⟩ amines.

5.08.3 2*H*-CHROMENES (2*H*-1-BENZOPYRANS)

A number of chromenes occur naturally, a feature which, coupled to the pharmacological activity and the photochromic behavior ⟨B-90MI 508-02⟩ exhibited by various derivatives, has ensued a healthy interest in their synthesis. The earlier work has been comprehensively reviewed ⟨75AHC(18)119, 77HC(31)11⟩. Reviews concerned with nitroalkenes ⟨86H(24)2645⟩, vinylphosphonates ⟨92S333⟩, and the Wittig reaction ⟨95H(41)2357⟩ refer to their value in the synthesis of chromenes.

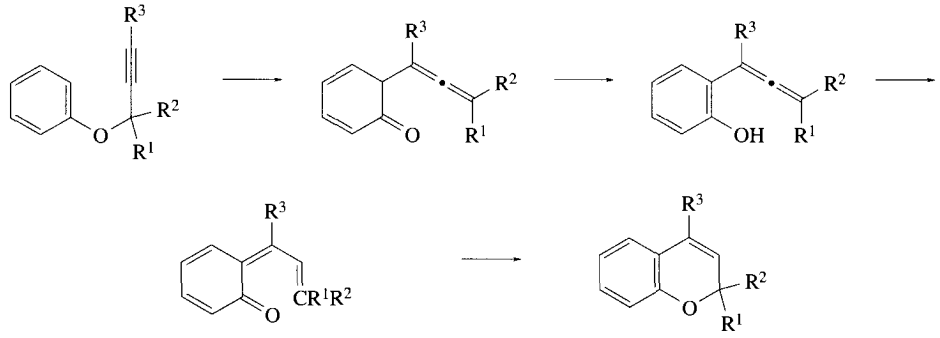
5.08.3.1 Formation of One Bond

5.08.3.1.1 Adjacent to the heteroatom

The facile cyclization of *o*-quinone allides to 2*H*-chromenes implies that any method of generation of the allide is a synthetic route to the heterocycle involving formation of the O—C(2) bond.

The synthesis of 2*H*-chromenes developed by Iwai and Ide ⟨62CPB926, 63CPB1062⟩ involving the thermal cyclization of aryl propargyl ethers proceeds through a series of pericyclic reactions. An initial [3,3]-sigmatropic rearrangement is followed by a [1,5]-hydrogen shift. The resulting *o*-quinone allide undergoes an electrocyclization to the chromene (Scheme 13) ⟨68HCA1510⟩. This route has many attractive features and has been widely used. The ethers themselves are readily available from the reaction of phenolic compounds with 3-halogenoalkynes or alkyn-3-ols. Copper(I) iodide has been advocated as a catalyst for this reaction ⟨95S707⟩. Furthermore, both components are easily accessible and are often cheap materials, and wide structural variation can be accommodated in the synthesis. The cyclization to the chromene is facile and can often be accomplished in a one-pot sequence. Indeed, chromene is occasionally present in samples of the propargyl ether. *N*,*N*-Diethylaniline has been widely used as the solvent, but other lower boiling solvents have also been used. The solvent can influence the course of the reaction, in the worst scenario leading to a different heterocyclic system, a benzofuran, possibly as a consequence of competition between a 1,5-shift in the allenic intermediate and addition to the central allenic carbon atom. Thus, whilst 2-methylbut-3-yn-2-yl 3,5-dinitrophenyl ether affords the chromene (79%) on boiling in xylene, the benzofuran

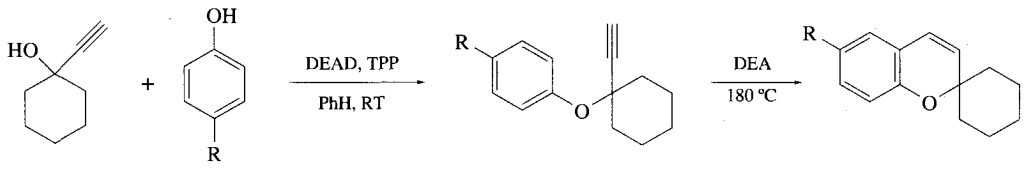
(61%) results in DMSO ⟨92JCS(P1)573⟩. Other effects include significant changes in yield and variation in isomer distribution from *m*-substituted phenyl propargyl ethers.



Scheme 13

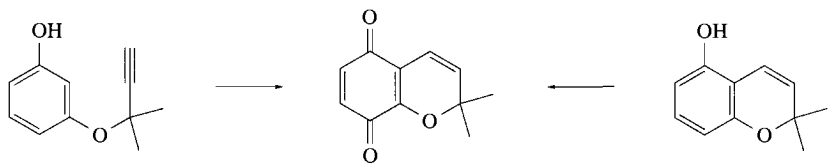
Earlier work concentrated on the synthesis of 2-alkyl- and 2,2-dialkyl-chromenes, but the propargyl ether route is especially valuable for the preparation of the corresponding aryl derivatives since other general chromene syntheses are often unreliable or inappropriate for these compounds. The requisite alkynols are accessible from diaryl ketones by reaction with lithium acetylide, although the use of trimethylsilylethynyllithium and subsequent desilylation is usually preferable. Application of this approach to 1- and 2-naphthols leads to naphtho[1,2-*b*]pyrans and the [2,1-*b*]isomers, respectively, and is particularly important because of the photochromic properties of the products ⟨94MIP22850⟩.

2-Spiro linked chromenes are also accessible from aryl propargyl ethers. The ethers obtained by Mitsunobu coupling of 1-ethynylcyclohexanol with phenols are readily cyclized in high yield (Scheme 14). The bridged analogue, 1-ethynyl-*endo*-2-norbornanol behaves similarly ⟨89TL2297⟩.



Scheme 14

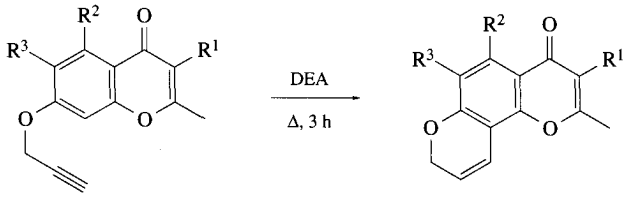
2*H*-1-Benzopyran quinones are available by manipulation of appropriate aryl propargyl ethers prior, during or after cyclization to the heterocycle. Thus, cyclization of 4-aryloxy-5-methoxy-1,2-benzoquinones in toluene yields benzopyran-5,8-quinones ⟨87S790⟩. Similar 1,4-quinones result from a Fremy salt oxidation of either the 3-hydroxyphenyl propargyl ether or 5-hydroxy-2,2-dimethylchromene (Scheme 15). The former route suggests that oxidation precedes cyclization, thereby preventing the expected cyclization to a 7-hydroxychromene. Electrolytic oxidation of the 2,5-dimethoxyphenyl propargyl ether in methanolic KOH also yields the quinone ⟨90JCS(P1)2979⟩.



Scheme 15

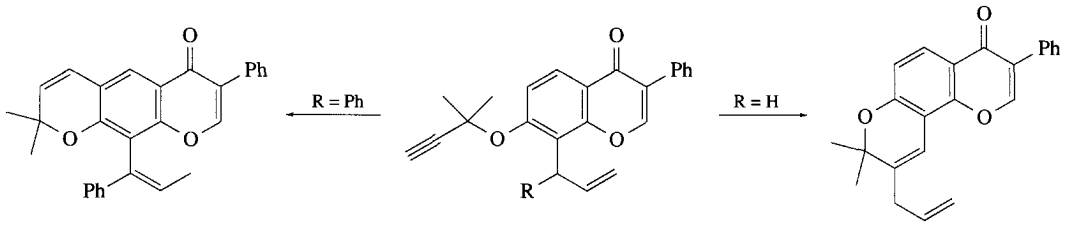
Hydroxy derivatives of several heterocyclic systems have been used as the phenolic component in the Iwai–Ide synthesis of a variety of hetero-fused pyrans. The propynyl ethers derived from 7-hydroxy-2-methylchromones afford 4*H*,8*H*-benzo[1,2-*b*][3,4-*b*']dipyran-4-ones on refluxing in *N*,*N*-diethylaniline. The angular isomer results even when the 6-position in the original chromone is unsubstituted (Equation (5)) ⟨89G481⟩. Application of this procedure to 5,7-dihydroxychromone is interesting in that propargylation occurs selectively at the 7-hydroxy group, presumably because 5-OH is hydrogen bonded to the carbonyl moiety, and on cyclization both angular and linear

chromenes are formed. 5-Hydroxy-8,8-dimethyl-8*H*-pyrano[2,3-*h*]chromone is obtained in five times the quantity of the linear [3,2-*g*] isomer ⟨85IJC250⟩. In ethanolic KOH, the angular compound is isomerized to the linear product.



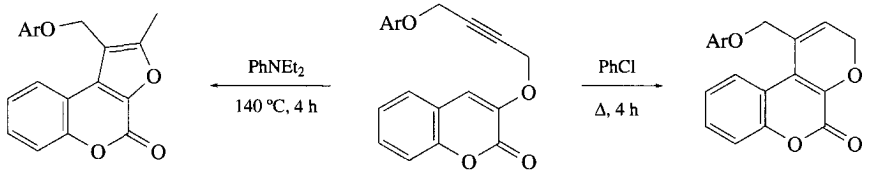
(5)

The Claisen rearrangement of 1,1-dimethylprop-2-ynyl ethers obtained from 7-hydroxyisoflavones is complex. The presence of an 8-methyl function in the isoflavone, introduced to direct cyclization to the linear benzodipyranone, effectively prevents formation of the new pyran ring, and leads instead to the cyclopenta[2,3-*h*]benzopyran-2,7-dione by way of an intramolecular Diels–Alder reaction. However, a prop-2-enyl substituent at the 8-position allows the formation of the angular benzodipyranone through a Cope rearrangement. Synthesis of the linear isomer can be achieved from 7-hydroxy-8-(1-phenylprop-2-enyl)isoflavone (Scheme 16) ⟨92T563⟩.



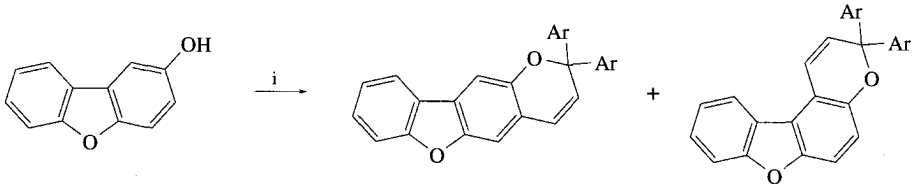
Scheme 16

1-Aryloxy-4-coumarin-3-yloxybut-2-ynes, derived from 3-hydroxycoumarin and 1-aryloxy-4-chlorobut-2-ynes, yield the pyrano[2,3-*c*][1]benzopyran-5(3*H*)-one exclusively on refluxing in chlorobenzene. However, in the presence of radical generators, a furanocoumarin is the major product, whilst it is the sole product under ionic conditions. It would appear that the intermediate allene which arises from an initial [3,3]-sigmatropic rearrangement is the critical species in determining the regiospecificity of the overall reaction (Scheme 17) ⟨89JCS(P1)1901⟩. The corresponding ethers derived from 4-hydroxycoumarin generally yield only the pyrano[3,2-*c*][1]benzopyran-5(2*H*)-one on heating in chlorobenzene, although the 2-methylphenoxy derivative affords the furocoumarin ⟨94IJC120⟩.



Scheme 17

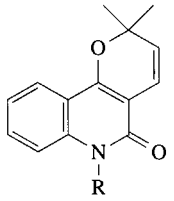
The reaction of 2-hydroxydibenzofuran with 3,3-diarylpropyn-1-ols, which can be catalysed by various acidic substances, yields a mixture of the linear and angular benzofurochromenes in which the latter predominates (Scheme 18) ⟨95MIP05382⟩.



i, $Ar_2C(OH)C{\equiv}CH$, Al_2O_3, PhMe, Δ

Scheme 18

Other hetero-fused pyrans synthesised by the propargyl ether route include the pyrano[3,2-*c*]quinoline alkaloids flindersine (**24**; R = H) and its *N*-alkylated derivative, haplophylline (**24**; R = $CH_2OOCCH=CMe_2$), and other examples obtained from 4-hydroxyquinolin-2-ones ⟨87JHC869, 93SC1087⟩, and the pyrano[2,3-*c*]carbazole (**25**) and the [3,2-*b*] isomer (**26**), glycomaurin and isoglycomaurin, respectively, from 2-hydroxy-7-methylcarbazole ⟨89AJC1375⟩.



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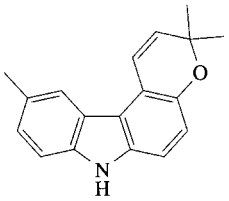

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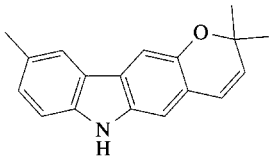
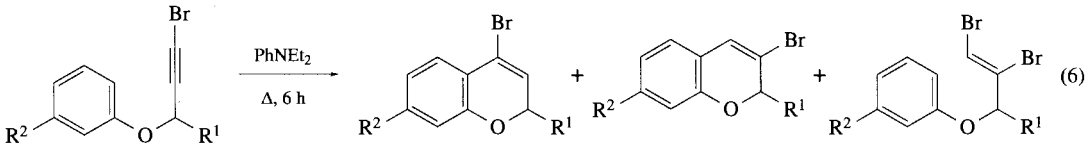


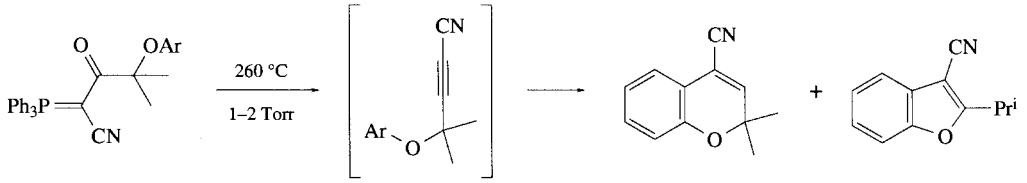
(26)

The scope of this reaction can be further enhanced by the inclusion of a functional group at the terminal position of the alkynyl moiety which subsequently becomes incorporated at the 4-position of the chromene. However, simple γ-bromo aryl propargyl ethers give a mixture of both the 3- and 4-bromochromenes together with a dibromoallyl aryl ether (Equation (6)). The presence of an α-methyl substituent accelerates the cyclization, thereby reducing the extent of competing side reactions and leads to good yields of the 4-bromochromene. The corresponding γ-chloro compounds give only the 4-chlorochromene in *N*,*N*-diethylaniline. It should be noted that when the cyclization is carried out in ethane-1,2-diol, the initially formed 4-halogenochromene is hydrolyzed to the chroman-4-one ⟨89T309⟩. 3-Bromochromenes result from a Claisen rearrangement of 2,3-dibromoallyl phenyl ethers ⟨94CC1177⟩.



(6)

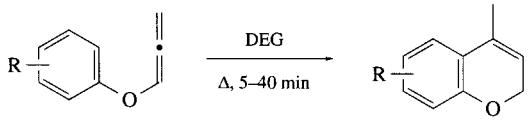
Thermolysis of (2-aryloxy-2-methylpropanoyl)cyanomethylenetriphenylphosphoranes results in an intramolecular Wittig reaction. A spontaneous Claisen rearrangement of the resulting aryl propargyl ether follows, affording a mixture of the 4-cyanochromene and the benzofuran (Scheme 19) ⟨87T5335⟩.



Scheme 19

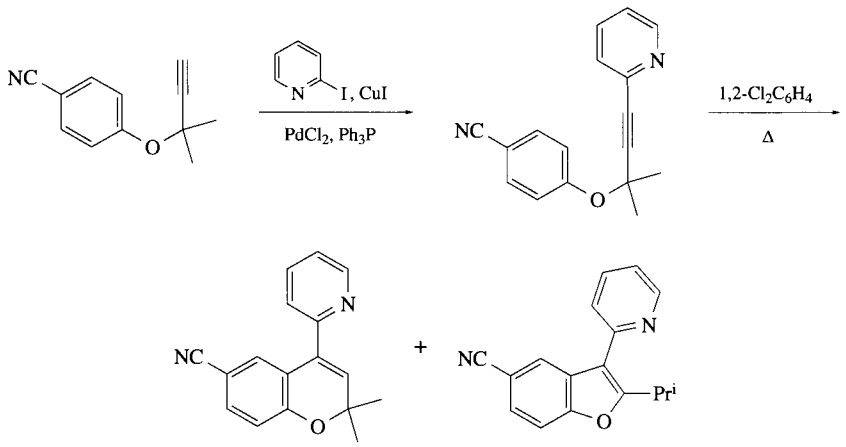
The 2-pyridylacetylene, derived from the aryl propargyl ether by a palladium catalyzed coupling process, is cyclized to the 4-pyridylchromene by refluxing a dilute solution in 1,2-dichlorobenzene. As the concentration of the ether is increased, increasing amounts of the benzofuran are formed (Scheme 20) ⟨92TL811⟩.

Closely related to these studies is the thermal Claisen rearrangement of aryl allenylmethyl ethers which yields the 4-methylbenzopyran in refluxing diethylene glycol. At lower temperatures, 2-(2-hydroxyaryl)buta-1,3-dienes are formed preferentially (Equation (7)) ⟨92CC1760⟩.



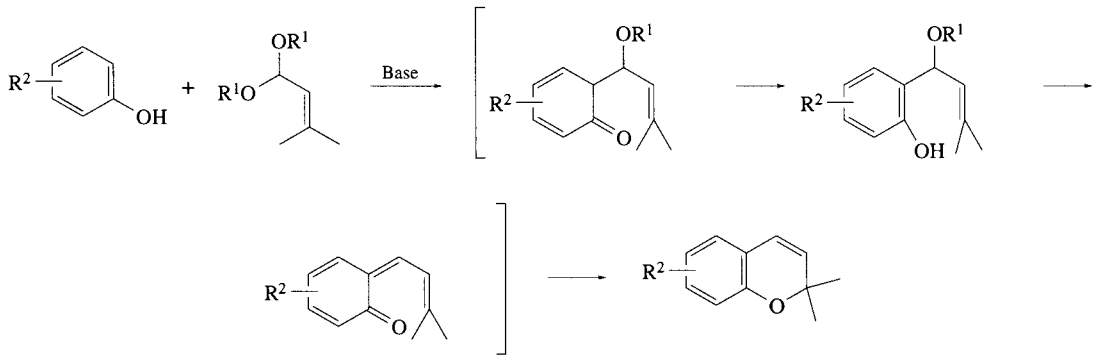
(7)

The condensation of α,β-unsaturated carbonyl compounds with phenols is a valuable route to chromenes, especially to examples bearing hydroxy and alkoxy functions, many of which are



Scheme 20

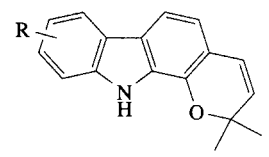
naturally occurring. The reaction is successful with protected forms of alkenals and it is also convenient to use acetals of hydroxyalkanals, introducing the double bond during the course of the reaction. Studies of the pyridine catalysed condensation have shown that the reaction proceeds by *C*-hydroxyalkenylation of the phenoxide ion and subsequent cyclization of the *o*-quinoneallide to the chromene (Scheme 21) ⟨74JCS(P1)1007⟩. Clearly this reaction will be facilitated by electron-releasing substituents in the phenolic moiety and both 3-methoxyphenol and 3,4-dimethoxyphenol react with 3-methylbutenal to give methoxychromenes, precocenes I and II respectively, in moderate yields ⟨91TL7251⟩. Both 1- and 2-naphthols behave similarly, but deactivated phenols (R^2 = Br, Cl, CHO, CO_2R) give much reduced yields. The use of 4-methylpyridine as catalyst offers some slight advantage, whilst the increased yields in the reactions with citral are probably associated with its greater stability ⟨93SC3019⟩. 2-Fluoro-1,1-dimethoxy-3-methylbut-2-ene gives satisfactory yields of 3-fluoro-2,2-dimethylchromenes with a wide variety of simple phenols ⟨80JHC1377⟩. It has been shown that this reaction is successful with phenols bearing electron-withdrawing groups provided only 0.25 molar equivalent of pyridine, or better 3-methylpyridine, is used and that ethanol is continuously removed from the reaction mixture ⟨95JOC3397⟩.



Scheme 21

This route has been used to synthesize a range of 2*H*-pyrano[2,3-*a*]carbazoles (**27**), isomers of the alkaloid girinimbine, from 1-hydroxycarbazoles ⟨94IJC479⟩, and naphtho[2,3-*b*]pyran-5,10-quinones, including α-caryopterone (**28**), have likewise been obtained from hydroxyjuglones ⟨88TL155⟩. The base-catalysed reaction of *trans,trans*-farnesal with 4,7-dihydroxycoumarin yields the pyranocoumarin (**29**) by way of a tandem aldol reaction and electrocyclization ⟨91HCA495⟩, and a double aldol condensation precedes cyclization in the formation of pyrano[2,3-*d*]pyrimidines (**30**) from uracils and acetone ⟨87SC1435⟩.

Several modifications have been made to this route. When the reaction is carried out in the presence of phenylboronic acid, a 1,3,2-benzodioxaborin is formed in high yield which decomposes



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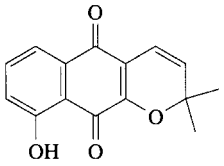

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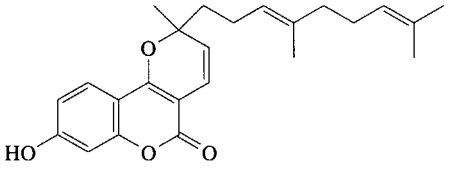

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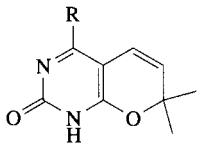
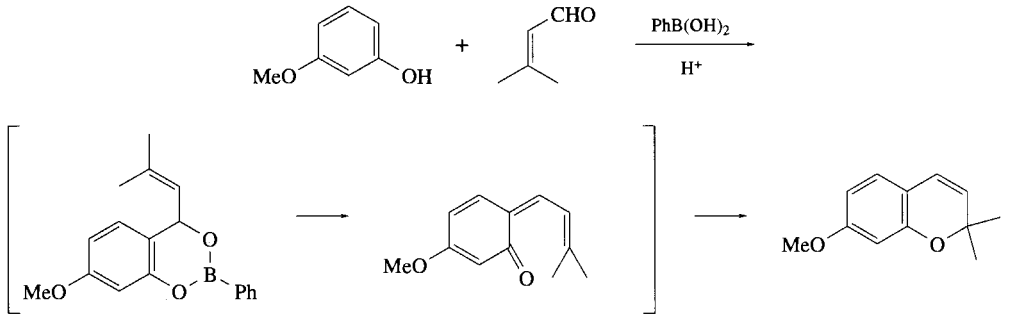


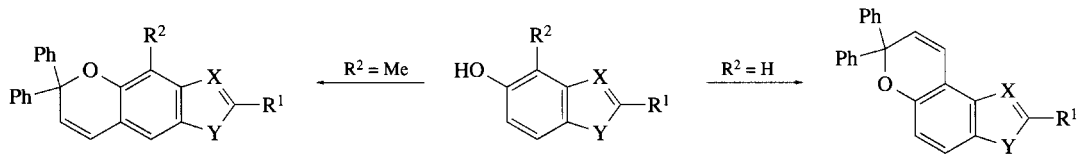
(30)

to a quinone methide on heating and hence a chromene is formed (Scheme 22). The robustadial framework has been assembled in this manner ⟨94CJC1866⟩.



Scheme 22

The reaction of metal (Ti, Mg) phenolates with α,β-unsaturated carbonyl compounds in toluene gives good yields of chromenes and is compatible with a wide variety of substituents in the aromatic ring. High regioselectivity is achieved, probably arising from the coordinating ability of the metal ⟨79JOC803⟩. This approach has been refined by the use of stoichiometric amounts of the phenol, unsaturated compound, and titanium(IV) ethoxide, leading to shorter reaction times and increased yields. Importantly, a range of heterocyclic phenols have yielded heteroannulated chromenes by this methodology. The regioselective nature of the process is retained, leading to the angular isomer, though suitable substitution in the starting phenol allows formation of the linear isomer (Scheme 23) ⟨94JCS(P1)2591⟩.

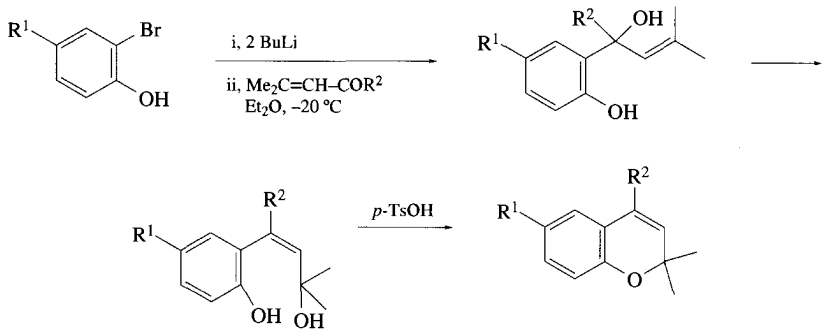


Reagents: i, $Ti(OEt)_4$, PhMe; ii, $Ph_2C{=}CHCHO$; iii, PhMe, Δ

Scheme 23

The 1,2-addition of protected aryllithium compounds to various α,β-unsaturated aldehydes affords carbinols which can be deprotected and cyclized to chromenes in the presence of a bentonite clay ⟨94H(37)759⟩. The dianion derived from *o*-bromophenols also adds to the carbonyl function of the α,β-enone. Cyclization after an allylic rearrangement of the diol yields the benzopyran (Scheme 24) ⟨83S845⟩.

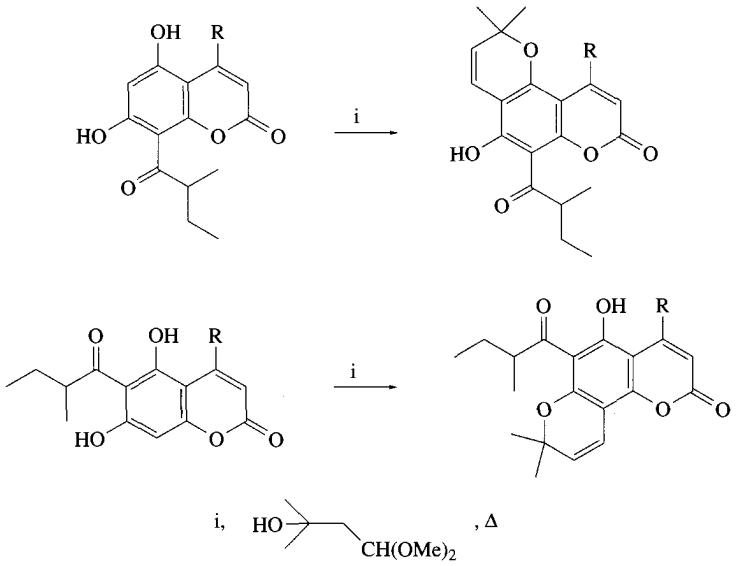
Efficient activation of the phenols towards electrophilic attack is provided by additional hydroxy groups and many natural products have been synthesized from polyhydric phenols and citral and 4,4-dimethoxy-2-methylbutan-2-ol ⟨71JCS(C)796, 71JSC(C)811⟩. However, such compounds may give



Scheme 24

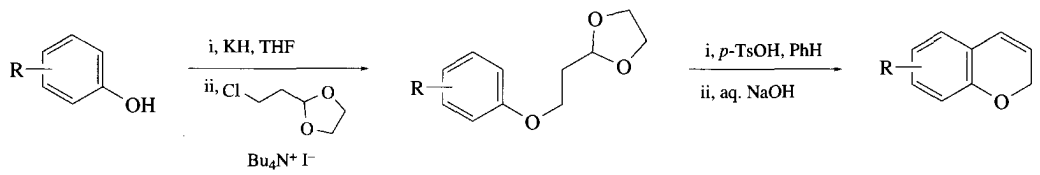
rise to isomeric products. Regiospecificity appears to be controlled by chelation, with only free hydroxyl functions being involved in chromene formation. Deuterium exchange provides a simple test for the suitability of a phenol to participate in the reaction ⟨64JA2084⟩. Additional directional control stems from resonance stabilization during the reaction sequence. The reactions of 2,4-dihydroxyacetophenone with but-2-enal, 3-methylbut-2-enal and cinnamaldehyde are illustrative ⟨72JCS(C)811, 74JCS(P1)1007⟩.

Judiciously placed substituents can be used to direct cyclization, as in the synthesis of chromenes present in extracts of tropical plants in the *Calophyllium* species (Scheme 25) ⟨94TL5363⟩.



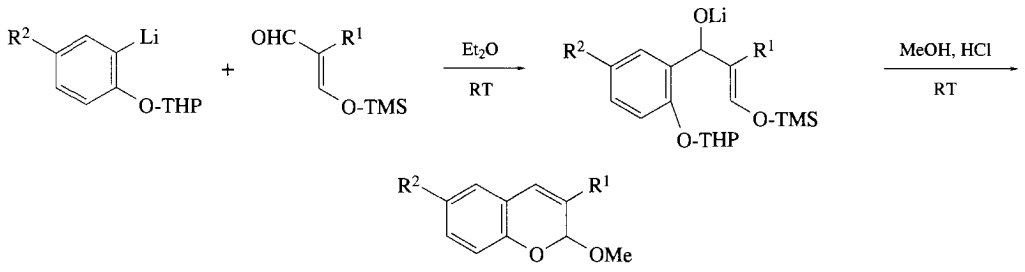
Scheme 25

A number of chromene syntheses involve construction of a side chain *ortho* to a phenolic function. Subsequent cyclization may be preceded or accompanied by double bond formation, typically by dehydration, according to the nature of the side chain. Reaction of a phenoxide with protected 3-halogenopropanals introduces a saturated side chain, but deprotection and cyclization is followed by dehydration to give chromenes in a highly regioselective manner (Scheme 26) ⟨84JHC669⟩.

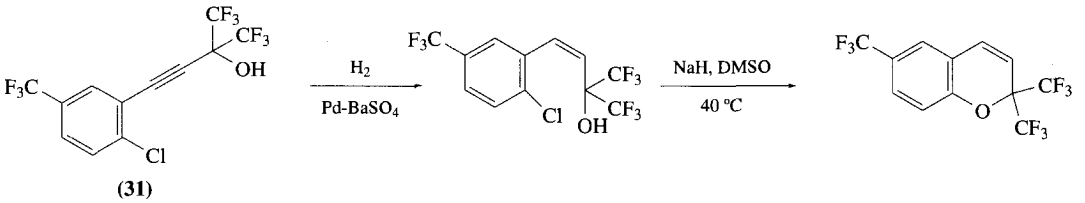


Scheme 26

3-Trimethylsilyloxyprop-2-enals are useful three-carbon annulation reagents and their reaction with protected *o*-hydroxyaryllithium compounds leads to good yields of 2-alkoxychromenes by way of hydrolysis of the intermediate γ-hydroxysilyl enol ethers (Scheme 27) ⟨87S951⟩. A further variation involves the partial hydrogenation of the alkyne (**31**) and cyclization of the resulting *cis*-allylic alcohol under basic conditions (Scheme 28) ⟨93TL1815⟩.



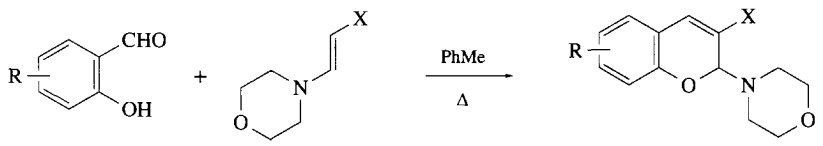
Scheme 27



(31)

Scheme 28

Both salicylaldehyde and *o*-hydroxyacetophenone feature in reactions with unsaturated systems which lead to chromenes in the presence of base, which promotes both the initial Michael addition and the subsequent cyclization ⟨75MI 508-02⟩. Examples include the formation of 3-nitrochromenes from nitroethene brought about by dibutylamine, which does not significantly polymerize the alkene ⟨90SC783⟩, and from nitroethanol ⟨84S348⟩. The use of β-nitrostyrenes leads to 2-aryl-3-nitrochromenes ⟨84H(22)1943, 86H(24)1647, 91H(32)33, 93CC1781⟩, a reaction which can be carried out on alumina without solvent and which is subject to sonic acceleration ⟨85H(23)139⟩. (Nitroethenyl)naphthalenes yield 2-naphthyl-3-nitrochromenes ⟨86S486⟩ and 6-formyl-7-hydroxy-2,2-dimethylchroman affords benzodipyrans with nitrostyrenes ⟨85BCJ3665⟩. Closely related are the reactions of salicylaldehydes with β-nitro-, β-cyano- and β-acyl- enamines, which yield 2-amino-3-substituted chromenes (Equation (8)) ⟨88MI 508-01⟩.



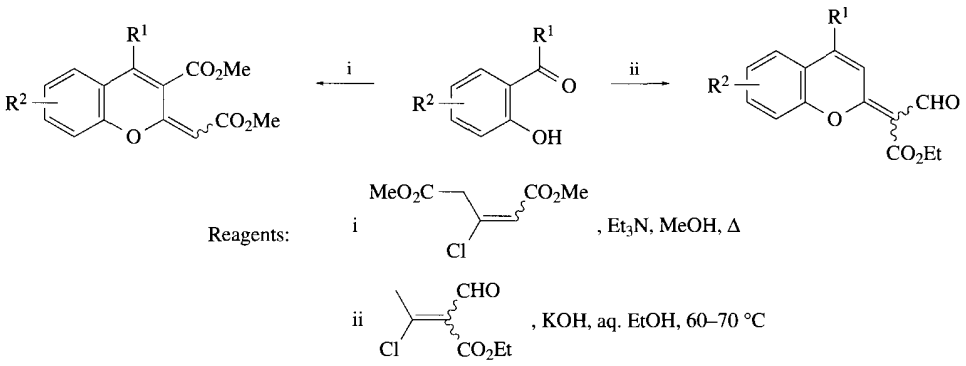
(8)

Dimethyl 3-chloropent-2-endioate and ethyl 3-chloro-2-formylbutenoate afford 2-alkoxycarbonylmethylenechromenes on reaction with salicylaldehydes and, in the latter case, with *o*-hydroxyacetophenone under mild conditions (Scheme 29) ⟨90ZC19, 94M61⟩.

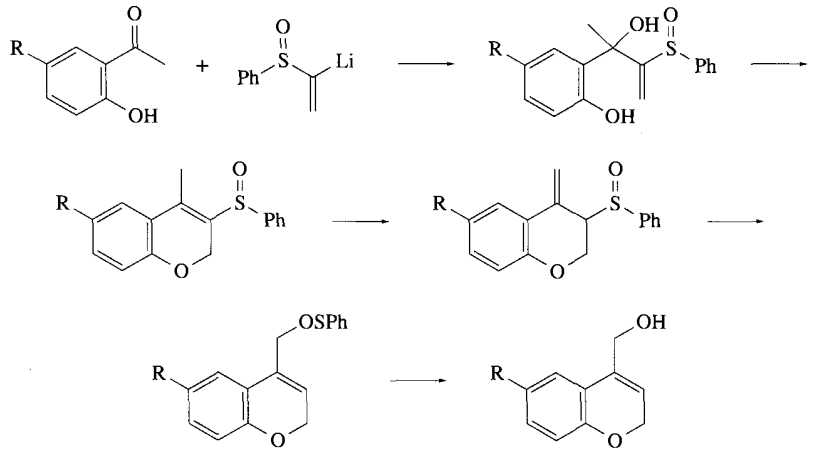
Benzyltrimethylammonium hydroxide effects the reaction of the allene dimethyl penta-2,3-dienedioate with salicylaldehyde, but potassium *t*-butoxide is needed with *o*-hydroxyacetophenone. The products have *Z*- and *E*-stereochemistry, respectively ⟨84JCR(S)380⟩.

In an extension of this method, the anion derived from phenyl vinyl sulfoxide reacts with *o*-hydroxyacetophenones to give 4-hydroxymethylchromenes after base-catalyzed cyclization of the initially formed β-hydroxysulfoxide. An intermediate 3-sulfinylchromene is proposed which isomerises to the *exo*-methylene species which then undergoes a sulfoxide → sulfenate rearrangement (Scheme 30) ⟨91S569⟩.

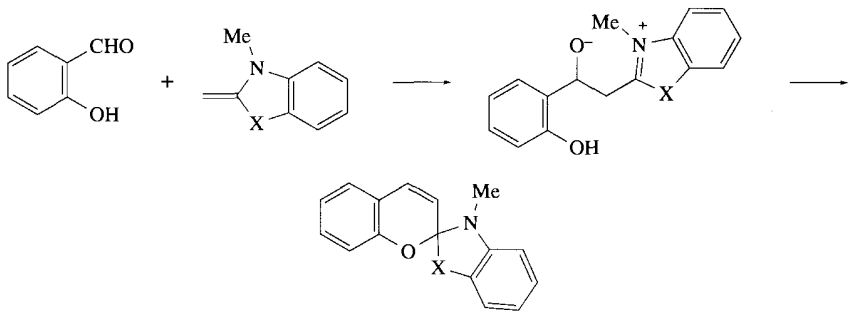
The spiro-linked chromenes resulting from the reaction of salicylaldehydes with derivatives of Fischer's base (Scheme 31) ⟨67BSF2824, 90HCA303, 90RCR663, 92JCS(P2)613⟩ and with 2-methylthiopyrylium salts (Scheme 32) ⟨90CC421⟩ exhibit photochromism.



Scheme 29



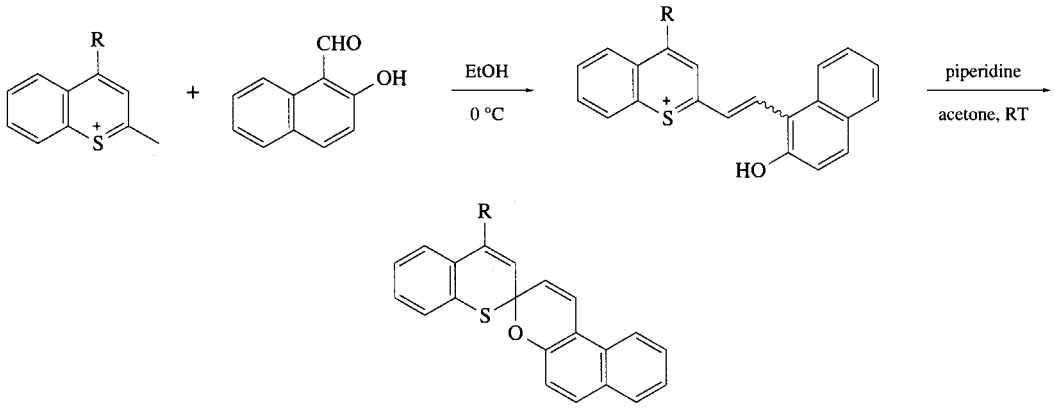
Scheme 30



Scheme 31

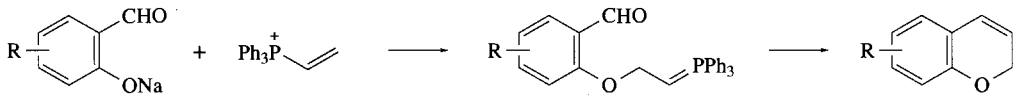
5.08.3.1.2 γ to the heteroatom

The application of Wittig methodology to the synthesis of chromenes has been developed by Schweizer and his co-workers. The sodium salt of salicylaldehyde reacts in a conjugate manner with vinyltriphenylphosphonium salts and the resulting ylid undergoes an intramolecular Wittig reaction to afford chromenes (Scheme 33), though a quinoneallide has been implicated in the process ⟨68JOC2416, 71JOC4028⟩. Substituted benzaldehydes generally give satisfactory yields and substituted vinylphosphonium salts may also be used ⟨73JOC1583⟩. In a related manner, the phosphonium salts derived from *o*-hydroxybenzyl halides and triphenylphosphine react with α-halogeno carbonyl

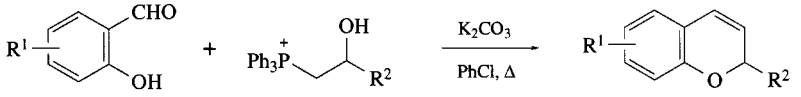


Scheme 32

compounds in the presence of base to yield chromenes. Initial halide displacement by the phenoxide ion is followed by an intramolecular Wittig reaction ⟨80T3409⟩. This approach has been developed on the basis of the formation of allylic ethers by treatment of 2-hydroxyethyltriphenylphosphonium chloride with an equimolar mixture of alcohol and aldehyde in the presence of potassium carbonate. Thus, the use of an *o*-hydroxybenzaldehyde as the source of both ROH and RCHO results in the formation of a vinyltriphenylphosphonium species and subsequent cyclization via an ylid. Whilst yields are not as high as in the two previous methods, and electronic and steric factors exert a pronounced effect on the process, this one-pot reaction has been successfully extended to 2-hydroxynaphthaldehyde and to heterocyclic analogues of salicylaldehyde (Equation (9)) ⟨93S881⟩.

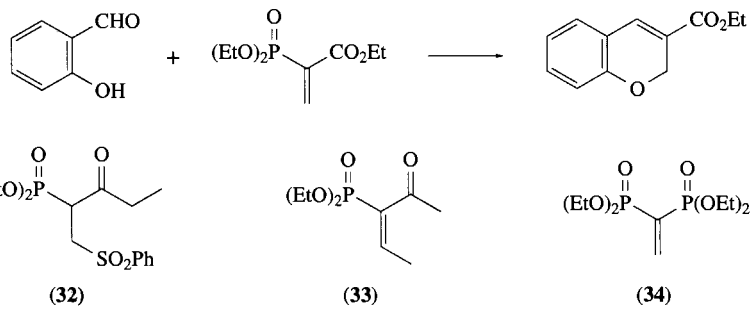


Scheme 33



(9)

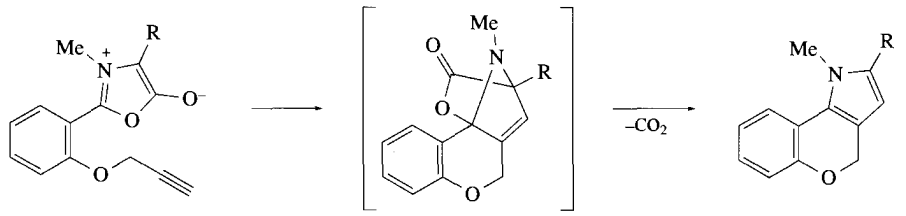
An intramolecular Horner–Emmons reaction features in the formation of chromene-3-carboxylic esters from salicylaldehyde and ethyl 2-diethylphosphonoacrylate (Equation (10)) ⟨78JOC1256⟩, whilst phosphonates (**32**) and (**33**) lead to 3-acylchromenes. Similarly, the *gem*-bisphosphonate (**34**) reacts with various *o*-hydroxybenzaldehydes to give good yields of 3-diethylphosphonochromenes ⟨92PS(70)255⟩.



(10)

(**32**) (**33**) (**34**)

An intramolecular cycloaddition of 2-[2-(prop-2-ynyloxy)phenyl]oxazolium-5-olates is followed by extrusion of CO_2 and leads to good yields of pyrano[4,3-*b*]pyrroles (Scheme 34) ⟨89JCS(P1)361⟩.



Scheme 34

5.08.3.2 From Other Heterocycles

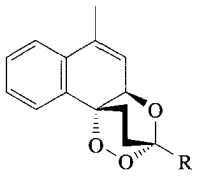
5.08.3.2.1 From benzofurans

2-Vinyldihydrobenzofurans undergo an acid-catalyzed isomerization and a rearrangement yielding benzofurans and chromenes. Careful choice of substrate and reaction conditions provides the chromene in good yield ⟨88T3587⟩.

2-(1-Bromo-1-methylethyl)benzofurans are electrolytically reduced to 2,2-dimethylchromenes in acetonitrile ⟨95CC615⟩.

5.08.3.2.2 From trioxanes

trans-Fused naphtho-1,2,4-trioxanes (**35**) rearrange to 2,2-disubstituted chromenes on treatment with trimethylsilyl trifluoromethylsulfonate. The electrophilic rearrangement proceeds by two 1,2-shifts, and an isomerization completes the sequence. The *cis*-isomers give a mixture of benzopyrans and benzofurans ⟨87CC713⟩.



(35)

5.08.3.2.3 From benzoxepins

The ring opening of benzoxepins with base yields a butadienylphenol which undergoes a 1,7-shift to the quinoneallide and thence a chromene ⟨69C108⟩.

5.08.3.3 From a Preformed Heterocyclic Ring

The accessibility of both coumarins and chroman-4-ones makes these compounds valuable precursors of chromenes.

5.08.3.3.1 From coumarins

Both Grignard and organolithium reagents open the lactone ring of coumarins, to give a tertiary alcohol which either spontaneously dehydrates to the chromene or does so on heating under acidic conditions ⟨39JOC575, 92JOC167⟩. However, the reaction of coumarins with Grignard reagents is complex and the nature of the products can vary with substrate, the organometallic reagent, the solvent and reaction conditions. Products include dihydrocoumarins and open-chain compounds as well as chromones as a result of competition between 1,2- and 1,4-addition and reduction processes. The initial stage of the synthesis is restricted to those coumarins which do not possess an

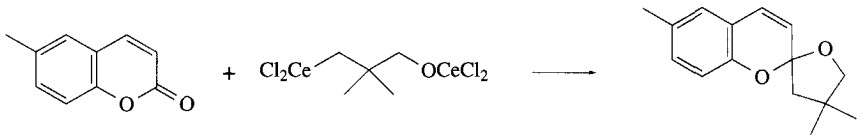
electrophilic substituent with which the organometallic reagent could react. Using normal procedures, two identical substituents are introduced into the 2-position of the chromene. However, reaction of a 3-halogenocoumarin with DIBAL-H followed by addition of a Grignard reagent leads to reasonable yields of a 2-monoalkylchromene ⟨94H(38)819⟩.

Whilst the earlier work on the second step favored an acid-catalyzed dehydration, later studies have shown that thermal cyclization is readily achieved. In general, substitution at C-2 favors the cyclization, with a primary alcohol requiring more energetic conditions (refluxing mesitylene). Similarly, a 4-substituent facilitates formation of the chromene ⟨83JHC715⟩. With careful control of conditions, a 3- or 4-halogen substituent is compatible with the synthesis and indeed may exert a beneficial effect on yields.

Exclusive reduction of the carbonyl function in coumarin is achieved using DIBAL-H and subsequent reaction with alcohols yields the racemic 2-alkoxychromene ⟨93HCA209⟩.

In the case of the reaction between 6-methylcoumarin and the cerium 2,2-dimethyl-3-cerio-propoxide obtained from 3,3-dimethyloxetane via the dilithium compound, the initial ring-opened product, a keto alkoxide, is protected as the dichlorocerium lactolate. Recyclization during acidic work leads to the chromene spiroketal (Equation (11)) ⟨90JA6389⟩.

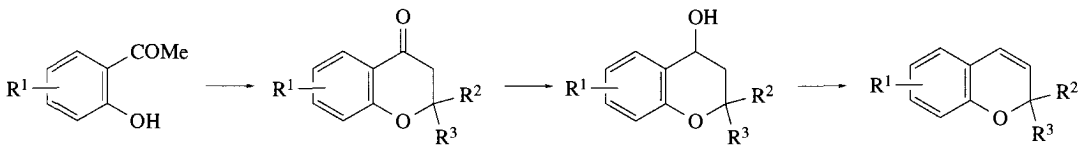
3,4-Diarylcoumarins are reduced to the chromene by the dimethyl sulfide—borane complex in good yield ⟨88S68⟩.



(11)

5.08.3.3.2 From chromanols

The synthesis of chromenes by the dehydration of chroman-4-ols has become increasingly significant as a result of improved routes to chroman-4-ones (see Section 5.08.26) and the consequent greater accessibility of the chromanols. Thus, chromenes can be obtained in three steps from aromatic precursors in good overall yield (Scheme 35). Furthermore, the final dehydration step may occur spontaneously during the reduction stage, thereby enhancing this route to chromenes. Dehydrating agents which have proved effective include anhydrous $CuSO_4$, *p*-TsOH, $KHSO_4$ and Al_2O_3, whilst pyrolysis of the derived acetate, tosylate, and mesylate is also successful.



Scheme 35

Variation of the substituents at C-2 is acceptable ⟨83JCS(P1)827⟩ and the reaction is compatible with a range of substituents in the aromatic ring and has been used to synthesize analogues of 7-methoxy-2,2-dimethylchromene (Precocene I). Examples include the 6-chloro, 6-*t*-butyl ⟨89ACH471⟩, 8-methyl ⟨88ACH617⟩, and 5-methyl ⟨88ACH457⟩ derivatives, whilst 6,8-dichloro-2-pentamethylenechromene has also been obtained in this way ⟨92RRC485⟩. Several alkoxy analogues of both Precocene I and Precocene II have been obtained by *O*-alkylation of the corresponding hydroxy 2,2-dimethylchroman-4-one followed by reduction and dehydration ⟨88ACH303, 89ACH149, 89ACH487⟩, an approach which has also been extended to the synthesis of polysubstituted chromenes ⟨89H(28)711⟩. Manipulation of phenolic groups also features in the preparation of some 7-alkylthio ⟨94S837⟩ and various arylsulfonyloxy derivatives of the precocenes ⟨90M403⟩. In a similar manner, 3-bromochroman-4-ols yield 3-bromochromenes ⟨94JCS(P1)1733⟩. An interesting variant on this theme is the synthesis of the linear and angular benzodipyrans from the dichromanones ⟨89H(28)711⟩.

The synthesis of heterofused 2*H*-pyrans, effectively heterocyclic analogues of chromenes, has also been accomplished using this methodology. Whilst the thieno[3,2-*b*]pyran system is accessible by dehydration of the corresponding pyranol, attempts to form the [2,3-*b*] and [3,4-*b*] isomers resulted

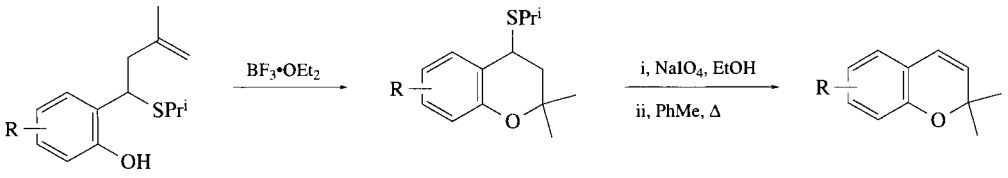
in the decomposition of the pyranols ⟨93JOC4629⟩. A halogen substituent in the thiophene ring exerts a stabilizing effect such that this route becomes viable for the [3,4-*b*]analogue.

The reaction of chroman-4-ones with Grignard reagents followed by dehydration of the tertiary alcohol is a useful extension of the simple chromanone → chromanol → chromene route which allows the introduction of a 4-substituent into the chromene moiety ⟨91S879, 94JOC6697⟩. The introduction of a 4-vinyl substituent through reaction of a chromanone with vinylmagnesium bromide is an interesting example ⟨84JCS(P1)2815⟩ which, like the simpler route, is compatible with a 3-substituent and offers a route to isoflavenes ⟨66JCS(C)629, 90JCR(S)4⟩. Closely related to the dehydration of chromanol is the elimination of alcohols from 4-alkoxychromans ⟨90SC641⟩.

It is less common to prepare chromenes from chroman-3-ols, though access to the latter from 3,4-epoxychromans and the current interest in the potassium channel activator cromakalim has prompted some activity in this approach. Reagents used include NaOH ⟨90JMC492, 90JMC2759⟩, NaH ⟨86JMC2194, 90JMC3028⟩, DAST ⟨91JCS(P1)63⟩, KOtBu ⟨92TL1109⟩, *p*-TsOH ⟨80JCS(P1)1804⟩, *p*-TsCl ⟨83JCS(P1)1431⟩, H_2SO_4 ⟨90M157⟩, and $Me(PhO)_3P^+I^-$ in HMPA ⟨84H(22)1951⟩. A chroman-3,4-diol has been converted into the 3-methoxychromene by successive treatment with DMF-DMA and CH_3I ⟨85P199⟩.

5.08.3.3.3 From chromans

The oxidation of chromans to chromenes is best achieved using DDQ and many examples are known ⟨84G359, 84H(22)709, 84IJC880, 90S1005⟩. Thermal elimination of isopropylsulfenic acid from the 4-isopropylthiosulfoxide derived from the 4-(isopropylthio)chroman gives the chromene (Scheme 36) ⟨87JOC5495⟩.



Scheme 36

The elimination of hydrogen halide from 3- or 4-halogenochromans can be achieved by treatment with sodium alkoxide ⟨71CB168⟩, whilst NaH in DMF has been applied to the synthesis of some 2*H*-pyrano[2,3-*b*]quinolines ⟨94JHC701⟩.

5.08.3.3.4 From chroman-4-ones

Treatment of chroman-4-ones with PCl_5 gives the 3,4-dichlorochromene via an initial α-chlorination, formation of the *gem*-dichloride and subsequent dehydrochlorination ⟨79TL3901⟩. Whilst no reaction occurs in boiling ether, a 98% conversion is achieved in CCl_4 ⟨85JCS(P1)1127⟩. The use of PCl_3 affords the monochlorochromene in just a few instances, but reaction with PBr_3 provides an excellent route to 4-bromochromenes. It is also possible to isolate some chromene-4-phosphonic acids during this process ⟨94T2507⟩.

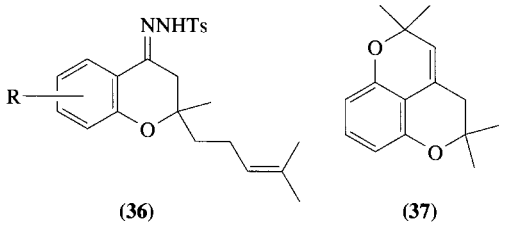
The reaction of the Vilsmeier reagent with chroman-4-ones is complex, being influenced especially by the steric consequences of substitution at C-2, which largely prevents 3-formylation. A minor product from treatment of some methoxy 2,2-dimethylchromenes with $POCl_3$ in DMF is the 4-chlorochromene-3-carbaldehyde, but the reaction affords high yields of 4-chlorochromenes ⟨85JCS(P1)1127⟩.

The tosylhydrazone derived from the 2-alkenyl-2-methylchromanone (**36**) yields the chromene by a Bamford–Stevens reaction ⟨89MI 508-01⟩.

5-Hydroxychroman-4-one is converted into the pyrano[4,3,2-*de*][1]benzopyran (**37**) on reaction with methallylzinc bromide and subsequent acid catalyzed cyclization ⟨93ACS314⟩.

5.08.3.3.5 From benzopyrylium salts

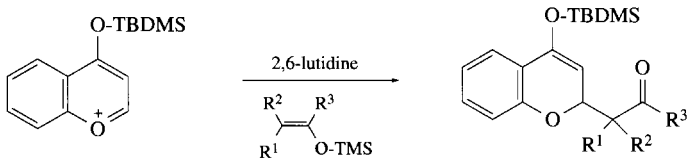
Chromenes result from the attack of nucleophiles at the 2-position of benzopyrylium salts. Thus, 3-substituted benzopyrylium salts yield 2*H*-chromenes on treatment with LAH ⟨68AJC2247⟩ and this



(36) (37)

approach constitutes a major route to isoflav-3-enes ⟨93TL3993⟩. However, reaction of isoflavylium salts with $NaBH_3CN$ leads to a mixture of the 2*H*- and 4*H*-chromenes ⟨81AJC2647⟩. Whilst simple benzopyrylium salts also show this behavior with secondary amines ⟨72JOC1069⟩, 7-methoxy-3-phenylbenzopyrylium perchlorate yields only the 2-substituted isoflav-3-ene ⟨78JCS(P1)88⟩. An intramolecular variation of this method leads to spirobi(2*H*-chromenes) ⟨26CB1377⟩.

Silyl enol ethers attack 4-silyloxybenzopyrylium salts at C-2 in the presence of lutidine, giving high yields of the 4-silyloxychromene (Equation (12)) ⟨91JOC2058⟩.



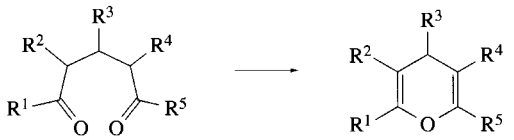
(12)

5.08.4 4*H*-PYRANS

5.08.4.1 Formation of One Bond

5.08.4.1.1 Adjacent to the heteroatom

The acid-catalyzed ring closure of 1,5-dicarbonyl compounds to 4*H*-pyrans (Equation (13)) discussed in CHEC-I ⟨84CHEC-I(3)757⟩ has been developed further.

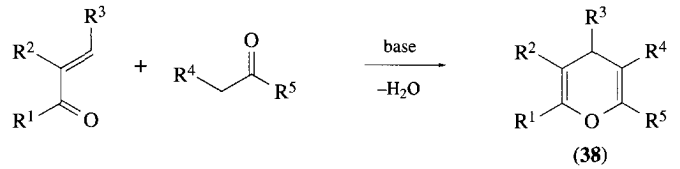


(13)

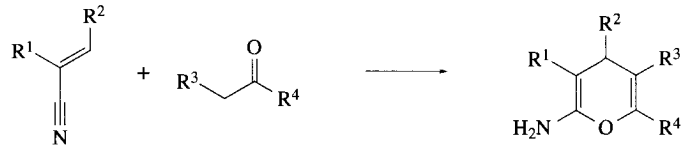
1,5-Dialdehydes afford 2,6-unsubstituted 4*H*-pyrans, a method which has been used to prepare 2,6-dideuterio-4*H*-pyran ⟨86OMS(21)459⟩, whilst 1,5-ketoaldehydes give the 6-unsubstituted analogues ⟨89AP(322)617⟩ and 1,5-diketones yield the 2,6-disubstituted pyrans. There are many examples in the latter category, including all the possible variations in substitution pattern ⟨92CHE266⟩, fused derivatives ⟨86H(24)1631, 92CHE266⟩, and spiro-linked 4*H*-pyrans ⟨92JCS(P2)1301⟩. The dehydrating reagents used include PPA ⟨89AP(322)617⟩, *p*-toluenesulfonic acid ⟨89CCC1854⟩, and a mixture of acetic anhydride and boron trifluoride etherate ⟨86H(24)1631, 92CHE266⟩. Cyclization with PCl_5 results also in chlorination at the 3- and 5-positions, whilst the Vilsmeier reagent $POCl_3$-DMF formylates the pyran at the same sites ⟨91TL3235, 92CCC2383⟩. The versatility of this route is further adumbrated by the cyclization of 5-oxonitriles which yields 2-amino-4*H*-pyrans ⟨87CCC2687⟩.

The 1,5-dicarbonyl system can be formed *in situ* from more readily available materials and the reaction of α,β-unsaturated carbonyl compounds with the carbanions derived from activated methylene groups has been utilized in the synthesis of 4*H*-pyrans (**38**) (Equation (14)) ⟨86H(24)935, 86JHC1203, 91JPR345⟩. When activation of the methylene function is provided by a nitrile group, a 2-amino-4*H*-pyran (**38**; $R^5 = NH_2$) results. If malononitrile is the carbanion precursor, then a 3-cyano group is also present in the product (**38**; $R^4 = CN$, $R^5 = NH_2$) ⟨85JCS(P1)2581, 86OPP227, 87CCC2687, 92T1581, 93LA801⟩. An interesting development of this route notes that the latter type of (**38**) reacts with further malononitrile to form a pyrano[2,3-*b*]pyridine ⟨88T5861⟩. In a similar fashion the reaction of α,β-unsaturated nitriles with carbanions has been extensively exploited to synthesise 2-aminopyrans (Equation (15)) ⟨86M247, 89LA585, 90JCR(S)310⟩. In all of the reaction types discussed,

extension to fused, heterocyclic, and spiro derivatives has been achieved ⟨85S432, 88TL2703, 90CCC718, 90LA101, 91LA827, 94S153, 95JCR(S)178, 95JCR(S)322, 95SC3211⟩.

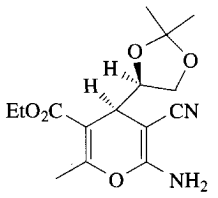


(38) (14)



(15)

The asymmetric synthesis of 4*H*-pyrans through Michael additions has been studied. Thus, the addition of malononitrile to enantiomerically pure α-acylacrylates leads to enantiomerically pure 4*H*-pyrans (**39**) ⟨93T7133⟩. Besides this chiral substrate control, a chiral auxiliary, Oppolzer's sultam, has been incorporated into a latent 1,3-dicarbonyl system prior to reaction with an α,β-unsaturated nitrile. Removal of the auxiliary from the resulting 4*H*-pyran (**40**) gave the enantiomerically pure pyran ⟨94T3509⟩. This approach has been extended to the use of chiral cyanoacetates, affording the 4*H*-pyrans in good diastereoisomeric excess ⟨95TA1435⟩.



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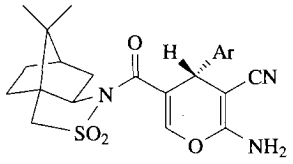

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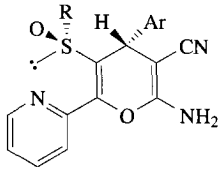
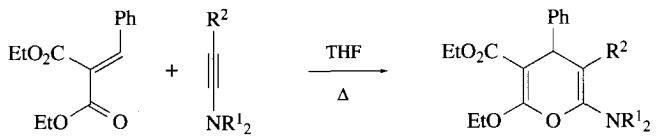


(41)

In a related synthesis, β-keto sulfoxides add to unsaturated nitriles in a highly stereocontrolled manner such that H-4 and the sulfoxide oxygen atom are in a *syn*-relationship (**41**) ⟨95JOC6678⟩.

5.08.4.2 Formation of Two Bonds

The hetero Diels–Alder reaction between α,β-unsaturated carbonyl compounds and alkynes leads to 4*H*-pyrans. Ynamines have usually been the dienophile and give satisfactory yields of pyrans, but other alkynes tend to give lower yields. The reaction is both regio- and chemo-selective (Equation (16)) ⟨86JOC1199, 91TL4051, 92TL699⟩. The method has been extended to 4-spirocyclic analogues ⟨89CB1285⟩. The use of enamines as the dienophile usually leads to mixtures of 2*H*- and 4*H*-pyrans ⟨84TL4503⟩.

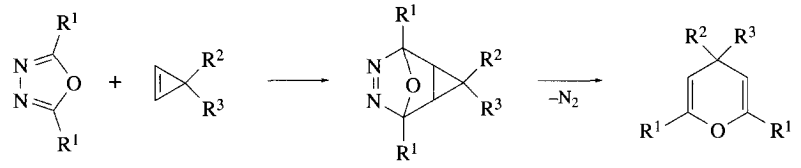


(16)

5.08.4.3 From Other Heterocycles

5.08.4.3.1 From oxadiazoles

The cycloaddition reaction between 1,3,4-oxadiazoles and cyclopropenes is followed by a retro Diels–Alder reaction which yields 4*H*-pyrans (Scheme 37) ⟨88TL3231⟩.



Scheme 37

5.08.4.4 From a Preformed Heterocyclic Ring

5.08.4.4.1 From pyrans

Dehydration of hydroxydihydropyrans leads to 4*H*-pyrans ⟨85AP(318)648, 86AP(319)704⟩.

5.08.4.4.2 From pyranones

Reduction of 2,6-di-*t*-butylpyran-4-one with DIBAL-H gives the pyran ⟨88OM1122⟩.

5.08.4.4.3 From pyrylium salts

Hydride ion reduction of pyrylium salts usually gives a mixture of a 4*H*-pyran and an acyclic dienone ⟨87TL1341⟩. When the reduction is radical-induced, using Zn in THF, dimeric 4*H*-pyrans are produced ⟨89BCJ2279⟩.

Organometallic reagents tend to give mixtures of 2*H*- and 4*H*-pyrans and ring-opened products, though some control can be achieved by choice of substitution pattern, reagent and reaction conditions ⟨89JCS(P1)683⟩.

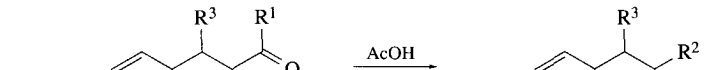
5.08.5 4*H*-CHROMENES (4*H*-1-BENZOPYRANS)

5.08.5.1 Formation of One Bond

5.08.5.1.1 Adjacent to the heteratom

The acid catalyzed cyclization of 3-(2-hydroxyphenyl)propan-1-ones affords 4*H*-chromenes (Equation (17)) ⟨42JA435, 63T839, 70JCS(C)1758, 71JOC600⟩ and probably features in a synthesis of pyrano[2,3-*d*]pyrimidines ⟨90SC1265⟩.

Functionalized enamines react with *o*-hydroxybenzyl alcohols on refluxing in acetic anhydride to form 4*H*-chromenes (Equation (18)) ⟨89S69⟩.



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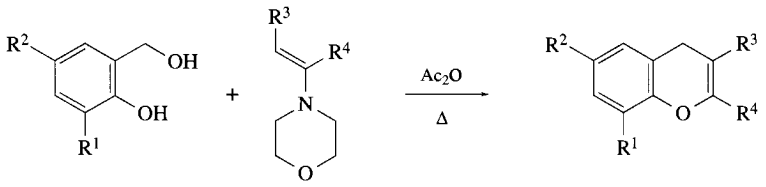
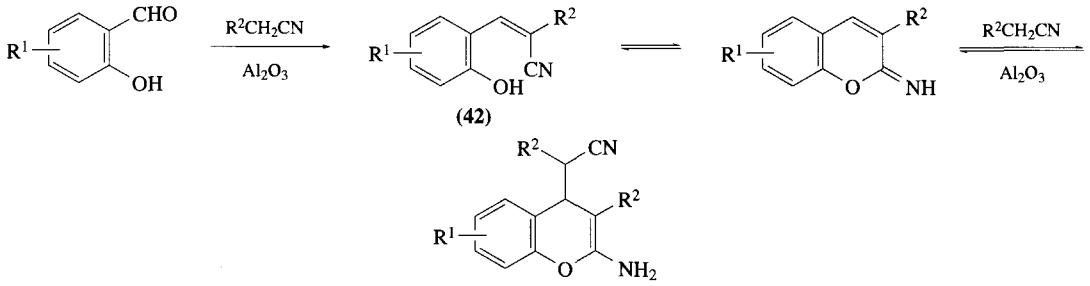


(18)

Although active methylene compounds react with salicylaldehydes to give coumarin derivatives, different behavior is shown when activation is brought about by a nitrile group. Thus, 3,5-dibromosalicylaldehyde gives 4*H*-chromenes on reaction with ethyl cyanoacetate ⟨77S871⟩. Malononitrile

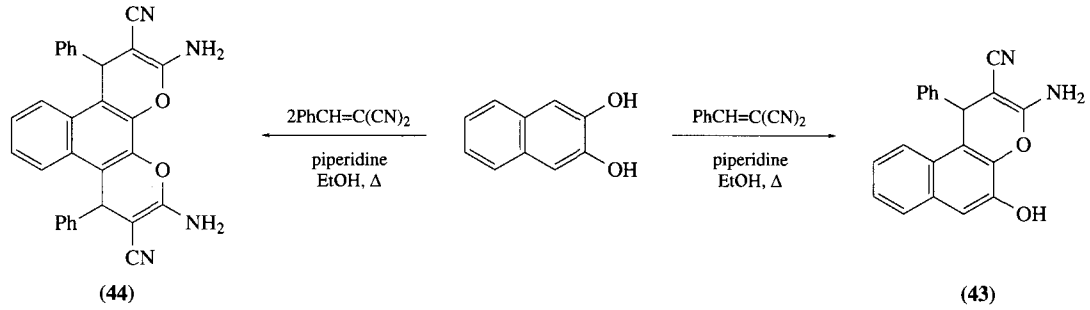
behaves similarly under heterogeneous catalysis by Al_2O_3. The benzylidene derivative (**42**), the product of a Knoevenagel reaction, is a known intermediate and the iminocoumarin may also play a part in the reaction which leads to diastereomers of 2-aminochromenes (Scheme 38) ⟨84S159⟩.



Scheme 38

Methylenemalononitrile, generated *in situ* from formaldehyde and malononitrile, affords naphthopyrans and naphthodipyrans on reaction with naphthols and naphthalenediols ⟨93BCJ464⟩.

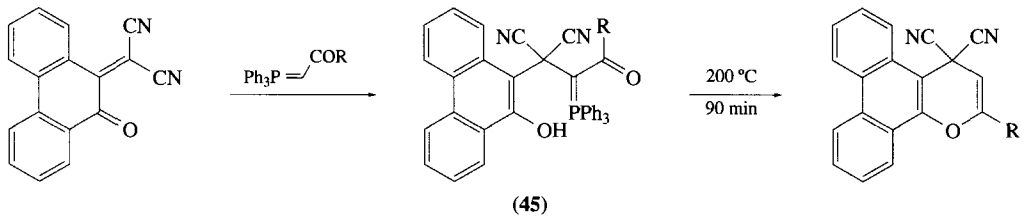
Cinnamonitriles react with phenols and naphthols to give 4*H*-naphthopyrans ⟨88CCC1534⟩, whilst dihydroxynaphthalenes afford either the naphtho[2,1-*b*]pyran (**43**) or naphthodipyrans (**44**) according to the reaction conditions (Scheme 39) ⟨90CCC524⟩.



Scheme 39

Although various 3-nitrobenzylidenemalononitriles react with 1-naphthol in the presence of piperidine to form the naphthopyran, a 4-fluoro substituent undergoes nucleophilic displacement by the amine ⟨94H(38)399⟩.

α,β-Unsaturated nitriles react with acylphosphoranes to give the stable 1,4-adducts (**45**). On heating, Ph_3PO is eliminated and 4*H*-chromenes are the final product (Scheme 40) ⟨91CI(L)217⟩.



Scheme 40

5.08.5.1.2 β to the heteroatom

A Wittig reaction also features in the synthesis of 4*H*-chromenes from *o*-acyloxybenzoyl bromides ⟨79TL2995⟩.

5.08.5.2 From a Preformed Heterocyclic Ring

5.08.5.2.1 From chromans

Elimination of ethanol from 2-ethoxychromans ⟨67CB1296⟩ and water from chroman-2-ols and 3-ols ⟨60CB1025⟩ or acetic acid from the corresponding acetates ⟨70JOC2282⟩ leads to 4*H*-chromenes.

5.08.5.2.2 From 2H-chromenes

Isomerization of 2*H*-chromenes to the 4*H*- compound is brought about by alkoxy- or phenoxy-magnesium halides ⟨71JCS(C)2546⟩.

5.08.5.2.3 From benzopyrylium salts

Nucleophilic attack at C-4 of flavylium salts leads to 4*H*-chromenes ⟨58JCS4040⟩.

5.08.6 1*H*-ISOCHROMENES (1*H*-2-BENZOPYRANS)

These compounds are not well known, as they are easily oxidized and polymerized.

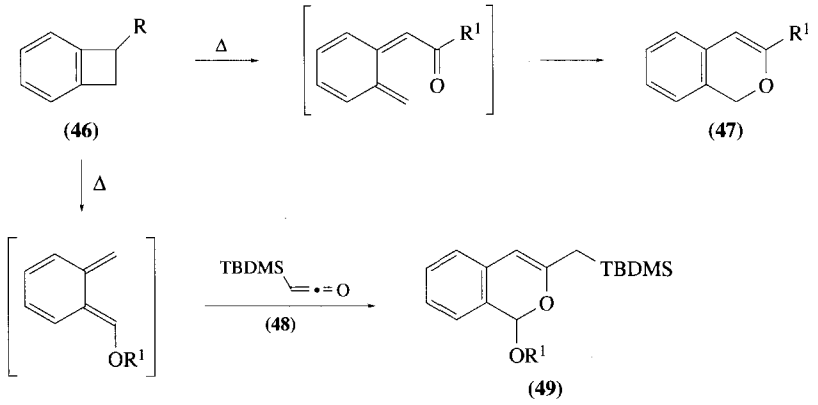
5.08.6.1 Formation of One Bond

5.08.6.1.1 Adjacent to the heteroatom

Cyclization of 2-(2-hydroxymethylphenyl)acetaldehyde, accessible from isocoumarin by reaction with LAH, leads to isochromene ⟨65CB3279⟩.

The acylbenzocyclobutene (**46**; R = COR^1) undergoes a thermal ring opening to the acylquinodimethane which cyclizes to the isochromene (**47**) ⟨72HCA10⟩. The silylketene (**48**) undergoes a [4 + 2] cycloaddition with (**46**; R = OR^1), to afford the isochromene (**49**) (Scheme 41) ⟨93TL6583⟩.

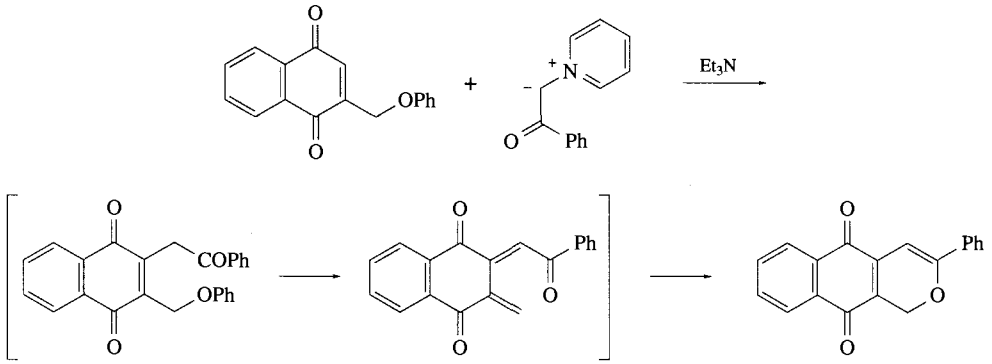
Naphtho[2,3-*c*]pyrandiones result from the reaction of 2-phenoxymethyl-1,4-naphthoquinone with acylated pyridinium ylides. Initial phenacylation is followed by cyclization *via* a quinone methide (Scheme 42) ⟨90JCS(P1)2163⟩.



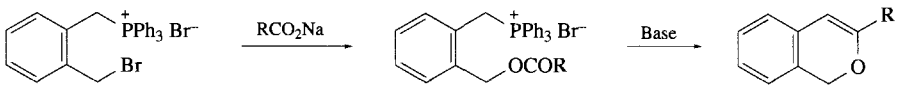
Scheme 41

5.08.6.1.2 β to the heteroatom

The monophosphonium salt derived from 1,2-di(bromomethyl)benzene undergoes an intramolecular Wittig reaction after conversion to the ester (Scheme 43) ⟨79TL2149⟩.



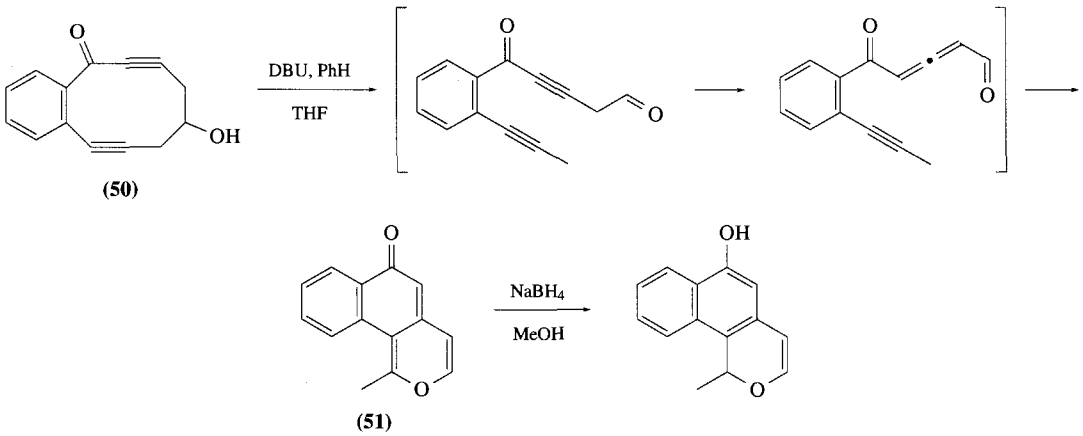
Scheme 42



Scheme 43

5.08.6.2 Formation of Two Bonds

An intramolecular cycloaddition follows treatment of the diynone (**50**), golfomycin A, with DBU, which initiates a retro-aldol reaction. Reaction of the tricyclic pyran (**51**) with borohydride leads to the isochromene (Scheme 44) ⟨90AGE1064⟩.

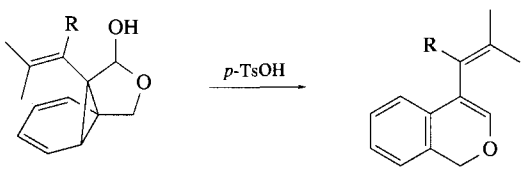


Scheme 44

5.08.6.3 From Other Heterocycles

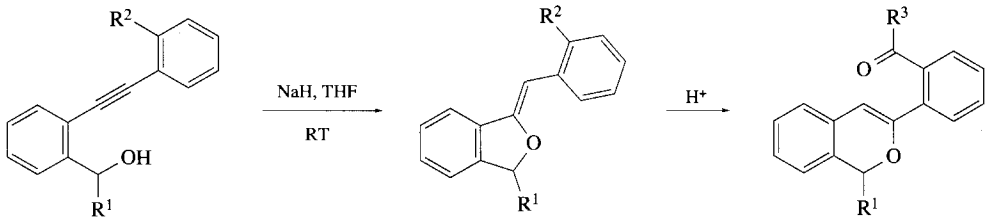
5.08.6.3.1 From furans

Cleavage of the 1,7-bond in a norcaradiene lactol under acid conditions is accompanied by a dehydrative aromatization which affords isochromens (Equation (19)) ⟨95TL553⟩.



(19)

Intramolecular addition of an anion to the C≡C bond in the diarylalkynols (**52**) leads to isobenzofurans (**53**) by a 5-*exo-dig* cyclization (Scheme 45). However, when R^2 in (**52**) is CHO or CO_2Et, a sequence of acid catalyzed rearrangements results in the formation of an isochromene during the work-up. Thus, 6-*endo-dig* cyclizations of this system are apparent rather than real ⟨95JOC5595⟩.



(**52**) (**53**)

Scheme 45

5.08.6.4 From a Preformed Heterocyclic Ring

5.08.6.4.1 From isochromanols

The dehydration of isochromanols is best achieved by distillation from potassium hydrogen sulfate ⟨87S497⟩, but *p*-TsOH has also been used. The overall yield from homophthalic acid is 48% and 69% from indanone, both routes involving three steps. The mesyl derivative is readily dehydrated in basic conditions ⟨90AP(323)493⟩.

5.08.6.4.2 From isocoumarins

Reduction of the tetracyclic isocoumarins with LAH leads to the fused isochromen ⟨56JCS4535⟩.

5.08.7 XANTHENES (9*H*-DIBENZO[*b*,*e*]PYRANS)

Some of the oldest known dyes are based on xanthene and many still have important applications, which accounts for the continued interest in this system. There are, however, few synthetic routes of value.

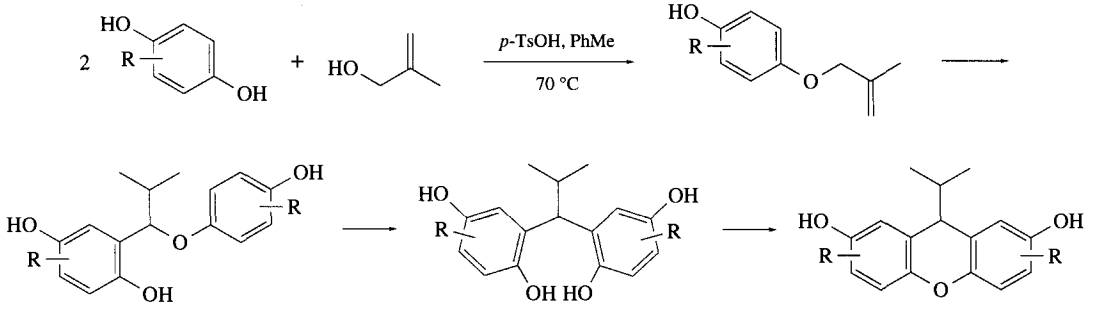
5.08.7.1 Formation of One Bond

5.08.7.1.1 Adjacent to the heteratom

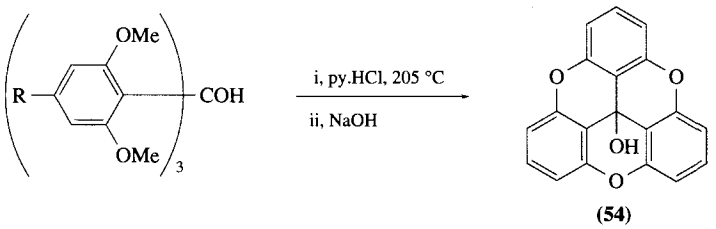
The cyclodehydration of 2,2′-dihydroxydiarylmethanes, achieved by heating with acids, leads to xanthenes ⟨43JOC316⟩. This approach features in a synthesis of the red fungal pigment, bikaverin, from a naphthoquinone ⟨92TL2805⟩. The requisite diarylmethanes are available from the condensation of electron-rich phenols with aldehydes ⟨12LA(391)308⟩.

The reaction of hydroquinones with 2-methylenepropan-1-ol leads to allyl ethers which react with a second molecule of the hydroquinone, forming the symmetrical xanthene via the 1,5-diol (Scheme 46) ⟨95S693⟩. This methodology has been used to synthesize the hexacyclic carbinol (**54**), a 4,8,12-trioxadibenzo[*cd*,*mn*]pyrene, the trioxatricornan system. If the cyclization product is treated with acid, the cation is formed ⟨64JA2252⟩.

Reduction of the 1,5-diketone (**55**) by borohydride leads to the *trans*-fused reduced xanthene derivative (**56**), but catalytic hydrogenation gives the *cis*-derivative (**57**) (Scheme 47) ⟨87ZOR521⟩.



Scheme 46



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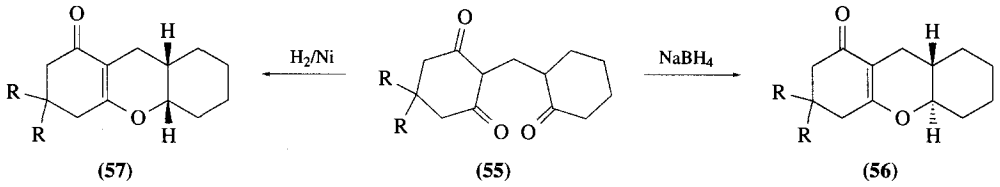


(57) **(55)** **(56)**

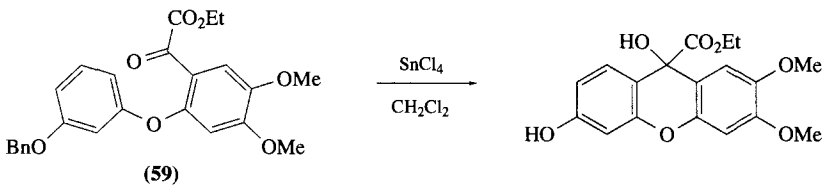
Scheme 47

5.08.7.1.2 γ to the heteroatom

As part of a synthesis of clavizepine, a dibenzopyranoazepine, the xanthone unit was constructed through a tandem intramolecular benzyne-enolate condensation using the diaryl ether (**58**) as substrate (Equation (20)) ⟨94SL433⟩. In a further approach to the alkaloid, the α-keto ester (**59**) undergoes an aromatic cyclization on treatment with tin(IV) chloride. Further manipulation affords the xanthene ester (Equation (21)) ⟨94SL49⟩.

(20)

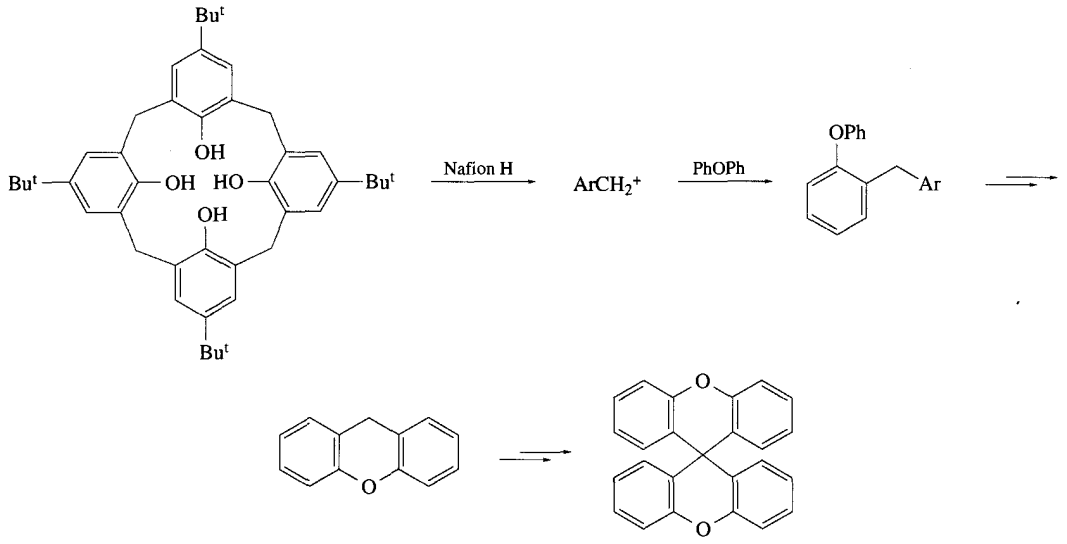
(58)



(21)

(59)

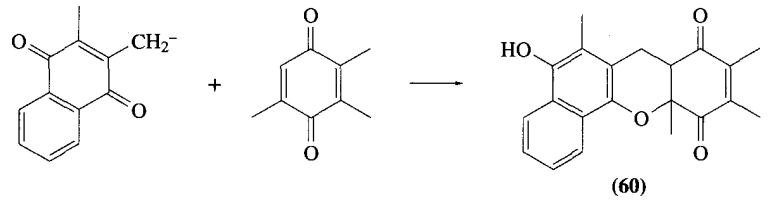
The formation of [9,9′]spirobixanthene during the reaction of *p*-*t*-butylcalix[4]arene with diphenyl ether in the presence of the perfluorinated sulfonic acid resin, Nafion H, is thought to involve four consecutive reactions of a benzylic cation on the ether moiety (Scheme 48) ⟨93TL4857⟩.



Scheme 48

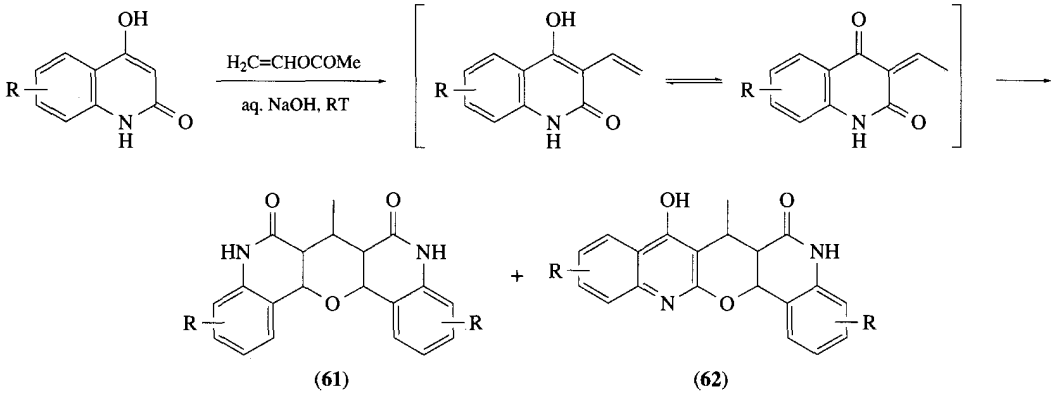
5.08.7.2 Formation of Two Bonds

The anion derived from 2,3-dimethyl-1,4-naphthoquinone functions as a quinone methide and undergoes a 1,4-cycloaddition with trimethylbenzoquinone to give the xanthene derivative (**60**) (Equation (22)) ⟨70JCS(C)722⟩. A quinone methide is also postulated as an intermediate in the formation of the pyranodiquinolines (**61**) and (**62**) from the reaction of 4-hydroxyquinolin-2-ones with vinyl acetate (Scheme 49) ⟨93IJC460⟩.



(22)

(**60**)



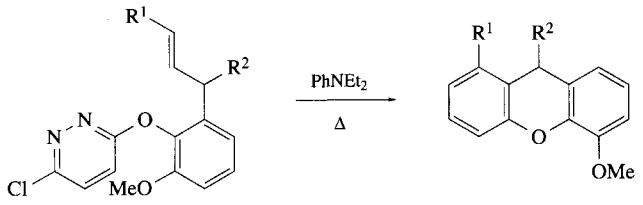
(**61**) (**62**)

Scheme 49

5.08.7.3 From Other Heterocycles

5.08.7.3.1 From pyridazines

Hydroxyxanthenes result from an intramolecular cycloaddition of 3-chloro-6-(2-substituted phenoxyallyl)pyridazines and the related 2-allyloxy derivatives (Equation (23)) ⟨80CPB198⟩.



(23)

5.08.7.4 From a Preformed Heterocyclic Ring

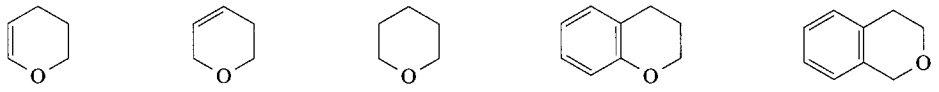
5.08.7.4.1 From xanthones

The reduction of xanthone to xanthene has been accomplished by means of LAH ⟨55JA4121⟩, diphenylsilane ⟨61JOC4817⟩ and the borane-THF complex ⟨92JOC4418⟩. Application of the Huang–Minlon modification of the Wolff–Kishner reduction also effects the conversion ⟨52JCS3741⟩.

A range of dibenzoxanthones has been converted into the 9-methylene derivatives by reaction with Grignard reagents, although in some instances the xanthenol is produced ⟨66CB1822, 83H(20)481⟩.

5.08.8 REDUCED PYRANS

The three reduced pyrans (**63**), (**64**), and (**65**) and their benzologues, chroman (**66**) and isochroman (**67**) are discussed in this section.



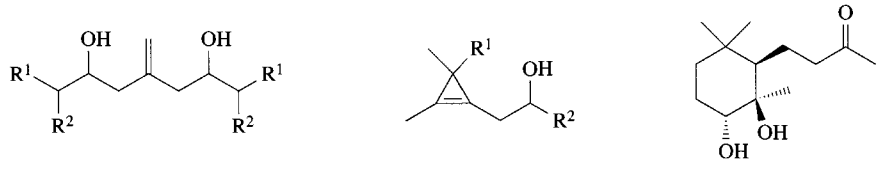
(**63**) (**64**) (**65**) (**66**) (**67**)

5.08.9 DIHYDROPYRANS

5.08.9.1 Formation of One Bond

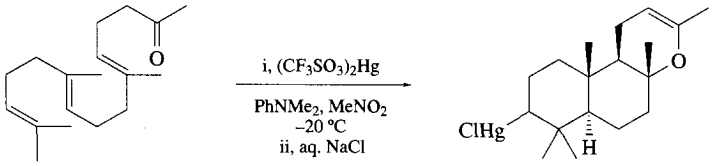
5.08.9.1.1 Adjacent to the heteroatom

Nucleophilic attack by a hydroxy group at an electrophilic centre, five carbon atoms remote, leads to dihydropyrans. Thus, the 1,5-diols (**68**) derived from 3-chloro-2-chloromethylpropene and carbonyl compounds by treatment with lithium naphthenide yield dihydropyrans when cyclized with concentrated HCl ⟨93T4117, 94T13269⟩. This also seems to be the scenario when the cyclopropenylethanol derivatives (**69**) are treated with bromine, when a 4-bromo-5,6-dihydropyran results ⟨90T5703⟩ and when the diol (**70**) derived from α-ionone via selective hydrogenation and epoxidation is cyclized to the fused 3,4-dihydropyran under acidic conditions ⟨89LA1195⟩.



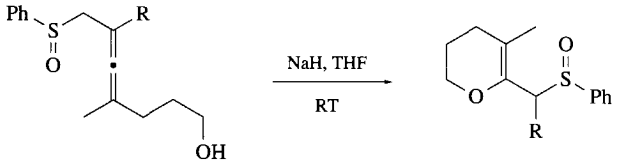
(**68**) (**69**) (**70**)

γ,δ-Unsaturated ketones undergo a halocyclization on reaction with NBS to give 3,5-dibromo-3,4-dihydropyrans ⟨94TL2619⟩, whilst the tricycle (**71**) results from a cascade of ring closures initiated by treatment of the polyalkene with an Hg(II) complex but completed by an oxy-cyclization (Equation (24)) ⟨92TL1679⟩. Epoxidation of the double bond most remote from the ketone group can also serve as the initiator for the cyclization sequence ⟨95JOC5726⟩. Intramolecular nucleophilic attack on the allene sulfoxides (**72**) gives excellent yields of the functionalized dihydropyrans (Equation (25)) ⟨87CC1718⟩.



(24)

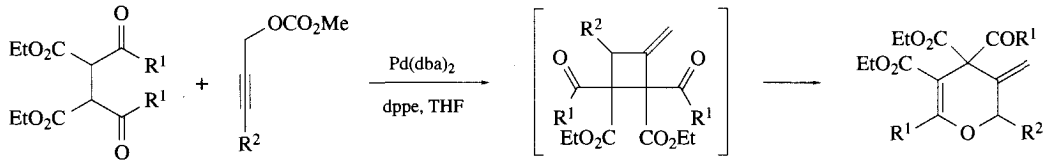
(71)



(25)

(72)

In the presence of Pd(0), 2,3-diacylsuccinates react with propargylic carbonates to give 3-methyl-enedihydropyrans. A cyclobutane intermediate is proposed (Scheme 50) ⟨90TL111⟩.

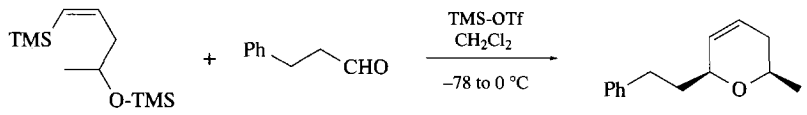


Scheme 50

5.08.9.1.2 β to the heteroatom

Good yields of dihydropyrans result from the condensation of vinylsilanes with aldehydes or acetals. An oxonium ion intermediate is involved in this stereoselective reaction (Equation (26)) ⟨94T7141⟩.

The reaction of formaldehyde with steroids possessing an α,β-enone function in ring A results in the fusion of a dihydropyran unit on to ring B (Equation (27)) ⟨88PJC269⟩.



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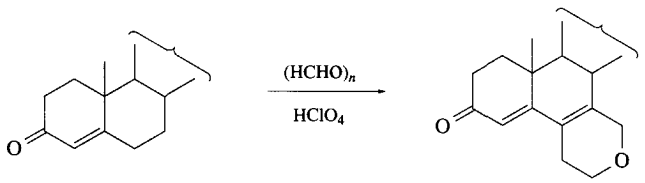
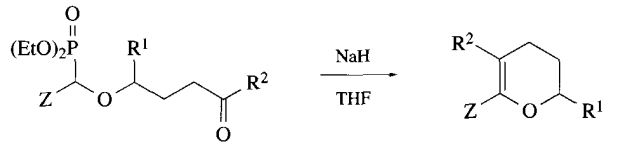


(27)

5.08.9.1.3 γ to the heteroatom

An intramolecular Wadsworth–Emmons reaction features in a conversion of phosphonates to dihydropyrans (Equation (28)) ⟨92T3991⟩.

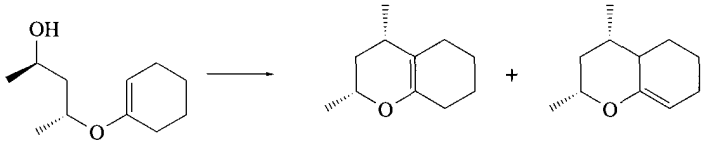
1-Cycloalkenyl 3-hydroxypropyl ethers undergo a regio- and stereo-selective cyclization when treated with triflic anhydride in the presence of tertiary amines.



(28)

Careful selection of the reaction conditions allows the selective formation of the *endo-* and *exo-*heterocyclic product to be accomplished (Equation (29)) ⟨95CC1117⟩.

Vinyl radicals derived from the propenyl ether (**73**) undergo a 6-*exo* cyclization to afford the dihydropyran (**74**) as a 2 : 1 mixture of the *E* and *Z* isomers (Equation (30)) ⟨94TL8445⟩.



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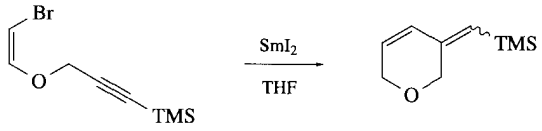
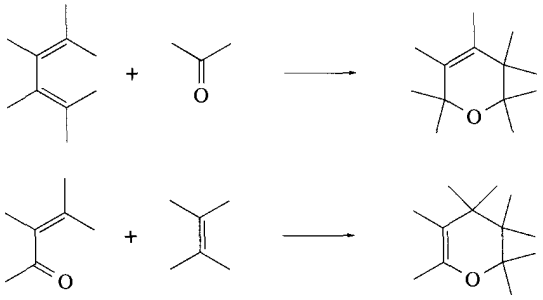


(30)

(**73**) (**74**)

5.08.9.2 Formation of Two Bonds

The Diels–Alder approach to dihydropyrans makes use of the two possible variations in the component parts. Thus, the cycloaddition of dienes to carbonyl compounds leads to 3,6-dihydropyrans, whilst reaction between an α,β-unsaturated carbonyl compound and an alkene results in 3,4-dihydropyrans (Scheme 51). Both types of reaction are well documented ⟨82T3087, 89CRV149, 93T5683, 94S535⟩ and a text details the value of the hetero Diels–Alder reaction in synthesis ⟨B-87MI 508-01⟩.

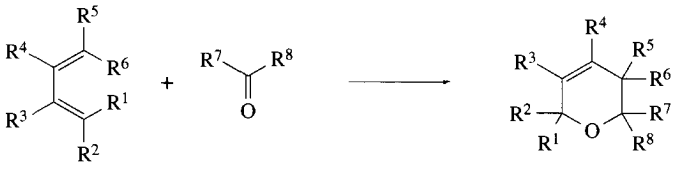


Scheme 51

Under normal circumstances, formation of 3,6-dihydropyrans by the Diels–Alder reaction is difficult because of the poor dienophilic character of the carbonyl group. However, the reaction can be promoted by activation of the diene through the incorporation of electron releasing groups, notably alkoxy functions ⟨86JA7060⟩, and by the introduction of electron-withdrawing functions in the carbonyl compound ⟨79JOC3347⟩. The reaction is also facilitated by an increase in pressure. Catalysis by Lewis acids assists the cycloaddition, often enabling reactions to be accomplished at low temperature (Table 1).

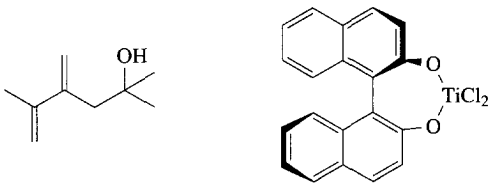
In addition to the hetero Diels–Alder reaction, a butadiene can react with a carbonyl compound to give the ene product (**75**). It has been shown the course of this reaction is influenced particularly by the catalyst and the reaction temperature ⟨95JOC5757⟩, Thus, copper(II) bisoxazoline complexes

Table 1 Synthesis of 5-6-dihydro-2*H*-pyrans from 1,3-dienes and carbonyl compounds.



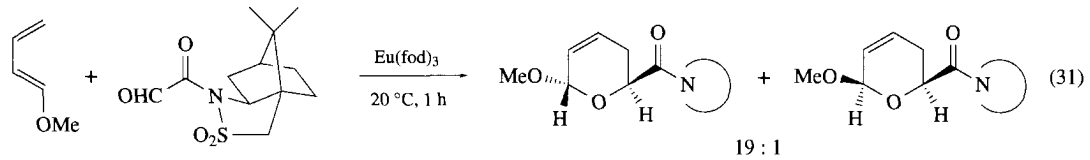
R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	*Conditions*	*Ref.*
H	H	H	H	OTMS	H	CF_3	CF_3	–	83JFC(22)1
OCH_2Ph	H	H	OTMS	H	H	CF_3	CF_3	THF, −45°C, 3h.	90JCS(P1)617
OTMS	H	H	Me	H	H	CO_2Et	CO_2Et	PhMe, 120°C, 3h.	90T5317
OMe	H	H	H	H	H	H	$CH_3CHN(Bn)BOC$	$Eu(fod)_3$, 10 kbar	89JOC759
OBu^t	H	Me	OTMS	R	H	H	Ph	$Eu(hfc)_3$, $CDCl_3$	83TL3451
Me	H	H	Me	H	H	H	CO_2H	H_2O, 100°C	94T10265

significantly increase the relative proportion of dihydropyran, buta-1,3-diene and isopropyl glyoxalate, for example, giving only the Diels–Alder product (55% yield) and furthermore with an *ee* of 87%.



(75) (76)

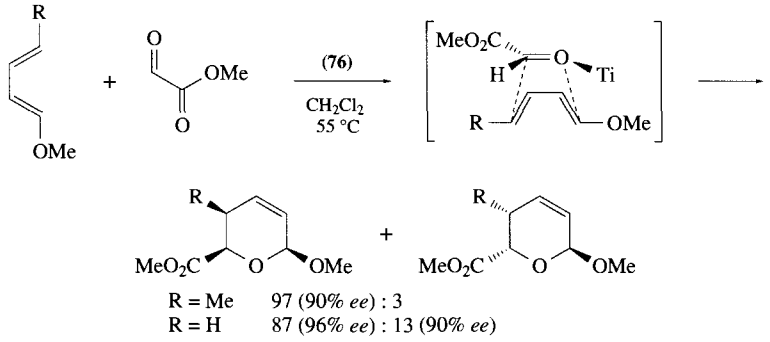
Initial attempts to effect asymmetric cycloaddition using glyoxylates of optically active alcohols were generally unsuccessful, resulting in low diastereoselectivity, though some enhancement was achieved at high pressures ⟨79JOC3347⟩. However, using Oppolzer's sultam as the chiral auxiliary, significant improvement in selectivity is observed which is further increased by the addition of $Eu(fod)_3$. At lower temperatures, still better asymmetric induction was obtained, but at the expense of yield (Equation (31)) ⟨89HCA482⟩.



19 : 1 (31)

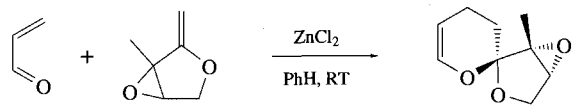
Chiral catalysts have been used to induce stereoselectivity in these cycloadditions ⟨87CC676, 91TL935⟩ with varied success. A titanium complex (**76**) derived from (*S*)-binaphthol controls the stereochemistry of the cycloaddition such that high enantioselectivity is achieved in the reaction of methoxydienes with methyl glyoxylate. It is proposed that the chiral catalyst complexes only to the aldehyde moiety and that the two carbonyl groups are disposed *anti* to each other in the *endo* transition state (Scheme 52) ⟨91TL935⟩. With isoprene, the ene product is formed in greater quantity than the Diels–Alder adduct, but a high *ee* is obtained in both reactions ⟨91TA643⟩.

The hetero Diels–Alder reaction of α,β-unsaturated carbonyl compounds with electron-rich dienophiles provides a valuable route to 3,4-dihydropyrans (Scheme 51), although the reaction of simple unsaturated carbonyl compounds with electron-rich alkenes is difficult to accomplish and requires high temperatures. Furthermore, the reaction shows little selectivity. However, both of these detractions have been largely overcome. The reaction is facilitated by electron withdrawing groups in the heterodiene ⟨93AG(E)131⟩ which lower the LUMO and hence promote overlap with the HOMO of the dienophile. The most reactive heterodienes have an EWG at the 3-position, but similar substituents at the 2- and 4-positions are also beneficial. The cycloaddition is also assisted



Scheme 52

by Lewis acids and by an increase in pressure ⟨88JA4065⟩, whilst the reaction of ketene acetals with α,β-unsaturated carbonyl compounds is facilitated by microwave irradiation ⟨94JCS(P1)3595⟩. The examples in Equations (32)–(37) ⟨85AP648, 89BCJ860, 94BCJ1912, 94T8035, 94T9037, 94TL8619⟩ are illustrative not only of the process but also of the means of imparting stereoselectivity to the reaction and supplement the data in Table 2.



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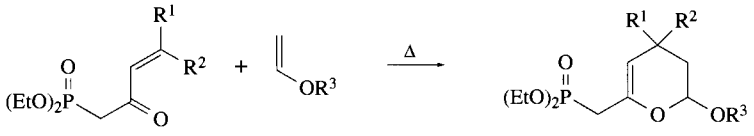

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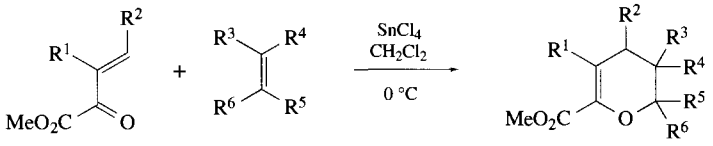

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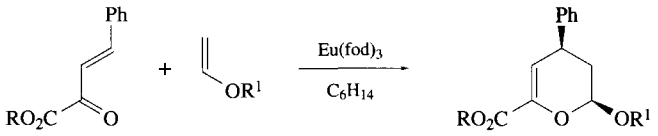

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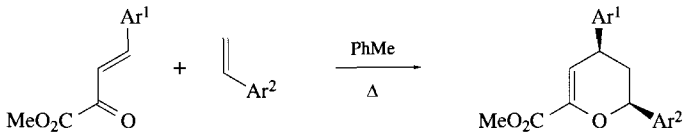

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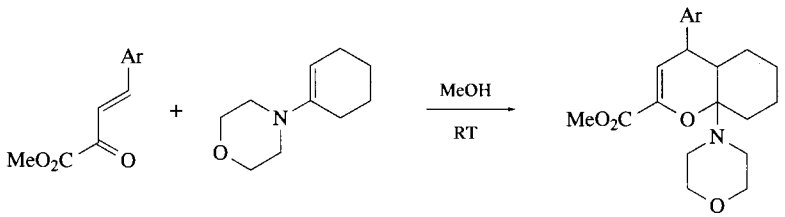
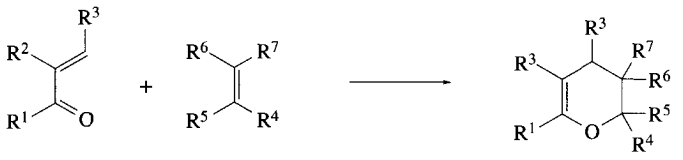


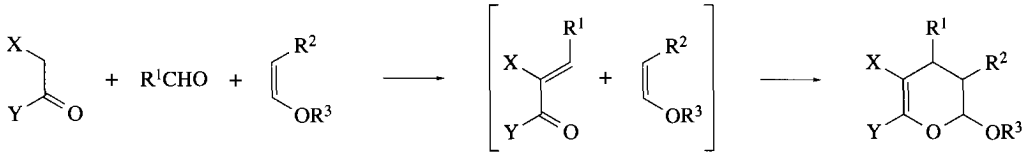
(37)

Table 2 Synthesis of 3,4-dihydro-2*H*-pyrans from α,β-unsaturated carbonyl compounds and alkenes.



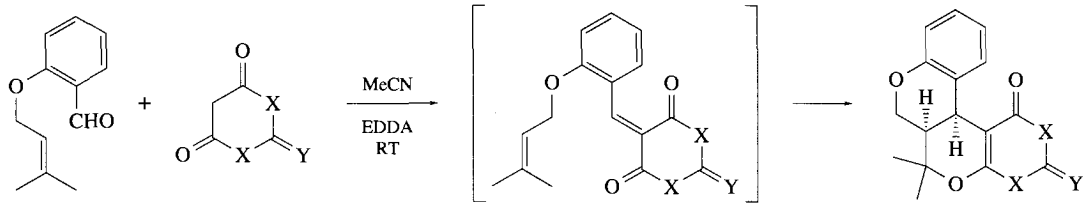
R^1	R^2	R^3	R^4	R^5	R^6	R^7	*Conditions*	*Ref.*
H	pTolS(O)	H	OEt	H	H	H	RT, 18 h	94SL409
$ROCH_2$	PhS	RC(O)	OEt	H	H	H	50–70 °C, 20–24 h, sealed tube	87S900
hetC(O)	H	OEt	OEt	H	OAc	H	various, range of catalysts	92S755
H	(O)C$(CH_2)_3$		OEt	H	H	H	20 °C, 3h	89TL1125
H	H	Me	$SCH=CH_2$	H	H	H	165 °C, 8h, sealed tube	87MI 508-02
X_3C, MeO_2C	H	HNPht	OEt	H	H	H	0.5–130 °C, pressure up to 7kbar	89CB1179
F_3C	H	OEt, OPh	OEt, OPh	H	H	H	80 °C, 30 h	89S215
F_3C, MeO_2C	PhS, H	NHPht	OEt	H	OAc	H	125 °C, 90 h	90TL1697
Ph	ROC(O)	Ar	piperidinyl	H	R, Ar	H	RT, 40 h	90AP(323)617
$EtO_2P(O)CH_2$	H	H, Me	RO	H	H	H	3–24h ($ZnCl_2$); 6–48 h ($ZnBr_2$)	89CL675
H	H, Me	Me	RO	H	Me	H, Me	16 h–3d, RT–50 °C, 15 kbar, $Eu(fod)_3$	95T8383
F_3C	$F_3CC(O)$	RO	RO, PhO	H, PhO	H	H	15 min–24 h	90S347
Ph	H	Ph	$OCH(Ph)CH_2O$		H	H	3 min, microwave irradiation	95JOC4160
MeO_2C	H	Ph	Chiral RO	H	H	H	70 °C, 72 h, $Eu(fod)_3$	93TA193
H	steroidal	H	$S(CH_2)_3S$		H	R	$Eu(fod)_3$	89AG(E)1359
X_3C, MeO_2C	H	ArC(O)NH, HNPht	RO	H	H	H	140 °C, 16 h	91CB881
H	H	H, EtO_2C	$OCH(tBu)OC(O)$		H	H	4 d	90SL145

This route to dihydropyrans has been extended and simplified by generating the α,β-unsaturated carbonyl compound in the presence of the dienophile. Such a tandem Knoevenagel/hetero-Diels–Alder approach involves reacting an aldehyde, a 1,3-dicarbonyl compound, and an alkene together in the presence of a catalyst, the most efficient of which appears to be fluoride ion (Scheme 53) ⟨89CB643, 90LA253⟩. The value of this methodology to natural product synthesis has been reviewed ⟨90JHC47⟩. Both components can be incorporated into the one molecule whereupon a highly stereoselective intramolecular hetero Diels–Alder reaction can occur ⟨84OR(32)1⟩. This variant leads directly to polycyclic compounds and features in syntheses of secoiridoid terpenes ⟨90H(30)583⟩ and indole alkaloids ⟨95JOC3236⟩. Furthermore, it can be combined with the tandem methodology mentioned above (Scheme 54) ⟨82AG(E)863, 87S700⟩ and as used in the synthesis of heterocyclic analogues of steroids ⟨90AGE527⟩ and iridoids ⟨91LA155⟩. An intramolecular cycloaddition has been combined with an intramolecular hetero Diels–Alder reaction in a synthesis of the tetracyclic the framework of the quassinoids (Scheme 55) ⟨94JOC5596⟩. By modification of this technique, stereochemical control can be achieved at eight centres.

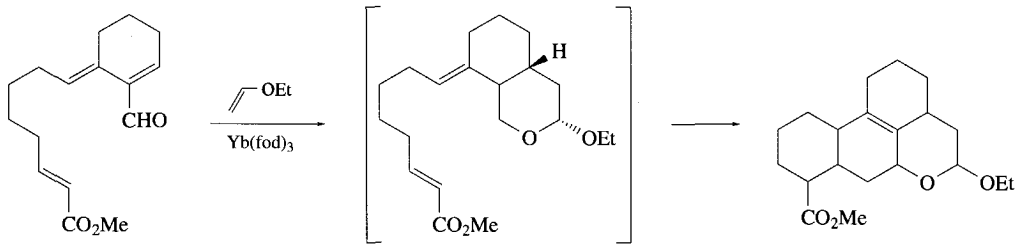


Scheme 53

Yields in these heterodiene Diels–Alder reactions are generally high provided that the heterodiene moiety is activated by electron withdrawing functions. The stereochemistry of the cycloaddition is controlled in part by substituents at sterically significant positions. The enantioselectivity is influenced by Lewis acid catalysts and by pressure ⟨93AGE1485⟩. The Lewis acid catalyst can also affect

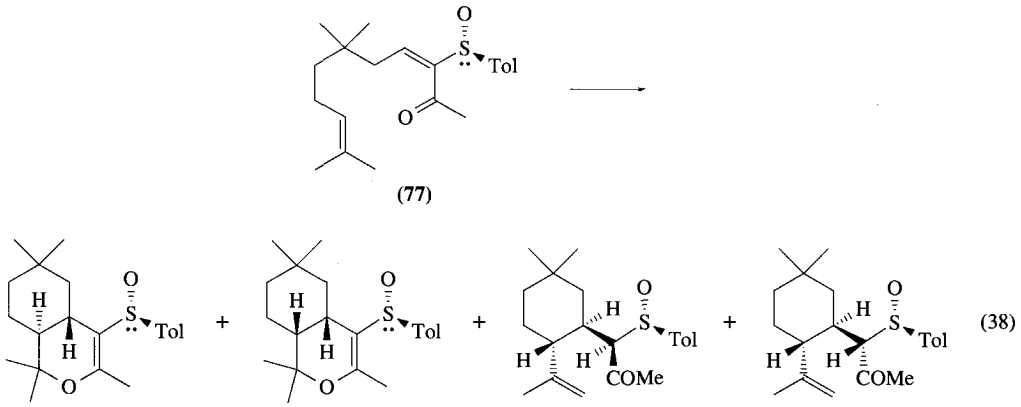


Scheme 54



Scheme 55

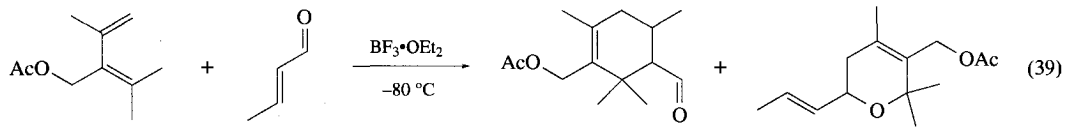
the mode of cyclization. Thus not only is a cycloaddition possible, but an ene reaction can also occur. For example, cyclization of the dienone (**77**) gives exclusively the dihydropyran when monodentate Lewis acids such as Et_2AlCl are used, but substantial quantities of the cyclohexane are formed with bidentate catalysts ($ZnCl_2$). In all cases, high optical yields result (Equation (38)) ⟨92TL7161⟩. The catalyst can also influence the diastereoselectivity ⟨94SL509⟩.



(38)

A copper(II) catalyst facilitates the reaction of dienes with glyoxylates and leads to high yields with a high enantiomeric excess, though both cycloaddition and ene reactions occur. The ratio of products is dependent on the ligand in the catalyst, the reaction conditions and the ester function ⟨95JOC5757⟩.

When an α,β-unsaturated aldehyde reacts with a diene, two adducts are again possible, a cyclohexene and a dihydropyran, but the normal Diels–Alder reaction usually prevails. However, a β-alkyl group in the dienophile not only hinders the cycloaddition but also increases the competition between normal and hetero Diels–Alder reactions such that significant amounts of dihydropyrans are formed (Equation (39)) ⟨95JOC8128⟩.

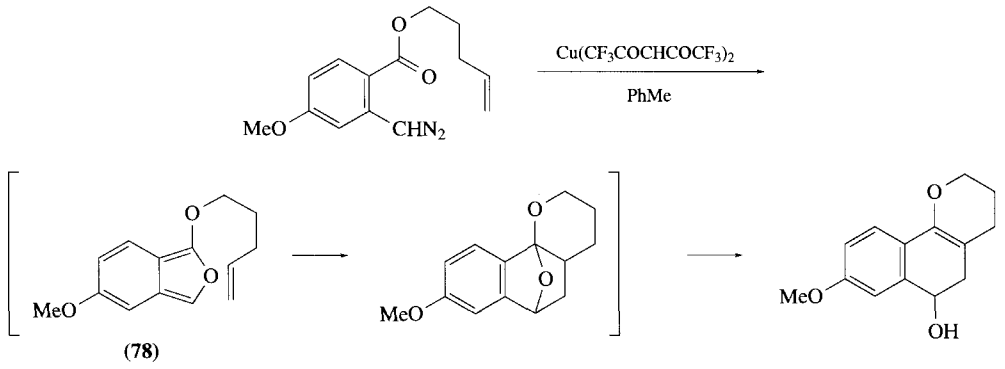


(39)

5.08.9.3 From Other Heterocycles

5.08.9.3.1 From furans

An intramolecular cycloaddition to the isobenzofuran (**78**) leads to the fused tetrahydropyran and forms part of a synthesis of an 11-oxasteroid (Scheme 56) ⟨89H(29)1243⟩.

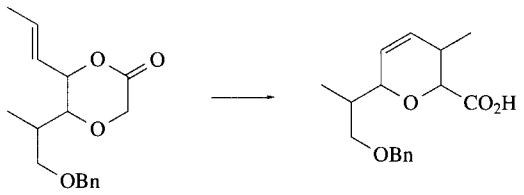


(78)

Scheme 56

5.08.9.3.2 From dioxans

An Ireland–Claisen rearrangement of the 1,4-dioxanone (**79**) gives the substituted dihydropyran carboxylic acid (Equation (40)) for use in a macrolide synthesis ⟨90TL5285⟩.



(79)

(40)

5.08.9.4 From a Preformed Heterocyclic Ring

5.08.9.4.1 From pyrans

Deprotonation and stannylation of a 2-benzenesulfonyltetrahydropyran leads to a 2-stannyl-2,3-dihydropyran, from which a bis-dihydropyran can be obtained through a Pd-catalyzed homo-coupling ⟨94S1275⟩.

5.08.9.4.2 From pyranones

The 1,2-addition of methylcerium dichloride to 2-butoxy-5,6-dihydropyran-4-one occurs with good diastereoselectivity, unlike the addition of methyllithium ⟨93JOC385⟩.

5.08.9.4.3 From coumarins

An epoxide is probably an intermediate in the conversion of 4-hydroxy-3-(3-oxoalkyl)coumarins into pyrano[3,2-*c*][1]benzopyran-5-one on treatment with dimethylsulfoxonium methylide. The linear pyrano[2,3-*b*][1]benzopyran-5-one resulted when an acid work-up procedure was followed ⟨86G501⟩.

5.08.10 TETRAHYDROPYRANS

The routes to tetrahydropyran and spiroketal units in polyether antibiotics ⟨87T3309⟩ and fruit fly pheromones ⟨95CRV789⟩ have been reviewed, as have methods of synthesis of 1,7-dioxaspiro-[5.5]undecanes ⟨86H(24)1699, 89CRV1617⟩. A general approach to spiroketals from lactones has been described ⟨90JOC5894⟩.

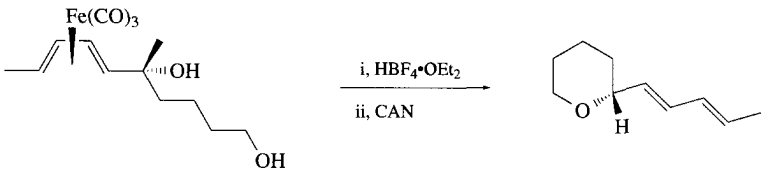
5.08.10.1 Formation of One Bond

5.08.10.1.1 Adjacent to the heteroatom

There are many examples of the synthesis of tetrahydropyrans which are based on the cyclization of 1,5-diols and compounds which can provide a similar electrophilic site for ring closure.

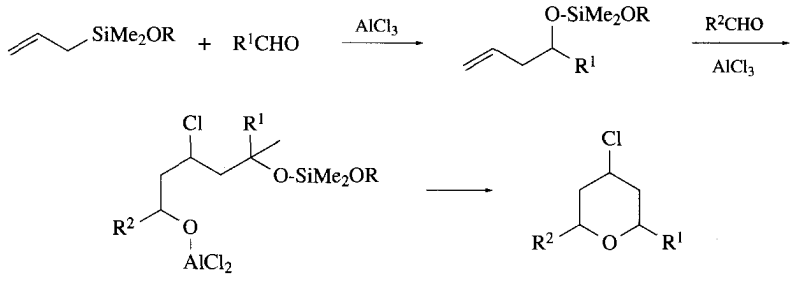
Pentan-1,5-diols can be quantitatively cyclized to the pyran in the presence of $BuSnCl_3$ in a simple experimental method ⟨88G483⟩.

Chiral tetrahydropyrans result from intramolecular trapping of the cations derived from iron tricarbonyl-butadiene complexes. Separation of stereoisomers and decomplexation are facile (Equation (41)) ⟨91SL895⟩.



(41)

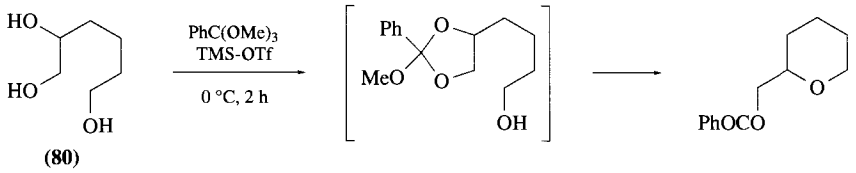
Alkylalkoxysilanes condense with aldehydes to give *cis*-2,4,6-trisubstituted tetrahydropyrans. The Lewis acid catalyzed process takes place in two stages and it is possible to use different aldehydes for each step, producing unsymmetrically substituted pyrans. The 4-substituent is derived from the catalyst (Scheme 57) ⟨89JOC5768⟩.



Scheme 57

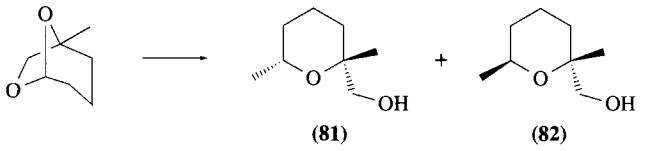
The triols (**80**) react with trialkyl orthoesters under acid conditions to form the 2-substituted tetrahydropyran by way of a cyclic orthoester (Scheme 58) ⟨93H(35)665⟩.

The stereochemistry of the tetrahydropyrans produced by reductive cleavage of bicyclic acetals can be controlled by the choice of reagent. Thus, DIBAL-H gives the *trans* isomer (**81**), whereas a mixture of $TiCl_4$ and triethylsilane affords mainly the *cis* compound (**82**) (Equation (42)) ⟨90T4595⟩.



(80)

Scheme 58



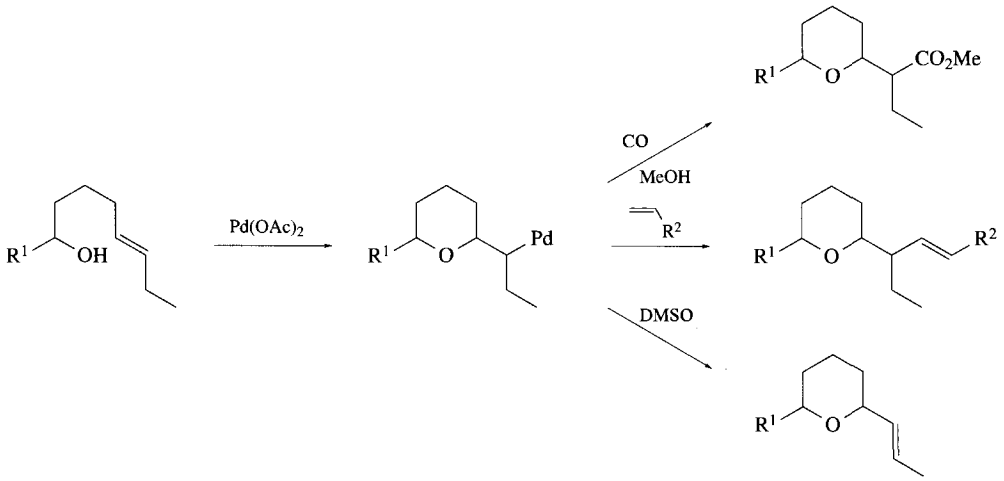
(81) (82) (42)

Several instances of halolactonization have been reported ⟨90JOC283, 93SL927, 94CC763, 95CC989⟩ including its use in the formation of an 11-oxasteroid ⟨89H(28)905⟩.

1,5-Diols are oxidatively cyclized to tetrahydropyran-2-ols using environmentally friendly reagents ⟨94TL8477⟩, whilst the oxidative cleavage of 1,2-diols features in another tetrahydropyran synthesis ⟨95JCS(P1)2989⟩. Tetrahydropyran-2-ols are also available from diketene and β-hydroxy-aldehydes ⟨94T2047⟩. δ-Silyloxy ⟨89CL259⟩ and δ-bromo ⟨89TL6571⟩ carbonyl compounds are alternative precursors. Polycyclic tetrahydropyrans can also be obtained using this approach ⟨93TL4105, 94TL97⟩.

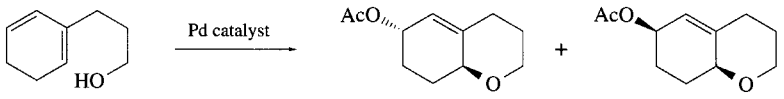
Tetrahydropyran syntheses based on cyclization of pent-4-en-1-ols are quite common and feature in syntheses of natural products ⟨93T5979, 93TL5739, 94TL323⟩. The cyclization can be assisted by sulfenylation ⟨95TL1909⟩, selenation ⟨90TL6535, 92LA261, 94T139, 95JOC4660, 95SL855⟩, iodination ⟨94CC1469, 95SL663⟩, and mercuriation ⟨90JA7407, 94CC767, 94T139⟩. Acid catalysis ⟨87CC1718, 88TL681, 89JOC4723, 92H(33)51, 94SL594, 95TL2453⟩, Lewis acid catalysis ⟨89CRC29⟩, and basic conditions ⟨92TL2399, 93SC1009, 93TL111⟩ are also effective.

Intramolecular palladium catalyzed cyclization of alkenols allows additional functionalization of the tetrahydropyran through the trapping of an intermediate palladium species. Thus, methoxycarbonylation ⟨84JA1496, 89JOC4485⟩, vinylation ⟨93TL7205⟩, and hydride elimination ⟨89JOC4483⟩ lead to 2-functionalized tetrahydropyrans (Scheme 59).



Scheme 59

The palladium-catalyzed cyclization of the dienols (**83**) involves a 1,4-oxidation and offers a route to fused tetrahydropyranols in a highly stereoselective manner which can be influenced by added nucleophile (Equation (43)) ⟨92JA6374, 95TL5397⟩. When the side chain is attached to the 1-position of the diene moiety, spirocyclization occurs. Added nucleophile can be incorporated into the product ⟨91JOC2274⟩.

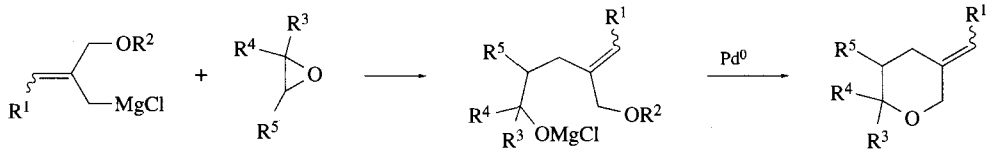


(83) (43)

A significant variation on the alkenol theme is the stereo- and regio- selective ring opening of hydroxyepoxides (Equation (44)) ⟨89JA5330⟩. 5-*exo*-Cyclization competes with the 6-*endo* mode but the latter is dominant when an electron-rich unsaturated function is present on the epoxide carbon atom remote from the hydroxy group. Similar controls apply to the next higher homologue of the hydroxy epoxides ⟨89JA5335⟩.

(44)

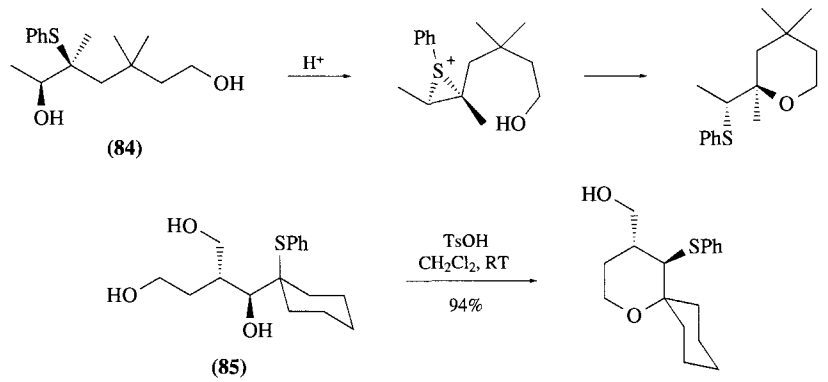
Other examples using the epoxide route to tetrahydropyrans include ⟨90TL4747, 92JOC50, 92TL4349, 93JA3558, 93TL5421, 93TL6925, 94TL2179⟩. Epoxides feature in a one-pot synthesis of 3-methylene-tetrahydropyrans in which the initial epoxide ring-opened product arising from attack by a Grignard reagent is cyclized by Pd(0) (Scheme 60) ⟨92T9901⟩.



Scheme 60

A 1,5-diene can be converted into a substituted tetrahydropyran by conversion into the diepoxide. Subsequent acidic hydrolysis is accompanied by cyclization. It is suggested that one epoxide is converted to the diol and the other undergoes intramolecular ring opening ⟨89SC1233⟩.

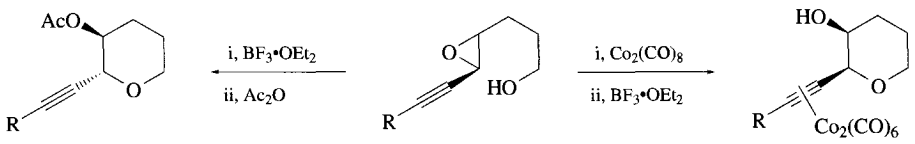
6-*exo*-Cyclization of the diol (**84**) proceeds via the episulfonium ion and involves attack at the more substituted carbon atom of the three-membered ring. Cyclization gives the *anti* product and this allows control of ring size when alternative nucleophiles are incorporated into the molecule, as in (**85**) (Scheme 61) ⟨92TL539⟩.



(84) (85)

Scheme 61

Cobalt complexes derived from alkynic epoxides undergo a Lewis acid catalysed 6-*endo* cyclization in which the configuration of the substrate is retained in the tetrahydropyran (Scheme 62) ⟨94TL2179⟩. In the absence of the catalyst, the mode of cyclization is determined by the terminal substituent on the alkyne moiety. Electron-releasing groups favor 6-*endo* cyclization over the 5-*exo* mode. Furthermore, inversion of configuration at the propynyl position is noted ⟨94TL2183⟩.

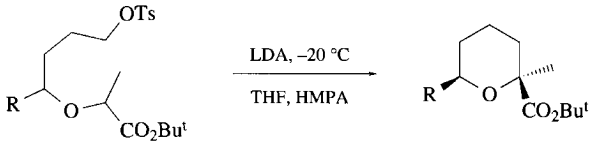


Scheme 62

The cyclization of 1,5-hydroxyketones has been extensively used to prepare tetrahydropyranols and, notably, spiroketals and consequently this methodology has been used in the synthesis of a number of naturally occurring molecules ⟨89T5935, 95TA397⟩.

5.08.10.1.2 β to the heteroatom

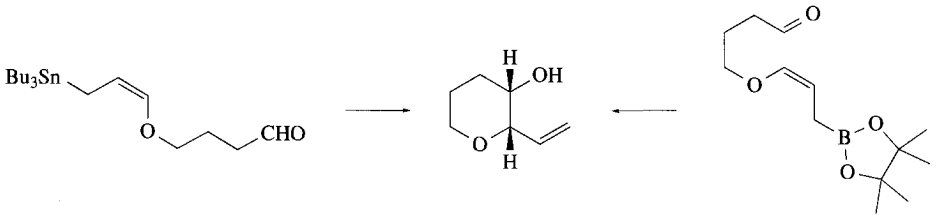
The enolates derived from α-alkoxy carboxylates can effect a highly stereoselective intramolecular alkylation to give tetrahydropyrans (Equation (45)) ⟨92BCJ3487⟩.



(45)

The intramolecular allylmetallation of aldehydes provides a useful route to tetrahydropyrans in which control of the stereochemistry of the product is usually possible. For instance, cyclization of the *Z*-ω-stannyl ether aldehyde (**86**) by Brønsted acids leads predominantly to the *cis*-2-ethenyltetrahydropyran-3-ol (Scheme 63), whereas the *E*-isomer affords *trans* product ⟨93TL1313⟩. In like manner, related acetal protected aldehydes afford the *trans* isomer under the influence of the Lewis acid system $TiCl_4$-PPh_3 ⟨91SL823⟩.

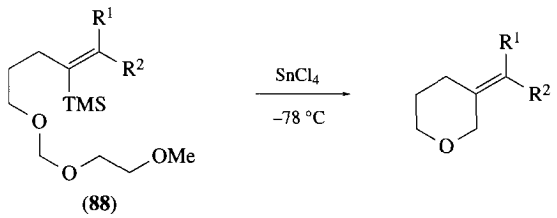
The γ-alkoxyallylboronates (**87**) undergo a *cis*-selective cyclization allowing a one-pot conversion of an allyloxyaldehyde to a *cis*-2-vinyltetrahydropyran-3-ol (Scheme 63) ⟨95TL1431⟩. This methodology gives access to the *cis*-fused pyrano[2,3-*b*]pyran and pyrano[2,3-*b*]pyrano[2,3-*e*]pyran systems.



(**86**) (**87**)

Scheme 63

Cyclization of the vinylsilane acetals (**88**) occurs in the *exo* mode, leading to 3-alkylidene tetrahydropyrans. Both stereoisomers are accessible by this route, in which the $SiMe_3$ moiety controls the stereochemistry (Equation (46)) ⟨89JOC5695⟩. Closely related is the $SnCl_4$ induced cyclization of 2-acetoxy-2-(3-alken-1-oxy)acetates ⟨94T7115, 94T7129⟩.

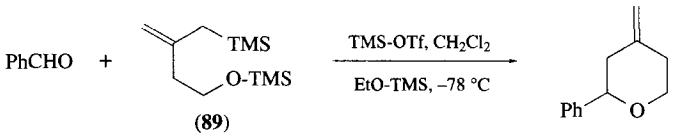


(**88**)

(46)

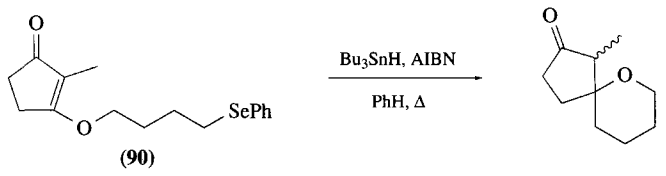
The Lewis acid catalyzed transacetalization of alkenols, which is followed by a spontaneous cyclization to the tetrahydropyran, offers a simplified routine to the above ⟨89JOC2748⟩.

4-Methylenetetrahydropyrans are formed in high yields from aldehydes by reaction with the allylsilane (**89**) in the presence of a trimethylsilyl ether, which prevents isomerization of the double bonds (Equation (47)). With cyclic ketones, spiroketals are produced ⟨92TL1799, 93BSB655, 95SL123⟩.

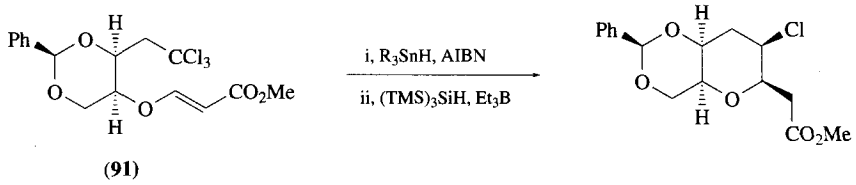


(47)

Cyclization of the selenides (**90**) proceeds via radical generation and leads to the spiro-linked pyran (Equation (48)) ⟨90T545⟩. The radical induced cyclization of the acrylate (**91**) proceeds with good steric control, a feature also utilized in a synthesis of the pyranopyran, dactomelyne (Equation (49)) ⟨95JA8017⟩.

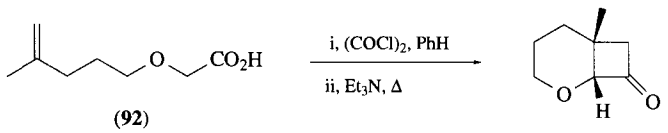


(48)



(49)

Ketenes derived from alkenyloxyacetic acids (**92**) undergo an intramolecular [2 + 2] cycloaddition during which a tetrahydropyran ring is formed (Equation (50)) ⟨85JA2194⟩.



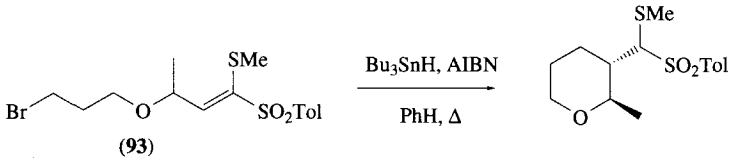
(50)

5.08.10.1.3 γ to the heteroatom

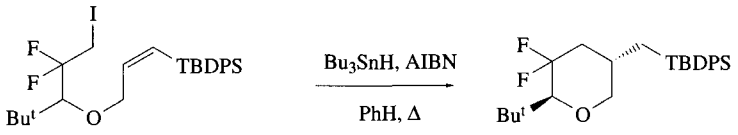
A number of approaches to the tetrahydropyran system are based on radical cyclizations.

The 6-*exo*-cyclization of the 7-bromo-4-oxahept-1-ene (**93**) via the terminal radical occurs exclusively in a *trans* manner to give a mixture of diastereoisomers (Scheme 63) ⟨93TL8313⟩.

High stereoselectivity is achieved in the cyclization of the radical derived from (**94**) only in the presence of a bulky substituent on the acceptor double bond. Again, the *trans* product is favored ⟨92T8915⟩.

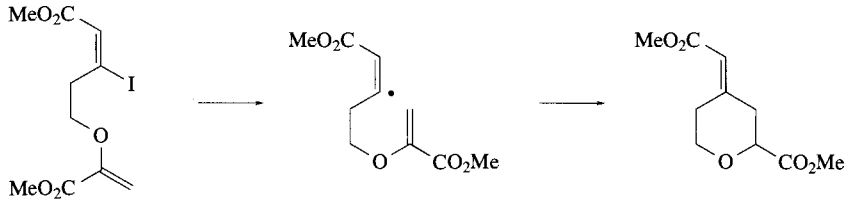


Preferential cyclization of the *Z*-radical derived from the vinyl pyruvate (**95**) leads to the tetrahydropyran (**96**) as the major product (Scheme 64). The *cis*-2,6-disubstituted 4-methoxy-



(94)

methylenetetrahydropyrans, the stereochemical array found in the bryostatins, can be obtained by a similar vinyl radical cyclization ⟨89CC480⟩.

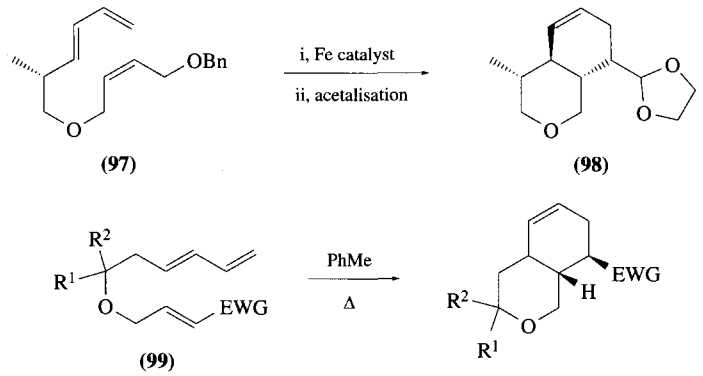


(95) (96)

Scheme 64

Concomitant C—C bond formation and cyclization can be effected through the mediation of transition metals. Cyclopentanone fused tetrahydropyrans result from an intramolecular reaction of alkynic chromium carbene complexes ⟨90JOC786⟩ and also from the amine oxide cyclization of alkenyl propargyl ether complexes ⟨93TL4023⟩.

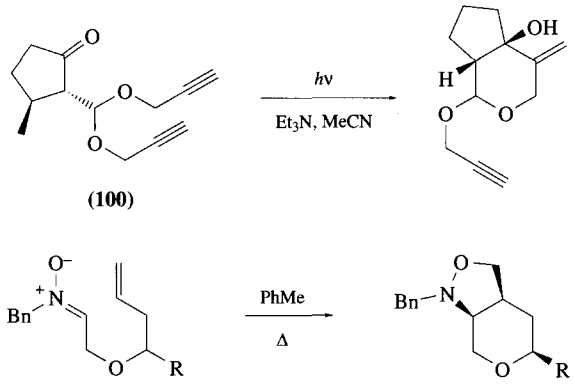
The iron-catalyzed cyclization of the chiral ene diene (**97**) forms the *trans*, *trans* substituted pyran (**98**) by way of a formal ene reaction (Scheme 65) ⟨87TL5627⟩ and fused tetrahydropyrans result from the thermal cycloaddition of the trienyl ether (**99**) in which activation is provided by an ester or sulfone group (Scheme 65) ⟨92SL757⟩.



(97) (98) (99)

Scheme 65

The photoreductive cyclization of the alkynyl ether (**100**) gives the *cis*-fused cyclopenta[*c*]pyran, the basic unit of the iridoids (Scheme 66) ⟨89TL4113⟩. The analogous *cis*-fused isoxazolopyran results from an intramolecular 1,3-dipolar addition (Scheme 66) ⟨94JCS(P1)1661⟩.



(100)

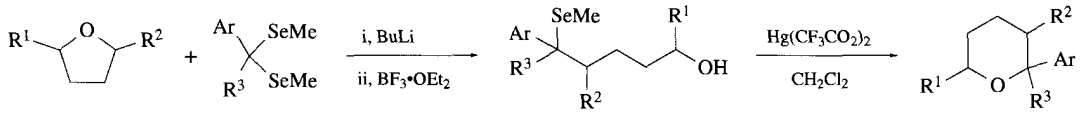
Scheme 66

5.08.10.2 From Other Heterocycles

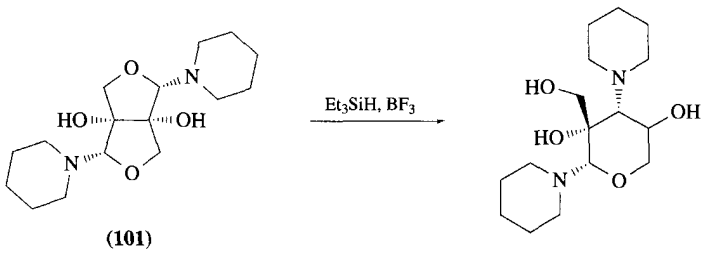
5.08.10.2.1 From furans

A two-step conversion of tetrahydrofurans to 2-aryltetrahydropyrans involves ring opening with α-selenoalkyllithium reagents and cyclization of the resulting 5-aryl-5-methylselenopentan-1-ols (Scheme 67) ⟨92SL320⟩.

The acid catalyzed rearrangement of the furofuran (**101**) leads to an epimeric mixture of pyrans (Equation (51)) ⟨94H(37)137⟩.



Scheme 67



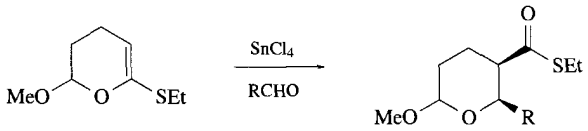
(51)

(**101**)

5.08.10.3 From a Preformed Heterocyclic Ring

5.08.10.3.1 From dihydropyrans

The reaction of 6-alkylthio-2-methoxy-3,4-dihydropyrans with aldehydes in the presence of a Lewis acid involves a ring-opening–ring-closure sequence which leads to tetrahydropyrans diastereoselectively (Equation (52)) ⟨95TL8255⟩.



(52)

Hydroboration—oxidation of dihydropyrans affords tetrahydropyrans, often with good stereochemical control ⟨86JA2049, 87JCS(P1)1123, 93JOC385, 94JOC4131⟩. Mercuriation is an alternative process ⟨86CCC1671⟩.

5.08.11 CHROMANS (3,4-DIHYDRO-2*H*-1-BENZOPYRANS)

There is an extensive literature on chromans and tocopherols, the chemistries of which are well covered in the text by Ellis and Lockhart ⟨81HC(36)⟩.

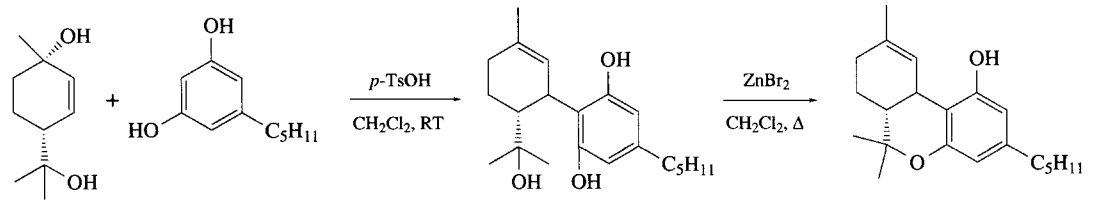
5.08.11.1 Formation of One Bond

5.08.11.1.1 Adjacent to the heteroatom

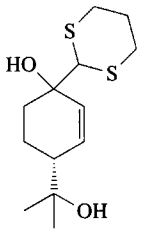
The cyclization of derivatives of 1-(2-hydroxyphenyl)propane (**102**) (Equation (53)) is a common feature of a number of chroman syntheses. A range of chromans has been synthesized by cyclization of chloropropane derivatives (**102**; X = Cl) ⟨39JOC311, 79S126⟩, but the acid catalyzed cyclization of

propanols (**102**; X = OH) is more common ⟨87SC829, 92SC23, 93H(36)1743, 94H(37)163, 94H(38)1487⟩. This approach has been used to synthesize dibenzo[*b*,*d*]pyrans, the cannabinoid ring system, from *cis*-*p*-menth-2-en-1,8-diol, thereby reducing the extent of by-product formation (Scheme 68) ⟨91SL553⟩. Use of the dithiane derivative (**103**) also offers advantages in the synthesis of cannabinoids ⟨89JOC5428⟩. The cyclization of the complex propanol (**104**) features in a synthesis of robustadial A ⟨88JOC3673⟩ and vitamin E has been prepared from phytol ⟨90SL451⟩ and (*S*)-*O*-benzylglycidol ⟨90TL3619⟩ using this methodology.

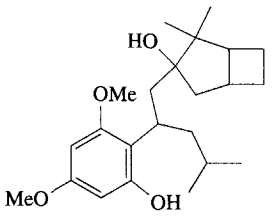
(102) (53)



Scheme 68

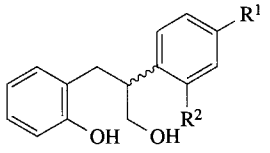


(103)



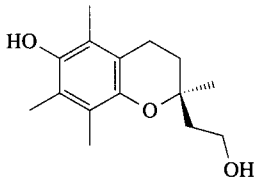
(104)

Use of oxazolidinones as chiral auxiliaries in the synthesis of the propanols (**105**) is fundamental to an enantioselective synthesis of isoflavans. Cyclization is best effected under Mitsunobu conditions ⟨95CC1317⟩.

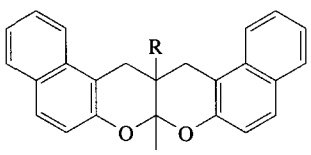


(105)

Several related syntheses proceed through the cyclization of 2-methoxyphenyl derivatives of propanol or methoxypropane ⟨81JOC783, 89CL465, 90SC3103⟩. An asymmetric synthesis of (*S*)-chromanethanol (**106**) is a pertinent example ⟨95SL1255⟩. An intramolecular acetalization features in the synthesis of the pyranopyran (**107**) from 2-naphthol and dimethylol ketones effected by ion exchange resins ⟨87T3505⟩.



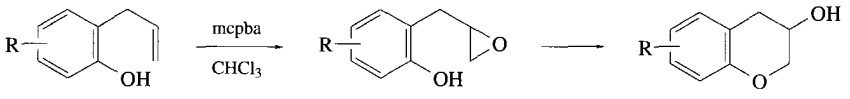
(106)



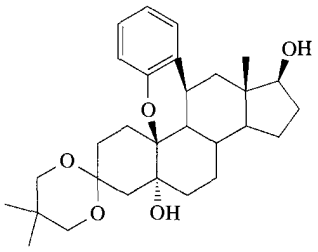
(107)

The nucleophilic ring opening of an epoxide is a further variant of this method, simultaneously introducing a hydroxy function into the product. Thus, *o*-allyl phenols yield chroman-3-ols via the

epoxides (Scheme 69) ⟨91SC1455⟩. There is no evidence of benzofuran formation. The oxygen bridged steroid (**108**) has been obtained in this manner ⟨93T2217⟩.

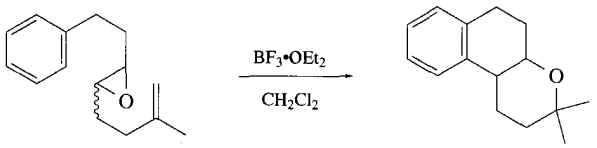


Scheme 69



(108)

In the case of the epoxyalkene (**109**), the Lewis acid catalyzed ring opening of the epoxide ring results in two cyclization processes and a reduced naphthopyran is formed (Equation (54)) ⟨93TL1283⟩. It is thought that alicyclic ring formation precedes heterocyclization. A cyclic bromonium ion serves a similar purpose to the epoxide ring ⟨95CJC1727⟩.



(54)

(109)

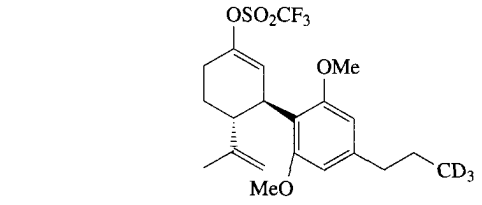
Activation of an aryl fluoride towards intramolecular nucleophilic attack is achieved by complexation with a cyclopentadienylrhodium catalyst. High yields of both simple chromans and a spirobichroman result from 3-(2-fluorophenyl)propan-1-ol ⟨84JCS(P1)925, 89JCR239⟩.

A C=C bond can serve as the focus for cyclization and there are many examples of chroman synthesis from *o*-hydroxyphenylpropene derivatives. Phosphoric acid effects the cyclization of 4-(2-hydroxyaryl)but-2-enes and similar compounds to chromans ⟨83S404, 84G501, 84G3549, 84M1059⟩ and promotes the direct formation of aminochromans from aminophenols and isoprene or 2-methylbut-3-en-2-ol ⟨84IJC129⟩. Flavans are similarly derived from phenols and cinnamyl alcohol ⟨84S346⟩ and their formation from phloroglucinol and acetaldehyde probably involves this mode of cyclization ⟨90TL2789⟩. Formic acid is an alternative cyclization medium ⟨88MI 508-02⟩ and montmorillonite clays bring about both the rearrangement of allyl phenyl ethers and the cyclization of the resultant *o*-allylphenols to chromans ⟨90TL3241⟩. An aluminosilicate is an effective Friedel–Crafts catalyst ⟨95CC519⟩. When 3,6-dihydro-4-methyl-2*H*-pyran is used as the alkene component, a Friedel–Crafts reaction with 2,3,5-trimethylhydroquinone leads to a useful precursor of α-tocopherol ⟨85CL1399⟩. Fluorinated analogues of vitamin E have been prepared using similar methodology ⟨88CPB515, 88CPB2950⟩.

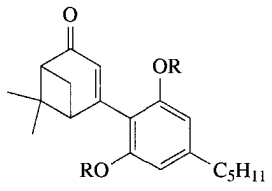
The tetrahydrocannabinol system results from the reaction of *p*-mentha-2,8-dien-1-ol with olivetol ⟨89CC62⟩ and by the demethylation and cyclization of (**110**) ⟨92T9173⟩. The cannabinoid nucleus is also accessible from (+)-apoverbenone via (**111**) ⟨89JOC4741, 90JOC5711⟩.

Control of the stereochemistry at C-6 can be achieved. Thus, although conventional acid catalysed cyclization of the alkenol (**112**) gives a 1 : 1 mixture of two isomers, a mercuration–demercuration sequence enables the individual stereoisomers to be obtained (Equation (55)) ⟨94T2671⟩. One of the chiral centres in 2,3-dimethylchroman-4-ol can also be induced using this mercuration technique; the others result from a borane reduction ⟨95S630⟩.

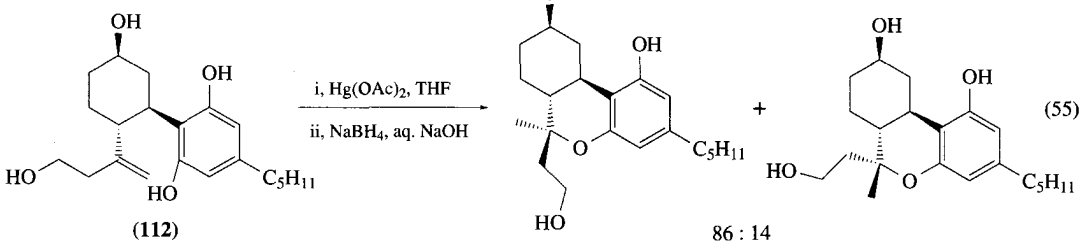
Both asymmetric alkylation and asymmetric epoxidation can be used to introduce the (*R*)-configuration at C-2 of the chroman unit of α-tocopherol ⟨90HCA1068⟩. A detailed study of the cycli-



(110)



(111)

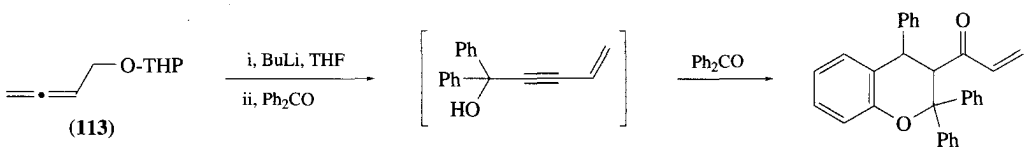


(112)

86 : 14

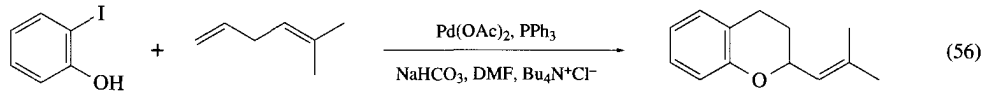
zation of a phytylhydroquinone to α-tocopherol brought about enzymatically has shown that *si*-protonation of the alkene unit and *re*-attack by the phenolic moiety occur concomitantly ⟨93HCA1729, 94HCA1721⟩.

The anion derived from the THP protected allene (**113**) reacts with benzophenone to give a tetrasubstituted chroman. A vinylacetylene intermediate is proposed which forms a tertiary alcohol on reaction with the ketone. A base initiated attack on a second molecule of benzophenone completes the sequence ⟨86JHC1195⟩. Similar products result from the reaction of phenylacetylene magnesium bromide with the ketone ⟨87JHC1705⟩. In this latter route, the tertiary alcohol can be condensed with a second aldehyde or ketone, giving greater scope to the method.



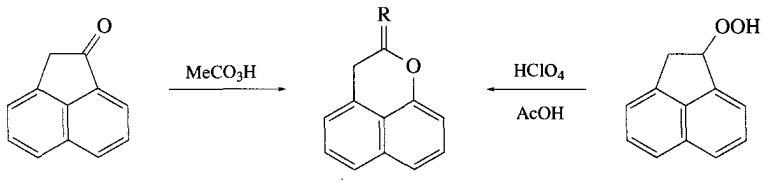
(113)

2-Alkenylchromans result from the palladium-catalyzed annulation of 1,4-dienes to *o*-iodophenols, arylation occurring at the less substituted double bond (Equation (56)) ⟨93JOC4509⟩.



(56)

Both Baeyer–Villiger and hydroperoxide rearrangements have been used to synthesize the 2,3-dihydronaphtho[1,8-*bc*]pyran ring system (R = O or H, OH) (Scheme 70) ⟨90S312, 93M331⟩.

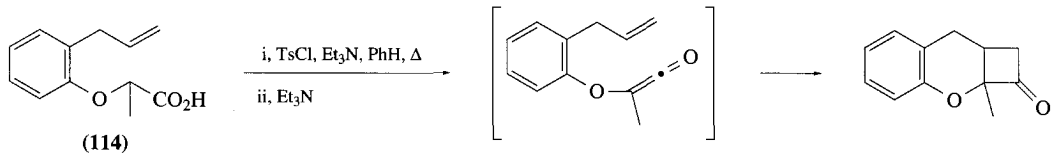


Scheme 70

5.08.11.1.2 β to the heteroatom

A spontaneous intramolecular [2 + 2] cycloaddition follows the generation of the ketene from the (*o*-propenylphenoxy)propanoic acid (**114**), producing the fused chroman (Scheme 71) ⟨87S395⟩.

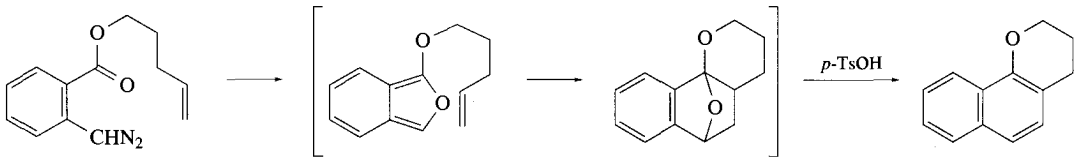
The photodecarboxylation of *o*-allylphenoxyacetic acids sensitized by methylene blue leads to chromans ⟨95TL1337⟩.



(114)

Scheme 71

An intramolecular Diels–Alder cycloaddition features in a multi-step synthesis of a naphtho[1,2-*b*]pyran from a 2-methylbenzoic acid derivative. A key step is the copper catalyzed decomposition of the diazo compound to the isobenzofuran (Scheme 72) ⟨89H(29)1243⟩.



Scheme 72

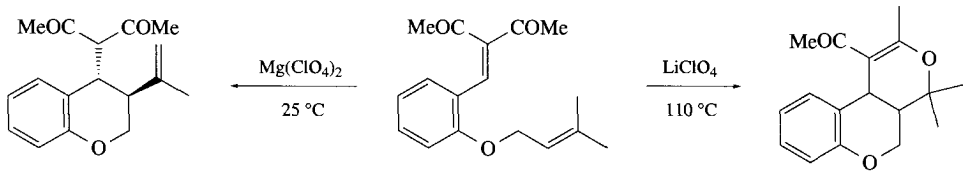
5.08.11.1.3 γ to the heteroatom

Several chroman syntheses are based on the cyclization of phenoxypropane derivatives, often under Friedel–Crafts conditions which implies the intermediacy of a carbocation.

The simplest example involves the cyclization of 1-chloro-3-phenoxypropanes, catalyzed by $SnCl_4$ ⟨52CR(234)1787⟩, but other substrates include 1,3-diphenoxypropanes ⟨65JCS5718⟩ and 3-phenoxypropan-1-ols ⟨66JOC3032⟩.

A related mechanism operates in the acid catalyzed cyclization of allyl ethers. Trifluoroacetic acid is recommended as the solvent and catalyst in preference to the usual Lewis acids ⟨92TL3795⟩. The alkylation of phenols with alkenols and alkenyl halides yields chromans directly in acidic media, a route which has been successfully applied to various 7-hydroxycoumarins ⟨90JHC995⟩. A Lewis acid catalyzed intramolecular cyclization also features in the synthesis of some chiral pyrano[2,3-*b*][1]benzopyrans ⟨93TL6757⟩.

A double cyclization is the predominant reaction when allyl arylidene ethers are heated in the presence of lithium or barium perchlorates, but with $Mg(ClO_4)_2$ an ene reaction is preferred (Scheme 73) ⟨95TL2855⟩.

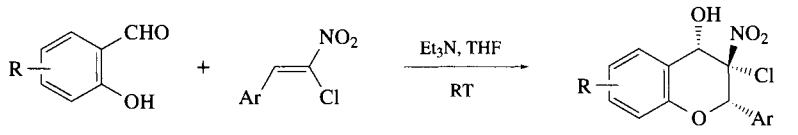


Scheme 73

Methanesulfonic acid effects the cyclization of (**115**), which presumably involves a cationic species. The intramolecular amidoalkylation shows some stereocontrol, with a distinct preference for (**116**) ⟨88TL5493⟩.

The chromanylamino acid (**118**) has been obtained in large quantities by the intramolecular alkylation of the oxazolidinone (**117**) and subsequent hydrolysis (Scheme 74) ⟨87JOC3587⟩.

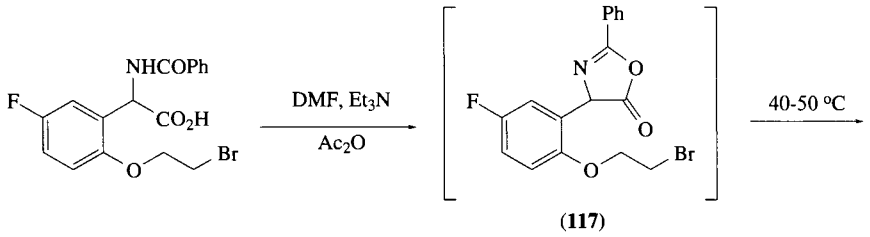
(115) (116)



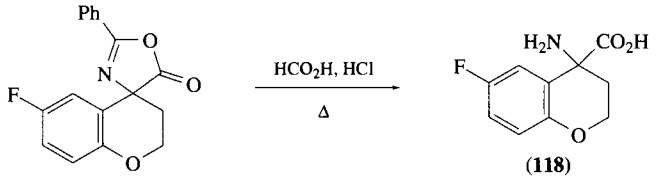
(57)

(2-Chloro-2-nitroethenyl)benzenes are stereoselectively converted into chromans on reaction with *o*-hydroxybenzaldehydes. Nucleophilic addition to the alkene and an intramolecular aldol condensation are implicated (Equation (57)) ⟨90S66⟩.

An intramolecular aldol reaction follows the Michael addition of cyanide ion to the acrylate (**119**) in a Stetter reaction which leads to an isomeric mixture of the chromanol (Equation (58)) ⟨95S1311⟩.

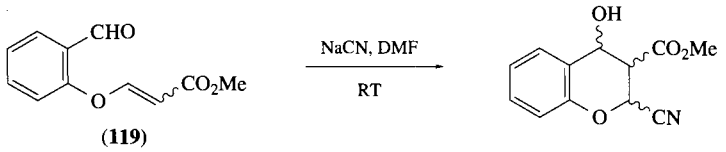


(**117**)



(**118**)

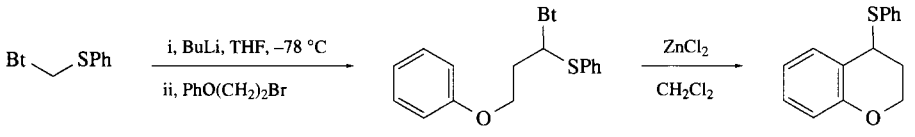
Scheme 74



(58)

(**119**)

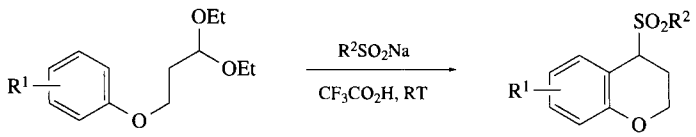
The value of the benzotriazolyl moiety (Bt) as a leaving group is utilised in a synthesis of 4-phenylthiochroman. On treatment with a Lewis acid, phenyl 3-(benzotriazol-1-yl)-3-phenylthiopropyl ether (**120**) generates the carbocation which spontaneously cyclizes to the chroman. It can be seen from Scheme 75 that benzotriazol-1-ylphenylthiomethane, $BtCH_2SPh$, functions as a 1,1-dipole equivalent ⟨93H(36)1367⟩.



(**120**)

Scheme 75

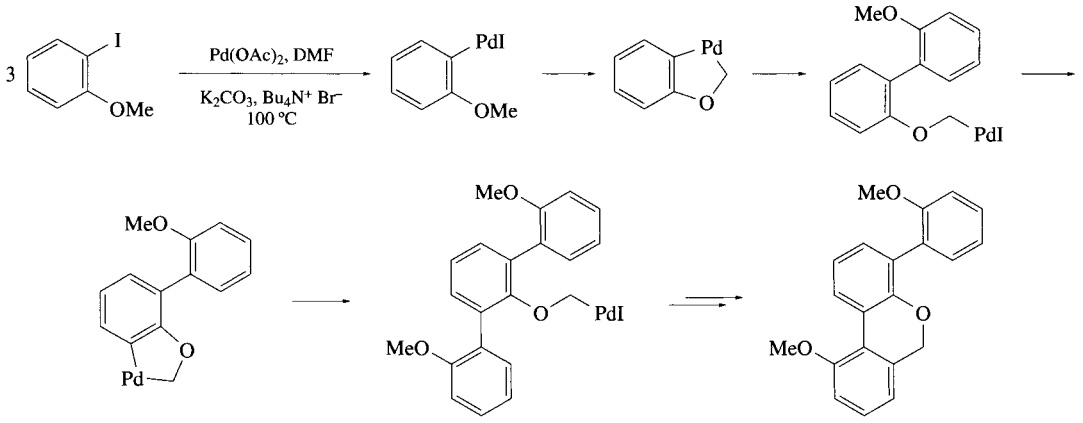
The cationic species implied in the cyclization sequences above can be trapped by sodium sulfinates and this provides an excellent route to 4-sulfonylchromans (Equation (59)) ⟨93TL8033⟩.



(59)

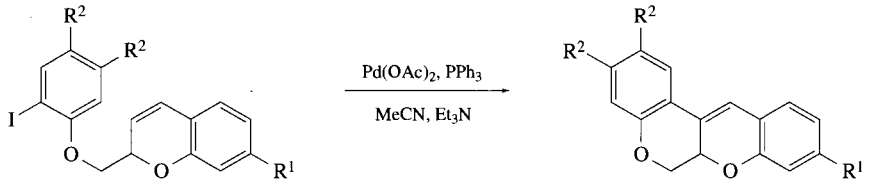
Various metal derivatives feature in the cyclization of aryl ethers to chromans. Application of the Parham cycloalkylation technique to 1-bromo-3-(2-bromophenoxy)propane leads to chromans via the aryllithium ⟨76JOC1184⟩.

Activation of a C—H bond in methoxy groups by palladium facilitates the homocoupling in *o*-iodomethoxybenzenes. Thus, 2-iodoanisole and various methoxylated derivates are converted into dibenzo[*b*,*d*]pyrans, involving the condensation of two or three molecules of the aryl iodide. It is proposed that initial insertion of palladium into the C—I bond is followed by cyclometallation to the five membered palladacycle. Sequential coupling and cyclometallation ensue in a repetitive manner as long as suitable sites remain in the substrate (Scheme 76) ⟨94CB739⟩. Benzofuran formation may compete.



Scheme 76

An intramolecular Heck reaction converts the iodoaryloxymethylchromene (**121**) into the chromeno[3,4-*b*]chroman (**122**), the tetracyclic unit of the rotenoids (Equation (60)). The cyclization can also be achieved photolytically under cobalt catalysis through a radical mechanism ⟨92JCS(P1)539⟩.

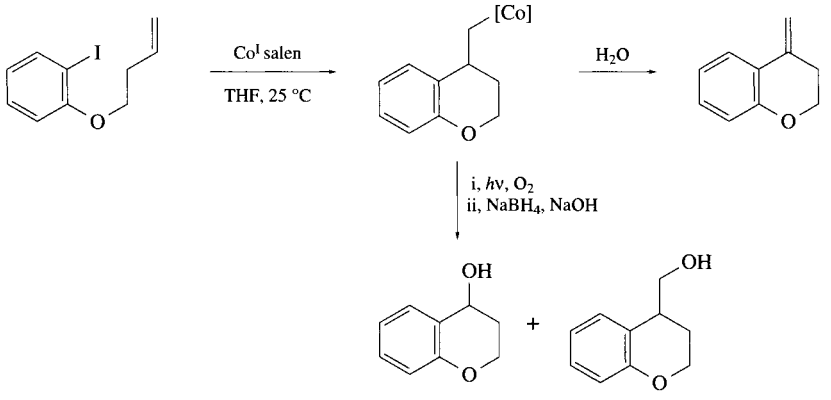


(60)

(**121**) (**122**)

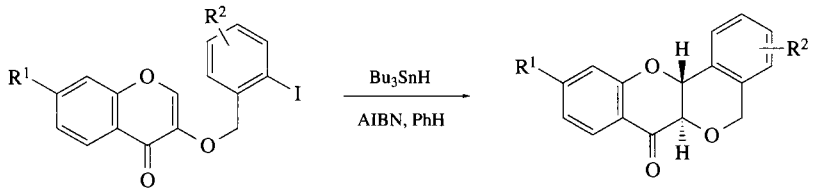
Cyclization of allyl *o*-vinylphenyl ethers is promoted by zirconium complexes and leads to mixtures of 3,4-*trans*- and *cis*-dimethylchromans in which the former isomer predominates ⟨95SL1237⟩.

The radical cyclization of (*O*-butenyl)iodophenol is mediated by Co(I) and leads to the chroman cobalt(III) complex. Subsequent β-elimination gives 4-methylenechroman, whilst oxidative photolysis followed by reduction of the peroxycobalt derivative leads to the chromanols (Scheme 77) ⟨90JCS(P1)2691⟩. But-1-yn-4-yl 2-iodophenyl ethers are cyclized to 4-methylenechromans ⟨94TL1601⟩ and a 4-spirocyclohexane derivative has been obtained in a like manner ⟨93JOC3877⟩.



Scheme 77

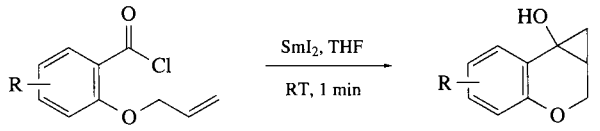
Construction of the peltogynol system utilizes a radical cyclization to form the *trans*-fused isochromano[4,3-*b*]chroman unit (Equation (61)) ⟨90JCS(P1)418, 92JCS(P1)675⟩.



(61)

An unusual double cyclization of 2-allyloxybenzoyl chlorides occurs on treatment with SmI_2 The products, which are formed rapidly, are fused cyclopropanols (Equation (62)) ⟨88TL6105⟩. Radical intermediates are proposed.

Allyl aryl ethers are also cyclized to chromans by Tl(III) salts, hydrolysis occurring simultaneously such that the final product is a chroman-3-ol ⟨90ACS1024⟩.



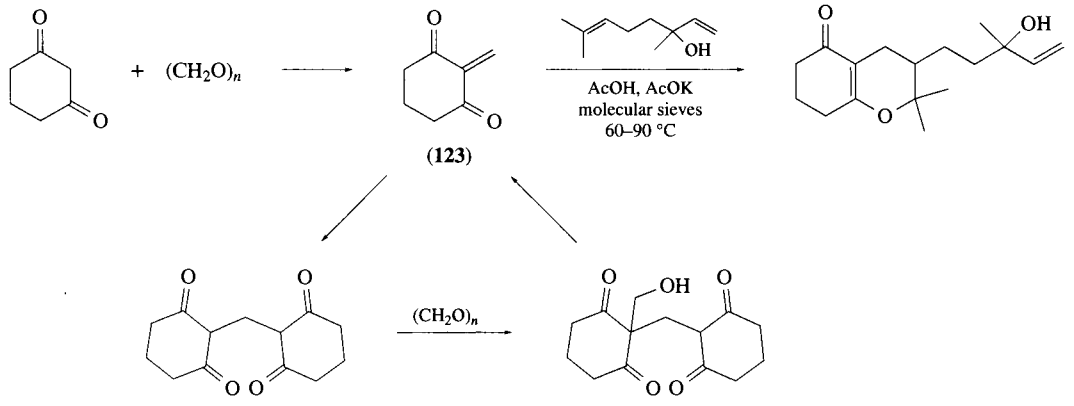
(62)

A pyran ring is constructed concomitantly with another heterocyclic unit in a number of syntheses which involve cycloaddition reactions, the 3,4-bond of the chroman moiety being one of the two new bonds formed ⟨89JOC1245, 89S57, 89T1661, 90IJC685⟩.

5.08.11.2 Formation of Two Bonds

o-Quinone methides ⟨B-74MI 508-01⟩ can function as the heterodiene components in hetero Diels–Alder reactions, the adducts from which are chromans. These unstable intermediates are generally more reactive than α,β-unsaturated carbonyl compounds, since aromatization is a consequence of the cycloaddition process. This behavior is apparent from the ease with which *o*-quinone methides dimerise, especially in the absence of an external diene or dienophile, to yield a spiroannulated chroman ⟨90JA5372⟩, thermal dissociation of which can be a good source of the methide ⟨81CJC2223⟩.

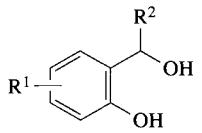
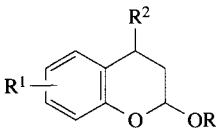
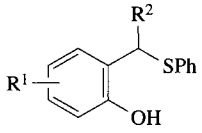
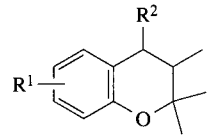
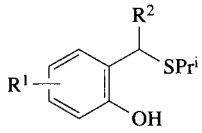
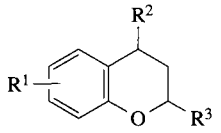
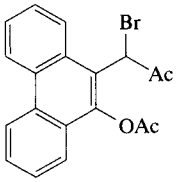
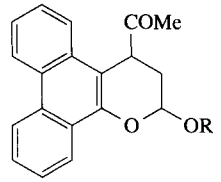
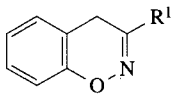
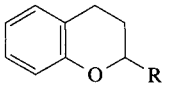
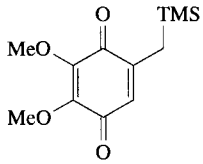
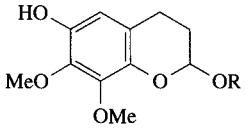
The related methylene ketone (**123**) derived from cyclohexan-1,3-dione and paraformaldehyde is so reactive that it is trapped readily as the Michael adduct. However, the adduct can be reconverted to the quinone methide which can be trapped by a range of monoterpenes. The reduced chromans are formed in a regio-, chemo-, and stereo-selective manner in a one-pot process (Scheme 78) ⟨93JOC6163, 94H(37)661⟩.



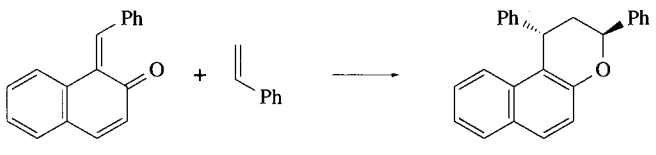
Scheme 78

There are a variety of methods available for the generation of *o*-quinone methides, each of which is a potential source of chromans. The examples collected in Table 3 are chosen to illustrate the diversity of the route.

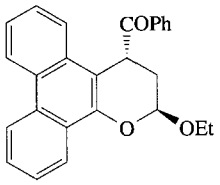
Table 3 Synthesis of chromans via *o*-quinone methides.

Source	*Conditions*	*Reactant*	*Product*	*Ref.*
	(a) Δ (b) hν, H_2O, MeCN			85T1695 95JA5369
	e⁻, $LiClO_4$, RNO_2			95CC1381
	(a) Ag_2O, RT (b) $BF_3 \cdot OEt_2$, RT			89CL653 90BCJ1647
	$LiOH_{aq}$, CH_2Cl_2, RT			92JCS(P1)2479
	≈90 °C			90JA5341
	H_2O, MeCN			90JA5372

The reaction of *o*-quinone methides with vinyl ethers is regiospecific, giving the 2-substituted chroman in an inverse electron demand Diels–Alder reaction. The LUMO of the quinone methide is considered to interact with the HOMO of the alkene moiety. The stereochemistry of the adduct is influenced by the structure of the quinone methide and by the conditions used in its formation. Thus, thermally generated *o*-quinone methides give a mixture of the *cis*- and *trans*-4-substituted 2-alkoxychromans in which the former isomer predominates ⟨85T3095⟩, whereas the *cis*-isomer is obtained virtually exclusively from *endo* attack on methides formed at room temperature ⟨90BCJ1062⟩. In the case of the naphthoquinone methide, the pseudo-*Z* form (**124**) is sterically favored and leads by *endo* cycloaddition to *trans*-isomers as the preferred products (Equation (63)) ⟨92S761⟩. Similar reasoning accounts for the predominance of the *trans*-phenanthro[9,10-*b*]pyran (**125**) in the complex reaction of phenanthroquinone with Ph_3P = CHCOPh in the presence of ethyl vinyl ether ⟨89JCS(P1)2329, 91JCS(P1)3159⟩.



(124) (63)

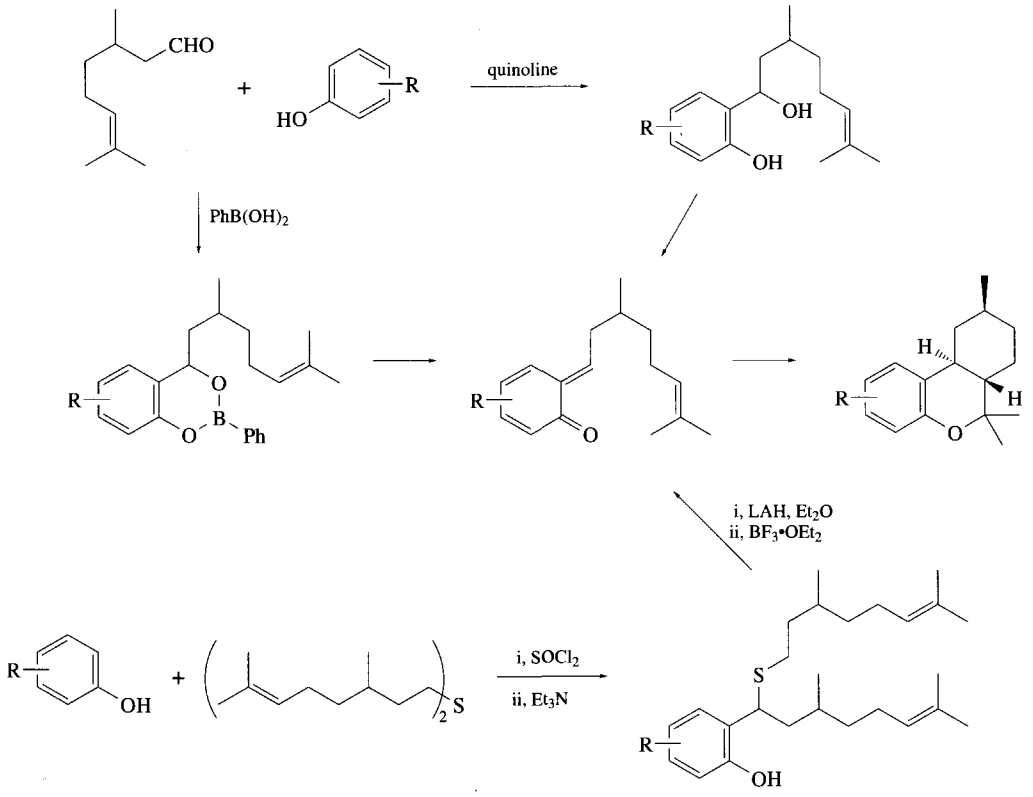


(125)

Mannich bases derived from a phenol, an aromatic aldehyde, and a cyclic secondary amine react with lactones, 1,3-diketones and related compounds to give 4-arylchromans incorporating either the amine or a hydroxy group at C-2, depending upon the conditions used ⟨88JHC89, 89JHC1349⟩. Cinnamaldehyde reacts directly with phenols and morpholine to form the 4-methylchroman ⟨91JHC983⟩.

Heterocyclic *o*-quinone methides also behave as reactive intermediates in cycloaddition reactions which lead to hetero-fused chromans ⟨90IJC707, 90S1005, 93G35, 93JCTB147⟩.

Both the heterodiene and dienophile moieties can be incorporated into the one molecule, whereupon an intramolecular cycloaddition becomes feasible. This approach has been used in elegant syntheses of hexahydrocannabinol from phenols, generating the *o*-quinone methide from benzylic alcohols ⟨89CC1171, 92JCS(P1)3397⟩, benzodioxaborins ⟨92JCS(P1)605, 93TL5527⟩ or [(alkylthio)alkyl]-phenols ⟨90BCJ1647⟩. Ring fusion is *trans*, with the 9-methyl substituent equatorially disposed (Scheme 79). A similar intermediate is proposed in the synthesis of the cannabinoid from citronellal and aluminum phenoxides which involves an *ortho*-directed electrophilic substitution ⟨89G329⟩. Various polycyclic chromans have been prepared using benzodioxaborins ⟨94TL3691⟩.

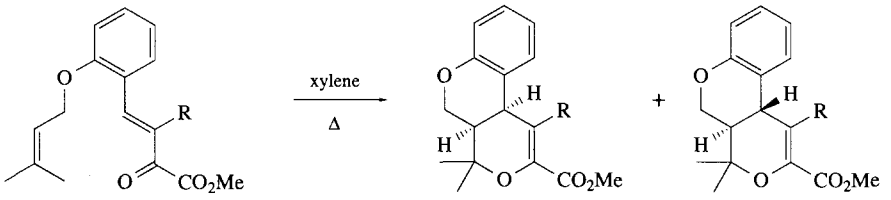


Scheme 79

When a dihydric phenol reacts with a two-fold excess of citronellal in the presence of phenylboronic acid, a bis-condensation occurs and a benzodipyran results ⟨92JCS(P1)605⟩.

The stereochemical result of the intramolecular Diels–Alder reaction of the heterodienes (**126**) is dependent on the C-3 substituent. When R = H, *trans*-annulation is favored, but the *cis*-fused isomer predominates when R = Me (Equation (64)) ⟨87S700⟩. Again *o*-quinone methides based on heterocyclic systems can feature ⟨94TL531⟩. The reaction of aldehydes with barbituric acid which

leads directly to benzopyrano[3,4-*d*]pyrimidine derivatives features a tandem Knoevenagel/hetero Diels–Alder sequence. The cycloaddition reaction results predominantly in the *trans*-fused product ⟨88CB499⟩. However, in the presence of a chiral titanium complex the *cis*-fused isomer is formed exclusively ⟨92SL281⟩.

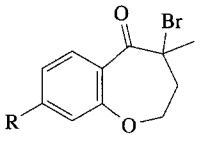


(126) (64)

5.08.11.3 From Other Heterocycles

5.08.11.3.1 From benzoxepines

On treatment with zinc chloride, the α-bromoketones (**127**) ring contract in a Favorskii-like rearrangement to give 4,4-disubstituted chromans. The acetals derived from the bromoketones undergo a similar rearrangement to the chroman-4-ester on heating with sodium acetate ⟨87S806⟩.



(127)

5.08.11.4 From a Preformed Heterocyclic Ring

5.08.11.4.1 From chromenes

The catalytic hydrogenation of 4*H*-chromenes ⟨35JCS646⟩ and 2*H*-chromenes ⟨94CJC1866, 94JOC6697⟩ leads to chromans. Tetrahydrobenzodipyrans have been obtained similarly, though the instability of the benzodipyrans can preclude their isolation ⟨91JCR154⟩. Mixed products result from the hydroboration–oxidation of chromenes ⟨84JCS(P1)1733⟩. 3-Nitro-2-arylchromenes and their benzologues are converted to the corresponding chromans by $NaBH_4$ in MeOH-THF ⟨86H(24)1647⟩ but to the 2-oximinochroman by $NaBH_4$ in EtOH or hydrazine ⟨91H(32)33⟩.

The addition of various reagents to the double bond leads to 3,4-disubstituted chromans. The usual stereochemistry associated with addition reactions of alkenes is manifested. Thus, halogens and hypohalous acids give the *trans*-product, whilst potassium permanganate and osmium tetroxide lead to the *cis*-diol and the 3,4-epoxychroman results from reaction with hydrogen peroxide and various peracids ⟨83JCS(P1)827, 90JOC1728, 91JCS(P1)2763, 93TL1815⟩. In the presence of a Mn(salen) complex, asymmetric epoxidation is observed ⟨91TL5055⟩. The oxirane itself is a source of a variety of chromans. *Cis*-addition of chlorosulfonyl isocyanate to the 2*H*-chromene gives the azetidinone, from which 3,4-*trans*-disubstituted chromans are accessible ⟨91JCS(P1)63⟩. Dichlorocarbene adds to both 4*H*- and 2*H*-benzopyrans to give the cyclopropane adduct ⟨82KGS163⟩.

5.08.11.4.2 From chromanones

The reduction of chromanones has been reviewed ⟨77HC(31)301⟩.

Hydride ion reagents reduce chromanones to chromanols, often stereospecifically ⟨70JCS(C)1006⟩. However, the reduction of 3-arylmethylchroman-4-ones gives a diastereoisomeric mixture. In

contrast, reduction by BH_3-THF affords the *cis*-chroman-4-ol ⟨90T1849⟩. Flavanone is converted to flavanol by $NaBH_3CN$ ⟨85SC1315, 89SC119⟩, but further reactions may follow ⟨91BSF939⟩.

Reductive amination of chroman-3-ones has been reported ⟨90ACS1024⟩.

5.08.11.4.3 From coumarins

Hydroboration and oxidation of various coumarins yields chromanols with little or no stereoselectivity ⟨90T1849⟩.

Dihydrocoumarins are converted into chromans on reaction with Grignard reagents ⟨81H(15)455, 82TL253⟩.

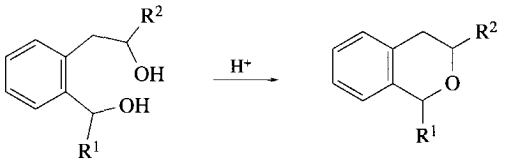
5.08.12 ISOCHROMANS (DIHYDRO-1H-2-BENZOPYRANS)

Isochromans do not occur commonly as natural products but nevertheless they are found in a number of plant and insect species. The chemistry of isochromans has been reviewed ⟨89RCR479⟩.

5.08.12.1 Formation of One Bond

5.08.12.1.1 Adjacent to the heteroatom

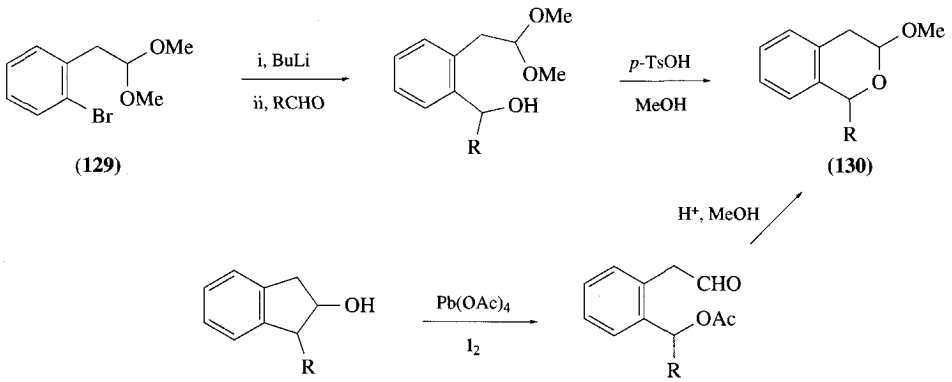
The acid catalyzed cyclodehydration of the 1,5-diols (**128**) leads to isochromans (Equation (65)) ⟨87S497, 93T3351⟩. There are a number of different routes to the diols and several variations on this synthesis have been developed.



(128) (65)

The organolithium compound derived from the acetal (**129**) reacts with aldehydes to form the corresponding benzyl alcohols, which are readily cyclized to the isochromans (**130**) or the related isochroman-3-ols (Scheme 80) ⟨90AP(323)493, 95LA1303⟩. Cyclization of an acetal features in a synthesis of a heteroanthracycline ⟨93TL3519⟩.

Oxidation of indanols provides a similar isochroman precursor (Scheme 80) ⟨83S595⟩ and extensive studies on the ozonolysis of indenes have provided routes to isochromans ⟨95JOC4755⟩.



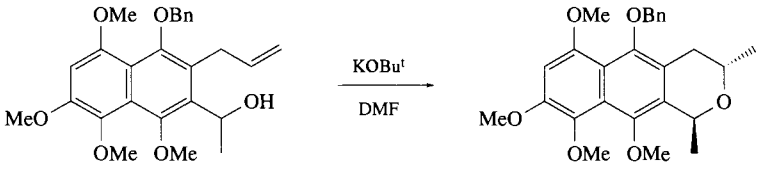
(129) (130)

Scheme 80

Whilst the cyclo-mercuriation of the alcohol (**131**) leads to a 1 : 1 mixture of the *cis* and *trans* isochromans, the base catalyzed cyclization affords the *trans* compound (**132**) exclusively (Equation

(66)). The isochromans are intermediates for the synthesis of naturally occurring ventiloquinones ⟨91JCS(P1)2743, 94JCS(P1)859⟩.

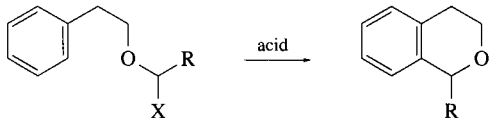
Naphtho[2,3-*c*]pyranoquinones are accessible from quinones by alkylation with 3-hydroxyhexanoic acid or *trans*-hex-3-enoic acid ⟨94SC2563⟩.



(131) (132) (66)

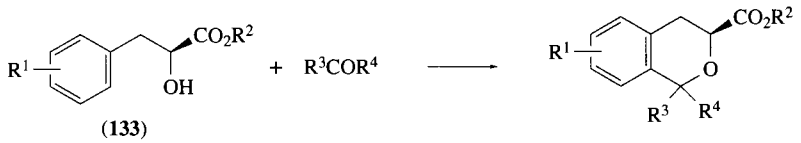
5.08.12.1.2 β to the heteroatom

A number of isochroman syntheses are based on intramolecular Friedel–Crafts alkylation processes, in which an ether side chain contains an electrophilic centre (Equation (67)). Thus X can be chlorine ⟨71MI 508-01⟩ or an acetal function ⟨87TL2567, 92SC1417⟩. The reaction of phenethyl alcohols with formaldehyde in the presence of acid is similar ⟨71AC253⟩.



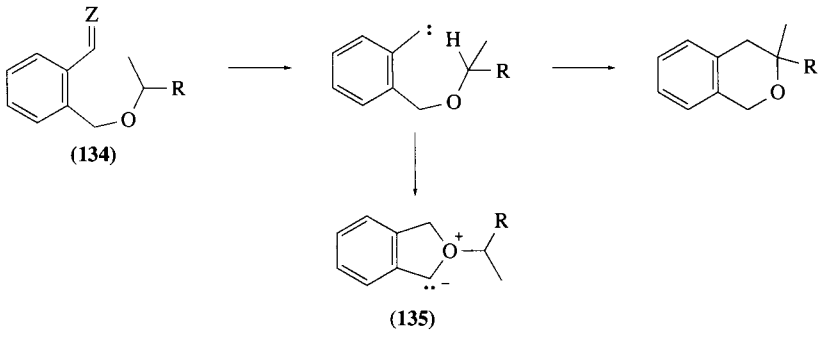
(67)

In an oxygen equivalent of the Pictet–Spengler tetrahydroisoquinoline synthesis, 3-aryllactic acids (**133**) react with aldehydes and ketones to form isochroman derivatives (Equation (68)). Activation of the phenyl ring in (**133**) facilitates the reaction, but the unsubstituted compound (**133**; $R^1 = H$) reacts only with aromatic aldehydes and then under more forcing conditions ⟨92LA39⟩.



(133) (68)

The carbenes derived thermally or photochemically from the tosylhydrazone (**134**; Z = NNHTs) or diazo compound (**134**; $Z = N_2$) can insert into a C—H bond to give isochromans. Competitve formation of the ylide (**135**) leads to various other products (Scheme 81) ⟨89JA1465, 94TL1699⟩.

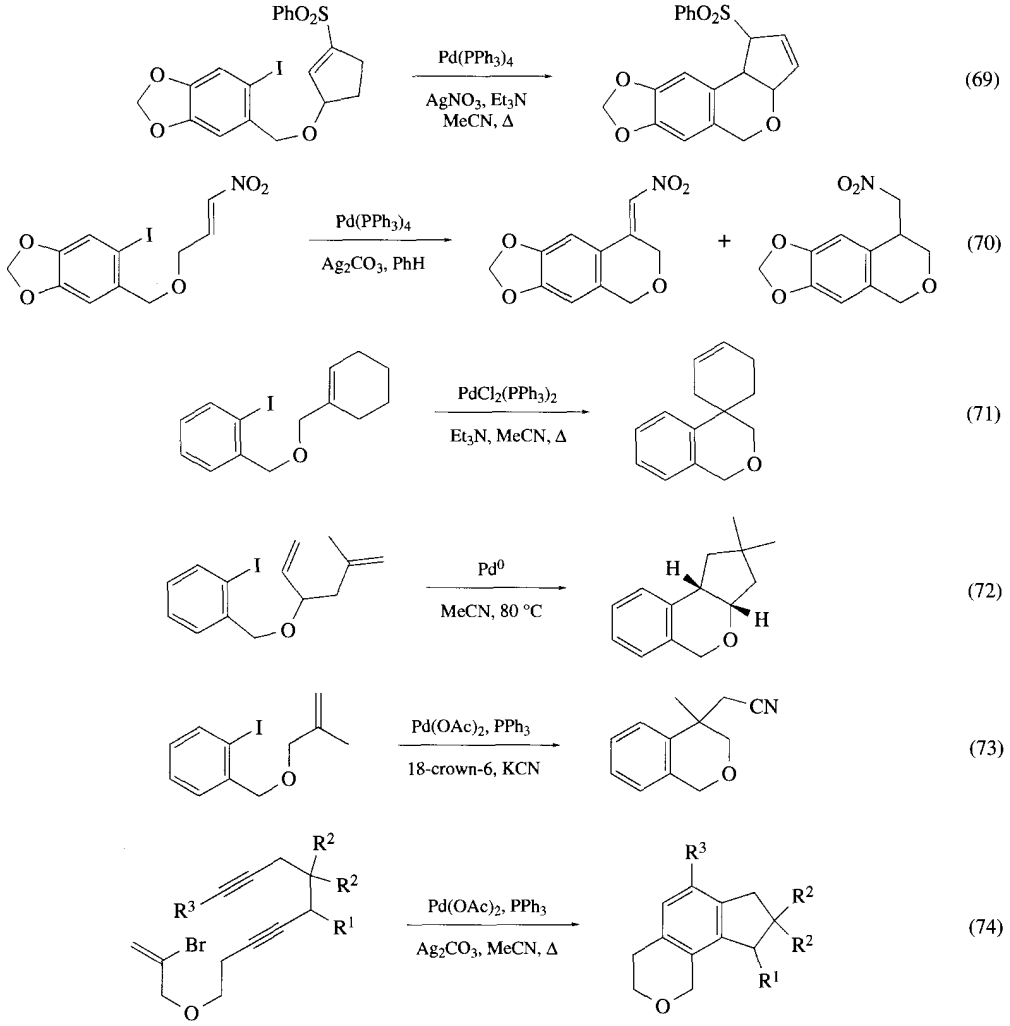


(134) (135)

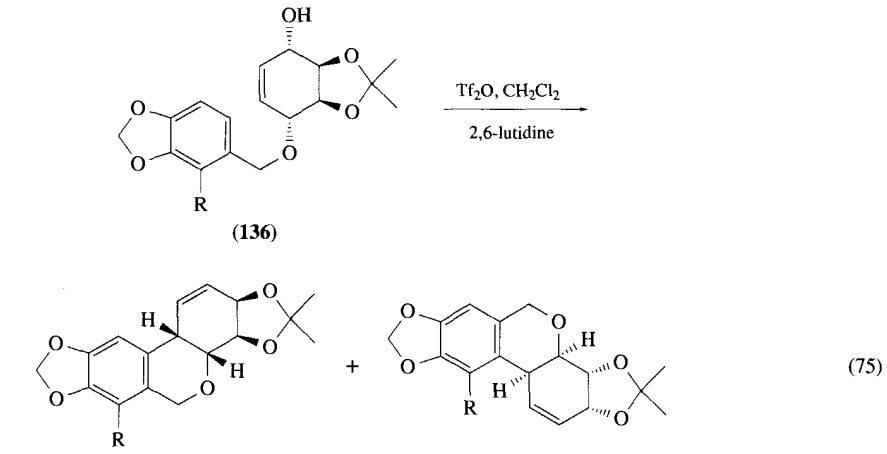
Scheme 81

5.08.12.1.3 γ to the heteroatom

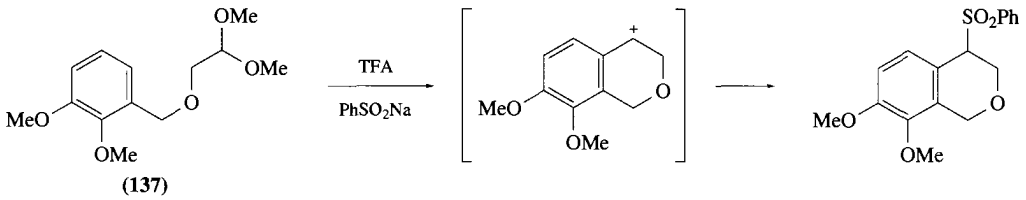
The palladium-catalyzed intramolecular addition of aryl halides to unsaturated systems has been widely used to synthesize isochromans. A selection of examples chosen to illustrate the diversity of products available using Heck methodology is given in Equations (69)–(74) ⟨89H(28)55, 90TL1343, 91SL777, 93TL3163, 93TL5205, 95JOC1013⟩.



The allyl aryl ethers (**136**) are cyclized at room temperature by triflic anhydride to isochromans, but the regiochemistry of the allylation is dependent on the nature of the substituent R (Equation (75)) ⟨95TL6197⟩.



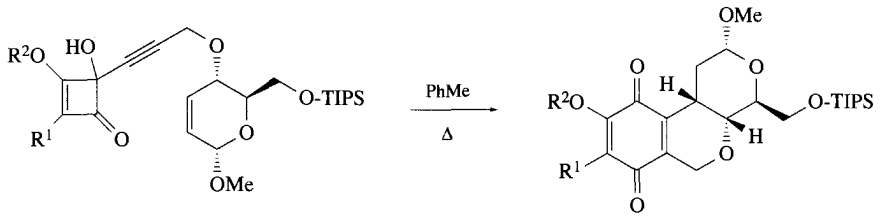
The acetal (**137**) yields the isochroman on reaction with sodium benzenesulfinate in TFA. It appears that a carbocation cyclization is followed by trapping of the heterocyclic cation by the sulfinate (Scheme 82) ⟨93TL8033⟩.



(137)

Scheme 82

A diradical mechanism is proposed for the ring expansion of 4-alkynylcyclobutenones to enantiomerically pure pyranoquinones (Equation (76)) ⟨95JOC6460⟩.

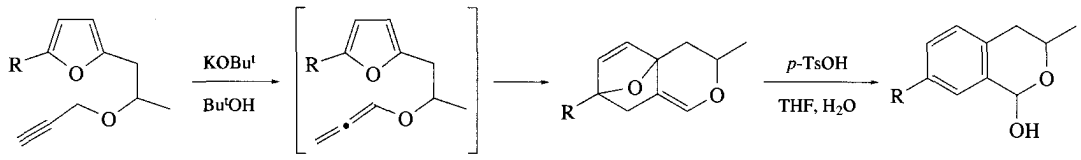


(76)

5.08.12.2 Formation of Two Bonds

The adducts from an intramolecular Diels–Alder reaction on the propargyl ether (**138**) are readily aromatized to the isochroman-1-ol (Scheme 83). It is considered that the intermediate allenyl ether is the dienophilic component ⟨94H(38)1507⟩.

Quinodimethanes and benzoyl cyanide yield isochromans as a result of a [4 + 2] cycloaddition ⟨92TL7277⟩.



(138)

Scheme 83

5.08.12.3 From Other Heterocycles

5.08.12.3.1 From furans

The oxidative rearrangement of furo[3,2-*b*]benzofuranones to furo[2,3-*b*][2]benzopyrans forms the basis of syntheses of several antibiotics ⟨90JCS(P1)881, 93TL5813⟩.

5.08.12.3.2 From dioxolanes

Both phenyl- and naphthyl- dioxolanes undergo a $TiCl_4$ promoted stereoselective isomerization to isochroman derivatives involving a 6-*endo-trig* ring closure of an intermediate oxonium ion ⟨91CC287, 94JCS(P1)865⟩.

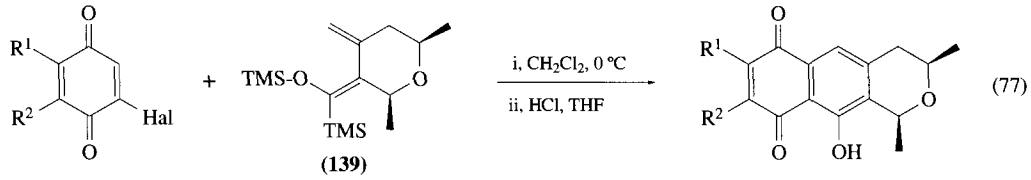
5.08.12.4 From a Preformed Heterocyclic Ring

5.08.12.4.1 From isochromanones

Reduction ⟨79AP(312)385, 82JOC2169⟩ and reaction with Grignard reagents ⟨56BSF1337, 93S211⟩ converts isochromanones into isochromans or isochromanols.

5.08.12.4.2 From pyrans

The 3,4-dimethylenetetrahydropyran derivative (**139**) undergoes facile and stereoselective cycloaddition to benzoquinones, providing naphtho[2,3-*c*]pyran-6,9-diones (Equation (77)) ⟨90JOC1466⟩.



(77)

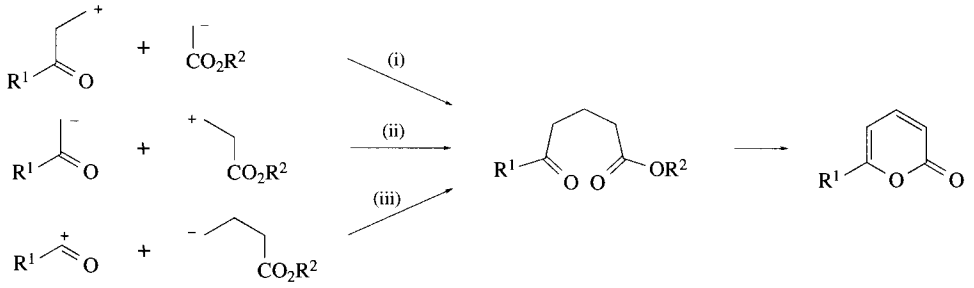
5.08.13 PYRANONES AND FUSED PYRANONES: PYRAN-2-ONES (2-PYRONES)

Interest in pyran-2-ones has been stimulated by the recognition of their value as synthetic intermediates and by the occurrence of the pyranone unit in various natural products ⟨93MI 508-01⟩. Several reviews cover the synthesis of pyran-2-ones ⟨47CRV(41)525, 67RCR175, 92C457⟩ and a review devoted to dehydroacetic acid and related compounds has been published ⟨92AHC(53)1⟩ and extended ⟨94H(37)585⟩.

5.08.13.1 Formation of One Bond

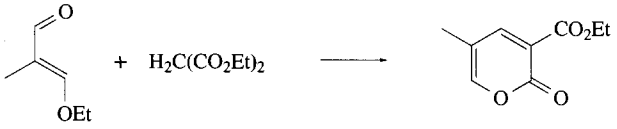
5.08.13.1.1 Adjacent to the heteroatom

A common feature of many syntheses of pyran-2-ones is the acid catalyzed ring closure of a 5-keto acid or acid derivative. The variation in these routes lies in the methods of formation of the five-carbon unit. Three major approaches have been developed involving the reaction of (i) an ester enolate with a 2-acyl vinyl cation equivalent; (ii) a ketone enolate with a 2-carbalkoxy vinyl cation precursor; and (iii) the 4-acylation of an ester dienolate or its equivalent. All are considered to involve formation of the O-C(2) bond in the cyclization step (Scheme 84).

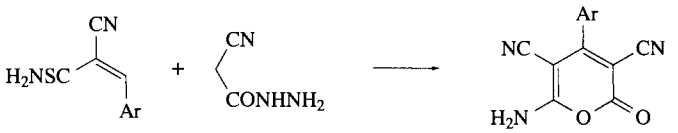


Scheme 84

The first type of reaction has been widely used and features the Michael addition of a carbanion derived from malonates, 1,3-keto esters and related compounds to α,β-unsaturated carbonyl compounds. In general, 3,6-disubstituted pyran-2-ones result but additional substitution is also possible at C-4 and C-5 through functionalization of the unsaturated system. Furthermore, the 3-substituent is normally capable of manipulation and removal. The examples collated in Equations (78)–(82) ⟨89MI 508-02, 90HCA883, 90S70, 92S453, 93SL741, 95H(41)1299⟩ illustrate the diversity of this approach to pyranones.



(78)



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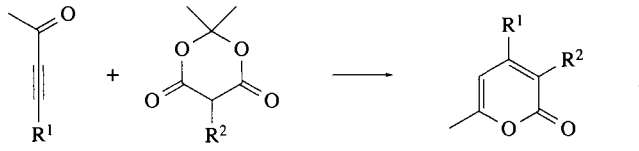

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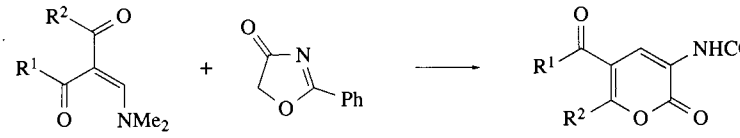

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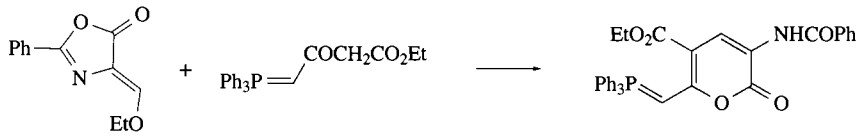
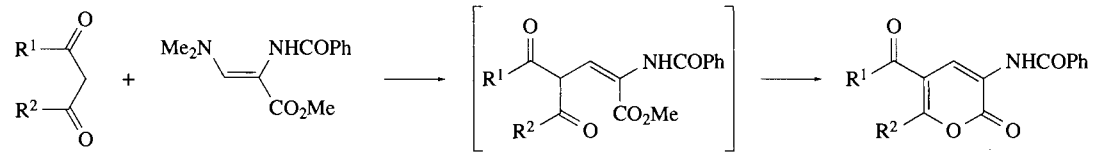


(82)

The self condensation of 1,3-dicarbonyl compounds is an established route to pyran-2-ones ⟨55OSC(3)231, 63OSC(4)201, 63OSC(4)549⟩ and constitutes a synthesis in category (ii). The formation of pyran-2-ones from the reaction of activated methylene compounds with an alkynic ester is a related approach which offers the possibility of greater variation in substituents ⟨76JCS(P1)2137, 87H(25)117, 89CP87⟩.

Unsaturated 3,3-dichloroaldehydes react in a similar manner with activated methylene compounds ⟨58IZV1445⟩ and several variants on this route have been described, including their self condensation ⟨59CI(L)992, 62IZV2096⟩, the use of cyclic active methylene compounds ⟨60CB2294⟩, and the reaction of the dichloro compounds with carbanions derived from activated alkynes ⟨75BSF751⟩.

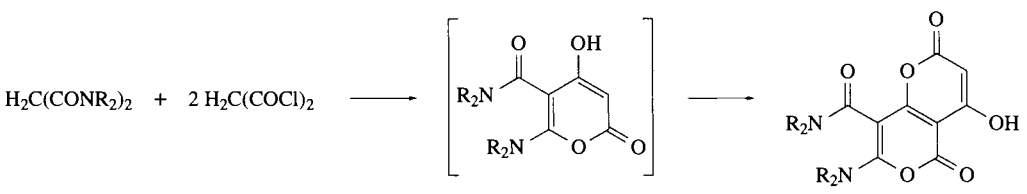
Methyl 2-benzoylamino-3-dimethylaminopropenoate functions as a three carbon atom component in its reaction with 1,3-dicarbonyl compounds, which leads to 3-benzoylaminopyran-2-ones (Scheme 85) ⟨90S70⟩. Enaminoesters, $R_2NCH{=}C(CO_2Me)_2$, react in a similar manner with ketone enolates ⟨91SC1433, 94H(37)1705⟩.



Scheme 85

The reaction of malondiamides with malonyl chloride results in two cyclizations, since the initially formed 4-hydroxypyran-2-one reacts with the dichloride to produce a pyrano[4,3-*b*]pyran-2,5-dione (Scheme 86) ⟨93CB841⟩ in a manner similar to the reaction of ethyl acetoacetate and 4-hydroxypyran-2-ones with malonyl dichloride ⟨58CB2849, 66JA624⟩.

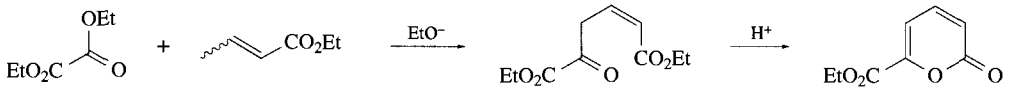
A further variant on the type (ii) synthesis utilizes pyridinium enolbetaines and cyclopropenones



Scheme 86

as the two three-carbon synthons. A similar result obtains with phosphonium and sulfonium betaines ⟨71LA(746)102⟩.

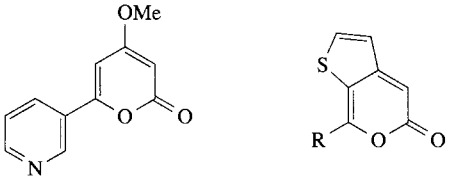
Unsaturated esters react with diethyl oxalate in the presence of base to form an unsaturated 5-keto ester in a type (iii) synthesis. Cyclization is sometimes spontaneous and invariably follows acidic hydrolysis (Scheme 87) ⟨41JOC566⟩.



Scheme 87

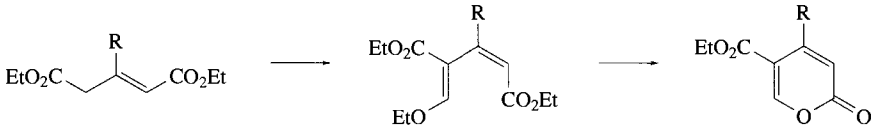
The dianion derived from benzoylacetone is carbonated at the methyl group and subsequent cyclization of the resulting dioxopentanoic acid leads to the 4-hydroxypyran-2-one ⟨58JA6360, 68JOC2399⟩. Reaction of the dianions with carbonyl sulfide offers an alternative approach to the hydroxypyranones ⟨69T2687⟩.

Acylation of the dianion derived from ethyl acetoacetate by an ester extends the scope of this type of pyranone synthesis ⟨71JA2506⟩, illustrated by a synthesis of anibine (**140**) from the β-keto ester and ethyl nicotinate ⟨83JOC3945⟩. The use of polyketone-derived anions in the synthesis of oxygen heterocycles has been reviewed ⟨77T2159⟩.



(140) **(141)**

Formylation of 3-substituted diethyl pent-2-enedioates can be accomplished with ethyl formate and a base and by using 4-methylmorpholine in the presence of titanium(IV) chloride. Cyclization of the ethoxymethylene derivatives under acidic conditions leads to 4-substituted 2-oxopyran-5-carboxylates (Scheme 88) ⟨90HCA411⟩.

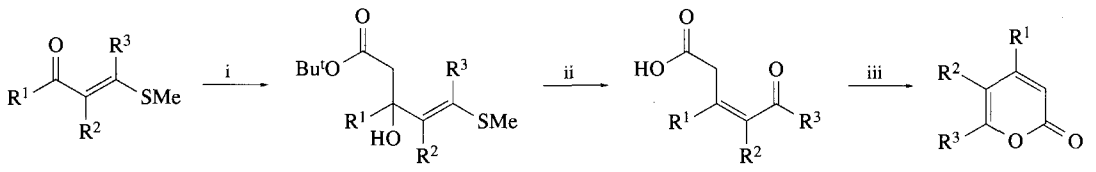


Scheme 88

The acylation of ethyl 3-thienylacetate is the initial step in synthesis of thieno[2,3-*c*]pyran-3-ones (**141**) and the isomeric [3,2-*c*] compounds ⟨90JCS(P1)2309⟩.

Vinylogous thioesters (**142**; R^3 = alkyl) and α-oxoketenedithioacetals (**142**; R^3 = SMe) are converted into highly substituted pyran-2-ones on reaction with *t*-butyl ester enolates followed by a somewhat sensitive 1,3-carbonyl transposition of the initially formed allylic alcohol (**143**) to the δ-keto acid (**144**) (Scheme 89). Further variation in substitution patterns can be achieved by the use of ketone and hydrazone enolates and the overall method is attractive ⟨88JOC2031⟩.

α-Oxoketenedithioacetals (**142**; R^3 = SMe) also yield pyran-2-ones on reaction with $BrZnCH_2$



(142) **(143)** **(144)**

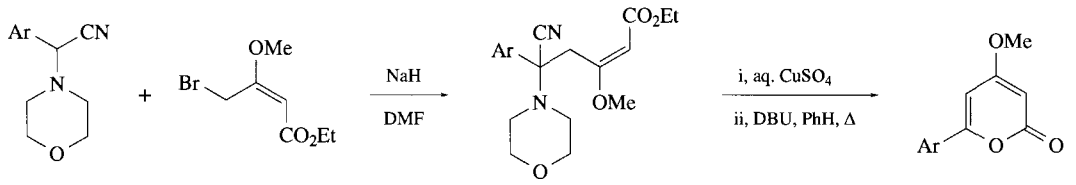
i, $LiCH_2CO_2Bu^t$, THF, −78 °C; ii, HBF_4, THF, H_2O; iii, $(CF_3CO)_2O$

Scheme 89

CO_2Et in the presence of copper(I) iodide. Coordination of Cu^+ to SMe is postulated to facilitate ring closure by attack of the ester function of the electrophilic bis(methylthio)carbon ⟨90JOC5589⟩. Application of a Reformatsky reaction to aroylketene *S,N*-acetals (**142**; $R^3 = NR_2$) results in a regioselective 1,4-addition leading to 4-amino-6-arylpyran-2-ones ⟨88S248⟩.

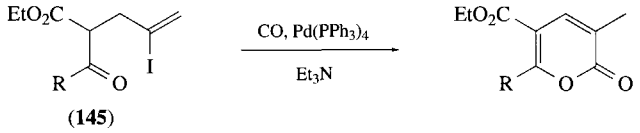
Various 3-cyanopyran-2-ones are available from the reaction of a ketene dithioacetal with acetophenones and related compounds ⟨84CB3384⟩.

Umpolung of the carbonyl group in ketones offers an alternative approach to pyran-2-ones in which the roles of the components in a type (iii) synthesis are reversed. Thus, alkylation of 4-bromo-3-methoxybut-2-enoate with the anion derived from α-aryl-α-(4-morpholino)acetonitrile and cyclization of the hydrolyzed product leads to good overall yields of 6-aryl-4-methoxypyran-2-ones (Scheme 90) ⟨89JOC3985⟩.



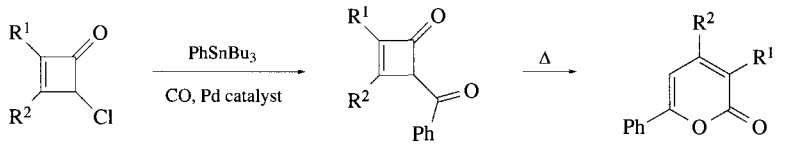
Scheme 90

There are a number of examples of the use of transition metal catalysts in the synthesis of pyran-2-ones. The palladium-catalyzed carbonylation of alkenyl iodides (**145**) is followed by *O*-enolate trapping rather than by carbon and 3,5,6-trisubstituted pyranones result (Equation (83)) ⟨90TL2841⟩.



(**145**) (83)

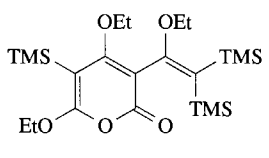
The palladium-catalyzed carbonylative cross coupling of 4-chlorocyclobut-2-enones with aryl and alkenyl tributylstannanes affords 4-acylcyclobutenones which are thermolysed to 3,4,6-trisubstituted pyran-2-ones (Scheme 91) ⟨93T5461⟩.



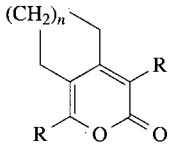
Scheme 91

The allyl diketoesters resulting from the palladium-catalyzed allylation of the copper complex of methyl 3,5-dioxohexanoate cyclize to pyran-2-ones with an allylic substituent at C-3 ⟨89TL3105⟩.

Carbon dioxide can provide the "ester" moiety of pyran-2-ones. The nickel-catalyzed co-oligomerization of ethoxy(trimethylsilyl)ethyne, $EtOC{\equiv}CSiMe_3$, and CO_2 affords the pyranone (**146**) in high yield ⟨90CC945⟩, whilst the use of diynes affords fused pyran-2-ones (**147**) ⟨88JOC3140, 89CC9, 90JOC2978, 90SC313⟩. Supercritical CO_2 serves as both solvent and reagent in the nickel catalyzed reaction with hex-3-yne which leads to 3,4,5,6-tetraethylpyran-2-one ⟨93C493⟩.



(**146**)

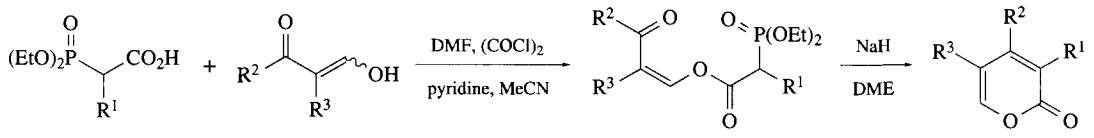


(**147**)

5.08.13.1.2 γ to the heteratom

The synthesis of fully substituted 4-hydroxypyran-2-ones by the cyclotrimerization of aliphatic acid chlorides is catalyzed selectively by $AlCl_3$. The reaction is considered to proceed via the self condensation of the acid chloride, which forms a 1,3-dicarbonyl intermediate, and further *O*-acylation follows ⟨93SL851⟩.

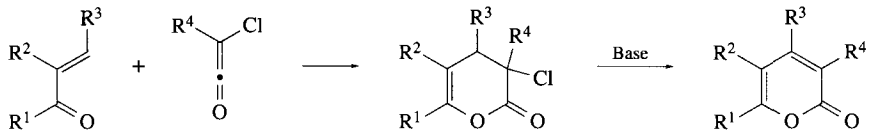
2-Diethylphosphinylalkanoic acids can be esterified by α-hydroxymethylene ketones in the presence of DMF and oxalyl chloride. The resulting esters undergo an intramolecular Wadsworth–Emmons reaction on treatment with base, providing a good route to 3,4,5-trisubstituted pyran-2-ones (Scheme 92) ⟨86S140⟩.



Scheme 92

5.08.13.2 Formation of Two Bonds

The hetero Diels–Alder reaction, so valuable in the synthesis of dihydropyrans, has been successfully adapted to the formation of pyran-2-ones. The dienophilic component most frequently utilized is a chloroketene, either generated in the normal way or used in a protected form such as the acetal ⟨72CC863⟩. The basic conditions used to form the ketene may suffice to effect the dehydrochlorination of the initially produced dihydropyranone (Scheme 93).



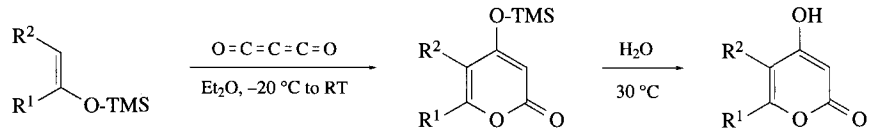
Scheme 93

In addition to α,β-unsaturated carbonyl compounds, enaminoketones are useful diene components which lead to 4-aminopyran-2-ones. The enaminoketone function has been incorporated into alicyclic molecules ⟨92F345⟩, heterocycles ⟨78JHC181, 80JHC61⟩ and steroidal systems ⟨89P227⟩ leading to complex fused pyran-2-ones.

Ketene itself reacts with enamines ⟨65JOC2642⟩, ketene *N,N*- and *N,O*-acetals ⟨64JOC2513⟩, and 1,1-bis(dialkylamino)ethenes ⟨64CB1266⟩ to give pyran-2-one derivatives.

Silylketenes afford pyran-2-ones through a [4 + 2] cycloaddition reaction with electron rich dienes. The isolation of acyclic material when the reaction is carried out at room temperature indicates that the reaction proceeds in a stepwise manner ⟨93TL6583⟩.

The reaction of carbon suboxide with silyl enol ethers derived from aldehydes and ketones provides a versatile route to 4-trimethylsilyloxypyran-2-ones and hence to the 4-hydroxy derivatives (Scheme 94) ⟨89H(29)913⟩.



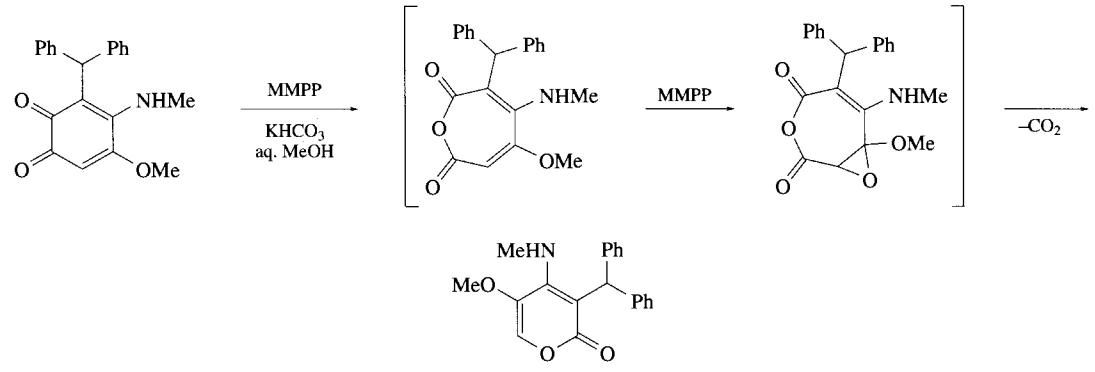
Scheme 94

5.08.13.3 From Other Heterocycles

5.08.13.3.1 From epoxides

The thermal rearrangement of cyclopentadienone epoxides to pyran-2-ones is considered to involve a cycloreversion and an electrocyclization ⟨81TL4553⟩ and the photochemical transformation of pyran-4-ones to pyran-2-ones may involve a similar sequence of reactions ⟨79JA7521⟩.

An epoxide is postulated as an intermediate in a conversion of 1,2-benzoquinones into substituted pyran-2-ones. The success of this synthesis hinges on steric protection of the 3,4-double bond in the initial Baeyer–Villiger product, the anhydride (Scheme 95) ⟨95TL6669⟩.

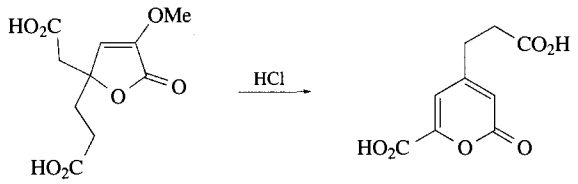


Scheme 95

5.08.13.3.2 From furans

A cycloreversion is also postulated in the thermal conversion of 5-arylfuran-2,3-diones to 3-aroylpyran-2-ones ⟨75KGS1468, 78JOU2245⟩.

Rearrangement of the butenolide (**148**) affords the pyranone, desaminostizolobic acid (Equation (84)) ⟨94TL6575⟩.



(84)

(**148**)

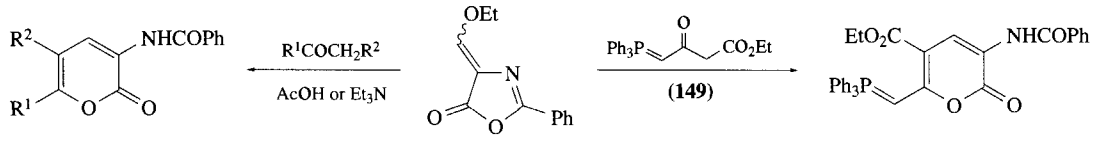
Oxidation of furanones with lead(IV) acetate gives 4-hydroxypyran-2-ones, but the pyran-4-ones result on treatment with iodosobenzene diacetate ⟨80TL1575⟩.

5.08.13.3.3 From pyrazolines

Both thermal and Ce(IV) catalyzed elimination of nitrogen from pyrazolines leads to pyran-2-ones ⟨02CB782, 85CJC3031⟩.

5.08.13.3.4 From oxazolones

Highly substituted 3-benzoylaminopyran-2-ones are accessible from 4-ethoxymethylene-2-phenyloxazol-5(4*H*)-one by reaction with activated methylene compounds under either acidic or basic conditions ⟨89SC1713, 92H(33)843⟩. The stabilized ylide, $Ph_3P{=}CHCOCH_2CO_2Et$, (**149**) behaves in a similar fashion (Scheme 96) ⟨92S453⟩.



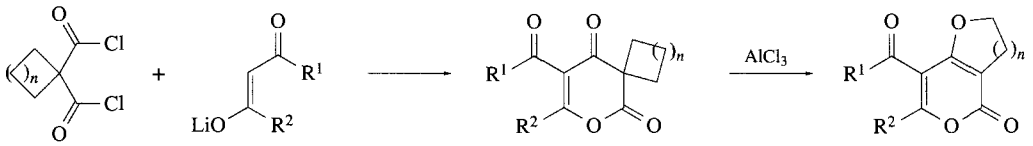
Scheme 96

5.08.13.4 From a Preformed Heterocyclic Ring

5.08.13.4.1 From reduced pyranones

Dehydrogenation of dihydropyranones has been achieved using DDQ ⟨81JHC363⟩ and by heating the substrate in the presence of palladized charcoal ⟨63JA3971⟩. However, it is more usual to effect the conversion indirectly by an initial halogenation and subsequent dehydrohalogenation ⟨56DOK(109)117, 76TL1903, 77OS(56)49⟩. The oxidative aromatization of 3-arylthio-3,4-dihydropyrans has been achieved using mcpba ⟨80H(14)163⟩.

The 3,4-dihydropyran-2,4-diones derived from the reaction of 1,1-dicarbonyl dichlorides with lithium enolates undergo isomerization to the hetero-fused pyran-2-ones on treatment with aluminum chloride (Scheme 97) ⟨90CB1175⟩.



Scheme 97

5.08.14 COUMARINS (2*H*-1-BENZOPYRAN-2-ONES)

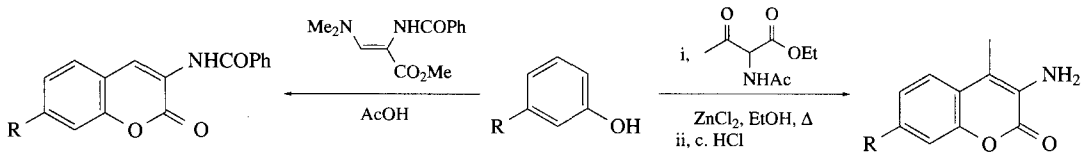
The literature concerning naturally occurring coumarins and related compounds is regularly reviewed ⟨95MI 508-01⟩.

5.08.14.1 Formation of One Bond

5.08.14.1.1 Adjacent to the heteroatom

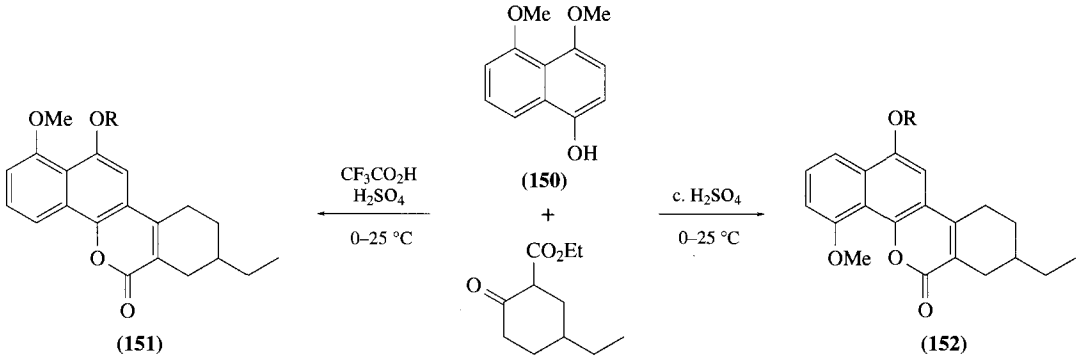
The value of the Pechmann reaction ⟨53OR(7)1⟩ for the synthesis of coumarins lies in its versatility and the availability of the reactants, phenols and 1,3-dicarbonyl compounds. The Pechmann reaction can be effected using zeolites in place of the normal acidic catalysts with obvious environmental advantages. Not only is the reaction between phenols and ethyl acetoacetate successful, but propenoic and propynoic acids ⟨95CC225⟩ and acetic anhydride ⟨93CC1456⟩ also give satisfactory yields of coumarins.

3-Aminocoumarins are readily prepared from phenols and ethyl 2-acetamido-3-oxobutanoate in the presence of $ZnCl_2$ ⟨90JCS(P1)2151⟩ and the reaction of methyl 2-benzoylamino-3-dimethylaminopropenoate with phenols ⟨89JHC1273⟩ and naphthols ⟨90JHC1021⟩ leads to 3-benzoylaminocoumarin derivatives (Scheme 98).



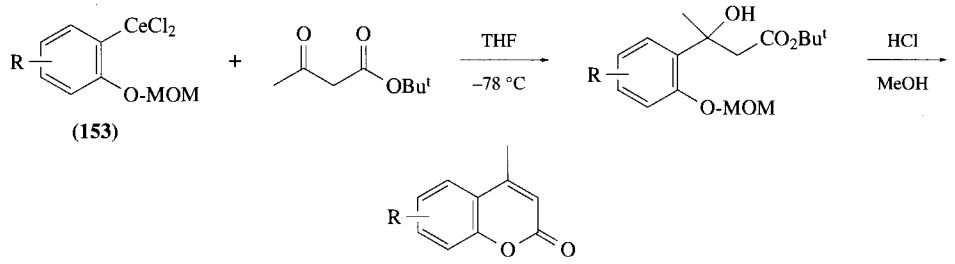
Scheme 98

One disadvantage of the method is the tendency for isomer formation with *m*-substituted phenols. For example, 5-methoxyresorcinol gives products arising from cyclization at both the 2- and 6-positions on reaction with benzoylacetates catalyzed by sulfuric acid ⟨90IJC422⟩. The acidic condensing medium can also influence the course of the Pechmann reaction. Condensation of 4,6-dimethoxy-1-naphthol with ethyl 5-ethyl-2-oxocyclohexanoate in H_2SO_4, for example, gave a mixture of benzonaphthopyranones (**151**), (**152**; R = H) and (**152**; R = Me) in which the last product formed only a minor part despite being the expected product. Presumably the 4-methoxy group is demethylated under the reaction conditions. Using CF_3CO_2H and H_2SO_4 as the cyclizing medium, (**151**) was formed in vast excess (Scheme 99) ⟨92JOC399⟩.



Scheme 99

A significant variation on Pechmann methodology involves the reaction of the organocerium compounds (**153**) with *t*-butyl acetoacetate. The ester obtained by 1,2-addition to the ketone is readily cyclised to the coumarin (Scheme 100) ⟨89H(28)703⟩.



Scheme 100

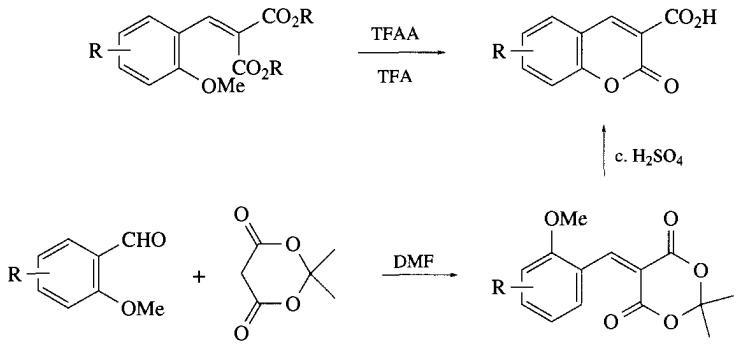
The Knoevenagel reaction ⟨67OR(15)204⟩, in which a benzaldehyde reacts with an activated methylene compound to form a cinnamic acid derivative, is readily adapted to coumarin synthesis by incorporation of a hydroxy group ortho to the aldehyde function. Intramolecular cyclization then follows formation of the unsaturated compound. This methodology constitutes a significant and widely used route to coumarins which has been adapted to incorporate alternative approaches both to the salicylaldehyde and to the cinnamate components. For convenience, such variations are discussed under the general context of Knoevenagel reactions.

A significant improvement in terms of convenience and yield of the conventional Knoevenagel reaction can be achieved by microwave irradiation. Thus, salicylaldehyde and diethyl malonate give an 82% yield of ethyl coumarin-3-carboxylate in three minutes compared to 73% after six hours under normal conditions ⟨90H(30)741⟩.

Syntheses of 3-nitro- ⟨83S836⟩, 3-(3-benzofuranyl)- ⟨90SC809⟩ and 3-(1-oxo-2-alkenyl)- coumarins ⟨84S859⟩, biscoumarins ⟨86DP13⟩, and a macrocyclic coumarin derivative ⟨93TL7465⟩ have been achieved using Knoevenagel methodology.

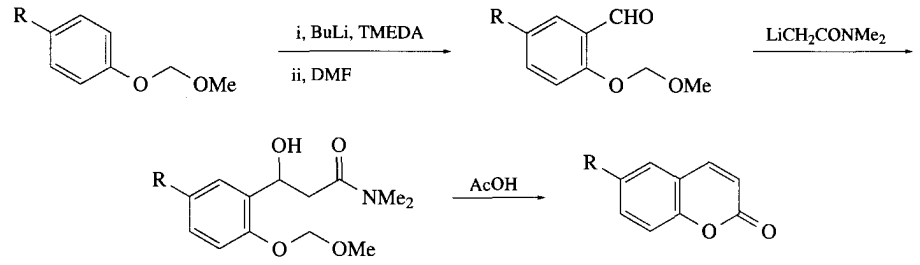
A mixture of TFA and TFAA is used to cyclize benzylidenemalonates and the reaction is thought to proceed via the malonic acid and the mixed anhydride (Scheme 101) ⟨91JCS(P1)219⟩. Coumarin-3-carboxylic acids are also available from Meldrum's acid, the Knoevenagel reaction being conducted in DMF solution (Scheme 101) ⟨88SC717⟩.

The role of DMF is quite different in a coumarin synthesis which involves directed metallation



Scheme 101

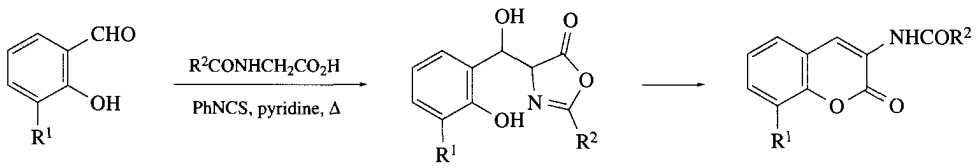
and an aldol reaction with the enolate from dimethylacetamide (Scheme 102). This method is generally applicable and has been used to synthesize polycyclic coumarin derivatives ⟨88JOC3936⟩.



Scheme 102

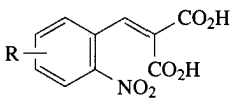
The complex formed between *N*,*N*-diethylacetamides, RCH_2CONEt_2, and $POCl_3$ reacts with salicylaldehydes to give 3-**R** substituted coumarins ⟨84SC407⟩. Thioacetonitriles $RSCH_2CN$ incorporating a heterocyclic function R react with *o*-hydroxybenzaldehydes to give 3-thiosubstituted coumarins via the coumarin imine ⟨89H(29)1729⟩.

The reaction of *N*-acylglycines with *o*-hydroxybenzaldehydes catalyzed by isothiocyanates involves initial formation of an oxazoline, which condenses with the aldehyde moiety. Hydrolysis, elimination, and lactonization lead to 3-*N*-acylaminocoumarins (Scheme 103) ⟨89JPC493⟩.



Scheme 103

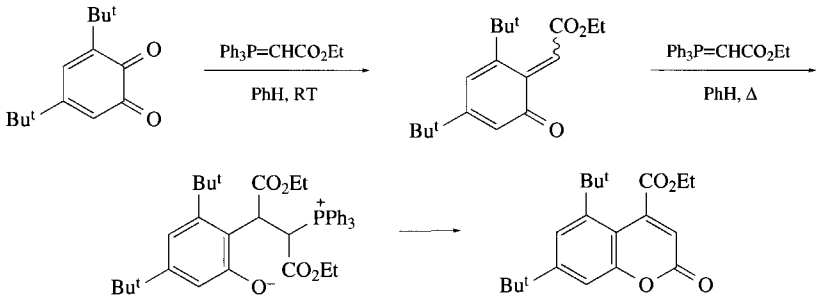
Coumarins are formed when *o*-nitrobenzylidenemalonic acids (**154**) are heated in quinoline, cyclization proceeding by nucleophilic displacement of the nitro group ⟨86S1026⟩. On the other hand, 3,8-dinitrocoumarins are formed directly from the reaction between alkyl 2-hydroxyphenyl ketones and acetic acid on the addition of nitric acid ⟨85S428⟩.



(154)

Phosphorus ylides can function as the carbanionic species in Knoevenagel like reactions. For example, substituted salicylaldehydes react with $Ph_3P{=}CHCO_2Et$ in boiling *N*,*N*-diethylaniline

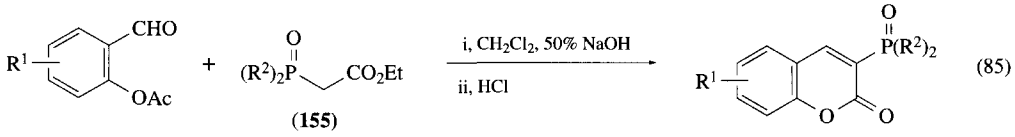
to give good yields of coumarins ⟨93CE245⟩, whilst 3,5-di-*t*-butyl-1,2-benzoquinone affords a 4-substituted coumarin (Scheme 104) ⟨91PS(61)91⟩.



Scheme 104

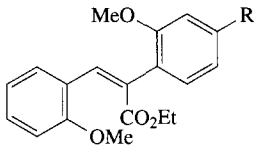
In a similar manner, 2-hydroxyacetophenones ⟨94JHC173⟩ and -benzophenones ⟨85M869⟩ yield 4-substituted coumarins.

When the hydroxy group of salicylaldehydes is protected, a Knoevenagel condensation between phosphonates (**155**; R^2 = OEt or Ph) and the aldehyde function proceeds and subsequent hydrolysis allows cyclization to the coumarin (Equation (85)) ⟨91TL5341⟩. Protection is not necessary when $TiCl_4$-pyridine ⟨95JHC1713⟩ or piperidine acetate and *β*-alanine ⟨93ZN(B)1391⟩ are used as the catalyst.



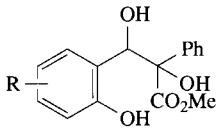
(85)

Directed lithiation and a Wittig reaction feature in the synthesis of the cinnamate (**156**) which is demethylated and cyclized to the coumarin with pyridinium chloride ⟨90SC1781⟩.



(**156**)

The radical, PhĊ(OH)CO_2Me, generated by the Ti(III)-reduction of methyl benzoylformate adds to salicylaldehydes to form the diol (**157**). Lactonization and dehydration leads to 4-hydroxy-3-phenylcoumarins in good overall yields ⟨93S99⟩.



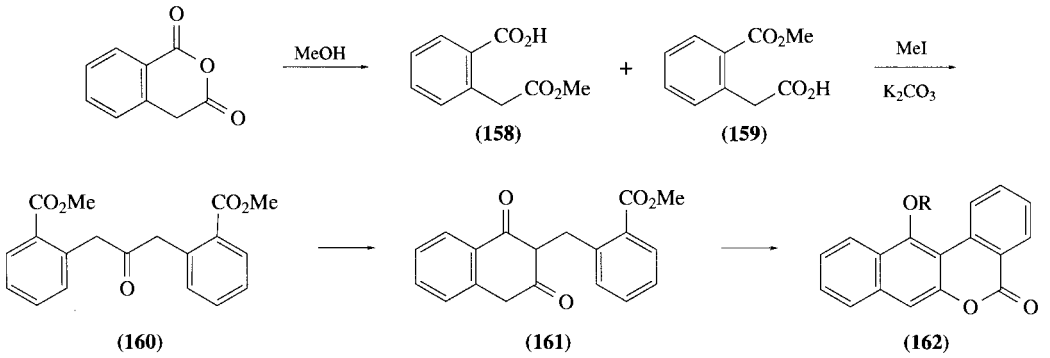
(**157**)

The enolate from *o*-hydroxyacetophenone is C-carbonylated by carbon monoxide in the presence of sulfur ⟨88S257⟩ or selenium ⟨85T4813⟩.

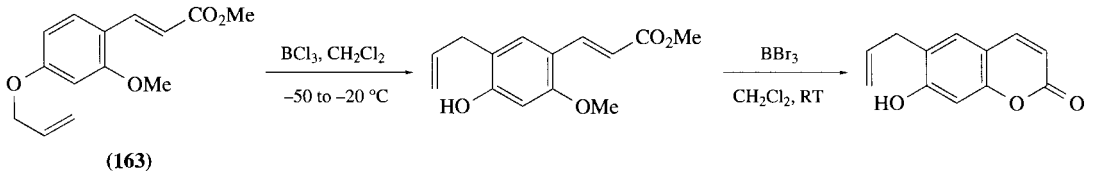
An unusual synthesis of the benzo[*d*]naphtho[2,3-*b*]pyran-5-one system (**162**) involves the sequential reactions of homophthalic anhydride with methanol and iodomethane with K_2CO_3. The former yields the esters (**158**) and (**159**) which then undergo an intermolecular condensation to give (**160**) and subsequently (**161**) (Scheme 105) ⟨91JCR(S)279⟩.

Careful control of conditions and substrate structure allows the synthesis of several naturally occurring coumarins to be achieved using thermal Claisen rearrangements. Thus a regioselective *ortho*-Claisen rearrangement of the 4-allyloxycinnamate derivative (**163**) in the presence of a Lewis acid gives the coumarin after demethylation of the ether (Scheme 106) ⟨94JCS(P1)3095⟩.

Multiple Claisen rearrangements enable 3-, 6-, and 8-allylated coumarins to be obtained in very

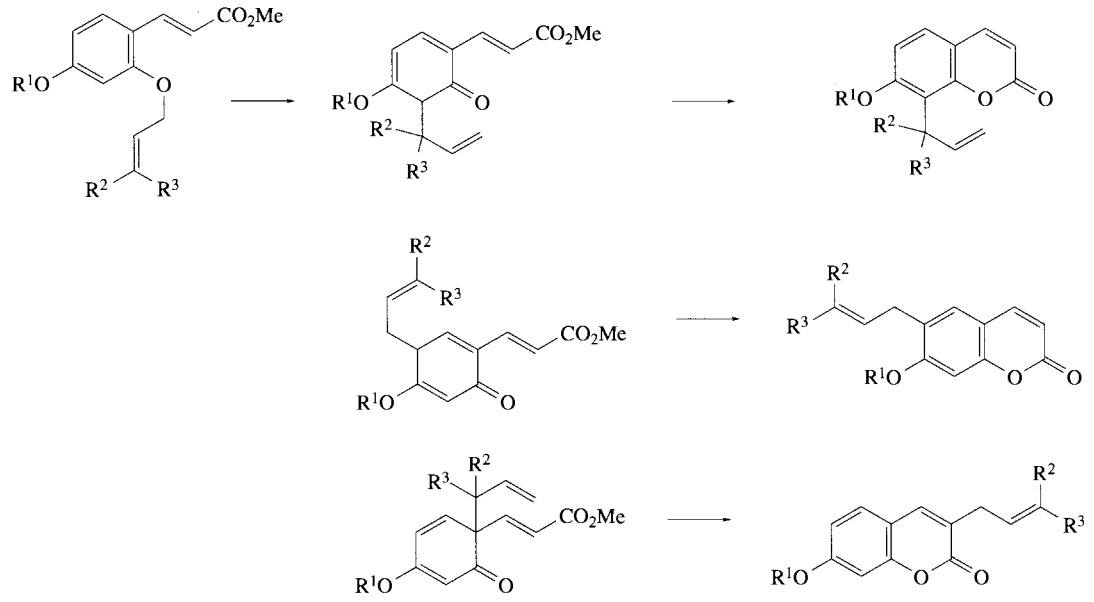


Scheme 105



Scheme 106

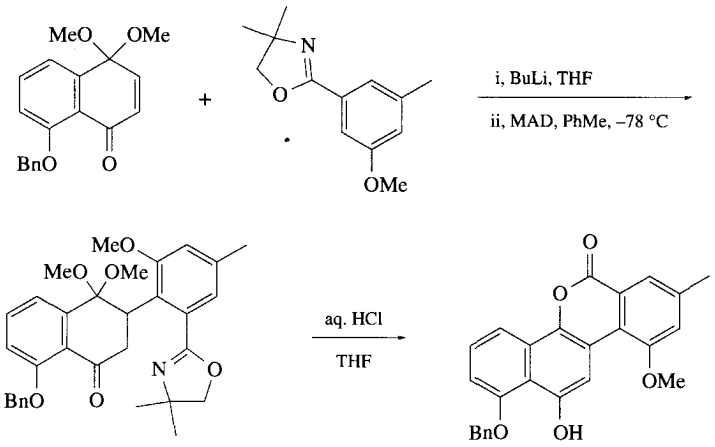
satisfactory yields from the cinnamates obtained from cleavage of 7-hydroxycoumarins. Allylation of the phenolic function and subsequent *para*-Claisen and side chain rearrangements and lactonization yield the products (Scheme 107) ⟨94JCS(P1)3101⟩.



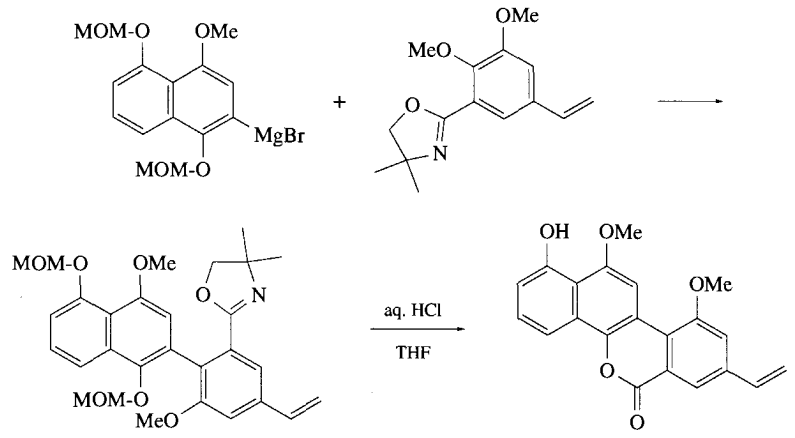
Scheme 107

Oxazolines feature in the synthesis of polycyclic coumarins. Directed metallation and aluminum-assisted coupling are used in the synthesis of the biaryl compound and subsequent hydrolysis generates the carboxylic acid function required for lactonization (Scheme 108) ⟨89TL5093⟩. An alternative approach to this gilvocarcin system is based on Meyer's coupling strategy (Scheme 109) ⟨88JOC1003⟩.

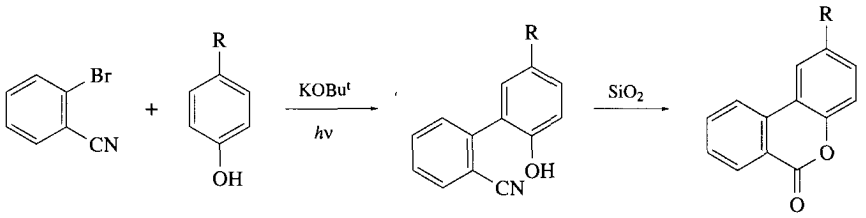
The reaction of phenoxides with *o*-bromobenzonitrile results in the formation of biaryls by a photolytic $S_{RN}1$ process. Cyclization to dibenzo[*b*,*d*]pyranones is catalyzed by SiO_2 (Scheme 110) ⟨93H(36)2723⟩.



Scheme 108



Scheme 109

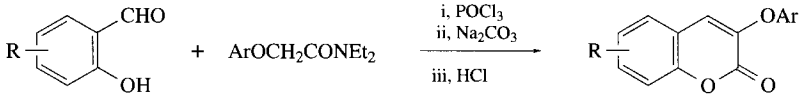


Scheme 110

5.08.14.1.2 γ to the heteroatom

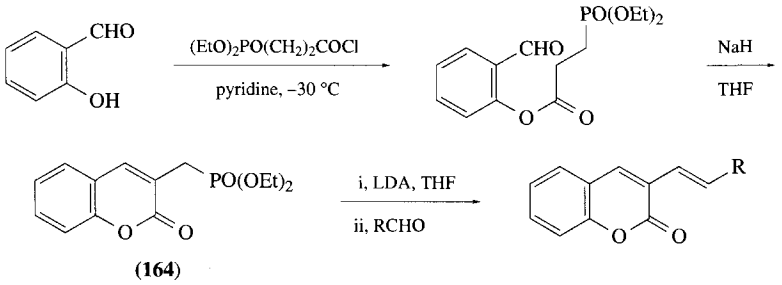
The synthesis of coumarins by the Perkin reaction ⟨42OR(1)210⟩ involves heating a salicylaldehyde with the sodium salt and anhydride of a carboxylic acid. Initial acylation of the phenolic function is followed by enolate attack at the aldehyde group, acylation, lactonization, and elimination.

Developments in the Perkin synthesis include the use of sodium fluoride ⟨91MI 508-01⟩ and dibenzo-18-crown-6 ⟨94MI 508-02⟩ as catalysts, and there are a number of variations in the reactants used. 3-Aryloxy-, 3-benzyl-, 3-chloro-, and 3-chloro-4-phenyl-coumarins can be prepared by the reaction of salicylaldehydes and *o*-hydroxybenzophenones with the complex formed between $POCl_3$ and substituted acetamides (Equation (86)) ⟨85S11, 87IJC1180, 90SC855⟩.



(86)

An intramolecular aldol condensation enables the phosphonate (**164**) to be prepared, from which 3-alkenylcoumarins are readily obtained (Scheme 111) ⟨89S506⟩.

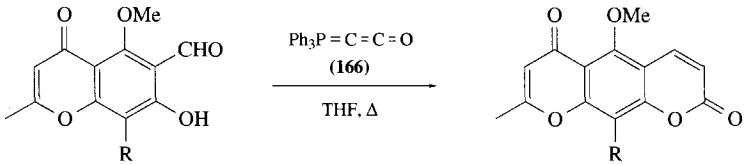


(**164**)

Scheme 111

Similarly, under phase transfer conditions, arylacetyl chlorides afford 3-arylcoumarins on reaction with aryl *o*-hydroxy carbonyl compounds ⟨87SC341⟩.

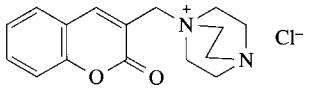
The fused salicylaldehyde (**165**) reacts with the phosphacumulene (**166**) to give an ylid which undergoes an intramolecular Wittig reaction on heating to produce the benzo[1,2-*b*][5,4-*b*′]dipyran-2,6-dione (Equation (87)) ⟨91PS(60)183⟩. Similarly, reaction of salicylaldehyde and *o*-hydroxyacetophenone with the ketene $(EtO)_2P(O)C(R)=C=O$ gives substituted coumarins ⟨90ZOK926⟩.



(87)

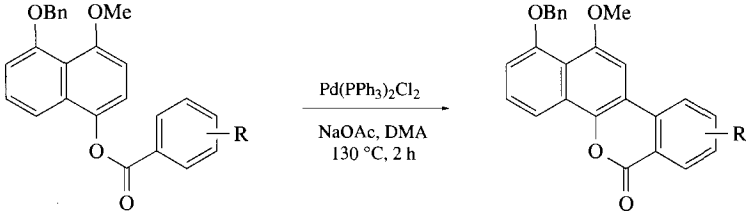
(**165**)

Isolation of the coumarin salt (**167**) has established that the intramolecular Baylis–Hillman reaction involves the Michael addition of DABCO to the acrylate ester. Protection of the hydroxy function in salicylaldehyde prior to reaction with methyl acrylate and DABCO enables other species to add in a 1,4-fashion, providing differently 3-substituted coumarins ⟨93SC2807⟩.



(**167**)

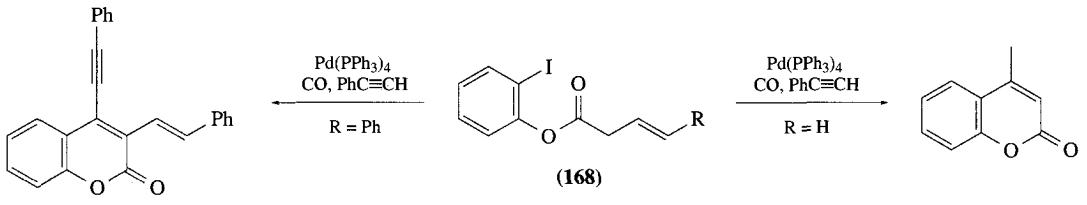
Palladium catalyzed intramolecular aryl coupling generates the pyranone ring in syntheses of the aglycone of the gilvocarcins, benzo[*d*]naphtho[1,2-*b*]pyran-6-ones (Equation 88) ⟨90TL6313⟩. A similar approach features in total syntheses of gilvocarcins themselves ⟨92JA3568, 94JA1004⟩. The same methodology is used in the synthesis of benzonaphtho- and dinaphtho-pyranones ⟨92LA225, 94LA91⟩.



(88)

The intramolecular cyclization of *o*-iodophenyl but-3-enoate (**168**; R = H) leads to 4-methylcoumarin only if the palladium-catalyzed process is carried out in the presence of CO and a promoter

such as phenylacetylene which can coordinate to the catalyst ⟨94TL5919⟩. However, when R is alkyl or aryl, the phenylacetylene is incorporated into the product (Scheme 112) ⟨94TL5923⟩.



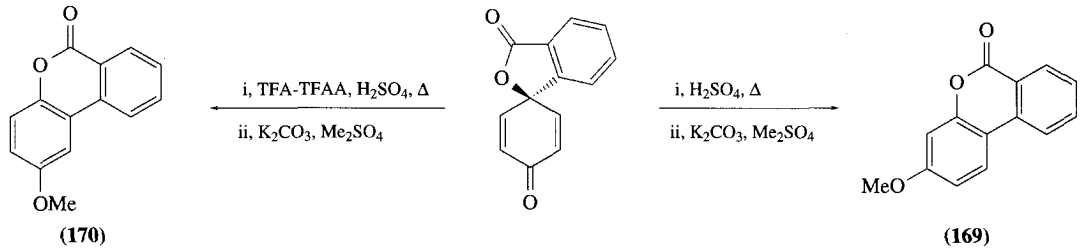
Scheme 112

Aryl coupling also results in the formation of dibenzo[*b*,*d*]pyran-6-ones during the decomposition of diaryl peroxides in phenols, thought to proceed by radical-substrate dimerization ⟨90JOC6312⟩.

5.08.14.2 From Other Heterocycles

5.08.14.2.1 From isobenzofurans

Spiro[2,5-cyclohexadiene-1,1′(3′*H*)-isobenzofuran]-3′-ones undergo an acid catalyzed dienone-phenol rearrangement. Using H_2SO_4, *O*-migration occurs exclusively leading to (**169**), whilst *C*-migration dominates in TFA-TFAA affording (**170**) (Scheme 113) ⟨92T8179⟩.

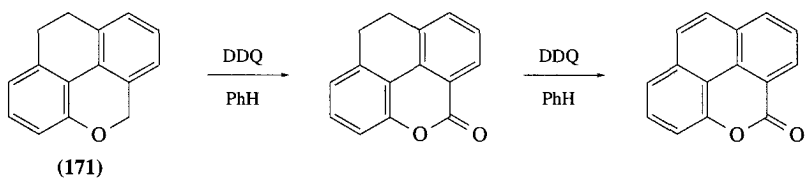


Scheme 113

5.08.14.3 From a Preformed Heterocyclic Ring

5.08.14.3.1 From chromans

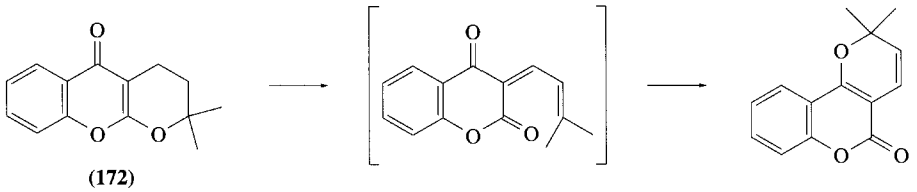
The reaction of the dihydrophenanthropyrans (**171**) with DDQ results in both oxidation and dehydrogenation (Scheme 114) ⟨93IJC975⟩.



Scheme 114

5.08.14.3.2 From chromones

On treatment with DDQ, the dihydropyranochromones (**172**) rearrange with concomitant dehydrogenation to pyranocoumarins. A quinone methide is implicated (Scheme 115) ⟨86SC1671⟩.



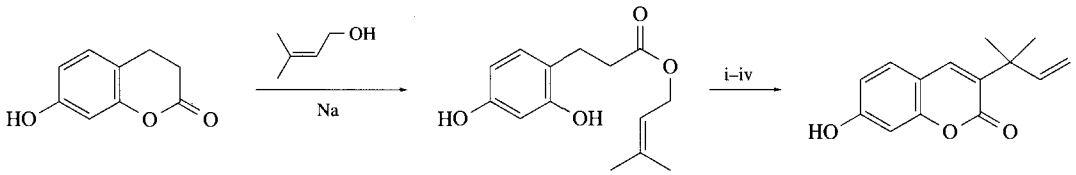
(**172**)

Scheme 115

5.08.14.3.3 From dihydrocoumarins

Aromatization of dihydrocoumarins is readily achieved using Pd-C ⟨88JA7419, 93T1701⟩, an oxidant ⟨88JA7419, 88TL5901⟩, or by reaction with NBS and subsequent dehydrobromination ⟨91JCS(P1)3159⟩.

On treatment with 3-methylbut-2-en-1-ol, the lactone ring of dihydrocoumarin is opened and a subsequent Claisen rearrangement and cyclization leads to 3-(1,1-dimethylallyl)coumarins (Scheme 116) ⟨93T1701⟩.



i, BzBr, K_2CO_3; ii, LDA, TMS-Cl; iii, BBr_3; iv, Pd-C, Ph_2O, Δ

Scheme 116

5.08.15 PYRAN-4-ONES

The few methods of synthesis of this system are generally reliable and of wide applicability. The early work on pyran-4-ones has been reviewed ⟨47CRV525⟩ and kojic acid has been the subject of a separate review ⟨82MI 508-03⟩.

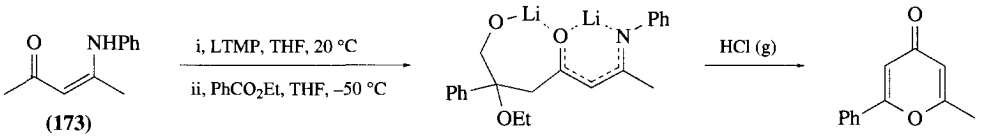
5.08.15.1 Formation of One Bond

5.08.15.1.1 Adjacent to the heteratom

Several routes to pyran-4-ones are based on the cyclization of 1,3,5-triketones and differ only in the synthetic approach to the carbonyl compound. The final cyclization step is normally carried out under acidic conditions although sometimes ring closure occurs spontaneously during the triketone synthesis under basic conditions. Cyclization using either Ph_3P-CCl_4 or DMSO-$(COCl)_2$ has been shown to occur without epimerization at any optically active centre and has been used to determine the absolute configurations of some naturally occurring pyran-4-ones ⟨93TL5781, 94TL9581, 95TL5357⟩.

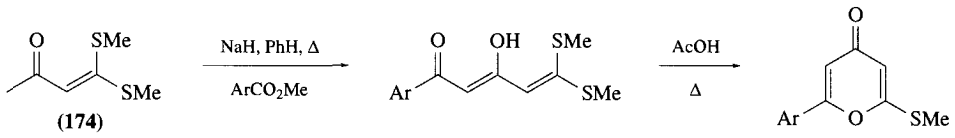
Aryl esters acylate the dianions derived from β-monosubstituted amino α,β-unsaturated ketones (**173**) and, provided conditions are chosen carefully, metallation, and subsequent cyclization of the

enaminodione affords pyran-4-ones. A competitive mode of ring closure leads to pyridin-4-ones (Scheme 117) ⟨93JCS(P1)2081⟩.

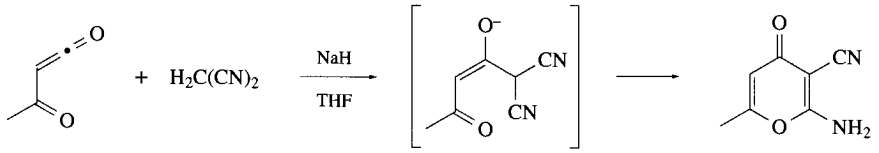


Scheme 117

The base-catalyzed condensation of the acylketene dithioacetal (**174**) with methyl benzoate affords aroylacetylketene dithioacetals which are efficiently cyclized to the 6-arylpyran-4-ones under acid conditions (Scheme 118) ⟨87S873⟩. The isomeric 5-aryl compounds result by a more elaborate route from cinnamoylketene dithioacetals, involving an epoxidation and subsequent Lewis acid catalyzed ring opening ⟨87S893⟩. α-Oxoketenes react with carbanions derived from activated methylene compounds to form pyran-4-ones (Scheme 119) ⟨84CPB2957⟩.



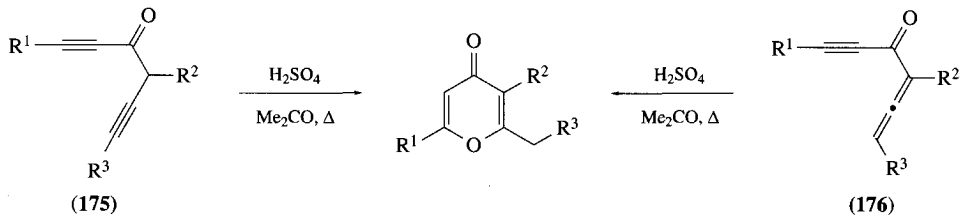
Scheme 118



Scheme 119

The acylation of ketones by alkynoate esters leads to an acetylenic β-diketone which cyclizes readily to the pyran-4-one ⟨86JHC1849⟩. In a similar manner, acetylenic β-keto amides afford 2-aminopyran-4-ones ⟨94S43⟩.

Both the diynone (**175**) and the allenynone (**176**) can be cyclized to di- and tri-substituted pyran-4-ones; (**175**) is thought to isomerize to (**176**), which is hydrated prior to ring closure (Scheme 120) ⟨93TL449⟩.

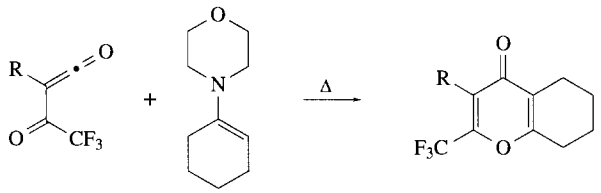


Scheme 120

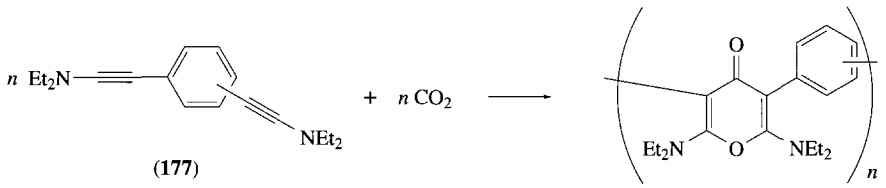
5.08.15.2 Formation of Two Bonds

α-Oxoketenes behave as the heterodiene component in [4 + 2] cycloaddition reactions which lead to pyran-4-ones. The dienophiles used include ynamines ⟨72TL1135⟩, silyl enol ethers ⟨93H(36)2139, 93MI 508-02⟩, and enol ethers ⟨89CHE126⟩. Trifluoroacetylketenes react with enamines to form fused pyran-4-ones (Equation (89)) ⟨95T2585⟩. However, electron-rich conjugated dienes add across the carbonyl function of the ketene leading to pyran-4-ones via the initial dihydropyran ⟨82S500⟩.

The aromatic bis(ynamines) (**177**) are copolymerized with CO_2 in DMF without the need for a catalyst to form the polypyran-4-ones (Equation (90)) ⟨95CC2417⟩.



(89)



(177)

(90)

5.08.15.3 From Other Heterocycles

5.08.15.3.1 From furans

The acid catalyzed rearrangement of a dihydrofurfuryl alcohol leads to a dihydropyran-3-one from which a pyran-4-one can be obtained. This approach is the basis of several syntheses of the flavoring agent maltol, 3-hydroxy-2-methylpyran-4-one ⟨80JOC1109⟩.

The oxidative rearrangement of furofurans leads to 3-formylpyran-4-ones ⟨94H(37)137⟩.

5.08.15.3.2 From oxazoles

Elimination of acetonitrile from the Diels–Alder adduct between an oxazole and diphenylcyclopropenone results in the formation of a pyran-4-one ⟨70JCS(C)552⟩.

5.08.15.4 From a Preformed Heterocyclic Ring

5.08.15.4.1 From reduced pyran-4-ones

Tetrahydropyran-4-ones can be oxidized to pyran-4-ones ⟨57JA156, 79JCS(P1)1806⟩.

5.08.15.4.2 From pyran-2-ones

The cleavage of the lactone ring of 4-hydroxy-6-acylmethylpyran-2-ones by strong acids is followed by recyclization to the pyran-4-one ⟨70T5255⟩.

5.08.16 CHROMONES (4*H*-1-BENZOPYRAN-4-ONES)

Chromones, in particular their 2- and 3-phenyl derivatives, the flavones and isoflavones, have an extensive chemistry and the earlier work is well documented. Specialized reviews include those on chromones with a 2,3-fused heterocyclic ring ⟨87H(26)1899⟩ and with fused rings containing nitrogen ⟨72MI 508-02⟩, and on styrylchromones ⟨93H(36)2601⟩.

5.08.16.1 Formation of One Bond

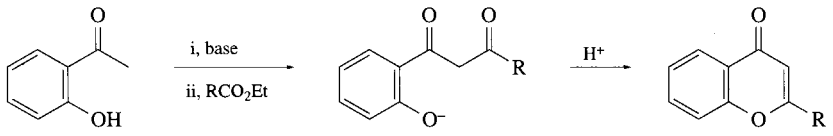
In general, chromones are derived from phenols and 2-hydroxyacetophenones by attaching a side chain which is subsequently used to construct the heterocyclic ring. Although the intermediate

acyclic material is sometimes not isolated, all of these syntheses are considered as involving the formation of only one bond. The use of *o*-hydroxyacetophenone in the synthesis of heterocycles has been reviewed ⟨94OPP159⟩.

5.08.16.1.1 Adjacent to the heteroatom

Several routes to chromones are based on the extension of the acyl group in *o*-hydroxyacetophenone by one carbon atom which, during subsequent cyclization, becomes C-2 of the heterocyclic product.

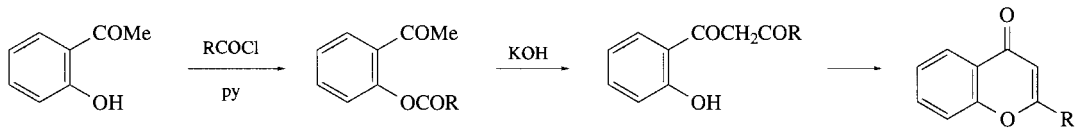
The base-catalyzed Claisen condensation of 2-hydroxyacetophenone with esters leads to a 1,3-diketone which can be isolated as its sodium salt. Cyclization to the chromone occurs readily under acidic conditions (Scheme 121). Since the reagents and reactants can be varied widely, there are many examples of this procedure, including a detailed preparation of 3-ethylchromone ⟨55OSC(3)387⟩. A comprehensive list of examples is given in the review by Ellis ⟨77HC(31)⟩ and syntheses of khellin ⟨89JOC3625⟩ and several naturally occurring pyranoflavones ⟨92ZN1021⟩ are illustrative.



Scheme 121

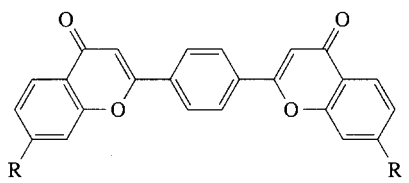
Variations on this theme include the use of diethyl oxalate to give ethyl 8-nitrochromone-2-carboxylate ⟨94JCS(P1)2113⟩ and ethyl oxalyl chloride to produce 5,7-dihydroxychromone-2-carboxylic acid ⟨91OPP390⟩, the related 3-alkoxy compound ⟨93JCS(P1)1153⟩ and 3-(2-benzothiazolyl)chromones ⟨94CHE405⟩. Application to 5-acetyl-2′,4′-dihydroxyacetophenone and related compounds results in a double Claisen condensation product, cyclization of which affords a benzodipyran-4-one ⟨87IJC766⟩. Use of ethyl methylthioacetate, $MeSCH_2CO_2Et$, as the ester component allows the introduction of the CH_3SCH_2 function at the 2-position of chromone ⟨84JOC5035⟩.

An alternative source of the 1,3-diketone chromone precursor is an *O*-acyloxyacylbenzene, readily accessible by the acylation of 2-hydroxyacetophenones. A base-catalyzed Baker–Venkataraman rearrangement affords the diketone intermediate (Scheme 122). Full experimental details are available for the preparation of flavone by this route ⟨63OSC(4)478⟩.



Scheme 122

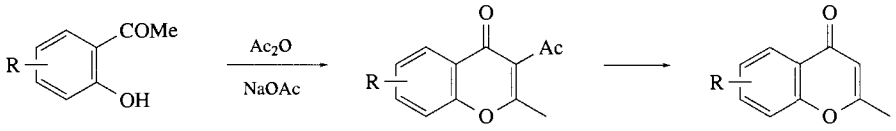
Wide variation in substrate, reagent, and reaction conditions is compatible with this approach to chromones. Examples include the use of a phase transfer catalyst ⟨90SC817, 92IJC335⟩, potassium *t*-butoxide ⟨93JOC7903⟩ and NaH/DMSO ⟨84S1076⟩ to effect the rearrangement, whilst a 6-coordinate cobalt Schiff base complex promotes cyclization of the 1,3-diketone in 2,2,2-trifluoroethanol ⟨92S839⟩. Use of terephthaloyl chloride with a two-fold excess of a hydroxyacetophenone leads to bischromonylarene derivatives (**178**) ⟨93AP(326)167⟩.



(178)

In the Kostanecki–Robinson synthesis of chromones and flavones, a 2′-hydroxyacetophenone is heated with the anhydride and sodium salt of an aliphatic acid. Alkaline cleavage of the 3-acyl

group in the product is facile and may occur during isolation of the product and a mixture of chromones may result (Scheme 123) ⟨36JCS215⟩. However, the reaction is compatible with a comprehensive range of substituents in the aromatic ring and has been widely used to synthesize chromones, and especially flavones. Details of the applications of this route to chromones are available ⟨77HC(31)⟩ and the earlier work has been reviewed ⟨54OR(8)59⟩. 3-Substituted chromones are produced when a substituent is present on the methyl group of the hydroxyacetophenone ⟨94BCJ1972⟩.

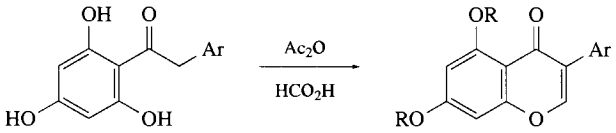


Scheme 123

The Kostanecki–Robinson reaction proceeds by both *C*- and *O*-acylation followed by a Baker–Venkataraman rearrangement to the 1,3-diketone and subsequent cyclization ⟨69T715⟩.

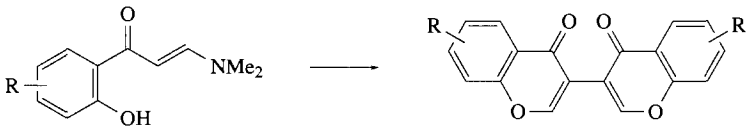
Improvements to the Kostanecki–Robinson reaction, which lead to increased yields under milder conditions, include catalysis by triethylamine ⟨77T1405⟩ and the use of a tertiary amine as solvent ⟨78JOC2344⟩.

The mixed anhydride of acetic and formic acids acts as a one carbon synthon and enables chromones unsubstituted at C-2 to be synthesized under mild conditions. This approach is exemplified by the formation of isoflavones (Equation (91)) ⟨91JHC1641, 92CHE497⟩ and 3-(2-benzothiazolyl)chromones ⟨94CHE405⟩.



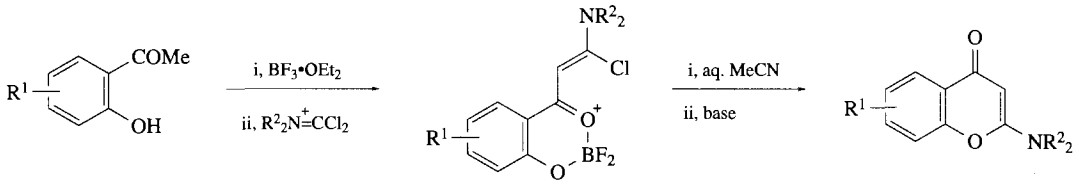
(91)

The use of triethyl orthoformate also yields chromones unsubstituted at the 2-position, a route which has been used to prepare 3-(3-isoxazolyl)chromones ⟨93CHE23⟩ and isoflavones ⟨92SC1735⟩. Related reagents include dimethylformamide and its acetal, often in the presence of $POCl_3$, BF_3, and $MeSO_2Cl$ ⟨71CB348, 72LA(765)8, 76CC78, 76S326, 93H(35)93, 94IJC847⟩. Deoxybenzoins, either isolated or formed *in situ* from phenols and arylacetic acids, are converted into isoflavones using DMF in methanesulfonyl chloride as the source of the additional carbon atom. An important feature of this route is its compatability with unprotected hydroxy groups ⟨91JCS(P1)3005⟩. Enaminones derived from 2′-hydroxyacetophenone and DMF-DMA undergo anodic oxidation to 3,3′-bichromones (Equation (92)) ⟨88MI 508-03⟩.



(92)

The formation of 2-aminochromones either by sequential treatment of 2-hydroxyacetophenone with BF_3 etherate and a phosgeneiminium salt or in a one-pot procedure occurs in a similar fashion, with the breakdown of the complex (**179**) generating the equivalent of a 1,3-diketone (Scheme 124) ⟨92JOC6502⟩. Salicylacetamides afford 2-aminochromones on cyclodehydration with triflic anhydride ⟨94SC849⟩.

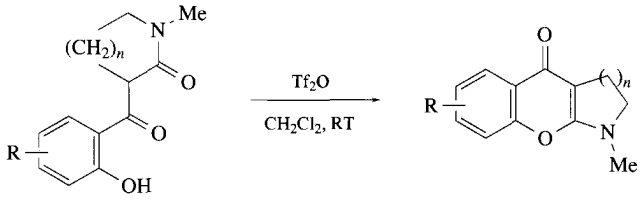


(**179**)

Scheme 124

Salicylic acid derivatives serve a similar purpose to 2′-hydroxyacetophenones, acting as precursors of 1,3-diketones in chromone syntheses. Thus, reaction of ethyl salicylates with sodium methylsulfinylmethide affords the substituted 2′-hydroxyacetophenone which with $HC(OEt)_3$ gives 3-methylsulfinylchromone ⟨72JHC171⟩. A synthesis of lanceolatin B, a flavonoid from *pongamia sp.*, is based on a Knoevenagel reaction between a β-ketosulfoxide and benzaldehyde. The resulting benzylidene derivative undergoes an intramolecular conjugate addition with loss of $MeSO_3H$ ⟨94TL6231⟩.

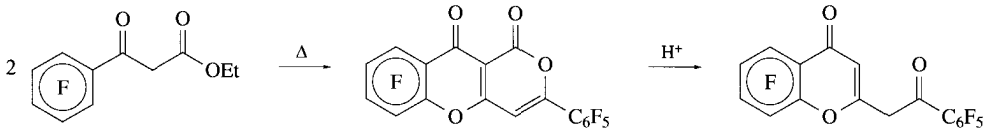
The lactam (**180**; n = 1) derived from methyl salicylate and the lithium enolate of *N*-methylpyrrolidinone behaves as a 1,3-diketone and is cyclodehydrated at room temperature on treatment with polyphosphoric ester or, better, triflic anhydride to the 2,3-fused chromone (Equation (93)). Thermal ring closure yields a coumarin ⟨93JOC7277⟩. The isoxazoles derived from *p*-hydroxybenzaldehyde oxime by 1,3-dipolar cycloaddition to tributylstannylacetylene and a palladium-catalyzed coupling to 2-iodophenols, afford 1,3-diketones, and hence flavones, on reductive ring cleavage ⟨92ACS494, 95ACS524⟩. The formation of 1,3-diketones by the reaction of acid chlorides with lithium enolates has also been used to prepare 2,3-fused chromones ⟨78JCS(P1)726⟩ and this approach is of value in the synthesis of hydroxylated flavones ⟨90TL497⟩.



(180)

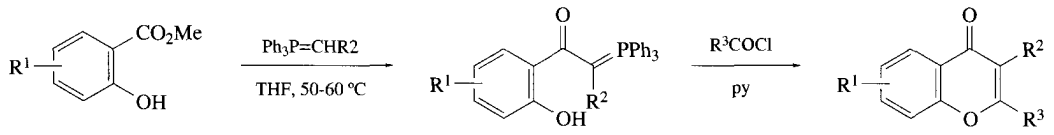
(93)

The 1,3-diketo side chain has been introduced using ethyl acetoacetate as, for example, in the synthesis of 2-methyl-8-phenylchromone ⟨93RRC1117⟩ and of polyfluorinated chromones ⟨70JOC930⟩. The self condensation of ethyl pentafluorobenzoylacetate involves a fluoride ion displacement, initially affording a pyrano[2,3-*b*]chromone which is hydrolyzed to the 2-pentafluorobenzoylmethylchromone (Scheme 125) ⟨93JFC37⟩.



Scheme 125

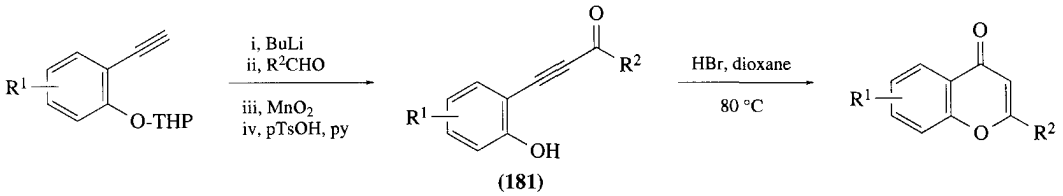
The role of the 1,3-diketone can be played by acyl phosphoranes, which react with acid chlorides to give 2-substituted chromones. Protection of phenolic functions is not necessary ⟨86TL2751, 86TL5503⟩. The acylphosphoranes are available from the reaction of triphenylphosphine with *o*-acetoxy or *o*-hydroxyphenacyl halides ⟨82S597, 91MI 508-02, 94IJC27⟩. The phosphonium salt or the phosphorane may be isolated, but a one-pot variant in which the phenacyl halide, acid chloride, and Ph_3P are heated together in toluene gives high yields of chromones. Alternatively, the reaction of methyl salicylates with alkylidenephosphoranes provides the acylated phosphorane (Scheme 126) ⟨91JHC2013, 92S375⟩.



Scheme 126

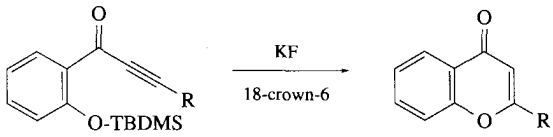
A C≡C bond can behave as the equivalent of a carbonyl group and this feature has been utilized in a number of chromone syntheses. Protected 2-hydroxyphenylacetylenes are the source of the acetylenic ketones (**181**) via reaction of the alkynyllithium with an aldehyde and oxidation of the resulting alcohol. Cyclization is best achieved with HBr, providing flavones and styrylchromones in good yields (Scheme 127) ⟨89HCA447⟩. 2-Hydroxyaryl ethynyl ketones are available from hydroxy-

protected salicyladehydes by reaction with a metal alkynide and oxidation to the ynone. After deprotection, cyclization can be achieved under basic conditions ⟨90TL2299⟩. However, a fluoride-induced cyclization is recommended since this favours a 6-*endo-dig* cyclization over the 5-*exo-dig* mode, which would lead to a benzofuranone (Equation (94)) ⟨94JOC4360⟩. In a related sequence, salicylic acid has been converted to flavone, a secondary amine effecting the cyclization of the ynone ⟨86ZOK1847⟩.



(181)

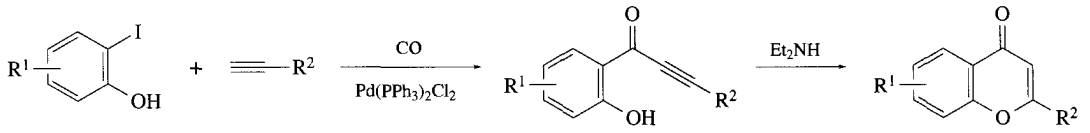
Scheme 127



(94)

The mode of cyclization of 2-hydroxyaryl phenylethynyl ketones is strongly dependent on the reaction conditions. Under acidic conditions, flavones are formed exclusively, but under basic conditions there is competition between 5-*exo-dig* and 6-*endo-dig* modes, leading to mixtures of aurones and flavones. Substituent effects on the mode of cyclization appear to be small. However, flavone formation is favored by the use of K_2CO_3 in acetone, whilst aurones are formed in significant amounts when cyclization is effected by NaOEt or K_2CO_3 in ethanol ⟨86JOC4432, 89JCS(P2)957⟩. Catalysis by silver(I) ions leads exclusively to aurones ⟨90JCS(P1)423⟩. In the related cyclization of 2′-acetoxychalcones, in which the side chain is bromoethoxylated, aurones are the major products unless electron withdrawing groups are present *para* to the side chain ⟨91M83⟩.

2-Iodophenols undergo a palladium-catalyzed carbonylation in the presence of terminal alkynes to give chromones directly. The intermediacy of *o*-hydroxyaryl ethynyl ketones is apparent (Scheme 128) ⟨93T6773⟩. In a related manner, protected iodophenols form 3-ethoxy-1-arylpropenones through a palladium-catalysed carbonylative coupling reaction with *Z*-1-ethoxy-2-(tributylstannyl)ethene. An acid catalyzed cyclization yields chromone ⟨92CPB1137⟩.



Scheme 128

Phenols are acylated by substituted propiolic acids in the presence of phosphorus pentoxide in methanesulfonic acid to give a mixture containing a chromone, a coumarin, and uncyclized material. When the phenol component bears methoxy groups, the chromone may be the sole product. Using alkylpropiolic acids, the uncyclized *o*-hydroxyaryl ethynyl ketones are the major product, but these are readily cyclized to chromones ⟨90JOC4349⟩. A good yield of 2-difluoromethylchromone results from cyclization of the corresponding phenoxyacrylic acid by PCl_5-$AlCl_3$ ⟨94JFC25⟩. Other fluoroalkylchromones have been obtained in a related manner ⟨94JFC263⟩.

An established route to flavones involving the oxidative cyclisation of 2′-hydroxychalcones has been well documented (Equation (95)) ⟨B-75MI 508-01⟩ and is particularly attractive because of the availability and variety of the chalcone precursors, *o*-hydroxyacetophenones, and aromatic aldehydes. Of the methods used to effect cyclization, mention can be made of DMSO containing catalytic amounts of iodine ⟨91CL445, 91IJC788, 93CHE728, 94TL5899⟩ or $NaIO_4$ ⟨93SC1021⟩. When molar quantities of halogen are used, cyclization is accompanied by electrophilic attack in the fused benzene ring ⟨94TL9459⟩. Selenium dioxide has been used in the synthesis of aminoflavones ⟨57JOC304, B-62MI 508-01⟩ and fluorinated flavones ⟨87IJC493⟩, whilst a bromination–debromination–dehydro-

bromination sequence is a suitable route to flavones ⟨63CB913, 81JOC638⟩ and to 3-aminoflavones via reaction of the chalcone dibromide with sodium azide ⟨79LA174⟩. Iodosobenzene diacetate converts chalcones with electron-rich phenolic rings directly to flavones ⟨95LA1711⟩.

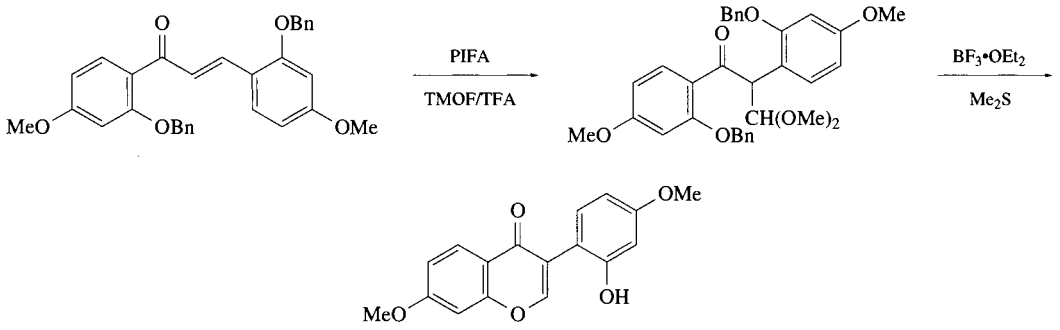
(95)

When the chalcone oxidation is conducted with hydrogen peroxide, a flavonol is usually formed through an Alger–Flynn–Oyamada reaction ⟨87IJC493, 93JHC1549⟩.

The oxidative cyclization of 2′-hydroxychalcones with DDQ leads to a mixture of flavone and aurone in which the former predominates ⟨87S199⟩.

A chalcone is presumably an intermediate in the synthesis of 2-arylcyclohepta[*b*]pyran-4,9-diones, the tropolone analogues of flavones, from 3-acetyltropolone ⟨90JHC891⟩.

Chalcones are also a source of isoflavones by virtue of a facile oxidative rearrangement. This can be accomplished in two distinct steps involving epoxidation and treatment with a Lewis acid, which effects a 1,2-aroyl shift ⟨56JA2278⟩. The oxidation and rearrangement occur simultaneously when 2′-benzyloxychalcones are treated with thallium(III) acetate in methanol; a 1,2-aryl shift is involved ⟨70JCS(C)125⟩. Protection of the 2′-hydroxy group is unnecessary when thallium(III) nitrate is used ⟨74JCS(P1)305, 84H(22)709, 86JCS(P1)1561, 89BCJ826, 92HCA457⟩. Phenyliodine(III) bistrifluoroacetate brings about the rearrangement of the chalcone to an acetal, which is cyclized to the isoflavone by $BF_3 \cdot OEt_2$ (Scheme 129) ⟨94SL1001⟩.

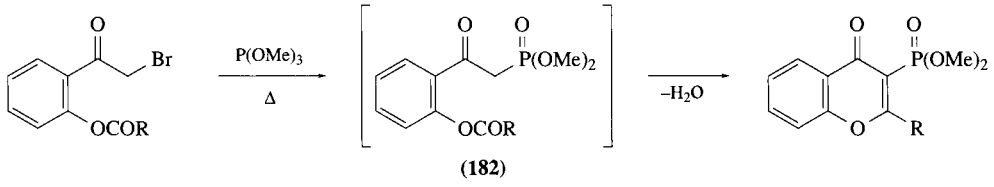


Scheme 129

5.08.16.1.2 β to the heteratom

Chromone syntheses which proceed by formation of the C-2—C-3 bond invariably involve organophosphorus chemistry.

The reaction of 2-bromo-2′-acetoxyacetophenone with trimethyl phosphite gives an arylvinyl phosphate by a Perkow reaction but 2-methylchromone-3-dimethylphosphonate by way of an Arbusov product (**182**), which spontaneously dehydrates (Scheme 130) ⟨92PS(71)67⟩.

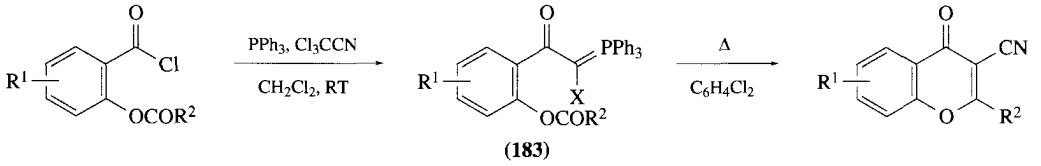


(**182**)

Scheme 130

2-Acyloxybenzoic acids afford 3-chloroflavones on reaction with triphenylphosphine and tetrachloromethane. The reaction is considered to proceed via the acid chloride and a reactive chloroylid

(**183**; X = Cl). When the acid chloride is treated with Ph_3P and trichloroethanonitrile, the ylid (**183**; X = CN) is formed which is thermally cyclized to the 3-cyanochromone (Scheme 131) ⟨90T3489⟩.

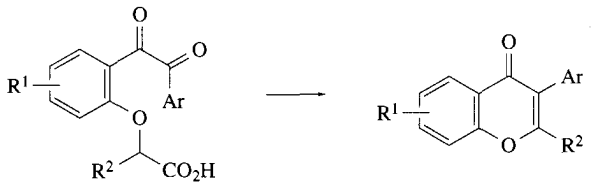


(**183**)

Scheme 131

Several 2-phenoxychromones have been prepared by the thermal cyclization of the phosphorane carbonates derived from *o*-hydroxypropiophenone ⟨81CC282, 81CC474⟩.

Phenoxyketenes derived from 2-(carboxyalkoxy)benzils undergo an intramolecular [2 + 2] cycloaddition to one or other of the carbonyl groups. The distribution of the products, isoflavones, and 3-aroylbenzofurans, varies with the substitution pattern of the benzils (Equation (96)) ⟨88JOC1353⟩.



(96)

5.08.16.1.3 γ to the heteratom

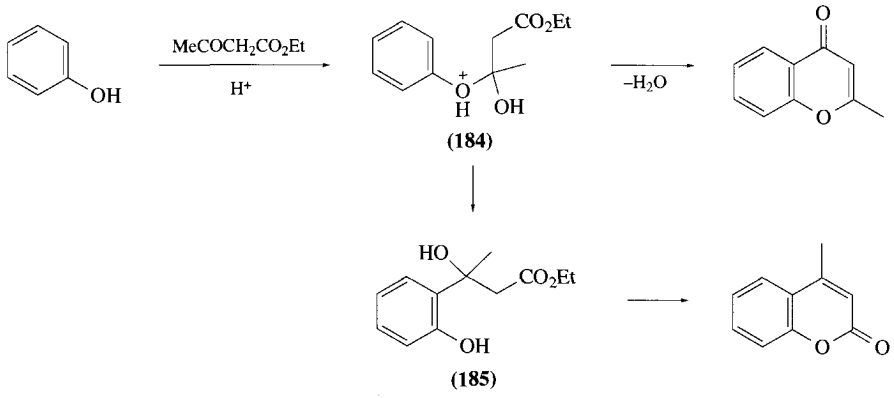
The synthesis of chromones from phenols is considered in this section despite the possible involvement of a Fries rearrangement, with the implication that the formation of the bond adjacent to the heteratom is the critical step.

The Simonis reaction ⟨53OR(7)1⟩ involves the reaction of a phenol with a 3-keto ester and is closely allied to the Pechmann synthesis of coumarins (see Section 5.08.14.1.1). Unfortunately, the initially formed ester can cyclize to either a chromone or a coumarin and in many cases both benzopyranones are formed. Various rules of thumb have been invoked to predict the likely product, but many exceptions to these rules have been noted. Whilst phosphorus pentoxide does generally improve the rather moderate yields achieved when sulfuric acid is used as the cyclizing agent, it does not always lead to a chromone as suggested. In the absence of a condensing agent, a fast thermal cyclization often leads to the chromone rather than the coumarin ⟨52BSF91, 57LA(603)169⟩.

The mechanisms of the Simonis and Pechmann reactions are still a matter of controversy, though a common intermediate oxonium ion (**184**) has been proposed. Dehydration to the phenoxyacrylic ester is followed by cyclization to the chromone, whilst the intervention of a Fries rearrangement leads to the substituted phenol (**185**) and thence to the coumarin (Scheme 132) ⟨50BSF1132, 54JCS854⟩. However, the formation of a chromone or a coumarin may simply be a consequence of preferential *O*-alkylation or *C*-alkylation, which is often subject to subtle changes in reaction conditions. Fortunately, the reliable differentiation of the two products by spectroscopic methods ensures that few, if any, errors in structural assignments are made, but care is needed in the interpretation of results from early work.

The reaction of a phenol with an unsaturated carboxylic acid ester is a useful route to chromone-2-carboxylic acids which is compatible with a wide range of substituents on the phenolic component. However, once again both chromones and coumarins can be formed and minor changes in the reaction conditions can alter the course of the reaction ⟨54LA(587)16, 57LA(605)158, 79SC129⟩. As illustration, 4-bromophenol yields a coumarin on reaction with dimethyl acetylenedicarboxylate in the presence of benzyltrimethylammonium hydroxide and subsequent hydrolysis and acid catalyzed cyclization. However, the use of $Bu_4N^+F^-$ in a similar sequence leads to a chromone ⟨87JCS(P1)2597⟩.

β-(Aryloxy)arylidenemalonates are a source of flavone-3-carboxylic acids and their esters. Cyclization with PPA affords the latter, whilst their hydrolysis prior to cyclization in H_2SO_4 or $(CF_3CO)_2O$ gives the acids ⟨87JOC5272⟩.



Scheme 132

5.08.16.2 From Other Heterocycles

5.08.16.2.1 From furans

Irradiation of 5-aryl-3*H*-furan-2-ones using a medium pressure mercury lamp leads to 2,3-dimethylchromones in benzene, but to the 3-ethoxycarbonylmethyl derivatives in ethanol solution ⟨81T2111, 81TL1749⟩.

The furan ring of the *O*-tosyl derivative of 2-acetylbenzofuran oxime is cleaved on treatment with an alcohol. Subsequent recyclization affords the chromone together with 2-coumaranone and a chromanone ⟨49JA2652⟩.

5.08.16.2.2 From isoxazoles

Reduction and hydrolysis of 3,5-diarylisoxazoles leads to flavones. The 2,8-diarylpyrano[3,2-*g*]chromene-4,6-diones have been similarly obtained ⟨94ACS61, 94ACS165⟩.

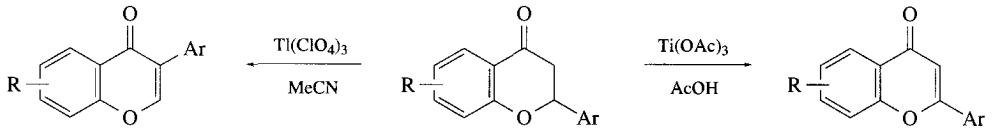
5.08.16.3 From a Preformed Heterocyclic Ring

The synthesis of chromones from other *O*-heterocycles is not commonly attempted because of their easy access from acyclic precursors. However, this approach can be helpful in preparing unusually substituted chromones and is of value in flavone and isoflavone synthesis.

5.08.16.3.1 From chroman-4-ones

The 2,3-double bond can be introduced into chromanones by dehydrogenation using Pd-C ⟨74CR(C)151⟩ and SeO_2 ⟨65JCS2743⟩, though neither reagent is totally reliable. DDQ is considered to effect the oxidation by an electron transfer process ⟨87S199⟩ and the photosensitized dehydrogenation using 2,4,6-triphenylpyrylium tetrafluoroborate probably proceeds in a similar manner ⟨89H(29)115⟩. Various oxidizing agents promote the conversion, of which DMSO-I_2 alone or in the presence of sulfuric acid appears to be particularly efficient ⟨91IJC367⟩. Thallium(III) salts and hypervalent iodine reagents are also effective, flavanones affording quantitative yields of flavones on treatment with $Tl(OAc)_3$ in AcOH ⟨92JCS(P1)2565, 95JCR(S)213⟩. Other thallium(III) salts bring about the oxidation, but may also cause a rearrangement of the flavanone to an isoflavone (Scheme 133). Examples include $Tl(NO_3)_3$ ⟨90TL7355⟩, thallium(III) *p*-toluenesulfonate ⟨92JCS(P1)2565⟩, and thallium(III) perchlorate ⟨93IJC911⟩. The last reagent succeeds even when the 2-aryl group contains electron withdrawing substituents (Scheme 133). This 1,2-aryl shift has also been observed when PhI(OH)OTs or iodosobenzene is used as the oxidant ⟨90S337, 95JCR(S)213⟩. The flavanone → isoflavone conversion can also be achieved by isoflavone synthase, a P-450 iron-containing enzyme ⟨92TL3663⟩. Both chemical and enzymatic induced rearrangements are considered to proceed via a spiro intermediate in which the initial 2-aryl substituent bridges the C-2 and C-3 sites. In an

interesting extension of these reactions, 2-spiroannulated chroman-4-ones are oxidatively rearranged to tetrahydroxanthones by TTN ⟨91TL5619⟩.



Scheme 133

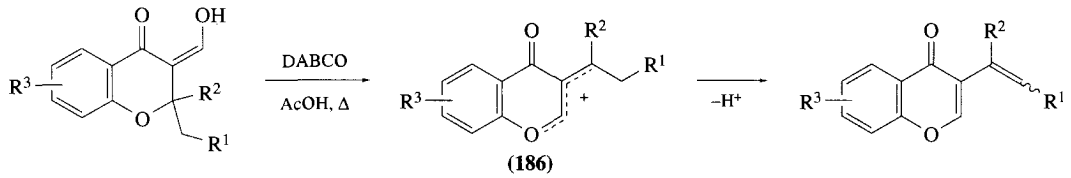
3-Arylideneflavanones are converted to 3-aroylflavones ⟨90BSF656⟩ and 3-benzylidenechroman-4-ones undergo an exocyclic → endocyclic bond transposition on treatment with rhodium chloride in ethanol ⟨77JCS(P1)1359⟩.

Dehydrohalogenation of 3-bromo- ⟨51JA4205⟩, 2,3-dibromo- ⟨58BSF329⟩, 3,3-dibromo- ⟨71AP(304)543⟩, and 3-chloro-3-nitro- ⟨95TL1845⟩ chroman-4-ones yields chromones, whilst flavones can be similarly obtained from 3-bromoflavanones ⟨59JOC567, 91JHC1047⟩. Dehydrogenation of chromanones is readily achieved by heating them with pyrrolidone hydrotribromide in DMSO, presumably via bromination α to the carbonyl function ⟨90JOC6161⟩.

3-Nitroflavones are produced by the dehydrochlorination of 3-chloro-3-nitroflavanones, readily available by the sonic-assisted PCC oxidation of flavanols ⟨92S677⟩.

Chromanone hemiacetals are converted into 2-methylchromones on acidic hydrolysis ⟨88H(27)1159⟩ and methanolic NaOH converts 2-(2-furyl)-3-hydroxychromanone into 2-(2-furyl)-3-hydroxychromone ⟨92SC327⟩.

2-Substituted derivatives of 3-hydroxymethylenechroman-4-ones undergo an acid-base catalyzed ring opening–ring closure sequence giving 3-alkenylchromones. It is proposed that a retro-Michael reaction is followed by ring closure and dehydration to give the carbocation (**186**), which may be intercepted by solvent (Scheme 134) ⟨85TL1879⟩.



(**186**)

Scheme 134

Various 3-substituted chroman-4-ones can be arylated at C-3 by aryllead(IV) triacetates. Subsequent oxidation with dimethyldioxirane or a palladium-catalyzed oxidative decarboxylation results in loss of the 3-substituent and formation of isoflavones in good yields ⟨93JCS(P1)1729, 93T7967⟩.

5.08.16.3.2 From chromenes

Oxidation of the 3-nitroflavenes with alkaline hydrogen peroxide gives the 3-hydroxyflavone ⟨84H(22)1943, 85BCJ3665⟩.

5.08.16.3.3 From coumarins

Nucleophilic attack of 4-methoxycoumarin leads to chromones with the incorporation of the nucleophilic moiety at C-2 ⟨78S208⟩.

5.08.16.3.4 From benzopyrylium salts

4-Alkoxybenzopyrylium salts are hydrolyzed to chromones, providing a facile route to 3-substituted chromones from 2-hydroxyphenacyl derivatives and triethyl orthoformate, whilst with

triethyl orthoacetate 2-methylchromones result ⟨90JCS(P1)418⟩. Flavylium salts yield flavones on oxidation by thallium(III) nitrate in methanol, probably via nucleophilic attack by the solvent ⟨68TL3859⟩.

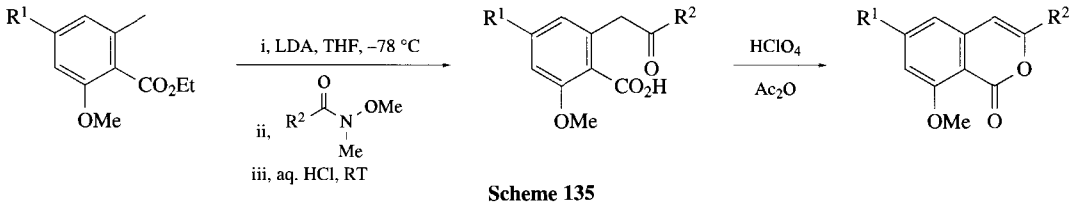
5.08.17 ISOCOUMARINS (1*H*-2-BENZOPYRAN-1-ONES)

5.08.17.1 Formation of One Bond

5.08.17.1.1 Adjacent to the heteroatom

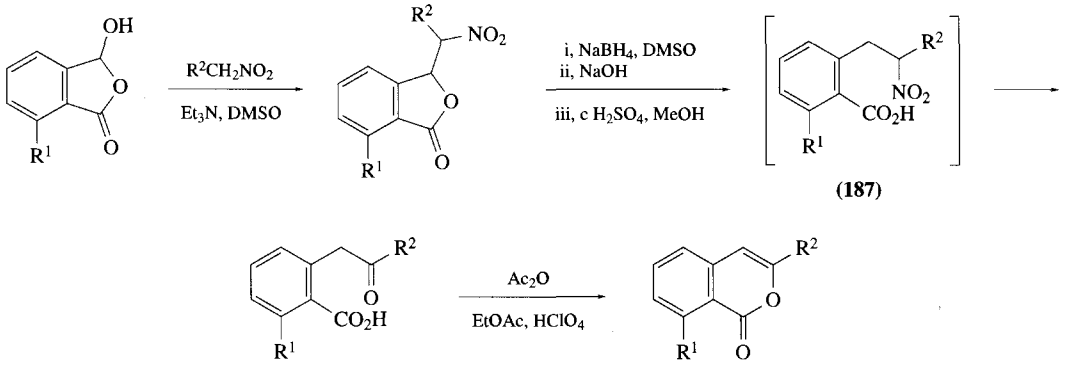
The cyclization of 2-carboxybenzyl ketones and related compounds features in several isocoumarin syntheses.

Acylation of the anion derived from 2-methylbenzoates by *N*-methoxy-*N*-methylamides gives the keto acids or the derived esters, depending on the work-up procedure, both of which cyclize to the isocoumarin (Scheme 135) ⟨86S945⟩. In a similar manner, acylation with diethyl oxalate and subsequent cyclization gives isocoumarin-3-carboxylates ⟨89H(28)71⟩.



Scheme 135

The 2-(nitroalkyl)benzoic acids (**187**), available from phthalaldehydic acids and nitroalkanes, undergo a Nef reaction to give the keto acids which are cyclized under acidic conditions. The whole sequence can be reduced to two steps, principally by not isolating the nitro- and keto-acids (Scheme 136) ⟨88JOC4676⟩.

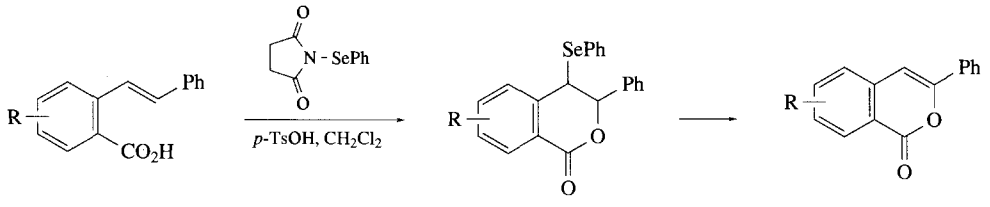


(187)

Scheme 136

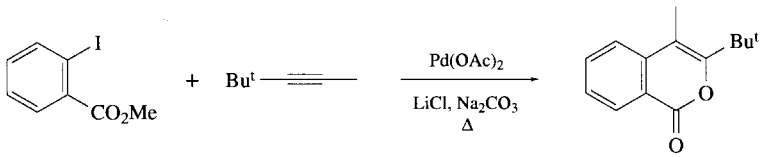
2-Styrylbenzoic acids are converted into the isocoumarin via the phenylseleno derivative. Although the product of selenolactonization, the dihydroisocoumarin, is formed, it spontaneously eliminates the phenylseleno moiety (Scheme 137) ⟨94JHC145⟩.

A number of isocoumarin syntheses are based on palladium-catalyzed coupling reactions. Methyl



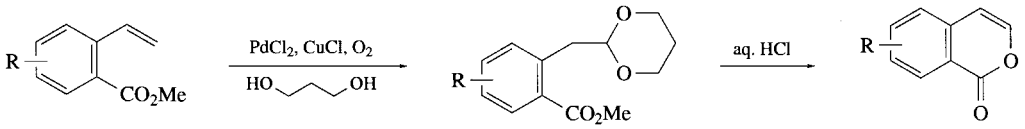
Scheme 137

2-iodobenzoate reacts with a variety of internal alkynes to form isocoumarins in good yields. The aryl moiety adds to the less hindered *sp* carbon atom (Equation (97)) ⟨95JOC3270⟩. Terminal alkynes give isocoumarins from 2-iodobenzoic acid only when the palladium-coupling process is mediated by $ZnCl_2$; otherwise the phthalide is formed ⟨95JOC3711⟩.



(97)

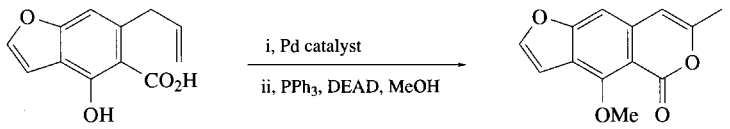
Methyl 2-ethenylbenzoates yield the acetal (**188**) following a palladium-catalysed, Cu(I) mediated oxidation. Treatment with acid furnishes the isocoumarin (Scheme 138) ⟨90JHC1419⟩.



(**188**)

Scheme 138

A total synthesis of the furoisocoumarin, coriandrin (**189**), involves palladium-catalysed cyclization of the acid to the alkene followed by a Mitsunobu reaction to produce the methyl ether (Equation (98)) ⟨94JOC4735⟩.

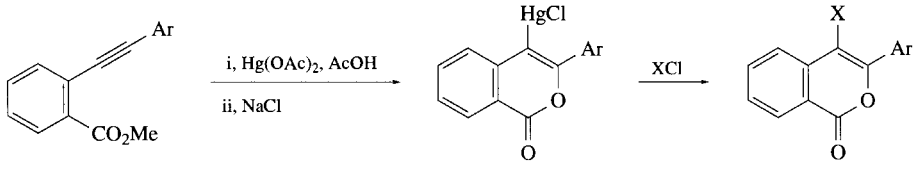


(98)

(**189**)

2-Alkynylbenzoates also undergo a mercury-mediated cyclization to isocoumarins. The initial product (**190**) provides access to a good variety of 4-substituted isocoumarins (Scheme 139) ⟨87IJC917⟩.

The oxidation of indanones to isocoumarins can be achieved with ozone ⟨89JOC4218⟩ and by way of a hydroperoxide rearrangement ⟨91JCS(P1)89⟩.

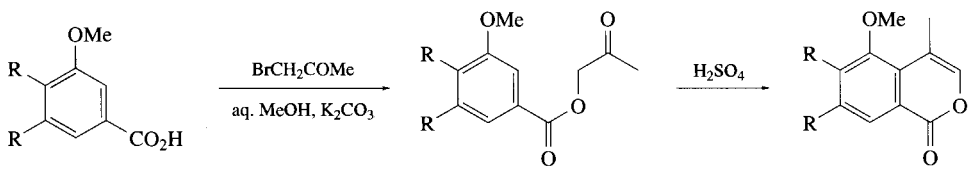


(**190**)

Scheme 139

5.08.17.1.2 γ to the heteroatom

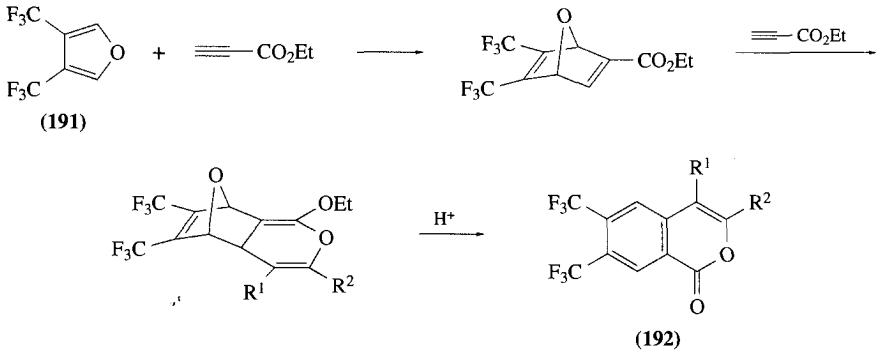
Esterification of substituted benzoic acids with bromoacetone and cyclization of the acetonyl ester affords isocoumarins (Scheme 140) ⟨85JHC383⟩.



Scheme 140

5.08.17.2 From Other Heterocycles

The furan (**191**) reacts with ethyl propynoate to give a mixture of the isocoumarin-3-carboxylate (**192**; $R^1 = H$, $R^2 = CO_2Et$) and its 4-isomer (**192**; $R^1 = CO_2Et$, $R^2 = H$). A double Diels–Alder sequence is proposed, followed by an acid catalyzed cleavage of the oxygen bridge (Scheme 141) ⟨92JFC359⟩.



Scheme 141

5.08.17.3 From a Preformed Heterocyclic Ring

5.08.17.3.1 From isochromanones

Bromination of isochroman-1-ones with NBS followed by dehydrobromination on heating with triethylamine or pyridine affords isocoumarins ⟨88JIC685, 88JOC4676⟩. Elimination of methanol from a 3,4-dihydro-3-methoxyisocoumarin is readily achieved under acidic conditions ⟨95G111⟩.

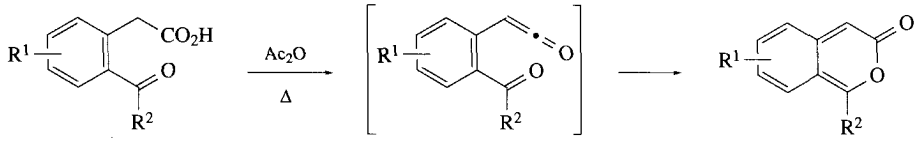
5.08.18 3*H*-2-BENZOPYRAN-3-ONES

Although 3*H*-2-benzopyran-3-one cannot be isolated and is best regarded as a reactive intermediate, for the sake of completeness methods used for its generation are included here. Several derivatives of the parent system are stable and have been fully characterized.

5.08.18.1 Formation of One Bond

5.08.18.1.1 Adjacent to the heteroatom

Generation of 2-benzopyran-3-ones is readily achieved by the dehydration of *o*-acylphenylacetic acids, normally accomplished by heating with acetic anhydride (Scheme 142) ⟨70JCS(C)536⟩. Indeed, the yellow color of 2-formylphenylacetic acid solutions in acetic anhydride is attributed to the formation of the benzopyranone.



Scheme 142

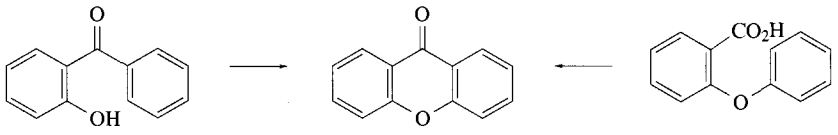
The pyranone is stabilised by electron releasing substituents and the 6- and 7-methoxy, 6,7-dimethoxy, and some 6,7-methylenedioxy derivatives have been isolated as yellow crystalline solids ⟨91JCS(P1)169⟩.

An improved method of generation uses 1,3-dicyclohexylcarbodiimide to effect the dehydration.

Rearrangement of the intermediate *o*-acyl isourea derivative is prevented by the addition of 2-pyridone in catalytic quantities. Under these mild conditions, 2-benzopyran-3-ones have been isolated and the formation of by-products substantially reduced ⟨91JCS(P1)639⟩.

5.08.19 XANTHONES (9*H*-DIBENZO)[*b*,*e*]PYRAN-9-ONES)

Xanthones are widely distributed in nature ⟨61CRV591⟩ and consequently synthetic routes to them are well established. Interest has been recreated as a result of the pharmacological activity of xanthone based antibiotics. Only two methods of synthesis are of any significance, involving ring closure on to either the hetero oxygen atom or the carbon atom of the carbonyl group (Scheme 143).



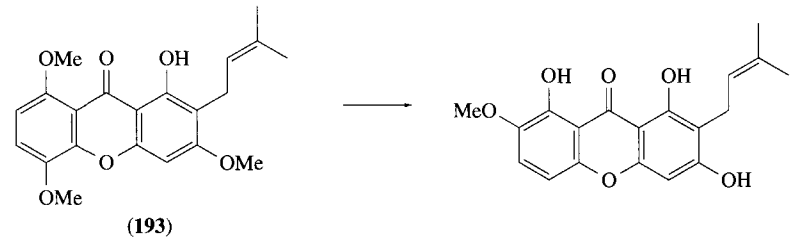
Scheme 143

5.08.19.1 Formation of One Bond

5.08.19.1.1 Adjacent to the heteroatom

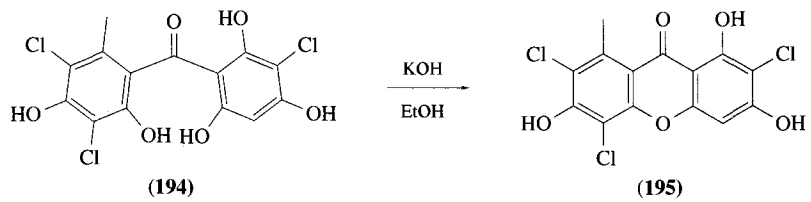
A number of xanthone syntheses are based on the cyclization of 2-hydroxybenzophenones. A 2′-substituent is not essential for success, but a good leaving group in that position facilitates the ring closure.

The Friedel–Crafts acylation of phenols with salicyclic acids leads to 2,2′-dihydroxybenzophenones, which under acid conditions or even spontaneously are cyclized to the xanthone derivative. The reaction conditions can influence the nature of the product ⟨55JCS3982⟩ and there is some evidence that the cyclization process may be reversible. For instance, the 1,3,5,8-tetraoxygenated xanthone (**193**) gives the 1,3,7,8-derivative when treated with hot aqueous morpholine. A ring opening–demethylation–recyclization sequence is probably the mechanism of the rearrangement (Equation (99)) ⟨89TL7265⟩. A high temperature, base catalyzed cyclization of dihydroxybenzophenones has been advocated, leading to enhanced yields of xanthones ⟨75CJC2054⟩. This mode of cyclization has been applied to the pentahydroxybenzophenone (**194**) which undergoes a selective transformation to 2,5,7-trichloronorlichexanthone (**195**), a lichen metabolite. The selectivity is attributed to differing strengths of intramolecular hydrogen bonds (Equation (100)) ⟨90AJC1291⟩.



(99)

(193)



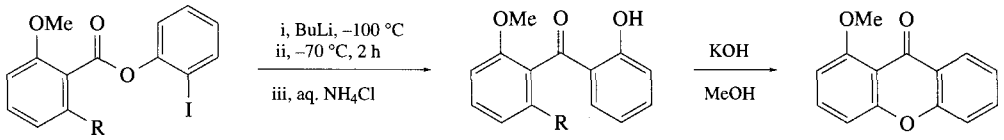
(100)

(194) (195)

Acylation of methoxybenzenes by aroyl chlorides is a reliable route to 2-hydroxy-2′-methoxybenzophenones. The initial acylation is followed by selective demethylation of the most electron-rich *ortho* ether function. Cyclization under basic conditions leads to high yields of xanthones and is considered to involve Michael addition of the phenoxide ion to the neighboring ring and subsequent loss of methoxide ⟨73JCS(P1)1329⟩. This approach has been utilized in total syntheses of the xanthone antibiotics, cervinomycin A_1 and A_2 ⟨94T11729⟩. Sodium trimethylsilanethiolate, Me_3SiSNa, has been used to demethylate and cyclize dimethoxybenzophenones ⟨94TL3545⟩.

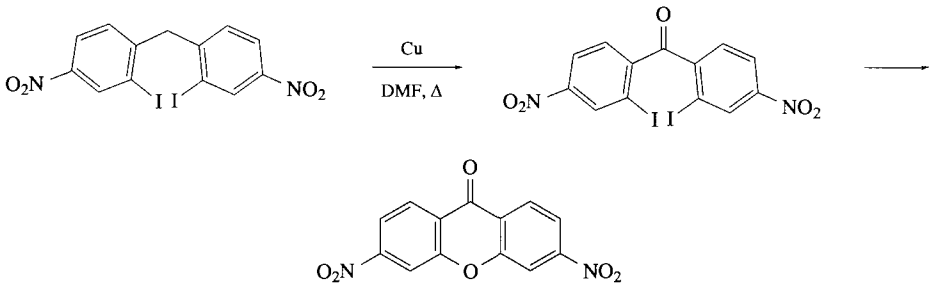
Displacement of chloride ion during the base catalyzed cyclization of 2-chloro-2′-methoxy- and 2-chloro-2′-hydroxybenzophenones has been observed ⟨92JOC5532⟩. The benzophenone is obtained from the reaction of 2-methoxyphenylmagnesium bromide with 3,6-dichlorophthalic anhydride.

The anionic Fries rearrangement features in syntheses of some naturally occurring xanthones, but is only really viable when a methoxy group is adjacent to the ester carbonyl group, implying the operation of a complex induced proximity effect (Scheme 144). The value of fluoride ion as a leaving group during cyclisation (R = F) is noted ⟨90JOC4520⟩.



Scheme 144

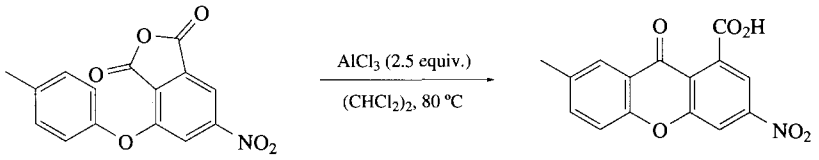
Bis (2-iodo-4-nitrophenyl)methane undergoes both oxidation to the benzophenone and cyclization to 3,6-dinitroxanthone on reaction with copper powder in boiling DMF. Copper catalyzed radical formation is probably involved in both steps (Scheme 145) ⟨93SC231⟩. Radicals are also invoked in the formation of xanthones by the irradiation of aromatic 1,2-diketones ⟨93MI 508-03⟩.



Scheme 145

5.08.19.1.2 γ to the heteroatom

The synthesis of a wide variety of xanthones has been achieved by the cyclodehydration of *o*-phenoxybenzoic acids (Scheme 143). Intramolecular acylation of the ether is accomplished in concentrated sulfuric acid ⟨89JA4522, 93SC2677, 94JA3680⟩, acetic anhydride containing H_2SO_4 ⟨94JPR429⟩, polyphosphoric acid ⟨92H(33)219, 93RTC376⟩, trifluoroacetic anhydride ⟨89SC2001⟩, *p*-TsOH ⟨91JMC2864⟩, and methanesulfonic acid ⟨92TL7437⟩. The phthalic anhydride is cyclized to the xanthone in the presence of an excess of $AlCl_3$ (Equation (101)) ⟨85HCA854⟩.



(101)

(196)

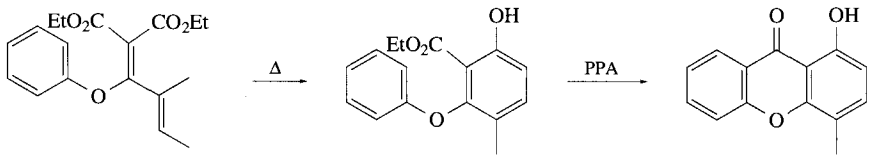
The phenoxybenzoic acids derived from *m*-substituted phenols can cyclize to give two isomeric xanthones. Whilst no systematic study has been carried out, it does appear that electron-withdrawing

substituents at the 3′-position promote cyclization at C-2′, whilst donor substituents lead to *para* cyclization ⟨58JCS4227⟩.

o-Aryloxybenzaldehydes also function as precursors of xanthones, undergoing a radical initiated cyclization when heated with copper(II) halides ⟨76JCS(P1)2241⟩. In a related fashion, the *o*-acylation of diaryl ethers provides a route to xanthones, although it is necessary to prevent acylation at the *para* position ⟨73JOC841, 74JOC2088⟩.

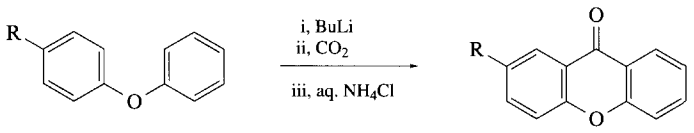
The pyrolysis of phenyl salicylate is a reliable route to xanthone ⟨41OSC(1)552⟩; the use of a high boiling solvent offers advantages in the synthesis of fused xanthones ⟨79JHC1663⟩.

A synthesis of 1-hydroxyxanthones which allows the regioselective introduction of a methyl group into the 4-position is based on the cyclization of the aryloxysalicylates. These compounds are readily derived from the thermolysis of the aryloxymethylenemalonates (Scheme 146) ⟨93TL6463⟩.



Scheme 146

The dimetallation of diphenyl ethers and subsequent carbonation with CO_2 leads directly to xanthones (Equation (102)) ⟨94JCR(S)82⟩.

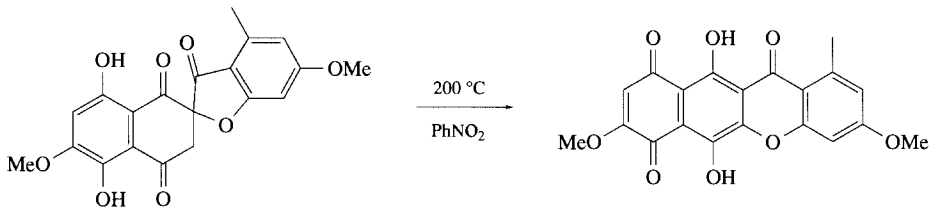


(102)

5.08.19.2 From Other Heterocycles

5.08.19.2.1 From benzofurans

A synthesis of bikaverin involves the pyrolytic isomerization of a spirobenzofurantrione (Equation (103)) ⟨88JCS(P1)3209⟩.



(103)

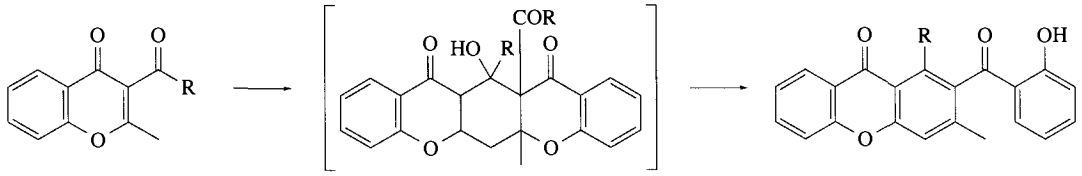
5.08.19.3 From a Preformed Heterocyclic Ring

5.08.19.3.1 From chromones

3-Acylchromones undergo a base catalyzed self condensation, the ultimate products of which are xanthones. An initial Michael addition is followed by a cyclization to the pentacyclic species (**197**) which then aromatizes with concomitant opening of the pyran ring (Scheme 147) ⟨93T4127⟩.

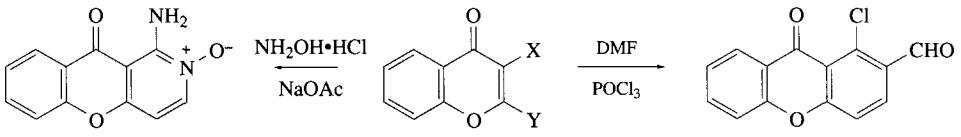
Both the chromone (**198**; X = Ac, Y = Me) and the derived enamine (**198**; X = Ac, Y = CH=CHNMe$_2$) afford xanthones in a Vilsmeier–Haack reaction ⟨93T4127⟩. The related enamines (**198**; X = CN, Y = CH=CHNMe$_2$) are a source of benzopyrano[3,2-*c*]pyridine derivatives (Scheme 148) ⟨89IJC448⟩.

Chromones react with the anion derived from (phenylsulfonyl)isobenzofuranones to give benzo[*b*]xanthones from which bikaverin was readily obtained (Equation (104)) ⟨88JOC223⟩.



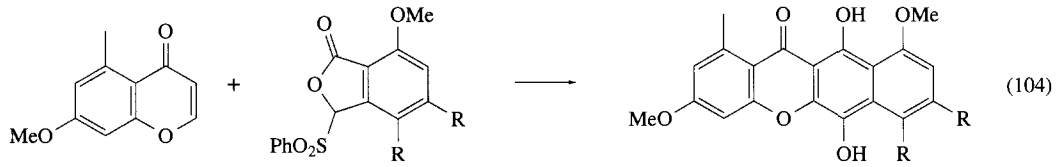
(196) (197)

Scheme 147



(198)

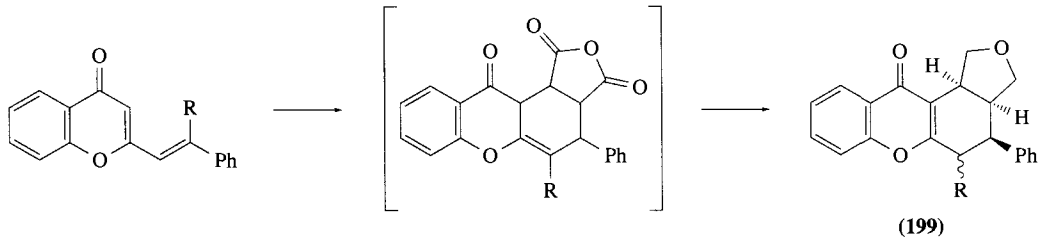
Scheme 148



(104)

The cycloaddition reaction between chromones and α,β-unsaturated ketones leads to partially reduced xanthones in excellent yields when catalyzed by *t*-butyldimethylsilyl triflate. A benzopyrylium salt is an intermediate ⟨89H(29)35⟩.

The Diels–Alder reaction between (*E*)-2-styrylchromones and maleic anhydride affords 1,2,3,4-tetrahydroxanthones (**199**). The initial cycloaddition is followed by a 1,3-hydrogen shift which restores the stable chromone subunit (Scheme 149) ⟨92JCR(S)248⟩. In a similar manner, 1-pyrrolidinylcyclopentene gives a xanthone (**202**) by way of an inverse electron demand Diels–Alder reaction and sigmatropic rearrangement ⟨92CC1310⟩. Replacement of the styrylchromone with a precursor, the pent-4-ene-1,3-dione (**200**), leads to the same product (**202**). However, this too is formed by rearrangement of the cyclopenta[*a*]xanthone (**201**) brought about by base ⟨93CC159⟩.

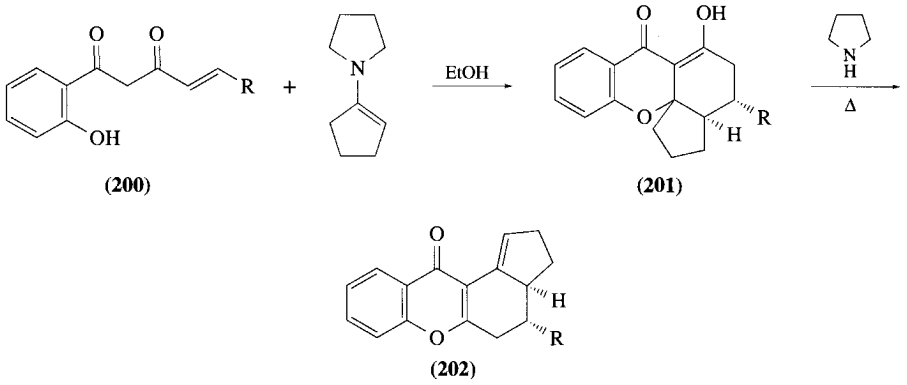


(199)

Scheme 149

5.08.19.3.2 From xanthenes

Xanthenes are oxidized to the thiones on heating with sulfur and subsequent hydrolysis affords xanthones ⟨45JCS858⟩. Oxidation of a benzo[*b*]xanthene to the xanthone by CrO_3 features in a synthesis of bikaverin ⟨92TL2805⟩. Other frequently used oxidants include Jones reagent ⟨89F547⟩, ceric ammonium nitrate ⟨94SC659⟩ and manganese(III) acetate ⟨92JOC3551⟩.



Scheme 150

5.08.20 REDUCED PYRANONES

The compounds discussed in this section include dihydropyranones, tetrahydropyranones and their benzologues, dihydrocoumarins, chromanones and isochromanones. Interest in this area stems from their occurrence in nature both as individual compounds and as part of larger molecules.

5.08.21 DIHYDROPYRAN-2-ONES

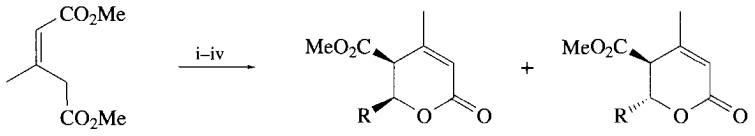
5.08.21.1 Formation of One Bond

5.08.21.1.1 Adjacent to the heteroatom

Lactonization as exemplified in Equation (105) provides a route to 5,6-dihydropyran-2-ones, unsaturated δ-lactones, and the various syntheses differ mainly in the route to the precursor.

(105)

A one-pot synthesis is based on a directed aldol condensation involving the reaction of aldehydes with dimethyl 3-methylpent-2-enedioate (Scheme 151). Careful choice of conditions allows spontaneous cyclization and prevents opening of the lactone ring. Both diastereoisomers are usually obtained, with a marked preference for the *syn* configuration although when R is Ph or Bu^t the *anti* product is obtained exclusively ⟨93SL507⟩.



i, $(TMS)_2NLi$, THF, –30 °C; ii, $ZnCl_2$, 4Å molecular sieves; iii, RCHO, –30 to –10 °C, 5 h; aq. NH_4Cl, –40 °C

Scheme 151

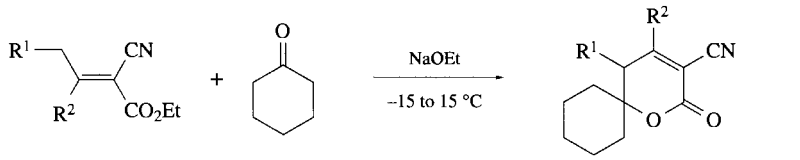
The aldol products derived from β-keto esters and aldehydes and ketones are δ-hydroxy-β-keto esters and these are readily lactonized to 5,6-dihydro-4-hydroxypyran-2-ones. Using similar methodology, 1,3-diketones afford δ-hydroxy-β-diketones which are cyclized under acidic conditions to 5,6-dihydropyran-4-ones ⟨88SC949⟩.

Alkynic compounds feature in several examples of chiral dihydropyran-2-one syntheses, being partially reduced to the alkene to provide the key intermediate, a 5-hydroxypent-2-enoic acid or ester ⟨78LA337, 89S539, 92TA533⟩.

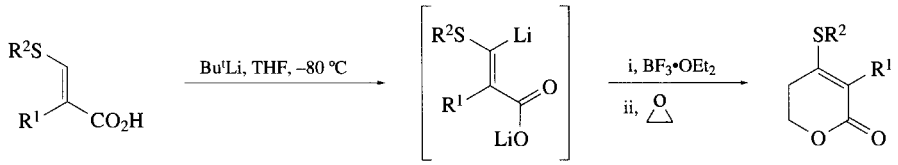
The formation of dihydropyranones by the palladium-assisted lactonization of alkenoic acids is strongly dependent on the solvent and base used. Thus, using NaOAc in THF, the 3,4-dihydro-

pyranone is formed exclusively, but under other conditions the regiospecificity is lost and furanones are also poduced ⟨93TL8545⟩.

Reaction of cyclohexanone with the anions derived from ethyl 2-cyanoalk-2-eneoates leads directly to spiroannulated 3-cyanodihydropyran-2-ones (Equation (106)) ⟨84S1075⟩, whilst the carbanion derived from 3-alkylthio- and 3-arylthio-prop-2-enoic acids reacts with epoxides in the presence of a Lewis acid to give 4-thio derivatives of dihydropyranones (Scheme 152) ⟨86S1067⟩.



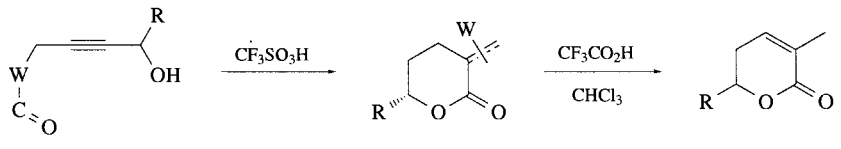
(106)



Scheme 152

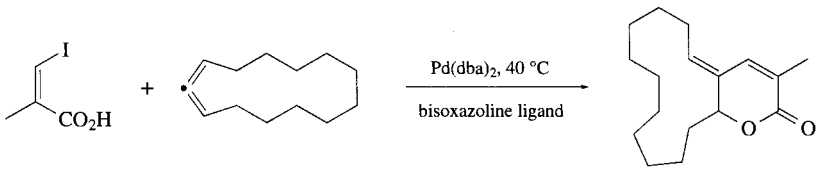
Cyclocarbonylation reactions have been utilized in the synthesis of dihydropyran-2-ones. The stereocontrolled synthesis of tungsten η^3-δ-lactones from the alkynols (**203**) is high yielding and the metal is easily removed (Scheme 153) ⟨95JA2933⟩.

In the presence of a chiral ligand, allenes undergo an asymmetric palladium-catalyzed annulation and 3-iodo-2-methylprop-2-enoic acid affords the fused pyran-2-one (**205**) on reaction with allene (**204**) (Equation (107)) ⟨95JOC482⟩.



(**203**)
W = CpW(CO)$_2$

Scheme 153

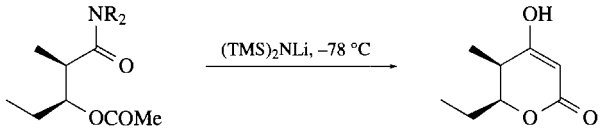


(107)

(**204**) (**205**)

5.08.21.1.2 β to the heteroatom

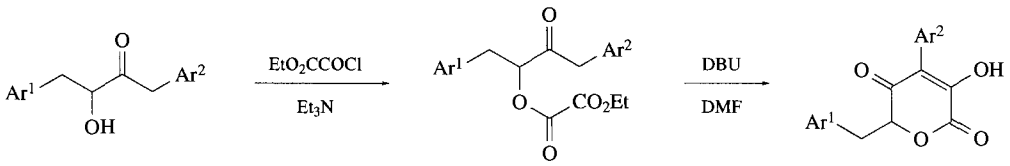
An intramolecular Claisen condensation involving β-acetoxy amides leads to 4-hydroxy-5,6-dihydropyran-2-ones. The use of a chiral auxiliary as part of the amide moiety gives an enantiomerically pure product (Equation (108)) ⟨92TL3025⟩.



(108)

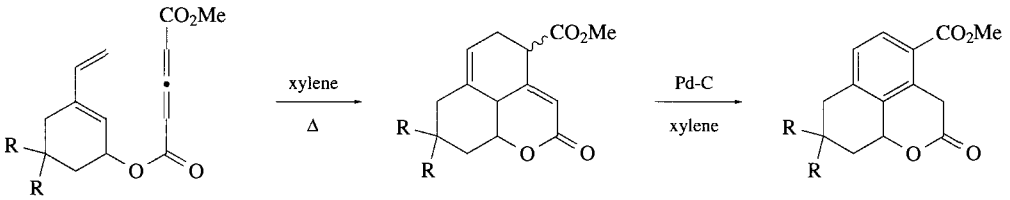
5.08.21.1.3 γ to the heteroatom

Benzylacyloins are suitable precursors for the synthesis of the fungal pigments, the grevillins. Conversion to the oxalate precedes ring closure to the dihydrogrevillins (Scheme 154) ⟨91JCS(P1)2363⟩.



Scheme 154

The allenic esters (**206**) undergo an intramolecular [4 + 2] cycloaddition during which the fused dihydropyranone (**207**) is formed. These products are readily aromatized to the fused isochroman-3-one (Scheme 155) ⟨88JA1232⟩.



(**206**) (**207**)

Scheme 155

Phosphonates derived from β-keto esters undergo an intramolecular Wadsworth–Emmons reaction on treatment with DBU to yield 5,6-dihydropyran-2-ones ⟨92TL2375, 94TL3753⟩.

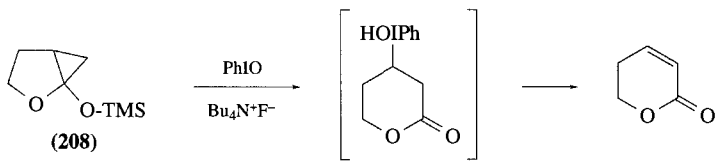
5.08.21.2 Formation of Two Bonds

High optical purities are observed when the cycloaddition of electron-rich dienes to aldehydes is mediated by a chiral boron complex derived from a tartaric acid derivative and phenylboronic acid ⟨94T979⟩, whilst with α-alkoxyaldehydes good yields of 6-substituted 5,6-dihydropyran-2-ones result under the influence of a Lewis acid. Only moderate diastereoselectivity results ⟨90JOC5058⟩.

5.08.21.3 From Other Heterocycles

5.08.21.3.1 From furans

Oxidation of the fused furan derivative (**208**) results in ring expansion to the 5,6-dihydropyran-2-one (Scheme 156) ⟨90TL197⟩.

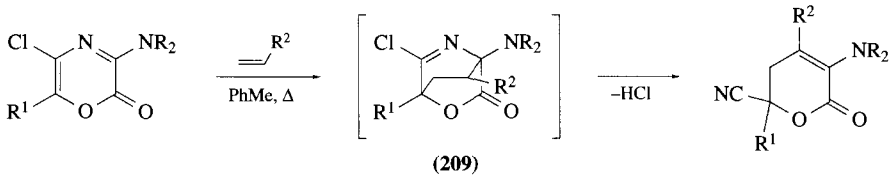


(**208**)

Scheme 156

5.08.21.3.2 *From oxazines*

The cycloadduct (**209**) from 3-amino-2*H*-1,4-oxazin-2-ones and alkenes undergoes a ring transformation by cleavage of the C—N bond, so providing a route to 2-oxopyran-6-carbonitriles (Scheme 157) ⟨92TL2049⟩.



(**209**)

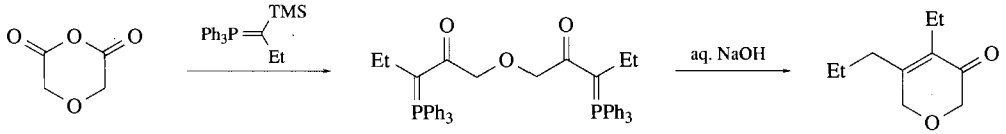
Scheme 157

5.08.22 DIHYDROPYRAN-3-ONES

5.08.22.1 Formation of One Bond

5.08.22.1.1 *γ to the heteroatom*

The phosphorane (**211**) derived from the anhydride (**210**) forms the 2,6-dihydropyran-3-one on basic hydrolysis (Scheme 158) ⟨93CB725⟩.



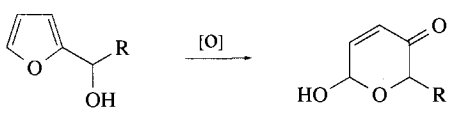
(**210**) (**211**)

Scheme 158

5.08.22.2 From Other Heterocycles

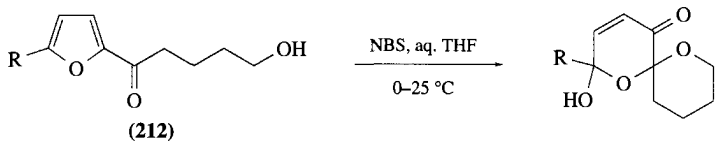
5.08.22.2.1 *From furans*

The oxidative ring expansion of furyl carbinols to 6-hydroxypyran-3(6*H*)-ones has been reviewed (Equation (109)) ⟨92OPP95⟩. Commonly used oxidants include Br_2/MeOH ⟨76T1051⟩, *m*-CPBA ⟨88JHC995, 89H(28)59, 89TL2885, 89TL3197, 90JCS(P1)1733, 92JA1438⟩, pyridinium chlorochromate ⟨89TL3141⟩, *N*-bromosuccinimide ⟨89JOC2044, 94JCS(P1)2091⟩, and *t*-butyl hydroperoxide ⟨89H(29)1247, 95CC743⟩. The mixed reagent iodobenzene diacetate/$Mg(ClO_4)_2$ in aqueous hexafluoropropan-2-ol is particularly effective and involves a radical cation in the single electron transfer process ⟨95TL3553⟩.

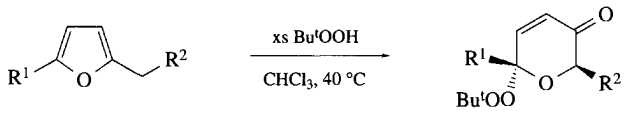


(109)

NBS converts the δ-hydroxyketofuran (**212**) into the spiroketal (Equation (110)) ⟨89JOC2044⟩ and the acid catalyzed oxidation of 2,5-dialkylfurans using an excess of Bu^tOOH gives good yields of 6-*t*-butylperoxy-*cis*-2,6-dialkylpyran-3-ones (Equation (111)) ⟨93TL7089⟩.



(110)

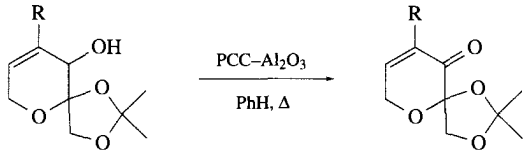


(111)

5.08.22.3 From a Preformed Heterocycle

5.08.22.3.1 From pyrans

Several enantiomerically pure dihydropyran-3-ones have been conveniently prepared from fructose derivatives. Oxidation of the pyran-3-ol (**213**) to the pyranone has been achieved with pyridinium chlorochromate (Equation (112)) ⟨85LA2454⟩.



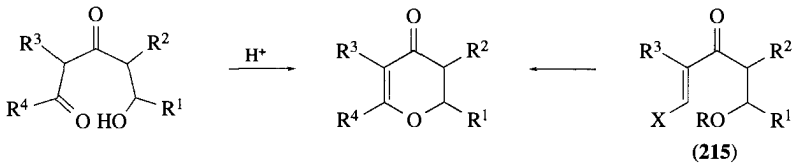
(112)

5.08.23 DIHYDROPYRAN-4-ONES

5.08.23.1 Formation of One Bond

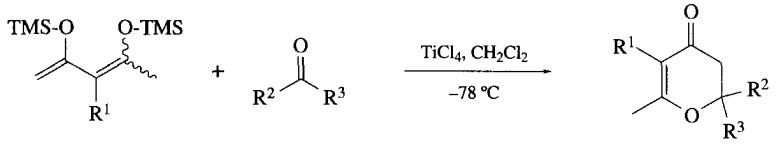
5.08.23.1.1 Adjacent to the heteroatom

The acid-catalyzed cyclization of 5-hydroxy-1,3-dione derivatives leads to dihydropyran-4-ones with good stereocontrol (Scheme 159). Syntheses of the acyclic precursors include the acylation of 1,2-keto acids ⟨86T5281⟩ and esters ⟨87JCR(S)302, 88G699⟩ and of a 2-pyrazolin-5-one ⟨83S844⟩. Epoxides ⟨81T709, 85TL1319⟩ and ozonides ⟨93SC87⟩ feature in multistage syntheses of pheromones.



Scheme 159

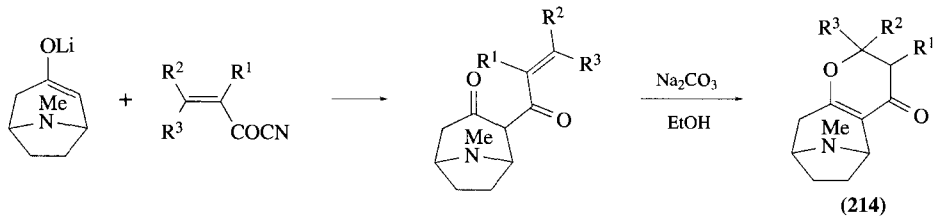
2,4-Bis(trimethylsilyloxy)penta-1,3-dienes function as masked β-keto dianions and condense with carbonyl compounds under Mukaiyama conditions. Cyclization is effected with TFA ⟨85JA1256⟩ or occurs spontaneously when an excess of $TiCl_4$ is used (Equation (113)) ⟨90SL394⟩.



(113)

C-Acylation of a tropinone enolate using unsaturated acyl cyanides provides the acyclic precursors

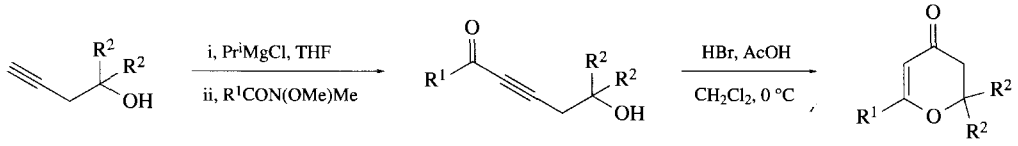
of the pyranotropane system (**214**) from which some tropane alkaloids can be obtained (Scheme 160) ⟨95JOC5825⟩.



(214)

Scheme 160

Acetylenic ketones are cyclized to dihydropyran-4-ones on treatment with acid, presumably through hydrolysis of the alkyne moiety which generates a 1,3-diketone ⟨89HCA447⟩. The use of HBr in acetic acid allows cyclization under mild conditions (Scheme 161) ⟨91HCA27⟩.

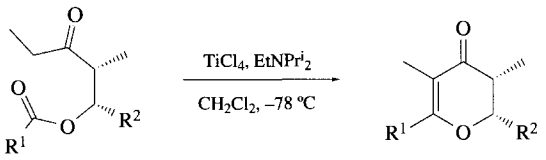


Scheme 161

The cyclization of 1-vinyl-3-hydroxyketones (**215**) results in the synthesis of dihydropyran-4-ones through nucleophilic displacement of a leaving group from the vinyl fragment (Scheme 159). Thus, β-methoxyvinyl derivatives (**215**; X = OMe) ⟨92TL6907⟩ and β-chlorovinyl compounds (**215**; X = Cl) ⟨90TL2213⟩ are suitable precursors.

5.08.23.1.2 β to the heteroatom

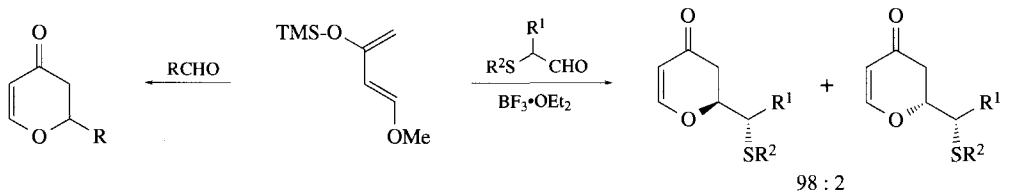
An intramolecular titanium-enolate–ester condensation features in the stereoselective synthesis of *cis*- and *trans*- dihydropyran-4-ones from β-acyloxyketones (Equation (114)) ⟨93HCA1282⟩.



(114)

5.08.23.2 Formation of Two Bonds

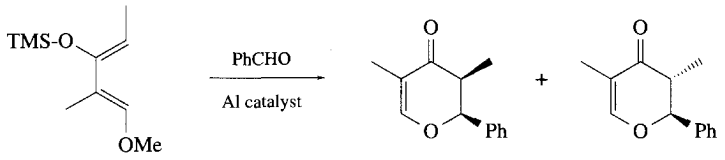
Considerable advances have been made in the Lewis acid catalysed hetero Diels–Alder reaction of aldehydes with electron rich dienes (Scheme 162). Good yields of dihydropyran-4-ones have been obtained from reactions catalyzed by ruthenium complexes ⟨89TL1189⟩, $BF_3 \cdot OEt_2$ ⟨94AJC1735⟩, $ZnBr_2$ ⟨91MI 508-03⟩, and SmI_2 ⟨94TL2545⟩. Attention has been directed towards the enantioselective formation of the pyranones using chiral catalysts such as the (*R*)-(+)-BINOL / $Ti(OPr^i)_4$ combination, which gives excellent enantiomeric excesses (ca. 97%) in good overall yields ⟨95JOC5998⟩.



Scheme 162

The reaction of Danishefsky's diene with racemic α- and β-thioaldehydes gives good yields and shows excellent diastereoselectivity when catalyzed by $BF_3 \cdot OEt_2$ (Scheme 162) ⟨92JOC3605⟩. However, $LiClO_4$ is the preferred catalyst for the reaction of the diene with α-amino- and α-alkoxy-aldehydes ⟨93T3605, 93TL5567⟩.

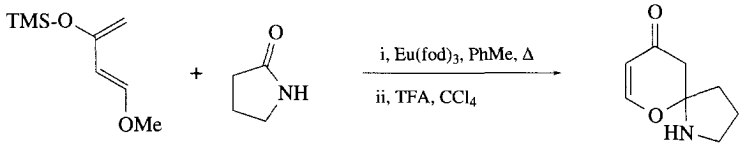
The *cis*-pyran-4-one (95% *ee*) is the predominant adduct from the cycloaddition of benzaldehyde to the 2,4-dimethyl derivative of Danishefsky's diene when catalyzed by chiral aluminum catalysts (Equation (115)) ⟨88JA310⟩.



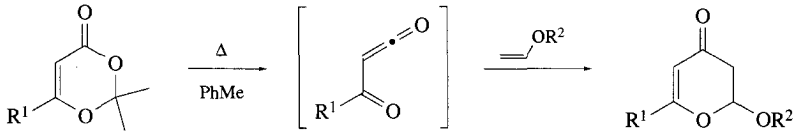
(115)

Lactams behave as hetero dienophiles in $Eu(fod)_3$-catalyzed reactions with silyloxydienes, giving spiro-annulated dihydropyran-4-ones. The best yields result when the *N*-atom is part of a 5- or 6-membered ring and is unsubstituted (Equation (116)) ⟨95JOC7724⟩.

Acyl ketenes undergo a [4 + 2] cycloaddition with electron rich alkenes to give 2,3-dihydropyran-4-ones (Scheme 163) ⟨90TL3677⟩.



(116)



Scheme 163

5.08.23.3 From a Preformed Heterocyclic Ring

5.08.23.3.1 From dihydropyrans

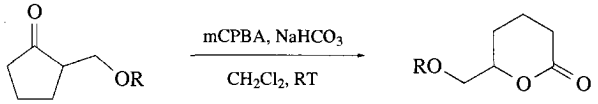
3,4-Dihydropyran is converted into dihydropyran-4-one on reaction with Koser's reagent, [hydroxy(tosyloxy)iodo]benzene, PhI(OTs)OH ⟨90JCS(P1)1481⟩.

5.08.24 TETRAHYDROPYRANONES

5.08.24.1 Formation of One Bond

5.08.24.1.1 Adjacent to the heteratom

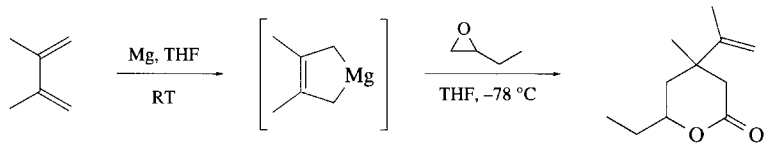
The Baeyer–Villiger oxidation of cyclopentanones provides a facile route to tetrahydropyran-2-ones ⟨93OR(43)351⟩ and is the key step in an efficient synthesis of hydroxyalkylpyranones (Equation (117)) ⟨90S589⟩. The most frequently used reagent is mcpba, generally in the presence of $NaHCO_3$ ⟨92G415, 93TL1149, 95JOC3052⟩, though it has also been successful in CF_3CO_2H ⟨89SC829⟩.



(117)

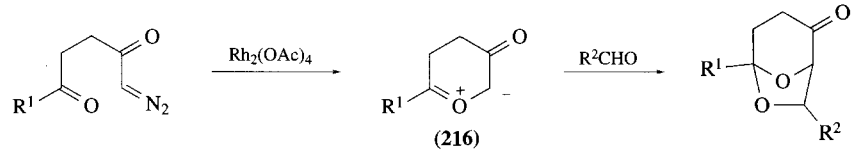
The synthesis of tetrahydropyran-2-ones by lactonization is widely used. The procedures chosen depend on the substrate structure, but include acidic ⟨88JCS(P2)431, 90JOC5977, 91HCA787, 92CE477, 92TL2823, 93JA6078, 93SL901, 93TL2327, 94T6603, 95JOC7774⟩ and basic conditions ⟨90T3463, 92JCS(P1)693, 95T1663⟩, iodolactonization ⟨90CJC620, 90JA3018, 91JCS(P1)133, 92TL6505, 94OPP671⟩, selenolactonization ⟨91JCS(P1)133⟩, catalytic hydrogenation ⟨95JOC6148⟩, homolytic cyclization ⟨89H(28)579⟩, and alkylative lactonization ⟨90H(31)215⟩.

Fused tetrahydropyran-2-ones have been obtained via the rhodium-catalyzed decomposition of diazocarbonyl compounds ⟨95JOC3035⟩ and the intramolecular cyclization of a metallocarbene onto an epoxide function furnishes 6-hydroxymethyl derivatives ⟨94TL6717⟩. The reaction of substituted (but-2-ene-1,4-diyl)magnesium complexes with epoxides leads to δ-lactones and spiro-δ-lactones (Scheme 164) ⟨95JOC5143⟩. The fluoride-induced carbonylation of 1,4-diiodobutane gives tetrahydropyran-2-one ⟨92CC1678⟩.



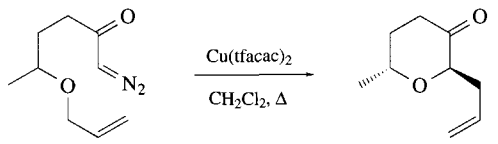
Scheme 164

Syntheses of tetrahydropyran-3-ones are based on the addition of a carbene to the oxygen atom of a carbonyl group. The carbenoid species is normally generated by treating a diazoketone with a rhodium(II) catalyst. The initial product is a carbonyl ylide (**216**) which undergoes further reaction to give a pyran-3-one derivative (Scheme 165). For example, cycloaddition reactions lead to bicyclic products, as used in a synthesis of brevicomin ⟨89TL1491⟩, whilst intramolecular versions of this tandem cyclization–cycloaddition sequence leads to oxapolycyclic systems ⟨91CRV263, 92JOC5747⟩.



Scheme 165

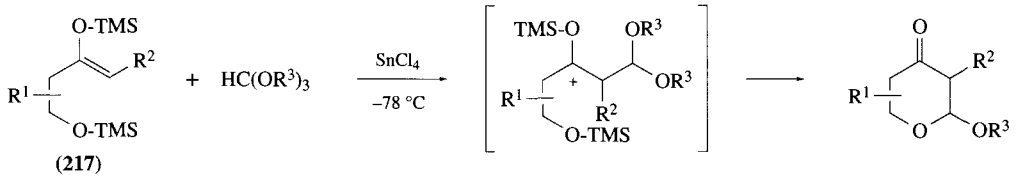
The use of copper(II) trifluoroacetylacetonate, $Cu(tfacac)_2$, and the hexafluoro analogue favors stereoselective oxygen insertion into the metal carbenoid rather than C—H insertion and, coupled with a rearrangement of the ylid, has been used in a synthesis of decarestrictive L (Equation (118)) ⟨93TL4385, 94TL6381⟩.



(118)

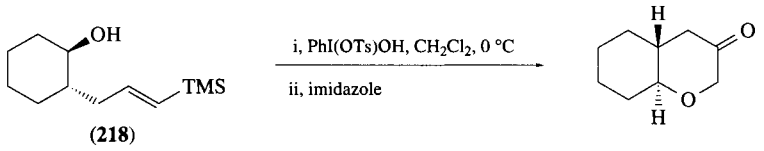
The acid catalyzed condensation of aromatic aldehydes with 3-oxopentanedioic acid is critically dependent on the purity of the reagents, but at −15°C gives largely the *cis*-2,6-diaryltetrahydropyran-4-one ⟨89OPP327⟩.

Treatment of β-silyloxy silyl enol ethers (**217**) with trialkyl orthoformates in the presence of Lewis acids gives good yields of 2-alkoxytetrahydropyran-4-ones (Scheme 166) ⟨90TL301⟩.



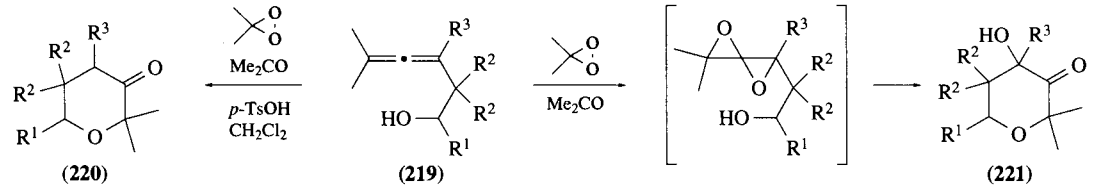
Scheme 166

Hypervalent iodine reagents favor a 6-*endo-trig* cyclization of the vinylsilanes (**218**), which leads predominantly to pyran-3-ones (Equation (119)) ⟨90JCS(P1)1481⟩.



(218) (119)

Oxidation of β-allenyl alcohols (**219**) by dimethyldioxirane results in sequential epoxidation of the double bonds. Under acidic conditions, the monoepoxide is intercepted and cyclization affords the tetrahydropyran-3-one (**220**). However, in the absence of acid, the spirodioxide is produced which spontaneously cyclizes to the pyranone (**221**) (Scheme 167) ⟨92T1427⟩.

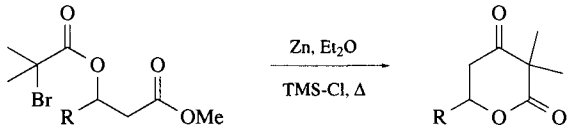


(220) (219) (221)

Scheme 167

5.08.24.1.2 γ to the heteroatom

The intramolecular Reformatsky reaction of bromodiesters derived from chiral β-hydroxy esters and β-bromo acyl halides is a facile route to pyran-2,4-diones (Scheme 120). The presence of an excess of TMS-Cl is essential for a successful reaction ⟨93TL277⟩.



(120)

5.08.24.2 Formation of Two Bonds

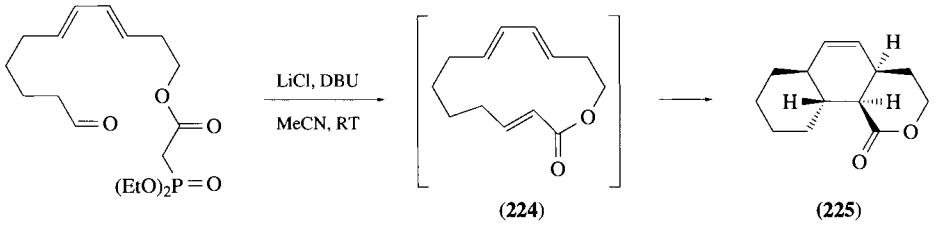
The *cis,trans*-fused tricyclic tetrahydropyran-2-one (**223**) results from a mild, Lewis acid catalyzed intramolecular Diels–Alder reaction of the *trans*-disubstituted cyclohexane (**222**) (Equation (121)) ⟨89T6203⟩.

(222) (223) (121)

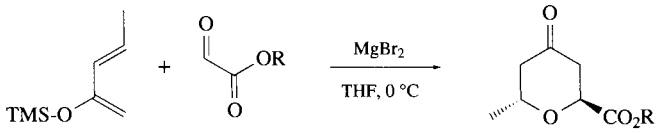
A transannular Diels–Alder reaction accounts for the formation of the *trans-anti-cis* tricyclic lactone (**225**) during attempts to synthesize the macrocycle (**224**) by an intramolecular Wadsworth–Emmons protocol (Scheme 168) ⟨95TL1051⟩.

The adduct from the hetero Diels–Alder reaction between a diene and a glyoxylic ester is

spontaneously converted into the *trans*-tetrahydropyran-4-one in the presence of Mg^{2+} ions, which exert stereocontrol by chelation (Equation (122)) ⟨95TL3503⟩.



Scheme 168



(122)

5.08.24.3 From Other Heterocycles

5.08.24.3.1 From benzoxepines

The acid catalyzed ring contraction of epoxyperhydrobenzoxepinones gives fused tetrahydropyran-2-ones and constitutes a synthesis from cyclohexanone derivatives ⟨92CJC1356⟩.

5.08.24.4 From a Preformed Heterocyclic Ring

5.08.24.4.1 From tetrahydropyranols

Oxidation of tetrahydropyranols to the pyranone can be accomplished using, amongst others, the mild oxidant Ag_2CO_3 ⟨88TL6901, 89H(29)445, 89TL5989, 90TL2393⟩, MnO_2 ⟨90T3535⟩, PDC ⟨90TL7343⟩, and PCC ⟨90CL1585, 93TL2945⟩. The latter reagent has been employed in the synthesis of (+)-isoiridomyrmecin ⟨92TL317⟩.

5.08.24.4.2 From pyranones

Catalytic hydrogenation of the unsaturated lactones is facile and has been used in a synthesis of (±)-invictolide ⟨93JOC338⟩ and other δ-lactones ⟨89HCA731, 92G395⟩.

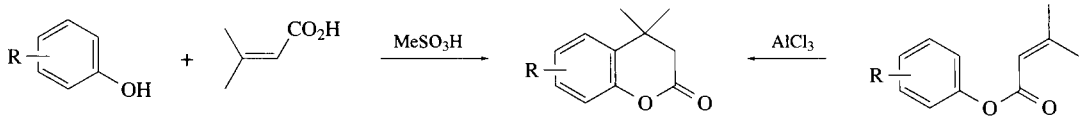
5.08.25 DIHYDROCOUMARINS

5.08.25.1 Formation of One Bond

5.08.25.1.1 Adjacent to the heteroatom

The condensation of phenols with α,β-unsaturated acids and their derivatives is complex, often yielding a mixture of products containing notably dihydrocoumarins, chroman-4-ones and indanones. However, careful selection of substrate, cyclizing medium, and reaction condition allows one or other of the products to be selectively obtained. In general, reactions of phenol, cresols, and halogenophenols give 3,4-dihydrocoumarins in good yields on reaction with 3-methylbut-2-enoic acid in methanesulfonic acid. In the case of hydroxy- and methoxy-phenols, the situation is less well

defined, with the 3-substituted compounds giving the chromanone in $MeSO_3H$, but the *o*- and *p*-isomers yielding dihydrocoumarins (Scheme 169) ⟨85TH 509-01, 89JOC3303⟩.

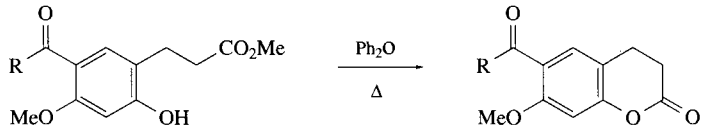


Scheme 169

A similar situation obtains with the Fries rearrangement of aryl 3-methylbut-2-enoates. Catalysis by polyphosphoric acid tends to produce chroman-4-ones through acylation, but the use of an excess of $AlCl_3$ to effect the rearrangement results in mainly alkylation to give the dihydrocoumarin (Scheme 169) ⟨85JHC363, 85TH 509-01⟩.

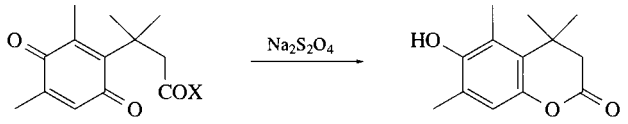
Other examples of dihydrocoumarin synthesis using this methodology include heating phenols with acrylic esters using LiH as catalyst ⟨92TL1161⟩, the reaction of Meldrum's acid with aromatic aldehydes to provide an α,β-unsaturated acid equivalent which reacts with phloroglucinol to give 4-aryldihydrocoumarins ⟨87SC723⟩, and the formation of 1-aroyl-1,2-dihydronaphtho[2,1-*b*]pyran-3-ones fom naphthols and β-aroylacrylic acids ⟨91IJC662⟩.

Dihydrocoumarins result from the cyclization of 3-(2-hydroxyphenyl)propanoate esters and related compounds. The esters themselves cyclize thermally (Equation (123)) ⟨92T7581⟩, but when an oxazoline moiety functions as a latent carboxyl group, acid catalysis is necessary ⟨88TL5901⟩.



(123)

Spontaneous cyclization accompanies reduction of the quinone (**226**; $X = NR_2$), and the transformation is the basis of the use of acid (**226**; X = OH) for amine protection (Equation (124)) ⟨95JOC539⟩.



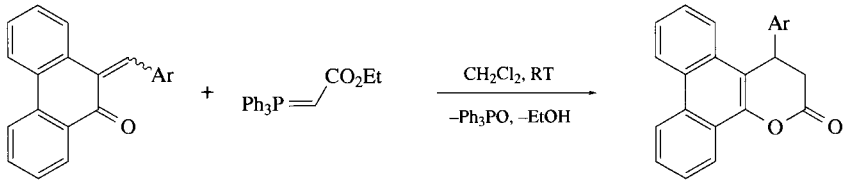
(124)

(**226**)

The Baeyer–Villiger oxidation of indanones leads to dihydrocoumarins ⟨94TA41⟩.

5.08.25.2 Formation of Two Bonds

The complex reaction of the quinone methide (**227**) with phosphorus ylides gives a good yield of the fused dihydrocoumarin when ethoxycarbonylmethylenetriphenylphosphorane is used as the reagent (Equation (125)) ⟨91JCS(P1)3159⟩.



(125)

(**227**)

5.08.25.3 From a Preformed Heterocycle

5.08.25.3.1 From coumarins

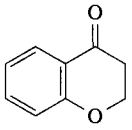
Catalytic hydrogenation of coumarins yields dihydrocoumarins ⟨93T1701⟩.

5.08.25.3.2 From chromans

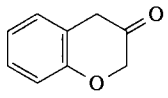
Oxidation of chroman-2-ols can be achieved with pyridinium chlorochromate ⟨89BCJ1198⟩.

5.08.26 CHROMANONES

This section considers the synthesis of chroman-4-ones (**228**), including the 2- and 3-phenyl derivatives, the flavanones and isoflavanones, and the less well known chroman-3-ones (**229**). The chemistry of chroman-3-ones has been reviewed ⟨91BSF189⟩.



(228)



(229)

5.08.26.1 Formation of One Bond

5.08.26.1.1 Adjacent to the heteroatom

The reaction between a phenol and an α,β-unsaturated acid or its derivatives has been extensively used to prepare chroman-4-ones. Its attractions are the ready availability and diversity of the two reactants and the variety of solvent, catalyst, and reaction conditions which can be used and which are illustrated in Table 4.

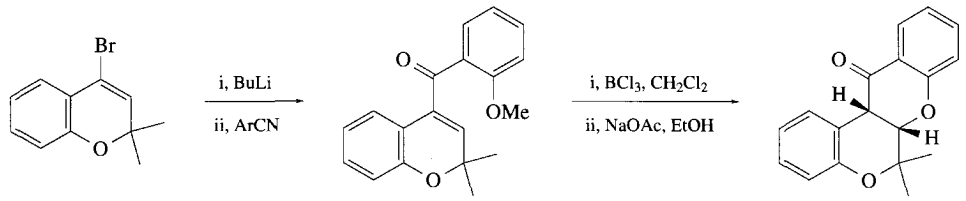
Table 4 Synthesis of chroman-4-ones from phenols and α,β-unsaturated acids or acid derivatives.

Phenol R	*Unsaturated Acid Derivative*	*Catalyst*	*Solvent*	*Yield (%)*	*Ref.*
3-OH	DMAA	TFA	TFA	85	92IJC338
4-Me	DMAA	PPA	PPA	48	89JHC1013
4-OMe	DMAC	$AlCl_3$	Et_2O	23	89JHC1013
3-OH, 5-Me	DMAC	$AlCl_3$	$POCl_3$	90	85S545
3,5-$(OH)_2$	DMAC	$FeCl_3$	$CHCl_3$	75	85JHC561
3,4,5-$(OMe)_3$	CC	$AlCl_3$	$PhNO_2$	–	87IJC564
1,2-$(OH)_2$	DMAA	$ZnCl_2$	$POCl_3$	80	88JHC871
3,4-$(OH)_2$	DMAA	P_2O_5	$MeSO_3H$	42	80S725
3,5-$(OH)_2$	DMAC	AlI_3	MeCN	35	90IJC661

DMAA = 3,3-dimethylacrylic acid; DMAC = 3,3-dimethylacryloyl chloride; CC = crotonyl chloride.

The initial step is a Friedel–Crafts acylation and leads to an *o*-hydroxy unsaturated ketone. In many instances, these spontaneously cyclize through an intramolecular conjugate addition to the enone, but the product from the reaction can be a mixture of cyclized and uncyclized material and on occasions may even be exclusively the latter. Subsequent cyclization can be effected under acidic or basic conditions ⟨85S545, 88JHC871⟩. This mode of cyclization is the final step in the synthesis of

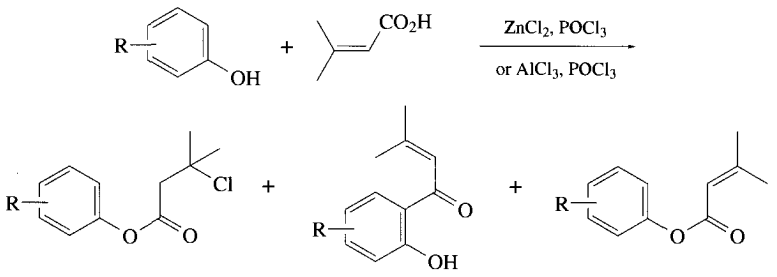
the rotenoid (**230**) from a 4-lithiochromene, aroylation being accomplished through reaction with a benzonitrile (Scheme 170) ⟨94JCS(P1)653⟩.



(230)

Scheme 170

However, the reaction is complex and a variety of products has been identified, some of which indicate that in addition to the Friedel–Crafts acylation, *O*-acylation occurs which may be followed by a Fries rearrangement. The reaction conditions as well as the substitution pattern of the phenol can influence the nature of the products. A study of the reaction of fourteen different phenols with 3-methylbut-2-enoic acid catalyzed by $ZnCl_2/POCl_3$ concluded that the major product was the ester (**231**) formed by addition of HCl to the alkene portion of the *O*-acylated phenol. Only in the cases of resorcinol and related compounds were significant amounts of chroman-4-one produced, accompanied by the uncyclized enone (**232**). Using $AlCl_3/POCl_3$ as catalyst, the resorcinols gave the enone again, but other phenols gave the α,β-unsaturated ester (**233**) (Equation (126)) ⟨94H(38)2099⟩.

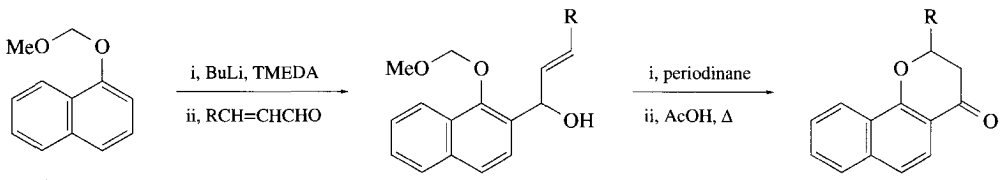


(126)

(231) (232) (233)

Interesting or unusual variations include the use of cycloalkylidene acetic acid which with *m*-dihydroxybenzenes yields spirobenzopyrans ⟨91T4775⟩, whilst a dimethoxybenzene may replace the phenol, as in the synthesis of 6-methoxy-2,2-dimethylchroman-4-one ⟨89JHC1013⟩. The reaction is readily extended to naphthols, which yield angular naphthopyranones ⟨58JCS2422⟩, whereas 2-hydroxyxanthene yields the linear pyranoxanthene ⟨94SC659⟩.

When 3-substituted phenols are used in this reaction, the formation of isomers is always possible and in some cases materializes. Thus, 1,3-dihydroxy-5-*n*-pentylbenzene affords both the 5- and 7-pentylchroman-4-ones when treated with 3-methylbut-2-enoic acid in the presence of BF_3 ⟨67JA5934⟩. Analogous behavior is shown by 3,5-dihydroxystilbene, whilst 3,3′,5,5′-tetrahydroxystilbene gives a mixture of three bis-chromanones ⟨90JHC535⟩. However, exclusive formation of the 7-substituted chromanone is generally observed. Directed metallation is the key feature in a synthesis of polycyclic chromanones and flavanones from aryl ethers which is outlined in Scheme 171 ⟨90JOC6161⟩.



Scheme 171

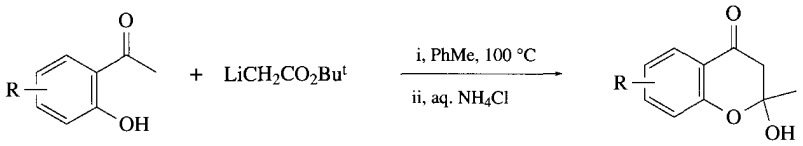
Provided that a good leaving group is present in the propanoyl moiety, the presence of unsaturation in the acid component is not essential for successful chromanone synthesis. Thus, the presence of a bromine atom at C-2 allows formation of a double bond by loss of HBr and spontaneous cyclization ensues ⟨24LA132⟩. Similarly, base catalyzed ring closure of 2′,4′-dihydroxy-3-chloro-

propiophenone affords 7-hydroxychroman-4-one. The chloroketone is prepared from resorcinol and 3-chloropropanoic acid in trifluoromethanesulfonic acid ⟨94JOC1216⟩.

2′-Hydroxyacetophenone and related compounds have been extensively used as precursors of chroman-4-ones. These syntheses generally involve the formation of an unsaturated side-chain on the acetyl function, utilizing the carbanionic potential of the methyl group. Cyclization follows through conjugate attack of the phenolic group on the α,β-enone unit. The Kabbe synthesis ⟨78S886⟩ is a particularly valuable route to chromanones which allows wide variation of substituents at the 2-position ⟨91AGE1709⟩ and is applicable to the synthesis of heterocyclic analogues ⟨88HCA596⟩.

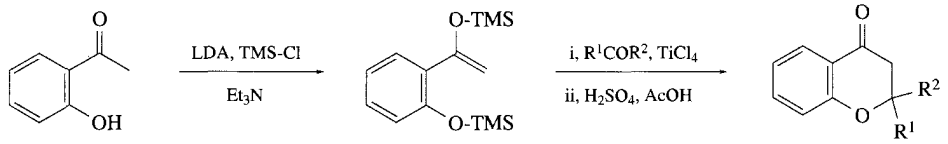
Problems associated with the reaction of formaldehyde with 2′-hydroxyacetophenone may be overcome by preforming the Mannich base hydrochloride, which can then be cyclized under basic conditions ⟨89S709⟩. Using basic conditions for the Mannich reaction leads to 3-aminomethyl- and 3,3-bis(aminomethyl)- chroman-4-ones ⟨83S579⟩. However, other workers have reported that only normal Mannich bases are formed and not chromanones ⟨88S830⟩.

Chroman-4-one hemiacetals result in good yield from the reaction of *o*-hydroxyacetophenones with *t*-butyl lithioacetate, which behaves as a two carbon homologation reagent (Equation (127)) ⟨88H(27)1159⟩.



(127)

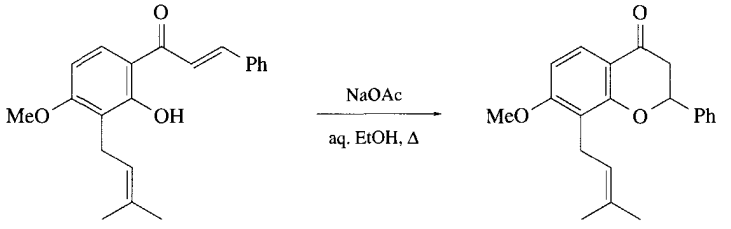
Enolisable carbonyl compounds react with the bis-silyl enol ether from *o*-hydroxyacetophenone to give β-hydroxyketones under Mukaiyama conditions. Cyclization leads to 2-substituted chroman-4-ones (Scheme 172) ⟨91JOC1325⟩.



Scheme 172

The base catalyzed reaction of 2′-hydroxypropiophenone with aqueous formaldehyde gives 3-methylchroman-4-one ⟨68T949⟩. However, the reaction is complex, proceeding via a mono- and bis-hydroxymethylated derivative followed by a 6-*endo-trig* cyclocondensation. Furthermore, 3-methylchroman-4-one itself adds formaldehyde to give 3-hydroxymethyl-3-methylchroman-4-one in high yield ⟨85S876⟩.

The cyclization of 2′-hydroxychalcones to flavanones is an extensively used route, the mechanism of which has been widely studied ⟨89JCS(P2)1623, 90CJC1780, 92JCS(P2)1571, 92JCS(P2)1603⟩. The synthesis is exemplified in Equation (128) ⟨90JOC1193⟩, but improvements include the use of KF-Celite ⟨90SC649⟩ and oxygen in the presence of a cobalt Schiff base complex ⟨89TL4145⟩. Some 2′-hydroxy-4′,6′-dimethylchalcones form flavanones in the solid state ⟨95JCS(P2)325⟩.



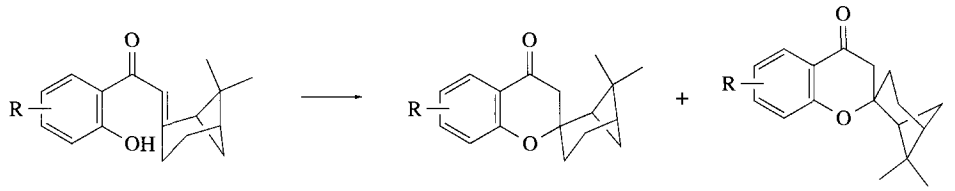
(128)

When the cyclization is conducted in the presence of an oxidant, 3-hydroxyflavanones are formed directly ⟨85S110⟩. Prior oxidation to the chalcone epoxide is an alternative approach to these compounds ⟨93TL5055⟩. The analogous 2-(2-furyl)-3-hydroxychromanones result from an oxidative cyclization with hypervalent iodine and hydrolysis of the resulting acetals ⟨92SC327⟩.

The condensation product from *o*-hydroxyacetophenone and 6-methylhept-5-en-2-one undergoes

a cyclodehydration in HMPT to give the chromanone. The more usual cyclizing agents give poor yields of chromanone as a consequence a retro-aldol reaction ⟨89SC159⟩.

The cyclization of the ketone (**234**) can be controlled to give either of the chromanones (**235**) and (**236**) in good yields by careful choice of base and solvent. The more stable product is considered to be (**236**) (Equation (129)) ⟨89TL6653⟩.

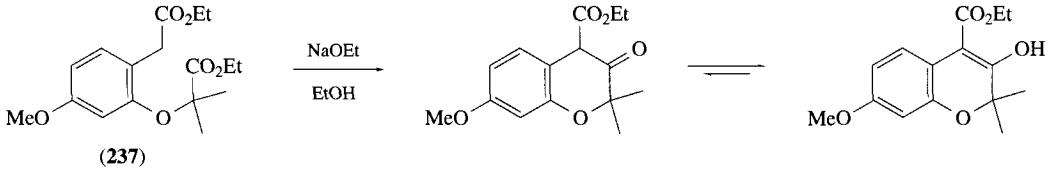


(234) (235) (236) (129)

5.08.26.1.2 β to the heteroatom

The irradiation of a mixture of *O*-allylsalicoyl chloride and triethylamine in acetonitrile generates acyl radicals which effect an intramolecular cyclization, giving 3-methylchroman-4-one ⟨94JCS(P2)1545⟩.

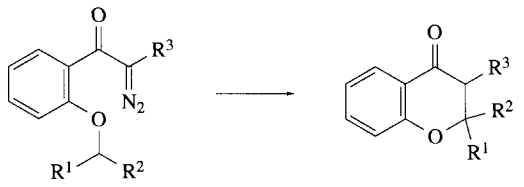
The Dieckmann condensation of *ortho*-substituted phenoxyacetates leads to chroman-3-ones. The diester (**237**), obtained in five steps from 3-methoxyphenol, affords 7-methoxy-2,2-dimethyl-3-oxochroman-4-carboxylate, which exists predominantly as the enol tautomer (Scheme 173) ⟨83JCS(P1)1431⟩.



(237)

Scheme 173

The rhodium-promoted decomposition of α-diazocarbonyl compounds results in insertion into the adjacent C—H bond, producing chromanones with little or no benzofuranone formation and with some enantioselectivity (Equation (130)) ⟨95JCS(P1)1373⟩.



(130)

5.08.26.1.3 γ to the heteroatom

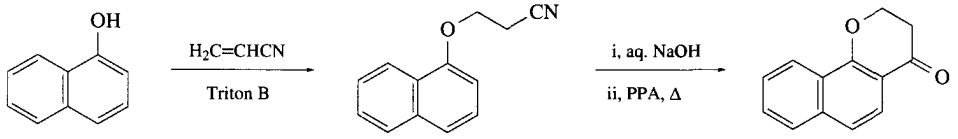
Chroman-4-ones can be synthesized by the cyclization of 3-phenoxypropanoic acid and its derivatives, which are usually prepared from a phenol and a 3-halogenopropanoic acid under basic conditions. A choice of cyclizing agents is available, polyphosphoric acid being particularly useful either alone or admixed with $AlCl_3$ ⟨62JA813, 87IJC786⟩, but hydrogen fluoride ⟨62CB1446⟩, sulfuric acid ⟨71JMC758⟩, and phosphorus pentoxide ⟨58BSF325⟩ are also effective. Generally, the cyclizing reagent has no effect on the nature of the product, but sulfonation may accompany cyclization using H_2SO_4 and 3-(3,5-di-*t*-butylphenoxy)propanoic acid yields different products with PPA and P_2O_5 ⟨68CJC3367⟩. The 3-(3-methylphenoxy)analogue gives a mixture of the 5- and 7-methylchroman-4-one, the composition of which varies with the cyclizing agent ⟨67AC(R)1045⟩. Chroman-3-ones can be synthesised in a similar way from *o*-substituted phenoxyethanoic acids ⟨63JCS5322⟩.

Introduction of substituents into the propanoic acid side chain gives access to substituted chro-

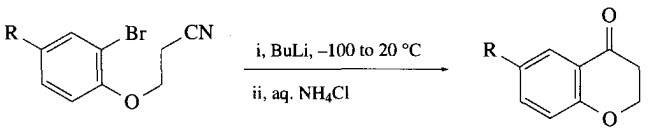
man-4-ones. Diethyl malonate reacts with aryloxymethyl chlorides to give aryloxymethylmalonates from which the monoacids and the derived acyl chlorides are obtained. Cyclization with $AlCl_3$ leads to the 3-alkyl-4-oxochroman-3-carboxylates (Equation (131)) ⟨87T93⟩. Extension of this route provides chiral 3-alkylchroman-4-ones through enzymatic hydrolysis of 2-substituted aryloxypropanoates and cyclization with $AlCl_3$ ⟨92TL2145⟩.

(131)

The use of 3-phenoxypropanonitriles as alternatives to the acids is attractive because of their ease of synthesis, though it is not uncommon to hydrolyze the nitrile prior to cyclization ⟨85JCR(M)2724⟩. The cyanoethylation of 1-naphthol with acrylonitrile in the presence of base is illustrative (Scheme 174) ⟨84S1063⟩ and a more exotic example is the synthesis of muscomosin, a benzocyclobutene isolated from *muscari sp.* ⟨92H(33)291⟩. A variation on this theme is based on the Parham cycloacylation process (Equation (132)) ⟨94JCR(S)82⟩.



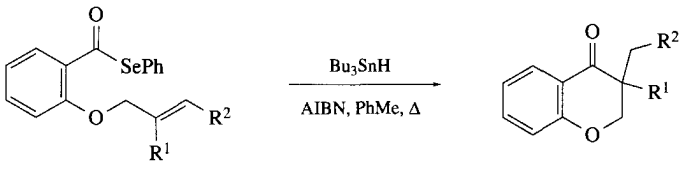
Scheme 174



(132)

The decomposition of 1-diazo-3-aryloxypropan-2-ones in the presence of bis[hexafluoroacetoacetonato]copper(II) proceeds by intramolecular addition of the ketocarbenoid species and leads to chroman-3-ones in high yield. Diazoketones derived from 1- and 2- naphthol yield the angular naphthopyranones ⟨84S268⟩. 1-Diazo-3-(2-methoxyphenyl)propan-2-ones yield chroman-3-ones on treatment with BF_3 ⟨70JHC197⟩.

On treatment with tri-*n*-butyltin hydride and a radical generator, the selenol esters yield chroman-4-ones through a 6-*exo-trig* cyclisation of the intermediate carbonyl radicals (Equation 133) ⟨89H(28)67, 89H(28)583⟩.



(133)

5.08.26.2 From Other Heterocycles

5.08.26.2.1 From furans

The reaction of dienophiles such as maleic anhydride, tetracyanoethylene, and DMAD with cycloheptatriene fused furanones is reported to produce chroman-3-ones by simple rearrangement of the substrate ⟨87H(26)2339⟩.

5.08.26.3 From a Preformed Heterocyclic Ring

5.08.26.3.1 From chromones

A variety of catalytic hydrogenation conditions have been found suitable for the selective reduction of the carbon–carbon double bond of chromones ⟨91JHC305, 92T9391, 93JOC1751⟩.

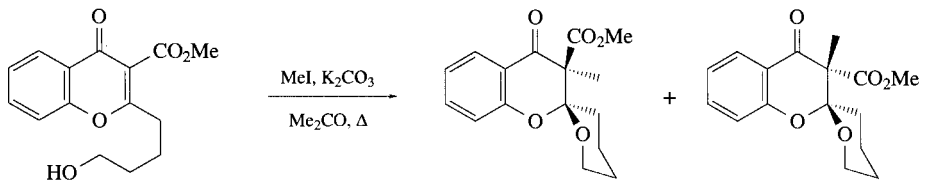
Chromones are α,β-enones and as such undergo conjugate addition reactions, notably when an electron-withdrawing group is present at C-3. Although some nucleophiles promote a ring-opening rearrangement sequence, organocopper reagents lead to 2,3-disubstituted chroman-4-ones. The reaction is compatible with an additional 2-substituent in the chromone ⟨90T3029⟩.

The 3-substituent can act as a chiral auxiliary. Thus, 3-*p*-tolylsulfinylchromones undergo diastereoselective 1,4-addition of lithium dimethylcuprate. Furthermore, the sulfoxide moiety can subsequently be removed, giving access to chiral 2-methylchromanones ⟨90T6553⟩.

The need for an electron withdrawing substituent in the chromone is obviated when methylcopper is used in the presence of BF_3. A combined sequence of conjugate addition, reoxidation to the chromone and a second addition of a copper reagent extends the scope of this reaction type to the synthesis of 2,2-disubstituted chromanones ⟨86TL91⟩.

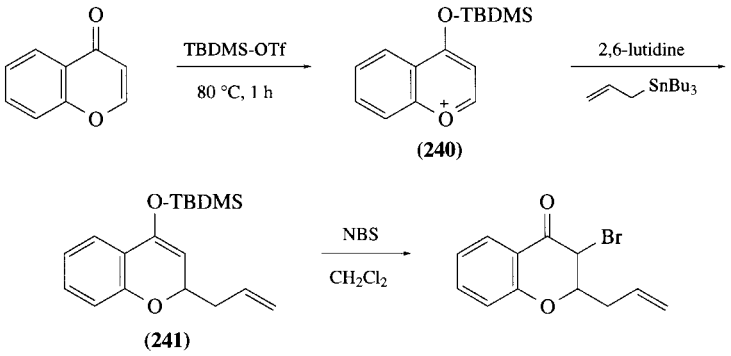
Conjugate addition of methanol to chromone-3-carboxylic acid is followed by decarboxylation and, unless the conditions are carefully controlled, loss of methanol such that the overall process is simply the decarboxylation of the starting material ⟨81S719, 91T9431⟩. An intramolecular alkylation follows the initial Michael addition when 2-haloethanols are reacted with suitable chromones under basic conditions, resulting in a heteroannulation to give a reduced furo[2,3-*b*]chromanone ⟨91T9431⟩.

Chromone esters can undergo spiroacetalization under alkylating conditions in which the first step is an intramolecular 1,4-addition to the enone system. Methylation of the resulting ester enolate leads to the chromanones (**238**) and (**239**) in a ratio of 5 : 1 (Equation (134)). A similar end product can be reached by epoxidation of the chromone and concomitant acid catalyzed acetal formation and cleavage of the epoxide ring ⟨93T3211⟩.



(237) (238) (239) (134)

Formation of 4-silyloxypyrylium salts (**240**) by treatment of chromone with *t*-butyldimethylsilyl triflate offers an alternative chromone–chromanone conversion. Subsequent reaction with silyl enol ethers and allyl organometallic reagents results in attack at C-2 to give chromene derivatives (**241**). Electrophiles convert (**241**) into 2,3-disubstituted chroman-4-ones (Scheme 175) ⟨91JOC2058⟩. The reaction sequence can be extended to produce 2,3-annulated products, reduced xanthones.



Scheme 175

3-Hydroxyflavones are converted into flavanone hemiacetals on treatment with various oxidizing agents in methanol ⟨92SC893⟩, whilst the hydrogen transfer reduction of isoflavones yields isoflavanones ⟨89H(28)183⟩.

5.08.26.3.2 From chromans

Oxidation of chromans to chroman-4-ones can be achieved using ceric ammonium nitrate ⟨90SC3259, 94CJC1866⟩ and the oxidative cleavage of a 4-(*N*-benzamide)chroman-4-carboxylic acid by NaOCl yields the chromanone. In the latter case, under controlled reaction conditions, the 3,3-dichloro derivative can be obtained ⟨92JHC431⟩.

5.08.26.3.3 From chromanols

The oxidation of simple chroman-4-ols to chroman-4-ones ⟨66JCS(C)2013, 94JCS(P1)1925⟩ and of chroman-3,4-diols to 3-hydroxychroman-4-ones ⟨65CB1498⟩ can be accomplished with chromium trioxide in acetic acid or pyridine respectively. Flavan-4-ols are oxidized to flavanones in high yield by phenyliodobistrifluoroacetate ⟨93OPP693⟩. Isoflavanols yield isoflavanones on oxidation, though the ketones may be accompanied by isoflavenes and polymeric material and 5-methoxyisoflavanols give coumarin derivatives ⟨66JCS(C)629⟩.

Formation of chroman-3-ones in this manner is less common ⟨90ACS1024⟩.

5.08.26.3.4 From chromenes

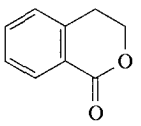
Controlled conditions are necessary to prevent cleavage of the heterocyclic ring during oxidation of chromenes. Neutral $KMnO_4$ ⟨77CJC2360⟩ and OsO_4-KIO_4 ⟨67BSF1164⟩ have been used with success.

The direct conversion of γ-bromopropargyl aryl ethers to chromanones, brought about by a mercury-catalyzed electrocyclization, probably proceeds by oxymercuration of the initially formed 4-bromochromene. The reaction is particularly facile when applied to the naphthyl ethers ⟨88CC34⟩.

Chroman-3-ones have been obtained from chromenes by epoxidation and Lewis acid catalyzed cleavage of the 3-membered ring and from 4-substituted chromenes via hydroboration and PCC oxidation ⟨91S879⟩. Reduction of 3-nitroflavenes with tin(II) chloride in acetone gives good yields of 2-arylchroman-3-one oximes ⟨86H(24)2581⟩.

5.08.27 ISOCHROMANONES

The three isomers which are discussed in this section are isochroman-1-one or 3,4-dihydroisocoumarin (**242**), isochroman-3-one (**243**), and isochroman-4-one (**244**). A few natural products contain an isochromanone moiety, but none of them have an extensive chemistry.



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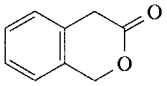

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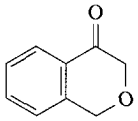


(244)

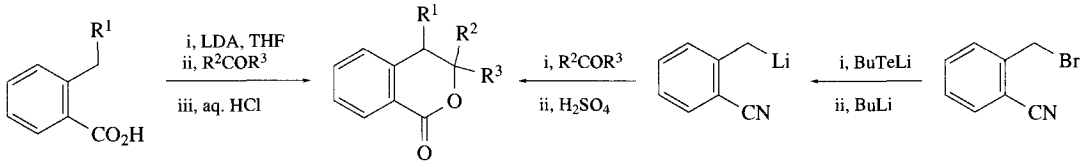
5.08.27.1 Formation of One Bond

5.08.27.1.1 Adjacent to the heteroatom

An established route to isochroman-1-one involves the reduction and cyclization of 2-carboxyphenylacetaldehyde, which is derived from indene by ozonolysis ⟨57JA3165⟩. This type of cyclization features in syntheses of naturally occurring dihydroisocoumarins ⟨93G669, 93LA1331, 95G111⟩.

The dianions derived from 2-methylbenzoic acid react readily with aromatic aldehydes and ketones to give hydroxy acids, which readily cyclize to the dihydroisocoumarin (Scheme 176)

⟨94SC779⟩. In a similar fashion, the anions from *o*-toluic esters ⟨87CC520, 92SC2757, 92TL7569⟩, *o*-toluamides ⟨84JOC742, 92G403⟩, and the related oxazolines ⟨85JOC1259⟩ have been utilized in dihydroisocoumarin syntheses. 2-Bromomethylbenzonitrile is an alternative starting material (Scheme 176) ⟨95S1102⟩.

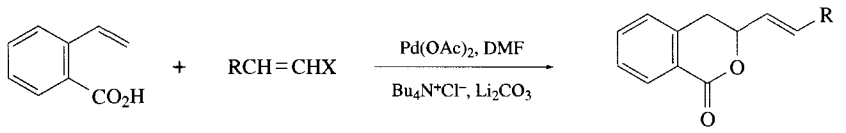


Scheme 176

2-Vinylbenzoic acids ring close to isochroman-1-ones on treatment with chlorine ⟨62AC(R)1070⟩ and $AlCl_3$ ⟨92CC883, 93IJC822⟩, and under acidic ⟨93H(35)289⟩ and basic conditions ⟨72JHC1255⟩. The formation of derivatives of 4,4-dimethylisochroman-1-one by the successive treatment of 2-phenacyl- and 2-acetonyl-benzoic acids with thionyl chloride and dimethylcadmium is a related approach ⟨62BSB394⟩ and methyl 2-acetonylbenzoates are reductively cyclized to isochroman-1-one ⟨77JOC1329⟩. Derivatives of methyl 2-hydroxyethylbenzoates also cyclize readily to the isocoumarin ⟨90T4503⟩.

Cyclization of 2-acylarylacetic acids leads to isochroman-3-ones ⟨62BSB379⟩ and the thermal ring closure of 2-(3,4-dimethoxyphenylacetyl)-4,5-dimethoxyphenylacetic acid and also affords an isochroman-3-one ⟨72JHC853⟩. Other substrates which yield isochroman-3-one derivatives on cyclization include nitriles ⟨81TL2797, 90JOC1471⟩ and hydroxyamides ⟨64JOC3514⟩. A detailed synthesis of the isochroman-3-one system from phenylacetic acids has been published ⟨76OS(55)45⟩ and extended to 4-substituted derivatives ⟨87IJC768⟩.

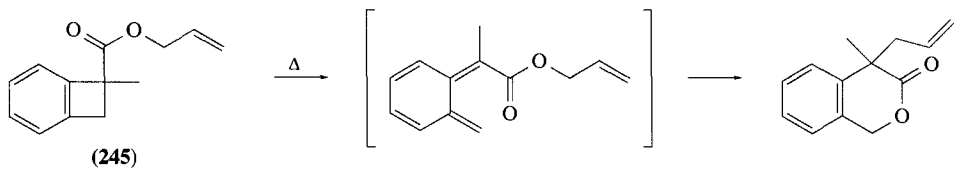
The palladium catalyzed coupling of vinyl halides and triflates to vinylbenzoic acids leads to vinyl substituted dihydrocoumarins together with varying, but small, amounts of the related phthalides (Equation (135)) ⟨94SL748⟩.



(135)

The carbonylation of 2-(2-bromophenyl)ethanol provides a suitable substrate for cyclization to isochroman-1-one ⟨79H(12)921⟩, whilst similar treatment of bromomethylbenzyl alcohols affords isochroman-3-ones ⟨80JA4193⟩.

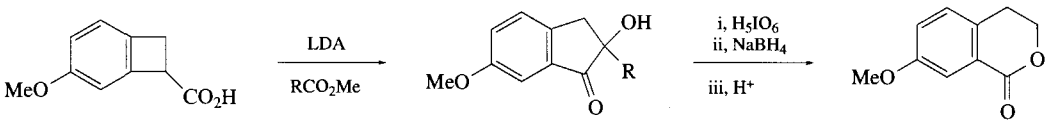
The thermolysis of allyl 1-alkylbenzocyclobutenyl-1-carboxylate (**245**) yields 4-alkyl-4-allyl-isochroman-3-one exclusively via electrocyclization of the *Z-o*-quinodimethane (Scheme 177). The alternative 1,5-sigmatropic reaction of the *E*-transition state is not observed ⟨85JA5810⟩. In an extension of this reaction, allyl 1-alkenylbenzocyclobutenyl-1-carboxylates afford a mixture of a naphthalene derivative via the *E-o*-quinomethane, an isochroman-3-one arising from a sequential electrocyclization and [3,3]-sigmatropic shift, and a 4-alkylideneisochroman-3-one derived from a Cope rearrangement ⟨87H(26)2361⟩.



(**245**)

Scheme 177

5-Methoxybenzocyclobutene-1-carboxylic acid is converted into the indanone (**246**) via reaction of the dianion with an ester. Oxidation of (**246**) followed by reduction and acidification leads to the 3,4-dihydroisocoumarin (Scheme 178) ⟨90H(30)253⟩.



(246)

Scheme 178

5.08.27.1.2 β to the heteroatom

Dieckmann cyclization of diesters derived from ethyl 2-chloromethylbenzoate yields isochroman-4-ones. An alternative, preferred approach involves an intramolecular Perkin reaction on the corresponding dicarboxylic acid ⟨71BSF13511⟩.

5.08.27.2 From Other Heterocycles

5.08.27.2.1 From benzofurans

Phthalides rearrange to dihydroisocoumarins on treatment with $AlCl_3$ ⟨92CC883⟩.

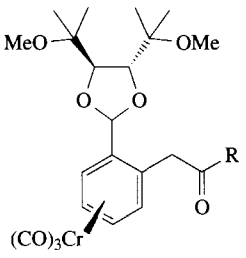
5.08.27.3 From a Preformed Heterocyclic Ring

5.08.27.3.1 From isochromans

Oxidation at C-1 can be accomplished using selenium dioxide ⟨56BSF1337⟩, chromium trioxide ⟨62JOC4337⟩, potassium permanganate ⟨56JCS3598⟩, PDC ⟨90AP(323)493⟩, and PCC ⟨94H(38)1507⟩. When the 1-position is fully substituted, oxidation occurs at C-4 ⟨69BSF915⟩.

Enantiomerically pure dihydroisocoumarins have been obtained by stereoselective reduction of chromium carbonyl complexes of ketones of the type (**247**). Hydrolytic decomplexation to the isochromanol and subsequent PCC oxidation cyclization complete the sequence ⟨94CC501⟩.

Photolysis of isochromanols or their hypoiodites gives good yields of the dihydroisocoumarin and is a further example of their synthesis from *o*-substituted toluenes (Scheme 179) ⟨93JCS(P1)111⟩.



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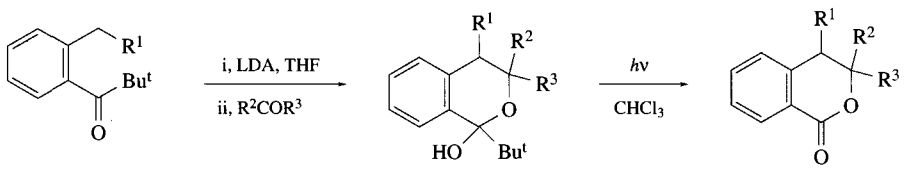


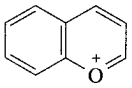
Scheme 179

5.08.27.3.2 From isocoumarins

Catalytic hydrogenation of isocoumarins affords the 3,4-dihydro compound ⟨81JCS(P1)2570, 89JOC4218⟩.

5.08.28 PYRYLIUM SALTS AND THEIR BENZO DERIVATIVES

In addition to the parent system, syntheses of 1-benzopyrylium (**248**) and its phenyl derivatives, the flavylium salts, 2-benzopyrylium (**249**) and xanthylium (**250**) salts are considered. Mention is also made of anthocyanidins, important as coloring materials in plants.



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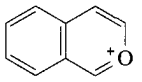

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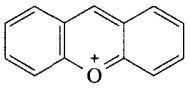


(250)

There is good coverage of pyrylium salts in the literature. Comprehensive reviews of the chemistry of pyrylium have been published ⟨69ACH(10)241, 82AHC(S2)⟩. Naturally occurring derivatives of the benzologues and related compounds are discussed by Dean ⟨B-63MI 508-01⟩ and the chemistry of benzo[*c*]pyrylium salts has been reviewed ⟨90AHC(50)158⟩.

The majority of syntheses of the pyrylium cation involve the cyclization of a C_5 unit, normally in the form of a pentan-1,5-dione or a pentenedione. It is not unusual, however, to generate the five-carbon moiety *in situ* from more readily available smaller molecules. All such syntheses are classified together, implying that the heterocycle results from the formation of only one bond.

5.08.28.1 Formation of One Bond

5.08.28.1.1 Adjacent to the heteroatom

Balaban ⟨82AHC(S2)⟩ has classified pyrylium syntheses according to the number of component molecules used to form the C_5 unit and this is shown in Figure 1. It can be seen that those approaches using three components will lead to symmetrically substituted pyrylium salts, but nevertheless the diverse choice of methods ensures that very few restrictions are imposed on the range of examples which is accessible.

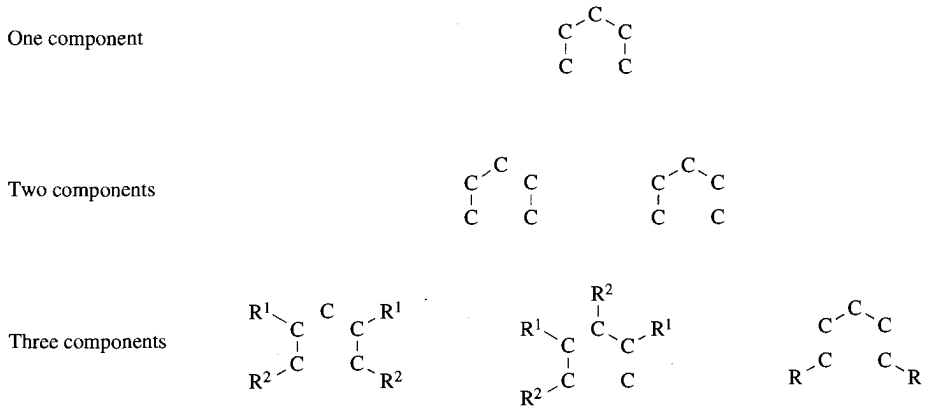


Figure 1 Pyrylium ring-forming processes.

Unsaturated 1,5-diones are in the correct oxidation state for direct conversion to pyrylium salts and cyclization is achieved under strongly acidic conditions. The mechanism of formation illustrated

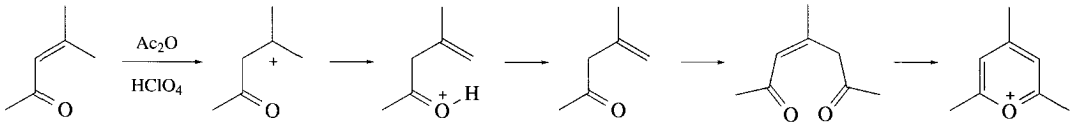
in Scheme 180 is supported by isotopic incorporation studies ⟨67MI 508-01⟩ and by kinetic studies ⟨71JA2733, 74CR(C)697⟩.

Scheme 180

The series of equilibria allow a change in the anion of a pyrylium salt to be accomplished. Treatment of the readily available pyrylium perchlorates and tetrafluoroborates with weak bases generates the pseudobases as either the cyclic or acyclic tautomer. Aryl substituted pseudobases are more stable than their aliphatic counterparts and generally react instantaneously with a range of acids to form the new pyrylium salts in high yield ⟨80T679⟩. Whilst alkyl substituted pyrylium salts behave similarly with strong acids, their reaction with weaker acids proceeds at a measurable rate leading to the new pyrylium salt only if the pK_a of the acid is below about four. It is considered that *cis–trans* equilibration of the pentendione is the critical, rate determining feature. Actual generation of the pseudobase is not always necessary, as when the solubilities of two salts differ widely in acid solution ⟨88OPP231⟩.

Although pyrylium salts are reduced to dihydropyrans by $NaBH_4$ in acetic acid, reduction is slower when stronger carboxylic acids are used. This allows perchlorate and tetrafluoroborate anions to be replaced by solvent acid anions such as trifluoroacetate. Acyloxyhydroborates remove the anion derived from a strong acid, allowing the pyrylium carboxylate to be formed ⟨91BSB665⟩.

The acylation of unsaturated ketones can lead to pyrylium salts ⟨19CB1195⟩. Yields are significantly better from β,γ-isomers than from α,β-unsaturated ketones and it may be that the latter compounds are isomerized to the former during the synthesis (Scheme 181) ⟨61JCS3573⟩. Aliphatic acid chlorides are the most efficient acylating agents and Lewis acid catalysis is usually necessary. A detailed preparation of 2,4,6-trimethylpyrylium perchlorate by this route has been published and its merits and alternative methods of synthesis discussed ⟨73OSC(5)1106⟩.



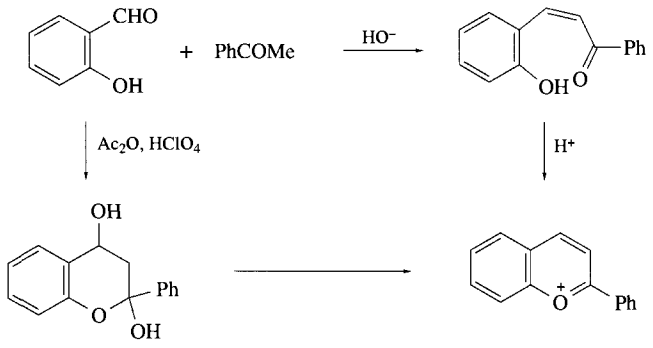
Scheme 181

The method allows considerable variation in substituents ⟨92ZN1011⟩ and lends itself to the formation of cyclic analogues of pyrylium salts ⟨67MI 508-02, 69ZOB716, 72KGS1461⟩. Successive treatment of 3-phenylpropanoic acid with polyphosphoric acid and carboxylic acids leads to a pentacyclic diindeno[*b*,*d*]pyrylium salt ⟨78KGS275⟩.

An unsaturated diketone is an intermediate in the formation of pyrylium salts by the acid catalyzed reaction of 1,3-diketones with methyl ketones ⟨24CB1653⟩. Thus, dibenzoylmethane and acetophenone give 2,4,6-triphenylpyrylium, whilst 2-methyl-4,6-diphenylpyrylium results from benzoxylacetone and acetophenones ⟨33JCS1197⟩. The use of 3-ketoaldehydes leads to 4-unsubstituted pyrylium salts ⟨65ZOB589⟩. A wide variety of substituents in the 1,3-dicarbonyl compound and variation in the structure of the methyl ketone are compatible with this synthetic route and many fused alicyclic and saturated heterocyclic derivatives of pyrylium have been obtained in this manner ⟨67T1821, 69CB1214⟩.

Salicylaldehyde reacts with methyl ketones under acidic conditions to give benzopyrylium salts (Scheme 182) and the same product arises from an initial base catalyzed condensation to the unsaturated ketone followed by cyclization in acid ⟨73BSF3421⟩. The triptycene fused pyrylium salt has been prepared in this way ⟨89RRC617⟩. β-Keto esters can function as the methyl ketone and *o*-hydroxyacetophenone can replace salicylaldehyde, in which case a 4-substituted benzopyrylium salt results. Reaction of salicylaldehydes with nitriles affords 2-aminobenzopyrylium salts ⟨81ZC408⟩. Flavylium salts are formed when arylmalondialdehydes react with phloroglucinol ⟨81AJC2647⟩ and 3-phenylbenzopyrylium salts can be synthesized from phenylacetaldehyde dimethyl acetal and salicylaldehydes ⟨82JHC97⟩.

Further potential of this method follows from the use of β-halovinyl ketones and aldehydes

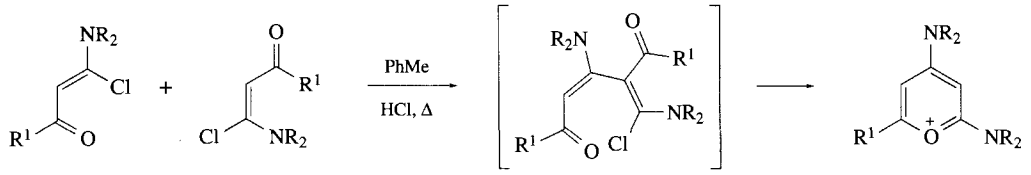


Scheme 182

and β-chlorovinyl immonium salts in place of the 1,3-dicarbonyl components ⟨63ZC266, 69CB1202, 71JPR1110, 73BSF2093, 76ZC337, 79S241⟩.

Enamines may replace the methyl ketone component, giving access to pyrylium salts which are unsubstituted at the 4- and 6-positions ⟨69CB575⟩. Cyclic analogues are available by this methodology ⟨69CB590⟩.

β-Acyl-α-chloroenamines are converted into 2,4-bis(dialkylamino)pyrylium salts in acidic conditions. It is considered that one molecule acts as a β-chlorovinylketone and the other as an enamine (Scheme 183). Under the neutral conditions, the 3-acyl derivative can be isolated ⟨89RRC271⟩.



Scheme 183

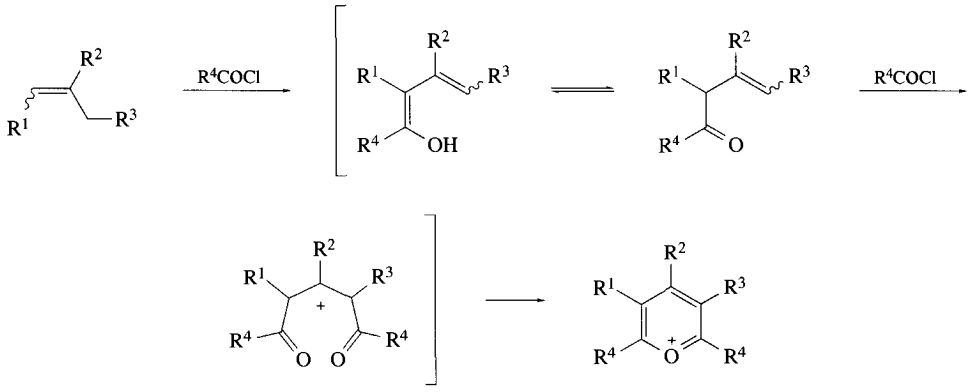
Alkynes, too, can replace the ketone moiety by virtue of their hydration to carbonyl compounds ⟨65CB334⟩. For example, phenylacetylene reacts with 3-chlorophenylprop-2-en-1-one to give 2,6-diphenylpyrylium.

The diacylation of alkenes provides an attractive route to alkyl substituted pyrylium salts and is exemplified by the preparation of 2,6-dimethyl-4-phenylpyrylium sulfoacetate from α-methylstyrene ⟨88OPP289⟩. The sulfoacetate anion has much to commend its use. The reaction is considered to proceed via a non-conjugated enone, which undergoes a second acylation which leads to the pyrylium salt (Scheme 184). Acyl anhydrides and halides in the presence of either Brønsted or Lewis acids are effective acylating conditions. The use of dicarboxylic acid derivatives leads to bicyclic pyrylium salts ⟨62T1079⟩, whilst double diacylation of *m*-diisopropenylbenzene gives the *meta*-phenylene bridged bispyrylium salt ⟨89RRC41⟩.

Reaction conditions can influence the nature of the product. Thus, 2-methylbut-2-ene affords 2,3,4,6-tetramethylpyrylium with acetic anhydride and perchloric acid, but acylation with acetyl chloride and a Lewis acid initiates an alkene isomerization and 4-ethyl-2,6-dimethylpyrylium is produced ⟨82OPP31⟩.

Alcohols and alkyl halides can function as an *in situ* source of the alkene, offering a practical simplification. Full preparative details have been published for 2,4,6-trimethylpyrylium ⟨73OSC(5)1106, 73OSC(5)1112, 73OSC(5)1114⟩ and the 2,3,4,6-tetramethyl derivative ⟨82OPP31⟩. Cyclic ⟨69KGS781⟩ and heterocyclic ⟨73KGS878⟩ tertiary alcohols afford fused and heterocycle substituted derivatives of pyrylium, respectively, and this route has been used to introduce a lipophilic alkyl side chain at C-4 ⟨91RRC229⟩.

In the presence of acids, alkyl orthoformates are converted into dialkoxycarbocations, which efficiently alkylate methyl ketones under mild conditions to yield unsaturated 1,5-diketones and hence 2,6-disubstituted pyrylium salts ⟨71CHE147⟩. Methylene ketones allow the introduction of substitutents at the 3- and 5-positions, whilst with *o*-hydroxyacetophenone and its *C*-acyl derivatives, benzopyrylium and flavylium salts are formed ⟨72CHE935, 72JOU2250⟩. Other sources of dialkoxy-carbocations, such as acetals, ethers, and esters, are equally acceptable in pyrylium synthesis.



Scheme 184

A mixture of an alkyl aryl ketone and an acylating agent yields pyrylium salts with identical substituents at the 2- and 4-positions ⟨65JOC1684⟩. Either a 1,3-diketone or an α,β-unsaturated ketone may function as intermediates. Further simplification of this approach features the acylation of aromatic hydrocarbons ⟨27CB716⟩ and alkoxybenzenes ⟨51JCS726⟩ under Friedel–Crafts conditions.

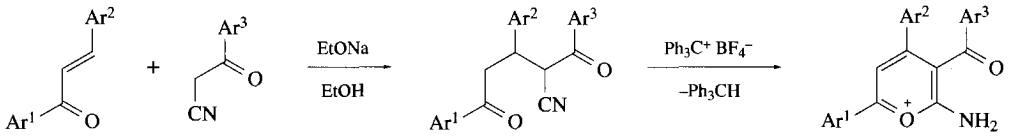
There are several pyrylium syntheses which involve the intermediacy of a pentan-1,5-dione and which therefore require an oxidation step.

Saturated 1,5-diketones themselves are cyclized to pyrylium salts by the triphenylmethyl cation ⟨90LA401⟩, but it is more usual to generate the dione *in situ*.

Michael addition of an aryl methyl ketone to an α,β-unsaturated ketone occurs in acetic anhydride under the influence of either a metal salt or a Lewis acid. Cyclization follows hydride ion abstraction by either the acetyl cation or the enone ⟨72BSF2312⟩. Syntheses of 2,4,6-triphenylpyrylium ⟨73OSC(5)1135⟩, naphtho[1,2-*b*]pyrylium, dibenzo[*c*,*h*]xanthylium ⟨80JCS(P1)1895⟩ and fused-⟨58JCS1978⟩ and bis-pyrylium salts ⟨68BSF4122⟩ exemplify this route. The reaction of an α-keto acid or ester with the enone results in the incorporation of a carboxyl function at C-2 of the pyrylium salt ⟨82JOC492⟩, whilst ethyl 3-oxobutanoate introduces a 3-ethoxycarbonyl group ⟨68JOC1102⟩.

Chalcones can be prepared *in situ* from a methyl ketone and an aldehyde which lacks an α-hydrogen atom. A wide range of substituted acetophenones and benzaldehydes have been utilized and, together with a choice of catalyst and solvent, this method is a convenient route to pyrylium salts with identical substituents at C-2 and C-6 ⟨84OPP407, 94OPP101⟩. When formaldehyde is used, the product is unsubstituted at the 4-position ⟨66BSF2959⟩.

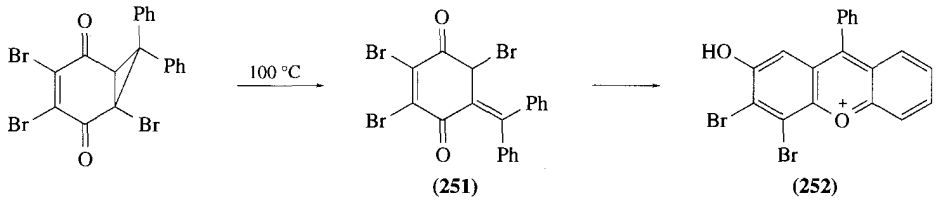
The reaction between an α,β-unsaturated aldehyde and an aryl methyl ketone under basic conditions leads to a 2,4-dienone and these too may be cyclized to a pyrylium salt by Ph_3C^+. Electrophilic attack at either C-2 or C-4 affords a carbocation species which undergoes an intramolecular cyclization. Aromatization involves the loss of triphenylmethane ⟨93BSF218⟩. Chalcones and aroylacetonitriles give 2-aroyl-3,5-diaryl-5-oxopentanenitriles from which 2-aminopyrylium salts can be obtained (Scheme 185) ⟨94JPR623⟩.



Scheme 185

A 2,4-dienone-like species (**251**) is formed when the diphenylhomobenzoquinones are thermolyzed. On heating, (**251**) undergoes an electrocyclization to give xanthylium salts (**252**) (Scheme 186) ⟨94JCS(P1)3325⟩. Xanthylium salts are also formed by the irradiation of the fused naphthoquinone ⟨94CC1681⟩.

As in those syntheses which did not require an oxidation step, synthetic equivalents of the methyl ketone and the α,β-unsaturated carbonyl compounds are acceptable, further extending the scope of pyrylium syntheses ⟨63RTC845, 65CB334⟩.



(251) (252)

Scheme 186

5.08.28.1.2 β to the heteroatom

Diaryl ethers undergo a Friedel–Crafts alkylation on reaction with dichloromethyl methyl ether, which leads to xanthylium salts ⟨73JCS(P1)1104⟩.

5.08.28.2 From Other Heterocycles

5.08.28.2.1 From pyridines

After electrophilic attack at nitrogen, the pyridinium ring is prone to nucleophilic attack at C-2 in much the same way as the pyrylium nucleus. Thus, ring opening of the sulfonate with hydroxide ion affords the enolate of penten-1,5-dial, subsequent acid-catalyzed ring closure of which affords the pyrylium salt ⟨53CB1327⟩.

5.08.28.2.2 From furans

Ring expansion of the hetero ring of benzofuran occurs when its adduct with chlorophenylcarbene is boiled with water. The initial product, benzopyrylium, is trapped as the bisacetal. In the absence of water, heating the cyclopropyl derivative in toluene leads to 2-(benzofuran-2-yl)-3-phenyl-2*H*-1-benzopyran through reaction of benzopyrylium with benzofuran ⟨90LA277⟩.

5.08.28.3 From a Preformed Heterocyclic Ring

5.08.28.3.1 From pyranones and their benzo derivatives

Pyrylium salts result from the reaction of pyranones with both electrophiles and nucleophiles. Alkylation of both 2- and 4-pyranones gives the alkoxypyrylium salt ⟨75T2229⟩ and pyranthiones behave similarly ⟨78JCS(P1)1373⟩. Acylation also effects conversion to pyrylium and in the case of pyran-4-ones even simple protonation to a 4-hydroxypyrylium is feasible. Nucleophilic attack is typified by the reaction of pyranones with organometallic compounds ⟨74JHC405⟩.

In a related manner, both coumarins and chromones take part in reactions with electrophiles and nucleophiles. Protonation of chromone is much more facile than that of coumarin ⟨25LA(446)155, 71CB348⟩. However, coumarins are considered a better source of benzopyryliums salts by way of nucleophilic attack ⟨92CHE283⟩.

Schiff bases derived from pyran-4-ones by reaction with reactive isocyanates form 4-amino-pyrylium salts with acids ⟨74JHC195⟩. Flavonol glycosides have been reduced to anthocyanins by zinc amalgam ⟨95TL4611⟩.

5.08.28.3.2 From pyrans and their benzo derivatives

Oxidation of 4*H*-pyrans to pyryliums is readily accomplished with triphenylmethyl perchlorate and is compatible with a wide variety of substituents ⟨73ACS1385, 76T2225⟩. Both 2*H*-1-benzopyrans ⟨72CR(C)650⟩ and isoflavenes ⟨82JCS(P1)193⟩ behave in a similar manner.

Derivatives of 2-methylenechromenes yield pyrylium salts with acids ⟨93CB823⟩ and chromones can be converted into benzopyrylium salts via their reaction with active methylene compounds ⟨81JHC863⟩.

Pyranols and their benzologues afford the corresponding pyrylium salts on treatment with acid ⟨68T949, 70CJC3388⟩.

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5.09
Pyrans and their Benzo Derivatives: Applications

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5.09.1 PHARMACEUTICALS

A large number of pharmaceutical agents containing the pyran unit that have been encountered in a survey of the literature, including patent applications and granted patents. A selection is thus required of the more pertinent for inclusion in this part of the chapter. Compounds that have reached the healthcare market in at least one country form the major part of this section and are joined by those compounds that await registration, or that have been registered, as they are likely to be launched in the near future. The inclusion of compounds that are currently in clinical trials has been restricted to those that are in the final phase. Such trials include administration to patients suffering from the disease targeted for the compound. Having passed to this stage of what is becoming an ever more rigorous process, compounds in this class are highly likely to be launched. However, no distinction is made between the different classes considered, as apart from post-launch, their status is not entirely clear. The pharmaceutical agents that contain the pyran ring are arranged by therapeutic area (disease state), and in each area they are grouped by structure and pharmacological mechanism of action.

5.09.1.1 Antibiotics and Antiinfectives

5.09.1.1.1 Macrolide antibiotics

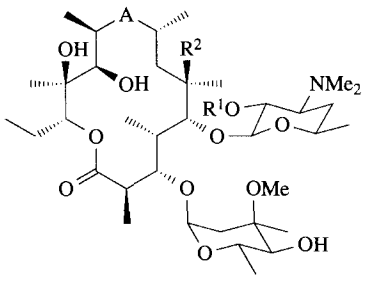
The macrolide antibiotics are part of a large and diverse class of natural products isolated from the culture broths of certain soil microorganisms. The fermentation-derived macrolides are classified by the ring size of the aglycone, the basic lactone ring system, to which are appended either or both amino and neutral sugar residues. The predominant subclasses are based on a 14- or 16-membered aglycone. Reviews have covered the 14-membered- ⟨B-93MI 509-01⟩ and 16-membered aglycones ⟨B-94MI 509-01⟩.

The archetypal 14-membered aglycone antibiotic, erythromicin (**1**), isolated from *Saccharopolyspora erythraea*, is the most widely used member of the macrolide class ⟨57JA6070⟩, being prescribed for the treatment of respiratory tract, skin and soft tissue infections, particularly in cases of penicillin allergy. However, erythromycin can cause intestinal discomfort, and its instability in the acidic environment of the stomach leads to unsatisfactory pharmacokinetics. Certain intramolecular reactions involving degradation of the aglycone occur in this environment that lead to inactive products, and in an effort to counter this tendency and to improve the palatability, a number of semisynthetic analogues has been developed. Roxithromycin (**2**) ⟨81FRP2473525⟩, azithromycin (**3**) ⟨84EUP101186⟩, clarithromycin (**4**) ⟨84JAN187⟩, flurithromycin (**5**) ⟨83JAN1439⟩, dirithromycin (**6**) ⟨90JAN1271⟩, and erythromycin carbonate (**7**) ⟨89EUP307177⟩ were designed to foil undesired transformation of the aglycone nucleus, while erythromycin acistrate (**8**) is a prodrug formulated as the stearate addition salt ⟨88MI 509-01⟩. Other salt derivatives of erythromycin are in development.

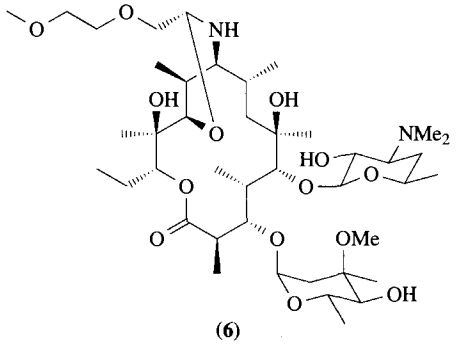
The 16-membered macrolides comprise two main families, the tylosins and the leucomycins, that are based on the substitution patterns of their aglycone units. While the former class has not as yet produced any compounds for human use, the latter has provided several drugs. Thus, josamycin (**9**) has been isolated from *Streptomyces narbonensis* ⟨67JAN174⟩, and midecamycin (**10**) from *Streptomyces mycarofaciens* ⟨71JAN319⟩. Miokamycin, diacetylated midecamycin (**11**) ⟨76JAN536⟩, and rokitamycin (**12**) ⟨81JAN1001⟩ are two semisynthetic analogues that have been prepared to improve absorption and palatability.

Although studies into the mechanism of action of the macrolides have concentrated on erythromycin, it is considered that they all possess the ability to penetrate the cell, bind to the 50S ribosomal subunit and disrupt protein synthesis.

Amphotericin B (**13**), first approved for use in 1958, remains the primary systemically administered fungicidal compound used today. Toxicity is a major side effect, and many complexes and formulations have been evaluated in an effort to reduce it while retaining the antifungal potency. One



(1) A = C=O, R^1 = H, R^2 = OH
(2) A = C=NOCH$_2$O(CH$_2$)$_2$OMe, R^1 = H, R^2 = OH
(3) A = N(Me)CH$_2$, R^1 = H, R^2 = OH
(4) A = C=O, R^1 = H, R^2 = OMe
(5) A = C=O, R^1 = H, R^2 = F
(8) A = C=O, R^1 = Ac, R^2 = H; stearate salt



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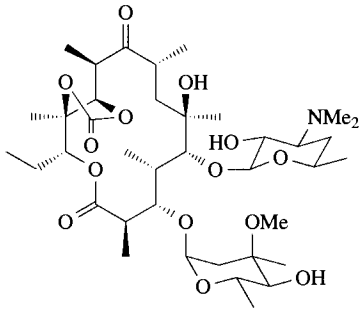

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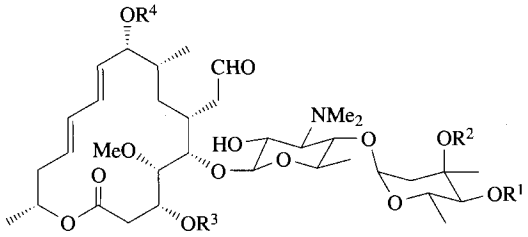
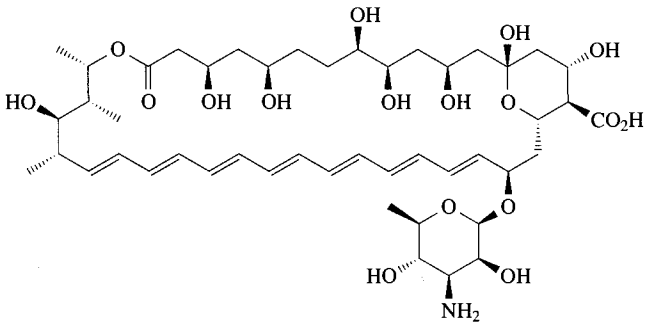


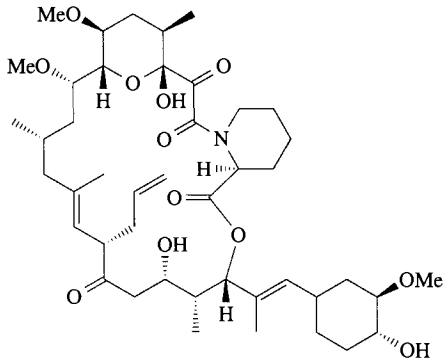
(9) R^1 = COBu^i, R^2 = R^4 = H, R^3 = Ac
(10) R^1 = R^3 = COEt, R^2 = R^4 = H
(11) R^1 = R^3 = COEt, R^2 = R^4 = Ac
(12) R^1 = COPr^n, R^2 = COEt, R^3 = R^4 = H

formulation that is reported to offer this advantageous profile is the 1 : 1 complex of amphotericin B with cholesteryl sulfate ⟨91MI 509-01⟩. The compound exerts its pharmacological effect by binding to ergosterol, which is commonly found in fungal cell membranes, thus leading to membrane instability and breakdown.



(13)

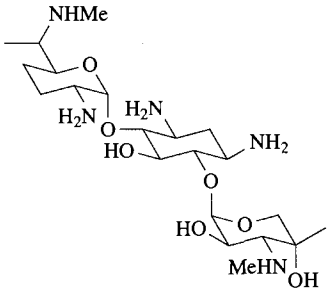
Extraction of the mycelia of *Streptomyces tsukubaensis* ⟨87JAN1249⟩ produces the novel macrolide immunosuppressant agent tacrolimus (**14**). It is particularly useful in combination with corticosteroids following liver or kidney transplantations, and is beneficial in countering graft rejection.



(**14**)

5.09.1.1.2 Aminoglycosides

Another important class of antibiotic agents is the aminocyclitol aminoglycosides exemplified by the gentamicin C complex (**15**) ⟨63USP3091572⟩, a Gram-negative bactericide. Like the macrolide antibiotics they are thought to act directly on the ribosome (but at the 30S unit) and thus to inhibit protein synthesis. Other closely related compounds isolated from natural sources are sisomicin (**16**; R = H) from *Micromonospora inyoesis* ⟨70JAN551⟩, micronomicin (**17**) from *Micronospora sagamiensis* ⟨74JAN793⟩, astromicin (**18**) from *Micromonospora olivoasterospora* ⟨77JAN552⟩, and the furanose ribostamycin (**19**) from *Streptomyces ribosidificus* ⟨70JAN173⟩. Semisynthetic analogues, designed to improve the spectrum of antibiotic activity, are netilimicin (**16**; R = Et) ⟨76CC206⟩ derived from sisomicin, dibekacin (**20**) ⟨71JAN485⟩, isepamicin (**21**) ⟨75GEP(O)2437159⟩, and arbekacin (**22**) ⟨80BEP879925⟩.



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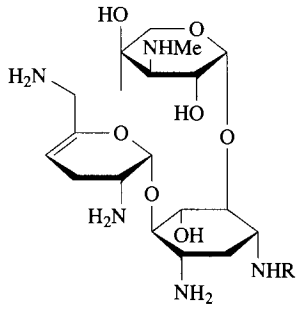

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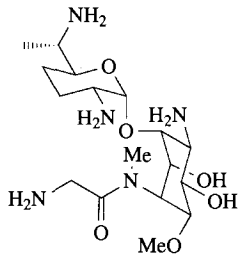

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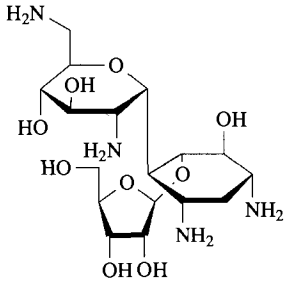

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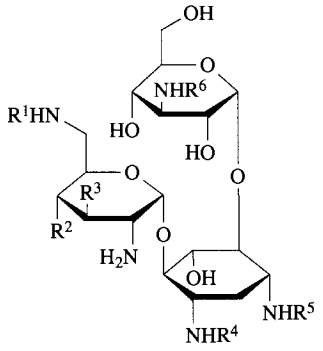
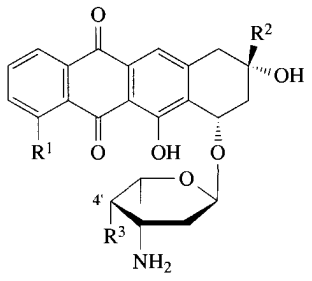


(**17**) R^1 = Ac, R^2–R^5 = H, R^6 = Me
(**20**) R^1–R^6 = H
(**21**) R^1–R^4 = H R^2 = R^3 = OH, R^5 = (*S*)-COCH(OH)CH_2NH_2, R^6 = Me
(**22**) R^1–R^4, R^6 = H, R^5 = (*S*)-COCH(OH)$(CH_2)_2NH_2$

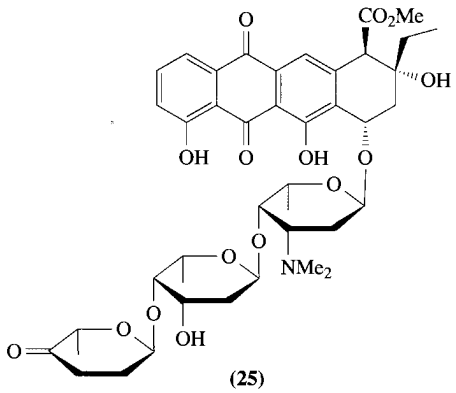
5.09.1.1.3 Anthracycline antibiotics

The members of the class of naturally occurring anthracycline antibiotics derived from anthraquinone that are reviewed here have been isolated from culture broths of *Streptomyces* species. They have a particular application as antitumor agents and exert their pharmacological activity by blocking the synthesis of RNA copies of DNA at the cellular level by binding to DNA.

Daunorubicin (**23**) ⟨64NAT706⟩ and doxorubicin (**24**) ⟨69MI 509-01⟩, are both produced by culturing *Streptomyces peucitus*. The latter is active against a whole range of cancers and has been one of the most widely used chemotherapeutic agents for human tumors. However two of the drawbacks of these agents are their level of cardiotoxicity and incidence of alopecia (hair loss). In order to improve the therapeutic ratio further natural analogues have been sought and aclarubicin (**25**), isolated from *Streptomyces galileus* ⟨75JAN830⟩, is particularly useful against some forms of lung cancer, with a lower incidence of side effects. Beside the search for natural analogues with improved side effect profile, several semisynthetic analogues such as zorubicin (**26**) ⟨74GEP(O)2327211⟩, pirarubicin (**27**) ⟨79JAN1082⟩, and idarubicin (**28**) ⟨76MI 509-01⟩ have been prepared. An interesting synthetic analogue is epirubicin (**29**) where the stereochemistry of the 4′-hydroxyl group in the sugar residue is inverted ⟨75JMC703⟩. The mode of antitumor action and efficacy of the compound class are retained in this compound while the cardiotoxicity is reduced.

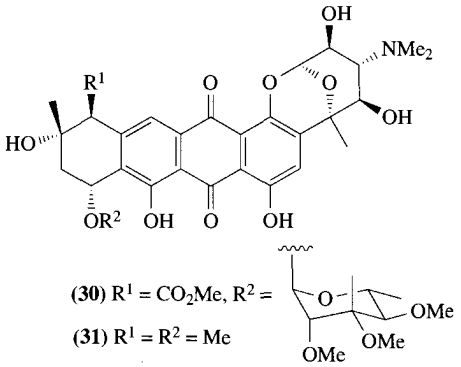


(**23**) R^1 = OMe, R^2 = Ac, R^3 = OH
(**24**) R^1 = OMe, R^2 = $COCH_2OH$, R^3 = OH
(**26**) R^1= OMe, R^2 = C(Me)=NHCOPh, R^3 = OH
(**27**) R^1= OMe, R^2 = $COCH_2OH$, R^3 = OTHP
(**28**) R^1 = H, R^2 = Ac, R^3 = OH
(**29**) R^1 = OMe, R^2 = $COCH_2OH$, R^3 = *epi*-OH



(**25**)

Undue levels of toxicity precluded the progression of the natural anthracycline nogalamycin (**30**), but a semisynthetic derivative menogaril (**31**) was used to overcome this problem ⟨77JAN628⟩. Potentially useful for the treatment of stomach and breast cancers, the compound exerts its pharmacological action by inhibiting DNA topoisomerase II.

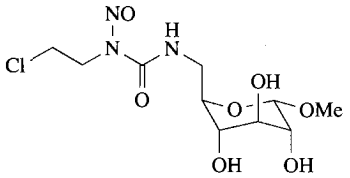


(**30**) R^1 = CO_2Me, R^2 =
(**31**) R^1 = R^2 = Me

5.09.1.1.4 Miscellaneous antibiotics

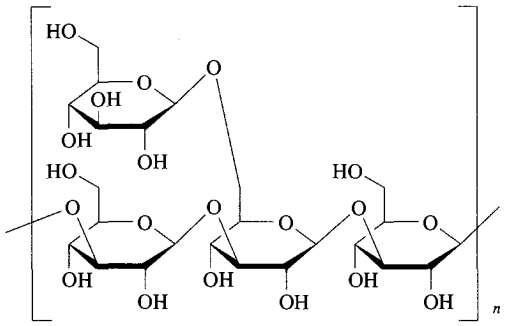
Nitrosoureas have emerged as an important group of antineoplastic agents with a wide spectrum of activity, including the treatment of lung cancers, brain tumors, and leukaemia. Ranimustine (**32**)

is a water soluble nitrosourea analogue ⟨79MI 509-01⟩ that exerts its pharmacological effect as an alkylating agent by inhibiting the last step in DNA repair.



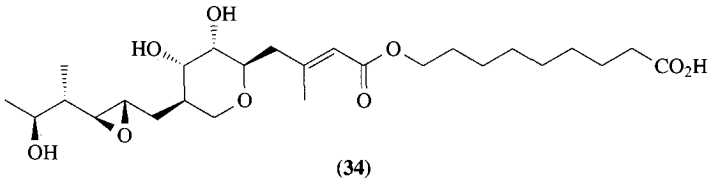
(32)

Schizophyllan (**33**) is a polysaccharide isolated from the fermentation broth of the microorganism *Schizophyllum commune* ⟨80MI 509-01⟩. Material of molecular weight 4.5×10^5 is used in the clinic for several forms of tumor, particularly cervical cancer.



(33)

Mupirocin (**34**) is the major component of a pseudomonic acid complex produced by *Pseudomonas fluorescens* ⟨78JCS(P1)561⟩ that is primarily active against Gram-positive organisms, exerting a bacteriostatic effect. It is used particularly for the treatment of dermal infections.



(34)

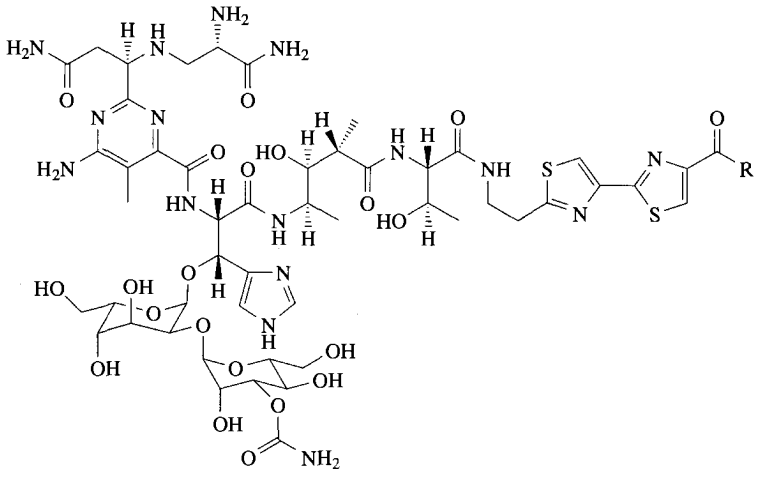
Peplomycin (**35**), an analogue of bleomycin (**36**), is isolated from the culture medium of *Streptomyces verticillis* ⟨74USP3846400⟩ when it is incubated in the presence of *N*-[(*S*)-1′-phenethyl]-1,3-diaminopropane. It is used for the treatment of oral, maxillofacial, and skin cancers, being as effective as bleomycin, but with milder side effects.

The antifungal agent siccanin (**37**), isolated from culture filtrates of *Helminthosporium siccans* ⟨62JAN161⟩, is reported to inhibit the aerobic respiration of various pathogenic fungi.

5.09.1.2 Cardiovascular Agents

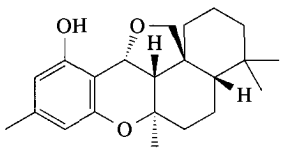
The β-adrenoceptor antagonists, or β-blockers, are one of the principal classes of drugs for the treatment of the cardiovascular diseases of elevated blood pressure, angina, and arrhythmias. Bucumolol (**38**) is used for the treatment of angina and arrhythmias ⟨72CPB905⟩, while nebivolol (**39**) lowers blood pressure ⟨85EUP145067⟩. In some cases acceptable levels of blood pressure cannot be achieved solely with β-blockers, and it is necessary to coprescribe an additional drug with an alternative pharmacological action. However, certain compounds, such as nipradilol (**40**), have been developed ⟨81EUP42299⟩ that possess an additional mode of action. Besides β-blockade, nipradilol has the ability to cause vasodilation reportedly by blockade of α-adrenoceptors. Interestingly, all three compounds (**38**)–(**40**) have been developed as racemates.

Hypocholesterolaemia is a primary risk factor for coronary heart disease. The fungal metabolite, lovastatin (**41**; R^1 = Me, R^2 = H) isolated from cultures of *Aspergillus terreus* ⟨80PNA3957⟩; a closely

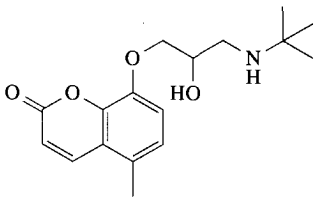


(**35**) R = (*S*)-$(CH_2)_3NHCH(Me)Ph$

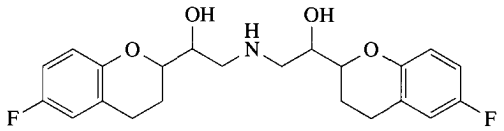
(**36**) R = $(CH_2)_3\overset{+}{S}Me_2 \cdot Cl^-$



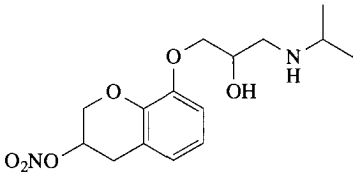
(**37**)



(**38**)



(**39**)

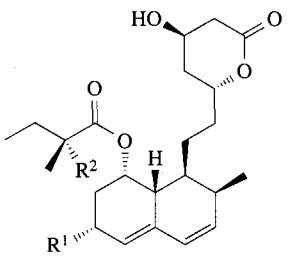


(**40**)

related semisynthetic derivative, simvastatin (**41**; $R^1 = R^2 = Me$) ⟨86JMC849⟩; and the synthetic compound dalvastatin (**42**) ⟨89MIP8905639⟩ are potent cholesterol-lowering drugs. They inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis, through the active hydroxyacid form derived by opening the lactone.

Cromakalim (**43**) was developed as an antihypertensive agent but as the vasodilatory activity resided almost exclusively in the (3*S*,4*R*) enantiomer, levcromakalim, it was decided to concentrate on this enantiomer ⟨86JMC2194⟩. The compound activates the ATP-dependent potassium channel in vascular smooth muscle and this subsequently leads to a relaxation of the muscle and hence of the blood vessel. In 1994, it was reported that levcromakalim has the additional property of increasing HDL-cholesterol while reducing LDL-cholesterol and plasma triglycerides in hypercholesterolemic patients ⟨94MI 509-02⟩, although the mechanism by which it exerts this effect is not known.

The flavone glycoside diosmin (**44**; R = H), isolated from a variety of natural sources such



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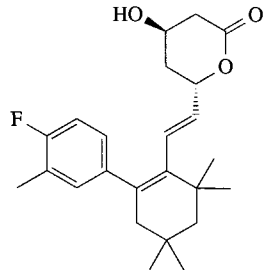

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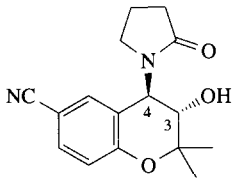
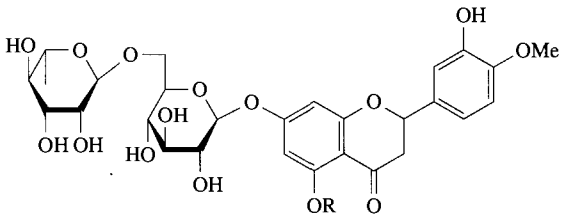


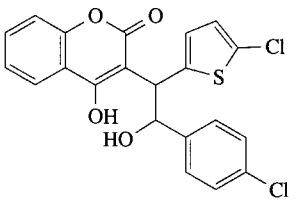
(43)

as *Sophora microphylla* ⟨60JCS1955⟩ protects fragile capillary blood vessels. Conversion to the hydroxyethoxy derivative hidrosmin (**44**; R = $(CH_2)_2OH$) enhanced the action of the compound on venous tone ⟨86MI 509-01⟩.



(44)

Tioclomarol (**45**) is an anticoagulant agent ⟨72MI 509-01⟩ related to warfarin (**46**), which inhibits epoxide reductase, an agent in the process of vitamin K regeneration needed for clotting factor synthesis.



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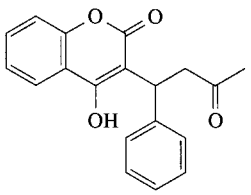
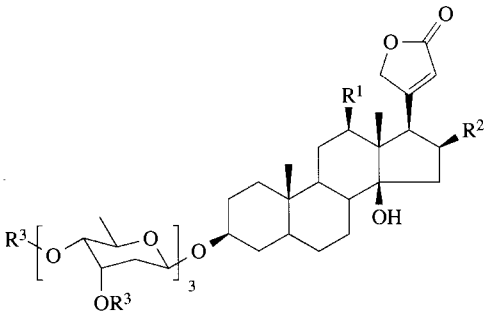


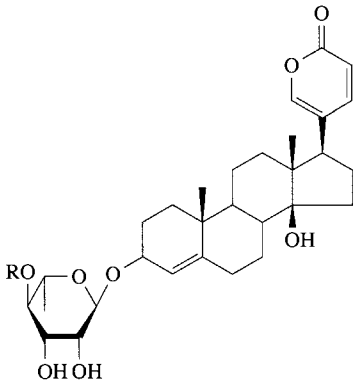
(46)

Although the cardiac glycosides represent one of the earliest classes of folklore medication, dating from about 1250, the pharmacological effect of the digitalis plant was only shown to be direct stimulation of the contractility of cardiac muscle as recently as 1938. Although their use has declined, digoxin (**47**) and to some extent, digitoxin (**48**), are still prescribed as cardiotonic agents. The major side effect, cardiac toxicity, has encouraged the search for analogues with improved therapeutic indices. Two such compounds, gitoformate (**49**) ⟨80MI 509-02⟩ and the the 4-methoxy derivative, meproscillarin (**50**; R = Me) ⟨78AF493⟩, of proscillaridin (**50**; R = H) have been derived by this approach.

Much research has also been directed towards novel nonglycosidic cardiotonic agents, to obviate the cardiotoxicity of the glycosides. Forskolin (**51**; R = H), a labdane-type diterpene isolated from the root of the *Coleus forskohlii* plant, increases both the intracellular cyclic AMP levels in the heart

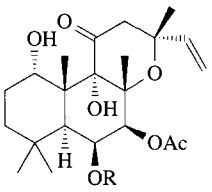


(47) R^1 = OH, R^2 = R^3 = H
(48) R^1 = R^2 = R^3 = H
(49) R^1 = H, R^2 = R^3 = CHO



(50)

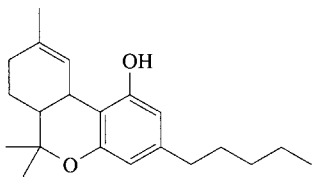
and the contractile force of heart muscle. Due to the low oral activity and poor water solubility of forskolin, the water soluble derivative NKH-477 (**51**; R = $CO(CH_2)_2NMe_2$) has been developed ⟨87EUP222413⟩.



(51)

5.09.1.3 Neurological Modulators

The medicinal use of cannabinoids began during the earliest days of general drug treatment. Thus Δ-9-tetrahydrocannabinol (**52**) exerts a sedative and relaxant effect in humans, but with unacceptable cardiovascular and CNS side effects. Nabilone (**53**) ⟨75GEP(O)2451932⟩ is a synthetic analogue that retains the useful actions but with reduced incidence of side effects.



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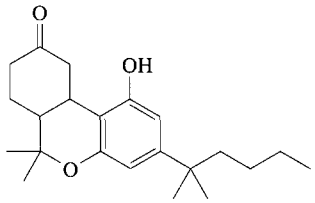

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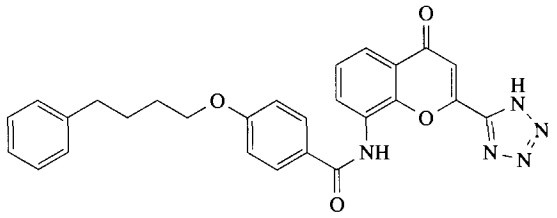
5.09.1.4 Antiallergic and Antiasthmatic Agents

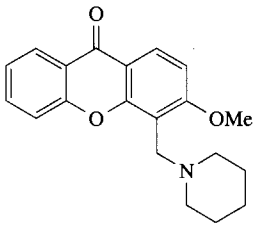
Pranlukast (**54**) is an antiallergic and antiasthmatic drug ⟨88JMC84⟩ that mediates its action as a selective orally active antagonist of peptido-leukotrienes. These compounds are arachidonic acid

metabolites that are potent bronchoconstrictors and modulators of mucosal production and transfer.



(54)

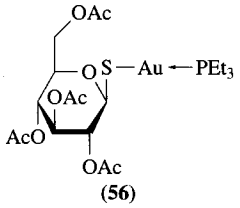
Mepixanox (**55**) was developed from a series of compounds originally prepared to evaluate CNS stimulatory properties ⟨70JMC527⟩. It has been found subsequently to possess respiratory stimulatory properties and to be useful for the treatment of chronic pneumopathy and other cardiorespiratory insufficiencies.



(55)

5.09.1.5 Antiinflammatory Agents

In vitro studies using models of human immune responsiveness have shown that auranofin (**56**) acts as an immunosuppresive agent ⟨88MIP144447⟩ and that its effectiveness in the treatment of rheumatoid arthritis may be due to interference with monocyte function, in a similar manner to other gold-containing antiarthritic drugs. Clinical trials have demonstrated its effectiveness in treating juvenile rheumatoid arthritis and progressive chronic arthritis, particularly when nonsteroidal antiinflammatory drugs have been found to be inadequate in controlling the disease activity. A major advantage is that unlike other gold drugs that have to be given intramuscularly, it may be taken orally.



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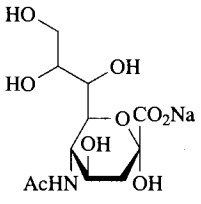
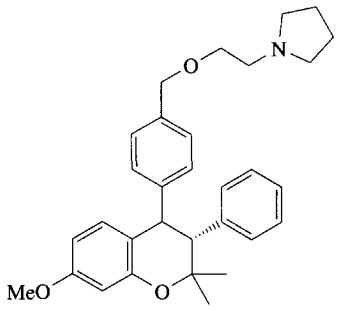
Sodium aceneuramate (**57**) ⟨91MI 509-02⟩ was originally promoted as an expectorant but has subsequently been developed as an arthritic agent.



(57)

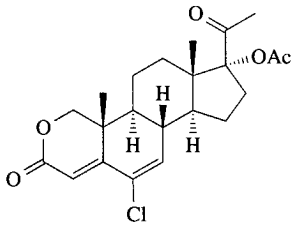
5.09.1.6 Reproduction and Genitourinary Agents

The search for nonsteroidal pregnancy-inhibiting agents has yielded centchroman (**58**) ⟨76JMC276⟩ that possesses weak oestrogenic and potent antioestrogenic actions. The contraceptive action of the drug may arise from the inhibition of oestrogen-sensitive events prior to the implantation of the fertilized egg in the uterus.



(**58**)

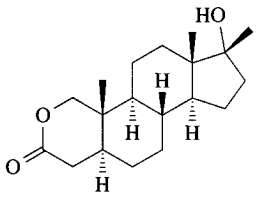
Enlargement of the prostate gland, a condition known medically as benign prostatic hyperplasia, is largely corrected by surgery. The more amenable course of drug treatment has prompted the search for drugs that, for example, are able to cause a shrinkage of the hyperplastic tissue of the human prostate. One strategy is to use an androgen receptor antagonist such as osaterone acetate (**59**) ⟨92CPB935⟩ to reduce androgen levels, as androgenic steroids are partly responsible for prostate growth.



(**59**)

5.09.1.7 Growth Promoters

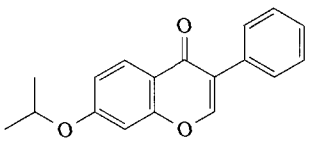
Use of the anabolic steroid oxandrolone (**60**) ⟨62TL365⟩ results in increased growth velocity in young men who have a delay in reaching adolescence. In combination with recombinant human growth hormone, the drug is effective in the treatment of short stature in young women with Turner syndrome, a form of mental retardation.



(**60**)

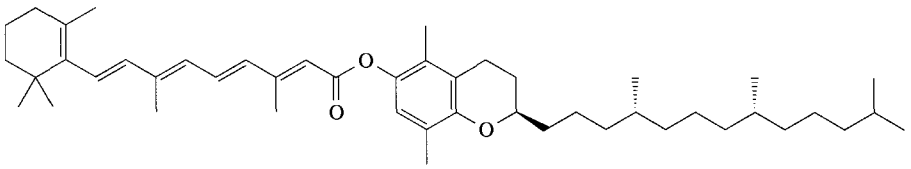
The original claim for the medicinal use of ipriflavone (**61**) was as an anabolic agent ⟨71GEP(O)2125245⟩. Subsequent investigation of its cardiovascular properties ⟨79MI 509-02⟩ suggested

a possible use for the treatment of angina. However, it is now marketed as an antiosteoporotic, as its action as a calcium regulator is manifested by its inhibition of calcium release from bone.



(61)

Tocoretinate (**62**) is a hybrid compound composed of retinoic acid esterified with α-tocopherol, that has pharmacological actions that cannot be reproduced by the individual constituents. The drug is effective in promoting cell growth in human intestinal mucosal cells by enhancing epidermal growth factor-induced DNA synthesis ⟨93MI 509-02⟩.

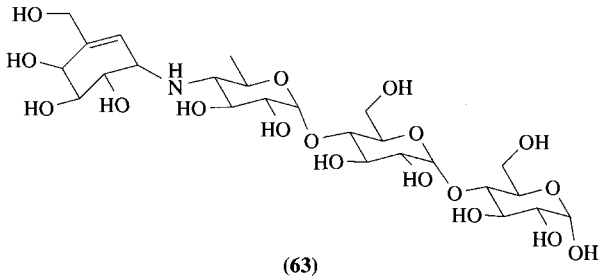


(62)

Although Δ-9-tetrahydrocannabinol (**52**) was found to have cardiovascular and CNS side effects that precluded its use as a sedative and relaxant under normal conditions, it can be used in certain circumstances. Hence it has been found to induce appetite stimulation and weight gain in patients with AIDS-related anorexia and weight loss ⟨93MI 509-03⟩.

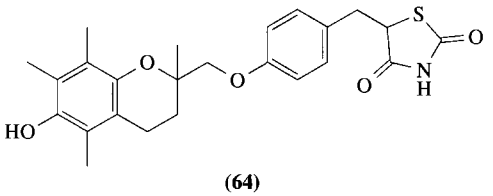
5.09.1.8 Antidiabetic Agents

Acarbose (**63**) is derived from a high molecular weight α-amylase inhibitor isolated from the culture broth of various *Actinoplanes* strains grown with D-glucose or maltose as the sole source of carbon, mild hydrolysis of which gives acarbose ⟨77N535⟩. The compound delays digestion of complex carbohydrates and disaccharides to absorbable monosaccharides, by inhibiting α-glucosidases. Clinical trials have shown that acarbose generally improves glycaemic control in patients with noninsulin-dependent diabetes mellitus.



(63)

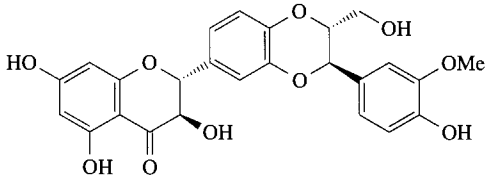
Troglitazone (**64**) ⟨89JMC421⟩ was designed to treat angiopathy, possessing either or both hypolipidemic and hypoglycaemic activity together with an ability to lower lipid peroxide levels, the latter action said to be attributed to the presence of the hindered phenolic group. It is particularly useful in obese and noninsulin-dependent diabetes mellitus.



(64)

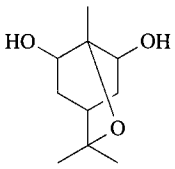
5.09.1.9 Miscellaneous

Certain members of the flavanolignans, a class of natural flavanoids, possess liver protection properties. Silybin (**65**) is a typical example but is poorly absorbed on oral administration. However, this problem is overcome as it forms a complex, IdB-1016, with phosphatidyl choline ⟨87EUP209038⟩ that possesses a surprisingly high lipophilicity. Silybin was found to have antioxidant activity and to enhance RNA-polymerase-1 activity.



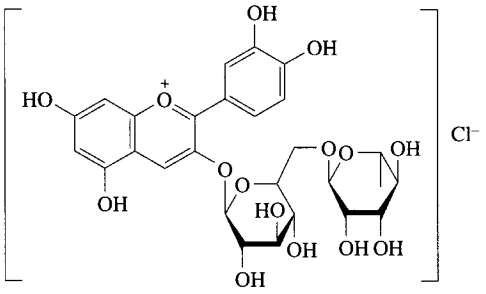
(**65**)

The preparation of the synthetic terpenoid epomediol (**66**) ⟨79PJC2213⟩ has been simplified and the yield increased ⟨87URP1346638⟩. The compound is reported to possess choleretic properties that are cytochrome *P*450 dependent.



(**66**)

Keracyanin (**67**), the 3-rhamnoglucoside of cyanidin chloride, has been isolated from a number of natural sources such as sour cherries ⟨56JA979⟩. It is used in the treatment of night blindness by reducing the time to adjust to darkness, but the mechanism of its pharmacological action remains undefined.

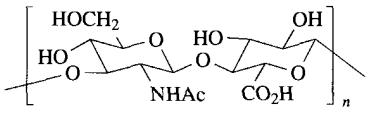


(**67**)

5.09.1.10 Healthcare

Hyaluronic acid (**68**) is a natural high-viscosity mucopolysaccharide that is found in the umbilical cord, in vitreous humour and in synovial fluid ⟨54JA1753⟩. The molecular weight of the synthetic material is between 5×10^4 and 8×10^6, depending on factors such as method of preparation. The compound is used as a viscoelastic protectant in ophthalmological surgery, permitting manipulation of ocular tissues, maintenance of the anterior chamber and protection of the corneal endothelium from damage. In patients with osteoarthritis, knee pain, and joint motion were improved with

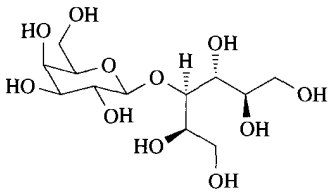
hyaluronic acid injected intraarticularly, suggesting a further use for high molecular weight hyaluronic acid.



(68)

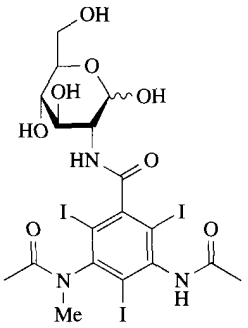
Povidone (polyvinylpyrrolidinone), formulated with β-D-fructofuranosyl α-D-glucopyranoside and iodine is an ointment preparation, KT-136, developed for the treatment of wounds such as bedsores and skin ulcers ⟨91MI 509-03⟩. It is suggested that the antioedema and granulation stimulating properties of KT-136 contribute to its wound healing potential. These are enhanced by antimicrobial properties, as certain species such as *Staphylococcus aureus*, *Staphylococcus epidermis*, *Candida albicans*, and *Pseudomonas aeruginosa* are susceptible to the effect of Povidone–iodine. The sugar portion (70%) is described as the healing agent ⟨91MI 509-04⟩.

Lactitol (**69**) is a disaccharide used in the management of hepatic encephalopathy. It has laxative properties and is used in the alleviation of constipation, being particularly useful in cases where the harsher laxatives are contraindicated ⟨89MI 509-01⟩.



(69)

Two diagnostic aids are metrizamide (**70**) ⟨71GEP(O)2031724⟩, a radiopaque medium used as an x-ray contrast agent, and echovist, D-galactose ⟨93MI 509-04⟩, an echogenic contrast agent that is used in color Doppler investigations of certain organs such as the cardiovascular and female reproductive systems.



(70)

Cyclodextrins, used to form stable, water-soluble inclusion complexes of a number of drugs are discussed in Section 5.09.9.1. Certain hydrogels find similar applications, and are considered in Section 5.09.5.1.2.

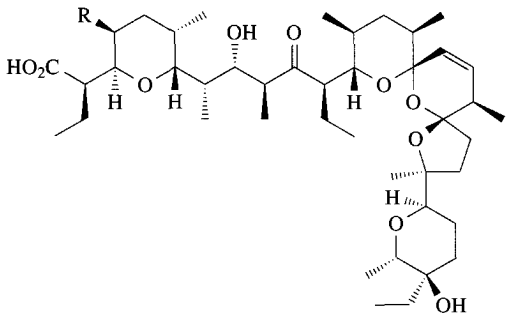
5.09.2 VETERINARY PRODUCTS

Compounds that are available for veterinary use are often administered prophylactically in animal foodstuff, and could therefore be classed as agrochemicals. However, it is appropriate to consider them in this section as they can be used at therapeutic doses for the amelioration of disease states,

particularly those that are amenable to antibiotic treatment. However, certain compounds that have application as pharmaceuticals and have already been considered in the earlier section will receive only a brief mention here.

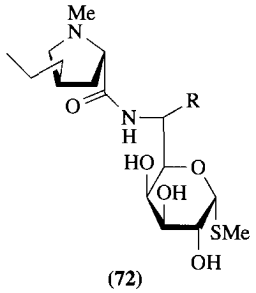
5.09.2.1 Antibiotics and Antiinfectives

Salinomycin (**71**; R = H), obtained by culturing a strain of *Streptomyces albus* ⟨72JAP(K)7225392⟩, and narasin (**71**; R = Me), 4-(*S*)-methylsalinomycin, the main component of a polyether complex produced by *Streptomyces aurofaciens* ⟨78JAN1⟩ are now used to prevent coccidiosis, particularly in broiler chickens. They are characterized by the presence of an unusual tricyclic spiroketal ring system.



(**71**)

Clindamycin (**72**; R = (*R*)—CHClMe) is a semisynthetic analogue ⟨70JMC616⟩ of lincomycin (**72**; R = (*S*)—CHOHMe), where the 7-(*R*) hydroxyl group is substituted by a 7-(*S*) chlorine atom. This enhances both the potency and the antibacterial activity spectrum, and increases absorption. The compound is used for the treatment of dental infections, abscesses and infected wounds, particularly those caused by Gram-positive organisms such as *Staphylococcus* species.



(**72**)

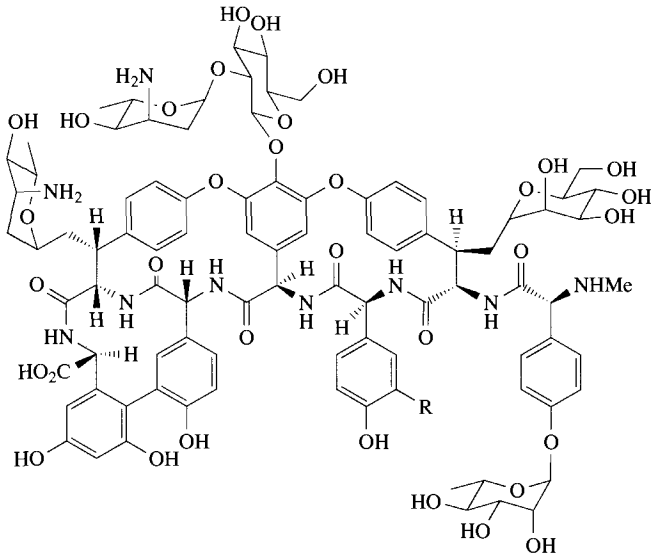
A glycopeptide antibiotic complex produced by the microorganism *Streptomyces candidus*, avoparcin ⟨68MI 509-01⟩, contains α-avoparcin (**73**; R = H) and its chlorinated analogue β-avoparcin (**73**; R = Cl) as major components. It is used principally as a growth promoter and antibacterial feed additive for cattle, pigs, and poultry.

Another antibiotic complex used to enhance growth and to improve the efficiency of feed conversion in pigs, poultry, calves, and fattening cattle is bambermycin ⟨65MI 509-01⟩, a mixture of at least four components, of which the major is meonomycin A (**74**) ⟨81AG(E)121⟩. The complex is obtained by culturing certain *Streptomyces* species, such as *S. bambergiensis*, *S. ghanaensis*, and *S. eclerensis*.

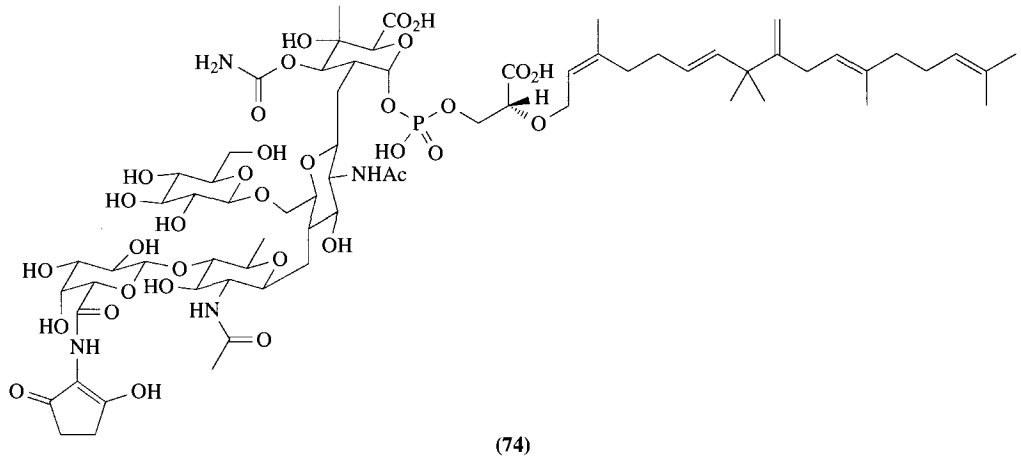
Haloxon (**75**) ⟨62BEP610896⟩ is an anthelmintic agent used to treat and control the spread of adult and immature ascarids.

5.09.2.2 Antiinflammatory Agents

Pentosan polysulfate (**76**), a semisynthetic sulfated analogue of polymeric β-D-xylopyranose residues is used as an anticoagulant ⟨53SZP293566⟩, provided certain properties such as degree of



(73)



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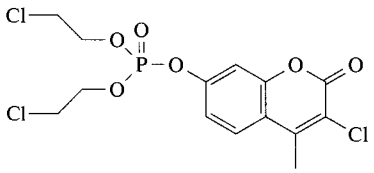
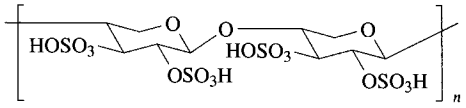


(75)

viscosity, molecular weight distribution and sulfur content are attained during its preparation. It is also used in canine osteoarthritis and allied musculoskeletal conditions, except when its major property is contraindicated, for example by the presence of wounds.

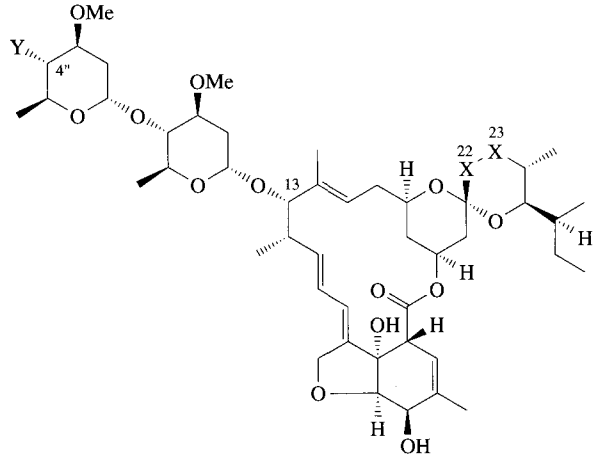


(76)

Hyaluronic acid (**68**) can be used for intraarticular treatment of inflammatory conditions of equine joints, and for the treatment of chip fractures.

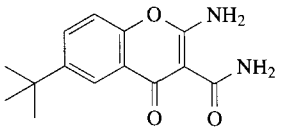
5.09.3 AGROCHEMICALS

The avermectins are a family of naturally occurring macrocyclic lactones with an α-L-oleandrosyl-α-oleandrosyl disaccharide attached at the 13-position ⟨81JA4216⟩. Since their initial discovery in the 1970s, there has been considerable interest in their total synthesis and chemical modification. Of the most effective analogues, abamectin (**77**; X—X = CH=CH, Y = OH) is the nonproprietary name for the natural product avermectin B_1, and is developed for use against agriculturally important insects and mites. The 22,23-dihydro analogue, ivermectin (**77**; X—X = CH_2—CH_2, Y = OH) is widely used as an anthelmintic agent in animals including cattle, sheep, swine, and horses ⟨B-89MI 509-02⟩. The 4″-methylamino-4″-deoxy analogues were found to have enhanced potency against insects. MK243 (**77**; X—X = CH=CH, Y = *epi*-NHMe) was thus selected for further development as an agricultural insecticide ⟨B-90MI 509-01⟩. A study of the 13-*epi* analogues of natural avermectins has also been described ⟨92JMC3873⟩. Biological evaluation revealed that avermectin analogues with inverted stereochemistry at C-13 retain full anthelmintic activity whilst having significantly lower toxicity. Thus the improved therapeutic index of 13-*epi*-avermectins may allow their use in a broader range of applications.



(**77**)

A new class of fungicidal chromone-3-carboxamides has been identified from a random screening program ⟨90MI 509-02⟩. In a follow up structure–activity relationship study, chromone (**78**) has been highlighted as a promising agent against major fungal diseases of the rice plant such as sheath blight, rice blast, and bakanae disease, curatively rather than preventively. Subsequent field evaluation has found (**78**) to be superior to ferimzone in efficacy against sheath blight without being phytotoxic to the host plant.

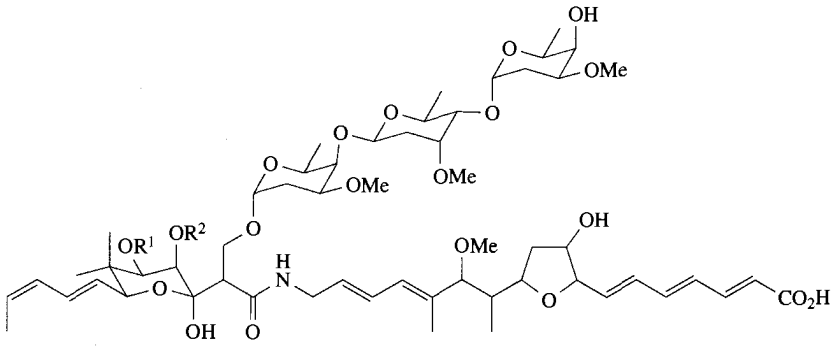


(**78**)

Ganefromycin-α (**79**; R^1 = H, R^2 = $COCH_2Ph$) and -β (**79**; R^1 = $COCH_2Ph$, R^2 = H) are antibiotics produced by *Streptomyces lydicus* ssp. *tanzanius* ⟨89JAN1489⟩. They have been found to have exceptional activity as growth promoting agents in livestock and represent a potential lead in the commercial development of performance enhancing agents ⟨93JOC6588⟩. A complete stereochemical assignment of these compounds has yet to be made.

5.09.4 TOXINS

This class of compound, derived from a variety of natural sources, provides a range of uses, for example serving as a chemical defence system for the producing organisms. These compounds also

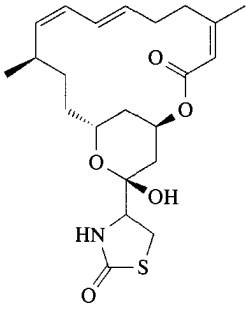


(79)

have a disadvantageous impact in certain food industries. Their study is of importance not only because of their obvious toxic and economic effects in humans, but also because of their mechanisms of biological action, which may have importance as pharmacological probes.

5.09.4.1 Marine Toxins

Among the most prolific sponges in the Red Sea is the red colored *Latrunculia magnifica* that enjoys an immunity from attack by fish. Two toxins, latrunculin A (**80**) and latrunculin B (**81**), isolated from this sponge, are known to be particularly toxic to fish. They are the first marine macrolides known to contain 16- and 14-membered rings, and are further characterized by the rare natural occurrence of the thiazolidinone group ⟨80TL3629⟩. Studies of their mode of action indicate that both compounds are able to disrupt microfilament organization in cultured cells ⟨83SCI493⟩. The stereochemistry of the 8-methyl group in latrunculin B is presently unknown.



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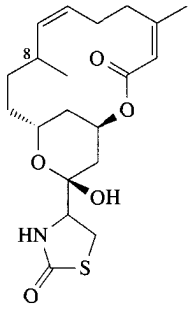
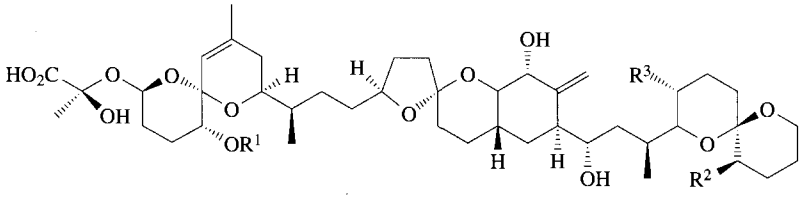


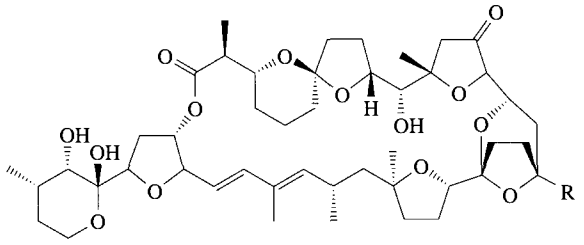
(81)

Diarrhetic shellfish poisoning, so named because of the predominant human symptom of gastroenteritis, was first confirmed in Japan. However, it has now been recognized as a major worldwide problem for the shellfish industry. It arises when normally edible fish and shellfish accumulate toxins as a result of ingesting toxic organisms such as the marine dinoflagellates. Two groups of polyethers identified as causative toxins of diarrhetic shellfish poisoning are okadaic acid (**82**) ⟨81JA2469⟩ and related dinophysistoxins 1-3 (**83**)–(**85**) ⟨85T1019, 92CC39⟩, and the polyether lactones known as pectenotoxins 1-3 (**86**)–(**88**) ⟨85T1019, 86ABC2693⟩. The former arise from *Dinophysis* and *Prorocentrum* dinoflagellate species, while the latter are named after the scallop *Patinopecten yessoensis* in which they have been identified.

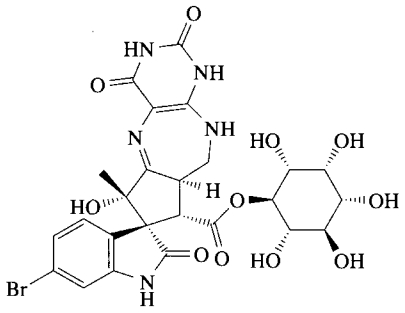
The Japanese ivory shell *Babylonia japonica* is commonly eaten in Japan, and is sometimes toxic, causing mydriasis. This illness has been ascribed to the presence of surugatoxin (**89**) and the analogous neosurugatoxin (**90**) ⟨82CPB3255⟩. The latter compound has been found to be of pharmacological interest as it appears to be a fairly specific antagonist of nicotinic receptors, particularly those located in the sympathetic ganglia ⟨84MI 509-01⟩.



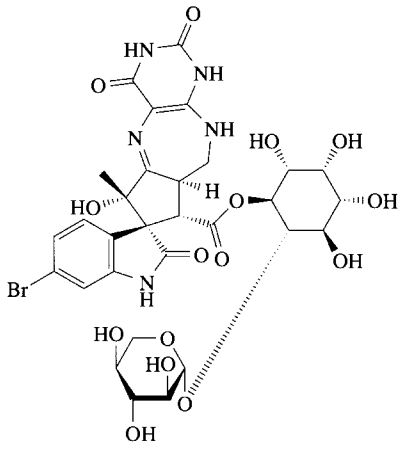
(**82**) R^1 = H, R^2 = H, R^3 = Me
(**83**) R^1 = H, R^2 = Me, R^3 = Me
(**84**) R^1 = H, R^2 = Me, R^3 = H
(**85**) R^1 = acyl, R^2 = Me, R^3 = Me



(**86**) R = CH_2OH
(**87**) R = Me
(**88**) R = CHO



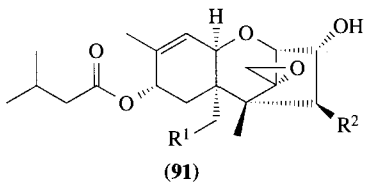
(**89**)



(**90**)

5.09.4.2 Terrestrial Toxins

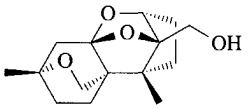
Tricothecenes are a group of more than 50 sesquiterpenoid mycotoxins produced by various genera of fungi, particularly *Fusarium* species ⟨B-81MI 509-01⟩. These mycotoxins have been responsible for human and animal toxicoses as a result of consumption of contaminated foodstuff ⟨B-83MI 509-01, 93MI 509-05⟩. There has been a considerable interest in T-2 toxin (**91**; R^1,R^2 = OAc) and related mycotoxins because of controversy over their alleged use in chemical and biological warfare ⟨86CEN23⟩.



(**91**)

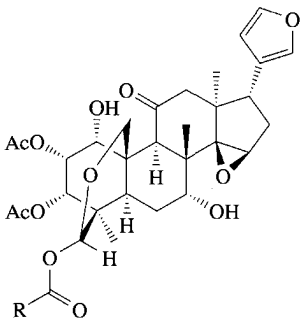
In 1986, two novel tricothecene mycotoxins, sporotrichiol (**91**; $R^1 = OH$, $R^2 = H$) and sporol (**92**), were isolated from *Fusarium sporotrichioides* ⟨86TL427⟩. Preliminary *in vitro* studies involving cytotoxicity levels indicate that both compounds are less toxic than T-2 toxin. The synthesis of sporotrichiol and other tricothecenes has been reported ⟨87JOC3468⟩.

Melia azedarach is a small, attractive deciduous tree often grown for shade or ornament on roadsides, parks, and other open situations in tropical and subtropical climates. Parts of the plant have been used medicinally for the treatment of a variety of human disorders ⟨B-62MI 509-01⟩. However, there are early records of the plant being poisonous to man and livestock ⟨B-74MI 509-01⟩, the great majority of cases following ingestion of the fruit. Death may not occur until some days later and is preceded by symptoms of nausea, vomiting, diarrhoea, and convulsions.



(92)

Four new tetranortriterpenes of the limonoid class, meliatoxins A_1 (**93**; R = Bu^s), A_2, (**93**; R = Pr^i), B_1 (**94**; R = Bu^s) and B_2 (**94**; R = Pr^i) have been isolated from the fruit of the Australian variety of *Melia azedarach*. These compounds have been shown to be responsible for acute nervous symptoms and death in pigs ⟨83P531⟩.



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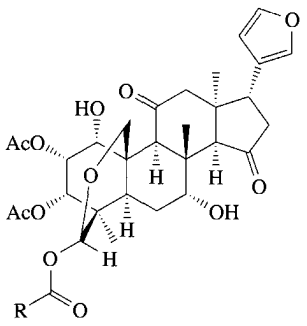


(94)

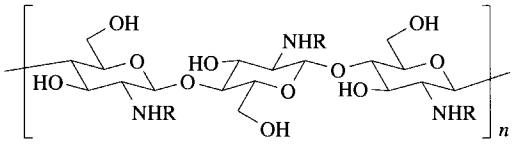
5.09.5 POLYMERS AND ADDITIVES

5.09.5.1 Polymers

5.09.5.1.1 Natural polymers

Interest in natural polymers such as the polysaccharides has been associated with the food, leather, paper, and textile industries. Research into these polymers, primarily in the biomedical and pharmaceutical industries, has resulted in much effort aimed at their chemical modification ⟨91MI 509-05⟩.

An important member in the field of natural polymers is chitin, which consists predominantly of unbranched chains of β-(1,4)-linked *N*-acetylglucosamine residues (**95**; R = Ac). The potential of chitin lies in its ubiquitous distribution in invertebrate exoskeletons. Annual synthesis in the biosphere is estimated at 100 billion tons ⟨B-79MI 509-03⟩. Research in improved isolation methods and the conversion of this insoluble material to its derivative chitosan (**95**; R = H), which results from deacetylation of sufficient amine groups, will enhance the exploitation of chitin as an industrial raw material ⟨92MI 509-01⟩. Interest in the use of chitin and chitosan has been associated with research in food ⟨91MI 509-06⟩, biodegradable plastics ⟨93MI 509-06⟩, crop protection ⟨88MI 509-02⟩, textiles ⟨94MI 509-03⟩, and cosmetics ⟨91USP5215759⟩.

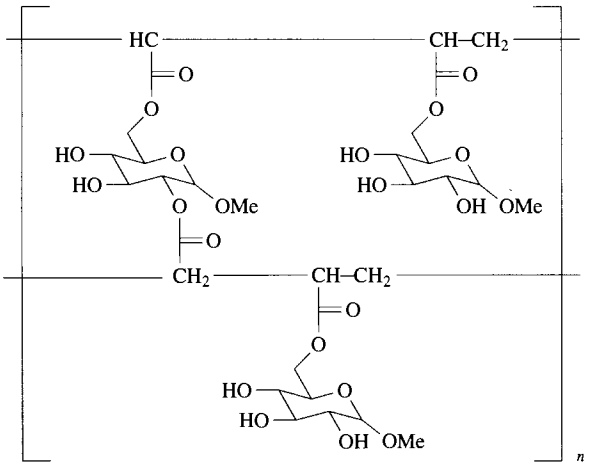


(95)

5.09.5.1.2 Hydrogels

Incorporation of sugars into synthetic polymers has significantly extended the application of these new materials into many areas ⟨92MM7081⟩. They often exhibit properties that are important for applicational and environmental reasons, such as their biodegradability, biocompatibility, specific chirality, and regularity. An additional reason for the use of sugar groups in the synthesis of swellable polymers is their hydrophilicity.

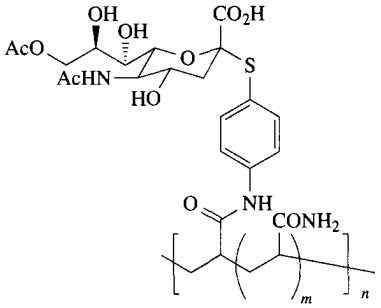
Hydrogels are lightly crosslinked polymeric materials that absorb large amounts of water and other polar solvents. Crosslinked hydrogels cannot dissolve in water because of their size; instead they absorb the water and swell. They find application as drug delivery matrices, bioimplantables, contact lens materials, and functional components of permselective membranes ⟨88MI 509-03, 91MI 509-07, 92MI 509-02⟩. With the aim of developing a nontoxic, biocompatible material that can absorb and tightly hold large amounts of water, Dordick *et al.* have described new glucose-based hydrogels (**96**) that absorb upwards of 300 times their weight in water and can operate at pH ranging from 4 to 9 ⟨94CT33⟩. These materials may have significant commercial potential for separation sciences involving biomolecules, as improved media for cell growth and as drug carriers for the transdermal sustained release of a variety of drugs, as well as the rectal delivery of narcotics and tranquilizers.



(96)

5.09.5.1.3 Glycopolymers

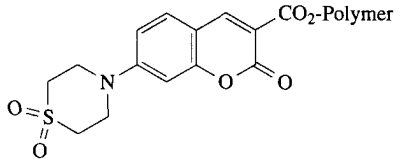
Synthetic glycoconjugates such as glycopolymers have been the subject of increased interest due to the recognition that the carbohydrate chains of glycolipids and glycoproteins serve as oncodevelopmental antigens and as receptors for infective agents ⟨87MI 509-01, 91JA686⟩. Glycopolymers containing multivalent sialic acid, such as (**97**), have been synthesized as tools for the development of esterase-resistant drugs designed to combat influenza C infections ⟨92AG(E)1478⟩. In order to develop new carbohydrate antigens useful for the screening and binding studies of monoclonal antibodies by radioimmunosorbent assays, researchers have engaged in the synthesis of polymers containing attachments of antigenic pseudopolysaccharide segments ⟨88MI 509-04, 91MI 509-08, 92MI 509-03⟩.



(97)

5.09.5.1.4 Photoactive polymers

Coumarin moieties are commonly incorporated into polymers for a wide variety of applications due to their favorable photochemical characteristics and relative ease of incorporation into the polymer matrix. The addition of the appropriate coumarin dye in the polymer-forming process can result in the polymeric product possessing either or both visible color and light absorption in the ultraviolet spectral region. These polymers, such as (**98**), are particularly designed for packaging materials where the desirability of colored or UV absorbing materials is sought without the drawback of extractability of the UV-screening or coloring agent ⟨92USP5091501⟩.

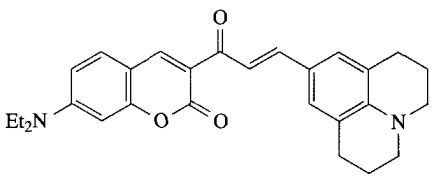


(98)

5.09.5.1.5 Photosensitizers and photoinitiators

Compounds capable of generating free radicals on exposure to light, and hence of inducing polymerization, are known as photoinitiators. However, the utility of many photoinitiators is limited because they are activated mainly by ultraviolet light. By adding a compound which absorbs incident light more efficiently, the photoinitiator may be activated to produce free radicals using visible light. Such compounds are known as photosensitizers. A laser light source is often used, and such technology finds application in direct laser writing of high resolution relief patterns in imaging science and microelectronics, holographic recording and storage of information, or the manufacture of holographic optical elements. 3-Ketocoumarins are well known photosensitizers, and are used in conjunction with diaryliodonium salts, halogenated triazines or triarylsulfonium salts as initiators.

It is reported that the coumarin (**99**) enhances the role of the photoinitiator system in high speed addition polymerization processes ⟨85USP4505793⟩. Coumarin analogues with general structure (**100**), where G^1 and G^2 are typically cyano, ketone, or ester substituents, have been applied as photosensitizers in allyl methacrylate–methacrylic acid copolymer compositions using epoxides as initiators ⟨88JAP(K)63165405⟩.



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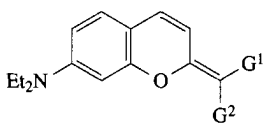
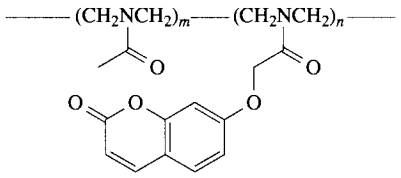


(100)

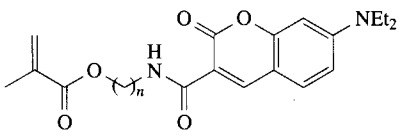
A photogelation process has been described involving polymers bearing photosensitive coumarins as pendant groups (**101**). Upon irradiation at above 310 nm, cross-linking occurs between the

coumarin groups on the polymer chains. This cross-linking step turns the soluble polymer into one which behaves as a hydrogel. The cross-linkage can be removed with irradiation at 254 nm. Hydrogels are used in a wide range of applications from household products to civil engineering materials ⟨90MM2693⟩.



(101)

Second-order nonlinear optical (NLO) materials have been the subject of extensive research ⟨89CT747, 92CT308⟩. Second-order nonlinear optical polymers are attractive because they provide durability, environmental protection, packaging advantages, and a broad spectrum of properties. These materials may find application in optical communications and computing components, frequency doublers for lasers, and laser resistant surfaces. One approach to the design of these polymers is to synthesize them with chromophores chemically attached as either pendant or main-chain substitutes, exemplified by (**102**) and (**103**). In the former, a variety of coumaromethacrylate monomers has been synthesized in which the alkyl "spacer" between chromophore and the methacrylate group was varied from ethyl to pentyl ⟨90MI 509-03⟩. Structure (**103**) is an example of the main-chain chromophore type in which the chromophore is also a part of the polymer backbone ⟨93USP5212269⟩.



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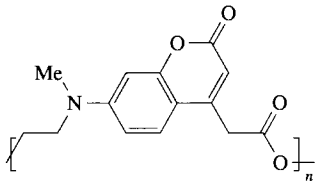
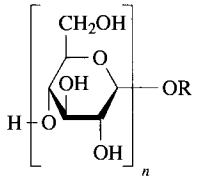


(103)

5.09.5.2 Surfactants

Glucosides are relatively new nonionic surfactants that are now commercially available. These are generally termed alkylpolyglucosides, with their general structures represented by (**104**). The glucose moiety, possessing multiple hydroxy groups, acts as the hydrophilic end of the molecule, whereas the alkyl chain R, generally being in the region of C_{12}–C_{13}, is the hydrophobic end.

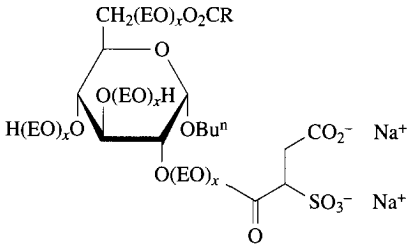


R = fatty chain C_8-C_{16}
n = 1,2 or 3

(104)

The commercial products are typically a complex mixture with (n = 1–3) and containing a number of geometrical isomers. Clearly there is large scope for improved chemical processes for the synthesis of these surfactant products. Their commercial importance is reflected by their presence in a wide variety of marketed products such as laundry detergents, dishwashing detergents, shower gel, and cosmetics. Developments include the chemical modification of existing alkylpolyglucosides to provide specialty surfactants. For example, new modified surfactants have been termed "sulfo-

succinates", (**105**), which are incorporated in dishwashing formulations. A large number of applications of these glucoside surfactants has been claimed by various manufacturers, and is the subject of a comprehensive summary ⟨94MI 509-04⟩.

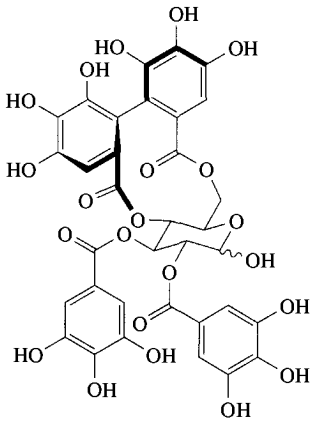


EO = Ethyleneoxy sub unit
R = fatty acid alkyl chain

(**105**)

5.09.6 FOOD PRODUCTS

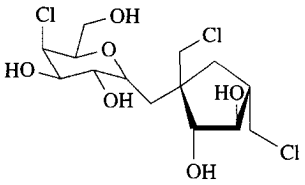
Ellagitannins, exemplified here by tellimargrandin I (**106**), are ubiquitous secondary metabolites present in the plant kingdom. Interest in these polyphenolic compounds has burgeoned as a consequence of their promising anticancer and antiviral properties ⟨91MI 509-09⟩. These compounds also display antioxidant activity ⟨93P557⟩ and play significant roles in the tea, food, and beverage industry, and as herbal medicines ⟨B-92MI 509-04, 93MI 509-07⟩. However, research progress in this field has been hampered by poor access to homogeneous samples of these natural products. With the success in the total synthesis of this class of compounds, increasing research activity is expected ⟨94JA1742, 94JOC2577⟩.



(**106**)

Despite the success of aspartame, there is a continuing search for noncaloric high intensity sweeteners in the food industry which is stimulated by the growing demand for low-calorie drinks and light foods. A successful candidate should possess negligible toxicological problems and superior flavor profile. A common approach in the discovery of these new agents is to begin from existing leads in nature. A long research program to identify a new nonnutritive sweetener based on sucrose was initiated by Tate & Lyle ⟨85CSR357⟩. It was shown that the selective chlorination of the sucrose molecule produced remarkable changes to the sweetness intensity and stability of sucrose, without compromising taste quality. The trichlorinated sucrose, Sucralose (**107**), is extraordinarily stable, with excellent physicochemical characteristics that will permit its use in a wide variety of foods and beverages ⟨B-91MI 509-10⟩.

Lactitol (4-*O*-(β-D-galactopyranosyl)-D-glucitol) (**69**) is also a new sweetener which has attracted much interest and is the subject of reviews ⟨87MI 509-02, B-91MI 509-11⟩. It is a sugar alcohol derived from lactose by hydrogenation of the glucose moiety. It provides food with the bulk and texture normally given by sucrose, but with only half of the calories. Lactitol is not as sweet as sugar and



(107)

has a clean taste closely resembling sucrose in sweetness character. In addition, Lactitol does not affect blood glucose and insulin levels, so it is valuable for diabetics. It does not cause dental caries and is thus suitable for products that are safe for the teeth, for example, sugar-free chewing gum and pastilles. Other applications of Lactitol include its use in hard-boiled sweets, ice-cream, instant beverages, jam, and toothpaste.

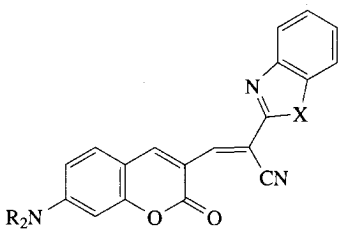
5.09.7 DYES AND PIGMENTS

Since 1982 technological progress has resulted in many new applications for existing dyes and pigments, and this has rather overshadowed the appearance of new chemical entities in this field. This has led to renewed importance for some older pyran-containing dyes, such as rhodamines and coumarins in laser technology. Three reviews have been published on modern applications of dyes ⟨88MI 509-05, 89MI 509-03, 89MI 509-04⟩.

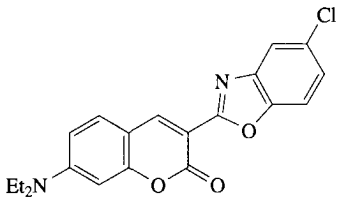
5.09.7.1 Fluorescent Dyes and Brighteners

Fluorescent dyes have been defined as materials that both absorb and emit strongly in the visible region of the spectrum, thereby distinguishing them from the fluorescent brighteners which emit visible light but absorb in the ultraviolet. Reviews are available specific to the former ⟨93MI 509-08⟩ and latter ⟨84DP109, 87MI 509-03⟩ categories.

Coumarins are one of the most commercially significant groups of fluorescent dyes and brighteners, most of which are 3,7-disubstituted. The dyes are characterized by the presence of electron-releasing substituents at the 7-position, and electron-withdrawing (often heterocyclic) substituents at the 3-position. Examples include the red dyes (**108**; R = alkyl, X = NH, O or S), and the greenish-yellow (**109**), all used for dyeing polyester.

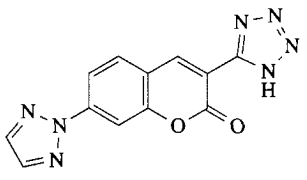


(108)



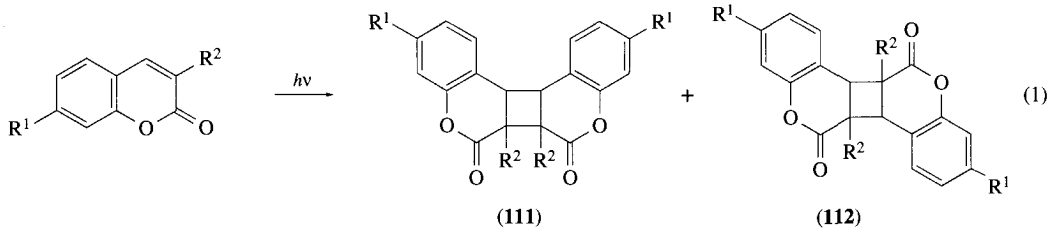
(109)

Coumarin fluorescent whiteners counteract the short wavelength visible light absorption of fibres, paper or plastics by having fluorescence maxima at 430–440 nm. The hydroxycoumarins formerly used have now been replaced by compounds having nitrogen-containing substituents at both the 3- and 7-positions. These are frequently heterocyclic in nature (e.g. **110**). Both nonionic coumarins for whitening polyester and water-soluble cationic coumarins for whitening polyacrylonitrile are available.



(110)

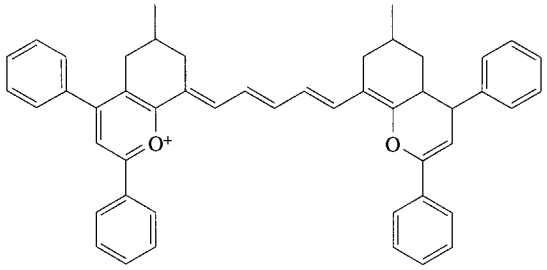
The usefulness of coumarins as fluorescent whiteners is limited by their susceptibility to photodimerization at the 3,4-position. All four products corresponding to the *syn-* and *anti-*isomers of the head-to-head (**111**) and head-to-tail (**112**) dimers are normally found, and all are nonfluorescent (Equation (1)). The major photochemical reactions of coumarin dyes have been reviewed ⟨92UK1243⟩.



(111) (112) (1)

5.09.7.2 Laser Dyes

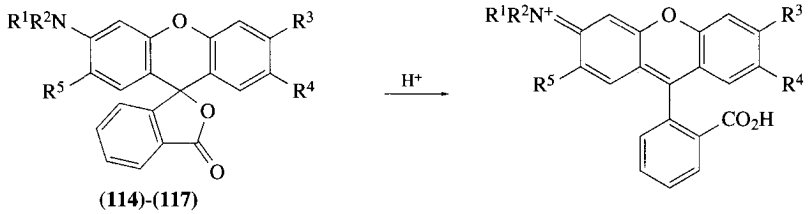
Dye lasers are of increasing technical importance, and are now being used in microsurgery and communications as well as scientific work. They are based on dyes which fluoresce with high quantum efficiency and show good photostability. A list of dyes used for this purpose has been published ⟨B-84MI 509-02⟩. Coumarins and xanthenes are important classes of dyes for laser use, having working ranges of 460–540 nm, and 510–700 nm respectively, but usually the older types of dyes are employed. A more recent development is the use of Q-switch dye cells to improve the energy output of solid state lasers. The dye (**113**) is suitable for use with the Nd:glass laser, emitting at 1060 nm ⟨72MI 509-02⟩.



(113)

5.09.7.3 Color Formers

Carbonless copy papers are based on the principle of colorant formation by the pressure of writing on the master sheet. On the reverse is a coating of microcapsules containing the color former. This is a chromogenic compound in its colorless form. The bottom sheet contains a co-reactive substance on the upper surface (usually a phenolic resin), which reacts with the color former released from the microcapsules by the writing pressure to form the dye (Equation (2)).



(114)-(117) (2)

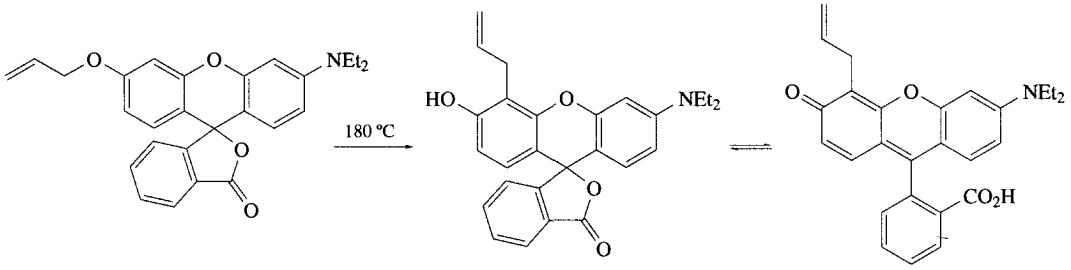
Fluorans are highly important color formers, and in the years under review the literature on dyes and pigments containing the pyran or fused pyran ring systems has been dominated by patents

describing the synthesis and properties of fluoran color formers. The 2,6-diaminofluorans containing an alkyl group at the 3-position are of particular commercial importance since the combination of steric and electronic effects results in the formation of black dyes. The same principle can be used in heat-sensitive paper, where a hot stylus melts the microcapsules, causing coloration on the underlying acidic surface. The chemistry of color formers has been reviewed by Raue ⟨B-83MI 509-02⟩, and a few typical structures of the dozens described in the literature are given in Table 1 and Equation (2).

Table 1 Color formers (see Equation (2)).

Structure	R^1	R^2	R^3	R^4	R^5	*Color*	*Ref.*
(114)	Bu^n	Bu^n	H	$N(CH_2Ph)_2$	H	Green	87JAP(K)6261983
(115)	Bu^n	Bu^n	Me	Br	H	Vermilion	90EUP356199
(116)	Et	H	H	$NH(2\text{-}ClC_6H_4)$	Me	Deep red	83JAP(K)58180557
(117)	Pr	Me	Me	NHPh	H	Black	84JAP(K)59120654

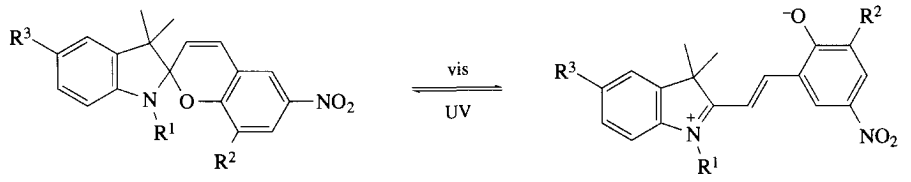
One problem associated with color formers is that to retain colorlessness before heating, the dyes must be protected from contact with the acid which converts them to the colored protonated form. Inouye *et al.* have introduced a class of purely thermally activated dyes, which self-color on heating, no other component being required (Scheme 1) ⟨92AG(E)204⟩. In this strategy, allyl aryl ethers undergo Claisen rearrangement to generate phenols, which are subject to intramolecular acid–base reaction involving opening of the lactone ring and coloration.



Scheme 1

5.09.7.4 Photochromism

The chemical process in which a compound changes its colour when exposed to light, and reverts to its original color in the dark is photochromism. One well known use of this property is in the control of radiation intensity in sunglasses, opthalmic lenses, and windows. This phenomenon is also finding application in the field of reversible optical data storage, and is of relevance to the design of molecular switches. The application of spiropyrans and related compounds based on these properties has been reviewed ⟨90MI 509-04⟩. In spiropyrans, on irradiation the C—O spiro bond is cleaved heterolytically and a merocyanine dye is formed. The photochromic behaviour of spiropyrans is based on the reversibility between the colorless spiropyran form and the colored merocyanine dye (Equation (3)). Although well established in the field, this type of molecule suffers from low thermal stability of the colored form, photochemical side reactions and competing thermochromic behavior. Nevertheless, advances continue to be made, and the introduction of a nitro group stabilizes the zwitterionic form to allow solution lifetimes of up to several hours ⟨93T8267⟩. Additionally, the chromone merocyanine dye (**118**) is reported to be stable in the coloured form ⟨92CC1188⟩.



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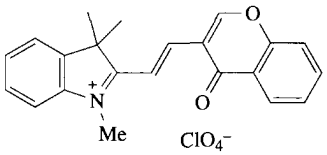
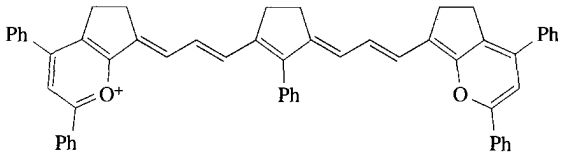


(118)

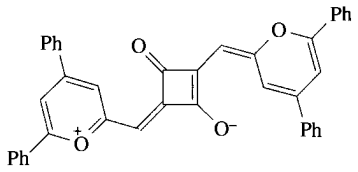
5.09.7.5 Infrared Absorbing Dyes

Infrared absorbing dyes are of importance as photoreceivers for laser light in optical recording systems, laser printing, infrared photography, and surgery ⟨92CRV1197⟩. Polymethine dyes having chalcogenopyrylium nuclei have particularly long wavelength absorption maxima [e.g. (**119**) > 1400 nm ⟨84GEP(O)3316666⟩].



(119)

Squarylium and croconium dyes are used as dye media in conjunction with a singlet oxygen quencher. Benzopyran squarylium and croconium dyes such as (**120**) have been synthesized for this purpose ⟨83JAP(K)58217558⟩.



(120)

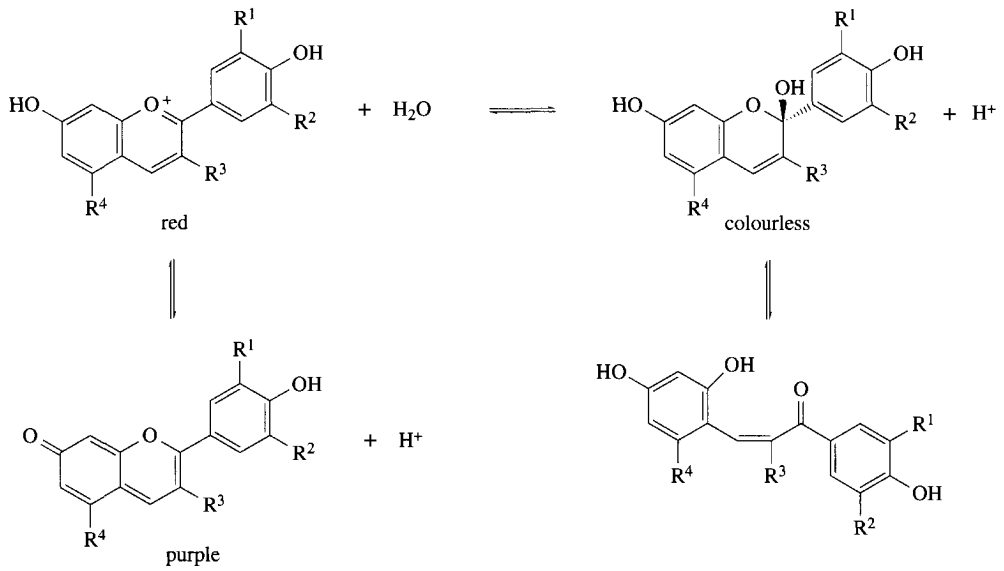
5.09.7.6 Natural Dyes

The use of natural substances for dyeing purposes begins the history of the subject. In most cases such substances have long since been replaced by synthetic dyes and pigments available in bulk quantities, and of superior color and fastness. However, renewed interest in this area has become evident, particularly in dyeing foods and drinks. The anthocyanins and flavonoids are classic examples of natural dyes. The anthocyanins are responsible for many of the reds and blues of flowers, fruit, and vegetables, and their intricate chemistry has been keenly studied for many years. Not only do they take part in complex acid/base equilibria (Scheme 2), but the exact color is also dependent upon self-association, copigmentation, intramolecular stacking, and complexation with metals ⟨91AG(E)17⟩.

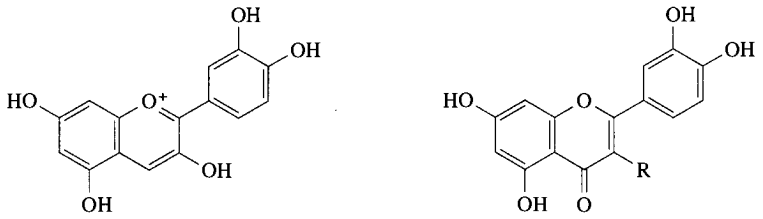
An assessment has been made of the color and fastness to washing of native Scottish wool dyes associated with the production of traditional tartans. Most of the reds, blues and purples were from anthocyanins such as cyanidin (**121**), and the yellows from flavonoids like quercitin (**122**; R = OH) and weld (**122**; R = H) ⟨85MI 509-01⟩.

5.09.8 USE IN CHEMICAL SYNTHESIS

Ley *et al.* have introduced the dispiroketal group (Dispoke) for the protection of vicinal diols. Not only is protection selective for vicinal diols in the presence of 1,3-diols but due to the domination of anomeric effects, only one stereoisomer of the dispiroketal is formed, (Equation (4)) ⟨92S52⟩.

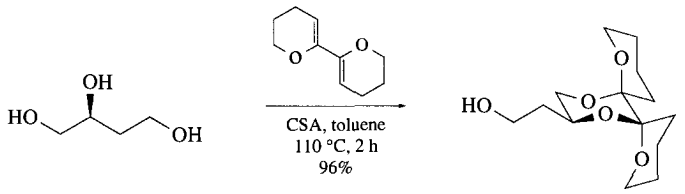


Scheme 2



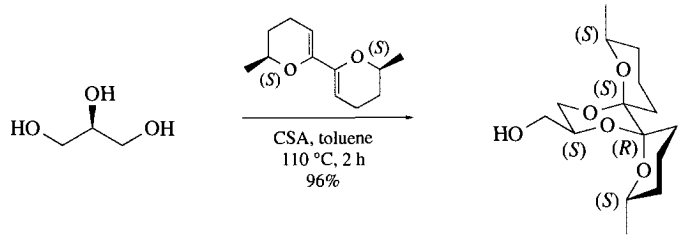
(121) **(122)**

Furthermore, differential anomeric stabilization allows selective protection of *trans* diequatorial vicinal diols in the presence of *cis* vicinal diols. This protecting group is therefore complementary to the existing *cis* selective ketals for carbohydrate chemistry, ⟨92TL4767, 93S689⟩. The protecting group may be removed by treatment with aqueous trifluoroacetic acid, by exchange with ethylene glycol, or use of an excess of iron(III) chloride ⟨94TL777⟩.



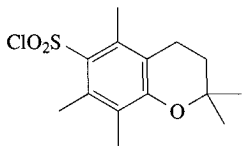
(4)

Incorporation of chirality into the *bis*-dihydropyan reagent allows the enantioselective desymmetrization and protection of glycerol in a single operation (Equation (5)) ⟨93TL5649⟩.



(5)

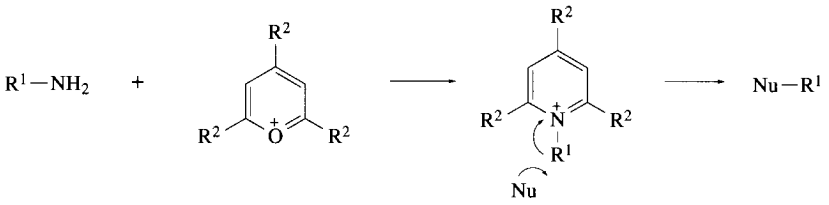
In peptide synthesis, 2,2,5,7,8-pentamethylchroman-6-sulfonyl chloride (Pmc) (**123**) has been developed as a trifluoroacetic acid labile protecting group for the guanidine side-chain function of arginine ⟨91T6353⟩.



(123)

Many carbohydrates and their derivatives such as D-fructose, D-galactose, D-glucose, and L-sorbose are polyfunctional molecules available in bulk quantities at low cost. As such they make excellent chiral educts for the synthesis of single enantiomers of complex target molecules. A book by Hanessian ⟨B-83MI 509-03⟩ discusses this subject in some detail. More specifically, the syntheses of a number of insect pheromones from D-glucose have been collated ⟨89T3233⟩.

Primary amino groups may be transformed into a wide variety of other functional groups through the intermediacy of *N*-pyridinium salts derived from pyrylium ions (Scheme 3), and this has been the subject of a comprehensive review ⟨84AG(E)420⟩.



Scheme 3

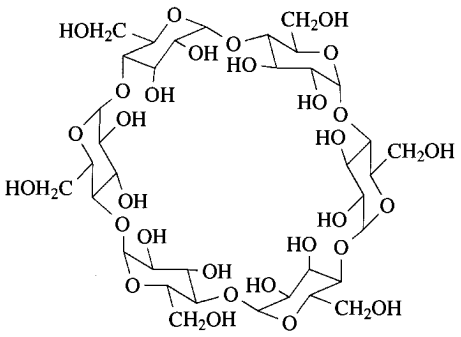
2*H*-Pyran-3(6*H*)-ones are versatile intermediates in the preparation of carbohydrates, polyether antibiotics, spiroketal pheromones, and other natural products. They are readily available from the oxidative rearrangement of 2-furylcarbinols (Equation (6)) ⟨92OPP95⟩.

(6)

5.09.9 CYCLODEXTRINS

Cyclodextrins are nonreducing oligosaccharides composed of α-(1,4)-D-glucopyranosyl units linked in a ring configuration. The most common members of this class of molecules are the α-, β-, and γ-cyclodextrins, consisting of 6-, 7-, and 8-glucopyranose units respectively. The dextrorotatory enantiomers are readily available from the enzymatic degradation of starch employing cyclodextrin glucosyl transferases of bacterial origin, for example from *Bacillus macerans* and alcaliphilic bacilli ⟨B-88MI 509-06⟩. Cyclodextrins are excellent chiral hosts for complexation with a wide range of substrates. They are of low toxicity ⟨B-91MI 509-12⟩, water-soluble and biodegradable, and since the natural enantiomers can be readily generated from renewable resources, they have attracted much attention in industry. Cyclodextrins are currently being produced and used widely throughout the world, with major producers located in Japan and Eastern Europe. Their low cost will undoubtedly provide further impetus for the discovery of new applications. The number of publications relating to the research in cyclodextrins has been increasing rapidly, including several review articles ⟨80AG(E)344, 87MI 509-04, 88MI 509-07, 94AG(E)803⟩.

Cyclodextrins, in particular β-cyclodextrin (**124**), are important products in a whole range of industries such as pharmaceuticals, agrochemicals, separation technology, foods, electronics, cosmetics and toiletries, dyestuff and printing, and polymers. Some of the important applications are discussed below.



(124)

5.09.9.1 Pharmaceuticals

Cyclodextrins have been shown to complex retinoids and are used for the treatment of hypervitaminosis A ⟨83LS719⟩. The ability of cyclodextrins to form stable and water-soluble inclusion complexes with a large number of reactive intermediates, thereby enhancing their solubilities, has been well recognized and applied to drug formulations, for example, in Prazosin ⟨86JAP(K)61129138⟩, Ibuprofen ⟨86MI 509-02⟩, and Rafoxanide ⟨80MIP18790⟩. Another feature of a cyclodextrin/drug inclusion complex is the stabilization of the labile drug while in transit to the therapeutic target site, for example, Ampicillin and Methicillin ⟨84MI 509-03⟩. A prostaglandin E_2/β-cyclodextrin complex is marketed under the name Prostarmon and the antihypertensive Alprostadil/α-cyclodextrin formulation as Prostandin 500. Clinical trials have been conducted for the anti-angina drug FR-46171, which consists of 6-chloro-2-pyridylmethyl nitrate formulated as a β-cyclodextrin complex for controlled release. Complexation with cyclodextrins has broadened the scope of the anticancer drug Carboplatin ⟨86MI 509-03⟩. Further applications of cyclodextrins in the field have been reviewed by Duchêne *et al.* ⟨86MI 509-04⟩, Uekama and Otagiri ⟨87MI 509-05⟩, and Szejtli and co-workers ⟨84MI 509-04, 94MI 509-05⟩. In 1994, cyclodextrins have been used in the design of drug-targeting vectors by their attachment to appropriate oligosaccharides ⟨94BMC1127⟩.

5.09.9.2 Agrochemicals

Szejtli has reported that grain pretreated with an aqueous solution of β-cyclodextrin before being sown results in retarded germination and reduced sensitivity of the plants to the phytotoxic effect of herbicides ⟨83MI 509-04⟩. Pyrethrins are highly active insecticides with their use greatly limited by their light-sensitivity and oily nature. Inclusion in β-cyclodextrin gives a powder form which is easy to handle and has increased duration of action ⟨76MI 509-02⟩. Controlled release forms of cyclodextrin-complexed bis(methyl 2,2-dichlorovinyl phosphate) are effective insecticides, acaricides, and anthelmintics ⟨86CE343⟩. β-Cyclodextrin complexation of Nevinphos selectively includes the more active (*E*)-isomer, powderizes the product and assists solubilization in water ⟨85MI 509-02⟩. Copper(II) complexes of β-cyclodextrin have been found to be effective fungicides for controlling downy mildew on grape ⟨90EUP401059⟩.

5.09.9.3 Flavors and Fragrances

Flavor ingredients and fragrances are often oils which may also exist only in short-lived forms. Many common essential oils (e.g., lemon, petitgrain, lavender, jasmine, cardamon) can be first rendered into crystalline cyclodextrin complexes before use to produce solid perfume compositions ⟨79JAP(K)7980433⟩. Cyclodextrins have been used in the detergent industry to inhibit the evaporation

of perfumes from detergent powders ⟨B-82MI 509-01⟩. The same approach has been employed in a wide range of products in the cosmetics, toiletries and proprietries industries.

Powdering of the oily aroma concentrates of tea and coffee has been reported ⟨81BEP887542, 86MI 509-05⟩. "Delayed bitterness" due to the presence of limonoids and flavanoids in citrus fruit juices is a major problem in the industry. These components can be removed with the aid of reusable cross-linked cyclodextrin polymers ⟨86MI 509-06⟩.

5.09.9.4 Reprographics and Phototechnological Applications

Some cyclodextrin-complexed reprographic materials have been shown to produce enhanced performance ⟨83JAP(K)58124692⟩. Cyclodextrins have also found applications in the photographic industry ⟨85GEP(O)3506955, 86JAP(K)61218513, 86JAP(K)6177846⟩. Other applications include textiles ⟨91MI 509-13, 92MI 509-05⟩, electronics ⟨86JAP(K)61158317⟩, adhesives ⟨91GEP(O)4009621⟩, polymeric thickening agents ⟨91EUP460896⟩, and molecular indicators ⟨92NAT136⟩.

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5.10
Thiopyrans and their Benzo Derivatives

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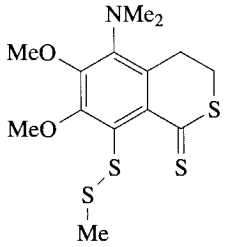
5.10.1 INTRODUCTION, REVIEWS AND NOMENCLATURE

5.10.1.1 General Introduction

The first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) covered the literature up to 1982. As was observed in the introduction to the chapter dealing with thiopyrans, whereas pyrans have received a vast amount of research attention, their sulfur-containing analogues are still, by comparison, poor relations. Oxygen heterocycles are continually being found as natural products, scores of new ones being identified each year, but a report of a naturally occurring thiopyran is an exceedingly rare event. Even the rich treasury of exotic structures found in onions and garlic does not yet contain even one example! Indeed, apart from a family of marine products (the polycarpamines, ⟨90TL2389⟩), no other group of biogenetically derived thiopyrans appears to have been reported since the mid 1980s.



Polycarpamine C

(1)

The principal natural source of thiopyrans remains crude oil and related deposits, in which the compounds found are the result of postbiotic transformations rather than biogenetic reactions. In keeping with the classical approach to the development of organic chemical methodology, in which the ultimate test is usually the synthesis of a defined natural product, relatively little synthetic effort has been directed towards thiopyrans as ends in themselves, unlike their pyran equivalents. Indeed, it is probably true to say that a significant proportion of the published effort in the area relates to the use of thiopyrans as intermediates in the preparation of nonsulfur-containing materials.

5.10.1.2 Reviews

That the thiopyran area is a minority interest is reflected in the rate of appearance of review articles. Prior to CHEC-I, while there were a number of papers reviewing aspects of the area, there

was only one extensive coverage of the literature, by Mayer *et al.* ⟨67AHC(8)219⟩. This picture has not changed: since 1980 there have been some 70 reviews published worldwide, but almost without exception they have been restricted to very specific aspects of the broader subject (e.g., the synthesis of 2,6-disubstituted thianes ⟨83CRV379⟩, or the chemistry of the little known "thiabenzenes" ⟨86MI 510-01⟩. The vast majority of these articles have been difficult of access, appearing in minor journals or unusual languages.

Only one comprehensive review article has appeared since 1982, but this was so soon after CHEC-I that it treated essentially the same material ⟨83AHC(34)145⟩.

5.10.1.3 Nomenclature

The root of systematic names for six-membered rings containing a single sulfur atom is "thiin", but *Chemical Abstracts* uses the common form "thiopyran" based upon the oxygen-containing system. In earlier publications the term "thi*a*pyran" may frequently be found, which, however, implies the replacement of a carbon atom by sulfur, not of the oxygen atom. This "replacement nomenclature" is more correctly applied in papers which deal with perhydrobenzothiopyrans or "thiadecalins." Figure 1 illustrates the range of monocyclic thiopyran structures possible and the names under which they can be found in *Chemical Abstracts*. Figure 2 shows the benzo-fused analogues of the compounds in Figure 1. Since 1983 there has been one change to these names: 1*H*-thiopyran is now indexed under 1λ^4-thiopyran. The numbering of the monocyclic and bicyclic compounds is systematic, but the tricyclic thioxanthenes are numbered in the same (irregular) manner as xanthenes.

Two thiopyran-derived systems have no stable counterpart among the corresponding oxygen heterocycles: λ^4-thiopyrans (thiabenzenes) and thiopyranium salts where the sulfur is alkylated.

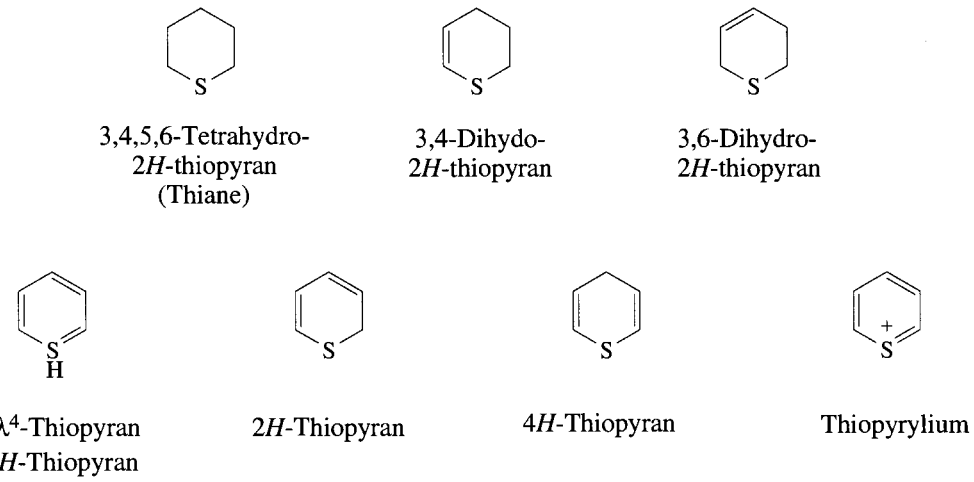


Figure 1 Monocyclic thiopyrans: structure and nomenclature.

5.10.2 THEORETICAL METHODS

The application of computational methods in chemistry has increased as the power of computers and the necessary algorithms have grown, so that structures of interest can now be handled in an almost routine manner. The earliest report of thiins being investigated in this way appeared in the early 1970s ⟨72TL4165, 73JPR690, 73T2009⟩, but only a handful of papers had appeared by 1980. Since that time not only has the number of publications been substantial, but the stage of doing calculations for their own sake is now past, and theoretically derived rationales of the properties and behavior of compounds are being used in the design of molecules for specific purposes. This has become possible because of the confidence that has been engendered by the degree of correlation exhibited between predicted and experimentally determined physical parameters. This success is the result of extensive refinement of methods by theoreticians and there have been several reports of detailed

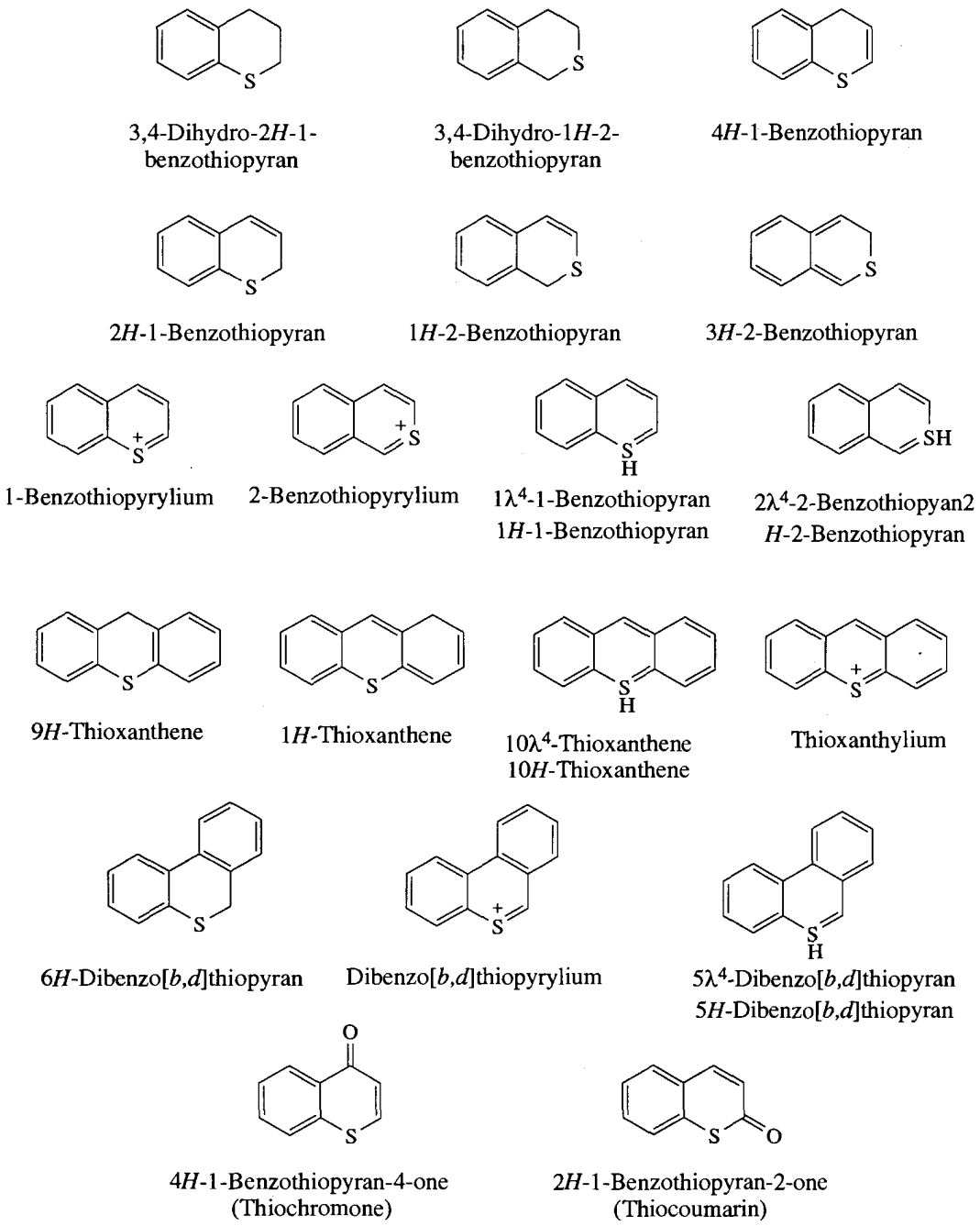


Figure 2 Benzo-fused bi- and tricyclic thiopyrans: structure and nomenclature.

investigations of a family of pyran- and thiopyran-4-ones and -thiones (Figure 3) making use of a number of different semiempirical techniques: one such compared the results from *ab initio*, CNDO/2, and MNDO/3 methods against experimentally derived data ⟨85MI 510-01⟩, while in a related study of the same group of structures STO-3G, STO-3G*, 3-21G, and 3-21G* were compared ⟨86IJQ1503⟩.

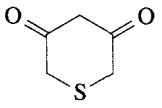
The majority of the reports of theoretical methods applied to thiopyran systems that have appeared use *ab initio* or the common semi-empirical methods including CNDO/2 and MNDO/3 (as mentioned previously), but other papers describe the application of STO-3G, STO-3G*, 3-21G, 3-21G*, and 4-31G, whilst the Pariser–Parr–Pople (PPP) method has been used in a number of specific cases.

Figure 3 Pyran- and thiopyran-4-ones and -thiones investigated by semiempirical techniques.

The types of problem tackled by these techniques range from those of a primarily theoretical interest, to those with "industrial" application. A brief overview of the publications includes:

(i) an investigation into the "aromatic energy" of heteroaromatic systems, including thiopyrylium and dihydrothiopyrylium species ⟨89H(28)1135⟩;

(ii) studies on electron-impact induced mass spectral fragmentations in structures related to dioxothianes (**2**) ⟨90MI 510-01⟩;



(**2**)

(iii) correlation of nuclear quadrupole coupling constants in thiopyrylium species ⟨92ZN(A)203⟩;

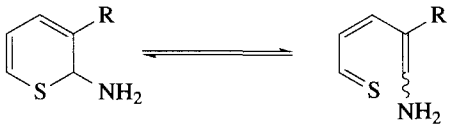
(iv) studies on the diastereotopic selectivity of deprotonation of thianes and related sulfonium species ⟨84CJC1470⟩;

(v) investigation of the regioselectivity of nucleophilic additions (2- vs. 4-) to thiopyrylium nuclei ⟨92JOC4431⟩;

(vi) investigation into the barrier to inversion in 9*H*-thioxanthenes (Equation (1)) ⟨91CJC927⟩;

(1)

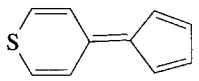
(vii) studies on the effect of solvent polarity on the ring-chain equilibrium of 2-amino-2*H*-thiins (Equation (2)) ⟨84JPR955⟩;



(2)

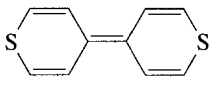
(viii) an investigation into the effects of ionization on molecular shape, and conversely the relationship between bond angles and ionization potential in thiins ⟨87MI 510-01, 91JST(249)305⟩;

(ix) studies on the biradical/zwitterionic nature of fulvene systems (**3**) on photoexcitation ⟨90T3803⟩;



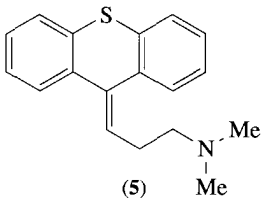
(**3**)

(x) studies on the closely related bithiopyranylidenes (**4**), which are the focus of much theoretical and experimental activity due to their potential applications as organic conductors ⟨84JCS(P2)239⟩;



(**4**)

(xi) an investigation of the interaction of a diverse range of neuroleptic drugs with the dopaminergic receptor in which a benzene ring in the molecule acts as an electron acceptor. Calculation correlated biological activity with the energy of the LUMO of the aromatic rings of the test compounds, including the thioxanthene (**5**) ⟨87EJM101⟩.



(**5**)

The foregoing is a lengthy list of published examples of the application of *ab initio* and semi-empirical computational methods to a whole range of questions surrounding thiins. The application of molecular mechanics to thiopyran systems is also almost routine. Many of the studies of conformational preferences by NMR spectroscopy, or related issues arising from x-ray crystallography, have been further clarified by its use, for example, in work in support of crystallographic studies on thianium compounds and thiopyran sulfoxides ⟨81ACS(B)607, 89H(28)937⟩. There are relatively few publications devoted solely to molecular mechanics calculations on thiins. The earliest paper discussing its application to thianes was by Allinger and Hickey ⟨75JA5167⟩, while a more recent publication treats similar material as a small part of a more extensive body of work, reporting that MM2 calculations suggest that the chair conformer of thiane is some 3.8 kcal mol^{-1} more stable than the twist chair, and 5.2 kcal mol^{-1} more stable than a boat arrangement ⟨88ACS(A)332⟩. Extensions of such calculations to more complex systems have appeared, including a most interesting paper discussing the problem of how ring systems including tetrahydrothiopyran accommodate the steric congestion of 3,3′,5,5′-tetrasubstitution ⟨88JA1220⟩.

5.10.3 EXPERIMENTAL STRUCTURAL METHODS

At the time of publication of CHEC-I, most of the structural determinations in thiin systems had relied very largely on the techniques of IR, UV, and ^1H NMR spectroscopy. Only a very few x-ray crystal structures had been published, and ^{13}C NMR work had only just begun to appear. The increasing sophistication of computer based techniques since the early 1980s for interpreting data from ever more sensitive detection systems has made both x-ray crystallography and ^{13}C NMR routine aids to structural assignment, and both are widely applied to thiopyran systems.

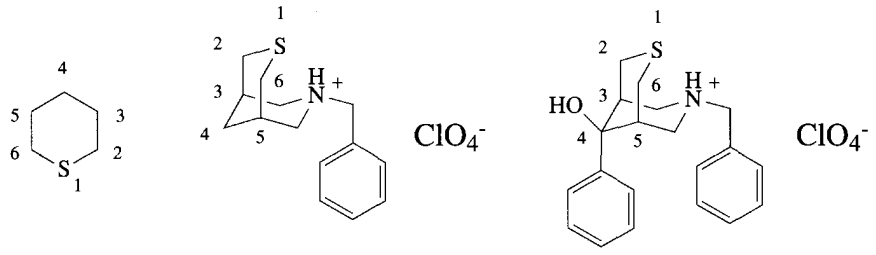
Methods that have newly been applied to the area under discussion include fluorescence, microwave, electron diffraction, and photoelectron spectroscopy, and NMR studies have been extended to include ^{33}S and ^{17}O nuclei. The nature of the information that each of these techniques provides differs. Results provided by these newer methods together with the older techniques will be discussed here, organized by structural subtype.

5.10.3.1 Thianes

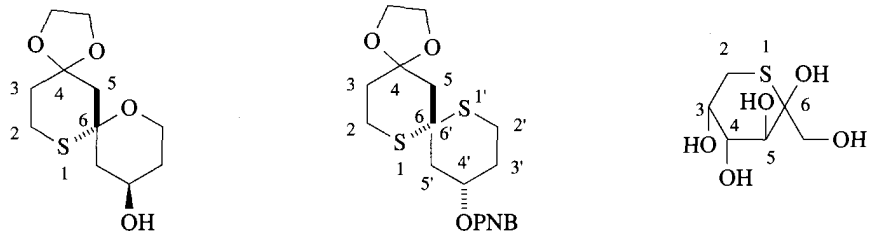
5.10.3.1.1 Electron diffraction spectroscopy

The data from electron diffraction experiments is consistent with the existence of tetrahydrothiopyran (**6**) as a chair conformer in the gas phase. While it was possible to measure the C—S—C bond angle as 97.6° (close to that in dimethyl sulfide (99.0°)), and to show that the C—C—C angles were opened out relative to cyclohexane, only a mean C—C bond length for the ring could be obtained (Table 1). With this proviso it is possible to derive a torsion angle (C—C—C—C) of 58.2° compared to 54.6° in cyclohexane and therefore recognize a greater degree of pucker in the heterocycle ⟨88ACS(A)332⟩.

Table 1 Bond lengths, angles, and torsion data in tetrahydrothiopyran and derivatives from molecular mechanics calculations, electron diffraction spectroscopy, and x-ray crystal structure determinations.



(6) (7) (8)



(9) (10) (11)

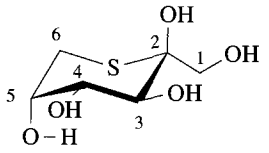
	Bond length (nm)						*Bond angle* (°)						*Torsion angle* (°)			*Ref.*
	S_1—C_2	C_2—C_3	C_3—C_4	C_4—C_5	C_5—C_6	C_6—S_1	C_6—S_1—C_2	S_1—C_2—C_3	C_2—C_3—C_4	C_3—C_4—C_5	C_4—C_5—C_6	C_5—C_6—S_1	C_6—S_1—C_2—C_3	S_1—C_2—C_3—C_4	C_2—C_3—C_4—C_5	
(6) (*molec. mech.*)	0.1816				0.1816		94.3	107.8			107.8					75JA5167
(6) (*electron diffn.*)	0.18098	0.15267	0.15267	0.15267	0.15267	0.18098	97.6	112.7	112.3	113.6	112.3	112.7	55.4	60.8	58.6	88ACS(A)332
(7) (*x-ray*)	0.1831	0.1503	0.1510	0.1547	0.1505	0.1820	99.3	114.7	111.9	109.6	111.4	114.5	45.4	59.9	67.2	84JMC758
(8) (*x-ray*)	0.1817	0.1533	0.1552	0.1547	0.1524	0.1825	99.8	115.5	111.7	106.7	112.4	113.8	44.2	59.6	67.4	84JMC758
(9) (*x-ray*)	0.181	0.1519	0.1511	0.1518	0.1526	0.1838	96.90	111.56	112.72	114.05	118.27	110.0		58.6		92JCS(P1)2223
(10) (*x-ray*)	0.1808/	0.1503/	0.1506/	0.1510/	0.1527/	0.1823/	98.49/	112.72/	112.11/	113.12/	116.29/	109.72/		56.5		92JCS(P1)2223
	0.1805	0.1517	0.1502	0.1514	0.1523	0.1826	99.33	113.42	110.73	113.69	115.96	109.77				
(11) (*x-ray*)	0.1807	0.1517	0.1529	0.1530	0.1535	0.1829	97.52	112.3	111.43	115.72	112.58	108.7				89CAR(193)1

5.10.3.1.2 X-ray crystallography

While use of electron diffraction spectroscopy allowed bond lengths to be derived, they were average figures across the molecule. Classical x-ray crystallography is the only method permitting the extraction of individual bond lengths and angles to a high degree of accuracy. Its limitation is the availability of suitable crystals, and the method clearly cannot be applied to thiane. Related molecules, however, can be examined. The general finding is that the saturated thiane ring behaves very much as cyclohexane: chair conformers are preferred, with substituents on carbon adopting equatorial orientations if possible. The situation with substituents on sulfur is more complex, and is discussed below.

In support of other investigations two bridged thiane analogues (**7**) and (**8**) (Table 1) were crystallized and subjected to x-ray analysis ⟨84JMC758⟩, as were two spiro-fused systems (**9**) and (**10**) (Table 1) ⟨92JCS(P1)2223⟩. Whereas the electron diffraction data experiment could only give average bond lengths etc., the x-ray data clearly shows variation in bond lengths and angles. In the symmetrically substituted bridged systems the difference in length for apparently equivalent bonds is quite marked and presumably reflects crystal packing effects.

An even less symmetrical analogue of thiopyran, that may be considered a thiosugar (materials that are still relatively uncommon, although a subject of increasing interest in the last decade), has also been crystallized and its structure determined by x-ray analysis. 6-Thio-β-D-fructopyranose (**11**) has been shown to exist in the $^2C_5$(D) chair conformation in the crystal ⟨89CAR(193)1⟩, which is also the predominant form in solution in D_2O ⟨83CAR(115)33⟩. As in the case of thiane, the thiosugar is more puckered than its oxygen analogue β-D-fructose, with the average torsion angle around the ring being some 4° greater. An interesting feature of the molecule is the finding of a hydrogen bond between the C(5)—OH and the ring sulfur atom (distance H—S 0.2791 nm, and the angle O(5)—H—S 106.55°).



(**11**)

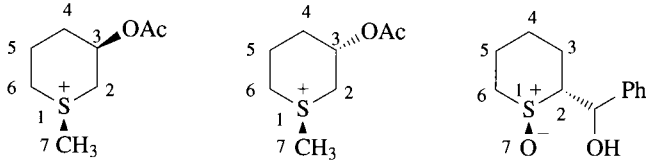
It is interesting to compare the figures for the bond lengths and angles derived from the different techniques. Table 1 brings together data for the compounds discussed above, and the broad agreement within the data is worthy of note.

The 3*d* orbitals of sulfur are responsible for the existence of a series of stable *S*-derivatives of thiopyrans which have no parallel in pyran chemistry. Thus, alkylation affords sulfonium salts, oxidation gives rise to sulfoxides and sulfones, and reaction with positive nitrogen sources produces thiane-imides. Conformational analysis of such species was first undertaken in the 1970s using NMR supported by IR spectroscopy ⟨77JA2337, 77T1149, 79JOC2863⟩. X-ray crystal structures have now appeared for a number of these sulfur-modified systems, and bond length and angle data are gathered in Table 2.

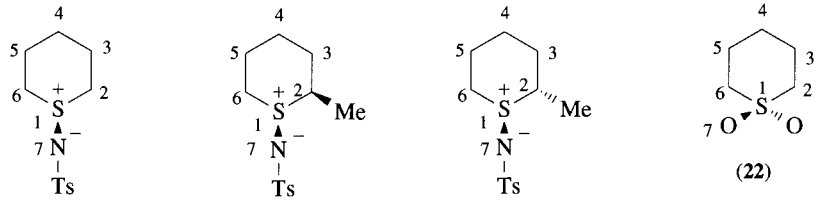
Considering firstly the sulfonium derivatives, the data in the table for 3-acetoxy-*S*-methylthianium systems shows that in the *trans*-disubstituted case (**17**) (Table 2) the acetoxy group adopts an axial position, and the atoms C_2, C_3, C_5, and C_6 are virtually in the best plane (deviation ± 2 pm); the structure is almost symmetrical. Symmetry is also found in the torsion angles around the ring, which lie in the range 57.8 to 62.6°. By contrast, the *cis* analogue (**16**) (Table 2), with axial acetoxy *and S*-methyl, is distorted: C_2, C_3, C_5, and C_6 deviate from the best plane by ±3 pm, and the internal angles of the ring are quite asymmetric. Torsion angles spread over 42.9 to 61.9° ⟨81ACS(B)607⟩. As can be seen, MM2 calculations were in excellent agreement with the experimental findings, including the distortion of the *cis* system, and were used to derive figures for the energy barrier to conformational inversion. A figure of 1–2 kcal mol^{-1} is supported by NMR studies. Similarly successful MM1 and MM2 studies have been applied to the analogous 4-acetoxy-*S*-methylthianium salts (**12**).

Turning to sulfoxide structures, conformational preferences are very strongly affected by factors other than simple steric interactions. The polar S—O moiety can participate in intramolecular hydrogen bonding, with significant effect upon molecular shape. However, x-ray crystallographic investigations are complicated by intermolecular forces in the crystal ⟨89H(28)937⟩. Thus (**13**) exists in a *trans*-diequatorially substituted chair, but in the unit cell there are two slightly different conformations. The bond length and angle data in Table 2 for this compound are averaged over

Table 2 Bond lengths and angles in sulfoxide, sulfilimine, and sulfonium derivatives of tetrahydrothiopyrans, from molecular mechanics calculations and x-ray crystallographic structure determinations.

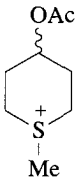


(16) **(17)** **(18)**



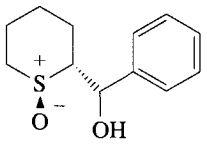
(19) **(20)** **(21)** **(22)**

	Bond lengths (nm)							*Bond angle* (°)							*Ref.*
	S_1—C_2	C_2—C_3	C_3—C_4	C_4—C_5	C_5—C_6	C_6—S_1	S_1—X_7	C_6—S_1—C_2	S_1—C_2—C_3	C_2—C_3—C_4	C_3—C_4—C_5	C_4—C_5—C_6	C_5—C_6—S_1	C_6—S_1—X_7	
(16) *X-ray*	0.1809	0.1518	0.1506	0.153	0.1524	0.1802	0.1804	101.46	116.23	114.2	114.1	112.64	113.5	103.8	81ACS(B)607
(16) *MM2*	(0.180)	(0.154)	(0.154)	(0.154)	(0.152)	(0.180)	(0.180)	(101.1)	(117.5)	(112.2)	(112.9)	(112.3)	(114.9)	(105.4)	81ACS(B)607
(17) *X-ray*	0.1821	0.1501	0.1511	0.1541	0.1521	0.1801	0.1781	98.65	108.67	113.2	114.4	112.3	108.97	103.5	81ACS(B)607
(17) *MM2*	(0.181)	(0.154)	(0.154)	(0.154)	(0.153)	(0.181)	(0.180)	(97.3)	(110.6)	(111.7)	(113.6)	(112.0)	(109.5)	(100.5)	81ACS(B)607
(18) *X-ray*	0.181	0.1525	0.153	0.1512	0.1528	0.1792	0.1504	96.1	109.8	112.4	112.4	112.0	111.0	105.4	89H(28)937
(19) *X-ray*	0.1796					0.1785	0.1649/ 0.1702 (disorder)	99/97	111.1/ 111.5	111.7/ 109.9	111.6/ 109.5	111.5	112.6/ 111.6	104.6/ 100.0	87JST(156)165
(20) *X-ray*	0.1763					0.1801	0.1639	99.4	113.7	111.4	114.2	112.1	111.6	102.1	87JST(156)165
(21) *X-ray*	0.1801					0.1817	0.1629	99.3	110.7	113.1	112.1	113.9	109.6	102.7	87JST(156)165
(22) *X-ray*	0.1756					0.1759	0.1439 ax	0.1447 eq	109.5					<O—S—O 116.9	88JA8512



(12)

the two forms. Torsion angles range from 58.4° to 64.2° in one and 57.6° to 62.7° in the other. Once again the experimental work was supported by molecular mechanics calculations (using MMP2(85)) to cast light upon the very interesting interplay of steric interactions and intramolecular hydrogen

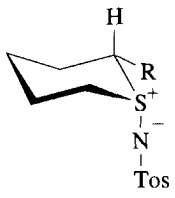


(13)

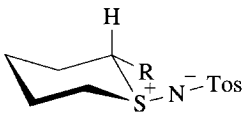
bonding effects which controls the rotational energy barriers within the molecule.

It is interesting that the equatorial disposition of the sulfoxide oxygen in (**13**) is not the most commonly observed state in such systems, and a preference for an axial orientation is usually seen. The origin of the tendency for polar substituents adjacent to the ring heteroatom to adopt an axial disposition is still the subject of dispute. Originally observed in sugars, whence is derived the term "anomeric effect," the phenomenon is frequently encountered in spiroketal systems (see Table 1). As part of an investigation into the anomeric effect the molecular parameters of thiane-1,1-dioxide were measured ⟨88JA8512⟩, and the data are shown in Table 2.

The structure of thiane-imides (sulfilimines) is closely related to that of the sulfoxides—the polar nitrogen substituent is frequently found axially disposed in otherwise unsubstituted systems. When further substituents are present these groups on sulfur appear subordinate to the preferences of the other moieties. Thus in the case of thiane-1-tosylimide derivatives bearing small alkyl groups, the imide is axial in *cis*-1,2-disubstituted compounds (**14**), but equatorial in *trans*-1,2-disubstituted cases (**15**). In all instances the carbon substituent was equatorial. Kucsman *et al.* have made extensive investigations of the thiane-sulfilimine area, as well as the sulfoxides, using both x-ray and *ab initio* SCF-MO methods. Some of the relevant data are abstracted in Table 2 ⟨87JST(156)165⟩.



(14)



(15)

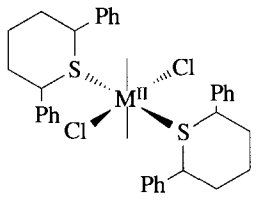
5.10.3.1.3 Microwave spectroscopy

The three rotational constants for the ground states of pyran and thiane have been determined by microwave spectroscopy over the frequency range 18–40 GHz. In both cases the spectra of a number of vibrationally excited states were also observed. Relative intensity measurements permitted the assignment of the satellite spectra to the individual ring skeletal modes. The values of the vibrational frequencies extracted by this method (224 to $\approx$500 cm^{-1} for thiane) were in good agreement with those derived by IR spectroscopy. Furthermore, the lack of fine structure in the microwave spectra suggested a high energy barrier to ring inversion, of the order of 12 kcal mol^{-1} for thiane ⟨86JST(147)67⟩.

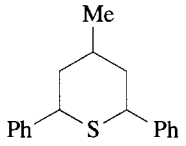
5.10.3.1.4 Infrared spectroscopy

The application of microwave spectroscopy to thiane systems was referred to above, and the estimate it gave for the barrier to inversion. Earlier studies of thianones and methylenethianes in comparison to pyran and cyclohexane analogues, used far-IR spectroscopy (over the range 50–450 cm^{-1}) to examine the skeletal vibrations, and in particular to identify the out-of-plane deformation modes for these systems. Ring inversion processes are closely connected to these motions ⟨83CJC1924, 84CJC1565⟩.

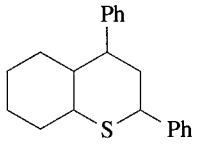
"Classical" IR spectroscopy has been applied to the characterization of a number of Pt^{II} and Pd^{II} complexes of thianes. These complexes, of the general form: *trans*-ML_2Cl_2 (**23**), had as ligands a number of mono-, di-, and tricyclic perhydrothiin ring systems (**24**), (**25**), and (**26**) ⟨83MI 510-01⟩.



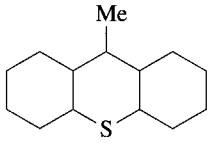
(**23**)



(**24**)



(**25**)



(**26**)

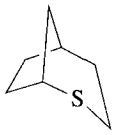
5.10.3.1.5 Optical rotation

While the use of x-ray crystallography can unambiguously define a complex molecular structure, and in particular its absolute stereochemistry, it is clearly limited by the need for a suitable crystal. Another phenomenon that can be used to elucidate absolute configuration is rotation of the plane of polarization of light. Theoretical studies on the circular dichroism properties of thianes and thiadecalins have been published, laying the foundations for accurate prediction of absolute structure ⟨81JCS(P2)1529, 90G223⟩.

Molecular rotation in thioglucopyranoses can be predicted in a simple manner with a high degree of confidence. As such thiosugars are only available by synthesis, such a prediction has great importance for confirming enantiopurity. It is necessary to take into account possible conformational influences of intramolecular hydrogen bonding, and solvent interactions ⟨84AJC971, 91JOC1668⟩.

5.10.3.1.6 Mass spectrometry

Mass spectrometric investigations of simple thianes has received relatively little specific attention. Bridged thiabicyclooctanes such as (**27**) have, on the other hand, been examined carefully, and both their positive and negative ion spectra have been analyzed in detail. It was found that negative ion spectra could give very specific information regarding substitution α to the sulfur, while the positive ion spectra were far less diagnostic ⟨83ZOR2561⟩.



(**27**)

There have been reports of GC-MS techniques being applied to the investigation of the perhydrothioxanthenes. Six isomers are possible (Figure 4) and all were identified unambiguously. Mass spectral fragmentations were characterised by cleavage principally of bonds in the central ring in *trans*-fused isomers, and of outer ring bonds in *cis*-fused systems ⟨92JCS(P2)965⟩.

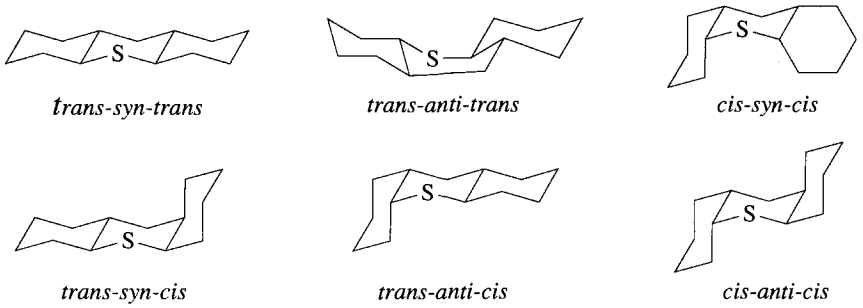
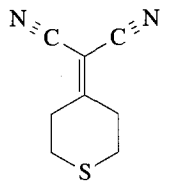


Figure 4 Perhydrothioxanthenes: structures and conformations.

5.10.3.1.7 Charge transfer absorption and emission spectroscopy

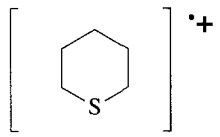
Charge transfer effects and the resulting absorption and emission spectra are perhaps most commonly thought of in connection with the intermolecular interaction of extensively delocalized structures. However, intramolecular charge transfer effects can be seen in systems wherein a sulfur atom can function as a donor separated from a suitable acceptor by a framework of σ bonds, as in (**28**). Preliminary work has appeared in which steric influences on this electronic behavior were investigated ⟨82JA5127⟩.



(**28**)

5.10.3.1.8 Electron spin resonance spectroscopy

ESR spectra of the cation radical of thiane (**29**) have been obtained. Its spectroscopic behavior is similar to its oxygen counterpart pyran, where the conformation adopted places two β protons in axial positions such that they can interact strongly, and couplings of 25 G were measured ⟨84JCS(P2)1681⟩.



(**29**)

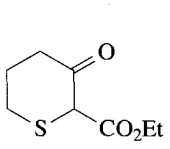
5.10.3.1.9 Dipole moment measurement

The dipole moments of thiane and 4-thianone have been determined to be 1.78 D and 1.46 D, respectively ⟨81AQ445⟩.

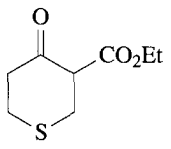
5.10.3.1.10 NMR spectroscopy

Of all the techniques for the elucidation of molecular structure and conformation, the most widely used is nuclear magnetic resonance spectroscopy. Since the early days when the only readily observable nucleus was the proton, instrumentation has advanced such that natural abundance ^{13}C spectra are routine aids to configurational and conformational assignment in thianes. Nitrogen-15 NMR spectroscopy has been used where appropriate, but is less commonly applied, while ^{17}O and ^{33}S have begun to be investigated and the foundations laid for their application to thiin systems.

The emphasis of NMR research in the thiane area since the early 1980s has been overwhelmingly on ^{13}C, and relatively few papers have appeared treating specifically ^{1}H NMR work. A study of the enolization of thianone-carboxylates (**30**) and (**31**) is one of the few ⟨81T2633⟩.



(**30**)



(**31**)

A more unusual ^{1}H NMR study has examined the effect of pressure on the resonances in the spectrum of *trans*-$PdCl_2$(thiane)$_2$ in methylene chloride as a means to probe the ligand exchange and ring inversion processes. Over the pressure range up to 220 MPa no significant variations in line shape or other parameters are observed, permitting an estimate of an upper limit for the activation volume of the exchange reaction $\Delta V^{\pm} = 0 \pm 2$ cm^3 mol^{-1}. Inversion rates were found to be 105 s^{-1}, in good agreement with theoretical predictions of 103 s^{-1} ⟨83JCS(D)1473⟩.

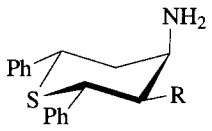
Extensive tabulations of ^{13}C chemical shift data observed in the thiane area have been published, and correlations with configuration and conformation have been extracted ⟨83IJC(B)1020, 86JOC677⟩. Low temperature studies have permitted the measurement of a range of thermodynamic parameters in such systems.

The sensitivity of ^{13}C to structural changes permits the investigation of configuration of a range of substituents on saturated six-membered rings including thianes from the chemical shifts of a *single* epimer, rather than requiring both isomers of the compound ⟨93MRC80⟩. Such configurational assignments, however, may be complicated in systems carrying polar groups, and, in particular, amino functions. Conformational analyses of 3-aminothiane analogues have derived the free energy contributions of a range of interactions between the sulfur (and its oxidized derivatives) and the (functionalized) nitrogen, from a "gauche-repulsive" steric interaction with a 3-NMe_2 substituent (0.26 kcal mol^{-1}), to the effect of protonation of NH_2 (−0.91 kcal mol^{-1}) where the equatorial : axial ratio switched from 2 : 1 to 1 : 2 ⟨88T1751⟩. The basicity of amino substituents is significantly affected by conformational effects in such systems. Solvation of protonated forms can be inhibited by steric interactions with adjacent groups, particularly when the ammonium center is in an axial orientation. Thus, in conformationally mobile species the free base may be favored, or the ring may twist. (Configurational assignments based on pK_a measurements should clearly be treated with caution ⟨83JOC1597⟩).

Another approach to the assignment of structure in amine-substituted thianes has made use of natural abundance ^{15}N NMR spectroscopy. The measured chemical shifts showed considerable sensitivity of the nitrogen nucleus to structural modification, as may be seen from the data collected in Table 3. However, scrutiny of the data would suggest that ^{15}N NMR spectroscopy needs to be used in association with other techniques, rather than for unequivocal identification of a single isolated structure, and for diagnosing deviations from normal behavior. To illustrate this latter point, Table 3 displays the ^{15}N chemical shifts of a number of simple 4-aminothiane analogues (**32**)–(**35**), and it may be seen that the shift value for compound (**34**; R = H) (δ 39.8) is not consistent with an axial orientation. While a simple ring flip might be invoked to explain the anomaly, strong 1,3-interactions would arise. A more distorted conformation is therefore to be expected and is shown as (**36**). Other anomalies are discussed in the paper ⟨82JOC1933⟩.

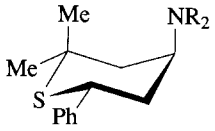
The application of ^{13}C NMR to the conformational analysis of sulfonium and sulfoxonium systems related to the thianes above has been widespread, and many of the papers already cited describe such work. Inevitably, as more research work is done, anomalous behavior and discrepancies are recognized. Such anomalous behavior may be illustrated by the issue of the relationship of vicinal ^{13}C–^{13}C coupling constant ($^3J_{(CC)}$) to dihedral angle. To be able to correlate one with the other clearly would have considerable utility for establishing dynamic solution structure in

Table 3 Nitrogen-15 chemical shift parameters for 4-aminothiane derivatives.

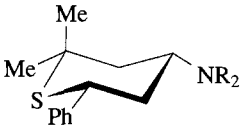


(32)

(33)



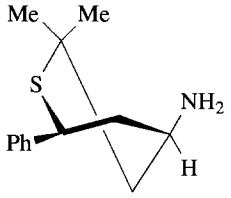
(34)



(35)

	(32)	(33)	(34)	(35)
R = H	33.6	27.4	39.8	42.7
Me	24.1	27.4	29.3	29.3
Et	22.9	26.0		

Shifts referred to anhydrous $^{15}NH_3$.



(36)

flexible heterocycles. The Karplus equation has been relied upon heavily for just such a purpose in ^{1}H NMR work for many years, but it is clear that a Karplus-type relationship does not hold for sulfonium species. The $^3J_{(CC)}$ data for a number of relevant structures have been tabulated, but no predictive solution has been reached ⟨81OMR(16)195⟩.

$^2J_{(CSC)}$ Coupling constants have also been tabulated for thiane and related systems, and those in the sulfone compounds are found to be of a magnitude not seen in sulfides and sulfoxides. The size of the coupling correlates well with the nature of the hybridization of the coupling carbon atoms, and the conformation of the ring (and hence dihedral angles) plays little part ⟨88OMR(26)1103⟩.

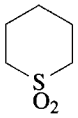
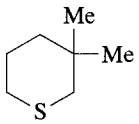
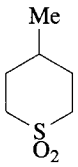
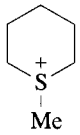
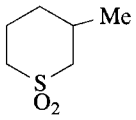
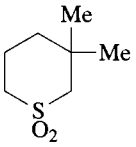
While the sensitivity of homonuclear couplings to conformational changes appears to vary from case to case, $^1J_{C-H}$ heteronuclear couplings do appear to be useful probes for molecular shape: $^1J_{C-H}$ is always larger for an equatorial than for an axial hydrogen in six-membered rings containing first or second row heteroatoms ⟨90CJC1051⟩.

As can be seen, investigation of thiin systems with ^{1}H and ^{13}C NMR spectroscopy has been, and continues to be, a very intensively used technique. By contrast, the ^{33}S nucleus (in natural abundance) has only been used since the early 1980s, due to difficulties of insensitivity and linewidth. The sensitivity of ^{33}S is only some 10% of that of ^{13}C, a consequence of a combination of unfavorable factors: low natural abundance (0.76%), small magnetic moment ($\mu = 0.8296\mu_N$) and a nuclear quadrupole moment of $Q = -0.06 \times 10^{-24}$ cm^2. Taken together with linewidths of hundreds or thousands of Hz (*cf* a few Hz for ^{13}C), the true relative signal intensity ^{33}S : ^{13}C is very low indeed. (Sulfones are an exception to this general rule as their linewidths are quite narrow and sharp signals may be obtained.) High field instruments do not completely overcome the problems, due to the low frequency at which ^{33}S resonates. Nevertheless chemical shift data and linewidth parameters have been determined for a range of thiopyran derivatives and a selection is presented in Table 4 ⟨84OMR(22)250⟩.

Similar studies have been directed at the ^{17}O nucleus, which does not suffer the same linewidth problem as ^{33}S. The chemical shift figures show significant variation with ring substitution in thiane oxides but somewhat less in the dioxide analogues. The figures in Table 5 may be taken as a basis for assigning the stereochemistry of the sulfoxide linkage in related compounds, and, in the sulfones, as a guide to the conformational preference of the ring ⟨84OMR(22)402⟩.

Further structural information may be derived from ^{17}O NMR spectroscopy by the use of lanthanide shift reagents ⟨90TL5835, 91JOC5589, 91PS(59)205⟩.

Table 4 Chemical shift and linewidth data for sulfur-33 NMR spctroscopy of thiane and related tetrahydrothiopyrans.

	δ (ppm)	$W_{1/2}$ (ppm)		δ (ppm)	$W_{1/2}$ (ppm)
	-30 ± 10	239 ± 10		321	4
	-33 ± 10	108 ± 5		321	3
	670 ± 50	390 ± 50		322	4
				320	5

Shifts referred to CS_2.

5.10.3.2 Dihydrothiopyrans

5.10.3.2.1 Photoelectron spectroscopy

It is possible to predict low energy ionization potentials in (substituted) five-membered rings containing sulfide or sulfone units within 0.1 eV through an empirical correlation scheme. The application of a similar method to the six-membered analogues fails as a consequence of their much greater deviation from planarity ⟨87JES147⟩.

5.10.3.2.2 Nuclear magnetic resonance spectroscopy

The conformational preferences of 5,6-dihydro-2*H*-thiopyran systems and their sulfoxide and sulfone analogues have been extensively investigated. Proton spectra were an unreliable guide to the molecular shapes, as there is insufficient difference in H—C—C—H dihedral angles in the half-chair and boat conformers for an unequivocal assignment of conformation. However, the predicted half-chair arrangement has been confirmed by both ^{13}C and ^{17}O experiments, and axial or equatorial dispositions of sulfoxide oxygen, or $>{}^{+}S-Me$, were readily apparent from the chemical shift data for those nuclei ⟨91T7677⟩. Table 6 collects some shift data for closely related compounds.

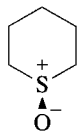
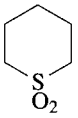
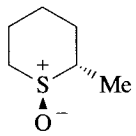
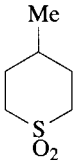
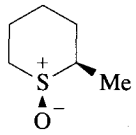
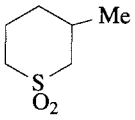
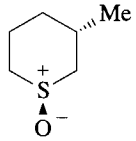
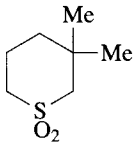
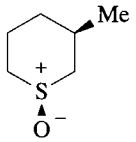
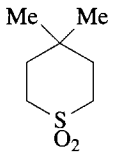
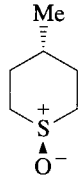
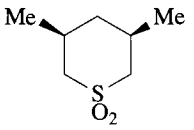
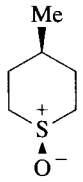
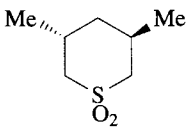
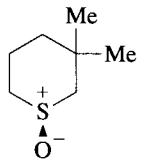
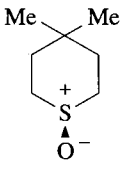
No comparable studies on 3,4-dihydro-2*H*-thiopyrans have been published, but other reports discussing the conformational equilibria of the sulfide system confirm that it too adopts a half-chair arrangement. Examination of a series of structures derived from 3,4-dihydro-2*H*-thiopyran-3-thioamides revealed a most unusual phenomenon: very large negative nOe correlations between the H-2 and H-3 protons when all others were positive ⟨92MI 510-01⟩.

5.10.3.3 Dihydrobenzothiopyrans

5.10.3.3.1 X-ray crystallography

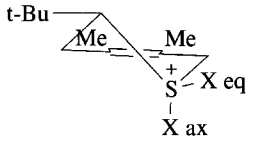
An x-ray crystal structure of the dihydrobenzothiopyran (**37**) has been reported. Examination of the data (Table 7) shows the significant asymmetry of the ring, and the opening up of the C—S—C bond angle compared to a thiane ⟨87BSB413⟩.

Table 5 Chemical shift data for oxygen-17 NMR spectroscopy of thiane sulfoxides and sulfones.

	δ (ppm)		δ (ppm)
	−4 ± 1		144 ± 1
	2 ± 1		146 ± 1, 138 ± 1
	−35 ± 1		150 ± 1, 139 ± 1
	−14 ± 1		151 ± 1
	13 ± 1		142 ± 1
	5 ± 1		149 ± 1, 139 ± 1
	−20 ± 1		154 ± 1
	2 ± 1		
	−14 ± 1		

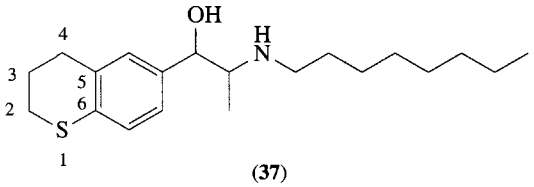
Shifts referred to $H_2{}^{17}O$.

Table 6 Carbon-13 and oxygen-17 NMR chemical shift parameters for axially and equatorially disposed sulfoxide and sulfonium derivatives of 5,6-dihydro-2*H*-thiopyrans.



X:	O^- $^{17}O\delta$ (ppm)	CH_3 $^{13}C\delta$ (ppm)
ax	−14	17.5
eq	+5	25.2

Table 7 X-ray crystallographic data for dihydro-1*H*-benzothiopyran (**37**).



(**37**)

Bond length (nm)		*Bond angle* (°)	
S_1—C_2	0.1800	C_6—S_1—C_2	103.0
C_2—C_3	0.138	S_1—C_2—C_3	117.9
C_3—C_4	0.1404	C_2—C_3—C_4	125.9
C_4—C_5	0.1509	C_3—C_4—C_5	118.9
C_5—C_6	0.1416	C_4—C_5—C_6	122.1
C_6—S_1	0.1756	C_5—C_6—S_1	123.6

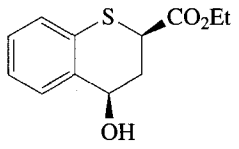
5.10.3.3.2 Electron paramagnetic resonance spectroscopy

As part of a study of the ability of compounds to trap peroxy radicals, a group of hydroxy substituted thiochromans have been examined by EPR spectroscopy. Interestingly, the outcome of the measurements implied that the sulfur compounds were less efficient than their oxygen analogues, trapping only 1–1.8 peroxy radicals per molecule rather than the stoicheiometric 2.0. UV-visible, EPR and ENDOR spectra of thiochromanoxyl radicals generated photolytically were also obtained: the radical has a UV-visible absorption band maximum at 488 nm, and an EPR g value 0.0008 greater than the oxygen analogue ⟨88JOC3739⟩.

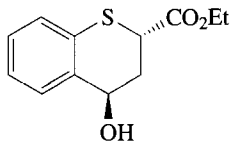
5.10.3.3.3 Infrared spectroscopy

Reference has been made earlier to the deep seated influence of intramolecular interactions of polar groups upon conformational preferences in the saturated thiopyran ring system. In the benzofused series extra rigidity is imposed by the aromatic nucleus and consequently the strain imposed by such distorting influences is much greater. A study of the conformations adopted by structures (**38**) and (**39**) utilizing the IR absorption bands of the hydroxyl group has been made. (A quasi-axial OH shows a single stretching band at ca. 3618 cm^{-1}, while a quasi-equatorial OH shows

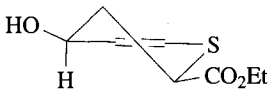
two such bands at ca. 3600 and 3622 cm^{-1}.) The preferred conformers for the two molecules were shown to be (**40**) and (**41**), respectively. These are as predicted for nonperturbed systems and therefore there was no evidence for any intramolecular hydrogen bonding ⟨84BCJ1695⟩.



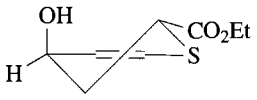
(**38**)



(**39**)



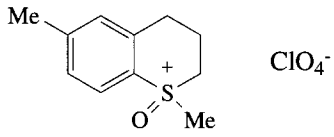
(**40**)



(**41**)

5.10.3.3.4 Circular dichroism

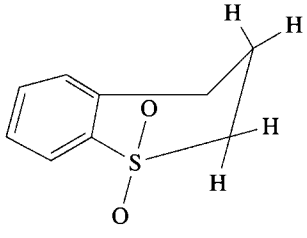
Application of circular dichroism measurements to the assignment of the absolute configuration of compounds has been extended to sulfoxide and oxosulfonium salts of dihydrobenzothiopyrans. The CD spectrum of the (−)-(*S*) enantiomer of (**42**) showed a strong negative Cotton effect at 234 nm, and negative weak effects at 273 and 281 nm. When the methyl was removed from the sulfur centre retaining the (−)-(*S*) configuration Cotton effects were observed at 203, 223, 254, 271, and 280 nm ⟨90PS(47)165⟩.



(**42**)

5.10.3.3.5 Nuclear magnetic resonance spectroscopy

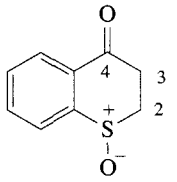
Basic ^1H NMR data permitting identification of conformational preferences in the thiochromans and 4-thiochromanones has been collected and analyzed. The hetero rings adopt half chair forms (**43**), as may be expected, but with somewhat less puckering than in the saturated monocyclic counterparts. Oxidation of the sulfur to the dioxide leads to *greater* puckering to relieve the strain inherent in the eclipsing of the S—O and adjacent C—H bond of the 2-methylene group ⟨82OMR(18)92⟩.



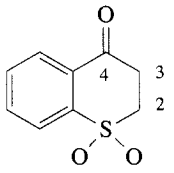
(**43**)

The related ^{13}C NMR data for the oxidized thianone systems (**44**) and (**45**) have similarly been collected ⟨84CJC586⟩, and a selection is given in Table 8.

Table 8 Carbon-13 chemical shifts in thiochromanone *S*-oxides.



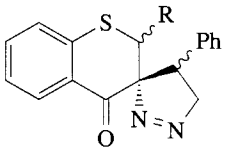
(**44**)



(**45**)

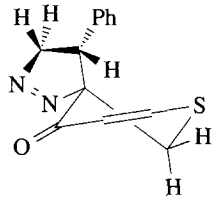
$^{13}C\delta$	C2	47.1	C2	49.3
	C3	30.7	C3	36.8
	C4	191.9	C4	190.1

Application of ^{13}C NMR to dihydrobenzothiopyrans has extended greatly the range of structures that can be investigated; the polycarpamines (**1**) referred to earlier were characterized by the use of ^{13}C NMR spectra ⟨90TL2389⟩. Even more complex problems are amenable to examination and solution in this way. Conformational analysis of spiro fused systems is common, and large amounts of valuable data may be assembled. For example, ^{13}C chemical shifts, $J_{(C-H)}$ coupling constants and long range ^{1}H—^{13}C correlations for the compounds (**46**) were measured, and used to investigate the regio- and stereoselectivity of the cycloaddition of arylidenethiochromanones with diazomethane which gives rise to them. The power of ^{13}C techniques may be illustrated by the identification of the preferred conformations of both the six- and five-membered heterocyclic moieties in the spiro-pyrazolines despite the extra complication of the flexibility of two ring systems ⟨93T863⟩. Structure (**47**) shows the result for the monophenyl substituted case.



R = H, Ph

(**46**)



(**47**)

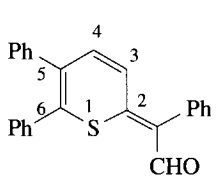
5.10.3.4 2H- and 4H-Thiopyrans

5.10.3.4.1 X-ray crystallography

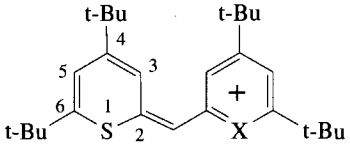
No x-ray crystal structure determination of a simple 2*H*- or 4*H*-thiopyran has yet been published, reflecting perhaps the lability of the parent compounds. However appropriate substitution with conjugative groups permits the acquisition of diffraction data. Molecules that have been examined include a 2*H*-thiopyranylidene compound (**48**) ⟨87MI 510-02⟩, a thiopyrylium dyestuff (**49**) ⟨91DP71⟩, a sulfoxide (**50**) ⟨67RTC1275⟩, and sulfone (**51**) ⟨92AX(C)1497⟩ and the relevant information is collected in Table 9. Dimensions of the 4*H*-thiopyranylidene nucleus in the nickel complex (**52**) are also included.

The rings containing sulfur in the sulfide state are only slightly distorted from a flat geometry, but this is not due to delocalization of sulfur electrons; rather, it is driven principally by the polyalkenic conjugation. It is also evident (from the C(2)—C(3) and C(5)—C(6) bond lengths) that there is no significant electron delocalization through the sulfoxide centre of 1-oxo-2,4,4,6-tetraphenyl-4*H*-thiopyran, and hence, as in the case of the dioxide (**51**), the molecule is boat shaped with pseudoaxial oxygen. The sulfur atom is 0.0237 nm above the best plane of C(2)C(3)C(5)C(6),

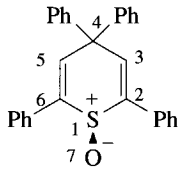
Table 9 Bond lengths and angles in 2*H*- and 4*H*-thiopyran systems.



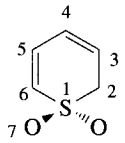
(48)



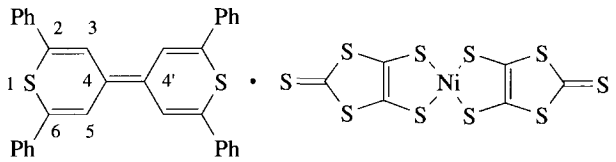
(49)



(50)



(51)



(52)

	Bond length (nm)								*Bond angle* (°)							
	S_1—C_2	C_2—C_3	C_3—C_4	C_4—C_5	C_5—C_6	C_6—S_1	S_1—O_7	C_4—$C_{4'}$	C_6—S_1—C_2	S_1—C_2—C_3	C_2—C_3—C_4	C_3—C_4—C_5	C_4—C_5—C_6	C_5—C_6—S_1	C_6—S_1—O_7	O_8—S_1—O_7
(48)	0.176	0.142	0.134	0.144	0.134	0.178			104.4	118.0	126.0	126.0	121.0	124.0		
(49; X = S)	0.1731	0.1432	0.1359	0.1428	0.1348	0.1740			105.0	120.0	126.0	121.1	126.4	121.5		
(49; X = O)	0.1724	0.1402	0.1384	0.1408	0.1354	0.1704			103.3	122.4	124.8	119.9	126.6	122.9		
(50)	0.1785	0.1325	0.1506	0.1512	0.1317	0.1802	0.1469		99.8	124.3	128.8	111.5	129.7	123.2	107.9	
(51)	0.1764	0.1494	0.1325	0.1450	0.1338	0.1730			102.6	112.6	123.1	123.2	123.8	120.8		116.9
(52)	0.1720	0.1370	0.1420	0.1412	0.1365	0.1723		0.1451	103.4	122.8	125.8	118.9	126.3	122.6		

while C(4) is 0.0116 nm above it. Furthermore the system is quite asymmetrical, with the phenyl groups at C(2) and C(6) lying at different dihedral angles to the best plane.

Reference has been made above to computational work relating to the potential of 2*H*- and 4*H*-thiopyran derivatives as organic conductors, and this has been supported by x-ray crystal structure determinations of the π-donor compounds 2-(thiopyran-4-ylidene)-1,3-dithiole and tetraphenyl-4,4-dithiopyranylidene in π-donor–π-acceptor complexes. Electrochemical properties and EPR spectra were also used to probe such systems ⟨89CM421, 91POL687⟩. The complex (**52**) shows distorted thiopyran rings, with the sulfur lying some 0.0097 nm above the plane of the rest of the organic ligand (see Table 9). Oxidation of the uncomplexed dithiopyranylidene moiety in (**52**) with iodine affords ion-radical salts, whose bond lengths etc are very similar to those seen in the complex.

5.10.3.4.2 Infrared spectroscopy

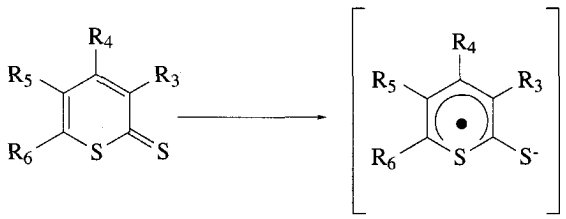
An investigation into carbonyl absorption data in thiopyran-2-ones, and comparison with the corresponding 2-pyridones, has revealed a general shift to lower frequencies in the thiin case. Variation of substituents at position 4 from Ph to Me_2N caused the absorption frequency to move from 1630 to 1619 cm^{-1} ⟨88PJS6⟩.

5.10.3.4.3 X-ray photoelectron spectroscopy

X-ray photoelectron spectroscopy has been applied to the study of "organic metals" including (**52**) ⟨82CPH355, 87ZOR505⟩.

5.10.3.4.4 Electron spin resonance spectroscopy

Radical anions of a group of 2*H*-thiopyran-2-thione derivatives have been generated and characterized (Equation (3)). The *g* values ranged between 2.00529 and 2.00670 ⟨86PS(26)257⟩.



(3)

5.10.3.4.5 Electron transmission spectroscopy

A comparison of electron transmission spectra within the group of thiopyranone, thiopyranthione and pyranthione in the range 0–6 eV showed the sulfur containing rings to have low energy Σ anion states ⟨86CPL(123)379⟩.

5.10.3.4.6 Nuclear magnetic resonance spectroscopy

The view of thiopyrans as much less delocalized species than pyrans as evidenced by techniques such as x-ray crystallographic structure determination is further strengthened by the results of investigations into π-electron densities in strongly polarized amino-substituted thiopyranthiones, and the barriers to rotation about the exocyclic C—N bonds. Endocyclic oxygen had a far more profound effect on molecular properties than S ⟨90JPR841⟩.

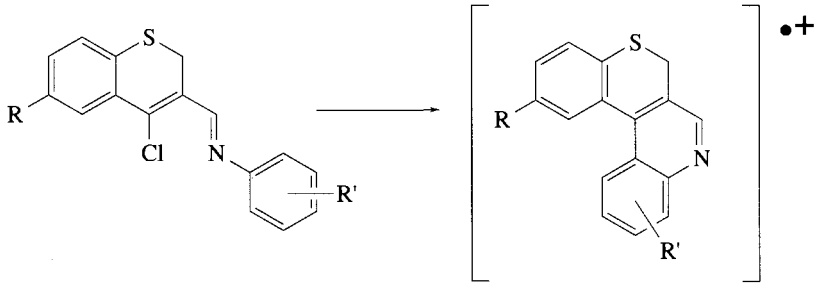
5.10.3.5 2H- and 4H-1-Benzothiopyrans and 1H- and 3H-2-Benzothiopyrans

5.10.3.5.1 X-ray crystallography

A number of crystal structures of 1-benzothiopyrans have been published ⟨89AX(C)1446, 91AX(C)1332⟩, while as yet none have appeared for the corresponding 2-benzothiopyrans. The bond length and angle data reported for the two simplest compounds (**53**) and (**54**) are collected in Table 10. There is little change in these figures in more highly condensed systems.

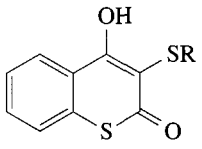
5.10.3.5.2 Mass spectrometry

The ionization of molecules in the mass spectrometer leaves them in a highly energetic state, which usually leads to decomposition processes, the smaller fragments from which can then be analyzed in order to identify the parent structure. An interesting example of such a "decomposition" process in which a more highly organized ion-molecule is formed has been found in the case of the 4-chloro-3-phenyliminomethyl 2*H*-1-benzothiopyrans (Equation (4)) ⟨87OMS(22)17⟩. As well as the cyclization process shown, the more destructive fragmentation of such structures was also fully analyzed.



(4)

A full analysis of the mass spectral behavior of compounds of the type (**55**) has been published ⟨83MI 510-02⟩.



(**55**)

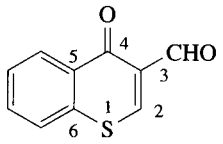
5.10.3.5.3 Photoelectron spectroscopy

He^{I} photoelectron spectra of thiochromone have been measured and interpreted with the aid of *ab initio* molecular orbital calculations. A total of four ionization energies were observed at 8.50, 9.16, 9.53, and 10.07 eV, corresponding to the π_1, n_1, π_2, and π_3 molecular orbitals respectively (n_1 is predominantly related to the carbonyl oxygen, while only π_1 has a substantial *p*-orbital coefficient on sulfur) ⟨85JCS(P2)1191⟩.

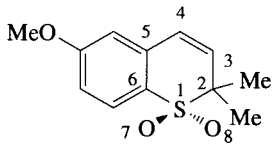
5.10.3.5.4 Electron spin resonance spectroscopy

A significant potential application of thiopyranoid systems is as electrically conducting "organic metals." As was mentioned in Section 5.10.3.4.1, the monocyclic compounds have been extensively investigated to this end, and the benzologues and more highly condensed systems have also received a considerable amount of attention. ESR studies of the "Weitz-type S-donors" (**56**) and (**57**) have

Table 10 Bond lengths and angles in 1-benzothiopyran derivatives.



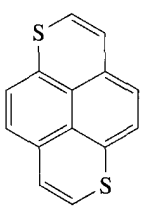
(53)



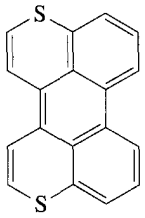
(54)

	Bond length (nm)								*Bond angle* (°)					*Ref.*
	S_1—C_2	C_2—C_3	C_3—C_4	C_4—C_5	C_5—C_6	C_6—S_1	S_1—O_7	S_1—O_8	C_6—S_1—C_2	S_1—C_2—C_3	C_2—C_3—C_4	C_3—C_4—C_5	C_4—C_5—C_6	
(53)	0.1712	0.1363	0.1459	0.1495	0.1422	0.1752			102.5	127.7	123.4	119.4	123.3	91AX(C)1332
(54)	0.1799	0.1506				0.1752	0.1429	0.1431	102.9	107.5	125.2			89AX(C)1446

appeared. ^{33}S coupling constants were derived for the two molecules (0.53 and 0.46 mT, respectively), which were in good agreement with theoretical predictions ⟨87HCA2065⟩.



(56)

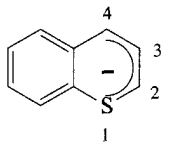


(57)

5.10.3.5.5 Nuclear magnetic resonance spectroscopy

An extensive tabulation of ^{13}C chemical shift data has been assembled for thiochromones and related systems ⟨83SA693⟩. Oxygen-17 chemical shift data has also been collected for analogous structures. When compared with that found in the chromone series broadly similar substituent influences were seen, but with a clearly smaller contribution of mesomeric effect for the sulfur atom compared to the oxygen ⟨92MRC65⟩.

The anion of 4*H*-benzothiopyran (**58**) is formally an 8π system, and therefore antiaromatic. It can be generated in liquid ammonia and, unlike the oxygen and NMe analogues, its ^1H NMR spectrum may be obtained. This shows three signals: δ5.6–6.4(5H multiplet – aromatic H + H3), δ3.88(1H dd, $J^1 = 7.0$ Hz, $J^2 = 1.5$ Hz, H4) and δ2.0(1H dd, $J^1 = 6.0$ Hz, $J^2 = 1.5$ Hz, H2) and the species clearly does not sustain a ring current in the heterocycle ⟨84TL5591⟩.



(58)

5.10.3.6 Dibenzothiopyrans

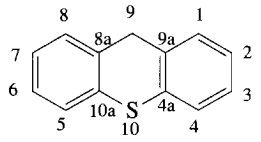
5.10.3.6.1 Electron diffraction spectroscopy

Thioxanthene (**59**) and thioxanthone (**60**) have been subjected to electron diffraction experiments and the results are shown in Table 11 ⟨87BCJ3887, 90JST(239)311⟩. Comparison of the figures with those derived from x-ray studies shows excellent agreement, within the limitations of the electron diffraction method. The pronounced folding of thioxanthene (**59**) is clearly seen, as is the flattening of the molecule when the sp^3 carbon becomes sp^2.

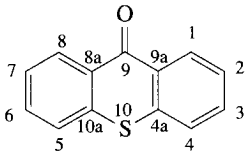
5.10.3.6.2 X-ray crystallography

A wide range of thioxanthene derivatives have been examined by x-ray crystallography. Table 12 brings together the results for the parent (**59**) and five related compounds including sulfoxide, sulfone, and sulfonium derivatives. In all cases the central thiin ring adopts a boat conformation, leading to a "V-shaped" molecule. The dihedral angle between the two arene rings is sensitive to the electronegativity of substituents, varying over a range of ca. 130–160° for simple groups, but is flattened further with the introduction of a carbonyl at C-9. The magnitude of the dihedral angle in thioxanthene appears to be only slightly influenced by crystal packing forces, as the magneto-optical rotation and molar Kerr constant suggest very similar figures in solution, and 3-21G(*) molecular orbital calculations produce molecular parameters very close to those found by x-ray analysis

Table 11 Bond lengths and bond angles of thioxanthene (**59**) and thioxanthone (**60**) from electron diffraction measurements.



(**59**)



(**60**)

	Bond length (nm)		*Bond angle* (°)		*Ref.*
	S_{10}—C_{4a}/C_{9a}	C_9—C_{9a}/C_{8a}	C_{10a}—S_{10}—C_{4a}	*Dihedral angle*	
(**59**)	0.1764	100.0	0.1520	131.3	90JST(239)311
(**60**)	0.1751	103.4	0.1498	169.0	87BCJ3887

⟨91CJC927⟩. Thioxanthones are much closer to being planar, showing dihedral angles of ca. 178° (**65**) ⟨93MI 510-01⟩, or 170° in the related sulfone (**66**) ⟨90AX(C)1178⟩ in the crystal. In solution thioxanthone may be essentially planar.

5.10.3.6.3 Ultraviolet spectroscopy

Arising from an important application of thioxanthones as sensitizers in the photoinitiation of polymerization, comprehensive studies of the mechanism of their sensitization behavior following excitation by UV light have been published ⟨92MI 510-02, 93MI 510-02⟩.

5.10.3.6.4 Photoelectron spectroscopy

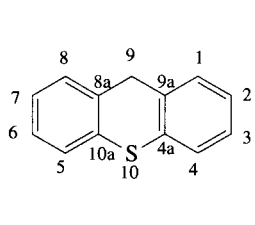
As in the cases of 2*H*- and 4*H*-thiopyrans and benzothiopyrans, thioxanthenes have attracted attention as potential "organic metal" components. The ability to participate in such behavior is related to the ease of charge transfer interactions with suitable acceptor or donor partners. A number of techniques have been applied to the study of the electronic properties of thioxanthene derivatives: the photoelectron spectra and ionization potentials of the parent molecule (**59**) have been described ⟨88MI 510-01⟩, as have luminescence spectra ⟨89MI 510-01⟩.

The absorption and emission properties of related thioxanthones have also been studied, with the finding that the S_1 state has primarily π–π^* character, and can readily participate in charge transfer interactions. Decay curves for this state are biphasic, showing involvement of the triplet state and a long lived ketyl radical. The T_1 state is itself quenched by electron transfer processes via "onium" species ⟨88JPR571⟩.

5.10.3.6.5 Electrochemical studies

The redox potentials of a group of bis-thioxanthene compounds linked via cumulene bonds have been measured by cyclic voltammetry at temperatures between −40 and −70°C. Unsymmetrically substituted compounds as well as symmetrical structures were examined, and comparison was made with a bis-thiopyranylidene analogue. Table 13 shows the results, from which may be seen the significant destabilizing effect of benzannelation on the thiopyrylium products of the oxidation step, and hence on electron transfer processes ⟨82CL1727⟩. The table also shows the equivalent data for some mixed hetero systems (compound (**70**) forms only a mono cation-radical). The ion-radical products of the first electron transfer step in materials of this type readily dimerize unless heavily substituted by electron donating groups ⟨84JOC2027⟩.

Table 12 Bond lengths and bond angles in thioxanthenes and thioxanthones.



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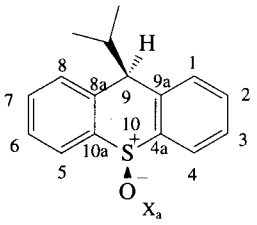

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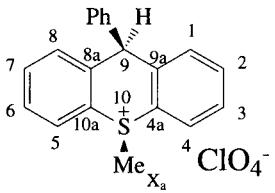

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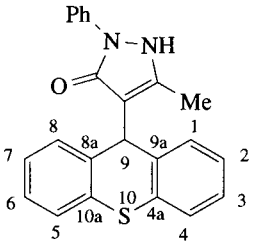

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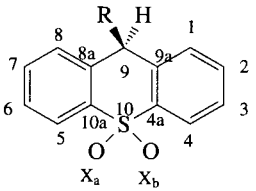

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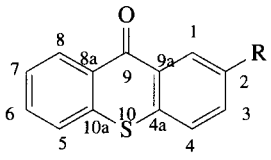

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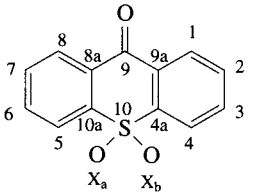
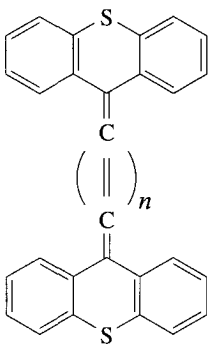


(66)

	Bond length (nm)								*Bond angle* (°)								*Ref.*
	S_{10}—C_{4a}	C_{4a}—C_{9a}	C_{9a}—C_9	C_9—C_{8a}	C_{8a}—C_{10a}	C_{10a}—S_{10}	S_{10}—X_a	S_{10}—X_b	C_{10a}—S_{10}—C_{4a}	S_{10}—C_{4a}—C_{9a}	C_{4a}—C_{9a}—C_9	C_{9a}—C_9—C_{8a}	C_9—C_{8a}—C_{10a}	C_{8a}—C_{10a}—S_{10}	X_a—S_{10}—C_{4a}	X_b—S_{10}—C_{4a}	*Dihedral angle* (°)	
(**59**)	0.1781	0.1390	0.1502	0.1522	0.1387	0.1759			99.2	119.1	120.2	111.4	119.1	120.4			135.3	73AX(B)2296
(**61**)	0.1793	0.1404	0.1514	0.1512	0.1382	0.1782	0.1505		98.2	112.3	119.5	110.8	121.0	122.5	109.7		136.5	83AX(C)648
(**62**)	0.1776	0.1392	0.1383	0.1529	0.1397	0.1755	0.1799		102.3	120.7	122.5	113.2	120.2	122.6	106.4		139.5	84JOC3151
(**63**)	0.1764	0.1396	0.1523	0.1513	0.1397	0.1759			101.9	122.9	122.9	112.9	123.7	121.9			143.4	86BCJ121
(**64**) R = H	0.1768		0.1509	0.1505		0.1764	0.1442	0.1436	101.5			113.7			107.3	112.4	136.6	87JHC143
(**64**) R = Me	0.1759		0.1539	0.1500		0.1755	0.1436	0.1424	102.6			112.5			108.8	112.0	142.9	87JHC143
(**64**) R = *i*-Pr	0.1776		0.1519	0.1510		0.1754	0.1444	0.1444	101.4			111.2			108.0	111.8	134.3	87JHC143
(**65**) R = Me	0.1743	0.1398	0.1489	0.1487	0.1415	0.1731			103.8	124.9	123.5	119.5	123.4	124.7			178	93MI 510-01
(**65**) R = Cl	0.1732	0.1406	0.1469	0.1467	0.1411	0.1734			104.0	124.5	123.2	120.8	123.2	124.3			179.0	76AX(B)2248
(**66**)	0.1757	0.1405	0.1499	0.1475	0.1405	0.1755	0.1439	0.1433	105.1	123.0	121.8	121.1	123.9	121.6	108.0	108.7	170.1	90AX(C)1178

Table 13 Redox potentials for some bis-thioxanthene and related systems.



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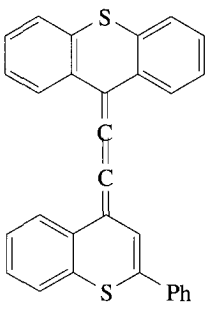

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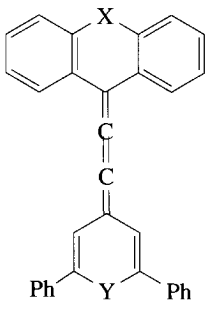

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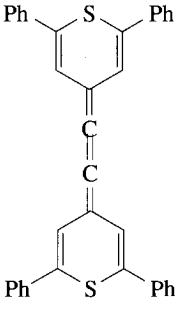


(70)

Compound	E_1^{ox}	E_2^{ox}	volts vs. SCE
(**67**; $n = 1$)	0.65	0.81	
(**67**; $n = 2$)	0.54	0.77	
(**68**)	0.54	0.84	
(**69**; X = S, Y = S)	0.37	0.72	
(**69**; X = S, Y = O)	0.14	0.49	
(**69**; X = SO_2, Y = O)	0.41	0.73	
(**70**)	0.73	—	

5.10.3.6.6 Mass spectrometry

The facile redox chemistry of thioxanthenes etc. is also apparent in mass spectral studies. Rapid redox transfer of hydrogen derived species between neutral moieties during the initial ionization/desorption processes (using a thermionic caesium ion source) may be observed in thioanthracyclines, and it has been suggested that this effect may be used to screen rapidly other biologically significant compounds for susceptibility to redox metabolic processes ⟨87MI 510-03⟩.

When methane negative ion chemical ionization is used thioxanthylidene species show an unusual MH^- ion, believed to be due to electron capture by the substrate followed by H-atom transfer from the reagent gas. It was proposed that the site of attachment of hydrogen was at the sulfur atom ⟨89OMS(24)385⟩.

5.10.3.6.7 Electron spin resonance spectroscopy

The cation-radicals derived from thioxanthenes etc by oxidative processes may be further characterized by ESR and CIDEP (chemically induced dynamic electron polarization) experiments. Such studies have been reported by Depew *et al.* ⟨88AG(E)1078⟩ and by Sugimoto *et al.*, respectively ⟨83JA2480⟩.

5.10.3.6.8 Photochemical studies

The photochemistry of thioxanthones and thiones has received a considerable amount of attention for reasons of theoretical interest and practical application. Theoretical studies on the thiones have looked at all aspects of their photochemical and photophysical behavior, including triplet lifetimes, phosphorescence quantum yields, and the influence of the nature of the solvent on their solution photoreactivity. Experimental work in this area has been described in a series of papers by Maciejewski and co-workers, who have shown that decay of the thione triplet state is dominated by intermolecular self-quenching interactions ⟨88CPH143, 88JPC2485, 88JPC6939⟩.

The oxygen analogues have been explored in a similar manner, and also from the point of view of their industrial application, where an important use is as photoinitiators of polymerization of

appropriate resins. Such photopolymerization is widely used in lithography, photoresists, and UV curing systems. To be of use in such situations the properties of the photoinitiator molecule must be tailored in a number of ways: the absorption maximum must complement the available irradiation sources, fast and efficient intersystem crossing to long-lived triplet species is desirable to facilitate activation of reactant molecules, and the photoinitiator must be compatible with, and soluble in, the resin matrix. Following excitation, *singlet* lifetime and hence rate of crossing to a triplet state has been shown to be strongly dependent on solvent, ranging from 0.1 ns in nonhydroxylic (though polar) solvents like acetonitrile up to ca. 4 ns in polar hydroxylic media such as ethylene glycol ⟨92MI 510-03⟩. Variation in the substituent pattern around the thioxanthone nucleus has equally dramatic effects on the behavior of the molecule. In a series of carboxylate ester derivatives the absorption maximum (λ_{max}) ranged from 330 nm to 420 nm (in CH_2Cl_2) and the extinction coefficient (ε) from 4300 to 7750 ($\times 0.1$ m^2mol^{-1}), with intersystem crossing quantum yields varying tenfold in a representative case ⟨86MI 510-05⟩. Thioxanthone-amines have been studied in the same way ⟨90ZC55⟩.

The combination of two ketones as a photoinitiator displays an interesting synergy ⟨87CPL(135)30⟩, whilst the interactions of two triplet species have been reviewed (and pertinent data assembled) by Carmichael and Hug ⟨86MI 510-02⟩.

5.10.3.6.9 Nuclear magnetic resonance spectroscopy

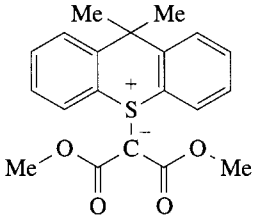
Proton NMR spectroscopy has been used to assist structural calculations (using STO-3G, STO-3G*, and 4-31G methods) on thioxanthene, as an aid to determining the dihedral angle between the benzene rings, and thence to estimate the barrier to inversion. Data from this work have been included in Table 11 ⟨91CJC927⟩.

The stereochemistry of 9-arylthioxanthene 10-oxides and 10,10-dioxides has also been investigated in this way ⟨84CPB3471⟩, complementing work on the alkyl analogues ⟨75JOC2993⟩. Significant deshielding of adjacent protons by the sulfinyl oxygen is a sensitive probe of the conformation of the system, and has permitted the recognition of the preferred pseudoequatorial arrangement of the oxygen atom. The 9-phenyl substituent occupied either the pseudoaxial or pseudoequatorial orientation, imposed by the sulfoxide. In the case of the sulfones, the phenyl substituent adopts the pseudoequatorial position.

Studies on the inversion of *S*-aryl sulfonium derivatives of thioxanthene (see Equation (5)), making use of dynamic proton NMR techniques, derived values for the enthalpy and entropy of activation of $\Delta H^{\ddagger} = 23.8$ kcal mol^{-1} and $\Delta S^{\ddagger} = 2.6$ cal mol^{-1} K^{-1}, respectively. The near zero entropy of activation of this process is interpreted to imply a single step mechanism, and is consistent with results from the application of other techniques to sulfonium compounds ⟨88BCJ1181⟩.

(5)

Studies of ylidic systems such as (**71**) using, in particular, variable temperature methods, has shown them to be more flattened than the related sulfoxides; the substituent occupies the most equatorial-like orientation of the two associated with the tricoordinate sulfur ⟨85JHC1261, 92PS(73)63⟩.



(71)

Full assignment of ^{13}C chemical shift data in thioxanthones and the derived sulfoxides has been made possible by the use of two-dimensional correlation techniques. Substitution on one benzenoid ring of the tricycle leads to electronic changes in the remote unsubstituted ring. The effects may be analyzed by PRDDO molecular orbital calculations, and it can be shown that substitution at C-2 alters electron density at C-4a, C-10a, C-6, and C-7. Transmission of substituent effects appears to involve a π-polarization mechanism through the sulfur atom ⟨87JHC1067, 89JCS(P2)325⟩. Related data on thioxanthenes has also been reported ⟨91JHC731⟩. Further evidence for "through-sulfur" electronic effects in 2-substituted thioxanthones, and their sulfoxides and sulfones, is provided by ^{17}O NMR chemical shift data. Examination of the spectra of ^{17}O-enriched materials, and application of Taft's dual substituent parameter treatment, revealed an excellent correlation of the carbonyl *oxygen* shift with the σ_I and $\sigma_R^{(+)}$ figures for the 2 (meta) group, but not of the carbonyl *carbon*. Substitution on sulfur was also well reflected by the carbonyl oxygen: $\delta^{17}O$ for thioxanthone is 462.7, for thioxanthone *S*-oxide it is 507.7 and for the *S,S*-dioxide it is 528.2; the corresponding carbonyl carbon shifts varied over only 1.7 ppm ⟨89JCS(P2)1657⟩.

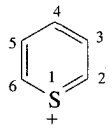
Comparison of ^{17}O NMR shifts of the sulfone oxygen of thioxanthone *S,S*-dioxides and of thioxanthene *S,S*-dioxides clearly shows a significant deshielding effect on the S—O group by the inductive action of the carbonyl ⟨87MRC305⟩.

5.10.3.7 Thiopyrylium Salts

5.10.3.7.1 Molecular dimensions

No crystal structures for simple thiopyrylium salts have been reported, but theoretical calculations for the parent molecule have been performed. The structure is predicted to be planar, and Table 14 lists the calculated bond lengths.

Table 14 Calculated bond lengths for the thiopyrylium ion.



(72)

Bond lengths (nm)	
S_1—C_2	0.1647
C_2—C_3	0.1391
C_3—C_4	0.1416
C—H bonds	0.1095

5.10.3.7.2 Electronic spectra

Major applications for thiopyrylium compounds are in dye stuffs and photoconductive materials. Studies on absorption and fluorescence behavior in relation to the substituent pattern on the nucleus and solvent effects revealed that one of the long wavelength absorption bands is related to an intramolecular charge transfer process ⟨85KGS198, 86MI 510-03, 92CJC2390⟩. Further work on intramolecular charge transfer has made use of x-ray photoelectron spectroscopy. When applied to solid state electron transfer phenomena in dialkylamino-substituted thiopyrylium systems (and their pyrylium and pyridinium analogues), well resolved spectra were obtained, in which the ionization of the donor nitrogen 1*s* orbital and the acceptor action of the hetero rings was clearly observed ⟨82MI 510-01⟩.

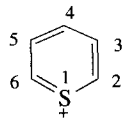
5.10.3.7.3 Mass spectrometry

The characterization of pyrylium, pyridinium, and thiopyrylium compounds by older mass spectral techniques is complicated by the fragmentation of the parent molecule. Fast atom bombardment ionization methods, however, using glycerol and bis(2-hydroxyethyl) sulfide matrices generally give rise to spectra with large peaks corresponding to intact molecular ions, and relatively little fragmentation. Low intensity, but diagnostically useful, fragment ions are observed for the substituents on the hetero nucleus. In certain cases, particularly nitro- or chloro-bearing substrates, FAB ionization-induced chemical conversions are seen, which differ from those found following electron impact ionization ⟨87JCS(P2)633⟩.

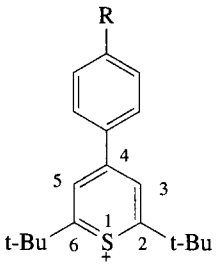
5.10.3.7.4 Nuclear magnetic resonance spectroscopy

The question of the electronic nature of thiopyrylium species has been addressed by a number of techniques, some of which have been outlined above, from theoretical calculations to photoelectron spectroscopy. NMR spectroscopy has also been used. Electron density changes in the ring can be well correlated with properties of substituents in a linear fashion, as reflected by ^{13}C chemical shifts, except in the case of groups like phenyl which exert effects by a π-polarization mechanism. Thus, an aryl group at C-4 carrying electron withdrawing substituents shields that carbon, but this relatively weak influence does not extend to C-2 or C-6. Table 15 shows illustrative data for ^{13}C chemical shifts in 4-phenyl-substituted thiopyrylium systems (**73**) and compares them with those for the parent thiopyrylium ion (**72**). The effect of ring substitution upon the chemical shift of C-2 is dramatic; the significant deshielding of the carbon atoms observed may be the consequence of steric interference with solvation of the charged sulfur by the CD_3CN solvent. Addition of methoxide to the 2,6, and 4 positions of such thiopyrylium salts has been used as a kinetic measure of the relative electron density at those centers, and correlates well with $\delta(^{13}C)$ values over a wide range of substitution patterns. However the correlation does not hold for aryl-substituted C-4 ⟨87PS(29)187, 88G291⟩.

Table 15 Carbon-13 NMR chemical shifts in thiopyrylium salts.



(**72**)



(**73**)

$\delta(^{13}C)_{CD_3CN}$	C-2	C-3	C-4	*Ref.*
(**72**)	158.8	138.3	150.8	87PS(29)187
(**73**) R = H	186.03	131.57	162.47	87PS(29)187
(**73**) R = NO_2	187.26	132.37	160.10	87PS(29)187
(**73**) R = Cl	186.31	131.50	161.10	88G291
(**73**) R = OMe	184.47	129.97	161.47	88G291
(**73**) R = NMe_2	179.26	126.19	159.30	88G291

Equally anomalous ^{13}C chemical shifts are found in the case of mesomerically interactive dialkylamino groups at positions 2 and 4. A considerable barrier to rotation about the exocyclic C—N bond (of the order of 50 kJ mol^{-1}) is seen, but the magnitude is very sensitive to further

conjugative and steric influences from adjacent groups. Comparison with the corresponding pyrylium compounds shows a higher mesomeric effect in the oxygen case consistent with the greater electronegativity of oxygen than sulfur ⟨88MRC707, 89MRC713⟩.

5.10.3.8 Benzothiopyrylium Salts

5.10.3.8.1 Infrared and ultraviolet spectral and other physical properties

Principal research interest in benzothiopyrylium salts is, as for thiopyrylium species, related to their electronic properties. Thus the electron transfer properties of 1-benzothiopyrylium compounds have been fully explored by cyclic voltammetry and electronic absorption spectra, supported by theoretical calculations ⟨87DP25⟩.

The powerful electron-withdrawing influence of the 1-benzothiopyrylium nucleus allied to an amino donor group may be used to make polymethine dyes which absorb in the near IR. Absorption bands with $\lambda_{(max)}$ between 600 and 900 nm (and ε ranging from 46,000 to 150,000 $dm^3\ mol^{-1}\ cm^{-1}$) can easily be realised ⟨90JCR(S)50⟩.

5.10.3.9 Thioxanthylium salts

5.10.3.9.1 Infrared spectroscopy

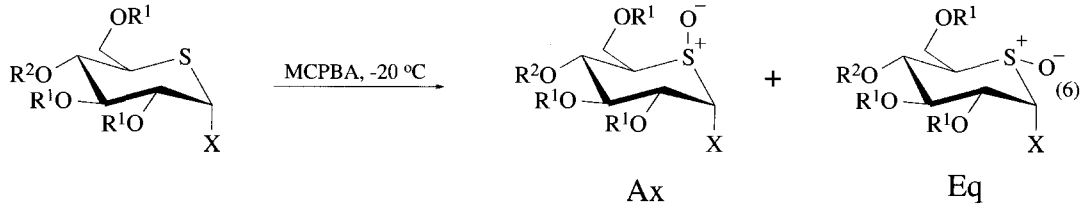
As in the case of thiopyrylium compounds, polymethine dyestuffs based on thioxanthylium nuclei have also been extensively investigated ⟨91MI 510-01⟩.

5.10.4 REACTIVITY OF RINGS: REACTIONS AT RING CARBON AND SULFUR ARRANGED BY RING SYSTEM

5.10.4.1 Thianes

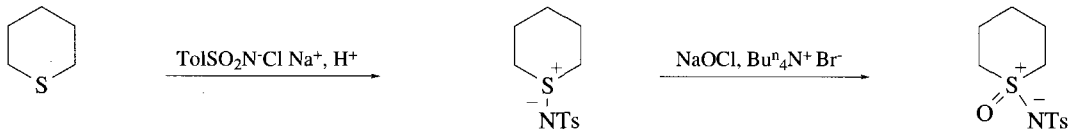
Reactions of thiane ring carbon atoms are closely analogous to those of the corresponding alicyclic materials: the influence of the sulfur atom in the thiane ring upon the ring carbons is largely restricted to the α positions, save for some interesting observations in solvolytic reactions of 3-, and to a much lesser extent 4-halo thianes. Transannular participation by sulfur lone pairs in such systems has a significant effect upon reaction rates and can lead to the formation of ring-contracted tetrahydrothiophene products. Intermolecular reactions of the electron rich S atom are common: electrophilic attack readily generates thianium salts from reagents such as alkyl halides, and ylidic products from carbenes and nitrenes. Equally facile is oxidation to the sulfoxide or sulfone, and a wide range of reagents may be employed, acting by one or other of two mechanistic pathways: direct oxidation by electrophilic oxygen as with peracids, or functionalization of the sulfur followed by a nucleophilic displacement by water as in the case of hypochlorites. If the product of the reaction is the sulfoxide then the stereochemical consequences of the two types of process are opposite, the hypochlorite-type oxidation proceeding via inversion of the configuration of the first-formed chlorosulfonium center. While this is of little consequence in the parent heterocycle, in substituted systems oxidation to the sulfoxide state introduces a new stereogenic center, and the ability to control the stereochemistry of the oxidation assumes considerable importance. The oxidation of conformationally fixed thianes (e.g., 4-*t*-butylthiane) affords axially oriented sulfoxides with peracids and equatorially arranged products from the two step process, following initial axial attack. However, more extensive substitution of the ring, particularly α to the sulfur, perturbs this simple picture and increasing amounts of equatorial product are observed from peracid oxidations as steric interactions increase. It is not only steric factors that influence the outcome of such reactions: stereoelectronic considerations also come into play if the α substituent is a heteroatom. A study of the oxidation of a 5-thioglucose derivative with *m*-chloroperbenzoic acid illustrates the situation well (Equation (6)) ⟨90BCJ3473⟩. If X = OMe the axial-equatorial product ratio (Ax : Eq) is ca. 5 : 1, as might be expected. However, if X = OAc the ratio changeses to ca. 1 : 2. The products of the

oxidation are under kinetic control, and their distribution may be taken to reflect the relative electron densities in the sulfur 3*p* orbitals, as influenced by the group X. In the absence of such perturbations, even with a carbon linked 2-substituent as large as isopropyl, the Ax : Eq ratio is usually > 15 : 1.



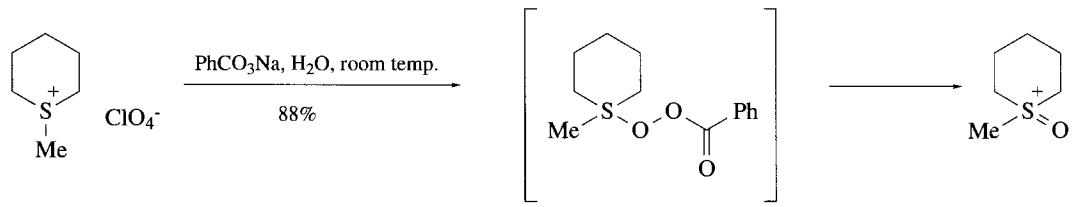
Oxidations using *t*-butyl hypochlorite, phenyltrimethylammonium tribromide or electrochemically generated halonium ions and proceeding via an initial halogenation at sulfur followed by nucleophilic displacement (with inversion) have been extensively investigated ⟨84TL4665, 90S847, 90S1037⟩. Photooxidation of thiane using molecular oxygen (acetone, room temperature, Rose Bengal sensitizer) is also an efficient process (rate constant $k_t = 0.47 \times 10^{-6}$ M^{-1} s^{-1}), and, unlike the case with tetrahydrothiophenes, does not yield any products of ring cleavage ⟨92JA3021⟩.

Acid-catalyzed reaction of thianes with chloramine-T and analogous reagents readily forms the sulfilimine ylides, probably via a similar process to the two-step oxidation above, i.e., initial chlorination of the sulfur atom and then nucleophilic displacement of the chlorine by the nitrogen anion ⟨82JCS(P2)1075⟩. However, stereoselectivity is poor, Ax : Eq ratios of ca. 1 : 1 being observed in fixed systems. The sulfilimines may be further oxidized by sodium hypochlorite (under phase transfer catalysis) to sulfoximines (Scheme 1) ⟨84JOC2282⟩.



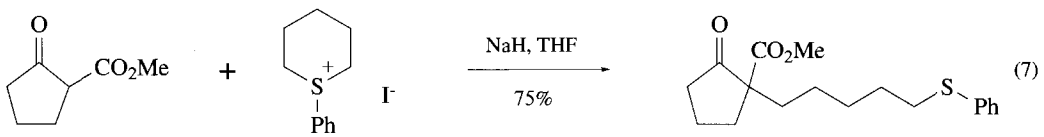
Scheme 1

Sulfonium salts may also be oxidized to oxosulfonium species ⟨90PS(47)157⟩ but this is a nucleophilic addition process rather than an electrophilic attack (Scheme 2); the stereochemistry of this conversion has yet to be determined.

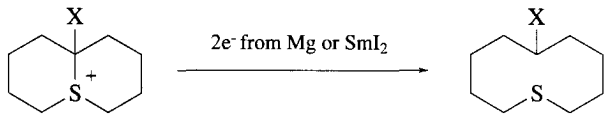


Scheme 2

The positively charged sulfur in thianium salts also renders the α carbon susceptible to nucleophilic attack, with rupture of the C—S^+ bond, leading to products carrying a 5-thiopentyl group. The reaction is not confined to the saturated heterocycle, both 5,6-dihydro-2*H*-thiopyranium and 3,4-dihydro-2-benzothiopyranium species undergoing such conversions with the formation of more highly functionalized products ⟨83JOC8⟩. The reaction shown in Equation (7) shows a carbon nucleophile but analogous reactions are seen with amines and thiols ⟨86BCJ2657, 88KGS1552⟩.

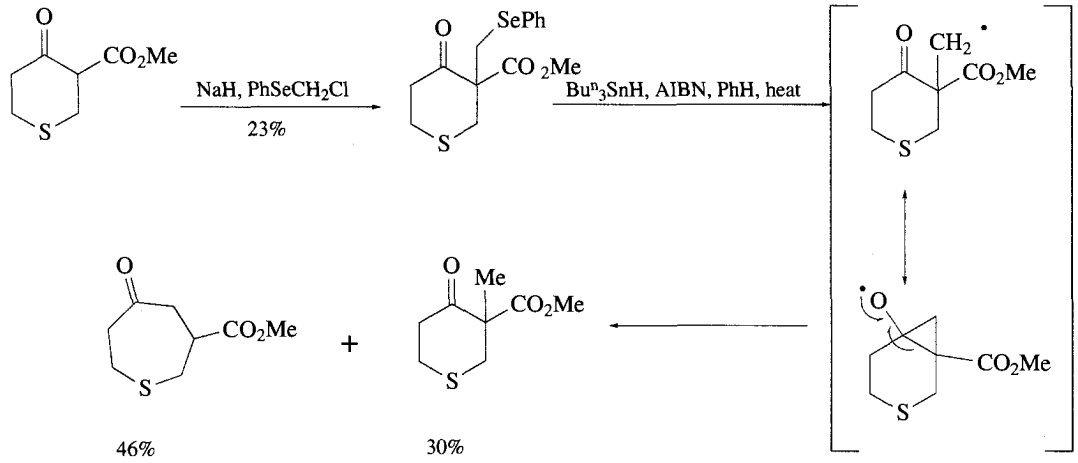


Reductive cleavage of thianium salts is equally facile with samarium iodide or magnesium, and has been used in the synthesis of medium ring sulfur compounds (Equation (8)). If X is a group capable of stabilizing negative charge, the bond breakage becomes specific ⟨90TL3027⟩. By contrast, the reductive cleavage of thiane sulfone with ultrasonically dispersed potassium gives rise to the pentylsulfonyl anion, which may be alkylated with methyl iodide to give methyl pentyl sulfone ⟨85TL4495⟩.



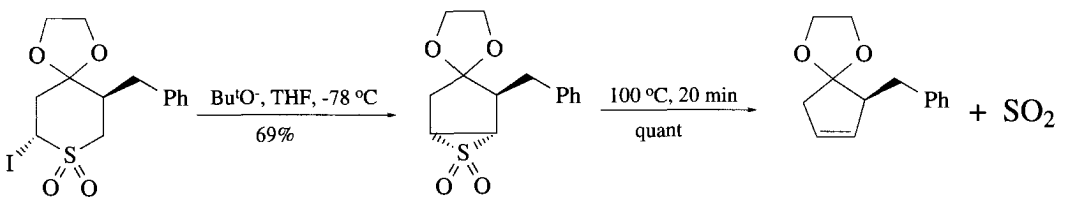
(8)

Whereas the reductive ring expansion reaction shown above may be used to expand a thiane to a cyclothiadecane, radical mediated ring expansion represents a new method of forming thiepanes from thianes. Scheme 3 shows the use of a carbonyl group to trap an exocyclic methylene radical as a cyclopropyloxy radical, which then reopens with ring expansion. While the overall yield is only modest, the analogous ring expansion of a tetrahydrothiophenone to a thianone is much more efficient, affording a 64% yield ⟨91T4847⟩.



Scheme 3

Ring contraction of the thiane sulfone, with extrusion of SO_2, is extremely well known under the name "Ramberg–Bäcklund reaction." First reported in 1940, it has seen considerable application for the synthesis of substituted cyclopentenes in recent years ⟨40MI 510-01⟩. The episulfone had long been postulated as an intermediate, but it was not until 1989 that the first example was isolated. While the bicycle (**74**) was moderately stable to storage at −18 °C, it slowly decomposed in solution at room temperature over a period of several weeks, or more usefully in 20 min at 100 °C. Analogous thianes with substituents at C-2 do not afford stable intermediates, giving rise directly to the cyclopentene in very high yield even at −78 °C. Steric strain in the bicyclic intermediate drives the cheletropic elimination of SO_2 (Scheme 4) ⟨89TL3267⟩.

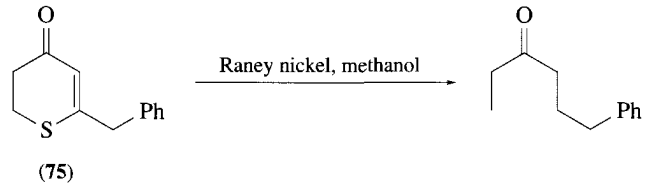


(74)

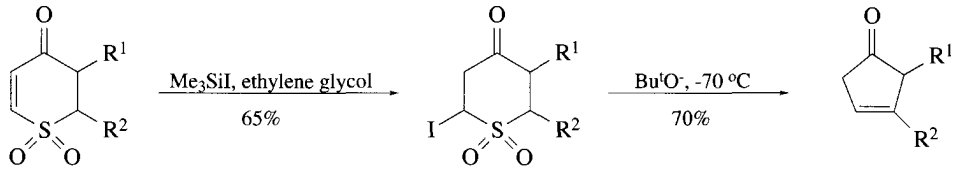
Scheme 4

5.10.4.2 Dihydrothiopyrans

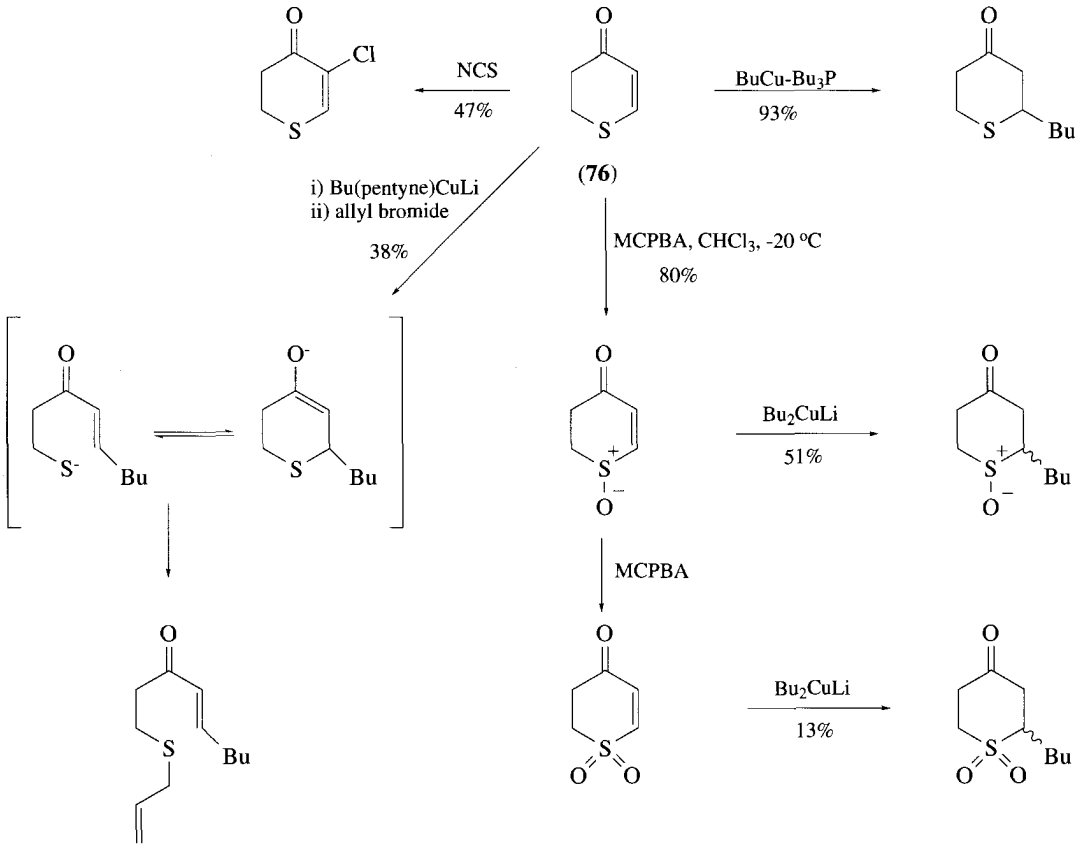
Dihydrothiins have received a considerable amount of attention as building blocks in natural product synthesis, summarized in a review by Vedejs ⟨87KGS1587⟩. Perhaps the most widely used core structure of this type is 5,6-dihydrothiopyran-4-one, for example (**75**). Equation (9) and Schemes 5–7 show a range of conversions for such derivatives ⟨82JCS(P1)1177, 84JCS(P1)703, 88CC454⟩.



(9)

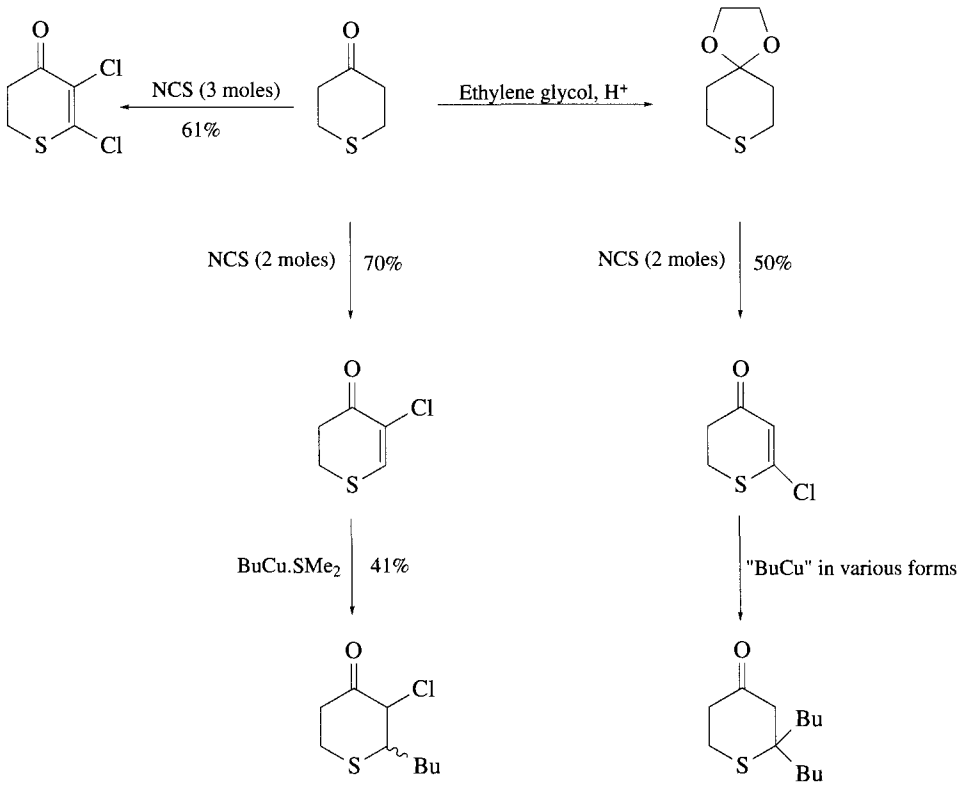


Scheme 5

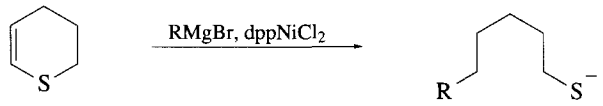


Scheme 6

Interestingly, while conjugate additions to the enone (**76**) generally afford addition products, attempted addition of Grignard reagents (catalyzed by dppNiCl$_2$) to 3,4-dihydro-2*H*-thiin (**77**) lead only to C—S bond cleavage, with the formation of 5-substituted-pent-5-enylthiolate anion, which can be trapped in high yield (Equation (10)) ⟨85JOC3828⟩.

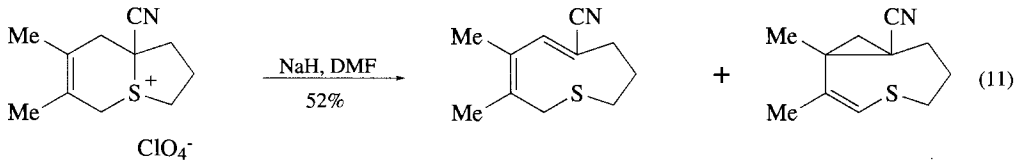


Scheme 7



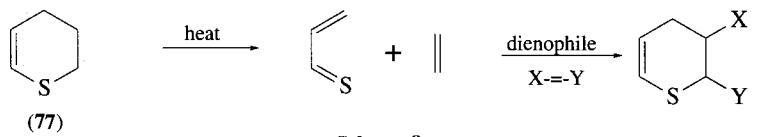
(77) (10)

The 3,6-dihydro-2*H*-thiopyranium system is also susceptible to base induced ring opening (Equation (11)) ⟨92JCR(S)393⟩.



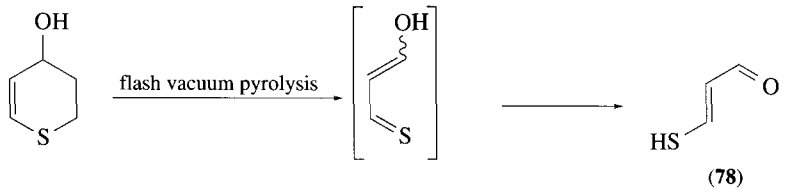
(11)

By contrast, the vinyl sulfide 3,4-dihydro-2*H*-thiin (**77**) is susceptible to acid-catalyzed hydrolytic ring opening under vigorous conditions, to a thiol-aldehyde. Of much greater importance is the retro-Diels–Alder fragmentation of this ring system (Scheme 8), the reversal of one of the most common synthetic processes for preparation of these compounds, and which has been used to prepare many novel structures by trapping of the short-lived enethioaldehyde product with a range of dienophiles (see, for example, ⟨86BCJ3279⟩). Flash vacuum pyrolysis of the functionalized ring is a source of otherwise difficultly accessible small molecules. Scheme 9 shows the preparation of 3-mercaptopropenal (**78**) ⟨91PS(59)121⟩.



(77)

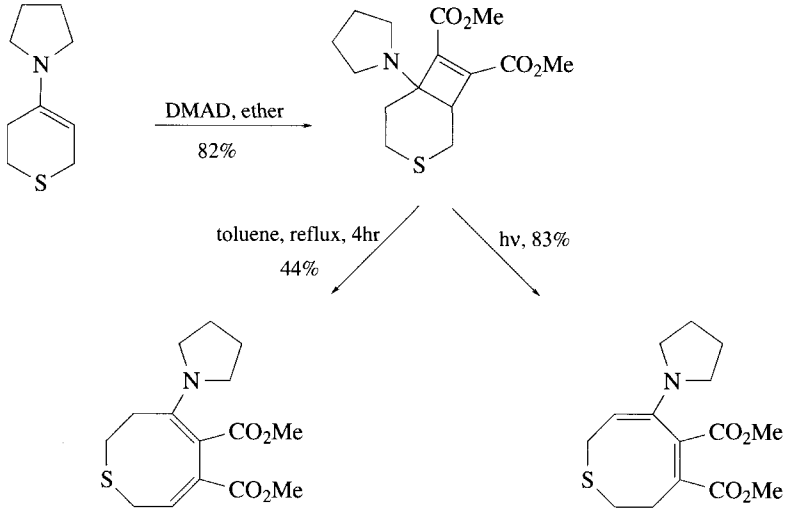
Scheme 8



(78)

Scheme 9

Electron-rich double bonds in dihydrothiins readily undergo [2 + 2] cycloaddition processes with reagents such as DMAD. The enamines derived from thian-4-one have frequently been employed in such reactions, from which the products are usually the result of ring-opening of the first formed cyclobutanes. This represents an efficient synthetic entré into functionalized thiocines (Scheme 10) ⟨84JA1341⟩.



Scheme 10

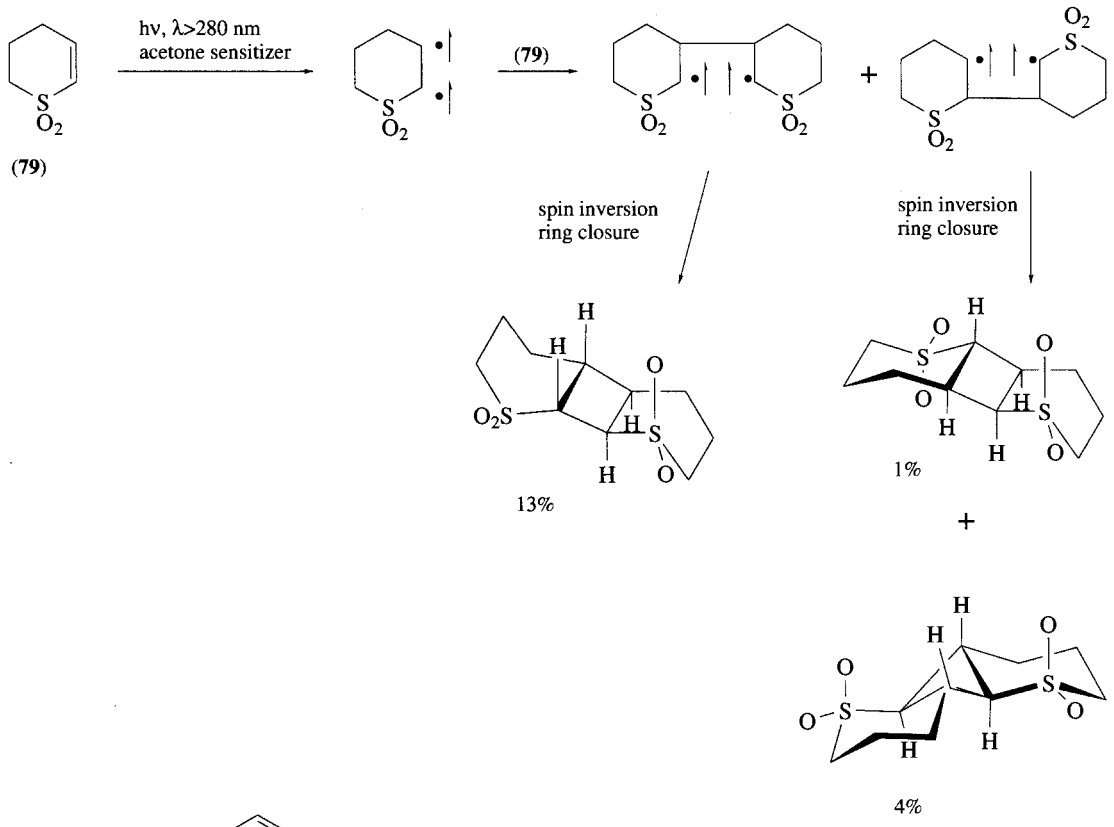
By contrast, the addition of 1,3-dipoles to *un*activated double bonds in dihydrothiins was precluded by the fragmentation of the ring during prolonged heating ⟨90BCJ3300⟩.

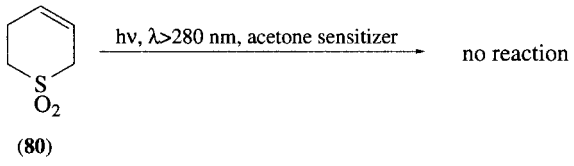
Photochemical reactions of a number of derivatives of dihydrothiins have been investigated. In the case of 3,4-dihydro-2*H*-thiopyran *S*,*S*-dioxide (**79**) there is inefficient formation of a number of isomeric products arising through [2 + 2] reactions of the alkenic bond. By contrast, 5,6-dihydro-2*H*-thiopyran *S*,*S*-dioxide (**80**) is inert to the same conditions (Scheme 11). Clearly the reactivity of (**79**) is dictated by the juxtaposition of the vinylic linkage and the sulfone, and this interaction may be observed in the IR absorption behavior of the alkene bond ⟨89T1667⟩.

The photochemistry of the enones is more varied: 5,6-dihydro-4*H*-thiopyran-4-one behaves as a simple enone, efficiently yielding head-to-head dimers or adding in [2 + 2] manner with isobutylene and other olefins when irradiated at 350 nm. The 2,6-dihydrothiopyran-3-ones (**81**) also efficiently undergo photoconversion, but to quite unusual products, vinyl thietanones. Solvent and substitution pattern have little influence on the reaction, and yields are typically 90%, offering a synthetically useful access to such structures (Scheme 12) ⟨85HCA1129, 92HCA1925, 92HCA2265⟩.

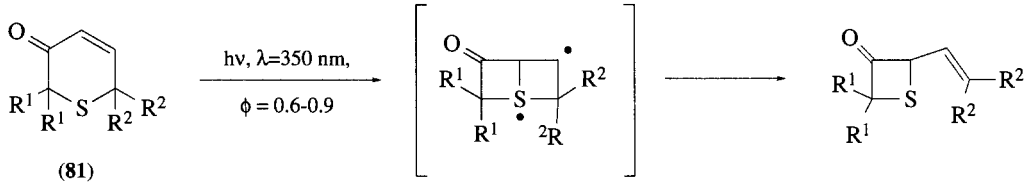
5.10.4.3 Dihydrobenzothiopyrans

S-Oxidation of thiane systems may be achieved with many reagents, but if the required product is the sulfoxide, problems may be encountered with over-oxidation to the sulfone and with the control of the stereochemistry of the product. Stereospecific oxidation of simple thianes is, as yet, not possible, but two approaches have shown promise for oxidation of the benzo-fused system: a titanium complex catalyzed reaction with *t*-butyl hydroperoxide gave a 15% *ee* of product ("L" stereochemistry complex affording "S" configuration sulfoxide), while an enzymatically mediated oxidation gave 77% *ee* product of "R" stereochemistry (Equation (12)) ⟨87JCS(P1)71, 90JCS(P1)1435⟩.

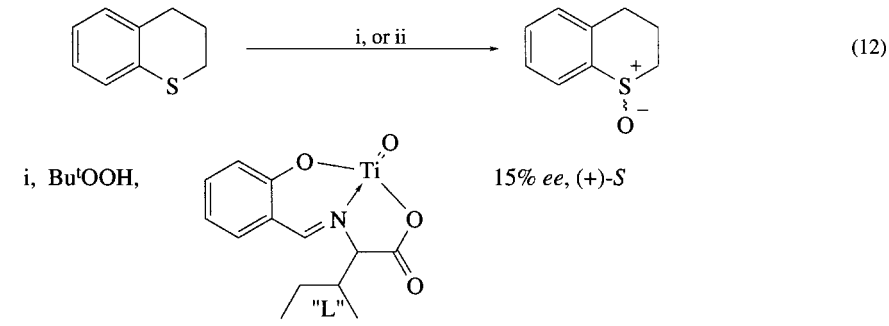




Scheme 11

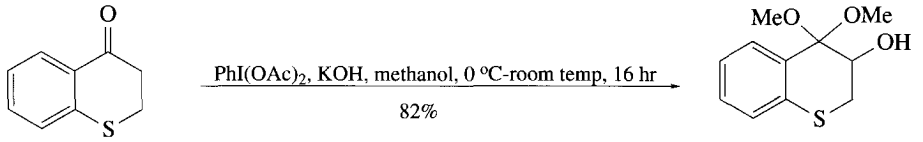


Scheme 12



(12)

Surprisingly, it is possible to hydroxylate C-3 of a thiochromanone *without* concomitant oxidation of the sulfur. The success of this application of the Moriarty reaction presumably is dependent upon the reactivity of the sulfur being sufficiently depressed by the adjacent electron-withdrawing acylbenzene moiety. If the substrate had been a 2-benzothiopyran derivative it might be expected that the product would have been a sulfoxide (Equation (13)) ⟨91TL711⟩.



(13)

Oxidative conversion of thiochromanones to the fully conjugated thiochromones would be expected to be a facile process, and catalytic dehydrogenation, or dehydrochlorination of Pummerer reaction-derived 2-chloro systems are commonly encountered methods. More unusual is the formation of a 3-formylthiochromone in the Vilsmeier formylation of a thiochromanone ⟨91T1303⟩.

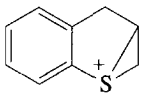
Functionalization of the position α to the sulfur may be achieved via sulfonium intermediates derived either from a thioacetal precursor, or a Pummerer reaction of a sulfoxide. Trapping of such species by nucleophiles gives rise to a variety of products. Scheme 13 illustrates the versatility of these reactions ⟨88CPB3453, 90CPB8⟩.

Cleavage of the heterocyclic ring of dihydro-1-benzothiopyrans can be brought about in a number of ways. Thermolytic fragmentation is a source of 6-methylene-2,4-cyclohexadiene-1-thione (**82**), which may be trapped by a number of added species, or may undergo a [4 + 4] dimerization (Scheme 14) ⟨91TL2013⟩.

Alternatively, treatment with strong base at elevated temperatures affords *o*-(prop-1-enyl)-thiophenylthiolate, which may be trapped as a thioether by electrophiles such as alkyl halides. Analogous cleavages of dihydro-2-benzothiopyran are not observed. Here the C—S bonds are usually broken following alkylation of the sulfur by reaction with nucleophiles, either in a direct displacement or in an electron transfer process ⟨90JCS(P1)3017⟩.

Thiochromanones (2,3-dihydro-4*H*-1-benzothiopyran-4-ones) readily undergo ring expansion to benzthiazepinones, either directly in a Schmidt reaction with azide, or in a two-step sequence via oximation and Beckmann rearrangement ⟨83IJC(B)300, 92IJC(B)803⟩. Two products are possible from these conversions, depending on the bond that migrates, and both are observed in the thiochromanone case, but interestingly Schmidt reaction of 1-thioflavanone *S*,*S*-dioxide (2-phenylthiochromanone *S*,*S*-dioxide) only gives the product from migration of the fused aryl moiety ⟨81ACH361⟩. The same migration is observed as a minor side reaction in the reduction of thiochromanone oxime with lithium aluminium hydride ⟨90MI 510-02⟩.

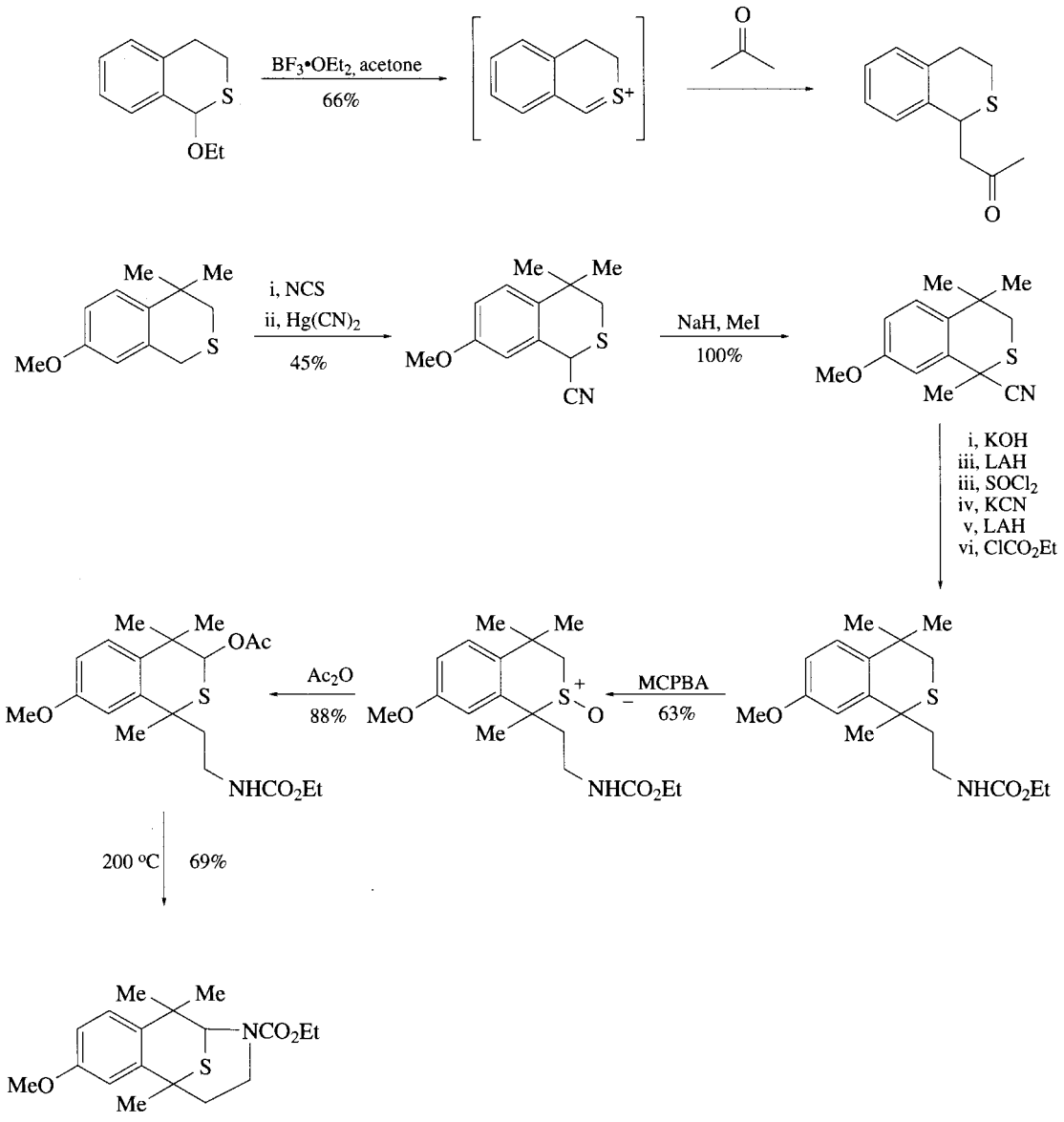
Ring contraction of 1-benzothiopyrans is frequently encountered when the constitution of the starting material (or intermediates) permits the formation of thiiranium species, for example, (**83**) ⟨82JCS(P1)395⟩, which on nucleophilic ring opening can lead to dihydrobenzothiophene derivatives ⟨88T2397, 90JCS(P1)3187⟩.



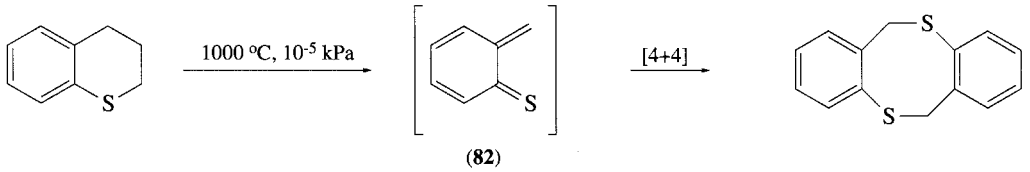
(**83**)

5.10.4.4 Thiopyrans

Unsubstituted 2*H*- and 4*H*-thiopyrans behave mainly as cyclic dienes. The 4*H*- species tautomerizes to the conjugated 2*H*- system under a variety of conditions. Kinetic studies on the interconversion catalyzed by thiopyrylium salts have reported the equilibrium constants for this hydride transfer process for a number of derivatives, as shown in Table 16. 2,6-Bis-aryl substituents facilitated the equilibration, while variation at the 4-position suggested steric effects to be the dominant influence there, affecting the approach of the thiopyrylium catalyst to the thiopyran in the rate determining step. Similar effects are observed in the interconversion of 4-methoxy-4*H*-thiopyran and 2-methoxy-2*H*-thiopyran. Extraction of the thermodynamic parameters from these



Scheme 13



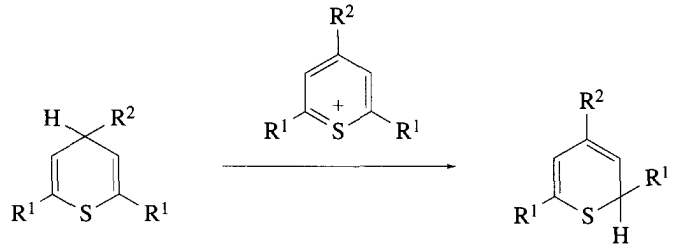
(**82**)

Scheme 14

experiments suggests that the 2*H*- system is only some 1 kcal mol^{-1} more stable than the 4*H*-analogue, rising to ca. 2 kcal mol^{-1} in the case of the 4-phenyl derivative ⟨91JOC1674⟩.

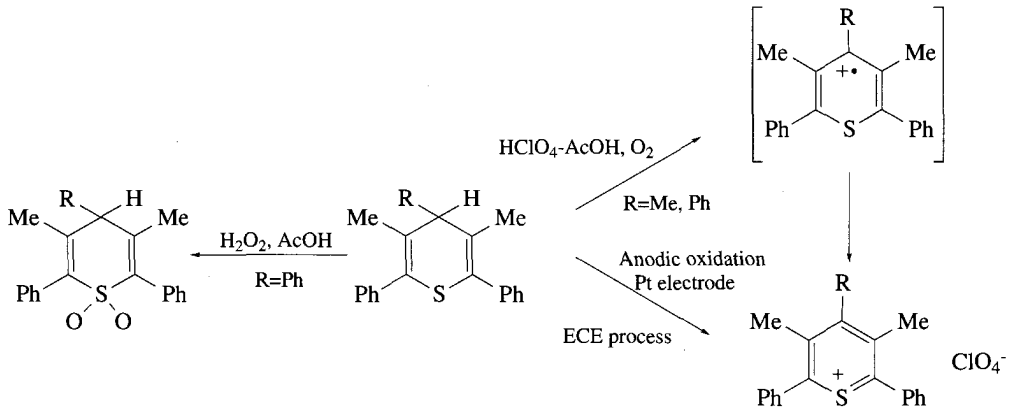
Treatment of thiopyrans with TFA results in disproportionation into thiopyrylium species and thianes, while reaction with triethylsilane in the presence of TFA efficiently reduces them to thianes ⟨91KGS181⟩. Oxidizing reagents give rise to a range of products, depending on their nature: oxygen transfer agents tend to react at the sulfur ⟨85KGS1042⟩, while electron transfer agents react at the

Table 16 Equilibrium constants for the 4*H*-thiopyran : 2*H*-thiopyran interconversion.

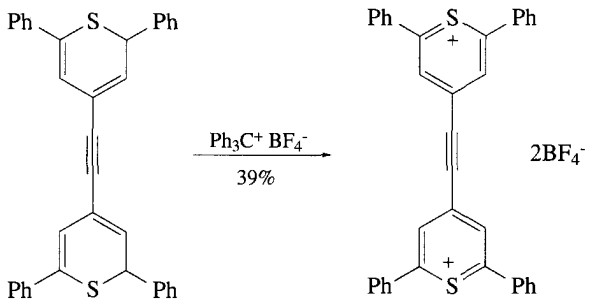


R^1	R^2	K_H
Ph	H	0.16
Ph	Ph	7.1
Bu^t	H	1.8
Bu^t	Ph	36

ring carbons (oxygen, ⟨83KGS1689⟩, anodic oxidation, ⟨84KGS318⟩, hydride abstraction, ⟨81CC1143⟩). Scheme 15 and Equation (14) illustrate the differences.

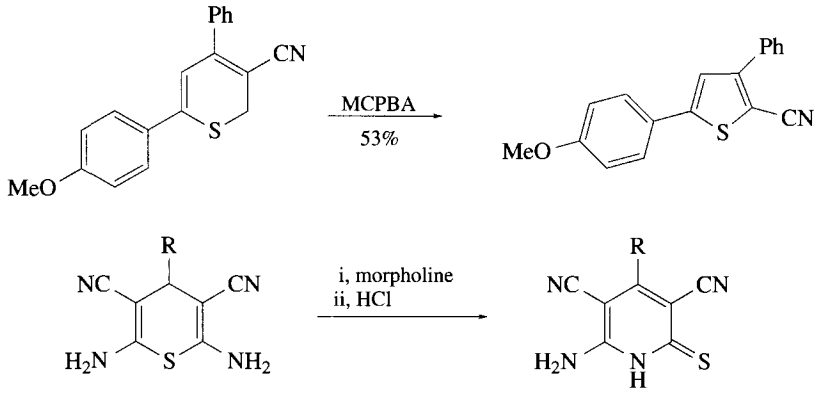


Scheme 15

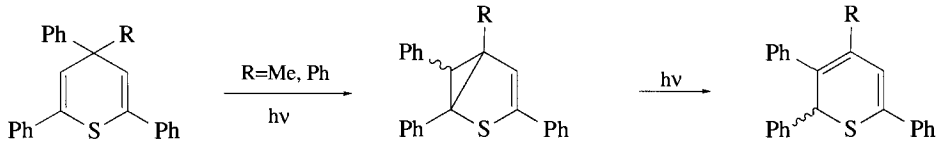


(14)

Sulfoxidation of 2*H*-thiins may be complicated by Pummerer rearrangements. In extreme cases further ring transformations may be observed (Equation (15)), ⟨84CL1973, 89KGS767⟩, as the intermediate thioacetal or related derivatives opens and recloses. Dimroth-type rearrangement is seen in the facile conversion of a 2-amino-4*H*-thiin to the isomeric pyridinethione (Equation (16), ⟨89ZOR1323⟩), and 2-azidothiins thermally rearrange to transient thiazepine intermediates which extrude sulfur to afford pyridines ⟨84T3559⟩.

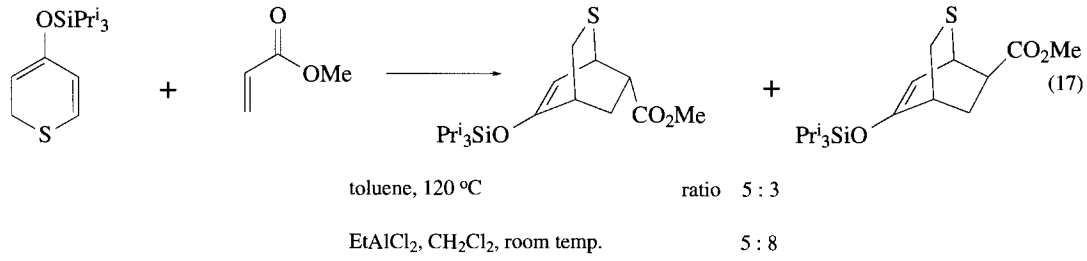


Photochemical transformations of 2*H*-thiins are not well known, but the 4*H*-systems undergo an interesting aryl migration with formation of a bicycle, analogous to that seen in 4*H*-pyrans and dihydropyridines. Further irradiation affords a monocyclic product (Scheme 16), ⟨91JCS(P2)2061⟩.



Scheme 16

The 2*H*-thiin system, as noted above, behaves in much of its chemistry as a conjugated diene, held in an 'all-*cis*' conformation. Diels–Alder reaction of such thiins followed by desulfurization has been extensively studied. The initial [4 + 2] addition is slow, and reactive dienophiles, or catalysis by Lewis acids is necessary to achieve synthetically useful yields. Uncatalyzed additions afford predominantly *endo* adducts, while the stereochemistry of the catalyzed process is dictated by the substitution pattern of the thiopyran: a group at C-4 favors *exo* products, while 5-substitution favors *endo*, as may be predicted from steric considerations. Equation (17) illustrates the outcome of the same cycloaddition with and without catalysis. The ease of the uncatalyzed addition is also controlled by the thiin substitution pattern: 4,6-disubstitution ≫ 5-substitution, 3,5-disubstitution ≫ 3-substitution ⟨90TL845, 91CJC1487, 92CJC2627⟩.



4*H*-Thiopyrans show interesting photochromic behavior that has been fully elucidated, with the isolation and full characterization of the various photoproducts ⟨92JCS(P2)1301⟩.

The fully unsaturated systems, as in 4-thiopyranones, behave as somewhat deactivated enones, and their chemistry may be broadly predicted from that of acyclic vinyl ketones. For example, efficient conjugate addition of organocopper species needs the assistance of further electron-withdrawing groups such as CO_2R in the heterocycle ⟨89T455⟩. Similarly, amino substitution, (enaminoketones) or hydroxy substitution (enolized β-diketones) facilitates a wide range of reactions with common electrophiles (see, for example ⟨83G17, 85S531⟩).

Alkylation of the sulfur of thiopyrans forms thiopyranium salts which may be deprotonated at a ring carbon adjacent to the heteroatom forming a neutral (formally fully unsaturated) system. Such compounds have frequently been referred to as thiabenzenes, but, unlike benzene, are not planar structures sustaining a ring current. Rather they are ylides, containing a planar five-carbon skeleton carrying 6π electrons with the positively charged sulfur atom significantly above that plane. Isolation is only possible if the thiabenzene is appropriately substituted with electron-withdrawing groups,

and there is little reported chemistry of the ring system. Protonation regenerates the thiopyranium salt, while the electron deficient acetylene DMAD undergoes cycloaddition reactions ⟨87YGK232⟩.

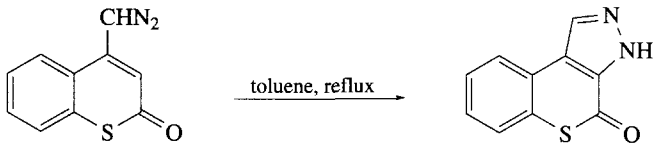
Another group of cyclic sulfur ylides contain sulfur in higher oxidation states than in 'thiabenzenes'. Again the free ring system is relatively unknown; better investigated are the transition metal carbonyl complexes. The metals most commonly bound to the heterocycle are chromium, tungsten, and molybdenum, which exert significant influence upon the reactivity of the ring and its substituents. The chemistry of this group of complexes has been reviewed ⟨83AG(E)516⟩, and Scheme 17 shows some typical facets of the chemistry of the ring. Not only is the heterocycle susceptible to reaction, but the metal may also interact with a variety of reagents without effect upon the ring. A particularly unusual observation is the product of the attempted alkylation of the sulfoxide complex (**84**); rather than the expected methoxysulfonium species, a Pummerer rearrangement product (**85**) was isolated ⟨83CB514⟩.

5.10.4.5 Benzothiopyrans

1-Benzothiopyrans (thiochromenes) are relatively infrequently reported species, whose chemistry is largely akin to that of the nearest acyclic analogue, for example, *o*-methylthiostyrene or phenylthioethylene. In the absence of stable blocking substituents thiochromenes are readily oxidized to the much more commonly encountered thiochromones or thiocoumarins. 2-Benzothiopyrans are even more infrequently reported, but they, too, behave similarly to the nearest noncyclic analogue and also readily form the isothiocoumarin system. The following discussion is therefore predominantly concerned with the unsaturated bicyclic ketonic compounds.

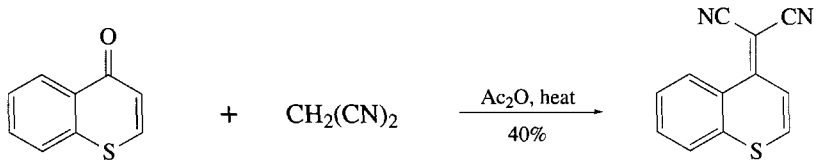
Scheme 18 collects typical reactions of thiochromones with electrophiles, and some further conversions of the products. It may be seen that the hetero ring has a generally deactivating influence upon the fused benzene, and electrophilic attack, even by a diazonium agent, is upon the "enone" part of the molecule. Conversion into the sulfone increases deactivation.

Thiocoumarins are less susceptible to electrophilic attack than thiochromones, unless substituted with hydroxy groups at position 4, when they may be viewed as acetoacetate enols, and readily condense with electrophiles at C-3. The reaction shown in Equation (18) is an example of such a process in an intramolecular sense ⟨88JHC1681⟩.



(18)

Nucleophilic attack can occur readily at both the carbonyl function or at C-2/C-4 in the thiochromones and thiocoumarins. Carbonyl attack gives rise to thiopyranylidene products (Equation (19)), while attack at C-2 of thiochromones frequently precedes cleavage of the S—C(2) bond, in an addition–elimination sequence.

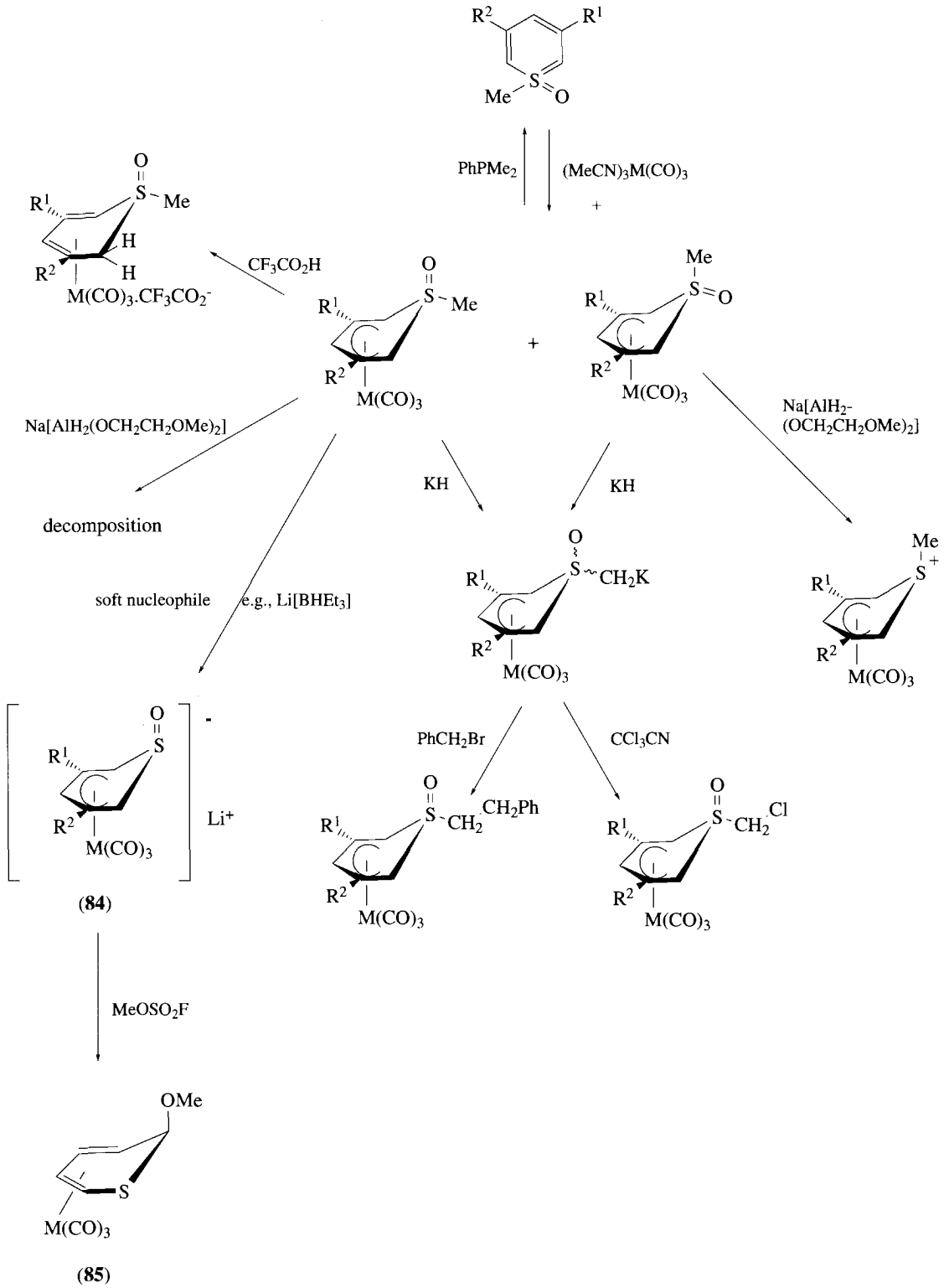


(19)

Reaction at C-2 is less facile than in the case of the corresponding chromones, but it can represent a useful means of generating 2-substituted thiochromones. A variety of heteronucleophiles and alkyl copper species may be used, and the resulting thiochromones are readily oxidized to the sulfone analogues (Scheme 19) ⟨86TL91, 88JHC1613⟩.

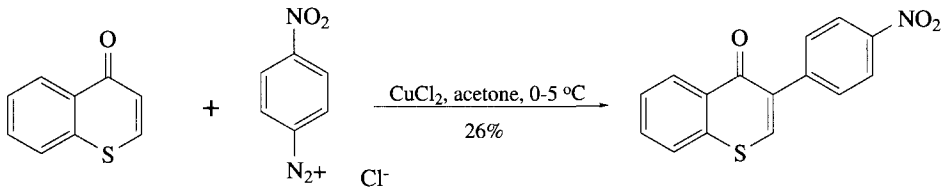
Thiochromone dioxides are particularly susceptible to nucleophilic ring opening at C-2 ⟨86JOC3282⟩. Thiocoumarins, being lactones, are readily opened by nucleophilic attack without the need for further activation at sulfur; in the presence of air the products are usually isolated as disulfides ⟨88JCR(S)49⟩. The thiochromone carbonyl group may be reduced with borohydride reagents to thiochromanols ⟨85AP(318)744⟩.

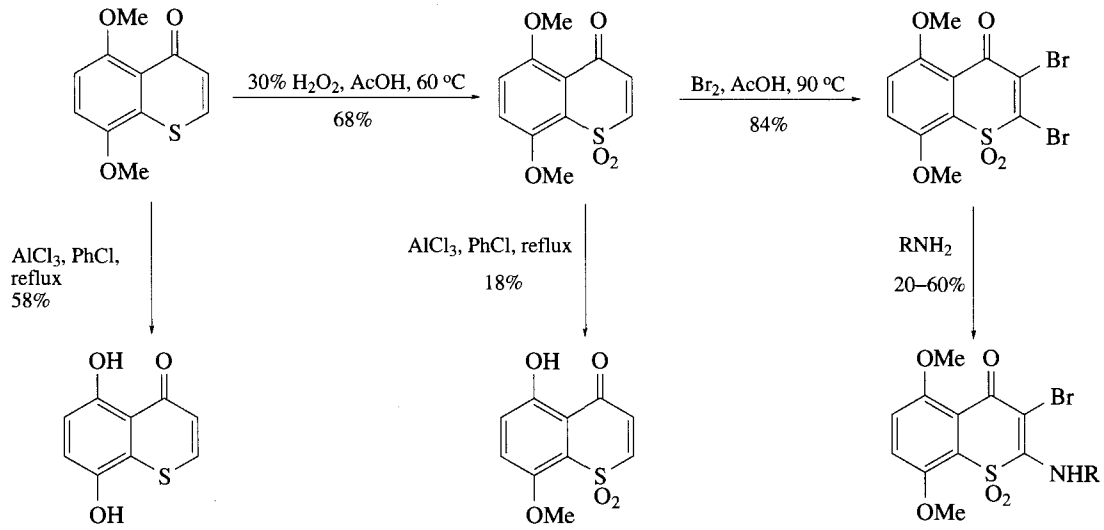
1-Benzothiopyran-3,4-diones exist as 3-hydroxythiochromones, and behave as simple enols,

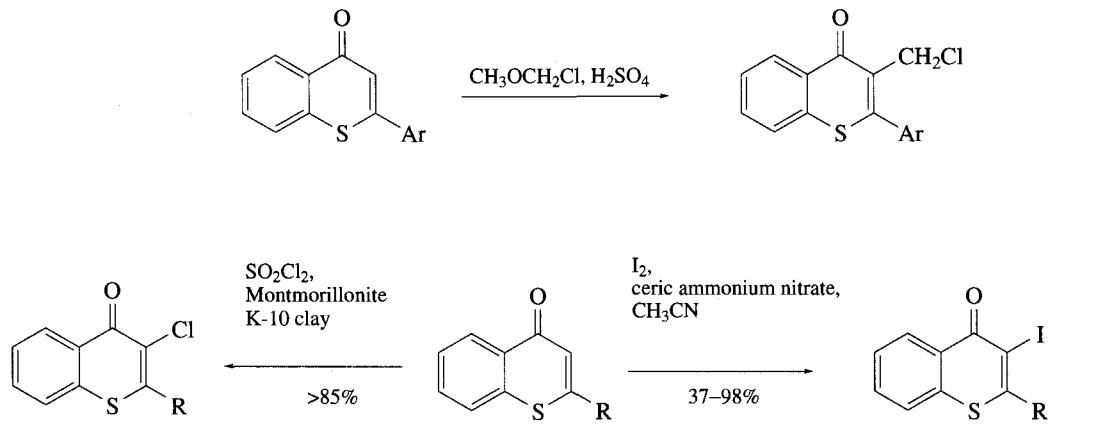


Scheme 17

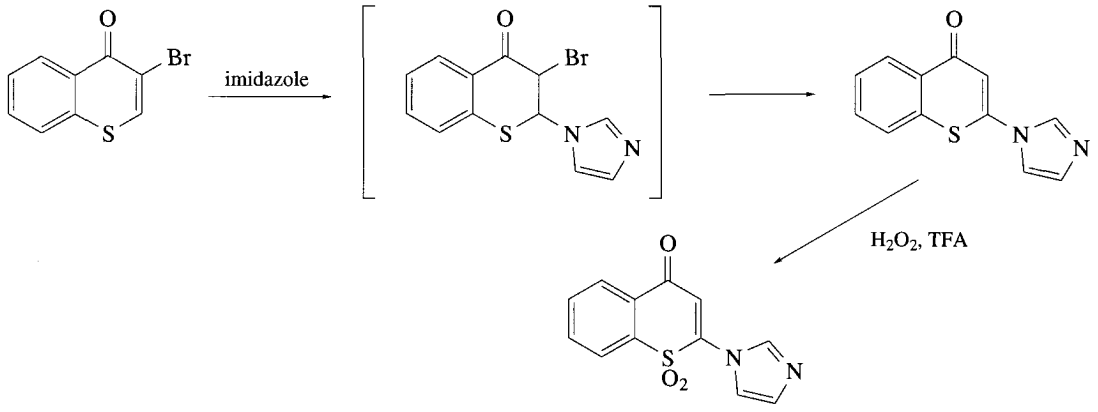
reacting with electrophiles at C-2 to afford for example the 2-aminomethyl product ⟨83AP(316)1034⟩. Similarly, 4-hydroxythiocoumarins are β-keto esters and may be C-alkylated with a range of electrophiles (e.g., ⟨81JHC1655⟩). More complex chemistry is displayed by 4-hydroxydithiocoumarins. The system may exist in two tautomeric forms, and it has been reported that both the


NO2
O
S
+
N2+
Cl-
CuCl2, acetone, 0-5 °C
26%
NO2


OMe O
S
OMe
30% H2O2, AcOH, 60 °C
68%
O2
Br2, AcOH, 90 °C
84%
Br
AlCl3, PhCl,
reflux
58%
AlCl3, PhCl, reflux
18%
RNH2
20–60%
OH
NHR


O
S
Ar
CH3OCH2Cl, H2SO4
CH2Cl
SO2Cl2,
Montmorillonite
K-10 clay
>85%
I2,
ceric ammonium nitrate,
CH3CN
37–98%
Cl
R
I

Scheme 18



Scheme 19

4-hydroxydithiocoumarin and the 2-thiolthiochromone form have been isolated and characterized by IR, UV, and NMR spectroscopy. Kinetic protonation of the monoanion of the system affords the coumarin, while treatment with strong acid tautomerizes it to the thiochromone form. In the solid state, and in aprotic solvents the tautomers are stable. Alkylation of either species takes place only at the exocyclic sulfur, but acylation gives mixtures of *O*- and *S*-acyl products. Oxidation of 2-alkylthiochromones takes place solely at the exocyclic sulfur. Unlike 4-hydroxycoumarins where *O*-acyl derivatives readily undergo 1,3-acyl migration to afford 3-acyl-4-hydroxycoumarins, the dithiocoumarins do not, even though electrophilic addition to C-3 is observed under other conditions. These various aspects are summarized in Scheme 20 ⟨87AJC1179⟩.

While the Fries rearrangement of *O*-acyl species (Scheme 20) does not proceed to any extent, the thia-Cope rearrangement of 2-propargylthio-thiochromones is a very efficient entry into the tricyclic thiopyranothiochromones (Scheme 21) ⟨92SC901⟩.

The utility of addition–elimination sequences to functionalize the 2-position of thiochromones has been described previously. A competing process is the cleavage of the ring by opening of the C—S bond. In the presence of appropriate substituents ring closure may lead to a benzothiophene and similar processes are seen with thiocoumarins. Two representative examples are shown in Schemes 22 and 23 ⟨85JHC89, 90CL679⟩.

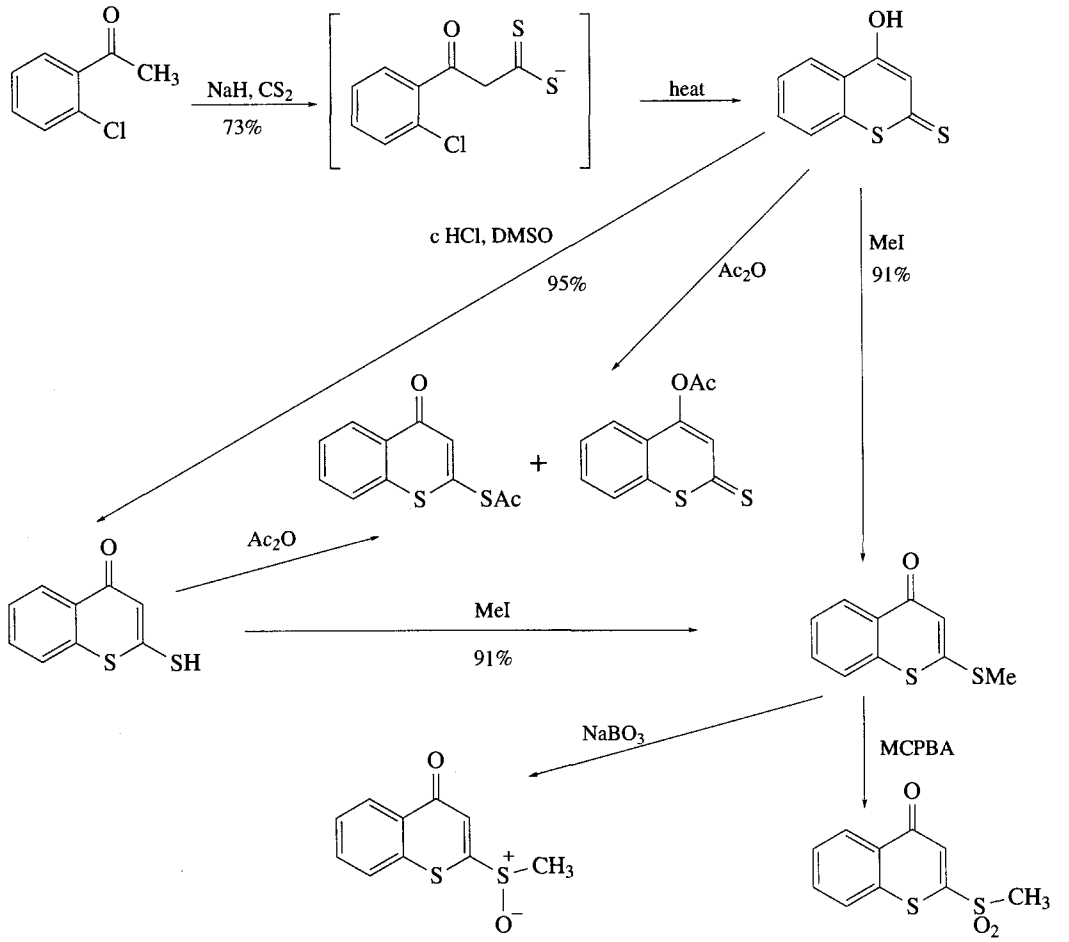
The photochemistry of the benzothiopyrans has received extensive attention since the mid 1970s. On irradiation thiocoumarin forms a single head-to-head [2 + 2] dimer in high yield from the T_1 state. In the presence of alkenes the reaction gives rise to the expected cyclobutane derivatives, but unusually as a mixture of *cis* and *trans* adducts. As has been observed with coumarins, addition to terminal alkenes produces the adduct with the unsubstituted carbon attached to C-3 of the heterocycle, but the sulfur system undergoes photocycloaddition significantly more readily than the oxygen analogue (Scheme 24) ⟨91MI 510-03⟩.

A synthetically useful application may be found in the photoaddition of isobutene to 4-methoxythiocoumarin which gives an adduct that, on treatment with boron trifluoride etherate, eliminates methanol, forming a cyclobutene. On thermolysis, the four-membered ring opens and a 3,4-dialkylated thiocoumarin is produced. Other alkenes may be used, though if the alkene is acrylonitrile, elimination of methanol requires *t*-butoxide. Side products from the sequence include small quantities of benzothiophenes, arising from electrocyclic opening of the thiocoumarin and its subsequent reclosure ⟨83JHC1275⟩.

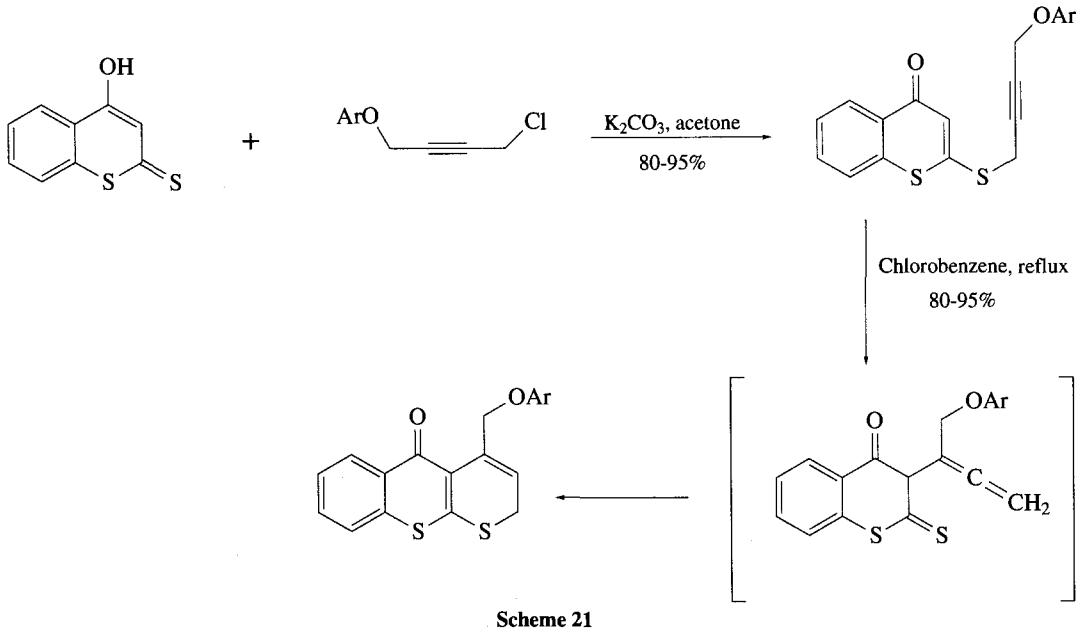
The photochemistry of thiochromones is very similar to that of the thiocoumarins, and is fully discussed in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨CHEC-I(3)918⟩. [2 + 2]-Photodimerization and intermolecular additions are facile, though the dimerization process is less specific. The three dimers are all head-to-head, but vary in the stereochemistry around the cyclobutane ring, as elucidated by x-ray crystallographic studies ⟨86AX(C)816⟩.

5.10.4.6 Thioxanthenes

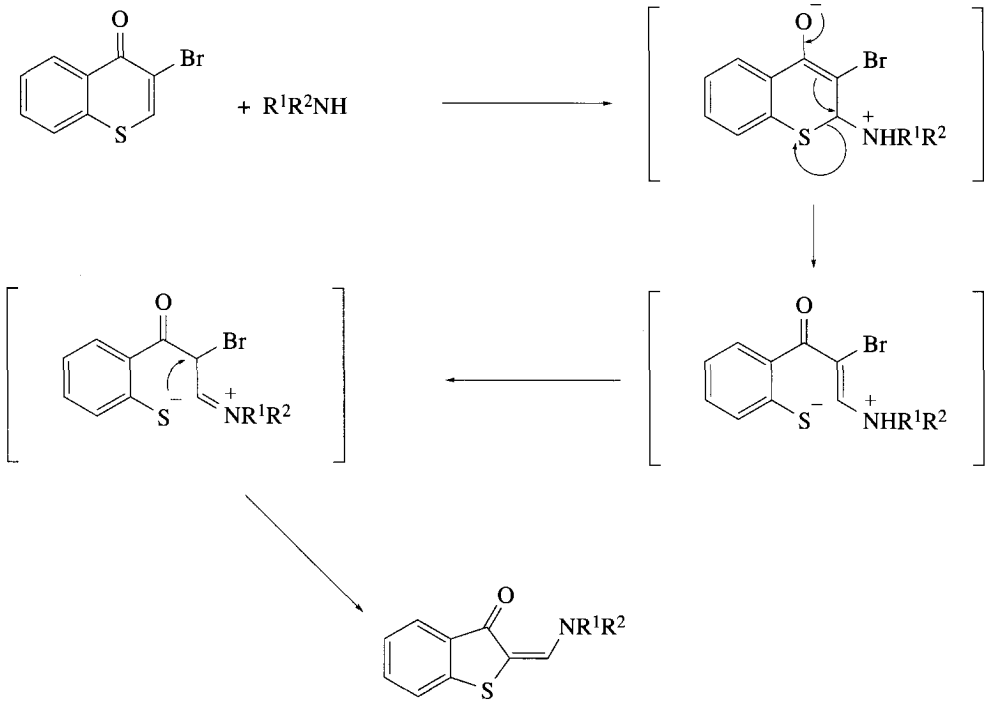
Thioxanthene behaves in its chemistry at the sp^3 center as a diarylmethane, and at the sulfur as diaryl sulfide. In fact there is a greater resemblance to the reactivity of thianes than of benzo-



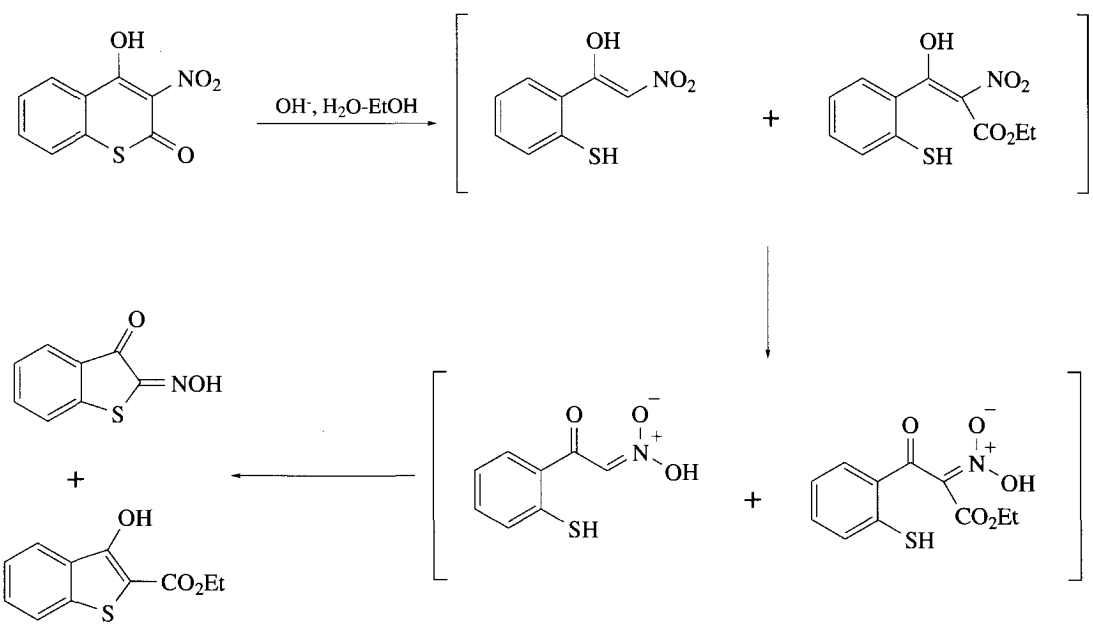
Scheme 20



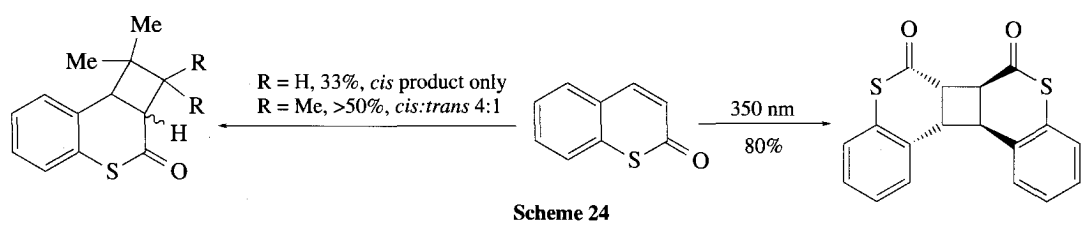
Scheme 21



Scheme 22



Scheme 23

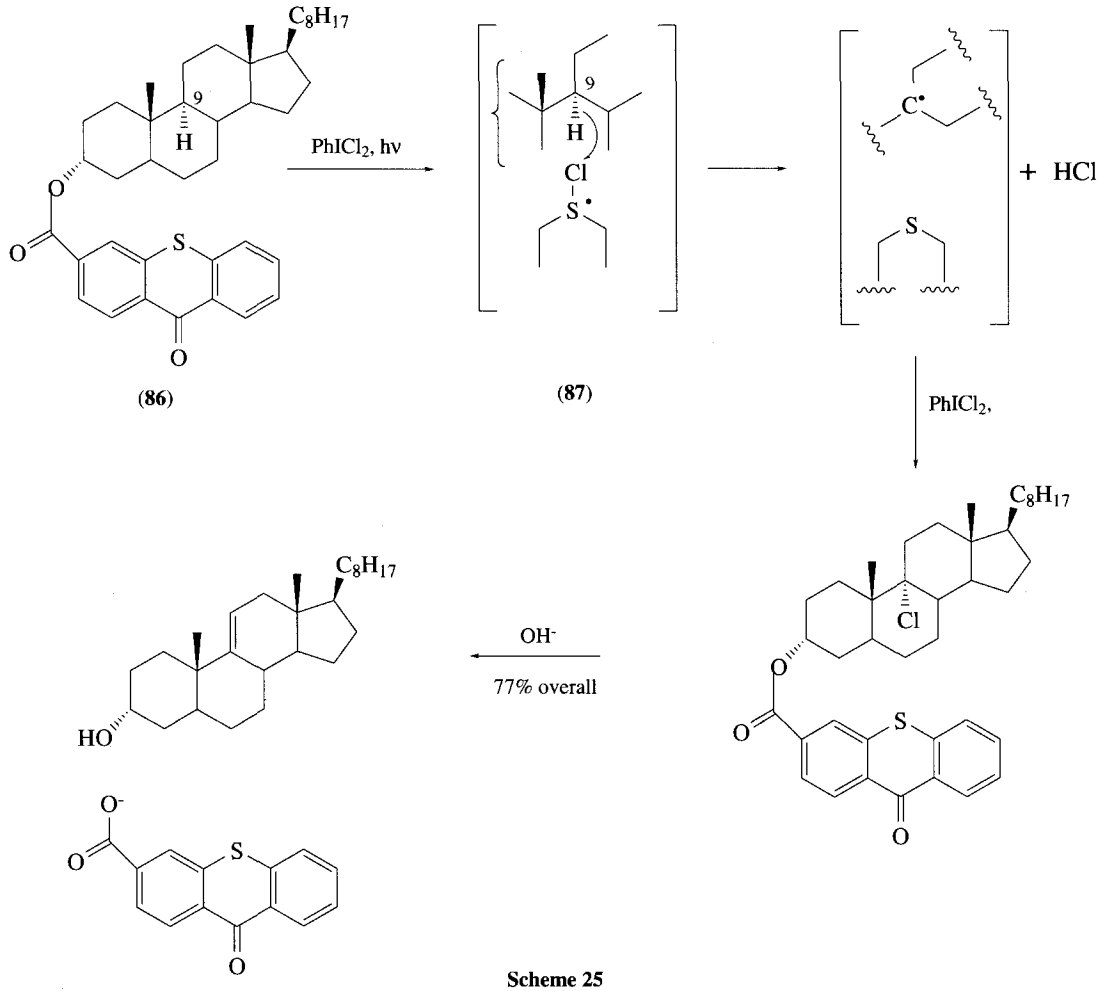


Scheme 24

thiopyrans. The sulfur forms ylides or sulfonium salts with alkylating agents or iminating species like chloramine-T, while the methylene group is readily deprotonated to form a very stable, though formally $4n$-π system, carbanion. This anomalous stability is further evidence for the non-participation of the sulfur lone pairs in any significant delocalization, a theme recurring frequently in the chemistry of the thiopyrans.

Hydride abstraction or electrochemical oxidation affords the thioxanthylium cation, which forms stable salts with nonnucleophilic counterions ⟨86JEC45⟩. The overriding feature of the chemistry of thioxanthene is the ease of oxidation of the methylene group, either to a carbonyl function, or other sp^2 form. The ready generation of thioxanthone (even through permanganate cleavage of a C=C bond ⟨86MI 510-06⟩) has made it readily available, and therefore a convenient nucleus with which to work. The published chemistry is extensive, and may be rationalized in the main by considering each portion of the molecule independently. The carbonyl group undergoes conventional nucleophilic chemistry: reduction, Grignard addition, Wittig reaction, etc. ⟨78BCJ2674, 79JHC679⟩; and the sulfur may be easily oxidized chemically to the sulfoxide or sulfone ⟨83MI 510-03, 89T3299⟩. Electrochemical oxidation affords the sulfoxide in a single irreversible 2 electron process with $E_{1/2} = +1.34$ V vs. SCE, somewhat higher than for thioxanthene (1.0 V vs. SCE) ⟨86JEC(210)45⟩. Reduction of the carbonyl electrochemically is a reversible process under anhydrous conditions, $E_{1/2} = 2$ V vs. Ag/Ag^+, becoming irreversible in the presence of water.

A rather unusual reaction in which the thioxanthone nucleus is used as a relay chlorinating agent for the site selective functionalization of a sterol is shown in Scheme 25 ⟨87TL3187⟩. Treatment of the thioxanthone ester (**86**) with $PhICl_2$ affords an intermediate (**87**), which is suitably disposed to abstract a hydrogen atom from C-9, leaving a carbon-centered radical, which is trapped by a second mole of the chlorinating agent. Base treatment to cleave the ester also eliminates HCl, affording in a regioselective manner the steroidal 9,11-alkene.



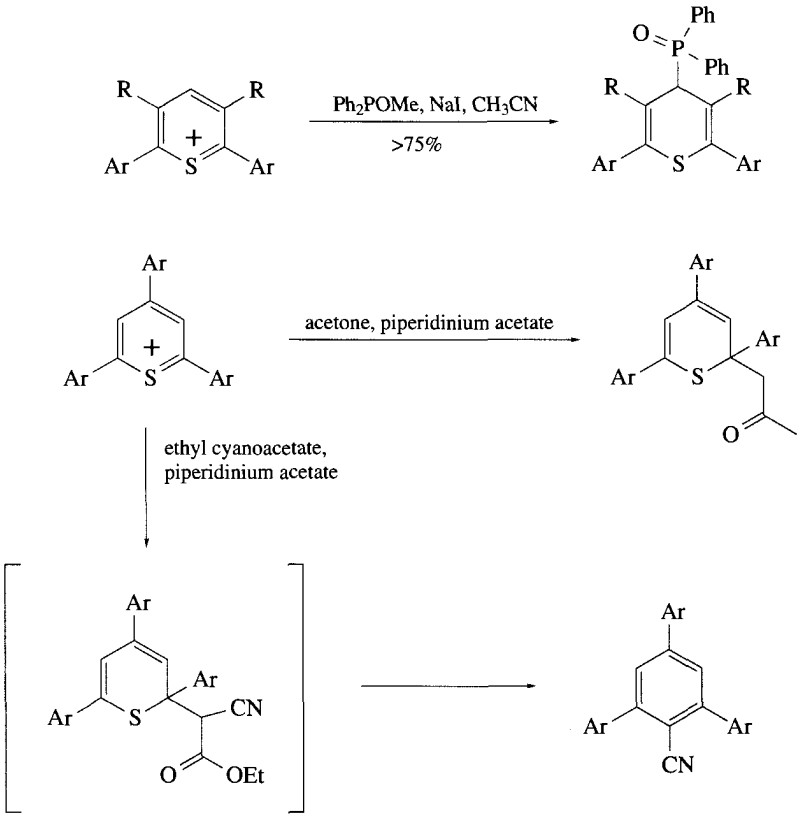
Scheme 25

5.10.4.7 Thiopyrylium Salts

The chemistry of the strongly electron deficient thiopyrylium system is dominated by the facile addition of nucleophiles to the ring. Addition occurs at both the 2- and 4-positions, but the initial kinetically controlled product mixture may equilibrate, particularly in the case of amines as nucleophiles, to the more stable 2-substituted system. While the bulk of the substituents at C-2 and C-4 has little influence on the addition of amine, increasing steric bulk of the amine (changing from primary to secondary amine) changes the rate determining step from the initial attack to the deprotonation of the first-formed adduct ⟨84JA7082, 89G205⟩. Analogous studies of the kinetics of addition of alkoxides have shown formation of a similar kinetically controlled mixture of 2- and 4-substituted products, which is transformed into the 2-substituted product on equilibration ⟨86JA3409, 86JCS(P2)271, 89JCS(P2)1393⟩. Interestingly, increasing the steric bulk of the incoming alkoxide also has profound effects on the reaction: the reactions of 2,4,6-triphenylthiopyrylium salts with isopropoxide or *t*-butoxide proceed via electron transfer processes, rather than by direct addition as seen with ethoxide ⟨86ZC400⟩.

Other nucleophiles also add at C-2 and C-4, but the ring substituents exert more steric influence on the course of the reaction than in the case of the nitrogen and oxygen reagents. Schemes 26 and 27 illustrate the range of such additions and some of the further transformations that are possible ⟨82TL3195, 83ZC333, 85CL1119, 86AG(E)635, 86JPR573, 88JPR35, 90ZOB1012⟩.

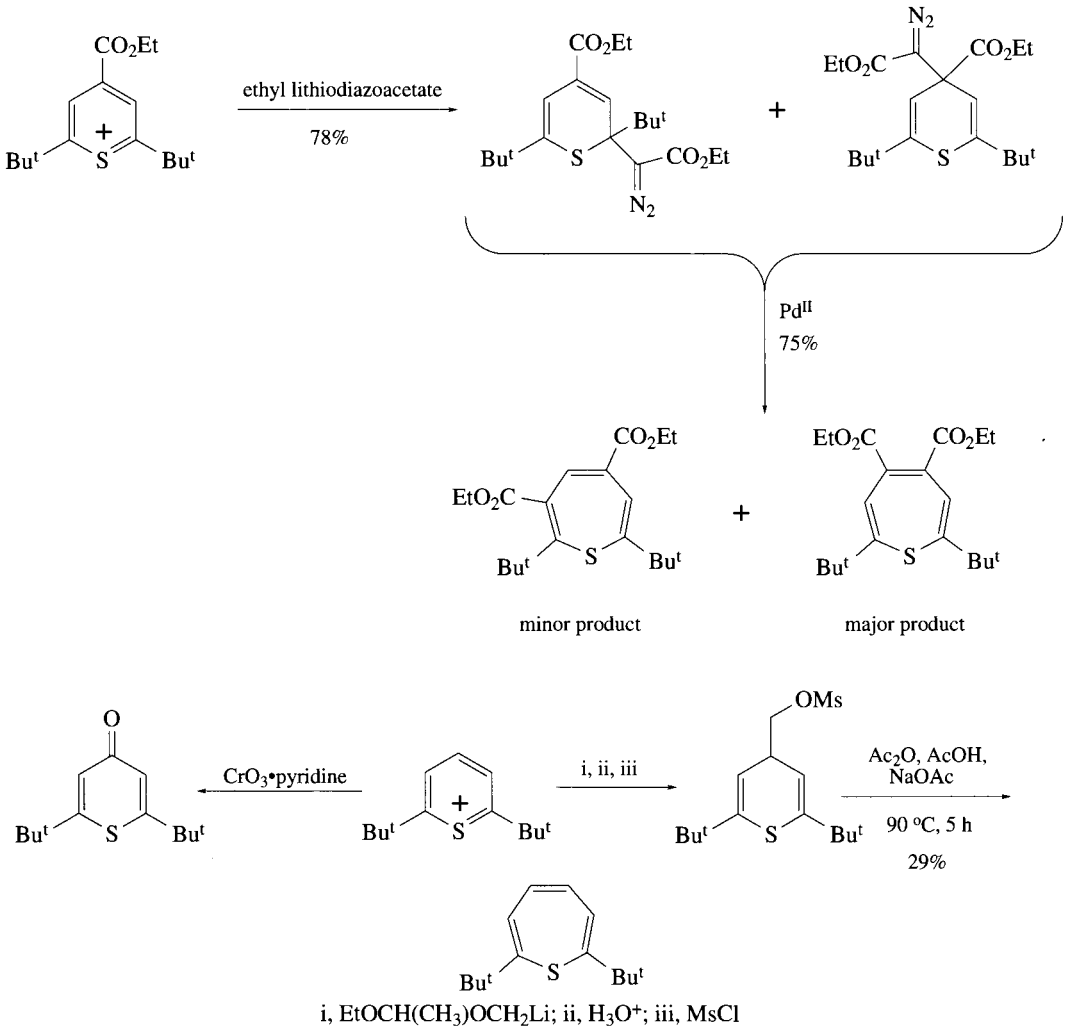
Catalytic reduction of thiopyrylium salts requires forcing conditions: $Pd/C/H_2$ at 50–100 bar saturates the system, forming thianes ⟨87KGS614⟩.



Scheme 26

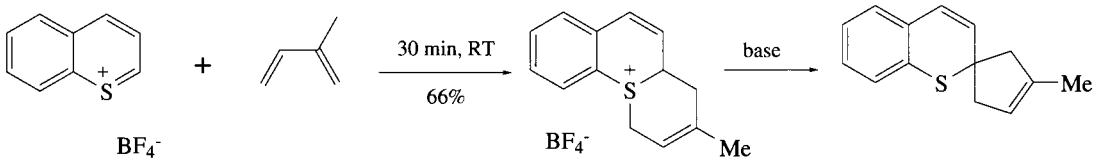
5.10.4.8 Benzothiopyrylium Salts

As expected, benzothiopyrylium salts are readily susceptible to nucleophilic addition reactions. They can also act as electron deficient dienes or dienophiles in cycloaddition reactions. As well as



Scheme 27

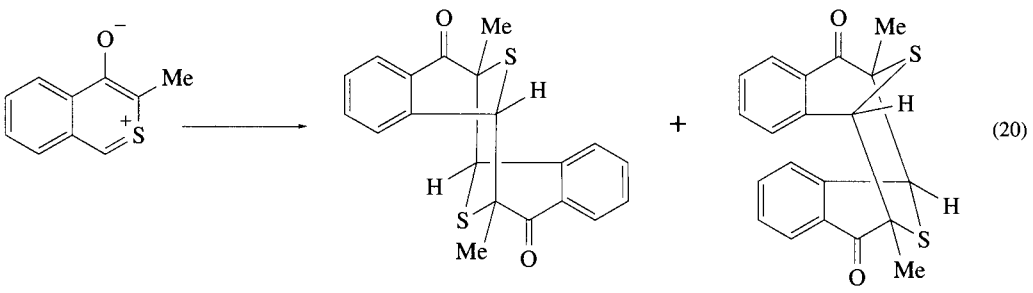
the carbon framework, the —C=S$^+$— moiety of 1- and 2-benzothiopyrylium systems may take part in such reactions, leading to bridgehead sulfonium salts (Scheme 28).



Scheme 28

Cycloaddition to the sulfonium linkage is generally regiospecific as shown in Scheme 28, and facilitated by further electron withdrawing substituents upon the heterocycle (e.g., a cyano group at C-4). Deprotonation of the cycloadducts leads to their rearrangement into 2,2-spiro-fused benzothiopyrans via [1,2] alkyl migration ⟨91TL5571, 92CC1586⟩.

The mesomeric betaine 2-benzothiopyrylium-4-olate is unstable, and rapidly self-condenses to give head-to-head and head-to-tail dimers (Equation (20)) ⟨84ACS(B)617⟩.



(20)

5.10.4.9 Thioxanthylium Salts

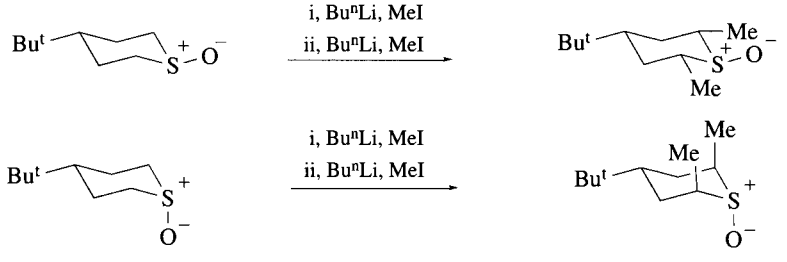
Thioxanthylium salts readily react at C-9 with nucleophiles such as amines, phenylthiolates and hydride ⟨86ZOR842, 88JCS(P1)2271⟩. Reaction with aryllithiums, however, is more complex: the addition of phenyllithium to 9-phenylthioxanthylium perchlorate gives eight products. As well as 9,9-diphenylthioxanthene, products of addition to the fused benzene rings and others such as a 9,9′-dimer (presumably derived from electron transfer processes) have been isolated ⟨87JCS(P1)187⟩.

5.10.5 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS: ARRANGED BY RING SYSTEM

5.10.5.1 Thianes

The tetrahydrothiin ring system is analogous to cyclohexane, and the chemistry of ring substituents at carbon may generally be inferred by reference to their alicyclic equivalents. Differences arise through the inductive effect of the sulfur (and its functional derivatives), and also as a consequence of transannular interactions available to the heteroatom. The inductive effect manifests itself most obviously in the ready formation of carbanions α to the sulfur, and even more easily when it is in the sulfoxide, sulfone, or sulfonium state. Transannular effects are revealed in instances of anomalous stereochemical outcomes of reactions.

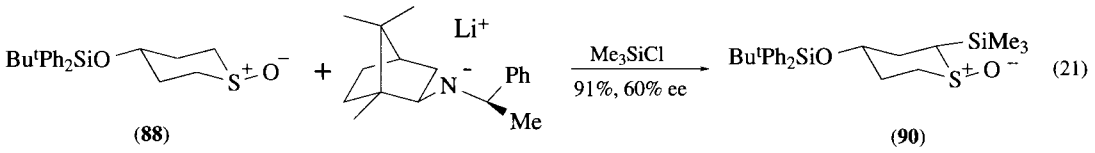
The stereochemistry of carbanion formation has been thoroughly investigated in both the sulfoxides and thianium salts. Deprotonation α to a sulfoxide generates an essentially planar carbanion which may be methylated in high yield, the methyl entering from the direction of least steric hindrance by the oxygen atom. Thus a conformationally rigid axial sulfoxide is methylated axially, and an equatorial sulfoxide is methylated equatorially. A second deprotonation/methylation sequence affords symmetrically dialkylated products (Scheme 29) ⟨84CHEC-I(3)897⟩. It can be demonstrated that under kinetic conditions the proton removed is usually axial in an equatorial sulfoxide, and equatorial in an axial sulfoxide. As may be expected, selectivity is greater in more rigid systems.



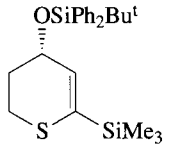
Scheme 29

A wide range of electrophiles may be used to trap α-sulfinyl carbanions, leading to a variety of interesting structures, (e.g., ⟨92JMC3613⟩). As well as the axial/equatorial control exerted by the sulfoxide configuration in functionalization reactions described above, the use of homochiral lithium amide bases also permits control of the absolute stereochemistry of the initial deprotonation. Equation (21) illustrates the high yielding (91%), enantioselective (60% *ee*) trimethylsilylation of a typical configurationally fixed thianeoxide (**88**). Interestingly the use of an "internal quench"—adding TMS-Cl *before* the homochiral amide base—leads to the formation of the unsaturated silane

(**89**) with 35% *ee*. This product arises from a Pummerer rearrangement of the first formed silane (**90**), and an *in situ* kinetic resolution ⟨92SL194⟩).

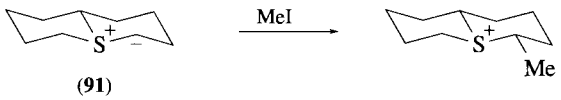


(**88**) (**90**) (21)



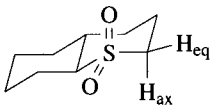
(**89**)

Analogous studies of thianium salts reveal similar behavior, but with the added complication that the stereochemistry of a carbanionic center adjacent to a sulfonium sulfur in monocyclic species may be planar or pyramidal depending on the presence or absence of the Li^+ cation. Interaction of Li^+ with C^- favors a nonplanar (though still flattened) geometry. As in the sulfoxide case, alkylation of a monocyclic ylide goes via the least hindered trajectory of approach. In bicyclic ylides such as (**91**) it is probable that deprotonation/alkylation proceeds with retention of configuration ⟨82TL763⟩ (Equation (22)).



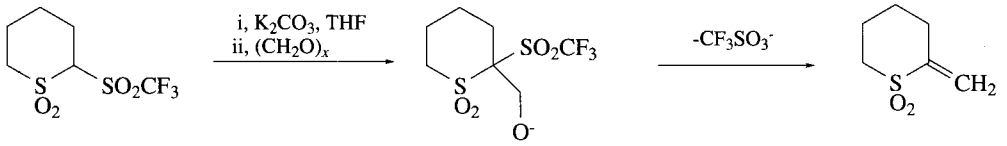
(**91**) (22)

The sulfone moiety is much less electron withdrawing than either a sulfoxide or sulfonium group. However, strong bases such as alkyllithium reagents will remove an adjacent proton. Studies in acyclic systems have shown that it is the C—H bond "bisecting" the O—S—O angle that is broken preferentially. In keeping with this observation, it is the α-equatorial hydrogens of (**92**) that exchange most rapidly in NaOD/D_2O (with a rate constant of ca. 10^{-6} M^{-1} s^{-1}), while the axial protons exchange some 100-fold slower ⟨90JA2001⟩.



(**92**)

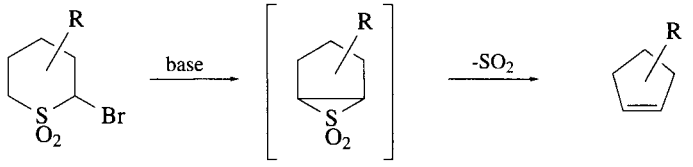
Synthetic utility of the deprotonation/alkylation sequence in thiane 1,1-dioxides has usually required the presence of an electron withdrawing substituent at the center to be functionalized, to control the regiochemistry of the reaction. In many cases this additional group may subsequently be unwanted, though Scheme 30 shows an example where it plays an important part in a further conversion. A formal [1,3] shift of the sulfonyl moiety from C to O permitted the elimination of trifluoromethanesulfonate anion, and the formation of a vinyl sulfone ⟨85TL2849⟩.



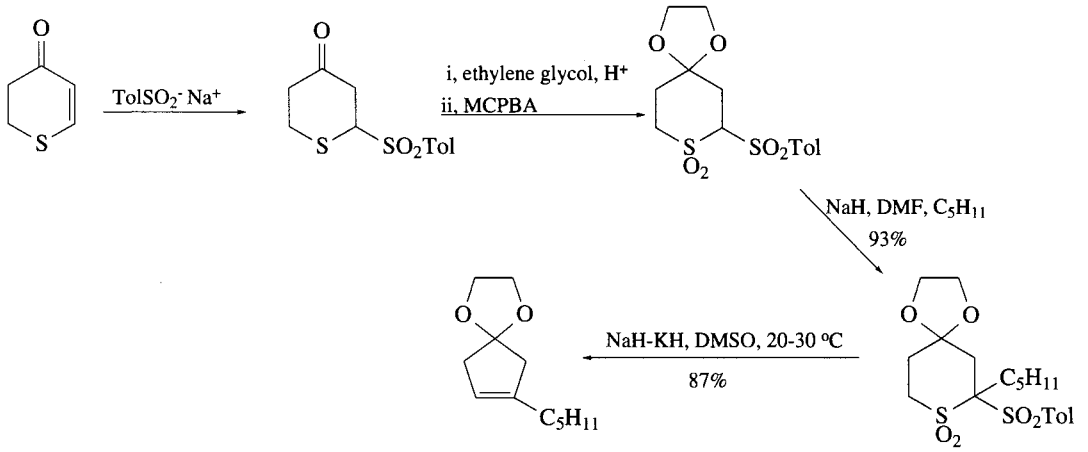
Scheme 30

If the electron withdrawing group is a good leaving group in its own right, it can divert the whole course of the reaction, and provide the key to a very significant interconversion: the Ramberg–

Bäcklund rearrangement. The archetypal example is the treatment of an α-halo sulfone with a nonnucleophilic base, which results in abstraction of an α′-proton, followed by transannular reaction of the carbanion and expulsion the halide anion. The intermediate bicycle undergoes cheletropic loss of SO_2, and a double bond is formed. When applied to the thiane dioxide system, the products are cyclopentenes (Scheme 31), and a number of investigators have made use of the conjugate addition of "activating-leaving groups" to dihydrothiopyranones, and subsequent ring contraction by the Ramberg–Bäcklund reaction, to set up appropriately substituted precursors of prostanoids and related compounds (Scheme 32) ⟨86CL433, 90DIS(B)4731⟩.

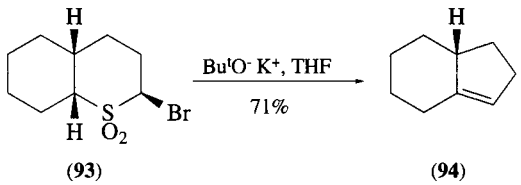


Scheme 31

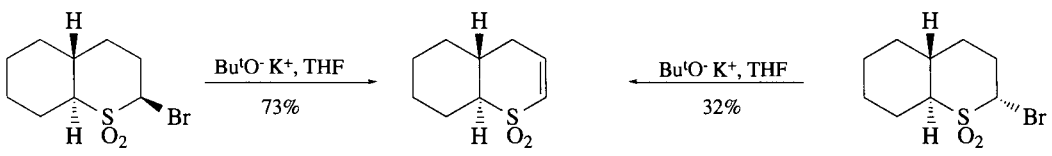


Scheme 32

When applied to bicyclic thiadecalin substrates, the Ramberg–Bäcklund reaction can give rise to bridgehead alkenes, but stereoelectronic considerations strongly influence the efficiency of such conversions. For example *cis-exo*-bromo sulfone (**93**) (with the ideal 'W' arrangement of the reacting atoms) gave 71% of the ring contracted product (**94**) (Equation (23)), while the *trans-exo*- and *trans-endo*-analogues gave negligible yields of Ramberg–Bäcklund products; elimination of HBr was the preferred pathway (Scheme 33) ⟨83HCA1090⟩.

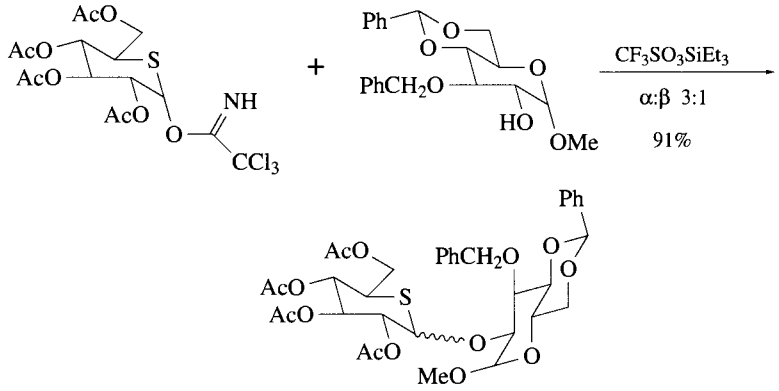


(93) (94) (23)



Scheme 33

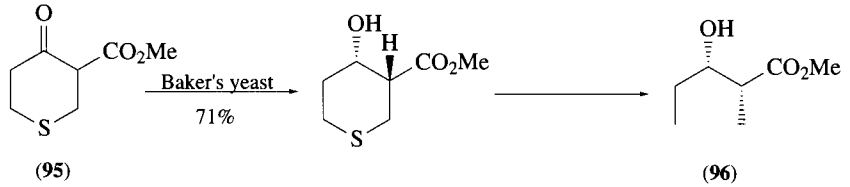
If the α-carbon bears a hydroxyl substituent, the system becomes a hemithioacetal, and a range of chemistry not seen in the carbocyclic analogues becomes possible. Stable hemithioacetals are found in thiosugars, a group of compounds which has received far less attention than the oxygen analogues, but which may offer considerable scope for manipulating the physical and biological properties of polysaccharides. A key conversion in such work is the controlled linking of monosaccharide units in a glycosylation reaction. Equation (24) shows an efficient (91% yield) stereoselective coupling of typical protected fragments to give a monothio disaccharide ⟨92TL7675⟩.



(24)

Carbonyl groups α to sulfur are part of thioester links and therefore readily attacked by nucleophiles, usually with subsequent opening of the ring. The β or γ analogues are simple ketones. Enolization of thian-3-one under both kinetic and thermodynamic conditions affords a double bond between C-2 and C-3 ⟨82SC333⟩. While thianones react qualitatively the same as in cyclohexanones, there are quantitative differences. For example, the rate of reaction of thian-3- or 4-ones with the lithium enolate of pinacolone is significantly faster (approximately one order of magnitude) than would be predicted from the rates for a range of other ketones, wherein field and inductive effects are believed to be the dominant influences. The reason for this unexpected acceleration is, as yet, unclear ⟨93JA1302⟩. Rate enhancement is also seen in the sodium borohydride reduction of 4-thianones, a phenomenon also noted in other 4-heteracyclohexanones. The rank order of rate enhancement in this group of analogues (O > N > S > Se) mirrors the ranking of electronegativities of the hetero atoms ⟨84IJC(B)623⟩. Related studies on semicarbazone formation have also been made ⟨83PS(17)331⟩.

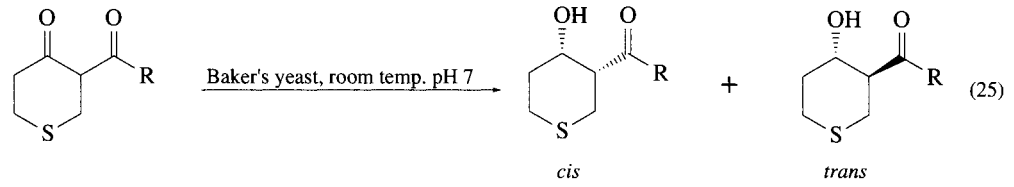
Enantioselective reduction of 4-thianones has received some attention, driven by the potential of thianes as precursors of biologically active cyclopentanes and cyclopentenes. Common baker's yeast reduced the thianonecarboxylic acid ester (**95**) in 71% yield (98% *de* and 85% *ee*), and the alcohol could be desulfurized to (**96**) (83% *ee*) (Scheme 34) ⟨84LA1170⟩. Reduction of the ester of the thianoneacetic acid analogue of (**95**) was also diastereo- and enantioselective ⟨91TL7055⟩.



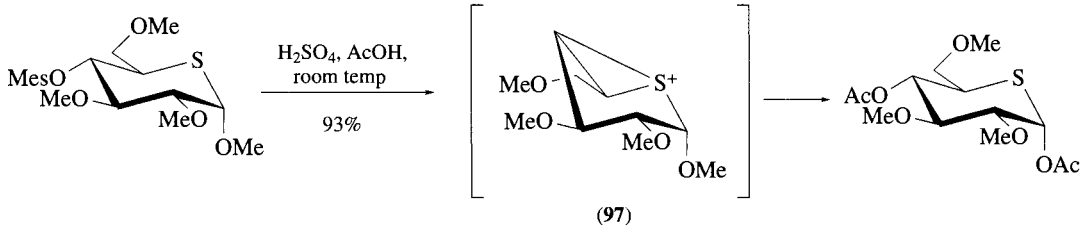
(**95**) (**96**)

Scheme 34

When applied to a mixed *endo*- + *exo*-cyclic β-diketone system, only the endocyclic carbonyl group is reduced (Equation (25)). The nature of the group R exerts a major influence on the reaction. If it is phenyl, the products are a 2 : 1 mixture of *cis* : *trans* hydroxy ketones; if R is a small alkyl moiety only the *cis* isomer is seen. The reduction is extremely efficient, and optical purities of individual products are typically 93–99%. The overwhelming formation of the *cis* products is presumed to arise from the facile interconversion of the antipodes of the diketone starting material, and the rapid enzymatic reduction of the (3*R*)-enantiomer ⟨92TL5567⟩.



The consequences of transannular effects are nicely illustrated in the solvolyses of sulfonate derivatives of thioglucose systems. Replacement of the leaving group occurs with retention of configuration via the fused episulfonium intermediate (**97**) (Scheme 35) ⟨88TL1939⟩.



Scheme 35

While the vast majority of the reported chemistry of thianes is polar, some investigation of radical mediated reactions has begun. Generation of a radical α to a sulfinyl center is expected to be straightforward, and its further reactions should be subject to stereocontrol by the adjacent S—O bond. Treatment of the 2-phenylselenyl derivatives of thiane oxide and dioxide with AIBN easily formed the radical intermediate which could be intercepted by deuterium or allyl radicals (from Bu^n_3SnD or $Bu^n_3SnC_3H_6$, respectively). The outcomes of the reactions are shown in Scheme 36. The orientation of attack is influenced by three factors: 1,2-steric; 1,3-steric; and stereoelectronic effects. In the case of the sulfinyl system 1,2-steric and stereoelectronic influences are in opposing directions: the 1,2-steric effect directs attack *anti* to the S—O bond, while the stereoelectronic effect favors approach *anti* to the sulfur lone pair (i.e., *syn* to the S—O bond). The stereoelectronic effect is most pronounced for reaction with small moieties (i.e., D·), while for larger groups it is the steric interactions which are most significant ⟨91HCA1305⟩.

5.10.5.2 Dihydrobenzothiopyrans

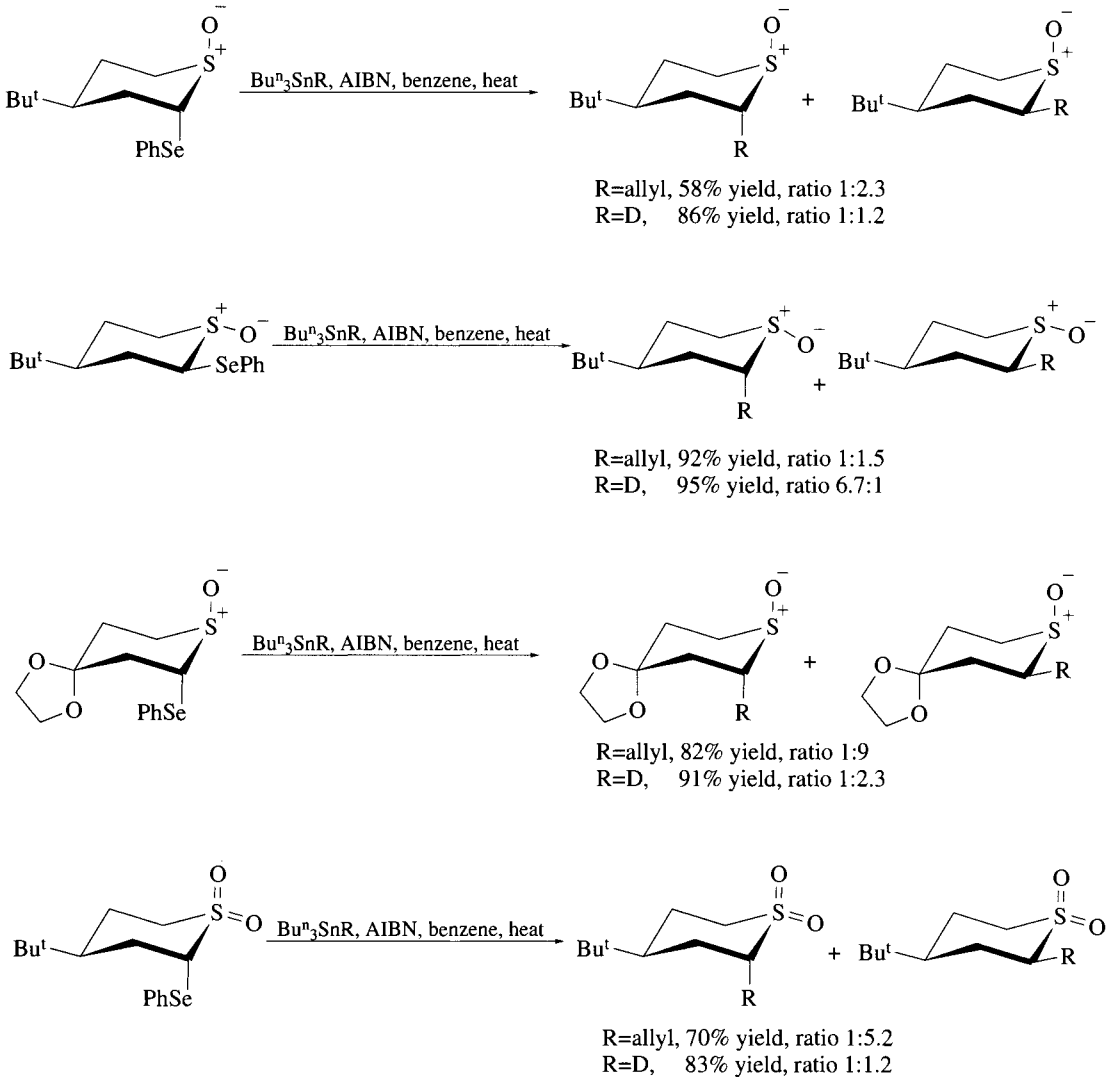
As for thianes the bulk of the chemistry of substituents on dihydrobenzothiopyrans may be readily inferred from that of the carbocyclic analogues. Differences arise, once again, through the inductive effect of sulfur, and through transannular interactions.

The inductive influence of sulfur makes α hydrogens acidic, but very strong bases are still necessary to make profitable use of this effect. Treatment of dihydro-2-benzothiopyran (**98**) with butyllithium followed by alkyl or silyl halides is an efficient source of functionalized derivatives. Scheme 37 shows some typical conversions ⟨82LA1643, 82PS(13)235⟩.

Similar functionalizations may also be achieved with the related sulfoxide analogues, but complications arise when the entering group is electron withdrawing. Acid-catalyzed Pummerer-type reactions can lead to the products of ring cleavage, or as in the case shown in Scheme 38, ring expansion ⟨82LA1643⟩.

By contrast Scheme 39 shows an interesting anionic rearrangement reaction of the dithioketene acetal (**99**) derived from a thiochromanone. These acetals, readily prepared from the unsubstituted carbonyl compound, are frequently used as intermediates for a wide range of annelation reactions. This unusual rearrangement is proposed to proceed as shown via the allylic anion (**100**) ⟨84JCS(P1)921⟩.

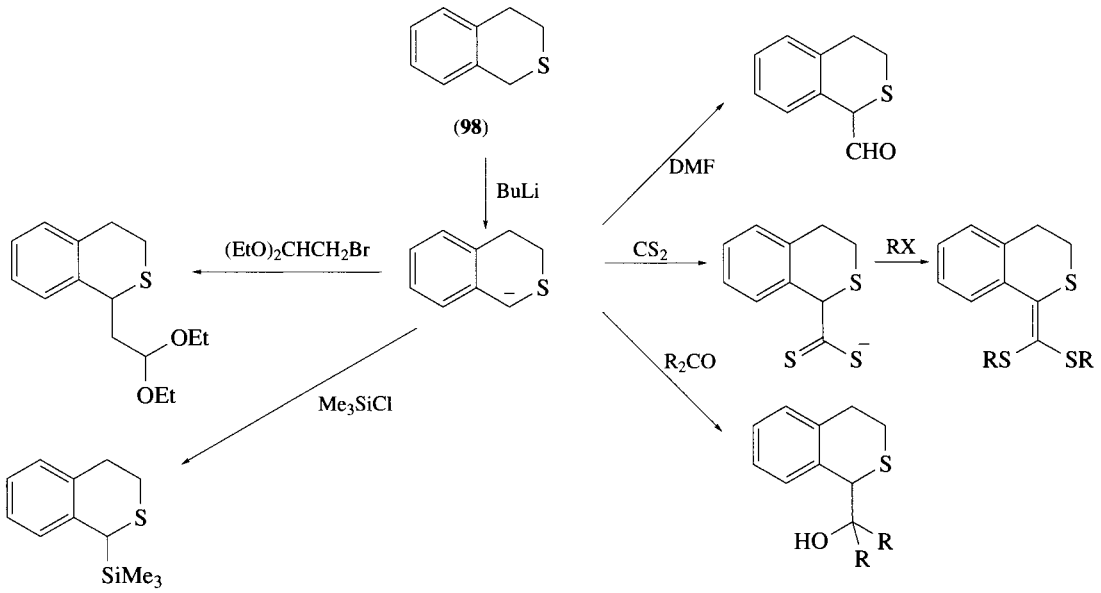
Combination of the activating influences of a carbonyl and a sulfoxide in a 1,3 orientation produces systems that are very easily deprotonated and alkylated. A thorough investigation of the stereochemistry of such alkylation reactions has been made, and has shown that alkylation on the methylene between the two activating groups proceeds with stereoselectivity of the incoming group of at least 9 : 1 in favor of the orientation *anti* to the sulfoxide oxygen, and is independent of the counterion. Bulkier electrophiles show essentially 100% *anti* approach. The carbanion derived from



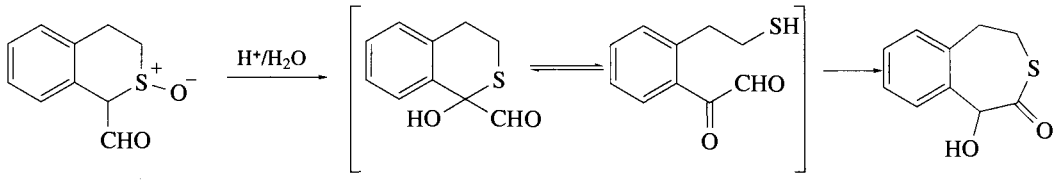
Scheme 36

the parent β-keto sulfoxide has been shown to exist in the enolate form, rather than as an isolated C^- center, and the direction of attack can be readily rationalized on this basis. Scheme 40 illustrates the puckered nature of the anion; it may be expected that repulsion between the sulfur lone pair and the perpendicular lobe of the enolate π-system will strongly favor conformer 1 over conformer 2. The normal preferential axial approach of an electrophile, leading to a pseudo chair transition state, therefore introduces the new substituent *anti* to the S—O bond. Double deprotonation of the unsubstituted β-keto sulfoxide affords the highly reactive dianion (**101**). Alkylation occurs first on the benzylic carbon, with stereochemical consequences dependent upon the electrophile, as shown in Scheme 41. The differing outcomes are consistent with the formation of a planar carbanion adjacent to a "lithiated" sulfinyl oxygen occupying an axial orientation: bulky alkylating agents approach from the opposite face of the ring, while delivery of D^+ is believed to be from a D_2O molecule coordinated through Li^+ to the sulfinyl oxygen, and therefore *syn* to the S—O ⟨84CPB891, 84CPB945⟩.

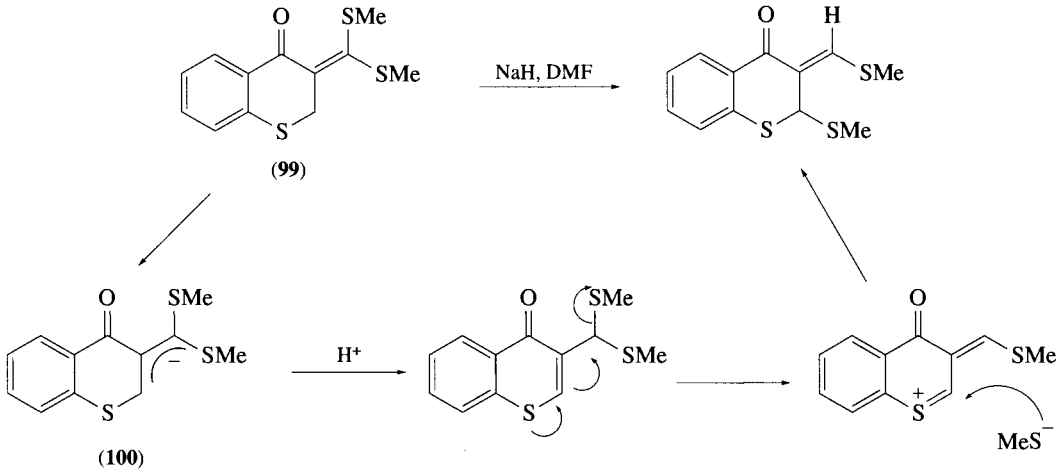
The reactions of the carbonyl group in thiochromanones and isothiochromanones with nucleophiles are largely predictable: Grignard addition, oximation, and hydride reductions all proceed normally. Stereospecific reduction has received some attention, and does warrant discussion. Differences may be expected when biological materials are used as reagents, and a good example is the failure of the alcohol dehydrogenase of *Lactobacillus kefir* (an enzyme that catalyzes many carbonyl reductions and tolerates a wide range of unusual functions) to reduce thiochromanone to thiochromanol ⟨92JOC1532⟩. By contrast, the fungus *Mortierella isabellini* (ATC 42613) is able to reduce



Scheme 37

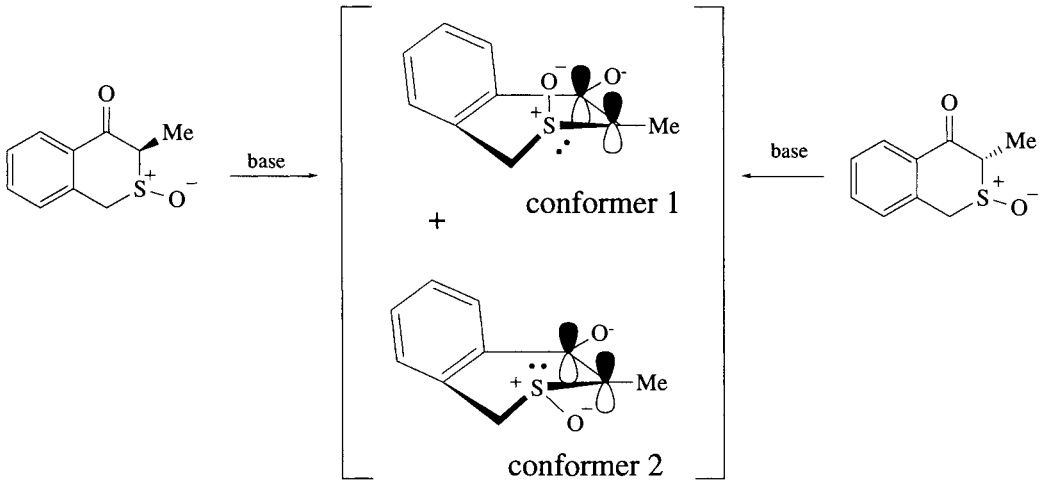


Scheme 38

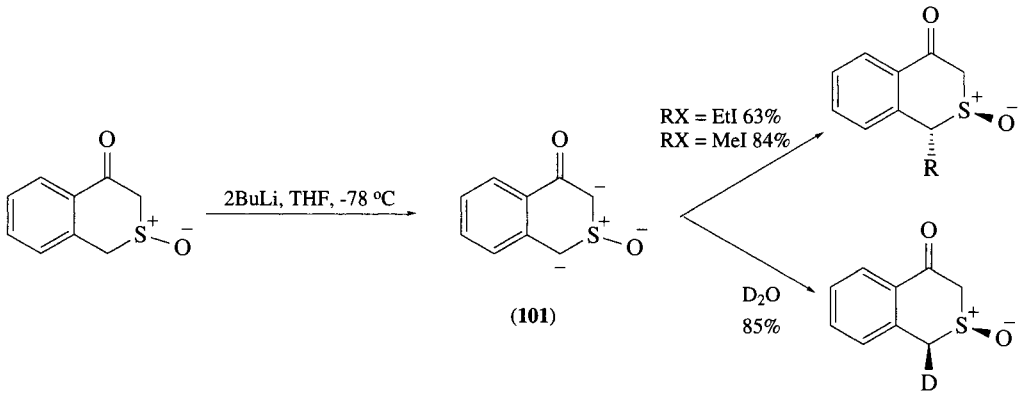


Scheme 39

the molecule to the (−)-alcohol (with (*S*)-configuration) in 82% yield and >98% *ee* ⟨91TA335⟩. Enantioselective chemical reduction of thiochromanones has been achieved by catalyzed hydrosilylation in the presence of a chiral ligand (Scheme 42). Enantiomeric excesses of around 60% were achieved readily under very mild conditions, but the asymmetric induction was not as efficient as in the reductions of the analogous chromanones or tetralones, where optical purities of 70–80% were found. The stereochemistry of the reduction, giving preferentially the (*R*)-alcohol, is controlled by

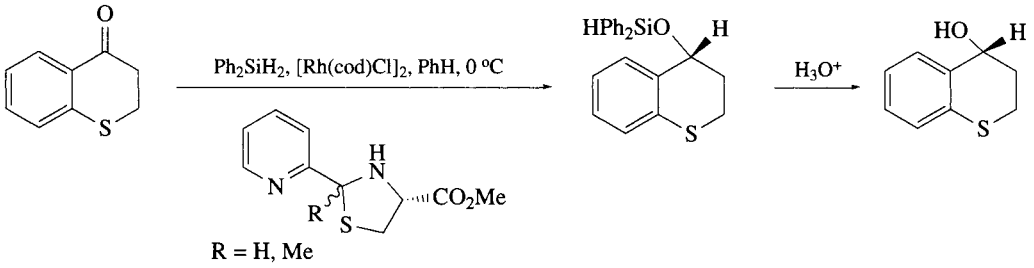


Scheme 40



Scheme 41

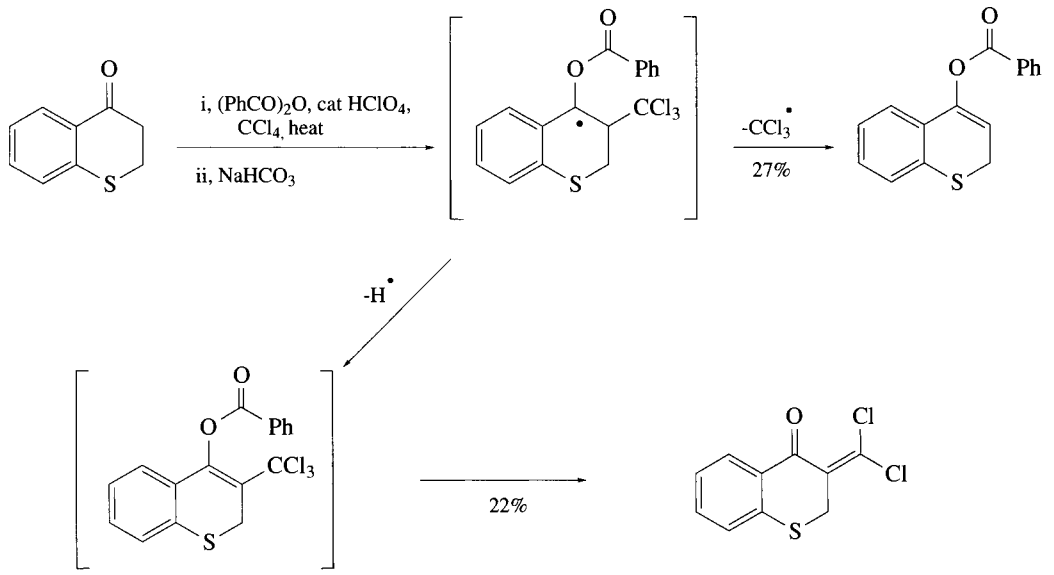
the chiral center derived from the cysteine unit of the chiral co-catalyst, while the configuration of the thiazolidine C-2 was unimportant ⟨88JOM(346)413⟩.



Scheme 42

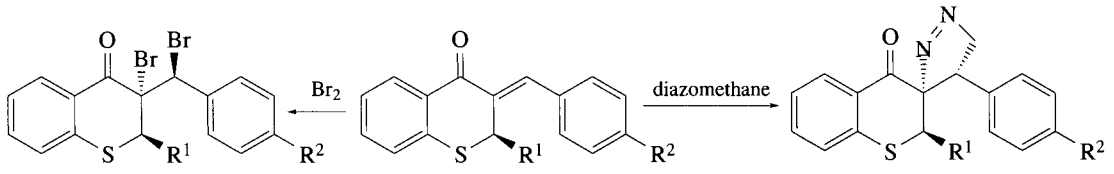
While the polar chemistry of thiochromanone is unsurprising, a most unusual radical mediated reaction was observed during an attempted preparation of its enol benzoate. Scheme 43 shows the diversion of the course of the reaction by the light induced formation of a radical intermediate which interacted with solvent, and gave, eventually, a dichlorovinyl product ⟨82JOC373⟩.

The imines of thiochromanones may be reduced by hydride agents to the amino compounds, but stereoselectivity in the conversion is somewhat less than in the carbocyclic analogue. It seems unlikely that this is a consequence of any transannular interaction, rather that it reflects the influence of the sulfur atom on ring shape ⟨88JCS(P1)611⟩.



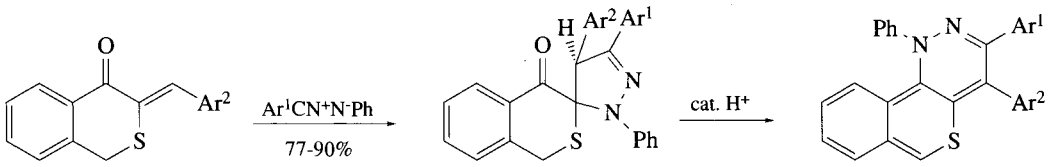
Scheme 43

$\alpha\beta$-Unsaturated derivatives of the dihydrobenzothiopyranones undergo a number of synthetically useful conversions, and there have been extensive studies of the stereochemical influences upon them. Bromination of (**102**) is diastereoselective when R^1 is phenyl; the group R^1 lies in a pseudo axial position, and approach of the bromonium ion is from the less hindered face *anti* to that group. The final opening of the epibromonium species by bromide occurs at the carbon remote from, but *syn* to, R^1 ⟨89LA651⟩. Similarly, the addition of diazomethane also takes place *anti* to R^1, with the orientation shown in Scheme 44, which was quite insensitive to variation in R^2 from alkyl to NO_2 ⟨86JCS(P2)1895⟩. The same regiochemistry is found in the addition of nitrilimines to arylidene-isothiochromanones (Scheme 45). Acid treatment rearranges the first formed spiropyrazoline adducts to [2]-benzothiopyranopyridazines ⟨90TL4145⟩.



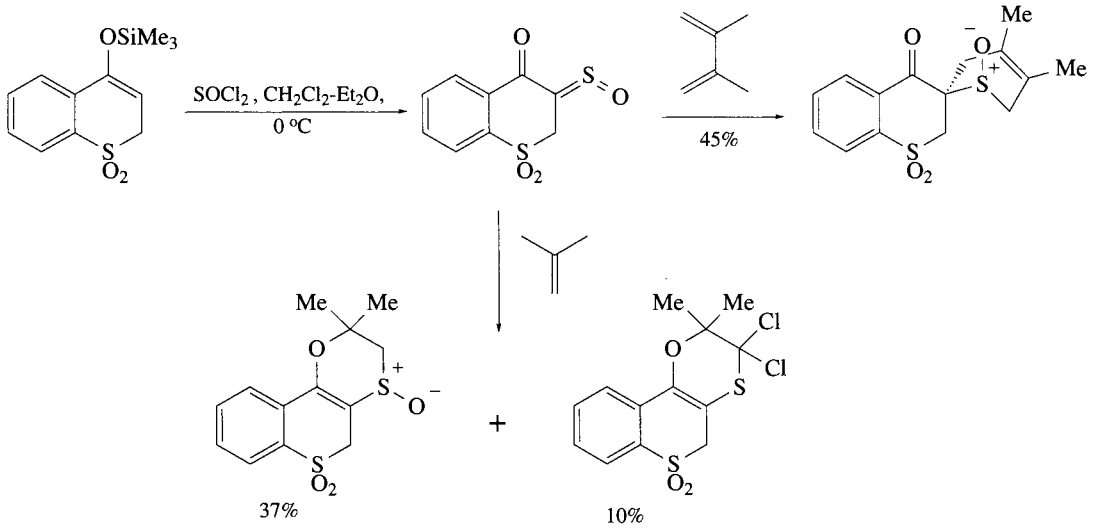
(**102**)

Scheme 44



Scheme 45

Cycloaddition reactions have also been reported for the α-oxo-sulfine of the *S,S*-dioxide of dihydrobenzothiopyranone, which can be prepared *in situ* from silyl enolates (Scheme 46), but with the added dimension that the oxo-sulfine can act as an ene or diene component. The chlorinated by-product presumably is derived from deoxygenation of the initial sulfoxide adduct by chlorine generated from residual trimethylsilyl chloride or thionyl chloride ⟨85CC524⟩.



Scheme 46

5.10.5.3 Dihydrothiopyrans

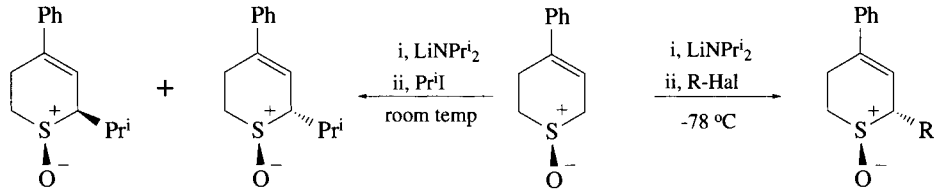
Dihydrothiopyrans behave as unsaturated sulfides, with very little evidence of influence from their cyclic nature, other than the normal imposed stereochemical imperatives. No transannular effects of the heteroatom are apparently to be observed. The lack of significant influence of the sulfur on the chemistry of this ring system may be seen in the absence of any complication in an elegant series of conversions wherein a dihydrothiopyranone bearing a vinylic iodide was taken as a starting material for a synthesis of vitamin D_3 analogues. Reactions carried out included a Pd(0) catalyzed coupling of the vinylic iodide with an alkynic unit, reduction, and silylation of the carbonyl function, metallation of the alkyne, and its coupling with another carbonyl compound, and finally its partial hydrogenation using Lindlar's catalyst. The sulfur did not interfere with any of these steps ⟨92JOC3846⟩.

The deprotonation of dihydrothiopyrans has been fully discussed in CHEC-I ⟨84CHEC-I(3)906⟩, and is a facile entry into alkylated derivatives of the parent system. *s*-Butyllithium efficiently removes the hydrogen α to the sulfur in 5,6-dihydro-2*H*-thiin; the regiochemistry of alkylation is determined by the electrophile: halides react at the α-position, while carbonyl compounds react at the γ-position. The corresponding sulfoxides have received less attention. The anions of (**103**) and (**104**) decompose rapidly even at −78 °C (presumably via ring opening reactions), and alkylation is only successful with methyl iodide, giving rise to the expected *trans*-diequatorial products. Stability is achieved by phenyl substitution at C-4, when the anions are stable up to 0 °C. Alkylation of these conformationally fixed structures is very rapid at −78 °C, giving only the 2-substituted products, and completely stereoselectively *trans* to the S—O bond except in the case of secondary halides such as 2-iodopropane, where room temperature was necessary, and two diastereomers were obtained, albeit in good yield. Even so, the major product had the *trans*-diequatorial configuration (Scheme 47).

(**103**) (**104**)

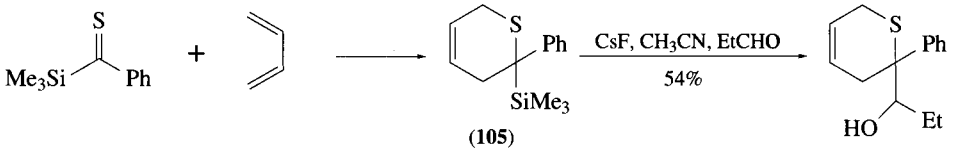
Carbonyl electrophiles likewise react at C-2, with little apparent stereoselectivity, probably as a result of epimerization of the initial product in the reaction mixture. The difference in regioselectivity of the reaction of ketonic substrates with the sulfoxide system compared to the sulfide case is believed to be driven by the conjugation afforded by the phenyl group ⟨85AJC119⟩.

Alkylation at the six position of 5,6-dihydro-2*H*-thiins may be achieved by carbanion generation via desilylation, the necessary α-silyl sulfides being readily available through cycloaddition reactions



Scheme 47

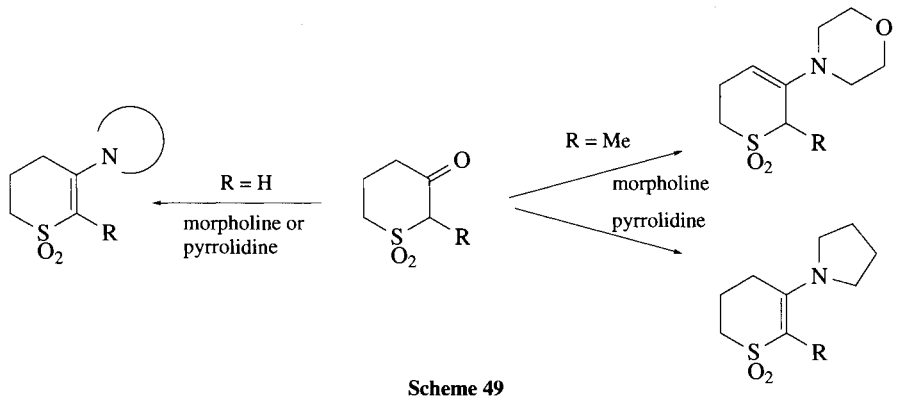
of silyl thioketones. Treatment of (**105**) with fluoride in the presence of a carbonyl compound, for example, affords adducts in yields of up to 70%, protiodesilylation being the other significant reaction observed (Scheme 48) ⟨91TL815⟩. Unsaturated aldehydes react at the C=O, while a cyclic enone gave only the conjugate addition product. If the silicon center was chiral, modest enantiomeric enrichments were seen in the reaction product from aromatic aldehydes, reflecting the diastereomeric purity of the dihydrothiopyran precursor. Alkylation is frequently achieved via enamines, particularly at centers remote from the sulfur. Enamines derived from thian-4-ones may be hydroborated to yield 5,6-dihydro-2*H*-thiopyran, but as no other substituents were present the regioselectivity of the reaction is uncertain ⟨91JOC1543⟩.



(**105**)

Scheme 48

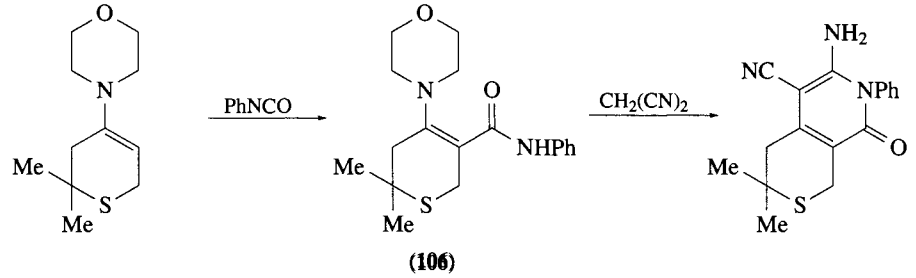
Turning to dihydrothiopyran-3-one *S*,*S*-dioxides, the enamines may exist either as a simple enamine, or as a vinylogous sulfonamide. In unsubstituted systems the Δ^2 isomer is preferred, but steric interactions (e.g., a 2-methyl group) reverse this preference as shown in Scheme 49. Reaction with dimethyl azodicarboxylate is low yielding in the morpholine enamine case, but more efficient in the pyrrolidino system, and occurs at the expected (C-2) position. Acylation with acetyl and benzoyl chlorides proceeds similarly ⟨83JCS(P1)2735⟩. Isocyanates and isothiocyanates react smoothly with the enamines and the products (**106**) can be easily trapped with nucleophiles such as malononitrile anion (Scheme 50) ⟨87AKZ587⟩.



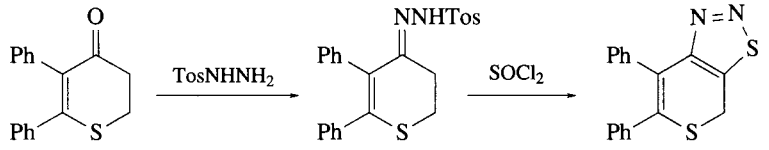
Scheme 49

An unusual enamine-like reaction of the hydrazone (**107**) with thionyl chloride affords the novel bicyclic product (**108**) (Scheme 51) ⟨90SUL67⟩.

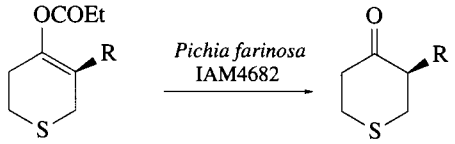
Enzymatic hydrolysis of dihydrothiin enol esters has been investigated as an entry into chiral tetrahydrothianones, mediated by enantioselective reprotonation. Unfortunately stereoselectivity was poorer than in the carbocyclic analogues (Equation (26)) ⟨92TL6367⟩. Chiral hydroboration of 3,4-dihydro-2*H*-thiin with (−)-diisopineocampheylborane gave a high yield of thian-3-ol with an optical purity >80% ⟨86JA2049⟩.



Scheme 50

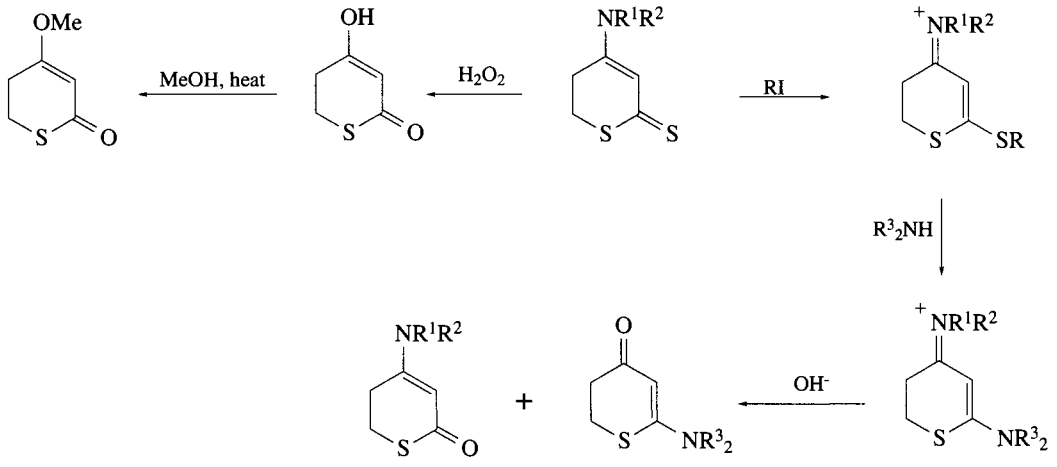


Scheme 51



(26)

The chemistry of 4-amino-5,6-dihydro-2*H*-thiopyran-2-thione is essentially that of a vinylogous dithiourethane. Alkylation occurs specifically at the thione sulfur, generating 4-imino products, which may be hydrolyzed etc. Scheme 52 illustrates this reaction and other typical conversions ⟨82M1283, 83M317, 92M33⟩.



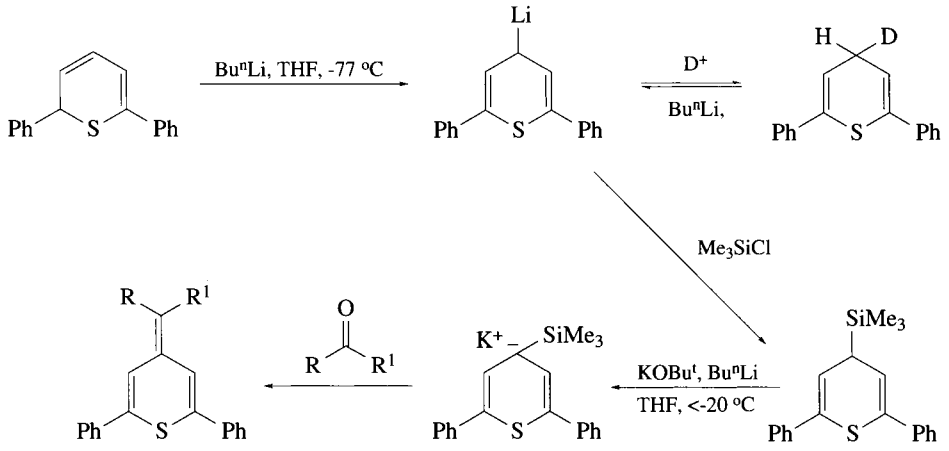
Scheme 52

5.10.5.4 2H- and 4H-Thiopyrans

The unsubstituted monocycles are only poorly stable, and they are most usually found in their (thi)one forms, or alkylidene substituted, affording a 6-π system. The sulfur does not participate significantly in any cyclic conjugation, and the parent 4*H*-thiopyran readily converts to the 2*H* tautomer on mild treatment with acetic acid. Deprotonation of the parent heterocycles affords a 6-

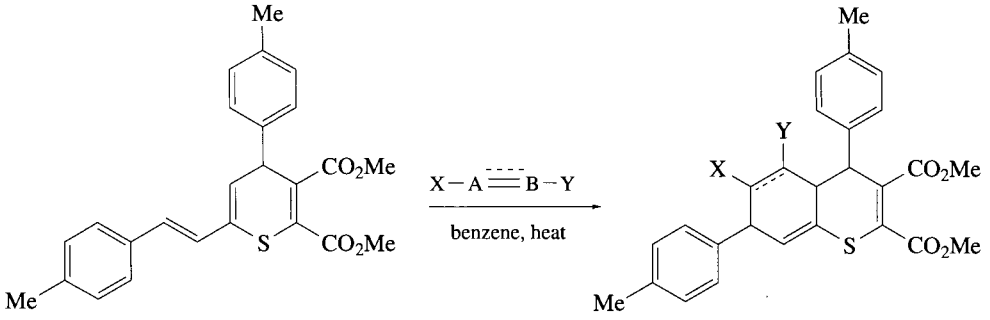
π anion, which may also be formed by sodium/liquid ammonia reduction of a thiopyrylium species. Alkylation is extremely fast with *t*-butyl iodide, possibly via an electron transfer mechanism. Mechanistic studies using the electrochemically generated anion gave a 3 : 1 mixture of 2- and 4-*t*-butylated products ⟨90ACS524⟩.

Phenyl substitution stabilizes the heterocycles, and permits useful deprotonation/functionalization reactions; Scheme 53 shows a silylation and Peterson alkenation sequence. The analogous Wittig–Horner reagent, and its use in alkenation, have also been described ⟨82JOC680⟩.



Scheme 53

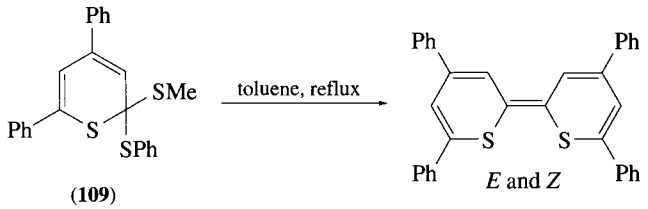
In the absence of "ylidene" substitution, the 4*H* isomer behaves as a vinyl sulfide, and Diels–Alder reactions are possible with a variety of electron deficient dienophiles (Equation (27)) ⟨90BCJ284⟩.



(27)

dienophile:	%
tetracyanoethylene	100
DMAD	73
DEAD	68

Much of the chemistry of the 2- and 4*H*-systems is driven by the formation of a fully unsaturated nucleus, which leads to some quite surprising conversions. The dimerization of **(109)** on heating in toluene is a good example (Equation (28)) ⟨86S916⟩.

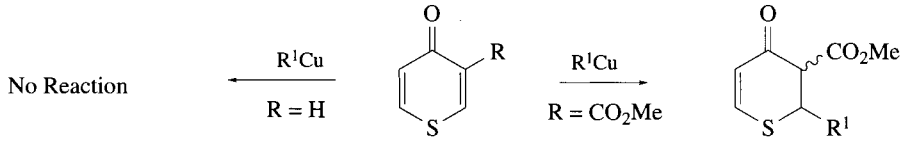


(109)

(28)

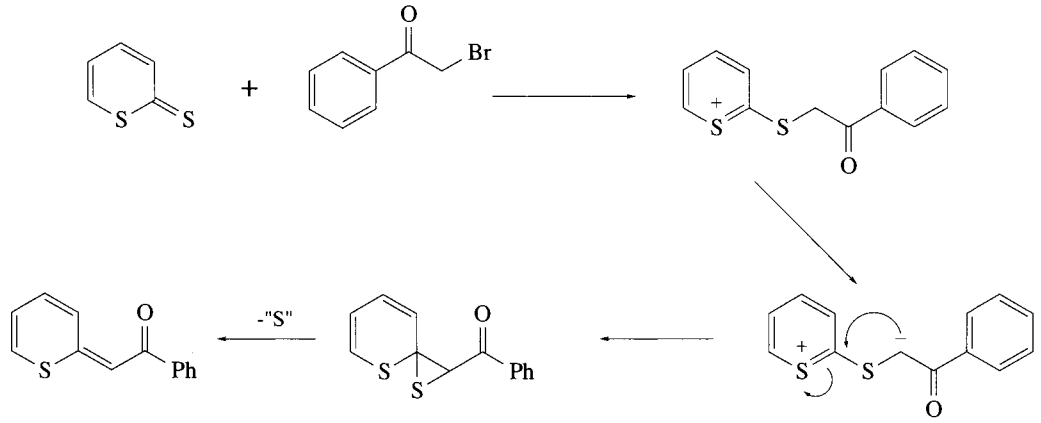
When the systems are fully unsaturated, as the 2- or 4-ones (or thiones), they behave predominantly as enones. Substitution reactions of halogens or methoxy groups, proceeding via

addition–elimination sequences, are a facile entry into 4-substituted 2-one compounds. The related conjugate additions of cuprates to thiin-4-ones requires more activation than the lone carbonyl can provide, and a further carbomethoxy group is necessary (Scheme 54). A range of cuprate species have been used, and it has been shown that yields are insensitive to the nature of the complex ⟨86JCS(P1)1397⟩.



Scheme 54

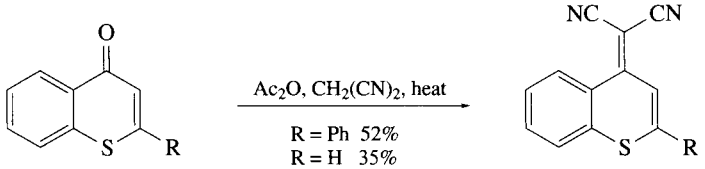
Alkylation of the 2-thiones occurs on the exocyclic sulfur, affording thiopyrylium products. Under basic conditions further reaction may be possible, and the initial thione can be replaced by an alkylidene moiety (Scheme 55) ⟨87FES465⟩.



Scheme 55

5.10.5.5 2H- and 4H-Benzothiopyrans

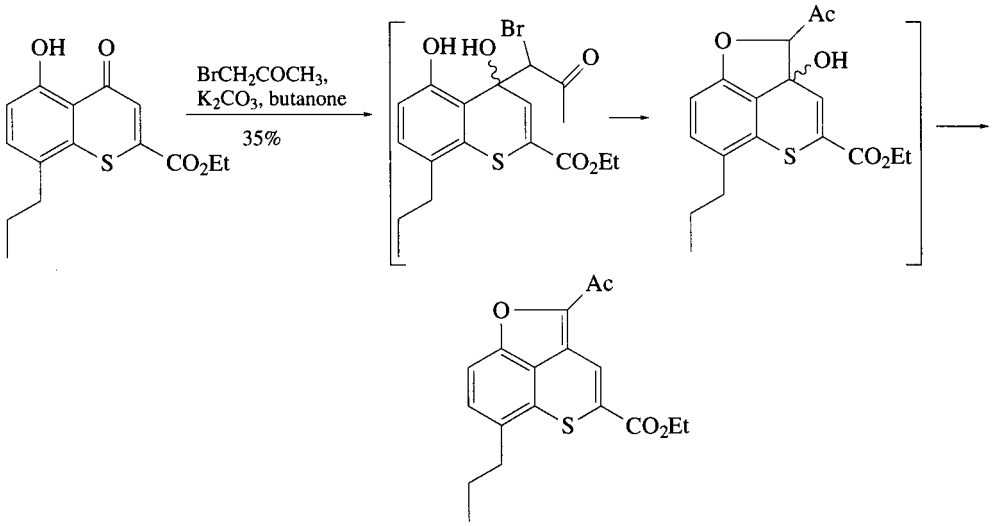
The chemistry of the parent benzothiopyrans is dominated by the drive to full unsaturation, and the majority of work has been performed on the (thio)carbonyl derivatives. The carbonyl group of 4*H*-1-benzothiopyranones is susceptible to condensation with carbon nucleophiles under Knoevenagel or Darzens-type conditions (Scheme 56 and Equation (29)) ⟨84JCS(P1)487, 86JOC3282⟩.



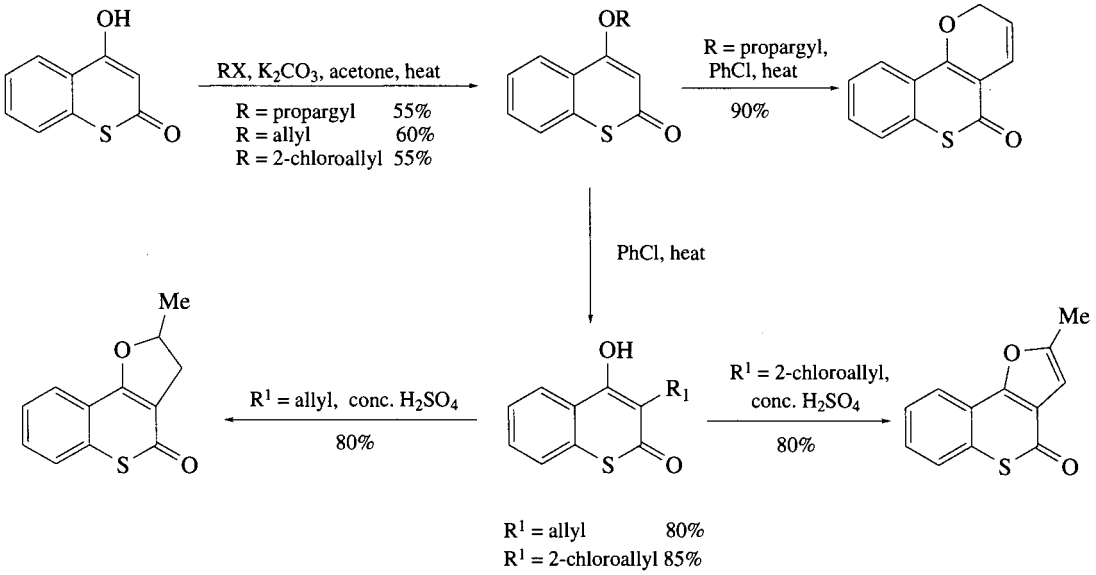
(29)

Reduction of the carbonyl group is usually complicated by conjugate addition reactions, leading to reduction of the ring as well. The tautomerically mobile 4-hydroxy-2-one system behaves differently; being an enolized β-diketone, it is acidic. The anion may be readily alkylated on carbon or oxygen. Reaction on oxygen at position 4 is facile and akin to the chemistry of phenols. Furthermore, allylic ethers undergo Claisen rearrangements on heating, the products from which can be further ring closed (either spontaneously or on acid treatment) to fused furans or pyrans (Scheme 57) ⟨89SC3249⟩.

A closely related reaction, wherein the β-diketone system is alkylated on carbon, is seen in the electrochemically driven synthesis of thiocoumestans via anodic oxidation of catechols to *o*-quinones (Scheme 58) ⟨90MI 510-02⟩.

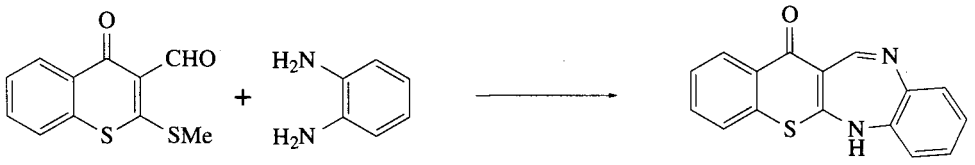


Scheme 56

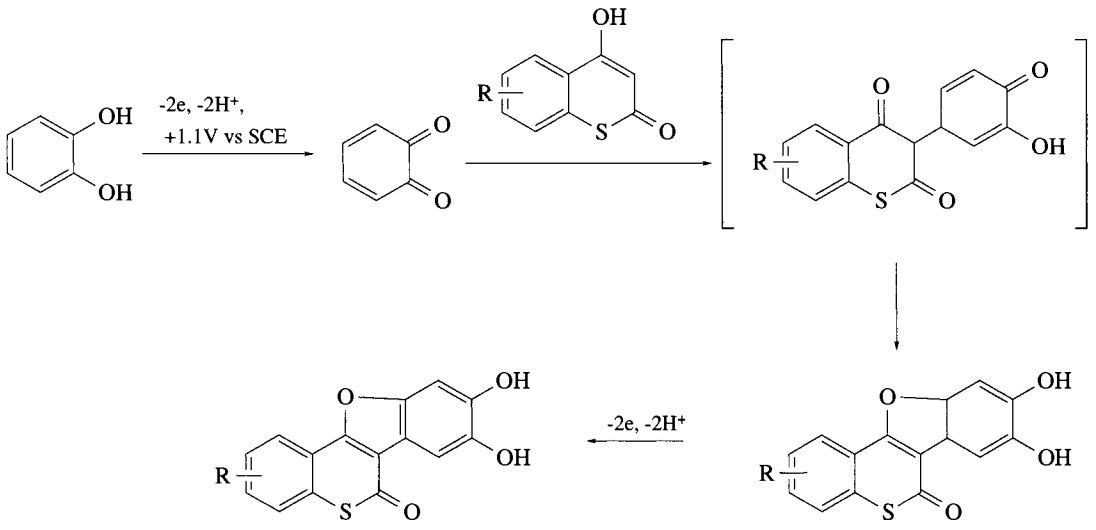


Scheme 57

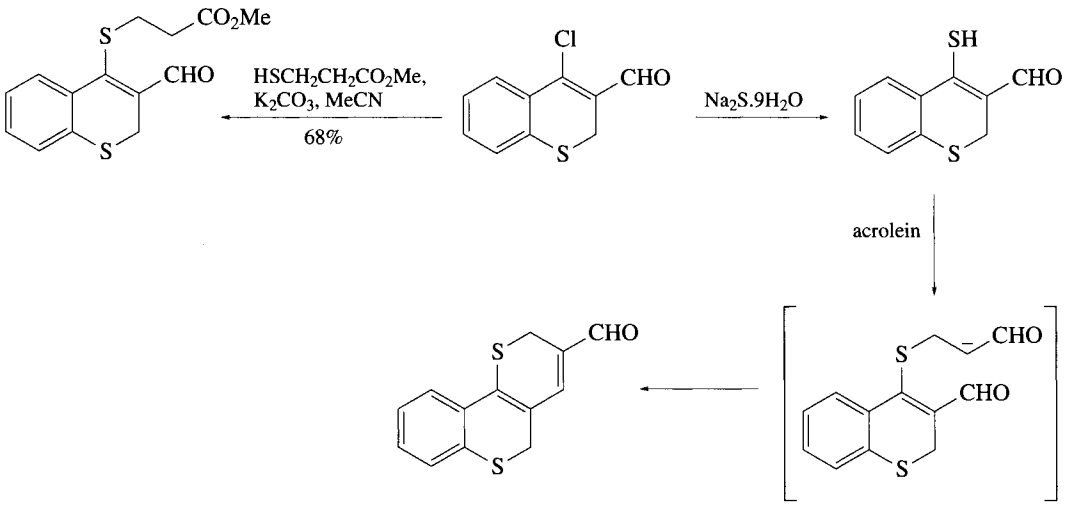
Halogens at C-2 of the 4-one system and at C-4 of the 2-one structure, in keeping with the β-diketonic nature of the compounds, are readily replaced by nucleophiles in an addition–elimination sequence. It is not essential that the carbonyl be endocyclic: an aldehyde group is also a very efficient activator of vinylic halogen displacement. Scheme 59 illustrates this process, and its use in the further elaboration of the compounds ⟨89MI 510-02, 89SUL149⟩. Equation (30) shows the analogous replacement of a sulfide substituent ⟨92SUL45⟩. An interesting alternative replacement process of a sulfide not involving an addition–elimination sequence is seen in the electrochemical carboxylation of 2-methylthiothiochromone, affording the thiochromone-2-carboxylic acid in 40–50% yield and on the gram scale (Equation (31)) ⟨88JPR147⟩.



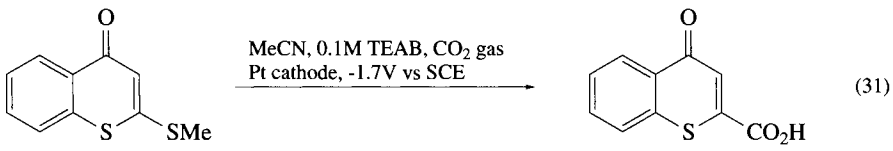
(30)



Scheme 58

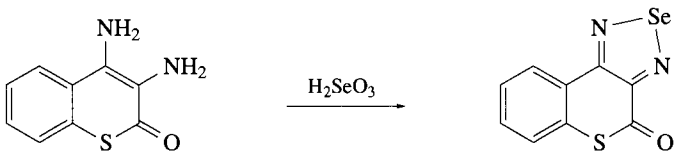


Scheme 59

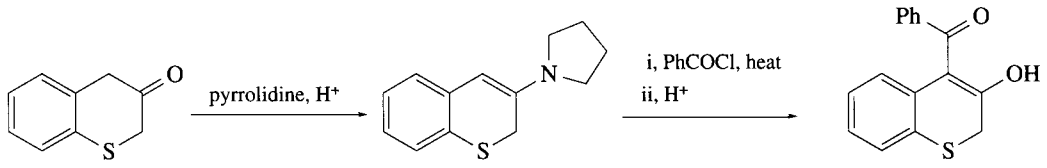


(31)

Amino substituents may be obtained by conventional reduction of nitro groups. Under milder conditions (CS_2/K_2CO_3 in the presence of solid–liquid phase transfer catalysts) moderate yields of oximes may also be produced ⟨90S333⟩. The amino groups behave as for anilines, forming imines etc, or in combination with other appropriate groups they can give rise to new fused heterocycles (Equation (32)) ⟨86KGS1000⟩. Enamine reactions are synthetically useful for entry into substituted systems (Scheme 60) ⟨92JCS(P1)3015⟩.



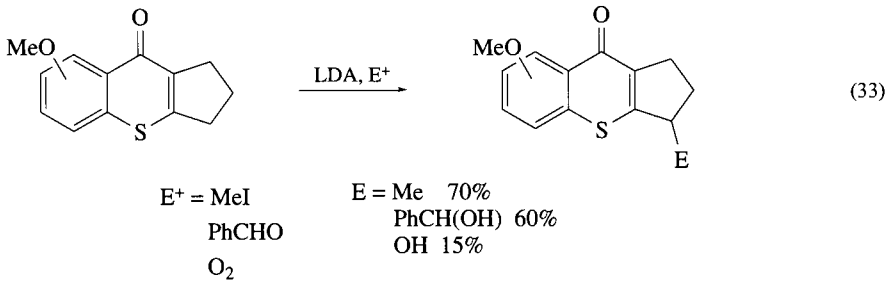
(32)



Scheme 60

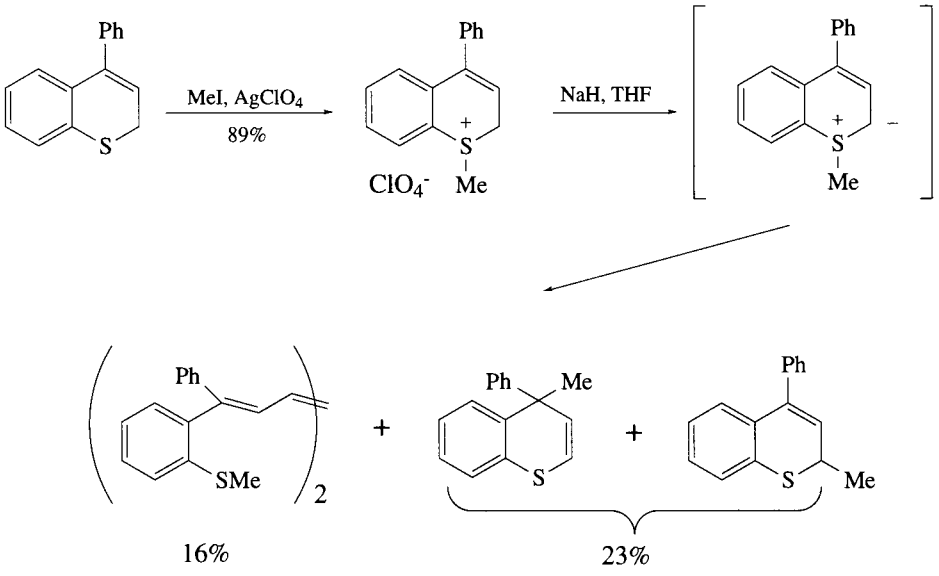
Simple thiones may be oxidized to sulfines under mild conditions. Under more vigorous conditions the thione is converted into its oxygen analogue ⟨87M1197⟩. Alkylation of the thione sulfur is facile if tautomerism to the thiol form is possible.

Alkyl groups on thiopyranones are activated toward oxidation by the generally electron withdrawing nature of the heterocycle. Selenium dioxide may be used to generate 2- and 4-aldehydo-1-benzothiopyranones ⟨88JHC511⟩. They are also prone to deprotonation, as shown in Equation (33) ⟨85BCJ2203⟩.



(33)

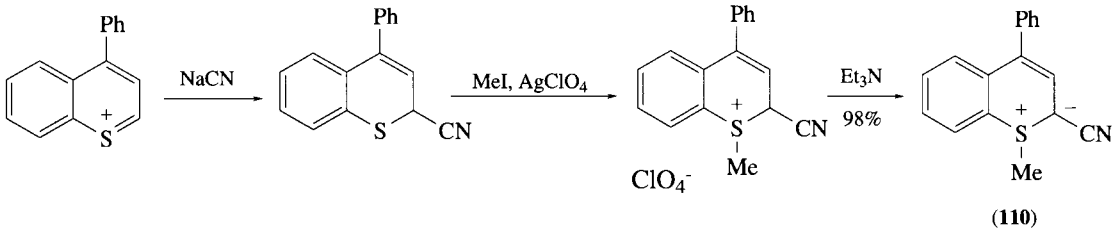
Metallation of benzothiopyrans is well known, and has been extensively studied. In the case of the 2*H* system deprotonation is not facile unless the sulfur is alkylated, when sodium hydride readily generates the unstable 8π "thianaphthalene." Decomposition via *S*-alkyl migration and ring opening is rapid (Scheme 61).



Scheme 61

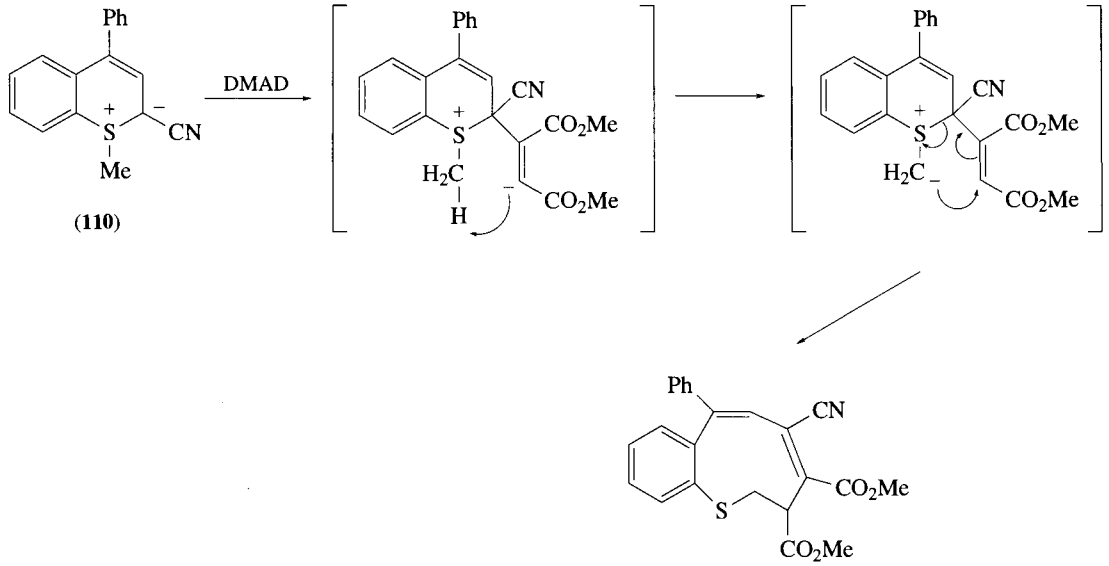
Anion stability requires the presence of another electron withdrawing group such as a nitrile, which so facilitates the deprotonation that triethylamine is sufficiently basic to generate ylides (e.g., **110**) (Scheme 62). While stable and fully characterizable at room temperature, heating (**110**) in

acetone causes the methyl to migrate to C-2 or C-4 (in about 40% yield). Electrophiles such as DMAD add readily, and further transformations are common, as shown in Scheme 63 ⟨88CPB3816⟩.



(110)

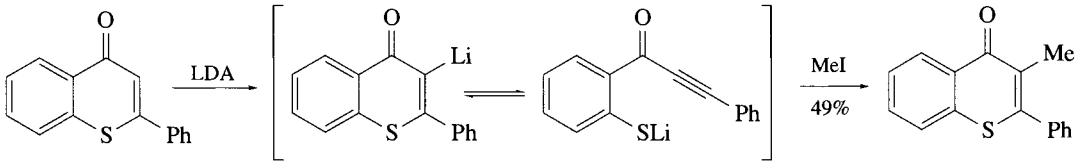
Scheme 62



(110)

Scheme 63

Lithiation of thiochromones and flavones has attracted much research, and is well understood. Metallation affords the 3-lithio compounds, which are in equilibrium with the ring opened alkynic anions (Scheme 64) ⟨88JOC1203⟩. Little use has been made of this potential approach to derivatization of thioflavones, which may indicate that reaction with electrophiles is not efficient.

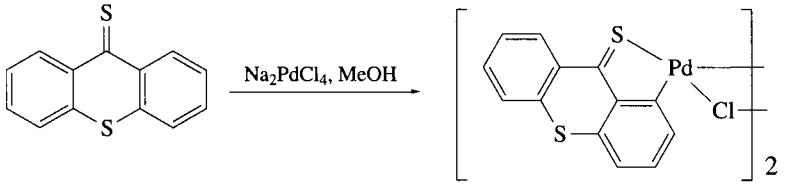


Scheme 64

5.10.5.6 Thioxanthenes

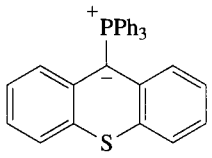
The chemistry of thioxanthenes, and the fully unsaturated thioxanthones, -thiones and thioxanthylidene compounds may be almost completely predicted from that of benzene and benzophenone. Substituents on the aromatic rings display little evidence of influence by the sulfur on their reactivity. The carbonyl group in thioxanthone permits nucleophilic displacement of halogen

substituents on its *ortho* benzenoid carbon ⟨88JMC1527⟩, and nitro groups *para* to the C=O may be displaced under mild conditions ⟨85HCA854⟩. The use of the thione permits replacement of an *ortho* hydrogen by cyclopalladation reactions (Equation (34)), and further elaboration of the aromatic nucleus is possible with such intermediates ⟨87JCR(S)280⟩.

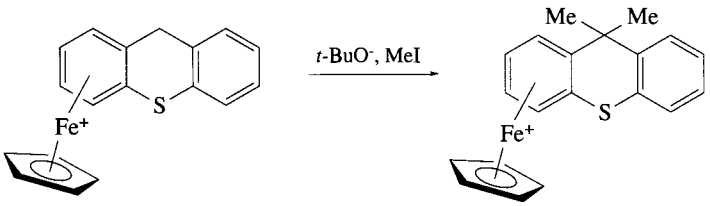


(34)

The chemistry of the nonbenzenoid carbon center of a thioxanthene is dominated by its "bis-benzylic" situation. Cations and anions are efficiently stabilized, such that the triphenylphosphorane (**111**) may be isolated ⟨88IJC(B)1⟩. The anion stabilizing action may be further enhanced by complexing one or both of the aromatic nuclei as η^6-arene-η^5-cyclopentadienyl iron cations. Both the thioxanthene and thioxanthene *S,S*-dioxide iron complexes have been prepared, and may be easily dimethylated by treatment with *t*-butoxide and methyl iodide (Equation (35)) ⟨86JOM(310)391⟩.



(**111**)



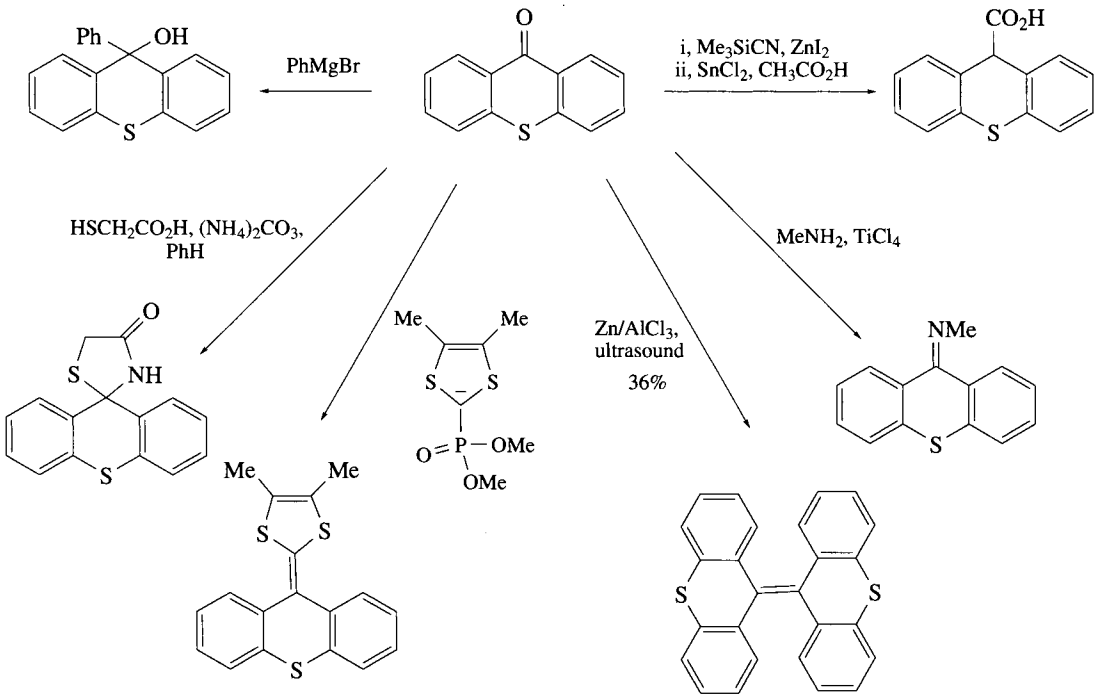
(35)

Halogens at C-9 are readily replaced, and the CH_2 group is also rapidly oxidized by a variety of agents to the thioxanthone system (see, for example, ⟨92BCJ2878⟩). Thioxanthone is readily attacked by nucleophiles ⟨87JPS848, 88NKK1977, 91JCS(P1)157, 92OPP81⟩, and may be reductively dimerized with Zn–$AlCl_3$ and ultrasound to bi-thioxanthylidene ⟨90TL4165⟩. Scheme 65 shows some of these reactions.

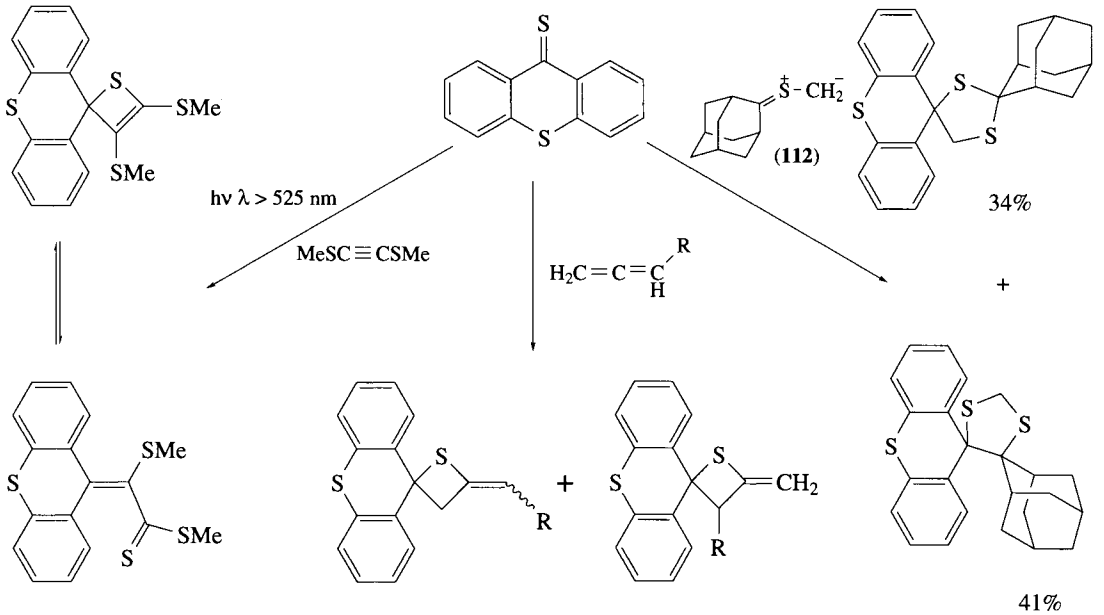
The thiocarbonyl compounds are readily converted into the carbonyl structures by a range of reagents including singlet oxygen, peroxo compounds, trifluoroacetic anhydride, and cuprous chloride in basic medium (see, for example, ⟨86TL3911, 91TL1195⟩). [2 + 2] Cycloaddition is observed upon photochemical excitation in the presence of alkylthio-substituted alkynes or allenes giving thietes (in equilibrium with dithioesters) and thietanes, respectively ⟨84RTC152, 85IJ120⟩, while the Schönberg dipole (**112**) adds nonregioselectively in a [1,3]-dipolar manner to the ground state thione affording dithiolanes (Scheme 66) ⟨85H(23)2201⟩.

9-Hydroxyl groups readily leave when protonated, forming thioxanthylium species. If this treatment is applied to 9-phenylthioxanthen-9-ol in the presence of H_2O_2, the peroxide adds to the thioxanthylium intermediate, and a Criegee type rearrangement is observed (Scheme 67) ⟨89JCS(P1)931⟩.

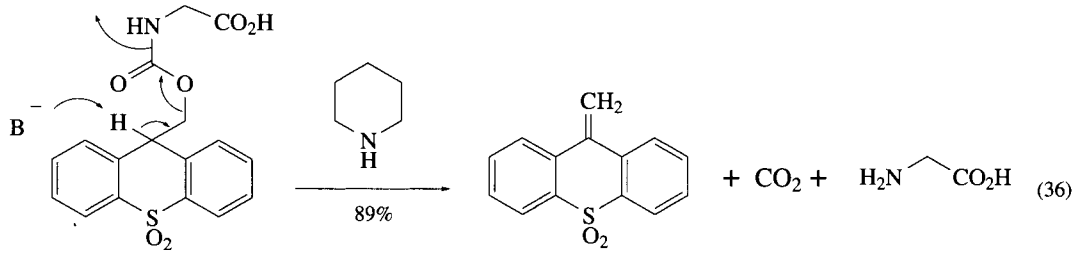
9-Hydroxymethyl groups can be dehydrated to the thioxanthylidene system, and this is even more facile in the *S,S*-dioxide case. Use may be made of this observation in the peptide protecting group "D-TMOC." The urethanes (**113**), prepared from the relevant chloroformate (a storage-stable, crystalline solid) in high yield, are efficiently deprotected on treatment with mild bases such as piperidine, or on simple dissolution in DMSO (Equation (36)) ⟨89JOC5887⟩.



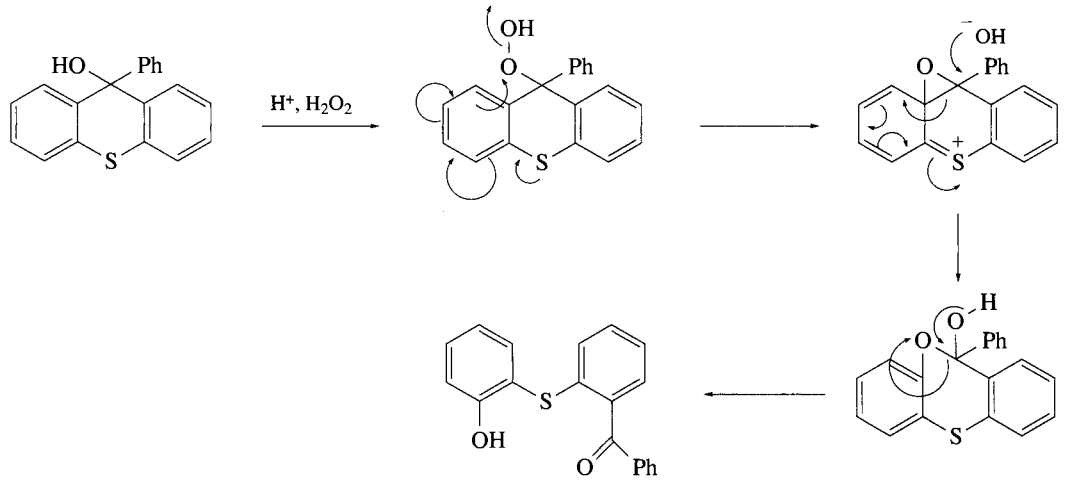
Scheme 65



Scheme 66



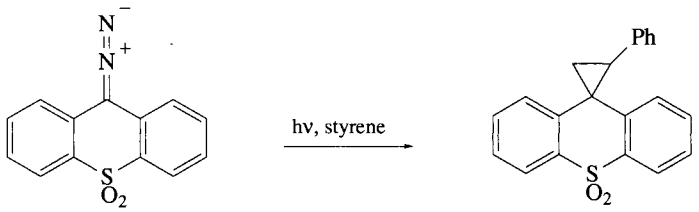
(113)



Scheme 67

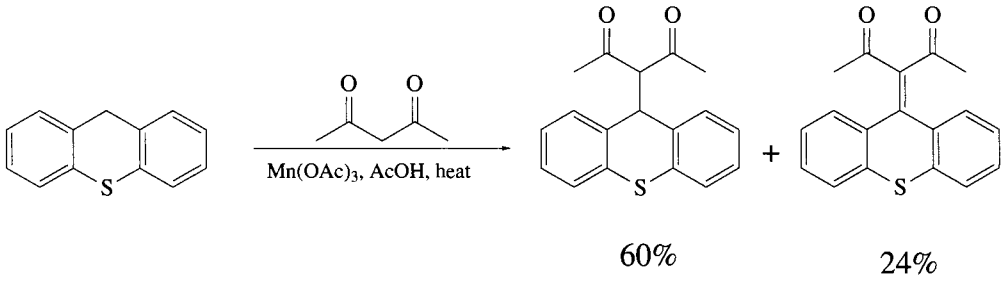
The 9-carbaldehyde exists completely in the enol form; reaction with amines affords the enamines, though a competing process is a retro-aldol cleavage to form thioxanthene ⟨89JOC4302⟩.

9-Diazothioxanthenes have been investigated as sources of the thioxanthylidene carbene. Trapping with fumarates and maleates gave a range of products, resulting from 1,3-dipolar cycloaddition (spiropyrazolines and cyclopropanedicarboxylates), and from C—H insertion. The *S,S*-dioxides even more readily give the carbene on photolysis, which may be trapped by styrenes in yields of 60–80% (Equation (37)) ⟨87JOC429⟩. A minor by-product of these reactions is the 9,9′-bis-thioxanthylidene dimer.



(37)

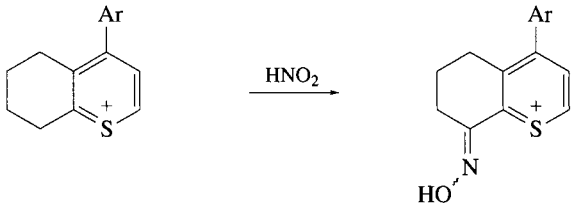
Oxidation of thioxanthene with manganese triacetate in refluxing acetic acid gives thioxanthylium, or 9-acetoxythioxanthene. In the presence of 1,3-dicarbonyl compounds, 9-substituted thioxanthenes are formed (Equation (38)) ⟨92JOC3551⟩.



(38)

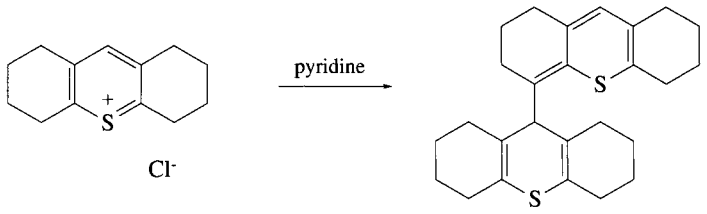
5.10.5.7 Thiopyrylium Salts

Substituents on thiopyryliums are powerfully influenced by the very strongly electron withdrawing nature of the heterocycle. Reactions akin to those of β-diketones are observed; for example, nitrosation (sodium nitrite in acetic acid) affords oximes in synthetically useful yields (Equation (39)) ⟨90ZOR405⟩.

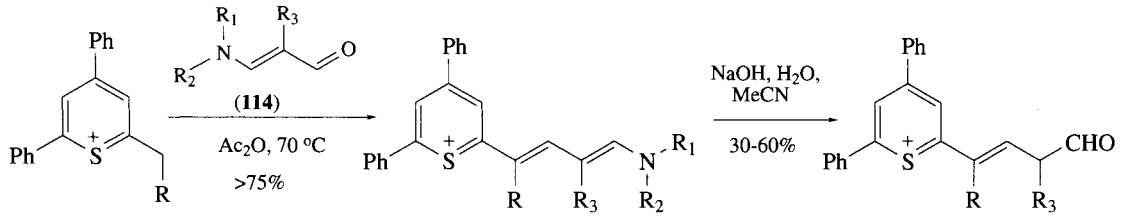


(39)

Treatment with base affords carbanions which may be trapped by a variety of electrophiles, including the parent thiopyrylium system (Equation (40)) ⟨89KGS479⟩, or the vinylogous amide (**114**) (Scheme 68). Base hydrolysis of the enamine product is greatly facilitated by the electron deficient heterocycle ⟨87ZC443⟩.

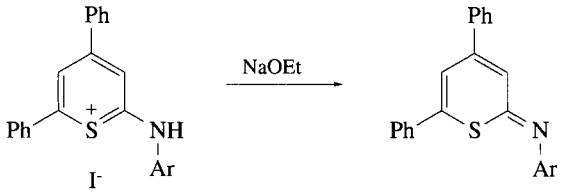


(40)



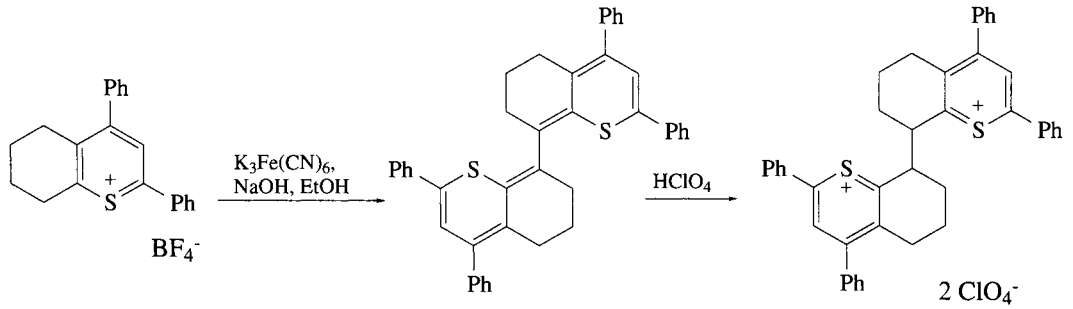
Scheme 68

In the absence of an appropriate trap the α-deprotonation of a 2-substituent can lead to the formation of 2*H*-thiopyrans (Equation (41)) ⟨90MI 510-04⟩.



(41)

Oxidation of α-carbanions with $K_3Fe(CN)_6$ affords dimers, for example (**115**), which on treatment with perchloric acid generates the bis-thiopyrylium salt almost quantitatively (Scheme 69) ⟨87ZOR2019⟩.



(**115**)

Scheme 69

5.10.5.8 Benzothiopyrylium and Thioxanthylium Salts

As in the case of thiopyrylium salts, the chemistry of benzothiopyrylium species is dominated by the strongly electron withdrawing nature of the heterocyclic ring. Alkyl groups are readily deprotonated and may be condensed with aldehydes etc. ⟨90CC421⟩. In the absence of a suitable external electrophile, deprotonation of a 2- or 4-alkyl group leads to the formation of the thiopyran. Nucleophiles add so readily to the heterocycle that other substituent interconversions are generally precluded. The same general comments apply to the thioxanthylium salts.

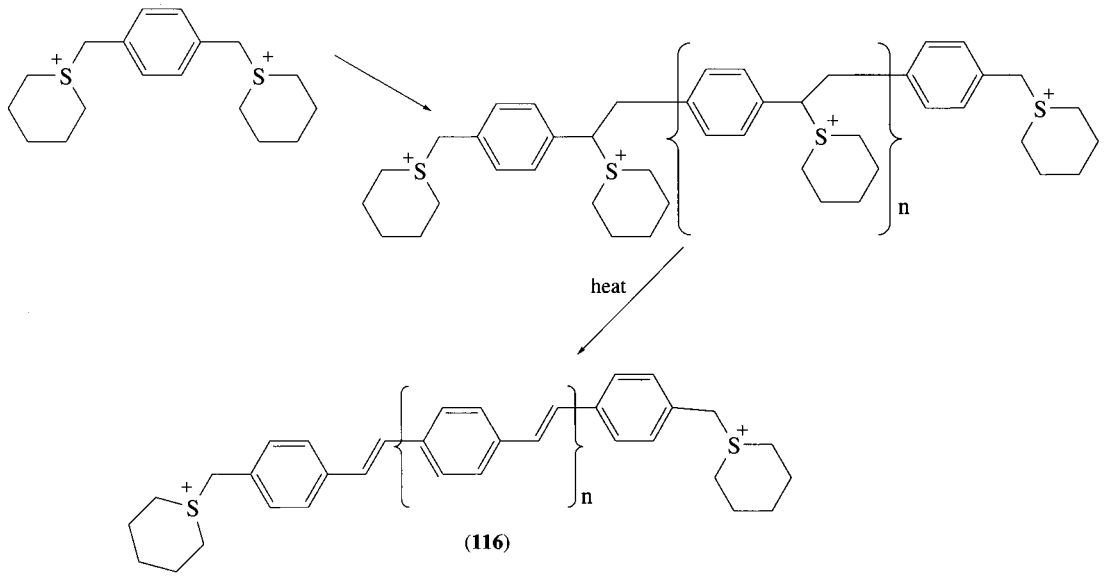
5.10.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

Substituents on the sulfur of stable derivatives of thiin rings are alkyl and aryl groups (sulfonium salts), oxygen (sulfoxides and sulfones), nitrogen (sulfilimines), and combinations of alkyl and oxygen (sulfoxonium compounds), and oxygen with nitrogen (sulfoximines). The reactivities of these groups are described according to the ring system.

5.10.6.1 Thianes

5.10.6.1.1 Thiane sulfonium salts

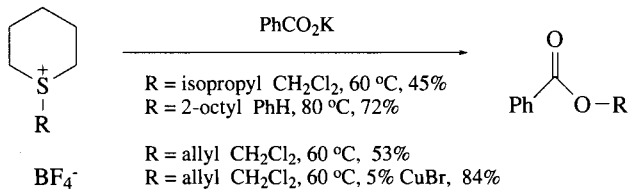
The reactions of an alkyl group attached to the S atom may be classified into two types: those in which the S—R bond is cleaved, and those in which it is retained. Looking firstly at those in which the bond breaks, the simplest case is thermal β-elimination of the sulfonium sulfur, leading to an alkene and a thiane. Use can be made of this reaction in the generation of polyunsaturated polymers such as (**116**). Creation of the highly conjugated system provides the driving force for the elimination process (Scheme 70) ⟨88JPS(A)3241⟩.



(**116**)

Scheme 70

An alternative transformation is the migration of the substituent to another atom, either inter- or intramolecularly. Sulfonium salts are powerful alkylating agents, with particular application in two-phase systems. While attack by a nucleophile can occur at each of the carbon atoms α to the sulfur, by suitable choice of the *S*-substituent group its transfer can be made the predominant reaction. Catalysis by Cu^{I} salts reinforces the preference for transfer of the *S*-alkyl group, and in the case of *S*-allylic thianium salts heavily favors S_N2' attack at the γ-carbon. Equation (42) shows some typical reaction conditions and yields ⟨83T3111⟩.

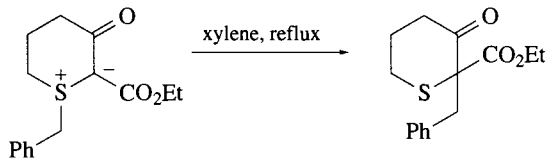


(42)

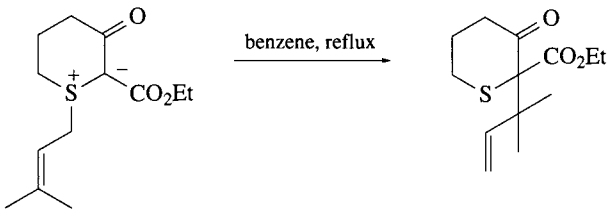
The use of a sulfonium compound as an alkylating agent has an important limitation: the nucleophile should not be so basic that it generates a zwitterion by deprotonation of the carbon α to the S^+ center. However, a significant potential advantage of such an alkylating species is the "soft" polarizable nature of the leaving group, akin to iodide. If used with an ambident nucleophile preferential reaction at the "soft" center is to be expected. Thus it may be predicted that alkylation of a β-dicarbonyl system would occur principally at carbon, rather than at the harder oxygen atom. Experiment bears this out ⟨83JOC1362⟩. The problem of nucleophile basicity may be avoided if protons adjacent to the S^+ center can be replaced by methyl groups etc. but it is then necessary to consider the acidity of the β-protons. If there is a 4-carbonyl substituent, base-catalyzed β-elimination (a retro-Michael reaction) competes with alkylation, resulting in ring cleavage.

The factors controlling the pathways actually followed are quite subtle. In the case of 1,2,2,6,6-pentamethyl-4-oxothianium tetrafluoroborate, treatment with the metal halides KCl or KBr *in the solid state* gave the products of β-elimination, but use of KI under the same conditions removed the *S*-methyl group. In aqueous solution all three gave ring cleavage products only ⟨87NKK1359⟩.

Substituent migration in an intramolecular sense may take place either by a Stevens type rearrangement, or in a [2,3] sigmatropic shift of allylic substituents. In both cases the reaction requires deprotonation of an endocyclic α-methylene, and is therefore facilitated by appropriately sited electron-withdrawing groups. While the simple 1,2-shift gives only moderate yields, the sigmatropic rearrangement is quite efficient. Equations (43) and (44) illustrate the two processes ⟨88TL6005, 90T6501⟩.



(43)

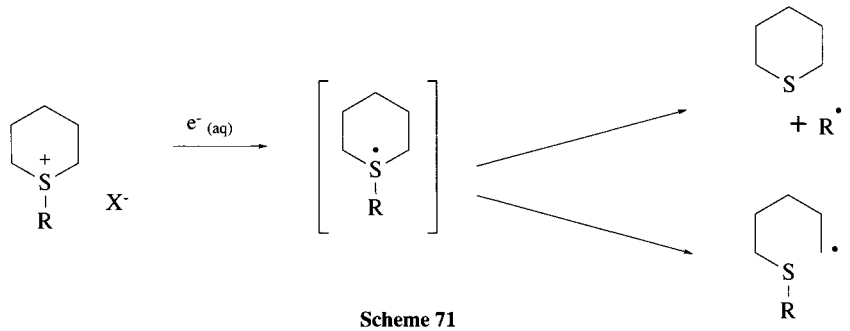


(44)

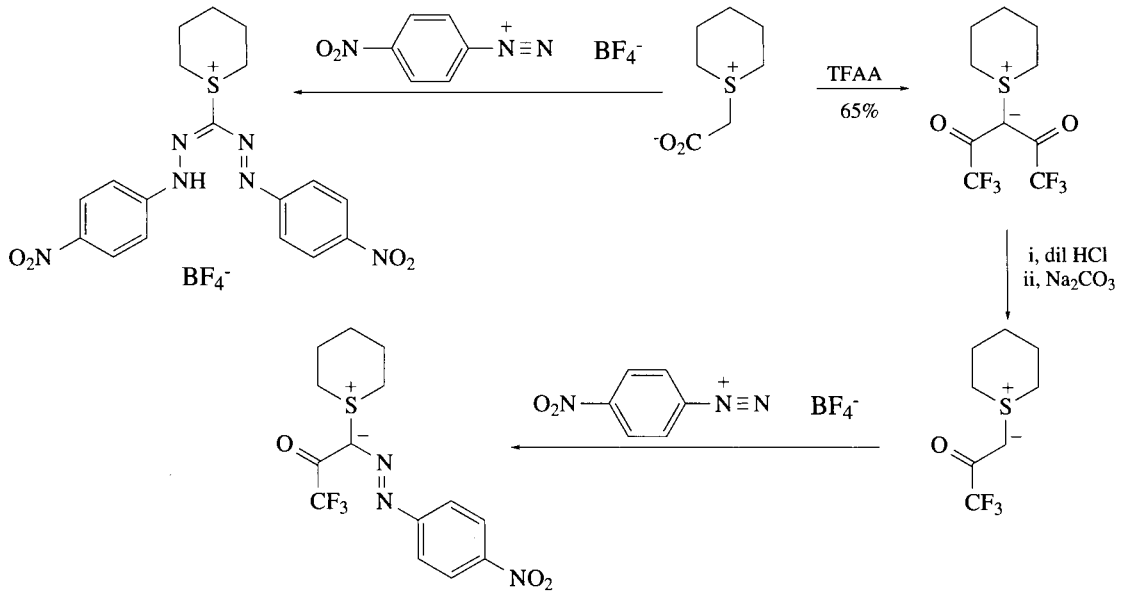
A third process that can remove a substituent from a sulfonium center is reduction. In fact, the principal course of interaction of hydrated electrons in aqueous systems (generated by pulse radiolysis techniques) is ring cleavage rather than ejection of methyl or ethyl radicals (Scheme 71). It is uncertain if larger *S*-substituents would be lost more easily, and thereby afford products in which the ring is retained. Rate constants for the one electron reduction with ring cleavage correlate with the inductive effect of the exocyclic substituent, and lie in the range 10^{-9} to 10^{-10} L mol^{-1} s^{-1} ⟨82JA4450, 91JCS(P2)243⟩.

Turning now to reactions in which an alkyl group on a sulfonium center reacts and is retained: processes under this heading all involve the intermediacy of a zwitterionic species, which is trapped by an electrophile, either inter- or intramolecularly. An interesting example of the use of a stable zwitterionic starting material for the creation of new reactive zwitterionic intermediates, and their trapping by electrophiles, is shown in Scheme 72 ⟨87M115⟩. Similar reactions are observed in acyclic sulfonium analogues, but yields are generally greatest in the five-membered thiolanium systems.

Perhaps the most widely reported application of the intramolecular trapping of the zwitterion is to be found in ring expansions generating nine-membered heterocycles. Two stereochemical outcomes of this [2,3]-rearrangement process are possible (Scheme 73), and it has been shown that the



Scheme 71



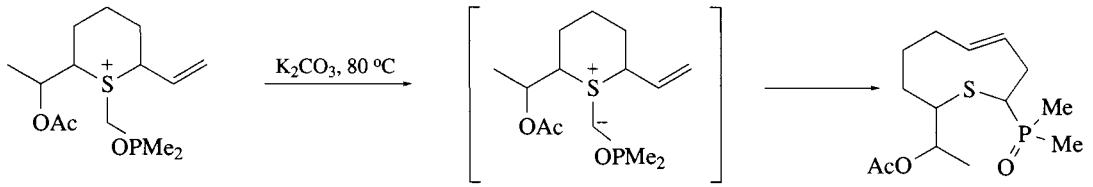
Scheme 72

course of the reaction is dictated by the means by which the zwitterionic intermediate is generated. With a base such as *t*-butoxide, used with a mixture of the *cis* and *trans* precursors of the zwitterions, the product mixture shows evidence of equilibration at the *allylic* hydrogen on C-2 of the ring in the starting thiane. On the other hand, if a base such as LDA is used no equilibration is seen, and the products closely reflect the stereochemical mix of the starting material. Deuterium labeling studies suggest that for *t*-butyllithium the S^+–Me protons are kinetically more acidic than the allylic hydrogens at C-2 by at least 100-fold, implying a nonparallelism of kinetic and thermodynamic acidities ⟨83TL839⟩. Less harsh conditions may be used if the *S*-substituent bears an electron withdrawing group, such as an ester, or a phosphine oxide (Scheme 74) ⟨81JOC5451, 82JA2046⟩.

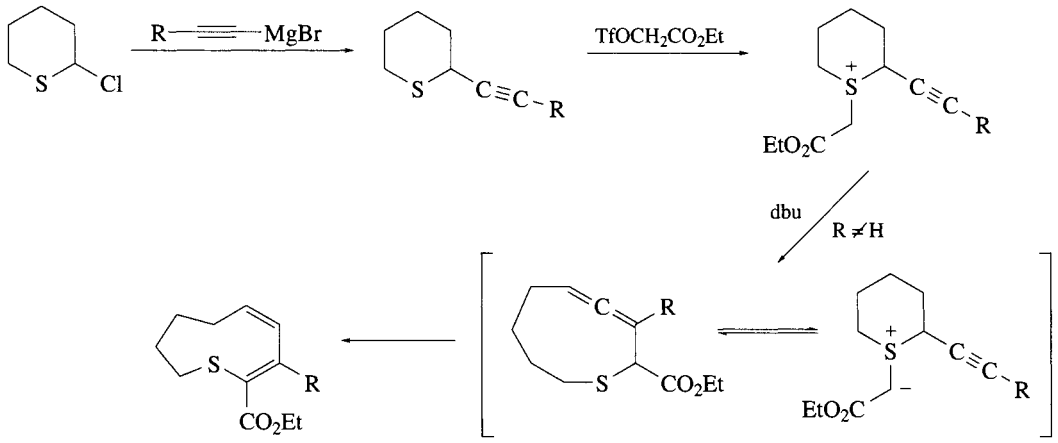
Scheme 73

Clearly the unsaturation required for the [2,3]-sigmatropic process need not be restricted to an alkene and Tsuchiya *et al.* have reported extensive studies on the related reaction involving alkyne groups as outlined in Scheme 75 ⟨86CPB3644⟩.

An obvious extension of the [2,3] rearrangement process is the analogous [3,3] reaction, which would lead to ten-membered systems. The difficulty lies in the generation of the necessary zwitterionic

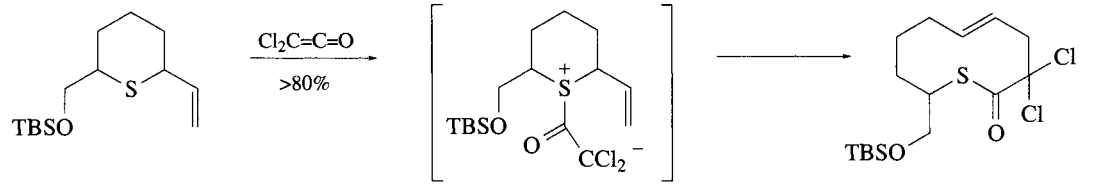


Scheme 74



Scheme 75

intermediate. One successful solution to this problem is to add dichloroketene to an α-vinyl thiane. There is transient formation of the anion (**117**) which efficiently expands to the ten-membered lactone in yields exceeding 80% (Scheme 76) ⟨84JOC1840⟩.



(**117**)

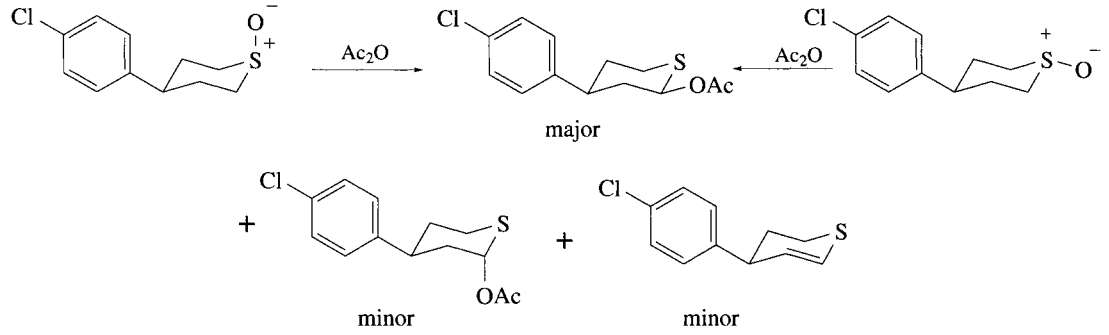
Scheme 76

5.10.6.1.2 Thiane S-oxides

Thiane *S*-oxides are readily reduced to the parent sulfides by a range of agents including $BH_3 \cdot THF$ ⟨93TL363⟩, and chloromethylsilanes/metal ⟨87H(26)2607⟩. While only moderate yields were reported for the borane reduction, the silane method afforded sulfide products in 80–90% recoveries, and was compatible with numerous functionalities including alkenes and hydroxy groups.

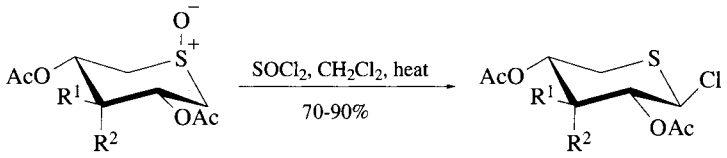
Perhaps the most widely applied reaction of thiane 1-oxides is the Pummerer rearrangement, which represents a synthetically useful entry into substituted thianes. Studies of the rearrangement have been made using acetic anhydride as electrophile, and the details of the mechanism and stereochemistry defined (Scheme 77). Using conformationally fixed 4-(*p*-chlorophenyl)thiane 1-oxides, and labeling with ^2H and ^{18}O, it has been shown that the reaction is *inter*molecular, with a significant kinetic isotope effect (2.8 for the *cis* and 3.4 for the *trans* system). In the presence of acid scavengers (2,6-lutidine or dcc) the product mix is kinetically controlled, with the equatorial acetate

in great preponderance. The product ratio is the same from both isomers of the starting material under all conditions. The rate limiting step is the E_2 elimination of acetic acid from the initially formed acetoxy sulfonium intermediate. If the substrate is made more rigid still, as in the thiadecalins, the preferred product under all conditions becomes the equatorial acetoxy compound ⟨83BCJ270⟩.



Scheme 77

Acetic anhydride is not a particularly efficient initiator of the Pummerer reaction, requiring harsh conditions of temperature and/or time, and the addition of an acid scavenger for more delicate substrates. Other commonly employed electrophiles, which do not suffer such shortcomings are trifluoroacetic anhydride, thionyl chloride and trimethylsilyl chloride. Thionyl chloride has been used to prepare a family of highly functionalized thiosugars, which would otherwise have been difficult of access (Equation (45)) ⟨88CAR(188)227⟩.



(45)

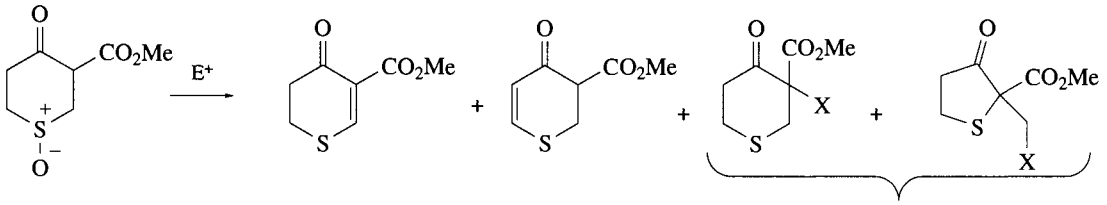
R^1	R^2
CO_2Et	CN
CN	CN
$CONH_2$	CN
NO_2	H

If the required product is the vinyl sulfide (see Scheme 77), trimethylsilyl chloride is usually the reagent of choice: the trimethylsilanol by-product is nonacidic, and is apparently too bulky to successfully add to the sulfenium intermediate. The presence of other substituents may further complicate the course of the reaction, and Scheme 78 shows some of the side reactions that have been observed. A thiiranium intermediate (**118**) may be invoked to explain the appearance of the "abnormal" products (Scheme 79) ⟨84JCS(P1)2549⟩.

While the Pummerer reaction is an example of a redox process involving a 1,2 oxygen shift, Scheme 80 shows a 1,3 example. The reaction is particularly facile if the α-substituent is a P^{III} species, when it is also catalyzed by iodine as shown and there is a *cis* relationship of the oxygen and phosphorus groups. The bicyclic structure (**119**) is a likely intermediate. In the case of the *trans* system, oxygen transfer is some 200-fold slower, and occurs overwhelmingly by an intermolecular mechanism ⟨81JOC5253⟩.

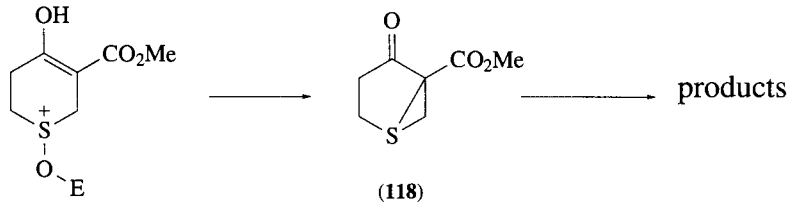
5.10.6.1.3 Thiane sulfilimines

While sulfilimines (**120**) are closely analogous to the sulfoxides, they have received much less attention. Easily prepared by the addition of a nitrene to a thiane, or through reaction with an *N*-halo reagent such as chloramine-T, they are stabilized by the presence of an electron-withdrawing group (acyl or arylsulfonyl) on the nitrogen.



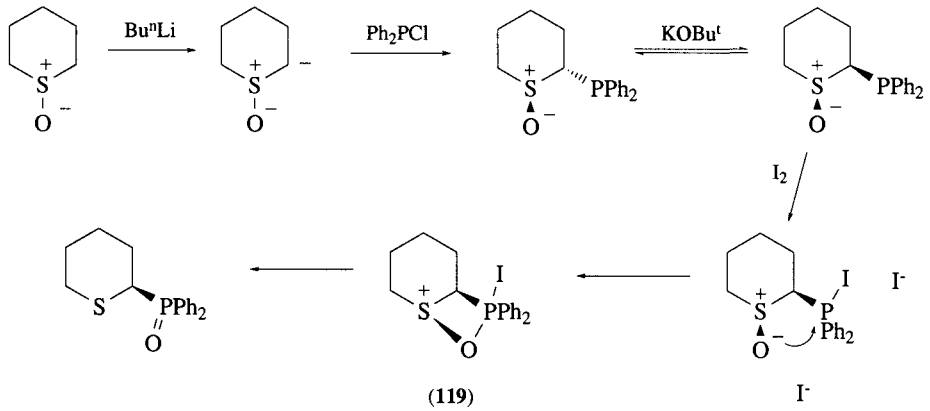
E^+:				
Me_3SiCl	74%	13%	12%, X = Cl
Ac_2O	–	–	87%, X = OAc
NCS (0 °C)	24%	7%	58% ,X = Cl
NCS (CH_2Cl_2, heat)	65%	27%	–

Scheme 76



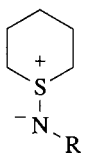
(**118**)

Scheme 79



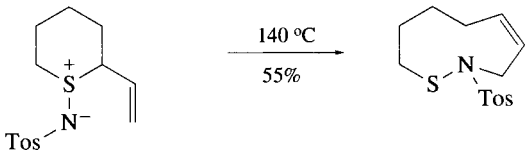
(**119**)

Scheme 80



(**120**)

The S—N bond may be cleaved reductively by P_4S_{10} or cyanide; transfer of the nitrogen substituent occurs easily to phosphines, and less cleanly to thiols. The most synthetically significant reaction of these species is their ring expansion to thiazonines via a [2,3]-sigmatropic rearrangement (Equation (46)) ⟨86CPB3682⟩.

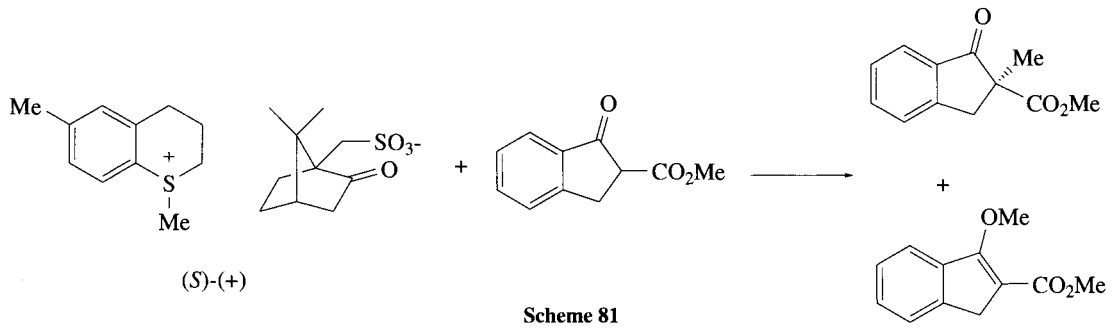


(46)

5.10.6.2 Dihydrobenzothiopyrans

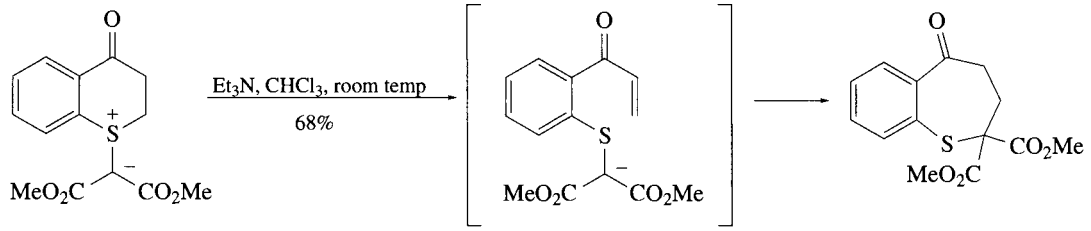
5.10.6.2.1 Dihydrobenzothiopyran sulfonium salts

Just as the use of *S*-alkyl thianium salts as alkylating agents has been investigated, so has the use of the corresponding *S*-alkyl dihydro-1-benzothiopyranium species. Under very mild conditions a 6 : 1 preference for *C*- over *O*-alkylation (in >90% total yield) has been observed in the alkylation of an indanone carboxylate. The use of a chiral sulfonium salt gave products with a small chiral induction, the degree of which varied inversely with temperature, rising from 4.5% *ee* (80% yield) at 25 °C to 8.9% *ee* (49% yield) at −28 °C. Over the same temperature range the yield of *O*-alkylated material only changed from 19 to 16% (Scheme 81) ⟨89JOC2374⟩.



Scheme 81

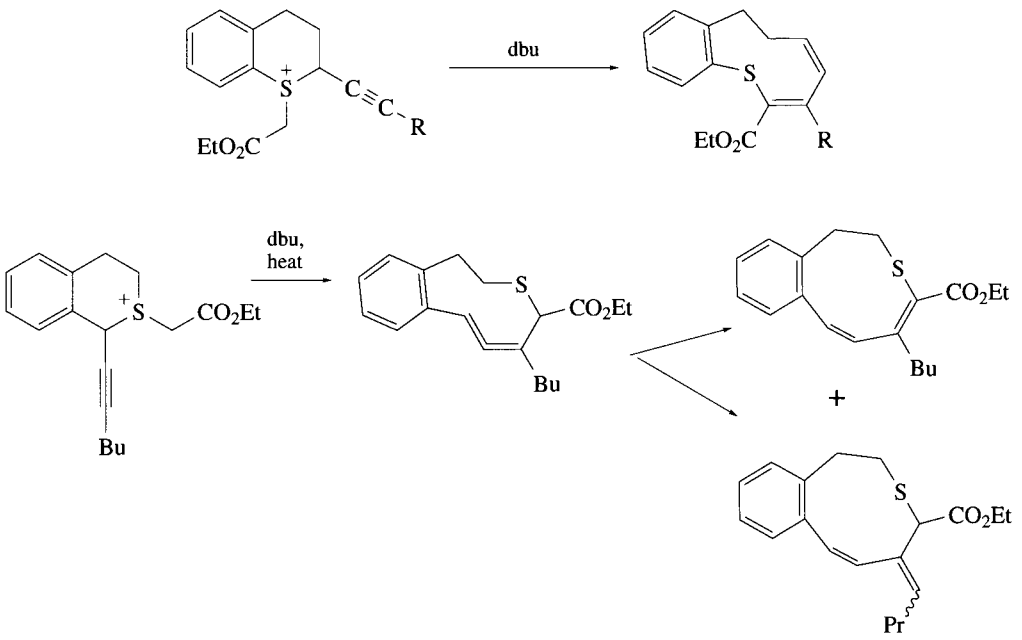
An important advantage of the use of a cyclic sulfonium salt as an alkylating agent over acyclic reagents is the chemoselective transfer of the exocyclic carbon center to the nucleophile. However, the presence of other functionality on the thiopyran or the *S*-substituent can markedly affect the course of such reactions. In particular, base-catalyzed ring expansion can be a facile process. For example, thiochroman-4-one bis-methoxycarbonylmethylides ring expand on base treatment, while no reaction is seen in the absence of the carbonyl group (Scheme 82). Substitution at the 2-position of the thiin ring has a marked influence on the rate of this reaction, as does the solvent. Disubstitution prevents the ring closure process, and only ring opened materials are recovered ⟨81JCS(P1)2978⟩.



Scheme 82

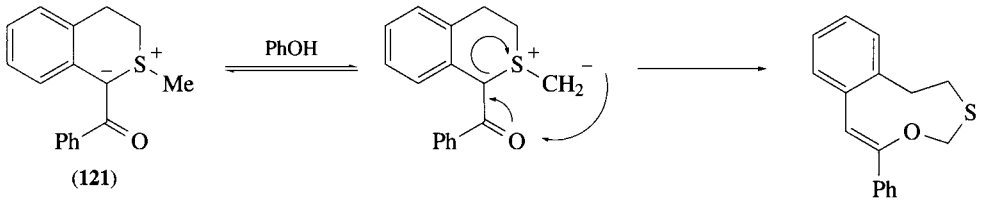
Bicyclic ring-expanded products are obtained by a [2,3] sigmatropic rearrangement in high yield from 1- and 2-thiochromans substituted by alkyne groups adjacent to the sulfur, on treatment with base. Only one diene is isolated from the former, but the 2-benzothiopyrans behave somewhat differently. The first-formed allenes were isolable in some cases, and two tautomeric products were obtained (Scheme 83) ⟨86CPB3644⟩.

Another intriguing example of ring expansion is found in the reaction of the zwitterionic sulfonium compound (**121**) with phenol. Rather than the alkylation or acylation of the phenoxide ion, as might be expected, the major product is a ring expanded benzoxathionine. The phenol catalyses the



Scheme 83

prototropic conversion of the initial betaine into the methylide form, which undergoes a [2,3] sigmatropic rearrangement (Scheme 84). Other weak acids such as succinimides also favor the ring expansion process ⟨82TL2597⟩.



Scheme 84

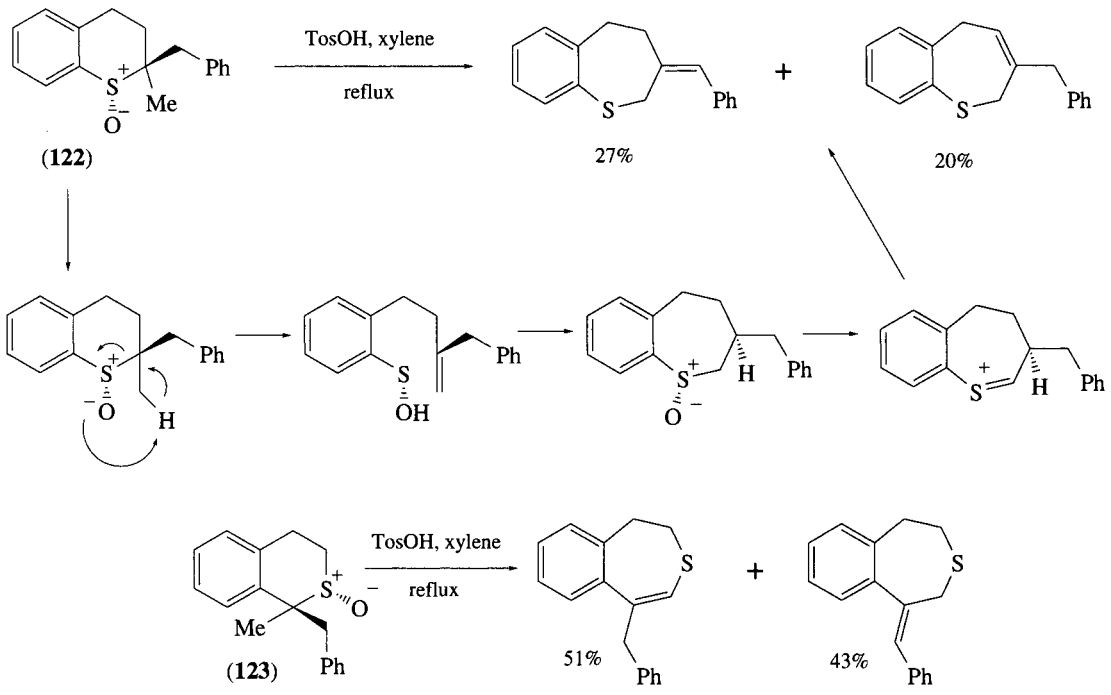
5.10.6.2.2 Dihydrobenzothiopyran sulfoxides

The Pummerer reaction of dihydrobenzothiopyran sulfoxides bearing α-hydrogen atoms with acetic anhydride gives rise to the expected products: α-acetoxydihydrobenzothiopyrans or, following elimination of acetic acid, benzothiopyrans. Blocking the α-position by dialkylation diverts the course of the reaction and ring expanded products are obtained. Scheme 85 shows the toluenesulfonic acid-catalyzed rearrangement of dihydro-1- and 2-benzothiopyrans (**122**) and (**123**). The reactions are stereospecific, and in each case the first step is a *syn*-elimination of a sulfenic acid (involving the carbon center *cis* to the sulfoxide oxygen), and its addition to the newly generated alkene to produce a tetrahydrobenzthiepin sulfoxide. Subsequent normal Pummerer reactions give the observed products ⟨84CPB2571⟩.

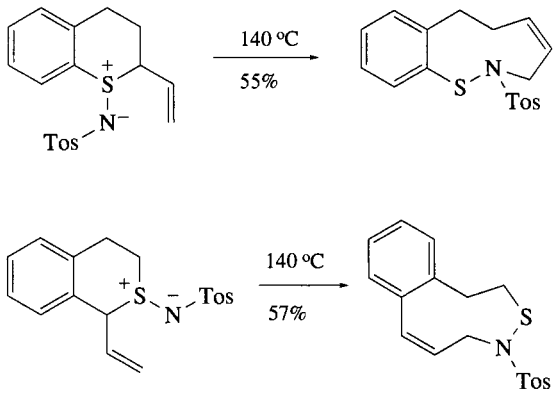
5.10.6.2.3 Dihydrobenzothiopyran sulfilimines

Dihydrobenzothiopyran sulfilimines undergo reactions closely similar to their isoelectronic methylide analogues, for example the nitrogen atom may be alkylated, creating new sulfilimines or azasulfonium salts. Vinyl substitution at the carbon α to sulfur enables [2,3]-sigmatropic ring expansion to benzothiazonine products (Scheme 86) ⟨86CPB3682⟩.

More interesting is the divergence of behavior of thiochroman-4-one *N*-tosylsulfilimines under



Scheme 85



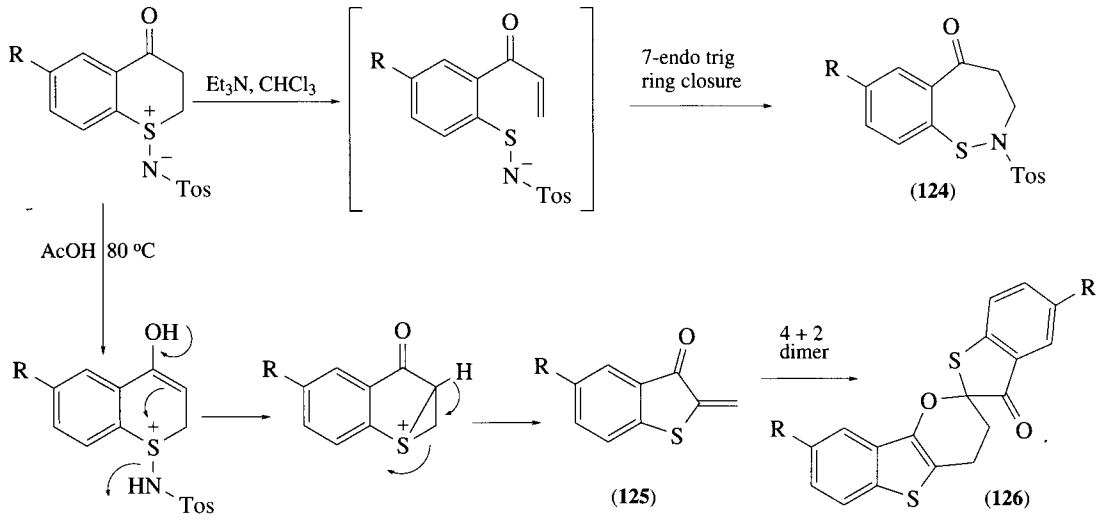
Scheme 86

base and acid conditions (Scheme 87). In base, β-elimination affords the intermediate sulfenamide, which may be isolated if the 2-position of the original heterocycle is substituted. Otherwise the ring closure to benzothiazepinone (**124**) occurs in very high yield. Under acid conditions, the S—N bond is cleaved and a benzothiophenone (**125**) is formed, probably via a thiiranium species. In sterically unhindered cases (**125**) may dimerize to (**126**) (Scheme 87) ⟨83MI 510-04⟩.

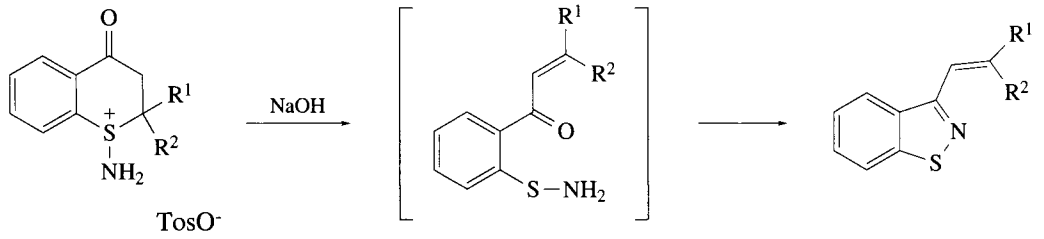
If the sulfilimine is not substituted on nitrogen, a different product may be observed on base treatment, namely a vinylbenzisothiazole (Scheme 88) ⟨83MI 510-05⟩.

5.10.6.3 Dihydrothiopyrans

Derivatives of dihydrothiopyrans modified at the sulfur are far less common than in the case of the saturated systems. The sulfoxide of the parent is known, and can be prepared under very mild

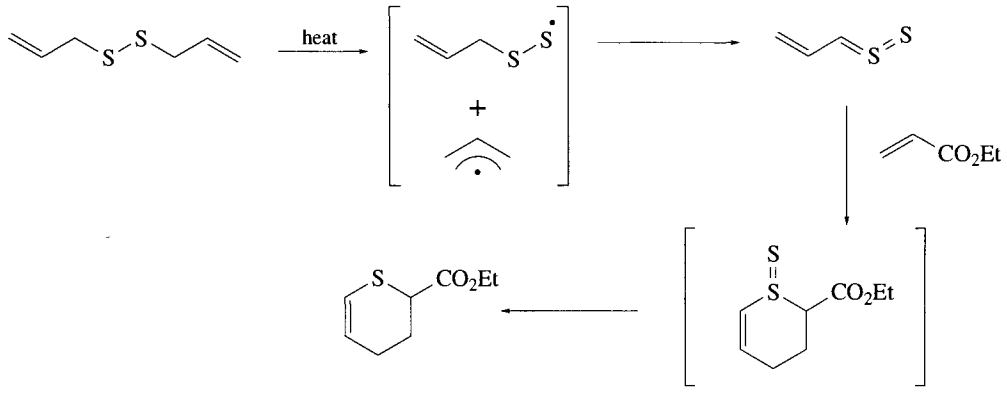


Scheme 87



Scheme 88

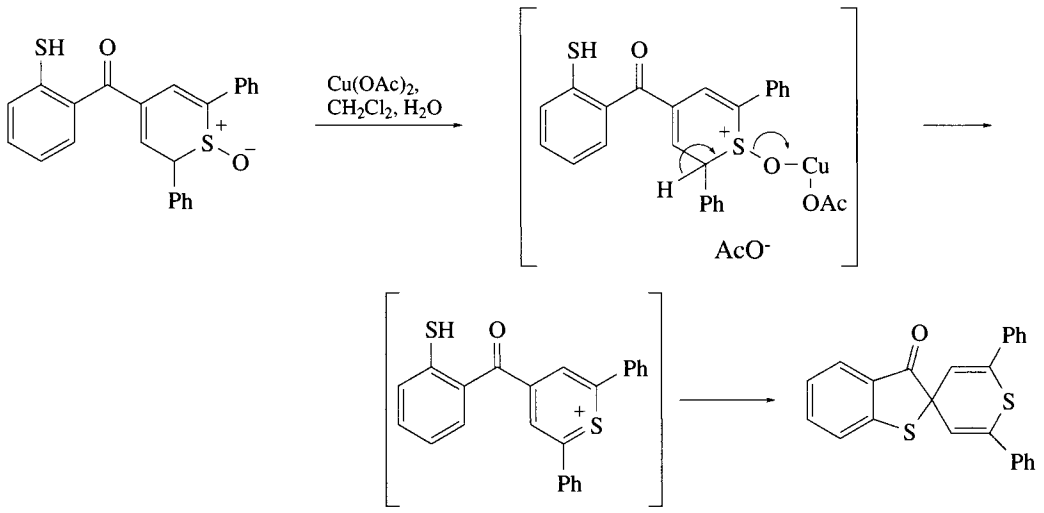
conditions. The corresponding *S*-sulfide compound has been postulated as a transient intermediate in the Diels–Alder cycloaddition of thioacrolein *S*-sulfide with acrylates, which extrudes elemental sulfur under the reaction conditions (Scheme 89) ⟨88JA7813⟩.



Scheme 89

5.10.6.4 Thiopyrans

Derivatives of the thiin ring system substituted on the sulfur are restricted to sulfoxides, and the chemistry reported for that substituent is only the Pummerer reaction. However the application of that transformation that has been described is interesting, leading to a 4-substituted product rather than the more usual 2-substituted compound (Scheme 90) ⟨84JOC5143⟩.

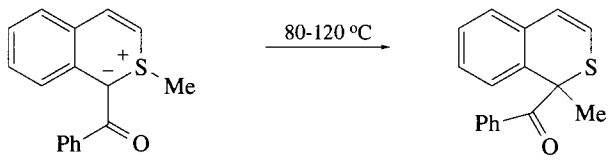


Scheme 90

5.10.6.5 Benzothiopyrans

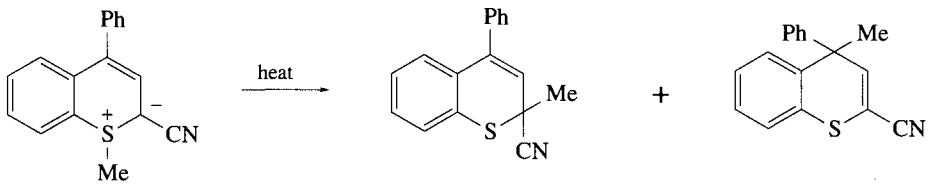
5.10.6.5.1 Benzothiopyran sulfonium salts

S-Alkyl or aryl zwitterions stabilized by electron-withdrawing groups have been prepared in the 1*H*-2-benzothiopyran series. Thermolysis (refluxing benzene or toluene) leads to the 1,2-transfer of a methyl group from sulfur to the adjacent carbon atom in high yield. Longer alkyl groups do not migrate, but undergo *β*-elimination under the same conditions. An *S*-phenyl moiety will also migrate, but only in low yield (Equation (47)) ⟨83JCS(P1)2913⟩.

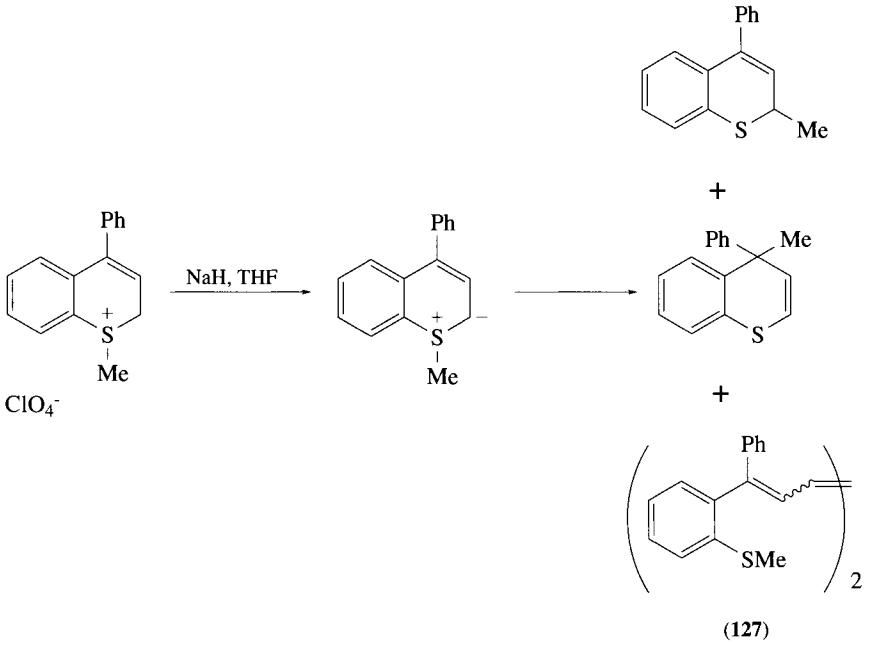


(47)

The chemistry of the 2*H*-1-benzothiopyran based sulfonium systems has been extensively investigated only since the mid-1980s. In the absence of stabilization by electron-withdrawing groups, base treatment leads to a range of products derived from 1,2- and 1,4-methyl migration, and dimerization (Scheme 91). Modification of the conditions of the reaction such that the presumed ylide coexists with the sulfonium species diverts the course of the reaction overwhelmingly in favor of the dimer (**127**) (68% yield), suggesting that it is derived from nucleophilic attack by the ylide upon the sulfonium salt, rather than via a carbene type intermediate. A second phenyl group, at position 2, modifies the reactivity to base. No *S*-methyl transfer is observed, only ring opening and dimerization. The ring opened products are favored by hydroxylic solvents, resulting from nucleophilic attack by alkoxide at C-2. With powerful electron-withdrawing groups at C-2 (particularly nitrile), treatment with base affords stable ylides, which have been termed "thianaphthalenes," in virtually quantitative yield. While these materials are quite stable, prolonged heating in acetone (50 h at reflux) leads to the 1,2- and 1,4-rearrangement products in 40% total yield (Equation (48)) ⟨88CPB3816⟩. The nonbenzannelated analogues behave in a closely similar fashion.



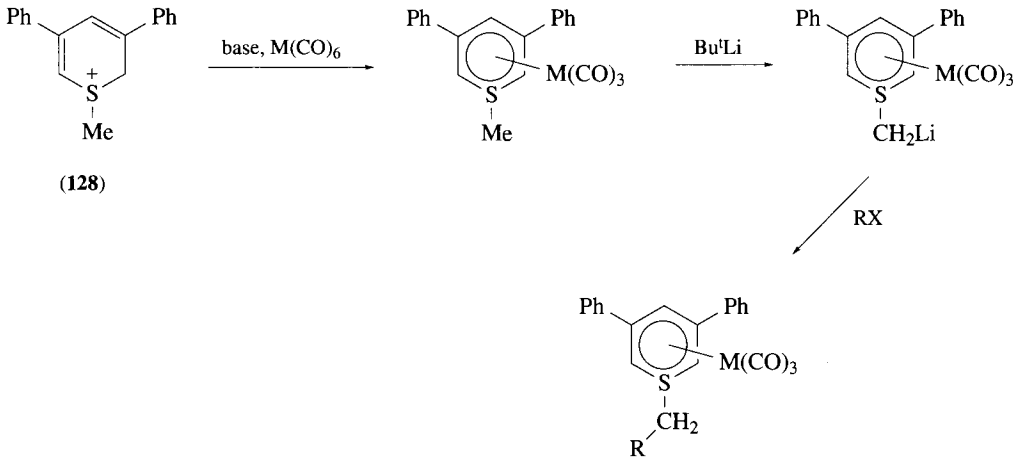
(48)



(127)

Scheme 91

Metallation of the methyl substituent of 2*H*-thiopyranium salt (**128**) is possible following complexation of the endocyclic ylide with tricarbonylchromium, -molybdenum, or -tungsten groups. The powerful base *t*-butyllithium is necessary, but once lithiated the complexes can be efficiently alkylated, silylated, or germylated (Scheme 92) ⟨82CB1775⟩.



(**128**)

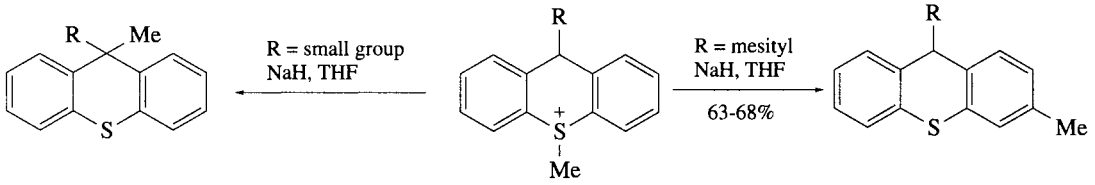
Scheme 92

5.10.6.6 Thioxanthenes

5.10.6.6.1 Thioxanthenium salts

S-Methylthioxanthenium tetrafluoroborate has been investigated as a solid state methylating agent for potassium salts of a wide range of carboxylic acids ⟨88YZ733⟩. Treatment of such thioxanthenium salts with non-nucleophilic bases leads to 1,4 shift of the sulfur substituent, giving 9-substituted thioxanthenes. However, if there is a particularly bulky substituent already at position

9, such as a mesityl group, an alternative migration is observed, placing the methyl group at C-3 (Scheme 93) ⟨84JOC2472, 88JCS(P1)1209⟩. However the 1,4 sigmatropic rearrangement of *S*-aryl substituents to position 9 is a facile process even in the presence of a 9-phenyl group ⟨92MI 510-04⟩.



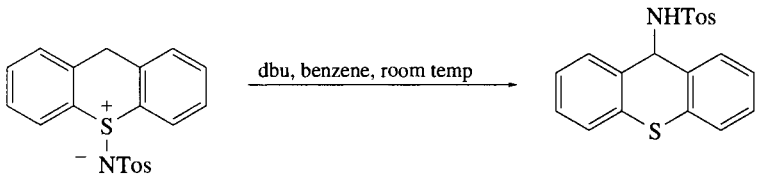
Scheme 93

5.10.6.6.2 Thioxanthene sulfoxides

Sulfoxides of thioxanthenes under Pummerer conditions efficiently form the thioxanthylium salts. The S—O bond may be cleaved electrolytically and a polarographic investigation showed a strong dependence of reduction potential on pH, varying between −0.609 V at pH 1.2 to −1.345 V at pH 12.7. Clearly protonation facilitates the reduction of the sulfoxide ⟨89PS(42)139⟩.

5.10.6.6.3 Thioxanthene sulfilimines

N-Tosyl thioxanthene sulfilimines may be reduced electrolytically as for the related sulfoxides ⟨89PS(42)139⟩. Rearrangement of the sulfilimines under acid conditions is not observed. However, treatment of the *N*-tosylsulfilimines of thioxanthenes with catalytic dbu in aprotic solvents brings about migration of the nitrogen group to position 9, presumably through deprotonation of C-9, elimination of the sulfur substituent with formation of a thioxanthylium species and readdition of the substituent (Equation (49)) ⟨82CPB4069⟩.



(49)

5.10.7 RING SYNTHESES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

5.10.7.1 Introduction

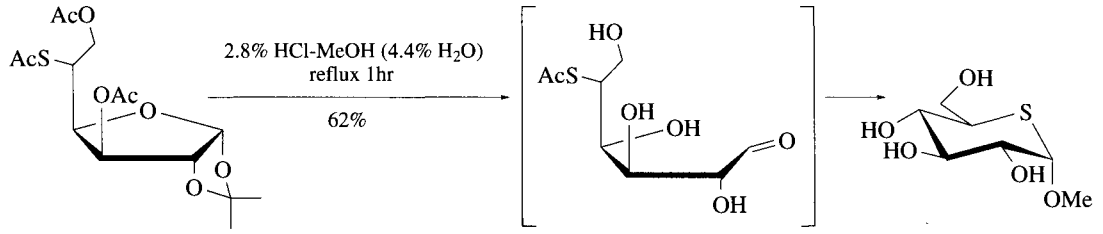
De novo ring synthesis is the usual means of access to thiopyrans, reflecting the few natural sources of such systems. Rings may be formed by closure α, β, or γ to the sulfur atom ([6 + 0] cyclization), or by simultaneous closure of two bonds between separate fragments. Of this latter method three cases may be recognized, defined by the number of atoms in each unit: [5 + 1], [4 + 2], and [3 + 3]. This last combination, and the conceptually possible 3-component couplings [1 + 1 + 4], [1 + 2 + 3], and [2 + 2 + 2] do not appear to have been realized in the formation of thiin systems.

5.10.7.2 Thianes

5.10.7.2.1 [6 + 0] Cyclization

Ring formation by closure of the bond α to the sulfur is well exemplified. Nucleophilic attack by the heteroatom on electrophilic centers has many variants, differentiated by the nature of the electrophile. Essentially the same method can be used to form sulfonium and *S*-oxidized derivatives. The electrophilic group may be an alkyl halide, an allylic halide (S_N2' attack), a carbonyl group, a (protonated) alkene, a carbene, and so on. The kinetic parameters for cyclizations of ε-halopentyl sulfides leading to sulfonium derivatives of thiane have been measured; as might be predicted, the major factor affecting the rate of closure is the halide leaving group (I > Br > Cl), while the bulk of the sulfur substituent exerts rather little influence. Changing the solvent from acetonitrile to methylene chloride has little effect ⟨88PS(40)99⟩. Similar observations may be expected for the formation of the underivatized thianes.

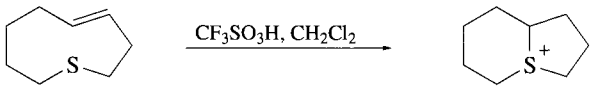
Closure of a thiol to a carbonyl group is the preferred route into thiosugar analogues. Typical of such preparations is the conversion of the 5-thiofuranose (**129**) (derived from 3-*O*-acetyl-1,2 : 5,6-di-isopropylidene-α-D-glucofuranose) into a thioglucoside on treatment with methanolic hydrogen chloride (Scheme 94) ⟨90JCS(P1)2763⟩.



(**129**)

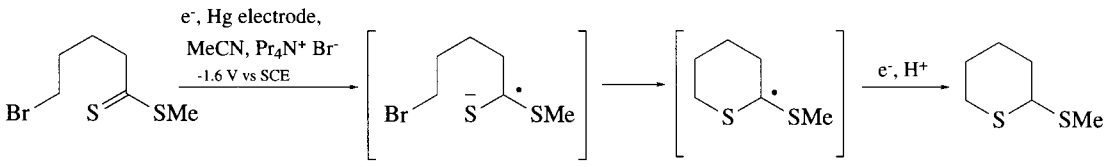
Scheme 94

Cyclization of sulfur onto alkenes under acid catalysis is frequently seen as a transannular process in medium ring systems, generating thioniabicyclo[4.3.0]nonane salts from thiacyclonon-4-enes (Equation (50)), or *cis*-1-thioniabicyclo[3.3.0]octanes from the respective cyclooctenes. Yields can be high, and the conversion is totally stereospecific, giving rise to only *cis*-fused products at the ring junction ⟨82JOC2861⟩.



(50)

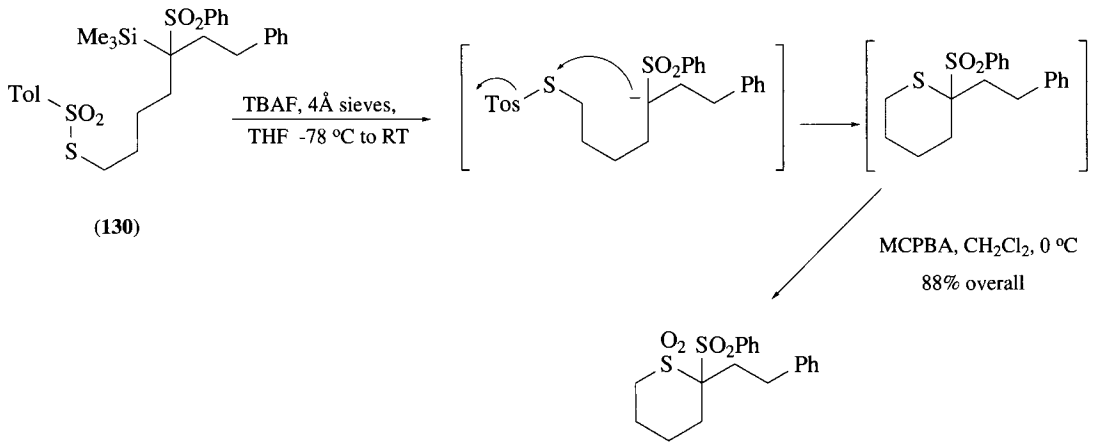
An interesting variant upon the use of a thiol as the nucleophile in these ring closures is the employment of a thiolate radical anion. Cathodic reduction of a dithioester inserts an electron into the C=S link, and cyclization follows. Though the yield is only modest (ca. 30%), and product composition sensitive to solvent, the reaction may have potential in synthesis (Scheme 95) ⟨90CB1733⟩.



Scheme 95

The reactions discussed above all cast sulfur in a nucleophilic role, but it may also behave electrophilically under appropriate conditions. Reaction of alkyllithium agents with disulfides or sulfenimides is a common sulfenylating process, but to use it in thiane preparation requires that the generation of the carbanion be compatible with the existence of an activated sulfur center. Fluoride ion mediated desilylation is a suitably mild source of (stabilized) carbanions, and Scheme 96 illustrates its application to the formation of tetrahydrothiopyrans. Here the sulfur atom is rendered

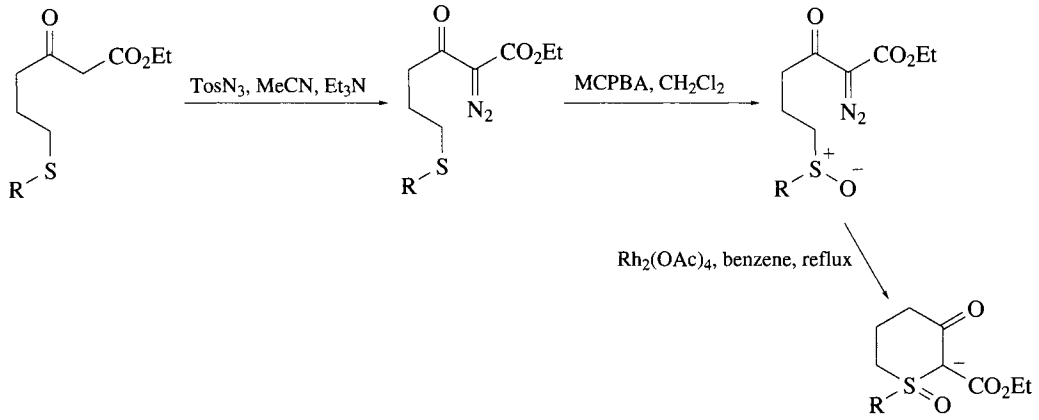
electrophilic by conversion into the tosylate (**130**), from which toluenesulfinate acts as a leaving group. Interestingly, the first formed 2-arylsulfonyl thianes were too unstable to be isolated, and had to be oxidized *in situ* to the bis-sulfones, which could then be fully characterized ⟨90JA8084⟩.



(**130**)

Scheme 96

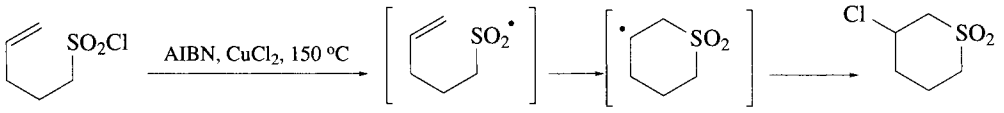
Turning from polar, heterolytic chemistry brings us to radical-based methods. Since the early 1980s thianes have begun to be prepared by homolytic type chemistry. Both carbenes and sulfur centered radicals have been used. Rhodium carbenoids may be trapped intramolecularly by sulfur centers such as sulfoxides, in reactions formally analogous to the formation of sulfoximides from electron deficient nitrenes and sulfoxides. The products are sulfoxonium ylides, and are formed in yields up 84%. Scheme 97 shows the essence of this preparative method, which tolerates a range of substitution on the carbon chain. Unsaturation in the group "R" does not interfere, even when it is an allyl unit ⟨90T6525⟩.



Scheme 97

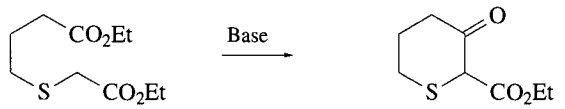
An example of the use of a sulfur centered radical is to be found in Scheme 98. Treatment of sulfonyl chlorides with a variety of radical initiators leads to the formation of sulfonyl radicals, which may be trapped by an appropriately positioned alkene, as in pent-4-enesulfonyl chloride. The process is not efficient, being in competition with the loss of sulfur dioxide and the generation of allyl radicals, and so the yield of cyclized products was only of the order of 20%. However the bulk of the sulfur containing products were predominantly derived from 6-*endo* cyclization, rather than the perhaps more commonly encountered 5-*exo* mode ⟨90TL6433⟩.

Ring closure of an acyclic precursor by completion of a bond β or γ to the sulfur is much less well known than the α closures described above. The earliest reported examples were based on Dieckmann-type reactions, as shown in Equation (51), while a related variant is given in Equation (52) ⟨85JCS(P2)833⟩. With more rigid systems chiral induction may be achieved in some cases. Scheme

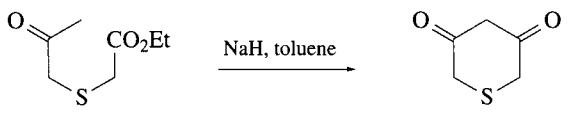


Scheme 98

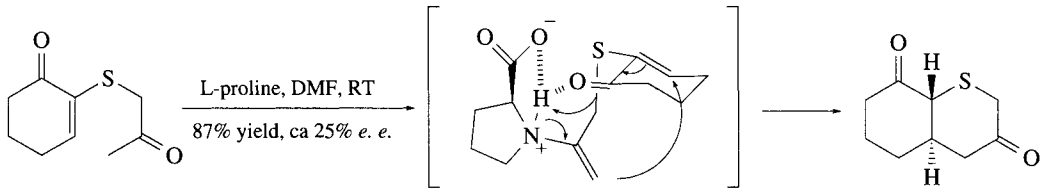
99 shows the use of a proline-catalyzed Michael addition step leading to products with ca. 25% *ee* ⟨89JOC2274⟩.



(51)

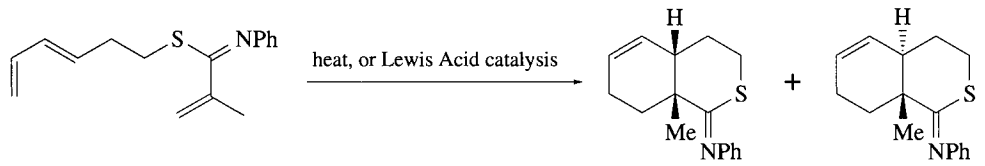


(52)



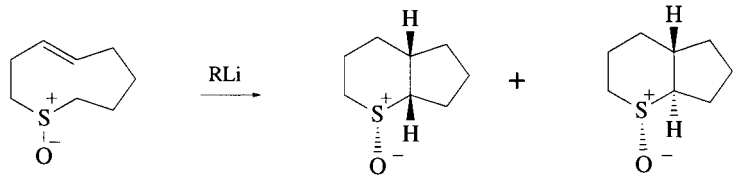
Scheme 99

If the acyclic precursor to a thiane contains appropriately positioned double bonds, an intramolecular Diels–Alder reaction can generate the heterocycle as shown in Equation (53). Thermal cyclization affords an 80 : 20 mixture of the *cis*- and *trans*-fused bicycles, but Lewis acid catalysis can be used to enhance the selectivity to essentially 100% *cis*. The reaction is high yielding, and the products are versatile precursors for a range of further sterically defined materials ⟨84TL3583⟩.



(53)

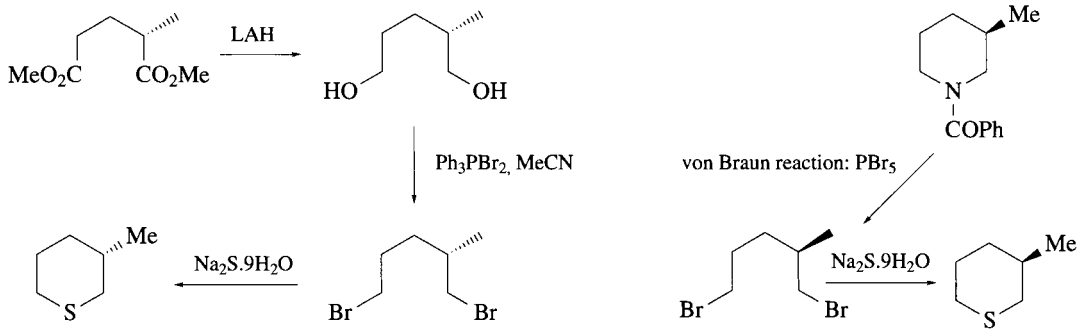
The acid-catalyzed transannular addition of sulfur to the alkenic bond in thiacyclonon-4-enes, generating bicyclic sulfonium compounds was described above. An equivalent anionic process is found in the cyclization of the α-lithio sulfoxides and sulfones of the same thiacyclonon-4-ene, proceeding via the highly unusual addition of a carbanion to an *un*activated double bond to afford the saturated bicycles (**131**-*cis*) and (**131**-*trans*) (Equation (54)). This very unusual reaction is facile and high yielding providing the double bond has the (*E*) configuration. It is insensitive to variation of solvent and concentration, and the presence of lithium salts does not exert any effect. Alkyllithium bases favor the ring closure, while lithium silylamides give substantially slower reaction rates. Approximately equal amounts of *cis*- and *trans*-fused bicycles are obtained initially, but the base permits epimerization until the final ratio is ca. 15 : 1 in favor of the *trans* form. Cyclization of the corresponding thiacyclodecene is equally facile and high yielding, giving products whose stereochemistry may be predicted from that of the medium ring precursor. If the sulfoxide is used the ratio is ca. 100 : 0 in favor of the *trans* system and ca. 9 : 1 *trans* : *cis* in the case of the sulfone, presumably reflecting the easy epimerization permitted by the oxidized sulfur and conformational influences of the sulfur substituents ⟨86JOC4880, 88JOC5689⟩.



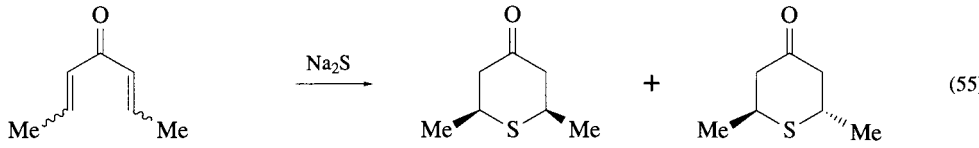
(131-*cis*) (131-*trans*) (54)

5.10.7.2.2 [5 + 1] Cyclization

Synthesis of thianes from two fragments has long been known. The most commonly applied method is a [5 + 1] coupling in which the "1" component is sulfide ion. It is a versatile reaction, limited only by access to the suitably functionalized C5 unit. A typical example of this methodology is the preparation of the enantiomers of a 3-substituted thiane. Scheme 100 shows the formation of the precursor dibromo compounds by bromination of a diol in one case, and through a von Braun functionalization of an amide in the other ⟨84HCA434⟩. Analogous reactions are possible in which the di-electrophile is a double Michael acceptor, or a mixed Michael acceptor/nucleofugic system. The double conjugate addition approach has enjoyed considerable popularity, as the required C5 component is very readily available. One example, reportedly displaying a degree of diastereoselectivity, is shown in Equation (55) ⟨87IZV1540⟩.



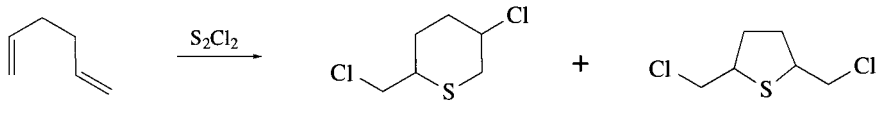
Scheme 100



(55)

The source of the sulfur nucleophile in these reactions is usually in the form of a metal sulfide, but such agents have a number of drawbacks. In particular they are basic, and frequently have poor solubility in organic systems. An interesting alternative that has been reported is the use of carbon–sulfur cathodes in electrolytic reactions, which have been shown to sulfurate a wide range of activated alkenes. While the yield of ring closed material from a "double Michael" type system was only modest, with further optimization the method may become of synthetic importance ⟨90BSF427⟩.

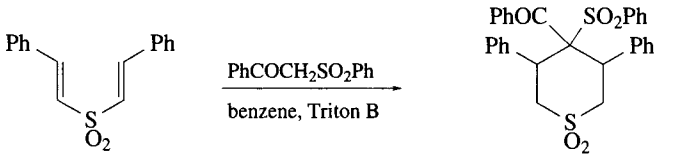
[5 + 1] Cyclization of unactivated dienes requires an electrophilic sulfur source. A good example of such a species is sulfur monochloride, and Equation (56) shows its use in this way. At equilibrium the product mix is about 2 : 1 in favor of the thiopyran ⟨83ZOR48⟩.



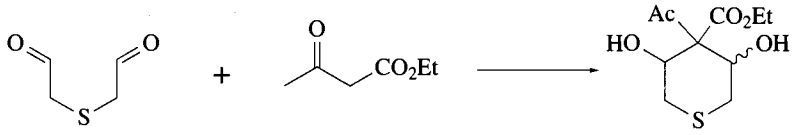
(56)

Less common are the ring formations where the "1" component is a carbon atom, but a number

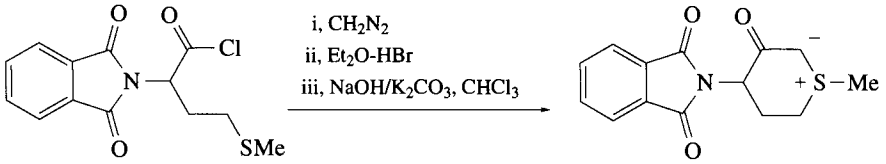
of variants are known. The most frequently used couples a gem-bifunctional alkylating agent with a bis-electrophile, and the most frequently used gem-bifunctional alkylators are malonates. As for the bis-electrophiles, dihalides and double Michael acceptors are best exemplified. Two somewhat more unusual variants are shown in Equations (57) and (58) ⟨87JCR(S)94, 91SUL123⟩. Even more unusual is the use of diazomethane, which functions (Equation (59)) as a geminal nucleophile/electrophile, cyclizing the protected methionine acid chloride to a sulfonium ylide ⟨89IZV974⟩.



(57)



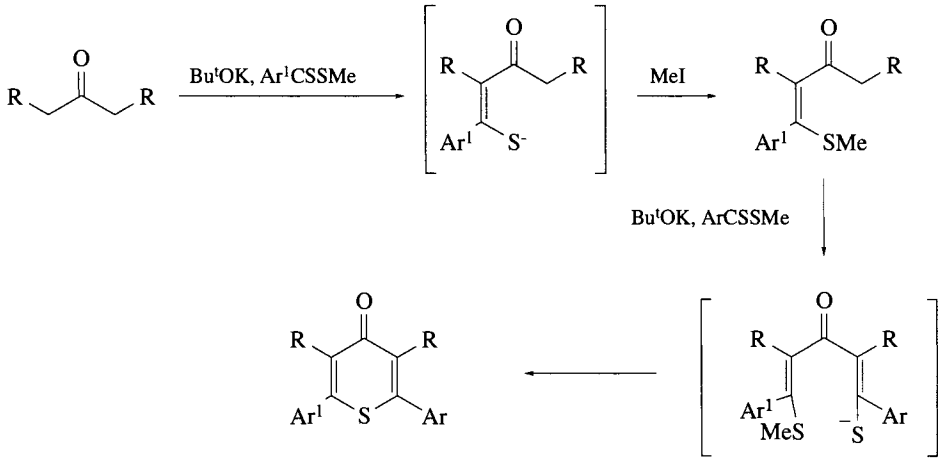
(58)



(59)

Another interesting example uses dithioesters as electrophilic/nucleophilic bifunctional centers, introduced by two thio-Claisen condensations. Yields are high (up to 90%) and the reaction is reportedly quite versatile (Scheme 101) ⟨93JOC3042⟩.

The synthesis of tetrahydrothiopyran-4-ones, -4-carboxaldehydes, and -4-carboxylates has been reviewed ⟨89AKZ99⟩.



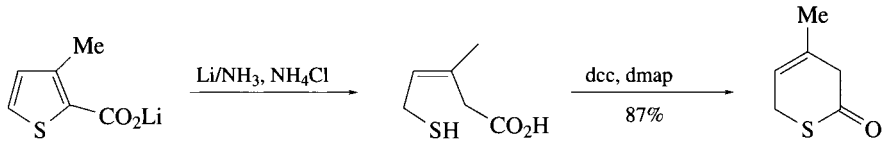
Scheme 101

5.10.7.3 Dihydrothiopyrans

5.10.7.3.1 [6+0] Cyclization

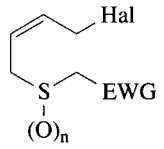
The *de novo* synthesis of 3,4- of 3,6-dihydro-2*H*-thiopyrans has received an enormous amount of attention since the early 1980s. However, the bulk of that research effort has been directed at the Diels–Alder type of entry into the system. Synthesis by closure of an acyclic precursor is unusual,

but the reactions employed are interestingly diverse. Formation of a bond α to sulfur is limited by access to a suitable precursor, but (*Z*)-5-thiolpent-3-enoic acids may be prepared by lithium/ammonia reduction of thiophene-2-carboxylates, and subsequent lactonization affords the dihydrothiopyranones (Scheme 102) ⟨83JOC3206⟩. Clearly the stereochemistry of the alkene has a crucial influence on the outcome of the reaction.



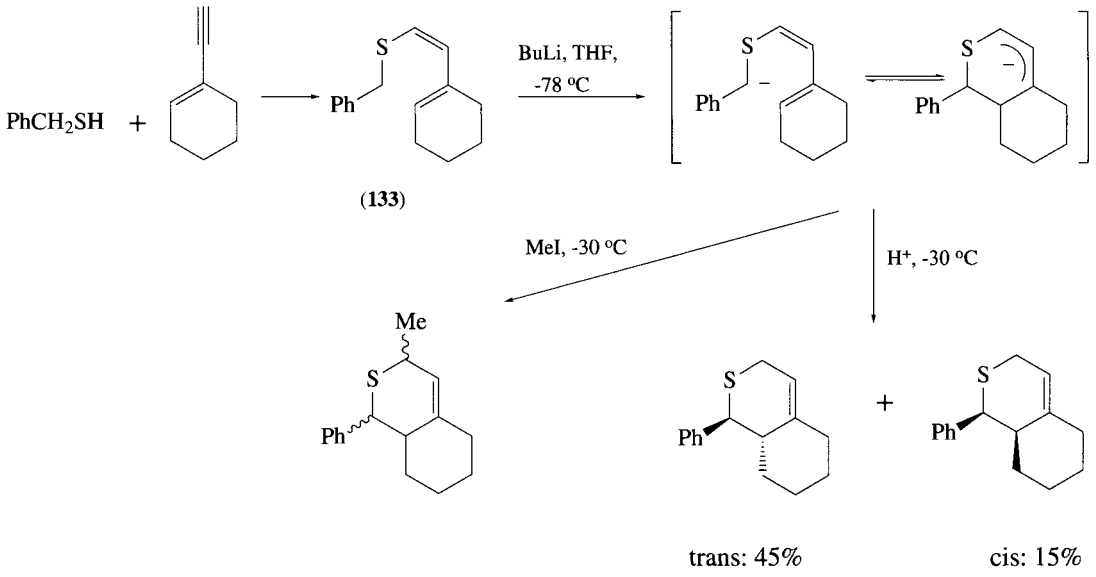
Scheme 102

Formation of a bond β to the sulfur could also be a useful cyclization process. A substrate such as (**132**) would be expected to be synthetically attractive, but accessibility is problematic.

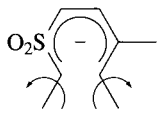


(**132**)

A more easily acquired precursor has proved to be (**133**). Its treatment with 1.2 eq. of *n*-butyllithium at −78 °C gave rise to a mixture of two products after protonation at −30 °C (Scheme 103). By contrast, the corresponding open chain sulfoxides and sulfones gave only the *cis* products (in 60–70% yields); the stereoselectivity may be formally rationalized as the consequence of a 6π disrotatory ring closure of a delocalized species (**134**) ⟨90BSF236⟩.



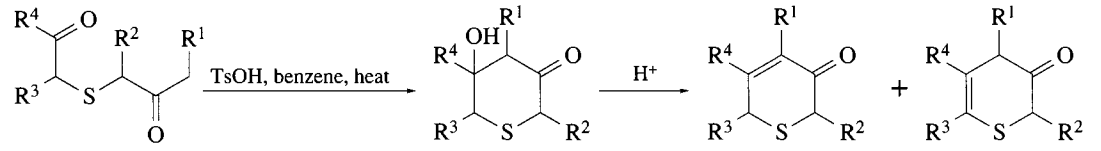
Scheme 103



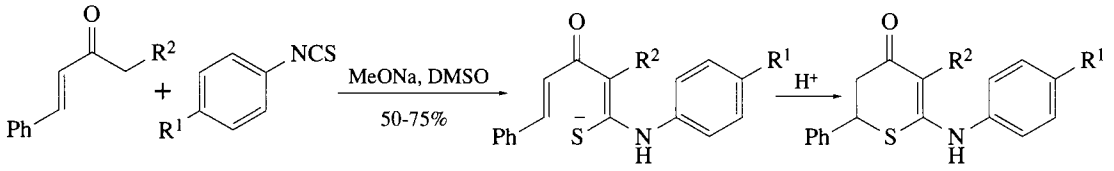
(**134**)

Formation of a γ bond has also been used, in an acid-catalyzed aldol condensation, to give dihydrothiopyran-3-ones (Scheme 104). The proportions of the products are strongly dependent on the substituents. When R^1 and R^4 are alkyl only the conjugated system is produced (in high yield), but with an aryl group at R^4 the nonconjugated isomer becomes a significant product, and with R^2,R^3,R^4 = Me it becomes the major product ⟨87H(26)1785⟩.

As in the case of thianes, closure to a Michael-accepting center may also be used (Scheme 105) ⟨86LA1109⟩.



Scheme 104



R^1 = H, Cl, OMe
R^2 = CN, CO_2Et, Ac

Scheme 105

5.10.7.3.2 [4 + 2] Cyclization

While dihydrothiopyran synthesis by coupling of two fragments rather than by cyclization of an open chain precursor has attracted a lot of attention, that attention has been directed almost entirely at one reaction type: the [4 + 2] coupling, and more specifically a [4π + 2π] Diels–Alder cycloaddition. Other conceptually possible condensation processes including [5 + 1] and [3 + 3] are essentially unknown. The Diels–Alder approach has seen much use since the 1960s, and many variants have been described. However, while there are 3 possible [4 + 2] arrangements (Figure 5), that using a positively charged sulfur species is not well exemplified. Most commonly used is the thiocarbonyl/diene combination. Variants are differentiated by the nature of the thiocarbonyl containing fragment, and its origin. Table 17 illustrates a range of these "thione" condensations.

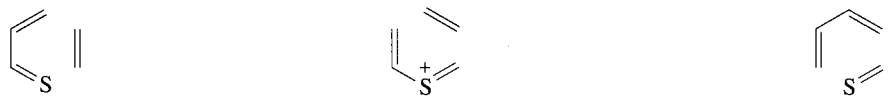


Figure 5 [4 + 2] Couplings affording dihydrothiopyrans.

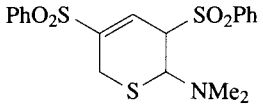
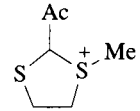
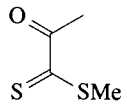
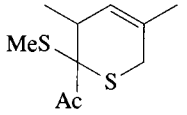
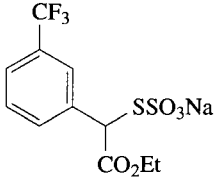
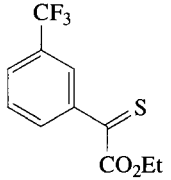
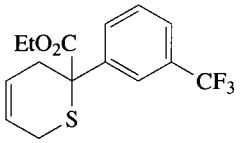
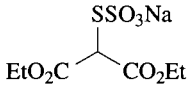
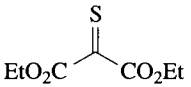
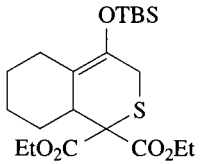
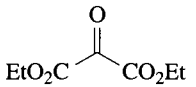
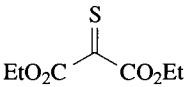
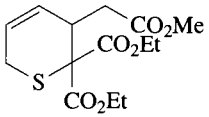
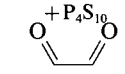
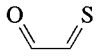
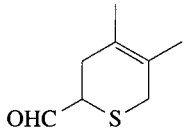
Virtually all thioaldehydes polymerize to trithianes on standing, and Table 17 reflects the preference for their preparation and trapping *in situ*. However, it is possible to prepare the thiocarbonyl compounds as isolable tungsten or chromium carbonyl complexes, and then to cycloadd the organic ligand to dienes, giving rise to metal carbonyl complexed sulfur heterocycles (Scheme 106) ⟨89JOM(364)155⟩.

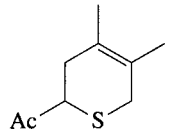
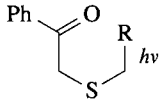
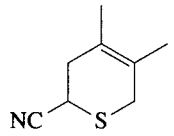
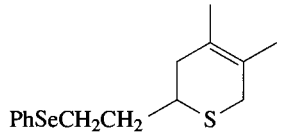
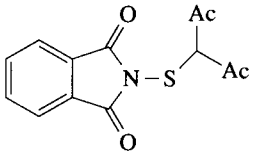
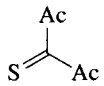
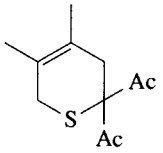
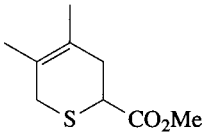
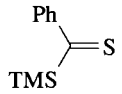
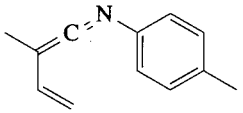
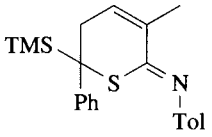
Vedejs *et al.* have investigated the diastereoselectivity of thioaldehyde cycloadditions with cyclopentadiene, and have shown that branching α to the aldehyde leads to *exo*/*endo* stereocontrol, while the presence of α-heteroatoms can give a degree of diastereoselectivity ⟨88JA5452⟩.

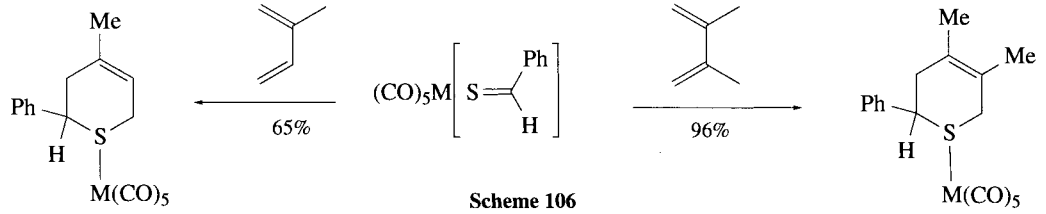
While the reactions described above are viewed as concerted cycloadditions, there are numerous examples of superficially similar reactions which are more correctly considered mechanistically as polar processes. Scheme 107 brings together two such cases ⟨90TL5237, 91SL487⟩.

Dihydrothiopyran synthesis by [4 + 2] coupling is also known for sulfides and sulfines. Scheme 108 shows a polar reaction leading to a sulfonium product ⟨86JCS(P1)1763⟩, while Scheme 109 collects

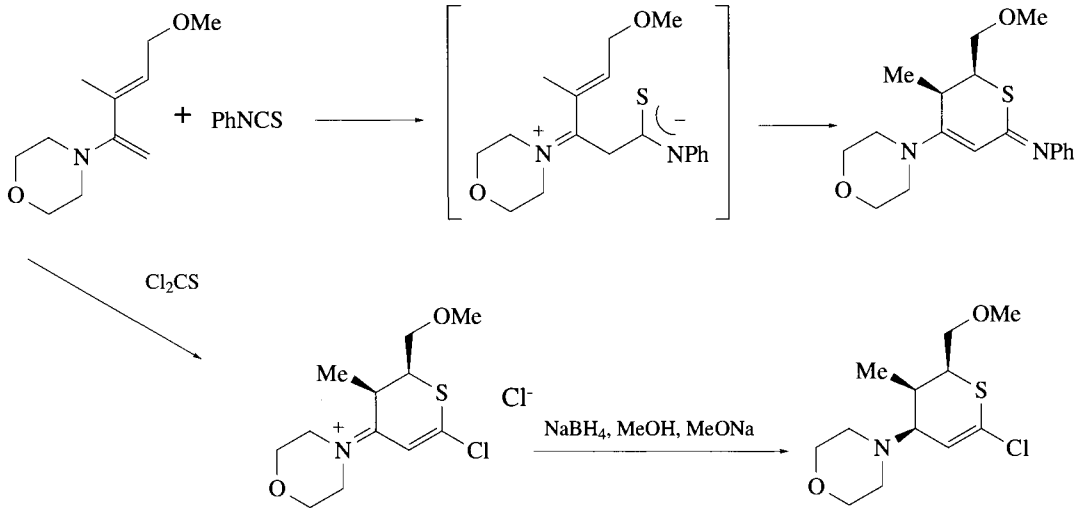
Table 17 Preparation of dihydrothiopyrans by thione/diene [4 + 2] couplings.

Source of $R^1R^2C{=}S$	$R^1R^2C{=}S$	R^3	R^4	R^5	R^6	*Product*	(%)	*Ref.*
	$HCSNMe_2$	H	SO_2Ph	H	SO_2Ph		70%	91JOC2713
		H	Me	H	Me			83JA127
		H	H	H	H		65%	92TL7597
		—$(CH_2)_4$—		OTBS	H		82%	88JA5932
		H	H	H	CH_2CO_2Me		69%	88JCS(P1)663
 $+(TMS)_2S$ $+CoCl_2 \cdot 6H_2O$		H	Me	Me	H		88%	91JOC7323

	RCH=S R = Ac	H	Me	Me	H		51%	
	R = CN	H	H	OTBS	H		70%	86JOC1556
	R = $PhSeCH_2CH_2$	OMe	H	OTBS	H		>70%	
		H	Me	Me	H		64%	92T9023
PPh_3=$CHCO_2Me$ + S_8	MeO_2CCHS	H	Me	Me	H		56%	88BCJ4323
							63%	87JCS(P1)2647

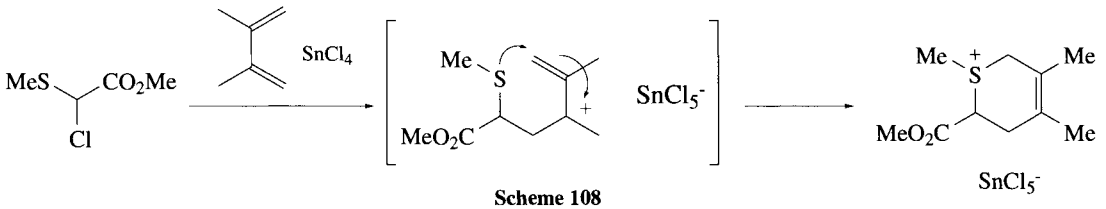


Scheme 106



Scheme 107

some representative examples of the concerted cycloadditions of sulfines ⟨88CB833, 90JCS(P1)3175, 91PS(58)129⟩. The stereochemistry of the latter processes has been thoroughly investigated for aryl sulfines, with the finding that the ratio of *cis*: *trans* dihydrothiopyran *S*-oxide products was dependent upon the initial proportions of sulfine and diene as a result of *Z*/*E* isomerization of the dienophiles ⟨91JOC2512⟩.



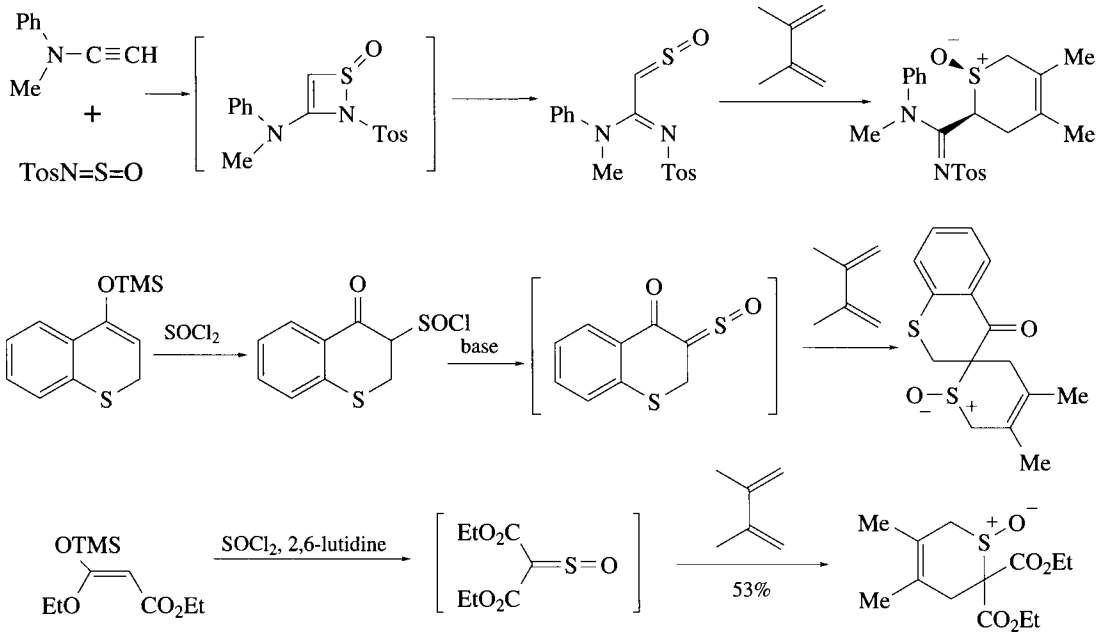
Scheme 108

The [4 + 2] coupling approaches to dihydrothiopyrans discussed above, wherein the "2" component is a thiocarbonyl moiety, only give rise to 3,6-dihydro-2*H*-thiopyrans. 3,4-Dihydro-2*H*-thiopyrans may be prepared in an alternative [4 + 2] process in which the sulfur is part of an enethione unit. Enethiones are usually found as stable dimers, although exceptions are known such as the captodatively stabilized β-thioxoenamine system. The dimeric species may be cleaved thermally (Scheme 110) and the monomers trapped *in situ* by dienophiles. Table 18 brings together some of the many reported examples of this process. A theoretical treatment of the reaction of the parent enethione 1-thiabutadiene with ethylene has been published ⟨93JOC1122⟩.

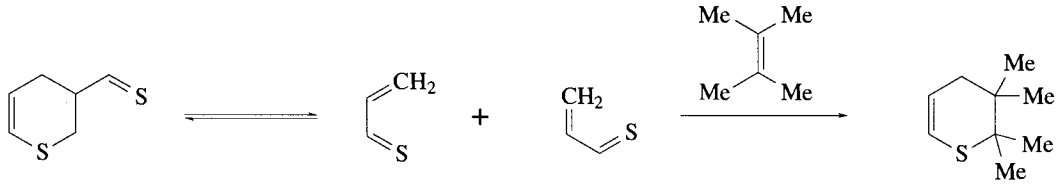
5.10.7.4 Dihydrobenzothiopyrans

5.10.7.4.1 [6 + 0] Cyclizations

The synthesis of benzannelated dihydrothiopyrans has made use of a more varied repertoire of reactions than is the case for the monocyclic system. Closure of an acyclic precursor by the formation

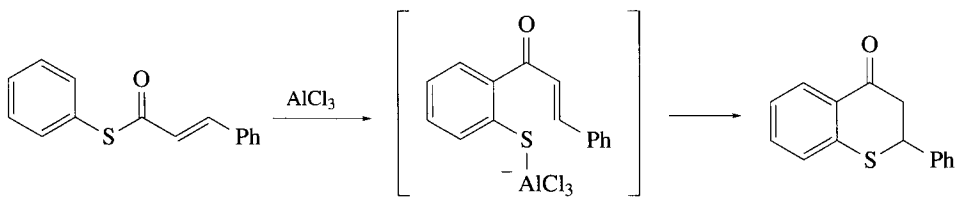


Scheme 109



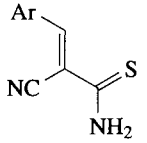
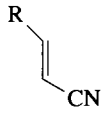
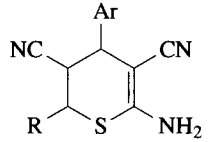
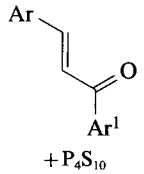
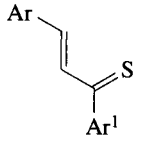
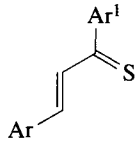
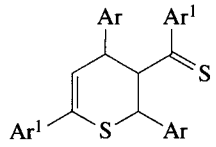
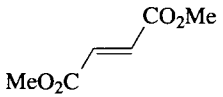
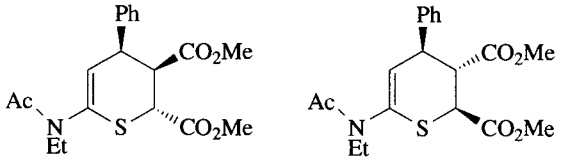
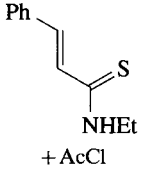
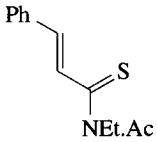
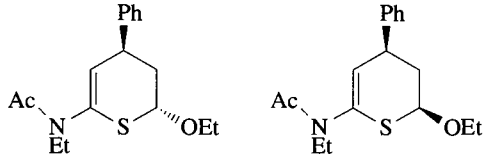
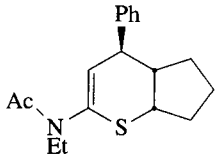
Scheme 110

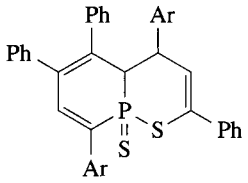
of a single bond is common, though, while nucleophilic attack by thiol on an electrophilic center is frequently employed, it is somewhat limited by difficulties in setting up the appropriate open chain structure. The problem may be overcome by masking the sulfur in some way whilst the electrophilic moiety is constructed, and then exposing the sulfur to give the immediate precursor of the dihydrobenzothiopyran. Two examples are shown in Schemes 111 ⟨91PS(61)373⟩ and 112 ⟨81KGS1191⟩, where a thioester is rearranged under Friedel–Crafts conditions, and an allylic sulfide is subjected to a thio-Claisen rearrangement respectively. Such thermal processes tend to be inefficient, giving rise to significant amounts of dihydrobenzothiophenes as competing products. Alternatively, a sulfide may be used as a nucleophile in its own right, leading to sulfonium products. If appropriately substituted the first formed compound may usefully undergo further reaction or rearrangement. The rhodium mediated carbene reaction shown in Scheme 113 is a nice example of this, in which the electrophilic (carbene) center is also masked as a diazonium unit until "deprotected" immediately prior to the cyclization reaction. The competing insertion of the carbene into the benzylic C—H bond, forming an indane, was only observed in about 10% yield, the thiin being by far the major product ⟨89JOC817⟩.

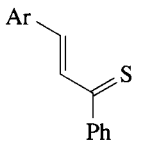


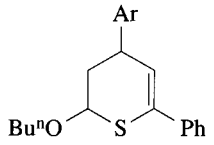
Scheme 111

Table 18 Preparation of dihydrothiopyrans by [4 + 2] coupling of enethiones.

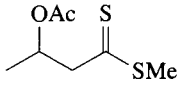
Source of enethione	*Enethione*	*Dienophile*	*Product* (%)	*Ref.*
				88IJC(B)472
				88CL717
			 83%, 4 : 1 ratio	
			 30%, 1 : 4 ratio	89T879
			 86%	

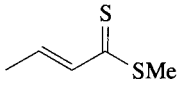


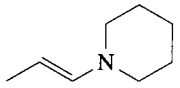


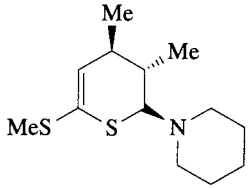


87BCJ1558

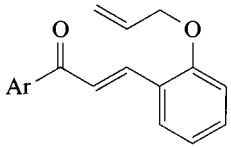




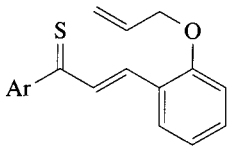


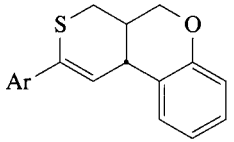


84JCS(P1)859



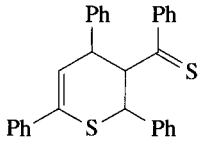
+P_4S_{10}/CS_2

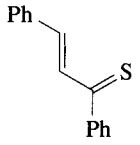


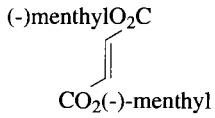


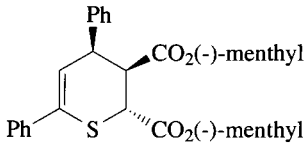
91%

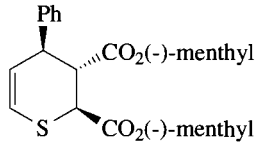
90CC1665



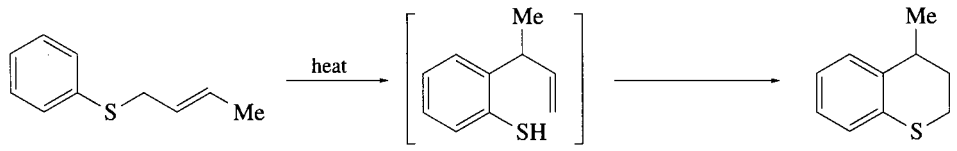




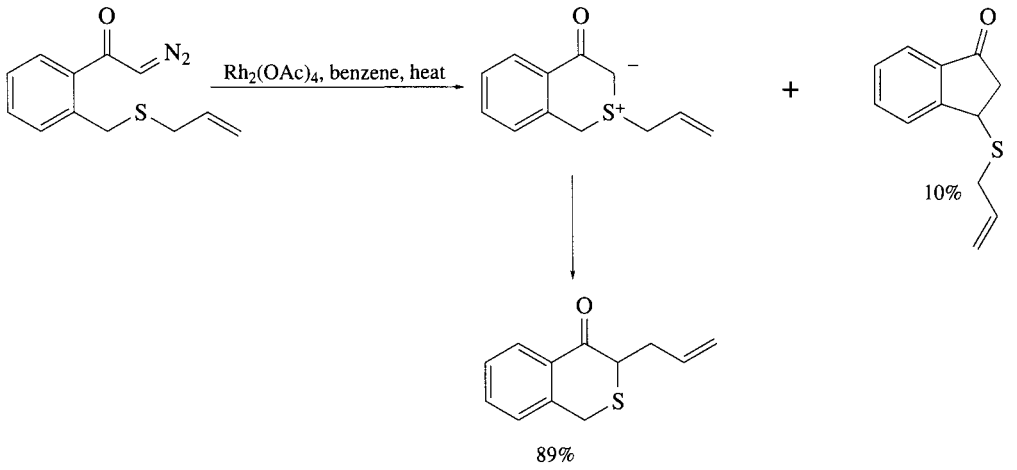




91JCS(P1)2281

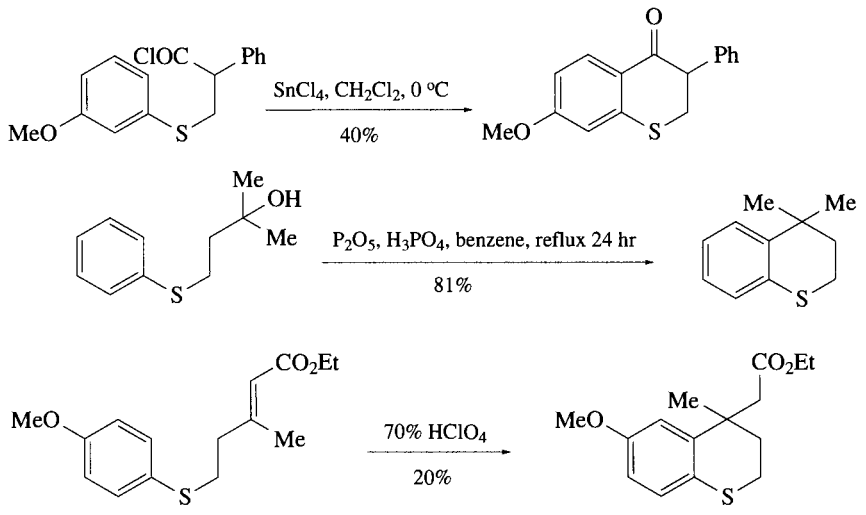


Scheme 112



Scheme 113

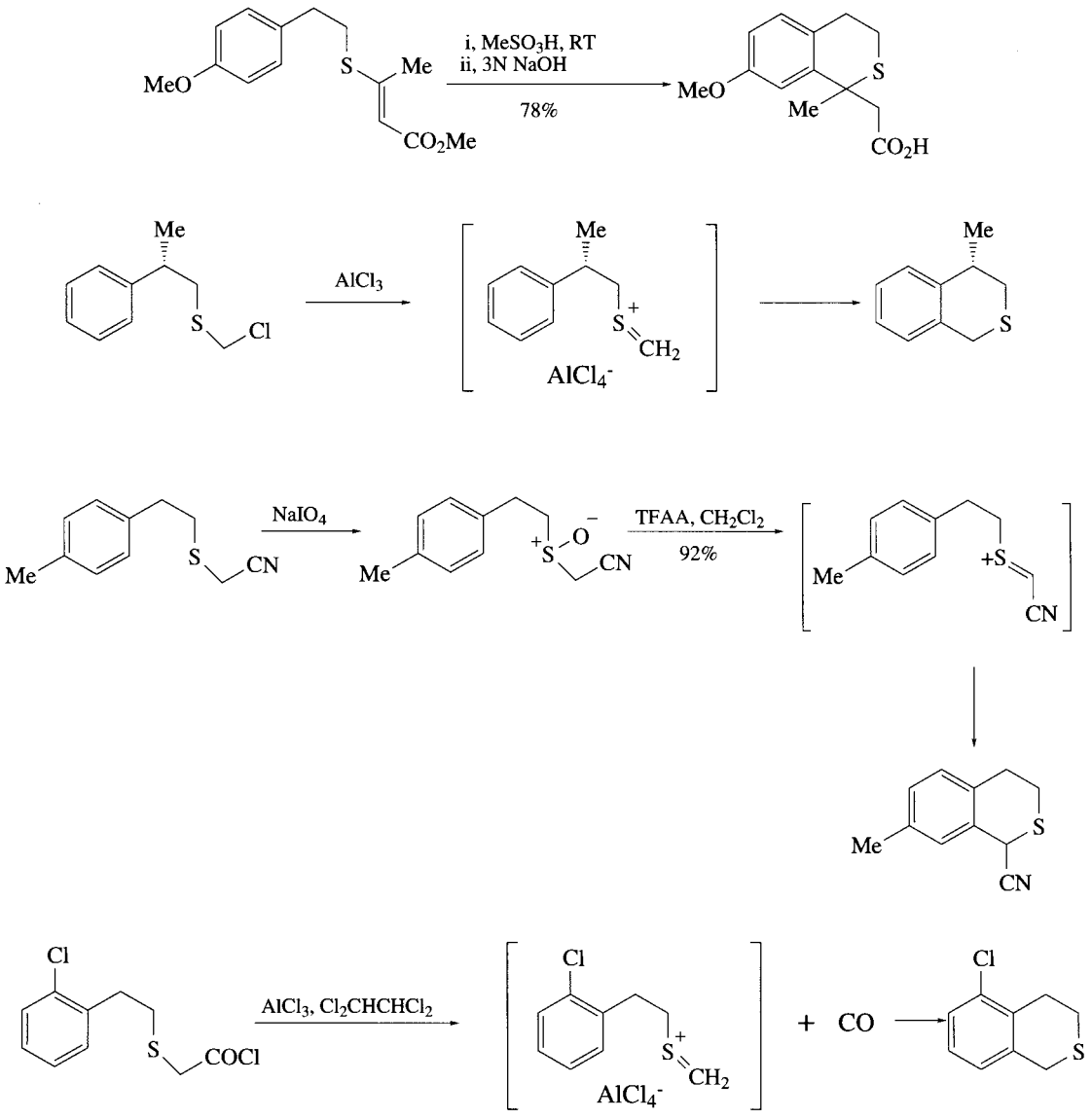
More commonly the bond formed is that to the aromatic nucleus, and γ to sulfur. Various Friedel–Crafts-type alkylations or acylations may be used and Scheme 114 shows three examples ⟨85H(23)1381, 85JMC116, 90OPP235, 93T939⟩.



Scheme 114

Turning to the 3,4-dihydro-1*H*-2-benzothiopyran system, ring closure methods analogous to those above may be used in its preparation, as well as the application of a β-bond formation on to the aromatic nucleus, which method is not available to the 2*H*-1-benzothiopyrans. A carbonium ion may be generated adjacent to the sulfur by a number of means, to be trapped in the cyclization. Scheme 115 shows four variants on the method ⟨87JCR(S)44, 88CPB1698, 90CCC2351, 90H(31)23⟩.

All of the foregoing preparative methods make use of the classical electrophilic attack upon a preformed benzene nucleus methodology to form a second ring. Only in the 1980s was the simultaneous formation of both the heterocycle and the benzene ring realized, as a result of inves-

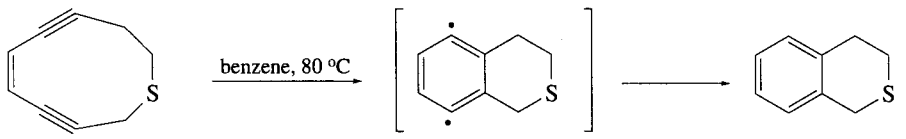


Scheme 115

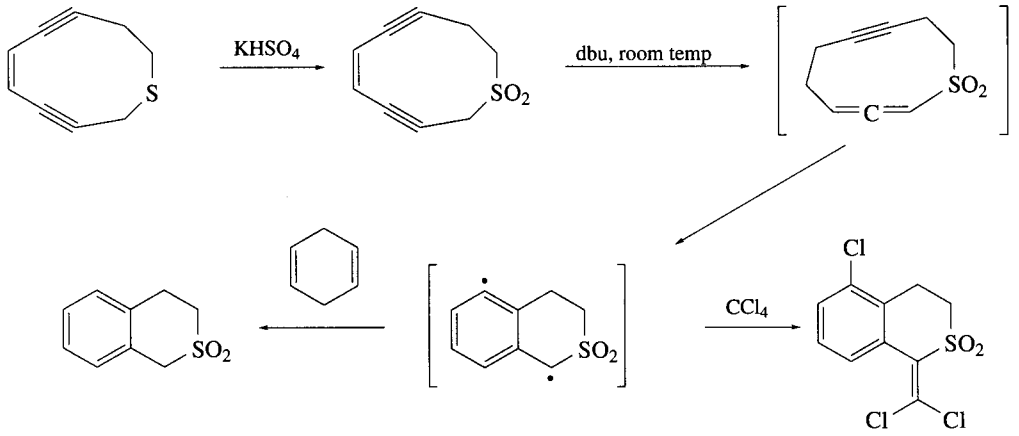
tigations of the antineoplastic activity of natural products such as calicheamycin. In these materials cyclodecane derived ene-diyne systems undergo a Bergmann cyclization to afford diradical products capable of interacting with DNA and inhibiting cell replication. The related thiacyclodecane ene-diynes have been examined as model compounds. Bicyclization may be initiated by a number of means: thermally (Scheme 116) ⟨91TL4363⟩, or by isomerization of one of the alkynic bonds to an allene. Isomerization and cyclization can be induced by base treatment of the sulfone system with dbu under mild conditions (Scheme 117) ⟨92TL957⟩, but more vigorous treatment with mineral base, or selenium dioxide is necessary for the unoxidized case (Scheme 118) ⟨91TL391, 91CC694⟩. Quenching of the diradical with different trapping agents can lead to a range of substituted systems.

5.10.7.4.2 [5 + 1] Cyclizations

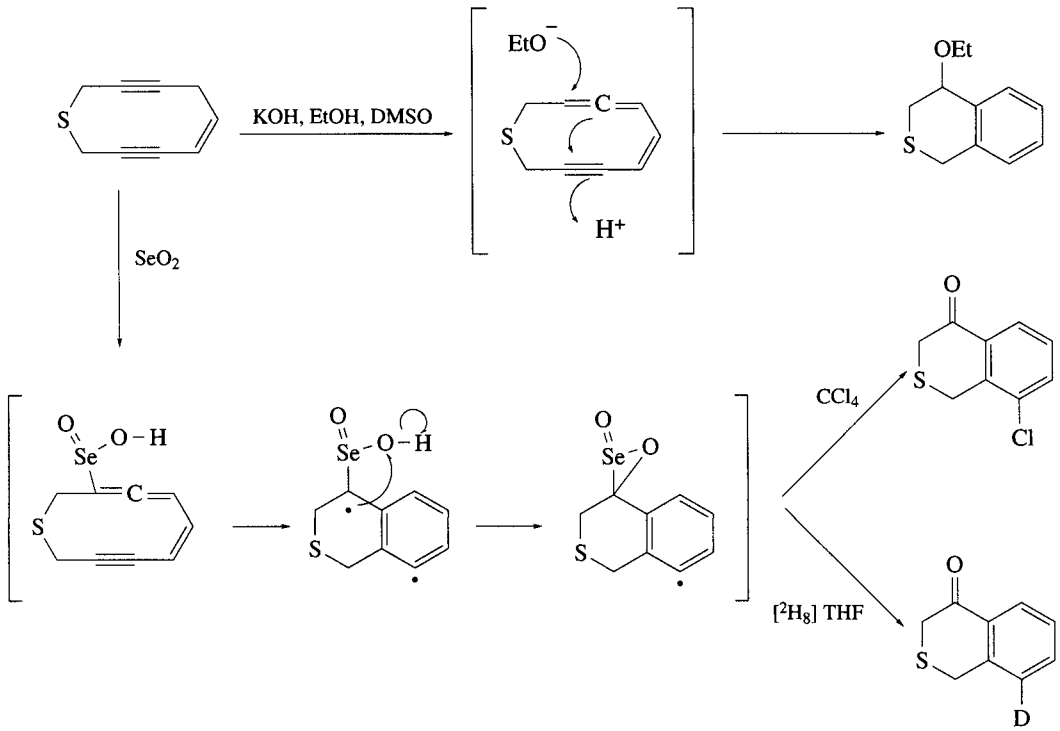
The first group of syntheses of dihydrobenzothiopyrans from two fragments are the [5 + 1] combinations. A good example of this type of coupling is the reaction of *o*-thiolacetophenones with



Scheme 116

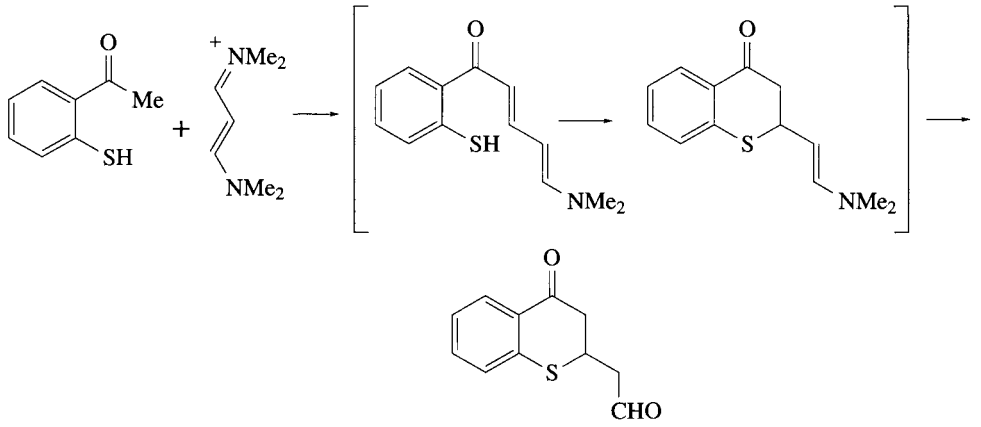


Scheme 117



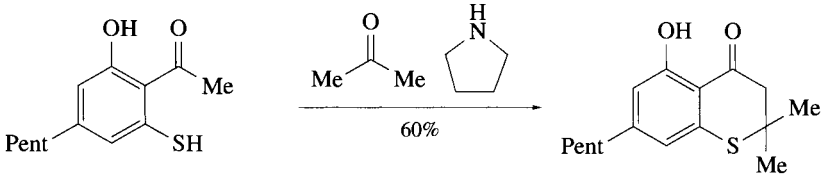
Scheme 118

a "doubly electrophilic" iminium species, forming *in situ* an enone, which spontaneously ring closes. The first formed enamine in the example shown in Scheme 119 hydrolyzes in the reaction mixture and the final product is the aldehyde (**134**) ⟨82CB2461⟩. Similarly, a carbonyl group may be the "doubly electrophilic" center (Equation (60)) ⟨90JMC2865⟩.



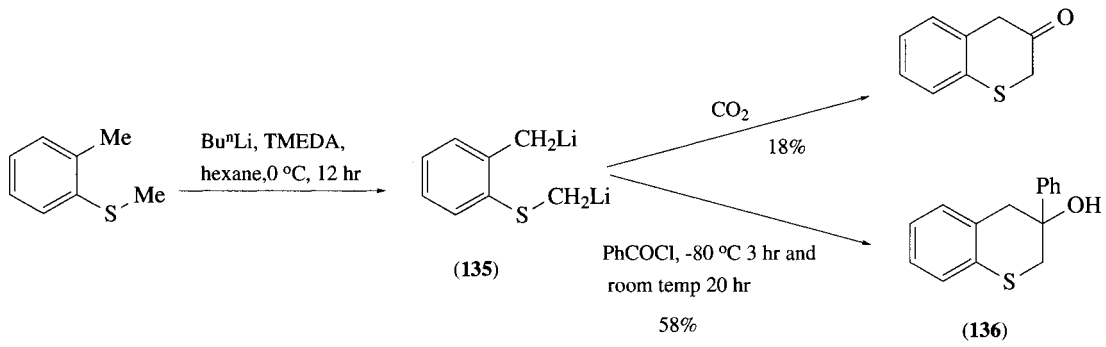
(134)

Scheme 119



(60)

The previous two examples (Scheme 119 and Equation (60)) rely upon the inherent nucleophilicity of the sulfur and the acetophenone enolate, and relatively weak bases are adequate to promote such couplings. In the absence of such activating influences stronger bases are necessary. Making use of the carbanion stabilizing ability of sulfur permits the formation of the dianion (**135**) with butyllithium, and its coupling with CO_2 to form benzothiopyran-3-ones (Scheme 120). While the reaction is not too efficient, the method makes accessible compounds otherwise very difficult to obtain. The electrophile may be varied: if an acid chloride is used, the products are dihydrothiochromanols (**136**), and in this case yields are higher ⟨89JOM(366)1⟩.

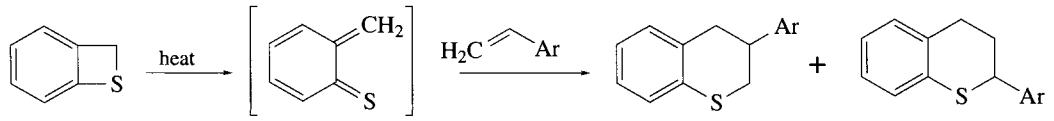


Scheme 120

5.10.7.4.3 [4 + 2] Cyclizations

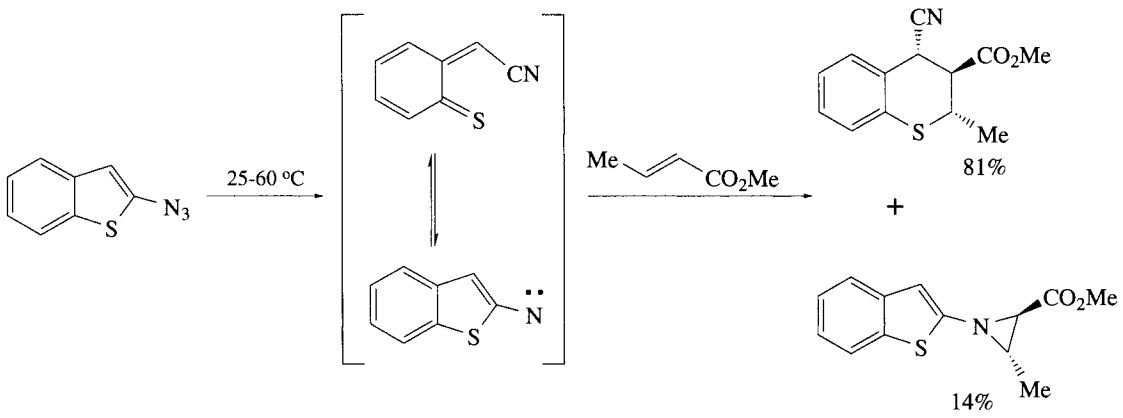
The [4 + 2] combination may be realized either by concerted cycloaddition or in polar stepwise fashion. Thermal ring opening of benzothietes affords thioquinone methides, which are also available from benzothiophene azides via a nitrene intermediate. Trapping of the thioquinone methide from benzothiete with styrenes has been extensively explored, and it has been shown that the cycloaddition is promoted by both electron donating and electron withdrawing substitution on the styrene *para* to the alkene (Scheme 121). The regiochemistry of the reaction is also styrene-substituent dependent: electron donating groups (OMe, NMe_2) favor 2-arylthiochromans, while the 3-aryl system is favored

by electron-withdrawing groups (NO_2, Ac). Typically, product isomer ratios fall in the range 1 : 2 to 2 : 1, but in the case of a *p*-NMe_2 moiety the ratio reaches 92 : 8 in favor of the 2-substituted heterocycle ⟨89CB1545⟩.



Scheme 121

The thermolysis of benzothiophene-2-azides at moderate temperatures is also a source of a cyano-substituted thioquinone methide, which in the presence of alkenes affords 4-cyano-dihydro-1-benzothiopyran adducts. Yields may be high (up to 80%), but addition of the postulated nitrene intermediate to the alkene affords aziridines competitively, and they can be significant by-products (Scheme 122) ⟨90JCS(P1)2971⟩.



Scheme 122

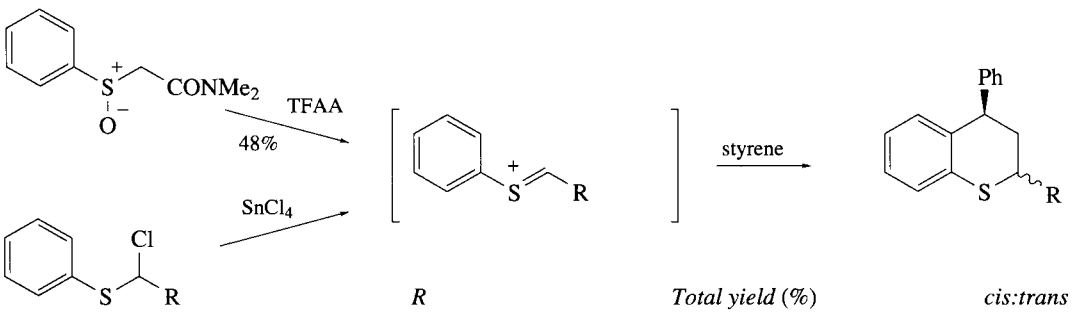
[4 + 2]-Combinations mediated by cationic species have been well exemplified by Ishibashi's group (Scheme 123). Generation of a carbonium ion α to the sulfur may be achieved in a number of ways, such as by the action of a Lewis acid upon an α chloro precursor, or from a sulfoxide in a Pummerer reaction. This electrophilic center may be trapped *in situ* by alkenes, generating a new electrophile, which can be trapped in turn by the adjacent aromatic nucleus. Studies using styrene have given an insight into the stereochemical aspects of the process, and have revealed a significant preference for *cis*-substituted products, being as great as 100% in the case where the α-chloro sulfide bears an amide group on the α-carbon. The table in Scheme 123 shows the diastereoselectivity for a range of such groups ⟨85CPB90⟩. The reaction is versatile, and has been applied to a variety of alkyl alkenic substrates, some of which are shown in Scheme 124 ⟨90CPB1233⟩.

5.10.7.5 2H- and 4H-Thiopyrans

5.10.7.5.1 Synthesis by redox methods and [6 + 0] cyclizations

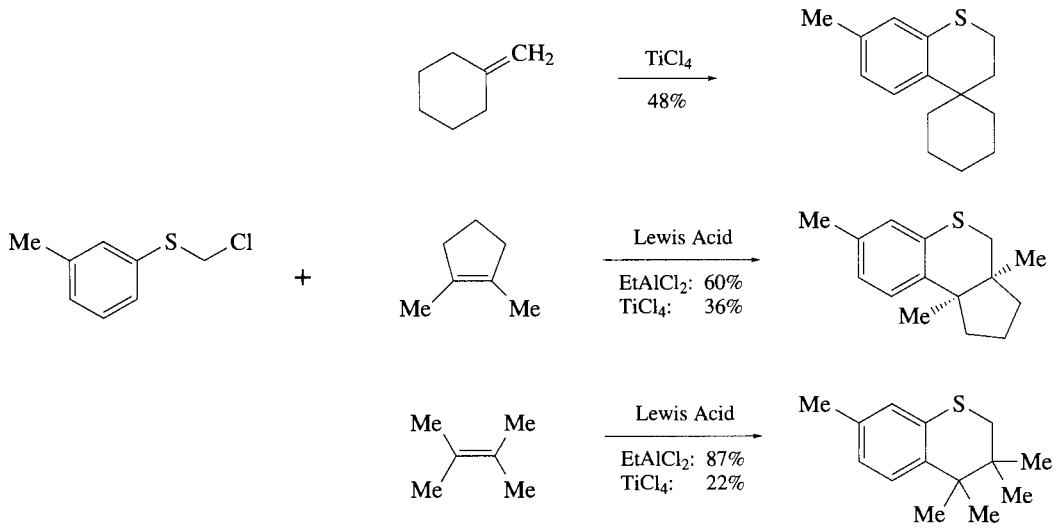
Reduction of thiopyrylium salts with metal hydride reagents gives mixtures of 2*H*- and 4*H*-thiopyrans, but as a preparative method it is clearly limited by considerations of compatibility of substituents with the reducing conditions, as well as its lack of specificity. A frequently adopted strategy is to make a suitably substituted dihydrothiopyran and then to dehydrate or deaminate it to introduce the second unsaturation. Obviously such a method is particularly attractive where a dihydrothiopyranone is readily accessible, and amenable to reduction to an alcohol. Less commonly applied is the dehydrogenation of tetrahydrothiopyran systems, where the severity of the reaction conditions is usually unacceptable.

De novo synthesis by closure of an acyclic precursor is also a rather restricted approach to thiopyrans, due to the difficulty of access of suitable structures, though a number of examples are known, (see, for instance, Scheme 125 ⟨73RTC667⟩).

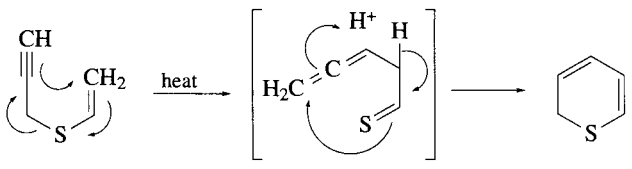


R	*Total yield (%)*	*cis:trans*
CONMe2	72%	100:0
CO_2Et	60%	7:3
CN	12%	7:3
COMe	19%	5:3
H	60%	

Scheme 123

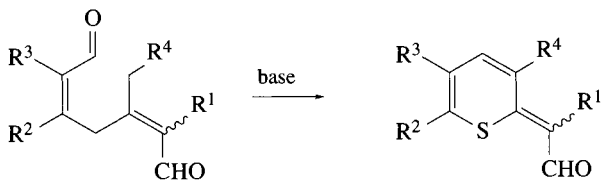


Scheme 124



Scheme 125

The picture is quite different if the thiopyran product bears a carbonyl, methylidene or imino group. The compounds are fully unsaturated and very stable, and suitable precursors are readily available, such as the bis-propenal shown in Equation (61) ⟨72T5197⟩. Frequently in such cyclizations the acyclic molecule is prepared *in situ*; the reaction then becomes a two (or more) component coupling.



(61)

5.10.7.5.2 [5 + 1] Cyclizations

Of the two component coupling approaches to thiopyrans the [5 + 1] case has found little use, save perhaps for the double Michael addition of H_2S to a dialkynic ketone leading to 2,6-diphenylthiopyran-4-ones ⟨82JOC1968⟩.

5.10.7.5.3 [4 + 2] Cyclizations

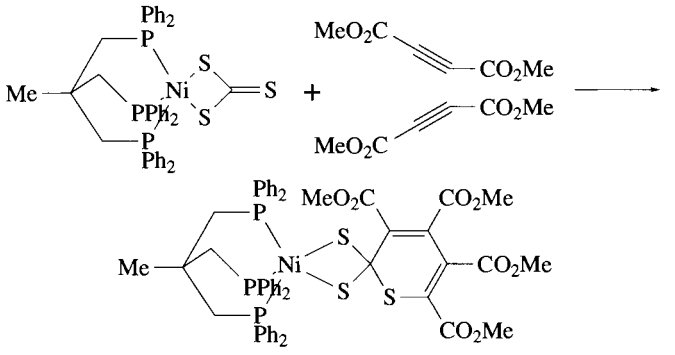
By contrast with the sparsity of examples of [5 + 1] cyclizations the [4 + 2] case has been very widely used, and Table 19 collects a range of examples. Most commonly the sulfur is introduced from the "4" unit, though carbon disulfide and isothiocyanates have seen frequent use as "2" components. Some of the couplings exemplified have been described as concerted cycloadditions, but it is probable that many follow polar pathways, particularly those involving enaminothione substrates.

5.10.7.5.4 [3 + 3] Cyclizations

Whereas the synthesis of six-membered rings by the [3 + 3] coupling process is usually rare, in the case of thiopyrans it is quite frequently encountered and Table 20 shows selected examples.

5.10.7.5.5 [2 + 2 + 2] Cyclization

Three component couplings are very unusual, but Equation (62) shows a case of the [2 + 2 + 2] combination. Such cyclizations seem to be restricted to certain reagents, of which DMAD appears to be the archetype. In this example a metal complexed trithiocarbonate functions as the C=S carrier ⟨82JOM(236)C75⟩.



(62)

5.10.7.5.6 Thiopyran synthesis by transformation of other heterocycles

Unlike the partially saturated thiins, thiopyrans are also available by transformation of other heterocycles:

(i) ring expansion of thiophenium ylides has received a significant amount of attention. The unstable 2*H* systems are the kinetic product of the expansion, but on prolonged reaction further

Table 19 Preparation of thiopyrans by [4 + 2] coupling reactions.

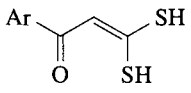
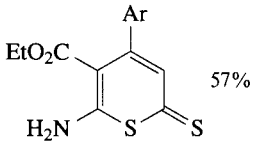
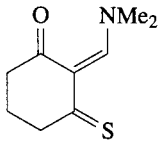
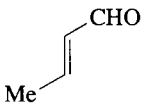
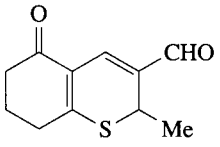
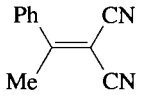
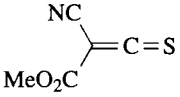
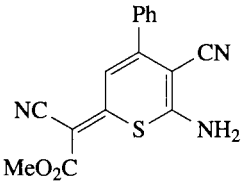
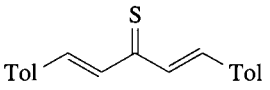
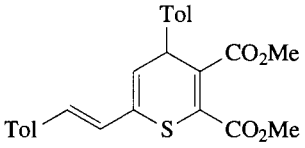
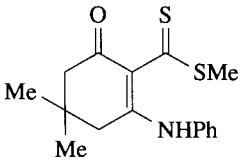
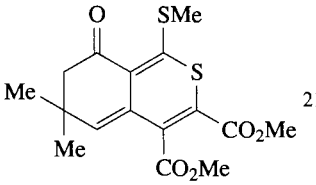
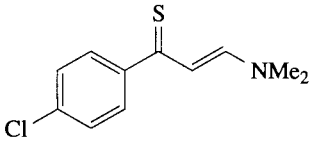
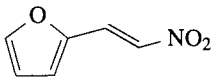
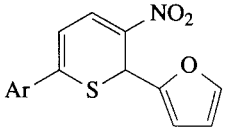
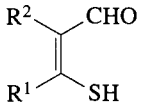
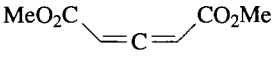
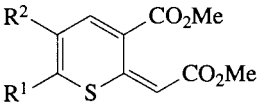
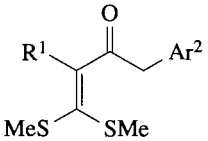
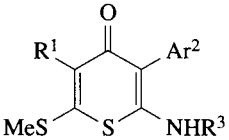
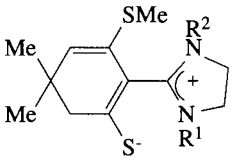
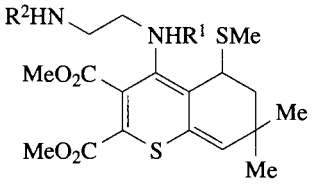
"4" component	*"2" component*	*Product* (%)	*Ref.*
		 57%	92PS(71)193
		 53%	92JCS(P1)2603
			83ZC406
	DMAD		88CL717
	DMAD	 21%	91JHC1245
		 60%	90T1951
		 50–60%	89JCR(S)300
	R^3NCS	 60–75%	85S531
	DMAD		91JOC4919

Table 19 (continued)

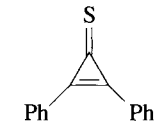
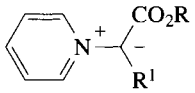
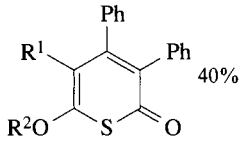
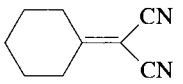
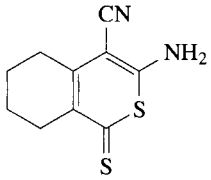
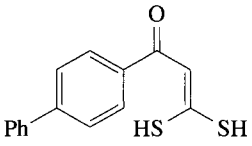
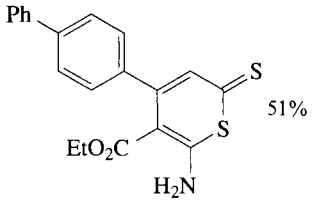
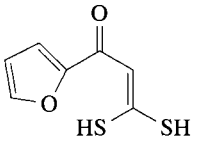
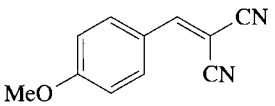
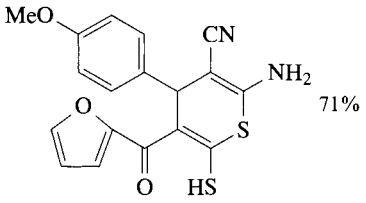
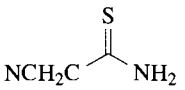
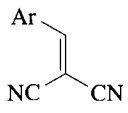
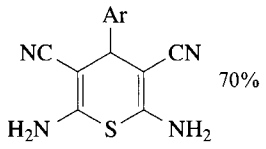
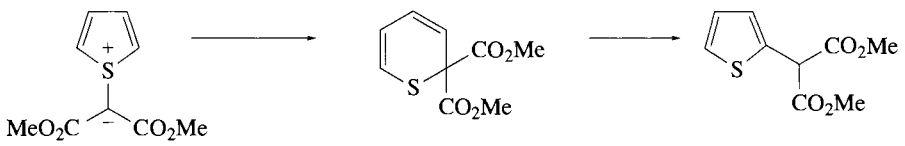
"4" component	*"2" component*	*Product* (%)	*Ref.*
		 40%	90JHC1597
	CS_2		89PS(44)203

Table 20 Preparation of thiopyrans by [3 + 3] coupling.

Component 1	*Component 2*	*Product* (%)	*Ref.*
	$NCCH_2CO_2Et$	 51%	92PS(71)193
		 71%	92PS(71)193
		 70%	86LA1639, 89BCJ3768, 91IZV1643

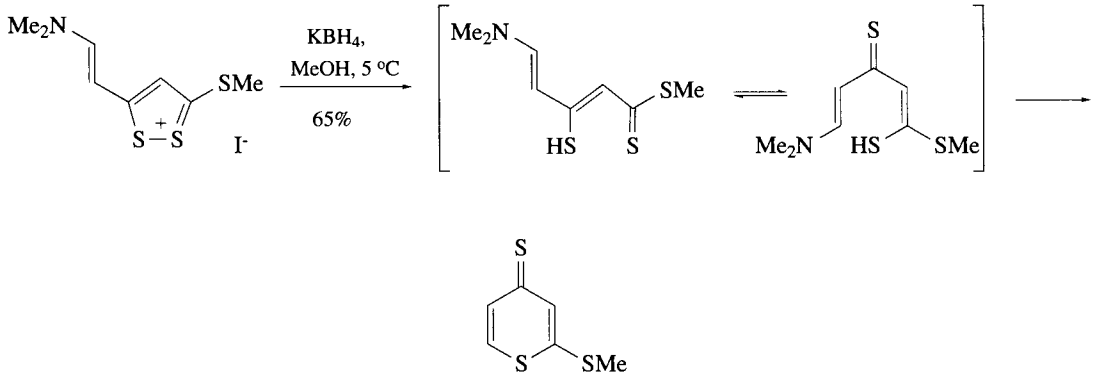
reorganizations may occur. In Scheme 126 for example, the first formed thiopyrandicarboxylate rearranges to a thiophene malonate ⟨88JCS(P1)803⟩.



Scheme 126

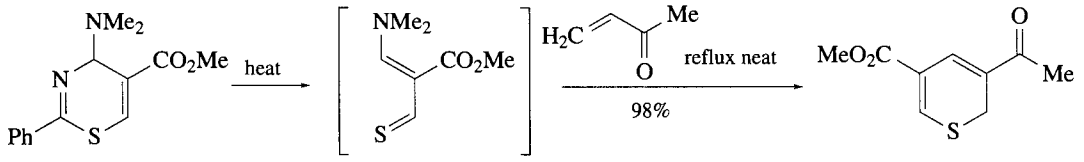
(ii) ring cleavages giving rise to thiopyran precursors are well known. Scheme 127 shows the reductive cleavage of a dithiolium salt to a β-dithione. With appropriate substitution ring closure in a new sense can lead to the thermodynamically more stable neutral six-membered species.

Additional driving force for the reaction may be available through elimination of a leaving group, an amine function in this case ⟨81TL4507⟩.



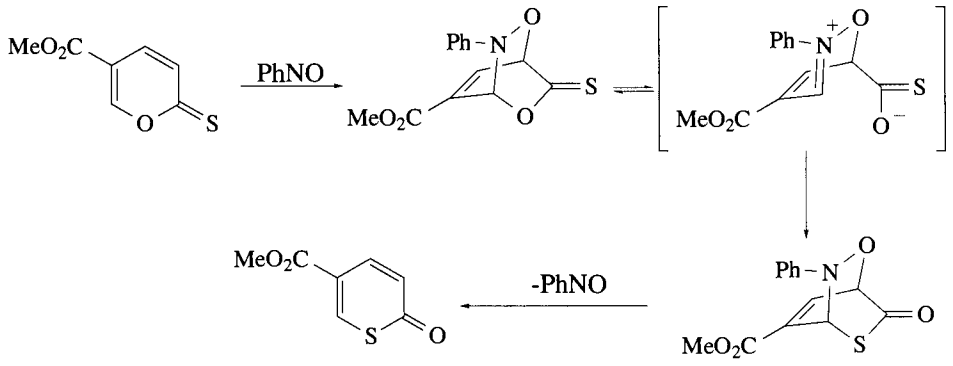
Scheme 127

More extensive cleavage of heteroring systems can give rise to fragments capable of taking part in [4 + 2] type couplings. Thiazines, for example, can be fragmented thermally to enaminothiones (Scheme 128) ⟨85JOC1545⟩; other examples may be found in the tables above.



Scheme 128

(iii) the conversion of pyrans into thiopyrans is well documented. Treatment of pyranones with thionating agents such as P_4S_{10} frequently produces mixtures of pyranthiones, thiopyranones, and thiopyranthiones. Presumably such interconversions proceed through acyclic intermediates. An interesting related conversion uses the cycloaddition of nitrosobenzene to a pyranthione to catalyze the O—S exchange process under relatively mild conditions (Scheme 129) ⟨85HCA1998⟩.



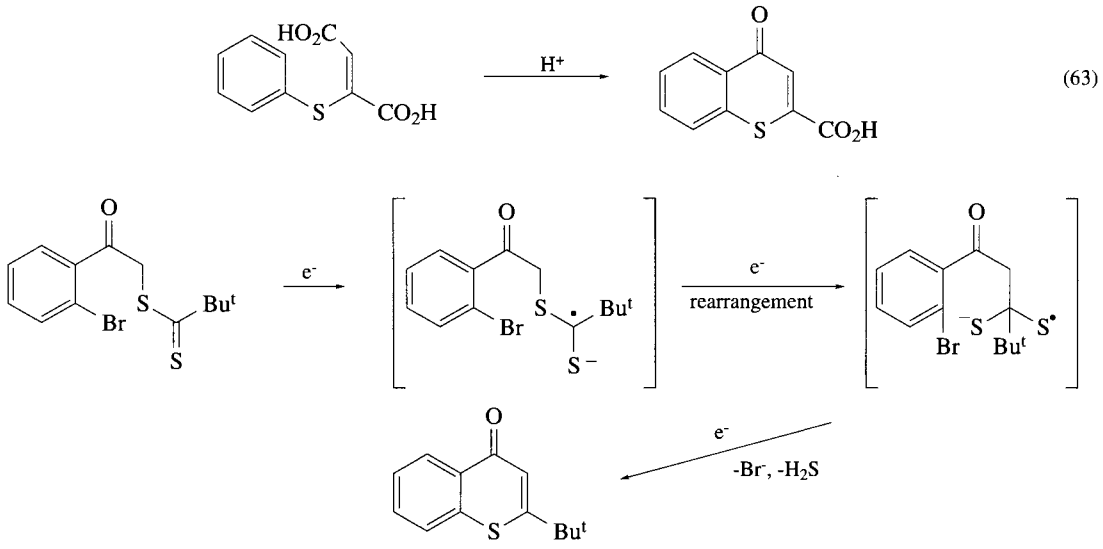
Scheme 129

5.10.7.6 Benzothiopyrans

5.10.7.6.1 [6 + 0] Cyclization

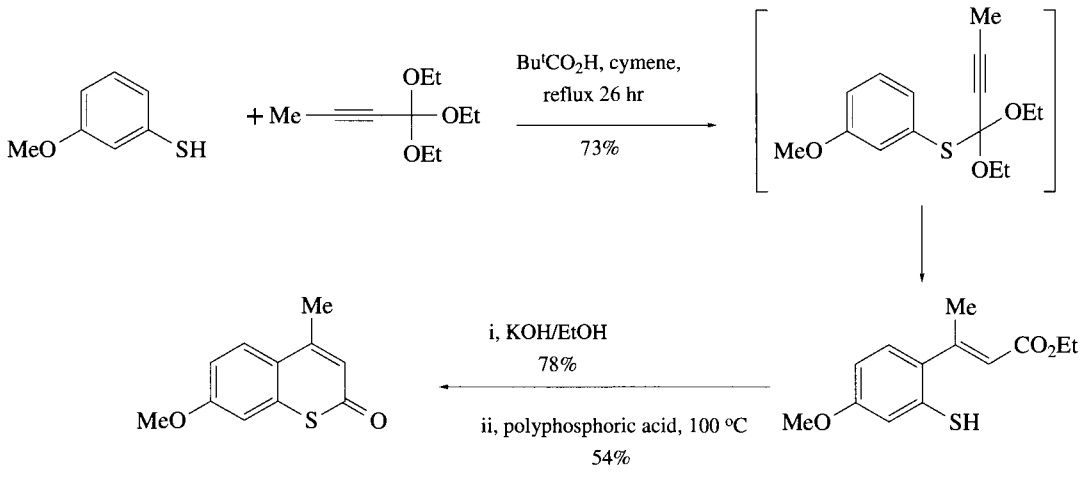
Cyclization of acyclic precursors to benzothiopyrans may involve the formation of bonds α, β, or γ to the sulfur atom. Making the γ bond, usually by an acylation of the aromatic moiety ortho to

the sulfur, is the most common means of preparing thiochromones (Equation (63)) ⟨71GEP2006196⟩. Nucleophilic closure onto the aromatic ring, rather than electrophilic, is unusual but has been realized electrochemically (Hg cathode, Pt anode, $Pr^n_4N^+Br^-$/DMF electrolyte, −1.75 V vs. Ag/Ag^+ ref) as shown in Scheme 130 ⟨92CB127⟩. Ejection of the halogen atom was facilitated by the adjacent carbonyl group, but even so the yield was only modest.



Scheme 130

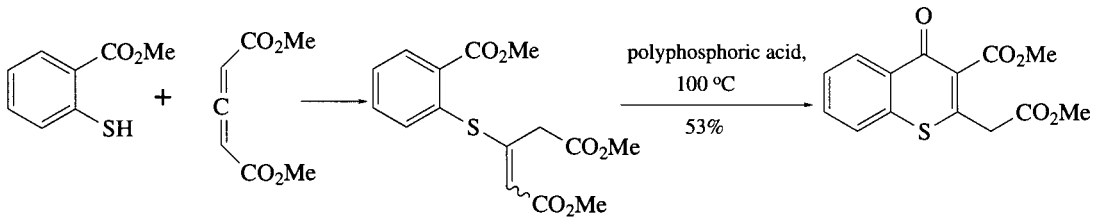
Closure of the bond α to the sulfur on the aliphatic side is much more facile. The limitation of this approach is access to the appropriate acyclic precursor. An interesting solution to that problem uses a thio-Claisen rearrangement of an orthoester to set up the carbon skeleton (Scheme 131). Subsequent acid-catalyzed closure permits the utilization of both the *cis* and *trans* alkenic intermediates ⟨82JOC2626⟩.



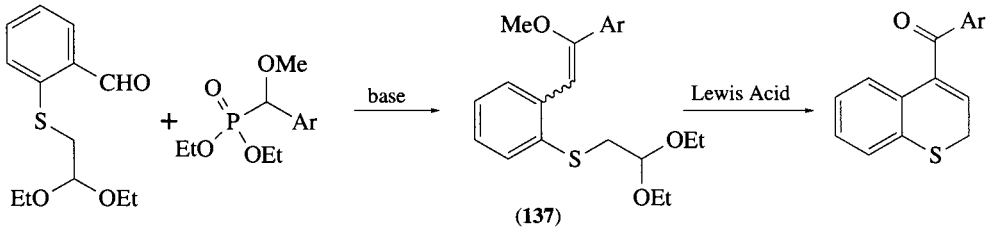
Scheme 131

Dieckmann-type cyclizations have frequently been applied, the source of the precursor being alkylation of a thiosalicylic acid with an acetic acid derivative ⟨82CJC243⟩ or an allene dicarboxylic ester (Scheme 132) ⟨85JOC1542, 88JCS(P1)2993⟩.

Closure of the 3,4-bond of a 2*H*-1-benzothiopyran has also been exemplified by Crombie's group, using a Mukaiyama reaction of the acetal and enol ether groups of (**137**) (Scheme 133) ⟨91CC972⟩.



Scheme 132



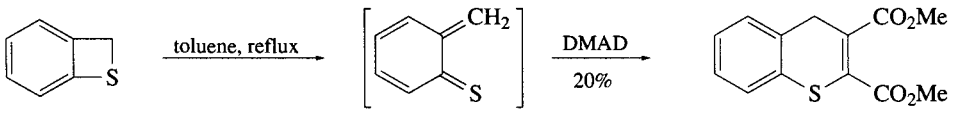
Scheme 133

5.10.7.6.2 [4 + 2] Cyclization

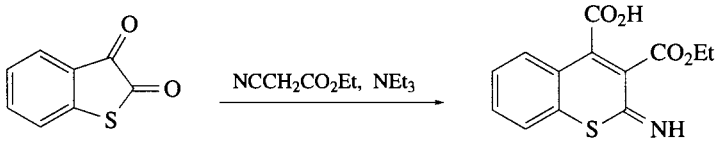
Two component couplings are essentially only reported for the [4 + 2] case. Table 21 lists various examples of this process.

5.10.7.6.3 Benzothiopyran synthesis by ring transformation

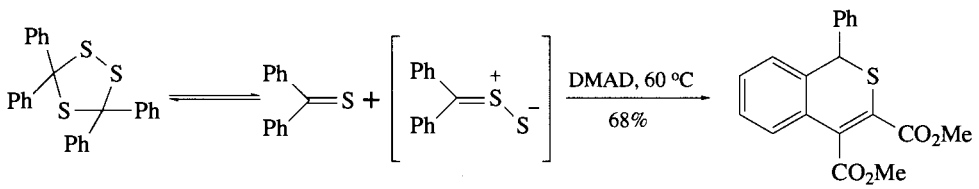
Ring transformations leading to benzothiopyrans are less versatile than in the case of thiopyrans. Ring expansions may be illustrated by the reaction of benzothietes with DMAD (Scheme 134) ⟨83JOC881⟩, and of benzothiophene-2,3-dione with ethyl cyanoacetate or malononitrile (Equation (64)) ⟨85JPR333⟩. The more extensive fragmentation of a heterocycle to a reactive intermediate may be exemplified by the formation of a thione-sulfide from a trithiolane, and its trapping by DMAD (Scheme 135) ⟨87JA902⟩.



Scheme 134

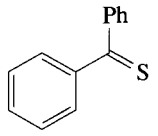
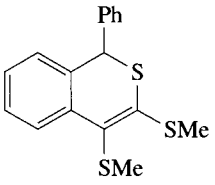
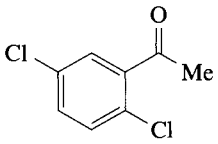
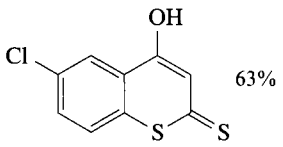
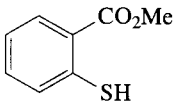
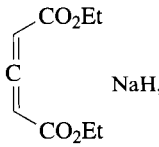
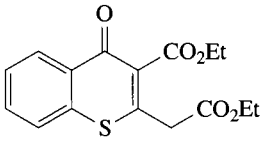
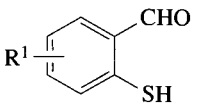
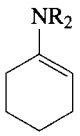
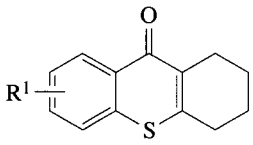
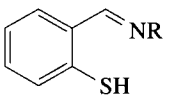
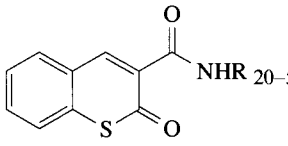
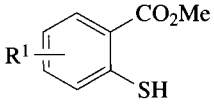
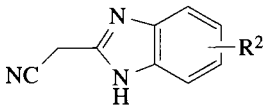
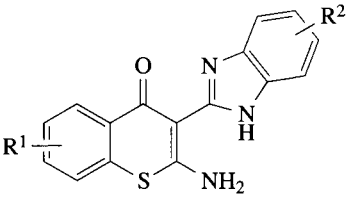
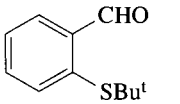
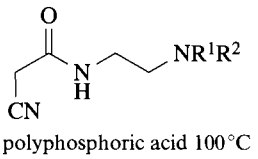
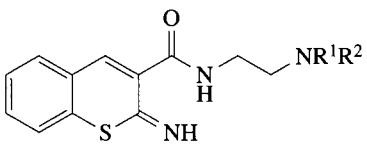


(64)



Scheme 135

Table 21 Preparation of benzothiopyrans by [4 + 2] coupling.

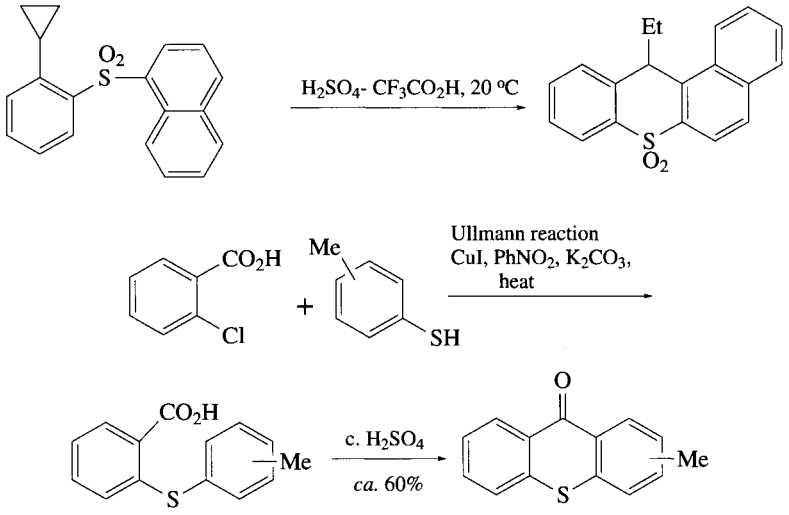
"4" component	*"2" component*	*Product* (%)	*Ref.*
	(hv, 589 nm)	 10%	83RTC91
	CS_2 (NaH)	 63%	87AJC1179
	 NaH, THF	 66%	85JOC1545
			85EUP163227
		 20–50%	85LA529
		 70–90%	83UKZ1202
	 polyphosphoric acid 100 °C	 70–90%	88JHC711

5.10.7.7 Thioxanthenes

5.10.7.7.1 [6 + 0] Cyclization

While a number of means of assembling thioxanthenes can be proposed, in practice only two are widely employed: electrophilic C—C bond formation and nucleophilic S—C bond closure of acyclic precursors. The electrophilic method is the method of choice and uses either an alkylation (Equation (65)) ⟨86ZOR2160⟩, or for thioxanthones an acylation (Scheme 136) ⟨83CJC1869⟩ of the aromatic nucleus. Many acylating species have been used such as carboxylic acids and benzohydroxamic acids ⟨86JOC4458⟩. If nitriles are used in this manner, the products are thioxanthene-imines ⟨88JMC254⟩. By

contrast, the alkylation method has seen less use, presumably because the reaction requires activation of the substrate by appropriate substituents, and vigorous reaction conditions.

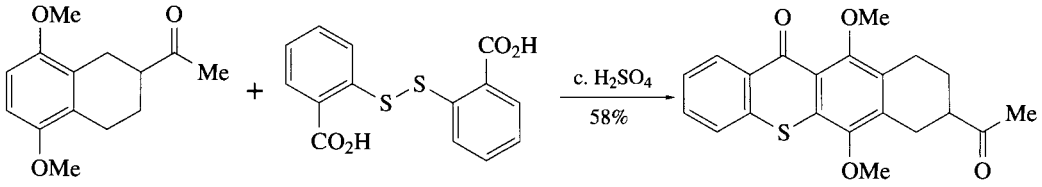


(65)

Scheme 136

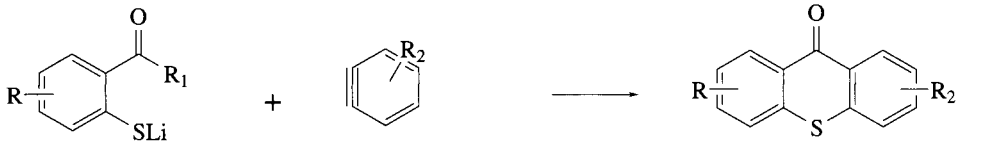
5.10.7.7.2 [4 + 2] Coupling

Two component couplings are unusual in the synthesis of thioxanthenes, but there are examples of the [4 + 2] case. Equation (66) shows an unusual electrophilic process, where the closure of the S—C bond occurs through an attack by the electron rich dimethoxy aromatic ring upon a sulfur atom of a protonated disulfide ⟨83CJC1600⟩.



(66)

The closest approach to a truly concerted ring formation is the regioselective formation of thioxanthenes in the reaction of benzynes with lithio salts of *o*-thiolbenzoic esters or amides, as shown in Equation (67) ⟨89CPB36⟩. This very versatile transformation complements the more common Friedel–Crafts acylation type approaches.



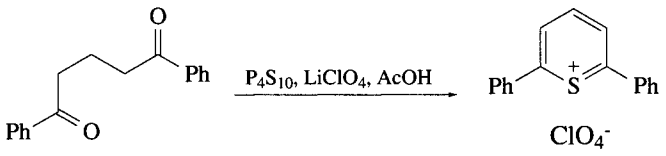
(67)

R	R^1	R^2	Yield (%)
H	OMe	H	73
OMe	NEt_2	H	50
OMe	NEt_2	OMe	38

5.10.7.8 Thiopyrylium Salts

5.10.7.8.1 [5 + 1] Cyclization

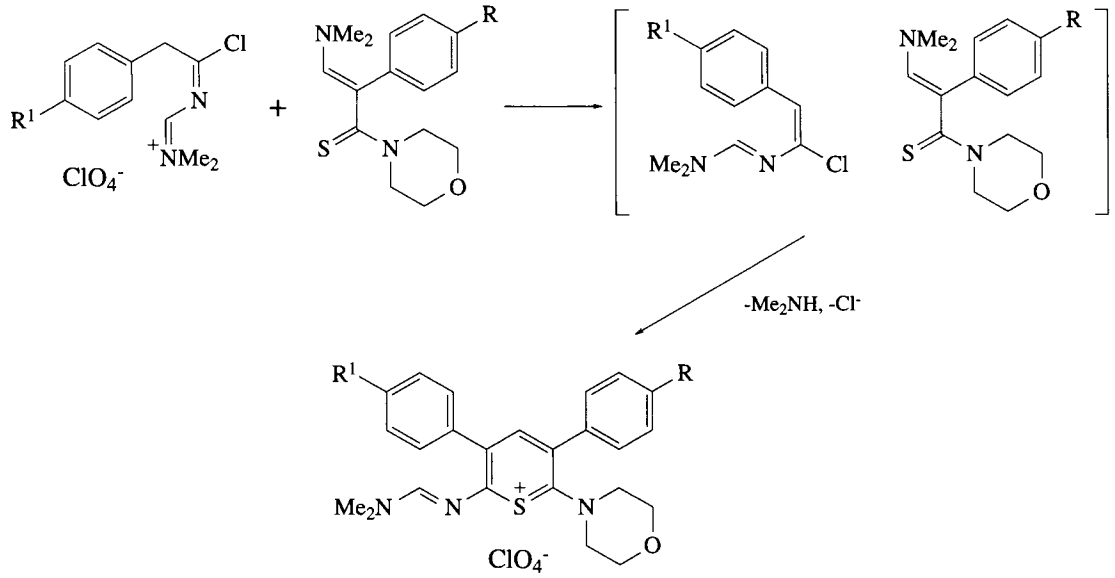
Perhaps the most common preparation of thiopyrylium species is the thionation of 1,5-diketones, and disproportionation of the first formed thiopyrans (Equation (68)). The reaction is facilitated by the presence of alkali perchlorates, the more so if they are present in substantial excess ⟨84SC775⟩. Closely related is the two component [5 + 1] coupling of hydrogen sulfide in perchloric acid with the same diketone ⟨85S789⟩.



(68)

5.10.7.8.2 [4 + 2] Cyclization

Two component couplings of the [4 + 2] class are known, probably proceeding through polar rather than concerted mechanisms, but ultimately relying on elimination of stable moieties to achieve the required oxidation state. Scheme 137 shows a rather complex example, but yields of 60–90% are easily obtained by this method ⟨83ZC403⟩.

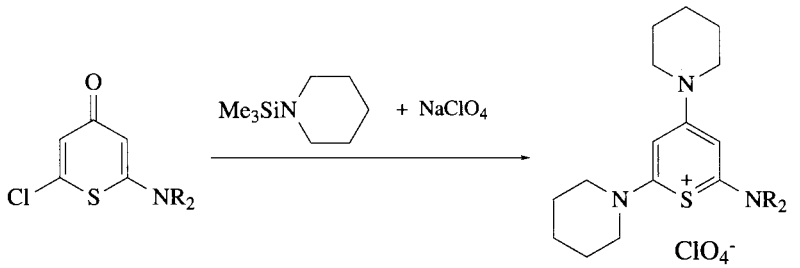


Scheme 137

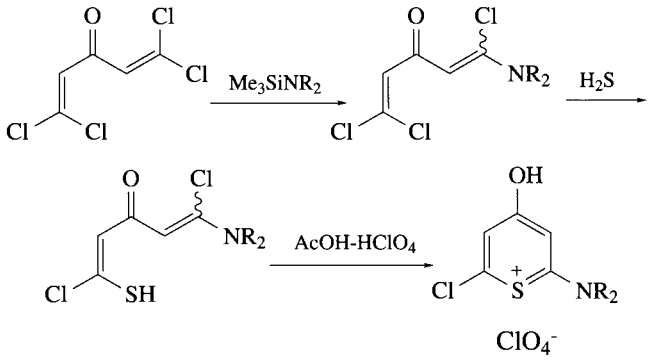
5.10.7.8.3 Thiopyrylium salt synthesis by transformation of other heterocycles

The direct oxidation of thiopyrans is the simplest conceptual preparation of thiopyrylium species, and may be achieved by electrochemical reactions ⟨91KGS47⟩, or with benzoquinones ⟨91KGS51⟩. Another common entry into these systems makes use of elimination of suitable leaving groups from

thiopyran derivatives. In Equation (69) it is a silyl ether that leaves ⟨88TL4695⟩, while in the transformation shown in Scheme 138 chlorine is the leaving group ⟨88TL4695⟩.



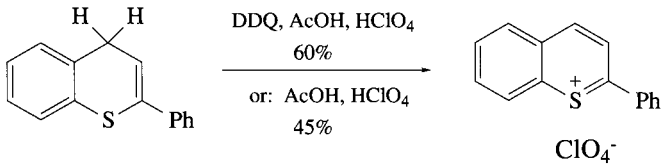
(69)



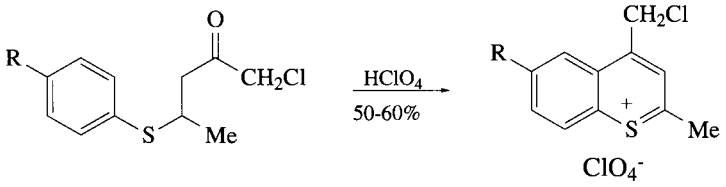
Scheme 138

5.10.7.9 Benzothiopyrylium Salts

The most common entry into the benzothiopyrylium salts is through oxidation of benzothiopyrans with perchloric acid, sometimes in the presence of quinone oxidizing agents (Equation (70)) ⟨83BCJ1251⟩. Cyclization of an acyclic precursor through an acid-catalyzed electrophilic alkylation of a benzene nucleus can also lead directly to the thiopyrylium system if the acid used is perchloric, which presumably oxidizes the intermediate benzothiopyran *in situ* (Equation (71)) ⟨87KGS766⟩.



(70)



(71)

5.10.7.10 Thioxanthylium Salts

The most common preparation of thioxanthylium salts is through the acid-catalyzed elimination of hydroxyl or amino functions from the appropriately substituted precursor. Less frequently used is the oxidation of thioxanthenes with perchloric acid. The perchloric acid mediated oxidations

produce perchlorate salts as products, which have been identified as the causes of a number of explosive incidents. Preparation of the perchlorate salts of thiopyrylium and benzannelated systems must always be conducted with extreme caution.

5.10.8 IMPORTANT THIOPYRANS AND APPLICATIONS ARRANGED BY RING SYSTEM

5.10.8.1 Thianes

There are no major thiane products in commercial use. However, the ring is frequently investigated alongside pyrans in research on pharmaceuticals, as the size, electronic properties, and lipophilicity of the sulfur atom allow subtle manipulation of the physical parameters of bioactive molecules. The radical-scavenging ability of sulfur heterocycles, including thiopyrans, has led to their investigation as radioprotective agents ⟨90MI 510-05⟩, while the photolytic and radiation-induced cleavages of sulfonium salts have been used as initiating mechanisms for polymerization processes ⟨90JAP(K)02178303⟩.

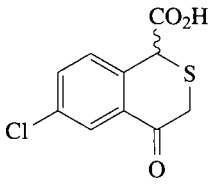
As mentioned in the Introduction, thianes are found, together with many other sulfur and other heterocycles, in oil deposits, and in many geological sediments. Analysis of the structural diversity of the organic content of such sediments permits identification of the biological sources of such materials, and hence affords an insight into prehistoric flora and fauna ⟨92MI 510-05⟩.

5.10.8.2 Dihydrothiopyrans

No significant applications of the dihydrothiopyran ring system appear to exist.

5.10.8.3 Dihydrobenzothiopyrans

As in the case of thianes, dihydrobenzothiopyrans are commonly used as replacements for their oxygen congeners in pharmaceutical research, though activity specifically residing in the sulfur compounds is relatively unusual. One example of such specificity is to be found in the activity of compounds such as (**138**) in the treatment of osteoporosis ⟨88EUP376197⟩.



(**138**)

5.10.8.4 Thiopyrans

Perhaps it is not surprising that the thiopyrans that have found any commercial application are the most stable, fully unsaturated compounds: the thiopyranones or thiopyranylidenes. Thiopyranylidenes conjugated to (thio)pyrylium nuclei have found use as dyestuffs, while similar compounds have been considered as possible phototherapeutic agents for the treatment of certain cancers ⟨90JA3845⟩. The ready photostimulation of electrons in such systems may also render them useful as components of photoconductive polymers, potentially important materials in optical information storage systems, and "organic metals" ⟨87JAP(K)6271965⟩.

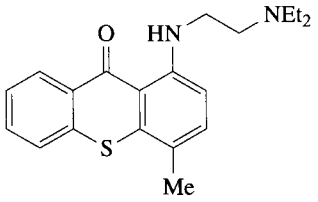
5.10.8.5 Benzothiopyrans

Benzothiopyrans and benzothiopyranylidene-containing compounds, such as thiochromones, being perhaps among the most stable and accessible of the thiins, have found numerous applications. Papers and patents have specifically described their use as pesticides ⟨88MIP8800197⟩, fungicides ⟨86JIC323⟩, antimalarials ⟨87AF647⟩, and antibiotics ⟨90EUP481441⟩, as well as the numerous more broadly drawn patents in which benzothiopyrans are one of several similar ring systems of interest.

Of nonbiological applications, benzothiopyrans have been used in dyes ⟨90MI 510-06⟩ and proposed as components of photochromic systems for recording devices, analogous to the thiopyrans ⟨92JAP(K)04279580⟩.

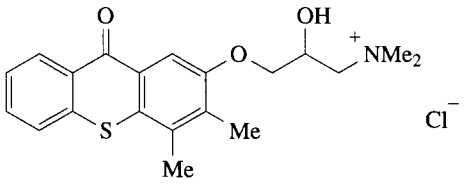
5.10.8.6 Thioxanthenes

The thioxanthenes and -xanthones are commonly used as isosteres for other tricycles in pharmaceutical and agrochemical research. Activity specifically requiring the sulfur heterocycle is reported in asthma ⟨77MIP523260⟩ and cancer studies: lucanthone (**139**) and many of its analogues have been extensively investigated as antineoplastic agents ⟨82JMC220⟩.



(**139**)

The photochemical properties of thioxanthones have been put to industrial application: appropriate substitution of the parent nucleus leads to the water-soluble UV/visible-responsive photocuring initiator "Quantacure" (**140**) for particular classes of vinyl monomers ⟨86MI 510-04⟩.



(**140**)

5.10.8.7 Thiopyrylium Salts

Once again it is the photochemical properties of thiopyrylium species that have excited interest in their industrial application. With appropriate conjugative substitution dyestuffs result, while when associated with other compounds, photoconductive polymers may be prepared for use in solar cells ⟨82MI 510-02, 89GEP(O)3832903⟩.

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5.11
Six-membered Rings with One Selenium or Tellurium Atom

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5.11.1 INTRODUCTION

Selenoxanthone (**22**) was known as early as 1914. However, the chemistry of six-membered heterocycles containing one selenium or tellurium atom only developed primarily during the 1970s and especially the 1980s when their potential industrial applications were noticed. As the topic was not covered in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) this chapter covers the main features prior to 1980 and is complete from that date until 1993. Several earlier general reviews are available on selenium and tellurium derivatives ⟨41CRV179, 50CRV279, B-73MI 511-01, B-74MI 511-01, B-77MI 511-01, 90HOU(E12.b), 91S793, 91S897, 94AHC(59)179, 94AHC(60)65⟩ and selenium and tellurium heterocycles ⟨B-84MI 511-01⟩. More specific works deal with selenanes and telluranes ⟨75CRV611⟩, the reactions and applications of selenopyrylium salts and dyes ⟨81YGK1⟩, and chalcogenoxanthylium salts ⟨83KGS435⟩.

The nomenclature system used for six-membered selenium heterocycles is shown below (Structures (1)–(28)) and is obviously the same for the tellurium analogues. Although IUPAC nomenclature is recommended many chemists still use the trivial system. The different generic names are given under the corresponding formulae and are used interchangeably.

Selenane
Terahydroselenopyran

(1)

3,4-Dihydro-2*H*-selenin
3,4-Dihydro-2*H*-selenopyran

(2)

5,6-Dihydro-2*H*-selenin
5,6-Dihydro-2*H*-selenopyran

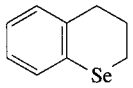
(3)

(4)

2*H*-Selenin
2*H*-Selenopyran

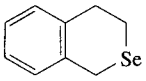
(5)

4*H*-Selenin
4*H*-Selenopyran



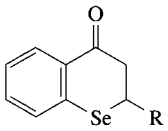
(6)

3,4-Dihydro-2*H*-1-benzoselenin
Selenochroman



(7)

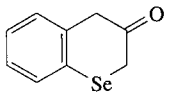
3,4-Dihydro-1*H*-2-benzoselenin
isoselenochroman



(8)

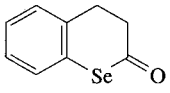
R = H, 2,3-Dihydro-4*H*-1-benzoselenin-4-one
1-Selenochroman-4-one

R = Ph, Selenoflavanone



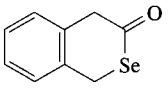
(9)

2*H*-1-Benzoselenin-3(4*H*)-one
Selenochroman-3-one



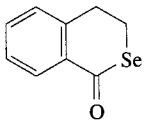
(10)

3,4-Dihydro-2*H*-1-benzoselenin-2-one
3,4-Dihydro-1-selenocoumarin



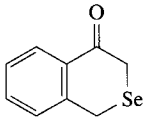
(11)

1,4-Dihydro-3*H*-2-benzoselenin-3-one
Isoselenochroman-3-one



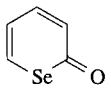
(12)

3,4-Dihydro-1*H*-2-benzoselenin-1-one
3,4-Dihydroisoselenocoumarin



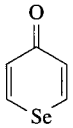
(13)

1*H*-2-benzoselenin-4(3*H*)-one
Isoselenochroman-4-one



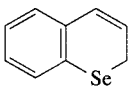
(14)

2*H*-Selenin-2-one
2*H*-Selenopyran-2-one
α-Selenopyrone



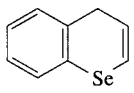
(15)

4*H*-Selenin-4-one
4*H*-Selenopyran-4-one
γ-Selenopyrone



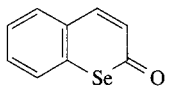
(16)

2*H*-1-Benzoselenin
2*H*-Selenochrom-3-ene



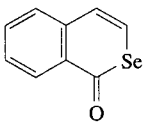
(17)

4*H*-1-Benzoselenin
4*H*-Selenochrom-2-ene



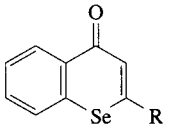
(18)

2*H*-1-Benzoselenin-2-one
1-Selenocoumarin



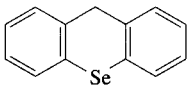
(19)

1*H*-2-Benzoselenin-1-one
Isoselenocoumarin



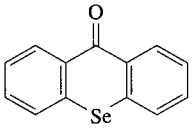
(20)

4*H*-1-Benzoselenin-4-one
R = H, Selenochromone
R = Ph, Selenoflavone



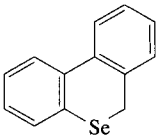
(21)

10*H*-Dibenzo[*b*,*e*]selenin
9*H*-Selenoxanthene



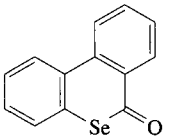
(22)

10*H*-Dibenzo[*b*,*e*]selenin-10-one
Selenoxanthone



(23)

6*H*-Dibenzo[*b*,*d*]selenin

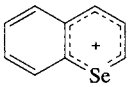


(24)

6*H*-Dibenzo[*b*,*d*]selenin-6-one
Benzo[*c*]selenocoumarin

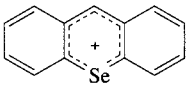
(25)

Seleninium cation
Selenopyrylium cation



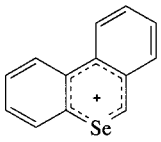
(26)

1-Benzoseleninium cation
Selenochromylium cation
1-Benzoselenopyrylium cation



(27)

Dibenzo[*b*,*e*]seleninium cation
Selenoxanthylium cation



(28)

Dibenzo[*b*,*d*]seleninium cation

5.11.2 THEORETICAL METHODS

Few theoretical works are devoted to six-membered heterocycles containing one selenium or tellurium atom and all of them consist of *ab initio* calculations. Investigations by spectral and polarographic measurements and quantum-chemical calculations in γ-pyrylocyanins were used for the characterization of the relative positions of the frontier MOs. A new parameter ΦB defining the electron donor ability in polymethine dyes has been proposed ⟨84DP295⟩. MO calculations from photoelectron spectra have provided for seleno- and telluro-substituted bipyranylidenes the orbital diagrams of the electronic levels, which seem to be delocalized over the whole ⟨87ZOB505⟩. In a careful and detailed spectral study of a series of chalcogenopyrylium dyes, Detty, a pioneer in this field, has shown that the aromaticity of the heterocycles decreases with the size of the chalcogen, whereas the bathochromic effect increases. Less positive oxidation and less negative reduction potentials follow the order O < S < Se < Te. The π donating character has been evidenced by

MNDO calculations ⟨88OM1131⟩. PPP-MO calculations on the first example of triphenylmethane dye ethynologues showed the contribution of resonance hybrids independent of the counter anions ⟨88JCS(P1)3155⟩.

5.11.3 EXPERIMENTAL STRUCTURAL METHODS

5.11.3.1 X-ray Structures

The electron diffraction structure of selenan-4-one shows a chair conformation with a C—Se bond length (1.92 Å) close to that of dialkyl selenides ⟨85JOC2580⟩. The x-ray structures of the full series of chalcogenopyran-4-ones have been investigated. As expected, these molecules are planar but the hexagonal ring becomes distorted with selenium and tellurium ⟨92OM2157⟩. Nevertheless, other molecules have been investigated with x-rays to confirm proposed structures without any general character, for example a new selenurane derived from selenoxanthene ⟨90CPB874⟩, a bicyclic Mannich reaction product of selenan-4-one ⟨87JMC780⟩, and the tetrahydroselenopyran-4-one derivative resulting from the condensation of benzylidenemalononitrile with cyanoacetamide ⟨89ZOB881⟩. Two distinct crystalline forms were obtained for clathrates derived from 4-(4′-hydroxyphenyl)-2,2,3-trimethylselenochroman; the α form has an undefined structure and the β form is rhombohedral ⟨87MI 511-01⟩. Halogen addition to telluropyrylium dyes led to a hypsochromic effect, and the structure of one of the derivatives formed has been confirmed by x-ray analysis ⟨86OM2250⟩. 4,4′-Biselenopyranylidenes doped with iodine show a compact, regular, segregated structure which is responsible for semiconducting behavior to 255 K ⟨88MCLC197⟩. The molecular structure of tetraphenyl-4,4′-biselenopyranylidene has also been reported ⟨86AX(C)312⟩, as have those of charge transfer complexes of TCNQ with 4,4′-bichalcogenopyranylidene derivatives ⟨88MCLC361⟩.

5.11.3.2 NMR Spectroscopy

The ^{13}C NMR chemical shifts of a single epimer in the six-membered saturated series lead to the assignment of the configuration at that carbon ⟨93MRC80⟩. A *trans* geometry has been proven by NMR (^{1}H, ^{13}C) for complexes of the type PdX_2L_2 where L is the tellurane ⟨91MI 511-01⟩. ^{1}H variable temperature measurements on palladium complexes of selenolane do not allow the observation of conformational changes, which are too fast, but the rates of inversion of the coordinated selenium atom are measurable ($\Delta G^{\ddagger} = 66$–78 kJ M^{-1}) ⟨86JCS(D)205⟩.

^{17}O chemical shifts have been used to correlate the stereochemistry with the heteroatom configuration in substituted heterocyclohexanones. These δ are shielded or deshielded according to the position of the substituent ⟨89JOC4758⟩.

In the ^{13}C NMR of 2,2-dimethylchalcogenan-4-ones, the γ *anti* and *gauche* effects depend on the polarity and electronegativity of the chalcogen ⟨81OMR(17)270⟩. From ^{1}H and ^{13}C NMR data, it was deduced that substituted selenan-4-ones as well as their corresponding cyanohydrins and alcohols are predominantly in the chair form ⟨80JOC4622⟩. An important substituent effect in selenanes and selenan-4-ones has been observed through ^{77}Se NMR measurements ⟨86MRC947⟩.

High resolution NMR studies (δ ^{1}H, $J^{1}H$—^{13}C, $J^{77}Se$-H, δ ^{13}C, $J^{77}Se$—^{13}C) have allowed a complete characterization of thi- and seleninium tetrafluoroborates and comparison with theoretical values ⟨81OMR(16)148⟩.

A ^{125}Te NMR and XPS study of several telluropyran, pyranone, and pyrylium salts has shown that the δ ^{125}Te is, as expected, highly sensitive to the formal positive charge (1304 ppm for di-Bu^{t} cation) and δ values for ^{125}Te of telluropyranones are downfield (139–188 ppm) compared with telluropyran. A linear correlation is found between $\delta^{125}Te$ and Te 3d 5/2 (XPS binding energy) ⟨89OM861⟩. Use of ^{1}H, ^{13}C, ^{77}Se, and ^{125}Te NMR spectroscopies is claimed to be a criterion for distinguishing between trigonal and bipyramidal structures for molecular complexes of cyclic chalcogenides and halogens ⟨83CL675, 90JPO358⟩.

A series of 27 chalcogeno(Se—Te)chroman-4-ones, chromones, and coumarins were investigated by ^{1}H NMR spectroscopy. The delocalization of the heteroatom lone-pair in these heterocycles has been discussed. An important heavy atom shielding effect is found in the ^{13}C spectra ⟨83SA(A)693⟩ as previously established ⟨80OMR(13)319⟩, as a general rule parallel to that existing for halo derivatives.

A complete structural study (IR, UV, ^{1}H, ^{13}C, and μ) of the chalcogenochromones has been

published ⟨81JOM(208)23⟩. The basicity of these heterocycles, based on ν N—H (IR) of pyrrole, decreases from O to Te, indicating a lower contribution to the polar form with increasing size of heteroatom. A careful study of J ^{1}H and δ ^{13}C enabled the stereochemistry to be assigned to isomeric 3-phenyl-2-selenabicyclo[4.4.0]decan-5-ones ⟨92ZOB2728, 92ZOB2055⟩. A dynamic NMR study of naphtho[1,9-*cd*]chalcogenopyrans showed that the increasing barrier to ring inversion with increasing size of the heteroatom is probably due to a bond angle strain ⟨82CC333, 88JCS(P2)469⟩. An excellent linear relationship is found for several heterocycles between ^{77}Se and ^{125}Te chemical shifts ⟨87MRC129⟩. Selenoxanthone shows extraordinarily large values for ^{2}J and $^{3}J^{77}$Se—^{13}C coupling constants. The three factors affecting these parameters (the orientational effect, the coordination number and the ring effect) have been discussed ⟨83BCJ1661⟩. The trigonal bipyramidal or molecular complex structure of the products resulting from the addition of halogen to chalcogenoxanthones (Se, Te) has been investigated by ^{1}H, ^{13}C, ^{77}Se, and ^{125}Te NMR and shown to be highly dependent on the nature of the halogen ⟨90JPO369⟩. Complete NMR data for 9*H*-telluroxanthene and 9*H*-telluroxanthone have been reported ⟨81JOM(208)39⟩. The 9-selenaanthracenide anion, generated from selenoxanthen and KNH_2/NH_3, shows a paratropic molecular frame. ^{1}H and ^{13}C NMR ⟨87JOC5461⟩ studies show a delocalization of the negative charge on the central ring.

5.11.3.3 Mass Spectrometry

A detailed study of fragmentations of a series of selenan-4-ones has shown three principal ways of bond rupture: C_3—C_4, C_4—C_5 and C_2—C_3, in addition to the loss of CO and selenium. Three- and four-membered ions are normally also observed ⟨83IJC(B)640⟩. Mass spectrometry has also been used in many other studies as proof of proposed structures.

5.11.3.4 Infrared, Ultraviolet, Raman, and Photoelectron Spectroscopies

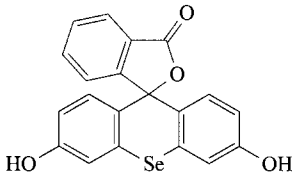
The out-of-plane deformations in the region of 950–980 cm^{-1} allow the identification of the *trans*-cinnamoyl moiety in several organochalcogenated compounds ⟨89UKZ465⟩. The absorption in the near IR of triphenylmethane dye ethynologues shows a red shift when going from O to Se ⟨87CC710⟩. The observation of ν-OH of phenol enabled the evaluation of the basicity of chalcogenan-4-ones, which decreases when the size of the heteroatom increases ⟨84MI 511-02⟩, to be compared with ⟨81JOM(208)23⟩. The IR spectrum of a new catalyst (9*H*-telluroxanthene)$_2$ RhCOCl has been reported ⟨84MI 511-03⟩.

The first excited energy level for singlet (S_1) and triplet (T_1) states decreases with the size of heteroatom in Se and Te xanthones as well as the energy splitting $S_1 \rightarrow T_1$. The difference of photophysical properties may be attributed to the $n\pi^*$ contribution ⟨89MI 511-01⟩.

The condensation of 2,6-di-*t*-butyl-4-methylseleno or telluropyrylium salts with squaric acid affords squarylium dyes which show batho- and hypsochromic effects ($\lambda_{max} = 847$ and 910 nm) ⟨93H(35)1149⟩. The bathochromic effect in 2,6-diphenyltelluropyrylium dyes has been empirically correlated with the metallic character of the chalcogen and follows the order Te > Se > S > O ⟨82JOC5235⟩. A wavelength of 1280 nm (ε_{max}) is claimed as the longest λ yet reported for a nonamethinepyrylocyanine ⟨83KGS1559⟩.

The kinetics of reductive elimination of Cl_2 from dichloro-Te^{IV} compounds have been followed by UV spectroscopy, the reduced species absorbing at a shorter wavelength. The driving force is the regeneration of the aromaticity ⟨93OM2496⟩. The same technique was used to determine the comparative rates of chalcogen oxidation by hydrogen peroxide. The oxophilicity in chalcogenopyrylium dyes increases normally from O to Te ⟨92OM2310⟩.

The quantum yields for the selenopyrylium dye-sensitized photodediazonation of 4-MeO$C_6H_4N_2^+$ are not affected by the concentration of micelles ⟨85ZC109⟩. A new selenium containing photosensitizer (**29**) for (*E*)–(*Z*) isomerization of trienes has been synthesized ⟨91JCS(P2)523, 91JCS(P2)527⟩.



(**29**)

5.11.3.5 Electron Spin Resonance

An ESR study of charge transfer complexes of telluranes with ddq shows a rather more ionic than molecular character ⟨91IJC(A)720⟩.

The radicals generated by reaction of chalcogenochromone-4-thiones with photolytically generated radicals ($R_3M^{\cdot}$) (Si, Ge, Sn) have an orthogonal conformation as for the 4-oxo derivatives. Some differences in behavior can be accounted for by the electronegativity values ⟨81JOM(221)47, 88T3693⟩.

4,4′-Bichalcogenopyranylidenes (Se, Te) show broad single lines in the ESR spectra. The g value increases with the size of the heteroatom X and there is a linear correlation between g and the spin orbit coupling constant of X (λ) ⟨85T4853⟩.

Reduction of 9-phenyl-9*H*-telluroxanthylium perchlorate with zinc dust in THF affords the corresponding radical, the ESR spectrum of which shows an interaction of the unpaired electron with hydrogens in positions 1, 3, 6, and 8. The radical can dimerize reversibly ⟨80KGS1421⟩.

5.11.3.6 Dipole Moments

A dipole moment study of selenopyran-4-ones, selenan-4-ones, and selenoxanthones was used as the basis of an approach to the aromaticity of these heterocycles ⟨86ZN(A)1250⟩. The contribution to a polar form in chalcogenochromanones is weaker than in the corresponding chromones, as established from dipole moment measurements. The contribution to a polar form decreases from O to Te ⟨80JST(67)251⟩.

5.11.3.7 Miscellaneous

Conductivity measurements of telluronium salts derived from tellurane have shown that they exist as ion-pairs in DMSO ⟨91MI 511-02⟩.

5.11.4 THERMODYNAMIC ASPECTS

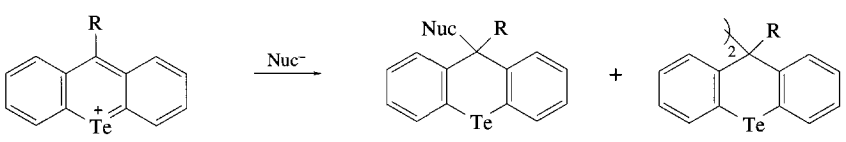
Microscale TLC separations of sulfur- and selenium-containing heterocycles have been realized with thio- and selenochromenes ⟨87MI 511-02⟩ and with thio- and selenoxanthenes or xanthones ⟨87MI 511-03⟩.

5.11.5 REACTIVITY OF FULLY CONJUGATED RINGS

The fully conjugated rings are seleninium and tellurinium derivatives, and few types of reactions are known.

5.11.5.1 Reactions with Nucleophiles

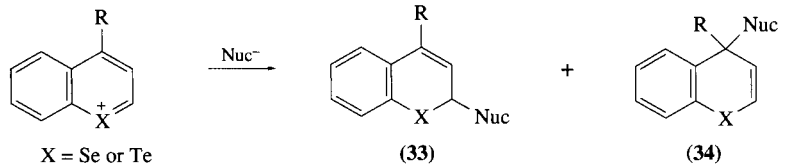
In the same way as with selenoxanthylium salts, telluroxanthylium salts (**30**) react with nucleophiles by addition to position 9, which gives telluroxanthene derivatives (**31**) together with some ditelluroxanthyls (dimeric form of telluroxanthene) (**32**) (Equation (1)). The nucleophiles may be N_3^- ⟨87KGS279, 88JCS(P1)2271⟩, halide, MeO^-, or OH^- ⟨89KGS691⟩.



(30) (31) (32) (1)

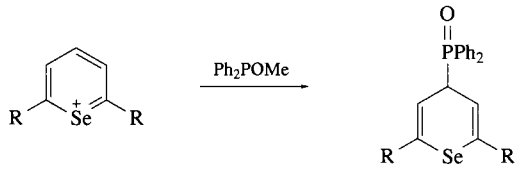
With chalcogenochromylium salts (X = Se, Te), the nucleophile may add at the 2 or 4 positions

to give, generally, a mixture of 2- and 4- substituted seleno- or tellurochromenes (**33**) and (**34**) (Equation (2)). In this case the nucleophile may be CN^- ⟨87H(26)2365⟩ or N_3^- ⟨84JHC1321⟩.



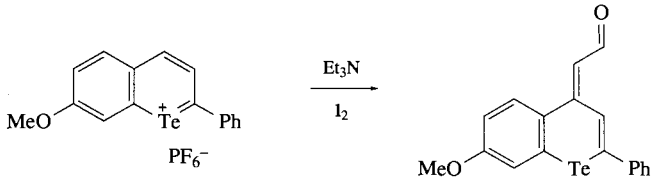
X = Se or Te (**33**) (**34**) (2)

Substituted seleninium perchlorates react with Ph_2POCH_3 to give addition products (**35**) (Equation (3)) ⟨90ZOB1012⟩.



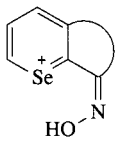
R = Bu^t, Ph (**35**) (3)

2-Substituted tellurochromylium salts react with tertiary amines in the presence of iodine to give α,β-unsaturated oxo-compounds such as (**36**), which can be used as starting materials for the synthesis of telluropyrylium polymethine dyes (Equation (4)) ⟨84JOC2676⟩.



(**36**) (4)

Telluropyrylium dyes act as catalysts for oxidations with hydrogen peroxide and as scavengers of singlet oxygen. First they add H_2O_2 (or $O + H_2O$) to the tellurium atom of the salt and the intermediate dihydroxytellurane is the true mild oxidation agent which gives faster reactions ⟨90JA4086, 92OM2147⟩. The nitrosation of cycloalkylselenopyrylium salts affords the (*Z*)-oxime (**37**) ⟨90ZOR405⟩.



(**37**)

9-Aryltelluroxanthylium perchlorates have been patented as analytical reagents for determination of water in aprotic solvents ⟨92URP1735295⟩.

5.11.5.2 Radical and Electrochemical Reactions

Polarographic half-wave reduction potentials were determined for one type of seleninium salt. They undergo a reversible electron transfer with dimerization ⟨86ZOB863⟩.

5.11.6 REACTIVITY OF NON-CONJUGATED RINGS

Most of the reactions carried out on six-membered heterocycles containing one selenium or tellurium atom are covered in this section and are presented in terms of the degree of saturation of the heterocycle.

5.11.6.1 Reactivity of 2*H*- and 4*H*-Chalcogenins and their Carbocyclic Condensed Derivatives

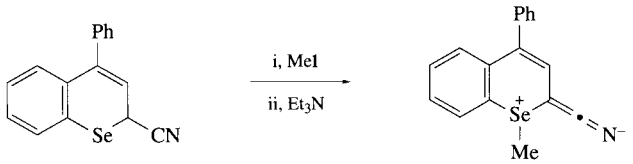
5.11.6.1.1 Thermal and photochemical reactions

Thermal or photochemical rearrangements of 9-azido-9-aryltelluroxanthenes (**38**) give dibenzo[*b*,*f*]1,4-tellurazepines (**39**) together with the corresponding phenanthridine arising from loss of the tellurium atom (Equation (5)) ⟨87KGS279⟩. The same type of reaction with a 9-(4-pyridyl)-selenoxanthene gave the unstable 4-pyridyldibenzo[*b*,*f*][1,4]-selenazepine ⟨84JHC1321⟩.

(38) (39) (5)

5.11.6.1.2 Reactions at the chalcogen atom

Classical addition of halogens to the chalcogen heterocycles gives dihalo compounds with tellurochromene ⟨88KGS1050⟩. The first stable selenabenzene derivative (**41**) was prepared by addition of iodomethane to selenochromene (**40**), followed by dehydroiodination with Et_3N (Equation (6)) ⟨87H(26)2365⟩.



(40) (41) (6)

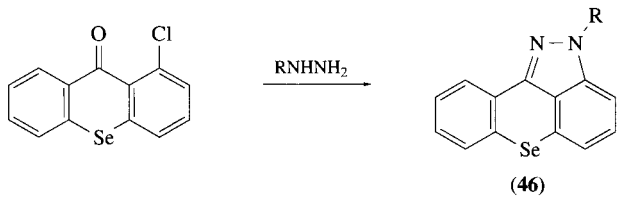
Telluropyran-4-one and tellurochromone are not oxidized to telluroxides by common oxidizing agents (H_2O_2, MnO_4^-, ...), but peracetic acid adds to the tellurium atom just as halogens do ⟨87JOC2123⟩.

The kinetics of halogen exchange in Te-dichlorotelluropyrylium dyes are first order in CD_3CN and second order in $CDCl_2CDCl_2$ ⟨86OM2250⟩. Selenoxanthene Se-oxides react with activated alkynes to give new selenium ylides ⟨83TL75, 84CPB2666⟩ and with chloramine-T to give isomeric seleninimines ⟨83PS(16)97⟩, the *cis*-form of which is the more stable.

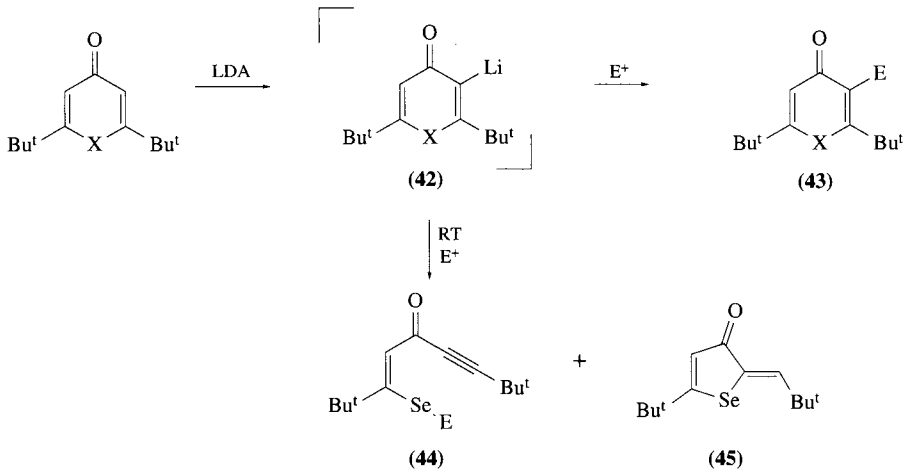
5.11.6.1.3 Reactions with nucleophiles

2-or 4-Oxo derivatives undergo reaction with carbanions to give the corresponding alcohols, from which the chalcogeninium salts are obtained by reaction with acids: selenoxanthone ⟨88JCS(P1)3155⟩, telluroxanthone ⟨81KGS343, 80KGS274⟩, and seleno- and telluropyran-4-ones ⟨92OM2157⟩. LDA metallates chalcogenopyran-4-ones and chromones. The 3-lithio intermediate (**42**) can be quenched in the cold with several electrophiles to give (**43**) but at room temperature it gives a mixture of ring-opened products (**44**) after action of an electrophile together with small quantities of the ring contracted derivative (**45**) (Scheme 1) ⟨88JOC1203⟩.

The reaction of 1-chloroselenoxanthone with substituted hydrazines was patented for the formation of antibacterial, antifungal, and antitumor compounds (**46**) (Equation (7)) ⟨86EUP170412⟩.

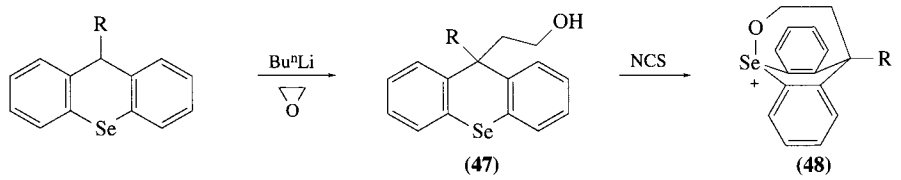


(46) (7)



Scheme 1

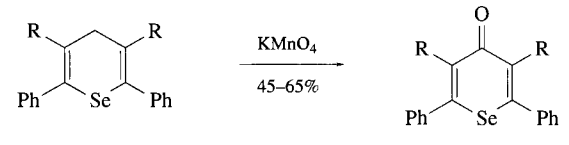
Bu^{n}Li deprotonation of 9-substituted selenoxanthenes, followed by reaction with oxirane gives the intermediate alcohols (**47**) which can be cyclized to the selenuranes (**48**) (Scheme 2) ⟨84H(22)1473⟩.



Scheme 2

5.11.6.1.4 Radical, electrochemical, and redox reactions

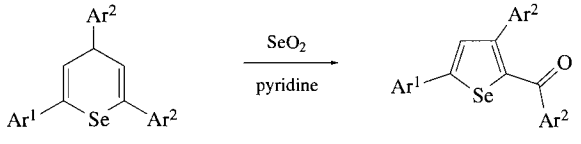
$KMnO_4$ in acetone oxidizes 4*H*-selenopyrans to the corresponding pyranones (**49**) (Equation (8)) ⟨91KGS996⟩ without affecting the selenium atom. Oxidation with SeO_2 in pyridine, however, affords the corresponding 2-acylselenophene (**50**) by a well-known ring contraction process (Equation (9)) ⟨89KGS767⟩. 2*H*-Tellurochromene is transformed by the same reaction into 2-formylbenzo[*b*]tellurophene (**51**) (Equation (10)) ⟨83JOM(258)163, 88KGS1050⟩.



(8)

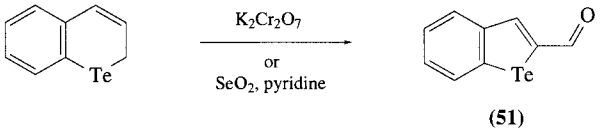
(**49**)

R = H or Me



(9)

(**50**)

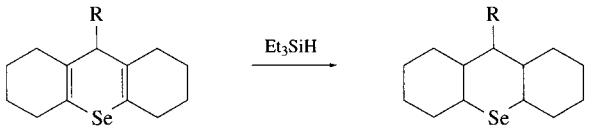


(10)

(**51**)

One-electron electrochemical oxidation of 9-substituted octahydroselenoxanthenes affords the corresponding salts ⟨91KGS47⟩. Oxidation of Te-dichlorotelluroxanthene with $K_2Cr_2O_7$ gives the corresponding telluroxanthone ⟨80KGS1342⟩. Surprisingly, when treated with trifluoroacetic acid, 9-aryloctahydroselenoxanthenes give the unsubstituted seleninium salts with loss of the aryl moiety ⟨91KGS900⟩, whereas use of ddq results in the expected dehydroaromatization ⟨91KGS51⟩. Electrochemical oxidation of selenoxanthene affords the corresponding seleninium salts in anhydrous solvents but selenoxanthydrol is obtained in the presence of water. Further oxidation leads to the selenoxanthone and then the oxide ⟨90MI 511-02⟩. When treated with strong acids, tellurochromene gives the corresponding salts ⟨86KGS1571⟩.

Somewhat surprisingly, the reduction of chalcogenopyran-4-ones with dibal-H gives the corresponding pyran together with some dimeric product ⟨88OM1122⟩. A DMSO solution of Se-dichloroselenoxanthone is claimed to undergo reduction to selenoxanthone, forming chloromethyl methyl sulfoxide ⟨83CL33⟩. The electrochemical reduction of halogen adducts of seleno- and telluroxanthones gives the expected 9-substituted heterocycle ⟨90ZOB847⟩. The reduction of octahydroselenoxanthenes (**52**) with triethylsilane affords the perhydro compounds (**53**) (Equation (11)) ⟨81KGS564⟩.

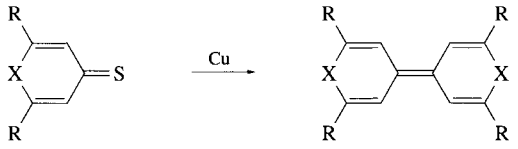


(11)

(52) (53)

R = Me, Et, CH_2Ph

Several 4,4′-bichalcogenopyranylidenes (**54**) have been prepared by reductive coupling of the corresponding chalcogenopyran-4-ones (Equation (12)) ⟨85T4853⟩. These dimeric compounds have proven to be good organic metals donors ⟨81TL2771, 84BSF(2)241⟩. Their oxidation potential increases with the size of X and their conductivity is highly dependent on the nature of the substituents ⟨83TL539⟩. Telluroflavone derivatives behave similarly ⟨82JOC1146⟩. The reductive condensation of selenopyran-4-thione with 1,3-dithiole-2-thione derivatives leads to new unsymmetrical electron donors ⟨88CC822⟩. The reaction of 2,6-di-*t*-butylselenopyrone with the lithium salt of ethyl diazoacetate gives the corresponding selenepin after ring enlargement ⟨90AG(E)424⟩.



(12)

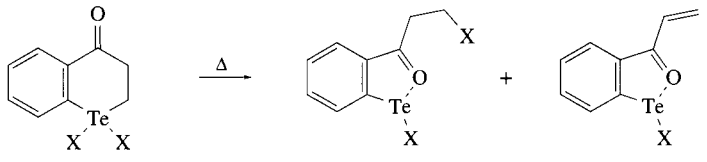
(54)

R = Me, Bu^t, Ph X = O, S, Se, Te

5.11.6.2 Dihydrochalcogenopyrans and Their Carbocyclic Derivatives

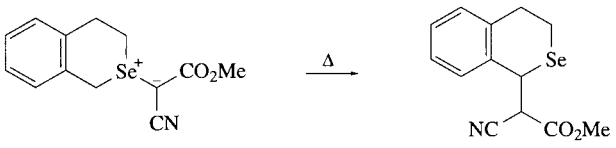
5.11.6.2.1 Thermal and photochemical reactions

The thermal decomposition of halogen adducts of tellurochromanone (**55**) leads to the stabilized tellurenyl derivatives (**56**) and (**57**) (Equation (13)) ⟨90ZOB2764⟩. The selenium ylide (**58**) rearranges under thermal conditions to give compound (**59**) (Equation (14)) ⟨90JCS(P1)39⟩, and the same reaction is observed with ylide (**60**) (Equation (15)) ⟨90JOC2458⟩. Thermolysis of the selenonium ylide (**61**) leads to formation of compounds (**62**) and (**63**) as the main products (Scheme 3). A mild reflux in ethanol affords the ring opened selenide (**64**) ⟨87JOC1397⟩.

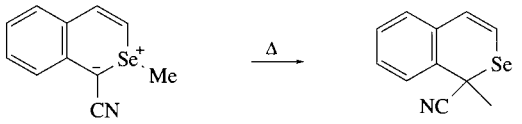


(13)

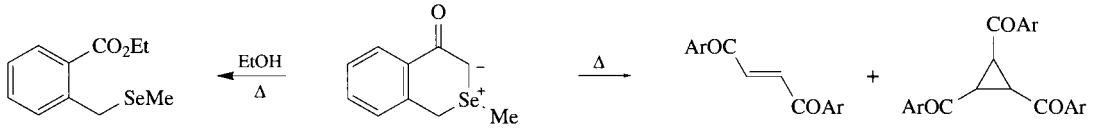
(55) (56) (57)



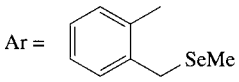
(58) (59) (14)



(60) (15)



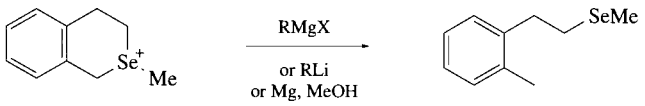
(64) (61) (62) (63)



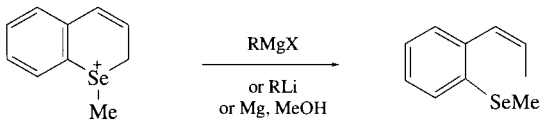
Scheme 3

5.11.6.2.2 Reaction with nucleophiles

The single electron transfer reaction of various selenonium salts derived from benzodihydroselenopyrans or pyran-4-ones with carbanions leads to a mixture of ring opened ⟨89TL981⟩ and other products ⟨90JCS(P1)3017⟩ whose structures are influenced by the counteranion (Equations (16) to (19)) ⟨90CPB779⟩. This type of reaction has been successfully applied to the synthesis of medium-sized selenium heterocycles ⟨90TL3027⟩. The condensation of selenochromanone with substituted benzaldehydes gives the corresponding (*Z*)-chalcones ⟨85ZOB367, 92JCR(S)393⟩.



(16)



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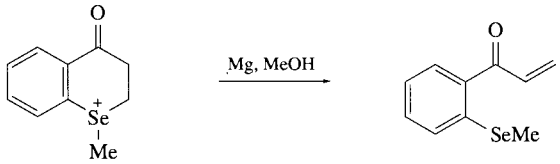

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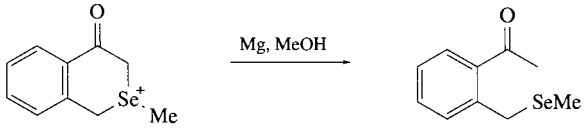


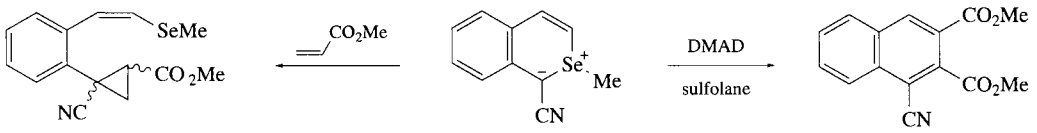
(19)

5.11.6.2.3 *Radical, electrochemical, and redox reactions*

The electrochemical oxidation of selenochromanes and selenochroman-4-one gives a cation radical which can be deprotonated and transformed into 4*H*-selenochromene, selenochromone, or the corresponding ring-opened diselenide ⟨87ZOB609, 89URP1456430, 89ZOB1349⟩.

5.11.6.2.4 *Cycloaddition reactions*

The reactions of the selenium ylide (**65**) derived from 1*H*-2-selenochromene with dimethyl acetylenedicarboxylate and with electron-deficient alkenes give different types of products (e.g. (**66**) and (**67**)) whose structure, especially in the case of the DMAD reactions, depends on the solvent (Scheme 4) ⟨90H(30)295, 90JOC2458⟩.



(*cis* + *trans*)
(**67**) (**65**) (**66**)

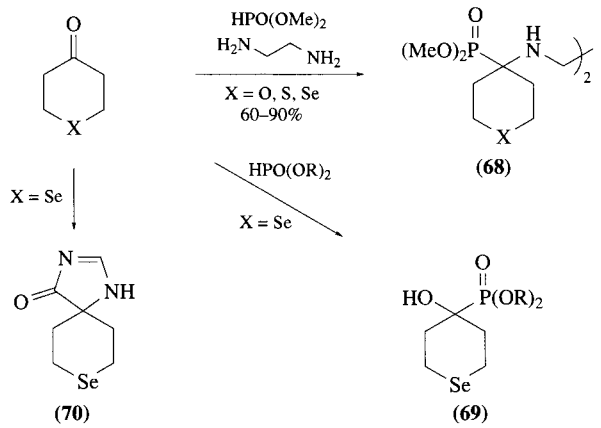
Scheme 4

5.11.6.3 Tetrahydrochalcogenopyrans and Their Carbocyclic Derivatives

5.11.6.3.1 *Reactions with nucleophiles*

Lithium aluminum hydride reacts normally with 3,6-dimethylselenan-4-one to give a mixture of stereoisomeric alcohols ⟨92ZOB1314⟩. It has been shown that the rate of reduction of tetrahydrochalcogenopyran-4-ones decreases from O to Se ⟨84IJC(B)623⟩. The relative rates of alkaline hydrolysis of tetrahydroselenopyran-4-ol acetate have been interpreted in terms of conformational and solvent effects, and conformations tentatively assigned on the basis of these kinetics ⟨84IJC(B)441⟩. The rates of acetylation of analogues of selenan-4-ols coupled with NMR arguments (^{1}H and ^{13}C) allow the determination of their conformations ⟨81JOC2542⟩.

A second order rate is observed for the formation of both the semicarbazone ⟨83IJC(B)403⟩ and the oxime ⟨83JCS(P2)49⟩ of tetrahydroselenopyran-4-one. Tetrahydrochalcogenopyran-4-ones react with ethylenediamine to give dimeric products (**68**) ⟨93ZOB938⟩ and with dialkyl phosphonates to give the normal products (**69**) which can be acetylated ⟨92ZOB2786⟩. Classical transformations of tetrahydroselenopyran-4-one allow the synthesis of spiroimidazolidinone (**70**) (Scheme 5) ⟨90OPP514⟩.



Scheme 5

The Mannich reaction with tetrahydroselenopyran-4-one gives unusual multicyclic compounds ⟨86OPP329, 88PS(39)91, 91CB423⟩. Some of them are claimed to have antiarrhythmic properties ⟨87JMC780⟩.

5.11.6.3.2 Radical reaction

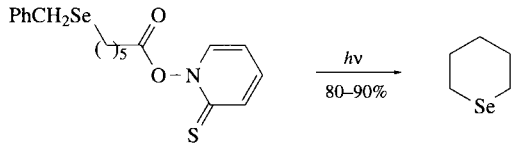
The reaction of *N*-bromosaccharin with tetrahydroselenopyran-4-one is first order with respect to the heterocycle ⟨86JCS(P2)957⟩ and gives the 3-bromo derivative.

5.11.7 RING SYNTHESIS

5.11.7.1 Formation of One Bond

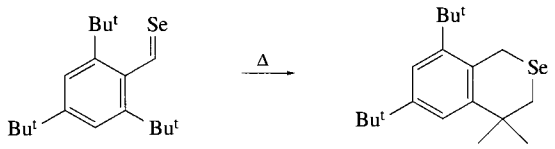
5.11.7.1.1 Se—C_2

Extrapolation of Barton's radical reaction allows the one-way cyclization of benzyl selenides (**71**) to selenanes (**72**) (Equation (20)) ⟨92CC57, 93T2557⟩.



(71) (72) (20)

The reaction of selenoneformate (R—O—CHSe) with highly hindered organolithium compounds can be used to prepare the stable blue selenoaldehyde (**73**) which undergoes thermal or photochemical cyclization to the isoselenochromane (**74**) (Equation (21)) ⟨86BCJ2529, 86CC71, 89JA5949⟩. A mechanism has been proposed ⟨87BCJ1037⟩.

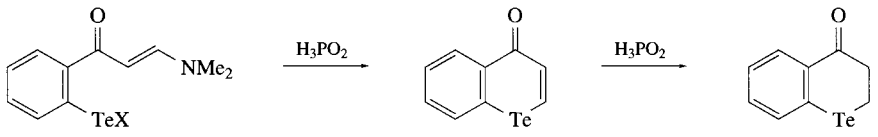


(73) (74) (21)

A new methodology has been designed for the synthesis of chalcogenochromone derivatives (**76**), consisting of the azeotropic HBr-induced cyclization of keto alkynes bearing an *ortho* alkylchalcogenide (**75**) (Equation (22)) ⟨85JOM(287)81⟩. A rather similar reaction is useful for the synthesis of tellurochromone and tellurochromanone (Scheme 6) ⟨81JOM(208)11⟩.

(75) (76) (22)

X = O, S, Se

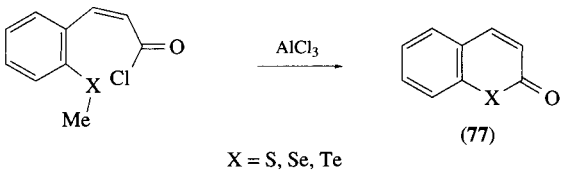


Scheme 6

The first example of a seleno-Claisen rearrangement of an allyl vinyl selenide is reported to give a 5,6-dihydro-2*H*-selenin ⟨92CC1680⟩.

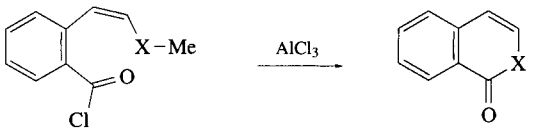
Chalcogenocoumarins (**77**) and their 3,4-dihydro derivatives are available through a chalcogen electrophilic ring closure (Equation (23)) ⟨84JHC1281⟩. In some more sophisticated cases, polyphosphoric silyl ester (PPSE) appeared to be the sole efficient reagent for the cyclization of the free acid ⟨91BSB1, 92H(34)1119⟩. The Simonis–Pechman reaction has also been applied to the synthesis of

selenocoumarin itself ⟨84IJC(B)328⟩. Isochalcogenocoumarins (**78**) have been obtained from *o*-chloro-carbonylarylalkenes following the same principle as for chalcogenocoumarins (Equation (24)) ⟨80JOC3535⟩.



(77)

X = S, Se, Te (23)



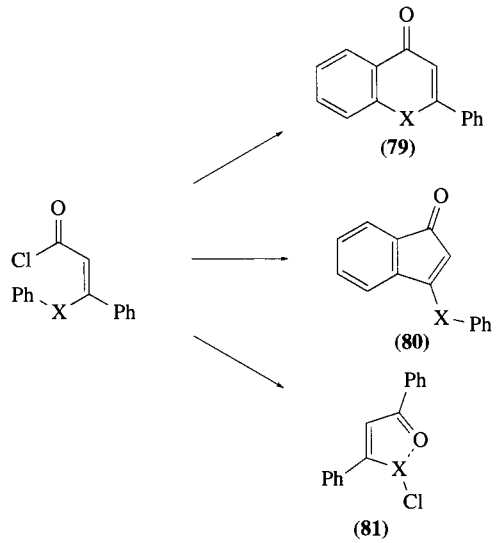
(78) (24)

The 1,6-diselenapyrene system has been synthesized and behaves as a relatively good electron donor ⟨93CL443⟩.

5.11.7.1.2 C_3—C_4

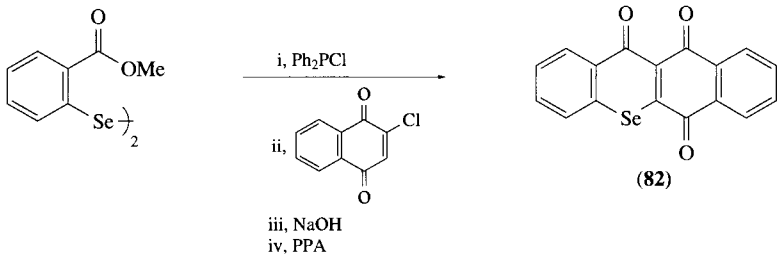
The electrophilic aromatic cyclization of appropriate carboxylic acid derivatives bearing an arylseleno function is the oldest method for the preparation of ketonic six-membered benzo-heterocycles and as early as 1914 ⟨14CB2510⟩ was used to obtain selenoxanthone. The general route has since been widely applied for the preparation of numerous heterocycles.

The factors controlling the cyclization of phenylchalcogenopropenoic acids have been studied and the formation of compounds (**79**), (**80**), or (**81**) has been discussed (Scheme 7) ⟨85JOM(287)81, 88OM2188⟩. When X = S, thioflavone derivatives (**79**) are obtained, whereas with X = Te the *ipso* attack predominates; with X = Se, the results are intermediate ⟨83JA883⟩. The best yields were obtained by reacting the mixture of $MeSO_3H$ and P_2O_5 with the free acid ⟨80JOC4611⟩. Japanese chemists have described the synthesis of quinonic selenochromones (**82**) by the reduction dialkyl diselenosalicylates with Ph_2PCl, followed by condensation with 2-chloro-1,4-naphthoquinone, then hydrolysis and cyclization (Equation (25)) ⟨92BCJ1291⟩. PPSE is claimed to be the best reagent for such cyclizations ⟨89JOC5642⟩.



X = S, Se, Te

Scheme 7

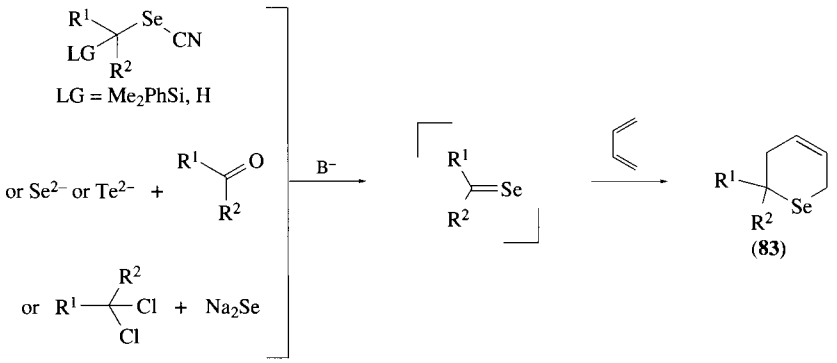


(25)

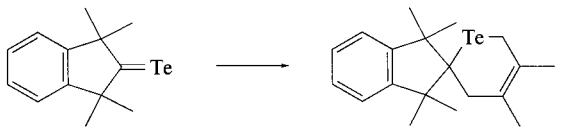
5.11.7.2 Formation of Two Bonds

5.11.7.2.1 Se—C_2 plus C_5—C_6

The [2 + 4] cycloaddition of selenoxo compounds across a diene is the most widely used reaction for the preparation of various 3,4-dihydro-2*H*-selenins (**83**), which are of course, inevitably substituted at the 2-position (Scheme 8). This method originated in 1986 with the first synthesis of a selenoaldehyde ⟨86JA1314⟩ and developed subsequently. The starting selenoxo compounds are generally prepared by elimination of a leaving group (LG) from a selenocyanate. In most of the cases, the base used is triethylamine. Diene components which have been used are anthracene ⟨91CB423⟩, 9,10-dimethylanthracene ⟨93TL4925⟩, 2,3-dimethyl-1,3-butadiene ⟨88JA624, 88JA8671, 88JCS(P1)1913, 88JPO59, 88TL6965, 89AG(E)179, 89JA8749, 89TL6047, 90AG(E)1067, 90BCJ1653, 92CL1843⟩, cyclopentadiene ⟨87TL6649, 88JA1976, 89TL2095, 91CL1053, 91TL7427, 92TL7865⟩, norbornadiene ⟨92TL1333⟩, 1,4-diphenyl-1,3-butadiene ⟨91TL7389⟩, 1,3-cyclohexadiene ⟨89CC667, 90CB725⟩, and 2-methyl-1,3-butadiene ⟨87TL4423, 88JOM(340)153⟩. The regioselectivity of the reaction has been discussed ⟨87TL3887, 87TL5121⟩, as has the stereoselectivity ⟨86CC1152⟩. Perfluoro derivatives ⟨88C265, 90JOM(386)321, 91CB51⟩ and diseleno esters undergo the same reaction ⟨93JA5823⟩. The first isolated telluroketone (**84**) behaves similarly (Equation (26)) ⟨93JA7019⟩. The reaction may be assisted by transition metal carbonyls, which stabilize the selenoxo compound. In such cases, the heterocycle which is obtained remains complexed with the metal carbonyl, for example $W(CO)_5$ ⟨86JOM(299)C7, 89JOM(364)155, 91JOM(415)211⟩; $Mo(CO)_5$ ⟨90JOM(385)351⟩.



Scheme 8



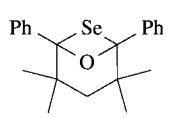
(26)

(**84**) (^{13}C : 301 ppm)

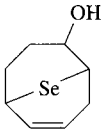
5.11.7.2.2 Se plus C_5 unit

In a particular reaction, $SeCl_2$ adds to a diketone monohydrazone to give the bicyclotetrahydroselenopyran (**85**) among other selenoorganic derivatives ⟨93BCJ1714⟩.

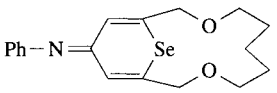
The oxidation of 1,5-cyclooctadiene with SeO_2 affords compound (**86**) in minor yield ⟨89ZN(B)1605⟩. Selenourea acts as selenium source in the synthesis of the ansa-bridged selenide (**87**) ⟨90JOC2567⟩. The same reagent reacts with *O*-benzylgeraniol to give a modest yield of a tetrahydroselenopyran-3-ol derivative ⟨86IZV2514⟩. $SeBr_4$ and $TeBr_4$ add to norbornadiene to give complex structures derived from selenane and tellurane ⟨81UKZ1293⟩.



(**85**)

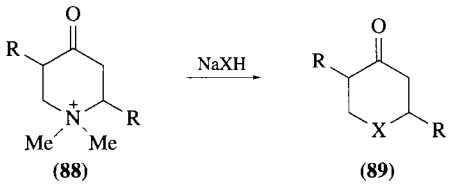


(**86**)

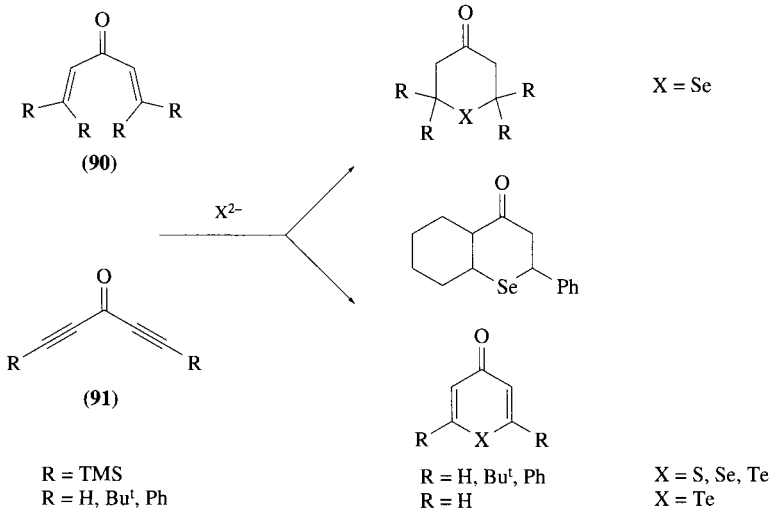


(**87**)

Among the most interesting syntheses are those involving Se^{2-} or Te^{2-} species in the final cyclization step. This situation has initiated several original types of ring closure. The reaction of NaSeH (Se, $NaBH_4$, EtOH) or NaTeH with quaternary piperidin-4-ones (**88**), for example, affords tetrahydroseleno- and -telluropyran-4-ones (**89**), R = H, X = Se, Te (Equation (27)) ⟨85JOC2580, 85TL5441⟩; R = Me, X = Se ⟨92ZOB851⟩ by a ring-opening-ring closure sequence. In related reactions, nucleophilic addition of selenide or telluride anions to activated alkenes (**90**) or alkynes (**91**) leads to seleno- and telluropyran-4-one derivatives in good yields (Scheme 9) ⟨80JOC4622, 87JOC3662, 89ZOB2644, 90ZOR2171, 92OM2147⟩. The use of Li_2X is claimed to minimize the formation of the isomeric five-membered ring ⟨82JOC1968⟩.



(**88**) (**89**) (27)



(**90**) (**91**)

R = TMS
R = H, Bu^t, Ph

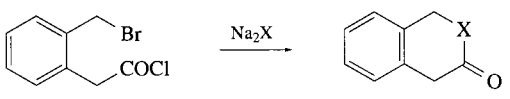
R = H, Bu^t, Ph
R = H

X = Se

X = S, Se, Te
X = Te

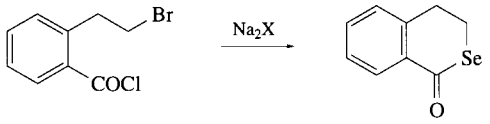
Scheme 9

Double nucleophilic substitutions by Na_2X on appropriate electrophilic substrates are useful for the preparation of benzo fused systems (Equations (28) ⟨83JHC811⟩ and (29)) ⟨81JHC343⟩, and when applied to either 2,2′-dichlorobenzophenone (**92**) ($n = 1$) or 2,2′-dichlorobenzil ($n = 2$) the same reaction gives selenoxanthone (Equation (30)). Attempted extension of this reaction to Na_2Te has so far proved unsuccessful ⟨94UP 512-01⟩.



(28)

X = S, Se, Te



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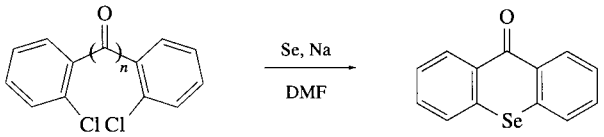
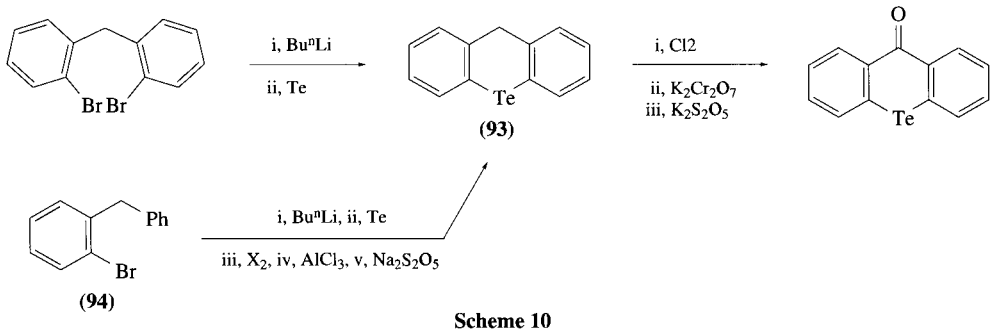


(30)

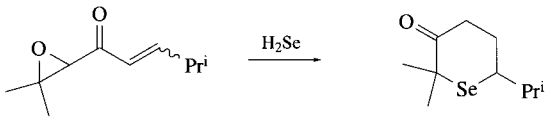
(92)

The reaction of 2,2′-dilithiodiphenylmethane with tellurium is claimed to afford telluroxanthene (**93**), which can be transformed into telluroxanthone by Te-chlorination, then oxidation and reduction (Scheme 10) ⟨81JOM(205)167⟩. Telluroxanthone can also be obtained from (**94**) as shown (Scheme 10) ⟨80KGS1342⟩. Another low yielding and more complicated method consists of the double nucleophilic substitution of 2,2′-bisdiazoniobenzophenone with Na_2Te ⟨79CZ265⟩. However, there is some discrepancy between the properties of the products reported in this paper and those from the bromo compounds.



Scheme 10

The reaction of epoxy ketone (**95**) with H_2Se is the sole direct synthesis of a tetrahydroselenopyran-3-ol derivative (**96**) (Equation (31)) ⟨91ZOR942⟩.

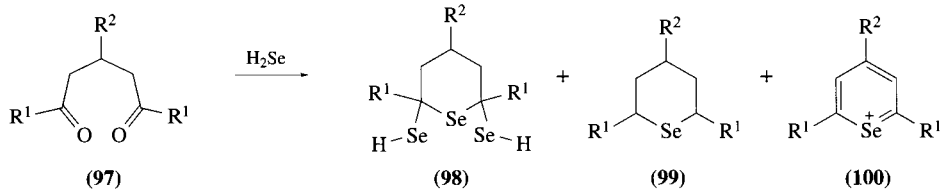


(31)

(95) (96)

The reaction of *p*-methoxyphenyltellurolate with 1,5-dibromopentane affords mainly a cyclic telluronium salt ⟨86JCS(D)2003⟩.

The general ring closure of 1,5-diketones (**97**) has been developed. Depending on the reaction conditions, it is possible to isolate the intermediate (**98**), the required tetrahydroselenopyran-4-one (**99**) or even the seleninium salt (**100**) (Equation (32)) ⟨80IJC(B)812, 81KGS640, 82KGS704, 82MI 511-01, 82ZOR2595, 84KGS1283, 84KGS1634⟩. This reaction has been patented ⟨85URP1167184⟩.



(32)

(97) (98) (99) (100)

5.11.7.2.3 *Se—C_2 plus C_3—C_4*

Ortholithiation methodology opens a new way to selenoxanthones by reaction of selenolate (**101**) with benzynes (Equation (33)) ⟨89CPB36⟩.

(101) (33)

5.11.7.2.4 *Se—C_2 plus C_4—C_5*

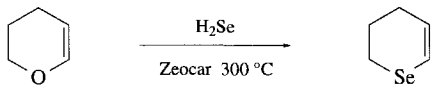
The reaction of cyanoselenoacetamide with benzylidenemalononitrile gives a 4*H*-selenopyran (**102**) which rearranges to a 2-selenopyridine derivative (**103**) (Equation (34)) ⟨89ZOB881⟩. The same reaction occurs with 3-pyridylidenemalononitrile ⟨87ZOB1662⟩.

(102) (103) (34)

Some 2*H*-selenochromenes with an acrolein moiety in the 2-position have been synthesized as building blocks for polymethine dyes ⟨83ZC145⟩.

5.11.7.2.5 *Ring transformations*

The reaction of H_2Se with oxygen heterocycles has been applied to the preparation of 3,4-dihydro-2*H*-selenin (**104**) (Equation (35)) ⟨86KGS1478⟩. Tetrahydrofurfuryl alcohol gives the same result.



(104) (35)

5.11.8 COMPOUNDS OF BIOLOGICAL INTEREST

Six-membered heterocycles with one selenium or tellurium atom have been described or patented in numerous and quite different areas of bioactivity. The photodynamic chemotherapy of tumors with selenium and tellurium heterocycles has been widely studied ⟨88JA5920, 90JA3845, 90JAP(K)02164825, 90JMC1108, 92MI 511-01⟩, while the anticancer and immunostimulating effects of selenoflavonoid derivatives have been demonstrated ⟨90EUP341104⟩. The mitochondrial toxicity of cationic photosensitizers for photochemotherapy has been demonstrated ⟨89MI 511-02, 90MI 511-03, 91MI 511-03⟩.

Some oximes derived from selenochroman-4-one have been claimed as inhibitors of the growth of bacteria ⟨89MIP147859⟩, and the A ring of some androstan-2-ones has been transformed into a selenane ⟨90JOC2170⟩.

Telluropyrylium dyes have been incorporated into glasses for eye protection against laser beam exposure ⟨88JAP(K)6368161⟩.

Bicyclic derivatives of tetrahydroselenopyran-4-one have been claimed to be antiarrhythmic agents ⟨88USP4778892⟩ while cardiovascular and circulation influencing effects have been found in selenochroman-4-one semicarbazones ⟨85GEP3416695, 87GEP85101799⟩. 5-Seleno-D-glycopyranose has been described ⟨80DIS(B)4774⟩.

Starting from 2,4-dibromo-1,5-dimethylbenzene (**105**), a new multistep methodology has been developed to provide access to all the sulfur and selenium analogues of psoralene (**106**; X = Y = O) (Equation (36)) ⟨92H(34)1119⟩. Some of these compounds appear to have interesting properties ⟨92MI 511-02⟩.

X = O, S or(and) Se

(105) (106) (36)

5.11.9 COMPOUNDS WITH POTENTIAL TECHNICAL UTILITY

Due to growing interest in their technical properties, there are now more than 80 patents on molecules containing a six-membered seleno or telluro heterocycle. It is not possible to present here a detailed coverage of the topic, but only to highlight some of the more important areas such as photographic and recording systems.

An important number of original molecules have been patented for use as photographic materials ⟨89EUP297871, 89JAP(K)01126655, 89MIP147859, 90JAP(K)02157760, 93MIP9303419⟩, optical recording systems ⟨87JAP(K)62163050, 88JAP(K)63189292⟩, and in IR laser recording media ⟨85JAP(K)60159087, 86JAP(K)6126044, 86USP4584258, 87JAP(K)62173461, 87JAP(K)6313792⟩.

New organic metals have been developed ⟨87USP4634553, 89JAP(K)01242583⟩, and highly sensitive polymerization photoinitiators have been claimed for particular pyrylium salts ⟨84BEP897694, 84JAP(K)59142205⟩. Even procedures for producing small molecules have been patented: those for selenopyrylium salts ⟨83URP1051089, 87URP1447824⟩, chalcogenochromones ⟨84USP4434098, 87URP1456431⟩, 2*H*-selenopyrans ⟨84GEP208804⟩ and chalcogenopyran-4-ones ⟨84USP4431586⟩.

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5.12
Six-membered Rings with One Phosphorus Atom

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5.12.1 INTRODUCTION

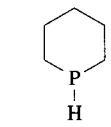
Six-membered rings containing one phosphorus atom were concisely covered as a small part of Volume 1 in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) ⟨84CHEC-I(1)493⟩. There are about 600 references which post-date 1980 and they show a steady development of both theoretical understanding of the aromatic phosphorins and of synthetic methods. Probably the most notable of these have been in the applications of multiply bonded phosphorus species in cycloaddition reactions, the carbene-induced ring-opening reactions of phospholes, and the exploitation of a general route for the synthesis of phosphorus analogues of sugars. A deliberate decision was made to exclude from this section papers of predominantly inorganic interest, bridged-ring systems and systems containing heterocyclic ring(s) fused to the phosphorus-containing ring.

General reviews relevant to this topic include "A decade of research in phosphinine chemistry" ⟨92HAC1⟩, "Cyclic phosphines" ⟨90MI 512-01⟩, and "Phosphabenzene and arsabenzene. Higher element homologs of pyridine" ⟨82MI 512-01⟩, "The λ^5-phosphorins" ⟨82ACR58⟩, "Phosphines and phosphonium salts" ⟨82MI 512-02⟩, and "Synthesis and heterocyclization of oxoalkoxyl derivatives of tricoordinate phosphorus acids" ⟨91ZOB10⟩. An early, but very comprehensive, summary was provided in 1978, by Atkinson ⟨78MI 512-0⟩. Reviews on specific sections are mentioned in appropriate sub-sections.

There is some disagreement in the literature as to the best nomenclature for these compounds. IUPAC ⟨83PAC409⟩ proposed that the six-membered saturated rings be named as derivatives of phosphinane and the unsaturated compounds as phosphinines. *Chemical Abstracts* prefers the older phosphorinane and phosphorin and has completely ignored the IUPAC recommendation. This also follows the lead set by Atkinson ⟨78MI 512-0⟩ and Dimroth ⟨84CHEC-I(1)493⟩. No authors seem to have used phosphinane, although phosphinine is quite common. For consistency, the *Chemical Abstracts* system is used throughout this chapter. IUPAC has no specific recommendations for the di- and tricyclic compounds, and the general line taken by *Chemical Abstracts* and the *Ring Index* is that the names be based on the corresponding non-systematic names used for the nitrogen analogues. In some special cases, the valence of the phosphorus atom, particularly in unsaturated molecules, is indicated by the designations λ^3, λ^4, and λ^5 (see (**1**) and (**2**)). λ^3-Phosphorin (**1**) is also widely referred to as phosphabenzene, a designation which reflects both its structure and the nature of many of its reactions. In an attempt to clarify this confusing situation, some of the names commonly used are summarized in Figure 1. The numbering is taken from *Chemical Abstracts*.

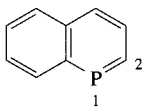
5.12.2 THEORETICAL METHODS

Most theoretical interest has been in questions of aromaticity in fully unsaturated molecules. It is generally concluded that λ^3-phosphorin (**1**) behaves as a fairly classical aromatic system, whereas λ^5-phosphorins (**2**) may be considered as either aromatic or as phosphonium ylides. Several papers concern the idea of aromaticity as a quantitative concept and the application of an aromaticity index. On a scale where benzene ranks 100, λ^3-phosphorin (74) ranks somewhat below pyridine (86) but λ^5-phosphorins with appropriate substituents on phosphorus may be comparable to pyridine according to this scale (R = OMe 81, R = NMe 69, R = Me 66) ⟨86T89, 90JPR885, 90T5697⟩. AM1 was used to calculate the aromatic energies of benzene (28.3 kcal mol^{-1}), phosphabenzene (26.0 kcal mol^{-1}), pyridine (25.6 kcal mol^{-1}), and other heterocycles ⟨89H(28)1135⟩ and CNDO/S methods showed good correlation of calculated transition energies with experimentally observed values. The calculated value for the dipole moment of phosphabenzene was 2.38 D compared with an experimental value of 1.46 ± 0.4 D. The CNDO method has the potential for wide application to the calculation of electronic states of many aromatic and heterocyclic compounds containing second-row elements ⟨85CPB3077⟩. Absolute hardness, related to the gap between HOMO and LUMO energies, also provides a theoretical parameter to recognise aromaticity. Using this measure phosphabenzene (1.66 eV) is a little less aromatic than benzene (2.27 eV) ⟨93OM5005⟩. The *ab initio* stabilization energy of phosphabenzene has been calculated ⟨90MI 512-02⟩. In a related study, calculations were made using *ab initio* molecular orbital (MO) theory to compare the properties of

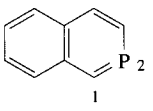


Phosphorinane[a]
Phosphinane[b]

(1)
Phosphorin[a]
Phosphinine[b]
Phosphabenzene
λ^3-Phosphorin



Phosphinoline[a]



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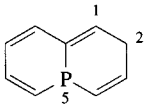
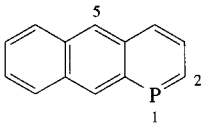


2*H*-Phosphinolizine



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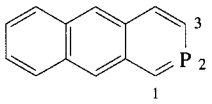

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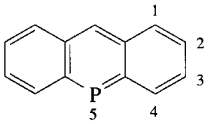
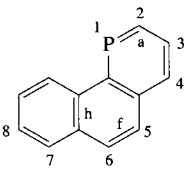
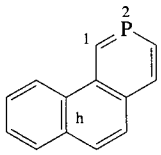


Acridophosphine



Benzo[*h*]phosphinoline



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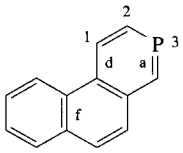
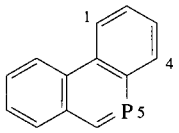
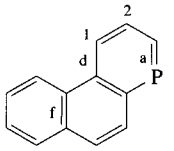


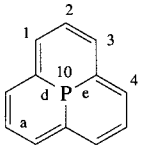
Benz[*f*]isophosphinoline



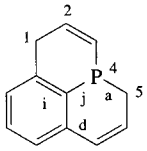
Phosphanthridine



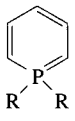
Benzo[*f*]phosphinoli
ne



Phosphorino[2,1,6-*de*]phosphinolizine



1*H*,5*H*-Phosphorino-
[3,2,1-*ij*]-phosphinoline



(2)
λ^5-Phosphorin

Figure 1 Nomenclature of six-membered heterocycles containing one phosphorus atom ([a] Chemical Abstracts; [b] IUPAC ⟨83PAC409⟩; where only one name is given, source is Chemical Abstracts).

heterabenzenes, with the heteroatoms taken from the block in the periodic table bounded by Groups IVA–VIA and periods 2–5. A small decrease in delocalization energy is found between benzene and phosphabenzene ⟨88JA4204⟩.

A Hartree–Foch SCF study concluded that electron population at P—C correlated strongly with bond length and bond order, integrated electron populations correlated with coordination number, and the integrated charge indicated a strongly polarized C—P bond in both saturated and unsaturated compounds ⟨89MI 512-01⟩. However, dipole moment calculations for some dicoordinated phosphorus compounds showed the C=P bond to be practically non-polar in phosphaalkenes but slightly polar in phosphabenzenes ⟨88ZOB1464⟩. Calculated polarizability for phosphabenzene agrees with experimental data ⟨94MP557⟩. Comparison of π-ionization energies of 28 compounds containing X=C double bonds (X = CH, N, P) revealed a larger similarity between carbon and phosphorus than between nitrogen and phosphorus. This suggested that although the strength of the P=C bond is significantly less than that of the C=C or C=N bond, in conjugative interactions P=C is more comparable to C=C than to C=N, which is consistent with similarity observed in reactions

⟨93JPC4011⟩. Theoretical studies of the gas-phase proton affinities of molecules containing phosphorus—carbon multiple bonds, including phosphabenzene, show a slight favour for protonation at phosphorus over carbon. The isomerization energy between the two sites is about 50 kJ mol^{-1}. In contrast, phosphaethyne shows a strong preference for protonation on carbon. Relationships with the basicity of the corresponding nitrogen compounds have been discussed ⟨84JPC1981, 931JQ343⟩.

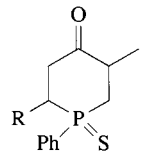
An *ab initio* study of a reaction important in the synthesis of phosphorinanes, the Diels–Alder reaction of aza- and phospha-1,3-butadienes with ethylene, indicated small activation energies (20–28 kcal mol^{-1}) and high exothermicity (about −43 kcal mol^{-1}). The 1-phospha compounds are a little more reactive than the 2-phospha compounds and both are substantially more reactive than the aza-analogues—so reactive, in fact, that the lightly substituted molecules may not be isolated, instead undergoing spontaneous [4 + 2] cycloaddition ⟨84CB3151, 91HAC651⟩. The method used was not able to determine the precise synchronicity of the reactions ⟨92JOC6736⟩.

5.12.3 EXPERIMENTAL STRUCTURAL METHODS

5.12.3.1 NMR Spectroscopy (^1H, ^{13}C, ^{31}P)

Most reports on the application of NMR spectroscopy have related to establishment of conformation and this is discussed under thermodynamic aspects (Section 5.12.4). In a brief review, Schmidpeter gave some examples of ^{31}P resonance frequencies for some phosphorins ⟨88PS(36)217⟩. The signal is at δ 200 ± 20 but is moved significantly by other heteroatoms in the ring and by complexation with metal carbonyls.

Spin-lattice relaxation of ^{13}C nuclei of the *ortho*, *meta*, and *para* carbons of the axial and equatorial phenyl substituents of rigid six-membered heterocyclic rings (**3**, R = H, Me) was used to calculate rotational diffusion constants characterizing the motion of the phenyl groups ⟨91IZV17⟩. Phenyl-group orientation was determined in six-membered saturated rings from ^{13}C longitudinal relaxation times. The spin-lattice relaxation time (T_1) of ^{13}C varies significantly as the phenyl group changes from axial to equatorial (**3**, R = H, Me) ⟨84ZOB1993, 871ZV75⟩. Equilibrium constants and ΔG values for the isomerization of the stereoisomers of 2,5-dimethyl-1-phenyl-1-thioxophosphorinan-4-one (**3**, R = Me) were estimated ⟨91ZOB864⟩. The phenyl orientation at the four-coordinate phosphorus atom in *trans*-isomers of 1-phenyl-1-seleno(thio, oxo)-2,5-dimethylphosphorinan-4-ones was determined. Ring proton chemical shifts vary with temperature differently according to the phenyl group orientation ⟨81MI 512-01⟩.



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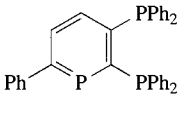

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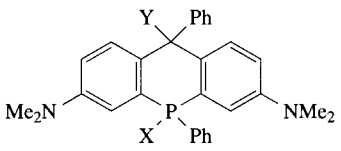

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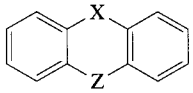

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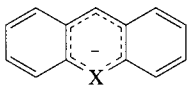


(7)

Spin-lattice relaxation for the ^{31}P via spin-rotation for some phosphines, phosphine oxides, and phosphine sulfides as a function of temperature and concentration has been investigated. The relaxation method for the 1-phenyl-1-thiophosphorinan-4-one has a definite spin-rotation component but the ^{31}P nucleus relaxes predominantly by the chemical shift anisotropy mechanism. This also participates in the relaxation of the phosphine oxides. Dipole–dipole relaxation is involved in all systems to some extent. The activation energies for molecular rotational re-orientation in systems where dipole–dipole relaxation makes a significant contribution fit reasonably well with the size and shape of the molecules and the T_1 values increase with a decrease in concentration ⟨81PS(11)199⟩.

NMR Spectra of heterocyclic aromatic ring systems oriented in liquid crystalline media were used to establish relationships between some geometric parameters and covalent or van der Waals radii of the heteroatom which agreed well with values established by more direct means ⟨80MI 512-01⟩. 2,3-Bis(diphenylphosphino)-6-phenyl-λ^3-phosphorin (**4**), the first example of a λ^3-phosphorin bearing phosphorus-containing side-chains, showed the largest value of 3 J_{PP} (178 Hz) found to

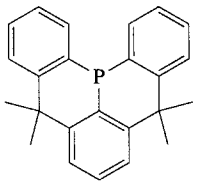
date for a system containing the P—C—C—P linkage, probably as a result of geometric factors placing the non-bonding electron pairs of the two side-chain phosphorus atoms in very close proximity to one another ⟨88JHC155⟩.

An NMR study of ring inversion in 3,7-bis(dimethylamino)-5,10-diphenyl-5,10-dihydroacridophosphine (**5**, Y = H, X = null) showed the free energy of activation to be about 29 kcal mol^{-1} with the conformer having an equatorial phenyl group being the more stable ⟨84ZOB2649⟩. Internal rotation of the cation (**5**, Y = +, X = S) was studied ⟨82ZOB1930⟩. ^{31}P and ^{29}Si NMR of phosphorus and silicon derivatives (**6**, Z = PPh, P(O)Ph, Me_2Si, Ph_2Si) of dihydroanthracene revealed significant differences in the chemical shifts of the phosphorus and silicon nuclei with the nature of the X group (O, NR, S, CR_2) showing effective transfer of electronic effects ⟨91ZOB2194⟩.

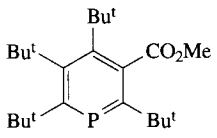
In NMR studies of 9-heteroanthracenide anions (**7**, X = Se, PPh, AsPh), only the selenium compound showed a paratropic molecular framework, the others showing no detectable paramagnetic ring current. In those cases, the NMR characteristics were probably caused by substantial delocalization of the carbanionic charge over the central ring containing the heteroatom ⟨87JOC5461⟩.

5.12.3.2 X-Ray Spectroscopy

X-ray studies have been primarily concerned with establishment or confirmation of molecular structures. Most structures are unexceptional in terms of bond angles and lengths. Minor variations occur in 1,1,6,6-tetramethyldibenzo[*b*,*e*]phosphajulolidine (**8**), in which the phosphorus atom is 0.81 Å out of plane of the three bonded carbon atoms. The P—C—P angles were 99.0°, 98.3°, and 108.5° ⟨85JOC2914⟩. The heavily substituted phosphorin (**9**) assumes an unsymmetrical twisted-boat conformation because of steric overcrowding ⟨87CB819⟩.



(**8**)



(**9**)

5.12.3.3 Mass Spectrometry

There seem to be no systematic studies of the mass spectra of six-membered phosphorus heterocycles, few significant reports having been unearthed. One provides a detailed analysis of the mass spectra of some peracetylated derivatives of sugar analogues having phosphorus in the hemiacetal ring. The molecules have pyranoid or furanoid rings and all showed molecular ions of higher intensity than did the O-containing analogues. The main fragmentation pathway was consecutive loss of the substituents from ring carbon atoms and C-6 to give 1,2-dihydro-λ^5-phosphorin or -phosphole oxide derivatives ⟨83PS(16)135⟩.

The ubiquitous phosphorinan-4-ones have also been subject to electron-impact fragmentation. One paper analyses the fragmentation of some 1-phenyl-1-oxo(seleno, thio)-2,5-dimethylphosphorinanes ⟨82IZV72⟩, another describes mass spectra of phosphorinanones with morpholine substituents, which provided the major fragment ions. The intensities of these fragments were claimed to exceed the ionization cross-section. This was attributed to migration of the positive charge in the electronically excited state of the molecular ion to the morpholino fragment and to the high stability of this fragment ⟨88MI 512-01⟩.

5.12.3.4 Miscellaneous Spectroscopic Methods

UV absorption and magnetic circular dichroism for phosphabenzene, arsabenzene, and stibabenzene show that in each case the lowest energy transition is due to an n–π^* transition. Three π–π^* transitions are also assigned and related to the aromatic six-electron perimeter. Analysis of

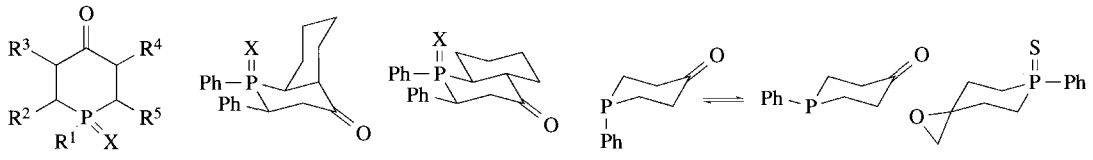
orbital splittings indicated that the effective π-orbital electronegativities of the heteroatoms are higher than that of carbon ⟨89OM2804⟩. The infrared and Raman spectra of phosphabenzene and arsabenzene have been studied and assignments made for all but five of the 54 fundamentals. The molecules show definite aromatic properties ⟨82JST(78)169⟩. ESCA studies of the charge distribution and bonding of λ^3- and λ^5-phosphorins support the theory that these compounds should be regarded as aromatic and as cyclic phosphonium ylides, respectively. Contrary to simple electronegativity considerations, the phosphorus atom in the λ^3-phosphorins is nearly neutral and not positively charged ⟨84ZN(B)795⟩. Electron transmission spectroscopy was used to study temporary negative ion formation in phosphabenzene, arsabenzene, and stibabenzene in the gas phase. Electron affinities were derived for the unstable states of these molecules. The trends in π^* electron affinities, including previous values for benzene and pyridine, were compared with those in the carbon—heteroatom bond lengths and heteroatom electronegativities. The ground anionic states of these heterobenzenes are stable. Anion states in addition to those associated with occupation of π^* orbitals were also observed ⟨82JA425⟩.

In the photoelectron spectra (PES) of stereoisomers of 1-phenyl-1-oxo(thioxo, selenoxo)-2,5-dimethylphosphorinan-4-one, the configuration did not effect the first ionization potentials appreciably but did affect the spectral band shapes in the high-energy region, providing another probe for conformational analysis ⟨87IZV28⟩. PES and quantum chemical calculations of 2-, 3-, and 4-chlorophosphorin, and 4-chloro-3-methyl- and 3,5-dimethylphosphorin showed them to have similar aromaticity to the corresponding benzene derivatives. The chloro-compounds were inert to nucleophiles even under forcing conditions ⟨94HAC131⟩.

5.12.4 THERMODYNAMIC ASPECTS

Aromaticity and stability of fully conjugated rings are covered in Sections 5.12.2 and 5.12.5. Other thermodynamic features, such as tautomerism, are only briefly mentioned in the literature and included here under reactivity of the appropriate systems.

There has been continued interest in the use of NMR spectra for conformational analysis of phosphorinanones (**10**). Particular emphasis has been placed on the establishment of orientation of substituents on the phosphorus atom and on the ring-carbon atoms, as well as interaction between the heteroatom and the carbonyl group in the 4-position. In all cases studied, the heterocyclic ring is in the chair conformation, sometimes flattened or twisted ⟨81IZV55, 85MI 512-01, 85IZV41, 88ZOB1030⟩, and substituents on both phosphorus and carbon favor equatorial orientation. NMR has been used for monocyclic ⟨80MI 512-02, 81IZV65, 81JOC1166, 81PS(11)199, 83OMR(21)345, 83OMR(21)457, 84IZV60, 85IZV41, 85ZOB817, 86IZV82, 88ZOB1030, 90MI 512-06⟩, bicyclic ⟨84IZV67, 86ZOB1978, 90ZOB319⟩, and bridged ⟨87MRC271, 89JOC4758, 90JOC1692⟩ systems. Interaction between phosphorus and a 4-carbonyl group is strongly dependent on ring size and molecular geometry ⟨83OMR(21)457, 87MRC271, 89JOC4758⟩ and shows strong effects on ^{17}O chemical shifts ⟨87MRC271⟩.



(10) (11) (12) (13) (14)

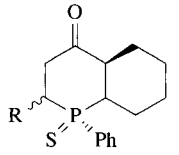
Bicyclic compounds exist in both *cis*- (**11**) and *trans*-fused forms (**12**). The *trans* form is more stable and has a twisted conformation of the P-containing ring ⟨90ZOB1970⟩. Base-catalysed isomerization from *cis* to *trans* occurs for both P=O and P=S compounds ⟨91ZOB678⟩ and is not reversible ⟨86ZOB1973⟩. Carbon-13 chemical shifts of phosphorinan-4-ones (**10**; X = null, O, S; R = Ph, Me) showed a linear relationship for carbons α and β to the phosphorus, as previously found for the analogous S, N, and O heterocycles, suggesting similar chair conformations.

In contrast to compounds with pentavalent phosphorus, ^{13}C and ^{31}P shielding and coupling constants of 1-phenyl-4-phosphorinanones (**13**) are consistent with the calculated conformational free energy of the phenyl group and its preference for axial orientation ($\Delta G^\circ = 0.81$ kcal mol^{-1}, ca. 80% axial) ⟨83OMR(21)345⟩. Plots for the γ atoms suggest transannular interactions between the trivalent phosphine groups and the carbonyl group ⟨83OMR(21)457⟩. A linear correlation was found between the ^{31}P NMR shifts of cyclic phosphines and the ^{17}O shifts of the corresponding phosphine

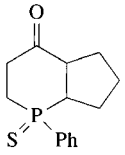
oxides, but there was no correlation between the ^{17}O and ^{31}P shifts of the phosphine oxides ⟨88PS(37)35⟩.

A number of x-ray studies have been made to determine the crystalline structure of substituted phosphorinanones (**10**) ⟨81JOC1156, 84MI 512-01, 85MI 512-02, 85MI 512-03, 87IZV79, 88IZV59, 89MI 512-02, 90MI 513-03, 90MI 512-06⟩. These all fit with the NMR data showing the molecules to have a chair conformation, as is found in solution, usually with the ring substituents in the axial position. All the pentavalent *P*-phenyl-substituted molecules preferred the form with an equatorial phenyl group. Depending on substituents, the ring adopted an idealized chair, a slightly twisted chair, or a chair somewhat flattened at the phosphorus end. Both 4-*t*-butoxy-1-phenoxy-1λ^5-phosphorinane-1-oxide ⟨87AX(C)282⟩ and 1-anilino-4-*t*-butyl-1λ^5-phosphorinane-1-oxide ⟨86AX(C)99⟩ have a chair conformation of the heterocyclic ring, slightly flattened at the P end to relieve steric strain. The 1- and 4-substituents are *trans* to each other and in equatorial positions. The bicyclic epoxide (**14**) also has a slightly flattened chair conformation with the phenyl group equatorial. The plane of the epoxide is virtually coincident with a pseudo-mirror plane and the phenyl group is rotated out of plane by 28.2°. Most bonds are of normal length but the P—Ph bond of 1.819 Å is longer than in some model systems. The C(4)—O bond in the epoxide is pseudo-axial ⟨84PS(19)113⟩.

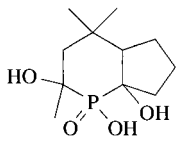
In the case of bicyclic molecules (**15**), the heterocycle has a twist conformation, while the carbocycle has an almost undistorted chair form ⟨88MI 512-02, 90IZV88, 90MI 512-05⟩. Two stereoisomers of (**15**, R = Ph) were examined. Both had *trans*-fused rings. In one, both rings had the chair conformation, the 1-phenyl group was equatorial, and the 2-phenyl group was axial. In the other, the carbocyclic ring had the chair conformation, the phosphorinane ring the twist conformation, and both phenyl groups were axial ⟨86IZV69⟩. The molecular structures of one of the stereoisomers of 2-thiono-2-phenyl-2-phosphabicyclo[4.3.0]nonan-5-one (**16**) ⟨88MI 512-03⟩ and its more heavily substituted derivative, 1,2,3-trihydroxy-2-oxo-3,5,5-trimethyl-2-phosphabicyclo[4.3.0]nonane (**17**) have been determined. In the latter, the six-membered phosphorinane ring exists in a distorted chair conformation, the five-membered ring is an envelope with C-8 at the flap, and the hydroxyl groups are *trans* to the phosphoryl group ⟨91AX(C)1752⟩.



(**15**)

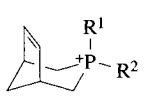


(**16**)

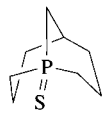


(**17**)

X-ray analysis shows that 3,3-diphenyl-3-phosphoniabicyclo[3.2.1]oct-6-ene bromide (**18**, R, R^1 = Ph) monohydrate and the corresponding saturated compound have the phosphorinanium ring in a chair conformation, substantially flattened at the phosphorus end ⟨88MI 512-04, 89MI 512-03⟩. The compound lacking the ethylene bridge, and the corresponding phosphine oxides with both *endo* and *exo* phenyl groups, are chairs and the torsional angles indicate them to be highly symmetrical ⟨83AX(C)383, 86AX(C)251⟩. In *exo*-3-*p*-nitrobenzyl-*endo*-3-phenyl-3-phosphoniabicyclo[3.2.1]octane bromide (**18**, R = Ph, R^1 = *p*-nitrobenzyl, no double bond) the heterocyclic ring adopts a chair conformation, flattened at the phosphorus end, and the respective *exo* and *endo* dispositions of the aromatic substituents were confirmed ⟨80JCS(P2)1467⟩.



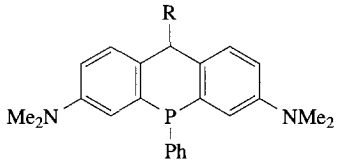
(**18**)



(**19**)

1-Phosphabicyclo[3.3.1]nonane-1-sulfide (**19**) adopts a chair–chair conformation with the central three-atom plane as a mirror plane. The phosphorinane rings are flattened by the repulsive interactions between their *endo*-methylene groups which exhibit a C—C transannular separation of 3.206 Å ⟨88AX(C)1435⟩. In the dibenzo compound (**20**) the precise conformation of the central ring depends on the character of the substituents on the central ring ⟨86ZOB1737⟩.

Gallagher ⟨87MI 512-01⟩ has summarized much of this data and reviewed the use of NMR in the analysis of conformation of heterocyclic systems. He has demonstrated that generalization to all



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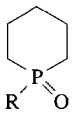


(21)

systems is far from simple. There are variations of ^{31}P chemical shift with ring size which are particularly marked in the case of phosphates but less so with phosphites. Rings containing P(III) are chair-shaped, somewhat flattened at the phosphorus end because of the longer C—P bond compared with C—C. Substituents at phosphorus prefer an axial orientation even in solution, although the energy difference between the two conformers is often quite small. Conformational bias seems to arise from substituents at carbon rather than phosphorus. Usually the axial isomer shows an upfield shift relative to the equatorial isomer, but this is reversed in the case of *P*-phenyl compounds for reasons which are not yet understood. The derived phosphoryl compounds (e.g. **21**) have a conformationally mobile chair-shaped ring, the precise stereochemical assignments often depending on the known specificity of oxidation, sulfuration, selenation, and alkylation of the P(III) precursor. The organic substituent at phosphorus commonly occupies the equatorial position with oxygen of the phosphoryl group axial in the more stable conformer. There are few ^{31}P data, most useful information coming from ^{13}C and ^{1}H NMR. Good examples are the sugar analogues which have been thoroughly studied by Inokawa and his co-workers ⟨82JOC191⟩.

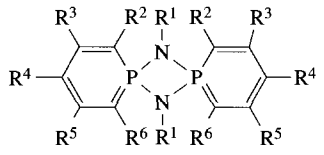
Quin and Hughes ⟨90MI 512-01⟩ have also discussed ring conformations with respect to the importance of the remarkable tendency of substituents on trivalent phosphorus in saturated rings to adopt an axial position. For example, as mentioned above, 1-phenylphosphorinan-4-one has an axial : equatorial ratio of the phenyl group of 4 : 1 ⟨83OMR(21)345⟩. Other conformational details are interpreted in terms of the length of the C—P bond (about 1.84 Å) and the C—P—C bond angle (about 100° in tertiary phosphines), as well the normal preference for equatorial orientation of substituents on the carbon atoms.

5.12.5 REACTIVITY OF FULLY CONJUGATED RINGS

5.12.5.1 Reactions at the Heteroatom

There are two main classes of fully conjugated rings, λ^3- and λ^5-phosphorins and a few examples of the much less-stable λ^4-phosphorins. In λ^3-phosphorins, the phosphorus can react as a base, a nucleophile, and an electrophile. They are moderately strong bases and the proton affinity of phosphabenzene was determined by ion cyclotron resonance techniques to be 195.8 kcal mol^{-1} (cf. ammonia 203.6 kcal mol^{-1} and pyridine 219.4 kcal mol^{-1}). Deuterium-labelling experiments demonstrate that phosphabenzene is protonated on phosphorus and arsabenzene is protonated on carbon ⟨85OM457⟩. The phosphorus atom in mono-, di-, and trisubstituted phosphorins effects nucleophilic substitution, to form the novel diazadiphosphetans (**22**), when treated with alkyl azides ⟨93TL3107⟩ and the sulfide (**23**) and selenide when reacted with sulfur or selenium ⟨88CC493⟩. Treatment of diazoalkanes with the phosphorin (**24**) in methanol gave the alkylmethoxyphosphorin (**25**), but similar reaction in ether gave the polycyclic 5s + 5s-[6 + 4]-cycloaddition product (**26**) ⟨87AG255⟩.

1,2,4,6-Tetraphenylphosphininium tetrachloroaluminate (**27**), the first phosphininium salt analogous to pyridinium salts, was prepared by treating 1-fluoro-1,2,4,6-tetraphenylphosphorin (**28**, R = F) with aluminum chloride. Reaction with methanol, ethanol, phenyllithium, or chloride ion gives the P-substituted λ^5-phosphorin (**28**, R = OMe, OEt, Ph, Cl) ⟨84AG984⟩. λ^3-Phosphorins can be arylated on phosphorus by reaction with aryllithiums, such as 2-thiophenyllithium, 2-benzofuryllithium, and ferrocenyllithium. The products, 1-substituted-1,2-dihydrophosphorins, then react with mercuric acetate in methanol to give 1-heteroaryl-1-methoxy-λ^5-phosphorins ⟨81TL1207⟩. Reaction of 4,5-dimethyl-2-phenylphosphorin with sulfur in refluxing xylene gave a transient *P*-sulfide which was trapped by cycloaddition with 2,3-dimethylbutadiene and dimethyl acetylenedicarboxylate to give the 1,2- (**29**) and 1,4-adducts (**30**), respectively ⟨84CC508⟩.



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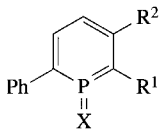

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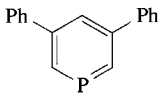

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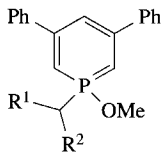

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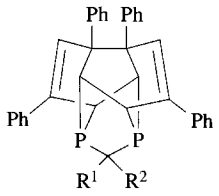

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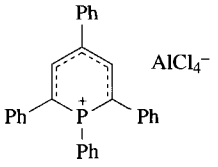

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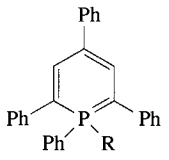

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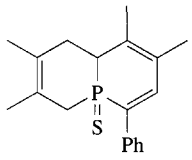

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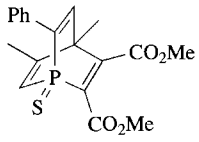
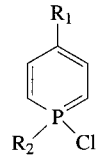


(30)

5.12.5.2 Reactions at Carbon

λ^5-Phosphorins (**31**) show some reactions similar to those of benzene and can be acylated on carbon with phosgene or acyl halides to give, for example, (**32**) ⟨83TL5051⟩.



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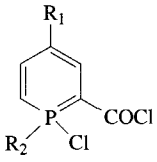

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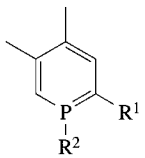
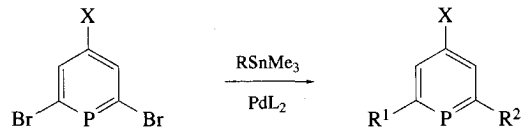


(33)

λ^3-Phosphorins behave more like pyridines. Nucleophilic substitution of 3-chloro- and 3-bromo-λ^3-phosphorins with lithium piperidide to give 3-piperidino-λ^3-phosphorin occurred via an addition–elimination mechanism. Similar results were obtained with lithium diisopropylamide ⟨83TL5055⟩. 2-Bromophosphorin can be further brominated at C-4 and C-5 by reaction with pyridinium perbromide and subsequent treatment with excess triethylamine. The λ^3-phosphorins also show reactions similar to benzenes, for example, organometallic derivatives are available from halogenated compounds and Ullmann-type coupling reactions are possible. Bromine atoms at all positions can be replaced by silyl substituents by reaction with magnesium and chlorosilanes in tetrahydrofuran near room temperature ⟨92BSF291⟩. The 2-iodo compound (**33**, R^1 = I, R^2 = null) can be converted into the corresponding zinc derivative (**33**, R^1 = ZnI, R^2 = null) and into the tungsten complex (**33**, R^1 = Li, R^2 = $W(CO)_5$), allowing further functionalization at the 2-position ⟨92TL3537⟩. Zirconocene can also be inserted into a carbon—halogen bond in the 2-position ⟨93CC789⟩. The functionalization of 2-halophosphorins has been reviewed ⟨93MI 512-02⟩. 4,4′,5,5′-Tetramethyl-2,2′-biphosphorin is formed by bis(triphenylphosphine)cobalt chloride coupling of 2-bromo-4,5-dimethylphosphorin. X-ray analysis suggests weak interaction between the two rings and a very low barrier to rotation. The biphosphorin is a strong ligand for electron-rich metals and is able to displace 2,2′-bipyridine from its chromium tetracarbonyl chelate ⟨92OM2475⟩. PdL_2 (L = triphenyl- or trifurylphosphine) catalyses cross-coupling of bromophosphorins (**34**, X = H, Br) to give 2,6-disubstituted (R^1, R^2 = 2-furyl, 2-thienyl, 2-methylpyrrolyl, phenylethynyl) or 2-monosubstituted (**35**, R^1 = 2-pyridyl,

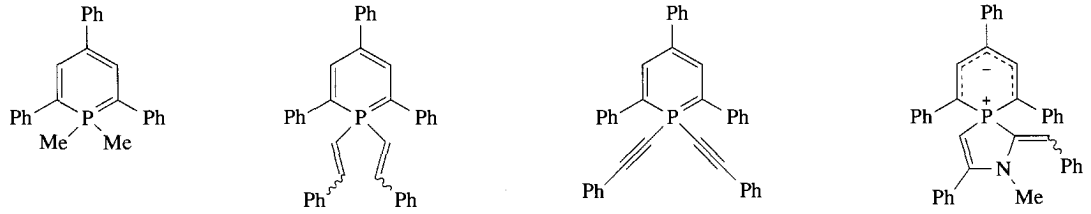
R^2 = Br) products ⟨93JA1065⟩ (Equation (1)). 2,2′-Biphosphorins are formed by sequential treatment of 2-bromophosphorins with trimethylstannylsodium and lithium tetramethylpiperidide ⟨94BSF330⟩.



(34) (35) (1)

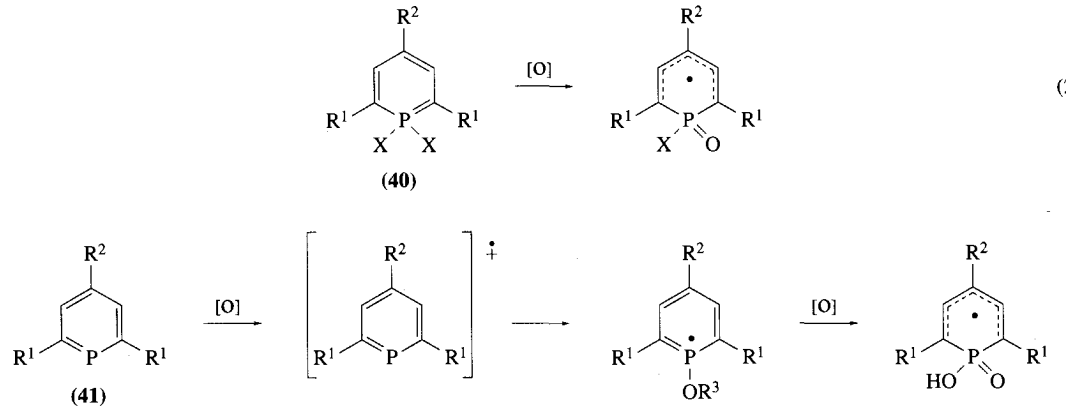
5.12.5.3 Reaction of *P*-Substituents

1,1-Dimethoxy-λ^5-phosphorins can be demethoxylated by dimethylsilane to the corresponding λ^3-phosphorins. *P*-alkyl groups are weak acids and butyllithium abstracts a proton from the *P*-methyl group. The resulting carbanions can be alkylated by electrophiles such as benzaldehyde ⟨81AG898⟩. Sequential aldol condensation of 1,1-dimethyl-2,4,6-triphenyl-λ^5-phosphorin (**36**) with benzaldehyde gave the alkenylphosphorin (**37**). The spirophosphorin (**39**) was prepared from 1,1-dihalo-2,4,6-triphenyl-λ^5-phosphorin via the dialkynyl compound (**38**) which was available from condensation of the 1,1-dihalo-λ^5-phosphorin with lithium phenylacetylide ⟨87CB1249⟩.



(36) (37) (38) (39)

λ^5-Phosphorin derivatives (**40**, X = OMe) can be oxidized chemically or electrochemically to form cation radicals which lose Me^+ to form stable, neutral radicals (Equation (2)). ESR data indicates that the cation radicals and neutral radicals are cyclohexadienyl-type and the phosphorus atom is not involved in delocalisation of the unpaired electron. ^{13}C Coupling constants were determined by preparation of labelled compounds ⟨81CB3004⟩. Chemical and electrochemical oxidation of λ^3-phosphorin (**41**) derivatives (Scheme 1) produces substituted radicals whose ESR spectra have been examined ⟨81CB3019⟩.



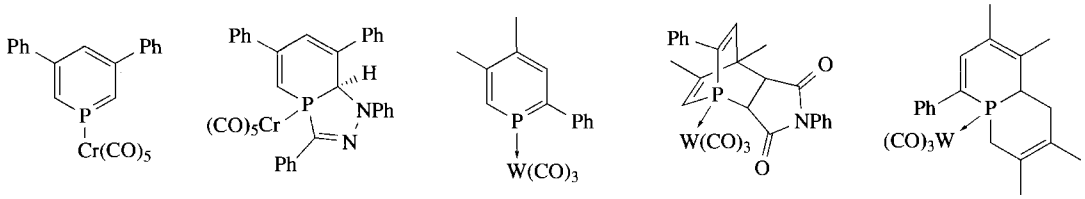
(2)

Scheme 1

5.12.5.3.1 Ring reactions

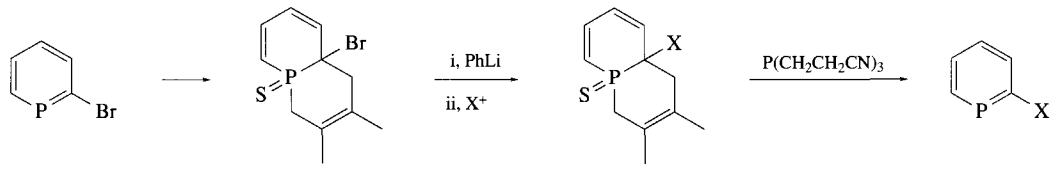
Chromium, molybdenum, and tungsten pentacarbonyls of 3,5-diphenyl-λ^3-phosphorins react with nitrilimines, nitrile oxides, and 1,3-dienes to give the corresponding 1,3-dipolar (**42**) and Diels–

Alder cycloadducts at a P=C double bond ⟨87TL3475⟩. 4,5-Dimethyl-2-phenylphosphorin can be activated by conversion into a phosphorin—tungsten complex which reacts easily as a dienophile with 2,3-dimethylbutadiene through its 1,6-positions (**44**) and as a diene with *N*-phenylmaleimide, dimethyl acetylenedicarboxylate, and cyclopentadiene through its 1,4-positions (**43**) ⟨84TL207⟩.



(**42**) (**43**) (**44**)

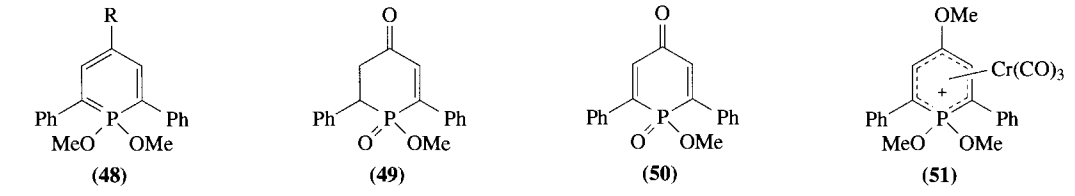
Two routes are described for the conversion of 2-bromophosphorins (**45**) into 2-functional phosphorins. In the first, a cycloadduct (**46**) between the 2-bromophosphorin and 2,3-dimethylbutadiene is formed in the presence of sulfur (Scheme 2). Br—Li exchange then permits reaction with an electrophile. The final product (**47**) is formed by a combined reduction–cycloreversion with $P(CH_2CH_2CN)_3$ as the reducing agent. In the second procedure, a Br—Li exchange is performed on a (2-bromophosphorin)pentacarbonyltungsten complex prior to reaction with an electrophile. The 2-functional phosphorin is recovered from its complex by heating with $Ph_2PCH_2CH_2PPh_2$ in toluene ⟨91OM2432⟩.



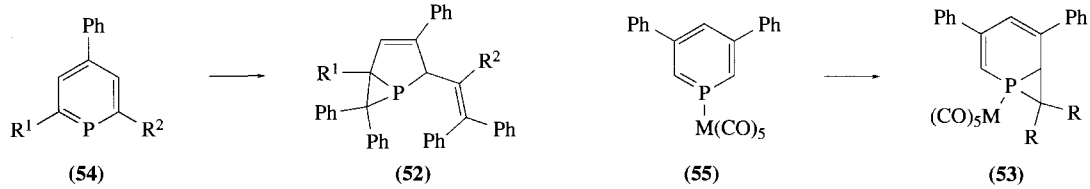
(**45**) (**46**) (**47**)

Scheme 2

4-Acetamido-1,1-dimethoxy-2,6-diphenyl-λ^5-phosphorin (**48**, R = NHAc) was hydrolyzed to give (**49**) and (**50**), which were deprotonated or reduced and methylated to give (**48**, R = OMe), characterised as the stable crystalline tricarbonylchromium complex (**51**) ⟨80CB3313⟩. Interesting products (**52**) and (**53**) were obtained from addition of carbenes to (**54**) ⟨90TL4849⟩ and the metal-complexed phosphorin (**55**) ⟨87AG1214⟩ (Scheme 3).



(**48**) (**49**) (**50**) (**51**)

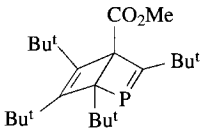


(**54**) (**52**) (**55**) (**53**)

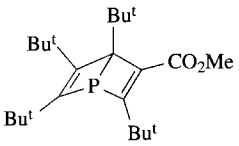
Scheme 3

5.12.6 REACTIONS OF NON-CONJUGATED RINGS

In some cases, there is a striking parallel between the reactions of phosphorins and benzene, for example the interconversions of the set of valence-bond isomers of a substituted phosphorin. Thermolysis of (**56**) gave (**57**) via (**58**). Photolysis of (**56**) gave (**59**) which underwent pyrolysis to give (**60**) and (**61**) ⟨87AG67⟩.



(**56**)



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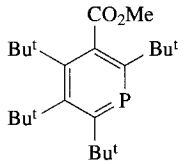
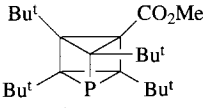


(**58**)



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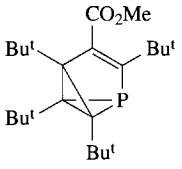
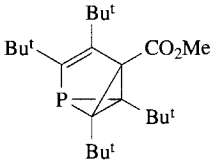


(**60**)

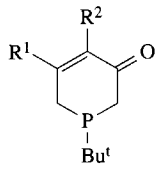


(**61**)

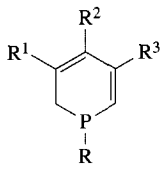
5.12.6.1 Dihydro Derivatives—Ease of Aromatization and Reactions

Generation of the thermally stable carbanions (**7**, X = PPh, P(O)Ph) was by treatment of the parent conjugate acid with potassium amide in liquid ammonia. Carbanionic charge is delocalized over the central ring ⟨87JOC5461⟩.

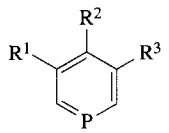
Tetrahydrophosphorinones (**62**) were prepared by reduction of the corresponding phosphine oxide with phenylsilane and gave dihydrophosphorins (**63**) on treatment with organolithium or Grignard reagents. Thermolysis of the dihydrophosphorins gave phosphorins (**64**) and treatment of (**63**, $R^1 = R^3 = Ph$, $R^2 = H$) with mercuric acid and then aryldiazonium fluoroborates produced diazo compounds (**65**, Ar = C_6H_4Me-*p*, C_6H_4OMe-*p*) ⟨84CB763⟩.



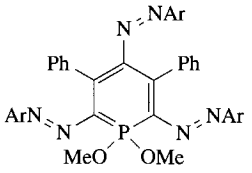
(**62**)



(**63**)



(**64**)

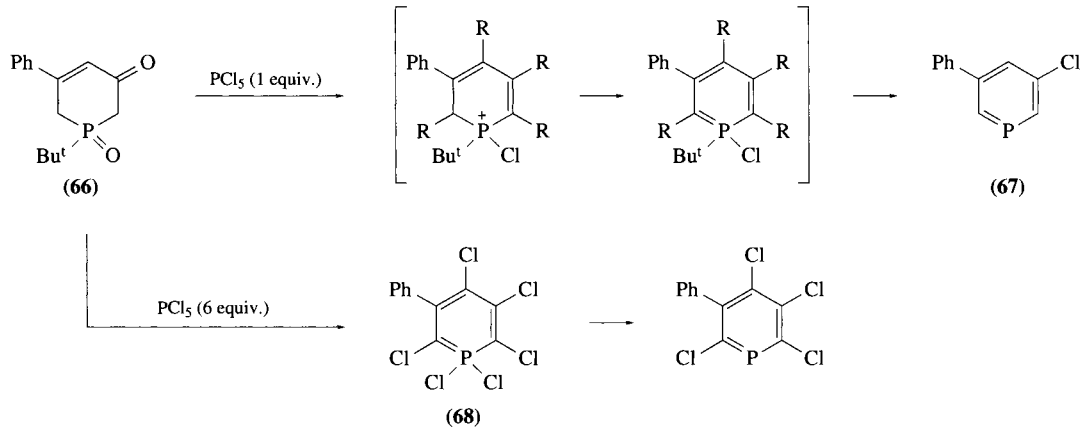


(**65**)

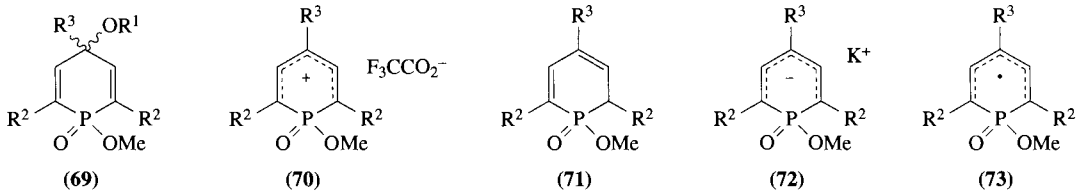
Halogen-substituted λ^3-phosphorins have been prepared by treatment of the tetrahydrophosphorinone (**66**) with phosphorus pentachloride. Use of one equivalent of PCl_5 gave, ultimately, (**67**). Use of six equivalents of reagent under more vigorous conditions gave a mixture of chlorinated products, including (**68**), which lost chlorine on heating to give 2,3,4,6-tetrachloro-5-phenylphosphorin ⟨83TL2645⟩ (Scheme 4).

Treatment of dihydrophosphorins (**69**) with trifluoroacetic acid gave carbocations (**70**) which reacted with alcohols to the give the corresponding (**69**). The cations (**70**) reacted with sodium borohydride to give (**71**), which with potassium hydride gave carbanions (**72**). Treating (**72**) with (**70**) gave radicals (**73**) ⟨84AG985⟩.

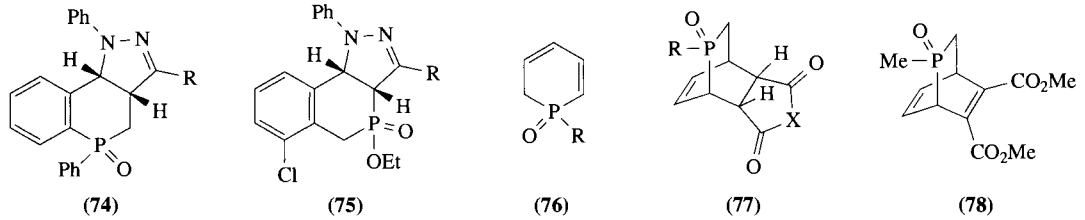
As expected, the 1,2-dihydro compounds act as both dienes and dienophiles in cycloaddition reactions. The regio- and stereoselective cycloaddition reactions of six-membered benzannelated phosphorus heterocycles, 1-phenyl-1,2-dihydrophosphinoline oxide, and 8-chloro-2-ethoxy-1,2-dihydroisophosphinoline oxide with diaryl nitrilimines gave (**74**) and (**75**) (R = Ph, C_6H_4OMe-*p*, C_6H_4Me-*p*), respectively ⟨92JCR(S)156⟩. 1,6-Dihydrophosphorin-1-oxides (**76**, R = Me, Ph), from dehydration of 3-hydroxy-1,2,3,6-tetrahydrophosphorin-1-oxides, underwent Diels–Alder reactions with maleic acid derivatives and dimethyl acetylenedicarboxylate to give (**77**) and (**78**) ⟨84CC1214,



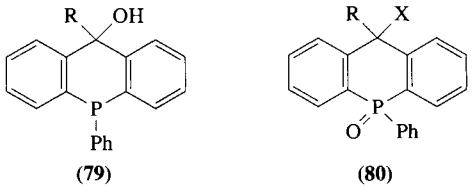
Scheme 4



88JOC1722〉. Removal of the phosphoryl oxygen was achieved under very gentle conditions, using trichlorosilane at −8 to 0 °C, to prevent fragmentation 〈88JOC1722〉. Ring expansion of regioisomeric 1,2-dihydrophosphorin 1-oxides can be achieved by treatment with dichlorocarbene under solid–liquid phase-transfer conditions. Dichlorocarbene addition to the 1-methoxydihydrophosphorin 1-oxides carrying one or two methyl groups on the skeleton gave a phosphabicyclooctene oxide as well as the phosphepin 1-oxide or a phosphabicyclooctadiene oxide, respectively 〈89MI S13-07〉.



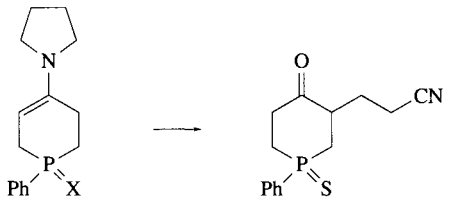
Treatment of the dihydroacridophosphine (**79**, R = Ph, $Me_2N(CH_2)_3$) with hydrochloric acid caused migration of oxygen from carbon to phosphorus to give (**80**, X = H) which was oxidized by hydrogen peroxide to (**80**, X = OH) 〈81ZOB2142〉.



5.12.6.2 Tetrahydro Derivatives

The reactions of tetrahydro derivatives are dominated by the double bond, and they generally behave in the manner expected of the homocyclic analogues. For example, the enamine, 1-(1,2,3,6-

tetrahydro-1-phenyl-4-phosphininyl)pyrrolidine *P*-sulfide (**81**, X = S), behaves in the standard manner in reactions with acrylonitrile and methyl vinyl ketone ⟨82PS(13)179⟩ (Equation (3)).

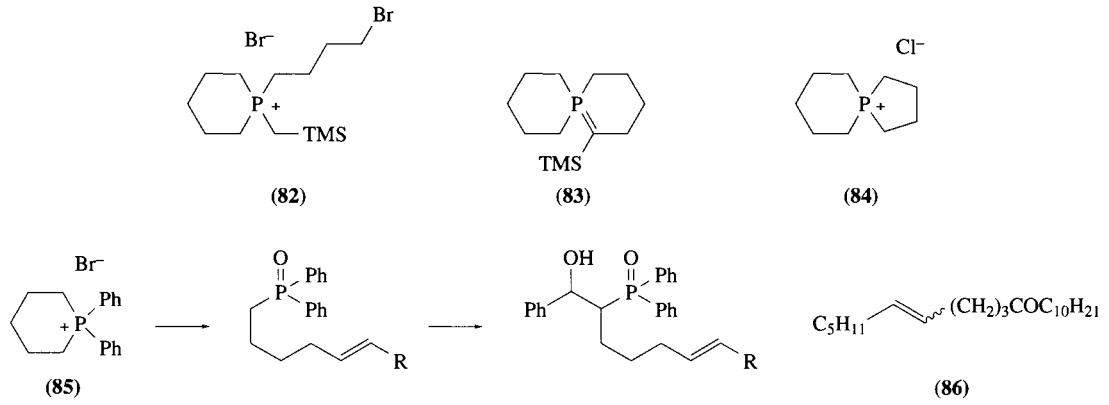


(81)

(3)

5.12.6.3 Hexahydro Derivatives—Phosphorinanes

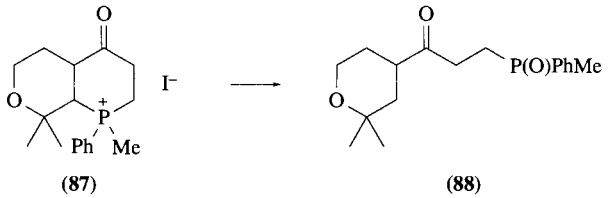
These compounds behave much in the same way as their acyclic analogues. As examples, the acidification of C—H groups adjacent to phosphonium centres (**82**) permits their use in cyclization reactions ⟨83ZC249⟩ and Wittig reactions to form (**83**) and (**84**). The cyclic phosphonium salt (**85**) reacted with aldehydes (RCHO) to give an acyclic product which reacted further with aldehydes and butyllithium ⟨87JCS(P1)1537⟩ (Scheme 5). This process was used in the synthesis of the Douglas fir tussock-moth sex pheromone (**86**) ⟨87NKK1227⟩. Hydrolytic cleavage of the quaternary phosphonium salts (**87**) leads to the pyran (**88**) ⟨86ZOB720⟩ (Equation (4)).



(82) (83) (84)

(85) (86)

Scheme 5



(87) (88)

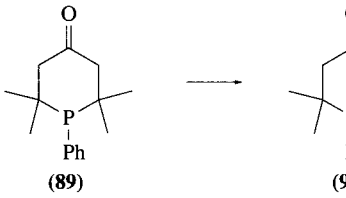
(4)

5.12.7 REACTIVITY OF SUBSTITUENTS ON RING CARBON ATOMS

In the case of fully saturated molecules, reactions of the ring substituents are largely unaffected by the heteroatom and follow the general trends observed in homocyclic systems. The carbonyl group in mono- and bicyclic phosphorinan-4-one *P*-oxides and *P*-sulfides is essentially indistinguishable in its reactions from the carbonyl of cyclohexanone. Thus, it undergoes bis- and mono-α-aminomethylation ⟨85IZV36, 88ZOB16, 88ZOB1030, 89IZV85, 92MI 512-01⟩ and it can be reduced to a mixture of epimeric alcohols ⟨85ZOB1285, 86ZOB1983, 88ZOB21, 89IZV79, 89ZOB1034, 90ZOB1745, 90ZOB371, 93ZOB674⟩. The α-substituents are predominantly equatorial. Similarly, the carbonyl is subject to Huang–Minlon reduction ⟨90ZOB80⟩, reaction with amines to form enamines ⟨82PS(13)179⟩ or Schiff bases which, if suitably substituted, can be cyclized to oxazolidines ⟨91ZOB868, 92ZOB767⟩, Grignard

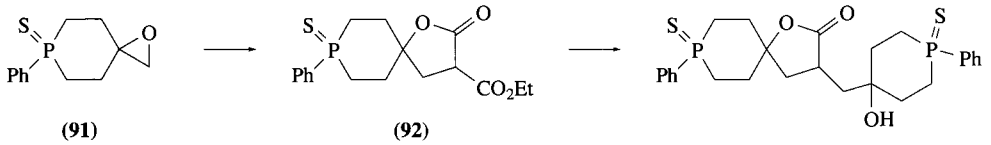
addition ⟨81IZV58, 89IZV80⟩ and ethynylation ⟨88ZOB26⟩. The Schiff bases, or related oxazolidine derivatives, are reduced by sodium borohydride to give mainly the equatorial amine ⟨92ZOB767⟩. Methyl groups α to the carbonyl group will also take part in Michael reactions with methyl methacrylate and acrylonitrile ⟨82AJC363, 90ZOB2473⟩ and cycloalkylation with $(BrCH_2)_2CHCO_2Me$ ⟨89ZOB1931⟩. The amino group of 4-alkylaminothioxophosphorinane gave the expected tertiary amines ⟨93IZV67⟩.

2,2,6,6-Tetramethyl-4-phosphorinanol (**90**) was prepared by sequential protection of the carbonyl of (**89**) with ethylene glycol, removal of the phenyl group with lithium, hydrolysis, and hydride reduction (Equation (5)). It was then oxidized with hydrogen peroxide to the phosphinic acid. Conformational analysis of the corresponding hydroxy compound showed the hydroxyl group to be equatorial and the P—H bond axial in solution ⟨84JOC2906⟩. Opening of the epoxide ring of (**91**) with diethyl malonate led to the spiro lactone (**92**) which could be further modified without complications from the phosphorus-containing function ⟨84PS(19)137⟩ (Scheme 6). 1-Halophosphorinanes were prepared by treatment of phosphines with dichlorophenylphosphine. These could be dimerised to form P—P-bonded compounds (**93**) by treatment with sodium ⟨88PS(36)165⟩ (Scheme 7).



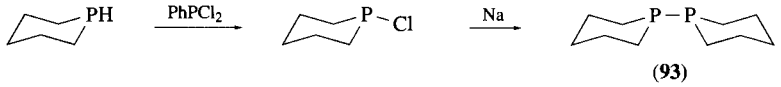
(5)

(89) (90)



(91) (92)

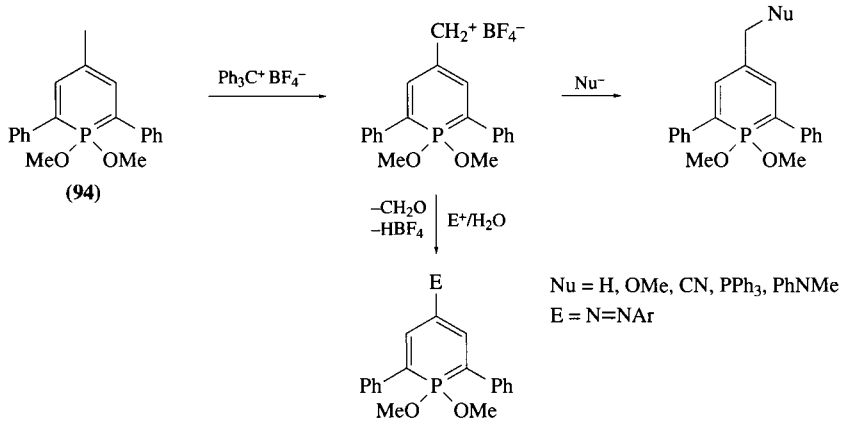
Scheme 6



(93)

Scheme 7

4-Methyl-1,1-dimethoxy-λ^5-phosphorins (**94**) undergo useful reactions as a result of the enhanced reactivity of the methyl group, which permits removal of a hydride ion by trityl salts ⟨87CB1245⟩ (Scheme 8).



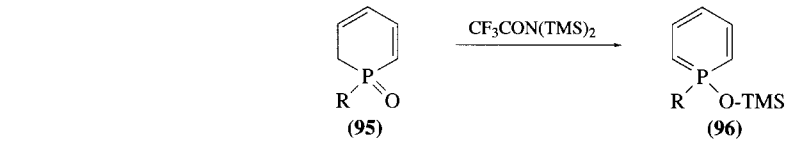
(94)

Nu = H, OMe, CN, PPh_3, PhNMe
E = N=NAr

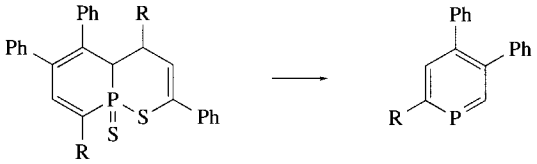
Scheme 8

5.12.8 REACTIVITY OF SUBSTITUENTS ON RING HETEROATOMS

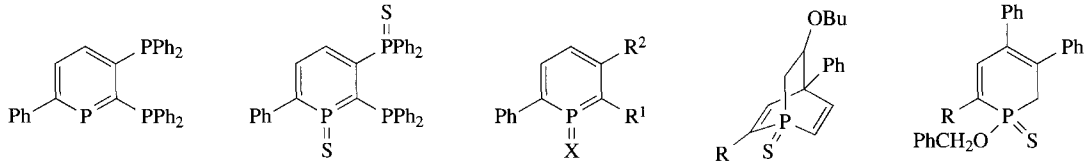
The phosphoryl oxygen of 1,6-dihydrophosphorin oxides (**95**) is silylated by bis(trimethylsilyl)trifluoroacetamide (Equation (6)). The product loses a ring proton to establish the resonance stabilized λ^5-phosphorin ring system (**96**). Similar reactions occur with a 3-keto derivative of tetrahydrophosphorin oxide, which also undergoes silylation of the keto oxygen ⟨90MI 512-04⟩. Phosphorins (e.g. (**97**)) react with sulfur at phosphorus. The λ^4 products (**98**) and (**99**) have only moderate stability but survive chromatography on silica gel ⟨88CC493, 90H(30)543⟩. Phosphorin sulfides (**100**, R = Ph, C_6H_4Me-*p*) reacted with triphenylphosphine to give the corresponding phosphorin (**101**) (Equation (7)), with dienophiles to give, for example, the phosphabicyclo-[2.2.0]octadiene sulfide (**102**), or with nucleophiles, such as benzyl alcohol, to form dihydrophosphorin sulfide (**103**) ⟨87BCJ1558⟩.



(95) (96) (6)



(100) (101) (7)



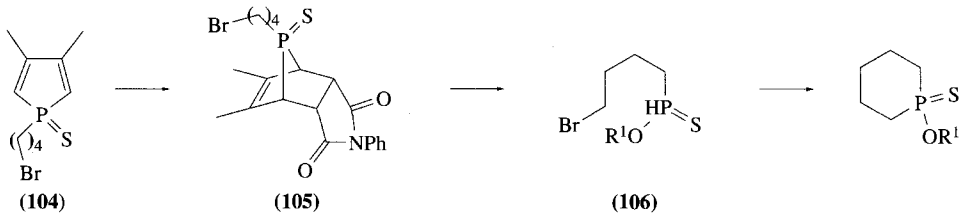
(97) (98) (99) (102) (103)

5.12.9 RING SYNTHESES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

5.12.9.1 PC_5 Cyclizations

5.12.9.1.1 Formation of the P—C bond

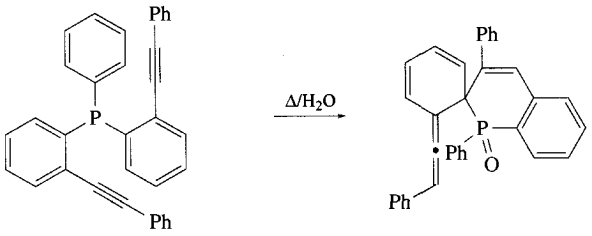
Photolysis in alcohol (R^1OH) of the *N*-phenylmaleimide adduct (**105**) of the phosphole sulfide (**104**) forms $Br(CH_2)_3P(S)(H)OR^1$ (**106**), which is easily cyclized by sodium hydride (Scheme 9). Five- and seven-membered ring compounds are also available by this route ⟨81JOC4386⟩.



(104) (105) (106)

Scheme 9

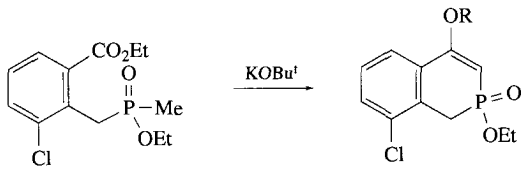
Heating (**107**) in organic solvents containing water gave the unusual spiro compound (**108**) ⟨82CB578⟩ (Equation (8)).



(107) (108) (8)

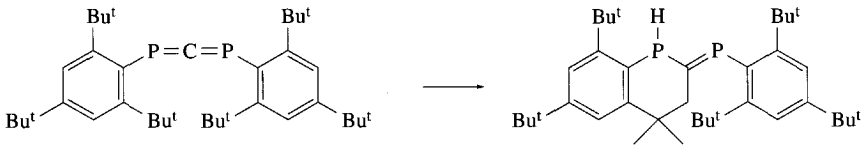
5.12.9.1.2 Formation of the C(2)—C(3) bond

Isophosphinolinone derivatives (**109**) were prepared by potassium *t*-butoxide cyclization of the aromatic esters (Equation (9)). The acyclic precursor was a useful post-emergent herbicide and the cyclized material could be used for selective protection of sorghum during herbicide treatment ⟨83USP4397790⟩.



(109) (9)

The carbodiphosphine, bis(2,4,6-tri-*t*-butylphenylphosphinidene)methane (**110**), reacts with electrophiles and undergoes thermolysis by C—H addition of an *ortho t*-butyl group to a P=C bond to give a 1,2,3,4-tetrahydrophosphinoline (**111**) ⟨88PS(36)213, 88TL333⟩ (Equation (10)).



(110) (111) (10)

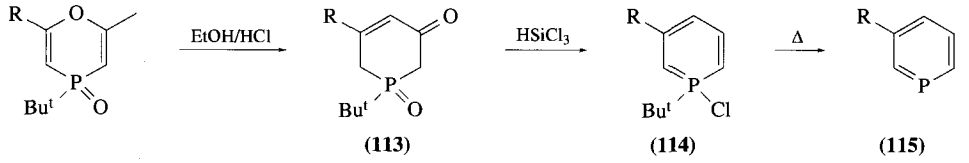
5.12.9.1.3 Formation of the C(3)—C(4) bond

The unsubstituted parent phosphorin (**1**) was obtained in moderate yield by flash vacuum pyrolysis of diallylvinylphosphine (**112**) ⟨93CC1295⟩ (Equation (11)).

(112) (1) (11)

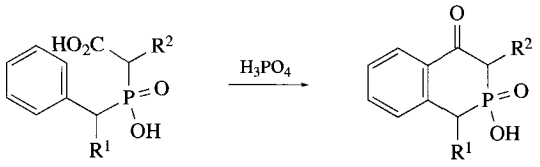
Oxophosphorin oxides were induced, by refluxing ethanolic hydrogen chloride, to undergo ether cleavage followed by aldol condensation to give (**113**), which was treated with trichlorosilane to give λ^5-phosphorin (**114**, R = H) (Scheme 10). This was thermolyzed at 250–280 °C to form the λ^3-phosphorins (**115**) in good yield ⟨83CB445, 83CB1756⟩. β-Nitroalkylphosphine oxides are converted into α-carboxyalkylphosphine oxides (**116**) by treatment with 85% phosphoric acid at 130 °C; the oxides (**116**) cyclize with the same reagent at 180 °C ⟨83ZOB56⟩ (Equation (12)). While these phosphinic acid derivatives with two alkyl substituents on phosphorus cyclized normally, a trisubstituted analogue cyclized with an intriguing migration of the methyl group to give (**117**). The tricyclic

compounds (**117**) and (**118**) were opened remarkably easily with sodium hydroxide under mild conditions (Scheme 11).

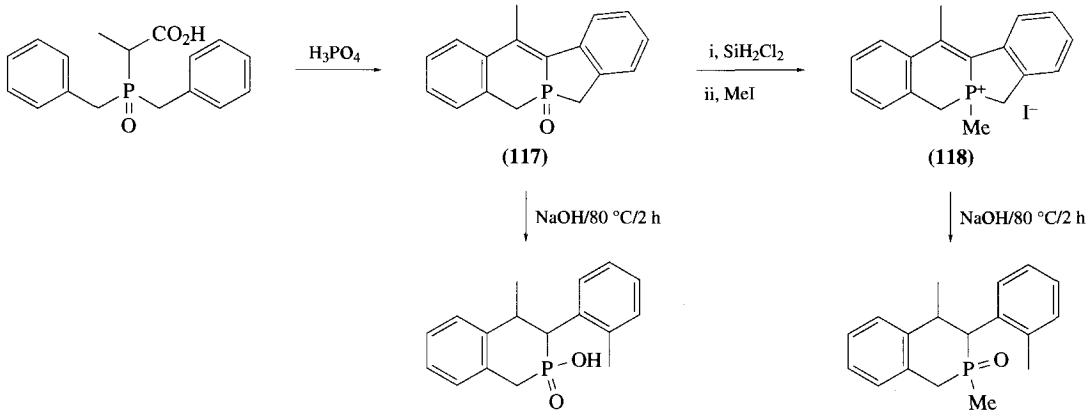


(113) (114) (115)

Scheme 10



(116) (12)



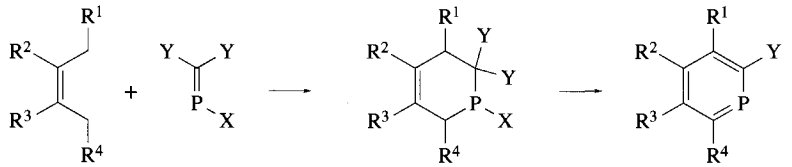
(117) (118)

Scheme 11

5.12.9.2 [2 + 4] Cycloadditions Involving P—C Multiple Bonds

5.12.9.2.1 PC + C_4 Cycloadditions

The Diels–Alder reaction provides an easy and general access to substituted phosphorus heterocycles with varying degrees of unsaturation (**119**) which may be aromatized to functionalized λ^3-phosphorins (**120**) (Scheme 12). The functional group may be derived either from the diene or the phosphaalkene. A brief review of the use of this approach for the synthesis of aromatic compounds has been published ⟨87PS(30)523⟩.

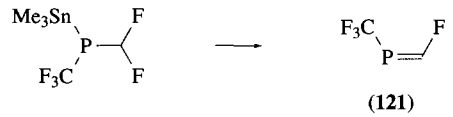


(119) (120)

Scheme 12

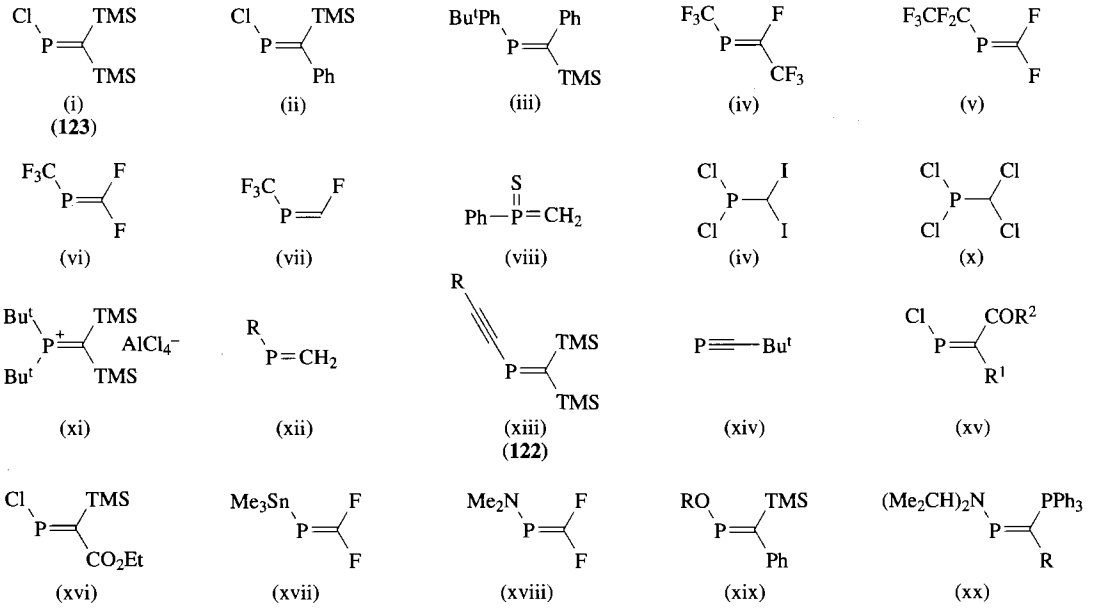
There has been a concerted effort to develop special multiple-bonded phosphorus-containing dienophiles which can react to form phosphorus heterocycles ⟨83TL3591, 84CB2693, 85CB814, 85TL3681, 85ZN(B)467, 85ZN(B)927, 85ZOB2795, 86TL5611, 86ZN(B)931, 87TL4299, 87TL5811, 87ZN(B)984, 88AG1541,

88ZN(B)427, 89CC988, 89TL817, 89ZN(B)175, 90CB935, 90IZV905, 90ZN(B)148, 91AG721, 91HAC439, 91T71, 93MI 512-02⟩ which can be aromatized, sometimes with 1,5-sigmatropic shift of a substituent ⟨89TL817, 91HAC439⟩. The dienophile may be prepared prior to use or generated *in situ* (e.g. (**121**)) ⟨89ZN(B)175⟩ (Equation (13)). The dienes may be electron-rich or electron-poor ⟨91T71⟩, acyclic, or cyclic (such as α-pyrone, cyclopentadienone, substituted dimethoxycyclopentadienones, or phospholes) ⟨82AG383, 86ZN(B)931, 88JHC155, 90CB935⟩. Some typical examples of the dienophiles or their precursors are shown in Figure 2.



(13)

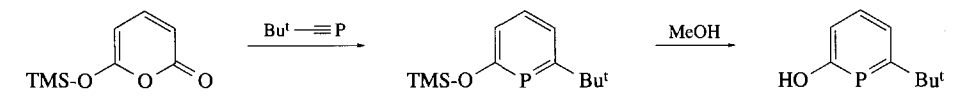
(121)



(i) (**123**) (ii) (iii) (iv) (v) (vi) (vii) (viii) (iv) (x) (xi) (xii) (xiii) (**122**) (xiv) (xv) (xvi) (xvii) (xviii) (xix) (xx)

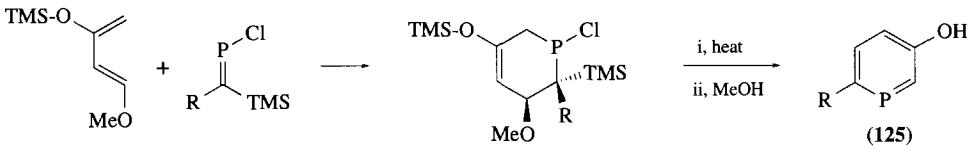
Figure 2 Phosphorus-containing dienophiles or precursors ((i) ⟨91HAC439⟩; (ii) ⟨85CB814⟩; (iii) ⟨85CB4068⟩; (iv) ⟨90ZN(B)148⟩; (v) ⟨90ZN(B)148⟩; (vi) ⟨87ZN(B)984⟩; (vii) ⟨89ZN(B)175⟩; (viii) ⟨84CC1214⟩; (ix) ⟨93MI 512-02⟩; (x) ⟨89TL817⟩; (xi) ⟨91AG721⟩; (xii) ⟨87TL5783, 87TL5811, 91HAC283, 94CC945⟩; (xiii) ⟨84CB2693⟩; (xiv) ⟨90CB935⟩; (xv) ⟨86TL5611⟩; (xvi) ⟨87TL4299⟩; (xvii) ⟨85TL3681⟩; (xviii) ⟨92ZN(B)321⟩; (xiv) ⟨83TL3591⟩; (xx) ⟨89AG768⟩).

The ethynylphosphaalkene (**122**) reacted selectively across the P=C bond ⟨84CB2693⟩. Adducts of dienophiles with chloro[bis(trimethylsilyl)methylene]phosphine (**123**) can be aromatized, providing access to phosphorins ⟨91HAC439⟩. This type of reaction was used to prepare 2- (**124**) and 3-hydroxy-λ^3-phosphorins (**125**) (Schemes 13 and 14). The crystalline 2-isomer, the first example of a 2-hydroxy-λ^3-phosphorin, behaved as a true heterocyclic phenol—there was no evidence for the presence of a keto tautomer, and it was soluble in 2 M sodium hydroxide and methylated exclusively on oxygen. The ring protons appear to be normally aromatic (δ 7.17–7.42) in the NMR spectrum ⟨89TL5245⟩.



(**124**)

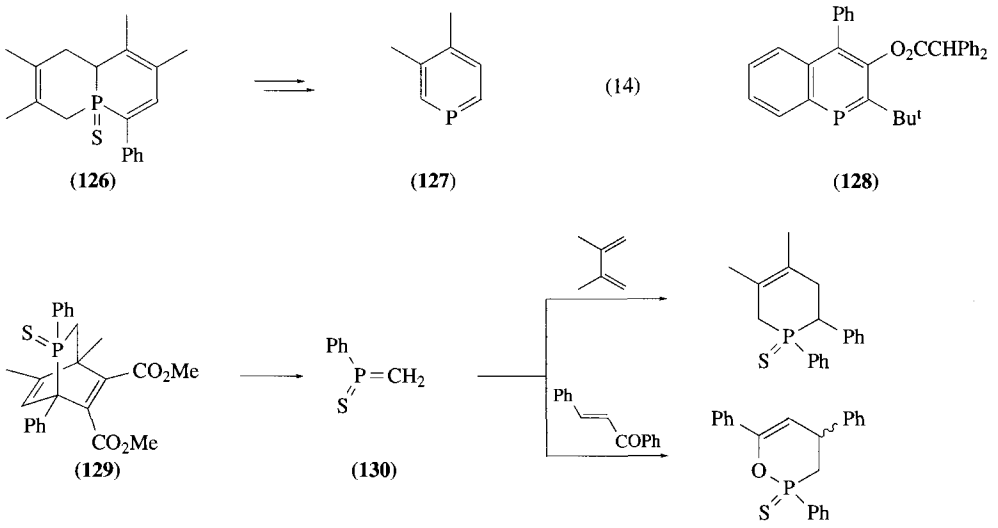
Scheme 13



(**125**)

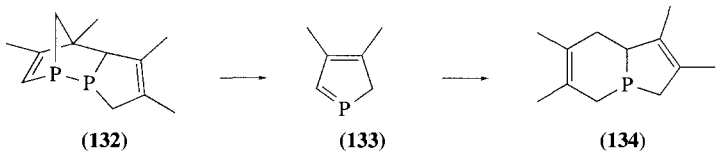
Scheme 14

3,4-Dimethylphosphorin (**127**) is formally equivalent to the aromatized [4 + 2] cycloaddition product of 2,3-dimethylbutadiene and HC≡P (Equation (14)). It was prepared in several steps from the bicyclic compound (**126**), which is a synthetic equivalent of HC≡P ⟨84TL4659⟩. Reaction of diphenylketene with *t*-butylphosphaethyne gives the 1-phosphinoline (**128**) ⟨92TL1597⟩. The unstable *C*-unsubstituted methylenephosphine sulfide, PhP(S)=CH_2 (**130**), was prepared by thermal decomposition of (**129**) (Scheme 15) (formed by addition of dimethyl acetylenedicarboxylate to (**131**) followed by thionation with P_4S_{10}) and was then trapped by 2,3-dimethylbutadiene or PhCH=CHCOPh ⟨84CC1214⟩.



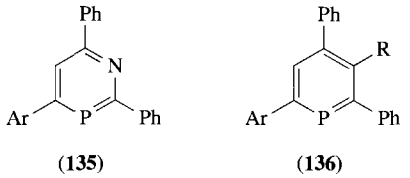
Scheme 15

The 3,4-dimethyl-2*H*-phosphole dimer (**132**) dissociates on heating into monomer (**133**) (Scheme 16). This reacts as both a diene and a dienophile, in the latter cases forming tetrahydrophosphorins (**134**) with, for example, 2,3-dimethylbutadiene ⟨82CC1272⟩.



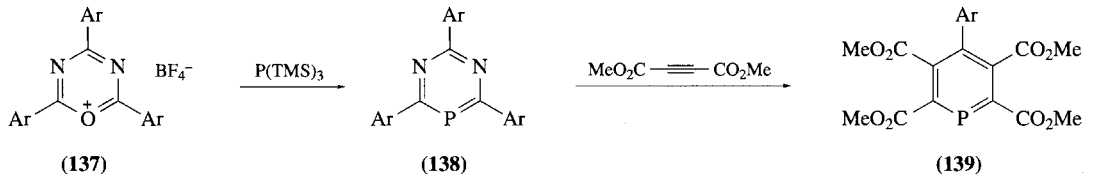
Scheme 16

[4 + 2] Cycloadditions of 1,3-λ^3-azaphosphorins (**135**) with alkynylphosphines under high pressure led to 1-phosphino-3-azabarrelenes which decomposed spontaneously by elimination of benzonitrile to give the phosphine-substituted λ^3-phosphorins (**136**) ⟨90TL4589⟩.



Oxadiazinium salts (**137**) can be converted into diazaphosphorins (**138**), which undergo two successive Diels–Alder additions via unstable heterobarrelene intermediates to give phosphorins (**139**) ⟨91AG82⟩ (Scheme 17).

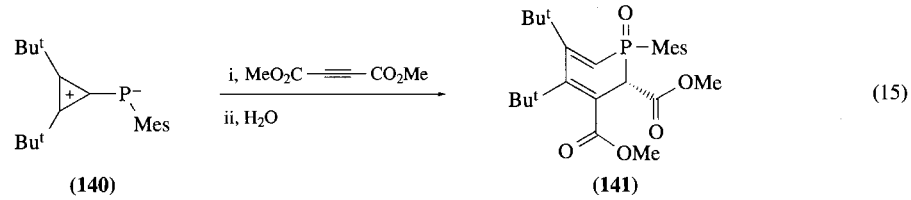
Dimethyl acetylenedicarboxylate reacts with (**140**) to form an unstable adduct which is trapped by water, giving the dihydrophosphorin (**141**) (Equation (15)). The kinetically controlled product subsequently rearranges slowly to give more stable isomers ⟨91S1099⟩. Dihydrophosphetes (**142**) react with Michael acceptors to form cycloadducts, apparently via zwitterionic species, to give



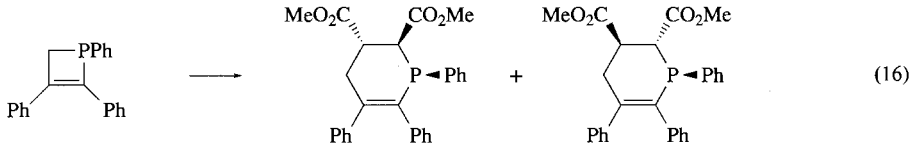
(137) (138) (139)

Scheme 17

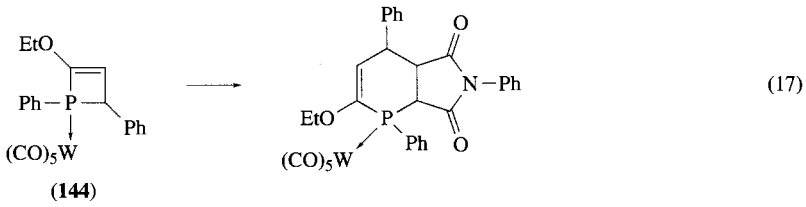
dihydrophosphorins (**143**) ⟨90CC1649⟩ (Equation (16)). They also react as masked 1-phosphabutadienes (**144**) and undergo the expected [4 + 2] cyclization with, for example, *N*-phenylmaleimide ⟨88TL3077⟩ (Equation (17)).



(140) (141) (15)



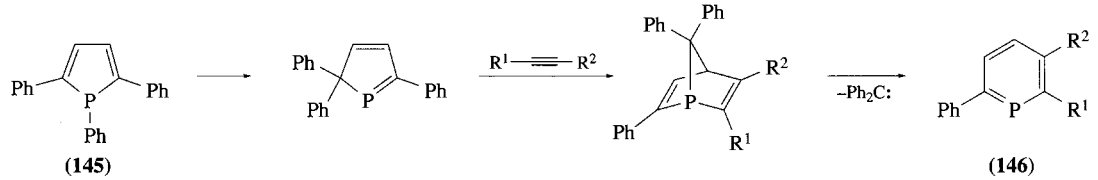
(142) (143) (16)



(144) (17)

5.12.9.2.2 $PC_3 + C_2$ Cycloadditions

When 1,2,5-triphenylphosphole (**145**) is heated for several days at 230 °C it is converted into 2,2′,3,3′,5,5′-hexaphenyl-1,1′-biphospholyl via a transient 2*H*-phosphole formed by a 1,5-phenyl migration ⟨81JA4595⟩ (Scheme 18). The 2*H*-phosphole intermediate may be trapped by alkynes, leading to a synthesis of phosphorins (**146**) after spontaneous loss of diphenylcarbene ⟨82JOC2376⟩. With unsymmetrical alkynes only one phosphorin is formed, with the less bulky substituent in the 2-position.



(145) (146)

Scheme 18

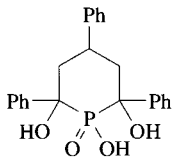
5.12.9.2.3 $P + C_5$ Cyclisations

Volume 1 of CHEC-I identified several key synthetic routes to six-membered phosphorus containing heterocycles ⟨84CHEC-I(1)493⟩. These can be summarized as: (i) reactions of 1,5 Grignard

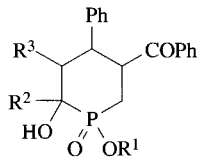
reagents with dichlorophosphines; (ii) reaction of 1,5-dihalocompounds with phosphites; (iii) addition of phosphines to 1,4-substituted 1,4-pentadien-3-ones; and (iv) free-radical addition of phosphines to 1,4-dienes and 1,4-diynes (as Quin, in his 1990 review, also identified) ⟨90MI 512-01⟩. These reactions continue to be used and only summary details of applications are included here.

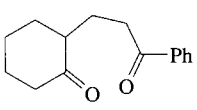
5.12.9.2.4 Addition of P(III) to 1,5-diketones

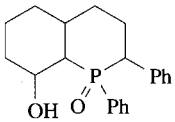
Reaction of 1,5-diketones with bis(trimethylsilyloxy)phosphine affords 2,6-dihydroxy-phosphorinanes (**147**), 1-hydroxy-5-oxopentyl-1-phosphinic acids, and 1,5-dihydroxy-1,5-pentadienyldiphosphinic acids. 1-Hydroxy-5-oxopentyl-1-phosphinic acids rearrange into tetrahydropyranyl-2-phosphinic acids upon refluxing in acetic acid ⟨91ZOB1315⟩. Some examples of the products formed in these reactions are indicated below ⟨83ZOB2206, 84ZOB1427, 85ZOB2475, 89ZOB2223, 90ZOB1282, 93ZOB358⟩.

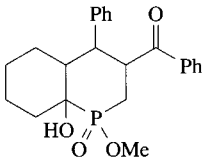


(**147**)



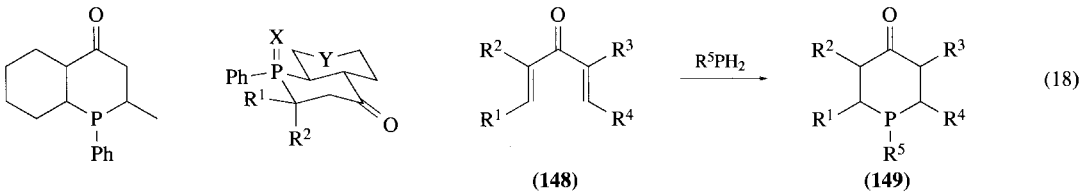




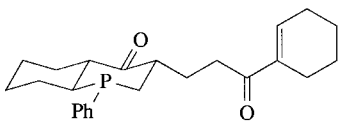


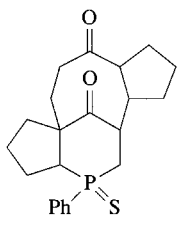
5.12.9.2.5 Addition of P(III) to alkene-unsaturated C=O

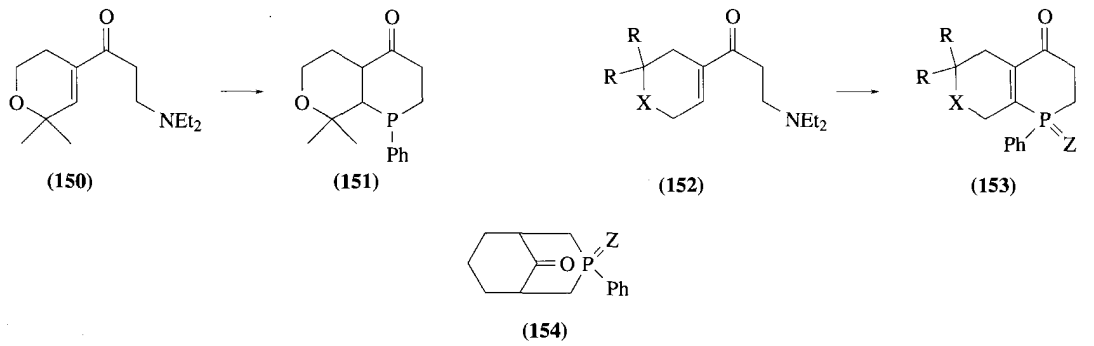
Some typical products are indicated below. Oxygen, sulfur, or selenium can be added to the phosphorus. In cases where a P—Ph group is present, this addition is usually stereoselective, leading to an equatorial phenyl group. Stereo-analysis of the bicyclic compounds shows them to be usually mixtures comprising predominantly the *trans*-fused compound with equatorial substituents ⟨83ZOB1050, 86ZOB2690, 88ZOB1530, 89ZOB338, 90ZOB814, 92ZOB762⟩. The effect of reaction conditions was studied for the cyclization of *β*-styryl cyclohexenyl ketone with phenylphosphine ⟨86IZV64⟩. Monocyclic compounds (**149**) were prepared by condensation of bis(hydroxymethyl)phenylphosphine with 1,5-diphenyl-2-methyl-1,4-pentadien-3-one or 1,4-diphenyl-2,4-dimethylpentadien-3-one (**148**) ⟨81JOC1166⟩, or phenylphosphine with CH_2=CHCOCMe=CH_2 ⟨84ZOB1995⟩ (Equation (18)). In some cases, a second molecule of the dienone adds in a double Michael addition to the first-formed heterocycle ⟨88ZOB946, 90ZOB537⟩. A modification of this process uses amino ketones ((**150**), (**152**)) with phenylphosphine to make bicyclic compounds containing fused six-membered rings (**151**) and (**153**, X = O, CH_2) ⟨82ZOB1919, 83ZOB1757, 85IZV43⟩ and heteraindenes (**153**, X = bond) ⟨86IZV57⟩ (Scheme 19). Similarly, 2,6-bis(dimethylaminomethyl)cyclohexanone reacted with phenylphosphine to form the bridged bicyclic phosphorin (**154**, Z = null) which was converted into the sulfide (Z = S) for characterization ⟨88ZOB233⟩.



(**148**) (**149**) (18)







(150) (151) (152) (153) (154)

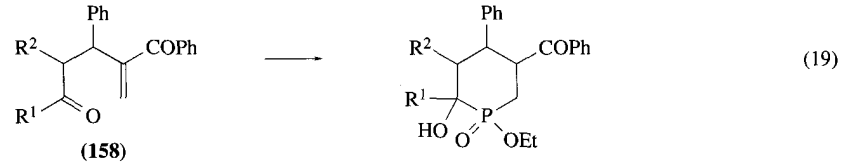
Scheme 19

5.12.9.2.6 Addition of P(III) to dienes

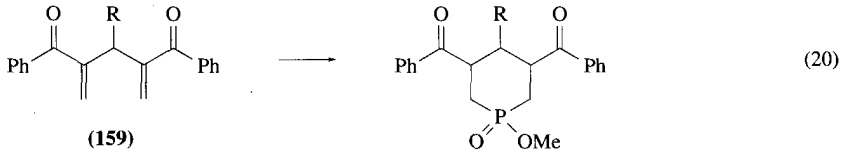
A mixture of *cis*- and *trans*-1-phosphabicyclo[4.4.0]decane (**156**) was prepared by free-radical cyclization of the diene (**155**) (Scheme 20a). Stereostructures were assigned by NMR. Equilibration of *cis* and *trans* isomers by UV irradiation gave ΔG° ca. 0 kcal mol^{-1}. Activation parameters for ring inversion were also measured for the *cis* compound and its *P*-sulfide as $\Delta G^{\circ} = 41.9$ and 39.7 kJ mol^{-1}, respectively ⟨87ZAAC(553)136⟩. Radical addition of Me_3SiPH_2 to 1,4-pentadiene, norbornadiene, $Ph_2PCH{=}CH_2$, or $PhP(CH{=}CH_2)_2$ yielded new organosilane synthons. Hydrolysis gave quantitative yields of the corresponding phosphines and provided a new general route for primary and secondary phosphine preparation ⟨84IC4130⟩. 9-Phosphorus heterocycles were prepared by adding substituted phosphines to 1,5-cyclooctadiene in the presence of radical-generating catalysts ⟨80JAP55122790, 80JAP55122791, 80JAP55122792⟩ and by intramolecular cyclization of 4-trimethylsilyloxy-4-phosphinomethylhepta-1,6-diene (**157**) ⟨93ZAAC(619)989⟩ and 4-phosphinocta-1,7-diene ⟨91ZAAC(600)195⟩ (Scheme 20b). One (**158**) ⟨83ZOB2645⟩ or both (**159**) of the double bonds may be conjugated with a carbonyl group ⟨93ZOB1530⟩ (Equations (19) and (20)).

(155) (156) (157)

Scheme 20a **Scheme 20b**



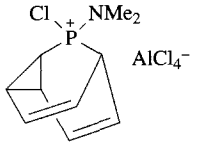
(158) (19)



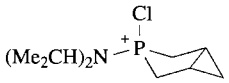
(159) (20)

Complexes of dihalophosphines with aluminum chloride ⟨81TL2695⟩ and $[Me_2N(Cl)P]^+AlCl_4^-$ ⟨86JA529⟩ add to 1,*n*-dienes, for example the 9-phosphabarbaralane (**160**) was obtained from cyclooctatetraene. Variable-temperature NMR confirmed that the solution-phase ground state corresponded to a localized structure, but the x-ray crystal structure suggested near symmetry and this molecule represented the closest approach to a bishomoaromatic system so far reported ⟨81TL2695, 86JA529⟩. Similar reactions occur with phosphenium ions, such as $(Me_2CH)_2NP^+$, which react with

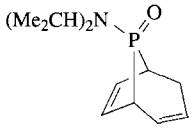
1,3- and 1,4-dienes to form some interesting cyclized products such as (**161**) from 1,4-pentadiene and (**162**) from cycloheptatriene ⟨84TL815, 86IC740, 88PS(35)353⟩.



(**160**)

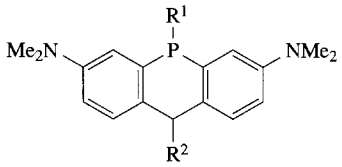


(**161**)



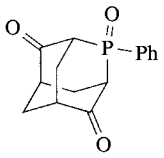
(**162**)

The dihydrophosphorins (**163**), obtained as mixtures of isomers in which the phosphorus lone pair is axial, were formed in reactions of aromatic aldehydes with bis(3-dimethylaminophenyl)arylphosphines. The product structure and yield was influenced by substituents on the aromatic aldehydes and the basicity of the phosphorus atom ⟨81ZOB1533, 90ZOB1558⟩.

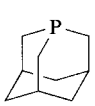


(**163**)

Another variation on this theme uses electrophilic addition to bisenamines. This has been particularly attractive to workers wishing to synthesize adamantane derivatives. For example, the 2-phosphaadamantane (**164**) was made by phosphorylation of 2,6-bis(morpholino)bicyclo[3.3.1]nona-2,6-diene with dichlorophenylphosphine ⟨84ZOB220, 85ZOB2475, 85ZOB2667, 89ZOB476, 89ZOB1451, 92ZOB2142⟩. Synthesis of 1-phosphaadamantane (**165**) involved as a key step the α,α-annulation of $(BrCH_2)_2CHCO_2Et$ and the enamine (**81**, X = O) ⟨82MI 512-03, 83PS(18)109, 83T4225⟩ (Equation 3). Phosphaadamantane syntheses have been reviewed ⟨83PS(15)51⟩.

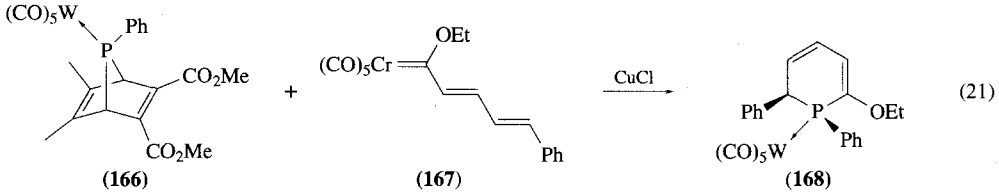


(**164**)



(**165**)

Reaction of (**166**), which is essentially a source of $PhP \rightarrow W(CO)_5$, with (**167**) in the presence of CuCl yields the complex (**168**) via the spontaneous cyclization of an intermediate 1-phosphahexatriene ⟨88TL4289⟩ (Equation (21)).

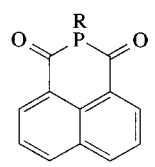


(**166**) (**167**) (**168**) (21)

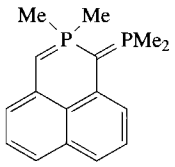
5.12.9.2.7 Addition of P(III) to 1,5-dihalo compounds

1-(4-Pentenyl)phosphorinane-1-oxide was formed in 15% yield by direct reaction of red phosphorus and 1,5-dibromopentane in aqueous dioxane ⟨92ZOB699⟩. The tricyclic skeletons (**169–171**) were formed by reaction of a bisacid chloride with bis(trimethylsilyl)phenylphosphine ⟨87CC1753⟩, 1,8-(bischloromethyl)naphthalene with trimethylphosphine ⟨87JCS(D)1647⟩, followed by cyclization and bisylide formation from the initial bisphosphonium salt, or of a 1,8-(bisbromomethyl)-naphthalene with diphenylsilylphosphine ⟨83JOM(250)171⟩. In the last case the product could be deprotonated with *t*-butyllithium to give (**172**), which is not a delocalized π-system, but rather a

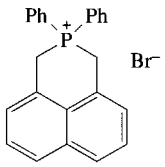
phosphonium bisylide. The cyclization reaction also works when the halogen atoms are directly attached to an aromatic ring, and (**173**) can be formed by reaction of suitable phosphorus reagents with a 2,2′-dibromo-4,4′-bis(dimethylamino)diphenylmethane ⟨84ZOB1995⟩. 3,7-Bis(dimethylamino)-5-phenyl-5,10-dihydroanthraphosphines were prepared by Grignard cyclization of the appropriate dibromodiphenylmethane with dichlorophenylphosphine. The reaction proceeds stereospecifically, giving only the isomer with axial orientation of the phenyl group on the phosphorus atom ⟨84ZOB1995⟩.



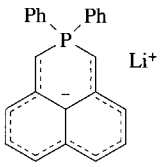
(**169**)



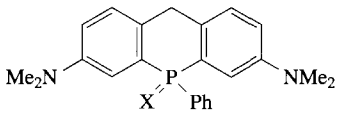
(**170**)



(**171**)



(**172**)

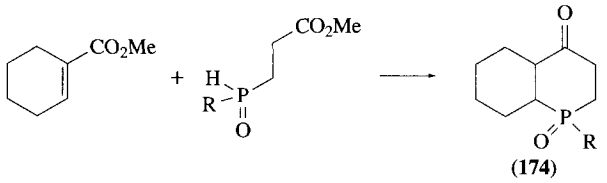


(**173**)

Simple phosphorinanes (**21**, R = $OSiMe_3$) are available in moderate yield by reaction of ammonium hypophosphite ($NH_4OP(O)H_2$) and hexamethyldisilazane with 1,5-dibromopentane. They were converted into the corresponding phosphinic acid (**21**, R = OH) by treatment with ethanol followed by distillation ⟨94ZOB419⟩.

5.12.9.3 $PC_2 + C_3$ Reactions

The 1,4-dioxo-2,3,4a,5,6,7,8,8a-octahydro-λ^5-phosphinoline system (**174**) was formed by a Claisen-type reaction of methyl (2-methoxycarbonylethyl)phosphinate with methyl 1-cyclohexenoate followed by cyclization (Equation (22)). The reactions appear to be stereoselective and give predominantly the *cis*-fused system ⟨87AJC1353⟩.



(**174**)

(22)

5.12.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

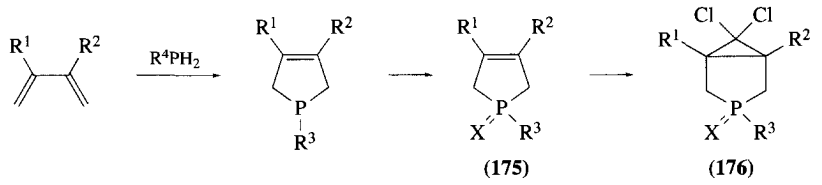
5.12.10.1 Synthesis via Ring Expansion

5.12.10.1.1 Synthesis via ring expansion of dihydrophospholes using carbenes

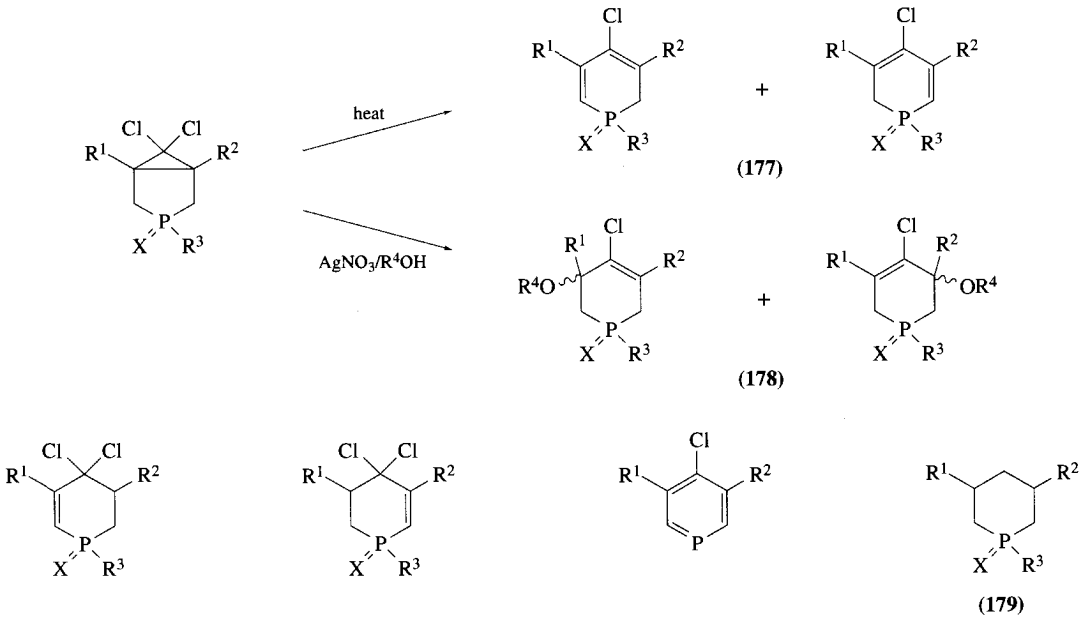
This area represents a major synthetic advance since Volume 1 of CHEC-I ⟨84CHEC-I(1)493⟩. Carbenes have been found to react easily with dihydrophospholes with ring expansion to form six-membered rings at various oxidation and substitution levels determined by substituents on the carbene and the phosphole.

The general procedure is summarized in Scheme 21. Dichlorocarbene is added to a dihydrophosphole (**175**, R^1, R^2 = H, Me, R^3 = Ph, OR). The bicyclohexane (**176**) may then spontaneously rearrange to a mixture of dihydrophosphorins (**177**). Alternatively, depending on the substitution on carbon and phosphorus, rearrangement may be induced by heating ⟨87JOC3983, 88JOC4106, 88MI 512-05, 88MI 512-07, 89MI 512-04, 89MI 512-05, 89AG768, 90HAC419, 93HAC61⟩ or by treatment with aqueous or alcoholic silver nitrate ⟨87JOC5721, 88MI 512-06, 93HAC61⟩. The alkoxytetrahydrophosphorins (**178**) may then be converted thermally into the dihydrophosphorins (**177**) (Scheme 22). Another option is to induce rearrangement by treatment of the bicyclic intermediates with mercuric acetate in acetic acid ⟨89MI 512-06, 88PS(36)61⟩. In the case of both thermal and ionic rearrangement, experimental data suggest the involvement of a cationic intermediate during the ring opening. The reaction of

dihydro-1*H*-phosphole oxides with dichlorocarbene takes a different course to give *P*-alkoxy-1,4-dihydrophosphorin oxides ⟨90JOC6361, 93HAC61⟩. A summary of this synthetic procedure has now been published by Keglevich ⟨93S931⟩.



Scheme 21



Scheme 22

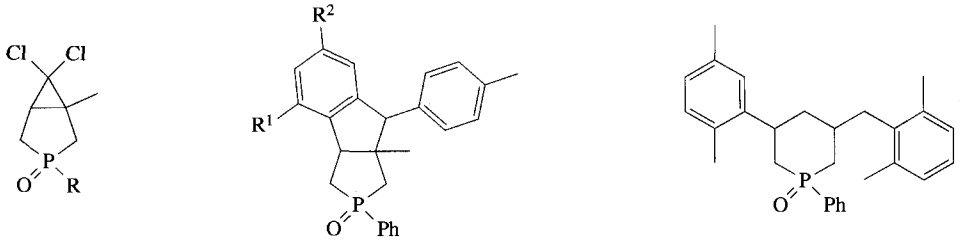
It is possible to make two diastereomers of the bicyclic intermediate (**176**, X = O, $R^3 = NAlk_2$, R^2 = H, R^1 = Me) by either adding dichlorocarbene to a 1-dialkylamino-3-phospholene-1-oxide or by substitution of the *P*-chloro derivative of the bicyclic system (**176**, X = O, R^3 = Cl, R^1 = H, R^2 = Me) ⟨94MI 512-01⟩.

The tetrahydrophosphorins can be hydrogenated to phosphorinanes. Conformational analysis of the products suggests a strong bias to those compounds (**179**, R^1 = H, R^2 = Me) with equatorial *C*-methyl groups. In contrast, the dimethyl compounds (**179**, $R^1 = R^2$ = Me) give an equilibrium mixture of two conformers ⟨92MI 512-01⟩ (Scheme 22). Alternatively, a three-step process involving conversion to phosphinic chlorides followed by deoxygenation and dechlorination led to the phosphorins ⟨92JOC977⟩.

Friedel–Crafts reaction of *P*-substituted 6,6-dichloro-3-phosphabicyclo[3.1.0]hexane-3-oxides (**180**, R = Ph, alkyl) with substituted benzenes may afford two benzophosphabicyclooctene derivatives (e.g. (**181**, R^1 = Me, R^2 = H; R^1 = H, R^2 = Me) as well as benzylphenylhexahydrophosphorin-oxides (e.g. **182**). The bicyclooctane (**181**) is formed by a rare opening of the cyclopropane ring, while (**182**) is formed by the more common ring expansion. Displacement of the two chlorine atoms without opening of the cyclopropane ring does not take place ⟨89MI 512-06, 91MI 512-01⟩.

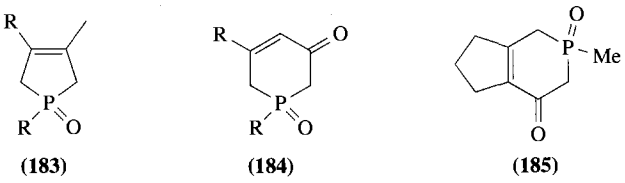
5.12.10.1.2 Synthesis via ring expansion

More traditional routes to the six-membered heterocycles include Quin's two-step 3-phospholene (**183**) to phosphorinanone (**184**) transformation by ozonolysis followed by aldol condensation ⟨85PS(22)35⟩. This process also works well in bicyclic systems to provide products such as (**185**)



(180) (181) (182)

⟨82JOC905, 90HAC93⟩. Another route involves aroylation of 1-phenylphosphole, followed by sulfurization with Lawesson's reagent and pyrolysis over nickel to give a 2-arylphosphorin. For example, 3,4-dimethyl-1-phenylphosphole reacted with thienoyl or furoyl chlorides to give (**186**, X = S, O) (Equation (23)) ⟨82TL1565, 84PS(19)45⟩. The reaction has also been used for ring expansion of 1-benzylphosphindole ⟨81NJC187⟩.



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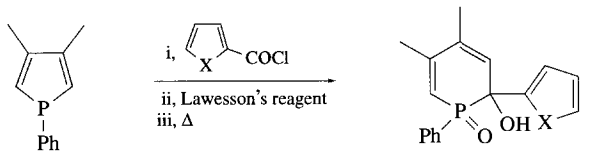
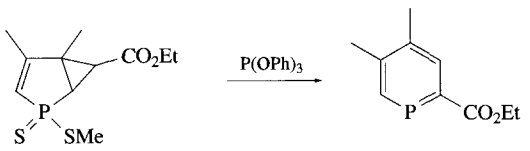


(23)

(186)

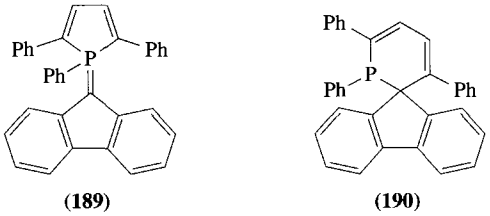
Ethyl diazoacetate reacts with 1-methylthio-3,4-dimethylphosphole-1-sulfide to produce (**187**), which was converted into (**188**) on reaction with triphenyl phosphite (Equation (24)). On the basis of x-ray data, the proposed mechanism includes the opening of the cyclopropane ring with selective phosphorus-assisted migration of the ethoxycarbonyl group. This chemistry was also used to prepare a 2,2′-biphosphorin from a 2,2′-biphosphole ⟨91JOC4031⟩.



(24)

(187) (188)

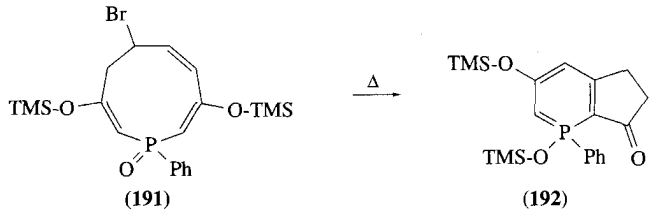
1-(Fluoren-9-ylidene)-1,2,5-triphenyl-λ^5-phosphole (**189**) and related compounds underwent a Stevens rearrangement in refluxing toluene to form spiro-ring-expanded compounds, e.g. (**190**) ⟨83PS(18)183, 84CC1217⟩.



(189) (190)

5.12.10.2 Synthesis via Ring Contraction

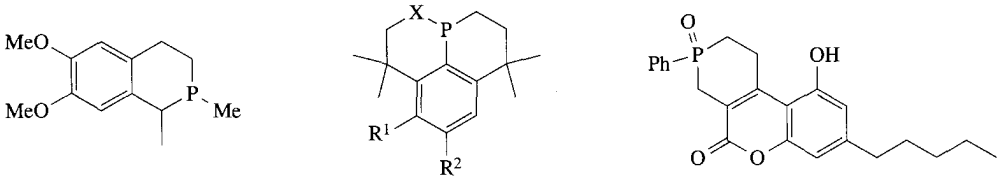
Silylation of 5,6-dibromo-1-phenyl-3,8-phosphonanedione-1-oxide occurs with bis(trimethylsilyl)trifluoroacetamide to give the 3,8-bis(trimethylsilyloxy) derivative (**191**) (Equation (25)). Heating this in an inert solvent resulted in intramolecular ring closure with an accompanying silyl migration from C—O to P—O to give the novel λ^5-cyclopentaphosphinin-7-one (**192**). Hydrolysis gave a crystalline diketophosphoryl derivative ⟨84JOC3157⟩. This procedure involves an intramolecular cycloaddition and is a variant on the preparation of (**185**) by intramolecular aldol condensation.



(191) (192) (25)

5.12.11 SYNTHESIS OF ANALOGUES OF NATURAL PRODUCTS

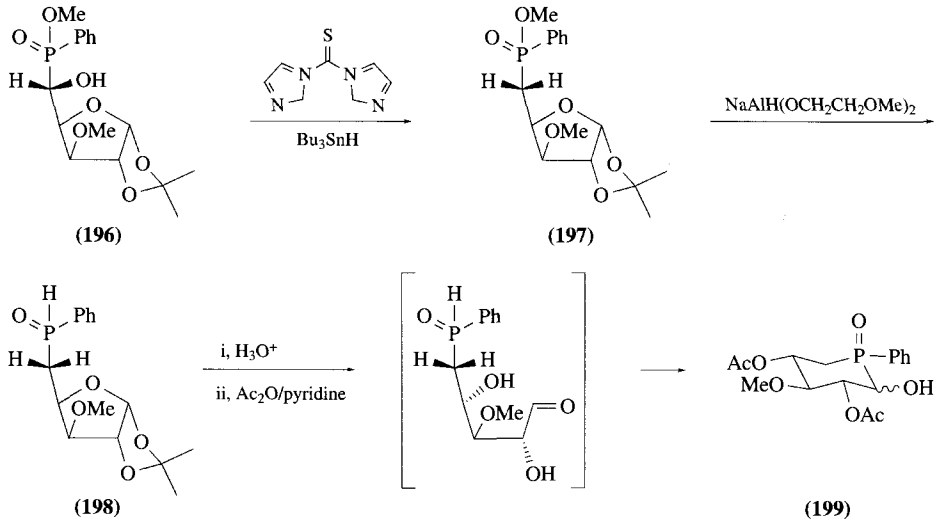
A computer-assisted synthesis of phosphacarnegine (**193**) (using PASCOP) was designed and executed. Some pathways were not appropriate but two successful routes are described and the limits of the computer program were discussed ⟨83PS(18)129, 84T2721, 84T2731⟩. Synthesis of phosphalilolidine (**194**, X = bond, R^1 = Me, R^2 = H) and phosphajulolidine (**194**, X = CH_2, R^1 = H, R^2 = Me) involved cyclization of 1-(methyl-*p*-tolylphosphinoyl)-3-methylbutan-2-ol, which produced an inseparable mixture of 1,4,4,7- and 1,4,4,6-tetramethylphosphinoline oxides via *ipso*-cyclization followed by migration of the phosphinoyl group ⟨81JOC361⟩. The phosphorus-containing phosphacannabinoid (**195**) precursor was prepared via methyl 4-oxo-1-phenyl-3-phosphorinanecarboxylate, available by cyclization of $Ph(CH_2CH_2CO_2Me)_2$. It represents the first example of this class of heterocycle ⟨81JA2032⟩.



(193) (194) (195)

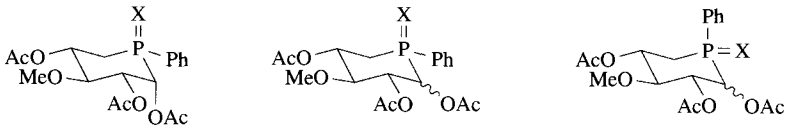
Considerable effort has been devoted to the synthesis of phosphorus-containing analogues of sugars which could well have intriguing biological properties. Unfortunately, the publications from Yamamoto's extraordinarily prolific team give little information on potential applications. All the synthetic methods involve modifications of Scheme 3. In essence, a furanose (**196**) is converted into a phosphonate (**197**) which is then reduced to a phosphinous acid (**198**) (Scheme 23). Hydrolysis of (**198**) followed by spontaneous recyclization gives the phosphapyranose (**199**). The technique is extraordinarily versatile and has been used to produce analogues of the ketohexose fructose ⟨91CL1439, 93JCS(P1)1663⟩, the aldohexoses fucose ⟨90CL1359, 92BCJ2922, 93BCJ2315⟩, galactose ⟨90CL1359, 91BCJ869, 91BCJ2398, 92BCJ2922⟩, glucose ⟨82CAR(102)159, 83JOC435, 84CAR(133)45, 85JAP60237093, 85JOC3516, 87NKK1207, 89CAR(193)9, 89MI 512-04, 91BCJ2398⟩, gulose ⟨90BCJ1174⟩, idose ⟨82CAR(106)31, 83CAR(113)31, 83CAR(122)C1, 83CAR(121)C4, 88JOC4790⟩, mannose ⟨89CL1471, 90BCJ1174⟩, and the aldopentoses ribose ⟨83CAR(122)81, 84CAR(127)35, 84CAR(125)172, 86CAR(148)168⟩, and xylose ⟨83CAR(114)83, 83CAR(119)101, 83CAR(124)156, 83CAR(124)195, 84CAR(128)C5, 85CAR(141)335, 87CL2081, 88BCJ2499, 89CL349, 90BCJ421, 91CAR(222)11⟩.

The structures and conformations of many of the products have been thoroughly analyzed. For example, 400 MHz proton nuclear magnetic resonance was used to establish that 5,6-dideoxy-5-*C*-



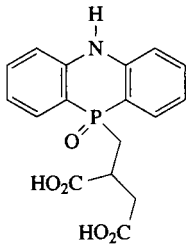
Scheme 23

[(*R* and *S*)-phenylphosphinyl]-L-*ido*-hexopyranoses have the L-*ido* configuration with the pyranoid ring in the 4C1(L) conformation ⟨82JOC191⟩. X-ray structure of the phosphaxylopyranoses (**200**, X = O, S) have been reported. In all three structures the pyranose rings had the 4C1(D) structure with substituents at C-1 axial and at C-2, C-3, and C-4 equatorial. The phenyl rings were oriented equatorially with their planes nearly parallel to the P=X bond. For the favored conformations in solution, the inclination of the equatorial phenyl in the α- and β-D-xylopyranose analogues (**201**) is similar to that observed in the solid, but the inclination of the axial phenyl ring of (**202**) is near 90° with respect to the equatorial P=X bond ⟨91CAR(222)11⟩. A simple method of calculating the molecular rotations of the sulfur, nitrogen, and phosphorus analogues of α-D-glycopyranoses having different substituents at the anomeric carbon atom was developed and gave results which agree satisfactorily with the corresponding literature values ⟨84AJC971⟩.



5.12.12 IMPORTANT COMPOUNDS AND APPLICATIONS

Six-membered phosphorus heterocycles have been referred to in a number of patents as useful catalysts for the polymerisation of carbon monoxide with alkenes ⟨92NEP9002688⟩, the hydroformylation of alkenes ⟨81JAP55113731, 81JAP56140940, 90MIP1043640, 91JAP03141234, 93USP5256827, 93USP5304691, 93USP5304686⟩, the preparation of ethylene glycol from synthesis gas ⟨85JAP61215338, 86JAP61215337⟩, and the preparation of ethanol and propanol from methanol and synthesis gas ⟨83EUP84833⟩. 1-Phosphanorbornadienes with chiral phosphorus at the bridgehead are useful in the asymmetric hydrogenation of dehydro amino acids ⟨89NJC369⟩ and double bonds ⟨85FPR8514638⟩. Cyclic and bicyclic phosphine oxides have been proposed as flame retardants ⟨85USP4503178, 86USP4623687, 87JAP62022791, 87JAP62022792⟩, for example (**203**) ⟨94JAP06100577⟩, and polymer antioxidants ⟨85JAP60097985⟩. "Classical" and "magnetic" aromaticities have been defined and applied to a number of heterocycles, including phosphabenzene, for the development of new pharmaceutical compounds using theoretical structure–activity relationships ⟨93QSAR146⟩.



(203)

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5.13
Six-membered Rings with One Arsenic, Antimony, or Bismuth Atom

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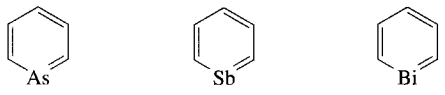
5.13.1 INTRODUCTION

The major contemporary interest in six-membered ring, Group 15 heterocycles centers on the aromaticity of the fully conjugated rings (the heterobenzenes). Therefore the major coverage in this

chapter is on arsenin (arsabenzene) (**1**), antimonin (stibabenzene) (**2**), and bismin (bismabenzene) (**3**). An attempt has been made to cover all material which has appeared since the publication of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) in 1984. Older material, particularly on theory, spectra, and structure, is included where it is judged that coverage in CHEC-I is inadequate. For clarity, the synthesis sections also deal with older material. Since the coverage of saturated and partially saturated rings in CHEC-I was satisfactory, only material discovered after 1984 is included.



(1) (2) (3)

Reviews by Ashe ⟨82TCC125⟩ and Märkl ⟨82MI 513-01⟩ were not noted in CHEC-I.

Nomenclature in this chapter follows the recommendations of the IUPAC, and is that which is used in the current *Chemical Abstracts*. The parent monocycles are therefore named arsenin (**1**), antimonin (**2**), and bismin (**3**). The arsenic analogue of acridine is assigned the name acridarsine. This was formerly called arsacridine (e.g., see ⟨B-50MI 513-01⟩), and a nonsystematic numbering was applied. In the first edition of this monograph, it was called dibenz[*b*,*e*]arsenin. The fully saturated rings are called arsenane, antimonane, and bismacyclohexane.

The replacement nomenclature system is also widely applied to these systems in the current literature: arsabenzene, stibabenzene, and bismabenzene are quite legitimate names, but it should be noted that, when substituted derivatives are involved, the numbering system may be different from that which applies to the Hantzsch–Widman names. In 4-arsatoluene, for instance, the arsenic atom is at the four position, while if it is named as 4-methylarsenin the methyl group occupies position four. Other names formed by analogy with the corresponding nitrogen ring systems (arsinoline, from quinoline; arsanthridine, from phenanthridine) have been coined, but they can be misleading, have not found much favor, and are for the most part obsolete (although in the five-membered ring series arsindole is accepted for the arsenic analog of indole).

5.13.2 THEORETICAL METHODS

The properties of arsenin and antimonin have been evaluated using various theoretical methods which range from completely empirical to *ab initio*. Most treatments also include pyridine (**4**) and phosphorin (**5**), although there is no published theoretical work on bismin up to 1995.

(4) (5)

Bird has defined an aromaticity index (*I*) based on the experimentally observed degree of bond alternation in an unsaturated ring ⟨86T89, 90T5697⟩. The following *I* values have been found: benzene, 100; pyridine, 80; phosphorin, 74; arsenin, 67. Herndon has used a graph theoretical model based on the experimentally observed UV photoelectron spectra to evaluate the aromaticity of the heterobenzenes ⟨79TL3283⟩. It was found that the resonance energies are as follows: benzene, 0.821 eV; pyridine, 0.618 eV; phosphorin, 0.661 eV; arsenin, 0.545 eV; antimonin, 0.607 eV.

The semi-empirical CNDO/2 method has been applied to phosphorin and arsenin by Schweig *et al.* ⟨73T475, 79TL3283⟩. The electron densities were found to decrease in the order C-2 > C-4 > C-3. The dipole moments could be calculated from the electron distribution. The calculated and experimental values of the dipole moments are: pyridine, 2.13 D (2.2 D), phosphorin, 0.94 D (1.54 D) and arsenin, 0.74 D (1.10 D).

Arsenin and phosphorin have been treated using *ab initio* methods with a STO-3G basis set using assumed (but realistic) geometries ⟨74JCS(F2)1222⟩. The electron distribution was also found to be C-2 > C-4 > C-3, although the calculated dipole moment of arsenin (3.18 D) emphasizes the inadequacy of the single ζ basis set. More recently, in the late 1980s, Baldridge and Gordon performed *ab initio* calculations using a 3-21G* basis set ⟨88JA4204⟩. Geometries were optimized and the calculated geometries matched the experimental values to within 0.03 Å. Using a homodesmic reaction based on bond fragmentation, the delocalization enthalpies were calculated as

follows: benzene, 61.3 kcal mol^{-1} (257 kJ mol^{-1}); pyridine, 64.0 kcal mol^{-1} (268 kJ mol^{-1}); phosphorin, 56.6 kcal mol^{-1} (237 kJ mol^{-1}); arsenin, 53.9 kcal mol^{-1} (226 kJ mol^{-1}); antimonin, 50.5 kcal mol^{-1} (211 kJ mol^{-1}).

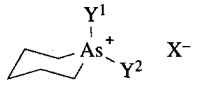
All the theoretical treatments find that arsenin and antimonin are significantly aromatic, although less so than benzene.

5.13.3 EXPERIMENTAL STRUCTURAL AND SPECTROSCOPIC METHODS

5.13.3.1 Structure

5.13.3.1.1 Arsenanes

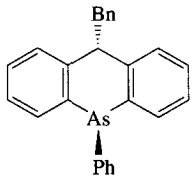
X-ray structures have been reported for the two derivatives of arsenane, (**6**) and (**7**) ⟨89CC829, 90MI 513-01⟩. In both cases the arsenane rings exist in chair conformations. The intraring As—C bonds are relatively short (1.89 Å for (**6**), 1.90 Å and 1.93 Å for (**7**)) although the As—C distance for the equatorial *t*-butyl group of (**7**)) is considerably longer (1.97 Å).



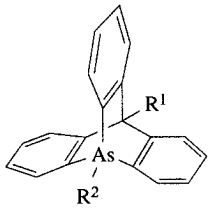
(**6**) $Y^1 = Y^2 = OH$, X = Cl
(**7**) $Y^1 = Me$, $Y^2 = Bu^t$

5.13.3.1.2 Dihydroarsenins

There are no reported structures for monocyclic dihydroarsenins. However, crystal structures of four derivatives of 9,10-dihydroarsacridine (**8**)–(**11**) have been reported by Stam and co-workers ⟨80AX(B)(36)455, 80AX(B)1247, 80AX(B)1252, 80AX(B)1254⟩. The dihydroarsenin rings are folded about the As—C-4 axis in each case. The arsenic(III) derivatives show As—C distances in the range of 1.94–1.96 Å while the C—As—C angles range from 90° to 94°. As expected, the As—C distances (1.88–1.91 Å) contract, while the C—As—C bond angles expand in quaternization to (**11**).



(**8**)

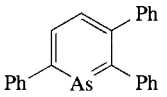


(**9**) $R^1 = H$, R^2 = nil
(**10**) $R^1 = Ph$, R^2 = nil
(**11**) $R^1 = H$, $R^2 = Me^+ Cl(H_2O)^-$

5.13.3.1.3 Structures of arsenins and antimonins

A crystal structure has been reported for 2,3,6-triphenylarsenin (**12**) ⟨72AG(E)630, 73JCS(D)511⟩. A gas phase structure of arsenin itself has been determined using electron diffraction ⟨75JST(25)65⟩. Similarly, analysis of the microwave spectra of arsenin and antimonin affords data on their structures in the gas phase ⟨75JSP(57)428, 78JSP(70)197⟩. Arsenin, 4-methylarsenin, and 4-methylantimonin show partial orientation in nematic solvents. Structural data has been obtained from NMR studies of these solutions ⟨78JST(48)219, 79JST(52)231⟩. The very labile bismin has not yet been subject to structural

study. However, its structure can be anticipated by extrapolation from the data on arsenin and antimonin. The structures are compared in Figure 1.



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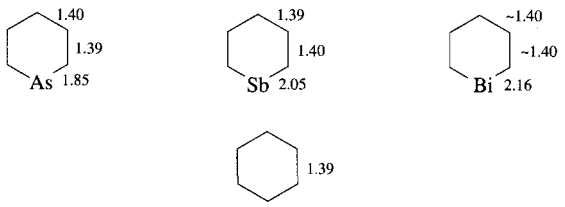


Figure 1 A comparison of the molecular dimensions of arsenin, antimonin, bismin, and benzene (distances shown in Å).

Arsenin and antimonin are planar within the expected C_{2v} symmetry. The C—C bond lengths are not significantly different, and their mean value of 1.395 Å is precisely that of benzene. The As—C bond length of arsenin (1.85 Å) is significantly shorter than those of the dihydroarsenins (~1.95 Å). Similarly, the Sb—C bond of antimonin (2.05 Å) is shorter than those found for trivalent antimony compounds (~2.20 Å). These bond lengths provide strong presumptive evidence for multiple C—As and C—Sb bonding.

The C—As—C bond angle of arsenin (97°) and the C—Sb—C bond angle of antimonin (93°) are similar to those found acyclic As(III) and Sb(III) compounds.

5.13.3.2 Spectroscopy

5.13.3.2.1 Vibrational spectroscopy

The IR and Raman spectra of arsenin have been analyzed, and a complete vibrational assignment has been made ⟨82JST(78)169⟩. Comparison of the spectra with those of pyridine and phosphorin indicates that the heterocycles have similar aromatic structures. The major trend is one of small shifts to lower frequency for the CH modes and larger shifts for the ring modes as the heteroatoms increase in size.

5.13.3.2.2 Mass spectrometry

Arsenin and antimonin derivatives show mass spectra which are typical of aromatic compounds ⟨71JA3293, 71JA6690⟩. The molecular ion is usually the base peak. While bismin and 4-*t*-butylbismin show significant molecular ions, the base peaks are due to bismuth atoms ⟨76TL415, 82JA5693⟩. Inspection of Table 1 shows that fragmentation to the heteroatom or by loss of the heteroatom becomes more important for the heavier heterocycles. This is consistent with weaker bonding and with the greater positive character of the heavier heteroatoms.

Table 1 The mass spectra fragmentation patterns of benzene, phosphorin, arsenin, antimonin, and bismin (C_5H_5E).[a]

Compound	*Parent ion (M^+)*	*$M—C_2H_2$*	*M—HCE*	*M—E*	*E*	*Ref.*
C_6H_6	78 (100)	52 (18)	—	—	—	
C_5H_5P	96 (100)	70 (24)	52 (8)	65 (0)	31 (0)	71JA3293
C_5H_5As	104 (100)	114 (24)	52 (1)	65 (1)	75 (3)	71JA3293
C_5H_5Sb	186 (100)[b]	160 (16)	52 (0)	65 (58)	121 (27)	71JA6690
C_5H_5Bi	274 (30)	252 (0)	52 (?)	65 (?)[c]	209 (100)	76TL415

[a]Ion *m/z* is followed by the relative intensity in parentheses. [b]The *m/z* and intensities are summed for the ^{123}Sb and ^{121}Sb. [c]Low *m/z* peaks were due to impurities.

5.13.3.2.3 NMR spectroscopy

The ^{1}H NMR spectra of arsenins, antimonins, and bismins (Table 2) show very low-field signals, invariably downfield from those of benzene ⟨76JA5451, 82JA5693⟩. The most characteristic feature of their spectra is the particularly low-field signals due to the proton α to the heteroatom. These shifts are progressive with atomic number. In the case of 4-*t*-butylbismin the α proton signal occurs at δ 13.5. This shift is apparently caused by the exceptionally large magnetic anisotropy of the π-bonded heteroatoms. Analysis of the spectra gives the anisotropies (Δχ) of π-bonded arsenic, antimony and bismuth as 103×10^{-6}, 202×10^{-6}, and 276×10^{-6}, respectively. These values are large when compared to the Pascal constants of σ-bonded atoms (e.g. 37×10^{-6} for bismuth) or even the (Δχ) values associated with benzocyclic aromatic rings (e.g. 55×10^{-6} for benzene). The signals for the protons β to the heteroatoms show similar but smaller shifts. The chemical shift values of the relatively remote γ protons show little variation. Their low-field position (δ 7.5–7.8) is consistent with a large ring current for these aromatic heterocycles.

Table 2 The ^{1}H chemical shifts (^{13}C chemical shifts in parentheses) of benzene, arsenin, antimonin, and bismin.

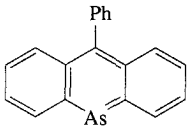
Compound	*H-α(C-α)*	*H-β(C-β)*	*H-γ(C-γ)*	*Ref.*
C_6H_6	7.37 (128.7)			
C_5H_5As	9.68 (167.7)	7.83 (133.2)	7.52 (128.2)	76JA5451
C_5H_5Sb	10.94 (178.3)	8.24 (134.4)	7.78 (127.4)	76JA5451
C_5H_5Bi	13.25 (211.7)[a]	9.8 (132.9)[a]	7.8 (–)[b]	82JA5693

[a] ^{13}C chemical shfts are for the more stable 4-*t*-butylbismin. [b] ^{13}C chemical shift could not be recorded. The trends for C_5H_5As and C_5H_5Sb suggest the δ(C-γ) would be close to 127.

The ^{13}C chemical shifts for the α-carbon atoms also occur at quite low field. This effect is probably the normal one shown by carbon atoms which are π bonded to heavier elements ⟨79AG(E)395⟩. The signals for the β- and γ-carbon atoms are in the normal aromatic range. The one-bond ^{13}C–H coupling constants for arsenin, antimonin, and bismin occur in the range of 150–161 Hz. These values are very close to the $^1J(^{13}C–H)$ of benzene (159 Hz), and imply that the hybridization is close to sp^2.

5.13.3.2.4 UV photoelectron spectroscopy and electron transmission spectroscopy

Heilbronner and co-workers have measured the UV photoelectron (UV PE) spectra of arsenin, antimonin, and bismin as a part of the study of the complete family of heterobenzenes ⟨73JA928, 76TL411, 76HCA1944⟩. Similarly, the UV PE spectra of 10-phenyl-9-arsacridine (**13**) was determined as a part of a series of analogous phosphorus and nitrogen compounds ⟨72AG(E)924⟩. The interpretation of both series is similar and is summarized in Figure 2 for the parent compounds.



(13)

The degenerate HOMO of benzene is split into a_2 and b_1 orbitals in the C_{2v} symmetry of the heterobenzenes. Since the a_2 orbital has a node at the heteroatom, its energy should not be affected by the nature of the heteroatom. Therefore, the a_2 orbital energies should be invariant in the series. On the other hand, the b_2 orbital, which has a maximum at the heteroatom, should vary strongly with the nature of heteroatom bonding.

Experimentally, the first ionization potentials of phosphorin, arsenin, antimonin, and bismin decrease as the atomic number of the heteroatom increases. Therefore, the HOMO must be the b_1 orbital. The second and third ionization potentials correspond to overlapping bands which shift only slightly in the series. These are assigned to the a_2 (π) orbital and a_1 (*n*) orbital. Since the a_2 orbital is the higher π orbital in pyridine, the order of the π MOs is inverted between pyridine and its heavier relatives.

The electron transmission spectra (ETS) have been measured for phosphorin, arsenin, and antimonin ⟨82JA425⟩. The ETS allow measurement of the electron affinities which correspond to

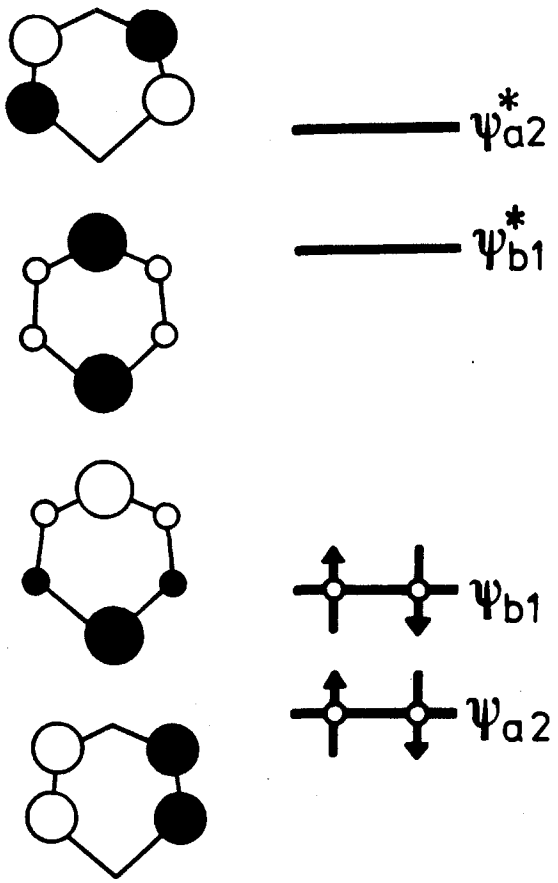


Figure 2 A schematic drawing of the frontier π molecular orbitals of arsenin, antimonin, and bismin (the heteroatom is located at the bottom vertex of each hexagon).

temporary filling of the virtual orbitals. The ETS results indicate that the LUMOs are b_1 orbitals. Thus, both frontier MOs of the heavier heterobenzenes have b_1 symmetry. This is consistent with both weaker carbon–heteroatom bonding and antibonding, an expected consequence of increasing carbon–heteroatom bond lengths in the series.

This ordering of the frontier MOs has been used to explain the enhanced chemical stability of 4-substituted antimonins (**14**) and bismins (**15**) and 10-substituted 9-arsacridines (**13**). Since the position of the substituent has the largest orbital coefficient, steric blocking of this most reactive site should greatly increase the kinetic stability of (**13**)–(**15**).

(14a) R = Me
(14b) R = Bu^t

(15a) R = Me
(15b) R = Bu^t

5.13.3.2.5 UV spectroscopy and magnetic circular dichroism

The solution UV spectrum of arsenin shows intense bands at 219 nm and 268 nm with a shoulder at 305 nm ⟨71JA3293⟩. It seems probable that the highest wavelength band corresponds to an $n \rightarrow \pi^*$ excitation while the more intense bands correspond to $\pi \rightarrow \pi^*$ excitations. Similarly, the spectrum of antimonin shows intense bands at 236 nm and 312 nm ⟨71JA6690⟩. The red shift of these $\pi \rightarrow \pi^*$ bands corresponds to a smaller gap between the bonding and antibonding levels for antimonin.

The magnetic circular dichroism (MCD) of the UV bands has been analyzed ⟨89OM2804⟩. From signs of the MCD bands, the ordering of HOMO and LUMO orbitals was shown to be $a_1^* > b_2^* > b_2 > a_1$ as had been inferred from the UV PE and ETS results above. In addition, it was concluded that π-bound arsenic and antimony atoms of (**1**) and (**2**) are more negative than π carbon.

5.13.3.3 Dipole Moments

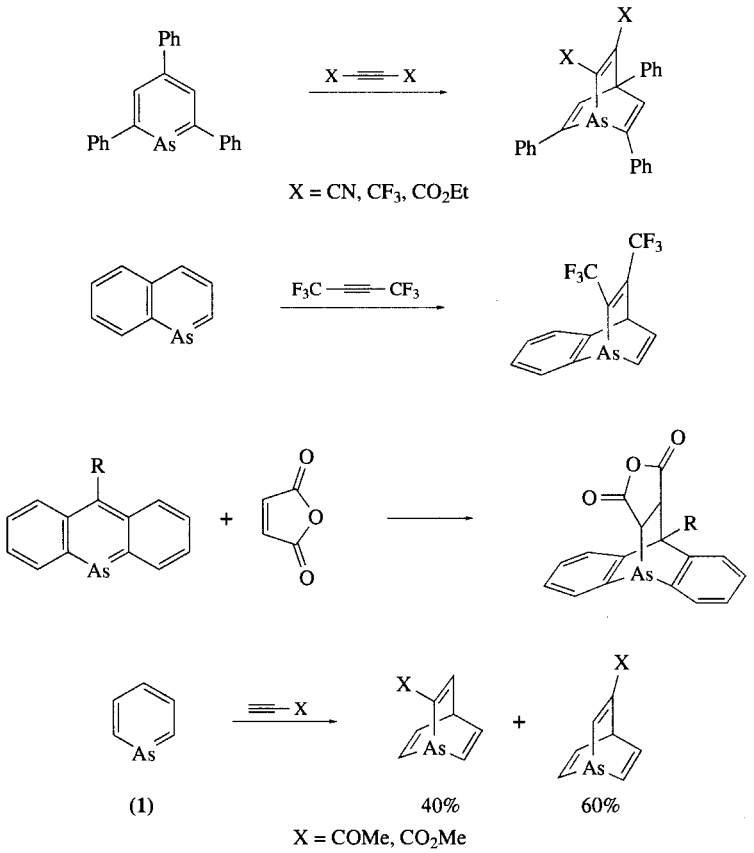
The gas phase dipole moment of arsenin was found to be 1.10 D from analysis of the microwave spectrum ⟨75JSP(57)428⟩. In cyclohexane solution it was measured as 1.02D ⟨75TL2749⟩. The dipole moment of 4-methylarsenin is 1.50 D. Since the 4-methyl group is more electron donating than the 4 proton, it reinforces the ring dipole. Thus the negative end of the dipole is at the arsenic atom, as had been predicted by theory.

There is no dipole moment data for antimonin and bismin.

5.13.4 REACTIVITY OF ARSENIN, ANTIMONIN, AND BISMIN

5.13.4.1 Cycloaddition Reactions

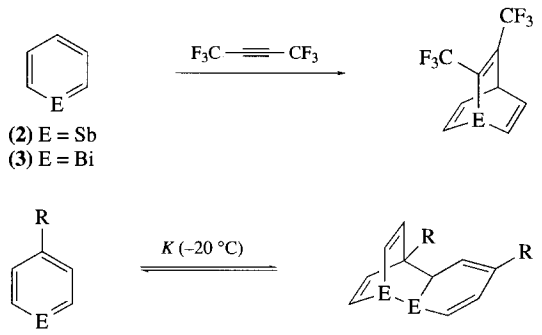
Arsenins react readily with dienophiles in the Diels–Alder reaction ⟨72JA7596, 72TL3961⟩ (Scheme 1). In all cases the products result from 1,4-addition at the arsenic atoms. Condensed ring systems containing an arsenin ring react in the same manner ⟨69AG(E)991, 75TL199, 79CC880⟩. In the case of unsymmetrical dienophiles there is little regioselectivity ⟨77TL1283⟩.



Scheme 1

Antimonin and bismin react faster but in the same manner as arsenin ⟨72JA7596⟩. Arsenin reacts with hexafluorobutyne at 25°C, while antimonin reacts at 0°C, and bismin at below −10°C. Antimonin and bismin are in equilibrium with their head-to-head Diels–Alder dimers at low

temperature ⟨76TL415, 82JA5693⟩. The equilibrium constants for the conversion of antimonin and bismin to their dimers at −20 °C are 19×10^5 and 2.9×10^5 l mol^{-1}, respectively. Dimer formation could not be detected for arsenin. Thus, formation of dimers is thermodynamically more favorable for the heavier heterobenzenes. Alkyl substitution at C-4 inhibits dimerization. Thus, dimer formation could not be observed for 4-methylantimonin. While 4-methylbismin does form a dimer, dimer formation could not be detected for 4-*t*-butylbismin (Scheme 2).



(2) E = Sb
(3) E = Bi

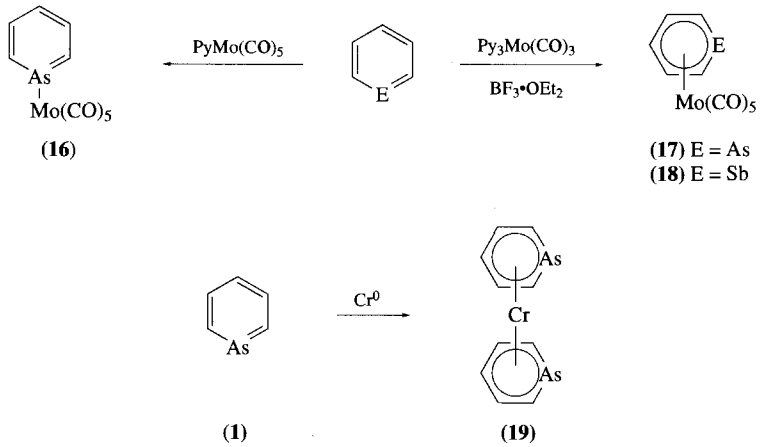
E = As, R = H, K = very small
E = Sb, R = H, K = 19 l mol^{-1}
E = Sb, R = Me, K = very small
E = Bi, R = H, $K = 2.9 \times 10^5$ l mol^{-1}
E = Bi, R = Me, $K = 2.5 \times 10^3$ l mol^{-1}
E = Bi, R = Bu^t, K = very small

Scheme 2

5.13.4.2 Reaction with Electrophilic Reagents

5.13.4.2.1 Transition metals

The sole example of the arsenic atom of arsenin acting as a nucleophile involves its reaction with pyridinemolybdenum pentacarbonyl to form arseninmolybdenum pentacarbonyl (**16**) ⟨77JA8099⟩ (Scheme 3). However, the complex (**16**) is fairly labile since heating causes loss of CO and formation of (η^6-arsenin) molybdenum tricarbonyl (**17**). This π complex is more easily formed by the direct reaction of tris(pyridine)molybdenum tricarbonyl with arsenin and $BF_3 \cdot OEt_2$. A similar π complex (**18**) is formed by antimonin, but the corresponding σ complex could not be obtained. The reaction of arsenin with chromium-metal vapor gave the bis sandwich complex (**19**). Interestingly, (**19**) is more difficult to oxidize than bis(benzene)chromium ⟨86AG(E)571⟩.



(16)

(17) E = As
(18) E = Sb

(1)

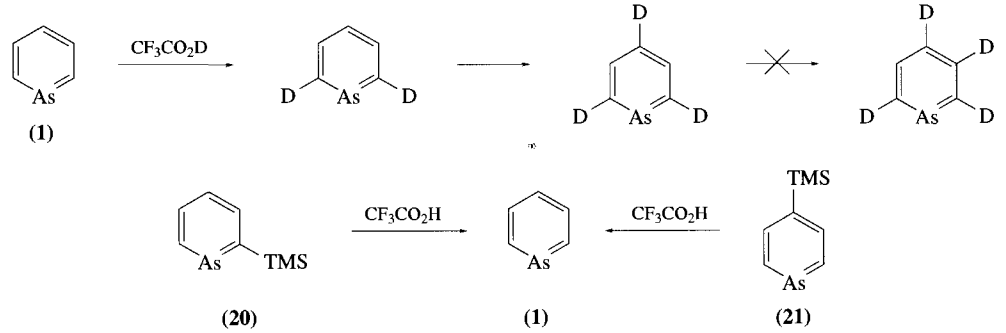
(19)

Scheme 3

5.13.4.2.2 Protonic acids

There is no evidence that the heteroatoms of arsenin, antimonin, or bismin have any basic properties. The gas phase proton affinity of arsenin has been determined by ion cyclotron resonance techniques to be 189.3 ± 0.1 kcal mol^{-1} (792.6 kJ mol^{-1}) ⟨85OM457⟩. However, deuterium labeling experiments demonstrate that protonation occurs at carbon rather than at arsenic. Since trimethylarsine has a proton affinity of 212.0 kcal mol^{-1} (887.6 kJ mol^{-1}), the protonation at the arsenic atom of arsenin is at least 23 kcal mol^{-1} (96 kJ mol^{-1}) less favorable than that of acyclic tertiary arsines. Results from x-ray photoelectron spectroscopy suggest that As protonated arsenin cannot undergo a necessary geometric relaxation, hence its low basicity ⟨79JA1764⟩.

In solution arsenin shows proton–deuterium exchange in trifluoroacetic acid-d_1 ⟨81JOC881⟩. Faster exchange occurs at C-2 and C-6, with slower exchange at C-4. No exchange occurs at C-3 and C-5 (Scheme 4). The rate of exchange is approximately 10^3 that of benzene. 2-Trimethylsilylarsenin (**20**) and 4-trimethylsilylarsenin (**21**) undergo protodesilylation with trifluoroacetic acid. Both compounds undergo protodesilylation approximately twice as fast as trimethylsilylbenzene. Antimonin and bismin yield intractable products when treated with acid.



Scheme 4

5.13.4.2.3 Other electrophiles

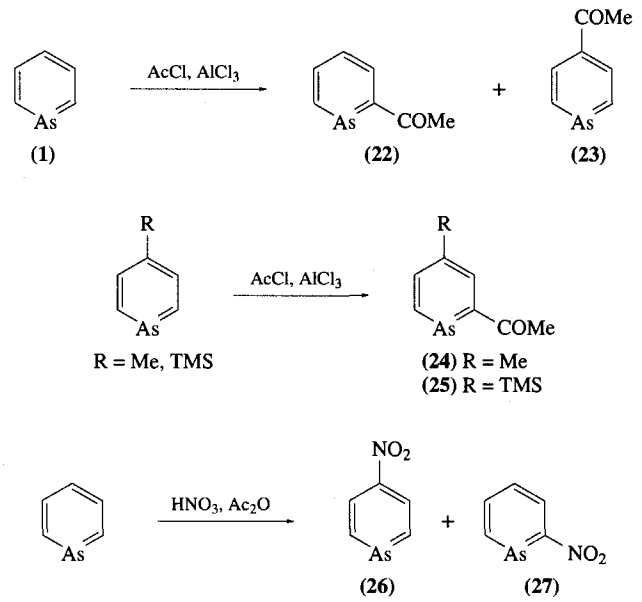
The Friedel–Crafts acylation of arsenin using acetyl chloride/$AlCl_3$ in methylene chloride affords a mixture of 2- and 4-acetylarsenins (**22**) and (**23**) ⟨81JOC881⟩ (Scheme 5). Competition experiments indicate that arsenin is acetylated twice as fast as mesitylene (approximately 10^3 faster than benzene). Acetylations of 4-methylarsenin and 4-trimethylsilylarsenin gave the corresponding 2-acetyl products (**24**) and (**25**). While the usual conditions for sulfonation and halogenation lead to intractable products when applied to arsenin, it may be nitrated with nitric acid in acetic anhydride at 0 °C. The products are 4-nitroarsenin (**26**) and 2-nitroarsenin (**27**).

5.13.4.3 Reaction with Organolithium Reagents

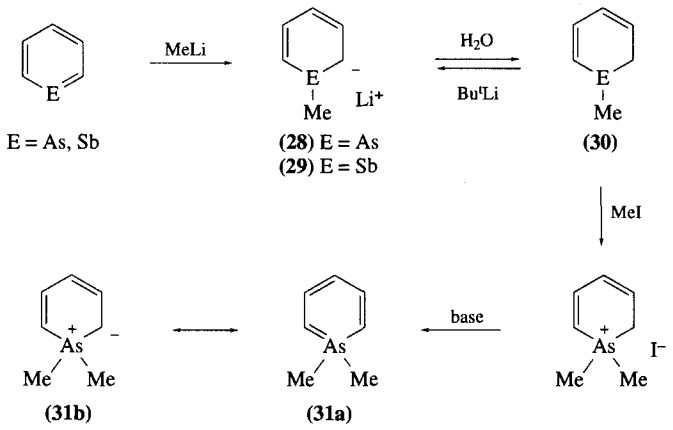
Arsenin and antimonin are attacked by organolithium reagents at the heteroatom, affording the corresponding lithium 1-alkyl-heterocyclohexadienides (**28**) and (**29**) ⟨77TL407⟩. Quenching (**28**) with water gives 1-methyl-1,2-dihydroarsenin (**30**), which can be reconverted into (**28**) by treatment with *t*-butyllithium (Scheme 6). Similar anions have been prepared from 9-phenyl-9,10-dihydroarsacridine ⟨87JOC5461⟩. Quaternization of (**30**) followed by treatment with base affords 1,1-dimethyl-λ^5-arsenin (**31a**) ⟨76JA7861⟩. The spectroscopic and chemical properties of (**31**) indicate that it has ylidic properties. Thus, resonance structure (**31b**) is dominant.

5.13.5 REACTIVITY OF SUBSTITUENTS

Although only a few alkyl-substituted antimonins and bismins are known, a variety of functionally substituted arsenins have been reported. The carbonyl chemistry is best developed. The three



Scheme 5

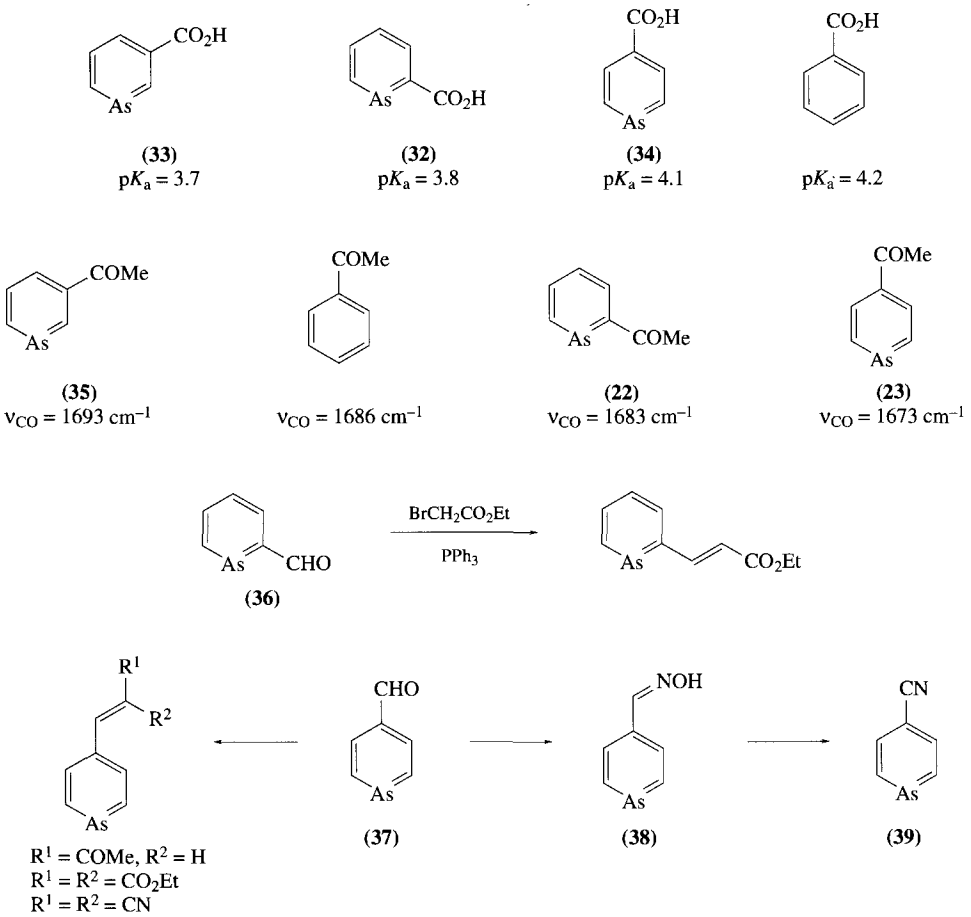


Scheme 6

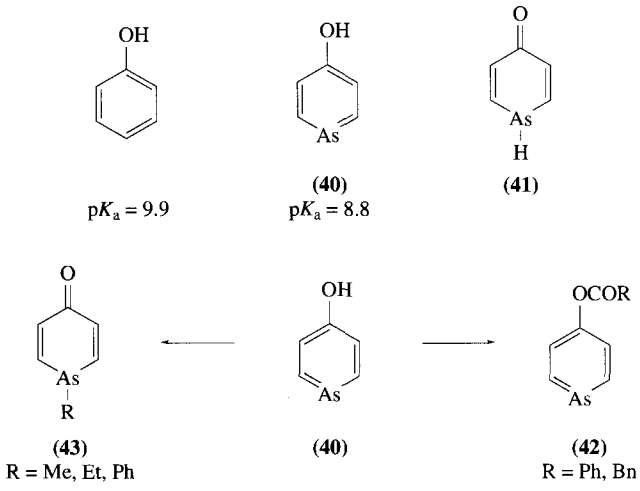
possible arsenin carboxylic acids (**32**), (**33**), and (**34**) have been prepared ⟨76TL665⟩, ⟨80JOC2016⟩. The order of acidity is (**33**) > (**32**) > (**34**) > benzoic acid. This suggests that the 3 position of arsenin is the most electropositive, as had been predicted by MO treatments. The three acetylarsenins (**22**), (**23**), and (**35**) are also available. The IR carbonyl stretching frequencies of (**22**) and (**23**) are lower than that of acetophenone, while (**35**) has a higher carbonyl stretching frequency. This data is also consistent with the 3 position being the most positive.

Arsenin-2-carbaldehyde (**36**) and arsenin-4-carbaldehyde (**37**) resemble benzaldehyde in their reactivity (Scheme 7). Compound (**36**) undergoes the Wittig reaction ⟨79JOC1409⟩, while its isomer (**37**) takes part in the aldol and Knoevenagel condensations ⟨74AG(E)668, 79TL3141⟩. The aldehyde (**37**) has been converted into an oxime (**38**), which was dehydrated to the nitrile (**39**).

4-Hydroxyarsenin (**40**) has distinct phenolic properties ⟨76TL4143, 76AG(E)690, 79TL1369⟩ and is more acidic than phenol (Scheme 8). Unlike 4-hydroxypyridine, which exists predominately as the pyridone tautomer, the arseninone tautomer (**41**) could not be detected. Acylation of (**40**) under basic conditions afforded products of *O*-acylation (**42**). However, alkylation usually gives *As*-alkylation products (**43**).



Scheme 7



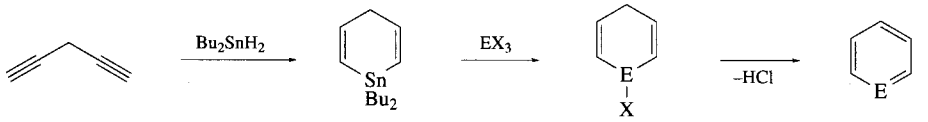
Scheme 8

5.13.6 SYNTHESES OF ARSENINS, ANTIMONINS, AND BISMINS

5.13.6.1 Arsenin, Antimonin, and Bismin

The parent arsenin, antimonin, and bismin are prepared by the route illustrated in Scheme 9. The thermal hydrostannation of 1,4-pentadiyne (**44**) gives 1,1-dibutyl-1,4-dihydrostannin (**45**)

⟨71JA1804⟩. The reaction of (**45**) with $AsCl_3$ gives arsenin in a single step, since gentle warming is sufficient to cause elimination of HCl from (**46a**) ⟨71JA3293⟩. Arsenin is an air-sensitive, but otherwise easy to handle, distillable liquid. Reaction of (**45**) with $SbCl_3$ affords (**46b**), which loses HCl on treatment with base (DBU) to give antimonin ⟨71JA6690⟩. Although antimonin can be isolated, the neat liquid polymerizes rapidly. It is best handled in dilute solution. The reaction of $BiCl_3$ with (**45**) gives (**46c**), which on treatment with base at −70°C gives bismin ⟨72JA7596, 76TL415⟩. Bismin is extremely labile, forming a dimer at low temperature and intractable products on warming above −20°C.

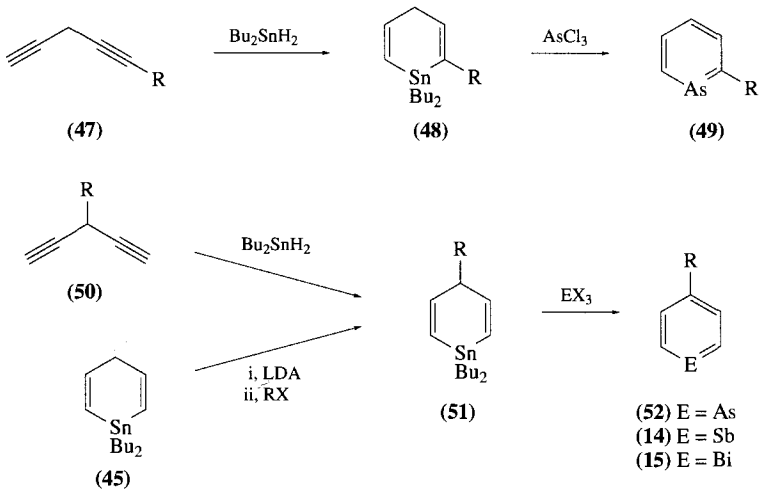


(**44**) (**45**) (**46a**) E = As (**46b**) E = Sb (**46c**) E = Bi (**1**) E = As (**2**) E = Sb (**3**) E = Bi

Scheme 9

5.13.6.2 Alkyl-substituted Arsenins, Antimonins, and Bismins

In general, 1,4-diynes (**47**) react with dibutyltin dihydride to give dihydrostannins (**48**) (Scheme 10), which have been converted into a variety of 2-alkylarsenins (**49**) ⟨75TL1083, 79JOC1409⟩. Similar hydrostannation of 3-alkyl-1,4-pentadiynes (**50**) gives 4-substituted dihydrostannins (**51**) ⟨75TL2749⟩. Alternatively, alkylation of (**45**) by the sequential treatment with LDA and alkyl halides also affords (**51**) ⟨78JOM(148)247, 83JOC767⟩, which have been converted into 4-substituted arsenins (**52**), antimonins (**14**), and bismins (**15**) ⟨82JA5693⟩. This latter modification is particularly useful since 4-alkylantimonins and -bismins are markedly more stable than the parent compounds.



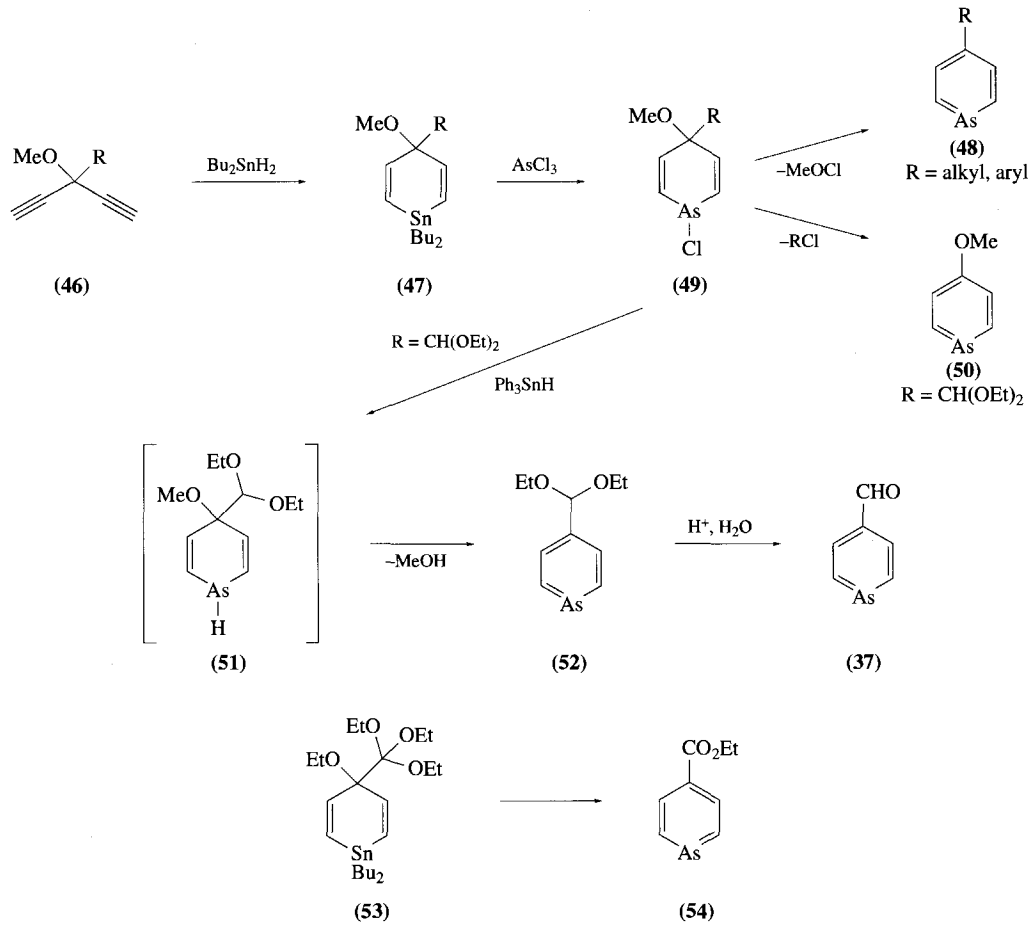
(**47**) (**48**) (**49**) (**50**) (**45**) (**51**) (**52**) E = As (**14**) E = Sb (**15**) E = Bi

Scheme 10

5.13.6.3 Substituted Arsenins

Several modified routes based loosely on Scheme 9 have been used to prepare arsenins bearing functional groups. 3-Substituted 3-methoxy-1,4-pentadiynes (**46**) react with Bu_2SnH_2 to give dihydrostannins (**47** (Scheme 11), which can be converted into the corresponding 4-substituted arsenins (**48**) by treatment with $AsCl_3$ ⟨73AG(E)931⟩. The intermediate (**49**) loses the elements of CH_3OCl on heating. However, heating the diethoxymethyl derivative (**49**) produces 4-methoxyarsenin (**50**)

〈74AG(E)667〉. Reduction of (**49**) gives the secondary arsine (**51**), which loses CH_3OH to give 4-diethoxymethylarsenin (**52**). Hydrolysis of this acetal gives arsenin-4-carbaldehyde (**37**) 〈74AG(E)668〉. A similar reaction sequence starting with the triethoxymethyl derivatives (**53**) allows the preparation of ethyl ester (**54**) 〈75TL2411〉.



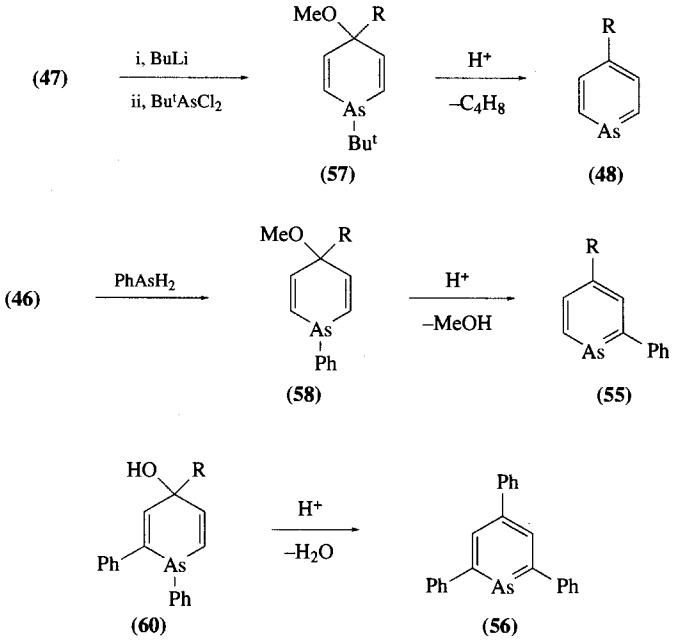
Scheme 11

The Märkl group has developed several related procedures which allow preparation of 4-, 2,4-, and 2,4,6-(alkyl, aryl)-substituted arsenins (**48**), (**55**), and (**56**). The approaches illustrated in Scheme 12 involve electrophilic rearrangements of 1,4-dihydroarsenins. When dihydroarsenins (**57**) are treated with acid, isobutylene and methanol are lost, affording 4-substituted arsenins (**48**) 〈81LA1610〉. However, acid treatment of the corresponding 1-phenyldihydroarsenins (**58**) results in 1,2-phenyl migration to produce the 2-phenyl-4-substituted arsenins (**59**) 〈77AG(E)637, 81LA1610〉. Similarly, the hydroxy compound (**60**) gives a trisubstituted arsenin (**56**) 〈83TL4079〉.

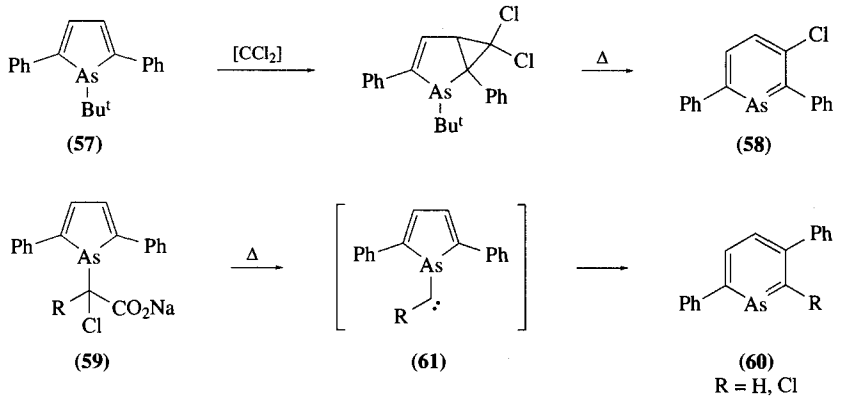
5.13.6.4 Syntheses of Arsenins from other Rings

5.13.6.4.1 From arsoles

The reaction of 1-*t*-butyl-2,5-diphenylarsole (**57**) with dichlorocarbene gives an adduct which on pyrolysis affords chloroarsenin (**58**) 〈74TL203〉 (Scheme 13). Similarly, the pyrolysis of the sodium salt (**59**) gives arsenin (**60**) 〈74TL203〉. This reaction probably involves the formation of the intermediate carbene (**61**) followed by ring expansion to give (**60**).



Scheme 12



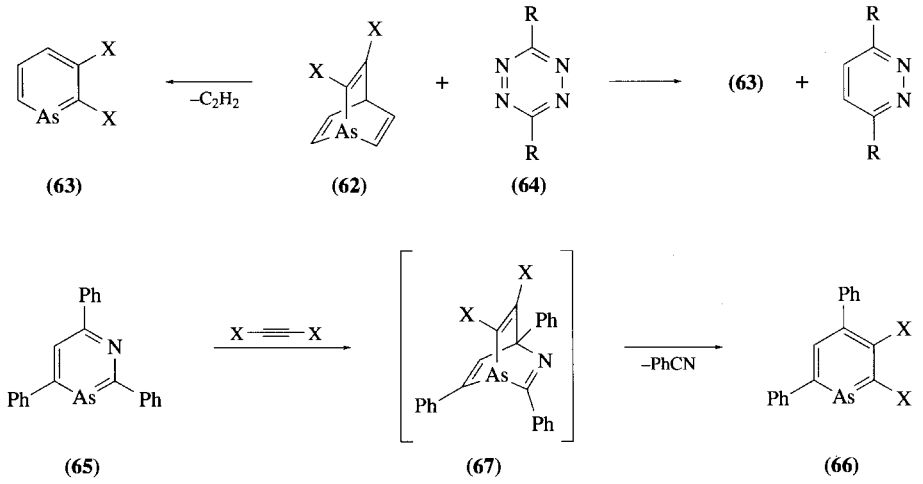
Scheme 13

5.13.6.4.2 From arsabarrelenes

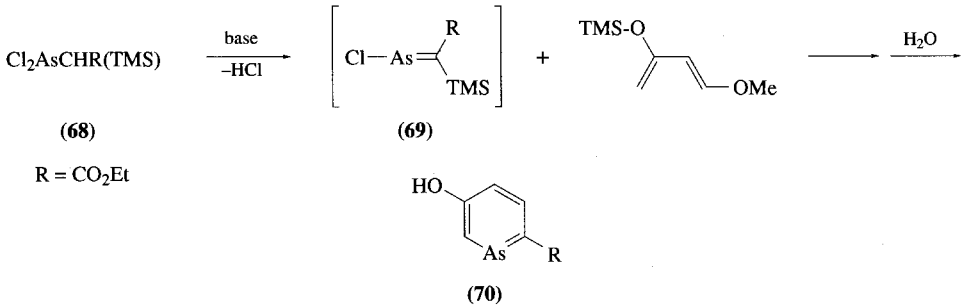
On pyrolysis, 1-arsabarrelenes (**62**) lose ethyne to form arsenins (**63**) ⟨77TL1283⟩ (Scheme 14). A milder, more convenient, method to effect the loss of ethyne involves treating (**62**) with 3,6-di(2′-pyridyl)-1,2,4,5-tetrazine (**64**) ⟨78TL2537, 79CC880, 81JOC881⟩. Since arsabarrelenes are available only from arsenins, the overall procedure amounts to a method of substitution of the arsenin ring. In a similar manner, 1,3-azarsenins (**65**) react with dienophiles to give arsenins (**66**) ⟨88TL539⟩. The intermediate (**67**) spontaneously loses benzonitrile.

5.13.6.5 From Acyclic Precursors

The reaction of the dichloroarsine (**68**) with base (DABCO) gives the labile arsalkene (**69**), which reacts *in situ* with the "Danishefsky diene" to produce arsenin (**70**) (Scheme 15). Overall, compound (**68**) is functioning as the equivalent of an arsaalkyne in this cycloaddition–elimination reaction ⟨89TL349⟩.



Scheme 14



Scheme 15

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References

EXPLANATION OF THE REFERENCE SYSTEM

Throughout this work, references are designated by a number–lettering coding of which the first two numbers denote tens and units of the year of publication, the next one to three letters denote the journal, and the final numbers denote the page. This code appears in the text each time a reference is quoted; the advantages of this system are outlined in the Introduction. The system has been used previously in the first edition of *Comprehensive Heterocyclic Chemistry*, eds A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984 and is based on that used in the following two monographs: (a) A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, New York, 1971; (b) J. Elguero, C. Marzin, A. R. Katritzky and P. Linda, "The Tautomerism of Heterocycles," in "Advances in Heterocyclic Chemistry," Supplement 1, Academic Press, New York, 1976.

The following additional notes apply:

1. A list of journal codes in alphabetical order, together with the journals to which they refer, is given immediately following these notes. Journal names are abbreviated throughout using the CASSI (Chemical Abstracts Service Source Index) system.
2. Each volume contains all the references cited *in that volume*; no separate lists are given for individual chapters.
3. The list of references is arranged in order of (a) year, (b) journal in alphabetical order of journal code, (c) part letter or number if relevant, (d) volume number if relevant, (e) page number.
4. In the reference list the code is followed by (a) the complete literature citation in the conventional manner and (b) the number(s) of the page(s) on which the reference appears, whether in the text or in tables, schemes, etc.
5. For nontwentieth-century references the year is given in full in the code.
6. For journals which are published in separate parts, the part letter or number is given (when necessary) in parentheses immediately after the journal code letters.
7. Journal volume numbers are *not* included in the code numbers unless more than one volume was published in the year in question, in which case the volume number is included in parentheses immediately after the journal code letters.
8. Patents are assigned appropriate three-letter codes.
9. Frequently cited books are assigned codes.
10. Less common journals and books are given the code "MI" for miscellaneous with the whole code for books prefixed by the letter "B-".
11. Where journals have changed names, the same code is used throughout, e.g. CB refers to both *Chem. Ber.* and to *Ber. Dtsch. Chem. Ges.*

Journal Codes

AAC	Antimicrob. Agents Chemother.
ABC	Agric. Biol. Chem.
AC	Appl. Catal.
AC(P)	Ann. Chim. (Paris)
AC(R)	Ann. Chim. (Rome)
ACH	Acta Chim. Acad. Sci. Hung.

ACR	Acc. Chem. Res.
ACS	Acta Chem. Scand.
ACS(A)	Acta Chem. Scand., Ser. A
ACS(B)	Acta Chem. Scand., Ser. B
AF	Arzneim.-Forsch.
AFC	Adv. Fluorine Chem.
AG	Angew. Chem.
AG(E)	Angew. Chem., Int. Ed. Engl.
AHC	Adv. Heterocycl. Chem.
AHCS	Adv. Heterocycl. Chem. Supplement
AI	Anal. Instrum.
AJC	Aust. J. Chem.
AK	Ark. Kemi
AKZ	Arm. Khim. Zh.
AM	Adv. Mater. (Weinheim, Ger.)
AMLS	Adv. Mol. Spectrosc.
AMS	Adv. Mass. Spectrom.
ANC	Anal. Chem.
ANL	Accad. Naz. Lincei
ANY	Ann. N. Y. Acad. Sci.
AOC	Adv. Organomet. Chem.
AP	Arch. Pharm. (Weinheim, Ger.)
APO	Adv. Phys. Org. Chem.
AQ	An. Quim.
AR	Annu. Rep. Prog. Chem.
AR(A)	Annu. Rep. Prog. Chem., Sect. A
AR(B)	Annu. Rep. Prog. Chem., Sect. B
ARP	Annu. Rev. Phys. Chem.
ASI	Acta Chim. Sin. Engl. Ed.
ASIN	Acta Chim. Sin.
AX	Acta Crystallogr.
AX(A)	Acta Crystallogr., Part A
AX(B)	Acta Crystallogr., Part B
B	Biochemistry
BAP	Bull. Acad. Pol. Sci., Ser. Sci. Chim.
BAU	Bull. Acad. Sci. USSR, Div. Chim. Sci.
BBA	Biochim. Biophys. Acta
BBR	Biochim. Biophys. Res. Commun.
BCJ	Bull. Chem. Soc. Jpn.
BEP	Belg. Pat.
BJ	Biochem. J.
BJP	Br. J. Pharmacol.
BMC	Bioorg. Med. Chem. Lett.
BP	Biochem. Biopharmacol.
BPJ	Br. Polym. J.
BRP	Br. Pat.
BSB	Bull. Soc. Chim. Belg.
BSF	Bull. Soc. Chim. Fr.
BSF(2)	Bull. Soc. Chim. Fr., Part 2
C	Chimia
CA	Chem. Abstr.
CAN	Cancer
CAR	Carbohydr. Res.
CAT	Chim. Acta Turc.
CB	Chem. Ber.

CBR	Chem. Br.
CC	J. Chem. Soc., Chem. Commun.
CCA	Croat. Chem. Acta
CCC	Collect. Czech. Chem. Commun.
CCR	Coord. Chem. Rev.
CE	Chem. Express
CEN	Chem. Eng. News
CHE	Chem. Heterocycl. Compd. (Engl. Transl.)
CHEC-I	Comp. Heterocycl. Chem., 1st edn.
CI(L)	Chem. Ind. (London)
CI(M)	Chem. Ind. (Milan)
CJC	Can. J. Chem.
CJS	Can. J. Spectrosc.
CL	Chem. Lett.
CLY	Chem. Listy
CM	Chem. Mater.
CMC	Comp. Med. Chem.
COC	Comp. Org. Chem.
COMC-I	Comp. Organomet. Chem., 1st edn.
COS	Comp. Org. Synth.
CP	Can. Pat.
CPB	Chem. Pharm. Bull.
CPH	Chem. Phys.
CPL	Chem. Phys. Lett.
CR	C. R. Hebd. Seances Acad. Sci.
CR(A)	C. R. Hebd. Seances Acad. Sci., Ser. A
CR(B)	C. R. Hebd. Seances Acad. Sci., Ser. B
CR(C)	C. R. Hebd. Seances Acad. Sci., Ser. C
CRAC	Crit. Rev. Anal. Chem.
CRV	Chem. Rev.
CS	Chem. Scr.
CSC	Cryst. Struct. Commun.
CSR	Chem. Soc. Rev.
CT	Chem. Tech.
CZ	Chem.-Ztg.
CZP	Czech. Pat.
DIS	Diss. Abstr.
DIS(B)	Diss. Abstr. Int. B.
DOK	Dokl. Akad. Nauk SSSR
DP	Dyes Pigm.
E	Experientia
EC	Educ. Chem.
EF	Energy Fuels
EGP	Ger. (East) Pat.
EJM	Eur. J. Med. Chem.
EUP	Eur. Pat.
FCF	Forstchr. Chem. Forsch.
FCR	Fluorine Chem. Rev.
FES	Farmaco Ed. Sci.
FOR	Fortschr. Chem. Org. Naturst.
FRP	Fr. Pat.
G	Gazz. Chim. Ital.
GAK	Gummi Asbest Kunstst.
GEP	Ger. Pat.
GEP(O)	Ger. Pat. Offen.

GSM	Gen. Synth. Methods
H	Heterocycles
HAC	Heteroatom Chem.
HC	Chem. Heterocycl. Compd.
HCA	Helv. Chim. Acta
HOU	Methoden Org. Chem. (Houben-Weyl)
HP	Hydrocarbon Process
IC	Inorg. Chem.
ICA	Inorg. Chim. Acta
IEC	Ind. Eng. Chem. Res.
IJ	Isr. J. Chem.
IJC	Indian J. Chem.
IJC(A)	Indian J. Chem., Sect. A
IJC(B)	Indian J. Chem., Sect. B
IJM	Int. J. Mass Spectrom. Ion Phys.
IJQ	Int. J. Quantum Chem.
IJS	Int. J. Sulfur Chem.
IJS(A)	Int. J. Sulfur Chem., Part A
IJS(B)	Int. J. Sulfur Chem., Part B
IS	Inorg. Synth.
IZV	Izv. Akad. Nauk SSSR, Ser. Khim.
JA	J. Am. Chem. Soc.
JAN	J. Antibiot.
JAP	Jpn. Pat.
JAP(K)	Jpn. Kokai
JBC	J. Biol. Chem.
JC	J. Chromatogr.
JCC	J. Coord. Chem.
JCE	J. Chem. Ed.
JCED	J. Chem. Eng. Data
JCI	J. Chem. Inf. Comput. Sci.
JCP	J. Chem. Phys.
JCPB	J. Chim. Phys. Physico-Chim. Biol.
JCR(M)	J. Chem. Res. (M)
JCR(S)	J. Chem. Res. (S)
JCS	J. Chem. Soc.
JCS(A)	J. Chem. Soc. (A)
JCS(B)	J. Chem. Soc. (B)
JCS(C)	J. Chem. Soc. (C)
JCS(D)	J. Chem. Soc., Dalton Trans.
JCS(F1)	J. Chem. Soc., Faraday Trans. 1
JCS(F2)	J. Chem. Soc., Faraday Trans. 2
JCS(P1)	J. Chem. Soc., Perkin Trans. 1
JCS(P2)	J. Chem. Soc., Perkin Trans. 2
JCS(S2)	J. Chem. Soc. (Suppl. 2)
JEC	J. Electroanal. Chem. Interfacial Electrochem.
JEM	J. Energ. Mater.
JES	J. Electron. Spectrosc.
JFA	J. Sci. Food. Agri.
JFC	J. Fluorine Chem.
JGU	J. Gen. Chem. USSR (Engl. Transl.)
JHC	J. Heterocycl. Chem.
JIC	J. Indian Chem. Soc.
JINC	J. Inorg. Nucl. Chem.
JLC	J. Liq. Chromatogr.

JMAS	J. Mat. Sci.
JMC	J. Med. Chem.
JMOC	J. Mol. Catal.
JMR	J. Magn. Reson.
JMS	J. Mol. Sci.
JOC	J. Org. Chem.
JOM	J. Organomet. Chem.
JOU	J. Org. Chem. USSR (Engl. Transl.)
JPC	J. Phys. Chem.
JPJ	J. Pharm. Soc. Jpn.
JPO	J. Phys. Org. Chem.
JPP	J. Pharm. Pharmacol.
JPR	J. Prakt. Chem.
JPS	J. Pharm. Sci.
JPS(A)	J. Polym. Sci., Polym. Chem., Part A
JPU	J. Phys. Chem. USSR (Engl. Transl.)
JSC	J. Serbochem. Soc.
JSP	J. Mol. Spectrosc.
JST	J. Mol. Struct.
K	Kristallografiya
KFZ	Khim. Farm. Zh.
KGS	Khim. Geterotsikl. Soedin.
KO	Kirk-Othmer Encyc.
KPS	Khim. Prir. Soedin.
L	Langmuir
LA	Liebigs Ann. Chem.
LC	Liq. Cryst.
LS	Life Sci.
M	Monatsh. Chem.
MAC	Macromol. Chem.
MC	Mendeleev Chem. J. (Engl. Transl.)
MCLC	Mol. Cryst. Liq. Cryst.
MI	Miscellaneous [book/journal]
MIP	Miscellaneous Pat.
MM	Macromolecules
MP	Mol. Phys.
MRC	Magn. Reson. Chem.
N	Naturwissenschaften
NAT	Nature
NEP	Neth. Pat.
NJC	Nouv. J. Chim.
NKK	Nippon Kagaku Kaishi (J. Chem. Soc. Jpn.)
NKZ	Nippon Kagaku Zasshi
NZJ	N. Z. J. Sci. Technol.
OCS	Organomet. Synth.
OM	Organometallics
OMR	Org. Magn. Reson.
OMS	Org. Mass Spectrom.
OPP	Org. Prep. Proced. Int.
OR	Org. React.
OS	Org. Synth.
OSC	Org. Synth., Coll. Vol.
P	Phytochemistry
PA	Polym. Age
PAC	Pure Appl. Chem.

PAS	Pol. Acad. Sci.
PB	Polym. Bull.
PC	Personal Communication
PCS	Proc. Chem. Soc.
PHA	Pharmazi
PHC	Prog. Heterocycl. Chem.
PIA	Proc. Indian Acad. Sci.
PIA(A)	Proc. Indian Acad. Sci., Sect. A
PJC	Pol. J. Chem.
PJS	Pak. J. Sci. Ind. Res.
PMH	Phys. Methods Heterocycl. Chem.
PNA	Proc. Natl. Acad. Sci. USA
POL	Polyhedron
PP	Polym. Prepr.
PRS	Proceed. Roy. Soc.
PS	Phosphorus Sulfur
QR	Q. Rev., Chem. Soc.
QRS	Quart. Rep. Sulfur. Chem.
QSAR	Quant. Struct. Act. Relat. Pharmacol. Chem. Biol.
RC	Rubber Chem. Technol.
RCM	Rapid Commun. Mass Spectrom.
RCP	Rec. Chem. Prog.
RCR	Russ. Chem. Rev. (Engl. Transl.)
RHA	Rev. Heteroatom Chem.
RJ	Rubber J.
RP	Rev. Polarogr.
RRC	Rev. Roum. Chim.
RS	Ric. Sci.
RTC	Recl. Trav. Chim. Pays-Bas
RZC	Rocz. Chem.
S	Synthesis
SA	Spectrochim. Acta
SA(A)	Spectrochim. Acta, Part A
SAP	S. Afr. Pat.
SC	Synth. Commun.
SCI	Science
SL	Synlett
SM	Synth. Met.
SR	Sulfur Reports
SRI	Synth. React. Inorg. Metal-Org. Chem.
SS	Sch. Sci. Rev.
SST	Org. Compd. Sulphur, Selenium, Tellurium [R. Soc. Chem. series]
SUL	Sulfur Letters
SZP	Swiss Pat.
T	Tetrahedron
T(S)	Tetrahedron, Suppl.
TA	Tetrahedron Asymmetry
TAL	Talanta
TCA	Theor. Chim. Acta
TCC	Top. Curr. Chem.
TCM	Tetrahedron, Comp. Method.
TFS	Trans. Faraday Soc.
TH	Thesis
TL	Tetrahedron Lett.
TS	Top. Stereochem.

UK	Usp. Khim.
UKZ	Ukr. Khim. Zh. (Russ. Ed.)
UP	Unpublished Results
URP	USSR Pat.
USP	US Pat.
WCH	Wiadom. Chem.
YGK	Yuki Gosei Kagaku Kyokaishi
YZ	Yakugaku Zasshi (J. Pharm. Soc. Jpn.)
ZAAC	Z. Anorg. Allg. Chem.
ZAK	Zh. Anal. Khim.
ZC	Z. Chem.
ZN	Z. Naturforsch.
ZN(A)	Z. Naturforsch., Teil A
ZN(B)	Z. Naturforsch., Teil B
ZOB	Zh. Obshch. Khim.
ZOR	Zh. Org. Khim.
ZPC	Hoppe–Seyler's Z. Physiol. Chem.
ZPK	Zh. Prikl. Khim.

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