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FURTHER ADVANCES IN THE CHEMISTRY OF MANNICH BASES

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CONTENTS

1. INTRODUCTION

Since the early studies of Mannich, Mannich bases have become important tools for the synthesis of new compounds. Mannich bases can be either directly employed or used as intermediates.

The most important application of these compounds is in pharmaceutical chemistry and at least 35% of the papers concerning Mannich bases are published in pharmaceutical journals. Research on antineoplastic drugs, analgesics, antibiotics etc. (see, e.g., refs. 1–9) including labelled molecules,[10–13] has received particular attention. In recent years a comparable importance has been

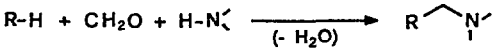
developed by the technological applications of Mannich bases in polymer chemistry[14] with respect to paints and surface active agents.

Reviews have also been devoted to the study of Mannich bases including the chemistry of phosphine[15] or benzotriazole[16] derivatives, the use of amino acids in the aminomethylation reaction[17] and the use of nitroalkanes in the synthesis of heterocyclic Mannich bases.[18] The stereoselective synthesis of diastereomeric amino-alcohols[19] as well as the cyclization to poly-pyridine derivatives by means of β-aminoketones[20] has been reviewed.

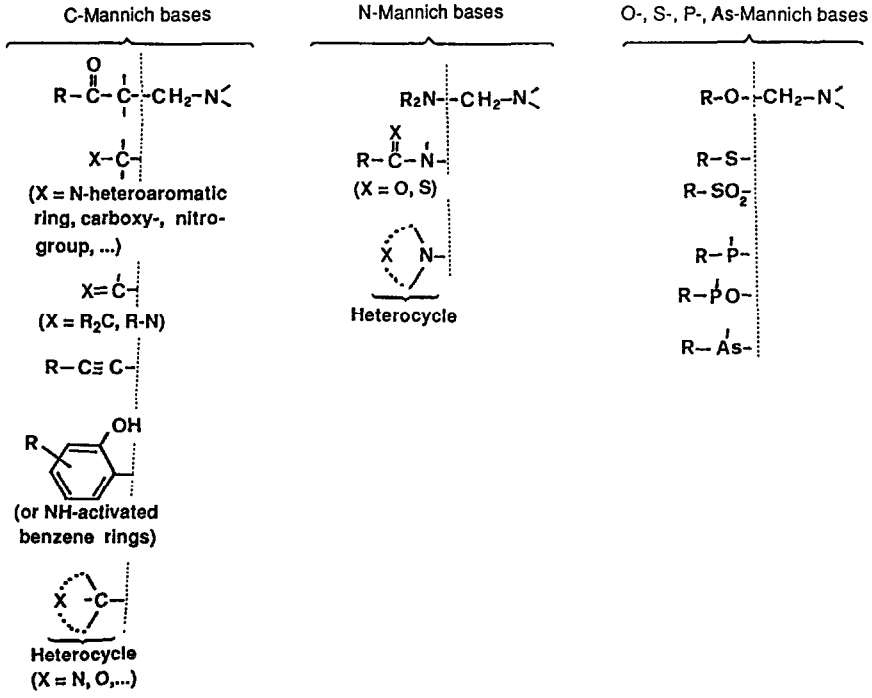
The number of papers on this topic has quadrupled since the last exhaustive review.[21] We shall therefore limit ourselves to those aspects of the chemistry of Mannich bases which represent novel advances or are relevant to synthesis. Present knowledge of chemo- and regioselectivity of the aminomethylation reaction, together with some selected syntheses of cyclic Mannich bases, will be treated. The properties of Mannich bases which are particularly relevant to the synthesis of interesting derivatives will be highlighted.

2. SYNTHESIS OF MANNICH BASES

The Mannich reaction is the condensation of a compound having active hydrogen atoms (the substrate) with formaldehyde and an amine:



The structures of the products depend on the nature of the substrate as the amine moieties of Mannich bases are frequently derived from quite common primary or secondary alkyl- and arylamines. A general classification of the substrates employed in Mannich reactions is reported in Scheme 1.[21]



Scheme 1. General classification of Mannich bases as based on substrate structure.

2.1. *Reagents*

2.1.1. *The substrate.* The substrates listed in Scheme 1 have been widely studied as reactants in Mannich synthesis; Table 1 summarizes a list of the substrates which are of interest for their novel structure, for the presence of unusual heteroatoms, or for belonging to scarcely investigated classes of compounds.

Among the CH-substrates of Table 1, there is renewed interest in alkyl derivatives activated by

Table 1 - Selected types of substrates submitted to aminomethylation (arrow indicates position of attack).

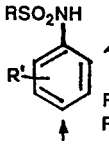
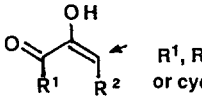
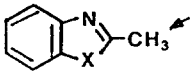
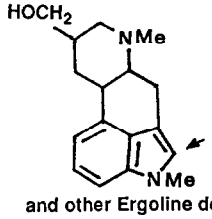
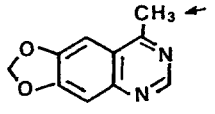
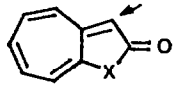
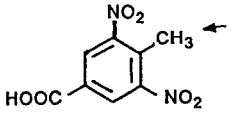
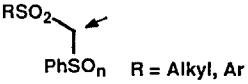
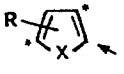
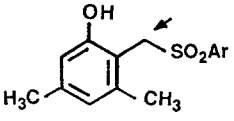
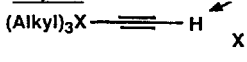
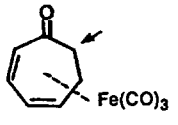
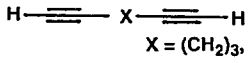
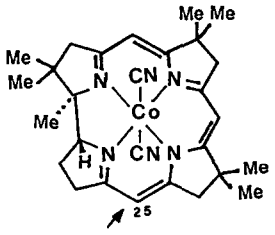
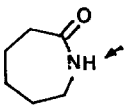
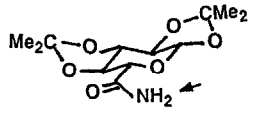
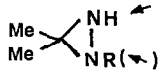
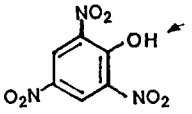
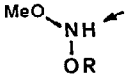
Substrates	References	Substrates	References
CH-SUBSTRATES		- NH-Activated Benzene Rings	
- Alkyl Ketones		 R = Me, Ar; R' = various substituents	40, 41
 R^1, R^2 = Alkyls, or cyclic	22, 23		
Ketosteroids	24-26		
- Other Activated Alkyl Substrates		- N-, O-, S-Heterocycles	
 X = S, CMe_2	27	 and other Ergoline derivatives	42
	28	 X = NH, O	43, 44
	29	Nucleoside and Nucleotide derivatives	45, 46
 R = Alkyl, Ar n = 1-2	30, 31	 X = O, S	47, 48
	32	Other furan and thiophene derivatives	49-52
- Alkenes	see Sect. 1.5.1		
- Alkynes		- Transition Metal Derivatives	
 X = Si, Ge	33, 34		53
 X = $(CH_2)_3$, $SiMe_2$, ...	33, 35-39		

Table 1-continued

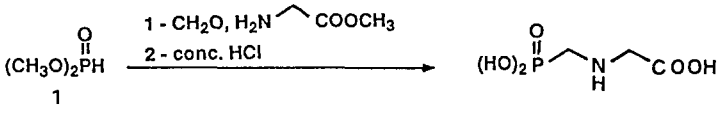
Substrates	References	Substrates	References
	54		58
			59
NH-SUBSTRATES			
Adenosine, Cytosine, Guanine	55	OH-, AsH-SUBSTRATES	
 R = H, Me	56		60
 R = Me, CH_2Ph	57	$(Alkyl)_2AsH$, Ph_2AsH	61

heteroaromatic nuclei (see also ref. 62) and benzene substrates activated by $-NHSO_2R$ groups. Several derivatives of transition metals are worth mentioning.

A novel aminomethylation reaction of arsines used as XH-substrates has been reported. Interesting studies on the N-aminomethylation of purine and pyrimidine bases (adenosine, guanine, cytosine) as well as on the N- and O-aminomethylation of caprolactam and picric acid have been made.

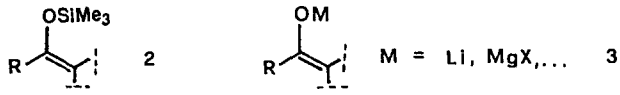
Bifunctional amines yield polymeric macromolecules.[14] Recently, such a reaction has been examined for alkylketones,[63] phenols,[64] nitroalkanes[65] and heterocycles.[63] Several polymeric substances have been successfully used as substrates in Mannich reactions.[14]

When the substrate in a Mannich reaction has a structure significantly unfavourable to direct aminomethylation, it is common practice to use a more suitable substrate which allows the reaction to occur more smoothly. Examples of this are the Mannich bases of phosphoric acid[66–68] which are useful as herbicides[66] and corrosion inhibitors.[67] These are obtained by aminomethylation of the alkyl ester **1** followed by acid hydrolysis of the ester groups.

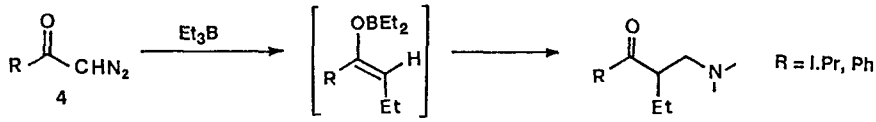


1

The substrate can be suitably activated so as to make the aminomethylation possible or to improve the yield. In many cases substrate activation affects the direction of attack by the aminomethylating agent, thus solving problems of chemo- or regioselectivity. The activation usually involves carbonyl substrates (esters and lactones included) which are modified as silyl enolethers **2**, with $(CH_3)_3SiCl$,[69–80] or as enolates **3**, by lithium alkyls, lithium amides or hydrides.[69,70,72,81,82]



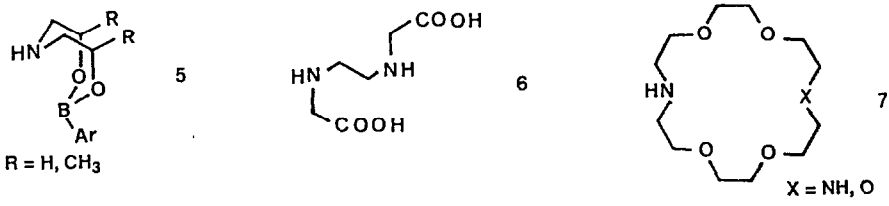
Enol-borates have been prepared from diazo-carbonyl compounds **4** or from α,β-unsaturated ketones.[83]



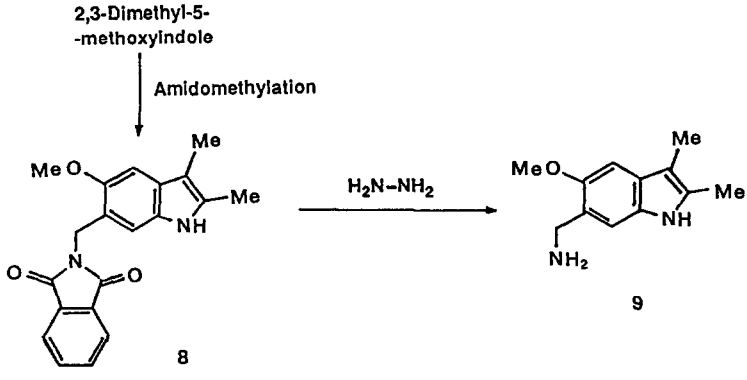
Substrates other than carbonyl derivatives, such as NH-heterocyclic compounds[84,85] or nitroalkanes,[84] have been activated as silyl derivatives.

2.1.2. *Amine, aldehyde and pre-formed aminomethylating reagents*

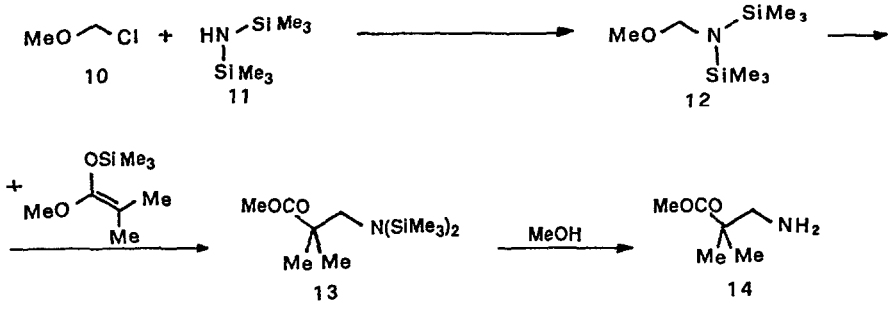
Amine. Besides the classical amines (dimethylamine, diethylamine, piperidine etc.), a remarkable number of other amines have been employed in the Mannich reaction to prepare products of pharmacological interest or for other purposes such as chelation. Thus, gentamicine[86] and bis-2-chloroethylamine,[2,87] or some amino derivatives of boron (**5**),[88,89] have been used in the preparation of antibiotics and antineoplastic drugs. Ribonucleosides[90] and enzymes[91] have been submitted to the Mannich reaction as amine components in researches of biological interest. Attractive chelating properties are shown by Mannich bases derived from amino acids **6**[92,93] or crown-ethers **7**.[57,94] Macromolecular amino derivatives provide further examples of unusual amine reagents usefully employed in Mannich synthesis.[14]



NH-amides, which are well known substrates in Mannich synthesis, can also behave as amine reactants. Phthalimide affords the amidomethylated product **8** by its reaction with 2,3-dimethyl-4-methoxyindole and formaldehyde. This permits the introduction of the $-CH_2NH_2$ group into the indole derivative by reductive hydrolysis with hydrazine (**9**).[95] In the phthalimidomethyl derivative **8** the position of amidomethylation may be noted. Further examples of similar syntheses are reported in ref. 96.

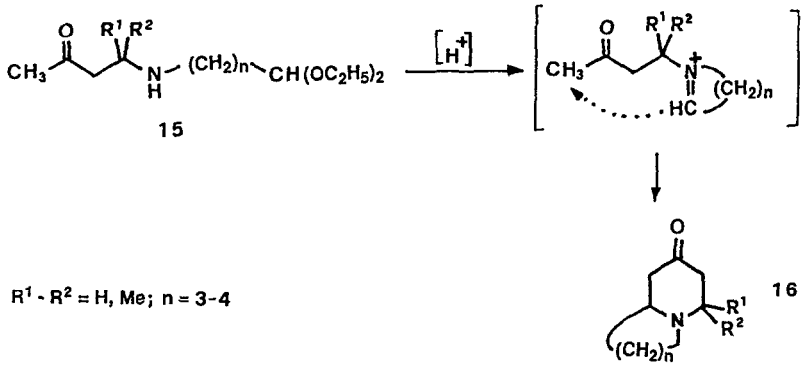


Disilylamine **11**,[97] by reaction with chloromethylether **10**, gives the aminomethylating reagent **12** which gives the Mannich base **13** which is easily transformed into the corresponding primary amine **14**.



Aldehyde. The usual aldehyde reagent, formaldehyde, has been successfully replaced in several cases by methylene dihalogenides CH_2XY ($X = /\neq Y = Cl, I$)[73,98,99] or by ether derivatives such as the chloromethylether **10**.[97] Frequently, aldehydes other than formaldehyde (mainly arylaldehydes) are used, so that aminoalkylation takes place. Glyoxylic acid and its derivatives are particularly interesting aldehyde reagents giving the synthesis of α-amino acids.[100,101] These compounds have also been obtained by aminoalkylation of hydrogen cyanide[102] or chloroform[103] with various aldehydes.

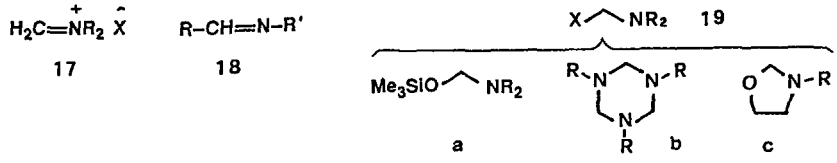
An example of intramolecular aminoalkylation is offered by the ketones **15** giving the cyclic derivatives **16**. The stereochemistry of the products **16** has been investigated.[104]



Analogous systems containing an amino group and two alkylcarbonyl moieties have been studied.[105] Related syntheses directed towards *Lycopodium* alkaloids have been performed.[106]

Pre-formed aminomethylating reagents. In many cases the aminomethylation reaction is carried out with pre-formed aminomethylating reagents. Various types of such reagents are known (**17** and **19**), together with few examples of azomethine derivatives **18**.

Methylene-imonium salts **17** are suitably synthesized from methylene-bis-amines,[107-110] formaldehyde N,O-acetals[111] or methylene halogenides.[54] The analogous $R'—CH=N^+R_2\ X^-$ salts have also been prepared.[101,112,113]



Oxidation of methylamine derivatives with triarylmethyl perchlorates[114] or electrochemical reactions on various alkylamines[77,115,116] have been used to produce methylene-imonium salts which can be also employed as aminomethylating agents with organometallic derivatives (Grignard reagents, organo-tin compounds[110,114,117–120]).

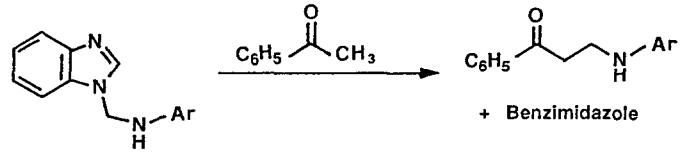
Reagents **17** have been used with alkylcarbonyl compounds, esters, lactones and other substrates activated as described before.[69–72,81,83,121–123] Good results have been obtained in the C-aminomethylation of non-activated aldehydes and ketones,[7,107–109,114,124–128] phenols[127,129–131] and heterocyclic substrates.[48,54,132,133] N-aminomethylation[134] and P- or As-aminomethylation[61] have been conveniently carried out by this method.

Methylene-imonium salts require anhydrous solvents and, in some cases, low reaction temperatures.[69,81] They have been prepared *in situ* with good results[73,135] either by using formaldehyde N,O-acetals in the presence of trimethylsilyl halide[74,78] or by treating **18** or **19b** with trimethylsilyl trifluoromethansulfonate.[79,80]

Solvent type[70,73,83,108,135] and reagent concentration[108] may be critical in the reactions with methylene-imonium salts. In addition, the type of anion can effect the chemo- or regioselectivity of the reaction and the stability of the product.[70,107–109]

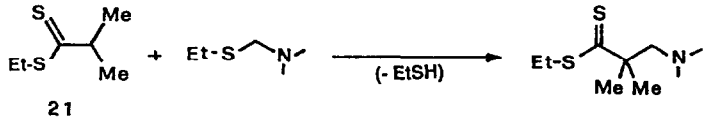
Azomethine reagents **18**, prepared by reaction of formaldehyde, or other aldehydes, with *tert*-alkylamines (*tert*-butylamine, 1-amino-adamantane), have proved to be useful aminomethylating agents of phenol or NH-amide substrates.[136,137]

Among the aminomethylating reagents **19**, which include the trimethylsilyl derivatives **19a** (actually O-Mannich bases of silanols[84,85]), the analogous trichlorotitanyl derivatives[82] and the disilylamino-derivatives **12**, the methylene-bis-amines and N,O-acetals are worth mentioning. Hexahydrotriazines **19b** are methylene-bis-amines which can be easily prepared both as alkyl-[138] or aryl derivatives.[139,140] With this reagent, ketones[140] as well as phenols[136,138] have been successfully aminomethylated, S-[138,139] and P-aminomethylations[66] have also been carried out. The cyclic N,O-acetal **19c** has been employed in order to obtain Mannich bases containing the ethanolamine group, including Mannich bases of ephedrine[141] and similar aminoalcohols.[142,143] Common Mannich bases of type **19** (X = N,S) can also be used as aminomethylating agents. The base of benzimidazole (**20**) is easily deaminomethylated, giving a reactive methylene-imonium salt which then reacts with acetophenone.[144] The compounds **20** are particularly useful when secondary Mannich bases are



20

desired as the final product. S-Mannich bases have been similarly used in the aminomethylation of several substrates. The Mannich base of the dithioic acid ester **21** has been synthesized by reaction with the aminomethyl derivative of ethyl mercaptan.[145]

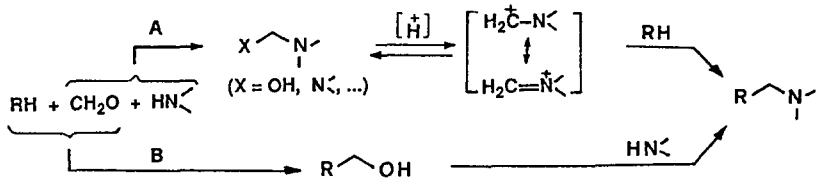


21

Analogous aminomethylations have been carried out on organometallics such as $C_4H_9(C_2H_5)C{=}CHCuMgX_2$, with the formation of allylamines.[146] Trans-amidomethylations by means of sulfonyl derivatives $ArSO_2{-}CH_2NHSO_2Ar'$ have also been performed.[147]

2.2. *Mechanism*

Mannich reaction can proceed through either of the two pathways depicted in Scheme 2 (see also ref. 21 and references therein) and is usually the result of a complex series of equilibria, related to the nature of the reactants and the reaction conditions, which determine the preferred reaction pathway.

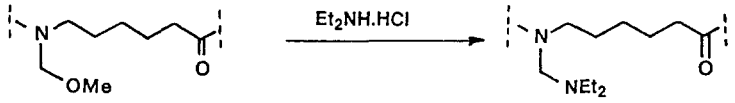


Scheme 2.

The main questions concerning the reaction mechanism are: (i), the relative importance of pathways A and B; (ii), the structure of the aminomethylating species in pathway A; (iii), the way of attack by this reagent on the substrate.

Pathway A is usually accepted as the preferred one. In the intramolecular aminomethylation of γ-carboxyglutamic acid with formaldehyde,[148] the study of the reaction has excluded an initial attack by formaldehyde on the substrate. In the C-aminomethylation of indole with glutamic derivatives, it has been confirmed that 3-hydroxymethylindole is unable to give a condensation reaction with the amine reactant.[149]

Several examples, however, have also been reported in which aminomethylated products are obtained from pre-formed methylol derivatives of the substrate. Thus, C-Mannich bases have been prepared from ferrocenyl derivatives[150] or nitroalkanes[65,151] and N-Mannich bases have been obtained from benzimidazoles[152] or benzotriazoles.[16] In one case, the polymeric substrate **22**, deriving from Nylon-6, reacts successfully with diethylamine[153] to give an N-Mannich base grafted to a polymeric backbone.

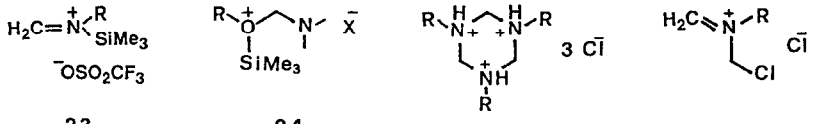


22 (NH substitution degree: 27%)

Some Mannich reactions on α-isonitroso ketones[154] as well as the aminoalkylation of benzotriazole with various aldehydes and arylamines[16] can be interpreted only on the basis of aldehyde attack on the substrate as the first step of the reaction. Nevertheless, pathway B is not usually relevant.

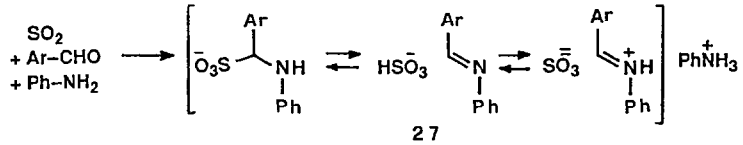
The nature of the aminomethylating species in pathway A has constituted the object of some important studies dealing with the reaction between formaldehyde and the amine in biological systems,[155] the aminomethylation of polyacrylamide[156] and the use of aldehydes other than formaldehyde.[100,157] All lead to the conclusion that aldehyde attack by the amine is the rate-determining step under acidic conditions. Under neutral or basic conditions the rate-determining step is hydroxyl elimination from the methylolamine HO—CH_2—NR_2 with the formation of the methylene-imonium cation.[155,157] The ratio amine/aldehyde also plays an important role in determining the nature of the aminomethylating agent.[100,158] Thus, ^{13}C-NMR measurements[156] have shown that methylolamine concentration is a maximum when this ratio is *ca.* 1. The formation of the methylene-bis-amine is favoured when the molar ratio increases. The Mannich reagent is therefore an equilibrium mixture of the species given in Scheme 2.

Other structures for the aminomethylating species have been proposed. In the reactions catalyzed by trimethylsilyl derivates Me_3SiX, employing hexahydrotriazines **19b** or N,O-acetals, the reactive agent would be the methylene-imonium salt **23**[79] or the oxonium cation **24**.[74] The intermediate trihydrochloride **25** could be formed by the action of anhydrous hydrochloric acid[138] on hexahydrotriazines **19b**. However, more recent studies[159] propose the formation, under the same conditions, of equimolecular amounts of methylene-imonium chloride (**17**) and the halogenated salt **26**.



23 **24** **25** **26**

An interesting reagent (**27**) which is an equilibrium mixture of ionic species, obtained from sulfur dioxide, aryl aldehyde and aniline, has been used in the aminomethylation of alkylketones and nitroalkanes.[160]



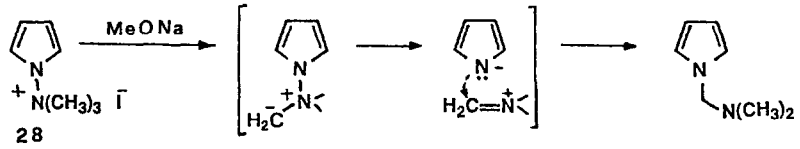
27

Studies on the reactivity of the aminomethylating agent, carried out in aprotic medium with acetylenic substrates[161] and in aqueous medium with polyacrylamide,[156] have shown that, unlike methylolamine, methylene-bis-amine possesses poor or no reactivity at all towards the above substrates. It can react with alkylketones only at very elevated pressures and exhibits very high steric requirements. It has therefore been proposed that methylene-bis-amine undergoes an S_N2 attack by an enolate ion deriving from the ketone, or participates in a cyclic transition state with the substrate in the enolic form.[162]

The C-aminomethylation of the CH_3 group of methyl-nitrooxazoles, investigated kinetically in hydroalcoholic solution, has been interpreted on the basis of an S_N2 mechanism involving anionic substrate and methylolamine when the reaction is carried out at alkaline pH. Under acidic conditions, an S_E2 attack by the substrate upon the methylene-imonium cation takes place.[163] On the other hand, the presence in the rate determining step of tautomeric structures of the type (H—Pyrr=CH_2) for substrates such as 2-methyl-pyrrole derivatives[62] or of carbonyl derivatives in the enolic form R—C(OH)=CR_2[108] has been demonstrated to be a necessary condition in order that the reaction may occur. This has also been proposed to be the case when glyoxylic acid is the aldehyde reagent.[100]

Enolization of the substrate can be rate-determining as it occurs at a rate comparable with that of reagent attack. A demonstration of this comes from an accurate study on the regioselective synthesis of Mannich bases from non-symmetric dialkylketones,[108] in which the possibility of kinetic or thermodynamic control of the reaction is extensively discussed and the relevance of steric hindrance upon the reaction pathway is considered. The correct choice of reagent concentration, temperature and reaction time, as well as suitable activation of the substrate as its enolate or enolether, can be very useful in solving problems of chemo- and regioselectivity.[70,72,135,164]

Finally, it is worth noting that the mechanism proposed[165] for the N-aminomethylation of pyrrole involves an intramolecular rearrangement of the quaternary ammonium salt **28**.



In this case, the action of a strong base such as sodium methoxide generates the methylene-imonium ion which can then react as a contact ion.

2.3. *Chemoselectivity and regioselectivity*

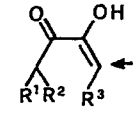
Chemoselectivity in Mannich synthesis usually involves substrates having more than one site for reaction with the aminomethylating agent. This is the case with alkyl-ketopyrroles,[166] alkyl-ketooximes,[167] N-propargyl anilines[168] and propargyl esters of phosphorous acid.[169] These cases are best considered on the basis of the relative reactivities of the functional groups present in each substrate.[21] Thus, the alkyl keto group reacts under acidic conditions, phenols under neutral or basic conditions and alkynes in the presence of copper salts.

Regioselectivity problems arise when aminomethylation may occur on either the α- or α′-CH of an asymmetrical ketone, the *ortho-* or *para*-positions of a phenol or the CH or NH groups of a heterocycle.

2.3.1. *Aliphatic ketones.* Several studies have examined[70,71,108] the selectivity of aminomethylation on dialkylketones, ketones with rather complex structures and steroidal derivatives. Open chain (**29**) and cyclic derivatives (**30**–**33**) (Table 2), which are conformationally more rigid, offer two non-equivalent positions to Mannich reaction. These are indicated by A (less substituted carbon atom) and B (more substituted carbon atom) in Table 2.

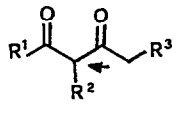
The results obtained show that Mannich bases deriving from attack on the less substituted carbon are obtained more frequently. B attack is preferred only under particularly selected reaction conditions, such as the use of methylene-imonium salts in dilute CF_3COOH solution for very long reaction times or with ethanolic primary arylamine hydrochlorides.[170] A few exceptions to this behaviour have been observed with some derivatives of **29**[170] and **30**.[78]

Substrates of the type **34**–**36**, which contain more than one carbonyl group, behave in a variable way so far as selectivity is concerned. α-Diketones **34** show a tendency to give bis-amino-methylation[22,23] even in the absence of excess aminomethylating agent. A mono-aminomethylated product on the less substituted carbon atom has been isolated in low yield in only one case.[23]



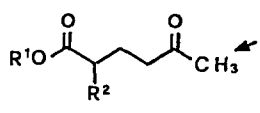
R^1 = Me, Ph
R^2, R^3 = H, or cyclic

34



R^1 = Me, Ph, O-Alkyl
R^2, R^3 = H, Alkyl

35



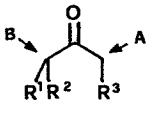
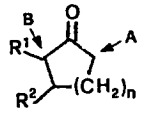
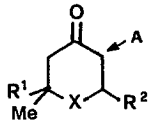
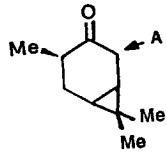
R^1, R^2 = H, Alkyl

36

When the second carbonyl or carboxyl group is in the β position (**35**), increased activation of the α carbon results, this position being the sole position of attack with rare exceptions.[179]

When the second activating group is further away, as in **36**, then the product is derived by aminomethylation of the less substituted carbon atom in the α position with respect to the keto-group.[180,181] The carboxyl group is unable to activate an adjacent carbon atom under the usual reaction conditions.

Table 2 - Regioselective aminomethylation reactions on non-symmetric dialkyl ketones.

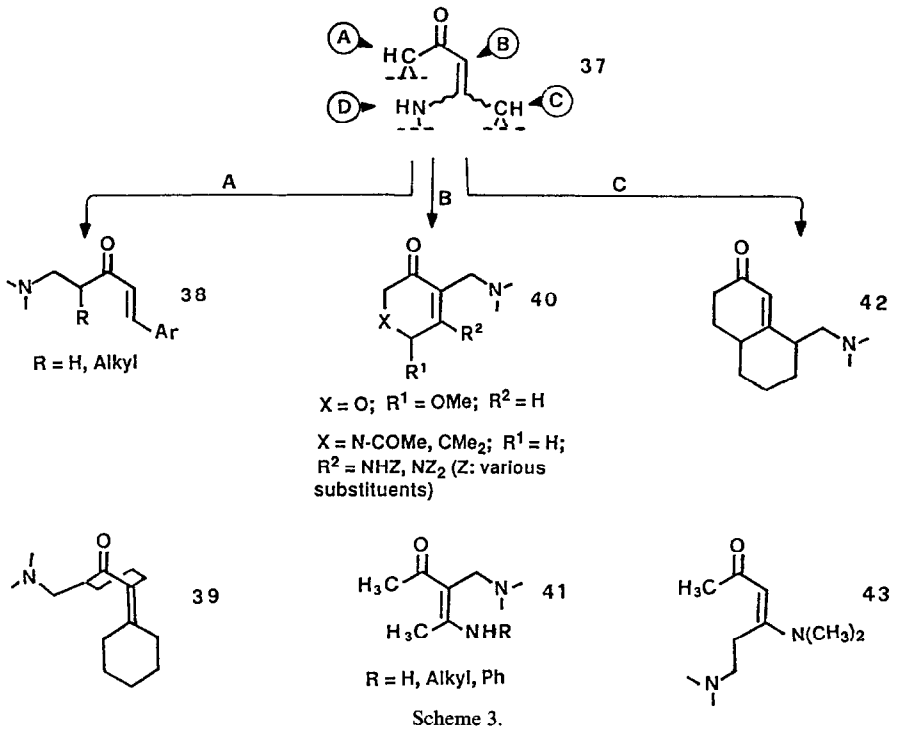
Dialkyl Ketones		Predominant attack	References
 29	$R^1 = R^3 = H$; R^2 = Alkyl	A[a]	70, 78, 98, 108, 170
	$R^1 = R^3 = H$; R^2 = Me, CH_2Ph, Ph	B	70, 73, 108, 170
	R^1, R^2 = Me, Me or $(CH_2)_{4\text{-}5}$ or polycyclic moieties (steroids bearing $CO\text{-}CH_3$ in 2 or 17 position, included); R^3 = H, Me	A B[a]	24, 25, 70, 78, 108, 162, 171-173 70, 108, 126, 170,
	$R^1 = R^2$ = Me, Ph; R^3 = Me	A B[a]	108 108
 30	n = 1 ; R^1, R^2 = H, $CH_2SC_4H_9$ or Alkyls	A	174, 175
	n = 1 ; R_1, R_2 = H, Me	B	107
	n = 2 ; R^1 = Me, Ph; R^2 = H	A B[a]	71, 73, 108 71, 78, 108
 31	X = CH_2, N-Me, O, S[b]; R^1 = H, Me; R^2 = H, Me, CH_2Ph, Ph	A	176-178
 32		A	125
 33		A or B	75

[a] Sometimes only slightly predominant. [b] The stereochemistry of the reaction has been also studied (ref. [178]).

With alkyl-vinyl-ketones, various reactions are observed (Scheme 3). Cases reported in the literature are summarized by the general structure **37**.

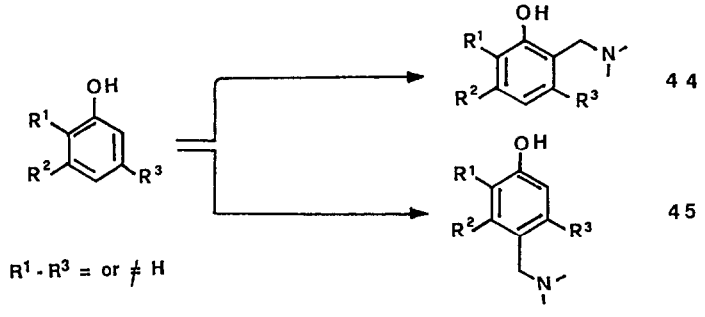
Styryl-ketobases **38**,[182,183] or the analogous unsaturated derivatives **39**,[184] are produced by attack of type A on acyclic or exocyclic unsaturated substrates in an acidic medium, or with preformed methylene-imonium salts. Vinylogous Mannich bases **42**[71,185] are obtained under the same conditions from cyclic α,β-unsaturated ketones (steroid derivatives included) through attack of type C. When aminomethylation is carried out with a free amine and formaldehyde, then the reaction involves the unsaturated C atom in the α position (**B** type attack) giving the Mannich bases **40** or **41**. This reaction occurs with cyclic[128,186,187] and acyclic[124,188,189] substrates bearing an NH group on the unsaturated C atom in the β position, the so-called 'push–pull olefines'. When the substrate bears an N,N-dimethylamino group, a vinylogous Mannich base **43** is produced (C type attack) with methylene-imonium salts.[190]

N-aminomethylations of type D will be discussed in Section 2.4.1.



Scheme 3.

2.3.2. *Phenols and NH-activated benzene substrates.* Phenols undergo aminomethylation predominantly in the *ortho* position (**44**); *para*-derivatives **45** are usually formed only when both the *ortho* positions are blocked.



para-Hydroxy Mannich bases (**45**) are obtained from substrates having one or both of the *ortho* positions unsubstituted. The reaction is influenced by the substituents in the substrate (with their electronic and/or steric effects), as well as by the reaction conditions and the reagents employed.

When aminomethylation is carried out with primary amines, using hexahydrotriazines **19b** in acidic medium as reagents, *para*-attack is favoured.[138] Phenol affords, in appreciable yield, the *para*-substituted Mannich base **45**.[159] A similar result is obtained with *ortho*- or *meta*-bromophenol.[191]

The Mannich reaction with cyclic secondary amines has been carefully investigated.[192] The results indicate that regioselectivity is affected by the position of substituents. The *ortho* position is usually favoured provided that the vicinal positions are unsubstituted. The attacking species shows considerable steric requirement.[192–194] With secondary acyclic amines (diallylamine,[195]

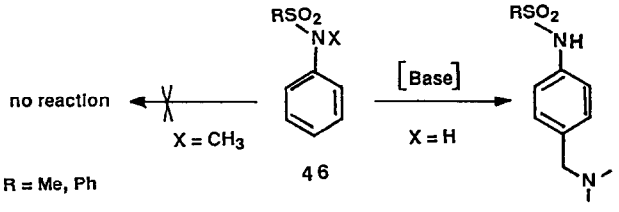
dicarboxymethylamine[196]), *ortho* attack is always preferred. The presence of substituents such as the nitro group or halogen atoms conditions both steric and electronic effects, making the interpretation of the data more difficult.[60,191–197]

Formation of *para* derivatives is clearly favoured when methylene-imonium salts are used.[130,159] Such behaviour has been attributed to a lack of influence by hydrogen bonding between the phenolic substrate and the aminomethylating agent in the transition state.[130]

The introduction of a second aminomethyl group usually occurs on the activated position less favoured in the first attack.[130,192,195] However, the reaction does not always proceed smoothly and in some cases a suitable choice of conditions (e.g. propionic acid as solvent[198]) is required in order to achieve satisfactory bis-aminomethylation.

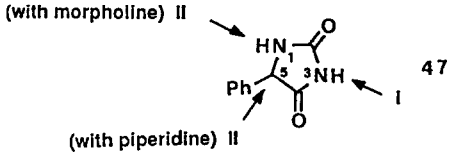
Regioselective aminomethylations of di- and poly-hydroxy phenolic substrates always take place first in the *ortho* position to the hydroxyl group. This can be interpreted on the basis of the orientating properties of the substituents.[199 202]

An interesting comparison with phenolic substrates is offered by the sulfonanilides (**46**), which largely undergo predominant aminomethylation in the *para*-position,[40,41] possibly due to *para*-quinonoid activation by dissociation of the NH proton.



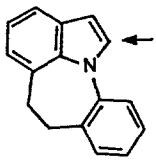
The corresponding NCH_3 derivative does not react at all and *para*-substituted derivatives of **46**, on aminomethylation, give Mannich bases in yields less than 10%.[41]

2.3.3. *Heterocyclic substrates.* Heterocyclic substrates, such as pyrroles, imidazoles or barbituric acids and uracils may undergo selective Mannich reactions which depend upon the reaction conditions employed. C-aminomethylation is favoured by acidic conditions whereas N-Mannich bases are produced when free amine and formaldehyde or O,N-acetals in anhydrous solvents are employed as aminomethylating agents. Heterocyclic N-Mannich bases, however, are not very stable and may therefore behave as aminomethylation agents (e.g. **20**, Section 2.1.2). Thus, the corresponding heterocyclic C-Mannich base can be obtained when reaction time and temperature are increased, as is observed with theophylline.[203,204] Aminomethylation of 5-phenyl-hydantoin (**47**) with one mole of aminomethylating reactant involves exclusively the N atom in position 3. The position of attack by the second aminomethyl group is influenced by the nature of reactant amine and, probably, by the medium basicity. When an excess of morpholine is employed, the second aminomethyl group is linked to the N atom in position 1, whereas with piperidine the second aminomethyl group is linked to the C atom in position 5.[205]

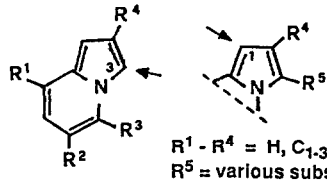


C-aminomethylation of five-membered heterocyclic substrates such as pyrrole and indole derivatives undergo reaction, as a rule, in positions 2 and 3, respectively, unless these are occupied by

substituents. Some exceptions, however, are observed, for example, with substrates **48**, in which the indole group is condensed with a benzazepine system where the preferred position of attack is the C atom adjacent to N.[206] Indolizine derivatives **49**, too, are aminomethylated in the C-3 atom of the five-membered ring: when this position is occupied, then reaction occurs in position 1.[132,207,208]



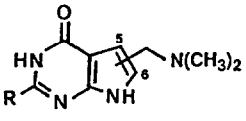
48



R^1 - R^4 = H, C_{1-3}Alkyl
R^5 = various substituents

49

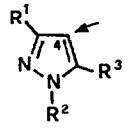
During research on the chromophore of ribonucleoside Q, the pyrimidino-pyrrole substrate **50** was submitted to aminomethylation and gave the 6-aminomethyl derivative when R = NH_2 and the 5-substituted derivative when R = H.[209] Both the 5- and the 6-positions are involved when R = $NHCOCH_3$.[210]



50

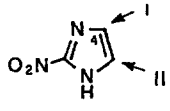
R = H : aminomethyl group in 5
NH_2 " " 6 (91 % yield)
NHAc " " 5 (37 %) and 6 (18 % yield)

With five-membered cyclic substrates containing more than one heteroatom aminomethylation appears to prefer position 4 as the site of attack in both the pyrazole (**51**)[211,212] and the imidazole (**52**)[213] system.



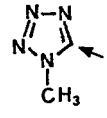
51

R^1 = H; R^2, R^3, cyclic or
R^1 = OH: R^2, R^3 = H, Alkyls

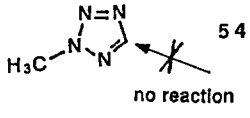


52

N-methyl-tetrazoles **53** and **54** undergo aminomethylation depending upon the position of N-methyl substituent.[214]



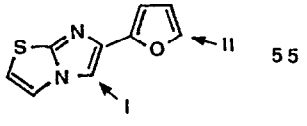
53



no reaction

54

The above examples demonstrate that five-membered rings present a very good class of substrates for C-aminomethylation. Moreover, the five-membered ring containing N is preferred for aminomethylation when the substrate is a condensed polycycle, as is observed for **49** and similar aza-derivatives.[212,215] Furyl-imidazothiazole **55**, significantly, affords a mono-aminomethyl derivative by reaction (I) in the imidazole ring. A bis-Mannich base is produced by attack of a second aminomethylating molecule upon the furane ring (II) when two molecular equivalents of reagent are employed.[216]



55

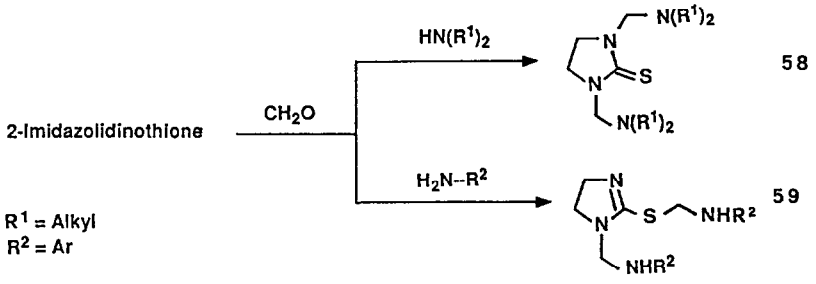
As regards six-membered heterocyclic substrates, most of them resemble the structure of the 'push–pull olefines' cited in Section 2.3.1. (Scheme 3). They show a behaviour similar to that of compounds **37**.[217,218]

In aza-phenol substrates such as 3-hydroxy-pyridines **56**,[219] the corresponding N-oxides,[220] 5-hydroxy-pyrimidine **57**[221] and pyridazine N-oxides,[222] C-aminomethylation is mainly oriented by the hydroxyl group towards the *ortho* and *para*-positions. The *ortho* position vicinal to N usually reacts first.

56 57

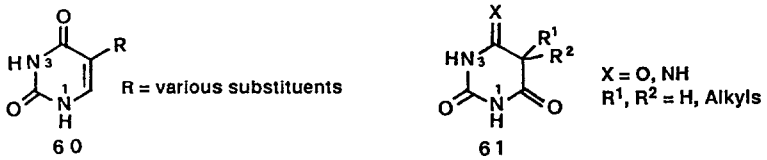
When the Mannich reaction is carried out on heterocyclic substrates under those conditions which favour N-aminomethylation, then the selectivity may be affected by tautomeric equilibria.[223] The Mannich reaction on benzotriazole has been studied[16,224] by ^{1}H- and ^{13}C-NMR spectrometry in order to determine the relative amounts of the 1- and the 2-isomers. It has been observed that the preference for aminomethylation in position 2 increases as the polarity of the reaction medium decreases. The maximum yield of 2-isomer is 43–47% in carbon disulfide.

The behaviour of 2-imidazolidinothione is influenced by tautomeric effects, as both the mobile H atoms of this substrate can be substituted by reaction with secondary dialkylamines and primary arylamines, to give, respectively, N,N- and N,S-bis-Mannich bases **58** and **59**.[225,226]



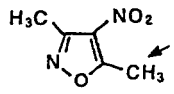
N-aminomethylation of six-membered heterocyclic substrates concerns the derivatives of uracil and barbituric acid which are both characterized by the presence of two reactive NH groups. Aminomethylation of the uracils **60** occurs on the N atom in position 3, although the reaction with formaldehyde alone shows an equilibrium constant for hydroxymethylation in position 1 which is about twice the value of the equilibrium constant associated with attack on the N atom in position 3.[227]

In barbituric acid derivatives **61** the position C-5 is the most reactive when it is unsubstituted. Otherwise, the reaction is directed towards the N-1 or the N-3 position.[228,229] With imino-barbituric derivatives, however, the largest reactivity is associated with position 3.[230] The imine NH group is the last to be attacked.

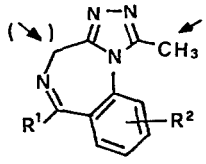


60 61

Some N-heterocyclic substrates are not directly aminomethylated, but act as activators of methyl or methylene groups attached to the ring. Dimethyl-nitrooxazine **62**, for example, reacts only on the methyl group in the α position with respect to the O atom.[231] The triazole-benzodiazepine **63** behaves similarly. Due to the pharmacological relevance[135] of this substrate, the mechanism of the reaction has been investigated. It has been found that mono- or bis-aminomethylation as well as aminomethylation of the methyl and the methylene group in the diazepine ring are remarkably affected by the type of solvent used and even by the order of addition of reactants.



62



63

R^1 = Ar
R^2 = H, Halogen, ...

2.4. *Synthesis of cyclic Mannich bases*

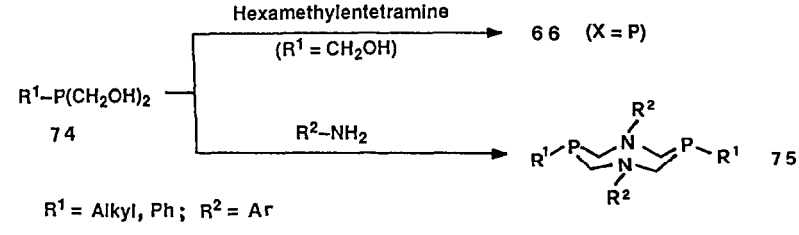
Two main strategies for the synthesis of N-heterocyclic Mannich bases have usually been followed.

(i) The classic Mannich reaction employing three components (bi- or polyfunctional substrate, primary amine and formaldehyde) (Section 2.4.1);

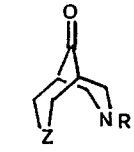
(ii) formaldehyde condensation (ring closure) of a compound containing both an active hydrogen group and an amine moiety (Section 2.4.2).

2.4.1. *Cyclization of polyfunctional substrates with amine and aldehyde.* Polyfunctional substrates may possess two or more active hydrogens on the same atom (**64**) linked to equal (**67**) or different (**71**) groups in the molecule (Table 3).

In the first case, the substrate XH_2 can react with formaldehyde and primary amine in the molar ratios 1:3:2, respectively, giving the heterocyclic products **65**. When the substrate molecule is trifunctional (XH_3), triaza-tricyclic derivatives **66** are obtained by reaction with ammonia. Similar polycyclic products are also given by the hydroxymethylated substrates **74** which afford, with primary amines, the diphospha-diaza-cyclooctanes **75** possessing attractive complexing properties.[250]

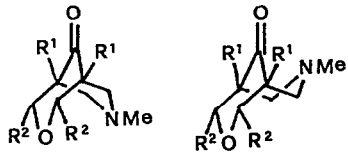


Substrates of the type $R(XH)_2$ (**67**, Table 3) constitute the starting material for the synthesis of products **68**–**70**. Among them, compounds **68**, which are mainly bicyclic derivatives having the structure **76**, are obtained in one case as a mixture of stable conformers (**77a** and **b**), which have been isolated and submitted to further reactions.[240]



Z = –, CR'_2, NR', O, S, Se

76

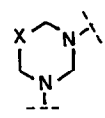
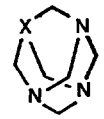
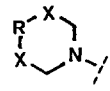
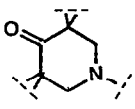
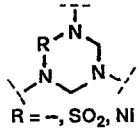
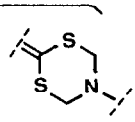
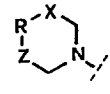
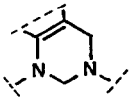
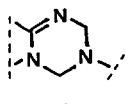


R^1 = COOAlkyl; R^2 = Ph

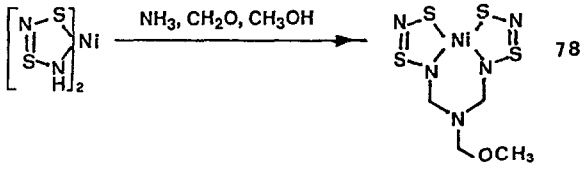
a b

77

Table 3 - Cyclic Mannich bases from polyfunctional substrates, formaldehyde and primary amines.

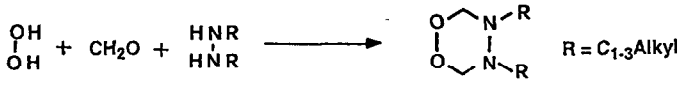
Substrates	Products
 64	+ 3 CH_2O + 2 H_2N–¦ →  X = R_2C, RN, S (65) [or  X = R-C, P (66)] from XH_3 and NH_3
References:	93, 138, 151, 232, 233 / 234, 235
 67	+ 2 CH_2O + H_2N–¦ →    R = –, SO_2, NI  68 69 70
References:	236-242 / 56, 243, 244 / 245
 71	+ 2 CH_2O + H_2N–¦ →    72 73
References:	128, 188, 190, 246-248 / 230, 249

Rather unusual heterocyclic compounds, which include seven- or eight-membered thia- and phospha-derivatives,[251-253] as well as the Mannich base **78**, which has a metal atom in the ring,[244] are noteworthy.



78

Hydrogen peroxide produces, with formaldehyde and the hydrazine derivative **79**, the dioxa-diaza-cyclohexanes **80**.[254]



79 80

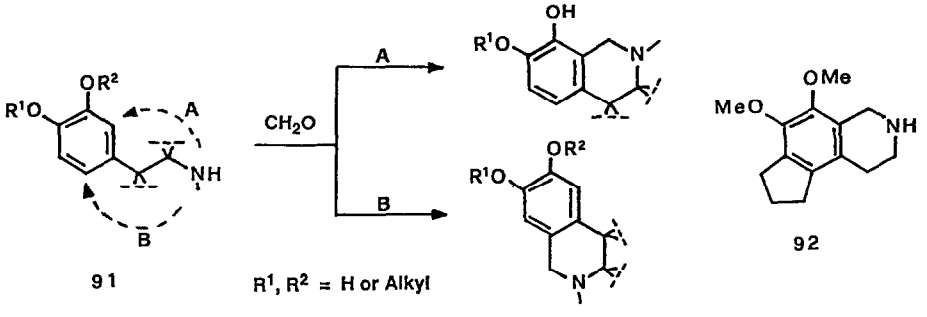
Substrates **71** (Table 3), including amino-heterocycles, 'push–pull olefines' and NH-imino-heterocycles, give respectively products **72** or **73**.

2.4.2. *Formaldehyde cyclization of aminic substrates.* The substrates **81** (Table 4) which contain primary or secondary amino groups, produce a variety of cyclic compounds depending on the nature and size of the R group.

When R is associated with a sequence of 2–3 atoms, then five- or six-membered N-heterocyclic rings (**82**, **83**) are usually formed. Larger heterocyclic rings may be produced in some cases[252,270] or even polycyclic structures[257,260,271] of the type **84**. It can be also observed that as the X group actually belongs to all classes of substrates, O-, S- and P-heterocyclic Mannich bases can be obtained, besides the usual C- and N-derivatives, by condensation with formaldehyde.

Phenolic substrates of the type **91** (Scheme 4) display different regioselective reaction pathways determined by the presence of substituents bonded to the O atom.

With only one exception,[272] pathway A is usually predominant when R^2 is H,[273,274] whereas pathway B is exclusively followed when R^2 is an alkyl group. This is observed in the cyclization of protoberberines[273] and similar substrates.[275,276] However, when no alternative way of condensation is offered, route A is again covered (**92**).[277]



91 92

R^1, R^2 = H or Alkyl

Scheme 4.

ortho-Phenylendiamines afford, by condensation with two moles of formaldehyde, N-methylbenzimidazoles **93**, due to an internal redox reaction.[278]

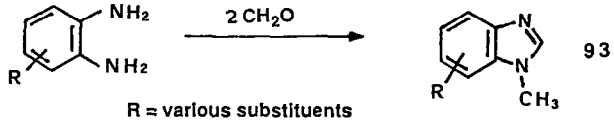
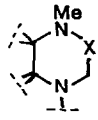
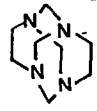
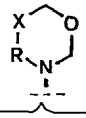
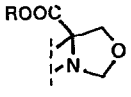
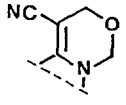
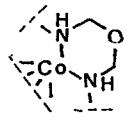
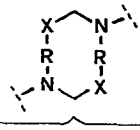
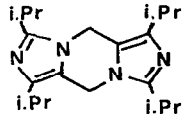
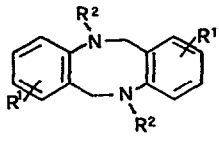
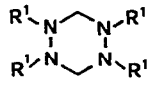
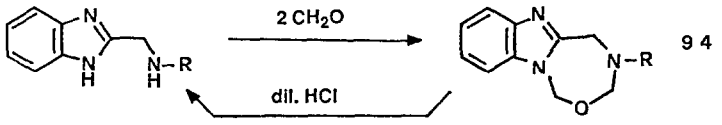


Table 4 - Cyclic Mannich bases from aminic substrates, and formaldehyde.

Substrates	Products		
 **81**	+ CH_2O 		
	 X = O, S, POOEt **82**	 X = N-Me, O **83**	 **84**
References:	252, 255-257	258, 259	260
	+ 2 CH_2O 		
	 **85**	 **86**	 **87**
References:	261, 262	263	264
	+ CH_2O (molar ratio, 2 : 2) 		
	 **88**	 **89**	 **90**
References:	265	266	267-269

When the R group of substrate **81** (Table 4) is very short in length so that excessively high ring strain would result in the cyclized product, the involvement in the reaction of two formaldehyde molecules occurs and five- or six-membered oxa-aza-derivatives **85–87** of α-amino acids,[261,262] 'push–pull olefines'[263] and cobalt complexes[264] are produced. Larger rings (see **94**) may also be formed when the expected derivative having two fused imidazole rings would be more strained.[279]



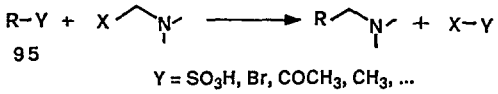
94

Alternatively, two molecules of substrate can react with formaldehyde so that stable six-membered ring products are formed. Imidazole gives the condensed tricyclic product **88** and the hydrazine derivatives give the tetra-aza derivatives **90** (Table 4). Dibenzo-diaza-cyclooctanes **89** originate by analogous self-aminomethylation starting from methylene-bis-arylamines $(ArNR^1)_2CH_2$ through the acid catalyzed formation of an intermediate methylene-imonium ion.[266]

2.5. *Mannich syntheses involving other concomitant reactions*

The introduction of an aminomethyl group may be accompanied by modifications of substrate molecule, such as rearrangements, cyclizations not involving the aminomethyl group, as well as reactions of the amine group.

Substitution of groups other than hydrogen by the aminomethylating agent in substrates **95** (Scheme 5) may take place; 1-amino- or 1-hydroxy-anthraquinone-2-sulfonic acids,[280] for example, give 2-aminomethylated derivatives. In the synthesis of protoberberines,[281] the substitution of a Br atom is observed in the *para* position with respect to an alkoxy group. The substitution of $COCH_3$ in aryl-butan-1,2,3-triones-2-arylhydrazones[282] has been reported.

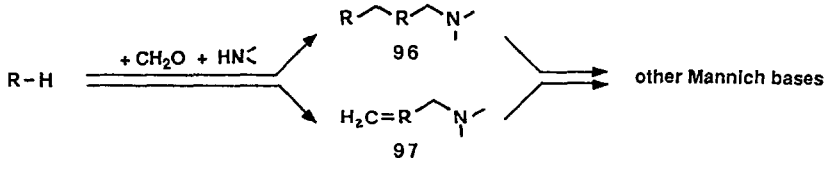


95

Scheme 5.

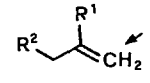
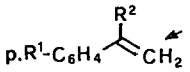
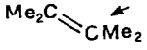
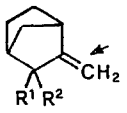
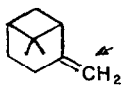
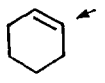
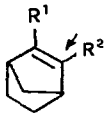
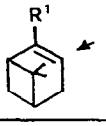
The methyl groups of dimethylsulfite $(CH_3)_2SO_3$ are similarly replaced by dimethylaminomethyl groups giving $^-O_3S—CH_2—N^+(CH_3)_2H$.[283]

When several mobile hydrogen atoms are present in the substrate, the possibility exists that formaldehyde reacts to give Mannich bases with a methylene bridge between two molecules of substrate (**96**).[284] Alternatively, unsaturated aminomethyl derivatives (**97**)[74,126] may be formed[285] (Scheme 6).



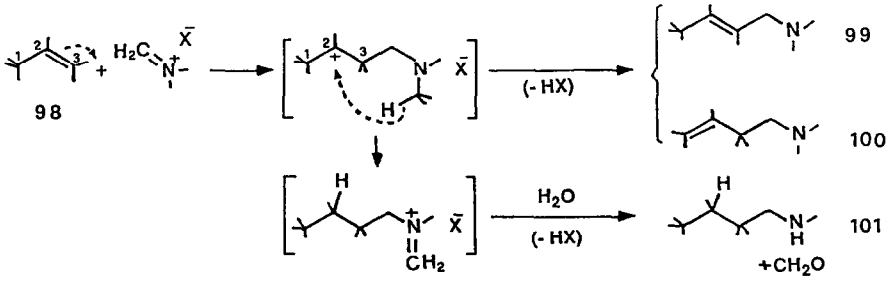
Scheme 6.

Table 5 - Aminomethylated products from Mannich reaction on alkenes.

Alkene 98			Aminomethylated product		References
	R^1	R^2	Predominant	Minor [a]	
	H, C_{1-11}Alkyl H, Pr	H Me, Et	101 99, 100	100, [b] 101	288
	H, Me OMe, H	H H, Me	101 99	99 101	288
			100		126
	H, Me Me	H Me	100 99	101, [b] b	289, 290 291
			100, 99	b	292
			101		288
	H Ph Me	H H H, Me	101, [b] 100	b b	286 293 289, 290
	H Me		101 100	b b	292

[a] Usually within 10 %. [b] Other products also obtained, e.g. deriving from N-methylation of **101** or from addition of ROH to the double bond in **99** or **100**.

2.5.1. *Aminomethylation of alkenes.* Aminomethylation of alkenes[75,126,286–293] (including some azulene derivatives[294,295]) can give a complex range of products. The main aminomethylated products obtained are reported in Scheme 7, although non-basic compounds are also formed.

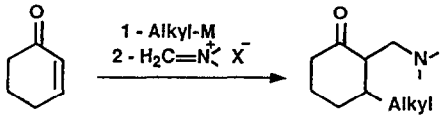


Scheme 7.

Alkenes **98**, employed as substrates, are quite various (Table 5). Dimethylamine is often used as the amine reagent but other amines[286,287] have been examined.

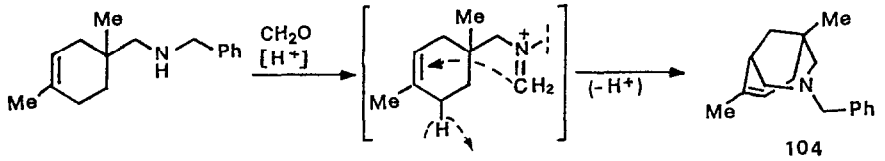
The reaction mechanism[126,287–289] shown schematically in Scheme 7 involves a methylene-imonium ion as the aminomethylating agent. This is generated by reaction conditions which are favourable to its formation (usually acetic acid as solvent). Attack by this reagent leads to an intermediate carbocation which can then follow various reaction pathways, depending upon the substrate structure. Thus, products **99** or **100** are produced by the loss of a proton from position 1 or 3. Cyclic substrates such as santene and 2-pinene give products with exocyclic double bonds. Products **101** can be formed by intramolecular hydride transfer followed by hydrolysis and the formation of formaldehyde. The use of primary amine (methylamine) in alkene aminomethylation gives products **99**:[293] tetrahydrooxazine derivatives are produced by shorter reaction times.

When the alkene double bond is conjugated, then the reaction proceeds much more smoothly. Unsaturated ketones[70,72] such as cyclohexenone **102** have been treated with alkylmetals in order to obtain the corresponding enolate which is then reacted with a methylene-imonium salt. Addition to the double bond takes place and alkyl- and aminomethyl groups are introduced in the β and α positions, respectively (**103**).



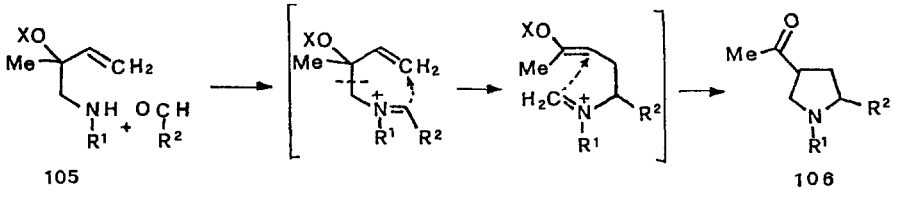
102 103

In some cases, aminomethylation of alkenes leads to cyclizations.[293,296,297] The aza-bicyclo-nonene derivative **104** is formed by double migration (cf. **100** in Scheme 7).



104

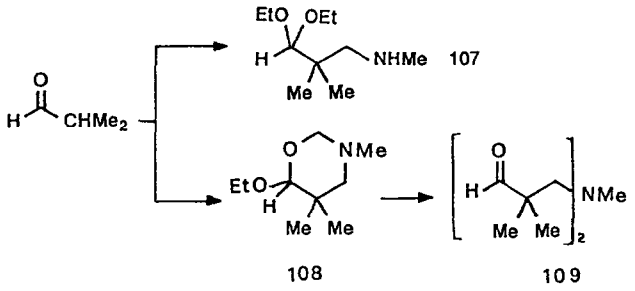
In 2-alkoxy (or 2-hydroxy) 3-alkenamines (**105**) cleavage of bond C(1)–C(2) in a tandem cationic aza-Cope rearrangement–Mannich cyclization[298] occurs, giving 3-acyl pyrrolidines **106**.



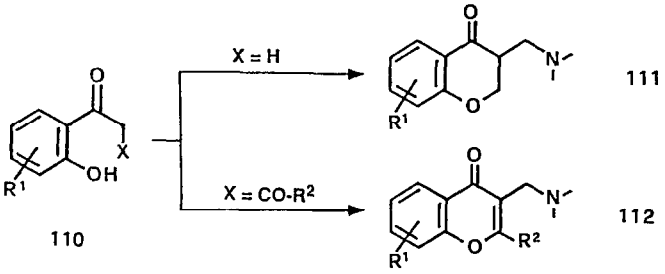
105 106

X = H, Me ; R^1 = Alkyl, Ar ; R^2 = H, Alkyl, Ar

2.5.2. *Aminomethylations with concomitant cyclization.* A number of aminomethylations are accompanied by cyclization reactions. Such reactions are affected by several factors including pH, the nature of aldehyde reactant and the type of solvent. The behaviour of isobutyraldehyde is typical. When ethanol is employed as the solvent for aminomethylation, then the diacetals **107** or **108** are formed. In the presence of $ZnCl_2$, **108** can then give the tertiary Mannich base **109**.[299]



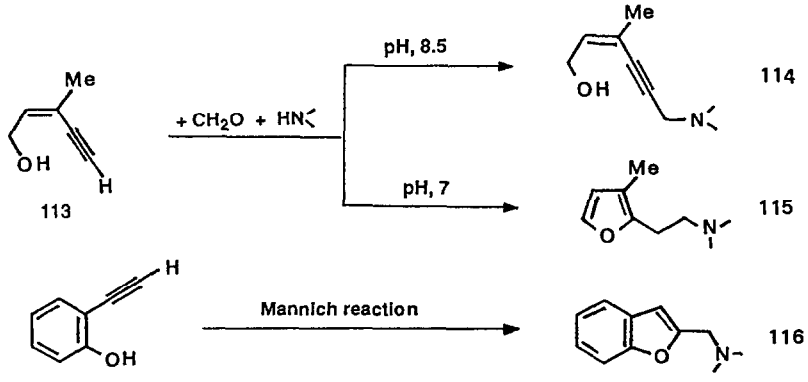
The effect of the reactant formaldehyde on aminomethylation is evidenced in the synthesis of Mannich bases **111**, starting from phenolic substrates **110**.[300,301]



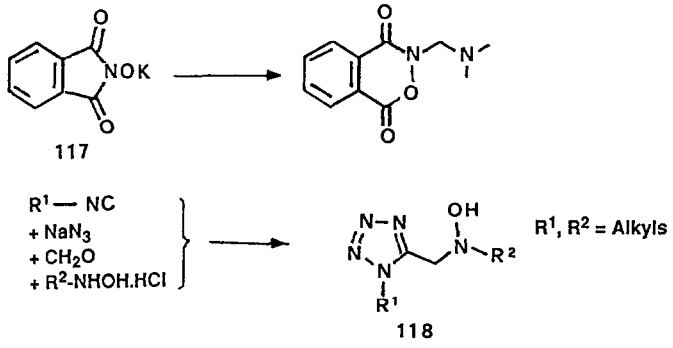
R^1 = various substituents ; R^2 = Alkyl, Ph

When suitable groups are present in the substrate, then chromone derivatives (**112**)[302] can be produced. Furan (**115**) or benzofuran (**116**) derivatives are produced when acetylenic substrates are submitted to the Mannich reaction. The reaction with the acetylenic alcohol **113** is influenced by pH and in addition to the expected Mannich base **114**, 2-aminoethyl-benzofuran **115** can also be obtained.[303,304]

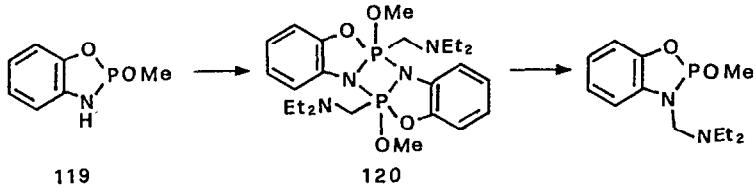
Aminomethylation of *ortho*-ethynyl-phenol produces only 2-aminomethyl-benzofuran **116**. No competition is observed by the phenolic ring towards the reagent.[305]



A ring expansion in the aminomethylation of N-hydroxy-phthalimide potassium salt **117**[123] has been observed. The synthesis of a tetrazole ring (**118**),[306] having the aminomethyl group linked in accordance with the reactive behaviour of N-methyl-tetrazoles **53**, **54** described in Section 2.3.3. have also been reported.

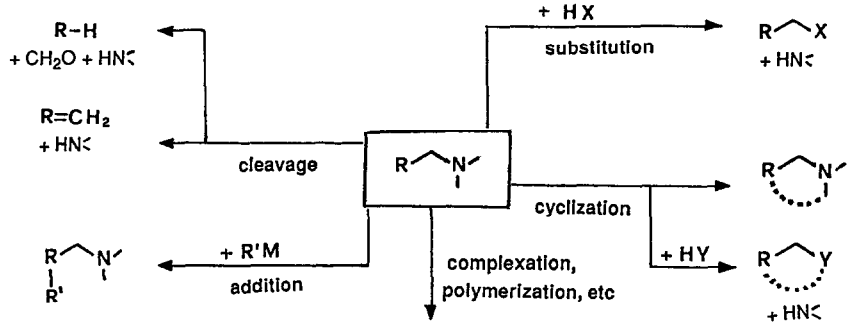


The polycyclic P-Mannich base, diaza-diphospha-tricyclodecane **120**, has been obtained from the oxazaphospholane **119**. On heating, **120** gives the expected N-aminomethylated oxazaphospholane.[307]



3. REACTIONS OF MANNICH BASES

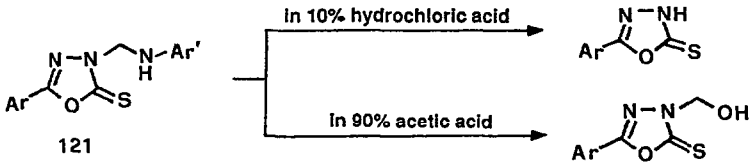
The remarkable number of reactions to which Mannich bases can be subjected (Scheme 8) demonstrates that these compounds are very useful intermediates in synthetic chemistry.



Scheme 8.

3.1. *Cleavage*

Cleavage of Mannich bases can take place either by deaminomethylation, that is a retro-Mannich reaction, or as a deamination producing the amine and an unsaturated derivative of the substrate. The type of cleavage taking place is particularly related to the class of Mannich base. C-Mannich bases, for example, are much more stable to deaminomethylation than to deamination. The pH value is also an important factor affecting cleavage. Heterocyclic Mannich bases **121** give deaminomethylation by treatment with hydrogen chloride, whereas an hydroxymethyl derivative is produced by deamination in acetic acid.[308]

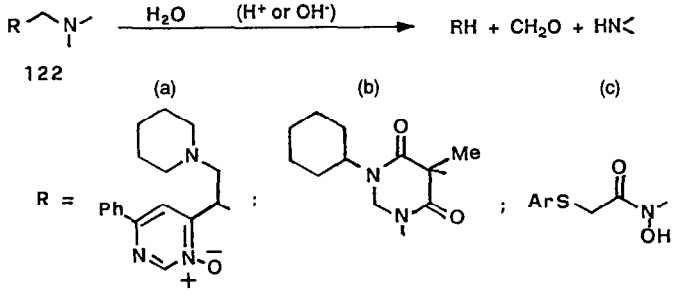


3.1.1. *Deaminomethylation.* Deaminomethylation is important in that it determines the stability of Mannich bases. The handling and storage of such compounds may lead to undesired transformations. In the synthesis of vincamine derivatives the occurrence of a racemization process is attributed to the equilibration induced by direct and reverse Mannich reactions.[309]

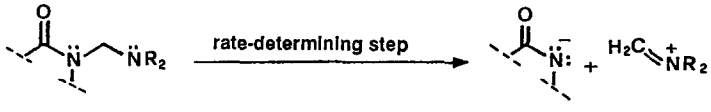
Deaminomethylation can be a side reaction in many transformations of Mannich bases giving trans-aminomethylation or methylene-bis-derivatives by inter- or intra-molecular aminomethyl group transposition. Trans-aminomethylation has some relevance in organic synthesis. Pharmacological interest[8,310] in amidic Mannich bases may yield useful pro-drugs of NH-acidic compounds (amides, urea derivatives etc.).[8] Deaminomethylation has been related to the antitumoral activity of Mannich bases.[2,311]

The elimination of the aminomethyl group has been investigated. C-Mannich bases are in general more stable to cleavage reactions. In compounds **122a**, the elimination of the aminomethyl group requires drastic conditions (heating at 90°C with dilute sulfuric acid[312]) whereas N-aminomethyl derivatives are decomposed much more easily, as shown by barbituric C,N-Mannich bases **122b**, in which only the C–N bond is cleaved.[228]

Acidic conditions result in the deaminomethylation of hydroxamic (**122c**),[313] five-membered heterocyclic Mannich bases[308,314] and of O-Mannich bases of adenosine, cytidine, etc.[90] Apart from a few exceptions, the acidic treatment requires some minutes at room temperature. Neutral or alkaline hydrolysis requires higher temperatures and/or much longer reaction times.[90,228,313]



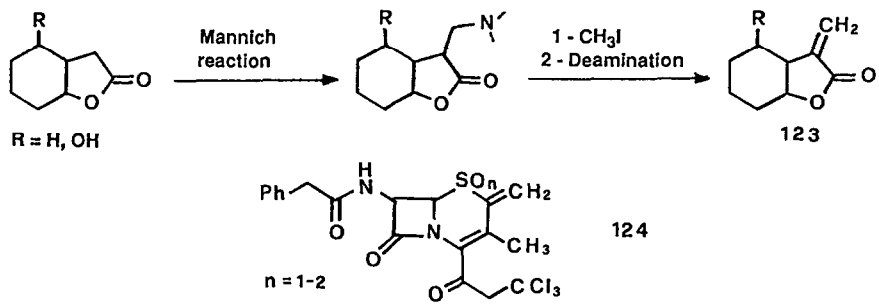
Studies on the mechanism of the hydrolytic cleavage of amidic Mannich bases show that the reaction is a deaminomethylation. The rate-determining step is the cleavage of the C–N bond between amido and methylene group of Mannich base.



The reaction is favoured by the steric hindrance of the amine moiety as well as by its basicity. The acidity of the amide moiety and the tendency to delocalize the negative charge operates in the same sense.[8]

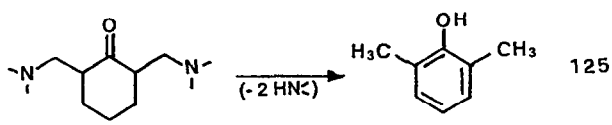
3.1.2. *Deamination.* Deamination of Mannich bases is connected with their stability, particularly when the base is in the free form. This is therefore of paramount importance so far as handling and storage are concerned. From the synthetic point of view deamination plays an important role because it frequently constitutes the first step of substitution reactions (Sections 3.2 and 3.4.2). Moreover, deamination has interesting implications in pharmacology (see, e.g., ref. 2). In technological applications the recently proposed[315] action of phenolic Mannich bases as well known hardeners of epoxy resins is worth mentioning.

β-Aminoketones and similar carbonyl derivatives (esters, lactones etc.) frequently undergo deamination. The reaction is often carried out by suitably modifying the conditions of Mannich synthesis, so that the α,β-unsaturated carbonyl derivative is formed directly. By such methods, the synthesis of D,L-vernolepin and D,L-vernomenin, which contain the α,β-unsaturated lactone moiety **123**, has been made possible.[69]

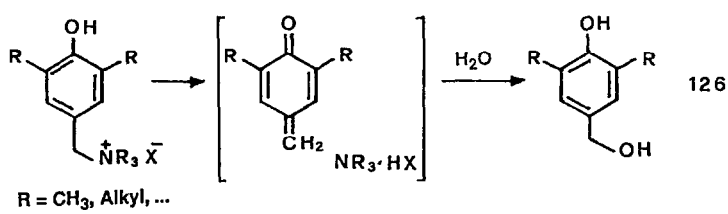


Mannich keto-bases of heterocyclic substrates such as flavanones,[316] pyrazolones and oxindoles[317] as well as some other C-Mannich bases (e.g. cephalosporin sulfoxides and sulfones **124**[318]) have been similarly submitted to deamination in order to obtain vinyl derivatives, or their dimers.

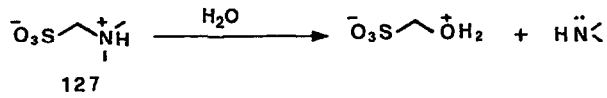
Other interesting reactions may also be shown by deamination products. Starting from bis-dimethylaminomethyl-cyclohexanone in phosphoric acid,[319] the dimethyl-phenol **125** has been obtained by a series of tautomeric equilibria.



Hydroxymethyl derivatives are, in many cases, reported to be formed instead of the unsaturated carbonyl product by cleavage of CH_2–N bond of Mannich bases. Thus, the deamination of *para*-aminomethylphenols leads to an intermediate methylenequinone which then reacts with water giving the hydroxymethyl phenol **126**.[320]



Hydroxymethyl derivatives are similarly produced in the deamination of the heterocyclic Mannich base **121**. Deamination of S-Mannich bases **127** derived from bisulfite ion proceeds by an S_N2 attack on the zwitterion structure of the Mannich base.[321]

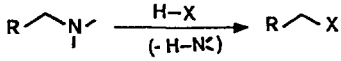


127

It has been suggested that in deamination of β-aminoketones, the elimination step would take place exclusively on the enolate–ammonium form, so that a cyclic transition state involving participation of a water molecule is unlikely. A linear structure, R—CO—CH=CH—CH_2—CH_2—CO—R, rather than the commonly proposed cyclic structure, has been attributed to the dimeric product of deamination.[322]

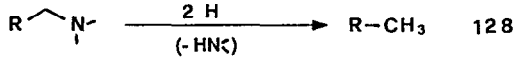
3.2. *Amino group substitution*

The amino group of Mannich bases can be replaced by various X substituents by reaction with nucleophilic H–X reactants.



The reaction may also be formally regarded as an X-alkylation by the R—CH_2— residue of Mannich base. It has considerable synthetic utility.

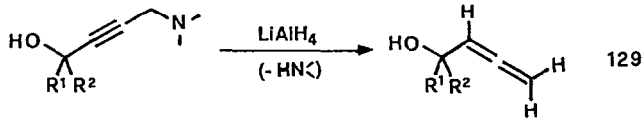
3.2.1. *Substitution by H.* Replacement of Mannich base amino group by H, leading to the products **128**, has been applied to a number of C-Mannich bases. This type of transformation on the 15-aminomethyl derivative of cyanocobalt-heptamethyl-corrin[54] is reported in Table 1.



Besides the usual reagents (hydrogen and catalyst, zinc and acid), some novel reducing agents have been recently introduced, including tin(II) chloride in an acidic medium,[323] some borohydrides[324,325] and tri-butyltin hydride.[326] In some cases the Mannich base is reduced as methiodide. Phenolic Mannich bases are employed with these reagents as they are particularly suited to this type of reaction. In one case the methyl derivative has been simply obtained on heating the Mannich base at 210°C in triethylamine without any reducing agent.[327]

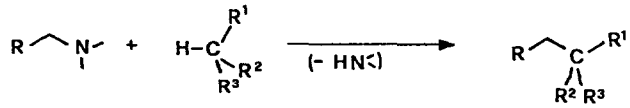
Diphenyl-arsine can also cause hydrogenolysis of the C–N bond, as reported in connection with As-alkylation attempts (Section 3.2.4.) by means of β-amino-propiophenones.[328]

When the reduction is carried out with metal hydrides on acetylenic methiodides of Mannich bases[329] an allene (**129**) is produced.



R^1, R^2 = H, Alkyl (also steroidal moieties), Ar

3.2.2. *Substitution by CH-derivatives.* When Mannich bases react with compounds containing nucleophilic CH groups (**130**) then substitution of amino group can take place.

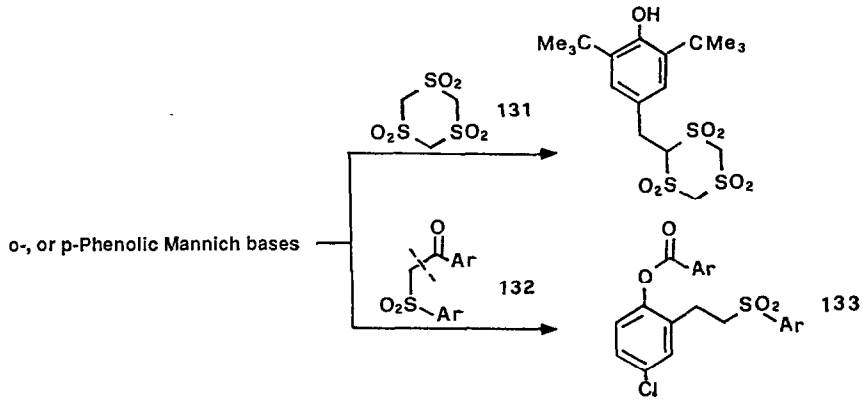


130

R^1 - R^3 = various substituents

Thus, molecules having a C atom activated by adjacent carbonyl, carboxyl or nitro groups may be employed as substrates for C-alkylation by Mannich bases. Sulfonyl derivatives may also be used, although at least two activating groups are required in the molecule, due to the lower activation by the sulfonyl group. Trithiane-hexaoxide **131**, for example, leads to the expected substitution product when allowed to react with a phenolic Mannich base.[330]

In some cases cleavage of the nucleophile reagent (**132**) can take place during the reaction, leading to C-alkylation and acylation of the phenolic hydroxyl group (**133**).[331]



Aldehydes may react with ketonic Mannich bases giving γ-diketones **134** following a mechanism unexplainable on the basis of the usual elimination–addition.[332]

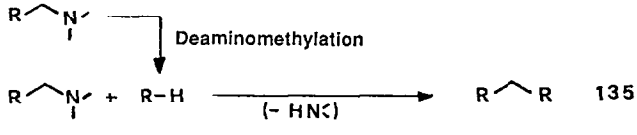
R^1 = Alkyl, Alkenyl, Ph ; R^2 = H, Alkyl, ; R^3 = Alkyl, Ar

NMR evidence on the reaction between 4-hydroxy-coumarins and some β-aminoketones, also, does not support an elimination–addition mechanism.[333]

A particular type of C-alkylation (Scheme 9) is found when two molecules of Mannich base react together with formation of a methylene-bis-derivative (**135**).

The reactions involved in self-condensation may differ from those depicted below. In the case of 4-aminomethyl-2,6-di-*t*-butyl-phenols[334] attack of methylenequinone on the Mannich base has been proposed.

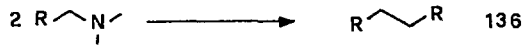
Self-condensation is usually a side-reaction of Mannich base formation which in some cases can produce methylene-bis-derivatives **135** as the predominant or even the unique product.[131,187,335,336] When such a reaction is desired, it can be favoured, starting from phenolic or heterocyclic Mannich bases, by means of high boiling reaction solvents.[336,337]



R = 2- or 4-hydroxyaryl , 3- or 4-hydroxycoumaryl group

Scheme 9.

Another type of self-condensation occurs by dimerization of the R—CH_2 residue formed by cleavage of CH_2–N bond.

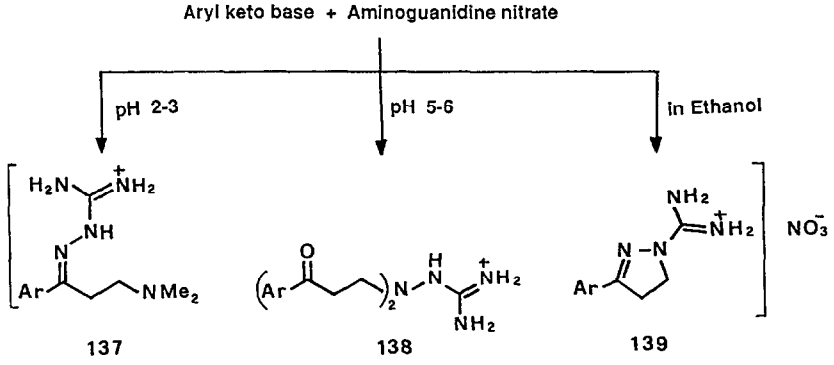


136

This reaction is observed with the methiodide derivative of azulene Mannich base, which, in the presence of zinc, gives bis-azulenyl-ethane (**136**, R = 1-azulenyl).[294] The presence of radical species is likely in this case, in analogy with photochemical reactions carried out on ketonic Mannich bases which produce similar dimeric products **136** (R = Ph—CO—CHPh).[338]

3.2.3. *Substitution by NH-derivatives.* Nucleophilic nitrogen-containing molecules, such as secondary amines, amides or NH-heterocyclic compounds, may be employed in the replacement of Mannich base amino groups. The reaction has been exploited with the aim of producing polymeric products from bis-Mannich bases and bis-amines.[14,63,65] Polycondensation with bifunctional N-derivatives is better than direct polyaminomethylation of a Mannich substrate.

N-Alkylation requires careful selection of experimental conditions. For instance, in the reaction of aryl ketobases with aminoguanidine,[339] the expected exchange product **138** is formed at pH 5–6 whereas hydrazone derivatives **137** or N-heterocyclic compounds **139** are formed under slightly different conditions.

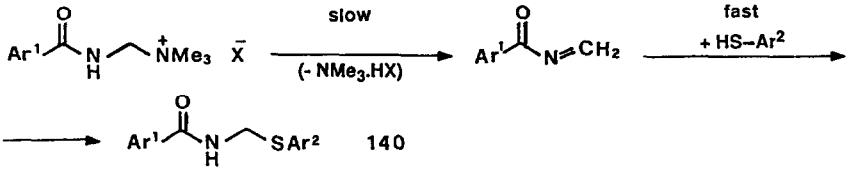


137 138 139

As far as the mechanism of amino group substitution is concerned, an elimination–addition is proposed for the reaction of β-aminoketones with uracils and a four-centered transition state for the same reaction of indole Mannich bases.[340]

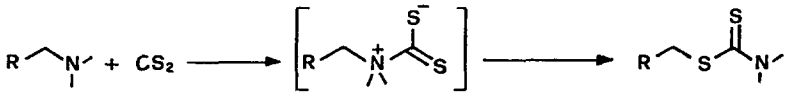
3.2.4. *Substitution by SH-, PH- and AsH-derivatives.* The substitution of Mannich base amino groups by S-derivatives has been investigated due to its pharmacological relevance.[7] This reaction has also been applied to the synthesis of sulfur-containing polymers starting from bis-Mannich bases and bis-thiols.[14]

Some comments on the mechanism for the reaction of amidic Mannich bases with thiols are noted. It has been established[341] that such bases react at neutral or basic pH only, with concomitant formation of the deaminomethylated product. In contrast, the corresponding quaternary ammonium salts give satisfactory results through a mechanism similar to that shown by β-aminoketones.



140

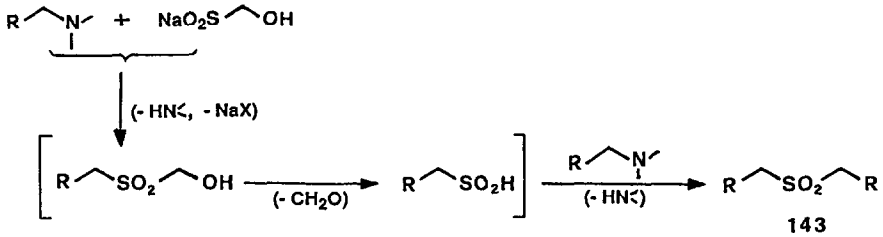
Dithiocarbamic acid esters **142** can also be obtained from Mannich bases and dithiocarbamic acids by insertion of CS_2 between the methylene and the amino group of various types of Mannich base. In this case, electrophilic attack by CS_2 on N atom should take place with formation of the adduct **141**, followed by an intramolecular rearrangement.[342]



141 **142**

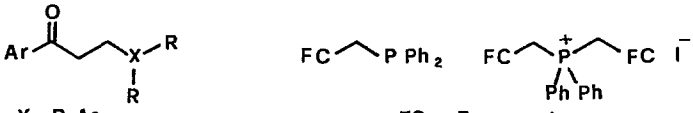
With *para*-aminomethyl-phenols, the participation of an intermediate *para*-methylene-quinone has been suggested.[343] The insertion of CS_2 has been achieved successfully on 2,6-dialkyl-phenols simultaneously with Mannich synthesis.[334]

The reaction with sulfinic acids, giving sulfones, has also been performed. An interesting synthesis of symmetric dialkyl sulfones **143** has been carried out using formaldehyde sulfoxylate.[344]



143

Mono- or disubstituted phosphines (or arsines) react with ketonic Mannich bases[328] giving products **144**. Similarly, Mannich base methiodides of ferrocene give the products **145**. Phosphonium salts **146** are also produced.[345]

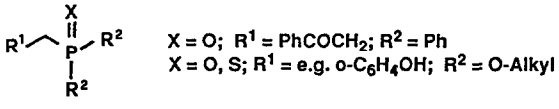


X = P, As
R = Cyclohexyl
144

FC = Ferrocenyl
145 **146**

Further examples of this substitution reaction are reported in a recent review paper on Mannich bases in phosphine chemistry.[15]

Analogous syntheses of derivatives of phosphine oxides[346] and dialkyl phosphites (**147**)[347,348] have been reported.

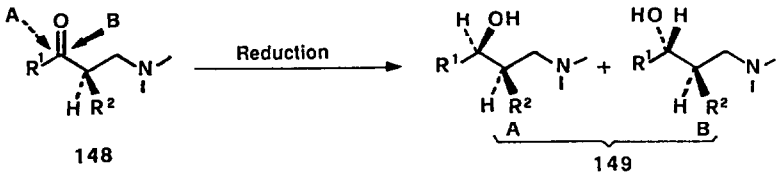


X = O; R^1 = $PhCOCH_2$; R^2 = Ph
X = O, S; R^1 = e.g. o-C_6H_4OH; R^2 = O-Alkyl

147

3.3. *Reduction and organometallic addition*

3.3.1. *Reduction.* Apart from hydrogenolysis of the aminomethyl group, described in Section 3.2.1, reduction of Mannich bases can involve the carbonyl group. This may be associated with a stereoselective reaction when a chiral center is present in the molecule (**148** → **149**, Scheme 10).[19]



Scheme 10.

The stereochemical course of the reduction of acyclic (**148**), homocyclic (**150**, **151**) and heterocyclic (**152**) β-aminoketones (Table 6) is generally in agreement with previous considerations[19] and confirms that acyclic aryl-ketobases **148** (R^1 = aryl) give predominantly aminoalcohol **149A**. The isomer **149B** may become predominant, although to a small extent, when R^1 is CH_3 or Ar—CH=CH—. Reduction of aminomethyl-tetralones **150** affords mainly the aminoalcohol B.

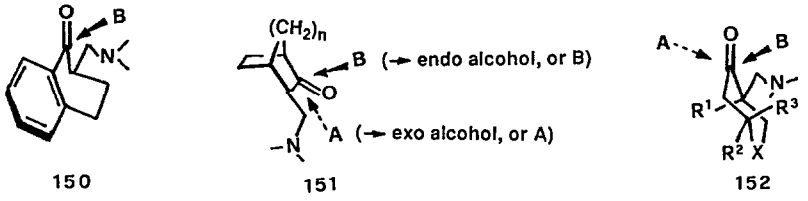


Table 6 - Stereoselective reduction of β-aminoketones.

β-Aminoketone R^1, R^2, Aminogroup or R^1 - R^3, Aminogroup		Reducing reagent [a]	Aminoalcohols ratio (A/B)	References
148	Me, Ph, Dimethylamino	LAH	40/60	349
	Ar-CH=CH-, C_5H_{11}, Dimethylamino	SBH	B predominant	350
	Ar, C_{1-3}Alkyl (or Ph), Piperidino (or Azacycloheptane)	LAH	A predominant	351, 352
150	-, -, N-Arylpiperazino	SBH	B predominant	353
151 (n = 1)	-, -, Dimethylamino (or Piperidino, Diisopropylamino)	LAH, SBH,...	12/88 - 42/58	125
151 (n = 2)	-, -, Dimethylamino	LAH, SBH, ...	59/41 - 64/36	125
152 (X = O)	H, Me, Me, Dimethylamino	Li/NH_3	2/98	354
		SBH	65/35	354
152 (X = S)	H (or Me), H, H, Dimethylamino	LAH	22/78	355
		AlP	71/29	355
	Me, H, Me, Dimethylamino	LAH	A predominant	355
		AlP	B predominant	355

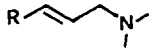
[a] Lithium Aluminum Hydride (LAH), Sodium Borohydride (SBH), Aluminum Isopropoxide (AlP).

Oxa- and thia-cyclohexanone derivatives **152** behave as follows (see pp. 611, 628, 633 in ref. 19): (i), in hydride reductions, the general rule of predominant B attack is always obeyed, provided the axial substituent R^3 is H; (ii), in aluminum isopropoxide reductions (Meerwein–Pondorf) the opposite direction of attack with respect to hydrides is preferred.

With aminomethyl-norbornanones **151** ($n = 1$) the prevailing attack takes place from the *exo* direction. However, the nature of the reducing agent as well as the type of amino group (particularly its steric hindrance) may affect the reaction course and reduce any selectivity. In Mannich bases of bicyclo/2.2.2/octan-2-one (**151**, $n = 2$) the stereoselectivity is inverted, and the *exo* aminoalcohol is predominantly produced.

An interesting example of solvent influence on reduction stereochemistry is offered by sodium borohydride reduction of conformers **77** (Section 2.4.1). In conformer **77b** the hydride attack occurs from the side of oxygenated ring, regardless the solvent employed, as expected on the basis of lower steric hindrance. On the other hand, with **77a** the predominant attack is influenced by the solvent. Attack occurs from the side of N-ring in water/dioxane and from the opposite side in methanol.[240]

Reduction of acetylenic Mannich bases displays several interesting aspects. Thus, the triple bond can be partially hydrogenated with diisobutyl-aluminum hydride, giving E-allylamines **153**. This reagent gives very good stereoselectivity, the mechanism of which has been investigated.[356]



153

R = Ph, Cyclohexenyl

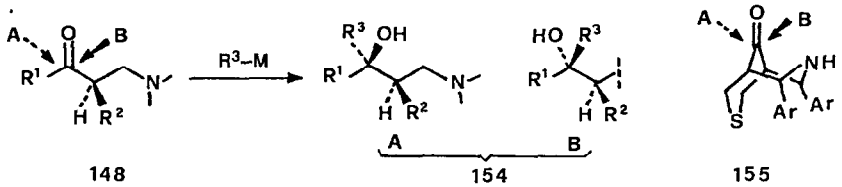
Selective hydrogenations of the heterocyclic ring of various Mannich bases have also been reported. The stereochemistry of indole[357] and tetrahydrocarbazole[358] derivatives has been studied.

3.3.2. *Organometallic addition reactions.* Organometallic addition to ketobases (Scheme 11) has many affinities with reduction and similar stereochemical features are present when chiral ketobases of the type **148**, **151**, **152** (Section 3.3.1) and **155** are employed. Diastereoisomeric products (**154**) are formed.

The most frequently employed reagents, organomagnesiums and organolithiums are discussed only as far as their stereochemical behaviour is concerned. The literature also reports on the Reformatsky reagent (zinc and α-halo-carboxyesters)[359,360] which allows the synthesis of derivatives **154**, having R^3 = CXY—COOAlkyl (see below).

Recent papers on the organometallic addition to Mannich bases report stereochemical results (Table 7) which are in agreement with the general considerations of ref. 19. Cyclic ketones **152** (X = CH_2, O, S) preferably undergo A attack, regardless of the substituent position, the type of amino group and the homo- or heterocyclic ring. The only exceptions are lithium-acetylene reagents with dimethylaminomethyl-cyclohexanone.[362] Attack A is also predominant on aza-thia-bicyclononanes **155**.

Mannich bases of norbornanone (**151**, $n = 1$) give mainly the product derived from reaction on the *exo* side (*endo*-alcohol prevailing), although with rather low stereoselectivity.[361]



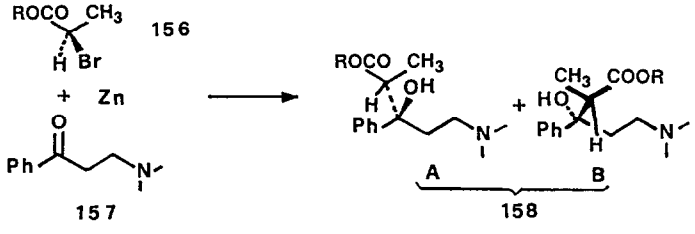
148 **154** **155**

Scheme 11.

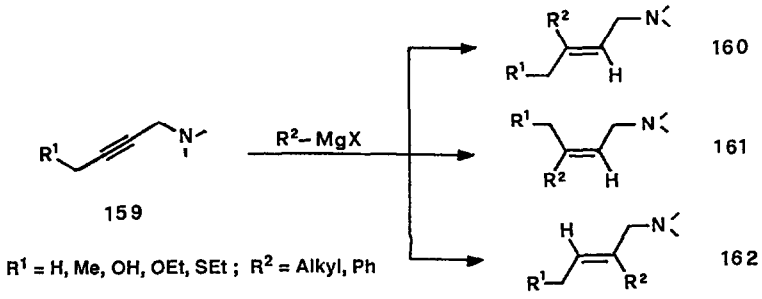
Table 7 - Stereoselective addition of organometal reagents to β-aminoketones

β-Aminoketone R^1 - R^3, Aminogroup		Organometal reagent	Aminoalcohols ratio A/B	References
151 (n = 1)	-, -, -, Dimethylamino (or Diethylamino)	PhMgBr	2/3	361
152 (X = CH_2)	H, H, H, Dimethylamino	Bu-C≡CLi, or Ph-C≡CLi	30/70 - 45/55	362
	H, H, H, Diethylamino	Bu-C≡CLi, or Ph-C≡CLi	55/45 - 60/40	
	H, H, H, Dimethyl- or Diethyl-amino	HC≡C-CH_2MgBr	70/30 - 80/20	
	H, H, H, Dimethylamino	ArMgBr	85/15	1
152 (X = O)	H, Me, Me, Diethylamino (or Piperidino, Morpholino, ...)	PhLi	A predominant	354, 355
152 (X = S)	Me, H, H (or Me), Dimethylamino			
and 2ax,5ax-Dimethyl-3eq-dimethylaminomethyl--tetrahydrothiapyran-4-one				
155		RMgX (R = Me, Ph)	only A	241
157	-, -, -, Dimethylamino (or Piperidino, Morpholino)	156 (R = Me, Ph)	23/77 - 33/67	360

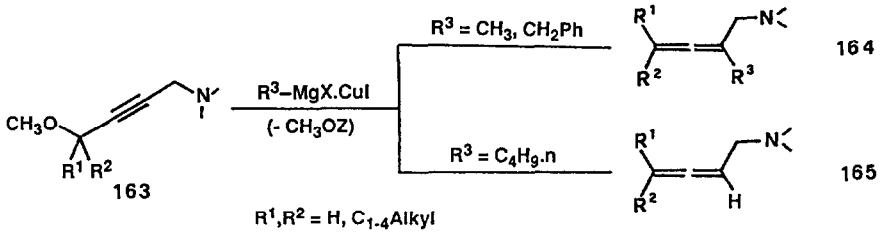
Table 7 lists reactions carried out with chiral organometallics derived from α-bromo esters **156** and zinc (Reformatsky reaction). This produces diastereoisomeric hydroxy-aminoesters **158** from achiral β-aminopropiophenones **157**. The mechanism has been carefully investigated assuming the presence of O-metal bonding in the reagent: the stereochemical results with B diastereomer prevailing have been interpreted on the basis of competing cyclic and open chain transition states.[360]



Acetylenic Mannich bases also give interesting reactions with organometallics which involve problems of regioselectivity and stereoselectivity. Allylamines **160** are the most frequently obtained from the Mannich bases **159**, through *anti* addition of the reagent and R^2 attack at the unsaturated C atom farthest away from aminomethyl group. The allylamines **161** and **162** are byproducts of the reaction.[146,363,364] The compounds **162** have been reported as the main product when the reaction is carried out with allylmagnesium reagents.[365,366]

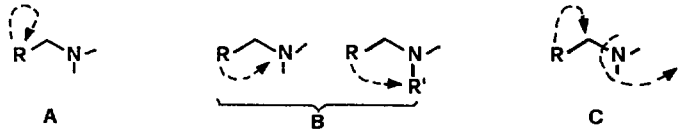


On the other hand, allene derivatives are formed from **159** when R^1 = Alkyl—X—CH_2— (X = O, S).[363,364] Elimination of the methoxyl group is the main reaction of Mannich bases **163** with Grignard reagents. The mechanism of this latter reaction has been investigated:[367] the determining influence of experimental conditions and steric factors on the amounts of the products **164** or **165**, given by Grignard addition or reduction has been stressed.



3.4. *Cyclization*

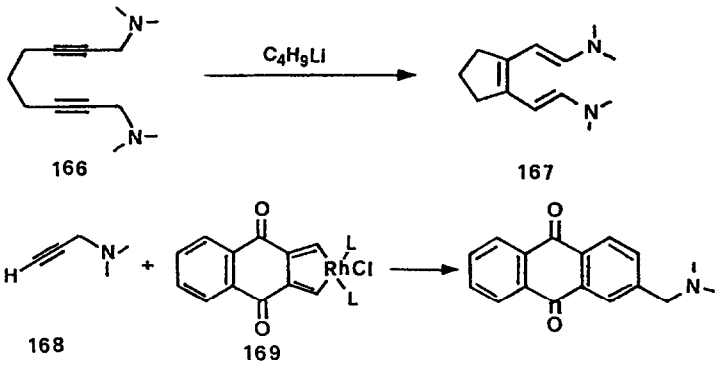
A remarkable number of cyclization reactions may take place with Mannich bases. The following types of ring closure have been reported in the literature.



(i) Reactions involving R group only (A) or the linking together of the R and amine groups (B) of the Mannich base without cleavage of CH_2–N bond (Section 3.4.1);

(ii) reactions involving ring closure at CH_2–N methylene group with elimination of amine (C) (Section 3.4.2).

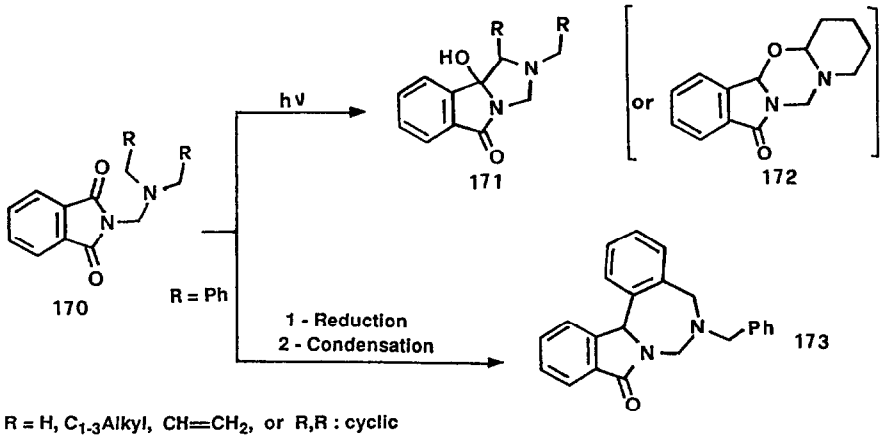
3.4.1. *Cyclization without amine elimination.* Most of the cyclization reactions that follow scheme A are based on classical methods of heterocyclic chemistry yielding heterocyclic compounds such as pyridine or hydropyridine derivatives,[368,369] indoles[370] or hydantoins.[371] Homocyclic products can also be prepared from acetylenic Mannich bases by reaction of the triple bond of mono- (**168**) or bis-propargylamines (**166**).



The reaction giving the cyclopentene derivative **167** strongly depends upon the amine nature of starting Mannich base **166**. The product is almost instantaneously formed with the dimethylamino derivative, whereas the diethylamino- or pyrrolidino-derivatives **166** do not react.[372] An aromatic ring is afforded by the Mannich base **168** by its reaction with rhodacyclopentadien-c-complexes **169** leading to anthraquinone derivatives.[373]

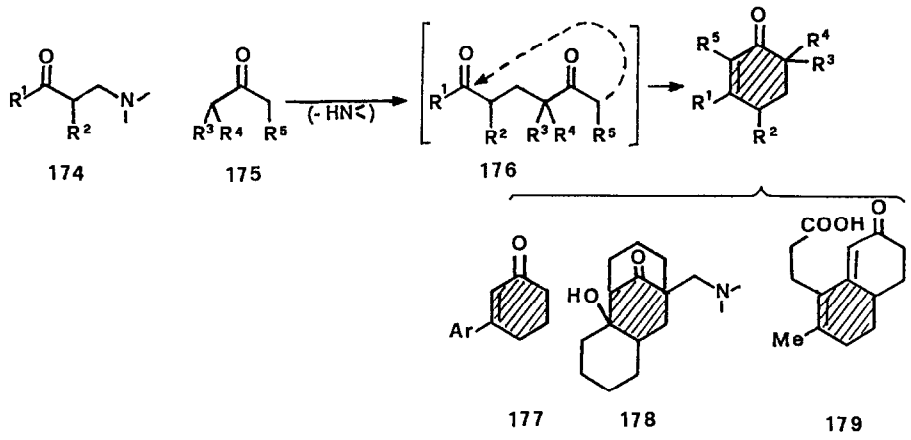
Several interesting examples of cyclization reactions following scheme B are reported in the literature. Thus, tertiary Mannich bases having a halogen atom in position 4 with respect to the amino group give heterocyclic quaternary salts;[134,374] NH-styryl ketobases afford piperidino derivatives.[375]

Phthalimide Mannich bases **170** and analogous cyclic imides have been submitted to photochemical reactions and the mechanism, as well as the stereochemistry, has been investigated.[376-378] The main reaction is bond formation between carbonyl and α-C atom of the substituent linked to the amino group. This produces the imidazoline derivative **171** in more or less consistent yield, but in some cases the reaction gives complex mixtures of products. The piperidino Mannich base **170** behaves differently,[376] as a C–O bond is formed, thus affording the perhydrooxazine derivative **172**.



Benzodiazepines (**173**) can be prepared from Mannich bases **170** by reduction with aluminum followed by condensation with sulfuric acid.[379]

3.4.2. *Cyclization with amine elimination.* Among homocyclic compounds the diene synthesis of spiro/5.5/-undeca-1,4,7-trienones, starting from phenolic Mannich bases and butadiene,[380] which occurs through an intermediate *para*-methylene-quinone is of interest. β-Aminoketones (**174**) are again the most studied and may give homocyclic as well as heterocyclic compounds. The former



Scheme 12.

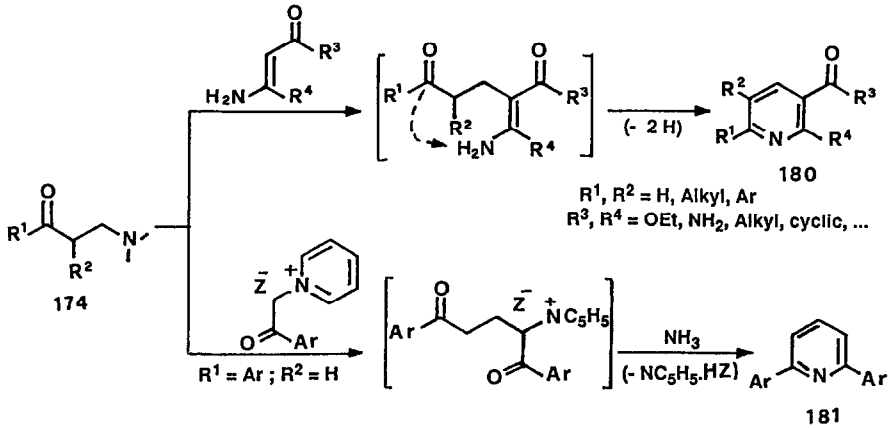
type of products derive from reactions such as that shown in Scheme 12, although different reaction steps may also be followed.

The cyclizing reagent **175** is usually a dialkylketone and products **177–179** are obtained (the hatching indicates the parts of the molecule which correspond). When **175** is an acetoacetic ester (R^4 = COOEt), a decarboxylation also occurs and **177** is formed.[381] When reagent **175** is another molecule of the starting ketobase, then the reaction gives product **178**.[382]

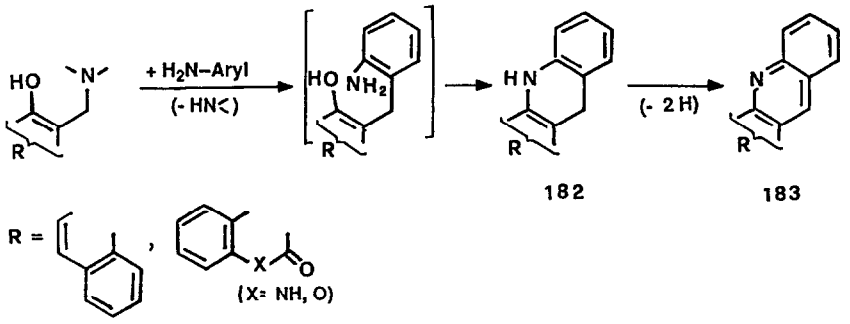
The Mannich base of acetone (**174**, R^1 = Me, R^2 = H) and 1,3-cyclohexanedione follow a slightly more complex reaction path.[383] In this case the intermediate species **176** ($R^1 = CH_3$; R^2,R^4 = H; $R^3 = CH_2CH_2COCH_3$; $R^5 = CH_2CH_2COOH$), which is considered to derive from dialkylation of position 2 of diketone by two molecules of the starting Mannich base, followed by hydrolytic ring opening at the CO–C(2) bond, leads to the final homobicyclic product **179**.

Six-membered heterocyclic products are mainly represented by compounds containing the pyridine ring (Scheme 13). Some of them derive from β-aminoketones **174** and enaminones, which give keto-pyridines **180** together with variable amounts of the corresponding dihydro-pyridines.[384,385]

A detailed review[20] on the synthesis of pyridines reports on the reaction of keto-pyridinium salts



Scheme 13.

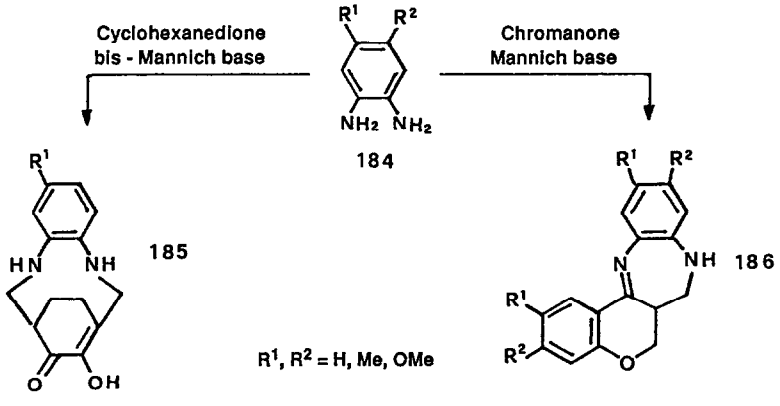


Scheme 14.

with Mannich bases **174** in order to obtain, in the presence of NH_3, a series of derivatives **181**. The products include some poly-pyridines which are used as complexing agents of heavy metals. The reaction involves an intermediate diketone which reacts with ammonia to give the final pyridine derivative.

In a similar manner, N-heterocyclic products are obtained from phenolic Mannich bases,[386] hydroxy-quinolones or hydroxy-coumarins[335] (Scheme 14). Dihydrophenazines, or similar derivatives **182**, are similarly formed and can be dehydrogenated in good yields, by common oxidation agents, to the corresponding aromatic derivatives **183**. The presence in the reaction mixture of reducible species may also lead directly to derivatives **183** as the predominant products.

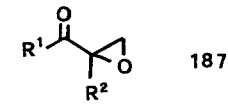
Macrocyclic derivatives may also be obtained from mono- or bis-Mannich bases. Thus, *ortho*-phenylendiamines **184**, in the presence of bis-Mannich bases of cyclohexandione, give a double substitution reaction leading to macrocycles **185**, instead of the expected condensation with the carbonyl groups.[387] *Ortho*-phenylendiamines can also afford seven-membered cyclic compounds (e.g. **186**) by condensation of chromanone with Mannich bases.[388]



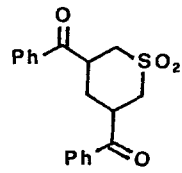
A few papers have been published on O- and S-cyclic derivatives obtainable from Mannich bases. An interesting synthesis of the epoxide ring has been reported[389] to occur by the deamination of methiodides of Mannich bases in the presence of hydrogen peroxide: acyl-epoxides **187** are thus prepared in good yields.

The tetrahydropyranone nucleus has been inserted into the androsterone molecule[26] and a large series of dihydropyran derivatives, mainly formed by dimerization of vinyl-ketones, has been

prepared.[386,390-392] Cyclic sulfones such as **188** can be obtained by reaction of sodium hydroxymethane sulfinate, $HOCH_2SO_2Na$, with the Mannich base of 1,5-diphenyl-pentandione.[393]



187

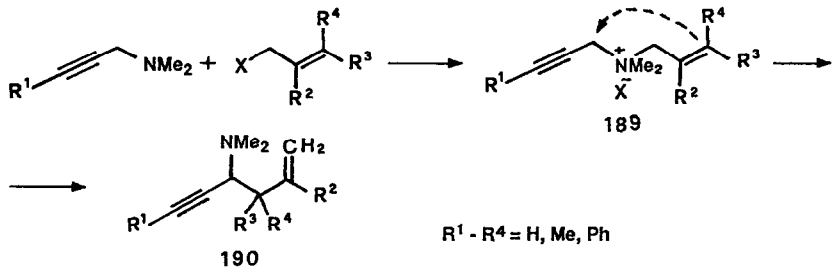


188

3.5. *Miscellaneous reactions*

This section deals with less common reactions given by particular functional groups present in some Mannich bases. In few cases the aminomethyl group is involved in reactions other than those described in preceding Sections.

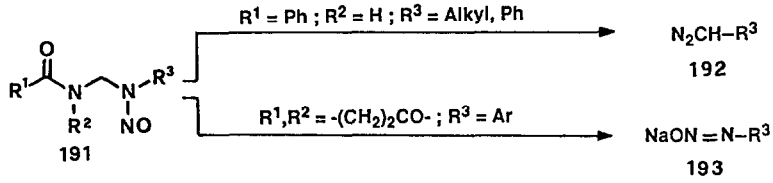
N-Alkylation. An interesting example of base-catalysed rearrangement is given by allylic ammonium salts **189**, obtained by N-alkylation of acetylenic Mannich bases with allyl halides.[394] In the presence of sodium hydride, the compounds **189** yield a wide range of 3-amino-5-hexen-1-yne derivatives **190**.



189

190

Acylation. Hydrogen atoms of Mannich bases, particularly those bonded to N in secondary bases, can be substituted by acyl groups. N-nitroso derivatives (**191**) display interesting properties related to the chemistry of azo-compounds, as they decompose in alkaline medium giving diazoalkanes **192**. The corresponding succinimide derivatives give sodium diazotates **193**.[395]



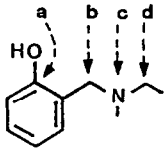
Oxidation and thionation. Among Mannich bases, aminomethyl-phenols have been treated with oxidizing agents. The reaction involves different positions (a–d) of the molecule depending on the reagent employed. Thus,

(a) the aromatic ring of hydroquinone derivatives can be oxidized by N-oxides with formation of aminomethyl-*para*-quinones,[396]

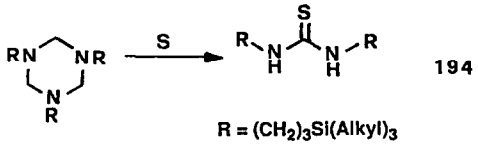
(b) chromic anhydride or mercuric oxide oxidize the methylene group to aldehyde producing *ortho*- and *para*-hydroxy-benzaldehydes;[397,398]

(c) hydrogen peroxide in methanol, or HgO, give the corresponding N-oxides in good yields.[399,400] In this connection, the rearrangement by thermolysis of N-oxides of acetylenic Mannich bases leading to allene derivatives[401] is to be mentioned;

(d) with disodium mercuric EDTA, the methylene group in position 2 of cyclic amines, such as piperidine, is oxidized to the corresponding lactam.[402]



The thionation reaction has been carried out on hexahydrotriazines and produces ring opening with formation of thiourea derivatives **194**.[403]



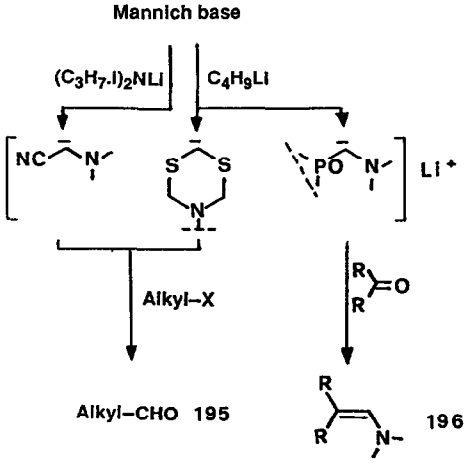
194

$R = (CH_2)_3Si(Alkyl)_3$

Metallation and complex formation. Metallation of Mannich bases has usually been performed with lithium reagents, such as butyl-lithium or lithium-diisopropylamide (Scheme 15). The metal is preferentially linked to the CH_2–N methylene group in Mannich bases derived from hydrogen cyanide,[404] phosphine oxides and phosphorous esters,[405,406] whereas in 3,5-dithia-piperidines the preferred position of metallation is at C(4).[407] In aminoalkyl-ferrocenes the five-membered ring is involved in metallation.[408]

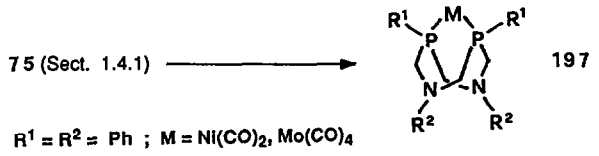
The aim of metallation is usually to attach an alkyl group to the Mannich base by reaction with halides, epoxides[404,407] or other alkylating reagents such as carbonyl derivatives.[405,406] Under proper conditions, aldehydes (**195**), ketones or enamines (**196**) can be prepared in this way.

The possibility of complex formation by Mannich bases has been widely investigated in connection with potential technological applications. Besides the substrate, the large choice of amines (see, e.g., amines **5**–**7**, Section 2.1.2.) allows the preparation of a large variety of suitably tailored compounds,[127,409,410] including macromolecular derivatives such as linear[64] and cross-linked[411] polymers.

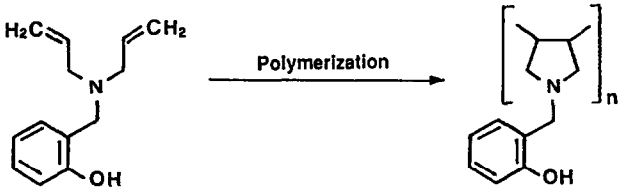


Scheme 15.

However, aminomethyl-phenols and, in particular, the 8-hydroxy-quinoline derivatives, which are very prone to complex formation, are certainly the most studied.[92,127,412–414] P-Mannich bases have also provided the object of many investigations (refs. in 15). A significant example (**197**)[250] of complex formation by this class of bases is reported here.



Polymerization. Mannich bases have been submitted to both step polymerization, through the substitution reactions described in Section 3.2, and to chain polyaddition. A wide number of



polymerizations have been reported in a review[14] recently devoted exclusively to this aspect of Mannich base reactivity. The interesting polymerization of diallylamino Mannich bases **198** leading to poly-pyrrolidines **199**[195] is worth mentioning.

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