Aminomethylated Pyrroles: Casting a Spotlight

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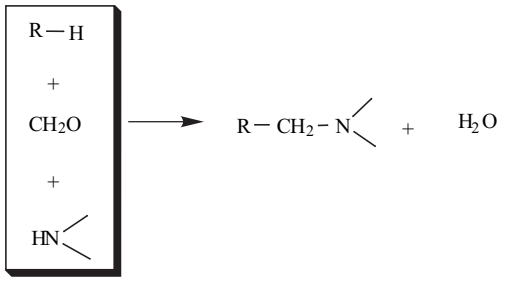
Abstract: The chemistry and applications of aminomethylated pyrroles are extensively reported by the present review. An overall account of the synthetic approaches to pyrrole Mannich bases is offered, with an emphasis on topics such as regioselectivity (α-aminomethylation over β-aminomethylation, *C*-Mannich reaction *versus* *N*-Mannich reaction), mono- and bis-aminomethylation, influence of substituents in the pyrrole ring, chemoselectivity, or the special mention of *N*-*tert*-butoxycarbonyl-2-[(*tert*-butyldimethylsilyl)oxy]pyrrole as a substrate. The scope and limitations of the aldehyde component and amine reagents in the Mannich reaction of pyrroles have been explored, the use of preformed aminomethylation reagents and catalysts with the view to improve yields or stereoselectivity has been surveyed, and the mechanism and by-products arising from the aminomethylation of pyrroles have been outlined. Pyrrole Mannich bases have been portrayed as excellent *H*-, *C*-, *N*-, *O*-, *S*-, and *P*-alkylating agents as a direct consequence of their ability to replace the easily leaving dialkylamino group with other nucleophiles, and the involvment in ring closure processes leading to porphyrins, or other miscellaneous reactions have also been included in the broad coverage of these compounds' reactivity. A particular attention has been paid to the contribution of pyrrole Mannich bases to drug discovery and advances in medicinal chemistry.

Keywords: Pyrrole, aminomethylation, Mannich bases, alkylation, amine displacement, ring closure, biological activity.

1. INTRODUCTION

Aminomethylations (also known as Mannich reactions [1]) are three-component condensations in which the substrate R-H, a compound containing an acidic hydrogen atom, reacts with formaldehyde and an amine to produce a derivative of the substrate, usually referred to as a Mannich base, in which the nitrogen atom of the amine is linked to the substrate through a methylene group (Scheme **1**). The substrates R-H employed in Mannich reactions may belong



Scheme 1.

to various structurally different classes of compounds, but they all share a high degree of nucleophilicity as a common feature. As the acidic hydrogen atom of the substrate could be located at a carbon atom or a heteroatom such as nitrogen, sulfur, oxygen, phosphorus, the aminomethylation may lead to the corresponding *C*-, *N*-, *S*-, *O*- and *P*-Mannich bases, respectively. Other aldehydes besides formaldehyde have been involved in Mannich reactions, which are more generally defined in this case as aminoalkylations. The amine reagent is not restricted to primary or secondary aliphatic or aromatic amines, but also comprises ammonia and its derivatives having at least one hydrogen atom, such as hydrazines or hydroxylamines, or even NH-heterocycles.

Pyrrole is a π-excessive monocyclic five-membered heterocycle with one heteroatom that exhibits a high tendency to undergo electrophilic substitution preferentially at the 2 (or α) position as a general feature of its chemistry. Pyrrole is a suitable substrate in Mannich reactions, reacting with the electrophilic species either preformed or generated *in situ* from the aldehyde and amine component [2] to give aminomethylated pyrroles useful as intermediates in organic synthesis or in the preparation of materials or biologically active compounds.

As the most recent extensive review on the synthesis and chemistry of Mannich bases goes back to the early '90s, and no particular attention has been given to pyrrole, it was considered interesting to review the ring aminomethylation of this specific five-membered heterocycle and highlight the recent advances regarding the reactions and applications of Mannich bases derived from pyrroles.

2. SYNTHESIS OF PYRROLE MANNICH BASES

The aminomethylation of a pyrrole derivative was first described [3] in 1925 as a part of Hans Fischer's ongoing research upon the pyrrole-containing biological pigments haemoglobin, chlorophyll and bilirubin, whereas the aminomethylation of pyrrole itself was investigated 20 years later in a study [4] aiming to define the generality of Mannich reaction in the heterocyclic series.

Pyrrole's electrophilic reactions generally lead to 2-substitution, whereas electrophilic substitutions at the nitrogen atom usually occur only under strong basic conditions, when the ambident anion which is generated may react either at the α carbon atom, the nitrogen atom, or both, depending on the nature of the reactants and the

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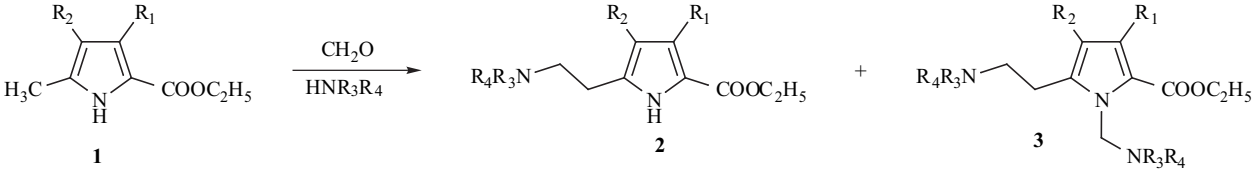
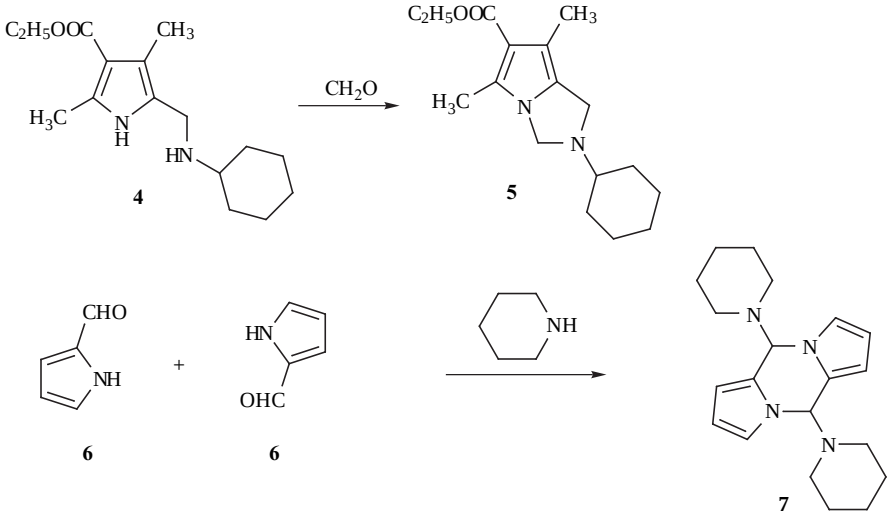


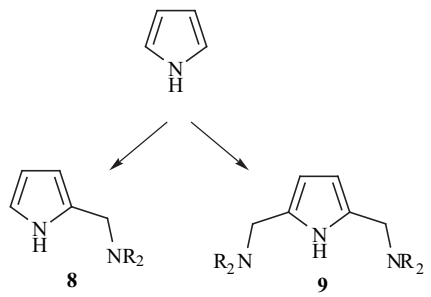
Scheme 2.



Scheme 3.

reaction conditions. Literature reports extensively show that aminomethylation of pyrroles takes place preferentially at a free α position; when both α positions are substituted, aminomethylation is directed to a free β position [5]. Nevertheless, a sterically bulkier *N*-substituent, such as triisopropylsilyl, can divert aminomethylations to a β position of the pyrrole ring, even if the α positions are unsubstituted [6]. *N*-Aminomethylations seem to be the least favored, even if position 1 is the only unsubstituted in the pyrrole ring, as proven by the Mannich reaction of 3,4,5-trisubstituted 2-methylpyrroles (**1**) which afforded more readily 2-dialkylaminoethylpyrroles (**2**) *via* side-chain aminomethylation [7] (Scheme **2**), probably through the corresponding α-methylenepyrroline as intermediate [8]; further aminomethylation to *C*,*N*-bis-Mannich bases (**3**) occurred only when the experiments were carried out in the presence of light. Even an attempt to *N*-aminomethylate pyrrole (as the related *in situ*-generated pyrrolyl anion) with Eschenmoser's salt failed [9]. However, fused heterocycles (**5**), obtained through intramolecular *N*-aminomethylation of the polyfunctional pyrrole (**4**) acting both as a substrate and as amine reagent [10], and (**7**), resulted from the intermolecular *N*-aminomethylation of two molecules of pyrrole-2-carboxaldehyde (**6**) acting in the same time as a substrate and as aldehyde reagent [11], are examples of pyrrole *N*-Mannich bases (Scheme **3**). Furthermore, the reported *N*-aminomethylation of 2,5-dimethylpyrrole [12] was later shown to had actually occurred at position β [5]. Recently, two papers have claimed the regioselective *N*-aminomethylation of 3-(2-pyrrolyl)-1*H*-indazole [13] and 2-(2-pyrrolyl)-1*H*-benzimidazole [14]. Taking into account that both these pyrrole derivatives have a free α position in the pyrrole ring, and that the *N*-1 atom in indazoles and benzimidazoles is well known for its reactivity towards aminomethylating species, it is difficult to conceive that the Mannich reaction occurred at the pyrrole nitrogen atom in the two reported cases. The direct aminomethylation does not seem to be the first choice for the synthesis of pyrrole *N*-Mannich bases, but these compounds may become available using different synthetic approaches [15].

As shown previously, pyrroles exhibit a certain degree of reactivity in the Mannich reaction at all available positions (except for N^1), and, consequently, reports of bis-aminomethylations are not unusual. Pyrrole itself has been reported to produce mono-Mannich bases (**8**) [16, 17] or bis-Mannich bases (**9**) [18, 19] in several papers (Scheme **4**), and even when only the less reactive β positions are free, monoaminomethylations [20, 21] and bis-aminomethylations [22] have been described. In the case of 1-(hetero)aryl-2,5-dimethylpyrrole, it was concluded that mono- or bis-aminomethylation of the investigated pyrroles depends on the nature of the *N*-substituent; the reactivity decreases in the order: *N*-(2-pyrimidinyl- > *N*-(2-pyridyl)- > *N*-phenyl- > *N*-(2-thiazolyl)-2,5-dimethylpyrrole [23], and could be quantitatively assesed through kinetic measure-ments [24]. Acknowledging that mono-aminomethylations occur mainly when the amine component is used in the Mannich reaction



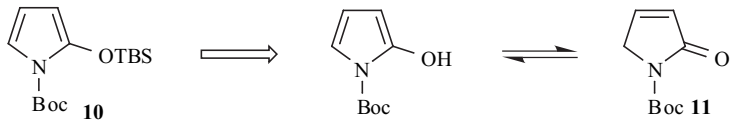
Scheme 4.

as a salt or when the process is conducted under acidic conditions, an attempted explanation argues that the pyrrole mono-Mannich bases produced as salts under these experimental conditions are significantly less nucleophilic than the initial substrate and do not undergo further aminomethylation, whereas the free pyrrole mono-Mannich bases are more nucleophilic than the starting pyrrole and subsequently react with the aminomethylating reagent to produce bis-Mannich bases [25].

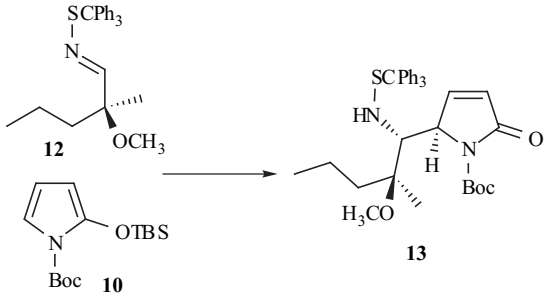
Pyrrole is sufficiently reactive to be aminomethylated under mild reaction condition. *N*-Methylpyrrole condenses readily with formaldehyde and amines to afford the Mannich bases in yields better than the ones recorded for pyrrole itself [26]. 3,4-Dimethylpyrrole [27], 3,4-diethylpyrrole [28, 29], and 2,5-dimethylpyrrole [5] also undergo aminomethylation smoothly to produce Mannich bases in high yields. These data confirm the activation of the pyrrole ring in the Mannich reaction by electron-donating groups irrespective of their position. On the other hand, 1-phenylpyrrole [26], 3,4-diphenylpyrrole [30], and 2,5-diphenylpyrrole [5] tend to react more sluggishly under the same conditions, and this trend becomes more obvious when strongly electron-withdrawing substituents (such as ester functions) deactivate the pyrrole ring in Mannich reactions [31], and require harsher reaction conditions only to provide moderate yields of aminomethylated pyrroles [32]. In the previous examples, electron-donating methyl group(s) counteract to some extent the deactivating effect of the ester function, but even the presence a single ester group (for example, in ethyl pyrrole-1-carboxylate) renders pyrrole aminomethylation unachievable [33]. Furthermore, in the case of diethyl 3-methylpyrrole-2,4-dicarboxylate, when two deactivating ester groups are present, the Mannich base could not be secured by direct aminomethylation [34].

A particular pyrrole substrate in Mannich reactions is *N*-*tert*-butoxycarbonyl-2-[(*tert*-butyldimethylsilyl)oxy]pyrrole (**10**), which can be pictured as a stable derivative of 2-hydroxypyrrole, the enolic form opposed to the keto form (**11**) from which the pyrrole-based silyloxydiene can be prepared (Scheme **5**) [35]. The versatile synthon (**10**) could be exploited in vinylogous Mannich-type addition to aldimines to gain easy access to biologically relevant chiral nitrogen-containing compounds through nucleophilic Lewis acid-assisted reactions at *C*-5 [36]. A pertinent example of this successful strategy is the preparation of the influenza neuraminidase inhibitor (**13**) [37] which comprises the stereoselective condensation of imine (**12**) and *N*-Boc-2-(*tert*-butyldimethylsilyloxy)pyrrole (**10**) as a pivotal step of the synthetic sequence (Scheme **6**). Other pyrrole substrates similar to silyloxypyrrole (**10**) were involved in reactions with preformed aldimines [38], or, in an even more classical approach, with aldehydes and amines [39] to give rise to the corresponding 5-aminoalkyl pyrrolidones.

Formaldehyde, both in the form of formalin or as paraformaldehyde, is the most used aldehyde component in the synthesis of pyrrole Mannich bases. The successful replacement of formaldehyde with dichloromethane for the aminomethylation of several substrates, including pyrrole, has been disclosed [40]. The small number of examples of pyrrole direct Mannich reactions that are based on reactions of aldehydes other than formaldehyde undoubtedly relates to the further reduction in reactivity of the weak electrophilic iminium intermediate species when the methylene group is substituted by an alkyl or aryl residue. Acetaldehyde was the aldehyde reagent of choice in a limited number of cases [41, 42], whereas the failure of benzaldehyde or acetone to react has been reported [43, 44]. Several intramolecular Mannich reactions can also be mentioned as examples of direct aminoalkylation employing aromatic aldehydes [11, 45, 46]. On the other hand, a suitably positioned electron withdrawing substituent would result in an increase in the reactivity of an iminium ion, such as (**15**) arising from aminol ether (**14**) upon treatment with a chlorosilane (Scheme **7**) and allowing the introduction of a methoxy-carbonylmethine unit, formally derived from methyl glyoxalate (**16**), *via* a Mannich reaction [25]. Furthermore, the use of a reactive pyrrole substrate and an appropriate catalyst may trigger aminomethylations even when the aldehyde component is an aliphatic enolisable or an aromatic aldehyde [39], and the use of aldimines can also be considered as an convenient approach [47] for implementing pyrrole aminoalkylations.



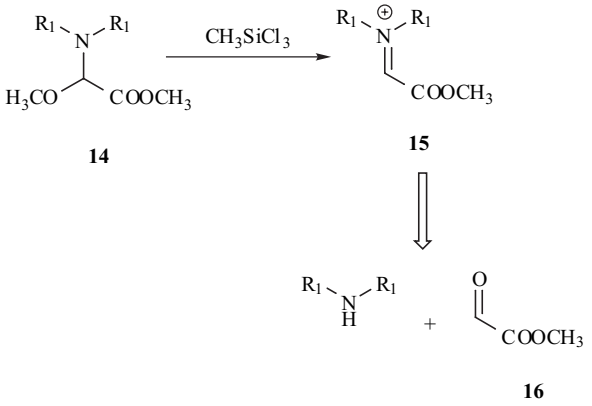
Scheme 5.



Scheme 6.

The amine reagents in the aminomethylation of pyrroles are mostly employed as free bases in the presence of acetic acid or as the easily accesible hydrochlorides, when the pyrrole free Mannich bases and, respectively, the corresponding hydrochlorides are formed. The use of free amines in the absence of any acidic catalyst is seldom described [48-50]. The extensive investigations into the preparation of pyrrole Mannich bases deal predominantly with the formation of tertiary aminomethylation products (**17**) derived from secondary amines, mainly because the use of a primary amine in aminomethylations may lead to a mixture of secondary and tertiary Mannich bases (**18**) and (**19**), respectively (Scheme **8**). Furthermore, even the

formation of a polymeric Mannich base from pyrrole, formaldehyde and methylamine or allylamine under the appropiate reaction conditions has been described [51].



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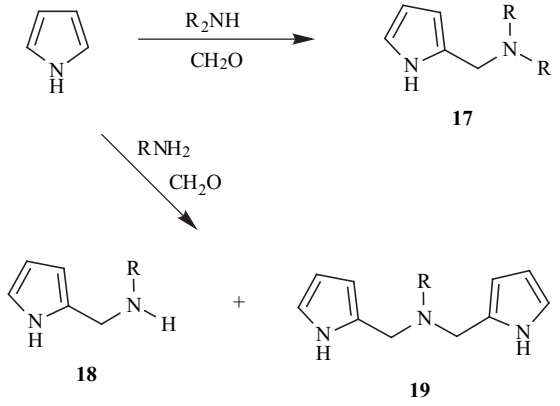
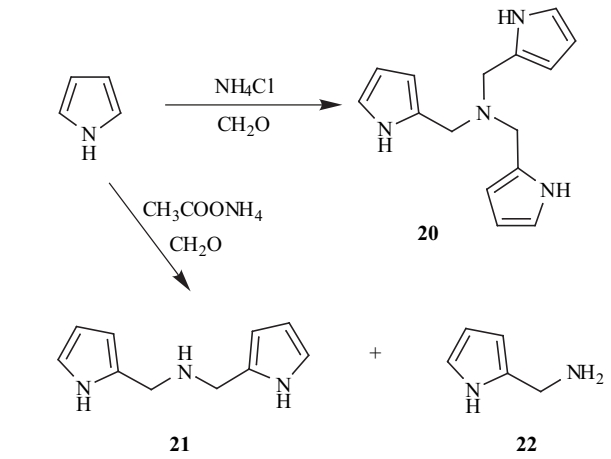


Scheme 8.

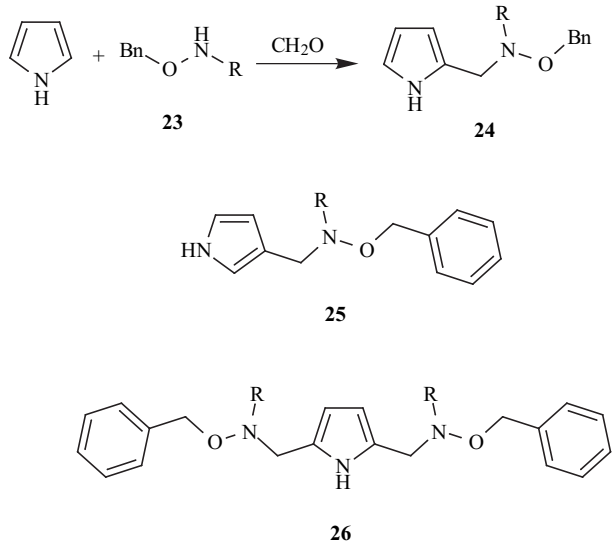
The use of ammonium chloride as a source of amine reagent in the aminomethylation of pyrrole affords the tertiary Mannich base (**20**) in good yield [52], whereas both the secondary Mannich base (**21**) and the primary Mannich base (**22**), albeit in low yield, have been obtained upon the use of ammonium acetate (Scheme **9**) [50]. Other synthetic approaches towards the preparation of pyrrole primary Mannich bases (**22**) are though available [49, 53, 54].

The preparation of secondary Mannich base (**18**) in high yields is often difficult to achieve. In the case of the direct pyrrole aminomethylation with primary alkylamines, the ratio of reactants and the steric factors dictate the relative amount in which the secondary and tertiary Mannich bases (**18**) and (**19**), respectively, are formed [55]. The use of primary amines having a bulky alkyl moiety (isopropyl, *tert*-butyl) at a substrate : amine ratio of 1 : 1 resulted in the exclusive formation of the secondary Mannich base (**18**). Attempts to find an improved method for the sole preparation of compounds (**18**) using bis(alkoxymethyl) alkylamines as preformed aminomethylation reagents were not quite successful, as the method seems to have an aplicability limited only to the use of bulky tertiary amines at very low temperatures [56]. A better approach towards the controlled formation of secondary aminomethylation products (**18**) relies on the transaminomethylation of pyrroles with *N*-alkylaminobenzotriazoles in the presence of a Lewis acid such as $ZnCl_2$ [57].

The use of secondary bifunctional amines such as piperazine in the Mannich reaction of pyrrole has been reported to lead to polymers arising from the bis-aminomethylation of the substrate [51]. Other particular amine reagents in the aminomethylation of pyrroles are the *O*-benzyl hydroxylamine derivatives (**23**) (Scheme **10**). The scope of these secondary hydroxylamines has been explored and shown to lead, *via* an oxyminium ion under the appropriate reaction conditions, mainly to the mono-α-Mannich bases (**24**), although the isomeric mono-β-Mannich bases (**25**) and the bis-aminomethylation products (**26**) could be identified in experiments run at room temperature [43].



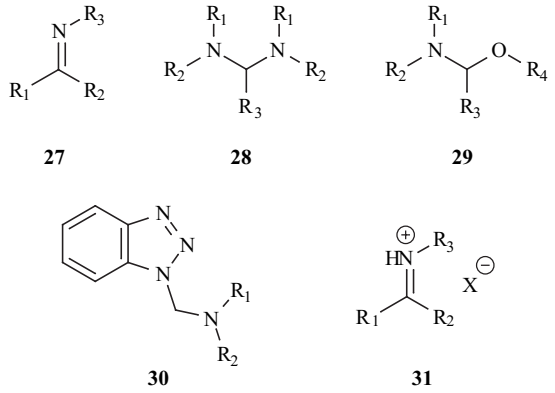
Scheme 9.



Scheme 10.

The limitations of the classical Mannich reaction have led to a search for more convenient synthetic methodologies. The use of preformed aminomethylation reagents (Fig. **1**) has often overcome these limitations, providing in the same time easy access to aminoalkylation reactions otherwise difficult to achieve [58]. Aldimines (**27**) represent a category of such preformed aminoalkylation reagents which have been used in the aminoalkylation of pyrrole substrates [37, 38, 42, 47]. Due to their lower electrophilicity compared to the original aldehyde, aldimines require activation either by a Lewis acid or a Bronsted acid in Mannich reactions which

often undergo with a high stereoselectivity. Aminals (**28**) and *N*,*O*-acetals (**29**) (also known as aminol ethers) illustrate two different classes of preformed aminomethylating reagents which resemble aldimines (**27**) with respect of their electrophilicity, accounting for the lack of reports concerning the non-mediated use of aminals and aminol ethers in the Mannich reaction of pyrroles. The easily accesible benzotriazole aminals (**30**) are a special case of preformed aminoalkylating reagents which enable a straightforward access to both secondary and tertiary pyrrole Mannich bases in the presence of Lewis acids [57]. Otherwise, aminals (**28**) and aminol ethers (**29**) have been widely exploited for the *in situ* generation of a more reactive electrophilic species, namely the iminium salts (**31**). The cleavage of aminals (**28**) with acetyl chloride [59], trimethylsilyl iodide [22], chlorosilanes [25], and sulfur dioxide [60, 61], or the conversion of aminol ethers (**29**) by the latter two reagents, ethereal HCl [56], or other various Lewis acids [62] into iminium salts, and subsequent Mannich reaction with pyrrole substrates represents a valuable alternative synthetic approach to the direct aminomethylation reactions. The typical iminium salt *N*,*N*-dimethyl-methylene-ammonium iodide (Eschenmoser's salt) has also been employed as a preformed aminomethylation agent in the Mannich reaction of pyrroles [6, 63].



27 **28** **29**

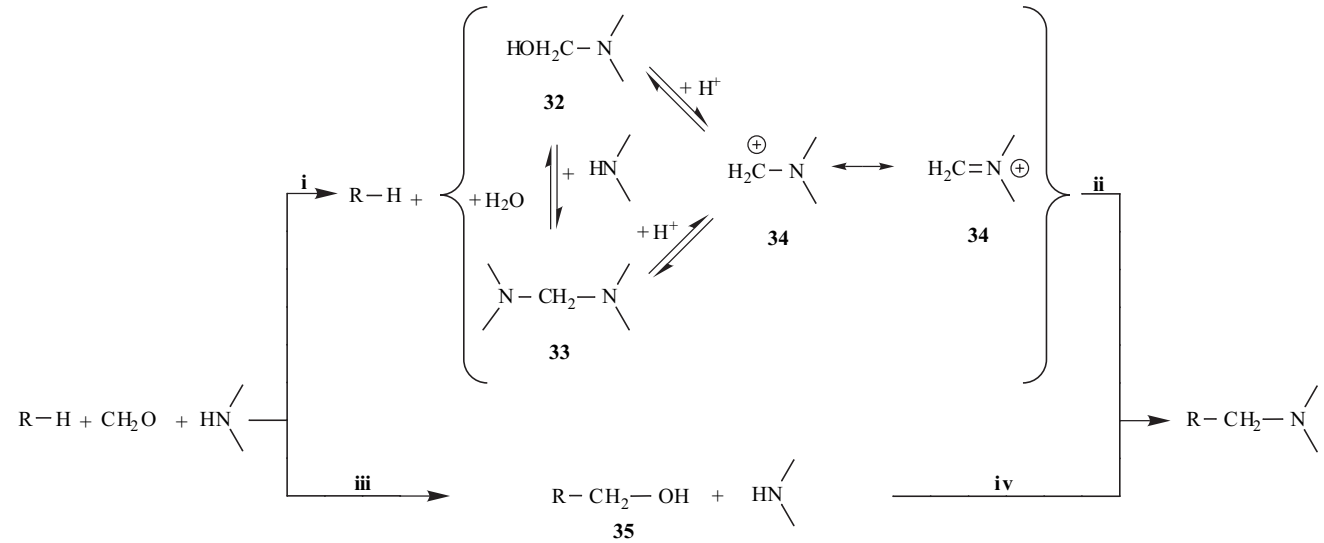
30 **31**

Fig. (1).

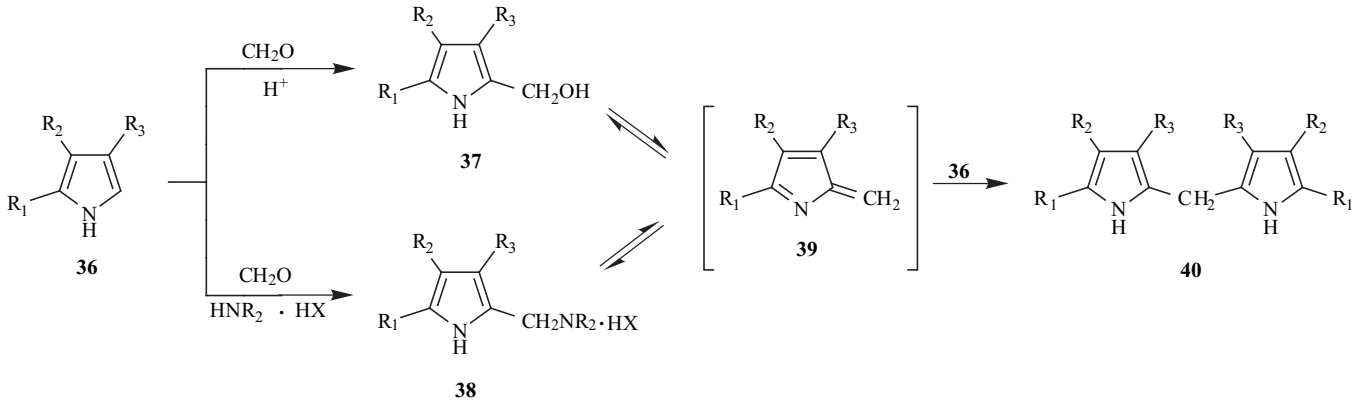
The direct Mannich reaction of pyrroles has been usually conducted in alcoholic solvents (methanol, ethanol) without the exclusion of water. The use of some preformed aminomethylation reagents may require anhydrous aprotic solvents (dichloromethane, chloroform, acetonitrile, nitromethane). The direct condensation usually takes place in the presence of an acidic catalyst, acetic acid being the most employed. A few of the latest approaches towards the aminomethylation of pyrroles have disclosed the use of the Lewis acids such lanthanides triflates as efficient catalysts for the direct Mannich reaction [44], but mostly in connection with the use of the preformed reagents [38, 47].

The mechanism of pyrroles aminomethylation is conform to the general mechanism of the Mannich reaction (Scheme **11**). Upon reacting the substrate, formaldehyde and the amine reagent, the condensation occurs in two steps: first, the amine reacts with formaldehyde to give a metilol derivative (**32**) of the amine in equilibrium with the corresponding aminal (**33**) and the reactive iminium salt (**34**) (step **i**), which then attacks the substrate (step **ii**). This pathway is supported by the well documented use of aminals, aminol ethers, and iminium salts as preformed aminomethylation reagents. Although it offers no experimental proof, a paper even reports the condensation of a metilol derivative of the amine with a pyrrole substrate [64]. A second possible mechanistic route for the aminomethylation of pyrroles (steps **iii** and **iv**), involving first the formation of a metilol derivative (**35**) of the substrate which subsequently reacts with the amine, although less probable, can not be completely excluded, as a successful condensation of a preformed pyrrolemethanol with an amine has been reported [65]. In the particular case of a pyrrole substrate having electron-withdrawing substituents which increase its acidity, the possible formation of *N*-hydroxymethylpyrrole as an intermediate should also be taken into consideration [66].

The formation of symmetric dipyrry1methanes (**40**) as by-products in Mannich reactions on pyrroles has been reported [50, 67]. These products could arise in the presence of acid catalysts either from a 2-(hydroxymethy1)pyrrole (**37**)



Scheme 11.



Scheme 12.

resulted from an initial condensation of the pyrrole substrate (**36**) and formaldehyde, or could be produced through *C*-alkylation of the pyrrole substrate with the Mannich base salt (**38**) priorly formed from the same substrate (Scheme **12**). In both cases, the involvement of an azafulvene-type intermediate (**39**) which condenses with another molecule of pyrrole (**36**) *via* a Michael-type addition can not be disregarded [68].

The ring Mannich reaction of pyrrole substrates appears to be chemoselective, at least with respect to the presence of an acetyl group. A few papers describing the selective ring aminomethylation of 3,5-dimethyl-2-acetylpyrrole [34] and 2,4-dimethyl-3-acetylpyrrole [50] are available. However, the reaction conditions seems to be essential in directing the aminomethylation towards one of the two active sites in methyl pyrryl ketones. Whereas the Mannich reaction in the pyrrole ring of methyl pyrryl ketones takes place under mild reaction conditions, a report [69] presenting the Mannich reaction of 2-acetylpyrrole in boiling isoamyl alcohol claims the reaction product melting at 170-171˚C as the hydrochloride of 2-acetyl-5-dimethyl-aminomethylpyrrole (**41**) (Fig. **2**) based on the not always reliable Ehrlich reaction. However, a compound showing a similar melting point (168-170˚C) and arising from the aminomethylation of the same substrate under identical harsh reaction conditions was assigned [70] the structure of the ketonic Mannich base 3-dimethylamino-1-(2-pyrrolyl)-1-propanone (**42**) which was subsequently proven by means of an amine exchange reaction leading to 3-phenylamino-1-(2-pyrrolyl)propan-1-ones (**43**), a process well documented in the case of ketonic Mannich bases, but reported to a lesser extent as far as pyrrole Mannich bases are concerned. The compound formed through the aminomethylation of 2-acetylpyrrole under the same conditions was finally established by means of NMR spectroscopy to be the ketonic Mannich base (**42**) [71].

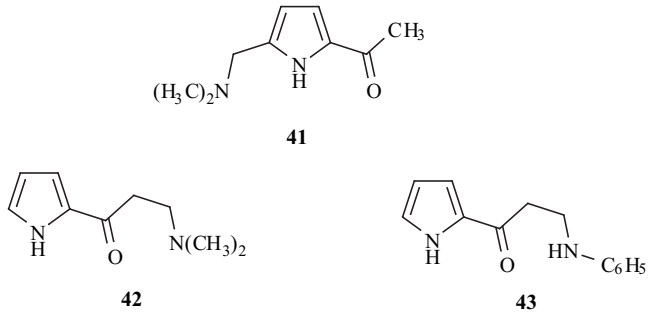
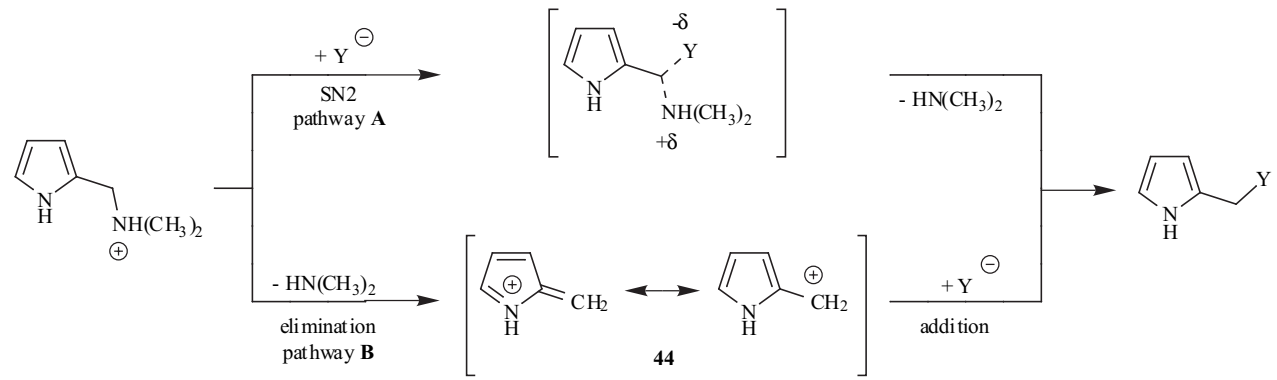


Fig. (2).

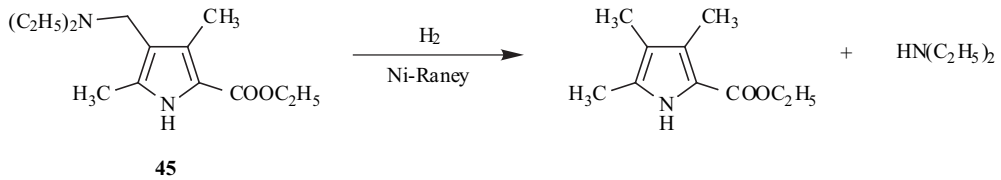
3. REACTIVITY OF PYRROLE MANNICH BASE

3.1. Alkylation with Aminomethyl-Substituted Pyrroles

The main type of reaction Mannich bases of pyrroles could take part in is the substitution of the easily displaceable dialkylamino group by a nucleophile. This most interesting property of Mannich bases, which can also be regarded as an alkylation of the nucleophile with the aminomethylated pyrrole, allows a simple and direct entry to structurally diverse chemical entities. From a mechanistic



Scheme 13.



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Scheme 14.

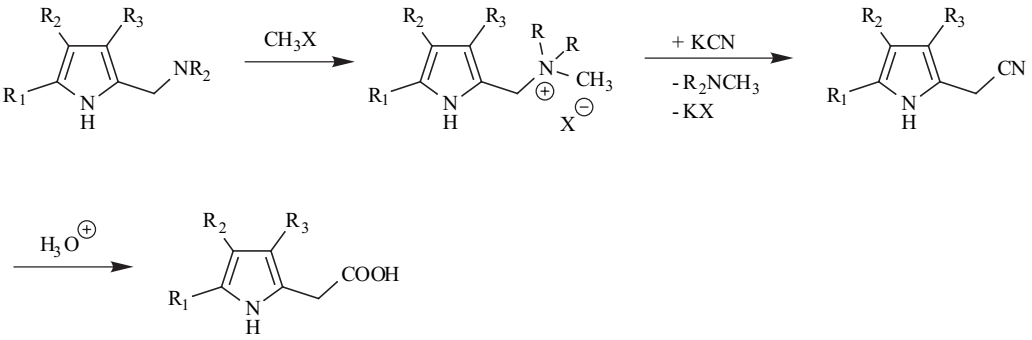
point of view, the substitution of the amino group in a Mannich base could take place either *via* a classical SN2 reaction (pathway **A**), or as a consecutive elimination-addition tandem (pathway **B**) having the hypothetical ambident azafulvenium cation (**44**) as intermediate (Scheme **13**), or as a combination of the two different pathways. Irrespective of the mechanistic pathway, the substitution of the dialkylamino group occurs better with Mannich base hydrochlorides, or Mannich bases methiodides obtained through quaternization with iodomethane or dimethyl sulfate.

H-Alkylation (Hydrogenolysis)

The substitution of the dialkylamino group for a hydrogen atom in a pyrrole Mannich base has been employed as a strategy for the preparation of polyalkylpyrroles *via* the introduction of methyl groups into a pyrrole ring (Scheme **14**), and represented in the past a way to determine the position of aminomethylation by means of comparing the physical properties of the methylpyrrole resulted from the hydrogenolysis of the corresponding Mannich base with those of a pyrrole unequivocally obtained through direct synthesis [5]. Treibs was the first to report the highly efficient catalytic reduction of free pyrrole Mannich bases using elevated hydrogen pressure and moderate temperature [50]; the hydrogenation of both the pyrrole ring and ester or ketone functions have not been observed under these conditions. The reduction of Mannich base (**45**) with zinc and acetic acid could not be accomplished. Milder reaction conditions can be employed for the hydrogenolysis of the Mannich bases methiodides: the treatment of these derivatives of aminomethylated pyrroles with sodium borohydride in ethanol at 50-60˚C afforded smooth access to several intermediates in the synthesis of the natural antifungal antibiotic pyrrolnitrin [32, 72].

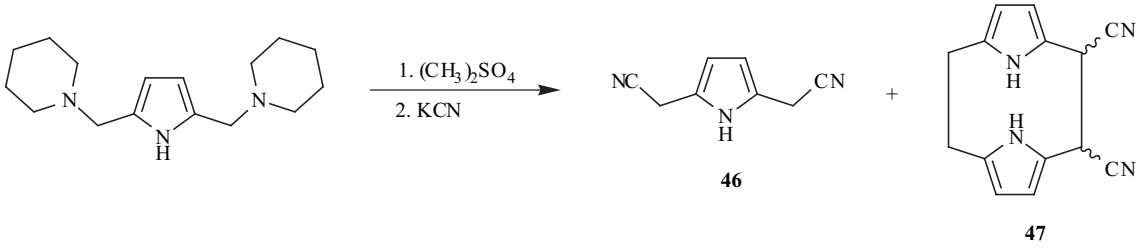
C-Alkylation

C-Alkylation is the most well documented reaction among alkylations with aminomethylated pyrroles, and the substitution of the dialkylamino group with a nitrile moiety as a result of the reaction of a pyrrole Mannich base with an alkaline cyanide is the most encountered type of *C*-alkylation. The process has found an extremely useful application in the multi-step sequence aiming at incorporating an acetic acid side chain (Scheme **15**), for example in the structure of several intermediates [63] required in the synthetic preparation of a common precursor in the biosynthesis of many natural porphyrin-containing pigments - uroporphyrinogen III [6].



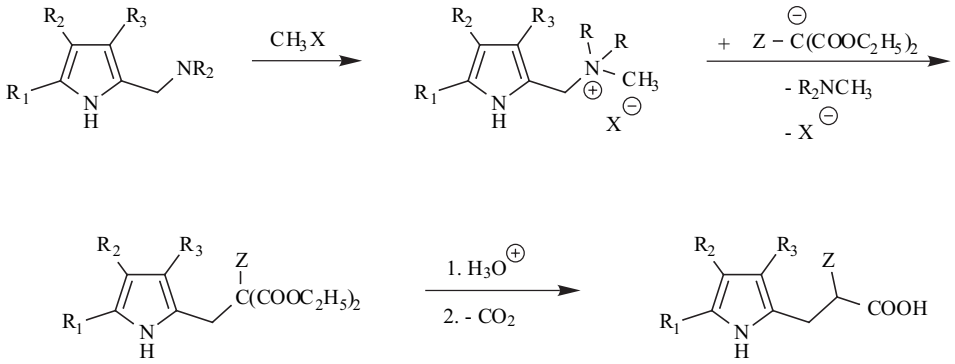
Scheme 15.

Pyrrole Mannich bases do not react with cyanide anions as free amines, but only as salts, usually methiodides (X = I) or methosulfates (X = CH_3SO_4) [49]. Such *C*-alkylation reactions occur readily in the case of Mannich bases derived from pyrroles substituted with electron-donating groups



46 **47**

Scheme 16.



Scheme 17.

(alkylpyrroles), and the presence of electron-withdrawing group in the structure of the such β-aminomethylated pyrroles does not influence the process [49]. The reaction is successful both in the case of pyrroles aminomethylated in position α or in position β. Some examples of α-aminomethylated pyrroles involved in *C*-alkylations with alkaline cyanides include the dimethylamine mono-Mannich base of pyrrole, [73, 74] 1-methylpyrrole and 1-phenylpyrrole, [26] 1-benzylpyrrole, [75] or 1-(2-hydroxyethyl)pyrrole [76]. The mono-Mannich bases derived from 1,2,5-trimethylpyrrole, 2,5-dimethyl-1-phenylpyrrole, [5] or methyl 5-chloropyrrole-2-carboxylate [63] illustrate the participation of simple β-aminomethylated pyrroles in reaction with cyanide anion. A large number of variously substituted 1-aryl-2,5-dimethyl- and 1,2-aryl-5-methyl-3-pyrroleacetonitriles have been obtained in a similar manner and reported as intermediates in the preparation of pharmacologically interesting pyrrole-3-acetic acids [21, 77]. In the case of pyrrole bis-Mannich bases, the stepwise replacement of the dimethylamino groups with nitrile functions is possible provided that the quaternization of the bis-aminomethylated pyrrole can be conducted to afford a mono-methiodide [6]. There is only one report to describe the reaction of an aminoalkylated pyrrole with cyanide anion, leading to the corresponding propionitrile substituted at position 2 with a pyrrole moiety [42]. The *C*-alkylation of cyanide anion with 2,5-bis(piperidinomethyl)pyrrole (Scheme **16**) deserves a special mention as it allowed, besides the isolation of the expected 2,5-bis(cyanomethyl)pyrrole (**46**), the identification of three diastereomeric pyrrole-containing cyclophanes (**47**), presumably arising from a ring closure of a diradical formed by head-to-head dimerization of the cyano-susbtituted 2,5-bis(methylen)-3-pyrrolenine produced from the dinitrile (**46**) through 1,6-elimination of one molecule of hydrogen cyanide [19].

Alkylation of CH groups activated by ester or nitrile functions is also of considerable practical interest. Pyrrole Mannich bases (as methiodides or methosulfates, X as above) *C*-alkylate malonic acid esters and the corresponding acylamino-substituted derivatives as part of a strategy devised to alow, after hydrolysis and decarboxylation, the introduction of a propionic acid side chain (Z = H) [48] or an alanine moiety (Z = NH_2), respectively (Scheme **17**) [78].

In the first attempt [79] to perform the *C*-alkylation of malonic acid esters with a pyrrole Mannich base, only the

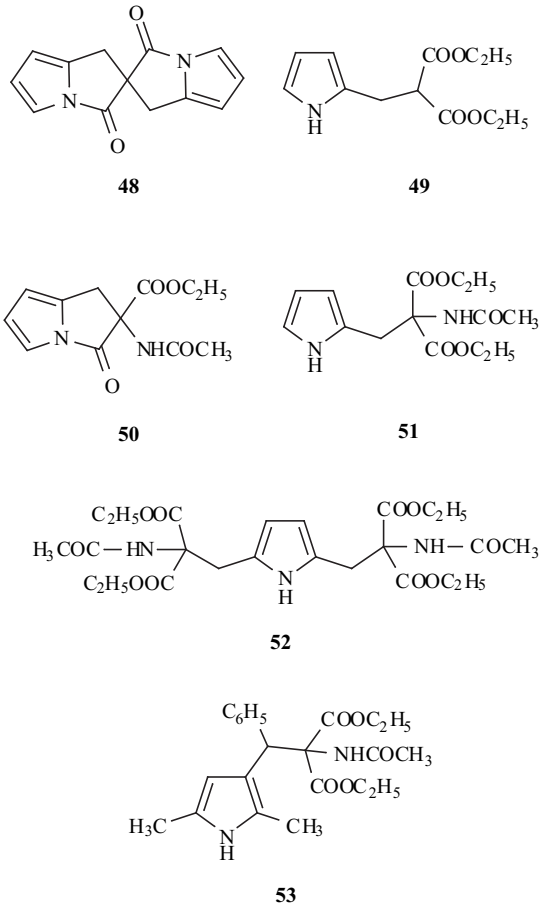
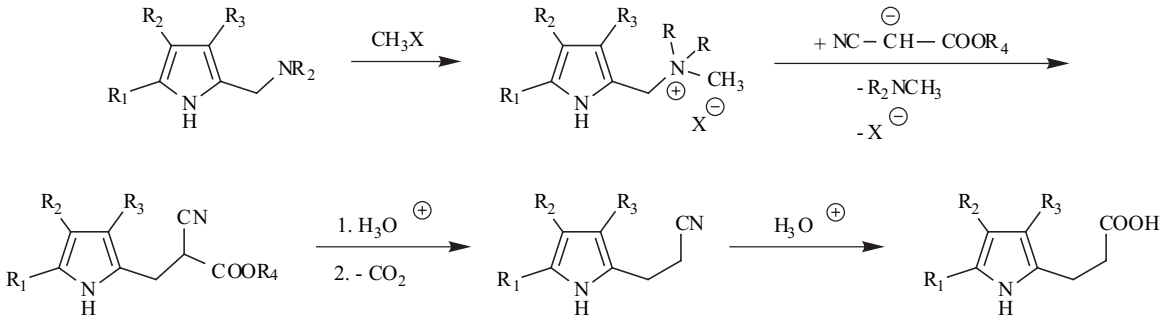


Fig. (3).

lactam (**48**) (Fig. **3**), resulted from a sequence comprising the bis-*C*-alkylation of diethyl malonate with 2-dimethylaminomethylpyrrole followed by an intramolecular ring closure, was isolated when the reaction was carried out with the free Mannich base in an apolar solvent such as toluene and using sodium hydroxide to generate the malonate carbanion. Diethyl (2-pyrrolyl)malonate (**49**) was however conveniently obtained, yet in moderate yields, by using ethanol as solvent in a one-pot reaction comprising the stepwise *in situ* formation of the required sodium diethyl malonate and pyrrole Mannich base methosulfate. Acknowledging that considerable amounts of both sodium diethyl malonate and dimethyl sulfate could be diverted in a competing methylating reaction to produce diethyl methylmalonate in the aforementioned procedure, improved



Scheme 18.

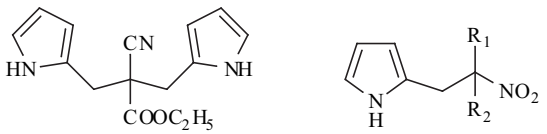
yields of such diesters (**49**) were achieved in a later study [80] by reversing the order of the *in situ* formation of the reactants. Another somehow better alternative for *C*-alkylating diethyl malonate with aminomethylpyrroles, preferably employed in the case of Mannich bases derived from *N*-substituted pyrroles, consists in the use of the previously prepared Mannich base methosulfate and the *in situ* formed sodium derivative of diethyl malonate, whose excess also acts as solvent [5, 26].

The replacement of diethyl malonate with diethyl acetamidomalonate in the *C*-alkylation process conducted in toluene with 2-dimethylaminomethylpyrrole as the free base produced the lactam (**50**) [79], which was also obtained from the reaction in dioxane with the corresponding Mannich base methiodide. The lactam (**50**) was later shown in a thorough investigation [17], meant to pinpoint the influence of the nature of the dialkylamino leaving group, the nature and the amount of the catalyst, the reaction temperature and the reaction time on the yields, to be accompanied by the normal reaction product, the diester (**51**). Compound (**51**) can be obtained more advantageously through the same one-pot reaction comprising the stepwise *in situ* formation of the required sodium diethyl acylaminomalonate and pyrrole Mannich base methosulfate described previously [5, 79]. The use of a pyrrole bis-Mannich base under identical reaction conditions also afforded the normal bis-*C*-alkylation product (**52**) [81]. In the case of 3-aminomethyl-2,5-disubstituted pyrroles, the formation of the undesired lactams (**49**) is no longer possible, but the advantage deriving from the use of the Mannich base methosulfate in ethanol over the employment of the free base in toluene was confirmed [5]. It is also worth mentioning the single report in the literature on the *C*-alkylation of diethyl acetamidomalonate with an aminoalkylated pyrrole to give compound (**53**) [42].

Another type of reagent involved in *C*-alkylations with pyrrole Mannich bases is illustrated by cyanoacetic acid esters. The reaction can be developed as an alternative (Scheme **18**) to the previously described strategy of grafting a propionic acid side chain *via C*-alkylation of malonates with pyrrole Mannich bases, and it has been incorporated in a protocol aiming to the insertion of a 2-cyanoethyl group in the structure of pyrroles serving as intermediates in the synthesis of uroporphyrinogen III octanitrile [6].

Ethyl cyanoacetate has been successfully *C*-alkylated with the priorly prepared Mannich bases methiodide of 1-methylpyrrole; the cyanoacetate carbanion has been produced using sodium, and the reaction was conducted in the excess ester as solvent [26]. The same approach has been employed to *C*-alkylate methyl cyanoacetate with the methiodide of 3,4-bis(dimethylaminomethyl)pyrrole [6]. Sodium hydride in DMSO can also act as a good carbanion generator from *t*-butyl cyanoacetate [63]. Even a bis-*C*-alkylation leading to compound (**54**) (Fig. **4**) has been reported when the *in situ* formed 2-dimethylaminomethylpyrrole methiodide and the carbanion derived from ethyl cyanoacetate were reacted in ethanol [79].

Other less represented *C*-alkylation reaction with pyrrole Mannich bases reffers to the replacement of the dialkylamino moiety with a cyanomethyl group by using lithium diisopropylamide to generate the required nucleophile from acetonitrile as a one-step method to create a propionitrile side chain in intermediates designed for the synthesis of uroporphyrinogen III octanitrile [6, 63]. Furthermore, one paper described the *C*-alkylation of sodium salts derived from nitroalkanes with pyrrole Mannich bases by following the general guidelines of the one-pot procedure that consists in the stepwise *in situ* formation of the required nucleophile and pyrrole Mannich base methosulfate, to give pyrrol-2-ylmethyl-substituted nitroalkanes (**55**) (Fig. **4**) suitable for the preparation of the related amines through reduction [42].



54 **55**

Fig. (4).

N-Alkylation

A limited number of examples are available to demonstrate the ability of pyrrole Mannich bases to alkylate nitrogen nucleophiles. The ammonolysis of 3-(4-cyanomethyl-5-dimethylaminomethylpyrrol-3-yl)propionitrile methiodide in liquid ammonia at -70°C afforded porphobilinongendinitrile (**56**) (Fig. **5**) as a precursor in the preparation of uroporphyrinogen III octanitrile [63]. The alkylation of the azide anion, a suprising omission in the arsenal of nucleophiles subjected to alkylation with Mannich bases, provided easy acces to 1-aryl-2-azidomethylpyrroles (**57**) as intermediates in the obtention of the corresponding 1-aryl-2-aminomethylpyrroles [53]. *N*-Alkylation of *N*-phenylhydroxylamine with an aminomethylated pyrrole lead to the expected substitution product (**58**) [34]. A series of 3-

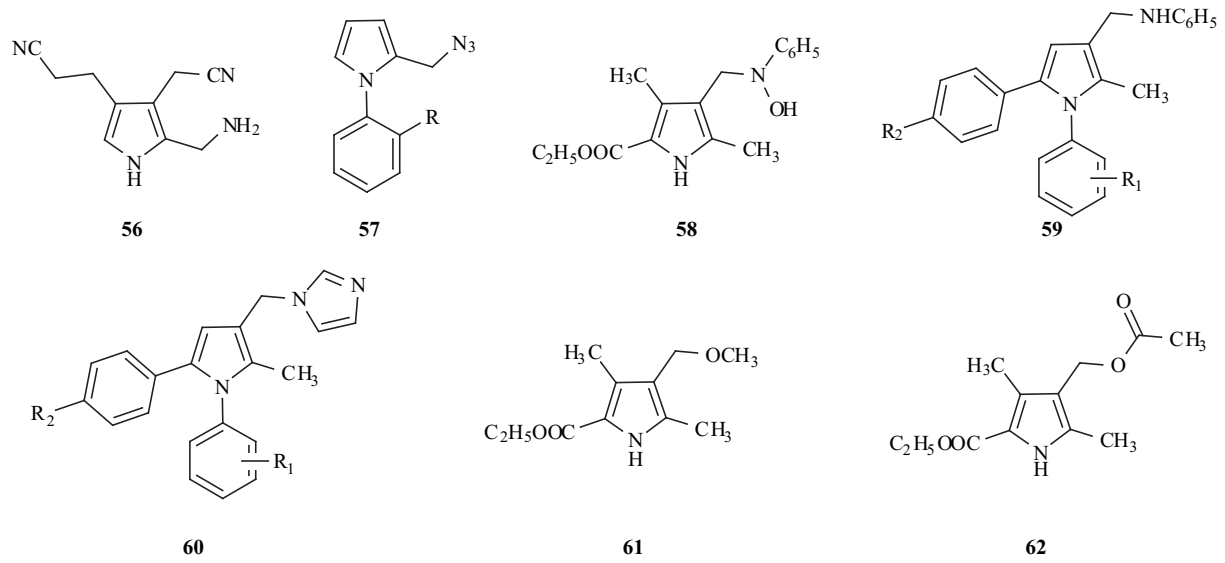


Fig. (5).

phenylaminomethylpyrroles (**59**) and 3-(imidazol-1-ylmethyl)pyrroles (**60**) have been obtained through an amine exchange reaction between a pyrrole Mannich bases methiodide and aniline or imidazole, respectively [82].

O-Alkylation

The *O*-alkylation with aminomethylated pyrroles has been scarcely investigated. The replacement of the pyrroles with sodium thiophenoxides in tetrahydrofuran to give thioethers (**63**) (Fig. **6**), which were subsequently turned into the related sulfones upon oxidation with *meta*-chloroperbenzoic acid. The sulfones (**64**) can be directly obtained through the replacement of the dialkylamino group in a pyrrole Mannich base by an arylsulfonyl moiety supplied by sodium arylsulfinate [84]. Cysteamine hydrochloride was selectively *S*-alkylated with the

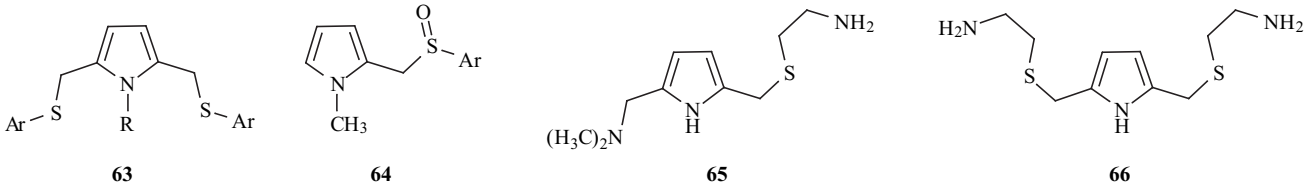


Fig. (6).

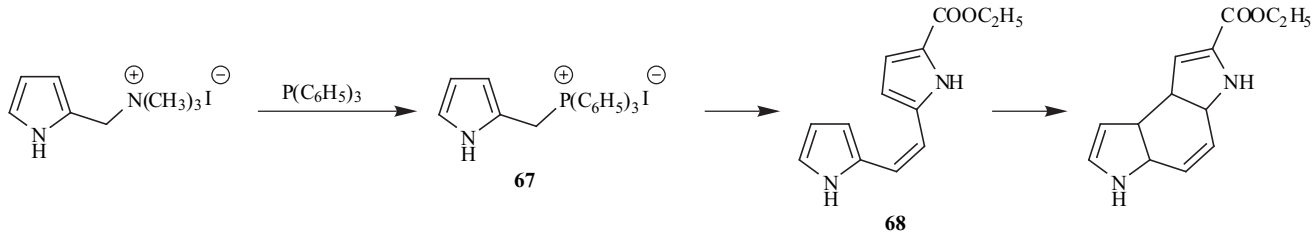
diethylamino group in the Mannich bases methosulfate derived from ethyl 3,5-dimethylpyrrole-2-carboxylate with a methoxide anion generated from methanol and sodium hydroxide gave methoxymethylpyrrole (**61**) (Fig. **5**), whereas substitution of the piperidine moiety in the Mannich base derived from the same pyrrole substrate with an acetoxy group led to compound (**62**) [34].

S-Alkylation

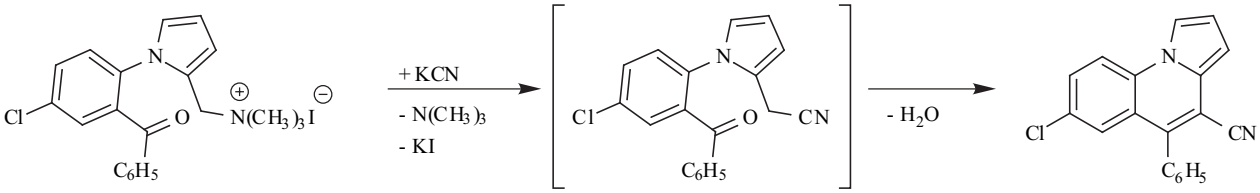
The substitution of the dialkylamino group in pyrrole bis-Mannich bases by an arylthio group has been achieved [83] by refluxing the methiodides of the aminomethylated methiodide of 2,5-bis(dimethylaminomethyl)pyrrole in the presence of sodium hydroxide to give 24% of amine (**65**) and the bis-displacement product (**66**) as the major fraction [85].

P-Alkylation

Triphenylphosphine acts as a strong nucleophile which displaces the quaternized dialkylamino group from pyrrole Mannich bases to yield (pyrrol-2-ylmethyl)triphenylphosphonium iodides (**67**) [86, 87], useful as starting materials in Wittig reactions with aromatic aldehydes [19]. The same approach led to the 1,2-dipyrryl substituted alkene (**68**) as



Scheme 19.



69 **70** **71**

Scheme 20.

precursor in a photochemical cyclization-based strategy allowing the rapid construction of the skeleton of the *Streptomyces* metabolites PDE-I and PDE-II (Scheme **19**) [88]. Sodium diethylphosphite is yet another example of phosphorous-containing nucleophile able to react with pyrrole Mannich bases [87].

3.2. Ring Closure Reaction of Aminomethylated Pyrroles

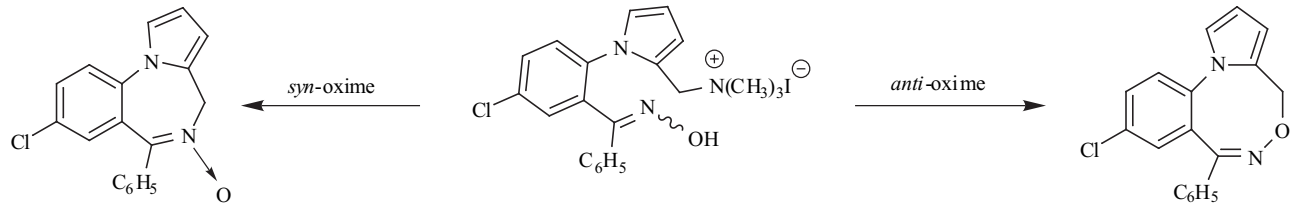
The chemistry of Mannich bases provides a large number of various ring closure reactions taking place either with or without the elimination of the dialkylamino group. The literature reports describing the cyclization reactions of pyrrole Mannich bases may not be so spectacular, abundant and diverse as in the case of other types of Mannich bases, yet these reactions offer entries to otherwise difficult to attain structures. For example, the pyrrole Mannich base methiodide (**69**) directly affords upon treatment with KCN pyrrolo[1,2-*a*]quinoline (**71**) *via* an initial replacement of the quaternized dimethylamino group with a nitrile function which activates the adjacent methylene group in the subsequent Claisen-like condensation with the ketone function in intermediate (**70**) (Scheme **20**) [89].

An intramolecular condensation with the loss of the quaternized dimethylamino group also occurs in the methiodide of the pyrrole Mannich base (**72**); the configuration of the oximino group is the essential factor in directing the ring closure either towards the formation of pyrrolobenzodiazepine (**73**) through *N*-alkylation in the case of the *anti*-oxime, or towards the building of pyrrolobenzoxadiazocine (**74**) *via O*-alkylation in the case of the *syn*-oxime (Scheme **21**) [89].

The most interesting ring closure reaction of pyrrole Mannich bases is the formation of macrocyclic tetrapyrrolic pigments belonging to porphyrins. Following the observation that the 3,4-disubstituted primary pyrrole Mannich base porphobilinogen (**75**) (Fig. **7**) is the natural precursor of uroporphyrin [90], Eisner and Linstead developed a general method for the tetramerization of 5-unsubstituted 2-aminomethylated pyrroles by refluxing the starting materials in xylene or *ortho*-dichlorobenzene with ethylmagnesium bromide [18]. Making use of the α-methylene group in the initial Mannich bases to provide the methine linker in porphyrins, this approach produces satisfactory yields of a mixture containing the corresponding porphin (**76**) (R = R_1 = H) and chlorin (**77**) (R = R_1 = H) as their magnesium complexes. The use of 3,4-dimethyl- and 3,4-diethyl-substituted pyrrole Mannich bases in similar procedures allowed the first direct entry to β-substituted chlorins (**77**) (R = H, R_1 = CH_3, C_2H_5) [27, 28], and even *meso*-tetramethylchlorin (**77**) (R = CH_3, R_1 =H) was accessible from 2-(1-dimethylaminoethyl)pyrrole [41]. The attempt to apply the same strategy to 3,4-diaryl-substituted pyrrole Mannich bases led only to porphins (**76**) (R = Ar, R_1 = H); the formation of the related chlorines can not be excluded, but their absence in the reaction mixture has been tentatively explained based on these compounds' high tendency to oxidize to porphins [30]. The Eisner-Linstead strategy for porphyrin synthesis also proved to be a source for tetrahydroporphyrins: when conducted in the absence of atmospheric oxygen, the procedure affords bacteriochlorine (**78**) and its isomer (**79**) having adjoining reduced pyrrole rings [91]. Furthermore, under the appropriate conditions, an aminomethylated pyrrole was shown to produce porphyrinogen (**80**), a hexahydroporphyrin in which the four pyrrole rings are linked through methylene bridges [92]. On the other hand, when a stream of oxygen was passed through the solution of 2-dimethylaminomethyl-3,4-diethylpyrrole in acetic acid, only porphin (**76**) (R = H, R_1 = C_2H_5) was formed [29]. In the end, it is worth mentioning the research conducted with porphobilinogen with the view of establishing the best reaction conditions for its cyclotetramerization and the resulting products [93], and the effect of the *C*-4 substituent on its reactivity in uroporhyrinogen formation [94].

3.3. Miscellaneous Reaction of Pyrrole Mannich Bases

Two methods for the preparation of pyrrole aldehydes starting from pyrrole Mannich bases have been developed. The first involves as the key step the transfomation of the



73 **72** **74**

Scheme 21.

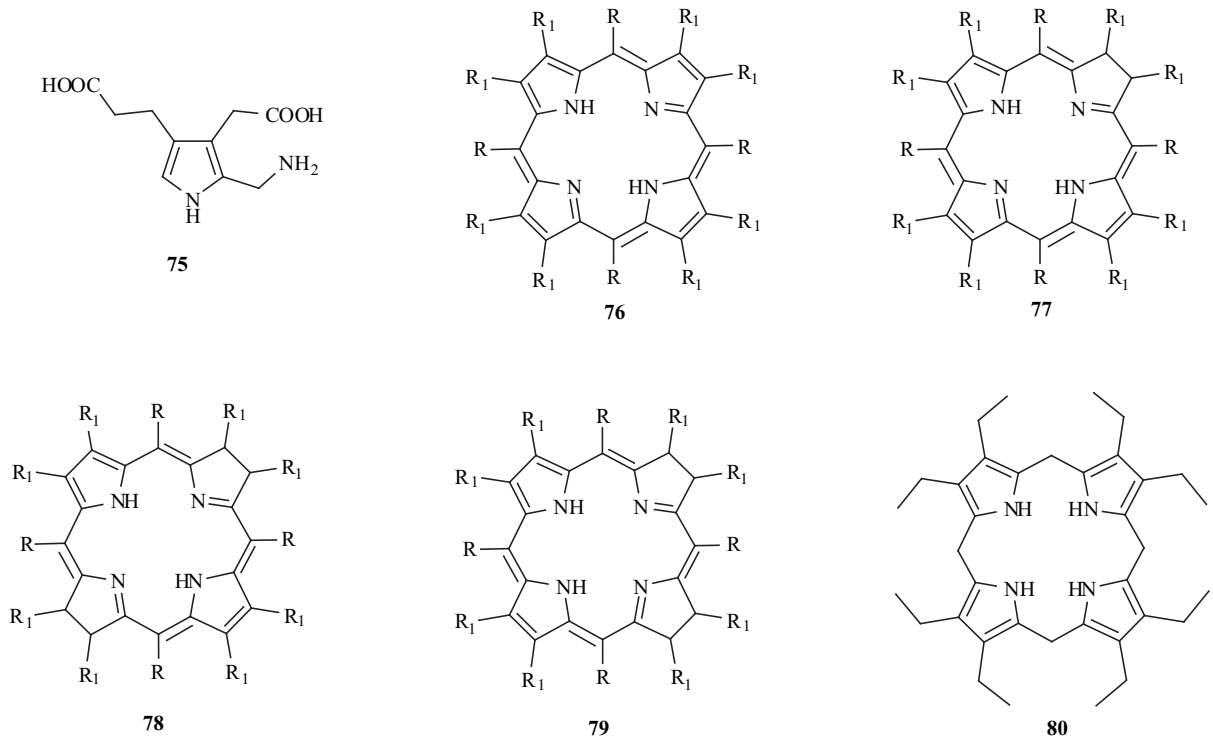
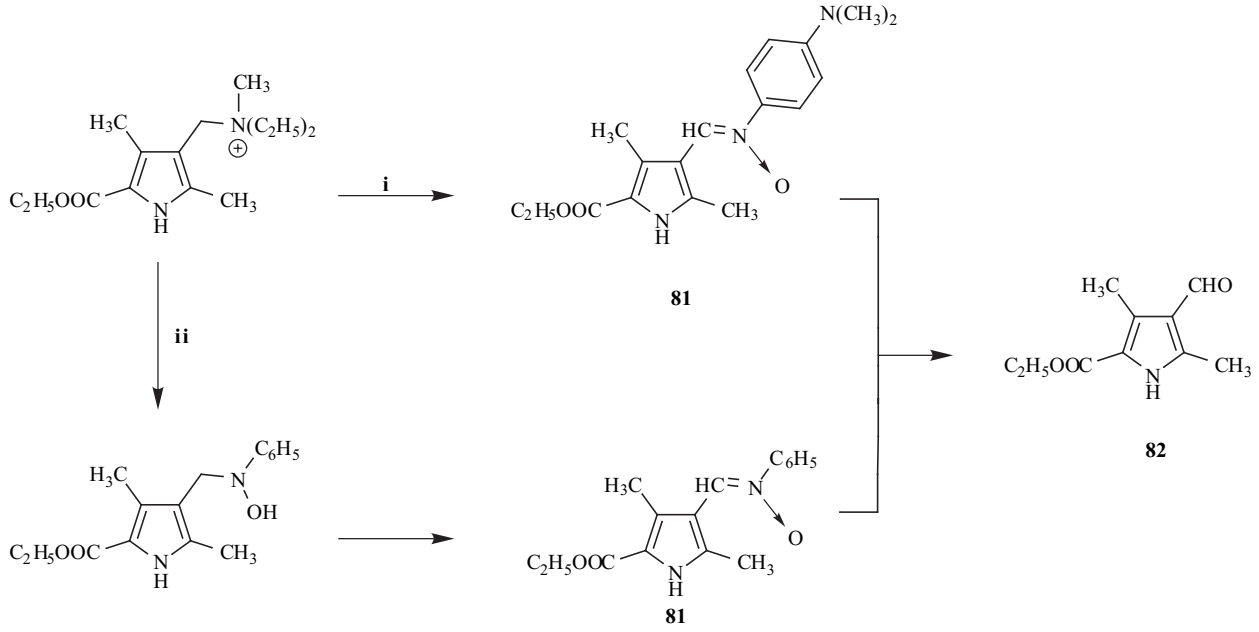


Fig. (7).

quaternized aminomethylated pyrrole into a nitrone (**81**) either upon direct reaction with *para*-nitrosodimethylaniline (pathway **i** in Scheme **22**), or upon treatment with phenylhydroxylamine followed by oxidation with lead dioxide (pathway **ii** in Scheme **22**) [34]; the nitrone is subsequently hydrolyzed to the related aldehyde (**82**) [95]. Although the hydrolysis of the nitrones (**81**) occurs smoothly in cold mineral acid, the scope of the approach is limited to aldehydes substituted with electron withdrawing groups, which have a higher stability in acidic medium; pyrrole-2-carboxaldehyde could not be obtained through this method. The synthesis of aldehyde (**82**) from the initial pyrrole Mannich base could also be achieved directly *via* a Sommelet-like reaction using hexamethylenetetramine, or employing the Duff variation of the aforementioned reaction [34].

Deaminomethylation processes involving the cleavage of the bond between the initial substrate and the dialkylamino group are known in the chemistry of Mannich bases. Although a reverse aminomethylation is conceivable for various types of Mannich bases, there is only one paper [34] presenting the removal of the dialkylaminomethyl moiety in



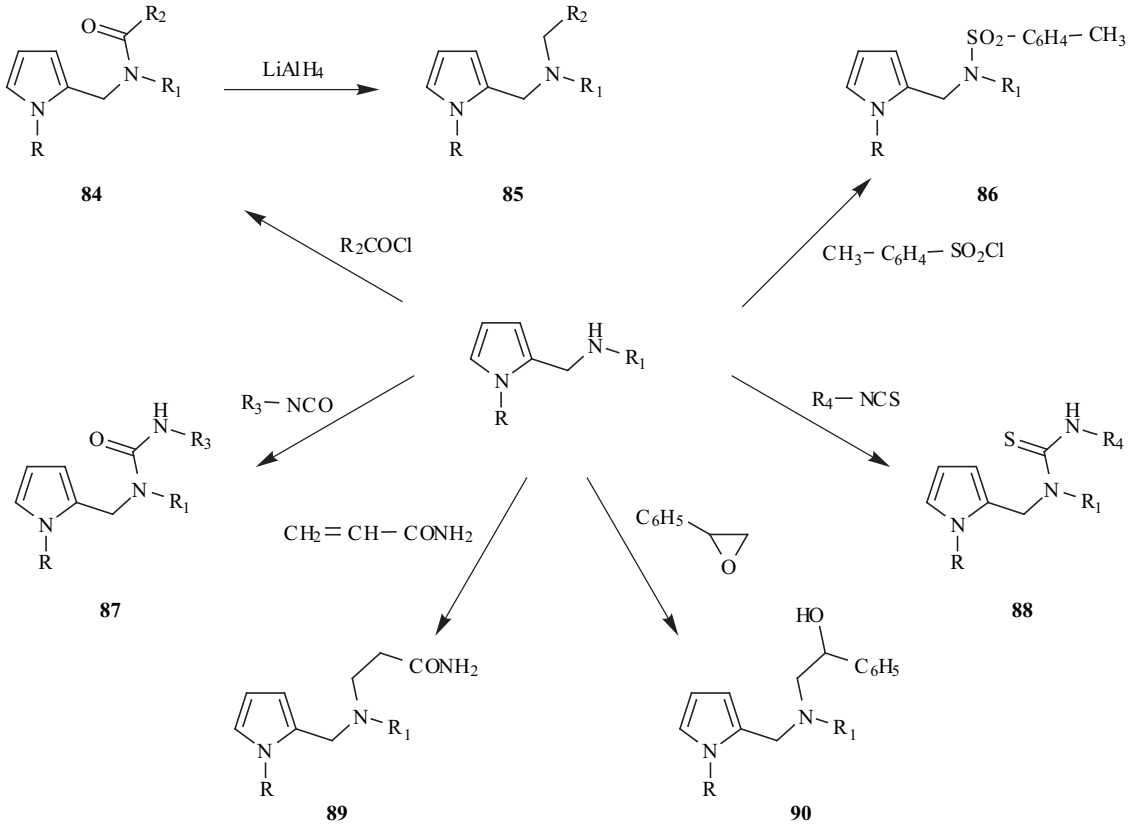
Scheme 22.

Scheme 23.

the case of aminomethylated pyrroles. The cleavage occurred upon treatment with diazonium salts (Scheme **23**), when the formation of the expected azo dye (**83**) was accompanied by release of formaldehyde and volatile amines. Pyrrole Mannich bases derived from less reactive substrates did not undergo the deaminomethylation under these conditions.

A series of secondary pyrrole Mannich bases were subjected to several types of common reactions involving the amine function [96]. Acylation of these compounds with both acid chlorides and anhydrides led to *N*,*N*-disubstituted amides (**84**), which could be in turn reduced to the corresponding tertiary amines (**85**) (Scheme **24**). Treatment of the Mannich bases with *para*-toluenesulfonyl chloride afforded the expected sulfonamides (**86**), whereas the addition to isocyanates, isothiocyanates, and acrylamide gave ureas (**87**), thioureas (**88**), and β-aminoacrylamide (**89**), respectively. The direction of ring opening of styrene oxide by these secondary pyrrole Mannich bases to produce amino alcohols (**90**) was also investigated.

Diallylamine pyrrole Mannich base (**91**) (Fig. **8**) has been copolymerized with acrylonitrile and fumarodinitrile to give polymers having pendant pyrrole rings [97, 98]. The homopolymerization of compound (**91**) initiated by $TiCl_3/H_2O_2$ led to cyclopolymers such as (**92**), whereas 2,5-



Scheme 24.

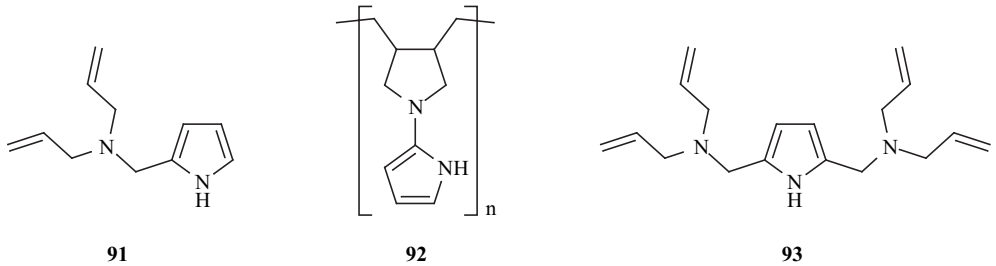


Fig. (8).

bis(diallylaminomethyl)pyrrole (**93**) produced under the same conditions crosslinked polymers [99].

4. USES OF PYRROLE MANNICH BASES

Far from being only important to theoretical research, Mannich bases also exhibit a wide range of practical uses. The most significant contributions of aminomethylation to applied research lie in the field of pharmaceutical chemistry, as 30-40% of the scientific papers on Mannich reaction are published in medicinal and pharmaceutical chemistry journals, but uses ranging from detergents, flocculants, chelators and anticorrosion chemicals to radical inhibitors and crosslinking agents have also been reported for Mannich bases. This remark holds true for pyrrole Mannich bases as well, as proven by the good deal of recent studies dealing

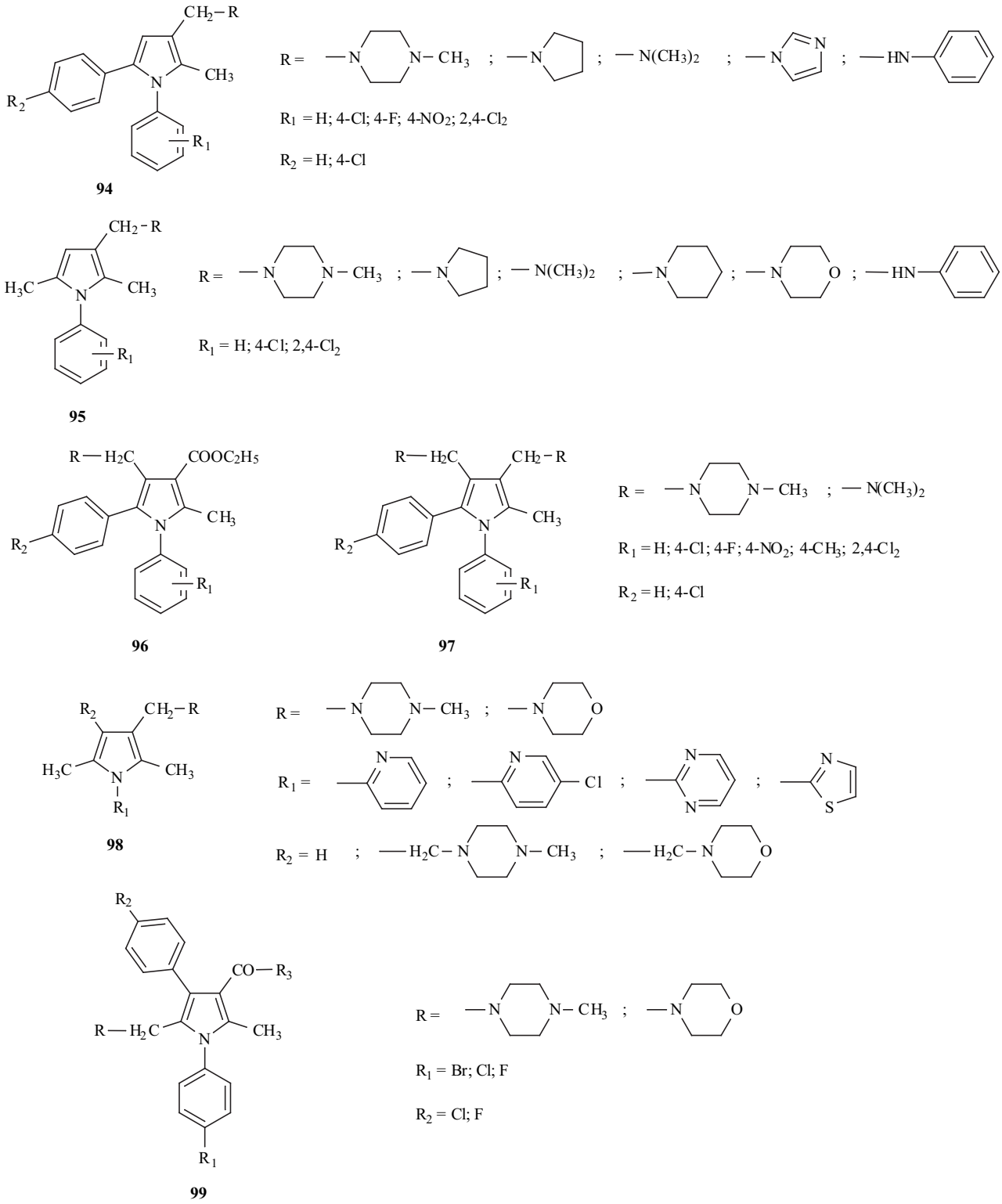
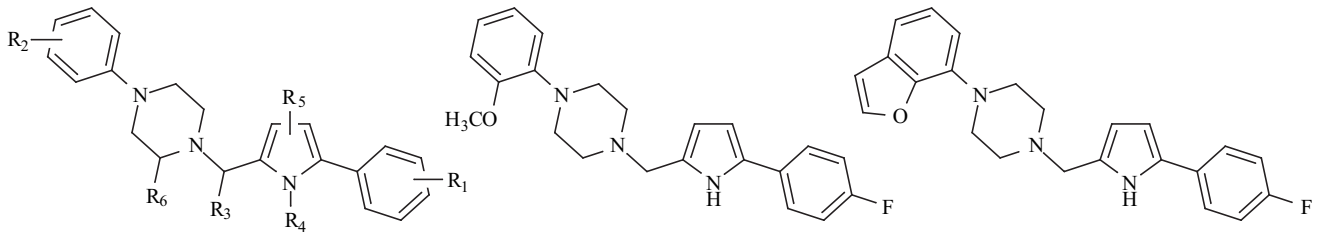


Fig. (9).



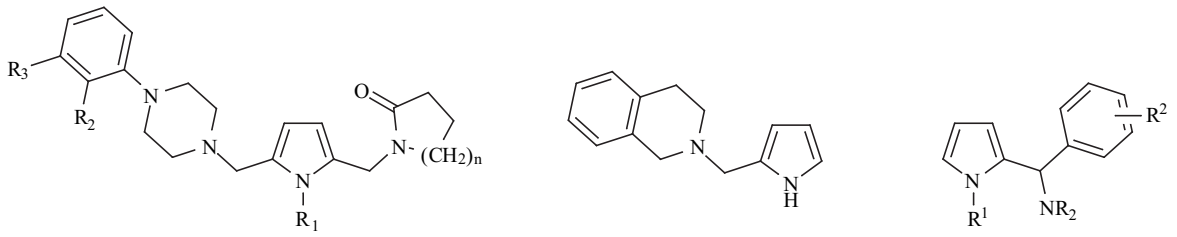
100 **101** **102**

Fig. (10).

with the aminomethylation of the pyrrole ring related to pharmacological applications.

A first group of papers related to drug discovery within pyrrole Mannich bases deals with their antibacterial and antifungal activities. The working hypothesis was that the mentioned pharmacological properties can be ascribed to the presence of non-bonded electrons of a nitrogen atom on a *C*-3 substituent. A series of β-aminomethylated 1,5-diaryl-2-methylpyrroles (**94**), containing the nitrogen atom of the *C*-3 substituent in a piperazine and pyrrolidine ring, as part of an acyclic secondary amine such as dimethylamine, or introduced by an aniline or an imidazole substituent with a lesser available nitrogen lone pair of electrons, have been synthesized (Fig. **9**) [82]. The dimethylaminomethyl derivatives exhibit the best anti-*Candida* activity, followed by the compounds having a 1-imidazolylmethyl and 4-methylpiperazinylmethyl moiety, and those containing a pyrrolidinylmethyl moiety. All phenylaminomethyl derivatives were inactive. As far as the substitution at position 5 is concerned, 4-chlorophenyl and 2,4-dichlorophenyl substituted aminomethylated pyrroles showed the highest microbiological activity. The replacement of the *C*-5 aryl substituent with a methyl group caused a significant decrease of anti-*Candida* activity, a finding that was confirmed in a later paper [20], which also pointed out that Mannich bases (**95**) derived 1-aryl-2,5-dimethylpyrrole and morpholine and piperidine as amine reagents were more active than the compounds having a similar structure, but containing a 4-methylpiperazine moiety instead. In order to further develop the QSAR study, another series of compounds (**96**) having the aminomethyl moiety at *C*-4 has been prepared, and their antiblastomycete activity has been investigated. The authors concluded that the shuffling of the 4-methylpiperazinylmethyl group from *C*-3 to *C*-4 does not markedly affect the antifungal effect, but the biological activity in *C*-4-dimethylaminomethyl Mannich bases (**96**) dropped significantly when compared to the activity of the similarly substituted *C*-3-substituted pyrrole Mannich bases [100]. Moreover, the bis-Mannich bases (**97**) exhibited a slightly lower antifungal activity then their *C*-3 monosubstituted analogues. Further modification of the *N*-1 substituent from a phenyl ring to an azaheteroaryl moiety in compounds (**98**) resulted in a complete loss of the antifungal activity [23], anyway already diminished considerably by the replacement of the *C*-5 aryl substituent of the most active pyrrole Mannich bases (**94**) with a methyl group. The repositioning of the *C*-5 aryl ring in compounds (**96**) to *C*-4 and the ensuing relocation of the dialkylamino-methyl group from *C*-4 to *C*-5 produced a new series of pyrrole Mannich bases (**99**) whose antifungal activity has not been altered drastically by the change; however, esters (**99**) (R_3 = OC_2H_5) were more active than the corresponding amides (**99**) (R_3 = 4-methylpiperazinyl), demonstrating that the introduction of a second basic group further decreases the antifungal activity of pyrrole Mannich bases [101].

A second group of papers describing the involvement of pyrrole Mannich bases in drug discovery deals with aminomethylated pyrroles as antipsychotic agents. In order to investigate the structural requirements for the interaction with D_2 receptors, a series of Mannich bases of 2-phenylpyrroles (**100**) (Fig. **10**) have been synthesized as bioisosteric conformationally restricted analogues of known antipsychotic benzamides eticlopride and raclopride, or butyrophenones haloperidol and fluanisone [102]. The combination of the 2-phenylpyrrole side chain with the tertiary amine containing moiety of fluanisone resulted in compound (**101**), which scored a high oral activity in apomorphine-induced climbing behavior and conditioned avoidance responding (CAR) tests, and exhibited selectivity towards D_2 receptors over α_1-adrenoceptors, making it the prototype of a new class of sodium-independent dopamine antagonists having a low propensity to induce acute



103 **104** **105**

Fig. (11).

extrapyramidal side effects [64]. The investigation on the influence of the substitution pattern of the 2-phenylpyrrole side chain and the nature of the aryl substituent in piperazine moiety led to the discovery of Mannich base (**102**) as an even more potent and selective D_2 antagonist [67].

A number of 35 compounds sharing the common structure (**103**) (Fig. **11**) have been synthesized, and their ability to block CAR in rat has been investigated as an indicator of antipsychotic potential [103]. The most promising agents have been also been examined for production of catalepsy in rat, a sign of extrapyramidal side effects liability, and for their binding interaction with dopamine D_1 and D_2, serotonin 5-HT_1 and 5-HT_2 and adrenergic α_1 receptors in rat brain. Mannich base (**103**) (R_1 = CH_3, R_2 = $OCH(CH_3)_2$, R_3 = H, n = 2) has emerged as an effective potential antipsychotic agent whose preclinical pharmacological profile (active in blocking CAR when administered po, produced little or no catalepsy at a dose 20 times higher than its ED_{50}, high affinity for 5-HT_1 and α_1 binding sites, no activity at D_1 or 5-HT_2 receptors) recommends it for further development [104]. The investigation for pyrrole Mannich bases with a better stability in aqueous medium started from these premises, and the preparation of a vast collection of structurally modified analogues was undertaken [105]. The change of the cyclic lactam to an open-chain equivalent or a sulfonamide group, the substitution of the pyrrole ring with an electron-withdrawing moiety, and even the replacement of the pyrrole ring with phenyl, thiophene, furan, isoxazole or pyridine in compounds (**100**) were explored. Some promising results were noticed for the replacement with a *N*-methylpyrrole moiety, and several candidates which were equipotent or slightly less potent in inhibiting CAR and showed a good stability in aqueous solution at pH 2 have been identified. Modification of the lactam and side chain segments in Mannich bases (**103**) resulted in compounds whose activity was either weaker or abolished. As a general feature, any structural change in compounds (**103**) has led to a decrease of D_1 binding, while giving rise to compounds which exhibit a high affinity for the 5-HT_1 receptor.

Other illustrations of pyrrole Mannich bases in the discovery of potential pharmacologically active compounds are available. An attempt to produce agents structurally related to the anorexic furfenorex, for which the central stimulating effect due to the methamphetamine-related tertiary amine moiety has subsided, led to the synthesis of pyrrole Mannich base (**104**) having a tetrahydroisoquinoline basic side chain which partially mimics methamphetamine's phenylethylamine structure [59]. Recently, a series of 1-substituted-2-(*N*,*N*-dialkylaminobenzyl)pyrroles (**105**) have been claimed to be suitable for pain treatment, and were showed to inhibit serotonin uptake and to be analgesic in the writhing test in mice [106]. Furthermore, pyrrole Mannich bases have been mentioned as intermediates in the preparation of drugs and drug-like molecules. For example, several derivatives of primary pyrrole Mannich bases exhibited a significant degree of central nervous system depressant activity [96], and the Mannich reaction of ethyl 4-(1-pyrrolyl)benzoate proved to be a valuable modification that allowed the scaling-up of the preparation of the angiotensin II receptor antagonist FR143187 [107]. Pyrrole-2-acetic acids [21], easily obtainable *via* pyrrole Mannich bases, have excellent analgesic and anti-inflammatory activities associated with good antipyretic action and a low toxicity [77], and 5-aroylpyrrole-2-acetic acids and their derivatives share the pharmacological profile with their aforementioned unsubstituted congeners [75]. Aminomethylated pyrroles have been involved as well in the preparation of Ketorolac analogues useful as anti-inflammatory, analgesic and fibrinolytic agents, platelet aggregation inhibitors, and smooth muscle relaxants [76]. It is worth mentioning that a highly diastereoselective vinylogous aminomethylation of *N*-Boc-2-*tert*-butyldimethylsilyloxypyrrole was the key step in the large scale asymmetric synthesis of the influenza neuraminidase inhibitor A-315675 [37].

Applications other than pharmacological have been scarcely described for pyrrole Mannich bases. The electrical properties of a polymeric aminomethylpyrrole obtained from pyrrole, formaldehyde and benzylamine have been investigated [108]. 2,5-Bis(dimethylaminomethyl)-1-hexylpyrrole was the starting material for the preparation of the intermediate 1-hexyl-2,5-bis(phenylthiomethyl)pyrrole [83], which afforded through a base-induced elimination/polymerization poly(1-hexylpyrrylene vinylene), a new conducting polymer whose electrical conductivity was measured in the neutral and doped state [109].

CONCLUDING REMARKS

The present review summarizes the up-to-date information on the chemistry and applications of pyrrole Mannich bases. Beyond the noteworthy interest to fundamental research initialy triggered by the progress in the chemistry of pyrrole and later fueled by their involvement in accomplishing the easy synthesis of various pyrrole-containing molecules, this particular type of aminomethylation products has shared the general trend of constant development of pertinent, improved synthetic methods in the Mannich reaction with the view to provide straightforward access to increasingly complicated structures. The preparation of pyrrole Mannich bases has undergone a smooth transition from direct aminomethylation to the era of preformed reagents and stereoselective synthesis, whereas the scope of these compounds' reactions widened and enriched in time. The high potential of aminomethylated pyrroles as pharmacophores or precursors in drug discovery has been long recognized, and the years to come will undoubtedly consolidate the special place pyrrole Mannich bases have earned in bioorganic and medicinal chemistry. This review modestly aims at pointing out the current stage of development in the chemistry and uses of Mannich bases with the more generous purpose of sparking off further theoretical advances and stimulating lucrative research in this field.

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