Use of β-(*N,N*-dialkylamino)Propiophenones in the Synthesis of Nitrogenated Heterocyclic Compounds

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Abstract: β-(*N,N*-dialkylamino)propiophenones ($ArCOCHR^1CH_2NR_2$) are compounds with special synthetic interest not only because many of them are biologically active, but also because they posses two different electrophilic reaction centers (i. e. carbonyl group and the β-carbon atom), which can be attacked by ambifunctional nucleophilic reagents. This property makes them attractive starting materials in medicinal chemistry as valuable building blocks for ring closure reactions to form mainly five, six and seven-membered heterocyclic compounds. Additionally, the presence of α-methylene active hydrogen atoms in such compounds also opens new possibilities for ring closure reaction as recently has been published. A selection of representative examples about structural and biological properties of the title compounds, synthetic methods and ring closure reactions leading to nitrogenated heterocyclic systems are described in this review.

Keywords: Mannich type reactions, aminomethylation, ketonic Mannich bases, α,β-unsaturated ketones, heterocyclizations.

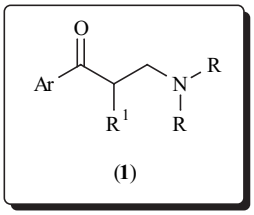
Dedicated to Our Colleague and Professor Emeritus of the Universidad del Valle Rodrigo Paredes for his Many Years Devoted to the Teaching of Chemistry

1. INTRODUCTION

Although several and exhaustive reviews and books has been devoted to the chemistry of Mannich bases in general [1-11], this review deals mainly with the precedent until up-to-date literature on the Mannich bases derived from propiophenones and related ketones. They are very interesting compounds not only for their practical biological and pharmacological properties displayed by themselves, but also for their capability to be transformed in other interesting organic compounds, specially in those that involve heterocyclic rings. A selection of representative examples about structural and biological properties of the title compounds, synthetic methods and ring closure reactions are described, including the most recent contributions on this topic.

2. STRUCTURE AND PROPERTIES OF THE β-(*N,N*-DIALKYLAMINO)PROPIOPHENONES

The β-(*N,N*-dialkylamino)propiophenones (**1**) also called β-(*N,N*-dialkylamino)ethylarylketones or 1-aryl-3-dialkylamino-1-propanones are Mannich bases derived from alkyl aryl ketones or analogous aromatic or hydro-aromatic ketones. Commonly, R^1 = H but some times can be an alkyl group. Generally, Ar is a phenyl or substituted phenyl group, but also can be a naphthyl group or a hydro-aromatic ring. The substituents R can be alkyl groups (methyl or ethyl), but also the carbonated part of five and six-membered alicyclic rings or heteroaromatic rings.



(**1**)

Compound (**1**) can exist as a free base but also in form of salt (commonly hydrochloride). The free base is soluble in both polar and non-polar solvents, but their salts are insoluble or sparingly soluble in non-polar solvents (i. e. toluene, ether, acetone, etc.) but soluble in polar solvents (alcohol, water, etc.) even at room temperature.

Many derivatives of compound (**1**) has been studied and reported as potent biologically active compounds. Dimmock and co-workers [12] have reported a study on several Mannich bases of cycloalkanones and related quaternary ammonium compounds, where their cytotoxic activities have been evaluated in order to examine the theory that sequential release of alkylating agents produces increased bioactivity compared to related compounds that contain only one potential alkylating site. Many of those compounds displayed significant activity against murine L1210 cells and various human tumors. Some correlations between structure and activity were noted in this study. Previously, these

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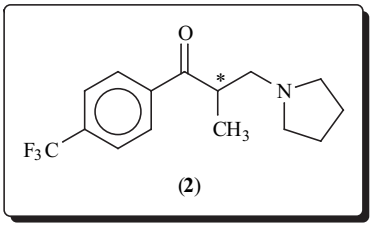
authors have reported studies on the evaluation of the cytotoxicity of some Mannich bases of acetophenone against the EMT6 tumor [13]. Similarly, some structure-effect interactions in Mannich bases have been studied on the basis of a cancerostatic-3-step test with transplantation tumors. Significant inhibition power toward some type of sarcomas was observed for some of them [14].

Shiozawa and co-workers [15] have synthesized some new 2-methyl-3-aminopropiophenones in order to evaluate their centrally acting muscle relaxant activities for an inhibitory effect on the flexor reflex in rats. The structure-activity relationships are discussed and they found that *(R,S)*-2-methyl-3-pyrrolidino-1-(4-trifluoromethylphenyl)-propan-1-one (**2**) showed significant centrally acting muscle relaxant activity. In addition, the racemic mixture was resolved and the activities of each enantiomer (**2**-(*S*) and **2**-(*R*)) were studied along with their acute toxicities. Compound **2** -(*R*) was found to exhibit more potent activity and weaker acute toxicity than **2**-(*S*). According to the results, compound **2**-(*R*) labeled as (NK433) is under development as a novel centrally acting muscle relaxant.



(**2**)

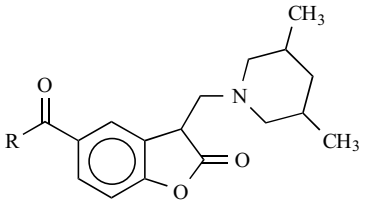
On the other hand, Erol and co-workers [16] have reported the synthesis of some new Mannich bases derived from 6-acyl-3-(3,5-dimethylpiperidinomethyl)-2(3H)-benzoxazolones (**3**). In the same work their biological activities were investigated.

Other pharmacologically active ketonic Mannich bases are listed in scheme 2. Falicain possess anesthetic properties and also acts as bronchomotor [17-19], BE-2254 is an important antihypertensive and a very selective α_1-adrenoceptor antagonist, precursor of the 3-[^{125}I]-derivative [20-23], Moban is a potent neuroleptic for psychosis and schizophrenia treatments [24,25], while, naphthyl derivatives α- and β-NETA are potent and selective fluorescent inhibitors of choline acetyltransferase [26].

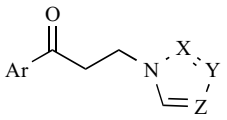
In the last years a series of Mannich bases (**4**) and (**5**), where the classical dialkylamino moiety is changed for a heterocyclic ring, have been synthetized owing to their biological activities as antifungal displayed. The most common heterocyclic rings used are imidazoles and 1,2,4-triazoles [27-30].

3. SYNTHETIC METHODS FOR β-(*N,N*-DIALKYLAMINO)PROPIOPHENONES AND RELATED COMPOUNDS

The classical method for the synthesis of β-(*N,N*-dialkylamino)propiophenones is the well known Mannich reaction between an alkyl aryl ketone, dialkylamine hydrochloride and polyformaldehyde in refluxing ethanol [31]. Alternatively, the common alkyl aryl ketones can be changed for acetylnaphtalenes, higher alkyl aryl ketones, alkyl hetaryl ketones, alkyl aryl ketones derived from aromatic azo compounds and anthraquinone dyes, methyl

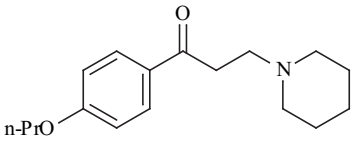


(**3**)

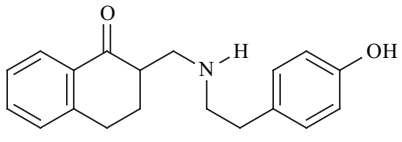


(**4**) X = CH, Y = CH, Z = N
(**5**) X = CH, Y = Z = N

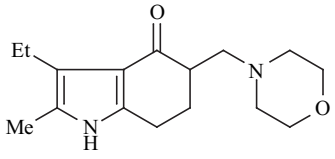
Scheme 1.



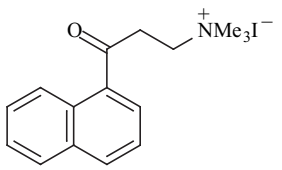
Falicain
Anaesthetic



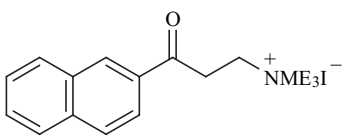
Be-2254
Antihypertensive



Moban
Neuroleptic



α-NETA



β-NETA

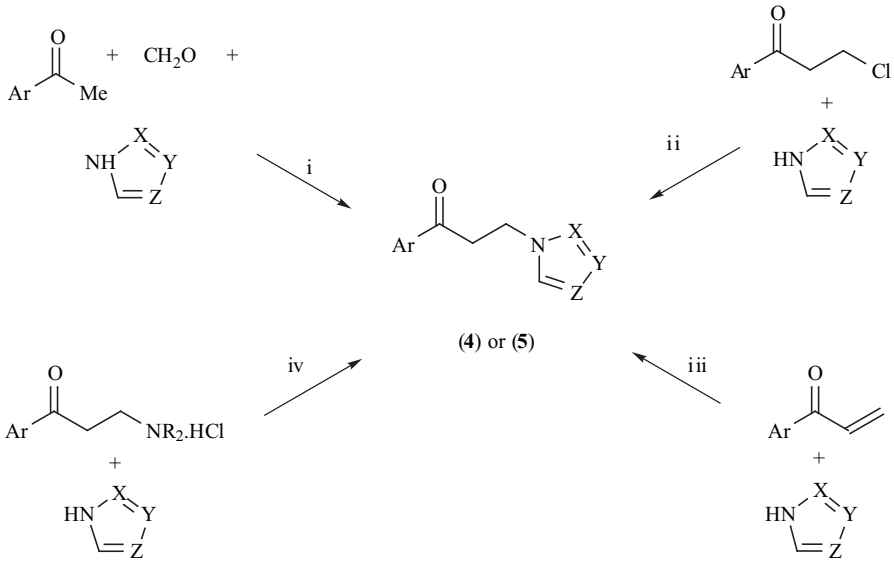
Scheme 2.

styryl ketones and alkyl cycloalkyl ketones. In this approach, *N,N*-dimethylmethyleneammonium chloride ($H_2C{=}NMe_2Cl$) is formed *in situ*, which suffers a Michael type addition from the methylene active ketone to render the expected Mannich adduct, with only a few exceptions where the C-aminoalkylation is the preferred process [32-34]. A variant of this methodology is that described by Kinast/Tietze [35], where the methylene active ketone is subjected to reaction with the commercially available *N,N*-dimethylmethyleneammonium chloride or *N,N*-dimethylmethyleneammonium iodide (Eschenmoser´s salt) to afford the corresponding Mannich bases (**1**) after a Michael type addition. A vast number of different ketonic Mannich bases synthetized from both above approaches is listed in reference [4].

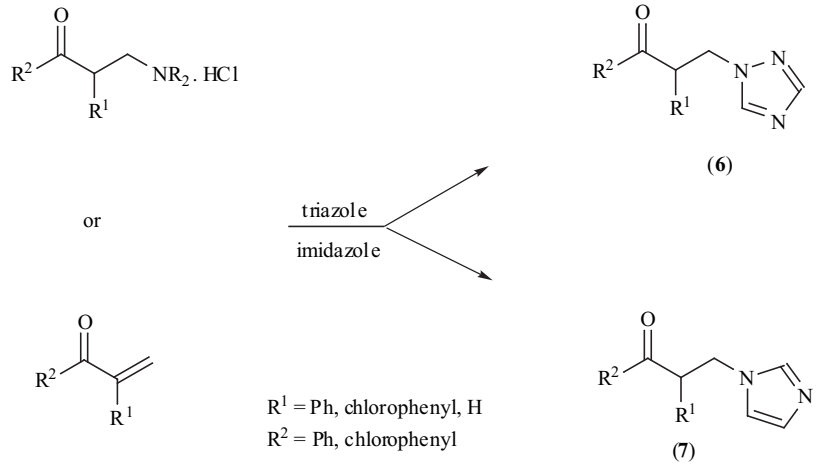
Although, dialkylamino group is the typical amino moiety in the Mannich bases (**1**), direct aminoalkylation of ketones can be achieved also with saturated heterocyclic rings such as piperidines, morpholines, pyrrolidines, piperazines and even with bi-cyclic secondary amines, just by replacing the dialkylamine for the hydrochloride of each of above amino compounds, according to the mentioned procedures [4, 31]. Contrary and except for few examples [36, 37] direct aminomethylation of ketones with heterocyclic aromatic rings (especially in azole series) to render the Mannich bases type (**4**) or (**5**) (entry i) (Scheme **3**), does not proceed as easily as it did with the saturated heterocyclic ones. For that reason, some more efficient procedures have been developed to obtain the desired compounds (**4**) or (**5**) in better yields. Namely, nucleophilic substitution of β-chloro ketones (entry ii) (Scheme **3**) [38, 39], addition of the hetero-aromatic ring to the activated carbon-carbon double bond in α,β-unsaturated ketones, (entry iii) (Scheme **3**) [28, 40, 41] or by amine exchange reaction from a dialkylamine Mannich base (entry iv) (Scheme **3**) [28, 42-45].

As an example, Takahashi and co-workers [28] have reported a convenient synthesis of the triazolyl and imidazolyl Mannich bases (**6**) and (**7**) (Scheme **4**), following the entries iii) and iv) of the Scheme **3** simultaneously.

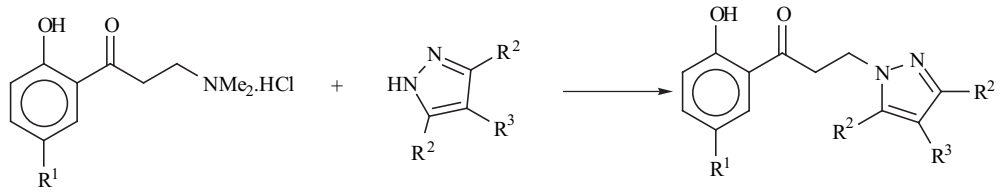
Roman and co-workers [43] recently have reported an efficient procedure for N-alkylation of a series of pyrazoles (**9**) with some special Mannich bases (**8**) following the entry iv) of the Scheme **3**.



Scheme 3.



Scheme 4.



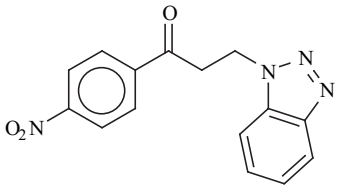
(**8**) (**9**) (**10 a-h**)

a-d R^1 = H; **e-h** R^1 = Me; **a, b, e** R^2 = H;
c, d, f-h R^2 = Me; **a** R^3 = H; **b, d, e, g** R^3 = I;
c, f R^3 = Cl **h** R^3 = NO_2

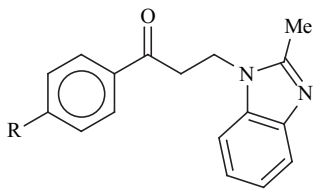
Scheme 5.

In this approach, compounds (**10 a-h**) were obtained in acceptable to good yields (41-96 %), *via* an amine exchange reaction, which involves treatment of molar amounts of the Mannich bases (**8**) with equimolar amounts of pyrazoles (**9**) in a refluxing mixture (ethanol-water 1:1) for one hour. According to these authors [43], this procedure when compared with others [27,46], offers the advantage of a simple separation of the products and the use of environmental friendly solvents, without need to use excess of pyrazole. A mechanistic explanation of the process is given for the authors.

Similarly, benzotriazole- and benzimidazole-containing Mannich bases (**11**) [44] and (**12**) [45] have recently been synthetized also by amine exchange reactions, from the respective *N,N*-dimethylaminopropiophenone hydrochlorides and benzotriazole or 2-methylbenzimidazole as nucleophiles (Scheme **6**). Both reactions were carried out heating equimolar amounts of the starting materials in water (for compound **11**) and refluxing ethanol (for compounds **12**) respectively. A complete structural study by X-ray diffraction was made for the Mannich base (**11**).



(**11**)

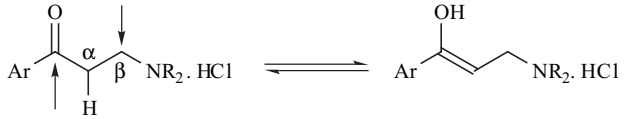


(**12**) R = Cl, OMe, NO_2

Scheme 6.

4. USE OF β-(*N,N*-DIALKYLAMINO)PROPIOPHENONES AS SYNTHETIC PRECURSORS FOR MORE ELABORATED COMPOUNDS

Ketonic Mannich bases have been widely used as good alkylating agents for acyclic and alicyclic ketones [47-55], β-ketoesters [53], phenols and aromatic amines [54]. However, the fact that β-(*N,N*-dialkylamino)propiophenones (**1**) possess two different electrophilic reaction centers (i. e. carbonyl group and the β-carbon atom) (Scheme **7**), which can be attacked for ambifunctional nucleophilic reagents, have made them to gain remarkable attention in synthesis and medicinal chemistry as valuable building blocks for ring closure reactions to form mainly five-, six- and seven-membered heterocyclic systems. Additionally, the presence of α-enolizable hydrogen atoms in compounds (**1**) (Scheme **7**), also opens new possibilities for ring closure reaction as recently have been published. A selection of representative examples is given in the following sections, specifically, those that led to the formation of nitrogenated heterocyclic rings.



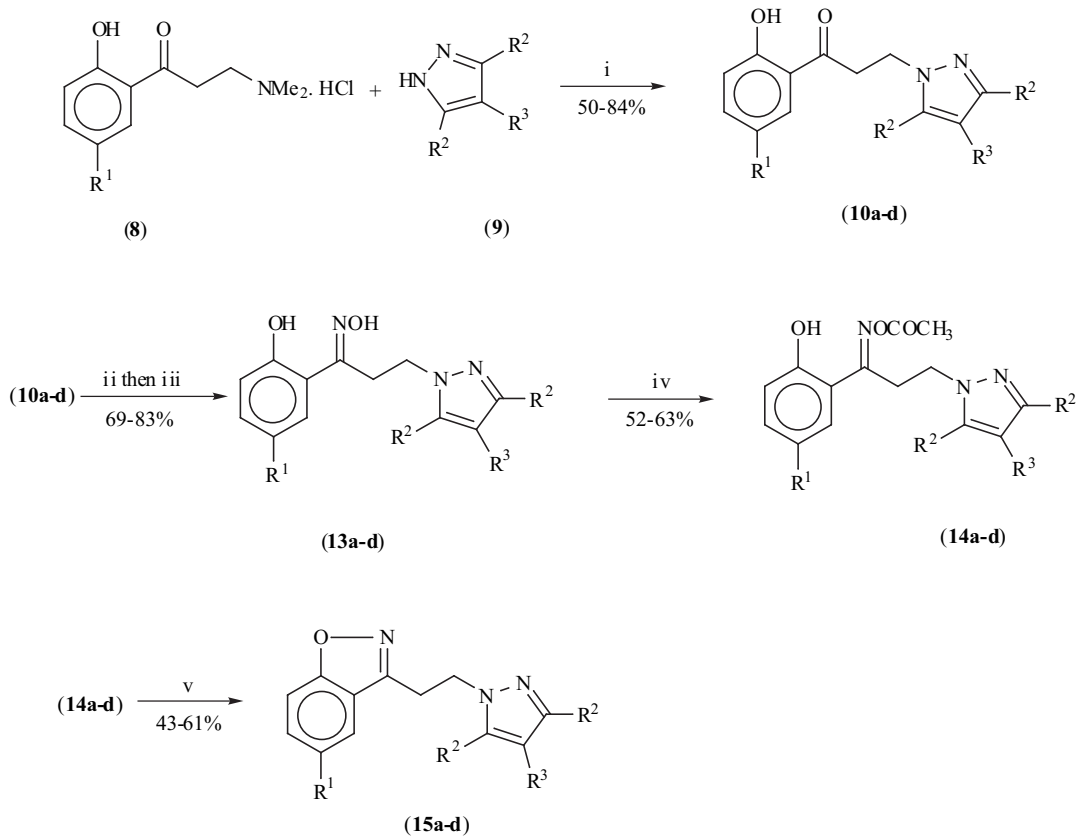
Scheme 7. Arrows indicates the two electrophilic reaction centers.

4.1. Formation of Five-membered Nitrogenated Heterocyclic Rings

Not many examples have been found where β-(*N,N*-dialkylamino)propiophenones are being used as building blocks for the synthesis of five-membered heterocyclic rings. However, a series of papers has recently been published by Roman and co-workers [55-57] where propiophenones type (**10**) are used as appropriate starting materials for an alternative synthetic method of biological and pharmacologically attractive 1,2-benzisoxazole-Mannich base derivatives [58-60].

In this approach, Roman group obtained 1,2-benzisoxazole derivatives in a sequence of four steps [57], starting with the synthesis of Mannich bases type (**10**) by an amine exchange reaction from the corresponding Mannich bases (**8**) as follows.

In this sequence, conversion of oximes (**13**) into oxime acetates (**14**) is recommended since the latter ones are more reactive towards cyclization reactions to 1,2-benzisoxazoles (under less drastic conditions), as is the case for the step v) in Scheme **8**. It is worth to indicate that in the Roman´s methodology just one of both electrophilic reaction centers of the Mannich base (**10**) (i. e. carbonyl group) is being

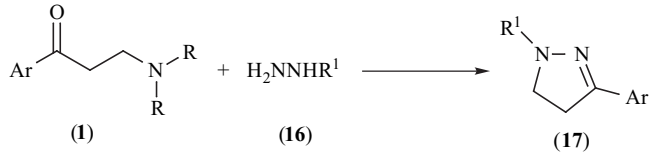


Scheme 8. i = reflux in 1:1 (v/v) EtOH-water for 1h; ii = $NH_2OH.HCl$, NaOH; iii = HOAc 10%; iv = Ac_2O/40-50 ^oC; v = K_2CO_3/benzene, reflux; **a** $R^1 = R^3 = H$, $R^2 = Me$; **b** $R^1 = Me$, $R^2 = R^3 = H$; **c** $R^1 = R^2 = Me$, $R^3 = H$; **d** $R^1 = R^2 = Me$, $R^3 = Br$.

used, which cyclizes with the strategically located hydroxyl group at the benzene ring of the propiophenone, to render the five-membered fused heterocyclic compounds (**15**).

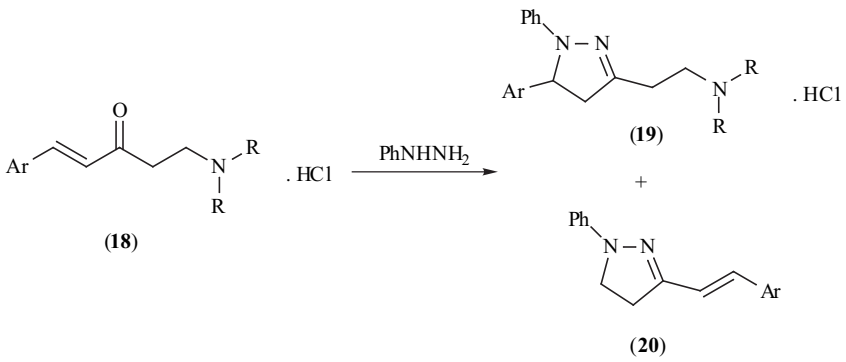
Contrary to the above reaction, treatment of the Mannich base (**1**) with hydrazine hydrate or arylhydrazines in ethanol or in acetic acid lead to the formation of the pyrazolines (**17**) (Scheme **9**). This is a current procedure for the synthesis of 1,3-disubstituted pyrazolines, which proceeds with elimination of the dimethylamino moiety [61-66].

In a similar way, treatment of the Mannich base salt (**18**) with phenylhydrazine leads to the formation of pyrazoline hydrochlorides (**19**), which involved the attack of the hydrazine over the α,β-unsaturated moiety [67].



Scheme 9. R = Me; R^1 = Ar [61], Ph [62], H [63, 64], 1-pyrazolyl [65], benzothiazol-2-yl [66].

The 1-phenyl-3-styrylpyrazolines (**20**), were also formed from the same reaction. It was observed that formation of one or another compound is strongly governed by the reaction conditions used. Thus, pyrazolines (**19**) were obtained as main products with only traces of (**20**) when phenylhydrazine was refluxed with the salts (**18**). Contrary, pyrazolines (**20**) were obtained almost exclusively along

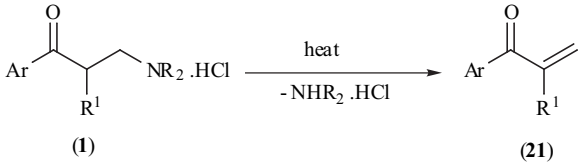


Scheme 10.

with traces of 1,5-diphenyl-3-vinylpyrazolines, when the reaction was carried out with the free base of (**18**). Formation of compounds (**19**) was not observed this time.

4.2. Formation of Six-membered Nitrogenated Heterocyclic Rings

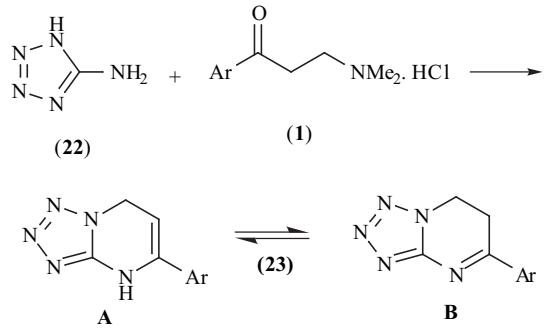
The β-(*N,N*-dialkylamino)propiophenones (**1**) can be visualized as synthetic equivalents of the less stable and more reactive α,β-unsaturated aryl vinyl ketones (**21**) (Scheme **11**). For instance, they can react with a series of 1,3-dinucleophiles through a Michael type addition with a subsequent cyclocondensation reaction, leading to the formation of simple or fused six-membered heterocyclic systems.



(**1**) (**21**)

Scheme 11.

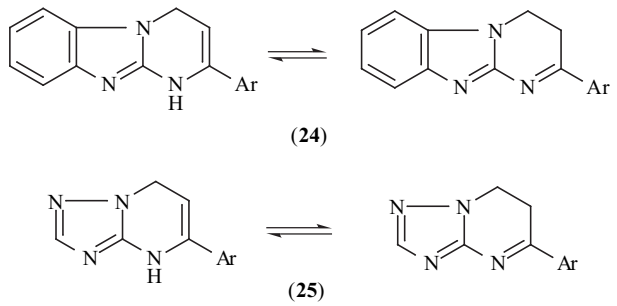
Desenko and co-workers [68], recently have reported a series of partially hydrogenated aryl substituted tetrazolo[1,5-*a*]pyrimidines (**23a-c**), where propiophenones (**1**) (R^1 = H) are forming part of the starting materials.



(**22**) (**1**) (**23**)

Scheme 12. **a**, **b**, **c** Ar = Ph, *p*-$MeOC_6H_4$, *p*-BrC_6H_4, respectively.

The reaction proceeded in refluxing isoamyl alcohol in acceptable to good yields (55-75%). Authors noticed that compounds (**23**) exist preferably as the enamine tautomeric form (**A**) in solid phase, but in solution, both enamine and imine tautomeric form (**A**) and (**B**) are observed for (**23a**) and (**23b**), while (**23c**) continue being in the enamine form (**A**).

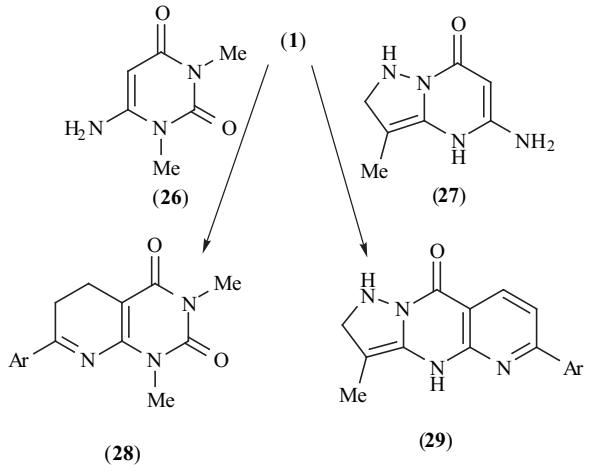


(**24**) (**25**)

Scheme 13. Ar = Ph, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-$O_2NC_6H_4$, *m*-MeC_6H_4.

In previous works, they also reported reactions of 2-aminobenzimidazole and 3-amino-1,2,4-triazole with ketonic Mannich bases to lead to tautomeric mixtures of dihydropyrimidobenzimidazoles (**24**) [69] and dihydrotriazolopyrimidines (**25**) [70,71] respectively.

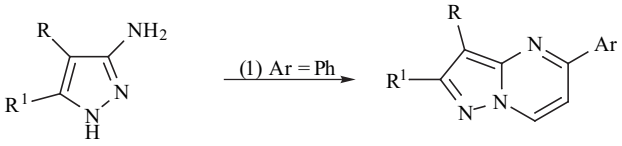
Alternatively, substitution of the azole amines by the uracil-amine (**26**) and pyrimidin-amine (**27**) lead to pyridopyrimidines (**28**) [72] and (**29**) [73] respectively.



(**26**) (**27**) (**28**) (**29**)

Scheme 14.

Similarly, Elnagdi/Erian [74] have reported the synthesis of a series of substituted pyrazolo[1,5-*a*]pyrimidines (**31**) in 62-76% yield, from the reaction of ketonic Mannich bases (**1**) and 3-aminopyrazoles (**30**).



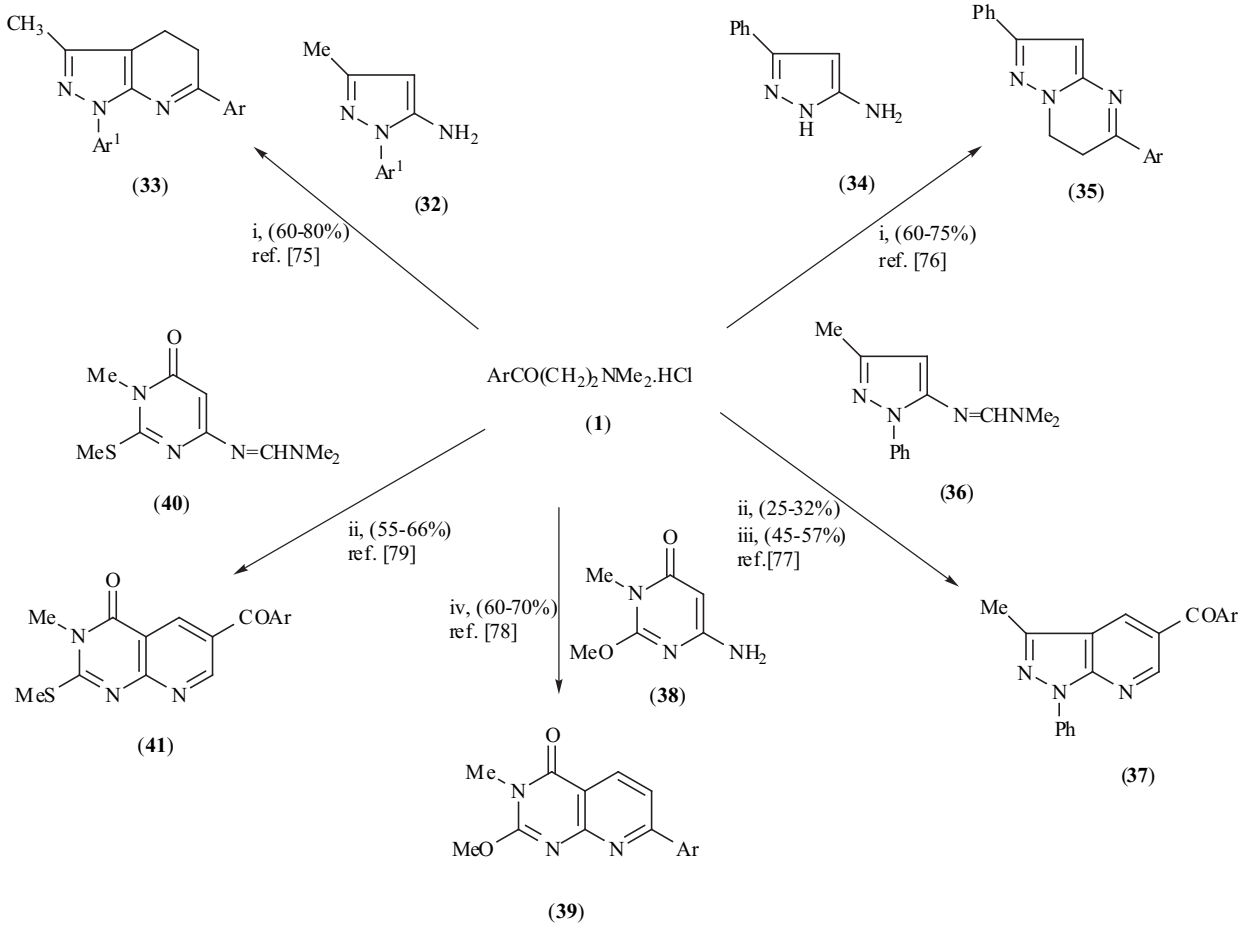
(**30**) (**31**)

Scheme 15. R = Ph, Me, NH_2; R^1 = H, C_6H_4N=N, Ph.

Reactions were carried out in refluxing DMF and accompanied by elimination of water, dimethylamine hydrochloride and hydrogen.

More recently, Quiroga and co-workers have reported a series of works leading to the formation of fused six-membered heterocyclic systems from reaction of ketonic Mannich bases with diverse 1,3-dinucleophiles [75-82] (Scheme **16**). Subsequently, new pyrazolopyridines (**33**) [75], (**37**) [77], pyrazolopyrimidines (**35**) [76], and pyridopyrimidines (**39**) [78], (**41**) [79] of biological and pharmacological interest [83-85] were regioselectively obtained in acceptable to good yields.

With regards to the above scheme, some representative compounds (**33**) were smoothly oxidized by treatment with N-bromosuccinimide in refluxing ethanol affording the respective pyrazolo[3,4-*b*]pyridines in 65-70% yield. Compounds (**35**) showed moderate anthelmintic *in vitro* activity against the *Nippostrongylus brasiliensis*. Formation of compounds (**37**) and (**41**) proceed by a hetero-Diels-Alder type reaction between the synthetically available dimethylaminomethylenamino compounds (**36**) and (**40**) and the *in situ* formed aryl vinyl ketones type (**21**), with a

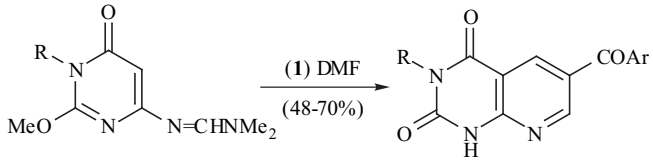


Scheme 16. i = Reflux in pyridine; ii = reflux in DMF; iii = microwave irradiation; iv = reflux in absolute ethanol.

subsequent aromatization process under the reaction conditions. A comparative study for compounds (**38**) showed that their formation proceeds faster and in better yields under microwave irradiation in dry media (2.5-3 min) than at reflux in DMF (120-145 min). For compounds (**39**), two key intermediates (**42**) and (**43**) were isolated and characterized confirming the proposed pathways for their formation, as follows:

A C-alkylation pathway to form (**42**) is preferred over the N-alkylation, due to the carbon atom at 5-position in (**38**) is the most nucleophilic center in these kinds of pyrimidines [72,86]. These finding are also experimental evidences for the proposed anti-Scraup direction of reactions of Mannich bases with aminoheterocycles which include as first step, an interaction of C- or N-endo-nucleophilic center of the heterocycle with β-C-atom of Mannich base followed by the cyclocondensation process as second step.

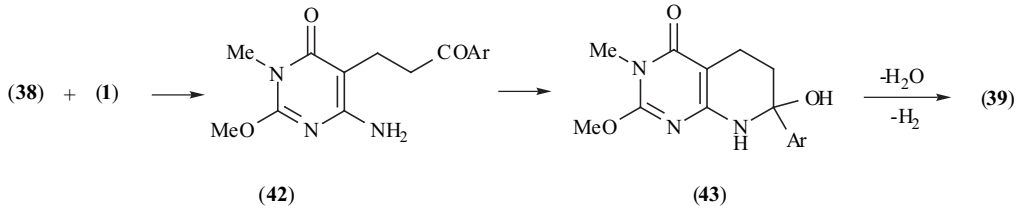
It is worth to mention that when pyrimidines (**44**) were treated with propiophenones (**1**) in refluxing DMF, pyridopyrimidin-2,4-diones (**45**) (R = H, CH_3) were obtained in good yields but not their analogues (**41**) [79].



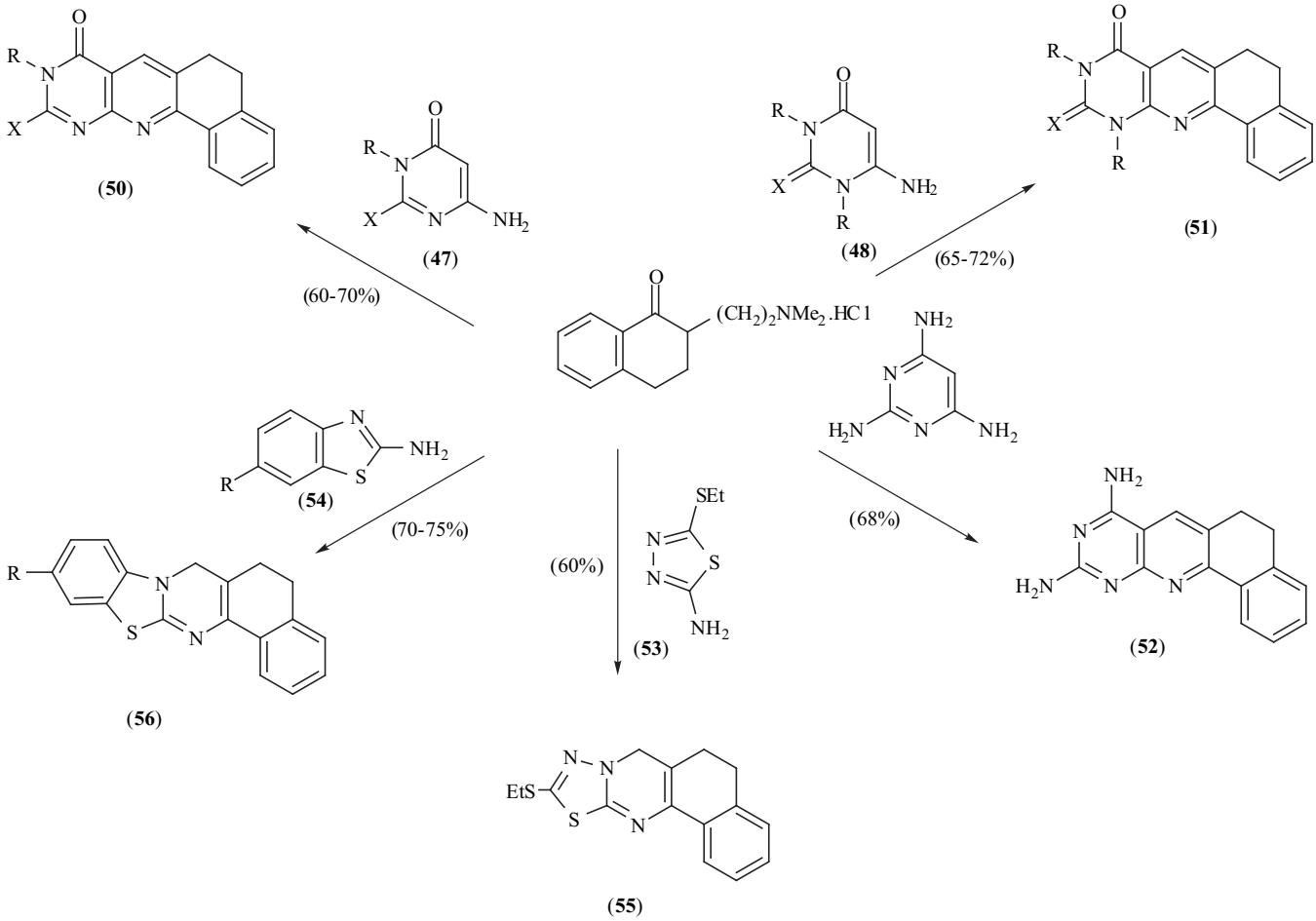
Scheme 18.

This process involves the loss of the dimethyl amino moiety under the drastic reaction conditions, which has also been observed elsewhere [87-89].

Mannich bases derived from tetralone (**46**) also react with aminopyrimidines (**47**), (**48**) and (**49**) affording



Scheme 17.



Scheme 19.

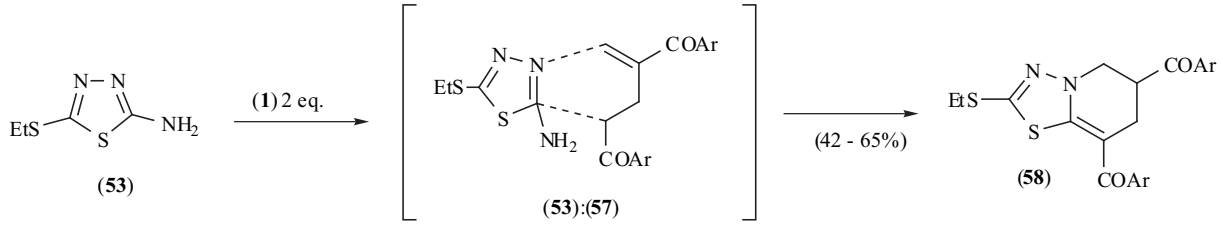
regiospecifically dihydrobenzo[*h*]pyrimido[4,5-*b*]quinolines (**50**) (R = H, Me; X = MeO, MeS, NH_2), (**51**) (R = H, Me; X = S, O) and (**52**) respectively [80] (scheme **19**). Alternatively, this Mannich base leads to the formation of benzothiazoloquinazolines (**55**) and (**56**) (R = H, Cl), from reaction with thiazoles (**53**) and (**54**) respectively [81].

All reactions were carried out refluxing equimolar amounts of pyrimidines or thiazoles and the Mannich base (**46**) in absolute ethanol. A complete NMR study as well as X-ray diffraction measurements confirmed the "linearity" of all obtained structures.

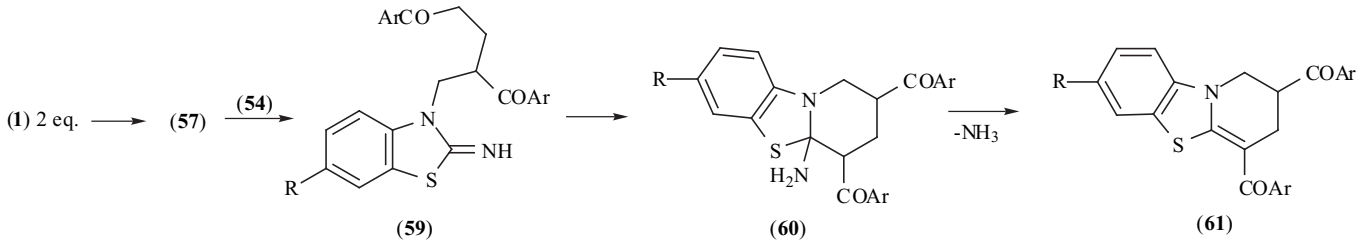
Some similar reactions with participation of two molecules of propiophenones (**1**) in the same pot of reaction are also reported (Scheme **20**). Unexpected 1:2 adducts of the dihydrothiadiazolopyridines (**58**) (Ar = Ph, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$O_2NC_6H_4$) were obtained in moderate yields from the reaction of the 2-aminothiadiazole (**53**) and propiophenones (**1**) in pyridine [82].

It is believed that the reaction proceed through the *in situ* pre-formed adduct (**53**):(**57**) from two molecules of (**1**), which subsequently reacts with the thiadiazole (**53**), involving the extrusion of a molecule of ammonia, although the process is more likely that proceed *via* a self-alkylation of the Mannich base in a similar way as shown in Schemes **21** and **22**. The proposed structures for compounds (**58**) are supported by a complete NMR study and by X-ray diffraction measurements.

In the same way, unexpected pyridobenzothiazoles (**61**) (R = H, Cl; Ar = H, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-HOC_6H_4) were obtained in 50-66% yield, from the reaction



Scheme 20.



Scheme 21.

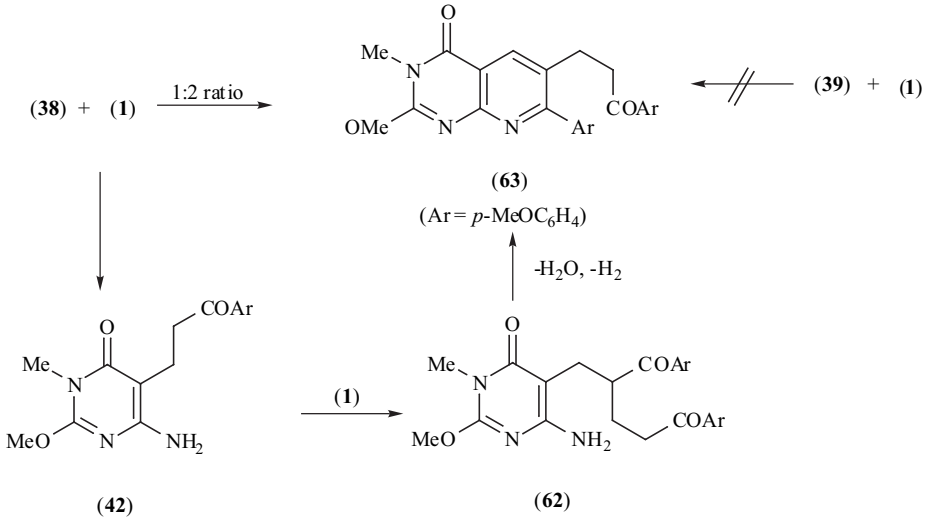
of 2-aminobenzothiazoles (**54**) with propiophenones (**1**) in refluxing ethanol (Scheme **21**). A sequence pathway that includes a self-alkylation reaction between two molecules of propiophenone (**1**) like Scheme **20** is proposed [81].

The exclusive formation of products (**55**) and (**56**) from the Mannich base (**46**) (Scheme **19**) is attributed to steric hindrance, which make impossible the formation of an adduct-intermediate like (**53**):(**57**) (Scheme **20**) from such a Mannich base. The contrary happens with the Mannich base (**1**), which leads to the formation of products type (**58**) and (**61**), through the mentioned intermediate.

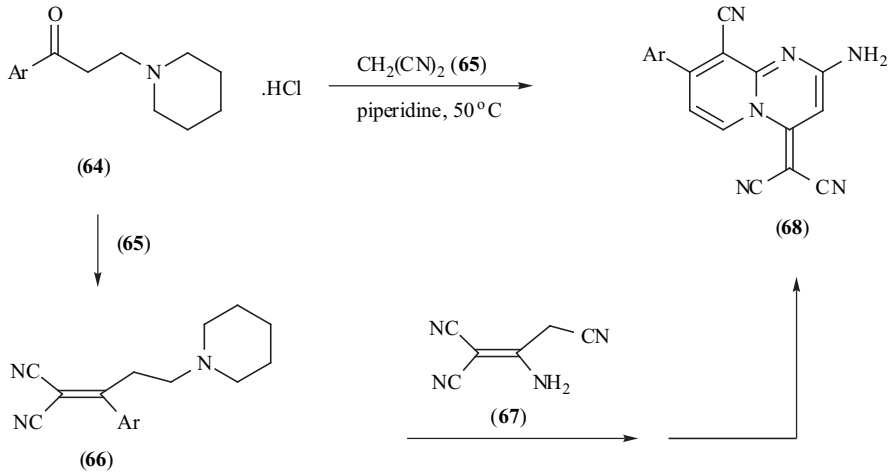
An interesting result was obtained when pyrimidine (**38**) was treated with propiophenone (**1**) (Ar = *p*-$MeOC_6H_4$) [78].

In this unique case, compound (**63**) is formed from the amine (**38**) but not from the pyridopyrimidine (**39**). These findings reinforces the pathway proposed for the formation of (**63**), through the intermediates (**42**) and (**62**). Alternatively, formation of compounds (**58**), (**61**) and (**62**) could occur, firstly, by a 1:1-interaction of Mannich bases and the respective monoamines (**53**), (**54**) and (**38**). Then the 1:1-adducts formed are attacked by a second molecule of Mannich base to render the cyclocondensated products.

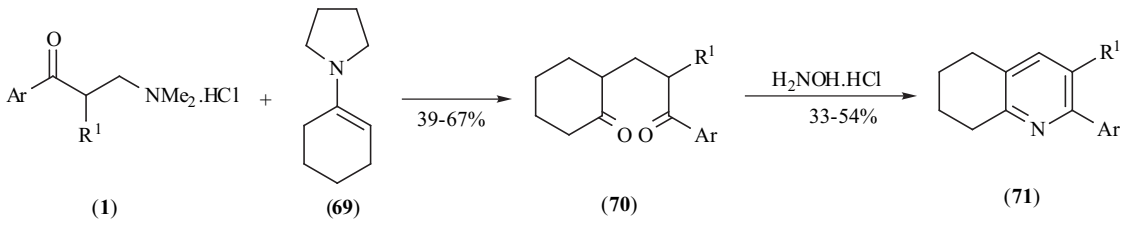
Recently Hammouda and co-workers [90], have reported some reaction of ketonic Mannich bases (**64**) with malononitrile (**65**) and malononitrile dimer (**67**) leading to the formation of six-membered fused heterocyclic systems



Scheme 22.



Scheme 23.



Scheme 24.

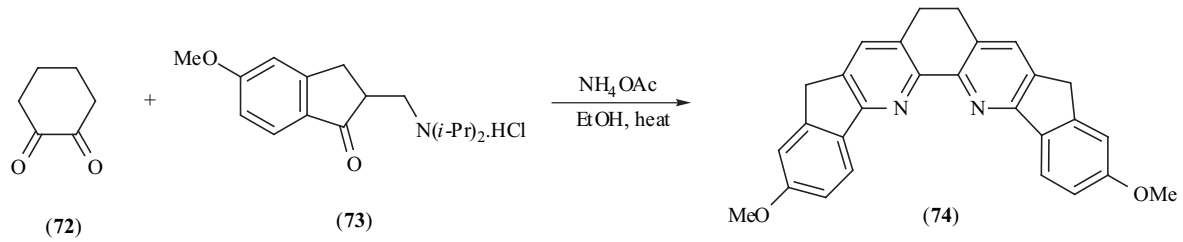
(**68**) (Ar = Ph, *p*-$MeOC_6H_4$, *p*-HOC_6H_4) in 60-62% yield.

This methodology was extended to other aryl and cycloalkyl ketonic Mannich bases with similar results. According to the authors these reactions could proceed through condensation products like (**66**) and the dimeric nitrile (**67**). Precedents for analogous reactions are scarcely known [91].

Risch and co-workers have reported an interesting route for the synthesis of functionalized pyridines [92-94] and the pharmaceutically attractive 5,6,7,8-tetrahydroquinolines (**71**) in acceptable yields, by starting with the enamine (**69**) and ketonic Mannich bases (**1**) (R^1 = H, Me, Ph; Ar = Ph, *p*-BrC_6H_4) [95].

An extension to the above methodology is the one-pot synthesis of the 3,3′-bridged bipyridine (**74**) in 12% yield, from 1,2-cyclohexanodione (**72**) and the ketonic Mannich base (**73**) [96].

This approach constitutes a domino reaction where several bonds are formed in only one sequence without the need to isolate intermediates. Formation of a bis-alkylated diketone (like intermediate **70** Scheme **24**) with subsequent closure of ring by reaction with the ammonium acetate, are part of this sequence. Attempts to increase the yield of compounds (**74**) were unfruitful. Some other pyridine and bipyridine derivatives were obtained in the same way and in better yields, by combination of the following ketonic Mannich bases (**75**)-(**77**) with ketones (7**8**)-(**82**):

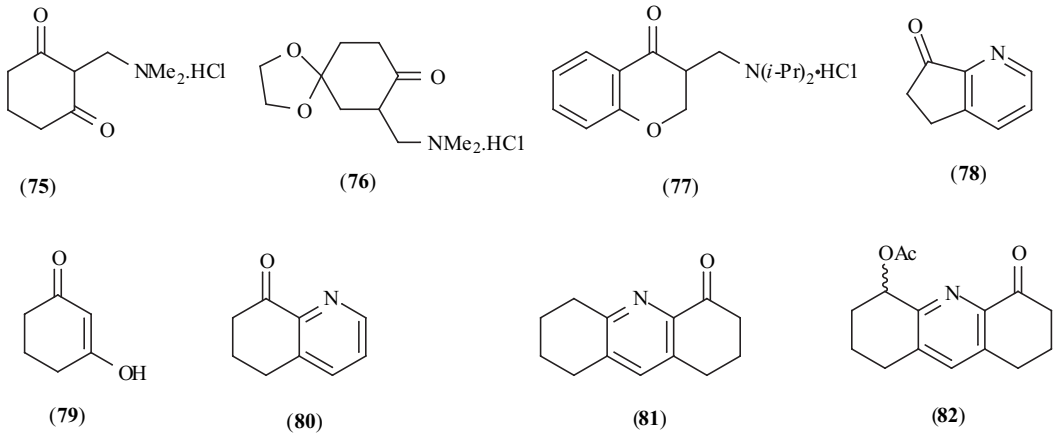


Scheme 25.

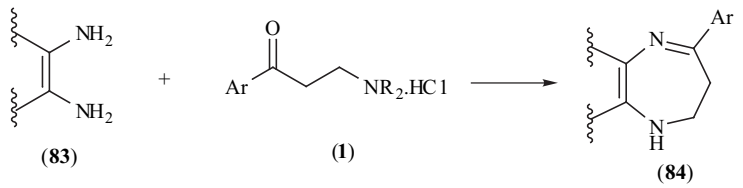
In this approach the Mannich bases (**1**) were obtained according to the method described by Kinast [35], in which they were subjected to reaction with the enamine (**69**) in refluxing dioxane to render the diketones (**70**). Subsequently, the treatment of (**70**) with hydroxylammoniun chloride in refluxing ethanol led to compounds (**71**). This methodology was extended to other aliphatic and alicyclic ketonic Mannich bases with similar results.

4.3. Formation of Seven-membered Nitrogenated Heterocyclic Rings

The discovery of diazepam followed by many other psychotropic agents sharing a 1,4-benzodiazepine skeleton has also promoted the studies on the isomeric 1,5-benzodiazepine ring systems. Several approaches have been developed with this purpose; one of them being the

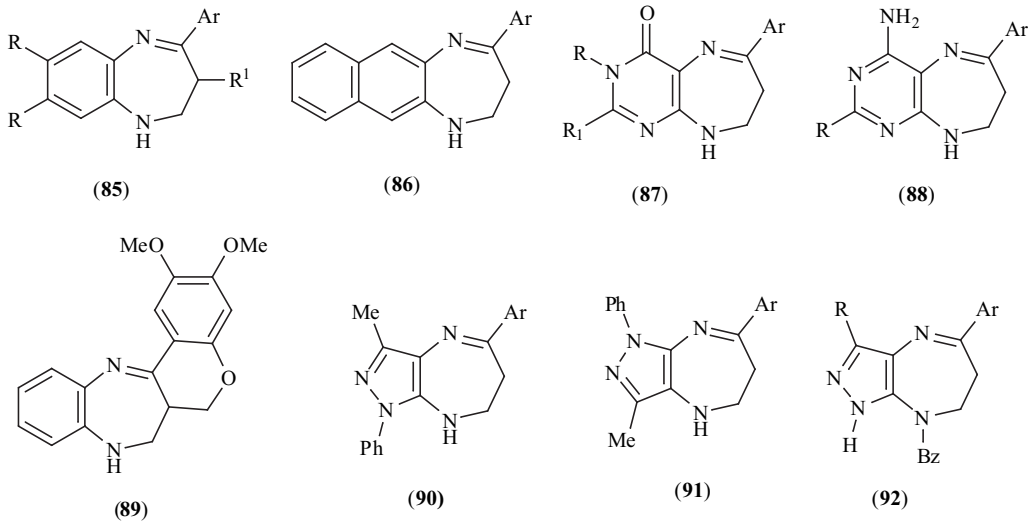


Scheme 26.



(**83**) (**1**) (**84**)

Scheme 27.



(**85**) (**86**) (**87**) (**88**)

(**89**) (**90**) (**91**) (**92**)

Scheme 28.

cyclocondensation of ketonic Mannich bases with homo- and heterocyclic aromatic *o*-diamines, leading to the formation of biological and pharmacologically attractive 1,5-benzodiazepine derivatives and analogue systems. This method is particularly appropriate when 1,5-benzo- or 1,5-hetero-diazepines substituted only at the 4-position of the azepinic ring representing the preparative target.

For instance, cyclocondensation reaction of *o*-phenylenediamines or *o*-heterodiamines (**83**) with ketonic Mannich bases (**1**) leads to the formation of diverse 1,5-diazepinic systems (**84**) (Scheme **27**). Reaction is accompanied by elimination of both dialkylammonium chloride and water molecules.

Representative examples of compounds prepared in this way are given in Scheme **28** and Table **1**.

Looking mainly for a synthetic application [97] compounds (**85e**) and (**85h**) were reduced to the

Table 1. Analytical Data for Diverse Diazepinic Systems Derived from Ketonic Mannich Bases (1)

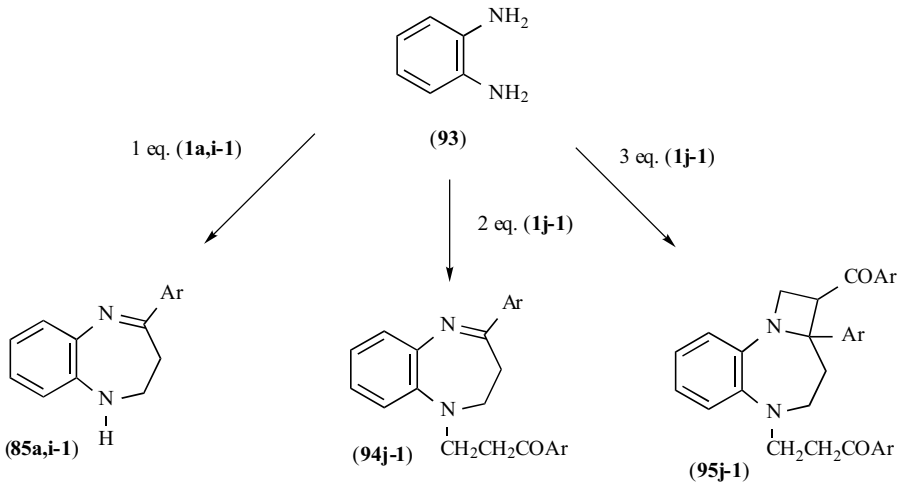
Comp.	Ar	R	R^1	Reaction conditions	Yield %	mp ^{0}C	Reference
85a	Ph	H	H	A B	60 60	42-3 129	[97] [98]
85b	Ph	7,8-di-Cl	H	A	48	45-6	[97]
85c	*p*-MeC_6H_4	Me	H	A	76	36-9	[97]
85d	*o*-HO_6H_4	H	H	A	90	119-20	[97]
85e	*o*-HO_6H_4	7,8-di-Me	H	A	87	134-6	[97]
85f	*m*-$MeOC_6H_4$	7,8-di-Me	H	A	65	47-8	[97]
85g	*p*-$O_2NC_6H_4$	7,8-di-Me	H	A	28	279-82	[97]
85h	*p*-$MeOC_6H_4$	7,8-di-Me	H	A	92	173-4	[97]
85i	*p*-$MeOC_6H_4$	H	H	B C	45 55	155 152-3	[98] [99]
85j	*p*-ClC_6H_4	H	H	B	68	130	[98]
85k	*p*-BrC_6H_4	H	H	B C	72 49	140 138-9	[98] [99]
85l	*p*-$O_2NC_6H_4$	H	H	B	60	129	[98]
85m	*p*-MeC_6H_4	H	H	C	41	138-9	[99]

(Table 1)contd.....

Comp.	Ar	R	R^1	Reaction conditions	Yield %	mp ^oC	Reference
85n	2-thienyl	H	H	C	45	109-10	[99]
85o	2-HO-5-MeC_6H_4	H	H	C	61	112-13	[99]
85p	3-Br-2-HO-5-MeC_6H_4	H	H	C	74	192-3	[99]
85q	3,4,5-$(MeO)_3$ C_6H_2	H	H	D			[100]
86a	2-HO-5-MeC_6H_4			C	55	182-3	[99]
86b	3-Br-2-HO-5-MeC_6H_4			C	81	237-9	[99]
86c	*o*-HO_6H_4			C	58	176-7	[99]
86d	2-HO-4-MeC_6H_4			C	62	180-1	[99]
87a	*p*-BrC_6H_4	H	MeS	E	26	219	[101]
87b	*p*-ClC_6H_4	H	MeS	E	35	228	[101]
87c	*p*-$O_2NC_6H_4$	H	MeS	E	60	250	[101]
87d	*p*-ClC_6H_4	Me	MeS	E	28	269	[101]
87e	*p*-$O_2NC_6H_4$	Me	MeS	E	58	327	[101]
87f	*p*-ClC_6H_4	Me	MeO	E	26	255	[101]
87g	*p*-$O_2NC_6H_4$	Me	MeO	E	51	260	[101]
88a	Ph	H		B	40	275	[102]
88b	*p*-ClC_6H_4	H		B	50	254	[102]
88c	*p*-BrC_6H_4	H		B	45	253	[102]
88d	*p*-$O_2NC_6H_4$	H		B	65	242	[102]
88e	Ph	NH_2		B	40	215	[102]
88f	*p*-MeOC_6H_4	NH_2		B	35	212	[102]
88g	*p*-ClC_6H_4	NH_2		B	55	250	[102]
88h	*p*-BrC_6H_4	NH_2		B	50	250	[102]
88i	*p*-$O_2NC_6H_4$	NH_2		B	65	285	[102]
89				D			[100,103]
90a	Ph			B	35	240	[104]
90b	*p*-ClC_6H_4			B	38	220	[104]
90c	*p*-BrC_6H_4			B	37	221	[104]
90d	*p*-$O_2NC_6H_4$			B	35	214	[104]
91a	Ph			B	30	95	[104]
91b	*p*-ClC_6H_4			B	32	154	[104]
91c	*p*-BrC_6H_4			B	30	177	[104]
91d	*p*-$O_2NC_6H_4$			B	33	209	[104]
92a	Ph	*p*-ClC_6H_4		E	50	238	[105]
92b	*p*-ClC_6H_4	*p*-ClC_6H_4		E	60	269	[105]
92c	*p*-BrC_6H_4	*p*-ClC_6H_4		E	65	265	[105]
92d	*p*-$O_2NC_6H_4$	*p*-ClC_6H_4		E	82	240	[105]
92e	*p*-MeOC_6H_4	*p*-BrC_6H_4		E	60	259	[105]
92f	*p*-ClC_6H_4	*p*-BrC_6H_4		E	62	256	[105]
92g	*p*-BrC_6H_4	*p*-BrC_6H_4		E	72	246	[105]
92h	*p*-$O_2NC_6H_4$	*p*-BrC_6H_4		E	80	222	[105]

^{A}Refluxing xylene, ^{B}refluxing EtOH, ^{C}refluxing EtOH/anh. Na_2OAc, ^{D}refluxing HOAc, ^{E}refluxing EtOH/HOAc.

corresponding tetrahydro-derivatives by treatment with $NaBH_4$. Compounds (**85q**) and (**89**) exhibited interesting activities as neoplasm inhibitors [100, 103]. Meanwhile the diazepinic 1:2- and 1:3-adducts (**94j-l**) and (**95j-l**) were



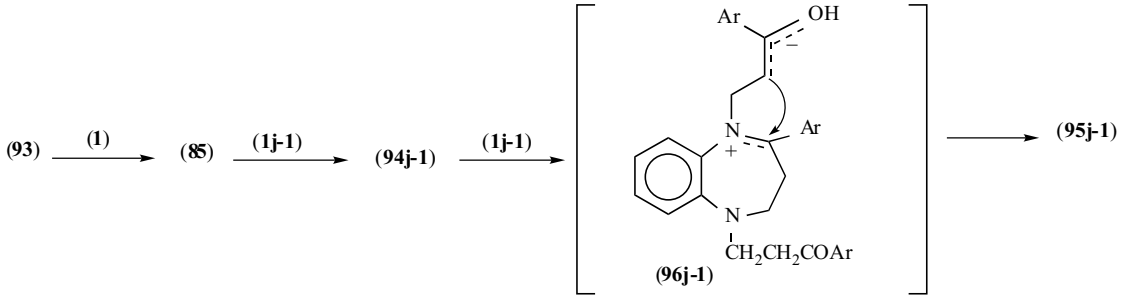
Scheme 29.

unexpectedly obtained along with diazepines (**85j-l**) in the same pot of reaction (Scheme **29**). After several reactions were carried out, it was established that compounds (**85a,i-l**) or adducts (**94j-l**) and (**95j-l**) can be selectively obtained each one as main product, just by controlling the stoichiometry of the starting materials and the reaction conditions.

A mechanistic pathway was proposed to explain the above results, which include formation of the alkyliminium intermediates (**96**) (Scheme **30**). Formation of adducts (**94**) and (**95**) is attributed not only to the ability of propiophenones (**1**) to serve as alkyling agents through the adducts (**94j-l**) and (**95j-l**) were obtained by treatment of diazepines (**85j-l**) with one and two equivalents of the propiophenones (**1j-l**) respectively, which constitute an important support for the proposed mechanism.

5. MISCELLANEOUS

A series of spiro-benzazepines (**98**) and (**99**) with potential biological activities [106,107] were obtained in 47–84% yields from the reaction of benzazepinediones (**97**) with some propiophenones (**1**) in ethanol and *t*-BuOK as

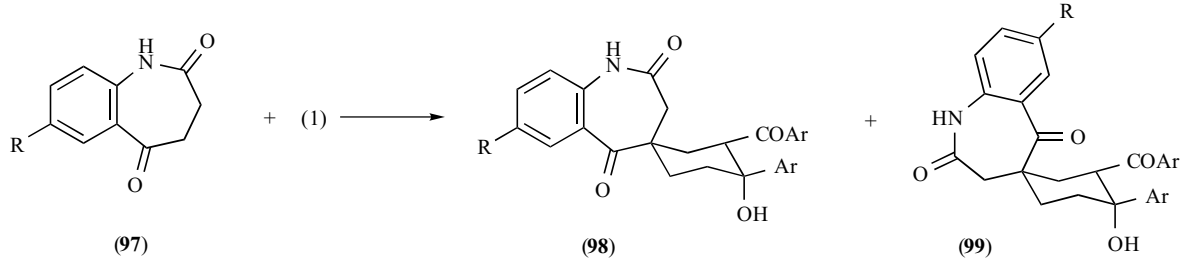


Scheme 30.

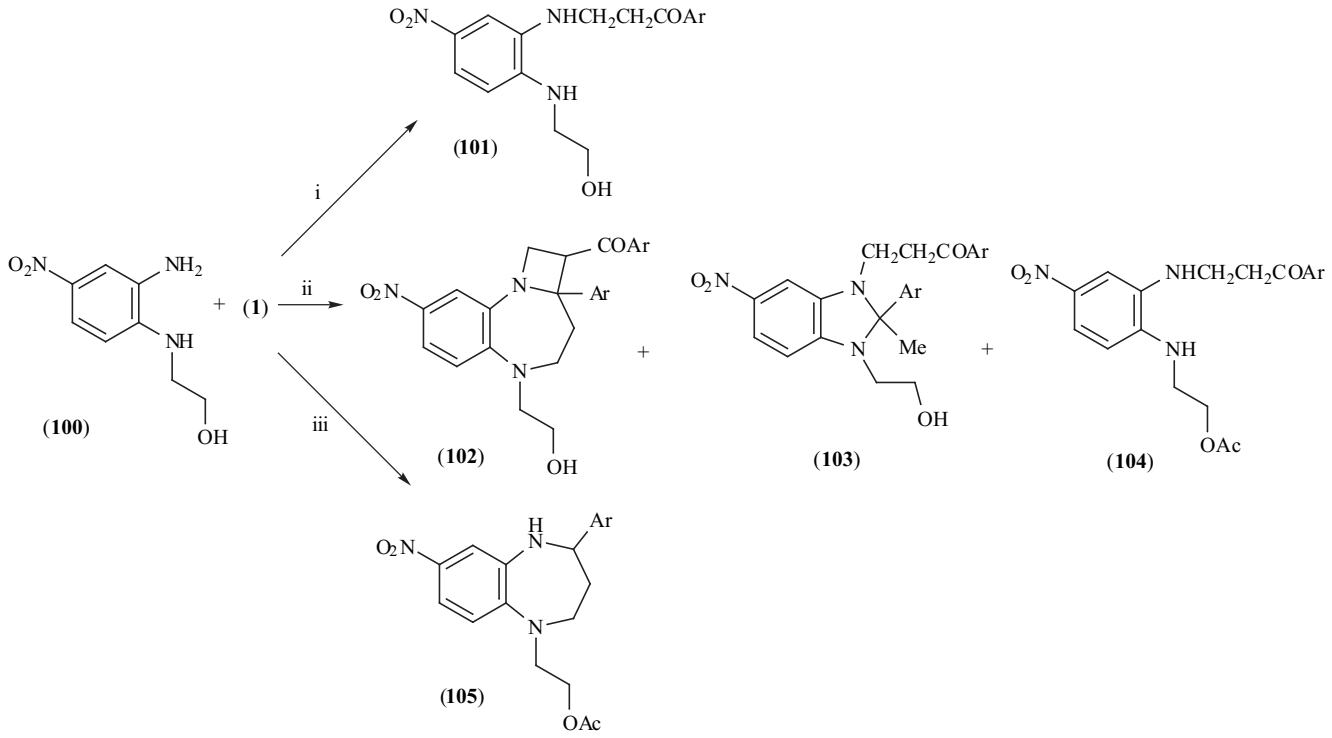
β-carbon atom, but also by the presence of acidic α-hydrogen atoms, which are in keto-enolic tautomerism, making this position suitable for nucleophilic additions as is the case of the 1:3-adducts (**95**).

It is worth to mention that 1:2- and 1:3-adducts only were formed when the *p*-substituent in propiophenones (**1**) are electron-withdrawing groups (i. e. Cl, Br, NO_2). This finding was attributed to electronic effects [98]. Alternatively catalyst [108]. Two molecules of propiophenones are involved in this process. Ratios of both racemic diastereomers were determined in each case by NMR studies.

Although formation of the six-membered spiro-ring does not lead to a nitrogenated heterocyclic system, nevertheless, structures (**98**) and (**99**) belong to this kind of systems by themselves. Moreover, this finding indicates the other facet of the propiophenones (**1**) acting not only as synthetic



Scheme 31. R = H, Br; Ar = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-BrC_6H_4, 2-naphthyl.



Scheme 32. i) EtOH, 2 h; ii) glacial acetic acid, 30 min; iii) glacial acetic acid, 6 h.
Ar = Ph, *p*-MeC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$O_2NC_6H_4$

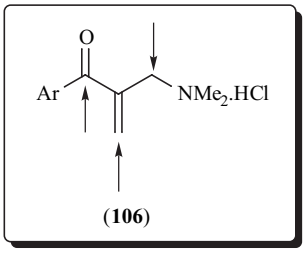
equivalent of α,β-unsaturated ketones for Michael type additions, but also as appropriate substrates for intramolecular aldol additions through the acidic α-hydrogen atoms.

Several alkylation and cyclization products (**101**)–(**105**) were obtained when nitrophenylenediamine (**100**) was treated with propiophenones (**1**) under different reaction conditions [109] (scheme **32**). Although the formation of some of them is in discussion, they reflect again the capability as alkylating and cyclocondensing agents showed by propiophenones (**1**) along this review.

6. CONCLUSION AND OUTLOOK

The aim of this short review has been to demonstrate the wide synthetic and preparative applications of a particularly versatile class of Mannich bases i.e. β-(*N,N*-dialkylamino)propiophenones for the generation of single or fused heterocyclic systems: pyrazoles, imidazoles, triazoles, pyrimidines, pyridines and diazepines. Most important procedures worked out for their synthesis are compiled up-to-date and their chemical transformation leading to the formation of biological and pharmacologically attractive heterocyclic systems are discussed as well. It is hoped that a greater understanding of their potential in the synthesis of nitrogenated heterocyclic systems of five-, six- and seven-membered rings will result.

The 1-aryl-2-dialkylaminomethyl-prop-2-en-1-ones (ADMP reagents) (**106**) closely related with the propiophenones (**1**) under study, are another promising group of ketonic Mannich bases, which are gaining increasing attention not only in medicinal chemistry but also because they can be visualized as valuable building blocks for ring closure reactions, owing to their three different electrophilic reaction centers, which can be attacked by ambifunctional nucleophilic reagents to afford diverse substituted heterocyclic compounds [8].



(**106**)

ABBREVIATIONS

Ac_2O	=	Acetic anhydride
ADMP	=	1-Aryl-2-dialkylaminomethyl-prop-2-en-1-ones
Anh.	=	Anhydrous
Ar	=	Aryl group
Bn	=	Benzyl
DMF	=	N,N-dimethylformamide
Et	=	Ethyl
EtOH	=	Ethanol
EtS	=	Ethylthio
HOAc	=	Acetic acid
i-Pr	=	Isopropyl
IR	=	Infrared

m-	=	meta-
Me	=	Methyl
min	=	Minutes
MeO	=	Methoxy
MeS	=	Methylthio
α-NETA	=	2-(α-Naphthoyl)ethyltrimethylammonium iodide
β-NETA	=	2-(β-Naphthoyl)ethyltrimethylammonium iodide
NMR	=	Nuclear Magnetic Resonance
n-Pr	=	n-Propyl
o-	=	ortho-
OAc	=	Acetate
p-	=	para-
Ph	=	Phenyl
R	=	Alkyl group
t-BuOK	=	Potassium *tert*-butoxyde
THF	=	Tetrahydrofuran

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REFERENCES

[1] Hellmann, H.; Opitz, G. *Angew. Chem.*, **1956**, *68*, 265.
[2] Thompson, B. *J. Pharm. Sci.*, **1968**, *57*, 715.
[3] Miocque, M. *Ann. Pharm. Franc.*, **1969**, *27*, 381.
[4] Tramontini, M. *Synthesis* **1973**, 703 and references cited therein.
[5] Arend, M.; Westermann, B.; Risch, N. *Angew. Chem.*, **1998**, *110*, 1096. *Angew. Chem. Int. Ed. Engl.*, **1998**, *37*, 1045.
[6] Moiseev, I.; Makarova, N.; Zemtsova, M. *Chem. Heterocycl. Compd.*, **1999**, *35*(6), 637.
[7] Roman, Gh.; Comanita, E.; Dumitrescu, L.; Andrei, M.; Ardeleanu, R. *Bull. Transilv. Univ. Brasov, Ser. B: Mathematics, Chemistry, Medicine, Philology*, **1999**, (6), 75.
[8] Girreser, U.; Heber, D. *J. Prakt. Chem*., **2000**, *342*(3), 230.
[9] Blicke, F. in *Org. Reactions 1. The Mannich Reaction*s, **1942**, pp. 303.
[10] Reichert, B. *Die Mannich Reaktion*, Springer-Verlag, Berlin, **1959**.
[11] Hellmann, H.; Opitz, G. *α-Aminoalkylierung*, Verlag Chemie, Weinheim, Germany, **1960**.
[12] Dimmock, J.; Sidhu, K.; Chem, M.; Reid, R.; Allen, T.; Kao, G.; Truitt, G. *Eur. J. Med. Chem.*. **1993**, *28*(4), 313.
[13] Dimmock, J.; Erciyas, E.; Raghavan, S.; Kirkpatrick, D. *Pharmazie* **1990**, *45*(10), 755.
[14] Werner, W.; Jungstand, W.; Gutsche, W.; Wohlrabe, K. *Pharmazie* **1977**, *32*(6), 341.
[15] Shiozawa, A.; Narita, K.; Izumi, G.; Kurashige, S.; Sakitama, K.; Ishikawa, M. *Eur. J. Med. Chem.*. **1995**, *30*(1), 85.
[16] Erol, D.; Rosen, A.; Erdogan, H.; Yulug, N. *Arzneim. Forsch.* **1989**, *39*(7), 851. *Chem. Abstr*., **1989**, 112, 118697s.
[17] Wilson, W.; Kyi, Z-Y. *J. Chem. Soc.*, **1952**, 1321.
[18] Marcus, R.; Gloye, E.; Florance, E. *Computers & Chemistry* **1997**, *1*(4), 235.
[19] Müller, E.; Vogel, J.; Kandt, D. *Z. Erkr. Atmungsorgane* **1976,** *145*(3), 339
[20] Pupo, A.; Uberti, M.; Minneman, K. *Eur. J. Pharmacol.*, **2003**, *462*, 1.
[21] Zhu, W.; Zhang, Y.; Han, Ch. *Eur. J. Pharmacol.*, **1997**, *329*, 55.
[22] Engel, G.; Hoyer, D. *J. Cardiovasc. Pharmacol.*, **1982**, *4*, S25.
[23] Hicks, P. *J. Auton. Pharmacol.*, **1981**, *5*, 391.
[24] Alper, K.; Barry, J.; Balabanov, A. *Epilepsy & Behavior* **2002**, *3*(5), 13.
[25] Szeszko, P.; Bilder, R.; Dunlop, J.; Walder, D.; Lieberman, J. *Biol. Psychiatry* **1999**, *45*(6), 680.
[26] Sastry, B.; Jaiswal, N.; Owens, L.; Janson, V.; Moore, R. *J. Pharmacol. Exp. Ther.* **1988**, *245*(1), 72.
[27] Rane, D.; Fishman, A.; Pike, R. *Synthesis* **1984**, 694.
[28] Takahashi. K.; Shimizu, S.; Ogata, M. *Synth. Commun.*, **1987**, *17*, 809.
[29] Rentzea, C.; Ammermann, E.; Pommer, E. (BASF A.-G.), DE 3,011,258; *Chem. Abstr.*, **1982**, *96*, 35250.
[30] Zirngibl, L. *Antifungal Azoles*, Wiley-VCH, New York, **1998**.
[31] Vogel´s Textbook of Practical Organic Chemistry, 4th ed., Longman Inc., New York, **1978**.
[32] Gautier, J.; Miocque, M.; Quan, D. *C. R. Acad. Sci.*, **1964**, *258*, 3731.
[33] Brandes, R.; Roth, H. *Arch. Pharm.*, **1967**, *300*, 1005.
[34] Okuda, T:, Matsumoto, U. *Yakugaku Zasshi* **1959**, 79, 1140. *Chem. Abstr.* **1960**, *54*, 3452.
[35] Kinast, G.; Tietze, L. *Angew. Chem.*, **1976**, 88, 261. *Angew. Chem. Int. Ed. Engl.*, **1976**, *15*, 239.
[36] Ran, H.; Ding, J. CN 1,107,474 **1994**; *Chem. Abstr.* **1996**, *124*, 261038.
[37] Ishmetova, R.; Kitaeva, V.; Rusinov, G.; Beresnev, D. *Russ. J. Org. Chem.*, **1995**, *31*(3), 392.
[38] Schaller, R.; Ehrhardt, H.; Sachse, B.; Buerstell, B.; Bieringer, H.; Klaus, K. (Hoechst A.-G.), EP 132,771. *Chem. Abstr.* **1985**, *103*, 160511.
[39] Popov, A.; Piskunova, Zh.; Matvienco, V.; Kondratenko, G.; Nikolenko, Y. *Khim. –Farm. Zh.*, **1989**, *23*, 1232. *Chem. Abstr.* **1989**, 112, 52089m.
[40] Maier, T.; Mildenberger, H. *Angew. Chem.* **1980**, *92*, 128.
[41] Dickens, J.; Ellames, G.; Hare, N.; Lawson, K.; McKay, W.; Metters, A.; Myers, P.; Pope, A.; Upton, R. *J. Med. Chem.*, **1991**, *34*, 2356.
[42] Andreani, F.; Andrisano, R.; Della Casa, C.; Tramontini, M. *Tetrahedron Lett.*, **1968**, 1059.
[43] Roman, Gh.; Comanita, E.; Comanita, B. *Chem. Heterocycl. Compd.*, **2002**, *38*(9), 1072.
[44] Low. J.; Cobo, J.; Nogueras, M.; Sánchez, A.; Cuervo, P.; Abonia, R. *Acta Cryst.*, **2002**, *E58*, 769.
[45] Abonia, R. Unplublished data.
[46] Montigoul, C.; Richard, M.; Vigne, C.; Giral, L. *J. Heterocyclic Chem.*, **1984**, *21*, 1489.
[47] House, H.; Kramar, V. *J. Org. Chem.*, **1970**, *28*, 3362.
[48] Austin, E.; Brown, H.; Buchanan, G. *Tetrahedron* **1969**, *25*, 5509.
[49] Buchanan, G.; Lay, G. *Chem. Commun.*, **1965**, 504.
[50] Haynes, N.; Timmons, C. *J. Chem. Soc. (C)*, **1966**, 224.
[51] Hammouda, M; Hamana, W.; Kandeel, E.; Afsa, E. *Pharmazie* **1988**, *43*, 529.
[52] Hammouda, M; Kandeel, E.; Hamana, W.; Afsa, E. *Arch. Pharm. Res.* **1993**, *16*(1), 88.
[53] Austin, E.; Brown, H.; Buchanan, G.; Raphael, R. *Tetrahedron* **1969**, *25*, 5517.
[54] Andreani, F.; Andrisano, R.; Della Casa, C.; Tramontini, M. *J. Chem. Soc. (C)*, **1970**, 1157.
[55] Popovici, I.; Comanita, E.; Roman, Gh.; Comanita, B. *Acta Chim. Slov.*, **1999**, *46*(3), 413.
[56] Comanita, E.; Popovici, I.; Roman, Gh.; Robertson, G.; Comanita, B. *Heterocycles* **1999**, *51*, 2139.
[57] Roman, Gh.; Comanita, E.; Comanita, B. *Tetrahedron* **2002**, *58*, 1617.
[58] Mizuta, H.; Naruto, S.; Suzuki, T.; Nagamoto, M.; Uno, H.; Nishimura, H. *Eur. J. Med. Chem.*, **1987**, *22*(3), 209.
[59] Villalobos, A.; Blake, J.; Biggers, C.; Butler, T.; Chapin, D.; Chen, Y.; Ives, J.; Jones, S.; Liston, D.; Nagel, A.; Nason, D.; Nielsen, J.; Shalaby, I.; White, W. *J. Med. Chem.*, **1994**, *37*(17), 2721.
[60] O'Malley, G.; Palermo, M. (Hoechst-Roussel Pharmaceuticals Inc.), US 5,494,908. *Chem. Abstr.*, **1996**, 124, 343282. See also O'Malley, G.; Palermo, M. (Aventis Pharmaceuticals Inc.) US 6,046,203.

[61] Drungilaite, V.; Chekuolene, L.; Shimkyavichene, V. 10th International Conference on Synthetic and Physiologically Active Compounds, **1990**, Erevan, p. 47.
[62] Chase, B.; Evans, J. *J. Chem. Soc. (C)*, **1964**, (12), 4825.
[63] Levin, Ya.; Kostin, V.; Gembitskii, P. *Zh. Obshch. Khim.*, **1961**, *31*, 1185; *Chem. Abstr.*
[64] Aubagnac, J.; Bouchet, P.; Elguero, J.; Marzin, C.; Jacquier, R. *J. Chim. Phys.*, **1967**, *64*, 1649.
[65] Judi, L.; Rivet, D.; Wilshire, J. *Austral. J. Chem.*, **1977**, *30*, 629.
[66] Dong, F.; Jiang, G.; Li, J. *Chem. J. Chin. Univ.*, **1990**, 11, 205; *Chem. Abstr.*
[67] Andrisano, R.; Chierici, L. *Gazz. Chim. Ital.* **1959**, *89*, 888.
[68] Desenko, S.; Gladkov, E.; Komykhov, S.; Shishkin, O.; Orlov, V. *Chem. Heterocycl. Compd.*, **2001**, *37*(6), 747.
[69] Desenko, S.; Orlov, V.; Lipson, V.; Estrada, Kh. *Chem. Heterocycl. Compd.*, **1991**, *27*(9), 976.
[70] Desenko, S.; Orlov, V.; Shishkin, O.; Borykin, K.; Lindeman, S.; Struchkov, Yu. *Chem. Heterocycl. Compd.*, **1993**, *29*(10), 1163.
[71] Desenko, S.; Orlov, V.; Lipson, V.; Shishkin, O.; Lindeman, S.; Struchkov, Yu. *Chem. Heterocycl. Compd.*, **1991**, *271*, 1242.
[72] Troschutz, R.; Roth, H. *Arch. Pharm. (Weinheim)*, **1978**, *311*, 406.
[73] Klein, H.; Troschutz, R.; Roth, H. *Arch. Pharm.*, **1985**, *318*, 353.
[74] Elnagdi, M.; Erian, A. *Bull. Chem. Soc. Jpn.*, **1990**, *63*(6), 1854. *Chem. Abstr.* **1990**, 113, 191279g.
[75] Quiroga, J.; Insuasty, B.; Cruz, S.; Hernández, P.; Bolaños, A.; Moreno, R. *J. Heterocyclic Chem.*, **1998**, *35*, 333.
[76] Quiroga, J.; Insuasty, B.; Abonia, R.; Hernández, P.; Nogueras, M.; Sánchez, A. *Heterocyclic Commun.*, **2000**, *6*(4), 345.
[77] Quiroga, J.; Insuasty, B.; Hormaza, A.; Gamenara, D.; Domínguez, L.; Saldaña, J. *J. Heterocyclic Chem.*, **1999**, *36*, 11.
[78] Quiroga, J.; Insuasty, H.; Insuasty, B.; Abonia, R.; Cobo, J.; Sánchez, A.; Nogueras, M. *Tetrahedron* **2002**, *58*, 4873.
[79] Quiroga, J.; Viveros, G.; Insuasty, B.; Nogueras, M.; Sánchez, A.; Cobo, J. *J. Heterocyclic Chem.*, **1999**, *36*, 501.
[80] Quiroga, J.; Insuasty, B.; Insuasty, H.; Abonia, R.; Ortíz, A.; Sánchez, A.; Nogueras, M. *J. Heterocyclic Chem.*, **2001**, *38*, 339.
[81] Quiroga, J.; Hernández, P.; Insuasty, B.; Abonia, R.; Cobo, J.; Sánchez, A.; Nogueras, M.; Low, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 555.
[82] Quiroga, J.; Insuasty, B.; Hernández, P.; Moreno, R.; De Almeida, R.; Meier, H. *Eur. J. Org. Chem.*, **1998**, 1201.
[83] Delia, T. In The Chemistry of Heterocyclic Compounds, Vol. 24. Fused Pyrimidines, Part 4, **1992**.
[84] Makamizawa, Y. Japan Patent 1,364,063, **1960**; *Chem. Abstr.*, **1964**, 60, 531.
[85] Hardy, C. *Adv. Heterocyclic Chem.*, **1984**, *36*, 343.
[86] Quiroga, J.; Insuasty, B.; Insuasty, B.; Sánchez, A.; Nogueras, M.; Meier, H. *J. Heterocyclic Chem.*, **1992**, *29*, 1045.
[87] García, J.; Sánchez, A.; Nogueras, M. *J. Heterocyclic Chem.*, **1989**, *26*, 1089.
[88] Melgarejo, M.; Rodríguez, C.; Nogueras, M.; Sánchez, A. *An. Quim.*, **1982**, *78*(3)C, 399.
[89] Nogueras, M.; Quijano, M.; Sánchez, A.; Melgarejo, M. *Nucleosides Nucleotides* **1989**, *8*, 117.
[90] Hammouda, M.; El-Ahl, A.; El-Toukhee, Y.; Metwally, M. *J. Chem. Research (S)* **2002**, 89.
[91] Otto, H.; Schmelz, H. *Monatsh. Chem.*, **1980**, *111*(1), 53.
[92] Keuper, R.; Risch, N.; Flörke, U.; Haupt, H.-J. *Liebigs Ann.*, **1996**, 705.
[93] Keuper, R.; Risch, N. *Liebigs Ann.*, **1996**, 717.
[94] Keuper, R.; Risch, N. *Eur. J. Org. Chem.*, **1998**, 2609.
[95] Sielemann, D.; Keuper, R.; Risch, N. *J. Prakt. Chem.*, **1999**, *341*(5), 487.
[96] Keuper, R.; Risch, N. *Eur. J. Org. Chem.*, **1998**, 2609.
[97] Hideg, K.; Hankovszky, H. *Acta Chim. (Budapest)* **1968**, *57*(2), 213; *Chem. Abstr.*, **1969**, *70*, 4082w.
[98] Insuasty, B.; Abonia, R.; Quiroga, J.; Salcedo, A.; Kolshorn, H.; Meier, H. *Eur. J. Org. Chem.*, **2000**, 2609.
[99] Roman, Gh.; Comanita, E.; Comanita, B. *Acta Chim. Slov.*, **2002**, *49*, 575.
[100] Werner, W.; Jungstand, W.; Gutsche, W.; Wohlrabe, K. Ger. (East) 122,247 20 Sep **1976**; *Chem. Abstr.*, **1977**, *87*, 39550a.
[101] Insuasty, B.; Argoti, J.; Gómez, S.; Quiroga, J.; Martínez, R.; Angeles, E.; Gabiño, R.; Nogueras, M.; Sánchez, A. *J. Heterocyclic Chem.*, **1998**, *35*, 1397.
[102] Insuasty, B.; Insuasty, H.; Quiroga, J.; Saitz, C.; Jullian, C. *J. Heterocyclic Chem.*, **2000**, *37*, 401.
[103] Werner, W.; Jungstand, W.; Gutsche, W.; Wohlrabe, K.; Römer, W.; Tresselt, D. *Pharmazie* **1979**, *34*, 394.
[104] Insuasty, B.; Insuasty, H.; Quiroga, J.; Saitz, C.; Jullian, C. *J. Heterocyclic Chem.*, **1999**, *36*, 635.
[105] Insuasty, B.; Rodríguez, R.; Quiroga, J.; Abonia, R.; Saitz, C.; Jullian, C. *Heterocyclic Commun.*, **2000**, *6*(3), 231.
[106] James, D.; Rees, H. *J. Med. Pharm. Chem.*, **1962**, *5*, 1234.
[107] Kunick, C. *Heterocycles* **1995**, *41*, 2299.
[108] Link, A.; Kunick, C. *Synthesis* **1997**, 297.
[109] Insuasty, B.; Caldas, Y.; Quiroga, J.; Abonía, R.; Sánchez, A.; Nogueras, M. Manuscript in preparation.

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