Dimethylformamide Dimethyl Acetal as a Building Block in Heterocyclic Synthesis

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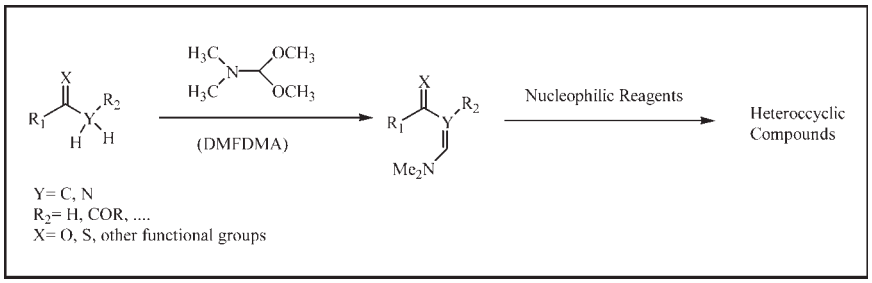

This review focuses on the use of dimethylformamide dimethyl acetal in the preparation of heterocyclic compounds *via* formylation of active methylene groups, methyl groups to give enamines, and formylation of amino groups to give amidines. These compounds are found to be useful intermediates in the formation and modification of heterocyclic compounds.

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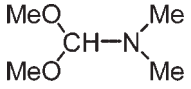
Contents

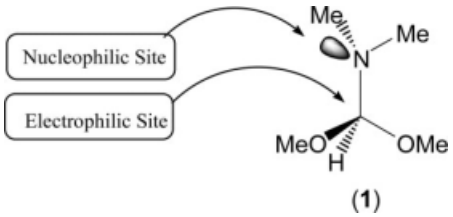
1. INTRODUCTION

N,*N*-dimethylformamide dimethyl acetal (DMFDMA) (**1**) is also called 1,1-dimethoxy-*N*,*N*-dimethylmethylamine and 1,1-dimethoxytrimethylamine. The molecular formula $(CH_3)_2NCH(OCH_3)_2$ and molecular weight 119.16. The Chemical Abstract Number is 4637-24-5.



(**1**)

DMFDMA (**1**) is a very important reagent in organic synthesis because of its higher reactivity. The DMFDMA molecule possesses a carbon atom attached to three electron withdrawing groups (2MeO and NMe_2) such that the carbon atom carries partial positive charge. While the nitrogen atom is attached to two methyl groups, the partially positive carbon atom, and carries a lone pair of electrons so that it ''looks'' like methyl amine. Therefore, DMFDMA carries two sites of reactivity, an electrophilic site and a nucleophilic site, respectively.



(1)

The main application of DMFDMA has been not only for functional group transformations but it may also be regarded as a one-carbon synthon in construction of the carbon skeletons.

Literatures referenced [1–10] highlight the methods of preparation and the major classes of reactions in which formamide acetals have been reported.

It has been found that reactions involving DMFDMA can be divided into two main categories, namely, methylation and formylation. DMFDMA acts as methylating agent [11,12] so that it has been used in the synthesis of methyl esters from acids, methyl ethers and thioethers from phenols and aromatic or heterocyclic thiols, and the methylation of active methines as shown in Scheme 1.

DMFDMA acts as formylating agent, so that it has been used in the synthesis of enamines from active methylenes and active methyl groups, and amidines from amines and amides or thioamide groups [12] as shown in Scheme 2.

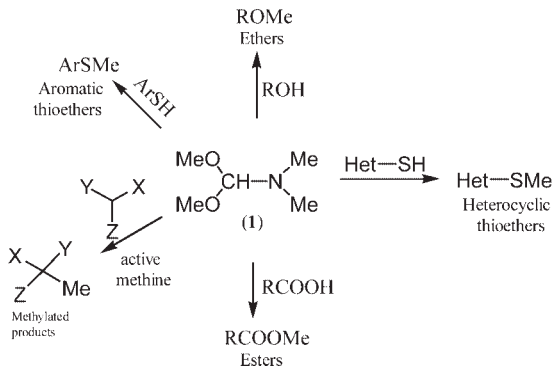
DMFDMA can also be used for cyclization of two functional groups to give heterocyclic compounds [11].

We will concentrate our review on the use of DMFDMA (**1**) for the preparation of heterocyclic compounds.

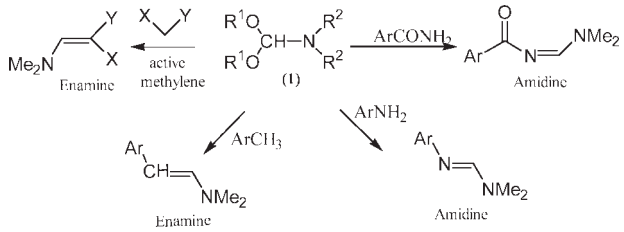
2. PREPARATION OF HETEROCYCLIC COMPOUNDS THROUGH THE FORMYLATION OF THE METHYLENE GROUP USING DMFDMA

2.1. Methylene of ethyl group. 4-Halopropiophenone (**2a–c**) condensed with DMFDMA to give the corresponding enamines (**3a–c**). 2,6-Bis(4-bromophenyl)-5-methylpyrimidine (**4**) was obtained by treatment of compound (**3a**) with *p*-bromobenzamidine. Compounds (**3a–c**) were subsequently treated with (4-sulfamoylphenyl)-hydrazine hydrochloride to provide pyrazoles (**5**), as in Scheme 3 [13,14]. The enamines (**3a–c**) are easily converted to the chloropropiniminium salt by the reaction with phosphorous oxychloride in dichloromethane which in turn is converted to the 2,3,4-trisubstituted pyrrole (**5′**) by condensation with ethyl *N*-methylglycinate in the presence of sodium hydride and DMF [15].

Scheme 1



Scheme 2



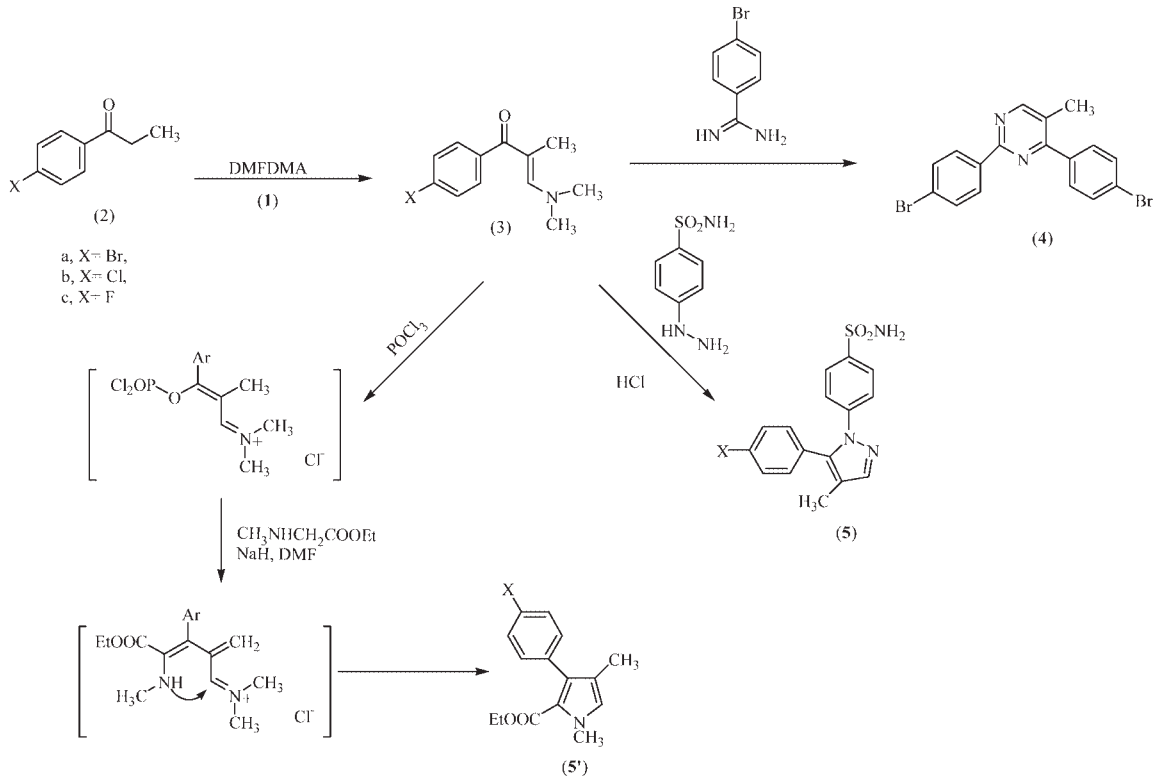
2.2. Active methylene group. DMFDMA was condensed with carbonyl compounds (**6**) yielding the corresponding enaminone (**7**), which reacted with cyanothioacetamide to yield polyfunctionaly substituted pyridines (**8**) [16–18]. Also the treatment of enaminone (**7**) with malononitrile dimer afforded 1,6-naphthyridine derivatives (**9**) [19], whereas treatment of the enaminones (**7**) with thiourea in the presence of sodium ethoxide affoded the corresponding 4,5-disubstituted pyrimidine-2-thiones (**10**) [20]. Although the treatment of enaminones (**7**) with hydrazine hydrate, phenyl, or alkyllhydrazine and hydroxylamine afforded 3,4-disubstituted azoles (**11**) as in Scheme 4 [21,22].

Consequently α-aryl or α-benzoylacetonitriles (**12a–c**) condensed with DMFDMA to afford enaminonitrile (**13a–c**). The reaction of enaminonitrile (**13a**) with 5-aminopyrazole afforded (**14**). Ring closure of enaminonitriles (**13a–c**) with hydrazine hydrate, and its derivatives and hydroxylamine in ethanol gave compounds (**15**) [23,24]. Although the reaction of enamine (**13c**) with hydrazine derivatives in the presence of HCl afforded 1-substituted-3-cyano-5-arylpyrazoles (**16**) as in Scheme 5 [14,25–27].

Also imidazo[1,2-*a*]pyridine derivative (**19**) could be obtained *via* reaction of (**17**) with DMFDMA. The reaction proceeds *via* the intermediate enamine derivative (**18**) as in Scheme 6 [28].

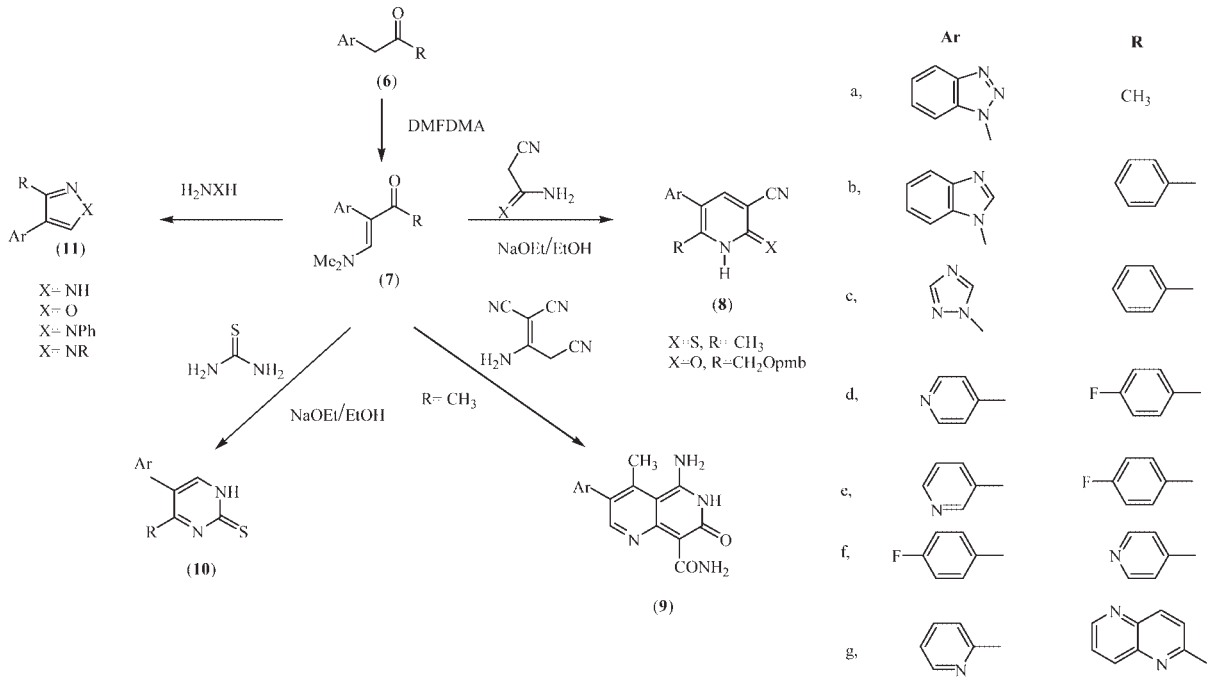
α-Phthaloylaminoacetophenone derivatives (**21a–c**) were obtained by the reaction of α-bromo- or α-chloroacetophenones (**20**) with phthalimide potassium salt in DMF. Reaction of (**21**) with 1.2 equivalents of DMFDMA gave the enamines (**22**), which on treatment with excess and one equivalent of hydrazine derivatives, produce (**23**) and (**24**), respectively, as in Scheme 7 [29,30].

Scheme 3

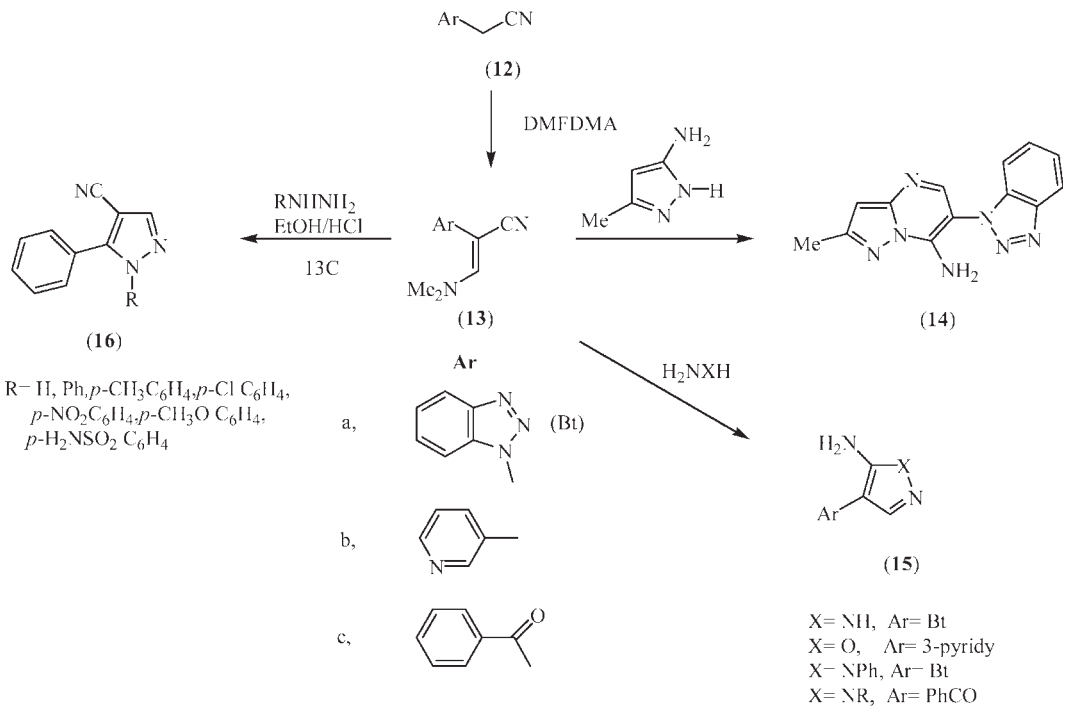


Refluxing of compound (**25**) with DMFDMA provided the enaminones (**26**), which were directly allowed to react with binucleophiles such as substituted guanidine and amino azoles (3-aminopyrazoles, 3-amino-1,2,4-triazole) to give the desired compounds (**27a,b**) and (**28a–d**), respectively, as in Scheme 8 [31,32].

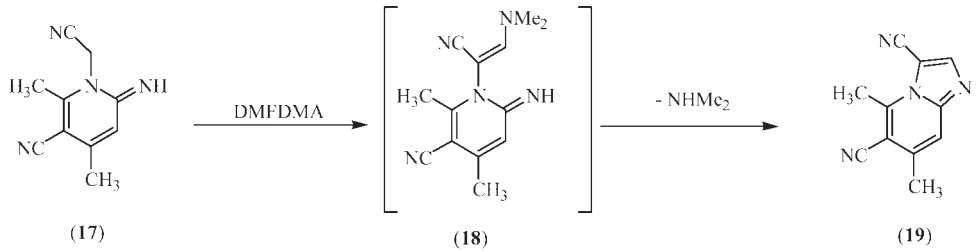
Scheme 4



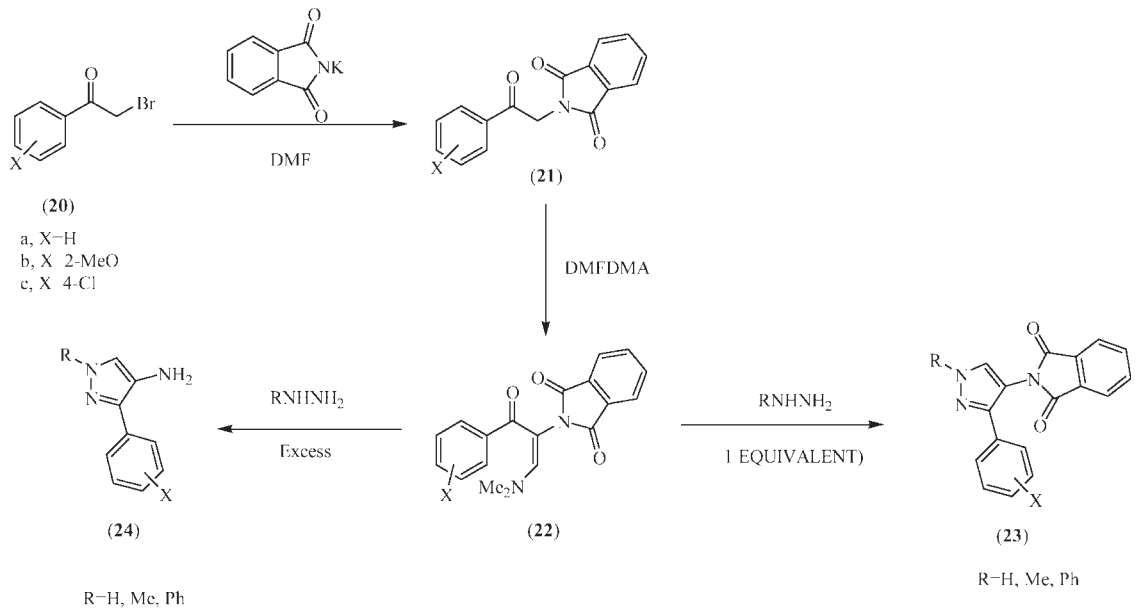
Scheme 5



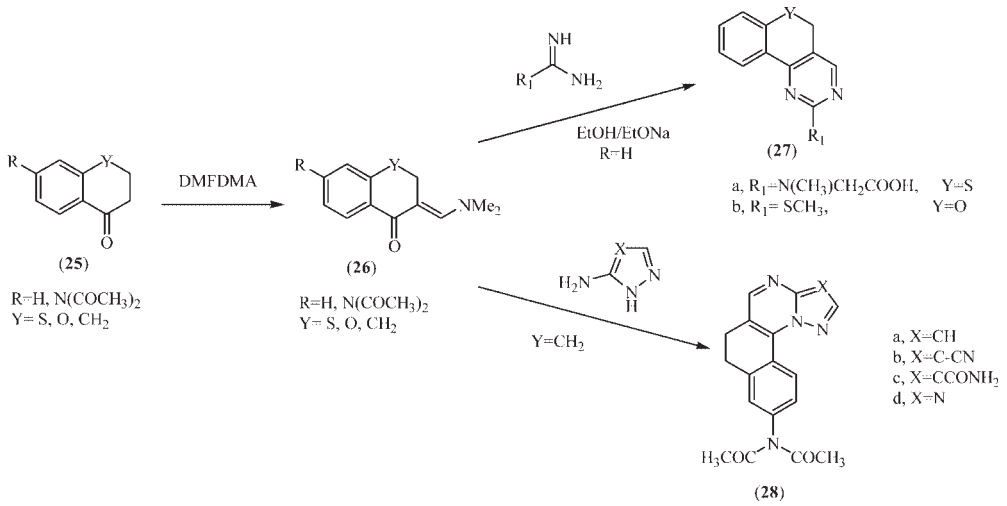
Scheme 6



Scheme 7



Scheme 8



(25) R=H, $N(COCH_3)_2$; Y= S, O, CH_2

(26) R=H, $N(COCH_3)_2$; Y= S, O, CH_2

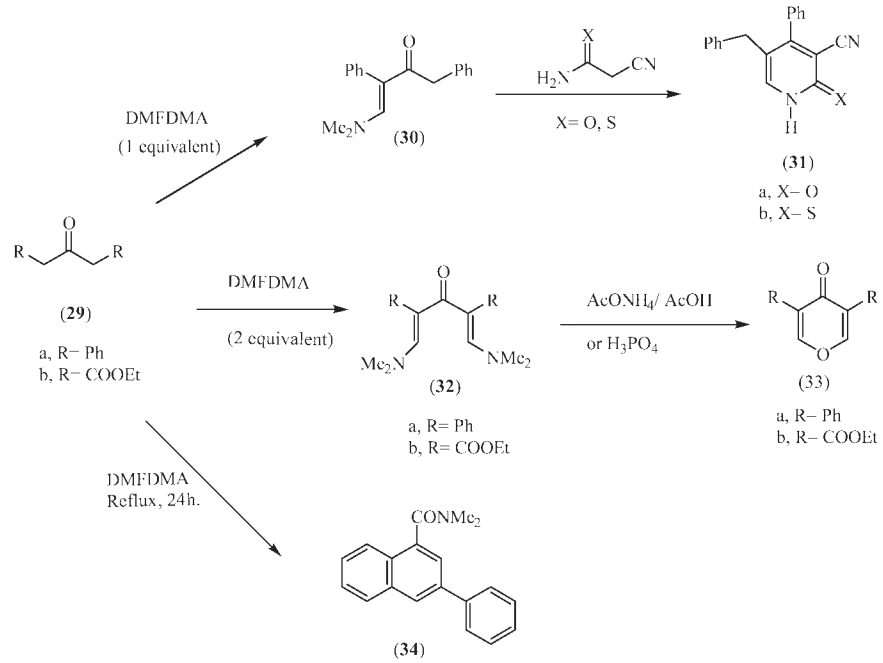
(27)

(28)

1,3-Diphenylacetone (**29a**) reacted with an equimolecular amount of DMFDMA to give the enaminone (**30**) which condensed with cyanoacetamide and with cyanothioacetamide to yield 2-oxo- and 2-thioxo-pyridine-3-carbonitrile derivatives (**31**). The 1,3-disubstituted acetones (**29a,b**) reacted with two molar equivalents of DMFDMA to give the dienaminones (**32**) which in turn reacted with an acetic acid ammonium acetate mixture or phosphoric acid to afford 3,5-disubstituted-pyrane-4-ones (**33a,b**) [33,34]. A mixture of 1,3-diphenylacetone and DMFDMA were left under reflux for 24 h to give the dimethylamide (**34**) as in Scheme 9 [35].

Abu-Shanab et al. [36–39] reported that, the reaction of 1,3-dicarbonyl compounds (**35a–f**) with DMFDMA in anhydrous DMF afforded the corresponding enaminones (**36a–f**) which reacted directly with the following nucleophiles using sodium hydride as a base in anhydrous DMF. Cyanoacetamide afforded 5,6-disubstituted-3-cyanopyridine-2(1*H*)-ones (**37a–d,f**). Cyanothioacetamide afforded 5,6-disubstituted-3-cyanopyridine-2(1*H*)-thiones (**38a–f**). Anion of malononitrile dimmer afforded 5,6-disubstituted-3-cyano-2-(dicyanomethylidene)-1,2-dihydropyridines (**39a–f**). Malonamide afforded 5,6-disubstituted-3-carboxamidopyridine-2(1*H*)-ones (**40a–c**). On the

Scheme 9



(29) a, R= Ph; b, R= COOEt

(30)

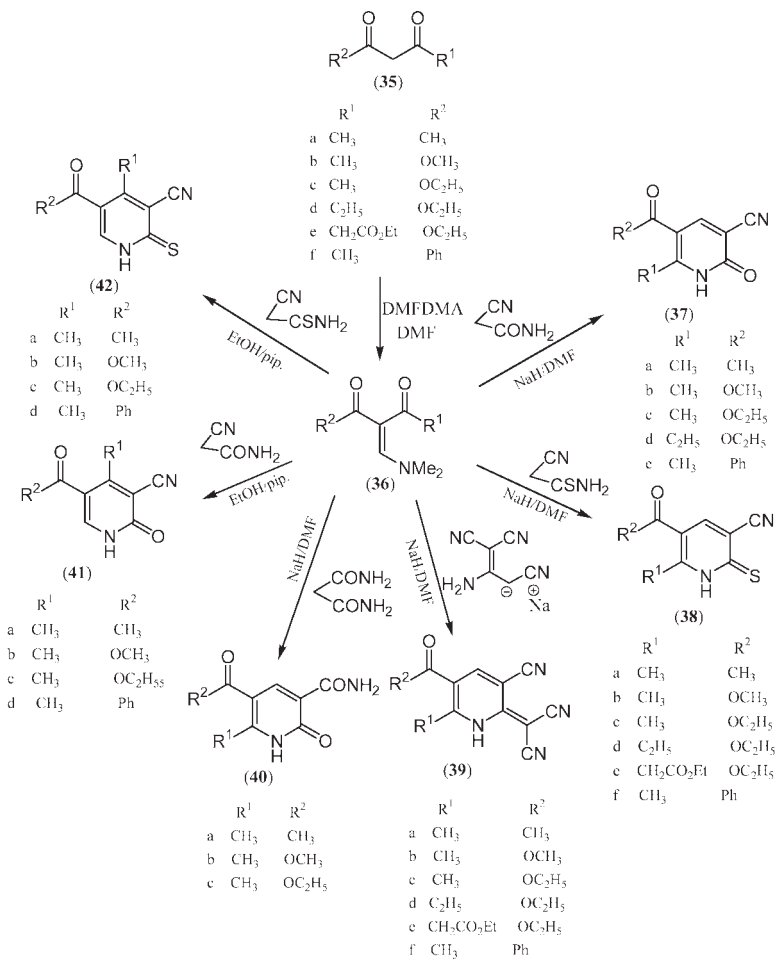
(31)

(32)

(33) a, R= Ph; b, R= COOEt

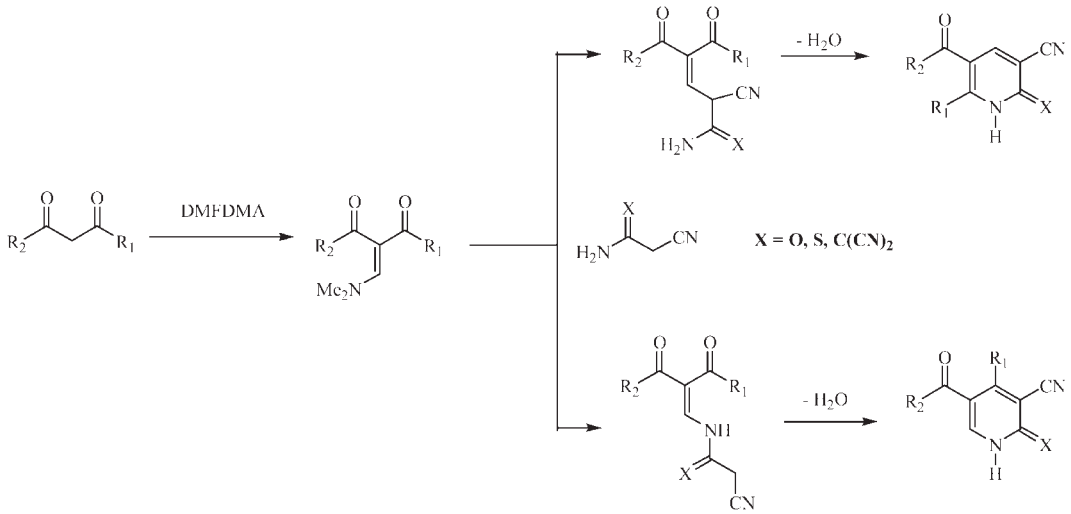
(34)

Scheme 10

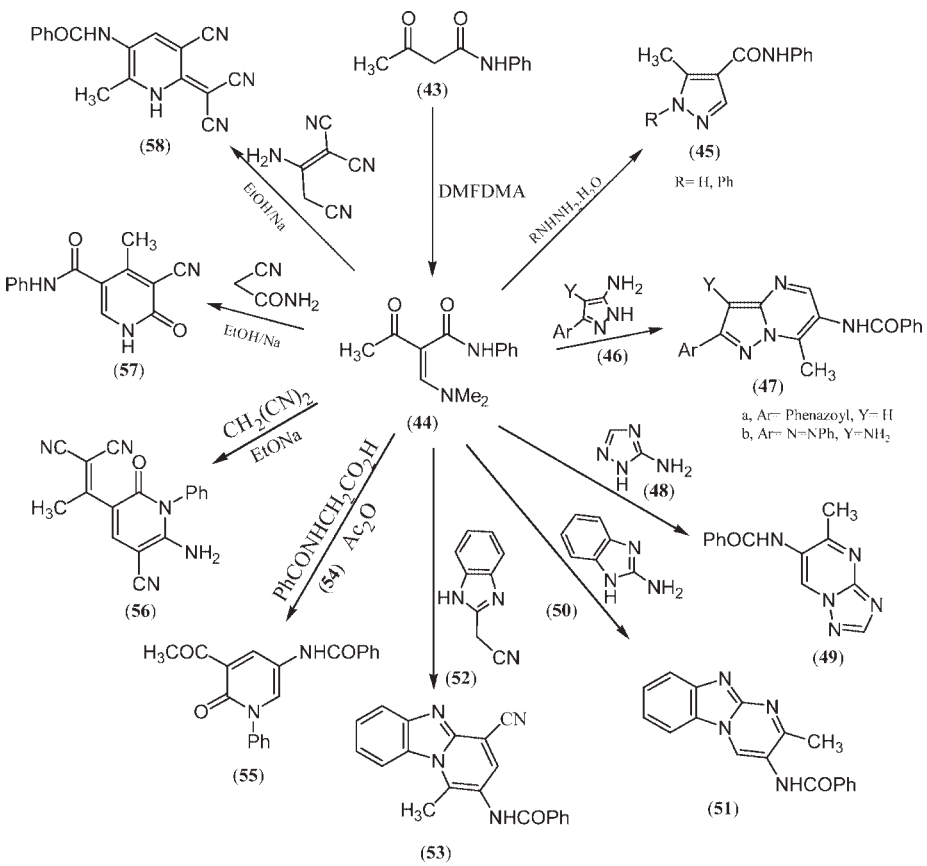


other hand, reactions analogous to those reported earlier, but using ethanol as a solvent and piperidine as a base, enaminones (**36**) reacted with the following nucleophiles: Cyanoacetamide to give 4,5-disubstituted-3-carboxamidopyridine-2(1*H*)-ones (**41a–c**). Cyanothioacetamide to give 4,5-disubstituted-3-carboxamidopyridine-2(1*H*)-thiones (**42a–d**) as in Scheme 10.

The structure of these compounds has been confirmed by X-ray crystallography [36,37]. The mechanism for the formation of the above products is as shown in the following.



Scheme 11



Also the reaction of DMFDMA with acetoacetanilide (**43**) gave enamine (**44**). Treatment of **44** with hydrazine hydrate and phenylhydrazine afforded pyrazoles (**45**). Pyrazolo[1,5-*a*]pyrimidines (**47**) were isolated when enamine (**44**) was reacted with pyrazoles (**46**). Enamine (**44**) reacted with 1,2,4-triazole (**48**) to produce triazolo[1,5-*a*]pyrimidine (**49**). 2-Aminobenzimidazole (**50**) reacted with (**44**) to give the pyrimido[1,2-*a*]benzimidazole (**51**). The reaction of enamine (**44**) with compound (**52**) afforded (**53**) and with hippuric acid (**54**) afforded the pyridine (**55**). Also the reaction of (**44**) with malononitrile, cyanoacetamide, and malononitrile dimer afforded (**56**), (**57**), and (**58**), respectively, as shown in Scheme 11 [40–47].

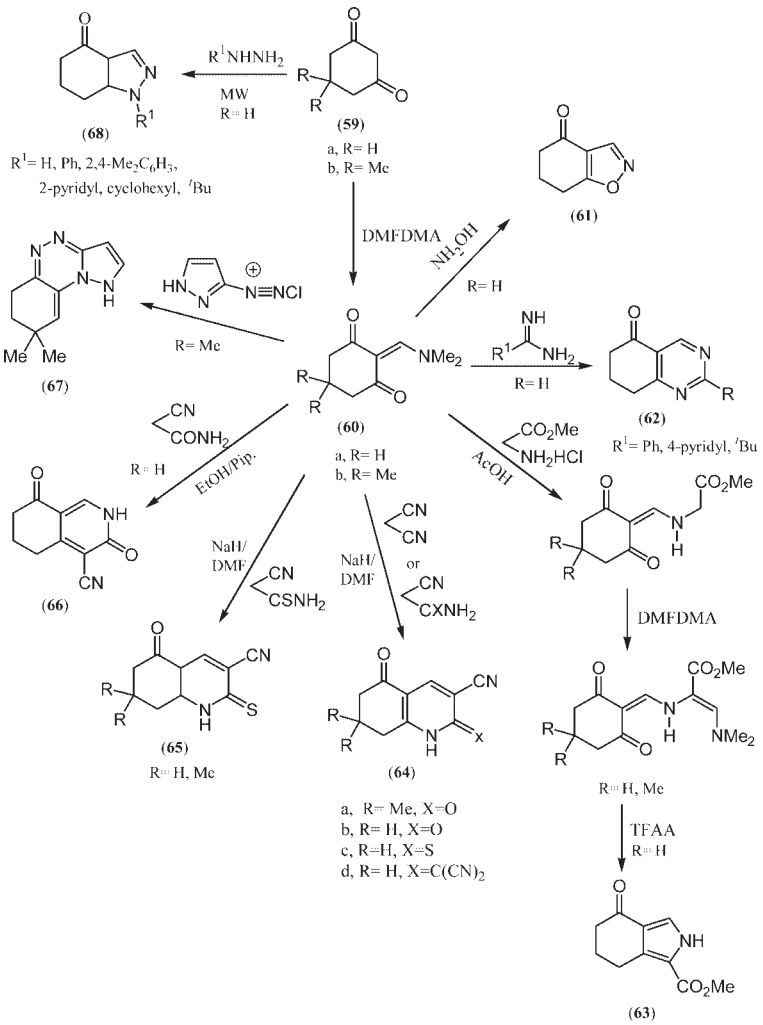
Further reactions for the preparation of heterocyclic compounds using DMFDMA are the condensation of 1,3-cyclohexanedione (**59a**) and 5,5-dimethyl-1,3-cyclohexanedione (**59b**) with DMFDMA to give the corresponding enaminones (**60a,b**). These compounds are also potentially valuable for the preparation of different types of heterocycles (**61–67**) as outlined in Scheme 12 [36,37,48–50]. Microwave irradiation of 1,3-cyclohexanedione (**59a**) with hydrazine hydrate and its derivatives afforded the corresponding pyrazole derivatives (**68**) [51]. The structure of these compounds has been confirmed by X-ray crystallography [36,37].

Diethyl ester (**69**) when refluxed with DMFDMA gave enamine (**70**), which was refluxed in DMF and ammonium acetate as a source of ammonia, the β-carboline (**71**) isolated Scheme 13 [52].

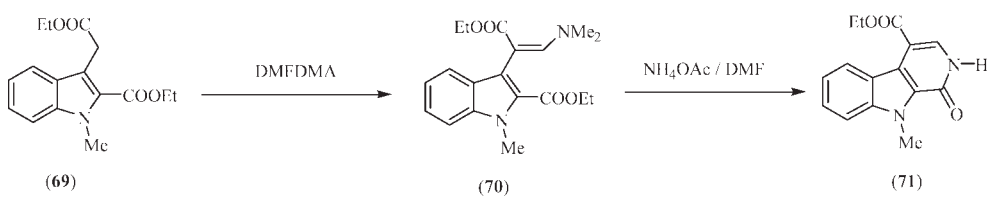
Enamines (**73a–c**) was obtained from (**72a–c**) with DMFDMA and converted directly to quinolinecarboxylic acid esters (**74**) by treatment with the requisite amines. Compounds (**75**) were prepared by reaction of (**73b**) with hydrogen sulfide in ethanol [53–55]. Also compound (**73a**) reacted with aryl hydrazine provided pyrazole (**76**) as shown in Scheme 14 [56,57].

Treatment of compounds (**77**) with excess DMFDMA gave compounds (**78**), which was cyclized to pyrrole ring (**79**) under various condition, EtOH in the presence of HCl (method A), AcOH (method B), AcOH and Ac_2O (method C), and $(CF_3CO)_2O$ (method D) as shown in Scheme 15 [58–60].

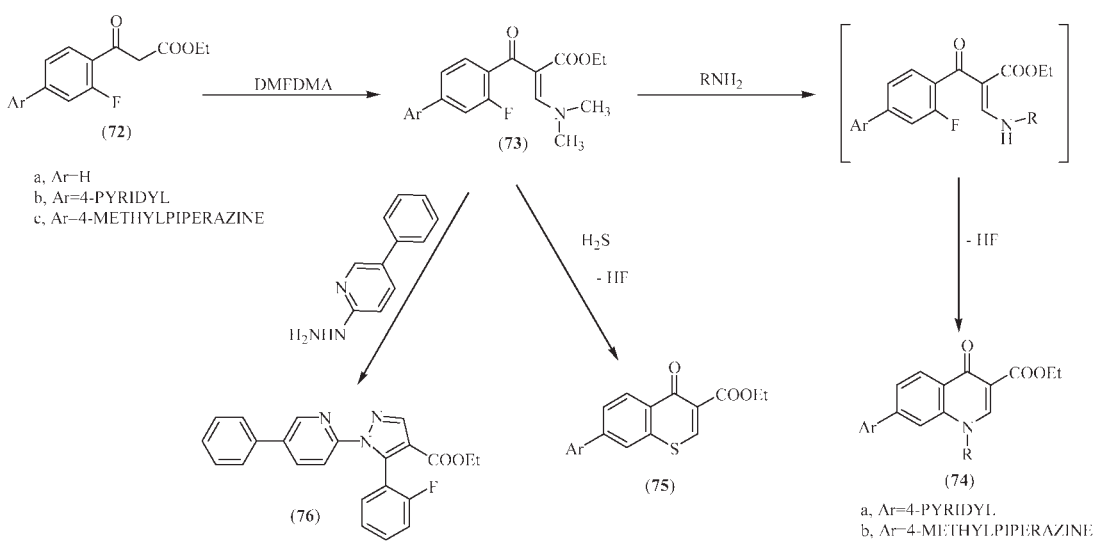
Scheme 12



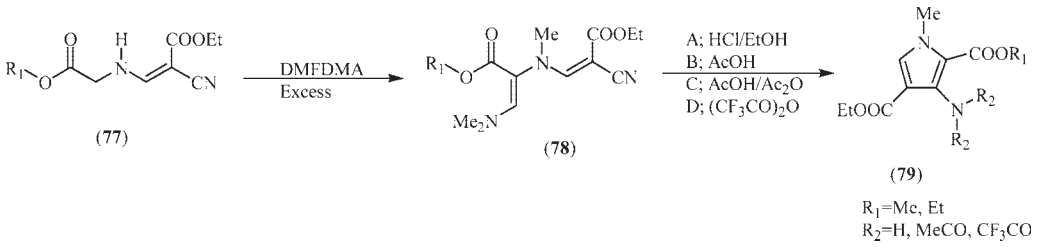
Scheme 13



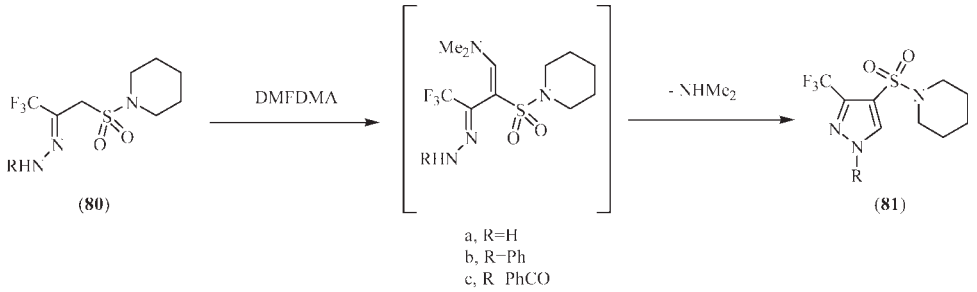
Scheme 14



Scheme 15



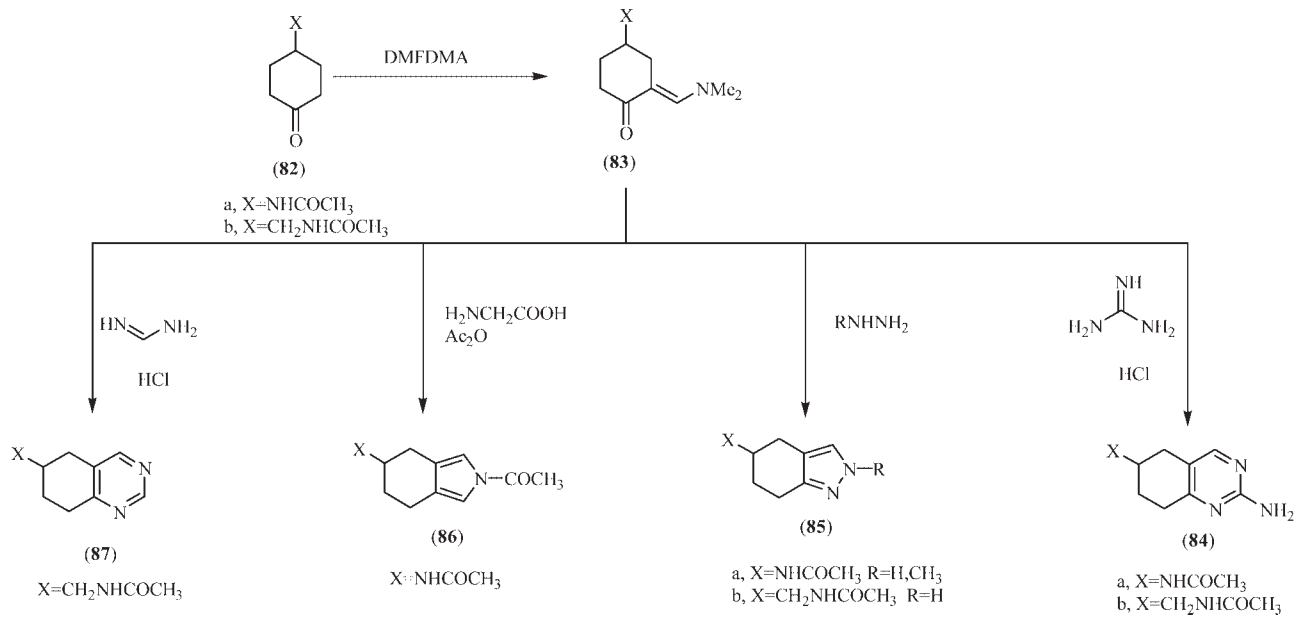
The reaction of hydrazones (**80**) with DMFDMA afforded 3-trifluoromethylpyrazole-4-sulfonamides (**81**) [61].



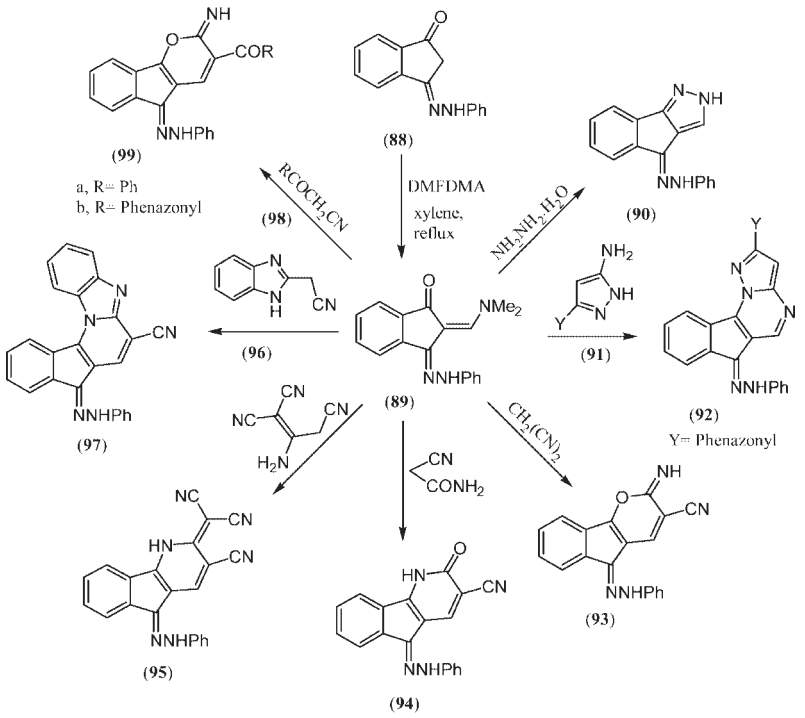
Condensation of 4-substituted cyclohexanones (**82a,b**) with DMFDMA provided enamino ketones (**83a,b**), which reacted with guanidine hydrochloride, hydrazine hydrate, *N*-methylhdrazine, glycine, and formamidine hydrochloride afforded heterocyclic compounds (**84a,b**), (**85a,b**), (**86**), and (**87**), respectively, as shown in Scheme 16 [18,62–67].

Also 3-(phenylhydrazono)indan-1-one (**88**) when reacted with DMFDMA gave the enaminone (**89**), which reacted with hydrazine hydrate to yield the indenopyrazole derivative (**90**). Treatment of (**89**) with pyrazole (**91**) gave the indenofluorene derivative (**92**). The reaction of compound (**89**) with malononitrile gave indenopyran derivative (**93**). When (**89**) reacts with cyanoacetamide, the

Scheme 16



Scheme 17

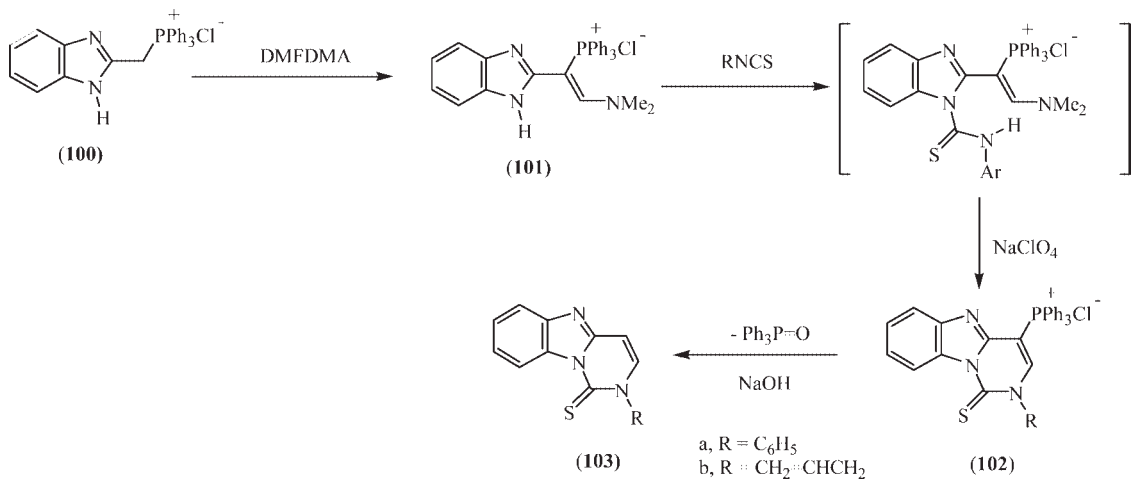


indenopyridine derivative (**94**) was formed. Also, compound (**89**) was reacted with malononitrile dimer to afford the trinitrile (**95**). Enaminone (**89**) reacted with compound (**96**) to afford the diazaindenofluorene derivative (**97**). The ω-cyano compounds (**98**) when reacted with (**89**) afforded compounds (**99a,b**) as shown in Scheme 17 [68].

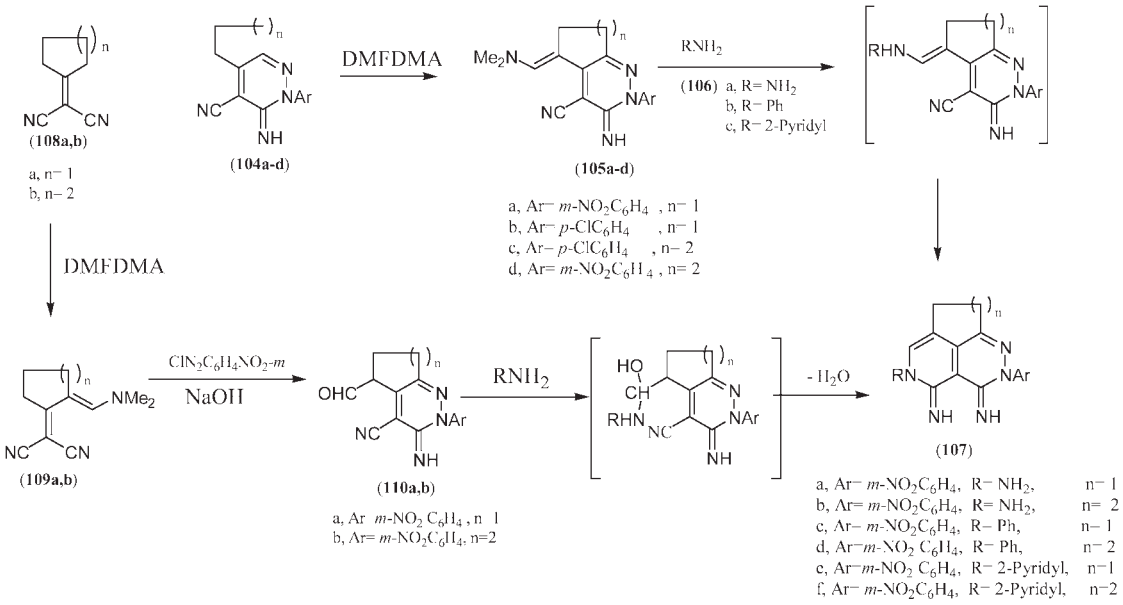
Treatment of the available phosphonium salt (**100**) with DMFDMA gives 2-vinylbenzimidazole derivatives (**101**) which on heating with phenyl or allyl isothiocyanate and sodium perchlorate afforded compounds (**102a,b**) followed by treatment with sodium hydroxide resulting thioxopyrimido[3,4-a]benzimidazoles (**103a,b**) as shown in Scheme 18 [69–72].

DMFDMA reacts with (**104a–d**) to give enamines (**105a–d**), which on treatment with hydrazine hydrate (**106a**) and aromatic amines (**106b,c**) gives pyridopyridazine derivatives (**107a–f**). The latter (**107a,b**) can also be prepared by treatment of (**108a,b**) with DMFDMA to give the corresponding enamines (**109a,b**) followed by coupling with diazonium salt of *m*-nitroaniline in sodium hydroxide to give the corresponding aldehyde derivatives (**110a,b**) followed by treatment with hydrazine hydrate and aromatic amines (Scheme 19) [73].

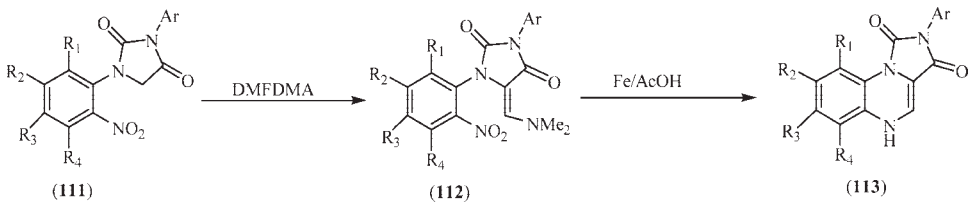
Scheme 18



Scheme 19

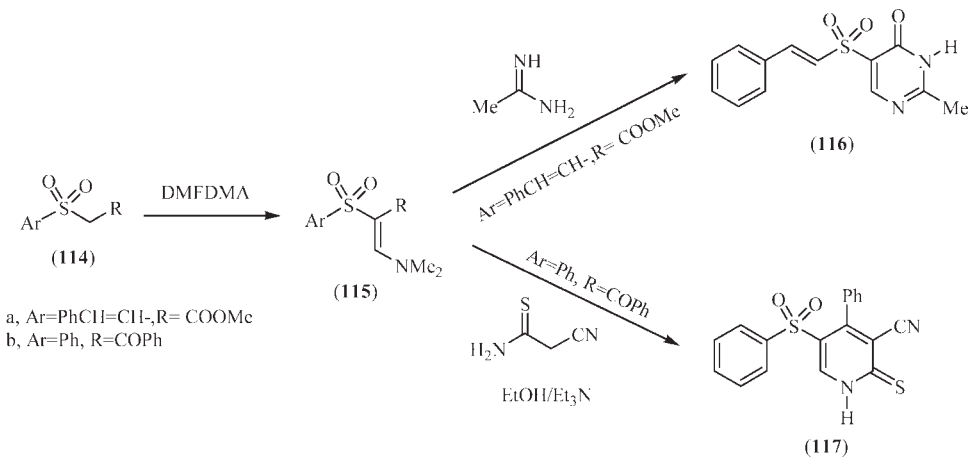


Imidazoquinoxalines (**113**) are biologically useful compounds, which can be prepared by the reaction of (**111**) with DMFDMA to give (**112**) followed by reductive cyclization using powdered Fe in AcOH [74].

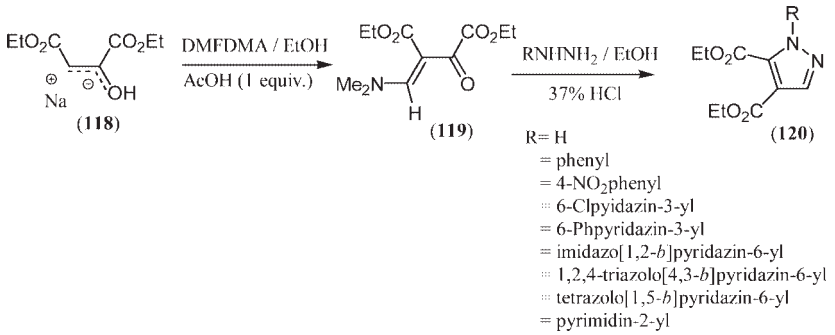


The treatment of compounds (**114a,b**) with DMFDMA afforded the corresponding arylsulfonylenamines (**115a,b**). Compound **115a** reacted with acetamidine to yield 5-styrylsulfonylpyrimidinone (**116**) [75]. Also compound **115b** reacted with cyanothioacetamide to give polysubstituted pyridine-2(1*H*)-thione in a good yield as shown in Scheme 20 [76].

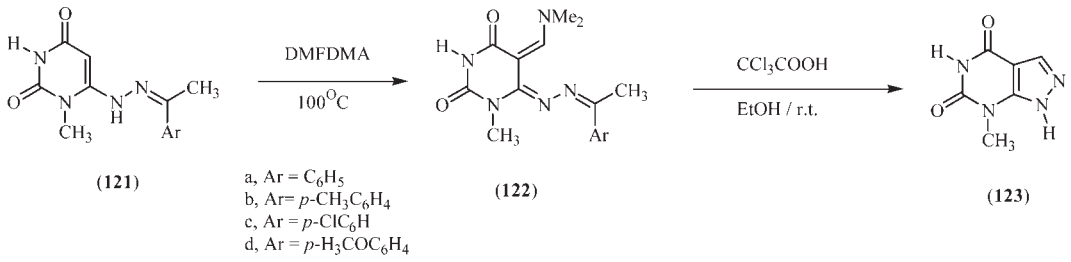
Scheme 20



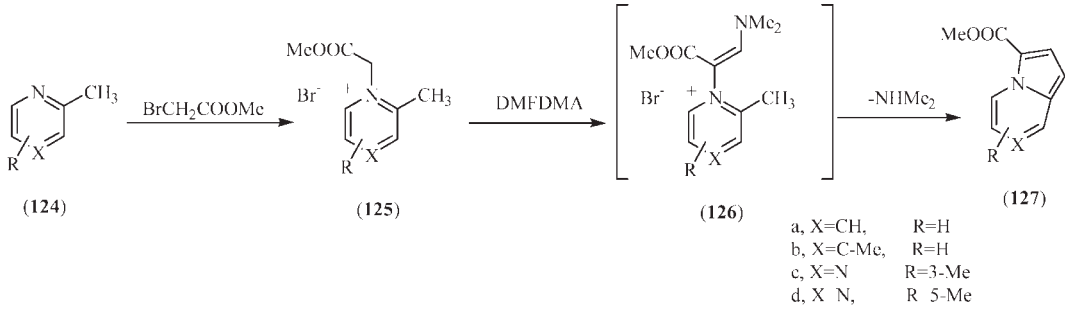
Enaminone (**119**) was prepared from the sodium salt of diethyl 2-oxosuccinate (**118**) by treatment with DMFDMA. Acid-catalyzed cyclocondensations of compound (**119**) were performed with hydrazine derivatives to give the corresponding 1-substituted diethyl 1*H*-pyrazole-4,5-dicarboxylates (**120**) [77].



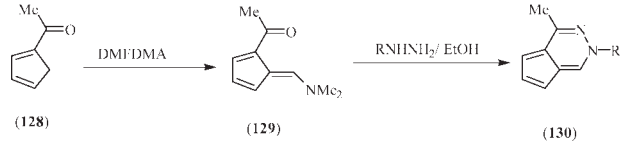
Heating of 6-(α-methylbenzylidenhydrazino)-1-methyluracils (**121a–d**) with an excess of DMFDMA at 100°C for 1 h led to the formation of enamines (**122a–d**) in good yields. Treatment of the products with trichloroacetic and hydrochloric acids (ethanol, room temperature, 15 min) gave rise to a ring closure with the loss of one mole of acetophenone and dimethylamine, affording 7-methylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*)-dione (**123**) [78].



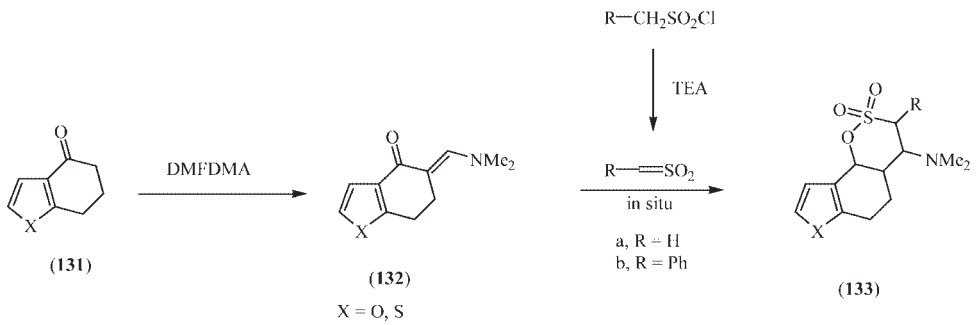
Quaternary salts (**125a–d**), which were prepared from (**124a–d**) and methyl bromoacetate, were treated with DMFDMA to afford fused heterocyclic compounds (**127a–d**) [26].



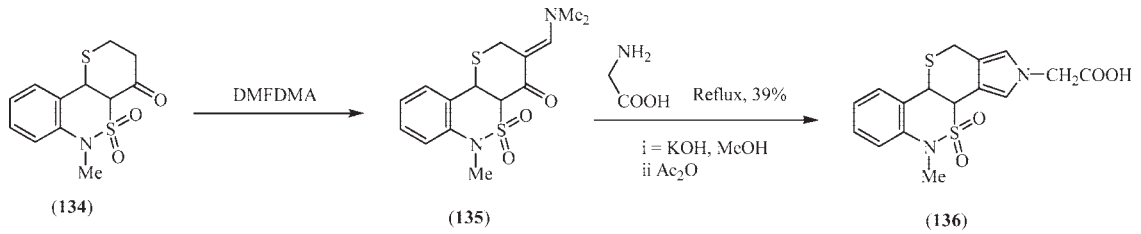
Also when the enamine and carbonyl functions are separated by a carbon, as in compound (**129**), which was prepared from compound (**128**) with DMFDMA, the reaction of (**129**) with a hydrazines gives a fused pyridazine ring, as cyclopenta[*d*]pyridazines (**130**) [79].



Treatment of compound (**131**) with DMFDMA afforded enaminones (**132**). A mixture of methanesulphonyl (or phenyl methylsulphonyl) chloride and triethyl amine produces a sulphene, RCH=SO_2 (R = H, Ph), which cyclizes enaminones (**132**) *in situ* at low temperature to an oxathiin ring (**133**) in high yields [80–85].

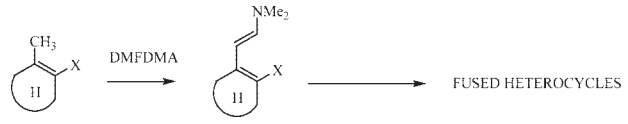


Reaction of (**134**) with DMFDMA afforded 2-keto-enamine (**135**) which reacts with glycine in alkali medium to form a pyrrole ring (**136**) [83].



3. PREPARATION OF HETEROCYCLIC COMPOUNDS THROUGH THE FORMYLATION OF THE METHYL GROUP USING DMFDMA

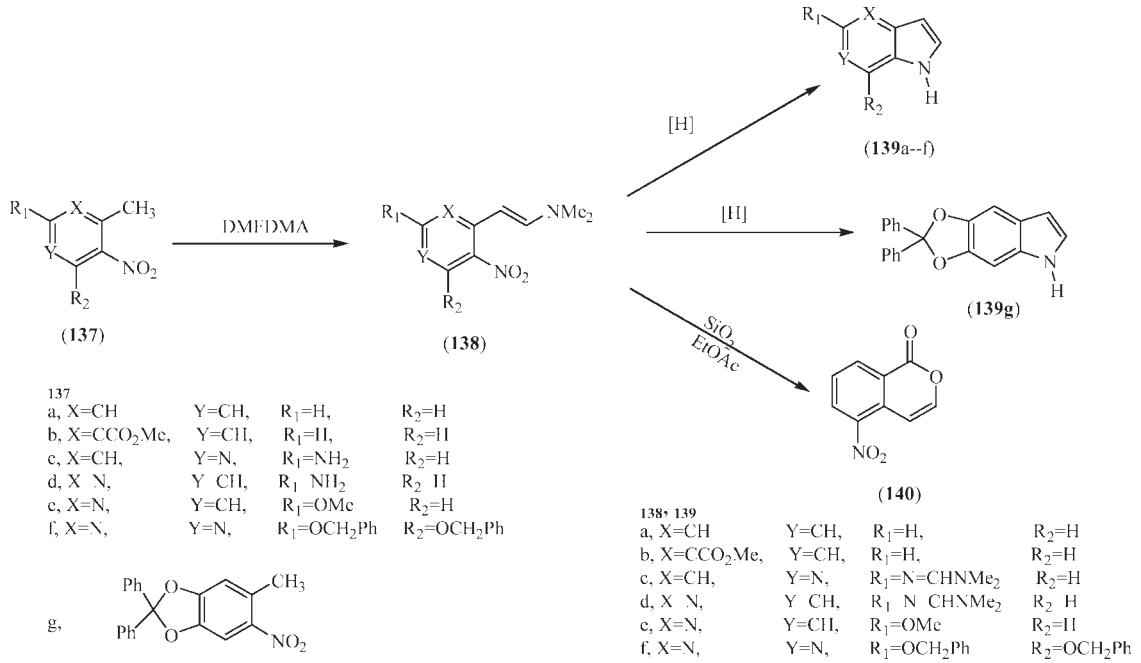
3.1. Ring methyl group. Abu-Shanab et al. reported the cyclization of the methyl group of azine compounds with different functional groups to give fused heterocycles using different organic reagents; DMFDMA is one of them [86].



Microwave irradiation of nitrotolune (**137a**) with DMFDMA in the presence of anhydrous CuI gave the corresponding enamine (**138a**). Treatment of compounds (**137b–f**) with DMFDMA provided enamine (**138b–f**). Reductive cyclization of enamines (**138a–f**) using H_2/Pd-C or Fe/AcOH or zinc in acetic acid or hydrazine hydrate in the presence of Raney-Ni as a catalyst gave compounds (**139a-f**). Also, treatment of enamine (**138b**) with silica gel provides sufficient acid catalysis to hydrolyze the enamine and cyclises the intermediate enol to the isocoumarine (**140**) as shown in Scheme 21 [4,87–101].

Treatment of pyridazinones (**141a–d**) with DMFDMA in dry DMF afforded (*E*)-dimethylaminoethylenes (**142a–d**) in good yields. Compounds (**142a–c**) reacted with aromatic amines in glacial acetic acid to yield the 2,7-diarylpyrido[3,4-*c*]pyridazinones (**143a–g**). The 1-unsubstituted pyrido[3,4-*c*]pyridazinones (**143h–j**) were also formed on treatment of (**142a–c**) with ammonium acetate in acetic acid. Compound (**142a**) also reacted with 5-methylpyrazol-3-amine (**144**) and with hydrazine hydrate to yield pyrido[3,4-*c*]pyridazinones (**143k,l**), respectively. Refluxing (**142a–c**) in HOAc-HCl afforded carboxylic acids that may be formulated as (**145a–c**) as shown in Scheme 22 [102,103].

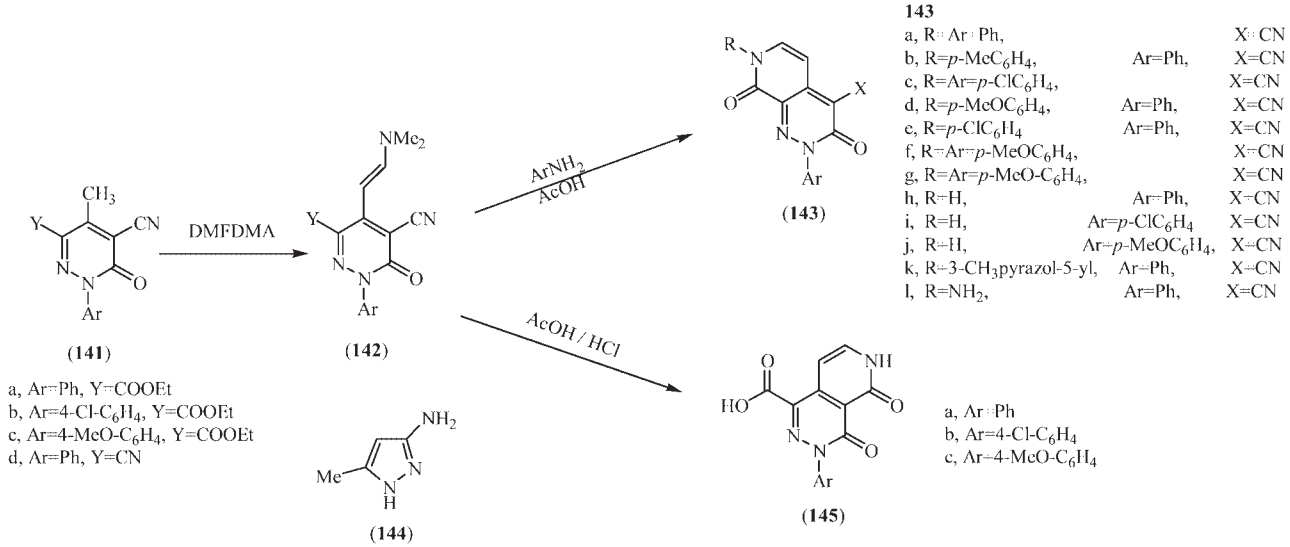
Scheme 21



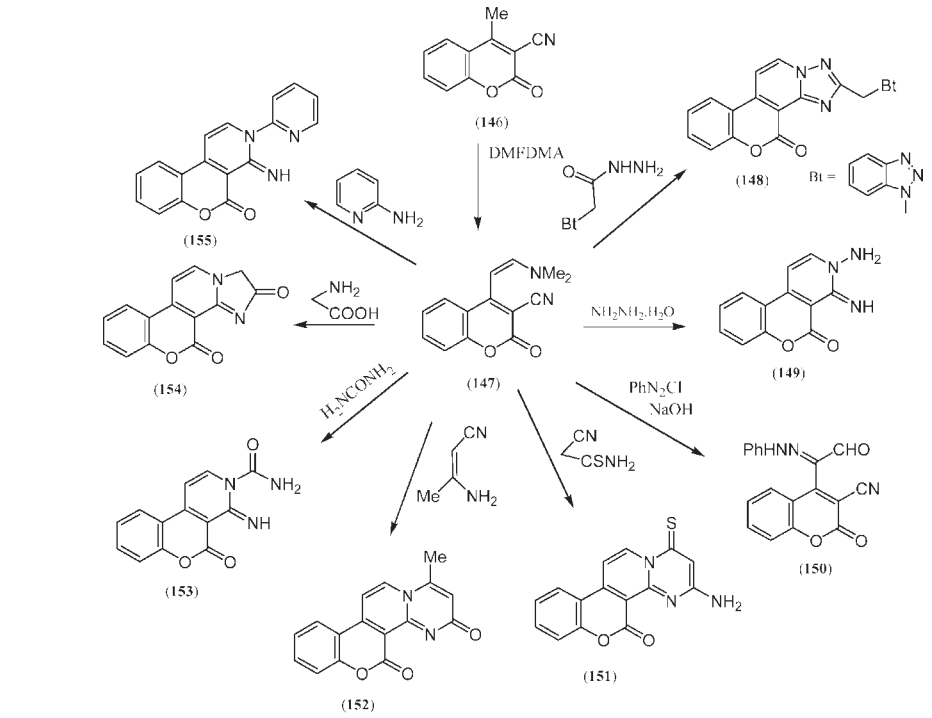
Also the treatment of 3-cyano-4-methylcoumarin (**146**) with DMFDMA in dry xylene afforded the (*E*)-dimethylaminoethylene derivative (**147**). Fusion of enamine (**146**) with benzotriazol-1-yl-acetic acid hydrazide afforded the corresponding [1,2,4]triazolo[1,5-*a*]pyrido[3′,4′-*c*]coumarin (**148**). Reaction of enamine (**147**) with hydrazine hydrate gave compound (**149**). Enamine (**147**) was also coupled with benzenediazonium chloride to afford 2-oxo-4-[2-oxo-1-(phenylhydrazono)-ethyl]-2*H*-chromene-3-carbonitrile (**150**). Treatment of (**147**) with cyanothioacetamide, 3-aminocrotononitrile, urea, glycine, and 2-aminopyridine affords fused heterocyclic compounds (**151–155**), respectively, as shown in Scheme 23 [104–106].

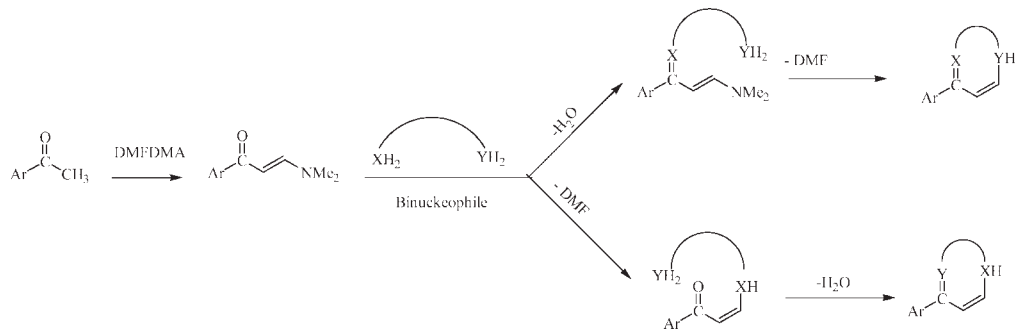
3.2. Methyl of acetyl group. In the acetyl group, the presence of the methyl group beside the carbonyl useful to give heterocyclic compounds using DMFDMA and different binucleophilic reagents. The general mechanism for this reaction is as shown in the following. The products of this reaction depend on the conditions under which the reactions were carried out and the type of the binucleophile used.

Scheme 22



Scheme 23



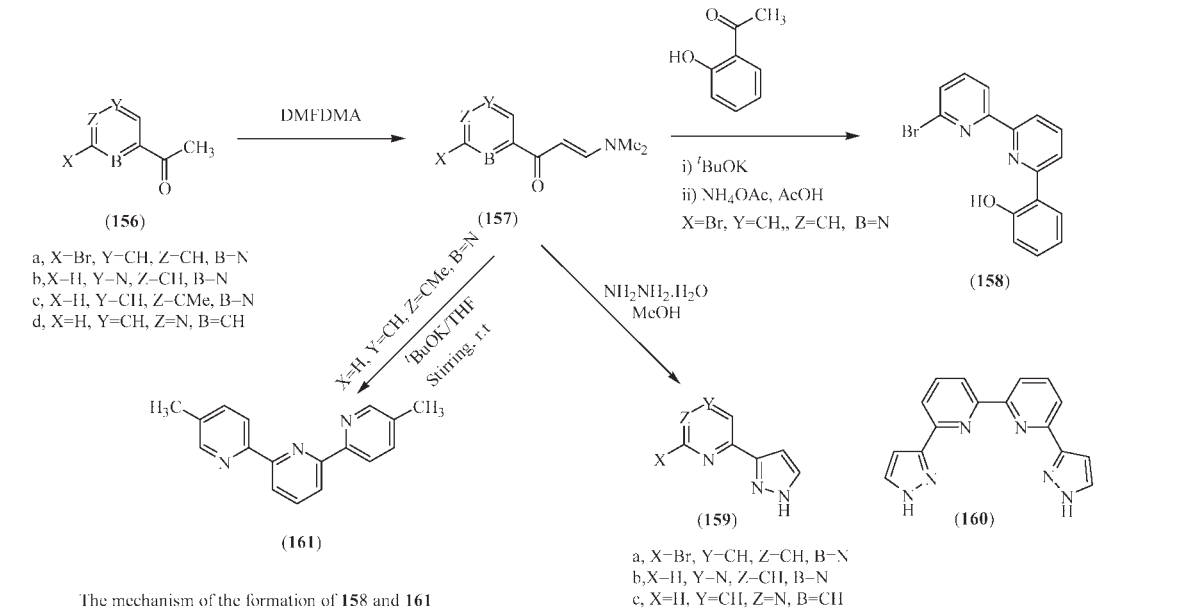


Reaction of acetyl azines (**156a–d**) with DMFDMA gave the corresponding enamines (**157a–d**). Compound (**157a**) reacted with 2-hydroxyacetophenone to afford 2,2′-bipyridine (**158**). When (**157a,b,d**) is reacted with hydrazine hydrate in hot methanol in a Schlenk tube, the pyrazolyl ring (**159a–c**) is formed. Also compound (**160**) is obtained similarly [107,108]. Also the reaction of (**157c**) with (**156c**) using potassium *t*-butoxide as a base gives 5,5'-dimethylterpyridine (**161**) as shown in Scheme 24 [109–112].

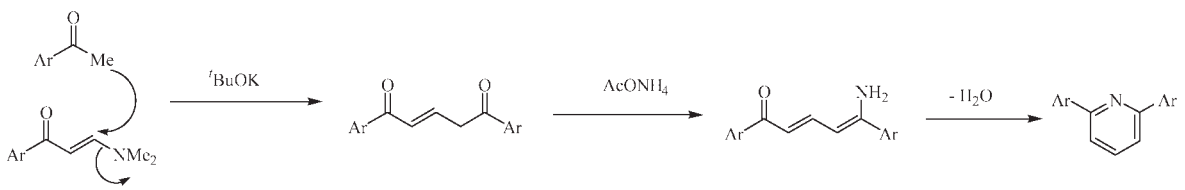
Also the treatment of some heterocyclic acetyl compounds (**162a–f**) with DMFDMA afforded *E*-1-heteroaryl-3-(*N*,*N*-dimethylamino)-2-propen-1-ones (**163a–f**). Cycloaddition of some nitrilimines and nitriles oxides (**164**) with the enaminone (**163a**) gave (**165**). Also the compound (**163a**) reacted with 1*H*-2-benzimidazoleacetonitrile (**166**) gave pyrido[1,2-*a*]benzimidazole (**167**). Also the enaminone (**163a**) reacted with 5-amino-3-phenylpyrazole (**168**) to yield pyrazolo[1,5-*a*]pyrimidine (**169**). Reaction of guanidine nitrate with (**163a,f**) afforded 2-amino-4-[2-benzothiazolyl]pyrimidine (**170, 171**), respectively. The reaction of (**163b,c**) with N-substituted guanidine carbonate at elevated temperature in alcoholic alkali afforded 2-[*N*-phenylamino]-4-[5-(2-substituted-4-methyl)thiazolyl]pyrimidine **172** and **173**, respectively. The treatment of **163c,d** with hydroxylamine or with alkylhydrazine afforded **174** and **175**, respectively, as shown in Scheme 25 [54,113–122].

Also, treatment of acetophenone and its derivatives (**176a–j**) with DMFDMA afforded 3-*N*,*N*-dimethylamino-1-aryl-prop-2-en-1-one (**177a–j**) in very good yield [123]. The reaction of enaminones (**177a–j**) with different nucleophiles afforded different heterocycles. Reaction of enaminone (**177a**) with 2-methoxyacetophenone

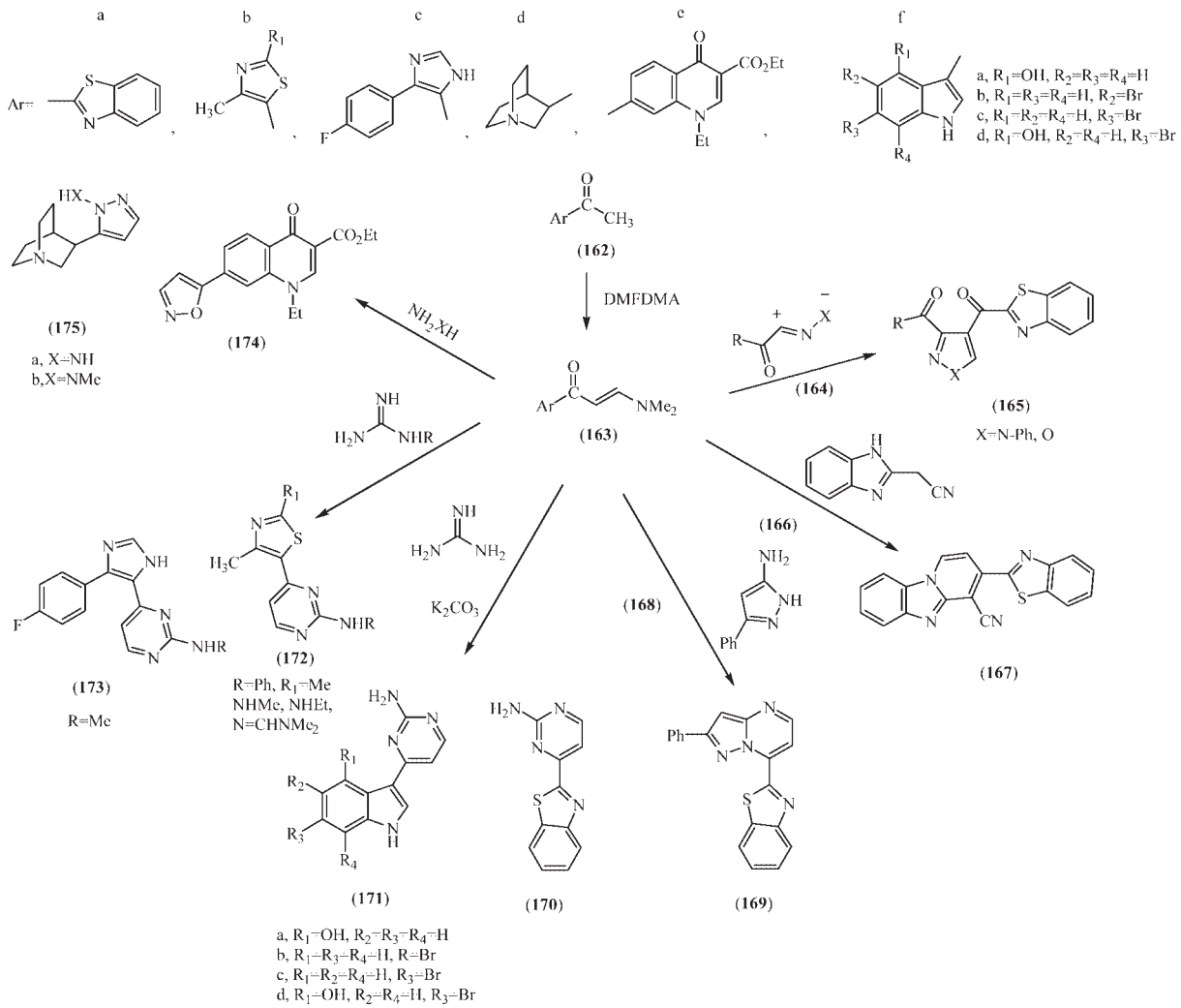
Scheme 24



The mechanism of the formation of **158** and **161**



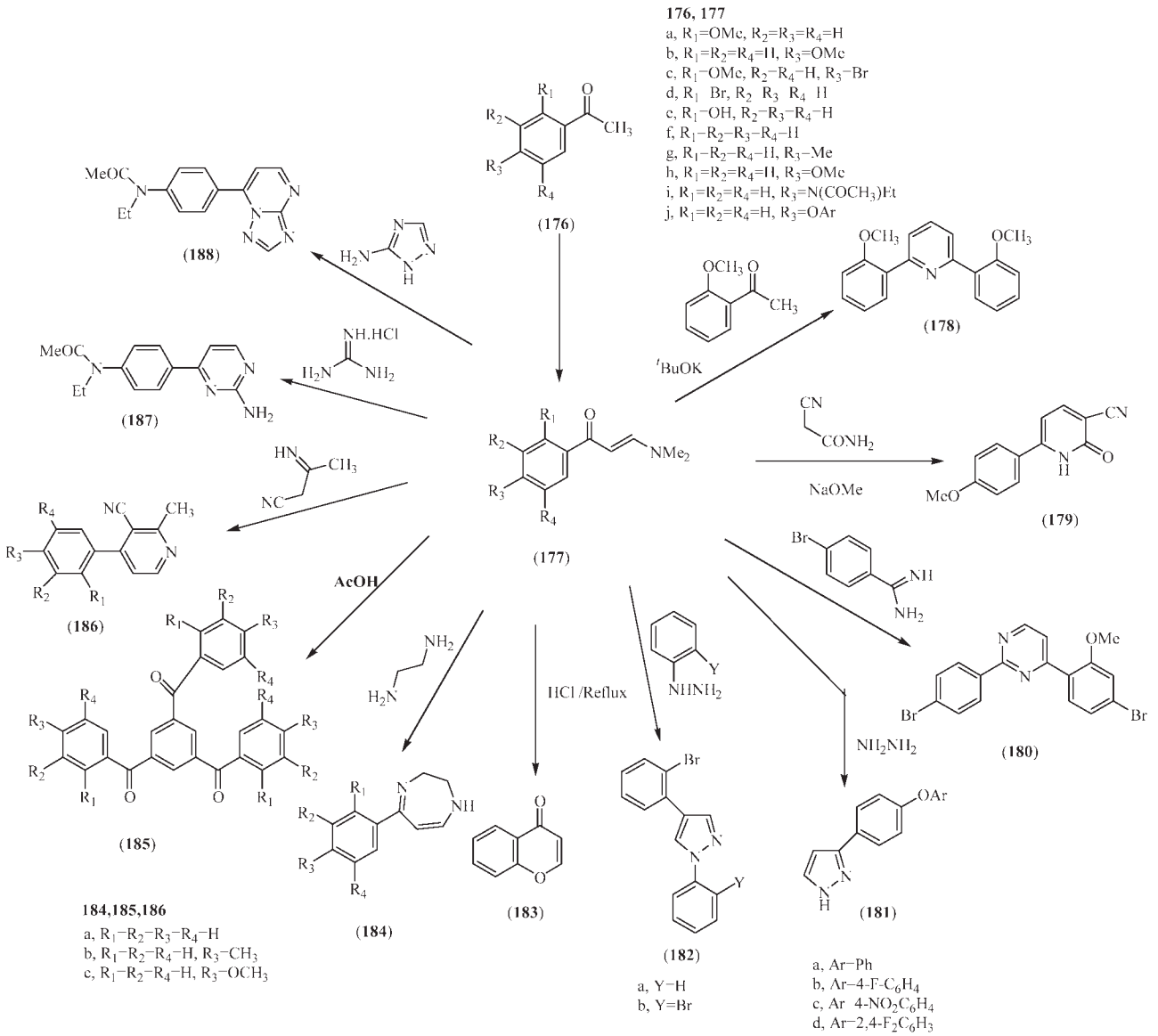
Scheme 25



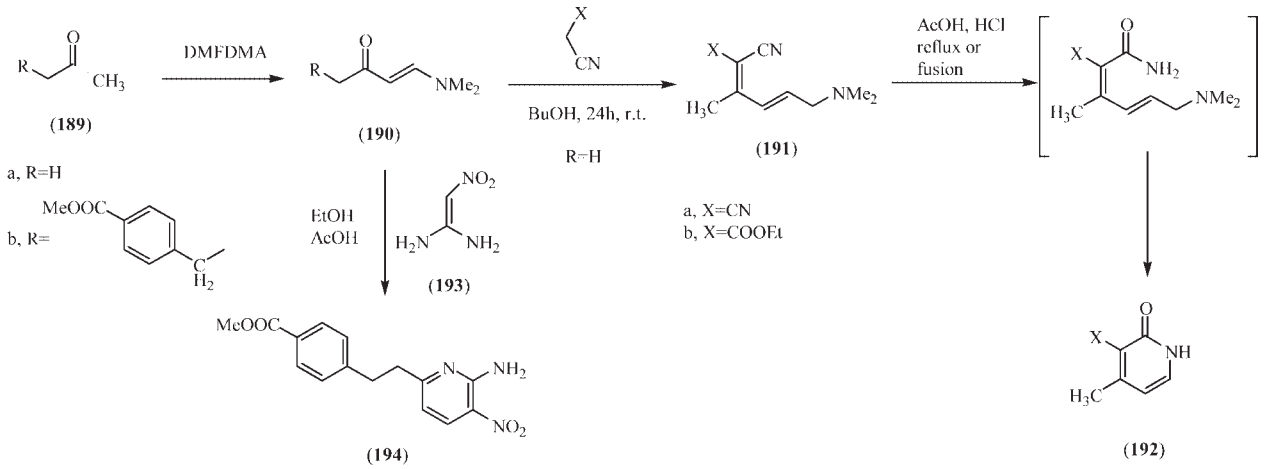
(**176a**) in the presence of potassium *t*-butoxide afforded pyridine derivative (**178**) [124]. The treatment of the dimethylaminopropenone (**177b**) with cyanoacetamide afforded pyridine-2(1*H*)-one (**179**) [125]. Formation of the pyrimidine ring (**180**) was achieved by the base-promoted condensation between 4-bromobenzamidine and 3-dimethylamino-1-(4-bromo-2-methoxyphenyl)-prop-2-en-1-one (**177c**) [126–128]. Enaminoketone (**177d**) was reacted with phenylhydrazine derivatives affording diarylpyrazoles (**182a,b**) [66,129]. Treatment of enaminone (**177e**) with hydrochloric acid under reflux gave 4*H*-benzopyran-4-one (**183**) [130,131]. The reaction of ethylenediamine with enaminones (**177f–h**) afforded the diazepenes (**184a–c**). Refluxing of enaminones (**177f–h**) in acetic acid gave (**185a–c**). The reaction of (**177f–h**) with 3-aminocrotononitrile afforded the pyridine derivatives (**186a–c**) [132]. 2-Amino-4-[4(*N*-acetyl-*N*-ethyl)aminophenyl]pyrimidine (**187**) was obtained by condensation of enaminone (**177i**) with guanidine hydrochloride. Enaminone (**177i**) reacted with 3-amino-1,2,4-triazole to give 1,2,4-triazolo[1,5-*a*]pyrimidine (**188**) [32,133] as shown in Scheme 26.

1-*N*,*N*-Dimethylaminobut-1-en-3-one (**190a**) and its derivatives (**190b**) were obtained by the reaction of acetone and its derivative (**189a,b**) with DMFDMA. The reaction of (**190a**) with either malononitrile or ethyl cyanoacetate afforded (**191a,b**) which was then refluxed in an acetic acid hydrochloric acid mixture to afford 3-substituted 4-methylpyridine-2(1*H*)-one (**192a,b**) in a good yield [134,135]. Treatment of phenethyl enaminone

Scheme 26

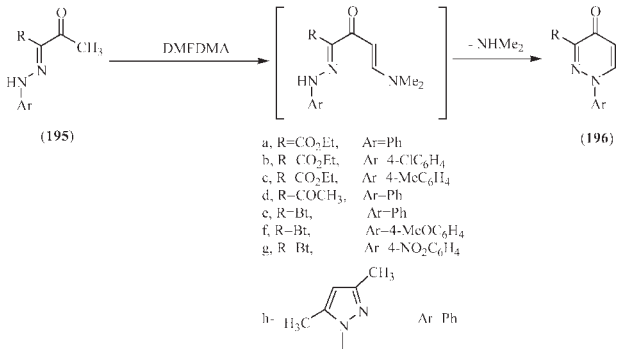


Scheme 27



(**190b**) with 2-nitroethene-1,1-diamine (**193**) gave pyridine (**194**) as shown in Scheme 27 [136].

Consequently arylhydrazones (**195a–h**) were condensed with DMFDMA to yield the pyrazolylpyridazine (**196a–h**) in good yields [137–139].

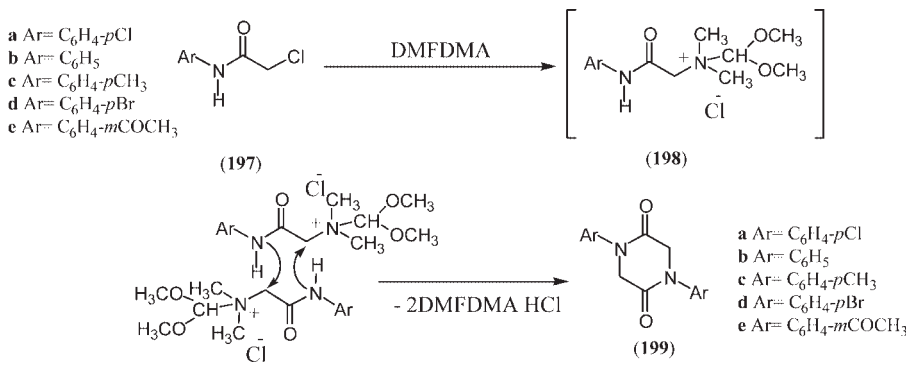


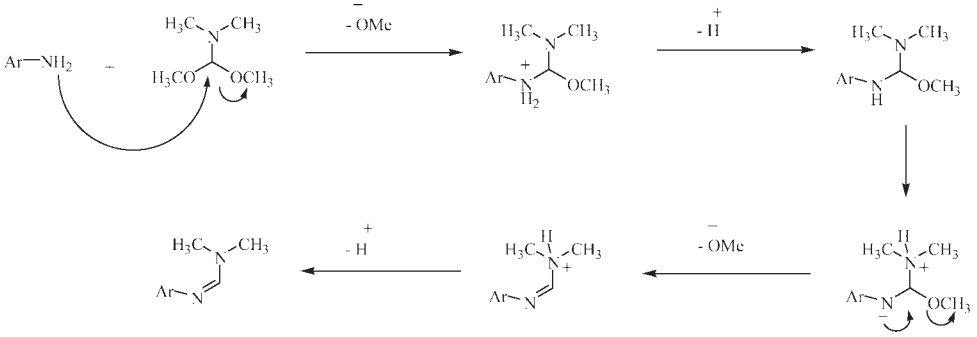
DMFDMA was found to react with α-chloroacetanildes (**197a–e**) to give the unexpected products 1,6-diarylpyrazine-2,5-diones (**199a–e**). Scheme 28 shows a possible alternative pathway, in which DMFDMA acts as a nucleophile which attacks the carbon carrying the chlorine in α-chloroacetamides (**197a–e**) to afford the salt (**198a–e**); dimerization with elimination of DMFDMA salt then gives 1,4-diarylpiperazine-2,5-diones (**199a–e**) [140].

4. PREPARATION OF HETEROCYCLIC COMPOUNDS THROUGH THE FORMYLATION OF THE AMINO GROUP USING DMFDMA TO GIVE AMIDINES

The reaction of the amino group with DMFDMA is easier and faster than the methyl and methylene groups because the amino group contains free lone pair of electrons, which make it a very good nucleophile. So that the reaction is nucleophilic substitution followed by elimination of methanol molecule to give the corresponding *N*,*N*-dimethylaminoamidine by the effect of NMe_2 group as shown in the following reaction mechanism.

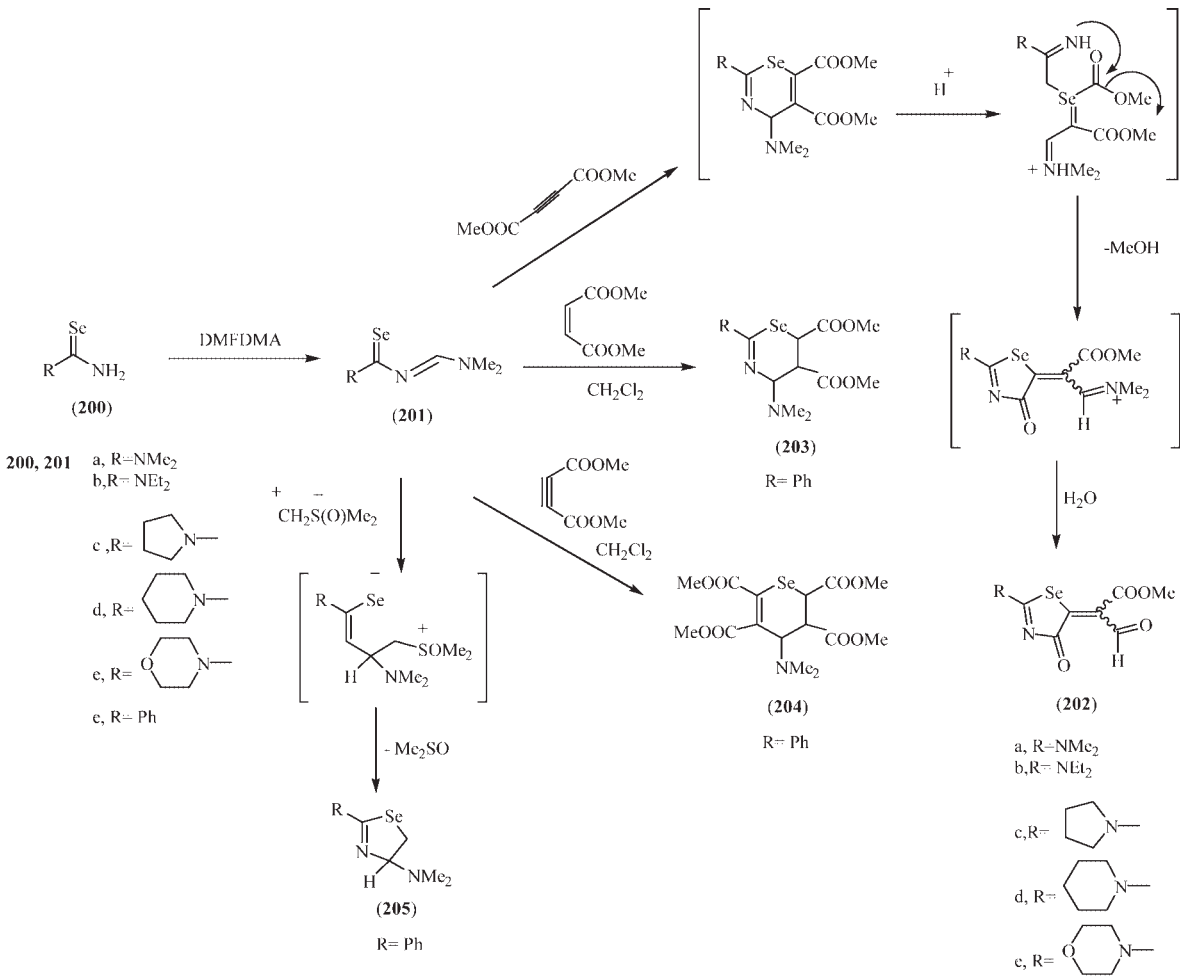
Scheme 28



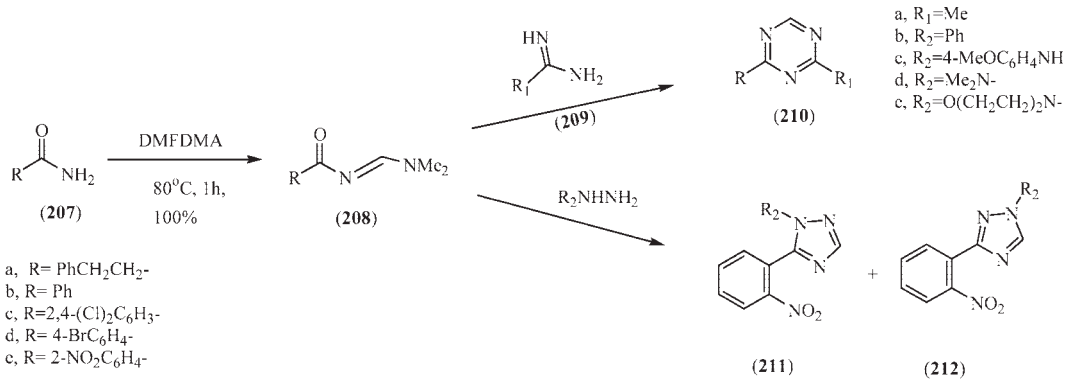


4.1. Amino of selenoamide group. Condensation of *N*,*N*-disubstituted selenourea (**200a–e**) with DMFDMA (1.5 equiv) at room temperature for 6 h afforded selenoazadienes (**201a–e**) in high yields. The presence of the selenium atom facilitates the cycloaddition reactions as a result of the presence of the vacant d-orbital which make it act as a Lewis acid. Interestingly, the reaction did not give the expected Diels-Alder adduct but a mixture of *E*/*Z* isomers of (**202**) was obtained. The reaction was carried out as shown in Scheme 29 [141]. The reactivity of the *N*-selenoacylamidine (**201e**) as 4π heterodienic system in [4 + 2] cycloaddition reactions with electrophilic dienophiles was investigated. Thus (**201e**) was quenched with an excess of methyl acrylate

Scheme 29



Scheme 30



affording 5,6-dihydro-4*H*-1,3-selenazine (**203**). The addition of dimethyl acetylenedicarboxylate (DMAD) afforded the 4*H*-selenopyran (**204**). Treatment of the trimethylsulfoxonium iodide with the *N*-selenoacylamidine (**201e**) gave the selenazol-2-ines (**205**) as shown in Scheme 29 [142].

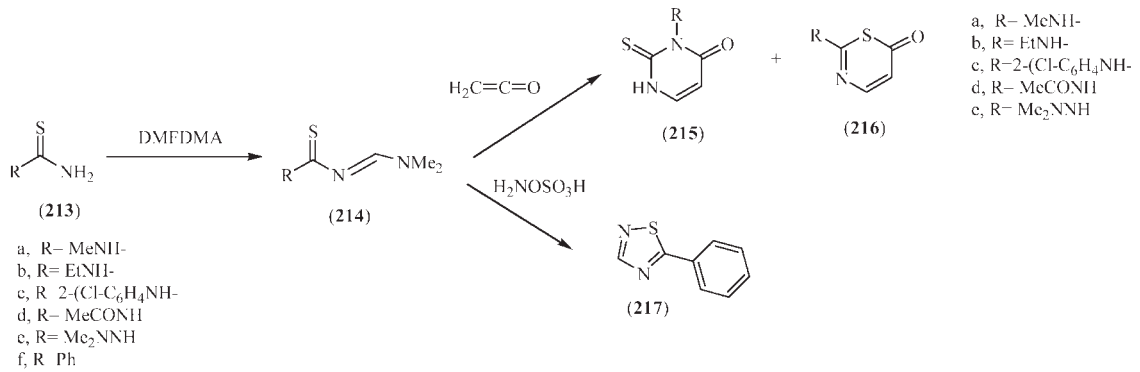
4.2. Amino of amide group. *N*′-Acyl-*N*,*N*-dimethylamidines (**208a–e**) were prepared in excellent yields by heating amides (**207a–e**) with DMFDMA. *N*′-Acyl-*N*,*N*-dimethylamidines (**208a–e**) were condensed with amidines or guanidines (**209a–e**) in aprotic solvent to give s-triazines (**210a–e**). Also 2-(2-nitrophenyl)-1,3,4-triazoles (**211**) and (**212**) were synthesized from treatment of (**208e**) with hydrazine derivatives Scheme 30 [143–146].

4.3. Amino of thioamide group. Treatment of thioamide (**213a–f**) with DMFDMA gave 2,4-diamino-1-thia-3-azabutadienes (**214a–f**). Thioxopyrimidinones (**215a–e**) and thiazinones (**216a–e**) were obtained from treatment of (**214a–e**) with ketene by [4 + 2] cycloaddition reaction [147]. 5-Phenyl-1,2,4-thiadiazole (**217**) was also synthesized from reaction of [dimethyl (amino)methylene]thiobenzamide (**214f**) with hydroxylamine-*O*-sulfonic acid at room temperature as shown in Scheme 31 [148].

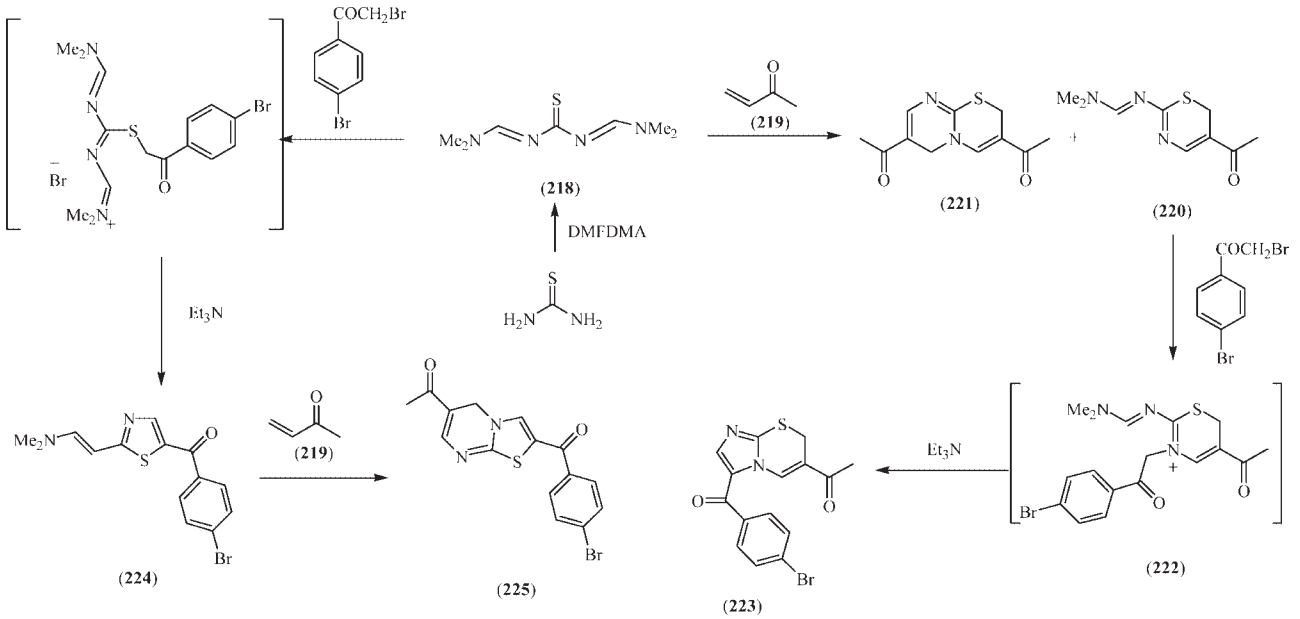
The reaction of thiourea with excess of DMFDMA in boiling dichloromethane afforded polyheteropolyene (**218**). The [4 + 2] cycloaddition reaction with methyl vinyl ketone (**219**), the thiazine (**220**), and pyrimido[2,1-*b*][1,3]thiazine (**221**) were formed. The alkylation of thiazine (**220**) by *p*-bromophenacyl bromide affected the endocyclic nitrogen atom providing the *N*-alkylated unisolated salt (**222**). Subsequent treatment with triethylamine afforded imidazo[2,1-*b*][1,3]thiazine (**223**). The reaction between polyheteropolyene (**218**) and *p*-bromophenacyl bromide afforded the corresponding S-alkyl bromide salt. This intermediate was deprotonated *in situ* by addition of triethylamine. Annulation proceeded spontaneously followed by loss of dimethylamine to provide thiazole derivative (**224**). The [4 + 2] cycloaddition reaction between thiazole (**224**) and methyl vinyl ketone (**219**) gave 5*H*-thiazolo[3,2-*a*]pyrimidine (**225**) as shown in Scheme 32 [149].

4.4. Amino group attached to the ring. Treatment of 2-aminoheterocyclic compounds (**226a–c**) with DMFDMA gave the corresponding amidines (**227a–c**). The treatment of (**227a–c**) with (*R*,*S*) isomer of *N*-trifluoroacetyl-5-bromo-4-oxonorvaline methyl ester (**228**) gave (**230a,b**) *via* the intermediate (**229**) as shown in

Scheme 31

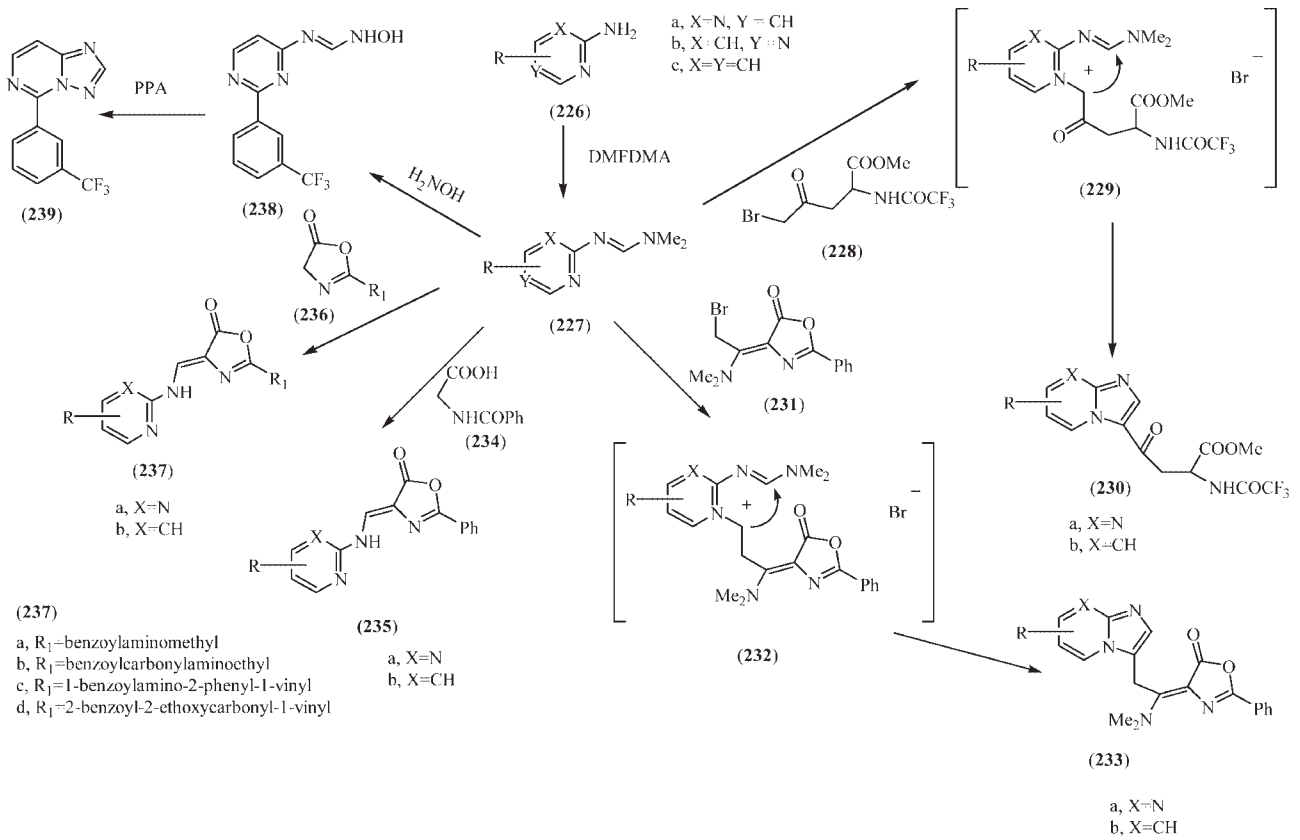


Scheme 32

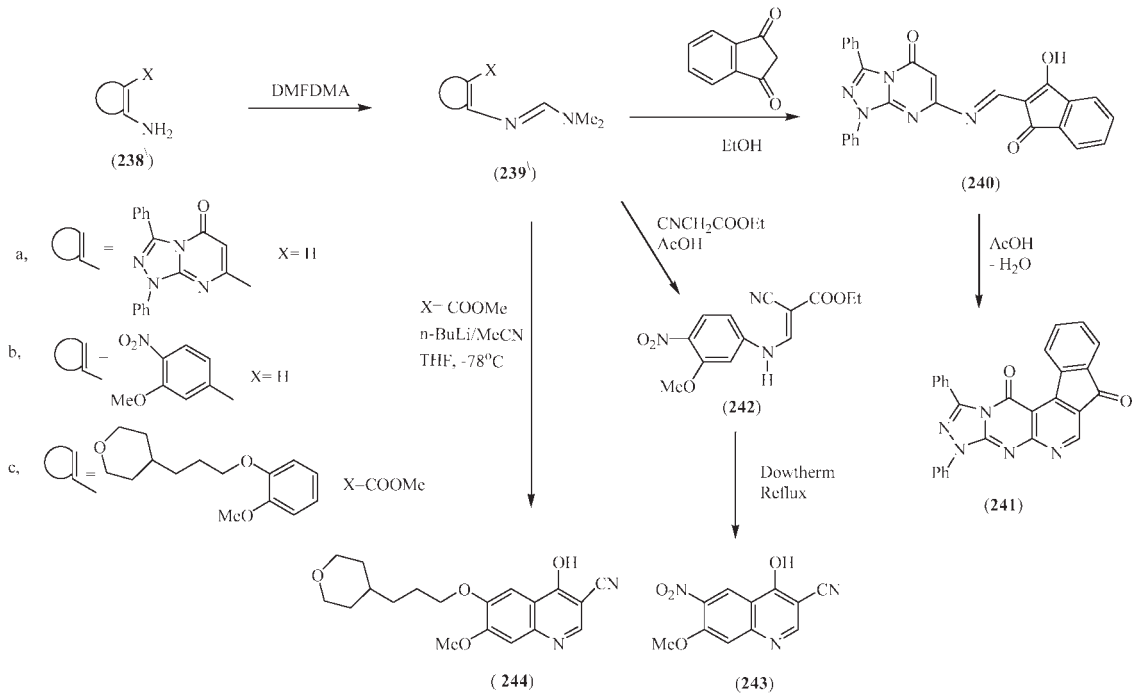


Scheme 33 [150]. Also the reaction of (**227a–c**) with 4-(2-bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**231**) in acetonitrile or DMF, the quaternary salt (**232**) was formed, which was cyclized into (**233a–c**) [151]. The reaction of (**227a–c**) with either huppuric acid (**234**) or oxazolones (**236**) afforded 2-substituted-4-

Scheme 33



Scheme 34



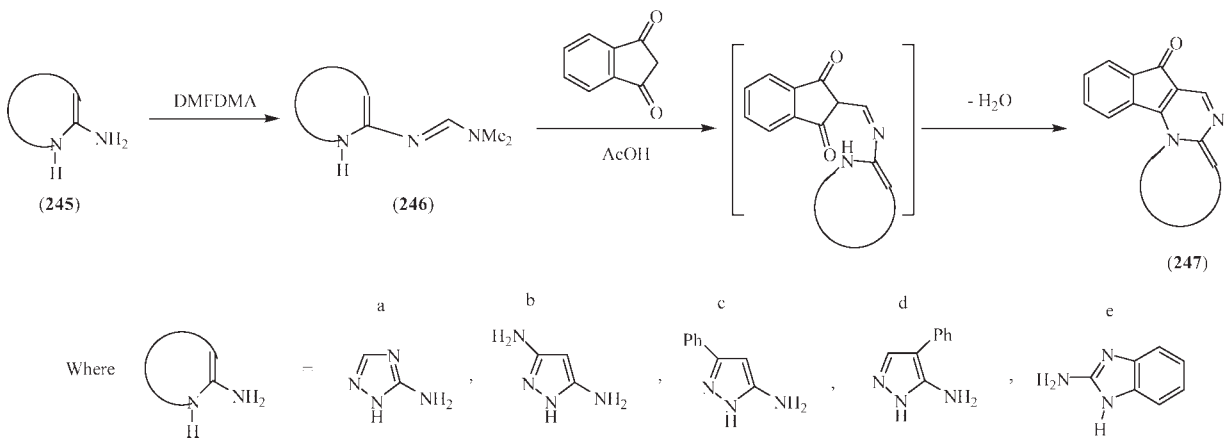
heteroarylaminomethylene-5(4*H*)-oxazolones (**235a–c**) and (**237**), respectively [152]. Triazolo[1,5-*c*]pyrimidine (**239**) was prepared by treatment of (**227b**) with hydroxylamine to give compound (**238**) followed by treatment with polyphosphric acid as is also shown in Scheme 33 [153,154].

Reaction of amino compounds (**238′a–c**) with DMFDMA yields the corresponding formamidine compounds (**239′a–c**). Treatment of compound (**239′a**) with indene-1,3(2*H*)-dione in boiling ethanol leads to the formation of acyclic structure (**240**), which is converted into cyclic compound (**241**) when boiled in glacial acetic acid [155]. Reaction of (**239b**) with ethyl cyanoacetate gave (**242**) as a mixture of isomers, which on thermal cyclization gave the 4-hydroxyquinoline (**243**). Hydroxyquinoline (**244**) was accomplished by treating (**239′c**) with the lithium anion of CH_3CN in THF at –78°C followed by quenching with AcOH, and warming to room temperature as shown in Scheme 34 [156].

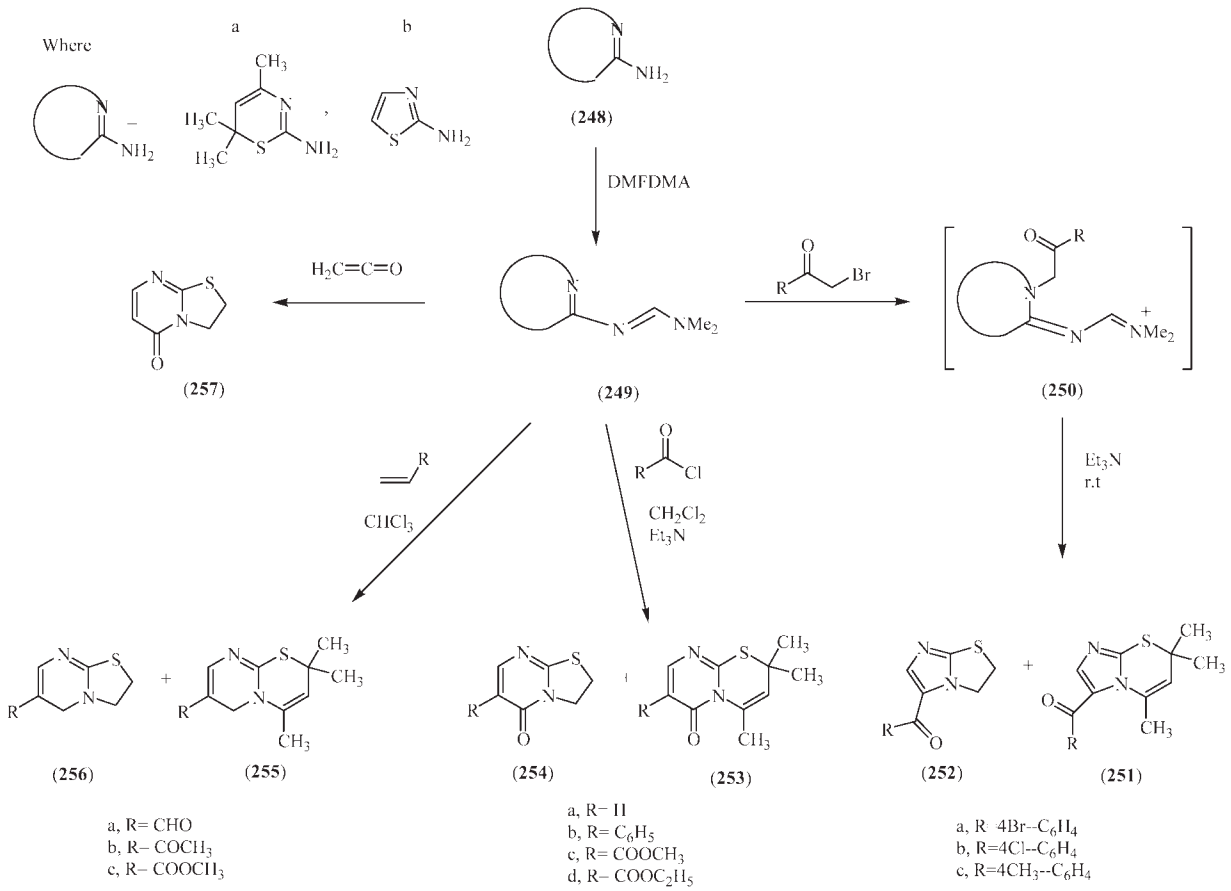
Also condensation of compounds (**246a–e**), which were prepared by reaction of (**245a–e**) with DMFDMA and indene-1,3-dione in boiling acetic acid leads to the formation of compounds (**247a–e**) as shown in Scheme 35 [155].

Treatment of 2-amino-4,6,6-trimethyl-6*H*-1,3-thiazine (**248a**) 2-aminothiazoline (**248b**) with DMFDMA

Scheme 35

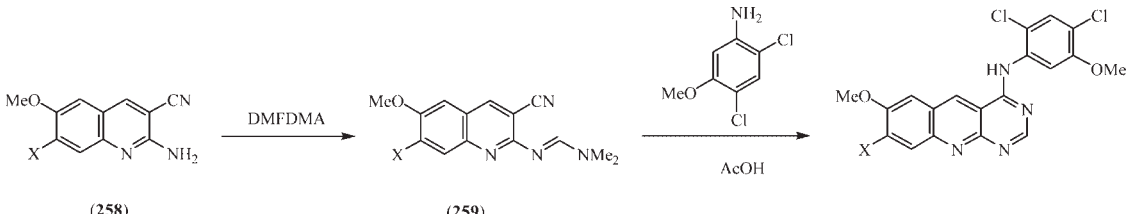


Scheme 36



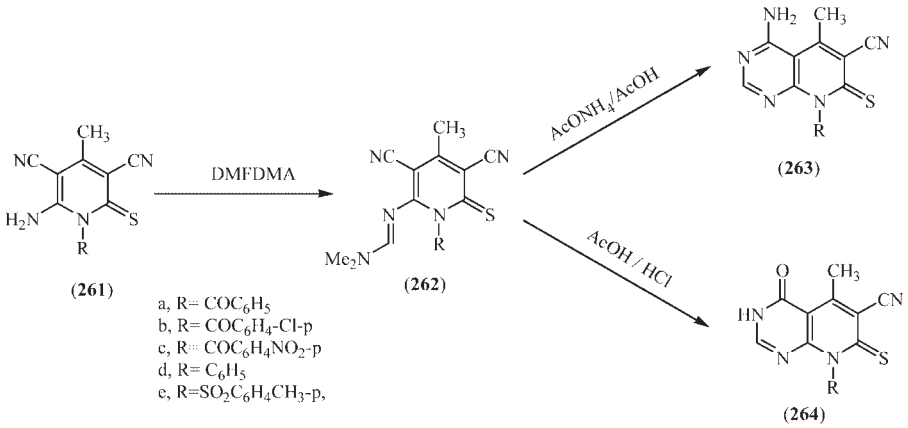
afforded (**249a,b**). Alkylation of compound (**249a,b**) with arylacyl bromides affected the intracyclic *N*-alkyl amidinium bromides (**250**). These salts transformed into 7*H*-imidazo[2,1-*b*][1,3]thiazines (**251**) imidazo[2,1-*b*]thiazoles (**252**), respectively, by addition of Et_3N. 2*H*,6*H*-Pyrimido[2,1-*b*][1,3]thiazin-6-ones (**253**) and (**254**) can be prepared from compounds (**249a,b**) with acid chlorides. 2*H*,6*H*-Pyrimido[2,1-*b*][1,3]thiazine derivatives (**255**) and thiazolo[3,2-*a*]pyrimidines (**256**) were obtained by the reaction of amidines (**249a,b**) with acrylic dienophiles in $CHCl_3$. Cycloaddition of amidine (**249b**) with ketene gave 6-unsubstituted thiazolo[3,2-*a*]pyrimidin-5-ones (**257**) as shown in Scheme 36 [157,158].

Treatment of quinoline derivatives (**258a,b**) with DMFDMA gave the corresponding amidines (**259a,b**). Subsequent addition of 2,4-dichloro-5-methoxyaniline in acetic acid provided the desired tricyclic derivatives (**260a,b**) as shown in the following [159].



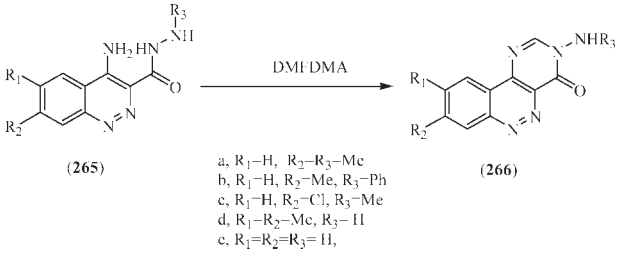
Also the treatment of 6-amino-3,5-dicyano-6-methyl-*N*-substitutedpyridine-2(1*H*)-thione (**261**) with DMF DMA in dry dioxane afforded the corresponding amidine (**262**) which on boiling with ammonium acetate in

Scheme 37

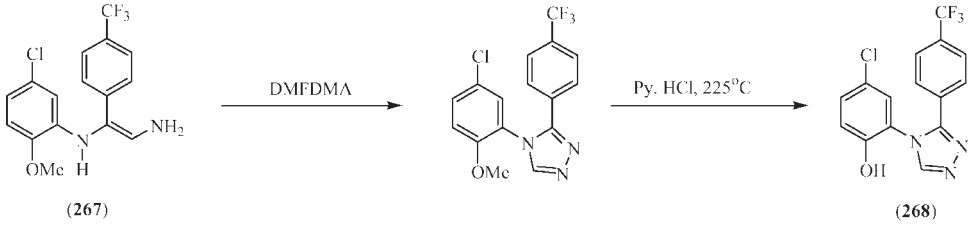


acetic acid and hydrochloric acid in acetic acid afforded pyrido[2,3-*d*]pyrimidine derivatives (**263**) and (**264**), respectively, as shown in Scheme 37 [160].

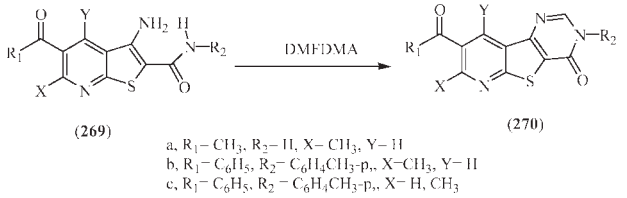
4.5. Cyclization of two amino groups by DMFDMA. Hydrazides (**265a–e**) were converted to 3-aminopyrimido[5,4-*c*]cinnolines (**266a–e**) by refluxing with DMFDMA in diethylene glycol dimethyl ether [161,162].



4-Chloro-2-[3-[4-(trifluoromethyl)phenyl]-4*H*-dihydro-1,2,4-triazol-4-yl]phenyl-phenol (**268**) was obtained by cyclization of compound (**267**) with DMFDMA to give triazole ring followed by hydrolysis [163].

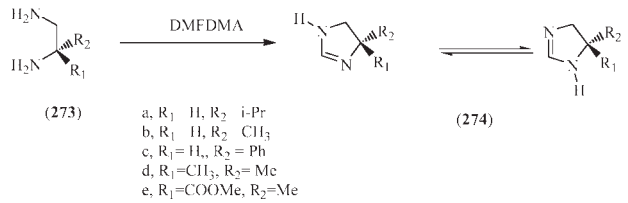


Thieno[2,3-*b*]pyridine derivatives (**269a–c**) on treatment with DMFDMA afforded a product that is formulated as pyrido[2,3-*b*]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (**270a–c**) [38,39,164].



Also, treatment of thieno[2,3-*b*]pyridine (**271**) when treated with DMFDMA afforded the tricyclic compound (**272**) [165].

Imidazolines (**273a–e**) were prepared from the treatment of diamines (**274a–e**) with DMFDMA [166].



5. CONCLUSIONS

The reactions considered in this review clearly demonstrate the high synthetic potential of DMFDMA. Many biologically active heterocyclic compounds have been obtained based on this reagent. This suggests that DMFDMA can be particularly used in the synthesis of functionalized carbo- and heterocyclic compounds used in the design of novel highly effective pharmaceuticals with a broad spectrum of bioresponses. The great interest of chemists in such reagent is confirmed by the facts that many articles cited in this review are recently obtained, along with a multitude of patents.

REFERENCES AND NOTES

[1] Meerwein, H.; Borner, P.; Fuchs, O.; Sasse, H. J.; Schrodt, H.; Spille, J. Chem Ber 1956, 89, 2060.

[2] Meerwein, H.; Florian, W.; Schon, N.; Stopp, G. Liebids Ann 1961, 641, 1.

[3] Stanovnik, B. Prog Heterocycl Chem 1993, 5, 34.

[4] Stanovnik, B. Molecules 1996, 123.

[5] Stanovnik, B. J Heterocycl Chem 1999, 36, 1581.

[6] Stanovnik, B.; Svete, J. Synlett 2000, 1077.

[7] Stanovnik, B.; Svete, J. Target Heterocycl Chem 2000, 4, 105.

[8] Stanovnik, B.; Svete, J.; Chem Rev 2004, 104, 2433.

[9] Negri, G.; Kascheres, A. J. J Heterocycl Chem 2004, 41, 461.

[10] Ostrowaska, K.; Kolasa, H. Sci Synth 2005, 22, 369.

[11] Granik, V. G.; Zhidkova, A. M.; Glushkov, R. G. Russ Chem Rev 1977, 46, 361.

[12] Abdulla, R. F.; Brinkmeyer, R. S. Tetrahedron 1979, 35, 1675.

[13] Boykin, D. W.; Kumar, A.; Bajic, M.; Xiao, G.; Wilson, W. D.; Bender, B. C.; McCurdy, D. R.; Hall, J. E.; Tidwell, R. R. Eur J Med Chem 1997, 32, 965.

[14] Penning, T. D.; Tallsy, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Buton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. J Med Chem 1997, 40, 1347.

[15] Gupton, J. T.; Krumpe, K. E.; Burnham, B. S.; Dwornik, K. A.; Petrich, S. A.; Du, D. X.; Bruce, M. A.; Vu, P.; Keertikar, M.; Hosein, K. N.; Jones, C. R.; Sikorski, J. A. Tetrahedron 1998, 54, 5075.

[16] Stochley, M.; Clegg, W.; Fontana, G.; Golding, B. T.; Martin, N.; Rigoreau, L. J. M.; Smith, G. C. M.; Griffin, R. J. Bioorg Med Chem Lett 2001, 11, 2837.

[17] Al-Saleh, B.; Abdel-Khalik, M. M.; El-Apasery, M. A.; Elnagdi, M. H. J Heterocycl Chem 2003, 40, 171.

[18] Finke, P. E.; Meurer, L. C.; Debenham, J. S.; Toupence, R. B.; Walsh, T. F. US PCT Int. Appl. WO 03 82,191, 2003; Chem Abstr 2003, 139, 307686f.

[19] Al-Omran, F.; Mohareb, R. M.; Abou El-Khair, A. J Heterocycl Chem 2002, 39, 877.

[20] Laufer, S. A.; Wagner, G. K. J Med Chem 2002, 45, 2733.

[21] (a) Gellibert, F. J.; Hartley, C. D.; Mathews, N.; Woolven, J. M. GB PCT Int Appl WO 02 62, 794, 2002; (b) Gellibert, F. J.; Hartley, C. D.; Mathews, N.; Woolven, J. M. Chem Abstr 2002, 137, 169515e.

[22] Abdel-Megid, M.; Elnagdi, M. H.; Negm, A. M. J Heterocycl Chem 2002, 39, 105.

[23] Olesen, P. H.; Swedberg, M. D. B.; Rimvall, K. Bioorg Med Chem 1998, 6, 1623.

[24] Al-Omran, F.; Abd El-Hay, O. Y.; Abou El-Kair, A. J Heterocycl Chem 2000, 37, 1617.

[25] Reidlinger, C.; Dworczak, R.; Junek H. Monatsh Chem 1998, 129, 1207.

[26] Svete, J.; Stanovnik; B. J Heterocycl Chem 1999, 36, 1147.

[27] (a) Fraley, M. E.; Peckham, J. P.; Arrington, K. L.; Hoffman, W. F.; Hartman, G. D. US PCT Int Appl WO 03 11,837, 2003; (b) Fraley, M. E.; Peckham, J. P.; Arrington, K. L.; Hoffman, W. F.; Hartman, G. D. Chem Abstr 2003, 138, 153548c.

[28] Elkholy, Y. M.; Erian, A. W. Heteroat Chem 2003, 14, 503.

[29] Chen, C.; Wilcoxen, K.; McCarthy, J. R. Tetrahydron Lett 1998, 39, 8229.

[30] Al-Mousawi, S.; John, E.; Al-Kandery, N. J Heterocycl Chem 2004, 41, 381.

[31] Bruno, O.; Schenone, S.; Ranise, A.; Mazzeo, F. Farmaco 1999, 54, 95.

[32] Mustazza, C.; Del Giudice, M. R.; Borioni, A.; Gatta, F. J Heterocycl Chem 2001, 38, 1119.

[33] Al-Mousawi, S.; Abdel-Khalik, M. M.; El-Sherbiny, S.; John, E.; Elnagdi, M. H. J Heterocycl Chem 2001, 38, 949.

[34] Abdel-Khalik, M. M.; Eltoukhy, A. M.; Agamy, S. M.; Elnagdi, M. H. J Heterocycl Chem 2004, 41, 431.

[35] Giardina, G. A.; Sarau, H. M.; Farina, C.; Medhurst, A. D.; Grugni, M.; Raveglia, L. F.; Schmidt, D. B.; Rigolio, R.; Luttmann, M.; Vecchietti, V.; Hay, D. W. P. J Med Chem 1997, 40, 1794.

[36] Abu-Shanab, F. A.; Redhouse, A. D.; Thompson J. R.; Wakefield, B. J. Synthesis 1995, 557.

[37] Abu-Shanab, F. A.; Aly, F. M.; Wakefield, B. J. Synthesis 1995, 923.

[38] Abu-Shanab, F. A.; Elkholy, Y. M.; Elnagdi, M. H. Synth Commun 2002, 32, 3493.

[39] Abu-Shanab, F. A.; Hessen, A. M.; Mousa, S. A. S. J Heterocycl Chem 2007, 44, 787.

[40] Svete, J.; Aljaz-Rozic, M.; Stanovnik, B. J Heterocycl Chem 1997, 34, 177.

[41] Simonic, I.; Stanovnik, B. J Heterocycl Chem 1997, 34, 1725.

[42] Malesic, M.; Krbavcic, A.; Golobic, A.; Golic, L.; Stanovnik, B. J Heterocycl Chem 1997, 34, 1757.

[43] Kepe, V.; Kozjan, V.; Polanc, S.; Kocevar, M. Heterocycles 1999, 50, 315.

[44] (a) Kim, G. C.; Kim, M. H.; Park, Y. J.; Lee, H. S. Repub. Korean Kongkae Taeho Kongbo KR 2000, 56, 672; (b) Kim, G. C.; Kim, M. H.; Park, Y. J.; Lee, H. S. Chem Abstr 2002, 137, 169544p.

[45] Abu Elmaati, T. M.; El-Taweel, F. M. A. J Chin Chem Soc 2002, 49, 1045.

[46] Elmaati, T. A.; Said, S.; Elenein, N. A.; Sofan, M.; Khodeir, N. Polym J Chem 2002, 76, 945.

[47] (a) Lambert, J. F.; Norris, T. US PCT Int Appl WO 02 44, 133, 2002; (b) Lambert, J. F.; Norris, T. Chem Abstr 2002, 137, 20372y.

[48] Menozzi, G.; Mosti, L.; Schenone, P. J Heterocycl Chem 1984, 21, 1437.

[49] Selic, L.; Grdadolnik, S. G.; Stanovnik, B. Heterocycles 2003, 60, 1317.

[50] Al-Mousawi, S.; Abdelkhalik, M. M.; John, E.; Elnagdi, M. H. J Heterocycl Chem 2003, 40, 689.

[51] Molteni, V.; Hamilton, M. M.; Mao, L.; Crane, C. M.; Termin, A. P.; Wilson, D. M. Synthesis 2002, 1669.

[52] Hu, X.-G.; Chen, H.; Hu, X.-Q.; Dai, H.; Bai, C.; Wang, J.; Zheng, Z. Tetrahedron Lett 2002, 43, 9179.

[53] Mazharuddin, M.; Thyagarajan, G. Tetrahedron Lett 1971, 12, 307.

[54] Wentland, M. P.; Perni, R. B.; Dorff, P. H.; Rrundage, R. P.; Castaldi, M. J.; Bailey, T. R.; Carabateas, Ph. M.; Bacon, E. R.; Young, D. C.; Woods, M. G.; Rosi, D.; Drozd, M. L.; Kullnig, R. K.; Dutko, F. J. J Med Chem 1993, 36, 1580.

[55] (a) Bellani, P. IT PCT Int Appl WO 95 11, 886, 1995; (b) Bellani, P. Chem Abstr 1995, 123, 111863m.

[56] Almansa, C.; Gomez, L. A.; Cavalcanti, F. L.; de Arriba, A. F.; Garcia-Rafanell, J.; Forn, J. J Med Chem 1997, 40, 547.

[57] (a) Merck Patent G.m.b.H. Ger Offen DE 10, 149, 370, 2003; (b) Merck Patent G.m.b.H. Chem Abstr 2003, 138, 304276r.

[58] Taylor, E. C.; Macor, J. E. J Heterocycl Chem 1995, 22, 409.

[59] Selic, L.; Stanovnik, B. J Heterocycl Chem 1997, 34, 813.

[60] Selic, L.; Stanovnik, B. Helv Chim Acta 1998, 81, 1634.

[61] Takahashi, M.; Muta, S.; Nakazato, H. J Heterocycl Chem 1997, 34, 1395.

[62] Chen, W.-Y.; Gilman, N. W. J Heterocycl Chem 1983, 20, 663.

[63] Chen, W.-Y.; Gilman, N. W. J Med Chem 1983, 26, 1589.

[64] (a) Bantick, J.; Perry M.; Thorne, P. GB PCT Int Appl WO 98 01,449, 1998; (b) Bantick, J.; Perry M.; Thorne, P. Chem Abstr 1998, 128, 140714x.

[65] Pelerlin-Masic, L.; Mlinsek, G.; Solmajer, T.; Trampus-Bakija, A.; Stegnar, M.; Kikelj, D. Bioorg Med Chem Lett 2003, 13, 789.

[66] (a) Maynard, G.; Yuan, J.; Rachwal, S. US PCT Int Appl WO 03 66,634, 2003; (b) Maynard, G.; Yuan, J.; Rachwal, S. Chem Abstr 2003, 139, 180059w.

[67] (a) Harrington, E. US Pat Appl Publ US 207,873, 2003; (b) Harrington, E. Chem Abstr 2003, 139, 364918g.

[68] Abu Elmaali, T. M. J Heterocycl Chem 2003, 40, 481.

[69] Kato, T. Acc Chem Res 1974, 7, 265.

[70] Kato, T.; Chiba T.; Okada, T. Chem Pharm Bull 1979, 27, 1186.

[71] Chemens, R. J. Chem Rev 1986, 86, 241.

[72] Smolii, O. B.; Muzychka L. V.; Drach, B. S. Russ J Gen Chem 2002, 72, 1315.

[73] Elassar, A. A.; El-Kholy, Y. M. Heteroat Chem 2003, 14, 427.

[74] (a) Shaw, K. Czech Rep CZ 280,796, 1996; (b) Shaw, K. Chem Abstr 1996, 125, 221868r.

[75] Takahashi, M.; Yamashita, I. Heterocycles 1990, 31, 1537.

[76] Abu-Shanab, F. A. J Sulfur Chem 2006, 27, 433.

[77] Hanzlowsky, A.; Jelencic, B.; Recnik, S.; Svete, J.; Golobic A.; Stanovnik, B. J Heterocycl Chem 2003, 40, 487.

[78] Youssif, S. Monatsh Chem 1997, 128, 493.

[79] Anderson, A. G.; Ko, R. P. J Org Chem 1984, 49, 4769.

[80] Gorvin, J. H.; Whalley, D. P. J Chem Soc Perkin Trans 1, 1979, 1364.

[81] Mosti, L.; Schenone, P.; Menozzi, G. J Heterocycl Chem 1979, 16, 913.

[82] Mosti, L.; Schenone, P.; Menozzi, G. J Heterocycl Chem 1982, 19, 1031.

[83] Cecchetti, V.; Fravolini, A.; Schiaffella, F. J Heterocycl Chem 1982, 19, 1045.

[84] Bargagna, A.; Bignardi, G.; Schenone, P.; Longobardi, M. J Heterocycl Chem 1983, 20, 839.

[85] Menozzi, G.; Mosti, L.; Schenone, P. J Heterocycl Chem 1984, 21, 1441.

[86] Abu-Shanab, F. A.; Wakefield, B. J.; Elnagdi, M. H. Adv Heterocycl Chem 1997, 68, 181.

[87] Senga, K.; Kanamori, Y.; Kanazawa, H.; Nishigaki, S. J Heterocycl Chem 1978, 15, 359.

[88] Kawase, M.; Sinhababu, A. K.; McGhee, E. M.; Milby, T.; Borchardt, R. T. J Med Chem 1990, 33, 2204.

[89] Showalter, H. D. H.; Sun, L.; Sercel, A. D.; Winters, R. T.; Denny, W. A.; Palmer, B. D. J Org Chem 1996, 61, 1155.

[90] (a) Oi, H. Jpn Kokai Tokkyo Koho JP10 279,538, 1998; (b) Oi, H. Chem Abstr 1998, 129, 330536j.

[91] Fauq, A. H.; Hong, F.; Cusack, B.; Tyler, B. M.; Ping-Pang, Y.; Richelson, E. Tetrahedron Asymmetry 1998, 9, 4127.

[92] Furneaux, R. H.; Tyler, P. C. J Org Chem 1999, 64, 8411.

[93] (a) Eturi, S. R.; Bashir-Hashemi, A.; Iyer, S. US Patent 5, 969,155, 1999; (b) Eturi, S. R.; Bashir-Hashemi, A.; Iyer, S. Chem Abstr 1999, 131, 271810k.

[94] Evans, C. B.; Furneaux, R. H.; Hutchison, T. L.; Kezar, H. S.; Morris, P. E.; Schramm, V. L., Jr.; Tyler, P. C. J Org Chem 2001, 66, 5723.

[95] (a) Hirose, K.; Imabori, H.; Yanase, T.; Ikejiri, S. Jpn Kokai Tokkyo Koho JP 26,579, 2001; (b) Hirose, K.; Imabori, H.; Yanase, T.; Ikejiri, S. Chem Abstr 2001, 134, 115852g.

[96] (a) Namie, K.; Takahashi, Y. Jpn Kokai Tokkyo Koho JP 288,168, 2001; (b) Namie, K.; Takahashi, Y. Chem Abstr 2001, 135, 303773b.

[97] Yang, C.; Wang, J.; Jiang, B. Tetrahedron Lett 2002, 43, 1063.

[98] Wong, S.; Shah, B.; Shah, P.; Butt, I. C.; Woon, E. C. Y.; Wright, J. A.; Thompson, A. S.; Upton, C.; Threadgill, M. D. Tetrahedron Lett 2002, 43, 2299.

[99] Filla, S. A.; Mathes, B. M.; Johnson, K. W.; Erickson, L. A.; Sckenck, K. W.; Wainscott, D. B.; Branchek, T. A.; Schaus, J. M. J Med Chem 2003, 46, 3060.

[100] Siu, J.; Baxendale, I. R.; Ley, S. V. Org Biomol Chem 2004, 2, 160.

[101] Zhu, J.; Wong, H.; Zhang, Z.; Yin, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T. Tetrahedron Lett 2006, 47, 5653.

[102] Abu-Shanab, F. A.; Wakefield, B.; Al-Omran, F.; Abdel Khalek, M. M.; Elnagdi, M. H. J Chem Res (S) 1995, 488.

[103] Abu-Shanab, F. A.; Wakefield, B.; Al-Omran, F.; Abdel Khalek, M. M.; Elnagdi, M. H. J Chem Res (M) 1995, 2924.

[104] Bruni, F.; Selleri, S.; Costanzo, A.; Guerrini, G.; Casilli, M. L.; Giusti, L. J Heterocycl Chem 1995, 32, 291.

[105] Al-Omran, F.; Elassar, A. A.; Abou El-Khair, A. J Heterocycl Chem 2003, 40, 249.

[106] Bruni, F.; Selleri, S.; Costanzo, A.; Guerrini, G.; Casilli, M. J Heterocycl Chem 1994, 31, 1193.

[107] Couchman, S. M.; Jeffery. J. C.; Ward, M. D. Polyhedron 1999, 18, 2633.

[108] Davies, G. M.; Jeffery, J. C.; Ward, M. D. New J Chem 2003, 27, 1550.

[109] Livoreil, A.; Sauvage, J. P.; Armaroli, N.; Balzani, V.; Flamigni, L.; Ventura, B. J Am Chem Soc 1997, 119, 12114.

[110] Mann, K. L. V.; Jeffery, J. C.; McCleverty, J. A.; Ward, M. D. Polyhedron 1999, 18, 721.

[111] Giblin, G. M. P.; Box, P. C.; Campbell, I. B.; Hancock, A. P.; Roomans, S.; Mills, G. I.; Molloy, C.; Tranter, G. E.; Walker, A. L.; Doctrow, S. R.; Huffman, K.; Malfroy; B. Bioorg Med Chem Lett 2001, 11, 1367.

[112] Chabonniere, L. J.; Ziessel, R. Tetrahedron Lett 2003, 44, 6305.

[113] Lowe, W. J Heterocycl Chem 1977, 14, 931.

[114] Plescia, S.; Daidone, G.; Sprio, V. J Heterocycl Chem 1982, 19, 1385.

[115] (a) Sisko, J. US PCT Int Appl WO 97 23,479, 1997; (b) Sisko, J. Chem Abstr 1997, 127, 135809g.

[116] (a) Bellani, P. US Patent 5,703,233, 1997; (b) Bellani, P Chem Abstr 1998, 128, 88929e.

[117] Sisko, J. J Org Chem 1998, 63, 4529.

[118] Dawood, K. M.; Kandeel, Z. E.; Farag, A. M. Heteroatom Chem 1999, 10, 417.

[119] Plae, R.; Plaum, M. J. M.; Hulst, R. G. A. V. D.; de Boer, T. Bioog Med Chem 2000, 8, 449.

[120] El-Taweel, F. M. A.; Elnagdi, M. H. J Heterocycl Chem 2001, 38, 981.

[121] Fresneda, P. M.; Molina, P.; Bleda, J. A. Tetrahedron 2001, 57, 2355.

[122] Wang, S.; Meades, C.; Wood, G.; Osnowski, A.; Anderson, S.; Yuill, R.; Thomas, M.; Mezna, M.; Jackson, W.; Midgley, C.; Griffiths, G.; Fleming, I.; Green, S.; McNae, I.; Wu, S.; McInnes, C.; Zheleva, D.; Walkinshaw, M. D.; Fischer, P. M. J Med Chem 2004, 47, 1662.

[123] Bulusu, M.; Ettmayer, P.; Weigand, K.; Woisetschlaeger, M. GB PCT Int. Appl. WO 03 63,871, 2003; Chem Abstr 2003, 139, 164802c.

[124] Silva, A. M. S.; Almeida, L. M. P. M.; Cavaleiro, J. A. S. Tetrahedron 1997, 53, 11645.

[125] Witherington, J.; Bordas, V.; Gaiba, A.; Garton, N. S.; Naylor, A.; Rawlings, A. D.; Slingsby, B. P.; Smith, D. G.; Takle, A. K.; Ward, R. W. Bioorg Med Chem Lett 2003, 13, 3055.

[126] (a) Baum, J. W.; Bamberg, J. T.; Grina, J. A. US PCT Int Appl WO 95 19,358,1995; (b) Baum, J. W.; Bamberg, J. T.; Grina, J. A. Chem Abstr 1995, 123, 340179k.

[127] Kumar, A.; Boykin, D. W.; Wilson, W. D.; Jones, S. K.; Bender, B. K.; Dykstra, C. C.; Hall, J. E.; Tidwell, R. R. Eur J Med Chem 1996, 31, 767.

[128] Bejan, E.; Ait-Haddou, H.; Daran, J.; Balavoine, G. G. A. Eur J Org Chem 1998, 12, 2907.

[129] Hernandez, S.; SanMartin, R.; Tellitu, I.; Dominguez, E. Org Lett 2003, 5, 1095.

[130] Reynolds, G. A.; Van Allan, J. A.; Seidel, A. K. J Heterocycl Chem 1979, 16, 369.

[131] Pleier, A.; Glas, H.; Grosche, M.; Sirsch, P.; Thiel, W. R. Synthesis 2001, 55.

[132] Hassanien, A. A.; Ghozlan; S. A. S.; Elnagdi, M. H. J Heterocycl Chem 2003, 40, 225.

[133] Molina, P.; Fresneda, P. M. J Heterocycl Chem 1984, 21, 461.

[134] (a) Julius, M. Ger Offen DE 4,418,155, 1994; (b) Julius, M. Chem Abstr 1995, 122, 132599z.

[135] Al-Mousawi, S. M.; George, K. S.; Elnagdi, M. H. Pharmazie 1999, 54, 571.

[136] Troschutz, R.; Karger, A. J Heterocycl Chem 1996, 33, 1815.

[137] Al-Omran, F.; Al-Awadl, N.; Yousef, O.; Elnagdi, M. H. J Heterocycl Chem 2000, 37, 167.

[138] Mohamed, M. H.; Abdel-Khalik, M. M.; Elnagdi, M. H. J Heterocycl Chem 2001, 38, 685.

[139] Abu-Shanab, F. A.; Nasr, H. M. D. Unpublished results.

[140] Abu-Shanab, F. A.; El-Harrasi, A.; Mousa, S. A. S. Synth Commun 2008, 38, 376.

[141] Koketsu, M.; Nada, F.; Mio, T.; Ishihara, H. Heterocycles 2003, 60, 1211.

[142] Purseigle, F.; Dubreuil, D.; Marchand, A.; Pradere, J. P.; Goli, M.; Toupet, L. Tetrahedron 1998, 54, 2545.

[143] Chen, C.; Dagnino, R., Jr.; McCarthy, J. R. J Org Chem 1995, 60, 8428.

[144] Speake, J. D.; Navas, F.; Bishop, M. J.; Garrison, D. T.; Bigham, E. C.; Hodson, S. J.; Saussy, D. L.; Liacos, J. A.; Irving, P. E.; Sherman, B. W. Bioorg Med Chem Lett 2003, 13, 1183.

[145] (a) Theis, C.; Friedrichs, P. Ger Offen. DE 10,212,053, 2003; (b) Theis, C.; Friedrichs, P. Chem Abstr 2003, 139, 292 274u.

[146] Ghozlan, S. A. S.; Abdelhamid, I. A.; Gaber, H. M.; Elnagdi, M. H. J Heterocycl Chem 2005, 42, 1185.

[147] Landreau, C.; Deniaud, D.; Reliquet, F.; Reliquet, A.; Meslin, J. C. Heterocycles 2000, 53, 2667.

[148] Pavlik, J. W.; Changtog, C.; Tantayanon, S. J Heterocycl Chem 2002, 39, 237.

[149] Landreau, C.; Deniaud, D.; Reliquet, A.; Meslin, J. C. Eur J Org Chem 2003, 421.

[150] Skof, M.; Svete, J.; Stanovnik, B. J Heterocycl Chem 1997, 34, 853.

[151] Bratusek, U.; Hvala, A.; Stanovnik, B. J Heterocycl Chem 1998, 35, 971.

[152] Aljaz-Rozic, M.; Svete, J.; Stanovnik, B. J Heterocycl Chem 1995, 32, 1605.

[153] Medwid, J. B.; Paul, R.; Baker, J. S.; Brockman, J. A.; Du, M. T.; Hallett, W. A.; Hanifin, J. W.; Hardy, R. A., Jr.; Tarrant, M. E.; Torley, L. W.; Wrenn, S. J Med Chem 1990, 33, 1230.

[154] (a) Sato, M.; Miyata, N.; Ishii, T.; Matsunaga, Y.; Amada, H. JP PCT Int Appl WO 02 88,071, 2002; (b) Sato, M.; Miyata, N.; Ishii, T.; Matsunaga, Y.; Amada, H. Chem Abstr 2002, 137, 353064h.

[155] Hassaneen, H. M., Abdallah, T. A.; Abdelhadi, H. A.; Hassaneen H. M. E.; Pagni, R. M. Heteroat Chem 2003, 14, 491.

[156] Wissner, A.; Floyd, M. B.; Rabindran, S. K.; Nilakantan, R.; Greenberger, L. M.; Shen, R.; Wang, Y.; Tsou, H. Bioorg Med Chem Lett 2002, 12, 2893.

[157] Landreau, C.; Deniaud, D.; Reliquet, A.; Meslin, J. C. Synthesis 2001, 2015.

[158] Landreau, C.; Deniaud, D.; Reliquet, A.; Meslin, J. C. Synthesis 2002, 403.

[159] Boschelli, D. H.; Powell, D.; Golas, J. M.; Boschelli, F. Bioorg Med Chem Lett 2003, 13, 2977.

[160] Abu-Shanab, F. A.; Hessen, A.; Gaber, H.; Mousa, S. A. S. J Sulfur Chem 2006, 27, 293.

[161] Stanczak, A.; Ochocki, Z; Pakulska, W. Pharmazie 1998, 53, 834.

[162] Elwan, N. M. J Heterocycl Chem 2004, 41, 281.

[163] Romine, J. L.; Martin, S. W.; Gribkoff, V. K.; Boissard, C. G.; Dworetzky, S. I.; Natale, J.; Gao, Y.; Li, Q.; Meanwell, N. A.; Starrett, J. E. J Med Chem 2002, 45, 2942.

[164] Molina, P.; Arques, A.; Hernandez, H. J Heterocycl Chem 1984, 21, 685.

[165] Abu-Shanab, F. A. J Chem Res (S) 1999, 430.

[166] Hsiao, Y.; Hegedus, L. S. J Org Chem 1997, 62, 3586.

[167] Mosti, L.; Schenone, P.; Menozzi, G. J Heterocycl Chem 1982, 19, 1057.

[168] Leysen, D. C.; Haemers, A.; Bollaert, W. J Heterocycl Chem 1984, 21, 1361.