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Application of guanidine and its salts in multicomponent reactions

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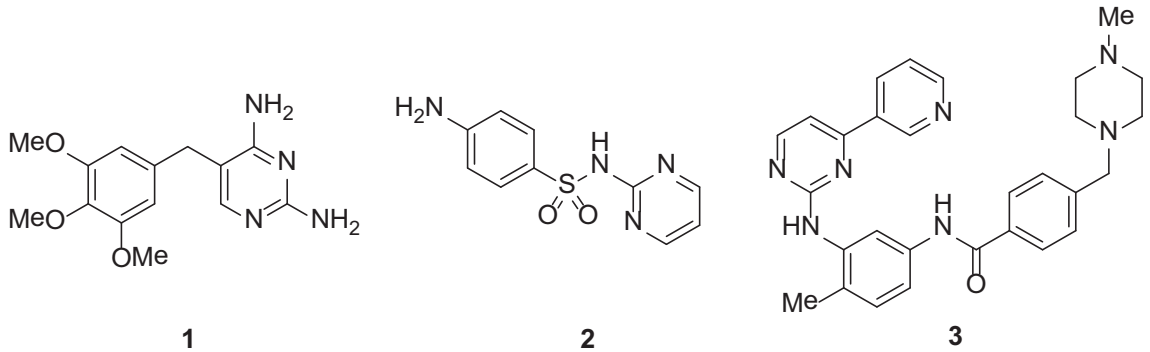
Abstract: This review gives an overview of the application of guanidine and its salts in multicomponent reactions. It can act as a catalyst or solvent for multicomponent reactions or as a reagent for synthesis of substituted diazines, triazines, and macroheterocycles by multicomponent reactions.

Key words: Guanidine, guanidinium salt, multicomponent reaction, pyrimidine, pyrimidinone, triazine

1. Introduction

Guanidine, also called carbamidine, is a strongly alkaline and water-soluble compound that plays a key role in numerous biological activities. The guanidine group defines chemical and physicochemical properties of many compounds of medical interest.[1] Trimethoprim[2] **1**, sulfadiazine[3] **2**, and Gleevec (imatinib mesilate)[4] **3** are examples of pharmaceutically important guanidine-containing heterocycles (Figure). In peptides, residue of arginine has a guanidine structure in the protonated form as guanidinium ion, which functions as an efficient identification moiety of anionic substrates such as carboxylate, nitronate, and phosphate functionalities.[5] The guanidinium ion is also involved in many enzymatic transformations, because it can orient specific substrates based on their electronic characteristic and it is able to form a transition state assembly with the substrates to reduce the activation energy or to stabilize anionic intermediates.[6]



1 **2** **3**

Figure. Typical compounds containing a guanidine substructure.

Multicomponent reactions are of increasing importance in organic and medicinal chemistry because this kind of reaction provides a powerful tool for the 1-pot synthesis of small heterocycles and complex compounds.[7,8]

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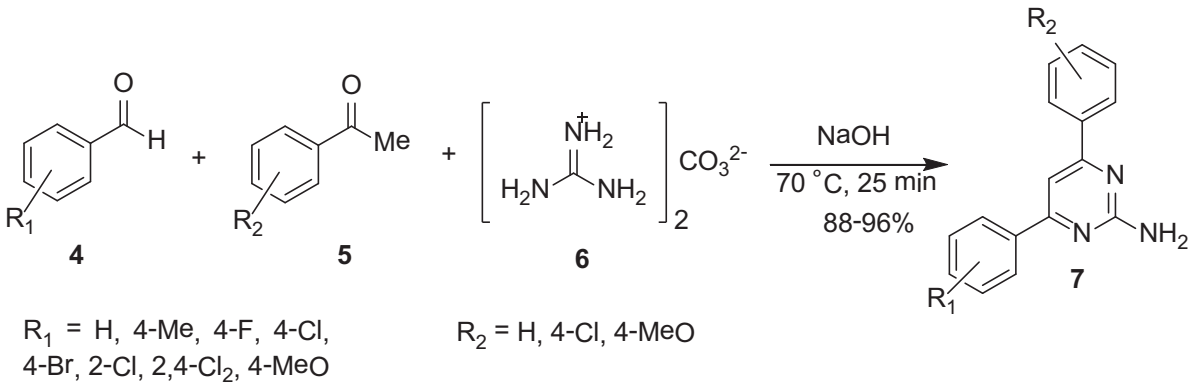
Using guanidine and its salt as reagent in multicomponent reactions usually leads to the formation of guanidine-containing heterocycles, which are a very important class of therapeutic agents, and they are suitable for the treatment of a wide spectrum of diseases.[1,9–11] Guanidinium salts are also environmentally friendly catalysts for some multicomponent reactions.[12,13] This review covers the application of guanidine and its salts from these points of view.

2. Guanidine as a reagent

2.1. Synthesis of 2-aminopyrimidine compounds

2.1.1. Synthesis of 4,6-diaryl compounds

One-pot synthesis of 2-amino-4,6-diarylpyrimidine **7** by multicomponent reaction of aromatic aldehydes **4**, acetophenones **5**, and guanidinium carbonate **6** in the presence of sodium hydroxide under solvent-free conditions was reported by Zhuang et al. (Scheme 1).[14]

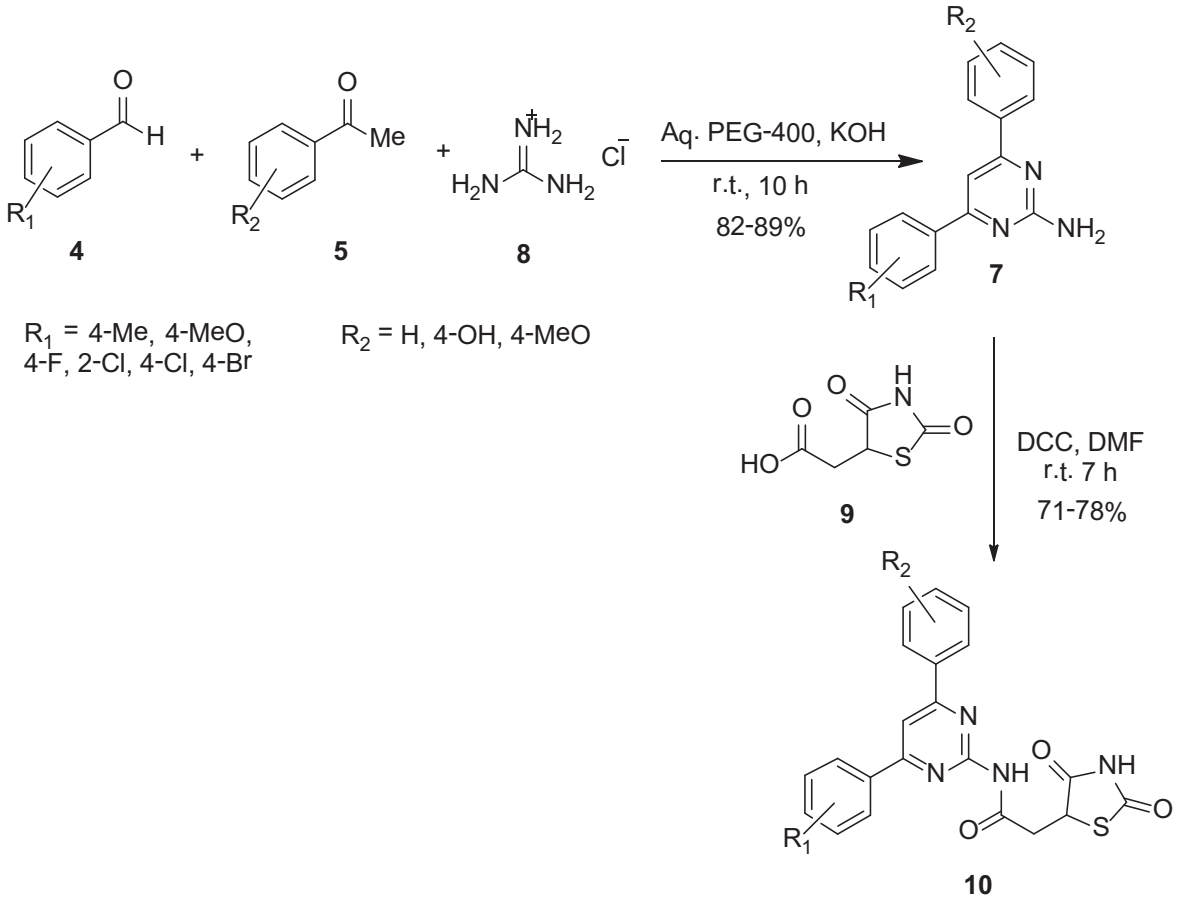


Scheme 1

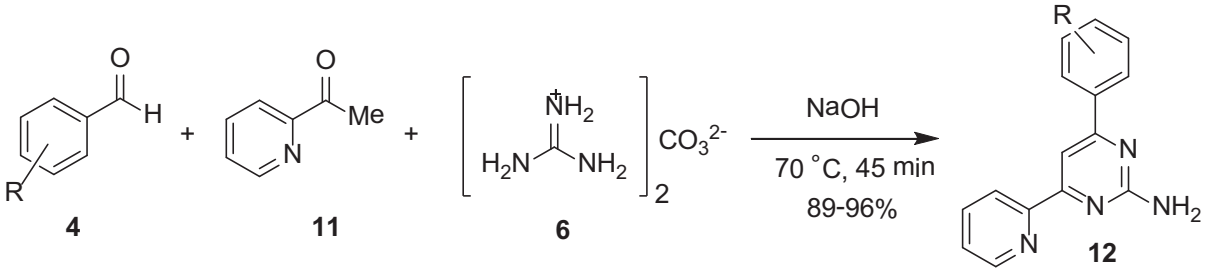
4,6-Diaryl amino pyrimidines **7** were also synthesized by 3-component condensation of aromatic aldehydes **4**, acetophenones **5**, and guanidinium chloride **8** in PEG-400 in the presence of KOH. A series of new dioxothiazolidin-5-yl)-N-(4,6-diphenylpyrimidin-2-yl) acetamides **10** has been prepared by condensing 2,4-thiazolidinedione acetic acid **9** with diaryl amino pyrimidines **7** in DMF using N,N-dicyclohexylcarbodimide (DCC) at room temperature (Scheme 2).[15]

Pyridylpyrimidine is a N,N'-chelating ligand that has 4 N-donors and can act as a neutral mono- or bidentate ligand and an anionic tridentate ligand. An easy and highly efficient 1-pot reaction for the preparation of 4-aryl-6-(pyridin-2-yl)pyrimidin-2-amine **12** via the reaction of different aromatic aldehydes **4**, acetylpyridine **11**, and guanidinium carbonate **6** in the presence of NaOH under solvent-free conditions was reported by Tao et al. (Scheme 3).[16]

Rong et al. reported a mild protocol for the synthesis of 4-naphthylpyrimidin-2-amine derivatives **14** (or **16**) by the reaction of aromatic aldehydes **4** (or 1-naphthaldehyde **15**), 2-acetylnaphthalene **13** (or acetophenones **5**) with guanidinium carbonate **6** in the presence of sodium hydroxide under solvent-free conditions (Schemes 4 and 5).[17]

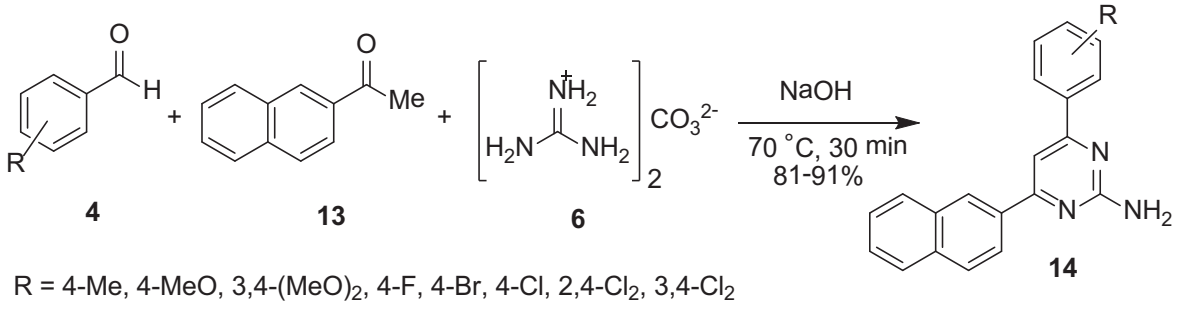


Scheme 2

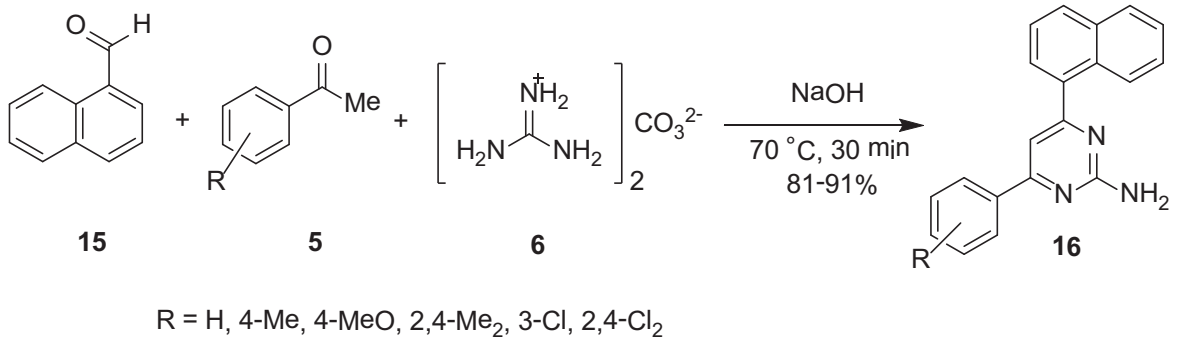


Scheme 3

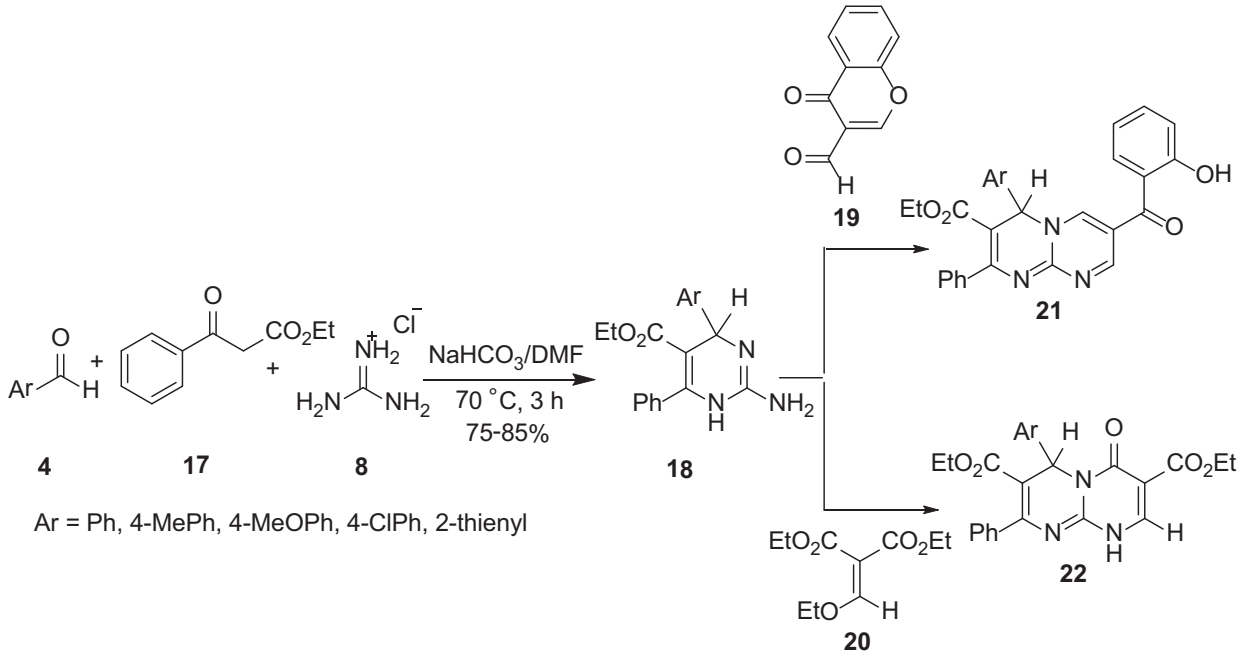
Eynde et al. described the synthesis of ethyl 2-amino-4-aryl-1,4-dihydro-6-phenylpyrimidine-5-carboxylates **18** from 1-pot cyclocondensation of arylaldehydes **4**, ethyl benzoylacetate **17**, and guanidinium chloride **8**. This amino-dihydropyrimidines can readily react under microwave irradiation and solvent-free conditions, with 3-formylchromone **19** or diethyl(ethoxymethylene)malonate **20** to yield novel pyrimido[1,2-*a*]pyrimidines **21** or **22**, respectively (Scheme 6).[18]



Scheme 4



Scheme 5

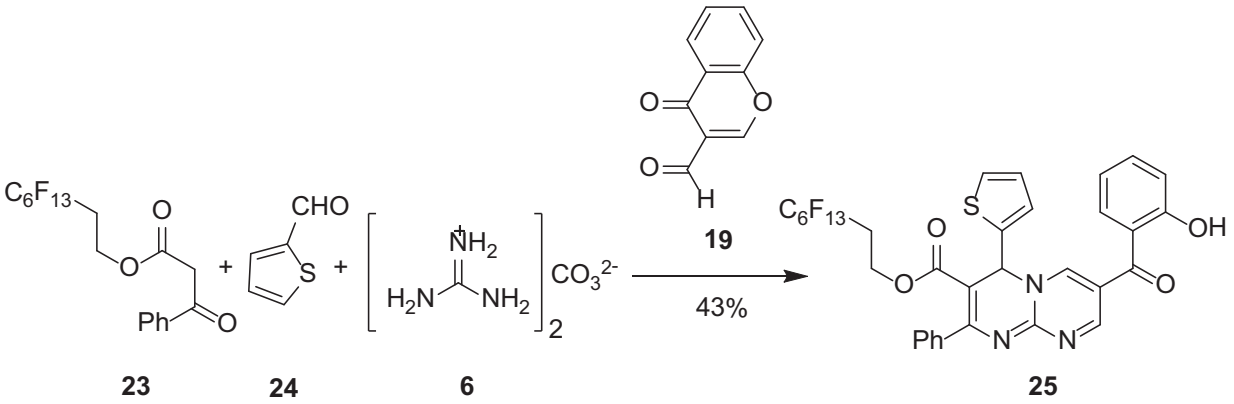


Scheme 6

2.1.2. Synthesis of pyrimidine-fused ring systems

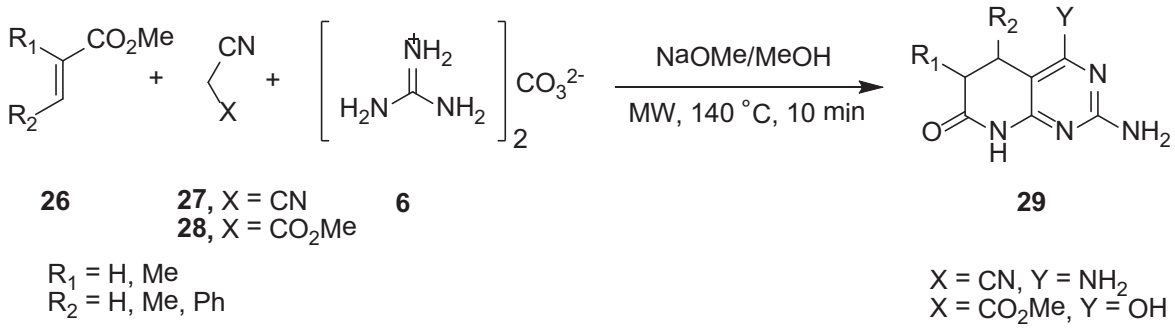
Spring et al. used a branching synthetic strategy to generate structurally diverse scaffolds such as pyrimido[1,2-a]pyrimidine that developed numerous biologically active compounds. Reaction of β-keto-ester **23**, thiophene-

2-carboxaldehyde **24**, and guanidinium carbonate **6** followed by reaction with 3-formylchromone **19** led to the formation of pyrimido[1,2-a]pyrimidine **25** (Scheme 7).[19]



Scheme 7

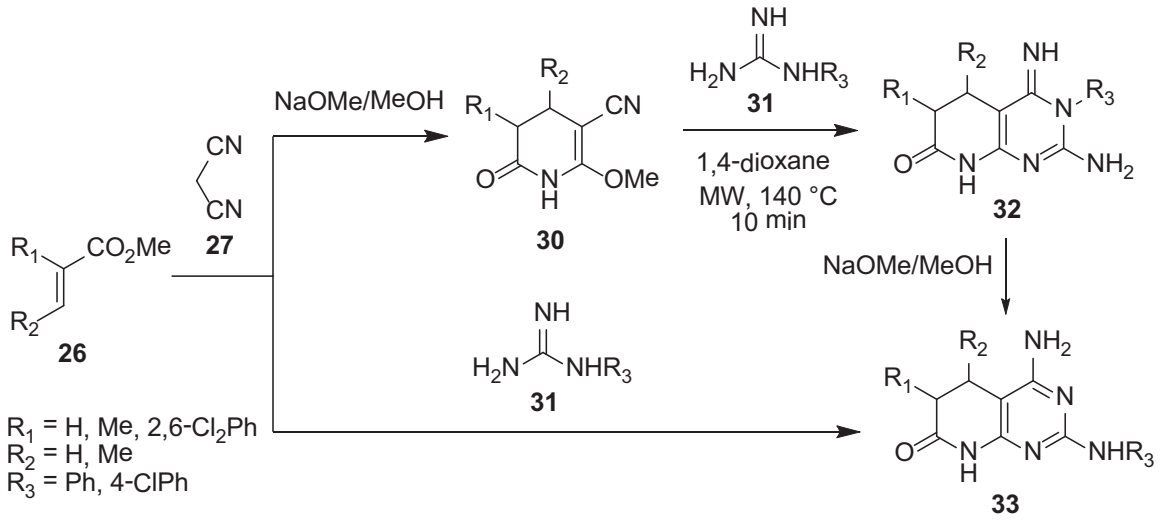
The heterocyclic pyrido[2,3-d]pyrimidines ring system represents several biological activities. Some analogues have been found to act as antitumor agents inhibiting dihydrofolate reductases or tyrosine kinases,[20–22] while others are known antiviral agents.[23] A simple and rapid multicomponent reaction providing multifunctionalized pyrido[2,3-d]pyrimidines **29** in a microwave-assisted 1-pot cyclocondensation of α,β-unsaturated esters **26**, malononitrile **27**, or methyl cyanoacetate **28** and guanidinium carbonate **6** was reported by Borrell et al. (Scheme 8).[24,25]



Scheme 8

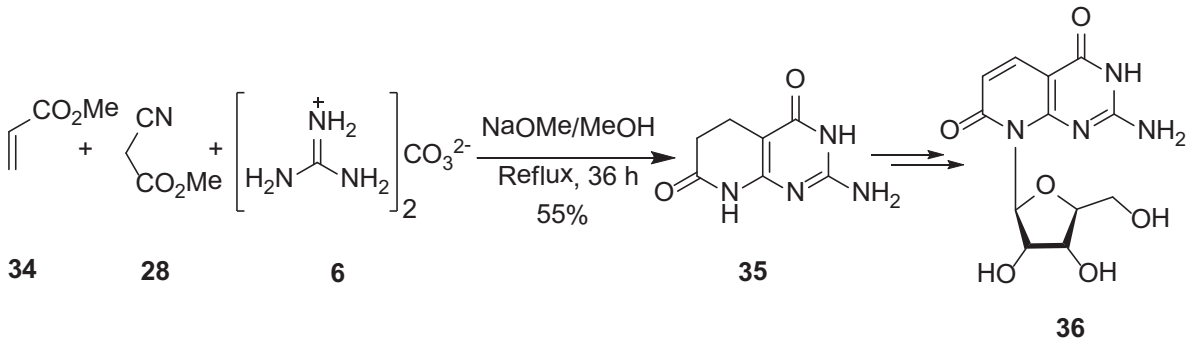
Use of guanidinium carbonate in the synthesis of pyrido[2,3-d]pyrimidines was previously described by Borrell et al. in 2 manners. In the first method, pyrido[2,3-d]pyrimidines were synthesized by treatment of isolated pyridones with guanidinium carbonate,[26,27] and the second method based on the reaction of guanidinium carbonate with isolated Michael adduct of acrylate and cyano-compounds.[28–30]

Galve et al. have developed a protocol for the synthesis of 2-arylamino substituted 4-amino-5,6-dihydropyrido[2,3-d]pyrimidin-7(8H)-ones **33** from treatment of pyridones **30** (synthesized from α,β-unsaturated esters **26** and malononitrile **27**) with the aryl guanidines **31** to form 3-aryl substituted pyridopyrimidines **32**, which underwent Dimroth rearrangement by NaOMe/MeOH. The overall yields of such a 3-step protocol are in general higher than those of the multicomponent reaction between an α,β-unsaturated ester **26**, malononitrile **27**, and an aryl guanidine **31** (Scheme 9).[31]



Scheme 9

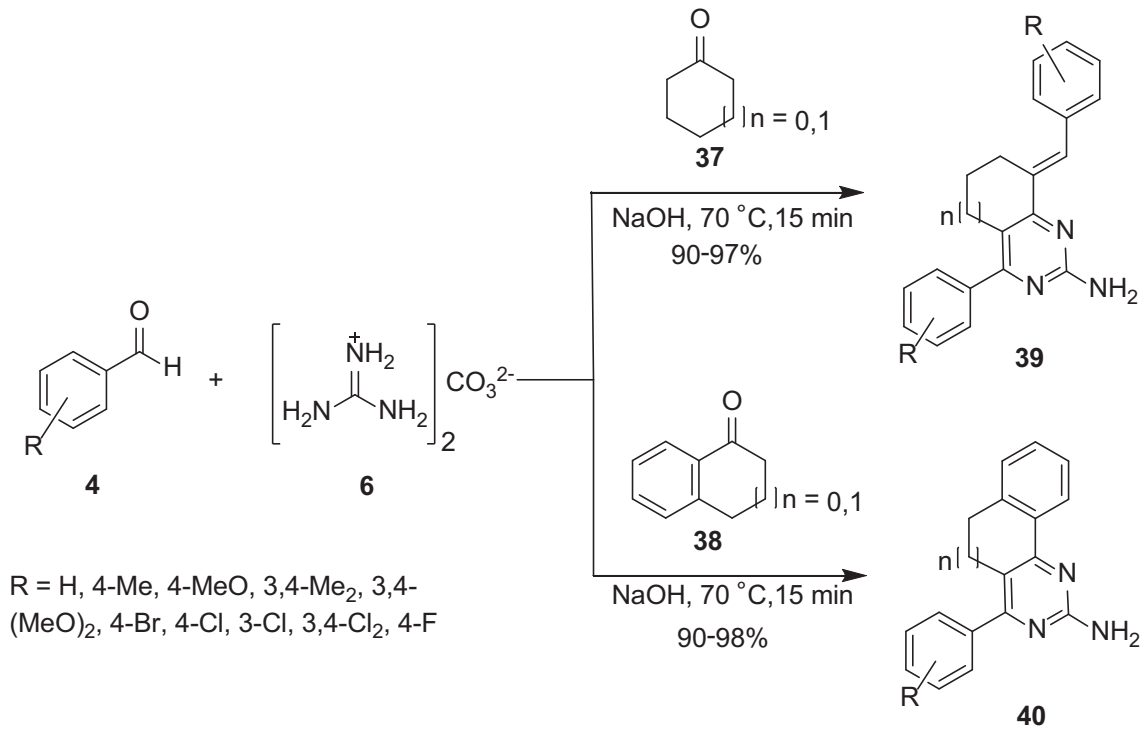
Jin et al. reported glycosylation of the pyrido[2,3-*d*]pyrimidine ring in the synthesis of the guanosine analogue system. Pyrido[2,3-*d*]pyrimidine ring system **35** has been synthesized by condensation of methyl acrylate **34** with methyl cyanoacetate **28** and guanidinium carbonate **6** in the presence of sodium methoxide. Dehydrogenation, glycosylation, and deprotection of pyrido[2,3-*d*]pyrimidine ring gave the desired guanosine analogue **36** (Scheme 10).[32]



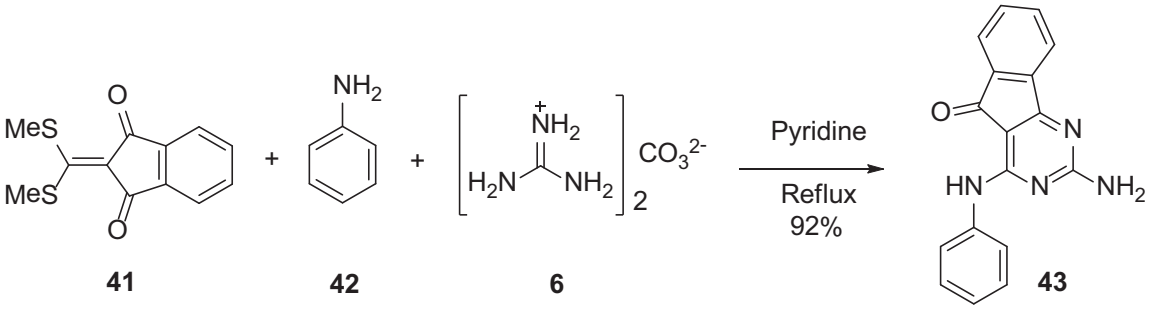
Scheme 10

An environmentally friendly method for the synthesis of pyrimidine-fused ring systems **39** or **40** by the 1-pot condensation of aromatic aldehydes **4**, guanidinium carbonate **6**, and cyclic ketones **37** or **38**, respectively, in the presence of NaOH under solvent-free conditions was reported by Rong et al. (Scheme 11).[33]

2-Amino-4-benzylaminoindeno[2,1-*d*]pyrimidin-5-one **43** was synthesized by condensation of α-oxoketene dithioacetal **41**,[34] aniline **42**, and guanidinium carbonate **6** by Tominaga et al. (Scheme 12).[35]

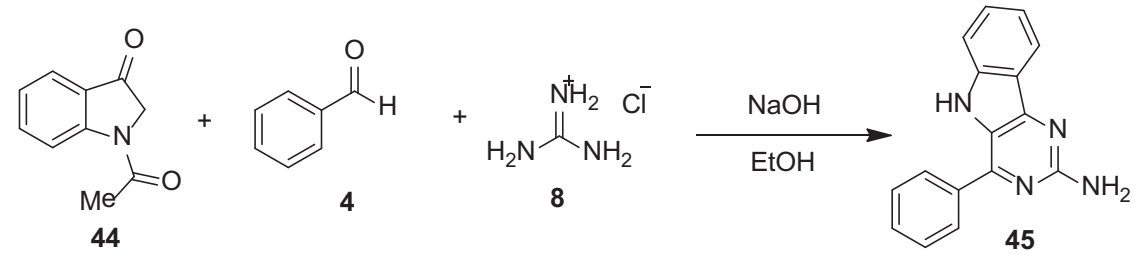


Scheme 11



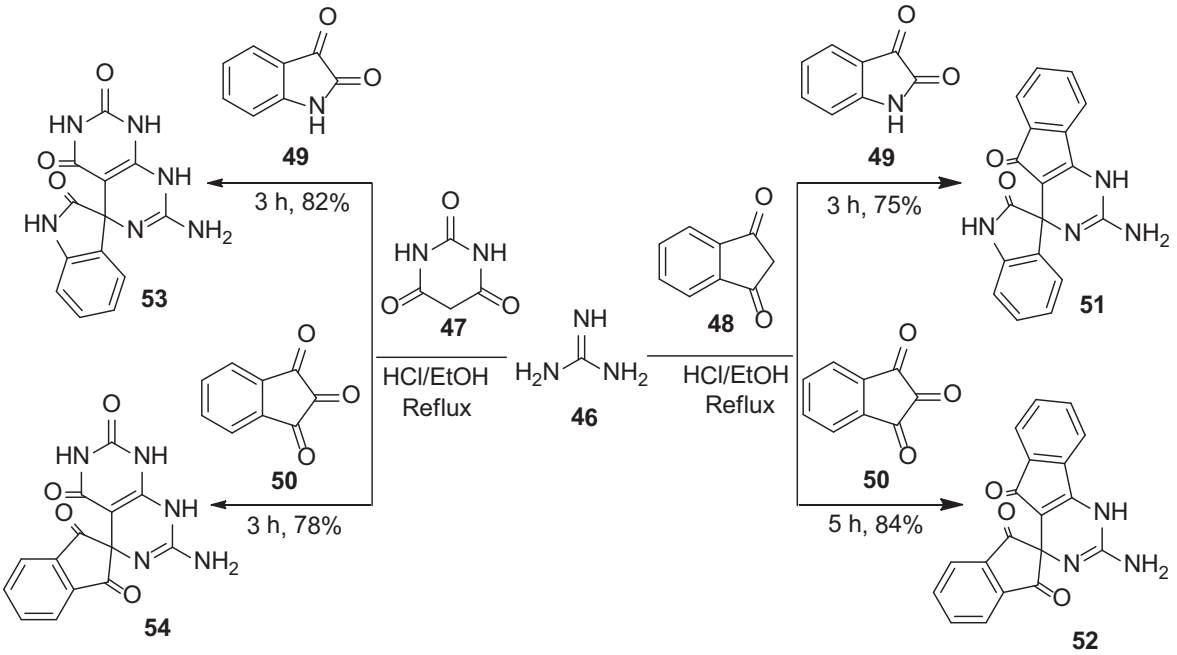
Scheme 12

The synthesis of 4-phenyl-5*H*-pyrimido[5,4-*b*]indol-2-amine **45** via a multicomponent reaction between 1-acetylindolin-3-one **44**, benzaldehyde **4**, and guanidinium chloride **8** (Scheme 13) and its antagonist activity of A_{2A} adenosine receptor were studied by Matasi et al.[36]



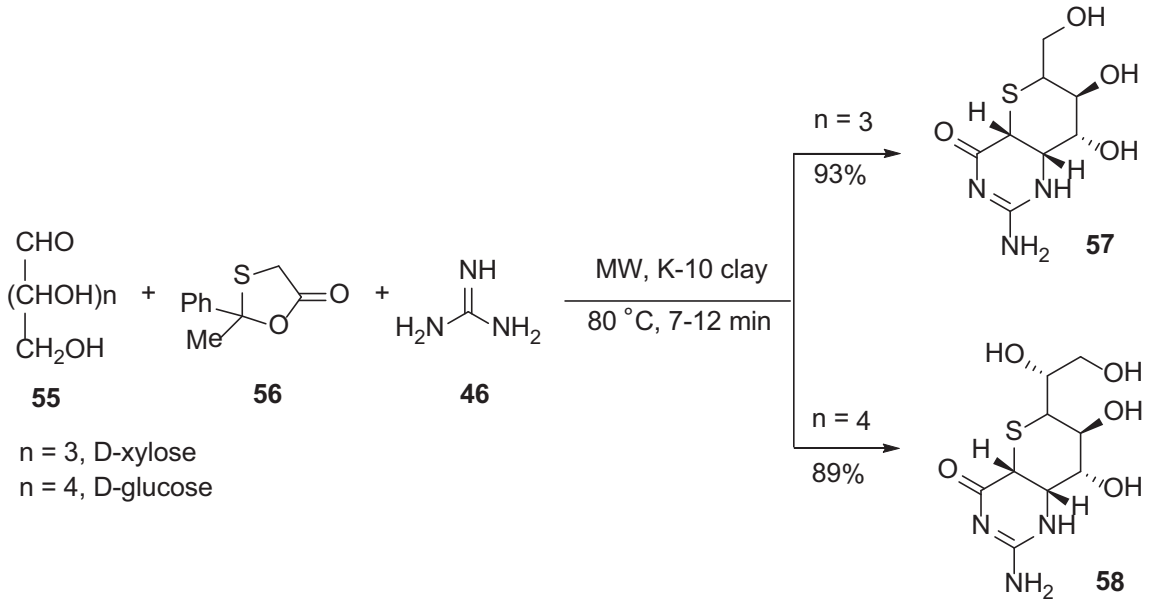
Scheme 13

Meshram et al. synthesized new spiro[indenopyrimidine] derivatives **51** and **52**, and spiro[pyrimidodiazine] derivatives **53** and **54** by a simple 1-pot 3-component reaction involving cyclic ketones **49** and **50**, guanidine **46**, and 1,3-dione **47** and **48** in the presence of HCl (10% mmol) in ethanol at reflux (Scheme 14).[37]



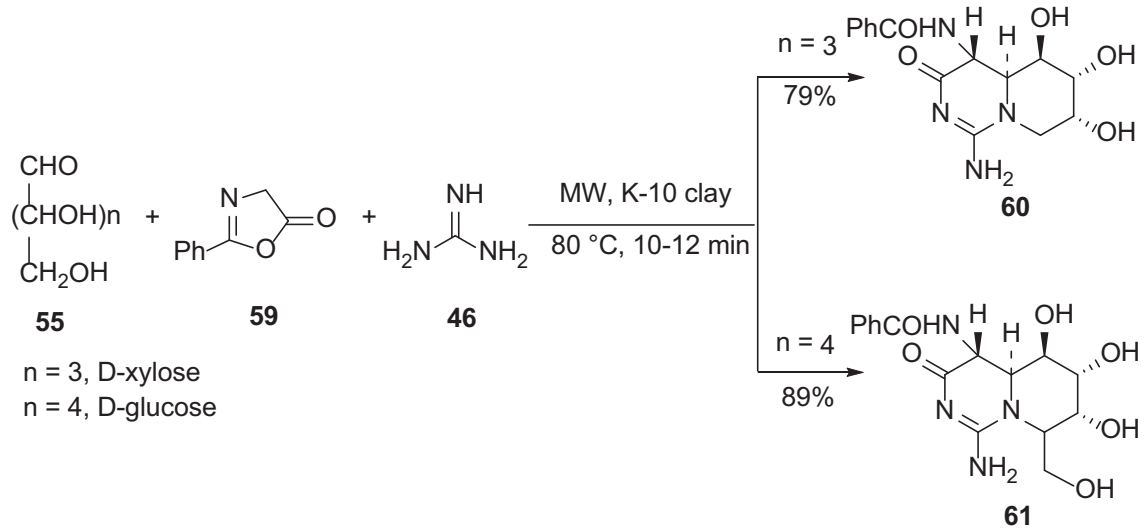
Scheme 14

The synthesis of thiosugar-fused bicyclic pyrimidines **57** and **58** with high *cis* diastereoselectivity at the ring junction has been developed by Yadav et al. using unprotected aldoses **55**, 2-methyl-2-phenyl-1,3-oxathiolan-5-one **56**, and guanidine **46** by a nanoclay catalyst under solvent-free MW irradiation conditions (Scheme 15).[38]



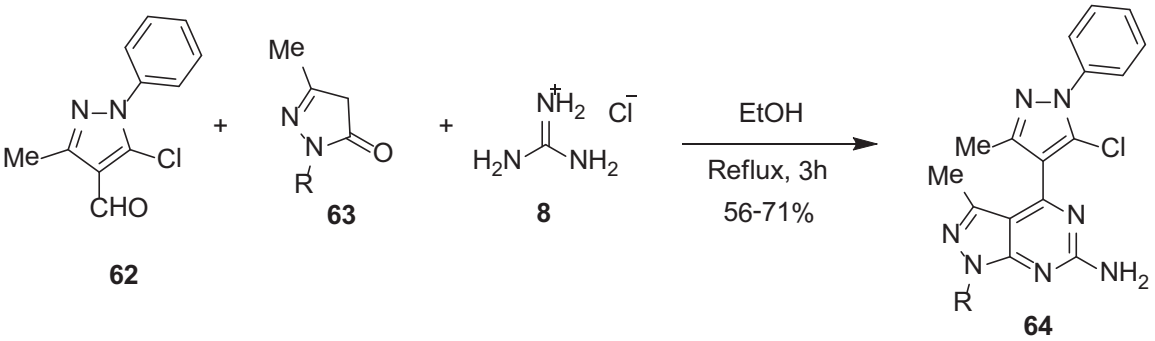
Scheme 15

Yadav et al. also reported the above 3-component reactions using 2-phenyloxazol-5(4*H*)-one **59** instead of 2-methyl-2-phenyl-1,3-oxathiolan-5-one **56** in the same conditions for synthesis of fused pyrimidines **60** and **61** (Scheme 16).[39]



Scheme 16

A facile 1-pot synthesis of pyrazolo[3,4-*d*]pyrimidines **64** by 3-component condensation of 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **62**, 3-methyl-1-(4-aryl)-5-pyrazolone **63**, and guanidine hydrochloride **8** (Scheme 17) and their antibacterial activity against *Mycobacterium tuberculosis* H37Rv was reported by Trivedi et al.[40]

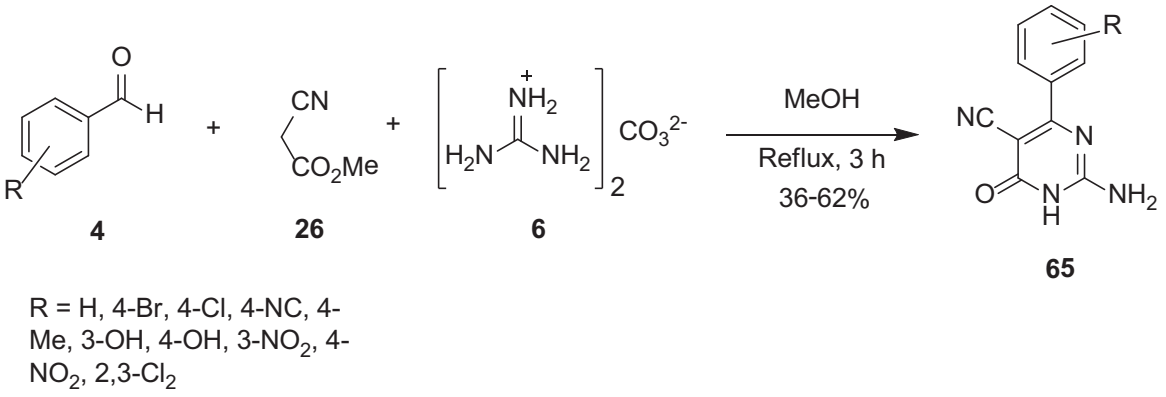


Scheme 17

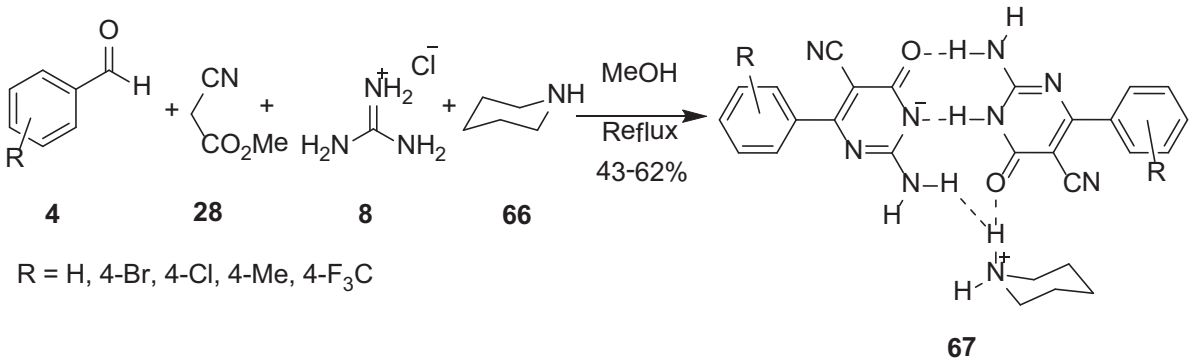
2.1.3. Synthesis of 5-carbonitrile compounds

A simple and efficient method for the 1-pot 3-component reaction of aromatic aldehydes **4**, methyl cyanoacetate **28**, and guanidinium carbonate **6** in the synthesis of 2-amino-4-aryl-1,6-dihydro-6-oxopyrimidine-5-carbonitriles **65** was reported by Bararjanian et al. (Scheme 18). They also attempted a 1-pot, 4-component condensation reaction of aromatic aldehydes **4**, methyl cyanoacetate **28**, guanidinium chloride **8**, and piperidine **66**, in

which piperidine acts both as a base and reagent (Scheme 19). The ^{1}H NMR data indicated the formation of zwitterionic product structures **67**.[41]

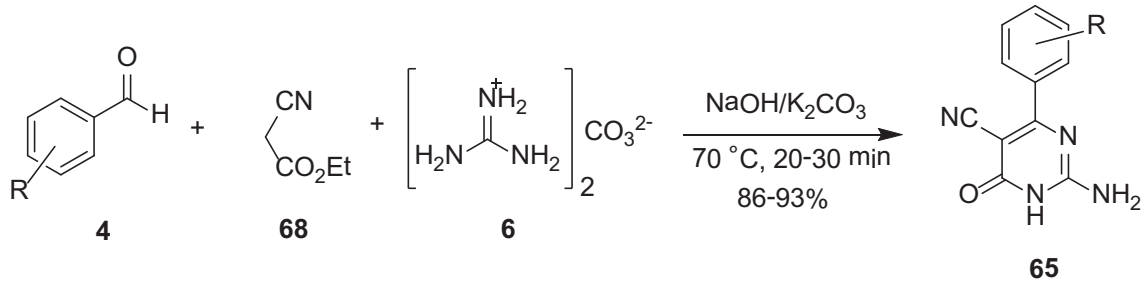


Scheme 18



Scheme 19

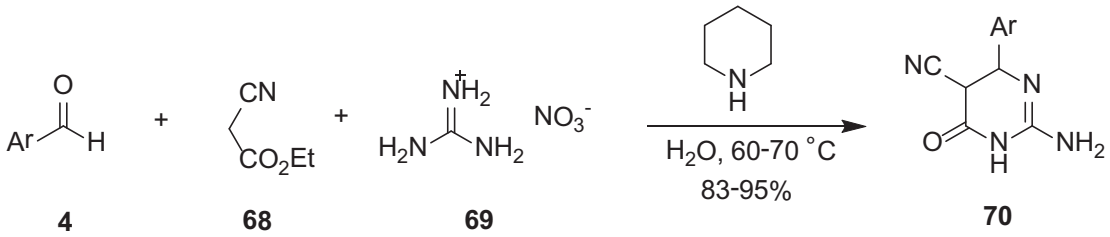
Rong et al. also reported an efficient and facile synthesis of 2-amino-4-aryl-1,6-dihydro-6-oxopyrimidine-5-carbonitriles **65** by the reaction of aromatic aldehydes **4**, ethyl cyanoacetate **68**, and guanidinium carbonate **6** in the presence of sodium hydroxide and potassium carbonate as catalyst under solvent-free conditions at 70 °C (Scheme 20).[42]



Scheme 20

Bhatewara et al. reported a simple and efficient method for synthesis of 2-amino-6-oxo-4-aryl-1,4,5,6-tetrahydropyrimidine-5-carbonitriles **70** via 3-component condensation of aldehydes **4**, ethyl cyanoacetate **68**,

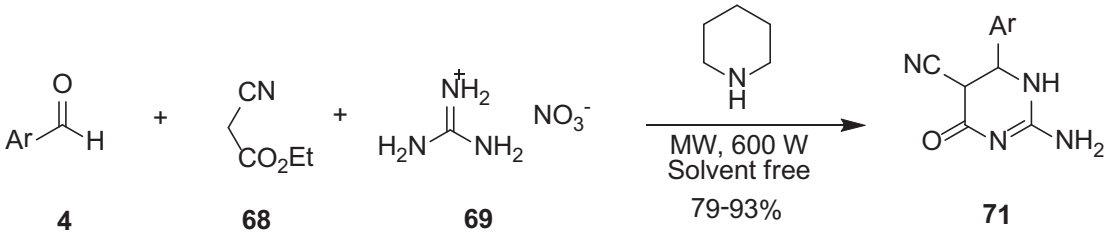
and guanidinium nitrate **69** using piperidine as a catalyst (Scheme 21).[43] They also reported a simple protocol for preparation of 2-amino-6-aryl-4-oxo-1,4,5,6-tetrahydropyrimidine-5-carbonitriles **71** using the same reactants and catalyst in solvent-free conditions under microwave irradiation (Scheme 22).[44]



4 **68** **69** **70**

Ar = Ph, 4-MeOPh, 3,4-$(MeO)_2$Ph, 4-NO_2Ph, 2-pyrrolyl,
2-furyl, 3-indolyl, N-methyl-2-pyrrolyl

Scheme 21

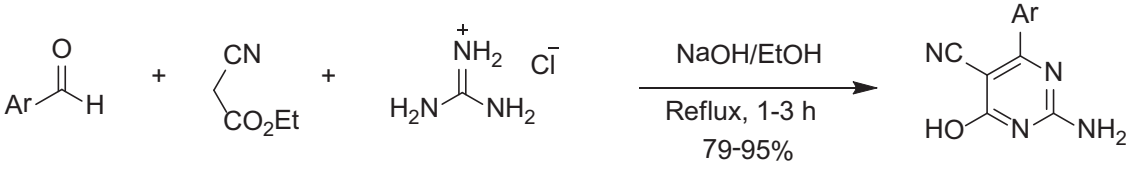


4 **68** **69** **71**

Ar = Ph, 4-MeOPh, 3,4-$(MeO)_2$Ph, 4-NO_2Ph, 2-pyrrolyl,
2-furyl, 3-indolyl, N-methyl-2-pyrrolyl

Scheme 22

Anbhule and co-workers have developed a simple and efficient approach toward 1-step synthesis of 2-amino-5-cyano-6-hydroxy-4-aryl pyrimidines **72** using condensation of aromatic aldehydes **4**, ethyl cyanoacetate **68**, and guanidinium chloride **8** in alkaline ethanol (Scheme 23). The antibacterial study of synthesized compounds showed good to excellent activity against tested gram-positive and gram-negative bacteria.[45]



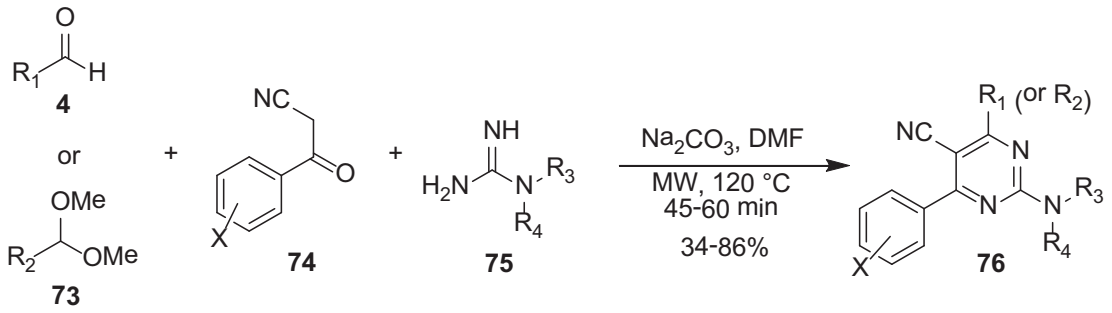
4 **68** **8** **72**

Ar = Ph, PhCH=CH, 3-NO_2Ph, 3,4-$(MeO)_2$Ph, 4-$(Me)_2$NPh, 4-MeOPh,
4-OHPh, 3-ClPh, 2-NO_2Ph, 3,4,5-$(MeO)_3$Ph, 2-ClPh, 2-thionyl

Scheme 23

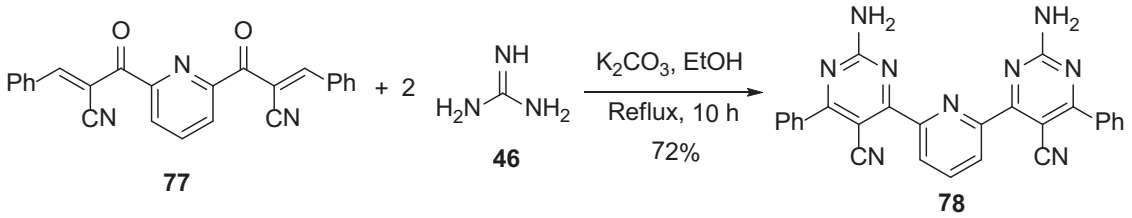
Val et al. reported a convergent and robust approach for synthesis of 2-aminopyrimidine-5-carbonitriles **76** from 3-component condensation of N-substituted guanidines **75**, α-cyanoketones **74**, and the corresponding

aldehydes **4** (or dimethyl acetals **73**) in the presence of DMF at 120 °C under microwave irradiation (Scheme 24).[46]



Scheme 24

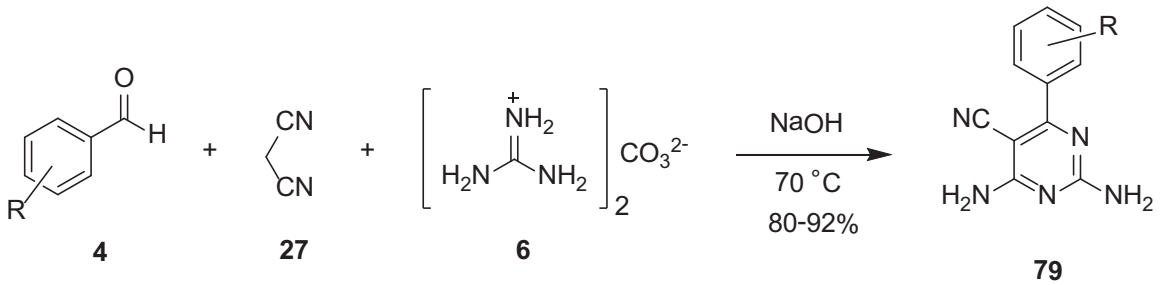
The synthesis of 2,6-bis(2-amino-5-cyano-6-phenylpyrimidin-4-yl)pyridine **78** was developed by the reaction of 2-benzylidene-3-oxopropanenitrile **77** and 2 guanidine **46** molecules in the presence of anhydrous potassium carbonate (Scheme 25).[47]



Scheme 25

2.1.3.1. Synthesis of 6-amino compounds

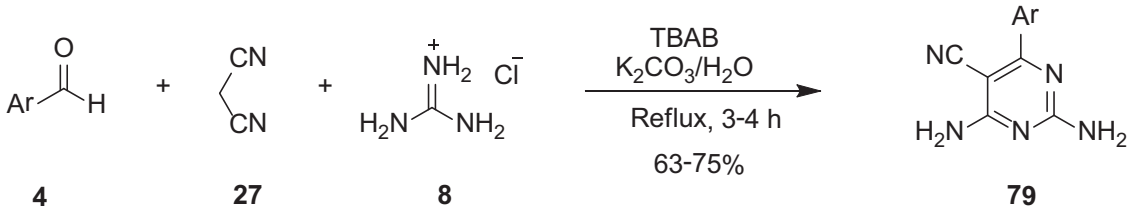
Rong and co-workers presented an environmentally friendly and mild method for synthesis of 2,6-diamino-4-arylpyrimidine-5-carbonitrile derivatives **79** via 1-pot cyclocondensation reaction of aromatic aldehydes **4**, malononitrile **27**, and guanidinium carbonate **6** using sodium hydroxide as catalyst at 70 °C in solvent-free conditions (Scheme 26).[48]



Scheme 26

Hekmatshoar et al. also reported an efficient and facile synthesis of 2-amino-4-aryl-1,6-dihydro-6-oxopyrimidine-5-carbonitriles **79** by the reaction of aromatic aldehydes **4**, malonitrile **27**, and guanidinium carbonate **6** in the presence of ZnO nanoparticles in water.[49] A method using granulated copper oxide nanocatalyst as a mild and efficient reusable catalyst for the 1-pot synthesis of 2-amino-4-aryl-1,6-dihydro-6-oxopyrimidine-5-carbonitriles **79** under aqueous conditions was also reported by Ahmadi and coworkers by the reaction of aromatic aldehydes **4**, malonitrile **27**, and guanidinium carbonate **6**.[50]

Furthermore, another 1-pot synthesis of 2,4-diamino-6-arylpyrimidine-5-carbonitriles **79** was reported by Deshmukh et al. via condensation of aromatic aldehydes **4**, malononitrile **27**, and guanidinium chloride **8** in aqueous medium using tetrabutyl ammonium bromide (TBAB) and potassium carbonate (Scheme 27).[51]

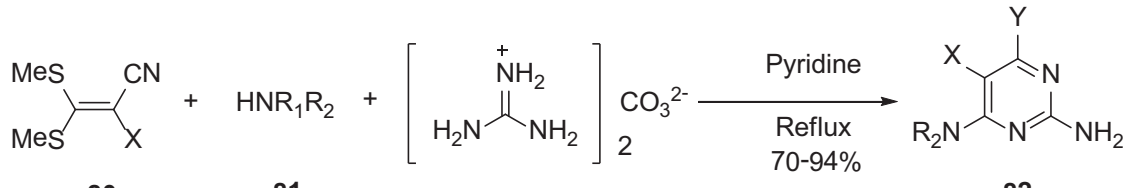


Ar = Ph, PhCH=CH, 3,4-$(MeO)_2$Ph, 4-$(Me)_2$NPh,
4-MeOPh, 4-OHPh, 2-OHPh, 3-ClPh

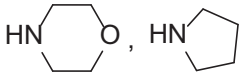
Scheme 27

2,6-Diamino-4-arylpyrimidine-5-carbonitriles **79** were also synthesized by 3-component reaction of malononitrile **27**, aldehydes **4**, and guanidinium chloride **8** in water at reflux or under microwave heating, in the presence of sodium acetate.[52] Sheibani and co-workers reported another method for synthesis of this class of compounds using high-surface-area MgO as a highly effective heterogeneous base catalyst.[53] Moreover, an efficient 1-pot synthesis of 2,6-diamino-4-arylpyrimidine-5-carbonitriles **79** has been achieved in excellent yields by the condensation of malononitrile **27**, aldehydes **4**, and guanidinium chloride **8** using ionic liquid under controlled microwave irradiation (100 W) at 60 °C.[54]

One-pot synthesis of 6-alkylamino-2,4-diaminopyrimidines **82** using ketene dithioacetals **80**,[55–56] alkyl amines **81**, and excess guanidinium carbonate **6** was developed under reflux conditions in pyridine (Scheme 28).[35]



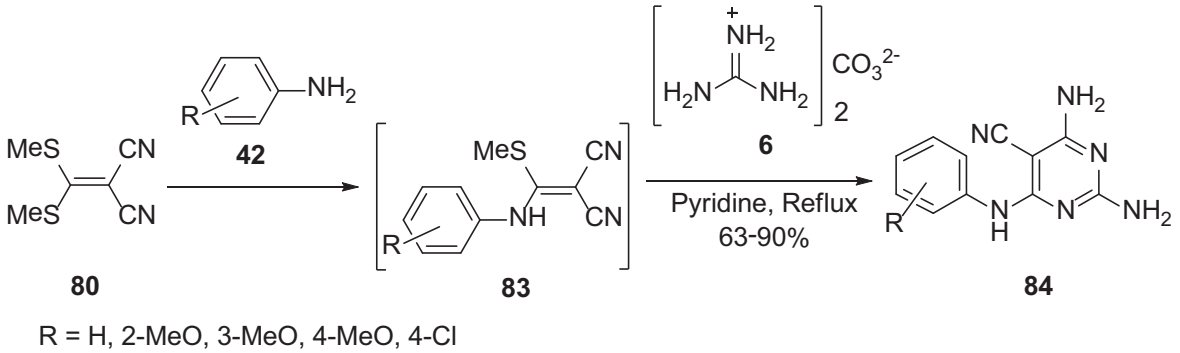
HNR_1R_2 = $HNCH_2Ph$, HNCH(Me)Ph,



X = CN, Y = NH_2
X = SO_2Ph, Y = NH_2
X = CO_2Me, Y = OH

Scheme 28

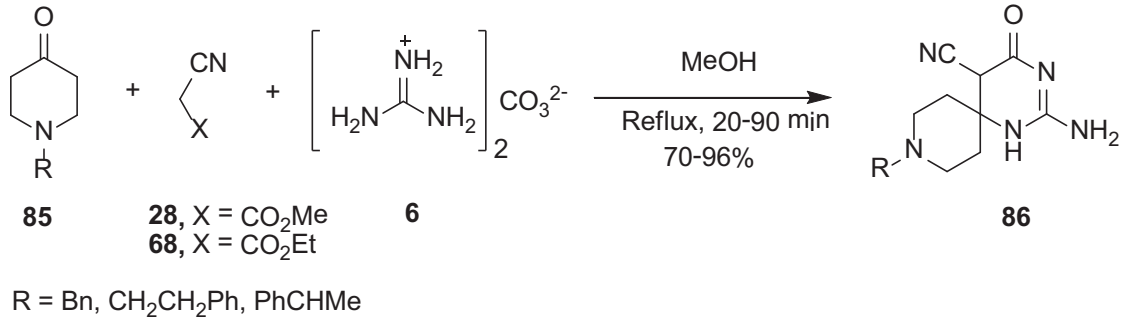
The reaction of aniline derivatives **42** with ketene dithioacetal **80** gave intermediates **83**, which were reacted with guanidinium carbonate **6** to provide 6-arylamino-2,4-diaminopyrimidines **84** (Scheme 29).[35]



Scheme 29

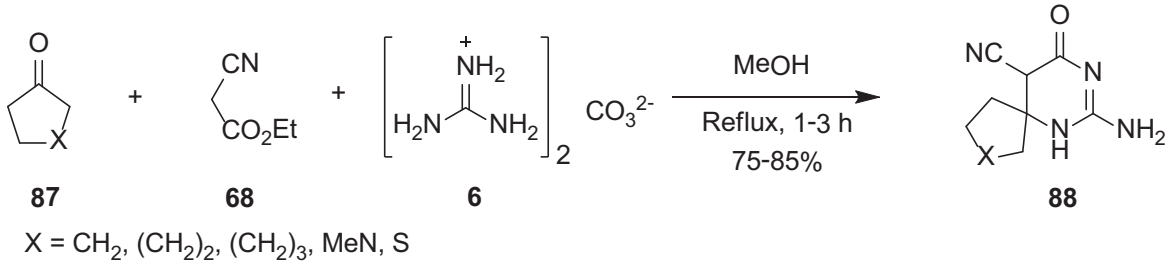
2.1.3.2. Synthesis of spiro compounds

Ramezanpour et al. developed an efficient protocol for the synthesis of various spiro-2-amino pyrimidinones **86** via a 3-component reaction of N-substituted piperidinones **85**, guanidinium carbonate **6**, and alkyl cyanoacetates **28** and **68** via domino Knoevenagel-cyclocondensation reaction (Scheme 30). This method has advantages such as high yields, neutral conditions, and short reaction times. This basic medium was suitable for deprotonation of alkyl cyanoacetates, which produced the desired alkene intermediate through Knoevenagel condensation on the reaction with carbonyl compound **85**. Michael addition of free guanidine into alkene and then cyclization led to the synthesis of spiro-2-amino pyrimidinones **86** in good yields.[57]



Scheme 30

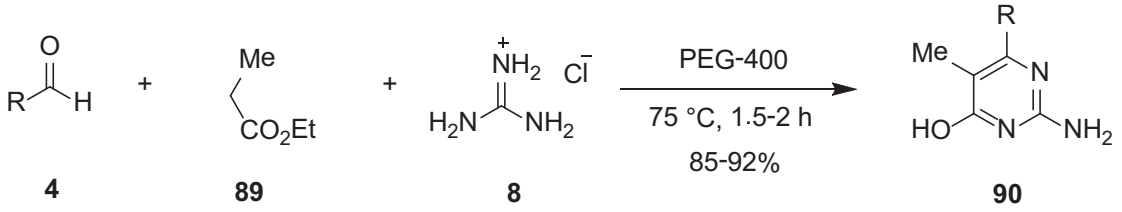
An efficient synthesis of spirocyclic 2-aminopyrimidinones **88** was achieved via a domino Michael addition–cyclocondensation reaction of a cyclic ketone **87**, ethyl cyanoacetate **68**, and guanidinium carbonate **6** in methanol (Scheme 31).[58]



Scheme 31

2.1.4. Synthesis of 5-alkyl compounds

Maddila et al. developed a simple and efficient approach for synthesis of 2-amino-6-aryl-5-methylpyrimidin-4-ol derivatives **90** by 3-component condensation of aldehydes **4**, ethyl propionate **89**, and guanidine hydrochloride **8** using PEG-400 at 75 °C (Scheme 32).[59]

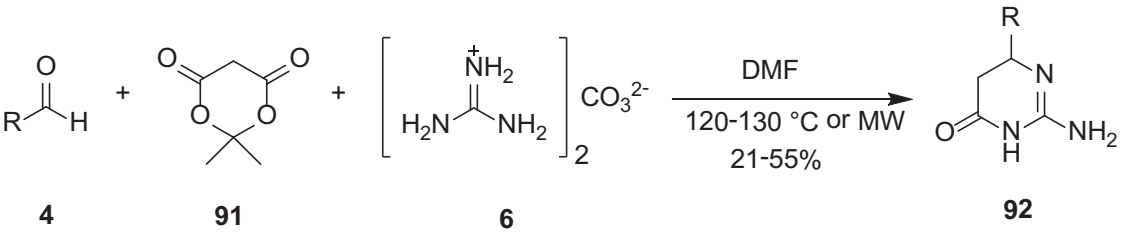


R = Ph, 2-ClPh, 3-ClPh, 3,4-$(MeO)_2$Ph, 3,4,5-$(MeO)_3$Ph,
PhCH=CH, 2-NO_2Ph, 3-NO_2Ph, 4-MePh, 4-OHPh, Et, *n*-Pr

Scheme 32

2.1.5. Synthesis of dihydropyrimidinone compounds

Gorobets et al. developed 2 different protocols (conventional and microwave conditions) in the synthesis of 2-amino-5,6-dihydropyrimidin-4(3*H*)-ones **92**. A multicomponent reaction between Meldrum's acid **91**, aliphatic or aromatic aldehydes **4**, and guanidinium carbonate **6** provided easy access to dihydropyrimidinones (Scheme 33). In comparison to the conventional heating method, microwave heating affords more advantages such as reduced reaction time, low cost, and simplicity in reaction progress, reduced pollution, and higher product purity.[60]



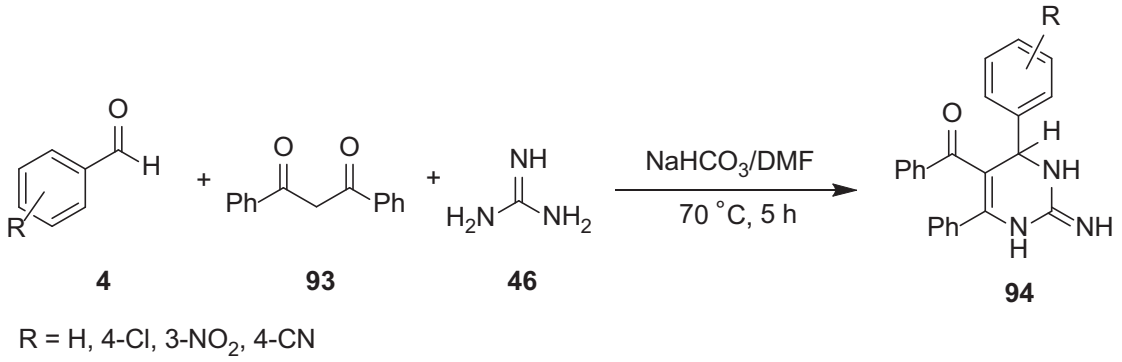
R = $CHMe_2$, CH_2Ph, Ph, 4-MeOPh, 2-MeOPh, 2,5-$(MeO)_2$Ph,
3-MeO-4-CHF_2OPh, 2-ClPh, 4-BrPh, 4-Me_2NPh

Scheme 33

There are 2 more methods for synthesis of the above 2-amino-5,6-dihydropyrimidin-4(3*H*)-ones **61**. Mohammadnejad and co-workers reported a 3-component reaction of Meldrum's acid **91**, aromatic aldehyde **4**, and guanidinium carbonate **6** in reflux of ethanol that leads to formation of 2-amino-5,6-dihydropyrimidin-4(3*H*)-ones **92**.[61] Mirza-Aghayan and co-workers also developed another method for the synthesis of these compounds from the 1-pot cyclocondensation of Meldrum's acid **91**, aldehydes **4**, and guanidinium carbonate **6** using MCM-41 catalyst functionalized with 3-aminopropyltriethoxysilane (MCM-41-NH_2) as an efficient nanocatalyst in DMF.[62]

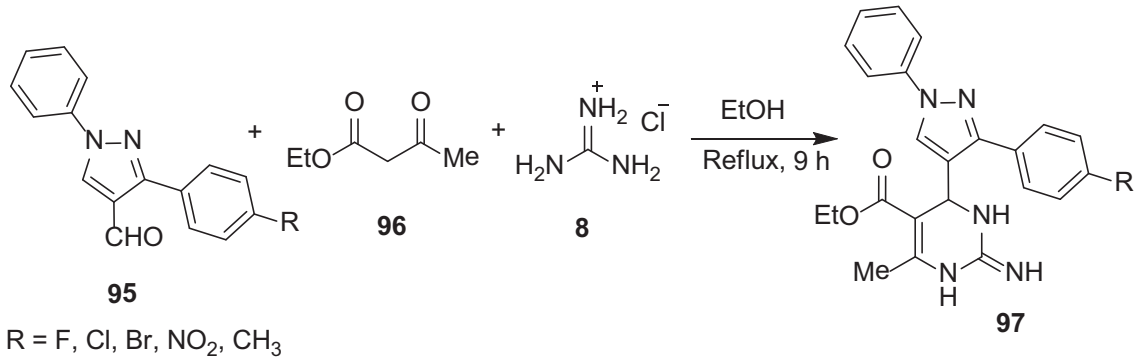
2.2. Synthesis of 2-iminopyrimidine compounds

2-Iminopyrimidines **94** were synthesized by Akbas et al. using 3-component cyclocondensation of arylaldehydes **4**, dibenzoylmethane **93**, and guanidine **46** (Scheme 34). The electrochemical properties of the novel systems were investigated by cyclic voltammetry (CV) and differential pulse voltammetry (DPV).[63]



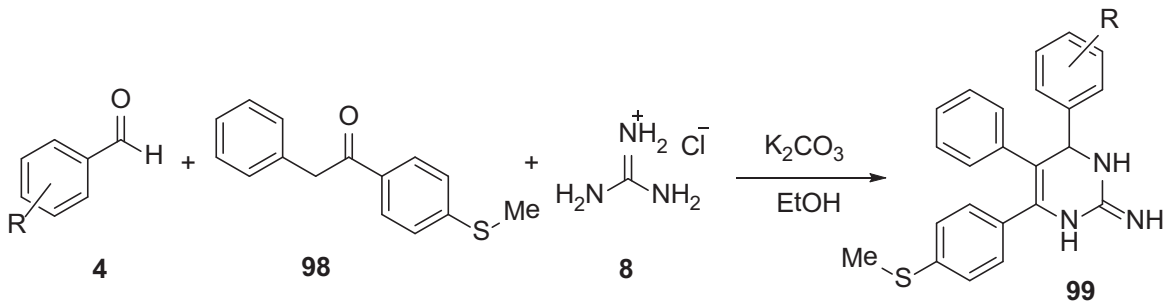
Scheme 34

Multicomponent Biginelli reaction of 3-(aryl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes **95**,[64] ethyl acetoacetate **96**, and guanidinium chloride **8** was reported by Shah et al. (Scheme 35). All synthesized dihydropyrimidines **97** were evaluated for their in vitro antitubercular activity against *Mycobacterium tuberculosis* H37Rv.[65]



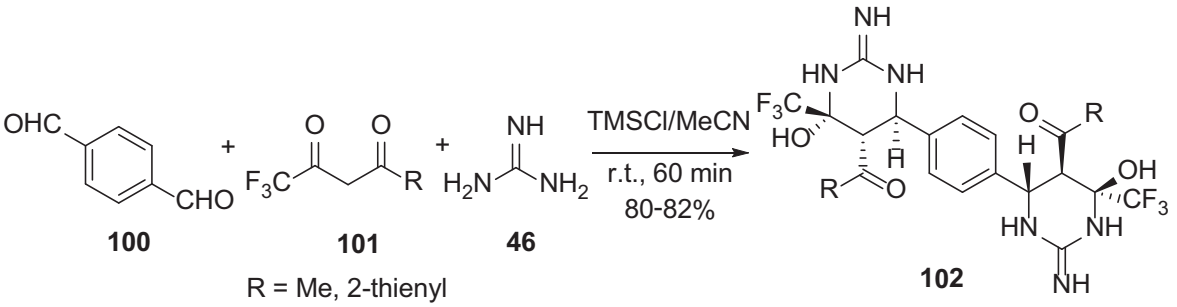
Scheme 35

4,5,6-Triphenyl-1,2,3,4-tetrahydropyrimidine derivatives **99** were synthesized by 1-pot reaction of 1-(4-(methylthio)phenyl)-2-phenylethanone **98**, aromatic aldehydes **4**, and guanidinium chloride **8** in the presence of potassium carbonate in ethanol (Scheme 36). In this reaction, at first chlorination of phenyl acetic acid by thionyl chloride yielded phenylacetyl chloride, which reacted with thioanisole in dichloromethane in the presence of $AlCl_3$ to give 1-(4-(methylthio)phenyl)-2-phenylethanone **98**. All the synthesized compounds were tested for their ability to inhibit cyclooxygenase-2 (COX-2).[66]



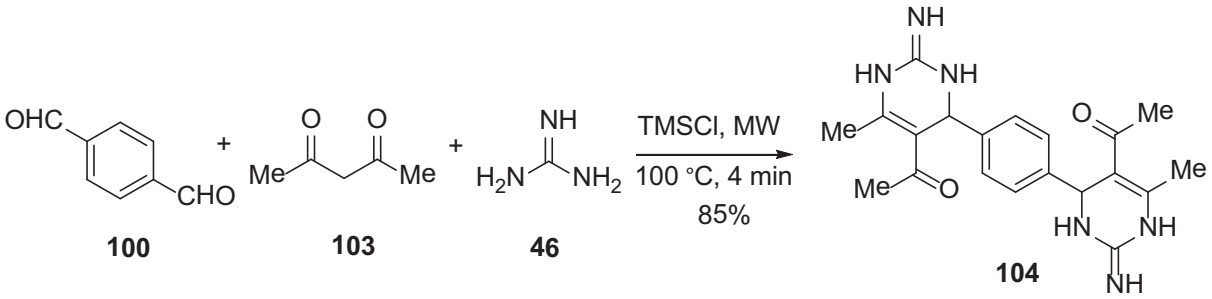
Scheme 36

A facile synthesis of novel trifluoromethyl derivatives of 4,4'-(1,4-phenylene)-bis(tetrahydro-pyrimidin-2(1*H*)-imine) **102** was reported by Azizian et al. via 1-pot 3-component condensation of terephthalaldehyde **100** with guanidine **46** and fluorinated 1,3-dicarbonyl derivatives **101** using chlorotrimethylsilane (TMSCl) as catalyst (Scheme 37).[67]



Scheme 37

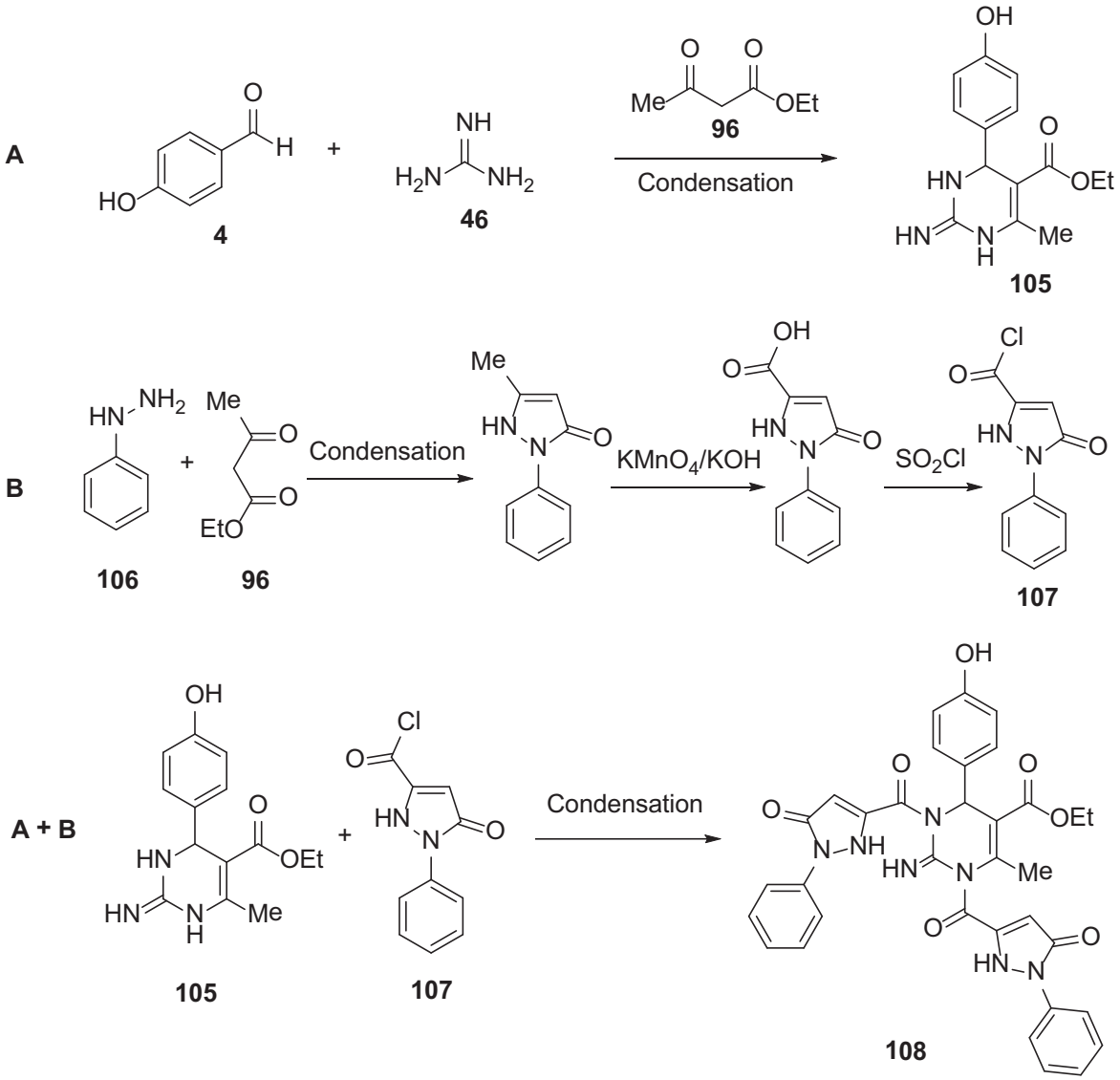
Miri et al. reported a Biginelli condensation reaction of terephthalaldehyde **100**, acetylacetone **103**, and guanidine **46** using chlorotrimethylsilane under microwave irradiation for 1-pot synthesis of 4,4'-(1,4-phenylene)-bis(3,4-dihydropyrimidin-2(1*H*)-imine) **104** (Scheme 38). The cytotoxicity of this compound was evaluated on 5 different human cancerous cell lines.[68]



Scheme 38

Pyrimidine derivative **105**, produced by condensation of 4-hydroxy benzaldehyde **4** with guanidine **46** and ethyl acetoacetate **96** (Scheme 39, A), has been condensed with acid chloride of phenyl substituted pyrazolone

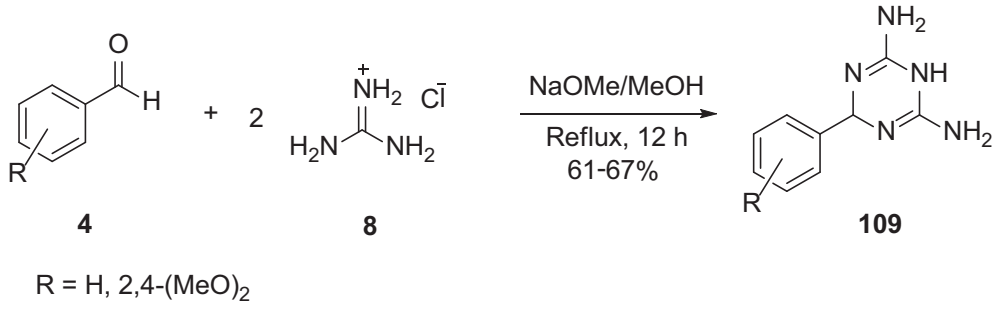
carboxylic acid **107**, which was synthesized by reaction of phenyl hydrazine **106** with ethyl acetoacetate **96** and then alkaline oxidation with $KMnO_4$/KOH (Scheme 39, B) to give compound **108** (Scheme 39, A+B).[69]



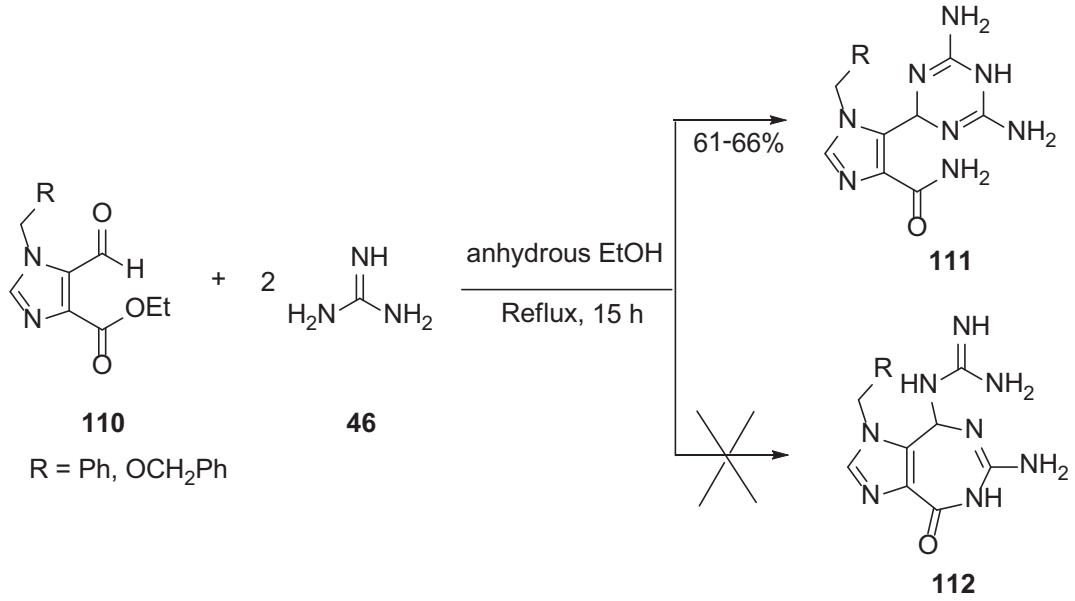
Scheme 39

2.3. Synthesis of triazine compounds

2,6-Diamino-3,6-dihydro-6-aryl-1,3,5-triazine **109** was synthesized by reaction of aromatic aldehydes **4** with 2 or more equivalents of guanidinium chloride **8** in the presence of sodium methoxide in methanol by Ujjinamatada et al. (Scheme 40). By this reaction, they have discovered a novel functional group transformation involving selective conversion of an ester group of imidazole ring **110** into the corresponding amide **111**, while simultaneously protecting the aldehyde group as dihydrotriazine (Scheme 41). In this transformation, alternative dihydrodiazepines **112** were not synthesized.[70]

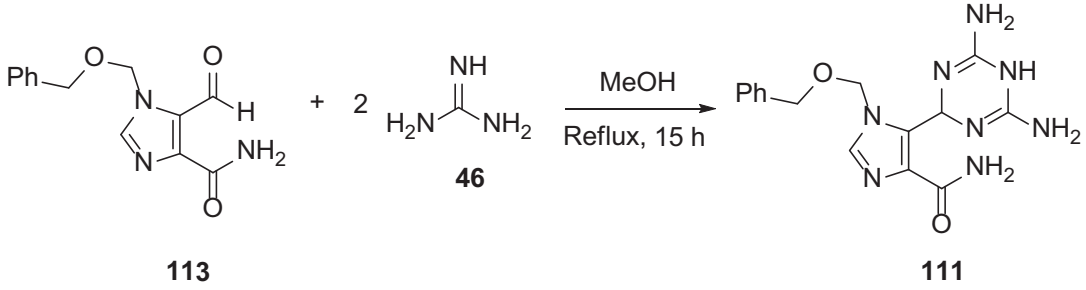


Scheme 40



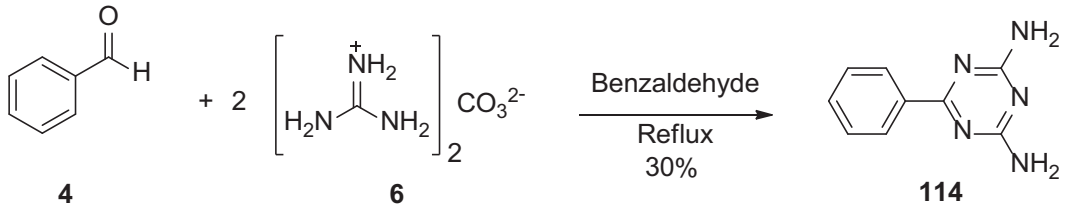
Scheme 41

The respective compounds **111** and **112** have the same molecular formula, the same methine signal of either the dihydrotriazine or the dihydrodiazepine ring, and with tautomerization the same number of amino/imino groups exchangeable with D_2O. In order to resolve this structural ambiguity, an unambiguous synthesis was performed of 1 of the 2 amide–triazines **111** by the reaction of amide–aldehyde **113** with excess guanidine **46** in methanol at reflux (Scheme 42).[70]



Scheme 42

Gund et al. reported the isolation of a fully aromatic product s-triazine **114** in low yield from a complex mixture of products by the reaction of excess benzaldehyde **4** (used as a solvent) with guanidinium carbonate **6** (Scheme 43).[71]

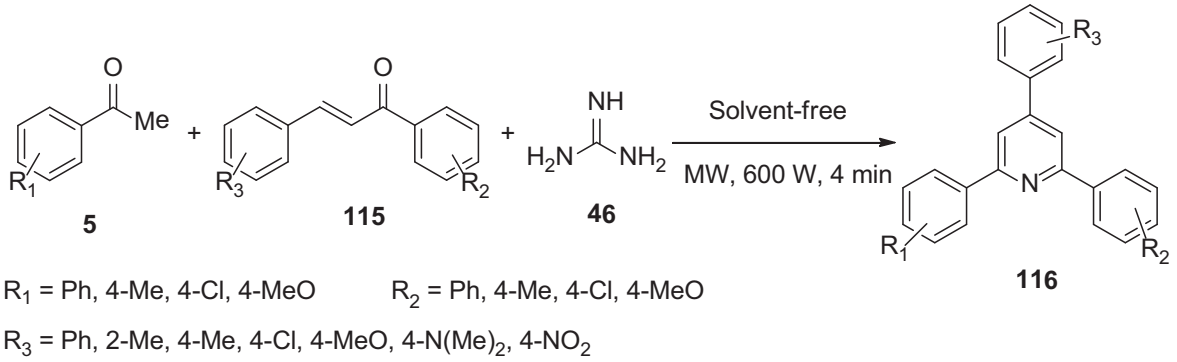


4 **6** **114**

Scheme 43

2.4. Synthesis of miscellaneous compounds

Zomordbakhsh et al. synthesized 2,4,6-triarylpyridine derivatives **116** by the reaction of chalcone derivatives **115** with guanidine **46** and acetophenones **5** in solvent-free conditions (Scheme 44).[72]



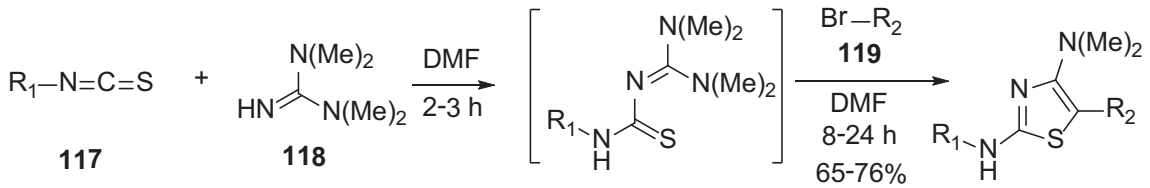
5 **115** **46** **116**

R_1 = Ph, 4-Me, 4-Cl, 4-MeO R_2 = Ph, 4-Me, 4-Cl, 4-MeO

R_3 = Ph, 2-Me, 4-Me, 4-Cl, 4-MeO, 4-$N(Me)_2$, 4-NO_2

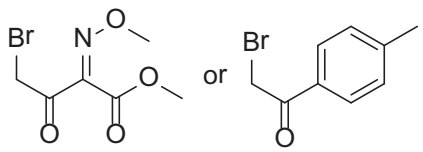
Scheme 44

Jalani et al. developed an efficient 1-pot domino method for the synthesis of 2-aminothiazoles **120** using isothiocyanates **117**, tetramethylguanidine **118**, and halomethylenes **119** in DMF (Scheme 45).[73]



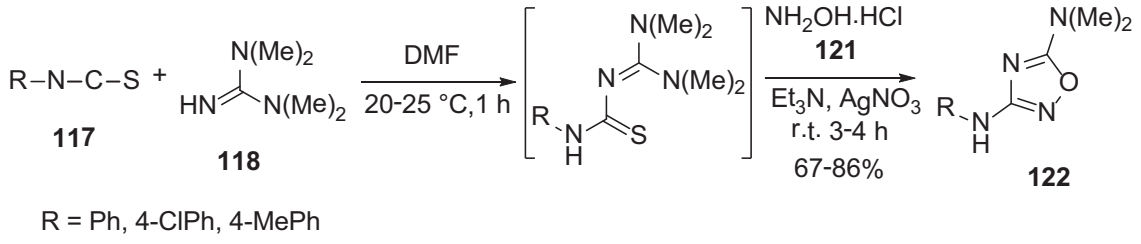
117 **118** **120**

R_1 = Ph, Bn, CO_2Et Br—R_2 =



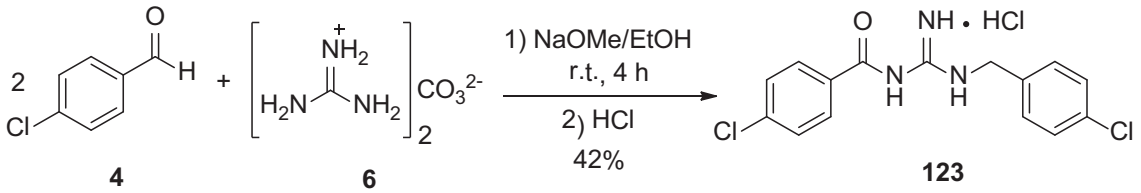
Scheme 45

Jalani et al. also reported another 1-pot domino method for synthesis of 1,2,4-oxadiazol-3-amines **122** using isothiocyanates **117**, tetramethylguanidine **118**, and hydroxylamine **121** in DMF (Scheme 46).[74]



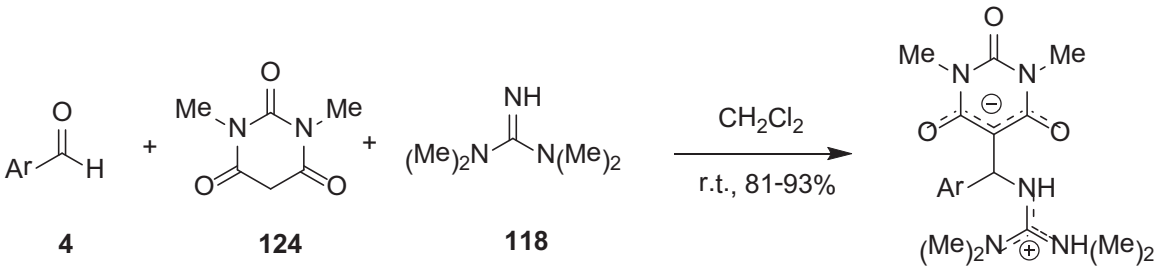
Scheme 46

The reaction of 4-chlorobenzaldehyde **4** and guanidinium carbonate **6** in the presence of sodium methoxide in ethanol after acidification with concentrated HCl gave noncyclic l-(*p*-chlorobenzoyl)-3-(*p*-chlorobenzyl)guanidine HCl **123** (Scheme 47).[71]



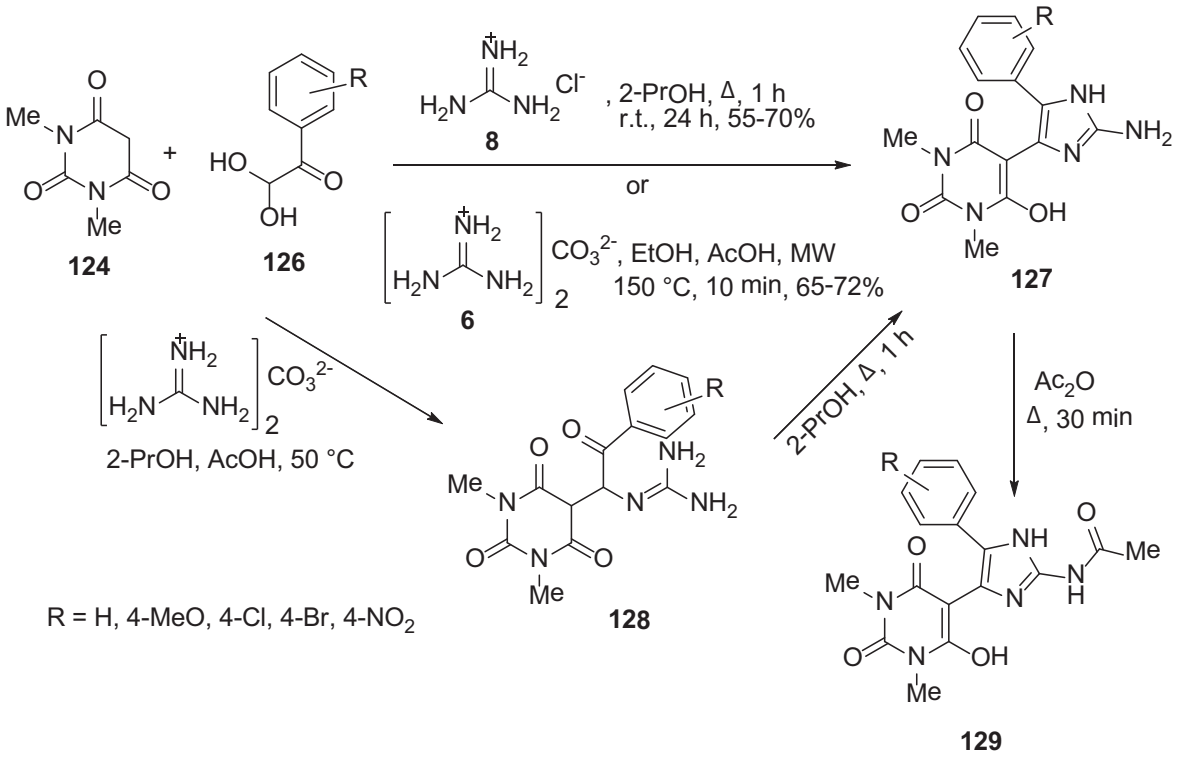
Scheme 47

Yavari et al. synthesized stable charge-separated tetramethylguanidinium-barbituric acid zwitterionic salts **125** through a 1-pot 3-component reaction of aromatic aldehydes **4**, N,N'-dimethylbarbituric acid **124**, and N,N,N',N'-tetramethylguanidine **118**. They also studied dynamic NMR of zwitterionic salts as a result of restricted rotation around the Me_2N–C bonds of the guanidine functional group (Scheme 48).[75]



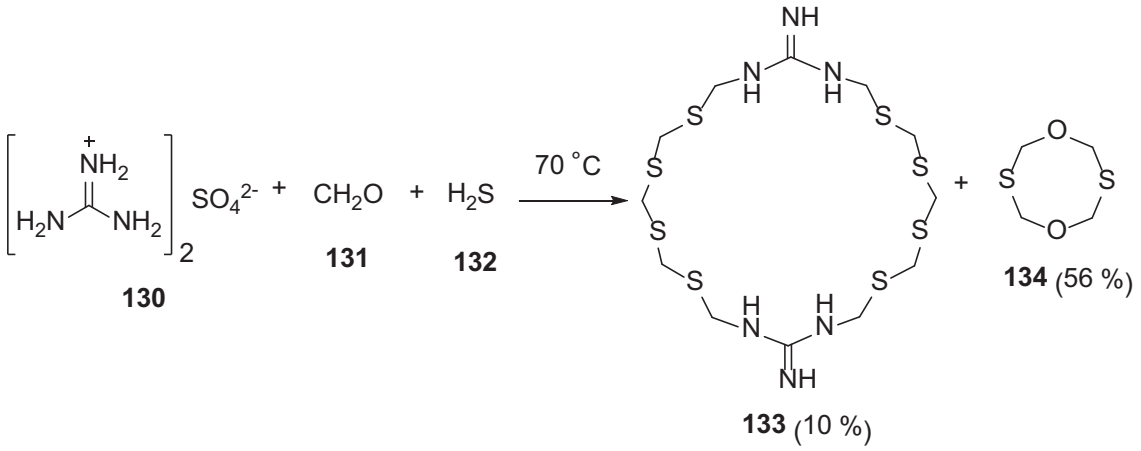
Scheme 48

Kolos et al. reported a thermally activated or microwave-induced 1-pot 3-component condensation of arylglyoxal hydrates **126**, 1,3-dimethylbarbituric acid **124**, and guanidine salts **6** and **8** for synthesis of 5-(2-amino-5-aryl-1*H*-imidazol-4-yl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **127**. Formation of the imidazole ring involved intermediates **128** that after heating in 2-propanol gave the desired imidazole **127**. The acetylation of pyrimidinediones **127** in acetic anhydride gave acetyl derivatives **129** (Scheme 49).[76]



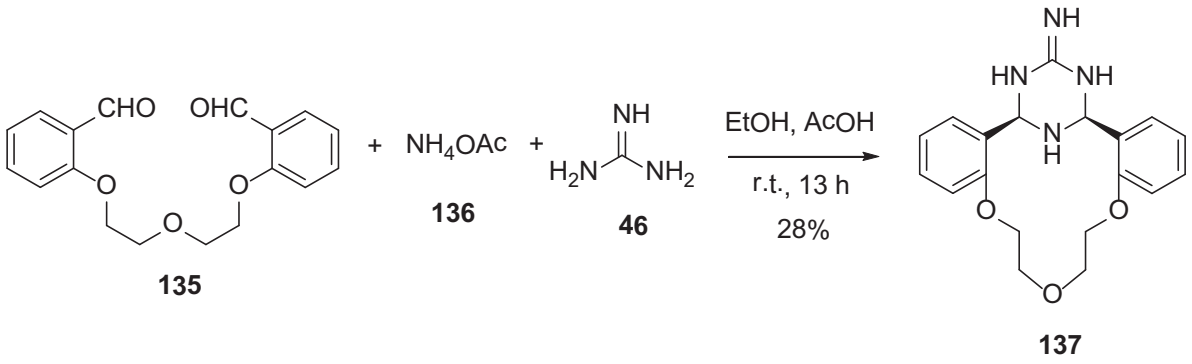
Scheme 49

The multicomponent condensation of guanidinium sulfate **130** with CH_2O **131** and H_2S **132** in more than 70 °C and in the concentration of the thiomethylating mixture (**130**:**131**:**132** = 1:10:9) led to the formation of target macroheterocycle **133** in 10% yield along with 1,3,5,7-oxatrithiocane **134** (Scheme 50). In the temperature range from 20 to 60 °C the guanidinium sulfate salt **130** is not involved in the reaction with CH_2O and H_2S.[77]



Scheme 50

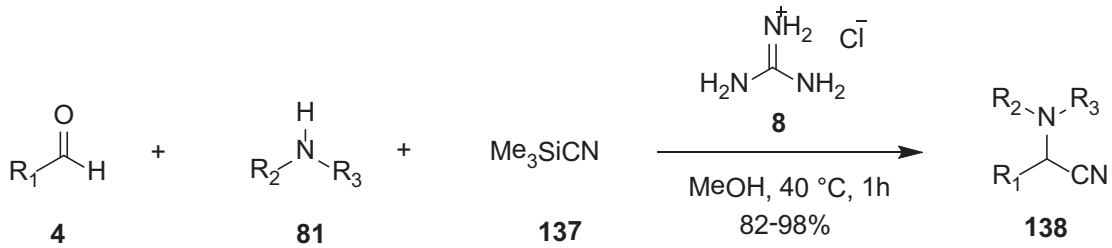
Synthesis of aza crown **137** was carried out by 3-component condensation of 1,5-bis(2-formylphenoxy)-3-oxapentane **135**, ammonium acetate **136**, and guanidine **46** in ethanol and acetic acid (Scheme 51).[78]



Scheme 51

3. Guanidine as a catalyst

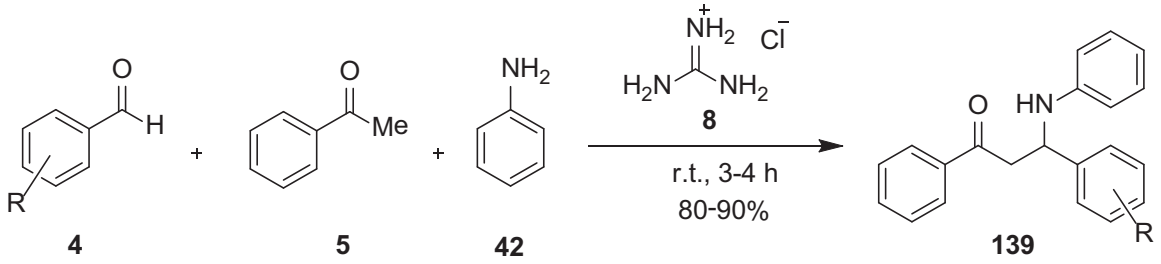
Guanidinium chloride **8** has been found to be a highly efficient catalyst for 1-pot 3-component Strecker reaction between various aldehydes **4**, amines **81**, and trimethylsilyl cyanide **137** for synthesis of α-aminonitriles **138** (Scheme 52).[13]



R_1 = *t*-Bu, Bn, *n*-pentyl, Ph, 4-ClPh, 2-furyl, 4-pyridyl, cinnamyl, *i*-propyl, 4-MeOPh R_2 = H, Et, Bn R_3 = Ph, Et, Bn

Scheme 52

Guanidinium chloride **8** is also an active and simple catalyst for Mannich-type reaction between various aldehydes **4**, acetophenone **5**, and aniline **42** for synthesis of β-carbonyl compounds **139** (Scheme 53).[12]

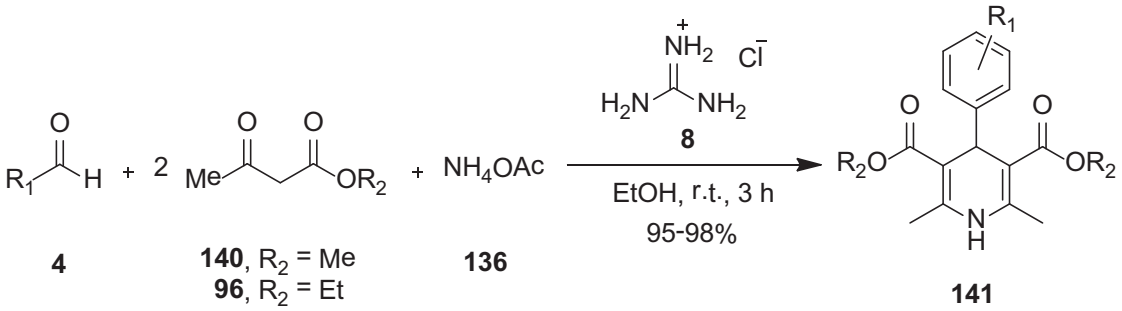


R = H, 4-Me, 4-F, 4-Cl, 4-NO_2, 4-MeO

Scheme 53

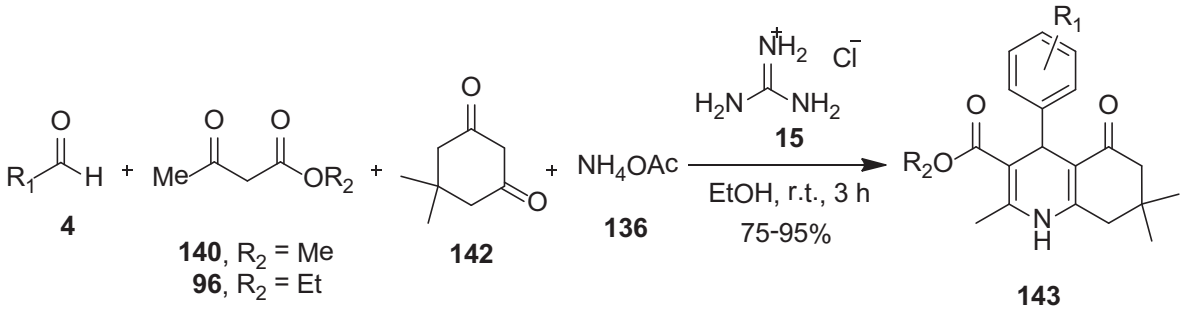
Baghbanian et al. have described an efficient methodology for synthesis of Hantzsch dihydropyridines **141** by 3-component condensation of aldehydes **4**, methyl acetoacetate **140** (or ethyl acetoacetate **96**), and ammonium acetate **136** by guanidinium chloride **8** as catalyst (Scheme 54). They also used guanidinium chloride **8** as catalyst for synthesis of octahydroquinoline derivatives **143** through Hantzsch reaction of aldehydes

4, methyl acetoacetate **140** (or ethyl acetoacetate **96**), dimedone **142**, and ammonium acetate **136** (Scheme 55).[79]



R_1 = Ph, 4-ClPh, PhCH=CH, cyclohexyl, 2-Furyl, 4-MePh, 4-BrPh, 4-OHPh, 4-NO_2Ph, *n*-pentyl

Scheme 54

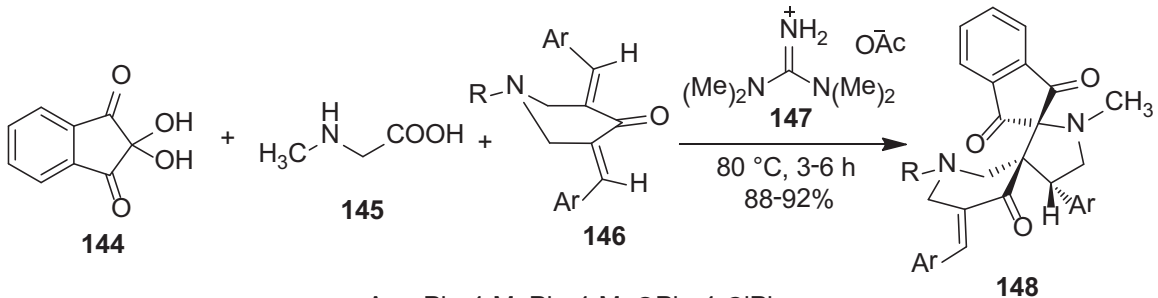


R_1 = Ph, 4-ClPh, PhCH=CH, 2-Furyl, 4-MePh, 4-MeOPh, 4-OHPh, 4-NO_2Ph, 3-pyridyl, 4-BrPh, *n*-Pr

Scheme 55

4. Guanidine as a solvent

1,1,3,3-Tetramethylguanidine acetate [TMG][Ac] ionic liquid **147** was used as solvent for the 3-component reaction between ninhydrin **144**, sarcosine **145**, and 1-benzyl/methyl-3,5-bis[(*E*)-arylidene]-piperidin-4-ones **146** for synthesis of dispiro heterocycles **148** (Scheme 56). The TMG-based ionic liquid is a reusable and environmentally benign solvent for synthesis of dispiropyrrolidines in high yields.[80]



R = Me, CH_2Ph

Ar = Ph, 4-MePh, 4-MeOPh, 4-ClPh, 4-BrPh, 4-FPh, 3,4-$(MeO)_2$Ph

Scheme 56

5. Conclusion

In this review, applications of guanidine and its salts in multicomponent reaction have been studied. Guanidine can be used as catalyst and also as a reactant in the synthesis of heterocycles in conventional, microwave, or solvent-free conditions. In most cases, using a base with guanidine salts is necessary for synthesis of heterocyclic compounds. Because of the ionic structure of guanidine salts, using microwave irradiation will be suitable for synthesis of heterocylic compounds.

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References

1. Wyss, P. C.; Gerber, P.; Hartman, P. G.; Hubschwerlen, C.; Locher, H.; Marty, H. P.; Stahl, M. *J. Med. Chem.* **2003**, *46*, 2304–2312.
2. Joffe, A. M.; Farley, J. D.; Linden, D.; Goldsand, G. *Am. J. Med.* **1989**, *87*, 332–338.
3. Petersen, E.; Schmidt, D. R. *Exp. Rev. Anti. Infect. Ther.* **2003**, *1*, 175–182.
4. Nadal, E.; Olavarria, E. *Int. J. Clin. Pract.* **2004**, *58*, 511–516.
5. Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609–1646.
6. Ube, H.; Uraguchi, D.; Terada, M. *J. Organomet. Chem.* **2007**, *692*, 545–549.
7. Weber, L. *Drug Discov. Today* **2002**, *7*, 143–147.
8. Domling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306–313.
9. Otzen, T.; Wempe, E. G.; Kunz, B.; Bartels, R.; Lehwark-Yvetot, G.; Hänsel, W.; Schaper, K. J.; Seydel, J. K. *J. Med. Chem.* **2004**, *47*, 240–253.
10. Peters, J. U.; Hunziker, D.; Fischer, H.; Kansy, M.; Weber, S.; Kritter, S.; Müller, A.; Wallier, A.; Ricklin, F.; Boehringer, M.; et al. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3575–3578.
11. Wyatt, E. E.; Galloway, W. R. J. D.; Thomas, G. L.; Welch, M.; Loiseleur, O.; Plowright, A. T.; Spring, D. R. *Chem. Commun.* **2008**, 4962–4964.
12. Heravi, M. M.; Zakeri, M.; Mohammadi, N. *Chinese Chem. Lett.* **2011**, *22*, 797–800.
13. Heydari, A.; Arefi, A.; Khaksar, S.; Shiroodi, R. K. *J. Mol. Catal. A: Chem.* **2007**, *271*, 142–144.
14. Zhuang, Q.; Han, H. X.; Wang, S.; Tu, S.; Rong, L. *Synth. Commun.* **2009**, *39*, 516–522.
15. Jawale, D. V.; Pratap, U. R.; Netankar, P. D.; Mane, R. A. *Chem. Biol. Interface* **2012**, *2*, 420–425.
16. Tao, S.; Xia, S.; Rong, L.; Cao, C.; Tu, S. *Res. Chem. Intermed.* **2012**, *38*, 2065–2073.
17. Rong, L.; Ji, H.; Xia, S.; Yin, S.; Shi, Y.; Tu, S. *J. Heterocycl. Chem.* **2012**, *49*, 696–699.
18. Vanden, E.; Jean, J.; Hecq, N.; Kataeva, O.; Kappe, C. O. *Tetrahedron* **2001**, *57*, 1785–1791.
19. Wyatt, E. E.; Fergus, S.; Galloway, W. R. J. D.; Bender, A.; Fox, D. J.; Plowright, A. T.; Jessiman, A. S.; Welch, M.; Spring, D. R. *Chem. Commun.* **2006**, 3296–3298.
20. Gangjee, A.; Adair, O.; Queener, S. F. *J. Med. Chem.* **1999**, *42*, 2447–2455.
21. Gangjee, A.; Vasudevan, A.; Queener, S. F.; Kisliuk, R. L. *J. Med. Chem.* **1996**, *39*, 1438–1446.
22. Hamby, J. M.; Connolly, C. J. C.; Schroeder, M. C.; Winters, R. T.; Showalter, H. D. H.; Panek, R. L.; Terry, C.; Olsewski, B.; Ryan, M. J.; Dahring, T. *J. Med. Chem.* **1997**, *40*, 2296–2303.
23. Nasr, M. N.; Gineinah, M. M. *Arch. Pharm.* **2002**, *335*, 289–295.
24. Mont, N.; Teixidó, J.; Borrell, J. I.; Kappe, C. O. *Tetrahedron Lett.* **2003**, *44*, 5385–5387.

25. Mont, N.; Teixidó, J.; Kappe, C. O.; Borrell, J. I. *Mol. Divers.* **2003**, *7*, 153–159.
26. Victory, P.; Borrell, J. I. *Trends Heterocycl. Chem.* **1993**, *3*, 235–247.
27. Victory, P. J.; Teixidó, J.; Borrell, J. I. *Heterocycles* **1992**, *34*, 1905–1916.
28. Borrell, J. I.; Teixidó, J.; Matallana, J. L.; Martínez-Teipel, B.; Colominas, C.; Costa, M.; Balcells, M.; Schuler, E.; Castillo, M. J. *J. Med. Chem.* **2001**, *44*, 2366–2369.
29. Borrell, J. I.; Teixidó, J.; Martínez-Teipel, B.; Serra, B.; Matallana, J. L.; Costa, M.; Batllori, X. *Collect. Czech. Chem. Commun.* **1996**, *61*, 901–909.
30. Berzosa, X.; Bellatriu, X.; Teixido, J.; Borrell, J. I. *J. Org. Chem.* **2009**, *75*, 487–490.
31. Galve, I.; Puig de la Bellacasa, R.; Sánchez-García, D.; Batllori, X.; Teixidó, J.; Borrell, J. *Mol. Divers.* **2012**, *16*, 639–649.
32. Jin, G.; Wu, C. C. N.; Carson, D. A.; Cottam, H. B. *Nucleos. Nucleot. Nucl.* **2006**, *25*, 1391–1397.
33. Rong, L.; Han, H.; Wang, H.; Jiang, H.; Tu, S.; Shi, D. *J. Heterocycl. Chem.* **2009**, *46*, 152–157.
34. Augustin, M.; Groth, C. H. *J. Prakt. Chem.* **1979**, *321*, 215–225.
35. Tominaga, Y.; Hirose, M.; Hagimori, M.; Shigemitsu, Y.; Mizuyama, N.; Wang, B. C. *Heterocycles* **2009**, *78*, 899–903.
36. Matasi, J. J.; Caldwell, J. P.; Hao, J.; Neustadt, B.; Arik, L.; Foster, C. J.; Lachowicz, J.; Tulshian, D. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1333–1336.
37. Meshram, G.; Wagh, P.; Deshpande, S.; Amratlal, V. *Lett. Org. Chem.* **2013**, *10*, 445–450.
38. Yadav, L. D. S.; Rai, A. *Carbohydr. Res.* **2009**, *344*, 2329–2335.
39. Yadav, L. D. S.; Rai, A. *Synthesis* **2009**, *2009*, 2802–2808.
40. Trivedi, A.; Dodiya, D.; Surani, J.; Jarsania, S.; Mathukiya, H.; Ravat, N.; Shah, V. *Arch. Pharm.* **2008**, *341*, 435–439.
41. Bararjanian, M.; Balalaie, S.; Rominger, F.; Barouti, S. *Helv. Chim. Acta.* **2010**, *93*, 777–784.
42. Liu, L.; Yin, S.; Xia, S.; Cai, P.; Rong, L. *Chinese J. Org. Chem.* **2012**, *32*, 612–615.
43. Bhatewara, A.; Jetti, S. R.; Kadre, T.; Paliwal, P.; Jain, S. *Arch. Appl. Sci. Res.* **2012**, *4*, 1274–1278.
44. Bhatewara, A.; Jetti, S. R.; Kadre, T.; Paliwal, P.; Jain, S. *Int. J. Med. Chem.* **2013**, *2013*, 1–5.
45. Deshmukh, M. B.; Salunkhe, S. M.; Patil, D. R.; Anbhule, P. V. *Eur. J. Med. Chem.* **2009**, *44*, 2651–2654.
46. Val, C.; Crespo, A.; Yaziji, V.; Coelho, A.; Azuaje, J.; El Maatougui, A.; Carbajales, C.; Sotelo, E. *ACS Comb. Sci.* **2013**, *15*, 370–378.
47. Ali, K. A. *Heterocycles* **2012**, *85*, 1975–1986.
48. Rong, L.; Han, H.; Gao, L.; Dai, Y.; Cao, M.; Tu, S. *Synth. Commun.* **2010**, *40*, 504–509.
49. Hekmatshoar, R.; Kenary, G. N.; Sadjadi, S.; Beheshtiha, Y. S. *Synth. Commun.* **2010**, *40*, 2007–2013.
50. Ahmadi, S.; Sadjadi, S.; Hosseinpour, M. *Monatsh. Chem.* **2011**, *142*, 1163–1168.
51. Deshmukh, M. B.; Anbhule, P. V.; Jadhav, S. D.; Jagtap, S. S.; Patil, D. R.; Salunkhe, S. M.; Sankpal, S. A. *Indian J. Chem. B* **2008**, *47*, 792.
52. Sheibani, H.; Saljoogi, A. S.; Bazgir, A. *Arkivoc* **2008**, *2*, 115–123.
53. Sheibani, H.; Seifi, M.; Bazgir, A. *Synth. Commun.* **2009**, *39*, 1055–1064.
54. Raghuvanshi, D. S.; Singh, K. N. *J. Heterocycl. Chem.* **2011**, *48*, 582–585.
55. Tominaga, Y.; Shigemitsu, Y.; Sasaki, K. *J. Heterocycl. Chem.* **2002**, *39*, 571–591.
56. Tominaga, Y.; Matsuda, Y. *J. Heterocycl. Chem.* **1985**, *22*, 937–949.
57. Ramezanpour, S.; Hashtroudi, M. S.; Bijanzadeh, H. R.; Balalaie, S. *Tetrahedron Lett.* **2008**, *49*, 3980–3982.
58. Amutha, P.; Nagarajan, S. *Helv. Chim. Acta.* **2010**, *93*, 430–434.

59. Maddila, S.; Jonnalagadda, S. B.; Chunduri, V.; Lavanya, P. *Heterocycl. Lett.* **2012**, *2*, 37–42.
60. Ostras, K. S.; Gorobets, N. Y.; Desenko, S. M.; Musatov, V. I. *Mol. Divers.* **2006**, *10*, 483–489.
61. Mohammadnejad, M.; Hashtroudi, M. S.; Balalaie, S. *Heterocycl. Commun.* **2009**, *15*, 459–466.
62. Mirza-Aghayan, M.; Baie Lashaki, T.; Rahimifard, M.; Boukherroub, R.; Tarlani, A. A. *J. Iran. Chem. Soc.* **2011**, *8*, 280–286.
63. Akbas, E.; Levent, A.; Guemues, S.; Suemer, M. R.; Akyazi, I. *Bull. Korean Chem. Soc.* **2010**, *31*, 3632–3638.
64. Prakash, O.; Pannu, K.; Naithani, R.; Kaur, H. *Synth. Commun.* **2006**, *36*, 3479–3485.
65. Trivedi, A. R.; Bhuva, V. R.; Dholariya, B. H.; Dodiya, D. K.; Kataria, V. B.; Shah, V. H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6100–6102.
66. Lokwani, D.; Shah, R.; Mokale, S.; Shastry, P.; Shinde, D. *J. Comput. Aided Mol. Des.* **2012**, *26*, 267–277.
67. Azizian, J.; Mirza, B.; Mojtahedi, M. M.; Abaee, M. S.; Sargordan, M. *J. Fluorine Chem.* **2008**, *129*, 1083–1089.
68. Azizian, J.; Mohammadi, M. K.; Firuzi, O.; Mirza, B.; Miri, R. *Chem. Biol. Drug Des.* **2010**, *75*, 375–380.
69. Chavda, D. R.; Modiya, P. R.; Marvaniya, H. M.; Sen, D. J. *Int. J. Drug Dev. Res.* **2010**, *2*, 348–355.
70. Ujjinamatada, R. K.; Hosmane, R. S. *Tetrahedron Lett.* **2005**, *46*, 6005–6009.
71. Gund, P.; Berkelhammer, G.; Wayne, R. S. *Tetrahedron Lett.* **1972**, *13*, 3983–3986.
72. Zomordbakhsh, S.; Anaraki-Ardakani, H.; Zeeb, M.; Sadeghi, M.; Mazraeh-Seffid, M. *J. Chem. Res.* **2012**, *36*, 138–140.
73. Jalani, H. B.; Pandya, A. N.; Pandya, D. H.; Sharma, J. A.; Sudarsanam, V.; Vasu, K. K. *Tetrahedron Lett.* **2013**, *54*, 5403–5406.
74. Jalani, H. B.; Sudarsanam, V.; Vasu, K. K. *Synthesis* **2012**, *44*, 3378–3386.
75. Yavari, I.; Aminkhani, A.; Arab-Salmanabadi, S. *Monatsh. Chem.* **2012**, *143*, 1195–1198.
76. Kolos, N. N.; Chechina, N. V.; Zamigailo, L. L.; Vashchenko, E. V. *Chem. Heterocycl. Comp.* **2013**, *49*, 872–881.
77. Akhmetova, V. R.; Khairullina, R. R.; Bushmarinov, I. S.; Tyumkina, T. V.; Yanybin, V. M. *Arkivoc* **2011**, *2011*, 149–162.
78. Hieu, C.; Anh, L.; Levov, A. N.; Nikitina, E. V.; Soldatenkov, A. T. *Chem. Heterocycl. Comp.* **2009**, *45*, 1406–1407.
79. Baghbanian, S. M.; Khaksar, S.; Vahdat, S. M.; Farhang, M.; Tajbakhsh, M. *Chinese Chem. Lett.* **2010**, *21*, 563–567.
80. Dandia, A.; Jain, A. K.; Sharma, S. *Tetrahedron Lett.* **2012**, *53*, 5859–5863.