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Current Organic Chemistry, 2013, *17*, 000-000

Application of Benzoylaceteonitrile in the Synthesis of Pyridines Derivatives

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Abstract: This review deals with synthetic potential and utility of benzoylacetonitrile in the synthesis of pyridine derivatives. The reactions are subdivided into groups that cover the synthetic methods of pyridine derivatives from benzoylacetonitrile e.g. self condensation, Friedlander reaction, Michael Addition reaction, addition to enaminones, reaction with enamino-nitriles or enamino-esters, and one-pot three component reactions. A brief account on the synthesis of benzoylacetonitrile was also displayed.

Keywords: Benzoylacetonitrile, pyridines, quinolines, naphthyridines.

1. INTRODUCTION

Benzoylacetonitrile, known as phenacylcyanide or ω-cyano-acetophenone, was named as 3-oxo-3-phenylpropanenitrile as using the IUPAC system. Benzoylacetonitrile is a versatile and convenient intermediate for preparation of various organic and six-membered heterocyclic compounds, especially pyridine derivatives, possessing diverse biological activities and many other practically useful properties e.g. antimicrobial [1-5]; anticancer agents [6]; anti-HCV, antioxidant, and peroxynitrite inhibitory activity [7]; and as electron-transporting layer [8], Despite this versatile importance, and in connection to our previous review articles [9], benzoylacetonitrile have not been previously reviewed. The present review aims to demonstrate the synthetic applications of benzoylacetonitrile in the synthesis of pyridine heterocyclic compounds from 1985 to the end of 2011 and provide useful and up-to-date data for organic and medicinal chemists.

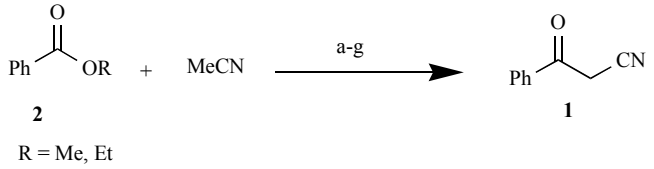
2. SYNTHESIS OF BENZOYLACETONITRILE

2.1. Claisen Condensation

Benzoylaceteonitrile **1** was synthesized in good to excellent yields either by reaction of aceteonitrile with benzoate ester **2** in the presence of different reagent [10-17] or through the electrochemical coupling of acetonitrile with methyl benzoate **2**. The reaction was catalyzed by samarium(III) chloride using *t*-Bu alcohol as a probase. Electrolysis was run under mild conditions in an undivided cell with a magnesium anode (Scheme **1**) [18].

2.2. From Haloacetophenone

Benzoylaceteonitrile **1** was prepared in excellent yield by reaction of haloacetophenones with sodium cyanide [19-21]. Reaction of 2-haloacetophenones with sodium cyanide in aqueous ethanol at 50 °C gave mixture of compound **1** and oxiranes **4**. The yields of **4** increased with increasing reaction temperature (Scheme **2**) [22].

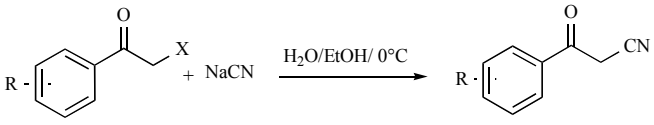


2 **1**

R = Me, Et

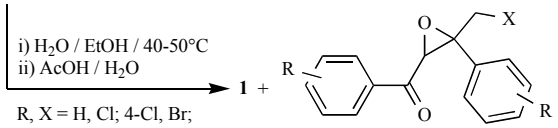
a; i) NaH/PhMe/reflux, ii) HCl/H_2O/pH 2-3 (89%)
b; $LiNEt_2$/THF (74%)
c;BuLi/THF/ -78°C (100%)
d; i) NaOMe/MeCN/ 90°C/ 1.5 h, ii) HCl/H_2O/pH 3 (98%)
e; EtONa, EtOH (65%)
f;Me_2CHCH_2OK/THF, MePh (99%)
g; t-BuOH, $SmCl_3$ (75%)

Scheme 1.



3 **1**

R = H, 2-F, 2-Me, 2-OMe, 3-F, 3-Cl, 3-Me, 2,5-diF, 2,5-diCl, 2,5-diMe, 2-MeO-5-Cl, 2-MeO-5-F; X = Cl, Br



4, 50%

Scheme 2.

2.3. From Enaminones, Benzonitrile or Acetophenone

Reaction of enaminones **5** with hydroxylamine hydrochloride in ethanol yielded aldoximes **6** which converted directly into 3-oxoalkanonitrile **1** (Scheme **3**) [23,24].

Treatment of benzonitrile with aceteonitrile led to compound **1** in 70% yields (Scheme **4**) [11].

Benzoylaceteonitrile **1** was obtained in high yield by treating aceteophenone with sodium cyanide (Scheme **5**) [19, 20, 25, 26].

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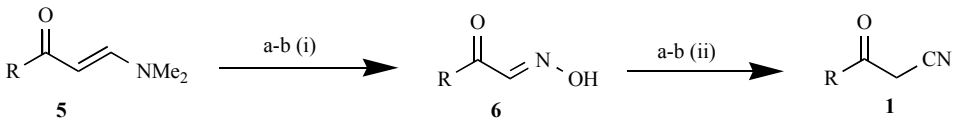
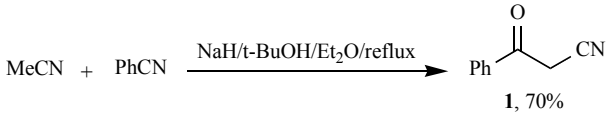


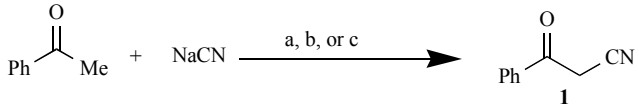
R = Ph, 4-ClC$_6$H$_4$, 2-thienyl, 2-furyl

a; i) KOH, NH$_2$OH.HCl, H$_2$O, EtOH, ii) HCl/H$_2$O
b; i) AcONa/NH$_2$OH.HCl, H$_2$O/EtOH; ii) (CO$_2$Et)$_2$/NaH, dioxane/rt

Scheme 3.

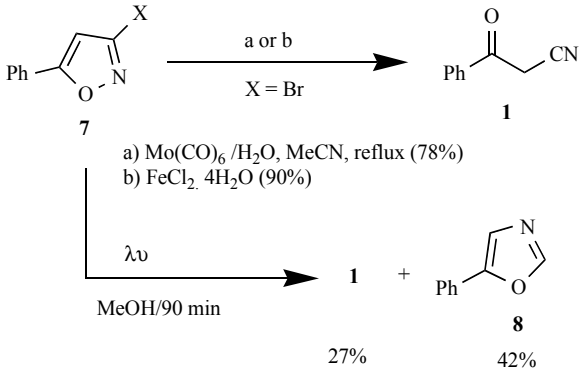


Scheme 4.



a; i) p-MeC$_6$H$_4$SO$_3$H/Chlorosuccinimide/MeCN; ii) H$_2$O/EtOH/ 0°C
b;p-tolylSO$_3$H, IC$_6$H$_4$OH/H$_2$O/MeCN
c; Br$_2$

Scheme 5.



Scheme 6.

2.4. Miscellaneous Methods

The synthesis of *β*-ketonitriles **1** from 3-bromoisoxazoles **7** has been reported. 3-bromoisoxazole **7** was ring opened with either molybdenum hexacarbonyl or iron(II) chloride tetrahydrate to give compound **1** in good yield [27]. On the other hand 5-Phenyl-isoxazole **7** underwent regioselective phototransposition to 5-phenyloxazole **8** and compound **1** (Scheme **6**) [28].

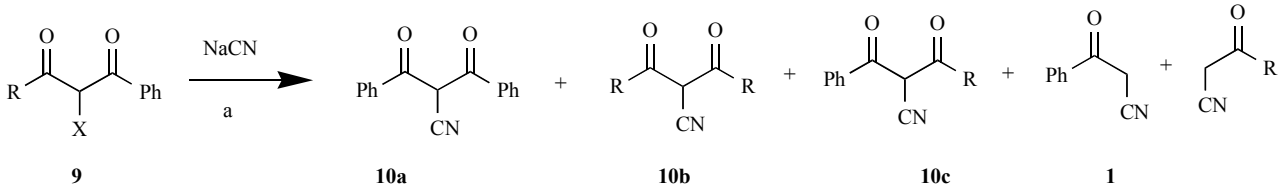
Reactions of 1,3-diaryl-2-chloropropane-1,3-diones **9** with nucleophiles-cyanide-induced retro-Claisen-Claisen condensation (Scheme **7**) [29].

One-step reaction of *N*-methoxy-*N*-methylbenzamide with acetonitrile in ether in the presence of lithium diisopropylamide led to **1** in excellent yield (Scheme **8**) [30].

3. SYNTHESIS OF PYRIDINES

3.1. Self Condensation

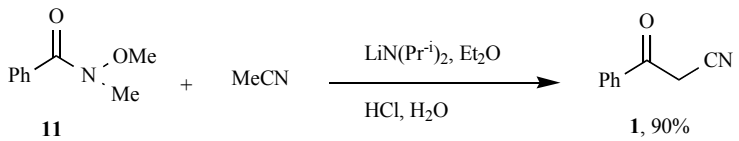
Elnagdi *et al.* [31] have been reported the self condensation of nitrile **1** to afford the dinitrile **12a**. While Abdelrazek *et al*. [32] revised the structure **12a** to **13**. The formation of **13** involved Knoevenagel self-condensation **1** to afford the tautomeric pair **12a**/**12b**, which then underwent 6-exo-dig cyclization [33] to afford the iminopyran **13**. Addition of ammonium acetate to **13** afforded a mixture of products **15** and **16** in 22% and 15% yields, respectively. The mechanism involved nucleophilic attack of ammonia to pyran ring then followed by ring opening to acyclic tautomeric pair **14a**/**14b**. Recyclization of **14a** through loss of water will lead to the iminopyridine **15a**, which can in principle tautomerize to the amino pyridine **15b**; while recyclization of **14b** *via* reelimination of ammonia gave 2-pyridone derivative **16**. Compound **15a** had been reported previously [34] The other possible direction is a Michael addition of the active methylene of one molecule of **1** to the cyano function of another to afford the 1,5-dione intermediate **17**, which is transformed into the pyridine derivative **18** under the effect of ammonia (Scheme **9**) [35].



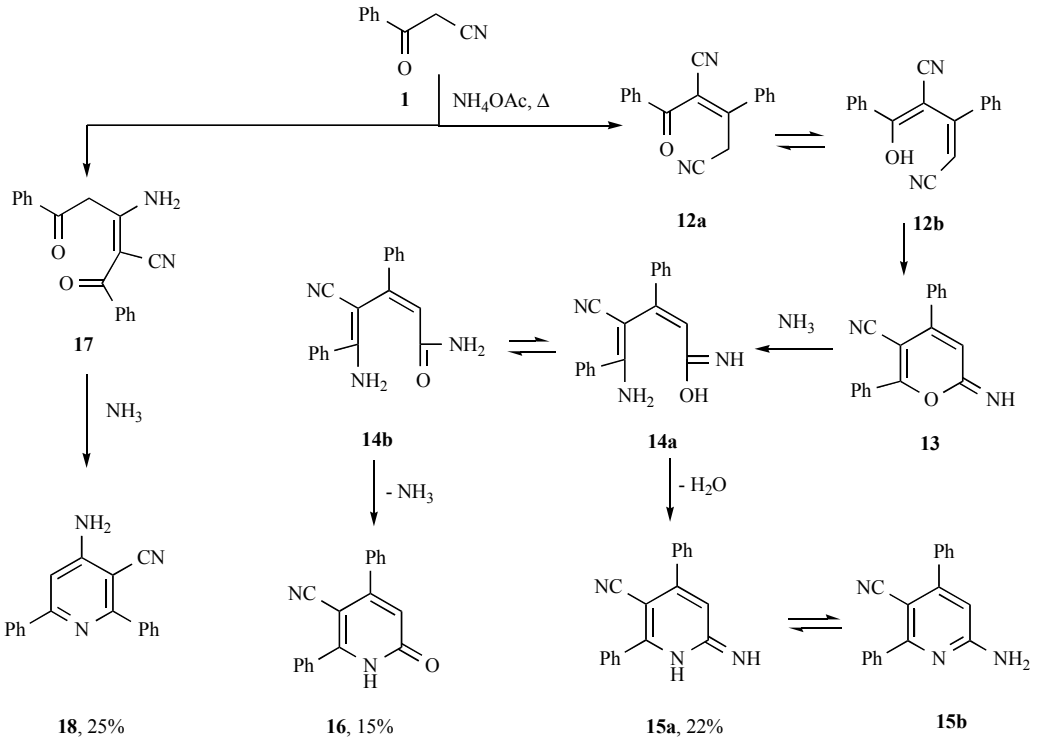
R = 4-ClC$_6$H$_4$; X = H, Cl

a; i) Chlorosuccinimide /CCl$_4$ / 12 h reflux; ii) DMSO/ 24 h rt - 0°C; iii) NaCl /H$_2$O / 0°C; iv) HCl /H$_2$O /pH 6

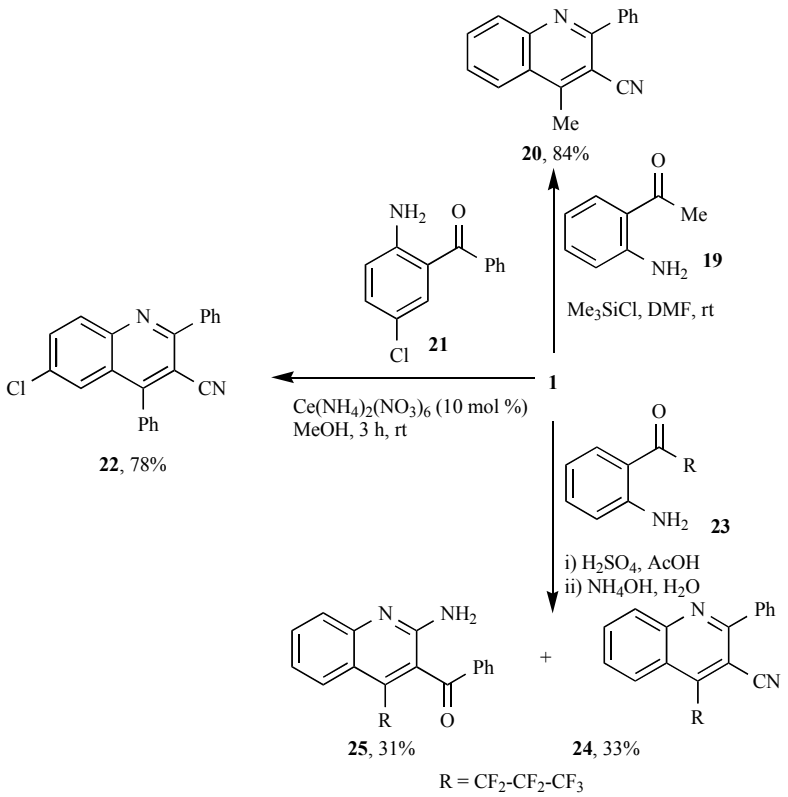
Scheme 7.



Scheme 8.



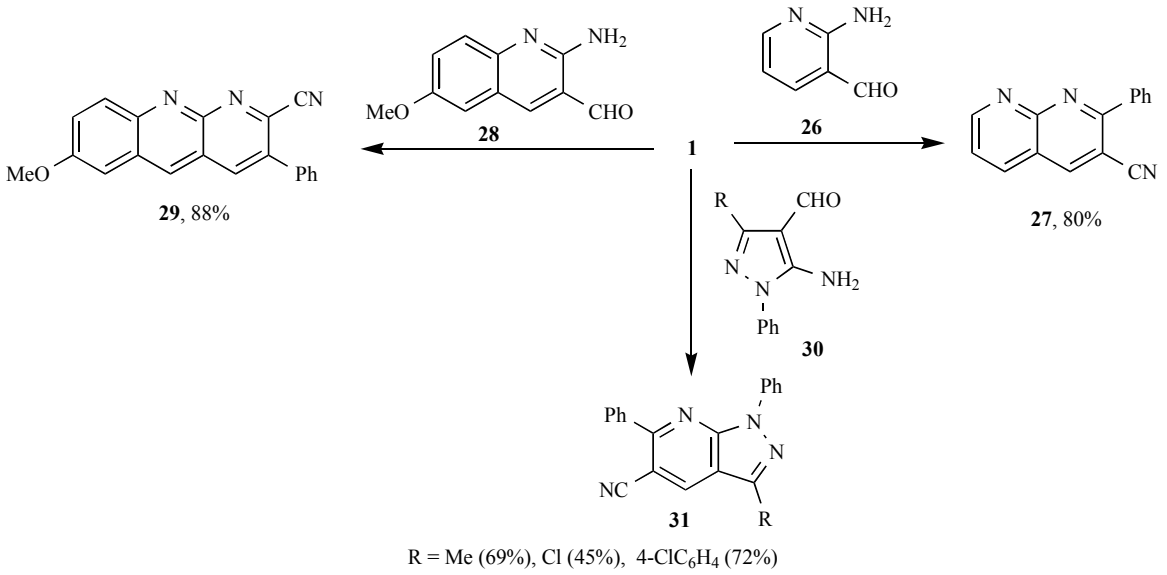
Scheme 9.



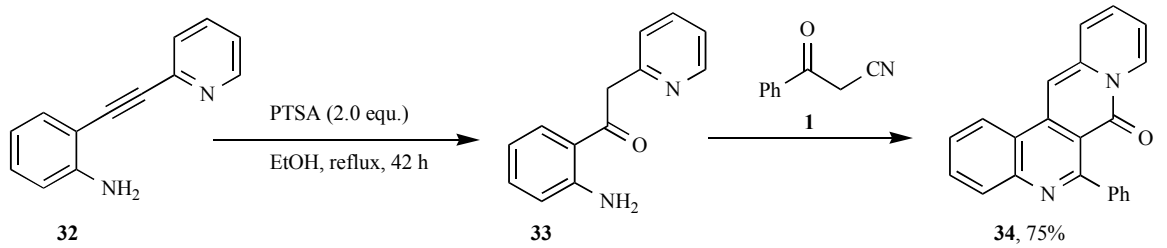
Scheme 10.

3.2. Friedlander Condensation Reaction

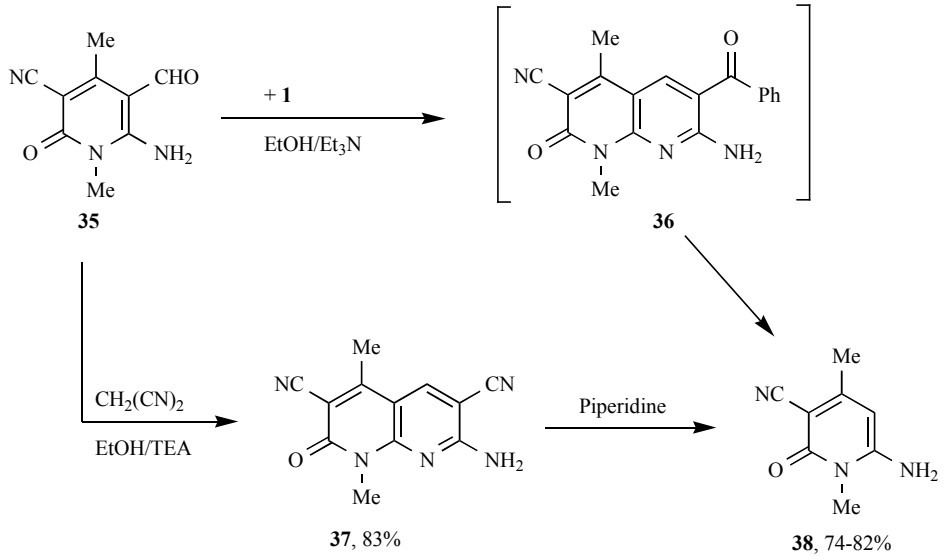
Chlorotrimethylsilane [36] or ceric ammonium nitrate [37] mediated Friedlander syntheses of polysubstituted quinolines was described. 2-phenylquinoline-3-carbonitrile **20** and **22** was readily prepared *via* reaction of 2-aminoaceteophenone **19** and 2-amino-5-chlorobenzophenone **21** with **1** using chlorotrimethylsilane as a promoter and water-acceptor agent or ceric ammonium nitrate as a catalyst at ambient temperature. 2,3-Disubstituted 4-(perfluoroalkyl)quinolines **24** and **25** were obtained by the acid-catalyzed condensation reaction of **1** with 2-(perfluoroacyl)anilines **23** [38] (Scheme **10**).



Scheme 11.



Scheme 12.

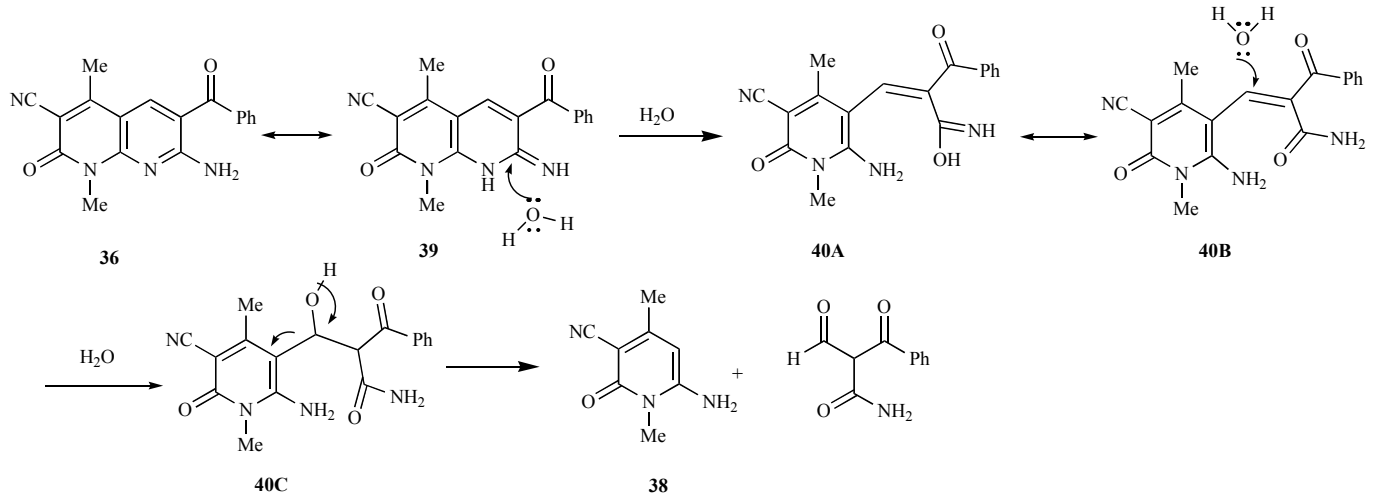


Scheme 13.

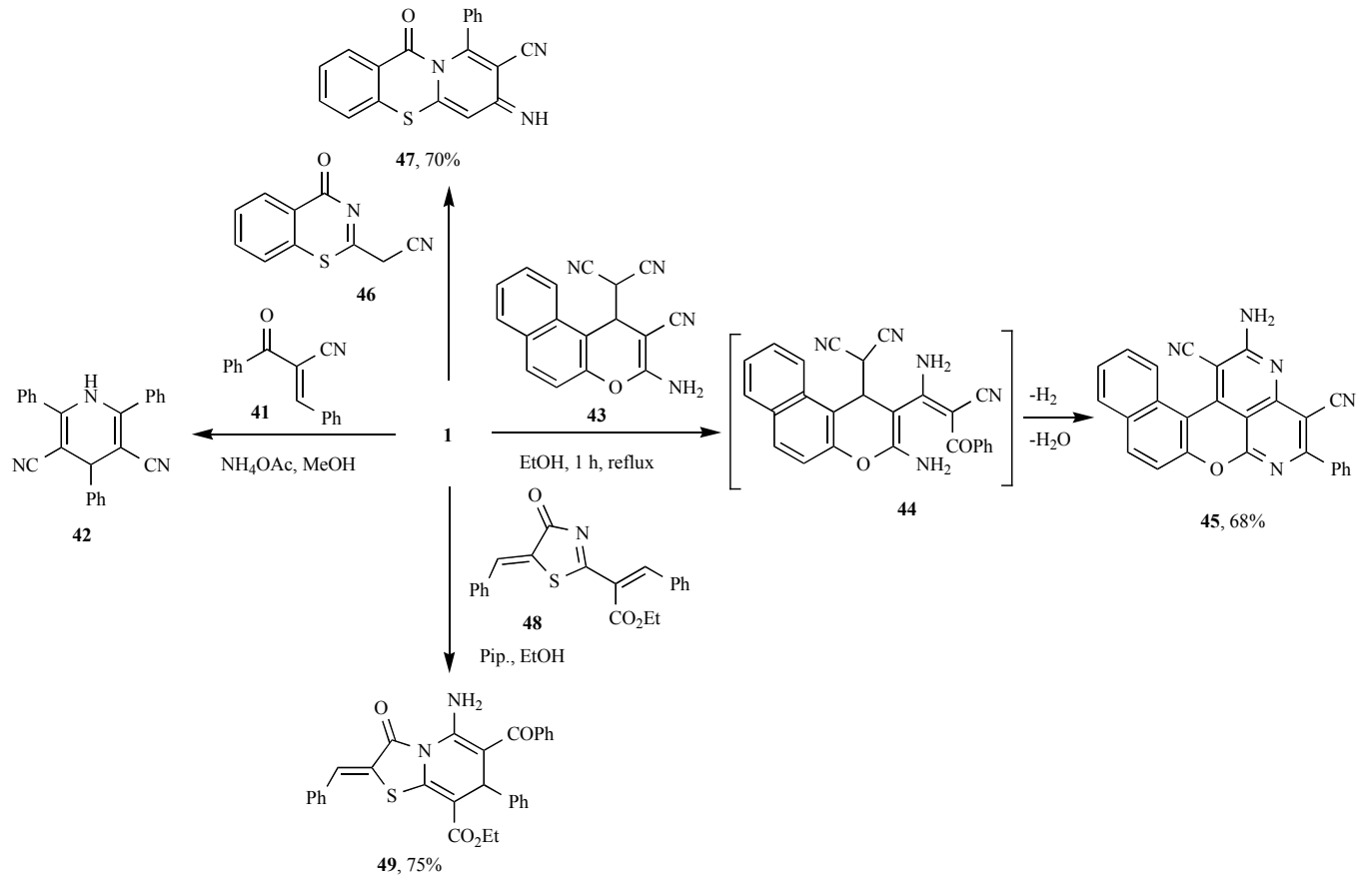
Cyclocondensation of 2-aminonicotinaldehyde **26** with **1** afforded 2-phenyl-1,8-naphthyridine-3-carbonitrile **27** in 80% yield [39]. Friedlander condensation reaction of **1** with 2-aminoformyl quinoline **28** gave benzonaphthyridine **29** in 88% yields [40]. Reaction of 5-amino-4-pyrazolecarbaldehyde **30** with **1** in ethanol in the presence piperidine as basic catalyst yielded pyrazolo[3,4-*b*]pyridine-5-carbonitriles **31** (Scheme **11**) [4,41-43].

The reaction of 2-(pyridin-2-ylethynyl)aniline **32** with **1**, promoted by *p*-toluenesulfonic acid in ethanol in one pot reaction to afford 6-phenyl-7*H*-benzo[*f*]pyrido[1,2-*b*][2,7]naphthyridin-7-one **34** in 75% yield via the intermediate **33** (Scheme **12**) [44].

6-Amino-5-formyl-1,4-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile **35** was reacted with **1**, to give 6-amino-1,4-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile **38**. The formation of **38** can be explained by the degradation of 1,8-naphthyridine-2-ones intermediate **36**. On the other hand, the formation of **37** from compound **35** and malononitrile under basic conditions implies that 1,8-naphthyridine-2-one **37** is more stable than **36** under these reaction



Scheme 14.



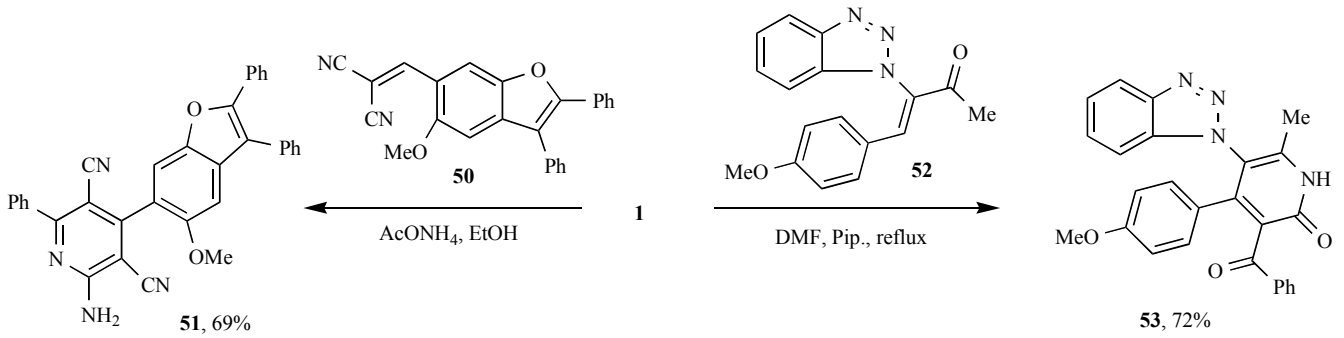
Scheme 15.

conditions. Refluxing **37** in piperidine for 30 minutes yielded 6-aminopyridone **38** as the sole product (Scheme **13**) [45].

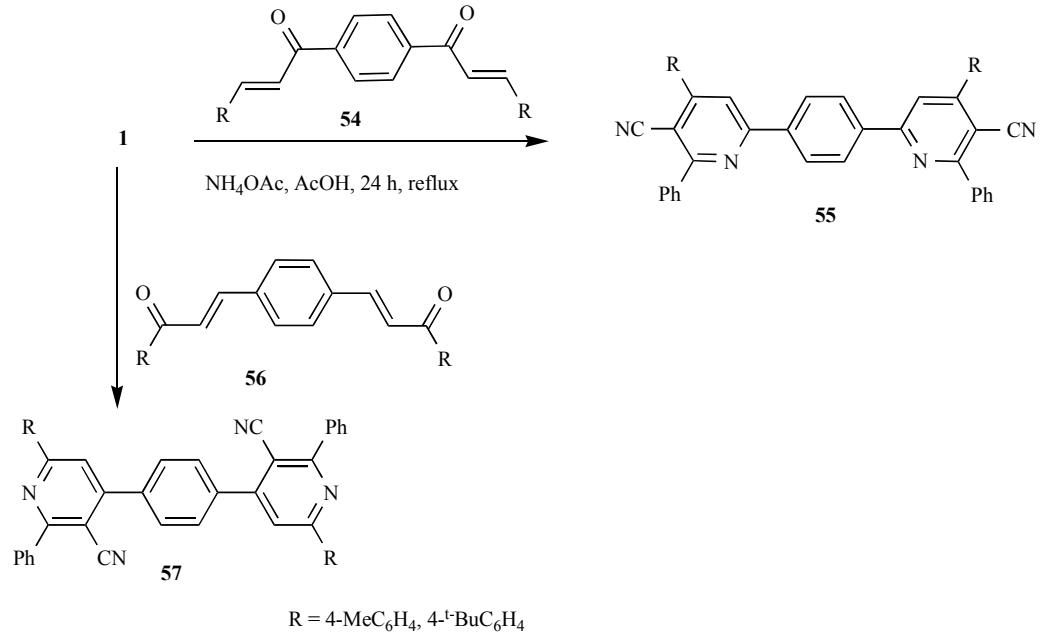
The probable mechanism leading to the formation of 6-aminopyridones **38** is outlined in Scheme 14. The formation of **38** is assumed to proceed *via* an initial nucleophilic attack by adventitious water on C-7 of **39**, tautomer of **36**, to form the non-isolable acyclic intermediate **40A**, which is in equilibrium with the tautomer **40B**. Further nucleophilic attack by another molecule of H_2O on the activated double bond in **40B** to yield intermediate **40C** followed by a proton shift and intramolecular rearrangement to give the final product **38** and the corresponding ester **40** (Scheme **14**) [46].

3.3. Michael Addition Reaction

Compound **1** was reacted with 2-benzoyl-3-phenylacrylonitrile **41** and ammonium acetate in acetic acid to give 2,4,6-triphenyl-1,4-dihydropyridine-3,5-dicarbonitrile **42** [47]. Cyclocondensation of 2-(3-amino-2-cyano-1*H*-benzo[*f*]chromen-1-yl)malononitrile **43** with **1**, gave benzo[5,6]chromeno[4,3,2-*de*][1,6]naphthyridine derivative **45** *via* intermediate **44** [48]. Michael addition of compound **1** to nitrile function of 2-(4-Oxo-4*H*-benzo[*e*][1,3]thiazin-2-yl)acetonitrile **46** followed by cyclization yielded 7-imino-11-oxo-9-phenyl-7,11-dihydrobenzo[*e*]pyrido[2,1-*b*][1,3]thiazine-8-carbonitrile **47** [49,50]. Ethyl 2-(5-benzylidene-4-oxo-4,5-



Scheme 16.



Scheme 17.

dihydrothiazol-2-yl)-3-phenylacrylate **48**, was reacted with compound **1** in ethanol under reflux in the presence of pipreidine to afford thiazolo[3,2-*a*]pyridine-8-carboxylate **49** (Scheme **15**) [51].

Reaction of 2-[(5-methoxy-2,3-diphenylbenzofuran-6-yl)methylene]malononitrile **50** with **1** in ethanol in the presence of ammonium acetate gave 6-phenylpyridine-3,5 dicarbonitrile **51** [52]. 3-(1-Benzotriazolyl)chalcone **52** was reacted with **1** in refluxing DMF in the presence of piperidine to afford benzotriazolyl pyridine **53**. The latter compound showed antimicrobial and antifungal activities (Scheme **16**) [2].

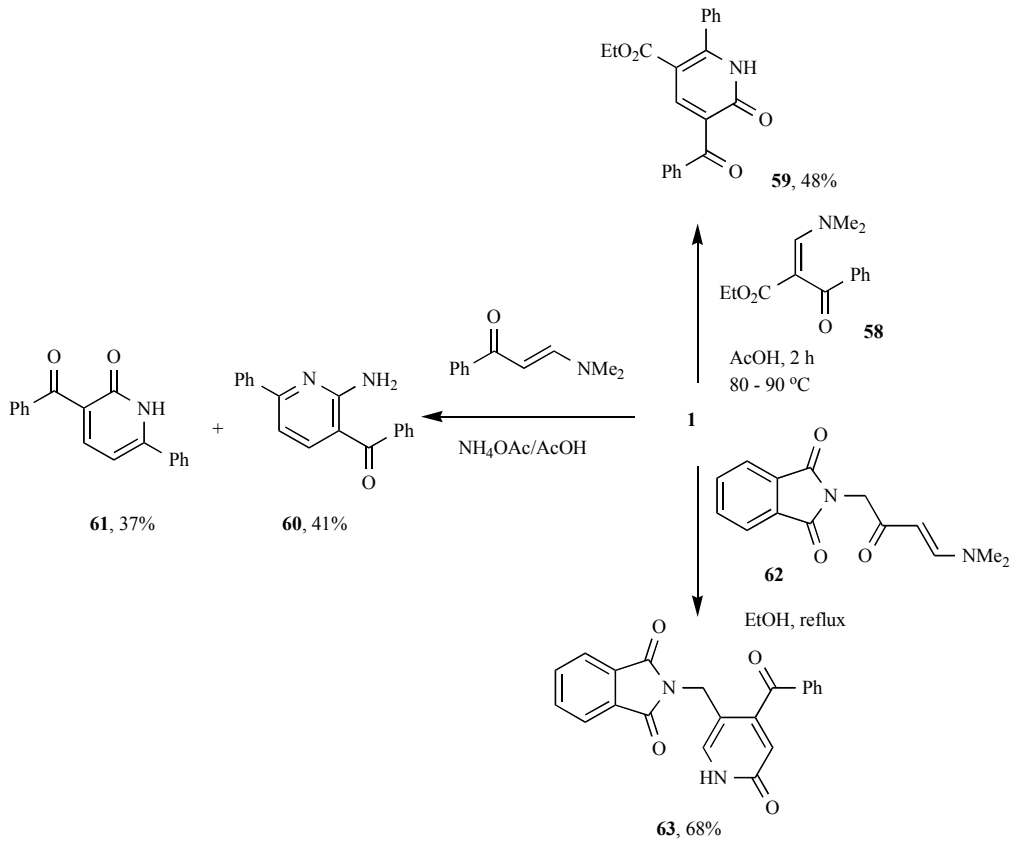
Substituted pyridine derivatives **55** and **57**, with good thermal properties and efficient deep-blue emissions, were designed from reaction of compound **1** with chalcones **54** and **56** respectively in acetic acid under reflux in the presence of ammonium acetate (Scheme **17**) [8a,b].

3.4. Addition to Enaminones

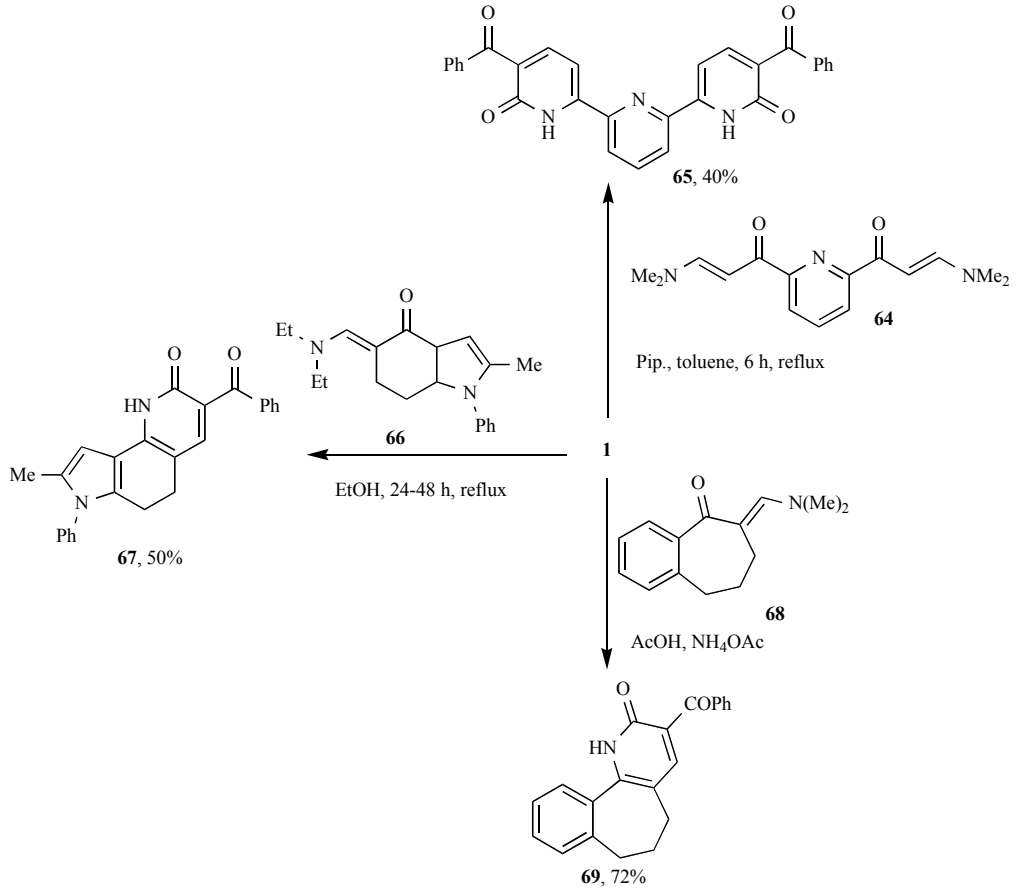
Compound **1** was reacted with ethyl 2-benzoyl-3-(dimethylamino)acrylate **58** in acetic acid to afford ethyl 5-benzoyl-6-oxo-2-phenyl-1,6-dihydropyridine-3-carboxylate **59** [53]. Similarly, the reaction of compound **1** with enaminone **60** in acetic acid/ammonium acetate proceeded *via* initial Michael addition across the double bond followed by cyclization to afford pyridine **60** and **61**[54]. 2-(4-(Dimethylamino)-2-oxobut-3-enyl)isoindoline-1,3-dione **62** was reacted with **1** in ethanol to afford 2-[(4-benzoyl-6-oxo-1,6-dihydropyridin-3-yl)methyl]isoindoline-1,3-dione **63**, which have antimicrobial activity (Scheme **18**) [3].

2,6-Bis[3-*N*,*N*-dimethylamino-1-oxopropen-1-yl]pyridine **64** was reacted with **1** in toluene containing piperidine to afford 6,6'-(pyridine-2,6-diyl)bis(3-benzoylpyridin-2(1*H*)-one) **65** [55]. Pyrrolo[2,3-*h*]quinolin-2-one **67**, as isosters of the angular furocoumarin Angelicin, was synthesized by reaction of **1** with indol-4-one derivative **66** [56]. In a similar manner, the enaminone **68**, which prepared from reaction of benzosuberone with dimethylformamide-dimethylacetal (DMF-DMA), was reacted with **1** in acetic acid in the presence of ammonium acetate to give pyridin-2-one **69** (Scheme **19**) [8].

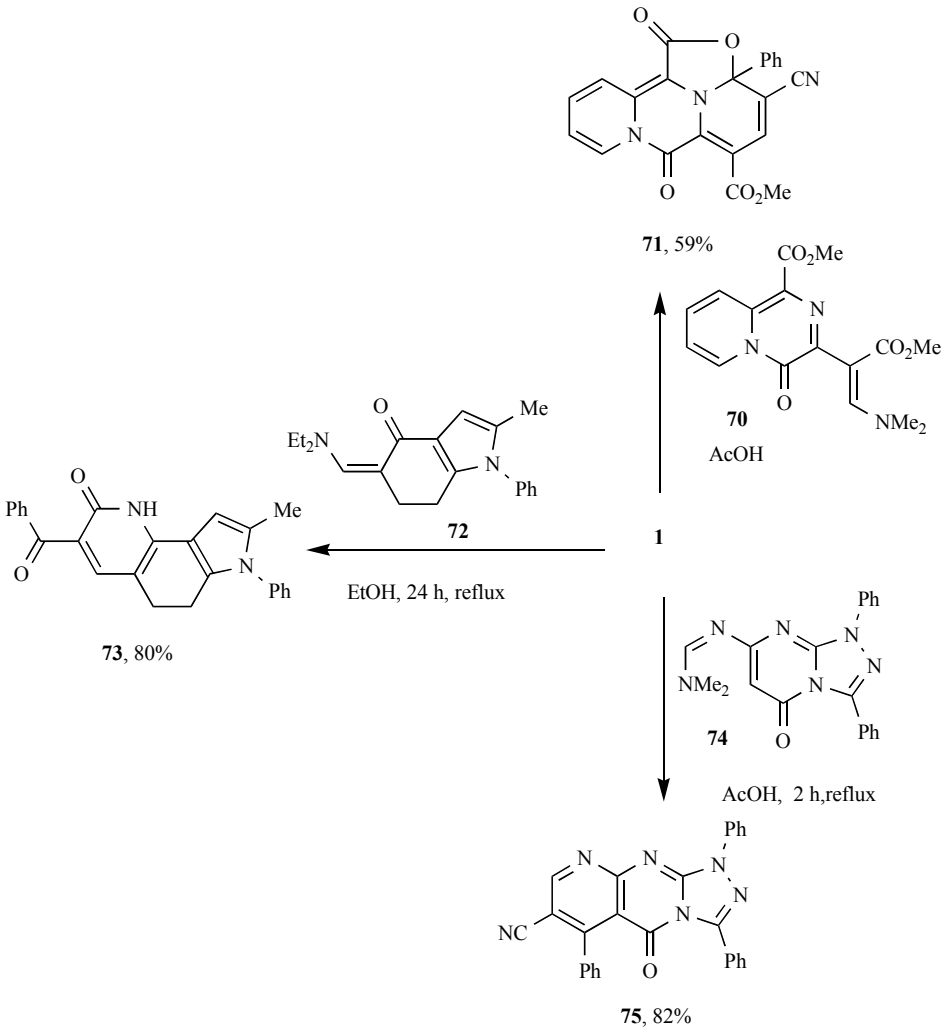
Transformations of methyl 3-(1-(dimethylamino)-3-methoxy-3-oxoprop-1-en-2-yl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrazine-1-carboxylate **70** into diazaaceanthrylene **71** by reaction with **1** was reported [57]. Synthesis of pyrrolo[2,3-*h*]quinoline-2-one **98**, as photo reagents toward cultured human tumor cells, was synthesized by reaction of **1** with 5-((diethylamino)methylene)-2-methyl-1-phenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one **72** in ethanol under reflux [4]. *N*,*N*-Dimethyl-*N*'-(5-oxo-1,3-diphenyl-1,5-dihydro-[1,2,4]triazolo[4,3-*a*]pyrimidin-7-yl)formimidamide **74** was reacted with **1** in acetic acid under reflux to give 5-oxo-1,3,6-triphenyl-1,5-dihydropyrido



Scheme 18.



Scheme 19.



Scheme 20.

[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-7-carbonitrile **75** by elimination of dimethylamine and water (Scheme **20**) [58].

Benzotriazolyl nicotinonitrile **77** was obtained by reaction of **1**with benzotriazoly-1-enaminone **76** in acetic acid under reflux in the presence of ammonium acetate at reflux temperature [59]. The enaminonitrile **78** was reacted with **1** to yield 3-benzoyl-4-imino-9,10-dimethoxy-6,7-dihydro-4*H*-pyrido[2,1-*a*]isoquinoline-1-carbonitrile **79** [60]. Treatment of 4-aminopent-3-en-2-one **80** with **1** in THF gave 3-benzoyl-4,6-dimethylpyridin-2(1*H*)-one **81** in 56% yield (Scheme **21**) [61].

Enaminone **82** or amidine **85** was reacted with **1** to yield 3-oxo-2,6-diphenyl-3,7-dihydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile **84** or 4-phenyl-2*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile **86**, respectively *via* condensation by elimination of dimethylamine and water. On the other hand, compound **86** was obtained from reaction of 3-aminopyrazole **88** with 2-benzoyl-3-(dimethylamino)acrylonitrile **87** [62]. The latter compound **87** was reacted with **1** in the presence of acetic acid and ammonium acetate to yield 5-benzoyl-6-hydroxy-2-phenylnicotinonitrile **90** *via* intermediate **89** (Scheme **22**) [63].

Compound **1** was converted into 3-amino-3-ethoxy-1-phenylprop-2-en-1-one hydrochloride **91** by reaction with ethanol in ether in the presence of HCl. The latter compound was treated with arylidenemalononitrile **92** in ethanol under reflux in the presence of triethylamine to give 2-amino-5-benzoylnicotinonitriles **93** (Scheme **23**) [64].

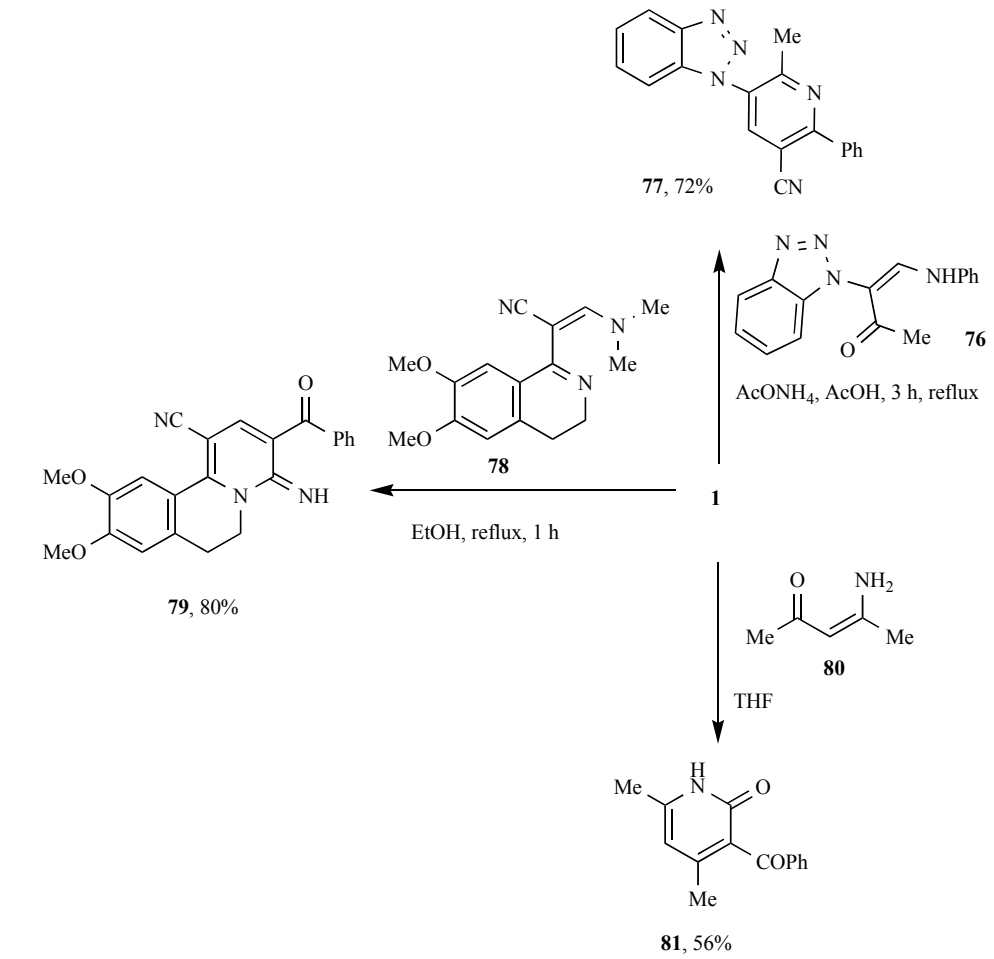
3.5. Reaction with Enamino-nitriles or Enamino-esters

Reactions of 2-amino-4*H*-chromen-3-carbonitrile **94** with **1** lead to tetrahydrochromeno[2,3-*b*]pyridine-3-carbonitrile **95** [65]. Thieno[2,3-*b*]pyridine **97**, has antimicrobial activity, was prepared by reaction of **1** with 2-amino-cycloalkane[*b*]thiophene-3-carbonitrile **96** [4,5]. 4-Amino-3-[(1,3-dioxoisoindolin-2-yl)methyl]-6-phenylthieno[2,3-*b*]pyridine-5-carbonitrile **58**, as antibiotic agents, was obtained from reaction of **1** with 2-amino-4-((1,3-dioxoisoindolin-2-yl)methyl)thiophene-3-carbonitrile **98** in ethanol under reflux in the presence of piperdine (Scheme **24**) [1].

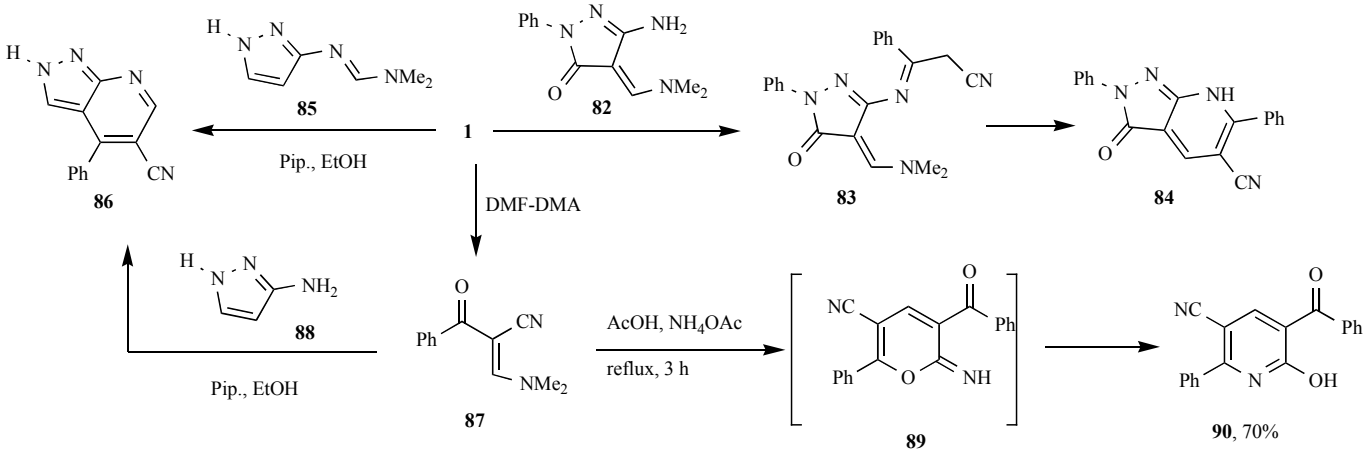
1,6-Diamino-3,5-dicyano-4-aryl-2-pyridone **100** was reacted regioselectively with **1** to give 1,8-naphthyridine **101** in 67% yield [66]. Ethyl 5-amino-1-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)-3-(methylthio)-1*H*-pyrazole-4-carboxylate **102** was reacted with **1** in ethanol containing sodium ethoxide to afford substituted pyrazolo[3,4-*b*]pyridine-5-carbonitrile **103** in 68% yield (Scheme **25**) [67].

3.6. One-pot three Component Reactions

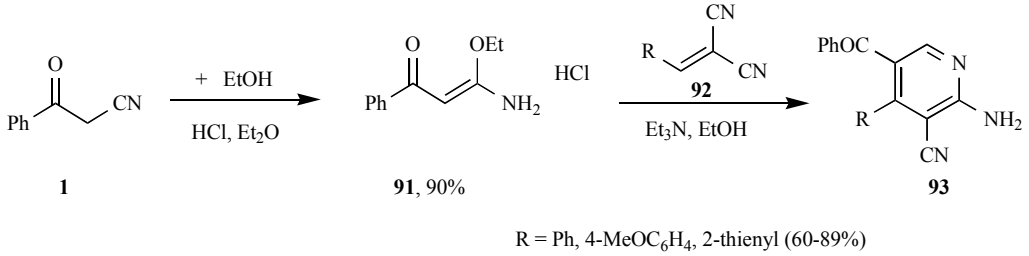
One pot three component reaction of **1**, 4-methoxybenzaldehyde, and thiourea led to tetrahydropyrimidine-2(1*H*)-thione



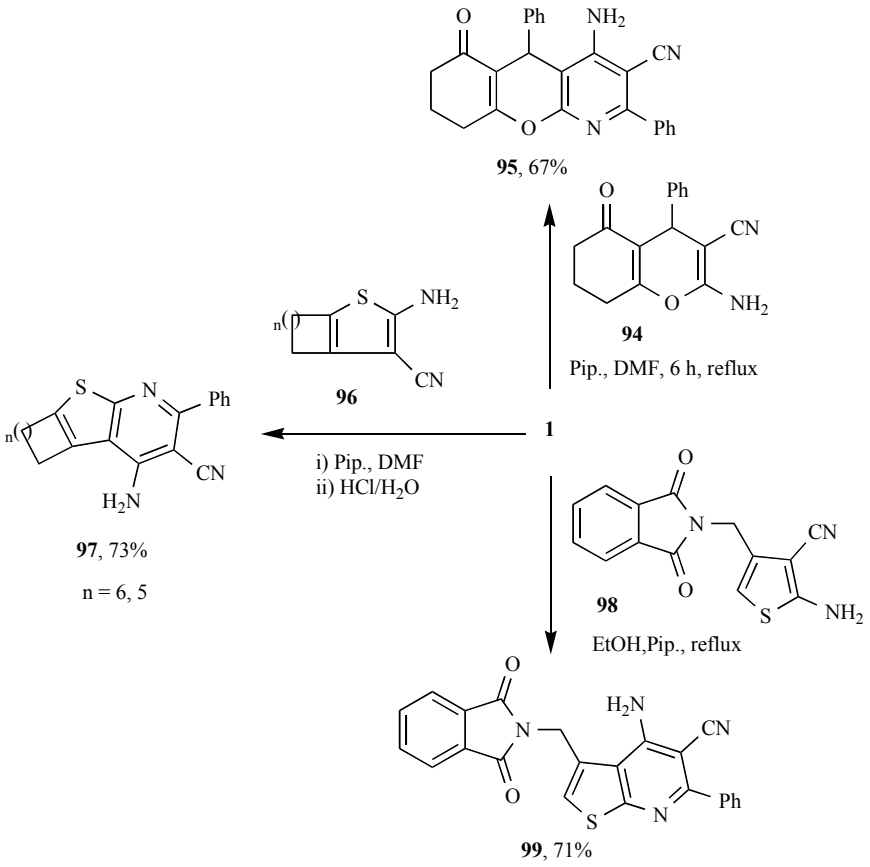
Scheme 21.



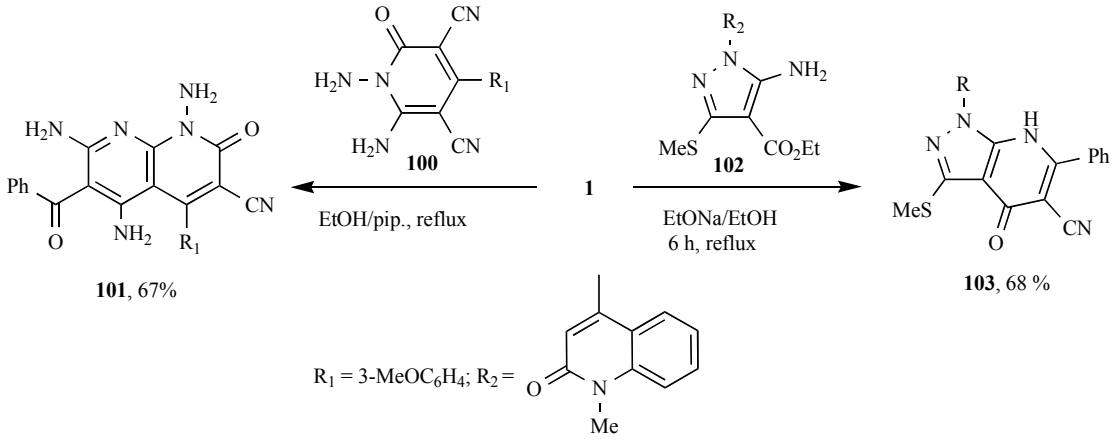
Scheme 22.



Scheme 23.



Scheme 24.



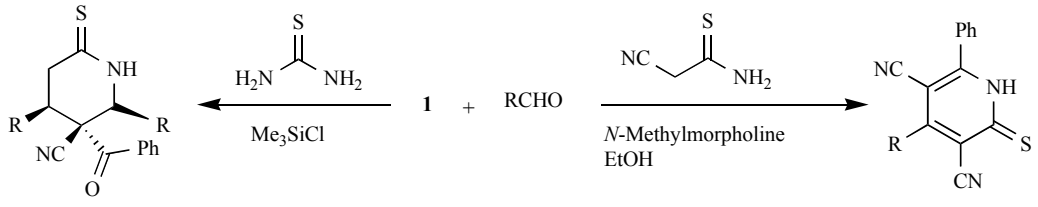
Scheme 25.

104 in 92% yield [68]. Similarly one-pot three component cyclocondensation reaction of compound **1**, cyanothioacetamide, and 4-methylpentanal in ethanol in the presence of *N*-methylmorpholine yielded pyridine-2(1*H*)-thione **105** (Scheme **26**) [69].

4,7-Dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles **107** were synthesized from one pot reaction of compound **1**, 3-methyl-1*H*-pyrazol-5(4*H*)-one **106**, and aromatic aldehyde in ethanol under reflux in the presence of ammonium acetate [4]. The synthesis of pyrazolo[3,4-*b*]pyridine-5-carbonitriles **109** in one-step by three-component cyclocondensation reaction of compound **1**, 5-aminopyrazolone **108**, and aromatic aldehydes in either ethanol under reflux or by microwave radiation in dry media (Scheme **27**) [70].

In a solvent-free system, regiospecific three-component one-step cyclocondensation to yield 4-oxo-7-phenyl-1,4,5,8-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitriles **111** starting from readily available aminopyrimidin-4(3*H*)-ones **110**, **1**, and aromatic or aliphatic aldehydes by microwave radiation in 75-91% yield [71-73]. A series of hexahydroquinoline derivatives **113** were synthesized by the three-component reaction of compound **1**; 5,5-dimethyl-3-aminocyclohex-2-enone **112**; aromatic aldehyde in ionic liquid without using any catalyst. This protocol has the advantages of easier work-up, milder reaction conditions, high yields, and environmentally benign procedure (Scheme **28**) [74].

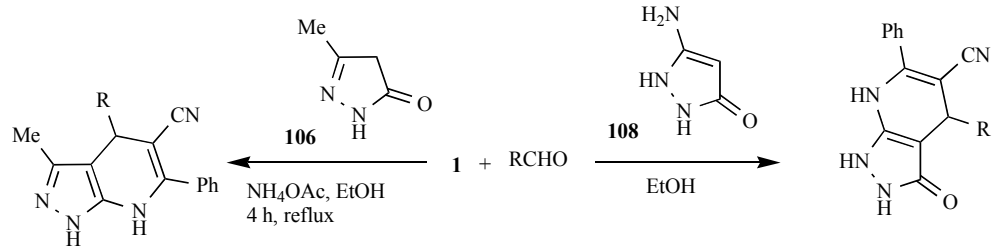
Compound **1** was reacted with formaldehyde, and enaminonitrile **114** in boiling ethanol containing catalytic amounts of triethy-



104, R = 4-$MeOC_6H_4$ (92%)

105, R = isopentyl (66%)

Scheme 26.

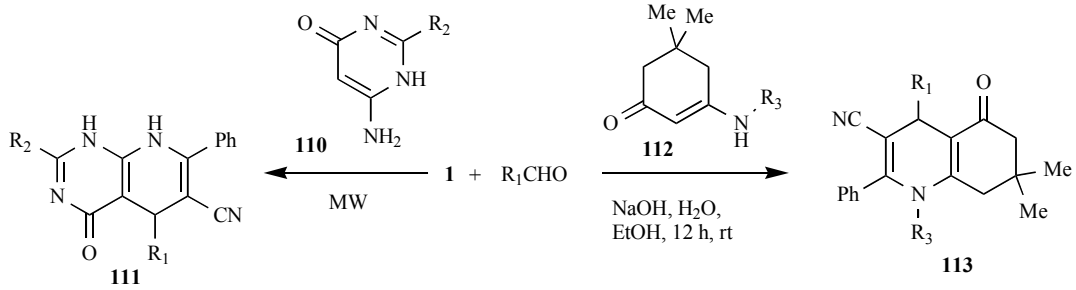


107, R = 4-$O_2NC_6H_4$ (76%)
R = 4-$(MeN)_2C_6H_4$ (49%)

109

R = C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$

Scheme 27.



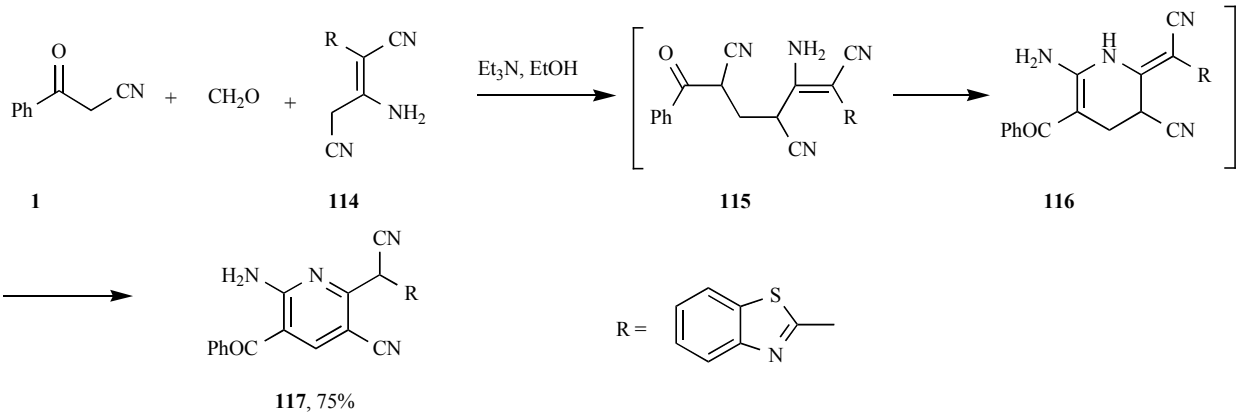
111

R_1 = Ph; R_2 = OMe (75%)
R_1 = 4-ClC_6H_4; R_2 = OMe (78%)
R_1 = Aromatic or aliphatic; R_2 = NH_2 (~ 91%)

113

R_1 = R_3 = 4-MeC_6H_4 (90%)
R_1 = 4-MeC_6H_4, R_3 = 2-$O_2NC_6H_4$ (95%)

Scheme 28.



1 **114** **115** **116**

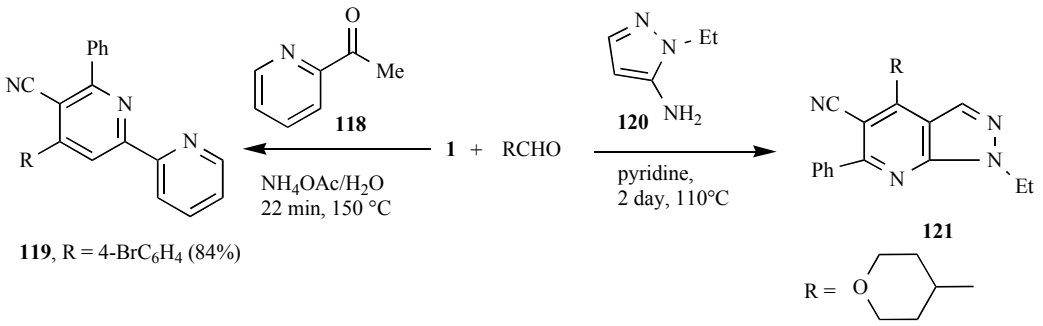
117, 75%

Scheme 29.

lamine to give 6-amino-2-(benzo[d]thiazol-2-yl(cyano)methyl)-5-benzoylnicotinonitrile **117** *via* intermediates **115** and **116** (Scheme **29**) [75].

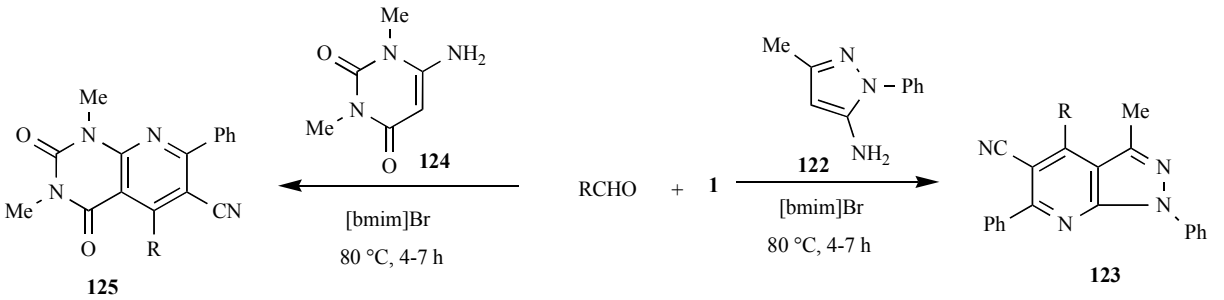
The regiospecific synthesis of 2,2'-bipyridine derivative **119** in high-temperature water *via* microwave-assisted multicomponent reactions of compound **1**, 2-acetylpyridine **118**, and 4-bromobenzaldehyde in the presence of ammonium acetate was reported [76]. Three-component cyclocondensation reaction of **1**, tetrahydro-2*H*-pyran-4-carbaldehyde, and 1-ethyl-1*H*-pyrazol-5-amine **120** led to pyrazolopyridine **121**, which act as inhibitors of phosphodiesterase-4 (PDE-IV) (Scheme **30**) [77].

Also, one-pot three-component synthesis of pyrazolo[3,4-*b*]pyridines **123** and pyrido[2,3-*d*]pyrimidines **125** have been achieved by reaction of **1**, aldehydes, and aminopyrazole **122** or aminouracil **124** in ionic liquid solvent (Scheme **31**) [78].



119, R = 4-BrC_6H_4 (84%)

Scheme 30.



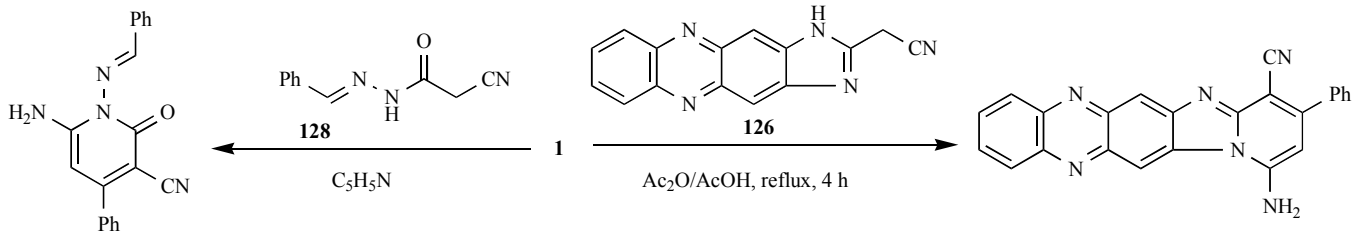
125

R = 3-pyridenyl (85%); 2-thienyl (90%); 3,4-$(OMe)_2C_6H_3$ (92%); 3-ClC_6H_4 (98%); 4-BrC_6H_4 (98%); 4-$OMeC_6H_4$ (94%); 3,4-$OCH_2OC_6H_3$ (90%)

123

R = Pr (90%); Et (98%); 3-pyridenyl (83%); 2-thienyl (95%); 4-$Me_2NC_6H_4$ (96%); 2,4-$O_2NClC_6H_3$ (91%); 3,4-$(OMe)_2C_6H_3$ (92%); 2-$O_2NC_6H_4$ (92%); 3-ClC_6H_4 (98%); 2-ClC_6H_4 (82%); 2-HOC_6H_4 (98%); 4-BrC_6H_4 (95%); 4-OHC_6H_4 (98%); 3,4-$OCH_2OC_6H_3$ (94%)

Scheme 31.



129, 65%

127, 81%

Scheme 32.

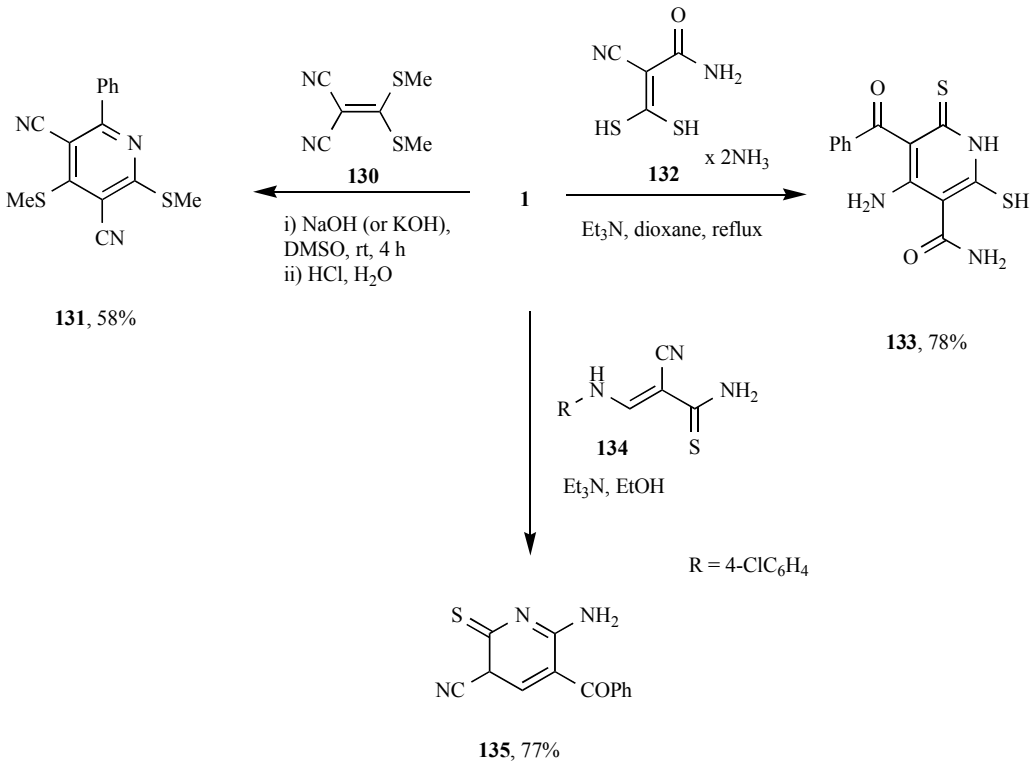
3.7. Miscellaneous Methods

Pyrido-imidazophenazine **127** was prepared by reaction of **1** with 2-(1*H*-imidazo[4,5-*b*]phenazin-2-yl)acetonitrile **126** [79]. Similarly, 6-amino-1-(benzylideneamino)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile **129** was obtained from reaction of **1** with *N*′-benzylidene-2-cyanoacetohydrazide **128** in pyridine under reflux (Scheme **32**) [80].

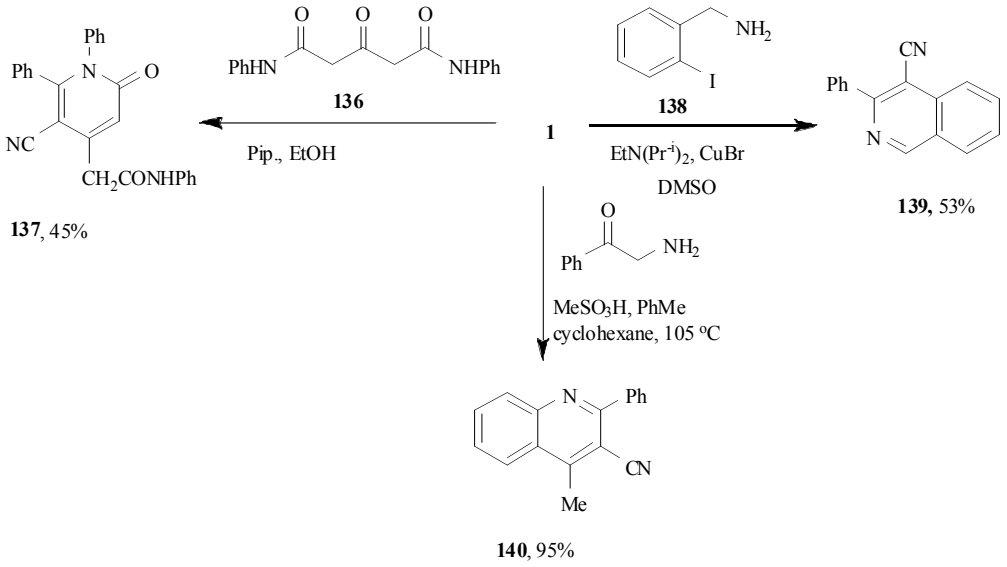
Polysubstituted pyridine **131** was synthesized by the reaction of ketene dithioacetal **130** with **1** in DMSO in the presence of either sodium hydroxide or potassium hydroxide as a base [81]. 2-Cyano-3,3-dimercaptoacrylamide **132** was reacted with **1** in dioxane in the presence of triethylamine to give 6-thioxo-1,6-dihydropyridine-3-carboxamide derivative **133** [82]. 6-Amino-5-benzoyl-2-thioxo-2,3-dihydropyridine-3-carbonitrile **135** was prepared from reaction of **1** with 3-(4-chlorophenylamino)-2-cyanoprop-2-enethioamide **134** in ethanol in the presence of triethylamine (Scheme **33**) [83].

3-Oxo-N^1,N^5-diphenylpentanediamide **136** was reacted with **1** in ethanol in the presence of piperidine to afford 2-(5-cyano-2-oxo-1,6-diphenyl-1,2-dihydropyridin-4-yl)-*N*-phenylacetamide **137** [84]. 3-Phenylisoquinoline-4-carbonitrile **139** was synthesized at room temperature by reaction of compound **1** with (2-iodophenyl)methanamine **138** in DMSO in the presence of copper(I) bromide and tertiary amine [85]. Cyclocondensation reaction of compound **1**, 2-aminoacetophenone, and methanesulfonic acid in a stirred mixture of toluene and cyclohexane then heated to 105 °C with removal of water to prepare 2-phenyl-4-methylquinoline-3-carbonitrile **140** [86] (Scheme **34**).

Reactions of 2-[(trimethylsilyl)ethynyl]aniline **141** with **1** promoted by *p*-toluenesulfonic acid afforded 4-methyl-2-phenylquinoline-3-carbonitrile **142** in good yield [87]. Naturally occurring secondary amines, (4a*R*,5*R*)-5-benzoyl-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinoline-5-carbonitrile **144** and (4a*R*,5*S*)-5-benzoyl-



Scheme 33.



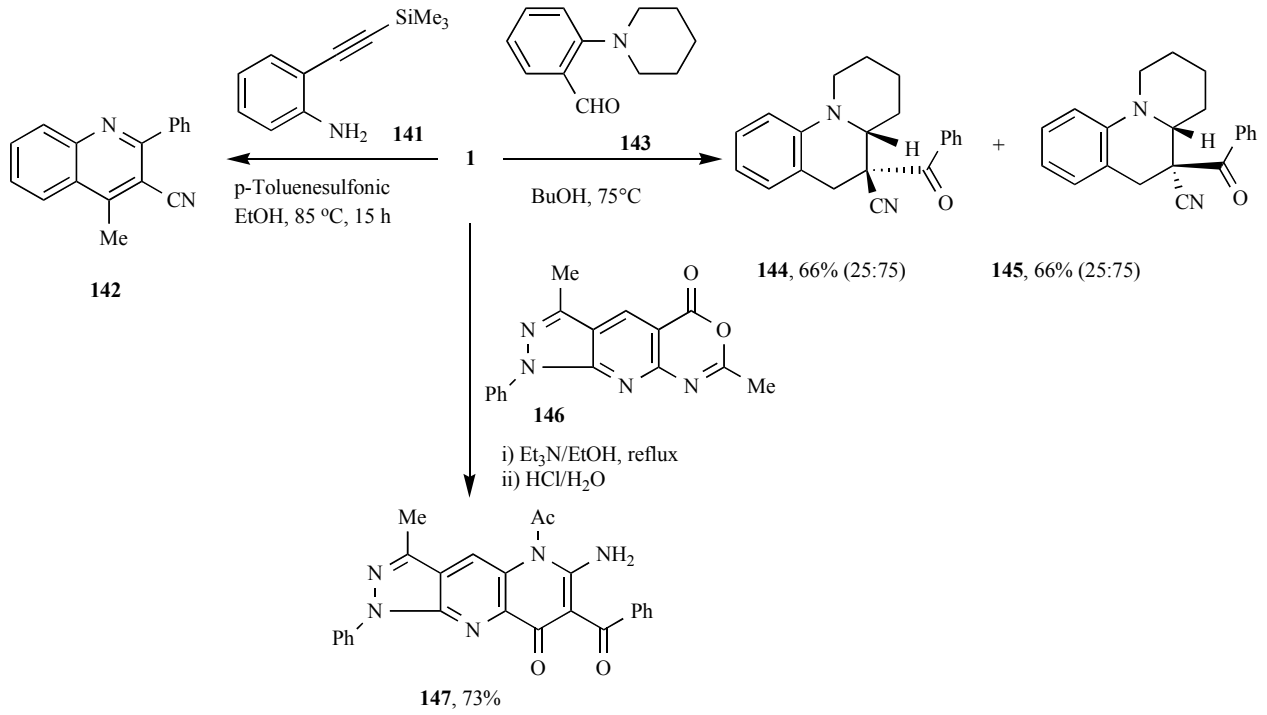
Scheme 34.

2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinoline-5-carbonitrile **145**, were prepared in 66% with relative stereochemistry by reaction of **1** with 2-(piperidin-1-yl)benzaldehyde **143** [88]. 1-Phenyl-1*H*-pyrazolo[3,4-*b*][1,5]naphthyridin-8(5*H*)-one **147** was obtained, in 73% yield, by reaction of compound **1** with oxazinone **146** [89] (Scheme **35**).

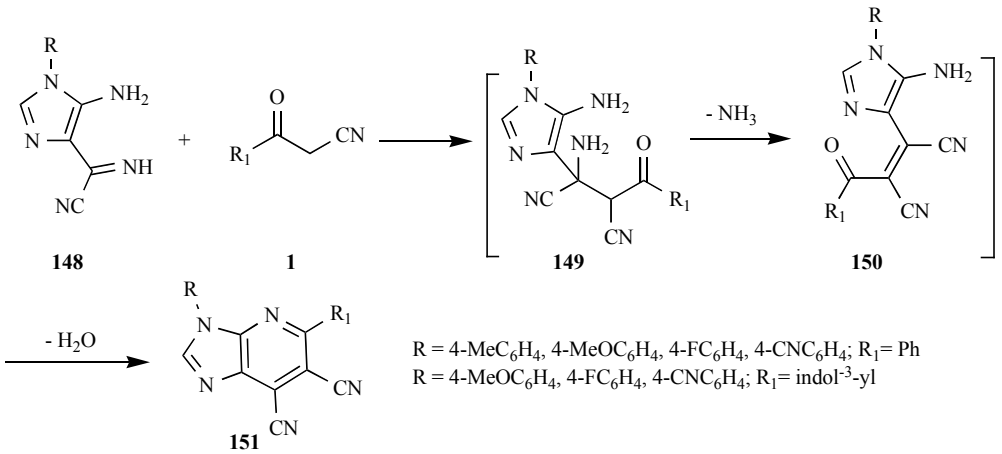
Imidazo[4,5-*b*]pyridines **151** were isolated in good yield from reaction of *N*-aryl-5-amino-4-(cyanoformimidoyl)-imidazoles **148** with **1**, in ethanol/acetonitrile or ethanol/DMF. The reaction must proceed through the formation of intermediate **150**, generated from adduct **149** by elimination of ammonia. Nucleophilic attack of the amino group in the 5-position to the acyl substituent was the only observed pathway, leading to the imidazo[4,5-*b*]pyridine **151** (Scheme **36**) [90].

CONCLUSIONS

Benzoylacetonitriles are easily available and have high chemical reactivity due to the presence of three active moieties nitrile, carbonyl, and active methylene functions. This survey is attempted to summarize the synthetic methods and synthetic potential of ben-



Scheme 35.



Scheme 36.

zoylacetonitriles, as starting precursor, in the synthesis of pyridine derivatives since 1985. We will publish the literature survey of the synthetic potential of benzoacetonitriles in the synthesis of pyrans, pyridazines, pyrimidines, pyrazines and triazine as a separate reviews article in the near future.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

Declared none.

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