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ORIGINAL PAPER

Production of pyrans, pyridazines, pyrimidines, pyrazines and triazine compounds using benzoylacetonitriles as a precursor

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Abstract Benzoylacetonitriles are easily available and have high chemical reactivity due to the presence of three active moieties; nitrile, carbonyl, and active methylene functions. This review article represents a survey covering the synthetic strategies leading to five six-membered heterocycles; pyrans, pyridazines, pyrimidines, pyrazines, and triazine compounds; utilizing benzoylacetonitriles as starting precursor since 1985. The reactions are subdivided into groups that cover the synthetic methods of these heterocycles.

Keywords Benzoylacetonitrile · Pyrans · Pyridazines · Pyrimidines · Triazines

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Introduction

Benzoylacetonitrile, known as phenacylcyanide or ω-cyanoacetophenone, 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, especially, six-membered heterocyclic compounds possessing diverse biological activities and many other practically useful properties, e.g. antimicrobial [1–5], photochemotherapic [6], antimalarial [7], anti-inflammatory [8], anti-HIV agents [9], anticancer agents [10], anti-*T. cruzi* activity [11], anti-HCV, antioxidant, and peroxynitrite inhibitory activity [12]; and as electron-transporting layer [13, 14]. Despite this versatile importance, and in connection to our previous review articles [15–19], benzoylacetonitrile have not been previously reviewed. The present review aims to demonstrate the synthetic potential of benzoylacetonitrile in the synthesis of pyrans, pyridazines, pyrazines and triazine compounds in the period from 1985 till now. The synthetic methods of benzoylacetonitriles and its utility in synthesis of pyridine derivatives were mentioned previously [18].

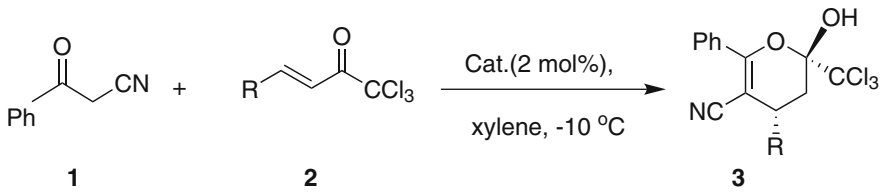
Pyrans and their fused derivatives

Michael addition reaction

The enantioselective Michael addition of **1** to α,β-unsaturated trichloromethyl ketones **2** was reported with a phenylalanine-derived bifunctional piperazine/thiourea catalyst, a series of α-trichloromethyldihydropyrans **3** were obtained with excellent yields (Scheme 1) [20].

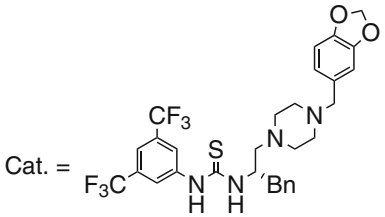
Similarly, enantioselective Michael addition of **1** to (*E*)-1,1,1-trifluoro-4-arylbut-3-en-2-one **4a,b** gave (2*S*,4*R*)-2-hydroxy-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-5-

Scheme 1 .



1 **2** **3**

R = Ph (94%); 4-FC$_6$H$_4$ (92%); 4-ClC$_6$H$_4$ (95%); 4-BrC$_6$H$_4$ (99%); 4-O$_2$NC$_6$H$_4$ (98%) ; 4-MeC$_6$H$_4$ (93%); 2-ClC$_6$H$_4$(98%); 3-ClC$_6$H$_4$(99%); 2,4-diClC$_6$H$_3$(97%); 1-naphthyl (97%); 2-furanyl (87%)



carbonitriles **5a,b** in 71–95 % yield (Scheme 2) [21, 22]. The structure of compound **5b** was established by the X-ray diffraction analyses.

In a similar fashion, an asymmetric Michael addition of **1** to β,γ-unsaturated α-keto ester to form chiral dihydropyrans was reported. Thus Michael addition of **1** to (*E*)-methyl 2-oxo-4-phenylbut-3-enoate **6** led to (2*S*,4*R*)-methyl 5-cyano-2-hydroxy-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-carboxylate **7** in 95 % yield (Scheme 3) [23].

The DABCO(1,4-diazabicyclo[2.2.2]octane)-catalyzed (3 + 3) annulations of **1** with 2-(acetoxymethyl)buta-2,3-dienoate **8** smoothly proceeded to construct benzyl 5-cyano-2-methyl-6-phenyl-4H-pyran-3-carboxylate **9** in excellent yields (Scheme 4) [24].

Three-component one pot reaction of compound **1**, 3-acetyl-1-ethyl-4-hydroxyquinolin-2(1*H*)-one **10**, and formaldehyde yielded 2-amino-3-benzoyl-6-ethyl-4*H*-pyrano[3,2-*c*]quinolin-5(6*H*)-one **11** in 80 % yield [25]. Similarly, 6-amino-5-(2,3-dihydrobenzo[*d*]thiazol-2-yl)-2-phenyl-4*H*-pyran-3-carbonitrile **12** was prepared by three-component one pot reaction of compound **1**, 2-cyanomethylbenzothiazole and, formaldehyde in refluxed ethanol containing triethylamine as catalyst [26]. 3-Methyl-6-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile **13** was synthesized via three-component one pot reaction of compound **1**; 2,5-dimethoxybenzaldehyde; and 3-methyl-1*H*-pyrazol-5(4*H*)-one in refluxed ethanol containing piperidine as catalyst (Scheme 5) [10].

Treatment of **1** with 2-[(3-oxo-3,4-dihydroquinoxalin-2-yl)methylene]malononitrile **14** gave 2-amino-4-(3-oxo-3,4-dihydroquinoxalin-2-yl)-6-phenyl-4*H*-pyran-3,5-dicarbonitrile **15** in 79 % yield (Scheme 6) [27].

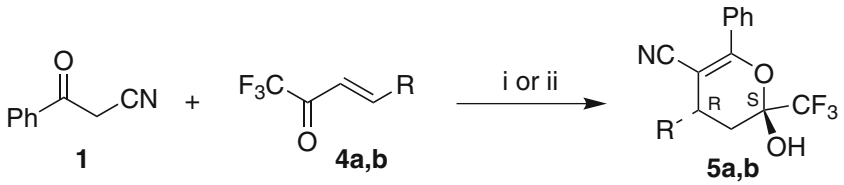
Benzylidenemalononitrile **16** was reacted with **1** in refluxed ethanol in the presence of piperidine to yield 2-amino-4,6-diphenyl-4*H*-pyran-3,5-dicarbonitrile **17** (Scheme 7) [28].

Pyrano[2,3-*c*]pyrazole-5-carbonitrile **19** was obtained from Michael addition cyclocondensation of **1** to 4-(furan-2-ylmethylene)-3-methyl-1*H*-pyrazol-5(4*H*)-one **18** in refluxed ethanol in the presence of piperidine (Scheme 8) [29].

Michael addition of compound **1** to 2,6-di(m-nitrophenylmethylene)cyclohexanone **20** followed by 6-exo-dig cyclization furnished (2-amino-8-(3-nitrobenzylidene)-4-(3-nitrophenyl)-5,6,7,8-tetrahydro-4*H*-chromen-3-yl)(phenyl)methanone **21** in 73 % yield (Scheme 9) [9].

The asymmetric Michael addition of **1** to α-cyanocinnamate **22** gave (*R*) **23** and (*S*) 2-amino-5-cyano-4,6-diphenyl-4*H*-pyran-3-carboxylate **24** in moderate diastereomeric mixture and good yield (Scheme 10) [30].

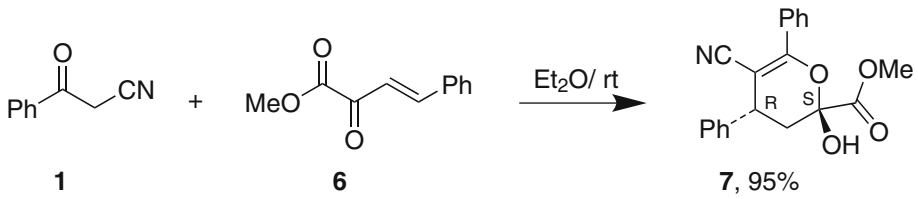
Scheme 2 .



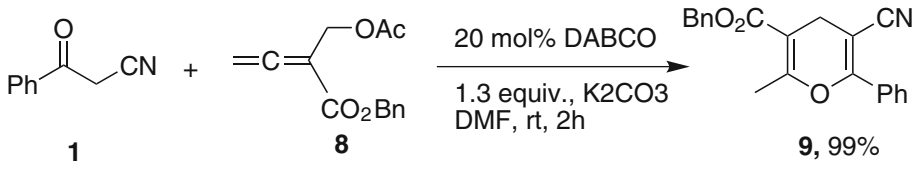
1 **4a,b** **5a,b**

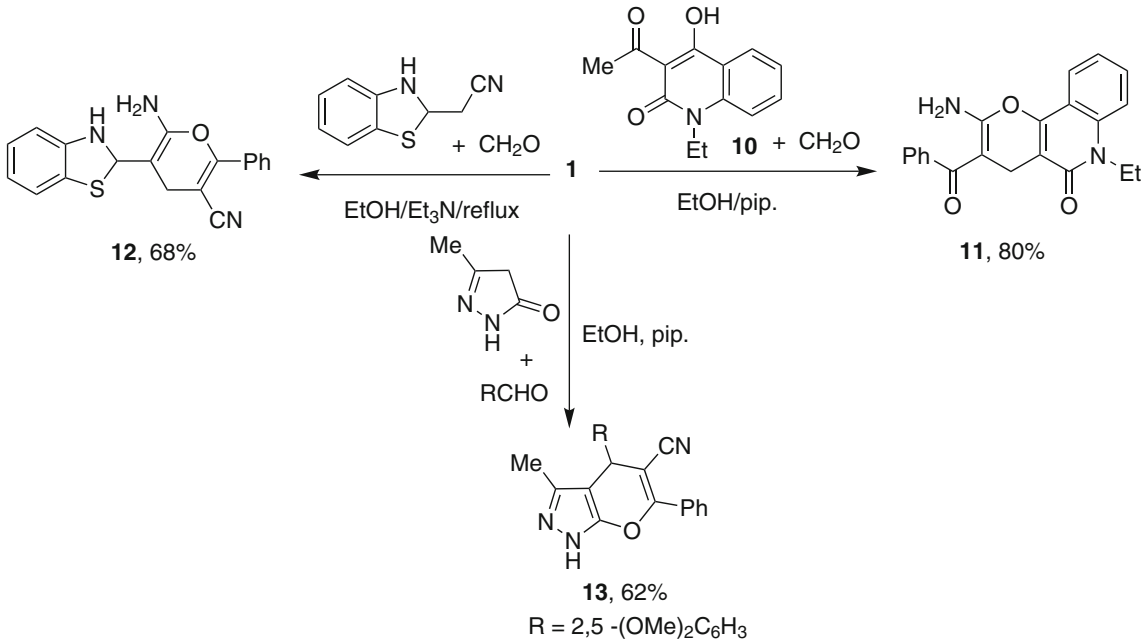
a, R = Ph (71%); i, $CHCl_3$/rt
b, R = 4-MeC$_6$H$_4$ (95%); ii, KF/Me_2CHOH/rt

Scheme 3 .



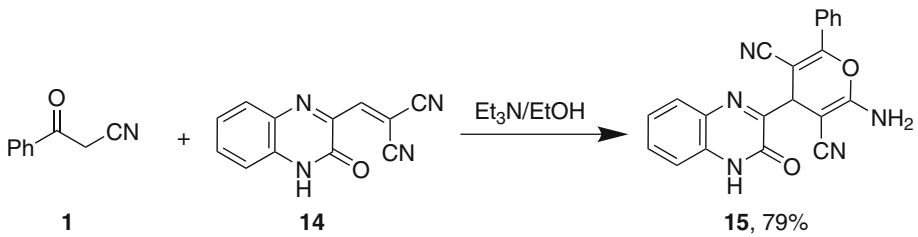
Scheme 4 .



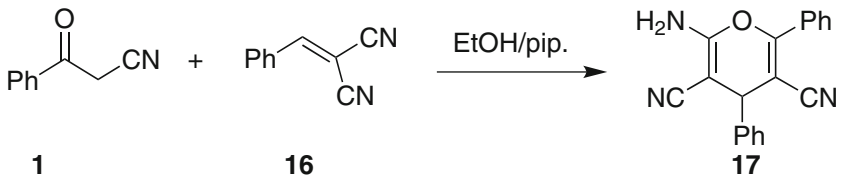


Scheme 5 .

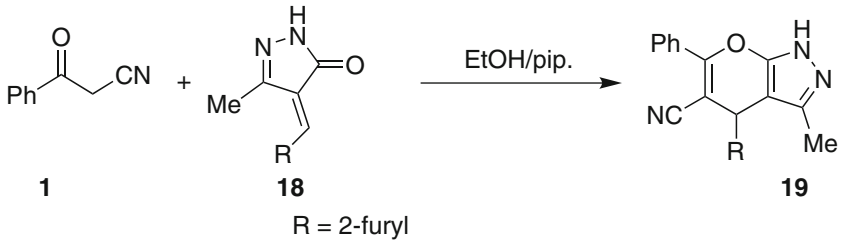
Scheme 6 .



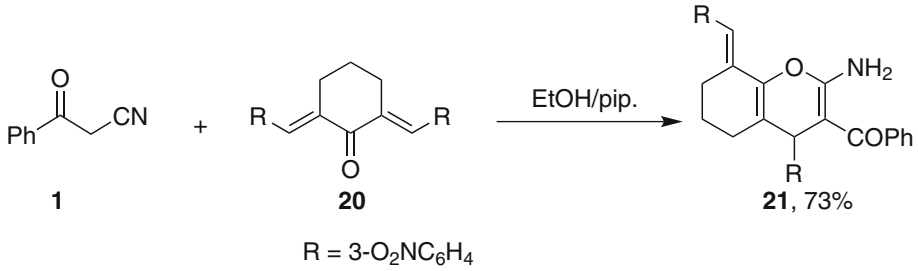
Scheme 7 .

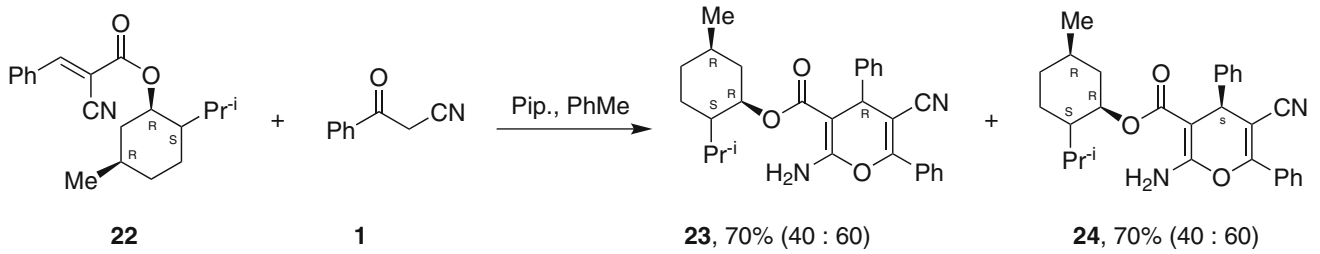


Scheme 8 .



Scheme 9 .





Scheme 10 .

4-(2-Oxo-1,2-dihydroquinolin-3-yl)-2,6-diphenyl-4*H*-pyran-3,5-dicarbonitrile **26** was synthesized via Knoevenagel reaction between **1** and 2-chloroquinoline-3-carbaldehyde **25** followed by Michael addition of second molecule of **1** and cyclization. The structure of compound **26** was confirmed by the X-ray diffraction analyses (Scheme 11) [8].

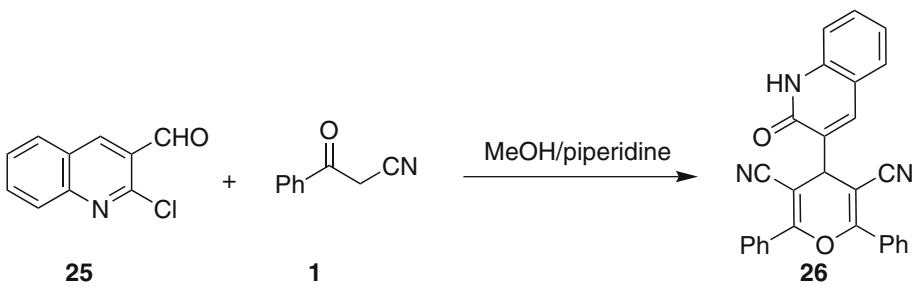
The mechanism of formation **26** probably takes place through a consecutive Michael addition of second molecule of compound **1**, to the initially formed α,β-unsaturated carbonyl compound **27** followed by cyclization and elimination of a molecule of H_2O and HCl to afford the target compounds **26** as describe in Scheme 12.

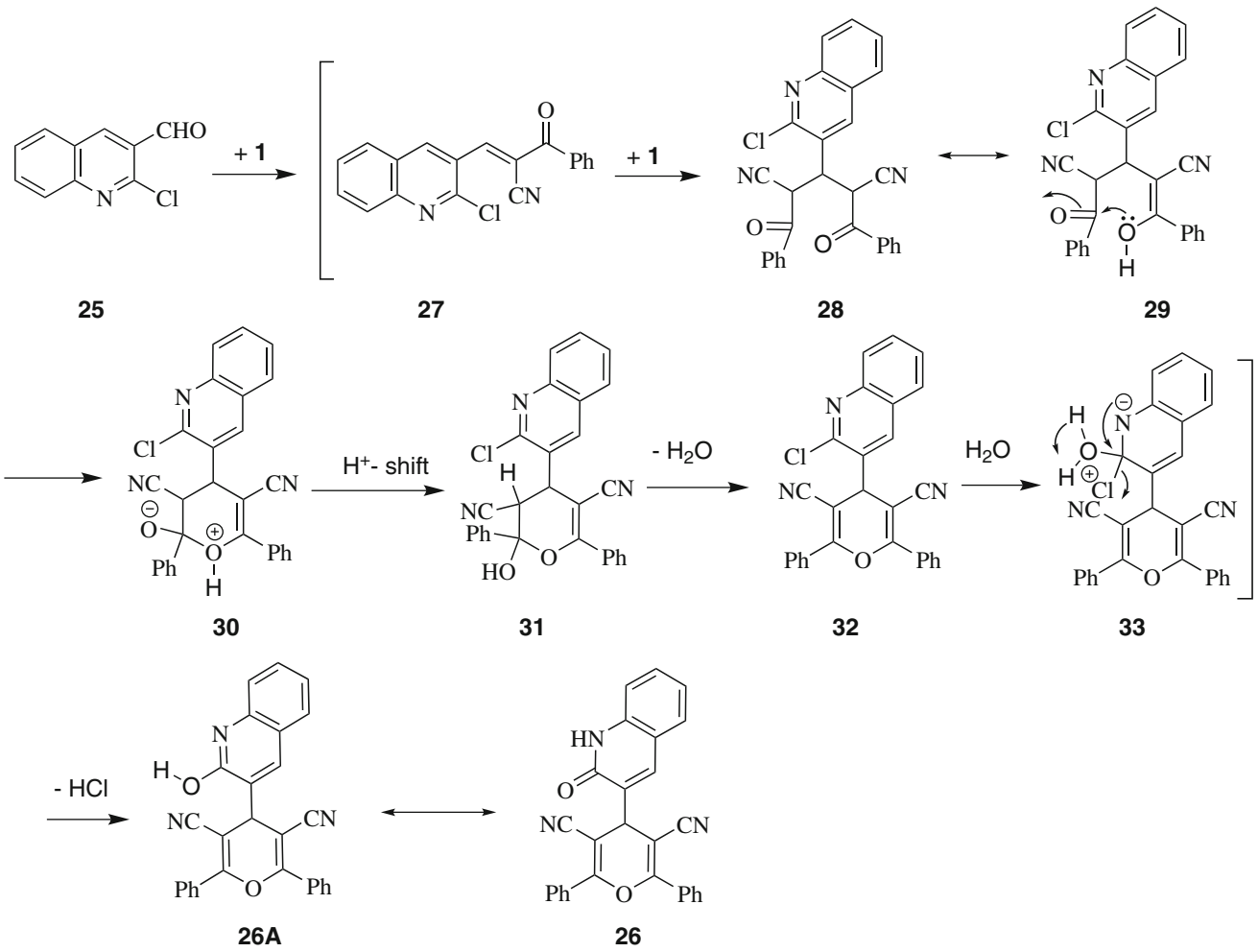
Cycloaddition reaction

Recently, enantioselective synthesis of substituted pyrans using compound **1** was reported. A variety of substituents compound, prepared from condensation of **1** and aldehyde, were well tolerated in *Cinchona*-based primary amine catalytic system, providing the substituted pyran adducts **35** in high yields, high diastereoselectivity (up to 9.0:1) and excellent enantioselectivities (up to 96 %) (Scheme 13) [31].

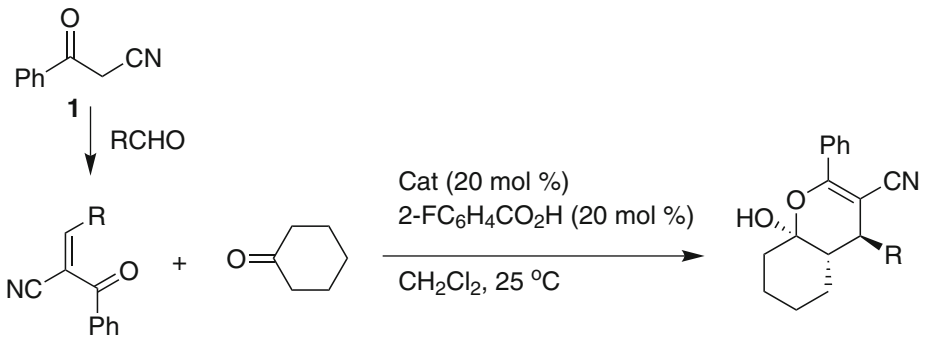
Catalyzed [4 + 2] annulation between activated terminal alkynes and oxo-dienes intermediated using triphenylphosphine catalyst (20 mol %) was reported. Thus, Diels–

Scheme 11 .





Scheme 12 .



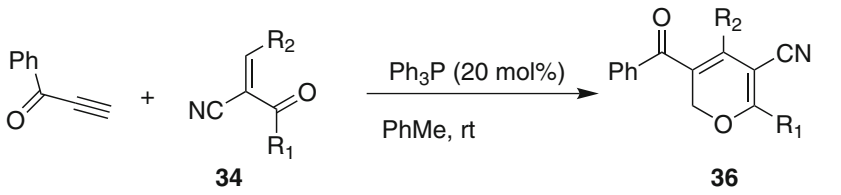
R = 4-CNC_6H_4 (90%), 4-BrC_6H_4 (84%), 4-$NO_2C_6H_4$ (77%), 4-ClC_6H_4 (85%), 3-$NO_2C_6H_4$ (79%), C_6H_5 (78 %), 4-MeC_6H_4 (81%), 4-$OMeC_6H_4$ (78%), 2-furyl (88%), 2-thienyl (85%), 2-naphthyl (82%)

Scheme 13 .

Alder reaction between 1-phenylprop-2-yn-1-one **34** and 1-phenylprop-2-yn-1-one gave the corresponding highly functionalized dihydropyrans **36** in good to excellent yields (Scheme 14) [32].

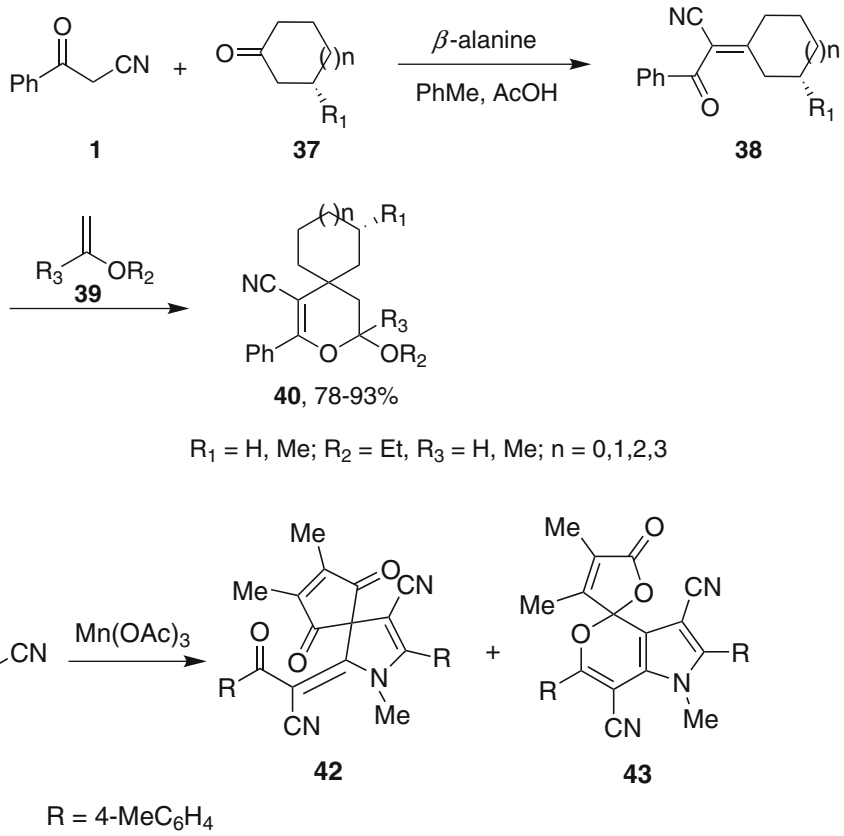
Knoevenagel condensation of compound **1** with appropriate cycloalkanone **37** in refluxing toluene or xylene for 4–6 h in the presence of β-alanine and acetic acid as catalyst gave 2-cycloalkylidene-3-oxo-3-phenylpropionitriles

Scheme 14 .



R_1= R_2 = Ph (88%); R_1 = Ph, R_2 = 2-furanyl (99%)
R_1 = Ph, R_2 = 4-BrC_6H_4 (99%); R_1 = Ph, R_2 = 4-MeOC_6H_4 (83%)
R_1 = Ph, R_2 = styrenyl (99%); R_1 = Ph, R_2 = 2-thienyl (90%)

Scheme 15 .



R_1 = H, Me; R_2 = Et, R_3 = H, Me; n = 0,1,2,3

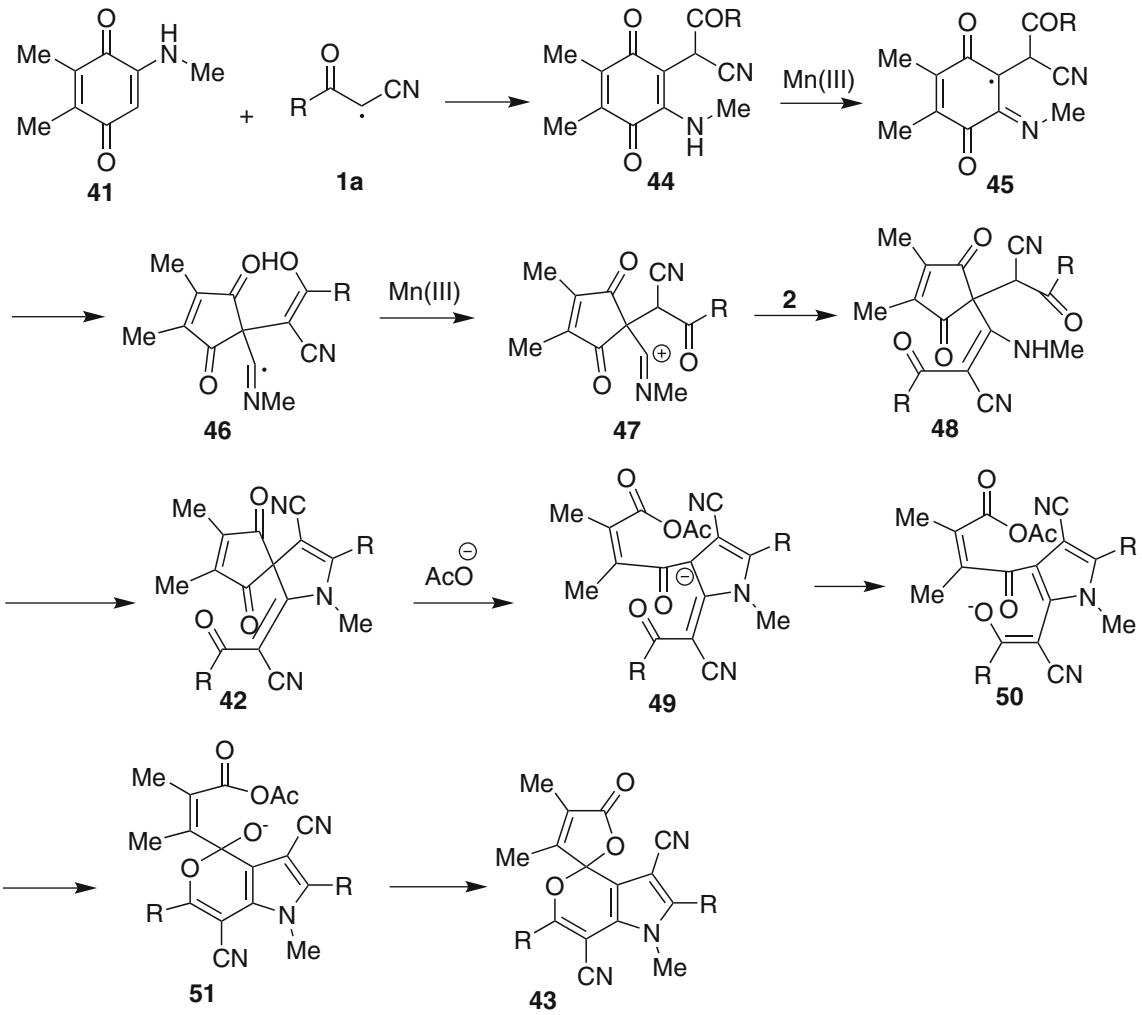
R = 4-MeC_6H_4

Scheme 16 .

38. The cycloaddition reaction of compound **38** with enol ethers **39** was performed in toluene solution at 110 °C for 24 h and the spiropyrans **40** were obtained in 78–93 % yields (Scheme 15) [33].

The manganese(III) initiated oxidative free radical reaction between 2-amino-1,4-benzoquinone **41** and **1** was reported. When 5,6-dimethyl-2-(methylamino)-1,4-benzoquinone **41** was treated with **1** and manganese(III) acetate in acetic acid at room temperature, a yellow product 1-(1-cyano-2-oxo-2-p-tolylethylidene)-2,7,8-trimethyl-6,9-dioxo-3-p-tolyl-2-azaspiro[4.4]nona-3,7-diene-4-carbonitrile **42** and 1′,3,4-trimethyl-5-oxo-2′,6′-dip-tolyl-1′*H*,5*H*-spiro[furan-2,4′-pyrano[4,3-*b*]pyrrole]-3′,7′-dicarbonitrile **43** were obtained in 55 % yield (Scheme 16) [34].

Initiation occurs with the manganese(III) acetate oxidation of **1** to produce radical **1a**. This radical intermediate undergoes intermolecular addition to quinone ring followed by oxidation to generate **44**, which was then oxidized by manganese(III) acetate to produce radical **45**. Radical **45** undergoes 1,2-carbonyl group migration followed by oxidation and intermolecular nucleophilic addition of another molecule of **1a** to give **46**, which then undergoes a further intramolecular condensation reaction to produce **42**. The solvent effects play an important role in the manganese(III) acetate initiated oxidative free radical reaction. Reaction between **1a** and **41** was next performed in other solvents. The change of solvent to benzene, 2,2,2-trifluoroethanol, and acetonitrile gave **42** as the only



Scheme 17 .

product. It gave best result (69 % yield) when acetonitrile was used as the solvent (Scheme 17) [34].

Reaction with 2-hydroxybenzaldehydes

Reaction of compound **1** with salicylaldehyde in isopropyl alcohol in the presence of piperidine afforded 3-benzoyl-2-iminocoumarin **52**. Treatment of the latter compound with HCl/EtOH gave the 3-benzoylcoumarins **53** (Scheme 18) [35, 36]. The cyclocondensation reaction of 7-hydroxy-5-methoxy-2-methyl-4-oxo-4*H*-chromene-6-carbaldehydes **54** with compound **1** in ethanol in the presence of piperidine yielded 7-benzoyl-8-imino-5-methoxy-2-methylpyrano[3,2-*g*]chromen-4(8*H*)-ones **55** (Scheme 18) [38, 39].

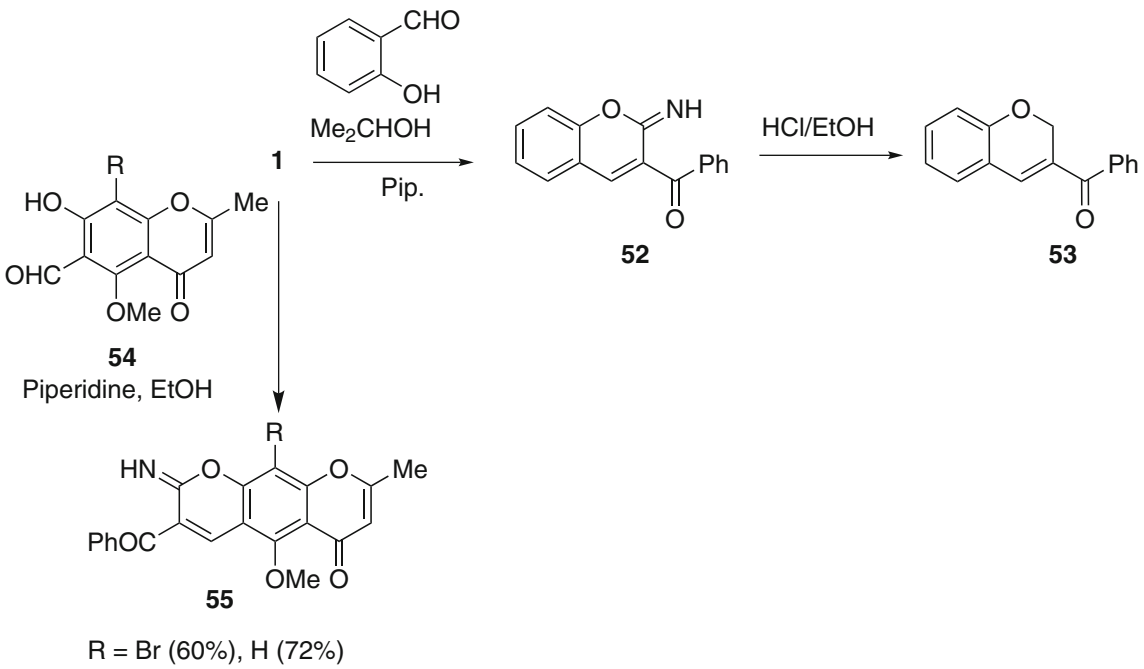
The reaction of 2-(allyloxy)benzaldehyde or 2-(allyloxy)-1-naphthaldehyde **56** with compound **1** carried out at room temperature gave rise to the formation of the Knoevenagel aduct **57** in good yield. The intramolecular hetero-Diels–Alder cycloaddition of **57** was accomplished in boiling xylene and afforded 3-phenyl-tetrahydropyrano[3,4-*c*]pyran-4-carbonitriles **58** in good yield (Scheme 19) [40].

A new strategy involving domino Knoevenagel hetero-Diels–Alder reaction is described for the preparation of the pyrano[3,4-*c*]chromene scaffold. Thus, reaction of 2-(prop-2-ynyloxy)benzaldehyde **59** with compound **1** in the presence of CuI and $(NH_4)_2HPO_4$ afforded pyrano[3,4-*c*]chromenes **61**, via intermediate **60**, with good yields (Scheme 20) [41].

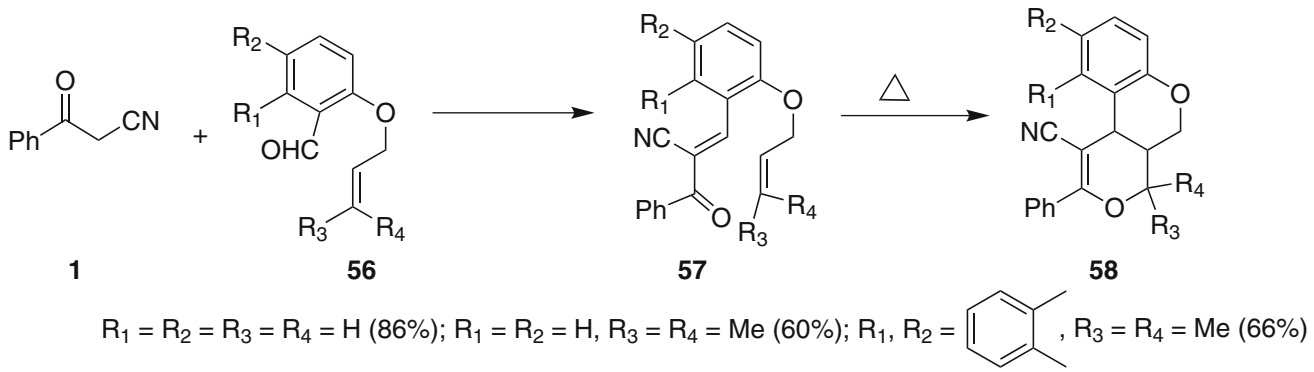
The condensation reaction of ethyl 3-ethoxy-3-imino-propanoate hydrochloride **62** with **1** gave ethyl 3-amino-4-cyano-5-oxo-5-phenylpent-3-enoate **63**. Then the latter compound was reacted with salicylaldehyde to afford 3-amino-2-benzoyl-3-(2-oxo-2*H*-chromen-3-yl)acrylonitrile **64** in 85 % yield (Scheme 21) [42].

Reaction with enaminones

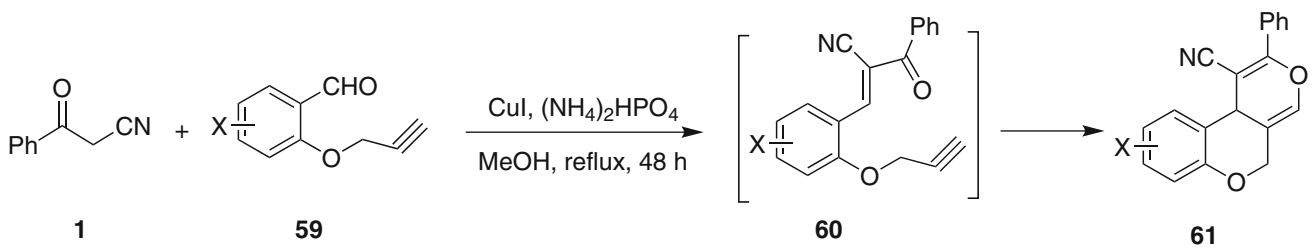
2-Dimethylaminomethylene-3-(phenylhydrazono)-indan-1-one **65** was allowed to react with compound **1** to afford



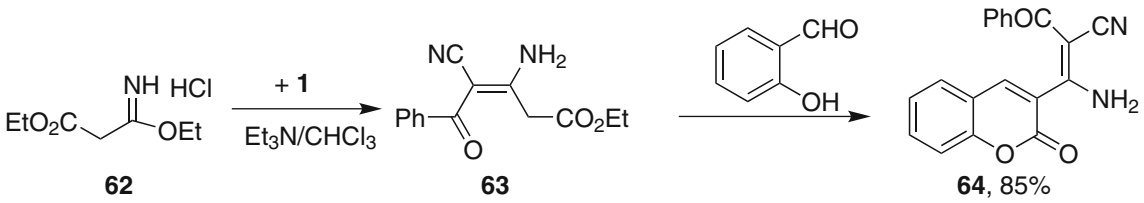
Scheme 18 .



Scheme 19 .

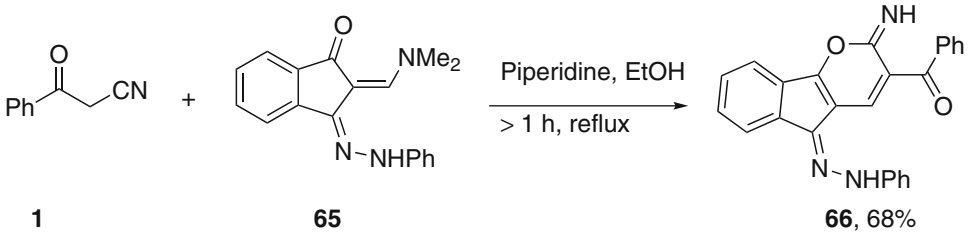


Scheme 20 .

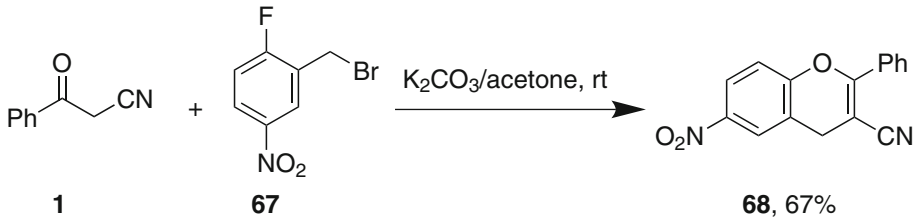


Scheme 21 .

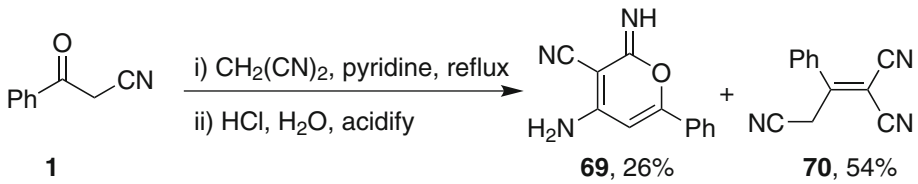
Scheme 22 .

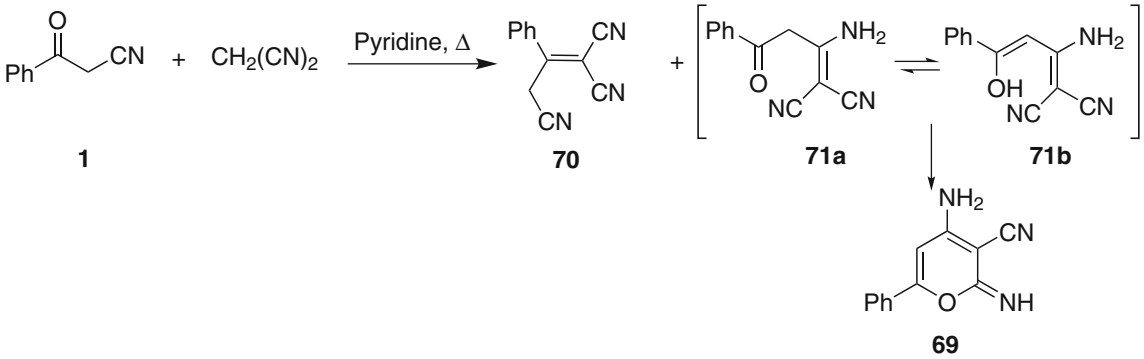


Scheme 23 .



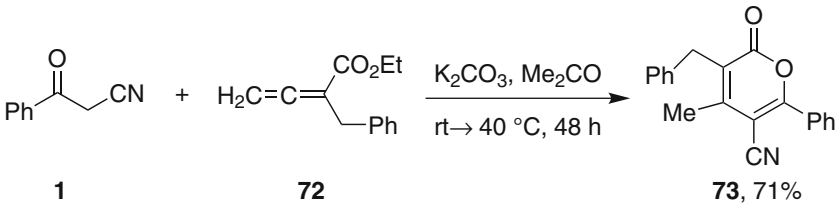
Scheme 24 .



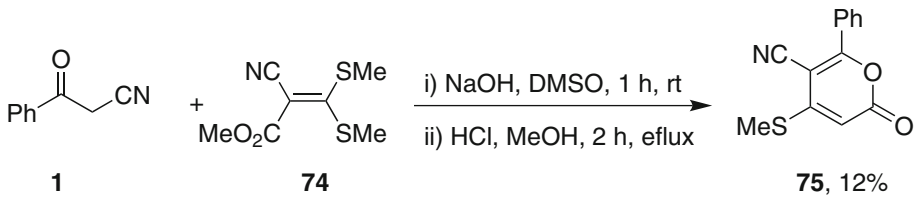


Scheme 25 .

Scheme 26 .

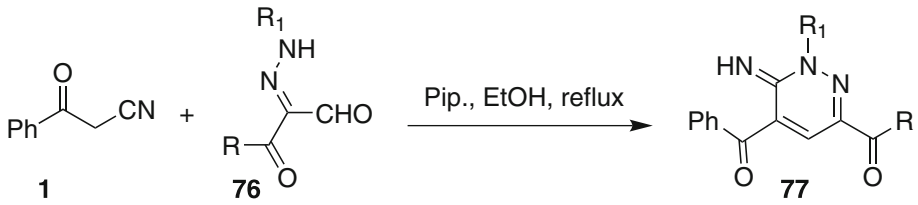


Scheme 27 .



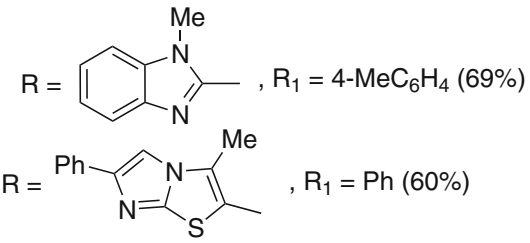
1 **74** **75**, 12%

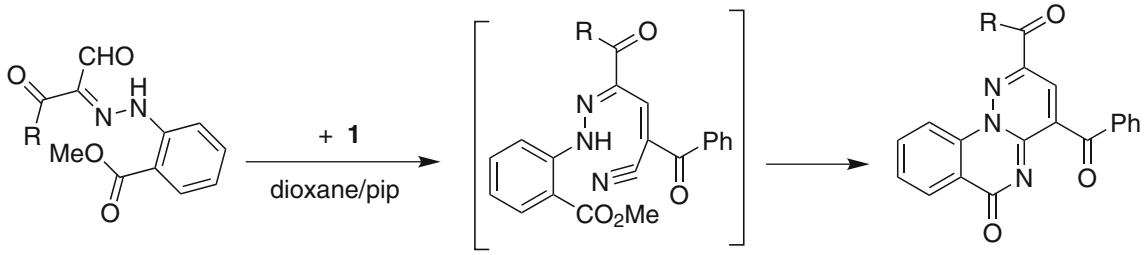
Scheme 28 .



1 **76** **77**

R = 2-thienyl, R_1 = Ph (78%); R = R_1 = 4-MeC_6H_4 (89%)



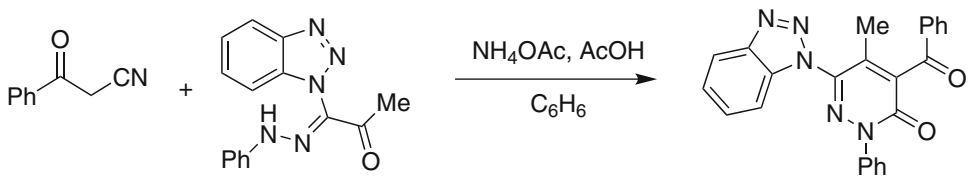


78 **79** **80**, 78%

R = 2-furyl

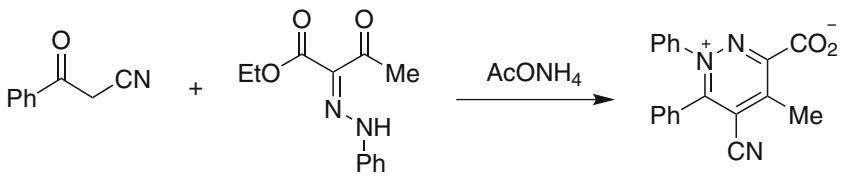
Scheme 29 .

Scheme 30 .

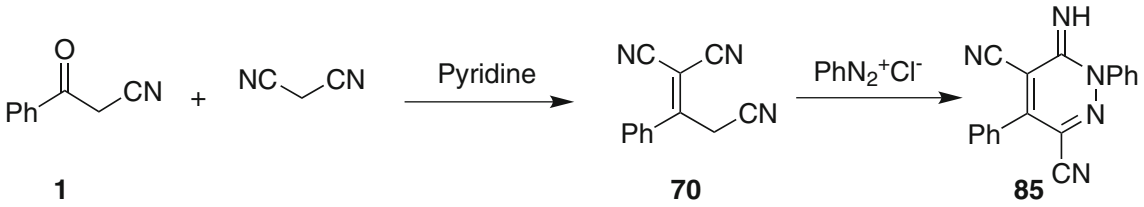


1 **81** **82**, 71%

Scheme 31 .



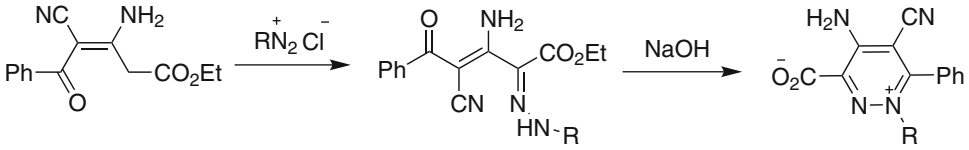
1 **83** **84**, 60%



1 **70** **85**

Scheme 32 .

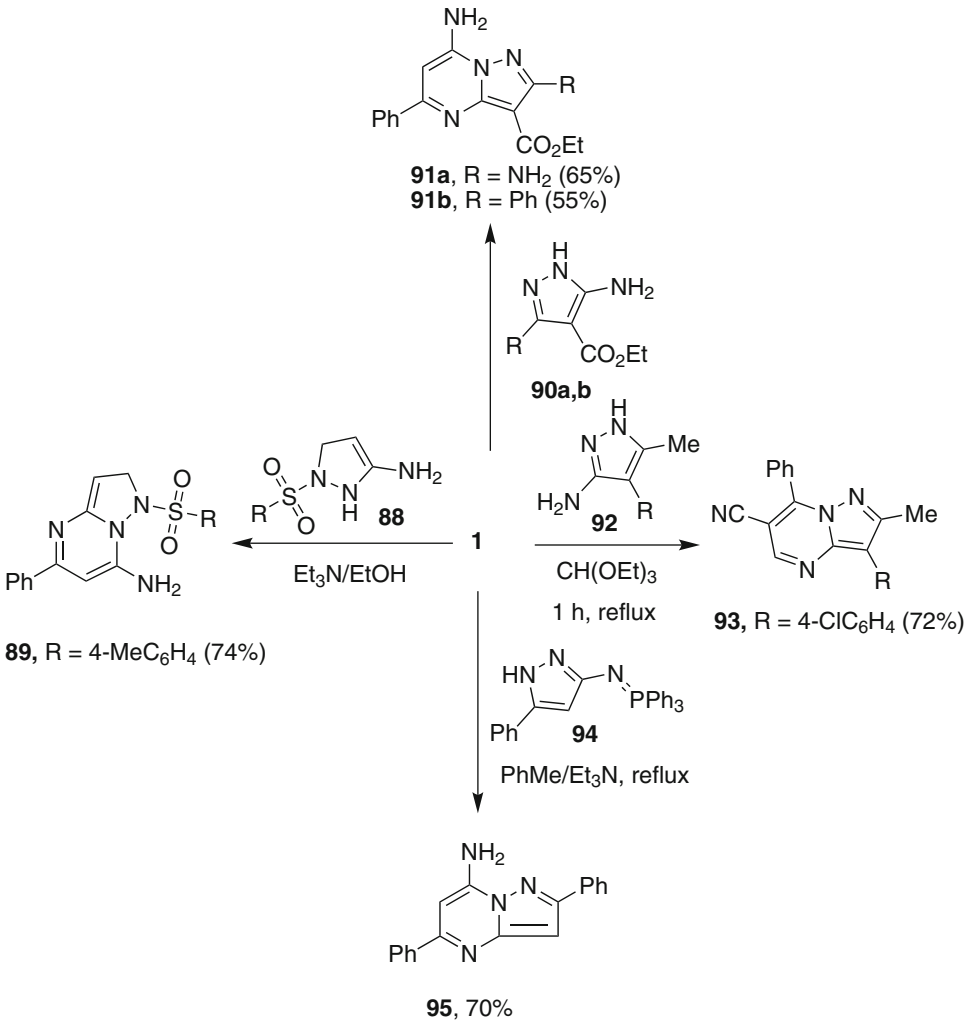
Scheme 33 .



63 **86** **87**

R = Ph, 4-MeC_6H_4, 4-ClC_6H_4

Scheme 34 .



91a, R = NH_2 (65%)
91b, R = Ph (55%)

90a,b

88

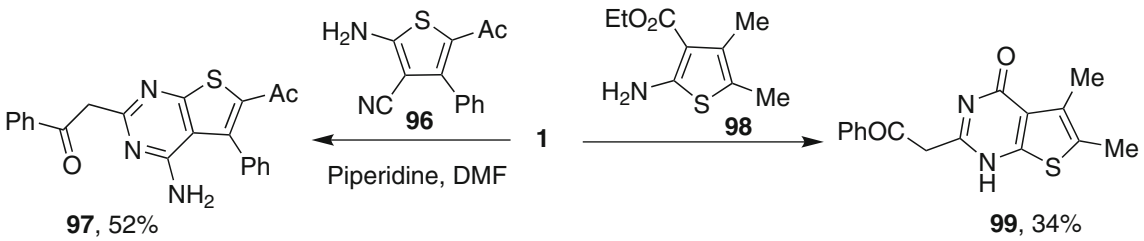
92

89, R = 4-MeC_6H_4 (74%)

93, R = 4-ClC_6H_4 (72%)

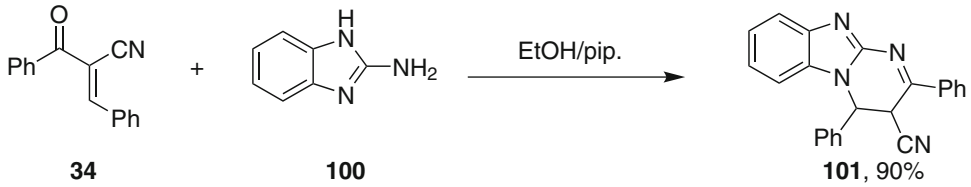
94

95, 70%

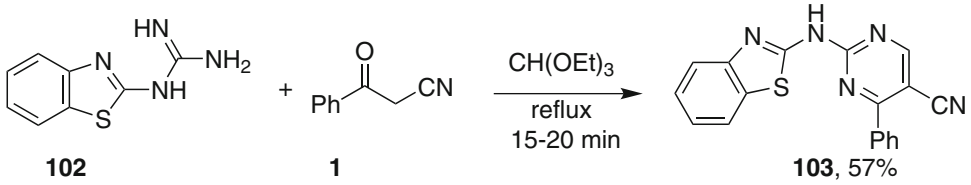


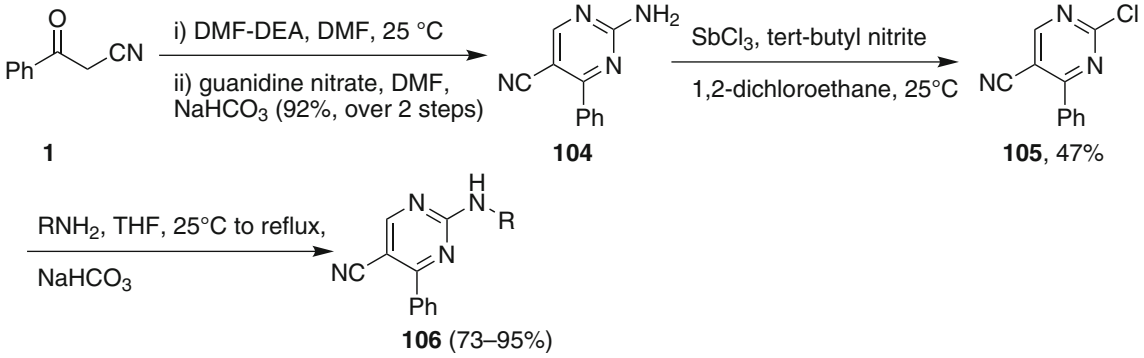
Scheme 35 .

Scheme 36 .



Scheme 37 .





Scheme 38 .

[2-imino-5-(2-phenylhydrazono)-2,5-dihydroindeno[1,2-*b*]pyran-3-yl](phenyl)methanone **66** (Scheme 22) [43].

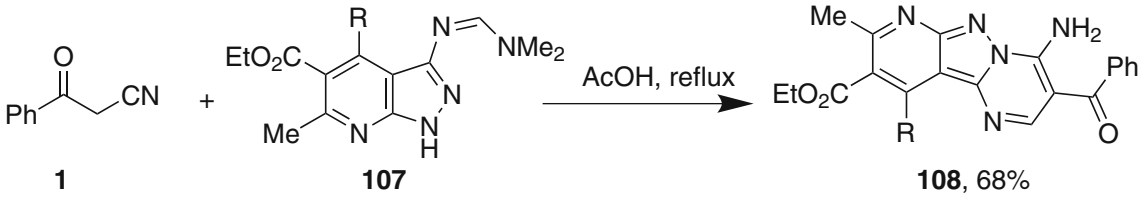
Miscellaneous methods

Treatment of 2-fluoro-5-nitrobenzyl bromide **67** with compound **1** in the presence of excess potassium carbonate led to the formation of 6-nitro-2-phenyl-4*H*-chromene-3-carbonitrile **68** (Scheme 23) [44].

Elgemeie et al. [45] reported the reaction of **1** with malononitrile in refluxing pyridine to give 2-phenylprop-1-ene-1,1,3-tricarbonitrile **70**. But Abdelrazek and Michael [46] reinvestigated the same reaction and a mixture of two products **69** and **70** was obtained (Scheme 24).

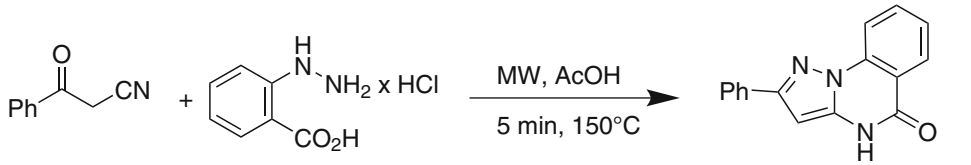
The formation of these two products **69** and **70** from compound **1** and malononitrile involved Knoevenagel condensation reaction which gave directly to compound **70** and Michael addition of the active methylene of malononitrile to the cyano function of **1** will lead to the tautomerized intermediate **71a/71b** which undergoes a 6-exo-dig cyclization [47] to afford the iminopyran **69** as shown in Scheme 25.

3-Benzyl-4-methyl-2-oxo-6-phenyl-2*H*-pyran-5-carbonitrile **73** was synthesized via reaction between ethyl



Scheme 39 .

Scheme 40 .



2-benzylbuta-2,3-dienoate **72** and **1** through a tandem nucleophilic addition/lactonization process (Scheme 26) [48].

4-(Methylthio)-2-oxo-6-phenyl-2*H*-pyran-5-carbonitrile **75**, showed very strong fluorescence in the solid state, was synthesized via reaction of compound **1** with ketene dithioacetal **74** in DMSO in the presence of sodium hydroxide (Scheme 27) [49].

Pyridazines and their fused derivatives

Reaction with α-diazo-β-diketones

Cyclocondensation reaction of **1** with α-hydrazonopropanal **76**, in refluxed ethanol containing pipreidine yielded pyridazin-6-imines **77** (Scheme 28) [50–52].

Similarly, 2-(2-furyl)-hydrazonopropanal **78** was condensed with **1** in dioxane in the presence of piperidine to yield 4-benzoyl-6*H*-pyridazino[1,6-*a*]quinazolin-6-one **80** via intermediate **79** (Scheme 29) [54].

6-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-4-benzoyl-5-methyl-2-phenylpyridazin-3(2*H*)-one **82** was obtained in 71 % yield from reaction between **1** and benzotriazolhydrazone **81** in benzene in the presence of acetic acid and ammonium acetate (Scheme 30) [55].

Ethyl 3-oxo-2-(2-phenylhydrazono)butanoate **83** was reacted with compound **1** in the presence ammonium acetate to yield 5-cyano-4-methyl-1,6-diphenylpyridazin-1-ium-3-carboxylate **84** (Scheme 31) [56].

Miscellaneous methods

Knoevenagel condensation of compound **1** with malononitrile afforded 2-phenylprop-1-ene-1,1,3-tricarbonitrile **70** which converted into 6-imino-1,4-diphenyl-1,6-dihydropyridazine-3,5-dicarbonitrile **85** when treated with benzene diazonium chloride followed by cyclization (Scheme 32) [45].

Coupling of compound **63** with substituted benzene diazonium chloride to give ethyl 3-amino-4-cyano-5-oxo-5-phenyl-2-(2-arylhydrazono)pent-3-enoate **86**. Then treatment of **86** with NaOH gave aminopyridazinium carboxylates **87** (Scheme 33) [46].

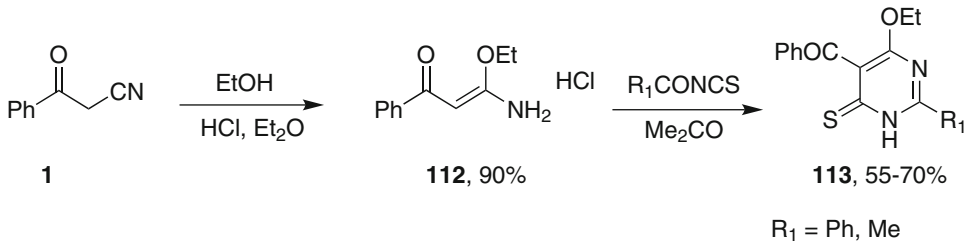
Pyrimidines and their fused derivatives

Reaction with 3(5)-aminopyrazoles, 2-aminothiophenes, 2-aminobenzimidazoles or 2-aminopyrimidines

Pyrazolo[1,5-*a*]pyrimidine **89** was synthesized by condensation of compound **1** with 3-amino-1,5-dihydro-1-(p-tosyl)pyrazole **88** in refluxed ethanol containing TEA [57]. Cyclocondensation of **1** with either ethyl 3,5-diamino-1*H*-pyrazole-4-carboxylate **90a** [58] or ethyl 5-amino-3-phenyl-1*H*-pyrazole-4-carboxylate **90b** [59] to give ethyl 7-amino-5-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate **91a**,**b**; respectively. One pot three-component cyclocondensation reaction of compound **1**, 4-(4-chlorophenyl)-5-methyl-1*H*-pyrazol-3-amine **92**, and triethylorthoformate gave 3-(4-chlorophenyl)-2-methyl-7-phenylpyrazolo[1,5-*a*]pyrimidine-6-carbonitrile **93** [60]. Pyrazolo[1,5-*a*]pyrimidine **95** was synthesized in70 % yield via aza-Wittig reaction of compound **1** with 5-(triphenylphosphoranylideneamino)-3-phenylpyrazole **94** (Scheme 34) [61].

2-(6-Acetyl-4-amino-5-phenylthieno[2,3-*d*]pyrimidin-2-yl)-1-phenylethanone **97** was synthesized, as inhibit the

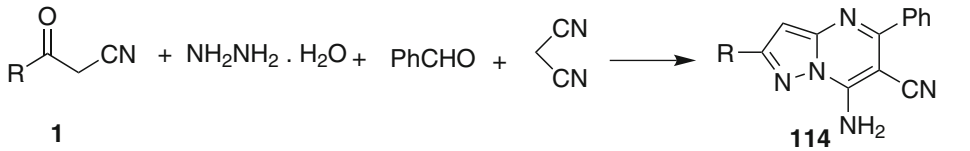
Scheme 41 .



1 **112**, 90% **113**, 55-70%

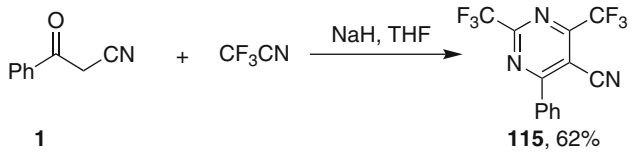
R_1 = Ph, Me

Scheme 42 .



1 **114**

R = Ph (71%), 4 -$(Me)_2NC_6H_4$ (75%)



1 **115**, 62%

Scheme 43 .

production of mycotoxins and fungal growth, from reaction of 5-acetyl-2-amino-4-phenylthiophene-3-carbonitrile **96** with compound **1** in DMF in the presence of piperidine [62]. 5,6-Dimethyl-2-(2-oxo-2-phenylethyl)thieno[2,3-*d*]pyrimidin-4(1*H*)-one **99** was prepared by treating aminothiophenecarboxylate **98** with **1** at room temperature (Scheme 35) [63].

2-Benzoyl-3-phenylacrylonitrile **132** was reacted with 2-aminobenzoimidazole **100** in refluxed ethanol in the presence of pipredine to give 2,4-diphenyl-3,4-dihydropyrimido[1,2-*a*]benzimidazole-3-carbonitrile **101** in excellent yield (Scheme 36) [64].

Three-component one pot cyclocondensation reaction of compound **1**, 1-(benzo[*d*]thiazol-2-yl)guanidine **102**, and triethylorthoformate afforded 2-(benzo[*d*]thiazol-2-ylamino)-4-phenylpyrimidine-5-carbonitrile **103** (Scheme 37) [65].

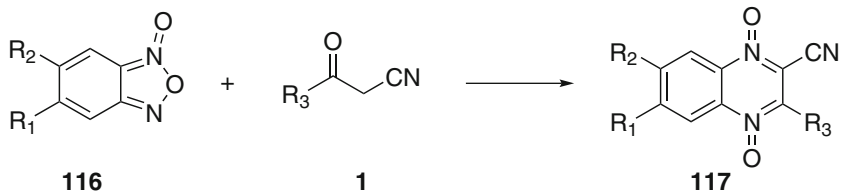
4-Phenyl-5-cyano-2-aminopyrimidines **106** were synthesized and found to have potent vascular endothelial growth factor (VEGF)-R2 kinase inhibitory activity. The key step involved reaction of a vinylogous amide with a guanidinium salt to form the pyrimidine ring. Specifically, treatment of **1** with *N*,*N*-dimethylformamide diethyl acetal (DMF-DEA) formed a vinylogous amide in situ that was reacted with guanidine nitrate in DMF at 100 °C to form the 2-amino-4-aryl-5-cyanopyrimidine **104**. The Sandmeyer reaction of the aminopyrimidine **104** was accomplished by treatment with antimony trichloride and *t*-butylnitrite in 1,2-dichloroethane at 25 °C to smoothly afford the 2-chloropyrimidine **105**. The displacement of the Cl of **105** with aliphatic amines proceeded at 25 °C and with aromatic amines in refluxing THF to afford the pharmacophores **106** (Scheme 38) [66].

Miscellaneous methods

Pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine **108** was prepared in 68 % yield by reaction of **1** with formamidine **107** (Scheme 39) [67].

The synthesis of substituted pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one **110**, as potent poly (ADP-ribose)polymerase-1 (PARP-1) inhibitors, has been reported. Thus, compound **1** was reacted with 2-hydrazinylbenzoic acid hydrochloride **109** under microwave condition in acetic acid to give 2-phenylpyrazolo[1,5-*a*]quinazolin-5(4*H*)-one **110** (Scheme 40) [68–71].

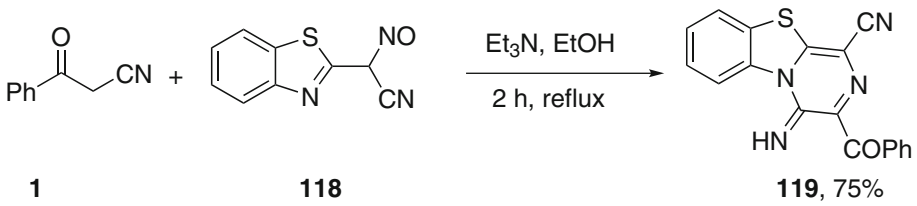
Scheme 44 .



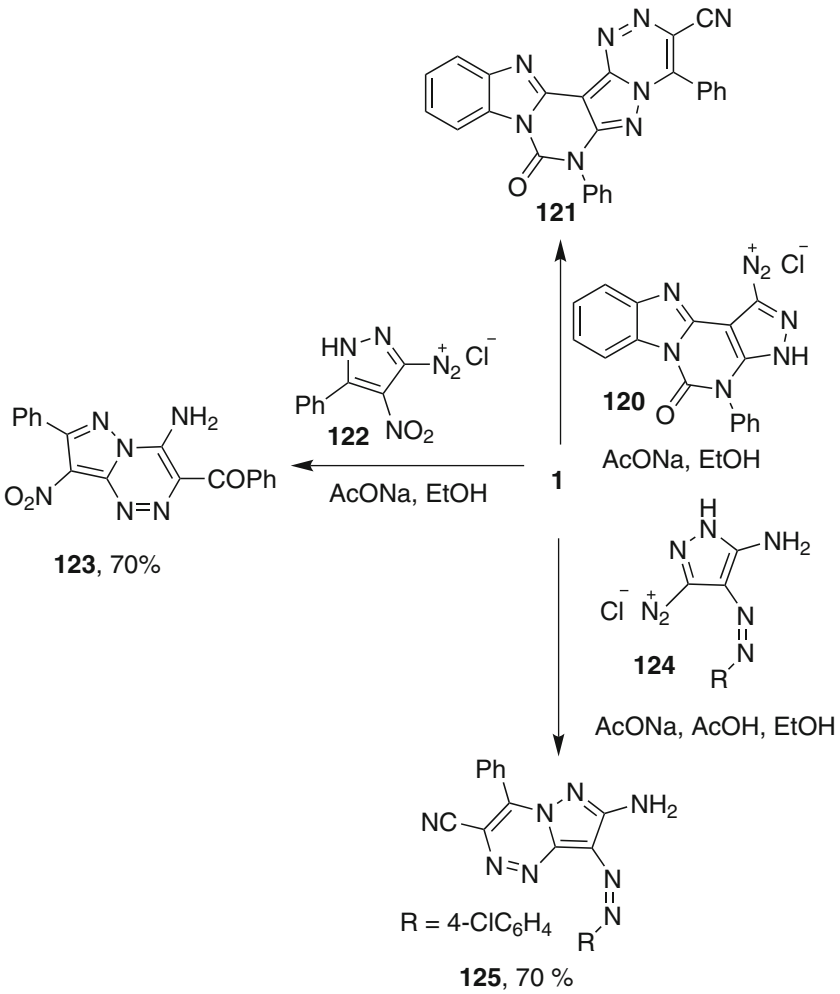
116 **1** **117**

R_1 = Me, F, H; R_2 = Me, F, H, F_3C, OMe; R_3 = Ph, 4-FC_6H_4, 4-$F_3COC_6H_4$

Scheme 45 .



Scheme 46 .



Pyrimidinethiones **113** were synthesized from reaction of 3-amino-3-ethoxy-1-phenylprop-2-en-1-one hydrochloride **112** with isothiocyanate in refluxing acetone (Scheme 41) [72].

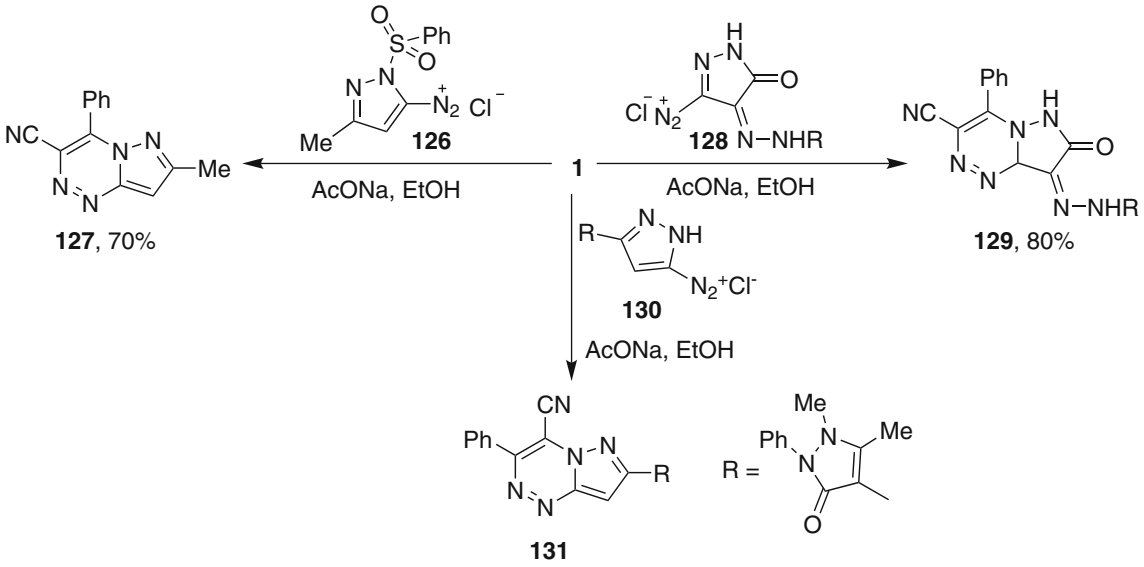
Multi-component one pot reaction of compound **1**, hydrazine hydrate, benzaldehyde, and malononitrile gave 7-amino-5-phenylpyrazolo[1,5-*a*]pyrimidine-6-carbonitrile **114** in good yields (Scheme 42) [73].

Treatment of compound **1** with NaH-THF for 30-40 min and then with trifluoroacetonitrile for 5 h gave 4-phenyl-2,6-*bis*(trifluoromethyl)pyrimidine-5-carbonitrile **115** in 62 % yield (Scheme 43) [74, 75].

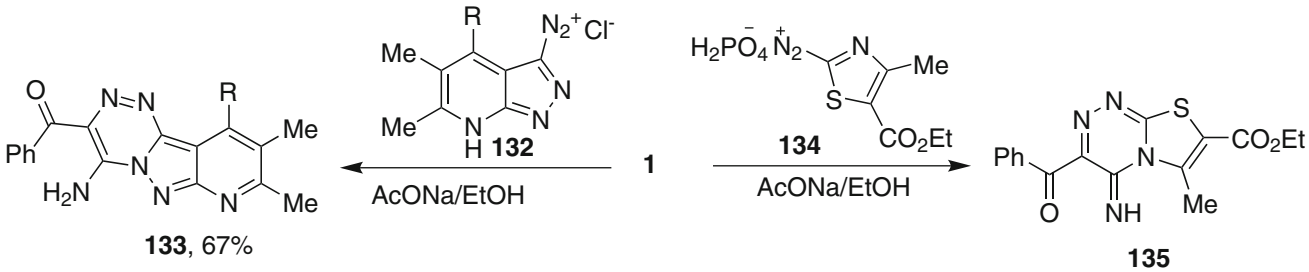
Pyrazines and their fused derivatives

Benzo[*c*][1,2,5]oxadiazole 1-oxides **116** were reacted with compound **1** in different solvent, such as chloroform [7], dichloromethane [11] ethanol [76] in the presence of triethylamine at room temperature to give 2-cyano-3-arylquinoxaline 1,4-dioxide **117** in 45–61 % yield (Scheme 44). Quinoxaline 1,4-dioxide derivatives showed superior antimalarial [7] and anti-*T. cruzi* activity [11].

Nitrosobenzothiazoleacetonitrile **118** was reacted with compound **1** in ethanol in the presence of triethylamine to yield 4-imino-3-(phenylcarbonyl)-4*H*-pyrazino[2,1-



Scheme 47 .



Scheme 48 .

b][1,3]benzothiazole-1-carbonitrile **119** in 75 % yield (Scheme 45) [77].

Triazines and their fused derivatives

Pyrazolo[5,1-*c*][1,2,4]triazines **121**, **123**, and **125** were synthesized from coupling of compound **1** with pyrazole diazonium chloride **120** [78], **122** [79], and **124** [80], respectively (Scheme 46).

In a similar fashion, coupling diazotized of compound **1** with pyrazolediazonium chlorides **126**, **128**, and **130** in ethanol in the presence of sodium acetate yielded pyrazolo[5,1-*c*][1,2,4]triazine **127**, [81] **129**, [82] and **131** [83] (Scheme 47).

Cyclocondensation reactions of compound **1** with pyrazole diazonium salt **132** afforded substituted triazine **288** [84]. 2-Thiazolediazonium salt **134** underwent coupling diazotized reaction with **1** to give ethyl 3-benzoyl-4-imino-6-methyl-4*H*-thiazolo[2,3-*c*][1,2,4]triazine-7-carboxylate **135** (Scheme 48) [85].

Conclusion

This survey is attempted to summarize the synthetic potential of benzoylacetonitrile in the synthesis five six-memderd ring heterocycles, pyrans, pyridazines, pyrimidine, pyrazines and triazine compounds, during the period from 1985 till now. The literature survey of the synthetic potential of benzoylacetonitrile in the synthesis of five-memberd heterocycles was submitted as a separate review article [19].

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