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Synthesis of 5-membered heterocycles using benzoylacetonitriles as synthon

Rizk Elsayed KHIDRE,[1,*] **Bakr Fathy ABDELWAHAB**[2]
[1]Chemistry Department, Faculty of Science, Jazan University, Saudi Arabia
[2]Shaqra University, Al-Dawadami, Saudi Arabia

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Abstract: This review article represents a survey covering the synthetic strategies leading to 5-membered heterocycles. The reactions are subdivided into groups that cover the synthetic methods of those heterocycles, i.e. pyrroles, furans, thiophenes, pyrazoles, isoxazoles, thiazoles, and others, utilizing benzoylacetonitriles as starting precursor from 1985 up to the present. The reactions are subdivided into groups that cover the synthetic methods for those heterocycles from benzoylacetonitriles.

Key words: Benzoylacetonitrile, pyrroles, furans, thiophenes, pyrazoles, isoxazoles, thiazoles

1. Introduction

Benzoylacetonitrile derivatives are easily available and have high chemical reactivity due to the presence of 3 active moieties: nitrile, carbonyl, and active methylene functions. Benzoylacetonitrile, known as phenacylcyanide or ω-cyanoacetophenone, was named as 3-oxo-3-phenylpropanenitrile using the IUPAC system. Benzoylacetonitriles are versatile and convenient intermediates in organic synthesis and have attracted a great deal of interest.[1] Benzoylacetonitriles opened up an important area of heterocyclic chemistry on account of the fact that many of them are subunits of natural products and pharmaceutical agents, e.g., antimicrobial,[2,3] antineoplastic,[4,5] antiviral,[6,7] and anti-inflammatory agents;[8,9] as inhibitors of poly(adp-ribose) polymerase (PARP);[10,11] as GABAB allosteric enhancers for treating CNS disorders[12] and pain;[13] and as allosteric enhancers at the human A1 adenosine receptor.[14–16] Despite this important versatility, and in connection with our previous review articles,[17] the utility of benzoylacetonitrile in the synthesis of 5-membered heterocycles has not been previously reviewed. The present review aims to demonstrate the synthetic applications of benzoylacetonitrile in the synthesis of 5-membered heterocycles from 1985 up to the end of 2011 and provide useful and up-to-date data for organic and medicinal chemists.

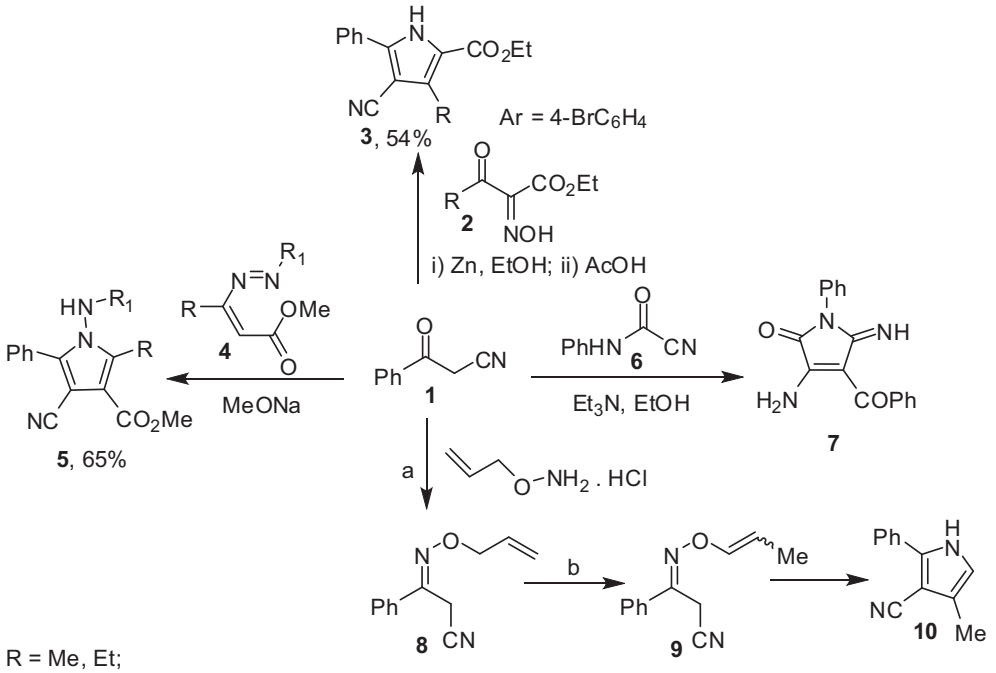
2. Synthesis of 5-membered rings with 1 heteroatom

2.1. Pyrroles and their fused derivatives

Synthesis of 4-cyanopyrroles via mild Knorr reactions with β-ketonitriles was achieved. Ethyl 3-(4-bromophenyl)-4-cyano-5-phenyl-1*H*-pyrrole-2-carboxylate **3** was prepared by reaction of ethyl 3-(4-bromophenyl)-2-(hydroxyimino)-3-oxopropanoate **2** with compound **1**.[18] Azoalkenes **4** were reacted with **1** to afford methyl 1-amino-4-cyano-5-phenyl-1*H*-pyrrole-3-carboxylates **5**.[19] 1-Cyanoformanilide **6** was reacted with **1** in refluxed ethanol in

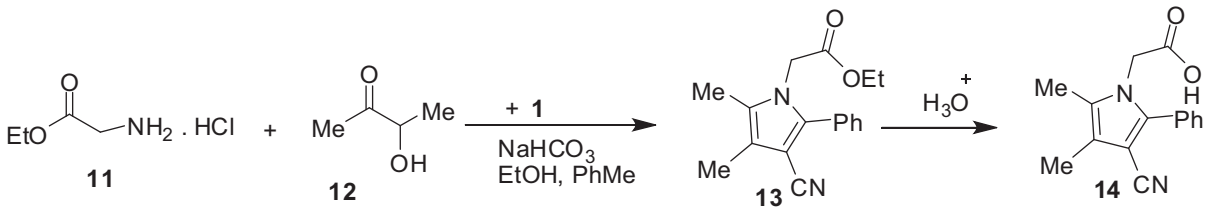
*Correspondence: rizkarein@yahoo.com

the presence of triethylamine to give 3-amino-4-benzoyl-5-imino-1-phenyl-1*H*-pyrrol-2(5*H*)-one **7**.[20] Regioselective synthesis of 2,3,4-trisubstituted pyrrole **10** has been achieved via [3,3] sigmatropic rearrangements of *O*-vinyl oximes **9**. *O*-allyl oximes **8** enable rapid access to *O*-vinyl oximes (Scheme 1).[21]



Scheme 1.

Three-component 1-pot condensation reactions of ethyl glycinate **11**, 3-hydroxybutan-2-one **12**, and **1** yielded ethyl 2-(3-cyano-4,5-dimethyl-2-phenyl-1*H*-pyrrol-1-yl)acetate **13**, which was consequently hydrolyzed to produce the corresponding carboxylic acid **14** (Scheme 2).[9]



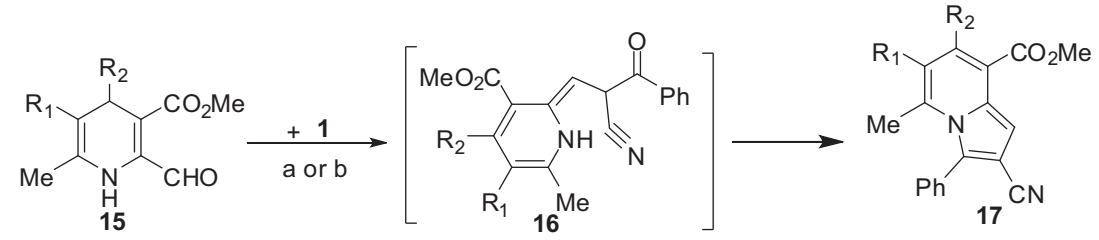
Scheme 2.

2-Formyl-1,4-dihydropyridines **15** underwent the tandem Knoevenagel condensation/aminonitrile cyclization with **1** to afford methyl 2-cyano-5-methyl-3-phenylindolizine-8-carboxylate **17** in 65%–93% yields (Scheme 3).[22]

2.2. Furans and their fused derivatives

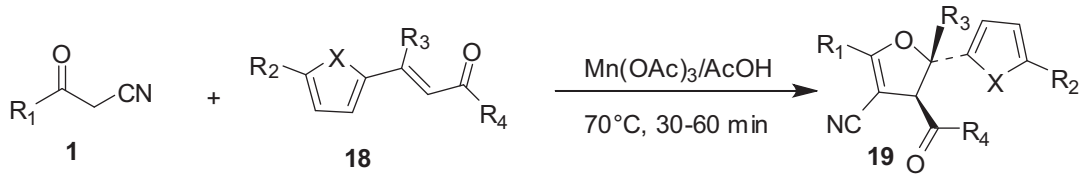
2.2.1. Michael addition reaction

4-Cyano-2,3-dihydrofuran-3-carboxamides **19** were obtained in moderate yields by the oxidative cyclization of **1** with unsaturated amides using manganese(III) acetate. Treatment of 3-oxopropanenitriles **1** with (2*E*)-3-(5-methyl-2-furyl)acrylamide **18** gave dihydrofuran-3-carboxamides **19** in moderate yields (Scheme 4).[23,24]



R_1, R_2 = EtO_2C, 2-$O_2NC_6H_4$ (93%); a, pip., EtOH
R_1, R_2 = MeCO, 3-$O_2NC_6H_4$ (88%); Me_2CHO_2C, 5-nitro-2-furyl (65%); b, AcOH, 30 min, reflux

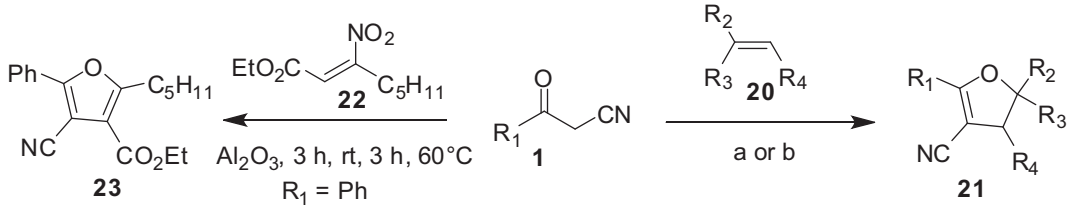
Scheme 3.



R_1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-thienyl, 2-benzofuryl, *t*-butyl
R_2 = Me, R_3 = H, R_4 = NH_2, X = O (42%-64%)
R_2 = R_3 = Me, H, R_4 = NH_2, OEt, X = S (45%-91%)

Scheme 4.

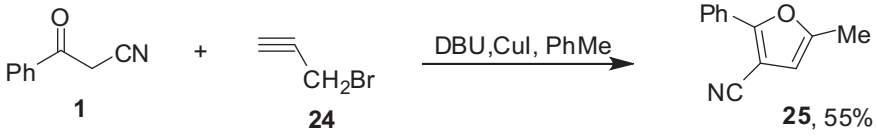
4,5-Dihydro-3-furancarbonitrile derivatives **21** were obtained through radical cyclization of **1**, mediated either by manganese(III) acetate in acetic acid[2,25,26] or by cerium(IV) ammonium nitrate in THF[27] with substituted ethylene **20**. Cerium(IV)/THF radical cyclization was compared with that performed with manganese(III) acetate/AcOH; the cerium(IV)/THF system turned out to be much more efficient. The synthesized compounds showed better results against test bacteria than some known antibiotics.[2] Similarly 1-pot synthesis of tetrasubstituted furan derivatives **23**, catalyzed by acidic alumina and in the absence of solvent, was reported from the reaction between compound **1** and ethyl 3-nitrooct-2-enoate **22** (Scheme 5).[28]



a) $Mn(OAc)_3$, AcOH, 80 °C; R_1 = Ph; R_2 = Ph, 2-thienyl; R_3 = Me, Ph, n-Pr, H; R_4 = Et, Ph, H (40-83%)
b) $Ce(NH_4)_2(NO_3)_6$, $NaHCO_3$,THF, 10 - 30 min, 60°C; R_1 = R_2 = R_3 = Ph, R_4 = H(97%);R_1 = R_2 = R_3 = Ph, R_4 = Et (83%); R_1 = Ph, R_2 = R_3 = 4-FC_6H_4, R_4 = H (86%); R_1 = 2-furanyl, R_2 = R_3 = Ph, R_4 = H (90%); R_1 = 1-benzofuran-2-yl, R_2 = R_3 = Ph, R_4 = H (96%); R_1 = R_2 = Ph,R_3 = R_4 = H (42%); R_1 = R_2 = Ph,R_3 = H, R_4 = Me (75%); R_1 = R_2 = Ph,R_3 = Me, R_4 = H (80%)

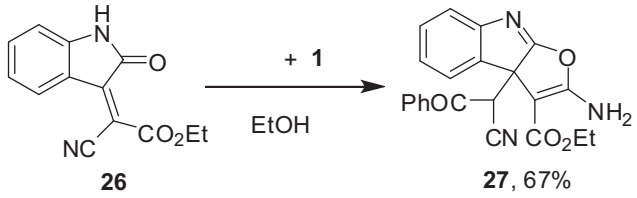
Scheme 5.

Propargyl bromide **24** was reacted with **1** in the presence of copper iodide and 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine (DBU) in toluene to give 5-methyl-2-phenyl-3-furancarbonitrile **25** in 55% yield (Scheme 6).[29]



Scheme 6.

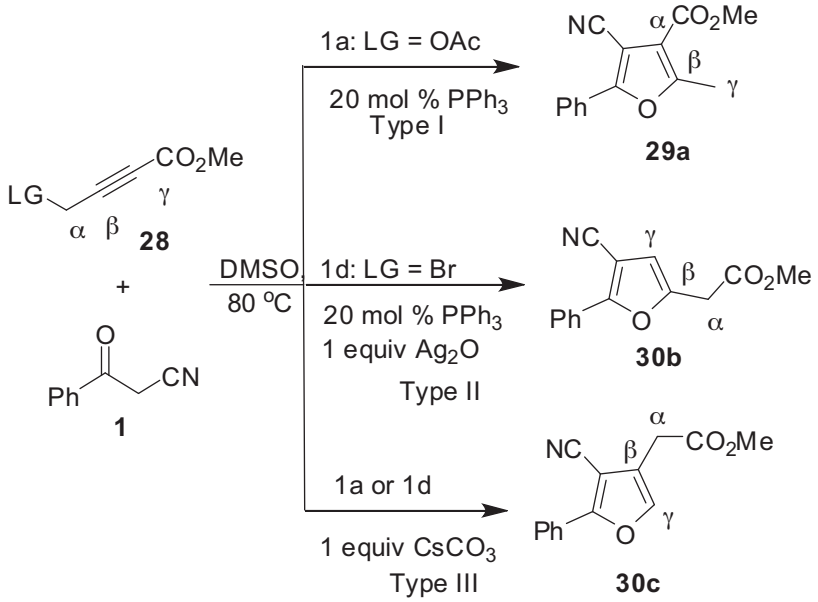
Furo[2,3-*b*]indole-3-carboxylate **27** was synthesized from the reaction between **1** and ethyl 2-cyano-2-(2-oxoindolin-3-ylidene)acetate **26** in ethanol at reflux (Scheme 7).[30]



Scheme 7.

2.2.2. [3+2]Cycloaddition

Reagent-controlled [3+2] annulation of γ-functionalized 2-butynoates and 1C, 3O-bisnucleophiles is reported, which leads to 3 distinct furan skeletons. A PPh_3 catalyst preferentially attached to the β-position of $AcOCH_2C{\equiv}CCO_2Me$, facilitating α-addition to furnish type I annulations. With the assistance of Ag_2O, type II annulations were achieved via selective γ-substitution. In the absence of the PPh_3 catalyst, the reagent Cs_2CO_3 promoted β-addition to realize type III annulations (Scheme 8).[31]

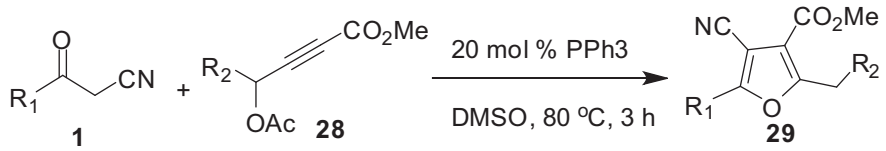


Scheme 8.

Polysubstituted furans **29** were synthesized by the reaction between methyl 4-acetoxybut-2-ynoate **28** and derivatives of compound **1** using type I annulations (Scheme 9).[31]

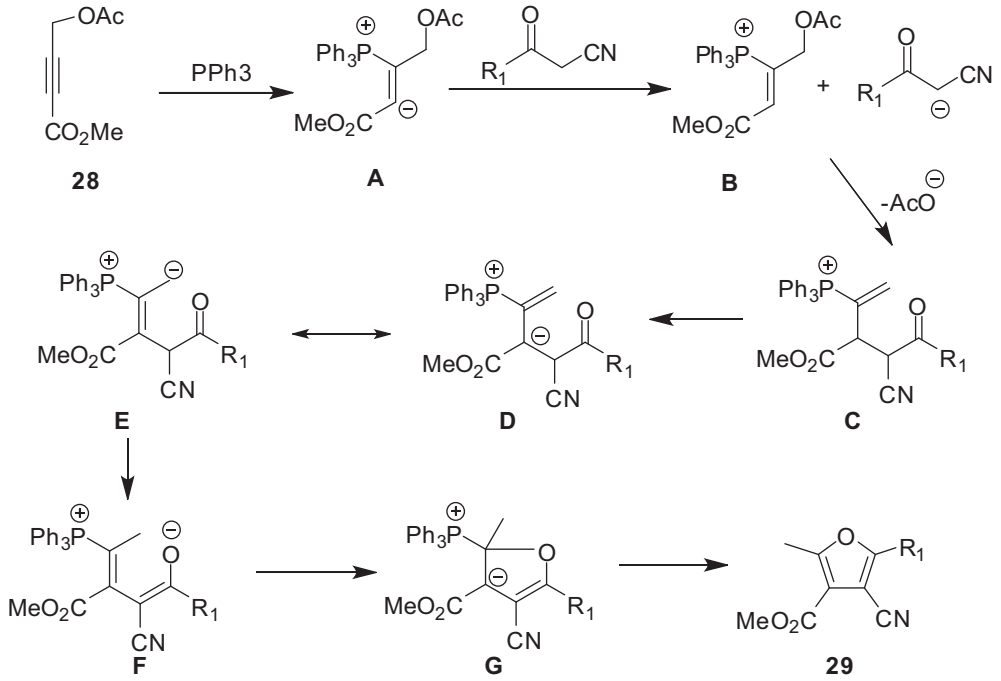
The mechanism of the above reaction is proposed. Addition of catalyst to **28** generates zwitterionic intermediate **A**. In the presence of **1**, **A** works as a base to initiate H-transfer, leading to the formation of

intermediate **B** and a nucleophile. Then addition and elimination of acetate produce intermediate **C**, which is converted to intermediate **F** via double continuous steps of H-transfer and isomerization. Finally, the addition–elimination process takes place to regenerate the catalyst and give product **29** (Scheme 10).



R_1 = Ph, R_2 = H (91%); R_1 = 4-$MeOC_6H_4$, R_2 = H (62%);
R_1 = 4-BrC_6H_4, R_2 = H (92%); R_1 = 4-ClC_6H_4, R_2 = H (94%);
R_1 = 2-furanyl,, R_2 = H (71%); R_1 = 2-thienyl , R_2 = H (82%);
R_1 = Ph, R_2 = Ph (56%); R_1 = Ph, R_2 = 2-thienyl (65%);
R_1 = Ph, R_2 = Bu (32%)

Scheme 9.



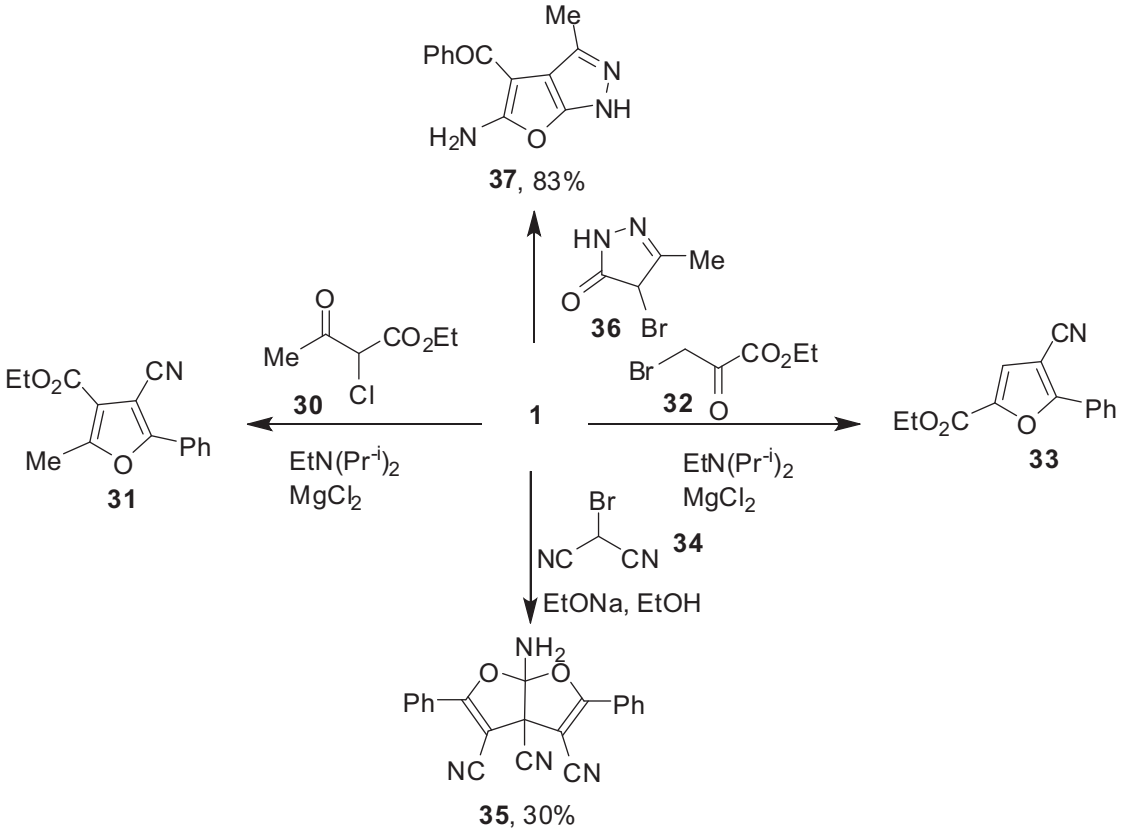
Scheme 10.

2.2.3. Miscellaneous methods

Alkylation of **1** with either ethyl 2-chloro-3-oxobutanoate **30** or ethyl 3-bromo-2-oxopropanoate **32** in the presence of ethyldiisopropyl amine and $MgCl_2$ gave furan derivatives **31** and **32**, respectively.[32] 6a-Amino-2,5-diphenyl-3a,6a-dihydrofuro[2,3-*b*]furan-3,3a,4-tricarbonitrile **35** was synthesized from the reaction of **1** with 2-bromomalononitrile **34** in refluxed ethanol containing sodium ethoxide.[33] Furo[2,3-*c*]pyrazole **37** was prepared in 83% yields by treating 4-bromo-3-methyl-2-pyrazolin-5-one **36** with **1** in EtOH in the presence of piperidine at reflux temperature (Scheme 11).[34]

5-Aryl-3-aminofuran-2-carboxylate esters **39**, key intermediates in pathways for synthesis of the amine substituted furan-2-carbonylguanidines, were prepared from the reaction of **1** with methyl glycolate under

Mitsunobu conditions to afford the vinyl ethers **38**, which upon treatment with sodium hydride cyclized to the 3-aminofurans **39** in 40%–60% yield (Scheme 12).[35]

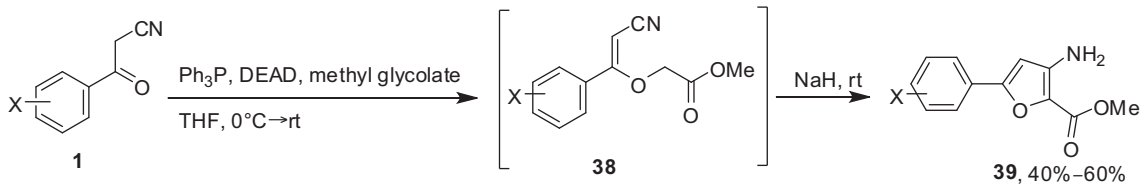


Scheme 11.

2.3. Thiophenes and their fused derivatives

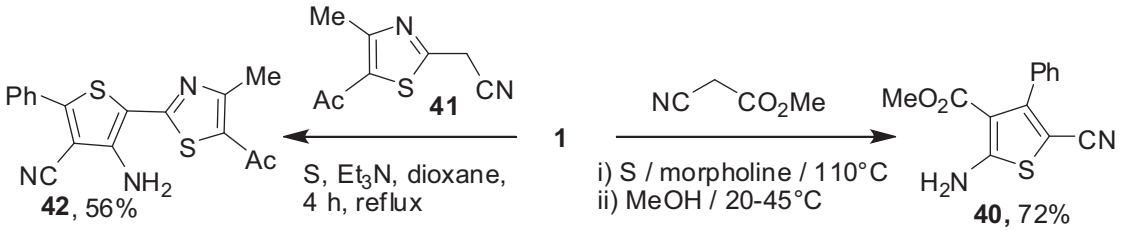
2.3.1. Gewald reaction

The synthesis of π-conjugated thiophenes starting from substituted 3-oxopropanenitriles via the Gewald reaction has been reported. Thus treatment of **1** with methyl cyanoacetate and elemental sulfur gave thiophene derivative **40** in 72% yields.[36] Similarly, 2-(5-acetyl-4-methylthiazol-2-yl)acetonitrile **41** was reacted with **1** in dioxane in the presence of sulfur to yield the 5-(5-acetyl-4-methylthiazol-2-yl)-4-amino-2-phenylthiophene-3-carbonitrile **42** (Scheme 13).[37]



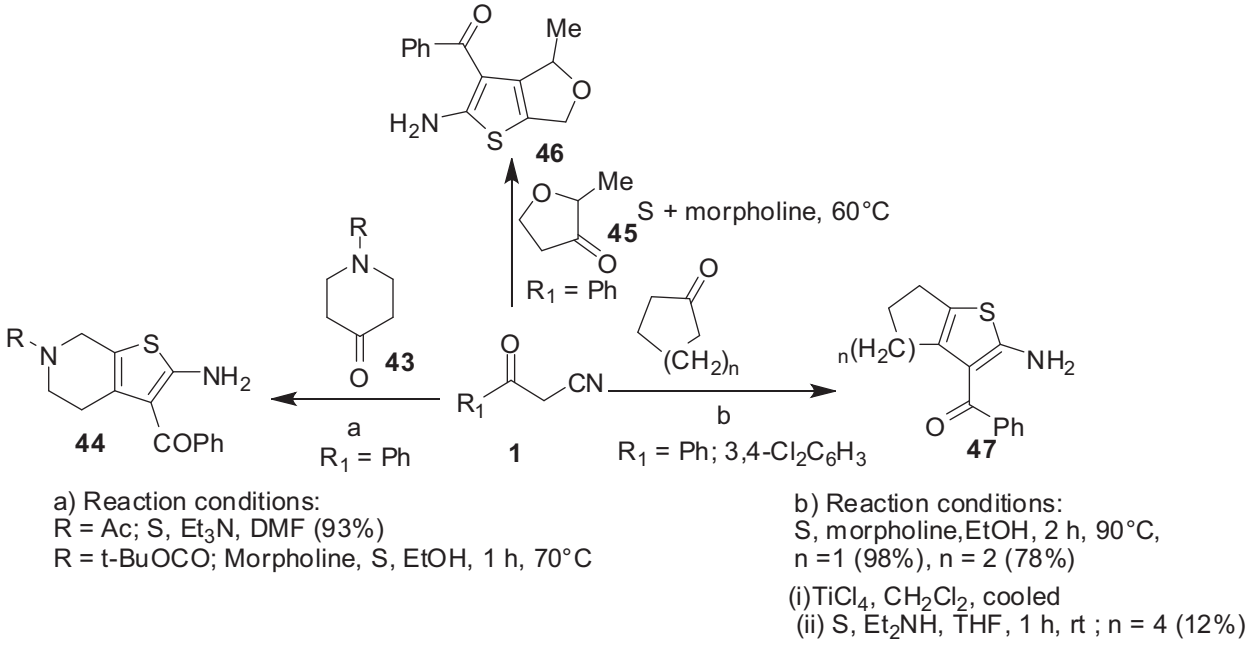
X = H, 2-F, 2-Me, 2-OMe, 3-F, 3-Cl, 3-Me, 2,5-F_2, 2,5-Cl_2, 2,5-Me_2, 2-MeO-5-Cl, 2-MeO-5-F

Scheme 12.



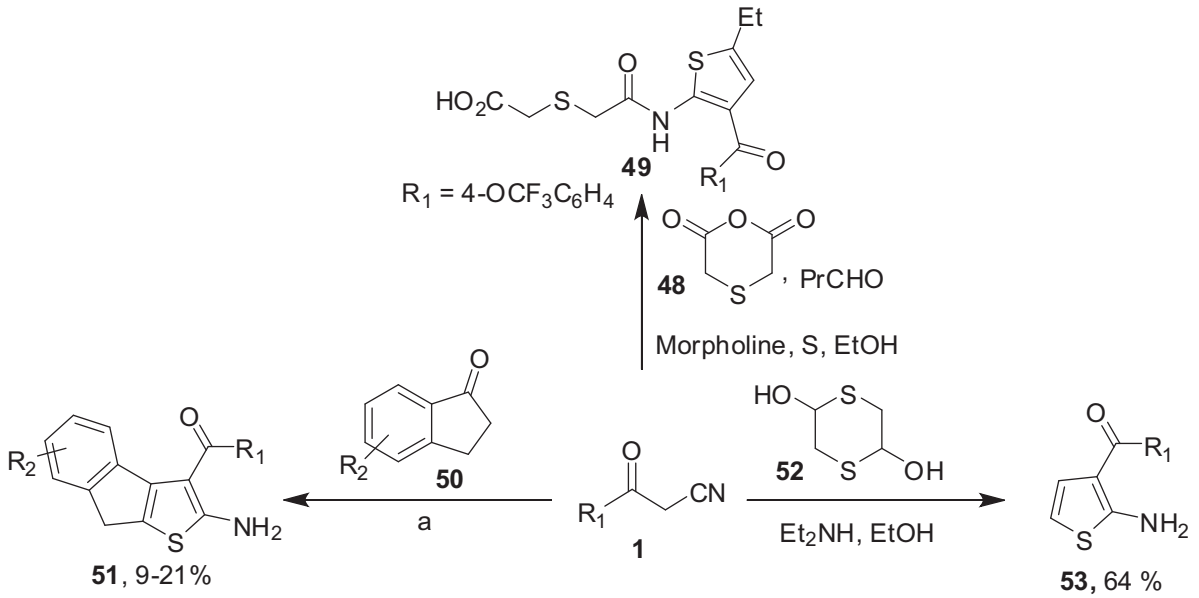
Scheme 13.

In the same fashion, compound **1** was reacted with 1-acetylpiperidin-4-one **43a** to give 1-(2-amino-3-benzoyl-4,5-dihydrothieno[2,3-*c*]pyridin-6(7*H*)-yl)ethanone **44a**, which was evaluated for its abilities to inhibit lipopolysaccharide (LPS)-stimulated production of TNF-α in rat whole blood.[38] On the other hand, the microwave-assisted aromatization method has been used for the synthesis of compound **44b**. The synthesized molecule has been evaluated as a potential new series of allosteric enhancers acting at the adenosine A1 receptor.[14] Thienofuran derivatives, as CB2 cannabinoid receptor ligands, were prepared by heterocyclization of compound **1** with 2-methyltetrahydrofuran-3-one.[39] The Gewald reaction of **1** with cyclopentanone,[7,12] cyclohexanone,[40] or cyclooctanone[41] and sulfur in ethanol in the presence of morpholine yielded thiophen-2-amines **47**. The latter compounds were evaluated as potential allosteric modulators of the A1 adenosine receptor (AR) (Scheme 14).[41]



Scheme 14.

Preparation of thiophene derivatives **49** as PPARδ agonists was reported. Cyclocondensation of **1** with butyraldehyde and sulfur was followed by acylation with thiodiglycolic anhydride **48**.[42] Similarly, 2-amino-3-benzoylthiophenes **51** and **53**, which have been widely reported to act as allosteric enhancers (AEs) at the A1 adenosine receptor (A1AR), were prepared from the reaction of **1** with substituted 1-Indanone **50** or 1,4-dithiane-2,5-diol **52**, respectively, as described in Scheme 15.[15,43]

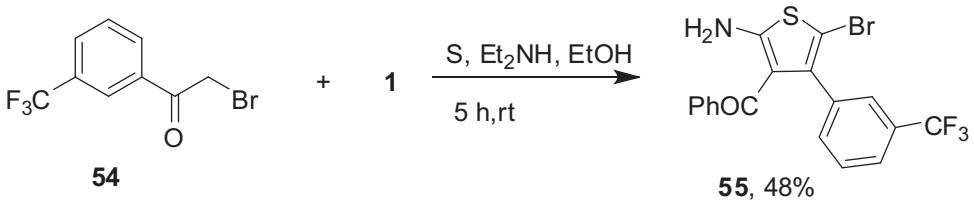


a: i)$TiCl_4$, pyridine; ii) S_8, Et_2NH, THF or i) β-ala, $PhCO_2H$, 110-120 °C; ii) S_8, morpholine, EtOH

R_1 = Ph, 4-ClC_6H_4; R_2 = H, 4-CF_3, 6-CF_3

Scheme 15.

Compound **1** was reacted with 2-bromo-1-(3-(trifluoromethyl)phenyl)ethanone **54** and sulfur in ethanol in the presence of diethylamine to afford (2-amino-5-bromo-4-(3-(trifluoromethyl)phenyl)thiophen-3-yl)(phenyl)methanone **55** in 48% yield (Scheme 16).[44]



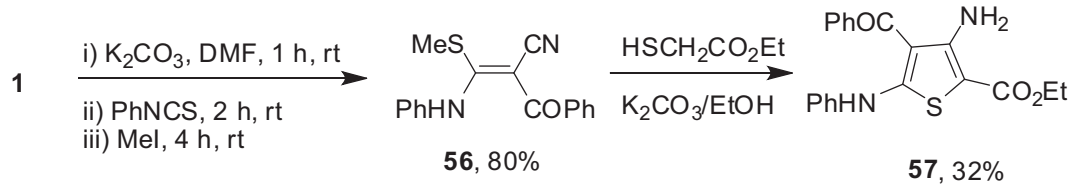
Scheme 16.

2.3.2. Miscellaneous methods

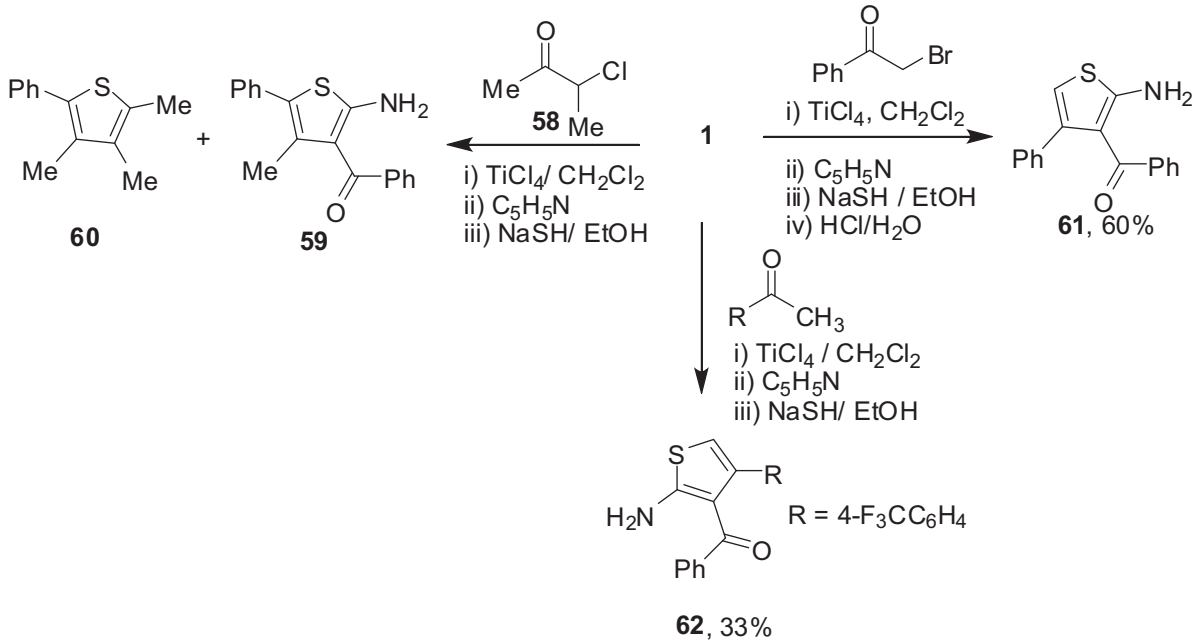
Ethyl 3-amino-4-benzoyl-5-(phenylamino)thiophene-2-carboxylate **57** was synthesized in 2 steps. The first step consisted of the formation of the *N*-phenyl *S*-methyl ketene-*N*,*S*-acetals **56**, obtained in a 1-pot reaction from **1**, phenyl isothiocyanate, and methyl iodide under basic conditions (K_2CO_3/DMF) in 90% yield. In the second step, ketene-*N*,*S*-acetals **56** were reacted with ethyl thioglycolate in ethanol containing potassium carbonate (Scheme 17).[45]

2,3,4-Trimethyl-5-phenylthiophene **60** and (2-amino-4-methyl-5-phenylthiophen-3-yl)(phenyl)methanone **59** were prepared in ratio 95:5 by regioselective Knoevenagel condensation of **1** with 3-chlorobutan-2-one **58** followed by intermolecular addition in pyridine and then the Gewald reaction.[46] Aminobenzoylthiophene **61**, as allosteric modulator of the adenosine A1 receptor, was prepared in 60% yield by alkylation of **1** with phenacyl bromide followed by cyclocondensation with sodium hydrosulfide.[16] 2-Amino-3-benzoyl-4-phenylthiophene deriva-

tives **62** as A1 adenosine receptor allosteric enhancers were prepared from the reaction of **1** with 3-trifluromethyl aceteophenone (Scheme 18).[13]

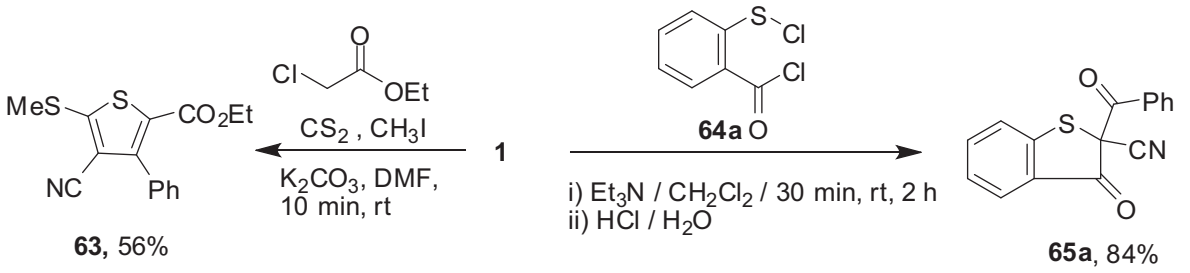


Scheme 17.



Scheme 18.

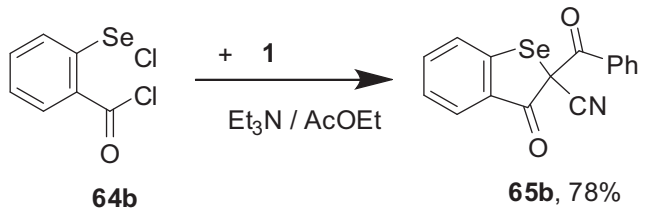
Disclosed are thiophene compounds of formula **63**, which are useful as therapeutics, especially in antineoplastic therapy and in other therapeutic regimes where cysteine protease inhibition is implicated. Compound **63** was prepared from the reaction of **1**, carbon disulfide, ethyl 2-chloroacetate, and methyl iodide.[4] Benzo[*b*]thiophene **65a** was prepared in 84% yield by sulfanylation–acylation of active methylene in compound **1** with 2-(chlorosulfanyl)benzoyl chloride **64a** in the presence of triethylamine (Scheme 19).[47]



Scheme 19.

2.4. Selenophene derivatives

Selenation–acylation of **1** with 2-(chloroseleno)benzoyl chloride **64b** afforded 2-benzoyl-3-oxo-2,3-dihydrobenzo[*b*] selenophene-2-carbonitrile **65b** in 78% yield (Scheme 20).[48]



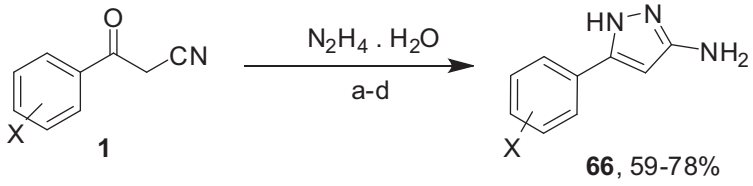
Scheme 20.

3. Synthesis of 5-membered rings with 2 heteroatoms

3.1. Pyrazoles and their fused derivatives

3.1.1. Reaction with hydrazines

5-Phenyl-1*H*-pyrazol-3-amine **66** was synthesized by the reaction of **1** with hydrazine in ethanol at reflux temperature.[49–54] Moreover, compound **66** was prepared in excellent yield using several conditions such as *p*-toluene sulfonic acid as catalyst in polyethylene glycol-400 as an efficient and recyclable reaction medium,[55] using *p*-toluene sulfonic acid at 100 °C under microwave conditions,[56] or using diimidazolyl ketone[57,58] (Scheme 21).

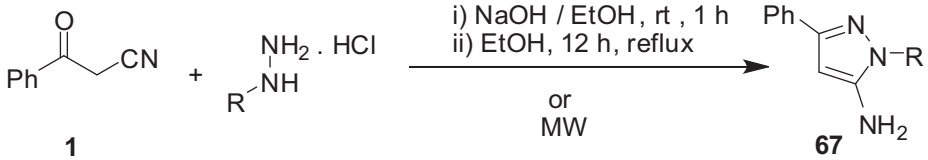


a: EtOH, 2 h, 85 °C; b: 4-$MeC_6H_4SO_3H$, $HOCH_2CH_2OH$ polymer;
c: 4-$MeC_6H_4SO_3H$, MW; d: diimidazolyl ketone

X = H; 2-Br; 2-OMe; 4-Cl; 4-Br; 4-OMe; 3-Cl; 3-Br;
3-OMe; 2,5-Cl_2; 3-Br; 3-I; 3-OMe; 3-CO_2Me, Pyridine

Scheme 21.

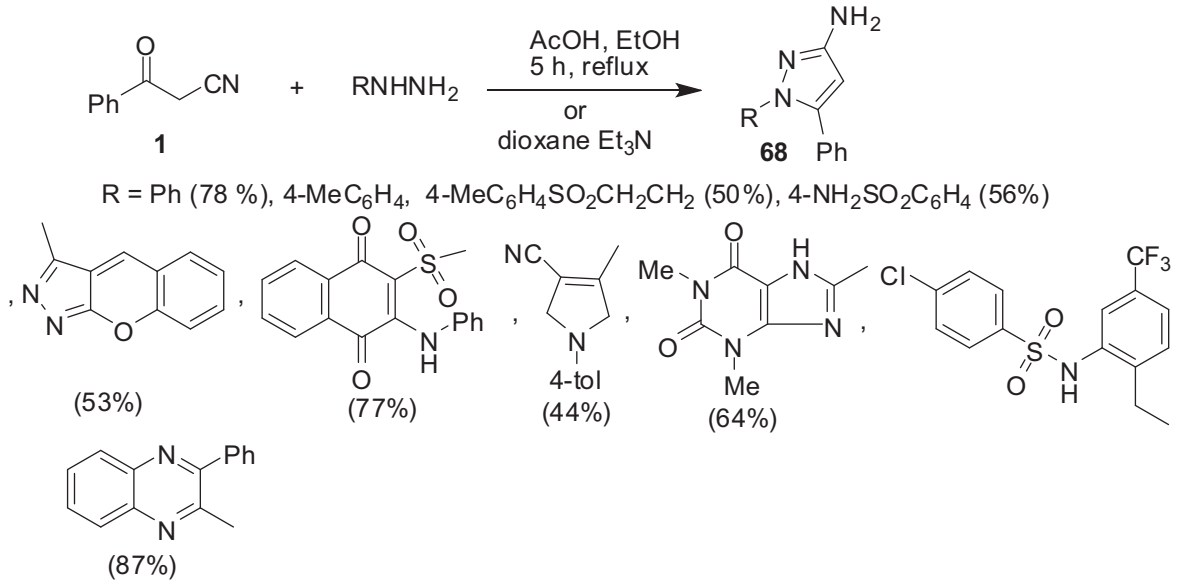
1-Substituted 5-aminopyrazole **67** was obtained in excellent yield by the reaction of **1** with substituted hydrazine such as *t*-butyl hydrazine hydrochloride,[59] 2-hydrazinylethanol hydrochloride,[60] and o-tolylhydrazine hydrochloride[61] either by the traditional method or using microwave irradiation (Scheme 22).



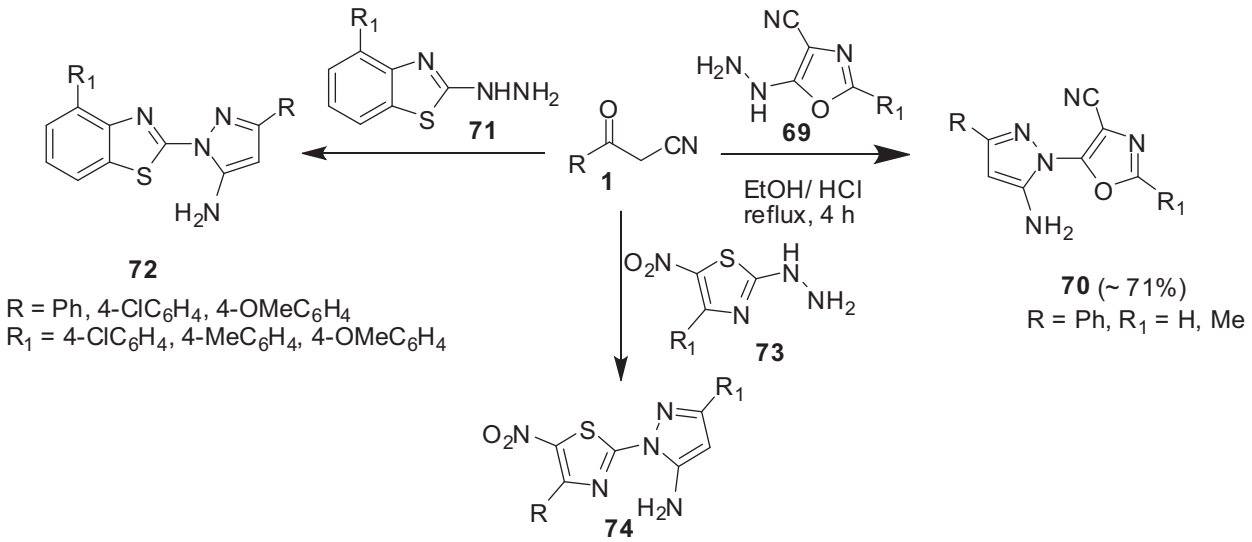
R = t-Bu (80%); $HOCH_2CH_2$ (79%); 2-MeC_6H_4 (81%)

Scheme 22.

Several aryl hydrazines[8,62–66] or heterocycle hydrazines such as 1,4-dioxo-3-(phenylamino)-1,4-dihydronaphthalene-2-sulfonohydrazide,[67] 4-hydrazinyl-1-p-tolyl-2,5-dihydro-1*H*-pyrrole-3-carbonitrile,[68] 8-hydrazinyl-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione,[69] 2-hydrazinyl-3-phenylquinoxaline,[3] 3-hydrazono-2,3-dihydrochromeno[2,3-*c*]pyrazole, or 4-chloro-*N*-(2-(hydrazinylmethyl)-5-(trifluoromethyl)phenyl)benzenesulfonamide[70] were reacted with **1** either by traditional methods or using microwave irradiation[71,72] to give 5-aminopyrazole in excellent yield (Scheme 23). The latter compound used as CCR2 chemokine receptor antagonists,[70] and as anti-HIV-1 and antimicrobial agent[69] (Scheme 23).



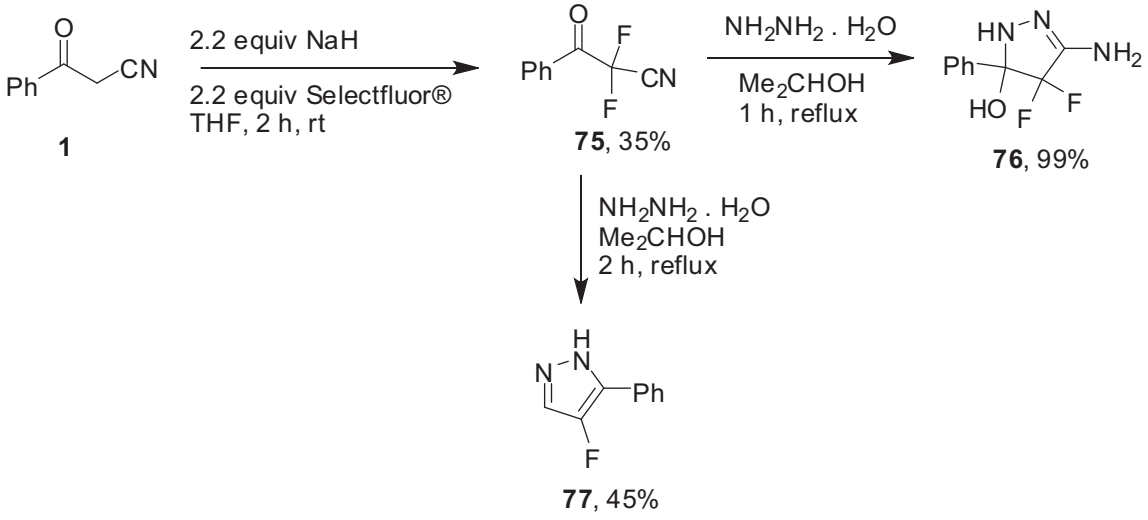
Scheme 23.



Scheme 24.

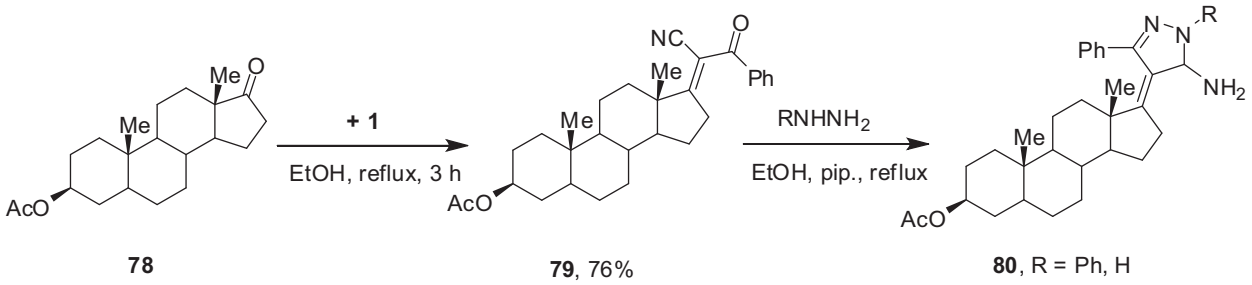
Similarly, 5-hydrazino-4-oxazolecarbonitriles **69**,[73] 2-hydrazinylbenzo[*d*]thiazole **71**,[5] and 2-hydrazino-5-nitrothiazoles **71**[74] were reacted with **1** to give 1-substituted-1*H*-pyrazol-5-amines **70**, **72**, and **74**, respectively. Some of the synthesized compounds show high antifungal activity[74] (Scheme 24).

Synthesis of fluorinated pyrazoles, a class of compounds with potential in medicinal chemistry, was described. The treatment of 2,2-difluoro-3-oxo-3-phenylpropanenitrile **75** with hydrazine hydrate yielded the expected 3-amino-4-fluoropyrazole **76** in 99% yield, while the analogous reaction of compound **75** with hydrazine hydrate in refluxing isopropanol surprisingly gave rise to 3-unsubstituted 4-fluoropyrazole **77** (Scheme 25).[75]



Scheme 25.

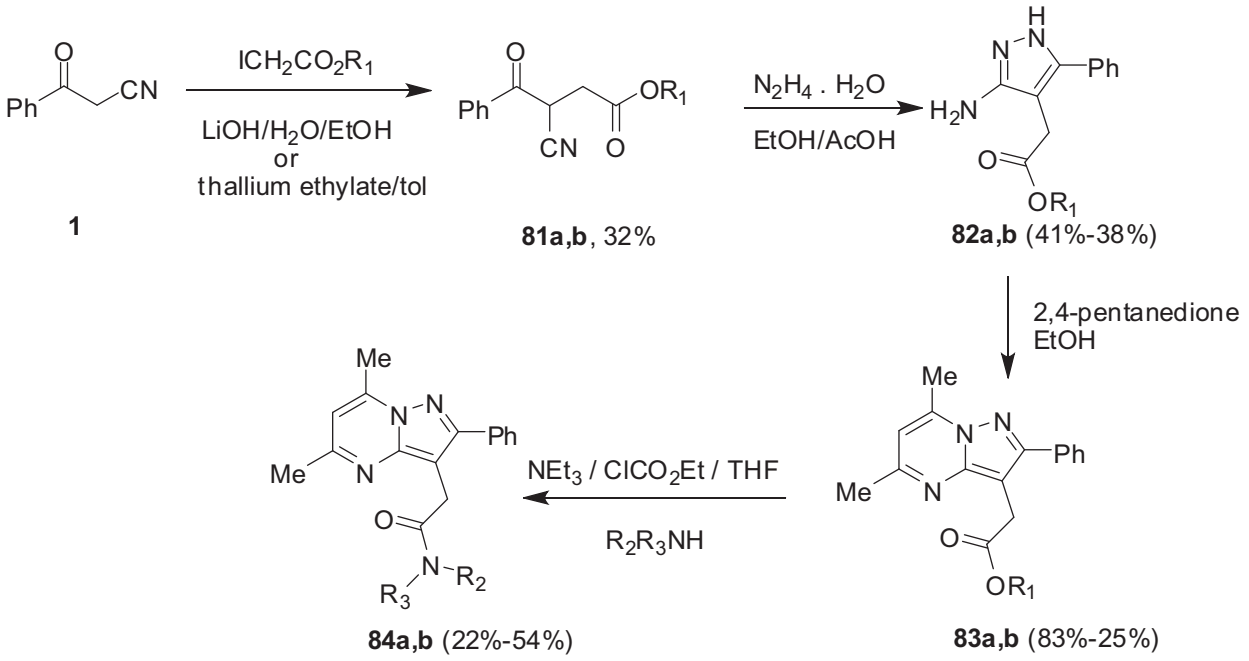
(3*S*,10*S*,13*S*)-10,13-Dimethyl-17-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate **78** was reacted readily with **1** in refluxing ethanol to afford the Knoevenagel condensed product 17-(2′-benzoylacetonitrile-2′-ylideno)androstane **79**. Compound **79** was reacted with hydrazine in refluxing ethanol/piperidine solution to afford the corresponding 17-(5′-aminopyrazol-4′-ylideno)-androstane derivatives **80** (Scheme 26).[76]



Scheme 26.

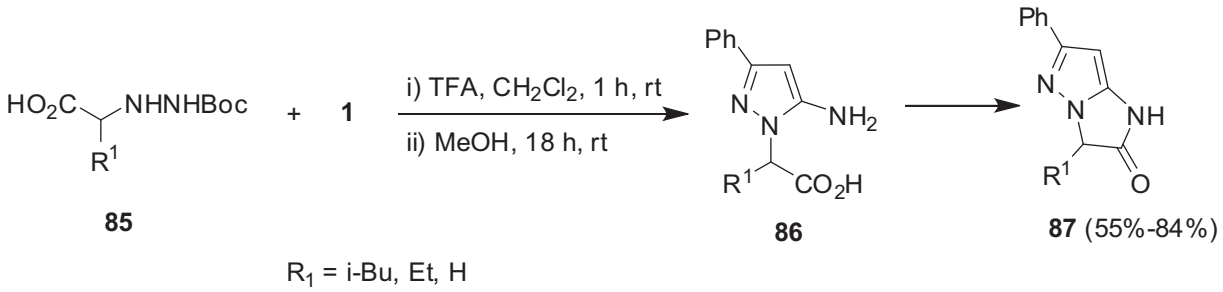
Compound **1** was reacted in basic medium ($LiOH/H_2O$) with iodoacetic acid or ethyl iodoacetate to give the corresponding acid **81a** and ester **81b**, respectively. 1,4-Dicarbonyl compounds **81a**,**b** were reacted in ethanol at reflux with hydrazine hydrate, in the presence of acetic acid, to give the corresponding 3-amino pyrazoles **82a**,**b** in good yield and purity. The condensation of the latter compounds with 2,4-pentanedione was carried out, which led to the closure of the pyrimidine ring, resulting in the intermediate **83a** and the final compound **83b**. Subsequently, the acid **83a** was converted into a mixed anhydride with ethyl chloroformate,

and this intermediate reacted with a large number of amines affording the corresponding amides **84** in good yields and in a short time (Scheme 27).[77]



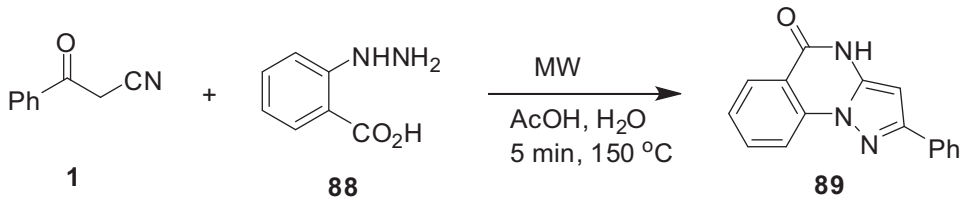
Scheme 27.

The heterocyclization of **1** with α-hydrazino acids **85** was reported to give 5-aminopyrazoles **86**, which underwent intramolecular cyclodehydration to give the corresponding imidazo[1,2-b]pyrazol-2-ones **87** (Scheme 28).[78]



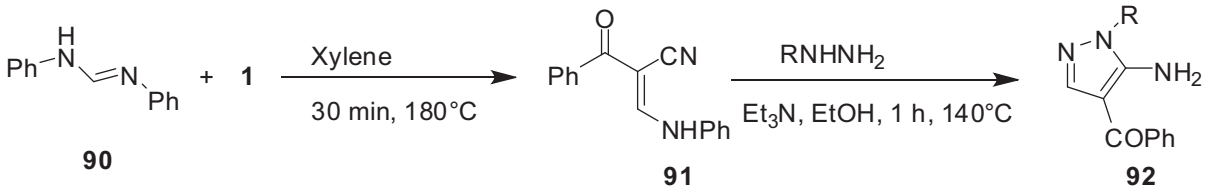
Scheme 28.

The 1-pot synthesis of 2-phenylpyrazolo[1,5-a]quinazolin-5(4H)-one **89** in good yield was reported by condensation of **1** with 2-hydrazino-benzoic acid **88** in acetic acid using microwave irradiation (Scheme 29).[10,11,79] The synthesized compound is used as inhibitor of the enzyme poly (ADP-ribose)polymerase (PARP).[10,11]



Scheme 29.

The pyrazolyl ketone, which exhibits good oral bioavailability and high selectivity for p38 MAPK, i.e. RK protein phosphorylating kinase over other kinases, is a key pharmacophore that could find application in the treatment of Werner syndrome. Microwave irradiation promoted the Knoevenagel condensation of **1** and N,N'-diphenylformimidamide **90**, to give β-aminovinyl ketones **91**, and their subsequent cyclocondensation with hydrazines provided pyrazolyl ketones **92** (Scheme 30).[80]

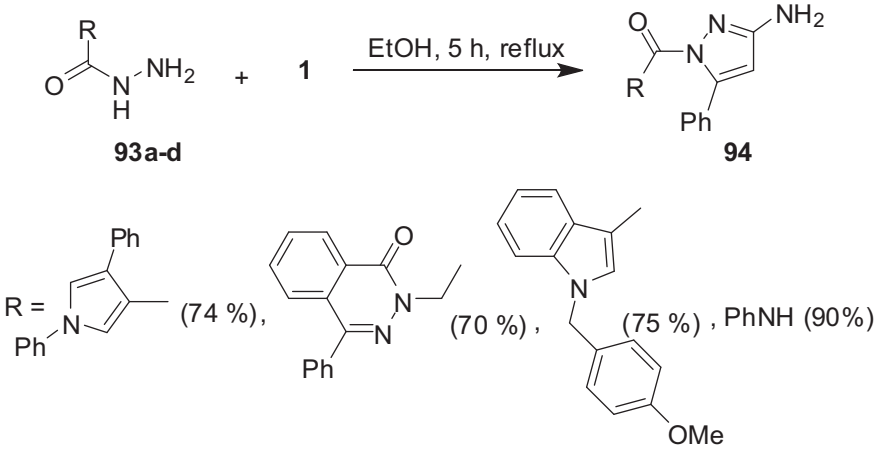


R = Ph, 4-FC_6H_4; 4-BrC_6H_4; 2,6-$Cl_2C_6H_3$; 2,4-$F_2C_6H_3$; 4-ClC_6H_4; C_6F_5; 2-FC_6H_4; 2,5-$Cl_2C_6H_3$; 4-IC_6H_4

Scheme 30.

3.1.2. Reaction with hydrazides

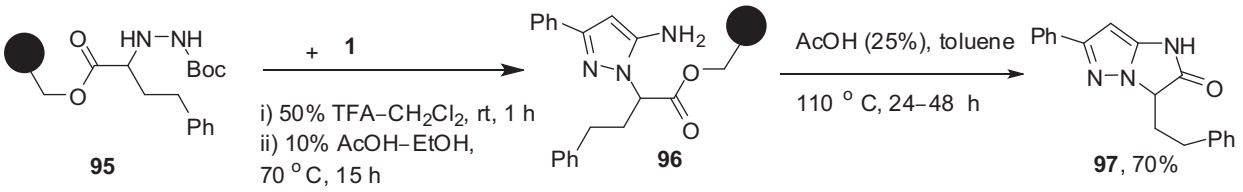
Condensation of compound **1** with hydrazides such as 2-(1-oxo-4-phenylphthalazin-2(1*H*)-yl)acetohydrazide **93a**,[81] 1-(4-methoxybenzyl)-1*H*-indole-3-carbohydrazide **93b**,[82] 1,4-diphenyl-1*H*-pyrrole-3-carbohydrazide **93c**,[6] and *N*-phenylhydrazinecarboxamide **93d**[83] in either acetic acid or ethanol at reflux temperature gave 1-aroyl-3-amino-5-phenyl-1*H*-pyrazoles **94**. The latter compounds were tested in vitro for tumor cell-growth inhibition (Scheme 31).



Scheme 31.

Resin-bound Boc protected α-hydrazino esters **95** were deprotected under standard conditions (50% TFA in dichloromethane) and were treated with **1** in ethanol in the presence of 10% acetic acid at 70 °C to provide

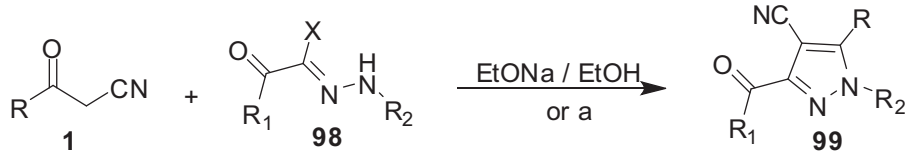
the requisite amino pyrazoles **96** on solid support. Treatment of the resin with 25% acetic acid solution in toluene at 110 °C provided the desired cyclized product **97** in good yield (Scheme 32).[84]



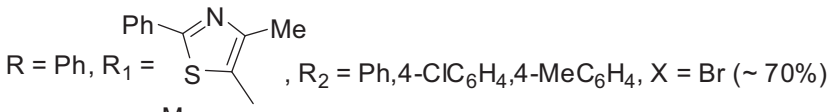
Scheme 32.

3.1.3. Reaction with hydrazonoyl halides

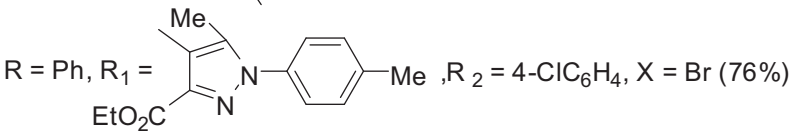
Hydrazonoyl halides, such as ethyl 4-(2-bromo-2-(2-(4-chlorophenyl)hydrazono)acetyl)-5-methyl-1-p-tolyl-1*H*-pyrazole-3-carboxylate,[85] *N*'-aryl-2-(4-methyl-2-phenylthiazol-5-yl)-2-oxoacetohydrazonoyl bromide,[86] 2-oxo-*N*′-m-tolylpropanehydrazonoyl chloride,[87] 2-oxo-*N*'-phenyl-2-(thiophen-2-yl)acetohydrazonoyl bromide, 2-oxo-*N*'-aryl-2-(phenylamino)acetohydrazonoyl bromide, ethyl 2-(2-(2-bromophenyl)hydrazono)-2-chloroacetate,[88] 2-(benzofuran-2-yl)-2-oxo-*N*'-phenylacetohydrazonoyl bromide,[89] *N*′-(aryl)-2-oxopropanehydrazonoyl bromide,[90] 1-bromo-2-(5-chlorobenzofuranyl)ethanedione-1-phenylhydrazone,[91,92] 2-oxo-*N*′-phenyl-2-(phenylamino) acetohydrazonoyl chloride,[93] and ethyl 2-(2-(2-bromophenyl)hydrazono)-2-chloroacetate,[94] were reacted with **1** in either ethanolic sodium ethoxide or $EtN(Pr\text{-}i)_2$ in acetonitrile at reflux to give substituted pyrazole-4-carbonitriles **99** (Scheme 33).



R = Ph, R_1 = Me, R_2 = 3-MeC_6H_4, X = Cl (70%); R_1 = 2-thienyl, R_2 = Ph, X = Br (78%)
R = Ph, R_1 = 2-benzofuryl, R_2 = Ph,4-ClC_6H_4,4-$MeIC_6H_4$, X = Br
R = Ph, R_1 = 5-chloro-2-benzofuryl, R_2 = Ph, X = Br (67%)
R = Ph, R_1 = PhNH, R_2 = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, X = Cl (~ 70%)



, R_2 = Ph,4-ClC_6H_4,4-MeC_6H_4, X = Br (~ 70%)

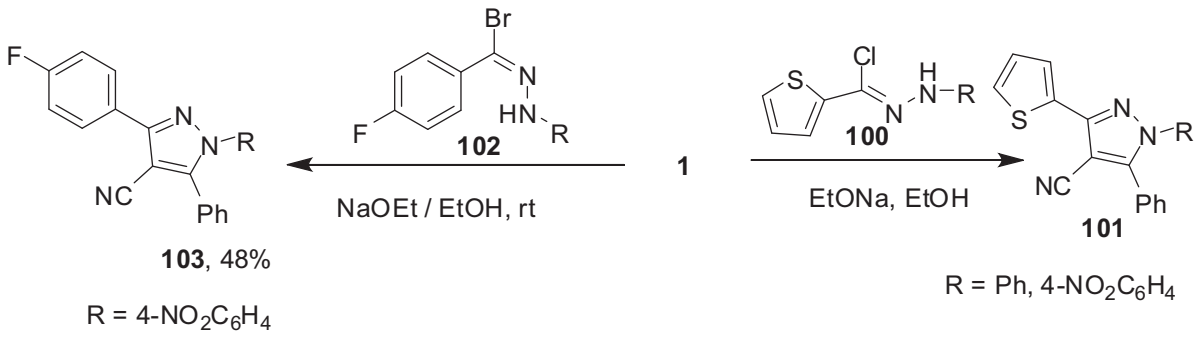


,R_2 = 4-ClC_6H_4, X = Br (76%)

R = Ph, 4-$OMeC_6H_4$, R_1 = OEt, R_2 = 2-BrC_6H_4, X = Cl; a: $EtN(Pr\text{-}i)_2$, MeCN, 16 h, reflux (12%)

Scheme 33.

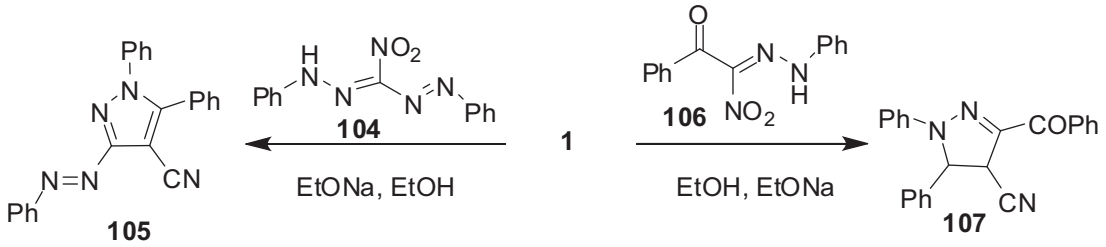
The reaction between compound **1** with either *N*'-arylthiophene-2-carbohydrazonoyl chloride **100**[95,96] or 4-fluoro-N'-(4-nitrophenyl)benzohydrazonoyl bromide **102**[97] in sodium ethoxide gave pyrazole-4-carbonitriles **101** and **103**, respectively (Scheme 34).



Scheme 34.

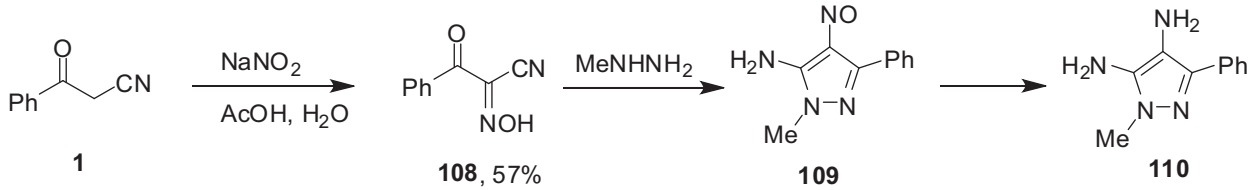
3.1.4. Miscellaneous methods

Compound **1** was reacted with either 3-nitro-1,5-diphenylformazan **104** or 2-nitro-1-phenyl-2-(2-phenylhydrazono) ethanone **106** in ethanol in the presence of sodium ethoxide to yield 1,5-diphenyl-3-(phenyldiazenyl)-1*H*-pyrazole-4-carbonitrile **105**[98] and 3-benzoyl-1,5-diphenyl-4,5-dihydro-1*H*-pyrazole-4-carbonitrile **107**,[99] respectively (Scheme 35).



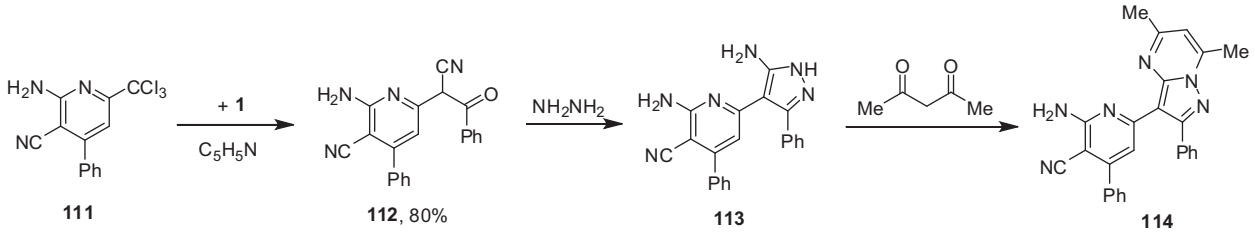
Scheme 35.

3-Phenyl-4,5-diaminopyrazole **110** was prepared by nitrosation of **1** followed by condensation of the resulting *N*-hydroxy-2-oxo-2-phenylacetimidoyl cyanide **108** with methyl hydrazine to form 5-amino-4-nitrosopyrazole **109** followed by catalytic hydrogenation (Scheme 36).[100]



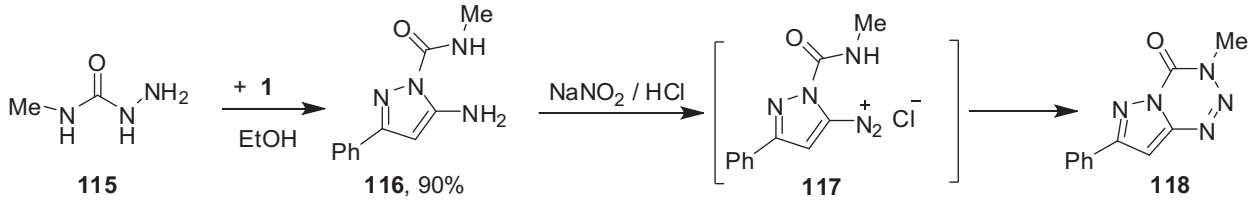
Scheme 36.

2-Amino-4-phenyl-6-(trichloromethyl)nicotinonitrile **111** was reacted with **1** in pyridine to give 2-amino-6-(1-cyano-2-oxo-2-phenylethyl)-4-phenylnicotinonitrile **112**, which was cyclized with hydrazine to afford aminopyrazolylpyridine **113**. The latter compound was cyclocondensed with acetylacetone to give 2-amino-6-(5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidin-3-yl)-4-phenylnicotinonitrile **114** (Scheme 37).[101]



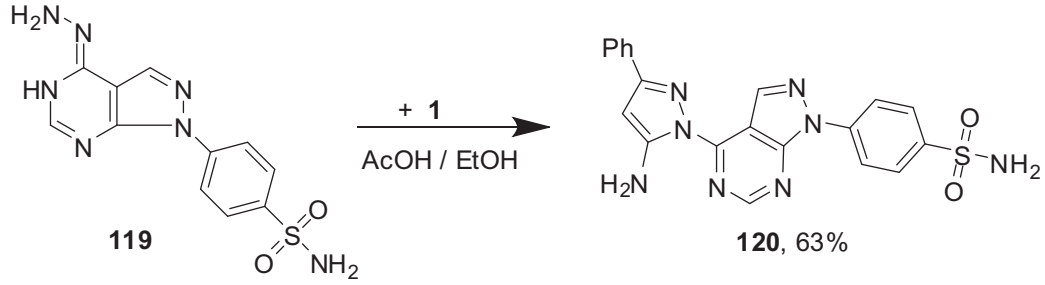
Scheme 37.

3-Methyl-7-phenylpyrazolo[5,1-*d*][1,2,3,5]tetrazin-4(3*H*)-one **118** was formed by cycloaddition of compound **1** with *N*-methylhydrazinecarboxamide **115** to afford 5-amino-*N*-methyl-3-phenyl-1*H*-pyrazole-1-carboxamide **116** followed by diazotization of the latter compound and subsequent intramolecular coupling (Scheme 38).[102]



Scheme 38.

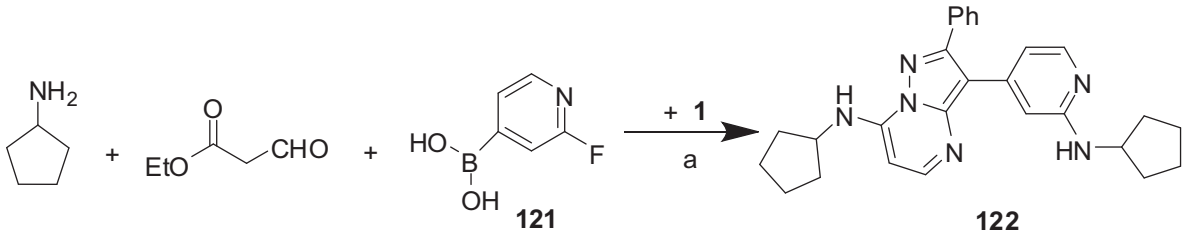
The synthesis of pyrazoles linked to pyrazolo[3,4-*d*]pyrimidine **120** incorporating benzenesulfonamide moiety as antimicrobial reagent was reported. 4-(4-Hydrazono-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)benzenesulfonamide **119** was reacted with **1** to give the target molecule (Scheme 39).[103]



Scheme 39.

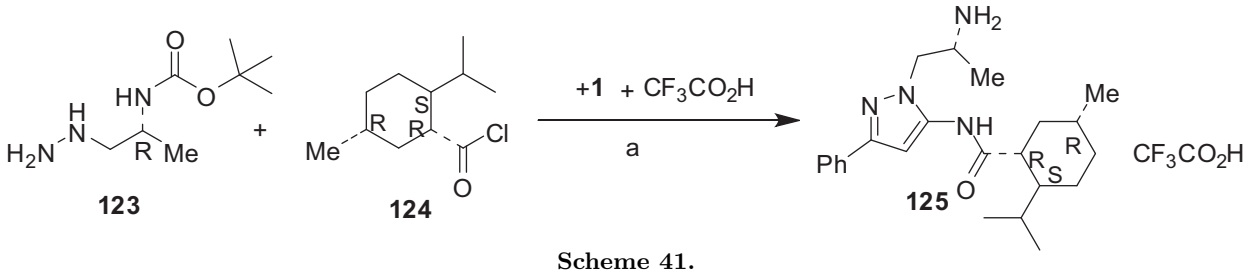
Pyrazolopyrimidine **122** was prepared, as orally bioavailable inhibitors of herpes simplex viruses, by 4-component reaction of **1**, ethyl 3-oxopropanoate, cyclopentanamine, and 2-fluoropyridin-4-ylboronic acid **121** (Scheme 40).[104]

(*R*)-*tert*-Butyl 1-hydrazinylpropan-2-ylcarbamate **123** was reacted with (1*R*,5*R*)-2-isopropyl-5-methylcyclohexanecarbonyl chloride **124** and **1** in the presence of triflouroacetic acid to afford (1*R*,5*R*)-N-(1-((*R*)-2-aminopropyl)-3-phenyl-1*H*-pyrazol-5-yl)-2-isopropyl-5-methylcyclohexanecarboxamide **12 5**, which acts as modulator of Trp-p8 (transient receptor potential-p8) activity (Scheme 41).[105]



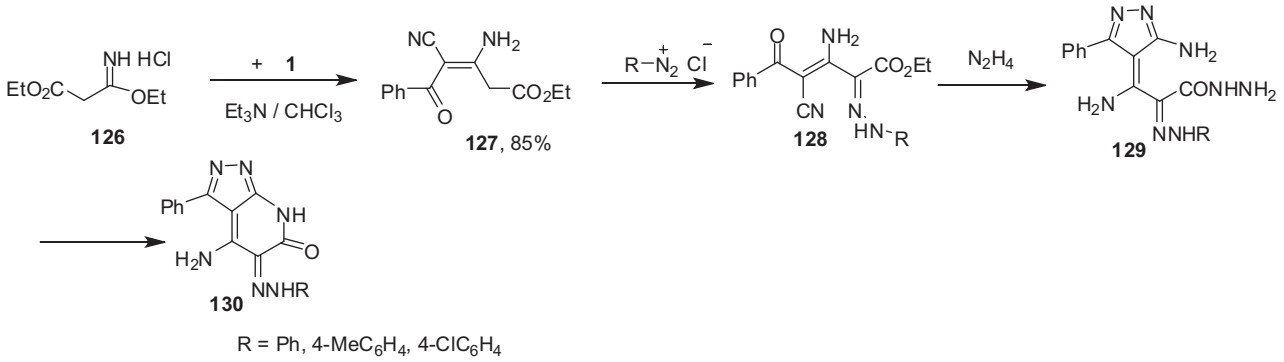
a: i) NH_2NH_2 . H_2O / EtOH / reflux; ii) Na / EtOH / rt ; iii) $POCl_3$ / 100°C
iv) *N*-bromosuccinimide / CH_2Cl_2; v) Na_2CO_3 / $PdCl_2(PPh_3)_2$

Scheme 40.



Scheme 41.

Condensation of compound **1** with ethyl 3-ethoxy-3-iminopropanoate **126** gave ethyl (*E*)-ethyl 3-amino-4-cyano-5-oxo-5-phenylpent-3-enoate **127**. Then the latter compound was coupled with aryldiazonium chloride to give hydrazones **128**, which on treatment with N_2H_4 gave hydrazides **129**. Compounds **129** were converted to pyrazolo[3,4-*b*]pyridines **130** by refluxing with AcOH-HCl (Scheme 42).[106]



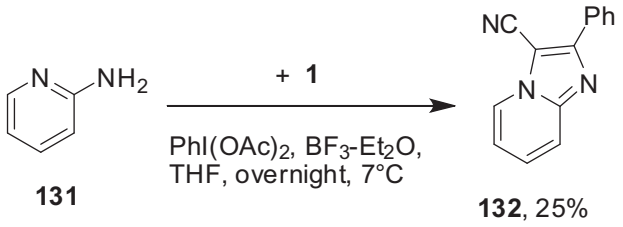
Scheme 42.

3.2. Imidazoles and their fused derivatives

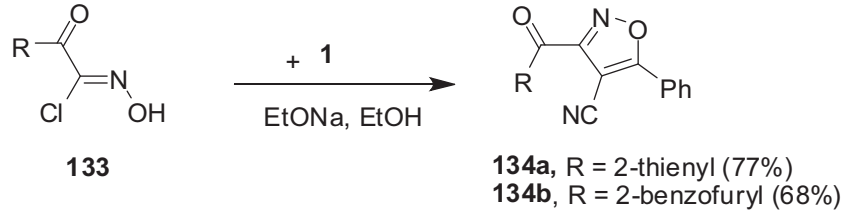
2-phenylimidazo[1,2-*a*]pyridine-3-carbonitrile **132** was prepared directly from the reaction of **1** with 2-aminopyridine **131** using bis(acetyloxy)(phenyl)-λ^3-iodane as an oxidant and boron trifluoride etherate as a catalyst (Scheme 43).[107]

3.3. Isoxazoles and their fused derivatives

Either 2-thenoylcarbohydroximoyl chloride **133a**[108] or benzofuroylhydroxamoly chloride **133b**[109] was reacted with **1** in ethanol in the presence of sodium ethoxide at reflux temperature to afford 5-phenylisoxazole-4-carbonitriles **134a**,**b**, respectively (Scheme 44).

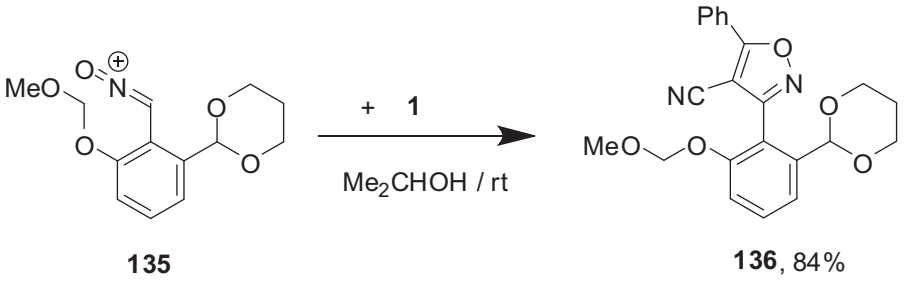


Scheme 43.



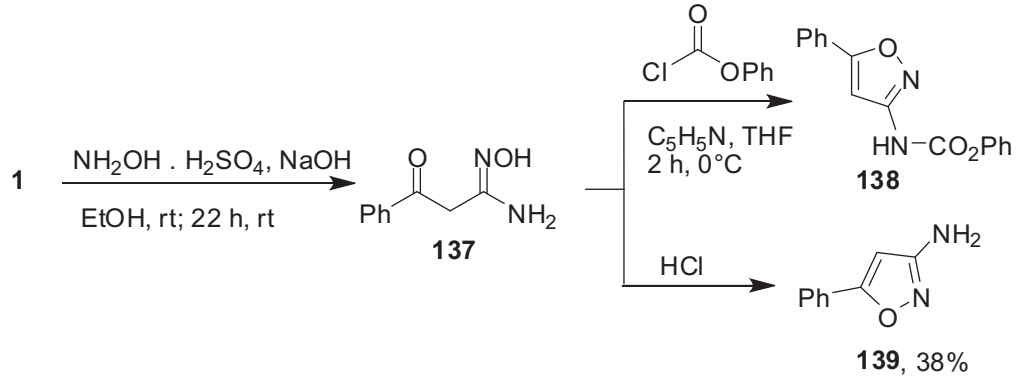
Scheme 44.

Base-promoted cyclocondensation of ortho-disubstituted benzonitrile oxide **135** with **1** afforded highly functionalized isoxazole **136** (Scheme 45).[110]



Scheme 45.

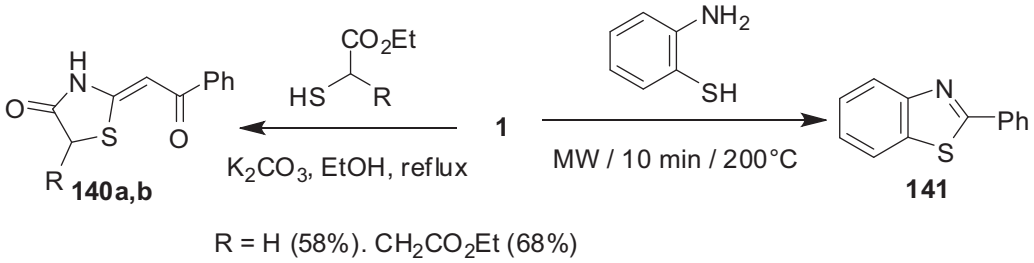
Regioselective reaction of **1** with hydroxylamine followed by treatment of the resulting 3-oxopentaneamidoxime **137** with either phenyl carbonochloridate or hydrochloride acid gave 5-phenylisoxazol-3-amine **138** and **139**, respectively, in poor yields (38%) (Scheme 46).[111]



Scheme 46.

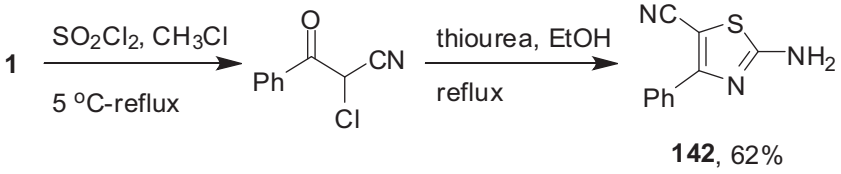
3.4. Thiazoles and their fused derivatives

Stereoselective base-catalyzed reaction of **1** with either ethyl 2-mercaptoacetate[112] or diethyl 2-mercaptosuccinate[113–117] in either ethanol containing potassium carbonate at reflux temperature or under solvent-free conditions and without solid support[118] afforded exclusively (*Z*)-2-(2-oxo-2-phenylethylidene)thiazolidin-4-ones **140**. Synthesis of benzothiazole **141** in excellent yield was achieved via microwave irradiation of a 1:1 mixture of compound **1** and o-aminothiophenol (Scheme 47).[119]



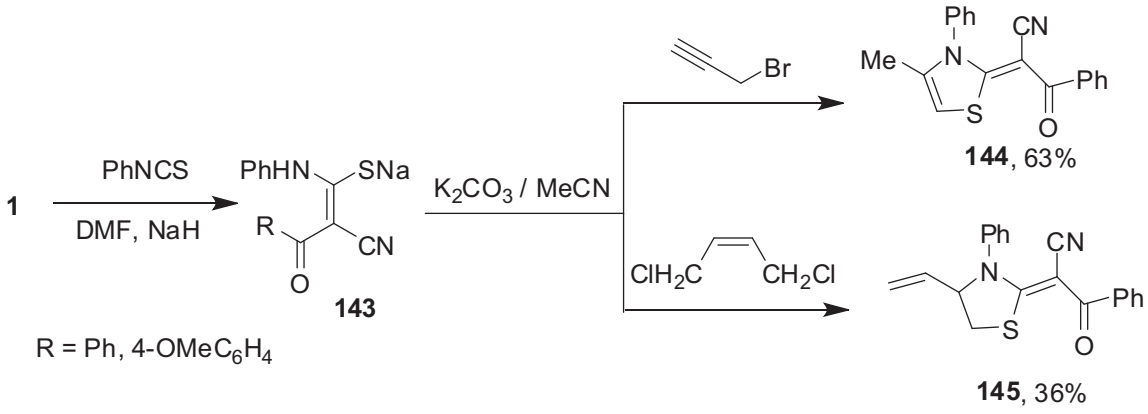
Scheme 47.

2-Amino-4-phenylthiazole-5-carbonitrile **142** was prepared in 62% yield from compound **1** by chlorination with sulfuryl dichloride followed by treatment with thiourea in refluxing ethanol (Scheme 48).[120]



Scheme 48.

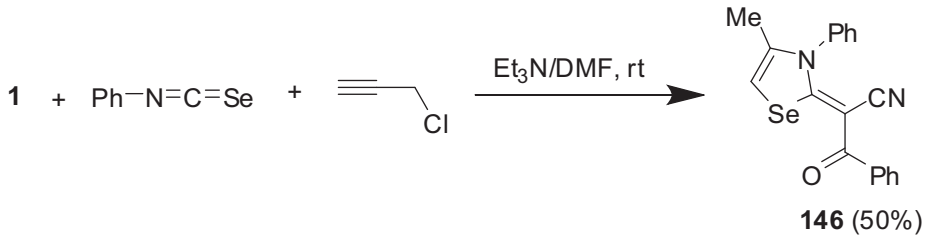
2-Alkylidene-3-phenylthiazoles were prepared as organic intermediates, useful in the synthesis of biological active substances. Compound **1** was treated with phenylisothiocyanate in DMF containing NaH to give **143**. The latter was reacted with either 3-bromoprop-1-yne **24**[121] or (Z)-1,4-dichlorobut-2-ene[122,123] in acetonitrile containing K_2CO_3 at reflux temperature to afford **144** and **145**, respectively (Scheme 49).



Scheme 49.

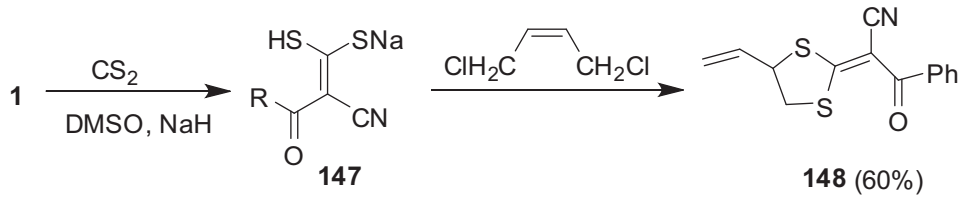
3.5. Selenazoles and dithiolanes and their fused derivatives

Phenylisoselenocyanate was reacted with **1** and 3-chloroprop-1-yne in DMF in the presence of triethyl amine to give (*Z*)-2-(4-methyl-3-phenyl-1,3-selenazol-2(3*H*)-ylidene)-3-oxo-3-phenylpropanenitrile **146** (Scheme 50).[124]



Scheme 50.

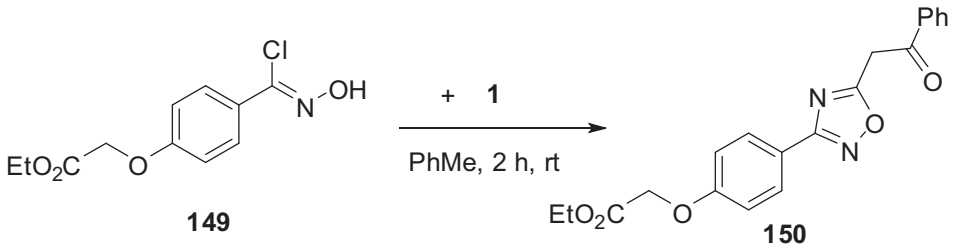
(3-Oxo-3-phenyl-2-(4-vinyl-1,3-dithiolan-2-ylidene)propanenitrile **148** in 61% yield was prepared by treating **1** with CS_2 in stirring Me_2SO containing NaH. Then the resulting **147** was cyclocondensed with 1,4-dichlorobut-2-ene (Scheme 51).[125,126]



Scheme 51.

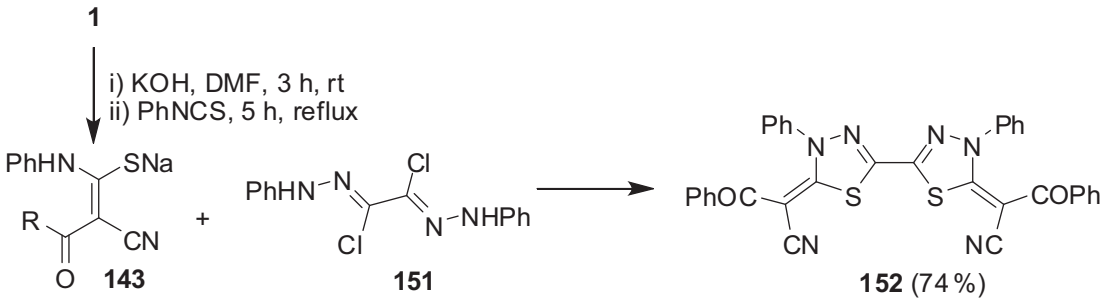
4. Others 5-membered rings with 3 or 4 heteroatoms

1,3-Dipolar cycloaddition of compound **1** with ethyl 2-(4-(chloro(hydroxyimino)methyl)phenoxy)acetate **149** gave 3,5-disubstituted 1,2,4-oxadiazole **150** (Scheme 52).[127]



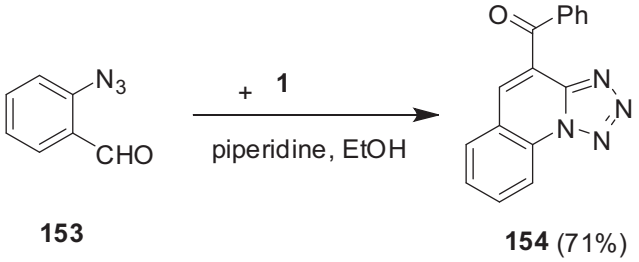
Scheme 52.

Bis-1,3,4-thiadiazolidine **152** was synthesized via cycloaddition of compound **143**, which was prepared from the reaction of **1** with phenylisothiocyanate with bis-hydrazonoyl chloride **151** in DMF containing potassium hydroxide (Scheme 53).[128,129]



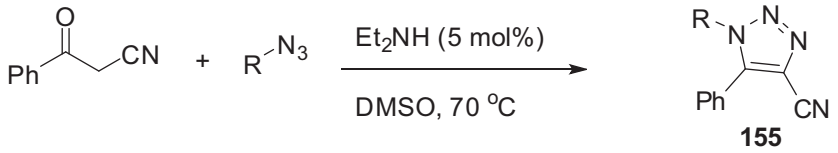
Scheme 53.

2-Azidobenzaldehyde **153** undergoes base-catalyzed condensation with **1** to yield tetrazolo[1,5-*a*]quinoline **154** (Scheme 54).[130]



Scheme 54.

1,4,5-Trisubstituted-1,2,3-triazoles **155** were regioselectively prepared via organocatalytic enamide-azide cycloaddition reaction of compound **1** with azide (Scheme 55).[131]



R = Ph (92%); 4-ClC_6H_4 (96%), 3-ClC_6H_4 (94%); 3-$CF_3C_6H_4$ (91%); 4-$CF_3C_6H_4$ (99%);4-$O_2NC_6H_4$ (91%); 3-Me,4-ClC_6H_3 (94%); 4-$OMeC_6H_4$ (87%); 4-OHC_6H_4 (98%); 3,5-$Me_2C_6H_3$ (91%);4-$iPrC_6H_4$ (95%); $PhCH_2$ (80%)

Scheme 55.

5. Conclusion

Benzoylacetonitriles are versatile and convenient intermediates for preparation of heterocyclic compounds due to the presence of 3 active moieties: nitrile, carbonyl, and active methylene functions. This survey attempted to summarize the synthetic potential of benzoylacetonitriles, as starting precursor, in the synthesis of 5-membered heterocycles since 1985. The synthetic methods and utility of benzoylacetonitriles in the synthesis of 6-membered heterocycles were covered in separate review articles.[17*f*,*g*]

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