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RING OPENING RING CLOSURE REACTIONS WITH 3-SUBSTITUTED CHROMONES UNDER NUCLEOPHILIC CONDITIONS

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Abstract – This review covers the ring opening ring closure (RORC) reactions of 3-substituted chromones with a variety of nitrogen and carbon nucleophiles. The nucleophilic reagent usually attack 3-substituted chromones at the C-2 position with γ-pyrone ring opening followed by further transformation during the course of the reaction producing a variety of products depending on the substrate at position 3, the nature of nucleophile and the reaction conditions.

CONTENTS

1. INTRODUCTION

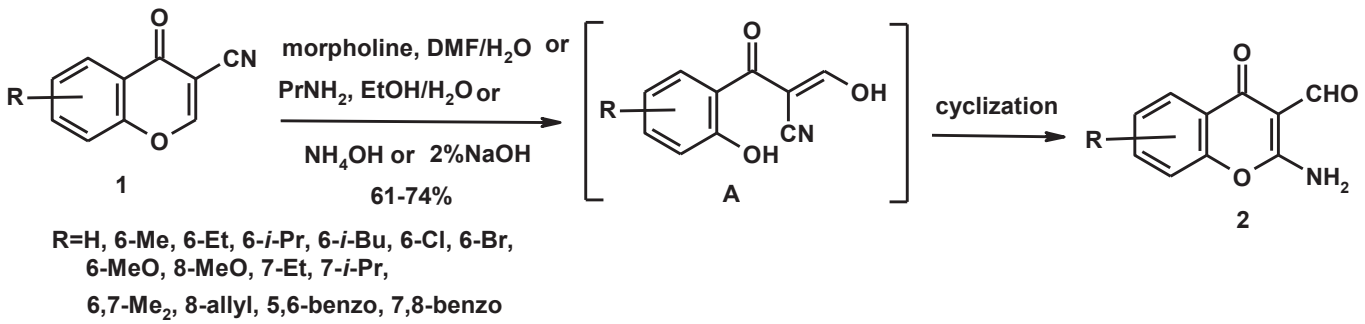
Chromones constitute one of the major classes of naturally occurring compounds,[1] and they are useful as biologically active agents.[2-6] The chromone moiety is an essential pharmacophore of a large number of bioactive molecules.[7-9] The biological activity of chromone derivatives include cytotoxic (anticancer).[10-13] neuroprotective,[14,15] HIV-inhibitory,[16,17] antimicrobial,[18-20] antifungal,[21] anti-inflammatory,[22] antiplatelet,[23] antidiabetics,[24] antitumor,[25] antiviral,[6] and antioxidant activity.[26] Also, chromones possess a broad diversity in treatment of ulcers,[27] and schizophrenia.[28] Due to their abundance in plants and their

low mammalian toxicity, chromone derivatives are present in large amounts in the diet of humans.[29,30] 3-Substituted chromones are very active substrates toward nucleophilic reagents. The chemical reactivity of 3-substituted chromones is widely different depending on the nature of the functional group present at position 3, nature of nucleophile and the reaction conditions. Among the 3-functionalized chromones, their 3-formyl derivatives are widely used in heterocyclic synthesis. Several reviews in the chemistry of 3-formylchromones are published.[31-36] Herein, the present review summarize the ring opening ring closure (RORC) reactions of other 3-substituted chromones with a variety of nitrogen and carbon nucleophiles. Introduction of electron-withdrawing [CN, $CONH_2$, CO_2H, CO_2R, NO_2, X (Cl, Br or I)] group at the 3-position of a chromone system increase significantly the reactivity of the γ-pyrone ring with respect to nucleophiles, and provides a broad synthetic potential for 3-substituted chromones.

2. RORC REACTIONS WITH CHROMONE-3-CARBONITRILES

Chromone-3-carbonitriles **1** being an α,β-unsaturated ketone and possess three electron deficient sites *viz*. C-2, cyano carbon and carbonyl carbon, the last one having obviously the least electrophilicity compared to the other two carbons.[37] An initial addition of the nucleophile to carbonitriles **1** and any subsequent transformations, if possible, of the adducts depend on the nature of the nucleophile as well as the reaction conditions.

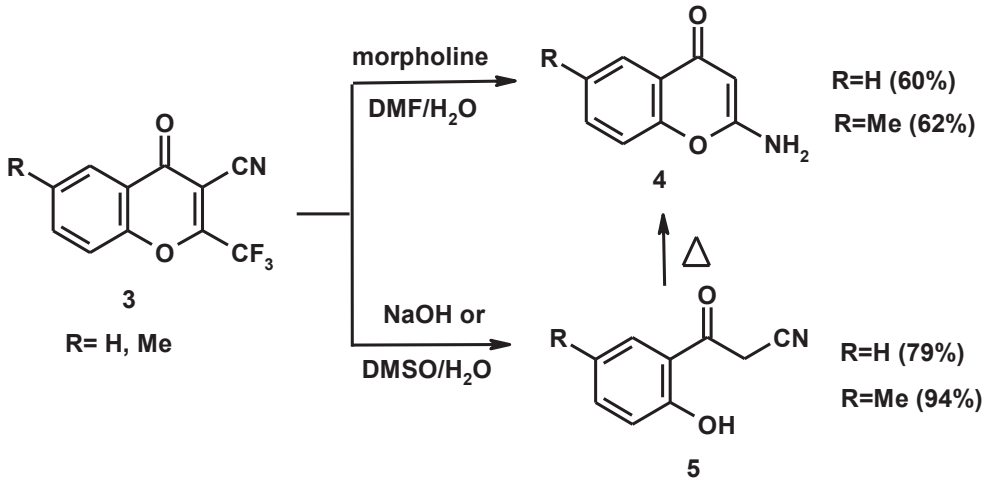
Among the diverse transformations of carbonitriles **1**, one of the most important, is their conversions on heating with morpholine in an aqueous DMF,[38] or with *n*-propylamine in an aqueous ethanol,[39] or with concentrated ammonia,[40] or with aqueous NaOH solution,[41] into 2-amino-3-formylchromones **2**, *via* the intermediate **A** (Scheme 1). This transformation was achieved *via* γ-pyrone ring opening followed by recyclization; in other words, the chromone-3-carbonitriles **1** are 'chemically equivalent' to 2-amino-3-formylchromones **2** under certain reaction conditions.



Scheme 1

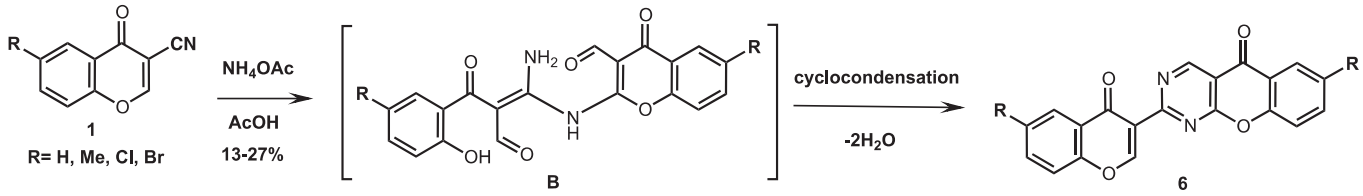
In marked contrast to the known behavior of chromone-3-carbonitriles **1**, 2-trifluoromethyl-chromone-3-

carbonitrile (**3**) under the same basic conditions undergoes facile detrifluoroacetylation giving either 2-aminochromone (**4**) with morpholine in an aqueous DMF, and salicyloylacetonitrile (**5**) with aqueous NaOH or DMSO/H_2O. The latter readily isomerizes on heating into 2-aminochromone **4** (Scheme 2).[42]



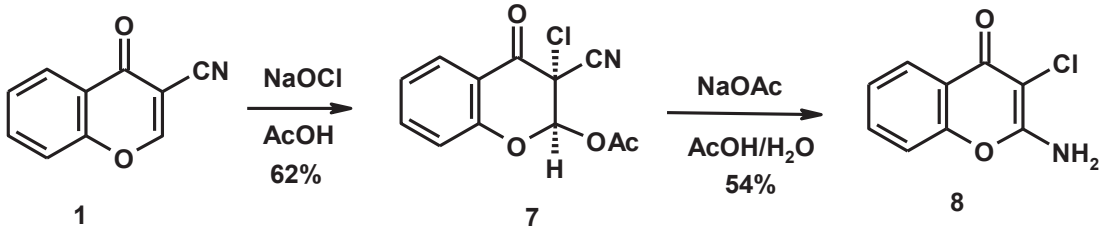
Scheme 2

Chromone-3-carbonitriles **1** when refluxed in ammonium acetate and acetic acid underwent self-condensation, through its tautomeric forms **2**, yielding 2-(chromen-3-yl)chromono[2,3-*d*]pyrimidines **6**, *via* the intermediate **B** (Scheme 3).[39,43]



Scheme 3

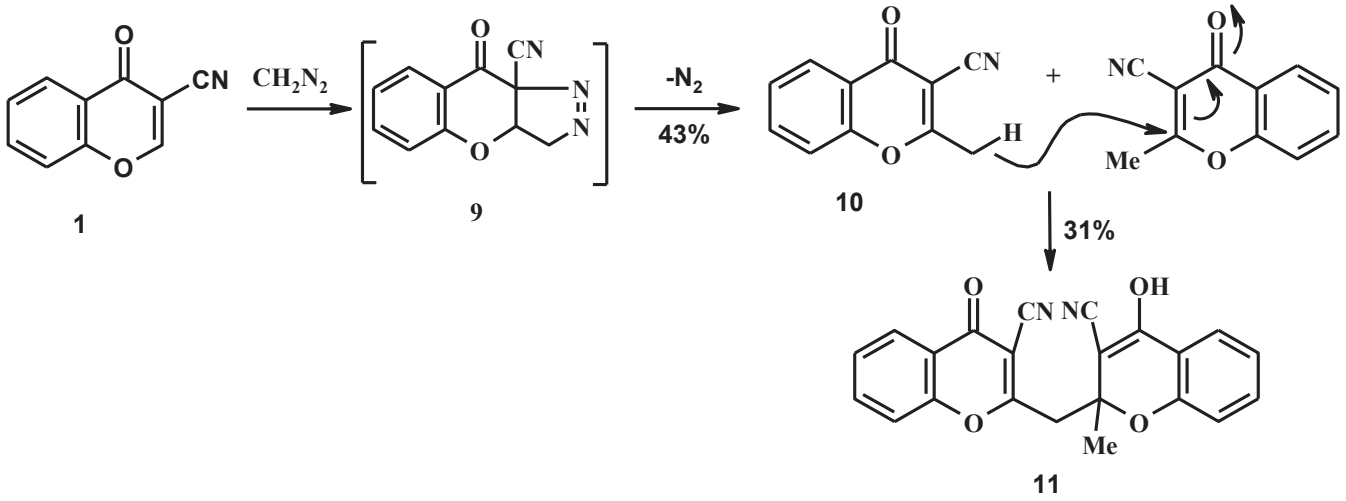
Carbonitrile **1** dissolved in acetic acid reacted with aqueous sodium hypochlorite solution producing 1,2-addition product **7** which upon hydrolysis with aqueous acetic acid in the presence of sodium acetate yielded the rearranged product, 2-amino-3-chlorochromone (**8**) (Scheme 4).[44]



Scheme 4

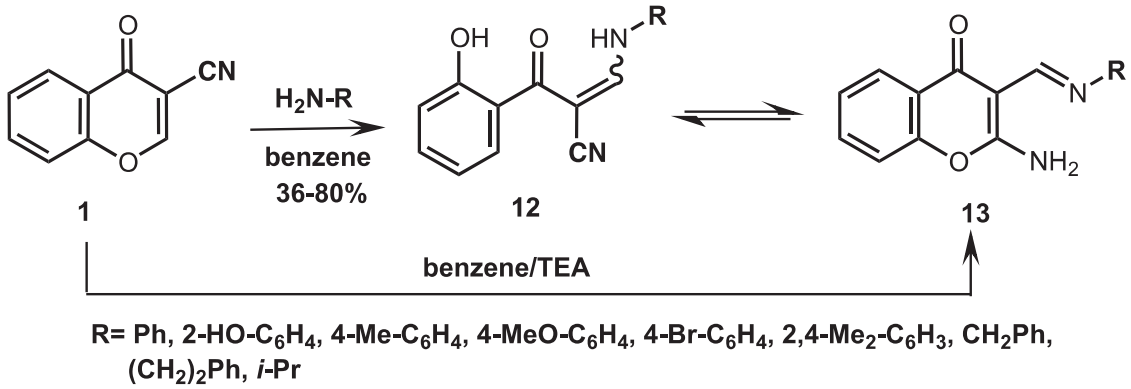
Diazomethane undergoes [3+2] cycloaddition with the 2,3-olefinic bond of carbonitrile **1** giving the 1-

pyrazoline intermediate **9** that by a concerted electrocyclic elimination of nitrogen molecule and migration of hydrogen yielded 3-cyano-2-methylchromone (**10**); base catalyzed *Michael* addition of compound **10** to the α,β-unsaturated keto function of a second molecule of compound **10** gave the dimeric product **11**, diazomethane or the pyrazoline **9** act as a base in the latter reaction (Scheme 5).[45]



Scheme 5

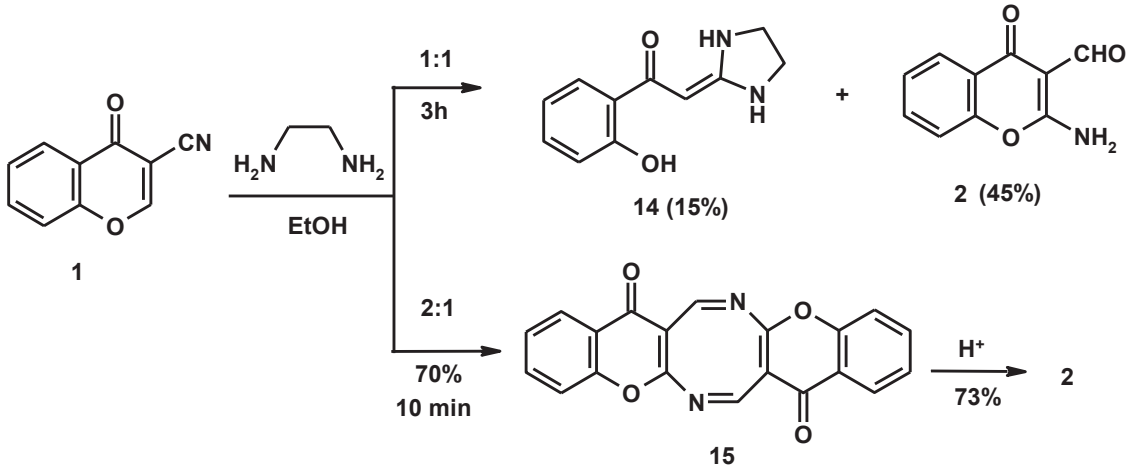
Reactions of carbonitrile **1** with primary aromatic amines in boiling benzene gave a mixtures of *Z*- and *E*-3-arylamino-2-(2-hydroxyaroyl)acrylonitriles **12** and 2-amino-3-(aryliminomethyl)chromones **13** (Scheme 6). The latter compounds **13** can easily be obtained in the individual state when the reaction was carried out in the presence of triethylamine, which accelerates the cyclization step *via* deprotonation of the phenolic hydroxyl group. In the case of primary aliphatic amines, the open chain product **12** immediately undergoes cyclization into 3-alkyliminomethyl-2-aminochromones **13** in good yields.[46-48]



Scheme 6

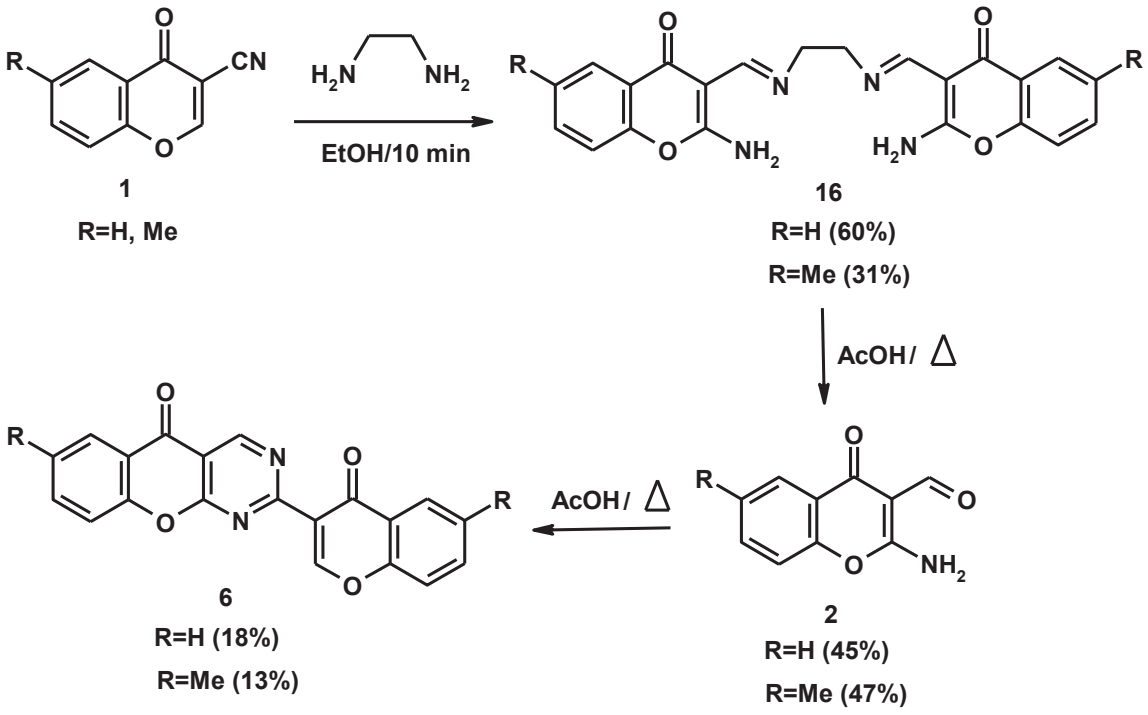
The reaction of carbonitrile **1** with ethylenediamine in boiling ethanol was firstly studied by Ghosh and Tewari,[39] and isolate 1-(2-hydroxyphenyl)-2-imidazolid-2-ylidene)ethanone (**14**) (15%) together with 2-amino-3-formylchromone **2** (45%); when the reaction was performed in boiling ethanol for 3 h in 1:1

molar ratio (Scheme 7). While, Ghosh *et al*.[49] postulated the formation of *bis*-chromeno[2,3-*b*:2',3'-*f*]-[1,5]diazocine (**15**) when the reaction was carried in boiling ethanol for 10 min in 2:1 molar ratio. Hydrolysis of compound **15** under acidic conditions afforded compound **2** (Scheme 7), in this reaction ethylenediamine, as aliphatic amine, induced self-condensation of carbonitrile **1**.



Scheme 7

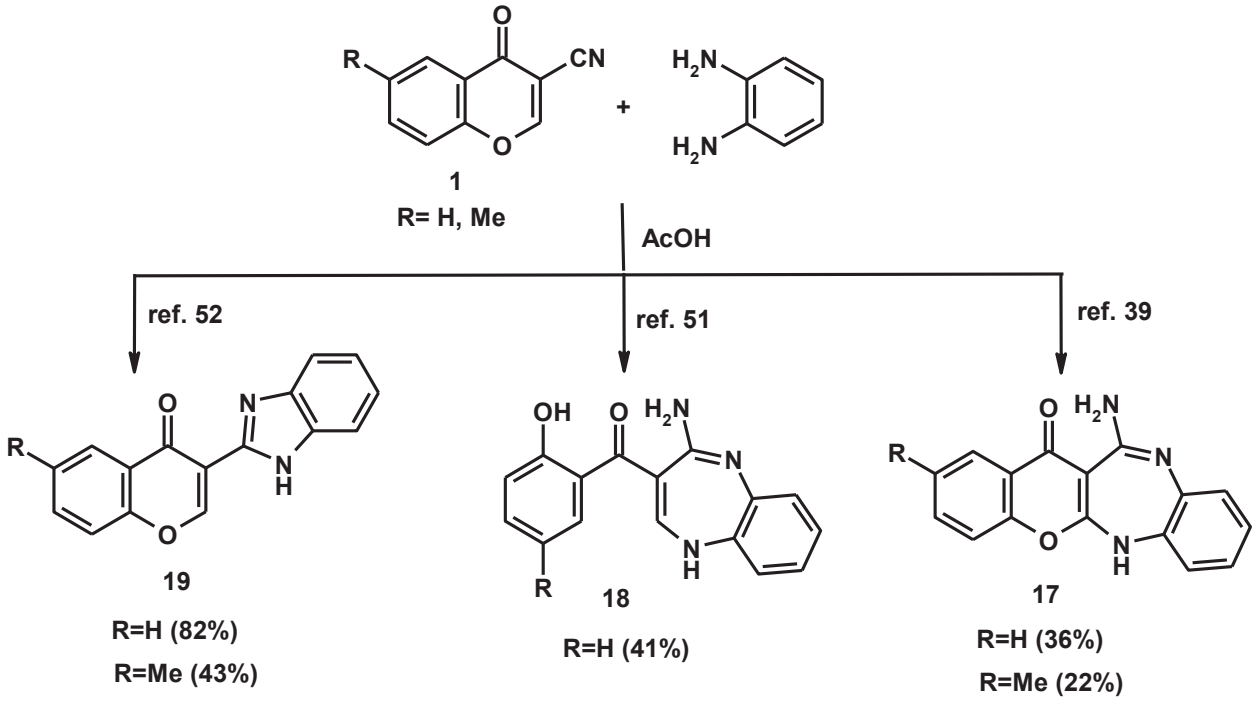
The previous reaction was next studied by Sosnovskikh *et al*.[50] and isolate *N*`,*N*`-ethylene-*bis*(2-amino-3-iminomethylchromones) **16**, when the reaction was performed in boiling ethanol for 10 min in 1:1 molar ratio. Depending on the time of refluxing in acetic acid, the later compound gave either 2-amino-3-formylchromones **2** or the products of their dimerization, 2-(chromen-3-yl)-5*H*-chromeno[2,3-*d*]-pyrimidin-5-ones **6** (Scheme 8).[50]



Scheme 8

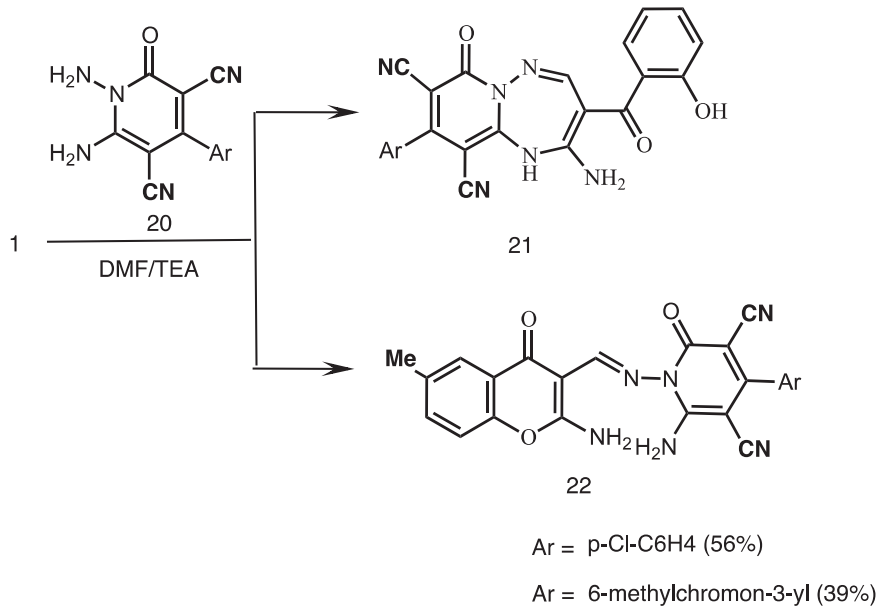
Also, there is contradictory information in literature regarding the structure of the product obtained from

the reaction between carbonitrile **1** and *o*-phenylenediamine. Hence, Ghosh and Tewari,[39] postulate the formation of chromeno[2,3-*b*][1,5]benzodiazepines **17**. While, Risitano and his coworkers [51] repeated the reaction and postulate the formation of benzodiazepines **18**. Next, the reaction was reinvestigated and the product was expected to be 3-(benzimidazol-2-yl)chromones **19** (Scheme 9).[52]



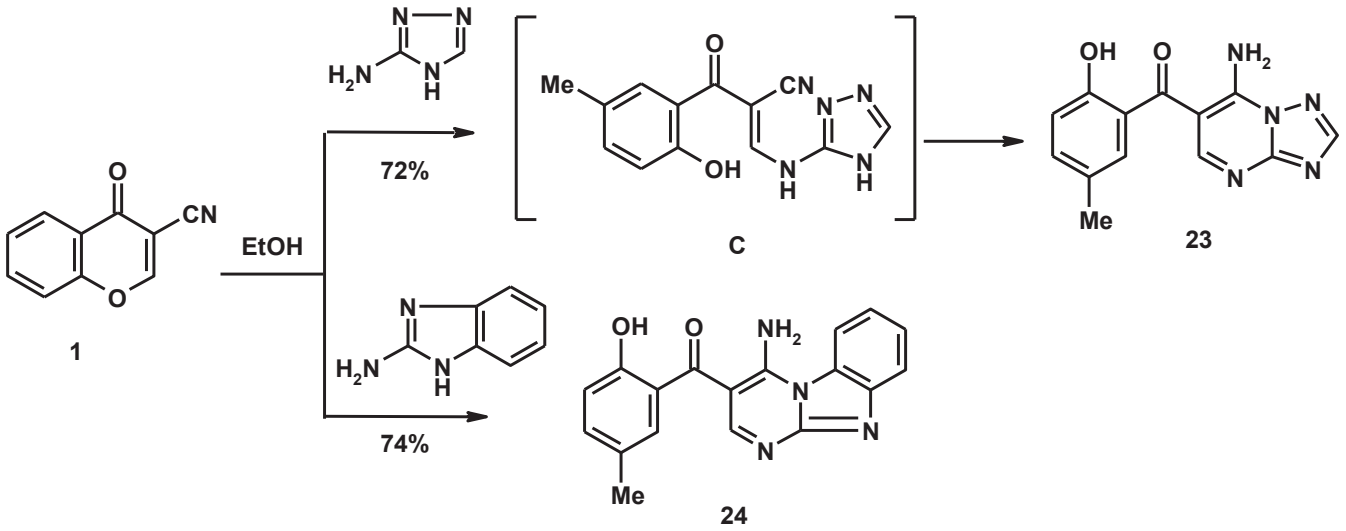
Scheme 9

Similar to the above behavior, reaction of carbonitriles **1** (R=H, CH_3) with 1,6-diaminopyridones **20** in boiling DMF containing triethylamine produced pyridotriazepine derivatives **21**,[53,54] these products were assumed to be the Schiff bases **22** as published by Sosnovskikh and Moshkin (Scheme 10).[55]



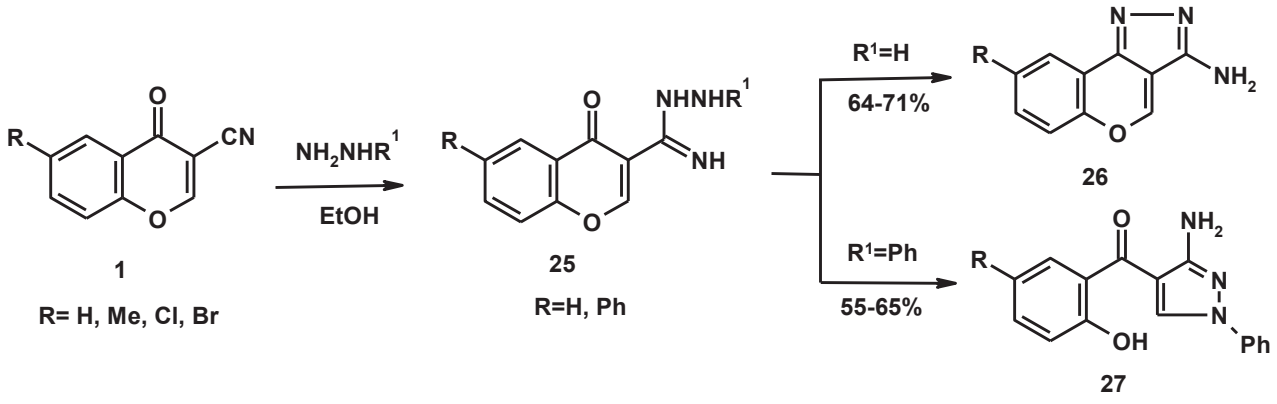
Scheme 10

Recently, the chemical transformations 6-methylchromone-3-carbonitrile (**1**) was studied towards a variety of heterocyclic nitrogen binucleophiles. Thus, treatment of carbonitrile **1** (R= Me) with 3-amino-1,2,4-triazole in absolute ethanol under reflux afforded 5-amino-6-(2-hydroxy-5-methylbenzoyl)-[1,2,4]triazolo[1,5-*a*]pyrimidine (**23**), *via* intermediate **C**, as depicted in Scheme 11. Similarly, reaction of carbonitrile **1** (R=Me) with 2-aminobenzimidazole in boiling ethanol yielded pyrimido[1,2-*a*]-benzimidazole derivative **24**. These reactions take place *via* γ-pyrone ring opening followed by intramolecular cycloaddition onto the nitrile function. (Scheme 11).[56]



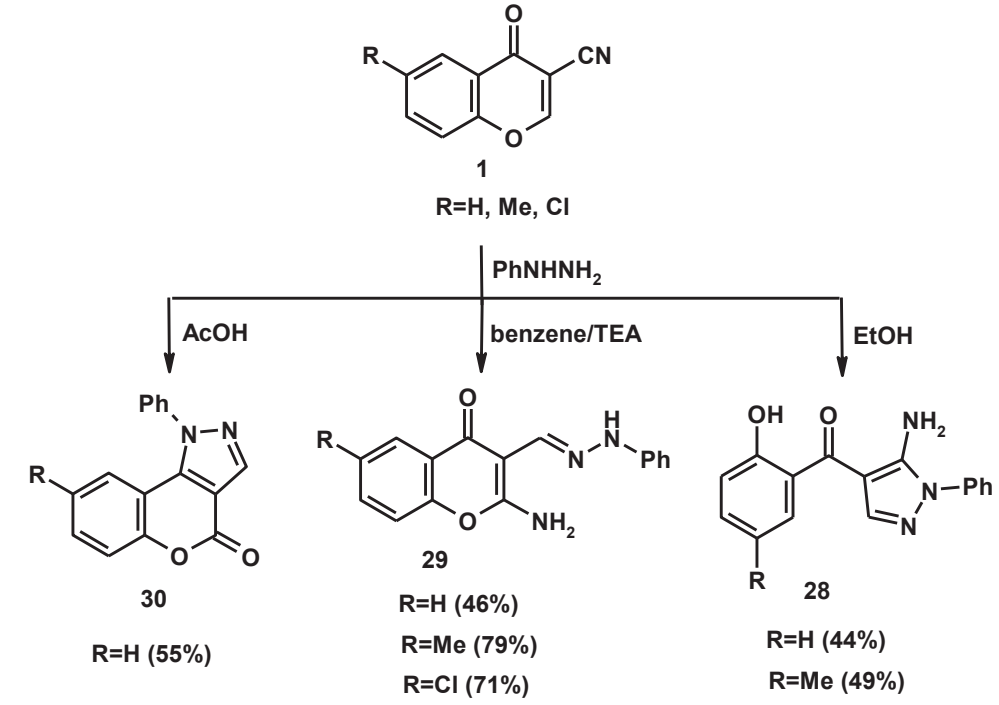
Scheme 11

Previously, the reactions of carbonitriles **1** with hydrazine hydrate and phenylhydrazine were believed to occur *via* 1,2-addition at the cyano group of carbonitrile **1**. Hydrazine undergoes 1,2-addition to the nitrile function in carbonitriles **1** in ethanol under reflux and the resultant iminohydrazine intermediate **25** (R=H; non-isolable) cyclized to the fused pyrazole **26**.[57] In case of phenylhydrazine, under similar conditions the iminiohydrazine **25** (R=Ph; isolable) was obtained and underwent, upon further heating in ethanol, intramolecular γ-pyrone ring opening producing benzoylpyrazole derivative **27** (Scheme 12).[57]



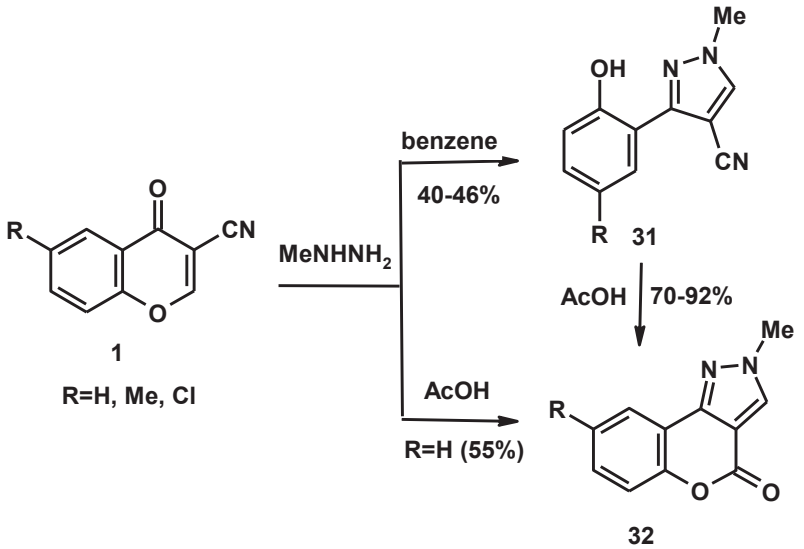
Scheme 12

The previous reactions were reinvestigated by Sosnovskikh *et al.*[58] and different products were isolated depending on the reaction conditions. Reactions of carbonitriles **1** with phenylhydrazine gave the corresponding 5-amino-4-salicyloyl-1-phenylpyrazoles **28** (in ethanol), 2-aminochromone-3-carboxaldehyde-*N*-phenyl-hydrazones **29** (in benzene/TEA), and 1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones **30** (in acetic acid), (Scheme 13).



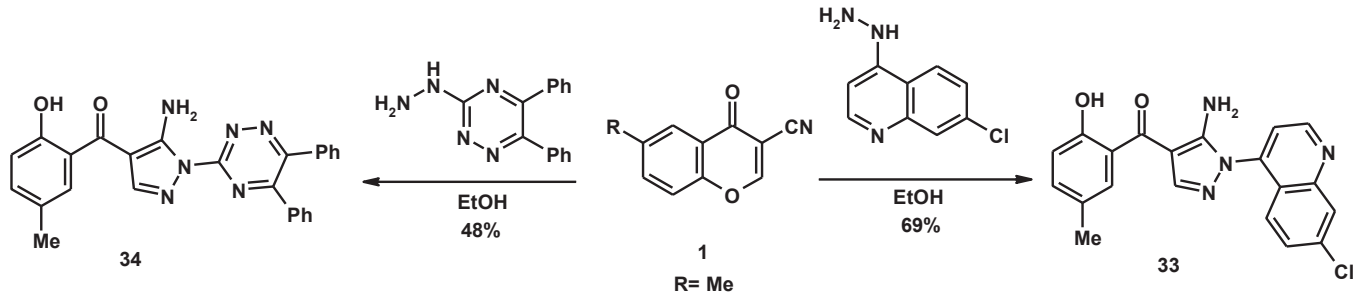
Scheme 13

Carbonitriles **1** reacted differently with methylhydrazine giving 3-(2-hydroxyaryl)-1-methylpyrazole-4-carbonitriles **31** (in benzene) and 2-methylchromeno[4,3-*c*]pyrazol-4(2*H*)-ones **32** (in acetic acid). Boiling pyrazole **31** in acetic acid produced compound **32** (Scheme 14).[58]



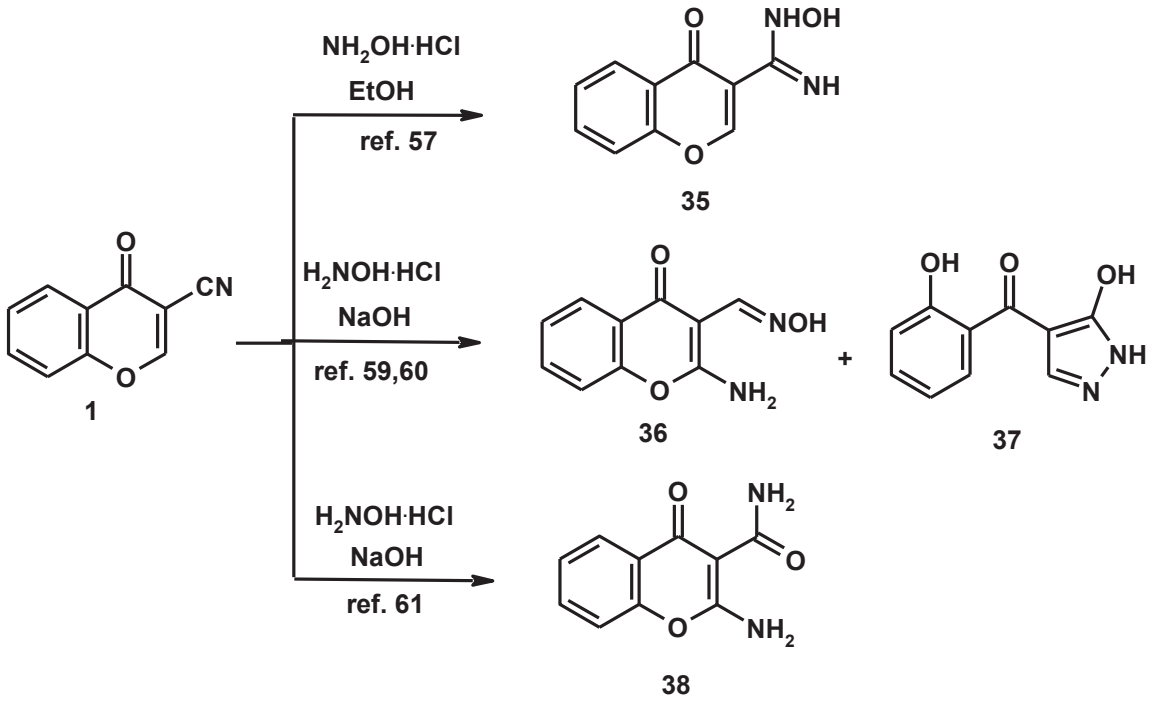
Scheme 14

Treating carbonitrile **1** with 7-chloro-4-hydrazinoquinoline and 3-hydrazino-5,6-diphenyl-1,2,4-triazine in refluxing ethanol led to the quinolinylpyrazole **33** and 1,2,4-triazinylpyrazole **34**, respectively (Scheme 15).[56]



Scheme 15

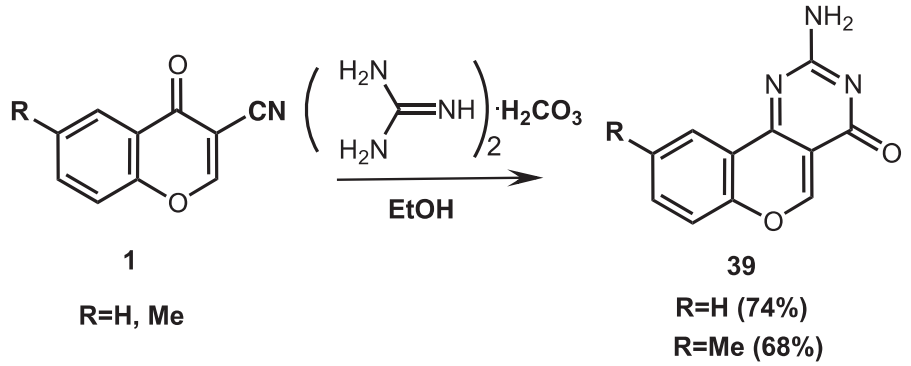
Previously, reaction of carbonitrile **1** and hydroxylamine hydrochloride in boiling ethanol was believed to occur *via* 1,2-addition onto the nitrile function to produce the 1,2-adduct **35** which undergoes no further transformation.[57] A Polish group[59,60] reported the formation of oxime **36** and pyrazolinone **37** by reaction of carbonitrile **1** with an aqueous solution of hydroxylamine hydrochloride and sodium hydroxide (Scheme 16). The reaction of carbonitrile **1** with hydroxylamine hydrochloride was repeated by Sosnovskikh *et al.*[61] and found the product was, in fact, 2-amino-3-carbamoylchromone (**38**) (Scheme 16).



Scheme 16

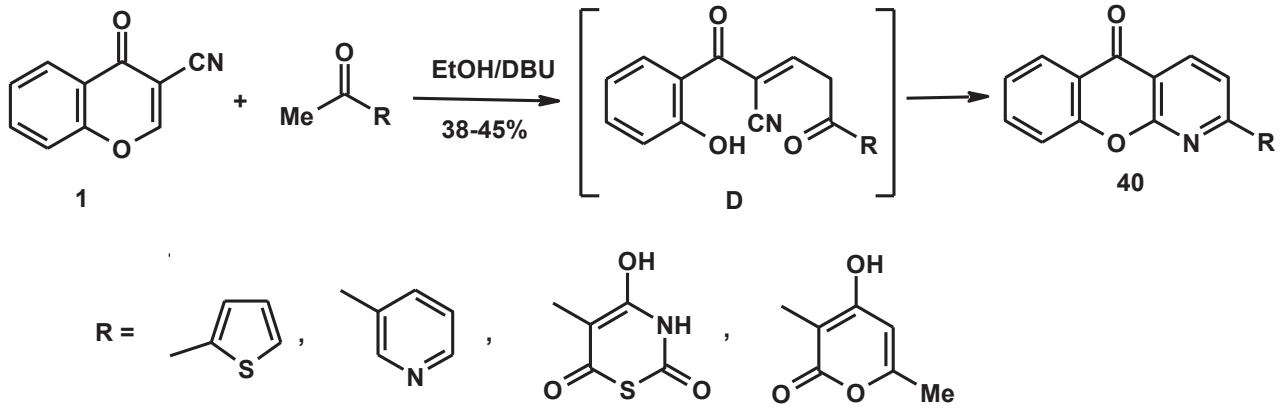
Reaction of carbonitriles **1** with guanidine carbonate in boiling ethanol afforded 2-aminochromeno[4,3-

d]pyrimidin-4(4*H*)-ones **39** (Scheme 17).[50]



Scheme 17

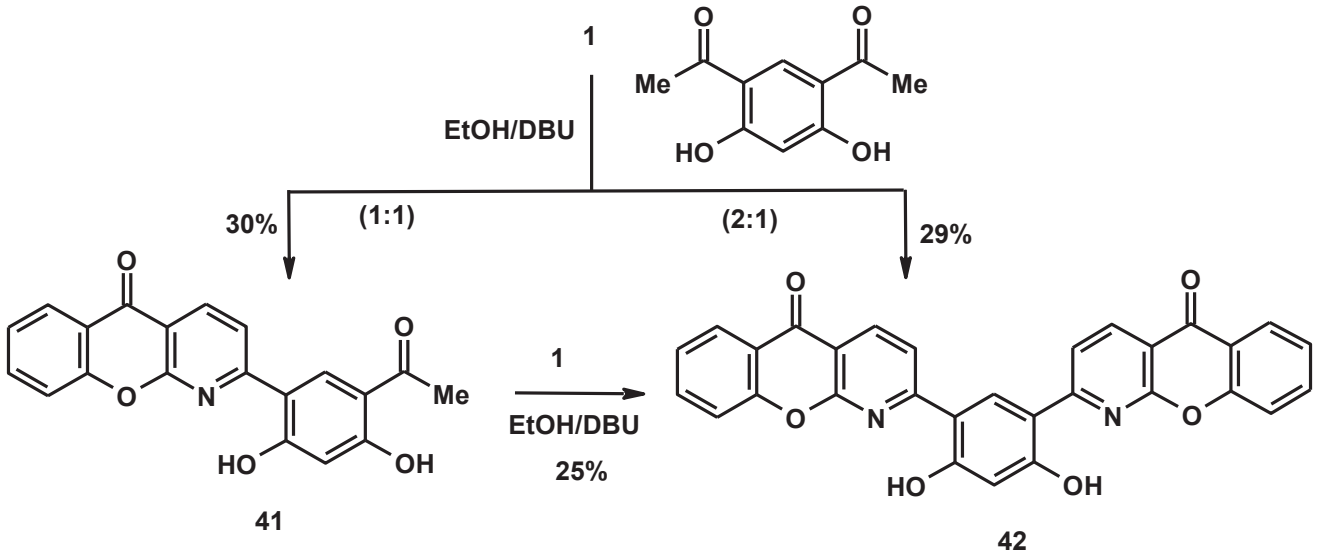
Heteroannulated chromones showed significant biological activity including pharmacological, anti-inflammatory and antiplatelet activities.[62] Chromone-3-carbonitriles **1** are useful intermediates in the synthesis of chromeno[2,3-*b*]pyridines **40** (trivial name: azaxanthones) with anti-inflammatory activity.[63] Reactions of carbonitriles **1** with some active methyl and methylene compounds were studied and a variety of chromeno[2,3-*b*]pyridines and related compounds were efficiently synthesized.[64] Condensation reaction of carbonitrile **1** with some acetyl heterocycles namely; 2-acetylthiophene, 3-acetylpyridine, 5-acetyl-4-hydroxy-2*H*-1,3-thiazine-2,6(3*H*)-dione and 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one, in absolute ethanol containing few drops of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a basic catalyst, afforded 2-heteroaryl-5-oxo-5*H*-chromeno[2,3-*b*]pyridines **40**, *via* the non isolable intermediate **D**, as described by Ibrahim (Scheme 18).[64] The transformation of carbonitrile **1** into chromeno[2,3-*b*]pyridines **40** can be regarded as a domino "*Michael*/retro-*Michael*/nitrile-addition/cyclocondensation".



Scheme 18

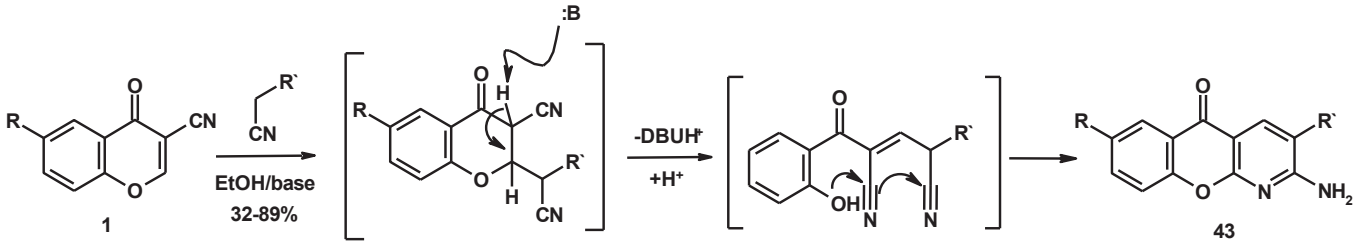
In a similar manner, condensation of carbonitriles **1** with 4,6-diacetylresorcinol in 1:1 and 2:1 molar ratios gave chromeno[2,3-*b*]pyridines **41** and **42**, respectively. 4,6-*Bis*(5-oxo-5*H*-chromeno[2,3-*b*]pyridin-2-yl)-resorcinols **42** were also obtained from the interaction of compounds **41** with carbonitriles **1** under the

same basic conditions (Scheme 19).[64,65]



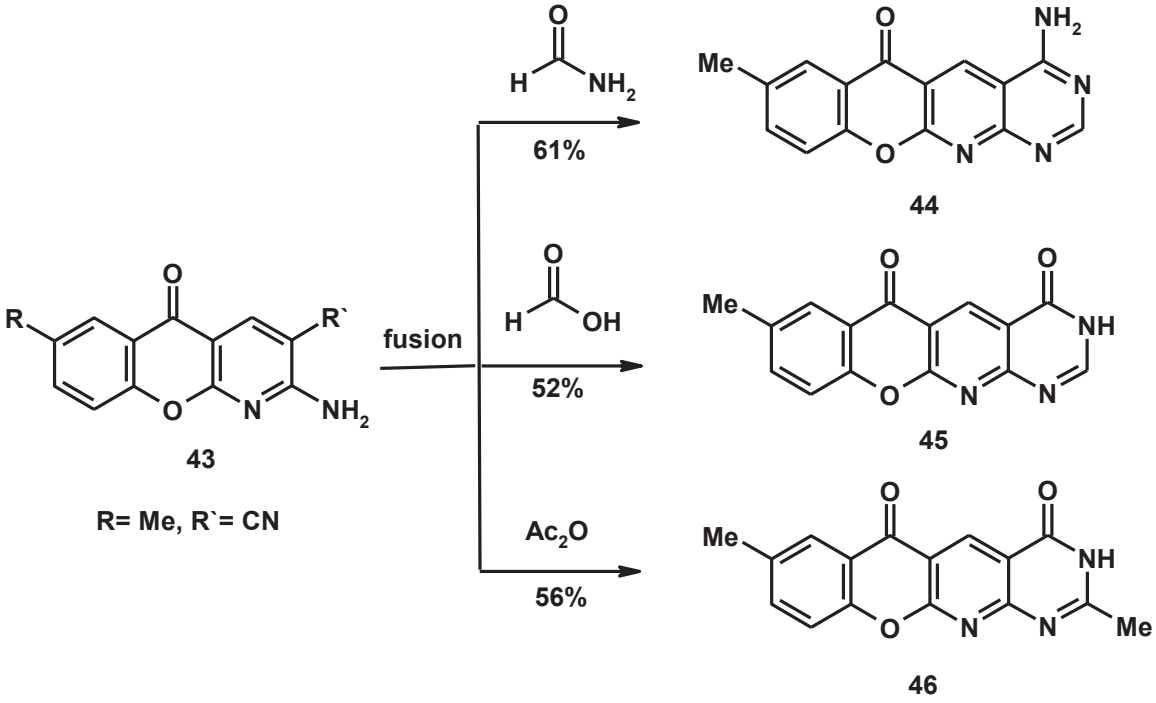
Scheme 19

Various 2-amino-5-oxo-5*H*-chromeno[2,3-*b*]pyridines **43** bearing different substituents at position 3 were synthesized from the reaction of carbonitrile **1** with some active methylenenitriles (-CH_2CN) namely: malononitrile, cyanoacetamide, *N*-benzyl-2-cyanoacetamide, *N*-phenyl-2-cyanoacetamide, ethyl cyanoacetate, phenylacetonitrile, and phenylthioacetonitrile in ethanol containing few drops of DBU (Scheme 20).[65,66]



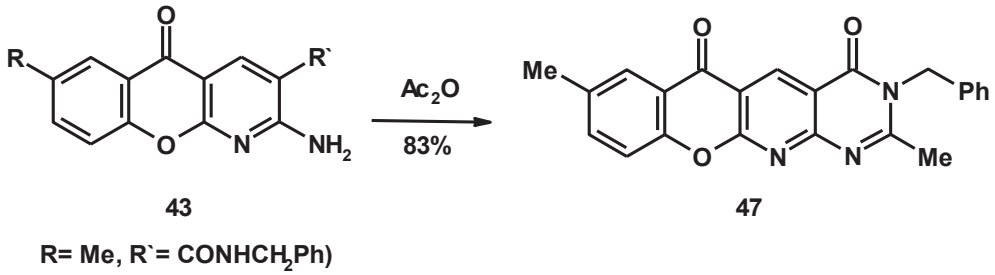
Scheme 20

Chromeno[2,3-*b*]pyridine **43** (R`= CN) was used as a good precursor to synthesize a novel series of heteroannulated chromones identified as chromeno[3',2':5,6]pyrido[2,3-*d*]pyrimidines.[66] Consequently, condensation of compound **43** (R`= CN) with formamide, formic acid and acetic anhydride under fusion conditions afforded 8-methyl-6-oxo-6*H*-chromeno[3',2':5,6]pyrido[2,3-*d*] pyrimidines **44-46**, respectively (Scheme 21).



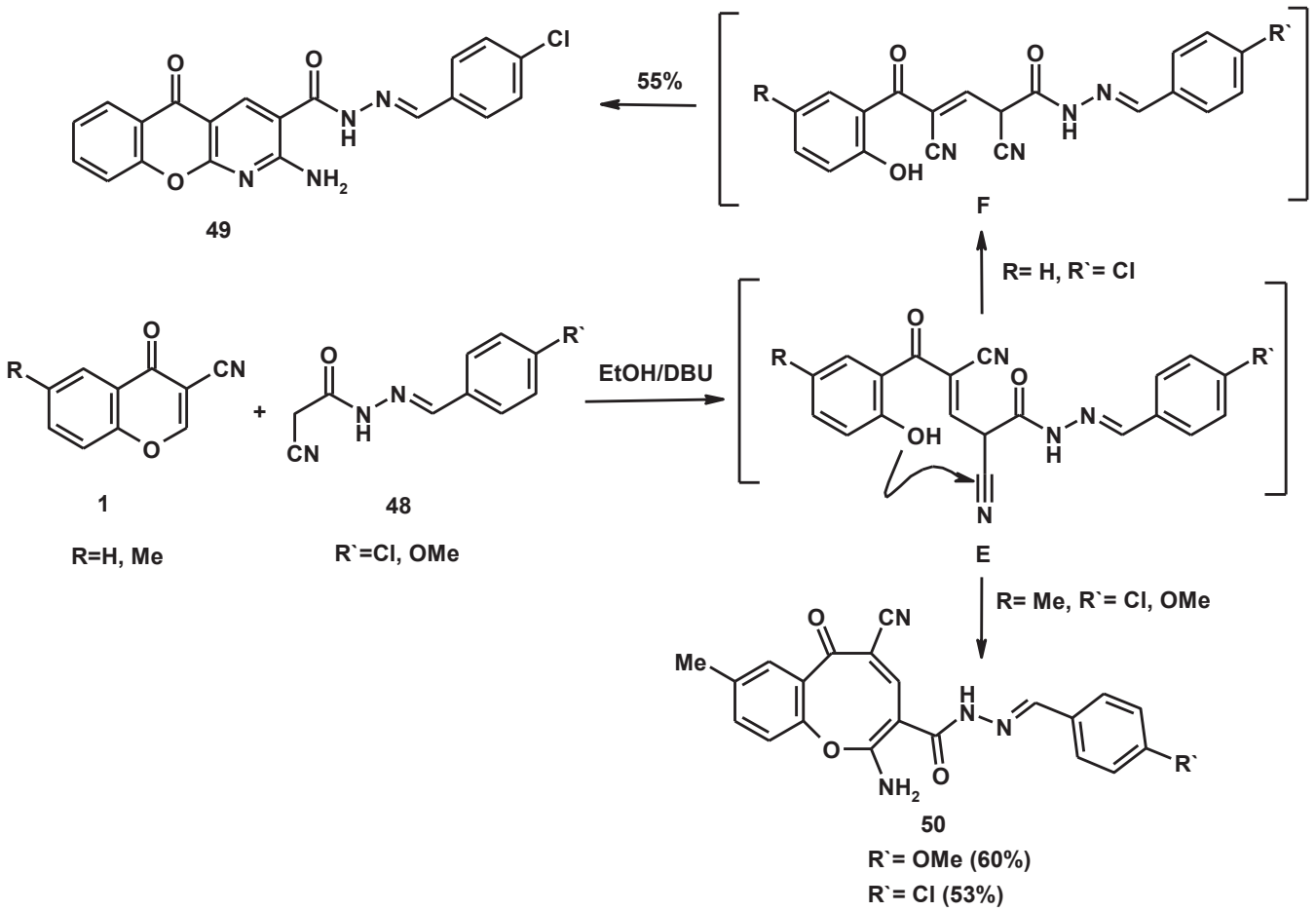
Scheme 21

Heterocyclization of compound **43** (R`=CONHCH$_2$Ph) with acetic anhydride afforded 3-benzyl-2,8-dimethyl-4*H*,6*H*-chromeno[3',2':5,6]pyrido[2,3-*d*]pyrimidine-4,6-dione (**47**) (Scheme 22).[66]



Scheme 22

On the other hand, reaction of carbonitrile **1** (R=H) with *N*`-[(4-chlorophenyl)methylidene]-2-cyanoacetohydrazide (**48**) in boiling ethanol containing DBU yielded the expected 2-amino-5-oxo-5*H*-chromeno[2,3-*b*]pyridine-3-carbohydrazide (**49**), *via* intermediates **E** and **F**.[64] While, the unexpected benzoxocine derivatives **50** were obtained from the reaction of carbonitrile **1** (R=CH$_3$) with *N*`-[(4-chloro/methoxyphenyl)methylidene]-2-cyanoacetohydrazide (**48**) under the same reaction conditions (Scheme 23).[56,66] Formation of benzoxocine derivative**s 50** may occur *via* the formation of intermediate **E** followed by an intramolecular nucleophilic addition of the hydroxyl group onto the nitrile function as shown in Scheme 23.



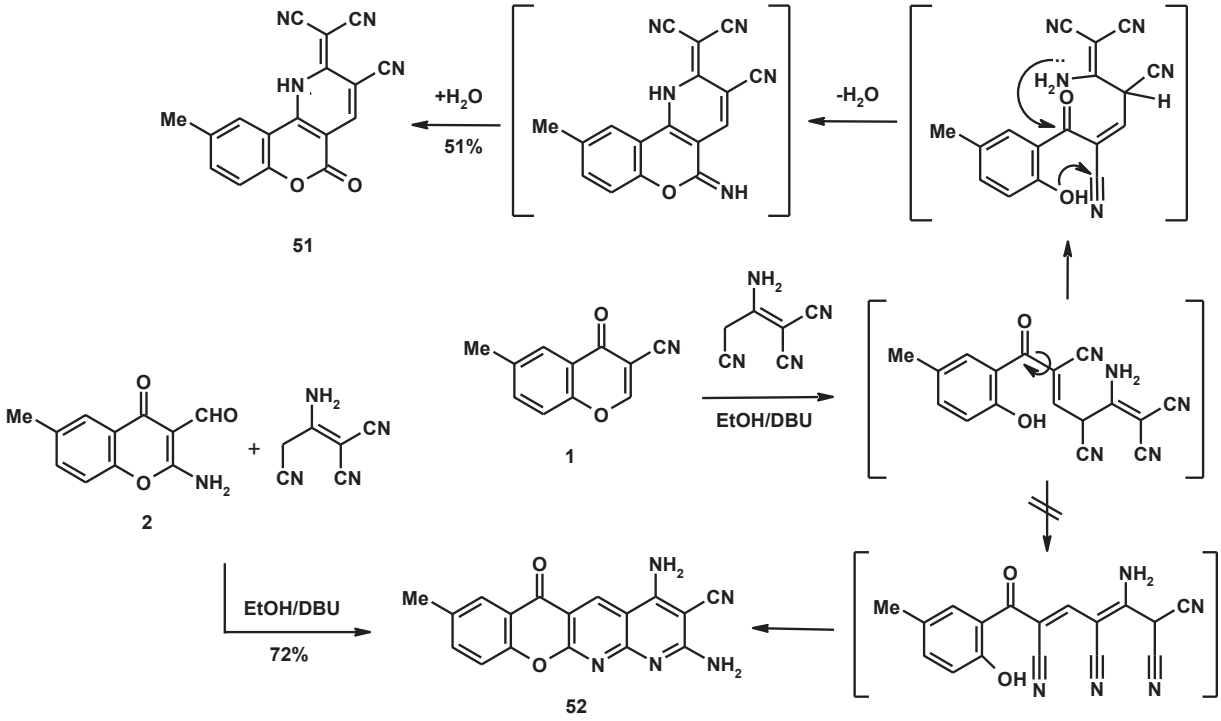
Scheme 23

Treatment of carbonitrile **1** (R= Me) with malononitrile dimer (2-aminoprop-1-ene-1,1,3-tricarbonitrile) in boiling ethanol containing DBU gave (3-cyano-9-methyl-5-oxo-1,5-dihydro-2*H*-chromeno[4,3-*b*]-pyridin-2-ylidene)-propanedinitrile (**51**).[67] Another expected product, 2,4-diamino-8-methyl-6-oxo-6*H*-chromeno[2,3-*b*][1,8]naphthyridine-3-carbonitrile (**52**) was ruled out (Scheme 24). Compound **52** was efficiently synthesized using an alternative pathway *via* the reaction of 2-amino-6-methylchromone-3-carboxaldehyde (**2**) with malononitrile dimer in boiling ethanol containing few drops of DBU.

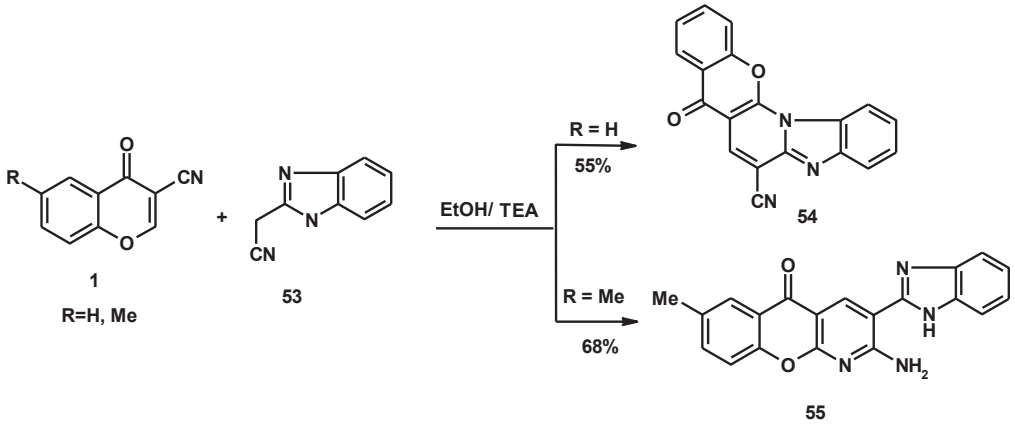
Reaction of carbonitrile **1** (R=H) with benzimidazol-2-ylacetonitrile (**53**) in boiling ethanol containing few drops of triethylamine, gave the angular heteroannulated chromone; chromeno[2,3:6,5]pyrido[1,2-*a*]benzimidazole-6-carbonitrile **54** (Scheme 25). While, the reaction of 6-methylchromone-3-carbonitrile (**1**; R=Me) with benzimidazol-2-ylacetonitrile (**53**) showed different behavior and the reaction proceeds in a different mechanism producing 2-amino-3-(1*H*-benzimidazol-2-yl)-7-methyl-5*H*-chromeno[2,3-*b*]-pyridin-5-one (**55**) (Scheme 25).[68]

Reaction of carbonitriles **1** with some symmetrical and unsymmetrical active methylene ketones namely; acetylacetone, dibenzoylmethane, deoxybenzoin, ethyl acetocetate, ethyl benzoylacetone, diethyl malonate, acetoacetanilide, dimethyl *β*-ketoglutarate and diethyl *β*-ketoadipate afforded 2,3-disubstituted-

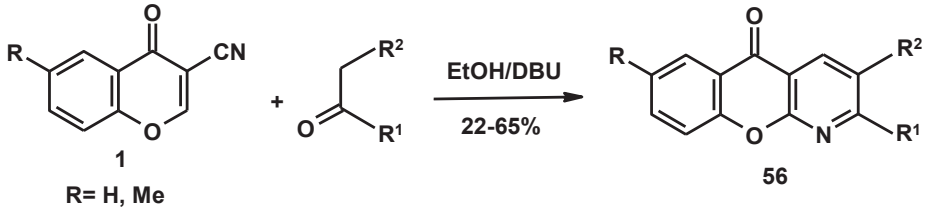
5-oxo-5*H*-chromeno[2,3-*b*]pyridines **56** (Scheme 26).[64,66,69-75] Recently, some chromeno[2,3-*b*]pyridines **56**, with antioxidant activity, were synthesized in high yields (78-86%) using ultra sound irradiation.[66]



Scheme 24



Scheme 25



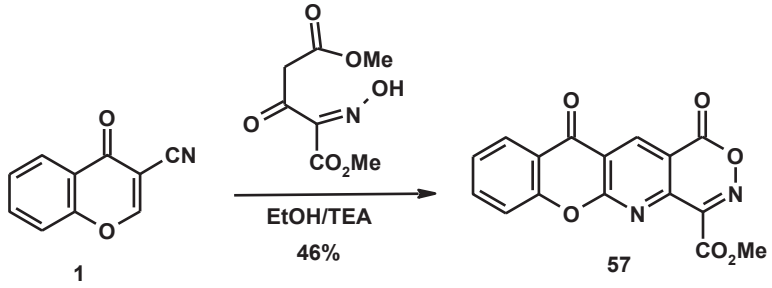
R^1=Me, R^2=COMe ; R^1=Ph, R^2=COPh ; R^1=Ph, R^2=Ph ; R^1=Me, R^2=CO_2Et

R^1=Ph, R^2=CO_2Et; R^1=OEt, R^2=CO_2Et ; R^1=Me, R^2=CONHPh

R^1=CO_2Me, R^2=CH_2CO_2Me ; R^1=CO_2Et, R^2=$CH_2CH_2CO_2$Et

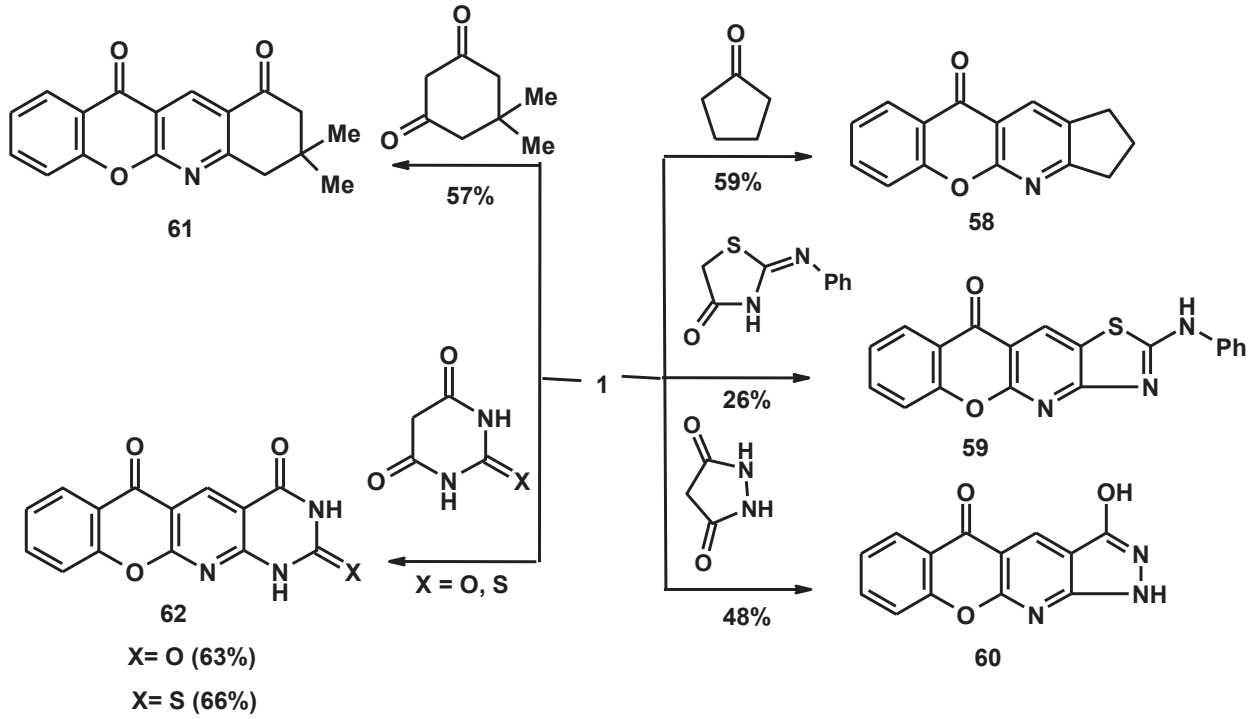
Scheme 26

Oxazine **57** was obtained, from reaction of carbonitrile **1** with *Z*-isomer of dimethyl *β*-keto-*α*-oximino-glutarate, in boiling ethanol containing triethylamine (Scheme 27).[71]



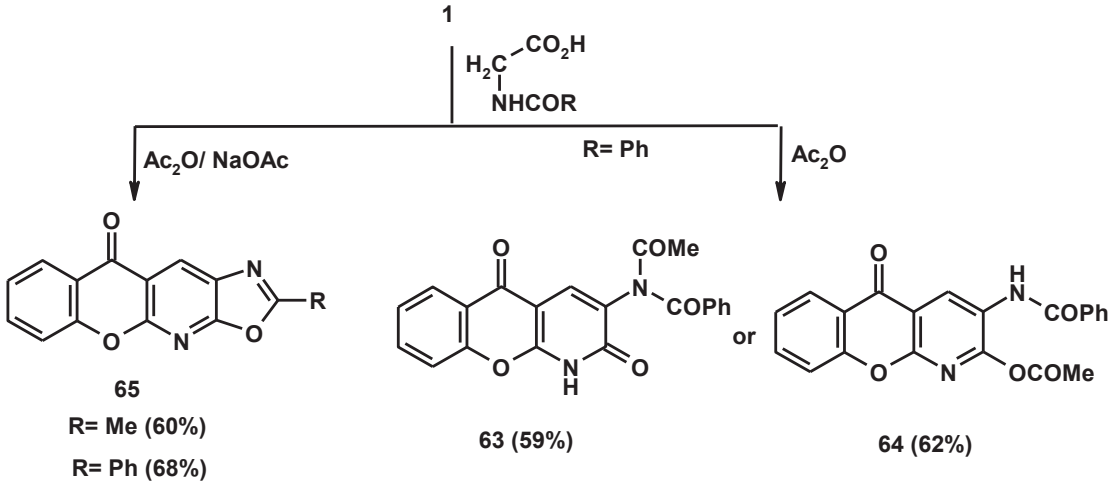
Scheme 27

Cyclic *α*-methylene ketones and cyclic 1,3-diketones also undergo smooth and efficient ring opening and ring closure (RORC) for carbonitrile **1** yielding heteroannulated chromone derivatives.[64] Thus, reaction of carbonitrile **1** with cyclopentanone, 2-phenyliminothiazolidin-4-one, pyrazoline-3,5-dione, 5,5-dimethylcyclohexane-1,3-dione, barbituric and thiobarbituric acids afforded a series of tetracyclic systems **58-62**, respectively (Scheme 28).[64]



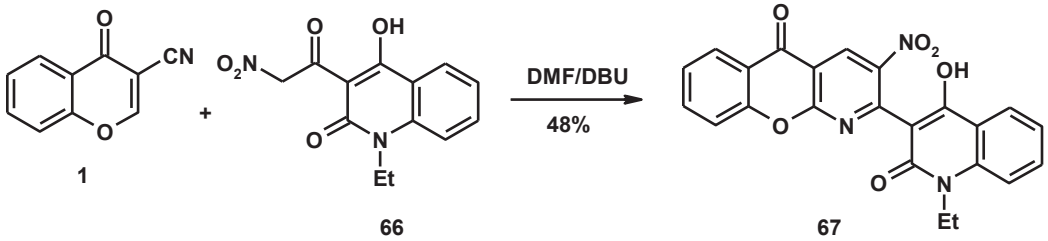
Scheme 28

The reaction of carbonitrile **1** with *N*-benzoylglycine, "hippuric acid", in acetic anhydride was reported to chromenopyridine derivative **63** as assigned by Ghosh and Tewari,[70] while the same reaction produced chromenopyridine derivative **64** as suggested by Ibrahim[64] (Scheme 29). On the other hand, boiling carbonitrile **1** with *N*-acetylglycine, "aceturic acid", and *N*-benzoylglycine, "hippuric acid", in acetic anhydride containing in the presence of freshly fused sodium acetate, the tetracyclic systems **65** was obtained (Scheme 29).[39, 64,70]



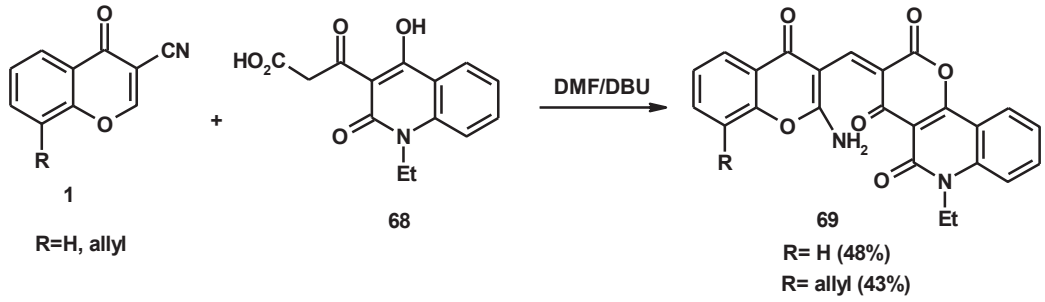
Scheme 29

Treating carbonitrile **1** with 3-nitroacetylquinolinone **66** in boiling DMF containing DBU as a catalyst afforded quinolinone derivative bearing chromeno[3,2-*b*]pyridine **67** (Scheme 30).[75]



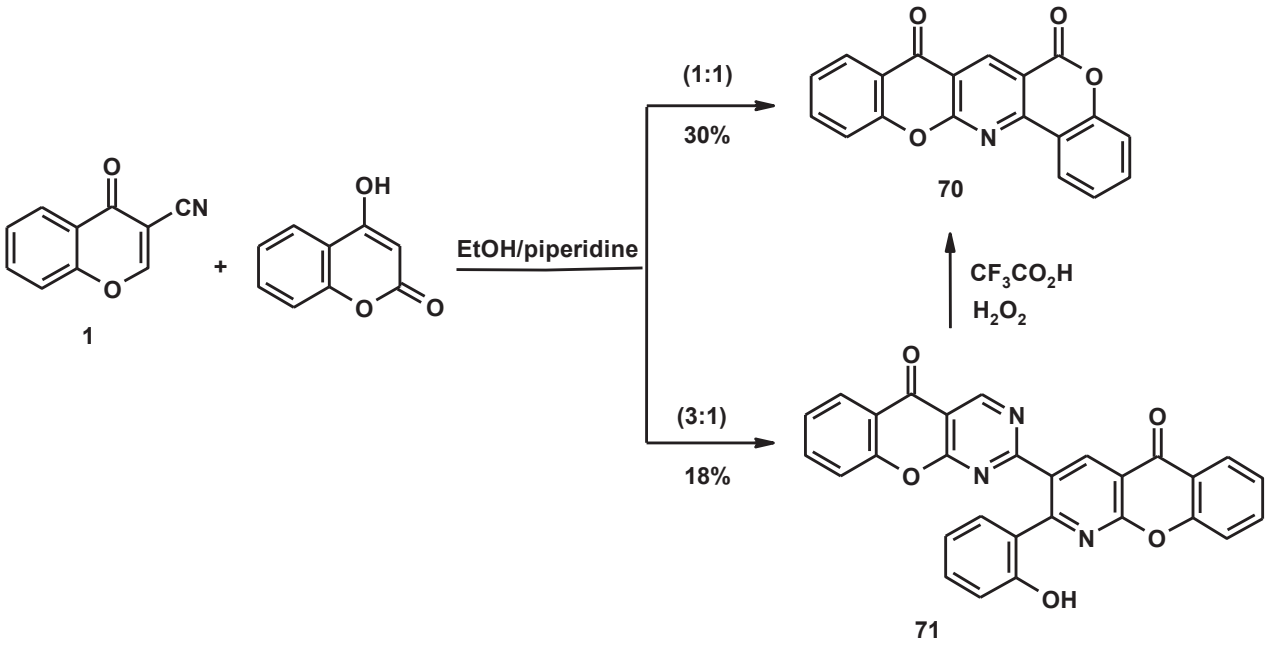
Scheme 30

Moreover, treating carbonitrile **1** (R=H, 8-allyl)) with β-ketoacid **68** in boiling DMF containing DBU afforded pyranoquinoline derivatives **69** (Scheme 31).[76]



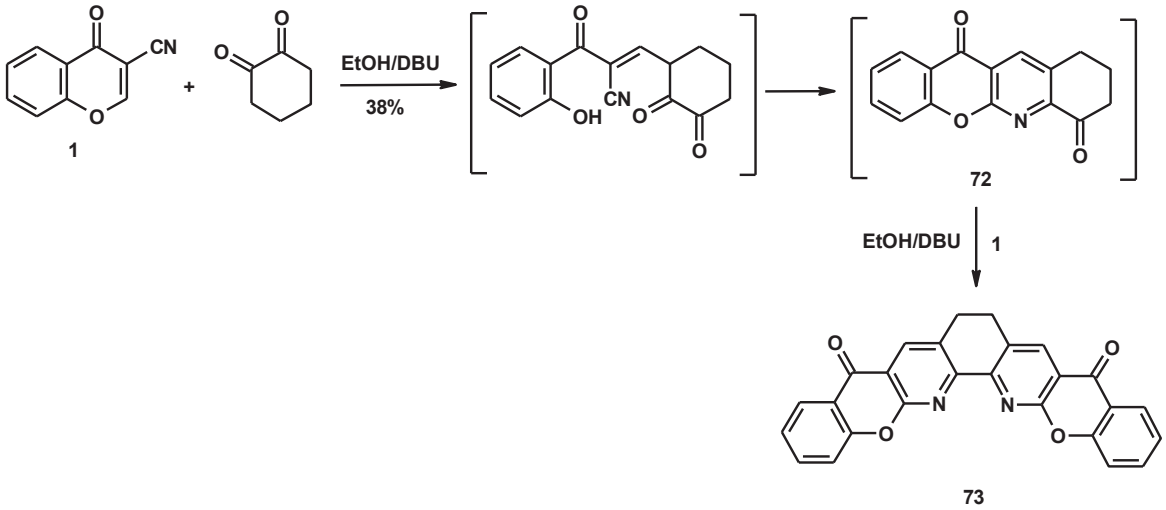
Scheme 31

Lactone **70** was obtained (30% yield) by reacting carbonitrile **1** with 4-hydroxycoumarin, in refluxing ethanol containing piperidine (Scheme 32).[77] Schurreit[78] has reported without giving any mechanism the formation of compound **71** (18% yield) by refluxing three molecules of carbonitrile **1** and 4-hydroxycoumarin under the same reaction conditions; 4-hydroxycoumarin having no role in the formation of compound **71**. Compound **71** when refluxed with 30% hydrogen peroxide in trifluoroacetic acid is converted into the lactone **70** (Scheme 32).



Scheme 32

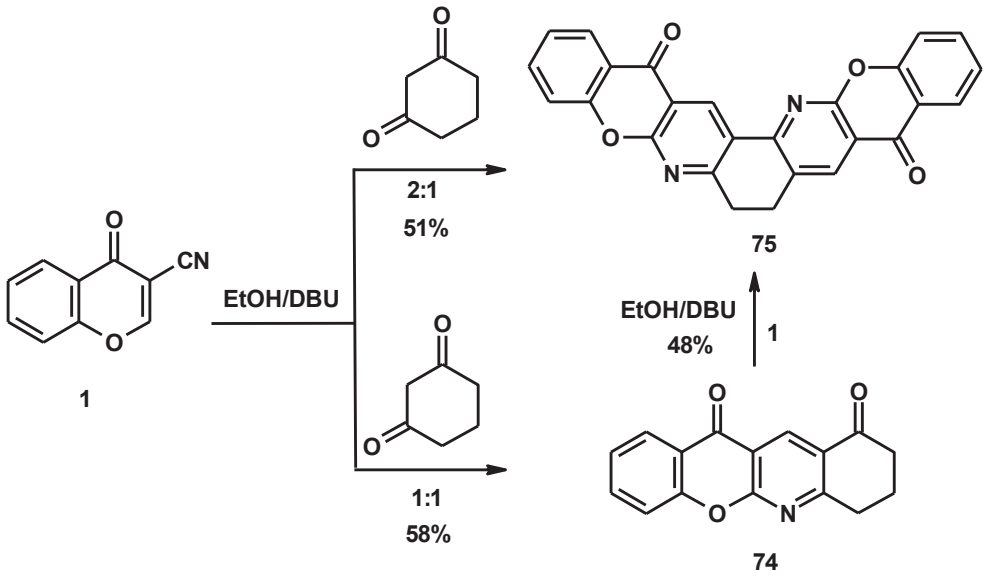
The chemical reactivity of chromone-3-carbonitrile (**1**) towards 1,2-, 1,3- and 1,4-cyclohexanediones was studied under different molar ratios. Three isomeric products of angular bis[1]chromenophenanthrolines were isolated.[79] Thus, base catalyzed reaction of carbonitrile **1** with 1,2-cyclohexanedione in 1:1 and 2:1 molar ratio resulted in the formation of the angular heptacyclic system, 7,8-dihydro-5*H*,10*H*-bis[1]chromeno[2,3-*b*:3`,2`-*J*][1,10]phenanthroline-5,10-dione (**73**). Isolation of chromeno[2,3-*b*]-quinolinedione derivative **72** was failed (Scheme 33).



Scheme 33

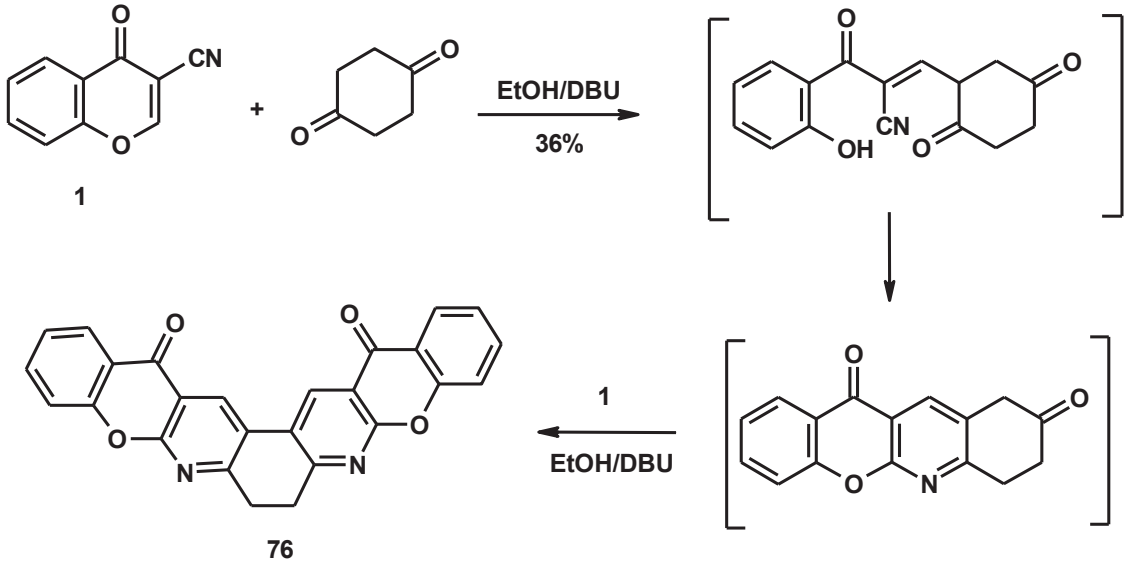
On the other hand, condensation of carbonitrile **1** with 1,3-cyclohexanedione, in absolute ethanol containing DBU, in 1:1 molar ratio resulted in the formation of chromeno[2,3-*b*]quinolinedione derivative

74 (Scheme 34). When the latter reaction occurs in 2:1 (carbonitrile **1**: 1,3-cyclohexanedione) molar ratio resulted in the formation of the angular heptafused system **75** containing two chromeno[2,3-*b*]pyridine moieties. Compound **75** was also obtained authentically from the condensation of compound **74** with carbonitrile **1**.[79]



Scheme 34

Next, condensation of carbonitrile **1** with 1,4-cyclohexanedione in 1:1 and 2:1 molar ratio resulted in the formation of the angular heptacyclic system, 7,8-dihydro-15*H*,18*H*-bis[1]chromeno[3,2-*b*:2`,3`-*J*][4,7]-phenanthroline-15,18-dione (**76**), *via* the non-isolable chromeno[2,3-*b*]quinolinedione derivative (Scheme 35).[79]

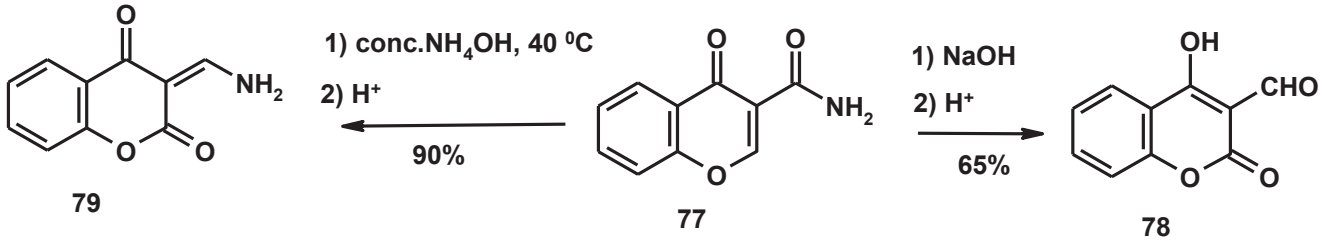


Scheme 35

3. RORC REACTIONS WITH CHROMONE-3-CARBOXAMIDES

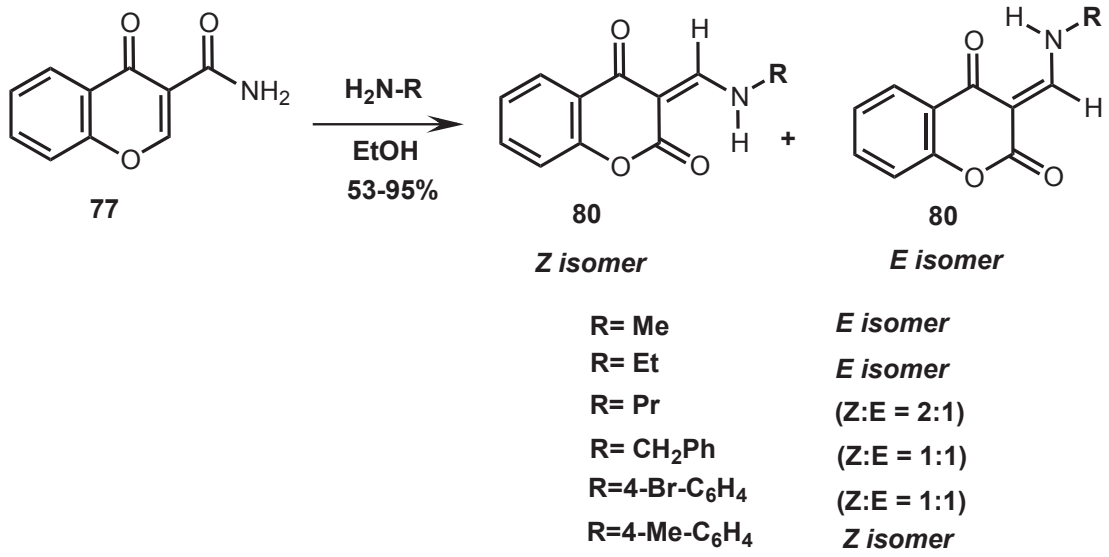
Chromone-3-carboxamide (**77**) has three electron deficient centers, C-2, C-4, and the amidic carbon at position 3. The nucleophilic reagent usually attack at the C-2 position with γ-pyrone ring opening followed by further transformation during the course of the reaction producing a variety of products depending on the nucleophile used. The chemistry of chromone-3-carboxamide (**77**) was studied in details by Ibrahim.[80,81] Reactions of chromone-3-carboxamide (**77**) with different nucleophiles resulted in the conversion of γ-pyrone ring into α-pyrone; on other words conversion of chromone into coumarin.

Treatment of carboxamide **77** with aqueous 1 *M* NaOH solution resulted in the facile rearrangement to 4-hydroxycoumarin-3-carboxaldehyde (**78**), while its reaction with concentrated ammonium hydroxide solution produced 3-aminomethylene-2*H*-chroman-2,4-dione (**79**) *via* ring opening followed by ring closing (RORC) reactions (Scheme 36).[80]



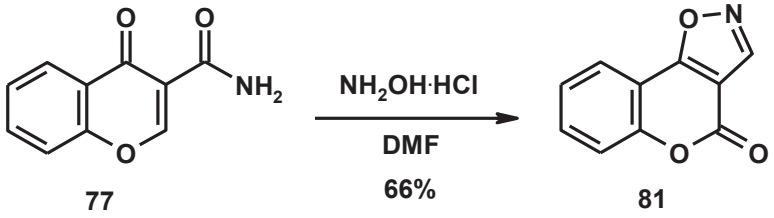
Scheme 36

Treatment of carboxamide **77** with some primary aliphatic and aromatic amines namely; methylamine, ethylamine, *n*-propylamine, benzylamine, *p*-bromoaniline and *p*-toluidine, resulted in ring transformation *via* γ-pyrone ring opening followed by lactonization with loss of ammonia to afford the corresponding geometrical isomeric chromane-2,4-diones **80** (Scheme 37).[80,81] The ratio of *Z*:*E* isomers depend on the type of amine used.



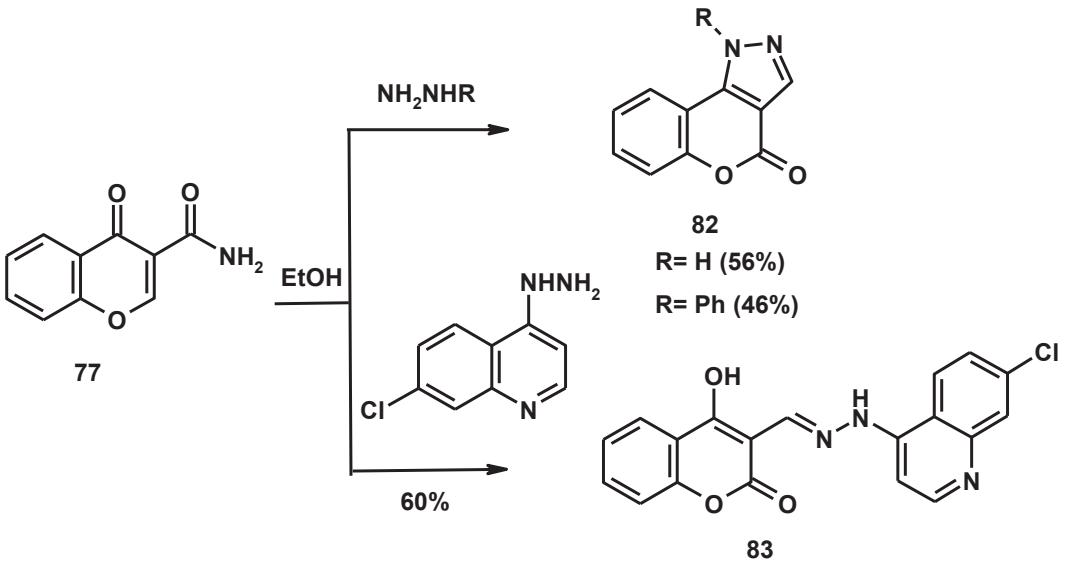
Scheme 37

Moreover, the chemical reactivity of carboxamide **77** was studied towards a variety of 1,2-binucleophiles. Condensation of carboxamide **77** with hydroxylamine hydrochloride in refluxing DMF produced chromeno[3,4-*d*]isoxazol-4(4*H*)-one (**81**) (Scheme 38).[81]



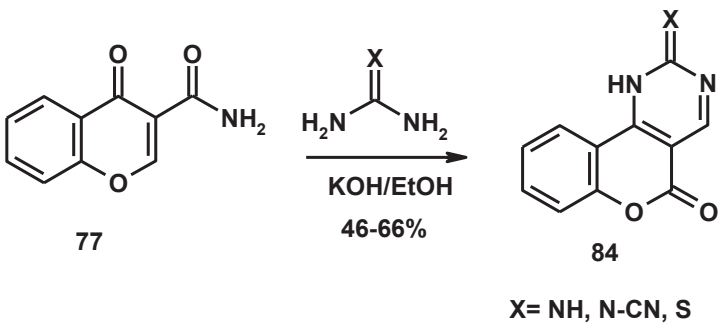
Scheme 38

Condensation of carboxamide **77** with hydrazine hydrate and phenylhydrazine in refluxing ethanol achieved ring transformation of carboxamide **77** producing chromeno[4,3-*c*]pyrazoles **82** (R=H, Ph). While, reaction of carboxamide **77** with 7-chloro-4-hydrazinoquinoline in boiling ethanol afforded the hydrazone derivative **83** (Scheme 39).[81]



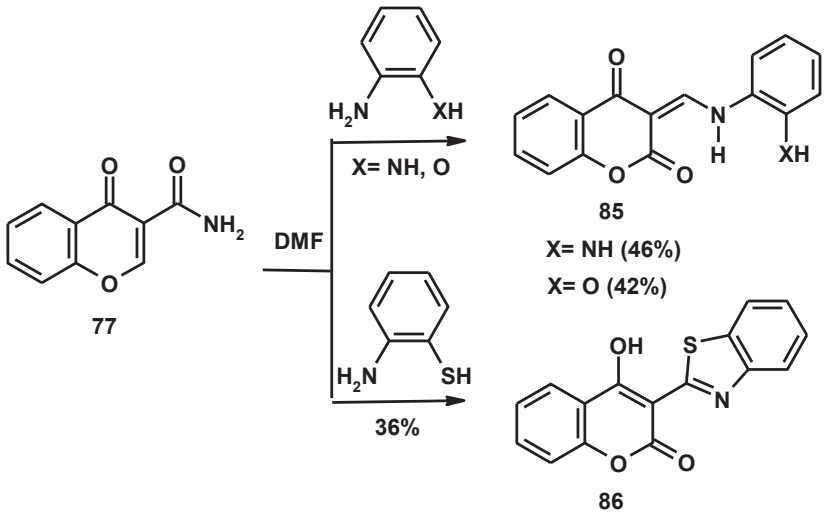
Scheme 39

Condensation of carboxamide **77** with guanidine hydrochloride, cyanoguanidine and thiourea in ethanolic potassium hydroxide solution produced chromeno[4,3-*d*]pyrimidine derivatives **84** (X= NH, N-CN, S) (Scheme 40).[81]



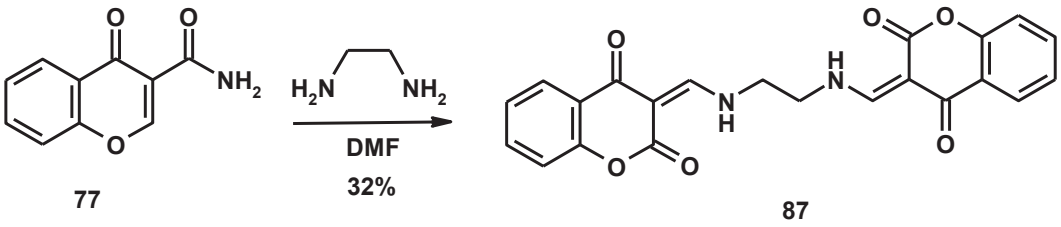
Scheme 40

Treatment of carboxamide **77** with *o*-phenylenedimine and *o*-aminophenol in refluxing DMF afforded chromane-2,4-dione derivatives **85** (X= NH, O), as *Z* isomers. While, treatment of carboxamide **77** with *o*-aminothiophenol in refluxing DMF achieved ring transformation producing benzothiazolylcoumarin derivative **86** (Scheme 41).[81]



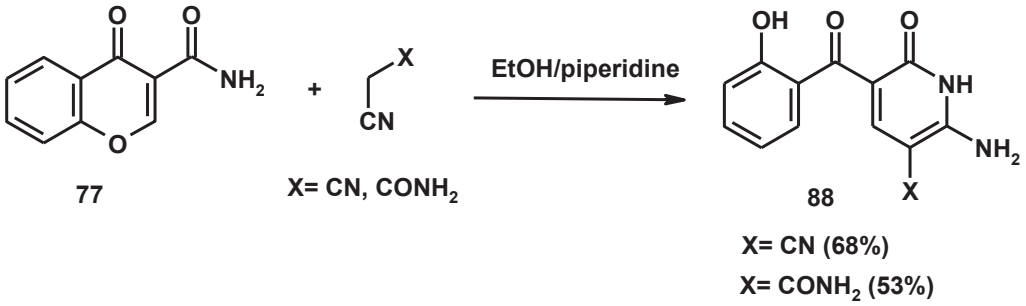
Scheme 41

Ethylenediamine showed different behavior when reacted with carboxamide **77** producing the *bis*-enaminone derivative **87** (Scheme 42).[81]



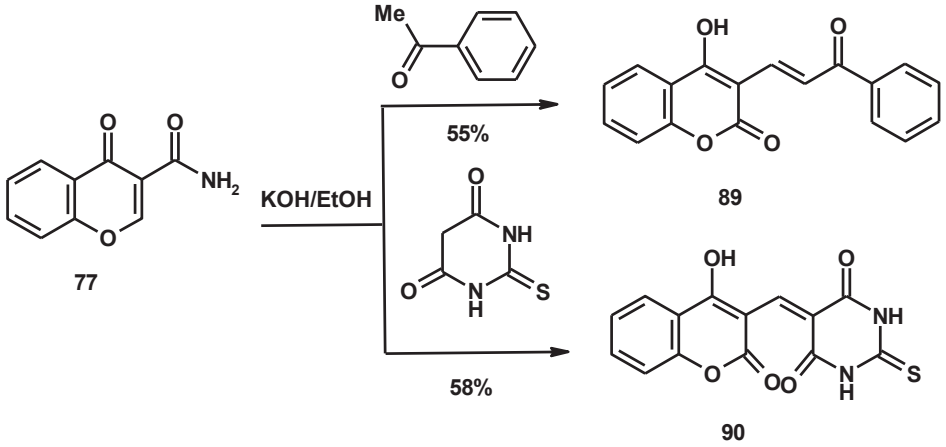
Scheme 42

Furthermore, the chemical reactivity of carboxamide **77** was studied towards a variety of carbon nucleophiles. Treatment of carboxamide **77** with malononitrile and cyanoacetamide in boiling ethanol containing piperidine afforded the pyridine derivatives **88** as depicted in Scheme 43.[81]



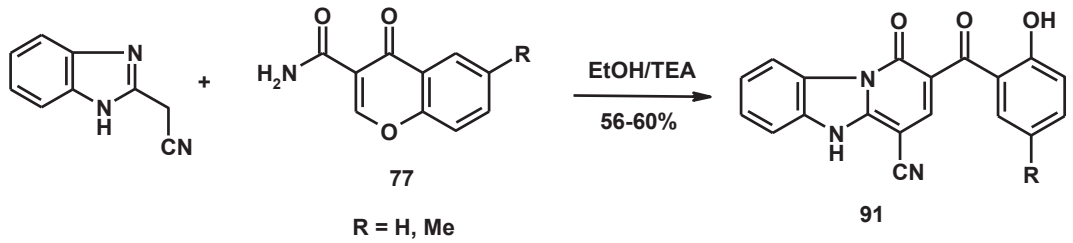
Scheme 43

The reaction of carboxamide **77** with acetophenone and thiobarbituric acid in ethanolic potassium hydroxide solution gave the corresponding α,β-unsaturated ketone **89** and pyrimidine derivative **90**, respectively (Scheme 44).[81]



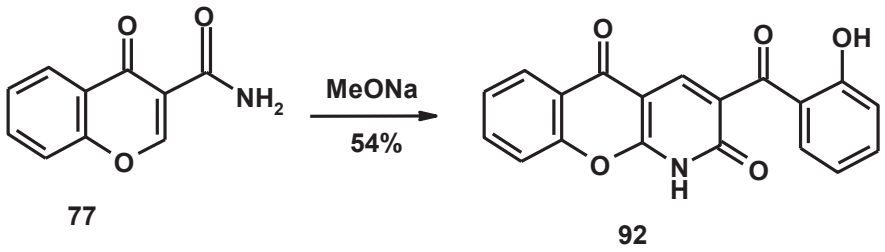
Scheme 44

Treating chromone-3-carboxamides **77** (R=H, Me) with 1*H*-benzimidazol-2-ylacetonitrile, in boiling ethanol containing triethylamine, produced pyrido[1,2-*a*]benzimidazoles **91** (Scheme 45).[68]



Scheme 45

Heteroannulated chromone, namely, 3-(2-hydroxybenzoyl)-2*H*-chromeno[2,3-*b*]pyridine-2,5(1*H*)-dione (**92**) was obtained from dimerization of carboxamide **77** with sodium methoxide solution (Scheme 46).[80]

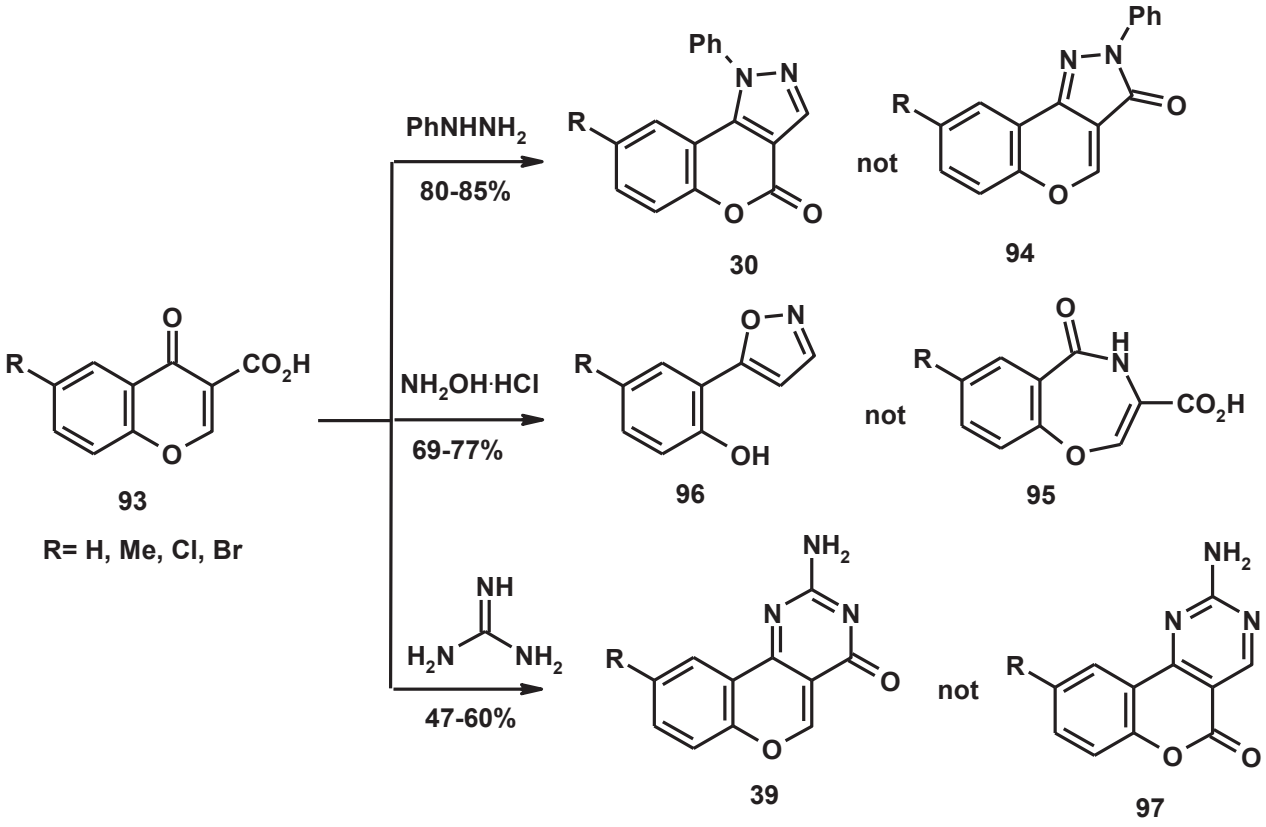


Scheme 46

4. RORC REACTIONS WITH CHROMONE-3-CARBOXYLIC ACIDS

The chemistry of nucleophilic reactions involving RORC of chromone-3-carboxylic acid (**93**) attracted attentions due to rare literature reports. Also, in these very few reports we face some encountering results.[82-84] The product obtained from the reaction of carboxylic acid **93** with phenylhydrazine had been established to be 4-oxo-1-phenylchromeno[4,3-*c*]pyrazole (**30**),[82] not the corresponding isomer 2-phenyl-

chromeno[4,3-*c*]pyrazol-3(2*H*)-one (**94**) as previously reported by Ghosh and Mukhopadhyay (Scheme 47).[83] Also, reaction of carboxylic acid **93** with hydroxylamine hydrochloride was reported to give 5-oxo-4,5-dihydro-1,4-benzoxazepine-3-carboxylic acid (**95**).[83] However, Chantegrel *et al.* found the same reaction gave 5-(2-hydroxyphenyl)isoxazole (**96**).[84] Reaction of carboxylic acid **93** with guanidine carbonate gave 2-aminochromeno[4,3-*d*]pyrimidin-4(4*H*)-one (**39**) not the corresponding isomer **97** (Scheme 47) as published by Chantegrel *et al*.[84]

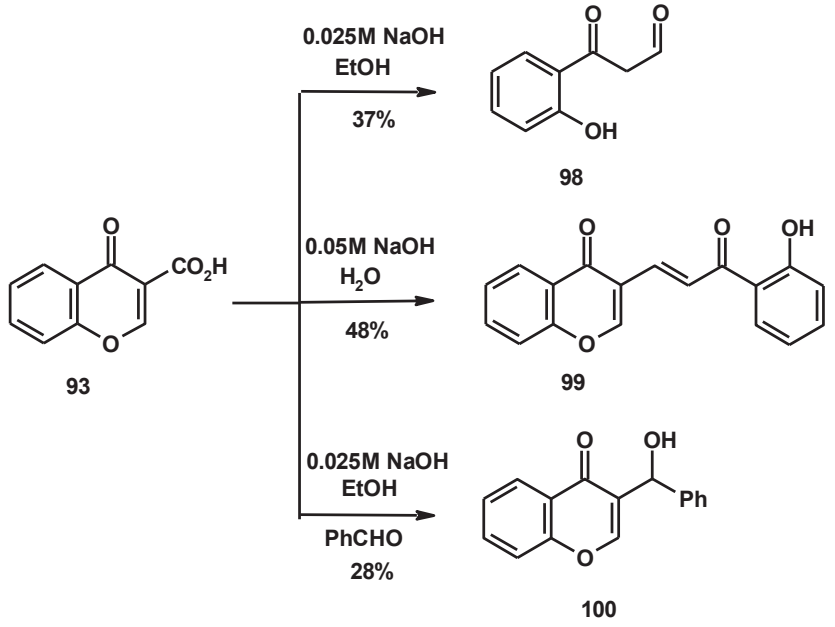


Scheme 47

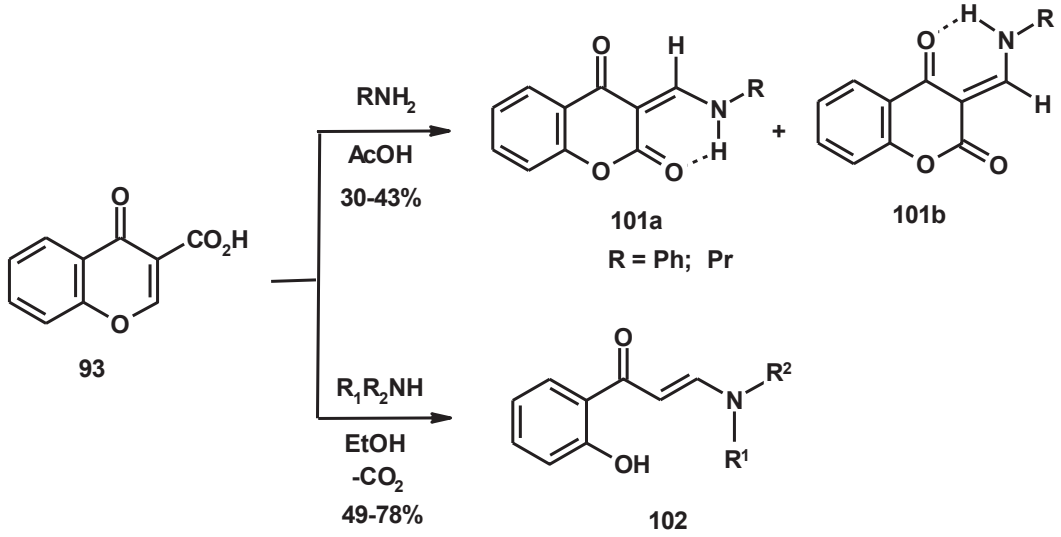
The chemistry of chromone-3-carboxylic acid (**93**) was studied in details by Ibrahim.[85] Carboxylic acid **93** in the presence of sodium hydroxide solution undergoes different reactions depending on the concentration of sodium hydroxide and reaction conditions. Treatment of carboxylic acid **93** with 0.025 M sodium hydroxide solution in refluxing ethanol afforded ω-formyl-2-hydroxyacetophenone (**98**), while when the reaction carried out using 0.05 M aqueous sodium hydroxide solution at 70 ºC afforded 1-(3-chromonyl)-2-(2-hydroxybenzoyl)ethene (**99**) (Scheme 48). Reaction of carboxylic acid **93** with benzaldehyde in ethanolic sodium hydroxide solution (0.025 M) afforded 3-(*α*-hydroxybenzyl)chromone (**100**) (Scheme 48).[85]

Reaction of carboxylic acid **93** with primary and secondary amines in ethanol afforded the enaminones **101**, when carboxylic acid **93** was allowed to react with aniline and *n*-propylamine in glacial acetic acid produced 3-(phenyl/*n*-propyl)aminomethylenechromane-2,4-diones **102** as stereoisomeric (*Z* and *E*)

mixtures (Scheme 49).[85] These results confirm the loss of CO_2 molecule after opening of pyrone ring in ethanol but no decarboxylation occurred in acetic acid medium.



Scheme 48



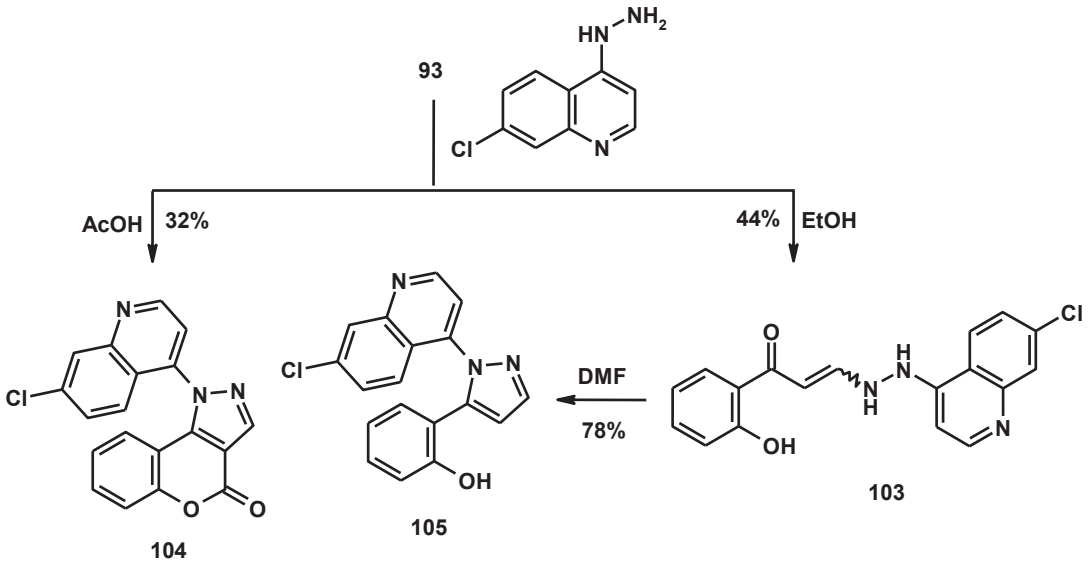
R^1= H, R^2 = Et; R^1 = H, R^2 = Pr; R^1 = H, R^2 = cyclohexyl;

R^1 = H, R^2 = Ph; R^1 = R^2 = Et; R^1 = Me, R^2 = Ph;

R^1R^2 = -$(CH_2)_5$-; R^1R^2 = -$(CH_2)_2$-O-$(CH_2)_2$-

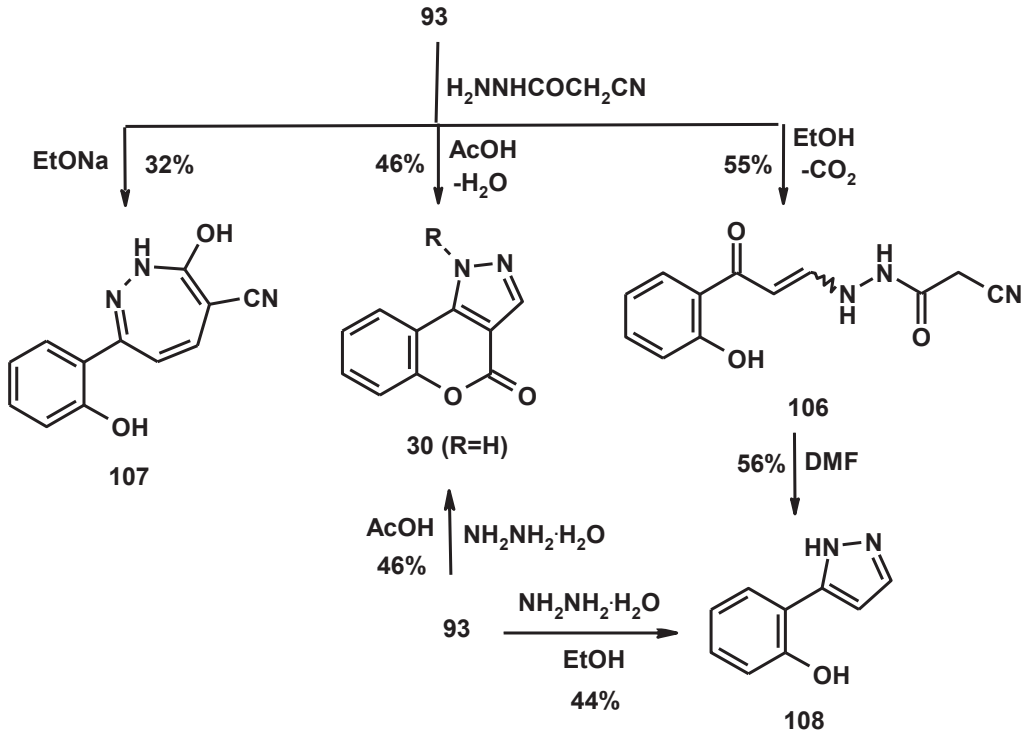
Scheme 49

3-[*N*'-(7-Chloroquinolin-4-yl)hydrazino]-1-(2-hydroxyphenyl)-prop-2-en-1-one (**103**) and 1-(7-chloroquinolin-4-yl)chromeno[4,3-*c*]pyrazol-4(1*H*)-one (**104**) were obtained from the reaction of carboxylic acid **93** with 7-chloro-4-hydrazinoquinoline in ethanol and acetic acid, respectively. Cyclization of compound **103** in DMF afforded the pyrazole derivative **105** (Scheme 50).[85]



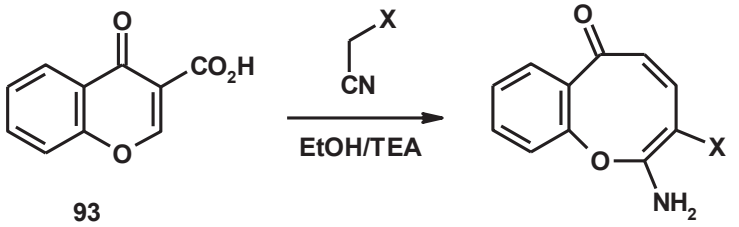
Scheme 50

Reaction of carboxylic acid **93** with cyanoacetohydrazide in ethanol and/or acetic acid gave compounds **106** and **30**, respectively. When the later reaction took place in sodium ethoxide, the diazepine derivative **107** was isolated (Scheme 51). Compounds **106**, **30** and **107** are produced during the ring transformation because cyanoacetohydrazide thereby acts as an ambient nucleophile, that is, as both *N*- and *C*-nucleophile.[85] Refluxing compound **106** in dimethylformamide afforded the well known 3-(2-hydroxyphenyl)-1*H*-pyrazole (**108**).[43] Compounds **30** and **108** were also obtained from the reaction of carboxylic acid **93** with hydrazine hydrate in acetic acid and ethanol, respectively (Scheme 51).[85]



Scheme 51

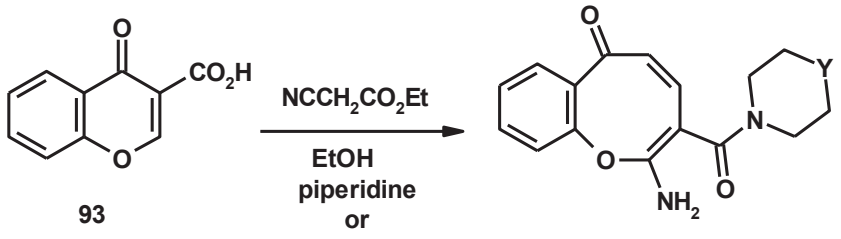
Reaction of chromone-3-carboxylic acid (**93**) with some carbon nucleophiles was studied. Reaction of carboxylic acid **93** with some acyclic active methylene nitriles namely; malononitrile, ethyl cyanoacetate, chloroacetonitrile and benzyl cyanide in absolute ethanol containing few drops of triethylamine led to the expansion of γ-pyrone ring in chromone-3-carboxylic acid (**93**) affording 2-amino-3-substituted-6*H*-benzoxocin-6-ones **110**–**113**, respectively (Scheme 52).[85,86] This transformation occurred by way a domino "Michael /retro-Micheal/ring opening/ decarboxylation/cycloaddition" reaction.



110, X=CN (38%)
111, X=CO_2Et (45%)
112, X=Cl (59%)
113, X=Ph (46%)

Scheme 52

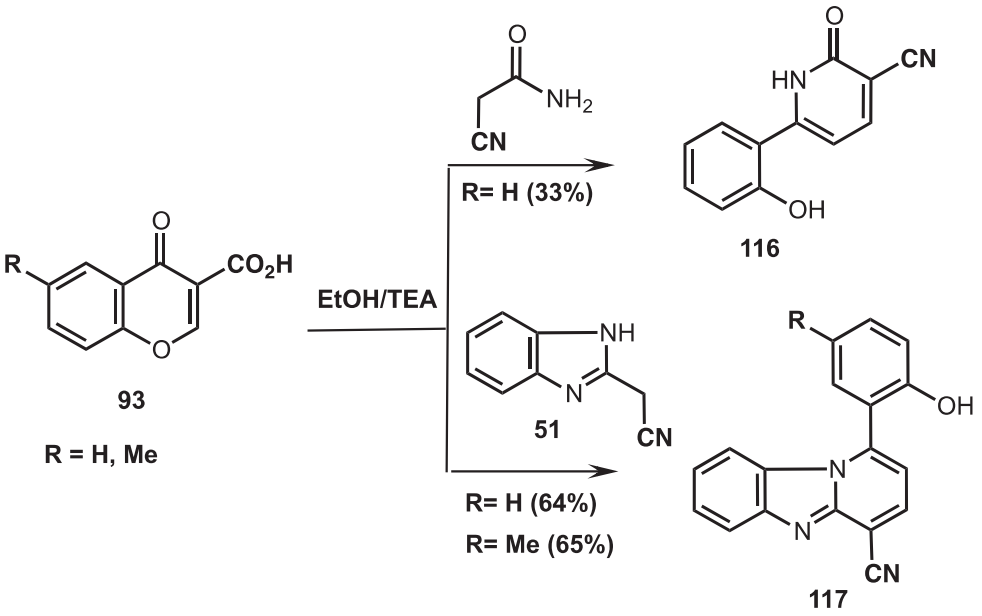
On the other hand, reaction of carboxylic acid **93** with ethyl cyanoacetate in absolute ethanol containing few drops of piperidine and morpholine afforded 2-amino-3-(piperidin/morpholin-1-ylcarbonyl)-6*H*-1-benzoxocin-6-ones **114** and **115**, respectively (Scheme 53). Compounds **114** and **115** were also synthesized from the reaction of ethyl ester **111** with equivalent amounts of piperidine and morpholine in boiling ethanol.[86]



114, Y=CH_2 (49%)
115, Y=O (53%)

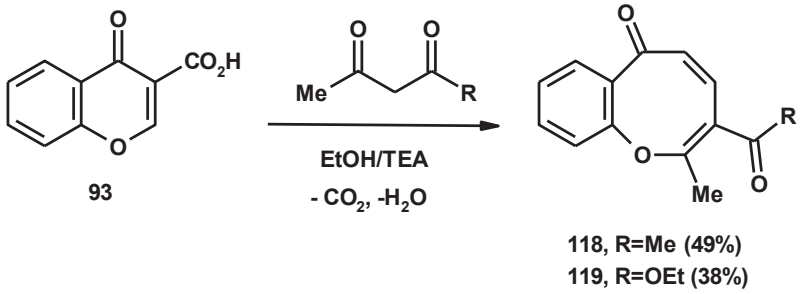
Scheme 53

Treatment of compound **93** with cyanoacetamide in ethanol containing few drops of triethylamine afforded 6-(2-hydroxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**116**) (Scheme 54).[85] Under similar conditions, treatment of carboxylic acids **93** (R=H, Me) with benzimidazol-2-ylacetonitrile, in boiling ethanol containing few drops of triethylamine as a basic catalyst, afforded the pyrido[1,2-*a*]-benzimidazole-4-carbonitriles **117** (Scheme 54).[68]



Scheme 54

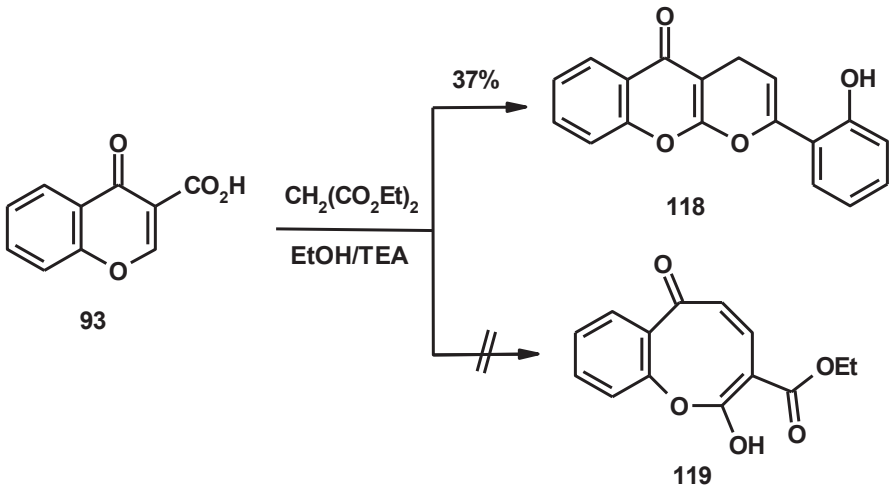
The chemical behavior of chromone-3-carboxylic acid (**93**) towards some acyclic active methylene ketones was studied. Boiling carboxylic acid **93** with acetylacetone and ethyl acetoacetate in absolute ethanol containing few drops of triethylamine afforded the corresponding 2-methyl-3-substituted-6*H*-1-benzoxocin-6-ones **118** and **119**, respectively (Scheme 55).[86]



Scheme 55

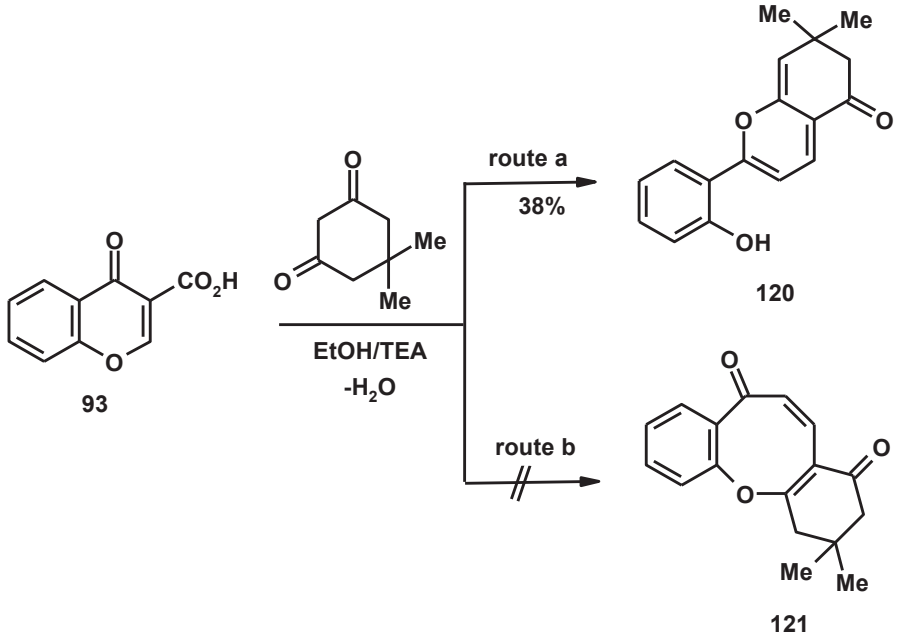
Interestingly, it was found that chromone-3-carboxylic acid (**93**) showed unexpected behavior towards diethyl malonate than the previous acylic active methylene compounds. Refluxing an equimolar amounts of carboxylic acid **93** with diethyl malonate in absolute ethanol containing few drops of triethylamine produced 2-(2-hydroxyphenyl)-4*H*,5*H*-pyrano[2,3-*b*]chromen-5-one (**118**) (Scheme 56). The expected benzoxocinone derivative **119** was excluded.[86]

In most of the previous mentioned reactions, the γ-pyrone ring in chromone-3-carboxylic acid (**93**) was expanded to oxocinone ring upon its reaction with acyclic active methylene compounds to produce 6*H*-benzoxocin-6-one derivatives.



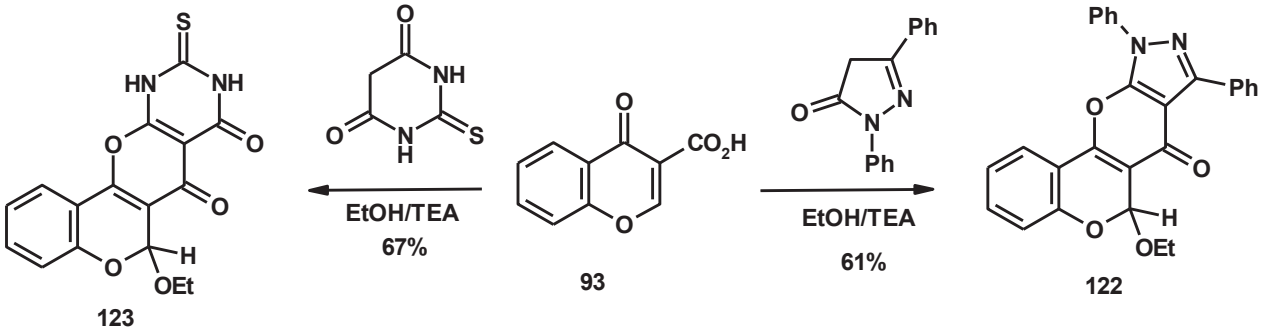
Scheme 56

Then, the chemical behavior of chromone-3-carboxylic acid (**93**) towards some cyclic active methylene compounds. Thus, treatment of carboxylic acid **93** with dimedone produced 2-(2-hydroxyphenyl)-7,7-dimethyl-6,7-dihydrochromen-5-one (**120**) and not the ring expanded product, 2,2-dimethyl-2*H*-dibenzo[*b,g*]oxocine-4,7(1*H*,3*H*)-dione (**121**) as depicted in Scheme 57.[86]



Scheme 57

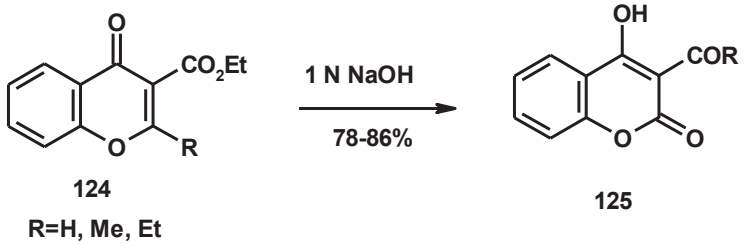
The reaction between carboxylic acid **93** and some heterocycles containing active methylene group was studied. Surprisingly, heating an ethanolic solution of the carboxylic acid **93** with 1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one and thiobarbituric acid under reflux produced the novel unexpected products identified as 1,3-diphenyl-5-ethoxy-5*H*-chromeno[3`,4`:5,6]pyrano[2,3-*c*]pyrazol-4 (1*H*)-one (**122**) and 6-ethoxy-2-thioxo-2*H*,6*H*-chromeno[3`,4`:5,6]pyrano[2,3-*d*]pyrimidine-4,5-(1*H*,3*H*)-dione (**123**), respectively (Scheme 58).[86]



Scheme 58

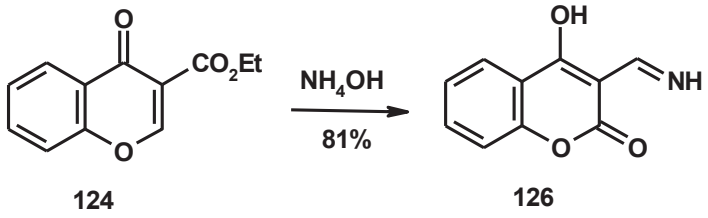
5. RORC REACTIONS WITH CHROMONE-3-CARBOXYLATES

The chemical reactions of chromone-3-carboxylates with nucleophilic reagents are rare. Basic rearrangement of ethyl chromone-3-carboxylates **124** in 1 *N* aqueous sodium hydroxide solution at room temperature produced 3-substituted-4-hydroxycoumarins **125** in good yield (78-86%) (Scheme 59).[87]



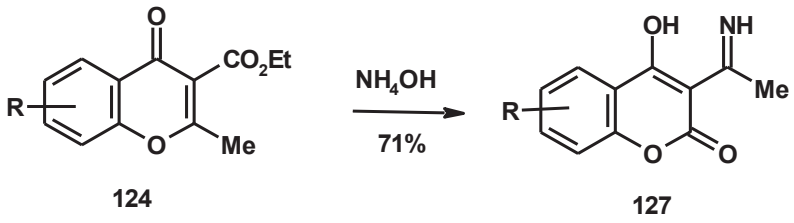
Scheme 59

An analogous transformation was observed when ethyl chromone-3-carboxylate (**96**) was heated with concentrated ammonium hydroxide solution, giving rise 3-(formimidoyl)-4-hydroxycoumarin (**126**) (Scheme 60).[87]



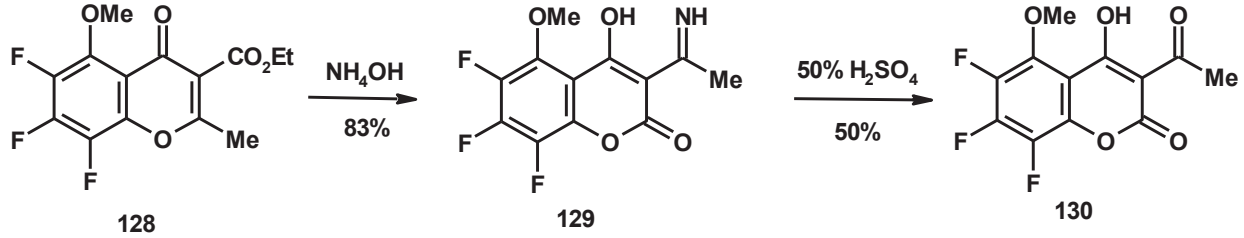
Scheme 60

Similarly, heating ethyl 2-methylchromone-3-carboxylate (**124**) with aqueous ammonia solution afforded 3-acetimidoyl-4-hydroxycoumarin (**127**) *via* ring opening ring closure reaction (Scheme 61).[88]



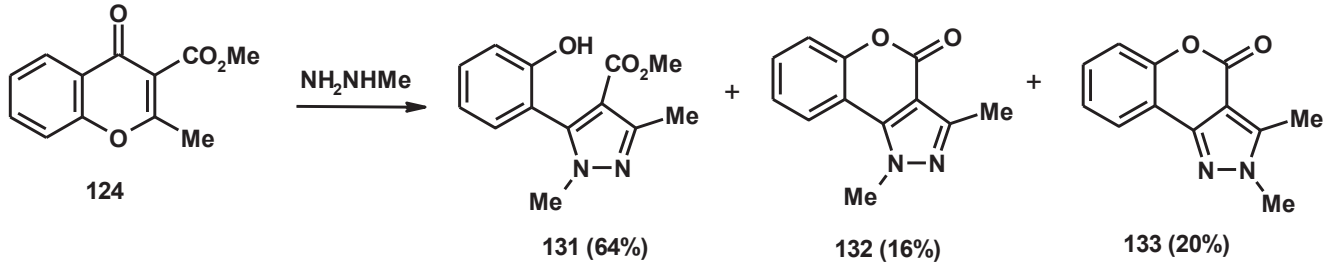
Scheme 61

Boiling chromone-3-carboxylate derivative **128** in aqueous ammonia solution yielded 3-acetimidoyl-4-hydroxy-5-methoxy-6,7,8-trifluorocoumarin (**129**) which upon heating with sulfuric acid afforded 3-acetylcoumarin analog **130** (Scheme 62).[89]



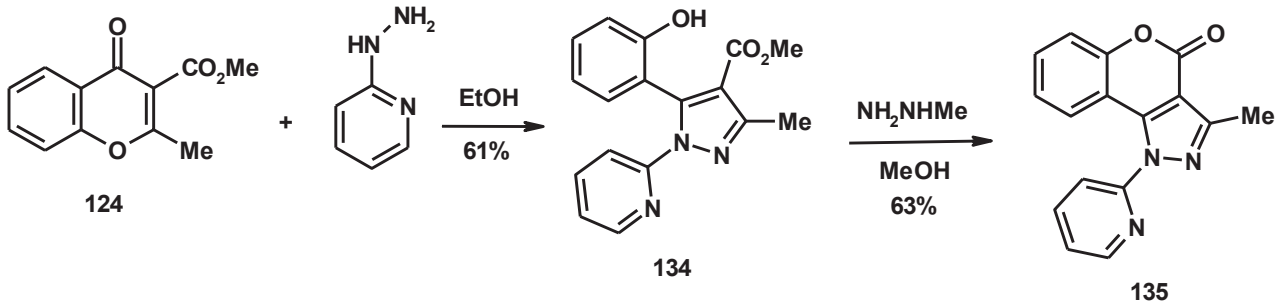
Scheme 62

Also, reaction of chromone-3-carboxylate **124** with methylhydrazine produced substituted pyrazole **131** and a mixture of chromeno[4,3-*c*]pyrazoles **132** and **133** (Scheme 63).[90]



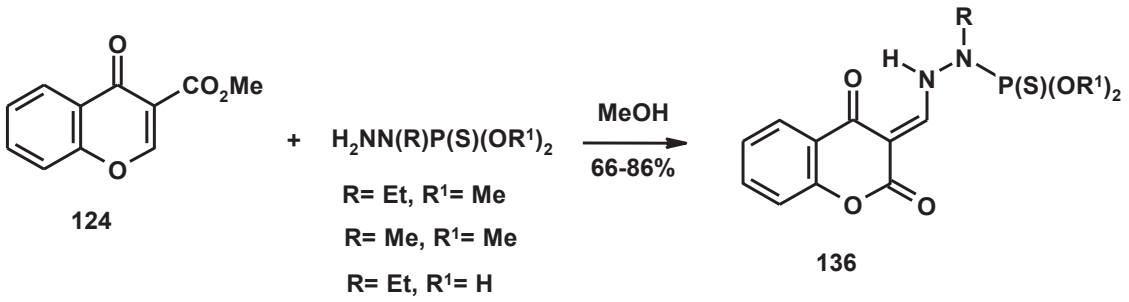
Scheme 63

On the other hand, methyl 5-(2-hydroxyphenyl)-1-(pyridin-2-yl)-1*H*-pyrazole-4-carboxylate (**134**) was synthesized in good yield (61%) from the reaction of chromone-3-carboxylate **124** with 2-hydrazinopyridine in boiling ethanol. Compound **134** underwent an intramolecular lactonization under the influence of methylhydrazine producing chromeno[4,3-*c*]pyrazol-4-one **135** (Scheme 64).[91]



Scheme 64

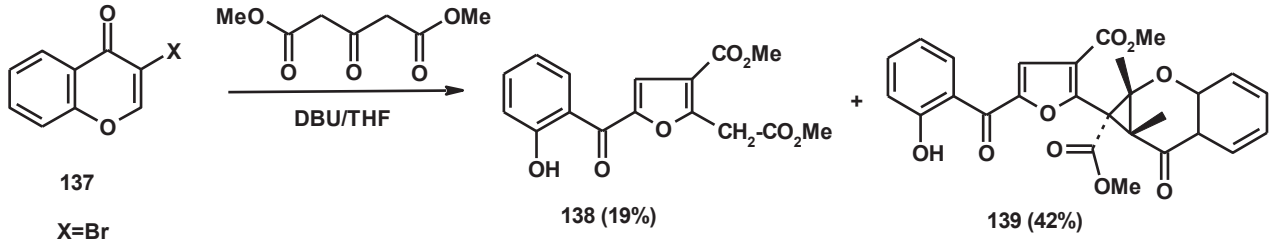
Treatment of methyl ester **124** with phosphorhydrazides afforded chromane-2,4-diones **136** *via* γ-pyrone ring opening followed by lactonization (Scheme 65).[92]



Scheme 65

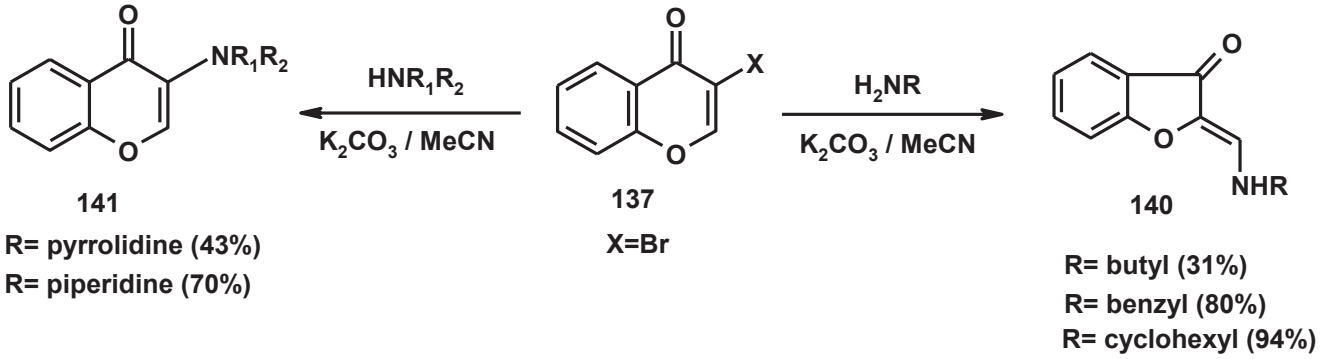
6. RORC REACTIONS WITH 3-HALOCHROMONES

Reaction of 3-bromochromone (**137**, X=Br) with equimolar amount of dimethyl acetonedicarboxylate in tetrahydrofuran (THF) in the presence of DBU as a basic catalyst afforded methyl furoate derivative **138** in 19% yield (expected product) along with furylcyclopropylchromene derivative **139** in 42% yield (unexpected product) (Scheme 66).[93]



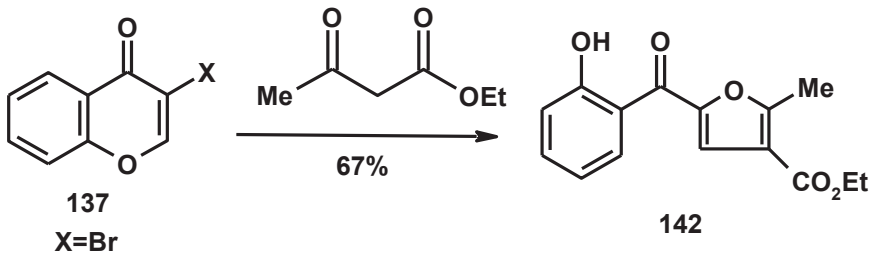
Scheme 66

Gammill and his coworkers[94] described the reaction of 3-bromochromone (**137**, X=Br) with amines and found that; the primary amines gave the ring contraction products **140**, while secondary amines gave 3-aminochromone (**141**). However, Huang and his coworkers[95] found that secondary amines gave also the ring contraction products (Scheme 67).



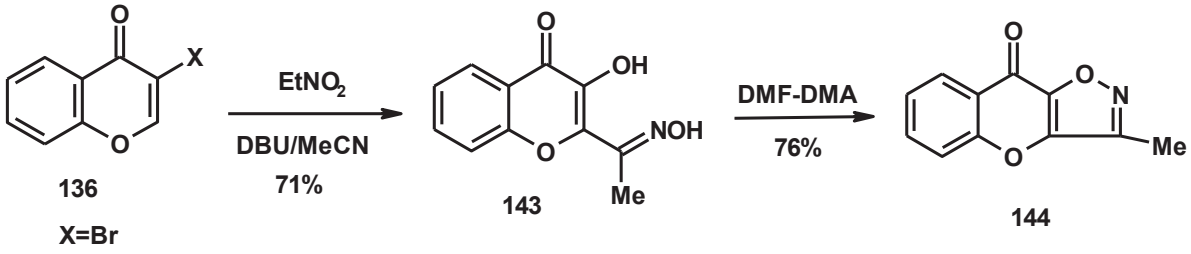
Scheme 67

Reaction of 3-bromochromone (**137**, X=Br) with ethyl acetoacetate in basic medium resulted in rupture of the γ-pyrone ring producing furan derivative **142** (Scheme 68).[94]



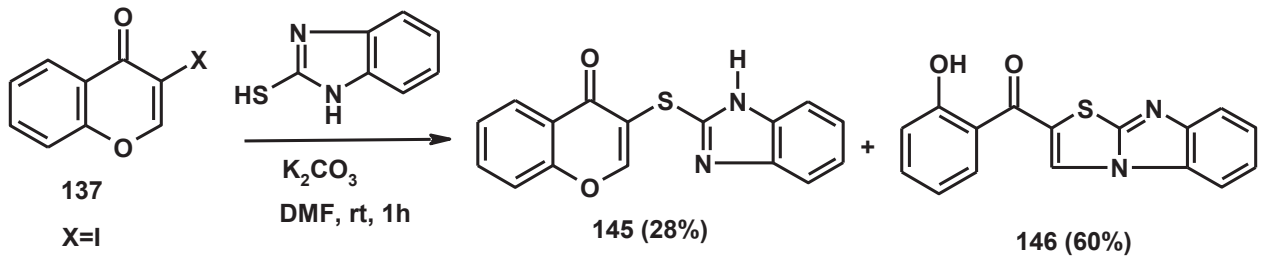
Scheme 68

Addition of nitroethane to 3-bromochromone (**137**, X=Br) in acetonitrile in the presence of DBU as a base gave 3-hydroxy-2-[1-(hydroxyimino)methyl]chromone (**143**) in 71% yield. Treatment of compound **143** with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) afforded the isoxazole derivative **144** in 76% yield (Scheme 69).[96]



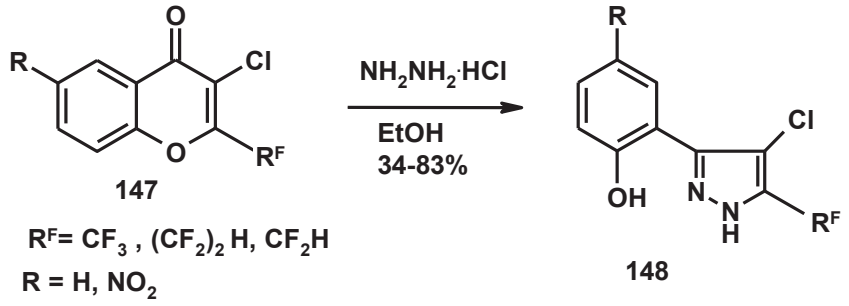
Scheme 69

Treatment of 3-iodochromone (**137**, X=I) with 2-mercaptobenzimidazole in the presence of potassium carbonate in DMF at room temperature gave a mixture of 3-(1*H*-benzimidazol-2-yl-thio)chromone (**145**) and benzimidazo[2,1-*b*]thiazole derivative **146** (Scheme 70).[97]



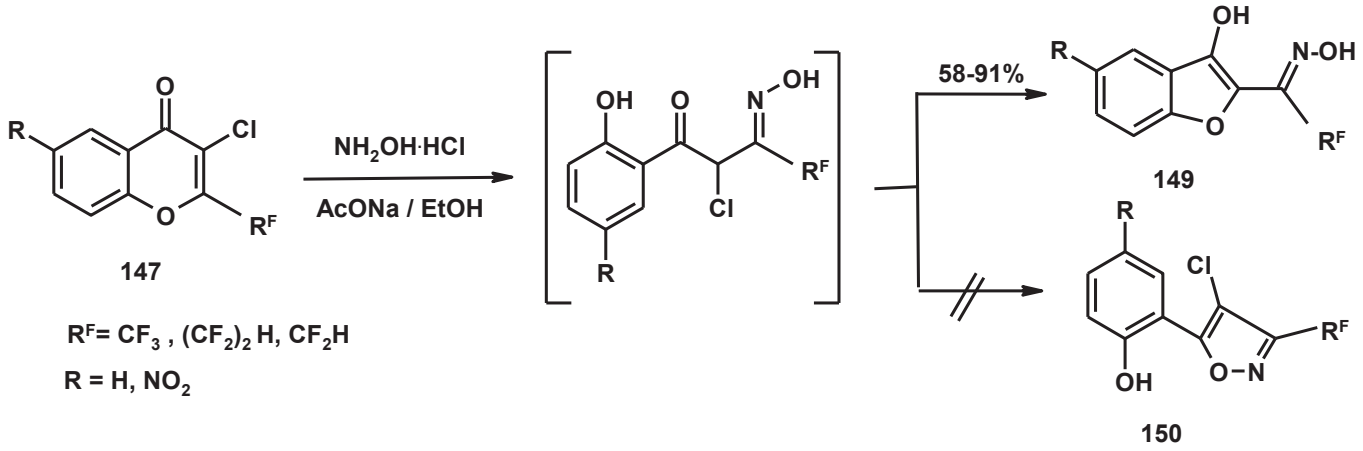
Scheme 70

Reaction of 3-chloro-2-(polyfluoroalkyl)chromones **147** with hydrazine hydrate hydrochloride in boiling ethanol afforded 4-chloro-3-(2-hydroxyphenyl)-pyrazoles **148** (Scheme 71).[98]



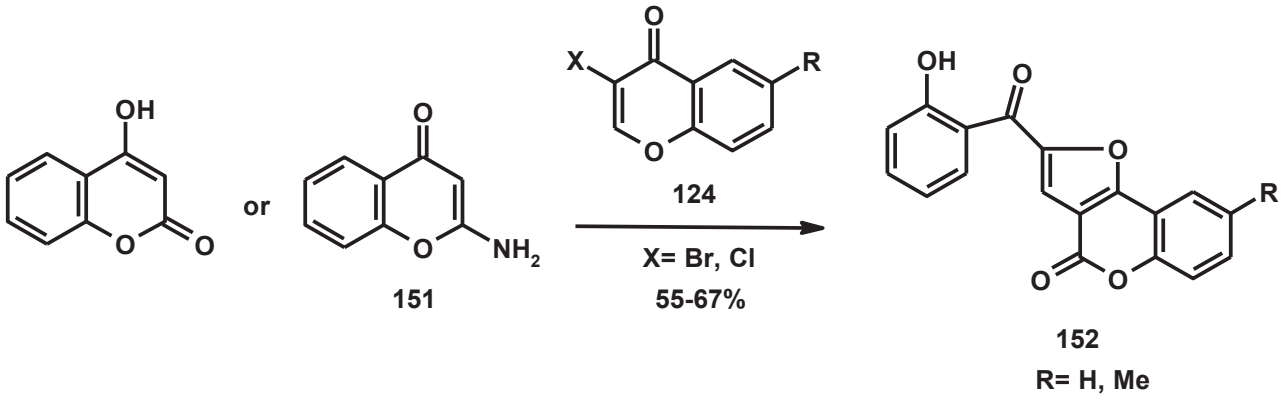
Scheme 71

On the other hand, reaction of 3-chloro-2-(polyfluoroalkyl)chromones **147** with hydroxylamine hydrochloride in boiling ethanol in the presence of sodium acetate produced benzofuran derivative **149** in high yield (58-91%) instead of isoxazoles **150** (Scheme 72).[99]



Scheme 72

A highly efficient synthesis of furo[3,2-*c*]coumarins **152** was achieved *via* base catalyzed reaction of 3-halochromones **124** (X=Br, Cl) with 4-hydroxycoumarin[100] or 2-aminochromone (**151**) (Scheme 73).[101]



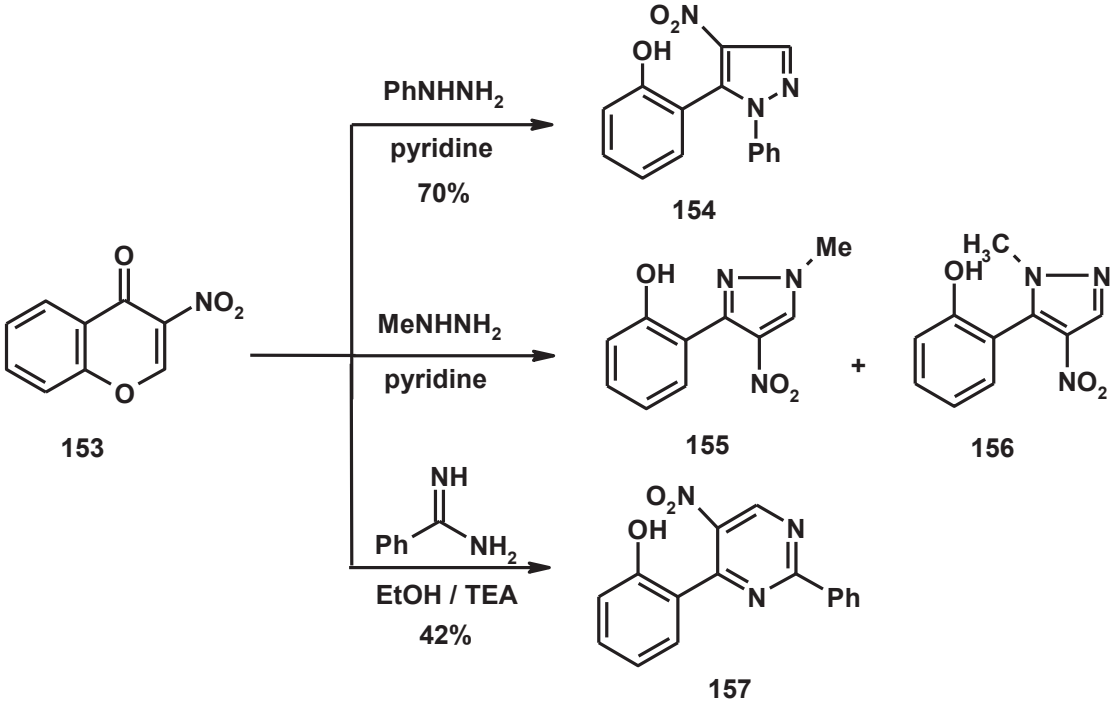
Scheme 73

7. RORC REACTIONS WITH 3-NITROCHROMONES

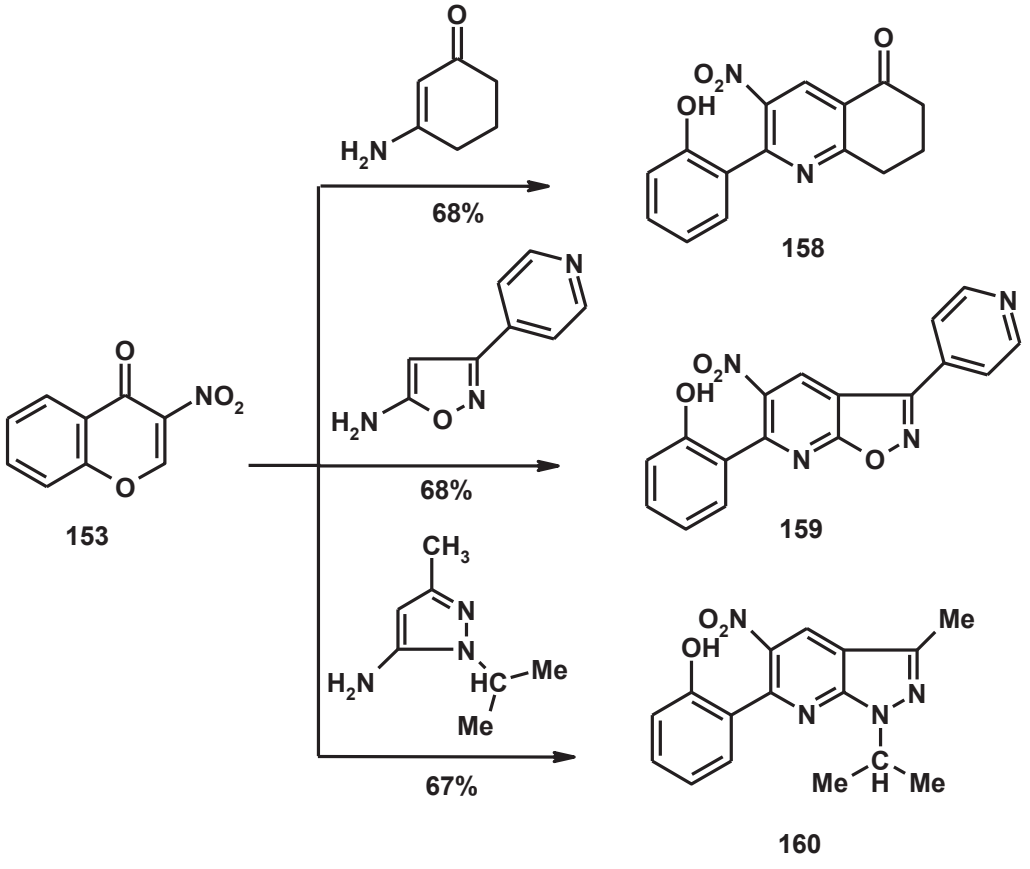
Reaction of 3-nitrochromone (**153**) with phenylhydrazine gave 5-(2-hydroxyphenyl)-4-nitro-1-phenylpyrazole (**154**),[102] while its reaction with methylhydrazine in boiling ethanol afforded the isomeric pyrazole derivatives **155** and **156** (Scheme 74).[103] Also, treatment of compound **153** with benzimidine in boiling ethanol containing triethylamine gave 6-(2-hydroxyphenyl)-5-nitro-2-phenylpyrimidine (**157**) (Scheme 74).[102]

Treatment of 3-nitrochromone (**153**) with some cyclic enamines namely 3-amino-2-cyclohexen-1-one**,** 5-amino-3-(4-pyridyl)isoxazole**)** and 3-amino-2-isopropyl-5-methylpyrazole afforded nitro derivatives of

quinolinone **158**, isoxazolo[5,4-*b*] pyridine **159** and pyrazolo[3,4-*b*]pyridine **160**, respectively, *via* γ-pyrone ring opening followed by ring closure (Scheme 75).[102]

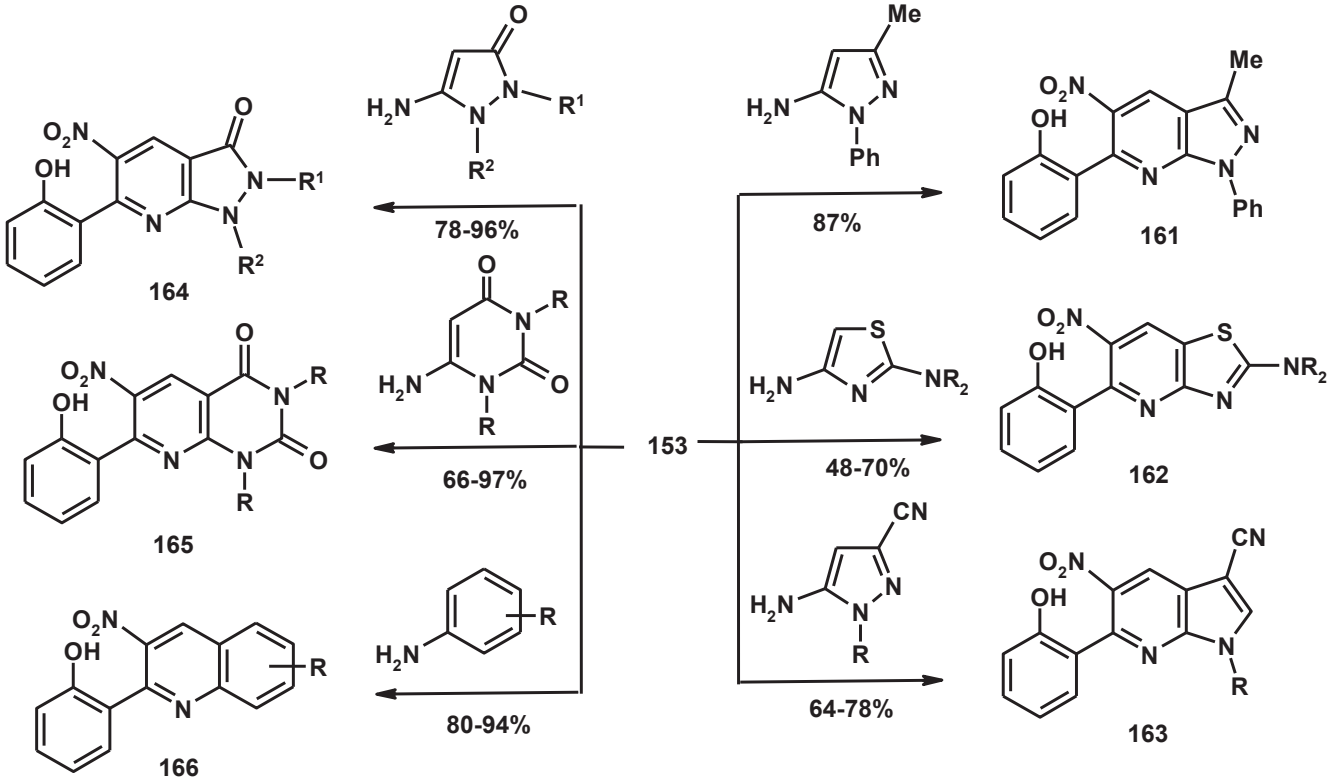


Scheme 74



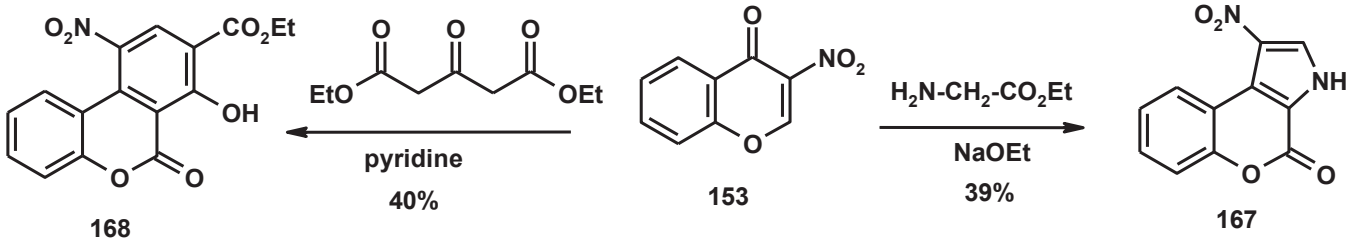
Scheme 75

Also, 3-nitrochromone (**153**) as 1,3-dielectrophile reacted with some electron rich aminoheterocycles (as 1,3-dinucleophiles) giving a variety of hetero(carbo)annulated 3-nitropyridines **161-166** (Scheme 76).[104] The reaction involve [3+3] cyclocondensation and proceeds in high yields and no influence greatly by the nature of the 1,3-*C*,*N*-dinucleophiles.[104]



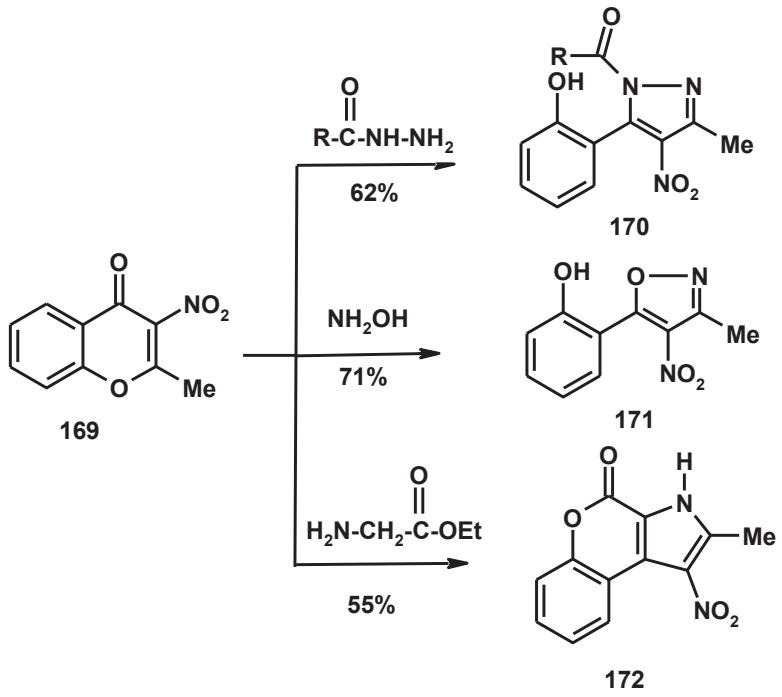
Scheme 76

Reaction of 3-nitrochromone (**153**) with ethyl glycinate hydrochloride in sodium ethoxide produced 1-nitropyrrolo[2,3-*c*]coumarin-4-one (**167**). Also, treating compound **153** with acetone dicarboxylic acid diethylester in pyridine gave ethyl 7-hydroxy-10-nitro-6-oxo-dibenzo[*b*.*d*]pyran-8-carboxylate (**168**) (Scheme 77).[102]



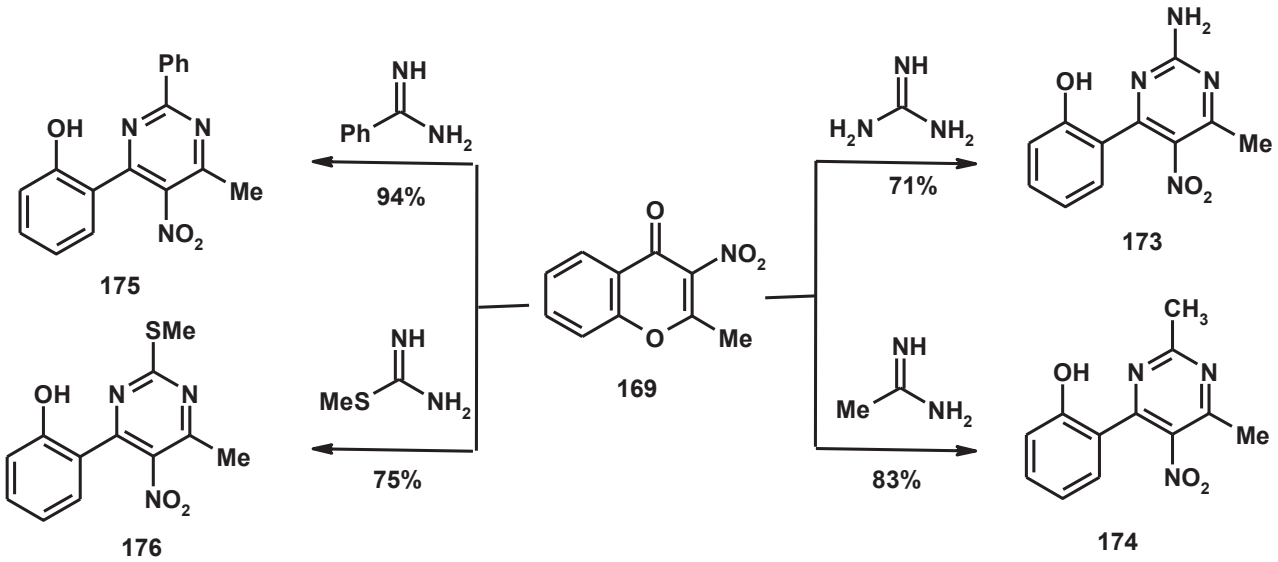
Scheme 77

2-Methyl-3-nitrochromone (**169**) reacted with acid hydrazides, hydroxyl amine and ethyl aminoethanoate to give the nitro derivatives of pyrazole **170**, isoxazole **171** and pyrrolo[2,3-*c*]coumarin **172**, respectively (Scheme 78).[105]



Scheme 78

Reaction of 2-methyl-3-nitrochromone (**169**) with guanidine, acetamidine, benzamidine and *S*-methylisothiourea, in sodium ethoxide, afforded the corresponding 2-substituted-6-(2-hydroxyphenyl)-4-methyl-5-nitropyrimidine **173-176** in good yields (Scheme 79).[105,106]



Scheme 79

8. CONCLUSION

In conclusion, the ring opening ring closure (RORC) reactions of 3-substituted chromones with nucleophilic reagents proceed preferentially at C-2 position through 1,4-*Michael* addition with γ-pyrone ring opening followed by new heterocyclization reaction leading to a variety of products depending on the substrate at position 3, nature of nucleophile used and the reaction conditions.

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