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Synthesis and Reactivity of 2-Aminochromone-3-carboxaldehydes towards Nucleophilic Reagents

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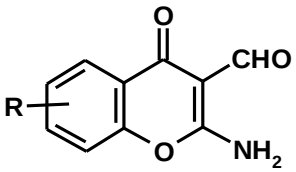
Abstract: The present review covers the methods developed for the synthesis and reactions of 2-aminochromone-3-carboxaldehydes. The chemical reactivity of 2-aminochromone-3-carboxaldehydes was summarized towards a variety of acyclic and cyclic active methylene compounds, in addition to a diversity of nitrogen nucleophiles.



Keywords: 2-Aminochromone-3-carboxaldehydes, chromeno[2,3-*b*]pyridines, annulated chromones, carbon nucleophiles.

1 Introduction

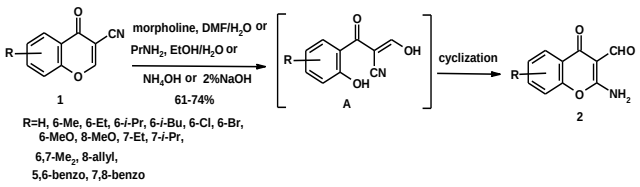
Chromones constitute one of the major classes of naturally occurring compounds [1], and they are useful as biologically active agents [2-6]. The chromone moiety is an essential pharmacophore of a large number of bioactive molecules [7-9].The biological activity of chromone derivatives includes cytotoxic (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 [31]. 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 [32-37].

The present review covers the methods developed for the synthesis and reactions of 2-aminochromone-3-carboxaldehydes. The chemical reactivity of 2-aminochromone-3-carboxaldehydes was summarized towards a variety of acyclic and cyclic active methylene compounds, in addition to a diversity of nitrogen nucleophiles.

2 Synthesis of 2-aminochromone-3-carboxaldehydes

Chromone-3-carboxasldehydes were used to synthesis a variety of 2-aminochromone-3-carboxaldehydes through their conversion into corresponding oximes or carbonitriles. Chromone-3-carbonitriles **1** are the most important substrate for the synthesis of 2-aminochromone-3-carboxaldehydes **2** through their reactions with a variety of nucleophilic reagents.

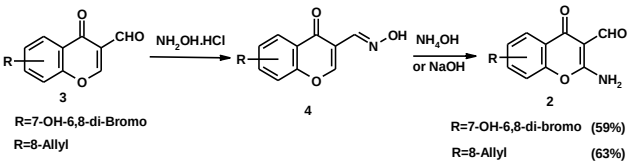


Scheme 1

2-Aminochromone-3-carboxaldehydes **2** were efficiently synthesized from heating carbonitriles **1** with morpholine in

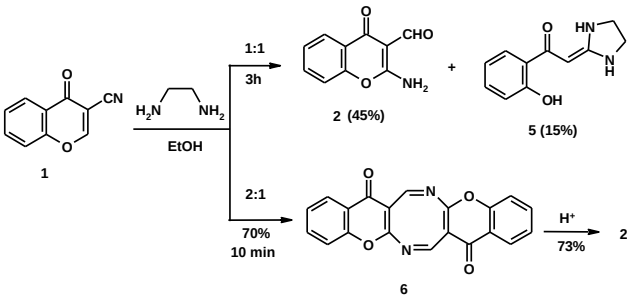
an aqueous DMF [38] or with *n*-propylamine in an aqueous ethanol [39] or with concentrated ammonia [40] or with aqueous sodium hydroxide solution [41], *via* the non-isolable intermediate **A** (Scheme 1).

Also, treatment of chromone-3-carboxaldehyd-oximes **4** [which was obtained from reaction between 3-formylcromones and hydroxylamine] in ethanol with ammonium hydroxide [42] or sodium hydroxide solution [43] produced 2-amino-3-formylchromone **2** (Scheme2).



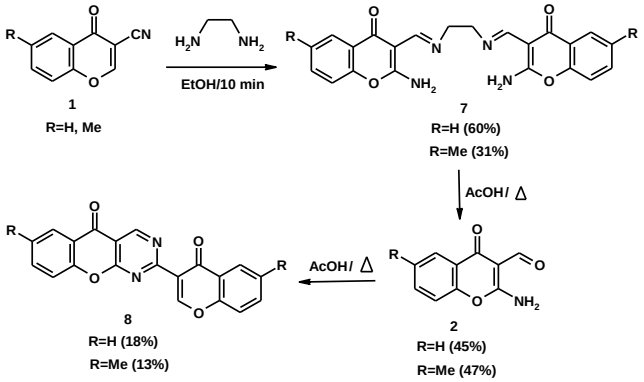
Scheme 2

2-Amino-3-formylchromone **2** was synthesized together with 1-(2-hydroxyphenyl)-2-imidazolidylidene)ethanone (**5**) from the reaction of carbonitrile**1** with ethylenediamine in boiling ethanol [3 h in 1:1 molar ratio] (Ghosh and Tewari) [39] (Scheme 3). While, Ghosh *et al*, [44] postulated the formation of *bis*-chromeno[2,3-*b*:2',3'-*f*][1,5] diazocine (**6**) when the reaction was carried in boiling ethanol for 10 min in 2:1 molar ratio, in this reaction ethylenediamine, as aliphatic amine, induced self-condensation of carbonitrile **1**. Hydrolysis of compound **6** under acidic conditions afforded compound **2** (Scheme 3).



Scheme 3

The previous reaction was next studied by Sosnovskikh *et al* [45] and isolate *N`*,*N`*-ethylene-*bis*(2-amino-3-iminomethylchromones) **7**, 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 **8** (Scheme 4) [45].



Scheme 4

3 Reactions of 2-amino-3-formylchromones

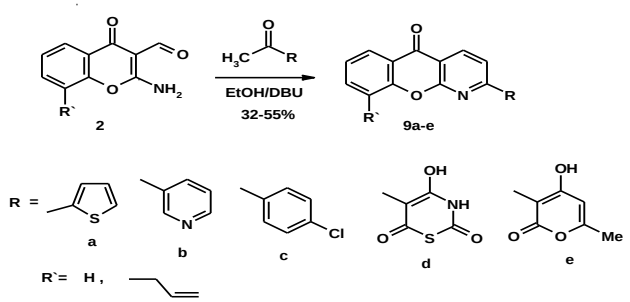
3.1 Reactions with carbon nucleophiles

2-Amino-3-formylchromones are good precursors for the synthesis of a variety of annulated chromones *via* Friedländer condensation reaction. Friedländer synthesis involves a condensation followed by cyclodehydration between an aromatic *ortho*-amino aldehyde or ketone and an aldehyde or ketone bearing α-methyl/α-methylene groups [46]. Also, Friedländer hetero-annulation reaction is highly efficient, simple and green solvent-free protocol for the preparation of poly-substituted quinolines in the presence of silica-supported P_2O_5 (P_2O_5/SiO_2) [Green Chemistry] [47]. Moreover, ionic liquid-promoted regiospecific Friedländer hetero-annulation reaction by using 1-butylimidazolium tetrafloroborate [Hbim]BF_4 was reported, where the ionic liquid acts as promoter for this regiospecific synthesis can be recycled [48]. The Friedländer condensation reaction of 2-amino-3-formylchromones with a variety of acyclic and cyclic carbon nucleophilic reagents is discussed below.

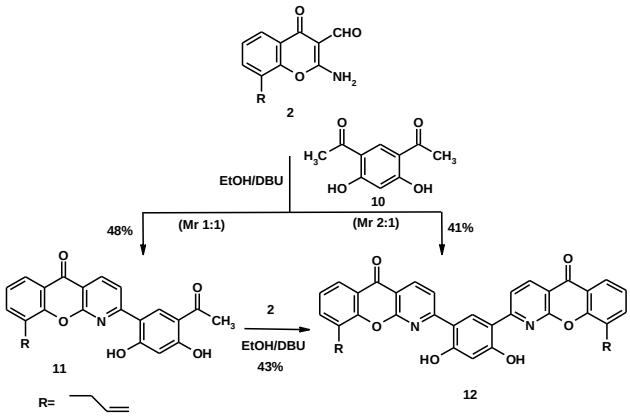
3.1.1 Reactions with active methyl and acyclic methylene compounds

Friedländer reaction of 2-amino-3-formylchromones **2** with a diversity of active methyl compounds namely; 2-acetylthiophene, 3-acetylpyridine, 4-chloroacetophenone, 5-acetyl-4-hyderoxy-3*H*-1,3-thiazine-2,6-dione and 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one under reflux in absolute ethanol containing few drops of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a basic catalyst, afforded chromeno[2,3-*b*]pyridine derivatives **9a-e** in good yields [32%-55%] (Scheme 5) [49,50].

Treatment of *o*-aminoaldehyde **2** with 4,6-diacetyl-resorcinol in 1:1 and 2:1 molar ratios gave chromeno[2,3-*b*] pyridines **11** and **12**, respectively. *Bis*(chromenopyridin-2-yl)resorcinol **12** was also obtained authentically from the reaction of compound **11** with aldehyde **2** under the same Friedländer reaction conditions (Scheme 6) [50].

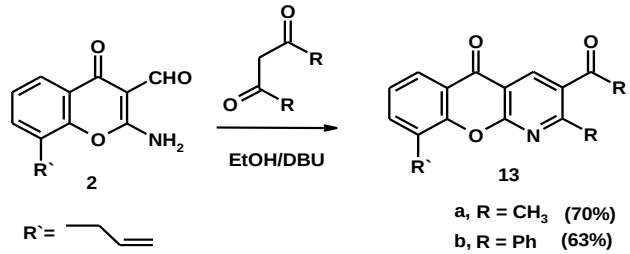


Scheme 5



Scheme 6

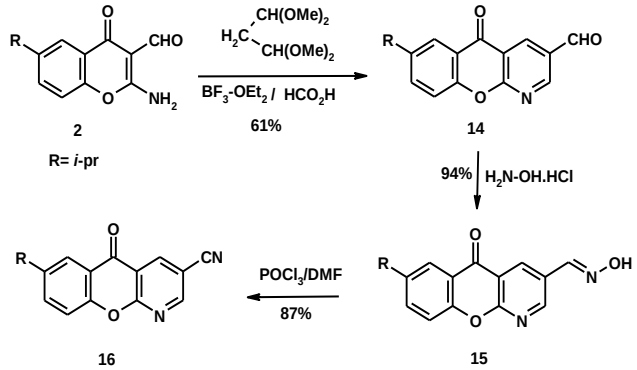
Cyclocondensation of *2*-amino-3-formylchromones **2** with acetylacetone and dibenzoylmethane, in boiling ethanol containing DBU, produced 5-oxo-5*H*–chromeno[2,3-*b*] pyridines **13a** and **13b**, respectively (Scheme 7) [50].



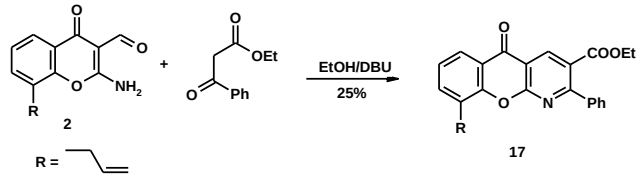
Scheme 7

Reaction of *o*-aminoaldehyde **2** with malonaldehyde *bis*(dimethy1acetal) in the presence of formic acid containing boron trifluorideetherate gave 7-isopropyl-5-oxo-5*H*-[1]chromeno[2,3-*b*]pyridine-3-carboxaldehyde (**14**) (Scheme 8). Reaction of carboxaldehyde **14** with hydroxylamine hydrochloride afforded the corresponding oxime **15** which upon dehydrated, using $POC1_3$ in DMF at room temperature, gave the corresponding carbonitrile **16** (Scheme 8) [51].

Refluxing *o*-aminoaldehyde **2** with ethyl benzoylacetate as unsymmetrical β-ketoester in boiling ethanol containing DBU afforded heteroannulated chromones, ethyl 9-allyl-2-phenyl-5-oxo-5*H*-chromeno[2,3-*b*]pyridine-3-carboxylate (**17**) (Scheme 9) [40]

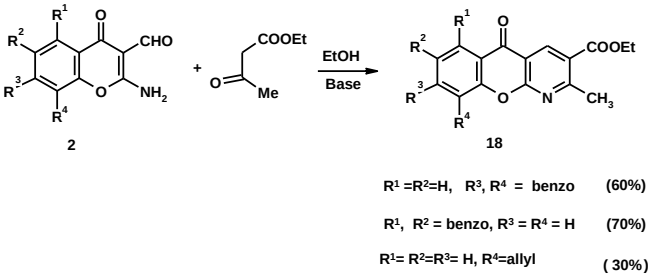


Scheme 8



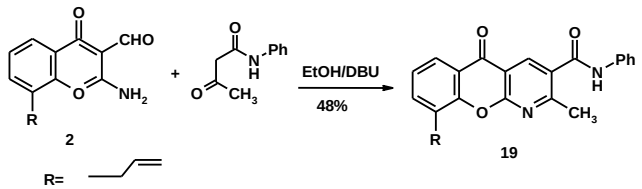
Scheme 9

In the same manner, reaction of *o*-aminoaldehydes **2** with ethyl acetoacetate in boiling ethanol under basic conditions afforded heteroannulatedchromones, ethyl 2-methyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carboxylates 18 (Scheme 10) [40,52]



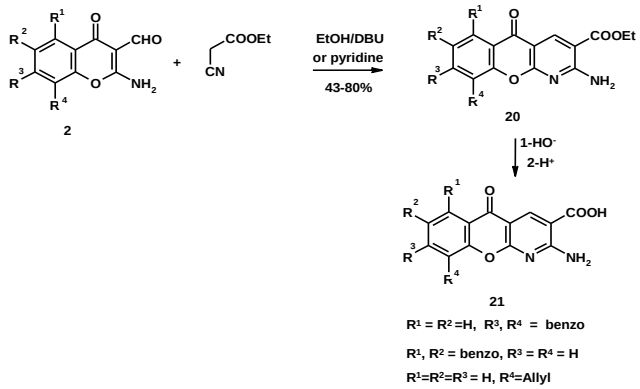
Scheme 10

Heating *o*-aminoaldehyde **2** with acetoacetanilide, in EtOH/DBU gave 9-allyl-2-methyl-5-oxo-*N*-phenyl-5*H*-chromeno[2,3-*b*]pyridine-3-carboxamides (**19**) (Scheme 11) [50].



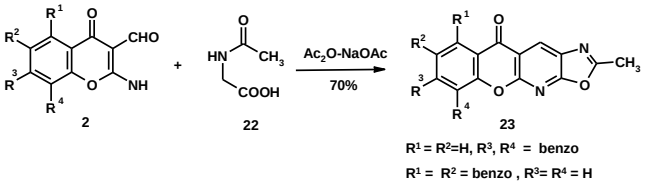
Scheme 11

The reaction of*o*-aminoaldehydes **2** with ethyl cyanoacetate produced ethyl chromeno pyridine-3-carboxylates **20**. Hydrolysis of the amino esters **20** in ethanolic sodium hydroxide solution afforded *o*-amino acids **21** in good yield (Scheme 12) [40,52]



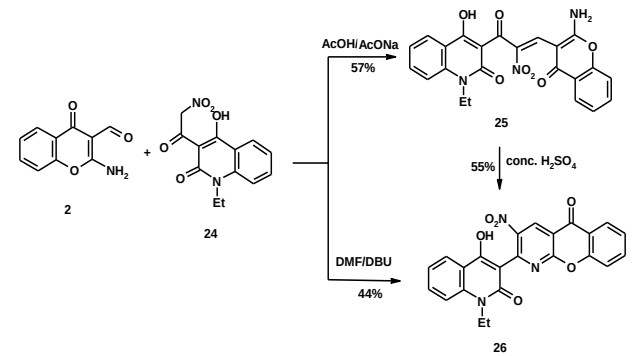
Scheme 12

Refluxing *o*-aminoaldehyde **2** with acetylglycine (**22**) in acetic anhydride in fused sodium acetate, afforded the oxazolochromenopyridine derivatives **23** (Scheme 13) [52].



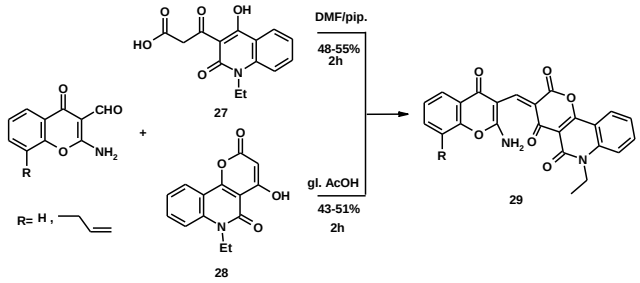
Scheme 13

Treatment of 2-amino-3-formylchromone (**2**) with 1-ethyl-4-hydroxy-3-nitroacetylquinolin-2(1*H*)-one (**24**), in glacial acetic acid containing freshly fused sodium acetate gave 3-[3-(2-amino-4-oxo-4*H*-chromen-3-yl)-2-nitroprop-2-enoyl]-1-ethyl-4-hydroxyquinolin- 2 (1*H*)-one (**25**). When the latter reaction took place in boiling DMF containing few drops of DBU as a basic catalyst afforded the Friedländer condensation product identified as 2-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-3-nitro-5*H*-chromeno[2,3-*b*]pyridin-5-one (**26**). The latter compound was obtained authentically *via* stirring of compound **25** in concentrated sulfuric acid (Scheme 14) [53].



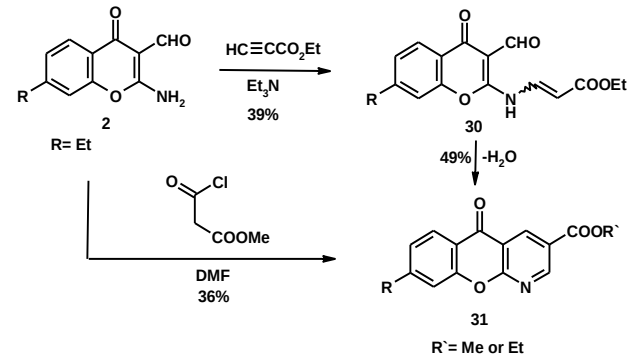
Scheme 14

Teatment of 2-aminochromone-3-carboxaldehydes **2** with *β*-keto acid **27** and/or pyranoquinoline**28** in boiling DMF containing few drops of piperidine as a catalyst afforded pyranoquinoline derivatives **29** bearing 2-amino-chromonylmethylidene moiety (Scheme 15) [54].



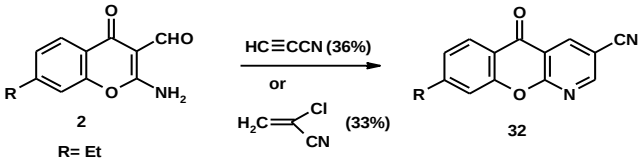
Scheme 15

The reaction of 2-aminochromone-3-carboxaldehyde **2**with ethyl propiolate in DMF containing triethylamine (TEA) initially afforded aminoacrylate **30** which was converted, by further heating, to ethyl 5-oxo-5*H*-[1]chromeno[2,3-*b*] pyidine-3-carboxylate (**31**) (R=Et). On the other hand, compound **31** (R=Me) was obtain directly from the reaction of compound **2** with methyl malonyl chloride in DMF (Scheme 16) [51].



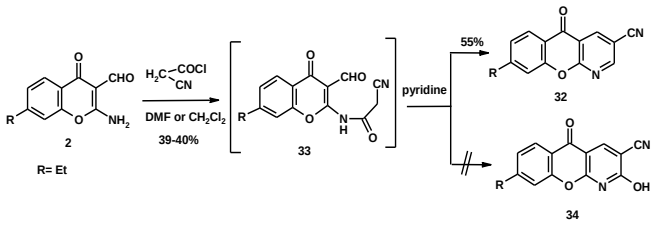
Scheme 16

Treating 2-amino-7-ethyl-3-formylchromone (**2**) with cyanoacetylene, gave ethyl-5-oxo-5*H*-[1]chromeno[2,3-*b*] pyridine-3-carbonitrile (**32**). However, because cyanoacetylene has several undesirable properties, i.e, sublimation at low temperature, instability and pungent odor. α-Chloroacrylonitrile reacted with *o*-aminoaldehyde **2** in the presence of trimethylamine and gave the same product **32**. Treating 2-amino-3-formylchromone **2** with cyanoacetyl chloride in DMF afforded the same product **32** (Scheme 17) [51].



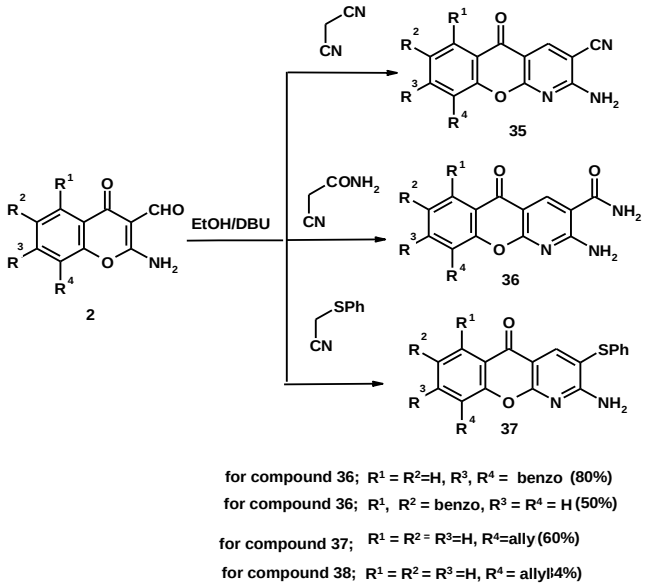
Scheme 17

Condensation of 2-amino-7-ethyl-3-formylchromone (**2**) with cyanoacetyl chloride in DMF or dichloromethane did not give the expected cyanoacetamide intermediate **33** or its cyclized product 2-hydroxy-3-cyanochromenopyridine derivative **34**, but gave the final product was identified as 5-oxo-5*H*-[1]chromeno[2,3-*b*]pyridine-3-carbonitrile **32**



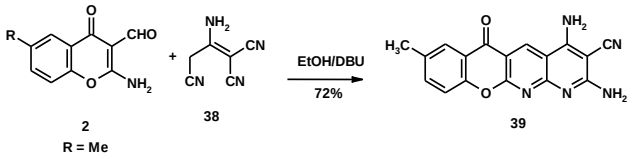
Scheme 18

Reaction of 2-aminochromone-3-carboxaldehyde **2** with active methylene compounds containing cyano group adjacent to methylene group (-CH_2CN) namely: malononitrile, cyanoacetamide, and phenylthioacetonitrile in absolute ethanol containing few drops of DBU afforded 2-amino-5-oxo-5*H*-chromeno[2,3-*b*]pyridines **35-37**, respectively, through condensation followed by cyclo-addition reactions (Scheme 19) [40,52].



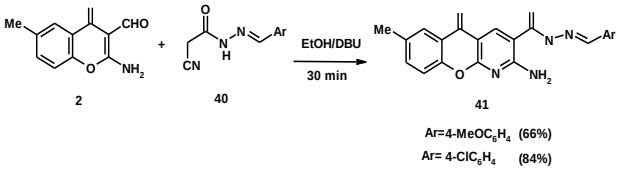
Scheme 19

Condensation reaction of 2-amino-6-methylchromone-3-carboxaldehyde(**2**) with malononitrile dimer **38** in boiling ethanol containing few drops of DBU afforded 2,4-diamino-8-methyl-6-oxo-6*H*-chromeno[2,3-*b*][1,8]naphthyridine-3-carbonitrile (**39**)(Scheme 20) [55].



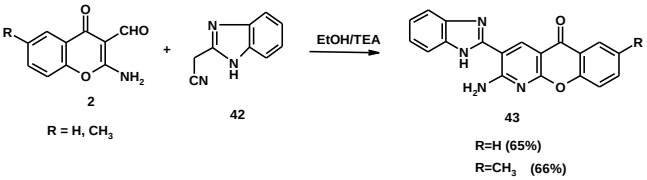
Scheme 20

Condensation reaction of 2-amino-6-methylchromone-3-carboxaldehyde (**2**) with *N`* [(4-methoxy/chlorophenyl) methylidene]-2-cyanoacetohydrazide **40** afforded 2-amino-[(4-methoxy/chlorophenyl)methylidene]-7-methyl-5-oxo-5*H*-chromeno[2,3-*b*]pyridine-3-carbohydrazides **41** (Scheme 21) [55,56]



Scheme 21

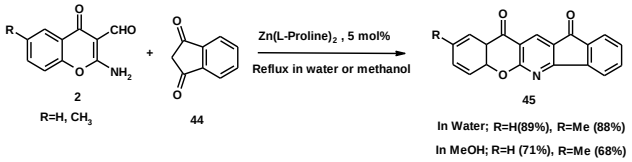
The reaction of 2-amino-3-formylchromones **2** with 1*H*-benzimidazol-2-ylacetonitrile (**42**), in boiling ethanol conaining few drops of TEA, produced 2-amino-3-(1*H*-benzimidazol- 2-yl)-7-methyl-5*H*-chromeno[2,3-*b*]pyridin-5-one (**43**) (Scheme 22) [57]



Scheme 22

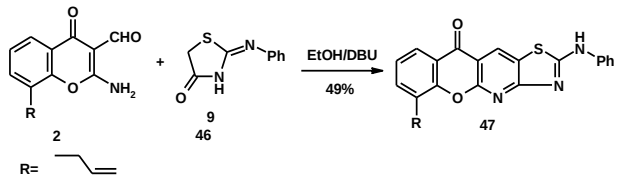
3.1.2 Reactions with cyclic methylene compounds

A facile and green synthetic route to new chromeno[2,3-*b*] pyridines in excellent yield *via* Friedlander condensation has been developed by the reaction of 2-amino-3-formylchromones **2** and cyclic active methylene compounds such as indandione**44** in the presence of Zn(L-proline)$_2$ as an efficient, stable and inexpensive Lewis acid catalyst in water, producing 4-oxo-4*H*-1-chromeno[2,3-*b*] indeno[2,3-*e*]pyridines (**45**) (Scheme 23) [58].



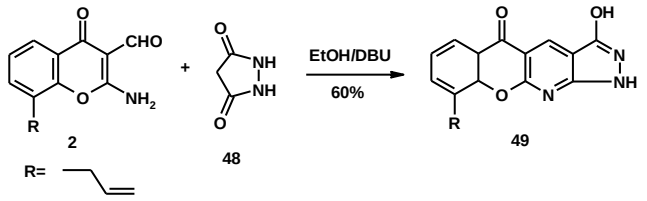
Scheme 23

Refluxing *o*-aminoaldehyde **2** with 2-phenylimino-1,3-thiazolidin-4-one (**46**) in absolute ethanol containing DBU gave 2-anilino-chromeno[2,3-*b*][1,3]thiazolo[5,4-*e*] pyridin-5-one (**47**) (Scheme 24) [50].



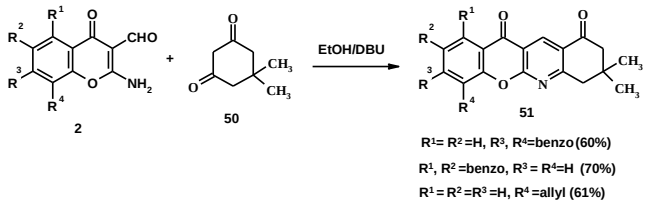
Scheme 24

Cyclic α-methylene ketones and cyclic 1,3-diketones also undergo smooth and efficient Friedländer reaction with compound **2** yielding heteroannulatedchromenes. Thus, refluxing *o*-aminoaldehydes **2** with pyrazolidine-3,5-dione (**48**) in ethanol containing DBU produced 3-hydroxy chromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridine-5(1*H*)one (**49**) (Scheme 25) [50].



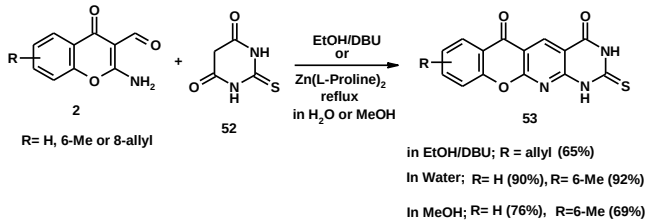
Scheme 25

Condensation of 2-amino-3-formylchromones **2** with 5,5-dimethylcyclohexane-1,3–dione (dimedone) (**50**) produced annulated chromeno[2,3-*b*]quinolinediones **51** (Scheme 26) [50,52,59].



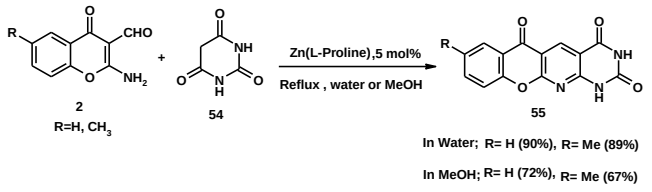
Scheme 26

The Friedlander condensation reaction of *o*-amino aldehydes **2** with thiobarbituric acid (**52**) in ethanol and DBU furnished 2-thioxo-4*H*-chromeno[2`,3:2,3]pyrido[5,6-*d*] pyrimidine-2,4,6-triones **53**,[50] this reaction occurring in presence of Zn(L-proline)$_2$ and gave the same product (Scheme 27) [58].



Scheme 27

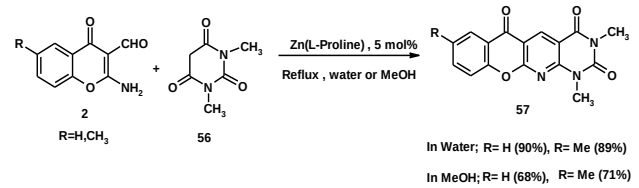
Tretment of o-aminoaldehydes **2** with barbituric acid (**54**) in the presence of Zn (L-proline)$_2$ gave chromeno[2`,3:2,3] pyrido[5,6-*d*]pyrimidine-2,4,6-triones **55** (Scheme 28) [58]



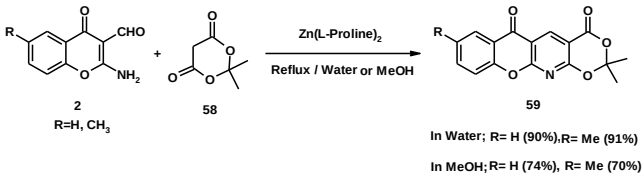
Scheme 28

Condensation of o-aminoaldehydes **2** with 1,3-*N*,*N*-dimethylbarbituric acid (**56**) afforded chromeno[2`,3:2,3]pyrido[5,6-*d*]pyrimidine-2,4,6-triones (**57**) (Scheme 29) [58].

Cyclocondensation of 2-amino-3-formylchromones **2** with 2,2-dimethyl-1,3-dioxane-4,6-dione (**58**) afforded 2,2-dimethyl-1,3-dioxane-6-methylchromeno[2,3-*b*]quinoline-4,6 (4*H*,6*H*)-dione (**59**) (Scheme 30) [58].

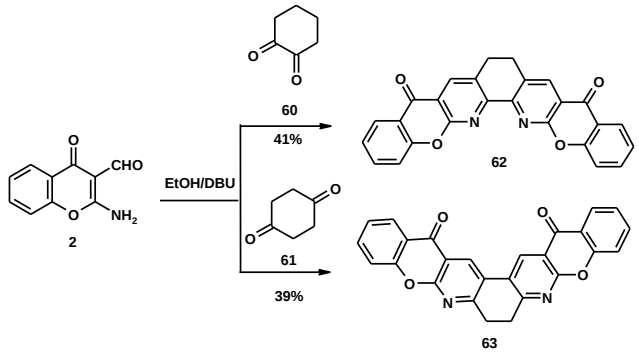


Scheme 29



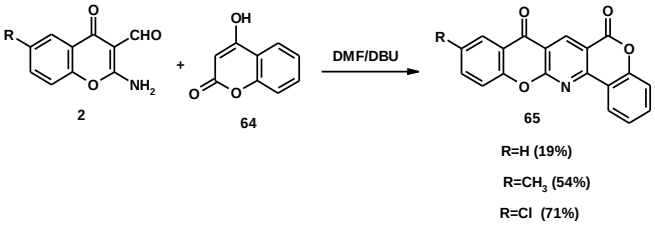
Scheme 30

Friedländer reaction of *o*-aminoaldehyde **2** with 1,2-cyclohexanedione (**60**) and 1,4-cyclohexanedione (**61**), in absolute ethanol and DBU, afforded the isomeric products, 7,8-dihydro-5*H*, 10*H*-*bis*[1]chromeno[2,3-*b*:3`,2`-*J*][1,10] phenanthroline-5,10-dione (**62**) and 7,8-dihydro-15*H*,18*H*-*bis*[1]chromeno[3,2-*b*:2`,3`-*J*][4,7] phenanthroline-15,18-dione (**63**), respectively (Scheme 31) [60].



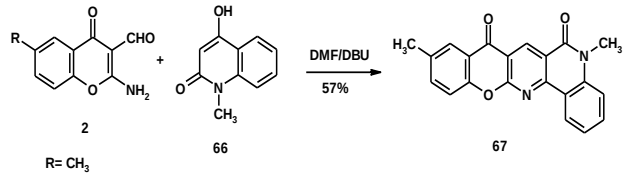
Scheme 31

2-Aminochromone-3-carboxaldehydes **2** were allowed to react with some heterocyclic enols. Thus, condensation of compound **2** with 4-hydroxycoumarin (**64**) in boiling DMF containing few drops of DBU afforded heteroannulated dichromeno[2,3-*b*:3',4'-*e*]pyridine-6,8-diones **65** (Scheme 32) [61,62, 63].



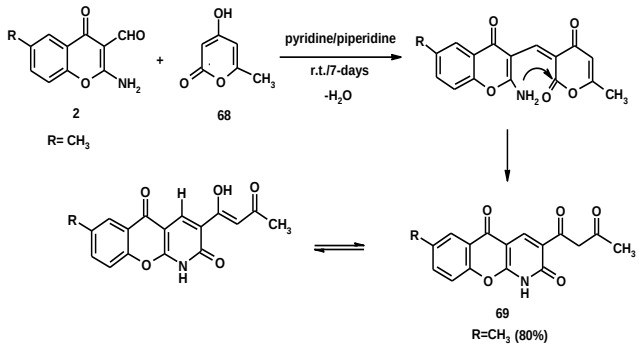
Scheme 32

Under the same reaction conditions, treatment of *o*-amino-aldehyde **2** with 4-hydroxy-1-methylquinolin-2(1*H*)-one (**66**) afforded 5,10-dimethyl-8*H*-benzo[*h*]chromeno[2,3-*b*] [1,6]naphthyridine-6(5*H*)-8-dione (**67**) (Scheme 33) [62].



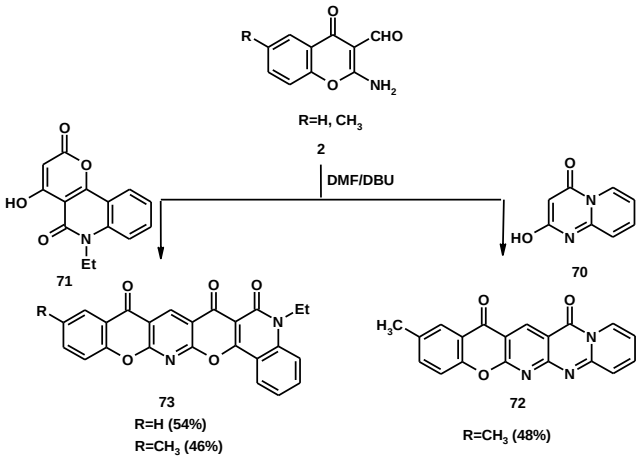
Scheme 33

Reaction of 2-aminochromone-3-carboxaldehyde **2** with 3-hydroxy-5-methylcyclohexa-2,4-dienone (**68**) gave 3-acetoacetyl-5-oxo-5*H*-[1]chromeno[3,2-*e*]pyridin-2-one (**69**) (Scheme 34) [63].



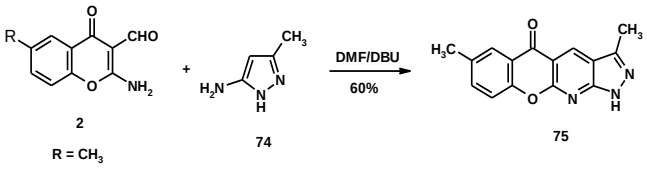
Scheme 34

Reaction of *o*-aminoaldehydes **2** with 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**70**) in refluxing DMF/DBU yielded the polyfused heterocyclic system; 2-methyl-13*H*,15*H*-chromeno[3",2":5',6']dipyrido[1,2-*a*:2',3'-*d*] pyrimidine-13,15-dione (**72**). Interestingly, 6-ethyl-4-hydroxy-2*H*-pyrano[3,2-*c*]quinoline-2,5(6*H*)-dione (**71**), when reacted with compound **2** produced the heteroannulated chromone 5-ethyl-11-H/methyl-7*H*,9*H*-chromeno[3",2":5',6']pyrido[3',2':5,6]pyrano[3,2-*c*] quinoline-6(5*H*),7,9-trione (**73**) (Scheme 35) [62,64].



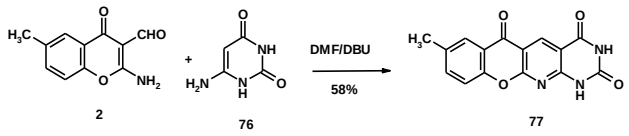
Scheme 35

The reactivity of compound **2** with some cyclic enamines was studied, thus treating *o*-amino aldehyde **2** with 5-amino-3-methyl-1*H*-pyrazole (**74**) in refluxing DMF/DBU resulted in 3,7-dimethylchromeno[2,3-*b*]pyrazolo[4,3-*e*] pyridin-5(1*H*)-one (**75**) (Scheme 36) [62].



Scheme 36

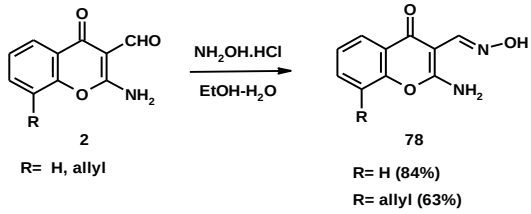
Refluxing *o*-aminoaldehyde **2** with 4(6)-aminouracil (**76**) in boiling DMF/DBU gave 8-methyl-6*H*-chromeno[3',2':5,6] pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*),6-trione (**77**) (Scheme 37) [62].



Scheme 37

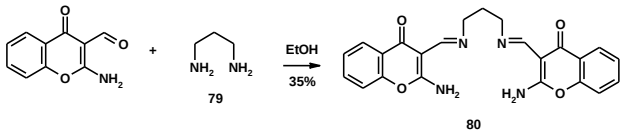
3.2 Reaction with nitrogen nucleophiles

Condensation of 2-amino-3-formylchromones **2** with hydroxylamine-hydrochloride in boiling ethanol afforded the corresponding oxime (**78**)(Scheme 38) [40,41]



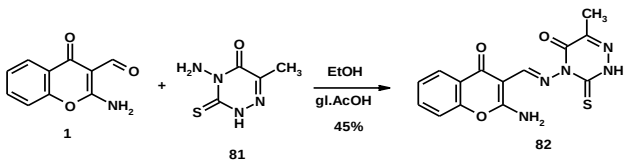
Scheme 38

The Schiff base **80** as a ligand was obtained from the condensation reaction of 2-amino-3-formylchromone (**2**) with 1,3-diaminopropane (**79**), in boiling ethanol (Scheme 39) [66].



Scheme 39

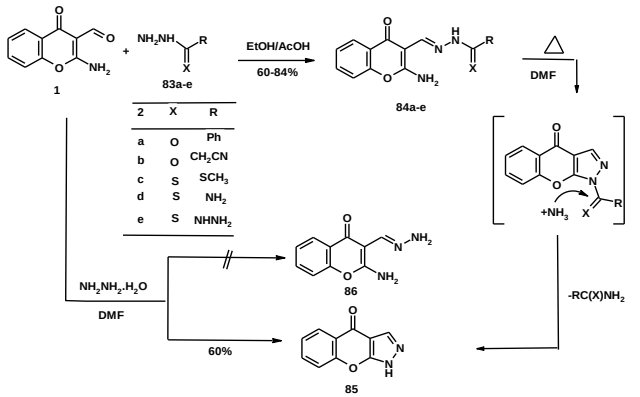
Condensing *o*-aminoaldehyde **2** with 4-amino-6-methyl-3-thioxo-3,4–dihydro-1,2,4-triazine-5(2*H*)-one (**81**), in EtOH/AcOH, afforded 4-{[(2-amino-4-oxo-4*H*-chromen-3-yl)methylene]amino}-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (**82**) (Scheme 40) [67].



Scheme 40

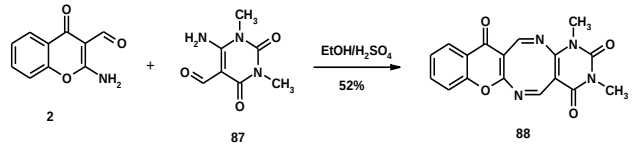
Condensation reaction of 2-amino-3-formylchromone (**2**) with some hydrazine derivatives **83a-e** namely

benzoylhydrazine, cyanoacetohydrazide, *S*-methyldithio carbazate, thiosemicarbazide and thiocarbohydrazide in boiling ethanol containing catalytic amount of acetic acid gave the corresponding hydrazones **84a-e**. Refluxing compounds **3a-e** in DMF yielded one product in all cases, which was identified as chromeno[2,3-*c*]pyrazol-4(1*H*)-one (**85**) (Scheme 38). Alternatively, condensation of *o*-amino-aldehyde **2** with hydrazine hydrate in boiling DMF produced compound **85** and not the hydrazone **86**. Formation of **85** was explained *via* cyclization of hydrazones **84a-e** with loss of one molecule of ammonia, followed by cleavage of amido and thioamido groups in high boiling solvents (Scheme 41) [67,68].



Scheme 41

Double condensation of *o*-amino aldehyde **2** with another type of *o*-aminoaldehyde namely, 6-amino-1,3-dimethyluracil-5-carboxaldehyde (**87**), in boiling ethanol containing catalytic amount of concentrated sulfuric acid, yielded the diazocine derivative **88** (Scheme 42) [67].

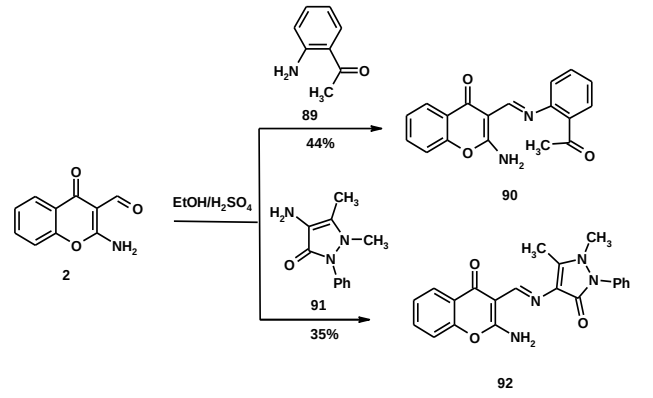


Scheme 42

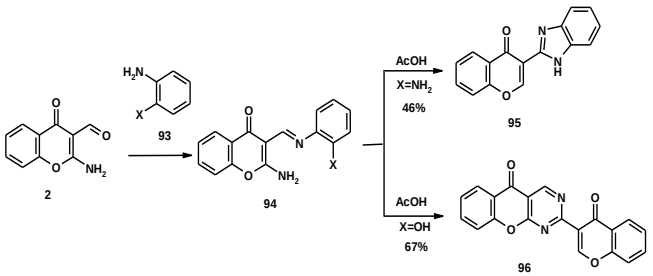
Under the same previous reaction conditions, condensation of *o*-aminoaldehyde **2** with 2-aminoacetophenone (**89**) and 4-aminoantipyrine (**91**) furnished 3-{([(2-acetylphenyl)imino]methyl}-2-aminochromone (**90**) and pyrazolyliminomethylchromone (**92**) (Scheme 43) [67].

Condensation reaction of 2-amino-3-formylchromone (**2**) with *o*-phenylenediamine and *o*-aminophenol **93** in boiling ethanol produced the corresponding Schiff bases **94a,b**. Refluxing Schiff base **94a** in boiling acetic acid furnished benzimidazolylchromone **95**, while boiling Schiff base **94b** in acetic acid gave chromeno[2,3-*d*]pyrimidin-5-one **96** in 67% yield (Scheme 44) [69].

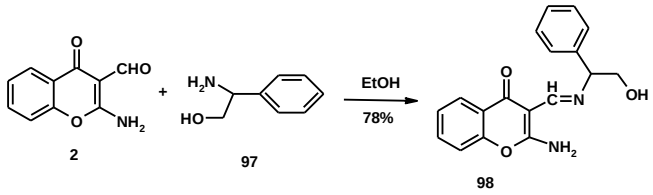
The Schiff base ligand **98** was obtained from the condensation reaction of 2-amino-3-formylchromone (**2**) with (R)-2-amino-2-phenylethanol (**97**) in ethanol as solvent in 1:1 stoichiometric ratio (Scheme 45) [70].



Scheme 43



Scheme 44



Scheme 45

4 Conclusion

2-Aminochromone-3-carboxaldehydes **2** represent a versatile substrate for the synthesis of a variety of heteroannulated chromones especially chromeno[2,3-*b*] pyridines and their related fused systems, *via* their reactions with a diversity of acyclic and cyclic active methyl and methylene compounds. In addition, 2-aminochromone-3-carboxaldehydes **2** used as a good synthone for a variety of Schiff bases and hydrazine ligands, which used for chelation with different metal ions leading to a diversity of metal complexes.

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