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SYNTHETIC APPROACHES FOR HETEROANNULATED CHROMONES FUSED VARIOUS HETEROCYCLIC SYSTEMS

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Abstract – The main focus of this review summarized the different methods utilized for the synthesis of chromone annulated with different heterocyclic rings such as pyrroles, furans, pyrazole, imidazole, benzene, naphthalene, quinolone.....and others.

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1. INTRODUCTION

Chromones (*4H*-chromen-4-one, *4H*-1-benzopyran-4-ones) serve as the basic structural motif of a highly important oxygen-containing heterocyclic systems, which are commonly found in various flavonoids that occur as natural products in the plant world.^{1,2} Many chromone derivatives exhibit strong biological activity^{3,4} such as antioxidants,⁵⁻⁷ antimicrobial,⁷ anti-HIV,⁸ anti-inflammatory,^{9,10} antitumor,¹¹ anticancer,¹² antiviral,¹³ antiparkinson,¹⁴ and have found applications as privileged structural motifs during the construction of various pharmaceutical molecules.^{15,16} Electronic absorption spectra, quantum chemical studies, DFT calculations, and optical properties were investigated for chromone derivatives.^{17,18} Heterocyclic ring fused on substituted chromones have become attractive targets in

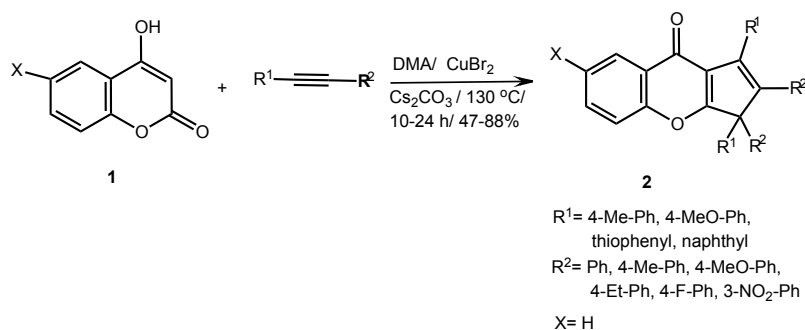
organic synthesis due to their significance in biological systems and wide occurrence in natural products.^{19,20}

2. SYNTHESIS OF HETEROANNULATED CHROMONES

2.1. Chromones-fused five membered rings

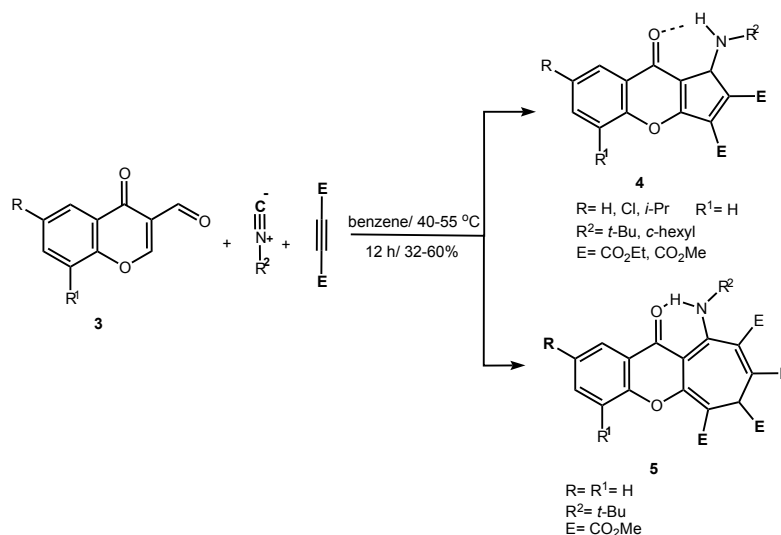
2.1.1. Chromones annulated with cyclopentadienes

Cascade reaction between 4-hydroxycoumarin (1) with disubstituted acetylene, in dimethylacetamide (DMA) in the presence of CuBr₂ as an oxidant and Cs₂CO₃ as base, afforded polysubstituted cyclopenta[*b*]chromen-9(3*H*)-one derivative 2 (Scheme 1).²¹



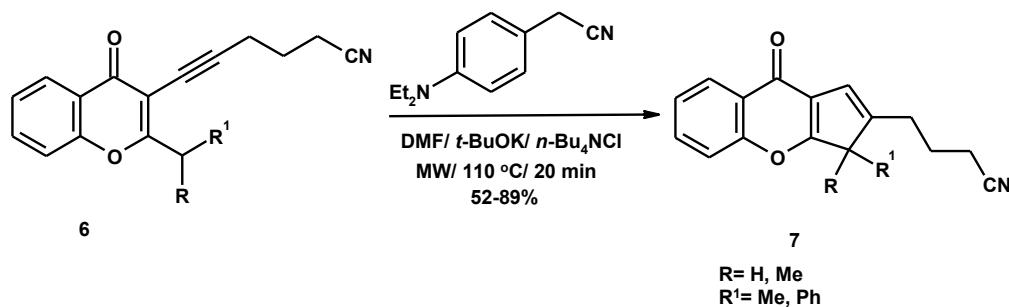
Scheme 1

Treatment of 3-formylchromones 3 with dialkyl acetylenedicarboxylate in the presence of butyl isocyanide, in benzene, led to the formation of the fused cyclopentachromenedicarboxylates 4. On the other hand, reaction of 3-formylchromone 3 with isocyanides and dimethyl acetylenedicarboxylate (DMAD), in benzene gave cycloheptachromenetetracarboxylate 5 (Scheme 2).²²



Scheme 2

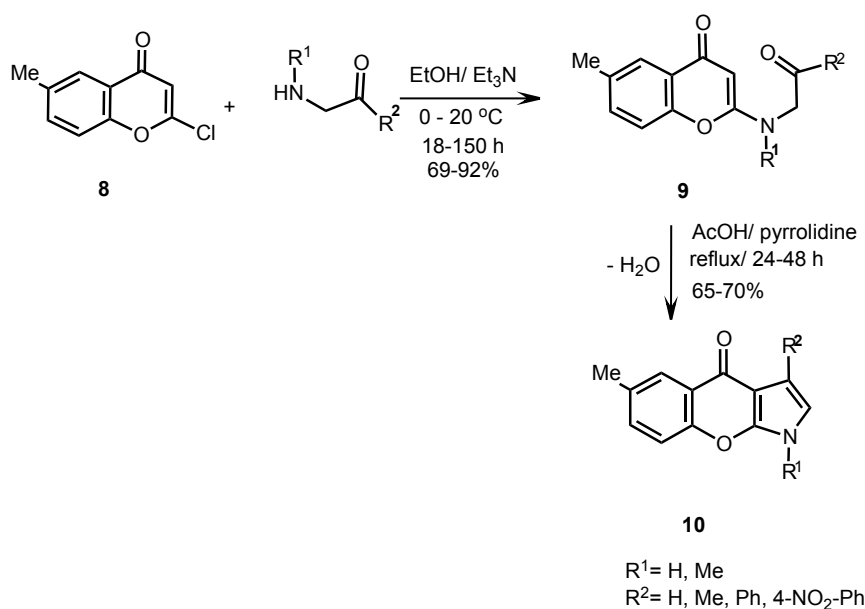
Substituted cyclopenta[*b*]chromen-9(3*H*)-ones **7** were produced in moderate to high yields by chemoselective cyclization of 2-substituted 3-alkynylchromones **6** with 4-diethylaminophenylacetonitrile in DMF containing potassium *t*-butoxide and tetrabutylammonium chloride as a catalyst. The phenylacetonitrile serves as an anion transfer reagent (Scheme 3).²³



Scheme 3

2.1.2. Chromones annulated with pyrroles

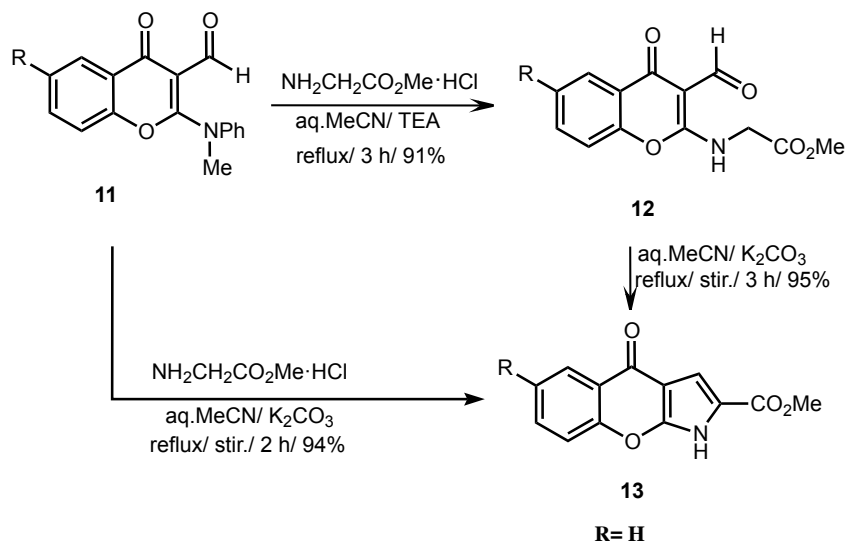
Alberola *et al.*²⁴ reported that condensation of 2-chloro-6-methylchromone **8** with α -amino ketones, in ethanol and trimethylamine, afforded 2-alkylaminochromones **9**. Boiling the latter compound with acetic acid and pyrrolidine led to chromeno[2,3-*b*]pyrrol-4(1*H*)-ones **10** (Scheme 4).



Scheme 4

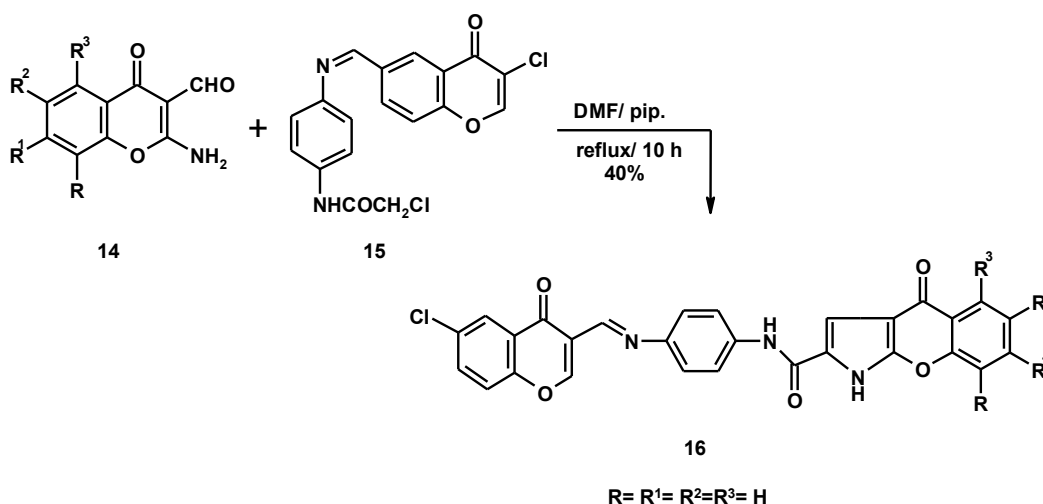
Refluxing 2-(*N*-methylanilino)-3-formylchromone (**11**) with methyl glycinate-hydrochloride, in aqueous acetonitrile in the presence of triethylamine, led to 2-methoxycarbonylmethylamino-3-formylchromone (**12**), in excellent yield (Scheme 5). Boiling compound **12** in aqueous acetonitrile in the presence of

potassium carbonate, gave 2-methoxycarbonylchromeno[2,3-*b*]pyrrol-4(1*H*)-one **13**. The latter compound **13** was obtained directly from the reaction of chromone derivative **11** with methyl glycinate-hydrochloride, in boiling acetonitrile containing potassium carbonate instead of trimethylamine (Scheme 5).²⁵



Scheme 5

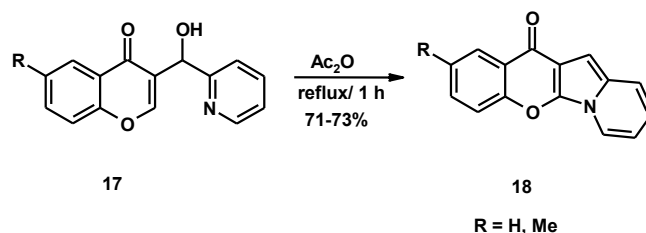
Cyclocondensation reaction between 2-amino-3-formylchromone (**14**) with chloroacetamide **15**, in boiling DMF containing piperidine, gave chromeno[2,3-*b*]pyrrole-2-carboxamide derivative **16** (Scheme 6).²⁶



Scheme 6

2.1.3. Chromones annulated with indolizine

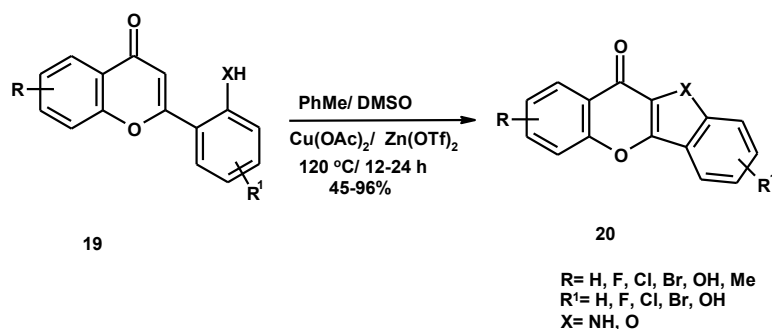
Heating 3-[hydroxy(pyrid-2-yl)methyl]chromones **17**, in acetic anhydride, provided 12*H*-chromeno[3,2-*b*]indolizin-12-ones **18**, in good yields (Scheme 7).²⁷



Scheme 7

2.1.4. Chromones annulated with benzopyrroles/benzofurans

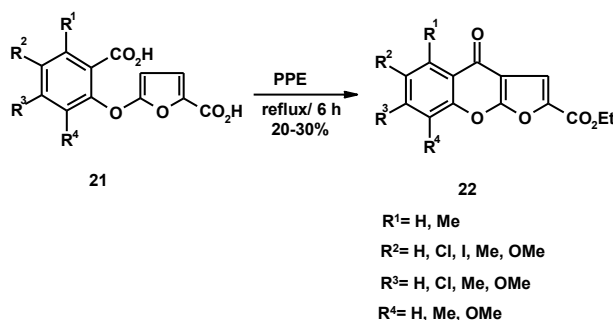
Cyclization reactions of 2-(2-substituted-phenyl)chromones **19** in boiling in toluene/dimethyl sulfoxide (PhMe/DMSO) using $Zn(OTf)_2$ combined with copper acetate, afforded chromones fused with benzofurans and/or benzopyrroles **20** (Scheme 8).²⁸



Scheme 8

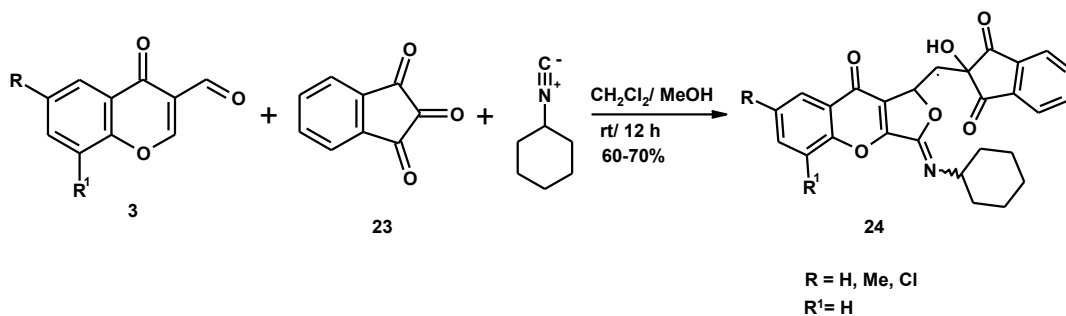
2.1.5. Chromones annulated with furans

Cyclization of 5-(2-carboxy-substituted-phenoxy)furan-2-carboxylic acids **21** with polyphosphoric acid ethyl ester (PPE), under reflux, produced substituted ethyl furo[2,3-*b*]chromone-2-carboxylates **22**, in low yield (Scheme 9).²⁹



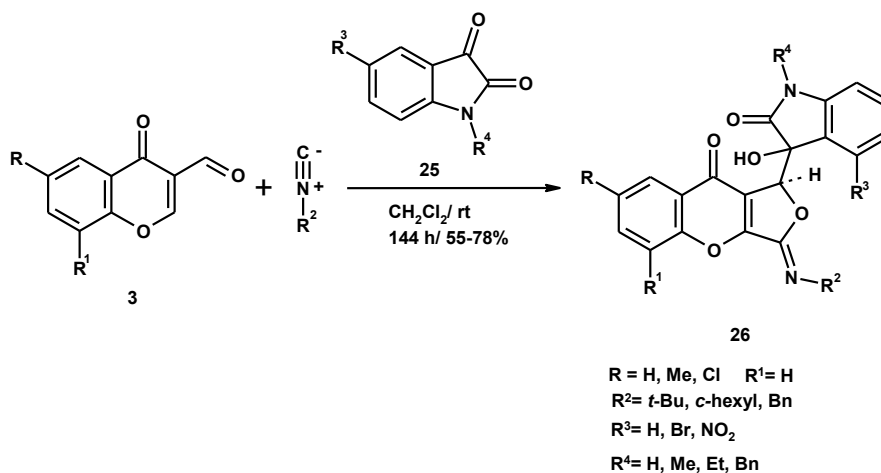
Scheme 9

Stirring an equimolar amount of 3-formylchromones **3**, ninhydrin **23** and cyclohexyl isocyanide, in mixture of dichloromethane/methanol (CH_2Cl_2 -MeOH) (7:1) at room temperature, produced furo[3,4-*b*]chromen-9-ones **24** (Scheme 10).³⁰



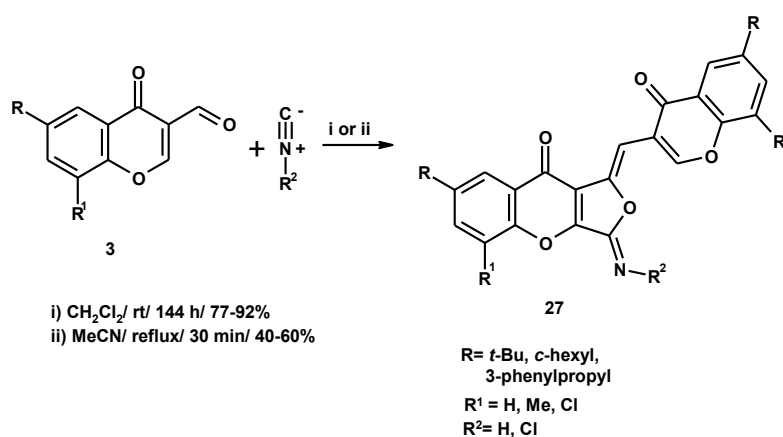
Scheme 10

Benchmark reaction between 3-formylchromones **3**, isocyanides and *N*-alkyl/benzylisatin **25**, in anhydrous dichloromethane (CH_2Cl_2), performed furo[3,4-*b*]chromen-1-ylindol-2-ones **26**, in 55-78% yields within 6 days at room temperature (Scheme 11).³¹



Scheme 11

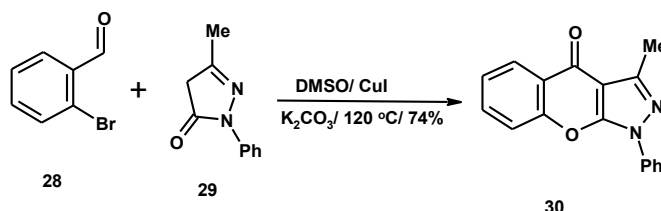
Reaction of 3-formylchromones **3** with isocyanides in molar ratio 2: 1, under different reaction conditions, furnished 1-[(chromon-3-yl)methylene]furo[3,4-*b*]chromen-9-ones **27** (Scheme 12).³⁰



Scheme 12

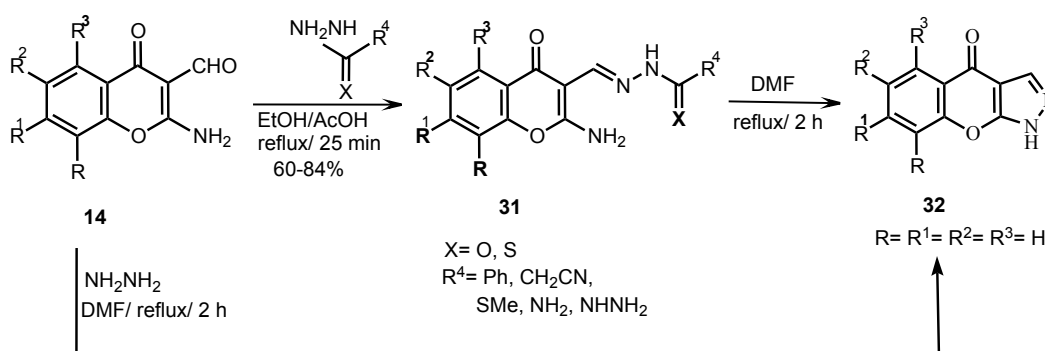
2.1.6. Chromones annulated with pyrazoles

Condensation of 2-bromobenzaldehyde (**28**) with 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**29**) in DMSO using CuI as a catalyst, and K₂CO₃ as a base afforded 3-methyl-1-phenylchromeno[2,3-*c*]pyrazol-4(1*H*)-one (**30**) (Scheme 13).³²



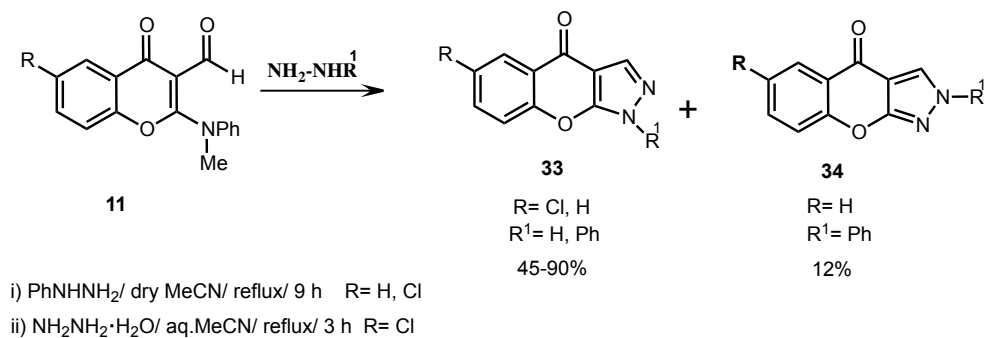
Scheme 13

Condensing 2-amino-3-formylchromone (**14**) with some hydrazine derivatives, in boiling ethanol containing catalytic amount of acetic acid, performed the corresponding hydrazones **31**. Boiling the latter compounds, in DMF, gave chromeno[2,3-*c*]pyrazol-4(1*H*)-one (**33**) (Scheme 14). Compound **32** can also be formed from refluxing aldehyde **14** with hydrazine hydrate in boiling DMF (Scheme 14).³³



Scheme 14

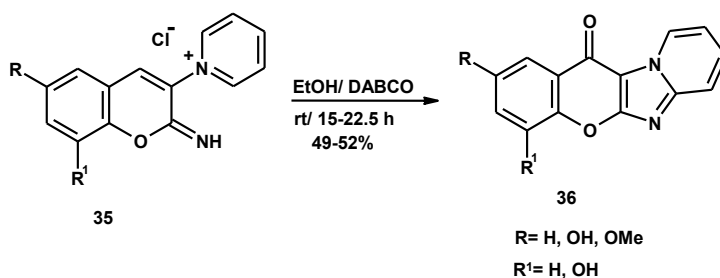
On the other hand, reaction of 2-(*N*-methylanilino)-3-formylchromones **11** (R = H) with phenylhydrazine, in refluxing dry acetonitrile, produced isomeric chromanopyrazoles **33** and **34**. Refluxing 2-(*N*-methylanilino)-3-formylchromone **11** (R = Cl) with hydrazine hydrate, in acetonitrile, afforded chromenopyrazole **33** (Scheme 15).^{25,34}



Scheme 15

2.1.7. Chromones annulated with imidazo-fused pyridine

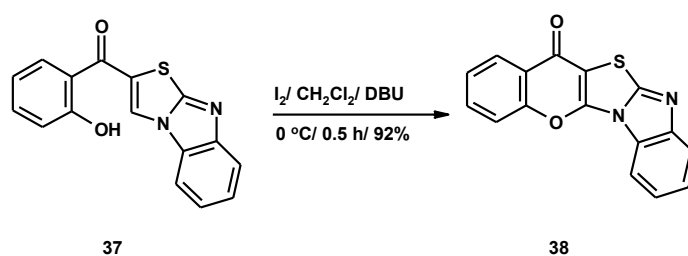
One-pot synthesis of 12*H*-chromeno[2',3':4,5]imidazo[1,2-*a*]pyridin-12-ones **36** were achieved, in moderate yield, from intramolecular cyclization of 1-(2-imino-2*H*-chromen-3-yl)pyridinium chlorides **35**, in boiling ethanol containing few drops of DABCO (1,4-diazabicyclo[2.2.2]octane) (Scheme 16).³⁵



Scheme 16

2.1.8. Chromone annulated with thiazolo-fused benzimidazole

Oxidation of benzimidazo[2,1-*b*]thiazole derivative **37** using iodine, in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), smoothly promoted the cyclized product; 5*H*-benzimidazo[2',1':2,3]thiazolo[4,5-*b*]chromone (**38**), in excellent yield (Scheme 17).³⁶

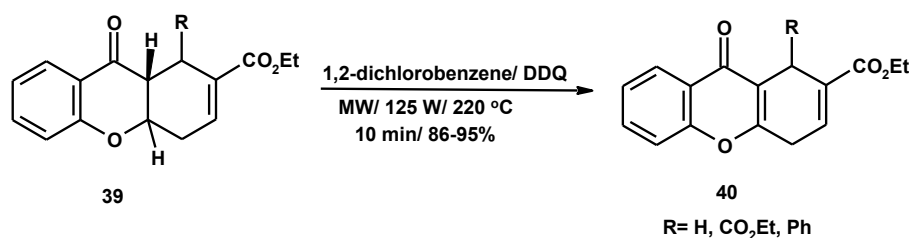


Scheme 17

2.2. Chromones-fused six membered rings

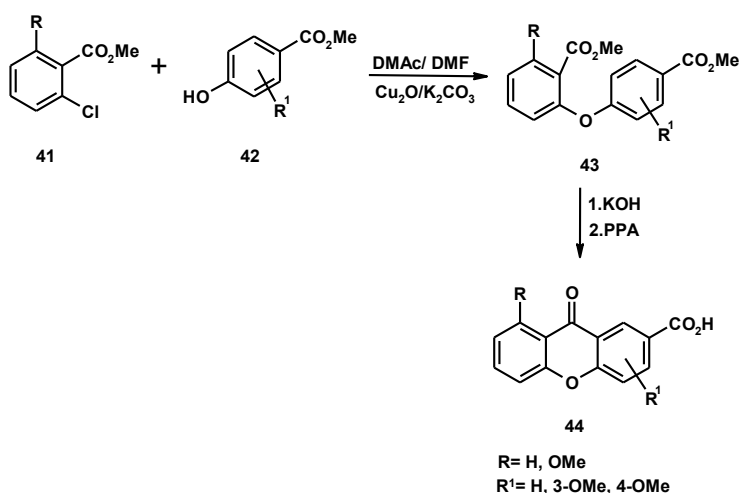
2.2.1. Chromone annulated with benzene

Also, oxidation of tricyclic chromones **39** with DDQ (2,3-dichloro-5,6-dicyanobenzoquinone), at 220 °C for 10 min under microwave conditions, provided 1,4-dihydroxanthones **40** in excellent yields (Scheme 18).³⁷



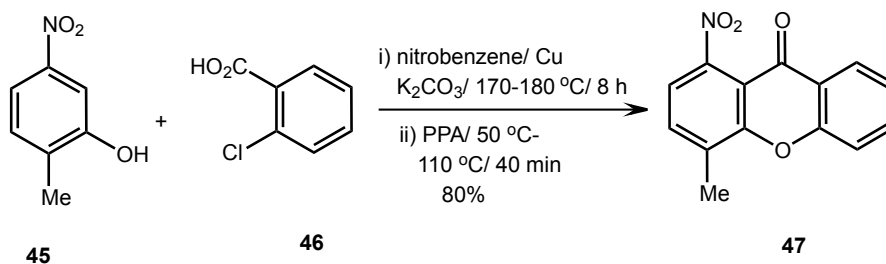
Scheme 18

Condensation of methyl 2-chlorobenzoates **41** with substituted phenols **42**, in mixture of dimethylacetamide (DMAc) and dimethylformamide (DMF) in the presence of cuprous oxide (Cu₂O) and potassium carbonate (K₂CO₃) yielded ether derivatives **43**, which were saponified and then cyclized by polyphosphoric acid to give xanthone-2-carboxylic acids **44** (Scheme 19).³⁸



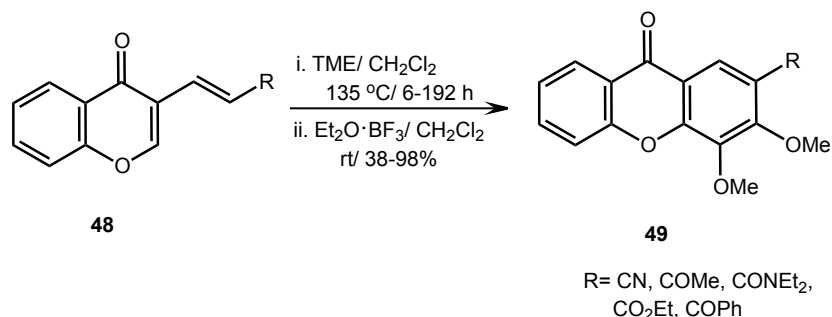
Scheme 19

4-Methyl-1-nitro-9*H*-xanthen-9-one (**47**) was synthesized from the reaction of 2-methyl-5-nitrophenol (**45**) with *o*-chlorobenzoic acid (**46**), in nitrobenzene and polyphosphoric acid (Scheme 20).³⁹



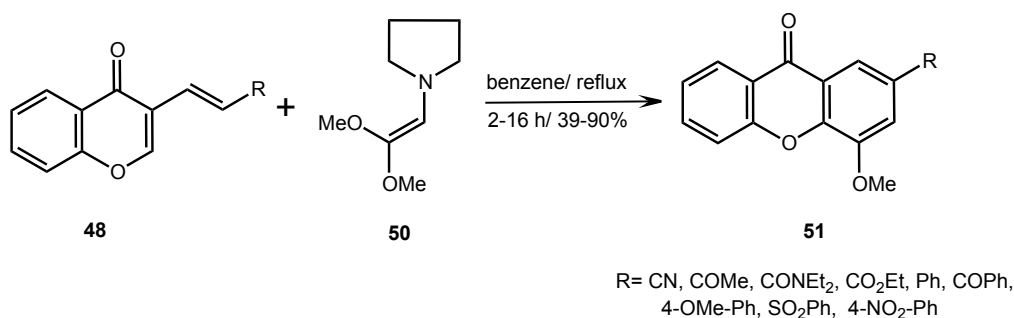
Scheme 20

Treating 3-alkenylchromone derivatives **48** with tetramethoxyethene (TME), in dichloromethane, followed by treatment with $Et_2O \cdot BF_3$ (4.0 equiv.) gave 3,4-dimethoxyxanthenes **49** (Scheme 21).⁴⁰



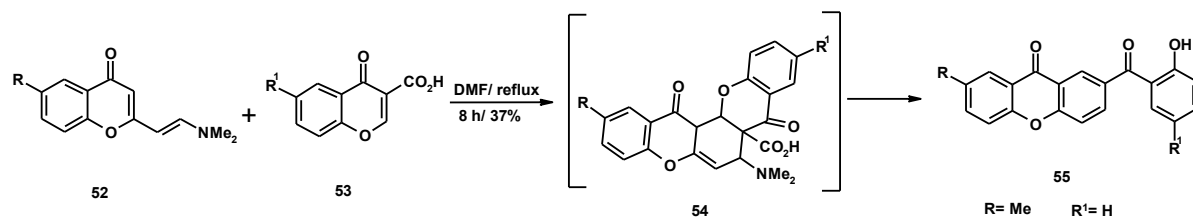
Scheme 21

Reaction of chromones **48** with freshly generated 1-(2,2-dimethoxyvinyl)pyrrolidine (**50**) (from dimethoxyacetaldehyde and pyrrolidine), in boiling benzene, resulted in xanthenes **51** in moderate to excellent yields (Scheme 22).⁴⁰



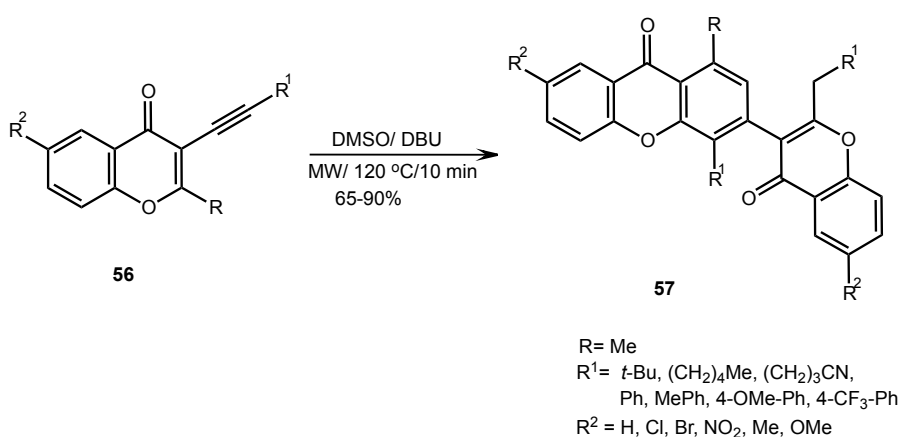
Scheme 22

Enamine derivatives **52** reacted smoothly with chromone-3-carboxylic acid (**53**), in boiling DMF, to give 2-salicyloylxanthone **55** via non-isolable cycloadduct **54** which underwent decarboxylative pyran ring opening and dedimethylamination (Scheme 23).⁴¹



Scheme 23

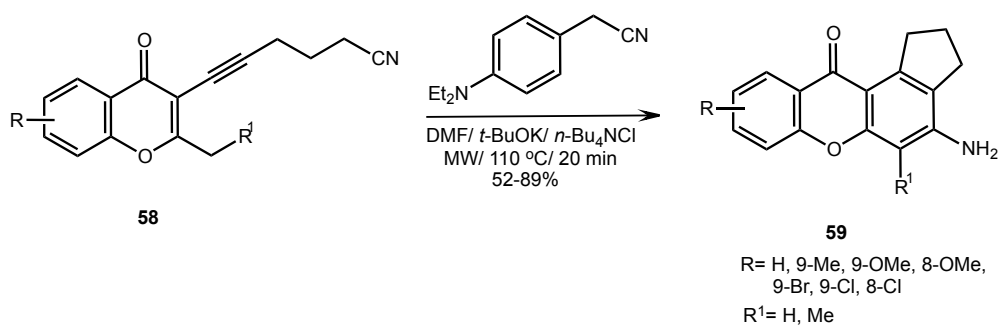
Dimerization reaction of 3-alkynyl-2-methylchromones **56**, in DMSO containing DBU in microwave irradiation at 120 °C for 10 min, led to xanthenes-linked chromones **57** (Scheme 24).⁴²



Scheme 24

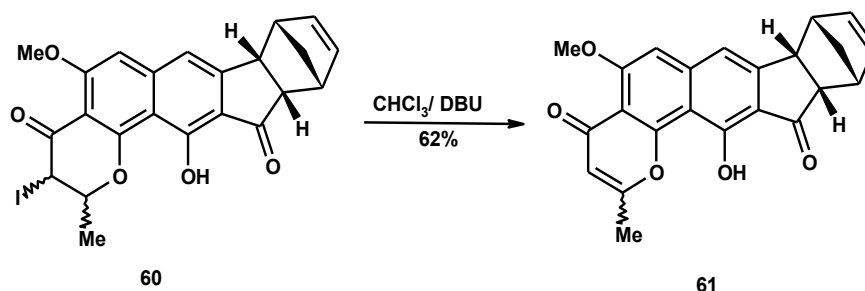
2.2.2. Chromones annulated with indenes

Reaction of 6-(chromon-3-yl)hex-5-ynenitriles **58** with 2-(4-(diethylamino)phenyl)acetonitrile, in the presence of *t*-BuOK and *n*-Bu₄NCl in DMF at 110 °C for 20 min under microwave irradiation, generated 4-amino-2,3-dihydrocyclopenta[*a*]xanthen-11(1*H*)-ones **59** (Scheme 25).²³



Scheme 25

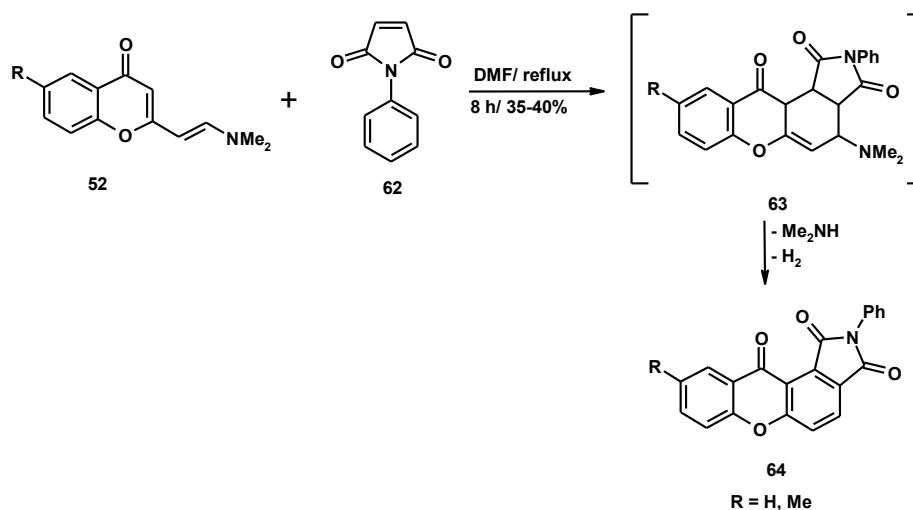
Also, dehydroiodination of annulated chromane **60**, in chloroform containing DBU, gave xanthone derivative **61** (Scheme 26).⁴³



Scheme 26

2.2.3. Chromones annulated with indole

Refluxing enamines **52** with *N*-phenylmaleimide **62**, in DMF under reflux, produced xanthone **64** through initially formed cycloadduct **63** which readily eliminated dimethylamine and dehydrogenated under the reaction conditions (Scheme 27).⁴¹



Scheme 27

2.2.4. Chromones annulated with isochromene

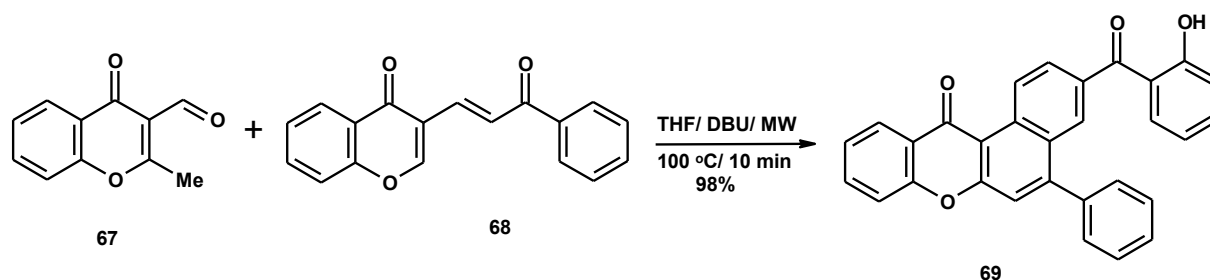
Tetracyclic pyranoxanthene derivatives **66** were prepared from oxidation of chromone derivatives **65** by using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) under microwave heating conditions at 220 °C for 10 min in 1,2-dichlorobenzene (Scheme 28).³⁷



Scheme 28

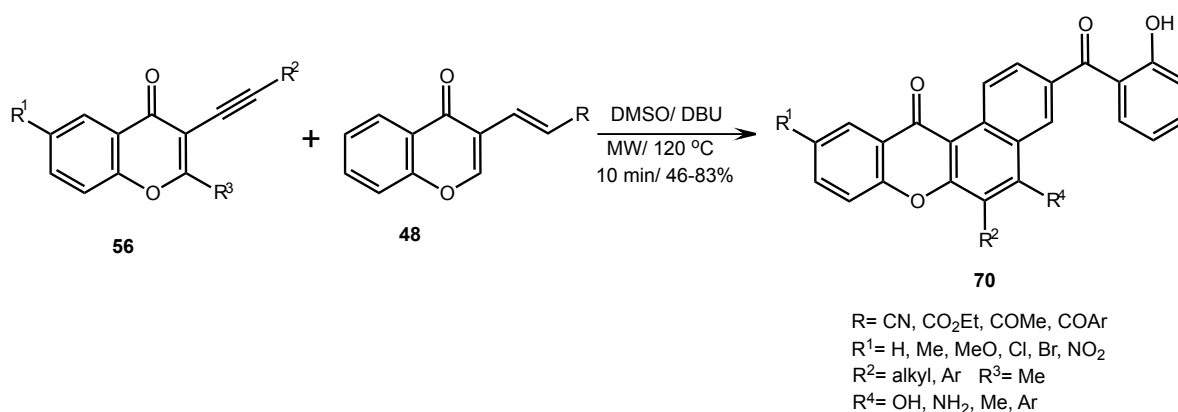
2.2.5. Chromones annulated with naphthalenes

3-[(2-Hydroxyphenyl)carbonyl]-5-phenyl-12*H*-benzo[*a*]xanthen-12-one (**69**) was obtained from cascade reaction between 2-methylchromone-3-carboxaldehyde (**67**) and 3-(3-oxo-3-phenylprop-1-enyl)chromone (**68**), in tetrahydrofuran (THF) containing DBU through microwave irradiation, in quantitative yield (Scheme 29).⁴⁴



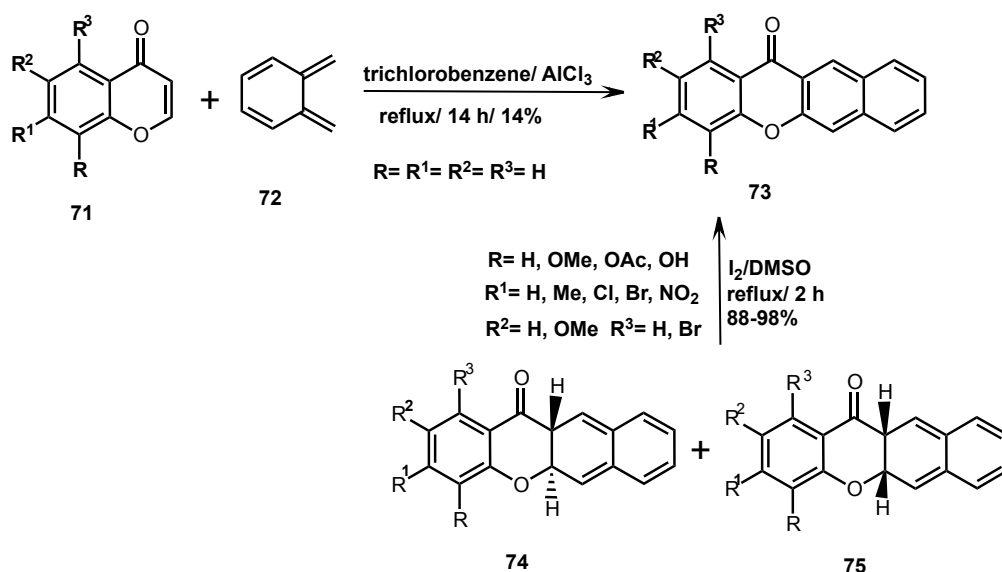
Scheme 29

Reaction of 2-methyl-3-(1-alkynyl)chromones **57** with electron-deficient chromone-fused dienes **48**, in DMSO using DBU as the base under microwave irradiation conditions, yielded benzo[*a*]xanthenes **70** (Scheme 30).⁴⁵



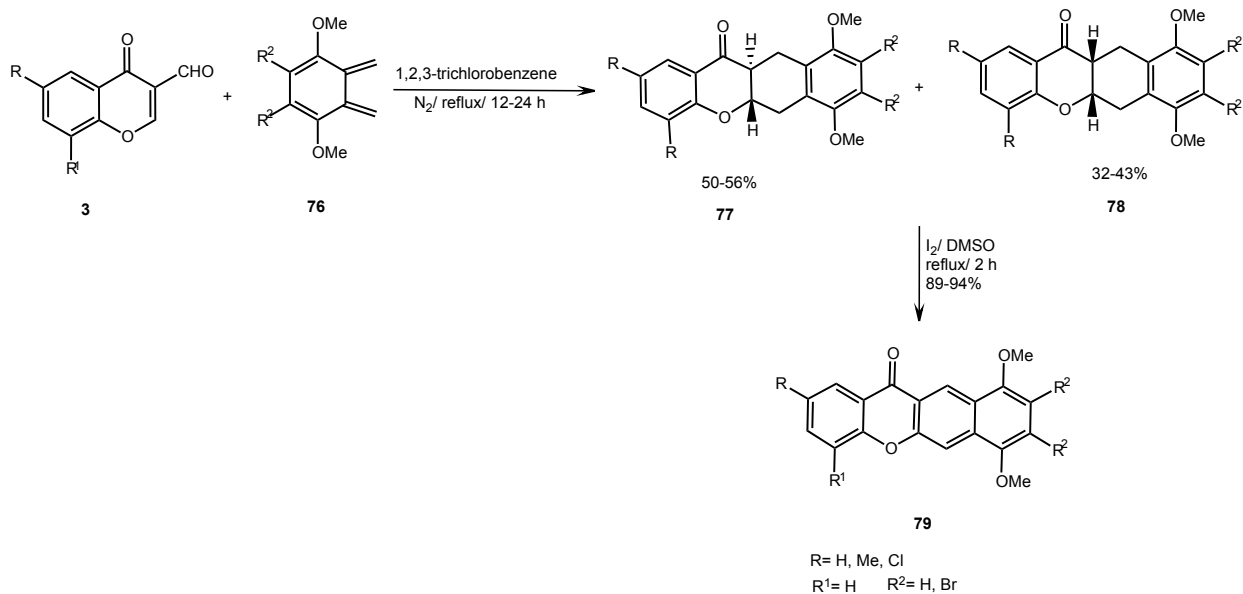
Scheme 30

Diels-Alder reaction of unsubstituted chromones **71** with *o*-benzoquinodimethane **72**, in 1,2,4-trichlorobenzene and anhydrous AlCl₃ as a Lewis acid, led to benzo[*b*]xanthenes **73**. While, oxidation of cycloadducts benzo[*b*]-1,6,6a,12a-tetrahydroxanthenes **74** and **75** by using iodine in DMSO gave compounds **73**, in excellent yields (Scheme 31).⁴⁶



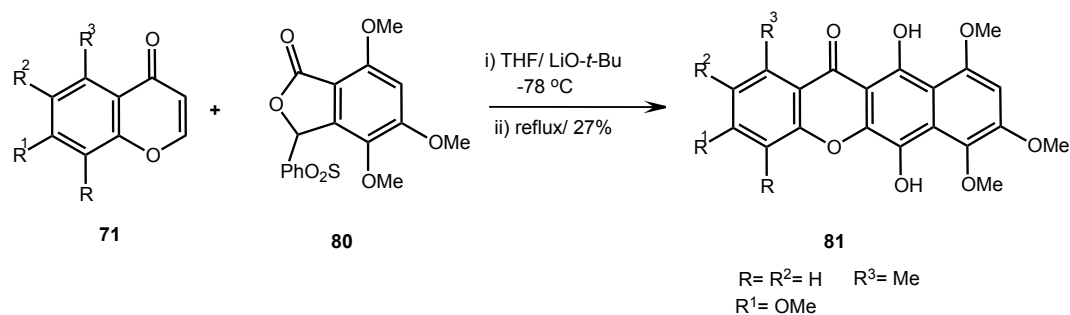
Scheme 31

Diels-Alder reactions of 3-formylchromones **3** with *o*-benzoquinodimethanes **76** gave rise a mixture of diastereomers **77** and **78** in excellent yields (88–93%). Oxidation of adducts **77** and **78**, with iodine in DMSO, gave benzo[*b*]xanthenes **79** in good yields (89–94%) (Scheme 32).⁴⁷



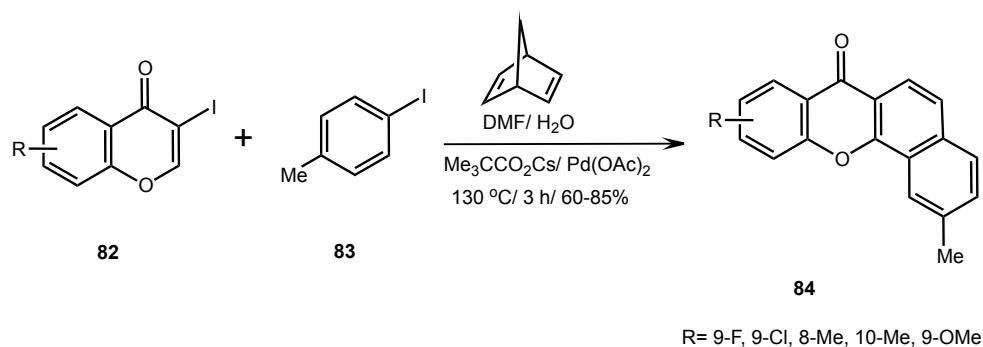
Scheme 32

Condensation reaction of chromone **71** with 4,5,7-trimethoxy-3-(phenylsulfonyl)isobenzofuran-1-(3*H*)-one (**80**), in THF in the presence of lithium *tert*-butoxide (LiO-*t*-Bu), furnished polysubstituted benzo[*b*]xanthone derivative **81**, in 27% yield (Scheme 33).⁴⁸



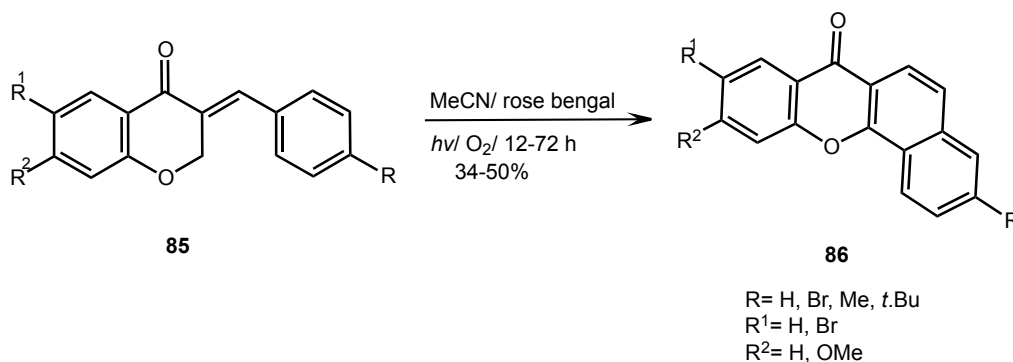
Scheme 33

Reaction of 3-iodochromones **82** with *p*-iodotoluene (**83**) in aqueous norbornadiene, promoted by Pd(OAc)₂, aqueous DMF, and cesium pivalate (Me₃CCO₂Cs), as the base, generated the desired benzoxanthenes **84** (Scheme 34).⁴⁹



Scheme 34

One-pot synthesis of benzo[*c*]xanthenes **86** were achieved from benzylidene-1-tetralones **85** under the ultraviolet radiation (Scheme 35).⁵⁰

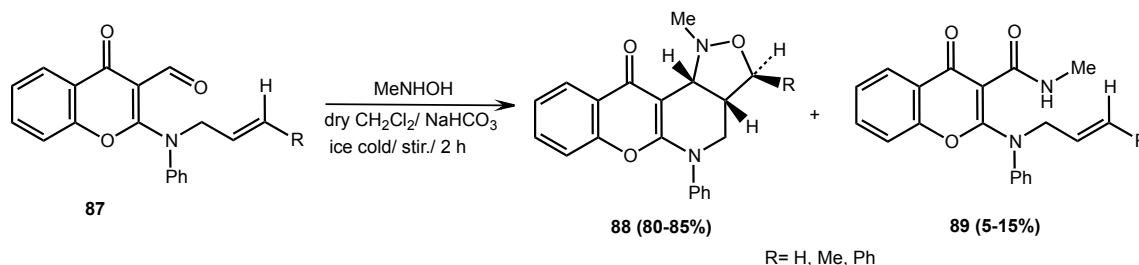


Scheme 35

2.2.6. Chromones annulated with pyridines

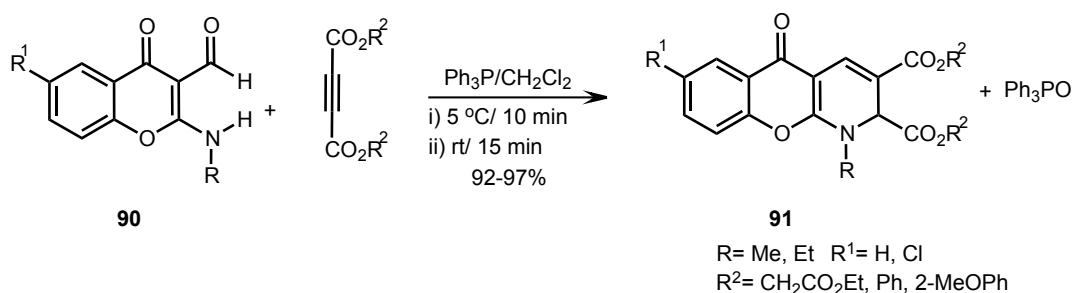
Reaction of 3-formylchromones **87** with *N*-methylhydroxylamine, in dichloromethane at an ice-cold

temperature, led to chromonopiperidine-fused isoxazolidines **88**, in excellent yields, in addition to the corresponding amides **89**, in low yields (Scheme 36).⁵¹



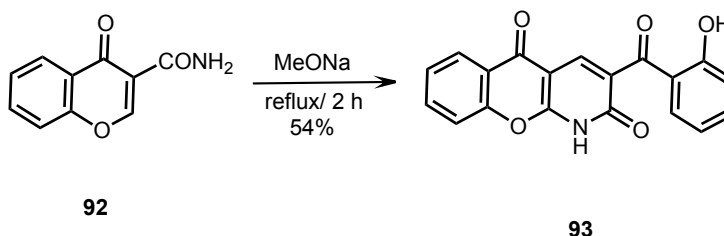
Scheme 36

Dialkyl chromeno[2,3-*b*]pyridine-2,3-dicarboxylates **91** were obtained from treatment of 2-(alkyl-amino)chromone-3-carboxaldehydes **90** with acetylenic esters and triphenylphosphine (Ph₃P) (Scheme 37).⁵²



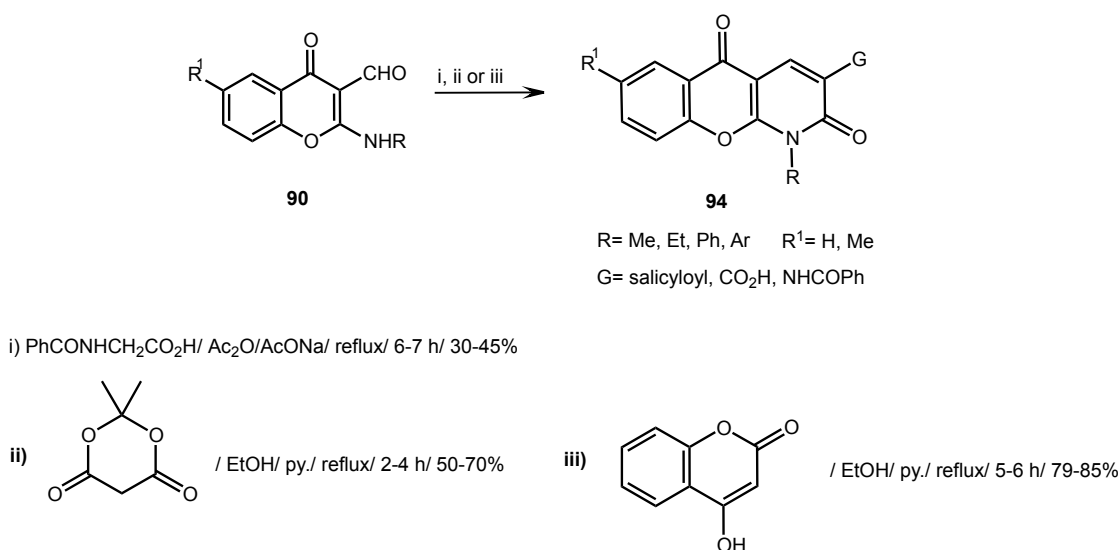
Scheme 37

3-(2-Hydroxybenzoyl)-2*H*-chromeno[2,3-*b*]pyridine-2,5(1*H*)-dione (**93**) was obtained from self-condensation of chromone-3-carboxamide (**92**), in sodium methoxide solution (Scheme 38).⁵³



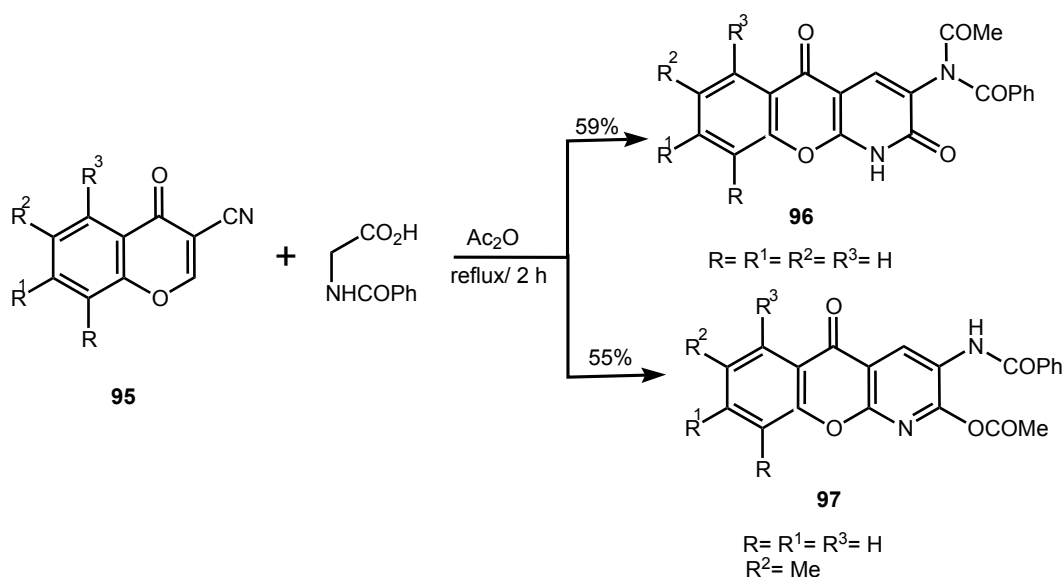
Scheme 38

2-(Alkyl/arylamino)chromone-3-carboxaldehyde **90** reacted with hippuric acid, Meldrum's acid and/or 4-hydroxycoumarin under different conditions produced chromeno[2,3-*b*]pyridine-2,5-diones **94** (Scheme 39).⁵⁴



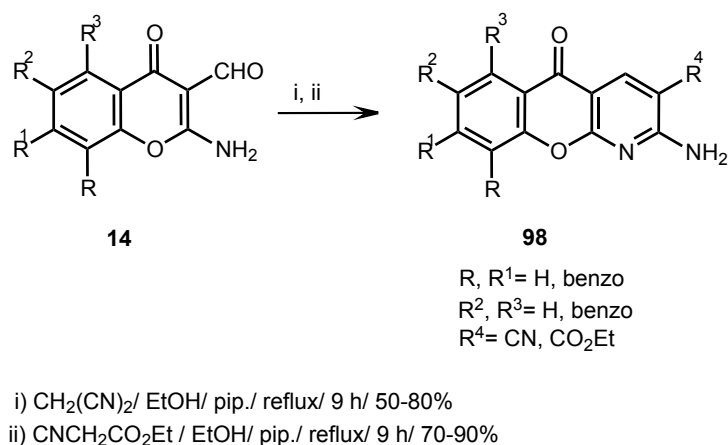
Scheme 39

Refluxing chromone-3-carbonitrile (**95**) with hippuric acid, in acetic anhydride, yielded *N*-acetylchromenopyridine derivative **96** (R²= H), in 59% yield (Scheme 41).³⁷ While, chromeno[2,3-*b*]pyridin-2-yl acetate **97** (R²= Me) was prepared from the reaction of 6-methylchromone-3-carbonitrile (**95**) with hippuric acid in boiling acetic anhydride (Scheme 40).⁵⁵



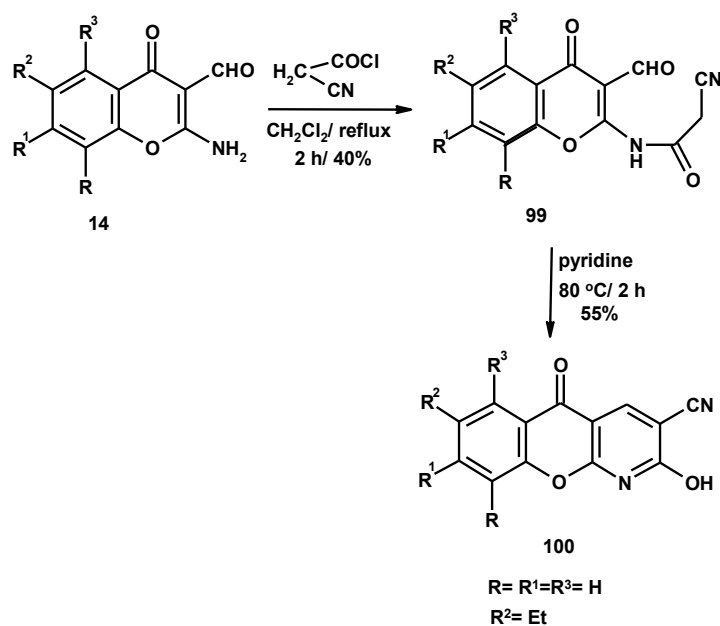
Scheme 40

Condensing 2-amino-3-formylchromones **14** with malononitrile and/or ethyl cyanoacetate, in boiling ethanol containing piperidine, furnished 2-amino-3-substituted chromeno[2,3-*b*]pyridines **98** (Scheme 41).⁵⁶



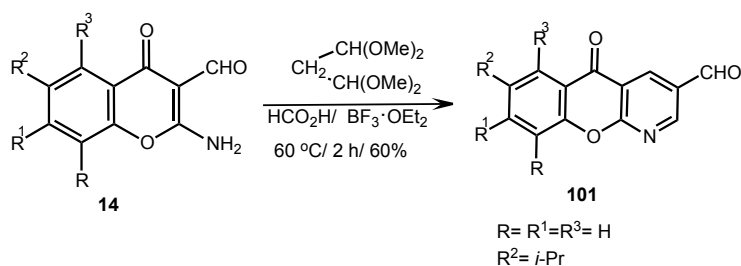
Scheme 41

Condensation reaction of 2-amino-3-formylchromone (**14**) (R²= Et) with cyanoacetyl chloride, in dichloromethane, gave cyanoacetamide derivative **99**, which by heating in pyridine converted to 7-ethyl-2-hydroxy-5-oxo-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (**100**) (Scheme 42).⁵⁷



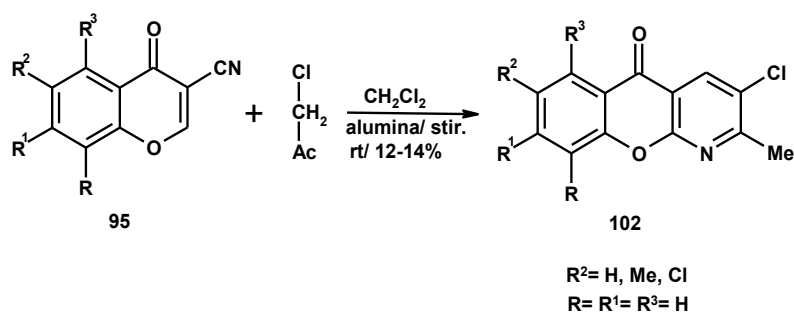
Scheme 42

Condensation of 2-amino-3-formylchromone **14** (R²= *i*-Pr) with malonaldehyde *bis*(dimethylacetal), in the presence of formic acid in boron trifluoride etherate, gave 7-isopropyl-5-oxo-5*H*-chromeno[2,3-*b*]pyridine-3-carboxaldehyde **101** (Scheme 43).⁵⁷



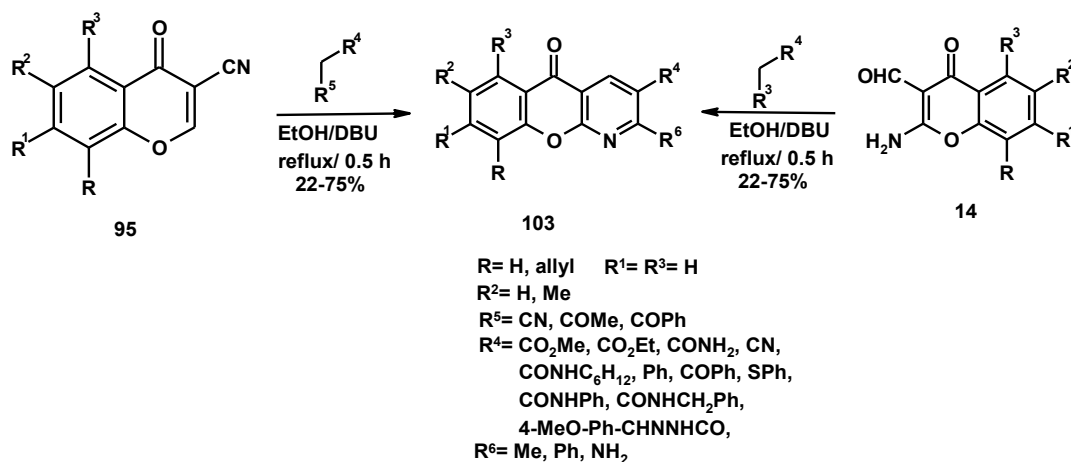
Scheme 43

Stirring chromone-3-carbonitriles **95** with chloroacetone, in dichloromethane in the presence of Brockman neutral alumina, led to chromeno[2,3-*b*]pyridines **102**, in very low yields (12 -14%) (Scheme 44).⁵⁸



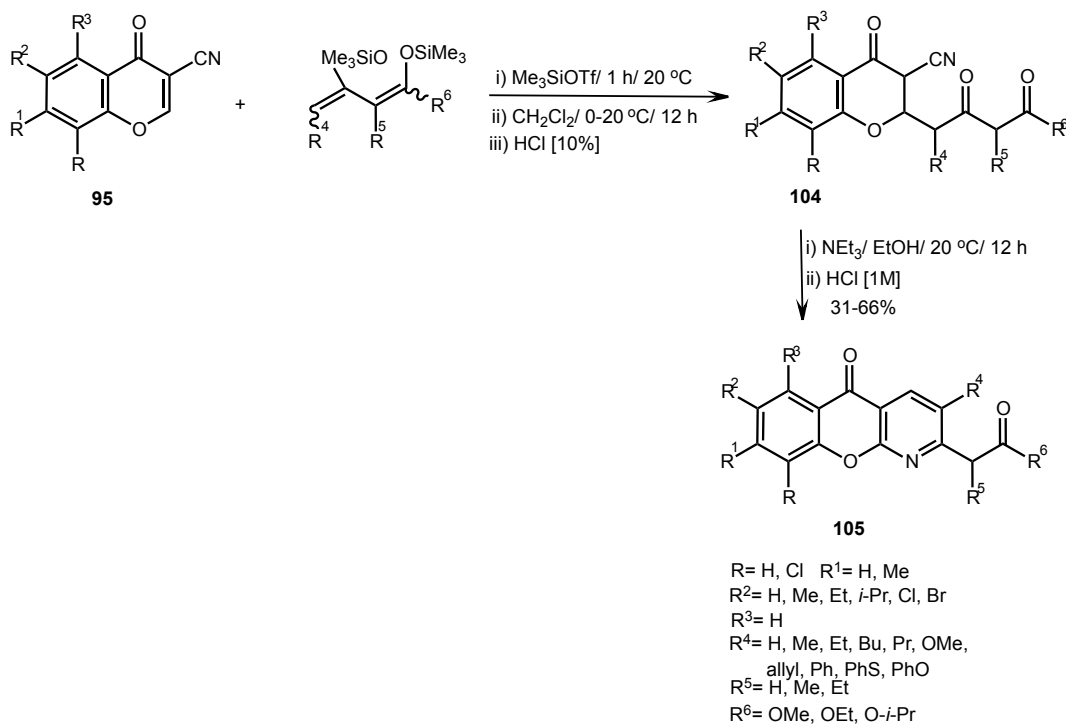
Scheme 44

Heteroannulated chromeno[2,3-*b*]pyridines **103** were synthesized by condensation of chromone-3-carbonitriles **95** with a variety of active methylene compounds, in the presence of ethanol containing DBU as a catalyst. Also, compounds **103** were synthesized from Friedländer reaction of 2-amino-3-formylchromone derivatives **14** with active methylene compounds under the same reaction conditions (Scheme 45).^{55,59-62}



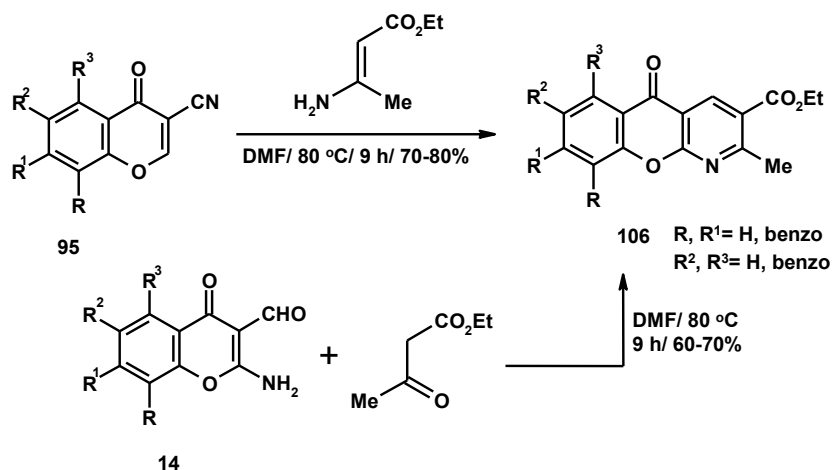
Scheme 45

Reaction of chromone-3-carbonitriles **95** with 1,3-*bis*(trimethylsilyloxy)-1,3-butadienes, in trimethylsilyl trifluoromethanesulfonate as Lewis acid, produced chromane derivatives **104**, which upon treatment with triethylamine resulted in 1-azaxanthenes (5-oxo-5*H*-chromeno[2,3-*b*]pyridines) **105** (Scheme 46).^{63,64}



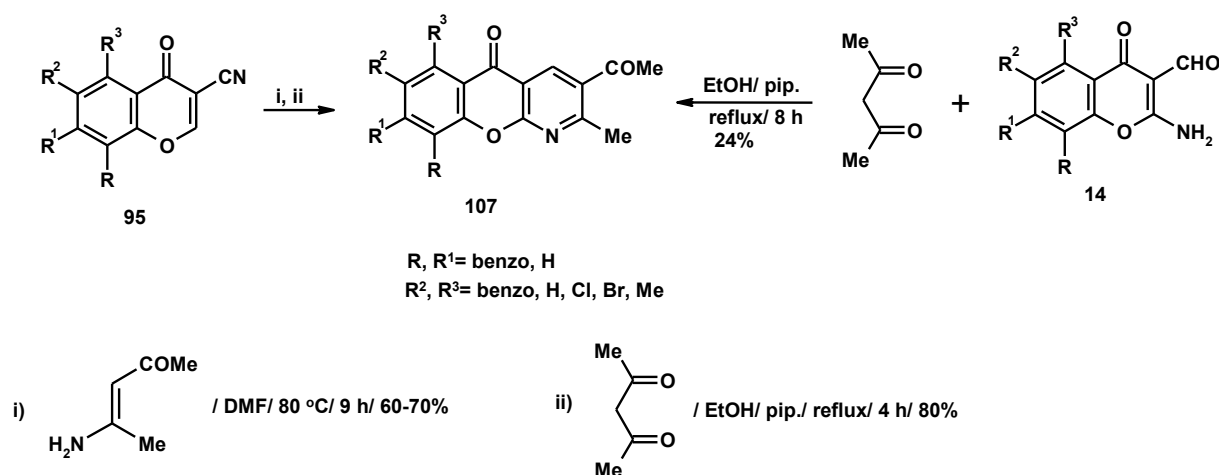
Scheme 46

Benzochromeno[2,3-*b*]pyridines **106** were obtained, in good yield, from treatment of chromone-3-carbonitriles **95** with ethyl 3-aminocrotonate. Compounds **106** were also be prepared from Friedländer reaction of 2-amino-3-formylchromones **14** and ethyl acetoacetate (Scheme 47).⁵⁶



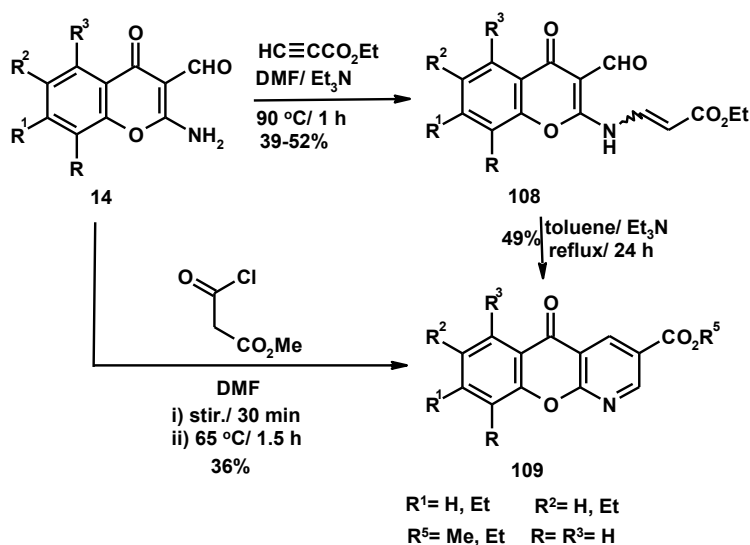
Scheme 47

Condensation reaction of chromone-3-carbonitriles **95** with acetylacetone and/or 4-amino-3-penten-2-one, under different reaction conditions, produced 2-methyl-3-acetyl-5-oxo-5*H*-chromeno[2,3-*b*]pyridines **107**. The latter compounds **107** were also be prepared from reaction of 2-amino-3-formylchromones **14** with acetylacetone, in boiling ethanol in the presence of piperidine (Scheme 48).^{56,65,66}



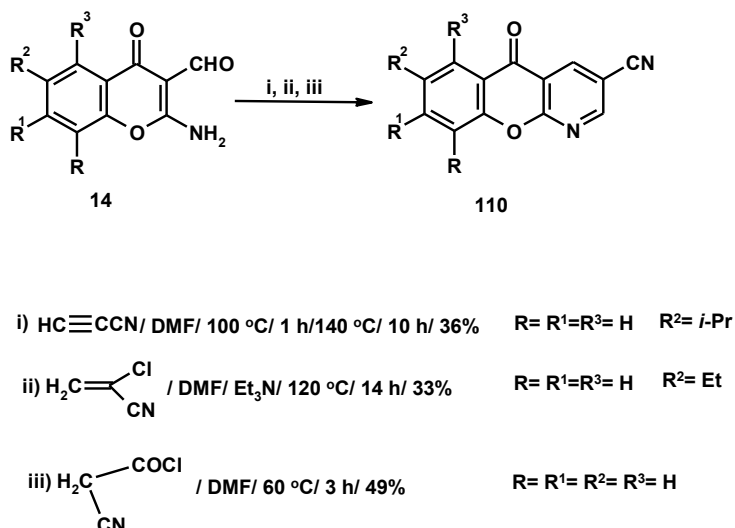
Scheme 48

Reaction of 2-amino-3-formylchromones **14** with ethyl propiolate, in DMF containing triethylamine (TEA), gave aminoacrylate **108** which was converted, by further heating, to ethyl 5-oxo-5*H*-chromeno[2,3-*b*]pyridine-3-carboxylates **109**. On the other hand, compounds **109** were obtained directly from the reaction of compounds **14** with methyl malonyl chloride, in boiling DMF (Scheme 49).⁶⁶



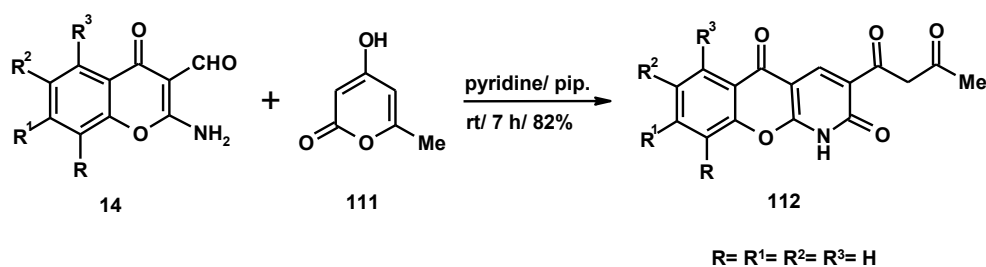
Scheme 49

Treating 2-amino-3-formylchromone **14** ($R^2=i\text{-Pr}$) with cyanoacetylene, gave 5-oxo-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile **110**. Also, compound **14** ($R^2= \text{Et}$) reacted with α -chloroacrylonitrile, in the presence of triethylamine, produced compound **110**. Treating aldehyde **14** ($R= \text{H}$) with cyanoacetyl chloride, in DMF, afforded the same product **110** (Scheme 50).⁶⁷



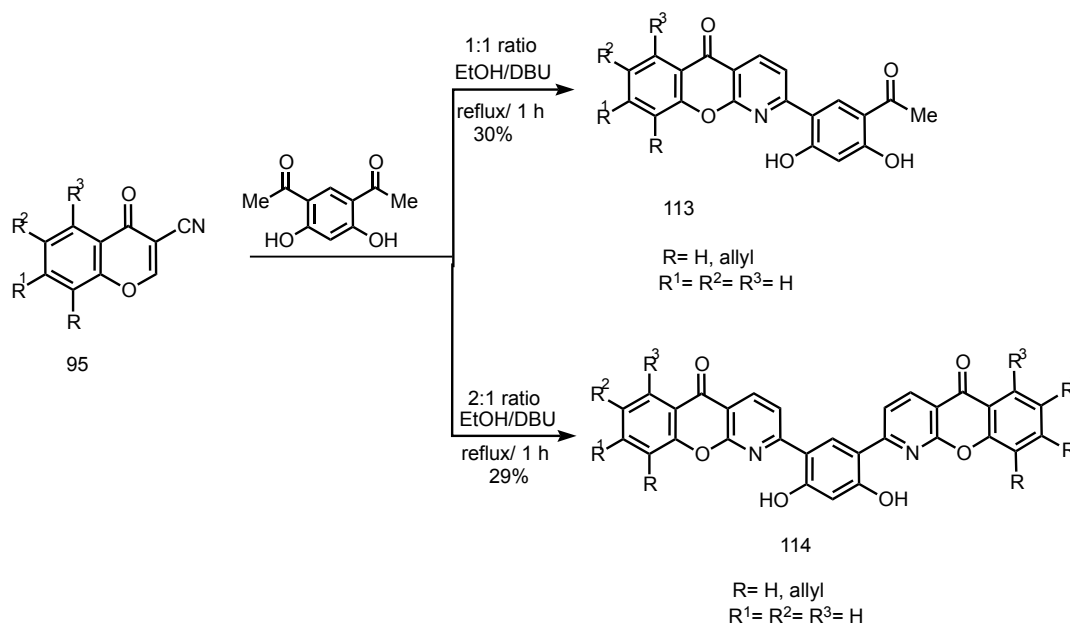
Scheme 50

Siddiqui *et al.*,⁶⁸ observed that 3-acetoacetyl-5-oxo-5*H*-chromeno[2,3-*a*]pyridine **112** was formed from the reaction of 2-amino-3-formylchromone (**14**) and triacetic acid lactone (**111**), in boiling pyridine containing piperidine. This reaction occurred through condensation followed by intramolecular translactonizations (Scheme 51).



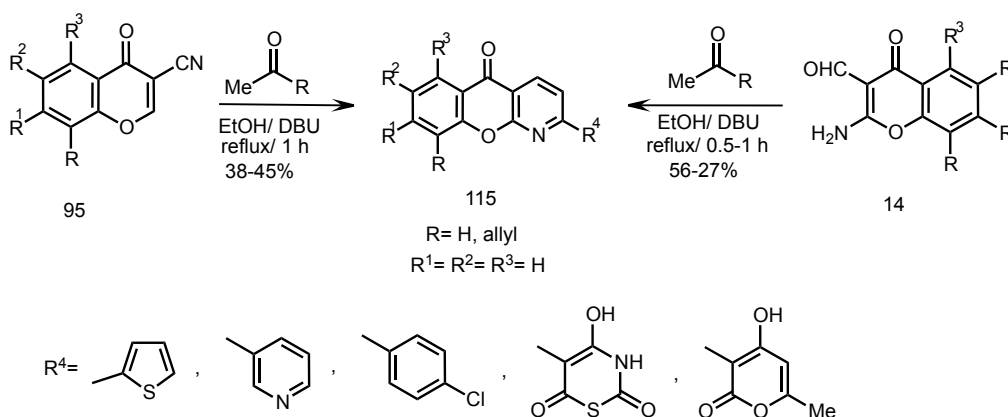
Scheme 51

Treatment of chromone-3-carbonitriles **95** with 4,6-diacetylresorcinol in 1:1 and 2:1 molar ratio, in absolute ethanol containing a few drops of DBU, gave 2-(5-acetyl-2,4-dihydroxyphenyl)-5-oxo-5*H*-chromeno[2,3-*b*]pyridine (**113**) and 4,6-bis(5-oxo-5*H*-chromeno[2,3-*b*]pyridin-2-yl)resorcinol (**114**), respectively (Scheme 52).^{59,69}



Scheme 52

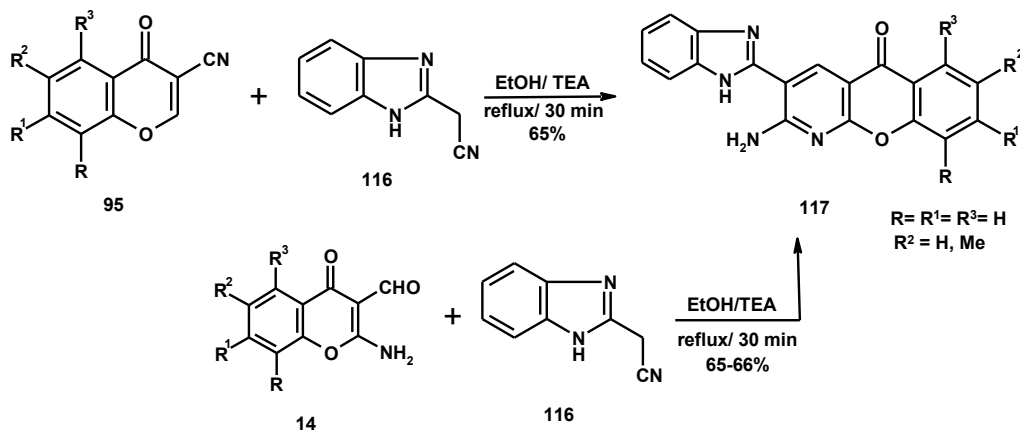
Condensation reaction of chromone-3-carbonitrile (**95**) with some acetyl heterocycles namely 2-acetylthiophene, 3-acetylpyridine, 5-acetyl-4-hydroxy-2*H*-1,3-thiazine-2,6(3*H*)-dione, 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one, 4-chloroacetophenone, in absolute ethanol containing DBU as a basic catalyst, afforded 2-heteroaryl-5-oxo-5*H*-chromeno[2,3-*b*]pyridines **115**. The transformation of carbonitrile **95** into chromeno[2,3-*b*]pyridines **115** can be regarded as a domino "Michael/retro-Michael/nitrile-addition/cyclocondensation reaction". Compounds **115** were obtained by the classical Friedländer condensation of 2-amino-3-formylchromone (**14**) ($R = \text{allyl}$) with the same acetyl derivatives under the same reaction conditions (Scheme 53).^{59,69}



Scheme 53

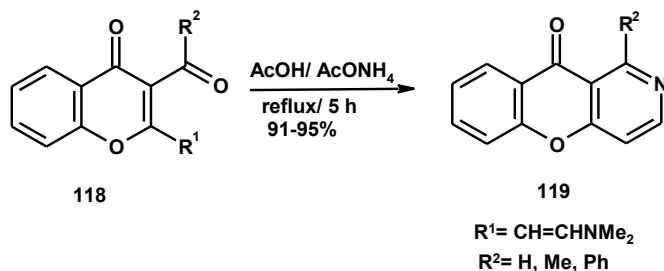
Treatment of chromone-3-carbonitrile (**95**) with (1*H*-benzimidazol-2-yl)acetonitrile (**116**) produced 2-amino-3-(1*H*-benzimidazol-2-yl)-7-methyl-5*H*-chromeno[2,3-*b*]pyridin-5-one (**117**). The latter

compound **117** can also be obtained from of 2-aminochromone-3-carboxaldehydes **14** with 1*H*-benzimidazol-2-ylacetonitrile (**96**) under the same conditions (Scheme 54).⁷⁰



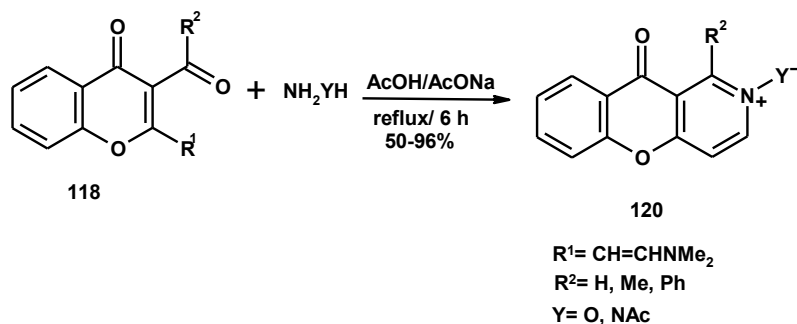
Scheme 54

Refluxing 3-acetylchromones **118**, in the presence of ammonium acetate as source of NH₃ in acetic acid, produced chromeno[3,2-*c*]pyridin-10-ones **119** (Scheme 55).⁷¹



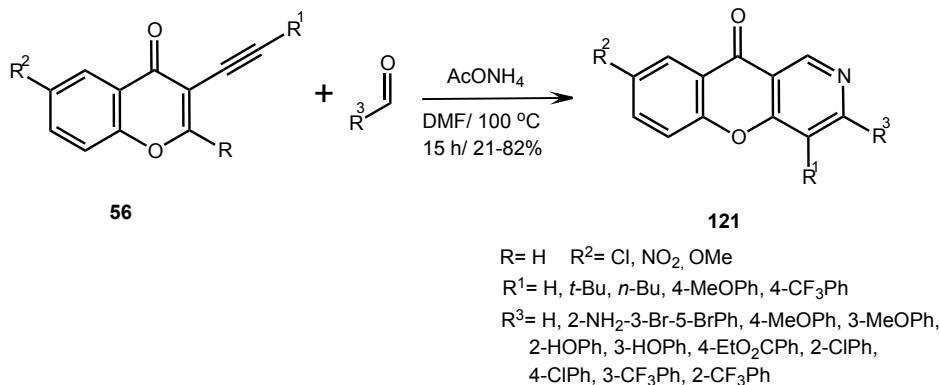
Scheme 55

Also, treatment of 3-acylchromones **118** with hydroxylamine and/or acetylhydrazine, in refluxing acetic acid containing fused sodium acetate, gave chromeno[3,2-*c*]pyridinium salts **120** (Scheme 56).⁷¹



Scheme 56

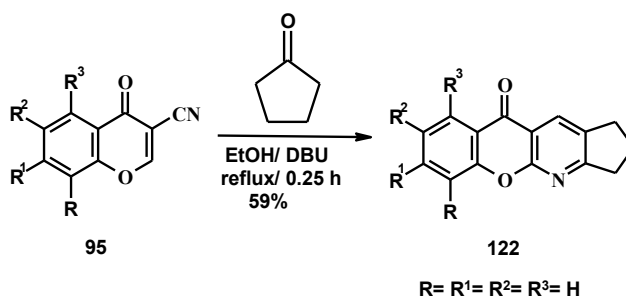
Chromeno[3,2-*c*]pyridines **121** were synthesized from reaction of 3-(1-alkynyl)chromones **56** and aromatic aldehydes (1.5 equiv.), in the presence of AcONH₄ in DMF (Scheme 57).⁷²



Scheme 57

2.2.7. Chromone annulated with pyrido-fused cyclopentene

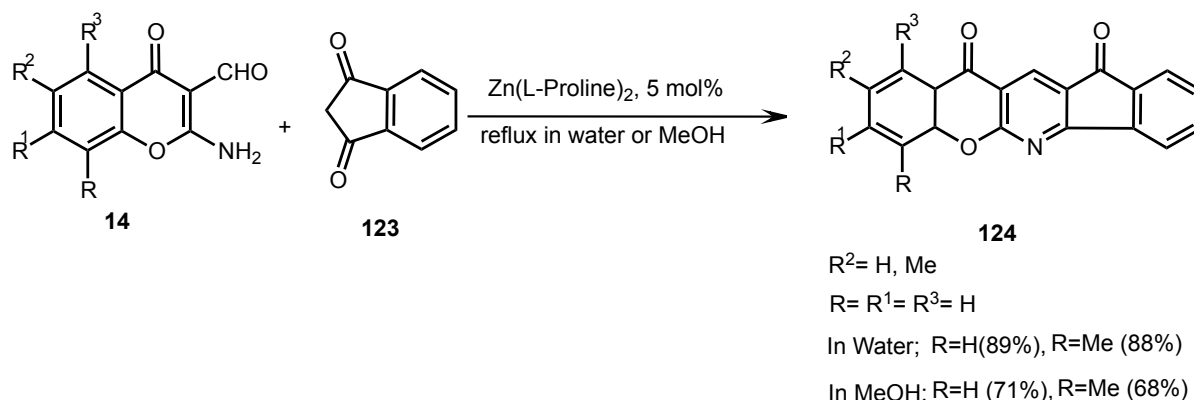
Cyclopenta[*b*]chromeno[3,2-*e*]pyridin-10-one (**122**) was obtained from condensation reaction of chromone-3-carbonitrile (**95**) with cyclopentanone, in boiling ethanol containing DBU (Scheme 58).⁵⁹



Scheme 58

2.2.8. Chromones annulated with pyrido-fused indene

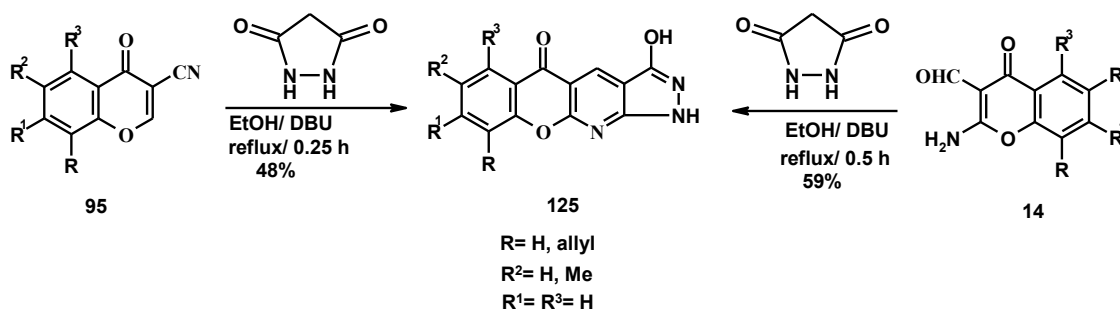
Friedländer condensation of 2-amino-3-formylchromones **14** and indanedione **123** in the presence of Zn(L-proline)₂ as an efficient, stable and inexpensive Lewis acid catalyst in water, produced 11,13-dioxochromeno[2,3-*b*]indeno[2,3-*e*]pyridines (**124**) (Scheme 59).⁷³



Scheme 59

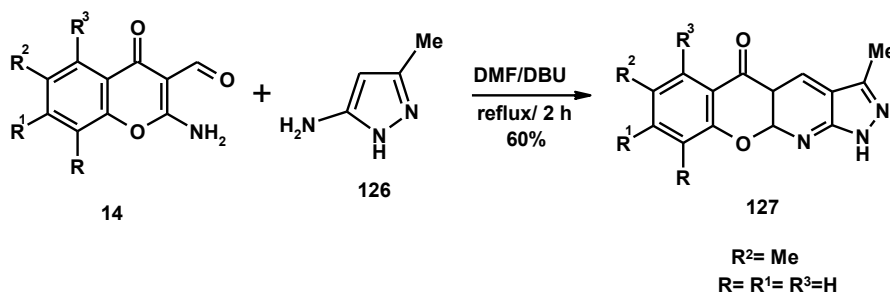
2.2.9. Chromones annulated with pyrido-fused pyrazole

Chromone-3-carbonitriles **95** reacted with pyrazoline-3,5-dione, in boiling ethanol containing DBU, yielded chromeno[2,3-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-ones **125**, in good yields. The latter compound **125** (R= allyl) was synthesized from condensation of 2-amino-3-formylchromone **14** with pyrazoline-3,5-dione under the same reaction conditions (Scheme 60).^{55,59,69}



Scheme 60

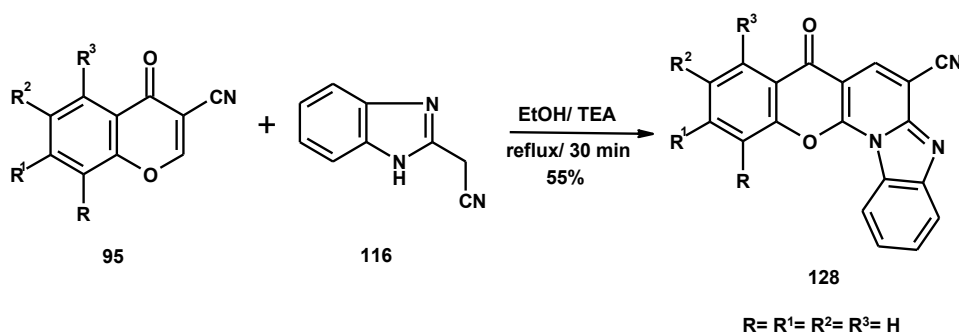
3,8-Dimethylchromeno[2,3-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (**127**) was obtained by reacting 2-amino-3-formylchromone **14** with 5-amino-3-methyl-1*H*-pyrazole (**126**) in refluxing DMF/DBU (Scheme 61).⁷⁴



Scheme 61

2.2.10. Chromone annulated with pyrido-fused benzimidazole

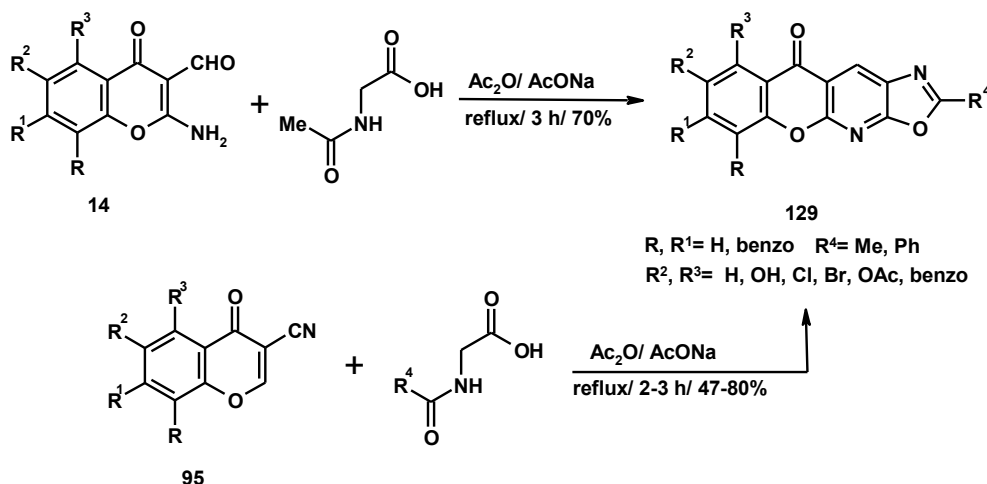
Reaction of chromone-3-carbonitrile (**95**) with (1*H*-benzimidazol-2-yl)acetonitrile (**116**), in boiling ethanol containing triethylamine (TEA), gave angular heteroannulated chromone; identified as chromeno[2',3':6,5]pyrido[1,2-*a*]benzimidazole-6-carbonitrile (**128**) (Scheme 62).⁷⁰



Scheme 62

2.2.11. Chromone annulated with pyrido-fused oxazole

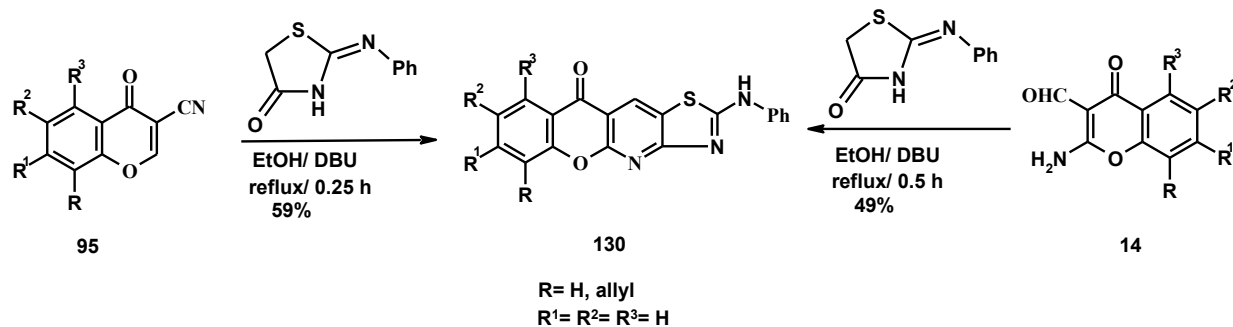
Chromenopyridoxazolones **129** were synthesized from reacting 2-amino-3-formylchromone **14** and *N*-acetylglycine, in boiling acetic anhydride containing fused sodium acetate. Compounds **129** were prepared from condensation of chromone-3-carbonitriles **95** with hippuric acid or aceturic acid under the same reaction conditions (Scheme 63).^{56,59,75}



Scheme 63

2.2.12. Chromones annulated with pyrido-fused thiazole

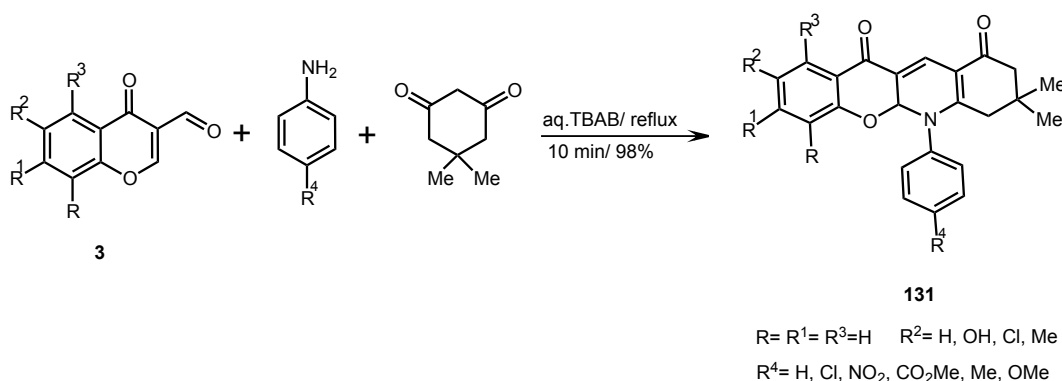
Treating chromone-3-carbonitrile (**95**) with 2-phenyliminothiazolidin-4-one, in ethanol containing DBU, led to 2-anilinochromeno[2,3-*b*][1,3]thiazolo[5,4-*e*]pyridin-10-one **130**. Friedländer condensation of 2-amino-3-formylchromones **14** (R = allyl) with 2-phenyliminothiazolidin-4-one afforded the same compound **130** (Scheme 64).^{59,69}



Scheme 64

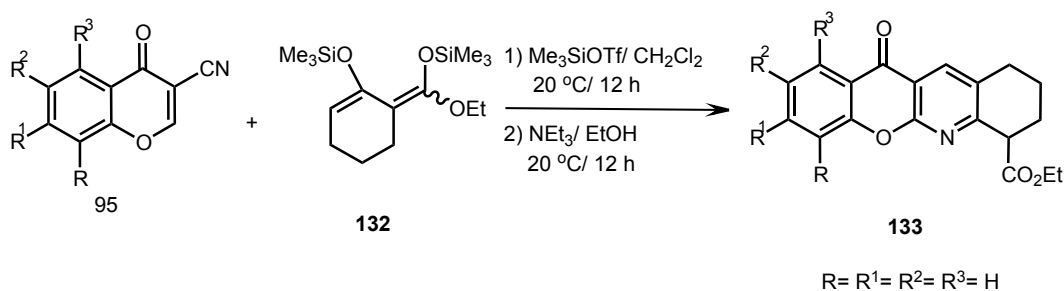
2.2.13. Chromones annulated with quinolines

Ghosh *et al.*⁷⁶ demonstrated that an efficient synthesis of 6-aryl-8,8-dimethyl-8,9-dihydro-5*aH*-chromeno[2,3-*b*]quinoline-10,12(7*H*,10*H*)diones **131** was achieved from a three-component reaction involving 3-formylchromones **3**, an aromatic amine, and dimedone in aqueous tetrabutylammonium bromide (TBAB) solution (Scheme 65).

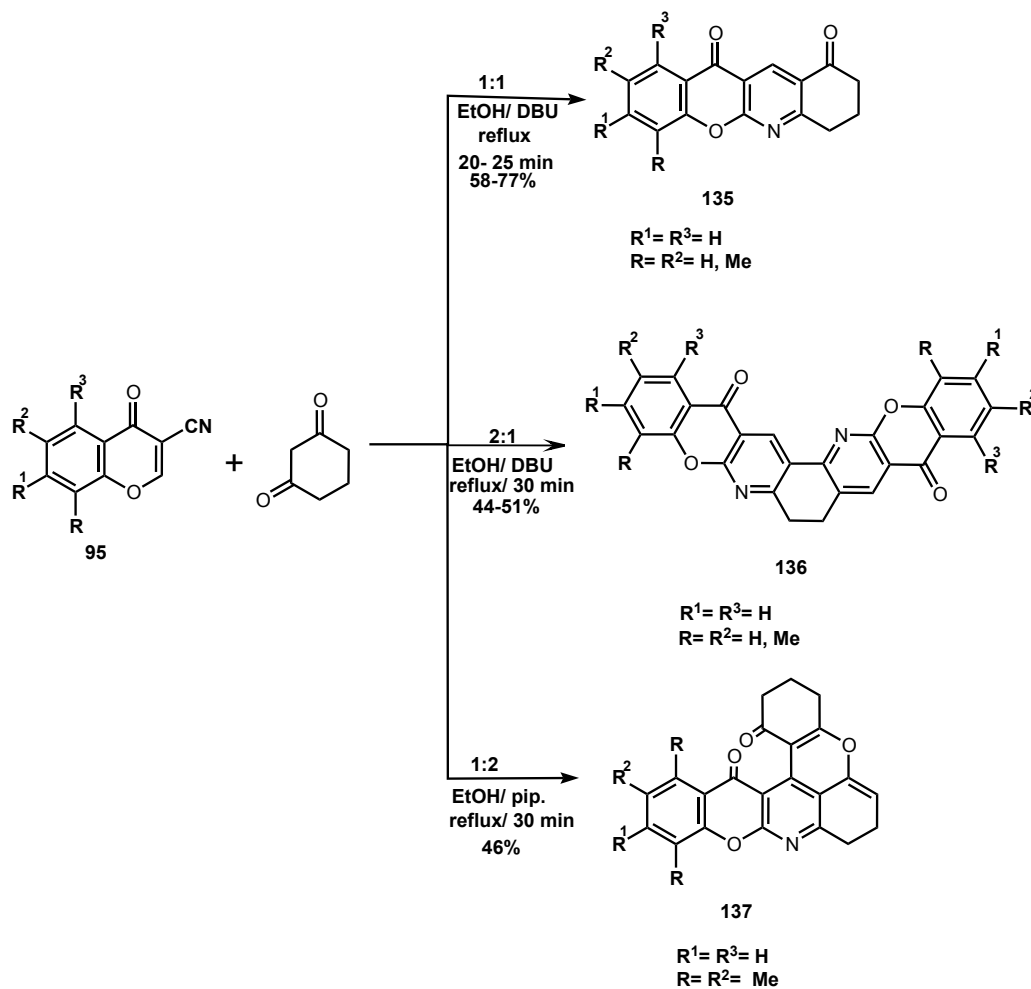


Scheme 65

Sequential reaction of chromone-3-carbonitrile (**95**) with 1,3-*bis*-silyl enol ethers **132**, afforded ethyl 8,9,10,12-tetrahydro-12-oxo-7*H*-chromeno[2,3-*b*]quinoline-7-carboxylate (**133**) (Scheme 66).⁶³

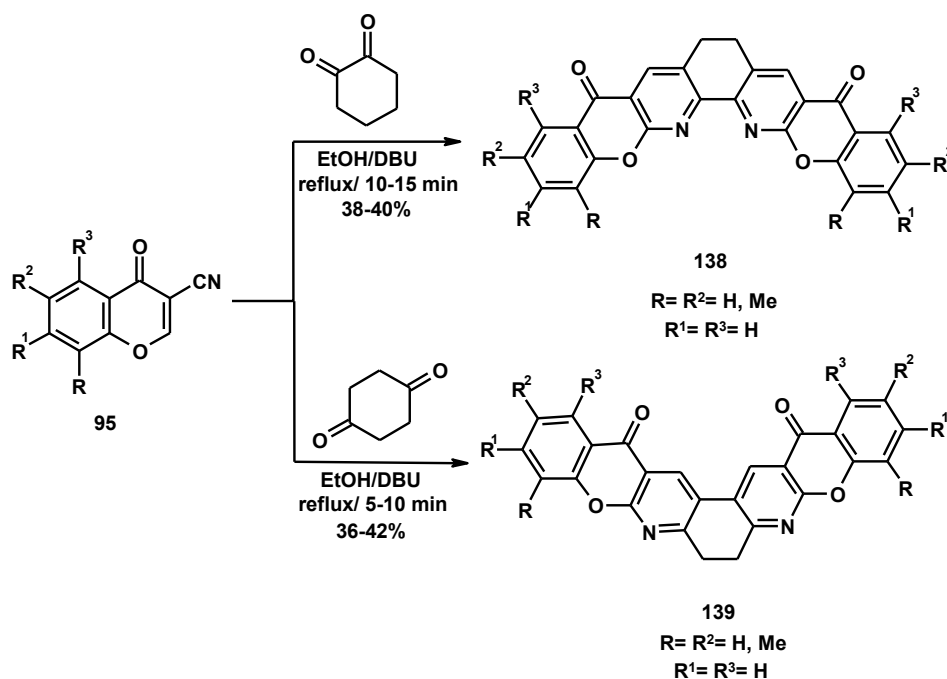


Scheme 66



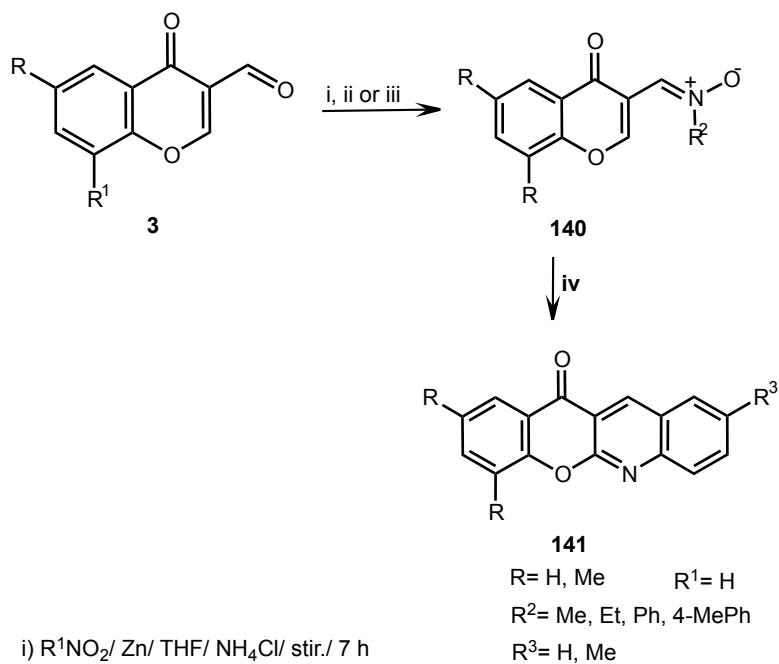
Scheme 68

Base-catalyzed reaction of carbonitrile **35** with 1,2-cyclohexanedione 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 (**138**) (Scheme 69). While, the isomeric product, 7,8-dihydro-15*H*,18*H*-bis[1]-chromeno[3,2-*b*:2',3'-*j*][4,7]phenanthroline-15,18-dione (**139**) was obtained from condensation reaction of carbonitrile **95** with 1,4-cyclohexanedione resulted in the formation of the angular heptacyclic system, (Scheme 69).^{77,78}



Scheme 69

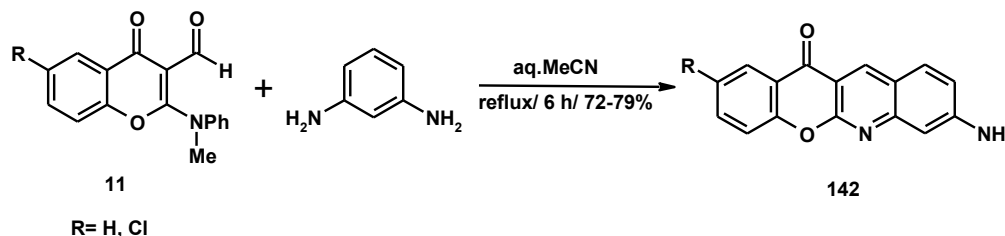
Condensation of 3-formylchromones **3** with nitroarene/nitroalkane under stirring or reflux conditions gave *C*-(chromon-3-yl)-*N*-substituted nitrones **140** which cyclized in ethanol containing few drops of piperidine to give chromoquinoline **141** (Scheme 70).⁷⁹⁻⁸⁴



- i) R^1NO_2 / Zn/ THF/ NH_4Cl / stir./ 7 h
 ii) R^1NHOH / dry C_6H_6 / stir./ 5 min/ 75%
 iii) R^1NO_2 / Zn/ EtOH/ AcOH/ reflux/ 55%
 iv) EtOH/ pip./reflux/ 3.5 h/ 65%

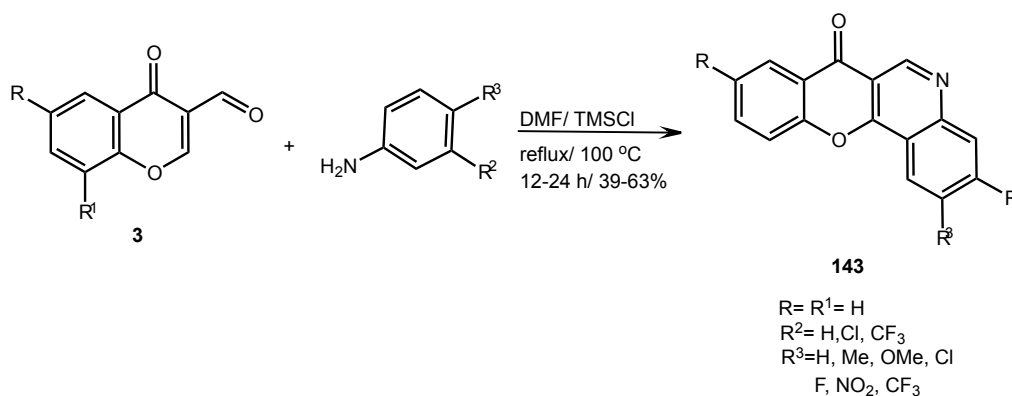
Scheme 70

Refluxing equimolar amounts of 2-(*N*-methylanilino)-3-formylchromones **11** with *m*-phenylenediamine, in aqueous acetonitrile solution led to 8-aminochromoquinolines **142**, in good yields (Scheme 71).⁸⁵



Scheme 71

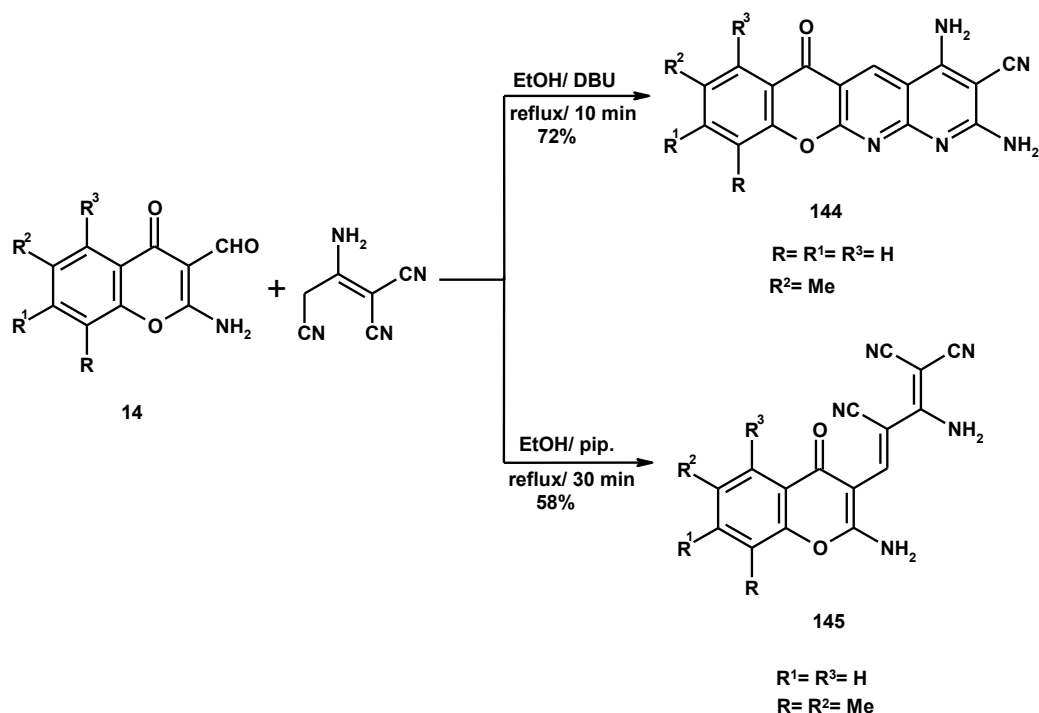
Reactions of 3-formylchromone (**3**) with aniline derivatives, in DMF and trimethylsilyl chloride (TMSCl), led to 7*H*-chromeno[3,2-*c*]quinolin-7-ones **143** in 39-63% yields (Scheme 72).⁸⁶



Scheme 72

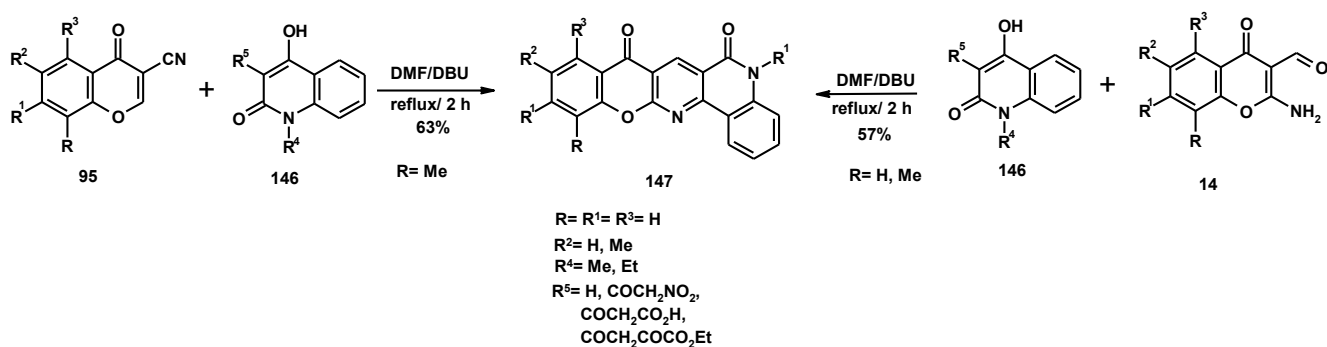
2.2.14. Chromones annulated with naphthyridines

2,4-Diamino-8-methyl-6-oxo-6*H*-chromeno[2,3-*b*][1,8]naphthyridine-3-carbonitrile (**144**) was synthesized *via* reaction of 2-amino-3-aminochromones (**14**) with malononitrile dimer (2-aminoprop-1-ene-1,1,3-tricarbonitrile), in boiling ethanol containing few drops of DBU (Scheme 73).⁶¹ On the other hand, reaction of aldehyde **3** with malononitrile dimer, in boiling ethanol containing few drops of piperidine, afforded buta-1,3-diene derivative **145** (Scheme 73).⁷⁸



Scheme 73

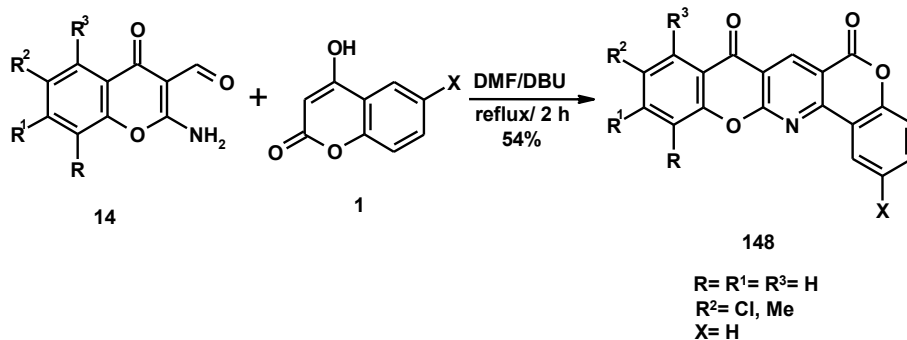
Benzo[*h*]chromeno[2,3-*b*][1,6]naphthyridines **147** were also synthesized from reaction of chromone-3-carbonitriles **95** with 1-ethyl-4-hydroxy-3-nitroacetylquinolin-2(1*H*)-one (**146**). Compounds **147** were also obtained from condensation of 2-aminochromone-3-carboxaldehydes **14** with 4-hydroxyquinolines and/or 4-hydroxy-3-substituted-acetylquinolin-2(1*H*)-ones **146** (Scheme 74).^{55,74,87}



Scheme 74

2.2.15. Chromones annulated with pyrido-fused coumarin

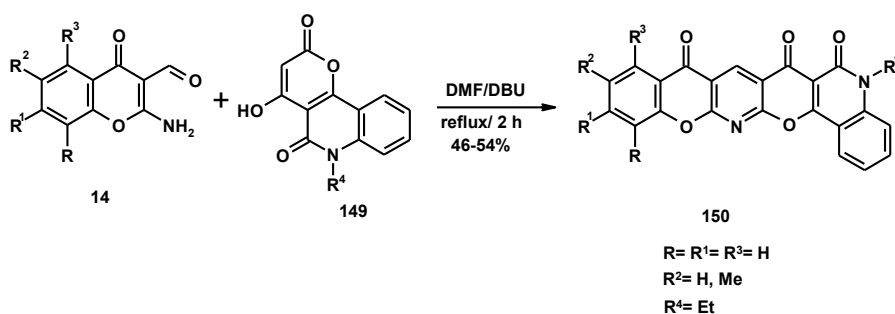
Friedländer condensation reaction of 2-amino-3-formylchromones **14** with 4-hydroxycoumarin (**1**), in boiling DMF containing few drops of DBU, afforded dichromeno[2,3-*b*:3',4'-*e*]pyridine-6,8-diones **148** (Scheme 75).^{74,88}



Scheme 75

2.2.16. Chromones annulated with pyrido-fused pyranoquinoline

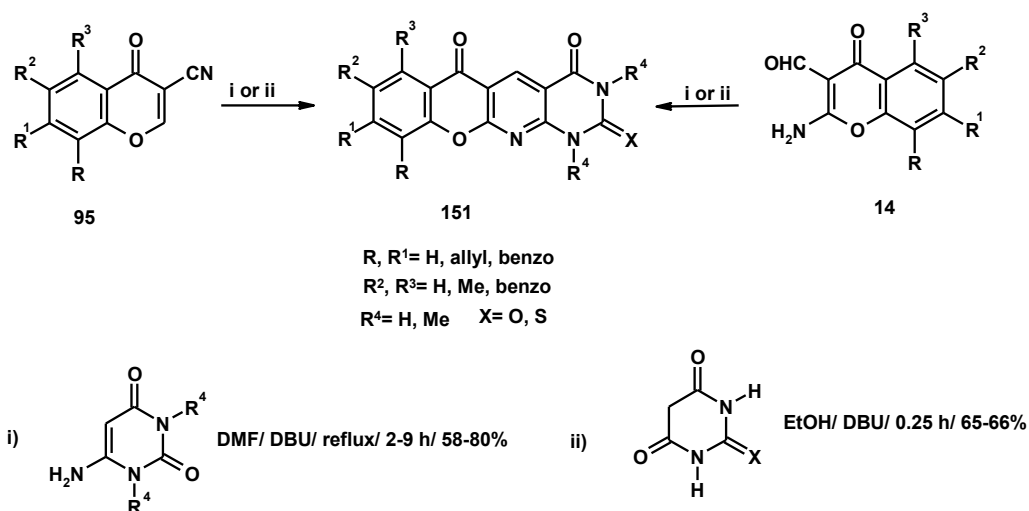
Chromeno[3'',2'':5',6']pyrido[3',2':5,6]pyrano[3,2-*c*]quinoline-6(5*H*),7,9-triones **150** were synthesized from DBU catalyzed condensation reaction of 2-aminochromone-3-carboxaldehydes **14** with 4-hydroxy-2*H*-pyrano[3,2-*c*]quinoline-2,5(6*H*)-dione (**149**) (Scheme 76).^{74,89}



Scheme 76

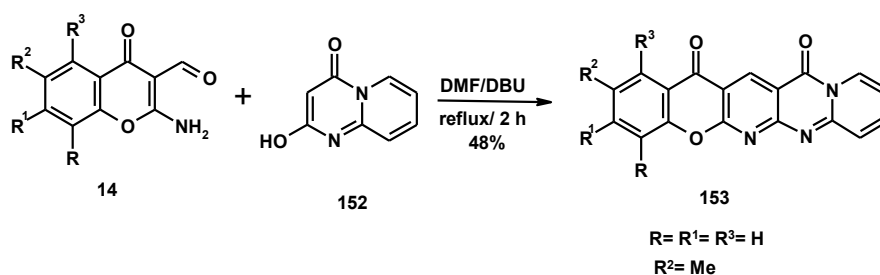
2.2.17. Chromone annulated with pyrido-fused pyrimidine

Chromeno[2',3':2,3]pyrido[6,5-*d*]pyrimidines **151** were obtained from condensation of chromone-3-carbonitriles **95** with 6-aminouracil, barbituric and/or thiobarbituric under different reaction conditions. Compounds **151** were prepared authentically from reaction of aldehyde **14** with 6-aminouracil and thiobarbituric acid, in DMF, in good yields (Scheme 77).^{56,59,69,74}



Scheme 77

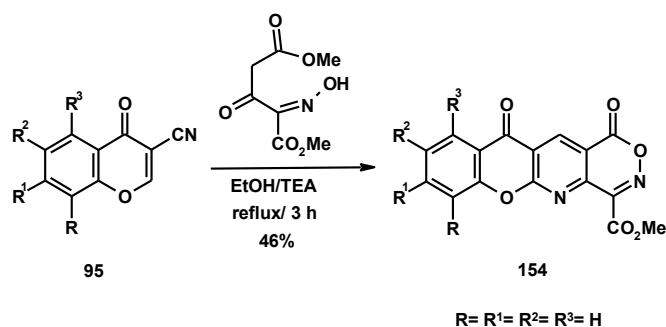
Reaction of 2-amino-3-formylchromone **14** with 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**152**) in refluxing DMF/DBU yielded polyfused 13*H*,15*H*-chromeno[3',2'':5',6']dipyrido[1,2-*a*:2',3'-*d*]-pyrimidine-13,15-dione (**153**) (Scheme 78).⁷⁴



Scheme 78

2.2.18. Chromone annulated with pyridoxazine

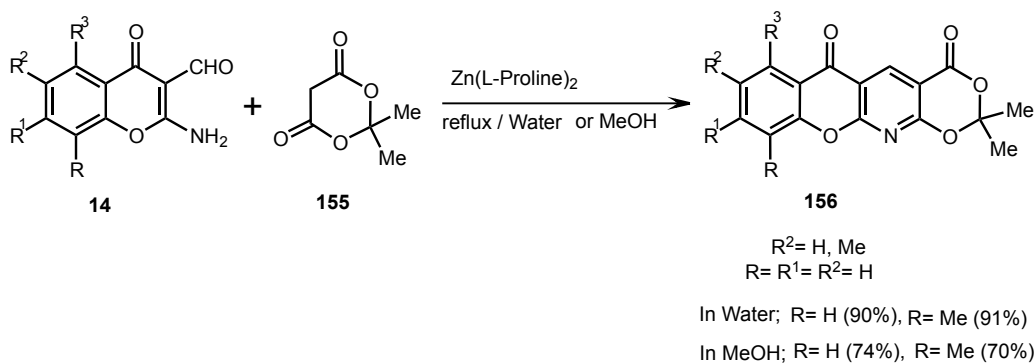
Fused oxazine **154** was obtained, from reaction of carbonitrile **95** with dimethyl β -keto- α -oximinoglutarate, in boiling ethanol containing triethylamine (Scheme 79).⁹⁰



Scheme 79

2.2.19. Chromones annulated with pyrido-fused dioxine

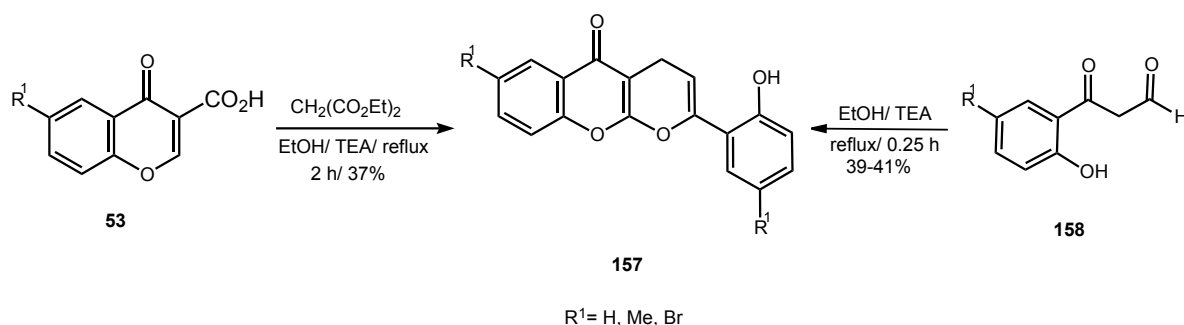
Cyclocondensation of 2-amino-3-formylchromones **14** with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (**155**) afforded 2,2-dimethyl-4*H*,6*H*-[1,3]dioxino[4,5-*b*]chromeno[3,2-*e*]pyridine-4,6-dione (**156**) (Scheme 80).⁷³



Scheme 80

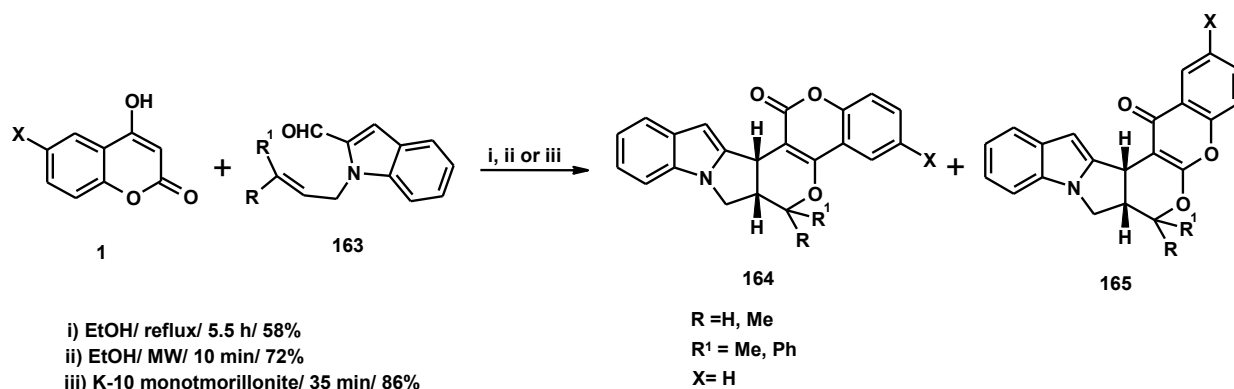
2.2.20. Chromones annulated with pyran

Refluxing an equimolar amount of chromone-3-carboxylic acids **53** with diethyl malonate, in absolute ethanol containing a few drops of triethylamine, produced 2-(2-hydroxyphenyl)-4*H*,5*H*-pyrano[2,3-*b*]chromen-5-ones **157** (Scheme 81).⁹¹ Pyrano[2,3-*b*]chromene derivatives **157** were also prepared from boiling ω-formyl-2-hydroxyacetophenones **158**, in ethanol containing drops of Et₃N (Scheme 81).⁹²



Scheme 81

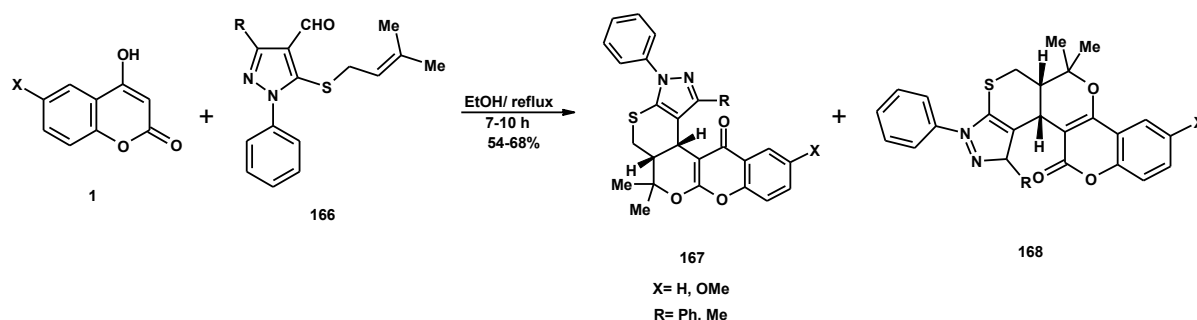
3-(Chromon-3-yl)-1-(*N*-cyclohexylimino)pyrano[4,3-*b*]chromones **159** were obtained, in moderate yields, by heating 3-formylchromones **3** with cyclohexyl isocyanide, (Mr 2:1), in acetonitrile (Scheme 82).⁹³



Scheme 84

2.2.23. Chromones annulated with pyrano-fused pyrazolothiothiopyran

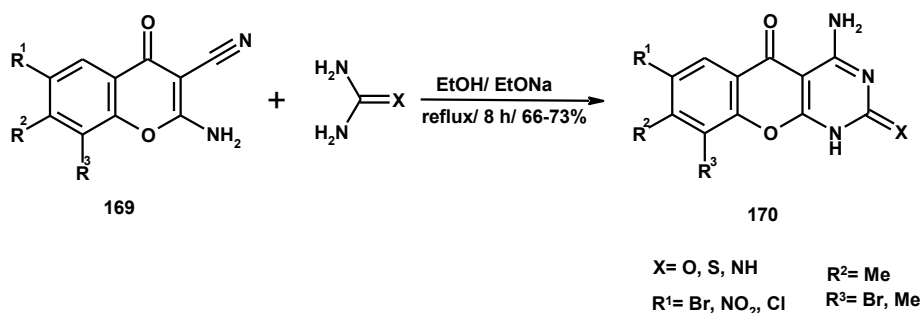
Thiopyrano[4',3':4,5]pyrano[2,3-*b*]chromenes **167** and thiopyrano[4',3':4,5]pyrano[3,2-*c*]coumarins **168** were prepared *via* domino Knoevenagel hetero Diels–Alder reactions between 4-hydroxycoumarins **1** and 3-methyl/phenyl-5-(3-methylbut-2-enylsulfanyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehydes **166**, in ethanol under reflux (Scheme 85).⁹⁶



Scheme 85

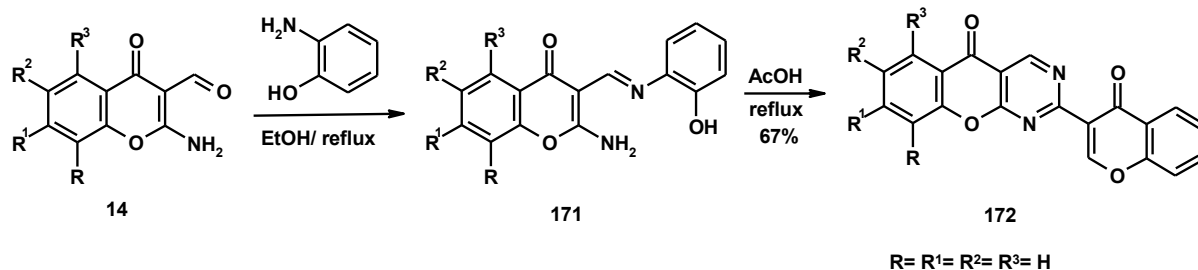
2.2.24. Chromones annulated with pyrimidines

Chromeno[2,3-*d*]pyrimidines **170** were synthesized from reaction of 2-aminochromone-3-carbonitriles **169** and urea, thiourea, and/or guanidine, in an ethanolic solution and sodium ethoxide (Scheme 86).⁹⁷



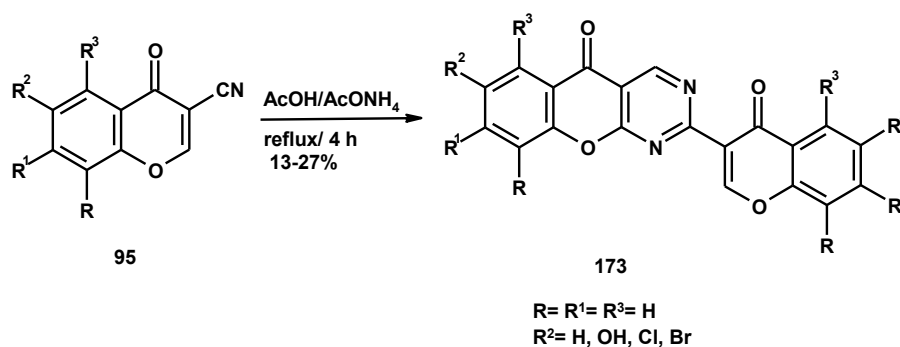
Scheme 86

Condensation reaction of 2-amino-3-formylchromone (**14**) with *o*-aminophenol in boiling ethanol produced the corresponding Schiff base **171**. Refluxing Schiff base **171** in boiling acetic acid furnished chromeno[2,3-*d*]pyrimidin-5-one **172** in 67% yield (Scheme 87).⁹⁸



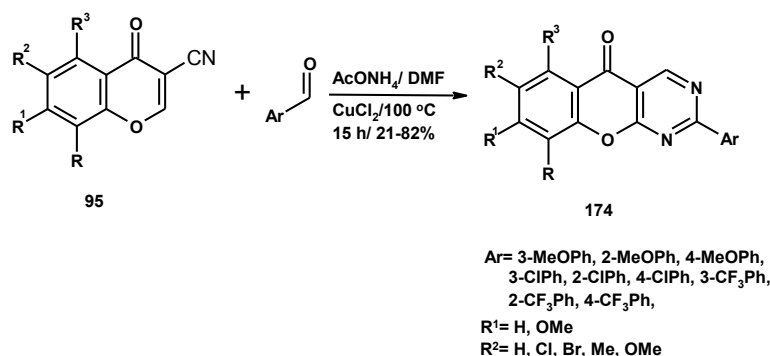
Scheme 87

When chromone-3-carbonitriles **95** were refluxed with a potential ammonia source such as ammonium acetate in acetic acid, produced 2-(chromon-3-yl)-5*H*-chromeno[2,3-*d*]pyrimidin-5-ones **173** (Scheme 88).⁹⁹



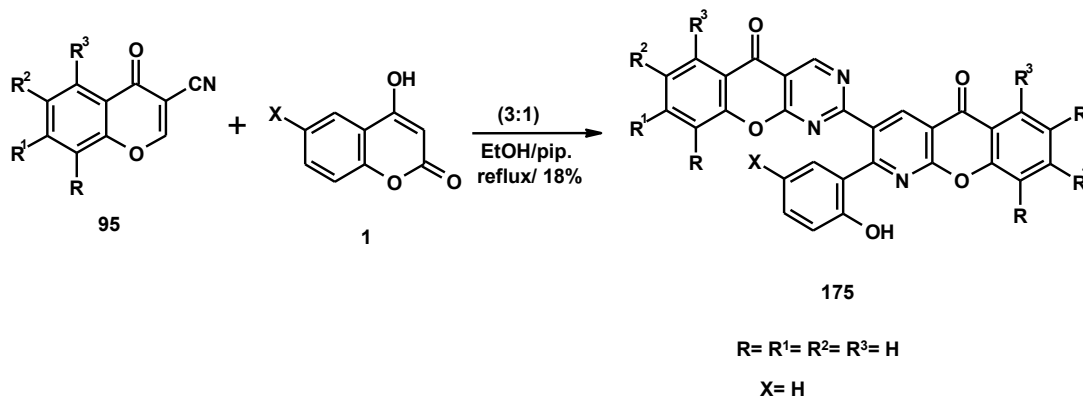
Scheme 88

Chromone-3-carbonitriles **95** reacted with aromatic aldehydes, in the presence of ammonium acetate and CuCl₂ to form chromeno[2,3-*d*]pyrimidines **174** (Scheme 89).⁷²



Scheme 89

Schurreit⁷⁹ has reported the formation of chromeno[2,3-*d*]pyrimidine linked to chromeno[2,3-*b*]pyridines **175** by refluxing three molecules of chromone-3-carbonitrile **95** and 4-hydroxycoumarin (**1**), in refluxing ethanol containing piperidine (Scheme 90).¹⁰⁰

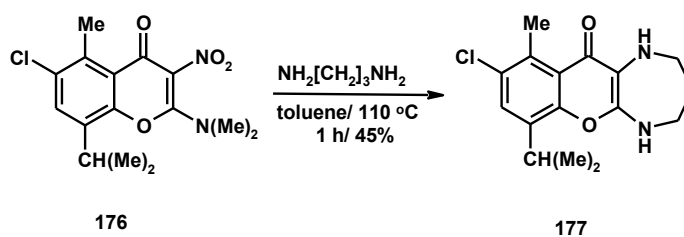


Scheme 90

2.3. Chromone-fused seven membered ring

2.3.1. Chromone annulated with diazepine

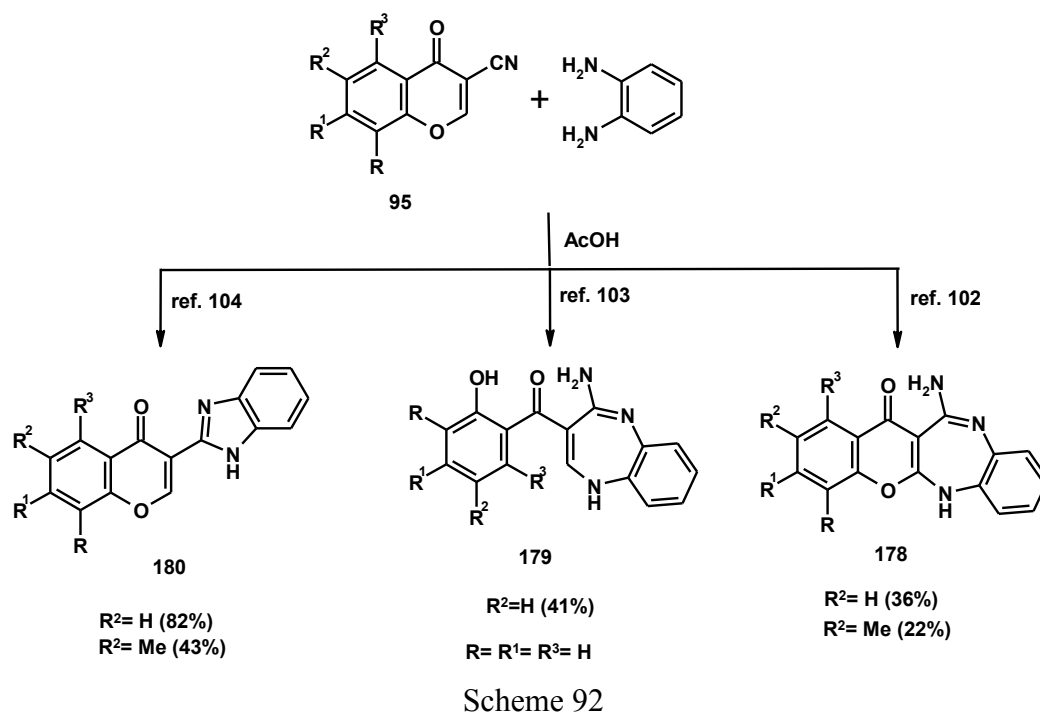
9-Chloro-2,3,4,5-tetrahydro-7-isopropyl-10-methylchromeno[2,3-*b*][1,4]diazepin-11(1*H*)-one (**177**) was synthesized from reaction of 2-(dimethylamino)chromone **176** with 1,3-diaminopropane, in boiling toluene (Scheme 91).¹⁰¹



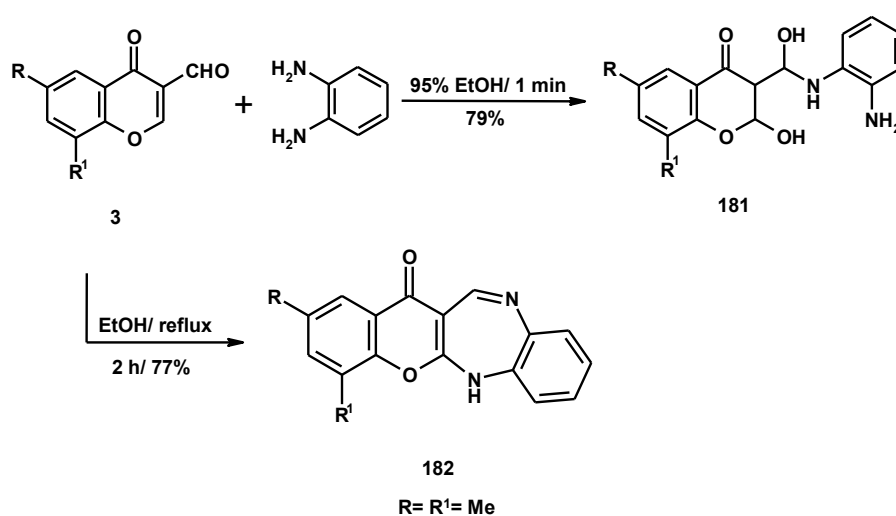
Scheme 91

2.3.2. Chromone annulated with benzodiazepine

There is contradictory information in literature regarding the structure of the product obtained from the reaction between carbonitrile **95** and *o*-phenylenediamine. Hence, Ghosh and Tewari,¹⁰² postulate the formation of chromeno[2,3-*b*][1,5]benzodiazepines **178**. While, Risitano and his coworkers,¹⁰³ repeated the reaction and postulate the formation of benzodiazepines **179**. Next, the reaction was reinvestigated and the product was expected to be 3-(benzimidazol-2-yl)chromones **180** (Scheme 92).¹⁰⁴

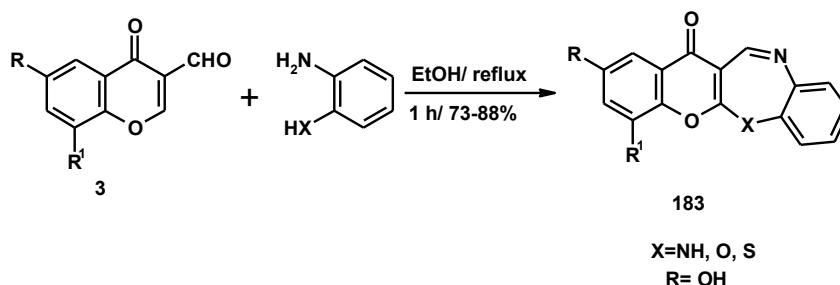


On the other hand, heating 3-formylchromone **3** with *o*-phenylenediamine, in 95% ethanol for 1 min, produced the addition product, 3-{[(2-aminophenyl)amino](hydroxy)methyl}-2-hydroxy-6,8-dimethyl-2,3-dihydro-4*H*-chromen-4-one (**181**), as an orange crystals in high yield (Scheme 93). Repeating the previous reaction under reflux for 2 h. Furnished the annulated benzochromenodiazepine derivative **182** *via* the formation of compound **181** followed by elimination of two molecules of water with subsequent dehydrogenation (Scheme 93).¹⁰⁵



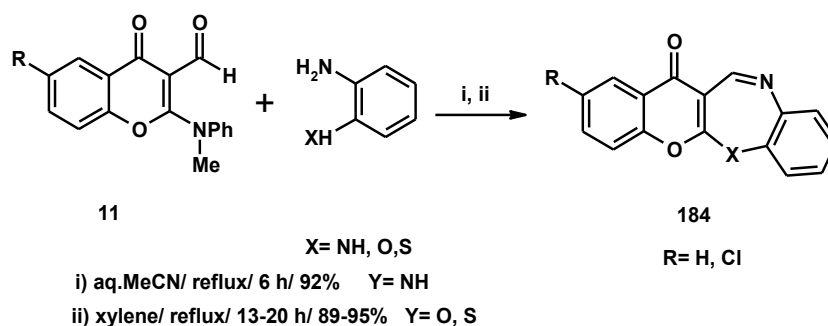
Scheme 93

Also, reaction of 3-formylchromones **3** with *ortho*-substituted anilines such as *o*-phenylenediamine, *o*-aminophenol and *o*-aminothiophenol, in boiling ethanol, afforded benzoazepine derivatives **183** (Scheme 94).¹⁰⁶



Scheme 94

Moreover, reaction of 2-(*N*-methylanilino)-3-formylchromones **11** with *ortho*-substituted anilines such as *o*-phenylenediamine, *o*-aminophenol, and *o*-aminothiophenol, furnished chromono-heterocyclic systems (chromono[2,3-*b*][1,5]benzodiazepine, chromono[2,3-*b*][1,5]benzoxazepine, and chromono[2,3-*b*][1,5]benzothiazepine **184**, respectively), in high yields (Scheme 95).^{107,108}

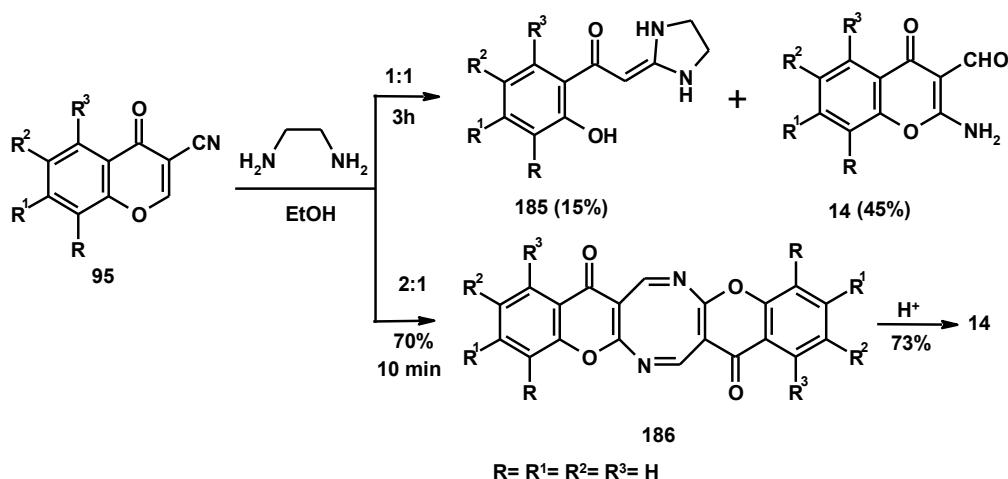


Scheme 95

2.4. Chromone-fused eight membered rings

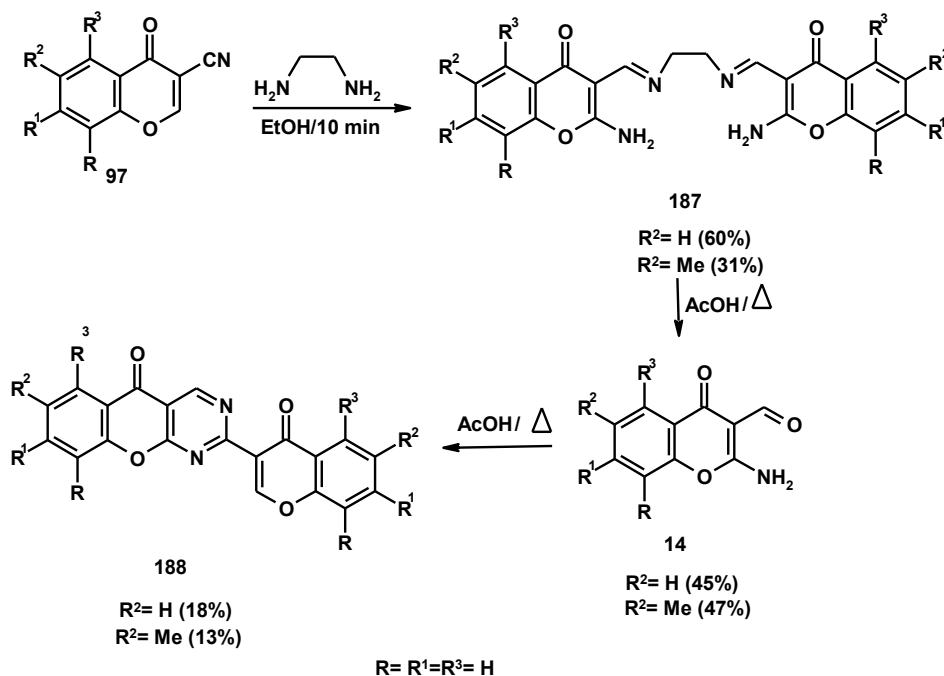
2.4.1. Chromones annulated with diazocine

Reaction of chromone-3-carbonitrile (**95**) with ethylenediamine in boiling ethanol was firstly studied by Ghosh and Tewari,¹⁰² and isolated 1-(2-hydroxyphenyl)-2-imidazol-2-ylidene)ethanone (**185**) (15%) together with 2-aminochromone-3-carboxaldehyde **14** (45%). When the reaction was performed in boiling ethanol for 3 h in 1:1 molar ratio (Scheme 96). While, Ghosh *et al.*¹⁰⁹ postulated the formation of *bis*-chromeno[2,3-*b*:2',3'-*f*][1,5]diazocine (**186**) when the reaction was carried in boiling ethanol for 10 min in 2:1 molar ratio. Hydrolysis of compound **186** under acidic conditions afforded compound **14** (Scheme 96), in this reaction ethylenediamine, as aliphatic amine, induced self-condensation of carbonitrile **95**.



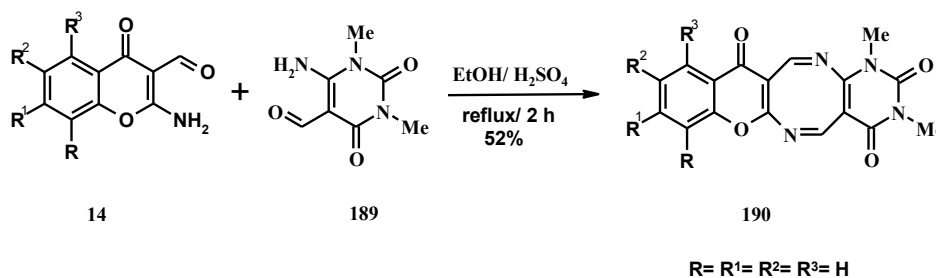
Scheme 96

The previous reaction was next studied by Sosnovskikh *et al.*,¹¹⁰ and isolated *N,N*-ethylene-*bis*(2-amino-3-iminomethylchromones) **187**, 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 **14** or dimerization products, 2-(chromen-3-yl)-5*H*-chromeno[2,3-*d*]pyrimidin-5-ones **188** (Scheme 97).



Scheme 97

Double condensation of 2-amino-3-formylchromone (**14**) with *o*-aminoaldehyde namely, 6-amino-1,3-dimethyluracil-5-carboxaldehyde (**189**), in boiling ethanol containing catalytic amount of concentrated sulfuric acid, yielded the diazocine derivative **190** (Scheme 98).^{33,111}



Scheme 98

3. CONCLUSION

Chromones are a group of compounds widely distributed in nature with a wide range of biological activities including antitumor, antimicrobial, antiviral, anti-inflammatory, antioxidant, and so on. Diverse synthetic methods were utilized to prepare a variety of heterocyclic rings using substituted chromones. The annulation of chromone moiety with different heterocycle scaffolds gives rise a new class of hybrid heterocycles with improved biological activity. In the future work, we hope to investigate the reactivity of chromone bearing electron withdrawing functional groups with a diversity of nucleophilic reagents aiming to synthesis a novel derivatives of annulated chromones, in addition to examine the biological properties of the new synthesized compounds.

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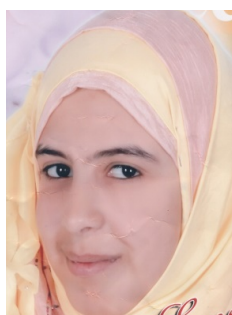
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