

Chemistry of 3-carbonyl-2-methyl-4-oxo-4*H*-1-benzopyrans

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Abstract

The review article gives a comprehensive survey of the synthesis and chemistry of the title benzopyrans covering the literature published during 1980 – August 2015.

Keywords: Chromones, acylation, Michael addition, [6+0]cyclization, radical cyclization, metal complex formation

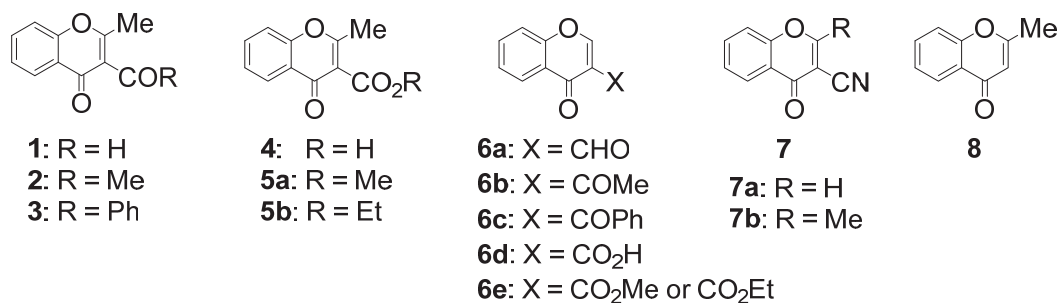
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1. Introduction

2-Methyl-1-benzopyran-4-ones **1-5** belong to the chromone family, and, like their respective 2-unsubstituted homologues **6**, possess an activated endocyclic olefinic bond, three electrophilic centres, namely pyran C-2, exocyclic carbonyl carbon and an endocyclic carbonyl carbon. In chromone **6**, C-2 is much more electrophilic than the exocyclic carbonyl carbon, and C-4 is the least electrophilic position. Electrophilicity at the methyl substituted C-2 of chromones **1-5** is evidently less than that at C-2 of their lower homologues **6** due to the positive inductive effect and hyperconjugation of the methyl group. The 2-methyl group in **1-5**, being vinylogous to two carbonyl groups, is more acidic than that in 2-methylchromone **8**, and functions as a nucleophile in the presence of an appropriate base. Because of these functionalities (activated olefinic bond, electrophilicity at three centres and nucleophilicity at the 2-methyl group), the chemistry of 2-methylchromones **1-5** is more varied than that of the lower homologues **6**. Of the several review articles on chromones, the latest one on 2-methylchromone **8**¹, two on the nitrile **7a**^{2,3} and three on 3-formylchromone **6a**⁴⁻⁶ are noteworthy. In contrast, a full, complete and up-to-date survey on the chemistry of the title chromones **1-5** is still lacking.



Research in the chemistry of the title topic started in 1921 with the synthesis of 3-acetyl-2-methylbenzo[*f*]chromone by treatment of 2-methoxynaphthalene with acetic anhydride and

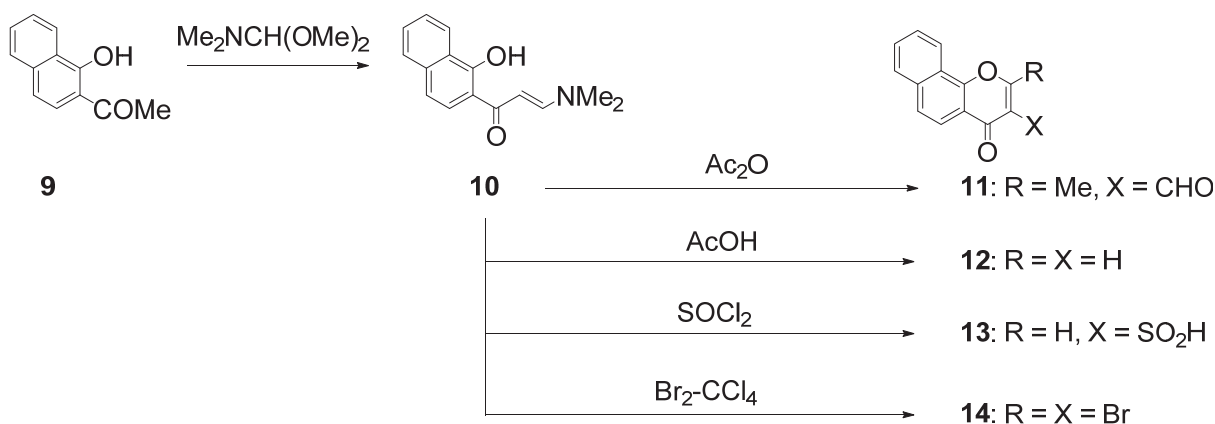
sulfoacetic acid. Here the methoxy group of the initially formed 1-acetyl-2-methoxynaphthalene probably undergoes hydrolysis under the reaction conditions and the resultant intermediate by further acetylation and cyclization gives the final product.⁷ Over the following six decades research has mainly revolved around the synthesis of 3-acylchromones **2** and **3** and their reactions with simple nitrogen nucleophiles. The present article is a comprehensive survey of the chemistry and applications of the chromones **1-5**, and covers the literature published during the period 1980 to August 2015. Patented works on the chromones **1-5** are excluded, and the biological activity of compounds **1-5** and the products obtainable therefrom are less emphasized. Most of the reactions described here for the chromones **1-5** generally do not affect any alkyl, alkoxy and halogeno substituents if present in the benzene ring, or on aromatic or heterocyclic rings if fused with the benzene ring of these chromones.

2. Synthesis

The easily available *o*-hydroxyacetophenone can serve as a synthon for the title chromones **1-5**.

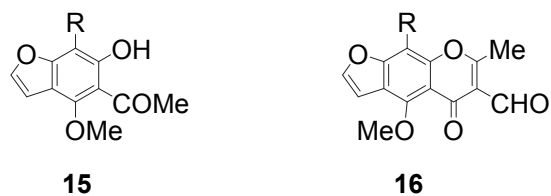
2.1. Synthesis of 3-formyl-2-methylchromone **1**

The chromone **1** is conveniently prepared by treating the enaminoketone, derived from *o*-hydroxyacetophenone and *N,N*-dimethylformamide dimethyl acetal, with acetic anhydride. This method has been adopted for the preparation of 3-formyl-2-methylbenzo[*h*]chromone **11** from 2-acetyl-1-naphthol **9** (Scheme 1).⁸ It is worth mentioning here that the enaminoketone **10** gives the chromone derivatives **12**, **13** and **14** by treatment with AcOH, SOCl₂ and Br₂, respectively.⁸

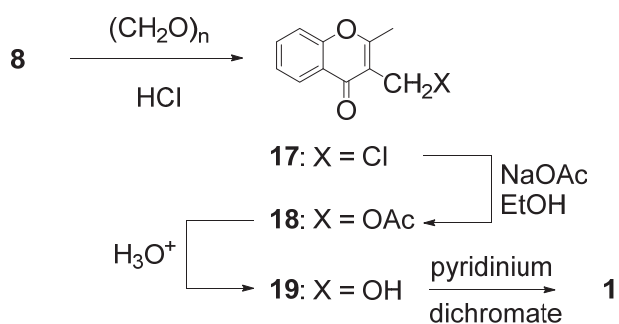


Scheme 1

Benzofuran derivatives **15a,b** have similarly been converted into 6-formylvisnagin **16a** and 6-formylkhellin **16b**, respectively.⁹

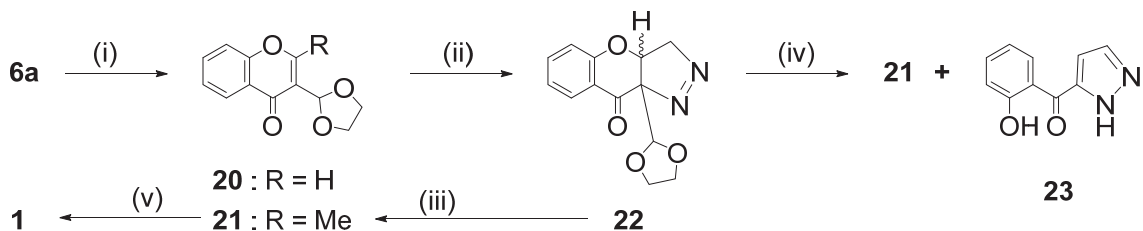
For **15** and **16****a** : R = H**b** : R = OMe

The aldehyde **1** has also been prepared from preformed 2-methyl-, 3-formyl- and 3-acetyl-chromone (**8**, **6a** and **6b**). 2-Methylchromone **8** is chloromethylated by paraformaldehyde-hydrogen chloride to **17** which is converted into **19** *via* **18**; pyridinium dichromate oxidizes the alcohol **19** to the aldehyde **1** (Scheme 2).¹⁰



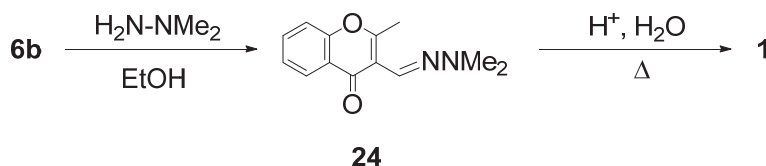
Scheme 2

Lithium dimethylcuprate causes conjugate addition of the methyl group to chromone-3-carbaldehyde **6a**, and the resultant 3-formyl-2-methylchromanone can be dehydrogenated by trityl tetrafluoroborate $[\text{Ph}_3\text{C}][\text{BF}_4]$ to the aldehyde **1** in 56% yield.¹¹ Treatment of the dioxolane **20**, derived from **6a** and ethylene glycol, with diazomethane gives the 1-pyrazoline **22** that gives exclusively 2-methylchromone **21** when heated under reflux in toluene but **21** admixed with a small amount of the aroylpyrazole **23** when heated neat. The compound **21** on treatment with aqueous acid gives 3-formyl-2-methylchromone **1** (Scheme 3).^{12,13}



Scheme 3. Reagents and conditions: (i) $\text{HOCH}_2\text{CH}_2\text{OH}$, PhH , PTSA , Δ ; (ii) CH_2N_2 , CH_2Cl_2 ; (iii) PhMe , Δ ; (iv) Δ ; (v) H_2O , H^+ , warm.

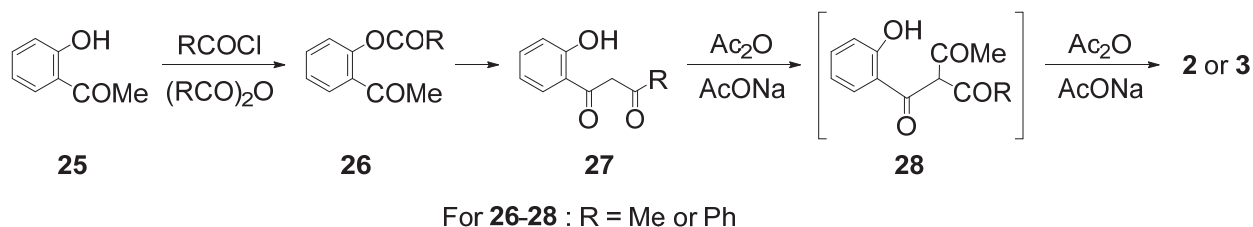
Another method for the preparation of the aldehyde **1** involves acid hydrolysis of the hydrazone **24** arising through an aza-Michael addition of 1,1-dimethylhydrazine to the α,β -unsaturated ketone functionality of **6b** with concomitant opening of the pyran ring and recyclization (Scheme 4).¹⁴



Scheme 4

2.2. Synthesis of 3-acetyl-2-methylchromone **2**

Synthesis of 3-acylchromones **2** and **3** from *o*-hydroxyacetophenone **25** involves a three-step process namely (i) *O*-acylation of **25** with acyl chloride RCOCl or acid anhydride (RCO)₂O to **26**, (ii) Baker-Venkataraman rearrangement of **26** to **27** and (iii) treatment of **27** with acetic anhydride, the final step involving the formation of the non-isolable intermediate **28** which spontaneously cyclizes to **2** or **3** (Scheme 5).

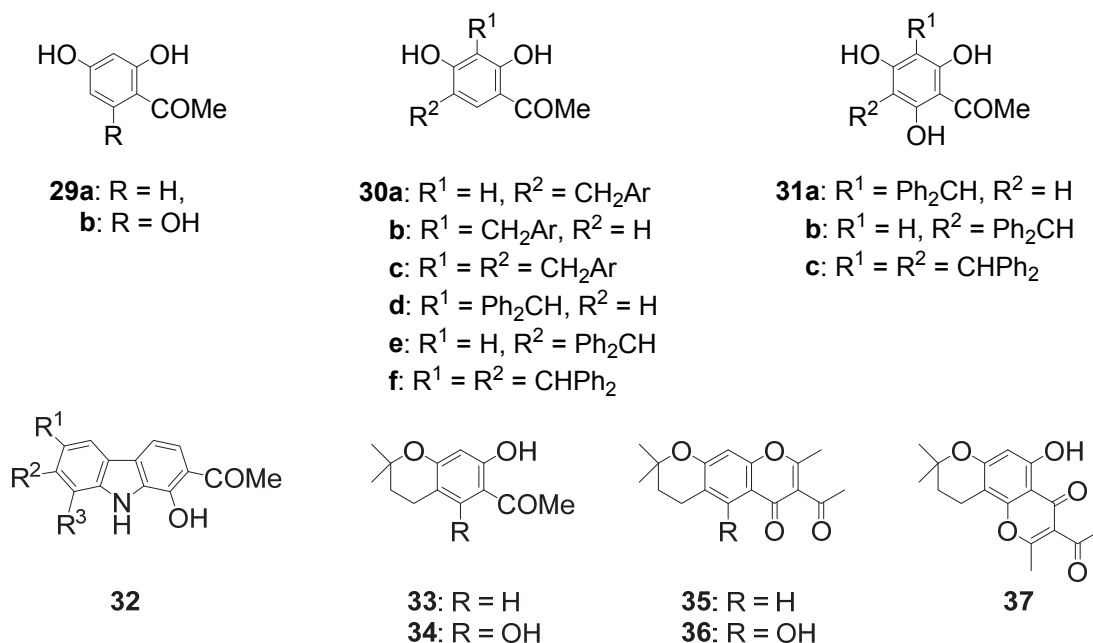


Scheme 5

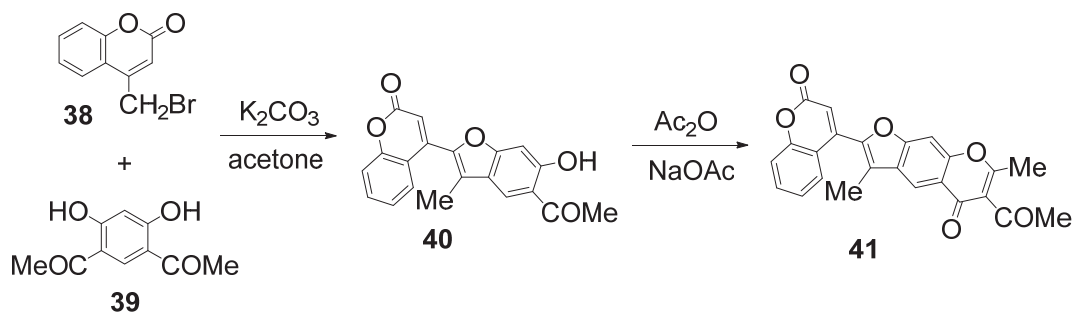
Kostanecki-Robinson synthesis of **2** by just heating **25** with Ac₂O-AcONa involves all the above three steps. 3-Acetyl-2-methylchromone **2** and its variously substituted analogues have been synthesized by the Kostanecki-Robinson method. Ganguly *et al.*¹⁵ have used MeCOCl in DBU-pyridine, instead of Ac₂O-AcONa, for preparing some 5- or 7-mono and 5,7-disubstituted analogues of **2** from the corresponding *o*-hydroxyacetophenones.

Resacetophenone (**29a**) on treatment with arylmethanol ArCH₂OH (Ar = Ph, 4-MeOC₆H₄) in the presence of BF₃-ether gives the mono- and di-benzylated acetophenone **30a-c**.^{16,17} Similar treatment of **29a** and phloracetophenone (**29b**) with Ph₂CHOH gives **30d-f**¹⁸ and **31a-c**,¹⁹ respectively. All these substituted acetophenones **30** and **31** have been heated with Ac₂O-AcONa to yield the corresponding 3-acetyl-2-methylchromones. 2-Acetyl-1-hydroxycarbazole **32** (R¹, R², R³ = H, Me) obtained along with 2,4-diacetyl-1-hydroxycarbazole by acylation of 1-hydroxycarbazole with AcCl in the presence of anhydrous AlCl₃ and POCl₃ has been subjected

to Kostanecki-Robinson reaction to give the corresponding chromone.²⁰ With Ac₂O-AcONa, the benzopyran **33** gives **35**,²¹ and **34** a mixture of **36** and **37**.²²

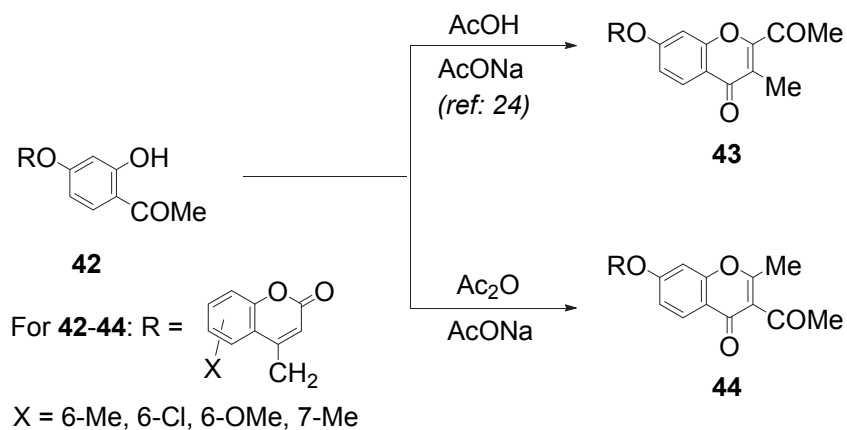


Ghate and Kulkarni²³ prepared the furo[3,2-g]benzopyran **41** containing a coumarin moiety at its 2-position by Ac₂O-AcONa treatment of **40**, derived from coumarin **38** and diacetylresorcinol **39** (Scheme 6) and assessed its anti-inflammatory and analgesic activity.



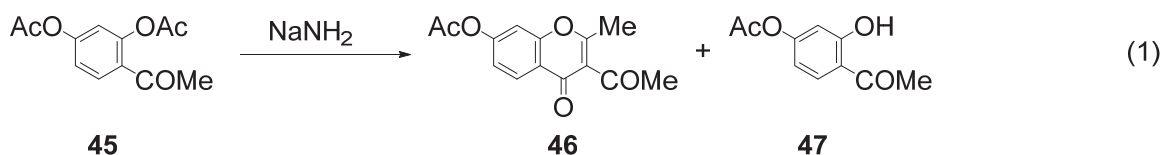
Scheme 6

Conversion of the acetophenone **42** to 2-acetylchromone **43** by treatment with either Ac₂O-AcONa as stated in the chemistry as well as experimental section or AcOH-AcONa as (perhaps erroneously) printed in the reaction scheme of a publication²⁴ is unlikely; the substrate **42** in Ac₂O-AcONa under reflux evidently affords the chromone **44** (Scheme 7).

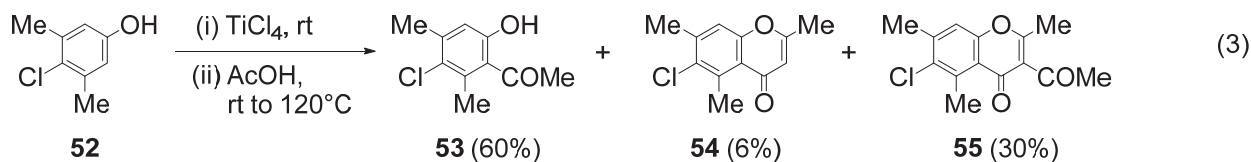
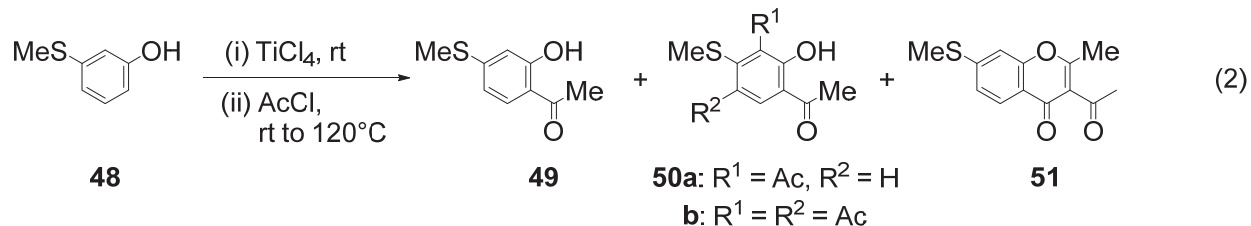


Scheme 7

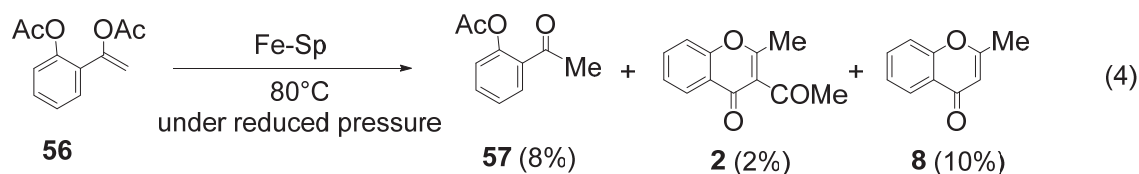
Treatment of the diacetoxyacetophenone **45** with sodamide results in cyclization and an intermolecular acetyl group transfer to give **46** admixed with **47**, the deacylated product from **45** (Equation 1).²⁵



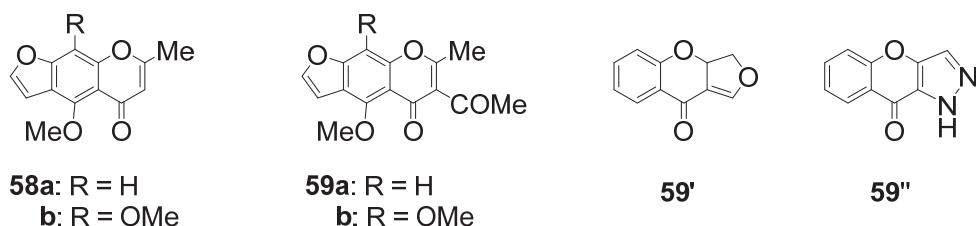
TiCl₄-catalyzed Friedel-Crafts acylation of some substituted phenols with either AcCl²⁶ or AcOH²⁷ is often followed by Allan-Robinson reaction to some extent so as to form 3-acetyl-2-methylchromones (Equations 2 and 3).



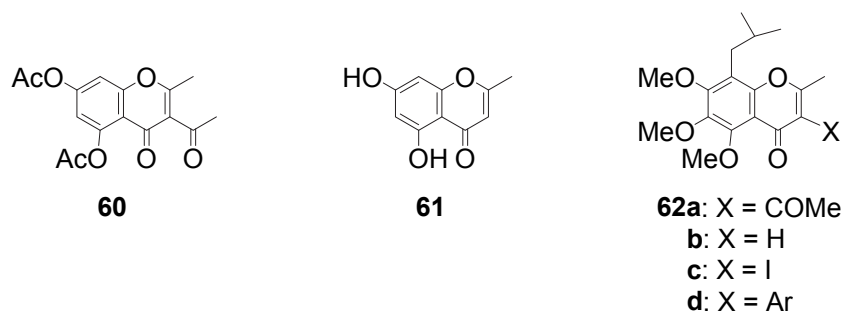
Iron(III) exchanged sepiolites (Fe-Sp) operate as Lewis acids in thermolysis of the styrene **56** under reduced pressure to 2'-acetoxyacetophenone **57** and chromones **2** and **8** (Equation 4).²⁸



Acetylation at the 3-position of 2-methylchromone **8** is also known. As for example, equimolar amounts of **8** and Ac₂O over a HBEA zeolite (Si/Al = 10) in a batch reactor or a fixed bed reactor at 60°C gives chromone **2**.²⁹ Acetylation of visnagin **58a** and khellin **58b** by Ac₂O-Zn dust to the respective 6-acetyl derivative **59a** and **59b** has also been achieved.³⁰ Diazomethane at -70 °C effects dual alkylation of 3-formyl-6-methylchromone yielding 3-acetyl-2,6-dimethylchromone,³¹ but in ice-cold ether or dichloromethane solution it converts 3-formylchromone **6a** into 3-acetyl-2-methylchromone **2** in only 2% yield together with furo[3,4-*b*][1]benzopyran **59'** (16%) and [1]benzopyrano[3,2-*c*]pyrazole **59''** (2%).³²



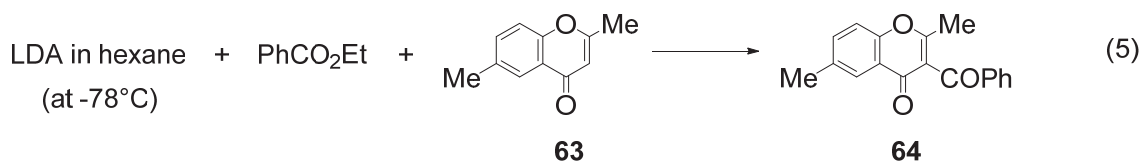
Deacetylation of several 3-acetyl-2-methylchromones by treatment with aqueous sodium carbonate is resorted to for preparation of otherwise difficultly accessible 2-methylchromones. For example, 5,7-dihydroxy-2-methylchromone **61**, needed for the synthesis of schumannio-phytine and isoschumannio-phytine, has been prepared by Na₂CO₃-H₂O treatment of the 3-acetylchromone **60**, obtainable from phloracetophenone **29b** and Ac₂O-AcONa.³³ The chromone **62b** obtained by similar deacetylation of 3-acetylchromone **62a** is treated with I₂-CF₃CO₂Ag to afford 3-iodochromone **62c**; the latter (**62c**) on Suzuki coupling with arylboronic acid leads to 3-aryl-2-methylchromones **62d** (Ar = Ph, 4-ClC₆H₄, 4-MeOC₆H₄, 2-naphthyl, C₆H₄Ph etc.).³⁴



2.3. Synthesis of 3-benzoyl-2-methylchromone (**3**)

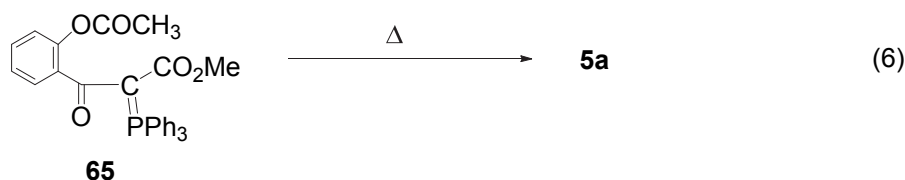
A general method for the synthesis of chromone **3** starting from *o*-hydroxyacetophenone *via* **26** and **27** (R = Ph) is shown in Scheme 5. Unsubstituted and various substituted 2'-hydroxyacetophenones,³⁵⁻³⁷ 3,6-diacetyl-5-hydroxyindole³⁸ and benzofuran **15b**³⁹ have been converted into the corresponding 3-benzoylchromones. Ac₂O-DMSO⁴⁰ and Ac₂O in DMAP/pyridine,⁴¹ instead of Ac₂O-AcONa, have also been used for the conversion of many 2'-hydroxy-*o*-benzoyl-acetophenones to chromones analogous to **3**.

3-Benzoyl-2-methylchromone **3** has also been prepared from 2-methylchromone **8** as well as 3-benzoylchromone **6c**. Lithium diisopropylamide (LDA, from diisopropylamine and butyl lithium) can cause vinylic deprotonation and classical deprotonation of the active methylene group. Costa *et al.*⁴² prepared 3-benzoyl-2,6-dimethylchromone **64** in 46% yield by sudden addition of ethyl benzoate to a LDA solution in hexane kept at -78°C followed immediately by the addition of 2,6-dimethylchromone **63** and quenching the reaction after 3 h with AcOH-H₂O (Equation 5). This is an example wherein vinylic deprotonation predominates over deprotonation of a sufficiently active 2-methyl group of chromone **63**. The chromone **3** along with three other products is obtained by treating 3-benzoylchromone **6c** with diazomethane.³²

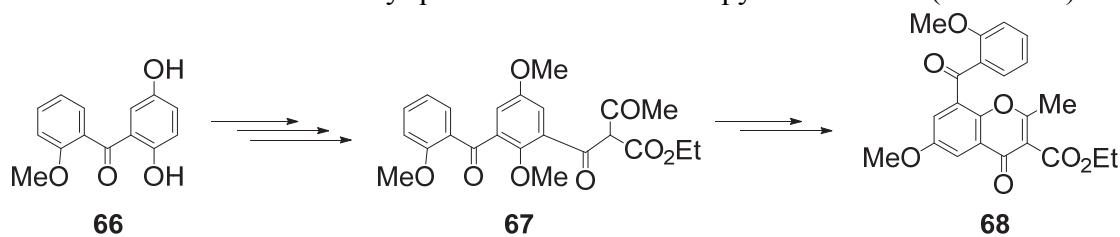


2.4. Synthesis of 3-hydroxycarbonyl- and 3-alkoxycarbonyl-2-methylchromone **4** and **5**

2-Hydroxy- and 2-fluoro-benzoic acid chlorides are synthons for the acid **4** and ester **5**. Ethyl acetoacetate in the presence of 40% NaOH⁴³ as well as its morpholino-enamine⁴⁴ gives with salicyloyl chloride the ester **5b** that on acid hydrolysis affords **4**. Thermal decomposition of the keto-ylid **65**, obtainable from *O*-acetylsalicyloyl chloride and Ph₃P=CHCO₂Me, gives the ester **5a** in 55% yield (Equation 6).⁴⁵



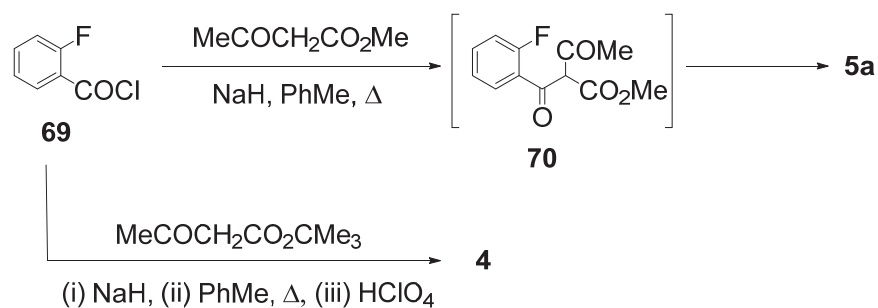
Kim⁴⁶ has converted the 2-arylquinol **66** into the benzopyran **68** via **67** (Scheme 8).



Scheme 8

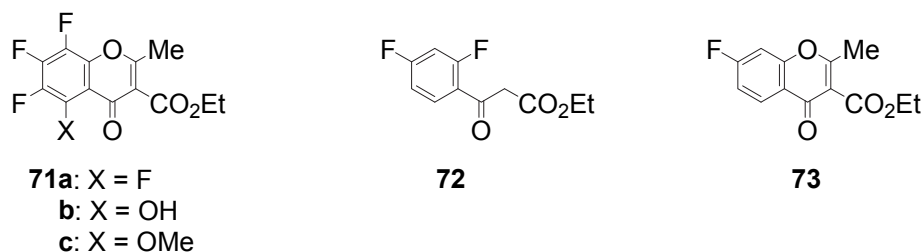
The intermediate β,β' -diketoester **70**, resulting from 2-fluorobenzoyl chloride **69** and methyl acetoacetate in the presence of sodium hydride, undergoes cyclization *via ipso*-fluorine

substitution to give the ester **5a**. When the acid chloride **69** is similarly reacted with *t*-butyl acetoacetate and the reaction mixture treated with HClO₄, the acid **4** results (Scheme 9).⁴⁷

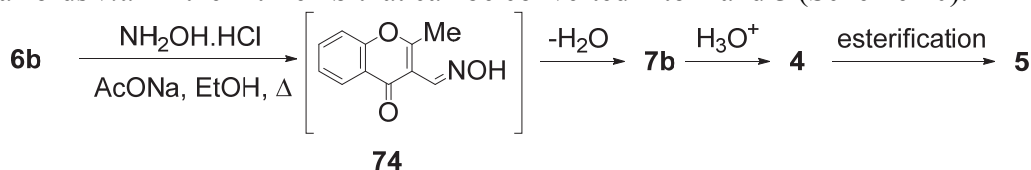


Scheme 9

A Russian group⁴⁸⁻⁵¹ adopted this method for the preparation of tetrafluoro- and trifluoro-chromones **71** and extensively studied their reactions with several nitrogen nucleophiles. Lin and Long⁵² subjected the β -ketoester **72** with AcCl in DMF containing K₂CO₃ and DIPEA to obtain the 7-fluorochromone derivative **73**.

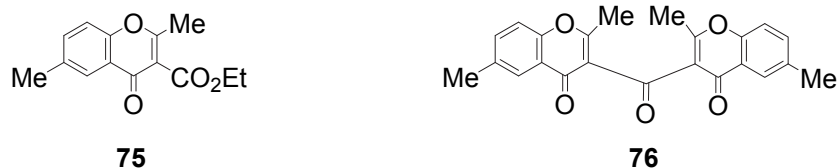


Preparation of the acid **4** and ester **5** from preformed chromone derivatives is also known. A mixture of 3-acetylchromone **6b**, NH₂OH.HCl and NaOAc on being heated under reflux in ethanol affords *via* **74** the nitrile **7b** that can be converted into **4** and **5** (Scheme 10).⁵³

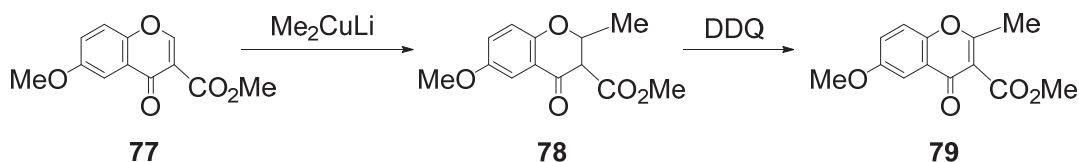


Scheme 10

Sequential rapid addition of diethyl carbonate and 2,6-dimethylchromone **63** to a solution of LDA at -78°C produces the ester **75** (42%) and the bis-hetaryl ketone **76** (17%) arising from acylation of the intermediate chromone carbanion with diethyl carbonate and the ester **75**, respectively.^{42,54}



The 2-unsubstituted chromone ester **77**, an analogue of **6e**, has been converted into the corresponding 2-methylchromone **79** by a sequential conjugate addition (through **78**) and dehydrogenation (Scheme 11).¹¹

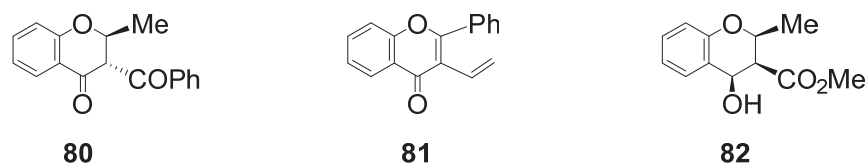


Scheme 11

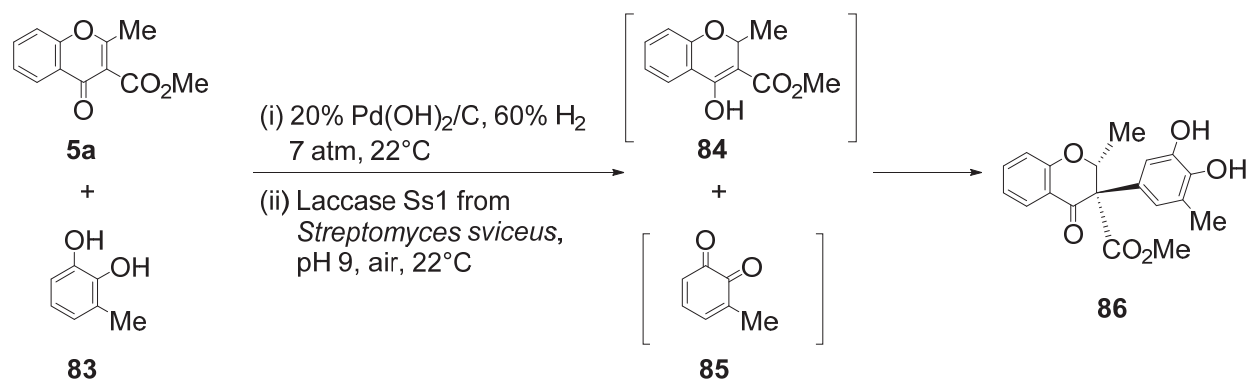
3. Conjugate Addition to the Pyran 2,3-Olefinic Bond of Chromones without Pyran Ring Opening

3.1. Conjugate reduction

Conjugate reduction of chromone **3** with sodium borohydride in pyridine at room temperature is both regio- and chemo-selective giving the chromanone **80**. Methanesulfonic acid triggers the pyranone ring opening of **80** followed by recyclization to give the 3-ethenylflavone **81**.³⁶ The ester **5a** with NaBH_4 in methanol gives **82**.⁵⁵



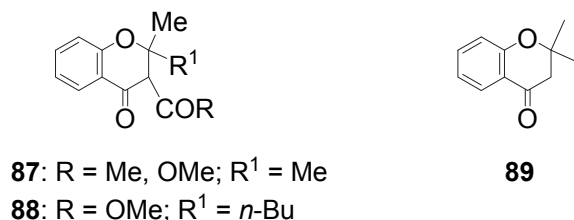
The conjugate reduction of the ester **5a** to **84** followed by its Michael addition to an α,β -unsaturated ketone **85**, derived from a biocatalytic oxidation of methylcatechol **83** in a H-Cube Pro flow system, leading to the trisubstituted chromanone **86** (96% yield; dr > 99:1) (Scheme 12) deserves special mention.⁵⁶



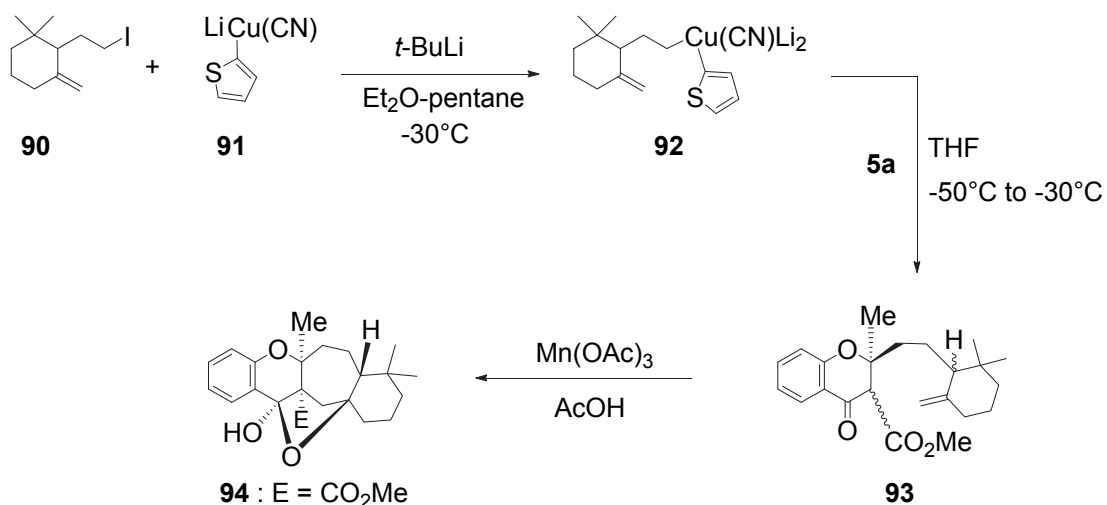
Scheme 12

3.2. Conjugate addition of alkyl and alkoxy groups

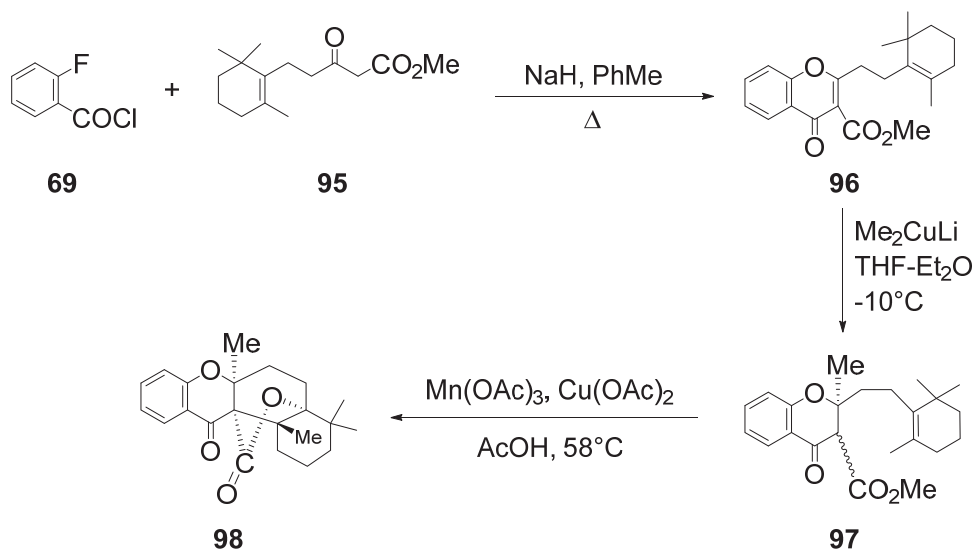
Lithium dimethylcuprate in THF at -10°C transforms 3-acyl- and 3-carbomethoxy-chromone **2** and **5a** to the corresponding 2,2-dimethylchromanone derivatives **87** (R = Me or OMe; R¹ = Me).^{11,57,58} Clarke *et al.*¹¹ have treated the ester **5a** with lithium *n*-butylcuprate to get the chromanone **88**, assumed to have the larger *n*-butyl and ester substituents in *trans*-diequatorial orientation. The compound **87** (R = OMe; R¹ = Me) on treatment with NaCl in DMSO at 155 °C gives 2,2-dimethylchromanone **89**,⁵⁷ the latter being also provided by treating 2-methylchromone with methylcopper-BF₃ complex.¹¹



Crombie *et al.*^{59,60} have developed a conjugate addition – radical cyclization approach to construct the naturally occurring sesquiterpene-phenol carbon framework. To an ether - pentane solution of the mixed ligand cuprate reagent **92**, derived from the alkyl iodide **90**, lithium cuprate **91** and *t*-butyllithium, was added the ester **5a** to obtain the chromanone **93** as a mixture of four stereoisomers. Treatment of this mixture with Mn(OAc)₃-HOAc affords the hemiacetal **94** in 30% yield (Scheme 13). In another approach the 2-alkyl ester **96** prepared from 2-fluorobenzoyl chloride **69** and the ester **95**, is converted into the 2,2-dialkylated chromanone **97** by treatment with Me₂CuLi. Radical cyclization of **97** as an unresolved stereoisomeric mixture affords the polycyclic lactone **98** in nearly 30% yield (Scheme 14).^{59,60}



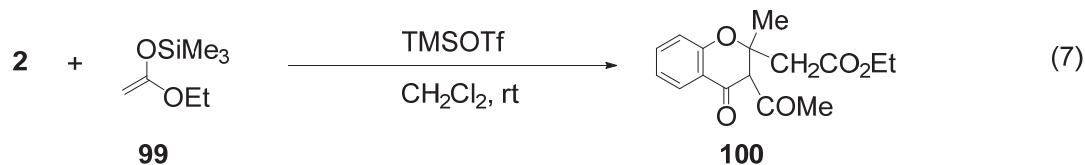
Scheme 13



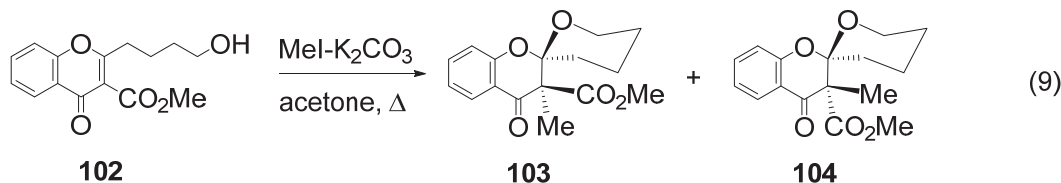
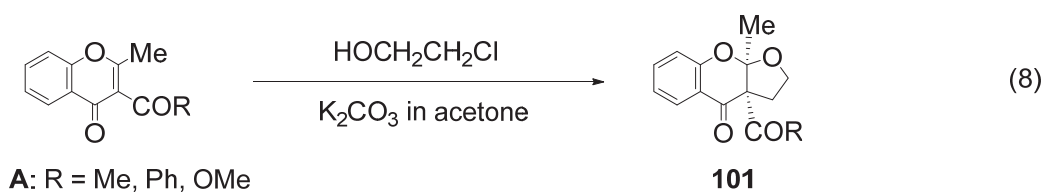
Scheme 14

A lithium dialkynylcuprate as $[(\text{TMS-C}\equiv\text{C})_2\text{CuLi}]$, though capable of transferring its alkynyl group in a conjugate addition to the ester **6e**, failed to react with 3-alkoxycarbonyl-2-methylchromone **5**.⁶¹

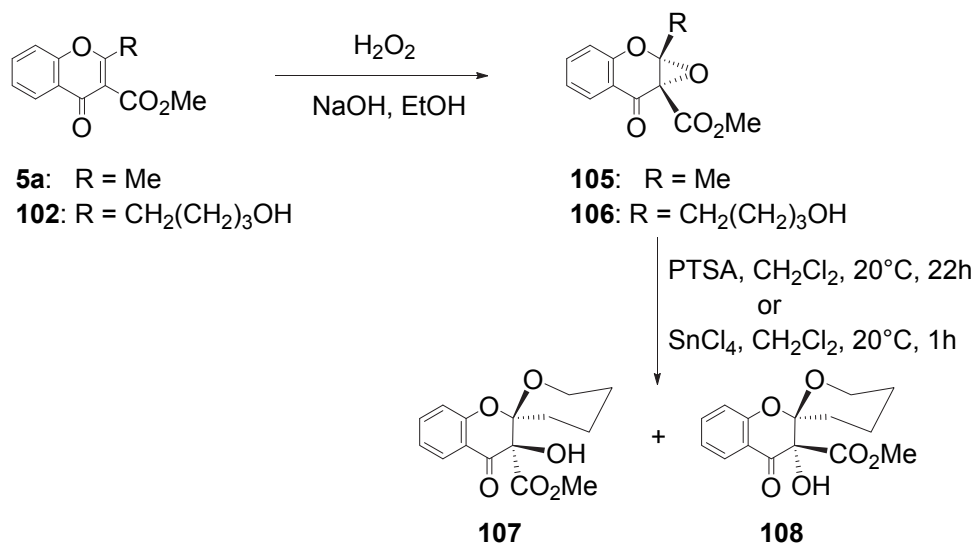
3-Acetylchromone **2** on treatment with the silyl enol ether **99** in the presence of trimethylsilyl triflate (TMSOTf) affords in 16% yield the chromonanone **100** as a diastereoisomeric mixture (Equation 7).⁶²



Heteroannulation of the chromone **A** (\equiv **2**, **3**, **5a**) with 2-chloroethanol in the presence of K_2CO_3 to the corresponding furobenzopyranone **101** (Equation 8) proceeds *via* the conjugate addition of the haloethanol to the chromone followed by intramolecular alkylation.⁶³ Transformation of the chromone ester **102** on treatment with MeI - K_2CO_3 in refluxing acetone into the spiroacetals **103** and **104** in a ratio of 5:1 (in 60% total yield) (Equation 9) also involves a sequential intramolecular conjugate addition and enolate alkylation.⁶⁴



Alkaline hydrogen peroxide with the esters **5a** and **102** forms the epoxides **105** and **106**, respectively. Acid catalyzed oxirane ring opening of **106** results in the formation of the spiroacetals **107** and **108** (Scheme 15).⁶⁴

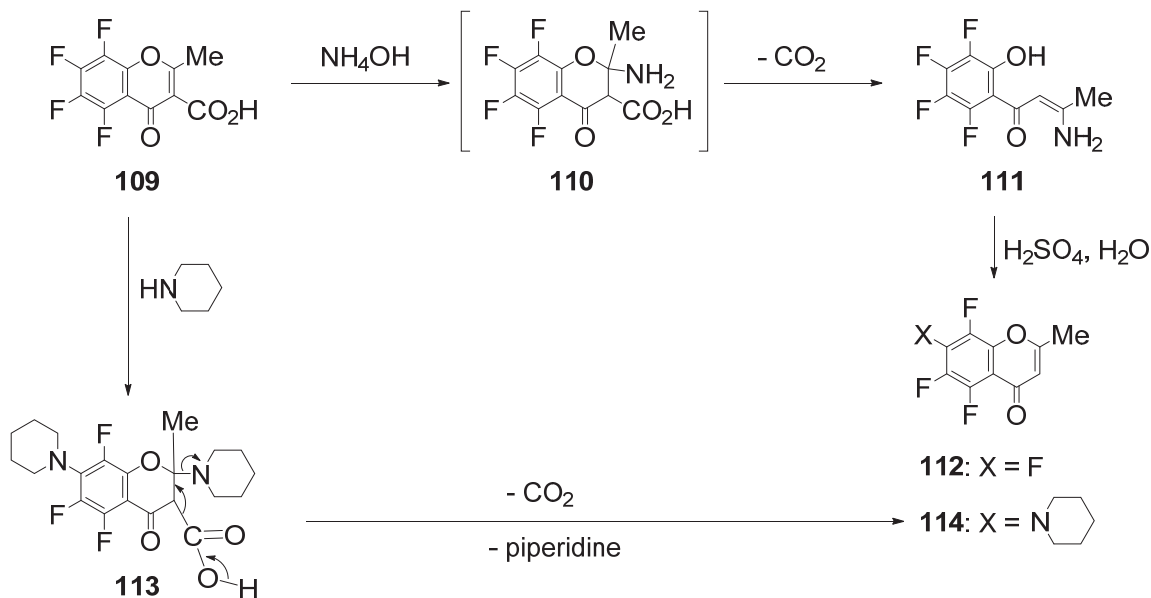


Scheme 15

4. Conjugate Addition with Other Concomitant Reactions

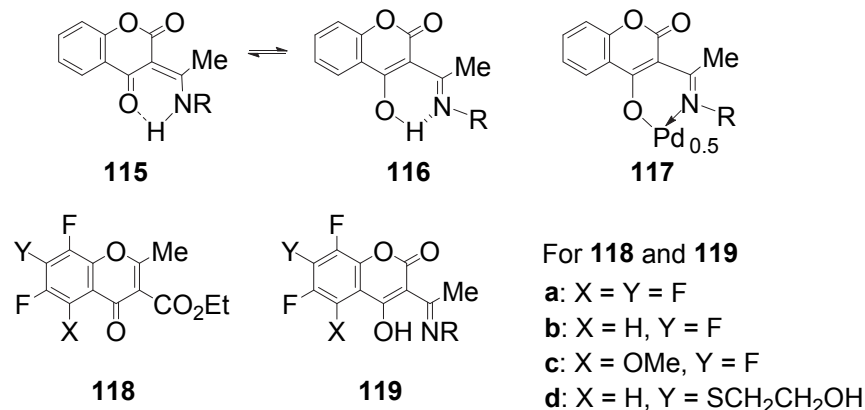
4.1. Addition of ammonia and amines

The aza-Michael adduct **110** resulting from tetrafluorobenzopyran-3-carboxylic acid **109** and ammonia undergoes decarboxylative pyran ring opening to give the enaminoketone **111** that on acid treatment affords 2-methylchromone **112** (Scheme 16).⁶⁵ Piperidine brings about substitution of fluorine at the 7-position of **109** and conjugate addition, the adduct **113** undergoing decarboxylative elimination of the piperidine moiety to give **114** (Scheme 16).⁶⁵



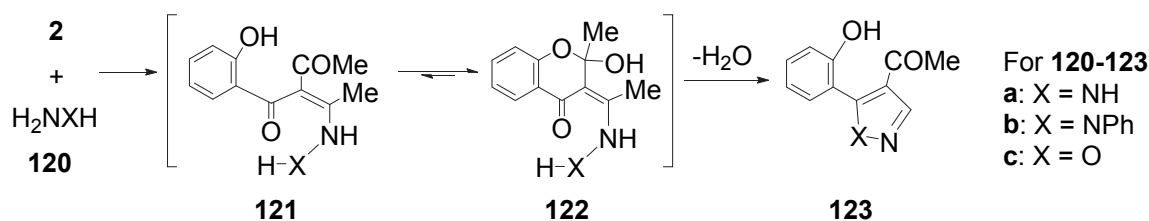
Scheme 16

The ester **5** with the amine RNH_2 ($\text{R} = \text{H}, \text{Me}, \text{PhCH}_2, \text{CH}_2\text{CH}_2\text{OH}$) gives the benzopyran-2,4-dione **115**, its enol tautomeric form **116** functioning as a ligand to form Pd(II) complex of the general formula PdL_2 ($\text{L} = \text{deprotonated } \mathbf{116}$).⁶⁶⁻⁶⁹ This four co-ordinated Pd(II) complex **117** exists in *cis*-isomeric form for the ligand L ($\text{R} = \text{H}$) and *trans*-form for L ($\text{R} = \text{other than H}$).^{67,68} Cytotoxic effects of the diones **115** and several of their Pd(II) complexes have been assessed against two leukemia cell lines HL-60 and NALM-6. On treatment with RNH_2 ($\text{R} = \text{H}, \text{Me}, \text{PhCH}_2, \text{hexyl}, \text{cyclohexyl}$ etc.), the fluorinated chromone-3-ester **118a** gives 4-hydroxycoumarin **119a**,^{48,51,70} **118b** affords **119b**,⁷¹ **118c** provides **119c**^{49,51} and **118d** the coumarin **119d**.⁷²



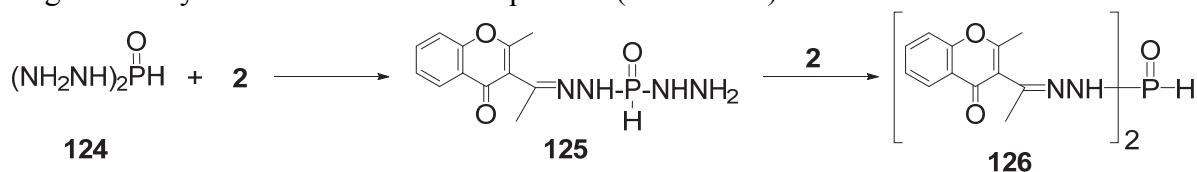
4.2. Addition of nitrogenous dinucleophiles

4.2.1. Dinucleophiles having adjacent nucleophilic centres. A dinucleophile as **120** undergoes aza-Michael addition to 3-acetyl-2-methylchromone **2** with concomitant opening of the pyran ring to form the intermediate **121** in *Z*-isomeric form so that its acetyl carbonyl group is protected as a hemiacetal **122**, the latter having no other way than to cyclize to the heterocycle **123** (Scheme 17).⁷³



Scheme 17

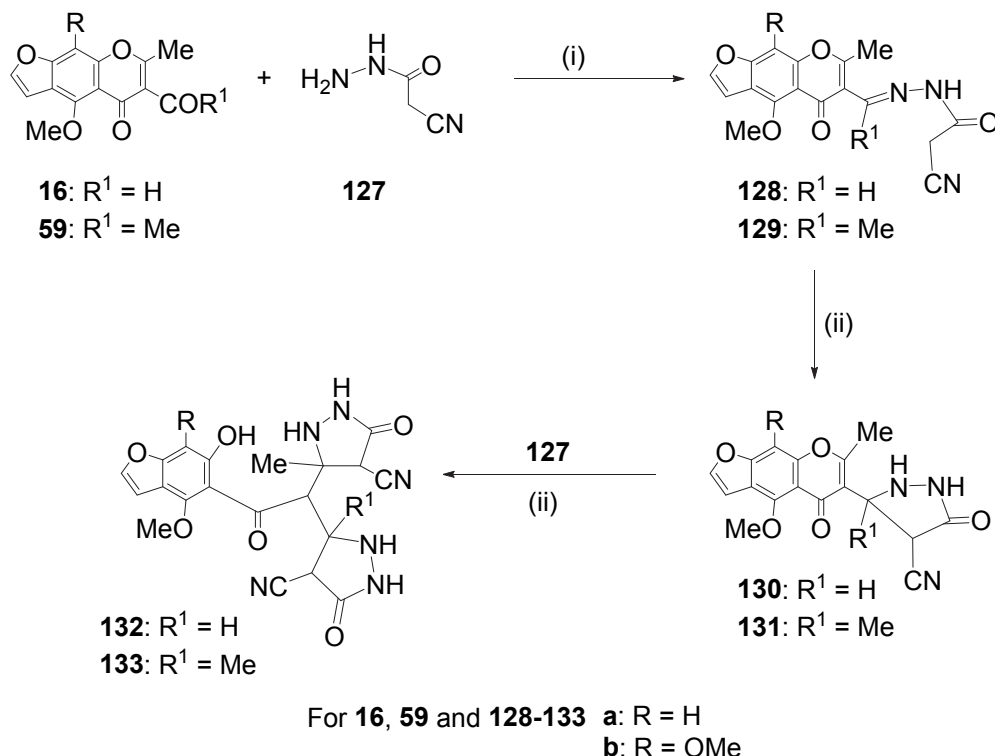
Reaction of phosphonic dihydrazide **124** and chromone **2** in a 1:2 molar ratio gives, probably through a domino aza-Michael addition – pyran ring opening – recyclization, the intermediate **125** that reacts further with a second molecule of **2** in the same reaction sequence giving the bis-hydrazone **126** as the final product (Scheme 18).⁷⁴



Scheme 18

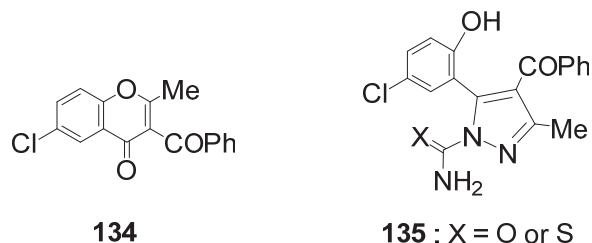
A mixture of 6-formylfurochromone **16** and 2-cyanoacetylhydrazide **127** in a 1:1 molar ratio on stirring in AcOH at ambient temperature gives the hydrazone **128** by direct derivatization of the aldehyde function of **16** with hydrazide **127**. The hydrazone **129** is formed on similar

treatment of the ketone **59** with the hydrazide **127** probably through a domino aza-Michael addition – pyran ring opening – recyclization sequence. When refluxed separately in acetic acid, the hydrazones **128** and **129** cyclize by intramolecular Michael addition giving respectively the benzopyran-3-ylpyrazolidones **130** and **131** which can further react with a second molecule of **127** in boiling acetic acid to yield the bis-pyrazolidones **132** and **133**, respectively (Scheme 19).⁷⁵



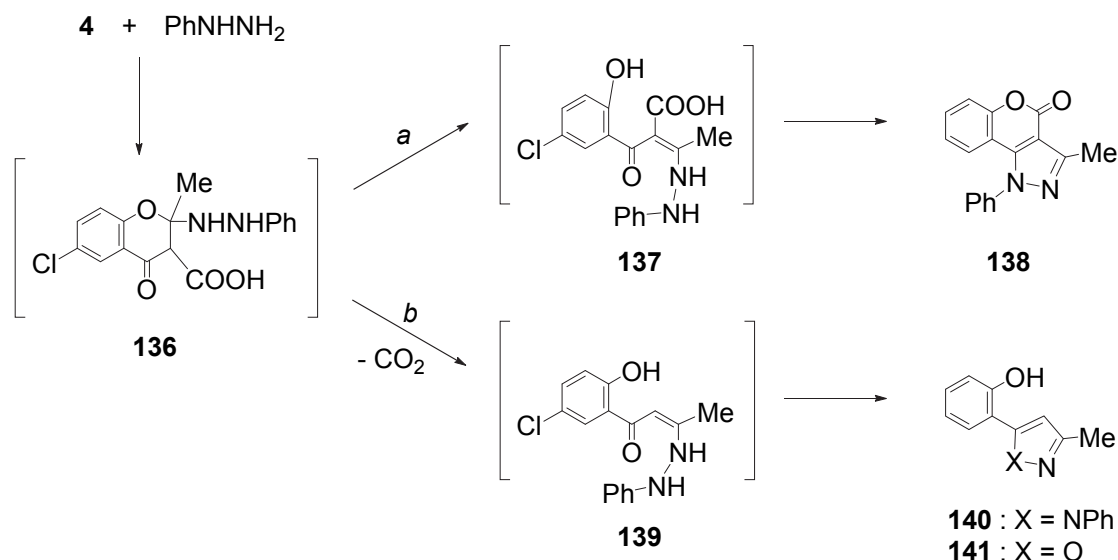
Scheme 19. Conditions : (i) Stirring in 95% AcOH, in a 1:1 molar ratio, rt; (ii) AcOH, reflux.

3-Benzoylchromone **3** behaves similarly to its 3-acetyl analogue **2** towards hydrazines. For example, the chromone **134** with semicarbazide or (thio)semicarbazide H₂NNHC(=X)NH₂ in refluxing methanol gives the tetrasubstituted pyrazole **135**.⁷⁶



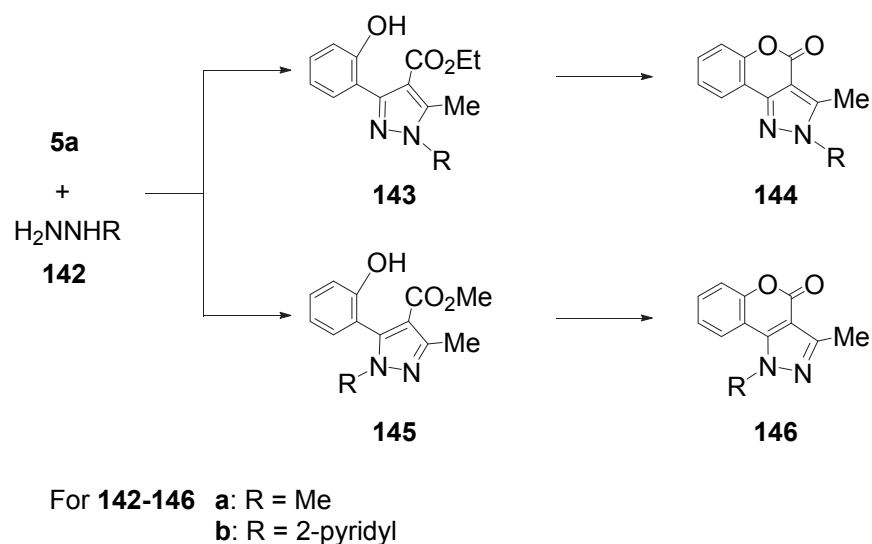
Phenylhydrazine undergoes 1,4-addition to the α,β -unsaturated acid **4**; the adduct **136** may give either the coumarinopyrazole **138** through its pyran ring opening (to **137**) and recyclization

(Scheme 20-path *a*) or the trisubstituted pyrazole **140** through a Grob fragmentation (to **139**) and cyclization (path *b*). A French group⁷⁷ have reported without disclosing the experimental details the formation of **138** in the said reaction, whereas Ghosh and Pal⁵³ obtained exclusively the pyrazole **140** by heating under reflux a mixture of **4** and PhNHNH₂.HCl in ethanol containing sodium acetate. The acid **4** with NH₂OH follows a reaction course similar to Scheme 20-path *b* to yield the isoxazole **141**.⁷⁸

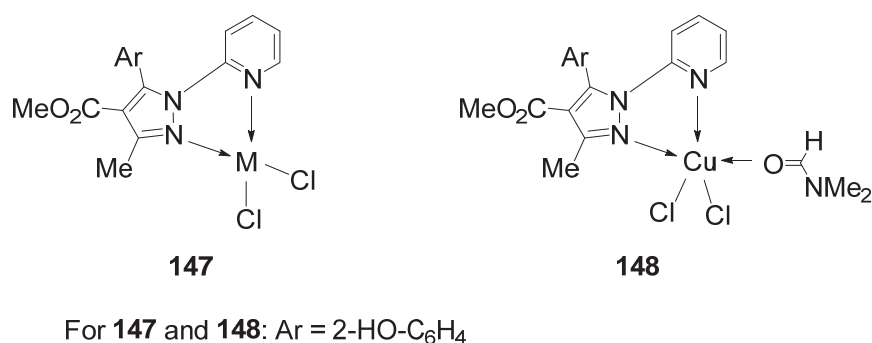


Scheme 20

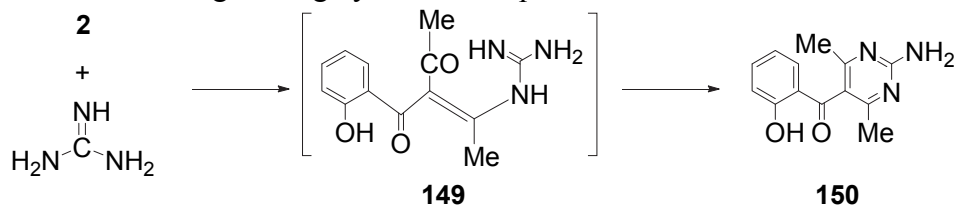
The ester **5a** with methylhydrazine **142a** gives **144a** (20%) and **145a** (64%), the former product (**144a**) arising by lactonization of the non-isolable intermediate **143a** and the latter (**145a**) lactonizing to **146a** only by base (like triethylamine) treatment (Scheme 21).^{79,80} Both **144a** and **145a** can serve as ligand L to form with Pd(PhCN)₂Cl₂ *trans*-PdL₂Cl₂ complexes, only the doubly-bonded nitrogen of L being co-ordinated to Pd(II).^{79,80} Treatment of the ester **5a** with 2-hydrazinopyridine **142b** gives exclusively the 1-(2-pyridyl)pyrazole **145b** that forms with K₂PtCl₄, K₂PdCl₄ and CuCl₂ the metal complex of the general formula **147**. A molecule of dimethylformamide can also coordinate with Cu(II) of the complex **147** (M = Cu) giving the pentacoordinated Cu(II) complex **148**.^{81,82} The structures of all these metal complexes have been confirmed by X-ray analysis.



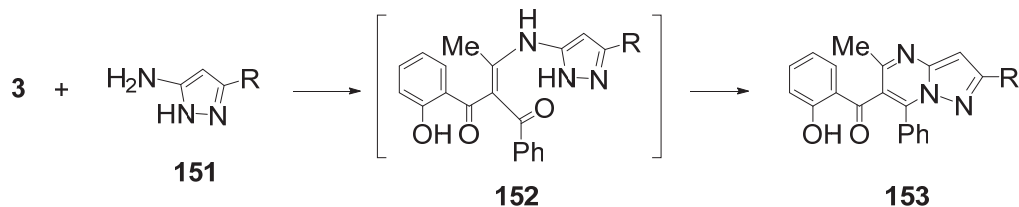
Scheme 21



4.2.2. Dinucleophiles with two nucleophilic centres separated by one carbon. Guanidine undergoes conjugate addition to the chromone **2** with concomitant opening of the pyran ring; the resultant intermediate **149**, unlike **121** arising from **2** and hydrazine or hydroxylamine, undergoes [6+0] cyclization involving the acetyl, not aroyl, group giving the pyrimidine **150** (Scheme 22).⁷³ In a precisely similar way, the amino group of 5-amino-1*H*-pyrazoles **151** attacks at C-2 of 3-benzoylchromone **3** with subsequent opening of the pyran ring; the resultant intermediate **152** cyclizes to the pyrazolopyrimidine **153** (Scheme 23).⁸³ This reaction under microwave irradiation and solvent free conditions gives high yields of the products.



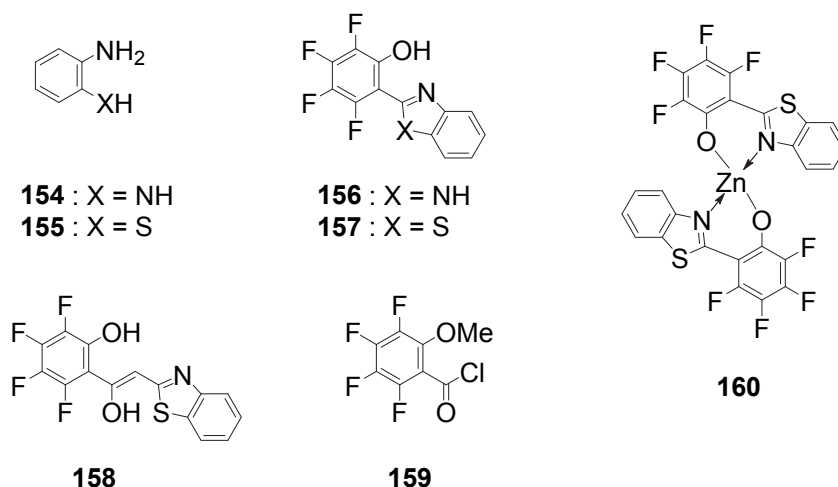
Scheme 22



For **151** - **153** : R = Me, *t*-Bu, Ph, 4-X-C₆H₄,
X = Me, MeO, Cl, Br

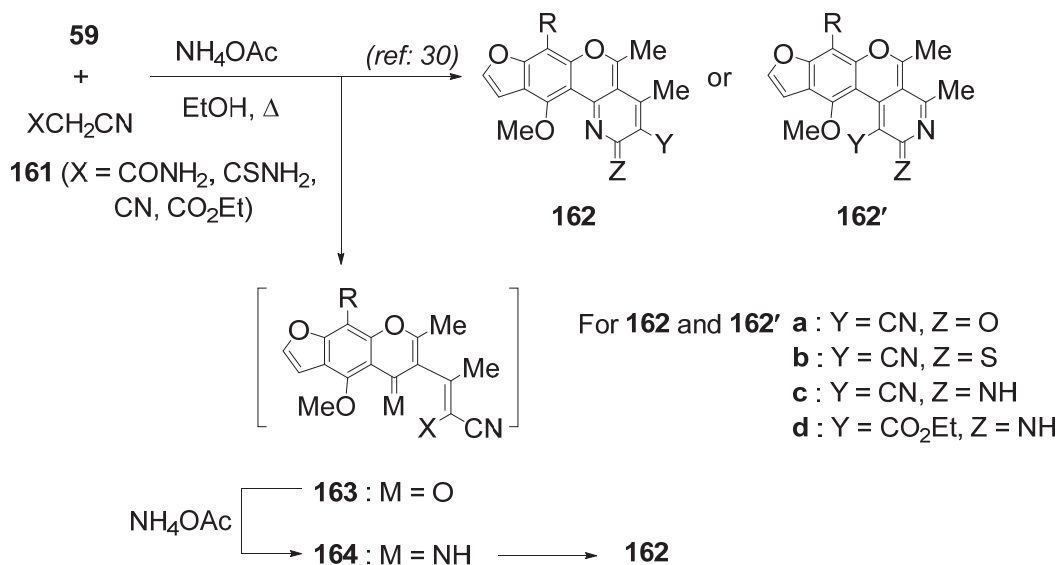
Scheme 23

4.2.3. Dinucleophiles with two nucleophilic centres separated by two carbons. No plausible mechanism has been suggested for the formation of the benzimidazole **156**⁸⁵ and benzothiazole **157**^{84,85} by treating the tetrafluorinated ester **118a** respectively with *o*-phenylenediamine **154** and 2-aminothiophenol **155** in boiling ethanol. Later Li *et al.*⁸⁶ reported that the product **157**, if prepared from **118a** and **155**, remains admixed with the benzothiazole **158**; it can be had exclusively by treating the acid chloride **159** with the thiophenol **155** in *N*-methyl-2-pyrrolidone at 100 °C. A mixture of Zn(OAc)₂ and potassium salt of thiazole **157** in a molar ratio of 1:2 in MeOH-H₂O forms the four coordinated Zn(II) complex **160**.⁸⁶



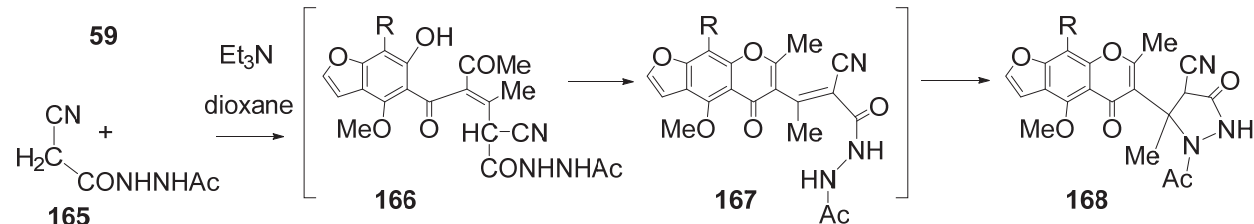
4.3. Addition of carbon nucleophiles

Miky and Sharaf³⁰ have reported, without giving any mechanistic interpretation, the reaction of 6-acetyl-visnagin and -khellin **59** separately with cyanoacetamide, α -cyanothioacetamide, malononitrile and ethyl cyanoacetate in the presence of NH₄OAc, yielding respectively the tetracyclic compounds **162a-d** or their isomers **162'a-d**. The formation of **162** is conceptualized by a domino base catalyzed conjugate addition of the active methylene compound **161** to **59** – pyran ring opening – recyclization (to **163**) – amination (to **164**) – cyclization sequence (Scheme 24). The formation of **162'**, necessitating a highly unlikely 1,2-addition of **161** to a very poor electrophilic centre C-5 of **59** is, therefore, ruled out.



Scheme 24

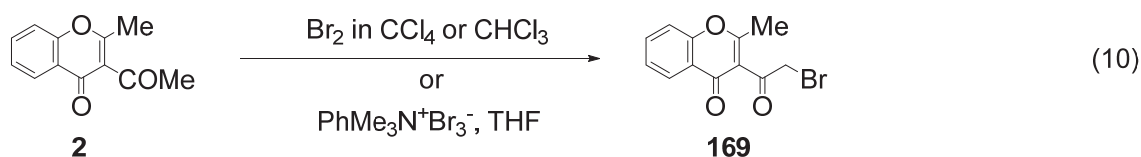
6-Acetylfurochromone **59** reacts with *N'*-acetyl-2-cyanoacetohydrazide **165** in dioxane containing triethylamine to afford the hetarylpyrazolidinone **168** via the intermediates **166** and **167** (Scheme 25).⁷⁵



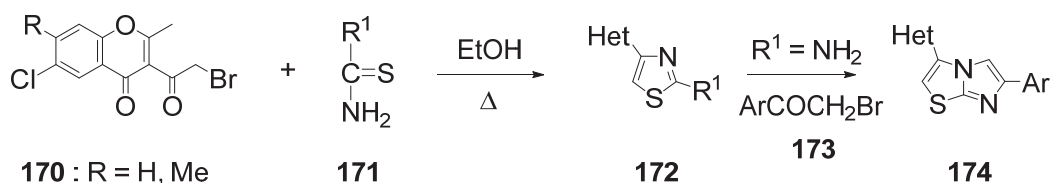
Scheme 25

5. Bromination of 3-Acyl-2-methylchromones **2** and **3**, and Reactions of the Resultant Bromo Derivatives

3-Acetyl-2-methylchromone **2** and its analogues on bromination with bromine^{30,87-90} as well as with phenyltrimethylammonium tribromide⁹¹ give the corresponding 3-bromoacetylchromones (Equation 10), the latter reagent being claimed to improve the yield.



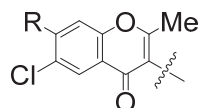
The chromone **170** involves only its bromoacetyl moiety, very rarely the pyran ring, in its reaction with thiourea as well as thio-acid amide **171** to give the benzopyran-3-ylthiazole **172**.⁸⁷ The thiazole **172** ($R^1 = NH_2$) condenses with aryl bromomethyl ketone **173** giving imidazolothiazole **174** (Scheme 26).⁸⁸



For **171** and **172**: $R^1 = NH_2, Ph, NHPH, 4-X-C_6H_4$; X = Me, Cl, NO_2

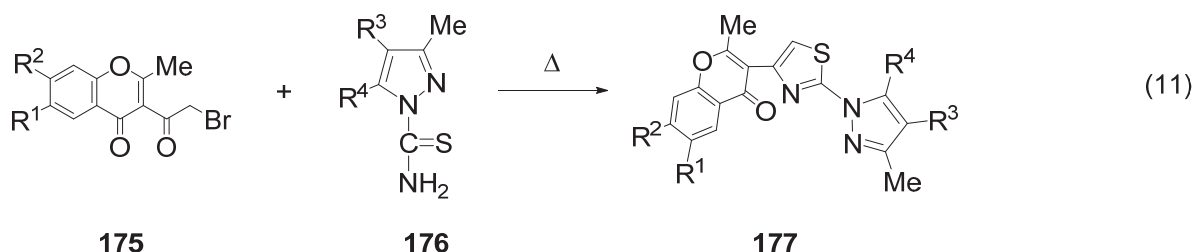
For **173** and **174**: Ar = Ph, $4-X-C_6H_4$; X = Me, Cl, NO_2

For **172** and **174**: Het =



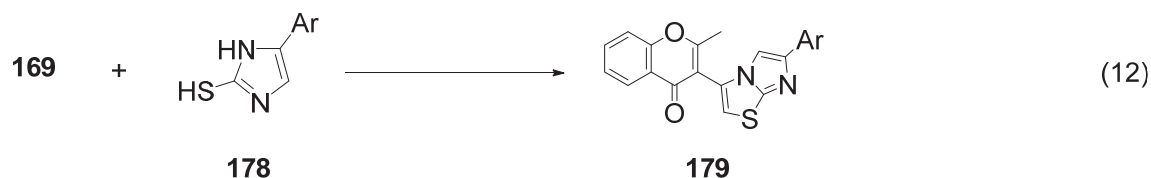
Scheme 26

The reaction between the chromone **175** and pyrazole-1-thiocarboxamide **176** leads to the product **177** incorporating three different heterocyclic systems (Equation 11).⁸⁹

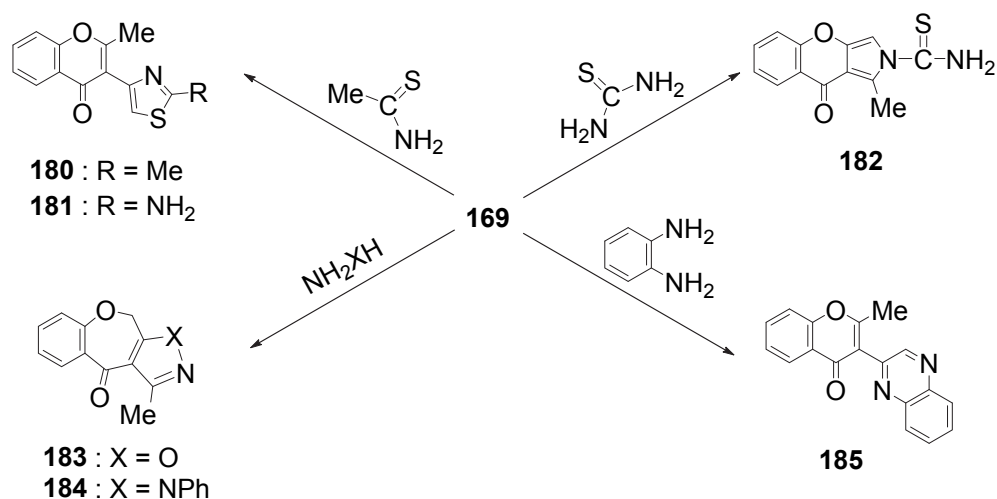


For **175** - **177**: $R^1 = H, Me, Cl$; $R^2 = H, Me$; $R^3 = H, Me, Et$; $R^4 = Me, 2\text{-thienyl}, 3\text{-furyl}$

The thiourea skeleton incorporated within the imidazole-2-thiol **178** condenses with the bromoacetyl moiety of **169** giving the imidazolothiazole **179** (Equation 12).⁹⁰ Bromine function of 7-fluoro-3-bromoacetyl-2-methylchromone can be substituted by primary and secondary alkyl or aryl amines.⁹¹

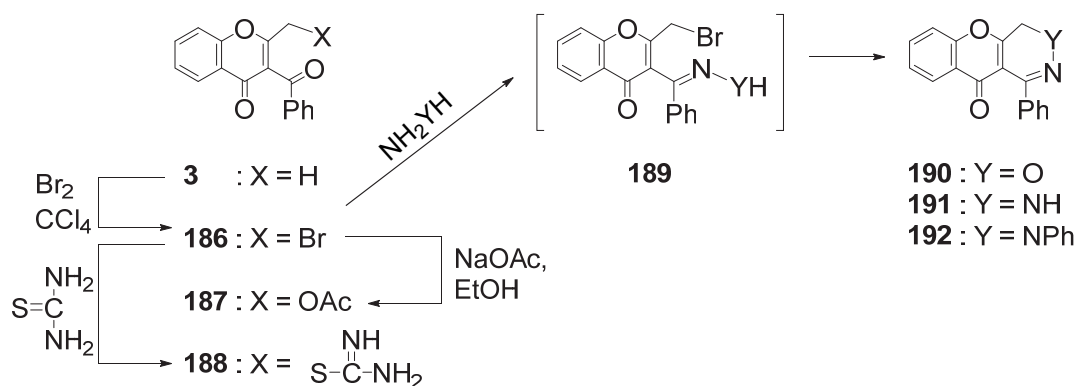


Ghosh *et al.*⁹² have studied the reactions of 3-bromoacetyl-2-methylchromone **169** with some dinucleophiles (Scheme 27). The chromone **169** with thioacetamide gives the expected thiazole **180**. In contrast, thiourea with **169** in refluxing ethanol containing AcONa gives the pyrrolobenzopyran **182** without any trace of **181**. The chromone **169** produces [1]benzoxepino-[4,3-*d*]isoxazole **183**, [1]benzoxepino[3,4-*c*]pyrazole **184** and quinoxaline **185** with hydroxylamine, phenylhydrazine and *o*-phenylenediamine, respectively.



Scheme 27

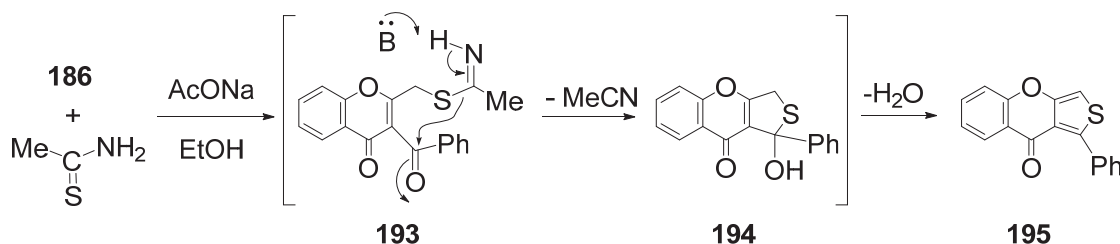
3-Benzoyl-2-methylchromone **3** is brominated by bromine to the 2-bromomethylchromone **186**; it can be transformed into **187** by treatment with AcONa in refluxing ethanol.⁹³ The chromone **186** gives *via* the intermediate **189** the pyrano-fused oxazine **190** with hydroxylamine, pyridazines **191** and **192** respectively with hydrazine and phenylhydrazine (Scheme 28).⁹³



Scheme 28

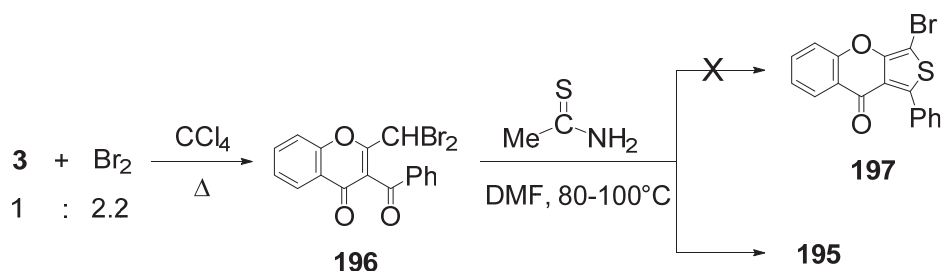
Thiourea brings about substitution reaction in **186** giving **188** (Scheme 28) that survives heating under reflux even in a high boiling solvent such as ethylene glycol. In contrast, a mixture

of **186** and thioacetamide on being heated under reflux in ethanol containing AcONa produces the thieno[3,4-*b*][1]benzopyranone **195**. Here the intermediate **193**, initially resulting from substitution of bromine by thioacetamide, undergoes base catalyzed acetonitrile eliminative cyclization (to **194**) and subsequent water elimination to **195** (Scheme 29).⁹³



Scheme 29

A Russian group⁹⁴ has treated the chromone **3** with 2.2 equivalents of bromine to obtain 3-benzoyl-2-(dibromomethyl)chromone **196** that condenses with thioacetamide to give the thienochromone **195**, instead of the normally expected bromothiophene **197** (Scheme 30); the formation of **195** is not rationalized.



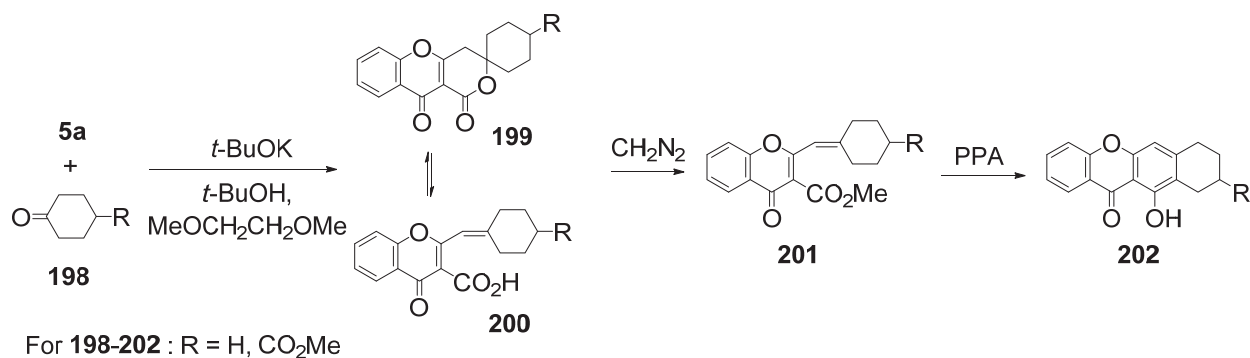
Scheme 30

6. Benzopyrans 1-5 as Nucleophiles

The 2-methyl group of the chromones **1-5**, being vinylogous to two carbonyl groups, functions as a nucleophilic centre even under weakly basic conditions so as to undergo addition to various electrophilic compounds as described in the following subsections.

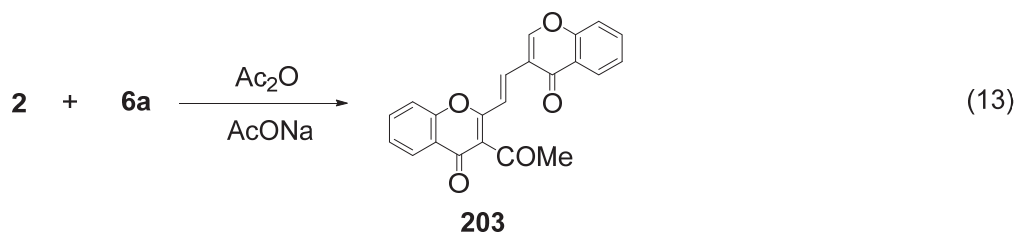
6.1. Addition to the carbonyl compounds

The ester **5a** condenses with cyclohexanone **198** in the presence of *t*-butoxide in butanol/dimethoxyethane giving the spiro lactone **199**; it in polar media exists in equilibrium with the acid **200** so that its treatment with diazomethane in diethyl ether leads to the cyclohexylidene ester **201** cyclizable by polyphosphoric acid to the tetrahydrobenzoxanthone **202** (Scheme 31).⁹⁵



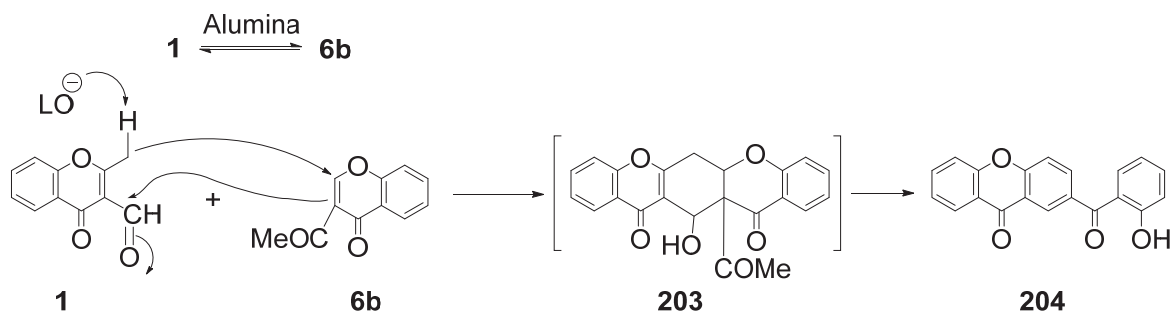
Scheme 31

3-Formylchromone **6a** functions as an aromatic aldehyde to condense with 3-acetyl-2-methylchromone **2** in Ac₂O-AcONa giving the 2-ethenylchromone **203** (Equation 13).³⁵ This mode of addition differs from the one described in the following subsection.



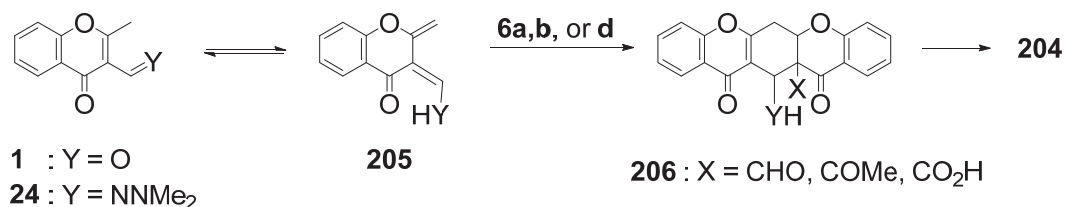
6.2. Addition to unsaturated carbonyl compounds

3-Acetylchromone **6b** dissolved in ethanol or dioxane on treatment with triethylamine or pyridine at room temperature or by percolation through Brockmann neutral alumina affords, without acid treatment, the xanthone **204**. Here **6b** undergoes acyl-acyl rearrangement under base catalysis to **1** and condensation between these two chromone derivatives leads to the xanthone **204**.¹⁴ Again the aldehyde **1** on treatment with alumina also affords the xanthone **204**.⁹⁶ The formation of **204** may be rationalized in the following way. Alumina (alumina lattice oxide anion, represented by LO⁻) catalyzed isomerization of **1** to **6b** and a subsequent Michael initiated ring closure between **1** and **6b** leads to the intermediate **203** that on base catalyzed deacylative hydroxy elimination and pyran ring opening (or deacylative pyran ring opening and water elimination) gives **204** (Scheme 32).⁹⁶



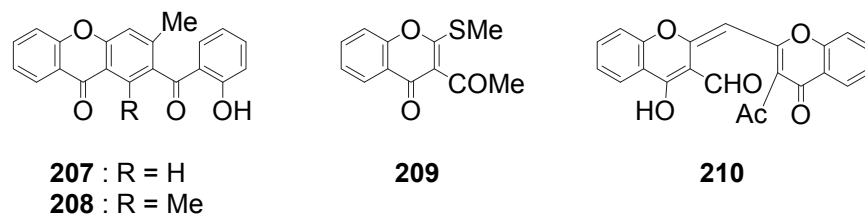
Scheme 32

Interestingly, when a mixture of the aldehyde **1** or the corresponding hydrazone **24** and any of the chromones **6a,b,d** is heated in dioxane in the absence of any catalyst, the xanthone **204** also results. Here **1** as well as **24** tautomerizes to **205** that having an *o*-quinodimethane structure undergoes a facile Diels-Alder reaction with the pyranodienophiles; the resultant adduct **206** gives **204** by an elimination process (Scheme 33).¹⁴



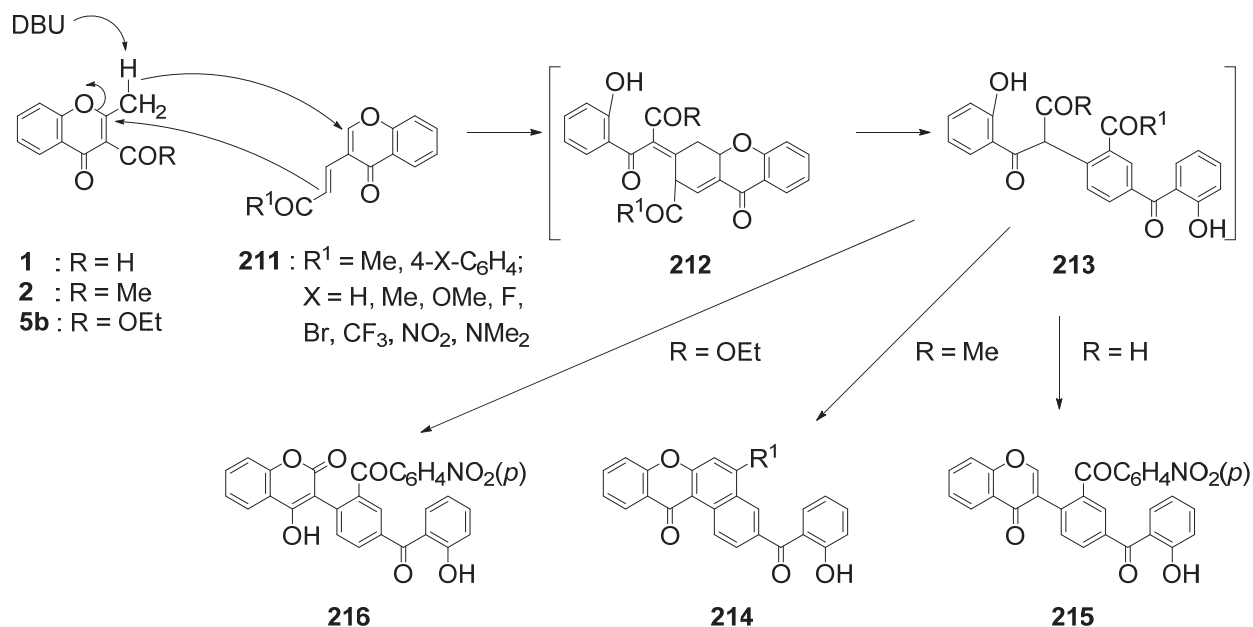
Scheme 33

Pyridine-piperidine, unlike alumina, brings about self-condensation of the aldehyde **1** to the xanthone **207** and pulverized sodium converts the ketone **2** into xanthone **208**.⁹⁷ The 2-methylchromone **2** in the presence of NaOMe undergoes Michael addition to 3-acetyl-2-(methylthio)chromone **209** followed by expulsion of thiomethanol to give the 2-(1-benzopyran-2-yl)methylene-1-benzopyran **210**; the later is accompanied by a small amount of 3-acetyl-4-hydroxycoumarin formed by base catalyzed hydrolysis of the unreacted chromone **209**.⁹⁷



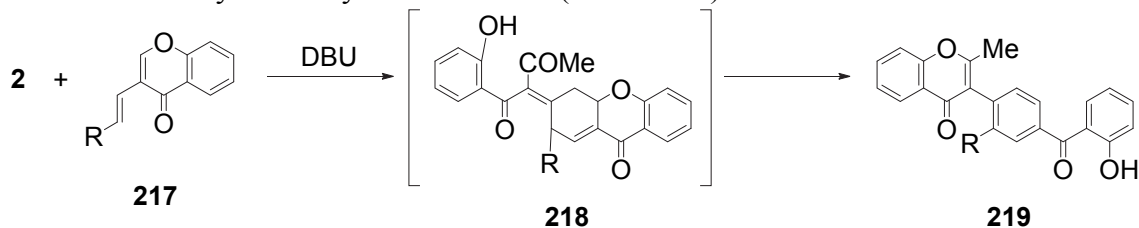
Gong *et al.*⁹⁸ have studied the DBU-catalyzed reactions of the aldehyde **1**, ketone **2** and ester **5b** with 3-(2-acylethenyl)chromone **211**. The carbanion generated from the 2-methyl group

of aforesaid chromone substrates undergoes under DBU catalysis domino 1,6-addition to the $\alpha,\beta,\gamma,\delta$ -unsaturated ketone functionality of **211** – intramolecular Michael addition to the 2-methylchromone moiety – pyran ring opening to give the intermediate **212**; the new six membered ring in **212** formed due to this [4+2]cyclization aromatizes to **213** by pyran ring opening and a 1,3-H shift. The intermediate **213** (R = Me) arising from **2** and **211** cyclizes to the xanthone **214**, that (**213**, R = H) from **1** and **211** ($R^1 = 4\text{-O}_2\text{N-C}_6\text{H}_4$) cyclizes to **215**, and the ketone-ester **213** (R = OEt; $R^1 = 4\text{-O}_2\text{N-C}_6\text{H}_4$) yields the 3-aryl-4-hydroxycoumarin **216** (Scheme 34).



Scheme 34

3-Alkenylchromone **217** behaves similarly to **211** towards 3-acetyl-2-methylchromone **2**, to give via **218** the 3-aryl-2-methylchromone **219** (Scheme 35).⁹⁸

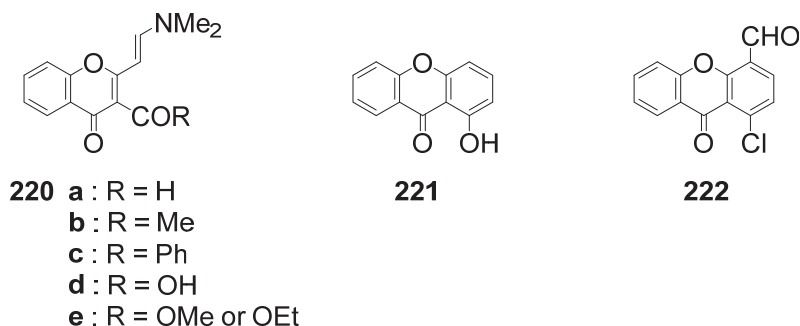


For **217-219** : R = CO₂Et, CN, Ph, 4-MeOC₆H₄, 4-O₂NC₆H₄

Scheme 35

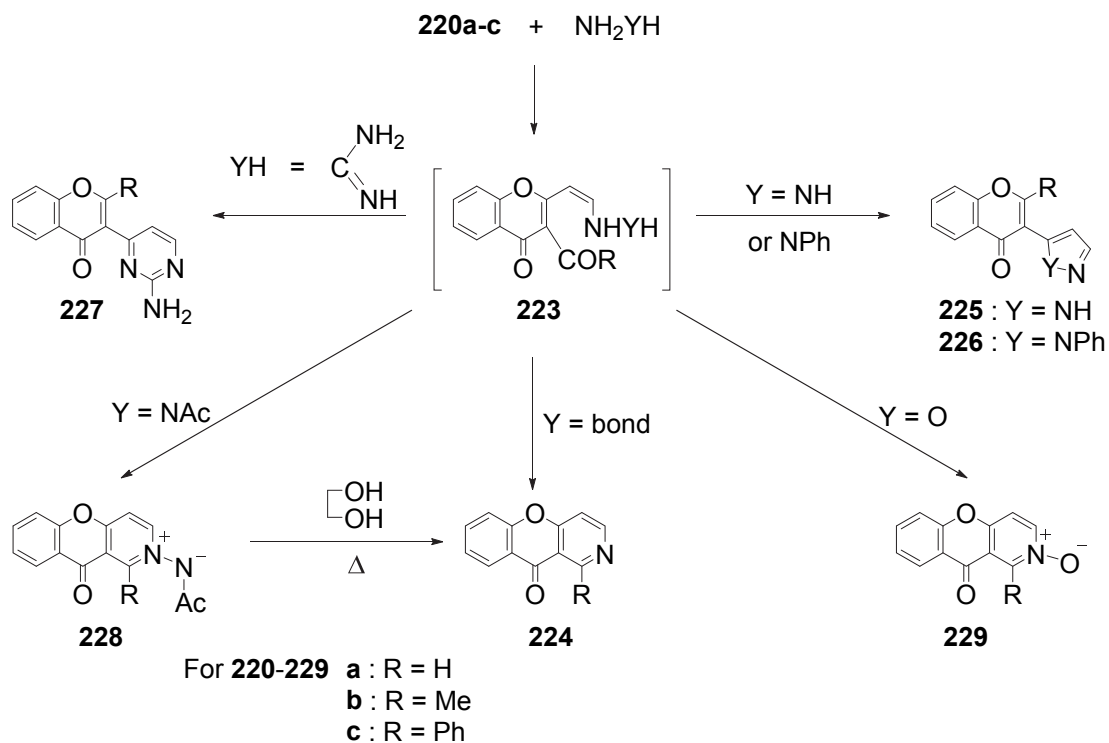
7. Aminomethylation of 2-Methylchromones 1 -5: Reactions of 2-(2-Dimethylaminoethenyl)chromones

Methylenation of 2-methylchromones **1-5** by *N,N*-dimethylformamide dimethyl acetal leads to the corresponding *trans*-enamines **220a-e**, respectively,^{97,99-101} the *cisoid* or *transoid* conformation of its diene system not being established. The chromone **220b** on being heated in DMF or with NaOMe in MeOH undergoes [6+0] cyclization with expulsion of the NHMe₂ giving 1-hydroxyxanthone **221**.¹⁰¹ DMF-POCl₃ converts **220b** into 1-chloro-4-formylxanthone **222**.⁹⁷

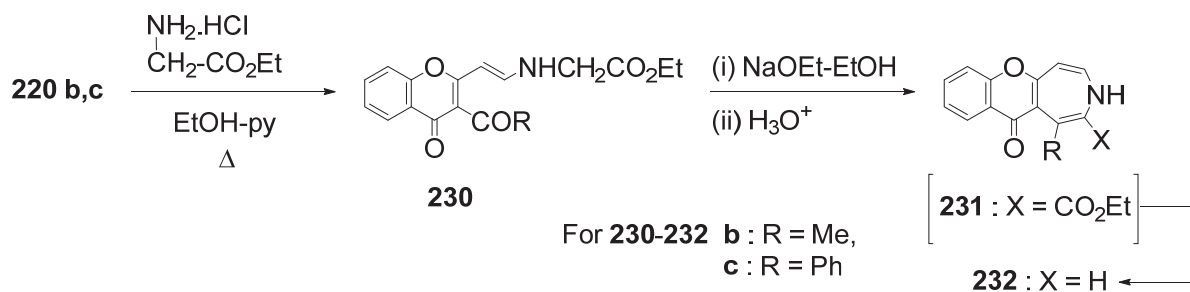


A nitrogen nucleophile of the general formula NH₂YH brings about transamination of the enamine **220** *via* a 1,6-addition — elimination sequence and the resultant enamine, due to prototropy, assumes a stereochemical configuration (*cisoid* diene with *cis* geometry around the exocyclic olefinic bond) as shown in the intermediate chromone **223**; the latter takes different reaction courses depending on the nature of its NHYH group. Thus, the enamine **220** (R = H, Me, Ph) gives the fused pyridine **224** with ammonia *via* the intermediate **223** (Y = bond). The compound **220a** gives intractable tar with hydrazine whereas the other two members **220b,c** give the pyrazoles **225** and **226** respectively with hydrazine and phenylhydrazine *via* **223** (Y = NH, NPh). Guanidine, acetylhydrazide and hydroxylamine convert **220** into the pyrimidine **227**, pyridine *N*-acetylimide **228** and pyridine *N*-oxide **229** *via* the corresponding intermediate **223**, respectively. The compound **228** on being refluxed in ethylene glycol thermolyses to the pyridine **224** (Scheme 36).⁹⁹

When refluxed with glycine ester hydrochloride in ethanol-pyridine, the enamines **220b** and **220c** give the enamino esters **230b** and **230c**, respectively. The substituted glycine ester **230** on being refluxed in ethanol-sodium ethoxide followed by acid treatment gives the azepine **232**, presumably by hydrolysis and subsequent decarboxylation of the [7+0] cyclization product **231** of **230** (Scheme 37).⁹⁹

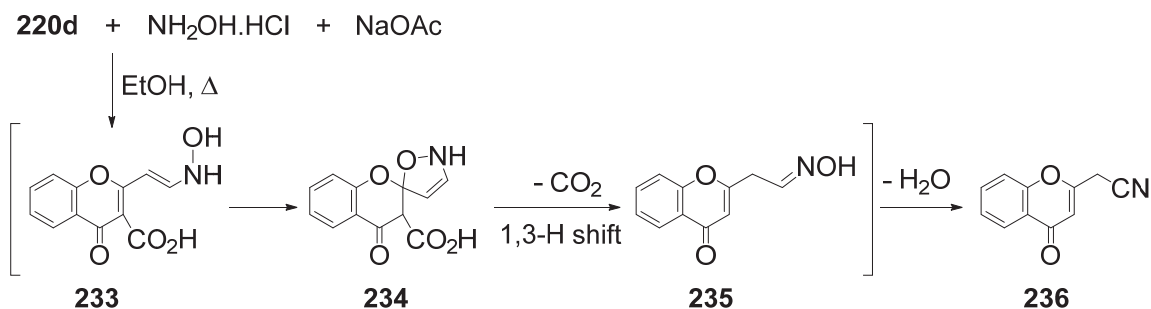


Scheme 36



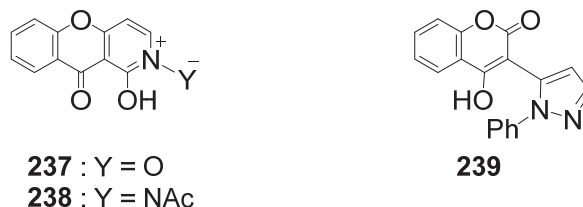
Scheme 37

A mixture of the enamino-acid **220d**, NH₂OH.HCl and NaOAc in refluxing ethanol affords chromone-2-acetonitrile **236** by a mechanism as shown in Scheme 38. The intermediate **223** resulting from transamination of **220d** by NH₂OH undergoes intramolecular 1,4-addition; the resultant spiro-compound **234** by decarboxylative isoxazoline ring opening followed by a 1,3-hydrogen shift gives the oxime **235** that is dehydrated under reaction conditions to the nitrile **236**.¹⁰⁰



Scheme 38

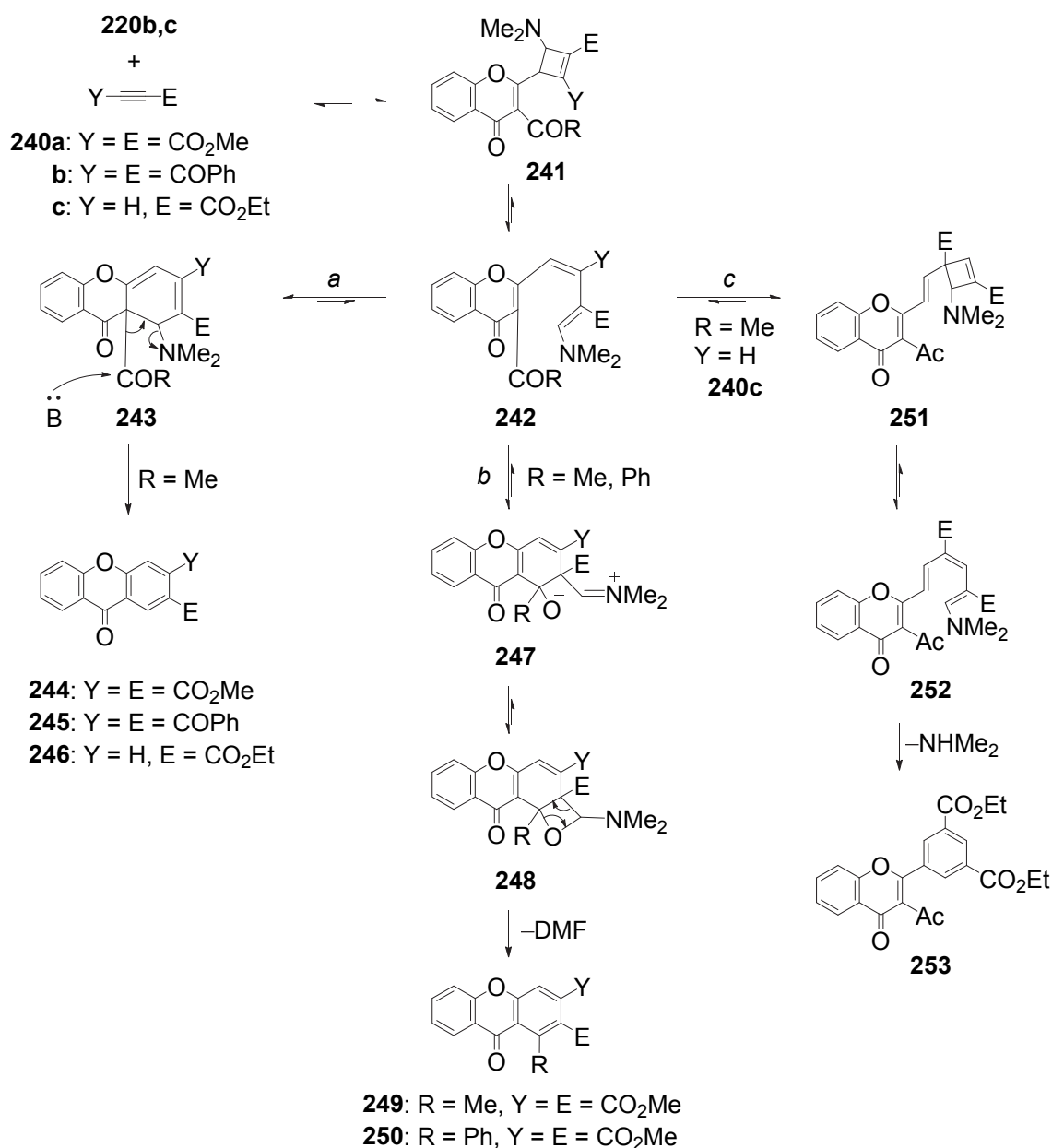
The ester **220e** (R = OMe) gives 1-benzopyranopyridine *N*-oxide **237** with hydroxylamine, benzopyranopyridine *N*-acetylimide **238** with acetylhydrazide and coumarin-3-ylpyrazole **239** with phenylhydrazine.¹⁰⁰



The dienaminoketone **220b** when heated with DMAD (**240a**) in DMF gives a mixture of the xanthone dicarboxylates **244** and **249** admixed with a small amount (~5%) of 1-hydroxyxanthone **221** whereas **220c** under similar conditions gives exclusively the xanthone **250**. Here the diene **220** behaves as an unconjugated enamine in undergoing [2+2] cycloaddition with the electron deficient acetylene **240** to give the adduct **241** (Scheme 39).¹⁰¹ The cyclobutene moiety in **241** having both an electron acceptor and an electron donor substituents in appropriate disposition undergoes symmetry allowed ring opening to **242** that takes different reaction courses dependent on the nature of its R, Y and E groups. Electrocyclization of **242** (R = Me, Y = E = CO₂Me) to **243** followed by base catalyzed deacylative deamination gives the xanthone **244**, **243** itself functioning as the base (path *a*). The zwitterion **247** formed from **242** (R = Me, Y = E = CO₂Me) by intramolecular 1,2-addition of enamine to the carbonyl group cyclizes to the oxetane **248** that undergoes thermal cycloreversion to the xanthone **249** (path *b*). In the reaction of **220c** with **240a**, the base catalyzed debenzoylation of the intermediate **243** (R = Ph, Y = E = CO₂Me) is not possible. So the intermediate **242** (R = Ph, Y = E = CO₂Me) follows the reaction path *b* to give the xanthone **250**.

The dienaminoketone **220b** is converted into **245** by dibenzoylacetone (**240b**), and a mixture of xanthone **246** and flavone **253** by ethyl propiolate (**240c**). The former two products (**245** and **246**) arise through the intermediates **243** (R = Me, Y = E = C(=O)Ph) and **243** (R = Me, Y = H, E = CO₂Et) (path *a*), respectively. The enamine **242** (R = Me, Y = H, E = CO₂Et) arising from **220b** and **240c** undergoes [2+2]cycloaddition with a second molecule of ethyl propiolate,

the resultant cyclobutene intermediate **251** by ring opening (to **252**) and recyclization giving the flavone **253** (path *c*).

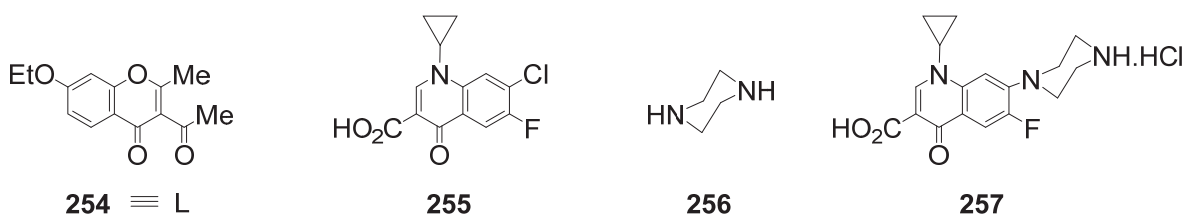


Scheme 39

8. 3-Acetyl-2-methylchromone as a Ligand in Mixed Ligand Metal Complexes

An Indian group¹⁰²⁻¹⁰⁴ have prepared novel six coordinated dimeric Fe(III) as well as five coordinated dimeric Fe(II) and Cu(II) complexes with 3-acetyl-7-ethoxy-2-methylchromone **254** as one ligand (L) along with two other ligands, namely 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **255** and piperazine **256** (abbreviated respectively as cip

and pip); the last named two ligands are obtained by splitting ciprofloxacin hydrochloride (cpf.HCl) **257** with alkali. This ligand mixture gives $[\text{Fe}_2\text{L}_2(\text{cip})_2(\text{OH})_2(\text{pip})]\cdot 5\text{H}_2\text{O}$ with ferric nitrate in the presence of alkali,¹⁰² $[\text{Fe}_2\text{L}_2(\text{cip})_2(\text{pip})]\cdot 5\text{H}_2\text{O}$ with ferrous sulfate¹⁰³ and $[\text{Cu}_2\text{L}_2(\text{cip})_2(\text{pip})]\cdot 5\text{H}_2\text{O}$ with cupric nitrate¹⁰⁴ having respectively the octahedral, distorted square pyramidal and square pyramidal geometry. Each metal in these complexes is coordinated to the deprotonated carboxylate oxygen and pyridine oxygen of cip, two carbonyl oxygens of chromone ligand L and one nitrogen of piperazine. Piperazine by coordination through its second nitrogen to the other metallic centre tethers two metal centres in the said dimeric complexes. The ferric ion in Fe(III) complex is additionally bonded to one hydroxyl anion. DNA binding activity as well as biological activities against several gram-positive and gram-negative bacterial cultures of the metal complexes have been assessed.



9. Conclusions

Syntheses of all the members **1-5** belonging to the title chromone family and their various reactions as electrophilic as well as nucleophilic substrates studied during the last thirtyfive years have been comprehended.

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