Chemistry of 3-carbonyl-2-methyl-4-oxo-4H-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

Table of Contents
1. Introduction
2. Synthesis
   2.1 Synthesis of 3-formyl-2-methylchromone 1
   2.2 Synthesis of 3-acetyl-2-methylchromone 2
   2.3 Synthesis of 3-benzoyl-2-methylchromone 3
   2.4 Synthesis of 3-hydroxycarbonyl- and 3-alkoxycarbonyl-2-methylchromone 4 and 5
3. Conjugate Addition to the Pyran 2,3-Olefinic Bond of Chromones without Pyran Ring Opening
   3.1 Conjugate reduction
   3.2 Conjugate addition of alkyl and alkoxy groups
4. Conjugate Addition with Other Concomitant Reactions
   4.1 Addition of ammonia and amines
   4.2 Addition of nitrogenous dinucleophiles
      4.2.1 Dinucleophiles having adjacent nucleophilic centres
      4.2.2 Dinucleophiles with two nucleophilic centres separated by one carbon
      4.2.3 Dinucleophiles with two nucleophilic centres separated by two carbons
4.3 Addition of carbon nucleophiles
5. Bromination of 3-Acyl-2-methylchromones 2 and 3, and Reactions of the Resultant Bromo Derivatives
6. Benzopyrans 1-5 as Nucleophiles
   6.1 Addition to carbonyl compounds
   6.2 Addition to unsaturated carbonyl compounds
7. Aminomethylenation of 2-Methylchromones 1-5: Reactions of 2-(2-Dimethylamino-ethenyl)chromones
8. 3-Acetyl-2-methylchromone as a Ligand in Mixed Ligand Metal Complexes
9. Conclusion

References

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, two on the nitrile 7a,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. 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). 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.

![Scheme 1](image)

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

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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](image)

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 \([\text{Ph}_3\text{C}]\text{[BF}_4\text{]}\) 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](image)

Scheme 3. Reagents and conditions: (i) \(\text{HOCH}_2\text{CH}_2\text{OH}, \text{PhH}, \text{PTSA}, \Delta\); (ii) \(\text{CH}_2\text{N}_2, \text{CH}_2\text{Cl}_2\); (iii) \(\text{PhMe}, \Delta\); (iv) \(\Delta\); (v) \(\text{H}_2\text{O}, \text{H}^+, \text{warm}\).
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-f18 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.\textsuperscript{20} With Ac\textsubscript{2}O-AcONa, the benzopyran 33 gives 35,\textsuperscript{21} and 34 a mixture of 36 and 37.\textsuperscript{22}

\begin{center}
\begin{tikzpicture}
\node at (0.0,0.0) {\includegraphics[width=0.9\textwidth]{structure.png}};
\end{tikzpicture}
\end{center}

Ghate and Kulkarni\textsuperscript{23} prepared the furo[3,2-\textit{g}]benzopyran 41 containing a coumarin moiety at its 2-position by Ac\textsubscript{2}O-AcONa treatment of 40, derived from coumarin 38 and diacetylresorcinol 39 (Scheme 6) and assessed its anti-inflammatory and analgesic activity.

\begin{center}
\begin{tikzpicture}
\node at (0.0,0.0) {\includegraphics[width=0.9\textwidth]{scheme6.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 6}

Conversion of the acetophenone 42 to 2-acetylchromone 43 by treatment with either Ac\textsubscript{2}O-AcONa as stated in the chemistry as well as experimental section or AcOH-AcONa as (perhaps erroneously) printed in the reaction scheme of a publication\textsuperscript{24} is unlikely; the substrate 42 in Ac\textsubscript{2}O-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

\[
\begin{align*}
\text{AcO} & \quad \text{OH} \\
\text{COMe} & \quad \text{AcO} \\
\text{45} & \quad \text{NaNH}_2 \\
\rightarrow & \quad \text{AcO} \quad \text{Me} \quad \text{Me} \quad \text{OH} \quad \text{COMe} \\
\text{46} & \quad \text{47}
\end{align*}
\]  

(Equation 1)

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).

\[
\begin{align*}
\text{MeS} & \quad \text{OH} \\
& \quad \text{(i) TiCl}_4, \text{rt} \\
& \quad \text{(ii) AcCl, \text{rt to 120°C}} \\
\text{48} & \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \\
\rightarrow & \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \\
\text{49} & \quad \text{50a: R}^1 = \text{Ac}, \text{R}^2 = \text{H} \\
& \quad \text{b: R}^1 = \text{R}^2 = \text{Ac} \\
& \quad \text{(2)}
\end{align*}
\]

\[
\begin{align*}
\text{MeS} & \quad \text{OH} \\
& \quad \text{(i) TiCl}_4, \text{rt} \\
& \quad \text{(ii) AcOH, \text{rt to 120°C}} \\
\text{52} & \quad \text{Cl} \quad \text{Me} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \\
\rightarrow & \quad \text{Cl} \quad \text{Me} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \quad \text{MeS} \\
\text{53} (60\%) & \quad \text{54 (6\%)} \\
& \quad \text{Cl} \quad \text{Me} \quad \text{Cl} \quad \text{Me} \quad \text{Cl} \quad \text{Me} \quad \text{Cl} \quad \text{Me} \\
& \quad \text{(3)}
\end{align*}
\]

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

\[
\begin{align*}
\text{AcO} & \quad \text{OAc} \\
\text{56} & \quad \text{Fe-Sp} \quad \text{80°C} \\
\rightarrow & \quad \text{AcO} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\text{57 (8\%)} & \quad \text{2 (2\%)} \\
& \quad \text{57 (8\%)} \\
& \quad \text{2 (2\%)} \\
& \quad \text{8 (10\%)} \\
\end{align*}
\]  

(Equation 4)
Acetylation at the 3-position of 2-methylchromone 8 is also known. As for example, equimolar amounts of 8 and Ac<sub>2</sub>O over a HBEA zeolite (Si/Al = 10) in a batch reactor or a fixed bed reactor at 60°C gives chromone 2. Acetylation of visnagin 58a and khellin 58b by Ac<sub>2</sub>O-Zn dust to the respective 6-acetyl derivative 59a and 59b has also been achieved. Diazomethane at −70 °C effects dual alkylation of 3-formyl-6-methylchromone yielding 3-acetyl-2,6-dimethylchromone, 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%).

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 schumanniophytine and isoschumanniophytine, has been prepared by Na₂CO₃-H₂O treatment of the 3-acetylchromone 60, obtainable from phloracetophenone 29b and Ac₂O-AcONa. 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.).

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, 3,6-diacyl-5-hydroxyindole and benzofuran 15b have been converted into the corresponding 3-benzoylchromones. Ac₂O-DMSO and Ac₂O in DMAP/pyridine, instead of Ac₂O-AcONa, have also been used for the conversion of many 2'-hydroxy-o-benzoylacetophenones 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.\textsuperscript{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-H\textsubscript{2}O (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.\textsuperscript{32}

\[
\text{LDA in hexane} \quad + \quad \text{PhCO}_2\text{Et} \quad + \quad \begin{array}{c}
\begin{array}{c}
\text{PhCO}_2\text{Me} \\
\text{Me}
\end{array}
\end{array} \quad \rightarrow \quad \begin{array}{c}
\begin{array}{c}
\text{PhCO}_2\text{Ph} \\
\text{Me}
\end{array}
\end{array}
\quad \text{(5)}
\]

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% NaOH\textsuperscript{43} as well as its morpholino-enamine\textsuperscript{44} 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 Ph\textsubscript{3}P=CHCO\textsubscript{2}Me, gives the ester 5a in 55% yield (Equation 6).\textsuperscript{45}

\[
\begin{array}{c}
\begin{array}{c}
\text{OCOCH}_3 \\
\text{Ph}\text{Ph}_3
\end{array}
\end{array} \quad \Delta \quad \begin{array}{c}
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{Ph}\text{Ph}_3
\end{array}
\end{array} \quad \quad \quad \quad \begin{array}{c}
\begin{array}{c}
\text{OCOCH}_3 \\
\text{Ph}\text{Ph}_3
\end{array}
\end{array} \quad \quad \quad \quad \begin{array}{c}
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{Ph}\text{Ph}_3
\end{array}
\end{array}
\quad \text{(6)}
\]

Kim\textsuperscript{46} has converted the 2-arylquinol 66 into the benzopyran 68 via 67 (Scheme 8).

\begin{align*}
\text{Scheme 8} & \\
\text{The intermediate } & \beta,\beta'-\text{diketoester 70, resulting from 2-fluorobenzoyl chloride 69 and methyl acetoacetate in the presence of sodium hydride, undergoes cyclization via ipso-fluorine}
\end{align*}
substitution to give the ester 5a. When the acid chloride 69 is similarly reacted with t-buty lacetoacetate and the reaction mixture treated with HClO₄, the acid 4 results (Scheme 9).⁴⁷

![Scheme 9](image)

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.

![Formulas 71a, 72, 73](image)

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](image)

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

The 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 NaBH₄ 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
3.2. Conjugate addition of alkyl and alkoxy groups

Lithium dimethylcuprate in THF at -10°C transforms 3-acyl- and 3-carbomethoxy-chromone \( \text{2} \) and \( \text{5a} \) to the corresponding 2,2-dimethylchromanone derivatives \( \text{87} \) (\( R = \text{Me or OMe}; \ R^1 = \text{Me} \)).\(^\text{11,57,58} \) Clarke et al.\(^\text{11} \) have treated the ester \( \text{5a} \) with lithium \( n \)-butylcuprate to get the chromanone \( \text{88} \), assumed to have the larger \( n \)-butyl and ester substituents in trans-diequatorial orientation. The compound \( \text{87} \) (\( R = \text{OMe}; \ R^1 = \text{Me} \)) on treatment with NaCl in DMSO at 155 °C gives 2,2-dimethylchromanone \( \text{89} \), the latter being also provided by treating 2-methylchromone with methylcopper-BF\(_3\) complex.\(^\text{11} \)

Crombie et al.\(^\text{59,60} \) 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 \( \text{92} \), derived from the alkyl iodide \( \text{90} \), lithium cuprate \( \text{91} \) and \( t \)-butyllithium, was added the ester \( \text{5a} \) to obtain the chromanone \( \text{93} \) as a mixture of four stereoisomers. Treatment of this mixture with Mn(OAc)\(_3\)-HOAc affords the hemiacetal \( \text{94} \) in 30% yield (Scheme 13). In another approach the 2-alkyl ester \( \text{96} \) prepared from 2-fluorobenzoyl chloride \( \text{69} \) and the ester \( \text{95} \), is converted into the 2,2-dialkylated chromanone \( \text{97} \) by treatment with Me\(_2\)CuLi. Radical cyclization of \( \text{97} \) as an unresolved stereoisomeric mixture affords the polycyclic lactone \( \text{98} \) in nearly 30% yield (Scheme 14).\(^\text{59,60} \)
A lithium dialkynylcuprate as \( [(TMS-C≡C)\text{CuLi}] \), 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 (≡ 2, 3, 5a) with 2-chloroethanol in the presence of K₂CO₃ to the corresponding furobenzopyranone 101 (Equation 8) proceeds via the conjugate addition of the haloethanol to the chromone followed by intramolecular alkylation. Transformation of the chromone ester 102 on treatment with MeI - K₂CO₃ 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.

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).

Scheme 15
4. Conjugate Addition with Other Concomitant Reactions

4.1. Addition of ammonia and amines

The aza-Michael adduct \( \text{110} \) resulting from tetrafluorobenzopyran-3-carboxylic acid \( \text{109} \) and ammonia undergoes decarboxylative pyran ring opening to give the enaminoketone \( \text{111} \) that on acid treatment affords 2-methylchromone \( \text{112} \) (Scheme 16).\(^6^5\) Piperidine brings about substitution of fluorine at the 7-position of \( \text{109} \) and conjugate addition, the adduct \( \text{113} \) undergoing decarboxylative elimination of the piperidine moiety to give \( \text{114} \) (Scheme 16).\(^6^5\)

![Scheme 16](image)

The ester \( \text{5} \) with the amine \( \text{RNH}_2 \) (\( \text{R} = \text{H, Me, PhCH}_2, \text{CH}_2\text{CH}_2\text{OH} \)) gives the benzopyran-2,4-dione \( \text{115} \), its enol tautomeric form \( \text{116} \) functioning as a ligand to form Pd(II) complex of the general formula \( \text{PdL}_2 \) (\( \text{L} = \text{deprotonated 116} \)).\(^6^6-6^9\) This four co-ordinated Pd(II) complex \( \text{117} \) exists in cis-isomeric form for the ligand \( \text{L} \) (\( \text{R} = \text{H} \)) and trans-form for \( \text{L} \) (\( \text{R} = \text{other than H} \)).\(^6^7,6^8\) Cytotoxic effects of the diones \( \text{115} \) and several of their Pd(II) complexes have been assessed against two leukemia cell lines HL-60 and NALM-6. On treatment with \( \text{RNH}_2 \) (\( \text{R} = \text{H, Me, PhCH}_2, \text{hexyl, cyclohexyl etc.} \)), the fluorinated chromone-3-ester \( \text{118a} \) gives 4-hydroxycoumarin \( \text{119a} \),\(^4^8,5^1,7^0\) \( \text{118b} \) affords \( \text{119b} \),\(^7^1\) \( \text{118c} \) provides \( \text{119c} \)\(^4^9,5^1\) and \( \text{118d} \) the coumarin \( \text{119d} \).\(^7^2\)
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-formyfurochromone 16 and 2-cyanoacetohydrazide 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

\[
\begin{align*}
&\text{O} \quad \text{O} \\
&\text{Me} \\
&\text{16: } R^1 = H \\
&\text{59: } R^1 = \text{Me}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{O} \\
&\text{Me} \\
&\text{127}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{O} \\
&\text{Me} \\
&\text{128: } R^1 = H \\
&\text{129: } R^1 = \text{Me}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{O} \\
&\text{Me} \\
&\text{130: } R^1 = H \\
&\text{131: } R^1 = \text{Me}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{O} \\
&\text{Me} \\
&\text{132: } R^1 = H \\
&\text{133: } R^1 = \text{Me}
\end{align*}
\]

For 16, 59 and 128-133 a: \( R = H \)

b: \( R = \text{OMe} \)

\textbf{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 \( \text{H}_2\text{NNHC} (=X)\text{NH}_2 \) in refluxing methanol gives the tetrasubstituted pyrazole 135.76

\[
\begin{align*}
&\text{134}
\end{align*}
\]

\[
\begin{align*}
&\text{135: } X = \text{O or S}
\end{align*}
\]

Phenylhydrazine undergoes 1,4-addition to the \( \alpha,\beta \)-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 group\(^{77}\) have reported without disclosing the experimental details the formation of 138 in the said reaction, whereas Ghosh and Pal\(^{53}\) obtained exclusively the pyrazole 140 by heating under reflux a mixture of 4 and PhNHNH\(_2\)HCl in ethanol containing sodium acetate. The acid 4 with NH\(_2\)OH follows a reaction course similar to Scheme 20-path b to yield the isoxazole 141.\(^{78}\)

![Scheme 20](image_url)

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)\(_2\)Cl\(_2\) trans-PdL\(_2\)Cl\(_2\) 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 K\(_2\)PtCl\(_4\), K\(_2\)PdCl\(_4\) and CuCl\(_2\) 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 pentacordinated Cu(II) complex 148.\(^{81,82}\) The structures of all these metal complexes have been confirmed by X-ray analysis.
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). In a precisely similar way, the amino group of 5-amino-1H-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). This reaction under microwave irradiation and solvent free conditions gives high yields of the products.
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 and benzothiazole 157 by treating the tetrafluorinated ester 118a respectively with o-phenylenediamine 154 and 2-aminothiophenol 155 in boiling ethanol. Later Li et al. 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 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.

\[
\begin{align*}
\text{NH}_2 & \quad XH \\
154 & : X = \text{NH} \\
155 & : X = \text{S} \\
156 & : X = \text{NH} \\
157 & : X = \text{S} \\
158 & \\
159 & \\
160 & 
\end{align*}
\]

4.3. Addition of carbon nucleophiles
Miky and Sharaf 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 bromine30,87-90 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. The thiazole 172 \( (R^1 = \text{NH}_2) \) condenses with aryl bromomethyl ketone 173 giving imidazolothiazole 174 (Scheme 26).

\[
\begin{align*}
    \text{Cl} \quad \begin{array}{c}
        \text{O} \\
        \text{O} \\
        \text{O} \\
        \text{O}
    \end{array}
    + \\
    \begin{array}{c}
        \text{C=S} \\
        \text{NH}_2
    \end{array}
    \rightarrow \\
    \begin{array}{c}
        \text{Het} \\
        \text{N} \\
        \text{R}^1
    \end{array}
    \rightarrow \\
    \begin{array}{c}
        \text{Het} \\
        \text{N} \\
        \text{Ar}
    \end{array}
\end{align*}
\]

\( 170 : R = \text{H, Me} \)

\( 171 \)

\( 172 \)

\( 173 \)

\( 174 \)

For 171 and 172: \( R^1 = \text{NH}_2, \text{Ph}, \text{NHPh}, 4-X-\text{C}_6\text{H}_4; X = \text{Me, Cl, NO}_2 \)

For 173 and 174: \( \text{Ar} = \text{Ph}, 4-X-\text{C}_6\text{H}_4; X = \text{Me, Cl, NO}_2 \)

For 172 and 174: \( \text{Het} = \begin{array}{c}
        \text{Cl} \\
        \text{O} \\
        \text{O} \\
        \text{O}
    \end{array} \)

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).

\[
\begin{align*}
    \begin{array}{c}
        \text{R}^2 \\
        \text{O} \\
        \text{O} \\
        \text{O} \\
        \text{O}
    \end{array}
    + \\
    \begin{array}{c}
        \text{R}^3 \\
        \text{Me}
    \end{array}
    \rightarrow \\
    \begin{array}{c}
        \text{R}^2 \\
        \text{O} \\
        \text{O} \\
        \text{O} \\
        \text{O}
    \end{array}
    \begin{array}{c}
        \text{N} \\
        \text{R}^1 \\
        \text{Me}
    \end{array}
    \begin{array}{c}
        \text{Me}
    \end{array}
    \begin{array}{c}
        \text{R}^3 \\
        \text{Me}
    \end{array}
    \begin{array}{c}
        \text{R}^4
    \end{array}
\end{align*}
\]

\( 175 \)

\( 176 \)

\( 177 \)

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

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

\[
\begin{align*}
    \begin{array}{c}
        \text{HN} \\
        \text{N} \\
        \text{Ar}
    \end{array}
    + \\
    \begin{array}{c}
        \text{Ar}
    \end{array}
    \rightarrow \\
    \begin{array}{c}
        \text{O} \\
        \text{O} \\
        \text{O} \\
        \text{O}
    \end{array}
    \begin{array}{c}
        \text{N} \\
        \text{Ar}
    \end{array}
\end{align*}
\]

\( 169 \)

\( 178 \)

\( 179 \)

(12)
Ghosh et al.\textsuperscript{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.

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {180: R = Me};
\node (B) at (1,0) {181: R = NH\textsubscript{2}};
\node (C) at (2,0) {169};
\node (D) at (3,0) {182};
\node (E) at (0,-1) {183: X = O};
\node (F) at (1,-1) {184: X = NPh};
\node (G) at (2,-1) {185};
\draw[->] (A) -- (C);
\draw[->] (B) -- (C);
\draw[->] (C) -- (D);
\draw[->] (E) -- (C);
\draw[->] (F) -- (C);
\draw[->] (G) -- (C);
\end{tikzpicture}
\end{center}

\textbf{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.\textsuperscript{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).\textsuperscript{93}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {3: X = H};
\node (B) at (1,0) {186: X = Br};
\node (C) at (2,0) {187: X = OAc};
\node (D) at (3,0) {188: X = S-C-NH\textsubscript{2}};
\node (E) at (4,0) {189};
\node (F) at (5,0) {190: Y = O};
\node (G) at (6,0) {191: Y = NH};
\node (H) at (7,0) {192: Y = NPh};
\draw[->] (A) -- (E);\draw[<->] (B) -- (E);\draw[->] (C) -- (E);\draw[->] (D) -- (E);
\draw[->] (E) -- (F);
\draw[->] (E) -- (G);
\draw[->] (E) -- (H);
\end{tikzpicture}
\end{center}

\textbf{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 \(\text{AcONa}\) 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 group\(^{94}\) 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 spirilactone \(199\); 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). 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
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).\textsuperscript{14}

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.\textsuperscript{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.\textsuperscript{97}

Gong \textit{et al.}\textsuperscript{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 α,β,γ,δ-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 (R1 = 4-N2O-C6H4) cyclizes to 215, and the ketone-ester 213 (R = OEt; R1 = 4-O2N-C6H4) 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

Scheme 35

For 217-219 : R = CO2Et, CN, Ph, 4-MeOC6H4, 4-O2NC6H4
7. Aminomethylenation 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, 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. DMF-POCl₃ converts 220b into 1-chloro-4-formylxanthone 222. 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).

When refluxed with glycine ester hydrochloride in ethanol-pyridine, the enamines 220b and 220c give the enaminoo 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).
Scheme 36

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

Scheme 38

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 dibenzoyleacetone (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 = COPh) 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 group\(^{102-104}\) 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 [Fe₂L₂(cip)₂(OH)₂(pip)].5H₂O with ferric nitrate in the presence of alkali,¹⁰² [Fe₂L₂(cip)₂(pip)].5H₂O with ferrous sulfate¹⁰³ and [Cu₂L₂(cip)₂(pip)].5H₂O 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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