Chemistry and application of 4-oxo-4H-1-benzopyran-3-carboxaldehyde

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Abstract
The publications on the title compound appearing mainly since 2007 to February 2014 are reviewed.

Keywords: 1-Benzopyran-4-one, 4-oxo-4H-1-benzopyran-3-carboxaldehyde, nucleophilic addition, dipolar cycloaddition, cyclization

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1. Introduction

The title aldehyde (trivial name: 3-formylchromone) 1, an intramolecular enol ether of the β-ketoaldehyde 2, possesses an endocyclic olefinic bond, an α,β-unsaturated carbonyl functionality, three electrophilic centres (C-2, aldehydic and ketonic carbons) and it can assume a pyrylium betaine structure in the presence of an appropriate reagent. These unique features make the chromone 1 amenable to various reactions as defunctionalisation, oxidation and reduction, radical and nucleophilic addition, and many types of annulations and cycloaddition reactions. The chemistry of 3-formylchromone has indeed evolved extensively since 1972. One aspect or the other of the compound 1 has been reviewed from time to time. As for example, Gasparova and Lacova1 published in 2005 an overview (with 59 references) of the condensation of 1 with active methylene compounds and a few reactions of the resultant condensates.
Condensation of 1 with only some binucleophiles\textsuperscript{2} covering the literature up to April 2011 and that with a number of carbon and nitrogen nucleophiles\textsuperscript{3} covering the literature up to 2012 have been reviewed and these two reviews contain 132 and 173 references, respectively. Only three reviews, one authored by Sabitha\textsuperscript{4} and the other two by the principal author\textsuperscript{5,6} of the present article, dealing extensively with the general chemistry and application of 3-formylchromone have appeared, the last one covering the literature available through Sci-finder up to December 2006. The present article, primarily designed to complement the earlier one\textsuperscript{6} is a comprehensive survey of the chemistry of 3-formylchromone and utilization of the compounds easily available therefrom for the preparation of different chemical systems, and covers the literature published during January 2007 to February 2014. A few earlier works which either remained unmentioned in the earlier review\textsuperscript{6} or are helpful for a better understanding of the present write-up are also briefly referred to. Patented works and the reactions of 2-substituted 4-oxo-4\textit{H}-1-benzopyran-3-carbaldehyde not directly derived from the 2-unsubstituted analogue 1 are not included, and the biological properties of the reported compounds are least emphasized. The 4-oxo-4\textit{H}-1-benzopyran-3-yl moiety is abbreviated as ‘Chr’ so that the title aldehyde 1 can be represented by ChrCHO. Alkyl, alkoxy and halogeno substituents in benzene ring of 1 remain unaffected in most of the reactions described here for the unsubstituted 3-formylchromone. The reactions of 1 are described in the following few sections and subsections based on the type of reactions and the nature of the reagents. One separate section is earmarked for annulation as well as cycloaddition reactions of 1 and its simple condensates, and another for one-pot multicomponent reactions involving 1 and two or more other reagents.

\begin{center}
\includegraphics[width=0.5\textwidth]{diagram.png}
\end{center}

2. Decarbonylation

Microwave irradiation of ChrCHO in EtOAc containing Pd(OAc)\textsubscript{2} (~10mol\%), K\textsubscript{2}CO\textsubscript{3} (1.5 eq.) and molecular sieves (4Å) brings about its decarbonylation.\textsuperscript{7} Decarbonylation of ChrCHO by using Pd(OAc)\textsubscript{2} does not need any exogenous ligand for palladium and any co-scavenger.\textsuperscript{8}

3. Oxidation, Reduction and Reductive Self Coupling

Treatment of a suspension of ChrCHO in CCl\textsubscript{4} with \textit{N}-bromosuccinimide under UV-irradiation affords after quenching with ammonia at 0 °C the chromone-carboxamide 3; a similar quenching at 40 °C yields the chroman-2,4-dione 4. Treatment of 3 as well as 4 with NaOH followed by acidification produces 3-formyl-4-hydroxycoumarin 5.\textsuperscript{9}
ChrCH₂OH, obtained by reduction of ChrCHO with 9-BBN has been converted to ChrCH₂Br, the phosphorus ylide of which has been reacted with several α,β-unsaturated and α,β,γ,δ-unsaturated aldehydes to get chromone based retenoids.¹⁰ 3-Formylchromone on being treated with Zn-Hg in AcOH under reflux¹¹ gives two 1,2-diol products 6 and 7; the major product identical with that obtained along with 3-hydroxymethylchromone and bis(chromon-3-yl)methane 8 by treating 1 with Zn-AcOH¹² is proved to the meso-1,2-diol 6.

 ChrCHO when heated with HMPA in benzene undergoes disproportionation to the alcohol 9 and acid 10. The same reaction in refluxing toluene produces cis-1,2-di(chromon-3-yl)ethylene 11. Pentacarbonyl iron in refluxing toluene brings about reductive dimerization of ChrCHO to the diol 7. Fe(CO)₅-HMPA, converts 1 into 3-methylchromone 12 and the dihydrobischromone 13 at different ratios dependent on the solvent. The reaction in refluxing benzene gives 13 as the major product whereas 12 prevails in refluxing toluene; these two products may sometimes be admixed with trace amounts of 8 and bis(chroman-3-yl)methane 14.¹³ The formation of these products is schematically shown in Scheme 1.

Scheme 1
4. Radical Addition

Diastereoselective tandem radical addition of an alkyl iodide to 3-formylchromone 1 (Scheme 2) has been reported by Zimmerman et al.\textsuperscript{14} The product distribution is dependent on the reaction time and equivalent of the radical initiator. Using 1.0-2.0 equivalent of triethylborane and short reaction time (<5 min) excellent yield of 15 is obtained. With excess triethylborane and long reaction time the tandem adduct 16 is produced as a single diasteroisomer in excellent yield. Zinc triflate (0.5 eq) is the preferable Lewis acid catalyst for the reaction. The boron enolate 16 is remarkably stable and convertible to the alcohol 17 by treatment with alkaline hydrogen peroxide.

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme2.png}
\end{center}

**Scheme 2**

5. Nucleophilic Addition

3-Formylchromone 1 is a good Michael acceptor towards most, if not all, nucleophiles. Thus, a nucleophile XH\textsubscript{2} such as an amine, hydrazine, monosubstituted hydrazine, hydroxylamine or an active methyl or methylene compound in conjugation with an appropriate base undergoes Michael addition to 1 with concomitant opening of the pyran ring and subsequent recyclization (i.e. domino Michael–retro-Michael–Intramolecular 1,2-addition) giving the hemiacetal A that
leads to B by water elimination (Scheme 3-A). The same reaction sequence of a nucleophile YH or ZH representing ROH, RSH etc. with 1 gives the intermediate C. Michael addition of the second nucleophile ZH to the $\alpha,\beta$-unsaturated carbonyl functionality of C with subsequent 1,4-elimination of water gives the final product D (Scheme 3-B); YH and ZH may be the same or different nucleophiles or two nucleophilic centres in a single reactant.

![Scheme 3](image)

5.1. Addition of oxygen and sulfur nucleophiles: protection and deprotection of carboxaldehyde group

Formation of acylal of ChrCHO with acetic anhydride involves reaction steps similar to those as written in Scheme 3-B. ChrCHO reacts readily with Ac₂O to give ChrCH(OAc)₂ in the absence of any Brønsted or Lewis acid catalyst in [bmim]BF₄ ionic liquid.¹⁵ The said acylal formation is also catalyzed by 1,3-dibromo-5,5-dimethylhydantoin under neutral condition.¹⁶ Titanium tetrafluoride,¹⁷ boric acid¹⁸ and alum¹⁹ catalyze the above reaction under solvent-free condition at room temperature. Titanium tetrafluoride¹⁷ also catalyzes deprotection of the gem-diacetate of ChrCHO in water. An efficient and solvent free synthesis of ChrCH(OAc)₂ and its deprotection to ChrCHO catalyzed by reusable Envirocat EPZ10R under microwave irradiation has been claimed by Shindalkar et al.²⁰ Conversion of ChrCHO into ChrCH(SCH₂CH₂OH)₂ with mercaptoethanol is catalyzed by silica supported sodium sulphate under solvent free condition.²¹ Indium trifluoride catalyzed protection of the aldehyde group of ChrCHO with MeOH, PhCH₂OH, 2,2-dimethylpropane-1,3-diol, PhSH, HSCH₂CH₂SH, HSCH₂CH₂CH₂SH in refluxing toluene is known.²² Acetal as well as thioacetal of ChrCHO when refluxed in MeCN-H₂O (4:1) in the presence of InF₃ is converted to 3-formylchromone.²²
The formation of the 1,2,4-dithiazole 24 by heating 1 with 2-phenyl-4-dimethylamino-1-thia-3-azabutadiene 18 in a sealed tube has been rationalized in the following way (Scheme 4).23 The first step involves thionation of 1 to 20 either through 19, the [4+2] cycloadduct of 1 and thiazadiene 18, or through the reaction of 1 with thiobenzamide 21; the latter may be generated by the hydrolysis of 18 with a small amount of moisture and further hydrolysis can occur due to in situ generation of water. The second step most likely involves the reaction of 3-thioformylchromone 20 with another molecule of 21 followed by oxidative cyclisation. The dithiazole 24 is indeed formed when ChrCHO is heated with 1 or 2 equivalent of thiobenzamide under identical conditions. Later on several 6-substituted and 6,7-disubstituted 3-formylchromones have been reacted with 2.0 equivalent thiobenzamide in refluxing toluene and the resultant dithiazoles evaluated for their cytotoxic activity against a number of human cancer cell lines.24,25

Scheme 4

5.2. Addition of nitrogen nucleophiles
5.2.1. Addition of aliphatic amines. The Schiff base as well as its precursor having respectively general structures B and A (X = NR), obtainable from ChrCHO and an aliphatic or aromatic amine RNH2 (Scheme 3-A) can function as a ligand for complexation with different metals. Many of these ligands as well as their metal complexes possess some biological activities. Cu(II), Ni(II) and Co(II) complexes with the chromone-based Schiff bases 26 (prepared from 1 and 25) and 27 (Scheme 5) have been subjected to various spectral studies.26
Scheme 5

Treatment of the Schiff base 28 with Me₂SnCl₂, Ph₂SnCl₂ and Ph₃SnCl gives respectively the organotin complexes 29a,b,c which exhibit electrostatic mode of binding preferably via oxygen of sugar phosphate backbone of DNA helix.²⁷

The formation of the pyrrole 30, pyridine 31 and pyranopyridine 32 by treating ChrCHO with methyl glycinate hydrochloride in refluxing toluene containing K₂CO₃ has been rationalized.²⁸ The pyrrole 30 is, however, the sole product when the above reaction is carried out in TMSCl-DMF at 100 °C.²⁹

TMSCl mediated reaction between 1 and hetarylmethylamine 33 strongly depends on their molar ratio. A 1:2 molar ratio of the aldehyde 1 and the amine 33 gives the pyrrole 35 in 68-91%
yields whereas a 2:1 molar ratio forms exclusively chromenopyrrole 37 in moderate yields. The
reaction of 1 with a secondary hetarylmethylamine 34 leads to 36 independent of the molar ratio
of the reactants.29

\[
\text{Het-NHR} \quad \text{Het-} \quad \text{Het-NHR} \quad \text{Het-}
\]

For 33-37 : Het = 2-, 4-pyridyl, 2-oxo-4-pyridyl, 2-(pyrid-1-yl)pyrid-4-yl, benzimidazol-2-yl, benzothiazol-2-yl,
benzoxazol-2-yl

A hot methanolic solution of furo[3,2-g]chromone-3-carbaldehyde 38 and benzimidazol-2-ylmethylamine 39 (Bim = benzimidazol-2-yl) gives the pyrrole 41 when treated with KOH but
42 with triethylamine, both arising through the Schiff base intermediate 40 (Scheme 6). Several
transition metal complexes of these pyrroles possess antiviral activity.30

\[
\text{CHO} \quad \text{OH} \quad \text{NH}_{\text{Bim}} \quad \text{OH} \quad \text{NH}_{\text{Bim}}
\]

Scheme 6

Iodine-catalyzed Pictet-Spengler condensation between ChrCHO and tryptamine yielding
1,2,3,4-tetrahydro-β-carboline 43 evidently through the Schiff base intermediate 42 has been
reported by Prajapati and Gohain (Scheme 7).31
Synthesis of the propenone 44 from 1 and piperidine has been achieved by conventional method\textsuperscript{32} as well as under ultrasound irradiation.\textsuperscript{33} Ultrasonication of a mixture of 1 and pyrrolidine affords the propenone 45.\textsuperscript{34} Here piperidine or pyrrolidine undergoes aza-Michael addition to 1; the resultant adduct by base catalyzed deformylative pyran ring opening gives the propenone 44 or 45.\textsuperscript{32}

5.2.2. Addition of aromatic amines. Ten aryl- and hetaryl- amines have been condensed with 3-formylchromone in refluxing water containing Zn[(L(-)-proline)]\textsubscript{2} (10 mol\%) as the catalyst to give the 2-hydroxychromanone 46.\textsuperscript{35} 2-Methoxychromanone derivatives 47-51 are obtained by reacting 3-formylchromone with the appropriate aniline in MeOH-PTS under reflux.\textsuperscript{36-38} X-ray crystallography shows the presence of methoxy groups and intramolecular hydrogen bonding in all these compounds. The compound 49 is stable up to 90 °C and decomposes in three stages where as 51 is stable up to 100 °C and decomposes in five stages.\textsuperscript{37} The compound 47 decomposes only when heated above 128 °C.\textsuperscript{38} Some of the chromone based sulphonamides 52, prepared from 3-formylchromones and the appropriate aminobenzenesulfonamide in refluxing EtOH containing catalytic amount of PTS are highly potent and selective inhibitors of alkaline phosphatase.\textsuperscript{39,40} 2-Ethoxychromanone 52d resulting from the reaction of 3-formylchromone and o-aminobenzenesulfonamide is always admixed with the benzothiadiazine derivative 53. X-ray study reveals that one water molecule of crystallization is present in the crystal of the compound 52a (R\textsubscript{1} = H).\textsuperscript{39} The compounds 52a-c (R\textsubscript{1} = H) possess excellent bovine carbonic acid anhydrase (BCA) inhibitory activities.\textsuperscript{40} Kamal \textit{et al.}\textsuperscript{41} have reported reductive amination of ChrCHO with several aromatic amines (ArNH\textsubscript{2}) to ChrCH\textsubscript{2}NHAr using sodium cyanoborohydride in methanol with a catalytic amount of acetic acid.

The Schiff bases prepared from 1 and several arylamines have been evaluated for their antibacterial activities.\textsuperscript{42-44} The Schiff base 54 has been prepared from 1 and 4-aminoantipyrine by conventional method\textsuperscript{45} as well as in an ionic liquid.\textsuperscript{46} Many other hetarylamines such as 1,3-diaryl-5-aminopyrazole 55,\textsuperscript{47} 3-aminoquinoxazolone 56,\textsuperscript{48} thiazolylcoumarin 57,\textsuperscript{49} 4-amino-1,2,4-triazole 58\textsuperscript{50} and aminophenazone 59\textsuperscript{51} have been condensed with ChrCHO to give the...
corresponding Schiff bases. Pandey et al.\textsuperscript{52} made a comparative study of conventional and microwave assisted synthesis of Schiff bases of ChrCHO.

\begin{center}
\includegraphics[width=\textwidth]{schiff_bases.png}
\end{center}

3-Formylchromones as well as Schiff bases obtainable therefrom can function as ligands towards many metal ions. The complexes of Mn(II), Co(II), Ni(II) and Zn (II) with unsubstituted 4-oxo-4\textsubscript{H}-1-benzopyran-3-carboxaldehyde \textsuperscript{1} are polycrystalline compounds with various formulae and different ratios of metal to ligand.\textsuperscript{53} The Schiff base obtainable from \textsuperscript{56} functions as a neutral bidentate ligand towards Co(II), Ni(II), Zn(II), Pd(II) and Cd(II), quinazolone carbonyl oxygen and azomethine nitrogen being involved in the corordination.\textsuperscript{48} The Schiff base corresponding to hetaryl amine \textsuperscript{57} coordinates as a neutral bidentate ligand with oxovanadium(IV), Co(II), Ni(II) or Pd(II) ions.\textsuperscript{49} The Schiff bases derived from 3-formylchromones and aminophenazone \textsuperscript{59} as well as their Ln(III) complexes can bind to DNA via an intercalation binding mode, the complexes having better DNA binding affinity than the free ligand alone.\textsuperscript{51} The Schiff base \textsuperscript{54} in its solid state as well as in solution has E-stereochemistry around its azomethine double bond and S-cisoid conformation for its α,β-unsaturated imine functionality. It functions as a fluorescent probe for Fe\textsuperscript{3+} in acetonitrile-water (1:9 by volume); while complexing with Fe(III) it assumes a conformation having S-transoid for CH=CH-CH=N and Z-stereochemistry around CH=N so that the metal can bind with azomethine nitrogen, chromone carbonyl oxygen and pyrazolinone oxygen.\textsuperscript{54} Same is the case for the condensate from \textsuperscript{1} and 2-aminothiazole; it assumes the conformation as shown in \textsuperscript{60} so as to function as an NNO coordinating ligand for several metal ions. Its Cu(II) complex possesses tetrahedrally distorted square planar geometry whereas Co(II), Ni(II) and Zn(II) complexes show distorted tetrahedral geometry and VO(IV) complex shows square pyramidal geometry.\textsuperscript{55} The azo-Schiff base \textsuperscript{61} forms complexes with VO(IV), Co(II), Ni(II), Cu(II) and Zn(II); octahedral geometry is proposed for all those complexes from their electronic spectra and magnetic
susceptibilities. The conductance data indicate non-electrolytic nature of the complexes except the VO(IV) one which is electrolytic in nature.\textsuperscript{56} Cu(II) complexes of 62 and 63 having metal to ligand ratio as 1:2 have been subjected to rigorous spectral analysis.\textsuperscript{57}

![Chemical structures](image)

Scheme 8

An aryl- or hetaryl- amine of general structure E undergoes [3+3] annulation with α,β-unsaturated aldehyde functionality of I in TMSCl-DMF promoted reactions to give ultimately either the chromenopyridine H or 3-(2-hydroxybenzoyl)pyridine I or both (Scheme 8). Here the
initially formed condensate having a structure akin to the Schiff bases F undergoes
electrocyclization to G, the latter aromatizing to H by air oxidation and to I by pyran ring
opening.

TMSCl mediated reaction of 1 with aniline or substituted aniline in DMF at 100 °C in a
sealed tube produces either 3-(2-hydrobenzoyl)quinoline 64 or the chromenofused pyridine 65
depending on the structure of the starting aniline.58,59 Substituents in aniline molecule that
withdraw electron from the ortho-position or increase electron density on nitrogen favour the
formation of 65; on the contrary, electron rich anilines give only 64. 4-Chloroaniline gives with 1
both 64 and 65.59 Similar reactions of 3-formylchromones with more than a dozen of
aminoheterocycles promoted by either AcOH or PTS or TMSCl leading to only the heterofused
pyridine H have been well documented in a Tetrahedron Report.2 Iodine catalyzed condensation
of ChrCHO with 1,3-disubstituted 5-aminopyrazole gives the pyrazolo[3,4-b]pyridine 66 (R, R^1
= alkyl, aryl).60 Microwave irradiated condensation of 1 with 2-aminopyridine 67 (R^1, R^2 = H,
Me, Br) in MeCN - PTS gives 68; indium triflate catalyzed cyclization of the latter with N-
arylopropargylamine 69 (Ar = Ph, substituted phenyl, naphthyl etc.) under microwave irradiation
furnishes the 2,10-dihydro-4aH-chromeno[3,2-c]pyridine 70 which has been evaluated for its
preliminary in vitro and in vivo activity against MTB and MDR-TB.61

5.2.3. Addition of aryl- and hetaryl- amine having a second nucleophilic group attached to
the ring. Dibenzotetraaza[14]annulene (DBTAA) 716,62 has been recently synthesized by
reacting 1 with o-phenylenediamine in an organised aqueous medium in the presence of a
surfactant (viz. DBSA) as catalyst and iodine as co-catalyst.63 Liquid crystalline DBTAA
derivative as 72 bearing four 3,7-dimethyloctoxy peripheral tails64 and its chiral variant 73
bearing four (S)- or (R)-enantiomeric 3,7-dimethyloctoxy groups have been prepared by
condensing 1 with the appropriate 4,5-disubstituted 1,2-diaminobenzene in methanol.\textsuperscript{65,66} DBTAA based lacunar type receptors 74-76 have been prepared by alkylation of both phenolic OH groups using the appropriate aliphatic dibromide or ditosylate.\textsuperscript{67} Esterification of 71 with octane-1,8-dicarboxylic acid and benzene-1,4-diacetic (or di-n-propanoic acid) gives respectively 77 and 78, 4-dimethylaminopyridine (DMAP) being used as an acylation catalyst and \textit{N,N}-diisopropylcarbodiimide (DIC) as a dehydrating agent.\textsuperscript{68}

\[
\begin{align*}
71: & \quad R = \ X = \ H \\
72: & \quad R = \ H; \quad X = \text{OCH}_2\text{CH}_2\text{CH(\text{CH}_3})(\text{CH}_2)_3\text{CH(\text{CH}_3)}_2 \\
73: & \quad R = \ H; \quad X = \text{OCH}_2\text{CH}_2\text{CH(\text{CH}_3})(\text{CH}_2)_3\text{CH(\text{CH}_3)}_2 \\
74: & \quad R = \text{(CH}_2)_6; \quad X = \ H \\
75: & \quad R = \text{(CH}_2)_10; \quad X = \ H \\
76: & \quad R = \text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{-}(p\text{-C}_6\text{H}_4)\text{-OCH}_2\text{CH}_2\text{-OCH}_2\text{CH}_2\text{-} \\
77: & \quad R = \text{OC(\text{CH}_2)_8\text{CO; \quad X = H}} \\
78: & \quad R = \text{OC-\{(CH}_2)_n-(p\text{-C}_6\text{H}_4)\text{-}(CH}_2)_n\text{CO; \quad n = 1 or 2; \quad X = H}}
\end{align*}
\]

The annule 71 on digestion in acetic acid or oxidation with chloranil gives the chromonylbenzimidazole (bzch) 79. A mononuclear rhenium(I) complex cuplex fac-
[Re(CO)$_3$bzchCl] is formed by treating [Re(CO)$_5$Cl] with bzch.$^{69}$ Grinding at ambient temperature a mixture of 1 and benzo[c][1,2,5]thiadiazole-4,5-diamine 80 with either xanthan sulphuric acid (XSA)$^{70}$ or cellulose sulphuric acid (CSA)$^{71}$ without any solvent affords the fused benzimidazole 81. ChrCHO with 4-(4-chlorophenyl)-1,6-diamino-2-oxypyridine-3,5-dicarbonitrile 82 in hot pyridine gives the pyrido[1,2-b][1,2,4] triazepin 83.$^{72}$ An Indian group$^{73}$ reports condensation of 1 with 3-alkyl(or aryl)-4-amino-5-mercapto-s-triazole 84 in the presence PTS to 4,5-dihydro-3-alkyl(or aryl)-s-triazolo[3,4-b][1,3,4]thiadiazole 85.

5.2.4. Addition of hydrazine. The hydrazone 86 and acylhydrazone 87 can function as ligands to coordinate with metal ions; these hydrazones and their metal complexes may have some biological activities. As for example, the hydrazone 86 ($R = \text{Ph}$) is a neutral bidentate ligand coordinating through its azomethine nitrogen and carbonyl oxygen with tripositive Fe, dipositive Fe, Ni, Cu and Pd ions.$^{73}$ DNA binding properties of the ligand 87 ($R = \text{Ph}$) and its complexes with several metals have been studied.$^{74,75}$ Many members of 87 ($R = \text{mono- or disubstituted phenyl}$) have been evaluated against cyanobacteria fructose-1,6-biphosphatase and sedoheptululose-1,7-biphosphatase.$^{76,77}$ Chromone-3-carboxaldehyde isonicotinylhydrazone 87 ($R = 4$-pyridyl) and lanthanide ions form mononuclear 10-coordinate complexes with 1:2 metal to ligand stoichiometry.$^{78}$ Acylhydrazone 88 ($R^1 = R^2 = H; R^1-R^2 = \text{bond}$) has been prepared by reacting the appropriate 6-oxopyridazine-3-carboxylic acid hydrazide with ChrCHO.$^{79}$ The thiosemicarbazone 89 forms complexes with Cu(II), Zn(II), Ni(II) nitrates having 1:1 metal to ligand stoichiometry; these complexes bind to calf thymus DNA via an intercalation binding mode.$^{80,81}$ Cytotoxicity activity and DNA binding of the semicarbazone 89 itself have also been studied.$^{82}$ PhNHNHCOCONHNH$_2$, obtainable by treating diethyl oxalate sequentially with phenylhydrazine and hydrazine has been condensed with ChrCHO to form the acylhydrazone 90. An octahedral geometry for its Co(II), Cu(II) and U(VI)O$_2$ and a tetrahedral structure for its Ni(II), Cd(II), Zn(II) and Hg(II) complexes have been proposed. The ligand 90 and its metal complexes have been screened against some gram (+)ve and gram (-)ve bacteria.$^{83}$ The hydrazone 86 ($R = 3$-chlorophenyl,$^{84}$ 2,4-dichlorophenyl,$^{85}$ fluorophenyl,$^{86}$ 2-pyridylphenyl$^{87}$) have been converted to the corresponding 4-salicyloyl-1-arylpyrazole 91. The pyrazole 91 ($Ar = \text{Ph}$) on treatment with $O,O$-diethylphosphochloridithioate gives the biologically active organophosphorus compound 92.$^{88}$ The ketoxime of 91 on treatment with phosphorus oxychloride undergoes Beckmann rearrangement and cyclization to the benzoxazole 93.$^{84,87}$ The hydrazone 94 in the presence of iodobenzene diacetate [Phl(OAc)$_2$] on solvent free microwave irradiation undergoes oxidative cyclization to 1,2,4-triazolo[4,3-a]-1,8-naphthyridine 95.$^{89}$ Azomethine functionality in acylhydrazone 87 ($R = \text{aryl or hetaryl}$) behaves similarly as that in a Schiff base towards mercaptoacetic acid and chloroacetyl chloride to give the corresponding thiazolidine and $\beta$-lactam, respectively.$^{90,91}$ The phosphorohydrazone 96 exhibits high in vitro antileukemic activity.$^{92}$
Scheme 9. Reagents and conditions: (i) 1 eq. ChrCHO, EtOH, Δ; (ii) 2 eq. ChrCHO, EtOH, Δ; (iii) HP(=O)(OEt)₂, EtOH, Δ.
An ethanolic solution of phosphonic dihydrazide 97 gives the hydrazones 98 and 99 with 1 and 2 equivalents of ChrCHO, respectively. Diethylphosphite converts 98 to the 1,2,3,4,5-triazadiphosphinane 101 most likely via the intermediate 100 formed by addition of diethylphosphate to the azomethine double bond of 98 followed by cyclization whereas it simply adds to 99 giving 102 (Scheme 9).\(^\text{93}\)

5.2.5. Reaction with hydroxylamine. Intricacy of the reaction between 1 and hydroxylamine has been discussed earlier.\(^\text{5}\) A later detailed study of the reaction by Sosnovskikh et al.\(^\text{94}\) gives interesting results (Scheme 10). The initially formed aldoxime 103 when treated with alkaline hydroxylamine gives the chromane-2,4-dione 106 via the isolable isoxazolocoumarin intermediate 105. Here the O-N bond in 105 is reduced by hydroxylamine to form 106. The amide 104 obtainable from 1 is also transformed into 106 under similar conditions. Reflux of 106 in acetic anhydride gives an \(E\), \(Z\)-isomeric mixture of the monoacetate 107. The chromanedione 106 (\(R = H, Me\)) is formed in 46-51% yield upon reflux of an ethanolic solution of 1 (\(R = H, Me\)) (1 eq) with aq NH\(_2\)OH.HCl (8 eq) in the presence of NaOH (14 eq) for 3 h, no intermediate as 104 and 105 (\(R = H, Me\)) being isolated. The reaction of 1 (\(R = Cl\)) with hydroxylamine under the same conditions furnishes a mixture of 106 and 105 in 7:3 proportion.\(^\text{94}\) Zirconium oxychloride (ZrOCl\(_2\).8H\(_2\)O) in aqueous acetone (1:1) can regenerate 3-formylchromone from its aldoxime 103.\(^\text{95}\)

**Scheme 10.** Reagents in hot conditions: (i) NH\(_2\)OH.HCl, EtOH; (ii) NH\(_2\)OH.HCl, pyridine-water; (iii) NH\(_2\)OH.HCl, NaOH, EtOH, H\(_2\)O; (iv) Ac\(_2\)O.
5.2.6. Reaction with guanidine. Reaction of 1 with cyanoguanidine 108 or metformine 109 gives biologically important pyrimidine 110 or 111.

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{N} \quad \text{H}_2\text{N} \\
\text{N} & \quad \text{C} \quad \text{NH} \\
\text{NMe}_2 & \quad \text{X} \\
108 & \quad 109 \\
\end{align*}
\]

\[110: \text{X} = \text{NHCN} \]

\[111: \text{X} = \text{NHC(NH)}\text{NMe}_2\]

5.3. Addition of phosphorus nucleophiles

Ammonium metavanadate (NH\(_4\)VO\(_3\)) catalyzes addition of triethyl phosphite to ChrCHO at room temperature under solvent free conditions yielding the \(\alpha\)-hydroxyphosphonate derivative 112. Potassium dihydrogen phosphate 97 and sulfamic acid 98 are also effective catalysts for the solvent free ultrasound irradiated synthesis of 112 from the above said two reactants.

\[
\begin{align*}
\text{Chr} & \quad \text{CH} \quad \text{P} \\
\text{O} & \quad \text{Et} \\
\text{OH} & \quad \text{Et} \\
112 & \\
\end{align*}
\]

5.4. Addition of carbon nucleophiles

5.4.1. Addition of active methyl and acyclic methylene compounds. The aryl(or hetaryl) methyl ketone \(J\) condenses with 3-formylchromone 1 under various conditions to give the chalcone \(K\) (Scheme 11). Several 2- or 4- substituted acetophenones have been condensed with ChrCHO in ethanol containing either pyridine 99 or sodium hydroxide 100 or under solvent free condition. 101 The hetaryl methyl ketones 113-116 have been used for preparation of chalcones in refluxing ethanol containing pyridine or water containing Zn(L-proline)\(_2\). Synthesis of chalcones by Claisen-Schmidt condensation of ChrCHO with ketones using ecofriendly nontoxic bismuth(III) chloride catalyst under solvent free conditions is also reported. Many of the chalcones and the products obtained therefrom by treatment with NH\(_2\)NHR (R = H, Ph) have been screened against many gram (+)ve and (-)ve bacteria and fungi. Gold(III) mediated condensation of 1 with aryl methyl ketone to produce the 1,5-diketone 118 admixed with a little amount of the chalcone 117 deserves special mention. Here the initially formed condensate 117 functions as a Michael acceptor towards a second molecule of aryl methyl ketone to give the adduct 118. The best result is obtained when the reaction is conducted in MeCN at ambient temperature using AuCl\(_3\) (5 mol%), AgSbF\(_6\) (15 mol%) and aryl methyl ketone (2.2 eq).
Interaction of 6-chloro-3-formylchromone with the pyridazinone 119 (1:1) in NaOEt-EtOH gives the corresponding chalcone 120 whereas the above reaction when carried out in EtOH containing piperidine gives the pyrano[2,3-c]pyridazone 121 via an intramolecular 1,4-addition in the compound 120 (Scheme 12).106

The methyl group directly linked to a very few aromatic or heterocyclic rings is sufficiently active to undergo condensation with ChrCHO giving ChrCH=CH-Φ (Φ = Ar, Het). This aspect mainly studied before 2000 has been the subject matter of seven publications well comprehended in a recent review.3 ChrCHO has been reacted with methoxy(methyl)pentacarbonyltungsten
carbene complex 122 in the presence of TMSCl and triethylamine; the carbanion generated from the carbene complex 122 condenses with the pyrylium salt generated from 1 and TMSCl to give the benzopyran Fischer carbene complex 123.\textsuperscript{107}

Several new catalysts have been used for the Knoevenagel condensation of 1 with active methylene compounds. As for example, ChrCHO has been condensed with XCH\textsubscript{2}CN (X = CN, COOH, COOEt, CONH\textsubscript{2}) under polyethylene glycol-400 (PEG-400) catalysis and microwave irradiation.\textsuperscript{108} Alum [KAl(SO\textsubscript{4})\textsubscript{2}.12H\textsubscript{2}O] mediated solvent free microwave induced clean process for preparation of \(\alpha,\beta\)-unsaturated carboxylates is known, only 10 mol\% of alum being sufficient for optimum yields.\textsuperscript{109} Knoevenagel condensation of 1 with ethyl cyanoacetate, Meldrum’s acid etc. using biosupported cellulose sulphuric acid (CSA) in the solid state under solvent free condition is reported.\textsuperscript{110} The condensate 124 resulting from 1 and XCH\textsubscript{2}Y (X = Y = COMe; X = Y = CO\textsubscript{2}Et; X = CN, Y = CO\textsubscript{2}Et; X = COPh, Y = CO\textsubscript{2}Et) undergoes chemoselectively reductive dimerisation to 125 with Sm in THF containing aq NH\textsubscript{4}Cl whereas Zn under similar conditions brings about chemoselective reduction of exocyclic olefinic bond.\textsuperscript{111} \(E\)-(chromon-3-yl)acrylic acid 126 obtained by conventional pyridine catalyzed Knoevenagel condensation of 1 with malonic acid\textsuperscript{112,113} has been subjected to molecular hybridization with isoniazide 128 using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and 1-hydroxybenztriazole (HOBt) under ultrasonication to afford the hydrazide 127.\textsuperscript{114} A mixture of allyl bromide and zinc dust in THF containing saturated NH\textsubscript{4}Cl converts ChrCHO to the homoallylic alcohol 129; the latter when heated with formalin in AcOH containing a few drops of H\textsubscript{2}SO\textsubscript{4} is reconverted to 3-formylchromone 1. Hydroxylamine converts 129 to the dioxime 130 (diastereoisomeric mixtures).\textsuperscript{115}
3-Formylchromone 1 when reacted with the substituted acetic acid 131 under Perkin reaction condition gives the pyranopyran 132 that on treatment with XOH (X = H or alkyl) in the presence of PTS affords 133 (Scheme 13). The compounds 132 and 133 when heated in aqueous acid at elevated temperature rearrange to 134 that can be alkylated to 135 by an alkanol in the presence of PTS. Another publication reveals the formation of small amounts of 5-(2-hydroxybenzoyl)pyran-2-one 136 along with the major product 132 in the above mentioned condensation of 1 with 131 under MWI. Recently several p-substituted phenylacetic acids have been condensed with 3-formylchromones in Ac<sub>2</sub>O-AcONa under reflux to give pyranochromone 132. Coumarin-3- or 4-acetic acid similarly condenses with 1 giving 132 (R = coumarin-3- or 4-yl).

**Scheme 13.** Reagents and conditions: (i) Ac<sub>2</sub>O, AcOK, Δ; (ii) XOH (X = H, Alkyl), PTS; (iii) H<sub>2</sub>O, H<sup>+</sup>, Δ; (iv) YOH (Y = alkyl), PTS; (v) Ac<sub>2</sub>O, AcOK, MWI.

The reaction of 1 with phenylacetic acid when conducted in the presence of t-BuOK under MWI, however, takes a different course; here initial condensation followed by decarboxylation produces only the E-isomeric form of 3-styrylchromone (E-137). Z-3-Styrylchromone (Z-137) can be conveniently prepared by reacting ChrCHO with benzylic ylid. Patonay et al. prepared the E-137 by exposing a mixture of 1 and phenylmalonic acid on solvent free NaOAc support to MWI. The compounds E-137 and 139 are obtained by treating 1 in dry pyridine-
'BuOK with phenylacetic acid and E-styrylacetic acid 138, respectively. A dichloromethane solution of dimethylidioxirane (DMD) brings about epoxidation of 3-styrylchromone with complete regio- and diastereo-selectivity, E-isomer giving the epoxide 140 and Z-isomer the epoxide 141; On the contrary, treatment with H₂O₂ under alkaline condition affords the corresponding 2,3-epoxy-3-styrylchromone. ChrCHO with benzisoxazole-3-acetic acid under MWI gives E-dihetaryl substituted ethene 142. In its reaction with urea, thiourea and guanidine, the α,β-unsaturated carbonyl functionality of 142 is involved, the hetarylvinyl moiety remaining unaffected. (p-Nitrophenyl)(tetrazol-5-yl)methane with 1 in dry pyridine gives the Z-isomer of trihetarylthene 143; similar condensation of 144 with 1 gives 145 having Z-stereochemistry around its exocyclic olefinic bond. Both the chromone based compounds 143 and 145 have been assayed against gram (+)ve and (-)ve bacteria.

Heating 3-formylchromone 1 with a variety of imidazole (146, R¹=R²=H) and benzimidazole 146 (R¹-R² = -CH=CH-CH=CH-) in DMF in the presence of TMSCl as a promoter and scavenger gives the 1,2-aza]pyridine 148. The reaction goes via an intermediate having a structure akin to 147 that by a domino aza-Michael – retro-Michael gives 148 (Scheme 14). The pyrido[1,2-α]benzimidazole 148 (R = CN; R¹-R² = -CH=CH-CH=CH-) is also obtained by reacting 1 with benzimidazole-2-acetonitrile under Perkin condition.™ TMSCl mediated cyclization of 1 with pyrimidinones 149 and 150 yields the pyridopyrimidinones 151 and 152, respectively.
For 146-148: R = CN, COPh, CONH₂, CONPh, CSNH₂, SO₂Me, SO₂Ph, Ph, SCH₂COOH, Cl, NHCOPh, OPh, H, etc.

\( R^1 = R^2 = H; R^1-R^2 = -\text{CH}=\text{CH}=\text{CH}- \)

Scheme 14

A few acyclic compounds having two active methylene groups have been condensed with 1. As for example, dimethyl acetonedicarboxylate functions as a 1,3-C,C-binucleophile in condensing with 1 in THF under DBU catalysis to give the benzophenone 153.¹²⁶ Wittig reaction of the ylid 154 with 1 in THF containing NaH gives 155.¹²⁷ The compound 156, obtained by condensing 1 with triethyl 3-methylphosphocrotonate under Wittig-Horner-Emmons reaction conditions, is sequentially subjected to reduction with LAH, oxidation with MnO₂, Wittig
reaction with (methoxycarbonylmethyl)triphosphonium bromide and hydrolysis by LiOH to give the benzophenone based retinoid 157. Acetoacetanilide functions as a 1,3-C,N-binucleophile towards 1 in CH₂Cl₂ containing FeCl₃.6H₂O, Cs₂CO₃ and MgSO₄ so as to form the pyridine 158.

![Chemical structures](image)

**5.4.2. Addition of cyclic active methylene compounds.** A methylene group incorporated in some cyclic, mostly heterocyclic, systems L is sufficiently active so as to condense with 3-formylchromone 1 giving the product M (Scheme 15). A number of such cyclic active methylene compounds that have been condensed with 1 and the condensation conditions with the appropriate references are given in Table 1.

![Scheme 15](image)

**Table 1. Condensation of 1 with the compound L**

<table>
<thead>
<tr>
<th>Active methylene compound L</th>
<th>Reaction conditions ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>(a) gl. AcOH, AcONa, Δ¹³⁰</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>(b) Zn nanobelts, Solvent free, Δ¹³¹a</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>(c) 1,13,3-tetramethyl-guanidine lactate [TMG][Lac] ionic Liquid, solvent free, ultrasonication¹³²</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>(d) PEG-400, MWI¹⁰⁸</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>Active methylene compound L</th>
<th>Reaction conditions[^ref]</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure 160" /></td>
<td>(a) NaHCO₃/MWI[^133a]</td>
</tr>
<tr>
<td><img src="image2" alt="Structure 161" /></td>
<td>(b) Solid state, Δ[^133b]</td>
</tr>
<tr>
<td><img src="image3" alt="Structure 162" /></td>
<td>AcOH, AcONa[^134]</td>
</tr>
<tr>
<td><img src="image4" alt="Structure 163" /></td>
<td>AcOH, AcONa, Δ[^135]</td>
</tr>
<tr>
<td><img src="image5" alt="Structure 164" /></td>
<td>(a) PEG-400/ MWI[^108]</td>
</tr>
<tr>
<td><img src="image6" alt="Structure 166" /></td>
<td>(b) solid state, Δ[^137]</td>
</tr>
<tr>
<td><img src="image7" alt="Structure 165" /></td>
<td>(c) solid state, MWI[^138]</td>
</tr>
<tr>
<td><img src="image8" alt="Structure 167" /></td>
<td>(d) cellulose sulphuric acid (CSA), solvent free[^110]</td>
</tr>
<tr>
<td><img src="image9" alt="Structure 168" /></td>
<td>(e) 1-Benzyl-3-methylimidazolium chloride [bnmim]Cl ionic liquid, room temp.[^139]</td>
</tr>
</tbody>
</table>

[^ref]: Additional references not provided in the image.
The compound 166 (X = O, S; Y = O; R = CH₂Ar), naphtho[2,1-b]furan-3-(or 2)-ones and 7-methoxychromanone have been condensed with 1 by one or other method mentioned in Table 1. 8-Allyl-3-formylchromone like its 8-unsubstituted analogue 1 has been condensed with hippuric acid in AcOH-AcONa, with barbituric acid and dimesione in dry pyridine to give the expected condensates. Condensation of 1-phenyl-3-methylpyrazolidin-5-one with CrhCHO either in aqueous medium containing B₂O₃-ZrO₂ solid catalyst or with PEG-400 under MWI or under MWI without any catalyst gives the normal condensate. A mixture of 1 and 168 in 1:2 molar ratio on MWI gives 170 that arises by a Michael addition of 168 to 169. Xanthan sulphuric acid (XSA) has also been used as a solid catalyst for the formation of 170 from 1 and 168. Similar condensation of 1 with triacetic acid lactone (4-hydroxy-6-methylpyran-2-one) and 4-hydroxycoumarin (2 eq) under conventional or solvent free conditions gives the trihetarylmethanes 171 and 172, respectively. The compound 172 is also formed from 1 and 3-bromo-4-hydroxycoumarin (1:2 molar ratio) in MeOH-pyridine under reflux. Shutov et al. have rectified their earlier report on the reaction of 1 with 2-aryl-4-hydroxy-1,3-thiazin-6(6H)-one 173 (Ar=Ph, p-MeOC₆H₄). The said reaction at 50-58 °C in THF.
containing pyridine as catalyst is now claimed to give a mixture of the pyrano fused heterocycles 174 and 175 admixed with a little amount of the byproduct 176. The condensates of I and different active methylene compounds as well as the products easily obtainable therefrom by reaction with some N-N, N-O, N-C-N binucleophiles have been evaluated for their biological activities.

5.4.3. Addition of enol ethers. The formation of benzophenones by reacting 3-formylchromone I with 1,3-\textit{bis}-silyl enolates of general formula 178 as the synthetic equivalent of 1,3-dicarbonyl compounds in the presence of trimethylsilyl triflate (TMSOTf) has been exploited by Langer and co-workers;\textsuperscript{153,154} the earlier works in this aspect has been accounted by Langer himself.\textsuperscript{155} Here the terminal carbon of the butadiene moiety of 178 undergoes Michael addition to the benzopyrylium triflate 177, generated from I and TMSOTf; the adduct 179 undergoes sequentially retro-Michael (→180), intramolecular aldol reaction (→181) and hydrolytic elimination of siloxane to give the product 182 (Scheme 16).

![Scheme 16](image_url)

The bis-silyl enolates 178 (R\textsubscript{1} = SC\textsubscript{6}H\textsubscript{4}-R\textsubscript{3}, R\textsubscript{3} = H, Me, Cl, OMe; R\textsubscript{2} = OEt)\textsuperscript{156} and 178 (R\textsubscript{1} = Cl; R\textsubscript{2} = OMe, OEt)\textsuperscript{157} have been similarly utilized for the formation of the corresponding benzophenones 182. Deprotonation of ethyl 3,5-\textit{bis}(trimethylsiloxy)-2,4-hexadienoate 183 with LDA and subsequent addition of TMSCl gives 1,3,5-tris(silyloxy)-1,3,5-triene 184. TMSCl catalyzed reaction of ChrCHO with 183 gives the benzophenone 185 and that with 184 gives 186, the latter product being a regioisomer of the former one.\textsuperscript{158} 182 (R\textsubscript{1} = H; R\textsubscript{2} = OMe) derived
from 1 and 178 (R¹ = H; R² = OMe) has been reacted with phenylboronic acid in the presence of Pd(PPh₃)₄, K₃PO₄ in 1,4-dioxane to get the 2,4'-diphenylbenzophenone 187.¹⁵⁹

5.4.4. Reaction with enamines. β-Aminocrotonic ester or β-aminocrotononitrile 188 (X = CO₂Et, CO₂Me, CN) with 1 in acetic acid¹⁶⁰ or in the presence of TMSCl¹⁶¹ forms only the Hantzsch type dihydropyridines 189. The keten-aminal 190 functions as an enamine to undergo Michael addition to 1 with pyran ring opening and ring closure (→191), water elimination (→192) and electrocyclization to the tetracyclic heterocycle 193 as the final product (Scheme 17).¹⁶²

Scheme 17
5.4.5. Electrophilic substitution reaction of aromatic and heterocyclic compounds with 3-formylchromone. 3-[(Bisaryl)methyl]chromone 194 (Ar = 4-N,N-dialkylaminophenyl) and 194 (Ar = 2,4-dimethoxybenzene) are prepared by treating 1 with N,N-dialkylaminobenzene in aq. H₂SO₄ and 1,3-dimethoxybenzene in CH₂Cl₂ containing BF₃·Et₂O, respectively. The chromone 194 on oxidation with p-chloranil followed by treatment with NaOMe gives the acetal 195. The pyrazoles derived from 195 and NH₂NH₂ as well as NH₂NHMe have also been subjected to oxidation by p-chloranil. Condensation of 1 with β-naphthol in the presence of CSA under solvent free condition affords the chromenyl-14H-dibenzo[a,j]xanthene 196.

Pyrrole and indole have been subjected to react with ChrCHO under different conditions. The reaction of 1 with pyrrole in DMF-PTS forms the meso-tetrakis(chromon-3-yl)porphyrin 197 whereas that in TFA gives the trisubstituted methane 198. The porphyrin 197 exhibits antioxidative activity against DNA damage induced by bleomycin-iron complex. The trihetarylmethane 198 on DDQ oxidation gives the chromanone 199 that can form a luminescent N,O-chelated chroman BF₂ complex 200 with BF₃-etherate in triethylamine. Sosnovskikh et al. reported the formation of 201 having E-stereochemistry around its exocyclic olefinic bond.
from the uncatalyzed reaction of 1 with 1-methylpyrrole under solvent free conditions; in a later publication\textsuperscript{167b} 1 is reported to form with indole as well as 1-methylindole the triheterarylmethane 202 under the same condition. A solid complex, conveniently prepared from sodium triphenylphosphine-m-sulfonate and carbon tetrachloride\textsuperscript{168} as well as XSA under solvent free conditions at room temperature\textsuperscript{169} has been used for the Friedel-Craft alkylation of indole with ChrCHO to produce 202 (R = H). (3,5-Dimethoxyphenyl)(3,5-dimethoxybenzyl)ether undergoes BF\textsubscript{3}.Et\textsubscript{2}O (10 mol\%) catalyzed alkylation with ChrCHO in CH\textsubscript{2}Cl\textsubscript{2} at room temperature to give 6,11-dihydrodibenzo[b,e]oxepine 203.\textsuperscript{170}

5.5. Baylis-Hillman reaction

Baylis-Hillman reaction of the electron deficient olefin 204 (X = CN, CO\textsubscript{2}Me) with 1 using as catalyst 3-hydroxyquinnuclidine (3HQ) or DBU in chloroform or DABCO in 1-methylpyrrolidine gives the adduct 205. DABCO catalyzed reaction in chloroform between 1 and acrylonitrile 204\textsuperscript{a} gives 205\textsuperscript{a} admixed with a small amount of 207\textsuperscript{a} whereas that between 1 and methyl acrylate 204\textsuperscript{b} gives exclusively the dimer 207\textsuperscript{b} (Scheme 18).\textsuperscript{171} The olefin 204 in the presence of the tertiary nitrogenous base catalyst undergoes Baylis-Hillman reaction with the aldehyde function of 1 to give the alcohol 205. A second Baylis-Hillman reaction involving Michael addition of the carbanion at C-3 of 1 to the exocyclic \(\alpha,\beta\)-unsaturated nitrile or ester functionality of 205 followed by elimination of HO\textsuperscript{−} (\(\rightarrow\)206) and base catalyzed deformylation gives the trisubstituted propene 207.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme_18.png}
\caption{Scheme 18}
\end{figure}

For 204-207\textsuperscript{a}: X = CN
\[\text{b}: X = CO_2\text{Me}\]
Synthesis of 3-hydrazinochromone 211 from 1 and azidodicarboxylate 208 (E = CO₂Et or CO₂Me) in the presence of DABCO (here written as NR₃) involves an aza-Baylis-Hillman type reaction (→209→210) followed by deformylation (Scheme 19). 172 ChrCHO and 208 in the presence of PPh₃ take a different reaction course (vide section 6.5).

Scheme 19

6. Cycloaddition

6.1. [2+2]Cycloaddition
2,4-Bis-(4-methoxyphenyl)-1,3,2,4-thiaphosphetane-2,4-disulfide (Lawesson’s reagent, LR) 212 capable of thiating a carbonyl group stays at elevated temperature in equilibrium with the monomeric 1,2-dipolar species 213. It can convert the Schiff base 214 into the chromonethione 215 and 1,3,2-thiazaphosphetidine derivative 216, the latter arising through [2+2]cycloaddition of 213 with the azomethine double bond of 215. LR under similar conditions converts 217 into 219a and 220; it also converts 218 to 219b that involves its NH₂ and ester groups to further undergo cyclization with a second molecule of 213. 173
6.2. [3+2]Cycloaddition
Reaction of ChrCHO with N-methylglycine (sarcosine) 221 is dependent on the reaction conditions. The reaction in refluxing toluene containing PTS forms 1-methyl-3-salicyloylpyrrole 223a. Here the dipolar compound 222 undergoes 1,5-electrocyclization with concomitant opening of the pyran ring (Scheme 20 – path a). The above reaction in refluxing toluene in the absence of any acid catalyst gives the pyrrolo[3,4-b]chroman 225 in addition to 223a. The compound 225 arises by 1,3-dipolar addition of the ylid 222 to the pyran 2,3-olefinic bond of 1 followed by deformylation (Scheme 20 – path b). ChrCHO and 221 together in DMF under reflux, however, produces the pyran ring opened form of 225. ChrCHO with N-benzylglycine hydrochloride in refluxing 1,4-dioxane containing K₂CO₃, however, gives only the pyrrole 223b.

Scheme 20
When the azomethine ylid 222 is generated in the presence of \(N\)-phenylmaleimide, the cycloadducts 226a and 226b are obtained in 60% yield as a mixture of cis/trans diastereoisomers, the pyrrole 223a also being formed in 27% yield. The ylid 222 fails to add to dipolarophiles as dimethyl fumarate, DMAD, 1,4-naphthoquinone, only pyrrole 223a being formed in nearly 80% yield.\(^{175a}\)

![Chemical Structures](image1)

The 1,3-dipole 227 generated in situ from the allene ester 227 and PPh\(_3\) adds to ChrCHO, the resultant adduct 228 undergoing deformylation to the cyclopentenobenzopyranone 229 (Scheme 21).\(^{176}\)

![Scheme 21](image2)

Scheme 21

Regio- and stereoactive 1,3-dipolar cycloadditions of \(C\)-(chromon-3-yl)-\(N\)-phenylnitrone 230 with several dipolarophiles in dry DCM at room temperature have been carried out. With \(R\) the dipolarophile 231 (R = OEt, Ph, i-BuO, CN, CO\(_2\)Me, CONH\(_2\), pyridyl) gives a mixture of exo- and endo- adducts 232 and 233, methyl \(\alpha\)-methylacrylate 234 only the exo-adduct 235, and \(N\)-phenylmaleimide a mixture of endo-236 and exo-237 adducts (Scheme 22).\(^{177}\) Many of these chromenylisoxazolidines possess excellent antiproliferative activity against some selected human cancer cells.

The allenic ester 238a with the nitrone 230 in benzene under reflux gives the benzindolizine 240a and a trace amount of the indole 241a whereas the ketone 238b and the nitrone 230 under the same conditions give indolizine 240b, no indole as 241b is detected; in both cases the products are admixed with varying amounts of the nitrone rearrangement product namely 3-
formyl-2-phenylaminochromone and both the products 240 and 241 arise through the initially formed [3+2] cycloadduct 239 of the nitrone 230 and the allene 238 (Scheme 23).\textsuperscript{178}

![Diagram of the reactions involving formyl-2-phenylaminochromone and the products 240 and 241.](image)

**Scheme 22**

For 231-233:
- R = OEt, Ph, O\textsuperscript{--}Bu
- CN, CO\textsubscript{2}Me,
- CONH\textsubscript{2}, pyridyl

**Scheme 23**

For 238-241:
- a = R\textsubscript{1} = H, Me; R\textsubscript{2} = OEt
- b = R\textsubscript{1} = H, Ph; R\textsubscript{2} = Me, CH\textsubscript{2}Ph, CH\textsubscript{2}C\textsubscript{6}H\textsubscript{4}OMe(\textit{p})
In the presence of the base DBU, tosylmethylisocyanide (TosMIC) 242A remains in equilibrium with the 1,3-dipole 242B; the latter is likely to undergo 1,3-dipolar cycloaddition to the olefinic bond of 1 and the resultant adduct 243 by base catalyzed deformedylative pyran ring opening and a subsequent 1,5-H shift to form 2-tosyl-4-(2-hydroxybenzoyl)pyrrole 244 (Scheme 24). DBU catalyzed reaction of 1 with TosMIC in THF at room temperature indeed gives the pyrrole 244 in ~60% yield. The pyrrole 244 is also obtained but in lower yield (~25%) when the above reaction is performed with K₂CO₃ in MeOH under reflux; use of a strong base like NaOH forms only a small amount of E-Chr-CH=N-CO-Tos along with a polymeric material.₁⁷⁹

Scheme 24

6.3. [4+1]Cycloaddition

An Indian group¹⁸⁰ reported the formation of the pyranochromene 246 (R¹ = H, Me, Cl; R² = c-hexyl) from the reaction of 3-formylchromone with cyclohexyl isocyanide 245 (R² = c-hexyl) in DCM at room temperature whereas Teimouri¹⁸¹ assigned the furochromene structure 247 (R¹ = H, Me, Cl; R² = n-Bu, t-Bu, c-hexyl, PhCH₂CH₂CH₂, Me₃C-CH₂-CMe₂, PhCH₂CH₂) to the product arising from ChrCHO and several alkyl isocyanides under identical reaction conditions, no unequivocal arguments being given in favour of these proposed structures. Later the Indian group¹⁸² subjected the product previously assigned by 246 [R¹ = H; R² = c-hexyl] to X-ray analysis and rectified its structure as 247 (R¹ = H, Me, Cl, Br; R² = t-Bu, C₅H₁₁, PhCH₂ etc) based on X-ray diffraction analysis and two dimensional NMR methods. Aryl isocyanides are found to be unreactive towards ChrCHO.¹⁸³ The mechanism for the formation of 247 from 3-formylchromone and an alkyl isocyanide is shown in scheme 25. The isocyanide 245 undergoes [4+1]cycloaddition with 3-formylchromone to give the adduct 248; its tautomer 249 functions as a dienamine to undergo Michael addition to the α,β-unsaturated carbonyl functionality of a second molecule of 1 with concomitant opening of the
pyran ring, recyclization (→250) and water elimination to give furo[3,4-b]chromene 247. The imine 247 in ethanol – conc HCl under conventional heating or MWI rearranges to the pyrrolochromone 251.\(^{183}\)

![Scheme 25](image)

**Scheme 25**

6.4. [4+2]Cycloaddition or annulation
6.4.1. ChrCHO as a \(2\pi\) component. ChrCHO can function as a dienophile. Its [4+2]cycloaddition with the appropriate four carbon components followed by \textit{in situ} deformylation leading to either xanthone or benzophenone derivatives or both has been compiled in a recent review article.\(^{184}\) The publications in this aspect appearing only since 2007 are briefly discussed here. [4+2]Cycloaddition of indole-\(\alpha\)-quinodimethane 252, generated by treating 1-benzoyl-2,3-\(\text{bis}\)(bromomethyl)indole with sodium iodide in DMF or PhMe containing 18-crown-6 under reflux, with 1 is neither regiospecific nor stereoselective in giving after in situ deformylation a stereoisomeric mixture of the dihydroxanthones 253 and 254.\(^{185}\) D-A reaction of 1 with pyrazole-\(\alpha\)-quinodimethane 255 is regiospecific giving only the stereoisomeric mixture of the deformylated cycloadduct 256. On air oxidation, 253 and 254 are aromatized to the corresponding chromenocarbazoles and 256 to chromeno[3,2-f]indazole.\(^{185}\)
Organocatalyzed reaction of 3-formylchromones with acetylenedicarboxylate depends on the nature of the substituents in the chromone substrates and that of the catalyst. The zwitterion 257 (E = CO₂Me or CO₂Et, X = Me or NMe₂) arising from acetylenedicarboxylate and the catalyst 4-picoline or 4-dimethylaminopyridine (DMAP) gets annulated with the 2,3-olefinic bond of 3-formylchromone having an electron-withdrawing bromo or nitro group at its 6-position and the resultant annihilated intermediate ultimately gives the xanthone 258 (R = Br or NO₂) by an organocatalyzed elimination process. In contrast, the organocatalyzed reaction of 3-formylchromone 1 and its 6-chloro- and 6-methyl-analogues with acetylenedicarboxylate leads to benzophenones 259 if catalyzed by DMAP or to pyrano[4,3-b]chromones 260 if catalyzed by 4-picoline. In the formation of 260, 3-formylchromone functions as a heterodiene to undergo [4+2]annulation with acetylenedicarboxylate in the presence of 4-picoline. 186,187

A cascade reaction sequence of [4+2] annulation of the zwitterion 262, generated by addition of tri-n-butylphosphine to the allene 261, with 3-formylchromone followed by deformylation affords in excellent yield and with good diastereoselectivity (~8:1) the tetrahydroxanthone 263.
that can be dehydrogenated by DDQ under microwave heating in 1,2-dichlorobenzene to the xanthone 264. \(^{188}\)

\[
\begin{align*}
\text{H}_2\text{C} & \equiv \text{C} - \text{R} \\
\text{H} & = \text{H, Ph, CO}_2\text{Et} \\
\end{align*}
\]

6.4.2. ChrCHO as \(4\pi\) component. ChrCHO when reacted with Lawesson’s reagent in boiling toluene gives a mixture of the thione 265 (20\%) and [1,3,2]-oxathiaphosphino[4,5-b]chromene-5-thione 266 (60\%), the former resulting from thiation of ChrCHO by LR and the latter by a \([4+2]\)cycloaddition of 1 with the monomeric 1,2-dipolar species 213 of LR followed by thiation.\(^{173}\)

\[
\begin{align*}
\text{265} & \quad \text{266 : Ar} = \text{C}_6\text{H}_4\text{OMe(\rho)}
\end{align*}
\]

\([4+2]\)-Ring annulation reaction of 1 with electron poor acetylene as 267 (R = H, Ph, CO\(_2\)Me,; R\(^1\) = Me, Et, \(t\)-Bu) in the presence of triphenyl(or tributyl)phosphine in toluene at 80 °C giving pyrano[4,3-b]chromone 268 has been reported by Waldman et al.\(^{189a}\) This organocatalyzed hetero-Diels-Alder type reaction proceeds well in PhH and PhMe but not in more polar solvents like DCM or THF, and tributylphosphine drives the reaction faster. This reaction also successfully performed by using DABCO\(^{189a}\) as well as 4-picoline\(^{186}\) generates a tricyclic benzopyran with one stereocentre. So an enantioselective version of this reaction has been attempted by using several chiral catalysts.\(^{189b}\) Five chiral phosphines and naturally occurring alkaloids like cinchonine, cinchonidine, \(O\)-methylhydroquinidine fail to catalyze the reaction whereas \(S\)-isomer of the fused pyran 268 (R = CO\(_2\)Me, R\(^1\) = Me) is formed in nearly 54\% ee when 1 is annulated with DMAD in the presence of \(\beta\)-isoquinidine.\(^{189b}\) Under mild acidic conditions (10\% TFA in CH\(_2\)Cl\(_2\), rt) the pyranochromone 268 rearranges to \(Z\)-269 or \(E\)-269\(^{190}\).
IEDDA reaction of 1 with ethyl vinyl ether leading to the endo-adduct 270 and its conversion by treatment with aqueous acid to $E$-$\beta$-(chromon-3-yl)acrolein 271 have been reported long back. 191 Similar cycloaddition of 6,6'-tethered bis(3-formylchromone) 272 with ethyl vinyl ether gives 273 that on treatment with NaOMe in MeOH followed by acidification affords the bis-acrolein derivative 274. 192 IEDDA reaction between 1 and $n$-butyl vinyl ether performed under inductive heating with superparamagnetic nanoparticles coated with silica (MAGSILICA) inside the flow reactor gives a mixture of endo-and exo-adducts 275. 193

Asymmetric IEDDA reaction of 1 with 3-vinylindole 276 ($R = H, Cl, Br, F, OMe$) as dienophile catalyzed by various chiral tertiary amine thiourea gives a mixture of endo and exo-adducts 277 (~3.4:1) with enantiomeric excess approaching to 97%. The endo-adduct 277 has been isomerized by Wilkinson’s catalyst [Rh(PPh3)3Cl] (5 mol%) and Et3SiH (7 mol%) in toluene under reflux to the pyranochromone 278. 194
6.4.3. [4+2]Cycloaddition of 3-(2-substituted vinyl)chromone. IEDDA reaction of the vinylchromone 279 (EWG = COMe, COPh, CO$_2$Et, CONEt$_2$, SO$_2$Ph, CN, Ar) with electron rich ethene 280 (R = R$^1$ = OMe; R = H, R$^1$ = NMe$_2$) is followed by elimination to produce the xanthone 281. 5-Hydroxychromone 282 with ethyl vinyl ether produces the xanthone 283 along with two other minor products. It is relevant to mention here that the reaction between 279 (EWG = CO$_2$Et) and several acyclic or cyclic enamine 284 (X = H, Y = Ph; X = Ph, Y = H; XY = CH$_2$(CH$_2$)$_{1-4}$CH$_2$) involves a domino IEDDA, elimination of dialkylamine and pyran ring opening to give benzophenone 285, no xanthone being formed at all.

Intermolecular [4+2]cycloaddition involving the diene system present in 3-(2-acetylvinyl)chromone 286 (X = COMe, Y = CO$_2$Me, Z = OMe) with the acetyl olefinic functionality (dienophile) of its second molecule has been utilized for the synthesis of naturally occurring vinaxanthone. When a solution of 286 in PhMe with 4.0 equivalent of 2,6-di-tert-butyl-4-methoxyphenol (DTBMP) is heated in a sealed tube at 200 °C for 24 h with air, the cycloadduct 287 (non-isolable) gives xanthone 289 (40%) by aromatization and benzophenone 288 by pyran
ring opening (Scheme 26-path a). This intermolecular cycloaddition is not regiospecific, the regioisomer 291 producing the deacylated products 292 and 293 respectively in 17% and 5% yields (Scheme 26-path b). The additive DTBMP is assumed to be oxidized to quinone that brings about aromatization of 287 to 289 and of 291 to 292. Demethylation of dimethoxyxanthone 289 by AlCl$_3$ in PhMe at 110 °C gives vinaxanthone 290.$^{198}$

Scheme 26
6.4.4. [4+2]Cycloaddition of 3-iminomethylchromone. 3-Iminomethylchromones function as azadienes to undergo [4+2]cycloaddition with several dienophiles. Cycloaddition of the tosylimine 294 with DMAD under PPh₃ or PBu₃ catalysis in boiling toluene gives the chromenopyridine 295 and salicyloylpyridine 296 (R = CO₂Me; R¹ = Me) in 50% and 40% yields whereas PPh₃ catalyzed reaction of 294 with methyl propiolate gives 296 (R = H, R¹ = Me) in 60% yield, the dihydropyridine 295 being obtained in trace amounts.¹⁸⁹b Chiral tertiary amine thiourea catalyzed IEDDA reaction of 294 with 3-vinylindole 276 (R as before) gives a mixture of exo- and endo- adducts 297.¹⁹⁴

A mixture of ChrCHO and 1,3-bis(dimethylaminomethylene)thiourea 298 (1:2) in toluene under reflux gives 5-(2-hydroxybenzoyl)pyrimidine 301 in 78% yield.¹⁹⁹ A plausible mechanism for the formation of 301 is shown in Scheme 27. The initially formed azadiene 299 undergoes IEDDA reaction with the azaenamine functionality of a second molecule of 298, the resultant intermediate 300 by an elimination – pyran ring opening sequence gives the pyrimidine 301. Several 6- or 7-monosubstituted 3-formylchromones have been subjected to react with 298 and the resultant pyridines have been evaluated for their antibacterial property.¹⁹⁹

Scheme 27
6.5. [4+3]-, [5+3]- and [5+4]-Annulation

The zwitterionic intermediates generated from dialkyl azidocarboxylates and triphenylphosphine undergo Mitsunobu reaction with 3-formylchromone in toluene under reflux to afford a mixture of chromeno[2,3-c]pyrazoline \( \text{305} \) and chromeno[2,3-e]tetrazepine \( \text{308} \).\(^{200}\) Here the Huisgen zwitterion \( \text{303} \) generated from azidocarboxylate \( \text{302} \) and \( \text{PPh}_3 \) undergoes [4+3]annulation with \( \text{ChrCHO} \) and the resultant intermediate \( \text{304} \) elides triphenylphosphine oxide to give fused the pyrazoline \( \text{305} \) (Scheme 28), this elimination of \( \text{OPPh}_3 \) being the driving force of the reaction. The zwitterion \( \text{303} \) adds on to a second molecule of the azo-ester \( \text{302} \) yielding the zwitterion \( \text{306} \) which by a domino [5+4]annulation with \( \text{1} \rightarrow \text{307} \) and elimination of \( \text{OPPh}_3 \) gives the seven membered ring compound \( \text{308} \) (Scheme 28).

\[
\begin{align*}
\text{E} & \text{N} \equiv \text{N} \equiv \text{E} \\
\text{302} & \quad \xrightarrow{\text{PPh}_3} \\
\oplus \text{N} & \equiv \text{N} \equiv \text{E} \\
\text{303} & \quad \xrightarrow{\text{[4+3]}} \\
\ominus \text{N} & \equiv \text{N} \equiv \text{E} \\
\text{302} & \quad \xrightarrow{\text{[5+4]}} \\
\ominus \text{N} & \equiv \text{N} \equiv \text{E} \\
\text{PhP} \equiv \text{N} & \equiv \text{E} \\
\text{306} & \quad \xrightarrow{\text{1}} \\
\text{E} & \equiv \text{N} \equiv \text{N} \equiv \text{E} \\
\text{305} & \quad \xrightarrow{\text{PhPO}} \\
\ominus \text{N} & \equiv \text{N} \equiv \text{E} \\
\text{304} & \quad \xrightarrow{\text{[4+3]}} \\
\ominus \text{N} & \equiv \text{N} \equiv \text{E} \\
\text{PhP} \equiv \text{N} & \equiv \text{E} \\
\text{306} & \quad \xrightarrow{\text{[5+4]}} \\
\ominus \text{N} & \equiv \text{N} \equiv \text{E} \\
\text{307} & \quad \xrightarrow{\text{PhPO}} \\
\ominus \text{N} & \equiv \text{N} \equiv \text{E} \\
\text{308} & \quad \xrightarrow{\text{[5+4]}} \\
\end{align*}
\]

Scheme 28

Baskar and coworkers\(^{201}\) have reported that an equimolar mixture of \( \text{1} \) and diisopropyl azidodicarboxylate (DIAD) \( \text{302} \ (E = \text{CO}_2\text{Pr}) \) in THF on treatment with \( \text{PPh}_3 \) gives \( \text{305} \) (26%)
and the tetracyclic compound 309 (27%). Increased amount of DIAD and phosphine in the above reaction gives a higher yield of 309. Evidently this is an example of stereoselective cascade double annulations, the initially formed pyranopyran 305 undergoing [3+2] cycloaddition with the Huisgen zwitterions 303 followed by elimination of triphenylphosphine oxide. Similar cascade double annulation of 1 first with 303 (E = CO$_2$Pr) and then with allenic ester 310 gives the tetracyclic pyranone 311 (Scheme 29). In contrast to the PPh$_3$ catalyzed regiospecific [3+2] cycloaddition of 310 with 305, that with 268 (R = H or CO$_2$Me, R$^1$ = Me), the [4+2] adduct of 1 and R-C≡C-CO$_2$Me (R = H, CO$_2$Me), gives the two regioisomers 312 and 313$^{201}$.

\[ \text{ChrCHO} + \text{DIAD} \xrightarrow{\text{THF, PPh}_3} 302 \xrightarrow{\text{305}} 303 \xrightarrow{[3+2]} -\text{Ph}_3\text{PO} \xrightarrow{\text{EtO}_2\text{C}} 309 (E = \text{CO}_2\text{Pr}) \]

\[ \text{310} \xrightarrow{\text{PPh}_3} \text{EtO}_2\text{C} \]

\[ \text{311} \]

\[ \text{312} \]

\[ \text{313} \]

Scheme 29

$^N$-Phenylnitron 314 reacts with DMAD in the presence of PPh$_3$ (1.2 eq.) to give the pyrido[4,3-b]chromone 317. Here the nitron 314 and the zwitterion 315 (E = CO$_2$Me) derived from DMAD and PPh$_3$ add initially in a [5+3]annulation mode (either in a concerted or stepwise manner) to give the intermediate 316 that by a sequential phosphine oxide elimination and a 1,3-H shift gives the fused pyridine 317 (Scheme 30).$^{202}$
7.3-Formylchromone as a Component in One Pot Multicomponent Synthesis

This section deals in the reaction of 3-formylchromone with at least two other different reactants, if not more, put together at a time in one reaction vessel. As ChrCHO contains three electropositive centres, most of the other reacting partners should function as nucleophiles either in the absence or in the presence of a suitable catalyst. The final product arises through a sequence of reactions between the reactants and the reaction intermediates. This reaction is further divided into a few subsections based on the number and nature of the components involved in the multi-component (M-C) reactions.

7.1. Three component condensation between ChrCHO, a nitrogen nucleophile and a third reactant

For the sake of brevity, a few examples of the title type of condensation involving an amine as the nitrogen nucleophile are tabulated in Table 2.

Table 2. Products from 3-C condensation of ChrCHO, an amine and a third reactant along with reaction conditions and references

<table>
<thead>
<tr>
<th>Entry No</th>
<th>Third Reactant</th>
<th>Amine component</th>
<th>Reaction conditions</th>
<th>Product</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P(OMe)₃</td>
<td>PhCH₂NH₂</td>
<td>Yittria-Zirconia, Lewis acid catalyst, aq. MeCN, 60 °C</td>
<td><img src="314.png" alt="Chemical structure" /> + <img src="315.png" alt="Chemical structure" /> → <img src="316.png" alt="Chemical structure" /> → <img src="317.png" alt="Chemical structure" /></td>
<td>203</td>
</tr>
</tbody>
</table>

Scheme 30
<table>
<thead>
<tr>
<th>Entry No</th>
<th>Third Reactant</th>
<th>Amine component</th>
<th>Reaction conditions</th>
<th>Product</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>PhCOMe</td>
<td>PhCH₂NH₂</td>
<td>-do-</td>
<td></td>
<td>204</td>
</tr>
<tr>
<td>3</td>
<td>PhC≡CH</td>
<td>MeCONH₂</td>
<td>MeCN–AcOH–TFA, AlCl₃, reflux</td>
<td></td>
<td>205a</td>
</tr>
<tr>
<td>4</td>
<td>β-Naphthol</td>
<td>RCONH₂ (R = Me or OEt)</td>
<td>Ethylammonium nitrate (EAN), neat, r.t.</td>
<td></td>
<td>206</td>
</tr>
<tr>
<td>5</td>
<td>X-C₆H₄NH₂ (X = H, Me, Cl, Br, NO₂)</td>
<td>In(OTf)₃, MeCN, Δ or MWI</td>
<td></td>
<td>207</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>RNH₂ (R = H, Me, Ph, PhCH₂ etc.)</td>
<td>PhMe, Δ</td>
<td></td>
<td>208</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>HSCH₂COOH</td>
<td>ArNH₂</td>
<td>MWI</td>
<td></td>
<td>209</td>
</tr>
<tr>
<td>8</td>
<td>HSCH₂COOH</td>
<td>2-Aminobenz-thiazole</td>
<td>ZnCl₂, PhH, Δ</td>
<td></td>
<td>210</td>
</tr>
<tr>
<td>9</td>
<td>NH₄OAc</td>
<td>EtOH, Δ</td>
<td></td>
<td></td>
<td>211</td>
</tr>
<tr>
<td>10</td>
<td>PhCOMe</td>
<td>NH₄OAc</td>
<td>EtOH, Δ</td>
<td></td>
<td>212</td>
</tr>
</tbody>
</table>
Table 2. Continued

<table>
<thead>
<tr>
<th>Entry No</th>
<th>Third Reactant</th>
<th>Amine component</th>
<th>Reaction conditions</th>
<th>Product</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Dimedone</td>
<td><img src="image" alt="image" /></td>
<td>TBAB, H2O, 70-80 °C</td>
<td><img src="image" alt="image" /></td>
<td>213</td>
</tr>
<tr>
<td>12</td>
<td>R^1COCH_2CO_2R^2</td>
<td>NH_4OAc</td>
<td>Wells-Dawson heteropolyacid</td>
<td><img src="image" alt="image" /></td>
<td>214</td>
</tr>
<tr>
<td>13</td>
<td>MeCOCH_2CO_2Et</td>
<td>NH_2OH.HCl</td>
<td>Sodium salt of saccharin, water, Δ</td>
<td><img src="image" alt="image" /></td>
<td>215</td>
</tr>
<tr>
<td>14</td>
<td>E-C≡C-E (E = CO_2Me, CO_2Et)</td>
<td>RNH_2 (R = alkyl or aryl)</td>
<td>PhMe, POCl_3, 80 °C</td>
<td><img src="image" alt="image" /></td>
<td>216</td>
</tr>
<tr>
<td>15</td>
<td>-do- ArNH_2</td>
<td>EtOH, Δ</td>
<td><img src="image" alt="image" /></td>
<td>208</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>CH_3O</td>
<td>H_2NCH_2COOH</td>
<td>MeOH, Δ</td>
<td><img src="image" alt="image" /></td>
<td>217</td>
</tr>
<tr>
<td>17</td>
<td>CH_3O</td>
<td>R = Me, CH_2CHMe_2, CH_2CH_2SMe</td>
<td>MeOH, Δ</td>
<td><img src="image" alt="image" /></td>
<td>217</td>
</tr>
</tbody>
</table>

*a* It is also obtained by SiCl_4-ZnCl_2 catalyzed 3-C condensation of ChrCHO, PhCOMe and MeCN in CH_2Cl_2 at r.t.,<sup>205b</sup> the product 322 is admixed with a little amount of 3-bis(indol-3-yl)methylchromone; *b* the product 329 is contaminated with the corresponding Hantzsch 1,4-dihydro-4-(chromon-3-yl)pyridine derivative.
One pot reaction of 3-formylchromone, alkyne 267 (R = H, CO₂Me; R¹ = Me, Et) and 3-(2-aminoethyl)indole 338 in the presence of PPh₃ gives the tetrahydroindolo[2,3-a]quinolizine (centrocountin) 339. Here the alkyne 267 gives with 1 in the presence of PPh₃ the pyranochromone 268. Aza-Michael addition of indole 338 through its primary amino group to 268 is succeeded by a domino sequence of reactions to give ultimately the indoloquinoizine 339 (Scheme 31). This 3-C condensation is also catalyzed by ZnCl₂ (1.2 equiv) in DMSO. Some chiral 1,1'-binaphthyl-2,2'-dihydrogenophosphates have been used to form 339 (R = CO₂Me, R₁ = Me) in 48-63% ee.

Scheme 31

ChrCHO when subjected to Biginelli reaction with a β-ketoester 340 and guanidine or urea or thiourea 341 behaves as a simple aldehyde to give the 1,4-dihydropyrimidine derivative 342 (Scheme 32). Thus ChrCHO, ethyl acetooacetate and guanidine together in DMF-NaHCO₃ at 70 °C gives 342 (R = Me, R¹ = Et; X = NH). PTS in ethanol, trifluoroethanol and xanthan sulphuric acid as well as TaBr₅ under solvent free condition can catalyze the formation of 342 (X = O, S) from ChrCHO, different β-ketoesters 340 (R = Me, R¹ = Me, Et) and 341 (X = O, S).

Scheme 32

When a methanolic solution of ChrCHO, DL-alanine, dimethyl fumarate and a few drops of acetic acid is refluxed for 1 h, proline 344a (60%) without any trace of the other diastereoisomer 345a is isolated. Here ChrCHO and alanine forms the syn-dipole 343 stabilized by double hydrogen bond formation that captures the dipolarophile dimethyl fumarate (Scheme 33).
When dimethyl fumarate is replaced by fumaronitrile, both the diastereoisomers 344b and 345b (4.5:1) are obtained. 3-C condensation involving ChrCHO, N-phenylmaleimide and an α-aminoacid also leads to a proline derivative; use of glycine, alanine and L-cysteine as the aminoacid in the above 3-C reaction yields 346a,b and c, respectively.225

\[
\text{ ChrCHO} + \text{H}_2\text{N} \rightarrow \text{ ECO}_2\text{Me} \quad \text{344a: } E = \text{CO}_2\text{Me} \\
\text{ ChrCHO} + \text{H}_2\text{N} \rightarrow \text{ ECN} \quad \text{344b: } E = \text{CN} \\
\]

\[
\text{ Scheme 33 }
\]

A mixture of ChrCHO, sarcosine 347 and ninhydrin 348 in methanol under reflux produces the dispiropyrrrolidines 350 and 351 sometimes admixed with dispiropiperazine 352.226 Ninhydrin being far more reactive than ChrCHO forms with sarcosine the azomethine ylid 349 that adds to ChrCHO to give 351; the compound 350 arises through the reaction of 349 with in situ generated formaldehyde followed by interaction with 1. Addition of formalin in the reaction mixture produces 350 exclusively.226 The piperazine 352 arises by dimerization of the ylid 349 (Scheme 34).

Formation of the pyrrolo[2,1-a]isoquinoline by stirring a mixture of 1, isoquinoline and phenacyl bromide (or ethyl bromoacetate) in water containing a surfactant as CTAB and a base as DBU has been reported by Naskar and co-workers.227 Here the isoquinolinium bromide 353, derived from isoquinoline and BrCH_2COZ (Z = Ph or OEt), gives in the presence of DBU the dipole 354 that undergoes [3+2]cycloaddition with the pyran-2,3-double bond of 1; the resultant adduct 355 (non-isolable) undergoes base catalyzed deformylation followed by pyran ring opening and air oxidation to give the fused isoquinolidine 356 (Scheme 35).
Scheme 34

Scheme 35

For 353-356: Z = Ph or OEt
The 1,4-dipole 357 derived from 3-methylisoquinoline and acetylene dicarboxylate undergoes [4+2] cycloaddition with the pyran 2,3-olefinic bond of 1 to give the chromenopyridoisoquinoline 358 (Scheme 36).\(^\text{228}\)

\[ \begin{align*}
  \text{CHO} & \quad \text{N} \quad \text{Me} \\
  \text{O} & \quad \text{E} & \quad \text{O} \\
  \text{N} & \quad \text{Me} & \quad \text{H} & \quad \text{X} & \quad \text{DMF} & \quad \text{r.t.} \\
  1 & & & & & \text{357} & \quad \text{358} & \quad \text{X} = \text{CHO} \\
\end{align*} \]

For 357 and 358: E = CO\(_2\)Me or CO\(_2\)Et

Scheme 36

[4+2]-Dipolar cycloaddition of the zwitterion generated from isoquinoline and DMAD in ionic liquid [bmim]BF\(_4\) at room temperature with pyran 2,3-olefinic bond of 1 followed by deformylation gives 359 and that with its aldehyde carbonyl group gives 360 (Scheme 37), the two products being formed in 8:2 proportion in 72% total yield.\(^\text{229}\)

\[ \begin{align*}
  \text{CHO} & \quad \text{N} \quad \text{Me} \\
  \text{O} & \quad \text{E} & \quad \text{O} \\
  \text{N} & \quad \text{Me} & \quad \text{H} & \quad \text{X} \\
  1 & & & & \text{[bmim]BF\(_4\)} & \text{r.t.} & \text{359} & \text{360} & \text{For 359 and 360: E = CO\(_2\)Me} \\
\end{align*} \]

Scheme 37

The 1,4-zwitterion derived from 4,5-dimethylthiazole and acetylenedicarboxylate has been shown to react at low temperature readily with 3-formylchromone 1 giving the thiazolo[3,2-a]pyridines 363 and 364. The said reaction with 1a as the substrate in DMF at -10 °C to r.t. gives 363a and 364a in 45 and 4% yield, respectively whereas 1b and 1c having electron donating substituents at p-position of the pyran oxygen, the yields of 363b,c and 364b,c being around 7 and 35%. However, at higher temperature the thiazolopyridine 362 is formed as a mixture of two rotamers presumably after a 1,2-aryl migration from 364 (Scheme 38).\(^\text{230}\)

An example of 3-C reaction involving 3-formylchromone and two nitrogen nucleophiles is also known. 2-(3-Chromenyl)-1-hydroxyimidazoles 365-368 have been prepared by one pot three component condensation of unsubstituted 3-formylchromone, AcONH\(_4\) and the appropriate α-hydroxyiminoketone in hot glacial acetic acid and their protropic tautomerism studied.\(^\text{231}\) C2-H of the chromone moiety of all these 1-hydroxyimidazoles in CD\(_2\)CN +CF\(_3\)SO\(_3\)H as well as in TFA appears as a narrow singlet (at δ ~ 9.50) precluding the tautomeric exchange process. 4,5-
Dimethylimidazole 365 exists in solution exclusively as the \( N \)-hydroxytautomer regardless of the nature of the solvent. In a hydrogen bond acceptor DMSO-\( d_6 \), 5-carbonylimidazoles 366-368 exist in the \( N \)-oxide form. In a weak hydrogen donor CDCl\(_3\), 366 also exists as the \( N \)-oxide tautomer whereas 367-368 exist in a tautomeric equilibrium, the \( N \)-oxide forms 367' and 368' prevailing over the \( N \)-hydroxy ones 367 and 368.

7.2. Three component reactions of 3-formylchromone with reagents other than a nitrogen nucleophile

Palladium catalyzed three component coupling reaction between 3-formylchromone, alcohol and allyl acetate leads to the highly substituted chromanone 369 (Scheme 39 – path a). This
reaction most probably proceeds via the formation of the benzopyrylium cation, generated from the Pd-catalyzed reaction between chromone 1 and allyl acetate. The subsequent trapping of the benzopyrylium cation by alcohol gives the corresponding product 369 in excellent yield. This alkoxy-allylation reaction is highly diastereo-selective and only one diastereoisomer is obtained. The chromanone 371 very much analogous to 369 is obtained by Pd-catalyzed decarboxylative aza-Michael addition – allylation reaction between 1 and allyl carbamate 370 (Scheme 39 – path b). The plausible formation of 371 by Pd-catalyzed three component coupling among 1, allyl acetate and ethyl N-phenylcarbamate has not been attempted.

Scheme 39

Diastereoselective synthesis of the pyrano-fused coumarin 372 via DBU catalyzed 3-C reaction of ChrCHO, 4-hydroxycoumarin and 3-bromo-4-hydroxycoumarin has been achieved. The compound 372 arises by a sequence of intramolecular lactonization-delactonisation of the initially formed bis(coumarin-3-yl)(chromon-3-yl)methane 172. An equimolar mixture of 1, dimedone and β-naphthol in hot AcOH gives the naphthopyran 373; use of Meldrum’s acid in place of dimedone in the above reaction produces the naphthopyrone 374 admixed with the pentacyclic compound 375. Proper mechanisms for the formation of 373-375 have been proposed. The heterodiene 376 (R1 = H, R2 = Ph; R1 = R2 = Me), preformed from 3-boronoacrolein pinacolate and hydrazine H2NNR1R2 (R1 = H, R2 = Ph; R1 = R2 = Me) is heated together with N-methylmaleimide and 3-formylchromone in toluene at 85 °C; the initially formed bicyclic allylic boronate intermediate 377 reacts with ChrCHO to give the highly substituted piperidine derivative 378 after hydrolytic workup. Passerini reaction involving ChrCHO, tosylmethylisocyanide and benzoic acid gives chromenyl-amido ester 379 that can be transformed into chromenylacetamide 380 by treatment with NaOEt-EtOH.
An equimolar mixture of ChrCHO, alkylisocyanide RNC (R = t-Bu, c-hexyl) and methyl (or ethyl) acetylenedicarboxylate in PEG-400 at room temperature is reported to give the chromenylfuran 381 but that in benzene at 40 °C a mixture of 381 and the cyclopentanochromone 382. The reaction of ChrCHO with the zwitterionic intermediate generated in situ from RNC and acetylenecarboxylate (1:2) in benzene at 40 °C affords an isomeric mixture of the cyclohepta[b]chromene carboxylates 383 and 384.
The formation of the furocoumarin 385 and biscoumarin 386 by treating ChrCHO with 4-hydroxycoumarin and cyclohexylisocyanide in ethanol-pyridine under reflux has been rationalized. The compound 386 is also obtained by reacting bis(coumarin-3-yl)(chromon-3-yl) methane 172 with cyclohexylamine under similar condition. An equimolar mixture of ChrCHO, cyclohexylisocyanide and ninhydrin in a boiling mixture of DCM and MeOH (7:1 by volume) affords the furochromone 387a that on hydrolysis by HCl-MeOH leads to the fused furanone 387b, no dehydration taking place. The one pot three component reaction of ChrCHO, 1,3-disubstituted barbituric acid and R2NC (R2 = alkyl) in DMF at room temperature furnishes the furo[2,3-d]pyrimidine 388. The product presumably arises via [4+1]cyclization of R2NC with the initially formed condensate of 1 and barbituric acid followed by a 1,3-H shift.

7.3. 3-Formylchromone as a component in the four component reactions

Application of the Hantzsch procedure for synthesis of 1,4-dihydropyridine in one-pot reaction of ChrCHO, dimedone, ethyl acetoacetate and ammonium acetate gives the cyclohexanopyridine derivative 389. An Ugi four component reaction of 3-formylchromone ArNH2, RNC (R = t-Bu, c-hexyl, 2,6-dimethylphenyl) and cyanoacetic acid at room temperature gives the diamide 390. Similar 4-C reaction involving 3-formylchromone, 2-haloaniline 391 (X = Cl, Br, I), RNC (R = t-Bu, c-hexyl) and R1COOH (R1 = Me, Et) provides the Ugi product 392 convertible into 1-benzopyrano[3,2-c]quinolin-12-one 393 by a ligand free Pd-catalyzed intramolecular C-H arylation protocol [PdCl2 or Pd(OAc)2, KOAc, DMF, Δ] at the C-2 position of the chromone moiety. Synthesis of chromone containing tripeptide 394 via a pseudo-five-component reaction between ChrCHO, Meldrum’s acid, alkylisocyanide RNC and ArNH2 (2-equivalent) in CH2Cl2 at room temperature has been achieved.
Marcaccini et al.\textsuperscript{247} have reported a diastereoselective, one-pot, two step synthesis of the spiropyrrolidinochromanone 397. Their method consists of an Ugi 4-C condensation of 3-formylchromone, ArNH\textsubscript{2} (Ar = Ph, substituted phenyl), RNC (R = t-Bu, c-hexyl, 2,6-diphenylphenyl) and glyoxylic acid 395 (Z = H, OMe) followed by an aza-Michael addition of a second amine R\textsuperscript{1}NH\textsubscript{2} (R\textsuperscript{1} = CH\textsubscript{2}C\textsubscript{6}H\textsubscript{4}-X; X = H, Cl etc.) to the resultant Ugi product 396 and subsequent cyclization (Scheme 40).\textsuperscript{247}

![Scheme 40](image-url)
One pot three component reaction of thiophene-2-carbaldehyde, the β-ketoester 398 and guanidine followed by addition of 3-formylchromone as the fourth component in the pot gives the pyrimidopyrimidine 400 evidently through the intermediacy of the 3,4-dihydropyrimidine 399 (Scheme 41).\textsuperscript{248}

\[
\text{Scheme 41}
\]

8. Conclusions

Interest in the chemistry of 3-formylchromone and its use as a synthon for several novel heterocyclic systems has been amply vindicated by a spate of publications. The present article, complementary to an earlier one\textsuperscript{6} is a comprehensive survey of a huge number of publications that have appeared mainly since 2007 to February 2014 and it provides a quick view of the research work already done in the title topic.

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Amarnath Chakraborty received his B.Sc. and M.Sc. in Chemistry from Vidyasagar University, India in 2002 and 2004 respectively. After obtaining Ph.D. in 2011 for his work on organometallic chemistry with Professor Amitabha Sarkar in Indian Association for the Cultivation of Science (IACS), Kolkata, he moved to Radboud University, Netherlands for his postdoctoral research with Professor Jan C. M. van Hest. Currently he is working as a Research Associate in the Department of Organic Chemistry at IACS, Kolkata. His current research interest is focused on synthetic organic and organometallic chemistry.