Chemistry of 4-oxo-4H-1-benzopyran-3-carbonitrile

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Abstract
The review article, primarily designed to complement an earlier one (J. Heterocycl. Chem. 2005, 42, 1035-1042), gives a comprehensive survey of the synthesis and chemistry of the title nitrile covering the literature published during 2005-2014.

Keywords: 4-Oxo-4H-1-benzopyran-3-carbonitrile, radical addition, nucleophilic addition, aza- and oxa-Michael allylation, cycloaddition, carbocyanation

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1. Introduction

The uniqueness of the title benzopyran (trivial name: 3-cyanochromone) 1, because of its diverse functionalities (an endocyclic olefinic bond with a keto and a nitrile functionalities at one end and a nucleofugal phenoxy group at the other end), its capability to assume a pyrylium betaine structure in the presence of an appropriate reagent and its ‘chemical equivalence’ to 2-amino-3-formylchromone 2 under certain reaction conditions, is mentioned in our earlier review article covering the literature on its synthesis and reactions reported up to 2004. Earlier syntheses reported up to 1986 of different heterocycles fused with the 2,3-bond of [1]benzopyran from 3-cyanochromone 1 or its equivalent 2-amino-3-formylchromone have been compiled. A critical account of the reactions of the nitrile 1 with amines, hydrazines and hydroxylamine appeared in 2012. The present article, primarily designed to complement our earlier one, is a comprehensive survey of the chemistry of 3-cyanochromone 1 covering the literature published from 2005 – 2014. Some earlier works which have later been either adversely criticized or rectified or are helpful for a better understanding of the present write-up are briefly referred to. Patented works and reactions of 2-substituted 3-cyanochromone are excluded, and the biological properties of the reported compounds are less emphasized. In this manuscript the 4-oxo-4H-1-benzopyran-3-yl moiety is abbreviated as ‘Chr’ so that the title nitrile 1 may be represented by ChrCN. Alkyl, alkoxy and halogeno substituents in the benzene ring of chromone remain unaffected in most of the reactions described here for the unsubstituted 3-cyanochromone. The reactions of the nitrile 1 are described here in the following sections and subsections based on the type of reactions and nature of the reagents. It is worth mentioning here that a closely related review article ‘Chemistry and application of 4-oxo-4H-1-benzopyran-3-carboxaldehyde’ has been recently published by the present authors.

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{Nitrile} \\
\text{CN} & \quad \text{NH}_2 & \quad \text{CHO} & \quad \text{X} \\
1 & \quad 2 & \quad 3 \quad X = O & \quad 4 \quad X = \text{NOH} & \quad 5 \quad X = \text{NOR (R = alkyl or aryl)}
\end{align*}
\]
2. Synthesis

3-Cyanochromone can be prepared from 4-oxo-4H-1-benzopyran-3-carboxaldehyde 3 via its oxime 4 or oxime O-alkyl (or aryl) ether 5. A convenient synthesis of 1 involves Vilsmeier-Haack reaction of 2-hydroxyacetophenone with DMF and POCl₃ at 0 °C and subsequent treatment of the reaction mixture in situ with NH₂OH.HCl at ambient temperature.¹²

3-Bromochromanone 6 has been converted into 3-cyanochromone 1. The former on KHMDS enhanced SmI₂-mediated cyanation by tosyl cyanide gives 3-cyanochromanone 7 which on dehydrogenation by DDQ affords the nitrile 1 (Scheme 1).¹³

![Scheme 1](image)

KHMDS = potassium salt of hexamethyldisilazane. (Me₃Si)₂N K

3. Radical Addition

An alkyl iodide such as 8 (R = ethyl, i-Pr, t-butyl, cyclopentyl, cyclohexyl) undergoes radical addition to the pyran 2,3-olefinic bond of 1 in the presence of triethylborane and oxygen, giving in an excellent overall yield (81-94%) a diastereoisomeric mixture of the chromanone 9, the trans-isomer predominating over the cis-isomer (Scheme 2); the diastereoselectivity is not improved by carrying out the reaction at low (~– 40 °C) temperature.¹⁴

![Scheme 2](image)

4. Transformation of the Nitrile Group of 3-Cyanochromone

Transformation of ChrCN to chromone-3-carboxamide, -3-N-t-butylcarboxamide and the 3-carboxylic acid has already been mentioned.¹ Ibrahim prepared the carboxamide 10 by treatment of a suspension of 3-formylchromone in carbon tetrachloride with NBS under UV irradiation followed by evaporation of the solvent and quenching the reaction mixture with ammonia, and subjected it to various transformations (Scheme 3). Thus, carboxamide 10 with aqueous NaOH (1M) rearranges to 4-hydroxycoumarin 12 via 11, with RNH₂ (R = Me, Et) in ethanol the 4-aminomethylenecoumarin 13, and with MeONa the azaxanthone derivative 14.
Addition of hydroxylamine to nitrile functionality of ChrCN is mentioned elsewhere (*vide* section 5.4)

\[
\begin{align*}
\text{OH} & \quad \text{CONH}_2 \\
\text{O} & \quad \text{OH} \\
\text{OH} & \\
\text{H} & \\
\text{N} & \quad \text{O} \\
\text{O} & \quad \text{OH} \\
\text{H} & \\
\text{CH}_2 & \\
\text{O} & \quad \text{CONH}_2 \\
\text{R} & \quad \text{NHR}
\end{align*}
\]

Scheme 3

5. Reaction with Nitrogenous Nucleophiles

5.1. Reaction with ammonia
ChrCN is prone to form the aldehyde 2 even under slightly alkaline conditions. ChrCN in ethanol containing a few drops of aqueous ammonia on warming produces the aldehyde 2. ChrCN when heated with ammonium acetate in acetic acid under reflux affords the self-condensation product 18 which is also obtained on refluxing the aldehyde 2 in acetic acid.\(^{16}\) Here the aminochromone 15 (X = NH or O) condenses with itself through a domino Michael – retro-Michael – heterocyclization reaction sequence giving the chromenopyrimidine 18 (Scheme 4).
5.2. Reaction with primary amines

The nature of the products resulting from the reaction of ChrCN with a primary amine depends on the stoichiometry of the reactants as well as the reaction conditions; a minor variation in the reaction conditions may drastically change the reaction course. We obtained 2-amino-3-formylchromone \(2\) (45\%) together with 2-methylenetetrahydro-imidazole \(22\) (15\%) by refluxing an equimolar mixture of \(1\) and ethylenediamine \(19\) in ethanol for 3 h,\(^\text{16}\) but got the diazocene \(27\), a dimer of ChrCN, by just warming an ethanolic solution of a 1:0.5 molar mixture of \(1\) and \(19\) for 10 min.\(^\text{17}\) In contrast, heating ChrCN (1 equiv) with ethylenediamine (0.5 equiv) in ethanol for 10 min is reported to produce the bis-imine \(29\).\(^\text{18}\) All these products \(2, 22, 27\) and \(29\) have been well characterized by analytical and spectral data beyond any doubt; hence the Russian group’s terse comment\(^\text{18}\) as the reported\(^\text{17}\) diazocene \(27\) being in fact the bis-imine \(29\) is unjustified.

![Scheme 5](image-url)
Plausible mechanisms for the formation of all the above named products are given in Scheme 5. The diamine 19 undergoes aza-Michael addition to the α,β-unsaturated nitrile 1; the adduct 20 by a base catalyzed elimination of HCN gives 21 (path a), the diamine 19 or the adduct 20 itself functioning as the base. The intermediate 21 by an intramolecular 1,4-addition with concomitant opening of the pyran ring gives the imidazole 22. The adduct 20 also undergoes retro-Michael to give 23 (path b), its cyclic isomer 24 taking up two different reaction courses. It functions as a nucleophile to a second molecule of ChrCN to give ultimately the diazocene 27 via 25 and 26 through an ANRORC mechanism (path ba). A 1,5-Hydrogen shift in the imino-enamine 24 leads to 28 that reacts with a second ChrCN molecule giving bis-chromone 29 again through an ANRORC mechanism (path bb). The formation of 2-aminochromone 2 as the major product obtained by refluxing ChrCN with ethylenediamine in ethanol16 may involve hydrolysis of any or/and all of the compounds 27-29.

An aromatic primary amine as ArNH2 (Ar = phenyl or substituted phenyl) with ChrCN in refluxing benzene gives in varying proportions the acrylonitrile 30 (Z, E- mixture) and the Schiff base 31, the latter being formed exclusively in the presence of a few drops of triethylamine in the reaction medium.18,19 The compound 31 (Ar = 4-MeC₆H₄) is, however, obtained by reacting ChrCN with p-toluidine in refluxing benzene.20 ChrCN reacts similarly with o-phenylenediamine and o-aminophenol yielding 32 and 33, respectively. Transformation of 32 in boiling acetic acid to 1-benzopyran-3-ylimidazole 34 has been rationalized.3,19 The erroneous structures 35 and 36, the former proposed to arise from 1 and o-phenylenediamine in hot ethanol and the latter by cyclization of the former and subsequent air oxidation,16 have been duly rectified by Sosnovskikh et al.3,19 as 32 and 34, respectively. The structure 37 assigned to the product similarly obtained by Risitano et al.21 from 1 and o-phenylenediamine should also be rectified as 32. In light of these data, the 1,2,4-triazine structure 39 proposed for the product obtained by refluxing ChrCN with 1,6-diamino-2-oxo-1,2-dihydropyridine 38 (R = p-chlorophenyl, 5-methyl-4-oxo-4H-1-benzopyran-3-yl) in DMF22-24 deserves further scrutiny; it may be assigned
the structure 40. The pyranopyrimidine 18 is obtained by heating 33 in AcOH\textsuperscript{19} as well as 31 (Ar = 4-MeC\textsubscript{6}H\textsubscript{4}) in DMF\textsuperscript{20} through a mechanism as depicted in Scheme 4, X in 15-17 representing the appropriate NAr.

5.3. Reaction with hydrazines

Our contention of 1,2-addition of phenylhydrazine 41 to the nitrile functionality of ChrCN and convertibility of the iminohydrazine adduct 42 to 3-aminopyrazole 43 (Scheme 6 – path a)\textsuperscript{25} has been convincingly refuted by Sosnovskikh et al.\textsuperscript{3,26} who have obtained a mixture of hydrazone 45 and 5-aminopyrazole 46 from the same reactants and under identical conditions evidently via the intermediate 44 (resulting from a domino Michael – retro-Michael reaction) (Scheme 6, path b); the hydrazone 45 is the exclusive product when the reaction is carried out in benzene or benzene-triethylamine and it can be converted to 46 under conditions as shown in Scheme 6. An acetic acid solution of 1 and 41 on heating affords via 44 the chromenopyrazolone 47.\textsuperscript{26}

Scheme 6

The nitrile 1 with methylhydrazine in boiling C\textsubscript{6}H\textsubscript{6} gives the pyrazole 48 admixed with a little amount of its isomer 49, whereas the same mixture in boiling acetic acid forms the pyrazolocoumarin 50 which is also obtainable by digesting 48 in acetic acid.\textsuperscript{26} A mixture of ChrCN and N,N-dimethylhydrazine in refluxing benzene forms the hydrazone 51 that in DMF heated under reflux undergoes self-condensation to the diazocene 27.\textsuperscript{20}
5.4. Reaction with hydroxylamine

We have reported the formation of the hydroxylamino-imine 52 by reacting ChrCN with an equivalent amount of NH₂OH.HCl in ethanol containing NaOAc.²⁵ As per a polish group’s report²⁷,²⁸ the same reaction in the presence of alkali gives in addition to the oxime 54 another compound assigned as 53 on the basis of a doubtful mechanism. A Russian group³,²⁹,³⁰ have asserted that the initially formed amino-aldoxime 54 under alkaline condition leads via 55 and 56 to 2-amino-3-carbamoylchromone 57 (Scheme 7), its structure being confirmed by detailed spectral studies. The chromone 57 on further treatment with NH₂OH gives the chroman-2,4-dione 60 through 58 and 59. In the conversion (59 → 60), NH₂OH brings about reductive cleavage of N-O bond of the isoxazole 59. The diamine 60 on acetylation forms an E, Z- mixture of the monoacetate 61 (Scheme 7).

A careful scrutiny of the reported IR and ¹H-NMR (DMSO-ᵈᴰ) of the three compounds 52, 53 and 57 reveals that the first two compounds show identical IR and ¹H-NMR spectra.
having three exchangeable hydrogens whereas 57 four exchangeable hydrogens. We feel that the so called compound 53 is indeed 52, particularly its mass spectral fragmentation \([m/e: 204 (27\%, M^+), 171 (100, M-NH_2OH) \text{ and } 144 (19, M-NH_2OH-HCN)]\) indicating it to arise from 1,2-addition of NH_2OH to cyano group of ChrCN. So the Russian group’s assertion\(^{3,29,30}\) that the structures 52 and 53 be rectified as 57 is not worth consideration. Furthermore, the chromone 52 in the presence of excess NH_2OH is likely to give the oxime 54 through the intermediates A and B (Scheme 8) and ultimately to 60 via 57 (Scheme 7). That is why Sosnovskikh\(^{29,30}\) failed to isolate the compound 52.

![Scheme 8](image)

**6. Reaction with Carbon Nucleophiles**

**6.1. Reaction with active methyl compounds**

The intermediate 63 resulting from the base catalyzed Michael – retro-Michael reaction of the hetaryl methyl ketone 62 with the nitrile 1 undergoes heterocyclization to 1-benzopyrano[2,3-b]pyridine 64 (Scheme 9).\(^{31}\)

![Scheme 9](image)

The reaction of ChrCN with diacetylresorcinol 65 depends on the stoichiometry of the reactants to give either 3-aryl-4-azaxanthone 66 or bis-azaxanthone 67 (Scheme 10).\(^{31}\)
6.2. Reaction with active methylene compounds

The title reaction reported since 2005 is being surveyed here. Ibrahim and his group\textsuperscript{31-34} have extensively studied the reaction of the cyanochromone 1 with various acyclic and cyclic methylene compounds. Thus, the nitrile 1 reacts with active methylene compounds as 68 (R = Ph, PhCO, CO\textsubscript{2}Et), 69 and 70 (R = Ph, PhS, CO\textsubscript{2}Me, CO\textsubscript{2}Et, CONH-N=CHC\textsubscript{6}H\textsubscript{4}Cl-4) in EtOH-DBU giving the azaxanthenes 71-73, respectively.\textsuperscript{31} Several cyclic $\alpha$-methylene ketones undergo smooth and efficient ring opening and ring closure (RORC) reaction with ChrCN yielding heteroannulated chromene systems. Thus, cyclopentanone, dimesdone, thiazolone 74, pyrazolidin-3,5-dione 75 and barbituric(or thiobarbuturic) acid 76 give with ChrCN the tetracyclic compounds 77-81, respectively.\textsuperscript{31}
8-allyl-3-cyanochromone 82 behaves similarly as the unsubstituted 3-cyanochromone 1 towards several active methylene compounds. Thus, the nitrile 82 gives with malononitrile, phenylthioacetonitrile, cyanoacetamide, ethyl cyanoacetate, ethyl acetoacetate and ethyl benzoyl acetate in ethanol-DBU the 4-azaxanthone 83a-f, respectively.32 Reaction between 82 and barbituric acid under the same conditions affords the benzopyrano-fused heterocycle 84.32 The nitrile 1 as well as the aldehyde 2 when heated with the β-ketoacid 85 in DMF containing a few drops of piperidine gives the pyranoquinoline 86 instead of any azaxanthone. Here the conversion of 1 with the acid 85 involves a tandem Michael – retro-Michael – cyclization involving phenolic OH and CN functionalities and lactonization of the intermediate.33 The nitrile 82 similarly gives with 85 a product analogous to 86.

\[
\begin{align*}
&\text{82} & \text{83} & \text{84} & \text{85} & \text{86} \\
&\text{X} & \text{Y} & \text{Et} & \text{NH}_2 & \text{Et} \\
&\text{83a} & \text{NH}_2 & \text{CN} & \text{H} & \text{CO}_2\text{Et} \\
&\text{83b} & \text{NH}_2 & \text{SPh} & \text{H} & \text{CO}_2\text{Et} \\
&\text{83c} & \text{NH}_2 & \text{CONH}_2 & \text{H} & \text{CO}_2\text{Et} \\
&\text{83d} & \text{NH}_2 & \text{CO}_2\text{Et} & \text{H} & \text{CO}_2\text{Et} \\
&\text{83e} & \text{Me} & \text{CO}_2\text{Et} & \text{H} & \text{CO}_2\text{Et} \\
&\text{83f} & \text{Ph} & \text{CO}_2\text{Et} & \text{H} & \text{CO}_2\text{Et}
\end{align*}
\]

Under basic condition (EtOH, NEt₃), benzimidazole-2-acetonitrile 87 gives the pentacyclic compound 91 with 3-cyanochromone 1a but the azaxanthone 93b with 3-cyano-6-methylchromone 1b (Scheme 11).34 Here the carbanion generated from the acetonitrile 87 undergoes Michael – retro-Michael to give the intermediate 88. Nucleophilicity of phenolic OH in 88 (R = H) is less than that of its imidazole NH; so its first cyclization (→ 90) involving NH and CN followed by a second one involving the phenolic OH and imine functionalities leads to the formation of the fused heterocycle 91 (path a). The intermediate 88 (R = Me) follows a different reaction course. Here the electron donating methyl group enhances the nucleophilicity of the phenolic OH of 88; so a process of double cyclization of 89 (≡88) initiated by its phenolic OH leads to 92 that by a 1,3-Hydrogen shift ultimately gives the imidazol-2-ylazaxanthone 93b (path b). The chromone-aldehyde 2 and its 6-methyl homologue, however, behave similarly towards the nitrile 87 in giving 93a and 93b, respectively.34
The cyanochromone 1 is reported to give the pyrido-oxazole 96 when refluxed along with aceturic acid 94 in Ac₂O containing fused AcONa but the chromenopyridine 98 with hippuric acid 95 presumably under identical conditions. Abdel-Rahman et al. have, however, claimed to get 96 and 97 by heating 1 in Ac₂O-AcONa with aceturic acid and hippuric acid, respectively. Later Ibrahim claimed that the reaction of 1 with hippuric acid 95 in Ac₂O gave 99 but 97 in Ac₂O in the presence of freshly fused AcONa. Now it seems that sodium acetate used for the preparation of 98 was not freshly fused. The product proposed to have the structure 98 or 99 has identical analytical and spectral (IR, NMR) data. An IR peak at ~ 1735 cm⁻¹ definitely points to the presence of an ester carbonyl group in the compound. Furthermore, N-acylation of an aromatic acid anilide as PhNHCOPh by Ac₂O-AcONa has not been realized though Ac₂O-NaH can bring about the said acylation. So the structure 98, not 99, should be attributed to the compound resulting from 1 and hippuric acid in refluxing acetic anhydride.
A recent report for the synthesis of ethyl azaxanthone-2-carboxylate by reacting the nitrile \( \text{1} \) with a \( \beta \)-keto ester \( \text{100} \) (Scheme 12) claims that yield of azaxanthone 101 is higher when the reaction is conducted under ultrasonication than that obtained by conventional heating.

\[
\begin{align*}
\text{1} & \quad + \quad \text{R} - \text{CO}_2\text{Et} \\
& \quad \xrightarrow{\text{DBU, EtOH, } \Delta \text{ or DABCO, sonication, 20 } \circ \text{C}} \quad \text{O} \\
& \quad \xrightarrow{\text{R = Me, Ph, CH}_2\text{CO}_2\text{Et}} \quad \text{N} \\
& \quad \xrightarrow{\text{O}} \quad \text{R} \\
& \quad \xrightarrow{\text{CO}_2\text{Et}} \quad \text{101}
\end{align*}
\]

**Scheme 12**

6.3. Reaction with enamines
The carbamimidoylacetic acid ester \( \text{102} \) in an aqueous medium containing NaOAc functions as an enediamine to undergo Michael – retro-Michael reaction; the resultant intermediate \( \text{103} \) by double cyclization, the first one involving phenolic OH and CN groups and the second one involving NH2 and CO groups, to \( \text{104} \) and subsequent hydrolysis gives the coumarinopyridine \( \text{105} \) (Scheme 13).

\[
\begin{align*}
\text{1} & \quad + \quad \text{EtOH-H}_2\text{O (4:1), AcONa or, DMSO-H}_2\text{O, NaOAc, 80 } \circ \text{C} \\
& \quad \xrightarrow{} \quad \text{H}_{2}\text{O} \\
& \quad \xrightarrow{} \quad \text{NH}_2 \\
& \quad \xrightarrow{} \quad \text{O} \\
& \quad \xrightarrow{} \quad \text{H}_{2}\text{O} \\
& \quad \xrightarrow{} \quad \text{NH}_3 \\
& \quad \xrightarrow{} \quad \text{N} \\
& \quad \xrightarrow{} \quad \text{O} \\
& \quad \xrightarrow{} \quad \text{102} \\
& \quad \xrightarrow{} \quad \text{103} \\
& \quad \xrightarrow{} \quad \text{104} \\
& \quad \xrightarrow{} \quad \text{105}
\end{align*}
\]

**Scheme 13**

Heating a mixture of the naphthopyran-3-nitrile \( \text{106} \) or its ‘chemical equivalent’ 2-amino-3-formyl naphthopyran-4-one \( \text{107} \) with the enamine \( \text{108} \) (X = Me, OEt) in DMF at 80°C affords the azaxanthone \( \text{109} \). A similar reaction of \( \text{106} \) with 6-amino-1,3-dimethyluracil \( \text{110} \) gives the pyridopyrimidine \( \text{111} \).

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6.4. Reaction with pyridinium phenacylide

Pyridinium phenacylide 112 undergoes [3+2]dipolar cycloaddition with the pyran-2,3-olefinic bond of ChrCHO as well as ChrCOOH; the resultant cycloadduct by base catalyzed deformylative or decarboxylative pyran ring opening and subsequent air oxidation gives the indolozine 113. In contrast, the phenacylide 112 with ChrCN gives the 1-azirine 114, its formation involving 1,2-addition of phenacylide carbanion to -C≡N of 1 followed by cyclization and a 1,3-hydrogen shift. Kornev et al. unfortunately failed to get the 1-azirine 114; they claimed to have got the ylid 115 by refluxing a mixture of ChrCN, phenacylpyridinium bromide and potassium carbonate (in 1:1:1 or 2 equivalent) in acetone. Here the phenacylide 112 also functions as a nucleophile to undergo Michael addition to the α,β-unsaturated nitrile functionality of 1 with concomitant opening of the pyran ring. We contend that this product proposed to be the ylid 115 should exist as the dipolar ion 116.

6.5. Reaction with 1,3-bis-silyl ethers of 1,3-dicarbonyl compounds

Reaction of 3-cyanochromone 1 with 1,3-bis-silyl enolates of general formula 118 as the synthetic equivalent of 1,3-dicarbonyl compounds in the presence of trimethylsilyl triflate (TMSOTf) has been extensively investigated by Langer et al. Here the terminal carbon of the butadiene 118 is captured by the 1-benzopyrilium triflate 117, generated from 1 and TMSOTf; the resultant adduct 119 (a diastereoisomeric mixture) by a base catalyzed retro-Michael gives
the acrylonitrile 120 that undergoes a two-step cyclization to the azaxanthone 121 (Scheme 14 – path a). An alternative mode of cyclization of 120 (R² = H, R³ = OMe, OEt) by an aldol-lactonization mechanism to the baryllactone 122 is also feasible (path b). Yields of the two types of compounds resulting from 1 and some selected members of 118 are given in Table 1.

**Table 1.** Yields (%) of the compounds 121 and 122 from the reaction of some bis-silyl ethers 118 with ChrCN

| Sl No. | Silyl ethers 118 | Azaxanthone 121 | Benzocoumarin 122 | Ref. |
|--------|-----------------|-----------------|-------------------|------|
| 1      | H H OMe        | 41              | –                 | 42,43|
| 2      | Me H OMe       | 52              | –                 | 42,43|
| 3      | Et H OEt       | 54              | 13                | 42,43|
| 4      | OMe H OMe      | 47              | 11                | 42,43|
| 5      | (CH₂)₃ OEt     | 36              | –                 | 42,43|
| 6      | 4-McC₆H₄ H OMe| 63              | –                 | 44   |
| 7      | H Cl OEt       | 58              | –                 | 45   |
| 8      | H F OEt        | 56              | –                 | 46   |
| 9      | n-Pr H OEt     | –               | 37                | 47   |
| 10     | n-Bu H OEt     | –               | 42                | 47   |

**Scheme 14.** Reagents and conditions: (i) TMSOTf, CH₂Cl₂, 0 °C, 1 h; (ii) CH₂Cl₂, 20 °C, 12 h, then HCl (10%); (iii) NET₃, EtOH, 20 °C, 12 h, then HCl (1M).
The enolate 118 (R₁R² = (CH₂)₄, (CH₂)₉; R₃ = OMe) as well as 118 (R₁ = R² = H; R₃ = Me or Ph) i.e. the bis-silyl ether prepared from acetyl(or benzoyl)acetone fails to react with ChrCN.⁴⁸ Interestingly, the reaction of 1 with 4-alkyl-2-fluorobutadiene 118 (R₁ = Me, n-Pr, n-Bu, n-pent, n-hex, n-oct; R² = F; R₃ = OEt) results in the biaryl 124 in ~ 70% yield accompanied by no or a little (0-20%) of azaxanthone 121; here the major product 124 arises by cyclization of the intermediate 120 to 123 and a subsequent 1,5-ester shift (Scheme 14 – path c).⁴⁹ Karapetyan⁵⁰ could isolate only the azaxanthone 121 (R₁ = n-oct; R² = H; R₃ = OEt) in 28% yield from the reaction mixture of 1 and 118 (R₁ = n-Oct; R² = H, R₃ = OEt).

7. Aza- and Oxa- Michael – Allylation

Allyl carbamate 125 undergoes palladium catalyzed decarboxylative and regioselective aza-Michael – allylation across the pyran 2,3-π bond of ChrCN to give the chromanone 126 in one diastereoisomeric form (Scheme 15).⁵¹ This chromanone 126 cannot be prepared by Pd(0) catalyzed three component coupling reaction between ChrCN, RNHR¹ and allyl acetate.

Scheme 15

Allyl carbonate 127 likewise the carbamate 125 reacts with ChrCN in the presence of the electron rich tetrabutylammonium ferrate Bu₄N[Fe(CO)₃NO] (TBAFe) and an N,N'-diphenyldihydrobenzimidazole derived carbene ligand L to give the 2-methoxychromanone 128 in 79% yield, the ratio of this diastereoisomer over the other one being >20:1 (Scheme 16).⁵²

Scheme 16

The reaction of chiral secondary allyl carbonate 129 with ChrCN under the aforesaid conditions results in the regioselective formation of the ipso-substitution product 130 albeit as a 1:1 mixture of the diastereoisomers.⁵² Fe-catalyzed three component coupling of ChrCN, allyl acetate and an external alcohol is possible (vide section 9).
8. Cycloaddition Reactions

8.1. [3+2]Dipolar cycloaddition

2,3-Olefinic bond of 1 participates in cycloaddition reaction with several 1,3-dipoles. Its reaction with several diazoalkanes ultimately leading to 2-alkyl-3-cyanochromone has been reviewed. A diarylnitrilmine exists as 1,3-dipolar species 131A and 131B; their [3+2] cycloaddition with ChrCN forms the adducts 132 and 133 which by a retro-Diels-Alder process gives respectively 4- and 5-cyanopyrazole 134 and 135 along with the ketoketene 136 that takes up water forming salicylic acid 137 (Scheme 17).

![Scheme 17](image)

**Scheme 17**
N-Tosyl-5,5-divinylazolidin-5-one 138 (R = CH=CH₂), prepared by sequential treatment of methyl N-Boc-glycinate with vinylmagnesium bromide, potassium t-butoxide and tosyl chloride, undergoes palladium catalyzed decarboxylative cyclization across the pyran-2,3-double bond of ChrCN to give the pyrrolo[2,3-b][1]benzopyran derivative 140 (Scheme 18). Here Pd(0) catalyst brings about decarboxylation of the oxazolidinone 138 to the 1,3-dipole 139 that undergoes stereoselective [3+2] dipolar cycloaddition to the α,β-unsaturated nitrile 1 giving the adduct 140.

![Scheme 18](image)

Scheme 18

The 1,3-dipolar cycloaddition of 3,4-dimethyl-2-phenyloxazolium-5-olate (münchone) 141a to ChrCN is reported by Cordaro et al.⁵⁵ to afford the pyrrole 145 together with salicylic acid by a mechanism as depicted in Scheme 19 – path a. Of all the resonating structures (141a-d, 142, 143, 144, 145).
of the said münchone, the predominating 1,3-dipolar species 141b forms with ChrCN the endo-adduct 142 that undergoes subsequent decarboxylative degradation to give the products via the intermediates 143 and 144. We feel that the formation of the pyrrole 145 and salicylic acid from 142 through a retro-Diels-Alder process and subsequent decarboxylation (path b) is also plausible.

The azomethine ylid 146, derived from sarcosine and paraformaldehyde, also undergoes diastereoselective [3+2] cycloaddition with ChrCN in refluxing benzene giving the adduct 147 accompanied by a small amount of 148 arising from a second [3+2] dipolar cycloaddition of the ylid 146 to the carbonyl group of 147 (Scheme 20).56 The compound 148 is obtained as a single diastereoisomer when ChrCN is reacted with excess sarcosine (6 equiv) and paraformaldehyde (10 equiv) and it on heating in HCl transforms into the tetracycle 149 through a sequence of opening of the semi-aminal methylene group, deformylation and intramolecular 1,2-addition of MeNH to CN group.

Scheme 20

Reaction of ChrCN with a few 1,3-dipolar species generated from isocyanide and acetylenic ester is described in section 9.

8.2. [4+2]Cycloaddition

Diels-Alder reaction of the unsaturated nitrile 1 with several oxygenated and non-oxygenated dienes extensively studied by Hsung et al57-60 has already been reviewed.1 A mixture of ChrCN and cyclohexadiene when heated under reflux in o-dichlorobenzene forms the endo-adduct 150, no catalyst being required.61,62 This adduct on UV irradiation undergoes intramolecular [2+2] alkene-arene photocyclization to 151. The diene system in 151 can capture in situ generated phenyl vinyl ketone yielding the D-A adduct 152; the latter (152) on UV irradiation in benzene triggers an intramolecular Paterno-Büchi reaction to give the oxetane 153 (Scheme 21). The conversion (1→153) involves a double-tandem [4+2],[2+2],[4+2],[2+2] cycloaddition process. The nature of the products resulting from the protolytic metathesis of the polycycle 153 has also been reported.61,62
Scheme 21

The nitrile 1 undergoes [4+2] cycloaddition with 2,4-hexadienals 154a-f in the presence of squaramide-based organocatalyst 155 to give respectively tetrahydroxanthones 156a-f in more than 20:1 diastereoisomeric ratio and in approximately 90% enantiomeric excess (Scheme 22).63

Scheme 22

The compound 156b has been subjected to various transformations.63 As for example, 156b by reduction with sodium borohydride gives 157 that on acid hydrolysis gives the lactone 158 in more than 20:1 d.r. The compound 156b on treatment with sodium triacetoxyborohydride followed by acid hydrolysis affords the fused pyranone 159 in >20:1 d.r. (Scheme 23).
9. 3-Cyanochromone as a Component in One-pot Multicomponent Synthesis

The synthesis of the cyclohexanoxanthone 78 by heating a mixture of the nitrile 1, dimedone and ammonium acetate in ethanol under reflux has been regarded as a three-component synthesis. Here ChrCN is converted under basic conditions to 2-amino-3-formylchromone 2 that condenses with dimedone giving the expected product 78.

A mixture of ChrCN, benzaldehyde 160 (R = H, electron withdrawing or electron donating group) and AcONH4 in DMF solution containing CuCl2 at 100 °C affords 2,4-diazaxanthone 164 (Scheme 24), its yield being increased to 85% when 1.2 equivalent of CuCl2 is present as an oxidant in the reaction mixture. It is assumed that the aldimine 161, generated in situ from the aldehyde 160 and AcONH4, serves as a nitrogen nucleophile in an efficient cascade aza-Michael – retro-Michael (→162) – cyclization (→163) – dehydrogenation (→164) reaction sequence. When benzaldehyde 160 is replaced by paraformaldehyde, the 3-unsubstituted diazaxanthone 164 (H in place of C6H4R) is obtained in 74% yield.

Palladium catalyzed three-component coupling reaction between the nitrile 1, alcohol 165 and allyl acetate 166 leads to the highly substituted chromanone 167 (Scheme 25). The
stereochemistry of the product 167 is given in comparison with similar amino – allylation of the unsaturated nitrile 1 with an allyl carbamate.\(^{51}\) It is to be noted that \(t\)-butanol does not participate in this (TCC) reaction and propargyl alcohol gives a complex mixture. An account of Pd-catalyzed alkoxy – allylation by an alcohol and allyl acetate and decarboxylative amino – allylation by allyl carbamates across the pyran 2,3-double bond of the nitrile 1 with plausible mechanisms has been published.\(^{67}\)

\[1\] + R\(^3\)OH + \(R^2\)-\(\equiv\)O\(\equiv\)Ac \(\xrightarrow{\text{Pd(PPh\(_3\))}_4, \text{THF, rt}}\) \(\text{OR}^1\)-\(\equiv\)R\(^2\)

\(R^3\)OH = MeOH, Me\(\_\_\)CH\(_2\)_OH, \(n\)-C\(_4\)H\(_9\)_OH, Ph\(\_\_\)OH, Ph\(\_\_\)OH, \(t\)-Bu\(\_\_\)OH, Ph\(\_\_\)OH, \(t\)-Bu\(\_\_\)OH, Me\(\_\_\)OH

Scheme 25

The reaction between ChrCN, acetylene carboxylate 168 and isocyanide 169 in a 1:1.2:1.2 molar ratio yields the spirobenzofuran 173 as the only product (Scheme 26).\(^{68}\) The 1,3-dipolar species 170, generated from acetylene carboxylate 168 and isonitrile 169, undergoes [3+2] dipolar cycloaddition (perhaps a two-step process – \textit{vide infra}); the cycloadduct 171 rearranges under base catalysis to the spirocompound 173 via the intermediate 172, isonitrile 169 functioning as the base. The product 173 (\(E = \text{CO}_2\text{Me}\) or \(\text{CO}_2\text{Et}\)) is obtained in 56-64% yield but 173 (\(E = \text{H}\), \(R^1 = \text{Me}\)) in less than 20% yield.

\[1\] + \(\text{CO}_2\text{R}^1\) \(\xrightarrow{\text{E} = \text{H}, \text{R}^1 = \text{Me}, \text{Et}}\) \(\text{E} = \text{CO}_2\text{R}^1; \text{R}^1 = \text{Me, Et}\)

Scheme 26
When 3-cyanochromone 1 as well its analogue having its benzene ring mono- or disubstituted with chlorine or methyl group is reacted with 2 equivalents each of alkyne 168 and isonitrile 169, in toluene at 40 °C for 12 h, the spirochromeno derivative 175 or 176 (but never a mixture of the two) is obtained in 60-80 % yield (Scheme 27). Of all the unsubstituted and different mono- and di-substituted 3-cyanochromones used in this five component reaction, only 1a-d can form the spirocompound 176 and that too only with 168 (E = CO₂Me, R¹ = Me) and 169 (R² = t-Bu). The nucleophilic end of the zwitterions 170 attacks preferentially C-2 of chromone 1 leading to the intermediate 174. Before its collapse to 171, the dipolar ion intermediate 174 is captured by a second dipolar molecule 170 to give the spirocompound 175. If the initial attack of 170 at pyran C-2 occurs from the up side of the chromone ring leading to the energetically activated intermediate 174, the next attack of a second molecule of 170 to the chromone-4-carbonyl would preferentially take place from the opposite (i.e. down side) of the chromone ring; hence the product should assume the stereoechemical feature as depicted in the structure 175, a 1,3-hydride shift in 175 leading to 176. The reason for only a few members of 175 isomerising to 176 is not ascertained. The compound 175 is very susceptible to acid; addition of a catalytic amount of p-toluenesulfonic acid (2 mol%) in toluene converts 175 to 177 in 71-90% yield.

Scheme 27

10. Carbocyanation of Alkyne with 3-Cyanochromone

Nickel - Lewis acid catalyzed hetaryl cyanation of 4-octyne 178 with 3-cyanochromone 1 to the disubstituted octene 179 in Z-isomeric form (Scheme 28) is known. The reaction has been carried out using Ni(cyclooctadiene)₂ (40 μmol) 1,4-bis(diphenylphosphino)butane (40 μmol) as
ligand and triphenylborane as the Lewis acid catalyst in toluene at 80°C for 20 h to give the product in 91% yield. A plausible mechanism of this carbocyanation has also been proposed.\(^7\) 

\[
\begin{align*}
1 + \text{Pr} &= \text{Pr} \\
178 &\xrightarrow{\text{Ni(cyclooctadiene)}_2, \text{Ph}_2\text{P-(CH}_2)_4\text{PPh}_2, \text{BPh}_3, \text{toluene, 80°C, 20 h}} 179
\end{align*}
\]

For 178 and 179 : Pr = n-propyl

Scheme 28

11. Conclusions

Publications mainly during 2005 to 2014 on the chemistry of 3-cyanochromone and its use as a synthon for several novel heterocycles have been comprehended. This review article together with an earlier one\(^1\) is likely to provide a quick overview of the work already done in the title topic.

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**Authors’ Biographies**

**Chandra Kanta Ghosh** got from the University of Calcutta his M.Sc., Ph.D. and D.Sc. degrees in Chemistry in 1965, 1970 and 1996, respectively. He did his postdoctoral research in the Department of Organic Chemistry, Karlsruhe University, Germany (1973-74) and in the Biology Division of Oak Ridge National Laboratory, USA (1979-80). He was a faculty member in Organic Chemistry Section in the Department of Biochemistry, Calcutta University during 1969-2007. Even after his formal retirement as a Professor in 2007, Dr. Ghosh has been contributing to many journals. His research interest lies mainly in the chemistry of 1-benzopyran-4-one (chromone) having an electron withdrawing group at its 3-position. He has so far sixty five publications in this field.
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. Then he joined the laboratory of Professor Amitabha Sarkar as a Research Associate in the Department of Organic Chemistry at IACS, Kolkata. Currently he is an Assistant Professor at the Department of Basic Sciences and Humanities in Institute of Engineering & Management (IEM), Salt Lake, Kolkata, India. His current research interest is focused on synthetic organic and organometallic chemistry as well as synthesis of novel heterocycles from 1-benzopyran-4-one system.