Chemistry of 4-oxo-4*H*-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-4*H*-1-benzopyran-3-carbonitrile, radical addition, nucleophilic addition, aza- and oxa-Michael allylation, cycloaddition, carbocyanation

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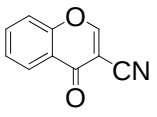
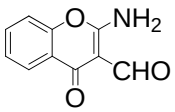
1. Introduction

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[1] 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.[2] A critical account[3] 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,[1] 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-4*H*-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-4*H*-1-benzopyran-3-carboxaldehyde' has been recently published by the present authors.[4]



1 ≡ ChrCN



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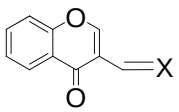
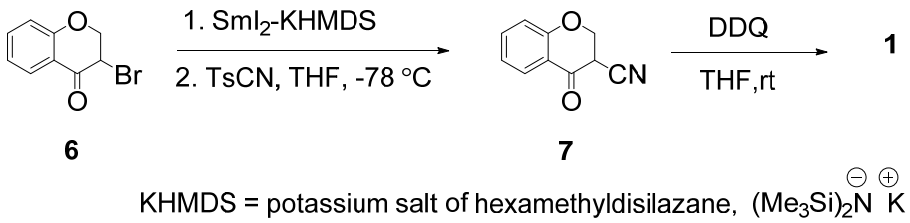


3 X = O
4 X = NOH
5 X = NOR (R = alkyl or aryl)

2. Synthesis

3-Cyanochromone can be prepared from 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde **3** *via* its oxime **4**[5-8] or oxime *O*-alkyl (or aryl) ether **5**.[9-11] A convenient synthesis of **1** involves Vilsmeier-Haack reaction of 2-hydroxyacetophenone with DMF and $POCl_3$ at 0 °C and subsequent treatment of the reaction mixture *in situ* with $NH_2OH.HCl$ at ambient temperature.[12]

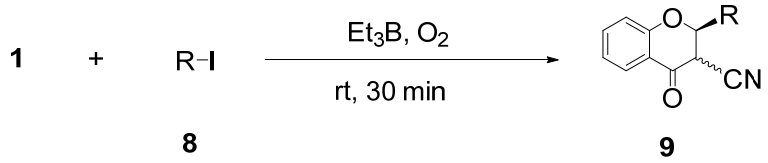
3-Bromochromanone **6** has been converted into 3-cyanochromone **1**. The former on KHMDS enhanced SmI_2-mediated cyanation by tosyl cyanide gives 3-cyanochromanone **7** which on dehydrogenation by DDQ affords the nitrile **1** (Scheme 1).[13]



Scheme 1

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]

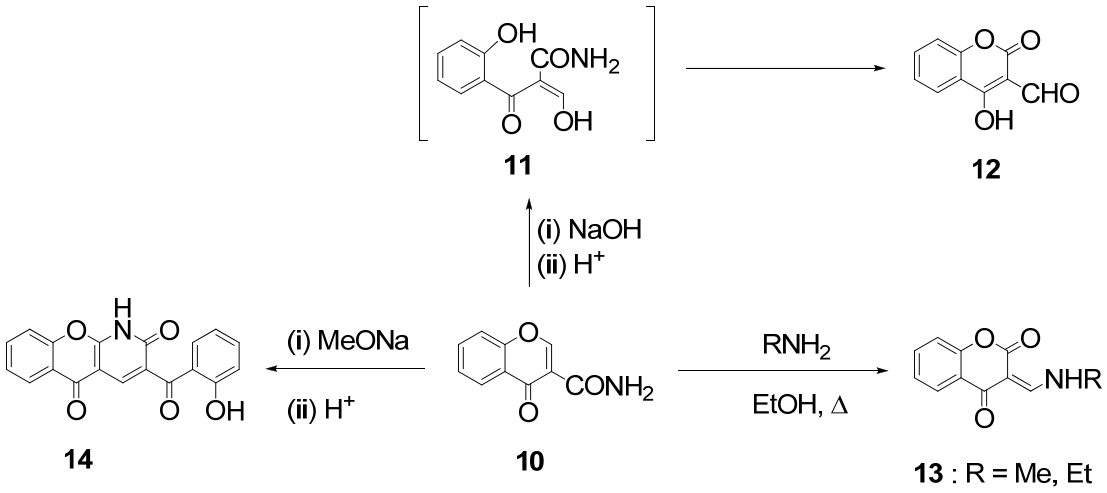


Scheme 2

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[15] 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 RNH_2 (R = Me, Et) in ethanol the 4-aminomethylenecoumarin **13**, and with MeONa the azaxanthone derivative **14**. 1,2-

Addition of hydroxylamine to nitrile functionality of ChrCN is mentioned elsewhere (*vide* section 5.4)

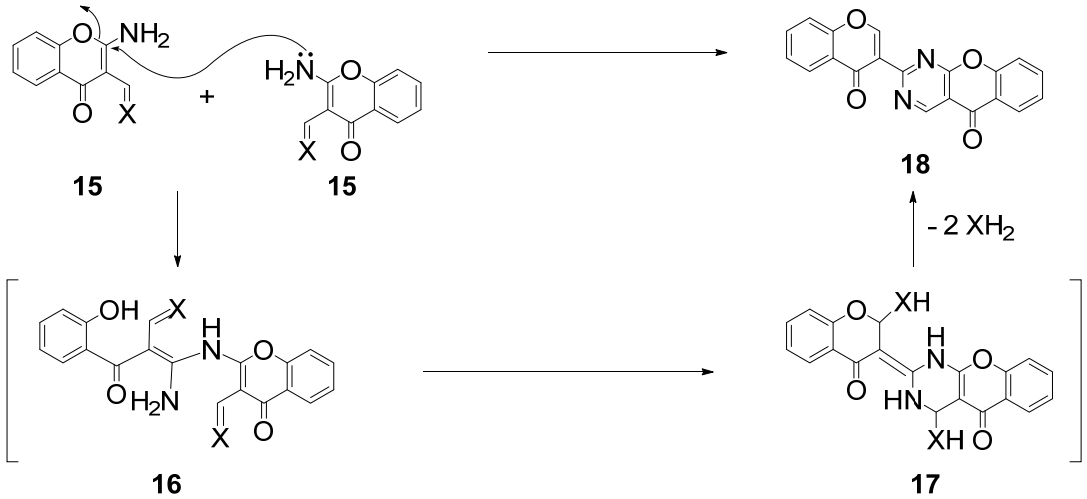


Scheme 3

5. Reaction with Nitrogeneous Nucleophiles

5.1. Reaction with ammonia

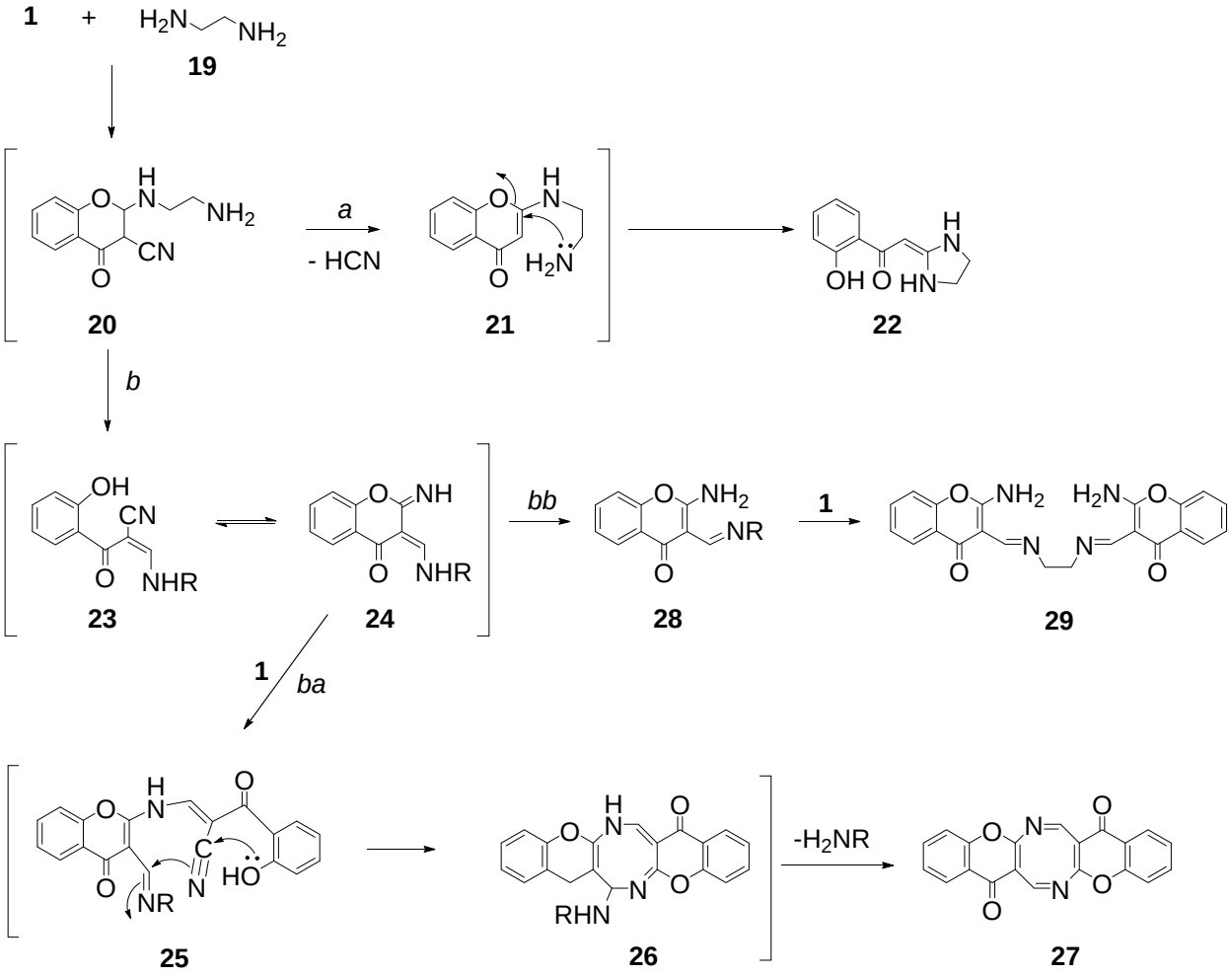
ChrCN is prone to form the aldehyde **2** even under slightly alkaline conditions. ChrCN in ethanol containing a few drops of aqueous ammonia on warming produces the aldehyde **2**. ChrCN when heated with ammonium acetate in acetic acid under reflux affords the self-condensation product **18** which 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).



Scheme 4

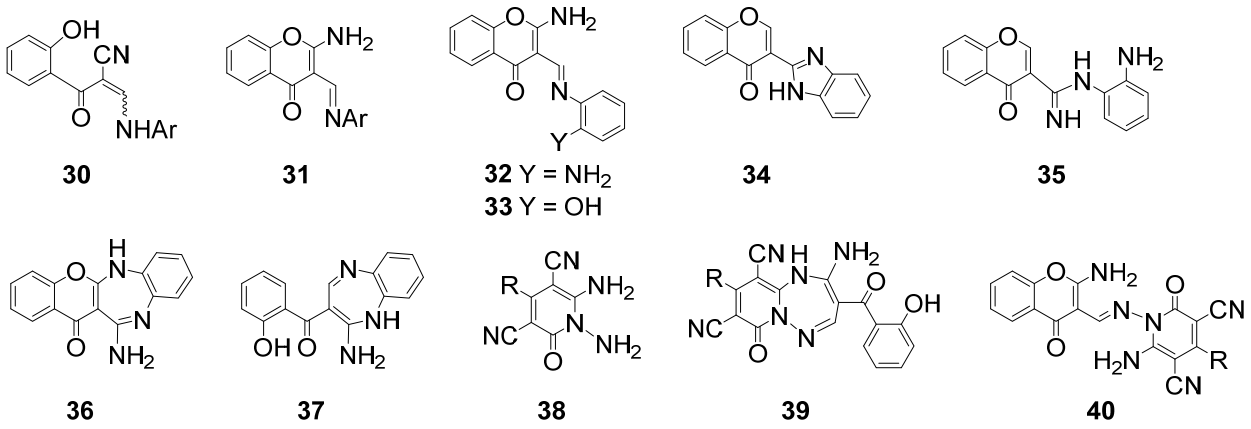
5.2. Reaction with primary amines

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,[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.[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**.[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[18] as the reported[17] diazocene **27** being in fact the bis-imine **29** is unjustified.



Scheme 5

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 ethanol[16] may involve hydrolysis of any or/and all of the compounds **27**-**29**.

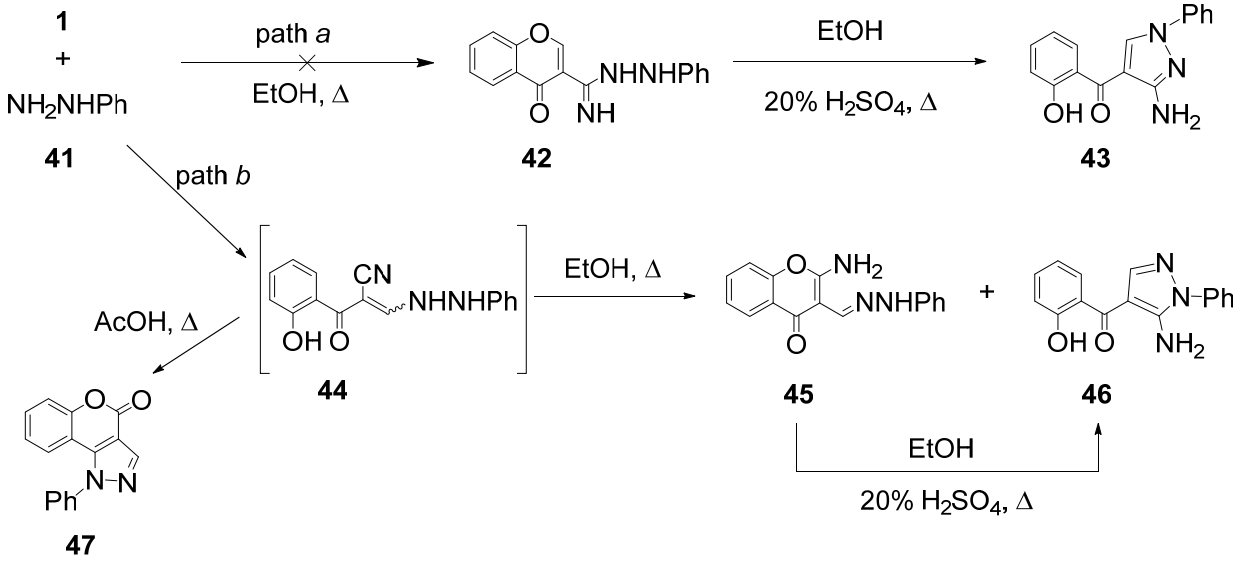


An aromatic primary amine as $ArNH_2$ (Ar = phenyl or substituted phenyl) with ChrCN in refluxing benzene gives in varying proportions the acrylonitrile **30** (*Z*, *E*- mixture) and the Schiff base **31**, the latter being formed exclusively in the presence of a few drops of triethylamine in the reaction medium.[18,19] The compound **31** (Ar = 4-MeC_6H_4) 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-4*H*-1-benzopyran-3-yl) in DMF[22-24] deserves further scrutiny; it may be assigned

the structure **40**. The pyranopyrimidine **18** is obtained by heating **33** in AcOH[19] as well as **31** (Ar = 4-MeC_6H_4) in DMF[20] through a mechanism as depicted in Scheme 4, X in **15-17** representing the appropriate NAr.

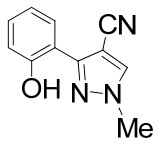
5.3. Reaction with hydrazines

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*)[25] has been convincingly refuted by Sosnovskikh *et al.*[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**.[26]



Scheme 6

The nitrile **1** with methylhydrazine in boiling C_6H_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.[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**.[20]



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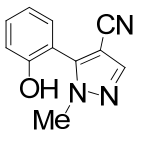

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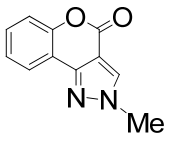

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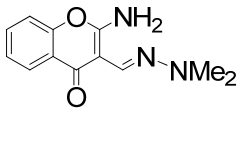
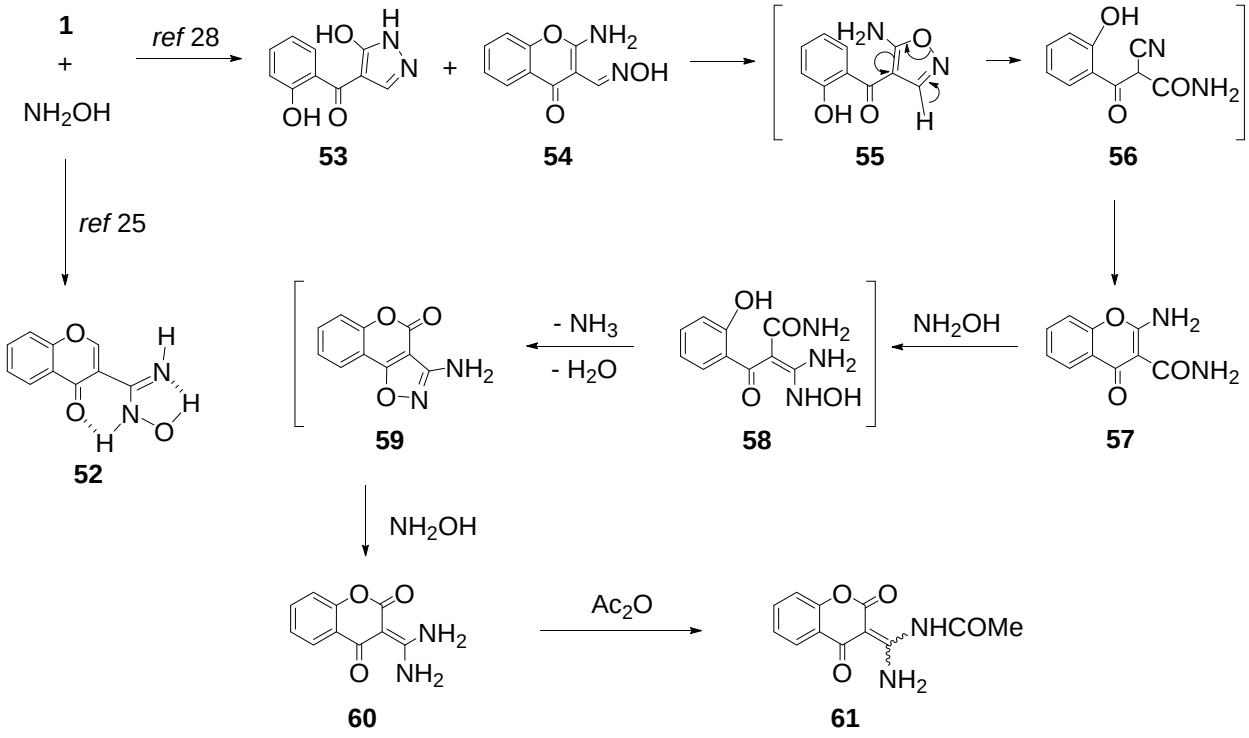


51

5.4. Reaction with hydroxylamine

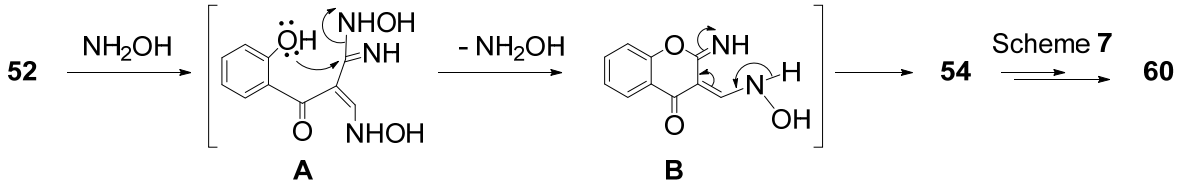
We have reported the formation of the hydroxylamino-imine **52** by reacting ChrCN with an equivalent amount of $NH_2OH.HCl$ in ethanol containing NaOAc.[25] As per a polish group's report[27,28] the same reaction in the presence of alkali gives in addition to the oxime **54** another compound assigned as **53** on the basis of a doubtful mechanism. A Russian group[3,29,30] 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 NH_2OH gives the chroman-2,4-dione **60** through **58** and **59**. In the conversion (**59** → **60**), NH_2OH 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).



Scheme 7

A careful scrutiny of the reported IR and ^{1}H-NMR (DMSO-d_6) of the three compounds **52**, **53** and **57** reveals that the first two compounds show identical IR and ^{1}H-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) 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**.

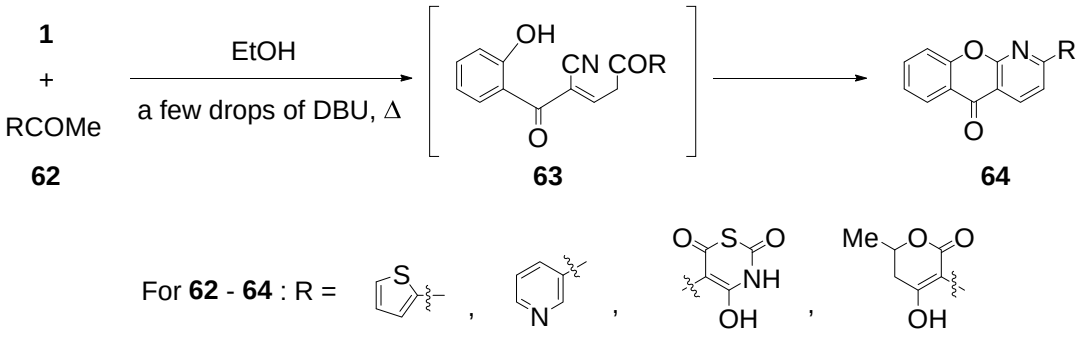


Scheme 8

6. Reaction with Carbon Nucleophiles

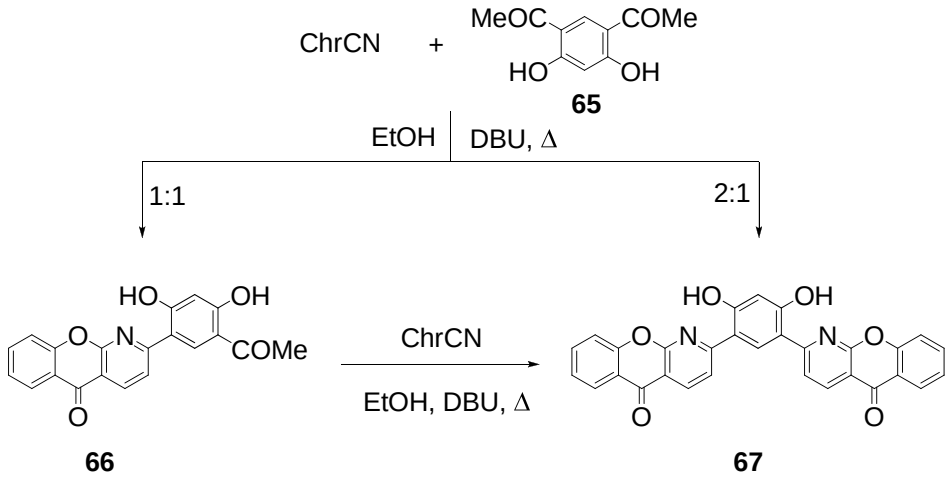
6.1. Reaction with active methyl compounds

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

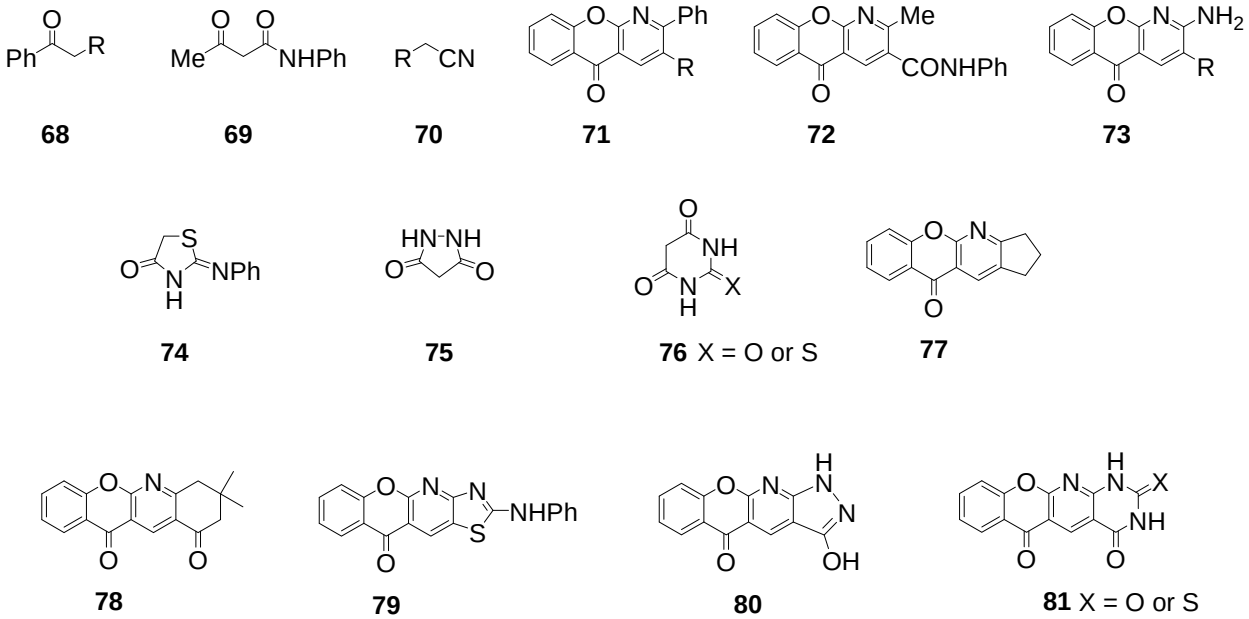
The reaction of ChrCN with diacetylresorcinol **65** depends on the stoichiometry of the reactants to give either 3-aryl-4-azaxanthone **66** or bis-azaxanthone **67** (Scheme 10).[31]



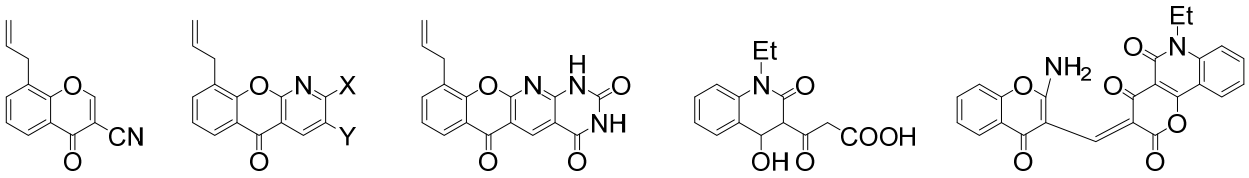
Scheme 10

6.2. Reaction with active methylene compounds

The title reaction reported since 2005 is being surveyed here. Ibrahim and his group[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_2Et), **69** and **70** (R = Ph, PhS, CO_2Me, CO_2Et, CONH-N=CHC_6H_4Cl-4) in EtOH-DBU giving the azaxanthones **71-73**, respectively.[31] Several cyclic α-methylene ketones undergo smooth and efficient ring opening and ring closure (RORC) reaction with ChrCN yielding heteroannulated chromene systems. Thus, cyclopentanone, dimedone, thiazolone **74**, pyrazolidin-3,5-dione **75** and barbituric(or thiobarbuturic) acid **76** give with ChrCN the tetracyclic compounds **77-81**, respectively.[31]



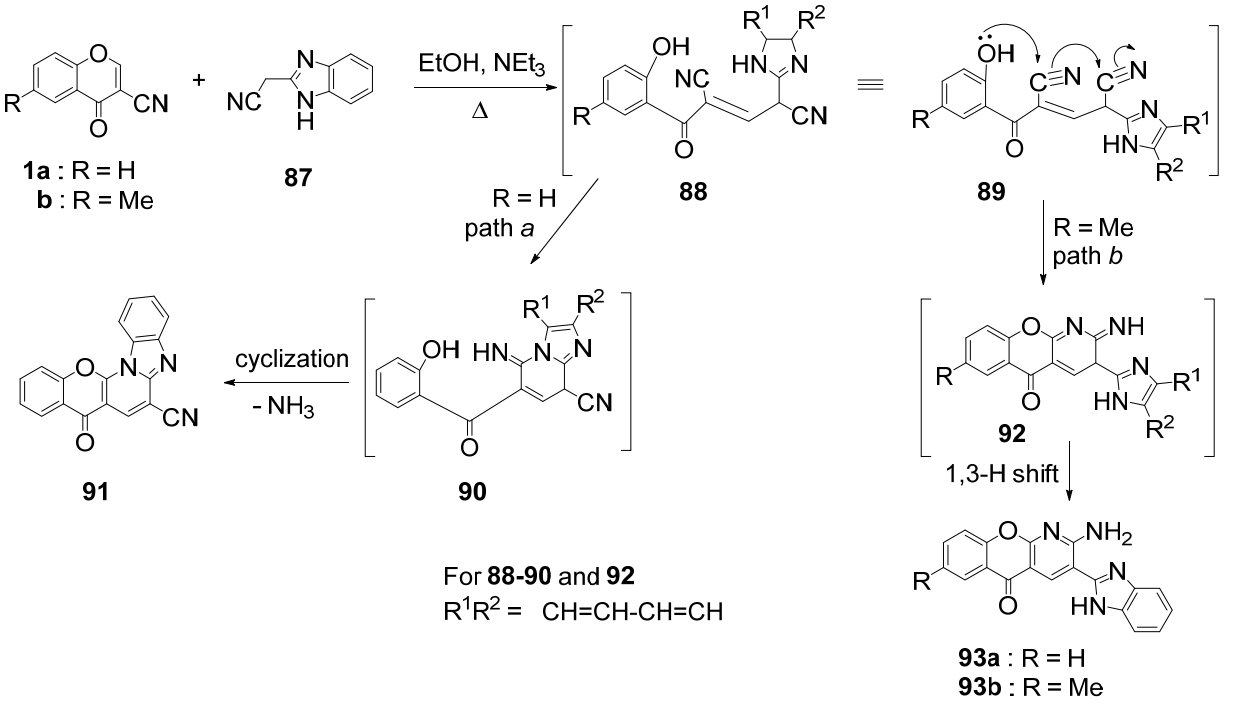
8-Allyl-3-cyanochromone **82** behaves similarly as the unsubstituted 3-cyanochromone **1** towards several active methylene compounds. Thus, the nitrile **82** gives with malononitrile, phenylthioacetonitrile, cyanoacetamide, ethyl cyanoacetate, ethyl acetoacetate and ethyl benzoyl acetate in ethanol-DBU 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**.



82 **83** **84** **85** **86**

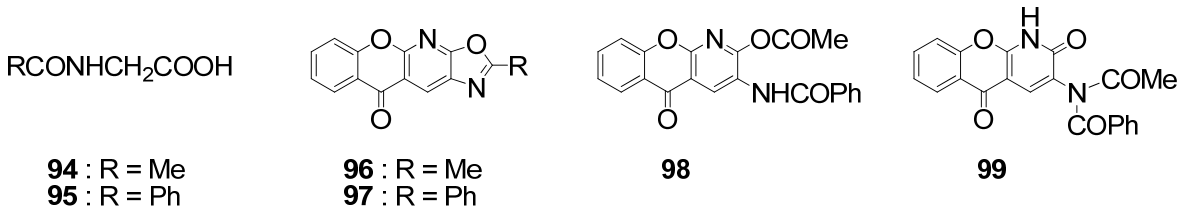
	X	Y
83 a	NH_2	CN
b	NH_2	SPh
c	NH_2	$CONH_2$
d	NH_2	CO_2Et
e	Me	CO_2Et
f	Ph	CO_2Et

Under basic condition (EtOH, NEt_3), 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]

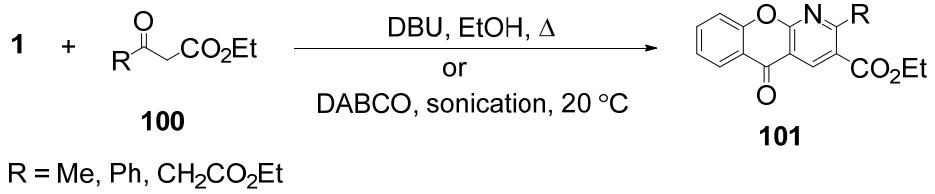


Scheme 11

The cyanochromone **1** is reported to give the pyrido-oxazole **96** when refluxed along with aceturic acid **94** in Ac_2O containing fused AcONa[16] but the chromenopyridine **98** with hippuric acid **95** presumably under identical conditions.[35] Abdel-Rahman *et al*[36] have, however, claimed to get **96** and **97** by heating **1** in Ac_2O-AcONa with aceturic acid and hippuric acid, respectively. Later Ibrahim[31] claimed that the reaction of **1** with hippuric acid **95** in Ac_2O gave **99** but **97** in Ac_2O in the presence of freshly fused AcONa. Now it seems that sodium acetate used for the preparation of **98** was not freshly fused.[35] 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 Ac_2O-AcONa has not been realized though Ac_2O-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.



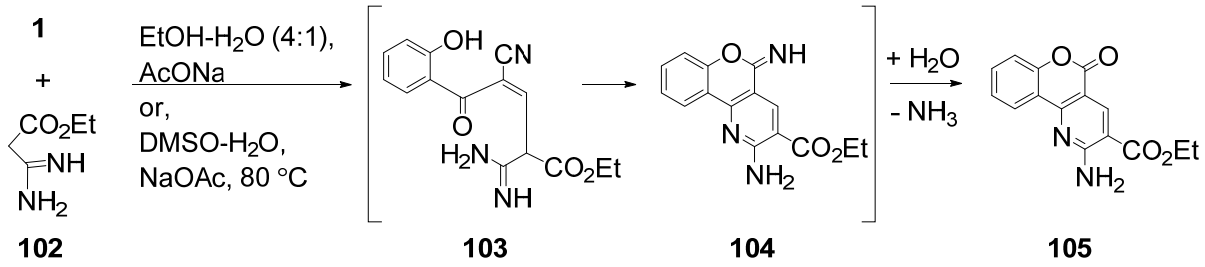
A recent report[37] for the synthesis of ethyl azaxanthone-2-carboxylate **101** by reacting the nitrile **1** with a β-keto ester **100** (Scheme 12) claims that yield of azaxanthone **101** is higher when the reaction is conducted under ultrasonication than that obtained by conventional heating.



Scheme 12

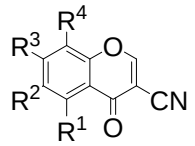
6.3. Reaction with enamines

The carbamimidoylacetic acid ester **102** in an aqueous medium containing NaOAc functions as an enediamine to undergo Michael – retro-Michael reaction; the resultant intermediate **103** by double cyclization, the first one involving phenolic OH and CN groups and the second one involving NH_2 and CO groups, to **104** and subsequent hydrolysis gives the coumarinopyridine **105** (Scheme 13).[38]



Scheme 13

Heating a mixture of the naphthopyran-3-nitrile **106** or its 'chemical equivalent' 2-amino-3-formylnaphthopyran-4-one **107** with the enamine **108** (X = Me, OEt) in DMF at 80°C affords the azaxanthone **109**. A similar reaction of **106** with 6-amino-1,3-dimethyluracil **110** gives the pyridopyrimidine **111**.[39]



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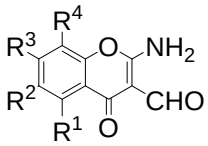

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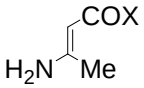
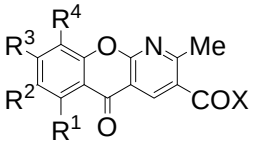


108



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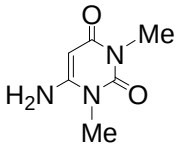

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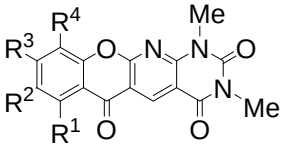
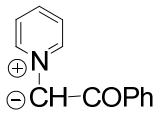


111

For **106**, **107**, **109** and **111**:
R^1, R^2 = H , R^3R^4 = CH=CH-CH=CH ; R^1R^2 = CH=CH-CH=CH , R^3, R^4 = H

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.[40] Kornev *et al*[41] 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**.



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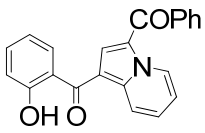

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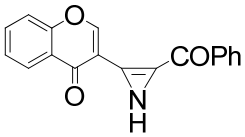

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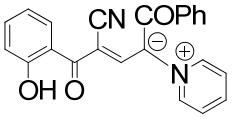

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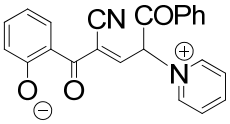


116

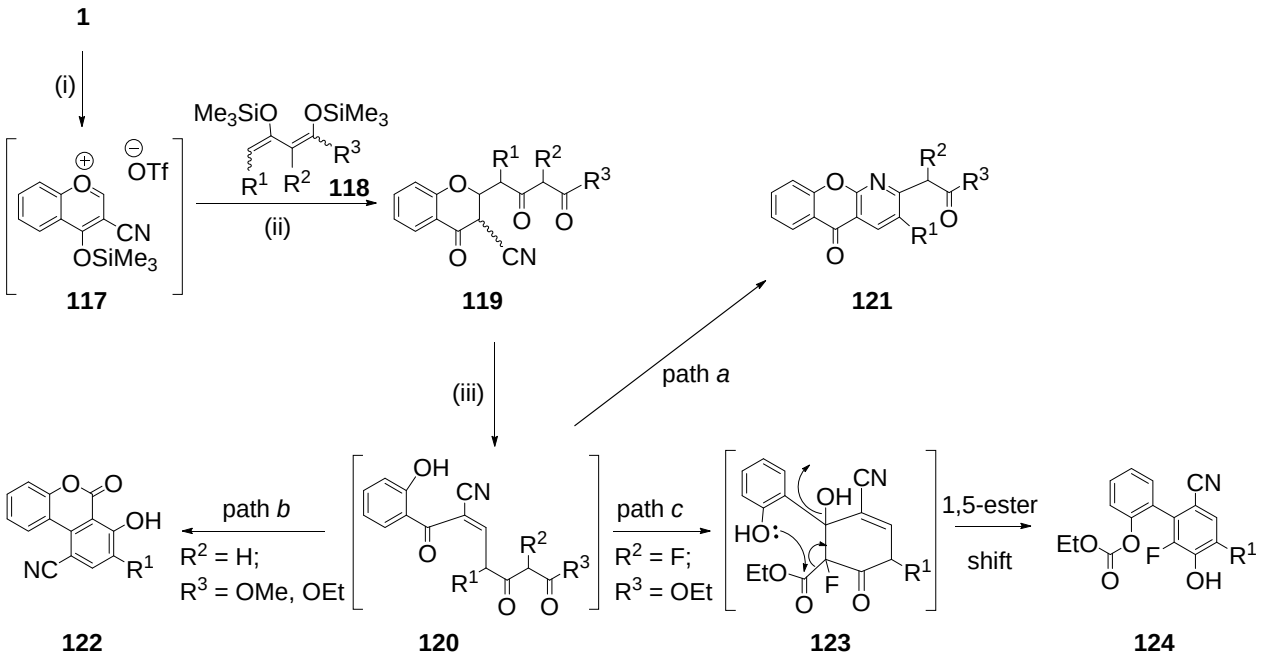
6.5. Reaction with 1,3-bis-silyl ethers of 1,3-dicarbonyl compounds

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.*[42-49] 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** (R^2 = H, R^3 = OMe, OEt) by an aldol-lactonization mechanism to the biaryllactone **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	Benzocoumarin	Ref.
	R^1	R^2	R^3	**121**	**122**	
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	$-(CH_2)_3-$		OEt	36	–	42,43
6	4-MeC_6H_4	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

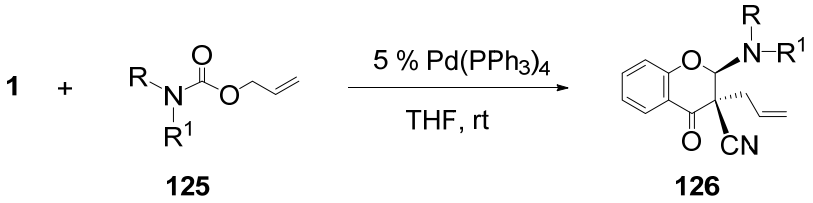


Scheme 14. Reagents and conditions: (i) TMSOTf, CH_2Cl_2, 0 °C, 1 h; (ii) CH_2Cl_2, 20 °C, 12 h, then HCl (10%); (iii) NEt_3, EtOH, 20 °C, 12 h, then HCl (1M).

The enolate **118** ($R^1R^2 = (CH_2)_4$, $(CH_2)_9$; R^3 = OMe) as well as **118** ($R^1 = R^2$ = H; R^3 = 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** (R^1 = Me, *n*-Pr, *n*-Bu, *n*-pent, *n*-hex, *n*-oct; R^2 = F; R^3 = 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] Karapetyan[50] could isolate only the azaxanthone **121** (R^1 = *n*-oct; R^2 = H; R^3 = OEt) in 28% yield from the reaction mixture of **1** and **118** (R^1 = *n*-Oct; R^2 = H, R^3 = OEt).

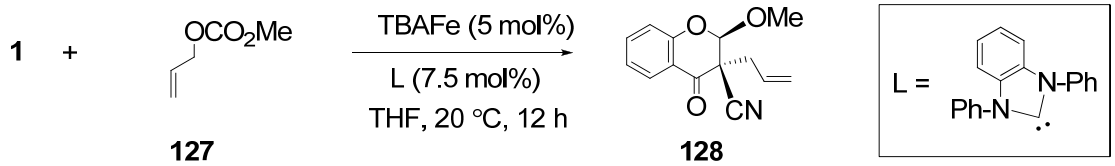
7. Aza- and Oxa- Michael – Allylation

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, $RNHR^1$ and allyl acetate.



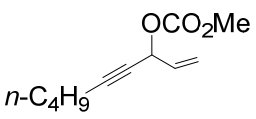
Scheme 15

Allyl carbonate **127** likewise the carbamate **125** reacts with ChrCN in the presence of the electron rich tetrabutylammonium ferrate $Bu_4N[Fe(CO)_3NO]$ (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).



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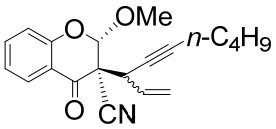
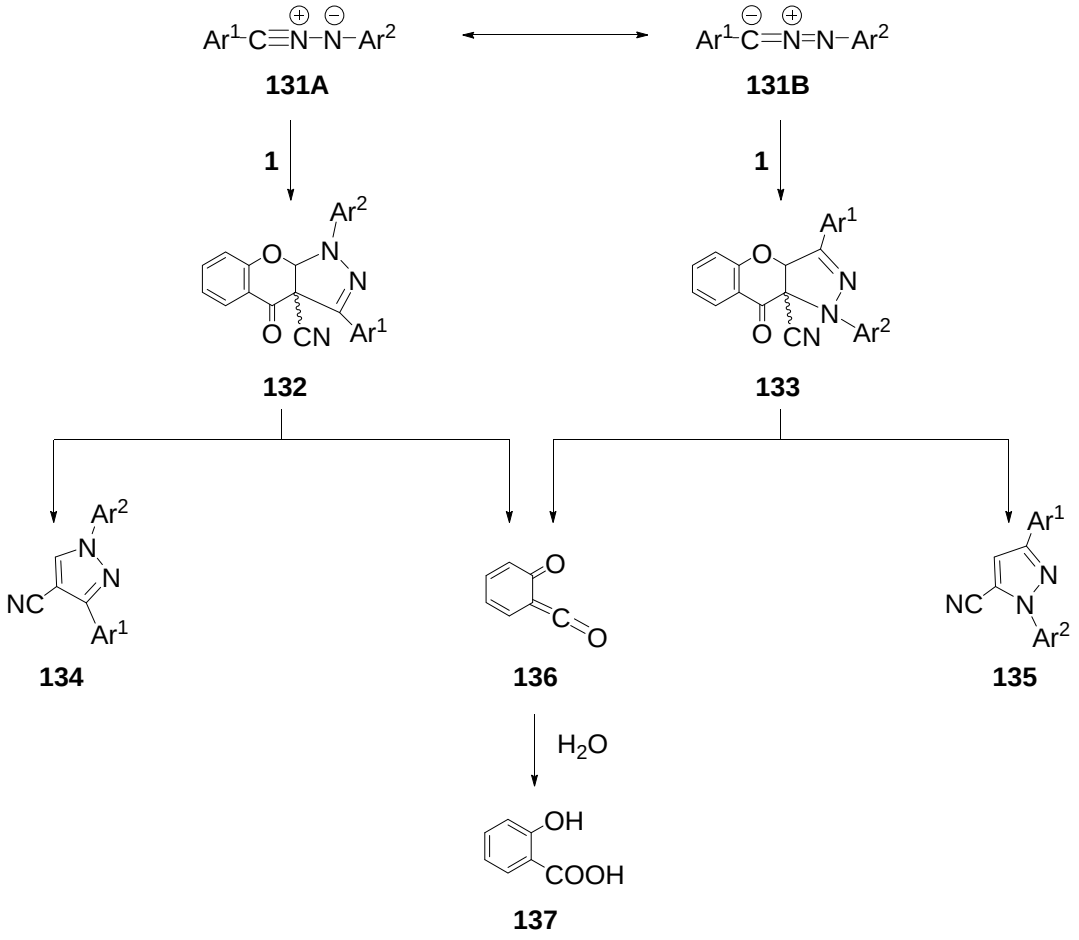


130

8. Cycloaddition Reactions

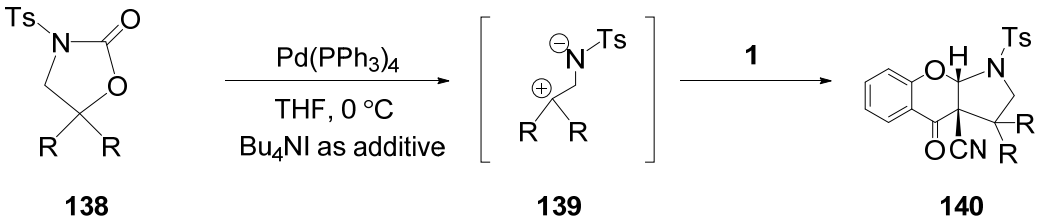
8.1. [3+2]Dipolar cycloaddition

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.[1] 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).[53]



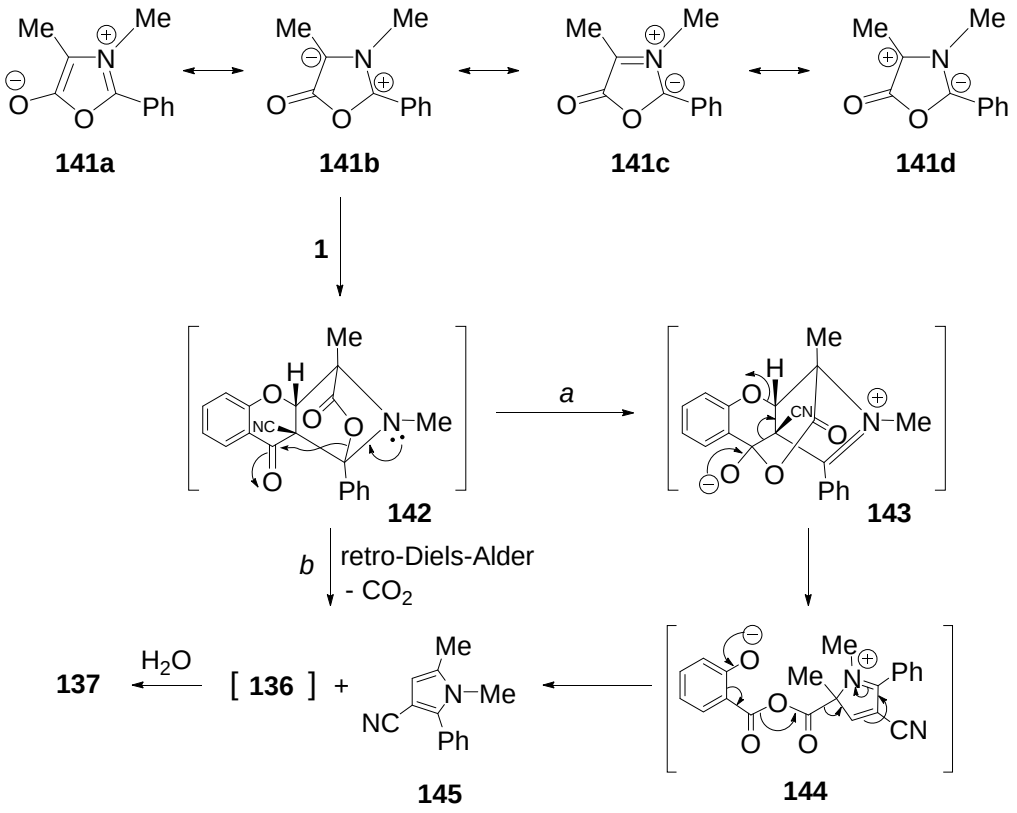
Scheme 17

N-Tosyl-5,5-divinyloxazolidin-5-one **138** (R = CH=CH_2), 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).[54] 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**.



138 **139** **140**

Scheme 18

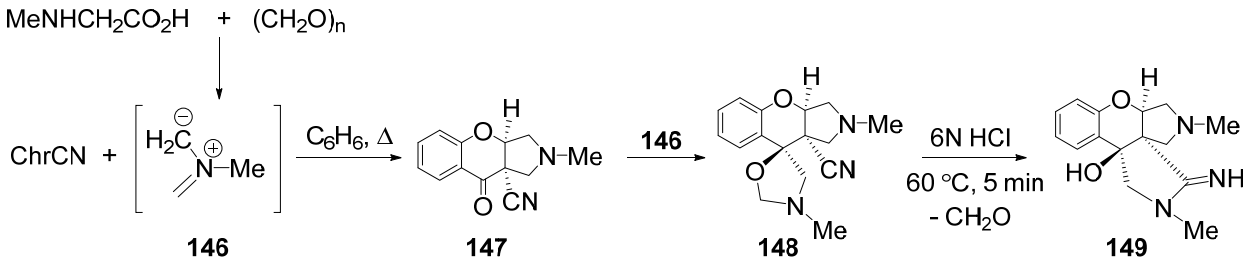


Scheme 19

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**)

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.

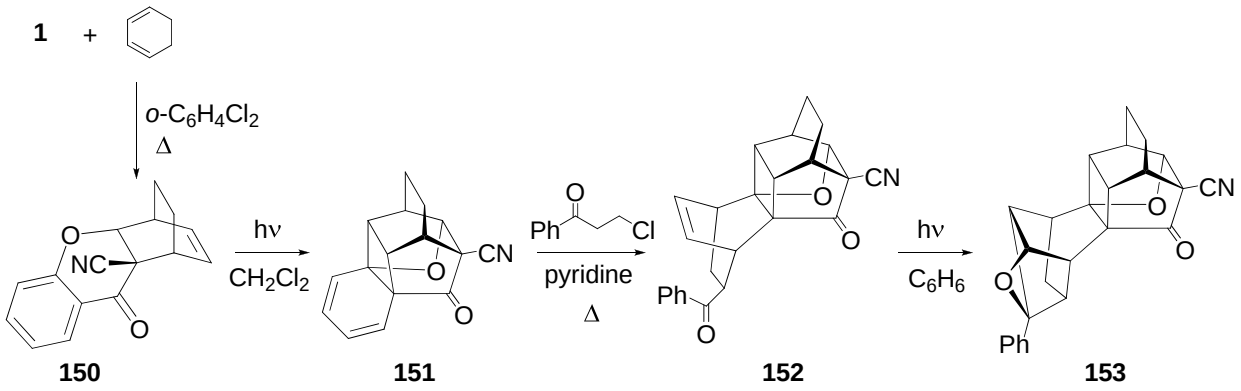


Scheme 20

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

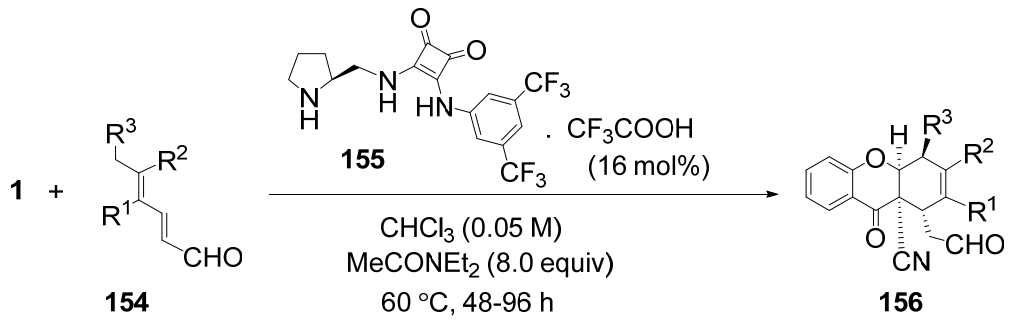
8.2. [4+2]Cycloaddition

Diels-Alder reaction of the unsaturated nitrile **1** with several oxygenated and non-oxygenated dienes extensively studied by Hsung *et al*[57-60] 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

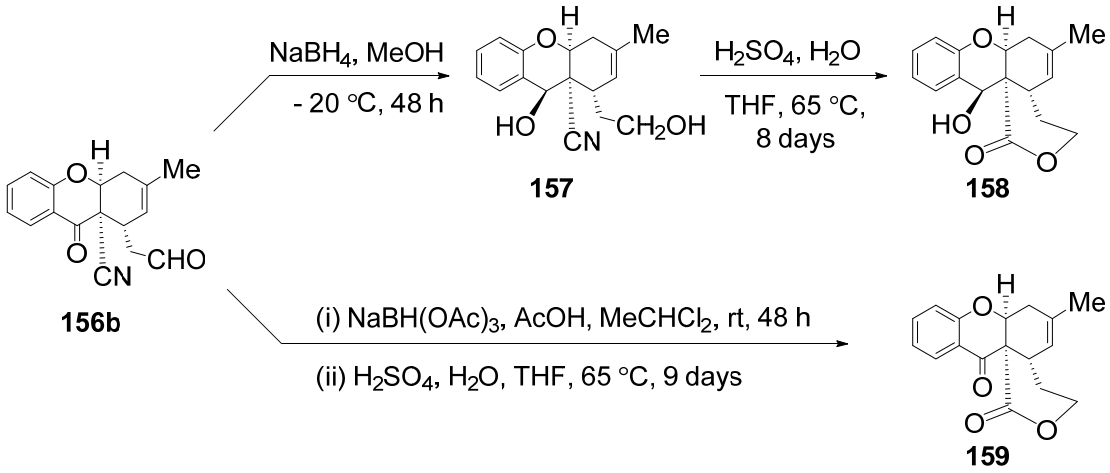
The nitrile **1** undergoes [4+2] cycloaddition with 2,4-hexadienals **154a-f** in the presence of squaramide-based organocatalyst **155** to give respectively tetrahydroxanthones **156a-f** in more than 20:1 diastereoisomeric ratio and in approximately 90% enantiomeric excess (Scheme 22).[63]



For **154** and **156** :	R^1	R^2	R^3
a	H	H	H
b	H	Me	H
c	Me	H	H
d	Ph	H	H
e	Ph	H	Me
f	Me	H	Me

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).

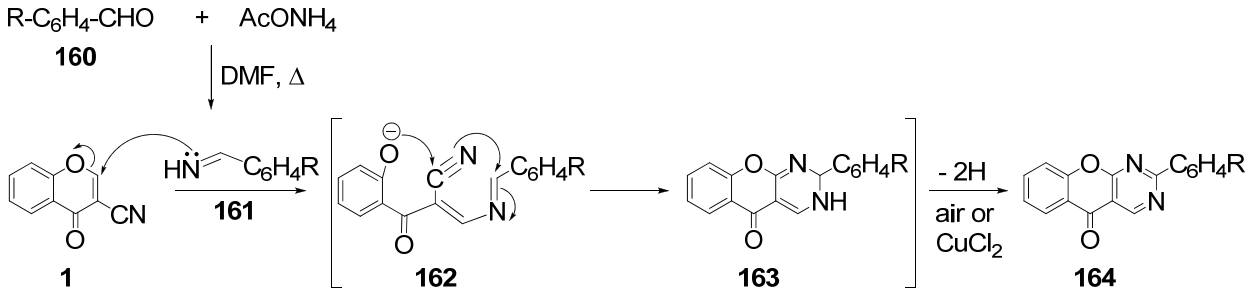


Scheme 23

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.[64] Here ChrCN is converted under basic conditions to 2-amino-3-formylchromone **2** that condenses with dimedone giving the expected product **78**.

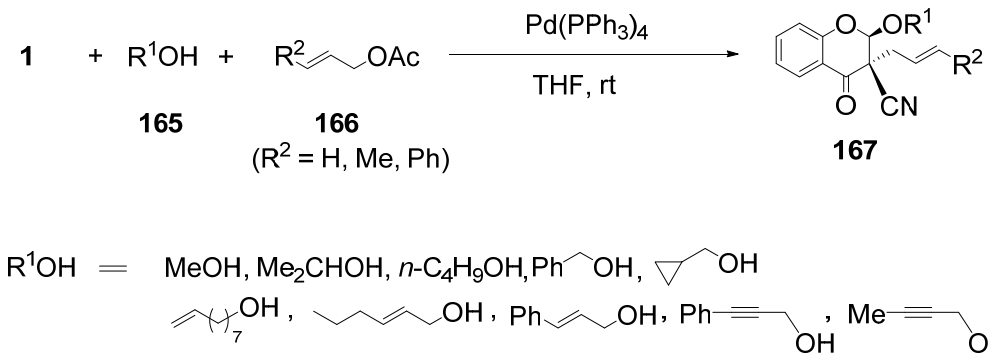
A mixture of ChrCN, benzaldehyde **160** (R = H, electron withdrawing or electron donating group) and $AcONH_4$ in DMF solution containing $CuCl_2$ at 100 °C affords 2,4-diazaxanthone **164** (Scheme 24), its yield being increased to 85% when 1.2 equivalent of $CuCl_2$ is present as an oxidant in the reaction mixture.[65] It is assumed that the aldimine **161**, generated *in situ* from the aldehyde **160** and $AcONH_4$, 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 C_6H_4R) is obtained in 74% yield.



Scheme 24

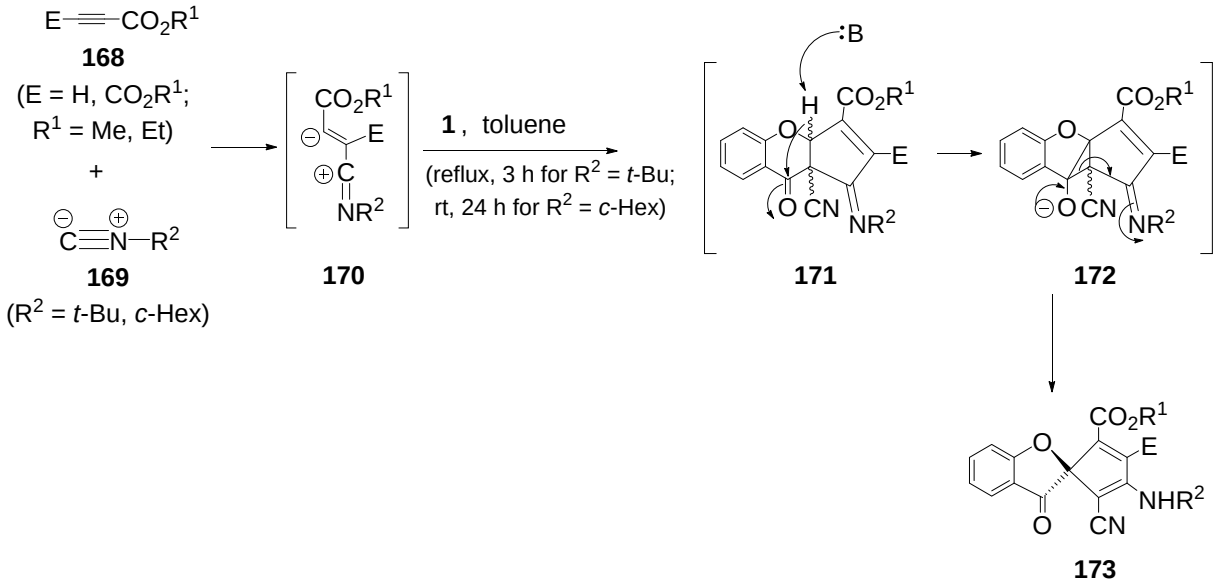
Palladium catalyzed three-component coupling reaction between the nitrile **1**, alcohol **165** and allyl acetate **166** leads to the highly substituted chromanone **167** (Scheme 25).[66] The

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]



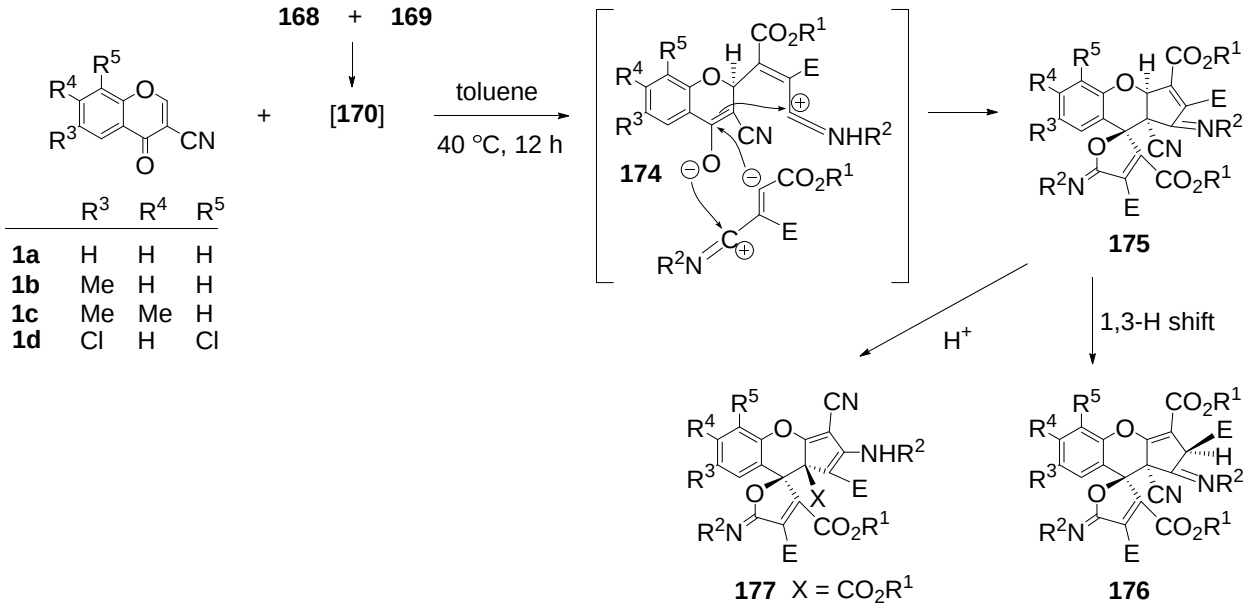
Scheme 25

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 – *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 = CO_2Me or CO_2Et) is obtained in 56-64% yield but **173** (E = H, R^1 = Me) in less than 20% yield.



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).[69] 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 = CO_2Me, R^1 = Me) and **169** (R^2 = *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 stereochemical 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.[69]



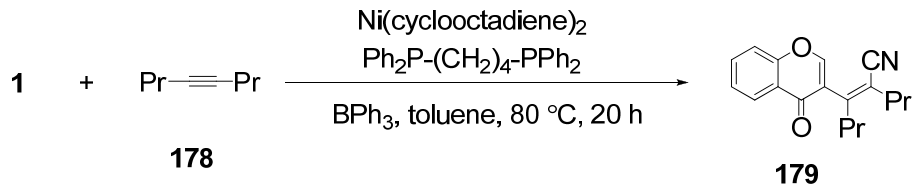
	R^3	R^4	R^5
1a	H	H	H
1b	Me	H	H
1c	Me	Me	H
1d	Cl	H	Cl

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.[70] 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.[70]



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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