Russian Chemical Reviews **72** (6) 489 – 516 (2003) © 2003 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2003v072n06ABEH000770

Synthesis and reactions of halogen-containing chromones

V Ya Sosnovskikh

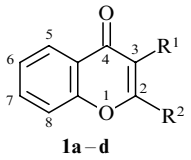
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Abstract. Published data on the synthesis and reactivity of halogen-containing chromones, flavones, thiochromones and furochromones are generalised. The bibliography includes 220 references.

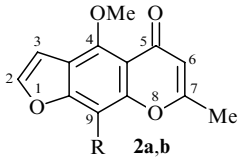
I. Introduction

Chromone (4*H*-chromen-4-one, 4*H*-1-benzopyran-4-one, **1a**) is a parent compound for an important class of oxygen-containing heterocyclic compounds with a benzoannelated γ-pyrone ring. This heterocyclic system is frequently encountered in the vegetable world, most often as flavone (2-phenylchromone, **1b**), flavonol (3-hydroxy-2-phenylchromone, **1c**) and isoflavone (3-phenylchromone, **1d**) derivatives, which form the group of flavonoids — flower and fruit pigments.[1] These compounds exhibit various types of biological activities[2] and find use as substrates in the preparation of many pharmaceuticals including some antitumour drugs.[3] Alkylchromones are less naturally abundant; nevertheless, some of them are also known to be biologically active. For example, of therapeutic interest are 3-methyl- and 2,5,8-trimethylchromones.[2] The natural furochromones khellin (**2a**) and visnagin (**2b**) are the active substances of the plant *Ammi visnaga L.*, known for its therapeutic properties since antiquity.[4,5]



1a – d

$R^1 = R^2 = H$ (**a**);
$R^1 = H$, $R^2 = Ph$ (**b**);
$R^1 = OH$, $R^2 = Ph$ (**c**);
$R^1 = Ph$, $R^2 = H$ (**d**).



2a,b

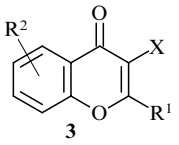
R = MeO (**a**), H (**b**).

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Received 30 September 2002
Uspekhi Khimii **72** (6) 550 – 578 (2003); translated by Z P Bobkova

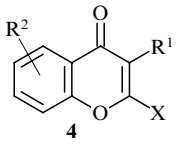
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Among halogen derivatives of chromone **1a**, compounds acting as stimulators for the central nervous system[6,7] and exhibiting high antiviral,[8] antimicrobial,[9,10] antimycotic,[9,10] antiallergic[11–13] and neuroleptic[14] activities have been found. The enhanced interest in the chromone chemistry is indicated by publication of a series of reviews[15–18] and monographs.[2] However, halogenated chromone derivatives (halochromones and haloalkylchromones) are the subjects of only one chapter in the book[2] published in 1977. In recent years, a fairly large number of studies dealing with the chemistry of halochromones containing halogen atoms attached directly to the carbon atoms of the chromone system and haloalkylchromones in which halogen atoms occur in the side chains have been reported. However these data have not yet been reviewed or analysed. This review is meant to fill this gap. Here we consider chromones **3** – **5**, where R^1, R^2 are any substituents containing no halogen atoms.



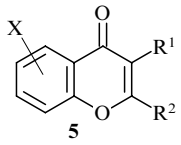
3

X = Hal, CH_2Hal, $COCH_2Hal$.



4

X = Hal, R^F, CCl_3, CH_2Hal.



5

X = Hal, CH_2Hal.

Derivatives **5**, containing a halogen or a halomethyl group in the benzene ring, differ little in methods of synthesis and reactivity from the appropriate halogenated benzene derivatives and are of secondary importance for the chromone chemistry, which is mainly determined by the γ-pyrone ring having two electrophilic centres, the C(2) and C(4) atoms. Therefore, attention will be focused on halo- and haloalkylchromones **3** and **4**, containing a halogen-containing substituent in the γ-pyrone ring. The presence in the ring of a halogen atom, which is a good leaving group, or a 2-polyhaloalkyl group, which increases the electrophilicity of the C(2) atom, extends appreciably the synthetic potential of chromones and makes them valuable substrates for the synthesis of new heterocyclic compounds with a broad range of useful properties.

To complete the picture, the review covers the most important publications of the 1960s – 1970s not included in the monograph[2] and also the sparse data available on halo-containing thiochromones and furochromones. The methods of synthesis and chemical properties of chromones with the perfluorinated benzene ring have been covered in a number of reviews;[2,18,19] therefore, we do not consider them here. The reactions of heteroanalogues of

isoflavones containing a trifluoromethyl group at the 2-position with alkalis, hydrazines, amidines and hydroxylamine have been described in a review published previously.[15]

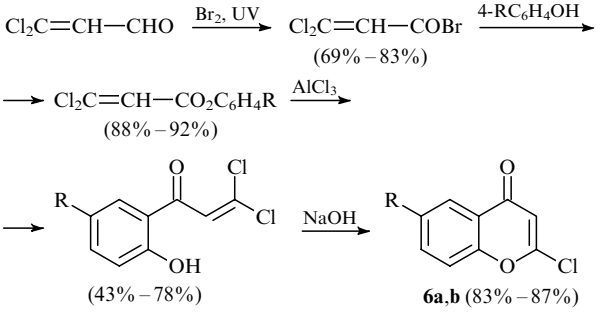
II. Methods for the synthesis of halochromones

The most convenient methods for the formation of the chromone system include the Claisen condensation of 2-hydroxyacetophenones with esters,[20] the Baker–Venkataraman rearrangement of *O*-acyl derivatives of 2-hydroxyacetophenones[21] and the Kostanecki–Robinson method, consisting of the reaction of the same ketones with carboxylic acid anhydrides.[14] This gives rise to compounds that exist either in the open β-diketone form or in the cyclic 2-hydroxychromanone form, depending on the conditions and the nature of the substituents. Upon dehydration in an acid medium, they yield the corresponding chromones. The introduction of halogen atoms into the pyrone and benzene rings and into the side chains can be performed both during the synthesis of chromones (by using halo-containing ketones and esters) and by treatment of chromones or their precursors (β-diketones) with halogenating agents.

1. Synthesis of 2-halochromones

2-Halochromones represent a group of halo-derivatives of chromone difficult to access, as the introduction of the halogen atom into the 2-position of the chromone system is usually a more complicated synthetic task than halogenation of the benzene ring activated by electron-donating groups.

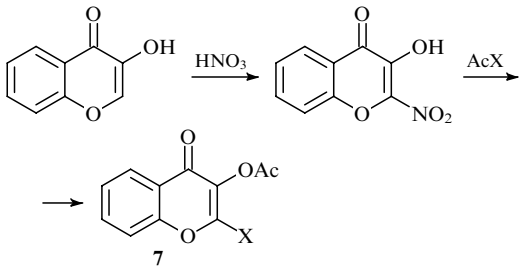
The first representatives of chromones containing a halogen atom at the 2-position [2-chloro- (**6a**) and 6-methyl-2-chlorochromones (**6b**)] were prepared in 1960 from β,β-dichloroacrolein and the corresponding phenols.[22] The key step of the synthesis is the Fries rearrangement of aryl dichloroacrylate on treatment with $AlCl_3$ at 130 °C followed by cyclisation of *o*-hydroxyketones in an alkaline medium to give 2-chlorochromones **6**.



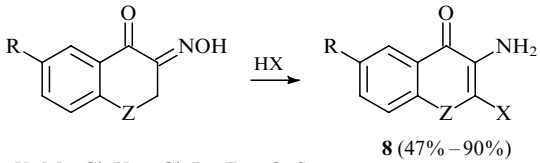
R = H (**a**), Me (**b**).

Subsequently, α,β,β-trichloro- and α-bromo-β,β-dichloroacroleins[23,24] and also α,β,β-trichloro- and α,β-dichloroacryloyl chlorides[25] have been involved in this reaction. The intra- and intermolecular acylation of phenols with these reagents resulted in the synthesis of 2- and 3-halo- and 2,3-dihalochromones. For example, 2,3-dichloro-7-methoxy- or 3-chloro-7-methoxychromones were prepared from 1,3-dimethoxybenzene and α,β,β-trichloro- or α,β-dichloroacryloyl chloride.[25]

Other methods for the introduction of a halogen atom into the 2-position are also known. The presence of the 3-hydroxy group facilitates the electrophilic attack on the C(2) atom; as a result, bromination of 3-hydroxychromone affords 2-bromo-3-hydroxychromone in a good yield,[2] while its nitration furnishes 3-hydroxy-2-nitrochromone. By treatment with acetyl halides, the latter product can be converted into 2-chloro- and 2-bromo-3-acetoxychromones (**7**).[26] The reactions of chromane-3,4-dione 3-oximes and thiochromane-3,4-dione 3-oximes with hydrogen halides yield 3-amino-2-chloro- and 3-amino-2-bromochromones and -thiochromones (**8**).[27]



X = Cl, Br.



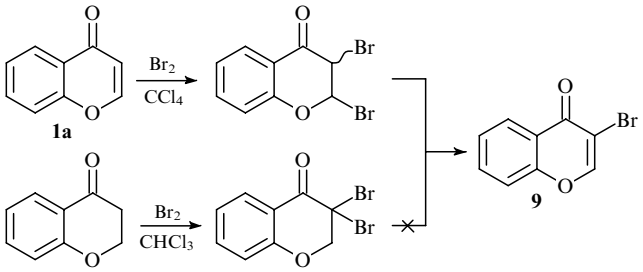
R = H, Me, Cl; X = Cl, Br; Z = O, S.

It is noteworthy that all the known methods for the synthesis of 2-halochromones proposed 30–40 years ago were based on initial compounds difficult to prepare and in most cases, the methods were not generally applicable. In recent years, no significant progress in the development of new approaches to the preparation of these compounds has been made either. Only in one study,[28] was the Fries rearrangement used to prepare 2-chloro-6-methylchromone,[22] which was then introduced in reactions with α-amino ketones and α-aminoacetals (see Section III.1).

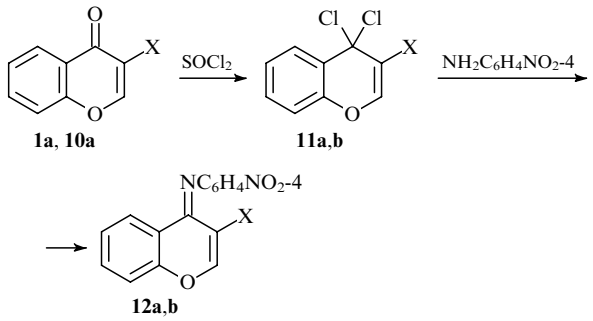
2. Synthesis of 3-halochromones

Due to the vigorous development of transition metal-catalysed cross-coupling reactions giving C–C bonds, which open up the way to complex natural molecules, the interest in the synthesis of 3-halochromones has been enhanced and they have become available compounds. 3-Halochromones can be prepared by halogenation of either chromones or their precursors, *i.e.*, β-diketones and β-aminovinyl ketones containing 2-hydroxyaryl substituents at the carbonyl group (in most cases, the latter route is preferred).

The reaction of chromones with halogens or some halogenating reagents usually starts with the halogen addition to the double bond of the pyrone ring, which is followed by dehydrohalogenation (either spontaneous or base-iduced), resulting in the target 3-halochromones. For instance, the reaction of chromone **1a** with bromine in CCl_4 gives 2,3-dibromochroman-4-one, which is readily converted into 3-bromochromone (**9**).[29] Chromanone reacts with bromine in $CHCl_3$ to give 3,3-dibromochromanone; however, this product could not be converted into chromone **9** in a plausible yield.[30]



Treatment of chromone **1a** with sulfuryl chloride with cooling gives rise to 2,3-dichlorochroman-4-one, which is smoothly converted into 3-chlorochromone (**10a**) on treatment with triethylamine.[31] Interestingly, chromones **1a** and **10a** react with thionyl chloride to give 4,4-dichloro- (**11a**) and 3,4,4-trichloro-4*H*-chromenes (**11b**), whose reaction with 4-nitroaniline affords the corresponding *N*-(4*H*-chromen-4-ylidene)anilines (**12a**,**b**), the first representatives of the chromeneimine series.[31]

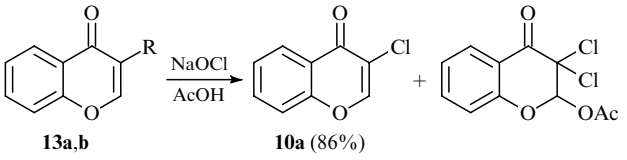


1a, **10a** **11a**,**b** **12a**,**b**

X = H (**1a**, **11a**, **12a**), Cl (**10a**, **11b**, **12b**).

The reaction of 6-nitrochromone with a potent electrophilic brominating agent, in particular, the dibromoisocuanuric acid–sulfuric acid system, results in the formation of 3,8-dibromo-6-nitrochromone, whereas chromone **1a** gives only 6-bromochromone under similar conditions due to protonation of the pyrone ring. With a greater amount of dibromoisocuanuric acid, the transformation of chromone **1a** yielded 5,6,8-tribromo- and 3,5,6,8-tetrabromochromones.[32]

Treatment of chromone-3-carbaldehyde (**13a**) or chromone-3-carboxylic acid (**13b**) with sodium hypochlorite in acetic acid gives 3-chlorochromone **10a** with a 2-acetoxy-3,3-dichlorochroman-4-one impurity.

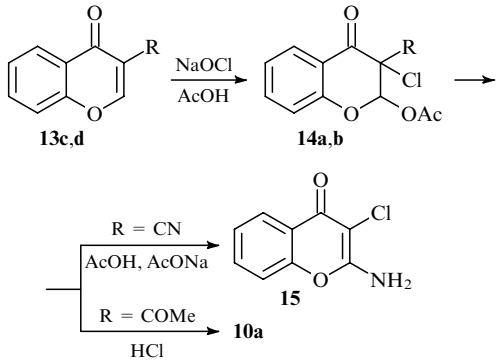


13a,**b** **10a** (86%)

R = CHO (**13a**), CO_2H (**13b**).

Under similar conditions, 3-formylchromones substituted in the benzene ring form the corresponding 3-chlorochromones in 43%–82% yields.[33, 34]

The transformation of 3-acetylchromone (**13c**) and chromone-3-carbonitrile (**13d**) under the same conditions gives 2-acetoxy-3-acetyl- (**14a**) and 2-acetoxy-3-cyano-3-chlorochroman-4-ones (**14b**). On treatment with HCl, the acetyl derivative **14a** furnishes chromone **10a**, while nitrile **14b** is converted into 2-amino-3-chlorochromone (**15**) in aqueous acetic acid in the presence of AcONa. In this case, the reaction is accompanied by opening of the pyrone ring followed by cyclisation involving the cyano group.[34]

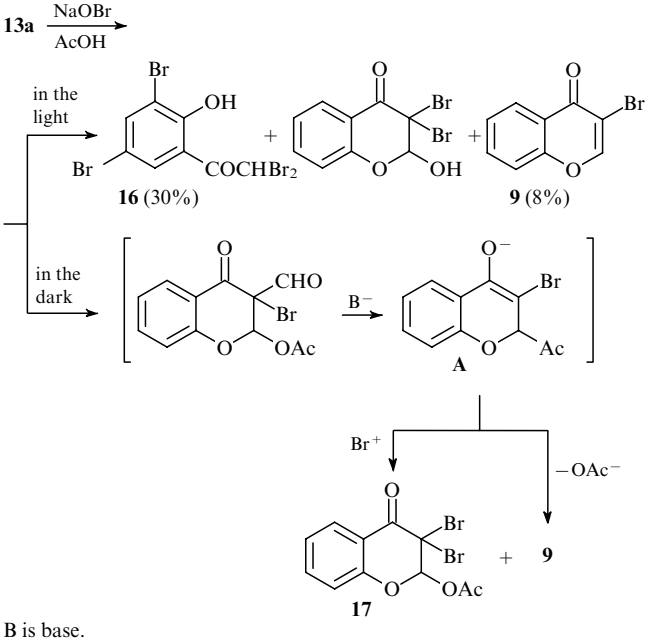


13c,**d** **14a**,**b** **15** **10a**

R = COMe (**13c**, **14a**), CN (**13d**, **14b**).

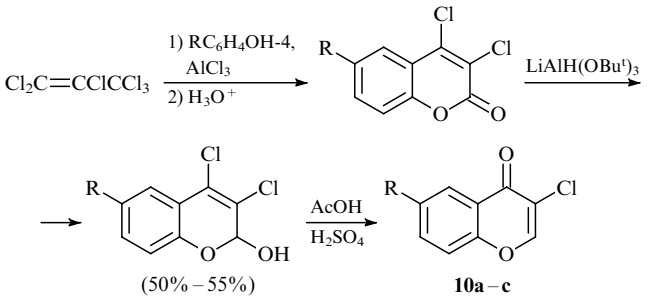
Chromone-3-carbaldehyde (**13a**) reacts with sodium hypobromite in the light to give a mixture of three products where 2,2,3′,5′-tetrabromo-2′-hydroxyacetophenone (**16**) is the major product (30%), while the expected 3-bromochromone **9** is formed in a low yield (8%). The researchers believe[34] that tetrabromoacetophenone results from radical opening of the pyrone ring, because the same reaction carried out in the dark gave only bromo-derivatives **9** and **17** in 32% and 29% yields, respectively (Scheme 1). The reaction mechanism includes the addition of acetyl hypobromite and subsequent elimination of the formyl group under the action of a base. The elimination of molecule AcOH from intermediate **A** affords chromone **9**, while its bromination leads to chromanone **17**.

Scheme 1



B is base.

The reduction of 3,4-dichlorocoumarins, prepared by treatment of phenols with perchloropropylene in the presence of aluminium chloride,[35] with lithium tri(*tert*-butoxy)aluminium hydride produces lactols, which are easily transformed into 3-chlorochromones **10a**–**c** when heated in acetic acid in the presence of catalytic amounts of H_2SO_4.[36, 37]

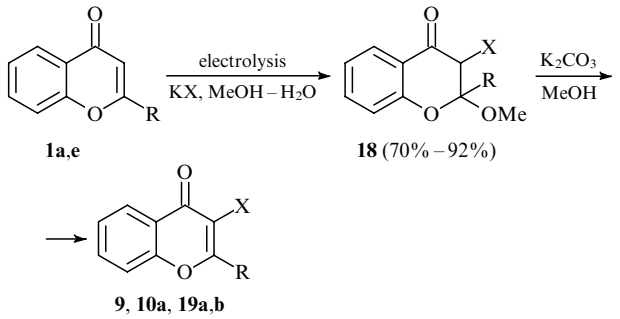


10a–**c**

R = H (**a**), Me (**b**), Cl (**c**).

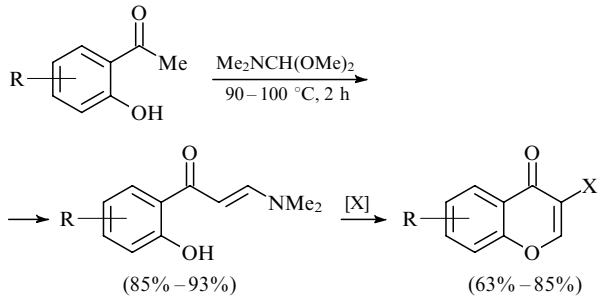
When chromone **1a** is subjected to oxidative chlorination (*m*-chloroperbenzoic acid, HCl, DMF, ~20 °C), 3-chlorochromone **10a** is formed in 96% yield.[38] This method is suitable for introducing chlorine into the α-position of both cyclic and acyclic α,β-enones.

Electrolysis of chromone (**1a**) and 2-methylchromone (**1e**) in a methanol–water mixture (4 : 1) containing potassium halide yields 3-halo-2-methoxychroman-4-ones **18**, which are unstable during storage. On treatment with K_2CO_3 in methanol, they pass almost quantitatively into the corresponding 3-chloro- (**10a**, **19a**) and 3-bromochromones (**9**, **19b**).[39]



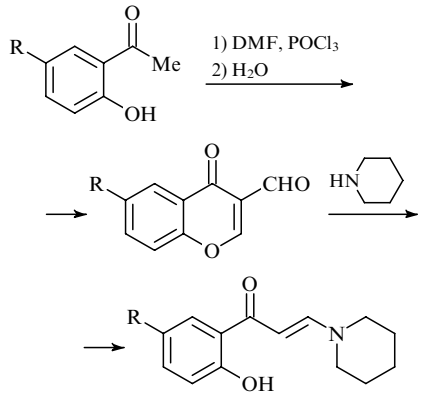
R = H, Me; X = Cl, Br.

The most general protocol used to prepare 3-halochromones (which also appears most attractive from the preparative standpoint) is halogenation of β-aminovinyl ketones containing a 2-hydroxyaryl group at the carbonyl carbon atom.[40] To prepare 3-halochromones containing no substituents at the 2-position, 2-hydroxyacetophenones are condensed with excess dimethylformamide dimethyl acetal. The 1-(2-hydroxyaryl)-3-dimethylaminoprop-2-en-1-ones thus formed are halogenated with *tert*-butyl hypochlorite, bromine or iodine in $CHCl_3$[40] or with *N*-fluoro-2,4,6-trimethylpyridinium triflate in a CH_2Cl_2 – MeCN mixture.[14]



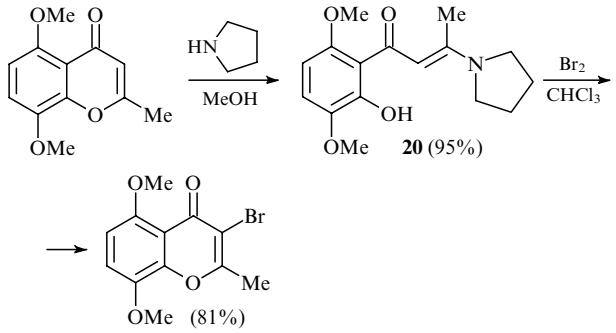
R = H, Me, Cl, MeO; X = F, Cl, Br, I.

When electrophiles with good leaving groups such as iodine chloride or trifluoro- and trichloroacetic anhydrides are used in the reaction with aminovinyl ketones, 3-chloro- and 3-trihaloacetylchromones are formed.[41] The use of expensive dimethylformamide dimethyl acetal can be avoided by preparing aminovinyl ketones in two steps *via* chromone-3-carbaldehydes,[42] which are readily deformylated by opening the heterocycle under the action of piperidine.[43]



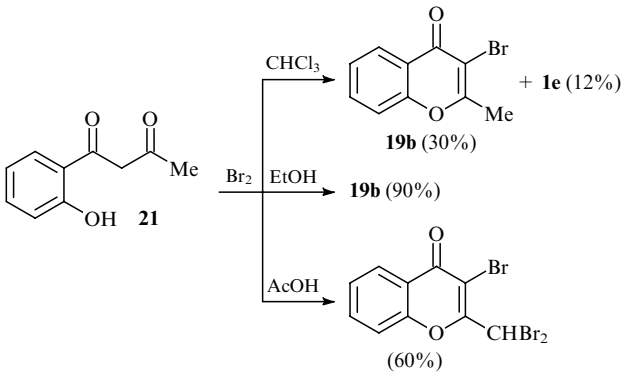
R = H, Me, Cl.

The reaction of 5,8-dimethoxy-2-methylchromone with pyrrolidine in boiling methanol yields aminovinyl ketone **20**, which reacts with bromine in $CHCl_3$ being converted into 3-bromo-5,8-dimethoxy-2-methylchromone.[40]

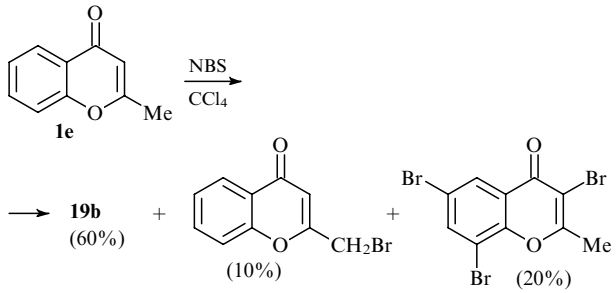


This reaction was used as an example to demonstrate that halogenation of enamines of 2-hydroxyacetophenones can be employed to obtain 2-substituted 3-halochromones.

3-Bromo-2-methylchromone (**19b**) was prepared in a relatively low yield, as a mixture with 2-methylchromone (**1e**) from β-diketone **21** under similar conditions (treatment with bromine in $CHCl_3$).[44] The outcome of this reaction proved to be substantially dependent on the nature of the solvent in which bromination took place. Indeed, when chloroform was replaced by ethanol, the yield of chromone **19b** increased to 90%, while the reaction performed in acetic acid in the presence of excess bromine led to 3-bromo-2-dibromomethylchromone.[45]



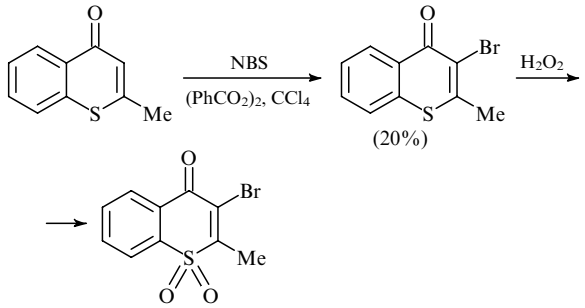
In the reaction of 2-methylchromone (**1e**) with bromine in AcOH, chromone **19b** is formed in a low yield (25%).[2] Upon an attempt to prepare compound **19b** from 2-methylchromone (**1e**) and *N*-bromosuccinimide in CCl_4, as described in an earlier publication,[46] three products were isolated, namely, chromone **19b**, 2-(bromomethyl)chromone and 3,6,8-tribromo-2-methylchromone.[47]



NBS is *N*-bromosuccinimide.

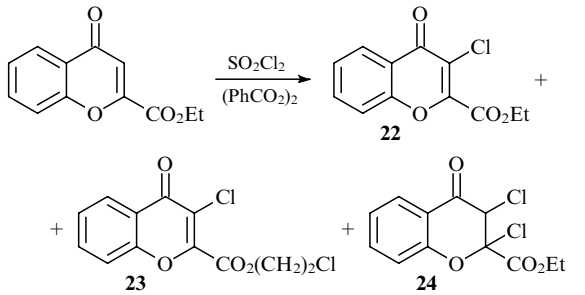
In the case of 6-methyl- and 6-methoxy-2-methylchromones, the reaction proceeds more unambiguously giving rise to 6-substituted 3-bromo-2-methylchromones (yields 90% – 92%), together with small amounts of 2-(bromomethyl)chromones (5% – 8%).[47] The reaction of 6-hydroxy-2-methylchromone with bromine in concentrated H_2SO_4 (25 °C, 6 h) gives 5-bromo-6-hydroxy-2-methylchromone (yield 73%). In acetic acid (45 – 50 °C, 8 h) and in the presence of excess bromine, 3,5-dibromo-6-hydroxy-2-methylchromone is formed (yield 53%).[48]

Ziegler bromination of 2-methylthiochromone gives 3-bromo-2-methylthiochromone, which is oxidised at sulfur on treatment with H_2O_2 to yield 3-bromo-2-methylthiochromone 1,1-dioxide.[49]



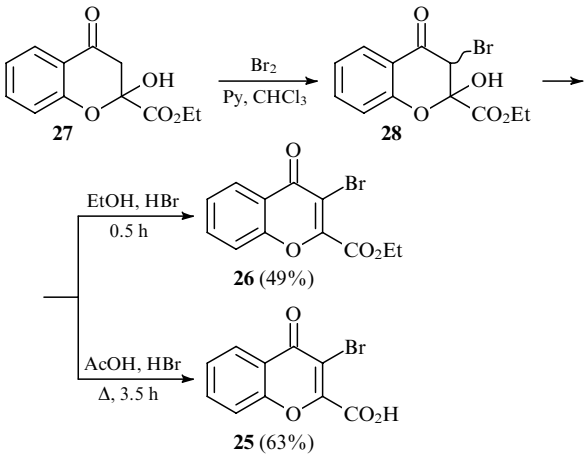
Treatment of 6-substituted 2-methylchromone and chromone-2-carbaldehyde with an aqueous solution of sodium hypochlorite in the presence of AcOH gives the corresponding 3-chlorochromones† in 61%–93% yield.[50] *N*-Trichloroacetyl- and *N*-ethoxycarbonyl-2-aminochromones are selectively chlorinated at the C(3) atom on treatment with SO_2Cl_2 in $CHCl_3$ at ~20 °C.[51] In the I_2–HIO_4 system, *N*-ethoxycarbonyl-2-aminochromone affords the 3-iodo-derivative in a yield of 78%.[52]

Refluxing a solution of ethyl chromone-2-carboxylate in sulfuryl chloride in the presence of benzoyl peroxide for 10 h gives a mixture consisting of approximately equal amounts of mono- (**22**) and di-chloro (**23**, **24**) derivatives.[53] Chromanone **24**, which is a product of free radical addition of chlorine at the double bond, easily loses an HCl molecule on treatment with pyridine, being thus converted into 3-chloro derivative **22**.



Under similar conditions, methyl chromone-2-carboxylate yields only methyl 3-chlorochromone-2-carboxylate (yield 69%)[54] and chromone-2-carbonitrile is converted into 3-chlorochromone-2-carbonitrile (yield 63%), which was used to prepare 3-chloro-2-(5-tetrazolyl)chromone, exhibiting an antiallergic activity.[55]

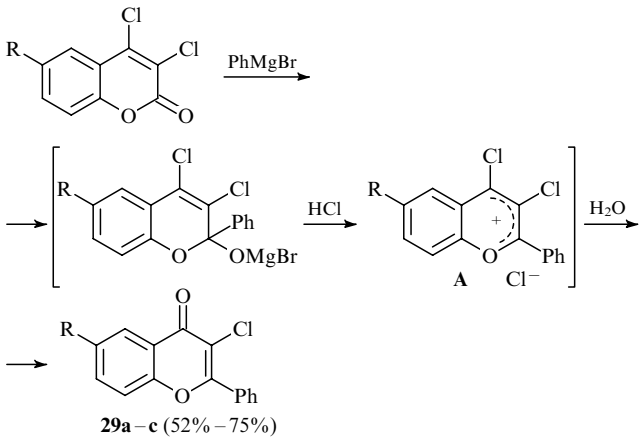
3-Bromochromone-2-carboxylic acid (**25**) and its ethyl ester (**26**) have been synthesised by two procedures.[54] According to one procedure, the condensation product obtained from 2-hydroxyacetophenone and diethyl oxalate and existing in the cyclic chromanone form **27** is made to react with bromine in chloroform in the presence of pyridine at −3 °C. This yields a mixture of *cis*- and *trans*-isomers of 3-bromochromanone **28** in 72 : 28 ratio. When compound **28** is refluxed in an EtOH–HBr mixture, ethyl 3-bromochromone-2-carboxylate (**26**) is formed in 49% yield, while refluxing of **28** in an AcOH–HBr mixture gives the acid **25**. The ester **26** can also be obtained by the above-described method[40] from ethyl chromone-2-carboxylate and pyrrolidine *via* aminovinyl ketone but in a lower yield.[54]



Bromination of ethyl 7-hydroxychromone-2-carboxylate with bromine in acetic acid (75–80 °C, 5 h) furnishes a mixture of 8-bromo-, 6,8-dibromo- and 3,6,8-tribromo-7-hydroxychromone-2-carboxylate, whereas bromination of the corresponding acid stops after the formation of 8-bromo-7-hydroxychromone-2-carboxylic acid under the same conditions (yield 94%).[56]

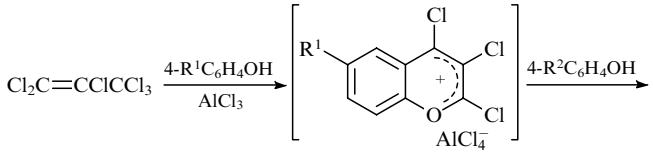
3. Synthesis of 3-haloflavones

Interestingly, 3-chloroflavones were first obtained[57] by the reaction of 3,4-dichlorocoumarins[35] with phenylmagnesium bromide rather than by chlorination of flavones. The key intermediate in this reaction is benzopyrylium salt **A**, which is hydrolysed at the 4-position to give 3-chloroflavones **29a**–**c**. This was the first example of direct transformation of the coumarin system into the chromone one.

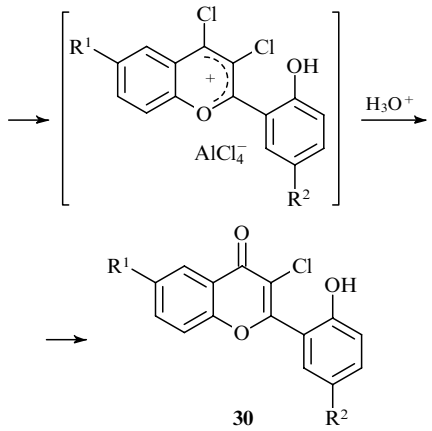


R = H (**a**), Me (**b**), Cl (**c**).

A modification of this method is treatment of the benzopyrylium salts formed *in situ* from phenols, perchloropropene and $AlCl_3$ with substituted phenols. This procedure was used to prepare 2′-hydroxy-3-chloroflavones **30**.[58]

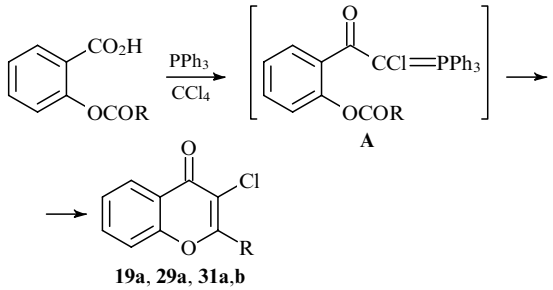


† In the case of 6-substituted chromone-2-carbaldehyde (unlike chromone-3-carbaldehyde[34]), the 2-formyl group is retained.



R^1, R^2 = Me, Cl.

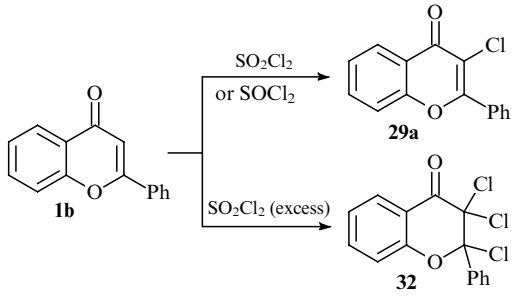
Acetylsalicylic acid and *O*-aroylsalicylic acids cyclise in the $PPh_3-NEt_3-CCl_4-CH_2Cl_2$ system at ~20 °C over a period of several hours to give 3-chloroflavone (**29a**) and its derivatives **19a** and **31a**,**b** (yields 43%–60%). In the researchers' opinion,[59] these products are formed *via* ylide type intermediate **A**. This reaction allows one to obtain 3-chlorochromone compounds in one step.



19a, **29a**, **31a**,**b**

R = Me (**19a**), Ph (**29a**), 4-ClC_6H_4 (**31a**), 3-C_5H_4N (**31b**).

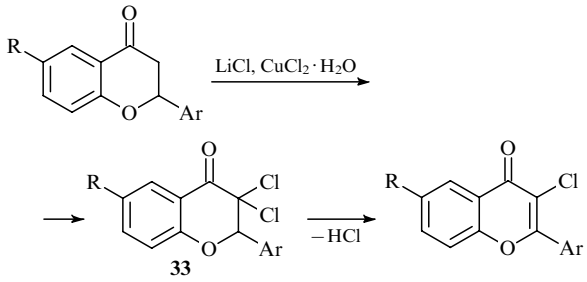
3-Chloroflavone (**29a**) is also formed on refluxing flavone (**1b**) with sulfuryl chloride ($CHCl_3$, 1 h, 65%)[31] or thionyl chloride (PhH, 15 h, 70%).[60] With excess SO_2Cl_2 in the presence of benzoyl peroxide (16 h, ~20 °C), flavone (**1b**) is converted into 2,3,3-trichloroflavanone **32** (67%).[31]



Compound **32** can also be prepared without benzoyl peroxide by refluxing flavone **1b** or **29a** with excess SO_2Cl_2 in benzene for 15 h.[61]

6- and 7-Chloroflavones react with thionyl chloride to give 3,6- and 3,7-dichloroflavones. 6-Chloroflavone reacts with sulfuryl chloride giving rise to 2,3,3,6-tetrachloroflavanone. The reaction of 7-hydroxyflavone with $SOCl_2$ in boiling benzene affords a mixture of 7-chloro- and 3,7-dichloroflavones, while its reaction with SO_2Cl_2 leads to 3,6,8-trichloro-7-hydroxyflavone.[62] When 6-methylflavone is refluxed with SO_2Cl_2 in CCl_4 for 15 h, 3-chloro-6-dichloromethylflavone is the major reaction product. 2,3,3-Trichloro-6-dichloromethylflavanone is formed as a minor product. The reaction of SO_2Cl_2 with 6-methoxyflavone results in a complex mixture of four chloro derivatives of flavone and flavanone.[63] A general and an efficient method for the synthesis of 3-chlorinated derivatives of flavone, chromone and thioflavone has been proposed. The procedure implies treatment with SO_2Cl_2 [64] and the use of montmorillonite K10 as the catalyst.

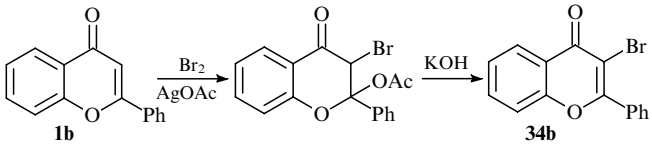
Oxidative chlorination of flavones has been carried out using LiCl as a source of chloride ions and $CuCl_2 \cdot 2H_2O$ [65,66] or $Mn(OAc)_3 \cdot 2H_2O$ [67] as the oxidant. The process afforded 3,3-dichloroflavanones **33**, which are readily dehydrogenated yielding 3-chloroflavones.



Ar = Ph: R = H, Me, OMe, Cl, Br; Ar = 4-$MeOC_6H_4$, 4-ClC_6H_4: R = H.

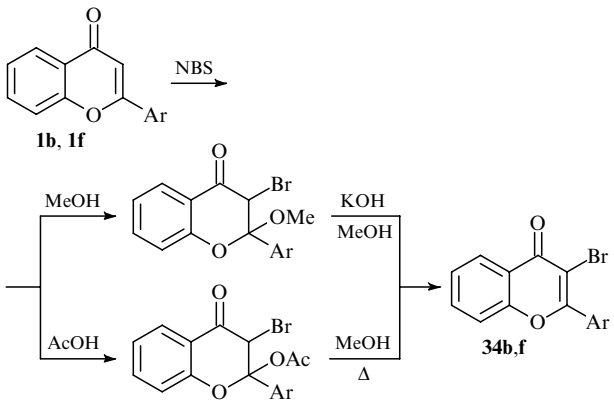
On refluxing in the $CuCl_2$–DMSO system, flavanones and their linear isomers, 2′-hydroxychalcones, are immediately converted into 3-chloroflavones **29** in 80%–85% yields. Dichloro derivatives are not formed under these conditions.[68]

Treatment of flavone **1b** with bromine in chloroform in the presence of silver acetate produces 2-acetoxy-3-bromoflavanone, which is easily transformed into 3-bromoflavone (**34b**) on treatment with KOH in aqueous alcohol.[69]



Upon direct bromination of flavone **1b** with bromine in boiling acetic acid, 3-bromoflavone **34b** (75%) and 3,8-dibromoflavone (10%) were isolated.[70] However, attempts to prepare substituted 3-bromoflavones and their heteroanalogues have not met with success.[71] During bromination of flavones in the Br_2–AcOH system, the addition of $Hg(OAc)_2$ is recommended.[72] Preparation of 3-bromoflavones by the reaction of flavone with bromine in pyridine has been reported;[73] the product yields were not given in the publication.

Good results have been attained by using *N*-bromosuccinimide as the brominating agent. For instance, 3-bromoflavones **34b**,**f** were prepared in high yields by the reaction of flavones **1b** and **1f** with *N*-bromosuccinimide in methanol or acetic acid.[74]

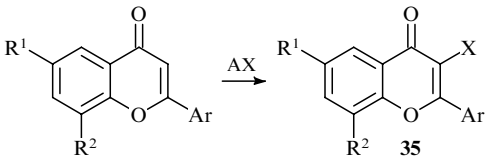


Ar = Ph (**b**), 4-$MeOC_6H_4$ (**f**).

This method was used successfully to prepare 3,8-dibromo-7-butoxy-6-nitroflavones. These compounds were used to demon-

strate that the introduction of a bromine atom in the 3-position of flavones increases their antibacterial activity.[75]

Substituted 3-bromoflavones **35** were prepared by treatment of appropriate flavones with *N*-bromosuccinimide in $CHCl_3$ or $CuBr_2$ in an AcOEt – $CHCl_3$ mixture (the yield of compounds **35** reached 50% – 80%).[71, 76–78]

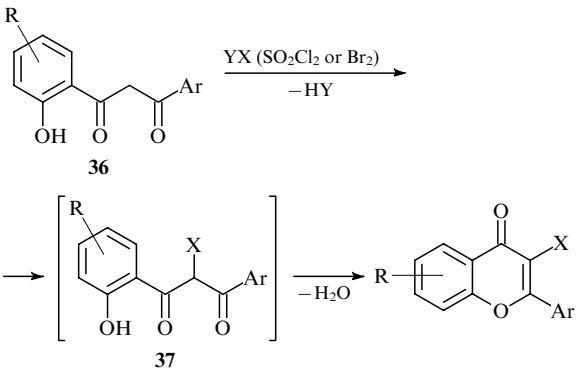


R^1 = H, Me, MeO, Cl, Br, F; R^2 = H, Me, Br; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 4-$AcNHC_6H_4$, 2-$MeOC_6H_4$, 2-C_4H_3O, 2-C_4H_3S; AX = NBS, $CuBr_2$, $C_5H_5NH^+Br_3^-$, $PhI(OAc)_2$ – Me_3SiX (X = Cl, Br).

Recently, it was found that the reaction of flavones with pyridinium tribromide in pyridine and CH_2Cl_2 (~20 °C, 16 – 48 h)[79] or with diacetoxy-λ^3-iodanylbenzene in the presence of trimethylsilyl halides and pyridine (0 °C, 4 h)[80] provides the corresponding 3-bromo- and 3-chloroflavones **35** in 60% – 86% yields. In the latter case, halogenation can be carried out on a polymer substrate.

Bromination of flavones with 2,4,4,6-tetrabromocyclohexa-2,5-dienone proceeds under mild conditions to give the corresponding 3-bromoflavone in good yields.[81]

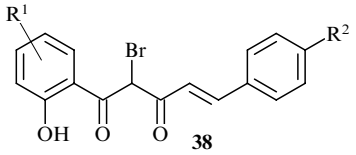
A facile and versatile method for the synthesis of 3-haloflavones is based on halogenation of flavone precursors, diketones **36**.[76, 82–86] For example, substituted 3-chloroflavones are formed on treatment of diketones **36** with sulfuryl chloride in dioxane and 3-bromoflavones, on treatment with bromine in dioxane.[82] The reaction involves intermediates **37**, which undergo cyclodehydration in the presence of the hydrogen halide evolved in the reaction to give 3-haloflavones in 60% – 70% yields. Subsequently, this procedure has been utilised to prepare 2-styryl-,[84] 2-(α-furyl)- (see Refs 71, 83) and 2-(α-thienyl)-3-halochromones,[71] as the double bond and the heterocyclic ring of 2-substituents are not halogenated under these conditions.



R = H, Me, Cl, Br; Ar = Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4, 2-C_4H_3O, 2-C_4H_3S, PhCH=CH, 4-$MeOC_6H_4CH$=CH; X = Cl, Br.

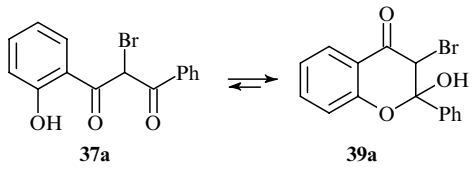
It should be noted that the reaction between 2-styrylchromones and pyridinium tribromide in AcOH at ~20 °C starts with bromination of the double bond of the styryl substituent; only after this, does bromination of C(3) take place.[87]

In the bromination of 5-aryl-1-(2-hydroxyaryl)pent-4-ene-1,3-diones in DMF (which traps the HBr evolved), intermediate α-bromodiketones **38**, existing in the linear form in $CDCl_3$ (according to ^1H NMR data), were isolated.[84]

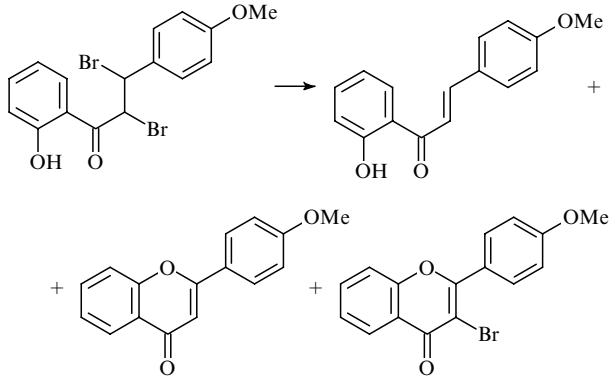


R^1 = H, Me; R^2 = H, MeO.

The same compounds are formed upon bromination of styryl diketones in the Br_2 – AcOH – AcONa system, whereas treatment with *N*-bromosuccinimide in CCl_4 yields a mixture of compounds **34** and **38** that are difficult to separate.[85] It is noteworthy that, unlike diketones **38**, 2-bromo-1-(2-hydroxyphenyl)-3-phenylpropane-1,3-dione (**37a**) produced in the reaction of diketone **36a** (R = H, Ar = Ph) with bromine in chloroform in the presence of K_2CO_3 exists in the crystalline state as cyclic semiketal **39a**, while in $CDCl_3$, it exists as a mixture of ring – chain tautomers **37a** and **39a** in a 3 : 11 ratio, respectively.[88]

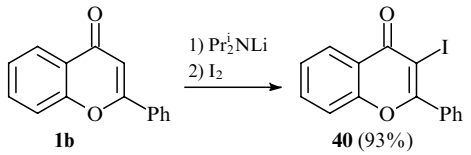


Treatment of flavanone with the complex $[(C_4H_7NO)_3 \cdot HBr \cdot Br_2]$ in THF is an efficient method for the synthesis of 3-bromoflavanone, which is formed as a mixture of *cis*- and *trans*-isomers. Treatment of 4′-methoxy- and 4′,7-dimethoxyflavanones with this complex in DMSO results in product mixtures consisting of the corresponding flavones and 3-bromoflavones.[89] Pyrolysis of 2′-hydroxy-4-methoxydihydrochalcone dibromide at 150 °C yields a mixture of three products, namely, 2′-hydroxy-4-methoxychalcone, 4′-methoxyflavone and 3-bromo-4′-methoxyflavone; the last-mentioned product is formed upon bromination of 4′-methoxyflavone under conditions of pyrolysis.[90]

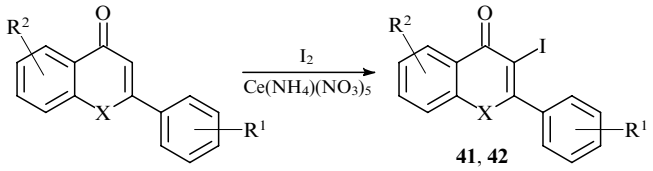


The reaction of 2′-benzyloxy-6′-hydroxychalcone and 2′-benzyloxy-6′-hydroxy-2-cinnamylideneacetophenone with bromine or iodine (DMSO, Δ, 0.5 h) represents a one-step synthesis of the corresponding flavones and 2-styrylchromones dihalogenated in the benzene ring, which is activated by the hydroxy group at the 5-position; 3-halochromones are not formed under these conditions.[91]

Data on the synthesis of 3-iodoflavones (which hold much promise as intermediates in the synthesis of diflavonoids) and 3-fluoroflavones are quite scarce. Unlike chromone **1a**, flavone **1b** is smoothly lithiated at the 3-position on treatment with lithium diisopropylamide (THF, −78 °C), which makes it possible to prepare 3-iodoflavone **40** by treating 3-lithioflavone with iodine.[92]

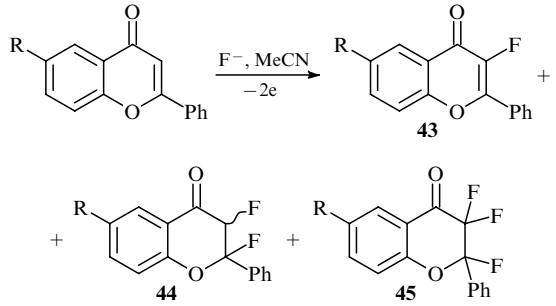


Recently, the first and still the only one rather general method for the synthesis of 3-iodoflavones **41**, 3-iodothioflavones **42** and 3-iodo-2-(methyl)thiochromones, has been developed.[93] The method consists of the treatment of flavones, thioflavones and thiochromones with the $Ce(NH_4)(NO_3)_5 - I_2$ system in anhydrous acetonitrile at 55–60 °C. The yields of 3-iodoflavones **41** vary over broad limits (24%–80%) and reach a maximum (71%–80%) when an electron-donating group occurs at the 4′-position. Thioflavones and 2-(methyl)thiochromones are iodinated under the same conditions almost quantitatively (95%–98%). These results are in good agreement with the mechanism of electrophilic substitution at C(3) involving I^+.



41: X = O: R^1 = H, 4-MeO, 4-BnO, 4-Cl, 2-MeO;
R^2 = H, 6-MeO, 7-MeO, 5,7-$(MeO)_2$;
42: X = S: R^1 = H; R^2 = H, 6-Me.

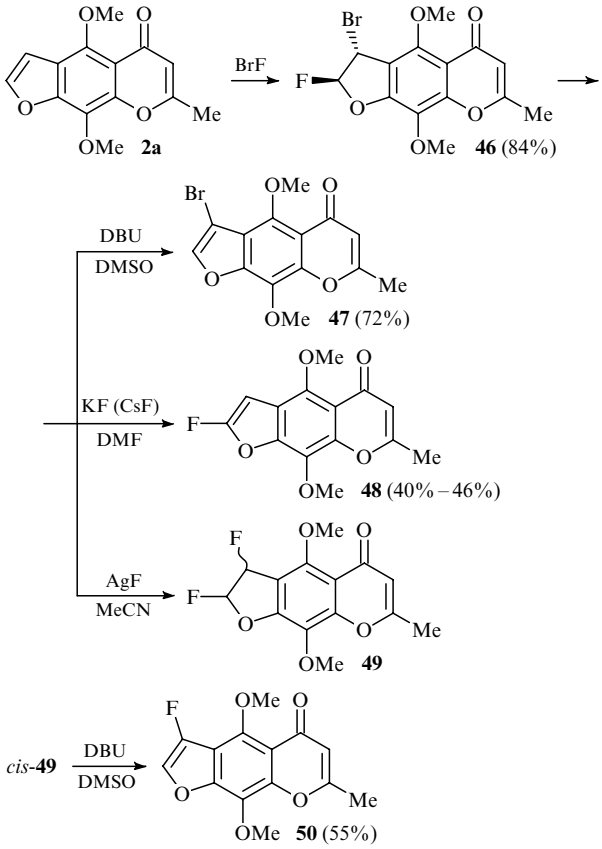
3-Fluoroflavone and its 6-substituted derivatives were prepared from appropriate flavones by electrochemical fluorination using the $Et_4NF \cdot 4\,HF$ or $Et_3N \cdot 3\,HF$ salts in acetonitrile as the source of fluoride anions.[94, 95] Anodic fluorination of flavones affords mono- (**43**), di- (**44**) and tri- (**45**) fluoro derivatives, whose ratio depends on the type of salt used and the temperature of electrolysis. 3-Fluoroflavones **43** are formed upon dehydrofluorination of compounds **44** under the action of triethylamine, while trifluoro derivatives **45** are the products of further fluorination of flavones **43**.



R = H, Me, Cl.

The yields of 3-fluoroflavones **43** vary over a broad range (25%–63%). Nevertheless, due to high regioselectivity, mild reaction conditions and the absence of toxic reagents, which are normally employed in the chemical fluorination, this method is an efficient tool for the synthesis of various fluorine-containing heterocycles.[95] By anodic fluorination of thioflavone under similar conditions, 3-fluorothioflavone (22%) and 2,3,3-trifluorothioflavanone (42%) have been synthesised.[96]

The synthesis of 3-bromo- and 2- and 3-fluorokhellins from khellin **2a** and BrF has been reported.[97] The protocol includes the formation of *trans*-3-bromo-2-fluoro-2,3-dihydrokhellin **46** in a high yield. On treatment with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in DMSO, compound **46** is smoothly converted into 3-bromokhellin **47**. The reaction of **46** with KF or CsF gives 2-fluorokhellin **48**, and the reaction with AgF in acetonitrile affords a mixture of *cis*- and *trans*-2,3-difluoro-2,3-dihydrokhellins **49** (51% and 36%, respectively). When the *cis*-isomer is treated with 1,5-diazabicyclo[5.4.0]undec-5-ene in DMSO, 3-fluorokhellin **50** is formed.

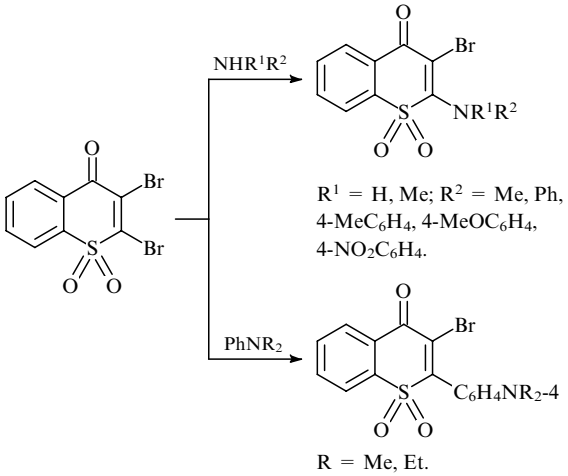


III. Chemical properties of halochromones

1. Reactions of 2-halochromones

As regards the ability of the halogen atom to act as a leaving group, 2- and 3-halochromones markedly surpass chromones halogenated at the benzene ring (except for 5,6,7,8-tetrafluorochromones in which the fluorine atom located in the *para*-position relative to the carbonyl group is susceptible to nucleophilic substitution [18]). The halogen atom situated in the β-position with respect to the carbonyl group is the most active; therefore, 2-halochromones surpass 3-halochromones and are similar to acid halides in reactivity.

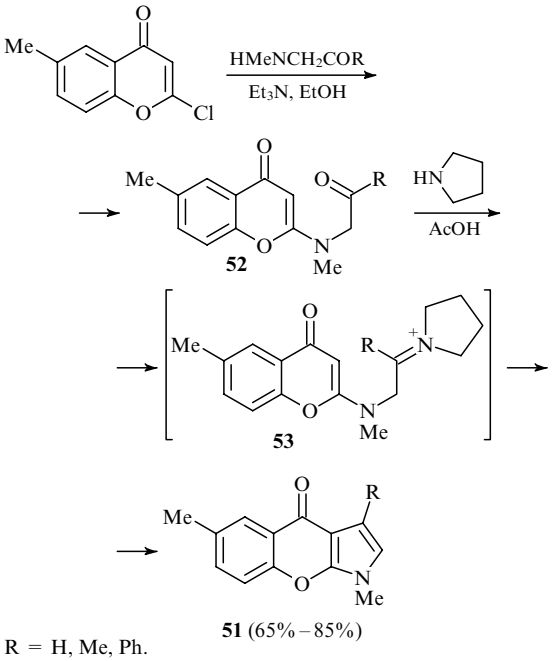
When 2,3-dibromothiochromone 1,1-dioxide is made to react with primary and secondary aliphatic and aromatic amines,[98] only one bromine atom is replaced, namely, that located at the



2-position. Tertiary aromatic amines behave in this reaction as C-nucleophiles.[98]

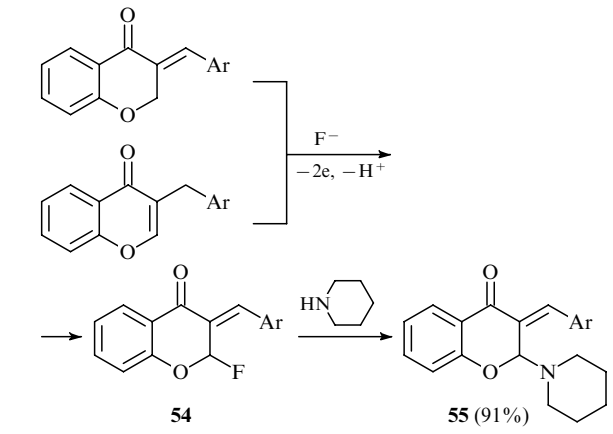
2-Chlorochromones are readily hydrolysed to 4-hydroxycoumarins when treated with water in the presence of acids or bases,[22] while 2-chloro-3-hydroxychromone reacts with methylamine, aniline or secondary amines yielding the corresponding 2-amino-3-hydroxychromones (yields 40% – 50%).[99]

Recently, chromeno[2,3-*b*]pyrrol-4(1*H*)-ones **51**, analogues of natural products useful for pharmacology, have been prepared from 2-chloro-6-methylchromone and α-aminocarbonyl compounds (as acetals, ketals or hydrochlorides).[28] The reaction follows the A_N-E mechanism proceeding through replacement of the chlorine atom by nitrogen giving rise to 2-aminochromone derivatives **52**, which cyclise on heating in a pyrrolidine – acetic acid mixture (1 : 1). Presumably,[28] pyrrolidine activates the carbonyl group through the formation of iminium salt **53** (in the presence of other acids or bases, this reaction does not occur).



R = H, Me, Ph.

The anodic fluorination of (*E*)-3-(4-chlorobenzylidene)-2,3-dihydrochroman-4-one or isomeric 3-(4-chlorobenzyl)chromone yields the same product — (*E*)-3-(4-chlorobenzylidene)-2-fluoro-2,3-dihydrochroman-4-one (**54**). On treatment with piperidine in acetonitrile at ~20 °C, compound **54** is converted into 3-(4-chlorobenzylidene)-2-piperidino-2,3-dihydrochroman-4-one (**55**).[100]

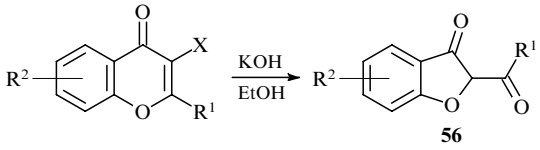


Ar = 4-ClC_6H_4.

2. Reactions of 3-halochromones

3-Halochromones contain a double bond with geminal arrangement of the carbonyl group and the halogen atom; thus, they can be regarded as geminally activated haloalkenes, which are highly reactive and are widely used in the synthesis of heterocycles and analogues of natural compounds.[101] The reactions of nucleophilic reagents with 3-halochromones containing two good leaving groups (the halogen atom at the α carbon atom and the phenolic fragment at the β carbon atom) are more diverse than reactions with haloalkenes. Indeed, haloalkenes react with *N*-nucleophiles along three major pathways including the formation of aziridines and aminoalkenes with a vicinal or geminal (*ipso*-substitution) activating group.[101] In the case of 3-halochromones, apart from these pathways, reactions associated with opening and transformation of the γ-pyrone ring can also take place. Note in addition that, whereas the reaction pathway with haloalkenes is governed by the nature of the activating group, in the case of 3-halochromones, the most important factor is the type of the nucleophilic species, together with the size and the electronic properties of the 2-substituent.

Among 3-halochromones, 3-haloflavones and their heterocyclic analogues are least reactive, which is due to the presence of the (het)aryl substituent at the 2-position. For example, the most typical reaction of 3-haloflavones is contraction of the γ-pyrone ring on refluxing with an ethanol solution of KOH to give compounds **56**.

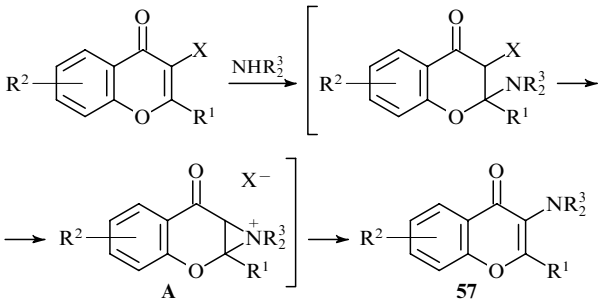


R^1 = Ar, Het, CH=CHAr; R^2 = H, Me, Cl; X = Cl, Br.

This ring transformation has been repeatedly used to confirm the structures of 3-bromoflavones,[82] 3-halo-2-hetaryl-[83] and 3-halo-2-styrylchromones.[84] However, in the case of 3-halochromones devoid of substituent at the 2-position, ring transformation occurs only on treatment with amines (see below). Worthy of note is also the possibility of replacement of the chlorine atom in 3-chloroflavones by a cyano group in the presence of copper(I) cyanide,[57, 102] which cannot be accomplished for other halochromones.

a. Reactions with N- and S-nucleophiles

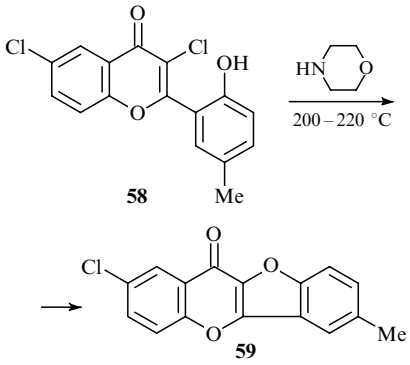
A very important reaction of 3-halochromones is its amination by secondary cyclic amines (pyrrolidine, piperidine, morpholine and *N*-methylpiperazine), which results in the corresponding 3-aminochromones **57**.[37, 46, 47, 70, 103, 104] Presumably, the *ipso*-replacement of the halogen atom observed in this case follows the 1,4-addition mechanism involving the formation of the aziridinium intermediate **A**, whose subsequent opening gives an amino group at the C(3) atom.[37, 105, 106]



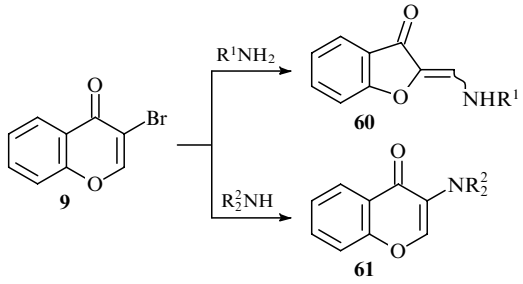
R^1 = H, Me, Ar; R^2 = H, Me, Cl; X = Cl, Br;

NHR_2^3 = HN⟨Z⟩ (Z = CH_2, O, NMe), HN⟨ ⟩.

The presence of a substituent at the 2-position of the chromone system hampers the reaction; amination of 3-haloflavones is carried out under rather drastic conditions. 3-Bromo derivatives are more reactive than analogous 3-chloro derivatives. 3-Bromoflavone is converted into amino derivatives **57** at ~100 °C in 60% – 80% yields (6 – 8 h),[70] while 3-chloroflavone enters into the reaction with morpholine or piperidine only on heating in *N*-methylpyrrolidone in a sealed tube (200 – 220 °C, 72 – 80 h) and the yield does not exceed 30% – 44%. Flavone **58** cyclises under these conditions to form tetracyclic derivative **59**.[104]

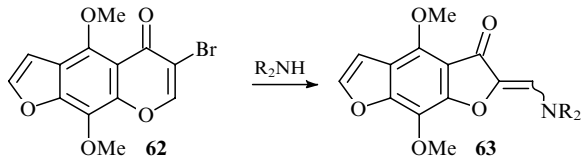


3-Chlorochromones,[37, 103] 3-bromo-2-methylchromone [46] and 3-bromoflavone [70] are aminated on heating without a solvent; however, an attempt to use these conditions for amination of 3-bromochromone (**9**) resulted in a complex mixture of products.[106] A study of amination of 3-halochromones devoid of substituents at C(2), which is the site of the initial nucleophilic attack, has shown that the reaction of 3-bromochromone (**9**) with primary amines in acetonitrile in the presence of K_2CO_3 (added for neutralisation of HBr evolved during the reaction) is accompanied by contraction of the γ-pyrone ring giving benzofuran (coumarone) derivatives **60**. The reaction with secondary amines under the same conditions gives the expected 3-aminochromones **61**.[106] The synthesis of compounds **60** proceeds *via* opening of the pyrone ring induced by the attack by the amine on the C(2) atom followed by replacement of the bromine atom under the action of the phenoxide anion (tautomerism and double bond configuration have not been discussed in the study cited [106]).



R^1 = Bu, Bn, cyclo-C_6H_{11}; R^2_2NH = HN⟨O⟩, HN⟨⟩.

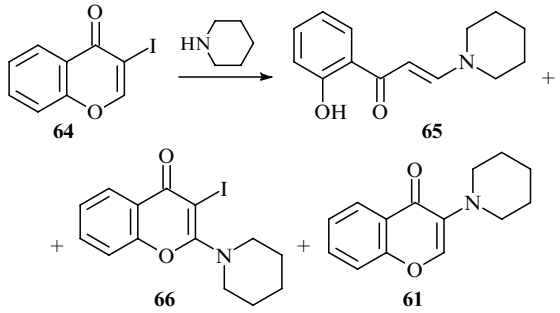
Note that 6-bromonorkhellin **62** reacts with primary and secondary amines with contraction of the pyrone ring to give furocoumarone derivatives **63**.[106]



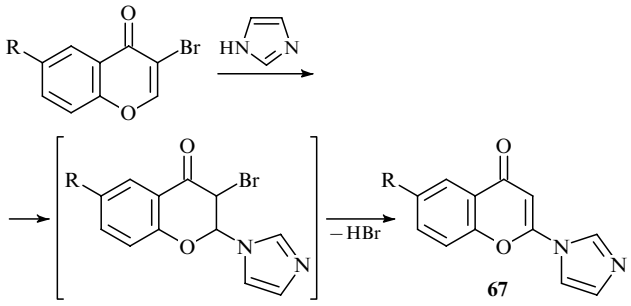
R_2NH = $BuNH_2$, cyclo-$C_6H_{11}NH_2$, HN⟨O⟩, HN⟨⟩.

Recently, it was shown [107] that replacement of acetonitrile by DMF changes the reaction pathway between secondary cyclic amines and 3-halochromones unsubstituted at the 2-position. Instead of 3-aminochromones **61**, the reaction affords benzofuranones **60** (yields 72% – 96%), *i.e.*, the reaction occurs in the same way as that with primary amines in MeCN.

Of 3-halochromones, 3-iodochromone (**64**) is the most reactive. For reactions of halochromones with imidazole, it was shown that on replacement of 3-iodochromone by 3-bromo- or 3-chlorochromone, the reaction rate and the product yield substantially decrease.[108] The reaction of 3-iodochromone with piperidine has been studied in detail.[107] The reaction carried out in MeCN in the presence of K_2CO_3 was found to yield aminovinyl ketone **65** (63%) and 3-iodo-2-piperidinochromone (**66**) (4%). In DMF in the absence of K_2CO_3, a mixture consisting of compounds **65** (51%), **66** (11%) and 3-piperidinochromone (**61**, $NR^2_2 = NC_5H_{10}$) (13%) is obtained. The diversity of reaction products is explained by a variety of transformations of the Michael adduct formed initially; in particular, iodine elimination with simultaneous ring opening affords compound **65**, iodination followed by elimination of HI gives chromone **66**, and intramolecular replacement of iodine *via* the aziridinium cation leads to chromone **61**. When 3-chloro- or 3-bromochromone is introduced in this reaction, products of types **65** and **66** are not formed.[107]



The reaction of 3-bromo- and 3-bromo-6-chlorochromones with excess imidazole in the presence of its silver salt (80 °C, 0.5 h) proceeds by Michael addition followed by dehydrobromination and results in 2-imidazolylchromones **67**.[108] Due to the electron-withdrawing nature of the imidazole ring, the acidity of the H(2) atom increases, and the formation of the aziridinium intermediate becomes impossible due to the reduced nucleophilicity of the imidazole nitrogen; apparently, this contributes to the change in the reaction route.

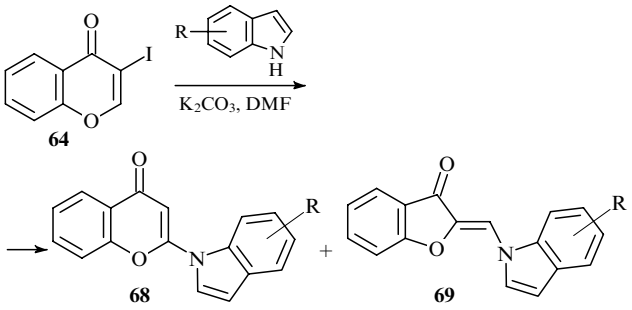


R = H, Cl.

3-Bromothiochromones react with imidazole or 2-alkylimidazoles giving rise to 2-imidazolylthiochromones and react with secondary amines (piperidine, morpholine and methylethylamine) to give 3-aminothiochromones, *i.e.*, 3-bromochromones and 3-bromothiochromones are equally reactive towards imidazoles and secondary amines.[109]

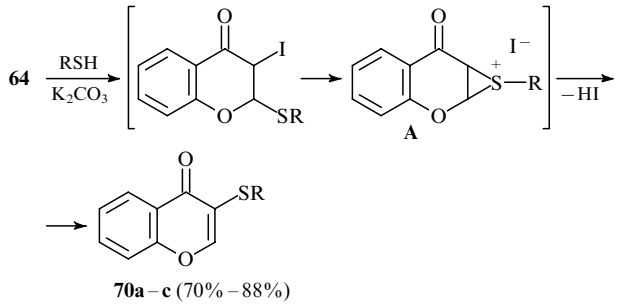
2-(*N*-Azolyl)chromones are prepared by heating 3-iodochromone (**64**) with azoles (imidazole, pyrazole, pyrrole, 1,2,4-triazole, benzimidazole, indazole) in DMF in the presence of K_2CO_3 (80 °C, 56% – 89%).[110] The reaction of 3-iodochromone (**64**)

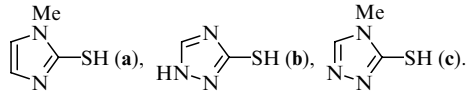
with indole carried out under the same conditions leads to a mixture of approximately equal amounts of 2-(1-indolyl)chromone (**68**) and 2-(1-indolyl)methylene-3(2*H*)-benzofuranone (**69**). Substituents in the indole system have a substantial influence on the **68** to **69** product ratio. In the presence of electron-donating groups (Me, MeO), the product ratio changes in favour of benzofuranones **69**, whereas electron-withdrawing substituents (Cl, NO_2) promote the proportion of chromones **68**, because in this case, the indole nitrogen atom is depleted of electrons.[110]



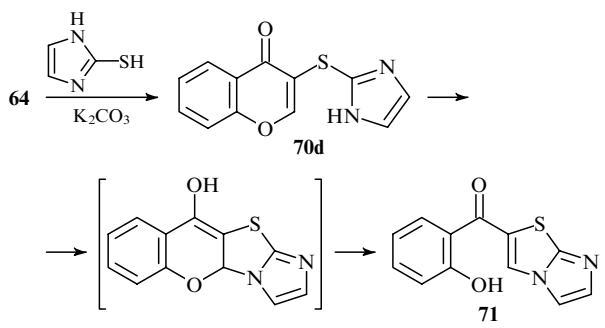
R = H, 3-Me, 5-Me, 5-MeO, 5-Cl, 5-NO_2, 6-NO_2.

The reactions of chromone **64** with 1-methyl-2-sulfanylimidazole, 3-sulfanyl-1,2,4-triazole or 4-methyl-3-sulfanyl-4*H*-1,2,4-triazole (DMF, K_2CO_3, ~20 °C) proceed differently from the reactions with azoles. In this case, 3-azolylsulfanylchromones **70** are formed instead of 2-substituted chromones or benzofuranones.[111] An analogous compound has also been obtained in the reaction of chromone **64** with 2-thiocytosine.[112] The substitution of a sulfur atom for iodine involves the formation of a three-membered episulfonium cation **A** (similarly to the substitution of nitrogen for halogen). The subsequent opening of the three-membered ring furnishes chromones **70a**–**c**.



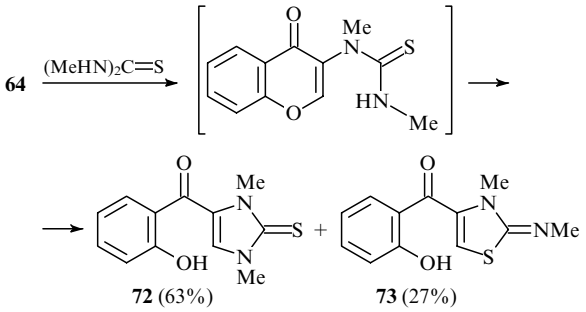
RSH =  SH (**a**), SH (**b**), SH (**c**).

Unexpectedly, the reaction of 3-iodochromone (**64**) with 2-sulfanylimidazole does not stop after the formation of chromone **70d** but proceeds further as an intramolecular ring transformation giving a mixture of products **70d** and **71** in 18% and 62% yields, respectively.[111]



2-Sulfanyl- and 5-methoxy-2-sulfanylbenzimidazoles react with chromone **64** to yield compounds of type **71** as the major products, whereas 5-nitro-2-sulfanylbenzimidazole gives only the corresponding chromone **70**.[111] When K_2CO_3 is replaced by Bu_4NCl, the reactions with 2-sulfanylimidazole and 2-sulfanylbenzimidazole stop after the formation of 3-substituted chromones **70**.[113]

Finally, the reaction of *N*,*N*′-dimethylthiourea with 3-iodochromone (**64**) produces a mixture of imidazoline **72** and thiazoline **73**; thiourea acts as an N-nucleophile in the first step of the reaction and as either an N- or S-nucleophile in the final step.[114]

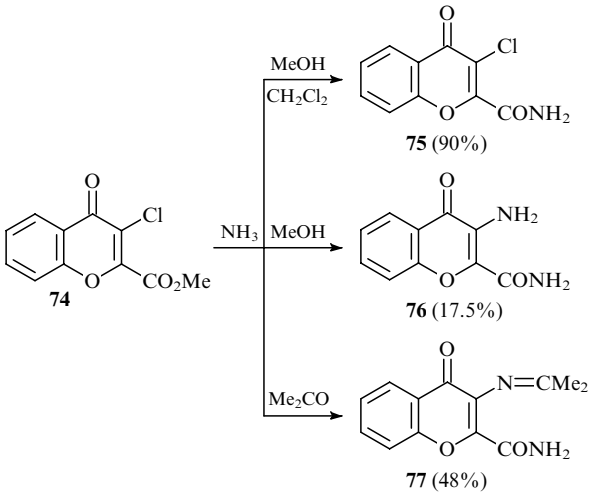


Thus, the transformations of 3-bromo- and 3-iodochromones induced by N- and S-nucleophiles demonstrate the broad synthetic potential of these compounds, the high reactivity of which ensures the existence of several pathways for particular reactions. On the one hand, this diversity of properties complicates prediction of the structures of the final products but, on the other hand, this makes 3-halochromones attractive objects for further investigations.

It should be noted that data on the reactions of 3-halochromones with bisnucleophiles (even with simple ones such as hydroxylamine or hydrazine) are very scarce.

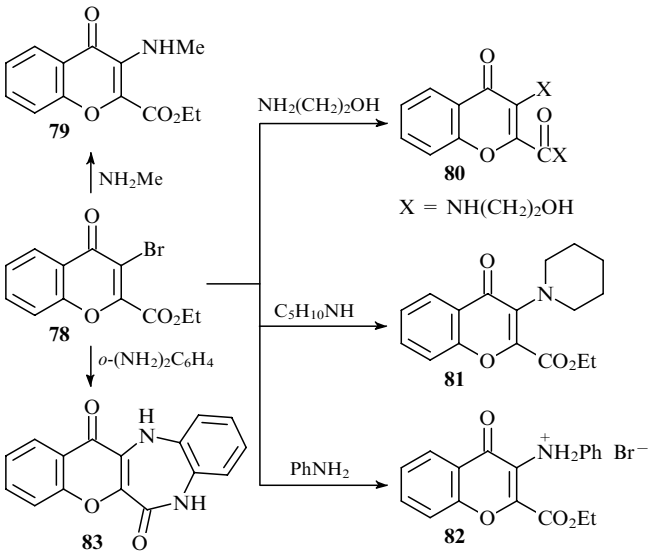
The reaction of 3-bromochromone (**9**) with hydroxylamine has been reported to give the oxime of 3-hydroxy-1-benzofuran-2-carbaldehyde, the structure of which was confirmed by X-ray diffraction data; however, neither the synthetic procedure nor the spectroscopic or physicochemical characteristics were described.[106]

Some data on the reactions of alkyl 3-chloro- and 3-bromochromone-2-carboxylates with ammonia and amines have been reported.[53, 54, 115] Depending on the reaction conditions, methyl ester **74** reacts with ammonia to give products **75**–**77**; this implies that the reaction first involves the ester group, and then the chlorine atom is replaced by the amino group, which is able to react with acetone to yield Schiff's base **77**.[54] The yield of amide **76** increases to 66% when the ethyl ester is used as the starting compound instead of the methyl ester, which is due to different solubilities of these compounds in methanol.[53]



Attempts to replace chlorine in 3-chlorochromone-2-carboxylate by an amino group on treatment with ammonia have failed. In 3-chlorochromone-2-carbonitrile, the group to be replaced is the cyano group; this gives 2-amino-3-chlorochromone, which is hydrolysed in an acid medium to 3-chloro-4-hydroxycoumarin.[53] On the basis of these data, it was concluded [53] that the reactivity of 2-substituted 3-chlorochromones decreases in the sequence 2-Me < 2-CO_2Et < 2-CN < 2-CO_2H.

The reactions of ethyl ester **78** with methylamine, 2-aminoethanol, piperidine, aniline and *o*-phenylenediamine proceed with replacement of the bromine atom and with retention of the pyrone ring, yielding products **79**–**83**.[54, 115]

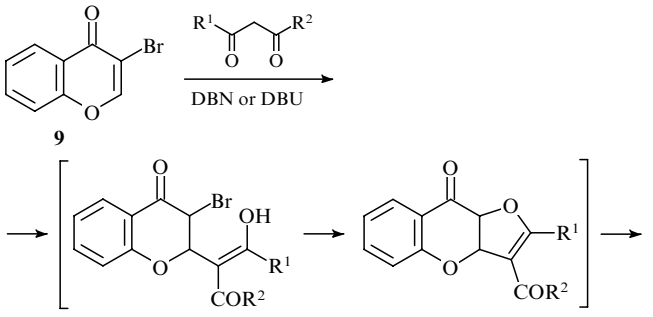


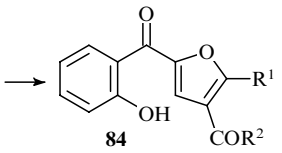
Ester **78** reacts with ammonia giving rise to amide **76** (yield 74%). Due to steric hindrance in the ester group, *tert*-butyl 3-bromochromone-2-carboxylate reacts only at the C(3) atom with replacement of bromine yielding *tert*-butyl 3-aminochromone-2-carboxylate (yield 55%).[115]

Thus, neither primary nor secondary amines react with 3-halochromone-2-carboxylate with contraction of the pyrone ring to form the furan ring. When secondary amines react with 3-bromo-2-methylchromone and 3-haloflavones, the pyrone ring is also retained.

b. Reactions with C-nucleophiles

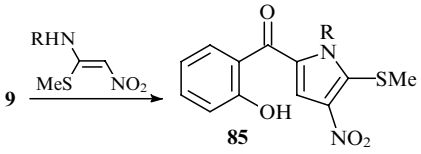
The reactions of bromochromone (**9**) with C-nucleophiles are highly significant, in particular, for the preparation of pharmaceutically valuable products. Thus the reactions of chromone **9** with β-diketones and β-ketoesters {1,5-diazabicyclo[4.3.0]non-5-ene (DBN) or DBU, $CHCl_3$, ~20 °C, 0.5–1 h} lead to highly functionalised furans **84**.[116] Completion of this reaction requires two equivalents of a base, while replacement of DBN or DBU by Et_3N results in the recovery of the starting compounds. The mechanism of this transformation involves 1,4-addition of the β-dicarbonyl compound to chromone **9** followed by intramolecular *O*-alkylation and opening of the pyrone ring to give 2-salicyloylfurans **84**.[116]





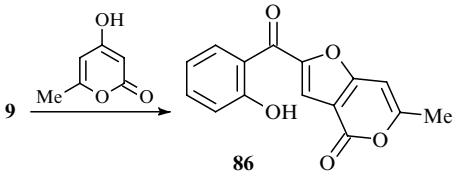
$R^1 = R^2 = Me$; $R^2 = OEt$: R^1 = Me, Ph, CH_2SPh, CH_2CO_2Et; $R^1–R^2 = CH_2CMe_2CH_2$.

The reaction of 3-bromochromone (**9**) with nitro enamines resulting in 2-salicyloylpyrroles **85** [117] is carried out in the MeCN–K_2CO_3 system (previously, this system was used in reactions with amines [106]).

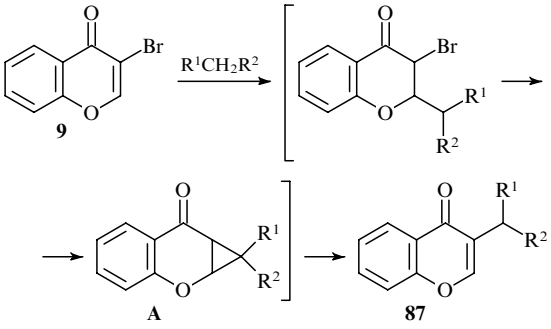


R = Me, Ph.

Heating of chromone **9** with 4-hydroxy-6-methyl-2*H*-pyran-2-one in pyridine for 4–5 h gives furopyrone **86**.[117]

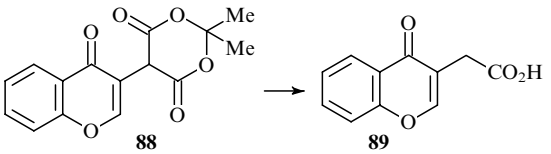


Unlike β-diketones and β-ketoesters, derivatives of malonic acid, more susceptible for C-alkylation, react with 3-bromochromone (DBU, MeCN, 20 °C) *via* the formation of the cyclopropane intermediate **A**. Owing to the anchimeric assistance from the neighbouring oxygen atom, the cyclopropane ring in compound **A** is easily cleaved to give 3-substituted chromones **87**.



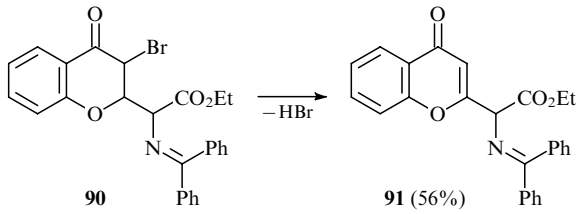
$R^1 = R^2 = CO_2Et$; $R^1 = CO_2Et$, R^2 = CN;
$R^1 = CO_2Bu^t$, R^2 = CN; R^1 = CN, $R^2 = SO_2Me$.

The reaction of 3-bromochromone (**9**) with Meldrum's acid affords chromone **88**, which is converted into acid **89**.[118]



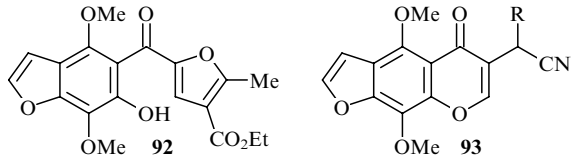
3-Bromo-2-methylchromone (**19b**) reacts with diethyl malonate in the presence of Et_3N in acetone being converted into diethyl (2-methylchromon-3-yl)malonate.[45] However, the reaction pathway between 3-bromochromone (**9**) and ethyl *N*-(diphenylmethylidene)glycine changes (apparently, for steric reasons). In this case, elimination of hydrogen bromide from the

protonated Michael adduct **90** results in the formation of 2-substituted chromone **91**.[118]



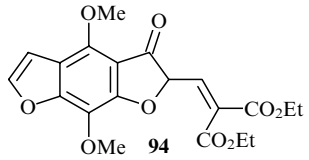
90 **91** (56%)

Notably, as in the reactions with amines, 6-bromonorkhellin **62** shows a specific behaviour in reactions with C-nucleophiles; in particular, it reacts with ethyl acetoacetate and ethyl and *tert*-butyl cyanoacetates in the same way as 3-bromochromone (**9**), *i.e.*, to give furan **92** and 6-substituted norkhellins **93**, whereas the reaction with diethyl malonate produces furocoumarone derivative **94**.[118] Thus, the pyrone fragment of compound **62** is also prone to contraction in reactions with C-nucleophiles.[106]



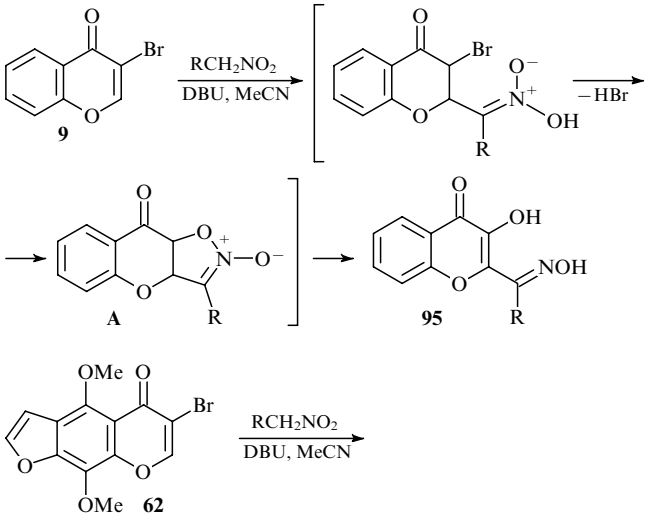
92 **93**

R = CO_2Et, CO_2Bu^t.



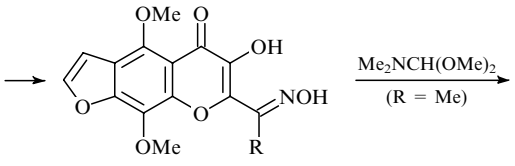
94

In reactions with the ambident nitronate anions generated from the corresponding nitro compounds, 3-bromochromone (**9**) and 6-bromonorkhellin (**62**) behave in the same way to give chromones **95** (yields 49%–74%) and **96** (yields 39%–90%) containing the oxime function at 2(7)-positions and the hydroxy group instead of the bromine atom.[119] As in the case of β-diketones and β-ketoesters, the reactions of nitronate anions with chromones start with the Michael addition, which is accompanied by intramolecular *O*-alkylation and gives intermediate **A**. Subsequently, under the action of the *N*-oxide fragment, the isoxazole (rather than the pyrone) ring in the intermediate **A** is opened, which gives oximes **95** and **96**.

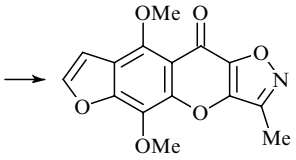


9 **A** **95**

62



96



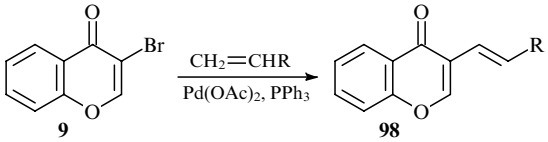
97

R = Me, Et, CO_2Me, Ph.

The khellin derivative **96** (R = Me) cyclises on heating with dimethylformamide dimethyl acetal at 100 °C for 0.5 h being thus converted into 5,9-dimethoxy-3-methyl-10*H*-furo[3′,2′:6,7]chromeno[2,3-*d*]isoxazol-10-one (**97**). Similar products were also obtained under the same conditions from chromones **95** (yields 49%–83%).[119]

c. Cross-coupling and cycloaddition reactions

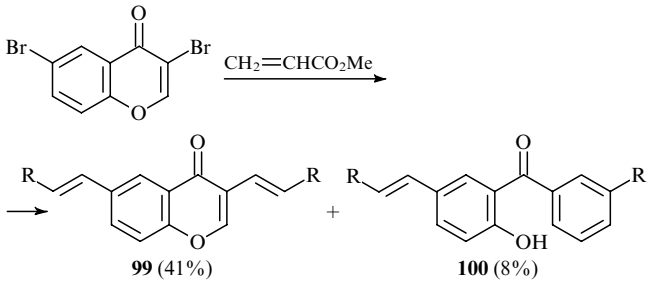
In recent years, studies dealing with the use of 3-halochromones in homo- and cross-coupling reactions catalysed by transition metal complexes have been appearing more and more often. These reactions open up a new route to the synthesis of complex molecules incorporating a chromone fragment. For example, derivatives **98**, otherwise difficult to prepare, have been synthesised by vinylation of 3-bromochromone (**9**) with methyl acrylate or styrene in the presence of catalytic amounts of palladium acetate and triphenylphosphine (DMF, Et_3N, 120 °C, 6 h).[120]



9 **98**

R = CO_2Me, Ph.

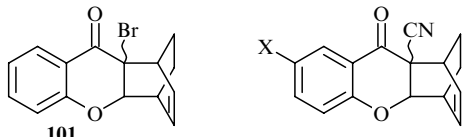
Cross-coupling of 3,6-dibromochromone with methyl acrylate involves both bromine atoms and affords a mixture of products — compounds **99** and **100**. The formation of substituted benzophenone **100** is a result of cycloaddition of methyl acrylate to chromone **99** followed by decarboxylation of the adduct, opening of the pyrone ring and dehydrogenation induced by palladium.[120]



99 (41%) **100** (8%)

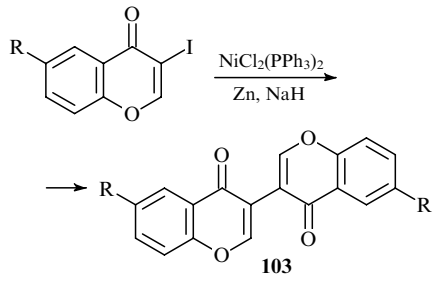
R = CO_2Me.

Chromone **9** proved to be a poor dienophile in the Diels–Alder reaction. Only with 1,3-cyclohexadiene and under rigorous conditions (300 °C, 120 h), does it form adduct **101** with a low stereoselectivity (the isomer ratio is equal to 2 : 1, yield < 16%). Chromone-3-carbonitrile and especially its 6-chloro- and 6-bromo-substituted derivatives proved to be more reactive. Compounds **102** were synthesised in 44%–50% yield and with 93% stereoselectivity.[121]



101 **102** (X = Cl, Br)

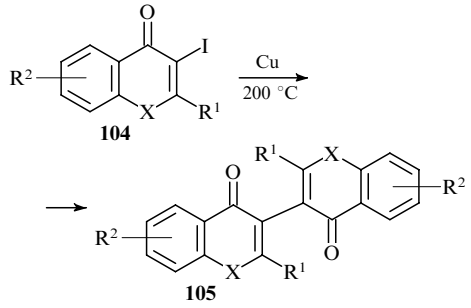
Homo-coupling of 3-iodochromones in the $NiCl_2(PPh_3)_2$–PPh_3–Zn–NaH–PhMe system occurs almost quantitatively giving rise to bischromones **103**, which are of interest for the synthesis of natural biflavonoids.[122, 123]



103

R = H, Me, MeO.

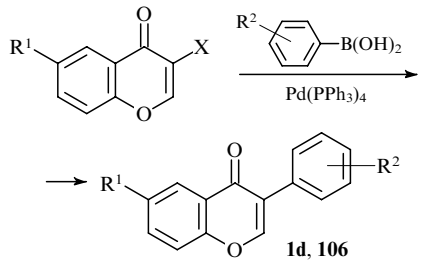
In order to develop a method for the synthesis of natural biflavonoids, homo-coupling of 3-iodo derivatives of flavones, thioflavones and thiochromones **104** under the Ullmann reaction conditions has been studied.[124] It was shown that heating of these compounds with copper powder at 200–210 °C under argon leads to products **105**, the yields of biflavones and bithioflavones being 71%–86% and the yields of bithiochromones being 31%–33%.



104 **105**

X = O: R^1 = Ph, 4-$MeOC_6H_4$; R^2 = H, 7-MeO;
X = S: R^1 = Ph, Me; R^2 = H, 6-Me.

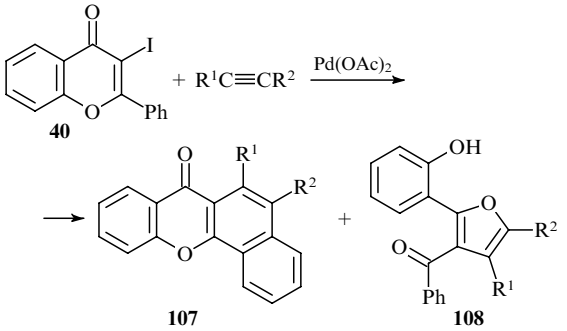
Isoflavone (**1d**) and its derivatives **106**[125, 126] have been prepared in high yields by cross-coupling of 3-bromo- and 3-iodochromones with arylboronic acids catalysed by tetrakis-(triphenylphosphine)palladium(0) in the presence of Na_2CO_3 (Suzuki reaction).



1d, **106**

R^1 = H, MeO, Cl; R^2 = H, Me, MeO, F, NO_2; X = Br, I.

Annelation of 3-iodoflavone **40** by internal alkynes catalysed by $Pd(OAc)_2$ in the presence of NaOAc and LiCl yields a mixture of compounds **107** and **108**. In this mixture, the expected benzoxanthenes **107** are the minor products,[127] while tetrasubstituted furans **108**, resulting from the electrophilic attack on the carbonyl oxygen atom by the vinylpalladium intermediate followed by pyrone ring opening, are the major products.



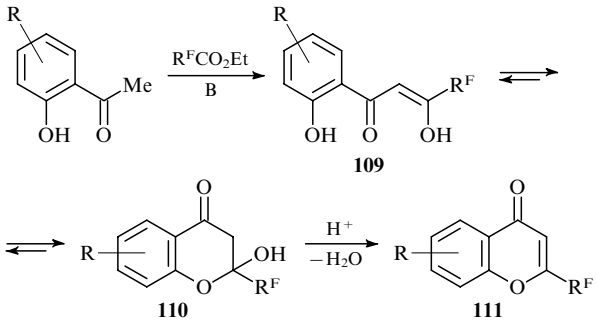
40 **107** **108**

R^1 = R^2 = Ph; R^1 = Me, R^2 = Bu^t.

IV. Methods for the synthesis of 2-polyhaloalkyl- and halomethylchromones

1. Synthesis of 2-polyfluoroalkylchromones

The first representatives of 2-trifluoromethylchromones were obtained in 1951 by condensation of substituted 2-hydroxyacetophenones with ethyl trifluoroacetate in the presence of sodium followed by dehydration of the initially formed β-diketones in an acid medium.[128] It has long been considered [129] that these diketones have a linear keto-enol structure **109**; however, subsequently, it has been found on the basis of ^{1}H NMR data [130, 131] that they exist as cyclic semiketals **110** both in solutions and in crystals. Cyclisation is facilitated by the presence of the electron-withdrawing trifluoromethyl group in the side chain and the hydroxy group in the *ortho*-position of the benzene ring. It was found that open tautomers start to appear in $CDCl_3$ solutions with an increase in the number of fluorine atoms in the polyfluoroalkyl group.[132, 133] Indeed, the condensation products of 2-hydroxy- and 2-hydroxy-5-methylacetophenones with $H(CF_2)_2CO_2Et$ in $CDCl_3$ represent a tautomeric mixture containing the keto-enol and semiketal forms in ~1 : 10 ratio.[133] Short-term refluxing of 2-hydroxychromanones **110** in ethanol [128] or acetic acid [134] in the presence of concentrated HCl results in 2-polyfluoroalkylchromones **111**.

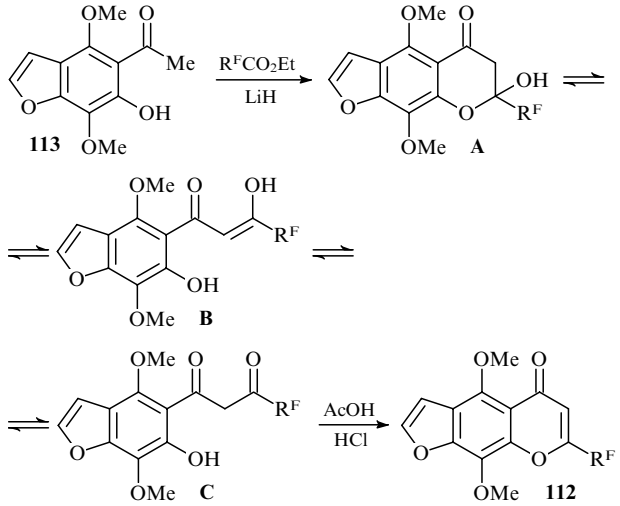


109 **110** **111**

R = H, Me, MeO, Cl, Br;
R^F = CF_2H, CF_3, $(CF_2)_2H$, C_2F_5, C_3F_7, C_4F_9.

Modification of natural products by replacing an alkyl group by a polyhaloalkyl group has long attracted the attention of researchers, because the electron-withdrawing effect of the halogenated substituent entails electron density redistribution in the molecule and thus changes its reactivity with respect to nucleophilic reagents.[135] In this connection, of obvious interest is the synthesis of 7-polyfluoroalkylnorkhellins **112**,[136, 137] which are fluorinated analogues of khellin **2a**, because it opens up the way for the synthesis of a broad range of fluorine-containing heterocyclic derivatives that incorporate the natural benzofuran fragment and are potentially biologically active.

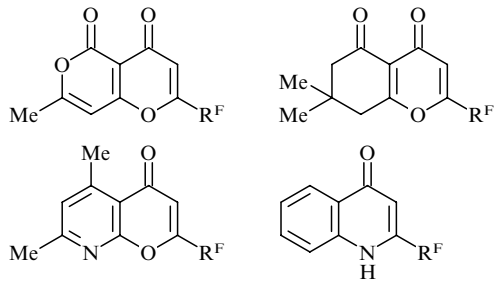
Fluorokhellins **112** were prepared by the reaction of khellinone **113** with R^FCO_2Et in the presence of LiH followed by dehydration of the condensation products, which exist as furochromanones **A** in crystals and in DMSO-d_6 solutions. In $CDCl_3$, these compounds (except for $R^F = CF_3$) are mixtures of tautomers **A**–**C**. Irrespective of length of the fluoroalkyl group, cyclic form **A** predominates (50%–78%), while the content of the diketone form **C** usually does not exceed 8%.[137]



$R^F = CF_2H, CF_3, (CF_2)_2H, C_2F_5, C_3F_7, C_4F_9$.

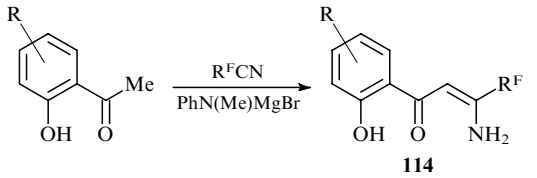
The Claisen condensation is the most convenient and efficient method for the synthesis of 2-R^F-chromones as it is based on simple and readily available initial compounds. This reaction can proceed in the presence of sodium [128] or other condensing reagents such as sodium hydride [131] or lithium hydride.[134] Ether [131] and THF [134] are commonly used as solvents. Due to the low solubility of phenolates, derivatives hydroxylated at the benzene ring are synthesised using hexamethylphosphorotriamide [138] or the Kostanecki–Robinson method. For example, 7-hydroxy-2-trifluoromethylchromone was prepared in 68% yield by heating 2,4-dihydroxyacetophenone with trifluoroacetic anhydride and sodium trifluoroacetate.[14]

If a heterocyclic or another 2-hydroxyacetophenone derivative such as dehydroacetic acid, 2-acetyldimedone, 3-acetyl-4,6-dimethyl-2-pyridone and 2-aminoacetophenone is used as the methylene component in the condensation with R^FCO_2Et, the reaction gives chromone, 7-methyl-2-polyfluoroalkylpyrano[4,3-*b*]pyran-4,5-diones,[139] 7,7-dimethyl-2-polyfluoroalkyl-7,8-dihydro-6*H*-chromene-4,5-diones,[140] 8-aza-2-polyfluoroalkylchromones [141] and 2-polyfluoroalkyl-4-pyridones.[142]



$R^F = CF_2H, CF_3, (CF_2)_2H$.

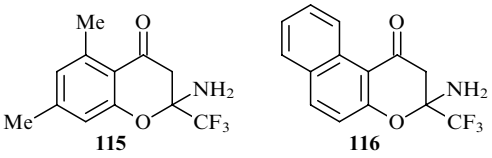
In addition to the Claisen condensation, other methods for the synthesis of 2-R^F-chromones have also been developed. For example, the reaction of 2-hydroxyacetophenones with R^FCN in the presence of *N*-methylanilinomagnesium bromide affords aminovinyl ketones **114** with geminal arrangement of the amino group and the fluorinated substituent (yields 35%–60%). Unlike diketones **109**, these compounds usually exist in the open form as *Z*-isomers having a coplanar *S-cis*-conformation stabilised by an intramolecular hydrogen bond.[143]



114

$R = H, Me, MeO, Cl; R^F = CF_2H, CF_3, (CF_2)_2H$.

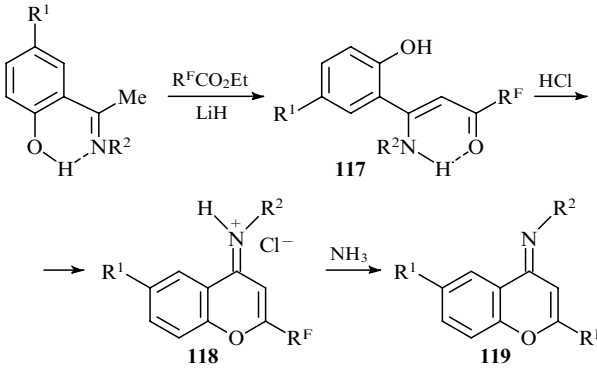
However, the products of condensation of CF_3CN with sterically hindered 2-hydroxy-4,6-dimethylacetophenone and 1-acetyl-2-naphthol exist predominantly as 2-aminochroman-4-ones **115** and **116**. In these compounds, the aminoenone form is destabilised due to unfavourable interactions between the vinylic hydrogen atom and the *ortho*-substituent in the benzene ring.[144, 145]



115 **116**

A similar ring–chain isomerism occurs also in the series of aliphatic hydroxyoxoenamines with a *gem*-dialkyl group in the α-position to the carbonyl group.[146–148] In an acid medium, compounds **114**–**116** are converted almost quantitatively into 2-R^F-chromones **111**.

The condensation of ketimines prepared from 2-hydroxyacetophenones and primary amines with R^FCO_2Et in the presence of LiH yields aminovinyl ketones **117** with γ-arrangement of the NHR and R^F groups, which exist only in the open form.[149, 150] In an ethanol solution of HCl (~20 °C, 2 h), these compounds cyclise to 2-polyfluoroalkyl-4*H*-chromene-4-iminium salts **118**, which can be neutralised with ammonia to form 2-polyfluoroalkyl-4*H*-chromene-4-imines **119**.

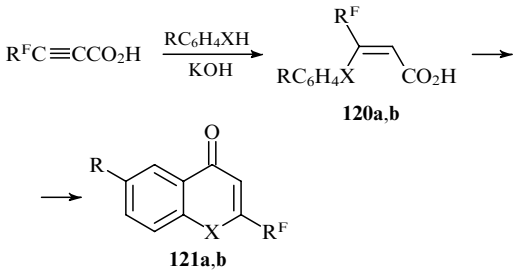


$R^1 = H, Me; R^2 = CH_2Ph, Pr^i, (CH_2)_2OH; R^F = CF_3, (CF_2)_2H$.

On treatment with aqueous acetic acid (~20 °C, 12 h or 80 °C, 1 h), compounds **117** and **119** are hydrolysed to chromanones **110**, which can be easily converted into chromones **111**. Chromeneimines **119** are of interest for synthesis by themselves, because they exist in an acid medium as highly reactive iminium cations **118**, which are more reactive than 2-R^F-chromones **111**.[151]

The reactions of polyfluoroalk-2-ynoic acids with a fivefold excess of ArOH and KOH in an aqueous solution are stereospecific and result in (*Z*)-β-polyfluoroalkyl-β-aryloxyacrylic acids **120a**. On treatment with concentrated H_2SO_4 at ~20 °C, compounds **120a** are converted into 2-R^F-chromones **121a** (yields 51%–76%).[152] Due to the higher nucleophilicity of arenethiols, a similar reaction involving arenethiols can be carried out in aqueous ethanol at a reactant molar ratio of 1 : 1. The resulting arylthioacrylic acids **120b** also have the *Z*-configuration of the

double bond; on successive treatment with PCl_5 and $AlCl_3$ in benzene at ~20 °C, they produce 2-R^F-thiochromones **121b** (yields 68%–87%).[152]

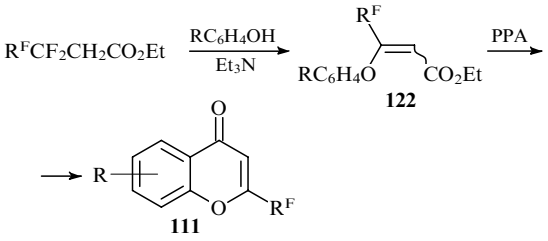


120a,b

121a,b

R^F = CF_2H, CF_3, $(CF_2)_3H$; R = H, Me, MeO, Cl; X = O (**a**), S (**b**).

A similar approach to the synthesis of 2-R^F-chromones has been described in a study[153] in which ethyl 2,2-dihydropolyfluorocarboxylates were used as the starting substrates. They were made to react with phenols in the presence of Et_3N in MeCN at 60 °C, which gave ethers **122**, most often, as mixtures of *Z*- and *E*-isomers. When heated with polyphosphoric acid (PPA) at 170 °C, they were converted into chromones **111** in high yields.

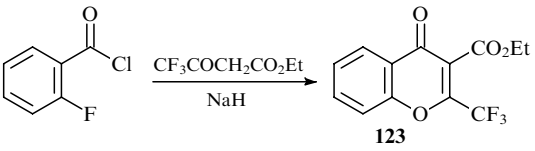


122

111

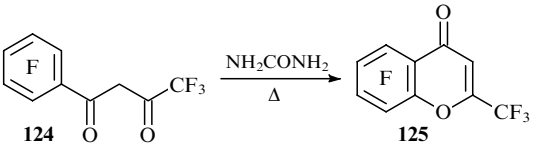
R^F = CF_2Cl, $(CF_2)_3Cl$, $(CF_2)_5Cl$; R = H, Me, Ph, Cl, Br.

The reaction of *o*-fluorobenzoyl chloride with β-ketoesters in the presence of NaH has been proposed as a method for the synthesis of 2-methylchromone-3-carboxylic acids and their esters;[154] in particular, this reaction proved to be suitable for the preparation of ethyl 2-trifluoromethylchromone-3-carboxylate (**123**).



123

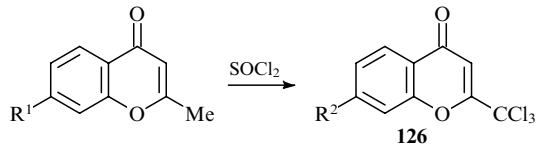
Heating compound **124**, containing an easily replaceable fluorine atom in the *ortho*-position to the carbonyl group, with urea results in 2-trifluoromethyl-5,6,7,8-tetrafluorochromone (**125**), instead of the expected pyrimidin-2(1*H*)-one derivative.[155]



124 **125**

2. Synthesis of 2-trichloromethylchromones and halomethylchromones

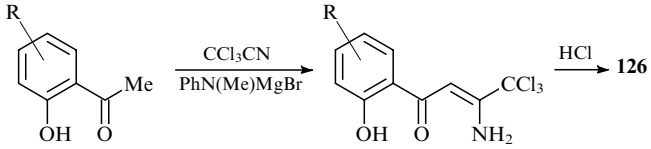
Esters of trichloroacetic acid undergo haloform cleavage under the Claisen condensation conditions in the presence of sodium alkoxides giving rise to chloroform[156] and dichlorocarbene.[157] Apparently, this is the reason why the first 2-trichloromethylchromones **126** were obtained only in 1972 by the reaction of 2-methylchromone or 7-hydroxy-2-methylchromone with thionyl chloride proceeding as chlorination of the side methyl group.[158] Later, this method has found no use.



126

R^1 = H, OH; R^2 = H, Cl.

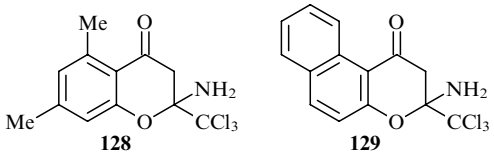
A simple and more general method for the synthesis of chromones **126** consists of condensation of 2-hydroxyacetophenones with CCl_3CN in the presence of *N*-methylanilinomagnesium bromide. This reaction affords aminovinyl ketones **127**, which are converted into chromones **126** on treatment with concentrated HCl at ~20 °C (yields 77%–96%).[143,159]



127 (33%–55%)

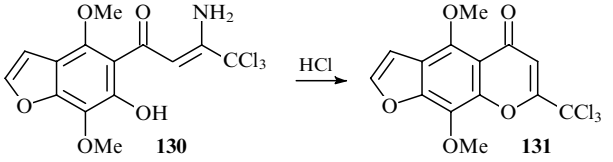
R = H, Me, MeO, Cl.

When sterically hindered ketones are used, the aminovinyl ketones formed initially cyclise spontaneously to yield 2-aminochromanones **128** and **129**.[144,145]



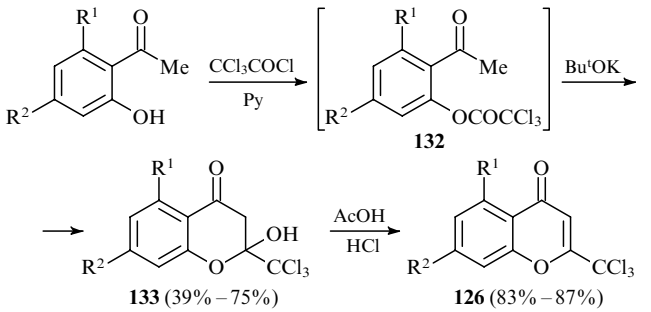
128 **129**

It is of interest that compound **130** exists only as the open form, despite the presence of the methoxy group in the *ortho*-position with respect to the carbonyl group. Acid hydrolysis of aminovinyl ketone **130**, prepared in 37% yield from 5-acetyl-6-hydroxy-4,7-dimethoxybenzo[*b*]furan (khellinone) and trichloroacetonitrile, gives 7-trichloromethylnorkhellin **131** in a yield of 87% (the overall yield over two steps was 32%).[136]



130 **131**

Recently,[160] we proposed a new method for the synthesis of chromones **126**, underlain by the Baker–Venkataraman rearrangement. When trichloroacetates **132** (prepared *in situ* by acylation of 2-hydroxyacetophenones with trichloroacetyl chloride) is treated with potassium *tert*-butoxide in THF at −30 °C, 2-hydroxy-2-trichloromethylchroman-4-ones **133** are formed; they represent the cyclic form of the corresponding β-diketones. Refluxing of these compounds in AcOH in the presence of concentrated HCl results in the corresponding chromones. In the synthesis of trichlorokhellin **131** by this procedure, an overall yield of 64% was attained.[160]



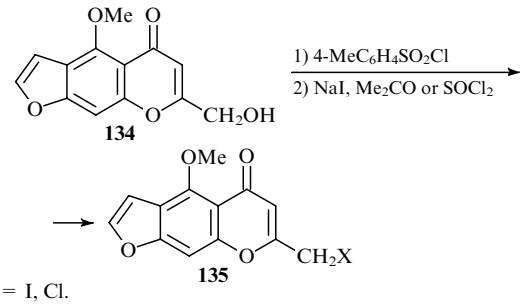
132

133 (39%–75%) **126** (83%–87%)

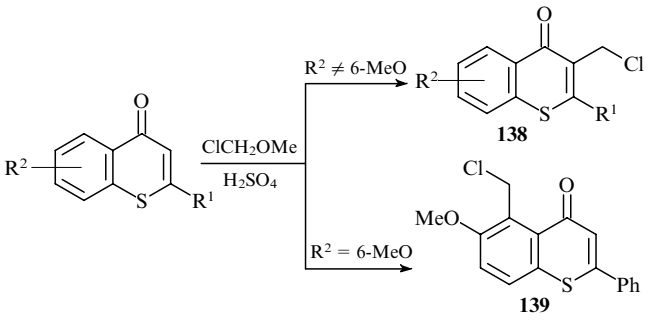
R^1 = R^2 = H; R^1 = MeO, R^2 = H; R^1 = R^2 = Me.

The Claisen condensation, which proceeds successfully with esters of polyfluorocarboxylic acids that contain $\geqslant 2$ fluorine atoms, proves to be inapplicable to alkyl trichloroacetates or monohaloacetates. In the latter case, this is due to the easy replacement of the halogen atom under the action of nucleophilic species. Therefore, 2-halomethyl chromone derivatives are more difficult to prepare than 2-polyhaloalkylchromones. Only a few examples of synthesis of these compounds have been reported. For example, treatment of 2-ethoxymehyl-7-methoxychromone (obtained by condensation of 2-hydroxy-4-methoxyacetophenone with ethyl ethoxyacetate) with a mixture of HBr and AcOH yields 2-bromomethyl-7-methoxychromone.[161] The bromination of 3-benzoyl-2-methylchromone with *N*-bromosuccinimide furnishes 3-benzoyl-2-bromomethylchromone.[162]

A natural furochromone — khellol **134** — was used to prepare 7-iodomethyl-[163] and 7-chloromethylnorvisnagins **135**.[164] 7-Methylthiomethylnorkhellin (**136**), obtained by condensation of khellinone **113** with ethyl methylthioacetate in the presence of NaH or NaOMe, reacts with methyl iodide to give 7-iodomethylnorkhellin **137**.[165]



3-Halomethylchromones are prepared by the reaction of 3-hydroxymethylchromones with $SOCl_2$, chloromethylation of chromones, or bromination of 3-methylchromones with *N*-bromosuccinimide.[2] When 2,3-dimethylthiochromone is treated according to Ziegler [NBS, $(PhCOO)_2$, CCl_4], only the hydrogen atom of the 3-methyl group is substituted, which gives 3-bromomethyl-2-(methyl)thiochromone (yield 74%).[49] The chloromethylation of 2-(methyl)thiochromone and thioflavones is carried out by treating these compounds with chloromethyl methyl ether in sulfuric acid. The reaction results in the formation of 3-(chloromethyl)thiochromones **138**; the only exception is 6-methoxythioflavone, which is converted into 5-chloromethyl derivative **139**.[166]



R^1 = Me, R^2 = H; R^1 = Ph, R^2 = 6-Me, 6-MeO, 8-Me, 8-CO_2Me.

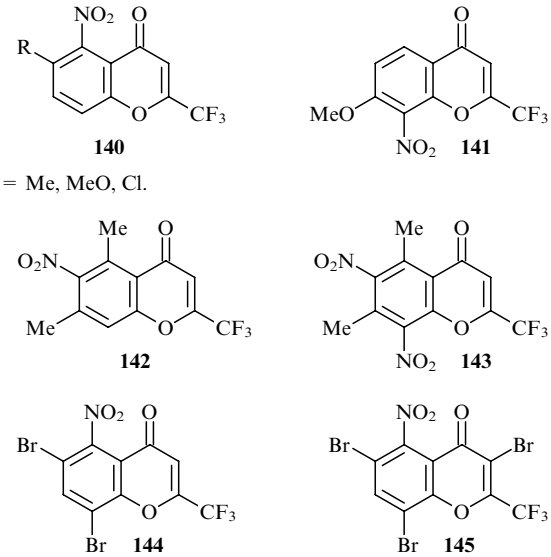
V. Chemical properties of 2-polyhaloalkyl- and halomethylchromones

1. Reactions of 2-polyfluoroalkylchromones

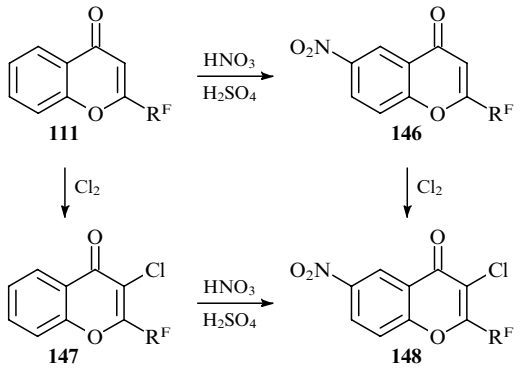
Unlike halochromones considered in Sections II and III, haloalkylchromones containing halogen atoms in the side chain have not received adequate attention. Transformations involving the active halogen atom in the halomethyl or haloacetyl substituent have been mainly considered. In recent years, a number of features of 2-polyfluoroalkyl- and 2-trichloromethylchromones important from the synthetic standpoint have been found; this allowed these compounds to be recommended as readily accessible highly reactive substrates for the synthesis of various heterocyclic derivatives including CF_3-containing compounds with a potential biological activity.[167, 168]

a. Nitration and halogenation

On heating with a mixture of nitric and sulfuric acids, 6- and 7-substituted 2-trifluoromethylchromones are nitrated into the 5- and 8-positions, which is in line with the directing effect of substituents, giving rise to compounds **140** and **141**.[134, 169] The reaction of 5,7-dimethyl-2-polyfluoroalkylchromones with a nitric–sulfuric acid mixture gives 6-nitro derivatives **142** as intermediates, which can be isolated at 0–3 °C and converted into 6,8-dinitrochromones **143** at 75 °C.[169, 170] 6,8-Dibromo-2-trifluoromethylchromone is nitrated at 75 °C at the 5-position to give chromone **144**. Under more rigorous conditions (100–160 °C), 6,8-dibromo-2-trifluoromethylchromone is unexpectedly converted into tribromochromone **145**, *i.e.*, the nitration is accompanied by oxidative destruction giving molecular bromine, which brominates derivative **144** to give **145**.[171]

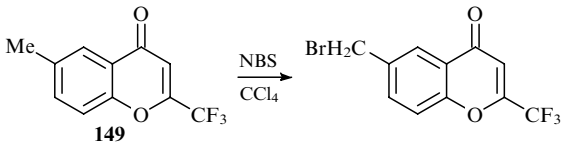


2-R^F-Chromones **111** unsubstituted in the benzene ring, like their non-fluorinated analogues,[32] are smoothly nitrated at the 6-position yielding chromones **146**. When treated with chlorine in the light (CCl_4, ~60 °C, 1 h), compounds **111** add a chlorine molecule at the double bond of the pyrone ring and, after elimination of HCl, they are converted into 3-chlorochromones **147**, which are readily nitrated at a high rate to give compounds **148**.[150, 169, 172] Chloronitrochromones **148** are also formed upon chlorination of compounds **146** but this takes a longer time (8 h).[150, 169, 172]



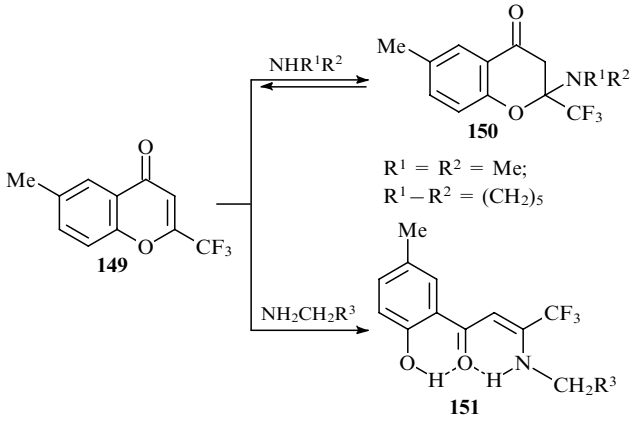
R^F = CF_2H, CF_3, $(CF_2)_2H$.

The bromination of 6-methyl-2-trifluoromethylchromone **149** with *N*-bromosuccinimide on refluxing in CCl_4 in the presence of azobis(isobutyronitrile) for 1.5 h is directed at the methyl group and results in 6-bromomethyl-2-trifluoromethylchromone (yield 49%).[173]



b. Reactions with mono-, di- and triamines

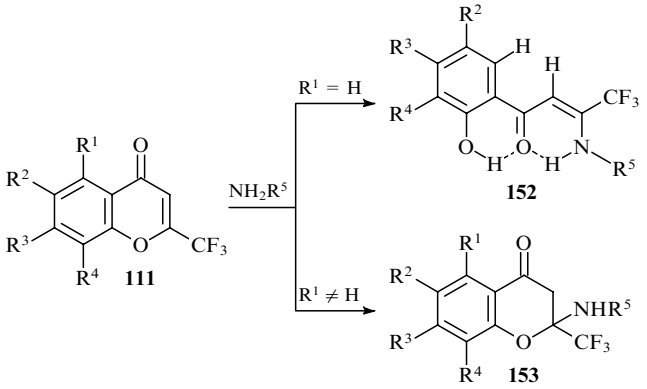
In 1981, an attempt at using chromone **149** as a protective group in the peptide synthesis was made, which showed for the first time [173] that secondary amines (dimethylamine and piperidine) add reversibly to the C(2) atom without opening of the pyrone ring to give unstable compounds **150** (in the case of sterically hindered diethylamine, the reaction does not proceed). However, even mere mixing of chromone **149** with primary amines (ethyl- and propylamines) induces opening of the pyrone ring, characteristic of the chromone system, to give aminovinyl ketones **151**.[174, 175]



R^3 = Me, Et, CO_2Et.

A similar transformation takes place (although at a lower rate) when the chromone **149** is treated with ethyl glycinate in MeCN and DMF but the methyl ester of alanine does not react with this chromone for steric reasons.

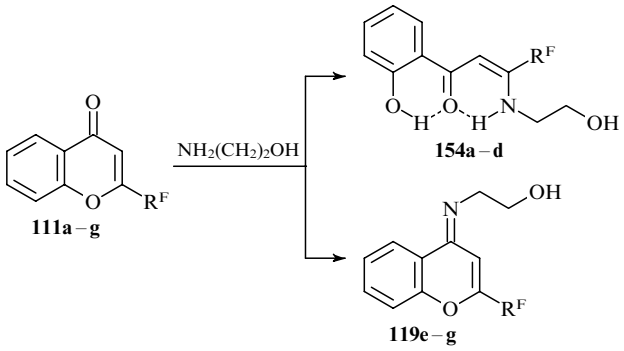
Subsequently, the significance of the steric factor in the reactions of 2-CF_3-chromones **111** (R^F = CF_3) with ammonia and primary amines was also demonstrated for other examples. The nature of the substituent at the 5-position of the chromone system influences the form of existence of the products of this reaction, which can be either ring or open. The attack by the amine on the C(2) atom of 2-CF_3-chromones **111** for R^1 = H is accompanied by opening of the pyrone ring and yields aminovinyl ketones **152**; when $R^1 \neq H$, the process stops after the nucleophilic addition of the amine, which gives 2-aminochromanones **153** stable on storage. This is due to destabilisation of the open form with $R^1 \neq H$ by the repulsion between the R^1 substituent located in the *ortho*-position to the oxo group and the vinylic hydrogen atom of the aminoenone system.[176]



R^1 = R^3 = Me, R^2 = R^4 = H; R^1–R^2 = 5,6-benzo, R^3 = R^4 = H; R^1 = R^2 = R^3 = R^4 = H; R^1 = R^2 = H, R^3–R^4 = 7,8-benzo; R^5 = H, Me, Bn.

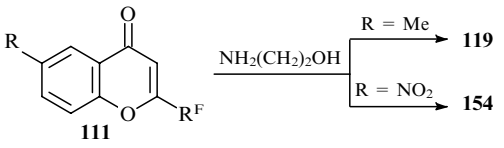
In spite of the presence of the methoxy group in the *peri*-position, fluorokhellins **112** also react with ammonia and primary amines mainly along the pathway of pyrone ring opening.[177, 178]

A change in the direction of nucleophilic attack has been found in a study of the reaction between chromones **111a–g** unsubstituted in the benzene ring and 2-aminoethanol at ~20 °C. This amine easily reacts with compounds **111a–d** yielding aminovinyl ketones **154a–d**, which precipitate from the reaction mixture over a period of 10–15 min; on long storage, they are hydrolysed to give the starting chromones. Completion of the reaction between 2-aminoethanol and chromones **111e–g** requires more than 24 h. In this case, chromeneimines **119e–g** are formed as products of transformation of 2-aminoethanol involving the carbonyl group.[179] This behaviour of compounds **111e–g**, difficult to explain and unusual for a chromone system, may be related to a specific combination of steric and electronic effects of the R^F groups in these molecules.



R^F = CF_3 (**a**), CF_2H (**b**), $(CF_2)_2OCF_3$ (**c**), C_4F_9 (**d**), $(CF_2)_2H$ (**e**), C_2F_5 (**f**), C_3F_7 (**g**).

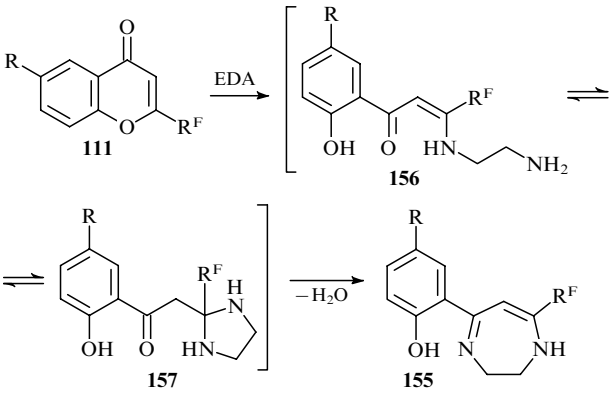
The reactivity of the C(2) and C(4) atoms in chromones **111** towards 2-aminoethanol depends on not only the length of the polyfluoroalkyl chain but also on the nature of the substituent at the 6-position. For example, aminoethanol reacts with 6-methyl-substituted chromone **111** at the C(4) atom (*i.e.*, at the carbonyl group) giving imine **119**, whereas its reaction with 6-nitro-substituted chromone **111** involves the C(2) atom and gives the corresponding aminovinyl ketone **154**, as the electron-withdrawing nitro group facilitates opening of the pyrone ring due to stabilisation of the leaving phenoxide anion.[180]



R = NO_2, Me; R^F = $(CF_2)_2H$, C_2F_5.

6-Nitro-2-trifluoromethylchromone, unlike 2-methyl- and 2-trifluoromethylchromones, reacts with aniline to give aminovinyl ketone. The bulky *tert*-butylamine does not react with 2-CF_3-chromones, and morpholine adds to the C(2) atoms to form 2-morpholino-2-trifluoromethylchroman-4-ones stable during storage. The formation of these products is facilitated by the nitro group present in the benzene ring of 2-CF_3-chromones.[134, 181]

Unlike non-fluorinated chromones, whose reactions with ethylenediamine give complex mixtures of products,[182] the reactions of 2-R^F-chromones **111** with excess ethylenediamine (EDA) in an ethanol solution (~20 °C, 3 h) are more unambiguous and give rise to 5-(2-hydroxyaryl)-7-polyfluoroalkyl-2,3-dihydro-1*H*-1,4-diazepines **155** (75%–91%).[183] The reaction is accompanied by opening of the pyrone ring with the formation of aminovinyl ketones **156**, which occur in equilibrium with imidazolidines **157**‡ and cyclise into the final dihydrodiazepines **155**.

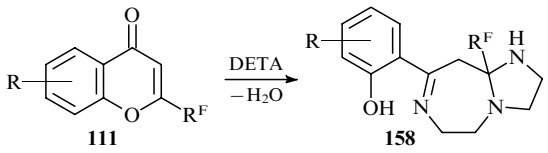


R = H, Me, MeO, Cl; R^F = CF_2H, CF_3, $(CF_2)_2H$.

Compounds **155** exist in $CDCl_3$ as the 1*H*-7-R^F-tautomers due to the formation of an intramolecular bond between the phenolic proton and the imine nitrogen atom of the heterocycle. This conclusion was based on the values of the $^3J_{H,F}$ spin–spin coupling constants, which are 2.8–4.5 Hz for molecules with the $HCF_2CF_2-C(X)=C$ fragments, where X = O, N.[184] The values $^3J_{H,F}$ = 3.2–3.4 Hz have been found for dihydrodiazepines **155**; thus, they contain this type of fragment.[183, 185]

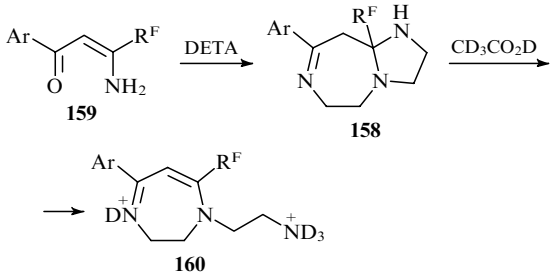
With diethylenetriamine (DETA), chromones **111** are converted into 5-(2-hydroxyaryl)-7-polyfluoroalkyl-1,4,8-triazabicyclo[5.3.0]dec-4-enes **158** (35%–91%), which represent the cyclic form of dihydrodiazepines containing a 2-aminoethyl group at the nitrogen atom located most closely to the fluorinated group. This reaction has virtually no limitations as regards the nature of the polyfluoroalkyl group or the nature and position of the substituent in the benzene ring. It is facilitated by the formation of a strong intramolecular hydrogen bond between the phenolic hydroxyl and the imine nitrogen atom (^{1}H NMR and X-ray diffraction data).[186, 187] The first step is nucleophilic addition of the primary amino group to the C(2) atom accompanied by opening of the pyrone ring yielding *N*-substituted aminovinyl ketones, which further cyclise to triazabicyclic products **158** with participation of both electrophilic centres.

‡ The cyclic products **157** formed in the reaction of ethylenediamine with 8-aza-5,7-dimethyl- and benzo[*h*]-2-trifluoromethylchromones have been isolated.



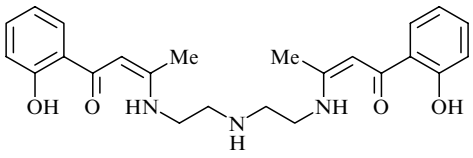
R = H, Me, MeO, Cl; R^F = CF_2H, CF_3, $(CF_2)_2H$, $(CF_2)_2OCF_3$, C_4F_9.

Note that similar products have been obtained from compounds **159** and diethylenetriamine. This reaction can be used to prepare bicyclic compounds **158** having no *o*-OH group in the aromatic ring. In the presence of CD_3CO_2D, the five-membered ring opens and compound **158** is transformed into dication **160**.[188, 189]

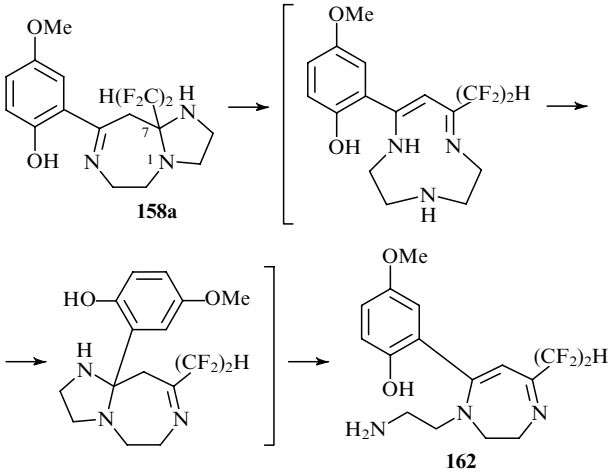


Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 2-HOC_6H_4, 2-C_4H_3S, 2-C_4H_3O; R^F = CF_3, $(CF_2)_2H$.

It should be emphasised that the formation of bicyclic products **158** is typical only of 2-R^F-chromones and R^F-aminovinyl ketones, where the polyfluoroalkyl group substantially increases the reactivity of the carbon atom that carries this group. This reaction does not proceed for non-fluorinated analogues. For example, 2-methylchromone reacts with diethylenetriamine under conditions used to prepare compounds **158** to give bisaminoenone **161**.[187]



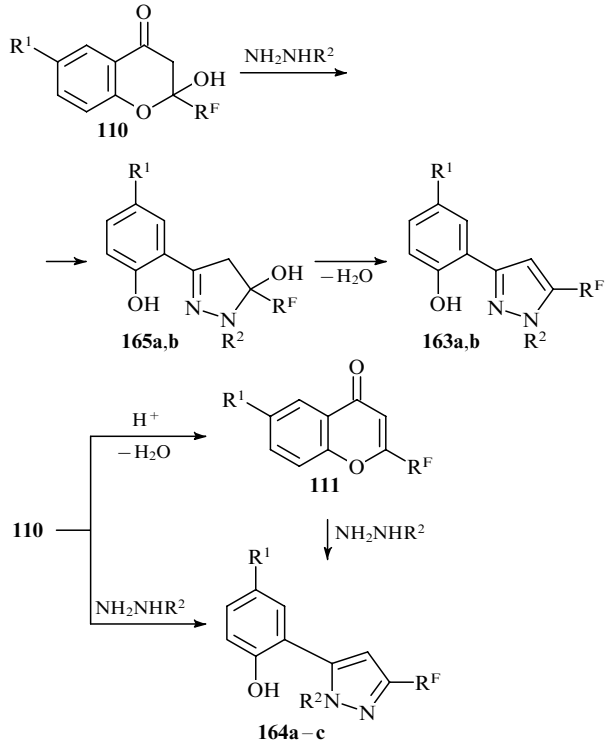
On keeping in ethanol for a week, compound **158a** [Ar = 2-HO-5-$MeOC_6H_3$, R^F = $(CF_2)_2H$] isomerises into dihydrodiazepine **162**; its structure was established by X-ray diffraction.[187, 190] This unusual rearrangement may start with cleavage of the C(7)–N(1) bond, while the triazacyclodecadiene thus formed may be converted into **162** by intramolecular transamination.



Thus, the reaction of 2-R^F-chromones with amines usually starts with the attack by the amino group on the C(2) atom. In the case of secondary amines or in the presence of a substituent at the 5-position, the reaction can stop after 1,4-nucleophilic addition; however, in most cases, it is accompanied by pyrone ring opening giving the corresponding aminovinyl ketones, whose structural features and subsequent transformations provide a variety of products. An exception is the reaction of 2-R^F-chromones with 2-aminoethanol; with $R^F = (CF_2)_2H$, C_2F_5 and C_3F_7, it gives chromeneimines **119**, pointing to the possibility of an attack by the amine on the carbonyl group.

c. Reactions with hydrazines, hydroxylamine and sodium azide

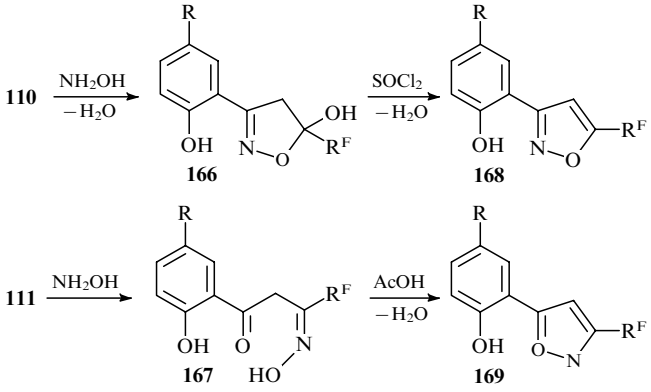
The reactions of chromanones **110** and chromones **111** with hydrazine hydrate resulted in the synthesis of 3(5)-(2-hydroxyaryl)-5(3)-polyfluoroalkylpyrazoles that have a planar conformation and mainly exist as 1*H*-5-R^F-tautomers **163a** in $CDCl_3$ and as 1*H*-3-R^F-tautomers **164a** in DMSO. The reaction with phenylhydrazine allows one to synthesise regioisomeric 5-R^F-pyrazole **163b** from compounds **110** and 3-R^F-pyrazoles **164b** from compounds **111**. With methylhydrazine, only the 3-R^F-regioisomers **164c** are formed. Under mild conditions, the reaction of chromanones **110** with hydrazines can be arrested after the formation of dihydropyrazoles **165**.[191]



R^1 = H, Me, MeO, Cl; R^2 = H (**a**), Ph (**b**), Me (**c**).

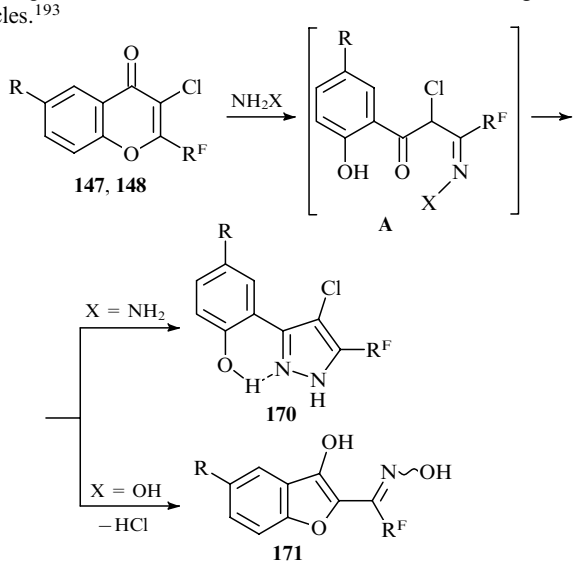
The products formed from chromanones **110** and hydroxylamine hydrochloride in the presence of AcONa are oximes existing in the ring isoxazoline form **166** owing to the high electrophilicity of the carbonyl carbon atom.[133] Under similar conditions, chromones **111** react at the C(2) atom rather than at the oxo group and give isomeric oximes **167**, which do not tend to cyclise, unlike the aliphatic analogues,[192] and exist in the linear oxime form. The change in the direction of the nucleophilic attack on passing from compounds **110** to **111** makes it possible to synthesise regioisomeric 5-R^F-isoxazoles **168** (refluxing of isoxazolines **166** in toluene with $SOCl_2$) and 3-R^F-isoxazoles **169** (refluxing of oximes **167** in AcOH with HCl). By investigating isoxazoles **168** and **169** by ^1H, ^{19}F and ^{13}C NMR spectroscopy, a number of specific features were revealed, which make it possible to distinguish between these regioisomers.[133]

Fluorokhellins **112** react with hydrazine and hydroxylamine in a similar way; they were used to prepare R^F-containing pyrazoles and regioisomeric isoxazoles of the benzofuran series.[177, 178]



R = H, Me; R^F = CF_2H, CF_3, $(CF_2)_2H$.

3-Chlorochromones **147** and **148** are resinified even at ~20 °C on treatment with hydrazine hydrate, while refluxing of these compounds in ethanol with hydrazine dihydrochloride for 4–48 h gives 4-chloropyrazoles **170** in good yields.[172] In view of the chemical reactivity of the 3-halochromones considered above (see Section III.2), this transformation does not appear evident, because it is the first example of a reaction of 3-halochromone with a nucleophile with retention of the halogen atom in the reaction product. When chromones **147** and **148** are refluxed with hydroxylamine hydrochloride in ethanol in the presence of AcONa, contraction of the pyrone ring to the furan ring, typical of 2-unsubstituted 3-halochromones, takes place to give derivatives **171** (58%–91%). These products are of interest as regards subsequent transformations into various R^F-containing heterocycles.[193]

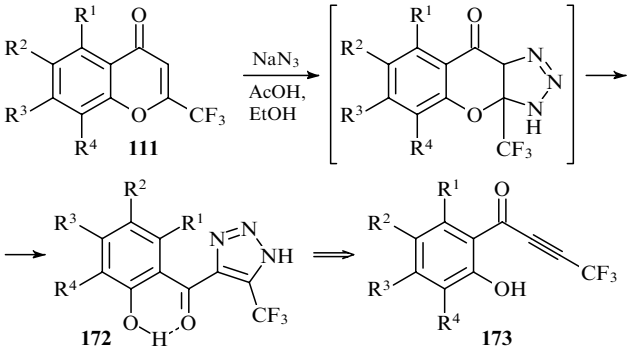


R = H (**147**), NO_2 (**148**); R^F = CF_2H, CF_3, $(CF_2)_2H$.

It has been suggested [193] that the reactions of chromones **147** and **148** with hydrazine and hydroxylamine involve intermediate **A** resulting from the attack of the NH_2 group on the C(2) atom with opening of the pyrone ring. This is followed by either an intramolecular A_N-E reaction between the C=O and NH_2 groups (for X = NH_2) or nucleophilic substitution of the phenolic hydroxyl for the chlorine atom (X = OH). According to the IR, ^1H NMR and ^{19}F NMR data, the isomer and tautomer composition of oximes **171** depends on the number of fluorine atoms in the R^F-substituent, the nature of substituents in the benzene ring and the solvent nature. The nitro derivatives exist almost entirely, both in the solid state and in solution in $CDCl_3$ or

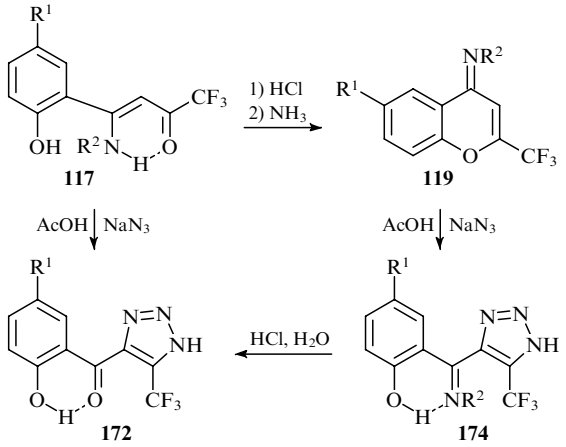
DMSO-d_6, as the enol form represented by the *Z*-isomer when $R^F = CF_3$, $(CF_2)_2H$ and by a *Z*- and *E*-isomer mixture when $R^F = CF_2H$. When the nitro group is missing, a mixture of two stable keto-enol tautomers of oximes **171** is formed.[193]

By the reaction of 2-CF_3-chromones **111** with sodium azide (AcOH, EtOH, 80 °C, 4–10 h), salicyloyltriazoles **172** were prepared (50%–86%); hence, the 2-CF_3-chromones **111** can be considered as synthetic equivalents of trifluoropropynyl ketones **173**, which are difficult to prepare.[151] This reaction is a novel transformation involving the chromone system. It should be noted that on replacement of the CF_3 group by H, CF_2H, $(CF_2)_2H$ or CCl_3, the reaction does not take place and without an electron-withdrawing group at the 6-position, the reaction slows down to such an extent that 2-trifluoromethylchromone is recovered unchanged after a 10-hour contact with NaN_3 under the conditions described above.[151]



$R^1 = R^3 = R^4 = H$, $R^2 = NO_2$; $R^1 = R^3 = R^4 = H$, $R^2 = Cl$; $R^1 = R^3 = H$, $R^2 = R^4 = Br$; $R^1 = R^3 = Me$, $R^2 = R^4 = NO_2$.

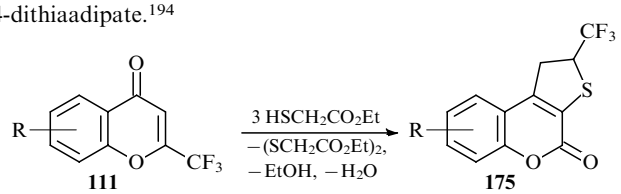
The reactivity of the pyrone ring with respect to NaN_3 can be increased by replacement of the C=O group by the C=NR group. It was shown[151] that the presence of an electron-withdrawing group in the benzene ring is not obligatory for chromeneimines **119**, and they easily react with NaN_3 in the presence of AcOH to give aryltriazolylketone imines **174**. This is due to the fact that, being rather strong bases, compounds **119** are protonated at the imine nitrogen atom even in the presence of AcOH,[179] thus generating iminium cations, which participate in the reaction. Hydrolysis of imines **174** affords triazoles **172**, which could not be synthesised from the corresponding 2-CF_3-chromones. Since the transformations **117** → **119** and **119** → **172** proceed *via* common iminium intermediate **118**, it comes as no surprise that aminovinyl ketones **117** are converted under these conditions into triazoles **172** as easily as chromeneimines **119**.



R^1 = H, Me; R^2 = CH_2Ph, $(CH_2)_2OH$.

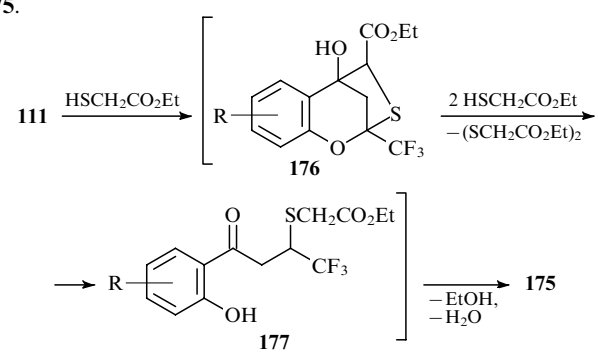
d. Reactions with alkyl sulfanylacetates

One of the most unexpected and interesting reactions of 2-CF_3-chromones **111** is the reaction with ethyl sulfanylacetate in the presence of Et_3N, which results in 1,2-dihydro-2-trifluoromethyl-4*H*-thieno[2,3-*c*]chromen-4-ones **175** (66%–93%) and diethyl 3,4-dithiaadipate.[194]



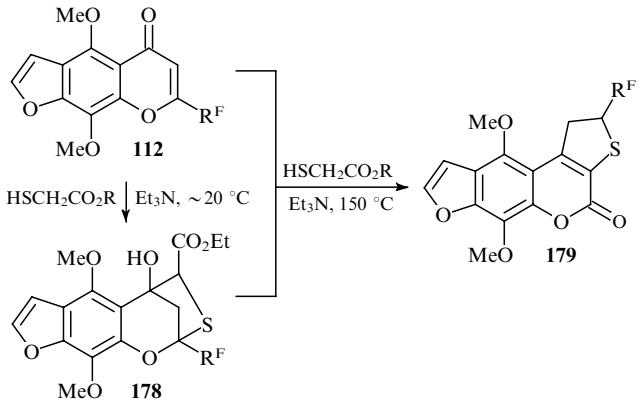
R = H, Me, MeO, NH_2, Cl, Br.

The formation of these products is indicative of the redox pattern of the given transformation. The nature and the positions of substituents in the benzene ring do not affect significantly the course of the reaction; however, as in the case of sodium azide, this reaction can be accomplished only with 2-CF_3-chromones. The reaction mechanism is not entirely clear but, most likely, as in the case of 3,3-dialkyl-6-trifluoromethyl-2,3-dihydro-4-pyrones,[195] the reaction starts with the formation of the benzo derivative of 2-oxa-7-thiabicyclo[3.2.1]octane **176**. The subsequent reductive opening of the pyrone ring in **176** induced by ethyl sulfanylacetate leads to ether **177**, which cyclises yielding dihydrothienocoumarin **175**.



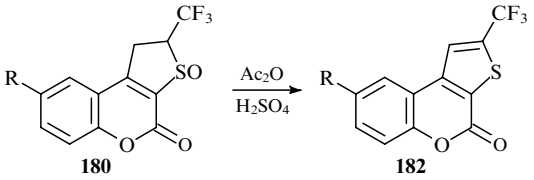
R = H, Me, MeO, NH_2, Cl, Br.

Interestingly, the reaction of alkyl sulfanylacetates with fluorokhellins **112**, although they are closely related to chromones, stops after the formation of products **178** (66%–85%), represented by a single diastereomer with *cis*-arrangement of substituents in the thiolane fragment (X-ray diffraction data).[150,196] Only under rigorous conditions (sealed tube, 150 °C), were 7-CF_3- and 7-CF_2H-norkhellins **112** converted into dihydrothienopsoralens **179**, which can also be synthesised from compounds **178**. This proves that compounds **178** are intermediates.[196]

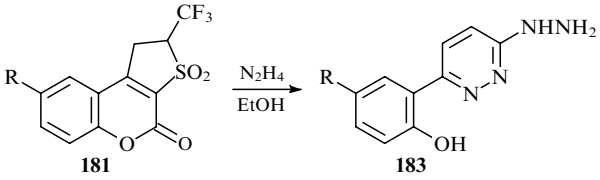


$R^F = CF_3$, CF_2H, $(CF_2)_2H$; R = Et, Me.

Selective oxidation of dihydrothienocoumarins **175** gives rise to highly reactive substrates, namely, sulfoxides **180** (NO_2, $CHCl_3$) and sulfones **181** (H_2O_2, AcOH). Under Pummerer rearrangement conditions, sulfoxides **180** produce thienocoumarins **182**,[150] and sulfones **181** are transformed into 3-hydrazino-6-(2-hydroxyaryl)pyridazines **183** under the action of hydrazine.[197] Previously, these pharmaceutically valuable products providing the basis for a series of 3-hydrazinopyridazine drugs,[198] were synthesised in seven steps starting from phenols and succinic anhydride.[199]

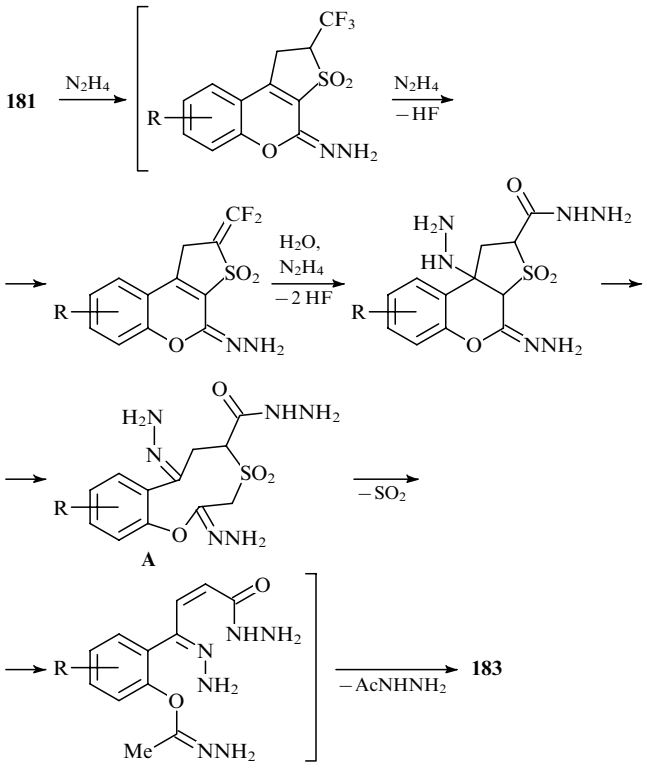


R = H, Me, Cl.



R = H, Me, MeO, NO_2, NH_2.

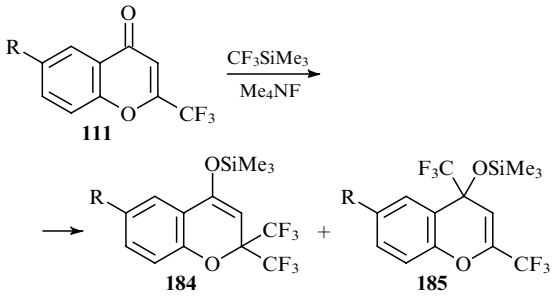
The reaction of 8-nitrosulfone with hydrazine has been used to elucidate the mechanism of the unusual transformation of sulfones **181** into pyridazines **183**. The reaction was arrested after an intermediate step that gave intermediate **A**. On the basis of spectroscopic data, the isolated intermediate **A** was identified as having a benzocyclononene structure, which allowed the researchers to propose a possible reaction pathway. It was suggested [197] that this reaction starts with the attack of the keto group of sulfone **181** by the hydrazine molecule, resulting in the replacement of the carbonyl oxygen atom by a hydrazone group. The subsequent hydrazinolysis and hydrolysis of the CF_3-group to $CONHNH_2$, the addition of a hydrazine molecule to the activated double bond and cleavage of the shared bond in the bicyclic structure furnish intermediate **A**. Further transformation of this intermediate involves elimination of SO_2 yielding the hydrazine derivative of β-aroylacrylic acid, which is then converted into pyridazine **183** upon an intramolecular cyclisation.



This reaction can find wide application, as it represents a new approach to the synthesis of 3-hydrazinopyridazines from readily available compounds, namely, 2-hydroxyacetophenones and ethyl trifluoroacetate.

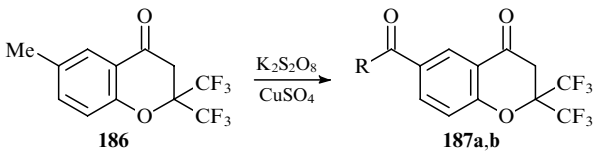
e. Reactions with C-nucleophiles

Nucleophilic trifluoromethylation of organic compounds is complicated by appreciable instability of the free trifluoromethyl anion, which tends to decompose giving the fluoride anion and difluorocarbene. By using trimethyl(trifluoromethyl)silane (Ruppert's reagent) in the presence of fluoride anions, one can avoid decomposition and accomplish direct insertion of the CF_3 group into the organic substrate. Ruppert's reagent easily reacts with both saturated and α,β-unsaturated carbonyl compounds according to the 1,2-nucleophilic addition pattern yielding the corresponding trifluoromethylated alcohols.[200–202] The reaction of R^FSiMe_3 with 2-R^F-chromones is the first example of preparative 1,4-trifluoromethylation of the α,β-enone system.[203,204] ^{19}F NMR monitoring of this system showed that in the presence of the nucleophilic initiator Me_4NF (THF, 0 °C, 4 h), chromones **111** react almost quantitatively and with high regioselectivity with CF_3SiMe_3 along the 1,4-addition route to give trimethylsilyl ethers **184** (the contents of 1,2-addition products **185** in the reaction mixture does not exceed 10%–12%). When the reaction mixture is treated with dilute HCl, only 1,4-addition products **184** are hydrolysed giving 2,2-bis(trifluoromethyl)chroman-4-ones.



R = H, Me.

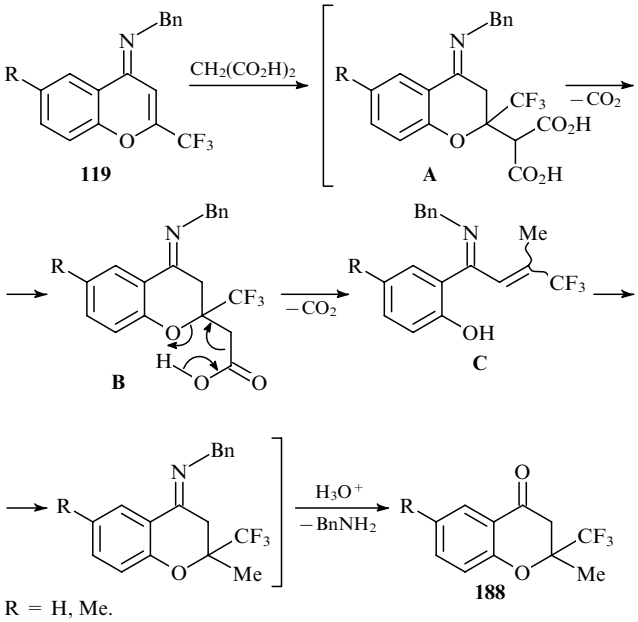
This reaction has been used [204] to prepare fluorinated analogues of naturally abundant chromanones with the *gem*-dimethyl group at the 2-position. Oxidation of the 6-Me group of chromanone **186** with a mixture of $K_2S_2O_8$ and $CuSO_4$ in aqueous acetonitrile provided the synthesis of aldehyde **187a** — an analogue of natural lactarochromal (a metabolite of the fungi *Lactarius deliciosus* [205]) in which both methyl groups have been replaced by trifluoromethyl groups. Apart from hexafluorolactarochromal **187a**, the corresponding acid **187b** was obtained, which is also a fluorinated analogue of the natural acid isolated from the plant *Chrysothamnus viscidiflorus*.



R = H (**a**), OH (**b**).

A fairly unexpected reaction has been reported.[206] By refluxing equimolar amounts of *N*-benzyl-2-trifluoromethylchromene-4-imines **119** and malonic acid in dioxane, 2-methyl-2-trifluoromethylchroman-4-ones **188** were obtained in ~60% yields. In this transformation, malonic acid functions as a methylating agent. Presumably,[206] the first step of the reaction is mutual activation of the starting compounds; in particular, malonic acid protonates the chromeneimine to give the iminium

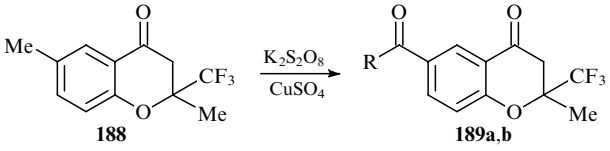
cation, which results in a higher electrophilicity of the C(2) atom, while chromeneimine, which is a rather strong base, deprotonates the activated CH_2 group of the acid, thus increasing its nucleophilicity. This mutual activation is crowned with the addition of malonic acid at the C(2) atom to form intermediate **A**, whose decarboxylation gives acid **B**. The ease of decarboxylation of the second CO_2H group is attributed to opening of the pyrone ring in intermediate **B**. As a result, intermediate **C** is produced. The subsequent cyclisation and hydrolysis of intermediate **C** in the presence of HCl afford chromanones **188**.



R = H, Me.

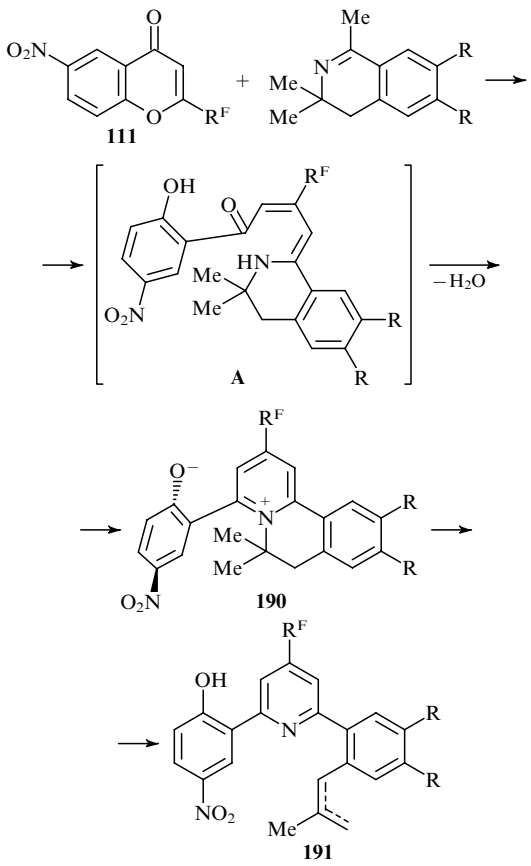
Methylmalonic and phenylacetic acids do not react with chromeneimines under similar conditions. Malonic acid does not methylate 2-CF_3 chromones in the presence of pyridine.

Oxidation of the 6-Me group in chromanone **188** by $K_2S_2O_8$ has yielded aldehyde **189a**, an analogue of lactarochromal in which, unlike aldehyde **187a**, only one of the methyl groups is replaced by the trifluoromethyl group. In addition to trifluorolactarochromal **189a**, the corresponding carboxylic acid **189b** was also isolated.[206]



R = H (**a**), OH (**b**).

The reaction of 6-nitro-2-R^F-chromones **111** with 1,3,3-trimethyl-3,4-dihydroisoquinolines (THF, 20 °C, 4 days) affords coloured (from orange to dark red) chiral zwitter-ions **190** in 50% – 80% yields; the structure of these products was confirmed by X-ray diffraction analysis.[150, 207] This reaction is typical only of 6-nitro derivatives, it involves an attack of the C(2) atom of chromone by the enamine tautomer of dihydroisoquinoline followed by cyclisation involving the carbonyl group with elimination of a water molecule. According to the ^{1}H NMR spectra of these compounds, the protons of the CH_2 group attached to the heterocyclic fragment are diastereotopic and account for an AB system with J_{AB} = 16.5 Hz. This attests to hindered rotation around the bond that connects the phenolate residue and the heterocycle and to the existence of the zwitterions **190** as atropoisomers. On heating or in the presence of sulfuric acid, the steric strain in the molecule is removed due to cleavage of the Me_2C-N bond, resulting in the formation of isomers **191**, differing in the position of the double bond in the alkenyl substituent.

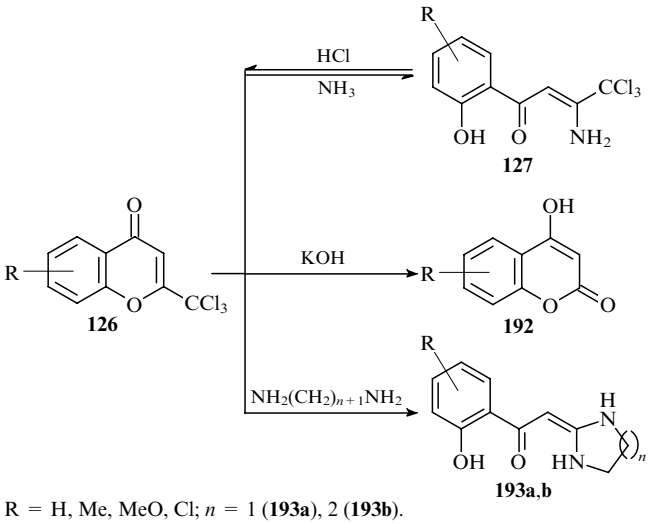


R^F = CF_3, CF_2H, $(CF_2)_2H$; R = H, Me, OMe.

Thus, as distinct from highly reactive 5,5,5-trifluoropent-3-en-2-one studied previously, which easily adds a variety of nucleophilic species to the C=C bond,[208] 2-R^F-chromones considered in this Section incorporate, apart from a similar fragment, a good leaving group at C(2), which increases appreciably the synthetic value of these compounds. Modification of 2-R^F-chromones by introducing electron-withdrawing substituents and/or a halogen atom into the 3-position of the benzene ring not only increases the reactivity of these compounds with respect to nucleophiles but also alters the route of some reactions. The replacement of the C=O group by a C=NR group further extends the synthetic potential of the chromone system. It is also noteworthy that the trifluoromethyl group occupies a special place among polyfluorinated substituents, because the most interesting and peculiar transformations with N-, S- and C-nucleophiles, such as addition of morpholine and reactions with sodium azide, ethyl sulfanylacetate and malonic acid can be carried out only for 2-CF_3-chromones and their derivatives.

2. The properties of 2-trichloromethylchromones and halomethylchromones

The trichloromethyl group is known to be a synthetic equivalent of the carboxy group to which it is transformed upon hydrolysis. For example, refluxing of 5-trichloromethylisoxazole with water or alcohols in the presence of sulfuric acid affords isoxazole-5-carboxylic acid and its esters in high yields.[209] However, the 2-trichloromethyl group in chromones cannot be hydrolysed in an acid medium, while on treatment with a methanol solution of KOH, this group is replaced by a hydroxy group, which results in the formation of 4-hydroxycoumarins **192**. On treatment with an alcohol solution of ammonia, the pyrone ring in 2-CCl_3-chromones **126** is opened, giving rise to aminoenones **127**, which are hydrolysed in hydrochloric acid giving again chromones **126**.[159]



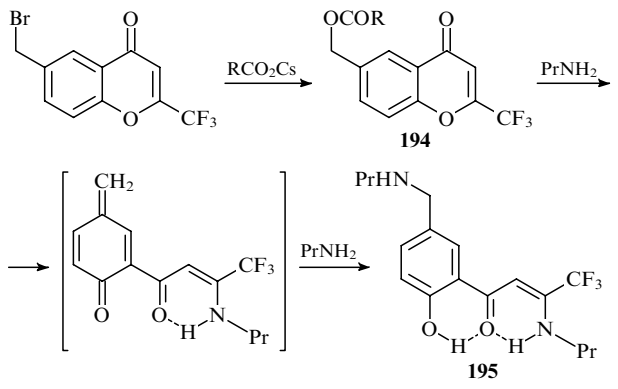
R = H, Me, MeO, Cl; n = 1 (**193a**), 2 (**193b**).

The 2-CCl_3-chromones **126** react with ethylene- and trimethylenediamines differently from 2-R^F-chromones. This reaction is a new convenient method for the synthesis of 2-phenacylideneimidazolidines **193a** and -hexahydropyrimidines **193b** (~20 °C, 3–5 h, yield 50%–95%),[210,211] which have been prepared formerly by cyclocondensation of diamines with α-oxoketene dithioacetals.[212] The reaction involves the intermediate formation of aminoenones with a 2-aminoethyl or 3-aminopropyl group at the nitrogen atom. Cyclisation of these aminoenones is accompanied by elimination of the CCl_3 group, which leads to products **193a**,**b**, existing in DMSO-d_6 and $CDCl_3$ solutions as ketoenamine tautomers.[210–212] The conjugation of the lone electron pairs of the nitrogen atoms with the carbonyl group markedly increases the electron density on the *exo*-methylene carbon atom of enediamines **193a**,**b**; as a consequence, this atom is the first to be attacked by electrophiles and 1,3-dipoles. The subsequent involvement of nitrogen or the carbonyl group in the reaction makes these substances valuable substrates for the synthesis of new heterocyclic systems that are difficult to obtain by other methods.[213,214]

7-Trichloromethylnorkhellin **131** reacts with ethylene- and trimethylene-diamines in a similar way, giving rise to enediamines of the benzofuran series. The reaction of compound **131** with a methanol solution of KOH gives a new khellin derivative, 7-methoxynorkhellin,[177] instead of the expected 4-hydroxyisopimpinellin.[215]

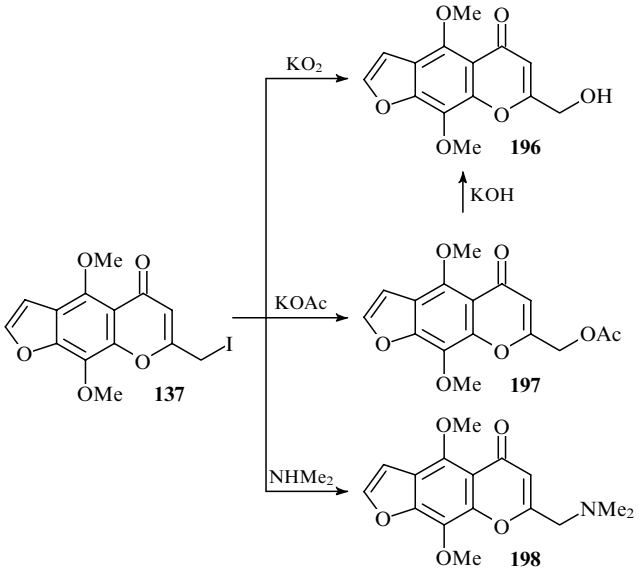
Thus, the high reactivity of 2-trichloromethylchromones, which is manifested as easy opening of the pyrone ring with simultaneous replacement of the CCl_3 group under the action of aliphatic diamines, makes these compounds useful substrates for the preparation of partially hydrogenated heterocycles, which are of synthetic interest by themselves.

The reactivity of halomethyl derivatives of chromones is similar to that of benzyl halides, which was reflected in a series of publications. For example, 6-bromomethyl-2-trifluoromethylchromone reacts with caesium salts of α-amino acids (DMF, 25 °C, 4 h) to give esters **194**, which have been proposed as protective groups for the carboxy function in the peptide synthesis.[173] The easy replacement of the carboxylate group in **194** on treatment with propylamine during the synthesis of aminovinyl ketones **195** was attributed[173] to the formation of the quinonemethide intermediate.

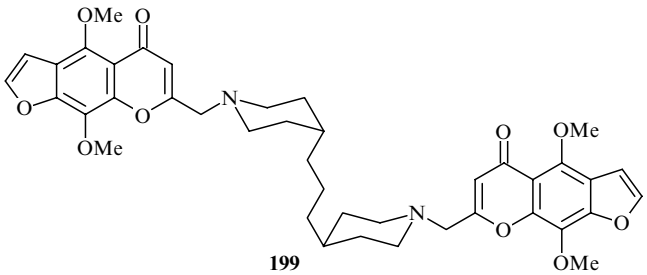


The bromine atom in ethyl 3-bromomethylchromone-2-carboxylate is readily replaced by an amino-, cyano- or acetate group, or can be involved in intramolecular cyclisation giving 1*H*-furo[3,4-*b*]chromene-3,9-dione.[53]

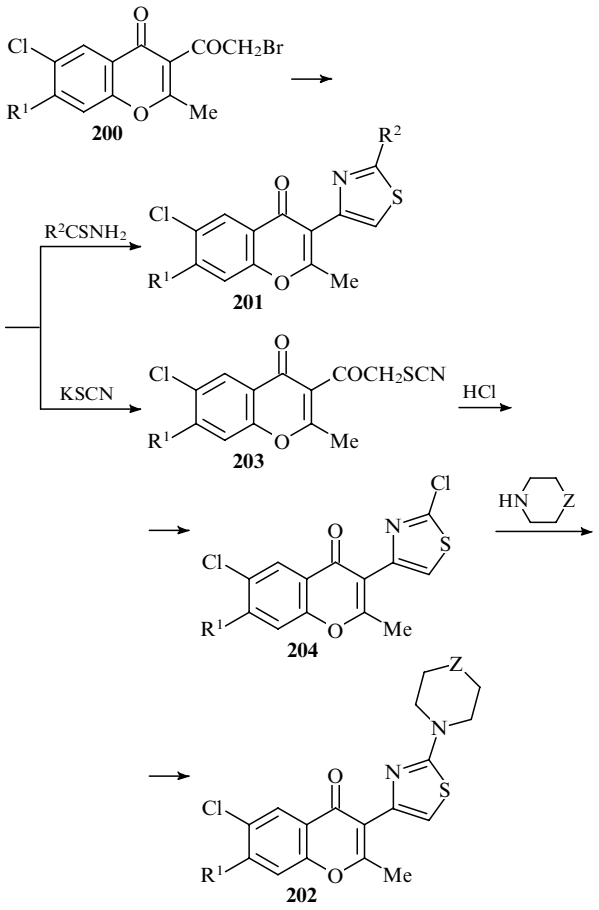
The reduction of 7-iodo- and 7-chloromethylnorvisnagins **135** by zinc dust in AcOH smoothly leads to visnagin.[163,164] Ammiol **196** — the natural furochromone least abundant of the furochromones isolated from the plant *Ammi visnaga L.*, — has been prepared from 7-iodomethylnorkhellin **137** *via* intermediate acetate **197** in a high final yield. Upon oxidation by potassium peroxide, 7-iodomethylnorkhellin **137** is directly converted into ammiol **196**, but the yield is low (27%). On treatment with dimethylamine, **137** is transformed into the amino-substituted khellin **198**.[165]



The reaction of iodokhellin **137** with 4,4′-trimethylenedipiperidine in MeCN in the presence of K_2CO_3 affords bisaminofurochromone **199**, which is a potential antiatherosclerotic agent.[216]



Bromoacetyl derivatives of chromones have found use in the synthesis of biologically active compounds. The condensation of 3-bromoacetyl-2-methylchromones **200** with thioamides and thiourea results in 3-(thiazol-4-yl)-2-methylchromone hydrobromides, which were converted into free bases **201** (69%–85%) by treatment with an aqueous solution of NH_3.[217,218] The reaction of chromone **200** with potassium thiocyanate allows one to obtain 3-thiazolylchromones **202**, which contain a residue of a cyclic secondary amine in the thiazole ring and exhibit a high antiinflammatory activity.[219] The last-mentioned reaction involves the intermediate formation of compounds **203** and 3-(2-chloro-4-thiazolyl)-2-methylchromones **204**.



R^1 = H, Me; R^2 = Ar, NH_2, NHAr, Het; Z = O, NH.

VI. Conclusion

Analysis of the published data demonstrates that of the diverse halogen-containing chromones, 3-halo- and 2-polyhaloalkylchromones, as well as chromones with the perfluorinated benzene ring have now been studied most comprehensively.[18] Data on 2-halochromones are quite scarce and data on 3-polyhaloalkylchromones are totally missing. The introduction of a halogen atom into the 3-position of the chromone system changes crucially the reactivity of the pyrone ring with respect to nucleophiles and stipulates the broad synthetic potential of 2-unsubstituted 3-halochromones. The diversity of properties of these compounds is due to the fact that, being actually highly reactive geminally activated haloalkenes [101] with a good leaving group at the β-carbon atom, they acquire the ability to undergo additional reactions related to opening and transformation of the γ-pyrone ring. In addition, 3-halochromones are valuable substrates in homo- and cross-coupling reactions catalysed by transition metal complexes. These reactions have been used to prepare various 3-substituted chromones, 3,3′-bischromones and isoflavones.

Strangely enough, but, despite the ready accessibility of 2-polyfluoroalkylchromones, these compounds have long remained out of sight of chemists engaged in synthesis, and their systematic study has started only in recent years. Nevertheless, it is already clear that 2-R^F-chromones and, in particular, fluorinated analogues of a natural furochromone, khellin **2a**, are valuable substrates for the synthesis of diverse fluorine-containing heterocycles with a potential biological activity. Indeed, a polyfluoroalkyl group present at the C(2) atom entails dramatic changes in the reactivity of the pyrone ring, which is manifested as a bunch of new transformations (this is especially pronounced for the CF_3 group) absolutely uncharacteristic of 2-alkylchromones. It is of interest that 2-R^F-chromones substantially differ in reactivity from 2-CCl_3-chromones, which tend to give off the trichloromethyl group on treatment with nucleophiles. In view of the fact that 20% to 30% of modern pharmaceuticals and 30% to 40% of agrochemical preparations contain at least one fluorine atom in the molecule,[220] the research dealing with modification and study of the reactivity of 2-R^F-chromones and their derivatives aimed at extending the synthetic scope of the chromone system appear to be a topical and promising line for the future research into fluorine-containing heterocyclic compounds and search for new biologically active substances.

The review was written with support from the Russian Foundation for Basic Research (Project No. 02-03-32706). The author is grateful to D V Sevenard and M A Shafeev for assistance in selection of publications.

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