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Synthesis and chemical properties of 2-acylchromones

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Methods of synthesis and reactivity of 2-formyl-, 2-alkanoyl-, 2-aroyl- and 2-trifluoroacetylchromones are summarized and systematized. It is shown that these chromone derivatives react mainly with N-, C- and P-nucleophiles, as well as undergo reduction and oxidation. The conditions of these reactions and the yields of the products are reported. Special attention is focused on biologically active derivatives.
The bibliography includes 84 references.

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I. Introduction

Chromones (benzo-γ-pyrones) — representatives of the most naturally abundant heterocyclic system — have long attracted the attention of chemists. This class of oxygen-containing heterocycles has been rather well studied. Reviews dealing with the biological activity of various chromone derivatives are available.[1–5] Many of them have addressed not only the valuable properties of chromones themselves but also their application in synthesis of different pharmaceuticals. The synthetic potential of the chromone system, *i.e.*, the possibility of using substituted chromones as substrates for subsequent chemical transformations, is largely determined by the nature and position of substituents in the pyrone ring.

Among numerous chromone representatives, the best studied one is 3-formylchromone, which has been addresses in five reviews only in recent years.[6–10] The synthetic value of this chromone is associated with its high reactivity due to the presence of three electrophilic sites — the C(2) and C(4) atoms and the CHO group — in the 3-position of its molecule. In addition, the phenol moiety is able to act as a good leaving group, so that the nucleophilic reactions of 3-formylchromone are usually accompanied by the opening of the pyrone ring and ring transformation involving carbonyl groups. Other 3-substituted chromones, such as 3-cyanochromones,[11–13] chromone-3-carboxylic acid and its functionalized derivatives,[14,15] are also of interest for chemists. Among 2-substituted chromones, noteworthy is 2-methylchromone, which has been discussed in reviews.[16,17]

At the same time, the methods of synthesis and chemical properties of 2-acylchromones have not been summarized and examined so far in the chemical literature. We intend to fill this gap in the present review dealing with the methods of synthesis and reactions of 2-formyl-, 2-alkanoyl-, 2-aroyl- and 2-trifluoroacetylchromones, including medically important 7-formylfuro[3,2-*g*]chromones, available by the beginning of 2016. Functionalized chromone-2-carboxylic acid derivatives, such as acid chlorides and esters, are mentioned in the review only as initial compounds for synthesis of 2-acylchromones. Yields are given for all the products characterized in original works, except those cases where they were not specified.

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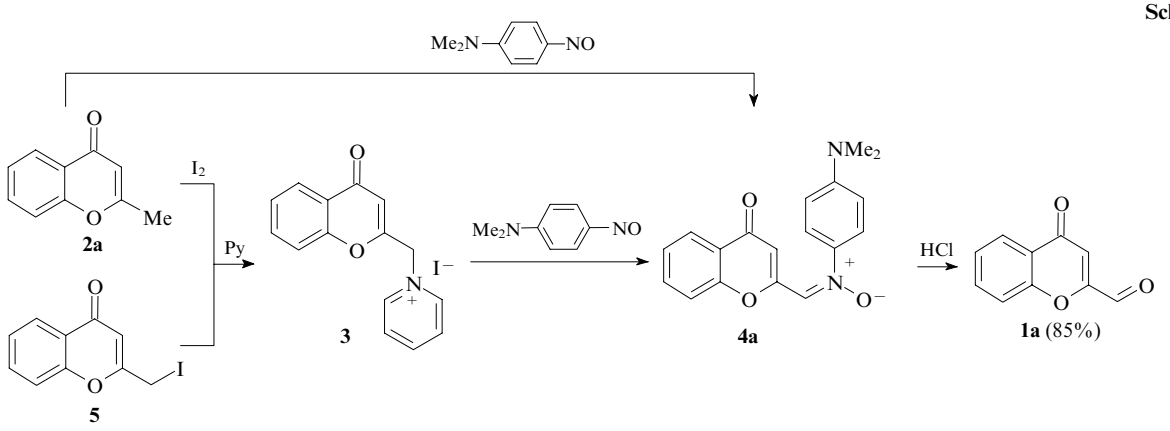
II. Synthesis and reactions of 2-formylchromones

II.1. Methods of synthesis of 2-formylchromones

Synthesis of 2-formylchromones is complicated by the high reactivity of the aldehyde group bonded to the electrophilic C(2) atom. Common approaches to producing a chromone system, such as the Claisen condensation of 2-hydroxyacetophenones with carboxylic acid esters, are inapplicable to

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Scheme 1



the direct synthesis of these compounds. That is why the available methods of synthesis of 2-formylchromones are based on modifications of different 2-substituted chromones.

II.1.a. Synthesis from chromon-2-yl-*N*-(*p*-dimethylaminophenyl)-nitrones

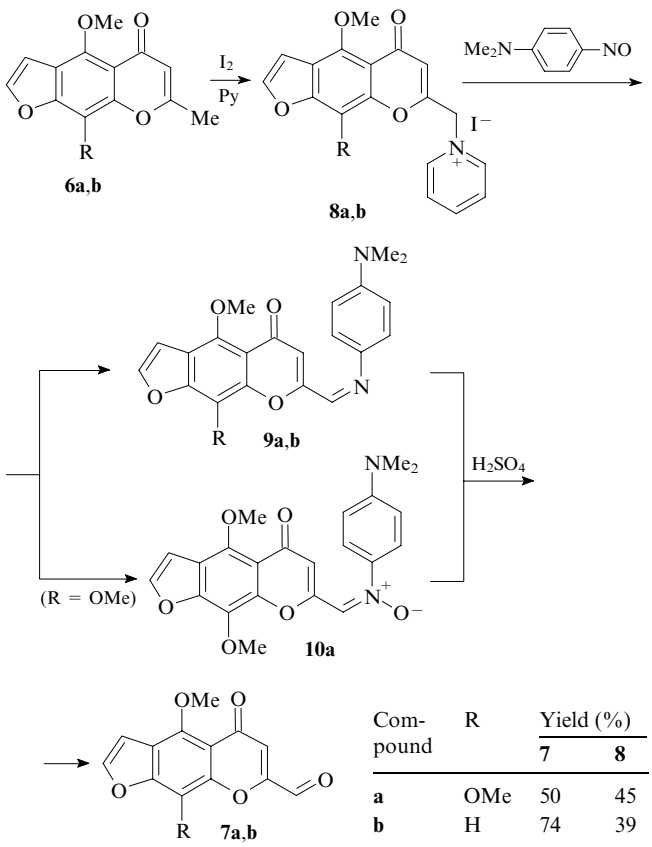
The first synthesis of 2-formylchromone (**1a**) from 2-methylchromone (**2a**) was described in 1952.[18] 2-Methylchromone (**2a**) reacts with iodine in pyridine (Py) to form 2-(pyridiniomethyl)chromone iodide (**3**) in 88% yield; the latter reacts with *p*-nitroso-*N*,*N*-dimethylaniline (1-dimethylamino-4-nitrosobenzene) to give chromon-2-yl-*N*-(*p*-dimethylaminophenyl)nitrone (**4a**) in nearly quantitative yield. Hydrolysis of this compound in hydrochloric acid leads to target 2-formylchromone (**1a**). Preliminarily synthesized 2-iodomethylchromone (**5**) can also be used as the starting compound in this chain of transformations, the yield of salt **3** in this case being 94%. In addition, nitrone **4a** is formed in low yield (9%) by the direct reaction of 2-methylchromone (**2a**) with *p*-nitroso-*N*,*N*-dimethylaniline; this allows one to reduce the number of stages of transformations to two, but leads to a considerable decrease in the yield of target product **1a** (Scheme 1).

An analogous procedure was used in 1964 to produce 6-nitro-2-formylchromone from 2-methyl-6-nitrochromone, but the hydrolysis was carried out in the presence of sulfuric acid.[19] The yields of the corresponding compounds at each of the three stages were 52%, 69% and 62%.

The same method was applied to synthesize formyl derivatives of natural chromones khellin (**6a**) and visnagin (**6b**) — 4,9-dimethoxy- (**7a**) and 4-methoxy-7-formylfuro[3,2-*g*]chromones (**7b**), which are of interest for medicinal chemistry (Scheme 2).[20]

The reaction of furochromones **6a**,**b** with iodine in pyridine leads to salts **8a**,**b**, which are condensed with *p*-nitroso-*N*,*N*-dimethylaniline in the presence of sodium carbonate to give azomethines **9a**,**b** (the yield of **9a** was 42%).[20] When treated with 10 M sulfuric acid, azomethines **9** convert into 7-formylfuro[3,2-*g*]chromones **7a**,**b**. Later in 1969, Renzi and Perini[21] carried out this reaction with salt **8a** under different conditions, including those described by Mustafa *et al.*,[20] and in all cases, the intermediate compound was nitrone **10a** rather than imine **9a** (Scheme 2). They obtained imine **9a** by reacting chromone **7a** with *N*,*N*-dimethyl-*p*-phenylenediamine.[21]

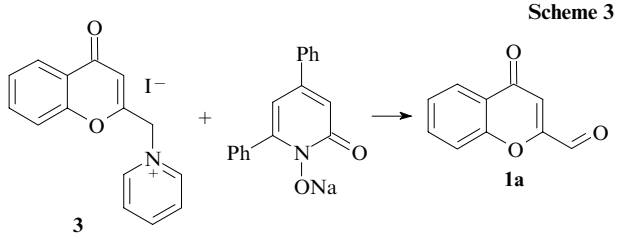
Scheme 2



Compound	R	Yield (%)	
		7	**8**
a	OMe	50	45
b	H	74	39

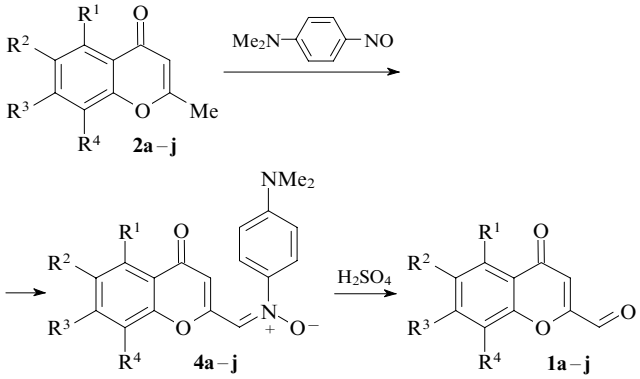
Katritzky *et al.*[22] have described the use of the sodium salt of 1-hydroxy-4,6-diphenyl-2-pyridone in synthesis of various carbonyl compounds. In particular, its reaction with pyridinium salt **3** gave 2-formylchromone (**1a**) in 11% yield. The reaction was carried out in 2,4,6-triphenylpyridine at 168 °C for 4 h (Scheme 3).

Scheme 3



Later, the method of synthesis of 2-formyl derivatives through the stage of formation of chromon-2-yl-*N*-(*p*-dimethylaminophenyl)nitrones **4** has been optimized and successfully used to prepare 2-formylchromones **1a – j**, substituted in the benzene ring.[23 – 26] Initial 2-methylchromones **2a – j** react with *p*-nitroso-*N*,*N*-dimethylanilines in the presence of sodium ethoxide to form nitrones **4a – j**, which are hydrolyzed by sulfuric acid into target 2-formylchromones **1**. This procedure has been used to synthesize furo[3,2-*g*]chromones **7a**,**b** (Scheme 4; a dash means that the yield has not been reported).[27, 28]

Scheme 4



Compound	R^1	R^2	R^3	R^4	Yield (%)		Ref.
					4	**1**	
a	H	H	H	H	58	–	24, 26
b	H	Me	H	H	–	68	23, 26
c	H	Cl	H	H	76	72	23, 26
d	H	Br	H	H	73	72	23, 24, 26
e	H	Cl	H	Cl	86	87	24
f	H	Me	H	Cl	78	81	24
g	H	Cl	Cl	H	86	77	24
h	H	Cl	Me	H	72	78	24
i	Benzo		H	H	92	87	23, 24
j	H	H	Benzo		100	91	24

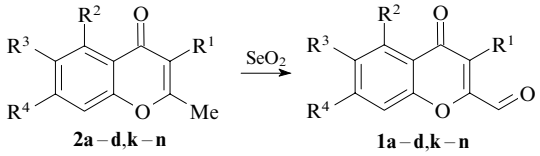
The ^{13}C NMR spectrum of 2-formylchromone (**1a**) has been considered in detail and compared with the spectra of other substituted chromones.[29]

II.1.b. Synthesis from 2-methylchromones

The second basic method of synthesis of 2-formylchromones is oxidation of 2-methyl derivatives. This method is complicated by further oxidation of the formyl group to chromone-2-carboxylic acid derivatives or formation of an intricate mixture of products,[18] which requires careful selection and maintenance of reaction conditions.

The most widely used oxidant is selenium(IV) oxide: in refluxing xylene, the oxidation leads to chromones **1a – d**,**k – n** in moderate yields (33% – 60%).[30 – 32] The higher yield (91%) has been achieved for chromone **1l** in a bromobenzene solution.[33, 34] On heating in dioxane in a sealed tube for 22 h, the reaction gives product **1m** in almost quantitative yield,[35] while 3-methyl-2-formylchromone (**1n**) is obtained only in refluxing dioxane in very low yield (Scheme 5).[18]

Scheme 5

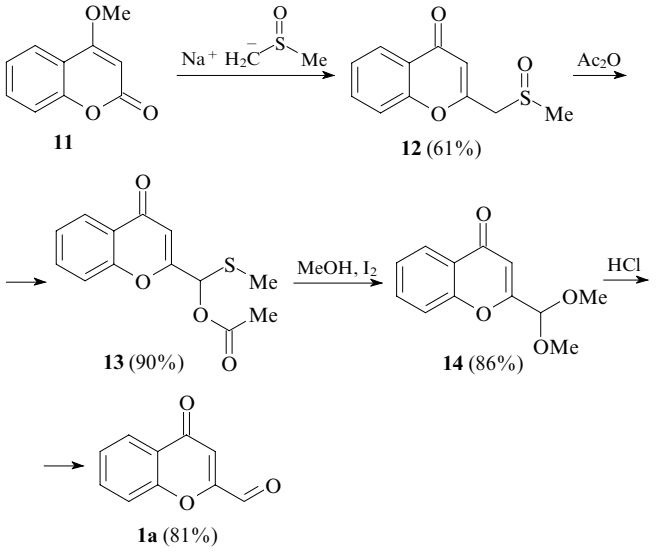


Compound	R^1	R^2	R^3	R^4	Yield (%)	Ref.
a	H	H	H	H	45 – 60	30 – 32
b	H	H	Me	H	45 – 60	31, 32
c	H	H	Cl	H	45 – 60	31, 32
d	H	H	Br	H	45 – 60	31, 32
k	H	Me	H	Me	33	30
l	H	OMe	OBn	H	91	33, 34
m	H	OH	H	Me	99	35
n	Me	H	H	H	9	18

II.1.c. Other methods

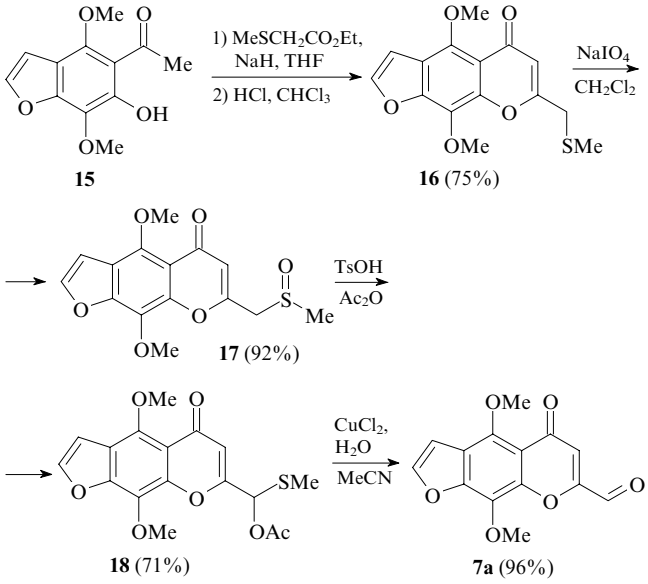
2-Formylchromone (**1a**) has been synthesized by the reaction of 4-methoxycoumarin (**11**) with sodium methanesulfinylmethide. The reaction involves the rearrangement to give 2-(methanesulfinylmethyl)chromone (**12**).[36] The Pummerer reaction of this intermediate with refluxing acetic anhydride leads to 2-[acetoxy(methylsulfanyl)methyl]chromone (**13**), which is converted to 2-dimethoxymethylchromone (**14**) by refluxing in methanol in the presence of iodine. Acid hydrolysis of **14** affords target 2-formylchromone (**1a**) in an overall yield of 38% (Scheme 6).

Scheme 6



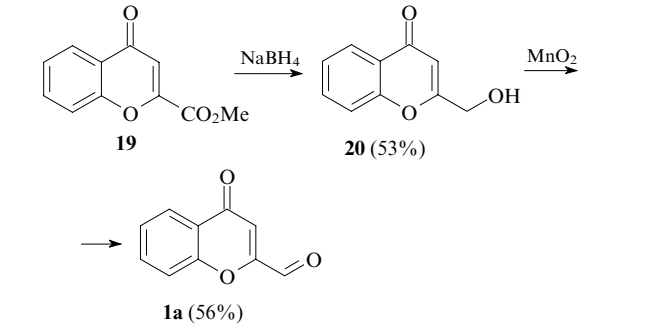
Analogously, the condensation of khellinone (**15**) with ethyl 2-(methylthio)acetate induced by sodium hydride in tetrahydrofuran followed by acid-catalyzed cyclodehydration in methanolic hydrochloric acid leads to methylthiokhellin **16**. Oxidation of **16** with sodium periodate gives sulfoxide **17**; when heated in acetic anhydride at 40 – 50 °C for 2 – 4 min in the presence of *p*-toluenesulfonic acid (TsOH), the latter converts into acetoxy sulfide **18**. Hydrolysis of this compound in refluxing $CuCl_2 – H_2O – MeCN$ system for 30 min affords aldehyde **7a** (Scheme 7).[37]

Scheme 7



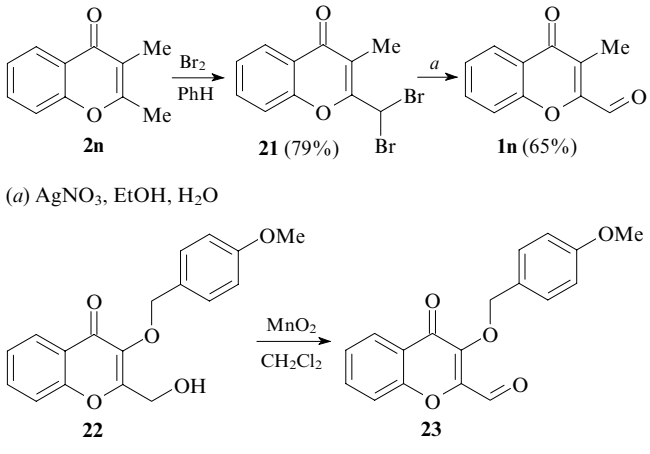
2-Formylchromone (**1a**) has also been synthesized in a two-stage reaction from methyl chromone-2-carboxylate (**19**).[38] This method is based on selective reduction of the ester group of **19** with sodium borohydride in methanol and subsequent oxidation of 2-hydroxymethylchromone (**20**) in chloroform by manganese(IV) oxide (Scheme 8).

Scheme 8



Data on the synthesis of 3-substituted 2-formylchromones are rather limited. The oxidation of 2,3-dimethylchromone leading to 3-methyl-2-formylchromone (**1n**) in low yield is mentioned above (see Scheme 5).[18] Another method of synthesis is based on bromination of 2,3-dimethylchromone (**2n**) with bromine in benzene followed by hydrolysis of the dibromomethyl group in chromone **21** in the presence of silver nitrate in aqueous ethanol.[39] Oxidation of 3-substituted 2-hydroxymethylchromone **22** by manganese(IV) oxide in dichloromethane gives aldehyde **23** (Scheme 9).[40]

Scheme 9



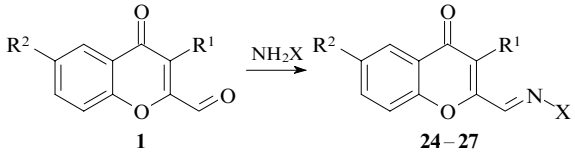
II.2. Reactions of 2-formylchromones

2-Formylchromones can be classified with 1,2,4-tricarbonyl compounds in which one of the carbonyl groups is in the latent form. Taking into account this fact as well as chemical properties of 3-formylchromones,[6–10] we can assume that 2-formylchromones will also be highly reactive compounds. However, since the aldehyde group in these compounds is directly bonded to the electrophilic C(2) atom ('latent' carbonyl group), it exhibits enhanced reactivity and determines the behaviour of 2-formylchromones as a whole. In addition, nucleophile approach to the C(2) atom, which usually starts reactions of the chromone system, turns out to be hindered. Therefore, in all known transformations of 2-formylchromones, they act as aromatic aldehydes activated by electron-withdrawing substituents. This fact evidently reduces the synthetic potential of 2-formylchromones as compared with 3-formyl derivatives, which hold a special place in the chemistry of chromones owing to the readily accessible and highly electrophilic site at the C(2) atom. Nevertheless, 2-formylchromones are valuable substrates in synthesis of 2-hetarylchromones, which are of interest for subsequent syntheses of biologically active molecules.

II.2.a. Reactions with N-nucleophiles

2-Formylchromones **1** readily react at the aldehyde group with N-nucleophiles through addition–elimination reactions. Nucleophiles can be primary aromatic amines (*o*-hydroxyaniline or α-naphthylamine, in refluxing ethanol, yields of imines **24** are 50% – 59%), hydroxylamine (in refluxing pyridine or ethanol for 5 min, yields of oximes **25** are ~75%), hydrazine and phenylhydrazine (in refluxing ethanol for 15 min, yields of hydrazones **26** are 45% – 52%), as well as semicarbazide and thiosemicarbazide (the synthesis conditions and the yields of semicarbazones and thiosemicarbazones **27** have not been reported).[18, 19, 23] No pyrone ring opening is observed, and the reaction consists of simple condensation involving the chromone aldehyde group and the primary amino group of the N-nucleophile (Scheme 10).

Scheme 10

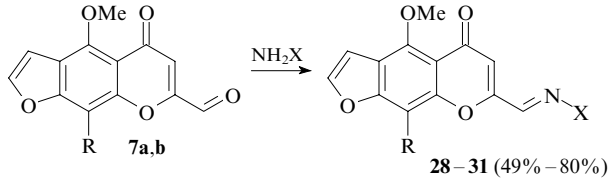


R^1 = H, Me; R^2 = H, Me, Cl, NO_2; X = C_6H_4OH-2, 1-Naph (**24**); OH (**25**); NH_2, NHPh (**26**); $NHC(O)NH_2$, $NHC(S)NH_2$ (**27**); Naph is naphthyl

The reactions of furo[3,2-*g*]chromones **7a**,**b** with hydroxylamine,[20] hydrazines,[20, 41] aromatic amines,[20, 21, 27, 41] semicarbazide[20] or thiosemicarbazide[41] in ethanol are analogous. These reactions give oximes **28** (in 80% yield),

hydrazones **29** (in 65% yield), imines **30** (in 49% – 63% yield), semicarbazones **31** (X = $NHC(O)NH_2$) and thiosemicarbazones **31** (X = $NHC(S)NH_2$, in 80%yield). Imines **30** are synthesized in the presence of acetic acid (Scheme 11).

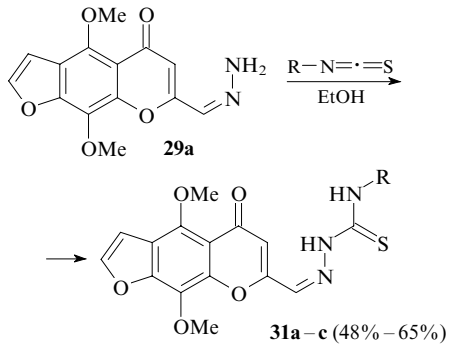
Scheme 11



R = OMe, H; X = OH (**28**); NH_2, NHPh (**29**); Ar (Ar = Ph, C_6H_4Me-2, C_6H_4Me-3, C_6H_4Me-4, C_6H_4Cl-4, C_6H_4OMe-2, $C_6H_4NMe_2$-4, $C_6H_3(NO_2)_2$-2,4) (**30**); $NHC(O)NH_2$, $NHC(S)NH_2$ (**31**)

Furo[3,2-*g*]chromone derivatives **29a** and **31** were used in synthesis of biologically active compounds **32** and **33**.[41] First, hydrazone **29a** was converted into substituted thiosemicarbazones **31a** – **c** by the reaction with ethyl, allyl and phenyl isothiocyanates in ethanol (Scheme 12).

Scheme 12

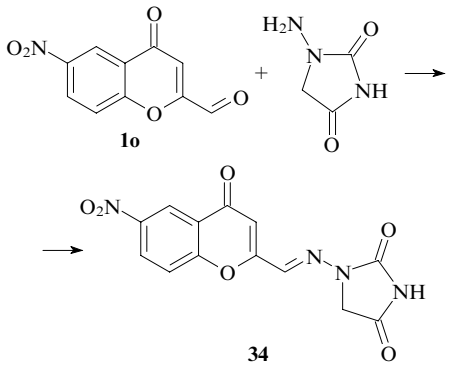


31: R = Et (**a**), All (**b**), Ph (**c**); All is allyl

The reaction of thiosemicarbazone **31a** – **d** with monochloroacetic acid leads to different products depending on conditions. In particular, the reaction in refluxing ethanol in the presence of sodium acetate gives 4-thiazolidinones **32** (in 52% – 71% yield), while the reaction in pyridine at room temperature for 15 min and then in ethanol at reflux for 4 h gives 4-oxoimidazolidine-2-thiones **33** in 50% – 80% yield (Scheme 13).[41]

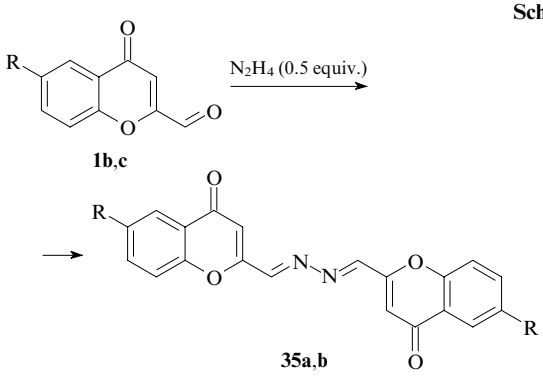
The reaction of 1-aminohydantoin with 6-nitro-2-formylchromone (**1o**) involves the primary amino group and leads to compound **34** — the product of addition – elimination at the aldehyde group without pyrone ring opening (Scheme 14).[19]

Scheme 14



The reaction of 2-formylchromones **1b**,**c** with 0.5 equiv. of hydrazine in refluxing ethanol for 15 min gives azines **35a**,**b** in 70% – 75% yield (Scheme 15).[23]

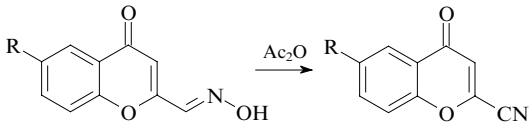
Scheme 15



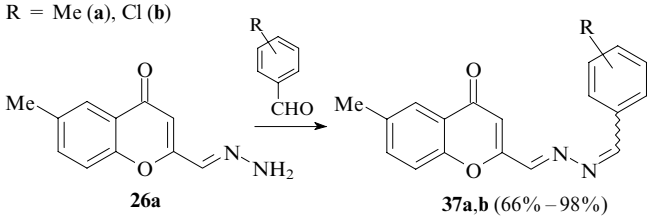
R = Me (**1b**, **35a**), Cl (**1c**, **35b**)

When heated in refluxing acetic anhydride for 3.5 h, oximes **25a**,**b** are dehydrated to form 2-cyanochromones

Scheme 16

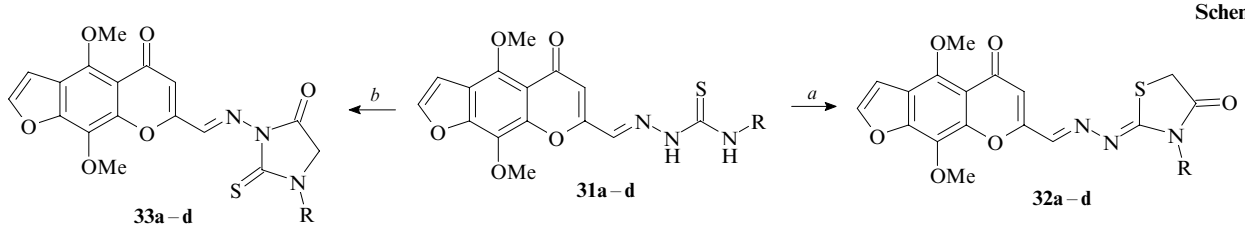


R = Me (**a**), Cl (**b**)



37: R = 4-OMe (**a**), 2-Cl (**b**)

Scheme 13

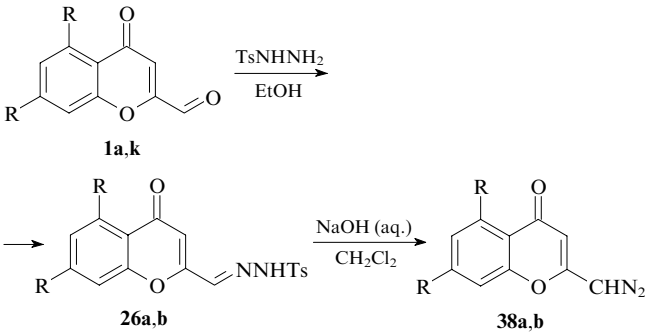


(*a*) $ClCH_2CO_2H$, AcONa, EtOH, Δ, 2 h; (*b*) 1) $ClCH_2CO_2H$, Py, rt; 2) EtOH, Δ, 4 h; R = Et (**a**), All (**b**), Ph (**c**), H (**d**)

36a,**b** (in 55% yield), while hydrazone **26a** reacts with aromatic aldehydes in refluxing ethanol for 1.5 h to give azines **37a**,**b** (Scheme 16).[23]

The reaction of 2-formylchromones **1a**,**k** with tosylhydrazine carried out under stirring in ethanol for 6 h gives tosylhydrazones **26a**,**b** (in 92% yield for R = H), and the treatment of their suspension in dichloromethane with a 0.2 M sodium hydroxide solution leads to 2-diazomethylchromones **38a**,**b** (in 75% yield for R = H) (Scheme 17).[42]

Scheme 17

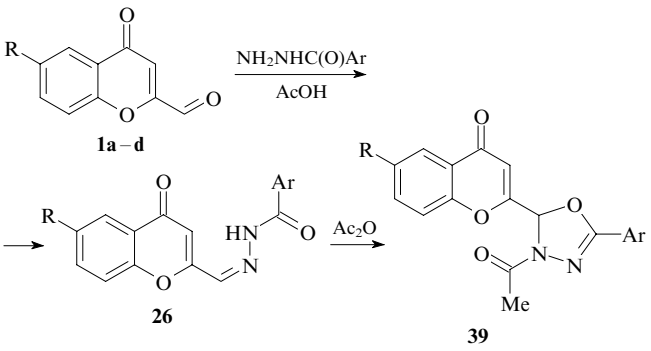


1a,**k** **26a**,**b** **38a**,**b**

26, **38**: R = H (**a**), Me (**b**)

With hydrazides of aromatic carboxylic acids in the presence of acetic acid at room temperature, chromones **1a** – **d** also react only at the aldehyde group to give aroylhydrazones **26** (X = NHC(O)Ar). The treatment of the latter in refluxing acetic anhydride leads to 2-(oxadiazolin-2-yl)chromones **39** in 64% – 81% yield (Scheme 18).[26]

Scheme 18



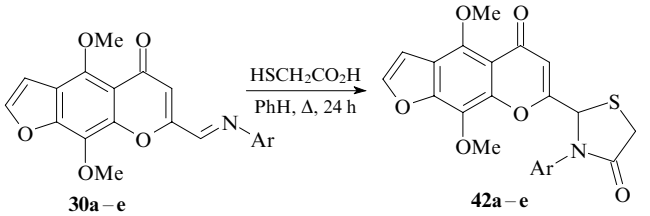
1a – **d** **26** **39**

R = H, Me, Cl, Br; Ar = Ph, C_6H_4Cl-2, C_6H_4Cl-4, C_6H_4OMe-4, $C_6H_4NO_2$-4

Yet another example of synthesis of 2-hetarylchromones by reacting 2-formylchromones with N-nucleophiles is the reaction of compounds **1b**,**c**,**p** with 2-amino-5-sulfanyl-1,3,4-thiadiazole. In this case, the reaction first gives imines **40a** – **c**, which react with sulfanylacetic acid in dioxane to form 4-oxothiazolidine derivatives **41a** – **c** (Scheme 19).[43]

An analogous reaction of 7-formylnorkhellin imines **30a** – **e** with sulfanylacetic acid in refluxing benzene for 24 h gives thiazolidin-2-ylchromones **42a** – **e** in 60% – 65% yields (Scheme 20).[41]

Scheme 20

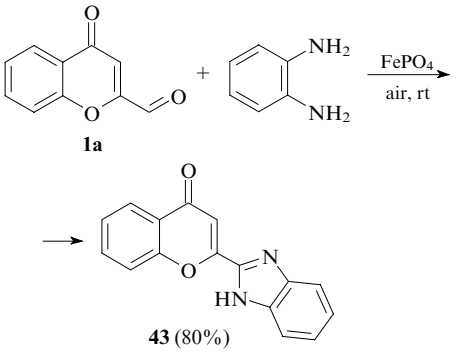


30a – **e** **42a** – **e**

Ar = Ph (**a**), C_6H_4Me-3 (**b**), C_6H_4Me-4 (**c**), C_6H_4Cl-4 (**d**), C_6H_4OMe-4 (**e**)

The solvent-free reaction of 2-formylchromone (**1a**) with *o*-phenylenediamine in the presence of anhydrous iron(III) orthophosphate at room temperature for 35 min leads to 2-(benzimidazol-2-yl)chromone **43** (Scheme 21).[44]

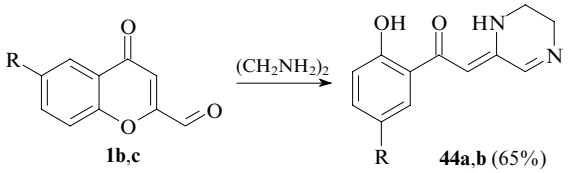
Scheme 21



1a **43** (80%)

It is worth noting that all above reactions of 2-formylchromones with N-nucleophiles involve only the aldehyde group without O – C bond cleavage in the chromone system. However, the reaction of compounds **1b**,**c** with ethylenediamine in ethanol at room temperature for 2 h is

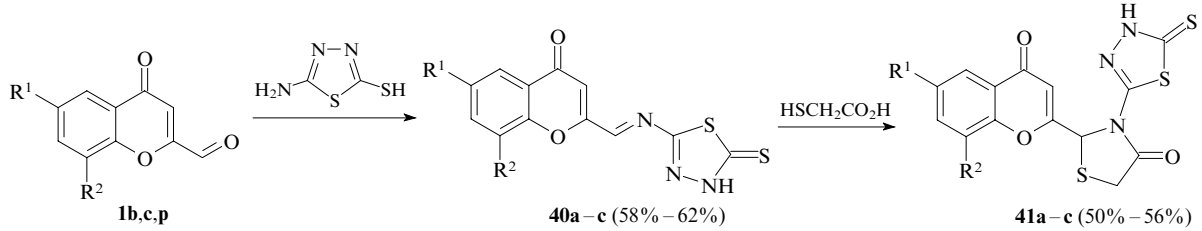
Scheme 22



1b,**c** **44a**,**b** (65%)

R = Me (**1b**, **44a**), Cl (**1c**, **44b**)

Scheme 19



1b,**c**,**p** **40a** – **c** (58% – 62%) **41a** – **c** (50% – 56%)

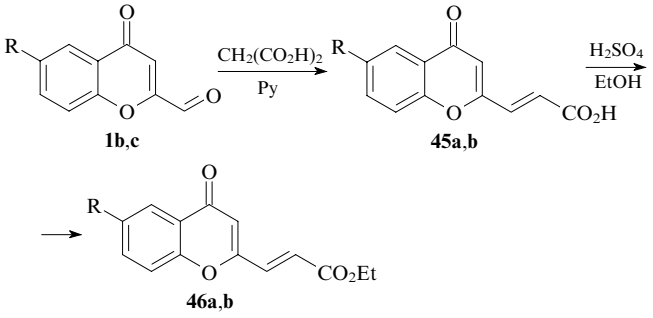
R^2 = H: R^1 = Me (**1b**, **40a**, **41a**), Cl (**1c**, **40b**, **41b**); R^1 = R^2 = Me (**1p**, **40c**, **41c**)

accompanied by pyrone ring opening to give 5,6-dihydropyrazines **44a**,**b** (Scheme 22).[23]

II.2.b. Reactions with C-nucleophiles

2-Formylchromones **1b**,**c** condense at the formyl group with malonic acid (Doebner reaction) in pyridine at 110 °C for 1.5 h. The reaction consists of decarboxylation to give acrylic acid derivatives **45a**,**b**. When refluxed in anhydrous ethanol for 5 h in the presence of concentrated sulfuric acid, these compounds give esters **46a**,**b** (Scheme 23).[23]

Scheme 23



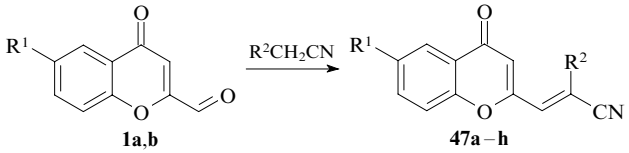
Compounds **45**, **46**	R	Yield (%)	
		45	**46**
a	Me	66	65
b	Cl	55	60

2-Formylchromones **1a**,**b** react analogously with other methylene-active compounds, such as malononitrile, ethyl cyanoacetate, cyanoacetic acid and cyanoacetamide, to give acrylonitriles **47a** – **h** (the Knoevenagel reaction). The reaction with malononitrile proceeds in aqueous ethanol with nearly quantitative yields of the adducts; with other methylene compounds, the reaction occurs under solvent-free conditions at 160 °C in 15 min (Scheme 24).[23]

The reaction of 6-methyl-2-formylchromone (**1b**) with hippuric acid is refluxing acetic anhydride in the presence of sodium acetate gives oxazolinone derivative **48** (Scheme 25).[23]

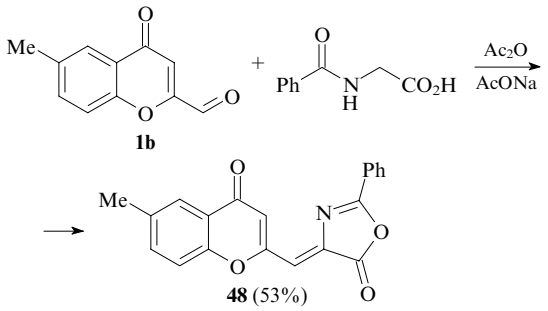
The same chromone reacts under the Perkin conditions (in acetic anhydride in the presence of potassium carbonate) with coumarin-4-acetic acid derivatives **49a**,**b**. The reaction involves aldol condensation followed by decarboxylation to give compounds **50a**,**b** in high yields (Scheme 26).[45]

Scheme 24

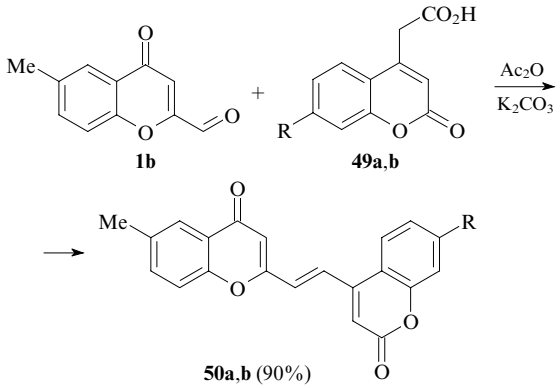


Compound **47**	R^1	R^2	Yield (%)
a	Me	CN	97
b	Cl	CN	98
c	Me	CO_2H	52
d	Cl	CO_2H	48
e	Me	CO_2Et	52
f	Cl	CO_2Et	62
g	Me	$C(O)NH_2$	65
h	Cl	$C(O)NH_2$	58

Scheme 25

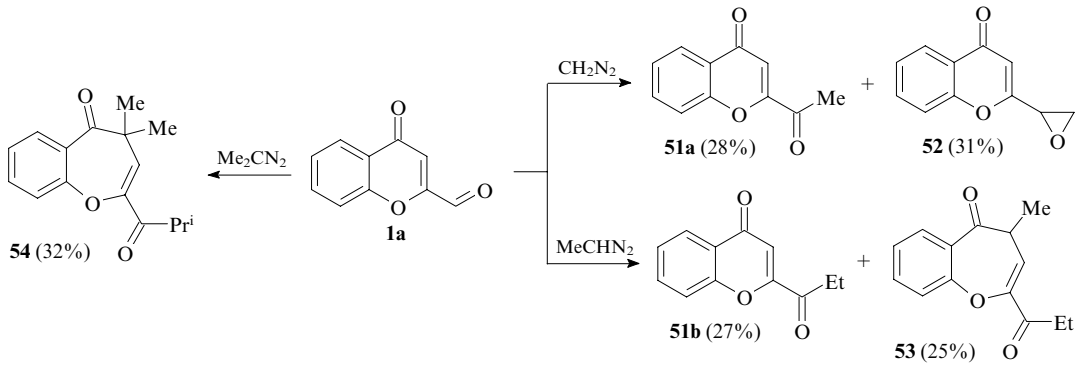


Scheme 26



R = Me (**49a**, **50a**), OH (**49b**), OAc (**50b**)

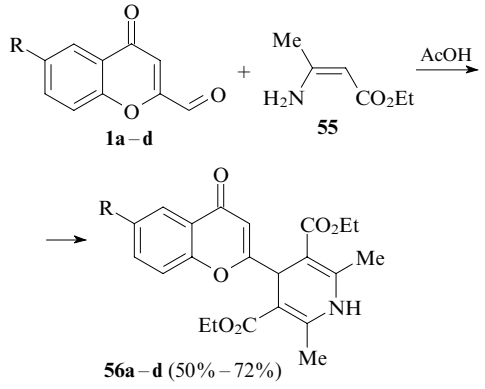
Scheme 27



2-Formylchromone (**1a**) reacts with diazomethane to give a mixture of 2-acetylchromone (**51a**) and 2-(oxiranyl)-chromone (**52**). The reaction of the same substrate with diazoethane leads to roughly equal amounts of 2-propionylchromone (**51b**) and methyl-substituted benzoxepine **53**, which forms by the reaction with two diazoethane molecules. At the same time, 2-diazopropane gives dimethylbenzoxepine **54** as the sole product (Scheme 27).[46]

The reaction of 2-formylchromones **1a – d** with ethyl 3-aminocrotonate (**55**) in acetic acid at room temperature affords 2-(1,4-dihydro-4-pyridyl)chromone **56a – d**.[31] The successive addition of two ethyl 3-aminocrotonate molecules at the aldehyde group to eliminate water and ammonia molecules is the most probable mechanism of this modification of the Hantzsch reaction (Scheme 28).

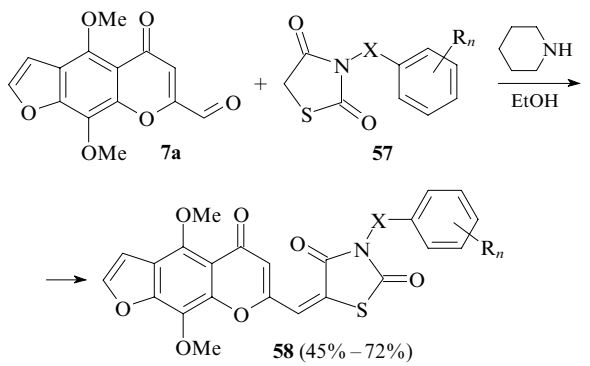
Scheme 28



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

7-Formylnorkhellin (**7a**) undergoes the Knoevenagel reaction with thiazolidine-2,4-diones **57** in the presence of piperidine in ethanol to give new furochromonylmethylene-thiazolidine-2,4-dione derivatives **58** (Scheme 29).[28] These compounds have been tested for insulinotropic activity.

Scheme 29

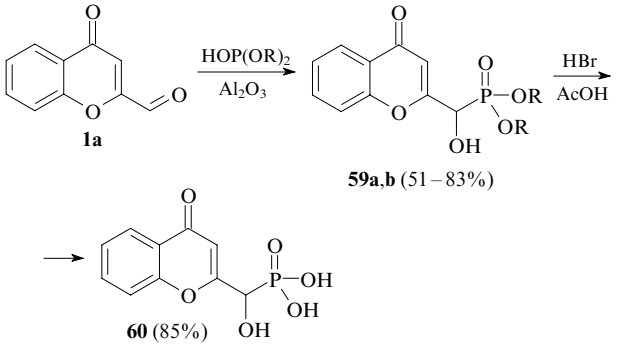


X = CH_2, $CH_2C(O)$; R_n = 4-F, 4-Cl, 4-Br, 4-NO_2, 4-OMe, 2,5-$(OMe)_2$

II.2.c. Reactions with P-nucleophiles

Kostka and Modranka[47] were the first who synthesized chromone-2-hydroxymethanephosphonic acid and its esters. 2-Formylchromone (**1a**) reacts with dialkyl phosphites in the presence of basic alumina to form dialkyl chromone-2-hydroxymethanephosphonates **59a**,**b**. Hydrolysis of these esters induced by HBr in acetic acid gives chromone-2-hydroxymethanephosphonic acid (**60**) (Scheme 30).

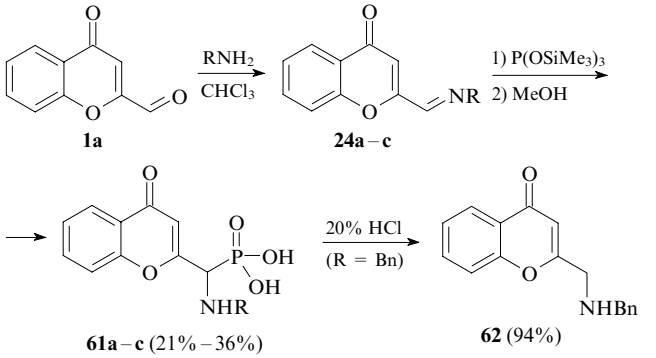
Scheme 30



59: R = Me (**a**), Et (**b**)

N-substituted chromone-2-aminomethanephosphonic acids **61a – c** have also been synthesized from 2-formylchromone (**1a**).The synthesis involved the reaction of imines **24a – c**, which form *in situ* from **1a** and corresponding amines, with tris(trimethylsilyl) phosphite in chloroform. The intermediate silylated aminophosphonates were not isolated; rather, they were immediately converted into target aminophosphonic acids **61** by adding methanol or ethanol (Scheme 31).[48,49]

Scheme 31



24, **61**: R = Bu^n (**a**), Bn (**b**), C_6H_4Me-4 (**c**)

It should be noted that compounds **61** are unstable in acidic aqueous solutions. On heating in hydrochloric acid or other mineral acids, derivative **61b** decomposes with C – P bond cleavage to form 2-(benzylaminomethyl)chromone **62** and phosphoric acid.[48]

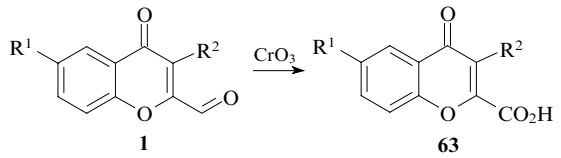
II.2.d. Other reactions

Oxidation of 2-formylchromones by the Jones reagent [chromium(VI) oxide in acetic or sulfuric acid] leads to chromone-2-carboxylic acid derivatives **63**.[18,23] Silver oxide can also be used as the oxidant. In the case of chromone **23**, the reaction is carried out in the presence of 10% sodium hydroxide in methanol; the oxidation is accompanied by elimination of the *p*-methoxybenzyl protective group in the 3-position and formation of chromone **64** (Scheme 32).[40]

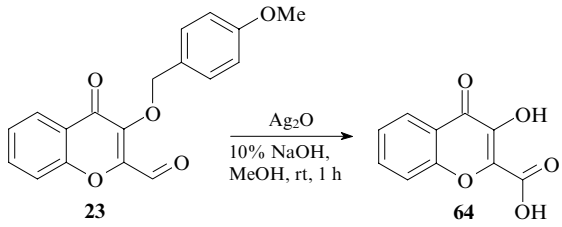
The reduction of 2-formylchromone (**1l**) by sodium borohydride in the presence of cerium(III) chloride hydrate leads to 2-hydroxymethylchromone derivative **65** (Scheme 33).[34]

Meerwein – Ponndorf – Verley reduction of furo[3,2-*g*]chromones **7a**,**b** with aluminium isopropoxide in isopropyl alcohol gives alcohols **66a**,**b** in roughly quantitative

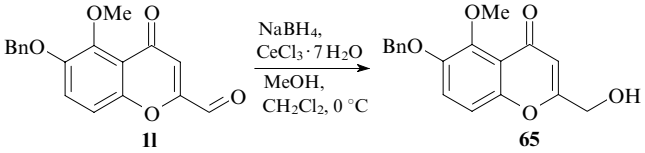
Scheme 32



R^1, R^2 = H, Me

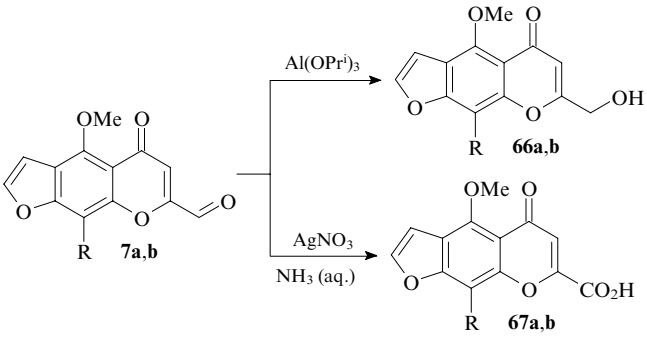


Scheme 33



yield (Scheme 34).[20,27] Reduction with zinc powder in glacial acetic acid leads to the same products in low yield. Alcohols **66a** (khellol) and **66b** (amminol), like khellin (**6a**) and visnagin (**6b**), are natural furochromones and can be isolated from the plant *Ammi visnaga* L. The treatment of 7-formylfurochromones **7a**,**b** with ammonia solution of silver nitrate leads to oxidation of the formyl group to form furochromone-2-carboxylic acids **67a**,**b** (the yield of **67a** is 57%).[20]

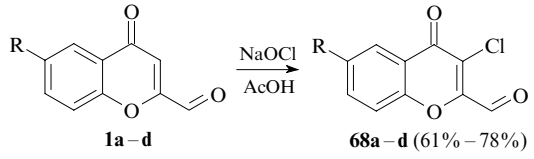
Scheme 34



R = OMe (**a**), H (**b**)

Selective monochlorination of 2-formylchromones **1a** – **d** at the C(3) atom was carried out by an aqueous sodium hypochlorite solution in acetic acid at room temperature.[32] The reaction afforded 2-formyl-3-chlorochromones **68a** – **d** in moderate yields (Scheme 35).

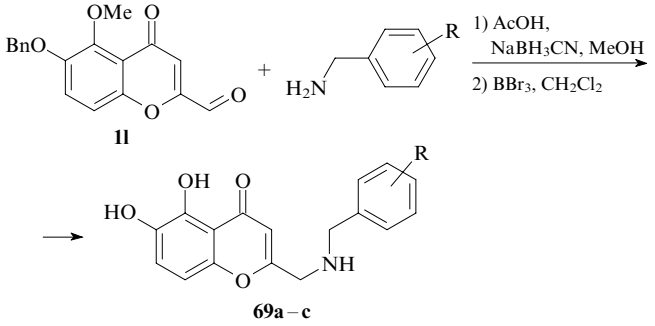
Scheme 35



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

2-Formylchromones have been used in synthesis of biologically active 2-aminomethyl derivatives **69a** – **c**. The reaction of aldehyde **1l** with substituted benzylamines under reductive amination conditions followed by removal of protective groups in the presence of BBr_3 in dichloromethane leads to target products in 31% – 38% yield (Scheme 36).[33]

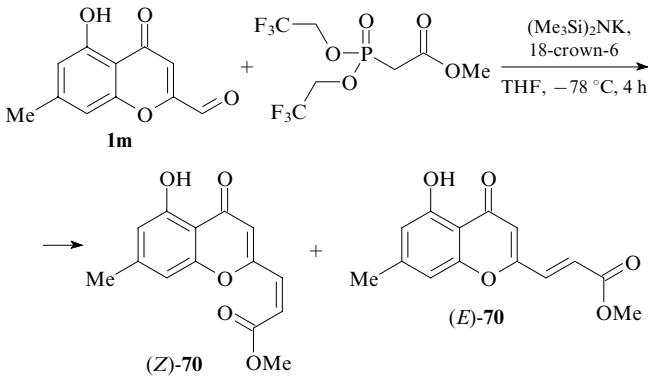
Scheme 36



R = 4-Cl (**a**), 3-Cl (**b**), 3-CN (**c**)

5-Hydroxy-7-methyl-2-formylchromone (**1m**) is alkenylated at the formyl group in the reaction with methyl *P*,*P*-bis(2,2,2-trifluoroethyl)phosphonoacetate.[35] The reaction

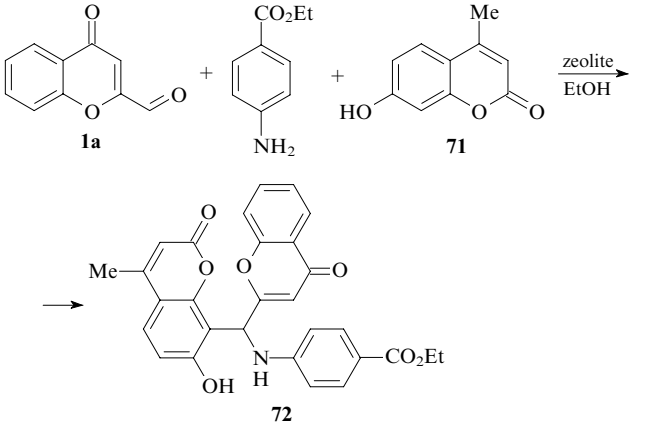
Scheme 37



proceeds in the presence of potassium bis(trimethylsilyl)-amide and 18-crown-6 in tetrahydrofuran at −78 °C for 4 h and leads to the mixture of the *Z* and *E* isomers of acrylic esters **70** with significant predominance of the former (*Z* : *E* = 6.7 : 1). Thus, this reaction is *Z*-selective, and the overall yield of the isomers, which are readily separated by column chromatography, is as high as 92% (Scheme 37).

The three-component reaction of 2-formylchromone (**1a**) with ethyl 4-aminobenzoate and 7-hydroxy-4-methyl-

Scheme 38



coumarin (**71**) in ethanol in the presence of zeolite first gives the corresponding imine followed by electrophilic substitution at the 8-position of coumarin to form adduct **72** in 90% yield (Scheme 38).[50]

III. Synthesis and reactions of 2-alkanoylchromones

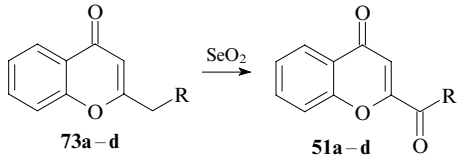
III.1. Methods of synthesis of 2-alkanoylchromones

This section summarizes data on the synthesis and 2-acetylchromone and its derivatives substituted at both the chromone system and the methyl group of the acetyl substituent in the 2-position. The methods of synthesis of 2-alkanoylchromones are mainly based on modification of 2-alkyl-substituted chromones, derivatives of chromone-2-carboxylic acid and 2-formylchromones.

III.1.a. Synthesis from 2-alkylchromones

As noted above, synthesis of 2-formylchromones **1** from 2-methyl derivatives **2** is complicated by oxidation of the aldehyde group to the carboxyl one. At the same time, synthesis of 2-acylchromones by this method becomes possible since the forming ketone function is much more stable to oxidation. In particular, the action of selenium(IV) oxide on 2-alkylchromones **73a – d** with a hydrocarbon substituent longer than methyl group leads to 2-alkanoylchromones **51a – d**, although in low yields (Scheme 39).[18]

Scheme 39



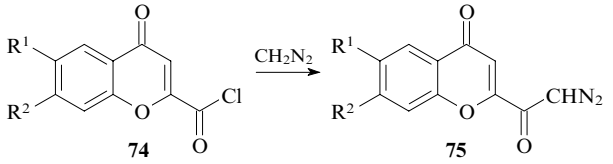
R = Me (**a**, 17% yield), Et (**b**, 8%), Pr^n (**c**, 9%), Pr^i (**d**, 22%)

III.1.b. Synthesis from 2-diazoacetylchromones

The most popular method of synthesis of 2-acetylchromones is based on transformations of diazo derivatives. First, chromone-2-carboxylic acid chlorides **74** react with diazomethane to give 2-diazoacetylchromones **75** (~80% yield, Scheme 40).[51 – 55]

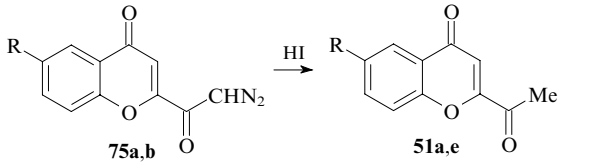
Chromones **75** can be used in synthesis of other 2-acetylchromone derivatives substituted at the methyl group of the acetyl substituent. In particular, 2-diazoacetylchromones **75a**,**b** have been used to synthesize 2-substituted chromones **51a**,**e**, **76 – 79** (Schemes 41, 42).[51]

Scheme 40



R^1 = H, F, Cl, Br, NO_2, Me; R^2 = H, OMe

Scheme 41



R = H (**a**), Br (**b**)

The reaction of compound **75a** with hydrogen iodide gives 2-acetylchromone **51a** (88% yield), and its reaction with hydrogen chloride and hydrogen bromide leads to, respectively, 2-chloroacetyl-[51, 54] and 2-bromoacetylchromones [51, 55] **76a**,**b** (up to 96% yields) (see Scheme 42).

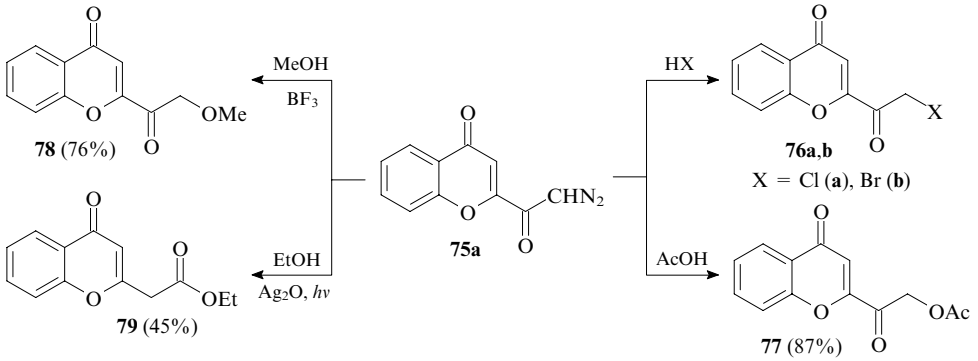
Treatment of this substrate with acetic acid gives 2-acetoxyacetylchromone **77**, and its reaction with boron trifluoride methanol complex gives methoxyacetylchromone **78**. In the reaction with ethanol in the presence of silver oxide in refluxing dioxane under irradiation, 2-diazoacetylchromone (**75a**) undergoes the Wolff rearrangement to give ethyl ester **79**. Later, the procedure of carrying out the reaction with HI has been optimized and used for synthesis of 2-acetyl-6-bromochromone **51e** (R = Br, see Scheme 41).[52] It is worth noting that microwave irradiation increases the yield of compounds **51** and **75**.[53]

III.1.c. Synthesis from 2-formylchromones and chromone-2-carbonyl chlorides

The synthesis of 2-alkanoylchromones from 2-formylchromone (**1a**) has been described by Dean and Johnson.[46] As shown above (see Scheme 27), this compound reacts with diazomethane and diazoethane to form 2-acetyl- (**51a**) and 2-propanoylchromones (**51b**), respectively, in yields no higher than 28%. By-products forming in the reaction are readily separated by chromatography and distillation.

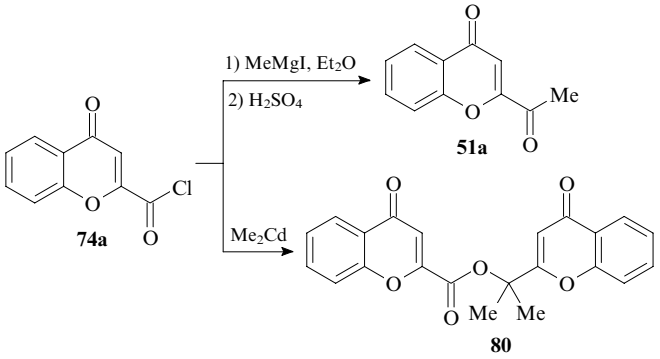
2-Acetylchromone (**51a**) was also obtained from chromone-2-carboxylic acid chloride (**74a**) through the Grignard reaction. The reaction of MeMgI with acid chloride **74a** in diethyl ether at temperature from −5 to 0 °C followed by

Scheme 42



acidification with dilute sulfuric acid leads to product **51a** in 72% yield.[56] It should be noted that treatment with dimethylcadmium leads to dimer **80** (47% yield) as a result of the reaction of intermediate tertiary alcohol with initial acid chloride **74a** (Scheme 43).

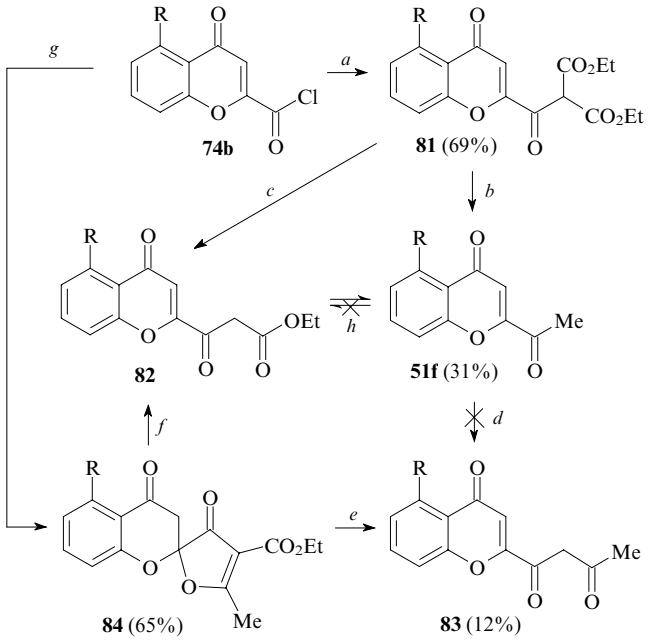
Scheme 43



2-Acetylchromone (**51a**)[57] and its 5-substituted analogue **51f** [R = O(CH$_2$)$_2$OEt][58] have been synthesized by the reaction of acid chlorides **74a**,**b** with diethyl ethoxymagnesiomalonate followed by acidification. In the second case, the reaction occurs through decarboxylation of intermediate **81**. Attempts to carry out ethoxycarbonylation or acylation of chromone **51f** to synthesize new 1,3-dicarbonyl derivatives **82** and **83** failed. Monodecarboxylation of compound **81** turned out to be either unsuccessful (only chromone **51f** was synthesized) or gave product **82** in low yield (24%, Scheme 44).[58] Compounds **82** and **83** have been synthesized through the formation of spiro[chromone-2,2′-furan] **84**, obtained by the reaction of acid chloride **74b** with ethyl ethoxymagnesioacetoacetate followed by acidification. Heating product **84** in refluxing ethanol in the presence of concentrated hydrochloric acid leads to the opening of the spiro system to form 1,3-dicarbonyl compound **82** (76% yield). Heating compound **84** in refluxing propionic acid in the presence of concentrated sulfuric acid leads to β-diketone **83** in low yield (see Scheme 44).

The yield of such a β-diketone is increased when acid chloride **74b** reacts with ethoxymagnesioacetylacetone (Scheme 45). Spiro compound **85** (R^2 = Me) is synthesized analogously. Treatment of this compound with refluxing ethanol – concentrated hydrochloric acid gives product **83** (R^2 = Me). The same method has been successfully used to synthesize analogue **86** with unsubstituted benzene ring (R^1 = H, R^2 = OEt) from chromone **74a** through the formation of spiro compound **87**.[58]

Scheme 44



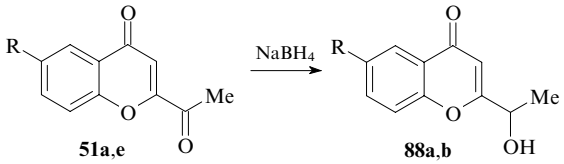
(*a*) 1) EtOMgCH(CO$_2$Et)$_2$, 2) HCl; (*b*) EtCO$_2$H, H$_2$SO$_4$, 3 h; (*c*) EtCO$_2$H, H$_2$SO$_4$, 0.5 h; (*d*) NaH, Ac$_2$O; (*e*) EtCO$_2$H, H$_2$SO$_4$; (*f*) HCl, EtOH; (*g*) 1) EtOMgCH(CO$_2$Et)Ac, 2) HCl; (*h*) ClCO$_2$Et, NaH; R = O(CH$_2$)$_2$OEt

III.2. Reactions of 2-alkanoylchromones

III.2.a. Reduction

It has been demonstrated that sodium borohydride reduces the acetyl carbonyl group of chromones **51a**,**e** to the hydroxyl group under stirring in methanol at room temperature for 2 h to give a racemic mixture of products **88a**,**b** (74% yield for R = H, Scheme 46).[57, 59]

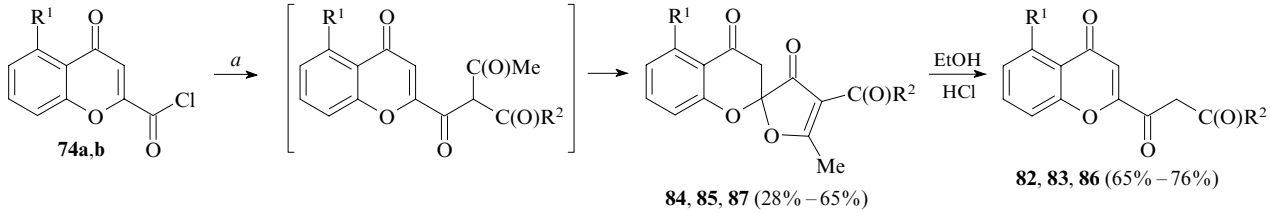
Scheme 46



R = H (**51a**, **88a**), Br (**51e**, **88b**)

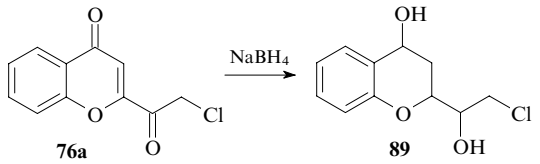
The reduction of 2-chloroacetylchromone (**76a**) with sodium borohydride at room temperature and atmospheric pressure proceeds further to give 4-hydroxychromane **89** (Scheme 47).[54]

Scheme 45



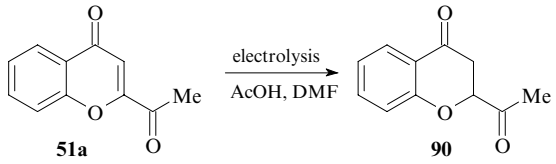
(*a*) 1) EtOMgCHAcC(O)R^2, 2) HCl; R^1 = O(CH$_2$)$_2$OEt (**74b**): R^2 = OEt (**82**, 76% yield; **84**, 65%), Me (**83**, 73%; **85**, 28%); R^1 = H (**74a**): R^2 = OEt (**86**, 65%; **87**, 50%)

Scheme 47



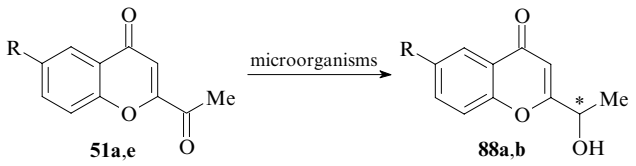
The electrochemical reaction of 2-acetylchromone (**51a**), monitored by cyclic voltammetry in dimethylformamide in the presence of a proton donor (acetic acid), leads to the selective reduction of the double bond in the pyrone ring to give chromanone **90** in 55% yield (Scheme 48).[60]

Scheme 48



In studying microbiological reduction of the carbonyl group in the 2-position of chromones **51a**,**e**, different microorganisms have been used [Scheme 49 (*ee* is enantiomeric excess)].[52, 59] Reduction gave both enantiomers of alcohols **88a**,**b** with high optical purity. The best experimental results (the highest yields and *ee* of the products) have been observed for *Saccharomyces cerevisiae* (SC), *Lactobacillus kefiri* (LK), *Zygosaccharomyces rouxii* (ZR) and *Yamadazyma farinosa* (YF).

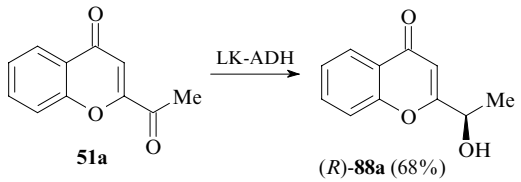
Scheme 49



Substrate	Product	R	Microorganism	Configuration	*ee* (%)	Yield (%)
51a	**88a**	H	SC	*R*	⩾98	87
51a	**88a**	H	LK	*S*	89	58
51e	**88b**	Br	ZR	*R*	⩾98	58
51e	**88b**	Br	YF	*S*	⩾98	69

Lactobacillus kefir (LK-ADH) alcohol dehydrogenase also catalyzed selective reduction of the acetyl carbonyl group of chromone **51a**. *R*-isomer of alcohol **88a** formed in 68% yield with 90% *ee* (Scheme 50).[61]

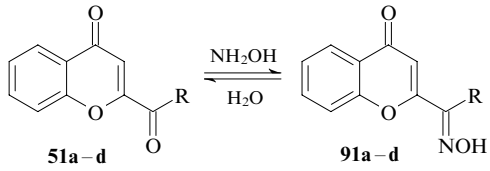
Scheme 50



III.2.b. Reactions with nucleophiles

The reaction of 2-alkanoylchromones **51a** – **d** with hydroxylamine involves only the carbonyl group in the 2-position to give oximes **91a** – **d**[18] (configuration, yields and conditions have not been reported), which can be hydrolyzed to initial chromones (Scheme 51).

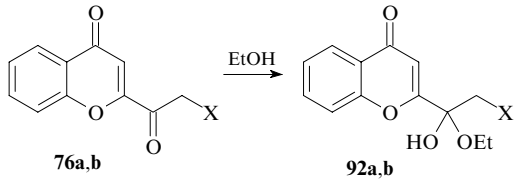
Scheme 51



R = Me (**a**), Et (**b**), Pr^n (**c**), Pr^i (**d**)

It has been shown that simple recrystallization of 2-chloroacetyl- and 2-bromoacetylchromones **76a**,**b** from ethanol leads to hemiacetals **92a**,**b**[51] (Scheme 52).

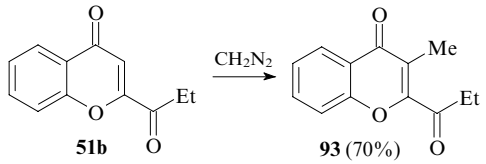
Scheme 52



X = Cl (**a**), Br (**b**)

2-Propanoylchromone (**51b**) reacts slowly but smoothly with diazomethane in a chloroform – diethyl ether mixture (1 : 10) for 45 h to form 3-methyl derivative **93** with retention of the chromone system (Scheme 53).[46]

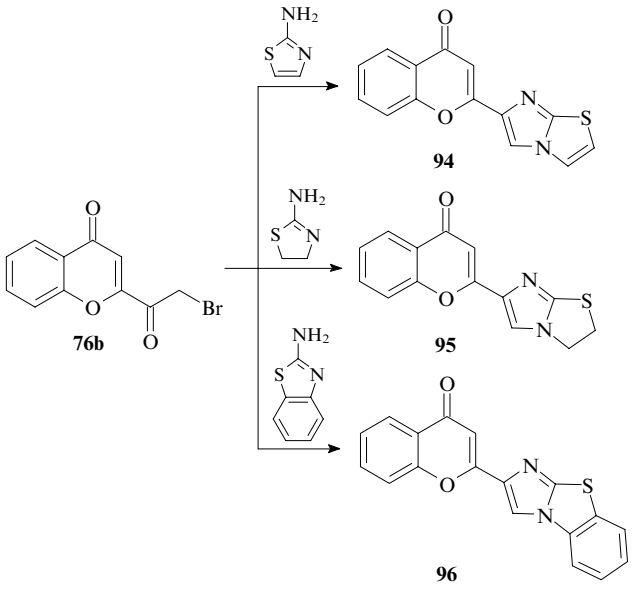
Scheme 53



III.2.c. Synthesis of 2-hetarylchromones

2-Alkanoylchromones, like 2-formylchromones, can be used in synthesis of 2-hetarylchromones. 2-Bromoacetylchromone (**76b**) undergoes the Chichibabin reaction with 2-aminothiazole, 2-amino-4,5-dihydrothiazole and 2-ami-

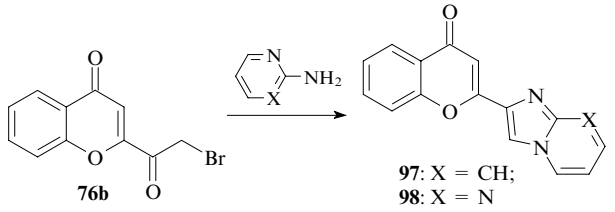
Scheme 54



nobenzo[*d*]thiazole to give chromone-substituted imidazo[2,1-*b*]thiazole (**94**), 2,3-dihydroimidazo[2,1-*b*]thiazole (**95**) and benzo[*d*]imidazo[2,1-*b*]thiazole (**96**) in 80%, 46% and 52% yields, respectively.[62] These compounds have been tested for antihelminthic activity (Scheme 54).

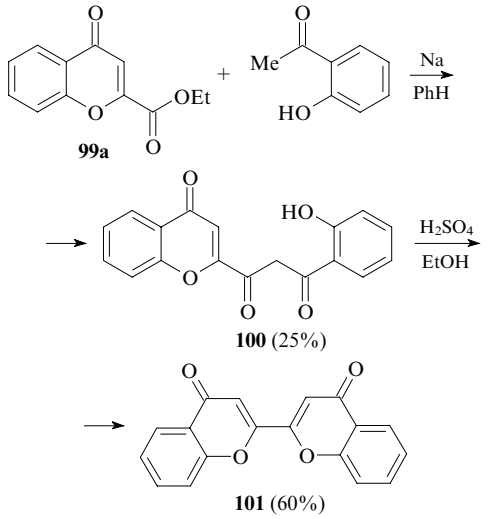
Analogous reactions of 2-bromoacetylchromone (**76b**) with 2-aminopyridine and 2-aminopyrimidine lead to chromone derivatives of imidazo[1,2-*a*]pyridine (**97**) and -pyrimidine (**98**) in 60% and 31% yield, respectively.[55] Such 2-hetarylchromones exhibit antihistamine activity (Scheme 55).

Scheme 55



Condensation of ethyl chromone-2-carboxylate (**99a**) with *o*-hydroxyacetophenone induced by sodium in benzene gives chromone **100** with β-dicarbonyl moiety in the 2-position. On heating with concentrated sulfuric acid in anhydrous ethanol, this chromone cyclizes into bischromone **101** (Scheme 56).[63]

Scheme 56



IV. Synthesis and reactions of 2-aroylchromones

IV.1. Methods of synthesis of 2-aroylchromones

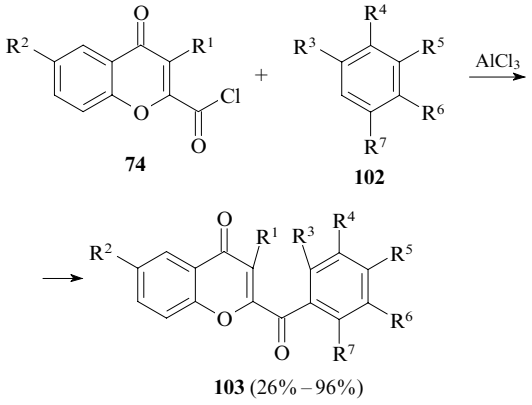
IV.1.a. Friedel – Crafts acylation of benzenes

Friedel – Crafts acylation of arenes **102** with chromone-2-carboxylic acid chlorides **74** is one of the most important methods of synthesis of 2-aroylchromones **103**. This procedure has been used to synthesize more than 30 related compounds; some of them exhibit noticeable analgesic, angioprotective and antiallergic activity.[52, 53, 57, 64, 65]

As a rule, 2-aroylchromones **103** are synthesized in the presence of aluminium chloride as a catalyst (Scheme 57).

Reaction conditions can be varied, and synthesized products can be modified with the aim to obtain new compounds. For example, they can be brominated at the benzene ring of the substituent to obtain bromo derivatives

Scheme 57



R^1 = H, Me; R^2 = H, Me, F, Cl, Br, NO_2; R^3 = H, OH, OMe, Cl; R^4 = H, Me, Cl, Br; R^5 = H, OH, OMe, F, Cl, Br; R^6 = H, Me, Br; R^7 = H, OH, OMe

of 2-aroylchromones. Because of the presence of MeO groups in arene **102**, the reaction should be carried out at low temperature. With increasing temperature, selective hydrolysis of methoxy groups occurs, leading to chromone derivatives with HO groups in the aroyl fragment. This additional stage of hydrolysis is often responsible for the decrease in the yield of the products to 28% – 40%. In the other cases, aroylchromone derivatives are produced in good to high yield (56% – 96%). Compounds **103**, which do not contain hydroxy groups or halogen atoms in the benzoyl moiety, are also synthesized at low temperatures. The most comprehensive study of this approach has been reported by Payard *et al.*[65]

IV.1.b. Oxidation

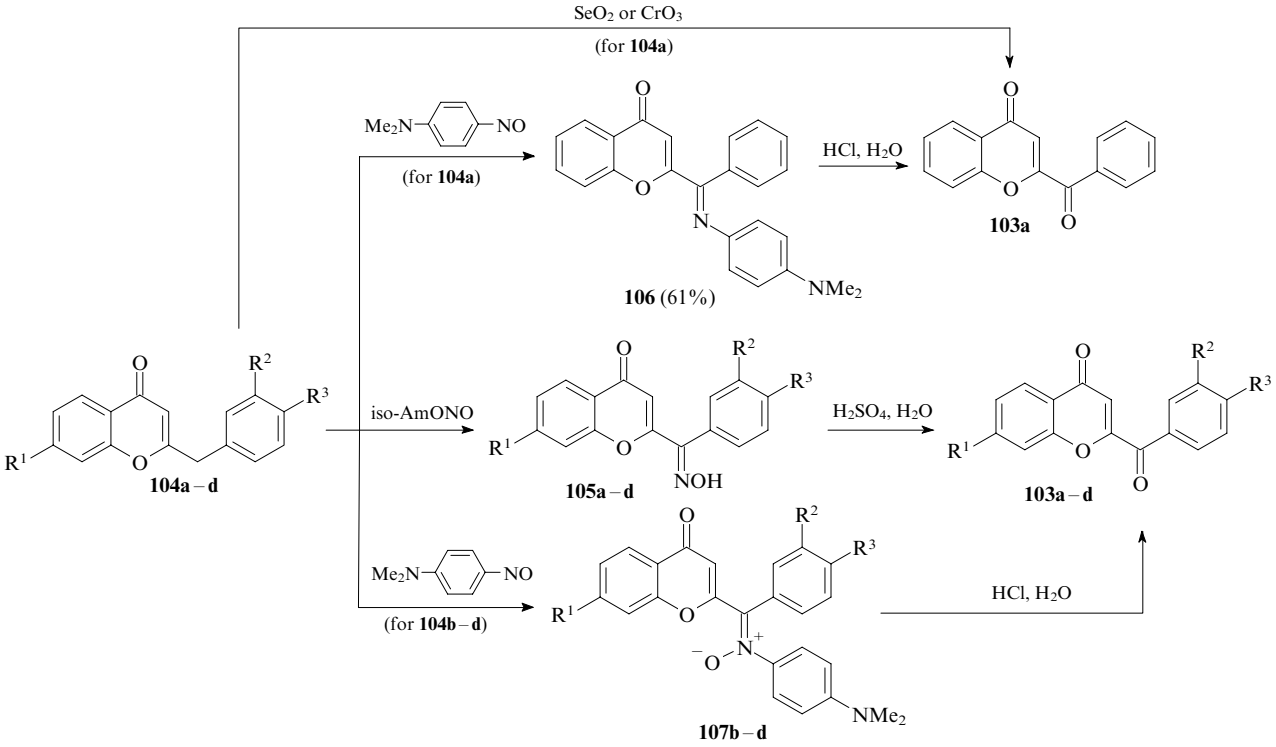
Unsubstituted 2-benzoylchromone (**103a**) is formed through direct oxidation of 2-benzylchromone (**104a**) with selenium(IV) oxide or chromium(VI) oxide in 51% or 42% yield.[18] Methoxy derivatives **103b – d** and unsubstituted 2-benzoylchromone (**103a**) can be synthesized through oximation of 2-benzylchromones **104a – d** under the action of isoamyl nitrite (iso-AmONO) followed by hydrolysis of oximes **105a – d** in the presence of sulfuric acid (Scheme 58).

The third approach consists of condensation of 2-benzylchromones with *p*-nitroso-*N*,*N*-dimethylaniline through the formation of (*p*-dimethylaminophenyl)imine **106** or (*p*-dimethylaminophenyl)nitrones **107b – d** (containing one or several methoxy groups). Then, intermediate compounds **106** and **107** are hydrolyzed in the presence of hydrochloric acid to corresponding 2-aroylchromones **103** in nearly quantitative yield (see Scheme 58).[18]

2-Aroylchromones **103** have been synthesized by oxidation and dehydrogenation of 2-aroyl-2*H*-chromanes **108**.[66, 67] 2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ) (3.0 – 3.5 equiv.) was used as an oxidant, and the reaction was carried out in refluxing dioxane in the presence of acetic acid and water (Scheme 59). Most of 2-aroylchromones **103** have been obtained in 57% – 86% yield. The presence of chloro substituents in compounds **108** leads to a decrease in yield to 34% – 48%. 3-Methylchromanes **108** (R^1 = Me) have been synthesized on the basis of 2-allylphenol.[66]

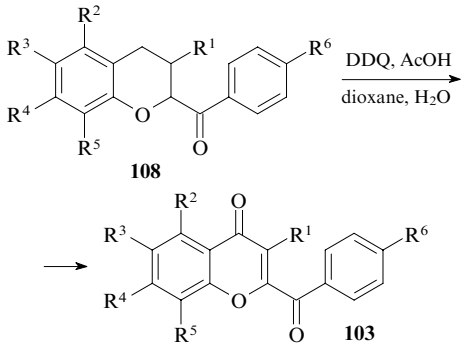
Initial chromanes **108** (R^1 = H) have been synthesized from salicylaldehydes **109** by one-pot synthesis through the formation of compounds **110**.[68] Aldehydes **109** are introduced into the reaction with methyltriphenylphosphonium

Scheme 58



Substrate	Product	R^1	R^2	R^3	Yield (%)	Substrate	Product	R^1	R^2	R^3	Yield (%)
104a	**105a**	H	H	H	89	**104d**	**107d**	H	OMe	OMe	78
104b	**105b**	H	H	OMe	93	**105a**	**103a**	H	H	H	84
104c	**105c**	OMe	H	H	90	**105b**	**103b**	H	H	OMe	70
104d	**105d**	H	OMe	OMe	89	**105c**	**103c**	OMe	H	H	83
104b	**107b**	H	H	OMe	76	**105d**	**103d**	H	OMe	OMe	–
104c	**107c**	OMe	H	H	85						

Scheme 59



R^1 = H, Me; R^2, R^4 = H, OMe; R^3 = H, Cl, Br, OMe; R^5 = H, Cl, OMe; R^6 = H, Me, Cl, Br, OMe

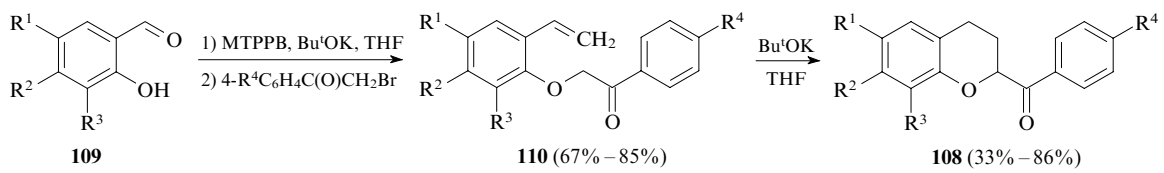
bromide (MTPPB) in the presence of potassium *tert*-butoxide in tetrahydrofuran, and then the corresponding phenacyl bromide is added. On heating with another portion of potassium *tert*-butoxide, intermediates **110** are cyclized into chromanes **108** (Scheme 60).

IV.1.c. Reactions with organometallic compounds

2-Benzoylchromones **103a**,**e** can be obtained by the Grignard reaction of phenylmagnesium bromide with ethyl chromone-2-carboxylates **99a**,**b** (Scheme 61).[69, 70]

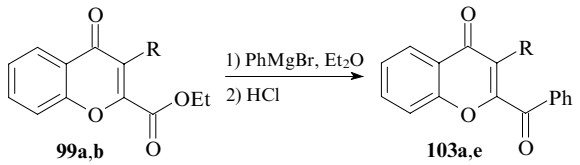
English chemists[71] have developed a method of synthesis of chromone **103f** from 3-formylchromone (**111**). The latter reacted with propane-1,3-diol to form acetal **112**, which reacted with lithium 2,2,6,6-tetramethylpiperidine (LTMP) in tetrahydrofuran at −78°C to give lithium derivative **113**. It was treated, without isolation, with

Scheme 60



R^1 = H, Cl, Br; R^2, R^3, R^4 = H, Cl, OMe

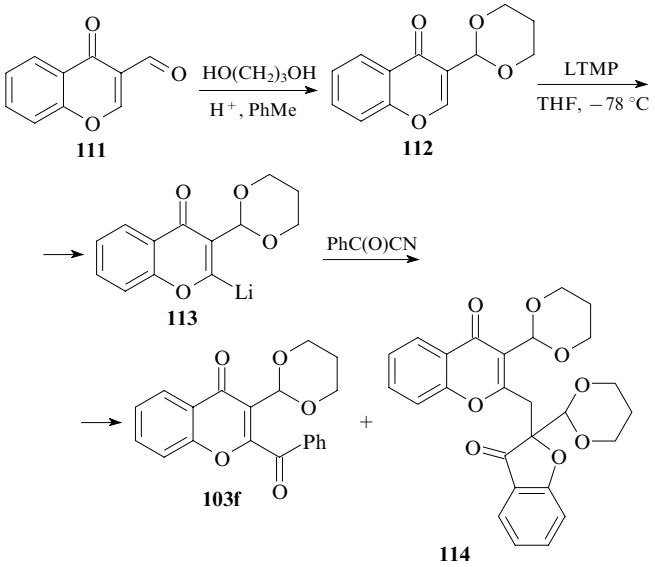
Scheme 61



R = H (**99a**, **103a**), Me (**99b**, **103e**)

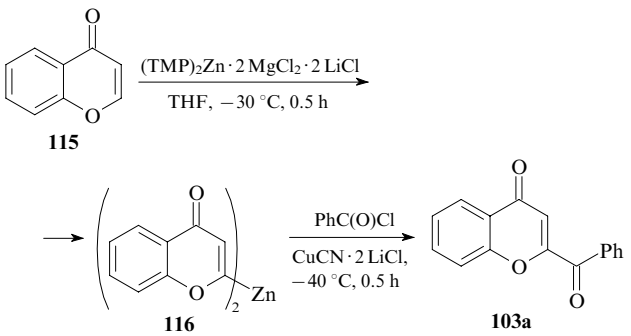
benzoyl cyanide to give chromone **103f** in 24% yield, while dimer **114** was isolated as a side product (Scheme 62).

Scheme 62



A method of C(2)-functionalization of chromones with the use of zinc compounds has been suggested.[72] In this case, 2-benzoylchromone (**103a**) was synthesized by the reaction of $(TMP)_2Zn \cdot 2\,MgCl_2 \cdot 2\,LiCl$ (TMP is 2,2,6,6-tetramethylpiperidyl) with unsubstituted chromone (**115**) in tetrahydrofuran on cooling in an argon atmosphere. Freshly prepared Zn chromone derivative **116** was introduced, without isolation, into the acylation reaction with benzoyl chloride in the presence of $CuCN \cdot 2\,LiCl$, which led to 2-benzoylchromone (**103a**) in 78% yield (Scheme 63).

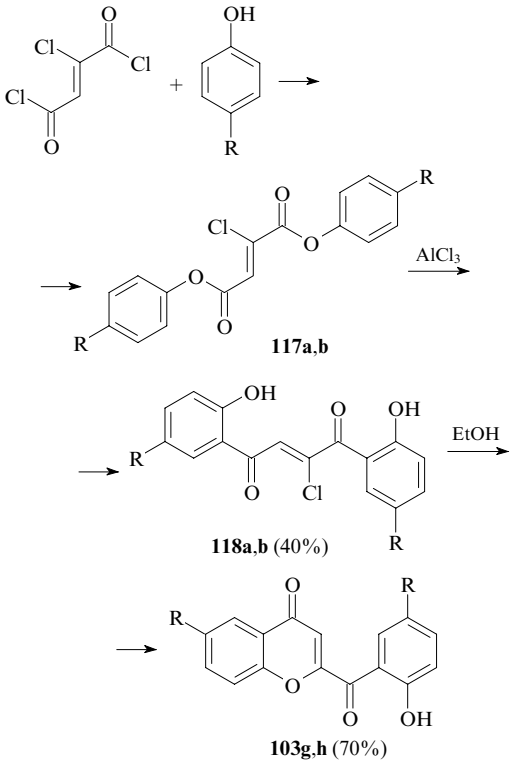
Scheme 63



IV.1.d. Miscellaneous methods

Synthesis of 2-salicyloylchromones **103g**,**h** is based on the Fries rearrangement of diphenyl chlorofumarates **117a**,**b** in the presence of aluminium chloride with subsequent cyclization of intermediate acetophenones **118a**,**b** in ethanol. For this reaction, the presence of substituent R in the *para*-position to the ester group is essential, since in the absence of the substituent rearrangement products are formed (Scheme 64).[73]

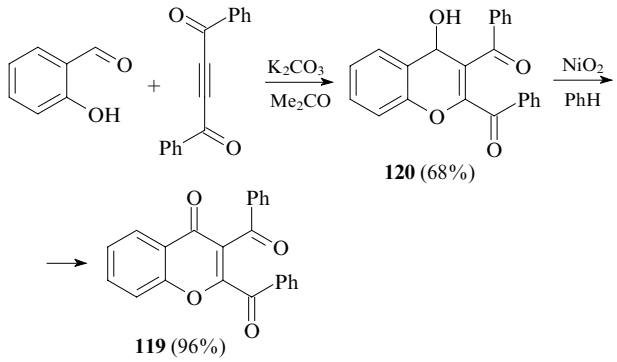
Scheme 64



R = Me (**117a**, 41% yield; **118a**, **103g**), Cl (**117b**, 37% yield; **118b**, **103h**)

2,3-Dibenzoylchromone (**119**) has been synthesized in two stages. Tandem condensation of salicylaldehyde with dibenzoylacetylene in the presence of anhydrous potassium carbonate in acetone at ~20 °C gives 4*H*-chromen-4-ol **120**, which is oxidized by nickel dioxide in benzene at room temperature to give chromone **119** in high yield (Scheme 65).[74]

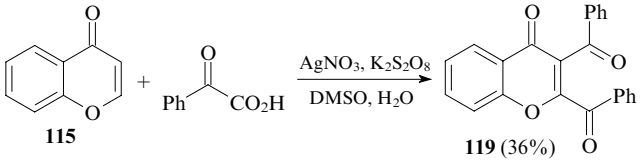
Scheme 65



Silver-catalyzed radical acylation of heterocycles has been suggested.[75] Unsubstituted chromone **115** reacts with 2-oxo-2-phenylacetic acid in the presence of $AgNO_3$ and

$K_2S_2O_8$ (inert atmosphere, aqueous DMSO, ~20 °C) to form 2,3-dibenzoylchromone (**119**) (Scheme 66).

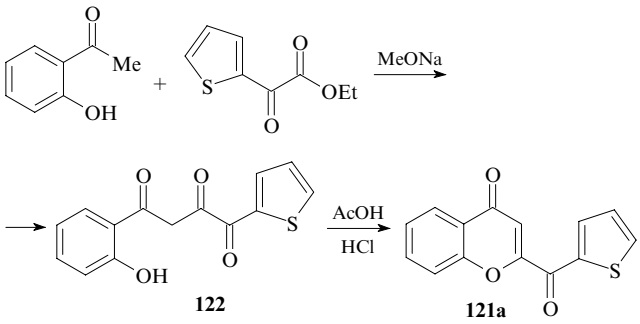
Scheme 66



IV.1.e. Synthesis of 2-(α-thenoyl)chromones

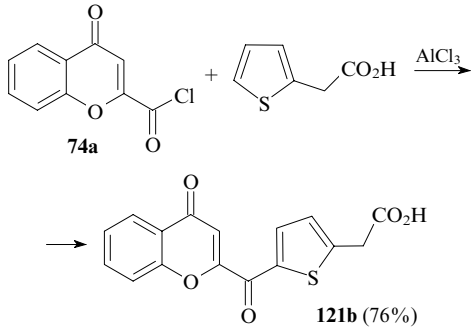
Synthesis of 2-(α-thenoyl)chromones has been reported. In particular, 2-(α-thenoyl)chromone (**121a**) is synthesized through the Claisen condensation of *o*-hydroxyacetophenone with ethyl (2-thienyl)glyoxalate in the presence of sodium methoxide in petroleum ether. The resulting triketone **122**, being treated with a mixture of acetic and hydrochloric acids, is cyclized into chromone **121a** in an overall yield of 60% (Scheme 67).[65]

Scheme 67



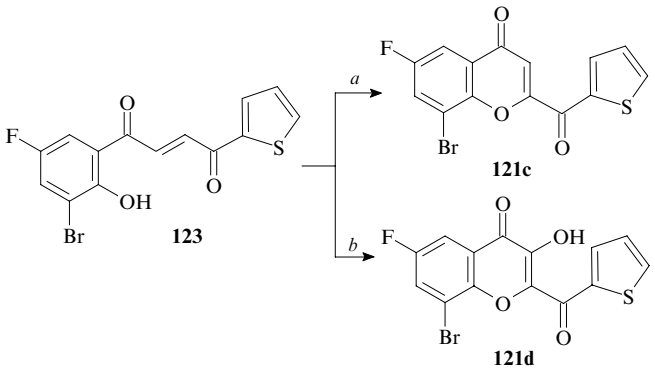
Compound **121b** has been synthesized analogously to 2-aroylchromones by direct acylation of 2-thienylacetic acid with chromone-2-carboxylic acid chloride (**74a**) at reduced temperature in the presence of a fourfold excess of aluminium chloride (Scheme 68).[65]

Scheme 68



Synthesis of substituted 2-(α-thenoyl)chromones has been accomplished from enedione **123**. Oxidation of this compound with selenium oxide in pentyl alcohol readily gives 8-bromo-2-thenoyl-6-fluorochromone (**121c**), and its reaction with hydrogen peroxide in the presence of NaOH gives 3-hydroxy-2-thenoylchromone **121d**. Chromones **121c**,**d** showed good antibacterial and antifungal activity (Scheme 69).[76]

Scheme 69



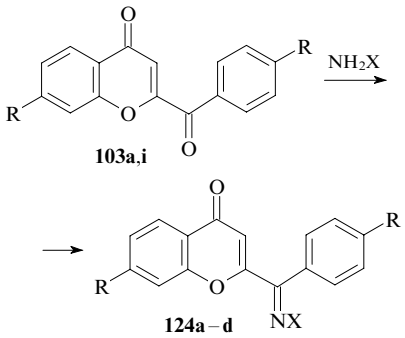
(*a*) SeO_2; (*b*) NaOH, H_2O_2

IV.2. Reactions of 2-aroylchromones

IV.2.a. Reactions with N-nucleophiles

2-Aroylchromones **103a**,**i** react with hydroxylamine and phenylhydrazine to form oximes (**124a**,**b**) and phenylhydrazones (**124c**,**d**), respectively (product configurations and yields, as well as synthetic conditions, have not been specified).[18] The reaction occurs only at the carbonyl group in the 2-position, while the chromone keto group is retained (Scheme 70).

Scheme 70



R = H (**103a**, **124a**,**c**), OMe (**103i**, **124b**,**d**);
X = OH (**124a**,**b**), NHPh (**124c**,**d**)

IV.2.b. Grignard reaction

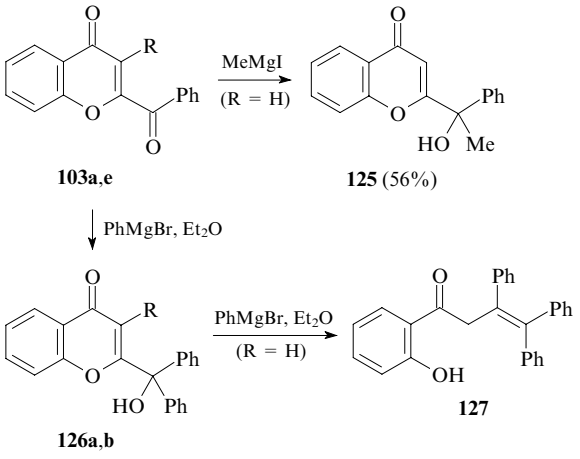
The reaction of 2-benzoylchromones **103a**,**e** with Grignard reagents (MeMgI, PhMgBr) also occurs at the benzoyl moiety and leads to tertiary alcohols **125** and **126**.[57, 69, 70] Alcohol **125** has been tested for antihistamine activity.[57] In the presence of a phenylmagnesium bromide excess, the pyrone ring of 2-benzoylchromone (**103a**) is opened to give 1-(2-hydroxyphenyl)-3,4,4-triphenylbut-3-en-1-one (**127**) (Scheme 71).[70]

IV.2.c. Reduction

2-Benzoylchromone (**103a**) reacts with sodium borohydride in methanol under stirring at room temperature for 2 h to give 2-(hydroxybenzyl)chromone (**128a**) as a racemic mixture (Scheme 72).[57] The resulting alcohol has been approved as antihistamine agent.

The use of various microorganisms for reducing 2-benzoyl- (**103a**) and 2-benzoyl-6-bromochromones (**103j**) allows one to selectively synthesize 2-(hydroxybenzyl)chromones **128a**,**b** as individual enantiomers in moderate yield

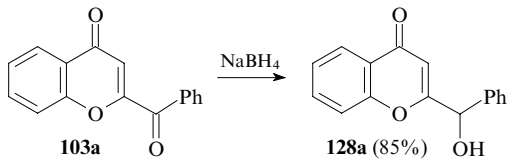
Scheme 71



103a,**e** **125** (56%) **126a**,**b** **127**

R = H (**103a**, **126a**), Me (**103e**, **126b**)

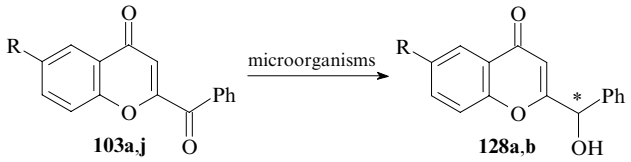
Scheme 72



103a **128a** (85%)

for R = H and in low yield for R = Br (the best results are shown in Scheme 73).[52]

Scheme 73

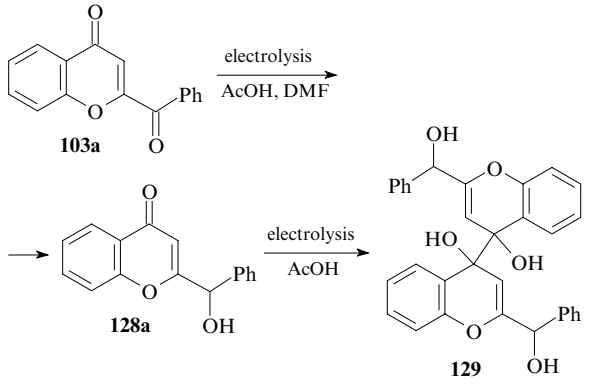


103a,**j** **128a**,**b**

Substrate	Product	R	Microorganism	Configuration	*ee* (%)	Yield (%)
103a	**128a**	H	LK	*R*	84	33
103a	**128a**	H	SC	*S*	94	60
103j	**128b**	Br	LK	*R*	57	3
103j	**128b**	Br	YF	*S*	⩾98	7

During electrolysis of 2-benzoylchromone (**103a**) in a mixture of acetic acid and dimethylformamide, the keto group of the benzoyl moiety is reduced to give alcohol **128a** (in 75% yield).[60] Further electrolysis in the presence of acetic acid leads to dimer **129** (Scheme 74).

Scheme 74



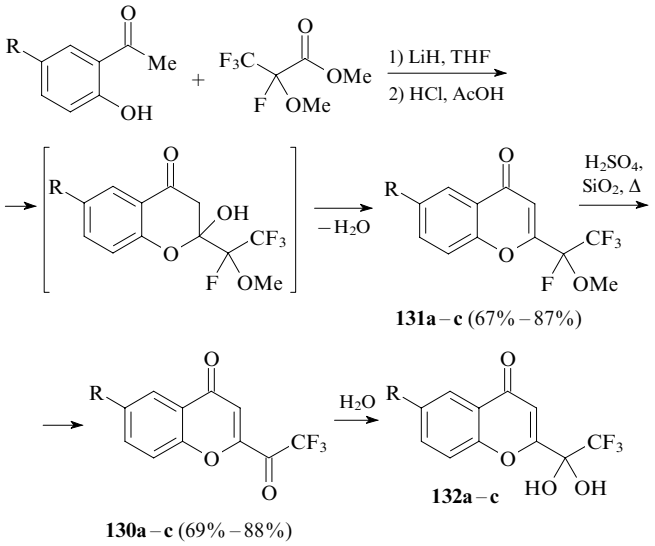
103a **128a** **129**

V. Synthesis and reactions of 2-trifluoroacetylchromones

V.1. Methods of synthesis of 2-trifluoroacetylchromones

2-Trifluoroacetylchromones are representatives of a new family of CF_3-containing chromones exhibiting the properties of highly active 1-trifluoromethyl-1,2-diketones. The first synthesis of these compounds was described by us in 2009.[77] 2-Trifluoroacetylchromones **130a**–**c** can be synthesized in two stages through the Claisen condensation of 2-hydroxyacetophenones with methyl 2-methoxy-2,3,3,3-tetrafluoropropionate (LiH, THF) followed by acid hydrolysis of intermediate chromones **131a**–**c** with the protected trifluoroacetyl group. The protection is readily removed when chromones **131a**–**c** are treated with concentrated sulfuric acid in the presence of silica, and the resulting 2-trifluoroacetylchromones **130a**–**c** are mainly in the hydrate form **132a**–**c**, stabilized by the electron-withdrawing trifluoromethyl group (Scheme 75).[77,78]

Scheme 75



131a–**c** (67%–87%) **130a**–**c** (69%–88%) **132a**–**c**

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

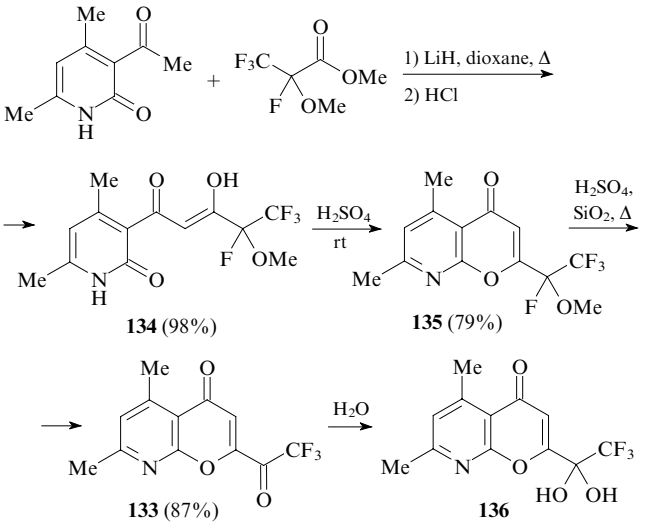
An analogous procedure affords 8-aza-5,7-dimethyl-2-trifluoroacetylchromone (**133**). Condensation of 3-acetyl-4,6-dimethyl-2-pyridone with methyl 2-methoxy-2,3,3,3-tetrafluoropropionate (LiH, dioxane) followed by hydrolysis with hydrochloric acid gives 1,3-diketone **134**, which is dehydrated by concentrated sulfuric acid to give 8-aza-5,7-dimethylchromone **135**. The treatment of the latter with concentrated sulfuric acid in the presence of silica leads to 8-aza-5,7-dimethyl-2-trifluoroacetylchromone (**133**), which is also in the hydrate form **136** (Scheme 76).[79]

V.2. Reactions of 2-trifluoroacetylchromones

V.2.a. Reactions with N-nucleophiles

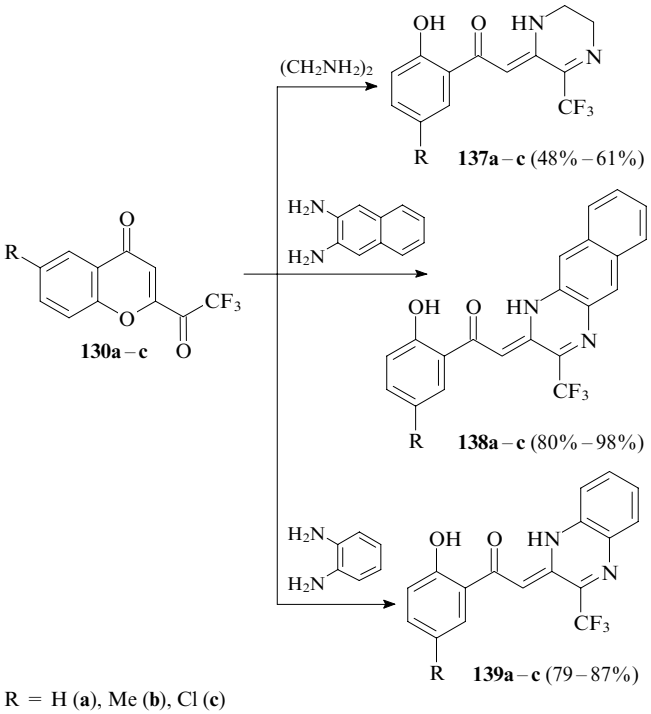
2-Trifluoroacetylchromones react with 1,2-diamines with pyrone ring opening to give different trifluoromethylated pyrazine derivatives.[77,78] In particular, the reaction of chromones **130a**–**c** with ethylenediamine in the presence of acetic acid in methanol at room temperature for 2 days gives 1,2,5,6-tetrahydropyrazine derivatives **137a**–**c**. An

Scheme 76



analogous reaction of chromones **130a – c** with aromatic 1,2-diamines, such as 2,3-diaminonaphthalene and *o*-phenylenediamine, in refluxing acetic acid for 4 h give, respectively, benzo[*g*]quinoxalines **138a – c** and quinoxalines **139a – c** in high yield (Scheme 77).

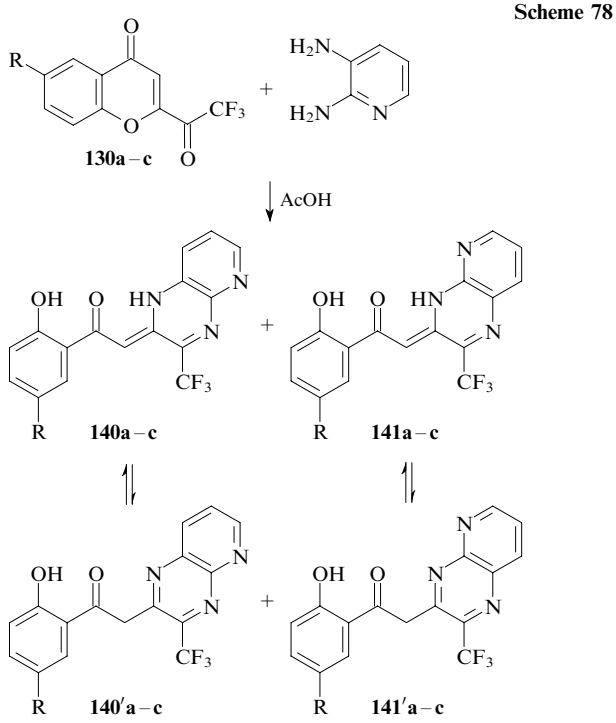
Scheme 77



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

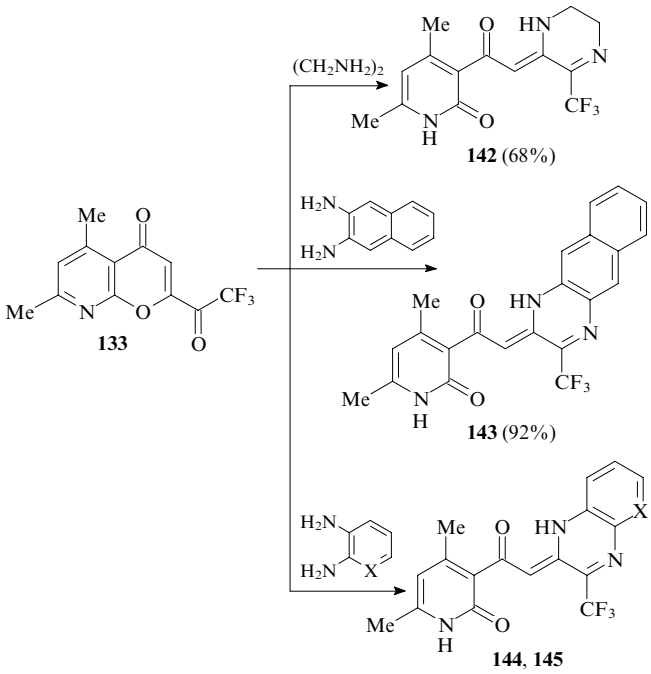
The reaction with 2,3-diaminopyridine under the same conditions gives a mixture of regioisomeric pyridopyrazines **140a – c** and **141a – c** being in imine – eneamine equilibrium with their tautomeric forms **140′a – c** and **141′a – c** (85% – 98% yields).[78] At the same time, carrying out the synthesis at ~20 °C for 7 days makes it possible to significantly improve its selectivity (the content of isomers **140** is as large as 85% – 94%). It is evident that the initial attack of the most active β-NH_2 group occurs mainly at the C(2) atom of the chromone system (Scheme 78).

Scheme 78



8-Aza-5,7-dimethyl-2-trifluoroacetylchromone (**133**) reacts with 1,2-diamines — ethylenediamine, 2,3-diaminonaphthalene, *o*-phenylenediamine and 2,3-diaminopyridine — in the same manner to give, respectively, 1,2,5,6-tetrahydropyrazine (**142**), benzo[*g*]quinoxaline (**143**), quinoxaline (**144**) and pyrido[2,3-*b*]pyrazine (**145**) derivatives (Scheme 79).[79]

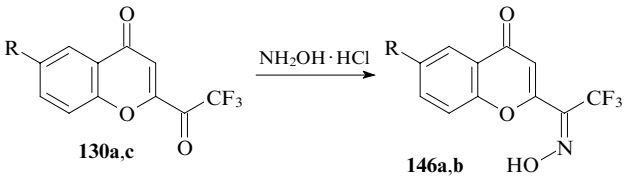
Scheme 79



X = CH (**144**, 84% yield), N (**145**, 89%)

The reaction of chromones **130a**,**c** with hydroxylamine hydrochloride is not accompanied by pyrone ring opening and leads to *E*-oximes **146a**,**b** (Scheme 80).[80]

Scheme 80

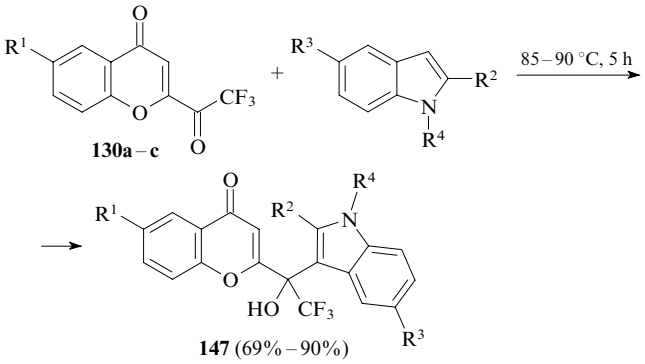


146: R = H (**a**, 83% yield), Cl (**b**, 90%)

V.2.b. Reactions with C-nucleophiles

Reactions of 2-trifluoroacetylchromones with C-nucleophiles have been described. In particular, compounds **130a – c** react with indole and its derivatives at 85 – 90 °C for 5 h (20 h in the case of 2-phenylindole) under solvent- and catalyst-free conditions to give (indol-3-yl)trifluoromethyl(chromon-2-yl)methanols **147** in moderate to high yield. This reaction can be treated either as nucleophilic addition at the trifluoroacetyl substituent of chromone or as Friedel — Crafts hydroxyalkylation of indoles (Scheme 81).[81]

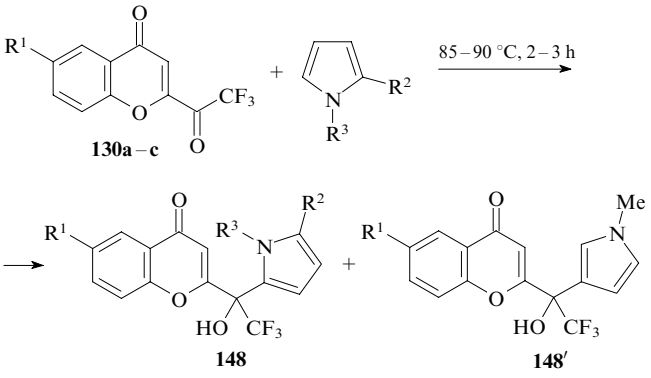
Scheme 81



R^1 = H, Me, Cl; R^2 = H, Me, Ph; R^3 = H, OMe; R^4 = H, Me

Pyrrole and its derivatives also enter into this reaction to give (pyrrol-2-yl)trifluoromethyl(chromon-2-yl)methanols **148** in 52% – 95% yield (Scheme 82).[81] In the case of *N*-methylpyrrole, small amounts (6% – 13%) of 3-substituted pyrroles **148′** are detected.

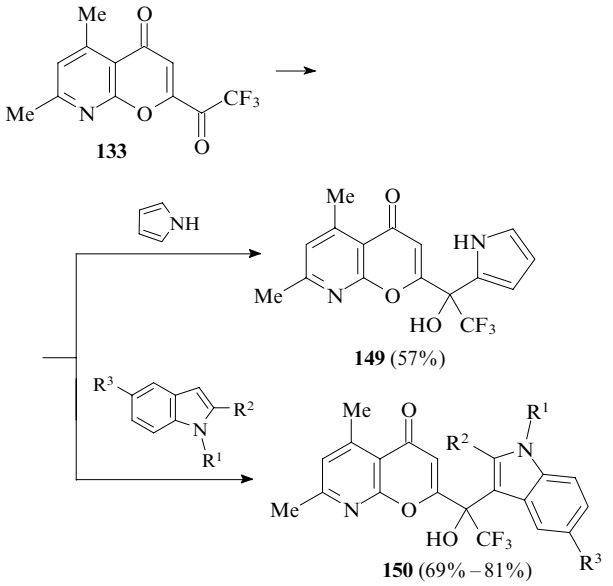
Scheme 82



R^1 = H, Me, Cl; R^2 = H, Ph; R^3 = H, Me

The analogous reaction of 8-aza-5,7-dimethyl-2-trifluoroacetylchromone (**133**) with pyrrole and indoles leads to adducts **149** and **150**, respectively (Scheme 83).[79]

Scheme 83



R^1, R^2 = H, Me; R^3 = H, OMe

VI. Conclusion

Thus, the most characteristic reaction for 2-acylchromones are reactions at the carbonyl group of the acyl substituent. In this case, the pyrone ring usually persists, and only a small part of reactions is accompanied by its opening due to the attack at the C(2) atom, followed by the formation of a new heterocyclic system. Based on 2-acylchromones, a number of methods have been developed for the preparation of 2-hetarylchromones, which are of interest to medicinal chemistry. In addition, analysis of the literature has shown that due to the increased activity of the carbonyl group of the acyl substituent, 2-acylchromones are often used in studying the reduction reactions and for synthesis of various biologically active molecules.

The electron-withdrawing trifluoromethyl group of 2-trifluoroacetylchromones significantly increases the reactivity of these compounds and makes them very promising substrates for subsequent transformations. However, unlike 2-trifluoromethylchromones[82, 83] and 3-trifluoroacetylchromones,[83, 84] chemical properties of which have been studied in sufficient detail, investigations of 2-trifluoroacetylchromones are just at their infancy. Nevertheless, it is already clear that such chromone derivatives behave in reactions with N- and C-nucleophiles as 1-CF_3-1,2-diketones with one protected carbonyl group, which is of undoubted interest for the preparation of various fluorine-containing heterocycles with biological activity.

In general, it can be concluded that the chemical properties of 2-acylchromones have not been fully studied to date, and their synthetic potential has been only partially elucidated. We hope that this review can serve as an additional impetus for the further development of the chemistry of 2-substituted chromones.

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