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Synthesis and properties of 3-nitro-2*H*-chromenes

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Abstract. Methods of synthesis and chemical properties of 3-nitro-2*H*-chromenes, including reactions with nucleophiles, cycloaddition, oxidation and reduction, have been reviewed. Enantioselective reactions involving 3-nitro-2*H*-chromenes, as well as the stereochemistry of the products, are discussed. The ways of practical use of these compounds are shown. The bibliography includes 115 references.

I. Introduction

3-Nitro-2*H*-chromenes (3-nitro-2*H*-1-benzopyrans), oxygen-containing heterocycles related to conjugated nitroalkenes, are highly reactive organic compounds, which have been extensively studied in recent years. The first report on the synthesis of one of the representatives of this family dates back to 1938;[1] however, systematic study of the chemical properties of 3-nitro-2*H*-chromenes began only in the 1970s. Nowadays, these studies continue to dynamically develop. This is due to the advent of simple methods of synthesis of 3-nitro-2*H*-chromenes from available salicylaldehydes and nitroalkenes and the discovery of useful properties of both nitrochromenes *per se* and the product of their reactions.

Owing to the availability and high reactivity of 3-nitro-2*H*-chromenes, as well as to the fact that many chromene and chromane (3,4-dihydro-2*H*-1-benzopyran) derivatives are widely distributed in the plant kingdom and have proven to be pesticides and promising medications,[2–4] interest in these compounds as starting substrates for production of more complex biologically active molecules is quite natural. Indeed, in the last twelve years, the number of publications dealing with 3-nitro-2*H*-chromenes and their enantiomerically pure forms increased almost fivefold as compared with the entire previous period. At the same time, no specialized reviews or monographs addressing these representatives of the chromene system are available. The known monograph by Ono,[5] in which synthetic aspects of the chemistry of nitro compounds have been comprehensively considered, as well as the recent review,[6] present information only on the methods of synthesis of some 3-nitro-2*H*-chromenes, including optically active compounds.

In the present review, we have systematized available literature data on the synthesis, chemical properties, and application of 3-nitro-2*H*-chromenes. Their methods of synthesis can be divided into three major groups. The first and the largest group includes condensation of salicylaldehydes or their imines with unsaturated nitro compounds (nitroalkenes, β-nitroenamines, β-nitroacetaldehyde dialkyl acetals). The second group of methods is based on modification of the already existing 2*H*-chromene skeleton by nitration of the double bond of the pyran ring. These methods are especially appropriate when natural compounds (for example, precocene or acronycine) are used for synthesizing 3-nitro-2*H*-chromenes. The third approach relies on the modification of the basic 3-nitro-2*H*-chromene structure by introducing a substituent into the 2-position (for example, by transamination) or into the chromene aromatic ring (for example, by nitration).

The reactivity of 3-nitro-2*H*-chromenes is mainly determined by the nitroalkene moiety; however, the substituent in the 2-position bonded to the sp^3-hybridized carbon atom can have a significant effect on the rate and direction of some reactions. Taking into account this fact, we divided our review into three sections. The first section deals with 2-unsubstituted 3-nitro-2*H*-chromenes and their poorly studied 2-amino and 2-alkoxy derivatives; the second section focuses on the chemistry of 2-alkyl- and 2-aryl-3-nitro-2*H*-chromenes, and the third section summarizes the results of studying 2-trifluoromethyl- and 2-trichloromethyl-3-nitro-2*H*-chromenes obtained by our team. The ways of

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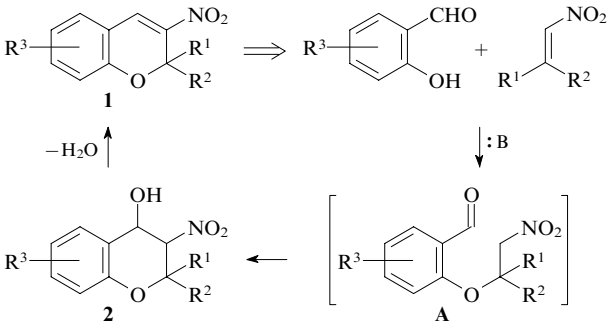
practical application of various 3-nitro-2*H*-chromene derivatives, although not widely implemented yet, are also discussed in this review in order to provide maximum possible information on this class of compounds.

II. 2-Unsubstituted and 2-amino(alkoxy)-3-nitro-2*H*-chromenes

1. Synthesis from salicylaldehydes and nitroalkenes

Synthesis of 3-nitro-2*H*-chromenes **1** by the reaction of salicylaldehydes with conjugated nitroalkenes in the presence of a base is most frequently used among the known methods for the preparation of these heterocycles, since the reagents (aliphatic and aromatic nitroalkenes) are relatively easily available. The synthesis occurs *via* tandem nucleophilic addition – Henry condensation: a phenolate anion is nucleophilically added to the nitroalkene molecule to give intermediate **A**, which undergoes intramolecular condensation into 4-hydroxy-3-nitrochromane **2**. The ease of further dehydration resulting in target product **1** is determined by different factors discussed below. This approach can be used for synthesizing a wide series of nitrochromenes **1** containing different substituents both in the 2-position of the pyran moiety and in the aromatic ring (Scheme 1).

Scheme 1

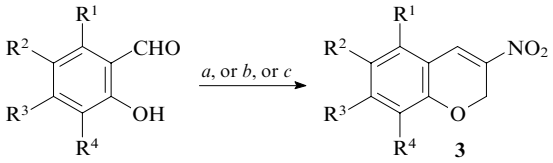


: B is base

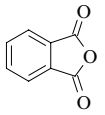
2-Unsubstituted 3-nitro-2*H*-chromenes **3** were synthesized for the first time in good yields from salicylaldehydes and 2-nitroethanol in the presence of dibutylamine hydrochloride in boiling isoamyl acetate for 5.5 – 8 h (Scheme 2, conditions *a*).[7] In addition, there are two versions of this method with the use of nitroethylene, which is either prepared immediately before the synthesis (conditions *b*)[8] or generated *in situ* through dehydration of 2-nitroethanol under the action of phthalic anhydride in boiling toluene (conditions *c*).[8–10] In both cases, the reaction is catalyzed by dibutylamine; in the presence of diisopropylamine or 1,4-diazabicyclo[2.2.2]octane (DABCO), the reaction leads to the partial or complete polymerization of nitroethylene (Scheme 2).

Naphthopyran nitro derivatives **4** and **5** have been synthesized in high yield from corresponding hydroxynaphthaldehydes and nitroethylene, prepared *in situ* from 2-nitroethanol in the presence of dibutylamine hydrochloride (Scheme 3).[8, 11]

Scheme 2

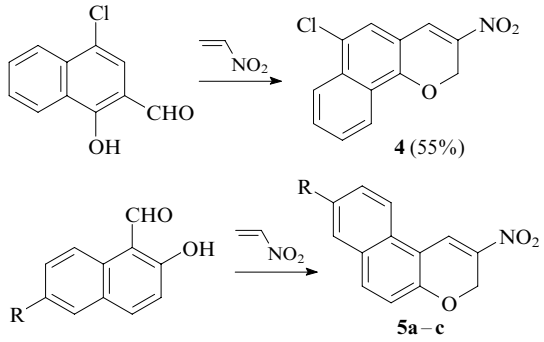


(*a*) $HO(CH_2)_2NO_2$, $Bu^n_2NH \cdot HCl$, iso-$C_5H_{11}OAc$, Δ;
(*b*) $H_2C{=}CHNO_2$, Bu^n_2NH, $CHCl_3$, 80 °C, 24 h;

(*c*) $HO(CH_2)_2NO_2$, Bu^n_2NH, PhMe,  , Δ, 12 h

R^1	R^2	R^3	R^4	Yield of **3** (%)		
				a	*b*	*c*
H	H	H	H	50	–	–
H	NO_2	H	H	45	–	–
H	Cl	H	H	47	–	–
H	Br	H	H	45	50	–
H	Br	H	Br	46	–	–
H	MeO	MeO	H	–	72	–
MeO	H	MeO	H	54	55	–
H	H	H	MeO	67	77	85
H	H	H	EtO	–	–	64
H	Br	H	EtO	–	–	74
H	H	MeO	H	63	67	57
H	MeO	H	H	66	72	85
MeO	H	H	H	63	49	24
H	OCH_2O		H	–	–	78

Scheme 3

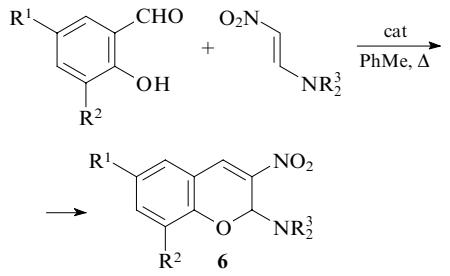


R = H (**a**, yield 52%), Br (**b**, 54%), MeO (**c**, 55%)

In the synthesis of 3-nitro-2*H*-chromenes, β-nitroenamines containing a tertiary amino group can act as a conjugated nitroalkene. 2-Dialkylamino-3-nitro-2*H*-chromenes **6** have been synthesized from salicylaldehydes and nitroenamines on heating in toluene for 15 h with the use of the related amine (R^3_2NH)[12] or *p*-toluenesulfonic acid as a catalyst (Scheme 4).[13]

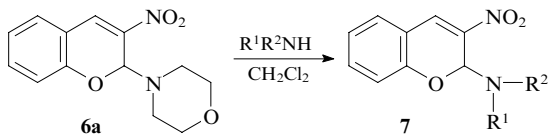
2-Arylaminochromenes **7** have been obtained in moderate yield by transamination of 2-morpholino-3-nitro-2*H*-chromene (**6a**) catalyzed by (+)-10-camphorsulfonic acid (Scheme 5).[14]

Scheme 4



R^1	R^2	R^3 or R^3-R^3	Yield of **6** (%)	Ref.
H	H	Me	18	12
Cl	H	Me	20	13
H	H	$(CH_2)_5$	31	12
MeO	H	$(CH_2)_5$	34	12
H	MeO	$(CH_2)_5$	31	12
Cl	H	$(CH_2)_5$	34	12
Br	H	$(CH_2)_5$	30	12
H	H	$(CH_2)_2O(CH_2)_2$	50	12
MeO	H	$(CH_2)_2O(CH_2)_2$	58	12
H	MeO	$(CH_2)_2O(CH_2)_2$	62	12
Cl	H	$(CH_2)_2O(CH_2)_2$	58	12
Cl	Cl	$(CH_2)_2O(CH_2)_2$	60	13
Br	H	$(CH_2)_2O(CH_2)_2$	50	12

Scheme 5

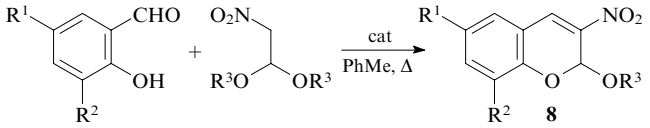


R^1	R^2	Yield of **7** (%)	R^1	R^2	Yield of **7** (%)
H	Ph	43	H	3-$MeOC_6H_4$	42
H	2-$O_2NC_6H_4$	12	H	4-$MeOC_6H_4$	24
H	3-$O_2NC_6H_4$	33	H	3,5-$(O_2N)_2C_6H_3$	21
H	4-$O_2NC_6H_4$	39	H	2,4-$(O_2N)_2C_6H_3$	53
H	2-$MeOC_6H_4$	55	CH=CH–CH=CH		28

2-Alkoxy-3-nitro-2*H*-chromenes **8** have been synthesized in low yield through condensation of β-nitroacetaldehyde dialkylacetals with salicylaldehydes in the presence of triethylammonium *p*-toluenesulfonate and triethylamine on heating for 1 h.[15] 2-Alkoxynitroethylenes presumably act intermediates (Scheme 6).

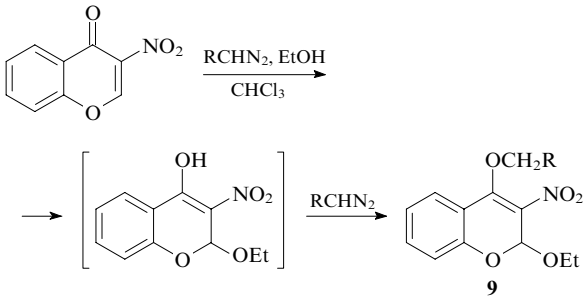
4-Alkoxy-3-nitro-2-ethoxy-2*H*-chromenes **9** have been synthesized by the reaction of 3-nitrochromone with diazoalkanes in chloroform containing 5% of ethanol.[16] It is assumed that diazo compounds, being bases, catalyze the nucleophilic addition of ethanol at the activated double bond of nitrochromone and then alkylate the intermediate enol (Scheme 7).

Scheme 6



R^1	R^2	R^3	Yield of **8** (%)	R^1	R^2	R^3	Yield of **8** (%)
H	H	Me	26	H	MeO	Et	28
H	Cl	Et	47	H	MeO	Pr^n	15
H	H	Pr^n	17	MeO	MeO	Me	13
MeO	H	Me	13	MeO	MeO	Et	18
MeO	H	Et	24	MeO	MeO	Pr^n	17
MeO	H	Pr^n	11	Cl	H	Me	13
H	MeO	Me	9	Cl	H	Et	8
				Cl	H	Pr^n	15

Scheme 7

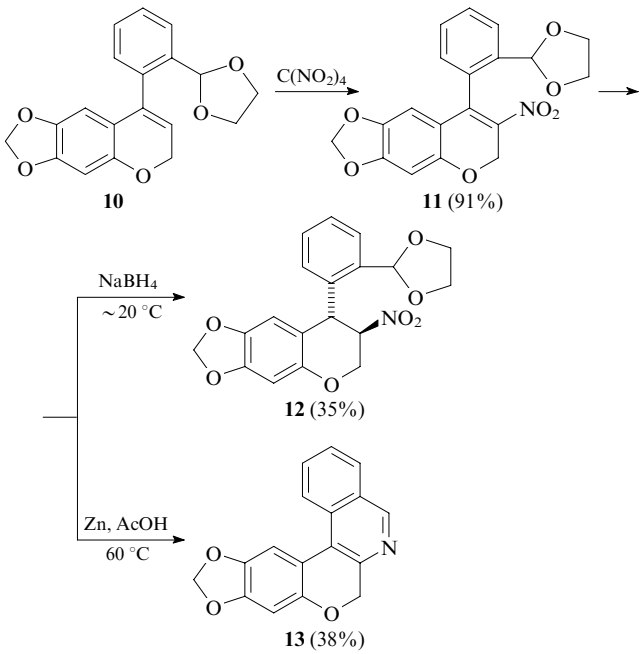


R = H (yield 17%), Me (18%)

2. Chemical properties and application

Selective nitration of the double bond in 2*H*-chromene **10** was accomplished by means of tetranitromethane in the pyridine – acetone system, which enabled the synthesis of nitrochromene **11** (Scheme 8).[17] With the aim of synthesizing doxanthrine (2,3-dihydroxy-6a,7,8,12b-tetrahydro-6*H*-

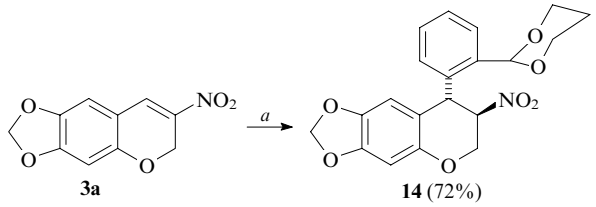
Scheme 8

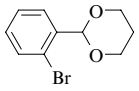


chromeno[3,4-*c*]isoquinoline), a known full agonist for the dopamine D1 receptor, the reduction of chromene **11** under different conditions was studied in the same work. It turned out that the reaction of **11** with sodium borohydride in ethanol yields nitrochromane **12** as an individual *trans* isomer, whereas the reduction of **11** with the Zn–AcOH system is accompanied by intramolecular heterocyclization and yields chromenoisoquinoline **13**, which is a precursor of doxanthrine (see Scheme 8).

2-Unsubstituted 3-nitrochromene **3a** stereoselectively adds to Grignard reagents. In particular, its reaction with arylmagnesium bromide with a protected aldehyde group leads to corresponding adduct **14** with *trans* arrangement of substituents in the pyran moiety (Scheme 9).[17]

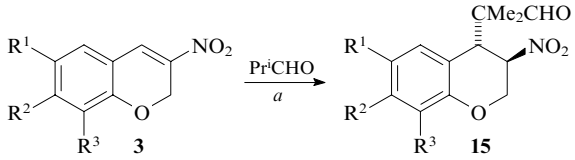
Scheme 9



(*a*) , Mg, THF, −78 °C

3-Nitrochromenes **3** add to isobutyraldehyde in the presence of racemic proline and sodium acetate to give *trans*-chromanes **15** in yields 20%–96% depending on the nature of the substituent in the aromatic ring (Scheme 10).[18]

Scheme 10

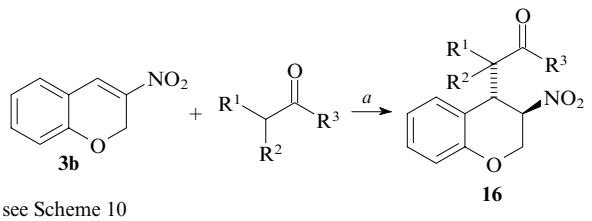


(*a*)  (20 mol.%), NaOAc (100 mol.%), MeOH, ~20 °C

R^1	R^2	R^3	Time /h	Yield of **15** (%)
H	H	H	5	96
H	H	MeO	6	92
H	MeO	H	6	89
MeO	H	H	6	85
Me	H	H	8	71
Cl	H	H	3	77
Br	H	H	2	81
Cl	H	Cl	2.5	40
Br	H	Br	4	31
NO_2	H	H	3.5	20

The reaction of the unsubstituted 3-nitrochromene (**3b**) with different aldehydes and ketonesc has been studied under the same conditions. The reaction produces compounds **16** in high yields, which also have the *trans* configurations of subsituents in the chromane ring. When $R^1 \neq R^2$, the reaction leads to two epimers that differ in the configuration of the exocyclic chiral centre (Scheme 11).[18]

Scheme 11

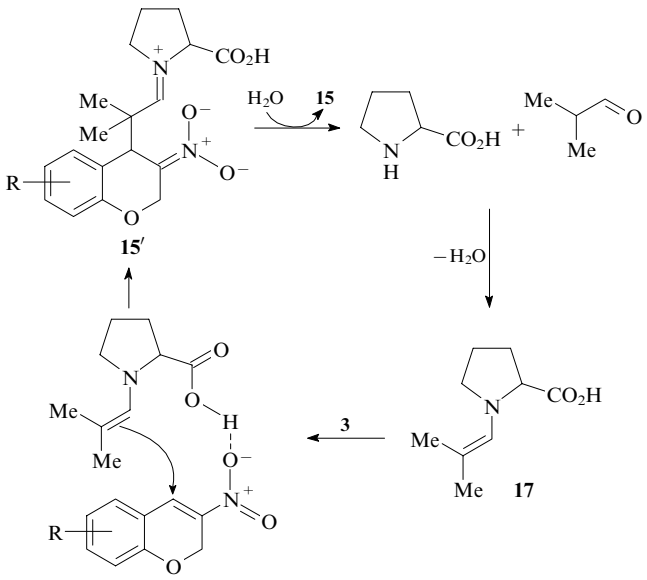


(*a*) see Scheme 10

R^1	R^2	R^3	Time /h	Yield of **16** (%)	Epimers (%)
H	H	H	18	20	
Me	H	H	0.1	90	71 : 29
Et	H	H	0.1	97	60 : 40
$(CH_2)_4$		H	5	88	
H	$(CH_2)_3$		5	92	84 : 16
H	$(CH_2)_4$		5	78	57 : 43
H	H	Me	5	56	
H	H	Ph	5	60	
H	MeO	Me	5	83	55 : 45
H	OH	Me	5	63	60 : 40

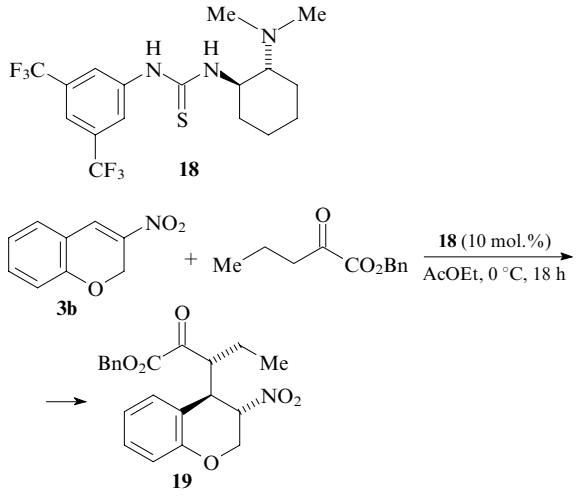
A probable mechanism of this catalytic reaction involves the formation of enamine **17** from proline and a carbonyl compound; this enamine activates chromene **3** through the formation of a hydrogen bond between the nitro and carboxyl groups in the transition state. The subsequent nucleophilic addition and hydrolysis of betaine intermediate **15′** afford product **15** and regeneration of the catalyst. The role of sodium acetate in this process is not completely clear, however, the decrease in its amount considerably reduces the yields of chromanes **15** and **16**. It is believed that sodium acetate promotes the formation of intermediate enamine **17** at the first stage of reaction (Scheme 12).

Scheme 12



The addition of benzyl-2-ketopentanoate to chromene **3b** in the presence of Takemoto's chiral catalyst **18** affords *anti*,*anti* isomer of keto ester **19** in 80% yield with 97% enantiomeric excess (Scheme 13).[19]

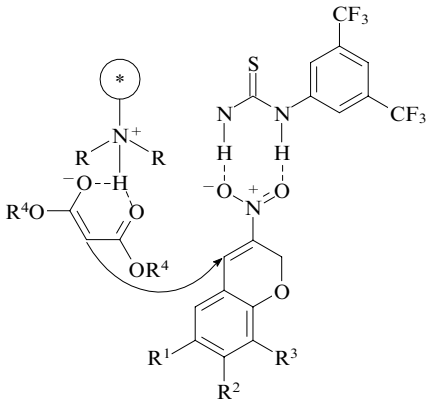
Scheme 13



The asymmetric nucleophilic addition of malonates to 2-unsubstituted nitrochromenes **3** in the presence of chiral catalysts has been studied.[20–22] To synthesize optically active chromanes **20**, Takemoto's catalyst **21**[20] or **22**[21] was used, and the reaction was carried in toluene at 0 °C. Under these conditions, products **20** were obtained in high yields (70% – 97%) and enantiomeric excesses (80% – 93%); in all cases, exclusively *trans* diastereomer was formed (Scheme 14). Under analogous conditions, 6- and 8-substituted *trans*-chromanes **20** were synthesized by the reaction of dimethyl and dibenzyl malonates with chromenes **3** catalyzed by chiral nickel complex **23** (81% – 96% yields, 80% – 95% *ee*) (see Scheme 14).[22]

The role of bifunctional Takemoto's catalysts is in activation of the substrate and reagent through the formation of hydrogen bonds between the functional groups of deprotonated malonate and nitrochromene and the corresponding amino groups of the catalyst in the transition state, so that the attack at the double bond with the nucleophile occurs on the sterically unhindered side (Scheme 15).

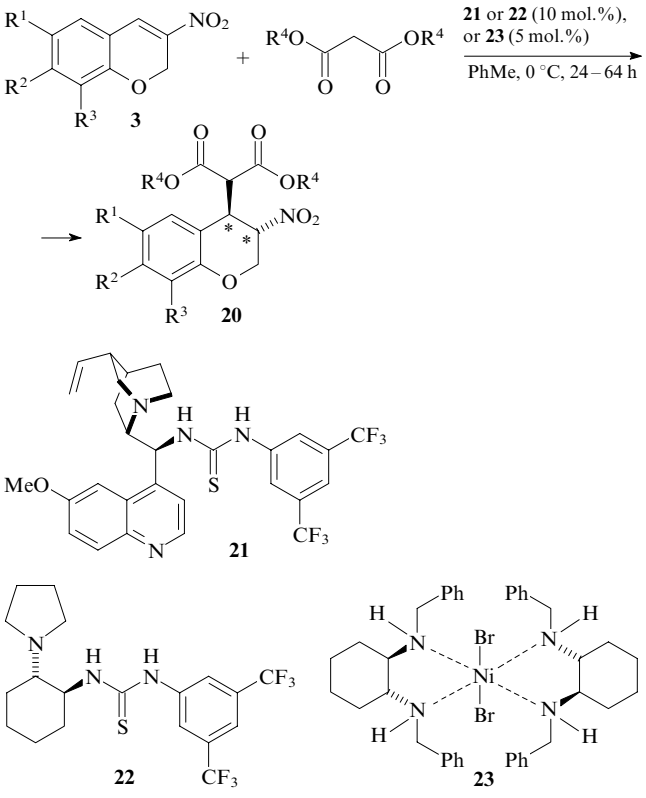
Scheme 15



An enantioselective Friedel – Crafts alkylation of indoles with nitrochromenes **3** has been described. To obtain optically active 4-(indol-3-yl)-3-nitrochromanes **24**, the reaction has been studied in the presence of catalysts based on Zn^{II} complexes with chiral organic ligands, a complex synthesized *in situ* from zinc triflate and diphenylamine derivative **25** being the best one.[23] The reaction was carried out in toluene at 0 °C for 46 – 60 h. These conditions were favourable for the predominant formation of (3*R*,4*S*)-*trans* isomer of chromanes **24**. The absolute configuration of the latter was confirmed by X-ray crystallography (Scheme 16).

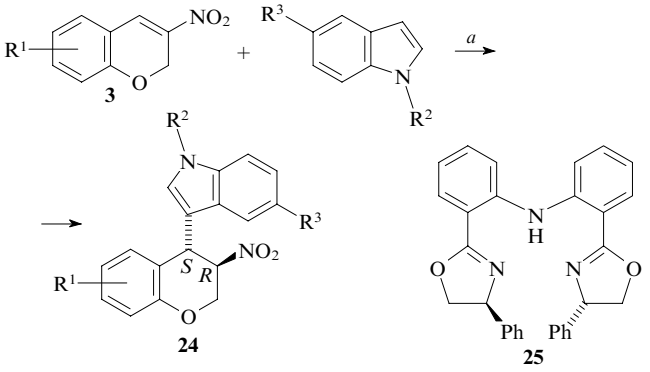
Reactions of [4 + 2]-cycloaddition are known in which 2-unsubstituted nitrochromenes **3** act as a dienophile. The enantio- and diastereoselective *endo*-[4 + 2]-cycloaddition of

Scheme 14



R^1	R^2	R^3	R^4	Yield of **20** (%)	*ee* (%)	Ref.
H	H	H	Me	86	88	20
H	H	H	Me	97	89	21
H	H	H	Et	50	87	21
H	H	H	Pr^i	71	91	21
H	H	H	Bn	88	85	20
Me	H	H	Me	82	81	20
Me	H	H	Me	73	89	21
Me	H	H	Bn	86	81	20
MeO	H	H	Me	78	82	20
MeO	H	H	Me	99	93	21
MeO	H	H	Bn	72	86	20
Br	H	H	Me	93	80	20
Br	H	H	Bn	84	84	20
Cl	H	H	Me	88	85	20
Cl	H	H	Me	85	88	21
Cl	H	H	Bn	82	85	20
H	MeO	H	Me	72	83	20
H	MeO	H	Me	74	88	21
H	MeO	H	Bn	70	87	20
H	H	Me	Me	84	80	20
H	H	Me	Bn	83	82	20
Br	H	Br	Me	94	87	21
Cl	H	Cl	Me	97	82	21

Scheme 16

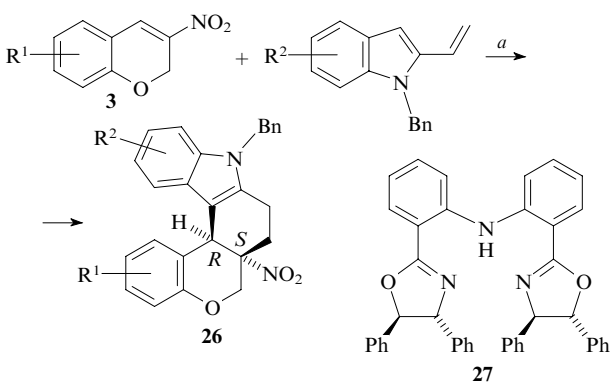


(*a*) $Zn(OTf)_2$ (5 mol.%), **25** (6 mol.%), PhMe, 0 °C

R^1	R^2	R^3	Yield of **24** (%)	*trans* : *cis*	*ee* (%)
H	H	H	80	89 : 11	94
6-Cl	H	H	80	88 : 12	83
6-Br	H	H	94	84 : 16	86
6-NO_2	H	H	80	90 : 10	54
8-MeO	H	H	84	89 : 11	89
8-EtO	H	H	92	92 : 8	88
6,8-Cl_2	H	H	90	90 : 10	83
6,8-Br_2	H	H	90	92 : 8	87
H	H	Me	88	94 : 6	92
H	H	MeO	92	91 : 9	93
H	H	Cl	68	82 : 18	62
H	Me	H	94	92 : 8	95

2-vinylindoles to chromenes **3** to form products **26** with the (6a*S*,13c*R*)-configuration has been described.[24] The addition is catalyzed by $Zn(OTf)_2$ and chiral ligand **27**. Diels–Alder adducts **26** were obtained in 82% – 94% yield, the diastereomeric excess of the 6a,13c-*cis* isomer was more than 90%, and the enantiomeric purity was 70% – 96%. The absolute configuration of compound **26** has been determined by X-ray crystallography (Scheme 17, locants at R^1 and R^2 are related to the initial compounds).

Scheme 17



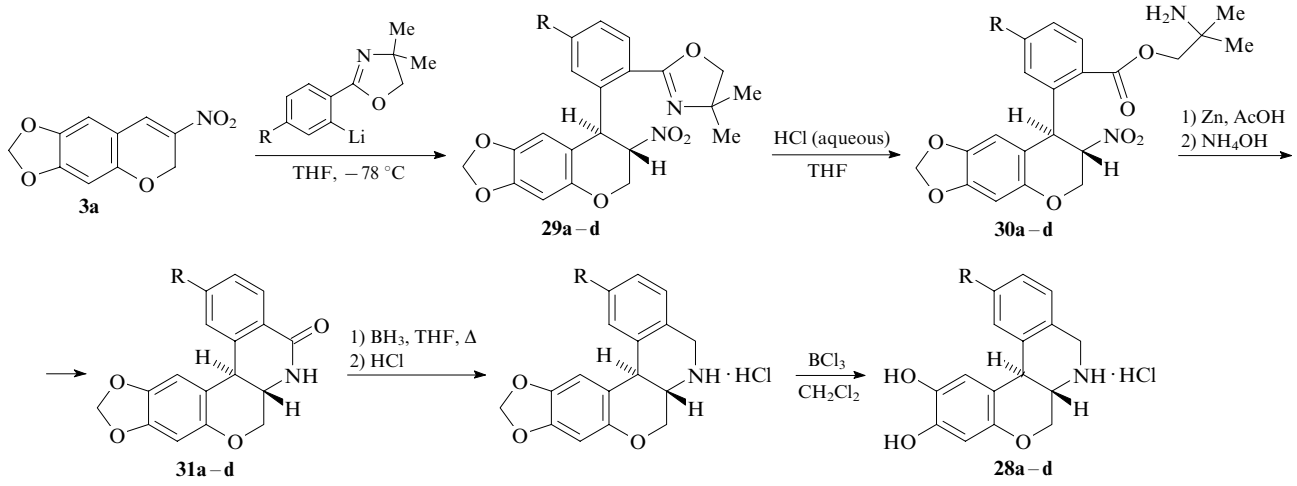
(*a*) $Zn(OTf)_2$ (10 mol.%), **27** (11 mol.%), PhMe, ~20 °C

R^1	R^2	Yield of **26** (%)	*ee* (%)	R^1	R^2	Yield of **26** (%)	*ee* (%)
H	H	92	92	8-MeO	H	82	92
6-F	H	90	89	6,8-Br_2	H	94	90
6-Cl	H	91	86	2-Naph	H	91	70
6-Br	H	90	86	H	5-F	93	78
6-Me	H	91	94	H	5-Cl	93	78
6-MeO	H	93	96	H	5-Me	92	92
7-MeO	H	91	75	H	5-MeO	91	94

Naph is naphthyl

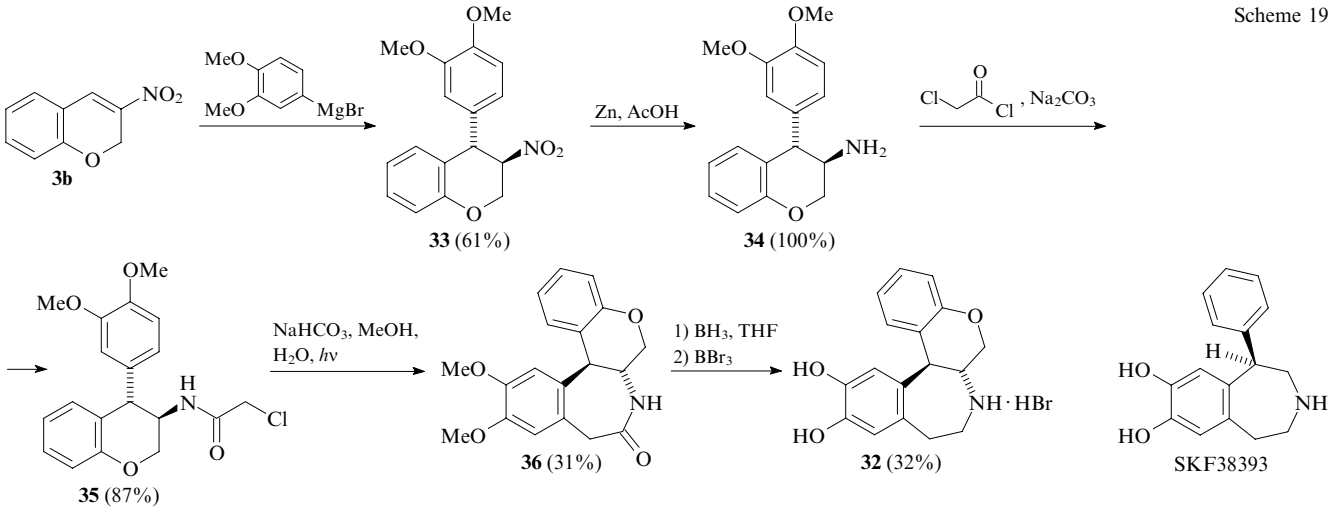
In recent years, studies have appeared focusing on synthesis of natural and biologically active compounds with the use of 2-unsubstituted 3-nitrochromenes. In particular, nitrochromene **3a** has been used to synthesize a series of analogues of doxanthrine (**28**, R = H) — a potent and selective synthetic agonist of dopamine D1-like receptors.[9] The reaction of **3a** with *o*-aryllithium salts of corresponding 2-aryloxazolines yields exclusively *trans* addition products **29a – d**, which are converted into amino esters **30a – d** through partial hydrolysis of the oxazoline ring. Then, the reduction of the nitro group in compounds **30** and subsequent intramolecular cyclization produce lactams **31a – d**;

Scheme 18



R = Me (**a**), Et (**b**), F (**c**), CF_3 (**d**)

Scheme 19



successive treatment of the latter with borane, dry HCl and anhydrous BCl_3 leads to hydrochlorides of target catecholamines **28a – d** with *trans* fusion of the chromane and tetrahydroisoquinoline systems (Scheme 18).

The synthesis of benzo[*d*]chromeno[3,4-*b*]azepine hydrobromide **32** — a conformationally restricted analogue of SKF38393, which is a dopamine D1-selective partial agonist, has been described.[25] To do this, at the first stage, 4-bromoveratrole-based Grignard reagent was stereoselectively added to nitrochromene **3b** to produce *trans*-nitrochromane **33**. The reduction of the nitro group in this compound with zinc powder in glacial acetic acid yielded quantitatively amine **34**, which was converted into chloroacetamide **35** through the treatment with chloroacetyl chloride. Then, amide **35** was photolyzed to lactam **36**, which was converted, as in the synthesis of compounds **28a – d**, into target product **32** by successive treatment with borane and anhydrous BBr_3 (Scheme 19).

6,7-Dimethoxy-3-nitro-2*H*-chromene (**3c**) has been used in synthesis of rotenoid munduserone (**37**), which is a natural insecticide.[26] The suggested synthetic route to munduserone uses, as initial components, relatively easily available nitrochromene **3c** and O-protected cyanohydrin **38**; the latter is obtained in two stages from 4-methoxysalicylaldehyde in 78% yield. The coupling reaction of chromene **3c** with cyanohydrin **38** gives a mixture of addition product **39** and dehydroadduct **40**. The treatment of this mixture first with dilute H_2SO_4 and then with triethtylamine leads to the isolation of ketone **41** and *cis*-12a-hydroxymunduserone (**42**). Treatment of these compounds with, respectively, 10% HCl and the Zn – AcOH reductive system leads to munduserone (**37**) in high yields (Scheme 20).

It has been recently shown that 2-unsubstituted 3-nitrochromenes **3** are efficient inhibitors of thioredoxin reductase (TRxR) and A549 carcinoma cells (Table 1).[27]

Successive treatment of 3-nitrochromene **3b** and its benzannelated analogue **5a** with sodium borohydride, hydrazine hydrate in the presence of Raney nickel and propyl iodide yields 3-*N*,*N*-dipropylaminochromanes **43** showing anxyolitic activity (Scheme 21).[28]

Scheme 20

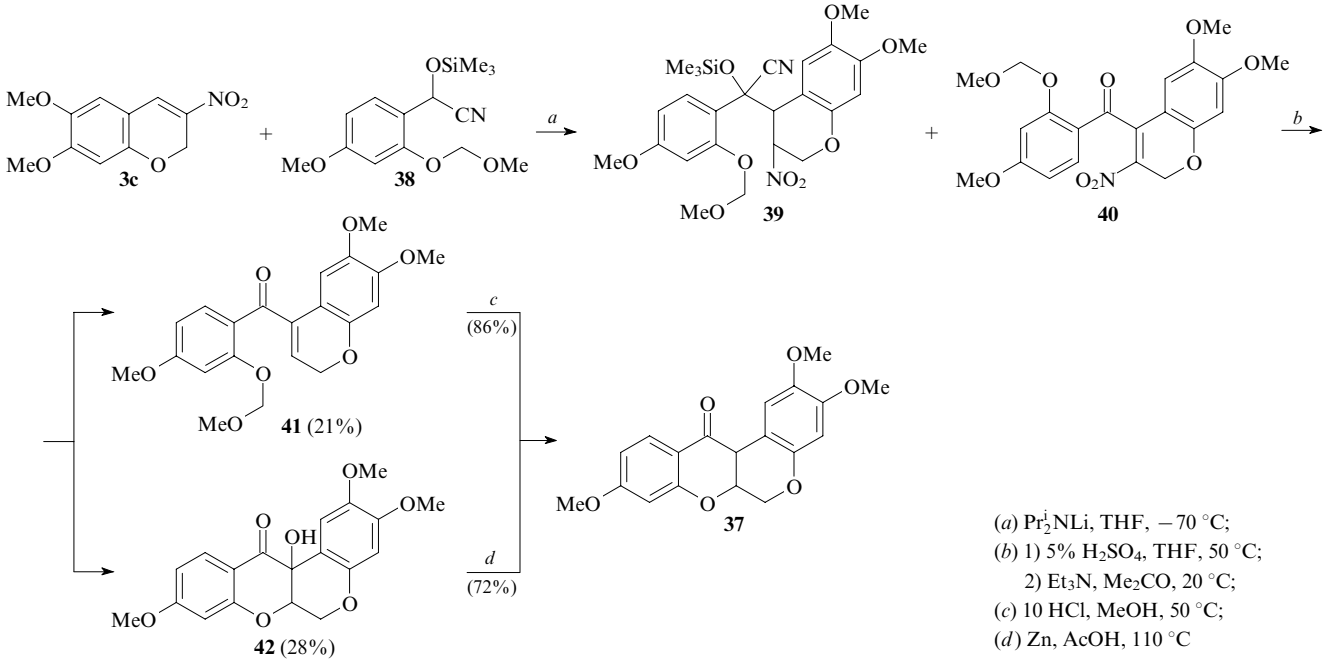
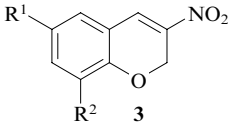


Table 1. Inhibition [a] of TRxR and A549 carcinoma cells with nitrochromenes **3**.[27]

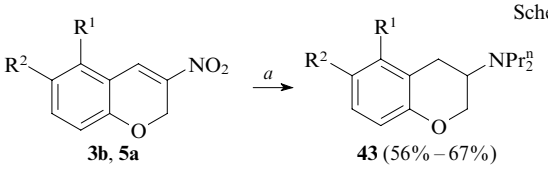


3

R^1	R^2	IC_{50} /μg ml^{-1}	
		TRxR	A549
H	H	4.01	5.84
F	H	1.68	1.42
Cl	H	2.18	1.52
Br	H	1.17	1.91
Cl	Cl	1.79	2.62
Br	Br	1.04	3.19
NO_2	H	2.41	1.81
MeO	H	2.82	5.64
H	MeO	4.52	10.46

[a] Here and hereinafter, half maximal inhibitory concentrations IC_{50} are given.

Scheme 21



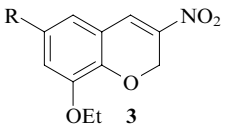
3b, **5a** **43** (56% – 67%)

$R^1 = R^2 = H$ (**3b**); $R^1 - R^2$ is benzo (**5a**);
(*a*) 1) $NaBH_4$, $CHCl_3 - Pr^iOH$ (35 : 1), SiO_2, ~20 °C;
2) Ni, N_2H_4, EtOH, 45°C; 3) Pr^nI, K_2CO_3, DMSO, 60 °C

Studying the antitumour activity of 3-nitro-8-ethoxy- and 6-bromo-3-nitro-8-ethoxy-2*H*-chromenes has shown that these compounds inhibit the proliferation of LP1 myeloma and K562 leukemia cells. The latter also exhibits antiproliferative activity against MDA-MB-231 breast tumour, B16 mouse melanoma and U87 human glioma cells (Table 2).[10]

In this study, it has been shown with the use of an inverted microscope that 6-bromo-3-nitro-8-ethoxy-2*H*-chromene taken in a concentration of 20 μmol litre^{-1}

Table 2. Inhibition [a] of cancer cell growth with nitrochromenes **3**.[10]

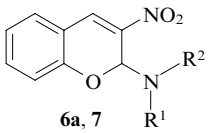


3

R	GI_{50} /μmol litre^{-1}				
	LP1	K562	MDA-MB-231	B16	U87
H	0.64	1.68			
Br	0.33	0.92	2.03	20.38	12.60

[a] Here and hereinafter, concentrations necessary to reduce the cell growth to 50% GI_{50} are given.

Table 3. Inhibition of phospholipase C in melanoma with nitrochromenes **6a** and **7**.[13]



6a, **7**

R^1	R^2	IC_{50} /μg ml^{-1}
$(CH_2)_2O(CH_2)_2$		5.0 ± 1.7
H	Ph	11.7 ± 0.4
H	2-$O_2NC_6H_4$	6.0 ± 0.1
H	3-$O_2NC_6H_4$	7.5 ± 2.3
H	4-$O_2NC_6H_4$	14.4 ± 3.1
H	2-$MeOC_6H_4$	4.5 ± 0.4
H	3-$MeOC_6H_4$	6.6 ± 0.2
H	4-$MeOC_6H_4$	12.9 ± 4.0
CH=CH–CH=CH		21.0

inhibits the proliferation of A549 lung cancer and HeLa uterine cervix cancer cells. In addition, it has been found that this compound also inhibits human umbilical vein epithelial cells migration and is a potential antimetastatic agent. 2-Aminochromenes **6a** and **7** have found to be inhibitors of phosphatidylinositol-specific phospholipase C of human melanoma cells (Table 3).[13]

III. 2-Aryl(alkyl)-3-nitro-2*H*-chromenes

1. Methods of synthesis and application

a. Tandem condensation of salicylaldehydes with nitroalkenes

Tandem condensation of salicylaldehydes with corresponding conjugated nitroalkenes is the most common method of synthesis of 3-nitro-2*H*-chromenes with an aryl or alkyl group in the 2-position. In particular, in synthesis of 2-aryl-3-nitro-2*H*-chromenes, easily available β-nitrostyrenes usually act as nitroalkenes.

In 1978, by keeping a mixture of salicylaldehyde (3 equiv.), β-nitrostyrene (1 equiv.) and triethylamine (0.2 equiv.) at room temperature for 16 h, Sakakibara *et al.*[29] obtained approximately equimolar amounts of 3-nitro-2-phenyl-2*H*-chromene (**44a**) and *trans,trans*-4-hydroxy-3-nitro-2-phenylchromane (**45a**, *tt*-isomer) in 69% yield. The presence of 4-hydroxychromane **45a** requires, as a rule, the introduction of additional purification stages, which complicates the isolation of the target product.

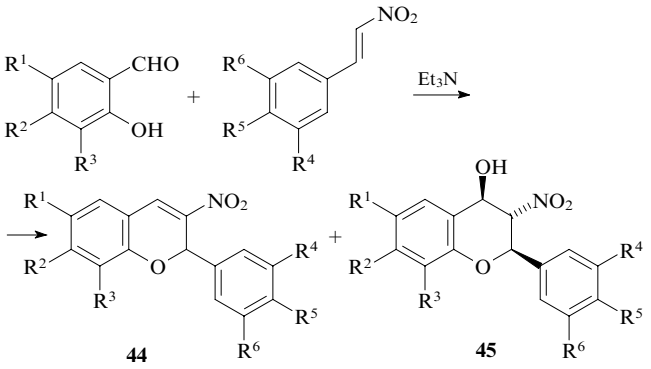
Later, this method, relying on the reaction of salicylaldehydes with conjugated nitroalkene under the action of triethylamine without heating and in the absence of a solvent, has been used for synthesizing a wide series of 2-aryl-3-nitro-2*H*-chromenes **44** in yields 27% – 81% (Scheme 22, Table 4).[30] Only in two cases was the formation of chromanols **45** ($R^1 = R^2 = R^3 = R^4 = R^6 = H$, $R^5 = H$ or Cl) in 30% yields observed in addition to chromenes **44**. The modified Sakakibara method,[31, 33, 34] in which the reactants were heated on a water bath for 30 min and then washed with water and the residue was recrystallized from ethanol, reduces the reaction time and results in complete dehydration of intermediate, 4-hydroxychromanes **45**. Rao *et al.*[32] prepared 6- and 7-methoxy-substituted chromenes **44** without impurities of 4-hydroxychromanes **45** by introducing triethylamine into a melt of equimolar

amounts of the reactants and keeping the reaction mixture at room temperature for 18 h.

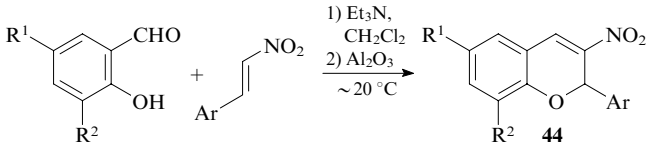
Basic alumina, as well as ultrasonication in the presence of Al_2O_3, has been successfully used for dehydration of intermediate chromanols **45** forming in synthesis of 2-aryl-3-nitro-2*H*-chromenes **44**.[35,36] This approach made it possible not only to reduce the reaction time to 2 – 4 h but also to carry out the reaction in one stage in the absence of a base and a solvent [37] (Scheme 23).

With the aim of studying biological activity, 2-aryl-3-nitro-8-ethoxy-2*H*-chromenes **44** have been synthesized in 74% – 87% yields from 3-ethoxysalicylaldehyde

Scheme 22



Scheme 23



R^1	R^2	Ar [a]	Yield of **44** (%)
H	H	Ph	84 (85) [b]
H	H	4-$MeOC_6H_4$	80
H	MeO	Ph	70 (76) [b]
H	MeO	4-$MeOC_6H_4$	84
H	H	3,4-$(EtO)_2C_6H_3$	68 [b]
H	MeO	3,4-$(EtO)_2C_6H_3$	42 [b]
Cl	H	Ph	68 (47) [b]
Cl	H	4-$MeOC_6H_4$	80
Cl	H	2-Th	73
Cl	H	3,4-$(MeO)_2C_6H_3$	78
H	H	1-Naph	78
H	MeO	1-Naph	84
H	H	2-Naph	75
H	MeO	2-Naph	74
Cl	H	1-Naph	75
NO_2	H	1-Naph	71

[a] Th is thienyl; [b] under ultrasonication (Ref. 37).

Table 4. Reaction conditions and yields of nitrochromenes **44**.

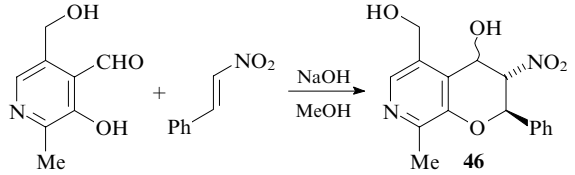
R^1	R^2	R^3	R^4	R^5	R^6	Time /h	Temperature /°C	Yield (%)	Ref.
H	H	H	H	H	H	16	20	42	30
H	H	H	H	H	H	0.5	100	65	31
H	H	H	H	Me	H	12	20	66	30
H	H	H	H	MeO	H	16	20	72	30
H	H	H	H	MeO	H	0.5	100	50	31
MeO	H	H	H	H	H	18	20	27	32
MeO	H	H	H	Me	H	18	20	33	32
MeO	H	H	H	MeO	H	18	20	29	32
H	MeO	H	H	H	H	18	20	76	32
H	MeO	H	H	Me	H	18	20	82	32
H	MeO	H	H	MeO	H	18	20	84	32
H	MeO	H	H	Cl	H	18	20	78	32
H	H	H	MeO	MeO	H	24	20	65	30
H	H	H	MeO	MeO	H	0.5	100	65	31
H	H	H	MeO	H	MeO	0.5	100	72	31
H	H	H	MeO	MeO	MeO	0.5	100	65	31
H	H	H	MeO	OH	H	24	20	51	30
H	H	H	H	BnO	H	0.5	100	70	31
H	H	H	OCH_2O		H	24	20	60	30
H	H	H	OCH_2O		H	0.5	100	65	31
H	H	H	H	Cl	H	2	20	45	30
H	H	H	H	Cl	H	0.5	100	60	31
H	H	MeO	H	H	H	20	20	see [a]	33
H	H	MeO	H	Me	H	20	20	see [a]	34
H	H	MeO	H	MeO	H	20	20	see [a]	34
H	H	H	EtO	EtO	H	20	20	see [a]	33
H	H	MeO	EtO	EtO	H	20 [b]	20	see [a]	33
H	H	MeO	H	Cl	H	20	20	see [a]	34
Cl	H	H	H	H	H	20	20	see [a]	33
NO_2	H	H	H	H	H	20	20	see [a]	33

[a] The yield was not given; [b] in dichloromethane.

(1 equiv.) and corresponding nitrostyrenes (1.2 equiv.) in the presence of L-proline (0.5 equiv.) as a catalyst and triethylamine (0.2 equiv.) as a cocatalyst upon refluxing in toluene for 24 h.[10] In addition, 2-aryl- and 2-alkyl-substituted 3-nitro-2*H*-chromenes have been synthesized in high yields by treating a mixture of the corresponding salicylaldehyde and nitroalkene with neutral alumina (1 g per 1 mmol aldehyde) at 50 °C in the absence of a solvent; alumina was preliminarily activated by microwaving (500 W) for 4 min.[38] A wide series of 2-aryl- and 2-hetaryl-3-nitro-2*H*-chromenes have been obtained by carrying out the reaction in pyridine at room temperature for 48 h.[39]

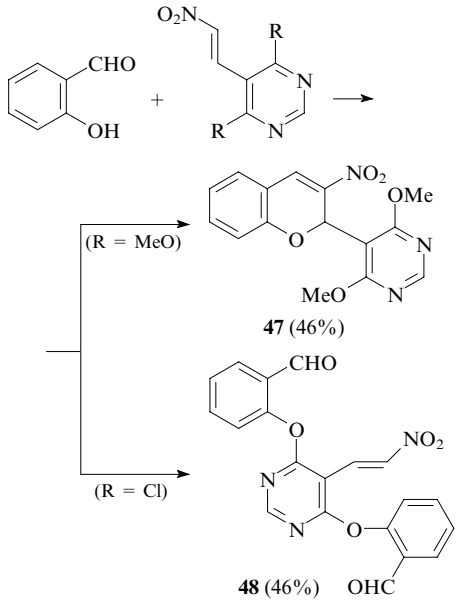
It is interesting that the reaction of pyridoxal hydrochloride with β-nitrostyrene in an aqueous methanol medium stops at the stage of azachromanol **46** forming as a mixture of *trans*,*cis* and *trans*,*trans* diastereomers in the 59 : 41 ratio (overall yield 49%). As distinct from carbon analogues **45**, azachromanol **46** is not dehydrated under acidic conditions (HCl, H_2SO_4, *p*-toluenesulfonic acid) (Scheme 24).[40]

Scheme 24



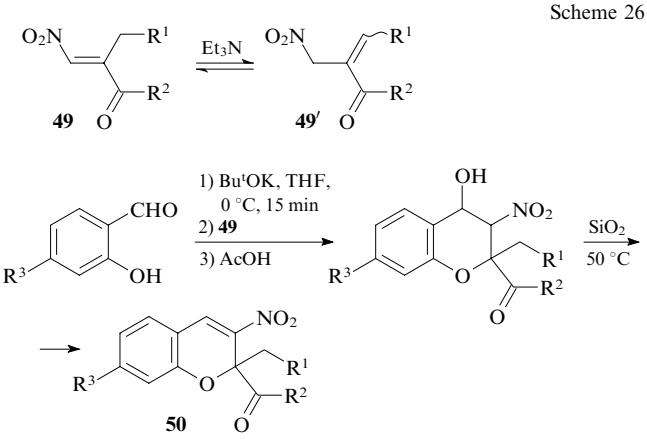
Nitrochromene **47**, which was not obtained with the use of triethylamine as a base, was synthesized from 4,6-dimethoxy-5-(2-nitrovinyl)pyrimidine and salicylaldehyde in DMSO in the presence of sodium 2-formylphenoxide (1.4 equiv.). The reaction of 5-(2-nitrovinyl)-4,6-dichloropyrimidine under analogous conditions occurred with substitution of two halogen atoms to give product **48** (Scheme 25).[29]

Scheme 25



An attempt to use nitroalkenes **49** for synthesis of 2-alkyl-2-acyl-3-nitro-2*H*-chromenes **50** in the presence of triethylamine as a base was unsuccessful since, under given conditions, alkenes **49** isomerized into nitroenones **49′**. Chromenes **50** have been obtained only by successive treatment of corresponding aldehydes with potassium *tert*-butoxide, nitroalkene **49**, acetic acid and silica gel (Scheme 26).[41]

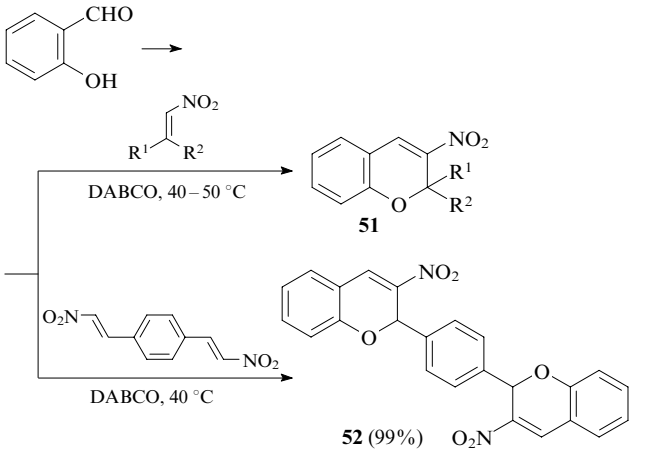
Scheme 26



R^1	R^2	R^3	Yield of **50** (%)	R^1	R^2	R^3	Yield of **50** (%)
H	Me	H	95	H	Me	Br	70
H	Et	H	91	H	Et	Br	66
Me	Me	H	87	Me	Me	Br	68
$(CH_2)_4$		H	54	$(CH_2)_4$		Br	30

The synthesis of 2-mono- and 2,2-disubstituted 3-nitro-2*H*-chromenes, including those containing the spiro C(2) atom, catalyzed by DABCO has been described [nitroalkene, salicylaldehyde (4 – 10 equiv.), DABCO (0.5 – 1 equiv.), without solvent — a modification of the Sakakibara method[29]].[42,43] It should be noted that DABCO surpasses triethylamine in selectivity and yields (75% – 99% for 2-aryl-3-nitro-2*H*-chromenes **44,** Ar = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-Th). Under analogous conditions, 2,2-disubstituted chromenes **51** and bis(nitrochromene) **52** form in yields from 31% to 99% (Scheme 27).[43]

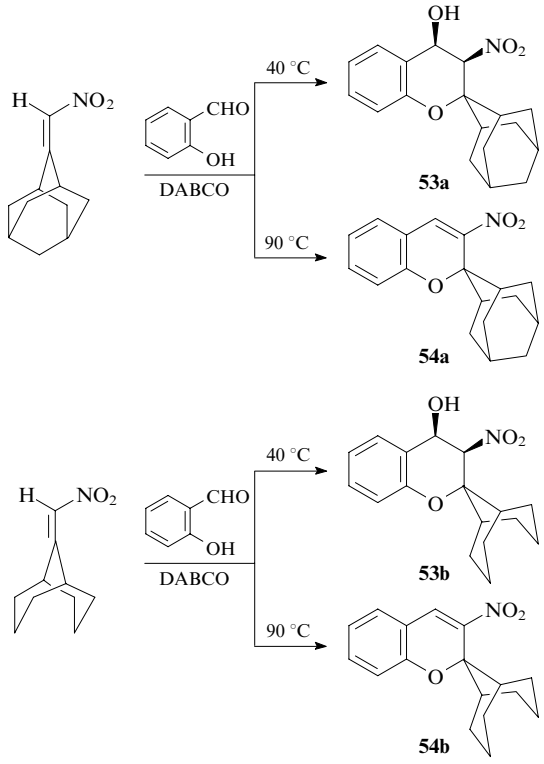
Scheme 27



R^1	R^2	Temperature /°C	Time /h	Yield of **51** (%)
Me	H	20	28	56
Me	Me	40	37	99
Me	CH_2CH_2Ph	40	16	32
Me	Bu^n	40	21	31
Ph	Ph	50	41	98

Under the above conditions, sterically hindered nitroalkenes formed only chromanols **53a**,**b**; the *cis* configuration of the latter was confirmed by X-ray crystallography. However, an increase in the reaction temperature to 90 °C afforded 2,2-dialkyl-3-nitrochromenes **54a**,**b** containing a spiro carbon atom. The higher resistance of 4-hydroxychromanes **53** to dehydration is, according to the authors, caused by the steric effect of the bulky substituent in the 2-position (Scheme 28).

Scheme 28

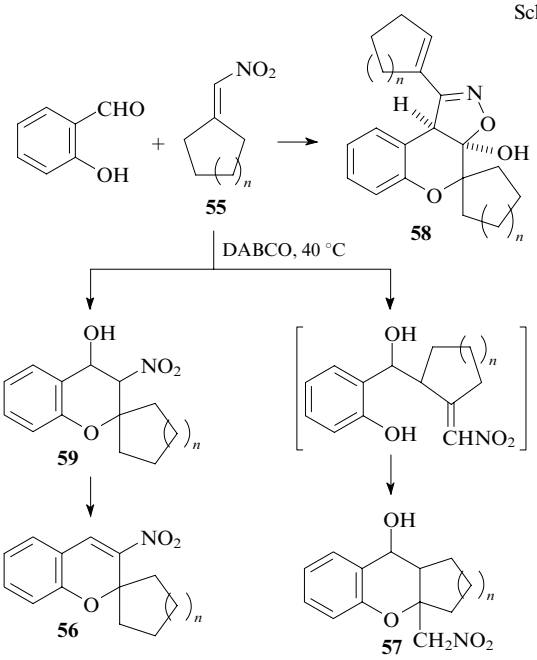


Product	Time /h	Yield (%)	Product	Time /h	Yield (%)
53a	15	96	**54a**	52	74
53b	7	98	**54b**	71	89

This method has limitations. In particular, an attempt to synthesize, from nitromethylenecycloalkanes **55**, 2-spironitrochromenes **56** led to a mixture of four products **56** – **59** structurally characterized by NMR. The formation of fused chromanol **57** is due to the increased CH-acidity of conjugated nitroalkenes **55** and their ability to act as a C-nucleophile in the presence of a base. Isoxazolines **58** are the products of interaction of spiro nitrochromenes **56** with nitrile oxides forming *in situ* from initial alkenes **55** (Scheme 29).[43]

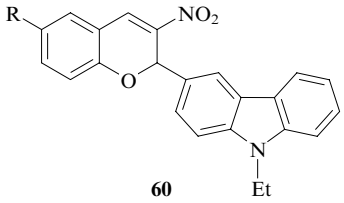
3-(3-Nitrochromen-2-yl)carbazole **60** was synthesized from β-nitrovinylcarbazole and corresponding salicylaldehydes in the presence of DABCO; the structure of the derivative with R = Br has been confirmed by X-ray crystallography.[44] Under similar conditions, bis(chromenyl)carbazoles **61** have been obtained as a mixture of two diastereomers; the concentration ratio between them has been determined by ^{1}H NMR. The reaction was carried out in an aldehyde medium at 70 °C for 30 min; at higher temperatures, 3,6-bis(β-nitrovinyl)carbazole polymerized.

Scheme 29

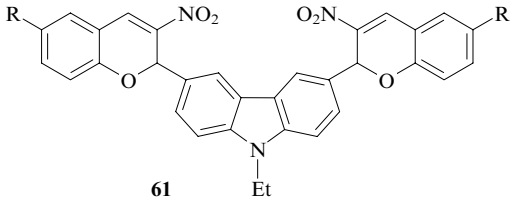


n	Yield (%)			
	56	**57**	**58**	**59**
1	12	51	4	24
2	14	–	22	8
3	traces	58	12	–

Structures **61**, **62**



R = H (yield 95%), MeO (100%), Me (85%), Br (79%), Cl (75%)

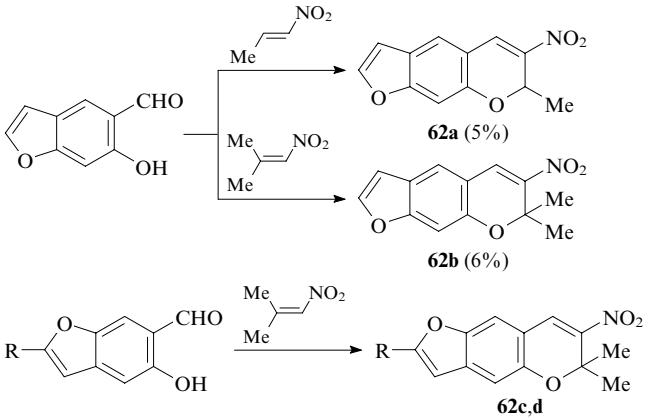


R = H (yield 90%, *dr* = 70 : 30), MeO (95%, 55 : 45), Me (80%, 80 : 20), Br (75%, 58 : 42), Cl (70%, 60 : 40)

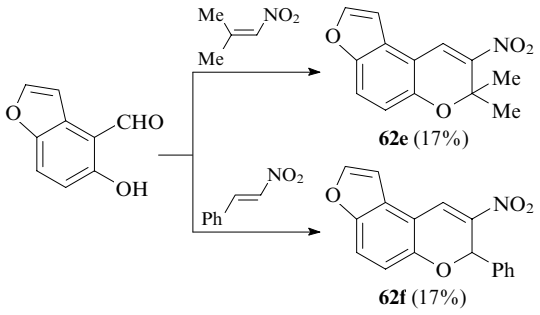
Six furochromenes **62a** – **f** have been synthesized in low yields from 6(5)-hydroxybenzo[*b*]furan-5(6)-carbaldehydes and 5-hydroxybenzo[*b*]furan-4-carbaldehyde and corresponding nitroalkenes in the presence KOH upon heating in different solvents.[45] Furochromenes **62** exhibit photosensitizing properties, their photodynamic effect depending on the presence of oxygen in a medium (Scheme 30).

The reaction of 7-hydroxy-2,2-dimethyl-6-formylchromane, 2-hydroxy-1-naphthaldehyde and β-nitrostyrenes in the presence of triethylamine at 100 °C for 30 min yields

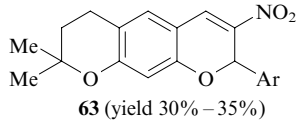
Scheme 30



R = H (**c**, yield 3%), Me (**d**, 11%)

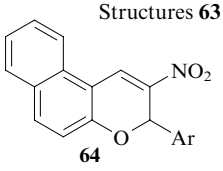


Structures **63** – **65**



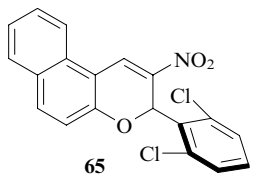
63 (yield 30% – 35%)

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$



64

Ar = Ph (yield 75%), 4-MeC_6H_4 (70%), 4-$MeOC_6H_4$ (72%), 3,4,5-$(MeO)_3C_6H_2$ (65%)



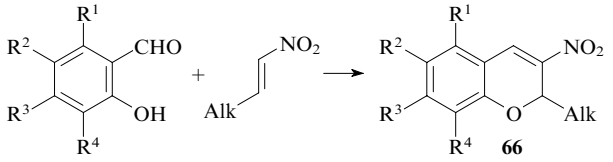
65

fused 2-aryl-3-nitro-2*H*-chromenes **63** and **64**.[46,47] Nitrochromene **65** acts as an inhibitor of TRPM7 protein regulating the magnesium ion concentration in cells and is a potential medication for ischemia treatment.[48]

In 1977, René *et al.*[49] described for the first time the synthesis of a wide series of 2-alkyl-2*H*-chromenes **66** from salicylaldehydes and 1-nitro-2-alkylethylenes (Scheme 31). These compounds exhibited inhibitory activity against *Staphylococcus aureus* (IC_{50} = 1 – 50 μg litre^{-1}), *Escherichia coli*, *Trichomonas vaginalis* and dysenteric amoeba *Entamoeba histolytica*. It has been shown that the inhibitory effect of a chromene depends on the length and bulk of the alkyl moiety, as well as on the nature of the substituent in the 6-position. In addition to the above kinds of activity, 6-bromo-2,2-dimethyl-3-nitrochromene exhibits antihelminthic activity.[49]

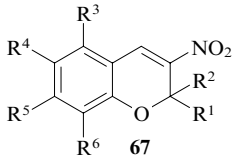
3-Nitro-2*H*-chromenes **67** exhibit radioprotective properties, their activity being independent of the presence of an alkyl or aryl group at the C(2) atom, or of the nature and position of the halogen atom or methoxy group.[50]

Scheme 31



R^1, R^2, R^3, R^4 = H, Me, MeO, Cl, Br, I, NO_2;
Alk = Me, Pr^n, n-C_6H_{13}, n-$C_{11}H_{23}$, $CHEt_2$, CH(Me)CH(Me)Et

Structures **67**

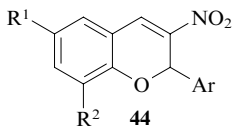


R^1 = H, Me; R^2 = Me, Ph;
R^3 = H, MeO; R^4 = MeO, Cl, Br;
R^5 = R^6 = H, MeO

2-Arylchromenes **44**,[30 – 39,51] which simultaneously contain electron-releasing and electron-withdrawing substituents in a common π-conjugated electronic system, are potential organic materials with second-order nonlinear optical properties. The latter can be used in development of laser telecommunications, optical storage devices and optical information processing devices. Ono *et al.*[35] studied the efficiency of second harmonic generation (SHG) in a series of such compounds by the powder method. Urea was used as a reference for estimating the SHG efficiency. The results listed in Table 5 show that the SHG efficiency of the last two chromenes is, respectively, 62 and 43 times higher than that of urea, which is a very good characteristic.

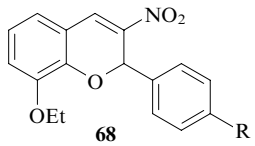
Many 2-aryl-substituted 3-nitro-2*H*-chromenes **44** are modulators of tyrosine kinase signal transduction and are capable of regulating, modulating and/or inhibiting cell proliferation. Pharmaceuticals based on these compounds can be used for treatment of cancer, fibrosis, psoriasis, atherosclerosis, arthritis and other diseases caused by rapid proliferation of pathogenic cells or by metabolic disorders.[39] Halogen derivatives of chromenes **44** are potential medications for infections caused by bacterium *Helicobacter pylori*, in particular, gastroduodenal ulcer.[52]

Table 5. Second harmonic generation efficiency of chromenes **44**.



R^1	R^2	Ar	SHG efficiency
H	H	Ph	0
H	H	4-$MeOC_6H_4$	0.013
H	MeO	Ph	0
H	MeO	4-$MeOC_6H_4$	0
Cl	H	Ph	0.091
Cl	H	3,4-$(MeO)_2C_6H_3$	0.013
Cl	H	4-$MeOC_6H_4$	62
Cl	H	2-Th	43

Table 6. Inhibition of tumour cell growth by nitrochromenes **68**.[10]



68

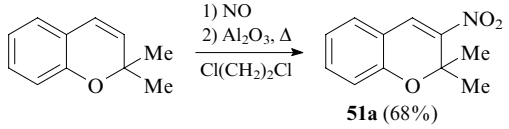
R	GI_{50} /μmol litre^{-1}				
	LP1	K562	MDA-MB-231	B16	U87
H	0.96	1.18			
CN	0.44	1.02			
MeO	3.16	4.86			
F	0.57	1.24	8.53	23.28	18.72

Study of antitumour activity of compounds **68** has shown that all of them inhibit the proliferation of LP1 myeloma and K562 leukemia cells. Nitrochromene **68** (R = F; S14161) also exhibits antiproliferative activity against MDA-MB-231 breast tumour, B16 mouse melanoma and U87 human glioma cells (Table 6).[10] Study of the mechanism of *in vivo* antitumour activity of compound S14161 has shown that it inhibits the activity of phosphoinositide 3-kinase and thus suppresses human myeloma and leukemia cell proliferation.[53]

b. Nitration of 2*H*-chromenes

The use of different nitrating agents enables the introduction of the nitro group into both the 3-position of 2*H*-chromenes and the aromatic ring of 3-nitro-2*H*-chromenes. Selective nitration of the double bond in 2,2-dimethylchromene leads to 3-nitrochromene **51a**, which is obtained by successive treatment with nitrogen monoxide at room temperature and then, for dehydration of the intermediate nitrochromanol, with acidic alumina with boiling for 30 min (Scheme 32).[54]

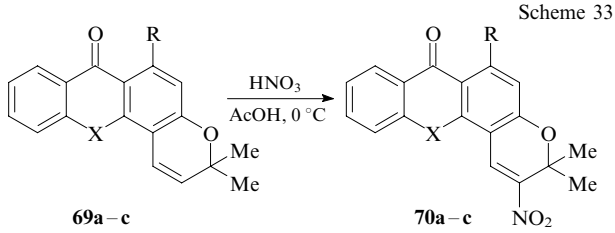
Scheme 32



51a (68%)

Nitration of pyranoacridone alkaloids acronycine (**69a**) and 6-demethoxyacronycine (**69b**) with nitric acid in glacial acetic acid at 0 °C afforded 2-nitroacronycine (**70a**) and 2-nitro-6-demethoxyacronycine (**70b**) in 90% and 49% yields, respectively.[55] Under similar conditions, chromene **69c** has been converted into nitro derivative **70c** in 56% yield (Scheme 33).[56]

Scheme 33



69a – c **70a – c**

X = NMe: R = MeO (**a**), H (**b**); X = O, R = OH (**c**)

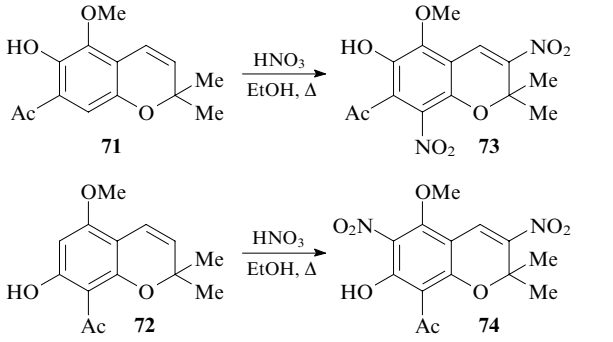
2-Nitroacronycine (**70a**) and 2-nitro-6-demethoxyacronycine (**70b**) are more cytotoxic against L1210 leukemia cells as compared to analogues without a nitro group **69a** and **69b**, respectively; in particular, the inhibitory effect of 2-nitroacronycine (**70a**) is 300-fold higher than that of acronycine (**69a**).[55]

Compound	IC_{50} /μg ml^{-1}
69a	27
69b	29.9
70a	0.09
70b	13.7

It has also been shown that 2-nitroacronycine (**70a**) exhibits antimalarial activity[57] and is toxic against milkweed bug, *Oncopeltus fasciatus*.[58]

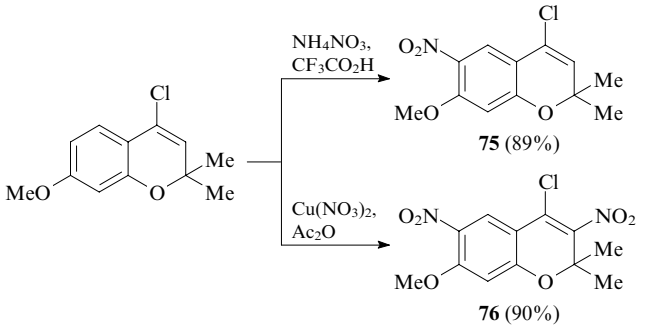
Treatment of evodionol[59] (**71**) and allevodionol[60] (**72**) with 68% nitric acid on heating in ethanol leads to the nitration of both the pyran ring and the aromatic ring, yielding dinitro derivatives **73** and **74**, respectively (Scheme 34).

Scheme 34



Information on 4-substituted 3-nitro-2*H*-chromenes is very meager. To introduce the nitro group into the 6-position of 2,2-dimethyl-7-methoxy-4-chloro-2*H*-chromene, its nitration with nitrates in acidic media has been studied.[61] It has been demonstrated that the treatment of this chromene with ammonium nitrate (1 equiv.) in trifluoroacetic acid at −15 °C (1 h) and then at room temperature (30 min) gives exclusively 6-nitro derivative **75**, while the treatment with a copper(II) nitrate excess (4.3 equiv.) in acetic anhydride at 60 °C for 2 h leads to 3,6-dinitro-4-chlorochromene **76** (Scheme 35).

Scheme 35



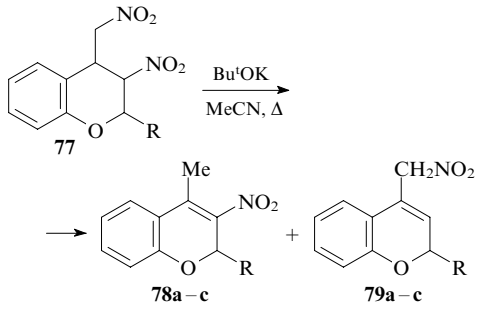
75 (89%)

76 (90%)

It is worth noting that the treatment of chromanes **77**, obtained by tandem condensation of β-nitrostyrenes with

2-(2-hydroxyphenyl)-1-nitroethene, with potassium *tert*-butoxide on heating under reflux in acetonitrile for 4–5 h yields mixtures of approximately equal amounts of 4-methyl-3-nitrochromenes **78** and 4-nitromethylchromenes **79** (Scheme 36).[62]

Scheme 36



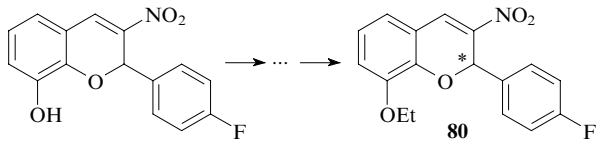
R = Pr (**a**), Ph (**b**), 4-ClC_6H_4 (**c**)

Compounds **78**, **79**	Yield (%)	
	78	**79**
a	39	33
b	29	22
c	40	34

c. Enantioselective synthesis

Optically active 3-nitro-2*H*-chromenes can be obtained by asymmetric synthesis with the use of chiral organic catalysts or through racemate separation. Enantiomerically pure 3-nitro-2-(4-fluorophenyl)-8-ethoxy-2*H*-chromenes **80** have been synthesized by etherification of the corresponding racemic 8-hydroxy derivative of (*S*)-(+)-α-methoxyphenylacetic acid with subsequent separation of diastereomers, hydrolysis and alkylation with iodoethane. Optically active chromenes **80**, as well as their pharmaceutically acceptable salts, can be used as antineoplastic medications for the treatment of leukemia and myeloma (Scheme 37).[63]

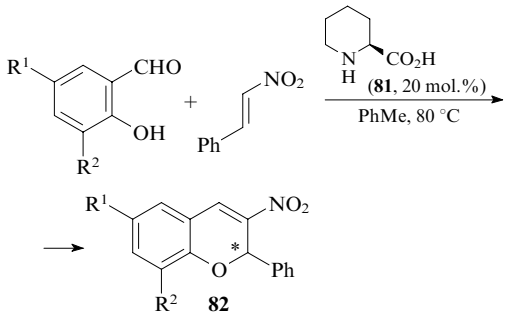
Scheme 37



There are several approaches to asymmetric synthesis of 3-nitro-2*H*-chromenes. One of them is based on the tandem reaction between salicylaldehydes and nitroalkenes catalyzed by chiral secondary amines (as a rule, derivatives of commercially available cyclic amino acids like proline are used). It is suggested that the role of the catalyst in this case is not only in the activation of the aldehyde formyl group through the formation of an iminium cation ('iminium activation') but also in the creation of conditions for selective approach of the nitroalkene molecule from the sterically unhindered side (asymmetric induction).

In enantioselective synthesis of 3-nitro-2-phenylchromenes, L-pipecolic acid (**81**) has been used as a catalyst of the Michael–Henry tandem reaction.[64] The best results were obtained when the reaction was carried out in toluene at 80 °C for 24 h. Under these conditions, products **82** were obtained in high yields, but the enantioselectivity was no more than 17% (Scheme 38).

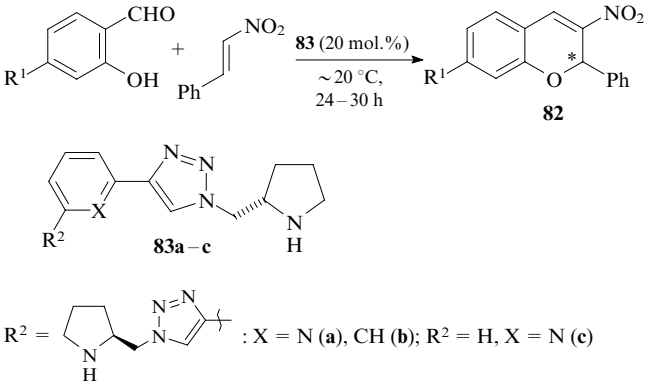
Scheme 38



R^1	R^2	Yield of **82** (%)	*ee* (%)
H	H	81	5
Cl	Cl	76	2
Cl	H	79	17
Br	H	80	16
OH	H	60	13

To obtain optically active nitrochromenes **82**, chiral pyrrolidine-triazole-based organocatalysts **83a–c** have been synthesized from ethynylbenzenes or ethynylpyridines and L-proline azide.[65] On their basis, asymmetric synthesis of compounds **82** has been accomplished; however, whatever the type of catalyst and solvent, the yields and enantioselectivity were low (Scheme 39, Table 7).

Scheme 39



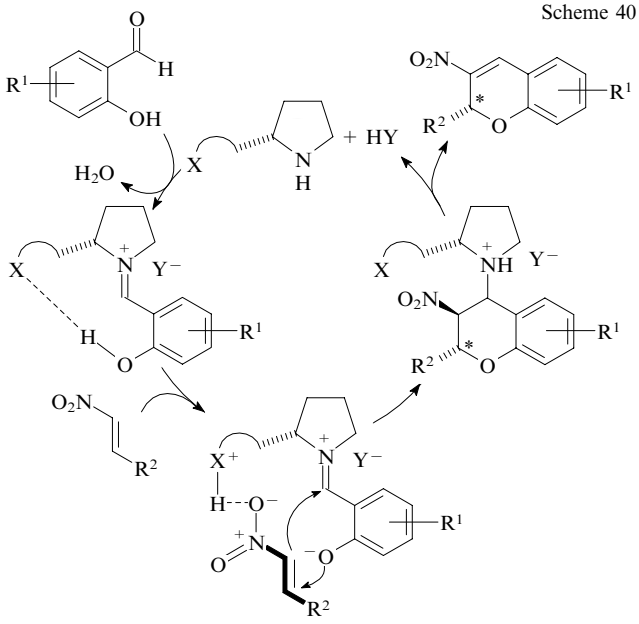
R² = : X = N (**a**), CH (**b**); R^2 = H, X = N (**c**)

With the aim of increasing the enantioselectivity of the process, proline-based chiral catalysts containing a Lewis base fragment (X) were used.[66] In addition, an acidic cocatalyst HY capable of forming hydrogen bonds with

Table 7. Reaction conditions and yields of nitrochromenes **82** (see Scheme 39).

R^1	Catalyst	Solvent	Yield of **82** (%)	*ee* (%)
H	**83a** + Et_3N	toluene	40	15
H	**83a**	DMF	30	24
H	**83a**	H_2O	22	19
H	**83b**	DMF	23	12
H	**83c**	DMF	27	11
MeO	**83a**	DMF	22	7

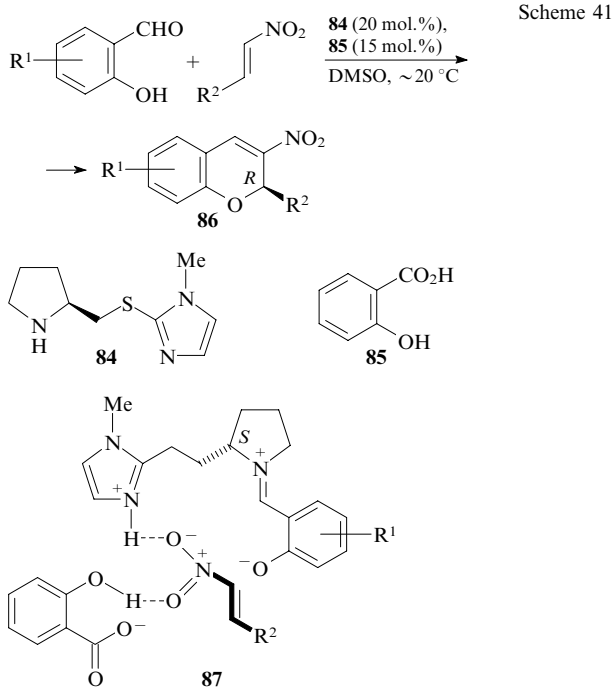
Scheme 40



both the basic fragment X and the oxygen atoms of the alkene nitro group was introduced into the reaction (Scheme 40).

This approach with the use of 1-methyl-1*H*-imidazol-2-yl-(2*S*)-pyrrolidin-2-ylmethyl sulfide (**84**) as a chiral catalyst and salicylic acid (**85**) as a cocatalyst afforded chromenes **86** in good yields and with high *R*-stereoselectivity upon the reaction in DMSO at ~20 °C for 96 h. It is believed [66] that the role of cocatalyst **85** is in the formation of strong intermediate complex **87** through an additional hydrogen bond involving a nitro oxygen atom and the hydroxy group of salicylic acid (Scheme 41, locants for R^1 are related to the initial compound).[66]

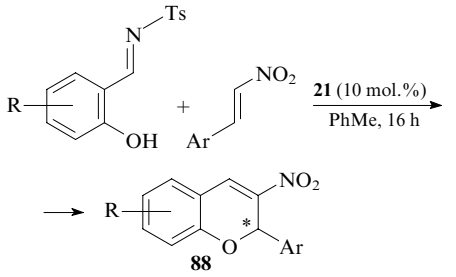
Scheme 41



R^1	R^2	Yield of **86** (%)	*ee* (%)	R^1	R^2	Yield of **86** (%)	*ee* (%)
H	Ph	72	51	5-Cl	Ph	72	62
H	4-MeC_6H_4	81	45	4-MeO	4-ClC_6H_4	57	69
H	4-$MeOC_6H_4$	87	52	4-MeO	4-BrC_6H_4	46	61
H	2-Naph	51	53	4-MeO	2-$MeOC_6H_4$	37	91
3-MeO	Ph	78	77	4-MeO	3-$MeOC_6H_4$	52	71
4-MeO	Ph	67	85	4-MeO	4-$MeOC_6H_4$	47	72
5-MeO	Ph	32	48	4-MeO	2-Naph	35	70

In an alternative approach,[67] the asymmetric synthesis of a series of 2-arylchromenes **88** was carried out from salicylaldehyde tosylimines (Ts is tosyl), which do not require additional activation of the formyl group. In this case, chiral thiourea-based catalysts were used, the best one being Takemoto's catalyst **21** (see Section II.2), containing chiral diamine and 1,3-bis(trifluoromethyl)benzene moieties. The reaction was carried out at both ~20 and 0 °C. The decrease in temperature significantly improves the optical purity, but the yield of the product decreased (Scheme 42).

Scheme 42

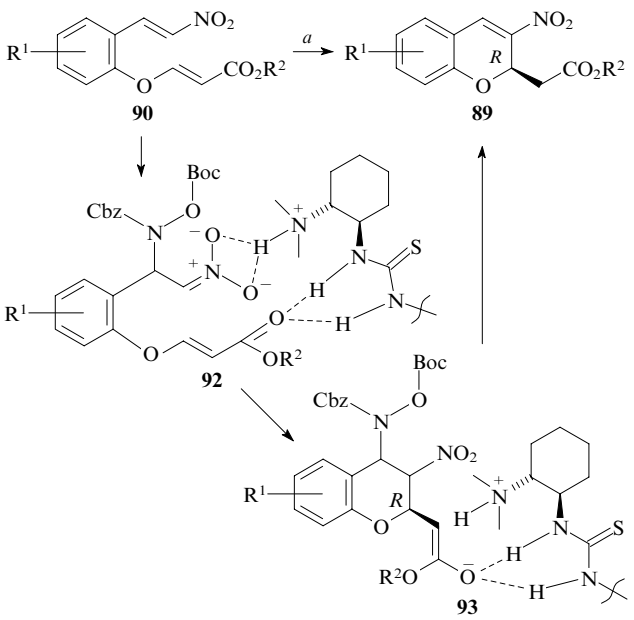


R	Ar	Yield of **88** (%) (see [a])	*ee* (%) (see [a])
H	Ph	52 (31)	49 (92)
H	2-$MeOC_6H_4$	70 (22)	29 (66)
H	4-$MeOC_6H_4$	56 (23)	50 (80)
H	4-MeC_6H_4	69 (22)	39 (96)
H	4-BrC_6H_4	83	35
H	2,3-$(MeO)_2C_6H_3$	81 (42)	48 (97)
H	2,6-$Cl_2C_6H_3$	34 (23)	37 (52)
H	3,4-$Cl_2C_6H_3$	93 (68)	31 (46)
H	2-Fu [b]	87 (54)	43 (51)
5-MeO	Ph	20	80
4-Br	Ph	75	41

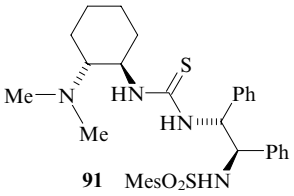
[a] Data at 0 °C are parenthesized; [b] Fu is furyl.

Recently,[68] an enantioselective method of synthesis of highly functionalized 2*H*-chromenes **89** from available nitroalkenes **90** has been developed. The method is based on the intramolecular crossed Rauhut – Currier reaction with the use of chiral catalyst **91,** able to selectively form intermolecular hydrogen bonds, and benzyl *tert*-butoxycarbonyloxycarbamate (BocONHCbz) as a nucleophilic promoter. The *R*-configuration of the products has been confirmed by X-ray crystallography. Calculation methods have shown that the high *R*-stereoselectivity of the process is caused by the lower Gibbs energy of the transition state with the *R*-configuration ($\Delta G = 5.6$ kcal mol^{-1}) that appears in the course of the intramolecular Michael reaction **92** → **93**, which is caused by the formation of stronger intermolecular hydrogen bonds between the substrate and the protonated form of catalyst **91** (Scheme 43, locants of substituent R^1 are specified for initial compounds **90**).

Scheme 43



(*a*) CbzNHOBoc (1.2 equiv.), **91** (20 mol.%), $CHCl_3$, from −40 to −20 °C, 6 days



91 $MesO_2SHN$ (Mes is mesityl)

R^1	R^2	Yield of **89** (%)	*ee* (%)	R^1	R^2	Yield of **89** (%)	*ee* (%)
H	Et	92	92	4-Cl	Et	95	93
4-Me	Et	93	92	4-Br	Et	98	91
4-MeO	Et	91	90	H	Me	87	98
5-MeO	Et	97	93	4-Me	Me	83	91
4-F	Me	86	91	4-MeO	Me	85	90

2. Chemical properties

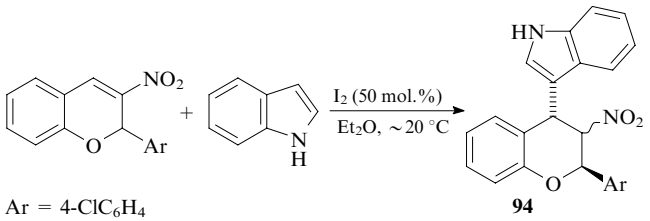
a. Reactions with C- and P-nucleophiles

The 3-nitro-2*H*-chromene molecules contain conjugated electrophilic alkene and heterodiene structural fragments, as well as the nitro group capable of different transformations, which are responsible for a wide spectrum of their chemical properties. In particular, 3-nitro-2*H*-chromenes act as active Michael acceptors toward C-nucleophiles and as dienophiles, dipolarophiles or heterodienes in cycloaddition reactions and are also involved in different redox and photochemical processes.

The best studied is the reaction of 2-aryl-3-nitro-2*H*-chromenes **44** with indoles as C-nucleophiles. The nucleophilic addition of indoles at the C(4) atom of these molecules (or Friedel–Crafts 'alkylation' of π-excessive indoles at the 3-position of chromenes) is a simple and widely used method of introduction of the biologically significant indole moiety into the pyran ring.[69–71] In the absence of a substituent in the 2-position of chromene, the reaction occurs *trans*-stereoselectively.[23] In the case of 2-monosubstituted chromenes, two of the four possible diastereomeric chromanes with the *trans* arrangement of the bulkiest substituents in the 2- and 4-positions are, as a rule, formed.

Molecular iodine has been used for activation of the initial components in the course of addition of indole to 3-nitro-2-(4-chlorophenyl)-2*H*-chromene.[69] This made it possible to carry out the reaction under mild conditions for 2.5 days and afforded chromane **94** as a mixture of *cis*,*trans* and *trans*,*cis* isomers, which were isolated in 73% and 26% yields, respectively, and their configuration was supported by X-ray crystallography data (Scheme 44).

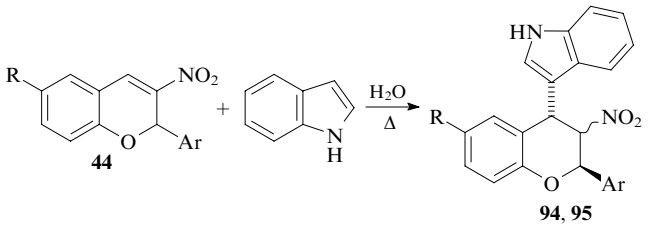
Scheme 44



Ar = 4-ClC_6H_4

Higher yields in shorter reaction times were achieved in 'alkylation' of indole with 2-aryl-3-nitrochromenes **44** in boiling water, which was, in this case, not only an environmentally safe medium but also promoted alkylation, activating the chromene molecule through the formation of hydrogen bonds with the oxygen atoms of the nitro group.[70] However, the diastereoselectivity of formation of compounds **94** and **95** was low (Scheme 45). A similar reaction of *N*-methylindole with 3-nitro-2-phenyl-2*H*-chromene (**44a**) yielded a mixture of *cis*,*trans* and *trans*,*cis* diastereomers (*ct* and *tc* isomers) in the 65 : 35 ratio; other indoles, such as 5-bromoindole and 2-carboxyindole, did not react with chromene **44a**.

Scheme 45

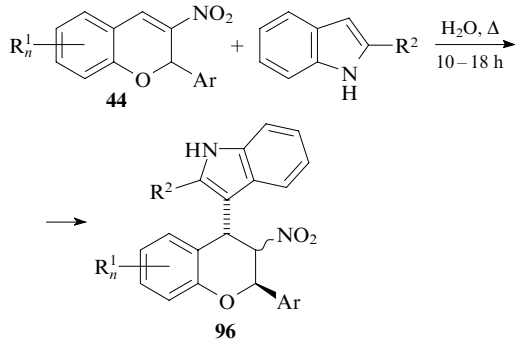


R	Ar	Time /h	Yield (%)	*ct* : *tc*
H	Ph	12	91	78 : 22
MeO	Ph	16	74	77 : 23
Br	Ph	10	84	71 : 29
H	4-MeC_6H_4	12	81	73 : 27
H	4-$MeOC_6H_4$	18	70	70 : 30
H	3-FC_6H_4	12	79	78 : 22
H	4-ClC_6H_4	12	82	75 : 25

Due to the presence of a bulky substituent in the 2-position, 2-methyl- and 2-phenylindoles react more selectively with 2-aryl-3-nitrochromenes **44,** and, in most cases, the content of the *cis,trans* isomer with the *trans* arrangement of the nitro group and indolyl substituent in compounds **96** exceeded 90% (Scheme 46, locants for R^1 are related to initial chromenes **44**). It is worth noting that the effect of steric factor is also manifested in the reactions of 2,2-dimethyl-3-nitro-2*H*-chromene (**51a**), which reacts with

indole to form a mixture of approximately equal amounts of *trans*- (yield 45%) and *cis*- (yield 43%) 4-(indol-3-yl)-3-nitrochromanes, whereas the addition of 2-methylindole leads exclusively to the *trans* isomer of the corresponding chromane in 84% yield.[70]

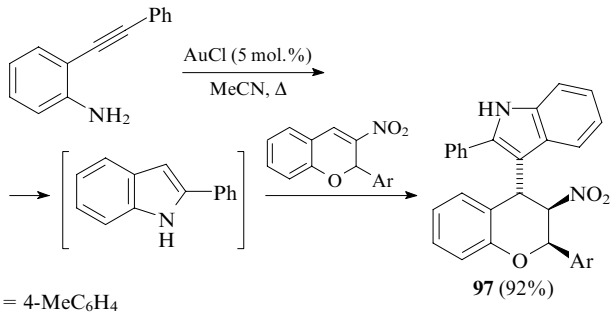
Scheme 46



R^1_n	R^2	Ar	Yield (%)	*ct* : *tc*
H	Me	2-$MeOC_6H_4$	69	92 : 8
H	Me	2-$CF_3C_6H_4$	78	> 99 : 1
H	Me	2-Th	73	> 99 : 1
6-MeO	Me	Ph	71	92 : 8
8-MeO	Me	Ph	73	> 99 : 1
6-Br	Me	Ph	82	93 : 7
6-Cl	Me	Ph	79	94 : 6
H	Me	4-$MeOC_6H_4$	54	> 99 : 1
6,8-Br_2	Me	Ph	86	99 : 1
H	Ph	Ph	73	> 99 : 1
H	Ph	3-FC_6H_4	83	> 99 : 1
H	Ph	4-ClC_6H_4	81	> 99 : 1
H	Ph	2-Th	76	96 : 4
6-MeO	Ph	Ph	71	> 99 : 1
8-MeO	Ph	Ph	73	> 99 : 1
6-Br	Ph	Ph	78	89 : 11
6,8-Br_2	Ph	Ph	81	96 : 4

A diastereoselective synthesis of 2-(4-methylphenyl)-3-nitro-4-(2-phenylindol-3-yl)chromane (**97**) has been accomplished through a domino gold(I) chloride catalyzed cycloisomerization of 2-(phenylethynyl)aniline into 2-phenylindole and its addition to 2-(4-methylphenyl)-3-nitro-2*H*-chromene; the reaction occurs in acetonitrile on heating under reflux for 12 h [71] (Scheme 47).

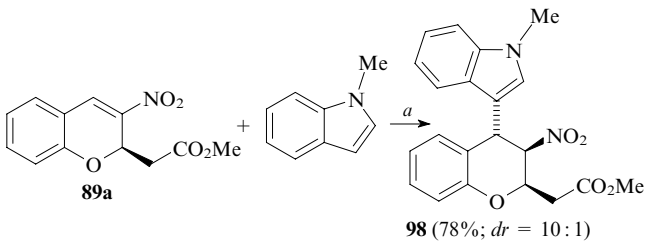
Scheme 47



Ar = 4-MeC_6H_4

The enantio- and diastereoselective addition of *N*-methylindole to methyl (2*R*)-3-nitrochromen-2-ylacetate (**89a**) in the presence of a catalyst obtained *in situ* from zinc triflate and chiral ligand **27** leads to chromane **98** (Scheme 48).[68]

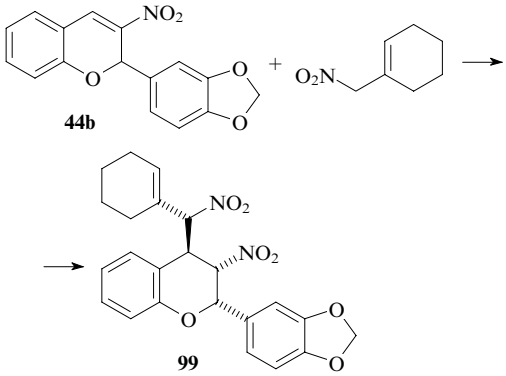
Scheme 48



(*a*) $Zn(OTf)_2$, **27** (15 mol.%), PhMe, ~20°C

2-(3,4-Methylenedioxyphenyl)-3-nitro-4-[(cyclohexen-1-yl)nitromethyl]chromane (**99**) has been synthesized by the reaction of nitrochromene **44b** with 1-nitromethyl-1-cyclohexene. The relative configurations of the C(2), C(3) and C(4) atoms of the pyran ring and the carbon atom of the nitroalkyl substituent in chromane **99** have been determined by X-ray crystallography (Scheme 49).[72]

Scheme 49

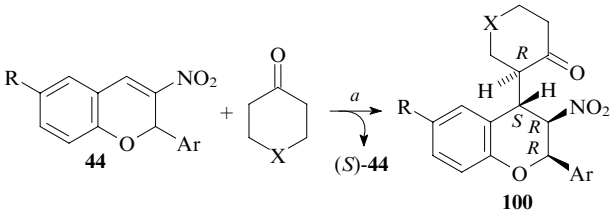


Recently, a synthesis of optically active 2,3,4-trisubstituted chromanes **100** has been described which is based on the catalytic Michael addition of cycloalkanones and their heterocyclic analogues to racemic 2-aryl-3-nitrochromenes **44** with the use as a catalyst of chiral sulfide **101**, containing the *trans*-4-hydroxypyrrolidine and borneol moieties.[73] Less reactive *S*-enantiomers of chromenes **44** by kinetic resolution were recovered in good yields and moderate optical purity (Scheme 50).

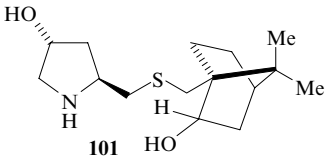
Of interest is the recently reported one-pot synthesis of highly functionalized 6-aryl-6*H*-dibenzo[*b*,*d*]pyran derivatives **102** achieved *via* a new domino reaction of (1-arylalkylydene)malononitriles with 2-aryl-3-nitrochromenes **44** catalyzed by a base.[74] The best results are achieved when the reaction is carried out in dichloromethane at room temperature in the presence of triethylamine. For R^4 = Me under the specified conditions, stable tautomers **103** and **104** are first formed and then they are converted into dibenzopyrans **102** by heating under reflux in ethanol in the presence of sodium acetate. This multistage synthesis involves the nucleophilic addition of α,α-dicyanoalkene to the chromene molecule accompanied by cyclization into intermediates **103** and **104**, which undergo the sigmatropic [1,5]-H-shift and elimination of nitrous acid to give target product **102** (Scheme 51).

The use of chiral bifunctional thiourea derivative **105** as a catalyst enables the enantioselective synthesis of compounds **103** and **104** from racemic 2-aryl-3-nitrochromenes under milder conditions.[75] In particular, the reaction of chromenes **44** with a dinitrile based on propiophenones at

Scheme 50

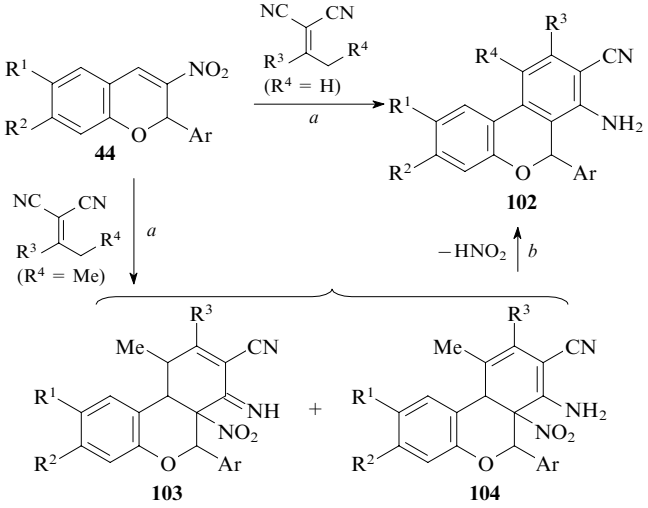


(*a*) **101** (20), AcOH (50 mol.%), 0 °C, 28 – 96 h



R	Ar	X	Yield (%) (*ee*, %)	
			(*S*)-**44**	**100**
H	Ph	CH_2	42 (64)	40 (90)
H	3-BrC_6H_4	CH_2	38 (72)	45 (93)
H	3-ClC_6H_4	CH_2	35 (70)	47 (80)
H	4-ClC_6H_4	CH_2	37 (54)	43 (80)
H	2-$MeOC_6H_4$	CH_2	37 (36)	41 (77)
H	3-$MeOC_6H_4$	CH_2	41 (72)	46 (81)
H	4-$MeOC_6H_4$	CH_2	39 (25)	33 (75)
H	4-MeC_6H_4	CH_2	39 (62)	38 (86)
H	2-Th	CH_2	36 (52)	39 (76)
H	2-Fu	CH_2	38 (35)	34 (76)
Cl	Ph	CH_2	35 (72)	42 (66)
MeO	Ph	CH_2	37 (48)	41 (88)
H	Ph	O	36 (45)	31 (66)
H	Ph	S	53 (12)	24 (71)

Scheme 51



(*a*) Et_3N (1 equiv.), CH_2Cl_2, ~20 °C, 48 h;
(*b*) NaOAc (1 equiv.), Bu^n_4NBr, EtOH, Δ

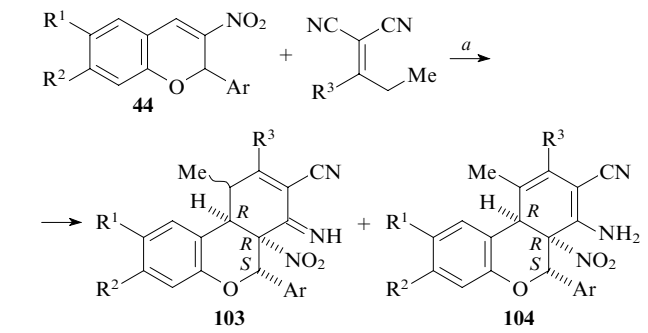
R^1	R^2	R^3	R^4	Ar	Yield of **102** (%)
H	H	Ph	H	Ph	71
H	MeO	Ph	H	Ph	58
F	H	Ph	H	Ph	76
Cl	H	Ph	H	Ph	72
H	H	Ph	H	4-$CF_3C_6H_4$	41
H	H	Ph	H	4-ClC_6H_4	73
H	H	Ph	H	4-MeC_6H_4	56
H	H	Ph	H	2-Fu	74
H	H	4-ClC_6H_4	H	Ph	62
H	H	4-BrC_6H_4	H	Ph	71
H	H	4-MeC_6H_4	H	Ph	65
H	H	2-$MeOC_6H_4$	H	Ph	52
Cl	H	Ph	Me	Ph	63 [a]
H	H	Ph	Me	4-ClC_6H_4	61 [a]
H	H	Ph	Me	4-MeC_6H_4	68 [a]
H	H	Et	Me	Ph	38 [a]

[a] Yield for two stages.

10 °C yields a mixture of products **103** and **104**, their (6*S*,6a*R*,10a*R*)-configuration being determined by X-ray crystallography (Scheme 52).

Under analogous conditions at 0 °C for 24 h, dinitriles based on acetophenones react with chromenes **44** to form

Scheme 52

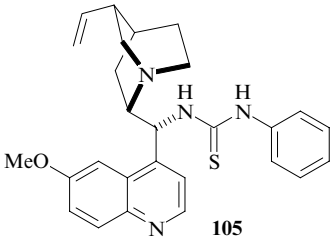


(*a*) **105** (20 mol.%), CH_2Cl_2, 10 °C, 36 h

R^1	R^2	R^3	Ar	Yield (%) (*ee*, %)	
				103	**104**
H	H	Ph	Ph	31 (92)	40 (92)
H	H	Ph	4-BrC_6H_4	35 (86)	38 (86)
H	H	Ph	4-MeC_6H_4	29 (78)	41 (74)
H	H	Ph	4-$MeOC_6H_4$	38 (68)	37 (66)
Cl	H	Ph	Ph	40 (84)	37 (84)
Br	H	Ph	Ph	23 (80)	44 (82)
H	MeO	Ph	Ph	30 (91)	43 (91)
H	H	4-MeC_6H_4	Ph	36 (89)	41 (89)
Cl	H	4-ClC_6H_4	4-MeC_6H_4	25 (88)	43 (86)
H	H	4-ClC_6H_4	Ph	30 (90)	46 (90)
H	H	4-ClC_6H_4	4-ClC_6H_4	32 (85)	44 (85)

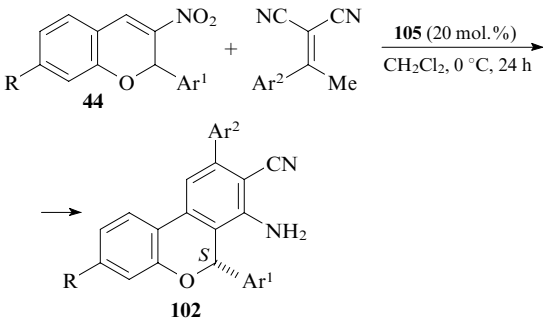
dibenzopyrans **102** with the *S*-configuration of the C(6) atom (Scheme 53).[75]

Structure **105**



105

Scheme 53



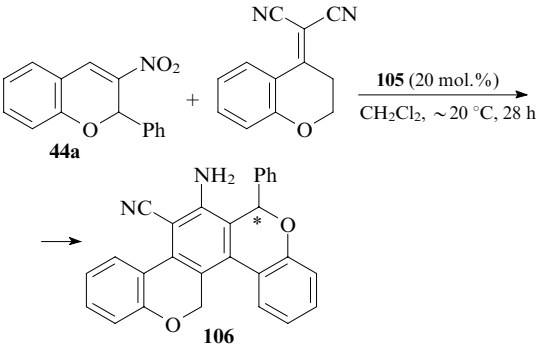
44

102

R	Ar^1	Ar^2	Yield of **102** (%) (*ee*, %)
H	Ph	$4\text{-}ClC_6H_4$	80 (86)
H	Ph	$4\text{-}BrC_6H_4$	71 (77)
H	$4\text{-}ClC_6H_4$	Ph	79 (92)
MeO	Ph	Ph	78 (83)

The reaction of chromene **44a** and chroman-4-ylidenemalononitrile catalyzed by **105** afforded pentacyclic product **106** in 30% yield and 90% enantioselectivity,[75] whereas in the presence of more basic triethylamine, the yield of racemic benzopyran **106** increased to 43% (Scheme 54).[74]

Scheme 54

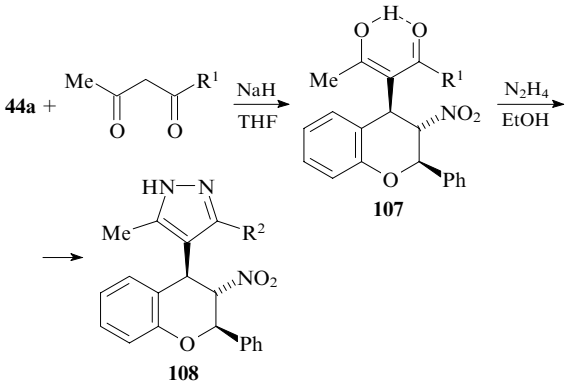


44a

106

Reactions of chromenes **44** with 1,3-dicarbonyl compounds and their enamines have been little studied. 3-Nitro-2-phenyl-2*H*-chromene (**44a**), in which thiols and arylamines do not add at the double bond, reacts with acetylacetone and acetoacetic ester in the presence of NaH to give *trans*,*trans*-chromanes **107** in 56% and 18% yields, respectively; the reaction of the latter with a 60% hydrazine hydrate solution in ethanol yields atropoisomeric 4-(pyrazol-4-yl)chromanes **108** (Scheme 55).[76]

Scheme 55



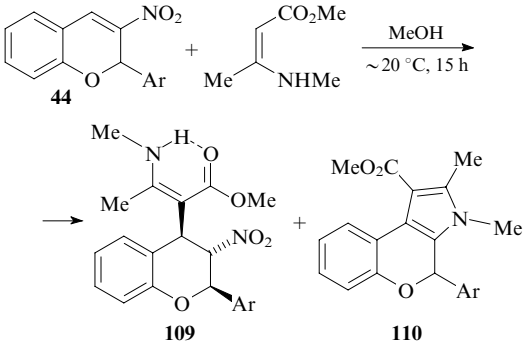
107

108

R^1 = Me, EtO; R^2 = Me (yield 79%), OH (80%)

The reaction of 2-aryl-3-nitrochromenes **44** with methyl 3-(methylamino)crotonate leading to mixtures of *trans*,*trans* isomer **109**, with the *Z*-configuration of the aminoenone moiety, and corresponding chromenopyrrole **110** has been described.[77] The latter is a result of the intramolecular Grob cyclization of the intermediate (*E*)-enamino ester not stabilized by intramolecular hydrogen bond (Scheme 56).

Scheme 56



44

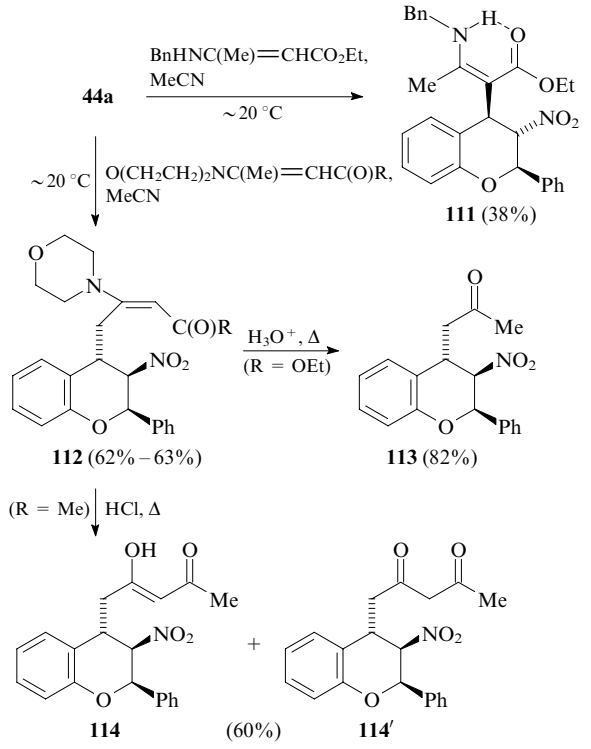
109 **110**

Ar = $4\text{-}MeOC_6H_4$, $4\text{-}ClC_6H_4$, $3,4\text{-}(OCH_2O)C_6H_3$

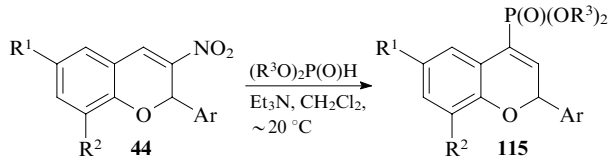
3-Nitro-2-phenylchromene (**44a**) reacts with ethyl 3-(benzylamino)crotonoate in a similar manner to give *trans*,*trans*-chromane **111**; however, the reaction of this chromene with enamines, synthesized from acetoacetic ester (or acetylacetone) and morpholine, occurs at the vinylogous β-methyl group of enamines and yields chromanes **112** as individual *cis*,*trans* diastereomers. The acid hydrolysis of these compounds affords acetonyl (**113**) and acetylacetonyl (**114**) derivatives (with retention of the chromane ring configuration); the latter compound is a 69 : 31 mixture of two tautomers (**114** and **114′**) (Scheme 57).[78, 79]

As distinct from the reactions with C-nucleophiles, the nucleophilic addition of dialkyl phosphites to 2-aryl-3-nitrochromenes **44** in the presence of triethylamine is accompanied by elimination of a nitrous acid molecule and leads to 4-phosphorylchromenes **115** in good yields (Scheme 58).[80]

Scheme 57



Scheme 58



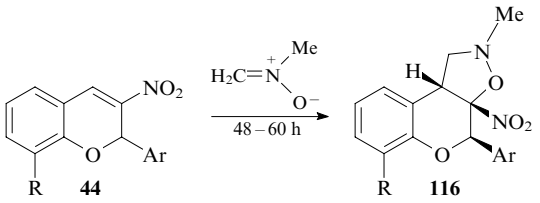
R^1	R^2	R^3	Ar	Yield of **115** (%)
H	Cl	Me	Ph	60
Cl	H	Me	4-$MeOC_6H_4$	64
H	MeO	Me	Ph	68
H	H	Et	Ph	78
Cl	H	Et	4-$MeOC_6H_4$	77
H	MeO	Et	4-$MeOC_6H_4$	70

b. Reactions of cycloaddition

Due to the presence of the activated C=C bond in 3-nitro-2*H*-chromene molecules, they act as dipolarophiles with respect to 1,3-dipoles, such as nitrones, sodium azide, diazoalkanes and azomethine ylides, in reactions of 1,3-dipolar cycloaddition. In particular, *N*-methylnitrone, prepared *in situ* by the reaction of *N*-methylhydroxylamine with sodium acetate in a dioxane – water mixture (19 : 1), reacts with 2-aryl-3-nitrochromenes **44** at room temperature to give 4-aryl-*N*-methylbenzopyrano[4,3-*d*]isoxazolidines **116** with the *cis* arrangement of the nitro group, aryl substituent and H(9b) atom (Scheme 59).[81]

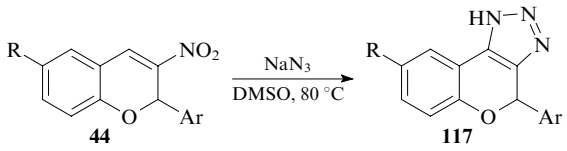
The reaction of chromenes **44** with sodium azide occurs in DMSO at 80 °C and yields 4-aryl-1,4-dihydrochromeno[3,4-*d*][1,2,3]triazoles **117** in 61% – 80% yields. Electron-withdrawing atoms and groups (F, Cl, CF_3) in the 2-aryl substituent have little effect on the substrate activity, whereas donor groups (Me, MeO) increase the reaction duration (Scheme 60).[64, 82]

Scheme 59



R	Ar	Yield of **116** (%)	R	Ar	Yield of **116** (%)
H	Ph	63	MeO	Ph	75
H	4-$MeOC_6H_4$	52	MeO	4-$MeOC_6H_4$	56
H	4-MeC_6H_4	60	MeO	4-MeC_6H_4	65
H	4-ClC_6H_4	68	MeO	4-ClC_6H_4	70

Scheme 60

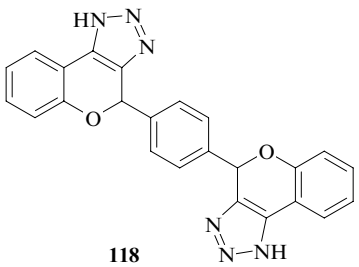


R	Ar	Time /min	Yield of **117** (%)
H	Ph	25	79
H	2-$MeOC_6H_4$	70	60
H	2-ClC_6H_4	50	82
H	2-$CF_3C_6H_4$	60	60
H	3-FC_6H_4	40	80
H	4-$MeOC_6H_4$	75	62
H	4-ClC_6H_4	35	74
H	4-MeC_6H_4	45	63
H	3,4-$(OCH_2O)C_6H_3$	70	69
H	1-Naph	60	64
H	9-anthranyl	90	60
H	2-Th	25	77
MeO	Ph	75	61
Cl	Ph	45	78

Through double cycloaddition, 1,4-bis(3-nitro-2*H*-chromen-2-yl)benzene (**52**), containing two nitrochromene moieties, was converted into 1,4-bis(1,4-dihydrochromeno[3,4-*d*][1,2,3]triazol-4-yl)benzene (**118**) in 61% yield. More sterically hindered 2,2-dimethyl-3-nitro-2*H*-chromene (**51a**) turned out to be less active and reacted with sodium azide more slowly (3 h) to form the corresponding cycloadduct in 58% yield; whereas 3-nitro-2,2-diphenyl-2*H*-chromene did not react.[82]

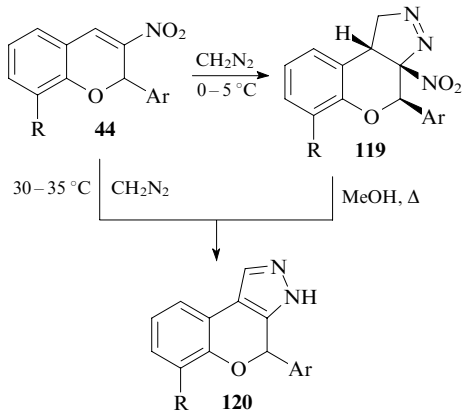
The reaction of chromenes **44** with diazomethane in a diethyl ether – dioxane mixture at 0 – 5 °C yields 4-aryl[1]-

Structure **118**



benzopyrano[3,4-*c*]-Δ^1-pyrazolines **119** as individual diastereomers with the *cis*-arranged H(9b) atom, nitro group and aryl substituent. Heating in methanol leads to the elimination of HNO_2 and hydrogen migration so that Δ^1-pyrazolines **119** are transformed into the more thermodynamically stable 4-aryl[1]benzopyrano[3,4-*c*]pyrazoles **120**. The latter can be obtained from chromenes **44** and diazomethane in one stage in 54% – 85% yields if the reaction is carried out at higher temperature (Scheme 61).[34]

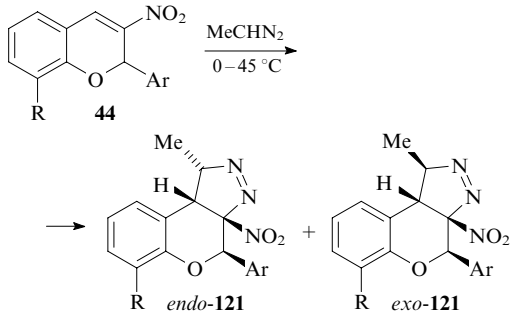
Scheme 61



R	Ar	Yield (%)		R	Ar	Yield (%)	
		119	**120**			**119**	**120**
H	Ph	90	62	MeO	Ph	80	80
H	4-$MeOC_6H_4$	82	65	MeO	4-$MeOC_6H_4$	84	85
H	4-MeC_6H_4	86	54	MeO	4-MeC_6H_4	65	78
H	4-ClC_6H_4	74	72	MeO	4-ClC_6H_4	70	70

A similar reaction of compounds **44** with diazoethane both at low temperature and on heating to 45 °C leads to stable Δ^1-pyrazolines **121** as a mixture of *endo* and *exo* diastereomers (with the prevalence of the former) distinguished by the arrangement of the methyl group in the 1-position relative to the chromane ring (Scheme 62).[34]

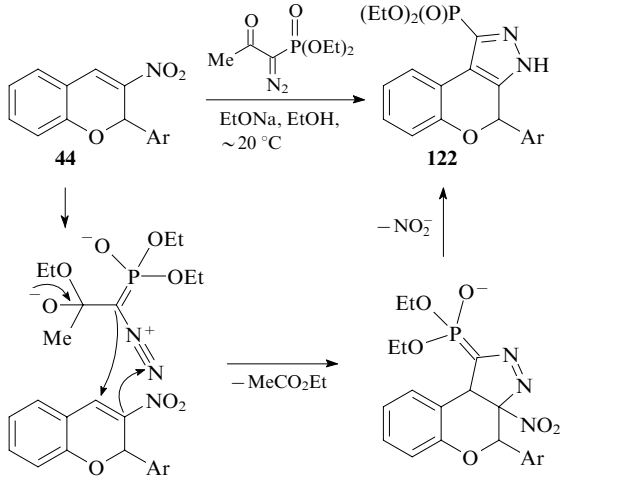
Scheme 62



R	Ar	Yield of **121** (%)	*endo* : *exo*
H	Ph	68	97 : 3
H	4-$MeOC_6H_4$	62	98 : 2
H	4-MeC_6H_4	65	88 : 12
H	4-ClC_6H_4	70	94 : 6
MeO	Ph	64	53 : 47
MeO	4-$MeOC_6H_4$	76	70 : 30
MeO	4-MeC_6H_4	48	64 : 36
MeO	4-ClC_6H_4	52	65 : 35

The reaction of chromenes **44** with diethyl 1-diazo-2-oxopropylphosphonate (Bestmann – Ohira reagent) in the presence of sodium ethoxide at room temperature in ethanol is complete in 5 – 10 min and leads to diethyl 4-aryl-3,4-dihydrochromeno[3,4-*c*]pyrazol-1-ylphosphonates **122** in good yield. In this case, the role of 1,3-dipole is played by the diethyl 1-diazomethylphosphonate anion generated at the first stage through the addition of the ethoxide anion to the carbonyl group of the diazo compound. The subsequent 1,3-dipolar cycloaddition, accompanied by elimination of ethyl acetate molecule, leads to intermediate Δ^1-pyrazoline, which loses nitrite anion and isomerizes into corresponding chromenopyrazole **122** (Scheme 63).[83, 84]

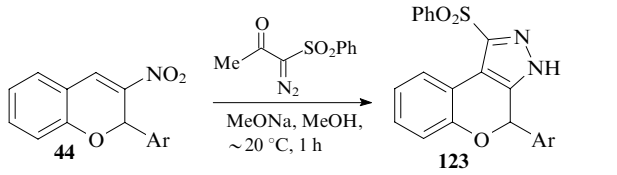
Scheme 63



Ar = Ph (yield 64%), 4-$MeOC_6H_4$ (57%), 2-Th (59%)

The reaction of chromenes **44** with phenyl-1-diazo-2-oxopropylsulfone in the presence of sodium methoxide occurs under analogous conditions and by a similar mechanism to give pyrazolylsulfones **123** in almost quantitative yield (Scheme 64).[85]

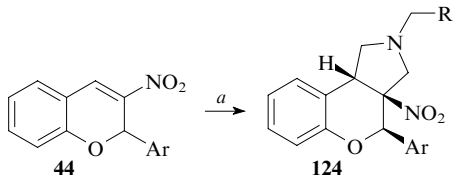
Scheme 64



Ar = Ph (yield 98%), 2-Th (95%)

The 1,3-dipolar cycloaddition of azomethine ylides to 2-aryl-3-nitrochromenes **44** has been studied.[86, 87] It has been demonstrated by $^1H-^1H$ NOE NMR experiments (NOE is nuclear Overhauser effect) that the reactions in all cases occur regio- and stereoselectively to form one diastereomer. In particular, the reaction of compounds **44** with azomethine ylides, generated *in situ* from paraformaldehyde and sarcosine or *N*-benzylglycine in boiling toluen, yields chromeno[3,4-*c*]pyrrolidines **124** as individual *cis* isomers (Scheme 65).

Scheme 65

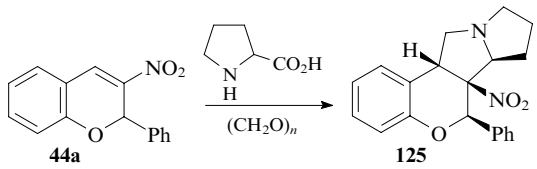


(*a*) $MeNHCH_2CO_2H$ (R = H) or $BnNHCH_2CO_2H$ (R = Ph), $(CH_2O)_n$, PhMe, 110 °C

R	Ar	Time /h	Yield of **124** (%)
H	Ph	3	93
Ph	Ph	5	72
H	2-$MeOC_6H_4$	7	79
H	4-$MeOC_6H_4$	5	94
Ph	4-$MeOC_6H_4$	5	85
H	3-$MeOC_6H_4$	7	76
Ph	3-$MeOC_6H_4$	11	68
H	2-ClC_6H_4	7	71
H	3-ClC_6H_4	5	89
Ph	3-ClC_6H_4	5	83
H	3-$BnOC_6H_4$	5	96
Ph	3-$BnOC_6H_4$	5	83
H	3,4-$(MeO)_2C_6H_3$	12	75
Ph	3,4-$(MeO)_2C_6H_3$	16	68
H	3,4-$(OCH_2O)C_6H_3$	12	66
H	4-$O_2NC_6H_4$	1	84
Ph	4-$O_2NC_6H_4$	1	79

A similar reaction with proline and paraformaldehyde has led to compound **125** in 40% yield; the stereochemistry of the product has been confirmed by the NOESY experiment (Scheme 66).[88]

Scheme 66

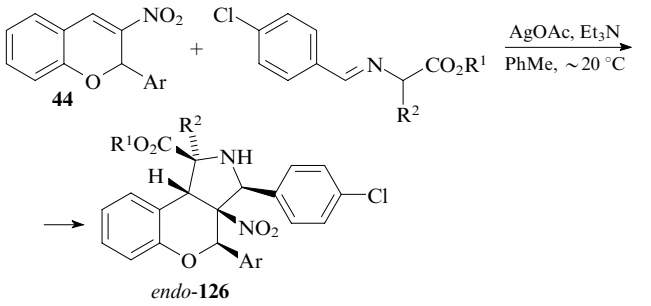


The 1,3-dipolar cycloaddition involving nitrochromenes **44** and *N*-unsubstituted azomethine ylides, synthesized from imines of ethyl esters of glycine, phenylalanine and aminomalonic acid in the presence of silver acetate and triethylamine under mild conditions, occurs as *endo*-addition (relative to the chromene nitro group) of (*E*,*E*)-ylide (relative to the CO_2R group and 4-chlorophenyl substituent) and gives products **126** in 60% – 75% yields (Scheme 67).[86,87]

The reaction of chromenes **44** with an asymmetric ylide generated from methyl sarcosinate and benzaldehyde upon boiling in toluene occurs regio- and stereoselectively. Whatever the nature of the aryl substituent, the reaction yields exclusively cycloadducts **127** as a result of the *endo*-cycloaddition of (*Z*,*E*)-ylide (Scheme 68).[86,87]

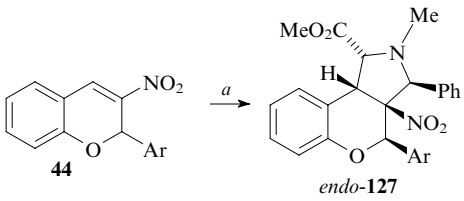
The 1,3-dipolar cycloaddition involving azomethine ylide, obtained from isoquinolinium salt **128** by treatment with Et_3N, leads to chromenopyrrolo[2,1-*a*]isoquinolines **129** in nearly quantitative yield. At Ar = Ph, cycloadduct **129** is readily oxidized by atmospheric oxygen to pyrrole **130** (Scheme 69).[86,87]

Scheme 67



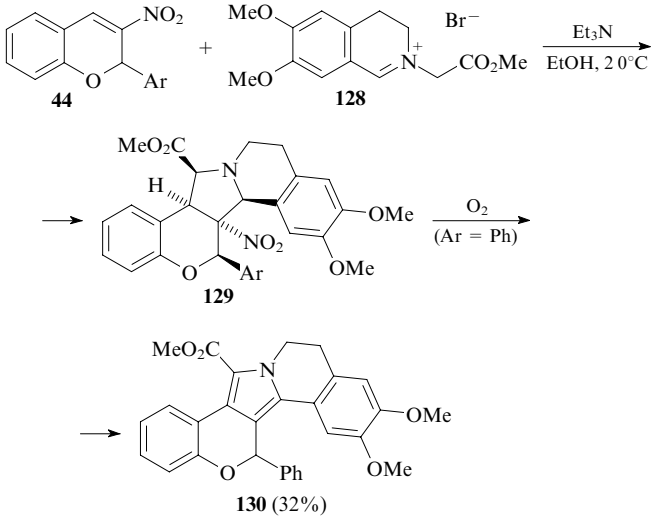
R^1	R^2	Ar	Yield of **126** (%)
Et	H	Ph	72
Me	Bn	Ph	75
Et	H	4-$MeOC_6H_4$	60
Me	Bn	4-$MeOC_6H_4$	65
Et	H	4-ClC_6H_4	70
Me	Bn	4-ClC_6H_4	72
Me	Bn	2-ClC_6H_4	60
Et	H	3,4-$(MeO)_2C_6H_3$	61
Me	Bn	3,4-$(MeO)_2C_6H_3$	62
Me	Bn	3-$O_2NC_6H_4$	75
Et	CO_2Et	Ph	48

Scheme 68



(*a*) $MeNHCH_2CO_2Me$, PhCHO, PhMe, 110 °C;
Ar = Ph (yield 57%), 2-$MeOC_6H_4$ (44%), 2-ClC_6H_4 (50%), 4-ClC_6H_4 (63%), 3,4-$(MeO)_2C_6H_3$ (47%), 3,4-$(OCH_2O)C_6H_3$ (38%)

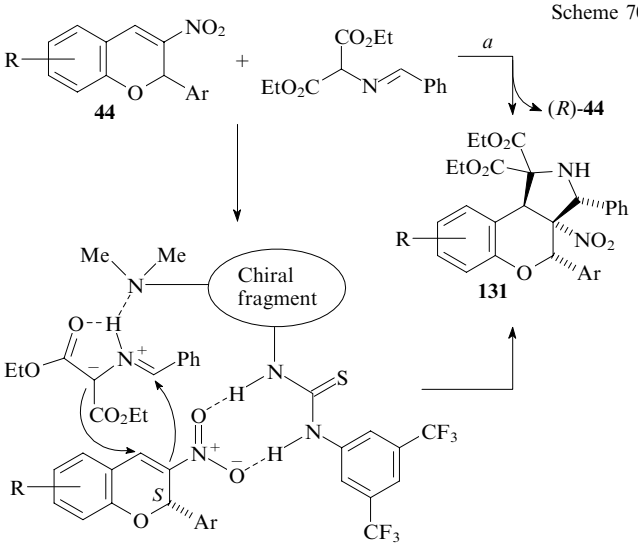
Scheme 69



Ar	Yield of **129** (%)
Ph	92
4-$MeOC_6H_4$	95
3,4-$(MeO)_2C_6H_3$	93

The asymmetric 1,3-dipolar cycloaddition of azomethine ylides in the presence of chiral Takemoto's catalyst **18** has been used for the kinetic resolution of racemic 2-aryl-3-nitrochromenes, which afforded *R*-enantiomers of corresponding chromenes **44** with an enantiomeric purity of 73% – 87%. Owing to a definite orientation of substituents in the chiral moiety of the catalyst, the latter selectively activates the *S*-isomer of the substrate, which then cycloaddition undergoes to form 4-aryl-3a-nitro-3-phenylbenzopyrano[3,4-*c*]-pyrrolidine-1,1-dicarboxylates **131**, while the *R*-enantiomer remains unaltered under the reaction conditions.[89] Unfortunately, the yields and enantiomeric purity of cycloadducts **131** are rather low. The absolute (3*R*,3a*R*,4*S*,9b*S*)-configuration of compounds **131**, containing four vicinal chiral centres, has been confirmed by X-ray crystallography (Scheme 70, locants for R are related to chromenes **44**).

Scheme 70



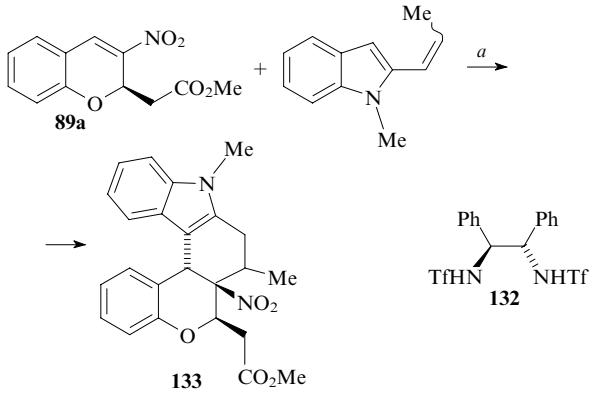
(*a*) **18** (10 mol.%), PhMe, 0 °C, 60 h

Ar	R	Yield (%) (*ee*, %)	
		(*R*)-**44**	**131**
Ph	H	41 (87)	25 (19)
4-ClC_6H_4	H	42 (77)	26 (17)
4-BrC_6H_4	H	41 (79)	40 (35)
4-$CF_3C_6H_4$	H	46 (85)	31 (49)
4-MeC_6H_4	H	47 (82)	27 (45)
4-$MeOC_6H_4$	H	49 (68)	23 (21)
Ph [a]	6-F	37 (73)	47 (53)
Ph [b]	7-MeO	43 (86)	29 (33)
4-MeC_6H_4 (see [b])	7-MeO	45 (87)	35 (57)
4-$MeOC_6H_4$ (see [b])	7-MeO	47 (83)	36 (70)
4-ClC_6H_4 (see [b])	7-MeO	45 (73)	41 (51)
4-BrC_6H_4 (see [b])	7-MeO	39 (82)	32 (13)

[a] At −10 °C, 12 h; [b] at −10 °C, 36 h.

The reaction of chiral (2*R*)-chromene **89a** acting as a dienophile with *N*-methyl-2-(1-propen-1-yl)indole catalyzed by optically active 1,2-di(trifluoromethylsulfonylamino)-1,2-diphenylethane (**132**) leads to [4 + 2]-cycloadduct **133** in 87% yield with a diastereomeric purity of > 90% (Scheme 71).[68]

Scheme 71

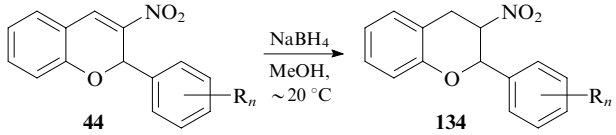


(*a*) **132** (10 mol.%), CH_2Cl_2, ~20 °C

c. Redox reactions

The reduction of the pyran ring of 3-nitro-2*H*-chromenes is in most cases chemoselective and leads to different products depending on the activity of the reducing agent. With sodium borohydride as a reducing agent, the C=C bond of the chromene pyran ring is subjected to hydrogenation, while the nitro group remains intact. As shown, the reduction of nitrochromenes **44** with sodium borohydride leads to a mixture of *cis*- and *trans*-chromanes **134** (with the prevalence of the *trans* isomer).[31] These isomers have been separated by column chromatography on silica gel with benzene as an eluent (Scheme 72).

Scheme 72

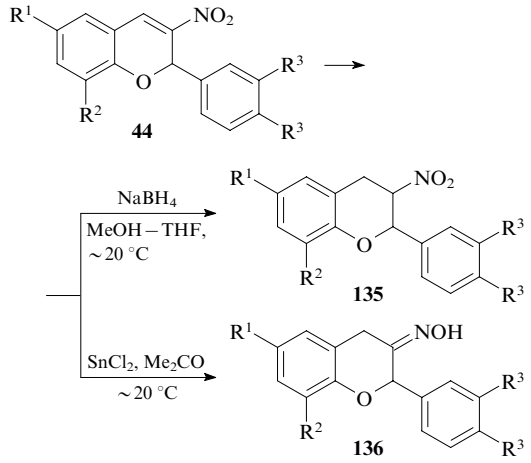


R_n	Yield (%)	
	cis-**134**	*trans*-**134**
H	10	75
4-BnO	20	70
3,4-$(MeO)_2$	15	65

A series of 2-aryl-3-nitrochromanes **135** have been obtained in 51% – 82% yields by treatment with $NaBH_4$ in the MeOH – THF system at room temperature for 20 h.[33,90] No information on the stereochemistry of these products is available. The reaction of chromenes **44** with more active $SnCl_2$ in acetone for 45 – 70 min is accompanied by partial reduction of the nitro group giving nitroso derivatives in the form of oximes **136** (Scheme 73).[91]

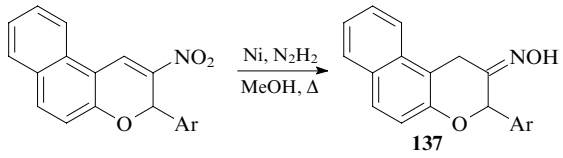
2-Naphthyl derivatives of 3-nitro-2*H*-chromenes undergo similar transformations in the reaction with $NaBH_4$ or $SnCl_2$ to give the corresponding 2-naphthyl-substituted 3-nitrochromanes or oximes.[33,90,91] Naphto[2,1-*b*]pyrans have been reduced to oximes **137** through catalytic hydrogenation using Raney nickel and hydrazine hydrate by refluxing in methanol for 6 h (Scheme 74).[47]

Scheme 73



R^1	R^2	R^3	Yield (%)	
			135	**136**
H	H	H	65	77
H	MeO	H	82	73
Cl	H	H	80	–
NO_2	H	H	51	68
H	H	EtO	67	–

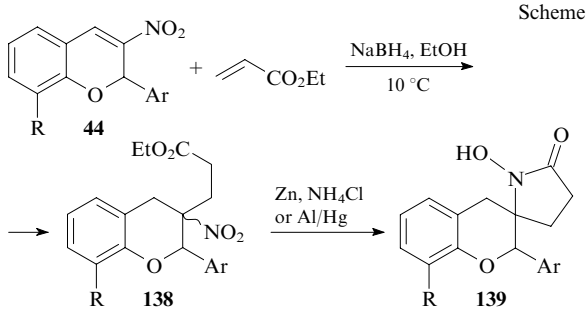
Scheme 74



Ar = Ph (yield 71%), 4-MeC_6H_4 (68%), 4-$MeOC_6H_4$ (70%), 3,4,5-$(MeO)_3C_6H_2$ (65%)

The selective action of $NaBH_4$ on the double bond of the 3-nitro-2*H*-chromene system has been used for reductive alkylation of nitrochromenes with ethyl acrylate. This reaction not only yielded propionates **138**, but also led to their transformation into spirocyclic *N*-hydroxypyrrolidin-2-ones **139** in the course of further reduction by the Zn – NH_4Cl system or aluminium amalgam (Scheme 75).[92]

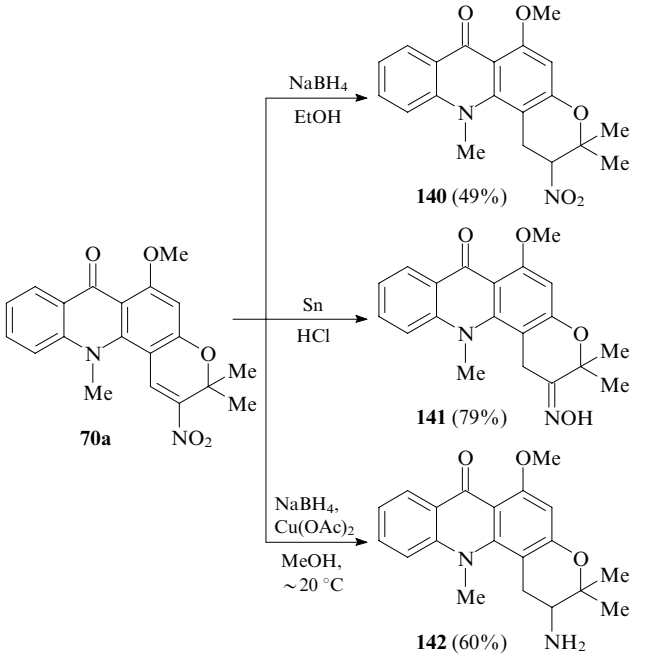
Scheme 75



Ar	R	Yield (%)	
		138	**139**
Ph	H	75	52
4-MeC_6H_4	MeO	78	54
4-$MeOC_6H_4$	MeO	67	49

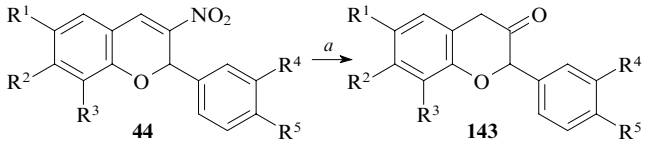
The reduction of 2-nitroacronycine (**70a**) occurs under mild conditions and, depending on the activity of the reducing agent, leads to products **140** – **142** in good yields.[55] In particular, the reaction of 2-nitroacronycine with sodium borohydride in ethanol or with tin in an HCl medium results in 2-nitro-1,2-dihydroacronycine (**140**) and 2-oxo-1,2-dihydroacronycine oxime (**141**), respectively. The $NaBH_4$ – $Cu(OAc)_2$ system completely reduces the pyran moiety to form 2-amino-1,2-dihydroacronycine (**142**) (Scheme 76).

Scheme 76



2-Arylbenzopyran-3(4*H*)-ones **143** were synthesized by successive treatment of chromenes **44** first with sodium borohydride at room temperature and then with chromium(II) chloride in 10% HCl on boiling for 2 – 2.5 h (the reductive Nef reaction), without isolation of the intermediate reduction product (yields 70% – 85%) (Scheme 77).[93]

Scheme 77

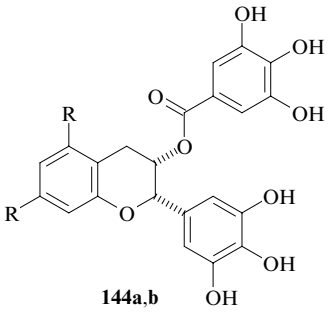


(*a*) 1) $NaBH_4$, EtOH – THF, ~20 °C; 2) $CrCl_2$ – HCl, Δ;
$R^1 = R^2 = R^3 = R^4 = R^5 = H$;
$R^1 = R^2 = R^3 = R^4 = H$: R^5 = MeO, Cl;
$R^1 = R^2 = R^3 = H$, $R^4 = R^5$ = MeO;
R^1 = MeO: $R^2 = R^3 = R^4 = R^5 = H$;
$R^2 = R^3 = R^4 = H$, R^5 = Me;
$R^1 = R^3 = R^4 = R^5 = H$, R^2 = MeO;
$R^1 = R^2 = R^4 = R^5 = H$, R^3 = MeO

Dideoxy analogue **144a** of natural epigallocatechin gallate **144b** has been synthesized from nitrochromene **44c**.[94] Both compounds exhibit anti-influenza A virus activity. In tests on infected kidney cells of cocker spaniel (MDSK), the

values $IC_{50} = 11.92 \pm 4.50$ and 41.25 ± 15.45 μg ml^{-1} have been obtained for compounds **144a** and **144b**, respectively.

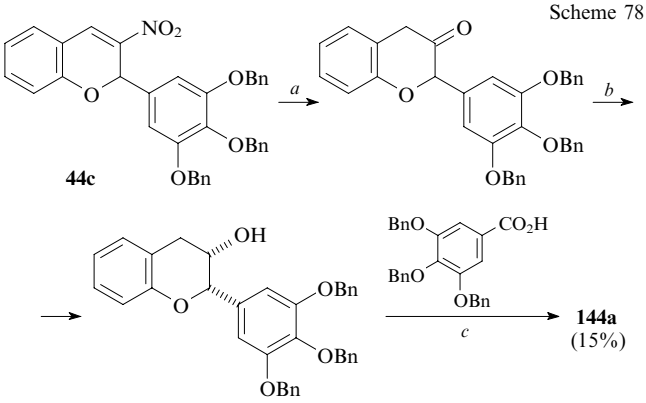
Structures **144**



144a,**b** R = H (**a**), OH (**b**)

A key stage of this synthesis was the conversion of the nitroalkene moiety into a keto group, which was achieved through the reductive Nef reaction with the use of $TiCl_3$ as a reagent. Further stages — stereoselective reduction of ketone with L-selectride, condensation with 3,4,5-tribenzyloxybenzoic acid and elimination of benzyl groups by catalytic hydrogenation — afforded **144a** in 15% yield (Scheme 78).

Scheme 78



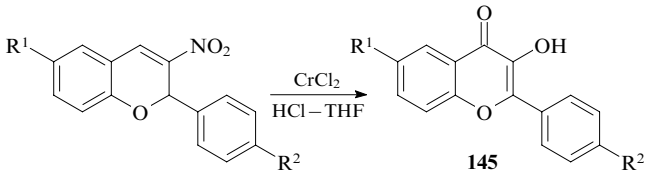
(*a*) $TiCl_3$ (5.0 equiv.), $AcONH_4$ (2.0 equiv.), dioxane (50%) – AcOH (5 : 1), ~20 °C; (*b*) L-selectride, THF, ~20 °C;
(*c*) 1) $EtN{=}C{=}N(CH_2)_3NMe_2$ (1.5 equiv.), 4-dimethylaminopyridine (0.1 equiv.), CH_2Cl_2, ~20 °C; 2) $Pd(OH)_2$, H_2, THF – MeOH (5 : 1), ~20 °C

The reaction of nitrochromenes in a THF – HCl (1 : 5) solution with chromium(II) chloride for 8 – 10 min produces flavonols **145** in yields 60% – 65%.[95] Analogous compounds can also be synthesized by oxidation with 15% hydrogen peroxide in an alkaline medium at ~ 20 °C for 10 min (yields 70% – 89%) (Scheme 79).[96]

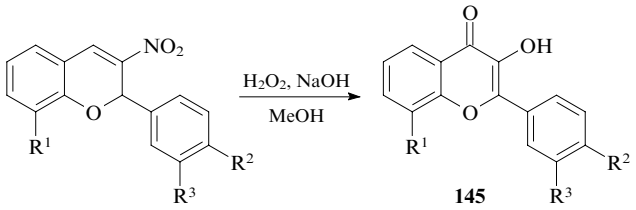
Flavonols **145** have been synthesized from 2-aryl-3-nitrochromenes **44** on irradiation of their methanol solutions containing catalytic amounts of HCl at room temperature.[96] In the absence of the acid, the reaction leads to a mixture of corresponding oximes **146** and **147**, and their acid hydrolysis also leads to flavonols **145** in 69% – 84% yields (Scheme 80).[97, 98]

When potassium superoxide in DMSO is used as an oxidant, the major process is the decomposition of chromene system **44** to give corresponding salicylic and benzoic acids, while flavonols **145** are only byproducts. Possible intermediates of the reaction can be dioxetane **148** and epoxide **149** (Scheme 81).[99]

Scheme 79

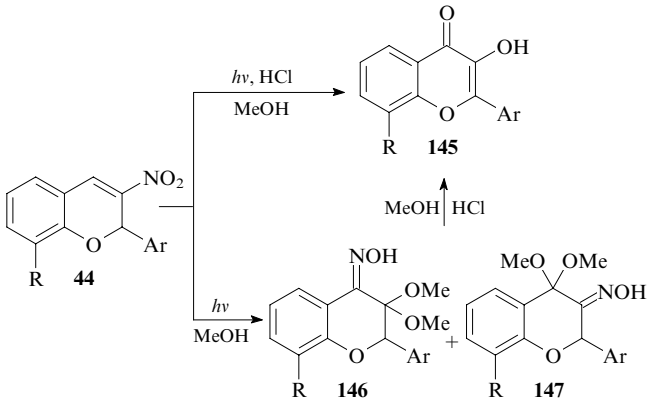


$R^1 = R^2 = H$; $R^1 = H$, $R^2 = MeO$; $R^1 = MeO$, $R^2 = Me$; $R^1 = R^2 = MeO$



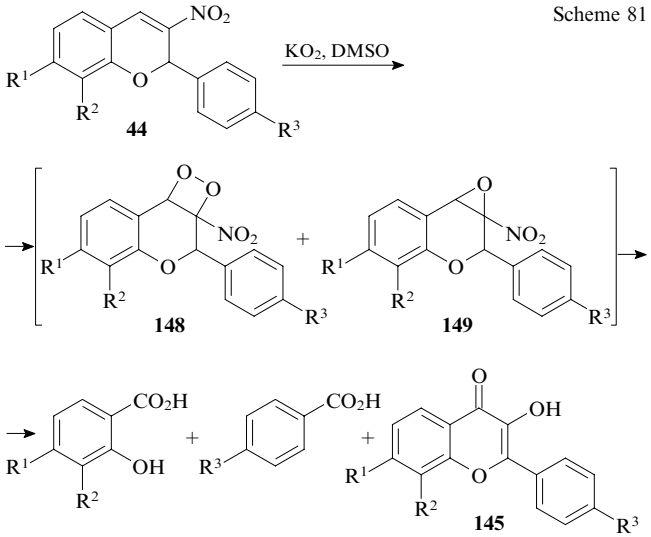
$R^1 = R^2 = R^3 = H$ (yield 76%); $R^1 = R^3 = H$: $R^2 = Me$ (72%), MeO (80%), Cl (70%); $R^1 = H$, $R^2 = R^3 = MeO$ (89%); $R^1 = MeO$: $R^2 = R^3 = H$ (79%), $R^2 = Me$, $R^3 = H$ (83%)

Scheme 80



145: R = H: Ar = Ph (yield 78%), 4-MeC_6H_4 (75%), 4-ClC_6H_4 (73%), 4-$MeOC_6H_4$ (84%); R = MeO: Ar = 4-MeC_6H_4 (73%), 4-$MeOC_6H_4$ (76%), Ph (69%)

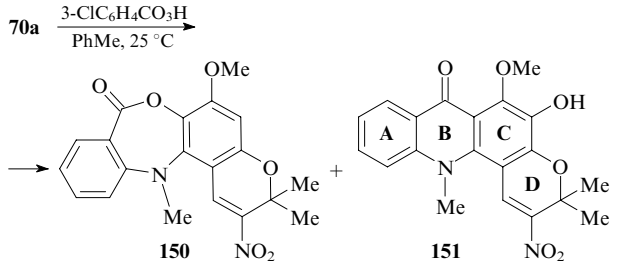
Scheme 81



$R^1 = R^2 = R^3 = H$; $R^1 = R^2 = H$: $R^3 = MeO$, Cl; $R^1 = MeO$, $R^2 = H$, $R^3 = Me$; $R^1 = R^3 = H$, $R^2 = MeO$; $R^1 = H$, $R^2 = R^3 = MeO$

The Baeyer – Villinger oxidation of 2-nitroacronycine (**70a**) is also not chemoselective and is accompanied by hydroxylation of aromatic ring **C**; the reaction gives a mixture of products **150** and **151** in yields 30% and 10%, respectively (Scheme 82).[100]

Scheme 82

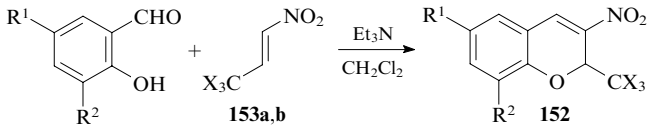


IV. 2-Trihalomethyl-3-nitro-2*H*-chromenes

1. Synthesis from salicylaldehydes and CX_3-nitroalkenes

2-Trihalomethyl-3-nitro-2*H*-chromenes **152** were synthesized for the first time from trifluoro(trichloro)nitropropenes (**153a**,**b**) and salicylaldehydes in dichloromethane in the presence of triethylamine at ~20 °C in yields 53% – 94%.[76, 101 – 103] The formation of intermediate 4-hydroxy-3-nitrochromanes was not observed (Scheme 83).

Scheme 83

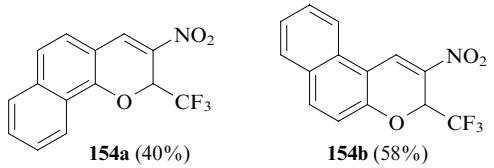


153: X = F (**a**), Cl (**b**)

X	R^1	R^2	Yield of **152** (%)	Ref.
F	H	H	76	101
F	MeO	H	55	76
F	Br	H	93	101
F	NO_2	H	75	102
Cl	H	H	94	101
Cl	MeO	H	61	76
Cl	Br	H	86	101
Cl	NO_2	H	78	76
Cl	H	NO_2	53	103

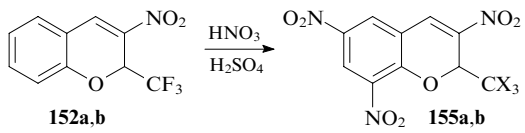
A similar reaction of 1-nitro-3,3,3-trifluoropropene (**153a**) with isomeric naphthaldehydes afforded benzannelated nitrochromenes **154a**,**b**.[104]

Structures **154**



3,6,8-Trinitro-2-trifluoro(trichloro)methyl-2*H*chromenes **155a**,**b** have been synthesized by nitration of chromenes **152a**,**b** with the nitrating mixture at 125 °C for 0.5 h in 81% and 89% yields, respectively (Scheme 84).[105]

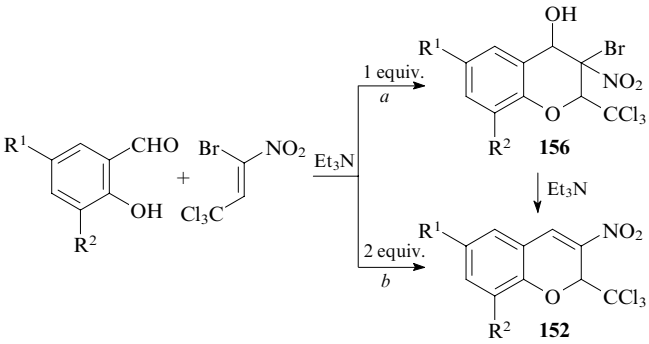
Scheme 84



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

3-Nitro-2-trichloromethyl-2*H*-chromenes **152** have been obtained from the corresponding aldehyde and 1-bromo-1-nitro-3,3,3-trichloropropene in chloroform or dichloromethane at 18 – 20 °C.[106] In the presence of 1 equiv. of triethylamine (path *a*), the reaction gives a mixture of chromanols **156** and chromenes **152**, whereas the use of a twofold excess of the base (path *b*) leads only to nitrochromenes **152** (Scheme 85).

Scheme 85



R^1	R^2	Yield (%)	
		156	**152** (path *b*)
H	H	33	28 (18)[a]
Br	H	19	33
Cl	H	23	40
Cl	Cl	27	39

[a] The yield of reaction along path *a* is parenthesized.

Synthesis of 6,6′-diisopropyl-8,8′-dimethyl-2,2′-dinitro-3,3′-bis(trifluoromethyl)-3*H*,3*H*′-9,9′- bi(benzo[*f*]chromene)-5,10,5′,10′-tetraol (**157**) has been described consisting in the reaction of gossypol (**158**) with trifluoronitropropene **153a** combined in a 1 : 2 molar ratio in diethyl ether in the presence of triethylamine at 20 – 25 °C (yield 80%) (Scheme 86).[107]

Nitrochromene **157** exhibits pronounced antitumour and fungicidal activity.[107] In particular, it causes irreversible death of HCT116 human colon tumour cells; IC_{50} is 4.6 ± 1.0 μmol litre^{-1}. This nitrochromene also exhibits activity against phytopathogenic fungi and oomycetes (Table 8). The maximal activity is observed against *Phoma betae* and *Botritys cinerea*. These data, as well as the fact that gossypol (**158**) (isolated from cotton seeds and roots) and nitroalkene **153a** are easily available, enables the use of chromene **157** in design of new antitumour drugs and fungicides.

Scheme 86

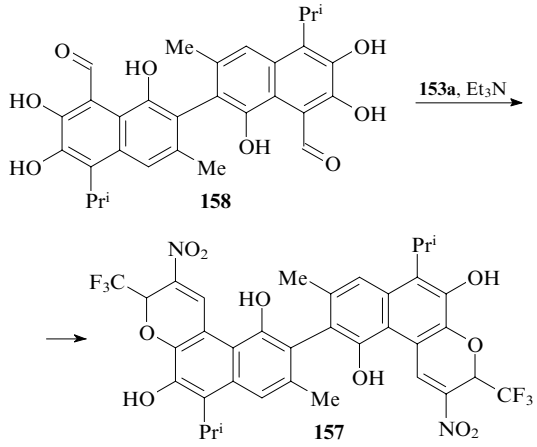
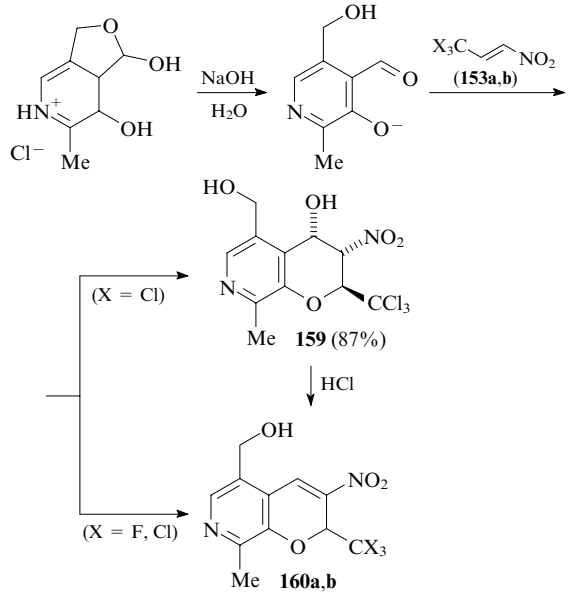


Table 8. Antifungal activity of nitrochromene **157**.[107]

Microorganism	IC_{90-100} /μg ml^{-1}	IC_{50} /μg ml^{-1}
Phoma betae	120	65
Botritys cinerea	65	48
Pythium debaryanum	–	65
Phytophthora infestans	–	96

It has been demonstrated that CX_3-nitropropenes **153a**,**b** react with pyridoxal hydrochloride in an aqueous medium in the presence of sodium hydroxide at 20 °C for 15 – 30 min to give 7-azachroman-4-ol **159** as the individual *trans*,*cis* isomer (from CCl_3-nitroalkene) and 7-azachromene **160a** (from CF_3-nitroalkene) in 87% and 56% yields, respectively.[40] In the presence of concentrated HCl, compound **159** is readily dehydrated to give 7-azachromene **160b** (yield 67%), which can also be directly obtained in the same yield if the reaction is carried out on heating to 45 – 50 °C (Scheme 87).

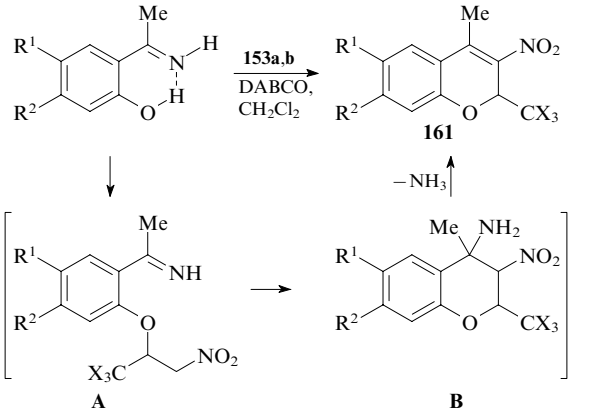
Scheme 87



160: X = F (**a**, yield 56%), Cl (**b**, 67%)

Attempts to synthesize 2-trihalomethyl-4-methyl-2*H*-chromenes from 2-hydroxyacetophenones did not lead to desired results. In all cases, the reaction mixtures contained, in addition to resinification products, considerable amounts of the initial compounds.[108] In this context, N-unsubstituted ketimines were used for synthesis of 4-methyl-3-nitro-2-trifluoro(trichloro)methyl-2*H*-chromenes **161**, and the reaction was carried out in boiling dichloromethane in the presence of DABCO (Scheme 88).

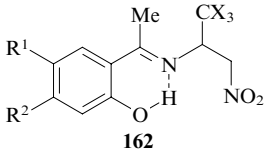
Scheme 88



R^1	R^2	X	Time /h	Yield of **161** (%)
H	H	Cl	5	66
Me	H	Cl	0.5	62
H	MeO	Cl	8	55
H	H	F	3	71
Me	H	F	2	68
Me	H	Cl	3	60

Under these conditions, small amounts of E imine isomers **162** (no more than 10%) formed in addition to target chromenes **161**. If benzene was used as a solvent, the addition of the imino group nitrogen atom to nitroalkenes **153a**,**b** was faster than the addition of the phenol hydroxyl group and mainly resulted in N-substituted imines **162** (yields 17% – 64%).[108]

Structure **162**



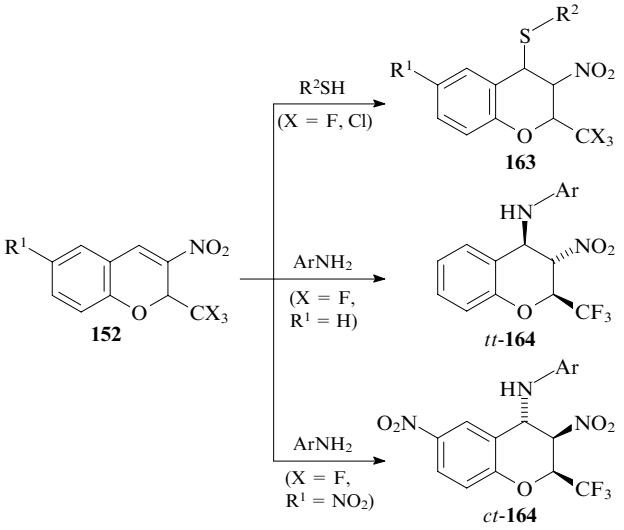
A probable mechanism of the reaction involves the formation of intermediate **A** through the nucleophilic addition of phenolate anion to nitroalkene **153** and its intramolecular cyclization into 4-amino-4-methylchromane **B** with subsequent elimination of ammonia molecule (see Scheme 88).

2. Chemical properties

The reaction of 2-trihalomethyl-3-nitro-2*H*-chromenes **152** with *p*-thiocresol, ethyl sulfanylacetate and 2-sulfanylethanol at 65 °C for 5 h (method A) or in CH_2Cl_2 in the presence of K_2CO_3 at 20 °C for 2 days (method B) occurs as nucleophilic addition of thiols to the activated double bond of chromenes **152** and leads to 2,3,4-trisubstituted chromanes **163** (Scheme 89, Table 9). The reactivity of chromenes **152** was judged by their conversion under the conditions of

methods A and B (see Table 9). 2-CF_3-Chromenes turned out to be more reactive than 2-CCl_3-chromenes, and the introduction of an electron-withdrawing substituent (NO_2, Br) into the 6-position of chromene system enhances the reactivity of both types of chromenes.[102, 109]

Scheme 89



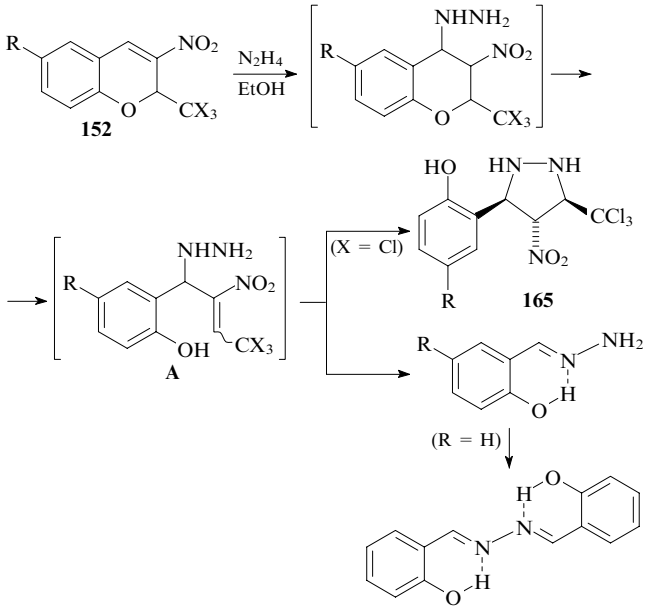
tt-**164**: Ar = Ph (yield 63%), 4-MeC_6H_4 (30%), 4-$MeOC_6H_4$ (47%); *ct*-**164**: Ar = Ph (65%), 4-MeC_6H_4 (70%)

In all cases, four stereoisomeric chromanes **163** were formed, with the *trans*,*trans* (*tt*), *trans*,*cis* (*tc*), *cis*,*trans* (*ct*) and *cis*,*cis* (*cc*) configurations relative to the C(2)–C(3) and C(3)–C(4) bonds, respectively; the isomer ratio in the reaction mixture depended on reaction conditions and the nature of the substrate and S-nucleophile. In some cases, individual diastereomers of chromanes **163** were obtained in 10%–70% yields by recrystallization.[102, 109]

More reactive 2-CF_3-chromenes also react with aromatic amines (aniline, *p*-toluidine and *p*-anisidine) on refluxing in benzene for 4–6 h to form the *tt* or *ct* isomers of 4-arylamino-3-nitro-2-trifluoromethylchromanes **164**; the latter were isolated as individual compounds in 30%–70% yields after recrystallization of the reaction mixtures from hexane or a hexane–dichloromethane mixture (see Scheme 89).[102, 109]

The reaction of 2-trichloromethylchromenes with hydrazine hydrate in ethanol at room temperatures leads to 3,4-*trans*-4,5-*trans*-3-(2-hydroxyaryl)-4-nitro-5-trichloromethylpyrazolidines **165** (yields 56%–73%) *via* the recyclization of the chromene system into N-unsubstituted pyrazolidines (Scheme 90). A secondary path of the reaction is the decomposition of intermediate A to salicylaldehyde hydrazone; this process becomes dominant with an increase in the hydrazine content or when the reaction occurs in boiling ethanol. Under similar conditions, 2-trifluoromethylchromenes react with hydrazine hydrate to give exclusively corresponding salicylaldehyde hydrazones or their mixtures with azines (see Scheme 90).[110]

Scheme 90



X = Cl: R = H, MeO, Br; X = F: R = H, MeO

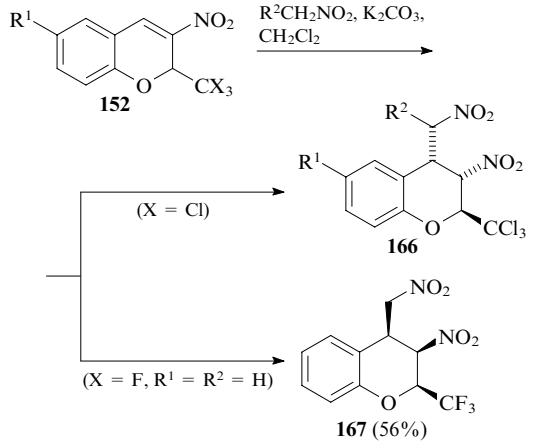
Table 9. Conversion of chromenes **152** in reactions with S-nucleophiles (see text).

X	R^1	R^2	Conversion (%)	
			method A	method B
F	H	4-MeC_6H_4	81	67
F	H	CH_2CO_2Et	95	91
F	H	$(CH_2)_2OH$	47	95
F	Br	4-MeC_6H_4	94	96
F	Br	CH_2CO_2Et	83	65
F	Br	$(CH_2)_2OH$	75	93
F	NO_2	4-MeC_6H_4	100	100
F	NO_2	CH_2CO_2Et	96	95
F	NO_2	$(CH_2)_2OH$	100	98
Cl	H	4-MeC_6H_4	41	30
Cl	H	CH_2CO_2Et	48	72
Cl	H	$(CH_2)_2OH$	12	34
Cl	Br	4-MeC_6H_4	98	86
Cl	Br	CH_2CO_2Et	78	81
Cl	Br	$(CH_2)_2OH$	76	79

2-CCl_3-Chromenes **152** add to nitromethane and nitroethane in the presence of K_2CO_3 at 20 °C for 2–3 days to form 3-nitro-4-nitroalkyl-2-(trichloromethyl)chromanes **166**. Individual *tc* isomers of chromanes **166** have been obtained in 50%–61% yields by recrystallization of the reaction mixture from hexane or a CH_2Cl_2–hexane mixture. The reaction of 3-nitro-2-trifluoromethyl-2*H*-chromene (**152a**) with nitromethnane under similar conditions leads to *cc*-chromane **167** in 56% yield (Scheme 91).[76]

The conjugated addition of acetylacetone and acetoacetic ester to 2-trihalomethyl-substituted chromenes **152** in the presence of NaH has been studied.[76] The reaction yields only *tt*-chromanes **168** with the β-dicarbonyl moiety in the 4-position, which exist in the enol form both in a $CDCl_3$ solution and in the crystalline form (Scheme 92). Only in one case, namely, in the reaction of 3,6-dinitro-2-trifluoromethyl-2*H*-chromene with acetylacetone, did partial elimination of a nitrous acid molecule occur, which led in low yield (11%) to a 31 : 69 mixture of corresponding chromane **168** and 2*H*-chromene **169**.

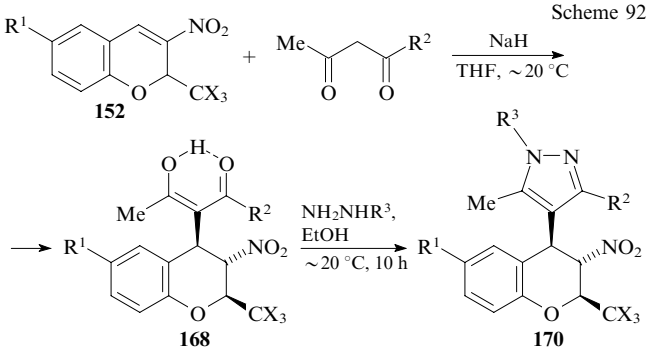
Scheme 91



166: $R^1 = R^2 = H$ (yield 50%); $R^1 = Br$, $R^2 = H$ (51%); $R^1 = H$, $R^2 = Me$ (61%); $R^1 = Br$, $R^2 = Me$ (57%)

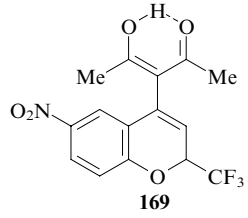
Treatment of chromanes **168** with a solution of hydrazine hydrate or methylhydrazine ($R^3 = H$, Me) in ethanol afforded *trans*,*trans*-4-pyrazolylchromanes **170** in 30% – 84% yields (see Scheme 92).

Scheme 92



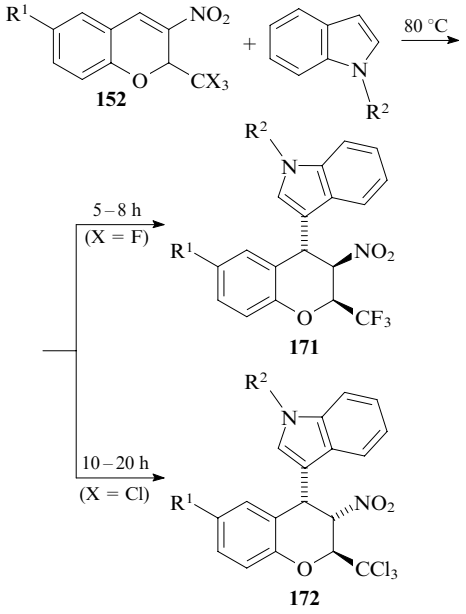
R^1	R^2	X	Yield of **168** (%)	R^1	R^2	X	Yield of **168** (%)
H	Me	F	50	H	OEt	F	52
MeO	Me	F	14	Br	OEt	F	37
Br	Me	F	32	H	OEt	Cl	74
H	Me	Cl	50	MeO	OEt	Cl	11
MeO	Me	Cl	59	Br	OEt	Cl	67
Br	Me	Cl	56	NO_2	OEt	Cl	54
NO_2	Me	Cl	40				

Structure **169**



2-Trifluoromethylchromenes **152** react with an excess of indole or *N*-methylindole at 80 °C for 5 – 8 h without a solvent and catalyst to give 2,3,4-trisubstituted chromanes **171**, isolated as individual *cis*,*trans* isomers in 68% – 84% yields (Scheme 93). These compounds are stable to epimerization on refluxing with DABCO in benzene, which points

Scheme 93



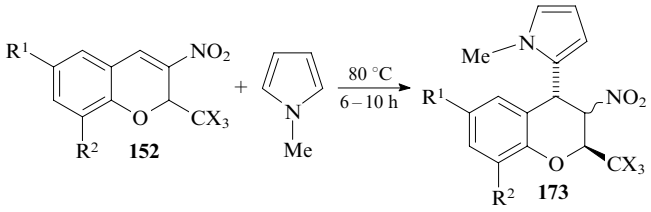
R^1	R^2	Time /h	Yield of **171** (%)	R^1	R^2	Time /h	Yield of **171** (%)
H	H	6	68	MeO	H	8	73
Br	H	8	84	H	Me	5	68
				Br	Me	5	68

R^1	R^2	Time /h	Yield of **172** (%)	*tc* : *ct*
H	H	20	30	100 : 0
Br	Me	15	61	85 : 15
NO_2	Me	10	70	87 : 13

to their high thermodynamic stability.[103] Under similar conditions, the nucleophilic addition of indoles to less reactive 2-CCl_3-substituted chromenes **152** occurs much more slowly (10 – 20 h) and in lower yields (30% – 70%). As distinct from 2-CF_3-chromanes **171** obtained exclusively as the *cis*,*trans* isomer, the *trans*,*cis* isomer is always predominant in 2-CCl_3 derivatives **172** (see Scheme 93).

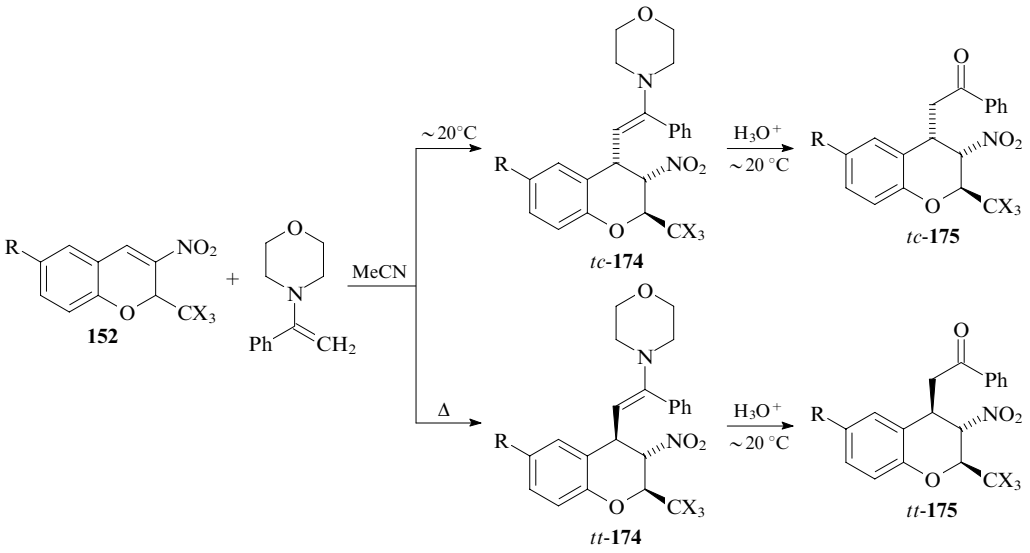
The same trend was observed in the reactions of 2-CX_3-chromenes **152** with *N*-methylpyrrole. In particular, the reaction of 2-CCl_3-chromenes containing electron-withdrawing substituents in the 6- and 8-positions of the

Scheme 94



X	R^1	R^2	Time /h	Yield of **173** (%)	*tc* : *ct*
Cl	Br	H	10	65	98 : 2
Cl	NO_2	H	6	52	96 : 4
Cl	H	NO_2	8	75	87 : 13
F	Br	H	6	72	0 : 100

Scheme 95



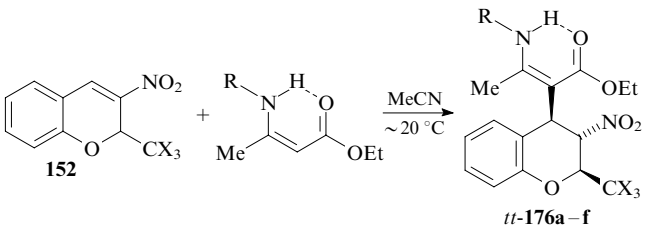
X	R	Yield of **174** (%)		Yield of **175** (%)		X	R	Yield of **174** (%)		Yield of **175** (%)	
		tc	*tt*	*tc*	*tt*			*tc*	*tt*	*tc*	*tt*
F	H	74	61	95	89	Cl	H	83	56	92	97
F	Br	69	47	100	74	Cl	Br	80	28	78	100
F	MeO	68	68	84	95	Cl	MeO	54	28	81	75

aromatic ring with *N*-methylpyrrole at 80 °C in the absence of a solvent mainly led to *trans*,*cis*-chromanes **173** (the content of the *cis*,*trans* isomer varied from 2% to 13%), whereas the analogous reaction with 2-CF_3-chromene **152** (R^1 = Br, R^2 = H) yielded only the *cis*,*trans* isomer of the corresponding chromane; the latter was not epimerized into the *trans*,*cis* isomer even on boiling in methanol in the presence of K_2CO_3 (Scheme 94).

The nucleophilic addition of α-morpholinostyrene to the activated double bond of chromenes **152** affords, depending on the conditions (acetonitrile, 20 °C or 80 °C), the *tc* or *tt* isomers of 2-trihalomethyl-4-[(*E*)-2-morpholino-2-phenylethenyl]-3-nitrochromanes **174** in good yields;[111] the stereochemistry of the products has been confirmed by X-ray crystallography (Scheme 95). The acid hydrolysis of these compounds under mild conditions yields 2-trihalomethyl-3-nitro-4-phenacylchromanes **175** with retention of the configuration.

The direction of the Michael reaction of 2-trihalomethyl-3-nitro-2*H*-chromenes **152** with enamines containing electron-releasing and electron-withdrawing substituents (so-called 'push – pull' enamines) depends on the configuration of the latter. The reaction of compounds **152** with ethyl 3-amino-, ethyl 3-methylamino- and ethyl 3-benzylaminocrotonates, which have *Z* configuration stabilized through intramolecular hydrogen bonds, occurs at the α-carbon atom of enamino ester and leads to corresponding addition products **176a – f** as individual *trans*,*trans* isomers (Scheme 96).

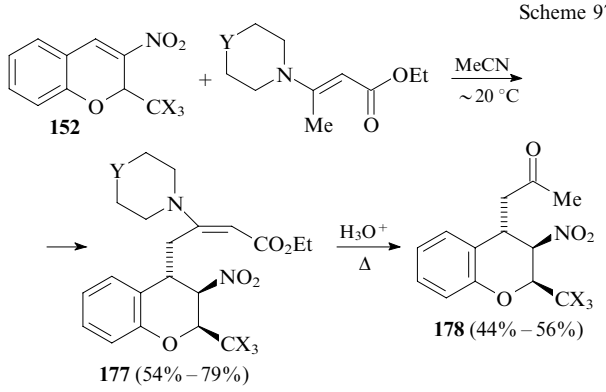
Scheme 96



X = F: R = H (**a**, yield 83%), Me (**b**, 38%), Bn (**c**, 70%);
X = Cl: R = H (**d**, 58%), Me (**e**, 76%), Bn (**f**, 73%)

The enamines prepared from acetoacetic ester and morpholine and having the *E* configuration of the double bond react with chromenes at the vinylogous β-methyl group to yield *cis*,*trans*-chromanes **177**, which are readily hydrolyzed to acetonyl derivatives **178** (Scheme 97). The stereochemistry of products **176** and **177** has been confirmed by X-ray crystallography.[76, 78]

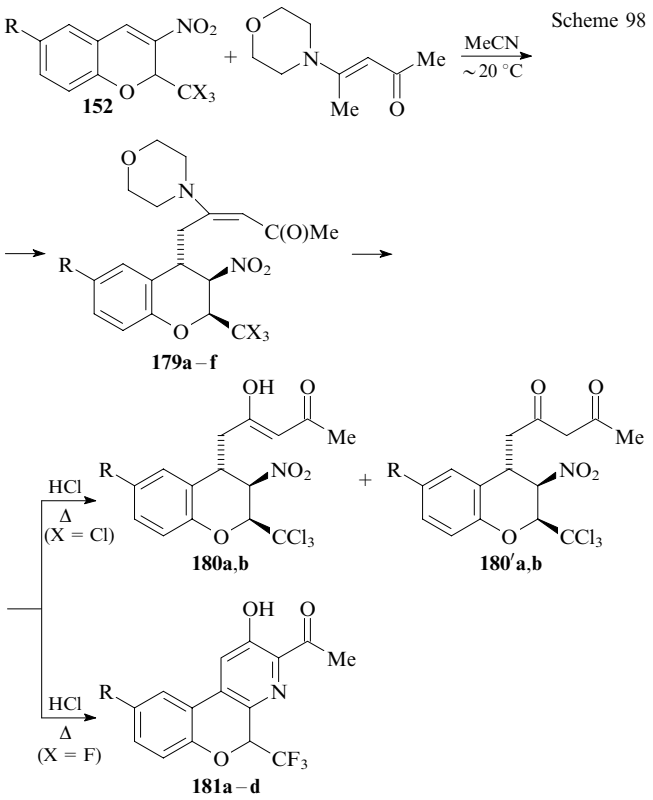
Scheme 97



X = F, Cl; Y = CH_2, O

The reaction of chromenes **152** with the enamine obtained from acetylacetone and morpholine also involves the β-methyl group and yields *cis*,*trans*-chromanes **179a – f**. It is interesting that the acid hydrolysis of 2-CCl_3-chromanes **179a**,**b** yields the expected β-diketones as a mixture of tautomers **180a**,**b** and **180′a**,**b**, whereas the hydrolysis of

Scheme 98



Compound **179**	X	R	Time /h	Yield (%)	Compounds **180**, **181**	Yield (%)
179a [a]	Cl	H	30	42	**180a** [a]	56
179b	Cl	Br	21	52	**180b**	63
179c	F	H	5	83	**181a**	33
179d	F	Br	3	80	**181b**	46
179e	F	NO_2	6	70	**181c**	42
179f	F	MeO	48	64	**181d**	34

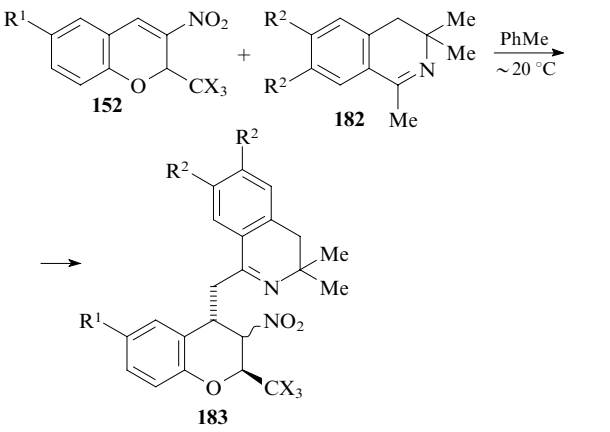
[a] *tc* Isomer.

2-CF_3-chromanes **179c – f** occurs in another way and leads to chromenopyridines **181a – d** in 24% – 46% yields (Scheme 98).[79]

A possible mechanism of formation of pyridines **181** is shown in Scheme 99. It involves the [1,4]-H-shift in the *aci*-form of the initially formed diketone **A** with subsequent cyclization of nitroso derivative **B**.

Recently, we have shown that 1,3,3-trimethyl-3,4-dihydroisoquinolines **182**, as a result of imine – enamine tautomerization, react with 2-trihalomethylchromenes **152** in toluene at room temperature to give corresponding Michael adducts **183** as a mixture of *tc* and *ct* isomers. The content of these isomers was determined by NMR and turned out to depend on the nature of substituents and deuterated solvent used for recording the spectrum (Scheme 100).[104, 112]

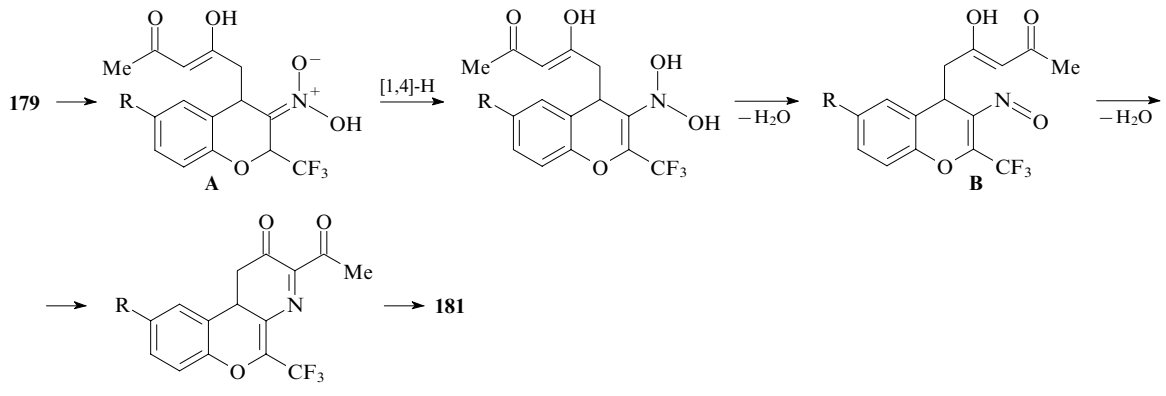
Scheme 100



X	R^1	R^2	Yield of **183** (%)	*tc* : *ct*	
				$CDCl_3$	DMSO-d_6
F	H	H	68	54 : 46	14 : 86
F	H	Me	73	50 : 50	16 : 84
F	H	MeO	81	53 : 47	14 : 86
F	MeO	MeO	84	55 : 45	10 : 90
F	Br	Me	39	54 : 46	16 : 84
F	Br	MeO	86	56 : 44	18 : 82
Cl	H	H	60	83 : 17	36 : 64
Cl	H	Me	78	84 : 16	35 : 65
Cl	H	MeO	71	84 : 16	–
Cl	MeO	MeO	62	86 : 14	30 : 70
Cl	Br	Me	52	84 : 16	35 : 65
Cl	Br	MeO	58	85 : 15	–

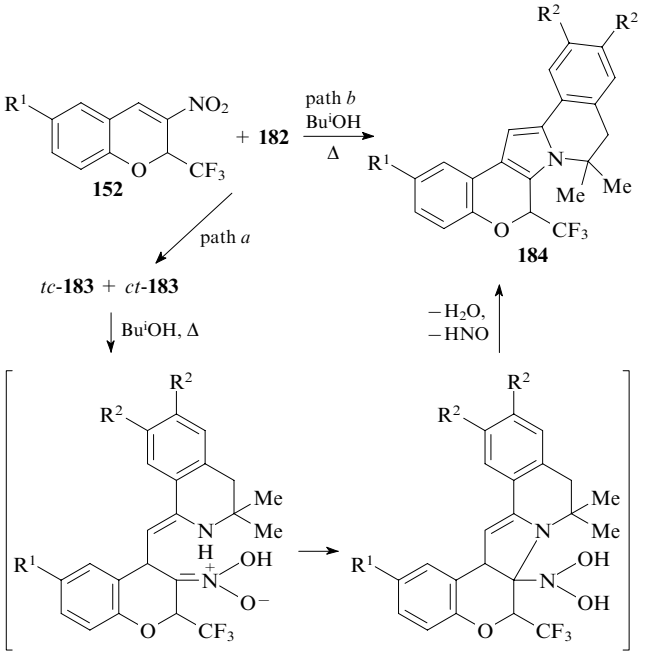
Refluxing of CF_3-containing adducts **183** in isobutyl alcohol for 1 h was accompanied by Grob cyclization to form 8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquino-

Scheme 99



lines **184** (path *a*) with the pentacyclic framework of lamellarin alkaloids exhibiting high biological activity (Scheme 101). Under the same conditions, compounds **184** can be synthesized directly from chromenes **152** and corresponding 3,4-dihydroisoquinolines **182**, but in lower yields (path *b*). The suggested mechanism implies that the nitro group in the *aci*-form of Michael adduct **183** is replaced through the intramolecular addition–elimination reaction accompanied by elimination of water and hyponitrous acid (see Scheme 101).[104]

Scheme 101



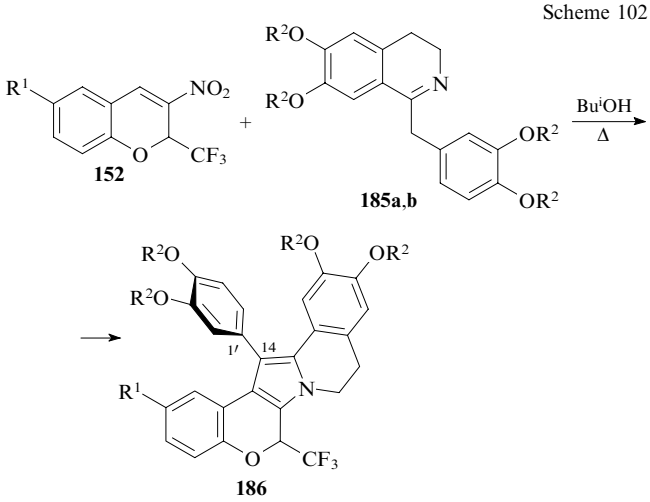
R^1	R^2	Yield of **184** (%)		R^1	R^2	Yield of **184** (%)	
		path *a*	path *b*			path *a*	path *b*
H	H	58	48	MeO	MeO	77	42
H	Me	67	60	Br	Me	63	26
H	MeO	56	25	Br	MeO	75	61

The reaction of 2-CF_3-nitrochromenes **152** with dihydropapaverine (**185a**) and drotaverine (**185b**) on refluxing in isobutyl alcohol yields 14-aryl-8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolines **186** as a mixture of rotamers (Scheme 102).[113]

As determined by dynamic ^1H and ^{19}F NMR, the barrier to rotation about the C(14)–C(1′) bond in compound **186** (R^1 = H, R^2 = Me) is 13.0 kcal mol^{-1}. Benzannelated chromene **154b** does not react with dihydropapaverine (**185a**) because of steric hindrances, whereas its isomer **154a** forms hexacyclic heterocyclization product **187** in 94% yield.[104]

With dihydrofuran, chromenes **152** react with high diastereoselectivity *via* the hetero-Diels–Alder reaction on heating in a dienophile medium to give *endo*-adducts **188**; only one compound **188** (R^1 = H, R^2 = NO_2, X = Cl) was obtained as a 85 : 15 mixture of *endo* and *exo* isomers (Scheme 103).[105]

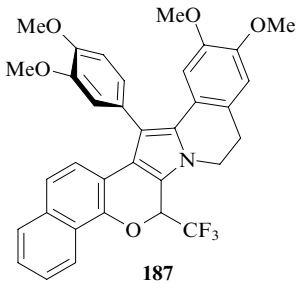
Scheme 102



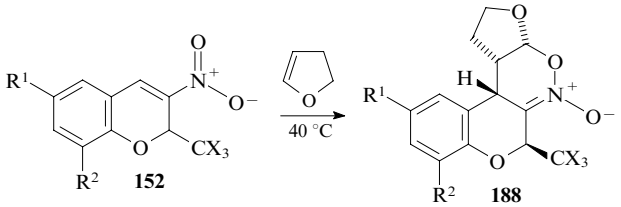
185: R^2 = Me (**a**), Et (**b**)

R^1	R^2	Yield of **186** (%)	R^1	R^2	Yield of **186** (%)
H	Me	78	H	Et	81
MeO	Me	66	MeO	Et	71
Br	Me	92	Br	Et	64

Structure **187**



Scheme 103

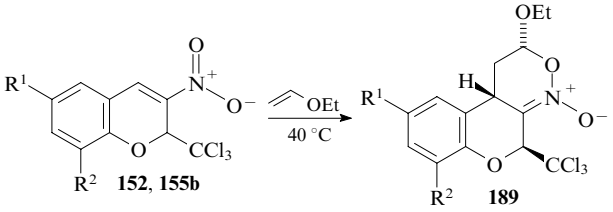


R^1	R^2	X	Time	Yield of **188** (%)
H	H	F	3 days	47
Br	H	F	2 days	67
NO_2	H	F	1 day	68
H	H	Cl	7 days	20
Br	H	Cl	4 days	49
NO_2	H	Cl	2 days	40
H	NO_2	Cl	2 days	30 [a]
NO_2	NO_2	Cl	3 h	56
MeO	H	Cl	10 h [b]	49

[a] Mixture of *endo* and *exo* diastereomers; [b] at 60 °C.

Vinyl ethyl ether reacts with 2-CCl_3-chromenes **152** and **155b** at 40 °C to form products **189**; the yield and reaction duration depend on the number of electron-withdrawing nitro groups in the chromene aromatic ring (Scheme 104). The *endo*-configuration of the oxazine ring and the *trans*-arrangement of the H(5) and H(10b) atoms in compounds **189** have been confirmed by X-ray crystallography.

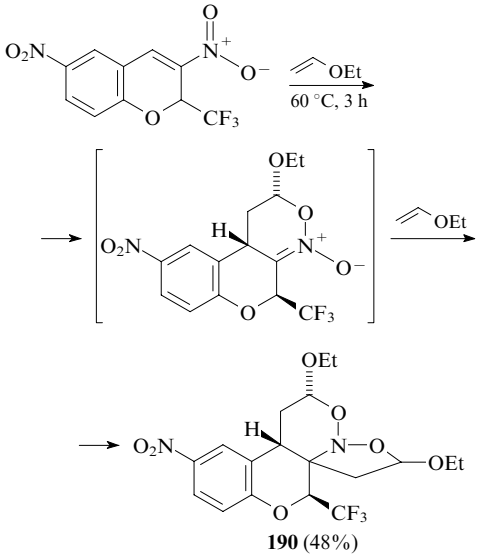
Scheme 104



R^1	R^2	Time	Yield of **189** (%)
H	H	3 days	15
NO_2	H	1 day	35
NO_2	NO_2	3 h	46

Under similar conditions, the most reactive 3,6-dinitro-2-trifluoromethyl-2*H*-chromene reacts with two molecules of vinyl ethyl ether to give tandem [4 + 2]/[3 + 2]-cycloaddition product **190** in 48% yield (Scheme 105).[105]

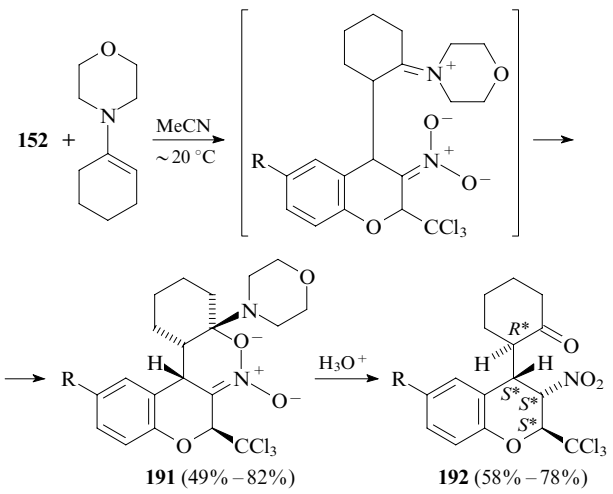
Scheme 105



The reaction of *N*-cyclohexen-1-ylmorpholine with 2-trichloromethylchromenes **152** in acetonitrile at ~20 °C occurs with high diastereoselectivity to give 1,2-oxazine *N*-oxides **191** in 32% – 82% yields. This process involves the nucleophilic addition of enamine to the activated double bond of chromene (Michael reaction) giving an intermediate betaine in which the ambident nitronate anion attacks the iminium carbon atom. The acid hydrolysis of compounds **191** in the presence of HCl at ~50 °C leads to corresponding ketones **192** in 58% – 78% yields; the relative configuration of the latter has been confirmed by X-ray crystallography (Scheme 106).[114]

Refluxing of CX_3-chromenes **152** with sarcosine and paraformaldehyde in toluene for 5 – 10 min with azeotropic water removal leads to benzopyrano[3,4-*c*]pyrrolidines **193**

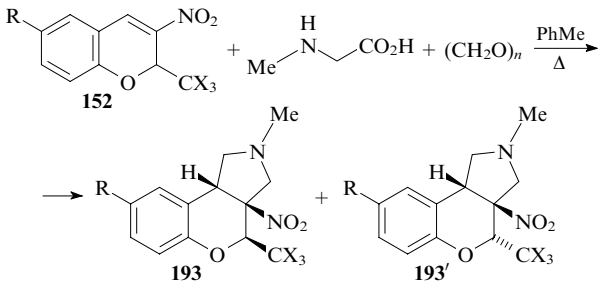
Scheme 106



R = H, MeO, Br

(yields 77% – 97%), isolated as free bases by crystallization from the dichloromethane – hexane system (Scheme 107). Like 2-aryl-3-nitro-2*H*-chromenes **44**,[86,87] compounds **193** are mainly formed as *cis* isomers relative to the NO_2 and CX_3 groups (X-ray crystallography data). *trans* Isomers **193′** were observed only in the crude product in amounts 3% – 20%.

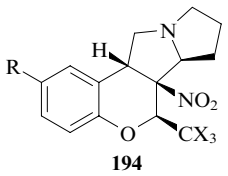
Scheme 107



R = H, Br, MeO, NO_2; X = F, Cl

The reaction of compounds **152** with proline and paraformaldehyde occurs analogously to give chromenopyrrolizidines **194** in 11% – 17% yields; the stereochemistry of the latter was confirmed by 2D $^1H-^1H$ NOESY experiments.[88]

Structure **194**

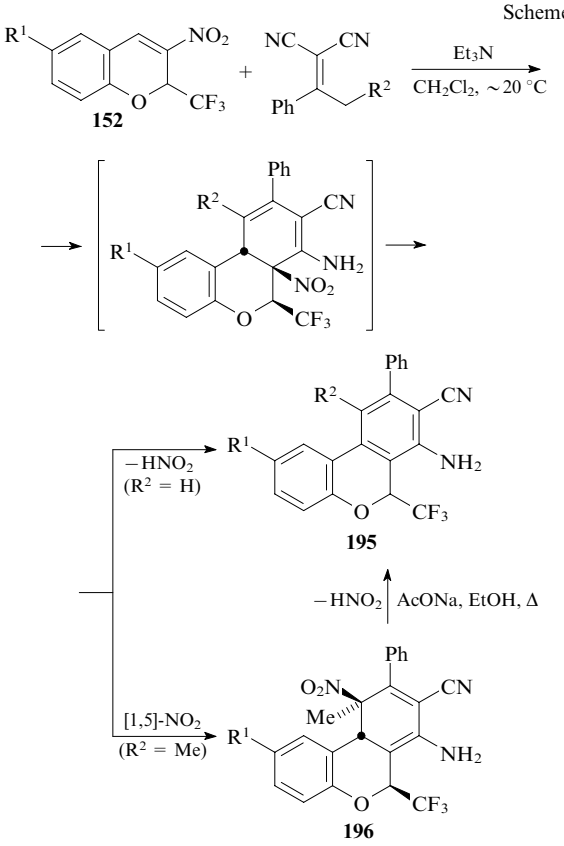


R = H, Br; X = F, Cl

Of special interest is the domino reaction of 2-CF_3-nitrochromenes **152** and (1-phenylalkylidene)malononitriles in the presence of triethylamine at ~20 °C. The reaction of chromenes **152** with (1-phenylethylidene)malononitrile was accompanied by spontaneous aromatization to give dibenzo[*b*,*d*]pyrans **195** (R^2 = H) in 33% – 64% yields, as in the case of 2-aryl-3-nitrochromenes **44**.[74,75] However, the reaction with (1-phenylpropylidene)malononitrile was accompanied by the rare [1,5]-sigmatropic shift of the nitro group

to give compounds **196** (yields 45% – 70%); the regio- and stereochemistry of the latter was confirmed by X-ray crystallography. In this case, the aromatization of products **196** occurred under more severe conditions (refluxing in ethanol with sodium acetate for 4 – 6 h), and the yields of corresponding dibenzo[*b*,*d*]pyrans **195** (R^2 = Me) were 72% – 89% (Scheme 108).[115]

Scheme 108



R^1 = H, MeO, Br, NO_2

V. Conclusion

Analysis of available literature data shows that, among the 3-nitro-2*H*-chromene derivatives, 2-aryl-3-nitro- and 2-trihalomethyl-3-nitro-2*H*-chromenes have been best studied to date. Information on 2-amino- and 2-alkoxy-3-nitro-2*H*-chromenes is rather scarce, while no information at all is available on derivatives containing a halogen atom or nitro or carboxyl group in the 2-position. In general, owing to the presence of the double bond conjugated with the nitro group in 3-nitro-2*H*-chromenes, they exhibit high reactivity toward different compounds. Reactions typical of these heterocycles are also diverse; most of them are distinguished by high regio- and stereoselectivity and lead to new compounds with useful properties. At the same time, the synthetic potential of 3-nitro-2*H*-chromenes is far from being exhausted since many reactions, for example, their reactions with nucleophiles and 1,3-dipoles, have not been fully explored yet.

The introduction of the trifluoromethyl group in the 2-position of the chromene system essentially changes the reactivity of the double bond of the pyran ring toward nucleophiles and is responsible for a wealth of synthetic possibilities of 2-trifluoromethyl-3-nitro-2*H*-chromenes. The enhanced reactivity of these compounds is presumably due to the negative inductive effect of the CF_3 group, which additionally activates the double bond and thus facilitates the addition of nucleophilic reagents. It is surprising, but despite the easy availability of 2-trifluoromethyl-3-nitro-2*H*-chromenes, these compounds have long remained out of sight of synthetic chemists, and their systematic studies have only recently been initiated. Nevertheless, it is clear that 2-CF_3-chromenes are more reactive than 2-aryl- and even 2-CCl_3-chromenes and are valuable substrates for diastereoselective synthesis of a wide series of 2,3,4-trisubstituted chromanes with potential biological activity.

Taking into account that many modern pharmaceutical and agrochemical products contain the chromane moiety,[2, 3] we believe that efforts at modifying and studying the reactivity of 2*H*-chromenes and their derivatives with the aim to extend the synthetic possibilities of the chromene system are important and promising for further research in the field of oxygen-containing heterocyclic compounds and for the search for new biologically active molecules. In our opinion, this review can stimulate synthetic organic chemists to further study the chemistry of these interesting and practically useful compounds.

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