DOI: 10.1070/RCR4756

Synthesis and properties of 2-mono- and 2,3-disubstituted thiochromones

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Data on the methods of synthesis, chemical reactivity and biological activity of 2-mono- and 2,3-disubstituted thiochromones are integrated and described systematically. Particular sections of the review address 2-arylthiochromones (thioflavones), 2-alkyl- and 2,3-dialkyl-substituted thiochromones and functionalized thiochromones with electron-donating (amino, hydroxy or mercapto group) or electron-withdrawing (cyano, nitro, formyl or carboxyl group or halogen atom) groups in positions 2 and/or 3. Analysis of published data indicates that chemical transformations of thiochromones, including functional derivatives, are rarely accompanied by thiopyrone ring opening, which distinguishes these compounds from representatives of the chromone system. Reaction conditions and product yields and data on the biological activities of some compounds of this class are given.
The bibliography includes 189 references.

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1. Introduction

The interest in the thiochromone chemistry has considerably grown in the last two decades — more than a half of all papers devoted to these derivatives since 1913, when the thiochromone system was described for the first time, appeared during this period.[1,2] However, in the number of publications, thiochromones lag much behind the oxygen analogues — chromones. This is due not only to the lower accessibility of the sulfur-containing building blocks, their unpleasant odour and the tendency to form disulfides, but also to the lower reactivity of the thiopyrone ring, which is a direct consequence of replacement of the oxygen atom by the less electronegative sulfur atom. The nucleophilic attack on the C(2) atom characteristic of pyrones and chromones, which is usually accompanied by ring opening and subsequent ring transformation, rarely occurs for the thio derivatives. It is evident that this sharp difference between the behaviours of these two related heterocyclic systems stems from the weak inductive effect ($-I$) of sulfur, resulting in low electrophilicity of the carbon atom attached to it and enhanced aromaticity of (benzo)thiopyrones compared with their oxygen analogues and, hence, a considerably lower synthetic potential of thiochromones.

Since the thiopyran system does not occur in nature, the biological activity of its derivatives is less studied than that for pyrans or benzopyrans. Nevertheless, judging by the increasing number of patents, substituted thiochromones are fairly promising compounds for medicinal chemistry. It is also noteworthy that owing to properties of the sulfur atom (variable oxidation states, easy oxidizability, both electron-donating and electron-withdrawing function), many representatives of the thiopyran series possess valuable spectral properties and are used to develop new dyes and modern materials for electronics.[3–6]

Recently we described[7] structural features, preparation methods and reactivity of 2,3-unsubstituted (**I**) and 3-substituted thiochromones (**II**). The present review covers data on the synthesis, chemical reactivity and biological activity of 2-mono- (**III**) and 2,3-disubstituted thiochromones (**IV**), including their functional derivatives. These reviews integrate virtually all currently available information on thiochromone chemistry (except for the data on 2,3-heteroannulated analogues, which will be considered elsewhere). The rather voluminous amount of information is

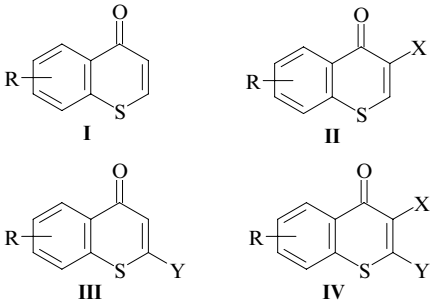
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Current research interests: organic synthesis, oxygen heterocycles, polyfunctional compounds.

Received 7 June 2017
Translation: Z.P.Svitanko

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arranged in terms of the substituent nature and position in the thiopyrone ring.

Structures I–IV

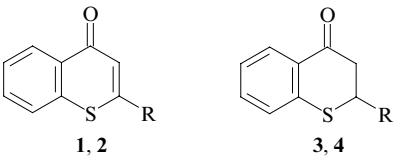


R, X, Y is alkyl (or aryl) substituent or functional group

Unlike the chromone chemistry, the chemistry of thiochromones, in which the heterocyclic system is not prone to S–C bond cleavage without an electron-withdrawing substituent in position 3,[7] is not so extensive and diverse. Therefore, the data on 2-mono- and 2,3-disubstituted derivatives can be considered within one review. Among compounds of this class, the best studied are 2-arylthiochromones (thioflavones) **1** and 2-alkylthiochromones **2**, which receive the most attention in this review. Thiochromones containing various functional groups (CN, NO_2, NH_2, SH, OH, CHO or halogen atom) in positions 2 and 3 are of great synthetic value for the design of heterocyclic systems and are discussed in a separate Section. The reaction conditions are presented in the review in considerable detail and the yields of products are indicated except for the cases where they are not given in the original source.

It is important to note that despite the abundance and diversity of representatives of thiopyrans such as 2*H*- and 4*H*-thiopyrans and benzothiopyrans, 2- and 4-thiopyrones and benzothiopyrones (thiochromones) and also their di- and tetrahydro derivatives, there is only one subject review [8] on the thioflavanone **3** and thiochromanone **4** chemistry. The data on 2-mono- and 2,3-disubstituted thiochromones have not yet been integrated and occur as a few mentions in the reviews devoted to (benzo)thiopyrans [3–6] and chromones.[9–12] In this review, hydrogenated compounds **3** and **4** are mentioned only as the starting reactants or products in the discussions of the preparation methods and chemical properties of thioflavones **1** and thiochromones **2**.

Structures 1–4



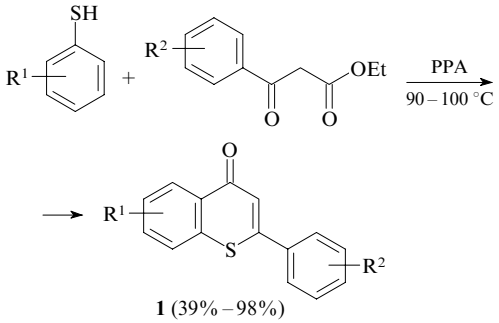
R = Ar (**1**, **3**), Alk (**2**, **4**)

2. Synthesis of 2-substituted thiochromones

2.1. Preparation of thioflavones

The condensation of arenethiols with aroylacetic esters is the most convenient and frequently used method for the synthesis of thioflavones (2-aryl-4*H*-thiochromen-4-ones, 2-aryl-4*H*-benzothiopyran-4-ones, **1**). These products are formed upon the addition of a mixture of a thiol and β-ketoester to polyphosphoric acid followed by stirring of the reaction mixture at 90–100 °C for 1–2 h. The yields of thioflavones vary over a broad range from moderate to nearly quantitative. Although no special studies have been carried out to elucidate the effect of the nature and positions of the groups R^1 and R^2 on the course of this reaction, evidently, the electrophilic cyclization to the thiopyrone system should be facilitated by the presence of electron-donating groups R^1 in the thiol, whereas the substituent R^2 in the ketoester is less significant (Scheme 1).[13–19]

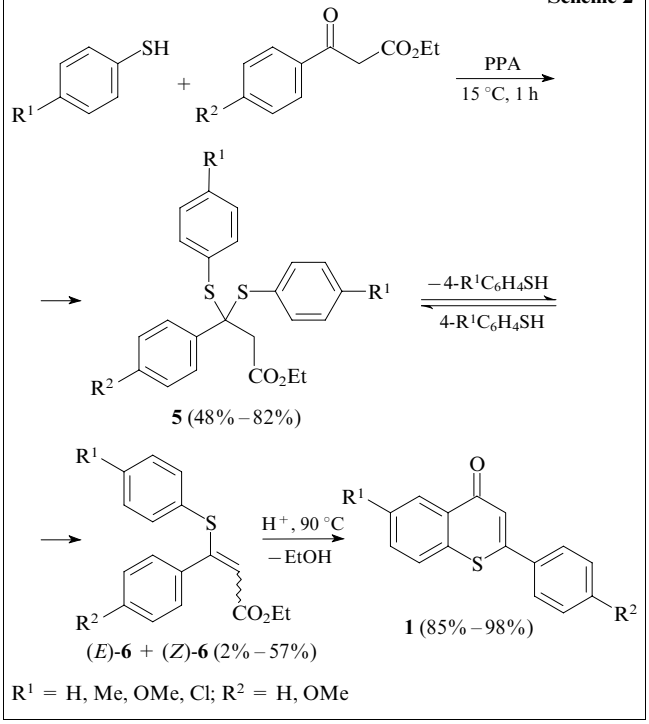
Scheme 1



R^1 = H, Me, OMe, Cl, Br (in different positions);
R^2 = H, Me, OMe, Cl, Br, NO_2 (in different positions)

The mechanism of this reaction has been studied by Japanese researchers,[20] who demonstrated that the reactions of arenethiols with ethyl aroylacetates in polyphosphoric acid at a temperature from 5 to 15 °C would mainly produce 3-aryl-3,3-bis(arylthio)propionates **5** in 48%–82% yields. Ethyl 3-(arylthio)cinnamates **6** as mixtures of *E*- and

Scheme 2

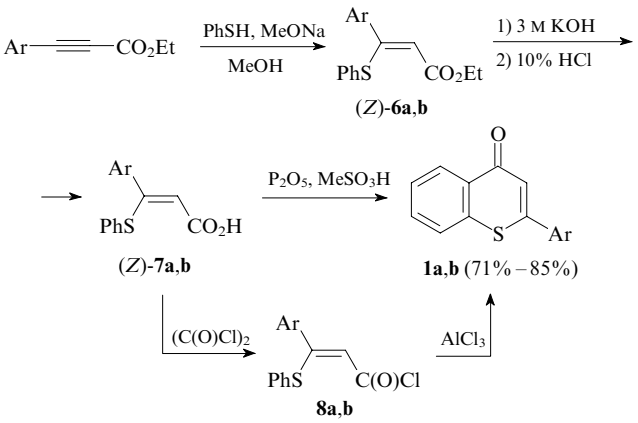


R^1 = H, Me, OMe, Cl; R^2 = H, OMe

Z-isomers were isolated as side products; they are formed as the major products when arenethiols are replaced by *tert*-butylthiobenzene.[21] Cinnamates **6** readily add arenethiols in dilute PPA at room temperature to give propionates **5**, while treatment of esters **5** or **6** with polyphosphoric acid (85% P_2O_5) or 98% sulfuric acid at 90 °C affords thioflavones **1** in high yields as a result of electrophilic substitution at the arylthio moiety. Therefore, compounds **5** and **6** can be considered as intermediates in this synthesis of thioflavones **1** (Scheme 2).[20]

The second classic and equally popular method for the preparation of thioflavones is the nucleophilic addition of benzenethiol to aryl propiolates in the presence of a base, which is directed at the β-carbon atom and affords cinnamates **6** mainly as *Z*-isomers.[1,2,22] Detty and co-workers[23,24] carried out this reaction with heating in methanol in the presence of sodium methoxide, immediately hydrolyzed intermediate esters **6a**,**b** (KOH, refluxing, 2 h) and, after addition of hydrochloric acid, isolated acids **7a**,**b** in 78% and 86% yields. The Friedel–Crafts cyclization of these acids to thioflavones **1a**,**b** can occur either in the presence of P_2O_5 and methanesulfonic acid[23] or *via* the reaction with oxalyl chloride followed by treatment of acid chlorides **8a**,**b** with aluminium chloride (Scheme 3).[24]

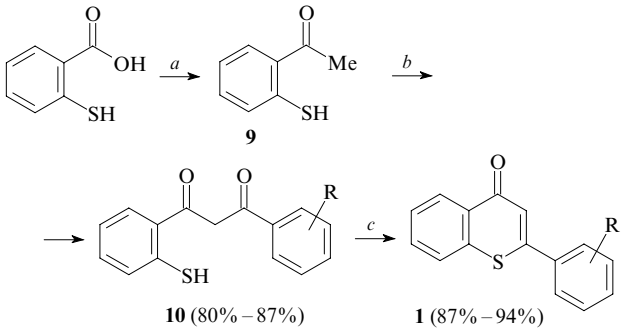
Scheme 3



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

In recent years, Lee and co-workers[25–27] have developed three new approaches to the synthesis of thioflavones **1**, two of the approaches being based on the use of thiosalicylic (2-mercaptobenzoic) acid. The reaction of this acid with methyllithium in monoglyme (dimethoxyethane, DME) gives 2-mercaptoacetophenone (**9**) in 80% yield;[28,29] aroylation of **9** results in the desired thioflavones **1**. The condensation of the lithium dianion, generated from ketone **9** and 2 equiv. of lithium diisopropylamide (LDA) in THF at −78 °C, with benzoyl chloride yields 2-mercaptobenzoylacetophenone (**10**) in only 15% yield. With benzoyl cyanide being used as the acylating agent, the yield of diketone **10** increases to 67%, and the yield of *N*-methyl-*N*-methoxybenzamide (Weinreb amide) after 16 h at room temperature increases to 84%. Substituted Weinreb amides have been used to prepare a broad range of 1,3-diketones **10**, which have been cyclodehydrated by treatment with sulfuric acid in acetonitrile at room temperature to furnish thioflavones **1** in high yields (Scheme 4).[25]

Scheme 4

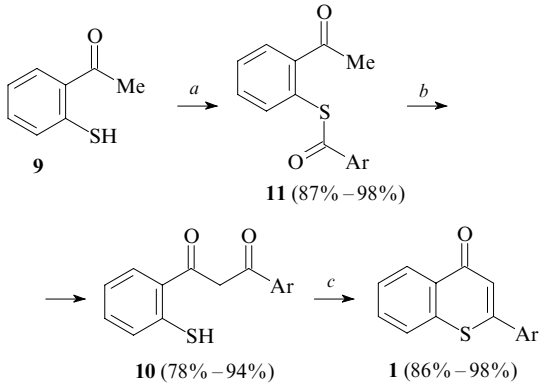


(*a*) 1) MeLi, DME; 2) H_3O^+; (*b*) $RC_6H_4C(O)N(Me)OMe$, LDA (2 equiv.), THF; (*c*) H_2SO_4, MeCN; R = H, Me, OMe, Cl (in different positions)

The aroylation of 2-mercaptoacetophenone (**9**) with aromatic acid chlorides in the presence of triethylamine in dichloromethane at 0 °C is directed at the sulfur atom and gives aroylthioacetophenones **11**. The intramolecular Baker–Venkataraman rearrangement of these compounds in the presence of 2 equiv. of lithium diisopropylamide in THF at a temperature from −15 to 0 °C over a period of 0.5 h gives 1,3-diketones **10**, which are readily converted, under these conditions, to thioflavones **1** containing either aromatic or heteroaromatic moieties in position 2 (Scheme 5).[26]

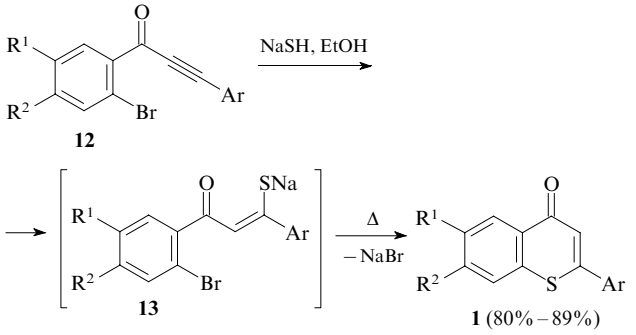
A drawback of the methods based on the use of thiosalicylic acid as the starting reactant[25,26] is the limited possibility for the preparation of thioflavones with substituents in the annulated benzene ring, since substituted mercaptobenzoic acids are poorly accessible. In 2015, Lee and Choi[27] extended the series of thioflavones **1** using acetylenic ketones with a halogen atom in the *ortho*-position of the benzene ring. For instance, 1-(2-bromophenyl)-3-(het)arylprop-2-yn-1-ones **12** react with sodium hydrogen sulfide in ethanol at room temperature being rapidly converted to unsaturated thiolates **13**, which are cyclized into thioflavones **1** in high yields on refluxing for several hours *via* intramolecular displacement of bromine (Scheme 6).

Scheme 5



(*a*) ArC(O)Cl, Et_3N, CH_2Cl_2; (*b*) 1) LDA (2 equiv.), THF; 2) H_3O^+; (*c*) H_2SO_4, MeCN; Ar = Ph, 2-ClC_6H_4, 4-ClC_6H_4, 2-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 2-Fu, 2-Th, 3-Py; Fu is furyl, Th is thienyl, Py is pyridyl

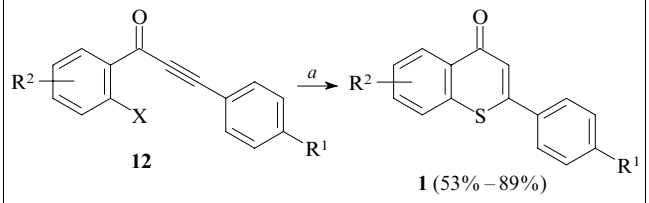
Scheme 6



Ar = Ph, 3-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3,5-$(MeO)_2C_6H_3$, 3-Th, 3-Py; R^1, R^2 = H, Me, OMe, Cl

Similar results, moreover, for a wider range of compounds, were reported back in 2012 by Yang *et al.*[30] The researchers showed that both 1-(2-alkoxyaryl)- and 1-(2-haloaryl)-3-arylprop-2-yn-1-ones **12** react with sodium sulfide nonahydrate on refluxing in ethanol for 24 h to give thioflavones **1**. The intramolecular nucleophilic substitution involves in this case not only halogen atoms, but also alkoxy substituents, which are poorer leaving groups; this results in S-arylation *via* C – Hal or C – O bond cleavage and does not require transition metal catalysis (Scheme 7). This method is also applicable for the preparation of 2-propyl- and 2-hexylthiochromones.[30]

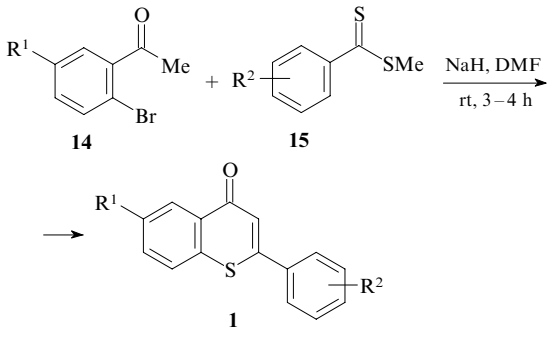
Scheme 7



(*a*) $Na_2S \cdot 9H_2O$, EtOH, Δ, 24 h; R^1 = H, Me, Et, OMe, OEt, Cl, Ac; R^2 = H, OMe, Cl; X = OMe, OEt, OPr^n, OPh, Cl, Br, I

A facile and convenient method for the synthesis of thioflavones **1** has been developed on the basis of condensation of *o*-bromoacetophenones **14** with methyl benzodithioates **15** in the presence of sodium hydride in DMF at room temperature for 3 – 4 h. The thiopyrone ring is formed as a result of nucleophilic displacement of the active bromine atom in one-pot intramolecular S-arylation. This reaction can be carried out for both substituted aromatic and heterocyclic dithio esters (*e.g.*, methyl thiophene-2-carbodithiooate), the product yields being 58% – 79% (Scheme 8).[31]

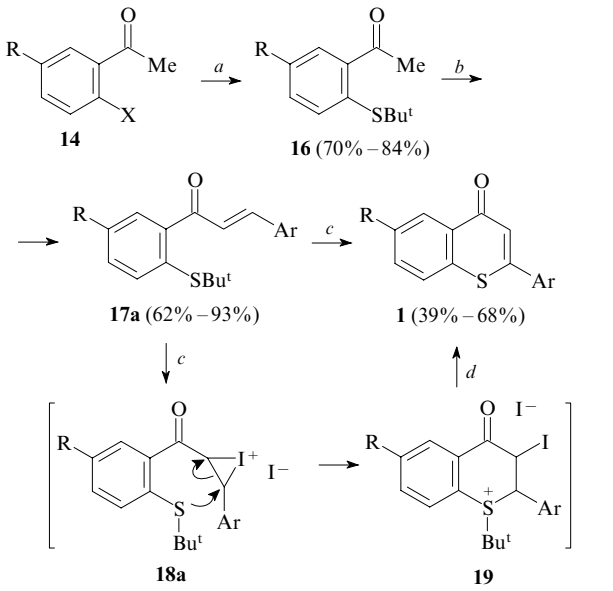
Scheme 8



R^1 = H, CF_3; R^2 = H, OMe

Recently Kobayashi *et al.*[32] proposed a new three-step method for the synthesis of thioflavones **1** from *o*-haloacetophenones **14**. First, ketones **14** react with 2-methylpropane-2-thiol in the presence of NaH in DMF at room temperature to give sulfides **16**, which condense with aromatic aldehydes in a solution of NaOH in aqueous ethanol to give *o*-*tert*-butylthiochalcones **17a** in high yields. Treatment of the latter compounds with iodine in refluxing propionitrile or *N*-methylpyrrolidin-2-one (NMP) affords the target products **1** in moderate to good yields. The last step proceeds *via* the formation of cyclic iodonium intermediate **18a**, which is ring-opened and cyclize to give thiochromanium cation **19**, and the latter eliminates hydrogen iodide and isobutylene (Scheme 9).[32]

Scheme 9

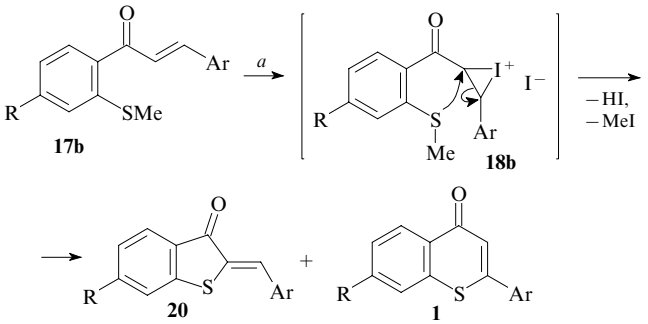


(*a*) Bu^tSH, NaH, DMF, rt; (*b*) ArCHO, NaOH, EtOH (aq.), rt; (*c*) I_2, $NaHCO_3$, EtCN or NMP, Δ; (*d*) elimination of 2 HI and $CH_2{=}CMe_2$; R = H, Cl, OMe; X = Cl, Br; Ar = Ph, 4-MeC_6H_4, 3-$MeOC_6H_4$, 3,4-$Cl_2C_6H_3$, 2,5-$(MeO)_2C_6H_3$, 1-Naph; Naph is naphthyl

It is noteworthy that upon iodination of *o*-methylthiochalcones **17b** in DMSO at 150 °C, opening of the iodonium intermediate **18b** follows mainly a different route, giving rise to a mixture of 2-arylidenebenzothiophen-3-ones (thioaurones, **20**) and thioflavones **1** in 40% – 73% yields, with thioaurones **20** markedly predominating; the **20** : **1** ratio varies from 73 : 27 to 94 : 6 (Scheme 10).[33]

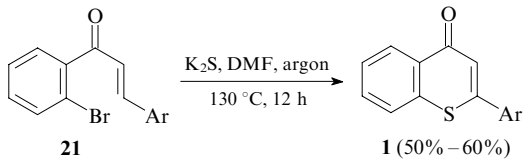
It has been shown [34] that on treatment with K_2S in DMF at 130 °C under argon, 2′-bromochalcones **21** cyclize to thioflavones **1** by a radical mechanism. The reaction is initiated by the $[S_3]^{-\cdot}$ radical anion,[35] which is formed in the K_2S solution in DMF. This is the first example of sulfur atom insertion with the use of K_2S without metal complex catalysts, usually employed for this purpose (Scheme 11).[36, 37]

Scheme 10



(*a*) I_2, DMSO, 150 °C, 8 – 12 h; R = H, F; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2,3-$(OCH_2O)C_6H_3$

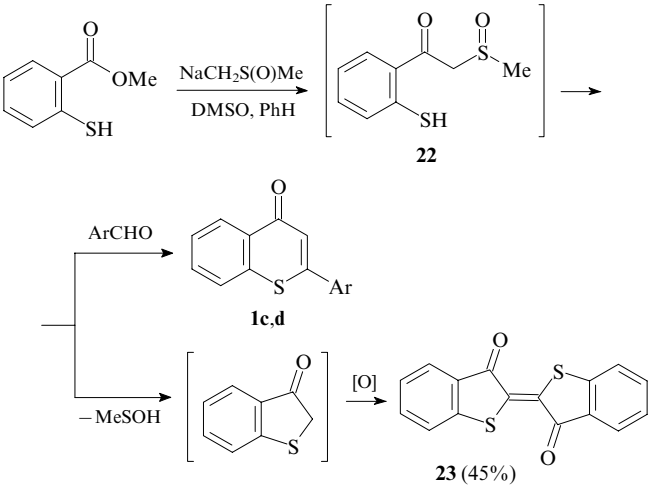
Scheme 11



Ar = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 2-Th

A synthetic route to chromones and flavones consists in condensation of salicylic acid esters with sodium methylsulfinylmethide in a mixture of DMSO and benzene giving rise to 2-hydroxy-ω-(methylsulfinyl)acetophenones. The latter react with formaldehyde or benzaldehydes to be cyclized to 3-(methylsulfinyl)chromanones, which then eliminate methanesulfenic acid (MeSOH).[38] This reaction was applied to methyl thiosalicylate and resulted in the formation of two thioflavones — compounds **1c**,**d**. Low product yields are attributable to instability of 2-mercapto-ω-(methylsulfinyl)-acetophenone (**22**), which readily eliminates MeSOH to give thioindoxyl, and the latter is spontaneously oxidized to thioindigo **23** (Scheme 12).[38]

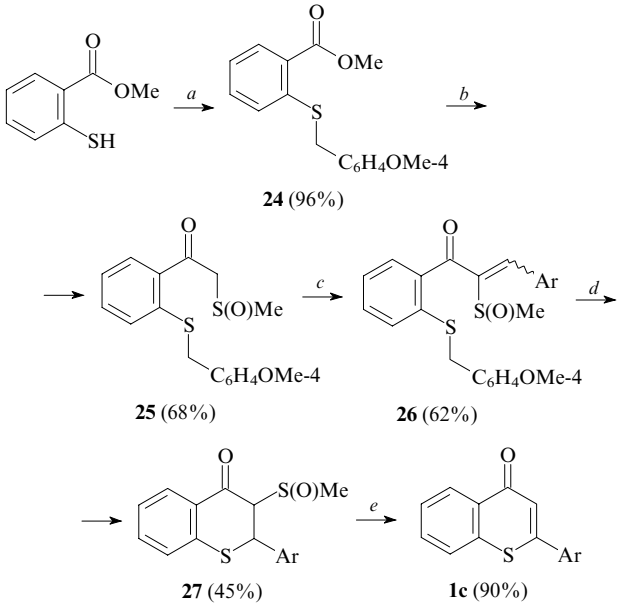
Scheme 12



Ar = 3,4-$(MeO)_2C_6H_3$ (**c**, 20% yield) , 4-Py (**d**, 14%)

Modification of the method described above[38] allowed Taylor and Dean[39] to synthesize 3′,4′-dimethoxythioflavone (**1c**) in a yield of 90%, which could not be attained by other methods. The key step of this route is protection of the thiol group in methyl thiosalicylate on treatment with 4-methoxybenzyl chloride (NaH, THF) to give ether **24** in a high yield. The condensation of compound **24** with sodium methylsulfinylmethide in THF gave β-keto sulfoxide **25**, which reacted with 3,4-dimethoxybenzaldehyde in the presence of piperidine to yield enone **26** as a mixture of *Z*- and *E*-isomers in 8 : 1 ratio. Treatment of this mixture with formic acid resulted in the removal of the benzyl protection and cyclization to form thioflavanone diastereomers **27** (45%), which eliminated MeSOH on refluxing in toluene to give the target 3′,4′-dimethoxythioflavone (**1c**) (Scheme 13). Unsubstituted thioflavone **1a** was synthesized in a similar way; however, its yield is not indicated in the original paper.[39]

Scheme 13

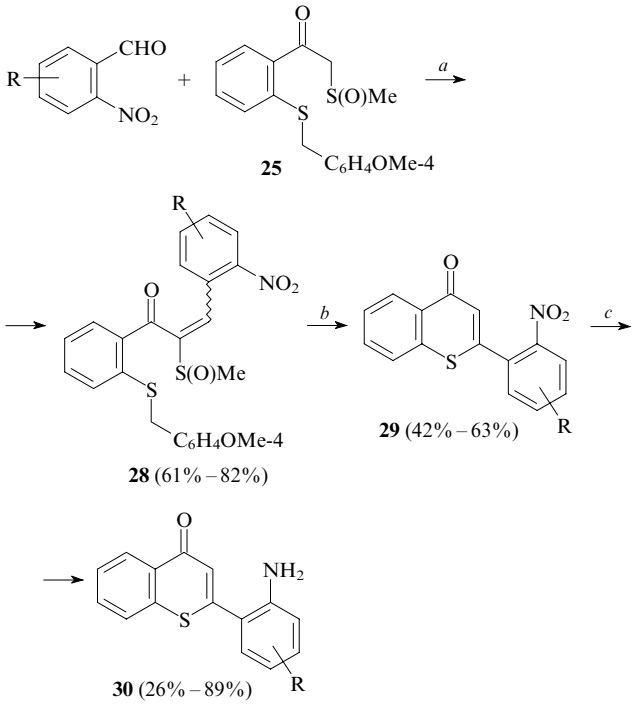


(*a*) 4-$MeOC_6H_4CH_2Cl$, NaH, THF, 60 °C, 1 h; (*b*) $NaCH_2S(O)Me$, THF, rt; (*c*) ArCHO, piperidine, PhMe, 110 °C, 1 h; (*d*) HCO_2H, 5 °C, 0.5 h; (*e*) PhMe, Δ, 2 h; Ar = 3,4-$(MeO)_2C_6H_3$

Kataoka *et al.*[40] used keto sulfoxide **25** to prepare 2′-nitro- and 2′-amino-substituted thioflavones, which were needed for biological testing and proved to be inaccessible by known methods. α-Sulfinylchalcones **28**, which were obtained in good yields from compound **25** and *o*-nitrobenzaldehydes, were treated with formic acid to be debenzylated and cyclize to give a diastereomeric mixture of thioflavanones, which eliminated MeSOH in refluxing benzene to give 2′-nitrothioflavones **29** in moderate yields. These products were reduced with tin in the presence of tetrafluoroboric acid to form 2′-aminothioflavones **30** in yields varying over a broad range depending on the nature of the group R, with the highest yields (83% – 89%) being obtained for R = 3′-OMe and 5′-OMe (Scheme 14).[40]

Beam and co-workers[41] demonstrated that the reaction of methyl thiosalicylate with *N*-alkoxycarbonyl- and *N*-benzoylhydrazones of methyl aryl ketones in the presence of lithium diisopropylamide (4 equiv.) in THF with cooling gives thioflavones **1** in moderate to high yields, instead of

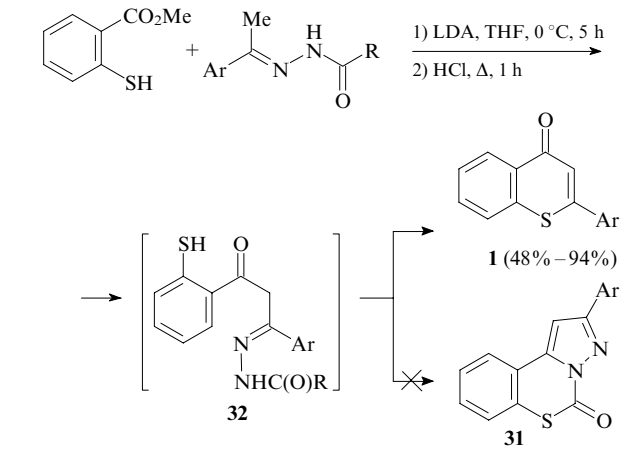
Scheme 14



(*a*) Piperidine, PhH, Δ, 0.5–1 h; (*b*) 1) HCO_2H, 5 °C, 0.5 h; 2) PhH, Δ, 0.5 h; (*c*) Sn, HBF_4, 80 °C, 0.5 h; R = H, Me, OMe, Cl (in different positions)

the expected 2-aryl-5*H*-benzo[*e*]pyrazolo[1,5-*c*][1,3]thiazin-5-ones **31**. It is worth noting that despite the broad range of obtained thioflavones, no correlation between the electronic nature of the substituent and the yield of the compound has been elucidated. The reaction includes the formation of intermediate **32**, in which the hydrazone group is not involved in the subsequent cyclization, but is displaced by the sulfur atom according to the A_N-E mechanism (Scheme 15).[41] A similar transformation with methyl salicylate gives rise to 2-aryl-5*H*-benzo[*e*]pyrazolo[1,5-*c*]-[1,3]oxazin-5-ones.[42]

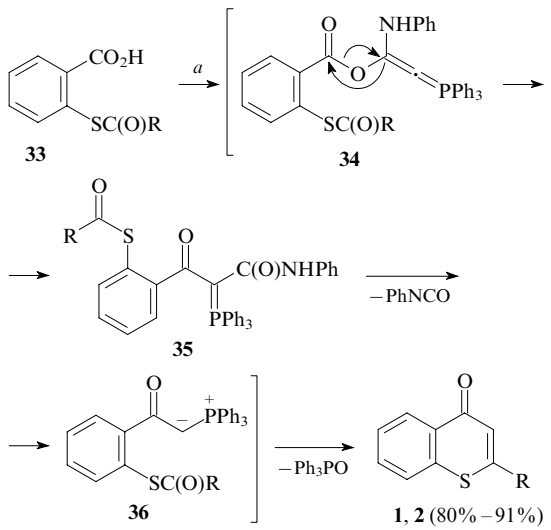
Scheme 15



R = OMe, OEt, Ph; Ar = 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-HOC_6H_4, 3,4-$(MeO)_2C_6H_3$, 2-Naph

In 1992, Kumar *et al.*[43] proposed a method for the synthesis of thiochromones, which proved to be equally efficient for the preparation of both thioflavones **1** and 2-alkylthiochromones **2**. The reaction of 2-acylthiobenzoic acids **33** with *N*-phenyl(triphenylphosphoranylidene)ethyleneimine[44] on refluxing in toluene or dioxane for 6–15 h affords acylphosphoranes, which are cyclized to thiochromones **1** and **2** in excellent yields. A possible mechanism of this reaction includes the addition of acid **33** to the imino group of phosphacumulene ylide intermediate **34** followed by migration of the aroyl moiety from the O to C atom. The subsequent extrusion of phenyl isocyanate from intermediate **35** results in the formation of acylphosphorane **36**, which undergoes the Wittig cyclization involving the S-carbonyl group to give the thiochromone system (Scheme 16).[43]

Scheme 16

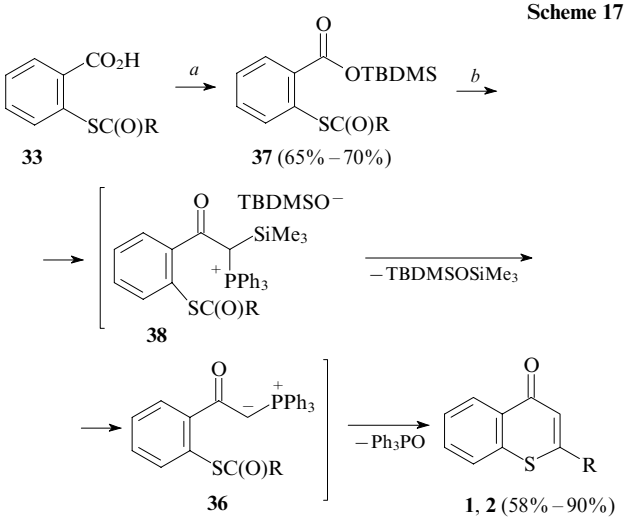


(*a*) $Ph_3P{=}C{=}C{=}NPh$, PhMe or dioxane, Δ, 6–15 h; for **1**: R = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$; for **2**: R = Me, Et

Kumar and Bodas[45] described one more method for the preparation of 2-aryl- and 2-alkylthiochromones starting from 2-acylthiobenzoic acids **33**. Acids **33** react with *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of imidazole to afford silyl esters **37**. Refluxing of a mixture of ester **37** and (trimethylsilyl)methylenetriphenylphosphorane in THF gives rise to target thiochromones **1** and **2** in good yields. The mechanism of this reaction was interpreted as the initial acylation of the ylide with silyl ester **37**, giving rise to phosphonium salt **38**, which is converted to acylphosphorane **36** upon migration of the trimethylsilyl group from the C to O atom of the $TBDMSO^-$ anion. The Wittig cyclization of compound **36** affords thiochromone (Scheme 17).[45]

In recent years, new methods for generation of the thiochromone system have been developed owing to broad use of metal complex catalysts in the practice of organic synthesis. Müller and co-workers[46,47] accomplished the three-component synthesis of thioflavones by the Sonogashira reaction of *o*-fluoro- and *o*-chloroaroyl chlorides, arylacetylenes and sodium sulfide nonahydrate under microwave (MW) irradiation. The acetylenic ketones

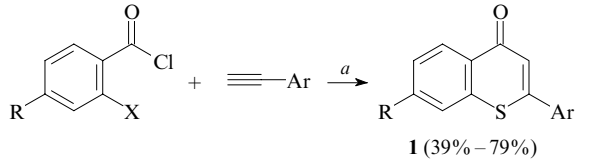
Scheme 17



(*a*) TBDMSCl, imidazole, CH_2Cl_2, 0°C → rt, 7–8 h; (*b*) $Ph_3P{=}CHSiMe_3$, THF, Δ, 16–38 h; for **1**: R = Ph, 2-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 2-ClC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 3,5-$(MeO)_2C_6H_3$; for **2**: R = Me, Et

formed in the first step rapidly add the hydrogen sulfide anion according to Michael to form intermediates **13** (see Scheme 6), which undergo S_NAr cyclization to give thiochromones **1** in moderate yields, the reaction being facilitated by Pd^{II} or Cu^{I} catalysts (Scheme 18). As was to be expected, the fluorine atom is a better leaving group for this reaction than chlorine. Similar transformations involving 2-chloronicotinoyl chloride and also 2,5-dichlorothiophene-3- and 3-chlorobenzo[*b*]thiophene-2-carboxylic acid chlorides resulted in the corresponding thioflavone heteroanalogues — 4*H*-thiopyrano[2,3-*b*]pyridin-4-ones (**39a**), 2-chloro-4*H*-thieno[2,3-*b*]thiopyran-4-ones (**39b**) and 4*H*-benzo[4,5]thieno[3,2-*b*]thiopyran-4-ones (**39c**) in low to moderate yields.[46, 47]

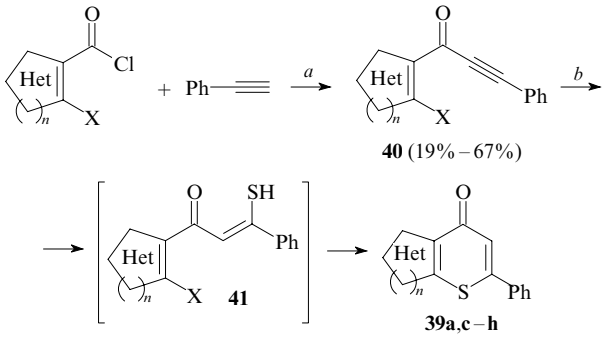
Scheme 18



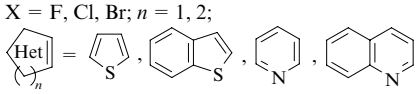
(*a*) 1) $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, rt, 1 h; 2) $Na_2S \cdot 9H_2O$, EtOH, MW, 90 °C, 1.5 h; R = H, Cl; X = F, Cl; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-$Bu^tC_6H_4$, 3,4-$(MeO)_2C_6H_3$

A wider range of thioflavone heteroanalogues have been described by Holzer and co-workers.[48] The authors demonstrated that Sonogashira cross-coupling of various *o*-halohetarenecarbonyl chlorides (palladium acetate, Et_3N) with phenylacetylene gives 1-(2-halohetaryl)-3-phenylprop-2-yn-1-ones **40** in yields ranging from 19% (for 3-chloro-4-pyridyl derivative) to 67% (for 2-bromo-3-thienyl derivative) (Scheme 19). Treatment of compounds **40** with sodium hydrogen sulfide in refluxing ethanol affords heteroannulated 2-phenylthiopyran-4-ones **39a**,**c**–**h** (Ar = Ph) *via* intermediates **41**, with the yields for products **39a**,**c**

Scheme 19



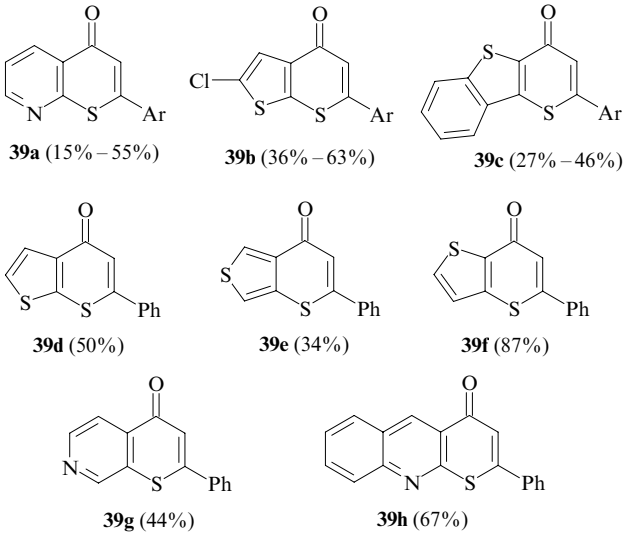
(*a*) $Pd(OAc)_2$, Et_3N, CH_2Cl_2, N_2, rt; (*b*) NaSH, EtOH, Δ; X = F, Cl, Br; *n* = 1, 2;



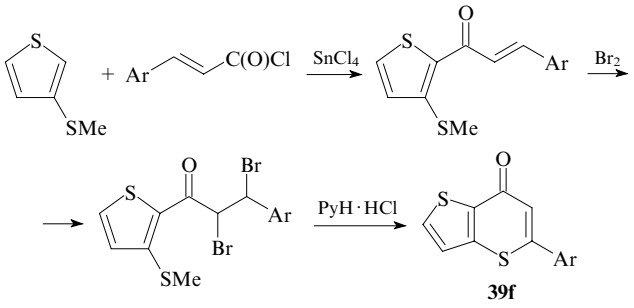
(Ar = Ph) being 93% and 82%, respectively. In the same publication, NMR spectroscopy data for previously unknown compounds are considered in detail.

5-Phenyl-7*H*-thieno[3,2-*b*]thiopyran-7-one (**39f**, Ar = Ph) and its derivatives with substituents in the benzene ring were synthesized in good yields by treatment of 3-(methylthio)thiophene with the chlorides of cinnamic acids followed by double bond bromination and cyclization in the presence of pyridine hydrochloride (Scheme 20).[49]

Structures 39



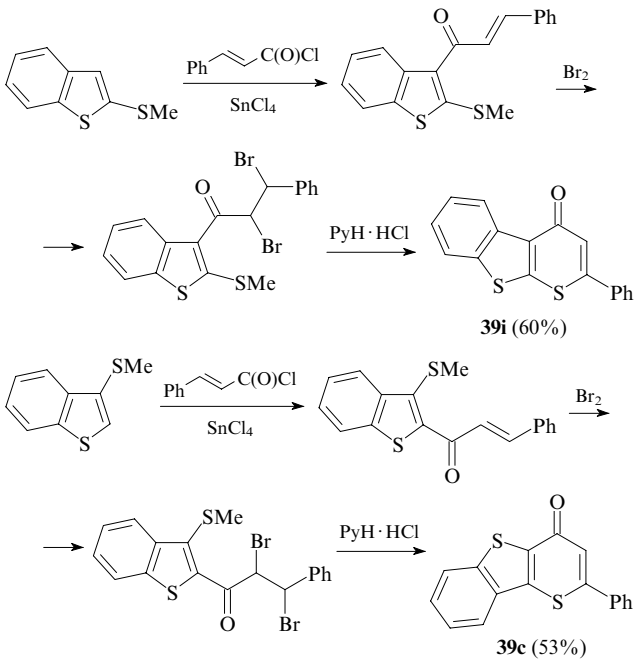
Scheme 20



Ar = Ph (65% yield), 3-$O_2NC_6H_4$ (70%), 4-HOC_6H_4 (50%)

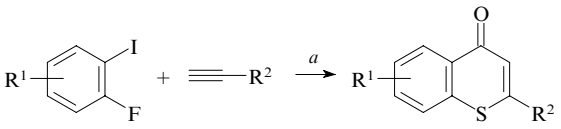
2-Phenyl-4*H*-benzo[4,5]thieno[3,2-*b*]thiopyran-4-one **39c** (Ar = Ph) and 2-phenyl-4*H*-benzo[4,5]thieno[2,3-*b*]thiopyran-4-one **39i** (Ar = Ph) were prepared by a similar route from 3- and 2-(methylthio)benzo[*b*]thiophenes, respectively (Scheme 21).[50]

Scheme 21



Recently, a four-component method has been developed [51] for the synthesis of thioflavones **1** and 2-alkylthiochromones **2** from 1-iodo-2-fluorobenzenes **42**, terminal acetylenes and sodium sulfide in a CO atmosphere in the presence of palladium acetate catalyst. A paraffin wax capsule was used for the controlled release of Na_2S to prevent catalyst poisoning and to avoid undesirable side reactions (Scheme 22).

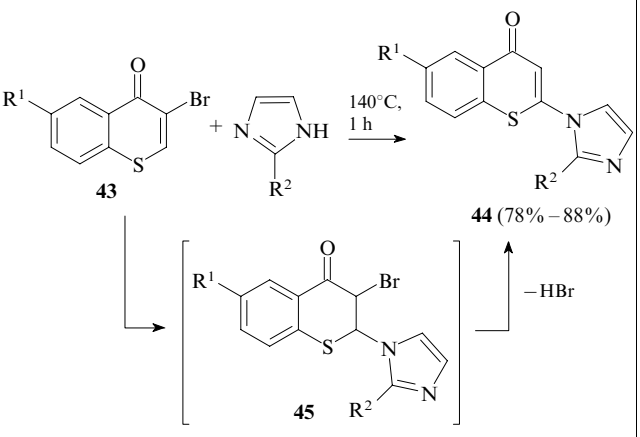
Scheme 22



(*a*) 1) CO, $Pd(OAc)_2$, $Bu^t_3P \cdot HBF_4$, Et_3N, MeCN; 2) $Na_2S \cdot 9H_2O$, 40 °C, 24 h; 3) 80 °C, 12 h; R^1 = H, Me, Cl, F; for **1**: R^2 = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-PhC_6H_4, 4-AmC_6H_4, 4-$MeOC_6H_4$, 4-$F_3C(O)C_6H_4$, 2-FC_6H_4, 4-FC_6H_4, 4-$F_3CC_6H_4$, 2-ClC_6H_4, 3,4-$Cl_2C_6H_3$, for **2**: R^2 = Am, n-C_8H_{17}; Am = n-C_5H_{11}

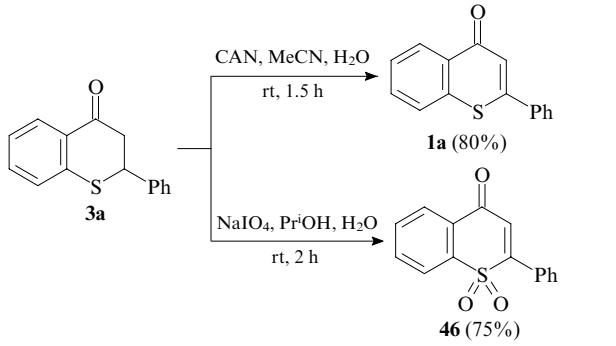
The essence of the all above-presented methods for the synthesis of 2-substituted thiochromones was to design the thiopyrone moiety in one or another way. Another approach to the preparation of these compounds is the use of substrates that already have a thiopyran ring in the molecule. For example, the reaction of 3-bromo-6-chloro- and 3-bromo-6-methylthiochromones **43** with an excess of imidazole or its 2-methyl and 2-isopropyl derivatives on heating at 140 °C for 1 h resulted in the synthesis of 2-(imidazolo)thiochromones **44**. The reaction starts with the Michael addition of imidazoles, after which primary adducts **45** easily eliminate a hydrogen bromide molecule to give products **44** in high yields (Scheme 23).[52]

Scheme 23



Treatment of thioflavanone (**3a**) with cerium ammonium nitrate in acetonitrile leads to dehydration of the substrate to thioflavone (**1a**) in 80% yield, while on treatment with sodium periodate in a water – isopropyl alcohol mixture at room temperature, dehydration is accompanied by oxidation of the sulfur atom, giving rise to thioflavone 1,1-dioxide (**46**) in 75% yield with no monoxide present (Scheme 24).[53]

Scheme 24

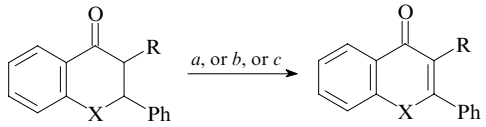


CAN is cerium ammonium nitrate

It has been shown [54] that thioflavanone (**3a**) can be converted to thioflavone (**1a**) by means of dehydrating agents such as 2,3-dichloro-5,6-dicyano-l,4-benzoquinone (DDQ, conditions *a*), iodosobenzene diacetate (IBDA, conditions *b*) or iodine in DMSO (conditions *c*) (Scheme 25). Irrespective of the reaction conditions, the yield of thioflavone (**1a**) is always quite high.[54, 55] A similar reaction of dioxide **3b** or 3-bromo derivative **3c** gave thiochromone **46** or **47**.

Somogyi [56] reported the Pummerer type transformation of thioflavanone 1-oxide (**48a**) to thioflavone (**1a**) or thioaurone (**20a**) induced by acetic anhydride under various conditions. The former product is generated from sulfoxide

Scheme 25



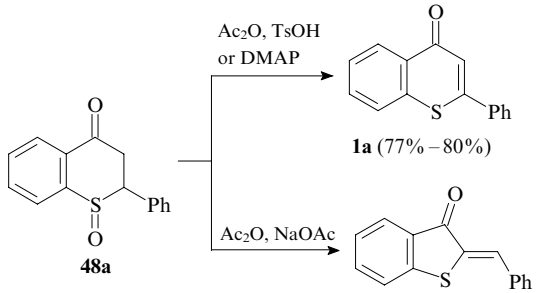
3a – c **1a**, **46**, **47**

(*a*) DDQ, PhH, Δ, 22 – 48 h; (*b*) IBDA, MeOH, Δ, 48 h; (*c*) I_2, DMSO, 100 °C, 18 – 42 h

Substrate	X	R	Conditions	Products	Yield (%)
3a	S	H	*a*	**1a**	85
3a	S	H	*b*	**1a**	86
3a	S	H	*c*	**1a**	93
3b	SO_2	H	*b*	**46**	50
3b	SO_2	H	*c*	**46**	91
3c	S	Br	*a*	**47**	67

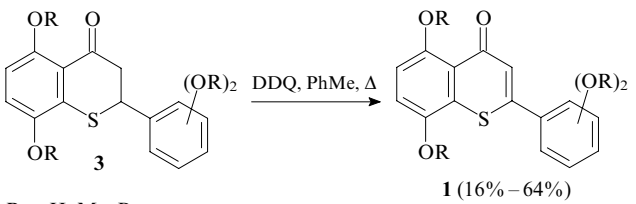
48a in a good yield in the presence of *p*-toluenesulfonic acid (TsOH) or 4-dimethylaminopyridine (DMAP). Note that the replacement of these catalysts by anhydrous sodium acetate induces ring contraction, resulting in the formation of product **20a**. The researchers[56] present a detailed discussion of the mechanisms of both reaction pathways depending on the reaction conditions (Scheme 26).

Scheme 26



Polyhydroxylated and polyalkoxylated thioflavanones **3** have been dehydrated to give the corresponding thioflavones **1** containing two hydroxy or alkoxy groups in different positions of the 2-aryl substituent in preparatively acceptable yields (16% – 64%) under the action of DDQ on refluxing in toluene for 2 h (Scheme 27).[57]

Scheme 27



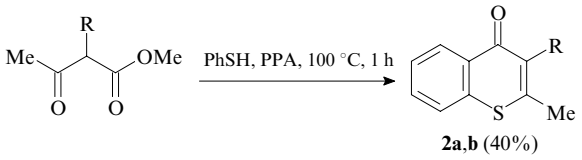
R = H, Me, Bn

2.2. Synthesis of 2(3)-alkylthiochromones

2.2.1. 2-Alkylthiochromones

As compared with thioflavones, 2-alkylthiochromones (2-alkyl-4*H*-thiochromen-4-ones, 2-alkyl-4*H*-1-benzothiopyran-4-ones, **2**) are less accessible and, hence, less studied. However, the range of synthetic routes to these thiochromones is rather broad, although the yields are rather low compared with those of flavones. Some known approaches considered in Section 2.1 have proved to be useful for the preparation of both 2-aryl- and 2-alkylthiochromones.[30, 41, 43, 49] In addition, the classical method based on the reaction of arenethiols with β-ketoesters is also applied in the synthesis of 2-alkylthiochromones **2**. 2-Methyl- (**2a**) and 2,3-dimethylthiochromones (**2b**) were prepared (both in 40% yield) from the corresponding acetoacetates and benzenethiol upon the addition of polyphosphoric acid and heating at 100 °C for 1 h (Scheme 28).[15, 58]

Scheme 28

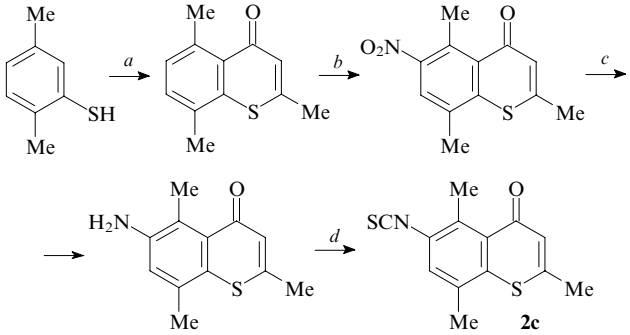


2a,**b** (40%)

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

For studying the fungicidal activity of chromone and thiochromone derivatives, 2-methylthiochromones **2**, containing various functional groups in position 6, have been prepared by this method. First, 2,5,8-trimethylthiochromone was obtained from ethyl acetoacetate and 2,5-dimethylbenzenethiol and then it was subjected to successive nitration and reduction reactions and reaction with thiophosgene to give 6-isothiocyanato-2,5,8-trimethylthiochromone (**2c**) (Scheme 29).[59]

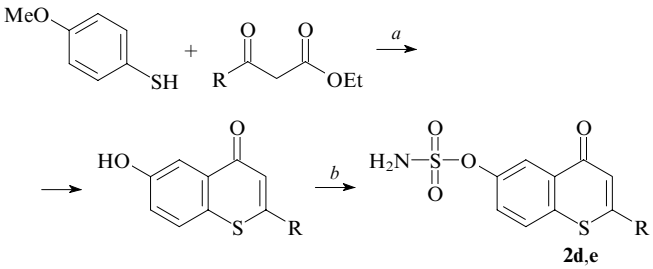
Scheme 29



(*a*) $AcCH_2CO_2Et$, PPA, 90 °C, 1.5 h; (*b*) HNO_3, H_2SO_4, rt, 1 h; (*c*) Fe, HCl, Pr^iOH, H_2O, Δ, 1.5 h; (*d*) $C(S)Cl_2$, Na_2CO_3, $CHCl_3$, H_2O, rt

2-*tert*-Butyl- (**2d**) and 2-(1-adamantyl)thiochromon-6-yl sulfamates (**2e**), which were subsequently used for biological assays, were prepared in a similar way from β-ketoesters and 4-methoxybenzenethiol *via* the formation of 6-hydroxythiochromones followed by sulfamoylation (Scheme 30).[60]

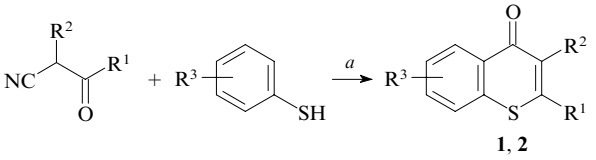
Scheme 30



(*a*) 1) PPA, 90 °C; 2) BBr_3, CH_2Cl_2; (*b*) $ClSO_2NH_2$, B, DMF, rt;
R = Bu^t (**d**, 85% yield), 1-Ad (**e**, 54%); B is base, Ad is adamantyl

2-Substituted thiochromones can also be obtained when β-ketoesters are replaced by β-ketonitriles. This reaction also proceeds in polyphosphoric acid on heating to 90 – 100 °C and is suitable for the synthesis of not only thiochromones **1** and **2**, but also their 3-substituted analogues (Scheme 31; the position of substituents in the product is indicated).[61]

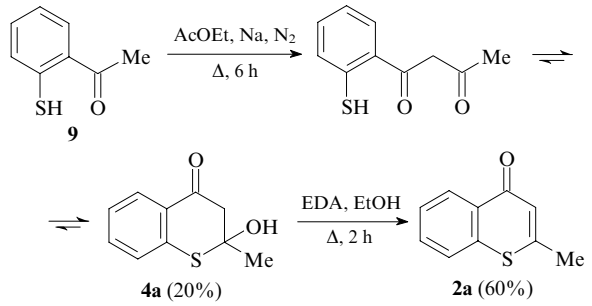
Scheme 31



(*a*) PPA, 90 – 100 °C; R^1 = Me, Ph; R^2 = H, Me, Ph;
R^3 = 6-Cl, 8-CO_2Me

Refluxing 2-mercaptoacetophenone (**9**) with ethyl acetate in the presence of sodium in a nitrogen atmosphere for 6 h gives a relatively low yield of the expected 1,3-diketone existing as 2-hydroxy-2-methylthiochroman-4-one (**4a**), which is readily dehydrated to 2-methylthiochromone (**2a**) when reacted with an ethanolic solution of ethylenediamine (EDA) (Scheme 32).[62]

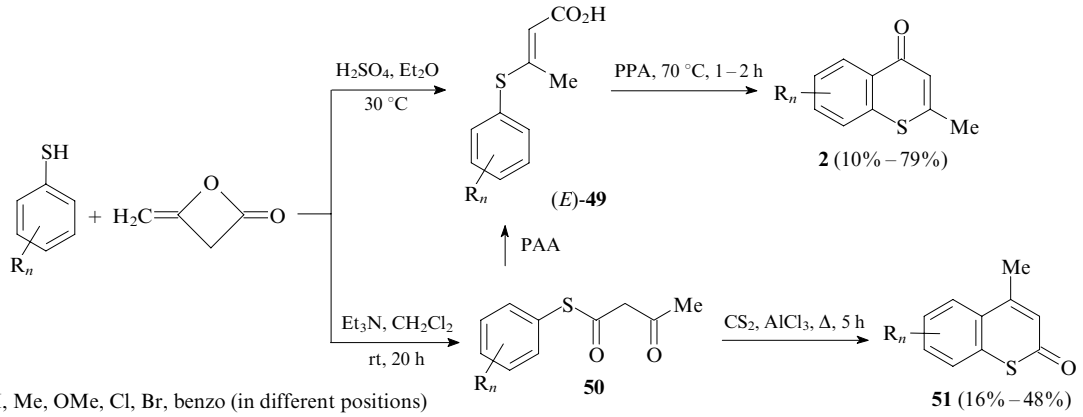
Scheme 32



Nakazumi *et al.*[63 – 65] have shown that the products resulting from the reaction of benzenethiols with diketene in the presence of H_2SO_4 are (*E*)-β-(arylthio)crotonic acids **49** rather than *S*-phenyl 3-oxobutanethioates **50**, as was considered earlier.[66] Under the action of PPA at 70 °C, *E*-isomers of acid **49**, are cyclized to 2-methylthiochromones **2**, with preliminary isomerization to the *Z*-form. Compounds **50**, which are precursors of thiocoumarins **51**, were obtained from benzenethiols and diketene in the presence of triethylamine in dichloromethane. It has been shown[63] that cyclization of *S*-phenyl 3-oxobutanethioates **50** to 4-methylthiocoumarins **51** occurs when anhydrous aluminium chloride is used, whereas heating of these substrates in PPA gives predominantly isomeric 2-methylthiochromones **2**. The transformation **50** → **2** is preceded by isomerization to acids **49**, which were isolated in low yields (4% – 10%) at 5 – 10 °C as intermediates. The spectral characteristics (NMR, IR, UV and mass spectra) of 2-methylthiochromones **2** and 4-methylthiocoumarins **51** have been described in detail,[63, 66] which is important for identification of these isomers (Scheme 33).

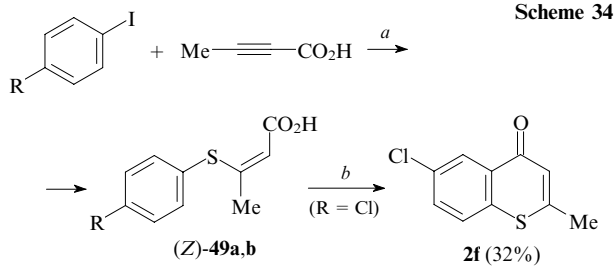
Palani *et al.*[67] developed a three-component synthesis of 2,3-unsubstituted thiochromones from aryl halides, sodium sulfide pentahydrate and propiolic acid in the presence of bis(triphenylphosphino)palladium chloride (2.5 mol.%), 1,4-bis(diphenylphosphino)butane (dppb, 5 mol.%) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2 equiv.) in DMSO with heating to 50 °C. Using a broad range of starting halides, it was shown that this reaction affords almost exclusively (*Z*)-3-arylthioacrylic acids; on treatment with sulfuric acid at 100 °C, they are converted to thiochromones substituted in the benzene ring in 51% – 80% yields. However, the reaction was very sensitive to steric factors; hence, in the case of but-2-ynoic acid, only two (*Z*)-β-(arylthio)crotonic acids **49a**,**b** could be obtained (Scheme 34).[67] Chloro derivative **49b** is cyclized to 6-chloro-2-methylthiochromone (**2f**) under the action of sulfuric acid during 1.5 h at 100 °C.

Scheme 33



R_n = H, Me, OMe, Cl, Br, benzo (in different positions)

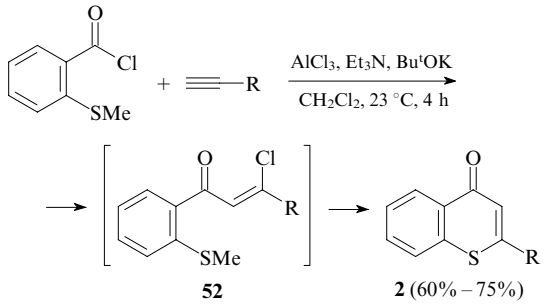
Scheme 34



(*a*) $Na_2S \cdot 5H_2O$, $Pd(PPh_3)_2Cl_2$, dppb, DBU, DMSO, 50 °C, 12 h; (*b*) H_2SO_4, 100 °C, 1.5 h; R = H (**49a**, 50% yield), Cl (**49b**, 35%)

Oh and co-workers[68] reported a new efficient method for the synthesis of 2-mono- and 2,3-disubstituted thiochromones, including 2-alkylthiochromones, under quite unusual conditions. The acylation of alkylalkynes with 2-(methylthio)benzoyl chloride took place in the presence of $AlCl_3$ with addition of a base (Et_3N or Bu^tOK) in dichloromethane in 4 h at room temperature. This furnished β-chlorovinyl ketones **52**, which were cyclized to give 2-alkylthiochromones **2** in good yields (Scheme 35).[68]

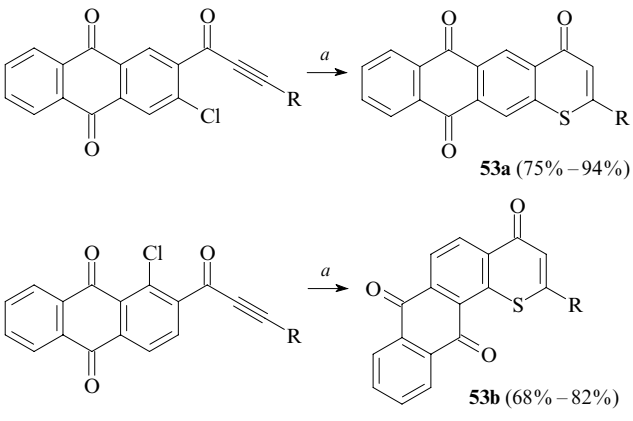
Scheme 35



R = Am, $(CH_2)_4Cl$, n-$C_{10}H_{21}$, Bn

Thiochromones annulated at the benzene ring, namely, naphtho[2,3-*g*]thiochromene-4,6,11-triones **53a** and naphtho[2,3-*h*]thiochromene-4,7,12-triones **53b** with linear and angular structures, respectively, containing alkyl, alkenyl and aryl substituents in position 2 were obtained by refluxing *o*-chloroacetylenic anthraquinone-derived ketones with sodium sulfide in ethanol for 10–20 min (Scheme 36).[69]

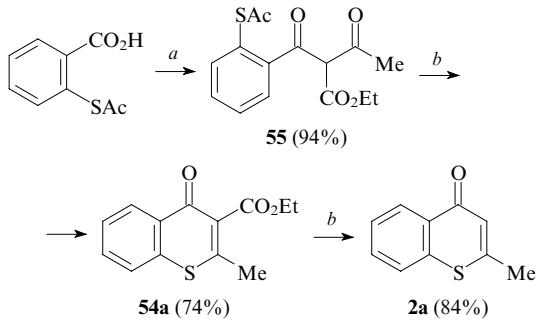
Scheme 36



(*a*) Na_2S, EtOH; R = Bu^n, CMe_2OH, C(Me)=CHMe, Ph, cyclohexen-1-yl

Jung *et al.*[70] reported the synthesis of 2-methylthiochromone (**2a**) by hydrogen chloride hydrolysis of 3-ethoxycarbonyl-2-methylthiochromone (**54a**), which was accompanied by decarboxylation and gave products in high yields. In turn, ester **54a** was obtained by refluxing ethyl 2-(2-acetylthio)benzoylacetoacetate (**55**) [resulting from condensation of 2-(acetylthio)benzoyl chloride with ethyl acetoacetate in the presence of NaH] in an ethanolic solution of hydrochloric acid (Scheme 37).

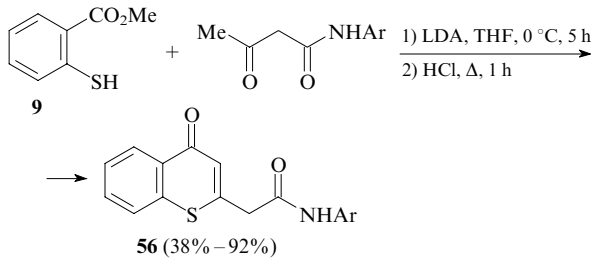
Scheme 37



(*a*) 1) $SOCl_2$, urea, PhMe; 2) NaH, $AcCH_2CO_2Et$; (*b*) HCl, EtOH, Δ, 3 h

Substituted acetoacetanilides react with lithium diisopropylamide in THF at 0 °C to be converted to trilithium intermediates, which condense with the lithium salt of methyl thiosalicylate under these conditions within 5 h. On treatment of the reaction mixture with hydrochloric acid and heating for 1 h, thiochromone-2-acetamides **56** are formed in moderate to high yields (Scheme 38).[71]

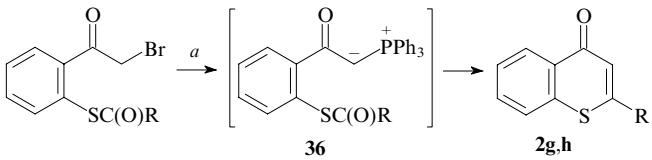
Scheme 38



Ar = Ph, 2-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 2,5-$(MeO)_2C_6H_3$, 2,5-$Me_2C_6H_3$

The intramolecular Wittig reaction involving phosphoranes **36**, which are formed in the reaction of 2-(acylthio)-phenacyl bromides with triphenylphosphine in the presence of 2,6-lutidine, affords 2-*tert*-butyl- and 2-hepthylthiochromones **2g**,**h** (Scheme 39).[72]

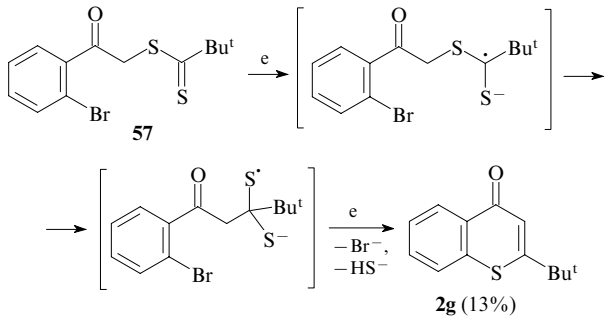
Scheme 39



(*a*) PPh_3, 2,6-lutidine; R = Bu^t (**g**), n-C_7H_{15} (**h**)

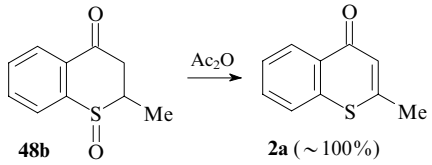
2-*tert*-Butylthiochromone (**2g**) has also been obtained, although in low yield, upon electrochemical reduction of dithioester **57** containing the *o*-bromoacetophenone moiety. The nucleophilic substitution of the bromine atom, which is carried out under electrochemical conditions (Hg cathode, Pt anode, Pr^n_4NBr + DMF electrolyte, −1.75 V), is preceded by rearrangement of the initially formed radical anion (Scheme 40).[73]

Scheme 40



The Pummerer reaction of sulfoxide **48b** as a mixture of two diastereomers gives 2-methylthiochromone (**2a**) in a nearly quantitative yield (Scheme 41).[74]

Scheme 41

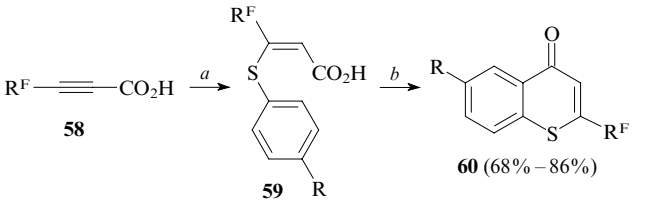


Thus, despite the large diversity of the described reactions, only few general methods for the preparation of 2-alkylthiochromones **2** are known. First of all, mention should be made of the reaction of benzenethiols with β-ketoesters in the presence of polyphosphoric acid [15, 58–60] and the intramolecular Wittig cyclization of acylphosphoranes **36**.[43, 45, 72]

2.2.2. 2-(Polyfluoroalkyl)thiochromones

Tamura *et al.*[75] have shown that, owing to high electrophilicity, polyfluoroalk-2-ynoic acids **58** can successfully react with arenethiols in the presence of KOH in aqueous ethanol within 0.5 h at room temperature. Unlike non-fluorinated alkynoic acids,[67] in this case, the steric factor is not crucial. The arylthioacrylic acids **59** thus formed have

Scheme 42

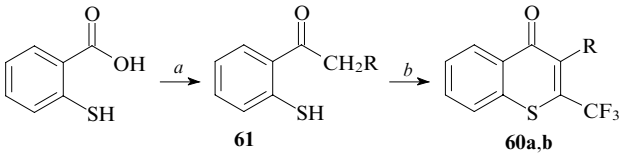


(*a*) 4-RC$_6$H$_4$SH, KOH; (*b*) PCl_5, $AlCl_3$, PhH, rt; R = H, Me, OMe, Cl; R^F = CF_2H, CF_3, $(CF_2)_3H$

Z-configuration at the double bond and, on the subsequent treatment with PCl_5 and $AlCl_3$ in benzene at room temperature, they are converted to 2-(polyfluoroalkyl)thiochromones **60** in high yields (Scheme 42).[75]

The modified Baker–Venkataraman reaction of alkyl 2-mercaptophenyl ketones **61**, obtained from thiosalicylic acid and methyl- or n-butyllithium,[29] with trifluoroacetic anhydride in the presence of triethylamine in refluxing THF

Scheme 43



(*a*) 1) RCH_2Li, 2) HCl; (*b*) $(CF_3C(O))_2O$, Et_3N;
R = H (**a**, 44% yield), Pr^n (**b**, 23%)

gives rise to 2-(trifluoromethyl)thiochromones **60a**,**b** in moderate yields (Scheme 43).[76]

2.2.3. 3-Benzylthiochromones

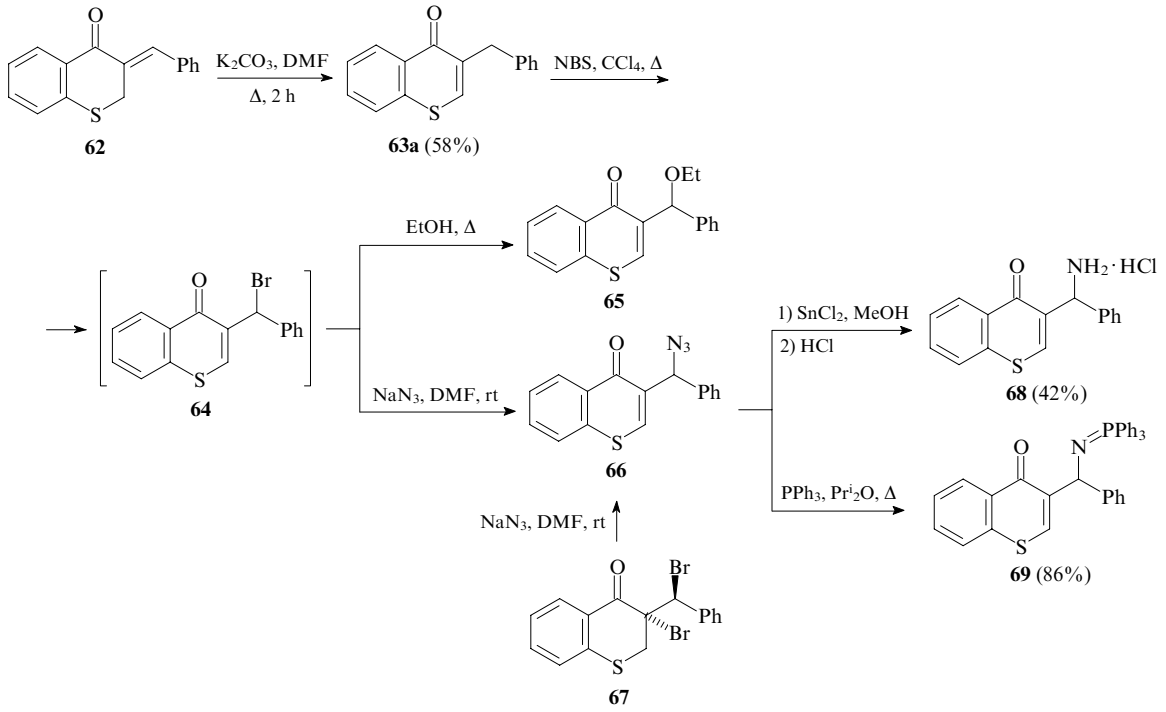
Along with 2-alkylthiochromones, considerable attention in the literature is paid to 3-benzylthiochromones (3-thiohomoisoflavones) and their functional derivatives. (*Z*)-3-Benzylidene-1-thiochroman-4-one (**62**), formed as the product of acid-catalyzed condensation of thiochroman-4-one with benzaldehyde,[77] readily isomerizes to 3-benzylthiochromone (**63a**) on refluxing in DMF in the presence of potassium carbonate, thus providing this product for further investigation (Scheme 44).[78]

The bromination of 3-benzylthiochromone (**63a**) with *N*-bromosuccinimide (NBS) gave rise to highly reactive bromide **64**, which was immediately treated without isolation with ethanol on heating or with sodium azide in DMF at room temperature. This gave compound **65** or **66** in 50% or 82% yield, respectively. 3-(α-Azidobenzyl)thiochromone (**66**), which has also been prepared from dibromide **67** in 83% yield, has a synthetic value of its own. Thus it is reduced with tin(II) chloride in methanol to form amine **68**, which has been isolated as the hydrochloride or is treated with triphenylphosphine on heating in diisopropyl ether giving rise to iminophosphorane **69** in high yield (see Scheme 44).[78]

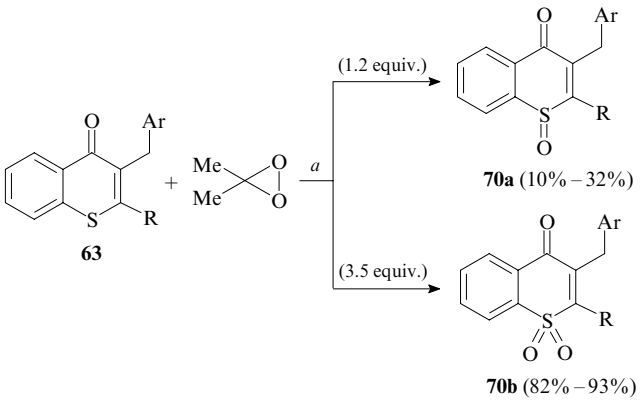
The oxidation of 3-benzylthiochromones **63** with dimethyldioxirane produces sulfoxides or S,S-dioxides, depending on the amount of the oxidant used. When the reaction is carried out in the dichloromethane–acetone system with cooling to 0–5 °C and with dimethyldioxirane taken in a slight excess (1.2 equiv.), sulfoxides **70a** are formed predominantly, with the conversion and yields being low. With a large excess of the oxidant (3.5–5.3 equiv.), dioxides **70b** are the major products (Scheme 45).[79]

Kataoka *et al.*[80] developed a method for the synthesis of 3-(α-hydroxybenzyl)thiochromones **71** based on the Morita–Baylis–Hillman reaction. The reaction of 1-(2-methylthiophenyl)propynone with boron trifluoride etherate leads to intermediate boron allenolate, which undergoes 6-*endo*-*dig*-cyclization followed by addition at the aldehyde group to be converted to thiochromones **71** in moderate yields (Scheme 46).[80, 81]

Scheme 44

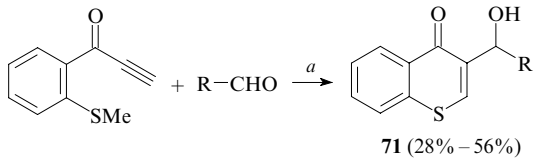


Scheme 45



(*a*) CH_2Cl_2, Me_2CO, 0 – 5 °C; R = H, Me, Ph; Ar = 4-XC_6H_4 (X = H, Cl, Br, CN, NO_2)

Scheme 46



(*a*) $BF_3 \cdot Et_2O$, CH_2Cl_2, −25 °C, 24 h;
R = 4-XC_6H_4 (X = H, Cl, CN, NO_2), $Ph(CH_2)_2$

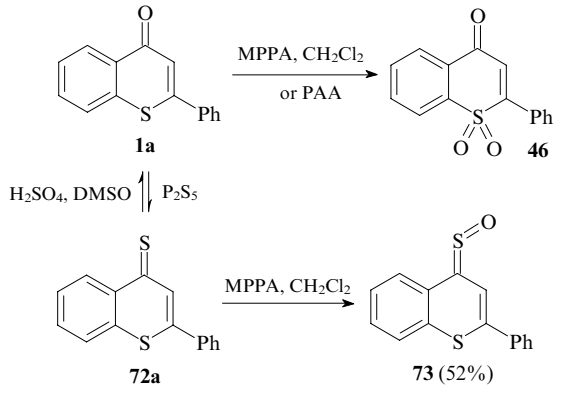
3. Properties of 2-substituted thiochromones

3.1. Chemical transformations of thioflavones

3.1.1. Reactions at the carbonyl group and sulfur atom

Bognár *et al.*[82] reported the oxidation of thioflavone (**1a**) with monoperoxyphthalic (MPPA) or peracetic acid (PAA) to thioflavone 1,1-dioxide (**46**) in 41% or 67% yield, respectively. A similar result has been reported in another paper,[83] but the yield of dioxide **46** obtained with peracetic acid was 76%. On treatment with P_2S_5, thioflavone (**1a**) is converted to dithioflavone (thioflavonethione, **72a**), which is converted to the starting compound in DMSO in the presence of sulfuric acid. The oxidation of dithioflavone **72a** with an equimolar amount of MPPA in dichloromethane affords sulfine **73**, which is not oxidized to 1-oxide or 1,1-dioxide even with excess MPPA (Scheme 47).[82]

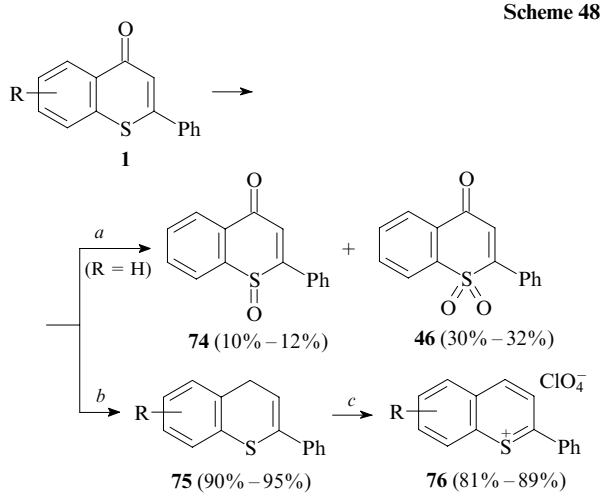
Scheme 47



Thioflavone 1-oxide (**74**) was obtained as a mixture with thioflavone 1,1-dioxide (**46**) upon the oxidation of thioflavone (**1a**) with hydrogen peroxide or *m*-chloroperoxybenzoic acid (MCPBA) and was isolated in a pure state in a low yield by column chromatography on silica gel.[11] The reduction of thioflavones **1** with lithium aluminium hydride in THF gives almost quantitatively 2-phenyl-4*H*-thiochromanes **75**, which form 2-phenylthiochromylium perchlorates **76** on treatment with 60% perchloric acid in the presence of DDQ in acetic acid (Scheme 48).[11,84]

It is noteworthy that thioflavones **1** do not directly react with amines; for the preparation of imines, they are first

Scheme 48



(*a*) H_2O_2 or MCPBA; (*b*) $LiAlH_4$, $AlCl_3$, THF; (*c*) $HClO_4$, DDQ, AcOH; R = H, OMe (in different positions)

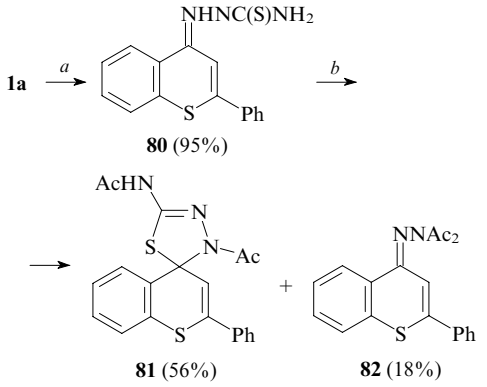
converted either to dithioflavones **72** by the reaction with phosphorus pentasulfide or to *gem*-dichloro derivatives **77** by the reaction with oxalyl chloride. For example, treatment of 6-halo-substituted dithioflavones **72**, obtained from thioflavones **1** by refluxing with P_2S_5 in toluene, with primary amines in refluxing anhydrous ethanol are converted to thioflavoneimines **78**. An alternative pathway to these compounds involves the formation of dichlorides **77**, which are not isolated in a pure state, but are immediately treated with amine and are thus converted to thioflavoneimines **78**, meant for biological assays, as hydrochlorides. The authors note that the latter synthetic route proved to be more advantageous, because in this case, the reaction with amines proceeded at lower temperature and the isolation of the target product was simpler (Scheme 49).[12]

German chemists[85] have demonstrated that dithioflavone (**72a**) reacts with ethyl diazoacetate and diazo-*p*-nitroacetophenone in the presence of copper powder to give 4-ethoxycarbonylmethylidene- and 4-(*p*-nitrobenzoylmethylidene)thioflavones **79a**,**b** in high yields. A similar reaction with diphenyldiazomethane in refluxing benzene in the presence of copper acetylacetonate gives 4-(diphenylmethylidene)thioflavone (**79c**) in 83% yield (see Scheme 49).[86]

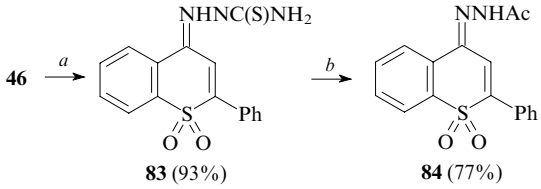
Unlike the reaction with primary amines, the reaction of thioflavone **1a** with thiosemicarbazide proceeds without carbonyl group preactivation, but on long-term refluxing in methanol with the addition of concentrated hydrochloric acid. The reaction results in a nearly quantitative formation of thiosemicarbazone **80**, which is converted to a mixture of thiochromene-containing spirothiadiazoline **81** and diacetylhydrazone **82** on heating with acetic anhydride in pyridine. Owing to solubility difference, these products could be isolated in a pure state. The corresponding thiosemicarbazide **83** prepared in a similar way from thioflavone 1,1-dioxide **46** reacts with acetic anhydride in a different manner to give thioflavone 1,1-dioxide acetylhydrazone **84** (Scheme 50).[87]

In a study of electrochemical properties of unsymmetrical bis(thiopyranylidene)ethenes,[88] thioflavone **1a** was

Scheme 50

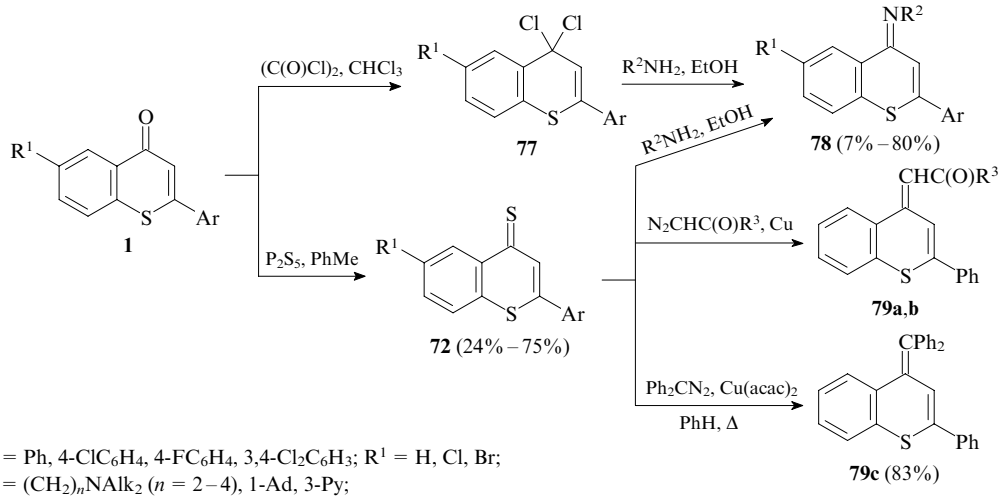


(*a*) $NH_2NHC(S)NH_2$, HCl, MeOH, Δ, 65 h; (*b*) Ac_2O, PyH, 100 °C, 3 h



(*a*) $NH_2NHC(S)NH_2$, HCl, MeOH, Δ, 9 h; (*b*) Ac_2O, PyH

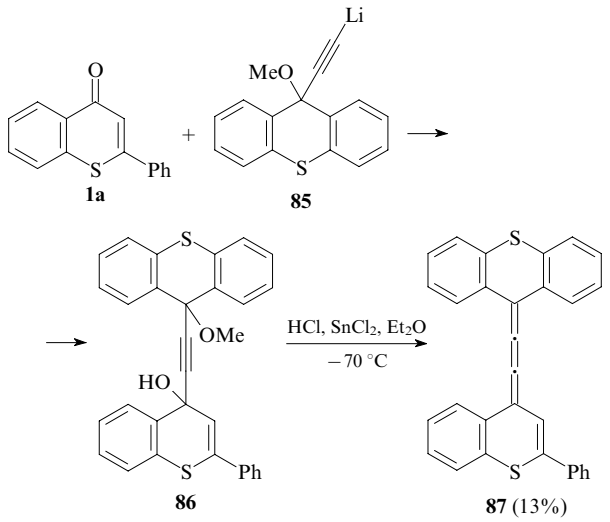
Scheme 49



Ar = Ph, 4-ClC_6H_4, 4-FC_6H_4, 3,4-$Cl_2C_6H_3$; R^1 = H, Cl, Br;
R^2 = $(CH_2)_nNAlk_2$ (*n* = 2–4), 1-Ad, 3-Py;
R^3 = EtO (**a**, 96% yield), 4-$O_2NC_6H_4$ (**b**, 87%); acac is acetylacetonate

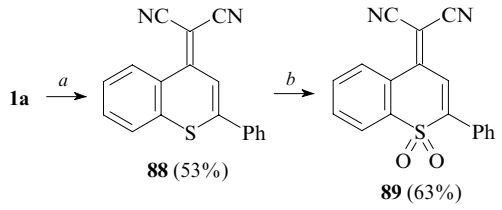
reacted with the lithium salt of 9-ethynyl-9-methoxythioxanthene (**85**) reported by Nakasuji *et al.*[89] As in the case of N-nucleophiles, this reaction involves the carbonyl group and affords acetylene glycol monomethyl ether **86**, which served for the preparation of cumulene **87** in a moderate yield upon treatment with $SnCl_2$ at −70 °C in hydrogen chloride-saturated diethyl ether (Scheme 51).[88]

Scheme 51



Reactions of thiochromones with methylene-active compounds also involve only the carbonyl group. For instance, thioflavone **1a** reacts with malononitrile on heating in acetic anhydride to furnish compound **88**, which is oxidized with peracetic acid at 90 °C, thus giving 1,1-dioxide **89** (Scheme 52).[83]

Scheme 52



(*a*) $CH_2(CN)_2$, Ac_2O, Δ; (*b*) 40% PAA, 90 °C, 15 min

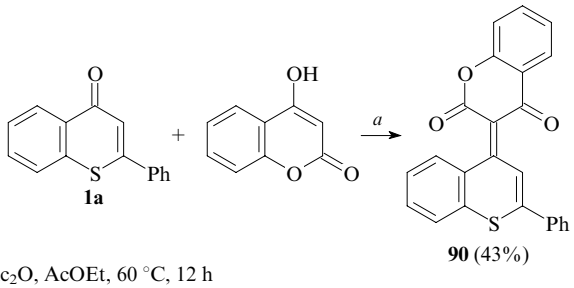
The condensation of thioflavone **1a** with 4-hydroxycoumarin as an active C-nucleophile in a mixture of acetic anhydride and ethyl acetate in 12 h at 60 °C gives a moderate yield of 3-(2-phenyl-4*H*-thiochromen-4-ylidene)-3*H*-chromene-2,4-dione (**90**), which is of interest as a reversible redox switch (Scheme 53).[90]

On refluxing in acetic anhydride, hippuric acid can react at the carbonyl group of both thioflavone **1a** and 2-methylthiochromone **2a**, giving rise to 4-(4*H*-thiochromen-4-ylidene)-2-phenyloxazol-5(4*H*)-ones **91a**,**b**, respectively (Scheme 54).[91]

3.1.2. Halogenation and chloromethylation

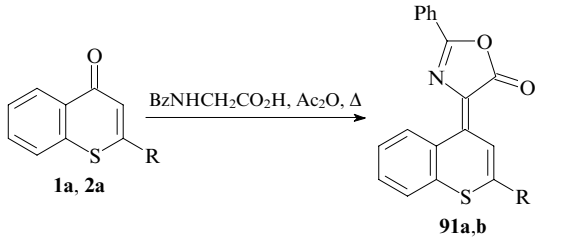
Halogenation of thioflavones occurs at position 3 of the thiopyrone ring and can be used to prepare 3-halothioflavones, where Hal = I, Br, Cl, F. In the known methods for the synthesis of 3-iodothioflavones, elemental iodine in the presence of oxidants is used most often. For example,

Scheme 53



(*a*) Ac_2O, AcOEt, 60 °C, 12 h

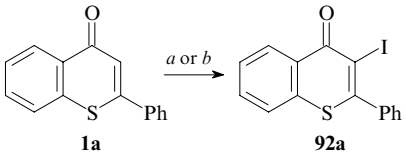
Scheme 54



R = Ph (**1a**; **91a**, 43% yield), Me (**2a**; **91b**, 40%)

treatment of thioflavone **1a** with the iodine–cerium(IV) ammonium nitrate iodinating system in anhydrous acetonitrile at 55–60 °C furnishes 3-iodothioflavone **92a** in an almost quantitative yield (98%).[51,92] The same product was also obtained, although in a lower yield (58%), using bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4) as the iodinating agent in the presence of trifluoromethanesulfonic acid (TfOH).[93] These results are well correlated with the mechanism of electrophilic substitution at C(3) involving the I^+ cation (Scheme 55).

Scheme 55

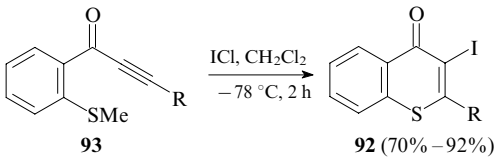


(*a*) I_2, CAN, MeCN, 55 °C; (*b*) IPy_2BF_4, TfOH, CH_2Cl_2, 20 h

It is noteworthy that a method for simultaneous introduction of the iodine atom and construction of the thiochromone system has been developed for 3-iodothioflavones. In 2006, Larock and co-workers[94] found that the ICl-initiated cyclization of [2-(methylthio)phenyl]alkynones **93**, which occurs in CH_2Cl_2 at −78 °C within 2 h, provides a facile and efficient approach to the synthesis of compounds **92** in high yields (Scheme 56).

The reaction of thioflavone **1a** with 2,4,4,6-tetrabromocyclohexa-2,5-dienone (**94**) in dichloromethane affords

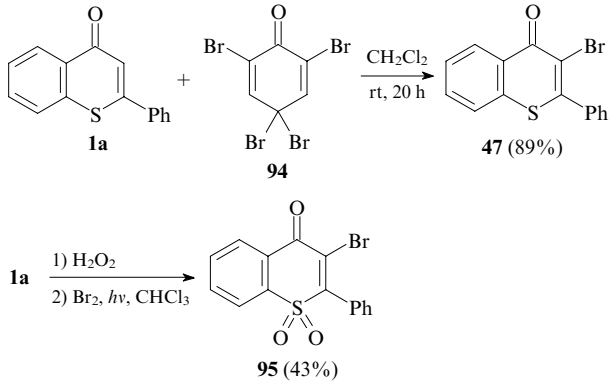
Scheme 56



R = Ph, 2-MeC_6H_4, 3,4-$(MeO)_2C_6H_3$, cyclohexen-1-yl

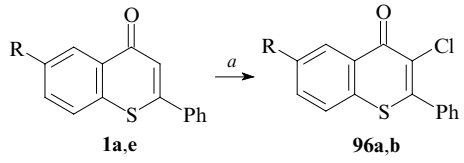
3-bromothioflavone **47**,[95] while the oxidation of compound **1a** with hydrogen peroxide followed by treatment with bromine in a UV reactor results in the formation of 3-bromothioflavone 1,1-dioxide **95** (Scheme 57).[58]

Scheme 57



A convenient and efficient method has been proposed[96] for the synthesis of 3-chlorothioflavones **96a**,**b** by the reaction of thioflavones **1a**,**e** with sulfuryl chloride in the presence of an inorganic solid acid — montmorillonite K-10. Note that without a catalyst, the yields of the target products do not exceed 60% (Scheme 58).

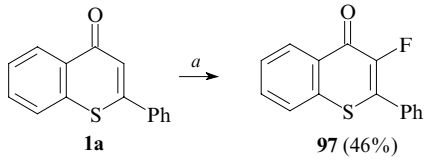
Scheme 58



(*a*) SO_2Cl_2, montmorillonite K-10, CH_2Cl_2, 15 min; R = H (**1a**; **96a**, 96% yield), Me (**1e**; **96b**, 90%)

The electrochemical fluorination of thioflavone **1a** at a low potential (E = 1.30 V) with the $Et_3N-3\,HF-MeCN$ system being used as the source of fluoride ion yields 3-fluorothioflavone **97** (Scheme 59).[97,98]

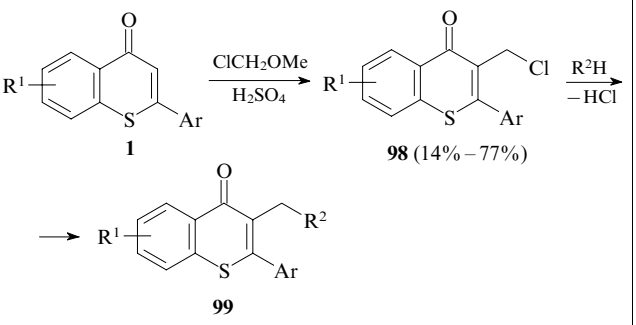
Scheme 59



(*a*) Electrochemical reaction, Et_3N, HF, MeCN

The reaction of thioflavones **1** with chloromethyl methyl ether in the presence of fuming sulfuric acid gives mainly 3-chloromethyl derivatives **98** in up to 77% yields. In a number of cases, 3-hydroxymethyl derivatives were obtained, and 6-methoxythioflavone was chloromethylated in position 5.[99–101] 3-Chloromethylthioflavones **98** react with aniline, morpholine or bis(2-hydroxyethyl)amine on refluxing in dioxane or ethanol to give 3-aminomethylthioflavones **99** (36%–77% yields) (Scheme 60).

Scheme 60

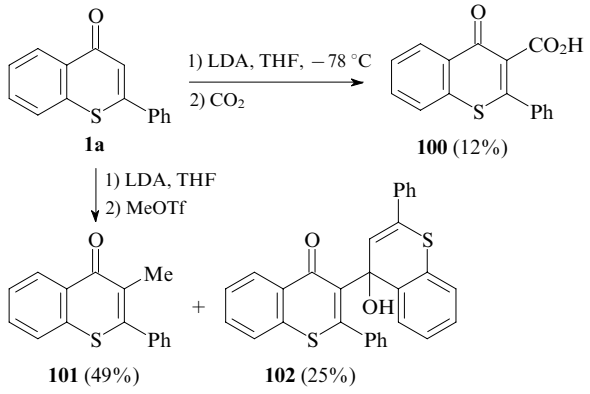


Ar = 4-XC_6H_4 (X = H, Me, OMe, NO_2); R^1 = H, Me, OMe (in different positions); R^2 = NHPh, cyclo-$N(CH_2CH_2)_2O$, $N(CH_2CH_2OH)_2$

3.1.3. Miscellaneous reactions

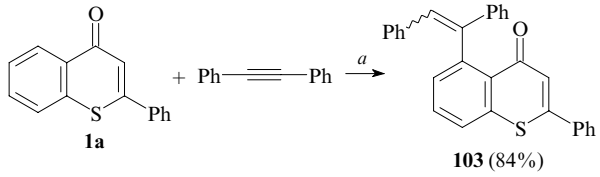
Costa *et al.*[102] have shown that thioflavone **1a** is lithiated at position 3 under the action of lithium diisopropylamide in THF at −78 °C; however, unlike the case of flavone, intermediate 3-lithiothioflavone does not readily react with carbon dioxide, which accounts for the low yield of thioflavone-3-carboxylic acid **100**. Meanwhile, the reaction of 3-lithiothioflavone with methyl triflate gives 3-methylthioflavone **101**, together with dimer **102**, which results from nucleophilic addition of a second thioflavone molecule to the carbonyl group (Scheme 61).[103]

Scheme 61



Transition metal-catalyzed hydroarylation of diarylacetylenes with chromones occurs at position 5 of the chromone system. Thioflavone **1a** also reacts with tolane (diphenylacetylene) in the presence of $AgSbF_6$ and AcOH in dichloroethane (DCE) at 100 °C to give compound **103** mainly as the Z-isomer ($Z:E$ = 92 : 8) (Scheme 62).[104]

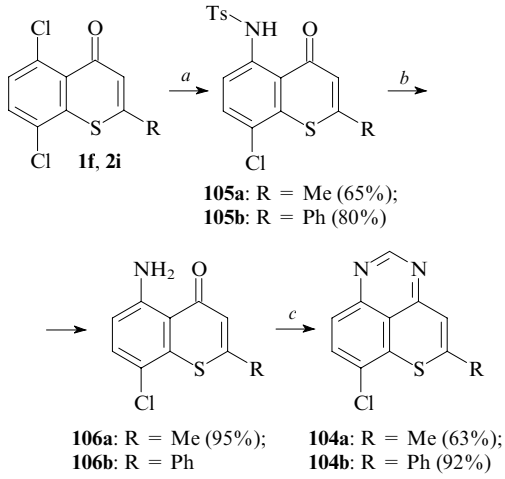
Scheme 62



(*a*) $AgSbF_6$ (20 mol.%), AcOH, DCE, 100 °C

The synthesis of 5-substituted 7-chlorothiopyrano[4,3,2-*de*]quinazolines **104a**,**b** based on 5,8-dichlorothiochromones **1f** and **2i** has been reported.[105] When the starting compounds are treated with *p*-toluenesulfonamide on heating with copper bronze in nitrobenzene, only one chlorine atom in position 5 is replaced to give tosylamines **105a**,**b**, which are converted to amines **106a**,**b** upon deprotection by treatment with concentrated sulfuric acid at 70–80 °C (the yield is indicated only for R = Me). The reaction of compounds **106a**,**b** with formamidinium acetate on heating to 160 °C leads to quinazolines **104a**,**b** (Scheme 63).[105]

Scheme 63



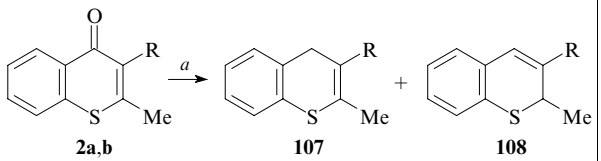
(*a*) $TsNH_2$, Cu, AcOH, $PhNO_2$, 180 °C, 4 h; (*b*) H_2SO_4, 70 °C, 1 h; (*c*) $NH_2CH{=}NH$, AcOH, 160 °C, 2 h; R = Ph (**1f**), Me (**2i**)

3.2. Chemical reactivity of 2-alkylthiochromones

3.2.1. Reduction and addition reactions

The first data on the reduction of 2-methylthiochromones **2a**,**b** appeared in 1981 in the publication of Akiba and coworkers.[106] The authors showed that sodium tetrahydroborate in methanol alone cannot induce the reaction, and only with addition of $CeCl_3 \cdot 7H_2O$, the carbonyl group is reduced to the methylene group. When the reactant ratio **2** : $NaBH_4$: $CeCl_3$ is 1.0 : 2.5 : 1.5, the reactions give mixtures of 4*H*-thiochromenes **107** and minor amounts of 2*H*-thiochromenes **108** in overall yields of 80% (R = H) and 69% (R = Me) (Scheme 64).

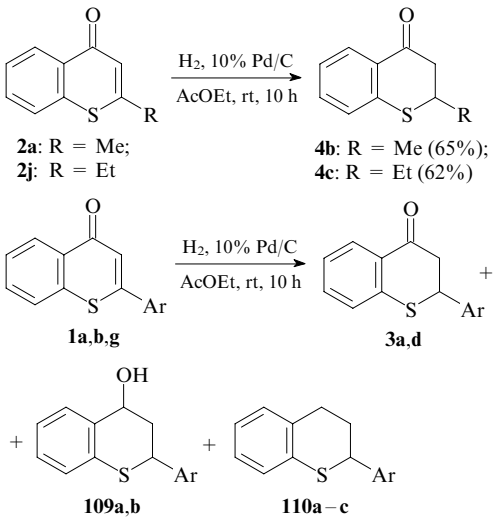
Scheme 64



(*a*) $NaBH_4$, $CeCl_3$, MeOH, rt, 5 h; R = H, Me

Hydrogen reduction of 2-methyl- and 2-ethylthiochromones **2a**,**j** in the presence of Pd/C in ethyl acetate at room temperature for 10 h involves only the carbon–carbon double bond and gives 2-alkylthiochromanones **4b**,**c** in 62%–65% yields. It is noteworthy that the reduction of 2-arylthiochromones **1a**,**g** under the same conditions, but for a longer period of time (15–20 h) proceeds ambiguously, giving rise to mixtures of thioflavanones **3a**,**d**, thioflavanols **109a**,**b** and thioflavanes **110a**,**b** (Scheme 65).[107] Meanwhile, substrate **1b** is regioselectively converted to thioflavane **110c**.

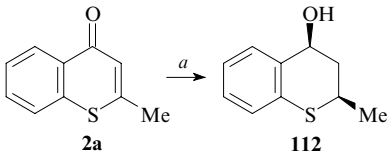
Scheme 65



Substrate	Ar	Products					
		3	yield (%)	**109**	yield (%)	**110**	yield (%)
1a	Ph	**a**	45	**a**	18	**a**	31
1g	4-ClC_6H_4	**d**	10	**b**	25	**b**	40
1b	4-$MeOC_6H_4$					**c**	66

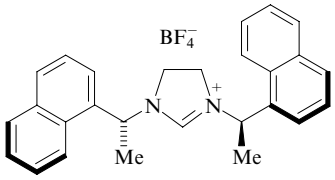
A study of asymmetric hydrogenation of chromones has shown that treatment with a combination of the bis(2-methylallyl)(cycloocta-1,5-diene)ruthenium(II) catalyst ([Ru(cod)(2-methylallyl)$_2$]) and imidazolinium salt **111** in the presence of potassium *tert*-butoxide with refluxing in hexane at a hydrogen pressure of 120–150 bar leads to reduction of 2-methylthiochromone (**2a**) to thiochromanol **112** with low diastereoselectivity [diastereomer ratio (*dr*) = 1.3 : 1] and high enantioselectivity [enantiomer ratio (*er*) = 91 : 9] for 92% conversion (Scheme 66).[108]

Scheme 66



(*a*) H_2, **111**, $KOBu^t$, [Ru(cod)(2-methylallyl)$_2$], hexane, 70 °C;

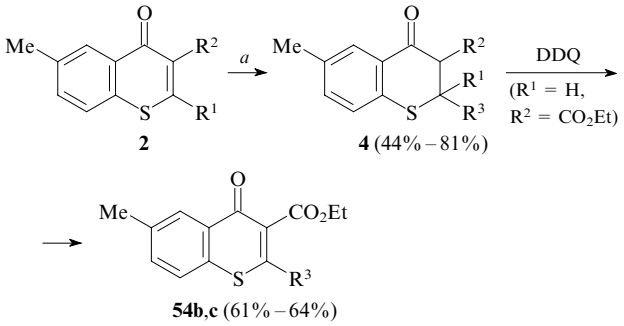
111 =



Using alkylcopper compounds, it is possible to perform conjugate addition of methyl or butyl group to the double

bond of compounds **2** to give thiochromanones **4**. The reaction was carried out by mixing a suspension of $Me_2S \cdot CuBr$ in diethyl ether with a solution of methyl(n-butyl)lithium in diethyl ether at −10 °C in a nitrogen atmosphere with subsequent addition of thiochromone at −40 °C and keeping the reaction mixture at this temperature for 30 min. Products **4** thus formed were isolated by flash chromatography. The oxidation of thiochromanones **4** (R^1 = H, R^2 = CO_2Et) under the action of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone furnishes ethyl 2-alkylthiochromone-3-carboxylates **54b**,**c** [R^3 = Me (**b**), Bu^n (**c**)] in good yields (Scheme 67).[109]

Scheme 67



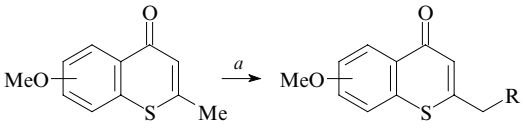
2 **4** (44%–81%) **54b**,**c** (61%–64%)

(*a*) R^3Li, $Me_2S \cdot CuBr$, Et_2O, N_2, −40°C; R^1 = H, Me, Bu^n; R^2 = H, CO_2Et; R^3 = Me, Bu^n

3.2.2. Reactions at the methyl and carbonyl groups

It has been shown [110] that treatment of 5-methoxy- (**2k**) and 7-methoxy-2-methylthiochromones (**2l**) with lithium diisopropylamide in THF at −78 °C in the presence of hexamethylphosphoramide (HMPA) leads to smooth lithiation of the methyl group, while the subsequent addition of various electrophilic reagents such as alkyl halides and aromatic aldehydes affords thiochromones **113** substituted at the methyl group (Scheme 68).

Scheme 68



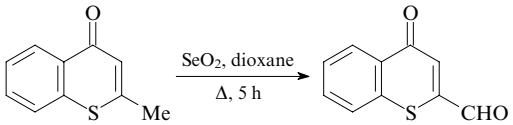
2k,**l** **113** (21%–71%)

(*a*) 1) LDA, HMPA, THF, −78°C; 2) electrophile; R = Me, All, EtO_2CCH_2, PhCH(OH), 4-$MeOC_6H_4CH(OH)$, 3,4-$(OCH_2O)C_6H_3CH(OH)$

Refluxing of thiochromone **2a** with selenium(IV) oxide in dioxane for 5 h leads to oxidation of the methyl group to the aldehyde group, thus giving 2-formylthiochromone **114** in 40% yield; the similar reaction in xylene gives the same product in a lower yield (26%) even after 6 h (Scheme 69).[111]

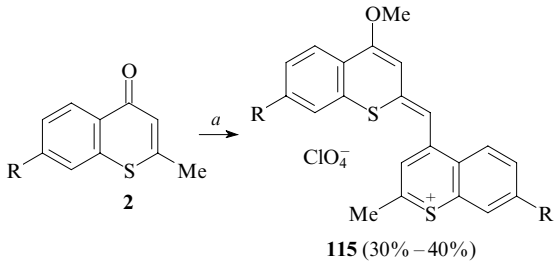
Upon methylation with dimethyl sulfate and reduction with aluminium hydride followed by treatment with perchloric acid, 2-methylthiochromones **2** are dimerized through the active methyl group to give light-blue-coloured thiochromylium salts **115** and **116** (Scheme 70).[112, 113]

Scheme 69



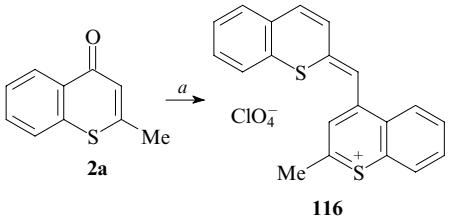
2a **114** (40%)

Scheme 70



2 **115** (30%–40%)

(*a*) 1) Me_2SO_4; 2) $HClO_4$; R = H, Me, OMe, Cl

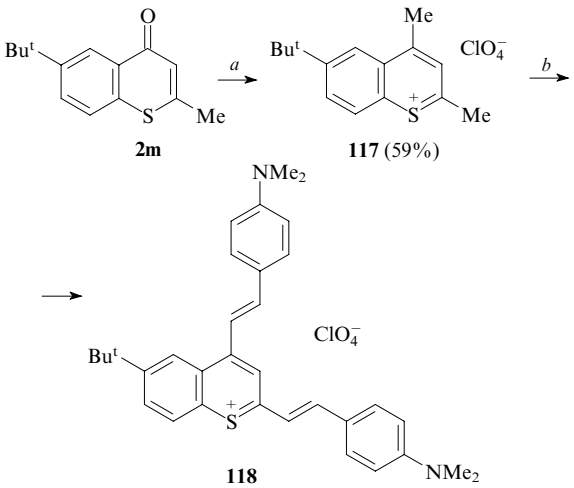


2a **116**

(*a*) 1) AlH_3, THF; 2) $HClO_4$

The reaction of thiochromone **2m** with methylmagnesium iodide with subsequent treatment of the reaction mixture with 20% $HClO_4$ at −20 °C yields thiochromylium salt **117**. The condensation of this salt with *p*-dimethylaminobenzaldehyde with refluxing in ethanol for 4 h involves simultaneously two activated methyl groups, giving rise to polymethine benzothiopyrylium dye **118** (Scheme 71).[114]

Scheme 71



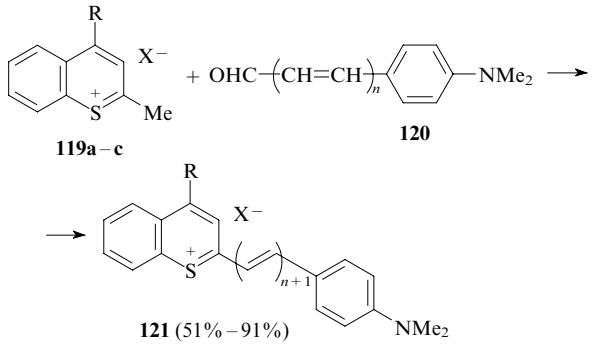
2m **117** (59%) **118**

(*a*) MeMgI, $HClO_4$; (*b*) 4-$Me_2NC_6H_4CHO$, EtOH, Δ

4-Hydroxy-2-methylthiochromylium perchlorate (**119a**), obtained by the reaction of 2-methylthiochromone **2a** with 60% perchloric acid in acetic acid, and 4-phenyl and

4-ethoxy derivatives of 2-methylthiochromylium **119b**,**c** are fused at the methyl group with *p*-dimethylaminobenzaldehyde and its vinylogues **120** to give infrared polymethine dyes **121** (dyes with the absorption peak in the infrared region) in good yields (Scheme 72).[115]

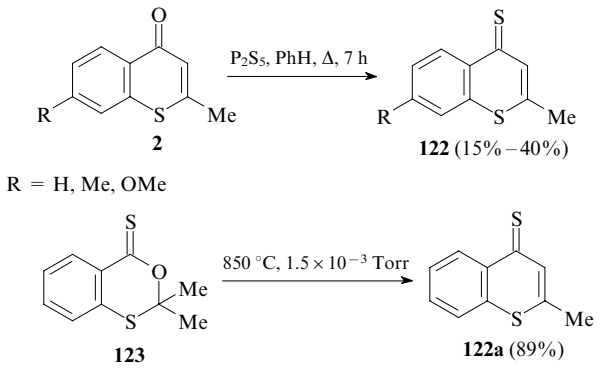
Scheme 72



119: R = OH (**a**), Ph (**b**), OEt (**c**); X = ClO_4, BF_4; *n* = 0–2

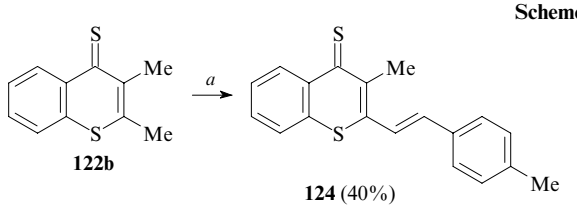
Upon refluxing of 2-methylthiochromones **2** with P_2S_5 in benzene for 7 h, dithiochromones **122** were isolated in a low yield.[113] Note that 2-methyldithiochromone (**122a**) unsubstituted in the benzene ring was also obtained in a high yield by thermolysis of 2,2-dimethyl-4*H*-3,1-benzoxathiine-4-thione (**123**) (Scheme 73).[116]

Scheme 73



It should be noted that, despite the replacement of carbonyl oxygen by sulfur in compounds **2**, high reactivity of the methyl group in position 2 is retained. Indeed, 2,3-dimethyldithiochromone (**122b**) reacts with anisaldehyde at the vinylogous 2-methyl group in the presence of piperidine to give the corresponding styryl derivative **124** in a moderate yield (Scheme 74).[117]

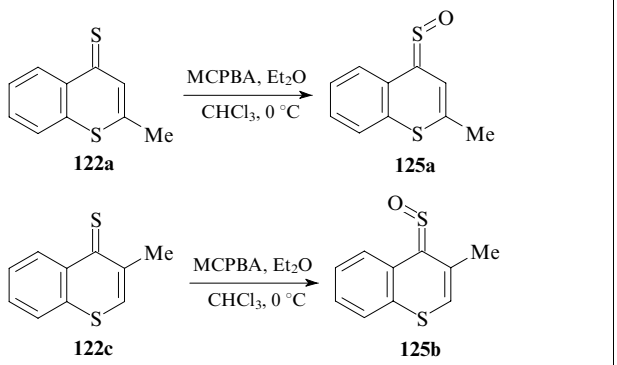
Scheme 74



(*a*) 4-MeOC$_6$H$_4$CHO, piperidine

The oxidation of 2- and 3-methyldithiochromones **122a**,**c** on treatment with *m*-chloroperoxybenzoic acid (1 equiv.) in diethyl ether at 0 °C involves the thione sulfur atom and affords sulfines **125a**,**b** (the yields are not indicated in the original paper, and the orientation of the S=O bond has not been strictly proved) (Scheme 75).[118]

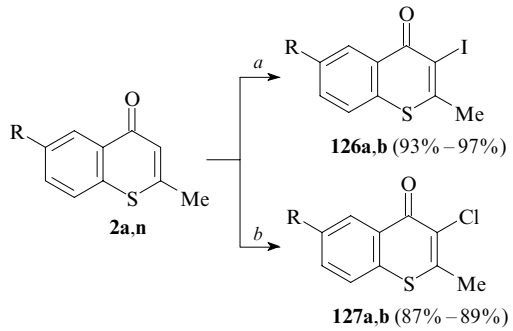
Scheme 75



3.2.3. Reactions at the C(3) atom

3-Iodo- (**126a**,**b**) and 3-chloro-2-methylthiochromones (**127a**,**b**) were prepared under the conditions proposed for the synthesis of the corresponding 3-halothioflavones. Treatment of thiochromones **2** with the iodine–cerium(IV) ammonium nitrate system in refluxing acetonitrile affords 3-iodo derivative **126**,[92] while the reaction with sulfuryl chloride in the presence of monmorillonite K-10 results in the formation of 3-chloro derivatives **127**.[96] Both reactions give products in nearly quantitative yields (Scheme 76).

Scheme 76

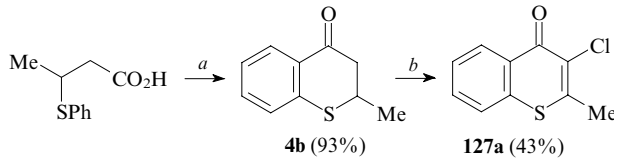


(*a*) I_2, CAN, MeCN, Δ; (*b*) $SOCl_2$, montmorillonite K-10, CH_2Cl_2, 15 min; R = H (**2a**, **126a**, **127a**), Me (**2n**, **126b**, **127b**)

The synthesis of 3-chloro-2-methylthiochromone (**127a**) by chlorination–dehydrochlorination of thiochromanone **4b** in acetic acid has been reported.[119] Chlorine was passed at a temperature of 20–25 °C for 3 h and then the reaction mixture was stirred at 30–34 °C for additional 34 h and product **127a** was isolated. The starting thiochromanone **4b** was prepared by cyclization of β-(phenylthio)butyric acid on treatment with PPA at 80 °C (Scheme 77).

The Ziegler radical bromination of 2-methylthiochromone (**2a**) (*N*-bromosuccinimide, benzoyl peroxide, CCl_4) affords 3-bromo-2-methylthiochromone (**128**), which is oxidized with H_2O_2 at the sulfur atom to give 3-bromo-2-methylthiochromone 1,1-dioxide (**129**). Bromination of 2,3-

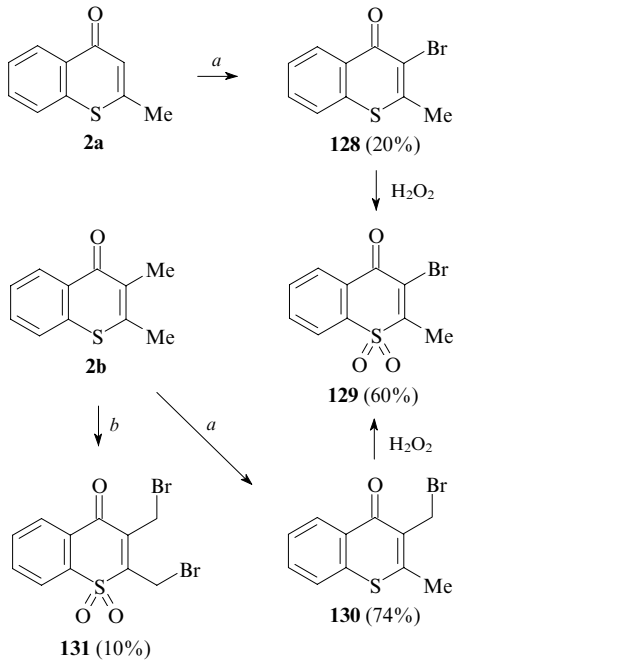
Scheme 77



(*a*) PPA, 80 °C, 2 h; (*b*) Cl_2, AcOH, 20–30 °C, 34 h

dimethylthiochromone **2b** under similar conditions involves the 3-Me group and affords 3-bromomethyl-2-methylthiochromone **130**, which is oxidized with hydrogen peroxide unexpectedly giving rise to dioxide **129**. This transformation is associated with the loss of the CH_2Br group to afford the bromonium cation, which attacks position 3. If the sequence of steps in the reaction of thiochromone **2b** is changed (oxidation followed by bromination) and an excess of NBS is used, thiochromone 1,1-dioxide **131** with two bromomethyl groups can be isolated in a low yield (Scheme 78).[58]

Scheme 78

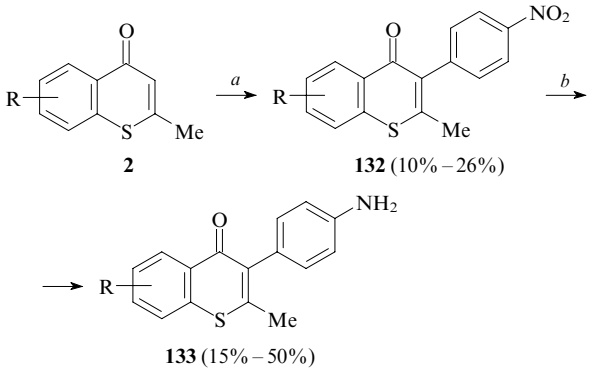


(*a*) NBS, $(BzO)_2$, CCl_4; (*b*) 1) H_2O_2; 2) NBS, $(BzO)_2$, CCl_4

Diazotization of benzene ring-methylated 2-methylthiochromones **2** with *p*-nitrophenyldiazonium chloride in acetone affords thioisoflavones **132** in low yields; the reduction of the nitro group in these products with iron in hydrochloric acid furnishes amino thioisoflavones, compounds **133**, necessary for biological assays (Scheme 79).[120]

Under the conditions used in the above-described chloromethylation of thioflavones **1** (see Scheme 60), 2-methylthiochromone **2a** is converted to 3-chloromethyl-2-methylthiochromone **134** and a minor amount of 3-hydroxymethyl-2-methylthiochromone **135**.[99] The latter product is also formed in the reaction of 3-bromo-2-methylthiochroman-4-one (**136**) with formaldehyde taken as 30% formalin in a methanol–water system in the presence of potassium

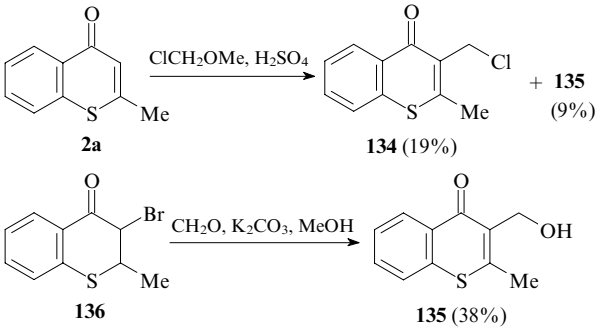
Scheme 79



(*a*) 4-$O_2NC_6H_4N_2Cl$, $CuCl_2$, NaOAc, Me_2CO, 0–5 °C;
(*b*) Fe, HCl, EtOH, Δ, 2 h; R = H, Me (in different position)

carbonate at 50 °C. This is accompanied by hydroxymethylation of the thiochromanone ring in position 3 followed by dehydrobromination to give thiochromone **135** in a moderate yield (Scheme 80).[121]

Scheme 80

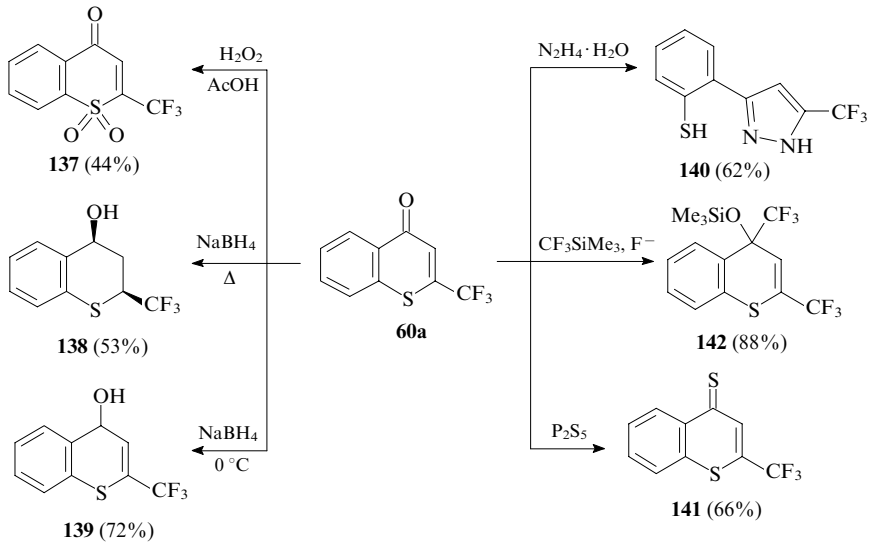


3.2.4. Reactions of 2-(trifluoromethyl)thiochromones

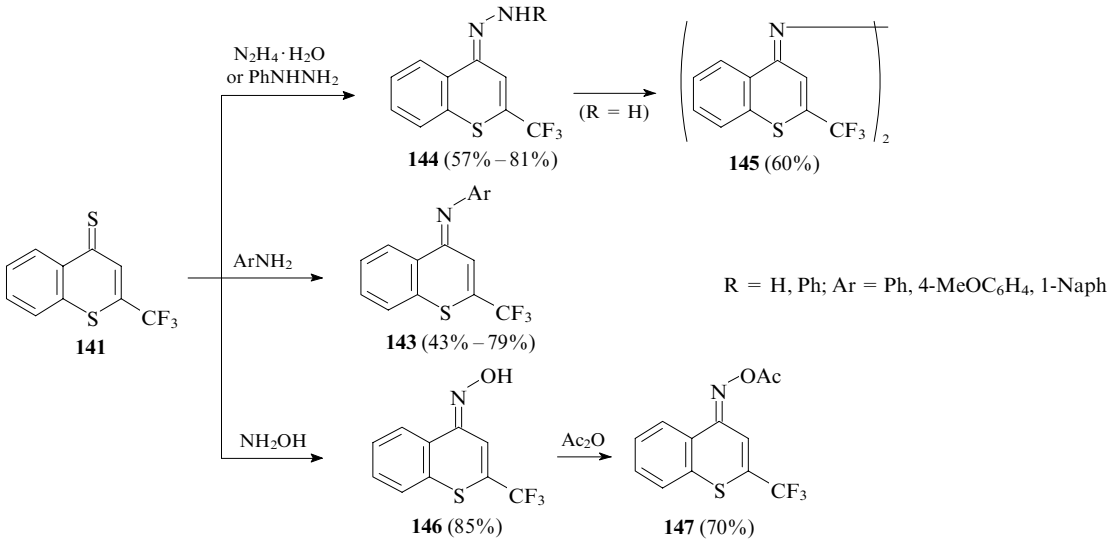
2-(Trifluoromethyl)thiochromone **60a** is oxidized with hydrogen peroxide on heating in acetic acid to give dioxide **137** and is reduced on treatment with an excess of $NaBH_4$ in isopropyl alcohol to form *cis*-2-(trifluoromethyl)thiochroman-4-ol (**138**). Under milder conditions (~0 °C) in the presence of a slight excess of $NaBH_4$, the reduction can be stopped after the formation of 2-trifluoromethyl-4*H*-thiochromen-4-ol (**139**).[122] Treatment of thiochromone **60a** with hydrazine hydrate at room temperature leads to pyrazole **140** (a rare example of thiopyrone ring opening),[76] while refluxing with P_2S_5 in toluene for 1 h affords dithiochromone **141**.[122] It was also found that compound **60a** reacts with the Ruppert reagent with involvement of the C=O group to give trimethylsilyl ether **142** as the only product in high yield (Scheme 81).[123] This result implies that 2-(trifluoromethyl)thiochromone **60a** reacts by the nucleophilic 1,2-addition mechanism, whereas 2-(trifluoromethyl)chromones react with CF_3SiMe_3 at the C(2) atom (1,4-addition).[10, 124]

Some chemical properties of 2-(trifluoromethyl)dithiochromone (**141**) have been reported.[122] This compound was found to react with aniline, *p*-anisidine and α-naphthylamine in refluxing butanol with the participation of the thione group, giving rise to anils **143** in good yields. Treatment of compound **141** with hydrazine hydrate and phenyl-

Scheme 81



Scheme 82



hydrazine affords hydrazones **144** and azine **145**, while the reaction with hydroxylamine results in the formation of oxime **146**, which is O-acetylated on treatment with acetic anhydride to be converted to product **147** (Scheme 82).

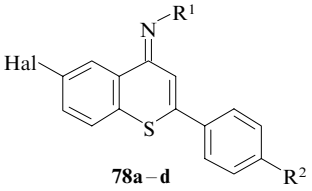
Thus, all reactions of dithiochromone **141** follow the nucleophilic 1,2-addition mechanism without thiopyrone ring opening and give the corresponding derivatives of 2-(trifluoromethyl)thiochromone **60a**. All attempts to obtain five- or six-membered heterocycles from compound **141** and various dinucleophiles such as hydroxylamine, hydrazines and amidines under the conditions that were used for 2-(trifluoromethyl)chromones proved unsuccessful. This means that, despite the presence of the strong electron-withdrawing CF_3 group at the C(2) atom, sulfur analogues of 2-(trifluoromethyl)chromone react with nucleophilic reagents almost exclusively at the C(4) atom, being thus markedly different from chromones, which are attacked most often at the C(2) atom and then undergo pyrone ring opening.[10, 124, 125]

3.3. Biological properties of 2-substituted thiochromones

Thioflavone (**1a**) and dithioflavone (**72a**), along with natural chromones, flavones and their thione derivatives have been studied[126] as photopesticides — compounds that become toxic only on exposure to light. It was shown that replacement of the carbonyl oxygen by sulfur decreases the photoactivation energy and chromonethiones start to behave as potential photopesticides. The authors claim that they were able to shift the light wavelength that activates the phototoxicity from the ultraviolet to visible range, thus creating prerequisites for the development of solar light-activated photopesticides. The activity of compounds was measured by inhibition of the growth of the fungus *Fusarium culmorum*.

A series of imines obtained from halo-substituted dithioflavones **72** have been tested[12] as potential antimalarial agents. Some conclusions concerting the structure – activity relationships (SAR) were drawn and the highest activity against *Plasmodium berghei* was found for 6-chloro- and 6-bromo-substituted thioflavoneimines **78a – d**, when tested on mice in 160 to 360 mg kg^{-1} doses.

Structures 78



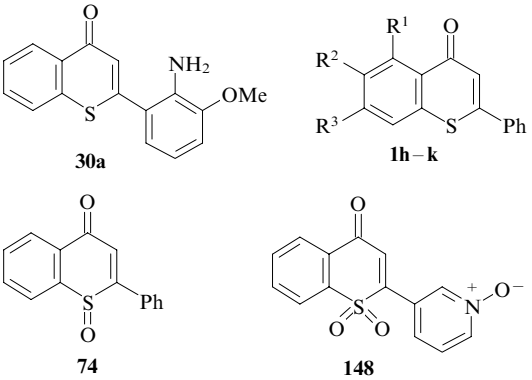
78a – d

Hal = Cl, R^1 = CH(Me)$(CH_2)_3NEt_2$, R^2 = H (**a**); Hal = R^2 = Cl: R^1 = $(CH_2)_3$[N$(CH_2CH_2)_2$NMe]-cyclo (**b**), $(CH_2)_3NMe_2$ (**c**); Hal = Br, R^1 = CH(Me)$(CH_2)_3NEt_2 \cdot 2$ HCl, R^2 = H (**d**)

Kataoka *et al.*[40] prepared nitro and amino thioflavone derivatives (see Scheme 14) and studied them for the ability to inhibit the activation of MAP-kinase ERK (MEK) signalling pathways. Among these compounds, (2-amino-3-methoxyphenyl)thioflavone (**30a**) was found to be the most potent agent inhibiting the Raf-1-induced MEK activation more efficiently than the corresponding flavone, which was known to strongly and specifically inhibit the MEK activity. Moreover, compound **30a** is an efficient and selective inhibitor of proliferation of some tumour cells, in which MAP-kinase ERK pathway activation has been identified.

Nakazumi *et al.*[13] investigated biological activities of a number of thioflavones and found that compounds **1h**,**j** and **74** exhibit a substantial inhibitory action on the growth of tumour cells, in particular, on the human ileocecal carcinoma (HCT-8), mouse leukaemia (P-388), human melanoma (RPMI) and human central nervous system tumour (TE671) cells. Thioflavones **1i**,**j** and **74** showed inhibitory activity *in vitro* towards DNA topoisomerase I, while compound **1k** inhibits *in vitro* DNA topoisomerase II. Thioflavone **1k** also proved to be the most active [half-maximum effective dose (ED_{50}) = 0.65 μmol litre^{-1}] against HIV in acutely infected H9-lymphocytes and had the therapeutic index ~5.

Structures 1h – k, 30a, 74, 148



30a **1h – k**

74 **148**

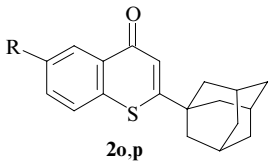
R^1 = R^3 = H, R^2 = OH (**h**); R^1 = NH_2, R^2 = R^3 = H (**i**); R^1 = H: R^2 = R^3 = OH (**j**), OAc (**k**)

Razdan *et al.*[14] studied the affinity of 6-methyl- and 6-methyl-3′-nitrothioflavones for the $GABA_A$-receptor benzodiazepine binding site using the binding of [^{3}H]- flumazenil to rat cortical membranes *in vitro*; however, no significant positive effect was revealed. The introduction of the chloromethyl group in position 3 of thioflavones (see compounds **98** in Scheme 60) gives rise to a substantial antimicrobial activity against the fungus *Trichophytons* [minimal inhibitory concentration (MIC) = 0.195 μg ml^{-1}]; a similar effect was found for 3-(alkoxymethyl)thioflavones, which can be easily prepared from 3-(chloromethyl)thioflavones **98**.[99, 100] The latter have also a slight insecticidal activity against the mite *Tetranychus urticae*.[127]

Transition from thioflavones to their sulfoxides and S,S-dioxides has been shown to markedly increase the antimicrobial activity of the compounds against yeast fungi and moulds.[13] In addition, thioflavone S,S-dioxides are potent inhibitors of the HCMV protease *in vitro* (HCMV is the human cytomegalovirus).[72] The enzymatic kinetic data obtained for compound **148** as the prototype of this class of inhibitors confirm a reversible inhibition mechanism that does not include the oxidative inactivation of the enzyme. SAR investigations have shown that thioflavones with electron-deficient aryl substituents in position 2 can be considered as a new class of CMV-protease inhibitors.[72]

Steroid sulfatase (STS) is a relevant target for the therapy of several diseases. 2-(1-Adamantyl)thiochromone 6-*O*-sulfamate (**2o**) with the half maximal inhibitory concentration (IC_{50}) of 0.34 nmol litre^{-1} is the most potent STS inhibitor discovered to date: it is approximately 170 times stronger than the reference estrone sulfamate.[60, 128] 2-(1-Adamantyl)thiochromone-6-carboxylic acid (**2p**) exhibited the behaviour of a potent reversible STS inhibitor, showing the inhibition constant (K_i) of 0.53 μmol litre^{-1} in a cell-free system with purified human STS.[129]

Structures 2o,p



2o,p

R = OSO_2NH_2 (**o**), CO_2H (**p**)

In conclusion, we would like to note that some substituted 2-methylthiochromones **2** and 2,7-dimethyldithiochromone (**122d**) showed a weak insecticidal activity against the mite *Tetranychus urticae*.[127]

4. 2,3-Disubstituted thiochromones

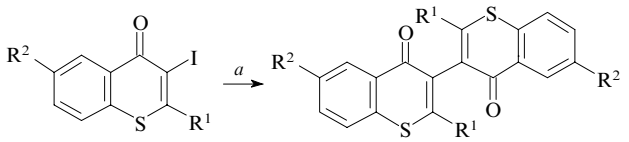
4.1. 2-Substituted 3-halothiochromones

The preparation of 3-halothioflavones and 3-halo-2-methylthiochromones is described in Sections 3.1.2 and 3.2.3, respectively; in this Section, we consider the chemical properties of these compounds. Note that there are numerous published examples of application of 2-substituted 3-halochromones in organic synthesis, especially in the Pd-catalyzed Heck, Sonogashira, Suzuki and Stille cross-coupling reactions;[10, 94] however, much less is known about similar reactions of thiochromones.

It has been shown[130] that under Ullmann reaction conditions (on heating with copper powder for 7 h at 200 – 210 °C under argon), 3-iodothioflavones **92** and 3-iodo-2-methylthiochromones **126** undergo homocoupling to give 3,3′-bis-products **149**. The yields of bis(thioflavones) were 80% – 83%, and the yields of bis(2-methylthiochromones) were only 31% – 33% (Scheme 83).

Thiochromone **126a** smoothly reacts with phenylboronic acid according to the Suzuki – Miyaura reaction pathway to

Scheme 83

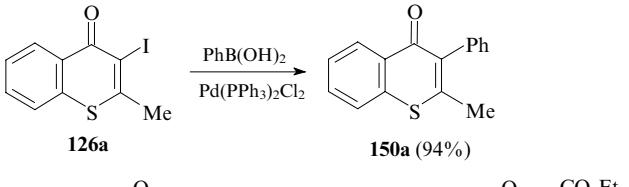


92, **126** **149** (31% – 83%)

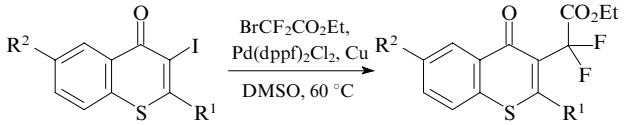
(*a*) Cu, argon, 200 – 210 °C, 7 h; R^1 = Me, Ph; R^2 = H, Me

give 2-methyl-3-phenylthiochromone **150a** — a starting compound for the synthesis of photolabile thiochromones — in a high yield.[131, 132] Palladium-catalyzed cross-coupling of 3-iodothiochromones **92** and **126** with ethyl bromodifluoroacetate in the presence of copper powder in DMSO proceeding in 4 – 5 h at 60 °C furnishes difluoro derivatives **151** in good yields (Scheme 84).[133]

Scheme 84



126a **150a** (94%)

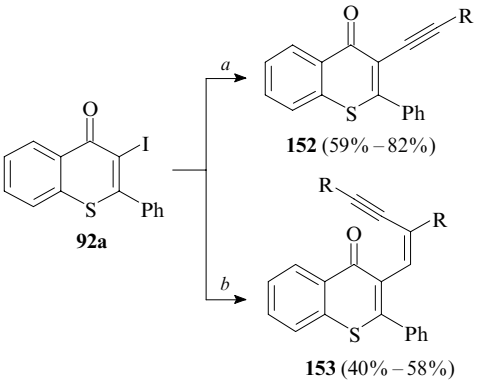


92, **126** **151** (71% – 91%)

R^1 = Me, Ph; R^2 = H, Me;
dppf is 1,1′-bis(diphenylphosphino)ferrocene

The cross-coupling reactions of 3-iodothioflavones catalyzed by palladium complexes involving the formation of new C – C bonds between the sp^2- and sp-hybridized carbon atoms have been recently studied in detail by Indian chemists.[134, 135] Using 3-iodothioflavone (**92a**) as an example, they explored the Heck and Sonogashira alkenylation and alkynylation coupling reactions with halogen displacement on treatment with various terminal alkynes containing hydroxyalkyl groups in the present of the $Pd(PPh_3)_2Cl_2$ complex as the catalyst (Scheme 85).

Scheme 85



92a **152** (59% – 82%) **153** (40% – 58%)

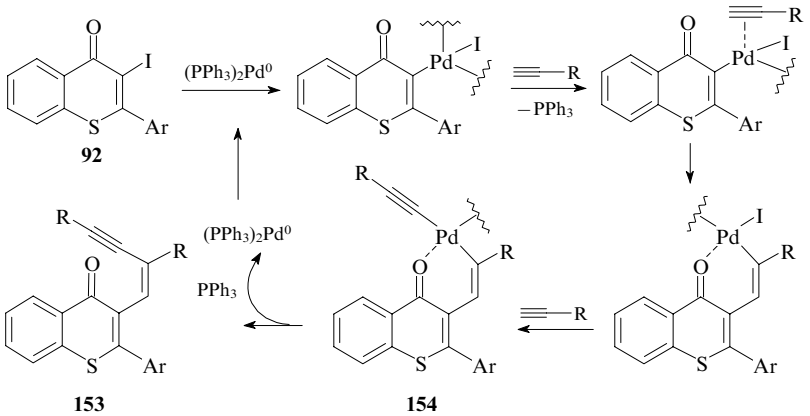
(*a*) RC≡CH (2 equiv.), $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF;
(*b*) 1) RC≡CH (1.5 equiv.), $Pd(PPh_3)_2Cl_2$; 2) RC≡CH (1 equiv.), CuI;
R = $C(OH)Me_2$, CH(OH)Me, CH_2OH, $(CH_2)_2OH$, CH(OH)Et, CH(OH)Ph, $CH_2OC_6H_4X$ (X = 4-CHO, 4-OMe, 4-NO_2, 2-Cl)

The Sonogashira reaction requires the simultaneous use of the Pd-catalyst and copper(I) halide in the presence of triethylamine and results in the formation of acetylene thioflavone derivatives **152** in moderate to high yields. In the Heck modification, the reaction is stepwise: first the same components are added to the reaction mixture, except for the copper cocatalyst, which is added 2 – 3 h later together with an additional amount of alkyne. In this case, enyne thioflavone derivatives **153** are formed in reasonable yields. Scheme 86 shows a probable mechanism of this coupled Heck – Sonogashira reaction that implies the formation of Pd-intermediates **154**.[134, 135]

Analysis of published data indicates that because of high activity of the halogen atom in position 2, 2-halo(thio)chromones are among the most poorly accessible halogenated chromones and thiochromones. Upon chlorination of 3-(hydroxymethylene)thiochroman-4-one (**155**), obtained *via* condensation of thiochroman-4-one with ethyl formate in the presence of sodium methoxide, under the action of *N*-chlorosuccinimide (NCS) in dichloromethane at 5 – 20 °C for 10 h, 2,3-dichlorothiochromone **156** was unexpectedly isolated in a relatively low yield (Scheme 87).[136]

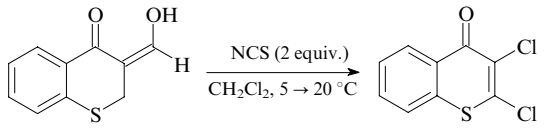
The reaction of 2,3-dibromothiochromone 1,1-dioxide (**157**) with primary and secondary aliphatic and aromatic amines in ethanol at −20 °C involves the replacement of only one bromine atom that is located in position 2, thus

Scheme 86



92 **153** **154**

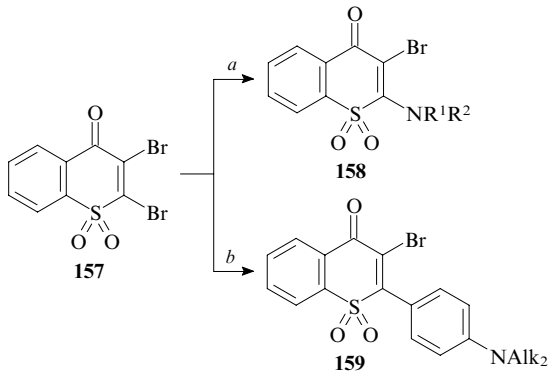
Scheme 87



155 **156** (24%)

affording amino derivatives **158** in 22% – 37% yields in the case of aliphatic amines and in 8% (for 4-$AcC_6H_4NH_2$) to 92% (for 4-$MeOC_6H_4NH_2$) yields in the case of anilines.[137] It is worth noting that this reaction can be carried out even for tertiary aromatic amines, which act in this case as C-nucleophiles; however, the yields of compounds **159**, which are of interest as chromophores,[138] are only 7% – 36%, depending on the amine structure (Scheme 88).

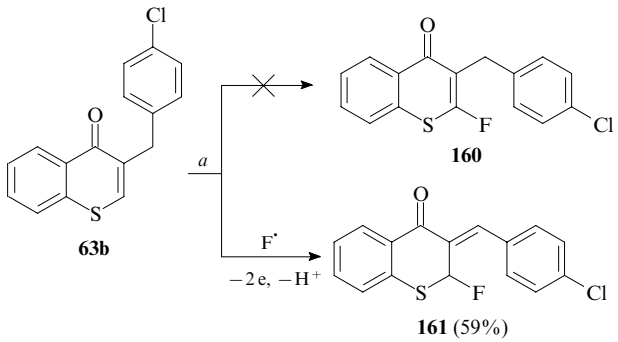
Scheme 88



(*a*) R^1R^2NH, −20 °C or $ArNH_2$, rt → Δ, EtOH; (*b*) $PhNAlk_2$, EtOH, Δ; R^1 = H, Me; R^2 = Me, 4-XC_6H_4 (X = H, Me, OMe, NO_2, Ac)

Instead of the expected 3-(4-chlorobenzyl)-2-fluorothiochromone (**160**), anodic fluorination of 3-(4-chlorobenzyl)thiochromone **63b** gives (*E*)-3-(4-chlorobenzylidene)-2-fluorothiochroman-4-one (**161**) as a result of [1,3]-hydrogen shift; di- and trifluorinated derivatives are formed as minor products (Scheme 89).[98]

Scheme 89



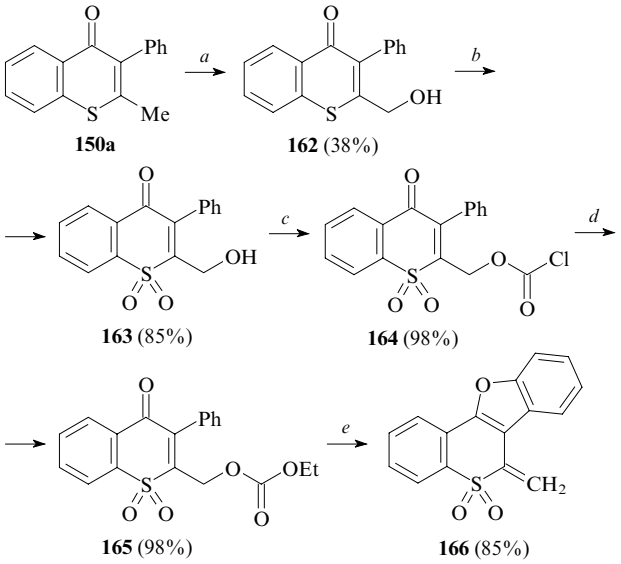
161 (59%)

(*a*) $Et_3N \cdot 3\,HF$, DME

4.2. Photolabile and other 2,3-dialkyl(aryl)thiochromones

In recent years, considerable attention has been devoted to photolabile protecting groups (PLPGs), which do not require any reagents for deprotection. In quite a few studies, Japanese researchers[131, 132, 139 – 141] demonstrated a broad scope of application of thiochromone fragments as PLPGs for alcohols, amines, phosphates and carboxylic and sulfonic acids. The reaction sequence used for this purpose is presented below. Allylic oxidation of the methyl group of thiochromone **150a** to the formyl group on treatment with SeO_2 followed by reduction with sodium tetrahydroborate leads to 2-hydroxymethyl-3-phenylthiochromone **162**. The subsequent oxidation of this compound with 2 equiv. of MCPBA results in the synthesis of thiochromone 1,1-dioxide **163**, which is treated with phosgene to give the target chloroformate derivative **164**, which reacts with ethanol in pyridine to form product **165**. The ethanol hydroxyl group is deprotected on exposure of compound **165** to monochromatic UV light at 313 nm, resulting in almost quantitative formation of tetracyclic product **166** with evolution of ethanol and carbon dioxide. This reaction sequence was successfully used to protect the functional groups in various aliphatic alcohols and amines. Note that unlike 1,1-dioxide **165**, the corresponding thiochromone derivative **162** proved to be stable on irradiation, indicating the crucial role of the oxidation state of the sulfur atom for the photolability of thiochromones (Scheme 90).[131]

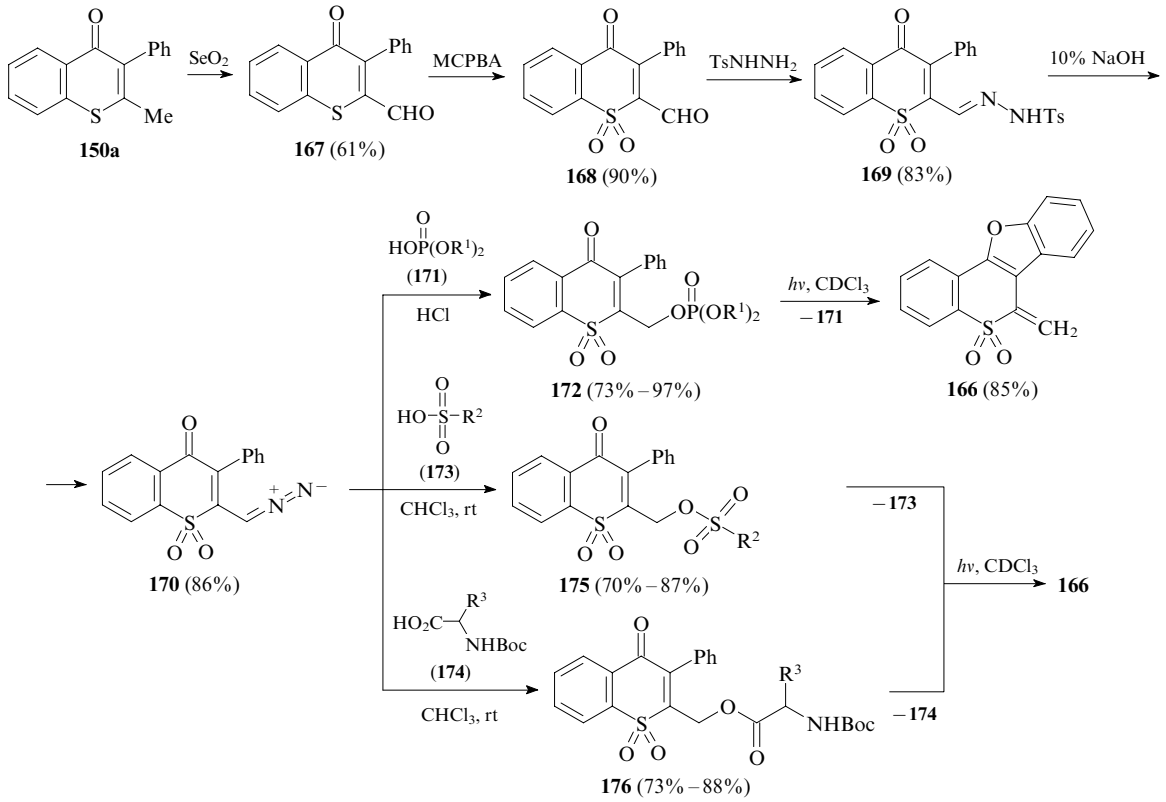
Scheme 90



(*a*) 1) SeO_2, PhCl, Δ; 2) $NaBH_4$, MeOH, 0 °C; (*b*) MCPBA, $CHCl_3$, rt; (*c*) $C(O)Cl_2$, PhMe, rt; (*d*) EtOH, PyH, rt; (*e*) *hν* (– EtOH, – CO_2)

Zhang *et al.*[132] proposed to protect the phosphate group by 2-diazomethyl-3-phenylthiochromone 1,1-dioxide (**170**), which was also prepared by oxidation of thiochromone **150a**, first with SeO_2 to aldehyde **167** and then with MCPBA to dioxide **168**. On treatment with tosylhydrazine, **168** was converted to tosylhydrazone **169**, which furnished diazoalkane **170** *via* the Bamford – Stevens reaction. This compound proved to be effective for the protection of the OH group in reactions of aliphatic, aromatic and cyclic phosphates **171** with diazoalkane **170** (1.25 equiv.) in the presence of a catalytic amount of 10% hydrochloric acid in chloroform at 60 °C. Products **172** isolated in high yields were relatively stable and insensitive to laboratory lighting,

Scheme 91



R^1 = Et, Bu^n, Ph; R^2 = Me, 4-MeC_6H_4, F_3C; R^3 = H, Me, Pr^i, Bn; Boc is *tert*-butoxycarbonyl

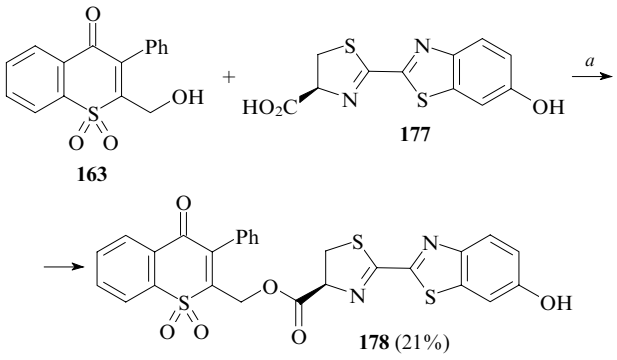
the deprotection being accomplished by irradiation with a high-pressure 500 W mercury lamp. As this was done, phosphates **171** were quantitatively recovered in several minutes together with tetracyclic compound **166** (Scheme 91).[132]

In another study, the same researchers[139] used a thiochromone **170** fragment as the PLPG for the protection of sulfonic acids **173** and amino acids **174**, which readily react with compound **170** in chloroform at room temperature to give S,S-dioxides **175** and **176**. Upon irradiation under the conditions indicated above, these products release acids **173** and **174** in a quantitative yield and are converted to compounds **166** (see Scheme 91).

Kakiuchi and co-workers[140] used thiochromone 1,1-dioxide **163** to protect the secondary carboxyl group in firefly luciferin (**177**). A combination of 4,4-dimethylaminopyridine and *N*,*N*′-diisopropylcarbodiimide (DIPC) was used as the condensing agent to obtain the target product **178** in a low yield as a result of luciferin self-condensation. The photochemical deprotection proceeded smoothly on irradiation of the product in an aqueous solution with light at 365 nm (Scheme 92).

Recently, a new thiochromone 1,1-dioxide with the 1,2-diol group in position 2 has been proposed for the protection of the carbonyl group of ketones and aldehydes.[141] The introduction of the methoxycarbonyl group into thiochromone **150a** for the preparation of compound **179** was performed by treatment with methyl cyanoformate in the presence of LDA and HMPA in THF at −78 °C. Hydroxylation of ester **179** with LDA and the Davis reagent afforded hydroxy ester **180**, which was reduced in two stages, first with lithium aluminium hydride to give the intermediate aldehyde and then with sodium tetrahydroborate to give diol **181**. At the final step, the target dioxide **182** was obtained by oxidation of the sulfur atom of diol **181** with MCPBA in dichloromethane. The carbonyl groups of aldehydes and ketones were protected in the presence of TsOH and $CuSO_4$ in benzene at room temperature. The deprotection of dioxolanes **183** was carried out by photoirradiation with an ultra-high pressure 500 W mercury lamp for 3 h (Scheme 93).[141]

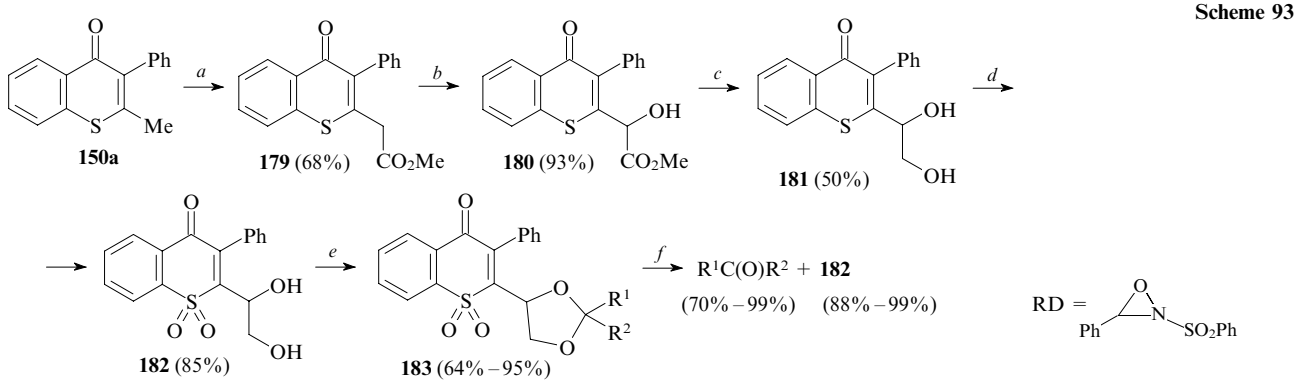
Scheme 92



(*a*) DMAP, DIPC, THF

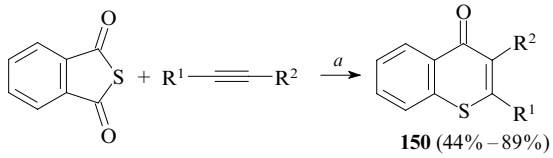
Matsubara and co-workers[142] have shown that the cycloaddition reactions of thiophthalic anhydride to alkynes catalyzed by nickel complexes are accompanied by decarbonylation and lead to the formation of thioisocoumarins, benzothiophenes and thiochromones. The selective formation of some 2,3-dialkyl(aryl)thiochromones **150** in reasonable to high yields took place in the reaction in benzene at 130 °C in the presence of bis(cycloocta-1,5-diene)nickel(0) and trimethylphosphine over a period of

Scheme 93



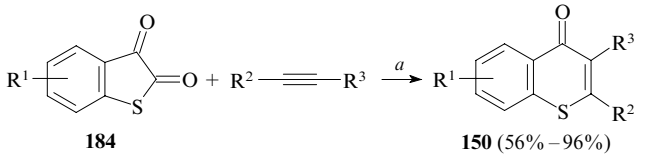
(*a*) $NCCO_2Me$, LDA, HMPA, THF, −78 °C, 2 h; (*b*) RD, LDA, HMPA, THF, −78 °C, 2 h; (*c*) 1) $LiAlH_4$, THF, −78 °C, 4 h; 2) $NaBH_4$, MeOH, 0 °C, 1 h; (*d*) MCPBA, CH_2Cl_2, rt, 8 h; (*e*) $R^1C(O)R^2$, TsOH, $CuSO_4$, PhH, rt; (*f*) *hv*, CD_3CN, D_2O, rt; R^1, R^2 = Me, Et; $R^1 - R^2 = (CH_2)_4$, $(CH_2)_5$; R^1 = Me: $R^2 = Pr^n$, n-$C_{10}H_{21}$; R^1 = H: R^2 = n-C_8H_{17}, Ph

Scheme 94



(*a*) $Ni(cod)_2$, PMe_3, PhH, 130 °C, 5 h; R^1 = Me, Pr^n, Bu^t, Am, Ph, 4-$MeOC_6H_4$; R^2 = Me, Pr^n, Ph, 4-$F_3CC_6H_4$, Me_3Si

Scheme 95



(*a*) $Ni(cod)_2$, PPh_3, PhMe, 50 °C, 6 h; R^1 = H, Me, MeO, F (in different positions); R^2 = Me, Pr^n, Am, $MeOCH_2$, $AcOCH_2$, $HOCH_2$, Ph, 4-$MeOC_6H_4$, 4-NCC_6H_4, 4-$O_2NC_6H_4$; R^3 = H, Me, Et, Pr^n, cyclo-C_3H_5, Me_3Si, $MeOCH_2$, $AcOCH_2$, $HOCH_2$, Ph, 4-$MeOC_6H_4$, 4-NCC_6H_4, 4-$O_2NC_6H_4$, 4-$F_3CC_6H_4$

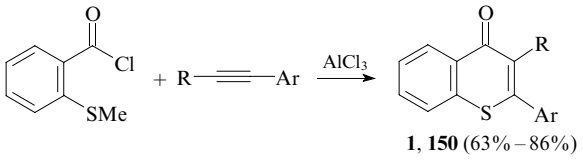
5 h (Scheme 94). The authors proposed a possible reaction mechanism.

An even wider range of 2,3-disubstituted thiochromones **150** was prepared under similar conditions from readily accessible thioisatins **184**, the reaction of which with alkynes is also accompanied by decarbonylation, proceeds at a lower temperature (50 °C) and provides high product yields (Scheme 95).[143]

The acylation of arylalkynes with *o*-methylthiobenzoyl chloride in the presence of $AlCl_3$ (2.5 equiv.) followed by quenching of the reaction mixture with water involves the intermediate formation of β-chlorovinyl ketones, which cyclize to thioflavones **1** (R = H) and 2,3-disubstituted thiochromones **150** (Scheme 96).[68]

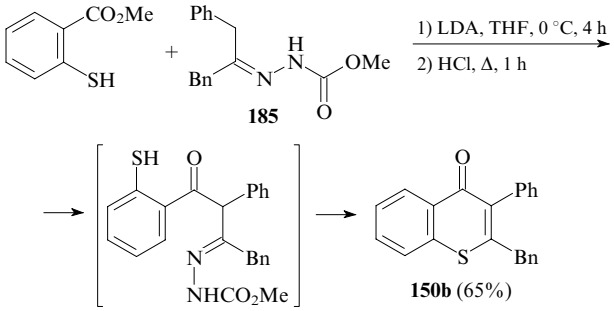
2-Benzylthioisoflavone (**150b**) was synthesized from methyl thiosalicylate and dibenzyl ketone *N*-methoxycarbonylhydrazone (**185**) in the presence of an excess of lithium diisopropylamide in THF (Scheme 97)[41] by analogy with thioflavones **1**.

Scheme 96



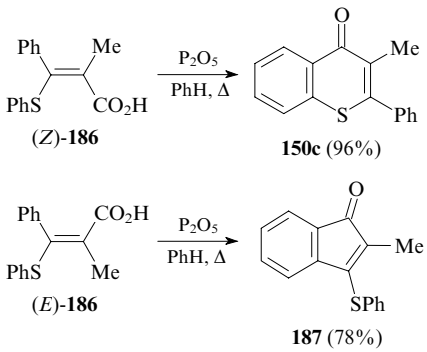
For **1**: R = H: Ar = Ph, 4-MeC_6H_4, 3-MeC_6H_4, 4-$Bu^tC_6H_4$, 4-$MeOC_6H_4$, 4-FC_6H_4; for **150**: Ar = Ph: R = Me, Ph

Scheme 97



Isomeric α-methyl-β-(phenylthio)cinnamic acids (*Z*)-**186** and (*E*)-**186** obtained from ethyl α-benzoylpropionate and benzenethiol[144] cyclize in high yields to 3-methylthioflavone **150c** and 2-methyl-3-phenylthioinden-1-one (**187**), respectively, under the action of P_2O_5 on refluxing in benzene for 3 h (Scheme 98).[145]

Scheme 98



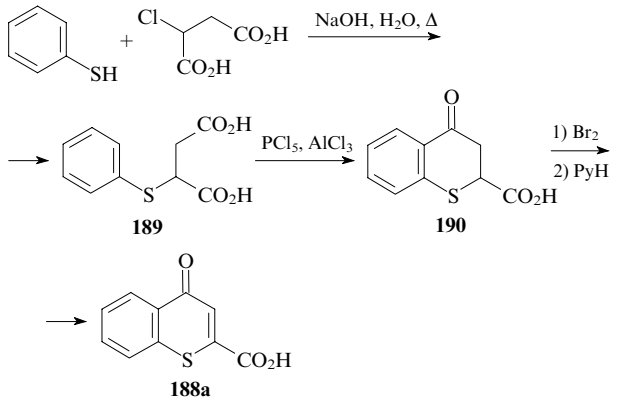
5. Functionally substituted thiochromones

5.1. Thiochromones with functional groups in position 2

5.1.1. Thiochromone-2-carboxylic acid and its derivatives

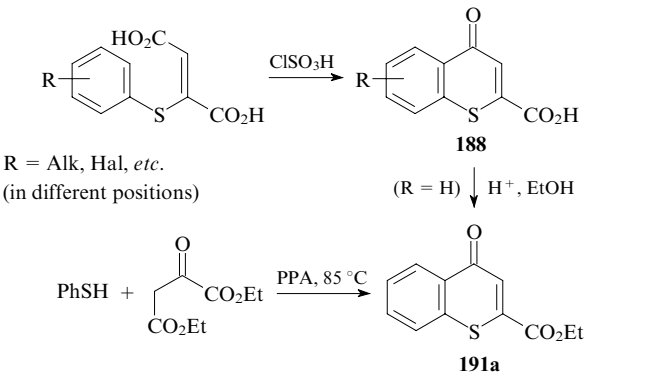
Apart from 2-halothiochromones (see Section 4.1), publications addressing thiochromones functionalized in position 2 also include data on 2-carboxy, 2-ethoxycarbonyl, 2-mercapto, 2-amino and 2-hydroxy derivatives. Thiochromone-2-carboxylic acid (**188a**) was first synthesized by three consecutive reactions that are depicted in Scheme 99. First, dicarboxylic acid **189** was prepared from benzenethiol and chlorosuccinic acid; then it was cyclized in the presence of PCl_5 and $AlCl_3$ to compound **190**, which was brominated and then dehydrobrominated by treatment with pyridine to afford the target acid **188a**.[146]

Scheme 99



The preparation of quite a number of derivatives of thiochromone-2-crboxylic acid (**188**) substituted in the benzene ring are presented in patents. Usually, they are prepared by treatment of the products of addition of arenethiols to acetylenedicarboxylic acid with Brønsted acids such as chlorosulfonic, polyphosphoric or sulfuric acid and Lewis acids (Scheme 100).[147–149] These compounds are of considerable interest for pharmaceutics, in particular, they have been proposed as additives to antiallergic drugs.[149]

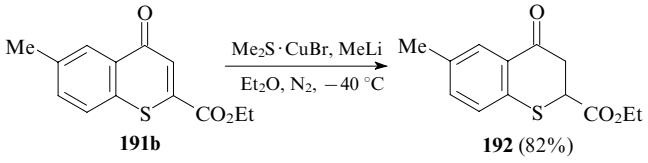
Scheme 100



Ethyl thiochromone-2-carboxylate **191a** can be obtained by esterification of acid **188a** or by cyclization of diethyl oxosuccinate with benzenethiol in the presence of PPA on heating to 85 °C (50% yield) (see Scheme 100).[15]

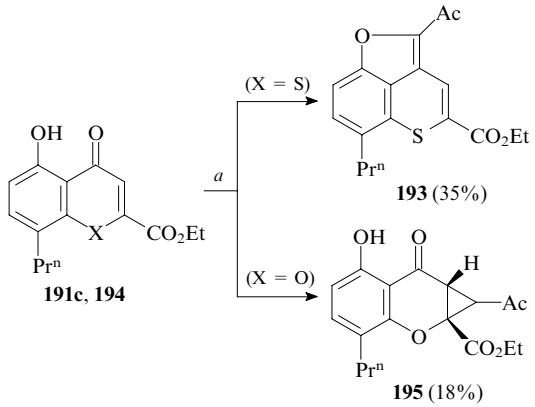
The literature data on the chemical properties of these esters are scarce. It is only known that compound **191b** does not add methylcopper under the conditions at which 2-alkylthiochromones **2** are methylated in position 2, but instead it is reduced to 2-ethoxycarbonylthiochromanone **192** in a good yield (Scheme 101).[109]

Scheme 101



The reaction of 5-hydroxythiochromone **191c** (X = S) with bromoacetone in the presence of K_2CO_3 on refluxing for 24 h in ethyl methyl ketone involves only the carbonyl group and affords tricyclic product **193**, whereas similar substituted chromone **194** (X = O) reacts mainly at the C(2) atom to give compound **195** (as a mixture of two diastereomers). It is evident that the stronger $-I$-effect of oxygen is responsible for the nucleophilic attack on position 2. This example illustrates well the fundamental difference between the reactivities of the two heterocyclic systems (Scheme 102).[150]

Scheme 102

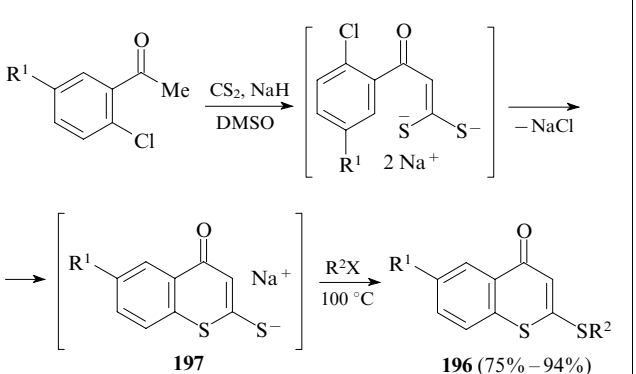


(*a*) $BrCH_2Ac$, K_2CO_3, AcEt, Δ, 24 h

5.1.2. 2-Sulfanylthiochromones

The first representatives of 2-sulfanylthiochromones were synthesized by Rudorf *et al.*[151] in 1979. The authors believed that *o*-haloacetophenones react with carbon disul-

Scheme 103

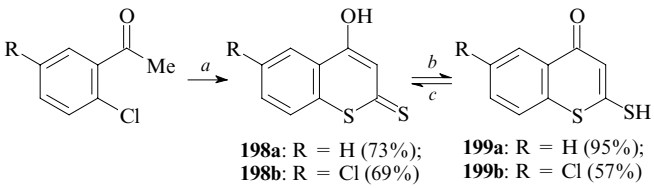


R1 = H, Cl; R2 = Me, Bn; X = Br, I

fide in the presence of NaH in DMSO to give the corresponding disodium salt, the treatment of which with alkylating agents at 100 °C affords 2-(methylthio)- and 2-(benzylthio)thiochromones **196** in good yields (Scheme 103). Most likely, alkylation takes place for the monosodium salt **197**.

An attempt was made [152] to isolate pure 4-hydroxydithiocoumarin (**198a**) or its tautomer, 2-mercaptothiochromone (**199a**), and to study them for the spectral and chemical properties. It was found that both tautomers are fairly stable compounds and are not easily interconverted. Dithiocoumarins **198a**,**b** were obtained from *o*-chloroacetophenones and CS_2 in the presence of NaH (1 equiv.) in the DMF – benzene system followed by heating to 115 – 130 °C and by acidification of the basic solution with hydrochloric acid. As hydrochloric acid is added to solutions of dithiocoumarins **198a**,**b** in a DMSO and MeOH mixture, or hydrogen peroxide is added to suspensions of **198a**,**b** in AcOH, the compounds are tautomerized to thiochromones **199a** ,**b**, which are converted back to coumarins **198a**,**b** on successive treatment with NaOH and HCl (Scheme 104).

Scheme 104



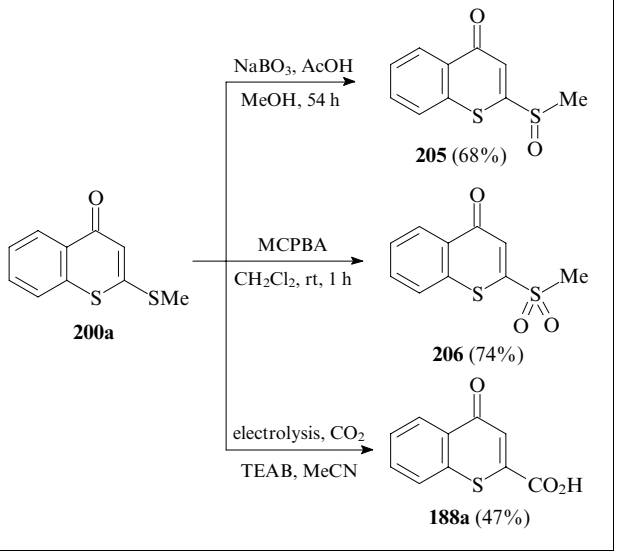
(*a*) 1) CS_2, NaH, DMF, PhH, rt; 2) HCl, AcOH, 115 – 130 °C, 1 h;
(*b*) DMSO, HCl, MeOH, rt or H_2O_2, AcOH, rt, 1 h;
(*c*) 1) NaOH, MeOH; 2) HCl

4-Hydroxydithiocoumarin (**198a**) reacts with iodomethane in the presence of K_2CO_3 in acetone or reacts with dichloromethane, giving rise to compounds **200a** and **200b**, the former of which was reported earlier by Rudorf *et al.*[151] The reaction of compound **198a** with 3,4-dihydro-2*H*-pyran smoothly gives tetrahydropyranyl sulfide **200c**. Unlike alkylation reactions that involve only the sulfur atom, acetylation of tautomers **198a** and **199a** under the action of acetic anhydride in THF affords a mixture of O- and S-acetylated products **201a** and **201b** (in the case of dithiocoumarin **198a**, the total yield of the isomers is 83% and the isomer ratio is 2.2 : 1.0).[152]

Allylation of 7-chloro-4-hydroxydithiocoumarin (**198c**) in chloroform in the presence of tetrabutylammonium bromide (TBAB) and a 1% NaOH solution at room temperature for 5 h leads to 2-(allylthio)thiochromones **202** in high yields. In the reaction with 2,3-dichloropropene, dithiocoumarin **198c** behaves as a C-nucleophile and gives, first, intermediate **203** and finally 7-chloro-2-methyl-4*H*-thieno[2,3-*b*]thiochromen-4-one (**204**) (Scheme 105).[153]

The oxidation of 2-(methylthio)thiochromone **200a** with sodium perborate in methanol affords exocyclic sulfoxide **205**, while the oxidation with MCPBA in dichloromethane yields exocyclic sulfone **206**.[152] Janietz *et al.*[154] studied the electrochemical carboxylation of cyclic ketene dithioacetals, including thiochromone **200a**. The latter was converted to acid **188a** by electrolysis in acetonitrile in the presence of tetraethylammonium bromide (TEAB) (Scheme 106).

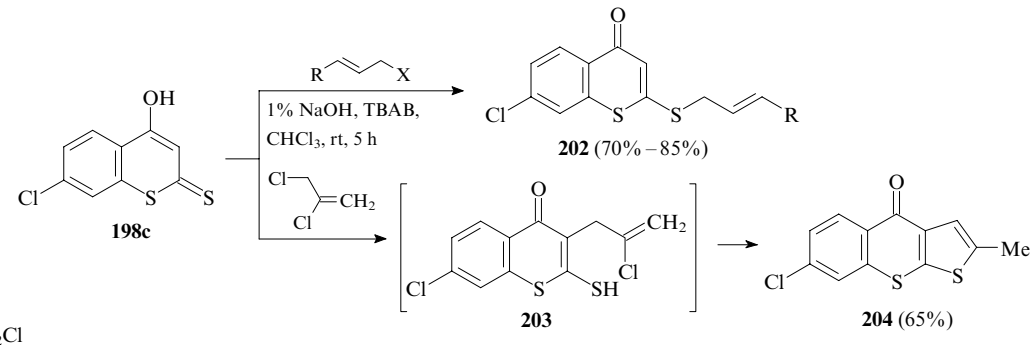
Scheme 106



5.1.3. 2-Amino- and 2-hydroxythiochromones

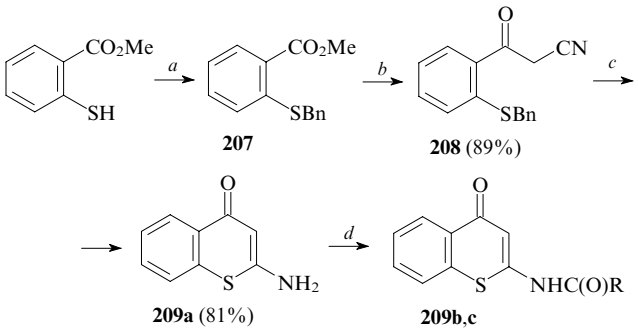
Zagorevskii and co-workers [155] accomplished the condensation of *o*-benzylthiobenzoate **207** with acetonitrile in the presence of sodium amide giving aroylacetonitrile **208** in high yield. Upon treatment with strong acids [CF_3CO_2H (TFA), $HClO_4$ or H_2SO_4] for 16 h at room temperature, this product was debenzylated and cyclized to 2-aminothiochromone (**209a**). The best result was observed in the reaction with trifluoroacetic acid (81% yield). The acylation of compound **209a** with acetic or benzoic anhydride in pyridine generated 2-acetamido- and 2-benzamidothiochromones **209b**,**c** in excellent yields (Scheme 107).[155]

Scheme 105



R = Me, Ph, CH_2Cl

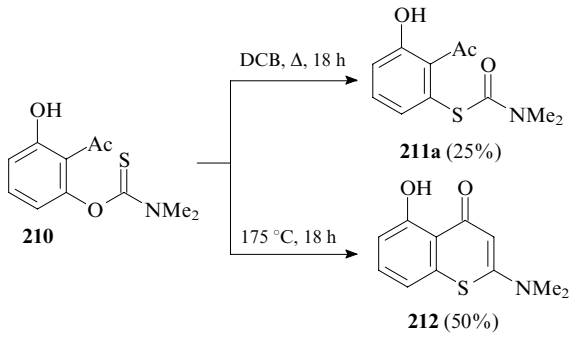
Scheme 107



(*a*) BnCl, MeONa; (*b*) MeCN, $NaNH_2$; (*c*) TFA, rt, 16 h; (*d*) $[RC(O)]_2O$, PyH; R = Me (**b**, 91% yield), Ph (**c**, 85%)

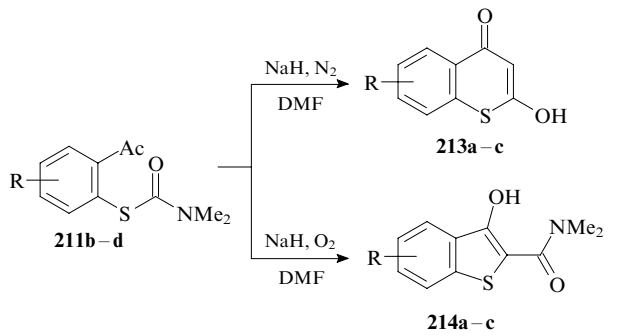
On refluxing in *o*-dichlorobenzene (DCB) for 18 h, *O*-(2-acetyl-3-hydroxyphenyl)dimethylthiocarbamate **210** undergoes the Newman – Kwart rearrangement to *S*-(2-acetylphenyl)dimethylthiocarbamate **211a**. Meanwhile, in the same reaction carried out without a solvent at 175 °C, only 5-hydroxy-2-(dimethylamino)thiochromone **212**, resulting from intramolecular cyclization involving the acetyl group, can be isolated instead of compound **211a** (Scheme 108).[156]

Scheme 108



S-(2-Acetylaryl)dimethylthiocarbamates **211b** – **d** proved to be valuable intermediates for subsequent transformations. On treatment with sodium hydride in DMF in a nitrogen atmosphere, they are cyclized to 2-hydroxythiochromones **213a** – **c**. Under the same conditions but in air, the reaction follows a different pathway and affords *N*,*N*-dimethyl-3-hydroxybenzothiophene-2-carboxamides **214a** – **c** (Scheme 109; the position of the substituent in the substrate is indicated).[156]

Scheme 109



Compounds	R	Yield of **213** (%)	Yield of **21** (%)
211b, **213a**, **214a**	H	43	39
211c, **213b**, **214b**	3-OMe	72	22
211d, **213c**, **214c**	5-OMe	79	33

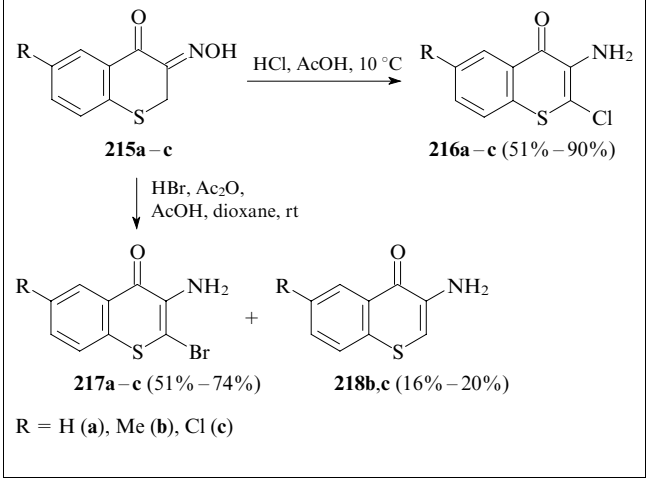
5.2. Thiochromones with functional groups in positions 2 and 3

5.2.1. Synthesis from 3-hydroxythiochromone

The presence of an electron-donating substituent such as the NR_2 or OR group in position 3 of thiochromones enables the synthesis of 2-chloro- and 2-bromothiochromones in which, as noted above (see Section 4.1), the halogen atom is characterized by high reactivity and is easily subjected to nucleophilic substitution reactions. Although this fact makes 2-halothiochromones valuable substrates for subsequent synthetic transformations, this issue is considered in a small number of publications, all being based on the reactions of 3-hydroxythiochromone (thiochromane-3,4-dione) derivatives.

In 1976, Eistert and Holzer [157] published one of the most significant studies on the chemistry of thiochromones with functional groups in positions 2 and 3. Thiochromane-3,4-dione 3-oximes **215a** – **c**, resulting from nitrosation of 6-substituted thiochroman-4-ones (the 3-hydroxyaminothiochromone tautomer is not mentioned), were converted to 2-chloro- and 2-bromo thiochromones on treatment with hydrohalic acids. 3-Amino-2-chlorothiochromones **216a** – **c** were formed in good yields when oximes **215a** – **c** were treated with a mixture of hydrochloric and acetic acids for 20 min at a temperature of ~10 °C. The reaction with 47% hydrobromic acid was carried out in a mixture of dioxane, acetic acid and acetic anhydride at room temperature; this gave 3-amino-2-bromothiochromones **217a** – **c** in moderate yields. In the case of oximes **215b**,**c**, 3-aminothiochromones **218b**,**c** were isolated as side products, as a result of reduction of thiochromones **217b**,**c** under the action of HBr (Scheme 110).[157]

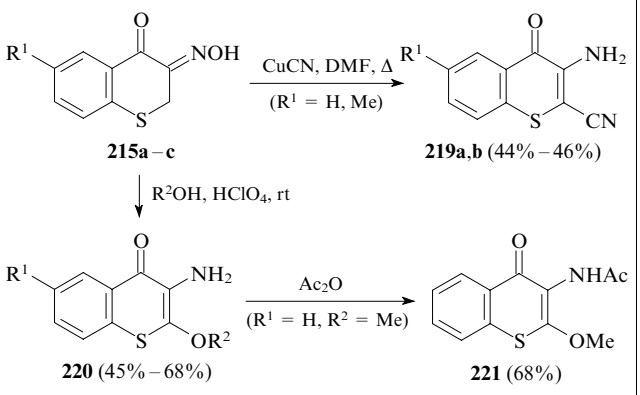
Scheme 110



Treatment of oximes **215a**,**b** with copper(I) cyanide in dimethylformamide results in the formation of 3-amino-2-cyanothiochromones **219a**,**b** in moderate yields, while the reaction of compounds **215a** – **c** with alcohols in the presence of 72% perchloric acid gives 2-alkoxy-3-aminothiochromones **220** (45% – 68% yields). Upon acylation of

3-amino-2-methoxythiochromone **220a** (R^1 = H, R^2 = Me) with acetic anhydride, 3-acetylamino-2-methoxythiochromone **221** is formed (Scheme 111).[157]

Scheme 111



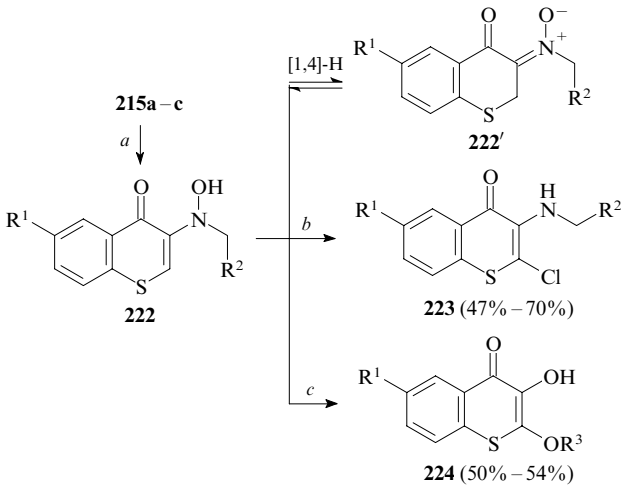
R^1 = H (**a**), Me (**b**), Cl (**c**); R^2 = Me, Et

The reaction of diazoalkanes with thiochromane-3,4-dione 3-oximes **215a–c** considerably extended the range of thiochromones functionalized in positions 2 and 3. The reaction with diazomethane or diazoethane in a methanol and diethyl ether mixture with cooling (0–10 °C) produced compounds **222** (31%–70% yields), which were prone to *N*-hydroxyenamine–nitrone tautomerization proceeding *via* the [1,4]H-shift. Hydroxyamines **222** react with a mixture of hydrochloric and acetic acids at room temperature to give 3-alkylamino-2-chlorothiochromones **223** and also react with alcohols in the presence of perchloric acid, being converted to 2-alkoxy-3-hydroxythiochromones **224** (R^1 = H, Me) in moderate yields (Scheme 112).[157]

The condensation of various 2-substituted thiochroman-4-ones with *p*-nitrosodimethylaniline yields thiochromane-3,4-dione 3-imines **225a–d**, the acid hydrolysis of which affords 3-hydroxythiochromones **226a–d**. The same compounds are formed on treatment of thioisatin (**184a**) with diazoalkanes, resulting in the insertion of the CHR group into the S–C bond and [1,3]H-shift (the product yields are not indicated in the original paper) (Scheme 113).[158]

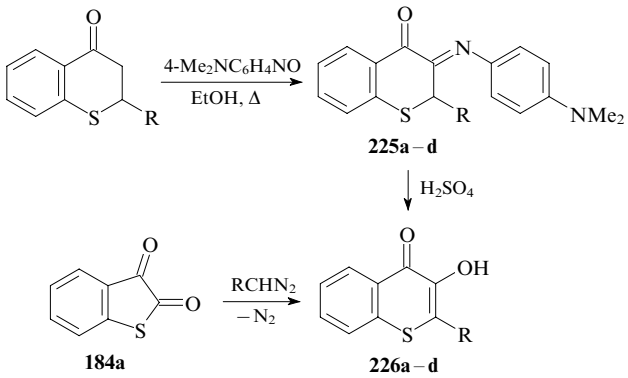
In 1983, Eiden *et al.*[159] described the synthesis and chemical reactivity of 3-hydroxythiochromone **226a** and its derivatives **227a**,**b**, which were used for the preparation of a broad range of new representatives of functionalized thiochromones. Compound **226a** was prepared by hydrolysis of

Scheme 112



(*a*) R^2CHN_2, Et_2O, MeOH, 0–10 °C; (*b*) HCl, AcOH, rt;
(*c*) R^3OH, $HClO_4$; R^1 = H, Me, Cl; R^2 = H, Me; R^3 = Me, Et

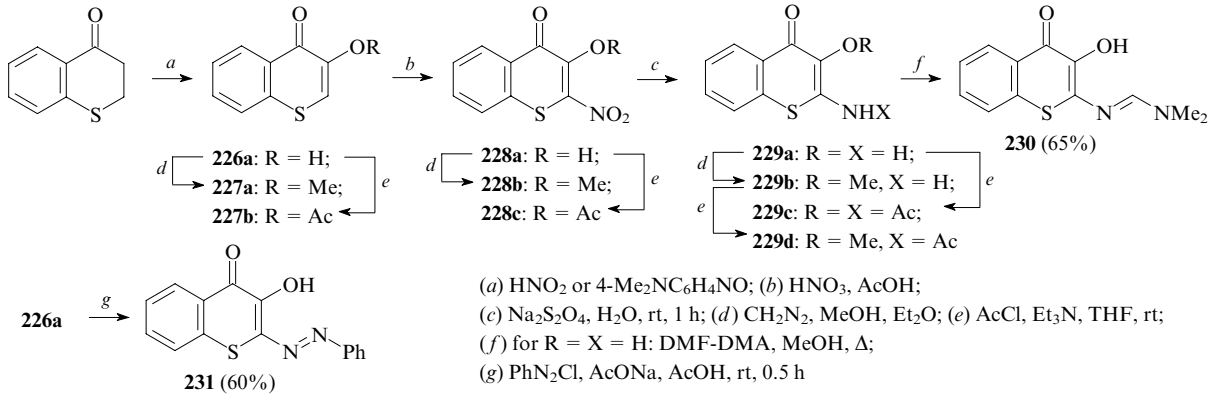
Scheme 113



R = H (**a**), Me (**b**), Ph (**c**), CO_2Et (**d**)

the products of reactions of thiochroman-4-one with nitrous acid or *p*-nitrosodimethylaniline. The nitration of **226a** with nitric acid (d = 1.52 g ml^{-1}) in acetic acid solution at 16–18 °C furnishes 3-hydroxy-2-nitrothiochromone (**228a**, 46% yield), while reduction of the latter product with sodium dithionite in water (~20 °C, 1 h) generates 2-amino-3-hydroxythiochromone **229a** in 79% yield. The treatment of 3-hydroxythiochromones **226a**, **228a** and **229a**

Scheme 114

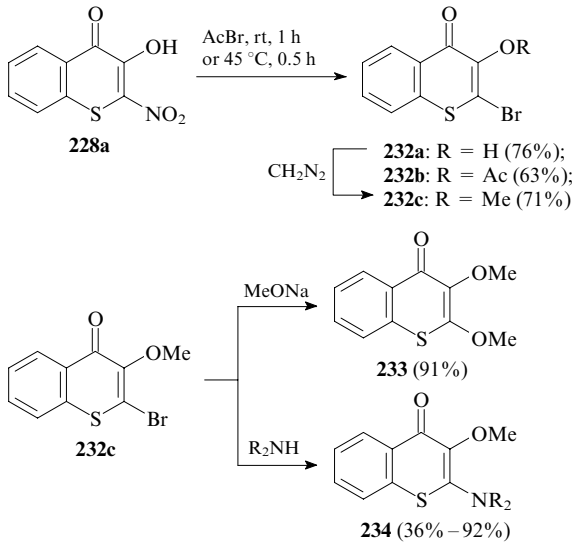


(*a*) HNO_2 or 4-$Me_2NC_6H_4NO$; (*b*) HNO_3, AcOH;
(*c*) $Na_2S_2O_4$, H_2O, rt, 1 h; (*d*) CH_2N_2, MeOH, Et_2O; (*e*) AcCl, Et_3N, THF, rt;
(*f*) for R = X = H: DMF-DMA, MeOH, Δ;
(*g*) PhN_2Cl, AcONa, AcOH, rt, 0.5 h

with diazomethane (MeOH, Et_2O) and acetyl chloride (Et_3N, THF) at room temperature provided the synthesis of their 3-methoxy (**227a**, **228b** and **229b**,**d**) and 3-acetoxy derivatives (**227b**, **228c** and **229c**) in 67% – 83% yields. Derivative **230** was obtained by the reaction of thiochromone **229a** with dimethylformamide dimethyl acetal (DMF-DMA) on heating in methanol, while diazotization of 3-hydroxythiochromone (**226a**) in acetic acid in the presence of sodium acetate (~ 20 °C, 0.5 h) affords 3-hydroxy-2-phenylazothiochromone **231** (Scheme 114).[159]

Depending on the temperature, the reaction of 3-hydroxy-2-nitrothiochromone **228a** with acetyl bromide gives either 2-bromo-3-hydroxythiochromone (**232a**, ~ 20 °C) or 3-acetoxy-2-bromothiochromone (**232b**, 45 °C). 2-Bromo-3-methoxythiochromone (**232c**) was obtained by treatment of compound **232a** with diazomethane in a methanol and diethyl ether mixture. As was to be expected, the bromine atom in these compounds is highly active and is easily replaced on treatment with nucleophiles. For example, the reaction of thiochromone **232c** with sodium methoxide was employed for the synthesis of 2,3-dimethoxythiochromone **233**, and the reaction with secondary amines resulted in the preparation of 2-dialkylamino derivatives **234** in reasonable to high yields (Scheme 115).[159]

Scheme 115



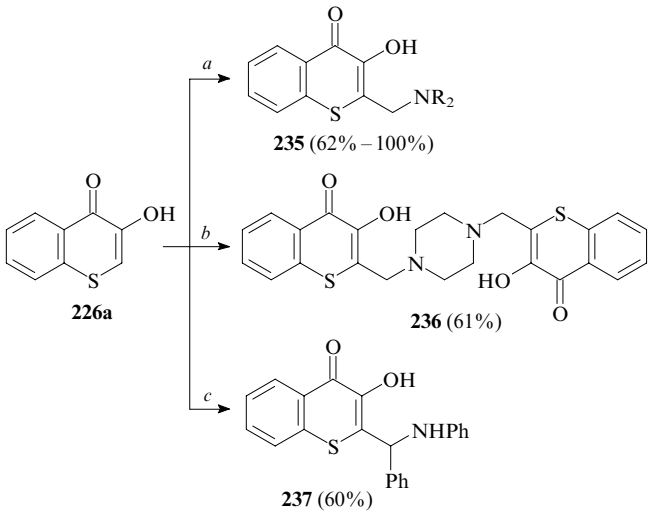
R_2N = Me_2N, piperidino, morpholino, *N*-methylpiperazino

The Mannich reaction of 3-hydroxythiochromone **226a** with formaldehyde and secondary amines readily proceeds in ethanol and gives thiochromones **235**; when compound **226a** reacts with piperazine, bis-adduct **236** is formed, while the reaction with benzaldehyde and aniline yields product **237** (Scheme 116).[160]

5.2.2. Synthesis from thiosalicylic acid

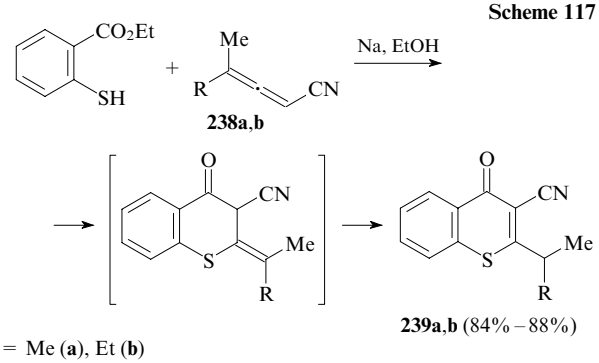
Apart from 3-hydroxythiochromones, thiosalicylic acid and its ester are key components for the synthesis of functionalized thiochromones. One of the first examples of these transformations is the reaction of ethyl thiosalicylate with 2,3-diene nitriles **238a**,**b** in the presence of sodium in ethanol, which gave good yields of 2-alkyl-3-cyanothiochromones **239a**,**b** (Scheme 117).[161]

Scheme 116



(*a*) CH_2O, R_2NH; (*b*) CH_2O, piperazine; (*c*) PhCHO, $PhNH_2$;
R_2N = Me_2N, Et_2N, piperidino, morpholino, *N*-methylpiperazino

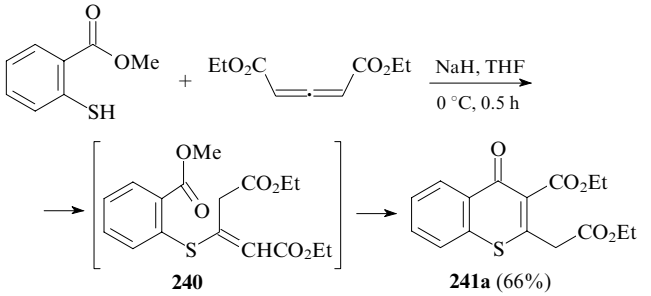
Scheme 117



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

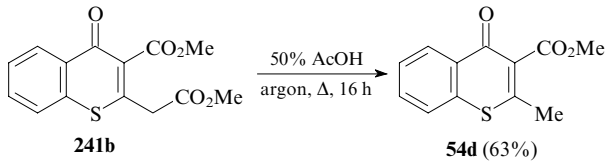
The reaction of methyl thiosalicylate with diethyl allene-1,3-dicarboxylate leads first to addition product **240**, which is then cyclized in THF in the presence of NaH under mild conditions to give diethyl ester **241a** in a moderate yield (Scheme 118).[162]

Scheme 118



A similar reaction of thiosalicylic acid with dimethyl allene-1,3-dicarboxylate has been reported.[163] The addition step was performed in a methanol solution at room temperature, and the cyclization of intermediate compound **240** to dimethyl ester **241b** occurred in the presence of potassium *tert*-butoxide in *tert*-butyl alcohol (36% yield). On treat-

Scheme 119

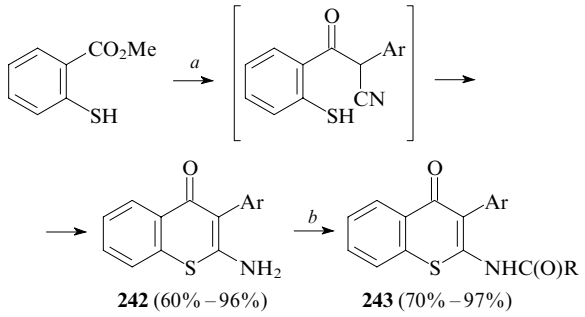


241b **54d** (63%)

ment with 50% acetic acid, diester **241b** was hydrolyzed and decarboxylated to give ester **54d** (Scheme 119).

It has been shown [164, 165] that arylacetonitriles react with methyl thiosalicylate in the presence of a base catalyst (sodium *tert*-butoxide) on refluxing in pyridine for 3 h, which results in the formation of 2-aminothioisoflavones **242**. When these compounds are treated with acetic anhydride or benzoyl chloride (refluxing in pyridine for 2–3 h) or with methyl isocyanate (refluxing in dioxane in the presence of a catalytic amount of *tert*-butoxide for 4 h), thioisoflavones **243** are formed in high yields (Scheme 120).

Scheme 120

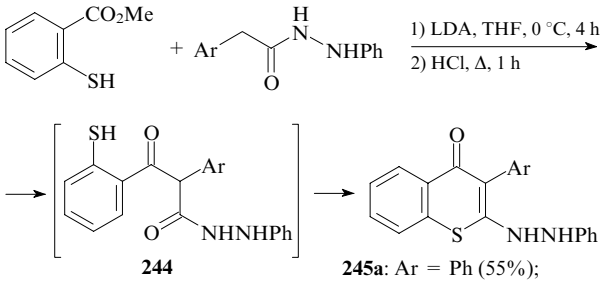


242 (60%–96%) **243** (70%–97%)

(*a*) $NCCH_2Ar$, Bu^tONa, PyH, Δ, 3 h; (*b*) RC(O)Cl or $(RC(O))_2O$, PyH, Δ, 2–3 h or MeNCO, Bu^tONa, dioxane, Δ, 4 h; Ar = Ph, 2-ClC_6H_4, 3-BrC_6H_4, 4-$EtOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 2,3,4-$(MeO)_3C_6H_2$, benzimidazol-2-yl; R = Me, Ph, MeNH

While studying the synthetic scope of the method proposed previously for the preparation of thioflavones and thiochromones,[41, 71] Beam and co-workers [166] have ascertained that the reaction of methyl thiosalicylate with phenylhydrazides of arylacetic acids in the presence of an excess of lithium diisopropylamide in THF at 0 °C involves the intermediate formation of aroylacetohydrazides **244**, which are converted, upon acidification, in moderate yields to thioisoflavones **245a**,**b** with the phenylhydrazine moiety in position 2 (Scheme 121).

Scheme 121

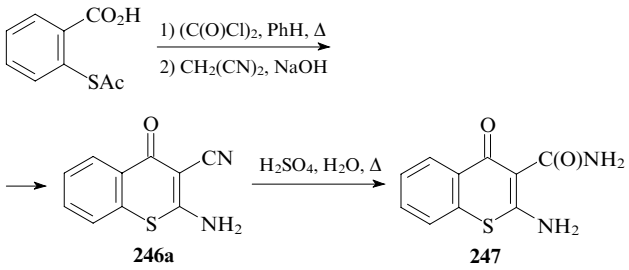


244

245a: Ar = Ph (55%);
245b: Ar = 4-$MeOC_6H_4$ (45%)

The treatment of *S*-acetylthiosalicylic acid with oxalyl chloride in refluxing benzene affords the corresponding acid chloride; the addition of malononitrile in an alkaline solution results in the formation of 2-amino-3-cyanothiochromone **246a**, which is hydrolyzed under the action of concentrated sulfuric acid to give 2-amino-3-carbamoylthiochromone **247** (Scheme 122).[167]

Scheme 122



246a **247**

Kikionis *et al.*[168] proposed to use ester **248**, formed from *S*-acetylthiosalicylic acid, *N*-hydroxysuccinimide and *N*,*N*′-dicyclohexylcarbodiimide (DCC), to prepare 2,3-disubstituted thiochromones. The treatment of methylene-active compounds such as methyl acetoacetate and methyl cyanoacetate with highly reactive acylating agent **248** in THF in the presence of sodium hydride furnishes thiochromones **54a** and **249**, which are formed *via* intramolecular attack by the sulfur atom on the acetyl or cyano group of intermediate **250**. In the case of malononitrile and dimethyl malonate, the preparation of compounds **246a** and **251** required additional treatment of the corresponding compounds **250**, which were not isolated in a pure state, with sodium in ethanol at room temperature. According to X-ray diffraction data, product **251** (67% yield) exists in the solid state as the thiocoumarin rather than thiochromone (**252**) tautomer (Scheme 123).[168]

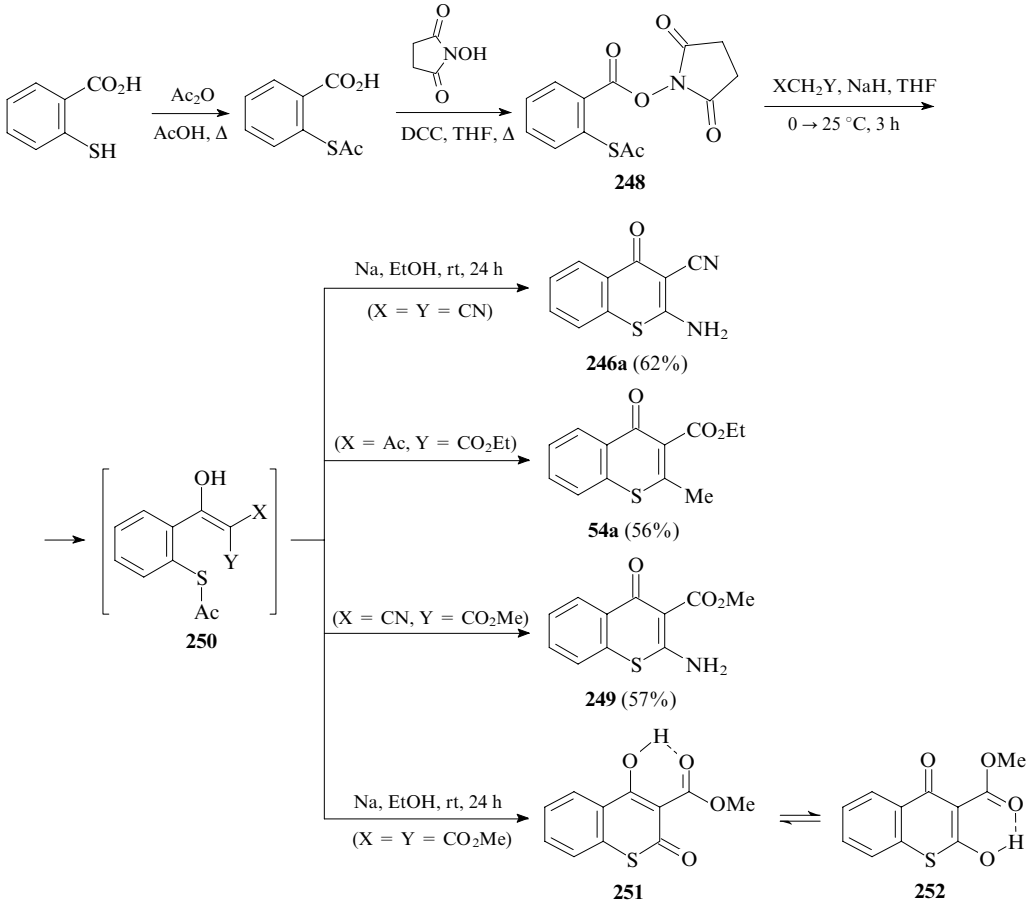
It has been shown [169] that thiosalicylic acids react with 2-substituted *N*,*N*-dialkylacetamides in the presence of phosphorus(V) oxychloride on heating in 1,1-dichloroethane or acetonitrile. This procedure was used to prepare a broad range of 2-aminothiochromones **253** containing an electron-withdrawing substituent in position 3, the products being formed in moderate yields (Scheme 124).

3-Acetamidothioflavones and 3-acetamido-2-methylthiochromones **254** are formed upon the reaction of α-acetamido-β-ketoesters with arenethiols on heating in polyphosphoric acid for 2–3 h at 90–100 °C. The acid hydrolysis of these compounds in ethanol gives 3-aminothiochromones **255** (Scheme 125).[170]

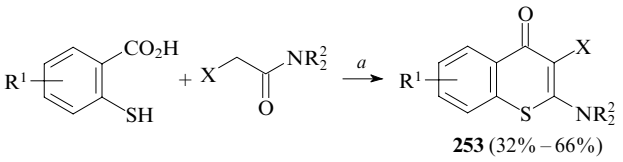
5.2.3. Synthesis from acylketene dithioacetals

Rudorf and co-workers [171–173] used acylketene dithioacetals to develop a general efficient approach to the preparation of thiochromones, which provided access to a broad range of their functionalized derivatives containing cyano, amino, mercapto and formyl groups in positions 2 and 3. The reaction of *o*-chlorobenzoylacetonitrile with carbon disulfide in the presence of sodium hydride in DMSO followed by alkylation of the intermediate sodium salt **256** with alkyl halides or α-haloketones gives rise to 3-cyano-2-sulfanylthiochromones **257** in moderate to good yields [171] (Scheme 126).

Scheme 123

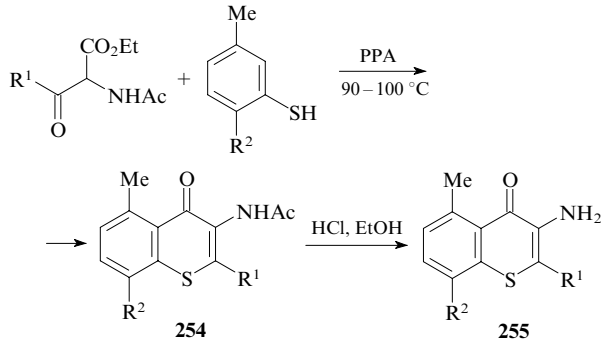


Scheme 124



(*a*) $POCl_3$, DCE or MeCN; X = CN, CO_2Me, CO_2Et, Cl, SO_2Ph, Ts; R^1 = H, Me, Cl; R^2_2N = Et_2N, pyrrolidino, piperidino

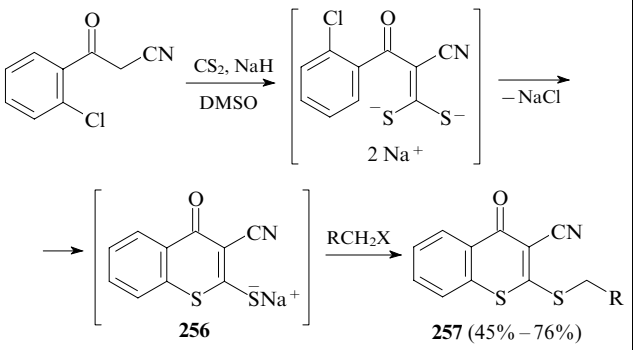
Scheme 125



R^1 = Me, Ph; R^2 = Me, OMe

Rudorf and Augustin [172] described the transformation of 3-cyano-2-methylthiothiochromone **257a** to 2-amino- and 3-cyano-2-methylaminothiochromones **246a**,**b** by treatment with ammonia and methylamine in DMF at elevated temperature. 2-(Methylthio)thiochromone **200a** reacts with hydroxylamine on refluxing in pyridine for 4 h to give oxime **258** in a high yield, while the similar reaction of 3-cyano-2-methylthiothiochromone **257a** leads to 2-amino-3-carbamoylthiochromone **259** *via* reduction of the cyclic intermediate with a hydroxylamine molecule (Scheme 127).

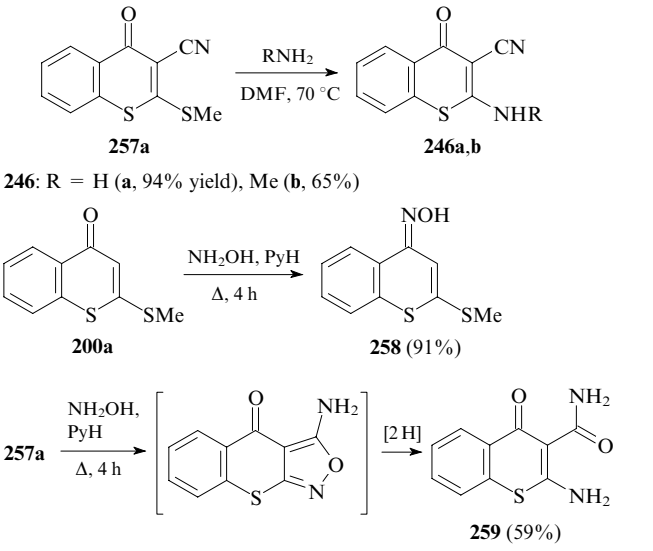
Scheme 126



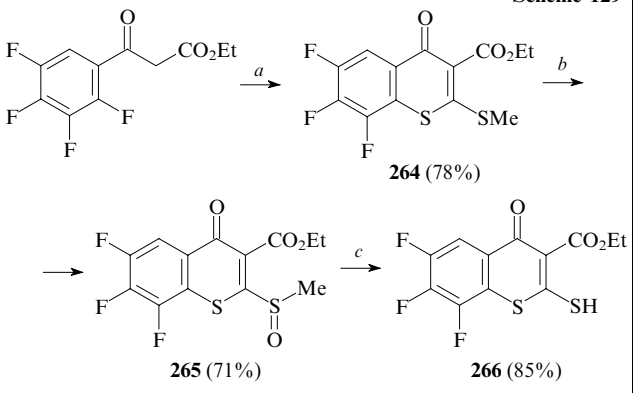
R = H, Me, Ph, Ac, Bz, 4-$O_2NC_6H_4$; X = Cl, Br

Rudorf and Köditz [173] carried out the first condensation of phenyl-substituted β-oxoenolates **260** with carbon disulfide in the presence of sodium hydride in DMF. After acid hydrolysis of the intermediate sodium salt **261**, 2-mercapto-3-formylthiochromone **262** was isolated. The alkylation of this salt with alkyl, benzyl, allyl and propargyl halides at

Scheme 127



Scheme 129



reduced temperature for 3 h gave 2-alkylthio-3-formylthiochromones **263** in moderate yields (Scheme 128; the substituent position in the product is indicated).

Using acylketene dithioacetals as the starting reactants, Cecchetti *et al.*[174] synthesized a series of 2-mercaptothiochromone-3-carboxylic acid derivatives. The reaction of 2,3,4,5-tetrafluorobenzoyl acetate with carbon disulfide in the presence of KOH in DMSO with subsequent methylation of the intermediate salt with dimethyl sulfate gave thiochromone **264**, which was converted to sulfoxide **265** (MCPBA oxidation in dichloromethane) and ethyl 2-mercapto-6,7,8-trifluorothiochromone-3-carboxylate **266** (substitution reaction with sodium hydrogen sulfide in THF) (Scheme 129).

5.2.4. Miscellaneous methods

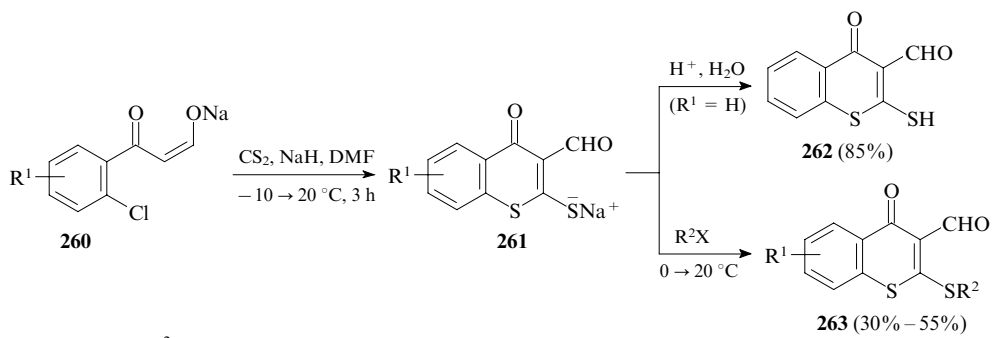
A research group including the author of this review has shown [175, 176] that the reaction of 3-cyanothiochromone (**267**), formed on treatment of 3-formylthiochromone with hydroxylamine,[120] with N-nucleophiles starts with the attack on the C(2) atom and is accompanied by thiopyrone ring opening, and the subsequent intramolecular cyclization involving the mercapto and cyano groups leads to the synthesis of 3-substituted 2-aminothiochromones. For example, the reaction with phenylhydrazine in refluxing benzene in the presence of triethylamine gives 2-amino-3-formylthiochromone *N*-phenylhydrazone **268**. 3-Cyanothiochromone **267** also reacts with *o*-phenylenediamine, *p*-anisidine and benzylamine on refluxing in toluene with a catalytic amount of Et_3N to give 2-aminothiochromones **269a**–**c**, respectively (Scheme 130).[175]

2-Amino- and 2-acetamidothiochromones **209a**,**b** are readily brominated into position 3 with bromine in an acetic acid solution to give bromo derivatives **270a**,**b**.[155] Mannich base **271** was obtained by aminomethylation of 2-aminothiochromone **209a** with a solution of bis(*N*,*N*-dimethylamino)methane in anhydrous ethanol and was isolated as the hydrochloride (Scheme 131).[155]

3-Hydroxymethylthioflavone **272**, described for the first time by Nakazumi *et al.*,[99] is oxidized with CrO_3 in pyridine to give 3-formylthioflavone **273**, which was isolated in a moderate yield and used as the starting compound for the preparation of 3-functionalized thioflavones.[120] Refluxing of this compound with hydroxylamine hydrochloride in ethanol affords 3-cyanothioflavone **274**, while oxidation with sodium chlorite in the presence of sulfamic acid in chloroform gives thioflavone-3-carboxylic acid **100**, and the reaction with malonic acid in pyridine furnishes 3-(thioflavon-3-yl)acrylic acid **275** (the product yields are 87%, 59% and 45%, respectively) (Scheme 132).[120]

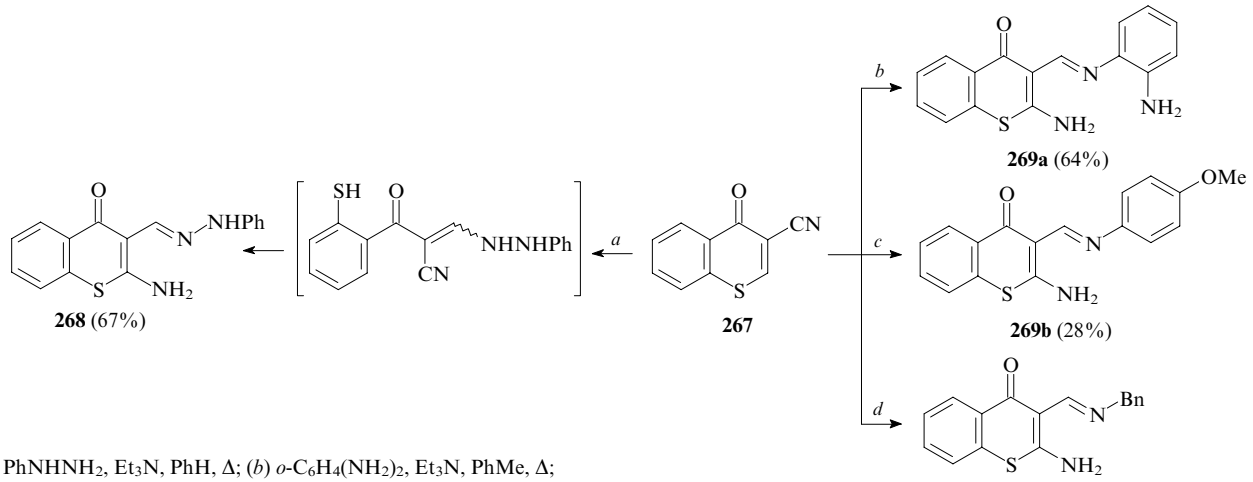
Recently, it has been shown [177] that the insertion of zinc into the C–H bond of unsubstituted thiochromone **276** under the action of the TMPZnCl·LiCl system (TMP is 2,2,6,6-tetramethylpiperidyl) in a Et_2O–THF mixture (1 : 2) occurs selectively at the C(2) atom to give zinc intermediate **277**. Transmetallation under the action of the CuCN·2 LiCl

Scheme 128



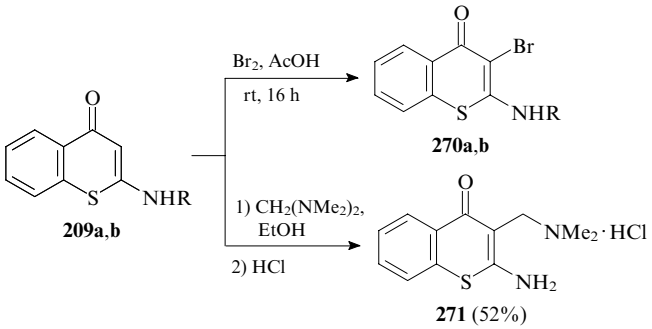
R^1 = H, 6-Cl, 7-Cl; R^2 = Me, Et, Pr^n, All, Bn, $CH{\equiv}CCH_2$; X = Cl, Br; All is allyl

Scheme 130



(*a*) $PhNHNH_2$, Et_3N, PhH, Δ; (*b*) *o*-$C_6H_4(NH_2)_2$, Et_3N, PhMe, Δ; (*c*) 4-$MeOC_6H_4NH_2$, Et_3N, PhMe, Δ; (*d*) $BnNH_2$, Et_3N, PhMe, Δ

Scheme 131



R = H (**a**, 55% yield), Ac (**b**, 100%)

salt followed by treatment with benzoyl chloride leads to 2-benzoylthiochromone (**278**) (Scheme 133).

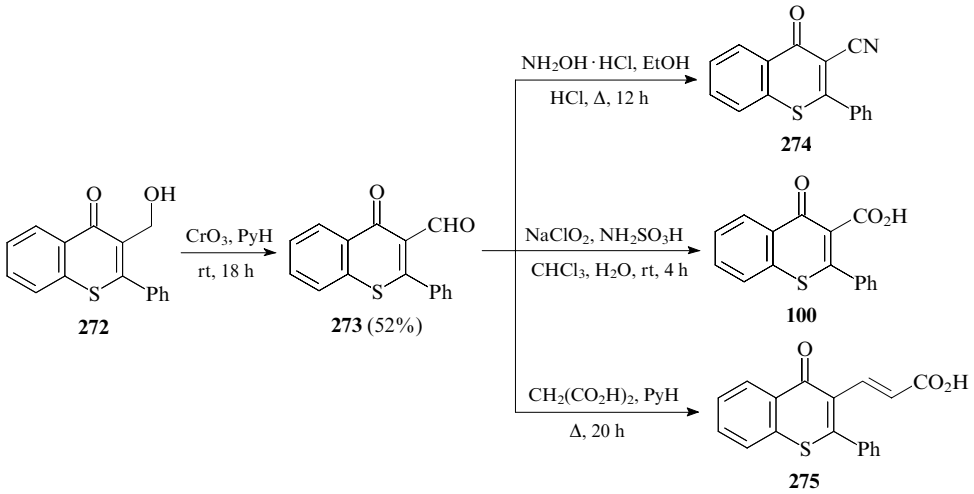
2,3-Disubstituted thiochromones **279** – **281** were prepared on the basis of compound **278**. Thus the introduction of zinc to the C(3) atom by means of the TMPZnCl · LiCl reagent provides the preparation of the intermediate 3-ZnCl-substituted thiochromone; in the presence of CuCN · 2 LiCl, it is allylated (compound **279**), acylated (**280**) or undergoes the Negishi cross-coupling reaction catalyzed by palladium complexes (**281**). Detailed conditions of these reactions are summarized in Scheme 133.[177]

3-Aroyl-2-furylthiochromones with photoinduced fluorescence were synthesized in three steps from *S*-aroyl-2-mercaptoacetophenones. The Baker – Venkataraman rearrangement of these ketones in the presence of LDA in THF with subsequent hydrolysis in a neutral medium first gave 1,3-diketones **282a**,**b** (in the enol form), which condensed with furfural or 5-methylfurfural in ethanol in the presence of piperidine to afford compounds **283**. These products were oxidized, without isolation, with SeO_2 in refluxing dioxane and this gave the target 3-aroyl-2-furylthiochromones **284a** – **c** in high yields (Scheme 134).[178]

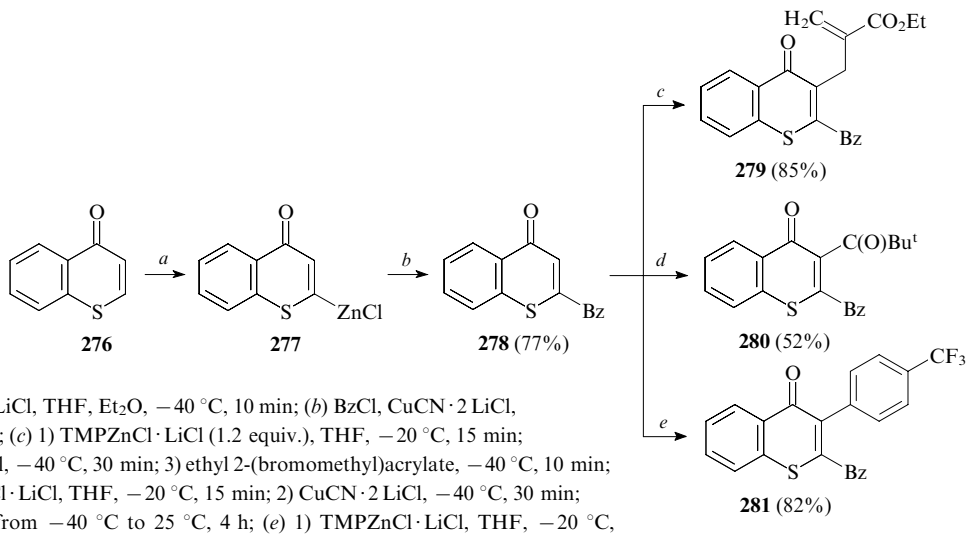
5.3. Biological properties of functionally substituted thiochromones

The high biological activity of thiochromones is often manifested only if they are incorporated into antibiotic molecules of known basic structures. Among the studies on this topic, mention should be made, first of all, of the publications addressing the synthesis of antimicrobial agents (mainly cephalosporins) based on 2-sulfanylthio-

Scheme 132

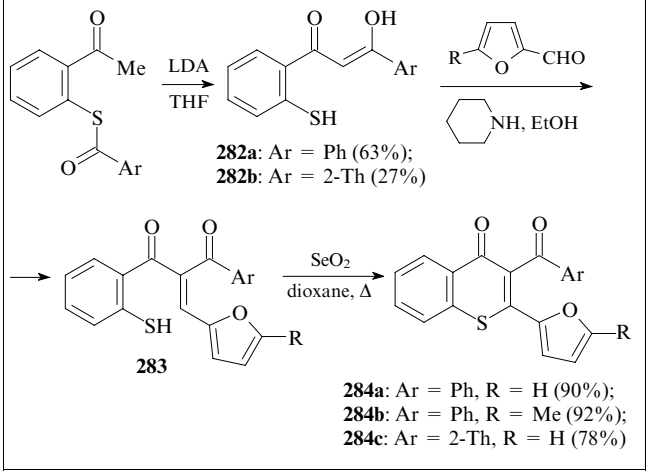


Scheme 133



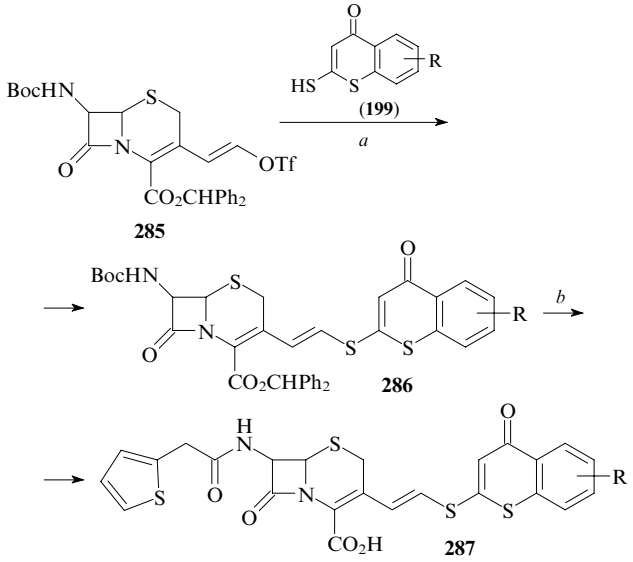
(*a*) TMPZnCl·LiCl, THF, Et_2O, −40 °C, 10 min; (*b*) BzCl, CuCN·2 LiCl, −40 °C, 30 min; (*c*) 1) TMPZnCl·LiCl (1.2 equiv.), THF, −20 °C, 15 min; 2) CuCN·2 LiCl, −40 °C, 30 min; 3) ethyl 2-(bromomethyl)acrylate, −40 °C, 10 min; (*d*) 1) TMPZnCl·LiCl, THF, −20 °C, 15 min; 2) CuCN·2 LiCl, −40 °C, 30 min; 3) $Bu^tC(O)Cl$, from −40 °C to 25 °C, 4 h; (*e*) 1) TMPZnCl·LiCl, THF, −20 °C, 15 min; 2) 4-$F_3CC_6H_4I$ (1.2 equiv.), $Pd(dba)_2$ (2 mol.%), tfp (4 mol.%), 25 °C, 1 h; dba is *trans*,*trans*-dibenzylideneacetone, tfp is tris(2-furyl)phosphine

Scheme 134



chromones and their heteroanalogues. Japanese researchers [179, 180] have prepared a broad range of cephalosporins, in particular, those containing 7-chloro-, 7-fluoro-, 6,7,8-trifluoro-, 5-trifluoromethyl- and 7-trifluoromethylthiochromone moieties. These compounds are highly active against penicillin-resistant forms of staphylococcus and against enterococcus. Of special note is the fact that cephalosporin with a 7-fluorothiochromone substituent showed the highest activity against a series of microbes. Vinyl triflate **285** served as the key intermediate for the synthesis of these derivatives; compound **285** reacted with 2-mercaptothiochromones **199** in the presence of diisopropylethylamine in DMF at room temperature to give intermediates **286**, which were converted to cephem antibiotics **287** in three steps (TsOH-induced deprotection, condensation with thiophen-2-ylacetic acid in the presence of 1,3-dicyclohexylcarbodiimide and removal of the benzhydryl protecting group in trifluoroacetic acid in the presence of anisole) (Scheme 135).[179]

Scheme 135

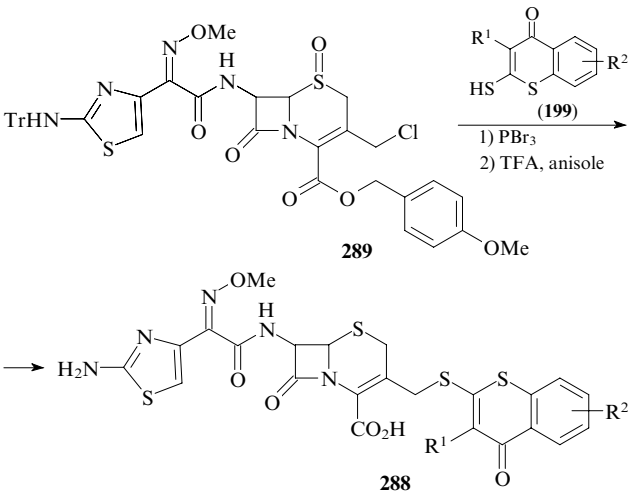


(*a*) Pr^i_2NEt, DMF, rt; (*b*) 1) TsOH; 2) 2-$ThCH_2CO_2H$, DCC; 3) TFA, anisole; R = H, 7-Cl, 7-F, 5-CF_3, 7-CF_3

Structurally related cephalosporins **288** with substituted thiochromone moieties have been proposed [181, 182] as efficient agents against streptococcus, staphylococcus, proteus and other pathogenic microflora. Compounds **288** were synthesized in three steps by coupling of sulfoxide **289** with 2-mercaptothiochromones **199** and deprotection under the action of PBr_3 and the TFA–anisole system (Scheme 136).[181]

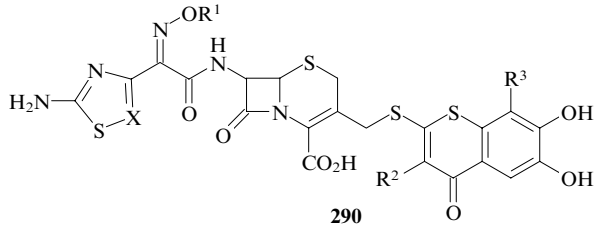
A similar route was used to prepare thiochromone cephalosporins **290**, which exhibit a broad range of antibacterial activity against gram-positive (including *Enterococcus faecalis*) and gram-negative bacteria (including *Pseudomonas aeruginosa*).[182, 183]

Scheme 136



R^1 = H, CO_2H, CO_2Et, CN; R^2 = H, F, OMe (in different positions); Tr = Ph_3C

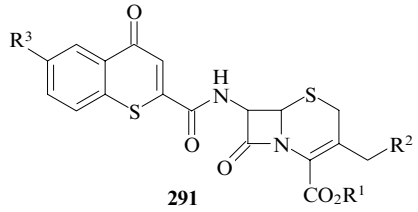
Structures 290



R^1 = Me, Et, CH_2Boc, CMe_2Boc; R^2 = H, Br; R^3 = H, Cl, Br; X = CH, N

A US patent [184] presents the synthesis of a wide range of cephalospirins **291** with a relatively simple structure containing a 6-substituted thiochromone moiety attached on the opposite side of the main skeleton of the molecule. This modification does not decrease the antimicrobial properties, and antibiotics of this type have been patented as active agents against a broad range of pathogenic microflora.

Structures 291



R^1 = H, Na, K, tert-Alk (C_4–C_6), tert-Alkenyl (C_5–C_6), tert-Alkynyl (C_5–C_7), Bn, $CHPh_2$, CH_2Bz, $SiMe_3$; R^2 = H, OC(O)Alk (C_2–C_4), OAlk (C_1–C_4), $SiAlk_3$; R^3 = H, F, Cl, Br, NO_2, NH_2, NHC(O)Alk

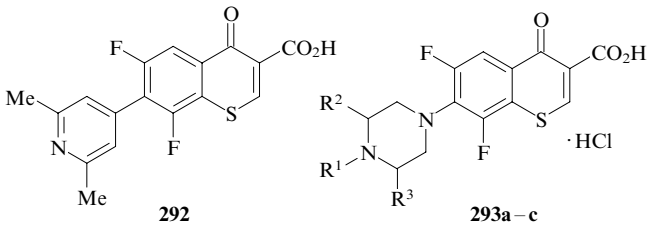
Along with the properties of various quinolone-3-carboxylic acids, Wentland *et al.*[185] have studied the inhibitory activity of 6,8-difluoro-7-(2,6-dimethylpyridin-4-yl)-4-oxo-4*H*-benzothio-pyran-3-carboxylic acid (**292**) towards mammal topoisomerase II. Interesting data about the antimicrobial activity of fluoro-substituted thiochromone-3-carboxylic acids **293a–c** were reported by Italian researchers.[174] It can be seen in Table 1 that not only thiochromone-based cephalosporins but also halo-substituted thiochromones themselves can possess clear-cut antimicrobial activity against a broad range of microflora (with nalidicsic acid, a known antimicrobial agent, used as the reference).[174]

Table 1. Data on the antimicrobial activities of thiochromones **293a–c**.[174]

Microbes	Thiochromones **293**			Nalidicsic acid (reference)
	a	**b**	**c**	
Staphylococcus aureus	32	32	128	64
Streptococcus faecalis	128	128	64	128
Escherichia coli	2	2	4	1
Enterobacter cloacae	16	8	64	4
Proteus vulgaris	128	128	128	128
Klebsiella pneumoniae	2	2	8	1
Shighella enteritidis	16	8	64	16
Pseudomonas aeruginosa	128	128	128	128

Note. The MIC values are given in μg ml^{-1}.

Structures 292, 293

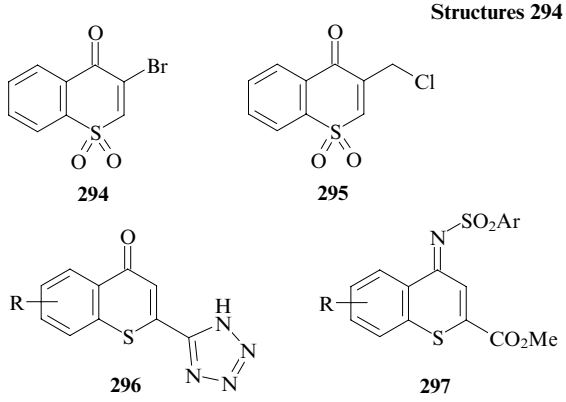


R^1 = Me, R^2 = R^3 = H (**a**); R^2 = Me, R^1 = R^3 = H (**b**), R^1 = H, R^3 = R^3 = Me (**c**)

S,S-Dioxides obtained from thiochromones, including 3-bromothiochromone (**294**) and 3-chloromethylthiochromone (**295**) *S*,*S*-dioxides,[58] possess anticancer activity and can be used, in particular, for the therapy of leukaemia. Of particular interest is dioxide **295**, which is a potent growth inhibitor for Erlich ascite carcinoma and a moderate growth inhibitor of the P-388 lymphocytic leukaemia.[186] A variety of thiochromones **296** mono- and polysubstituted in the benzene ring containing a tetrazole ring in position 2 were patented as antiasthmatic agents.[187] 4-Arenesulfonyliminothiochromone-2-carboxylates **297** are interleukin-1 (IL-1) inhibitors and, hence, they are suitable for the treatment of rheumatoid arthritis, multiple sclerosis, diabetes mellitus, atherosclerosis and septic shock.[188]

Thiochromones with a sulfamoyloxy group in side-chain positions 6 or 7 behave as steroid sulfatase inhibitors.[189] Thiochromones with a nitrogen-containing heterocyclic moiety as the 2- or 3-substituent proved to be useful for the treatment of the stress sexual dysfunction; these compounds demonstrate antioedema behaviour and show antitumour activity *via* inhibition of the matrix metalloproteinase in the human fibrosarcoma cells.[3] Also, a pronounced action of 2-(4-methylpiperazino)-3-methoxy-

Structures 294 – 297



294 **295**

296 **297**

R = H, Alk, Ar, Hal, OAlk (in different positions)

thiochromone (**234**), obtained by the reaction of 2-bromo-3-methoxythiochromone (**232c**) with *N*-methylpiperazine, on the central nervous system should be noted (see Scheme 115).[159]

6. Conclusion

Analysis of the published data indicates that the development of new methods for the synthesis of thioflavones and 2-alkylthiochromones has received considerable attention in recent years; as a result, these compounds became much more accessible for comprehensive exploration. However, no substantial progress has been achieved to date in the studies of thiochromone reactivity. The most typical transformations of these compounds are still nucleophilic addition – elimination reactions at the carbonyl group, electrophilic substitution in position 3 and oxidation of the sulfur atom and double bond reduction; in the case of 2-methylthiochromones, this list can be supplemented by reactions at the vinylogous methyl groups. Conditions favouring thiopyrone ring opening at the S – C bond without the obligatory presence of a strong electron acceptor in position 3 have not been found as yet; this reaction could open a new page in the (benzo)thiopyrone chemistry and make them equivalent to pyrones and chromones in the synthetic potential.

An important place in the thiochromone series is occupied by 2- and 3-substituted derivatives, among which new photolabile protecting groups and compounds with high biological activities have been identified. A special group comprises mono- and disubstituted thiochromones containing both electron-donating (amino, hydroxy and mercapto groups) and electron-withdrawing (halogen atom or cyano, nitro, carboxy and formyl groups) substituents in positions 2 and 3 of the thiopyrone ring. Owing to the enhanced stability of the (benzo)thiopyrone system, these compounds are of particular interest as valuable building blocks for the preparation of 2,3-heteroannulated thiochromones; this subject would be covered in a dedicated paper. High and diverse biological activities of some thiochromones stimulate further investigations in this area, which would be facilitated, as we hope, by the present review.

This review was prepared with financial support of the Russian Foundation for Basic Research (Project No. 17-03-00340).

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