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Efficient synthesis of 4-sulfanylcoumarins from 3-bromo-coumarins *via* a highly selective DABCO-mediated one-pot thia-Michael addition/elimination process†

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A facile and efficient protocol for the highly selective direct sulfanylation of 3-bromocoumarins under DABCO promotion, was developed. The transformation took place with aromatic and aliphatic thiols as well as with α,ω-dithiols, affording the expected products in very good to excellent yields. Simple and convenient ways to access 4-((ω-mercaptoalkyl) thio)coumarins and the dimeric 4,4′-(alkane-1,4-diylbis(sulfanediyl))bis(coumarins) were also devised with the use of α,ω-alkanedithiols in different ratios with regards to the starting 3-bromocoumarin. The transformation seems to proceed through the DABCO-mediated thia-Michael stereoselective addition of the thiolate anion to the α,β-unsaturated carbonyl system of the coumarin, followed by a DABCO-assisted stereoselective dehydrobromination of the resulting α-bromo carbonyl intermediate.

Introduction

The coumarin core is a privileged scaffold and a ubiquitous heterocyclic structure among natural products, bioactive synthetic compounds and technologically interesting materials. The introduction of sulfur as a heteroatom in many molecules has been demonstrated to be an effective method for changing their characteristics, by endowing them with new properties useful for materials science or conveying significant biological activity.[1]

The 4-sulfanylcoumarin core is found in many relevant natural products, such as in the cytotoxic pheofungins (**Ia–d**), the tricyclic lactone iotrochotazine A (**II**), a chemical probe to study Parkinson's disease and other heterocycles, like **IIIa–d**.[2] They are also interesting structural motifs in the area of functional materials, as exemplified by the selective fluorescent probes **IV** and **V**.[3] It is also known that upon reaction with glutathione, compound **IV** affords the 4-thiocoumarin adduct **VI**.

In addition, 4-thiocoumarins have ample applications in medicinal chemistry, exhibiting a wide range of biological and pharmacological activities. These include inhibition of vitamin K epoxide reductase[4a] and pyruvate kinase M2,[4b] to inhibition of the benzodiazepine receptors[4c] and the incorporation of DIG-11-dUTP to BS-C-1 cells modified/infected with vaccinia virus,[5a] as well as inhibition of interleukin 2 (ref. 5*b*) and the TNF-α induced expression of ICAM-1 (**VII**).[5c] 4-Sulfanylcoumarins like **VIII** and **IX**[6a–c] have been tested as cytotoxic and anti-proliferative agents and some of them proved to be interestingly bioactive.[6a,b] Others displayed anti-Hepatitis C virus activity (Fig. 1).[6d]

Despite the importance and usefulness of the 4-sulfanyl coumarins, methods for accessing these compounds are scarce, suffer from multiple synthetic steps and harsh reaction conditions, in addition, the available methodologies often use toxic agents and high temperatures, and also display poor substituent tolerance.

They mainly comprise formation of the C–S bond by 4-sulfanylation through nucleophilic vinylic substitution of suitable 4-substituted heterocyclic precursors, such as 4-hydroxycoumarins,[7a] and their sulfonates,[7b–d] 4-halocoumarins[8] and 4-bromomethyl coumarins.[9a,b] An oxidative cross-coupling on 3-aminocoumarin has been reported as an alternative.[9c]

In addition, elemental sulfur, inorganic sulfides, KSCN, CS_2 and thiourea have also served as sources of the sulfur atom,[6c,8b,10] whereas the alkylation of the resulting 4-mercaptocoumarins[11] and their arylation through the use of electrochemical means[12] have been disclosed as other options.

An exhaustive literature search revealed that there are also few and scattered cases related to the use of 3-bromocoumarins as starting materials;[13] however, their use seems discouraging, since the transformations proceed under rather harsh

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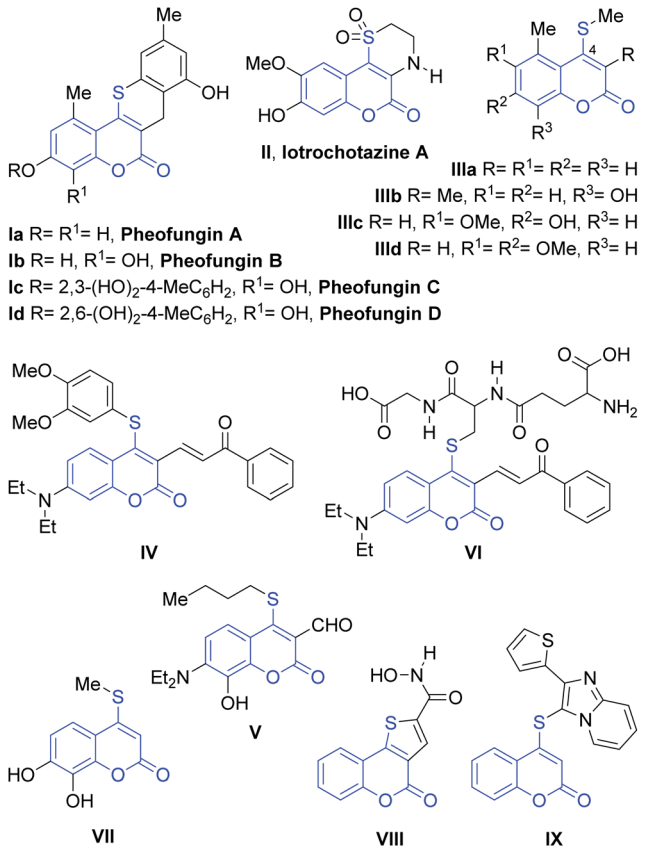


Fig. 1 Examples of relevant coumarin derivatives carrying C4–S bonds.

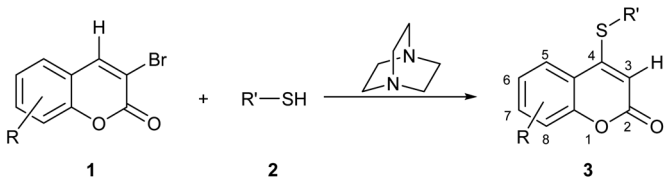
conditions and with low selectivity, resulting in poor to moderate product yields and/or giving mixtures of the isomeric 3- and 4-sulfanyl coumarins. These characteristics seriously limit their general applicability.

We have reported the synthesis of different compounds through functional group transposition,[14] such as between C-3 and C-4 among tetrahydroisoquinoline derivatives and have disclosed a vinylic nucleophilic substitution approach toward the synthesis of 4-aryl- and 4-benzyl-selanylcoumarins.[15]

To the best of our knowledge, despite some scattered precedents,[13] there have been no systematic studies of the functional transposition of 3-bromocoumarins toward their corresponding 4-sulfanyl congeners. Therefore, due to our continued interest in the preparation of new coumarin derivatives,[15,16] herein we report a facile and metal-free, selective direct 4-sulfanylation of 3-bromocoumarins (**1**) with aromatic and aliphatic thiols (**2**), under DABCO promotion. The transformations resulted in the synthesis of diverse novel 4-organylsulfanyl-coumarins (**3**), as shown in Scheme 1.

Results and discussion

The required 3-bromocoumarin[17] starting materials **1a** (R = H) and **1c** (R = 8-Me) were conveniently obtained by bromination of the corresponding coumarins with the HBr/oxone reagent system,[18] whereas the derivative **1b** (R = 6-Cl) was prepared by



Scheme 1 Proposed DABCO-promoted approach for the sulfanylation of **1** toward 4-organyl sulfanyl-coumarin derivatives (**3**).

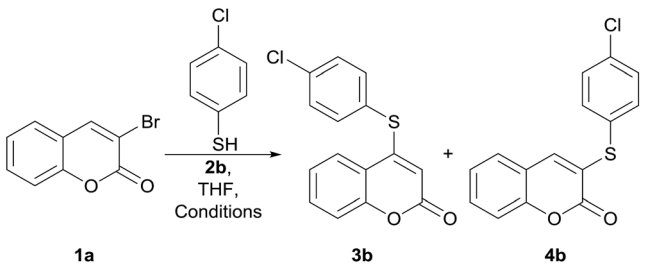
bromo-decarboxylation of 6-chlorocoumarin-3-carboxylic acid with NBS.[19]

At the outset of our debromosulfanylation studies, we employed the reaction between 3-bromocoumarin (**1a**) and 4-chlorobenzenethiol (**2b**) as model system.

Therefore, with the intention of developing a more efficient and selective protocol, we tested a small set of bases as promoters, including inorganic (KOH,[20a] K_2CO_3 (ref. 20*b* and *c*)) and organic (pyridine,[13b,c] DMAP, Et_3N,[13a,20d] DBU[20e] and DABCO[20f]) examples, under different reaction conditions (Table 1).

At first, the transformations were performed at room temperature and monitored by GC/MS. Under these conditions, a white precipitate began to form after *ca.* 10 min and the

Table 1 Optimization of the reaction conditions[a]



Entry no.	Base	Temp. (°C)	Yield[b] (%)	(**3b** : **4b**)[c]
1	K_2CO_3	r.t	82	46 : 54
2	K_2CO_3	70	—[d]	28 : 72[d]
3	KOH	r.t	68	35 : 65
4	Pyridine	r.t.	—[e]	—
5	Pyridine	70	—[f]	—
6	DMAP	r.t.	44	96 : 4
7	DMAP	70	74	92 : 8
8	Et_3N	r.t.	71	64 : 36
9	Et_3N	60	—[d]	63 : 37[d]
10	DBU	r.t	82	66 : 34
11	DBU	70	—[d]	66 : 34[d]
12	DABCO	r.t	72	97 : 3
13	DABCO	70	86	100 : 0

[a] Reaction conditions: 3-bromocoumarin (**1a**, 1 mmol), *p*-chlorothiophenol (**2b**, 1.5 mmol), THF (5 mL), base (1.5 mmol), 2 h. [b] Isolated yields by column chromatography. [c] Determined by GC/MS. [d] The yield was not determined; only the isomer ratio was estimated by GC. [e] No precipitate was formed after 3 h at room temperature. [f] No precipitate was formed after 3 h. The GC-MS analysis of the crude mixture revealed the formation of the disulfide, coumarin and **1a**.

obtention of mixtures of C-3 and C-4 isomers was consistently observed in the presence of the tested promoters, except pyridine.

The ^{1}H NMR and GC/MS analyses of the products revealed that the C-3 isomer (**4b**) prevailed in case of the inorganic bases K_2CO_3 (46 : 54, entry 1) and KOH (35 : 65, entry 3), whereas the opposite was detected for the organic promoters Et_3N (64 : 36, entry 8) and DBU (66 : 34, entry 10); however, when pyridine (1.5 equiv.) was employed as base, the expected reaction product was not observed[13b,c] even under the heating condition (entries 4 and 5). Instead, the disulfide related to **2b**, coumarin and **1a** was the detected products when the reaction was executed at 70 °C. It is worth noting that a similar process was reported to proceed at 140 °C in refluxing pyridine, employed both, as solvent and base.[13b–d]

Gratifyingly, however, although not fully suppressing the formation of the undesired C-3 isomer, the use of DMAP (96 : 4, entry 8) and DABCO (97 : 3, entry 12) resulted in a comparatively larger preference for the expected C-4 isomer **3b**, with the latter affording higher product yields.

Therefore, the performances of the reactions with these bases were examined at higher temperatures, where formation of a white precipitate was observed almost immediately; however, these also furnished mixtures of isomers (entries 2, 9 and 11). After some trial and error experiments, it was observed that heating a mixture of **1a**, the thiol **2b** and DMAP gave a 92 : 8 mixture of **3b** and **4b** in a satisfactory 74% overall yield (entry 7).

Luckily, however, the use of DABCO in THF at 70 °C, led to the exclusive formation of **3b**, the product substituted at C-4, in an improved 86% yield (entry 13). Interestingly, to the best of our knowledge, despite the use of DABCO as a promoter of a similar transformation has been recorded,[20f] this is the first time the reaction is explored under DMAP assistance. The differences between DABCO and DMAP as organocatalysts have been examined.[21a]

The ^{1}H NMR signals of the vinylic protons of the starting material and product where compared with those of the unsubstituted coumarin ($\delta_{H\text{-}3}$ 6.43 ppm, doublet; $\delta_{H\text{-}4}$ 7.72 ppm, doublet), and taken as the diagnostic signals of this outcome.

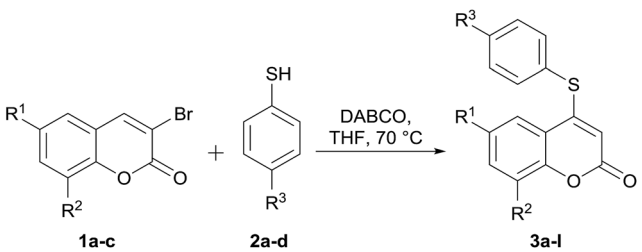
The H-4 resonance of **1a** was observed as a highly deshielded singlet resonating at δ 8.11 ppm, whereas the product exhibited a considerably more shielded singlet at δ 5.62 ppm, consistent with structure **3b**. The reason for this upfield shift could only be assigned to H-3 in the presence of an adjacent sulfur-containing group, due to its electron-donating character.

Since only mixtures of C-3 and C-4 isomers were observed with the different bases other than DABCO, it was concluded that use of the latter in THF at 70 °C was the best choice for the proposed transformation. Once suitably optimized conditions were obtained, the scope of the reaction was examined with four different 4-substituted thiophenols (**2a–d**) and three coumarins (**1a–c**).

As shown in Table 2, the use of DABCO as promoter systematically resulted in the expected 4-substituted heterocycles (**3a–l**) in consistently high yields (71–97%).

From the analysis of these results, no clear trend emerged with regards to the effect of the substituents of both reaction

Table 2 Synthesis of 4-arylthiocoumarins[a]



1a-c 2a-d 3a-l

Entry no.	Coumarin no.	R^1	R^2	Thiophenol no.	R^3	Product no.	Yield[b] (%)
1	**1a**	H	H	**2a**	H	**3a**	90
2	**1a**	H	H	**2b**	Cl	**3b**	86
3	**1a**	H	H	**2c**	Me	**3c**	84
4	**1a**	H	H	**2d**	OMe	**3d**	90
5	**1b**	Cl	H	**2a**	H	**3e**	78
6	**1b**	Cl	H	**2b**	Cl	**3f**	97
7	**1b**	Cl	H	**2c**	Me	**3g**	84
8	**1b**	Cl	H	**2d**	OMe	**3h**	79
9	**1c**	H	Me	**2a**	H	**3i**	80
10	**1c**	H	Me	**2b**	Cl	**3j**	78
11	**1c**	H	Me	**2c**	Me	**3k**	71
12	**1c**	H	Me	**2d**	OMe	**3l**	87

[a] Reaction conditions: 3-bromocoumarin (0.5 mmol), arenethiol (**2**, 0.75 mmol), THF (5 mL), DABCO (1.0 equiv.), 2 h. [b] Isolated yields by column chromatography.

components on the performance of the transformation. However, it was observed that electron-donating and electron-withdrawing substituents on the thiol side were well tolerated.

Furthermore, the data revealed that the more acidic 4-chloro thiophenol (**2b**, pK_a = 5.46)[21b] performed better with 6-chlorocoumarin (**1b**) than with its congeners, the heterocycles **1a** and **1c** (entry 6 *vs.* entries 2 and 10). Analogously, the less acidic 4-methoxythiophenol (**2d**, pK_a = 6.21) gave better results in the presence of the coumarins **1a** and **1c** than with **1b** (entries 4 and 12 *vs.* entry 8).

Taking advantage of the good performance of the transformation when arenethiols were employed, and in order to expand its scope, the reaction was also carried out with α,ω-dithiols (**5a**,**d**). Rewardingly, it was observed (Table 3) that in the presence of the α,ω-dithiols in excess, the reaction furnished the expected 4-((ω-mercaptoalkyl)thio)coumarins **6a**,**d**.

Thus, in the presence of 3.0 equiv. of the dithiols with three (**5b**) and six (**5d**) carbon atoms and 1.5 equiv. of the dithiol with five carbon atoms (**5c**), the coumarin **1a** afforded good yields of the expected coumarin thiols **6b–d** (71–79%, entries 2–4), with slightly decreased with the increase of the chain length. Contrastingly, however, only a meagre 39% yield of **6a** was isolated (entry 1), despite the use of 3.0 equiv. of the more reactive 1,2-ethanedithiol (**5a**).

Encouraged by these results, the scope of this selective sulfanylation was also explored in the presence of excess of the coumarin **1a**, aiming to obtain the more challenging 4,4′-(alkane-α,ω-diylbis(sulfanediyl))bis(coumarins). As shown in Table 4, under our optimized conditions, the corresponding reactions of **1a** with **5c** and **5d** gave good yields of the expected products **7a** and **7b**, respectively. Sadly, however, when analogous transformations were attempted with the more reactive 1,2-ethanedithiol (**5a**) and 1,3-propanedithiol (**5b**), they met with failure, giving insoluble white solids, which could not be analyzed by NMR.

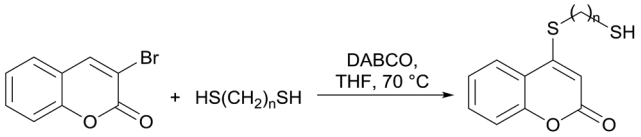
Noteworthy, compounds such as **7a** and **7b** are very rare. A related 4,4′-sulfanediyl-biscoumarin was prepared as a side product of the reaction of 4-mercaptocoumarin with diphenylketene.[22]

On the other hand, their synthesis complements earlier work by Drozd and coworkers who prepared analogous heterocycles in a more cumbersome way, by vinylic substitution on 3-nitro-4-halocoumarins.[23]

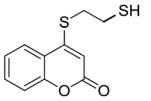
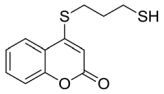
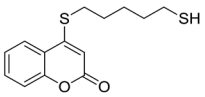
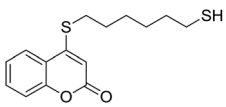
Further, these authors also found out that the presence of a good leaving group on C-3 enables short chain dithiols to displace the leaving group, resulting in intramolecular cyclization, to afford tricyclic products which carry 1, n + 2 dithiane motifs (n = number of carbon atoms of the α,ω-dithiol), and bear sulfur atoms attached to both positions, C-3 and C-4. In addition, they discovered that 4-((ω-mercaptoalkyl)thio) coumarins can be preferentially obtained (<40% yield) by running the transformation at low temperature.

It was reported that α-bromo Michael acceptors such as ketones and esters, react with thiols to undergo *ipso*-

Table 3 Synthesis of 4-((ω-mercaptoalkyl)thio)coumarins[a]

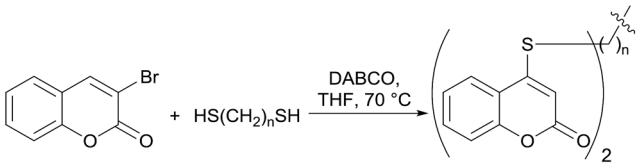


1a 5a-d 6a-d

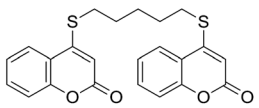
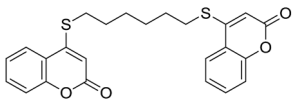
Entry no.	α,ω-Dithiol no.	α,ω-Dithiol (equiv.)	n	Product	Product no.	Yield[b] (%)
1	**5a**	3.0	2		**6a**	39
2	**5b**	3.0	3		**6b**	79
3	**5c**	1.5	5		**6c**	74
4	**5d**	3.0	6		**6d**	71

[a] Reaction conditions: 3-bromocoumarin (**1a**, 1 mmol), α,ω-dithiol, THF (5 mL), DABCO (1.5 equiv.), 2 h. [b] Isolated yields by column chromatography.

Table 4 Synthesis of 4,4′-(alkane-α,ω-diylbis(sulfanediyl))bis(coumarins)



1a 5c-d 7a-b

Entry no.	α,ω-Dithiol no.	*n*	Product	Product no.	Yield[a] (%)
1	**5c**	5		**7a**	86
2	**5d**	6		**7b**	65

[a] Isolated yields by column chromatography, based on the α,ω-dithiols. Excess 3-bromocoumarin **1a** (3.0 equiv.) and DABCO (3.0 equiv.) were employed.

substitution, furnishing the α-sulfanyl derivatives alone or in mixtures with the corresponding dithiosubstituted compounds.[20c,24a,b] Further, cyclic α-haloenones react with thiols providing mainly the α-sulfanyl derivatives,[24c] and α-haloenals derived from crotonaldehyde and cinnamaldehyde gave moderate yield of the *ipso*-substitution product upon reaction with butanethiol.[24d,e]

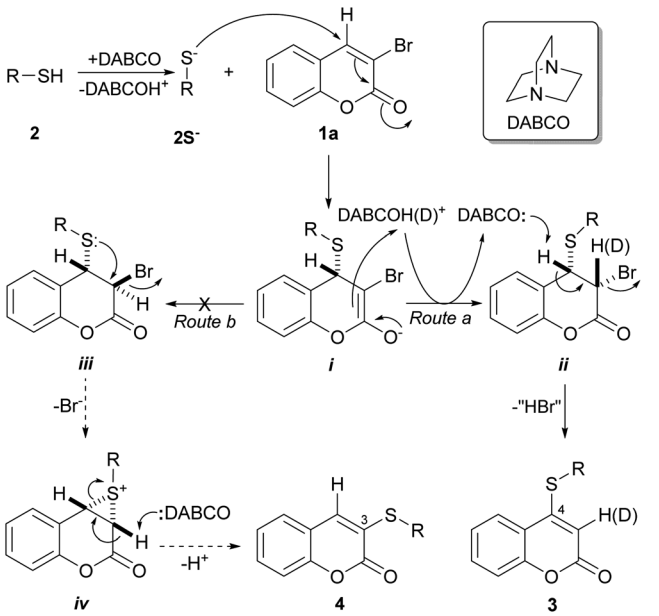
The actual case is different and, although the exact reaction mechanism of the disclosed transformations remains unknown, a good mechanistical picture can be drawn based on literature precedents.[25a] As shown in Scheme 2, it can be assumed that the addition of DABCO effects deprotonation of the acidic thiol moieties **2** and results in the formation of the thiolate anions (**2S**$^-$), which are stronger nucleophiles and can react with the α,β-unsaturated carbonyl system of **1a**.

In general, the α,β-unsaturated carbonyl system of coumarins is prone to undergo a Michael type (C-4) addition, and it has been observed that the latter transformation takes place preferentially in these heterocycles when they are 3,4-disubstituted with good leaving groups, such as halides and sulfonates.[7b,25b]

This in sharp contrast with the reactivity of the neighbor C-3 position. It is known that in α,β-unsaturated carbonyl systems like those of coumarins, when an halogen atom is placed at the α-position to the carbonyl moiety (C-3), the activation of the α-carbon atom is usually too low to afford a substitution product *via* an addition–elimination mechanism. Therefore, all the reactivity characteristics of the coumarin unsaturated system strongly favor a C-4 attack.

Accordingly, the thiolate anions might trigger a thia-Michael addition, where the incoming nucleophile becomes attached to the β-end of the double bond (C-4) system, resulting in the enolate intermediate **i**. In turn, the latter may capture a proton (from DABCOH$^+$), furnishing a 3,4-disubstituted 3,4-dihydro coumarin intermediate and returning the nucleophilic catalyst DABCO to the reaction medium. If the transformation path takes the Route a, the structure of this intermediate is **ii**, which can then undergo a base-mediated dehydrohalogenation to furnish the expected 4-sulfanylcoumarin **3**.

Some literature precedents suggest that, at least in the case of the coumarins, both stages, the formation intermediate **ii** as well as its dehydrohalogenation, should be stereospecific processes, with the latter stage being an 1,2-*anti*-type elimination.[25c] In view of the observed results, it is most likely that



Scheme 2 Plausible reaction mechanism for the DABCO-promoted selective sulfanylation of 3-bromocoumarins to afford 4-sulfanylcoumarins **3**.

the bulk of DABCO, a sterically hindered tertiary amine, may play some key role in inducing the delivery of the proton to intermediate **i** in an *anti*-fashion to the incoming sulfur reactant, to selectively afford the intermediate **ii**.

Notably, when the transformation of **1a** with thiol **2b** was performed in the presence of a small amount of D_2O ($\approx$0.1 mL), it was observed that the product **3b** exhibited deuteration on C-3 (δ 5.62 ppm),[25c,d] as stemmed from the reduction of its ^{1}H NMR resonance integral, clearly demonstrating the participation of intermediates **i** and **ii** in the reaction. Furthermore, a GC/MS analysis of the reaction products confirmed this observation, and indicated over 90% deuterium incorporation.

Interestingly, Nambara found out that the reaction between thiophenol and 3-bromothiachromone-1,1-dioxide affords 2-phenylsufanylthiachromone-1,1-dioxide. Despite the reaction may take place through an analogous mechanism, it is noteworthy that the transformation was performed in KOH,[20a] which proved to give unsatisfactory results in the case of **1a**. In addition, a similar mechanism may be at the heart of a recently reported modification of Fiesselmann's thiophene synthesis.[25e]

Alternatively, the reaction could take place through Route b and proceed through the intermediacy of **iii**, which has the proper geometric array for an intramolecular attack by the sulfur moiety of the sulfanyl group from behind to the bromine atom, to furnish the episulfonium (thiiranium) ion intermediate **iv**.[20e] This step entails a 3-*exo-tert* process,[24e] which is favorable according to Baldwin's rules. In turn, the intermediate **iv** could suffer an attack of the base on the most acidic α-carbonyl hydrogen, resulting in opening of the strained episulfonium ion ring, to finally give the 3-sulfanylcoumarin **4**.

The same outcome could be achieved by means of either a thiolate-mediated nucleophilic ring opening of intermediate **iv**, or a nucleophilic bromide substitution on intermediate **iii**, followed in both cases by elimination of a molecule of thiol,[20e,24c,24e] which would result in a formal *ipso*-substitution of the halogen atom. This sequence of events is reminiscent of intracellular reactions of molecules containing the α-haloacryloyl motif with biological thiols in living organisms, which generate episulfonium ion intermediates; the latter are DNA-alkylating agents and play a key role in processes of DNA-damaging and cytotoxicity.[26]

Contrastingly, however, in the actual case and under DABCO promotion in refluxing THF, no 3-thio-substituted coumarin derivatives **4** were isolated in any of the studied cases. Furthermore, the high yields recorded in most of the examples suggest that the reaction takes place exclusively through Route a or that involvement of Route b, if any, should be minimal.

Experimental

General information

The solvents were purified and dried according to usual procedures.[27] The reagents for synthesis were obtained commercially and were used as received, without further purification. The progress of the reactions was monitored by thin layer chromatography on silica gel GF_{254} plates. For detection of the spots the plates were exposed to UV light (254 and 365 nm), I_2 or H_2SO_4/vanillin solution. The chromatographic purifications were carried out by column chromatography employing silica gel (230–400 mesh, 40–63 μm) and eluting with hexane–EtOAc (10 : 1, v/v).

Equipment

The melting points were taken on a MQAPF-301 melting point apparatus and are reported uncorrected.

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer, with the samples dissolved in $CDCl_3$, unless otherwise noted. The chemical shifts are informed in ppm downfield from the signal of TMS, used as internal standard, and the coupling constants (J) are expressed in Hertz (Hz).

The high-resolution mass spectral data were obtained on a LTQ Orbitrap Discovery mass spectrometer (Thermo Fisher Scientific), using sodium formate as reference.

3-Bromo-6-chlorocoumarin (1b).[19] A stirred mixture of salicylaldehyde (1.22 g, 10 mmol) and $TsOH\cdot H_2O$ (3.8 g, 20 mmol) in MeCN (100 mL) was treated with NCS (1.33 g, 10 mmol) and the system was stirred at room temperature for 4 h. The reaction was diluted with H_2O (20 mL) and extracted with EtOAc (4 × 25 mL). The combined extracts were dried over $MgSO_4$, concentrated under reduced pressure. The residue was chromatographed affording 4-chloro salicylaldehyde (1.29 g, 81%), as a white solid. ^{1}H NMR δ 10.9 (s, OH), 9.85 (s, 1H), 7.53 (d, J = 2.6, 1H), 7.47 (dd, J = 2.6, 8.9, 1H) and 6.96 (d, J = 8.9, 1H).[28a] Without further purification, the aldehyde (3.13 g, 20 mmol) was mixed with meldrum acid (2.88 g, 20 mmol) in H_2O (100 mL) and the stirred reaction was warmed to 75 °C for 2 h. Then, the reaction was cooled to room temperature and the solid obtained was filtered employing a sintered glass funnel. The solid was washed with ice water (5 mL) and Et_2O (5 mL) and further dried under high vacuum to afford 6-chlorocoumarin-3-carboxylic acid (3.57 g, 80%), as a white solid. ^{1}H NMR δ 10.01 (s, 1H), 8.64 (s, 1H), 7.73 (d, J = 2.4, 1H), 7.63 (dd, J = 2.5, 8.9, 1H), 7.35 (d, J = 8.9, 1H).[28b] Next, the coumarin (0.898 g, 4 mmol) and LiOAc (0.397 g, 4.8 mmol) were dissolved in a MeCN/H_2O mixture (10 : 1, v/v). After 5 minutes, the stirred reaction was treated with NBS (0.748 g, 4.2 mmol) and allowed to further stir overnight at room temperature. Then, the reaction was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 25 mL); the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Chromatographic purification of the residue afforded **1b** (0.838 g, 81%), as a white solid, mp 174 °C (lit. 172–174 °C). ^{1}H NMR δ 8.02 (s, 1H), 7.51 (dd, J = 2.4, 8.8, 1H), 7.44 (d, J = 2.4, 1H), 7.29 (d, J = 8.8, 1H).[19]

8-Methylcoumarin.[28c] Propiolic acid (1.26 g, 18 mmol) was added to a stirred solution of *ortho*-cresol (1.62 g, 15 mmol) and $Ce(OTf)_3$ (0.587 g, 1 mmol) in $MeSO_3H$ (15 mL) at room temperature. The system was heated at 90 °C and stirred overnight. Then, H_2O (20 mL) was added and the product was extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography of the

residue gave 8-methylcoumarin (0.721 g, 30%), as a white solid, mp 106 °C (lit. 106–107 °C). ^{1}H NMR δ 7.68 (d, J = 9.5, 1H), 7.39–7.35 (m, 1H), 7.33–7.29 (1H), 7.17 (t, J = 7.6, 1H), 6.40 (d, J = 9.5, 1H) and 2.45 (s, 3H).

3-Bromocoumarin (1a) and 3-bromo-8-methylcoumarin (1c).[18] Oxone (7.4 g, 12 mmol) was added to a solution of the corresponding coumarin (10 mmol) in CH_2Cl_2 (40 mL) and the system was treated dropwise with 48% HBr (2.5 mL, 22 mmol) dissolved in H_2O (15 mL). The reaction was stirred at room temperature for 4 h, when Et_3N (8.7 mL) was added and then, it was allowed to stir overnight. The reaction was diluted with H_2O (40 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and chromatographically purified to afford **1a** (R = H; 1.88 g, 84%), as a white solid, mp 110 °C (lit. 110–111 °C). ^{1}H NMR δ 8.11 (s, 1H), 7.60–7.55 (m, 1H), 7.49–7.45 (m, 1H) and 7.37–7.29 (m, 2H). Compound **1c** (R = 8-Me) was obtained in a similar fashion (1.62 g, 68%), as a yellowish solid, mp 128 °C (lit. 127–129 °C). ^{1}H NMR δ 8.07 (s, 1H), 7.41–7.38 (m, 1H), 7.30–7.26 (m, 1H), 7.20 (t, J = 7.6, 1H) and 2.46 (s, 3H).

General procedure for the 4-sulfanylation of 3-bromocoumarins

The coumarin (0.5 mmol) was transferred to a 25 mL two-necked round bottomed flask containing THF (3 mL) and the mixture was heated to 70 °C. Then, the thiol (0.75 mmol) and DABCO (0.5 mmol) were successively added (specific modifications to the amounts of the reagents of this protocol are given in the tables). The reaction was monitored by TLC. Upon complete consumption of the starting material, the reaction was diluted with H_2O (10 mL) and the products were extracted with EtOAc; the combined organic extracts were washed with 10% w/v Na_2CO_3 solution, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography. In the labelling experiment, D_2O (0.1 mL) were mixed with the thiol and the coumarin, before adding DABCO.

4-(Phenylthio)-2*H*-chromen-2-one (3a).[7d,29a–c] White solid (114 mg, 90%), mp 150–152 °C. ^{1}H NMR δ 7.88–7.84 (m, 1H), 7.63–7.49 (m, 6H), 7.37–7.29 (m, 2H) and 5.64 (s, 1H). ^{13}C NMR δ 159.7, 158.1, 152.3, 136.2 (2C), 132.4, 131.0, 130.6 (2C), 126.3, 124.3, 123.8, 117.9, 117.3 and 108.5.

4-((4-Chlorophenyl)thio)-2*H*-chromen-2-one (3b).[29a,c] White solid (124 mg, 86%), mp 103–104 °C. ^{1}H NMR δ 7.83–7.79 (m, 1H) 7.59–7.46 (m, 5H), 7.34–7.28 (m, 2H) and 5.62 (s, 1H). ^{13}C NMR δ 159.3, 157.2, 152.3, 137.7, 137.4 (2C), 132.5, 130.8 (2C), 124.8, 124.3, 123.7, 117.7, 117.3 and 108.7.

4-(*p*-Tolylthio)-2*H*-chromen-2-one (3c).[7a] Yellowish solid (113 mg, 84%), mp 142–144 °C. ^{1}H NMR δ 7.86 (dd, J = 7.9, 1.5, 1H), 7.59–7.53 (m, 1H), 7.50–7.43 (m, 2H), 7.36–7.29 (m, 4H), 5.63 (s, 1H) and 2.43 (s, 3H). ^{13}C NMR δ 159.7, 158.5, 152.4, 141.6, 136.1 (2C), 132.3, 131.3 (2C), 124.2, 123.8, 122.7, 118.0, 117.3, 108.3 and 21.5.

4-((4-Methoxyphenyl)thio)-2*H*-chromen-2-one (3d). White solid (128 mg, 90%), mp 154–156 °C. ^{1}H NMR δ 7.88–7.83 (m, 1H), 7.59–7.53 (m, 1H), 7.52–7.47 (m, 2H), 7.36–7.29 (m, 2H), 7.05–7.00 (m, 2H), 5.62 (s, 1H) and 3.88 (s, 3H). ^{13}C NMR δ 161.9, 159.8, 159.0, 152.4, 137.8 (2C), 132.4, 124.2, 123.8, 118.1, 117.3, 116.5, 116.2 (2C), 108.3 and 55.7. HRMS: m/z calcd for $C_{16}H_{13}O_3S$ $[M + H]^+$: 285.0580; found: 285.0573.

6-Chloro-4-(phenylthio)-2*H*-chromen-2-one (3e).[29a] Yellowish solid (113 mg, 78%), mp 202–204 °C. ^{1}H NMR δ 7.82 (d, J = 2.4, 1H), 7.62–7.49 (m, 6H), 7.30–7.27 (m, 1H) and 5.66 (s, 1H). ^{13}C NMR δ 159.0, 156.9, 150.8, 136.2 (2C), 132.4, 131.2, 130.7 (2C), 129.8, 125.8, 123.5, 119.0, 118.7 and 109.2.

6-Chloro-4-((4-chlorophenyl)thio)-2*H*-chromen-2-one (3f). White solid (156 mg, 97%), mp 164–166 °C. ^{1}H NMR δ 7.76 (d, J = 2.4, 1H), 7.54–7.47 (m, 5H), 7.26 (d, J = 8.8, 1H) and 5.63 (s, 1H). ^{13}C NMR δ 158.6, 156.1, 150.7, 137.9, 137.3 (2C), 132.4, 130.9 (2C), 129.8, 124.2, 123.3, 118.7, 118.7 and 109.4. HRMS: m/z calcd for $C_{15}H_9O_2SCl_2$ $[M + H]^+$: 322.9695; found: 322.9687.

6-Chloro-4-(*p*-tolylthio)-2*H*-chromen-2-one (3g).[7a] White solid (127 mg, 84%), mp 190–191 °C. ^{1}H NMR δ 7.82 (d, J = 2.4, 1H), 7.51 (dd, J = 8.8, 2.4, 1H), 7.48–7.42 (m, 2H), 7.35–7.30 (m, 2H), 7.27 (d, J = 8.8, 1H), 5.65 (s, 1H), 2.44 (s, 3H). ^{13}C NMR δ 159.1, 157.4, 150.9, 141.9, 136.1 (2C), 132.3, 131.5 (2C), 129.8, 123.5, 122.3, 119.1, 118.7, 109.2 and 21.5.

6-Chloro-4-((4-methoxyphenyl)thio)-2*H*-chromen-2-one (3h). White solid (126 mg, 79%), mp 106–108 °C. ^{1}H NMR δ 7.81 (s, 1H), 7.52–7.46 (m, 3H), 7.29–7.25 (m, 1H), 7.05–7.00 (m, 2H), 5.64 (s, 1H), 3.88 (s, 3H). ^{13}C NMR δ 162.1, 159.0, 157.8, 150.9, 137.8 (2C), 132.3, 129.8, 123.5, 119.1, 118.7, 116.3 (2C), 116.0, 109.0 and 55.7. HRMS: m/z calcd for $C_{16}H_{12}O_3SCl$ $[M + H]^+$: 319.0190; found: 319.0185.

8-Methyl-4-(phenylthio)-2*H*-chromen-2-one (3i). White solid (106 mg, 80%), mp 149–151 °C. ^{1}H NMR δ 7.71 (d, J = 8.0, 1H), 7.62–7.49 (m, 5H), 7.42 (d, J = 7.4, 1H), 7.21 (t, J = 7.7, 1H), 5.64 (s, 1H), 2.45 (s, 3H). ^{13}C NMR δ 159.8, 158.4, 150.8, 136.2 (2C), 133.7, 130.9, 130.5 (2C), 126.8, 126.7, 123.8, 121.5, 117.7, 108.4 and 15.9. HRMS: m/z calcd for $C_{16}H_{13}O_2S$ $[M + H]^+$: 269.0631; found: 269.0628.

4-((4-Chlorophenyl)thio)-8-methyl-2*H*-chromen-2-one (3j). White solid (118 mg, 78%), mp 160–162 °C. ^{1}H NMR δ 7.69–7.64 (m, 1H), 7.55–7.46 (m, 4H), 7.44–7.40 (m, 1H), 7.21 (t, J = 7.7, 1H), 5.62 (s, 1H) and 2.45 (s, 3H). ^{13}C NMR δ 159.5, 157.7, 150.8, 137.7, 137.4 (2C), 133.9, 130.8 (2C), 126.9, 125.2, 123.8, 121.4, 117.6, 108.6 and 15.9. HRMS: m/z calcd for $C_{16}H_{12}O_2SCl$ $[M + H]^+$: 303.0241; found: 303.0244.

8-Methyl-4-(*p*-tolylthio)-2*H*-chromen-2-one (3k). White solid (98 mg, 71%), mp 141–143 °C. ^{1}H NMR δ 7.73–7.67 (m, 1H), 7.48–7.43 (m, 2H), 7.43–7.39 (m, 1H), 7.33–7.29 (m, 2H), 7.21 (t, J = 7.7, 1H), 5.62 (s, 1H), 2.45 (s, 3H) and 2.43 (s, 3H). ^{13}C NMR δ 159.8, 158.9, 150.8, 141.5, 136.1 (2C), 133.6, 131.3 (2C), 126.8, 123.7, 123.1, 121.5, 117.8, 108.2, 21.5 and 15.9. HRMS: m/z calcd for $C_{17}H_{15}O_2S$ $[M + H]^+$: 283.0787; found: 283.0799.

4-((4-Methoxyphenyl)thio)-8-methyl-2*H*-chromen-2-one (3l). White solid (129 mg, 87%), mp 199–201 °C. ^{1}H NMR δ 7.72–7.69 (m, 1H), 7.52–7.46 (m, 2H), 7.44–7.39 (m, 1H), 7.21 (t, J = 7.7, 1H), 7.04–7.00 (m, 2H), 5.61 (s, 1H), 3.88 (s, 3H) and 2.45 (s, 3H). ^{13}C NMR δ 161.9, 159.8, 159.3, 150.8, 137.8 (2C), 133.6, 126.7, 123.7, 121.4, 117.7, 116.8, 116.2 (2C), 108.0, 55.6 and 15.9. HRMS: m/z calcd for $C_{17}H_{15}O_3S$ $[M + H]^+$: 299.0736; found: 299.0739.

4-((2-Mercaptoethyl)thio)-2*H*-chromen-2-one (6a). White solid (92 mg, 39%), mp 138–140 °C. ^{1}H NMR δ 7.77–7.71 (m, 1H), 7.59–7.52 (m, 1H), 7.37–7.26 (m, 2H), 6.16 (s, 1H), 3.32–3.26 (m, 2H), 2.96–2.88 (m, 2H), 1.79 (t, J = 8.4, 1H). ^{13}C NMR δ 159.3, 155.3, 152.4, 132.5, 124.3, 124.0, 118.2, 117.4, 107.2, 34.6 and 23.0. HRMS: m/z calcd for $C_{11}H_{11}O_2S_2$ $[M + H]^+$: 239.0195; found: 239.0198.

4-((3-Mercaptopropyl)thio)-2*H*-chromen-2-one (6b). White solid (99 mg, 79%), mp 79–81 °C. ^{1}H NMR δ 7.73 (dd, J = 8.0, 1.5, 1H), 7.56–7.51 (m, 1H), 7.35–7.31 (m, 1H), 7.30–7.24 (m, 1H), 3.18 (t, J = 6.5, 2H), 2.75–2.70 (m, 2H), 2.14–2.08 (m, 2H) and 1.45 (t, J = 8.2, 1H). ^{13}C NMR δ 159.3, 156.0, 152.3, 132.3, 124.2, 124.0, 118.3, 117.4, 107.2, 31.6, 29.0 and 23.5. HRMS: m/z calcd for $C_{12}H_{13}O_2S_2$ $[M + H]^+$: 253.0351; found: 253.0345.

4-((5-Mercaptopentyl)thio)-2*H*-chromen-2-one (6c). White solid (103 mg, 74%), mp 89–91 °C. ^{1}H NMR δ 7.73 (dd, J = 8.0, 1.5, 1H), 7.56–7.50 (m, 1H), 7.33–7.23 (m, 2H), 6.13 (s, 1H), 3.02 (t, J = 7.3, 2H), 2.60–2.52 (m, 2H), 1.86–1.79 (m, 2H), 1.73–1.56 (m, 4H) and 1.37 (t, J = 7.8, 1H). ^{13}C NMR δ 159.2, 156.4, 152.1, 132.1, 124.0, 123.8, 118.2, 117.1, 106.8, 33.3, 30.7, 27.6, 27.2 and 24.3. HRMS: m/z calcd for $C_{14}H_{17}O_2S_2$ $[M + H]^+$: 281.0664; found: 281.0674.

4-((6-Mercaptohexyl)thio)-2*H*-chromen-2-one (6d). White solid (104 mg, 71%), mp 89–90 °C. ^{1}H NMR δ 7.77–7.72 (m, 1H), 7.57–7.50 (m, 1H), 7.34–7.30 (m, 1H), 7.29–7.24 (m, 1H) 6.14 (s, 1H), 3.02 (t, J = 7.3, 2H), 2.58–2.51 (m, 2H), 1.85–1.80 (m, 2H), 1.67–1.62 (m, 2H), 1.52–1.48 (m, 4H) and 1.35 (t, J = 7.8, 1H). ^{13}C NMR δ 159.4, 156.7, 152.3, 132.2, 124.2, 124.0, 118.4, 117.3, 106.9, 33.8, 30.9, 28.5, 27.9, 27.7 and 24.5. HRMS: m/z calcd for $C_{15}H_{19}O_2S_2$ $[M + H]^+$: 295.0821; found: 295.0823.

4,4′-(Pentane-1,5-diylbis(sulfanediyl))bis(2*H*-chromen-2-one) (7a). White solid (364 mg, 86%), mp. 164–165 °C. ^{1}H NMR δ 7.74–7.70 (m, 2H), 7.56–7.50 (m, 2H), 7.32–7.23 (m, 4H), 6.14 (s, 2H); 3.05 (t, J = 7.2, 4H), 1.92–1.84 (m, 4H) and 1.76–1.72 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 159.2 (2C), 156.3 (2C), 152.2 (2C), 132.2 (2C), 124.1 (2C), 123.9 (2C), 118.2 (2C), 117.2 (2C), 106.9 (2C), 30.6 (2C), 28.3 (2C) and 27.3 (1C). HRMS: m/z calcd for $C_{23}H_{21}O_4S_2$ $[M + H]^+$: 425.0876; found: 425.0857.

4,4′-(Hexane-1,6-diylbis(sulfanediyl))bis(2*H*-chromen-2-one) (7b). White solid (247 mg, 65%), mp 185–187 °C. ^{1}H NMR δ 7.68 (d, J = 8.0, 1.4, 2H), 7.50–7.44 (m, 2H), 7.28–7.24 (m, 2H), 7.23–7.17 (m, 2H), 6.08 (s, 2H), 2.97 (t, J = 7.3, 4H), 1.83–1.74 (m, 4H) and 1.55–1.49 (m, 4H). ^{13}C NMR δ 159.5 (2C), 156.6 (2C), 152.4 (2C), 132.3 (2C), 124.2 (2C), 124.0 (2C), 118.4 (2C), 117.4 (2C), 107.0 (2C), 30.8 (2C), 28.6 (2C) and 27.7 (2C). HRMS: m/z calcd for $C_{24}H_{23}O_4S_2$ $[M + H]^+$: 439.1032; found. 439.1036.

Conclusion

In conclusion, we have developed an efficient DABCO-promoted approach for the direct 4-sulfanylation of 3-bromocoumarins, to afford a ready access to different 4-organylsulfanyl-coumarin derivatives in good yield. This methodology entails a one-pot thia-Michael addition/dehydrobromination process and results in a direct C–S bond formation.

In the presence of DABCO, the introduction of the sulfanyl moiety is highly stereospecific, in such a way that it favors the following *anti*-elimination step and precludes thiirane formation, to afford only 4-substituted coumarins. This approach is simple and metal-free; therefore, it may find application in the synthesis of other relevant compounds from the biological, functional or structural points of view.

Conflicts of interest

There are no conflicts of interest to declare.

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