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MeONH$_2$·HCl-Mediated α-Methylenation/Conjugate Addition of α-Sulfonyl *o*-Hydroxyacetophenones with Methyl Sulfoxides: Route to 3-Sulfonylchroman-4-ones

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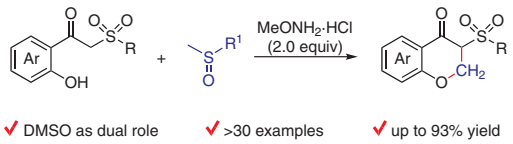

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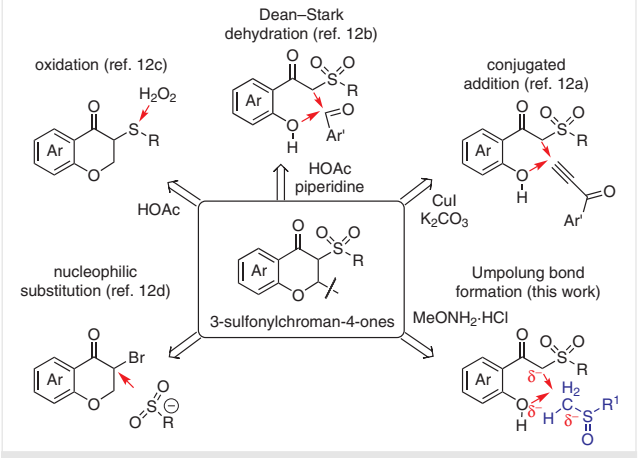
Abstract A novel and efficient route for the synthesis of 3-sulfonylchroman-4-ones from α-sulfonyl *o*-hydroxyacetophenones with methyl sulfoxides *via* a MeONH$_2$·HCl-mediated sequential methylenation/conjugate addition is described. Plausible reaction mechanisms are proposed and discussed. Various reaction conditions for this novel, one-pot, environmentally friendly conversion were investigated.

Key words chroman-4-ones, *o*-hydroxyacetophenones, methylenation, methyl sulfoxides, sulfonyl compounds

In the field of organic synthesis, solvents as reactants or reagents for the efficient installation of a methylene moiety have attracted the continuous attention of many chemists on the basis of cost and easy availability perspectives.[1] Therefore, the development of diversified reaction systems involving a 'CH_2 synthon' in the construction of functionalized molecules from purchased solvents would be highly valuable. Generally, CH_2Cl_2 is one of the most common methylene bridges for carbon–heteroatom bond formation.[2] By using DMF and DMA, transition-metal-catalyzed oxidative methylene-linked dimerizations of bicyclic heteroarenes have been performed.[3] The bridging methylenation of two aromatics has been described by choosing DMSO as a one-carbon (CH_2) source to afford symmetric or asymmetric products.[4] Other solvents, such as toluene, MeCN and $MeNO_2$, have been employed as conjugated CH_2 units to insert into the desired target blocks.[5–7] Among these solvents, DMSO exhibits high polarity, low toxicity and relative stability, resulting in a number of synthetic applications.[8] Compared with these reported synthetic variations of different methods, there has been little focus on DMSO-mediated, one-pot methylene bond formations.[9] To the best of our knowledge, no examples have been reported for the tandem α-methylenation/conjugate addition process to establish the core skeleton of sulfonylchroman-4-ones.

Substituted chroman-4-ones are versatile skeletons common in useful synthetic intermediates[10] and bioactive molecules.[11] Representative synthetic routes toward 3-sulfonylchroman-4-ones are shown in Scheme 1, including our previous reports on (i) double conjugated addition of α-sulfonyl *o*-hydroxyacetophenones with alkynones[12a] and (ii) Dean–Stark dehydration of α-sulfonyl *o*-hydroxyacetophenones with aryl aldehydes.[12b] Two common and classic examples have been described, namely (i) H_2O_2-mediated oxidation of α-sulfenylchroman-4-ones[12c] and (ii) nucleophilic substitution of α-bromochroman-4-ones with sodium sulfinates (RSO_2Na).[12d] As a result of recent finding,[12] new methods for the preparation of 3-sulfonylchroman-4-ones are needed. For their preparation, no routes using Umpolung bond formation have been studied.[13,14]



Scheme 1 Synthetic routes toward 3-sulfonylchroman-4-ones

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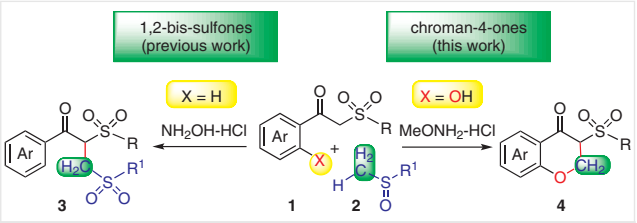
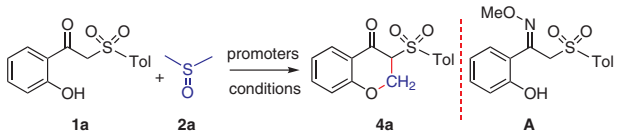
Very recently, we reported the synthesis of α,β-bis-sulfonyl aryl ketones **3** *via* NH_2OH·HCl-mediated Umpolung α-methylsulfonylation of α-sulfonyl ketones **1** (X = H) with methyl sulfoxides **2**, as shown in Scheme 2.[15] Continuing our research on α-sulfonyl *o*-hydroxyacetophenones **1** (X = OH),[12a,b] herein we present the synthesis of 3-sulfonylchroman-4-ones **4** *via* a $MeONH_2$·HCl (2.0 equiv) mediated, one-pot (5+1) annulation process. These results highlight that DMSO with the dual role of reagent and solvent plays a key role in effecting different kinds of products.



Scheme 2 DMSO-mediated reactions

On the basis of our previous NH_2OH·HCl/DMSO combination conditions, the investigation commenced with treating model substrate **1a** (Ar = C_6H_4, R = Tol, X = OH; 1.0 mmol), NH_2OH·HCl (1.1 equiv) and DMSO (**2a**, 2 mL) at 100 °C for 10 hours.[15] In the initial concept, the desired product **3a** (Ar = Ph, R = Tol, R^1 = Me) was anticipated in a modest yield. Unexpectedly, only a complex mixture was produced. Then, after changing the promoter from NH_2OH·HCl to $MeONH_2$·HCl, **4a** was isolated in 52% yield under the reported conditions (Table 1, entry 1). By adjusting the temperature from 100 °C to 25, 80 and 150 °C, for 10 hours, **4a** was isolated in 0%, 42% and 50% yield, respectively (entries 2–4). Under room temperature conditions, the reaction could not be initiated, and starting material **1a** was recovered as the major material. Controlling the temperature at 100 °C, extended reaction times (15 and 20 h) enhanced the isolated yield of **4a** (63%, 60%; entries 5, 6). Accordingly, 15 hours and 100 °C should be the optimal reaction time and temperature, and could be applied to switching the loading of $MeONH_2$·HCl for the (5+1) annulation process. Fortunately, higher yields of **4a** (92% and 89%) were observed with both 2.0 and 3.0 equivalents of $MeONH_2$·HCl (entries 7, 8). Thus, 2.0 equivalents of $MeONH_2$·HCl could provide a better yield of **4a** (92%). Furthermore, the reaction concentration was studied. When the volume of DMSO was changed from 2 mL to 1 or 4 mL, the isolated yields of **4a** (88%, 85%; entries 9, 10) were similar to entry 7 (92%). These results demonstrated that the reaction concentration (1.0, 0.5 and 0.25 M) has little influence on the formation of **4a**. Then, three alternative promoters (Et_3N·HCl, C_5H_5N·HCl, DMPU·HCl; 2 equiv) were used in our investigation of the reaction conditions. In two cases, however, only **1a** was recovered, and no expected **4a** was observed (entries 11, 12). DMPU·HCl provided only a 15% yield of **4a** (entry 13). When the small methyl group of $MeONH_2$·HCl was changed to a bulkier benzyl group, $BnONH_2$·HCl, a lower yield of **4a** was provided (78%, entry 14). To check other methylene sources, four reported solvents were chosen as reagents to screen the reaction conditions (entries 15–18). By replacing DMSO with DMF, DMA, $MeNO_2$ or toluene, however, **4a** could not be generated. With the removal of HCl, only an oxime product was isolated, in 88% yield (entry 19). Free $MeONH_2$ did not promote the Umpolung reaction successfully, so the desired **4a** was not produced. From these observations, we conclude that alkoxy-linked primary amine ($MeONH_2$ or $BnONH_2$), protic acid (HCl) and DMSO are the three key factors that effect the formation of 3-sulfonylchroman-4-ones. The molecular structure of **4a** was determined by single-crystal X-ray analysis.[16]

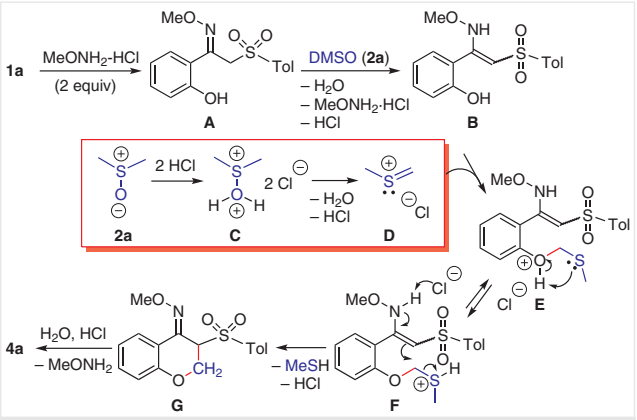
Table 1 Investigation of the Reaction Conditions[a]



Entry	Promoter	Solvent	Time (h)	Temp (°C)	Yield (%) of **4a**[b]
1	$MeONH_2$·HCl	DMSO	10	100	52
2	$MeONH_2$·HCl	DMSO	10	25	–[c]
3	$MeONH_2$·HCl	DMSO	10	80	42
4	$MeONH_2$·HCl	DMSO	10	150	50
5	$MeONH_2$·HCl	DMSO	15	100	63
6	$MeONH_2$·HCl	DMSO	20	100	60
7	$MeONH_2$·HCl[d]	DMSO	15	100	92
8	$MeONH_2$·HCl[e]	DMSO	15	100	89
9	$MeONH_2$·HCl[d]	DMSO[f]	15	100	88
10	$MeONH_2$·HCl[d]	DMSO[g]	15	100	85
11	Et_3N·HCl[d]	DMSO	15	100	–[c]
12	C_5H_5N·HCl[d]	DMSO	15	100	–[c]
13	DMPU·HCl[d]	DMSO	15	100	15
14	$BnONH_2$·HCl[d]	DMSO	15	100	78
15	$MeONH_2$·HCl[d]	DMF	15	100	–[c]
16	$MeONH_2$·HCl[d]	DMA	15	100	–[c]
17	$MeONH_2$·HCl[d]	$MeNO_2$	15	100	–[c]
18	$MeONH_2$·HCl[d]	toluene	15	100	–[c]
19	$MeONH_2$[d]	DMSO	15	100	–[h]

[a] Reaction conditions: **1a** (1.0 mmol), promoter (1.1 equiv), solvent (2 mL); reactions were monitored by TLC.
[b] Isolated yields.
[c] No reaction.
[d] 2.0 equivalents.
[e] 3.0 equivalents.
[f] 1 mL.
[g] 4 mL.
[h] Oxime product **A** (88%) was isolated.

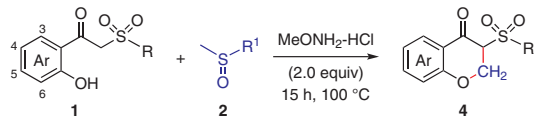
Based on the above experimental results (Table 1), a plausible mechanism for the formation of **4a** is proposed, as illustrated in Scheme 3. Initially, intermolecular condensation of **1a** with 1 equivalent of $MeONH_2$·HCl yields oxime **A** and H_2O. After tautomerization of oxime **A**, enamine **B** with *Z*- and *E*-isomers is generated, and DMSO (**2a**) can trap the released 2 equivalents of HCl (formed *in situ* from $MeONH_2$·HCl) to produce methylsulfonium methylide salt **D** by the removal of HCl and H_2O.[4a] Following the intermolecular conjugation of **B** and **D**, the oxygen atom on the phenol attacks the methylide moiety of **D** to achieve **E**. Furthermore, proton exchange between the oxonium ion and sulfonium ion triggers the transformation from **E** to **F**. After the resulting chloride ion mediated deprotonation of **F**, the enamine forces the elimination of methyl mercaptan (MeSH) such that **G** with a six-membered ring is provided *via* a sequential intramolecular annulation. With the releasing of H_2O and HCl, subsequent hydrolysis of **G** spontaneously forms **4a**. Finally, $MeONH_2$ can be regenerated for the next cycle. From the above reaction pathways, basically, catalytic amounts of $MeONH_2$·HCl are enough to promote the overall reaction, but the reaction efficiency is poor compared with stoichiometric amounts of $MeONH_2$·HCl.



Scheme 3 Plausible mechanism

To study the scope and limitations of this approach, **1a–1y** were reacted with $MeONH_2$·HCl in methyl sulfoxides **2a–2c** to afford products **4a–4y**, as shown in Table 2, entries 1–27. With optimal conditions established (Table 1, entry 7) and a plausible mechanism proposed (Scheme 3), we found that this route allowed direct, one-pot Umpolung cross-couplings under mild conditions in good to excellent yields. By maintaining the Ar group as phenyl (Ar = C_6H_4, entries 1–11) in the reaction of **1a–1k** with DMSO (**2a**, R^1 = Me), sulfonyl group variation showed that R substituents with aliphatic (Me, *n*Bu) or electron-neutral, electron-donating oxygenated or electron-withdrawing aromatic groups were tolerated, and **4a–4k** were obtained in 84–93% yield. Furthermore, by controlling the sulfonyl group as tosyl (R = Tol), the Ar group was changed to other aromatic rings with electron-neutral, electron-donating oxygenated or electron-withdrawing groups. The yields of the provided **4l–4y** (73–87%, entries 12–25) were slightly lower than for **4a–4k**. From these results, we understood that good yields of **4a–4y** can be maintained with different Ar and R groups, which have little influence on the yield outcome. Next, by changing the R^1 group from Me to Ph, the $MeONH_2$·HCl-mediated reaction of **1a** with **2b** was studied (entry 26). However, only an 11% yield of **4a** was isolated along with generation of the major product, oxime **A** (70%). On elongating the time

Table 2 Synthesis of **4a–4y**[a]



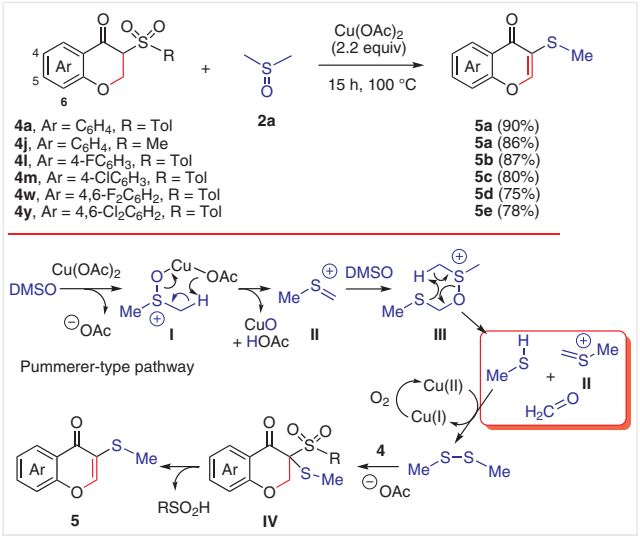
Entry	**1**, Ar, R	**2**, R^1	Yield (%) of **4**[b]
1	**1a**, C_6H_4, Tol	**2a**, Me	**4a**, 92
2	**1b**, C_6H_4, Ph	**2a**, Me	**4b**, 90
3	**1c**, C_6H_4, 4-FC_6H_4	**2a**, Me	**4c**, 86
4	**1d**, C_6H_4, 4-$MeOC_6H_4$	**2a**, Me	**4d**, 87
5	**1e**, C_6H_4, 3-MeC_6H_4	**2a**, Me	**4e**, 87
6	**1f**, C_6H_4, 4-EtC_6H_4	**2a**, Me	**4f**, 90
7	**1g**, C_6H_4, 4-*i*PrC_6H_4	**2a**, Me	**4g**, 93
8	**1h**, C_6H_4, 4-*t*BuC_6H_4	**2a**, Me	**4h**, 86
9	**1i**, C_6H_4, 4-*n*BuC_6H_4	**2a**, Me	**4i**, 84
10	**1j**, C_6H_4, Me	**2a**, Me	**4j**, 84
11	**1k**, C_6H_4, *n*Bu	**2a**, Me	**4k**, 90
12	**1l**, 4-FC_6H_3, Tol	**2a**, Me	**4l**, 87
13	**1m**, 4-ClC_6H_3, Tol	**2a**, Me	**4m**, 84
14	**1n**, 4-BrC_6H_3, Tol	**2a**, Me	**4n**, 87
15	**1o**, 4-MeC_6H_3, Tol	**2a**, Me	**4o**, 86
16	**1p**, 4-$MeOC_6H_3$, Tol	**2a**, Me	**4p**, 87
17	**1q**, 3-$MeOC_6H_3$, Tol	**2a**, Me	**4q**, 80
18	**1r**, 5-$MeOC_6H_3$, Tol	**2a**, Me	**4r**, 83
19	**1s**, 5-*n*BuOC_6H_3, Tol	**2a**, Me	**4s**, 82
20	**1t**, 4-PhC_6H_3, Tol	**2a**, Me	**4t**, 78
21	**1u**, 4-(4-$MeOC_6H_4$)C_6H_3, Tol	**2a**, Me	**4u**, 76
22	**1v**, 4-(4-FC_6H_4)C_6H_3, Tol	**2a**, Me	**4v**, 75
23	**1w**, 4,6-$F_2C_6H_2$, Tol	**2a**, Me	**4w**, 74
24	**1x**, $C_{10}H_6$ (2-naphthyl), Tol	**2a**, Me	**4x**, 73
25	**1y**, 4,6-$Cl_2C_6H_2$, Tol	**2a**, Me	**4y**, 80
26	**1a**, C_6H_4, Tol	**2b**, Ph	**4a**, 11[c]
27	**1a**, C_6H_4, Tol	**2c**, *t*Bu	**4a**, 6[c]

[a] Reaction conditions: **1a–1y** (1.0 mmol), **2a–2c** (2 mL), $MeONH_2$·HCl (167 mg, 2 equiv), 15 h, 100 °C.
[b] Isolated yields.
[c] Oxime product **A** (entry 26, 70%; entry 27, 75%) was isolated.

to 30 hours, the yield of the desired product **4a** was decreased to trace amounts (<5%). On the other hand, treatment of **1a** with *tert*-butyl methyl sulfoxide (**2c**, R^1 = *t*Bu) produced trace amounts of **4a** (6%, entry 27). These results show that a phenyl or *tert*-butyl group on methyl sulfoxide **2** possesses bulkier steric hindrance than the methyl group such that the poor reactivity provides a low yield of **4a**. All products **4a–4y** were obtained as racemates. The molecular structures of **4f** and **4x** were determined by single-crystal X-ray analysis.[16]

With these results in hand, the synthetic application of **4** with **2a** in the presence of $Cu(OAc)_2$ was screened next (Scheme 4). Initially, the $Cu(OAc)_2$-mediated reaction of starting material **4a** with **2a** provided 3-sulfanylchromen-4-one **5a** in 90% yield *via* an α-sulfanylative desulfonylation process. Based on the literature,[17] we understood that the combination of $Cu(OAc)_2$ and DMSO could trigger the generation of three components, namely methyl mercaptan (MeSH), formaldehyde (HCHO) and methylsulfonium methylide ion **II**, *via* the six-membered-ring transition states **I** and **III**. By the involvement of DMSO, the regenerated **II** could be converted into **III** for the overall reaction cycle. Under a Pummerer-type pathway, suspended brownish-black copper oxide (CuO) particles were observed. Subsequently, the *in situ* formed MeSH could be oxidized to dimethyl disulfide (Me_2S_2) by molecular oxygen mediated dimerization.[18] Jain and co-workers have reported a similar phenomenon for the formation of Me_2S_2 *via* $Cu(OAc)_2$-mediated thermal decomposition of DMSO.[19] Then, α-sulfanylation of **4a** with the resulting Me_2S_2 provides **IV**. Subsequent removal of RSO_2H generates **5a**. For the *in situ* desulfonylation,[20] similar results have been reported for the introduction of an unsaturated conjugation system in the synthesis of the quinoxaline skeleton.[5a] After changing the R group from Tol to Me, **4j** was also converted into **5a** (86% yield) based on this synthetic route.[21] Furthermore, by controlling R as the tolyl group, different Ar groups were tested. Treatment of **4l**, **4m**, **4w** and **4y** under the $Cu(OAc)_2$-mediated conditions produced **5b–5e** in 75–87% yield (Scheme 4). The molecular structures of **5a** and **5b** were determined by single-crystal X-ray analysis.[16]

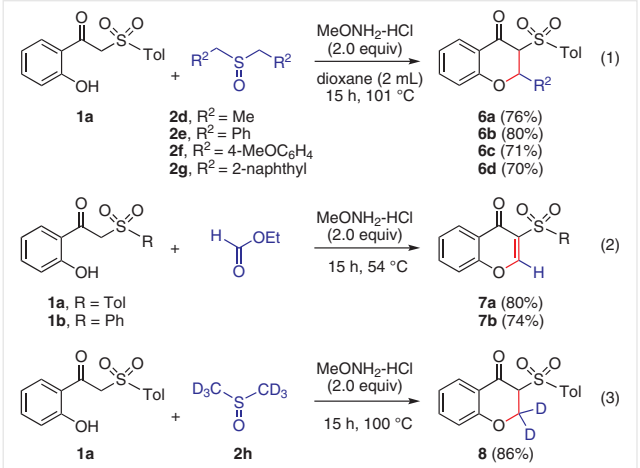
Encouraged by the above results, we chose to replace methyl sulfoxides **2a–2c** by the symmetrical diethyl or dibenzyl sulfoxides **2d–2g** (R^2 = Me, Ph, 4-$MeOC_6H_4$, 2-naphthyl) as the carbon source, as shown in Scheme 5, eq 1. Because sulfoxides **2d–2g** with high boiling points are hard to remove, we used 1.4 equivalents of **2d–2g** to examine the reaction in refluxing dioxane (101 °C). The temperature was similar to the above-mentioned conditions (100 °C). Under the optimal conditions, the expected 3-sulfonylflavan-4-ones **6a–6d** with major *trans*-isomers were afforded in 70–80% yield. By changing the substituents of sulfoxides **2**, chroman-4-ones can be converted into flavan-4-ones. As an extension of the $MeONH_2$·HCl-mediated reaction of **1a**



Scheme 4 Synthesis of **5a–5e**

with DMSO, ethyl formate (a carbonyl synthon) was examined next (eq 2). Using **1a**, **1b** as model substrates, two Knoevenagel cycloadducts **7a**, **7b** with a chromen-4-one skeleton were isolated in 80% and 74% yield, respectively.[22,23] In a subsequent reaction with **1a**, when DMSO (**2a**) was changed to DMSO-d_6 (**2h**, eq 3), **8** was isolated in 86% yield. This important result confirms the proposed reaction mechanism.

In summary, we have developed a facile, one-pot route for synthesizing 3-sulfonylchroman-4-ones *via* $MeONH_2$·HCl-mediated intermolecular Umpolung α-methylenation and sequential intramolecular conjugate addition of α-sulfonyl *o*-hydroxyacetophenones with methyl sulfoxides. Related plausible reaction mechanisms have been proposed. The structures of the key products were confirmed by X-ray crystallography. The effects of various reaction conditions were investigated to optimize this environmentally friendly



Scheme 5 Synthesis of **6a–6d**, **7a**, **7b** and **8**

transformation. Further investigations regarding synthetic applications of α-sulfonyl *o*-hydroxyacetophenones will be conducted and the results reported in due course.

All reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry air, with magnetic stirring. A heating mantle was used to provide a stable heat source. Products in organic solvents were dried with anhydrous $MgSO_4$ before concentration in vacuo. Melting points were determined with an SMP3 melting point apparatus. ^1H and ^{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer operating at 400 and at 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are given in hertz. High-resolution mass spectra were measured with a Finnigan/ThermoQuest MAT 95XL mass spectrometer. X-ray crystal structures were obtained with an Enraf-Nonius FR-590 diffractometer (CAD4, Kappa CCD).

Skeleton 1; General Procedure[12b]

$CuBr_2$ (450 mg, 2.0 mmol) was added to a solution of commercially available, substituted *o*-hydroxyacetophenone (1.0 mmol) in EtOAc (30 mL) at 25 °C. The reaction mixture was stirred at reflux for 10 h. Then, the reaction mixture was cooled to 25 °C, filtered, neutralized with saturated aq $NaHCO_3$ (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure to afford crude product. Without further purification, substituted sodium sulfinate (2.1 mmol) was added to the resulting substituted α-bromo-*o*-hydroxyacetophenone in a cosolvent of dioxane and water [20 mL, 1:1 (v/v)] at 25 °C. The reaction mixture was stirred at reflux for 3 h. Then, the reaction mixture was cooled to 25 °C and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexanes/EtOAc, 10:1–2:1) afforded skeleton **1**, known compounds whose analytical data are consistent with the literature.[12b]

Oxime A and Compounds 4a–4y; General Procedure

$MeONH_2$·HCl (167 mg, 2 mmol) was added to a solution of **1a**–**1y** (1.0 mmol) in **2a**–**2c** (2 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 10 min, then at 100 °C for 15 h. The reaction mixture was cooled to 25 °C, diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexanes/EtOAc, 20:1–10:1) afforded **A** and **4a**–**4y**.

1-(2-Hydroxyphenyl)-2-(toluene-4-sulfonyl)ethanone *O*-Methyloxime (A)

Synthesized from **1a** (290 mg, 1.0 mmol) using $MeONH_2$ (Table 1, entry 19).

Yield: 281 mg (88%); white solid; mp 136–137 °C (recrystallized from hexanes/EtOAc).

^1H NMR (400 MHz, $CDCl_3$): δ = 10.5 (br s, 1 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 7.54 (dd, *J* = 1.6, 8.0 Hz, 1 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.27 (dt, *J* = 1.2, 7.6 Hz, 1 H), 6.96 (d, *J* = 8.4 Hz, 1 H), 6.91 (t, *J* = 7.6 Hz, 1 H), 4.73 (s, 2 H), 3.61 (s, 3 H), 2.43 (s, 3 H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 157.7, 149.9, 145.1, 136.2, 131.5, 129.3 (2 ×), 128.7, 128.6 (2 ×), 119.4, 117.4, 116.1, 62.5, 52.3, 21.6.

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{18}NO_4S$: 320.0957; found: 320.0960.

3-(Toluene-4-sulfonyl)chroman-4-one (4a)

Synthesized from **1a** (290 mg, 1.0 mmol).

Yield: 278 mg (92%); white solid; mp 184–185 °C (recrystallized from hexanes/EtOAc).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (dd, *J* = 1.6, 8.0 Hz, 1 H), 7.70 (d, *J* = 8.4 Hz, 2 H), 7.45 (dt, *J* = 1.6, 8.4 Hz, 1 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 6.99 (dt, *J* = 1.2, 8.4 Hz, 1 H), 6.87 (dd, *J* = 1.2, 8.4 Hz, 1 H), 5.26 (dd, *J* = 2.8, 12.8 Hz, 1 H), 4.70 (dd, *J* = 4.0, 13.2 Hz, 1 H), 4.00 (dd, *J* = 2.8, 4.0 Hz, 1 H), 2.37 (s, 3 H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 182.7, 160.8, 145.6, 136.9, 134.8, 129.5 (2 ×), 129.2 (2 ×), 127.4, 122.0, 120.4, 118.0, 68.6, 65.9, 21.6.

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{15}O_4S$: 303.0691; found: 303.0697.

Single-crystal X-ray analysis: crystals of **4a** were grown by slow diffusion of EtOAc into a solution of **4a** in CH_2Cl_2, which yielded colorless prisms. Compound **4a** crystallized in the monoclinic crystal system, space group $P2_1/c$, *a* = 10.8297(6) Å, *b* = 6.8348(4) Å, *c* = 19.1877(10) Å, *V* = 1372.38(13) $Å^3$, *Z* = 4, d_{calcd} = 1.463 g/cm^3, *F*(000) = 632, 2θ range 1.946–26.423°, *R* indices (all data) R_1 = 0.0333, wR_2 = 0.0756.

3-(Benzenesulfonyl)chroman-4-one (4b)

Synthesized from **1b** (276 mg, 1.0 mmol).

Yield: 259 mg (90%); white solid; mp 141–142 °C (recrystallized from hexanes/EtOAc).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.79 (m, 3 H), 7.57 (dt, *J* = 1.2, 8.4 Hz, 1 H), 7.47–7.45 (m, 3 H), 6.99 (dt, *J* = 1.2, 8.4 Hz, 1 H), 6.86 (dd, *J* = 0.8, 8.4 Hz, 1 H), 5.28 (dd, *J* = 2.8, 12.8 Hz, 1 H), 4.71 (dd, *J* = 4.0, 12.8 Hz, 1 H), 4.04 (dd, *J* = 2.8, 4.0 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 182.5, 160.8, 137.8, 137.0, 134.4, 129.3 (2 ×), 128.9 (2 ×), 127.4, 122.1, 120.4, 118.0, 68.7, 65.9.

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}O_4S$: 289.0535; found: 289.0539.

3-(4-Fluorobenzenesulfonyl)chroman-4-one (4c)

Synthesized from **1c** (294 mg, 1.0 mmol).

Yield: 263 mg (86%); white solid; mp 149–150 °C (recrystallized from hexanes/EtOAc).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.83 (m, 2 H), 7.81 (dd, *J* = 1.6, 8.0 Hz, 1 H), 7.46 (dt, *J* = 2.0, 8.8 Hz, 1 H), 7.14–7.08 (m, 2 H), 7.01 (dt, *J* = 1.2, 8.0 Hz, 1 H), 6.87 (dd, *J* = 0.4, 8.4 Hz, 1 H), 5.29 (dd, *J* = 2.8, 12.8 Hz, 1 H), 4.72 (dd, *J* = 4.0, 12.8 Hz, 1 H), 4.03 (dd, *J* = 2.8, 4.0 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 182.5, 166.2 (d, *J* = 257.0 Hz), 160.7, 137.2, 133.8, 132.3 (d, *J* = 9.8 Hz, 2 ×), 127.5, 122.3, 120.4, 118.1, 116.2 (d, *J* = 22.7 Hz, 2 ×), 68.8, 66.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –105.32 (s, 1 F).

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{12}FO_4S$: 307.0440; found: 307.0449.

3-(4-Methoxybenzenesulfonyl)chroman-4-one (4d)

Synthesized from **1d** (306 mg, 1.0 mmol).

Yield: 277 mg (87%); white solid; mp 117–118 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (dd, *J* = 1.6, 8.0 Hz, 1 H), 7.79 (d, *J* = 8.8 Hz, 2 H), 7.45 (dt, *J* = 2.0, 8.8 Hz, 1 H), 6.99 (dt, *J* = 1.2, 8.0 Hz, 1 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 6.87 (dd, *J* = 2.0, 8.4 Hz, 1 H), 5.26 (dd, *J* = 2.8, 12.8 Hz, 1 H), 4.70 (dd, *J* = 4.0, 12.8 Hz, 1 H), 3.99 (dd, *J* = 2.8, 4.0 Hz, 1 H), 3.82 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.8, 164.3, 160.8, 136.9, 131.6 (2 ×), 129.2, 127.4, 122.0, 120.5, 118.0, 114.1 (2 ×), 68.8, 66.1, 55.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}O_5S$: 319.0640; found: 319.0648.

3-(Toluene-3-sulfonyl)chroman-4-one (4e)

Synthesized from **1e** (290 mg, 1.0 mmol).

Yield: 263 mg (87%); white solid; mp 117–118 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (dd, *J* = 2.0, 8.0 Hz, 1 H), 7.64 (d, *J* = 6.8 Hz, 1 H), 7.63 (s, 1 H), 7.45 (dt, *J* = 1.6, 8.4 Hz, 1 H), 7.38–7.31 (m, 2 H), 7.00 (dt, *J* = 1.2, 8.0 Hz, 1 H), 6.87 (dd, *J* = 0.4, 8.4 Hz, 1 H), 5.28 (dd, *J* = 2.4, 12.8 Hz, 1 H), 4.70 (dd, *J* = 4.0, 12.8 Hz, 1 H), 4.02 (dd, *J* = 2.4, 4.0 Hz, 1 H), 2.35 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.6, 160.8, 139.3, 137.6, 137.0, 135.1, 129.5, 128.8, 127.4, 126.5, 122.1, 120.5, 118.0, 68.7, 66.0, 21.2.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}O_4S$: 303.0691; found: 303.0698.

3-(4-Ethylbenzenesulfonyl)chroman-4-one (4f)

Synthesized from **1f** (304 mg, 1.0 mmol).

Yield: 284 mg (90%); white solid; mp 142–143 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (dd, *J* = 2.0, 8.0 Hz, 1 H), 7.73–7.71 (m, 2 H), 7.42 (dt, *J* = 2.0, 8.8 Hz, 1 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 6.97 (dt, *J* = 1.2, 8.0 Hz, 1 H), 6.84 (dd, *J* = 0.8, 8.4 Hz, 1 H), 5.26 (dd, *J* = 2.4, 12.8 Hz, 1 H), 4.69 (dd, *J* = 4.0, 12.8 Hz, 1 H), 4.01 (dd, *J* = 2.4, 4.0 Hz, 1 H), 2.65 (q, *J* = 7.6 Hz, 2 H), 1.18 (t, *J* = 7.6 Hz, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.6, 160.7, 151.6, 136.9, 134.9, 129.4 (2 ×), 129.3 (2 ×), 127.4, 122.0, 120.4, 118.0, 68.7, 66.0, 28.8, 15.0.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}O_4S$: 317.0848; found: 317.0855.

Single-crystal X-ray analysis: crystals of **4f** were grown by slow diffusion of EtOAc into a solution of **4f** in CH_2Cl_2, which yielded colorless prisms. Compound **4f** crystallized in the triclinic crystal system, space group $P\bar{1}$, *a* = 8.2604(4) Å, *b* = 8.4159(4) Å, *c* = 11.1927(6) Å, *V* = 723.83(6) Å^3, *Z* = 2, d_{calcd} = 1.452 g/cm^3, *F*(000) = 332, 2θ range 2.505–26.432°, *R* indices (all data) R_1 = 0.0721, wR_2 = 0.1749.

3-(4-Isopropylbenzenesulfonyl)chroman-4-one (4g)

Synthesized from **1g** (318 mg, 1.0 mmol).

Yield: 307 mg (93%); white solid; mp 127–128 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (dd, *J* = 1.6, 8.0 Hz, 1 H), 7.73 (d, *J* = 8.4 Hz, 2 H), 7.41 (dt, *J* = 2.0, 8.4 Hz, 1 H), 7.26 (d, *J* = 8.8 Hz, 2 H), 6.97 (dt, *J* = 0.8, 8.0 Hz, 1 H), 6.82 (dd, *J* = 0.8, 8.4 Hz, 1 H), 5.28 (dd, *J* = 2.4, 12.8 Hz, 1 H), 4.69 (dd, *J* = 4.0, 12.8 Hz, 1 H), 4.01 (dd, *J* = 2.4, 4.0 Hz, 1 H), 2.94–2.87 (m, 1 H), 1.19 (d, *J* = 6.8 Hz, 6 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.6, 160.7, 156.1, 136.9, 135.0, 129.5 (2 ×), 127.4, 126.9 (2 ×), 122.0, 120.5, 118.0, 68.8, 66.2, 34.2, 23.5, 23.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}O_4S$: 331.1004; found: 331.1015.

3-(4-*tert*-Butylbenzenesulfonyl)chroman-4-one (4h)

Synthesized from **1h** (332 mg, 1.0 mmol).

Yield: 296 mg (86%); white solid; mp 158–159 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (dd, *J* = 1.6, 8.0 Hz, 1 H), 7.72 (d, *J* = 8.8 Hz, 2 H), 7.39 (d, *J* = 8.8 Hz, 2 H), 7.37 (dt, *J* = 2.0, 8.4 Hz, 1 H), 6.94 (dt, *J* = 0.8, 7.6 Hz, 1 H), 6.78 (dd, *J* = 0.8, 8.4 Hz, 1 H), 5.25 (dd, *J* = 2.4, 12.8 Hz, 1 H), 4.67 (dd, *J* = 4.0, 12.8 Hz, 1 H), 4.02 (dd, *J* = 2.4, 4.0 Hz, 1 H), 1.25 (s, 9 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.6, 160.6, 158.3, 136.8, 134.5, 129.2 (2 ×), 127.3, 125.8 (2 ×), 121.9, 120.4, 117.9, 68.8, 66.2, 35.1, 30.8 (3 ×).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{21}O_4S$: 345.1161; found: 345.1169.

3-(4-*n*-Butylbenzenesulfonyl)chroman-4-one (4i)

Synthesized from **1i** (332 mg, 1.0 mmol).

Yield: 289 mg (84%); white solid; mp 136–137 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (dd, *J* = 1.6, 8.0 Hz, 1 H), 7.72 (d, *J* = 8.8 Hz, 2 H), 7.42 (dt, *J* = 1.6, 8.4 Hz, 1 H), 7.22 (d, *J* = 8.8 Hz, 2 H), 6.98 (dt, *J* = 0.8, 8.0 Hz, 1 H), 6.84 (dd, *J* = 0.4, 8.4 Hz, 1 H), 5.28 (dd, *J* = 2.8, 12.8 Hz, 1 H), 4.69 (dd, *J* = 4.0, 13.2 Hz, 1 H), 4.02 (dd, *J* = 2.8, 4.0 Hz, 1 H), 2.63–2.59 (m, 2 H), 1.57–1.49 (m, 2 H), 1.33–1.24 (m, 2 H), 0.91 (t, *J* = 7.2 Hz, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.6, 160.7, 150.4, 136.9, 134.9, 129.4 (2 ×), 128.9 (2 ×), 127.4, 122.0, 120.5, 118.0, 68.8, 66.1, 35.6, 33.0, 22.1, 13.8.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{21}O_4S$: 345.1161; found: 345.1164.

3-(Methanesulfonyl)chroman-4-one (4j)

Synthesized from **1j** (214 mg, 1.0 mmol).

Yield: 190 mg (84%); white solid; mp 145–146 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.55 (dt, *J* = 1.6, 8.4 Hz, 1 H), 7.09 (dt, *J* = 0.8, 8.0 Hz, 1 H), 7.03 (dd, *J* = 0.8, 8.4 Hz, 1 H), 5.20 (dd, *J* = 4.0, 12.8 Hz, 1 H), 4.77 (dd, *J* = 4.4, 12.8 Hz, 1 H), 3.98 (t, *J* = 4.0 Hz, 1 H), 3.12 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 183.5, 161.2, 137.5, 127.7, 122.4, 120.2, 118.4, 66.4, 64.5, 42.0.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{11}O_4S$: 227.0378; found: 227.0383.

3-(*n*-Butane-1-sulfonyl)chroman-4-one (4k)

Synthesized from **1k** (256 mg, 1.0 mmol).

Yield: 241 mg (90%); colorless gum.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (dd, *J* = 1.6, 8.0 Hz, 1 H), 7.55 (dt, *J* = 2.0, 7.6 Hz, 1 H), 7.08 (dt, *J* = 0.8, 8.0 Hz, 1 H), 7.03 (dd, *J* = 0.8, 8.4 Hz, 1 H), 5.22 (dd, *J* = 4.0, 12.8 Hz, 1 H), 4.77 (dd, *J* = 4.4, 12.8 Hz, 1 H), 3.95 (t, *J* = 4.0 Hz, 1 H), 3.33–3.21 (m, 2 H), 1.93–1.79 (m, 2 H), 1.53–1.43 (m, 2 H), 0.96 (t, *J* = 7.2 Hz, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 183.8, 161.3, 137.4, 127.6, 122.3, 120.4, 118.4, 64.6, 64.5, 53.8, 23.5, 21.6, 13.5.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}O_4S$: 269.0848; found: 269.0852.

6-Fluoro-3-(toluene-4-sulfonyl)chroman-4-one (4l)

Synthesized from **1l** (308 mg, 1.0 mmol).

Yield: 278 mg (87%); white solid; mp 186–187 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.4 Hz, 2 H), 7.46 (dd, *J* = 3.2, 8.0 Hz, 1 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.19 (ddt, *J* = 3.2, 4.0, 9.2 Hz, 1 H), 6.89 (dd, *J* = 4.0, 9.2 Hz, 1 H), 5.28 (dd, *J* = 2.4, 12.8 Hz, 1 H), 4.68 (dd, *J* = 4.0, 12.8 Hz, 1 H), 3.99 (dd, *J* = 2.4, 4.0 Hz, 1 H), 2.40 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.1, 157.4 (d, *J* = 241.9 Hz), 157.1, 145.8, 130.3, 129.65 (2 ×), 129.3 (2 ×), 124.6 (d, *J* = 25.1 Hz), 120.8 (d, *J* = 6.8 Hz), 119.9 (d, *J* = 7.6 Hz), 112.3 (d, *J* = 23.5 Hz), 68.3, 66.1, 21.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –122.12 (s, 1 F).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}FO_4S$: 321.0597; found: 321.0602.

6-Chloro-3-(toluene-4-sulfonyl)chroman-4-one (4m)

Synthesized from **1m** (324 mg, 1.0 mmol).

Yield: 282 mg (84%); white solid; mp 154–155 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 2.8 Hz, 1 H), 7.69 (d, *J* = 8.4 Hz, 2 H), 7.40 (dd, *J* = 2.8, 9.2 Hz, 1 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 6.88 (d, *J* = 8.8 Hz, 1 H), 5.31 (dd, *J* = 2.8, 12.8 Hz, 1 H), 4.69 (dd, *J* = 4.0, 12.8 Hz, 1 H), 3.98 (dd, *J* = 2.4, 4.0 Hz, 1 H), 2.41 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 181.8, 159.3, 145.9, 136.8, 134.7, 129.7 (2 ×), 129.2 (2 ×), 127.7, 126.6, 121.1, 119.9, 68.2, 66.0, 21.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}ClO_4S$: 337.0301; found: 337.0308.

6-Bromo-3-(toluene-4-sulfonyl)chroman-4-one (4n)

Synthesized from **1n** (368 mg, 1.0 mmol).

Yield: 331 mg (87%); white solid; mp 190–191 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 2.4 Hz, 1 H), 7.69 (d, *J* = 8.0 Hz, 2 H), 7.54 (dd, *J* = 2.4, 8.8 Hz, 1 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 5.30 (dd, *J* = 2.4, 12.8 Hz, 1 H), 4.68 (dd, *J* = 4.0, 12.8 Hz, 1 H), 3.98 (dd, *J* = 2.4, 4.0 Hz, 1 H), 2.41 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 181.7, 159.7, 145.9, 139.5, 134.6, 129.74, 129.71 (2 ×), 129.2 (2 ×), 121.6, 120.2, 114.8, 68.2, 66.0, 21.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}BrO_4S$: 380.9796; found: 380.9805.

6-Methyl-3-(toluene-4-sulfonyl)chroman-4-one (4o)

Synthesized from **1o** (304 mg, 1.0 mmol).

Yield: 272 mg (86%); white solid; mp 172–173 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.4 Hz, 2 H), 7.60 (dd, *J* = 1.2, 1.6 Hz, 1 H), 7.28–7.25 (m, 3 H), 6.79 (d, *J* = 8.4 Hz, 1 H), 5.23 (dd, *J* = 2.4, 12.8 Hz, 1 H), 4.67 (dd, *J* = 4.0, 12.8 Hz, 1 H), 3.97 (dd, *J* = 2.8, 4.0 Hz, 1 H), 2.39 (s, 3 H), 2.37 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.8, 159.0, 145.5, 138.1, 135.0, 131.6, 129.6 (2 ×), 129.2 (2 ×), 126.9, 120.1, 117.9, 68.6, 65.9, 21.6, 20.3.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}O_4S$: 317.0848; found: 317.0853.

6-Methoxy-3-(toluene-4-sulfonyl)chroman-4-one (4p)

Synthesized from **1p** (320 mg, 1.0 mmol).

Yield: 289 mg (87%); white solid; mp 152–153 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.4 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 7.21 (d, *J* = 3.2 Hz, 1 H), 7.07 (dd, *J* = 3.2, 8.8 Hz, 1 H), 6.81 (d, *J* = 8.8 Hz, 1 H), 5.23 (dd, *J* = 2.8, 12.8 Hz, 1 H), 4.66 (dd, *J* = 4.0, 12.8 Hz, 1 H), 3.98 (dd, *J* = 2.8, 4.0 Hz, 1 H), 3.77 (s, 3 H), 2.39 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.7, 155.7, 154.5, 145.6, 135.0, 129.6 (2 ×), 129.5, 129.3 (2 ×), 126.5, 119.4, 107.3, 68.5, 66.1, 55.8, 21.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}O_5S$: 333.0797; found: 333.0805.

5-Methoxy-3-(toluene-4-sulfonyl)chroman-4-one (4q)

Synthesized from **1q** (320 mg, 1.0 mmol).

Yield: 266 mg (80%); white solid; mp 132–133 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.4 Hz, 2 H), 7.35 (t, *J* = 8.4 Hz, 1 H), 7.26–7.23 (m, 2 H), 6.48 (d, *J* = 8.4 Hz, 2 H), 5.19 (dd, *J* = 2.8, 12.8 Hz, 1 H), 4.64 (dd, *J* = 4.0, 12.8 Hz, 1 H), 3.96 (dd, *J* = 2.8, 4.0 Hz, 1 H), 3.87 (s, 3 H), 2.38 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 190.7, 162.3, 161.2, 145.3, 139.6, 136.9, 135.3, 129.5 (2 ×), 129.2 (2 ×), 109.9, 104.3, 69.7, 65.4, 56.2, 21.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}O_5S$: 333.0797; found: 333.0789.

7-Methoxy-3-(toluene-4-sulfonyl)chroman-4-one (4r)

Synthesized from **1r** (320 mg, 1.0 mmol).

Yield: 276 mg (83%); white solid; mp 133–134 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.8 Hz, 1 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 7.2 Hz, 2 H), 6.57 (dd, *J* = 2.4, 8.8 Hz, 1 H), 6.32 (d, *J* = 2.4 Hz, 1 H), 5.27 (dd, *J* = 2.8, 12.8 Hz, 1 H), 4.69 (dd, *J* = 4.0, 12.8 Hz, 1 H), 3.94 (dd, *J* = 2.8, 4.0 Hz, 1 H), 3.82 (s, 3 H), 2.40 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 181.0, 166.9, 163.0, 145.4, 135.0, 129.6 (2 ×), 129.3, 129.2 (2 ×), 114.4, 111.1, 100.6, 68.4, 66.1, 55.7, 21.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}O_5S$: 333.0797; found: 333.0806.

7-*n*-Butoxy-3-(toluene-4-sulfonyl)chroman-4-one (4s)

Synthesized from **1s** (362 mg, 1.0 mmol).

Yield: 307 mg (82%); white solid; mp 63–64 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 9.2 Hz, 1 H), 7.70 (d, *J* = 8.4 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 6.54 (dd, *J* = 2.4, 8.8 Hz, 1 H), 6.29 (d, *J* = 2.4 Hz, 1 H), 5.24 (dd, *J* = 2.4, 12.8 Hz, 1 H), 4.67 (dd, *J* = 4.0, 12.4 Hz, 1 H), 3.98–3.92 (m, 3 H), 2.39 (s, 3 H), 1.79–1.72 (m, 2 H), 1.51–1.42 (m, 2 H), 0.97 (t, *J* = 7.2 Hz, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 180.9, 166.4, 162.9, 145.4, 135.0, 129.5 (2 ×), 129.2 (3 ×), 114.2, 111.4, 101.0, 68.4, 68.3, 66.1, 30.8, 21.6, 19.1, 13.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}O_5S$: 375.1266; found: 375.1275.

6-Phenyl-3-(toluene-4-sulfonyl)chroman-4-one (4t)

Synthesized from **1t** (366 mg, 1.0 mmol).

Yield: 295 mg (78%); white solid; mp 191–192 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 2.4 Hz, 1 H), 7.74–7.70 (m, 3 H), 7.54–7.52 (m, 2 H), 7.45–7.42 (m, 2 H), 7.37–7.33 (m, 1 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 6.98 (d, *J* = 8.8 Hz, 1 H), 5.33 (dd, *J* = 2.8, 13.2 Hz, 1 H), 4.74 (dd, *J* = 4.0, 12.8 Hz, 1 H), 4.03 (dd, *J* = 2.8, 4.0 Hz, 1 H), 2.38 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.8, 160.2, 145.6, 139.1, 135.6, 129.6 (2 ×), 129.1 (2 ×), 129.0 (3 ×), 128.9, 127.6, 126.7 (2 ×), 125.4, 120.5, 118.6, 68.7, 66.0, 21.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}O_4S$: 379.1004; found: 379.1015.

6-(4-Methoxyphenyl)-3-(toluene-4-sulfonyl)chroman-4-one (4u)

Synthesized from **1u** (396 mg, 1.0 mmol).

Yield: 310 mg (76%); white solid; mp 115–116 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 2.4 Hz, 1 H), 7.73 (d, *J* = 8.4 Hz, 2 H), 7.66 (dd, *J* = 2.4, 8.4 Hz, 1 H), 7.44 (d, *J* = 8.8 Hz, 2 H), 7.27–7.25 (m, 2 H), 6.99–6.94 (m, 3 H), 5.31 (dd, *J* = 2.8, 12.8 Hz, 1 H), 4.73 (dd, *J* = 4.0, 12.8 Hz, 1 H), 4.02 (dd, *J* = 2.8, 4.0 Hz, 1 H), 3.85 (s, 3 H), 2.38 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.8, 160.0, 159.8, 145.6, 135.3, 135.0, 129.6 (2 ×), 129.5, 129.3 (2 ×), 129.0, 128.2, 127.8 (2 ×), 124.7, 118.5, 114.3 (2 ×), 68.7, 66.0, 55.4, 21.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{21}O_5S$: 409.1110; found: 409.1118.

6-(4-Fluorophenyl)-3-(toluene-4-sulfonyl)chroman-4-one (4v)

Synthesized from **1v** (384 mg, 1.0 mmol).

Yield: 297 mg (75%); white solid; mp 164–165 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 2.4 Hz, 1 H), 7.73 (d, *J* = 8.0 Hz, 2 H), 7.66 (dd, *J* = 2.4, 8.4 Hz, 1 H), 7.50–7.46 (m, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.14–7.10 (m, 2 H), 6.99 (d, *J* = 8.8 Hz, 1 H), 5.34 (dd, *J* = 2.8, 12.8 Hz, 1 H), 4.74 (dd, *J* = 4.0, 12.8 Hz, 1 H), 4.02 (dd, *J* = 2.8, 4.0 Hz, 1 H), 2.39 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.8, 162.6 (d, *J* = 245.6 Hz), 160.2, 145.7, 135.5, 134.9, 134.4, 129.7 (2 ×), 129.5, 129.3 (2 ×), 129.0, 128.3 (d, *J* = 8.3 Hz, 2 ×), 125.3, 118.7, 115.8 (d, *J* = 21.9 Hz, 2 ×), 68.6, 66.0, 21.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{18}FO_4S$: 397.0910; found: 397.0917.

6,8-Difluoro-3-(toluene-4-sulfonyl)chroman-4-one (4w)

Synthesized from **1w** (326 mg, 1.0 mmol).

Yield: 250 mg (74%); white solid; mp 173–174 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.4 Hz, 2 H), 7.31–7.28 (m, 3 H), 7.08–7.03 (m, 1 H), 5.37 (dd, *J* = 2.4, 13.2 Hz, 1 H), 4.74 (dd, *J* = 4.0, 12.8 Hz, 1 H), 4.03 (dd, *J* = 2.4, 4.0 Hz, 1 H), 2.40 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 181.1, 159.1, 156.0 (dd, *J* = 9.8, 244.8 Hz), 151.4 (dd, *J* = 11.3, 253.2 Hz), 146.0, 134.5, 129.7 (2 ×), 129.3 (2 ×), 122.0, 111.8 (dd, *J* = 21.2, 28.0 Hz), 107.6 (dd, *J* = 3.8, 22.7 Hz), 68.5, 66.8, 21.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –122.38 (dt, *J* = 1.5, 8.6 Hz, 1 F), –124.16 (dt, *J* = 1.9, 10.9 Hz, 1 F).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}F_2O_4S$: 339.0503; found: 339.0506.

3-(Toluene-4-sulfonyl)benzo[*h*]chroman-4-one (4x)

Synthesized from **1x** (340 mg, 1.0 mmol).

Yield: 257 mg (73%); white solid; mp 185–186 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (dd, *J* = 0.4, 8.4 Hz, 1 H), 7.75–7.73 (m, 2 H), 7.68 (d, *J* = 8.4 Hz, 2 H), 7.62 (dt, *J* = 1.2, 8.0 Hz, 1 H), 7.52 (dt, *J* = 1.2, 8.0 Hz, 1 H), 7.36 (d, *J* = 8.4 Hz, 1 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 5.54 (dd, *J* = 2.4, 12.8 Hz, 1 H), 4.89 (dd, *J* = 4.0, 12.8 Hz, 1 H), 4.08 (dd, *J* = 2.4, 4.0 Hz, 1 H), 2.18 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.0, 159.3, 145.5, 134.6, 130.3, 129.6, 129.4 (2 ×), 129.2 (2 ×), 127.7, 126.5, 124.3, 123.7, 121.8, 121.5, 120.3, 68.4, 66.6, 21.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{17}O_4S$: 353.0848; found: 353.0852.

Single-crystal X-ray analysis: crystals of **4x** were grown by slow diffusion of EtOAc into a solution of **4x** in CH_2Cl_2, which yielded colorless prisms. Compound **4x** crystallized in the monoclinic crystal system, space group $P2_1/c$, *a* = 14.1887(5) Å, *b* = 5.9979(2) Å, *c* = 19.5252(7) Å, *V* = 1626.57(10) Å^3, *Z* = 4, d_{calcd} = 1.487 g/cm^3, *F*(000) = 758, 2θ range 2.131–26.373°, *R* indices (all data) R_1 = 0.0409, wR_2 = 0.0976.

6,8-Dichloro-3-(toluene-4-sulfonyl)chroman-4-one (4y)

Synthesized from **1y** (358 mg, 1.0 mmol).

Yield: 296 mg (80%); white solid; mp 120–121 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.68 (m, 3 H), 7.51 (d, *J* = 2.4 Hz, 1 H), 7.27 (d, *J* = 7.6 Hz, 2 H), 5.42 (dd, *J* = 2.4, 12.8 Hz, 1 H), 4.74 (dd, *J* = 4.0, 12.8 Hz, 1 H), 4.02 (dd, *J* = 2.4, 4.0 Hz, 1 H), 2.40 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 181.2, 155.0, 146.1, 136.3, 134.4, 129.7 (2 ×), 129.3 (2 ×), 127.3, 125.3, 124.2, 121.9, 68.1, 66.6, 21.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}Cl_2O_4S$: 370.9912; found: 370.9921.

Compounds 5a–5e; General Procedure

$Cu(OAc)_2$ (200 mg, 1.1 mmol) was added to a solution of **4a**, **4j**, **4l**, **4m**, **4w** or **4y** (0.5 mmol) in DMSO (**2a**, 2 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 10 min, then at 100 °C for 15 h. The reaction mixture was cooled to 25 °C, diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexanes/EtOAc, 20:1–10:1) afforded **5a–5e**.

3-(Methylsulfanyl)chromen-4-one (5a)

Synthesized from **4a** (151 mg, 0.5 mmol) or **4j** (113 mg, 0.5 mmol).

Yield from **4a**: 86 mg (90%); yield from **4j**: 83 mg (86%); white solid; mp 87–88 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (dd, *J* = 1.6, 8.0 Hz, 1 H), 8.04 (s, 1 H), 7.67 (dt, *J* = 1.6, 8.8 Hz, 1 H), 7.44 (d, *J* = 8.4 Hz, 1 H), 7.41 (dt, *J* = 1.2, 8.0 Hz, 1 H), 2.40 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 175.6, 156.2, 153.9, 133.8, 126.0, 125.4, 123.1, 121.8, 118.0, 16.2.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_9O_2S$: 193.0323; found: 193.0330.

Single-crystal X-ray analysis: crystals of **5a** were grown by slow diffusion of EtOAc into a solution of **5a** in CH_2Cl_2, which yielded colorless prisms. Compound **5a** crystallized in the monoclinic crystal system, space group $P2_1/n$, *a* = 10.3835(5) Å, *b* = 7.5647(5) Å, *c* = 12.3143(7) Å, *V* = 878.12(9) Å^3, *Z* = 4, d_{calcd} = 1.454 g/cm^3, *F*(000) = 400, 2θ range 2.165–26.425°, *R* indices (all data) R_1 = 0.0441, wR_2 = 0.1018.

6-Fluoro-3-(methylsulfanyl)chromen-4-one (5b)

Synthesized from **4l** (160 mg, 0.5 mmol).

Yield: 91 mg (87%); white solid; mp 135–136 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (s, 1 H), 7.86 (ddd, *J* = 0.4, 3.2, 8.0 Hz, 1 H), 7.47 (ddd, *J* = 0.4, 4.4, 9.2 Hz, 1 H), 7.39 (dt, *J* = 3.2, 9.2 Hz, 1 H), 2.39 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 174.9 (d, *J* = 2.3 Hz), 159.6 (d, *J* = 245.6 Hz), 153.9, 152.5, 124.2 (d, *J* = 7.6 Hz), 122.1 (d, *J* = 25.0 Hz), 121.4, 120.2 (d, *J* = 8.3 Hz), 110.8 (d, *J* = 23.5 Hz), 16.2.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_8FO_2S$: 211.0229; found: 211.0232.

Single-crystal X-ray analysis: crystals of **5b** were grown by slow diffusion of EtOAc into a solution of **5b** in CH_2Cl_2, which yielded colorless prisms. Compound **5b** crystallized in the triclinic crystal system, space group $P\bar{1}$, *a* = 3.9228(5) Å, *b* = 5.7519(9) Å, *c* = 19.400(3) Å, *V* = 436.52(11) Å^3, *Z* = 2, d_{calcd} = 1.599 g/cm^3, *F*(000) = 216, 2θ range 1.051–26.516°, *R* indices (all data) R_1 = 0.0956, wR_2 = 0.2494.

6-Chloro-3-(methylsulfanyl)chromen-4-one (5c)

Synthesized from **4m** (168 mg, 0.5 mmol).

Yield: 90 mg (80%); white solid; mp 132–133 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (dd, *J* = 0.4, 2.8 Hz, 1 H), 8.03 (s, 1 H), 7.61 (dd, *J* = 2.8, 8.8 Hz, 1 H), 7.42 (dd, *J* = 0.4, 8.8 Hz, 1 H), 2.40 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 174.5, 154.6, 153.7, 134.0, 131.4, 125.4, 124.0, 122.2, 119.8, 16.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_8ClO_2S$: 226.9934; found: 226.9941.

6,8-Difluoro-3-(methylsulfanyl)chromen-4-one (5d)

Synthesized from **4w** (169 mg, 0.5 mmol).

Yield: 86 mg (75%); white solid; mp 163–164 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (s, 1 H), 7.70–7.67 (m, 1 H), 7.28–7.22 (m, 1 H), 2.41 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 173.8, 158.4 (dd, *J* = 9.1, 247.9 Hz), 153.3, 152.9, 151.4 (dd, *J* = 11.4, 256.2 Hz), 125.1 (d, *J* = 7.6 Hz), 122.5, 109.3 (dd, *J* = 19.7, 28.1 Hz), 106.2 (dd, *J* = 4.5, 23.5 Hz), 16.0.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_7F_2O_2S$: 229.0135; found: 229.0143.

6,8-Dichloro-3-(methylsulfanyl)chromen-4-one (5e)

Synthesized from **4y** (185 mg, 0.5 mmol).

Yield: 101 mg (78%); white solid; mp 121–122 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 2.4 Hz, 1 H), 8.05 (s, 1 H), 7.72 (d, *J* = 2.4 Hz, 1 H), 2.40 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 173.8, 152.9, 150.6, 133.9, 131.1, 124.6, 124.3, 124.2, 123.1, 15.8.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_7Cl_2O_2S$: 260.9544; found: 260.9550.

Compounds 6a–6d; General Procedure

$MeONH_2$·HCl (84 mg, 1 mmol) was added to a solution of **1a** (145 mg, 0.5 mmol) and **2d**–**2g** (0.7 mmol) in dioxane (2 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 10 min, then at reflux (101 °C) for 15 h. The reaction mixture was cooled to 25 °C, diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexanes/EtOAc, 20:1–10:1) afforded **6a**–**6d**.

2-Methyl-3-(toluene-4-sulfonyl)chroman-4-one (6a)

Yield: 120 mg (76%); two isomers, ratio >10:1; colorless solid; mp 59–61 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ (major isomer) = 7.76 (ddd, *J* = 0.4, 1.6, 8.0 Hz, 1 H), 7.63 (d, *J* = 8.4 Hz, 2 H), 7.43 (ddd, *J* = 1.6, 7.2, 8.8 Hz, 1 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 6.94 (dt, *J* = 1.2, 8.4 Hz, 1 H), 6.79 (dd, *J* = 0.4, 8.4 Hz, 1 H), 5.61 (dq, *J* = 1.2, 6.8 Hz, 1 H), 3.82 (d, *J* = 1.6 Hz, 1 H), 2.35 (s, 3 H), 1.44 (d, *J* = 6.8 Hz, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.6, 158.2, 145.5, 137.2, 134.3, 129.4 (2 ×), 129.2 (2 ×), 126.8, 121.5, 119.8, 118.5, 73.6, 71.9, 21.6, 18.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}O_4S$: 317.0848; found: 317.0840.

2-Phenyl-3-(toluene-4-sulfonyl)chroman-4-one (6b)

Yield: 151 mg (80%); colorless solid; mp 131–133 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.70 (m, 3 H), 7.46 (dt, *J* = 1.6, 8.4 Hz, 1 H), 7.27–7.19 (m, 7 H), 6.95 (dd, *J* = 0.8, 7.6 Hz, 1 H), 6.91 (dd, *J* = 0.8, 8.4 Hz, 1 H), 6.57 (s, 1 H), 4.39 (d, *J* = 1.6 Hz, 1 H), 2.38 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.0, 159.0, 145.7, 137.4, 136.2, 134.2, 129.6 (2 ×), 129.4 (2 ×), 129.0 (2 ×), 128.7, 126.9, 126.1 (2 ×), 121.7, 120.8, 118.2, 76.2, 73.0, 21.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}O_4S$: 379.1004; found: 379.1009.

2-(4-Methoxyphenyl)-3-(toluene-4-sulfonyl)chroman-4-one (6c)

Yield: 145 mg (71%); colorless solid; mp 121–123 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.68 (m, 3 H), 7.42 (dt, *J* = 1.6, 8.4 Hz, 1 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 6.92 (dt, *J* = 0.8, 8.0 Hz, 1 H), 6.85 (dd, *J* = 0.8, 8.4 Hz, 1 H), 6.77 (d, *J* = 8.8 Hz, 2 H), 6.50 (s, 1 H), 4.38 (d, *J* = 0.8 Hz, 1 H), 3.71 (s, 3 H), 2.37 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.3, 159.7, 158.8, 145.6, 137.2, 134.3, 129.5 (2 ×), 129.3 (2 ×), 128.0, 127.6 (2 ×), 126.8, 121.6, 120.7, 118.3, 114.3 (2 ×), 76.0, 72.8, 55.2, 21.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{21}O_5S$: 409.1110; found: 409.1117.

2-(Naphthalen-2-yl)-3-(toluene-4-sulfonyl)chroman-4-one (6d)

Yield: 150 mg (70%); colorless solid; mp 141–143 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.68 (m, 6 H), 7.58 (br s, 1 H), 7.48–7.39 (m, 4 H), 7.26 (d, *J* = 8.8 Hz, 2 H), 6.96–6.91 (m, 2 H), 6.73 (s, 1 H), 4.57 (d, *J* = 1.2 Hz, 1 H), 2.39 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.1, 158.9, 145.7, 137.4, 134.3, 133.4, 132.9, 132.7, 129.6 (2 ×), 129.4 (2 ×), 129.2, 128.1, 127.5, 126.9, 126.8, 126.7, 125.5, 123.6, 121.8, 120.8, 118.3, 76.2, 72.6, 21.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{21}O_4S$: 429.1161; found: 429.1169.

Compounds 7a, 7b; General Procedure

$MeONH_2$·HCl (84 mg, 1 mmol) was added to a solution of **1a** or **1b** (0.5 mmol) in HCO_2Et (2 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 10 min, then at reflux (54 °C) for 15 h. The reaction mixture was cooled to 25 °C, diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexanes/EtOAc, 20:1–10:1) afforded **7a**, **7b**.

3-(Toluene-4-sulfonyl)chromen-4-one (7a)

Synthesized from **1a** (145 mg, 0.5 mmol).

Yield: 120 mg (80%); white solid; mp 230–231 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.89 (s, 1 H), 8.16 (dd, *J* = 1.6, 8.0 Hz, 1 H), 8.05 (d, *J* = 8.4 Hz, 2 H), 7.72 (dt, *J* = 2.0, 8.8 Hz, 1 H), 7.52 (dd, *J* = 0.8, 8.4 Hz, 1 H), 7.44 (dt, *J* = 1.2, 8.0 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 2.41 (s, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 171.5, 160.2, 156.0, 145.0, 136.7, 134.9, 129.5 (2 ×), 129.0 (2 ×), 126.7, 126.6, 126.2, 124.6, 118.4, 21.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}O_4S$: 301.0535; found: 301.0542.

3-(Benzenesulfonyl)chromen-4-one (7b)

Synthesized from **1b** (138 mg, 0.5 mmol).

Yield: 106 mg (74%); white solid; mp 211–212 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.91 (s, 1 H), 8.20–8.15 (m, 3 H), 7.73 (dt, *J* = 2.0, 8.8 Hz, 1 H), 7.63 (dt, *J* = 1.6, 8.8 Hz, 1 H), 7.57–7.52 (m, 3 H), 7.46 (dt, *J* = 0.8, 8.0 Hz, 1 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 171.4, 160.4, 156.0, 139.6, 135.0, 133.9, 128.93 (2 ×), 128.89 (2 ×), 126.8, 126.4, 126.3, 124.6, 118.5.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}O_4S$: 287.0378; found: 287.0385.

3-(Toluene-4-sulfonyl)chroman-4-one-2,2-*d*$_2$ (8)

$MeONH_2$·HCl (167 mg, 2 mmol) was added to a solution of **1a** (290 mg, 1.0 mmol) in DMSO-d_6 (**2h**, 2 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 10 min, then at 100 °C for 15 h. The reaction mixture was cooled to 25 °C, diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexanes/EtOAc, 20:1–10:1) afforded **8**.

Yield: 261 mg (86%); white solid; mp 181–182 °C (recrystallized from hexanes/EtOAc).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.82 (ddd, *J* = 0.6, 1.8, 7.8 Hz, 1 H), 7.72 (d, *J* = 8.4 Hz, 2 H), 7.46 (dt, *J* = 1.8, 8.4 Hz, 1 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 7.00 (dt, *J* = 0.6, 7.8 Hz, 1 H), 6.88 (dd, *J* = 0.6, 8.4 Hz, 1 H), 4.00 (s, 1 H), 2.39 (s, 3 H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 182.7, 160.8, 145.6, 136.9, 134.9, 129.6 (2 ×), 129.3 (2 ×), 127.5, 122.1, 120.5, 118.1, 68.5, 65.4 (quintet, *J* = 19.0 Hz, CD_2), 21.6.

^{2}H NMR (92 MHz, CH_2Cl_2): δ = 4.89 (d, *J* = 47.7 Hz, 2 D).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}D_2O_4S$: 305.0815; found: 305.0820.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707245. Included are scanned photocopies of NMR spectra for all compounds and X-ray analysis data of **4a**, **4f**, **4x**, **5a** and **5b**.

References

(1) Xiang, J.-C.; Gao, Q.-H.; Wu, A.-X. *The Applications of DMSO*, In *Solvents as Reagents in Organic Synthesis: Reactions and Applications*; Wu, X.-F., Ed.; Wiley-VCH: Weinheim, **2017**, Chap. 7.

(2) Recent examples for CH_2Cl_2, see: (a) Liu, Y.; Song, R.-J.; Luo, S.; Li, J.-H. *Org. Lett.* **2018**, *20*, 212. (b) Zhao, Y.; Chen, X.; Chen, T.; Zhou, Y.; Yin, S.-F.; Han, L.-B. *J. Org. Chem.* **2015**, *80*, 62. (c) Chen, X.; Chen, T.; Zhou, Y.; Au, C.-T.; Han, L.-B.; Yin, S.-F. *Org. Biomol. Chem.* **2014**, *12*, 247. (d) Yu, D.; Zhang, Y. *Adv. Synth. Catal.* **2011**, *353*, 163.

(3) Recent examples for DMF and DMA, see: (a) Pu, F.; Li, Y.; Song, Y.-H.; Xiao, J.; Liu, Z.-W.; Wang, C.; Liu, Z.-T.; Chen, J.-G.; Lu, J. *Adv. Synth. Catal.* **2016**, *358*, 539. (b) Modi, A.; Ali, W.; Patel, B. K. *Adv. Synth. Catal.* **2016**, *358*, 2100. (c) Kaswan, P.; Nandwana, N. K.; DeBoef, B.; Kumar, A. *Adv. Synth. Catal.* **2016**, *358*, 2108.

(4) Recent examples for DMSO, see: (a) Ebule, R.; Mudshinge, S.; Nantz, M. H.; Mashuta, M. S.; Hammond, G. B.; Xu, B. *J. Org. Chem.* **2019**, *84*, 3249. (b) Wen, Z.-K.; Liu, X.-H.; Liu, Y.-F.; Chao, J.-B. *Org. Lett.* **2017**, *19*, 5798. (c) Xue, L.; Cheng, G.; Zhu, R.; Cui, X. *RSC Adv.* **2017**, *7*, 44009. (d) Sun, K.; Zhu, Z. H.; Sun, J. J.; Liu, L. L.; Wang, X. *J. Org. Chem.* **2016**, *81*, 1476. (e) Li, P. F.; Weng, Y. X.; Xu, X. X.; Cui, X. L. *J. Org. Chem.* **2016**, *81*, 3994. (f) Patel, O. P. S.; Anand, D.; Maurya, R. K.; Yadav, P. P. *J. Org. Chem.* **2016**, *81*, 7626. (g) Liu, P.; Shen, Z. Y.; Yuan, Y.; Sun, P. P. *Org. Biomol. Chem.* **2016**, *14*, 6523. (h) Sun, K.; Wang, X.; Jiang, Y.; Lv, Y.; Zhang, L.; Xiao, B.; Li, D.; Zhu, Z.; Liu, L. *Chem. Asian J.* **2015**, *10*, 536. (i) Mahajan, P. S.; Tanpure, S. D.; More, N. A.; Gajbhiye, J. M.; Mhaske, S. B. *RSC Adv.* **2015**, *5*, 101641. (j) Sun, K.; Lv, Y.;

Zhu, Z.; Zhang, L.; Wu, H.; Liu, L.; Jiang, Y.; Xiao, B.; Wang, X. *RSC Adv.* **2015**, *5*, 3094. (k) Wang, J.; Rochon, F. D.; Yang, Y.; Hua, L.; Kayser, M. M. *Tetrahedron: Asymmetry* **2007**, *18*, 1115.

(5) Recent examples for toluene, see: (a) Luo, W. K.; Shi, X.; Zhou, W.; Yang, L. *Org. Lett.* **2016**, *18*, 2036. (b) Li, K.; Wu, Q.; Lan, J.; You, J. *Nat. Commun.* **2015**, *6*, 8404.

(6) Recent examples for MeCN, see: (a) Wang, C.; Li, Y.; Gong, M.; Wu, Q.; Zhang, J.; Kim, J. K.; Huang, M.; Wu, Y. *Org. Lett.* **2016**, *18*, 4151. (b) Bunescu, A.; Wang, Q.; Zhu, J. *Org. Lett.* **2015**, *17*, 1890. (c) Li, Y.; Liu, B.; Li, H.-B.; Wang, Q.; Li, J.-H. *Chem. Commun.* **2015**, *51*, 1024.

(7) Recent examples for $MeNO_2$, see: (a) Padilla-Salinas, R.; Walvoord, R. R.; Tcyrulnikov, S.; Kozlowski, M. C. *Org. Lett.* **2013**, *15*, 3966. (b) Akagawa, K.; Kudo, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 12786.

(8) Reviews on DMSO-mediated reactions, see: (a) Jones-Mensah, E.; Karki, M.; Magolan, J. *Synthesis* **2016**, *48*, 1421. (b) Wu, X.-F.; Natte, K. *Adv. Synth. Catal.* **2016**, *358*, 336. (c) Tashrifi, Z.; Khanaposhtani, M. M.; Larijani, B.; Mahdavia, M. *Adv. Synth. Catal.* **2020**, *362*, 65.

(9) Examples of DMSO-mediated α-methylenation, see: (a) Zhu, H.; Meng, X.; Zhang, Y.; Chen, G.; Cao, Z.; Sun, X.; You, J. *J. Org. Chem.* **2017**, *82*, 12059. (b) Liu, Y.-F.; Ji, P.-Y.; Xu, J.-W.; Hu, Y.-Q.; Liu, Q.; Luo, W.-P.; Cuo, C.-C. *J. Org. Chem.* **2017**, *82*, 7159. (c) Pothikumar, R.; Sujatha, C.; Namitharan, K. *ACS Catal.* **2017**, *7*, 7783.

(10) Examples of 3-substituted chroman-4-one syntheses, see: (a) Tang, L.; Yang, Z.; Chang, X.; Jiao, J.; Ma, X.; Rao, W.; Zhou, Q.; Zheng, L. *Org. Lett.* **2018**, *20*, 6520. (b) Hu, H.; Chen, X.; Sun, K.; Wang, J.; Liu, Y.; Liu, H.; Fan, L.; Yu, B.; Sun, Y.; Qu, L.; Zhao, Y. *Org. Lett.* **2018**, *20*, 6157. (c) Lu, D.; Wan, Y.; Kong, L.; Zhu, G. *Org. Lett.* **2017**, *19*, 2929. (d) Rafiński, Z.; Kozakiewicz, A. *J. Org. Chem.* **2015**, *80*, 7468. (e) Ankner, T.; Fridén-Saxin, M.; Pemberton, N.; Seifert, T.; Grøtli, M.; Luthman, K.; Hilmersson, G. *Org. Lett.* **2010**, *12*, 2210. (f) de Alaniz, J. R.; Kerr, M. S.; Moore, J. L.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 2033.

(11) Examples of biologically active 3-substituted chroman-4-ones, see: (a) Basavarajappa, H. D.; Lee, B.; Lee, H.; Sulaiman, R. S.; An, H.; Magaña, C.; Shadmand, M.; Vayl, A.; Rajashekhar, G.; Kim, E.-Y.; Suh, Y.-G.; Lee, K.; Seo, S.-Y.; Corson, T. W. *J. Med. Chem.* **2015**, *58*, 5015. (b) Seifert, T.; Malo, M.; Kokkola, T.; Engen, K.; Fridén-Saxin, M.; Wallén, E. A. A.; Lahtela-Kakkonen, M.; Jarho, E. M.; Luthman, K. *J. Med. Chem.* **2014**, *57*, 9870. (c) Amato, E.; Bankemper, T.; Kidney, R.; Do, T.; Ma, L. *Bioorg. Med. Chem.* **2014**, *22*, 126. (d) Guo, H.; Zhao, H.; Kanno, Y.; Li, W.; Bai, H. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3137. (e) Conti, C.; Monaco, L. P.; Desideri, N. *Bioorg. Med. Chem.* **2011**, *19*, 7357.

(12) Examples of sulfonylchroman-4-one syntheses, see: (a) Chang, M.-Y.; Wu, Y.-S.; Chen, H.-Y. *Org. Lett.* **2018**, *20*, 1824. (b) Chang, M.-Y.; Chen, H.-Y.; Tsai, Y.-L. *J. Org. Chem.* **2019**, *84*, 326. (c) Yang, D.-T.; Meng, Q.-Y.; Zhong, J.-J.; Xiang, M.; Liu, Q.; Wu, L.-Z. *Eur. J. Org. Chem.* **2013**, 7528. (d) Wan, J.-P.; Zhong, S.; Guo, Y.; Wei, L. *Eur. J. Org. Chem.* **2017**, 4401.

(13) Reviews on Umpolung reactions, see: (a) Miyata, O.; Miyoshi, T.; Ueda, M. *ARKIVOC* **2013**, *(ii)*, 60. (b) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 11686.

(14) Selected examples of Umpolung conjugation of C–S bonds. For α-sulfenyl ketones, see: (a) Hatcher, J. M.; Kohler, M. C.; Coltart, D. M. *Org. Lett.* **2011**, *13*, 3810. (b) Gabillet, S.; Lecerclé, D.; Loreau, O.; Carboni, M.; Dézard, S.; Gomis, J. M.; Taran, F. *Org. Lett.* **2007**, *9*, 3925. For β-sulfenyl ketones, see: (c) Fan, J.; Zhao, Y.; Zhang, J.; Xie, M.; Zhang, Y. *J. Org. Chem.* **2020**, *85*, 691. (d) Mizota, I.; Ueda, C.; Tesong, Y.; Tsujimoto, Y.; Shimizu, M. *Org. Lett.* **2018**, *20*, 2291. For β,β-disulfenyl ketones, see: (e) Lai, J.; Tian, L.; Huo, X.; Zhang, Y.; Xie, X.; Tang, S. *J. Org. Chem.* **2015**, *80*, 5894.

(15) Chang, M.-Y.; Chen, H.-Y.; Tsai, Y.-L. *Org. Lett.* **2019**, *21*, 1832.

(16) CCDC 1938200 (**4a**), 1938201 (**4f**), 1945748 (**4x**), 1938202 (**5a**) and 1938203 (**5b**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(17) (a) Chu, L.; Yue, X.; Qing, F.-L. *Org. Lett.* **2010**, *12*, 1644. (b) Luo, F.; Pan, C.; Li, L.; Chen, F.; Cheng, J. *Chem. Commun.* **2011**, *47*, 5304. (c) Wang, M.; Tang, B.-C.; Ma, J.-T.; Wang, Z.-X.; Xiang, J.-C.; Wu, Y.-D.; Wang, J.-G.; Wu, A.-X. *Org. Biomol. Chem.* **2019**, *17*, 1535.

(18) Traynelis, V. J.; Hergenrother, W. L. *J. Org. Chem.* **1964**, *29*, 221.

(19) Sharma, P.; Rohilla, S.; Jain, N. *J. Org. Chem.* **2015**, *80*, 4116.

(20) Review on desulfonylation reactions, see: Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547.

(21) Reviews on sulfur chemistry, see: (a) Wang, M.; Li, Y.; Jiang, X. *Aldrichimica Acta* **2020**, *53*, 19. (b) Qiaz, Z.; Jiang, X. *Org. Biomol. Chem.* **2017**, *15*, 1942. (c) Liu, H.; Jiang, X. *Chem. Asian J.* **2013**, *8*, 2546.

(22) Review on the Knoevenagel reaction, see: Majumdar, K. C.; Taher, A.; Nandi, R. K. *Tetrahedron* **2012**, *68*, 5693.

(23) Selected examples of Knoevenagel reactions, see: (a) Yang, D.-S.; Ke, S.; Du, X.; Gao, P.; Zhu, H.-T.; Fan, M. J. *Tetrahedron* **2017**, *73*, 5522. (b) Kumpf, J.; Schwaebel, S. T.; Bunz, U. H. F. *J. Org. Chem.* **2015**, *80*, 5159. (c) Lakshmi, V.; Ravikanth, M. *J. Org. Chem.* **2013**, *78*, 4993. (d) Srinivas, V.; Koketsu, M. *J. Org. Chem.* **2013**, *78*, 11612.

