Application of the Acetate of Baylis-Hillman Adducts in the Synthesis of 3-Carbomethoxy-2*H*-thiochromenes

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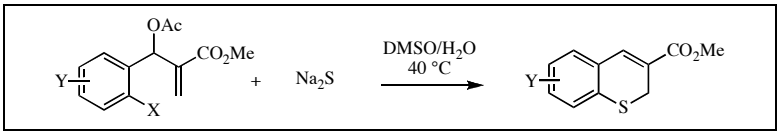

A new route to 2*H*-thiochromenes using the tandem S_N2' and S_NAr reaction of several Baylis-Hillman acetates having an *ortho*-substituent, such as a halogen or nitro group, with sodium sulfide in aqueous dimethyl sulfoxide has been described.

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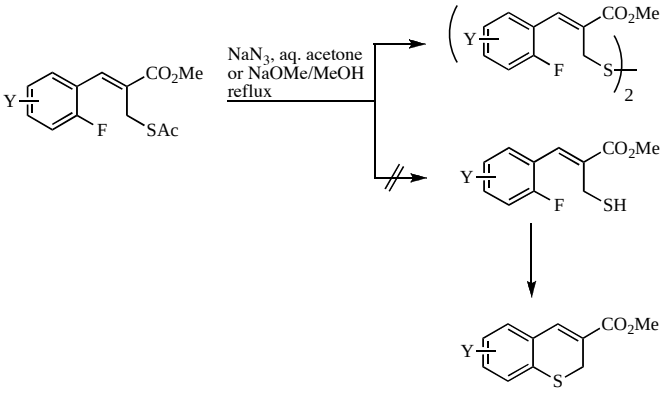
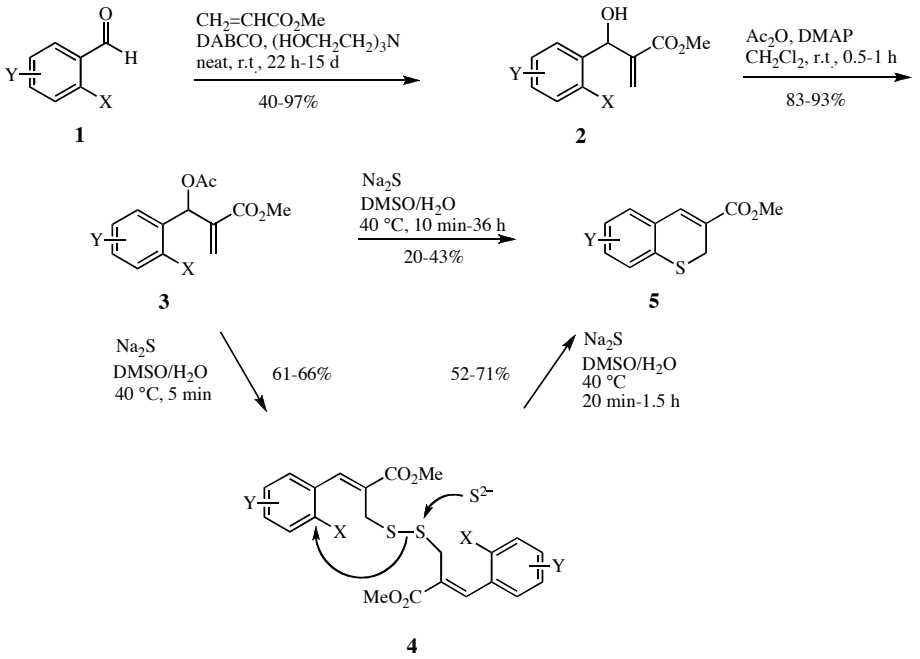
Recently, several studies have examined thiochromene units, sulfur-containing analogues of benzopyran, because they demonstrate a wide range of biological activities. For instance, thiochromenes exhibit anti-inflammation [1], anti-HIV [2], anti-bacteria [3], anti-hyperplasia [4], anti-psychiatric [5] and anti-cancer [6] activities. Therefore, it is important to develop new and more efficient synthetic pathways to achieve a diverse array of thiochromene pharmacophores. The main synthetic route involves an initial condensation of thiophenols with acrylic acid derivatives, followed by reduction and dehydration [7], and a magnesium amide-induced sequential conjugate addition-Aldol type condensation reaction between 2-mercaptoacetophenone and α,β-unsaturated carboxylic acid derivatives and subsequent dehydration [8]. A similar method to produce chiral 2*H*-thiochromenes through tandem Michael-Aldol reactions between 2-mercaptobenzaldehyde and α,β-unsaturated aldehydes has been reported [9]. In addition, several other synthetic methods are available such as reacting (2-mercaptophenyl)methyltriphenylphosphonium bromide with α-haloketones [10].

The Baylis-Hillman (BH) reaction has been the subject of recent reviews [11] and continues to elicit attention. Studies have focused on the S_N2' nucleophilic substitution of the BH adducts with a variety of nucleophiles. Many heterocycles have been synthesized including quinolines [12], dihydroquinolines [13], quinolones [14], pyrrolidines [15], cumarines [16] and indoles [17]. It was reported that 2,2′-dithiodibenzaldehyde could be used as a masked thiosalicyl aldehyde in the BH reaction with activated alkenes in the presence of 1,8-diazabicyclo-[5,4,0]undec-7-ene (DBU) to give thiochromenes [18]. However, the most obvious drawback is that the starting material of dithiodibenzaldehyde is not available commercially. In principle, compounds having the thiol group at the allylic position of 3-arylpropenoates after hydrolysis of the thiolester group might be extended further to build thiochromene derivatives *via* an intramolecular nucleophilic aromatic substitution reaction (S_NAr). However, after a hydrolysis reaction of 2-acetylthiomethylpropenoates, no traces of the intended allyl thiols were produced. Instead, symmetrical diallyl disulfides were produced *via* autooxidation of thiols [19] as shown in Scheme 1. At this stage, a one-pot procedure might be used to obtain 3-carbomethoxy-2*H*-thiochromenes using bis-nucleophile sodium sulfide. We herein describe a new route to 2*H*-thiochromenes by the tandem S_N2'nucleophilic substitution reaction, autooxidation of thiols, and intramolecular S_NAr nucleophilic substitution reaction of several BH acetates having *ortho*-substituents with sodium sulfide in an aqueous dimethyl sulfoxide.

Scheme 1



Scheme 2



1 **2** **3** **5** **4**

1,2,3,4	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	**l**
X	F	Cl	Br	NO_2	F	NO_2	Cl	Cl	Cl	F	Br	Cl
Y	H	H	H	H	5-MeO	5-MeO	3-Cl	5-Cl	6-Cl	4,5-F_2	4,5-OCH_2O	5-NO_2

5	**a**	**b**	**c**	**d**	**e**	**f**	**g**
Y	H	6-MeO	8-Cl	6-Cl	5-Cl	6,7-F_2	6,7-OCH_2O

Table 1

3-Carbomethoxy-2*H*-thiochromenes **5a**-**g**

Entry	Reactant	Reaction Time	Product	Yield (%)
1	**3a**	1.5 h	**5a**	41
2	**3b**	3 h	**5a**	26
3	**3c**	1.5 h	**5a**	30
4	**3d**	10 min	**5a**	43
5	**3e**	2.5 h	**5b**	34
6	**3f**	1 h	**5b**	37
7	**3g**	30 min	**5c**	28
8	**3h**	2 h	**5d**	22
9	**3i**	36 h	**5e**	23
10	**3j**	10 min	**5f**	20
11	**3k**	2.5 h	**5g**	23

Accordingly, BH acetates **3a**-**l** were synthesized as starting materials whose preparation has been previously described [19], except for **3e**, **3f**, **3h**, **3i** and **3k**. Treatment of BH acetate **3a** with 1.5 molar equivalents of sodium sulfide in aqueous dimethyl sulfoxide at 40 °C for 1.5 hours produced the desired 3-carbomethoxy-2*H*-thiochromene **5a** in a 41% yield after separation by column chromatography on silica gel. The spectral data of **5a** were identical to reported infrared, ^{1}H and ^{13}C nmr spectral values [18]. This result led to the examination of the effect of the leaving group of the aromatic moiety. Table 1 summarizes the results of the synthesis of 3-carbomethoxy-2*H*-thiochromenes. When the reactions of BH acetates bearing halogen and nitro leaving groups were conducted under similar reaction conditions, **3d** containing a nitro group gave an acceptable yield (43%) of **5a**. Meanwhile, in the cases of **3b**,**c** with chloro and bromo groups, **5a** was obtained in relatively lower yields (26% and 30%, respectively). Also, substituents *ortho* and/or *para* to the leaving group in the aromatic ring influenced the reaction. In general, the requirement of the presence of certain electron-withdrawing groups such as a halogen or nitro group *ortho* and/or *para* to the leaving group limits the generality of the S_NAr reaction by the addition-elimination mechanism. It did not work well with halogen-substituted compounds (Entries 7-10). Moreover, the reaction of nitro-substituted BH acetate **3l** was not successful and only complex inseparable

decomposition mixtures were obtained. However, the reactions of electron-donating methoxy-substituted BH acetates **3e** and **3f** led to relatively reasonable yields (34% and 37%, respectively) of **5b**, as shown in Table 1 (Entries 5 and 6). However, the BH acetate **3k** containing a methylenedioxy group produced a lower yield (23%) of **5g**.

Although the exact reaction mechanism has not yet been confirmed, we suggest that the conversion of **3** into **5** would appear to proceed through an S_N2' nucleophilic substitution reaction with sulfide ion followed by the formation of diallyl disulfides **4** by autooxidation and a subsequent intramolecular S_NAr nucleophilic substitution reaction of allyl thiolate ion, which is generated from diallyl disulfide **4** by the attack of the sulfide ion. The easy oxidation of thiols on exposure to air is well known [20]. It is also known that autooxidation of thiols is accelerated by bases [21]. For example, in the course of the synthesis of **5b**, careful examination of the reaction progress by thin layer chromatography (TLC) found that all starting BH acetate **3f** was converted to the diallyl disulfide **4f** in a 66% yield within 5 minutes. Compared with the reference sample prepared according to the literature method [19], both products were identical. In addition, treatment of **4f** with 1.5 molar equivalents of sodium sulfide in aqueous dimethyl sulfoxide at 40 ℃ for 1 hour gave the expected thiochromene **5b** in 52% yield. Also, several diallyl disulfides **4a**, **4c,** and **4d** produced the 3-carbomethoxy-2*H*-thiochromene **5a** in 59-71% yields under the same reaction conditions (Scheme 2).

In summary, we developed a new strategy for the synthesis of 3-carbomethoxy-2*H*-thiochromenes from easily accessible BH acetates and sodium sulfide. Although satisfactory results in product yields were not obtained, the efficacy of BH chemistry in heterocycle synthesis was demonstrated.

EXPERIMENTAL

Silica gel 60 (70-230 mesh ASTM) used for column chromatography was supplied by E. Merck. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} TLC plates. Melting points were measured by an Electrothermal melting point apparatus and were uncorrected. Microanalysis was obtained using a Thermo Electron Corporation Flash EA 1112 element analyzer. Infrared spectra were recorded with a Nicolet Magna 550 FTIR spectrometer. Electron impact (EI) mass spectra were obtained using a Jeol SX102 mass spectrometer. The ^{1}H and ^{13}C NMR spectra were measured on a Gemini 300 spectrometer using deuteriochloroform. All chemical shifts are reported in parts per million relative to tetramethylsilane. The coupling constants (*J*) are expressed in Hertz.

The known BH adducts **2a-c**, **2f**, **2g**, **2j**, **2l** [19], **2d** [22], BH acetates **3a-c**, **3g**, **3j** [19], **3d** [22] and disulfides **4a**, **4c** [19] were prepared according to literature procedures.

Methyl 2-[(2-Fluoro-5-methoxyphenyl)(hydroxy)methyl]-acrylate (2e). 1,4-Diazabicyclo[2,2,2]octane (DABCO) (0.22 g, 2 mmoles), triethanolamine (0.24 g, 1.6 mmole) and methyl acrylate (0.52 g, 6 mmoles) were added to a stirred solution of 2-fluoro-5-methoxybenzaldehyde (**1e**, 0.31 g, 2 mmoles) at room temperature. After stirring for 48 hours the reaction mixture was diluted with water (20 ml) and extracted with dichloromethane (3 × 50 ml). The combined organic layers were dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel that was eluted with hexane/ethyl acetate (5:1) to produce 0.45g (94%) of **2e** as a white solid: mp 51-52 °C; ir (potassium bromide): 3502, 1709, 1636, 1498, 1439 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.30 (d, J = 5.5 Hz, 1H), 3.76 (s, 3H), 3.79 (s, 3H), 5.73 (s, 1H), 5.84 (d, J = 5.5 Hz, 1H), 6.34 (s, 1H), 6.76-6.81 (m, 1H), 6.93-7.02 (m, 2H). *Anal.* Calcd. for $C_{12}H_{13}FO_4$: C, 60.00; H, 5.45. Found: C, 59.72; H, 5.63.

Methyl 2-[(2,5-Dichlorophenyl)(hydroxy)methyl]acrylate (2h). DABCO (0.22 g, 2 mmoles), triethanolamine (0.24 g, 1.6 mmole) and methyl acrylate (0.52 g, 6 mmoles) were added to a stirred solution of 2,5-dichlorobenzaldehyde (**1h**, 0.35 g, 2 mmoles) at room temperature. After stirring for 22 hours, the aforementioned procedure was followed to produce **2h**. Yield: 0.51 g (97%); colorless oil; ir (dichloromethane): 3437, 1720, 1631, 1462, 1440 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.30 (d, J = 4.6 Hz, 1H), 3.81 (s, 3H), 5.57 (s, 1H), 5.92 (d, J = 4.6 Hz, 1H), 6.36 (s, 1H), 7.21-7.31 (m, 2H), 7.58 (d, J = 2.4 Hz, 1H). *Anal.* Calcd. for $C_{11}H_{10}Cl_2O_3$: C, 50.60; H, 3.86. Found: C, 50.71; H, 3.93.

Methyl 2-[(2,6-Dichlorophenyl)(hydroxy)methyl]acrylate (2i). DABCO (0.22 g, 2 mmoles), triethanolamine (0.24 g, 1.6 mmole), and methyl acrylate (0.52 g, 6 mmoles) were added to a stirred solution of 2,6-dichlorobenzaldehyde (**1i**, 0.35 g, 2 mmoles) at room temperature. After stirring for 27 hours, the aforementioned procedure was followed to produce **2i**. Yield: 0.31 g (60%); white solid; mp: 74.5-75.5 °C; ir (potassium bromide): 3500, 1706, 1634, 1577, 1560, 1434 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.34 (d, J = 8.2 Hz, 1H), 3.75 (s, 3H), 5.78 (s, 1H), 6.35 (d, J = 8.2 Hz, 1H), 6.41 (s, 1H), 7.18 (dd, J = 8.5 and 7.2 Hz, 1H), 7.32 (d, J = 7.2 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H). *Anal.* Calcd. for $C_{11}H_{10}Cl_2O_3$: C, 50.60; H, 3.86. Found: C, 50.84; H, 4.01.

Methyl 2-[(2-Bromo-4,5-methylenedioxy)(hydroxy)methyl]-acrylate (2k). DABCO (0.22 g, 2 mmoles), triethanolamine (0.24 g, 1.6 mmole) and methyl acrylate (0.52 g, 6 mmoles) were added to a stirred solution of 2-bromo-4,5-methlenedioxybenzaldehyde (**1k**, 0.46 g, 2 mmoles) at room temperature. After stirring for 15 days, the aforementioned procedure was followed to produce **2k**. Yield: 0.25 g (40%); colorless oil; ir (dichloromethane): 3434, 1721, 1629, 1502, 1478 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.14 (d, J = 4.0 Hz, 1H), 3.79 (s, 3H), 5.62 (s, 1H), 5.86 (d, J = 4.0 Hz, 1H), 5.99 (s, 2H), 6.35 (s, 1H), 7.00 (s, 1H), 7.02 (s, 1H). *Anal.* Calcd. for $C_{12}H_{11}BrO_5$: C, 45.74; H, 3.52. Found: C, 45.90; H, 3.77.

Preparation of BH Acetates 3: General Procedure. Acetic anhydride (3 mmoles) and 4-(dimethylamino)pyridine (0.4 mmoles) were added to a stirred solution of BH adduct **2** (2 mmoles) in dichloromethane (5 ml) at room temperature. After stirring for 10-40 minutes the reaction mixture was diluted with water (20 ml) and extracted with dichloromethane (3 × 50 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*. The

resulting mixture was chromatographed on silica gel and eluted with hexane/ethyl acetate (3:1) to produce **3** as an oil or solid.

The physical and spectral data of **3** prepared by this general method follows.

Methyl 2-[Acetoxy(2-fluoro-5-methoxyphenyl)methyl]-acrylate (3e). Reaction time: 10 minutes; white solid; yield: 83%; mp: 53 °C; ir (potassium bromide): 1750, 1728, 1635, 1596, 1501, 1227 cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.12 (s, 3H), 3.74 (s, 3H), 3.77 (s, 3H), 5.82 (s, 1H), 6.46 (s, 1H), 6.78-6.85 (m, 2H), 6.89 (s, 1H), 6.95-7.02 (m, 1H). *Anal.* Calcd. for $C_{14}H_{15}FO_5$: C, 59.57; H, 5.36. Found: C, 59.68; H, 5.22.

Methyl 2-[Acetoxy(5-methoxy-2-nitrophenyl)methyl]-acrylate (3f). Reaction time: 30 minutes; white solid; yield: 89%; mp: 93.5-94.5 °C; ir (potassium bromide): 1747, 1716, 1638, 1614, 1581, 1515, 1231 cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.15 (s, 3H), 3.80 (s, 3H), 3.91 (s, 3H), 5.48 (s, 1H), 6.41 (s, 1H), 6.93 (dd, J = 9.2 and 2.7 Hz, 1H), 7.04 (d, J = 2.7 Hz, 1H), 7.40 (s, 1H), 8.19 (d, J = 9.2 Hz, 1H). *Anal.* Calcd. for $C_{14}H_{15}NO_7$: C, 54.37; H, 4.89; N, 4.53. Found: C, 54.49; H, 4.78; N, 4.84.

Methyl 2-[Acetoxy(2,5-dichlorophenyl)methyl]acrylate (3h). Reaction time: 25 minutes; white solid; yield: 93%; mp: 60-61 °C; ir (potassium bromide): 1748, 1711, 1635, 1465, 1440, 1295, 1225 cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.14 (s, 3H), 3.76 (s, 3H), 5.69 (s, 1H), 6.59 (s, 1H), 6.97 (s, 1H), 7.24 (dd, J = 8.5 and 2.4 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H). *Anal.* Calcd. for $C_{13}H_{12}Cl_2O_4$: C, 51.51; H, 3.99. Found: C, 51.36; H, 3.85.

Methyl 2-[Acetoxy(2,6-dichlorophenyl)methyl]acrylate (3i). Reaction time: 30 minutes; colorless oil; yield: 87%; ir (dichloromethane): 1747, 1727, 1580, 1563, 1436, 1229 cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.13 (s, 3H), 3.75 (s, 3H), 5.73 (s, 1H), 6.49 (s, 1H), 7.19 (dd, J = 8.7 and 7.3 Hz, 1H), 7.31-7.33 (m, 3H). *Anal.* Calcd. for $C_{13}H_{12}Cl_2O_4$: C, 51.51; H, 3.99. Found: C, 51.63; H, 3.75.

Methyl 2-[Acetoxy(2-bromo-4,5-methylenedioxy)methyl]-acrylate (3k). Reaction time: 40 minutes; colorless oil; yield: 86%; ir (dichloromethane): 1740, 1712, 1636, 1504, 1484, 1233 cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.12 (s, 3H), 3.76 (s, 3H), 5.67 (s, 1H), 5.99 (s, 2H), 6.46 (s, 1H), 6.82 (s, 1H), 6.91 (s, 1H), 7.03 (s, 1H). *Anal.* Calcd. for $C_{14}H_{13}BrO_6$: C, 47.08; H, 3.67. Found: C, 47.22; H, 3.81.

Preparation of 3-Carbomethoxy-2*H*-thiochromenes 5: General Procedure. Sodium sulfide (3 mmoles) was added to a stirred solution of BH acetate **3** (2 mmoles) in aqueous dimethyl sulfoxide (7.7 ml, v/v= 10/1) at 40 °C. After stirring for the time indicated in Table 1, the reaction mixture was diluted with water (20 ml) and extracted with diethyl ether (3 × 50 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel and eluted with hexane/ethyl acetate (10:1) to produce **5** as an oil or solid.

The physical and spectral data of **5** prepared by this general method follow.

3-Carbomethoxy-2*H*-thiochromene (5a). [18] Compound **5a** was obtained from BH acetates **3a**-**d** in 41, 26, 30 and 43% yields, respectively. Yellow solid; mp 34.5-35.5 °C; ir (potassium bromide): 1707, 1631, 1586, 1558, 1436, 1239 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.74 (d, J = 1.2 Hz, 2H), 3.85 (s, 3H), 7.10-7.28 (m, 4H), 7.55 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 24.0, 52.2, 123.0, 125.8, 127.1, 130.2, 130.6, 131.3, 134.0, 137.4, 166.4.

3-Carbomethoxy-6-methoxy-2*H*-thiochromene (5b). Compound **5b** was obtained from BH acetates **3e** and **3f** in yields of 34% and 37%, respectively. Yellow solid; mp 38-39 °C; ir (potassium bromide): 1706, 1631, 1595, 1560, 1235 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.70 (d, J = 1.2 Hz, 2H), 3.80 (s, 3H), 3.84 (s, 3H), 6.79-6.83 (m, 2H), 7.18-7.21 (m, 1H), 7.52 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 24.2, 52.2, 55.4, 115.6, 116.3, 124.0, 124.5, 128.0, 132.3, 137.4, 157.8, 166.3. *Anal.* Calcd. for $C_{12}H_{12}O_3S$: C, 61.00; H, 5.12; S, 13.57. Found: C, 60.77; H, 5.02; S, 13.74.

3-Carbomethoxy-8-chloro-2*H*-thiochromene (5c). Yellow solid; yield: 28%; mp: 88-89 °C; ir (potassium bromide): 1698, 1645, 1439, 1415, 1250, 1220 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.78 (d, 2H, J = 0.9 Hz, 2H), 3.86 (s, 3H), 7.06 (t, J = 7.6 Hz, 1H), 7.15 (dd, J = 7.6 and 1.5 Hz, 1H), 7.29 (dd, J = 7.6 and 1.5 Hz, 1H), 7.53 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 24.2, 52.4, 123.2, 125.7, 128.8, 130.9, 131.7, 132.8, 133.9, 137.0, 166.0. *Anal.* Calcd. for $C_{11}H_9ClO_2S$: C, 54.89; H, 3.77; S, 13.32. Found: C, 54.71; H, 3.75; S, 13.18.

3-Carbomethoxy-6-chloro-2*H*-thiochromene (5d). Yellow solid; yield: 22%; mp: 75-76 °C; ir (potassium bromide): 1705, 1631, 1464, 1435, 1235 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.73 (d, J = 1.2 Hz, 2H), 3.85 (s, 3H), 7.15-7.23 (m, 3H), 7.48 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 23.9, 52.3, 124.3, 128.1, 129.8, 129.9, 131.2, 132.3, 132.7, 136.1, 166.0. *Anal.* Calcd. for $C_{11}H_9ClO_2S$: C, 54.89; H, 3.77; S, 13.32. Found: C, 54.82; H, 3.51; S, 13.54.

3-Carbomethoxy-5-chloro-2*H*-thiochromene (5e). Yellow oil; yield: 23%; ir (dichloromethane): 1712, 1629, 1591, 1579, 1433, 1240 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.69 (d, J = 0.9 Hz, 2H), 3.87 (s, 3H), 7.09-7.23 (m, 3H), 7.97 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 23.6, 52.4, 124.4, 125.7, 126.8, 129.2, 130.2, 133.2, 135.4, 136.9, 166.1. *Anal.* Calcd. for $C_{11}H_9ClO_2S$: C, 54.89; H, 3.77; S, 13.32. Found: C, 54.68; H, 3.97; S, 13.14.

3-Carbomethoxy-6,7-difluoro-2*H*-thiochromene (5f). Yellow solid; yield: 20%; mp: 76-77 °C; ir (potassium bromide): 1695, 1582, 1490, 1438, 1253 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.72 (s, 2H), 3.85 (s, 3H), 7.04-7.13 (m, 2H), 7.45 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 23.8, 52.4, 115.8, 116.1, 118.7, 118.9, 123.5, 128.0, 135.6, 149.0, 149.1, 150.1, 152.3, 166.0. *Anal.* Calcd. for $C_{11}H_8F_2O_2S$: C, 54.54; H, 3.33; S, 13.24. Found: C, 54.37; H, 3.43; S, 13.38.

3-Carbomethoxy-6,7-methylenedioxy-2*H*-thiochromene (5g). Yellow solid; yield: 23%; mp: 103-104 °C; ir (potassium bromide): 1692, 1609, 1584, 1499, 1481, 1242 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.68 (d, J = 0.9 Hz, 2H), 3.83 (s, 3H), 5.97 (s, 2H), 6.74 (s, 1H), 6.78 (s, 1H), 7.44 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 24.1, 52.1, 101.5, 107.6, 110.2, 120.4, 125.4, 127.9, 137.3, 146.2, 149.1, 166.5. *Anal.* Calcd. for $C_{12}H_{10}O_4S$: C, 57.59; H, 4.03; S, 12.81. Found: C, 57.78; H, 4.26; S, 12.57.

Preparation of Diallyl Disulfides 4.

Method A.

(2*Z*,2´*Z*)-Dimethyl 2,2´-Disulfanediylbis-(methylene)bis[3-(2-nitrophenyl)acrylate] (4d). Sodium sulfide (0.23 g, 3 mmoles) was added to a stirred solution of BH acetate **3d** (0.56 g, 2 mmoles) in aqueous dimethyl sulfoxide (7.7 ml, v/v= 10/1) at 40℃. After stirring for 5 minutes, the reaction mixture was diluted with water (20 ml) and extracted with diethyl ether (3 ×

50 ml). The combined organic layers were dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel and eluted with hexane/ethyl acetate (3:1) to produce 0.31 g (61%) of **4d** as a white solid: mp: 142-143 ℃; ir (potassium bromide): 1710, 1604, 1530, 1435, 1353, 1272, 1259 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.43 (s, 2H), 3.82 (s, 3H), 7.47-7.57 (m, 2H), 7.66-7.71 (m, 1H), 7.93 (s, 1H), 8.13-8.17 (m, 1H); ^{13}C NMR (deuteriochloroform): δ 30.0, 52.4, 125.0, 130.0, 130.3, 130.7, 131.1, 133.8, 137.8, 147.4, 166.7; ms: m/z (%) No M^+, 486 (21), 337 (17), 250 (100), 218 (82), 188 (59), 164 (58). *Anal*. Calcd. for $C_{22}H_{20}N_2O_8S_2$: C, 52.37; H, 4.00; N, 5.55; S, 12.71. Found: C, 52.52; H, 3.86; N, 5.63; S, 12.54.

(2*Z*,2′*Z*)-Dimethyl 2,2′-Disulfanediylbis(methylene)bis[3-(5-methoxy-2-nitrophenyl)acrylate] (4f). Sodium sulfide (0.23 g, 3 mmoles) was added to a stirred solution of BH acetate **3f** (0.62 g, 2 mmoles) in aqueous dimethyl sulfoxide (7.7 ml, v/v= 10/1) at 40℃. After stirring for 5 minutes, the aforementioned procedure was followed to produce 0.37 g (66%) of **4f** as a white solid: mp: 165-166 ℃; ir (potassium bromide): 1713, 1600, 1585, 1508, 1242 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.45 (s, 2H), 3.82 (s, 3H), 3.93 (s, 3H), 6.93 (d, J = 2.4 Hz, 1H), 6.98 (dd, J = 9.2 and 2.4 Hz, 1H), 7.97 (s, 1H), 8.21 (d, J = 9.2 Hz, 1H); ^{13}C NMR (deuteriochloroform): δ 30.2, 52.4, 56.2, 115.2, 127.6, 129.7, 133.6, 138.8, 138.9, 140.2, 163.5, 166.7; ms: m/z (%) No M^+, 472 (2), 426 (42), 252 (19), 220 (98), 188 (100), 134 (100), 115 (54). *Anal*. Calcd. for $C_{24}H_{24}N_2O_{10}S_2$: C, 51.06; H, 4.28; N, 4.96; S, 11.36. Found: C, 51.27; H, 4.20; N, 4.73; S, 11.55.

Method B [19].

(2*Z*,2′*Z*)-Dimethyl 2,2′-Disulfanediylbis(methylene)bis[3-(2-nitrophenyl)acrylate] (4d). Thiolacetic acid (0.17 g, 2.2 mmoles) and triethylamine (0.24 g, 2.4 mmoles) were added to a stirred solution of **3d** (0.56 g, 2 mmoles) in dichloromethane (5 ml) at room temperature. After stirring for 30 minutes, the reaction mixture was diluted with water (5 ml) and extracted with dichloromethane (2 × 10 ml). The combined organic layers were dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The resulting crude product, methyl (Z)-2-(acetylthiomethyl)-3-(2-nitrophenyl)acrylate, was dissolved in 50% aqueous acetone (10 ml), and NaN_3 (0.20 g, 3 mmoles) was added and stirred at reflux temperature for 4 hours. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with dichloromethane (2 × 10 ml). The organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*. The reaction mixture was chromatographed on silica gel and eluted with hexane/ethyl acetate (10:1) to produce 0.31 g (62%) of **4d** as a white solid. The melting point and spectral data were identical to those of the **4d** obtained from method A.

(2*Z*,2′*Z*)-Dimethyl 2,2′-Disulfanediylbis(methylene)bis[3-(5-methoxy-2-nitrophenyl)acrylate] (4f). Thiolacetic acid (0.17 g, 2.2 mmoles) and triethylamine (0.24 g, 2.4 mmoles) were added to a stirred solution of **3f** (0.62 g, 2 mmoles) in dichloromethane (5 ml) at room temperature. After stirring for 30 minutes, the reaction mixture was diluted with water (5 ml) and extracted with dichloromethane (2 × 10 ml). The combined organic layers were dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The resulting crude product, methyl (Z)-2-(acetylthiomethyl)-3-(2-nitrophenyl)-acrylate, was dissolved in 50% aqueous acetone (10 ml), and NaN_3 (0.20 g, 3 mmoles) was added and stirred at reflux temperature for 4 hours. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with dichloromethane (2 × 10 ml). The organic layers were dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The reaction mixture was chromatographed on silica gel and eluted with hexane/ethyl acetate (10:1) to produce 0.41 g (72%) of **4f** as a white solid. The melting point and spectral data were identical to those of the **4f** obtained from method A.

Synthesis of Thiochromenes 5 from Diallyl Disulfide 4: General Procedure. Sodium sulfide (3 mmoles) was added to a stirred solution of diallyl disulfides **4a**, **c**, **d**, **f** (2 mmoles) in aqueous dimethyl sulfoxide (11 ml, v/v= 10/1) at 40℃. After stirring for 20 minutes to 1.5 hours, the reaction mixture was diluted with water (20 ml) and extracted with diethyl ether (3 × 50 ml). The combined organic layers were dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel and eluted with hexane/ethyl acetate (10:1) to produce **5a** or **5b** as a solid.

Spectroscopic data were identical to the **5a** or **5b** obtained from the one-pot procedure. For **4a**, reaction time: 1.5 hours; yield: 60%. For **4c**, reaction time: 1 hour, yield: 58%. For **4d**, reaction time: 20 minutes, yield: 71%. For **4f**, reaction time: 1 hour, yield: 52%.

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