One-Pot Synthesis of 2*H*-Thiochromenes *via* $TiCl_4$-Promoted Reaction of 2-*tert*-Butylthiobenzaldehydes with Activated Alkenes

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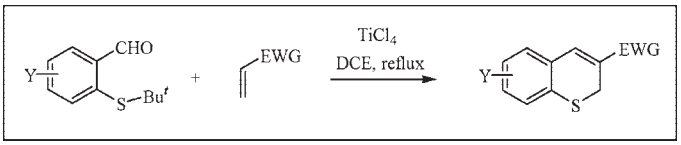

A facile synthesis of 2*H*-thiochromenes through $TiCl_4$-promoted reaction of 2-*tert*-butylthiobenzaldehydes with activated alkenes is described.

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INTRODUCTION

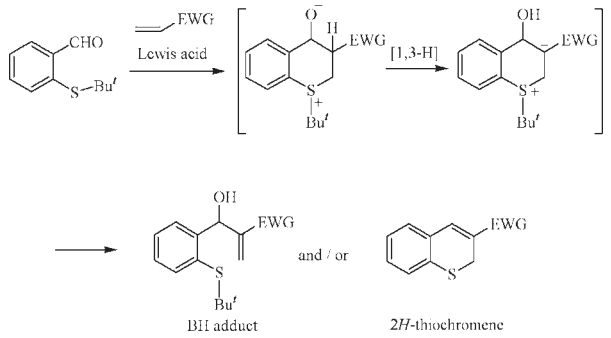
Thiochromenes are of considerable pharmacological and material interest because they display a wide range of biological activities [1] and are occasionally used as scaffolds [2] or synthetic intermediates of functional dyes [3]. In recognition of their importance, several efforts have been made to synthesize this class of molecules so far, but the development of more efficient and general method still remains a continuing challenge. The main synthetic routes involve an initial condensation of thiophenols with acrylic acid derivatives, followed by reduction and dehydration [4], 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 [5]. 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 [6]. In addition, several other synthetic methods are available such as the cyclization of 3-(2-*tert*-butylthiophenyl)-prop-2-en-1-ols [7] and the Baylis-Hillman (BH) reaction of 2,2′-dithiodibenzaldehyde with activated alkenes [8]. However, most of these routes suffer from main drawbacks such as multistep processes, the poor availability of starting material, and the limited scope of substrates. Recently, we also reported a tandem S_N2' and S_NAr reaction of BH acetates having an *ortho*-leaving group with sodium sulfide, leading to the formation of 2*H*-thiochromenes, which gave unsatisfactory product yields [9]. In continuation of our ongoing studies on the synthesis of heterocycles, including thiochromenes, using BH methodology [10], we herein describe $TiCl_4$-promoted reaction of 2-*tert*-butylthiobenzaldehydes with activated alkenes, which serves as a facile method for the synthesis of 2*H*-thiochromenes.

RESULTS AND DISCUSSION

The chalcogeno-Baylis-Hillman reaction [11] is well known as a coupling reaction of activated alkenes with electrophiles such as aldehydes [12], activated ketones [13], and acetals [14] catalyzed by a mixture of Lewis acid and base, typically using titanium (IV) chloride ($TiCl_4$)/methyl sulfide [12,13] to give highly functionalized olefins. We envisioned that the reactions of 2-*tert*-butylthiobenzaldehydes with activated alkenes in the presence of $TiCl_4$ could produce the thiochromenes alone or together with the BH adducts, after loss of the *tert*-butyl group under acidic conditions without addition of extra Lewis base such as sulfide, because aldehydes have a chalcogenyl group which might serve as a Lewis base (Scheme 1).

Accordingly, we first synthesized 2-*tert*-butylthiobenzaldehydes **2a–e** as starting materials, following a slightly modified literature procedure [15,16]. The reaction of benzaldehydes **1a–e** with 1.2 equiv of *tert*-butylthiol in the presence of 1 equiv of potassium carbonate in *N*,*N*-dimethylformamide at reflux temperature gave 2-*tert*-butylthiobenzaldehydes **2a–e** in 64–97% yields. Treatment of **2a–e** with 2 equiv of methyl vinyl ketone (MVK) in the presence of 1 equiv of $TiCl_4$ in 1,2-dichloroethane at reflux temperature gave the expected 3-acetyl-2*H*-thiochromenes **4a–e** in low to acceptable yields (8–51%) without the production of BH adducts. The spectral data of **4a** were identical to the reported infrared, ^1H, ^{13}C NMR spectral values [8]. As

Scheme 1



shown in Table 1, the presence of electron-withdrawing chloro- or nitro-substituents in benzene ring of aldehyde **2** demanded a prolonged reaction time to afford the corresponding thiochromenes. For instance, the synthesis of **4b** and **4c** (Entries 7 and 8) having chloro-substituent required longer reaction time than that of **4a** (Entry 6) (2–4 h *vs.* 0.5 h). Nitro-substituted aldehyde **2d** with MVK also gave desired thiochromene **4d** in low yield (8%) after relatively long reaction time (4 h). We consider that the reduced nucleophilicity of the sulfur atom in aldehyde **2** by electron-withdrawing chloro- or nitro-substituent decelerated the reaction. Next, we examined the reaction of **2a–e** with methyl acrylate or acrylonitrile. Using 2 equiv of methyl acrylate, the corresponding thiochromenes **4f–h** and **4j** were produced in 35–70% yields. However, the reaction of **2d** having nitro-substituent with methyl acrylate was unsuccessful, and very complex mixture of unidentified products was observed by thin layer chromatography. The spectral data of **4f–h** and **4j** were identical to the reported infrared, ^{1}H, ^{13}C NMR spectral values [9]. In the cases of acrylonitrile, thiochromenes **4k** and **4l** were produced in relatively low yields (25 and 18%, respectively) and were taken long reaction times (Entries 16 and 17). Because of low yields, additional reactions of **2c–e** with acrylonitrile were not undertaken. A plausible mechanism based on Kataoka's work [12] is shown in Scheme 2. A β-sulfonium-$TiCl_4$-stabilized enolate **3a** is produced by conjugate addition of sulfur atom in aldehyde **2** to $TiCl_4$-activated Michael acceptor, followed by carbon–carbon bond formation through transition state **3b** to give the $TiCl_4$-stabilized alkoxide **3c** and subsequent proton migration to afford **3d**, which gives *2H*-thiochromene **4** by dehydration and loss of the *tert*-butyl group. A similar Michael-aldol process catalyzed by Lewis acid/chalcogenide [11(b)], amine [17], and bifunctional thiourea [18] is well known. It is also known that the *tert*-butyl thioethers are easily cleaved under Lewis [19] or Brønsted [20] acidic conditions.

CONCLUSIONS

In conclusion, a new method for the synthesis of 2*H*-thiochromenes has been developed through $TiCl_4$-promoted reaction of 2-*tert*-butylthiobenzaldehyde derivatives with activated alkenes. Although some products were obtained in low yields, compared with other routes, this synthetic method apparently allows a facile approach to 2*H*-thiochromenes.

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. Microanalyses were obtained using a Thermo Electron Corporation Flash EA 1112 element analyzer. Mass spectra were obtained using a ThermoQuest Polaris Q mass spectrometer operating at 70 eV. Infrared spectra were recorded on a Nicolet Magna 550 FTIR 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.

Preparation of 2-*tert*-butylthiobenzaldehyde derivatives 2: General procedure. To a stirred solution of aldehyde **1** (40 mmol) and *tert*-butyl thiol (5.40 mL, 48 mmol) in dimethylformamide (40 mL) was added potassium carbonate (5.53 g, 40 mmol) and the mixture was heated to reflux temperature for 1–7 days. After cooling to room temperature, the reaction mixture was diluted with water (300 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The resulting mixture was

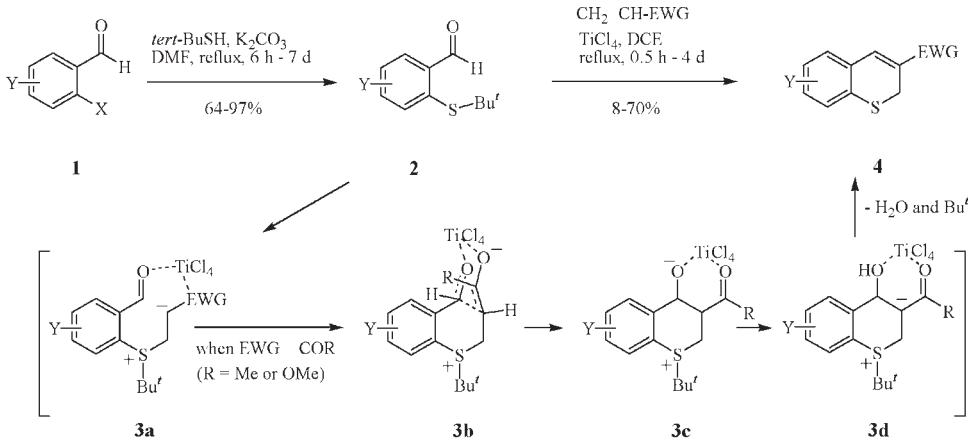
Table 1

Aldehydes **2a–d** and 2*H*-thiochromenes **4a–j.**

Entry	Reactant	Olefin	Reaction time	Product	Yield (%)
1	**1a**	–	1 day	**2a**	84
2	**1b**	–	4 days	**2b**	97
3	**1c**	–	7 days	**2c**	94
4	**1d**	–	6 h	**2d**	64
5	**1e**	–	4 d	**2e**	73
6	**2a**	MVK	0.5 h	**4a**	51
7	**2b**	MVK	2 h	**4b**	22
8	**2c**	MVK	4 h	**4c**	24
9	**2d**	MVK	4 h	**4d**	8
10	**2e**	MVK	0.5 h	**4e**	32
11	**2a**	MA	0.5 h	**4f**	69
12	**2b**	MA	2.5 h	**4g**	70
13	**2c**	MA	4 h	**4h**	42
14	**2d**	MA	3 days	**4i**	–
15	**2e**	MA	1 h	**4j**	35
16	**2a**	AN	4.5 h	**4k**	25
17	**2b**	AN	4 days	**4l**	18

MVK, methyl vinyl ketone; MA, methyl acrylate; AN, acrylonitrile.

Scheme 2



1,2	a	b	c	d	e
X	NO_2	Cl	Cl	Cl	F
Y	H	3-Cl	5-Cl	5-NO_2	5-OMe

4	a	b	c	d	e	f	g	h	i	j	k	l
EWG	COMe	COMe	COMe	COMe	COMe	COOMe	COOMe	COOMe	COOMe	COOMe	CN	CN
Y	H	8-Cl	6-Cl	6-NO_2	6-OMe	H	8-Cl	6-Cl	6-NO_2	6-OMe	H	8-Cl

chromatographed on silica gel eluting with hexane/ethyl acetate (20:1) to produce **2** as an oil or a solid.

The physical and spectral data of **2** prepared by this general method are as follows.

2*-tert-*Butylthiobenzaldehyde (2a). [15] Yellow oil; yield: 84%; IR (neat): 1692, 1583, 1455, 1363 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.30 (s, 9H), 7.50–7.65 (m, 3H), 7.98–8.01 (m, 1H), 10.80 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 30.8, 47.5, 128.0, 129.5, 133.5, 136.5, 139.4, 139.9, 193.6; ms: *m/z* (%) 194 (M^+, 100), 138 (14), 137 (6), 109 (12), 104 (8).

2*-tert-*Butylthio-3-chlorobenzaldehyde (2b). [16] White solid; yield: 97%; mp: 52–54°C; IR (potassium bromide): 1680, 1571, 1458, 1366 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.32 (s, 9H), 7.46 (t, J = 7.9 Hz, 1H), 7.78 (dd, J = 7.9 and 1.5 Hz, 1H), 7.91 (dd, J = 7.9 and 1.5 Hz, 1H), 10.77 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 31.1, 50.7, 126.7, 130.3, 135.0, 135.5, 142.0, 143.4, 193.5; ms: *m/z* (%) 230 (M^+, 41), 228 (M^+, 100), 173 (5), 172 (7), 171 (6).

2*-tert-*Butylthio-5-chlorobenzaldehyde (2c). Yellow oil; yield: 94%; IR (neat): 1695, 1570, 1454, 1363 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.29 (s, 9H), 7.52–7.59 (m, 2H), 7.96 (d, J = 2.1 Hz, 1H), 10.71 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 30.8, 47.9, 128.1, 133.5, 134.8, 136.3, 140.4, 141.2, 192.4; ms: *m/z* (%) 230 (M^+, 39), 228 (M^+, 100), 227 (6), 226 (7), 225 (8). Anal. Calcd. for $C_{11}H_{13}ClOS$: C, 57.76; H, 5.73; S, 14.02. Found: C, 57.59; H, 5.55; S, 13.87.

2*-tert-*Butylthio-5-nitrobenzaldehyde (2d). Yellow oil; yield: 64%; IR (neat): 1696, 1598, 1525, 1458, 1345 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.38 (s, 9H), 7.85 (d, J = 8.5 Hz, 1H), 8.39 (dd, J = 8.5 Hz and 2.7 Hz, 1H), 8.78 (d, J = 2.7 Hz, 1H), 10.75 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 31.0, 49.5, 123.2, 126.9, 139.9, 140.1, 144.6, 148.2, 191.0; ms: *m/z* (%) 239 (M^+, 8), 210 (9), 183 (100), 182 (14), 136 (43). Anal. Calcd. for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85; S, 13.40. Found: C, 55.32; H, 5.60; N, 5.84; S, 13.26.

2*-tert-*Butylthio-5-methoxybenzaldehyde (2e). Yellow oil; yield: 73%; IR (neat): 1683, 1589, 1473, 1375 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.27 (s, 9H), 3.88 (s, 3H), 7.13 (dd, J = 8.5 and 3.1 Hz, 1H), 7.49 (d, J = 3.1 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 10.73 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 30.7, 47.1, 55.5, 110.9, 121.1, 128.0, 140.3, 141.3, 160.5, 193.7; ms: *m/z* (%) 224 (M^+, 100), 222 (3), 221 (2), 220 (2) 168 (2), 167 (1). Anal. Calcd. for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19; S, 14.29. Found: C, 64.41; H, 7.22; S, 14.03.

Preparation of 3-substituted 2*H*-thiochromenes 4: General procedure. To a stirred solution of aldehyde **2** (3 mmol) and alkene (6 mmol) in 1,2-dichloroethane (10 mL) was added $TiCl_4$ (0.33 mL, 3 mmol) at room temperature, and then the mixture was heated to reflux temperature for 0.5–96 h. After cooling to room temperature, the reaction mixture was quenched by aqueous saturated $NaHCO_3$ solution (50 mL), diluted with water (150 mL), and extracted with dichloromethane (2 × 150 mL). The combined organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel eluting with hexane/ethyl acetate (10:1) to produce **4** as an oil or a solid.

The physical and spectral data of **4** prepared by this general method are as follows.

3*-Acetyl-2H-*thiochromene (4a). [8] Yellow oil; yield: 51%; IR (neat): 1641, 1616, 1439, 1378, 1305, 1281, 1235, 1217 cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.47 (s, 3H), 3.72 (d, J = 0.9 Hz, 2H), 7.12–7.31 (m, 4H), 7.40 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 22.8, 25.3, 125.7, 127.3, 130.5, 130.8,

131.4, 131.7, 135.0, 137.8, 196.7; ms: *m/z* (%) 190 (M^+, 63), 189 (62), 149 (8), 148 (23), 147 (100).

3-Acetyl-8-chloro-2H-thiochromene (4b). Yellow oil; yield: 22%; IR (neat): 1656, 1625, 1412, 1372, 1238, 1214 cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.49 (s, 3H), 3.76 (d, J = 0.9 Hz, 2H), 7.09 (t, J = 7.6 Hz, 1H), 7.20 (dd, J = 7.6 and 1.2 Hz, 1H), 7.33 (dd, J = 7.6 and 1.2 Hz, 1H), 7.39 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 22.9, 25.4, 125.7, 129.0, 131.2, 131.6, 131.9, 132.9, 134.8, 137.5, 196.5; ms: *m/z* (%) 226 (M^+, 23), 225 (20), 224 (M^+, 59), 223 (25), 183 (37), 181 (100), 146 (11), 145 (25). Anal. Calcd. for $C_{11}H_9ClOS$: C, 58.80; H, 4.04; S, 14.27. Found: C, 58.71; H, 3.87; S, 14.04.

3-Acetyl-6-chloro-2H-thiochromene (4c). Yellow solid; yield: 24%; mp: 85–86°C; IR (potassium bromide): 1662, 1632, 1461, 1369, 1235, 1208 cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.48 (s, 3H), 3.71 (d, J = 0.9 Hz, 2H), 7.18–7.27 (m, 3H), 7.33 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 22.8, 25.4, 128.3, 130.1, 130.2, 131.2, 132.7, 132.8, 133.3, 136.6, 196.5; ms: *m/z* (%) 226 (M^+, 28), 225 (27), 224 (M^+, 78), 223 (27), 183 (38), 181 (100), 146 (12), 145 (18). Anal. Calcd. for $C_{11}H_9ClOS$: C, 58.80; H, 4.04; S, 14.27. Found: C, 58.67; H, 3.87; S, 14.03.

3-Acetyl-6-nitro-2H-thiochromene (4d). [3(a)] Yellow solid; yield: 8%; mp: 143–144°C; IR (potassium bromide): 1662, 1598, 1558, 1510, 1336, 1226 cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.52 (s, 3H), 3.81 (d, J = 0.9 Hz, 2H), 7.42 (d, J = 8.5 Hz, 1H), 7.45 (s, 1H), 8.06 (dd, J = 8.5 Hz and 2.4 Hz, 1H), 8.15 (d, J = 2.4 Hz, 1H); ^{13}C NMR (deuteriochloroform): δ 22.8, 25.4, 124.6, 125.0, 127.5, 131.6, 132.6, 135.9, 144.4, 145.5, 196.2; ms: *m/z* (%) 235 (M^+, 68), 234 (8), 192 (90), 176 (19), 146 (100).

3-Acetyl-6-methoxy-2H-thiochromene (4e). Yellow solid; yield: 32%; mp: 100–102°C; IR (potassium bromide): 1653, 1620, 1485, 1459, 1316, 1247, 1223 cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.48 (s, 3H), 3.69 (d, J = 0.9 Hz, 2H), 3.81 (s, 3H), 6.82–6.85 (m, 2H), 7.21–7.24 (m, 1H), 7.37 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 23.1, 25.4, 55.5, 115.7, 116.7, 125.5, 128.2, 132.4, 132.7, 137.9, 157.8, 196.8; ms: *m/z* (%) 220 (M^+, 87), 219 (33), 177 (100), 162 (8), 134 (33). Anal. Calcd. for $C_{12}H_{12}O_2S$: C, 65.43; H, 5.49; S, 14.56. Found: C, 65.62; H, 5.47; S, 14.31.

3-Carbomethoxy-2H-thiochromene (4f). [8,9] Yellow solid; yield: 69%; mp: 34–35°C; IR (potassium bromide): 1704, 1628, 1586, 1552, 1438, 1239 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.73 (d, J = 0.9 Hz, 2H), 3.84 (s, 3H), 7.09–7.28 (m, 4H), 7.54 (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; ms: *m/z* (%) 206 (M^+, 73), 205 (62), 191 (100), 175 (8), 147 (35).

3-Carbomethoxy-8-chloro-2H-thiochromene (4g). [9] Yellow solid; yield: 70%; mp: 94–95°C; IR (potassium bromide): 1699, 1641, 1436, 1415, 1247, 1220 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.78 (d, J = 1.2 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, 52.3, 123.2, 125.7, 128.8, 130.9, 131.7, 132.8, 133.9, 137.0, 166.0; ms: *m/z* (%) 242 (M^+, 21), 241 (23), 240 (M^+, 56), 239 (31), 227 (39), 225 (100), 183 (12), 181 (34).

3-Carbomethoxy-6-chloro-2H-thiochromene (4h). [9] Yellow solid; yield: 42%; mp: 75–76°C; IR (potassium bromide): 1705, 1628, 1464, 1433, 1235 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.73 (d, J = 0.9 Hz, 2H), 3.85 (s, 3H), 7.16–7.23 (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; ms: *m/z* (%) 242 (M^+, 25), 241 (20), 240 (M^+, 67), 239 (22), 227 (38), 225 (100), 183 (15), 181 (42).

3-Carbomethoxy-6-methoxy-2H-thiochromene (4j). [9] Yellow solid; yield: 35%; mp: 38–39°C; IR (potassium bromide): 1704, 1628, 1599, 1561, 1236 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.70 (d, J = 1.2 Hz, 2H), 3.80 (s, 3H), 3.85 (s, 3H), 6.75–6.82 (m, 2H), 7.18–7.21 (m, 1H), 7.53 (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; ms: *m/z* (%) 236 (M^+, 86), 235 (25), 221 (100), 205 (4), 177 (20), 134 (12).

3-Cyano-2H-thiochromene (4k). [8] Yellow solid; yield: 25%; mp: 87–88°C; IR (potassium bromide): 2208, 1616, 1461, 1436, 1415, 1254 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.58 (d, J = 0.9 Hz, 2H), 7.15–7.26 (m, 5H); ^{13}C NMR (deuteriochloroform): δ 25.8, 103.7, 118.3, 126.3, 127.5, 130.06, 130.11, 130.9, 132.7, 142.2; ms: *m/z* (%) 173 (M^+, 64), 172 (100), 147 (7), 146 (4), 145 (10).

3-Cyano-8-chloro-2H-thiochromene (4l). Yellow solid; yield: 18%; mp: 116–117°C; IR (potassium bromide): 2202, 1620, 1442, 1413, 1282 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.64 (d, J = 1.2 Hz, 2H), 7.10–7.18 (m, 3H), 7.32–7.35 (m, 1H); ^{13}C NMR (deuteriochloroform): δ 26.0, 104.1, 117.9, 126.2, 128.4, 131.5, 131.7, 132.1, 132.8, 141.9; ms: *m/z* (%) 209 (M^+, 22), 208 (38), 207 (M^+, 59), 206 (51), 181 (5), 172 (100). Anal. Calcd. for $C_{10}H_6ClNS$: C, 57.83; H, 2.91; N, 6.74; S, 15.44. Found: C, 57.91; H, 2.70; N, 6.56; S, 15.28.

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