A New Synthesis of Thioflavanones from Thiosalicylic Acid

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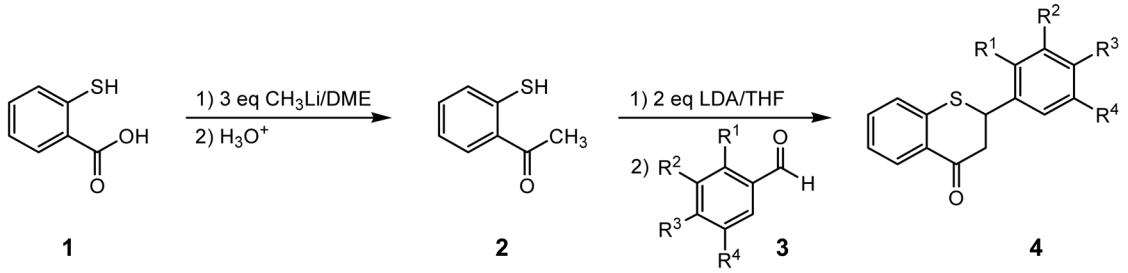
The thioflavanones (2-phenylthiochroman-4-ones), the thio analogues of flavanones, are an important class of heterocycles[1] and serve as precursors of biologically active benzothiazepins and thiochroman-4-one 1,1-dioxides.[2] The synthesis of thiochroman-4-ones has been generally accomplished by the intramolecular Friedel-Crafts acylation of 3-arylthiopropanoic acid derivatives with H_2SO_4[3] or Lewis acids[4] such as $SnCl_4$ and $Bi(NTf_2)_3$. However, this method is not suitable for the synthesis of thioflavanones with 2-substituted phenyl groups. The direct condensation of thiophenol with α,β-unsaturated acids proceeds at high temperature to give thiochroman-4-ones in low to moderate yields with side products such as the corresponding disulfides and enol thioethers.[5] The construction of thiochroman-4-one rings is also performed by the acyl radical cyclization of 2-allylthiotriphenylhydrazides[6] at high temperature in multiple steps from thiosalicylic acid. Alternatively, thioflavanones are synthesized by the catalytic hydrogenation[7] of thioflavones, derived from the condensation of thiophenols and β-keto esters[8] or the intramolecular Wittig cyclization of salicilate thioesters,[9] with H_2/Pd-C, but the desired products are obtained in low yields with side products.

Although some types of reaction to synthesize thiochroman-4-ones have been known, reports of the synthesis of thioflavanones have been scarce, presumably because 2'-mercaptoacetophenone is not commercially available. As part of our continuing studies of flavonoids,[10] we wish to extend these studies to the sulfur-containing analogues of flavanones since thioflavanones would be expected to be biologically active agents. 2'-Mercaptoacetophenone **2**, a pivotal key intermediate for the synthesis of thioflavanones **4**, were newly prepared by the treatment of thiosalicylic acid **1** with 3 equiv of methyllithium in DME for 1 h between −15 °C and 0 °C (Scheme 1). After completion of the reaction, the light yellow mixture containing white precipitate was quenched with 1.0 N-HCl and isolated by usual workup. The condensed residue was purified by vacuum distillation using Kugelrohr apparatus to give **2** in 80% yield as a light yellow liquid and could be stored in a refrigerator for several months.

The condensation of **2** with benzaldehyde derivatives **3** was initially studied using 4-chlorobenzaldehyde **3e** as a model substrate. The addition of **3e** to a solution of the lithium anion, generated from **2** and 1 equiv of lithium diisopropylamide in THF for 1.5 h between −15 °C and −10 °C, afforded 4'-chlorothioflavanone **4e** in 68% after 12 h between −10 °C and room temperature. However, the use of 2 equiv of lithium diisopropylamide accelerated the rate of the corresponding reaction and **4e** was obtained in 84% yield after 2.5 h between −10 °C and room temperature. The direct condensation seems to occur by the intramolecular nucleophilic attack of sulfur anion to the β-carbon atom of chalcone which are produced from the nucleophilic addition of the lithium dianion of **2** to **3e**, accompanying elimination of lithium hydroxide. This is similar with the result that 2'-hydroxyacetophenone is condensed with benzaldehyde with alkali metal hydroxide to give a mixture of chalcone and flavanone and furtheremore the ratio of flavanone is increased according to the amount of metal hydroxide.[11]

As shown in Table 1, various thioflavanones were synthesized in high yields (76-91%) from 2'-mercaptoacetophenone. The reaction worked well both for the electron withdrawing group (**4d**-**4f**) and electron donating (**4g**-**4j**) of benzaldehydes regardless of the kind and the position of substituents under the present reaction conditions. The ortho substituted methoxy group (**4b**) of benzaldehyde didn't influence the condensation of **2**. Furthermore, 3'-hydroxy-



Scheme 1

Table 1. Preparation of thioflavanones from 2'-mercaptoacetophenone and benzaldehydes

Thioflavanones **4**	R^1	R^2	R^3	R^4	Isolated yields, %[a]
a	H	H	H	H	87
b	OMe	H	H	H	82
c	H	OH	H	H	76
d	H	NO_2	H	H	78
e	H	H	Cl	H	84
f	H	H	F	H	81
g	H	H	Me	H	86
h	H	H	OMe	H	91
i	H	OMe	OMe	H	85
j	H	OMe	OMe	OMe	80

[a]Yields from 2'-mercaptoacetophenone.

thioflavanone **4c** was synthesized by this method without the protection of hydroxyl group. The addition of a solution of 3-hydroxybenzaldehyde pretreated with 1 equiv of lithium diisopropylamide to a solution of lithium dianion of **2** in THF gave **4c** in 76% yield after 2 h between −10 °C and room temperature.

In conclusion, the present method provides (i) a new synthesis of **2** (ii) the direct condensation of **2** with **3** without the isolation of the corresponding chalcones, and (iii) a new synthesis of **4** from **2** in high yields.

Experimental Section

Preparation of 2'-mercaptoacetophenone. To a solution of thiosalicylic acid (771 mg, 5.0 mmol) in DME (20 mL) was slowly added methyllithium (1.5 M in Et_2O, 10.5 mL, 15.8 mmol) under argon atmosphere at −15 °C. After being stirred for 1 h between −15 °C and 0 °C, the resulting light yellow mixture containing white precipitate was quenched with 1.0 N-HCl (3 mL) and DME was evaporated *in vacuo*. The mixture was poured into 1.0 N-HCl (30 mL), extracted with methylene chloride (3 × 25 mL), and washed with sat. aqueous $NaHCO_3$ (30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The residue was purified by vacuum distillation using Kugelrohr apparatus to give **2** (609 mg, 80%) as a light yellow liquid. bp 92-97 °C/0.3 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.8 Hz, 1H), 7.29-7.34 (m, 2H), 7.17-7.25 (m, 1H), 4.46 (s, 1H), 2.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 137.5, 132.7, 132.3, 132.1, 131.7, 124.7, 27.7; FT-IR (film) 3059, 2974, 2539 (S-H), 1671 (C=O), 1588, 1467, 1360, 1254, 1055, 755 cm^{-1}; Ms *m/z* (%) 154 (M^++2, 4), 152 (M^+, 87), 151 (13), 138 (12), 137 (100), 109 (61).

Preparation of thioflavanone 4a (General procedure). To a solution of **2** (304 mg, 2.0 mmol) in THF (9 mL) was added lithium diisopropylamide (2.0 M, 2.2 mL, 4.4 mmol) under argon atmosphere at −15 °C. The resulting light tan mixture was stirred for 1.5 h between −15 °C and −10 °C and a solution of benzaldehyde (212 mg, 2.0 mmol) in THF (5 mL) was added. After being stirred for 2 h between −10 °C and room temperature, the resulting reddish mixture was quenched with 0.5 N-HCl (3 mL) and THF was evaporated *in vacuo*. The mixture was poured into 0.5 N-HCl (30 mL), extracted with methylene chloride (3 × 20 mL), and washed with sat. aqueous $NaHCO_3$ (30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The residue was purified by silica gel column chromatography using 20% EtOAc/*n*-hexane to give **4a** (418 mg, 87%) as a light yellow solid. mp 56-57 °C (lit.[12] 55-56 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (dd, J_1 = 8.0 Hz, J_2 = 1.3 Hz, 1H), 7.31-7.46 (m, 6H), 7.18-7.31 (m, 2H), 4.72 (dd, J_1 = 12.8 Hz, J_2 = 3.3 Hz, 1H), 3.32 (dd, J_1 = 16.4 Hz, J_2 = 12.8 Hz, 1H), 3.20 (dd, J_1 = 16.4 Hz, J_2 = 3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 142.1, 138.4, 133.7, 130.4, 129.2, 129.0, 128.5, 127.4, 127.2, 125.2, 46.7, 45.5; FT-IR (KBr) 3060, 2946, 1677 (C=O), 1586, 1435, 1285, 1085, 756, 697 cm^{-1}; Ms *m/z* (%) 240 (M^+, 51), 163 (20), 136 (100), 108 (50), 97 (33), 83 (33).

2'-Methoxythioflavanone (4b). mp 130-131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (dd, J_1 = 7.9 Hz, J_2 = 1.2 Hz, 1H), 7.36-7.46 (m, 2H), 7.25-7.34 (m, 2H), 7.16-7.22 (m, 1H), 6.89-7.00 (m, 2H), 5.21 (dd, J_1 = 12.2 Hz, J_2 = 3.3 Hz, 1H), 3.84 (s, 3H), 3.29 (dd, J_1 = 16.5 Hz, J_2 = 12.2 Hz, 1H), 3.14 (dd, J_1 = 16.5 Hz, J_2 = 3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 156.6, 142.6, 133.4, 130.4, 129.4, 129.1, 127.7, 127.4, 126.7, 125.0, 120.8, 110.9, 55.6, 45.9, 38.5; FT-IR (KBr) 3079, 2968, 2939, 1672 (C=O), 1588, 1462, 1243, 1107, 1027, 756 cm^{-1}; Ms *m/z* (%) 270 (M^+, 100), 237 (19), 163 (30), 136 (90), 108 (99).

3'-Hydroxythioflavanone (4c). mp 160-161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (s, 1H), 8.01 (dd, J_1 = 7.9 Hz, J_2 = 0.8 Hz, 1H), 7.48-7.56 (m, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.24-7.30 (m, 1H), 7.14-7.22 (m, 1H), 6.86-6.93 (m, 2H), 6.71-6.76 (m, 1H), 4.91 (dd, J_1 = 12.6 Hz, J_2 = 2.8 Hz, 1H), 3.36 (dd, J_1 = 16.4 Hz, J_2 = 12.7 Hz, 1H), 3.05 (dd, J_1 = 16.4 Hz, J_2 = 2.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1, 157.9, 141.8, 140.6, 134.2, 130.4, 130.2, 128.8, 127.6, 125.6, 118.3, 115.5, 114.7, 46.1, 44.3; FT-IR (KBr) 3662 (O-H), 3109, 1659 (C=O), 1584, 1455, 1281, 1156, 757, 689 cm^{-1}; Ms *m/z* (%) 256 (M^+, 48), 239 (7), 163 (15), 136 (100), 120 (37), 108 (46), 91 (24).

3'-Nitrothioflavanone (4d). mp 116-117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30-8.37 (m, 1H), 8.25 (dd, J_1 = 8.1 Hz, J_2 = 1.4 Hz, 1H), 8.15 (dd, J_1 = 8.0 Hz, J_2 = 1.4 Hz, 1H), 7.78 (J = 8.0 Hz, 1H), 7.55-7.63 (m, 1H), 7.41-7.50 (m, 1H), 7.20-7.32 (m, 2H), 4.82 (dd, J_1 = 11.9 Hz, J_2 = 3.6 Hz, 1H), 3.36 (dd, J_1 = 16.4 Hz, J_2 = 11.9 Hz, 1H), 3.25 (dd, J_1 = 16.4 Hz, J_2 = 3.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2, 148.5, 140.8, 140.6, 134.0, 133.5, 130.3, 130.1, 129.3, 127.3, 125.7, 123.5, 122.6, 46.1, 44.6; FT-IR (KBr) 3066, 1678 (C=O), 1585, 1528, 1436, 1350, 1084, 763, 728 cm^{-1}; Ms *m/z* (%) 285 (M^+, 49), 163 (14), 136 (100), 108 (47).

4'-Chlorothioflavanone (4e). mp 126-127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (dd, J_1 = 7.9 Hz, J_2 = 1.2 Hz, 1H), 7.38-7.47 (m, 1H), 7.29-7.31 (m, 4H), 7.18-7.29 (m, 2H), 4.69 (dd, J_1 = 12.2 Hz, J_2 = 3.6 Hz, 1H), 3.28 (dd, J_1 = 16.4

Hz, J_2 = 12.2 Hz, 1H), 3.18 (dd, J_1 = 16.4 Hz, J_2 = 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 141.6, 136.9, 134.3, 133.8, 130.3, 129.2, 129.1, 128.8, 127.2, 125.4, 46.5, 44.7; FT-IR (KBr) 3059, 2986, 1674 (C=O), 1590, 1491, 1435, 1288, 1088, 829, 760 cm^{-1}; Ms *m/z* (%) 276 (M^++2, 10), 274 (M^+, 31), 163 (23), 136 (100), 108 (44), 91 (49).

4'-Fluorothioflavanone (4f). mp 99-100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (dd, J_1 = 7.9 Hz, J_2 = 1.3 Hz, 1H), 7.33-7.47 (m, 3H), 7.16-7.30 (m, 2H), 7.01-7.11 (m, 2H), 4.70 (dd, J_1 = 12.4 Hz, J_2 = 3.6 Hz, 1H), 3.28 (dd, J_1 = 16.4 Hz, J_2 = 12.4 Hz, 1H), 3.18 (dd, J_1 = 16.4 Hz, J_2 = 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1, 162.5 (d, J_{CF} = 246.2 Hz), 160.9, 141.8, 134.2, 133.7, 130.3, 129.2, 127.2, 125.3, 116.1, 115.8, 46.7, 44.7; FT-IR (KBr) 3060, 2893, 1676 (C=O), 1592, 1508, 1435, 1286, 1228, 1084, 838, 761 cm^{-1}; Ms *m/z* (%) 258 (M^+, 22), 163 (10), 136 (100), 108 (26), 96 (23).

4'-Methylthioflavanone (4g). mp 67-68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (dd, J_1 = 8.0 Hz, J_2 = 1.3 Hz, 1H), 7.36-7.43 (m, 1H), 7.12-7.35 (m, 6H), 4.68 (dd, J_1 = 12.9 Hz, J_2 = 3.2 Hz, 1H), 3.30 (dd, J_1 = 16.4 Hz, J_2 = 12.9 Hz, 1H), 3.17 (dd, J_1 = 16.4 Hz, J_2 = 3.2 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 142.2, 138.3, 135.4, 133.6, 130.4, 129.6, 129.2, 127.3, 127.2, 125.1, 46.8, 45.2, 21.1; FT-IR (KBr) 3052, 2947, 1678 (C=O), 1590, 1435, 1285, 1085, 821, 759 cm^{-1}; Ms *m/z* (%) 254 (M^+, 52), 163 (21), 136 (100), 118 (58), 105 (74), 91 (49).

4'-Methoxythioflavanone (4h). mp 93-94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (dd, J_1 = 9.0 Hz, J_2 = 1.2 Hz, 1H), 7.32-7.44 (m, 1H), 7.35 (d, J = 8.7 Hz, 2H), 7.15-7.30 (m, 2H), 6.90 (d, J = 8.7 Hz, 2H), 4.68 (dd, J_1 = 12.9 Hz, J_2 = 3.1 Hz, 1H), 3.81 (s, 3H), 3.29 (dd, J_1 = 16.4 Hz, J_2 = 12.9 Hz, 1H), 3.17 (dd, J_1 = 16.4 Hz, J_2 = 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 159.6, 142.3, 133.6, 130.4, 130.1, 129.2, 128.6, 127.2, 125.2, 114.3, 55.3, 46.9, 44.9; FT-IR (KBr) 3004, 2955, 1676 (C=O), 1609, 1511, 1435, 1251, 1029, 832, 759 cm^{-1}; Ms *m/z* (%) 270 (M^+, 95), 163 (12), 136 (52), 121 (100), 108 (72).

3',4'-Dimethoxythioflavanone (4i). mp 140-141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (dd, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 1H), 7.40-7.46 (m, 1H), 7.21-7.28 (m, 1H), 7.15-7.21 (m, 1H), 6.92-7.00 (m, 2H), 6.86 (d, J = 8.0 Hz, 1H), 4.68 (dd, J_1 = 12.7 Hz, J_2 = 3.4 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.30 (dd, J_1 = 16.4 Hz, J_2 = 12.7 Hz, 1H), 3.19 (dd, J_1 = 16.4 Hz, J_2 = 3.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 149.1, 149.0, 142.1, 133.6, 130.8, 130.3, 129.2, 127.2, 125.2, 119.6, 111.2, 110.4, 55.9 (overlapped O**C**H$_3$), 46.9, 45.3; FT-IR (KBr) 3003, 2961, 2941, 1678 (C=O), 1591, 1458, 1265, 1141, 1026, 870, 810, 768 cm^{-1}; Ms *m/z* (%) 300 (M^+, 99), 163 (13), 151 (100), 136 (30), 108 (28).

3',4',5'-Trimethoxythioflavanone (4j). mp 159-160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (dd, J_1 = 8.0 Hz, J_2 = 1.4 Hz, 1H), 7.37-7.43 (m, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.15-7.21 (m, 1H), 6.65 (s, 2H), 4.67 (dd, J_1 = 12.2 Hz, J_2 = 3.8 Hz, 1H), 3.87 (s, 6H), 3.86 (s, 3H), 3.29 (dd, J_1 = 16.4 Hz, J_2 = 12.2 Hz, 1H), 3.20 (dd, J_1 = 16.4 Hz, J_2 = 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 153.5, 141.9, 138.0, 134.0, 133.7, 130.3, 129.2, 127.2, 125.3, 104.4, 60.9, 56.2, 47.0, 45.9; FT-IR (KBr) 3060, 2937, 2837, 1674 (C=O), 1589, 1506, 1457, 1241, 1126, 840, 762, 729 cm^{-1}; Ms *m/z* (%) 330 (M^+, 96), 194 (44), 181 (100), 163 (9), 136 (34), 108 (20).

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References

1. (a) Schneller, S. W. *Adv. Heterocycl. Chem.* **1975**, *18*, 59. (b) Ingall, A. H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, U. K., 1984; Vol. 3, p 885.
2. (a) Philipp, A.; Jirkovsky, I. *J. Med. Chem.* **1980**, *23*, 1372. (b) Holshouser, M. H.; Loeffler, L. J.; Hall, I. H. *J. Med. Chem.* **1981**, *24*, 853.
3. (a) Truce, W. E.; Milionis, J. P. *J. Am. Chem. Soc.* **1952**, *74*, 974. (b) Robillard, B.; Slaby, H. M.; Lindsay, D. A.; Ingold, K. U. *J. Org. Chem.* **1986**, *51*, 1700.
4. (a) Ponticello, G. S.; Freedman, M. B.; Habecker, C. N.; Holloway, M. K.; Amato, J. S.; Conn, R. S.; Baldwin, J. J. *J. Org. Chem.* **1988**, *53*, 9. (b) Cui, D. M.; Kawamura, M.; Shimada, S.; Hayashi, T.; Tanaka, M. *Tetrahedron Lett.* **2003**, *44*, 4007.
5. Clayton, S. E.; Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M. *Tetrahedron* **1993**, *49*, 939.
6. Bath, S.; Laso, N. M.; Lopez-Ruiz, H.; Quiclet-Sire, B.; Zard, S. Z. *Chem. Commun.* **2003**, 204.
7. Kumar, P.; Rao, A. T.; Pandey, B. *Synth. Commun.* **1994**, *24*, 3297.
8. (a) Wang, H. K.; Bastow, K. F.; Cosentino, L. M.; Lee, K. H. *J. Med. Chem.* **1996**, *39*, 1975. (b) Horvath, A.; Nussbaumer, P.; Wolff, B.; Billich, A. *J. Med. Chem.* **2004**, *47*, 4268.
9. (a) Kumar, P.; Rao, A. T.; Pandey, B. *J. Chem. Soc., Chem. Commun.* **1992**, 1580. (b) Kumar, P.; Bodas, M. S. *Tetrahedron* **2001**, *57*, 9755.
10. Lee, J. I.; Jung, M. G.; Jung, H. J. *Bull. Korean Chem. Soc.* **2007**, *28*, 859.
11. (a) Poonia, N. S.; Chhabra, K.; Kumar, C.; Bhagwat, V. W. *J. Org. Chem.* **1977**, *42*, 3311. (b) Moorthy, N. S. H. N.; Singh, R. J.; Singh, H. P.; Gupta, S. D. *Chem. Pharm. Bull.* **2006**, *54*, 1384.
12. Cadogan, J. I. G.; Ley, S. V.; Pattenden, G.; Raphael, R. A.; Rees, C. W. *Dictionary of Organic Compounds*; Chapman & Hall: London, U. K., 1997; p 2313.