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SYNTHESIS AND CHARACTERIZATION OF 2-METHYLSULFONYL-4*H*-4-CHROMENONES

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Abstract: 2-Methylsulfonyl-4*H*-4-chromenones which are important intermediate of 2-substituted 4*H*-4-chromenones, equivalent to 2-halo-4*H*-4-chromenone, were synthesized and first characterized.

In nitrogen heterocyclic chemistry, displacement of the sulfonyl group by nucleophiles such as amino, alkoxy, or thioalkoxy groups is well documented.[1] Compared with the sulfinyl group, the sulfonyl group has been used more frequently due to higher reactivity toward nucleophiles.[2] For the synthesis of 2-substituted 4*H*-4-chromenones, however, the sulfinyl group has been used more generally although the reactivity is low. Until now, 2-methylsulfonyl-4*H*-4-chromenones have not been characterized because these compounds were rapidly hydrolyzed by atmospheric moisture.[3] Here we report the general synthetic method and the first chracterization of 2-methylsulfonyl-4*H*-4-chromenones.

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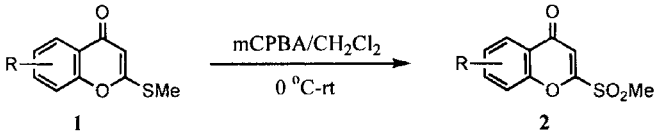
Table 1. Oxidation of 2-methylthio-4*H*-4-chromenones with mCPBA.



1 2

Entry	R[a]	Isolated yield (%)
1	H	91
2	6,8-2Cl	90
3	6-Cl,8-CH_3	94
4	7-MeO	96

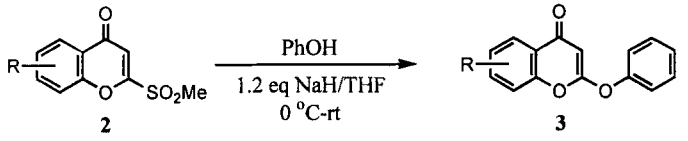
[a] Numbering is based on 2-methylthio-4*H*-4-chromenone.

2-Methylthio-4*H*-4-chromenones were readily prepared from 2'-hydroxyacetophenones in very good yields through the one-pot reaction.[4] These compounds were treated with 2.5 equiv of mCPBA in CH_2Cl_2 at 0 °C, followed by warming to room temperature, and the reaction mixture was concentrated *in vacuo* to afford crude sulfones along with m-chlorobenzoic acid.[5] Very pure sulfones were obtained in high yields (90-96%) as white crystals when diethyl ether/n-hexane (1/1, v/v) was added to crude adducts (Table 1).

Regardless of substituents, electron-donating or electron-withdrawing, the oxidation step is general. All sulfones are very stable for several weeks at room temperature. Characterization of sulfones was done after recrystallization with isopropanol (see Experimental Section).

When the sulfinyl group was used as the leaving group, yields of displacement reaction with phenol were very low.[3] With sulfones, however, yields

Table 2. Reaction of 2-methylsulfonyl-4*H*-4-chromenones with phenol.



2 3

Entry	R[a]	Isolated yield (%)
1	H	91
2	6,8-2Cl	95
3	6-Cl,8-CH_3	93
4	7-MeO	94

[a] Numbering is based on 2-methylthio-4*H*-4-chromenone.

were very high (91-95%) and results are shown in Table 2. This reaction may have utility by providing an alternative synthetic route for the synthesis of naturally occurring polyalkoxy-2-aryloxy-4*H*-4-chromenones.[6]

In summary, this method provides an efficient, facile, and simple preparation of 2-methylsulfonyl-4*H*-4-chromenone, equivalent to 2-chloro-4*H*-4-chromenones, that are important common intermediates to synthesize diverse 2-substituted 4*H*-4-chromenones. Further studies on the reaction of 2-methylsulfonyl-4*H*-4-chromenones with various nucleophiles such amines, alcohols, and thioalcohols are underway.

Experimental Section

General. Melting points were measured in open capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75.4 MHz,

respectively, unless otherwise specified, in $CDCl_3$ solution using tetramethylsilane as internal standard. Analytical thin-layer chromatography was performed on precoated silica gel plates (0.25-mm 60 F-254 E. Merck). THF was dried over sodium benzophenone prior to use.

Representative Procedure

Preparation of 7-Methoxy-2-methylsulfonyl-4*H*-4-chromenone. To a stirred solution of 7-methoxy-2-methylthio-4*H*-4-chromenone (44.5 g, 0.2 mol) in CH_2Cl_2 (700 mL) was added portionwise mCPBA (57-86%, 151.4 g) over 30 min at 0 °C. After 30 min, the reaction mixture was allowed to warm to room temperature, and the stirring was continued for an additional 2 h. The reaction mixture was concentrated *in vacuo* to afford a white solid. Diethyl ether (200 mL) and n-hexane (200 mL) were added to the residue and the mixture was kept at 0 °C for several hours. The insoluble white solid was filtered, washed with cold diethyl ether/n-hexane (v/v, 1/1), and dried to give a white solid (48.8 g, 96%) which was only one spot on TLC. Analytical sample was obtained by recrystallization with isopropanol as white needle-type crystals.

TLC R_f 0.44 (hexane/EtOAc; 1/1); mp 181-182 (isopropanol); ^{1}H NMR (300 MHz) δ 8.01-8.09 (m, aromatic, 1 H), 6.90-7.04 (m, aromatic, 2 H), 6.97 (s, 1 H), 3.90 (s, 3 H), 3.21 (s, 3 H); ^{13}C NMR (75.4 MHz) δ 175.9, 165.2, 160.2, 157.6, 127.4, 117.8, 116.0, 112.3, 100.6, 56.1, 40.8; IR (KBr) 3072, 3006, 2922, 1658 (CO), 1604, 1506, 1434, 1255, 1236, 1155, 1058, 879, 842 cm^{-1}; MS *m/e* (rel intensity) 254 (M^+, 87), 119 (100), 63 (33). Anal. Calcd for $C_{11}H_{10}O_5S$: C, 51.96; H, 3.96. Found: C, 52.05; H, 3.85.

Other sulfones were synthesized by the same reaction scale as described in the representative procedure mentioned above.

6,8-Dichloro-2-methylsulfonyl-4*H*-4-chromenone: Yield 90%; TLC R_f 0.70 (hexane/EtOAc; 1/1); mp 179-180 (isopropanol); ^{1}H NMR (300 MHz) δ 8.03-8.08 (m, aromatic, 1 H), 7.80-7.83 (m, aromatic, 1 H), 7.09 (s, 1 H), 3.27 (s, 3 H); ^{13}C NMR (75.4 MHz) δ 175.0, 161.2, 150.0, 135.3, 132.7, 125.8, 124.9, 124.3, 111.7, 40.5; IR (KBr) 3081, 3021, 3002, 2919, 1662 (CO), 1463, 1357, 1163, 1160, 970, 775 cm^{-1}; MS *m/e* (rel intensity) 293 (M^+, 12), 292 (73), 201 (38), 157 (84), 69 (100). Anal. Calcd for $C_{10}H_6Cl_2O_4S$: C, 40.98; H, 2.06. Found: C, 41.08; H, 2.11.

6-Chloro-8-methyl-2-methylsulfonyl-4*H*-4-chromenone: Yield 94%; TLC R_f 0.62 (hexane/EtOAc; 1/1); mp 214-215 (isopropanol); ^{1}H NMR (300 MHz) δ 7.94-8.00 (m, aromatic, 1 H), 7.50-7.60 (m, aromatic, 1 H), 7.04 (s, 1 H), 3.22 (s, 3 H), 2.51 (s, 3 H); ^{13}C NMR (75.4 MHz) δ 176.0, 160.8, 152.7, 136.2, 132.3, 130.2, 124.9, 123.1, 111.8, 40.9, 15.5; IR (KBr) 3080, 3005, 2922, 1666 (CO), 1563, 1332, 1153, 971, 773 cm^{-1}; MS *m/e* (rel intensity) 272 (M^+, 100), 181 (30), 137 (77), 101 (35). Anal. Calcd for $C_{11}H_9ClO_4S$: C, 48.45; H, 3.33. Found: C, 47.99; H, 3.41.

2-Methylsulfonyl-4*H*-4-chromenone: Yield 91%; TLC R_f 0.49 (hexane/EtOAc; 1/1); mp 119-120 (isopropanol); ^{1}H NMR (300 MHz) δ 8.10-8.20 (m, aromatic, 1 H), 7.70-7.80 (m, aromatic, 1 H), 7.35-7.60 (m, aromatic, 2 H), 7.03 (s, 3 H), 3.23 (s, 3 H); ^{13}C NMR (75.4 MHz) δ 176.8, 160.7, 155.7, 135.3, 126.7, 126.2, 124.0, 118.5, 112.0, 40.7; IR (KBr) 3095, 3010, 2913, 1705 (CO), 1658, 1610, 1321,

1197, 765 cm^{-1}; MS *m/e* (rel intensity) 224 (M^+, 51), 89 (100), 63 (35). Anal. Calcd for $C_{10}H_8O_4S$: C, 53.57; H, 3.60. Found: C, 53.60; H, 3.48.

Representative Procedure

Reaction of 6,8-dichloro-2-methylsulfonyl-4*H*-4-chromenone with phenol. To a stirred solution of sodium phenoxide, prepared from phenol (1.13 g, 12.0 mmol) and NaH (60% dispersion in mineral oil, 12.0 mmol) in dry THF (10 mL), was added dropwise a solution of 6,8-dichloro-2-methylsulfonyl-4*H*-4-chromenone (2.93 g, 10.0 mmol) in dry THF (10 mL) for 5 min at 0 °C. After 5 min, the reaction mixture was allowed to warm to room temperature, and the stirring was continued for an additional 20 min. The reaction mixture was concentrated *in vacuo* to afford a pale yellow sticky material. Flash column chromatography (SiO_2, n-hexane/EtOAc; 5/1 ,v/v) gave 6,8-dichloro-2-phenoxy-4*H*-4-chromenone (2.92 g, 95%) as a white crystal.

TLC R_f 0.49 (hexane/EtOAc; 5/1); mp 106-107; ^1H NMR (300 MHz) δ 8.04 (d, J = 2.5 Hz, aromatic, 1 H), 7.71 (d, J = 2.5 Hz, aromatic, 1 H), 7.15-7.53 (m, aromatic, 5 H), 5.47 (s, 1 H); ^{13}C NMR (75.4 MHz) δ 177.1, 167.6, 151.1, 148.1, 133.6, 131.3, 130.5, 127.3, 125.0, 124.1, 123.6, 120.8, 90.3; IR (KBr) 3099, 3050, 1649 (CO), 1614, 1564, 1461, 1070, 845, 822 cm^{-1}; MS *m/e* (rel intensity) 307 (M^+, 18), 118 (100), 77 (68), 51 (37). Anal. Calcd for $C_{15}H_8Cl_2O_3$: C, 58.66; H, 2.63. Found: C, 58.41; H, 2.59.

Other phenoxychromenones were synthesized by the same reaction scale as described in the representative procedure mentioned above.

2-Phenoxy-4*H*-4-chromenone: Yield 91%; TLC R_f 0.39 (hexane/EtOAc; 5/1); mp 80.5-81.5; ^{1}H NMR (300 MHz) δ 8.18 (dd, J = 7.9, 1.7 Hz, aromatic, 1 H), 7.68 (ddd, J = 10.2, 7.2, 1.7 Hz, aromatic, 1 H), 7.14-7.53 (m, aromatic, 7 H), 5.46 (s, 1 H); ^{13}C NMR (75.4 MHz) δ 179.3, 167.5, 153.8, 151.5, 133.5, 130.4, 126.9, 125.9, 125.5, 123.0, 120.8, 117.4, 90.4; IR (KBr) 3066, 3039, 3010, 1618 (CO), 1562, 1475, 1216, 991, 767 cm^{-1}; MS *m/e* (rel intensity) 238 (M^+, 70), 120 (45), 77 (100). 69 (70), 50 (65). Anal. Calcd for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23. Found: C, 75.81; H, 4.24.

6-Chloro-8-methyl-2-phenoxy-4*H*-4-chromenone: Yield 93%; TLC R_f 0.52 (hexane/EtOAc; 5/1); mp 122-123; ^{1}H NMR (300 MHz) δ 7.97 (d, J = 2.6 Hz, 1 H), 7.16-7.52 (m, aromatic, 6 H), 5.46 (s, 1 H), 2.45 (s, 3 H); ^{13}C NMR (75.4 MHz) δ 178.3, 167.4, 151.3, 150.6, 134.4, 130.9, 130.4, 129.1, 127.1, 123.9, 122.9, 120.9; IR (KBr) 3093, 3062, 1658 (CO), 1575, 1458, 1379, 1225, 812, 764 cm^{-1}; MS *m/e* (rel intensity) 286 (M^+, 74), 168 (51), 140 (28), 118 (100), 90 (16), 77 (58), 69 (15), 51 (36). Anal. Calcd for $C_{16}H_{11}ClO_3$: C, 67.03; H, 3.87. Found: C, 67.22; H, 3.95.

7-Methoxy-2-phenoxy-4*H*-4-chromenone: Yield 94%; TLC R_f 0.41 (hexane/EtOAc; 5/1); mp 151-152; ^{1}H NMR (300 MHz) δ 8.06 (d, J = 8.8 Hz, aromatic, 1 H), 7.15-7.55 (m, aromatic, 5 H), 6.97 (dd, J = 8.8, 2.4 Hz, aromatic, 1 H), 6.86 (d, J = 2.4 Hz, aromatic, 1 H), 5.39 (s, 1 H), 3.91 (s, 3 H); ^{13}C NMR (75.4 MHz) δ 178.8, 167.3, 164.0, 154.4, 151.6, 130.3, 127.1, 126.8, 120.8, 116.6, 114.0, 100.4, 90.1, 55.8; IR (KBr) 3066, 3016, 2949, 2839, 1622 (CO), 1564, 1444, 1392,

1352, 1219. 1024, 935, 802 cm^{-1}; MS *m/e* (rel intensity) 268 (M^+, 85), 151 (55), 118 (100). 77 (53). Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.88; H, 4.41.

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