An Efficient Synthesis of 2-Phenyl-4*H*-1-benzothiopyran-4-ones from Thiosalicylic Acid

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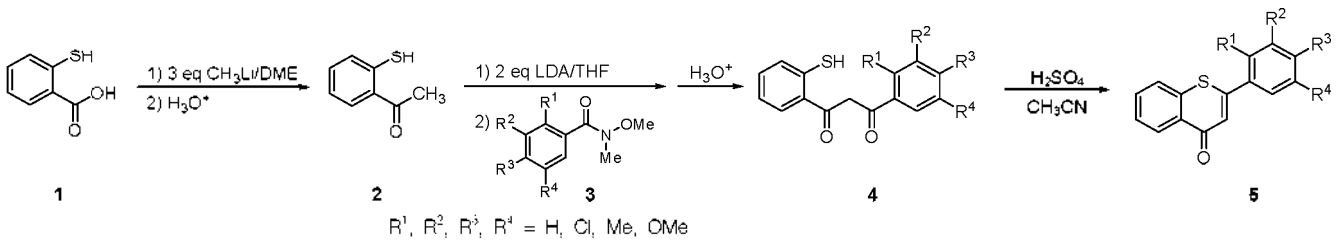
2-Phenyl-4*H*-1-benzothiopyran-4-ones (thioflavones) are the thio analogues of flavones[1] which are a class of naturally occuring pharmacologically active compounds. The thioflavones also exhibit various pharmacological activities[2] such as antimalarial, antimicrobial, and antifungal activity and are useful as potent inhibitors of steroid sulfatase.[3] In general, 2-phenyl-4*H*-1-benzothiopyran-4-ones are synthesized by the condensation of thiophenols with ethyl benzoylacetates in polyphosphoric acid at 90 °C, but the yields are low to moderate.[4] The cyclization of ethyl β-(arylthio)cinnamates, derived from Michael addition of thiophenols to ethyl phenylpropiolates, with stannic chloride or phosphorus pentoxide/methanesulfonic acid gives 2-phenyl-4*H*-1-benzothiopyran-4-ones.[5] However, this method could not be applied for the synthesis of methoxy substituted thioflavones because competitive cyclization into the cinnamyl aromatic ring, rather than the sulfur-bearing ring, occurs when cinnamyl ring is activated by methoxy substituents. The reaction of *S*-aroyl derivatives of thiosalicylic acid with *N*-phenyl(triphenylphosphoranylidene) ethemine[6] or (trimethylsilyl)methylenetriphenylphosphorane[7] leads to the acylphosphoranes which undergo subsequent intramolecular Wittig cyclization in refluxing THF to afford 2-phenyl-4*H*-1-benzothiopyran-4-ones, but the separation of phenyl isocyanate is tedious. Alternatively, the condensation of methyl thiosalicylate with trilithiated acetoacetanilides[8] or dilithiated *N*-benzoylhydrazones[9] with excess lithium diisopropylamide gives the *C*-acylated intermediates which undergo subsequent cyclodehydration and hydrolysis with 3 N-HCl under reflux to afford 2-phenyl-4*H*-1-benzothiopyran-4-ones in moderate to high yields.

Herein, we describe a new efficient synthesis of 2-phenyl-4*H*-1-benzothiopyran-4-ones *via* 2'-mercaptoacetophenone in overall high yields under the mild conditions. 2'-Mercaptoacetophenone **2** was directly prepared from thiosalicylic acid **1** and methyllithium in DME in 80% yield according to our previous method[10] (Scheme 1). The condensation of the dilithiated anion of **2** with benzoylating reagent was initially studied using benzoyl chloride. The addition of benzoyl chloride to a solution of the lithium dianion, generated from compound **2** and two equivalents of lithium diisopropylamide in THF, at -78 °C and on stirring for 2 h between -78 °C and room temperature gave 1-(2-mercaptophenyl)-3-phenyl-1, 3-propanedione **4a** in only 15% yield. The use of benzoyl cyanide increased the yield of **4a** to 67% under the same reaction conditions. However, the reaction of the lithium dianion of **2** with *N*-methoxy-*N*-methyl benzamide **3a** at room temperature for 16 h proceeded well to give **4a** in 84% yield. Interestingly, ^{1}H NMR spectra of **4** showed C_2 methylene signals at 3.22-3.98 ppm with two doublets, indicating that **4** exist mostly as keto forms.

The cyclodehydration of **4a** was attempted using 1 equiv of sulfuric acid in various solvents such as HOAc, CH_3CN, EtOH, and THF. Under these conditions, the desired 2-phenyl-4*H*-1-benzothiopyran-4-one **5a** was obtained in 93%, 94%, 92%, and 91% yield, respectively, after 0.5 h, 1 h, 36 h, and 48 h, respectively. Although the use of acetic acid as a solvent gave excellent yield of **5a** in very short time (*vide supra*), acetic acid is corrosive, irritant, and pungent, and troublesome to separate and therefore CH_3CN was chosen as a suitable solvent for the cyclodehydration. The cyclodehydration of **4a** using 1 equiv of polyphosphoric acid in CH_3CN was also tested at room temperature. However, the reaction was rather sluggish and after 48 h the yield was 92%. Thus, 1 equiv of sulfuric acid in CH_3CN at room temperature for 1 h is considered as optimum reaction conditions for obtaining high yield (94%) of product **4a**. The same reaction conditions were adopted for the synthesis of other products.

As shown in Table 1, various 2-phenyl-4*H*-1-benzothiopyran-4-ones were synthesized in overall high yields (58-65%) from the starting **1**. The reaction worked well both for the



Scheme 1

Table 1. Preparation of compounds **4** and 2-phenyl-4*H*-1-benzothiopyran-4-ones (**5**) from thiosalicylic acid

Entry	R^1	R^2	R^3	R^4	Isolated yields, %	
					4[a]	**5**[b]
a	H	H	H	H	84	94
b	Cl	H	H	H	87	91
c	OCH_3	H	H	H	84	93
d	H	Cl	H	H	84	91
e	H	H	Cl	H	85	89
f	H	H	CH_3	H	85	87
g	H	H	OCH_3	H	87	93
h	H	OCH_3	OCH_3	H	80	91
i	H	OCH_3	OCH_3	OCH_3	81	90

[a]Chromatographic yields. [b]Recrystallized yields.

electron withdrawing substituent such as chloro group (**5d**, **5e**) and electron donating substituents such as methyl (**5f**) and methoxy group (**5g**-**5i**). The reaction also proceeded well regardless of the number and the position of methoxy substituents under the present reaction conditions. Furthermore, the ortho substituted chloro (**5b**) and methoxy group (**5c**) did not affect the efficacy of the cyclodehydration of **4**.

In conclusion the present method provides a new efficient synthesis of 2-phenyl-4*H*-1-benzothiopyran-4-ones from the starting **1**. It has the advantage of high yield synthesis, convenience and versatility of the reaction under the mild conditions and, therefore, may be widely utilized for the synthesis of 2-phenyl-4*H*-1-benzothiopyran-4-ones.

Experimental Section

Preparation of 1-(2-mercaptophenyl)-3-phenyl-1,3-propanedione 4a (General procedure). To a solution of 2'-mercaptoacetophenone (609 mg, 4.0 mmol) in THF (12 mL) was added lithium diisopropylamide (2.0 M, 2.1 mL, 4.2 mmol) at -20 °C. The stirring was continued for 1.5 h between -20 °C and -10 °C and then a solution of *N*-methoxy-*N*-methyl benzamide (661 mg, 4.0 mmol) in THF (6 mL) was added to the light tan solution. The mixture was allowed warm to room temperature and stirred for 16 h. The resulting light yellow mixture was quenched with 1 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 × 25 mL), and washed with brine (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 30% EtOAc/*n*-hexane to give **4a** (861 mg, 84%), mp 116-118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (dd, J_1 = 8.2 Hz, J_2 = 1.5 Hz, 1H), 7.66-7.71 (m, 2H), 7.38-7.47 (m, 4H), 7.20-7.26 (m, 2H), 3.44 (d, J = 16.3 Hz, 1H), 3.25 (d, J = 16.3 Hz, 1H), 3.09 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.5, 142.6, 138.8, 134.0, 129.6, 128.9 (overlapped), 128.8, 127.6, 125.5, 124.9, 85.5, 53.7; FT-IR (KBr) 3058, 2914, 1658 (C=O), 1582, 1435, 1296, 1093, 760, 690 cm^{-1}; MS *m*/*z* (%) 256 (M^-, 20), 238 (100), 223 (51), 151 (50), 136 (60), 105 (77).

Preparation of 2-phenyl-4*H*-1-benzothiopyran-4-one 5a (General procedure). To a solution of **4a** (769 mg, 3.0 mmol) in CH_3CN (20 mL) was added *conc* H_2SO_4 (160 μL, 3.0 mmol) at room temperature. The resulting mixture containing precipitate was stirred for 1 h and CH_3CN was evaporated *in vacuo*. The mixture was poured into saturated $NaHCO_3$ solution (30 mL) and extracted with methylene chloride (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was recrystallized twice from 10% EtOAc/*n*-hexane to give **5a** (672 mg, 94%) as a pale yellow solid, mp 125-126 °C (lit.[7] 126 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, J = 7.7 Hz, 1H), 7.60-7.71 (m, 4H), 7.52-7.59 (m, 1H), 7.48-7.52 (m, 3H), 7.24 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.8, 153.0, 137.7, 136.5, 131.6, 130.9, 130.8, 129.3, 128.6, 127.8, 126.9, 126.5, 123.4; FT-IR (KBr) 3066, 1620 (C=O), 1587, 1335, 1098, 759, 696 cm^{-1}; MS *m*/*z* (%) 238 (M^+, 100), 210 (95), 136 (46), 108 (22).

2-(2'-Chlorophenyl)-4*H*-1-benzothiopyran-4-one (5b). mp 129-130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, J = 7.8 Hz, 1H), 7.61-7.65 (m, 2H), 7.50-7.59 (m, 2H), 7.34-7.46 (m, 3H), 7.02 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.4, 150.4, 138.1, 135.2, 132.6, 131.7, 131.1, 130.9, 130.7, 130.5, 128.7, 127.9, 127.2, 127.1, 126.3; FT-IR (KBr) 3059, 1615 (C=O), 1590, 1327, 1100, 863, 764 cm^{-1}; MS *m*/*z* (%) 274 (M^-+2, 34), 272 (M^+, 98), 246 (44), 244 (100), 136 (40), 108 (24).

2-(2'-Methoxyphenyl)-4*H*-1-benzothiopyran-4-one (5c). mp 130-131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 7.5 Hz, 1H), 7.57-7.62 (m, 2H), 7.51-7.55 (m, 1H), 7.42-7.47 (m, 2H), 7.16 (s, 1H), 7.00-7.08 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.8, 156.4, 150.3, 138.8, 131.6, 131.3, 130.9, 130.3, 128.5, 127.5, 126.8, 126.2, 125.4, 120.9, 111.7, 55.7; FT-IR (KBr) 3050, 2983, 1627 (C=O), 1589, 1463, 1251, 1015, 733 cm^{-1}; MS *m*/*z* (%) 268 (M^-, 100), 137 (60), 136 (29), 131 (31), 108 (20).

2-(3'-Chlorophenyl)-4*H*-1-benzothiopyran-4-one (5d). mp 144-146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J = 7.6 Hz, 1H), 7.63-7.68 (m, 3H), 7.52-7.57 (m, 2H), 7.41-7.51 (m, 2H), 7.20 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.6, 151.2, 138.3, 137.3, 135.3, 131.8, 130.8, 130.7, 130.5, 128.6, 128.0, 127.1, 126.5, 125.1, 123.9; FT-IR (KBr) 3057, 1634 (C=O), 1593, 1327, 1102, 885, 768, 731 cm^{-1}; MS *m*/*z* (%) 274 (M^-+2, 35), 272 (M^+, 100), 246 (35), 244 (86), 136 (45), 108 (24).

2-(4'-Chlorophenyl)-4*H*-1-benzothiopyran-4-one (5e). mp 168-169 °C (lit.[9a] 161-165 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, J = 7.6 Hz, 1H), 7.61-7.66 (m, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.52-7.58 (m, 1H), 7.47 (d, J = 8.7 Hz, 2H), 7.19 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.7, 151.5, 137.3, 137.1, 135.0, 131.7, 130.8, 129.6, 128.6, 128.2, 127.9, 126.5, 123.5; FT-IR (KBr) 3015, 1630 (C=O), 1588, 1326, 1088, 828, 706 cm^{-1}; MS *m*/*z* (%) 274 (M^-+2, 33), 272 (M^+, 100), 246 (41), 244 (98), 136 (49), 108 (22).

2-(4'-Methylphenyl)-4*H*-1-benzothiopyran-4-one (5f). mp 118-119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J = 7.7 Hz, 1H), 7.51-7.65 (m, 3H), 7.61 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 7.23 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.9, 153.1, 141.3, 137.7, 133.7, 131.5, 130.9, 130.0, 128.6, 127.7, 126.8, 126.5, 122.8, 21.4; FT-IR (KBr) 3056, 1618 (C=O), 1589, 1441, 1332, 1102, 816, 778 cm^{-1};

MS *m/z* (%) 252 (M^+, 100), 251 (29), 224 (96), 136 (42), 108 (22).

2-(4'-Methoxyphenyl)-4*H*-1-benzothiopyran-4-one (5g). mp 124-125 °C (lit.[7] 126-127 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, J = 7.7 Hz, 1H), 7.65 (d, J = 8.9 Hz, 2H), 7.58-7.65 (m, 2H), 7.50-7.58 (m, 1H), 7.19 (s, 1H), 7.00 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ180.9, 161.8, 152.7, 137.6, 131.5, 130.9, 128.8, 128.5, 128.3, 127.6, 126.4, 122.2, 114.7, 55.5; FT-IR (KBr) 3063, 2989, 1626 (C=O), 1604, 1508, 1435, 1267, 1017, 771 cm^{-1}; MS *m/z* (%) 268 (M^+, 100), 240 (66), 225 (49), 132 (42), 108 (18).

2-(3',4'-Dimethoxyphenyl)-4*H*-1-benzothiopyran-4-one (5h). mp 149-150 °C (lit.[9a] 145-148 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, J = 7.5 Hz, 1H), 7.61-7.66 (m, 2H), 7.51-7.59 (m, 1H), 7.31 (dd, J_1 = 8.4 Hz, J_2 = 2.2 Hz, 1H), 7.21 (s, 1H), 7.19 (d, J = 2.2 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.9, 152.8, 151.4, 149.5, 137.6, 131.5, 130.9, 129.1, 128.5, 127.7, 126.4, 122.3, 120.0, 111.3, 109.6, 56.1 (overlapped OCH_3); FT-IR (KBr) 3012, 2939, 1614 (C=O), 1587, 1509, 1439, 1265, 1143, 1019, 849, 784 cm^{-1}; MS *m/z* (%) 298 (M^+, 100), 270 (16), 255 (23), 162 (24).

2-(3',4',5'-Trimethoxyphenyl)-4*H*-1-benzothiopyran-4-one (5i). mp 111- 112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J = 7.4 Hz, 1H), 7.62-7.68 (m, 2H), 7.53-7.61 (m, 1H), 7.23 (s, 1H), 6.92 (s, 2H), 3.95 (s, 6H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.5, 153.7, 153.0, 140.3, 137.5, 132.0, 131.7, 131.0, 128.6, 127.8, 126.4, 123.0, 104.2, 61.0, 56.3; FT-IR (KBr) 3026, 2950, 1630 (C=O), 1586, 1507, 1450, 1328, 1245, 1131, 1003, 773, 732 cm^{-1}; MS *m/z* (%) 328 (M^+, 100), 313 (74), 285 (16), 257 (17).

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