A Novel and Efficient Method for the Synthesis of New Hydroxythioxanthone Derivatives

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Abstract: We describe the synthesis of some new hydroxythioxanthones by treatment of thiosalicylic acid (TSA) with various substituted phenols in the presence of Al₂O₃–CH₃SO₃H (AMA). Most of the reactions show high regioselectivity and produce thioxanthones in good yields.

Keywords: thioxanthone, thiosalicylic acid, methansulfonic acid, alumina

Thioxanthone derivatives have been studied extensively owing to their medicinal properties such as antihistaminic, antiparasitic, neuroleptic, and antitumor activities. In addition, various derivatives of thioxanthones are used as activators or sensitizers in the photopolymerization of ethylene-derived unsaturated monomers, particularly acrylate derivatives. Moreover, alkyl-, alkoxy- and hydroxyl- substituted thioxanthones are particularly useful as heat and ultraviolet stabilizers for polyolefins.

The syntheses of thioxanthone and substituted thioxanthones have been carried out by different methods. These compounds are generally synthesized by condensation of appropriately substituted potassium 2-chlorobenzoates with thiophenoles, or condensation of substituted thiosalicylic acids with benzene derivatives followed by cyclization of the intermediate 2-phenylmercaptobenzoic acids in sulfuric acid, AlCl₃, or PPA. However, these methods have some disadvantages such as low yields, long reaction times, the use of large amount of concentrated sulfuric acid, and lack of regiochemical control in the ring closure step. Moreover, some of these methods require two steps and are limited to specific benzoic acids or benzene derivatives having electron-withdrawing groups and are not applicable to a large number of starting materials.

We have recently reported that a mixture of Al₂O₃–CH₃SO₃H (AMA) is an effective reagent for Fries rearrangement, Beckmann rearrangement, direct conversion of aromatic aldehydes to the corresponding glycol monoesters, dehydration of nitriles into amides, and synthesis of macrocyclic polyether-diesters. We report herein that AMA also works as a good reagent for the synthesis of hydroxythioxanthones by heating thiosalicylic acid (TSA) and phenol in AMA to give the corresponding hydroxythioxanthones in high yield (Scheme 1). To develop an efficient reagent for the synthesis of hydroxythioxanthone derivatives, we initially examined the reaction of TSA with resorcinol (Scheme 1) in the presence of various reagents. The reaction was monitored via TLC and ¹H NMR spectroscopy (Table 1).

As shown in Table 1, the best results were obtained using a mixture of Al₂O₃ (0.300 g) and CH₃SO₃H (1 mL) at 110 °C for five minutes. The results also show the importance of using both Al₂O₃ and CH₃SO₃H (compare entries 9 and 10 with 11). The use of two equivalents of phenol and one equivalent of TSA (2) for 1-hydroxythioxanthone (3) does not improve the yield of thioxanthone in comparison with the case where one equivalent of phenol (1) and one equivalent of TSA (2) were used. Because of this initial observation, it seemed advantageous to investigate this method as a new and more suitable way to hydroxythioxanthones synthesis. The experimental procedure for the preparation of hydroxythioxanthones is remarkably simple and does not require the use of any solvent or inert atmosphere.

To establish the generality and applicability of this method, various substituted phenols were subjected to the same reaction condition to furnish the corresponding thioxanthones in good yields (Table 2, Scheme 2).
As illustrated in Table 2, when 3-hydroxy-5-methylphenol (2b) and 3,5-dihydroxyphenol (2c) were employed, 1-hydroxy-3-methylthioxanthone (3b) and 1,3-dihydroxythioxanthone (3c) were isolated as regiospecific isomers in 67% and 70% yields, respectively (Table 2, entries 2 and 3). Similar regiochemical behavior was observed in the reaction of pyrogallol (2g) with TSA (1) affording 1,2,3-trihydroxythioxanthone (3i) in 65% yield (Table 2, entry 7).

In the case of phenols that can form two products, the major product is the thioxanthone that has one hydroxyl group in position 1 (entries 4, 5, and 8). The regiochemical control in these reactions can be rationalized in terms of the hydrogen-bond formation between the hydroxyl and the carbonyl group in the corresponding thioxanthones. The 1H NMR signal of the H-bonded OH group was observed at δ = 14 ppm. Reaction of 2-hydroxy-4-methyltoluene (2f) afforded isomer 3h in 70% yield. 4-Hydroxy-2-methylphenol (2e) gives 3f and 3g in equal yields and they were readily separated by column chromatography (entry 5). Some phenols having an electron-withdrawing group such as NO2 and/or Cl did not produce any thioxanthone (Table 2, entries 9 and 10). Increase of the reaction time to 24 hours or more did not improve the yield of the reaction.

In conclusion, we have found a new, efficient, and regio-selective method for the preparation of some new hydroxythioxanthones in the presence of Al2O3–CH3SO3H.

Table 2 The Results of Reaction of 1 (1 mmol) and 2 (1 mmol) in the Presence of AMA Reagent

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phenol 2</th>
<th>Time/min</th>
<th>Mp/°C</th>
<th>Thioxanthone 3</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>R2</td>
<td>R3</td>
<td>R4</td>
<td>R5</td>
<td>R1</td>
</tr>
<tr>
<td>1</td>
<td>2a</td>
<td>OH</td>
<td>H</td>
<td>OH</td>
<td>H</td>
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<tr>
<td>2</td>
<td>2b</td>
<td>OH</td>
<td>H</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>OH</td>
<td>H</td>
<td>OH</td>
<td>H</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>OH</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>OH</td>
<td>Me</td>
<td>H</td>
<td>OH</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>Me</td>
<td>OH</td>
<td>H</td>
<td>Me</td>
</tr>
<tr>
<td>7</td>
<td>2g</td>
<td>OH</td>
<td>OH</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>8</td>
<td>2h</td>
<td>OH</td>
<td>H</td>
<td>OH</td>
<td>H</td>
</tr>
<tr>
<td>9</td>
<td>2i</td>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>NO2</td>
</tr>
<tr>
<td>10</td>
<td>2j</td>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
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As illustrated in Table 2, when 3-hydroxy-5-methylphenol (2b) and 3,5-dihydroxyphenol (2c) were employed, 1-hydroxy-3-methylthioxanthone (3b) and 1,3-dihydroxythioxanthone (3c) were isolated as regiospecific isomers in 67% and 70% yields, respectively (Table 2, entries 2 and 3).
MS: (KBr); δ = 32.50 (s), 1640 (s), 1590 (s), 1440 (s), 1270 (s), 1200 (s), 1160 (s), 1020 (s), 900 (s), 840 (s), 750 (s) cm⁻¹.

1H NMR (DMSO-d₆): δ = 6.31 (s, 1 H), 6.50 (s, 1 H), 7.52 (t, 1 H), 7.72 (m, 2 H), 8.70 (d, 1 H), 11.05 (s, 1 H), 14.36 (s, 1 H).

13C NMR (DMSO-d₆): δ = 101.4, 103.3, 107.8, 126.0, 126.9, 127.6, 128.7, 133.4, 136.6, 140.3, 164.2, 166.9, 183.3.

MS: ml/z (% = 244 (10) [M⁺], 216 (5), 187 (10), 115 (11), 85 (17), 69 (50), 43 (100).

UV: λₑₘₓ = 267, 390 nm.


1-Hydroxy-3,4-dimethylthioxanthone (3d)

Yield: 65%: yellow needles; mp 171–173°C.

IR (KBr): 1620 (s), 1575 (s), 1550 (s), 1450 (s), 1350 (s), 1280 (s), 1210 (s), 1100 (s), 920 (s), 840 (s) cm⁻¹.

1H NMR (CDCl₃): δ = 2.30 (s, 3 H), 2.37 (s, 3 H), 6.78 (s, 1 H), 7.46 (t, 1 H), 7.58 (d, 1 H), 7.62 (t, 1 H), 8.55 (d, 1 H), 14.13 (s, 1 H).

13C NMR (CDCl₃): δ = 15.2, 21.8, 115.9, 122.0, 126.3, 129.4, 133.0, 137.0, 138.0, 145.7, 160.0, 163.5.

MS: ml/z (% = 256 (32) [M⁺], 135 (31), 122 (71), 107 (100), 91 (32), 77 (47), 43 (51).

UV: λₑₘₓ = 257, 272, 316, 412 nm.

Anal. Calcd for C₁₅H₁₅O₂S (256.32): C, 70.29; H, 4.72. Found: C, 70.16; H, 4.69.

4-Hydroxy-1,2-dimethylthioxanthone (3e)

Yield: 8%: green needles; mp 230–232°C.

IR (KBr): 1620 (s), 1580 (s), 1440 (s), 1400 (s), 1310 (s), 1230 (m), 1200 (m), 1100 (s), 950 (s), 870 (s), 800 (s), 750 (s) cm⁻¹.

1H NMR (CDCl₃): δ = 2.20 (s, 3 H), 2.53 (s, 3 H), 7.01 (s, 1 H), 7.46 (t, 1 H), 7.67 (d, 1 H), 8.55 (d, 1 H), 10.68 (s, 1 H).

13C NMR (CDCl₃): δ = 17.9, 20.9, 118.9, 123.0, 126.4, 128.7, 129.1, 130.9, 131.5, 132.2, 135.2, 136.1, 141.2, 149.9, 183.1.

MS: ml/z (% = 256 (36) [M⁺], 135 (34), 122 (70), 107 (100), 77 (50), 43 (52).

UV: λₑₘₓ = 264, 311, 390 nm.

Anal. Calcd for C₁₅H₁₅O₂S (256.32): C, 70.29; H, 4.72. Found: C, 70.26; H, 4.76.

1,4-Dihydroxy-3-methylthioxanthone (3f)

Yield: 40%: yellow needles; mp 232–233°C.

IR (KBr): 3450 (w) 1640 (s), 1580 (s), 1360 (s), 1300 (s), 1230 (s), 1160 (s), 1100 (s), 920 (s), 840 (s) cm⁻¹.

1H NMR (CDCl₃): δ = 2.41 (s, 6 H), 6.71 (s, 1 H), 6.83 (s, 1 H), 7.51 (m, 3 H), 8.53 (d, 1 H), 14.00 (s, 1 H).

13C NMR (CDCl₃): δ = 22.3, 115.3, 116.5, 118.3, 125.9, 126.5, 128.1, 129.6, 133.1, 138.4, 144.0, 147.8, 164.2, 185.2.

MS: ml/z (% = 242 (100) [M⁺], 213 (21), 184 (13), 43 (14).

UV: λₑₘₓ = 268, 313, 405 nm.


1,3-Dihydroxythioxanthone (3e)

Yield: 70%: orange cubes; mp 232–233°C.

UV: λₑₘₓ = 255, 273, 324, 422 nm.


1,4-Dihydroxy-2-methylthioxanthone (3g)

Yield: 40%: yellow needles; mp 219–220°C.

IR (KBr): 3300 (w), 1630 (s), 1600 (s), 1430 (s), 1390 (s), 1300 (s), 1090 (s), 750 (s) cm⁻¹.
Novel Method for Synthesis of New Hydroxythioxanthone Derivatives

2-Hydroxy-1,4-dimethylthioxanthone (3h)
Yield: 70%; red needles; mp 210–212 °C.

2,4-Dihydroxythioxanthone (4)
Yield: 5%; green needles; mp 220–222 °C.

References