One-pot synthesis of novel thioxanthone crown ethers

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Abstract
The reaction of thiosalicylic acid (TSA) and benzocrown ethers in concentrated sulfuric acid affords a general and efficient way to prepare thioxanthone crown ethers. This chemistry presumably proceeds by intermolecular sulfur electrophilic reaction and subsequently intramolecular electrophilic cyclization. Most of the reactions show high regioselectivity in good yields.

Keywords: Thioxanthone, thiosalicylic acid, crown ether

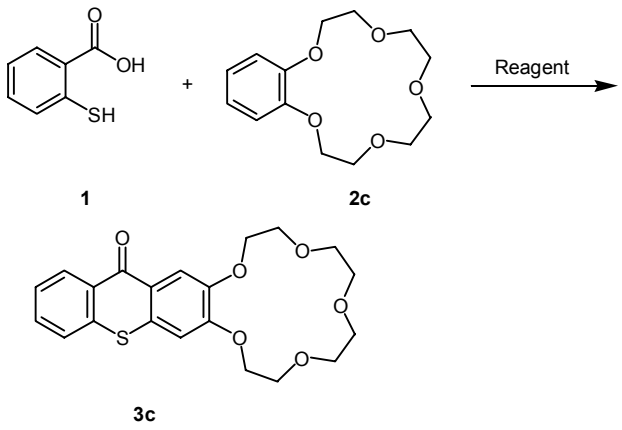
Introduction

Thioxanthones are an important class of molecules and are a common heterocyclic scaffold in biologically active and medicinally significant compounds. The thioxanthone ring is the core structure of a wide variety of naturally occurring and synthetic compounds that exhibit extraordinary anti-tumor[1-3,6,9] anti-parasitic[4,5] and anti-cancer activity[6,7,10]. Thioxanthone derivatives are potential anti-cancer drugs and some thioxanthones containing plant extract are directly used in traditional medicines.[5-7] Crown ethers have enjoyed widespread use in various areas of science and technology[11] ever since the first preparation of the ligands by Pederson.[12]

Results and Discussion

Standard syntheses of the thioxanthones skeleton typically involve multi-step procedures which generally involve the intermediacy of a benzophenone or a diarylthioether, plus harsh reaction conditions, and/or strong acids are often employed.[6-8] Other methods for the synthesis of thioxanthones are used of concentrated sulfuric acid at room or high temperature.[13,14] Also we have recently reported preparation of hydroxythioxanthone derivatives and some of their applications.[15,16, 17]

We now wish to report a novel and efficient one-pot method for synthesis of thioxanthone crown ether under concentrated sulfuric acid at room temperature (Scheme 1).



Scheme 1

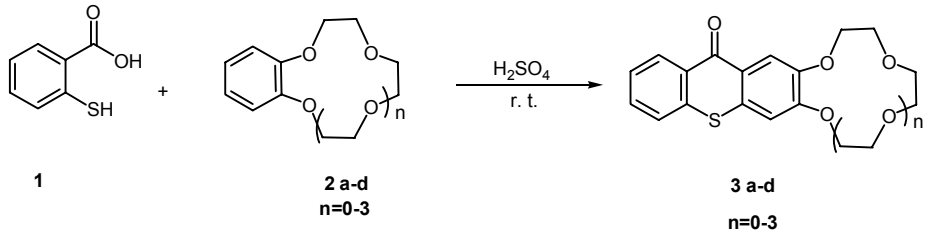
To develop an efficient reagent for the synthesis of thioxanthone crown ethers, we initially examined the reaction of thiosalicylic acid (TSA) with benzo-15-crown-5 (**2c**) in the presence of various reagents. The reaction monitored via TLC (n-hexane/CH_2Cl_2) and ^{1}H NMR spectroscopy (Table 1).

Table 1. The results of the reaction of **1** (1 mmol) and **2c** (1 mmol) in the presence of various reagents

Entry	Conditions	Time (h)	Temp. ^oC	Yield (%)[a]
1	CH_3SO_3H	24	r. t.	-
2	CH_3SO_3H	1.5	100	-
3	CH_3SO_3H+Al_2O_3[14]	10	110	-
4	CH_3SO_3H+Al_2O_3[14]	1.5	140	-
5	H_3PO_4	24	r. t.	-
6	PPA[6]	24	100	-
7	PPA+Al_2O_3	24	100	-
8	P_4O_{10}+CH_3SO_3H	16	100	-
9	H_2SO_4 70%	12	80	-
10	Conc. H_2SO_4 98%	2	0	25
11	Conc. H_2SO_4 98%	2	r. t.	40
12	Conc. H_2SO_4 100%	2	r. t.	40
13	Conc.H_2SO_4 98% [b]	2	r. t.	70
14	Conc. H_2SO_4 98%	2	90	30

[a] Isolated yield, [b] ratio 1:7 of TSA/Crown ether were used

As is shown in Table 1 the best results were obtained using concentrated sulfuric acid at room temperature for 2 hours. The ratio TSA/crown ether is 1:7 (Table 1: Entry 13). No increase in the yields was observed with improving the temperature. To establish the generality and applicability of this method, various crown ethers were subjected to the same reaction conditions to furnish the corresponding thioxanthone crown ethers in good yields (Scheme 2) (Table 2).



1 **2 a-d** n=0-3 **3 a-d** n=0-3

Scheme 2

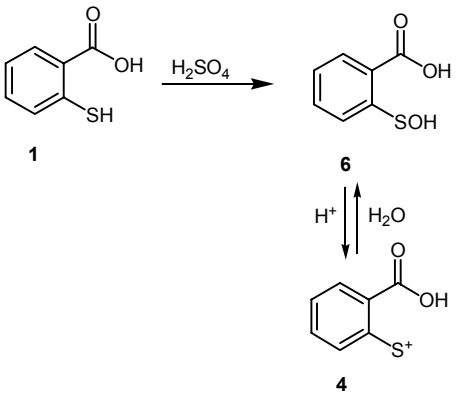
Table 2. The results of reaction of **1** (1 mmol) and **2a-d** (7 mmol) in the presence of concentrated sulfuric acid

Entry	n	Time/h	Product	Yield [a] (%)
1	0	2	**3a**	70
2	1	2	**3b**	70
3	2	2	**3c**	68
4	3	2	**3d**	63

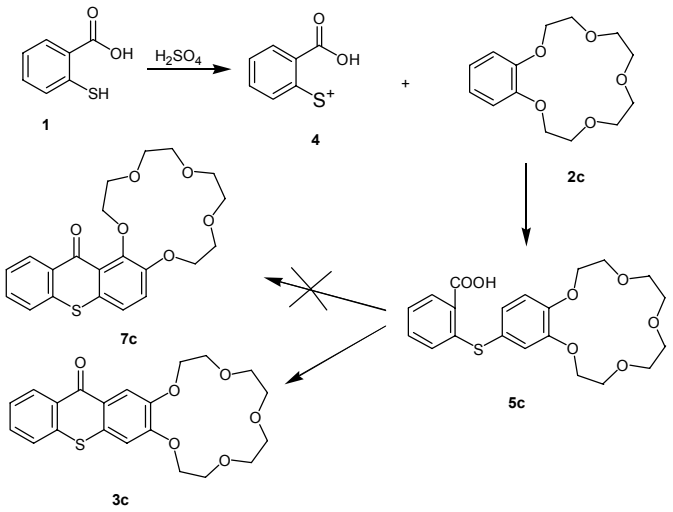
[a] Isolated yield

No attempt has been made to probe the mechanism of the reaction. We assume that the mercapto group **1** (TSA) is oxidized to sulfenic acid which immediately decomposes to a sulfenium ion **4** [14a] (Scheme 3). Electrophilic substitution of sulfenium ion with the benzo-15-crown-5 (**2c**) would then give intermediate thioether and the cyclization of thioether gives the thioxanthone-15-crown-5 ether (**3c**) (Scheme 4). Thioxanthone crown ether yields depended directly upon the sulfuric acid concentration because sulfonation of **2c** competes with the generation of sulfenium ion (**4**) and subsequent electrophilic substitution [14].

The experimental procedure for the preparation of thioxanthone crown ethers are remarkably simple and does not require the use of any solvent or inert atmosphere and does not require the purification of products by column chromatography**.**



Scheme 3



Scheme 4

Experimental Section

General Procedure. Thiosalicylic acids, benzocrown ethers and sulfuric acid (98%), were purchased from Fluka and Merck in high purity. The preparation of the benzo-9-crown-3 used as precursors has been described and it was purified by chromatography on silica-gel, eluted with 1:1 CH_2C1_2: diethyl ether (See reference 18). NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker Advanced Dpx-250 (^{1}H NMR 250 MHz and ^{13}C NMR 62.9 MHz) spectrophotometer using TMS as internal standard. Infrared spectra were recorded on a Perkin Elmer IR-157G spectrometer, UV spectra were recorded on a Pharmacia Biotech (Ultrospec 3000) UV/Visible spectrometer and melting points were taken on a Büchi melting apparatus. The TLC was performed on plates coated with silica gel (silica gel 60 GF_{254}, Merck).

Preparation of 2,3,5,6-tetrahydro-1,4,7-benzotrioxonine [18] (**2a**). A 2-L round-bottom flask was charged with catechol (16.3 g, 0.148 mol), water (1700 mL), and LiOH (12.4 g, 0.296 mol), and the mixture was stirred for 5 min. To this was added dropwise 1,5-dichloro-3-oxapentane (21.7 g, 0.148 mol) and the reaction mixture was refluxed for 86 h. Upon cooling, the mixture was acidified to pH=2 by an addition dilute H_2S0_4 and were extracted with CH_2C1_2 (3×100 mL). After washing with 5% NaOH (3×100 mL), saturated NaCl (100 mL), and water, the extracts were dried over anhydrous Na_2S0_4. After solvent removal, the resulting reddish slurry was purified by column chromatography on silica gel (grade 60, 230-400 mesh). Elution with 1:1 CH_2C1_2: diethyl ether yielded, in the initial fractions, 8.0 g (30%) of 2,3,5,6-Tetrahydro-1,4,7-benzotrioxonine (**2a**), mp 70-72°C (lit.[18] mp (for protio analog) 69-71°C); ^{1}H NMR ($CDCl_3$ 250 MHz): δ 3.91 (m, 4H); 4.34 (m, 4H); 6.98 (m, 4H); ^{13}C NMR ($CDCl_3$ 62.9 MHz): δ 74.1, 76.6, 120.7, 124.0, 151.4; IR (KBr, cm^{-1}): 3315 (s), 1579 (s), 1494 (s), 1446 (s),1365 (s), 1024 (s), 999 (s), 761 (s), 490 (s); Mass m/z (%): 180 (M^+, 40.9); 136 (100), 80 (38.8), UV ($CHCl_3$) λ_{max}/nm (ε): 241.5 (610), 274.6 (1782); Anal. Calcd for $C_{10}H_{12}O_3$ (180.1): Calc. C 66.65%, H 6.71%; found C 66.55%, H 6.67%.

General procedure for the synthesis of thioxanthone crown ethers. To a stirring mixture of concentrated sulfuric acid 98% (2 mL) and thiosalicylic acid (TSA) (0.154 g, 1 mmol) in a round-bottomed flask was gradually added (60 min) the appropriate crown ether (7 mmol) at room temperature and then the mixture was stirred for one hour. The reaction progress was monitored by TLC. After completion of the reaction, the mixture was poured onto ice and the product was filtered, washed with water and then washed with a saturated aqueous solution of sodium hydrogen carbonate or cesium carbonate until alkali-free and dried under vacuum over night at room temperature to yield product as shown in Table 2.

2,3,5,6-Tetrahydro-14*H*-thioxantheno[2,3-*b*][1,4,7]trioxonin-14-one (**3a**). Compound **3a** was obtained as yellow crystal in 70% yield. Mp=178-180°C, ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.91 (m, 4H), 4.30 (m, 2H), 4.70 (m, 2H), 7.08 (s, 1H), 7.51 (m, 3H), 8.25 (s, 1H), 8.56 (d, 1H, J=7.4 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 71.6, 71.8, 72.8, 76.5, , 117.2, 124.7, 124.9, 125.8, 126.0, 127.1, 129.7, 131.9, 133.4, 137.1, 150.6, 155.8, and 178.7; IR (KBr, cm^{-1}): 2900 (s), 1640 (s), 1580 (s), 1490 (s),1300 (s), 1125 (s), 1030 (s), 880 (s), 740 (s); Mass m/z (%): 314 (M^+, 26.5); 270 (17.6), 214 (29.4), 186 (34.8), 158 (25.5) and 57 (100%); UV ($CHCl_3$) λ_{max}/nm (ε): 253.6 (2029), 318.8 (2537), 363.4 (2446), 395.3 (2420); Anal. Calcd for $C_{17}H_{14}O_4S$ (314.36): Calc. C 64.95%, H 4.49%; found C 64.72%, H 4. 43%

2,3,5,6,8,9-Hexahydro-17*H*-thioxantheno[2,3-*b*][1,4,7,10]tetraoxacyclododecin-17-one (**3b**). Compound **3b** was obtained as yellow crystal in 70% yield. Mp=286-288 °C (decomposed); ^{1}H NMR ($CDCl_3$,250 MHz): δ 3.79 (s,4H), 3.86 (m, 4H), 3.93 (m, 2H), 4.30 (s, 2H), 7.05 (s, 3H), 7.47 (t, 1H, J=7.2 Hz), 7.57 (m, 2H), 8.22 (s, 1H), 8.58 (d, 1H J=7.4 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 69.5, 71.0, 71.4, 72.9, 111.9, 118.6, 124.1, 125.8, 126.2, 128.6, 129.7, 131.8, 132.7, 137.0, 149.7, 155.4, 178.8; IR (KBr, cm^{-1}): 2873 (s), 1635 (s), 1593 (s), 1504 (s), 1440 (s), 1292 (s), 1269 (s), 1253 (s), 1147 (s), 1114 (s) 742 (s); Mass m/z (%): 358 (M^+, 4.1); 270 (9.4), 214 (8.2), 186 (7.1), 149 (21.3) and 57 (100); UV ($CHCl_3$) λ_{max}/nm (ε): 253.5 (2123), 314.6 (2501),

368.2 (2565), 389.1 (2373); Anal. Calcd for $C_{19}H_{18}O_5S$ (358.41): Calc. C 63.67%, H 5.06%; found C 63.51%, H 5.13%.

2,3,5,6,8,9,11,12-Octahydro-20*H*-thioxantheno[2,3-*b*][1,4,7,10,13]pentaoxacyclopentadecin-20-one (**3c**). Compound **3c** was obtained as yellow crystal in 68%.yield. Mp=157-158 °C; ^{1}H NMR ($CDCl_3$): δ 3.34 (s, 8H), 3.64 (s, 4H), 3.82 (s, 2H), 4.20 (s, 2H), 7.34 (s, 3H), 7.57 (t, 1H, J=7.5 Hz), 7.73 (t, 1H, J=7.5. Hz), 7.81 (d, 1H, J=7.9. Hz), 7.87 (s, 1H), 8.54 (d, 1H, J=7.9. Hz); ^{13}C NMR ($CDCl_3$): δ 68.7, 68.9, 69.0, 69.8, 69.9, 70.9, 108.7, 111.0, 122.4, 126.7, 126.8, 128.2, 129.1, 131.0, 132.5, 136.8, 148.3, 153.5, 177.7; IR (KBr, cm^{-1}): 2873 (s), 1591 (s), 1506 (s), 1446 (s), 1407 (s), 1261 (s), 1215 (s), 1137 (s), 1083 (s), 935 (s) 740 (s), Mass m/z (%): 402 (M^+, 28.3);270 (50.5), 214 (18.7), 97 (10.8) and 43 (100); UV ($CHCl_3$) λ_{max}/nm (ε): 253.6 (2022), 319.3 (2566), 364.3 (2483), 395.0 (2368); Anal. Calcd for $C_{21}H_{22}O_6S$ (402.46): Calc. C 62.67%, H 5.51%; found C 63.49%, H 5.46%.

2,3,5,6,8,9,11,12,14,15-Decahydro-23*H*-thioxantheno[2,3-*b*][1,4,7,10,13,16]hexaoxacyclooctadecin-23-one (**3d**). Compound **3d** was obtained as yellow crystal in 63% yield. Mp=289-291 °C (decomposed); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.76 (s, 8H), 3.98 (s, 2H), 4.28 (s, 2H), 6.91 (s, 1H), 7.50 (m, 2H), 7.57 (s, 1H), 8.03 (s, 1H), 8.61 (d, 1H, J=7.5. Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 67.0, 68.4, 68.8, 68.9, 69.0, 70.3, 70.4, 70.5, 70.6, 70.7 107.5, 109.7, 111.2, 115.8, 123.1, 125.8, 126.1, 129.3, 129.7, 131.5, 137.0, 153.0, 178.5; IR (KBr, cm^{-1}): 2923 (s), 2860 (s), 1681 (s), 1589 (s), 1504 (s), 1411 (s), 1259 (s), 1126 (s), 950 (s), 742 (s); Mass m/z (%): 446 (M^+, 12.0);270 (61.7) 214 (26.8), 84 (80.4) and 57 (100); UV ($CHCl_3$) λ_{max}/nm (ε): 253.7 (2072), 315.6 (2195), 374.2 (2942), 385.6 (2000); Anal. Calcd for $C_{23}H_{26}O_7S$ (446.51): Calc. C 61.87%, H 5.87%; found C 61.98%, H 5.64%.

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