Halogenation of Methylthiomethyl *p*-Tolyl Sulfone

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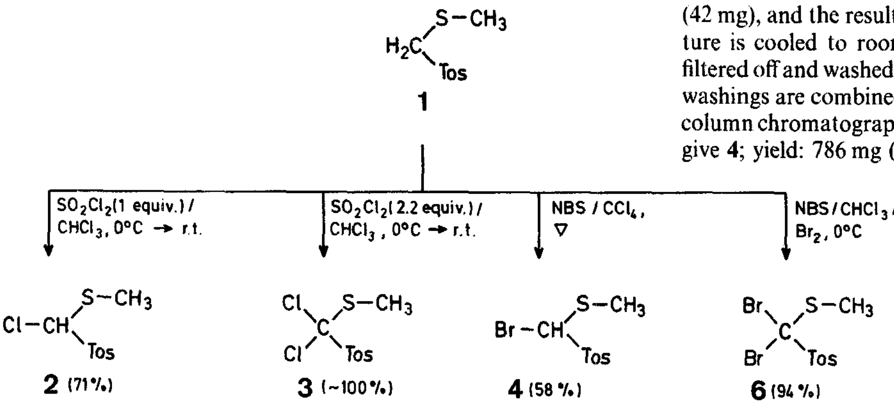
Recently it has been shown that methylthiomethyl *p*-tolyl sulfone (**1**), easily obtainable from dimethyl sulfoxide[1], is a useful reagent for preparing various kinds of organic compounds[2,3]. In order to exploit further utilization of this reagent, we have now investigated halogenation of **1** leading to its halo derivatives **2**–**6**. To date, many reports have revealed that α-halo-α-methylthio carbonyl compounds **7** serve as the sources of the α-carbenium cations of α-methylthio carbonyl compounds by the action of Lewis acids such as tin tetrachloride and aluminium chloride[4,5,6]. From the structural analogy between **7** and the monohalo derivatives **2**, **4** and **5**, it is anticipated that **2**, **4** and **5** could serve as precursors for generating a methyl cation having methylthio and *p*-toluenesulfonyl groups.

First, we have found that sulfuryl chloride smoothly reacts with **1** and that either monochloro derivative **2** or dichloro derivative **3** can be formed predominantly in a controlled fashion simply by limiting the amount of sulfuryl chloride added. When **1** was treated with 1.0 equiv of sulfuryl chloride in chloroform at 0°C to room temperature, the expected monochloro derivative **2** was obtained in 71 % yield together with unreacted **1** (15%) and the dichloro compound **3** (12 %). Use of an excess amount of sulfuryl chloride did not improve the yield of **2**, but increased the yield of **3**. For example, **2** and **3** were produced in 70% and 24% yields, respectively, with 1.26 equiv of sulfuryl chloride. When 2.2 equiv of sulfuryl chloride were used, **3** was produced quantitatively. Thus, chlorination of **1** with sulfuryl chloride provided efficient synthetic methods for **2** and **3**.

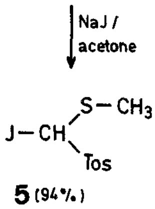
Bromination of **1** encountered some trouble. In the reaction of **1** with bromine in chloroform (room temperature/68 h), **1** remained unchanged. When **1** was allowed to react with 2.1 equiv of bromine in the presence of 1.2 equiv of pyridine (0°C/3 h → r.t./17 h), the bromination proceeded to some extent to give **4** and **6** in 16% and 30% yields, respectively, in addition to unchanged **1** (43%). As observed in the α-bromination of sulfoxides[7], the addition of 1.2 equiv of *N*-bromosuccinimide (NBS) to the above reaction system facilitates the bromination to afford **6** in a high yield of 94%. Furthermore, we found that a free radical-chain bromination with NBS was suitable for the preparation of **4**. After NBS (1.5 equiv) and benzoyl peroxide (0.04 equiv) were added to a 1.5 mol/l solution of **1** in carbon tetrachloride and the resulting mixture was refluxed for 5 h, the usual workup afforded **4** in 58% yield. It should be noted that the concentrations of **1** and NBS are crucial to the smooth formation of **4** in the present bromination; the reaction using a 0.3 mol/l solution of **1** (reflux/18 h) resulted in the formation of a 1 : 1 mixture of **1** and **4**.

For the preparation of the iodo derivative **5**, we used the so-called "halogen-exchange" method. The reaction of **2** with sodium iodide or potassium iodide in refluxing acetone was very slow and a prolonged heating of the reaction mixture resulted in the formation of a complicated mixture. However, when **4** was used as the starting material, the halogen exchange promptly took place. In the reaction of **4** with potassium iodide in acetone, **5** was obtained in 80% yield after warming the reaction mixture at 45–55°C for 18 h. The use of sodium iodide instead of potassium iodide shortened the reaction time. The reaction of **4** with sodium iodide in acetone at 45–55°C was completed within 1 h to afford **5** in 94% yield.

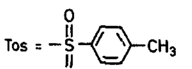
In a preliminary experiment, we observed the formation of benzaldehyde (60% yield) on treatment of **2** with tin tetrachloride (1.1 mol-equiv) in benzene at room temperature followed by an aqueous workup, implying that monohalo derivatives **2**, **4** and **5** can serve as a source of formyl cation.

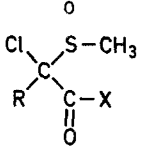


2 (71%) **3** (~100%) **4** (58%) **6** (94%)



5 (94%)





7 R = H, CH₃
Y = OCH₃, OC₂H₅

Further, the dihalo derivatives **3** and **6** are regarded as a synthetic equivalent of carbonic acid. Detailed studies on these reactions are in progress in our laboratory.

Chloro-(methylthio)-methyl *p*-Tolyl Sulfone (2):

To a solution of **1** (9.99 g, 46.3 mmol) in chloroform (80 ml), is added dropwise sulfuryl chloride (6.97 g, 51.6 mmol) over 45 min under ice-cooling, and the resulting mixture is stirred under ice-cooling for 5 h and then at room temperature for 12 h. After the addition of water (100 ml), followed by extraction with diisopropyl ether (4 × 60 ml), the organic layer is washed with water (200 ml), dried with magnesium sulfate, and evaporated in vacuo. Recrystallization of the residue from benzene/hexane gives **2** (6.93 g). Evaporation of the mother liquor and subsequent column chromatography on silica gel using benzene/hexane (1 : 1) as an eluent gives **1** (666 mg), **2** (1.55 g), and **3** (1.66 g). The total yield of **2** is 8.48 g (73%): m.p. 100.5-101 °C.

$C_9H_{11}ClO_2S_2$	calc.	C 43.11	H 4.42
(250.8)	found	43.32	4.41

I.R. (KBr): ν = 1595, 1315, 1170, 1150, 1085, 820, 650, 560 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 2.44 (s, 3 H); 2.47 (s, 3 H); 5.55 (s, 1 H); 7.45 (d, 2 H, J = 8.4 Hz); 7.94 ppm (d, 2 H, J = 8.4 Hz).

Dichloro-(methylthio)-methyl *p*-Tolyl Sulfone (3):

Using 2.2 equiv of sulfuryl chloride, the above procedure is repeated and **3** is obtained in quantitative yield as colorless crystals; m.p. 82-82.6 °C.

$C_9H_{10}Cl_2O_2S_2$	calc.	C 37.90	H 3.53
(285.2)	found	37.97	3.60

I.R. (KBr): ν = 1595, 1430, 1420, 1340, 1320, 1300, 1150, 1080, 820, 800, 765 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 2.50 (s, 3 H); 2.64 (s, 3 H); 7.47 (d, 2 H, J = 8.4 Hz); 8.05 ppm (d, 2 H, J = 8.4 Hz).

Bromo-(methylthio)-methyl *p*-Tolyl Sulfone (4):

To a solution of **1** (998 mg, 4.6 mmol) in carbon tetrachloride (3 ml), are *N*-bromosuccinimide (1.23 g, 6.9 mmol) and benzoyl peroxide (42 mg), and the resulting mixture is refluxed for 5 h. After the mixture is cooled to room temperature, the deposited succinimide is filtered off and washed with carbon tetrachloride. The filtrate and the washings are combined and evaporated. The residue is subjected to column chromatography on silica gel using benzene/hexane (1 : 2) to give **4**; yield: 786 mg (58%); m.p. 106-106.5 °C.

$C_9H_{11}BrO_2S_2$	calc.	C 36.62	H 3.76
(295.2)	found	36.84	3.69

I.R. (KBr): ν = 1595, 1310, 1170, 1150, 1080, 820, 650, 560 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 2.44 (s, 3 H); 2.48 (s, 3 H); 5.66 (s, 1 H); 7.45 (d, 2 H, J = 8.4 Hz); 7.95 ppm (d, 2 H, J = 8.4 Hz).

Dibromo-(methylthio)-methyl *p*-Tolyl Sulfone (6):

To a solution of **1** (455 mg, 2.1 mmol) in chloroform (5 ml), are added *N*-bromosuccinimide (441 mg, 2.5 mmol), pyridine (211 mg, 2.7 mmol) and bromine (585 mg, 3.7 mmol) under ice-cooling, and the resulting mixture is stirred at the same temperature for 1 h. After the addition of water (50 ml) and extraction with dichloromethane (3 × 30 ml), the extract is washed with 10% aqueous solution of sodium thiosulfate (100 ml) and water (100 ml). The extract is dried with magnesium sulfate and evaporated to afford **6** as colorless crystals; yield: 741 mg (94%). An analytical sample of **6** is obtained by recrystallization from benzene/hexane; m.p. 102-103.5 °C.

$C_9H_{10}Br_2O_2S_2$	calc.	C 28.89	H 2.69
(342.1)	found	28.73	2.61

I.R. (KBr): ν = 1595, 1430, 1410, 1330, 1315, 1295, 1150, 1080, 820, 720 cm^{-1}.

Iodo-(methylthio)-methyl *p*-Tolyl Sulfone (5); Typical Procedure:

A mixture of **4** (586 mg, 1.99 mmol) and sodium iodide (685 mg, 4.6 mmol) in acetone (10 ml) is stirred at 45-55 °C for 1 h, and then water (50 ml) is added. After extraction with dichloromethane (4 × 20 ml), the organic layer is washed with 10% aqueous solution of sodium thiosulfate (100 ml) and water (100 ml). The extract is dried with magnesium sulfate, evaporated, and subjected to column chromatography on silica gel using benzene/hexane (3 : 1) as an eluent to give **5** as a colorless oil which soon crystallizes; yield: 639 mg (94%); m.p. 62-63 °C.

$C_9H_{11}JO_2S_2$	calc.	C 31.59	H 3.24
(342.2)	found	31.67	H 3.24

I.R. (KBr): ν: 1600, 1335, 1150, 1090, 820, 790, 720 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 2.33 (s, 3 H); 2.47 (s, 3 H); 5.93 (s, 1 H); 7.44 (d, 2 H, J = 8.4 Hz); 7.92 ppm (d, 2 H, J = 8.4 Hz).

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