

# Swern Oxidation of Alcohols with Ion-Supported Methyl Sulfoxide and Oxalyl Chloride

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**Abstract:** The oxidation of primary and secondary alcohols with ion-supported methyl sulfoxide and oxalyl chloride in the presence of triethylamine in dichloromethane efficiently proceeded to give the corresponding aldehydes and ketones, respectively, in good yields with high purity. Isolation of the product was achieved very easily by simple diethyl ether extraction of the reaction mixture and subsequent removal of solvent from the extract. The reaction did not produce any unpleasant odor. Furthermore, ion-supported methyl sulfide was recovered in good yield and could be re-oxidized to ion-supported methyl sulfoxide for reuse in the same oxidation.

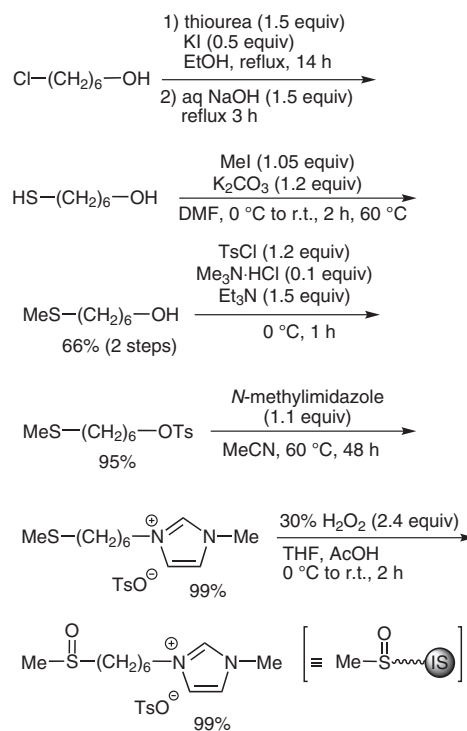
**Key words:** Swern oxidation, ion-supported methyl sulfoxide, alcohol, aldehyde, ketone, reuse

Organic synthesis that features high efficiency, low toxicity, minimal odor, atom economy, and the production of low amounts of waste is important for clean chemistry. In this regard, efficient organic synthesis with less toxic reagents has been explored actively.<sup>1</sup> The oxidation of alcohols to aldehydes or ketones is one of the most fundamental, widespread, and important reactions in both research laboratories and production plants. The Swern oxidation is one of the most efficient and selective oxidation methods available for the preparation of aldehydes or ketones from alcohols, because the reaction does not require any toxic metals, and proceeds under mild and neutral conditions.<sup>2</sup> These characteristics have paved the way for the extensive use of the Swern oxidation in the synthesis of natural products and pharmaceuticals.<sup>2g</sup> However, dimethyl sulfide, a co-product in the Swern oxidation, is a highly malodorous volatile compound and it is very difficult to handle or isolate the desired product without being exposed to the unpleasant odor. As an alternative, odorless Swern oxidation procedures that use modified dimethyl sulfoxides (DMSO), such as 6-(methylsulfinyl)hexanoic acid,<sup>3</sup> polyfluoroalkyl methyl sulfoxide,<sup>4</sup> dodecyl methyl sulfoxide,<sup>5</sup> and polymer-supported methyl sulfoxide,<sup>6</sup> were studied with the aim of producing aldehydes and ketones in high yields. However, there are still several drawbacks, such as the complicated separation of the desired product from methyl sulfide, the use of a large amount of solvent, the occurrence of side reactions such as the Pummerer reaction, differences in reactivity from the original Swern oxidation conditions with DMSO, and the presence of trace amounts of polymeric

species when polymer-supported methyl sulfoxides are used.

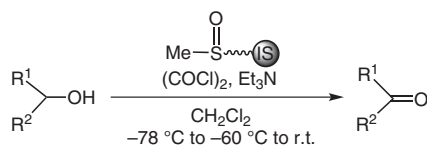
Based on our previous reports on ion-supported reagents, such as ion-supported  $\text{PhI}$ <sup>7</sup> and ion-supported  $\text{Ph}_3\text{P}$ ,<sup>8</sup> we expected that the use of ion-supported methyl sulfoxide for the Swern oxidation would remove the unpleasant odor and make possible both easy separation of the desired product from the reaction mixture and reuse of the ion-supported methyl sulfoxide. Here, we would like to report the Swern oxidation of alcohols with novel ion-supported methyl sulfoxide and oxalyl chloride.

Ion-supported methyl sulfoxide was prepared from commercially available 6-chlorohexanol in 62% overall yield as shown in Scheme 1.<sup>9</sup>



**Scheme 1** Preparation of ion-supported methyl sulfoxide

The reaction was carried out as follows:<sup>10</sup> oxalyl chloride was added dropwise to a solution of ion-supported methyl sulfoxide in  $\text{CH}_2\text{Cl}_2$  at  $-70\text{ }^\circ\text{C}$  and the mixture was stirred for 30 minutes at the same temperature. Then, a solution of alcohol in  $\text{CH}_2\text{Cl}_2$  was added dropwise to the solution at  $-70\text{ }^\circ\text{C}$  and the obtained mixture was stirred for 30 minutes. Triethylamine was added dropwise to the solution at

**Table 1** Oxidation of Alcohols to Aldehydes or Ketones with Ion-Supported Methyl Sulfoxide,  $(\text{COCl})_2$ , and  $\text{Et}_3\text{N}$ 

Entry	Product	Yield <sup>a</sup>	Purity
1		92	99
2		84	88
3		99	98
4 <sup>b</sup>		95	99
5		99	99
6		99	98
7		83	82
8		85	90
9		96	99
10		76	95
11		74	67
12		99	99
13		99	99
14		99	99
15		88	99

<sup>a</sup> Isolated yield.<sup>b</sup> Ion-supported methyl sulfoxide that was recovered and regenerated in entry 3, was used.

$-70\text{ }^\circ\text{C}$ , and the mixture was stirred for one hour at the same temperature. The resulting mixture was warmed to  $-60\text{ }^\circ\text{C}$  and  $-50\text{ }^\circ\text{C}$  for one hour each. Finally, the mixture was warmed to room temperature by removing the cooling bath and stirred for two hours. The mixture was quenched with water and extracted with diethyl ether. After removal of diethyl ether solvent, aldehyde or ketone was obtained in good yield with high purity without any unpleasant odor at all. The results shown in Table 1 indicate that various benzylic and allylic, and primary and secondary alcohols could be efficiently oxidized to aldehydes and ketones in high yields with high purity. During the reactions and operations, no unpleasant odor was detected at all. After the oxidation, ion-supported methyl sulfide, which is a co-product of the present reaction, was recovered in approximately 73% yield by chloroform extraction of the aqueous solution and re-oxidized to ion-supported methyl sulfoxide in quantitative yield. Once ion-supported methyl sulfoxide was obtained, it could be reused for the same Swern oxidation to generate the corresponding aldehyde in good yield with high purity again, by simple diethyl ether extraction from the reaction mixture (entry 4).

In conclusion, an efficient and odorless protocol for the Swern oxidation with ion-supported methyl sulfoxide has been developed. Using this protocol, various benzylic and allylic alcohols, as well as primary and secondary alcohols were oxidized to the corresponding aldehydes and ketones, in high yields with high purity without any unpleasant odor. The isolation of aldehydes or ketones from the reaction mixture was easily accomplished. Moreover, ion-supported methyl sulfide was recovered in good yield and re-oxidized to ion-supported methyl sulfoxide for reuse in the same reaction. Further synthetic studies using the present ion-supported methyl sulfoxide are underway in this laboratory.

**Supporting Information** for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

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- (9) (a) **Preparation of 6-mercaptohexan-1-ol**: Thiourea (270 mmol) and KI (90 mmol) were added to a solution of 6-chlorohexan-1-ol (180 mmol) in EtOH (150 mL) at r.t., and the mixture was heated at reflux for 14 h. Then, aq NaOH (2.7 M, 270 mmol, 100 mL) was added to the mixture, which was then heated at reflux for 3 h. The reaction mixture was cooled to r.t., and neutralized with aq HCl (1 M, 200 mL). The mixture was extracted with Et<sub>2</sub>O (2 × 300 mL) and the combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated in vacuo. The residue was dissolved in Et<sub>2</sub>O (200 mL) and the mixture was filtered. The filtrate was concentrated to give 6-mercaptohexan-1-ol as an oil. IR (neat): 3348, 2555, 1054 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.34–1.47 (m, 5 H), 1.54–1.67 (m, 4 H), 1.84 (s, 1 H), 2.54 (q, *J* = 7.4 Hz, 2 H), 3.64 (t, *J* = 6.6 Hz, 2 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 24.49, 25.17, 28.05, 32.53, 33.86, 62.76.
- (b) **Preparation of 6-(methylthio)hexan-1-ol**: MeI (189 mmol) was added to a solution of 6-mercaptohexan-1-ol (180 mmol) and K<sub>2</sub>CO<sub>3</sub> (198 mmol) in DMF (160 mL) at 0 °C, and the mixture was stirred for 2 h. The reaction mixture was filtered and concentrated, then H<sub>2</sub>O (150 mL) was added to the residue, which was extracted with EtOAc (3 × 200 mL). The combined organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. Purification of the residue by distillation (85–95 °C/1.0 mmHg) gave 6-(methylthio)hexan-1-ol (66% yield from 6-chlorohexan-1-ol) as an oil. IR (neat): 3365, 1055 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.34–1.47 (m, 4 H), 1.55–1.67 (m, 5 H), 2.10 (s, 3 H), 2.50 (t, *J* = 7.4 Hz, 2 H), 3.64 (t, *J* = 6.6 Hz, 2 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 15.47, 25.32, 28.49, 29.01, 32.57, 34.14, 62.76.
- (c) **Preparation of 6-(methylthio)hexyl 4'-methylbenzenesulfonate**: *p*-TsCl (72 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (60 mL) was added to a solution of 6-(methylthio)hexan-1-ol (60 mmol), Et<sub>3</sub>N (90 mmol) and Me<sub>3</sub>N·HCl (6.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (60 mL) at 0 °C, and the obtained mixture was stirred for 1 h. H<sub>2</sub>O (100 mL) was added to the reaction mixture, which was neutralized with 1 M HCl and extracted with EtOAc (2 × 200 mL). The combined organic layer was washed with H<sub>2</sub>O, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 4:1; *R*<sub>f</sub> = 0.4) to give 6-(methylthio)hexyl *p*-toluenesulfonate (95% yield) as an oil. IR (neat): 1360, 1175 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.31–1.37 (m, 4 H), 1.51–1.68 (m, 4 H), 2.07 (s, 3 H), 2.44 (t, *J* = 7.3 Hz, 2 H), 2.45 (s, 3 H), 4.02 (t, *J* = 6.5 Hz, 2 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 7.79 (d, *J* = 8.1 Hz, 2 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 15.39, 21.52, 24.89, 27.92, 28.60, 28.72, 33.93, 70.41, 127.75, 129.72, 133.05, 144.60.
- (d) **Preparation of 1-Methyl-3-[6'-(methylthio)hexyl]-1*H*-imidazol-3-ium *p*-Toluenesulfonate (Ion-Supported Methyl Sulfide)**: 1-Methylimidazole (33 mmol) was added to a solution of 6-(methylthio)hexyl *p*-toluenesulfonate (30 mmol) in MeCN (30 mL) at r.t., and the mixture was stirred at 60 °C for 48 h. The reaction mixture was concentrated in vacuo, and the residue was washed with Et<sub>2</sub>O (3 × 100 mL) to give ion-supported methyl sulfide (99% yield) as an oil. IR (neat): 1191, 1034 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.19–1.38 (m, 4 H), 1.48–1.56 (m, 2 H), 1.73–1.81 (m, 2 H), 2.07 (s, 3 H), 2.34 (s, 3 H), 2.43 (t, *J* = 7.3 Hz, 2 H), 3.93 (s, 3 H), 4.14 (t, *J* = 7.6 Hz, 2 H), 7.15 (d, *J* = 7.8 Hz, 2 H), 7.31 (t, *J* = 1.8 Hz, 1 H), 7.41 (t, *J* = 1.8 Hz, 1 H), 7.74 (d, *J* = 7.8 Hz, 2 H), 9.59 (s, 1 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 15.41, 21.20, 25.64, 27.87, 28.62, 29.95, 33.89, 36.25, 49.63, 121.81, 123.52, 125.71, 128.61, 137.51, 139.36, 143.56.
- (e) **Preparation of 3-Methyl-1-[6'-(methylsulfinyl)hexyl]-1*H*-imidazolium *p*-Toluenesulfonate (Ion-Supported Methyl Sulfoxide)**: H<sub>2</sub>O<sub>2</sub> (30% in H<sub>2</sub>O, 1.47 mL, 48 mmol) was added dropwise to a solution of ion-supported methyl sulfide {1-methyl-3-[6'-(methylthio)hexyl]-1*H*-imidazol-3-ium *p*-toluenesulfonate; 7.69 g, 20 mmol} in AcOH–THF (2:1, 45 mL) at 0 °C, and the mixture was stirred at r.t. for 2 h. The reaction mixture was quenched with aq sat. Na<sub>2</sub>SO<sub>3</sub>, and concentrated in vacuo. The obtained mixture was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. After removal of the solvent, ion-supported methyl sulfoxide was obtained (99% yield) as an oil; IR (neat): 1034 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 1.28–1.49 (m, 4 H), 1.67–1.86 (m, 4 H), 2.34 (s, 3 H), 2.55 (s, 3 H), 2.68 (t, *J* = 7.6 Hz, 2 H), 3.93 (s, 3 H), 4.19 (t, *J* = 7.4 Hz, 2 H), 7.15 (d, *J* = 7.9 Hz, 2 H), 7.36–7.38 (m, 2 H), 7.74 (d, *J* = 8.2 Hz, 2 H), 9.63 (s, 1 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 21.21, 22.06, 25.37, 27.59, 29.59, 36.25, 38.30, 49.49, 53.79, 121.96, 123.38, 125.71, 128.64, 137.63, 139.48, 143.43; HMRS (APPI): *m/z* [M<sup>+</sup>] calcd for C<sub>11</sub>H<sub>21</sub>ON<sub>2</sub>S: 229.1369; found: 229.1357.
- (10) **General Procedure for the Swern Oxidation using Ion-Supported Methyl Sulfoxide**: Oxalyl chloride (0.34 mL) was added dropwise to a solution of ion-supported methyl sulfoxide (1.60 g, 4.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) at –70 °C and the mixture was stirred for 30 min at the same temperature. A solution of alcohol (2.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added dropwise at –70 °C and the obtained mixture was stirred for 30 min. Triethylamine (1.66 mL, 12 mmol) was added dropwise at –70 °C and the mixture was stirred for 1 h at the same temperature. The resulting mixture was warmed to –60 °C and stirred for 1.5 h at the same temperature. The mixture was warmed to –50 °C and stirred for 1 h at the same temperature. Finally, the mixture was warmed to r.t. by removing the cooling bath and stirred for 2 h at the same temperature. The reaction mixture was quenched with H<sub>2</sub>O (10 mL), neutralized (pH 6–7) with aq 1 M HCl, and extracted with Et<sub>2</sub>O (2 × 40 mL). The organic layer was washed with H<sub>2</sub>O (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. After removal of the solvent, aldehyde or ketone was obtained. The purity was estimated by <sup>1</sup>H NMR analysis.

Most of the aldehydes and ketones obtained in this study are commercially available and were identified by comparison with the authentic materials (see the Supporting Information; mp, IR,  $^1\text{H}$  NMR, and  $^{13}\text{C}$  NMR). The aqueous layer was concentrated in vacuo. After the addition of aq sat.  $\text{NaHCO}_3$ , ion-supported methyl sulfide was extracted with  $\text{CHCl}_3$  ( $3 \times 40$  mL). The organic layer

was dried over  $\text{Na}_2\text{SO}_4$  and filtered. After removal of the solvent, the residue was washed with  $\text{Et}_2\text{O}$  ( $2 \times 10$  mL), and concentrated in vacuo to provide ion-supported methyl sulfide (~73% yield). The recovered ion-supported methyl sulfide was quantitatively oxidized to the corresponding ion-supported methyl sulfoxide with hydrogen peroxide in a mixture of AcOH and THF, as described above.

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