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New odorless protocols for the Swern and Corey–Kim oxidations

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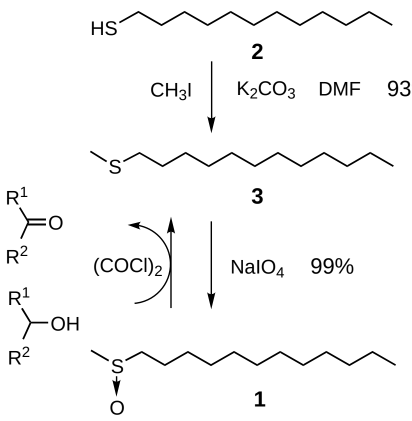
Abstract—New odorless protocols for the Swern oxidation as well as the Corey–Kim oxidation using dodecyl methyl sulfoxide (**1**) or dodecyl methyl sulfide (**3**) are described. © 2002 Elsevier Science Ltd. All rights reserved.

The Swern oxidation [dimethyl sulfoxide (DMSO)–oxalyl chloride][1] is the most commonly used of several activated DMSO methods[2] for oxidation of primary or secondary alcohols to aldehydes or ketones. Among its many advantages are mild conditions, stability of acid sensitive functional groups, no epimerization of the α-carbon of the carbonyl group, easy work-up, gaseous byproducts (carbon dioxide and carbon monoxide), and rapid reaction rate.[2] Nevertheless, one important drawback is the foul odor of the volatile dimethyl sulfide produced, which is regulated by the offensive odor control law. From an environmental standpoint, the need for odorless substitutes for foul-smelling molecules like dimethyl sulfide is therefore great. In order to circumvent this problem, substitutes for the original dimethyl sulfoxide, like 6-methylsulfinylhexanoic acid and its polymer-supported derivatives,[3] are constantly being sought. Recently, Crich and Neelamkavil devised a fluorous Swern oxidation using tridecafluorooctyl methyl sulfoxide for this purpose.[4] The development of a new odorless Swern oxidation is, however, still needed for researchers in the laboratory as well as in the chemical industry setting.

Recently, we have also been involved in a program aimed at developing odorless thiols and sulfides that can be used in organic reactions as substitutes for the usual foul-smelling thiols[5] and sulfides. We have performed a study on a formal asymmetric Michael addition of hydrogen sulfide to α-substituted α,β-unsaturated carbonyl compounds using odorless 10-mercaptoisoborneol and 1-dodecanethiol.[6] In this study, we found that the dodecyl methyl sulfide was also odorless and used it in the debenzylation of esters. This result prompted us to develop a new odorless Swern oxidation. Herein we report *new protocols for odorless Swern oxidation and Corey–Kim oxidation* using dodecyl methyl sulfoxide or sulfide, respectively.

The process of a new odorless Swern oxidation is illustrated in Scheme 1. Dodecyl methyl sulfoxide (**1**)[7] was easily prepared in high yields by methylation of 1-dodecanethiol (**2**) with methyl iodide followed by oxidation with sodium periodate in chloroform–water catalyzed by a phase transfer catalyst. The dodecyl methyl sulfide (**3**)[6,7] and the sulfoxide **1** are odorless, namely, this modified Swern oxidation procedure is free from the malodorous dimethyl sulfide produced in the original Swern oxidation. In addition, the less polar and fairly high boiling-point sulfide **3** (bp 110°C/0.2 mmHg) is easily separable by silica gel chromatography and can be reused by re-oxidation to the sulfoxide **1**.



Scheme 1. A new odorless Swern oxidation.

Keywords: odorless Swern oxidation; dodecyl methyl sulfoxide; odorless Corey–Kim oxidation; dodecyl methyl sulfide.

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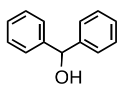
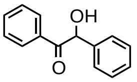
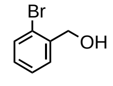
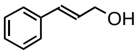
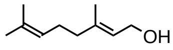
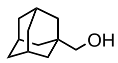
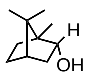
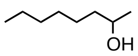
In order to optimize the reaction conditions for a new odorless Swern oxidation [sulfoxide **1**–oxalyl chloride], an oxidation of benzhydrol was carried out first under the original Swern oxidation conditions[1] (−60°C to rt, 2 h, after addition of triethylamine) to give benzophenone (51%) accompanied by the recovered alcohol (42%). It was suggested that longer reaction times and keeping the reaction temperature at about −40°C after addition of triethylamine were necessary to generate a sufficient amount of the sulfonium ylide intermediate and to prevent the undesired Pummerer rearrangement.[3a] A high yield (95%) of benzophenone was obtained under a prolonged reaction time (200 min) at −60 to −40°C after addition of triethylamine. The reactions in other solvents (THF, toluene, ether) afforded benzophenone in moderate to low yields (49, 53 and 10%), respectively. The results of the new odorless Swern oxidation[8] using the sulfoxide **1** and oxalyl chloride are summarized in Table 1. All benzylic, allylic, and aliphatic primary and secondary alcohols were oxidized smoothly to aldehydes or ketones in high yields.

The other oxidation of alcohols using dimethyl sulfide and *N*-chlorosuccinimide is known as the Corey–Kim oxidation.[9] Instead of using the dimethyl sulfide, we applied the dodecyl methyl sulfide (**3**) to this oxidation. The results of the new odorless Corey–Kim oxidation[10] were compiled in Table 2. From the standpoint of the chemical industry setting, toluene as a solvent was tested instead of dichloromethane. The yields of the corresponding aldehydes or ketones were excellent in both solvents.

The two protocols described for the oxidation of alcohols were performed without foul smelling in the laboratory. Since dodecyl methyl sulfide (**3**) has a higher boiling point than volatile dimethyl sulfide, the products of the oxidation were isolated by column chromatography in the case of neutral alcohols.[11] However, chromatographic isolation of the products should be avoided in large-scale reactions. In the case of acidic alcohols, for example, odorless Swern oxidation of mandelic acid gave phenylglyoxylic acid in 96% yield by sequential extraction of the reaction mixture after basification and acidification.[12]

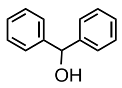
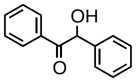
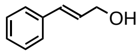
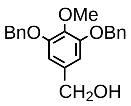
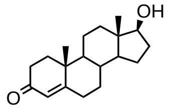
In conclusion, we were able to provide new *odorless protocols* for the Swern oxidation and the Corey–Kim oxidation using the dodecyl methyl sulfoxide (**1**) or the dodecyl methyl sulfide (**3**), respectively. These protocols furnish the products under odorless experimental conditions at minimal cost. The starting material 1-dodecanethiol (**2**) for the synthesis of the odorless sulfoxide (**1**) and the sulfide (**3**) is inexpensive (about $20/kg) because it is used in bulk as a vulcanizing agent for rubber. The odorless reagents **2** and **3** can therefore be prepared at a more moderate price than the other new sulfoxides[3,4] or the new oxidizing reagent[13] recently developed. We believe that the odorless feature of these protocols is important for environmental chemistry as well as for organic chemistry. Further studies utilizing odorless sulfides and sulfoxides are underway in our laboratory.

Table 1. Odorless Swern oxidation of alcohols using dodecyl methyl sulfoxide (**1**)

substrate	conditions (temp. and time after Et$_3$N addition)	yield (%)[a] aldehyde or ketone (lit.)[b]	 recovery of Dod-S-Me
	-60°C ~ -40°C (3.33 h) -40°C ~ r. t. (1 h)	95 (98)	100
	-60°C ~ -40°C (2 h) -40°C ~ r. t. (40 min)	91 (95)	94
	-60°C ~ -40°C (2 h) -40°C ~ r. t. (40 min)	95	95
	-60°C ~ -40°C (2 h) -40°C ~ r. t. (40 min)	93 (98)	93
	-60°C ~ -40°C (2 h) -40°C ~ r. t. (40 min)	93 (95)	89
	-60°C ~ -40°C (5 h) -40°C ~ r. t. (1 h)	93 (99)	99
	-60°C ~ -40°C (2 h) -40°C ~ r. t. (40 min)	91 (95)	91
	-60°C ~ -40°C (2 h) -40°C ~ r. t. (40 min)	81 (98)	95

a) Isolated yields. b) See ref. 2c.

Table 2. Odorless Corey–Kim oxidation of alcohols using dodecyl methyl sulfide (**3**)

alcohols	NCS (3 equiv.) Dod-S-Me (**3**, 3 equiv.) → aldehydes or ketones Et$_3$N (5 equiv.) -40°C (14 h) yield (%)[a] in CH$_2$Cl$_2$	 in toluene
	95	98
	99	—[b]
	91	90
	99	95
	91	97

a) Isolated yields. b) The starting material was insoluble.

Acknowledgements

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6. Nishide, K.; Ohsugi, S.; Shiraki, H.; Tamakita, H.; Node, M. *Org. Lett.* **2001**, *3*, 3121–3124.
7. Dodecyl methyl sulfoxide (**1**) and dodecyl methyl sulfide (**3**) will be available in the near future from Wako Pure Chemical Industries, Ltd.
8. *A typical procedure for the new odorless Swern oxidation using dodecyl methyl sulfoxide* (**1**): To a dichloromethane (4 ml) suspension of dodecyl methyl sulfoxide (**1**) (95 mg, 0.41 mmol) was added dropwise oxalyl chloride (1.0 M dichloromethane solution, 0.41 ml, 0.41 mmol) at −60°C, and the resulting mixture was stirred for 15 min. A dichloromethane (1 ml) solution of benzhydrol (50 mg, 0.27 mmol) was added dropwise at −60°C. The mixture was stirred for 30 min, triethylamine (189 μl, 1.36 mmol) was added dropwise, and the resultant mixture was gradually warmed to −40°C in 200 min. The reaction mixture was then warmed to room temperature by removing the cooling bath and stirred for 1 h. The mixture was quenched with water (10 ml), and neutralized with an 1N HCl (0.5 ml) solution, then extracted with chloroform (40 ml×3). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/ethyl acetate = 40/1) gave benzophenone (47 mg, 95% yield) and dodecyl methyl sulfide (**3**) (60 mg, 100% yield).

   The 10-times scale-up experiment under the above conditions using benzhydrol (500 mg, 2.7 mmol) gave benzophenone (460 mg, 93% yield), accompanied with dodecyl methyl sulfide (**3**) (540 mg, 92% yield).
9. Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586–7587.
10. *A typical procedure for the new odorless Corey–Kim oxidation using dodecyl methyl sulfide* (**3**): To a dichloromethane or toluene solution (10 ml) of *N*-chlorosuccinimide (108 mg, 0.81 mmol) was added a dichloromethane or toluene solution (2 ml) of dodecyl methyl sulfide (**3**) (176 mg, 0.81 mmol) dropwise at −40°C, and the resulting mixture was stirred for 30 min. A dichloromethane or toluene solution (2 ml) of benzhydrol (50 mg, 0.27 mmol) was added dropwise at −40°C. After the mixture was stirred for 2 h, triethylamine (189 μl, 1.36 mmol) was added dropwise at −40°C. After stirring for 14 h, water (20 ml) was added to the reaction mixture. The mixture was neutralized with 1N HCl (0.5 ml), followed by extraction of the aqueous layer with chloroform (40 ml×3) or ethyl acetate (40 ml×3). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Silica gel chromatography of the residue (hexane/ethyl acetate = 40/1) gave benzophenone (47 mg, 95% yield in dichloromethane or 49 mg, 98% yield in toluene, respectively).

    The 20-times scale-up experiment under the above conditions using benzhydrol (1.0 g, 5.43 mmol) gave benzophenone (953 mg, 96% yield).
11. Depending on the physical property and the amounts of the products, extraction, crystallization, or distillation could be used for isolation of the products.
12. The same extraction in the case of Corey–Kim oxidation gave a mixture of phenylglyoxylic acid and succinimide.
13. (a) Matsuo, J.; Iida, D.; Tatani, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 223–234; (b) Mukaiyama, T.; Matsuo, J.; Iida, D.; Kitagawa, H. *Chem. Lett.* **2001**, 846–847; (c) Matsuo, J.; Kitagawa, H.; Iida, D.; Mukaiyama, T. *Chem. Lett.* **2001**, 150–151; (d) Mukaiyama, T.; Matsuo, J.; Yanagisawa, M. *Chem. Lett.* **2000**, 1072–1073.