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En relación con el expediente de la referencia, y en particular con el oficio número 1904 del 12 de Febrero de 2010, por medio del presente escrito y estando dentro del término legal, me permito dar respuesta al mismo acompañando lo siguiente:

- Los documentos completos de las anterioridades de materia relacionadas con esta solicitud de patente, tal y como lo solicita esa División, como resultado del examen de búsqueda efectuado; en virtud de lo establecido en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina.

Teniendo en cuenta lo anterior, solicito agregar este escrito y su anexo al expediente para continuar con el trámite de la solicitud.

De usted atentamente,


LUIS FELIPE CASTILLO GIBSONE
C.C. 79.397.879 de Bogotá
TP No 68.995 del C.S.J



New odorless protocols for the Swern and Corey–Kim oxidations

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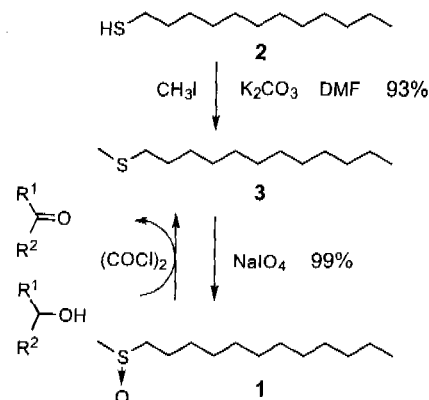
Abstract—New odorless protocols for the Swern oxidation as well as the Corey–Kim oxidation using dodecyl methyl sulfoxide (**1**) or dodecyl methyl sulfide (**3**) are described. © 2002 Elsevier Science Ltd. All rights reserved.

The Swern oxidation [dimethyl sulfoxide (DMSO)–oxalyl chloride]¹ is the most commonly used of several activated DMSO methods² 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 fluoros 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 thiols⁵ 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 debenzoylation 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 conditions¹ (–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 oxidation⁸ 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 oxidation¹⁰ 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 reagent¹³ 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.) 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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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 $\times$ 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).
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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 $\times$ 3) or ethyl acetate (40 ml $\times$ 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.
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Modification of the Swern Oxidation: Use of a Soluble Polymer-Bound, Recyclable, and Odorless Sulfoxide

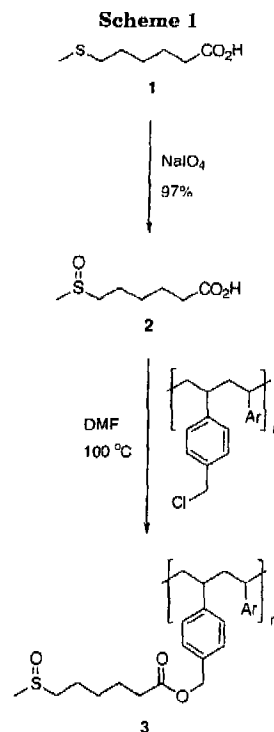
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The Swern procedure, using oxalyl chloride activation of dimethyl sulfoxide (DMSO), is one of the most widely used methods of oxidizing primary and secondary alcohols to aldehydes and ketones.¹ Although very effective, this process produces the unpleasant-smelling, volatile (bp 37 °C) byproduct, dimethyl sulfide. We have previously reported the use of 6-(methylsulfinyl)hexanoic acid (**2**) as an efficient substitute for DMSO in Swern oxidation reactions.² This modification generates the non-volatile sulfide **1**, which is easily separable from the reaction mixture by extraction or filtration through silica gel. Also described was preliminary work on the attachment of **2** to commercial chloromethyl polystyrene beads (Merrifield resin) to form a polymer-bound reagent **3** (Scheme 1). The present study expands on these investigations and reports the attachment of **2** to soluble poly(ethylene glycol) (PEG) supports to form polymer-bound reagents that can be easily removed from the reaction mixture by precipitation and filtration. After use in the Swern procedure, the PEG-bound reagent can be readily recycled by periodate oxidation, with no observable loss of oxidation capacity.

Initial studies on supports to bear the sulfoxide functionality necessary for Swern oxidation focused on insoluble solid-phase polymers such as Merrifield resin. Use of a 2-fold excess of polymer-supported sulfoxide **3** in the Swern process quantitatively oxidizes *endo*-borneol to camphor, with no residual alcohol remaining. However, after regeneration by sodium metaperiodate oxidation,³ the oxidation capacity of the polymer-bound reagent is reduced from 92% to 78%. This may be due to cross-linking of the polystyrene backbone by reaction with oxalyl chloride. Clearly, if the reagent is to be recyclable, the polymer-support must be inert to the reaction conditions for both the Swern oxidation and periodate regeneration of the sulfoxide functionality. A rapidly expanding area of polymer-supported chemistry is the use of soluble scaffolds.⁴ These have the advantage of forming a homogeneous phase in the reaction medium, but having polymeric properties that simplify product separation and reagent recovery. One of the most versatile and widely



used polymer supports for such liquid-phase synthesis is poly(ethylene glycol) (PEG).⁵ PEG is soluble in a wide-range of organic solvents and water, thereby facilitating homogeneous reaction, but is insoluble in hexane, diethyl ether, and *tert*-butyl methyl ether.⁶ It is therefore easily separated from the reaction mixture by precipitation and filtration.

When choosing a polymer for liquid-phase synthesis a compromise must be made between loading capacity and solubility. PEG is commercially available in a range of molecular weights up to 20 000; those between 2 000 and 20 000 are crystalline with loading capacities between 1 and 0.1 mmol/g, whereas the lower molecular weight PEG's exist as liquids at room temperature. A number of different size PEG's (with hydroxyl functionalities at both ends) and MeO-PEG's (with the polyether terminated by a methoxy group at one end and a free hydroxyl at the other) were investigated in an attempt to optimize the reaction conditions and loading capacity. Reagent **2** is easily coupled to PEG in the presence of DCC and DMAP.⁷ The reduced sulfide acid **1** can be similarly coupled and subsequently oxidized to the sulfoxide **5** with sodium metaperiodate (Scheme 2).³ Although they have higher loading capacities, the low molecular weight (below 2 000) liquid polymers present problems with

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6-(Methylthio)hexanoic Acid (1) and 6-(Methylsulfinyl)hexanoic Acid (2) were synthesized as described previously.²

Poly(ethylene glycol) Bis(6-(Methylthio)hexanoate) (4). A solution of PEG-2000 (10.0 g, 5.0 mmol), sulfide acid 1 (2.80 g, 17.5 mmol), and DMAP (0.21 g, 1.7 mmol) in dichloromethane (50 mL) was treated with DCC (3.60 g, 17.5 mmol) and stirred overnight. The white urea precipitate was removed by filtration through Celite and washed with CH₂Cl₂. The filtrate was concentrated to ~15 mL, and diethyl ether (150 mL) was added with vigorous stirring to precipitate the polymer. The precipitation was enhanced by stirring in an ice bath for 2 h. The precipitate was removed by filtration, washed with diethyl ether, and dried in vacuo to give 11.17 g (98%) of polymer-bound sulfide 4 as a white solid: IR (CH₂Cl₂ cast) 1733 (m), 1113 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.21 (t, 2H, J = 4.8 Hz), 3.64 (s, 8H), 2.48 (t, 2H, J = 7.3 Hz), 2.33 (t, 2H, J = 7.4 Hz), 2.08 (s, 3H), 1.63 (m, 4H), 1.42 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 173.44, 70.45, 69.06, 63.30, 33.90, 28.65, 28.09, 24.37, 15.39.

Poly(ethylene glycol) Bis(6-(Methylsulfinyl)hexanoate) (5). A solution of 4 (10.5 g, 4.6 mmol) in methanol (80 mL) and water (20 mL) at 0 °C was treated with 0.50 M sodium metaperiodate (19.4 mL, 9.7 mmol) overnight, during which time a white precipitate formed. The methanol was removed in vacuo below 10 °C, and the residue was extracted with CH₂Cl₂ (5 × 50 mL). Combined extracts were dried (Na₂SO₄) and evaporated to give 10.6 g (99%) of polymer-bound sulfoxide 5 as a white solid: IR (CH₂Cl₂) 1732 (m), 1114 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.20 (t, 2H, J = 4.7 Hz), 3.61 (s, 8H), 2.66 (m, 2H), 2.53 (s, 3H), 2.33 (t, 2H, J = 7.3 Hz), 1.76 (m, 2H), 1.65 (m, 2H), 1.48 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 173.08, 70.37, 68.93, 63.30, 54.17, 38.44, 33.56, 27.99, 24.20, 22.09.

General Procedure for the Modified Swern Oxidation. A solution of 5 (1.74 g, 0.75 mmol) in dichloromethane (30 mL) is cooled to -50 to -60 °C, oxalyl chloride (0.098 mL, 1.125 mmol) is added dropwise, followed after 15 min by a solution of the alcohol (0.75 mmol) in CH₂Cl₂ (5 mL). The mixture is stirred for 45 min, triethylamine (0.63 mL, 4.5 mmol) is added, and the

solution is kept at -45 °C for 2.5 h before warming to room temperature. Workup involves concentration of the reaction mixture to approximately 10 mL, followed by addition of diethyl ether (100 mL) to precipitate the polymer. The precipitation is accelerated by cooling to -20 °C for 10 min. After filtration the filtrate is concentrated in vacuo to give the oxidized product, which typically contains a trace of polymer contamination (1%). This is easily removed by passing an ethereal suspension through a pad of silica. The solid polymer reagent, which is a 1:1 mixture of the sulfide and sulfoxide, is contaminated with triethylammonium hydrochloride. Although this does not affect the subsequent periodate oxidation, it can be removed by washing a dichloromethane solution with water to give recovered polymer-bound reagent in a 98% yield. The product was analyzed by ¹H NMR spectrometry, which showed complete oxidation with no trace of alcohol. All the carbonyl products obtained from the Swern oxidation were characterized by comparing chromatographic and/or spectral properties (¹H NMR, IR, MS) with the authentic samples or literature.

In experiments to determine the recyclability of the PEG-bound sulfoxide, limiting conditions were used. Thus, 1 equiv of *endo*-borneol was used for the reaction with 0.6 equiv of polymer-supported sulfoxide 5 and 1.1 equiv of oxalyl chloride: 96% of the alcohol was oxidized to give camphor with 4% left unchanged. The polymer-bound reagent recovered was a 6:1 mixture of sulfide:sulfoxide. It was reoxidized by the above procedure for periodate oxidation, giving a 91% recovery of PEG-bound sulfoxide 5.

Acknowledgment. These investigations were supported by Merck Frosst Ltd., the Natural Sciences and Engineering Research Council of Canada, and the Alberta Heritage Foundation for Medical Research (postdoctoral fellowships J.M.H. and M.D.A.). Y.L. acknowledges support from an Izaak Walton Killam Scholarship.

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Additions and Corrections

Vol. 62, 1997

Matthias Köck* and Jochen Junker. How Many NOE Restraints Are Necessary for a Reliable Determination of the Relative Configuration of an Organic Compound: Application to a Model System.

Page 8614. The configuration of compound 1 is correctly designated as 1*R*,6*R*,8*R*,11*R*,12*S*,16*R* in the text. The centers 6, 8, 11, and 12 should be switched in the 2D drawing of 1.

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It should be noticed the position of the saddle point moves out monotonically toward the $F + H_2$ channel as this height decreases. This should be expected in general for nonthermoneutral reactions¹⁰ and should be a caution against emphasizing¹¹ a prediction of the geometry of the saddle point when its height is not predicted correctly.

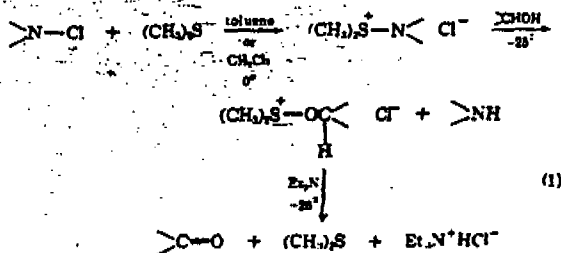
(18) See, e.g., G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955); M. H. Mok and J. C. Polanyi, *J. Chem. Phys.*, **51**, 1431 (1969); and C. A. Parr and D. G. Truhlar, *J. Phys. Chem.*, **75**, 1844 (1971).

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Sir:

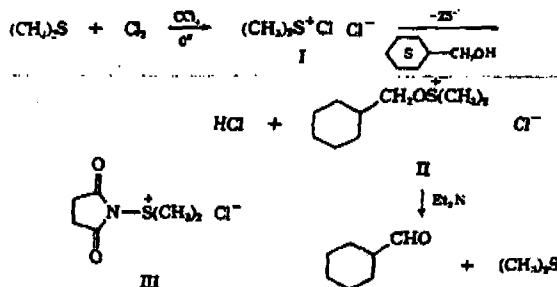
We report here a new process for the oxidation of alcohols to ketones or aldehydes which is operationally simple, highly selective, and efficient. It is expected that the method will find widespread use and that in many instances it will be found superior to currently important procedures such as those using the reagents CrO_2 -pyridine complex,¹ CrO_2 -acetone,² and dimethyl sulfoxide with various coreactants.³⁻⁵ An overall representation of the new method, which is clearly related to the dimethyl sulfoxide based processes, is given in sequence I.



The long-known complexes which result from the reaction of halogens with sulfides,⁶ $R_2S^+Hal^-$, might be expected to react with an alcohol to form a type of sulfoxonium complex, $R_2S^+OCH<Hal^-$,^{6b} which judging from previous work^{6a-c} should under suitable condi-

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- (6) See, for example, (a) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. II, Chemical Publishing Co., New York, N. Y., p. 48, and also (b) H. Meerwein, K.-F. Zenger, and R. Gipp, *Justus Liebig's Ann. Chem.*, 687, 67 (1965). The question of tetravalent or sulfonium sulfur in these complexes merits further study, but is not crucial to the present application.

tions undergo elimination to form a carbonyl compound. This process would effectively allow an overall transformation such as: $RR'CHOH + Cl_2 \rightarrow RR'CO + 2HCl$, which is mediated by a sulfide. The operability of this scheme has now been demonstrated. For example, treatment of dimethyl sulfide in carbon tetrachloride at 0° with 1 equiv of chlorine in carbon tetrachloride at 0° results in rapid formation of the partially insoluble complex I, which when cooled to -25° (Dry Ice-carbon tetrachloride bath) and treated with cyclohexylcarbinol for 2 hr at -25° with stirring is converted to the sulfoxonium complex II. Addition of 2 equiv of triethylamine, removal of the cooling bath, and isolation after 5 min affords pure cyclohexylcarboxaldehyde in ca. 80% yield after distillation.



The oxidation of cyclohexylcarbinol can be effected even more cleanly and efficiently (93% yield) using the recently reported complex III from dimethyl sulfide and *N*-chlorosuccinimide^{7,8} under carefully controlled conditions. Most of this work has been performed using the complex III, since the use of *N*-chlorosuccinimide for small-scale laboratory work is convenient, since the formation of hydrogen chloride is avoided (in contrast to the use of I), giving a milder and probably more generally useful method, and, finally, since the reaction products are somewhat cleaner.

The simplicity and the key details of the new oxidation process are illustrated by the following procedures for the preparation of a ketone and an aldehyde.

A. 4-*tert*-Butylcyclohexanone. To a stirred solution of 400 mg (3.0 mmol) of *N*-chlorosuccinimide in 10 ml of toluene (analytical grade) was added at 0° 0.3 ml (4.1 mmol) of methyl sulfide under argon. A white precipitate appeared immediately after addition of the sulfide. The mixture was cooled to -25° (carbon tetrachloride-Dry Ice), and a solution of 312 mg (2.00 mmol) of 4-*tert*-butylcyclohexanol (mixture of *cis* and *trans*) in 2 ml of toluene was added dropwise. The stirring was continued for 2 hr at -25°, and then a solution of 303 mg (3.0 mmol) of triethylamine in 0.5 ml of toluene was added dropwise. The cooling bath was removed and after 5 min, 20 ml of ether was added. The organic layer was washed with 5 ml of 1% aqueous hydrochloric acid and twice with 15 ml of water. Removal of dried (magnesium sulfate) solvents produced 310 mg (~100%) of 4-*tert*-butylcyclohexanone as white

- (7) E. Vilsmaier and W. Sprügel, *Tetrahedron Lett.*, 625 (1972).
(8) Other examples of azasulfonium salts have been reported by (a) P. G. Gassman, G. Grunzacher, and R. H. Smith, *ibid.*, 497 (1972), and (b) C. R. Johnson, C. C. Bacon, and W. D. Kingsbury, *ibid.*, 501 (1972). The latter group has also reported the isolation of unsable sulfonium salts from alcohols and the complexes of sulfides with *N*-chlorobenzotriazole.

plates which melted at 44–47° (an authentic sample from Aldrich Chemical Co. had mp 45–50°). The infrared and nmr spectra were identical with those of an authentic sample, and the nmr spectrum showed that no more than 1% of the methylthiomethyl ether of 4-*tert*-butylcyclohexanol was present. Vapor chromatographic analysis indicated a yield of 97% (xylene as internal standard with a 10% SE-30, 10-ft column).

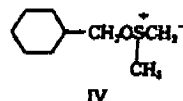
B. Octanal. The complex III (3 mmol) was generated following the procedure described above. To this stirred suspension of III was added a solution of 260 mg (2.0 mmol) of 1-octanol in 1 ml of toluene at –25°. After stirring at –25° for 90 min, a solution of 303 mg (3.0 mmol) of triethylamine in 1 ml of toluene was added. The cold bath was then removed, and after 5 min, 20 ml of ether was added. The organic layer was washed with 5 ml of 1% aqueous hydrochloric acid and then twice with 15 ml of water. The organic layer was dried (magnesium sulfate) and concentrated under reduced pressure to 10 ml and analyzed by vapor phase chromatography (10% SE-30, 10-ft column with xylene as the internal standard) (96% yield). Removal of all solvents under reduced pressure produced 250 mg of 1-octanal as a colorless liquid which was spectroscopically identical with an authentic sample.

Using the method detailed above, benzyl alcohol and 2-octanol were converted respectively to benzaldehyde (90% yield) and 2-octanone (91% yield). 1,2-Diphenyl-1,2-propanediol gave 2-hydroxy-1,2-diphenyl-1-propanone in 86% yield indicating that the sulfonium method may be valuable for the avoidance of C–C bond cleavage in the oxidation of *sec*, *tert*- α -glycols to α -ketols.

An important limit on the scope of the new oxidation process has been observed, however. Benzhydrol and 2-cyclohexenol suffer replacement of hydroxyl by chlorine instead of oxidation using III under the standard conditions. The conversion of alcohols to halides is very efficient for such cases involving alcohols which correspond to stabilized carbocations.^{9,10} Fortunately the oxidation of allylic or benzylic alcohols is readily effected by other mild, highly selective oxidizing agents, including manganese dioxide and various quinones, and consequently there is no pressing need for the sulfonium reagents in such cases.

Still another reaction may occur in more polar media, viz. the transformation of the alcohol ROH to the corresponding methylthiomethyl ether ROCH₂SCH₃. Thus, although cyclohexylcarbinol is converted cleanly to the corresponding aldehyde using complex III at –25° in *toluene* with less than 1% of methylthiomethyl ether formation, the methylthiomethyl ether is formed to the extent of ca. 18% in *methylene chloride* at –25° and 45% in *methylene chloride-dimethyl sulfoxide* (1:1) at –25°. It seems likely that the ylide IV is an intermediate¹¹ in the formation of the methylthiomethyl ether

and that its formation and/or further reaction can be avoided in nonpolar media.



The oxidation process which is described herein should be extremely useful for complex or polyfunctional molecules, the reaction conditions being so mild as to minimize the possibility of involvement of most functional or protecting groups. As is clear from the examples cited above the yields of carbonyl compounds are remarkably high and there is little variation in optimal conditions.¹²

We are currently exploring other applications of reagents such as III, for example to carboxyl activation. The use of inexpensive halogen-derived reagents such as I for large scale oxidation is also under study.

Acknowledgment. This research was supported in part by grants from the National Science Foundation and the National Institutes of Health.

(12) A number of bases other than triethylamine have been used in oxidations of alcohols with the reagent III, including 1,3-diazabicyclo-[4.3.0]nonene-5 and 1,4-diazabicyclo[2.2.2]octane, but triethylamine appears to be the amine of choice.

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Photosensitized Aquation of the Hexacyanochromate(III) Ion. Evidence against the Doublet Mechanism

Sir:

Two principal mechanisms have been proposed in order to account for the photochemistry of Cr(III) complexes.¹ The first mechanism² assumes that the lowest spin-forbidden excited state (⁴E_g, Figure 1) is that one responsible for the photoreactivity, whereas the alternative mechanism³ involves the lowest quartet excited states (⁴T_{1g} and ⁴T_{2g}, Figure 1) as direct precursors to the photochemical reactions. Neither direct photolysis¹ nor sensitization experiments^{4–6} has as yet given a definitive answer to the above alternative, whereas quenching experiments carried out on Cr(NH₃)₆(NCS)₃[–] have clearly shown that its photoaquation originates, at least in part, from the lowest quartet excited state.⁷ These latter experiments as well as some studies^{8,9} on the temperature dependence of the phosphorescent lifetime for some

(1) V. Balzani and V. Carassiti, "Photochemistry of Coordination Compounds," Academic Press, London, 1970.

(2) R. A. Plane and J. P. Hunt, *J. Amer. Chem. Soc.*, **79**, 3343 (1957); H. L. Schlifer, *J. Phys. Chem.*, **69**, 2201 (1965).

(3) A. W. Adamson, *ibid.*, **71**, 798 (1967).

(4) A. W. Adamson, J. E. Martin, and F. D. Camassai, *J. Amer. Chem. Soc.*, **91**, 7530 (1969); J. E. Martin and A. W. Adamson, *Theor. Chim. Acta*, **20**, 119 (1971).

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(7) S. N. Chen and G. B. Porter, *Chem. Phys. Lett.*, **6**, 41 (1970).

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TETRAHEDRON

New odorless method for the Corey–Kim and Swern oxidations utilizing dodecyl methyl sulfide (Dod-S-Me)

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Abstract—Development of the odorless dodecyl methyl sulfide (Dod-S-Me, 1) as an alternative for dimethyl sulfide (DMS) and new odorless methods for the Corey–Kim and Swern oxidations are described. These reactions have been developed with a view toward green chemistry, utilizing Dod-S-Me (1) and common solvents instead of dichloromethane.
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1. Introduction

Thiols and sulfides are useful reagents for organic syntheses.¹ However, because of their general malodorous nature, they are widely known to contribute to environmental pollution as well as to the physical stress of the researchers working with them. Development of odorless substitutes for commonly used foul-smelling thiols and sulfides would greatly improve or, in some cases, eliminate these objectionable features. Demethylations of phenyl methyl ethers^{2a} and methyl phosphates^{2b} using either an odorless bulky thiol or an odorless sodium dithiocarboxylate have been reported. Studies of a novel reaction using chiral 1,3-mercapto alcohols (odorless)³ prompted us to exploit odorless thiol substitutes for ethanethiol,⁴ benzyl mercaptan,^{4,5} benzenethiol⁵ and hydrogen sulfide,⁶ which we have applied to dealkylation and the Michael addition. Dimethyl sulfide (DMS) is also commonly used for organic reactions, e.g. dealkylation⁷ and the Corey–Kim oxidation⁸ (NCS–DMS, Et₃N). However, due to its foul smell, industrial use of DMS is regulated by the offensive odor control law. Recently, odorless versions of the Corey–Kim oxidation⁹ and the Swern oxidation^{10,11} have been published. We report herein the development of dodecyl methyl sulfide¹² (Dod-S-Me, 1), which was easily prepared as an odorless alternative for DMS, and new odorless versions of the oxidations mentioned above in an application of green chemistry.¹³

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

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2. Result and discussion

2.1. Odor of alkyl methyl sulfides

We tested the odor of a number of alkyl methyl sulfides. The relative odor index of these sulfides compared to foul-smelling dimethyl sulfide perceived by the human nose⁶ of three test subjects is listed in Table 1, with 5 being the most malodorous and 0 an odorless sulfide. All the alkyl methyl sulfides were commercially available except for undecyl methyl sulfide and Dod-S-Me (1), which were synthesized from the corresponding 1-undecanethiol and 1-dodecanethiol, respectively (Scheme 1).

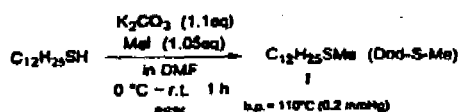
These sulfides were purified by distillation and HPLC on

Table 1. Odor scale for alkyl methyl sulfides

Entry	Sulfides	Carbon length	Odor scale		
			A	B	C
1	CH ₃ SCCH ₃	1	5	5	5
2	CH ₃ CH ₂ SCCH ₃	2	5	5	5
3	CH ₃ (CH ₂) ₂ SCCH ₃	3	4	4	4
4	CH ₃ (CH ₂) ₃ SCCH ₃	4	4	4	4
5	CH ₃ (CH ₂) ₄ SCCH ₃	5	4	3	4
6	CH ₃ (CH ₂) ₅ SCCH ₃	7	2	2	3
7	CH ₃ (CH ₂) ₆ SCCH ₃	8	2	2	2
8	CH ₃ (CH ₂) ₇ SCCH ₃	10	1	1	2
9	CH ₃ (CH ₂) ₈ SCCH ₃	11	1	1	0
10	CH ₃ (CH ₂) ₁₁ SCCH ₃ (1)	12	0	0	0
11	CH ₃ (CH ₂) ₁₃ SCCH ₃	14	0	0	0
12	CH ₃ (CH ₂) ₁₅ SCCH ₃	16	0	0	0
13	C ₁₂ H ₂₅ SC ₁₂ H ₂₅	6+6	1	1	1

Odor scale: stench 5–0 odorless.

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Scheme 1. Synthesis of dodecyl methyl sulfide (1).

GPC columns. Among the alkyl methyl sulfides, Dod-S-Me (1) was found to be odorless, while lower carbon-chain sulfides were malodorous. These results suggest that the alkyl methyl sulfides with longer chains have lower volatility than DMS and that the sulfides having more than 12 carbons become odorless due to their lower volatility.

2.2. Odorless Corey–Kim oxidation using dodecyl methyl sulfide (Dod-S-Me)

We next used Dod-S-Me (1) as an odorless substitute for foul-smelling DMS in the Corey–Kim oxidation,⁸ which is a useful method for oxidation of alcohols to aldehydes or ketones. Oxidation of benzhydrol was carried out first under the original Corey–Kim oxidation conditions (-20°C to room temperature, 6 h after addition of triethylamine) to give benzophenone (50%). Benzophenone was obtained in high yield under optimized reaction conditions, while maintaining the reaction temperature at -40°C for longer reaction times (14 h after addition of triethylamine). This result suggested that it was necessary to generate a sufficient amount of the sulfur ylide intermediate and to prevent the undesired Pummerer rearrangement.^{11a} The results of the new odorless Corey–Kim oxidation using the sulfide 1 are summarized in Table 2. Toluene was also tested as a solvent instead of dichloromethane, following the original Corey–Kim oxidation⁸ from the standpoint of industrial chemistry. The yields of the corresponding aldehydes or ketones were excellent in both solvents.

Table 2. Odorless Corey–Kim oxidation using dodecyl methyl sulfide (1)

Entry	Alcohols	Yield (%)	
		in CH_2Cl_2	in toluene
1		99	95
2		91	97
3		99	— ^a
4		95	98
5		91	90

^a No reaction.

Applying this new odorless Corey–Kim oxidation to industrial scale experiments, we considered using common solvents instead of dichloromethane and toluene (Table 3). All the solvents tested were applied to the new Corey–Kim oxidation and gave excellent yields, with acetone being the most suitable solvent for industrial use.

Table 3. Odorless Corey–Kim oxidation using 1

1) 1 (3eq) -40°C		2) Et_3N (5eq) -40°C 2.5 h	
NCS (3eq) 2 h		Yield (%)	
Solvent	Yield (%)	Solvent	Yield (%)
Toluene	83	THF	99
CH_2Cl_2	96	CH_3CN	93
AcOEt	97	Acetone	100

The new odorless Corey–Kim oxidation of alcohols having a heteroaromatic substituent also proceeded in good to excellent yields (Table 4). Tetrahydrofuran (THF) was found to be the best solvent for oxidation of these alcohols.

Table 4. Odorless Corey–Kim oxidation of heteroaromatics using dodecyl methyl sulfide (1)

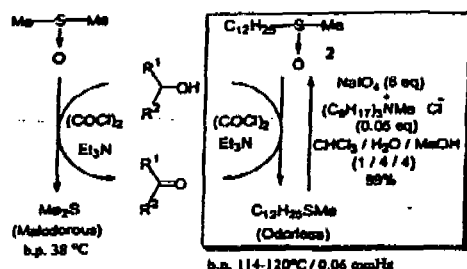
1) 1 (3eq) -40°C		2) Et_3N (5eq) -40°C 2.5 h	
NCS (3eq) 2 h		Yield ^a (%)	
Alcohols	Yield ^a (%)	Alcohols	Yield ^a (%)
1	77	4	86
2	71	5	85
3	99	6	92

^a Yield was determined by GC.

2.3. Odorless Swern oxidation using dodecyl methyl sulfoxide

The Swern oxidation¹⁴ (DMSO–oxalyl chloride, Et_3N) is also a useful method for oxidation of alcohols to aldehydes or ketones. However, one serious drawback is the foul odor of the volatile DMS which is produced during the reaction. In order to overcome this problem, we planned a new odorless Swern oxidation using dodecyl methyl sulfoxide (2), as illustrated in Scheme 2.

Dodecyl methyl sulfoxide (2) could be prepared in high yield from Dod-S-Me (1) by oxidation with sodium periodate. In our strategy, Dod-S-Me was recovered as an odorless byproduct instead of DMS, and was reused by re-oxidation to the sulfoxide 2. The optimized reaction conditions of the new Swern oxidation for benzhydrol (-60 to -40°C for 200 min after addition of triethylamine, then warming to room temperature for 40 min) gave benzophenone (95%) along with the recovered Dod-S-Me (1).



Scheme 2. Strategy of a new odorless Swern oxidation.

98%). The reaction in other solvents such as THF,¹⁵ toluene, and ether afforded benzophenone in moderate to low yields (49, 53 and 10%, respectively). The results of the new odorless Swern oxidation using the sulfoxide 2 and oxalyl chloride are summarized in Table 5. All benzylic, allylic, and aliphatic primary and secondary alcohols were oxidized smoothly to aldehydes or ketones in high yields.

The two protocols described for the oxidation of alcohols were carried out without creating a foul smell in the laboratory. Since Dod-S-Me (1) has a higher boiling point than the volatile DMS, the products of the oxidations were isolated by column chromatography in the case of neutral products.¹⁶ However, chromatographic isolation of the product could 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 extraction¹⁷ of the reaction mixture after basification and acidification.

In conclusion, we were able to provide new odorless methods for the Corey–Kim and Swern oxidations using Dod-S-Me (1)¹⁸ or dodecyl methyl sulfoxide (2)¹⁶ as substitutes for the foul-smelling DMS and the sulfoxide DMSO. These protocols furnish the products under

odorless conditions at minimal cost. The starting material, 1-dodecanethiol, for the synthesis of the odorless sulfide 1 and the sulfoxide 2 is inexpensive (about \$20/kg) because it is used in bulk as a vulcanizing agent for rubber. The odorless compounds 1 and 2 can therefore be prepared at a moderate price without using a foul-smelling reagent (MeSSMe and MeSH are regulated by the offensive odor control law). We anticipate that the odorless feature of these methods will be important for green chemistry as well as for organic chemistry in general. Further studies utilizing odorless sulfides and sulfoxides are underway in our laboratory.

3. Experimental

3.1. General

¹H NMR spectra were obtained with a VARIAN GEMINI 2000/200, XL-300, INOVA-400NB or JEOL JNM-AL300 spectrometer with tetramethylsilane as the internal standard. Infrared spectra were measured with a SHIMADZU FTIR-8300 spectrometer. Low and high-resolution mass spectra were determined on either a JEOL JMS GC-mate (EI) or a JEOL JMX SX 102A QQ (FAB) mass spectrometer. Gas chromatographic analyses were performed on a DB-1 column (0.25 mm×30 m J & W Scientific) with SHIMADZU GS-2010 and FID. High performance liquid chromatography was performed on a SHIMADZU LC-10A series, chiral column (Chiralcel OD, OJ), Wakogel C-200 (Wako Pure-Chemical Industries), Silica gel 60N (Kanto Chemical) was used for column chromatography. Silica gel F254 plates (Merck) were used for TLC. Visualization was performed using UV light, iodine and 12-molybdo(VI) phosphoric acid *n*-hydrate in EtOH. Sulfides were further purified by a recycle HPLC (LC-908, Japan Analytical Industry Co., Ltd.) on GPC columns (JAIGEL 1H and 2H) after purification by distillation. Dichloromethane was distilled from CaH₂.

Table 5. Odorless Swern oxidation using dodecyl methyl sulfoxide

Entry	Alcohols	Isolated yield (%)		Entry	Alcohols	Isolated yield (%)	
		Aldehydes or ketones (lit.) ^a	Recovery of 1			Aldehydes or ketones (lit.) ^a	Recovery of 1
1		95 (98)	100	5		93 (95)	99
2		91 (95)	94	6		93 (99)	99
3		95	95	7		91 (95)	91
4		93 (98)	93	8		81 (98 ^b)	95

^a Swern et al. *Synthesis* 1980, 165.

^b GC yield.

after washing with water. Other solvents were dried by general methods.

3.1.1. Dodecyl methyl sulfide (1). To a DMF (3 ml) suspension of potassium carbonate (751 mg, 5.43 mmol) was added a DMF solution of 1-dodecanethiol (1000 mg, 4.94 mmol) and methyl iodide (736 mg, 5.19 mmol) at 0°C, and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was filtered, then 1N HCl was added to the solution, which was concentrated in vacuo. The residue was added to distilled water, then extracted with ethyl acetate. The organic layer was washed with sodium thiosulfate solution, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification of the residue by silica gel column chromatography gave dodecyl methyl sulfide (1) (922 mg, 86%).

The scale-up reaction under the above conditions using a DMF (300 ml) solution of potassium carbonate (75.1 g, 543.5 mmol) and a DMF (200 ml) solution of 1-dodecanethiol (100 g, 494.1 mmol) and methyl iodide (73.6 g, 518.8 mmol), gave dodecyl methyl sulfide (1) (91.4 g, 81%) by distillation in vacuo.

Colorless oil; bp 110°C (0.2 mm Hg); ¹H NMR (300 MHz, CDCl₃): δ 2.49 (t, *J*=7.4 Hz, 2H), 2.10 (s, 3H), 1.59 (sextet, *J*=7.4 Hz, 2H), 1.43–1.19 (m, 15H), 0.88 (t, *J*=6.9 Hz, 3H); MS (20 eV) *m/z*: 216 (M⁺, 60), 201 (100), 125 (11), 111 (30), 103 (24), 97 (50), 83 (51), 71 (25), 70 (36), 69 (38), 61 (12), 57 (35); HRMS calcd for C₁₃H₂₈S (M⁺): 216.1912, found 216.1914.

3.1.2. Dodecyl methyl sulfoxide (2). To a CHCl₃/MeOH/H₂O (1/4/4, 9 ml) solution of dodecyl methyl sulfide (50 mg, 0.23 mmol) was added triethylmethylammonium chloride (20 ml, 0.04 mmol) and sodium periodate (296 mg, 1.38 mmol) at 0°C, and the resulting mixture was stirred at room temperature for 10 min. The reaction mixture was added to distilled water (10 ml) and stirred for 2 h. The reaction mixture was concentrated in vacuo then extracted with ethyl acetate. The organic layer was washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification of the residue by silica gel column chromatography gave dodecyl methyl sulfoxide (2) (53 mg, 99%).

White powder; ¹H NMR (300 MHz, CDCl₃): δ 2.81–2.57 (m, 2H), 2.52 (s, 3H), 1.76 (quintet, *J*=7.9 Hz, 2H), 1.57–1.19 (m, 15H), 0.88 (t, *J*=6.7 Hz, 3H); IR (CHCl₃): 3550–3150 (br), 2997, 2928, 2855, 1466, 1408, 1034, 934 cm⁻¹; MS (20 eV) *m/z*: 233 (M⁺+H, 1), 232 (M⁺, 1), 216 (43), 215 (100), 201 (40), 187 (2), 168 (3), 140 (3), 125 (4), 111 (13), 97 (24), 85 (19), 83 (30), 71 (32), 69 (25), 57 (52); HRMS calcd for C₁₃H₂₈SO (M⁺): 232.1861, found 232.1865.

3.2. A typical procedure for the new method of the Corey–Kim oxidation using dodecyl methyl sulfide (1)

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 (1) (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 an alcohol

(0.27 mmol) was added dropwise at –40°C. After the mixture was stirred for 2 h, triethylamine (0.19 ml, 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 (Na₂SO₄), filtered and concentrated in vacuo. Silica gel chromatography of the residue (hexane/ethyl acetate=40/1) gave an aldehyde or a ketone. The resulting products were analyzed by comparing their NMR spectra and TLC with those of authentic samples.

3.2.1. 3,5-Dibenzoyloxy-4-methoxybenzaldehyde (Table 2, entry 1). Using CH₂Cl₂ as a solvent. According to the general procedure, the reaction was performed using 3,5-dibenzoyloxy-4-methoxybenzyl alcohol (50 mg, 0.14 mmol), dodecyl methyl sulfide (94 mg, 0.43 mmol), *N*-chlorosuccinimide (58 mg, 0.43 mmol), triethylamine (0.10 ml, 0.72 mmol), and dichloromethane (10 ml) to give 3,5-dibenzoyloxy-4-methoxybenzaldehyde (49 mg, 99%).

Using toluene as a solvent. According to the general procedure, the reaction was performed using 3,5-dibenzoyloxy-4-methoxybenzyl alcohol (50 mg, 0.14 mmol), dodecyl methyl sulfide (94 mg, 0.43 mmol), *N*-chlorosuccinimide (58 mg, 0.43 mmol), triethylamine (0.10 ml, 0.72 mmol), and toluene (10 ml) to give 3,5-dibenzoyloxy-4-methoxybenzaldehyde (47 mg, 95%).

3.2.2. 4-Androsten-3,17-dione (Table 2, entry 2). Using CH₂Cl₂ as a solvent. According to the general procedure, the reaction was performed using testosterone (50 mg, 0.17 mmol), dodecyl methyl sulfide (113 mg, 0.52 mmol), *N*-chlorosuccinimide (69 mg, 0.52 mmol), triethylamine (0.12 ml, 0.86 mmol), and dichloromethane (14 ml) to give 4-androsten-3,17-dione (45 mg, 91%).

Using toluene as a solvent. According to the general procedure, the reaction was performed using testosterone (50 mg, 0.17 mmol), dodecyl methyl sulfide (113 mg, 0.52 mmol), *N*-chlorosuccinimide (69 mg, 0.52 mmol), triethylamine (0.12 ml, 0.86 mmol), and toluene (14 ml) to give 4-androsten-3,17-dione (48 mg, 97%).

3.2.3. Benzil (Table 2, entry 3). Using CH₂Cl₂ as a solvent. According to the general procedure, the reaction was performed using benzoin (50 mg, 0.24 mmol), dodecyl methyl sulfide (153 mg, 0.71 mmol), *N*-chlorosuccinimide (94 mg, 0.70 mmol), triethylamine (0.16 ml, 1.18 mmol), and dichloromethane (14 ml) to give benzil (49 mg, 99%).

3.2.4. Benzophenone (Table 2, entry 4). Using CH₂Cl₂ as a solvent. According to the general procedure, the reaction was performed using benzhydrol (50 mg, 0.27 mmol), dodecyl methyl sulfide (176 mg, 0.81 mmol), *N*-chlorosuccinimide (108 mg, 0.81 mmol), triethylamine (0.19 ml, 1.35 mmol) and dichloromethane (14 ml) to give benzophenone (47 mg, 95%).

Using toluene as a solvent. According to the general procedure, the reaction was performed using benzhydrol

(50 mg, 0.27 mmol), dodecyl methyl sulfide (176 mg, 0.81 mmol), *N*-chlorosuccinimide (108 mg, 0.81 mmol), triethylamine (0.19 ml, 1.35 mmol) and toluene (14 ml) to give benzophenone (48.5 mg, 98%).

3.2.5. Cinnamaldehyde (Table 2, entry 5). Using CH_2Cl_2 as a solvent. According to the general procedure, the reaction was performed using cinnamyl alcohol (50 mg, 0.37 mmol), dodecyl methyl sulfide (242 mg, 1.12 mmol), *N*-chlorosuccinimide (149 mg, 1.12 mmol), triethylamine (0.26 ml, 1.86 mmol), and dichloromethane (14 ml) to give cinnamaldehyde (45 mg, 91%).

Using toluene as a solvent. According to the general procedure, the reaction was performed using cinnamyl alcohol (50 mg, 0.37 mmol), dodecyl methyl sulfide (242 mg, 1.12 mmol), *N*-chlorosuccinimide (149 mg, 1.12 mmol), triethylamine (0.26 ml, 1.86 mmol), and toluene (14 ml) to give cinnamaldehyde (44.5 mg, 90%).

3.3. A typical procedure for the new method of the Corey–Kim oxidation using dodecyl methyl sulfide for heteroaromatic alcohols

To a tetrahydrofuran solution (30 ml) of *N*-chlorosuccinimide (324 mg, 2.43 mmol) was added a tetrahydrofuran solution (6 ml) of dodecyl methyl sulfide (1) (526 mg, 2.43 mmol) dropwise at -40°C , and the resulting mixture was stirred for 30 min. A tetrahydrofuran solution (6 ml) of an alcohol (0.81 mmol) was added dropwise at -40°C . After the mixture was stirred for 2 h, triethylamine (410 mg, 4.05 mmol) was added dropwise at -40°C . After stirring for 14 h, the reaction mixture gave an aldehyde or a ketone. The resulting products were analyzed by comparing their GC with those of authentic samples.

3.3.1. 2-Pyridinecarboxaldehyde (Table 4, entry 1). According to the general procedure, the reaction was performed using 2-pyridinemethanol (88 mg, 0.81 mmol). Yield: 77%.

3.3.2. 3-Pyridinecarboxaldehyde (Table 4, entry 2). According to the general procedure, the reaction was performed using 3-pyridinemethanol (88 mg, 0.81 mmol). Yield: 71%.

3.3.3. 3-Acetylpyridine (Table 4, entry 3). According to the general procedure, the reaction was performed using 2-(1-hydroxyethyl)pyridine (100 mg, 0.81 mmol). Yield: 99%.

3.3.4. 2-Thiophenecarboxaldehyde (Table 4, entry 4). According to the general procedure, the reaction was performed using 2-thiophenemethanol (92 mg, 0.81 mmol). Yield: 86%.

3.3.5. 3-Thiophenecarboxaldehyde (Table 4, entry 5). According to the general procedure, the reaction was performed using 3-thiophenemethanol (92 mg, 0.81 mmol). Yield: 85%.

3.3.6. Furfural (Table 4, entry 6). According to the general

procedure, the reaction was performed using furfuryl alcohol (79 mg 0.81 mmol). Yield: 92%.

3.4. A typical procedure for the new method of the Swern oxidation using dodecyl methyl sulfoxide (2)

To a dichloromethane (4 ml) suspension of dodecyl methyl sulfoxide (2) (95 mg, 0.41 mmol) was added dropwise oxalyl chloride (41 μl , 0.41 mmol) at -60°C , and the resulting mixture was stirred for 15 min. A dichloromethane (1 ml) solution of an alcohol (0.27 mmol) was added dropwise at -60°C . The mixture was stirred for 30 min, triethylamine (0.19 ml, 1.36 mmol) was added dropwise and the resultant mixture was gradually warmed to -40°C over 200 min. The 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), neutralized with an 1N HCl (0.5 ml) solution then extracted with chloroform (40 ml $\times$ 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 an aldehyde or a ketone and dodecyl methyl sulfide (1). The resulting products were analyzed by comparing their NMR spectra and TLC with those of authentic samples.

3.4.1. Benzophenone (Table 5, entry 1). According to the general procedure, the reaction was performed using benzhydrol (50 mg, 0.27 mmol), dodecyl methyl sulfoxide (95 mg, 0.41 mmol), oxalyl chloride (36 μl , 0.52 mmol), triethylamine (0.19 ml, 1.36 mmol), and dichloromethane (5 ml), to give benzophenone (47 mg, 95%).

The 10-times scale-up experiment under the above conditions using benzhydrol (500 mg, 2.7 mmol) gave benzophenone (460 mg, 93%), along with dodecyl methyl sulfide (1) (340 mg, 92%).

3.4.2. Benzil (Table 5, entry 2). According to the general procedure, the reaction was performed using benzoin (50 mg, 0.24 mmol), dodecyl methyl sulfoxide (82 mg, 0.35 mmol), oxalyl chloride (45 μl , 0.70 mmol), triethylamine (0.16 ml, 1.18 mmol) and dichloromethane (6 ml) to give benzil (46 mg, 99%).

3.4.3. *o*-Bromobenzaldehyde (Table 5, entry 3). According to the general procedure, the reaction was performed using *o*-bromobenzyl alcohol (50 mg, 0.27 mmol), dodecyl methyl sulfoxide (93 mg, 0.40 mmol), oxalyl chloride (35 μl , 0.40 mmol), triethylamine (0.19 ml, 1.34 mmol), and dichloromethane (5 ml) to give *o*-bromobenzaldehyde (47 mg, 95%).

3.4.4. Cinnamaldehyde (Table 5, entry 4). According to the general procedure, the reaction was performed using cinnamyl alcohol (50 mg, 0.37 mmol), dodecyl methyl sulfoxide (129 mg, 0.56 mmol), oxalyl chloride (39 μl , 0.56 mmol), triethylamine (0.26 ml, 1.86 mmol), and dichloromethane (6 ml), to give cinnamaldehyde (46 mg, 93%).

3.4.5. Geranial (Table 5, entry 5). According to the general procedure, the reaction was performed using geraniol

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(50 mg, 0.32 mmol), dodecyl methyl sulfoxide (113 mg, 0.49 mmol), oxalyl chloride (43 μ l, 0.49 mmol), triethylamine (0.23 ml, 1.62 mmol), and dichloromethane (14 ml), to give geranial (46 mg, 93%).

3.4.6. 1-Adamantanecarboxaldehyde (Table 5, entry 6). According to the general procedure, the reaction was performed using 1-adamantanemethanol (50 mg, 0.30 mmol), dodecyl methyl sulfoxide (104 mg, 0.45 mmol), oxalyl chloride (40 μ l, 0.45 mmol), triethylamine (0.21 ml, 1.50 mmol), and dichloromethane (6 ml), to give 1-adamantanecarboxaldehyde (46 mg, 93%).

3.4.7. Camphor (Table 5, entry 7). According to the general procedure, the reaction was performed using borneol (50 mg, 0.32 mmol), dodecyl methyl sulfoxide (113 mg, 0.49 mmol), oxalyl chloride (43 μ l, 0.49 mmol), triethylamine (0.23 ml, 1.62 mmol) and, dichloromethane (14 ml), to give camphor (45 mg, 91%).

3.4.8. 2-Octanone (Table 5, entry 8). According to the general procedure, the reaction was performed using 2-octanol (50 mg, 0.38 mmol), dodecyl methyl sulfoxide (134 mg, 0.58 mmol), oxalyl chloride (40 μ l, 0.58 mmol), triethylamine (0.27 ml, 1.92 mmol) and dichloromethane (6 ml) to give 2-octanone (40 mg, 81%).

3.5. Manipulation of odorless Swern oxidation of acidic alcohol (mandelic acid) using dodecyl methyl sulfoxide (2)

To a $\text{CH}_2\text{Cl}_2/\text{THF}$ (3/1, 90 ml) solution of dodecyl methyl sulfoxide (1680 mg, 7.23 mmol) was added dropwise a $\text{CH}_2\text{Cl}_2/\text{THF}$ (3/1, 5 ml) solution of oxalyl chloride (0.63 ml, 7.23 mmol) at -60°C , and the resulting mixture was stirred for 15 min. Then, a $\text{CH}_2\text{Cl}_2/\text{THF}$ (3/1, 5 ml) solution of mandelic acid (500 mg, 3.23 mmol) was added dropwise at -60°C . The mixture was stirred for 2 h, triethylamine (2.29 ml, 16.4 mmol) was added dropwise, and the resulting mixture was gradually warmed to -40°C over 2 h. The mixture was then warmed to room temperature by removing the cooling bath and stirred for 40 min. The mixture was quenched with 10% NaOH solution, and concentrated in vacuo. The residue was washed with ether, a 1N HCl solution was added, then the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Without further purification, the pure phenylglyoxylic acid (466 mg, 96%) was obtained. The product was analyzed by comparing the NMR spectrum and TLC with those of the authentic sample.

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- Depending on the physical property and the amounts of the products, extraction, crystallization, or distillation could be used for isolation of the products.
- The same extraction in the case of Corey–Kim oxidation gave a mixture of phenylglyoxylic acid and succinimide.
- Both Dod-S-Me (1) and dodecyl methyl sulfoxide (2) are now available from Wako Pure Chemical Industries, Ltd.

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