The Reactivity of Silyl Ethers to the Swern Reagent

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The activated Me_2SO reagent [$Me_2SO-(COCl)_2$, 'Swern reagent'] oxidises the trimethylsilyl ethers of primary and secondary alcohols directly to the corresponding carbonyl compound. Useful selectivity is possible where competing ether groups possess large differences of steric hindrance. Dimethyl-t-butylsilyl ethers are unaffected by this reagent.

It is well known that trimethylsilyl ethers are unstable in the presence of halide ions and especially so under even very mildly acidic conditions. At lower temperatures, however, it may be supposed that they would be more stable and perhaps sufficiently so to survive the relatively mild conditions encountered during a Swern oxidation.[1] The Swern reagent is a useful selective oxidising agent (*e.g.* does not oxidise sulphides[2]) and functions at relatively low temperatures (-60 °C). Intrinsically, however, it also furnishes chloride ions and the formation of traces of hydrogen chloride by decomposition of the active agent, a chlorodimethylsulphonium salt, is also a possibility [Equation (1)].

$$R^1CH(OSiMe_3)R^2 \xrightarrow{(Me_2SCl)^+Cl^-} R^1COR^2 \quad (1)$$
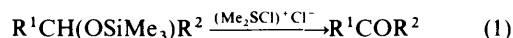
In order to test the stability of trimethylsilyl ethers to the Swern reagent we treated cyclohexyl trimethylsilyl ether to Swern's recommended conditions for alcohol oxidations (-60 °C, 15 min; triethylamine). This resulted in a 60% conversion into cyclohexanone. From this result it is evident that the trimethylsilyl ethers are not stable under these conditions. This is probably due to attack by one or both of the aforementioned reactive species.

Considerable interest[3] has been shown over the years in methods for the direct oxidation of trimethylsilyl ethers to aldehydes and ketones. We therefore attempted to optimise the conditions for direct oxidations with the Swern reagent in order to obtain acceptable yields of carbonyl products. From the cyclohexyl trimethylsilyl ether reaction we knew that the product was contaminated only with the starting material and we reasoned that a higher temperature and a longer initial reaction period was probably necessary in order to complete the liberation of the alcohol. A reaction temperature of -30 °C and a time of 30—45 min. afforded good yields of carbonyl products

both for primary and secondary alcohol trimethylsilyl ethers, in almost all of the examples studied (normally above 80%), Table 1. The only relative failure occurred with the allylic trimethylsilyl ether, entry 5. The more forcing conditions necessary confirmed our initial suspicions that the slow step is the removal of the trimethylsilyl group to liberate the free alcohol. This then reacts rapidly with the chlorosulphonium salt to form an alkoxysulphonium salt which, with base, results in oxidation.

A recent publication[4] described an investigation of the selectivity in the oxidation of mixtures of primary and secondary alcohols by the Swern method. In a similar study we subjected a mixture of equimolar quantities of octan-1-yl and octan-2-yl trimethylsilyl ethers to our oxidation conditions and we obtained a mixture of octan-2-one and octanal in the ratio of 2.5:1 respectively, as estimated by n.m.r. spectroscopy. Removal of the trimethylsilyl group from the primary alcohol is expected to be more rapid. Hence the product distribution is not that predicted if the deprotection of the alcohol is implicated in product control. After slow exposure of the alcohol and rapid formation of the alkoxysulphonium salt there is probably an equilibration as in Equation (2), resulting in a thermodynamically controlled mixture. This is in accord with the results of the aforementioned study.[4]

$$Me_2S^+OR^1 + R^2OH \rightleftharpoons Me_2S^+OR^2 + R^1OH \quad (2)$$
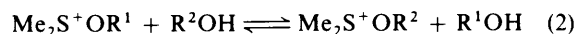
We next attempted to selectively oxidise the 3-hydroxy group of methyl deoxycholate, the 12α-hydroxy group of which is severely hindered. Oxidation of the unprotected 3,12-diol (**5**), using Swern's conditions and one equivalent of oxidant, afforded, after chromatography (SiO_2), 40% of the required ketone (**2**), 12% of the 12-oxo compound (**3**) with the remainder

Table 1. Oxidation of the trimethylsilyl ethers of primary and secondary alcohols[5]

Entry	Trimethylsilyl ether	Yield of product as 2,4-DNP (%)	M.p. of 2,4-DNP °C (lit. value)
1	Cyclohexyl	83	158—159 (160—162)[6]
2	Octan-1-yl	92	100—102 (106—96)[6]
3	Octan-2-yl	88	55—57 (58)[6]
4	$Me_2C=CHCH_2CH_2CHMeCH_2CH_2$	80	83—85 (78)[6]
5	$Me_2C=CHCH_2C(Me)=CHCH_2$	40	107—111 (108—110)[6]
6	Cholest-5-en-3-yl	94	226—230 (232)[7,a]
7	Cyclopentadecyl	83	106—107 (108—109)[8]
8	Benzyl	86	239—240 (239—241)[9]
9	(**1**)	74	137—140 (140—142)[10,b]

[a] M.p. for cholest-4-en-3-one 2,4-dinitrophenylhydrazone. The underivatised ketone gave m.p. 80—82 °C., lit.,[12] 81—82 °C. [b] Underivatised ketone.

Table 2. Attempted oxidation of dimethyl-t-butylsilyl ethers (3) [13]

| R in (3) Y=OSiMe$_2$Bu^t	Yield (%)	Product	M.p. (°C)
Me(CH$_2$)$_6$CH$_2$Y	90	Starting material	
Cyclohexyl-Y	90	Starting material	
(6)^a	80	(7)	142—144

^{a} Contained 0.5 mol of ethyl acetate of crystallisation.

consisting of a mixture of starting material (5) and the diketone (4). When the readily available methyl deoxycholate 3,12-bis-(trimethylsilyl ether) (1) was treated according to our modified conditions, followed by rapid hydrolysis (MeOH–HCl), to remove all remaining trimethylsilyl protection, and chromatography, the required 12-hydroxy-3-oxo-compound (2) was isolated in 74% yield and the starting diol (5) in 14% yield. The other oxidation products (3) and (4) were also identified in the remainder by comparison with authentic samples.

Unprotected methyl deoxycholate has previously been selectively oxidised to the 12-oxo compound (3) (97% crude yield) by chromic acid,[11] and to the 3-oxo material (2) (57%) by the Oppenauer method.[12] Since the preparation of the bis(trimethylsilyl ether) (1) is almost quantitative this represents a good method for the preparation of (2).

Finally, we treated some dimethyl-t-butylsilyl ethers according to Swern's conditions and found them to be completely stable. Thus the 3-dimethyl-t-butylsilyl ether of methyl deoxycholate (6) was cleanly converted into the 12-oxo compound (7). The results of these experiments are summarised in Table 2.

The Swern reagent serves as a useful reagent for the direct oxidation of trimethylsilyl ethers to the corresponding carbonyl compound. It does not exhibit useful selectivity in the oxidation of mixtures of primary and secondary alcohol trimethylsilyl ethers, however under certain conditions of severe steric impediment, useful selective oxidations of one latent hydroxy group in the presence of another is possible. Dimethyl-t-butylsilyl ethers are completely stable to the Swern reagent. Other trialkylsilyl
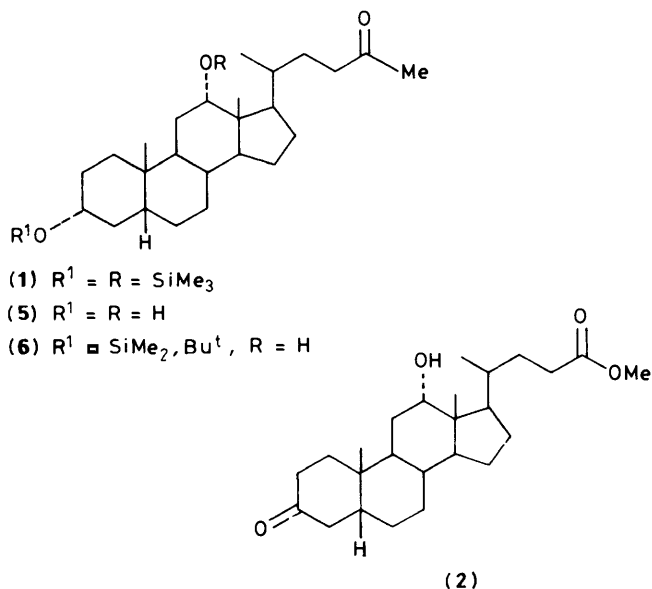
(3) R = H
(7) R = Me$_2$Bu^{t}Si

(4)
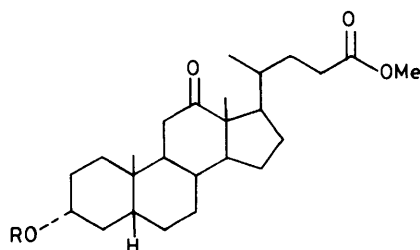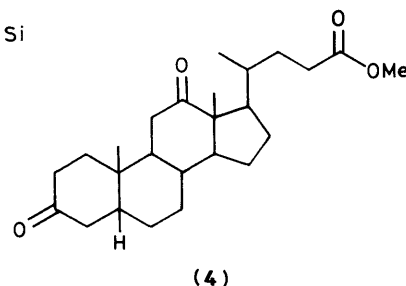
Experimental

All reagents were purified by standard procedures prior to use. The oxidations were carried out under an atmosphere of argon. Reagent transfers were performed using glass syringes. The n.m.r. spectra were measured on a Varian EM 360 L and the chemical shifts calculated in p.p.m. using tetramethylsilane as the internal standard reference 0. Specific rotations were determined using a Bellingham and Stanley non-automatic polarimeter, melting points with a capillary apparatus and infrared spectra were obtained using a Perkin Elmer 683 spectrophotometer. Low pressure column chromatography was performed using Merck Kieselgel 60 H.

The following experiment demonstrates the general procedure for the direct oxidation of simple trimethylsilyl ethers.

Oxidation of Octan-1-yl Trimethylsilyl Ether to Octanal.—A solution of oxalyl chloride (0.95 g, 7.6 mmol) in dry dichloromethane (10 ml) contained in a 25 ml two-necked flask fitted with a septum, was cooled to −60 °C. Dimethyl sulphoxide (1.1 ml, 15.44 mmol) was carefully added and after 5 min, octan-1-yl trimethylsilyl ether (1.01 g, 5 mmol) in dichloromethane (2 ml) was injected into the mixture, still at −60 °C. The temperature of the reaction was allowed to rise to −44 °C over 15 min and then maintained between −30° and −40 °C for a further 30 min. A chloroform–liquid nitrogen bath was then applied in order to cool the mixture rapidly, once more, to −60 °C; triethylamine (3.5 ml, 25.11 mmol) was then added. After a few minutes the temperature of the mixture was allowed to rise naturally to room temperature. For the preparation of the 2,4-dinitrophenylhydrazone a 10% excess of 0.1M aqueous 2,4-dinitrophenylhydrazine was added to the crude reaction products. The crystals of the 2,4-dinitrophenylhydrazone resulting after removal of the dichloromethane by evaporation under vacuum, were filtered off and recrystallised (ethanol–water) to give in this case octanal 2,4-DNP (1.42 g, 92%), m.p. 100—102 °C (lit.,[6] 96 and 106 °C).

Oxidation of a Mixture of Octan-1- and -2-yl Trimethylsilyl Ethers.—Dry Me$_2$SO (0.83 ml, 17.7 mmol) was added to a solution of oxalyl chloride (0.50 ml, 5.85 mmol) in dichloromethane (8 ml) at −60 °C. After 15 min, a mixture of octan-1-yl trimethylsilyl ether (1.18 g, 5.8 mmol) and octan-2-yl trimethylsilyl ether (1.18 g, 5.8 mmol) in dichloromethane (2 ml) was added. The temperature of the mixture was allowed to rise to

(1) R^1 = R = SiMe$_3$
(5) R^1 = R = H
**(6)** R^1 = SiMe$_2$Bu^t, R = H

(2)

groups of intermediate stability have not been tested but are expected to show greater promise than the trimethylsilyl group for selective oxidations. The reactivity of the halogenodimethylsulphonium fluorides may also be interesting in this context.

−40 °C over 15 min and then maintained at this temperature for a further 30 min. After recooling to −60 °C, trimethylamine (3.26 ml, 35.4 mmol) was added and the temperature allowed to rise to ambient.

2,4-Dinitrophenylhydrazine (0.1M; 65 ml; 10% excess) was added as in the previous experiment and the precipitated mixture of the 2,4-dinitrophenylhydrazones removed by filtration. ^{1}H N.m.r. analysis of the imine-H and aromatic-H indicated a mixture of octan-2-one:octanal of ratio 2.5:1 respectively. Although the recovery of carbonyl compounds was not investigated for this mixture the individual compounds could be readily recovered from the crude reaction product mixture as their 2,4-dinitrophenylhydrazones. There is, therefore little evidence to indicate that one of the dinitrophenylhydrazones was selectively precipitated from the mixture.

Oxidation of Methyl Deoxycholate (5).—The procedure of Swern ^{9} was followed and the quantities of reagents used were as follows: Methyl deoxycholate (5) (1.0 g, 2.46 mmol), oxalyl chloride (0.21 ml, 2.46 mmol), Me$_2$SO (0.35 ml, 4.92 mmol), and triethylamine (1.13 ml, 8.12 mmol). The product mixture after washing with brine was chromatographed using silica to give the 3-oxo compound (2) (0.34 g, 40%) m.p. 136—141 °C (methanol–water), the 12-oxo compound (3), (0.12 g, 12%, and the remainder consisted of a mixture of starting material (5) and the 3,12-dioxo compound (4) as verified by chromatographic comparison with authentic samples.

Oxidation of Methyl Deoxycholate 3,12-Bis(trimethylsilyl Ether) (1).—In a 10 ml two-necked flask were mixed oxalyl chloride (0.24 g, 1.93 mmol) and dimethyl sulphoxide (0.28 ml, 3.94 mmol) in dichloromethane at −60 °C in the usual manner. The bis(trimethylsilyl ether) (1) (1.07 g, 1.93 mmol) in dichloromethane (2 ml) was added rapidly and the temperature of the reaction mixture allowed to rise to −40 °C during 15 min and then maintained at about this value for a further 30 min. The mixture was recooled to −60 °C as usual and triethylamine (0.89 ml, 6.38 mmol) was added. After 5 min at −60 °C the temperature of the mixture was allowed to rise to that of its surroundings. To remove remaining trimethylsilyl ether groups the crude mixture was poured into an excess of 5% methanolic hydrogen chloride. When the methanolysis was complete (t.l.c.) the solution was diluted with water and extracted with dichloromethane. After silica gel chromatography compound (2) was obtained (0.58 g, 74%) m.p. 137—140 °C (aqueous acetone) (lit.,^{12} 140—142 °C), along with compound (5) (0.11 g, 14%) m.p. 92—94 °C (lit.,^{14} 95—100 °C) and compound (4) (4%), m.p. 130—131 °C (lit.,^{15} 129—130 C). Thin layer chromatography of the crude methanolysis products indicated the presence of a small quantity of the 3-hydroxy-12-oxo compound (3), however no attempt was made to isolate it.

Oxidation of Methyl Deoxycholate 3-Dimethyl-t-butylsilyl Ether (6).—To a solution of oxalyl chloride (0.15 ml, 1.63 mmol) in dry dichloromethane (10 ml) at −60 °C was added slowly Me$_2$SO (0.25 ml, 3.59 mmol). After 5 min, a solution of compound (6) (0.804 g, 1.50 mmol) in dichloromethane (1 ml) was added and the temperature of the mixture then allowed to rise to −40 °C over 25 min and maintained at this temperature for a further 20 min. The mixture was again cooled to −60 °C and triethylamine (1.14 ml, 8.16 mmol) was carefully added. The mixture was then allowed to warm to room temperature over a period of 20 min. Dichloromethane was added to dilute the solution and this was washed twice with water. The organic phase was dried (MgSO$_4$) and the solvent evaporated to afford a solid. Recrystallisation (ethyl acetate) gave the ketone (7) (0.58 g, 79%) m.p. 142—144 °C, [x]$_D^{25}$ 87.3 ± 2.3° (*c* 4.2, in CCl$_4$). The alcohol (3) was obtained by hydrolysis of the silyl ether with 10% methanolic hydrogen chloride for 24 h at room temperature; m.p. 106—108 °C (lit.,^{16} 106—107 °C).

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