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Sodium Sulphide as a Mild and Selective Desilylating Reagent

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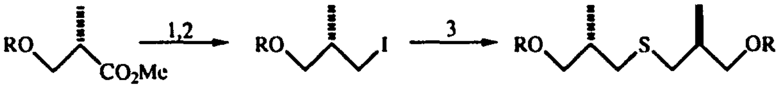
Abstract: diphenyl-t-butoxysilyl (i.e. DPTBOS) derivatives of alcohols are selectively cleaved by nonahydrated sodium sulphide in ethanol, the order of reactivity being: primary≈secondary>>tertiary. The corresponding t-butyldimethylsilyl and diphenyl-t-butylsilyl derivatives remain unaffected in these conditions.

As part of an ongoing synthetic programme, we needed to prepare optically pure sulphide **1a**. Accordingly, the commercially available methyl ester of (*S*)-3-hydroxyisobutyric acid, **2a**, was reacted with diphenyl-*t*-butylsilyl chloride (*i.e.* DPTBSCl). Reduction by LAH of the resulting DPTBS derivative, **2b**, was followed by tosylation and treatment with NaI in acetone, to afford iodide **3b**. Conversion of this iodide into the desired sulphide **1a** was then achieved by stirring **3b** with commercial hydrated (9 H_2O) sodium sulphide in ethanol,[1] to give **1b**. Removal of the protecting group in **1b** was then achieved classically (moist TBAF in THF).



2a-c **3b-c** **1a**, R=H
1b, R=DPTBS
1c, R=DPTBOS

Reagents (on **2b**, **2c**): 1- LAH, THF; 2- tosyl chloride, pyridine, 0-4°C, overnight; 2- NaI, acetone, r.t., 2 days; 3- $Na_2S, 9H_2O$ (0.5 eq.), ethanol, r.t., 6 days

Since this product was required in a larger amount, we attempted to substitute diphenyl-*t*-butoxysilyl chloride (*i.e.* DPTBOSCl) to the rather expensive DPTBSCl reagent; DPTBOSCl can be easily prepared on a large scale from the inexpensive diphenyldichlorosilane[2] and DPTBOS derivatives of alcohols have been shown to display a stability close to that of the corresponding DPTBS ethers.[3,4] Both protection of the starting ester with this reagent and the reduction/halogenation sequence, precedently used with **2b**, proceeded well; several grams of the DPTBOS-protected iodide **3c** could thus be prepared.

However, stirring this iodide with sodium sulphide in the same conditions as above resulted directly -*i.e.* without the need to treat the product by TBAF- in the formation of the corresponding *bis*-hydroxysulphide **1a**. The apparent sensitivity of the Si-O bond to these conditions was confirmed as follows: treatment of the *bis*-hydroxysulphide **1a** by DPTBOSCl gave the expected *bis*-DPTBOS derivative, **1c**, which gave the starting diol when stirred with hydrated sodium sulphide in EtOH for two days. Since the corresponding DPTBS derivatives, *i.e.* **1b** and **2b**, proved stable under these sulphuration conditions, it turned out that the use of Na_2S-9 H_2O in alcoholic media could be developed as a convenient means for deprotecting selectively these *bis*-alkoxysilanes. Experiments aimed at shedding some light on the mechanism of action of sodium sulphide and at delineating the scope of the method are presented herein.

Obviously, both aqueous and alcoholic solutions of hydrated sodium sulphide are alkaline: pH values of *c.a* 11.9 were recorded (standard pH-meter measurement) for both 1N aqueous and 1N ethanolic (or methanolic) solutions of hydrated Na_2S. Therefore, it could be supposed that hydroxide ions were responsible for the observed hydrolysis; the sensitivity of DPTBOS derivatives of alcohols in aqueous alkaline media has already been identified.[3] However, stirring the DPTBOS derivative of *n*-undecanol, **4**, used as a model substrate, in a pH 11.9 solution of sodium hydroxide in either ethanol or methanol did not induce, as shown, such a significant hydrolysis of the protecting group as that observed with Na_2S.[5]

$$\underset{\textbf{4}}{n\text{-}C_{11}H_{23}\text{-ODPTBOS}} \xrightarrow[\text{ethanol (or methanol) r.t., 3 days}]{Na_2S\text{-}9\ H_2O\ (1\ eq.),} \underset{\text{100\% conversion}}{n\text{-}C_{11}H_{23}\text{-OH}}$$

$$\xrightarrow[\text{ethanol (or methanol), r.t., 3 days}]{NaOH\ (0.04\ eq.),\ H_2O\ (9\ eq.)} \quad \underset{\text{8\% conversion}}{''}$$

Though sodium sulphide dissolved progressively during the reaction, a small amount of residual solids could be isolated by filtration after the hydrolysis. Stirring **4** with these solids in ethanol did not allow the hydrolysis to proceed, but adding **4** to the clear solution obtained by prolonged stirring of commercial sodium sulphide in ethanol, followed by filtration, resulted in the quantitative formation of *n*-undecanol after a few days at room temperature. Therefore, sodium sulphide had to be considered as the actual catalyst.[6]

Subsequent experiments in which various amounts of Na_2S-9 H_2O were used showed that a molar-equivalent of sulphide was necessary to induce full hydrolysis of the silyloxy group; curiously, the conversion did not exceed 50% when using 0.5 eq.. Attempts to detect the transient formation of an adduct in which the silicon atom would be bonded to a sulphur atom by performing the reaction in a NMR tube using deuterated solvents (*i.e.* CD_3OD) proved disappointing, the only observable signals being those of either the starting ether or the resulting alcohols (*i.e.* *n*-undecanol and *t*-butyl alcohol). When sodium thiophenoxide or NaSH (with or without added water (9 eq.)) were substituted to Na_2S, *n*-undecanol was formed in only trace amounts.[7]

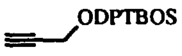
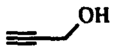
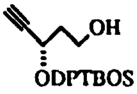
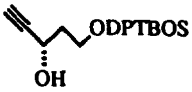
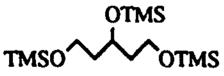
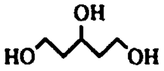
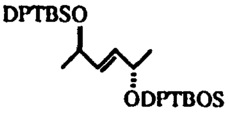
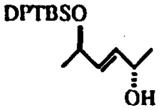
The incidence of the solvent conditions on the course of the reaction was also studied, still using compound **4** as substrate. Whereas the hydrolysis went to completion after three days when the solvent was methanol or ethanol (*v. supra*), almost no reaction occurred in using the following mixtures: 9/1 (or 8/2) THF/H_2O; 1/1 CH_2Cl_2/H_2O (with added NBu_4Cl); 20/1 DMF/H_2O. Moreover, diluting ethanol with water (10%) reduced consistently the rate of hydrolysis; in that case, the conversion amounted for only 40% after three days. At the moment, we are unable to present a mechanism which accommodates these diverse facts.[8]

The unique effect of sodium sulphide in these hydrolyses being ascertained, experiments were then devised in order to precise the incidence of the substitution pattern of both the alcohol and the silyl group on the ease with which the desilylation process would take place. Various substrates were submitted to the original conditions (table).[9]

Hydrolyses of the DPTBOS ethers formed from primary alcohols (entries 1-4) occurred very cleanly, the corresponding alcohol being obtained in high yield in each case. It is worth noting that the ester functionality was unaltered (entry 4) and that no racemisation occurred in these conditions.[10]

As it can be seen (entries 5 and 6), the rate is affected by increasing branching of the alcohol moiety, the order of reactivity being: primary≈secondary>>tertiary.

Table: Na_2S-9 H_2O promoted hydrolyses of alkoxysilanes in ethanol.

Entry	Substrate	time (hours)	Conversion (%)	Product
1	$n\text{-}C_8H_{17}ODPTBOS$	18	100	$n\text{-}C_8H_{17}OH$
2	$Ph\text{-}CH_2ODPTBOS$	12	100	$Ph\text{-}CH_2OH$
3		12	100	
4*	2c	12	100	2a
5		18	40	  (ratio: 3/2; see note 11)
6		72	0	
7		12	100	
8	$n\text{-}C_{10}H_{21}OTBDMS$	16	<5	
9		12	70	

* *in methanol*

The *t*-butyldimethylsilyloxy group remains largely unaffected (entry 8), whereas the trimethylsilyl (TMS) derivatives are cleaved very rapidly, whatever the branching of the alcohol is (entry 7). The stability of diphenyl-*t*-butylsilyl ethers in these conditions has already been mentioned. This authorised, for instance, a selective hydrolysis of a *bis*-protected diol (entry 9).

In conclusion, hydrated sodium sulphide, used in either ethanol or methanol, appears to be a convenient reagent for deprotecting selectively diphenyl-*t*-butoxysilyl derivatives of primary and secondary alcohols in mild conditions.

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References and Notes

1- Gasmann, P. G.; Bonser, S. M.; Mlinaric-Majerski, K. *J. Am. Chem. Soc.* **1989**, *111*, 2652-2662.

2- Diphenyl-*t*-butoxysilyl chloride was prepared following essentially the procedure described by Gillard and Morton (ref. 3). Though this chloride can be prepared on a large scale (100 g) and kept in a dry atmosphere several days without any inconvenience, we have noticed the formation, on standing, after one month, of unidentified solids at the bottom of the flask. We recommend distillation of the product prior to each utilisation ($Bp_{0.2}$ 112°C), in order to obtain a clear colourless oil.

3- Gillard, J. W.; Fortin, R.; Morton, H. E.; Yoakim, C.; Quesnelle, C. A.; Daignault, S.; Guindon, Y. *J. Org. Chem.* **1988**, *53*, 2602-2608.

4- TBDMS (Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190-6191), DPTBS (Hanessian, S.; Lavallée, P. *Can. J. Chem.* **1975**, *53*, 2975-2977) and DPTBOS (ref. 3) derivatives have been classically prepared by stirring the alcohol and the appropriate silyl chloride (1 eq.) in DMF and in presence of an excess of imidazole (2 eq.) overnight, at room temperature. Standard work-up involved: dilution with brine and extraction with hexane, followed by washing (brine), and drying ($MgSO_4$). After evaporation of the solvents, the products were purified by flash-chromatography on 60H silica gel (hexane/CH_2Cl_2). Yields were in the range 92-96%.

5- Standard protocol for the Na_2S-promoted desilylation process: the DPTBOS derivative (5 mmol) was diluted with ethanol or methanol (20 ml) and the resulting solution was thoroughly deaerated. Then Na_2S-9 H_2O (purissim, Fluka; 1.22 g (5 mmol)) was added an the mixture was stirred for the indicated time, at room temperature, under an argon atmosphere. Progress of the reaction was monitored by TLC on silica gel (1/1 hexane/CH_2Cl_2). The reaction mixture was diluted with CH_2Cl_2 (100 ml), then filtered on Celite. The solvents were evaporated *in vacuo* and the residue was chromatographed on silica gel (hexane/CH_2Cl_2). The alcohol was distilled, when appropriate. Starting from ether **4**, *n*-undecanol was obtained in 91% yield, after distillation.

6- It is interesting to note that lithium sulphide has been shown to catalyse, in aprotic media, the silylation of alcohols by silyl halides (Olah, G.; Balaram, B. G. B.; Narang, S. C.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 4272-4275).

7- In a different context, transient formation of a pentavalent species in nucleophilic substitutions at silicon atom has been substantiated by Corriu (Corriu, R. J. P. *J. Organomet. Chem.* **1990**, *400*, 81-106). Should the formation of any pentavalent adduct be the rate-limiting step in the present hydrolyses, the non-observation of such a hypothetical adduct between the DPTBOS derivative and a sulphide ion will be not really conclusive. However, the failure of thiophenoxide ion to accelerate the hydrolysis of these ethers makes this hypothesis questionable, in the present case.

8- A general acid-base catalysis (or a "bifunctional catalysis"), as argued in a related context (Dietze P. E., *J. Org. Chem.* **1993**, *58*, 5653-5662; for general discussion, see also: Bøe B. *J. Organomet. Chem.* **1976**, *107*, 139-217), though conceivable presently, seems difficult to conciliate with the observed retardation induced by added water.

9- Experimental conditions were as in ref. 5. Identification of the products was ensured by GLC and/or ^1H NMR analyses. The yields (related to the unrecovered starting ether) were in the range 87-94% (Entries 1-5, 7, 9).

10- The $[\alpha]_D$ value of the hydroxyester **2a**, thus obtained was identical to that of the commercial product used to prepare **2c** ($[\alpha]_D$ +32; c=2, MeOH). The DPTBOS derivative **2c** had $[\alpha]_D$ +4 (c=10, CH_2Cl_2).

11- The observed selectivity did not result, as verified independently, from scrambling of the protecting group.

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