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Sodium sulfide in methanol: a two-in-one reagent for deprotection of silyl and formation of propargyl sulfide

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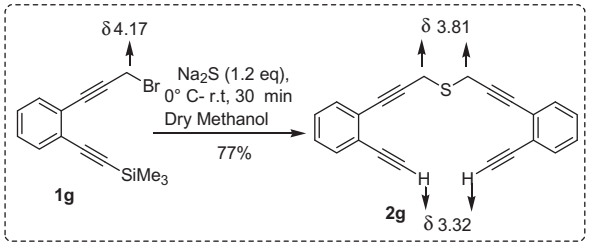
ABSTRACT

A new reagent Na_2S/MeOH for silyl deprotection has been developed. The reagent has several advantages which include deprotection of C-TMS, O-TMS, O-TBS, and O-TBDPS, selective removal of C-TMS and O-TMS in the presence of O-TBS and simultaneous desilylation and sulfide formation in one pot.

Efficiency of a synthetic protocol is measured by several yardsticks which include product yield, atom economy, reagent availability, ease of separation, energy requirement, green character etc.[1] While reagent development and that too under environmentally benign conditions has been a constant endeavor of synthetic chemists, carrying out multiple reactions in a single pot[2] or in domino fashion[3] also helps make a synthetic protocol for a target molecule more efficient. Another option which certainly has an edge over others is to develop a single reagent for carrying out multiple reactions in a single step. Herein we report one such development of a reagent, namely sodium sulfide in methanol (Na_2S/MeOH), which carries out sulfide formation along with silyl deprotection in high yields. A plethora of reagents exist for deprotection of various silyl groups. These include the fluoride sources[4] (TBAF, KF/18-C-6, KF/Al_2O_3, and KF/tetraethylene glycol), acids[5] (HF and CSA), strong bases[6] NaOH/nBuNHSO$_4$, K_2CO_3/ethanol, K_2CO_3/kryptofix/CH_3CN), organic bases[7] Tetramethylguanidine (TMG) and tetraethyl amine N-oxide,[8] LiOAc[9] and phosphate.[10] However, to the best of our knowledge, none of these reagents have been used for dual purposes. On the other hand, use of Na_2S/MeOH for simultaneous desilylation and sulfide formation has not been explored except for one example of *O*-silyl deprotection using Na_2S/MeOH.[11] However the versatility of the reagent was not explored.



Scheme 1. Initial observation.

The possibility of using the reagent for deprotection of silyl first occurred in our mind while trying to prepare[12] the bis-propargyl sulfide from the bromide **1g** (Scheme 1). The procedure involved stirring a methanolic solution of the bromide with Na_2S (1.2 equiv) at 0 °C for 10 min followed by chromatographic purification. This led to the isolation of a product which was clearly a sulfide as the characteristic methylene signal adjacent to the bromine has shifted upfield to appear at δ 3.81. At the same time, the product did not show the presence of a TMS signal which was replaced by a singlet at δ 3.32 characteristic of a terminal alkyne C–H. This confirmed the simultaneous deprotection of TMS under the reaction conditions to provide the compound **2g** whose structure

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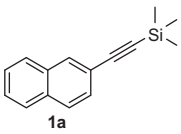
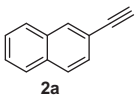
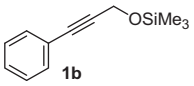
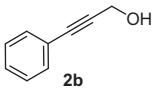
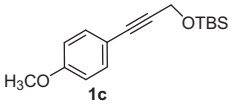
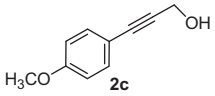
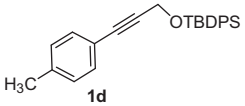
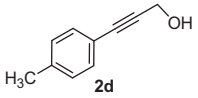
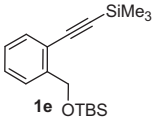
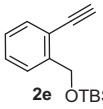
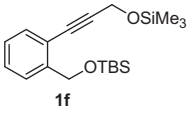
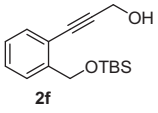
Table 1
Desilylation of TMS, TBS, and TBDPS

Substrate	Product	Percent yield (method, reaction time)	
 **1a**	 **2a**	90 (a, 10 min)	95 (b, 10 min)
 **1b**	 **2b**	80 (a, 30 min)	90 (b, 30 min)
 **1c**	 **2c**	55 (c, 12 h)	65 (d, 12 h)
 **1d**	 **2d**	67 (c, 24 h)	80 (d, 24 h)
 **1e**	 **2e**	80 (a, 10 min)	90 (b, 10 min)
 **1f**	 **2f**	78 (a, 30 min)	90 (b, 30 min)

a = Na_2S (1.0 equiv), dry MeOH, 0 °C to rt.
b = Na_2S (1.0 equiv), 5% moist MeOH, 0 °C to rt.
c = Na_2S (3.0 equiv), dry MeOH, 50 °C.
d = Na_2S (3.0 equiv), moist MeOH, 50 °C.

was further confirmed by mass spectrometry (appearance of MH^+ peak at m/z 311).

Before embarking on to make an elaborate study on the dual reactivity of Na_2S/MeOH, we proceeded to investigate the reactivity of different silyl groups with this reagent. Thus various silyl—protected substrates were treated with Na_2S/MeOH under different conditions. The effects of solvent and temperature on this desilylation reaction were also included in our study. In addition, the scope of the reaction was extended to other silyl groups like TBS and TBDPS ethers. Results are summarized in Table 1. Analysis of the results reveals that both C-TMS and O-TMS underwent efficient deprotection with Na_2S (1 equiv) at 0 °C. The reaction took 10 min for completion. When carried out at room temperature, the reaction took an even shorter time (5 min); however, the yield was slightly less (85% for **1b**) as compared to 95% when carried out at 0 °C. Deprotection of TBS-ether (**1c**) or TBDPS ether (**1d**) required higher temperature and longer reaction time. Typically, these had to be stirred in methanol at 50 °C for 12 or 24 h respectively. As regard to the solvent effect, moist methanol (5%) was found to be best medium affording the highest yield followed by dry methanol and then THF/water (10%).

The difference in the reaction conditions for C-TMS/O-TMS and O-TBS allowed us to chemo selectively deprotect the former in the presence of the latter as shown in Table 1 (conversion of **1e** to **2e** and **1f** to **2f**).

After the establishment of Na_2S/MeOH as an efficient reagent for silyl deprotection, we turned our attention to study the concomitant formation of sulfide as well as silyl deprotection with this reagent. Thus various TMS-protected propargyl bromides (**1g**–**1j**) were treated with Na_2S (1.2 equiv)/MeOH, which coupled two reactions in one pot to form the sulfides with a free terminal alkyne in very good yields.

Since the reagent is carrying out two reactions in one pot, it is of interest to know which step namely desilylation or sulfide formation is occurring first. Thus the bromoenediyne **1g** and Na_2S were dissolved in MeOH-d_4 in an NMR tube and kept well-shaken at 0 °C. The ^1H NMR was recorded at different time intervals (Fig. 1a). Appearance of the methylene signal at δ 3.9 with simultaneous reduction in intensity of the bromomethylene peak indicated immediate sulfide formation followed by the desilylation (increase in the signal at δ 3.3). It may be pointed out that the acetylenic C–H and the residual protiated methanol peak both appeared at the same position at δ 3.3. However, the integration under the peak gradually increased with time and became stationary after 30 min while the peak for the bromomethyl disappeared within 5 min (Fig. 1b).

We have thus developed a new reagent (Na_2S/MeOH) for deprotection of the TMS group attached to alkyne termini. The method also works for deprotection of O-TMS, O-TBS, and O-TBDPS. The desilylation method was further explored for chemoselective deprotection of alkyl silyl against silyl ether. In general the method is simple, high yielding, and carried out at 0 °C to room temperature (for TMS deprotection). The utility of the reagent has been further extended by carrying two reactions in

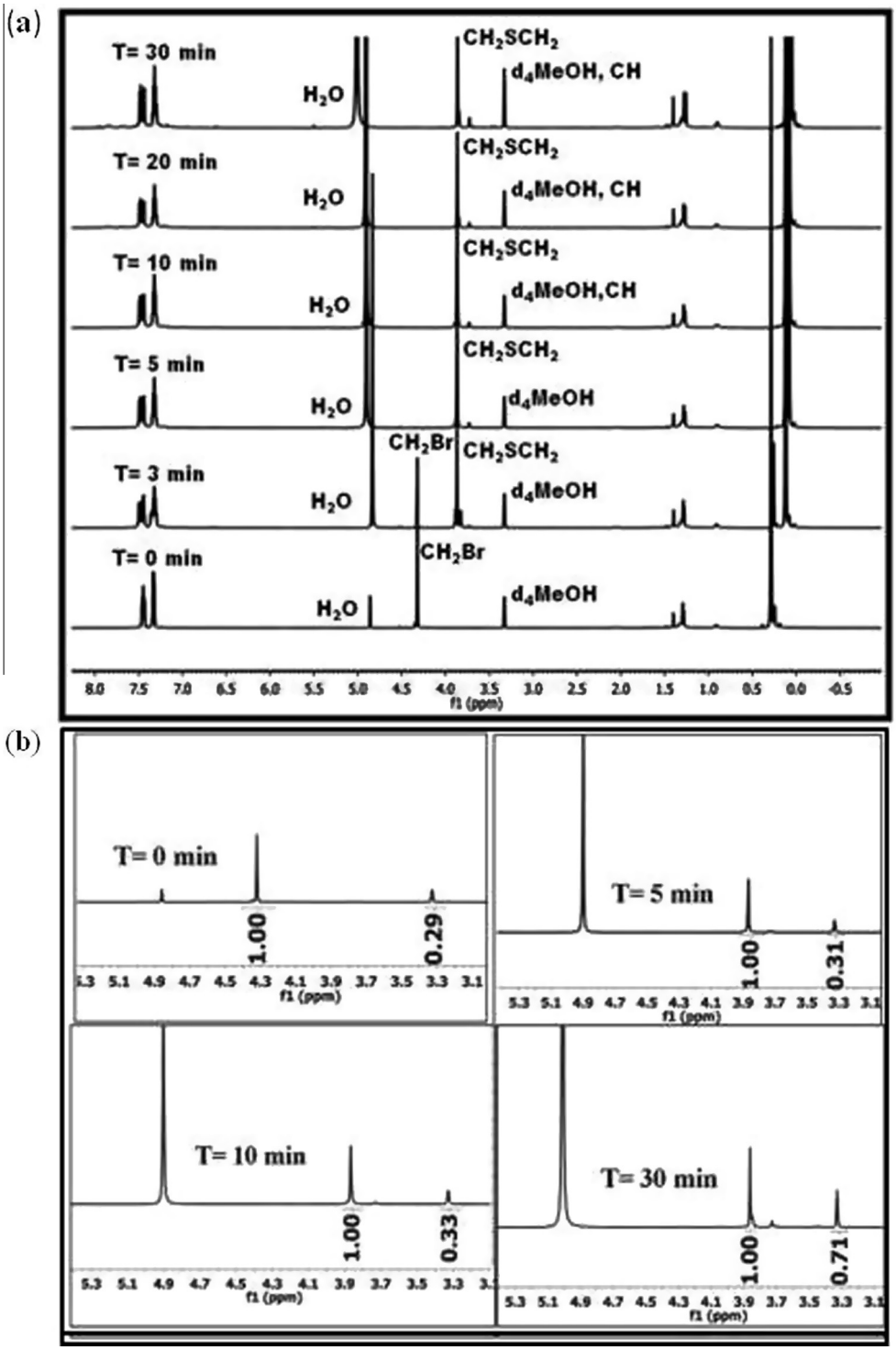
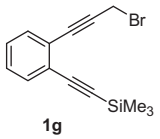
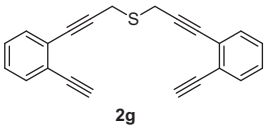
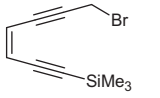
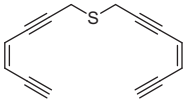
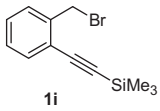
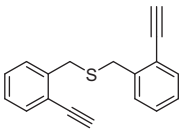
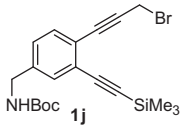
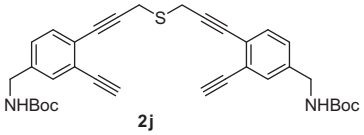
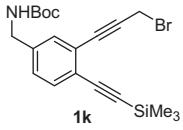
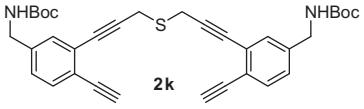


Figure 1. ^{1}H NMR of a MeOH-d_4 solution of **1g** and Na_2S (a) the entire spectrum at different time points (top); (b) the spectra at different time points in the window ($\sim\delta$ 5.3–3.1) showing a gradual increment of peak at δ 3.3 (bottom).

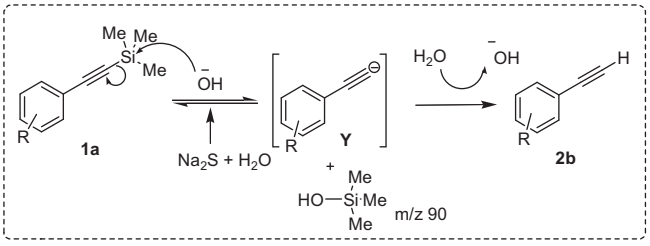
a single pot (Scheme 1), namely deprotection of TMS attached to alkyne termini along with formation of bis-propargyl sulfides in high yields (Table 2). It is interesting to mention that the versatility of Na_2S as reagent for deprotection of TMS-alkyne, first reported by Schmittberger et al.[11], has been established and it may find further application in the design of cascade alkyne transformations.

Regarding the mechanism of the deprotection, two possibilities could have been considered: one involving a nucleophilic attack by sulfide on to the silicon or else attack by hydroxide (reportedly generated from sodium sulfide and moist methanol).[14] We believe that the reaction proceeds by attack of hydroxide and not by sulfide owing to the following reasons: the obligatory requirement of moisture for the reaction and more importantly the observation

Table 2
Desilylation and sulfide formation by Na_2S

Substrate	Product	Percent yield[e]
 1g	 2g	77
 1h	 2h	80
 1i	 2i	72
 1j **	 2j	75
 1k	 2k	

** Contained with regioisomer 1 k and 2 k respectable.
[e] = Na_2S (1.2 equiv), dry MeOH, 0 °C to rt, 30 min.



Scheme 2. Plausible mechanism of deprotection.

of the peak at m/z 91 (MH^+, spectrum in SI) for the trimethyl silanol (Scheme 2).

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.04.104.

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14. (a) General procedure for silyl group deprotection
To the ice cold solution of TMS protected alkyne or aryl silyl ether (0.1 mmol, 1.0 equiv) in dry MeOH (3 mL) sodium sulfide was added (1 mmol, 1 equiv and 0.3 mmol, 3 equiv for TMS alkyne and silyl ether respectively) stirred at 0 °C/room temperature/50 °C (as required) at a specified time. After completion of the reaction (monitored by TLC) it was quenched with water (5 mL) and diluted with DCM (10 mL). The organic layer was washed with water (3 × 5 mL) 3 times, dried over Na_2SO_4, and evaporated under vacuum. The desired product was purified by silica gel column chromatography using petroleum ether/EtOAc as eluent.
(b) General procedure for one pot chemo selective TMS group deprotection and concomitant sulfide formation
To the ice cold solution of TMS-protected propargyl bromide (**1g**–**1j**) (0.1 mmol, 1.0 equiv) in dry MeOH (3 mL) sodium sulfide was added (0.12 mmol, 1.2 equiv) and stirred about 30 min. Then the reaction mixture was quenched with water (5 mL) and diluted with EtOAc (10 mL). The organic layer was separated, washed with brine solution (3 × 5 mL), dried over Na_2SO_4, and concentrated under vacuum. The product was purified by silica gel column chromatography using petroleum ether/EtOAc as eluent.
(c) Spectral data of unknown compounds are included in SI. For the known compound please see Ref. 13.