# Hexamethyldisilazane (HMDS) Promotes Highly Efficient Oxidative Coupling of Thiols by DMSO Under Nearly Neutral Reaction Conditions

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**Abstract:** A variety of thiols were efficiently converted to their disulfides using DMSO in the presence of hexamethyldisilazane (HMDS) under almost neutral reaction conditions. Due to the neutrality of the reaction medium in this protocol, acid sensitive functional groups survived intact.

**Key words:** oxidation, oxidative coupling, thiols, disulfides, hexamethyldisilizane, DMSO

Oxidative conversion of thiols to disulfides is of importance from both biological[1] and synthetic point of view,[2] as shown by a plethora of procedures and methods that have been devised for this transformation.[2,3] Among this, it has been shown, that DMSO in combination with a variety of acidic co-reagents can be used for this purpose.[4] However, many of these protocols suffers from drawbacks such as long reaction times, use of acidic catalysts, and in certain cases, moderate to low yields of the desired disulfides. Consequently, it seems that the development of new improved protocols for high yielding oxidative coupling of thiols to disulfides using inexpensive reagents are being pursued. Application of DMSO in organic transformations is of interest because of its stability, ease of handling, none corrosive and safe nature and inexpensiveness. However, the major limitation of the use of DMSO is its low oxidizing power. This problem can be circumvented by prior treatment of DMSO with a variety of oxophilic co-reagents under acidic conditions as shown by the pioneer work of Swern et al.[5] 1,1,1,3,3,3-hexamethyldisilazane (HMDS) is a stable, weak oxophilic, commercially available and cheap reagent that has generally been used for trimethylsilylation of hydrogen labile substrates,[6] and giving ammonia as the only byproduct. On the other hand, reactions using this silazane-type reagent are nearly neutral and do not need special precaution. In development of new methods for functional group transformation, we especially interested in exploring the potential use of various types of neutral or nearly neutral catalysts.[6d,7] With this strategy in mind, we hypothesized that HMDS might increase the reactivity of DMSO to a reasonable level to carry out the oxidation of thiols under nearly neutral reaction conditions. We first examined the oxidative coupling of thiophenol using DMSO (3 equiv) in $CH_2Cl_2$ in the absence of any additives. At room temperature the reaction was very sluggish and no detectable product was formed even after 12 hours. Once again, we attempted a similar reaction in the presence of HMDS (1.2 equiv). Interestingly, in this case the reaction proceeded smoothly to afford almost quantitative yield of the corresponding disulfides (Table, entry 1).[8] Among the various solvents such as $CH_3CN$, THF, and $CH_2Cl_2$, $CH_3CN$ turned out to be a suitable solvent for this transformation. It is worth mentioning that at least 1.2 equivalents of HMDS were required to obtain good results. Similarly, different types of aromatic thiols were efficiently converted to the corresponding disulfides in excellent yields under similar reaction conditions (Table, entry 2–4). By this method including acyclic, benzylic and cyclic mercaptanes were effectively oxidized to afford the corresponding disulfides in good to excellent yields (Table, entries 5–9). In order to show the neutrality of the reaction, we used 2-(1-phenylpropxy)-tetrahydropyran as a model for THP ethers under the reaction conditions described above. Interestingly, we observed that the THP group survived intact even after 24 hours. Furthermore, due to the neutrality and mildness, this method tolerates a range of functional groups such as organic sulfides, aromatic ethers, THP ethers, furan rings and hydroxy groups of alcohols. In sharp contrast to the Swern oxidation, the HMDS/DMSO protocol only protects hydroxy functions in alcohols. To the best of our knowledge this method can be considered as the first example of the oxidative coupling of thiols using DMSO under nearly neutral reaction conditions.

The actual mechanism of the protocol and the precise role of HMDS are not clear at this stage. However, it is plausible that at the first stage HMDS reacts with the first molecule of thiol in the presence of DMSO to produce a reactive species **1** and trimethylsilyl amine. Intermediate **1** in turn reacts with the second molecule of thiol in the presence of trimethylsilylamine with concomitant release of $NH_3$ to afford the corresponding oxonium intermediate **2**. The rapid collapse of intermediate **2** then results the formation of the corresponding disulfide along with the evolution of dimethylsulfide and hexamethyldisiloxane as by-products (Scheme).

Further applications of this reagent for functional group transformations are currently ongoing in our laboratories.

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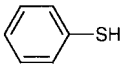
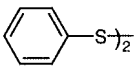
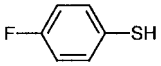
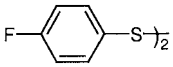
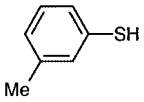
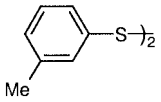
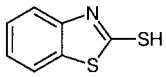
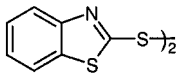
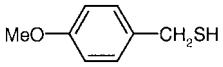
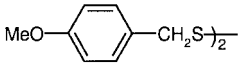
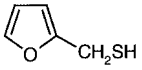
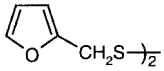
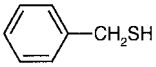
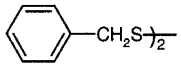
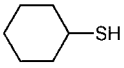
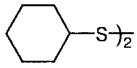
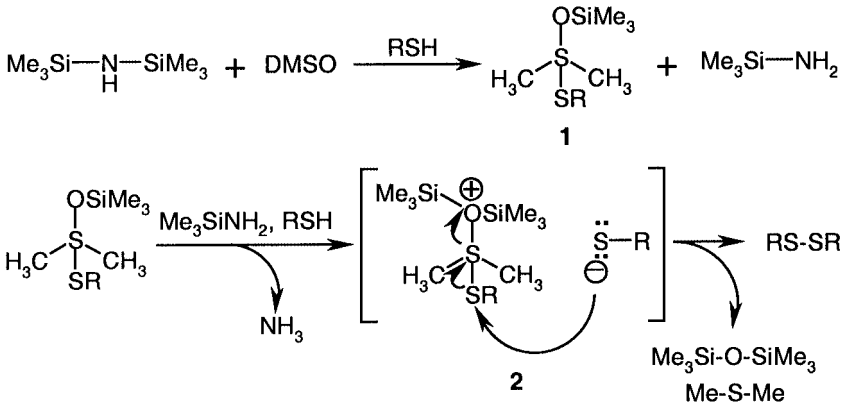
**Table** Oxidative Coupling of Thiols to Disulfides Using HMDS/DMSO in $CH_3CN$ Under Nearly Neutral Conditions

| Entry | Substrate | Product | T (min) | Yield[a,b] (%) |
|---|---|---|---|---|
| 1 |  |  | 45 | 96 |
| 2 |  |  | 80 | 98 |
| 3 |  |  | 80 | 90 |
| 4 |  |  | 225 | 76[c] |
| 5 | n-Bu—SH | n-Bu—S)$_2$ | 250 | 82 |
| 6 |  |  | 50 | 86 |
| 7 |  |  | 70 | 90 |
| 8 |  |  | 90 | 97 |
| 9 |  |  | 95 | 96 |

[a] Yields refer to isolated pure products.
[b] The ratios of thiol:DMSO:HMDS were 1:3:1.2, respectively and all reactions were performed in $CH_3CN$ (5 mL per mmol of substrate).
[c] Reaction was performed under reflux.




**Scheme**

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(8) **General Procedure for Oxidative Coupling of Thiols to Disulfides**: To a solution of thiol (3 mmol) and DMSO (9 mmol) in anhyd acetonitrile (5 mL), HMDS (3.6 mmol) was added and the resulting solution was magnetically stirred at r.t. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into 10% aq NaOH solution. The organic layer was separated and the aq phase was extracted with ether ($3 \times 50$ mL). The organic extracts were combined together and was washed successively with 10% NaOH (25 mL) and water ($2 \times 50$ mL) and dried over anhyd $Na_2SO_4$. Evaporation of the solvent under reduced pressure gave the almost pure disulfide. Further purification of the product was achieved by re-crystallization or column chromatography through a short silica-gel column.