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An alternative to the Swern oxidation

Alakesh Bisai, M. Chandrasekhar and Vinod K. Singh*

Department of Chemistry, Indian Institute of Technology, Kanpur 208 016, India

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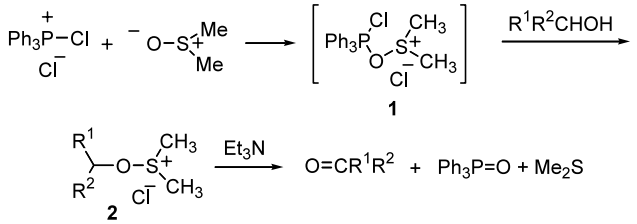
Abstract—A variety of alcohols have been oxidized under mild conditions by the DMSO–$Ph_3P{\cdot}X_2$ complexes. The reaction does not produce any Pummerer product. A mechanism for the reaction is proposed.

The oxidation of alcohols to the corresponding carbonyl compounds is a very important and frequently used transformation in organic synthesis.[1] One of the most common methods for this oxidation is via activated DMSO (Swern oxidation),[2,3] which involves a variety of electrophilic reagents as activators such as oxalyl chloride,[4] acid anhydrides,[5] phosgene,[6] bis(trichloromethyl)carbonate,[7] cyanuric chloride,[8] and others.[9] The reaction proceeds via alkoxysulfonium salts that react with a base to give the carbonyl compound and dimethyl sulfide. The major disadvantage of the reaction is the formation of methylthioalkyl ethers as a by-product due to the Pummerer rearrangement of the alkoxysulfonium ylid. Amongst all activators, oxalyl chloride was found to be the best as high yields of carbonyl compounds were obtained with minimal Pummerer product. Although DMSO–oxalyl chloride is routinely used, the method is still associated with some disadvantages such as a violent reaction during the formation of the ylid and toxicity associated with vapors of the latter. While working on the reaction of activated DMSO with epoxides and other strained rings,[10] we discovered that triphenylphosphine dibromide ($Ph_3P{\cdot}Br_2$)[11] and dichloride ($Ph_3P{\cdot}Cl_2$)[12] in combination with DMSO are good alternatives to the classical Swern oxidation. Details of this work are described in this paper. Based on a ^{31}P NMR study of the reagent, we also propose a mechanism for the reaction.

At the outset, 1-phenyl-1-butanol was treated with a reagent prepared from DMSO and $Ph_3P{\cdot}Br_2$ in CH_2Cl_2 at −78°C followed by Et_3N under the conditions of the Swern oxidation (Scheme 1). The ketone was obtained in a 98% isolated yield (entry 1). Similarly, the use of $Ph_3P{\cdot}Cl_2$ gave the product in high yield (entry 1). However, the oxidation did not proceed when $Ph_3P{\cdot}I_2$ was used. In order to show the scope of the reaction, a variety of alcohols was oxidized with these reagents and the results are summarized in Table 1. All kinds of alcohols such as primary, secondary, allylic, and benzylic alcohols could be oxidized to carbonyl compounds in high yields. A noteworthy feature of the reaction is that an alcohol having a sulfur atom in the molecule could also be oxidized in a reasonably good yield (entry 8). The oxidation could also be carried out in a molecule having silyl ethers which were inert to these conditions (entries 22 and 23). Although ethers are known to be cleaved[13] with $Ph_3P{\cdot}Br_2$, we did not observe any such cleavage under our oxidation conditions (entries 22–26). Similarly, the reagent is known to convert alcohols into halides;[14] however, we did not observe any halo compounds under our reaction conditions.

In order to see whether we would obtain any Pummerer product and to understand the mechanism, the oxidation of 2-*tert*-butyldimethylsilyloxy-1-phenylethanol (entry 22) was tried at different temperatures. At −78, −70, and −60°C, the reaction was complete and a high yield (~95%) of the oxidized product was obtained. On increasing the temperature to −50, −40, and −30°C, the



Scheme 1. Proposed mechanism for oxidation of alcohols.

* Corresponding author. Fax: 91-512-597436; e-mail: vinodks@iitk.ac.in

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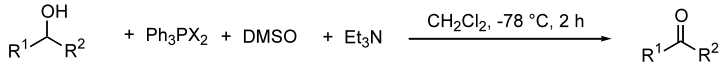
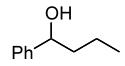
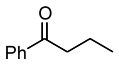
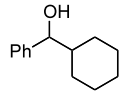
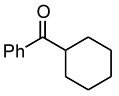
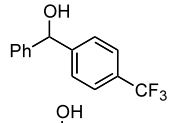
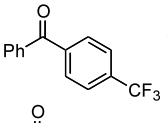
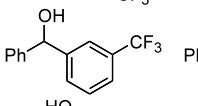
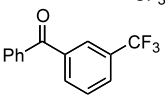
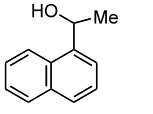
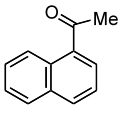
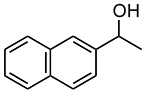
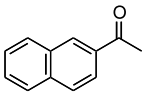
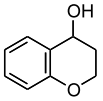
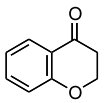
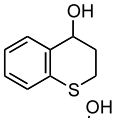
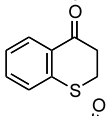
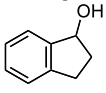
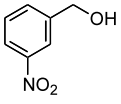
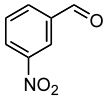
Table 1. Oxidation of alcohols to ketones



S. No.	Substrate	Product	Isolated Yield (%) Ph_3PBr_2	Isolated Yield (%) Ph_3PCl_2
1.			98	94
2.			79	84
3.			76	78
4.			74	82
5.			85	90
6.			88	92
7.			76	80
8.			64	70
9.			89	88
10.			83	70
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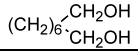
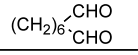
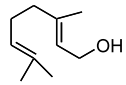
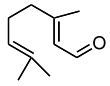
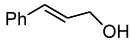
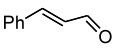
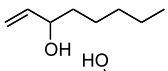
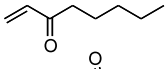
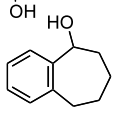
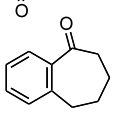
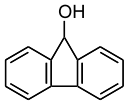
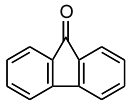
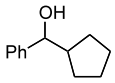
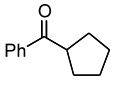
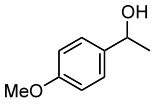
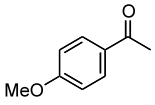
12.	4-*t*-butylcyclohexanol	4-*t*-butylcyclohexanone	73	80
13.			77	80
14.			86	89
15.			90	86
16.			85	91
17.			87	88
18.			82	90
19.			89	90
20.			82	75
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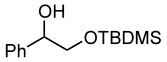
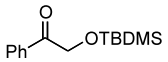
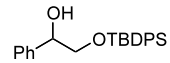
22.			89	93
23.			86	94
24.			81	78
25.			65	68
26.			63	70

yield dropped to 85, 64, and 13%, respectively. In all these cases, the lower yield was due to incomplete oxidation and unreacted alcohol was recovered. It was observed that there was no reaction at −20 and 0°C and the starting material was recovered in a quantitative manner. It was gratifying to know that even at these temperatures, no Pummerer product was formed. Based on a ^{31}P NMR spectrum of a mixture of DMSO and $Ph_3P{\cdot}Cl_2$ in CD_2Cl_2 at −55°C, it is proposed that the reaction does not proceed via the chlorodimethyl sulfide ion as in the classical Swern oxidation (no signal at δ 27 for $Ph_3P{=}O$), instead a signal at δ 46 was seen and was assigned to species **1**.[15] There was no change in the spectrum when the sample was warmed to room temperature. It was also noted that there was not much change in the ^{31}P NMR spectrum on addition of an alcohol to the reagent. No change in the ^{31}P NMR signal could be seen because of a similar environment to the phosphorus in all the species. It was assumed that the species **1** might be undergoing an irreversible change at the higher temperatures (−20°C to rt), because of which oxidation is not observed at these temperatures. However, when **1** was prepared and treated with an alcohol at −78°C, dimethylalkoxysulfonium salt **2** is assumed to be formed, which on treatment with a base, decomposes to the carbonyl compound, Me_2S, and $Ph_3P{=}O$ (δ 27 in ^{31}P NMR).

In conclusion, we have described a mild method for the oxidation of alcohols using DMSO–$Ph_3P{\cdot}Cl_2$ and DMSO–$Ph_3P{\cdot}Br_2$. We also propose a suitable mechanism for the reaction. It was observed that some func-

tional groups, which could react with these reagents, remained unaffected under the reaction conditions.

General procedure for oxidation reactions. DMSO (3 mmol) was added to a solution of PPh_3X_2 (1.5 mmol) in CH_2Cl_2 (6 mL) was cooled at −78 °C. The color of the solution turned yellow when PPh_3Br_2 was used and it was milky white with PPh_3Cl_2. After one hour, 1 mmol of an alcohol solution in CH_2Cl_2 (2 mL) was added and the reaction mixture was stirred at the same temperature for 15 min when 3 mmol of Et_3N were added. The reaction mixture was allowed to warm to rt (2 h). Most of the CH_2Cl_2 was removed in vacuo, and a 1:1 mixture of Et_2O and *n*-hexane was added to the flask in order to precipitate $Ph_3P{=}O$, which was filtered off. The filtrate was evaporated and the crude product was purified by column chromatography over silica gel to provide pure ketones in high yields (Table 1). All the carbonyl compounds are either commercially available or known in the literature. They were characterized by the usual spectral data and compared with authentic samples.

Acknowledgements

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