Conversion of Alcohols to Chlorides by TMSCl and DMSO

Dudley C. Snyder

Department of Chemistry, The Pennsylvania State University/Wilkes-Barre Campus, Lehman, Pennsylvania 18627

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It has been well established that alcohols can be converted to their corresponding iodides¹ or bromides² by the action of trimethylsilyl halides, TMSI or TMSBr, respectively. The same reaction does not occur with the less reactive TMSCl alone, although it has been shown that the transformation can be accomplished with TMSCl when a catalytic quantity of SeO₂ is employed.³ Recent work in this laboratory has found that both 1° and 3° alcohols can be readily converted to alkyl chlorides by TMSCl and a catalytic quantity of DMSO. The facile, high-yield reaction is postulated to take place through a mechanism similar to that proposed for TMSI and TMSBr (Scheme 1).

The reaction shown in Scheme 1 is highly dependent on the electrophilicity of the silicon in the TMSX species. This allows the formation of the critical silicon-oxonium intermediate by the nucleophilic attack of the alcohol oxygen. (In these reactions a 2/1 excess of the TMSX is used due to the unavoidable reaction of the trimethylsilyl alcohol product with TMSX to generate the stable hexamethyldisiloxane.) It has been postulated that the lower electrophilicity of the TMSCl silicon is the reason for the failure of TMSCl to react as well as either TMSI or TMSBr. An effort to facilitate the first step of the Scheme 1 mechanism by the use of a dipolar aprotic solvent, specifically DMSO, led to the discovery that even a catalytic quantity of the DMSO was all that was required for the rapid formation of the alkyl chlorides and hexamethyldisiloxane. The reaction proved to be general for a variety of 1° and 3° alcohols, as summarized in Table 1.

A possible mechanism for the reaction, based on Scheme 1, is shown in Scheme 2. In Scheme 2 it is postulated that the electrophilicity of the TMSCl silicon is enhanced by the initial transformation of the TMSCl to a new, much more reactive Si-O-S intermediate formed from the reaction with the DMSO. This intermediate can then enter into the same general reaction as in Scheme 1 to generate the specified products, as well as to regenerate the DMSO as a true catalyst. Some evidence for the existence of the intermediate can be found in ¹H NMR data. Addition of an approximately equimolar quantity of DMSO to an NMR tube containing TMSCl resulted in a strong exotherm and the formation of a fine white solid. There was also the complete loss of the δ 0.4 signal of the TMSCl, with the appearance of a signal at δ 2.4 that appeared to overlap the DMSO resonance. No further analysis was done on the unstable suspension, but the data suggest a definite change in the nature of the silicon species that could be involved when even a small amount of DMSO is used. The high



Table 1. Formation of Alkyl Chlorides from Alcohols and TMSCI/DMSO

 $ROH + 2(CH_3)_3SiCl/DMSO \rightarrow RCl + (CH_3)_3SiOSi(CH_3)_3$

R	% yield
PhCH ₂	95
$CH_3(CH_2)_6CH_2$	95
$CH_3CH_2CH_2$	93
$PhCH_2CH_2$	93
$CH_3(CH_2)_3CH(CH_2CH_3)CH_2$	92
$CH_3CH_2CH_2CH_2CH_2$	96
$(CH_3)_2CHCH_2$	95
$c-C_6H_{11}$	6 (after 4 h of reflux)
$CH_3(CH_2)_5CHCH_3$	0
(CH ₃) ₃ C	89
$CH_3CH_2C(CH_3)_2$	88
$(CH_3CH_2)_2CCH_3$	94
Scheme 2	
<u> </u>	ÇH₃
/	
ÇH₃ +	н о-
H	
$(CH_3)_3SiOR + CI $	

reactivities of the 1° and 3° alcohols relative to 2° systems (see Table 1) can be explained in terms of the last step of the reaction. This is simply analogous to the cleavage of an ether by either an $S_N 2$ pathway for 1° centers or an $S_N 1$ for the 3° systems. A 2° carbon, however, having poor reactivity to either $S_N 2$ or $S_N 1$, particularly with a weaker nucleophile like chloride ion, would tend instead to show reaction at the more receptive silicon. Thus the reaction would simply be reversed.

A strong case can be made that the key TMS intermediate in Scheme 2 is at least as reactive as TMSI. This can be demonstrated by the fact that TMSI is itself more reactive than TMSBr, transforming TMS-protected alcohols as well as unprotected alcohols to alkyl iodides¹ while TMSBr can react only with the alcohols themselves. Like TMSI, the TMSCI/DMSO combination will also react just as readily with TMS-protected alcohols to give the chlorides in the same high yields. Although it is assumed that alcohols will make the most convenient starting materials for the alkyl chloride syntheses, the reactivity with the TMS-protected derivatives could prove useful in some cases.

In conclusion, the new reaction described here offers a quick, convenient, and inexpensive alternative to other methods for the synthesis of alkyl chlorides. In addition, the reactive TMSCI/DMSO combination may prove a useful alternative to other reactions which require the somewhat difficult-to-handle TMSI, such as epoxide openings. Further investigations in these areas are now underway, and preliminary evidence indicates an extremely fascile opening of epoxides with the TMSCI/ DMSO.

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Notes

Experimental Section

General. All reagents were used as commercially supplied from Aldrich Chemicals. Generally products were isolated by distillation and identified by bp and matching of distillate IR⁴ and ¹H NMR⁵ with literature spectra without need for further purification. All alcohols were reacted in the manner shown below for the representative benzyl alcohol.

Reaction of Benzyl Alcohol with TMSCI/DMSO. A 10 mL flask was charged with a mixture of 0.01 mol (1.1g) of benzyl alcohol and 0.02 mol (2.2g) of TMSCl. To the stirred solution was added 0.2 g (0.0026 mol) of DMSO in a single portion. The flask grew warm immediately, vented HCl(g) and within 1 min a two-phase system had formed. The mixture was stirred for an additional 10 min and then distilled through a short-path. mircohead to remove the volatiles (81-98 °C) and leave 1.2 g of material whose IR and ¹H NMR matched the literature spectra of pure benzyl chloride (95% yield).

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