METHYLTRICHLOROSILANE AS AN EFFECTIVE ACTIVATION AGENT FOR SWERN OXIDATION

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GRAPHICAL ABSTRACT

Abstract A practical and efficient alternative version of the Swern oxidation has been successfully developed. Methyltrichlorosilane was used as an efficient activator of dimethylsulfoxide, which could oxidize a wide range of primary and secondary alcohols to the corresponding carbonyl compounds with good to excellent yields.

Keywords Alcohols; carbonyl compounds; MeSiCl3–DMSO; silicon reagents; Swern oxidation

INTRODUCTION

Carbonyl compounds are of great importance in organic synthesis because they can be transformed into various functionalized compounds through many different reactions.1 For the preparation of carbonyl compounds, oxidation of the corresponding alcohols is one of the most important and frequently used transformations.2 So far numerous methods have been developed to implement this transformation, among which the metal-free Swern oxidation represents the most widely used one. Typically, the Swern oxidation uses a strong electrophile such as oxaly chloride as the activator of dimethylsulfoxide (DMSO).3,4 Recently, we demonstrated that methyltrichlorosilane (MeSiCl3) could serve as an effective activator of both DMSO

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and sodium phenylsulfonate (PhSO₂Na), on the basis of which highly efficient methods for chlorination of enamides and sulfinylation of enecarbamates have been developed.\[5\] We speculated that MeSiCl₃ could also be used as an activator of DMSO for the Swern oxidation and that an alternative recipe for the Swern oxidation could be developed (Scheme 1).

Initially, we tested the Swern oxidation of benzyl alcohol using MeSiCl₃ as the activator of DMSO. The reaction was carried out at different temperatures with triethylamine as base and dichloromethane as solvent. To our delight, the desired product benzaldehyde was obtained in moderate yield if the temperature was maintained at -20°C during the whole reaction process (Table 1, entry 1). The yields were further increased to 76% and 80% when the temperatures for the oxidation step

![Scheme 1. Proposed mechanism for the oxidation of alcohols by MeSiCl₃–DMSO system.](image)

Table 1. Screening of reaction conditions

| Entry | Temp. (°C) | Chlorosilane | Yield (%) |
|-------|------------|--------------|-----------|
| 1     | -20        | MeSiCl₃      | 52        |
| 2     | -78        | MeSiCl₃      | <5        |
| 3     | -20 to -40 | MeSiCl₃      | 76        |
| 4     | -20 to -60 | MeSiCl₃      | 80        |
| 5     | -20 to -78 | MeSiCl₃      | 90        |
| 6     | -20 to -78 | SiCl₄        | 85        |
| 7     | -20 to -78 | AllylSiCl₃   | 85        |
| 8     | -20 to -78 | HSiCl₃       | 79        |
| 9     | -20 to -78 | Me₂SiCl₂     | 78        |
| 10    | -20 to -78 | Me₂SiCl      | 10        |

\[a\]Conditions: [I] = 0.3 M, [chlorosilane] = 0.3 M, [DMSO] = 1.2 M, [Et₃N] = 2.4 M.
\[b\]All chlorosilanes were used directly without purification.
\[c\]The yield was determined with HPLC.
were decreased to −40°C and −60°C, respectively (Table 1, entries 3 and 4). Some other chlorosilanes were also found to be effective activators of DMSO, furnishing the oxidation with moderate to good yields (Table 1, entry 6–9). MeSiCl3 and SiCl4 showed almost identical activities and gave 86% and 85% yields, respectively.

We next explored the substrate’s scope and the limitations of the Swern oxidation using MeSiCl3 as the activator of DMSO. The oxidations of a variety of aryl and alkyl primary and secondary alcohols were examined under the optimal conditions. As shown in Table 2, all the testing substrates could be efficiently oxidized to the corresponding carbonyl compounds with good to excellent yields.

| Entry | Substrate | Product | Yield (%) |
|-------|-----------|---------|-----------|
| 1     | ![Substrate 1](image1) | ![Product 1](image2) | 80        |
| 2     | ![Substrate 2](image3) | ![Product 2](image4) | 76        |
| 3     | ![Substrate 3](image5) | ![Product 3](image6) | 99        |
| 4     | ![Substrate 4](image7) | ![Product 4](image8) | 71        |
| 5     | ![Substrate 5](image9) | ![Product 5](image10) | 92        |
| 6     | ![Substrate 6](image11) | ![Product 6](image12) | 70        |
| 7     | ![Substrate 7](image13) | ![Product 7](image14) | 84        |
| 8     | ![Substrate 8](image15) | ![Product 8](image16) | 83 (75)   |
| 9     | ![Substrate 9](image17) | ![Product 9](image18) | 88 (78)   |
| 10    | ![Substrate 10](image19) | ![Product 10](image20) | 99 (83)   |
| 11    | ![Substrate 11](image21) | ![Product 11](image22) | 96        |
| 12    | ![Substrate 12](image23) | ![Product 12](image24) | 96 (84)   |
| 13    | ![Substrate 13](image25) | ![Product 13](image26) | 80 (89)   |
| 14    | ![Substrate 14](image27) | ![Product 14](image28) | 85 (99)   |

*Conditions: [Alcohol] = 0.5 M, [MeSiCl3] = 0.5 M, [DMSO] = 2 M.*

*The yield was determined with 1H NMR.

*Reaction was carried out at −20°C.*
The substituted benzylic alcohols could be oxidized to the corresponding benzaldehydes (Table 1, entries 1–3). More interestingly, thiophen-2-ylmethanol, which has a sulfur atom in the aromatic ring, could also be effectively oxidized to the corresponding aldehyde with 71% yield (Table 2, entry 4). Secondary alcohols were also tested to see if they could be oxidized to ketone in the current oxidation system. It turned out that even greater yields could be obtained for either aryl or alkyl secondary alcohols comparing to primary alcohols (Table 2, entries 8–14). Notably, good yields could also be obtained for these substrates even if the temperature was maintained at $-20^\circ$C for the oxidation step.

Finally, the oxidation of alcohols by the MeSiCl$_3$–DMSO system has been compared with literature reports of other Swern oxidations. Results of the oxidation of the selected relatively simple primary and secondary alcohols are summarized in Table 3. Reactions were carried out according to the procedures described by the original workers. No substantial difference in the yield of the different oxidation methods has been found for the tested alcohols except 1-(pyridin-4-yl) ethanol, which has a nitrogen atom in the aromatic ring. It seems that the MeSiCl$_3$–DMSO system is more suitable for the oxidation of alcohols that contain heteroaromatic

| Entry | Substrate | Activator | Yield (%)$^e$
|-------|-----------|-----------|------------|
| 1     | \((\text{COCl})_2\)^a | TFAA$^b$ | 99$^{[3h]}$ |
|       |           | TCT$^c$ | 90$^{[4c]}$ |
| 2     | \((\text{COCl})_2\) | TFAA | 99$^{[3h]}$ |
|       |           | TCT | 94 $^{[4c]}$ |
| 3     | \((\text{COCl})_2\) | TFAA | 90$^{[4c]}$ |
|       |           | TCT | 93 $^{[4c]}$ |
| 4     | \((\text{COCl})_2\) | TFAA | 90$^{[4c]}$ |
|       |           | TCT | 95 $^{[4c]}$ |
| 5     | \((\text{COCl})_2\) | TFAA | 90$^{[4c]}$ |
|       |           | TCT | 93 $^{[4c]}$ |
| 6     | \((\text{COCl})_2\) | TFAA | 90$^{[4c]}$ |
|       |           | TCT | 7 $^{[4c]}$ |

$^a,b,c$See Refs. [3b], [3h], and [4c] for all the reaction conditions. TCT = 2,4,6-trichloro-1,3,5-triazine.  
$^d$Conditions: [alcohol] = 0.5 M, [MeSiCl$_3$] = 0.5 M, [DMSO] = 2 M.  
$^e$The yield was determined with $^1$H NMR.
rings because both the thiophen-2-ylmethanol and 1-(pyridin-4-yl) ethanol could be oxidized with good to excellent yields. In conclusion, we have developed a mild and practical method for the oxidation of alcohols with the MeSiCl₃–DMSO system. A wide range of alcohols such as aryl and alkyl primary and secondary alcohols could be oxidized to the corresponding aldehydes and ketones with good to excellent yields. These results demonstrated that the MeSiCl₃–DMSO could be a useful alternative system for the Swern oxidation.

**EXPERIMENTAL**

DMSO (2 mmol) in DCM was added to a solution of MeSiCl₃ (0.5 mmol) in DCM at −20°C. The mixture was stirred at the same temperature for 3 h and cooled to −78°C, followed by slow addition of 1 equivalent of alcohol in DCM. The reaction continued to stir at −78°C for 3 h, and then 8 equivalents of Et₃N were slowly added. After completion of the reaction, the mixture was warmed to the room temperature and extracted with DCM. The combined organic solvent was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography. Dibromomethane or benzyl methyl ether was used as internal standard for quantitative ¹H NMR analysis.

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**SUPPORTING INFORMATION**

Supplemental data for this article can be accessed on the publisher’s website.

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