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Reductive etherification of carbonyl compounds with alkyl trimethylsilylethers using polymethylhydrosiloxane (PMHS) and catalytic $B(C_6F_5)_3$

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Abstract—A facile synthesis of symmetrical and unsymmetrical ethers is achieved by reductive coupling of carbonyl compounds with alkoxysilanes. This reaction is performed using inert polymethylhydrosiloxane as the hydride source and $B(C_6F_5)_3$ as the catalytic activator of the PMHS. © 2004 Elsevier Ltd. All rights reserved.

Ethers are generally prepared by O-alkylation of alkoxides under basic conditions using various alkyl halides.¹ Chloroimidates have also been used for etherification reagents under acidic conditions.² Alternatively, reductive coupling between carbonyl compounds in the presence of trialkylsilane has been used for symmetric ethers as communicated by Doyle and co-workers.³ Other popular methods include Noyori's trimethylsilyl triflate catalyzed reaction of acetals⁴ and the use of Mukaiyama's trityl perchlorate catalyst.⁵ Olah and co-workers have reported a more general synthesis of both symmetric and unsymmetrical ethers catalyzed by TMSI.⁶ High pressure hydrogenation of carbonyl compounds in the presence of alcohols⁷ and trimethylsilane mediated reductive etherification,^{8,9} are other useful protocols. Our research group has a long term programme on the utilization of polymethylhydrosiloxane (PMHS),¹⁰ a silicon industry by-product as a safe source of hydride. Towards this end, the results pertaining to reductive etherification of carbonyl compounds with alkoxytrimethylsilanes are presented herein.

Initially trimethyl(3-phenylpropoxy)silane was subjected to reductive etherification with benzaldehyde in the presence of $1 \text{ mol } \% B(C_6F_5)_3$ catalyst and poly-

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methylhydrosiloxane (2 equiv) in dichloromethane, to give the ether in 85% yield (Scheme 1). This success promoted us to expose the aldehyde to other TMS ethers (Table 1, entry 1). In all cases, uniformly consistent results were obtained. 4-Nitrobenzaldehyde also participated in the reaction without affecting the nitro group.

Mechanistically, we believe, coordination of the carbonyl compound with $B(C_6F_5)_3$ followed by formation of an acetal intermediate, which abstracts hydride from PMHS to release the product is involved. In a generalization to other TMS ethers and carbonyl compounds, the benzyl alcohol TMS ether was exposed to acetophenone (entry 2) to yield 2-phenylethyl benzyl ether without any cleavage of the benzyl ether, which is typical of PMHS in presence of Pd–C. Entry 4 [(4-methoxybenzyloxy)trimethylsilane] demonstrates the stability of a conjugated olefinic system with product yields always over 70%. A natural product substrate, a steroid TMS ether (entry 7), and a terpene (entry 6) also



R, R" = Alkyl, Aryl R', R"' = Alkyl, H

Scheme 1.

| Entry | Substrates | | Product | Yield (%) ^a | |
|-------|---|---|--|----------------------------|--|
| | I II | | - | | |
| 1 | R ¹ OTMS R ¹ = | <i>p</i> -MeOC ₆ H ₄ CHO C ₆ H ₅ CHO C ₆ H ₁₁ CHO <i>p</i> -NO ₂ C ₆ H ₄ CHO 3-C ₆ H ₅ CH ₂ CH ₂ CHO | $\begin{array}{c} R^{1}OPMB \\ R^{1}OBn \\ R^{1}OCH_{2}C_{6}H_{11} \\ R^{1}OCH_{2}C_{6}H_{4}\text{-}p\text{-}NO_{2} \\ R^{1}O(CH_{2})_{3}C_{6}H_{5} \end{array}$ | 85 85 81 84 88 | |
| 2 | OTMS | C ₆ H ₅ COCH ₃ | OBn | 78 | |
| 3 | MeO | C ₆ H ₅ COCH ₃ | ОРМВ | 70 | |
| 4 | MeO | СНО | CH ₂ OPMB | 75 | |
| 5 | R ² OTMS R ² = COTHP | <i>p</i> -MeOC ₆ H ₄ CHO C ₆ H ₅ CHO C ₆ H ₁₁ CHO | R^2OPMB R^2OBn $R^2OCH_2C_6H_{11}$ | 80 83 82 | |
| 6 | R ³ OTMS R ³ = | <i>p</i> -MeOC ₆ H ₄ CHO C ₆ H ₅ CHO C ₆ H ₁₁ CHO | $R^{3}OPMB$ $R^{3}OBn$ $R^{3}OCH_{2}C_{6}H_{11}$ | 82 82 80 | |
| 7 | R ⁴ OTMS | <i>p</i> -MeOC ₆ H ₄ CHO C ₆ H ₅ CHO C ₆ H ₁₁ CHO | R ⁴ OPMB R ⁴ OBn R ⁴ OCH ₂ C ₆ H ₁₁ | 85 90 80 | |

| Table | 1. Reductive | e etherification | of carbonyl | compounds | with alkyl | trimethylsilyl | l ethers using | PMHS and | $B(C_6F_5)$ | 4 |
|-------|--------------|------------------|-------------|-----------|------------|----------------|----------------|----------|-------------|---|
| | | | | | | 2 2 | | | (0 2/2 | |

^a Isolated yields of the product is after purified by column chromatography.

furnished the corresponding ethers with both aliphatic and aromatic aldehydes with excellent yields.

In conclusion, PMHS in the presence of $1 \mod \%$ B(C₆F₅)₃ has been proved to be a useful system for reductive etherification of carbonyl compounds with various TMS ethers.

General experimental procedure. To a stirred solution of the carbonyl compound (2 mmol) and the TMS ether (2 mmol) in dry dichloromethane (5 mL) was added $B(C_6F_5)_3$ (10 mg, 0.02 mmol) and PMHS (240 mg, 4 mmol). The reaction mixture was stirred at room temperature for 5 h. After completion of the reaction, water was added to the reaction mixture, which was extracted with dichloromethane (3×5 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, concentrated in vacuo and purified by column chromatography.

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