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A Simple and Cost Effective Synthesis of Chloromethyl Methyl Ether

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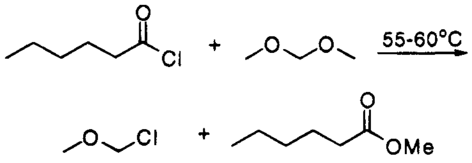
Chloromethyl methyl ether is a reagent commonly employed for the protection of alcohols as the methoxymethyl (MOM) ether.[1] Although chloromethyl methyl ether itself is a suspected mild carcinogen, commercial preparations of this reagent often contain significant amounts of the more toxic and carcinogenic bis(chloromethyl) ether.[2] Although several alternative methods for the methoxymethylation of alcohols have been been developed,[3] many thermally unstable or acid sensitive alcohols are not amenable to the formation of MOM ethers by these routes. The protection of (α-hydroxyalkyl)trialkylstannanes is an example of such a class of sensitive alcohols. The derived MOM-protected stannanes are useful reagents for the preparation of (α-alkoxyalkyl)lithio[4] and cuprate reagents.[5] In the preparation of the functionalized organometallic reagents from the corresponding stannane, the MOM ether or other acetal functionality has proven to be the protecting group of choice.

Chloromethyl methyl ether was originally prepared by Henry in 1893 from formaldehyde, methanol, and hydrogen chloride by essentially the same procedure later reported by Marvel and Porter.[6] Purification of the product from this reaction requires a difficult and time consuming fractional distillation to remove the bis(chloromethyl) ether byproduct. Small, yet significant, amounts of the bis-ether remain in the distilled material. Although several patents have reported modifications of the classic procedure, such as the reaction of dimethoxymethane and anhydrous hydrogen chloride,[7] these modifications do not solve the problem of byproduct formation or the difficulties associated with purification of the product. Amato and co-workers reported a method using dimethoxymethane, anhydrous methanol, and acetyl chloride which provided chloromethyl methyl ether as a solution in methyl acetate contaminated by a small amount of acetyl chloride.[8] Although this procedure solved the problem of how to prepare chloromethyl methyl ether free from bis(chloromethyl) ether, the method required very careful control of the amount of hydrogen chloride (evolved by the initial reaction of methanol and acetyl chloride) present in order to prevent a strongly exothermic and difficultly controlled reaction. An additional alternative preparation of chloromethyl methyl ether free of bis(chloromethyl) ether, the decarbonylation of methoxyacetic acid in refluxing thionyl chloride, has been reported by Jones.[9] Although chloromethyl methyl ether can be obtained in reasonable yield after multiple fractional distillations, the method is not consistently reproducible.

Scheme 1



We sought to eliminate the inherent technical problems associated with the above procedures while still maintaining the desirable feature of not producing the carcinogenic byproduct, bis(chloromethyl) ether. We examined several acid chlorides as potential substitutes for acetyl chloride in the reaction with dimethoxymethane. We anticipated that a high boiling methyl ester byproduct would be readily separated from the chloromethyl methyl ether produced by *simple* distillation. In addition, a cost effective route for the synthesis was also needed, thereby requiring an inexpensive carboxylic acid chloride. With these criteria in mind, hexanoyl chloride was ultimately identified as the acid chloride of choice.

The reaction of dimethoxymethane and hexanoyl chloride (Scheme 1) at 55–60 °C was conveniently monitored by ^{1}H-NMR integration of the methylene signals for chloromethyl methyl ether at 5.45 ppm and dimethoxymethane at 4.57 ppm. Approximately 50% conversion was noted within 2 h; however, to obtain complete conversion (>95%) required heating the solution for 18 h at 55–60 °C. As anticipated, simple distillation of the reaction mixture provided chloromethyl methyl ether in 97% yield. The chloromethyl methyl ether produced in this reaction is typically ≥93% pure, containing only dimethoxymethane as a contaminant. No trace of bis(chloromethyl) ether was detected in the ^{1}H-NMR spectrum (bis-ether CH_2 singlet at 5.56 ppm absent) of crude or distilled product. Continued distillation of the pot residue provided methyl hexanoate in 91% yield, ≥96% pure (by ^{1}H-NMR). Commercially available dimethoxymethane (99%) was employed without further purification. Hexanoyl chloride was prepared from the acid using thionyl chloride and distilled prior to use. The acid chloride was assayed as ≥95% pure by ^{1}H-NMR, with hexanoic acid as the sole contaminant (integration of the CH_2CO signals for the acid chloride at 2.86 ppm and hexanoic acid at 2.35 ppm, respectively). Alternatively, commercially available hexanoyl chloride (tech) may be used if distilled prior to the reaction. No special precautions were taken to exclude traces of hydrogen chloride which may have been present in the acid chloride.

In summary, the synthesis of chloromethyl methyl ether by a very simple and efficient route is reported.

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(2) Van Duuren, B. L.; Goldschmidt, B. M.; Katz, C.; Langseth, L.; Mercado, G.; Sivak, A. *Arch. Environ. Health* **1968**, *16*, 472.

(3) For several procedures which do not involve chloromethyl methyl ether, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons, Inc.: New York, 1991.

(4) See, *inter alia*: (a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (b) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842. (c) Chong, J. M.; Chan, P. C. M. *Tetrahedron Lett.* **1990**, *31*, 1985. (d) Linderman, R. J.; Graves, D. M.; Kwochka, W. R.; Ghannam, A. F.; Anklekar, T. V. *J. Am. Chem. Soc.* **1990**, *112*, 7438. For an example of γ-alkoxyallylicstannanes, see: (e) Marshall, J. A.; Seletsky, B. M.; Luke, G. P. *J. Org. Chem.* **1994**, *59*, 3413, and earlier references therein.

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(9) Jones, M. *Synthesis* **1984**, 727.

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The technical problems associated with safety issues and tedious purification procedures of the previously reported methods have been eliminated. In addition, this new procedure provides chloromethyl methyl ether at a material cost of only \$10.60/mol.[10]

Experimental Section

Chloromethyl Methyl Ether. Freshly distilled hexanoyl chloride (139.1 mL, 134.0 g, 0.995 mole) and dimethoxymethane (88.1 mL, 75.7 g, 0.995 mol) were combined (neat) in a 500 mL round-bottom flask fitted with a reflux condensor. The mixture was placed under an inert atmosphere (Ar) and heated to 55–60 °C (water bath) for 18 h. After cooling to room temperature, the reflux condensor was removed and the flask was fitted with a simple distillation head. Distillation was carried out at atmospheric pressure under Ar. After discarding a small forerun, chloromethyl methyl ether was collected at 58–60 °C (77.7 g, 97% yield). Distillation was continued and methyl hexanoate was collected at 148–150 °C (118.5 g, 91% yield) after discarding a small forerun.

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(10) Cost calculated from hexanoic acid, thionyl chloride, and dimethoxymethane using current Aldrich Chemical Co. catalog prices. For comparison, a mole of chloromethyl methyl ether from Aldrich costs \$138.00.