

SYNTHESIS COMMUNICATIONS

Concise, complete papers on

- New or improved synthetic methods
- Key intermediates for organic synthesis

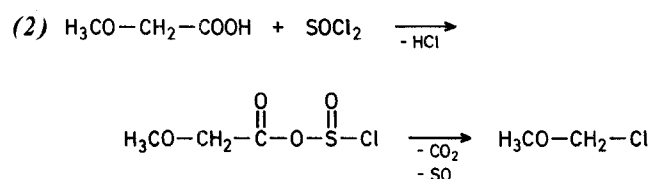
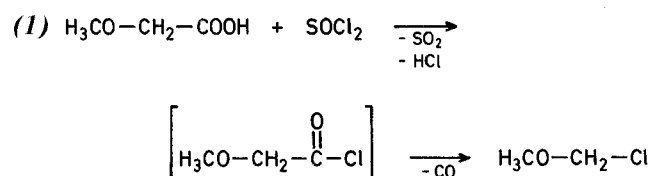
Including full experimental and analytical data

A Novel, Convenient Synthesis of Chloromethyl Methyl Ether

Martin JONES

Department of Chemistry, University of North Dakota, Grand Forks, North Dakota 58202, U.S.A.

We have recently found that a number of chloromethylating agents react with aromatic nuclei to yield high-melting, insoluble polymers¹. During the course of this study, we had occasion to examine the use of methoxyacetyl chloride, which has been shown to effect not only chloromethylation, but also diarylmethane formation, depending on the starting aromatic moiety². Preparation of methoxyacetyl chloride entailed refluxing methoxyacetic acid with thionyl chloride for ~ 1 h followed by slow fractional distillation, with the desired product collected between 106–112°C³. A disappointingly low yield was received from this reaction. When the reflux time was extended to 2 h, no fraction corresponding to methoxyacetyl chloride was obtained. Rather, all but the residue in the boiling flask distilled below 70°C. Spectral analysis of the material revealed that it was chloromethyl methyl ether, which may have resulted from decarbonylation of the acid chloride (Reaction 1) or by nucleophilic attack of chloride (S_Ni or S_N2) on the initially formed acyl chlorosulfite (Reaction 2).



Although mechanistic features of the reaction were not investigated, the apparent time dependence of the product distribution would tend to favor decarbonylation as the route to the ether. Thermally induced loss of carbon monoxide from acid chlorides is uncommon; the usual technique involves treatment with some type of transition metal complex, such as Wilkinson's catalyst⁴.

Chloromethyl methyl ether has been previously prepared from a variety of starting materials, including aqueous formaldehyde, methanol, and hydrogen chloride^{5,6}; dimethoxymethane and anhydrous hydrogen chloride⁷; dimethoxymethane and acetyl chloride⁸; and anhydrous dimethoxymethane, anhydrous methanol and acetyl chloride⁹. The latter synthesis has the advantage of giving chloromethyl methyl ether free of the bis[chloromethyl] ether (this is an

important consideration, since the bis-ether is strongly carcinogenic¹⁰). However, the material is obtained as a solution in methyl acetate with a very small amount of acetyl chloride present. Furthermore, complete conversion requires 36 h and careful control of temperature to prevent an overly exothermic reaction.

The synthesis we report herein also produces material free of the bis[chloromethyl] ether (as determined by N.M.R. and G.L.C.). Side products of the reaction are gaseous (HCl, SO₂ or SO, and CO or CO₂) and the chloromethyl methyl ether is obtained in pure form after a relatively short reflux time (2 h) followed by fractional distillation. Minimal handling of the product is required. We have found this to be a safe and convenient preparation, and expect that it may be of some value, given the synthetic utility of chloromethyl methyl ether¹¹.

Chloromethyl Methyl Ether:

Because of the lachrymatory nature of the chemicals involved, this reaction must be carried out in an efficient hood.

A mixture of methoxyacetic acid (Aldrich Chemical Co.; 50.0 g, 0.56 mol) and freshly distilled thionyl chloride (97.7 g, 0.82 mol) is refluxed in a 250 ml round-bottom flask for 2 h followed by fractional distillation through a 15-cm Vigreux column. The fraction which boiled at 58–65°C was collected, then slowly redistilled through the Vigreux column. Pure chloromethyl methyl ether [as determined from analysis by I.R., ¹H-N.M.R., and G.L.C. (2 m, 3% OV-17 on Chromosorb WAP 80/100)] is obtained; yield: 36.7 g (81%)¹².

The author thanks Daniel Stanley and Steven Balaban for acquisition of I.R. and N.M.R. spectra and Professors Neil Woolsey and Donald Bergstrom for helpful discussions.

Received: March 5, 1984

¹ M. B. Jones, N. Nystuen, D. Stanley, S. P. Rao, C. E. Brown, NW Regional ACS Meeting, June, 1984, Moscow, Idaho.

² A. McKillop, F. A. Madjidabadi, D. A. Long, *Tetrahedron Lett.* **24**, 1933 (1983).

³ J. H. van Boom, P. M. J. Burgers, C. A. G. Haasnoot, *Recl. Trav. Chim. Pays-Bas* **96**, 91 (1977).

⁴ J. Tsuji, K. Ohno, *Synthesis* **1969**, 157.

⁵ C. S. Marvel, P. K. Porter, *Org. Synth. Coll. Vol. I* 377 (1941).

⁶ V. D. Pascu et al., *Rom. RO* 67 136, 1979; *C. A.* **98**, 106 797 (1983).

⁷ L. A. Ens, *Ger. Offen.* 2 431 778, 1975; *C. A.* **83**, 27 558 (1975).

⁸ N. Natrass, *J. Natl. Inst. Metall., Repub. S. Afr., Rep.* **1977**, 1853; *C. A.* **86**, 190 699 (1977).

⁹ J. S. Amato, S. Karady, M. Sletzing, L. M. Weinstock, *Synthesis* **1979**, 970.

¹⁰ B. L. Van Duuren et al., *Arch. Environ. Health* **16**, 472 (1968).

¹¹ M. Fieser, R. L. Danheiser, W. Roush, *Fieser and Fieser's Reagents for Organic Synthesis*, Vol. 9, Wiley-Interscience, New York, 1981, p. 107 and references therein.

¹² Difficulty in reproducing this synthesis was encountered by a student. Subsequent attempts by the author were successful. The product distribution may be sensitive to as yet undetermined factors, perhaps including reflux rate.