A New Efficient Synthesis of Iodomethyl Methyl Ether

Michael E. Jung*, Monica A. Mazurek**, Richard M. Lim**

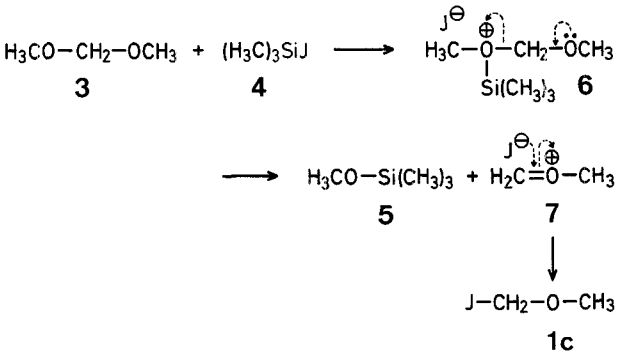
Department of Chemistry, University of California, Los Angeles, California 90024, U.S.A.

Halomethyl methyl ethers (**1a, b, c**) are useful reagents for the protection of alcohols (as methoxymethyl ethers) and for the halomethylation of aromatic systems. The most highly employed of these compounds is the commercially available chloromethyl methyl ether (**1a**) which has certain undesirable properties. Although **1a** is only mildly carcinogenic itself, it is usually contaminated with small quantities of bis-chloromethyl ether (**2a**) which is strongly carcinogenic[1]. Since the general conditions for the formation of the halomethyl methyl ethers, treatment of formaldehyde and methanol with the appropriate hydrogen halide, also cause the production of the bis-halomethyl ethers[2], it is of great interest to devise new methods for the preparation of these compounds which would eliminate the possibility of forming the dangerous bis-ethers. We wish to report an extremely facile synthesis of iodomethyl methyl ether (**1c**) from commercially available materials which avoids the formation of bis-iodomethyl ether (**2c**).

$X-CH_2-O-CH_3$		$X-CH_2-O-CH_2-X$	
1a	X = Cl	**2a**	X = Cl
1b	X = Br	**2b**	X = Br
1c	X = J	**2c**	X = J

In an extension of our work on the conversion of acetals into carbonyl compounds[3], an excess of the dimethyl acetal of formaldehyde (methylal, **3**) was treated with trimethylsilyl iodide[4] (**4**) at room temperature under nitrogen. A very rapid reaction occurred to afford methyl trimethylsilyl ether (**5**) and iodomethyl methyl ether (**1c**) in high yield. The reaction can be carried out on a large scale to furnish the desired compound in yields ranging from 75% to 93%.

The probable mechanism of the reaction is shown below.



Nucleophilic displacement of iodide from trimethylsilyl iodide (**4**) by the lone pair of one of the O-atoms of methylal (**3**) should produce the silylated ether salt **6**. The lone pair on the other O-atom should assist in the ejection of the silyl ether **5** from **6** with the formation of the second intermediate **7**. Attack of the iodide ion at the unhindered, very electrophilic C-atom in **7** should then produce iodomethyl methyl ether (**1c**). The reason that no simple dealkylation occurs (leading to methyl iodide and formaldehyde), as is seen in the case of other acetals[3], is probably that the attack of iodide ion at the methylene center in **7** is now totally unhindered. When there are alkyl groups at this center, direct attack of iodide ion is hindered and the dealkylation occurs instead.

Iodomethyl methyl ether has been used to methoxymethylate various organic substrates[5]. In the presence of zinc iodide or tin(IV) iodide it has been employed to iodomethylate aromatic systems[6]. An example of the enhanced reactivity of **1c** as compared to the chloro analogue **1a** is its very rapid reaction (25°, 30 min) with triphenylphosphine (**8**) to afford methoxymethyltriphenylphosphonium iodide (**9**) in 80% yield. The corresponding reaction with **1a** to give the chloride salt has been reported to require warming for 60 h[7]. Treatment of **9** with phenyllithium in diethyl ether furnishes the well-known methoxymethylenetriphenylphosphorane (**10**) which can be used to convert carbonyl compounds into the homologous aldehydes (**11**).

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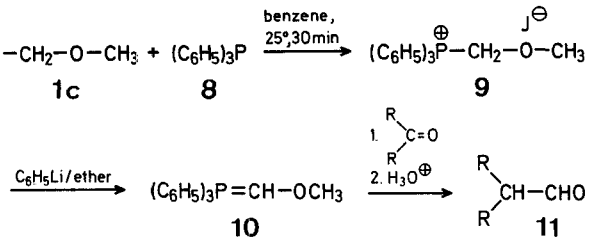

Iodomethyl Methyl Ether (1c):

Freshly prepared trimethylsilyl iodide[3] (**4**; 12.0 g, 0.06 mol) is added all at once via a nitrogen-flushed Luerlock 10 ml syringe to methylal[8] (**3**; 45.6 g, 0.6 mol) in a 100 ml round-bottom flask with vigorous stirring at 25° under a nitrogen atmosphere. Although the reaction of **3** with **4** is essentially complete upon addition, the mixture is stirred for an additional 30 min. The excess, unreacted methylal is distilled off (b.p. 41–42°) at atmospheric pressure using a 6" Vigreux column. Additional warming of the Vigreux column during the distillation is necessary so as to avoid very high pot temperatures and subsequent decomposition of the undistilled product in the reaction flask. After removal of the methylal, the fraction boiling at 90–115° is collected; yield: 9.6 g (93%). The product thus obtained is pure according to G.L.C. and N.M.R. analyses. [In eight separate preparations, the yield ranged from 75% to 93%].

^{1}H-N.M.R. ($CDCl_3$): $\delta = 5.73$ (s, 2H); 3.27 ppm (s, 3H).

Methoxymethyltriphenylphosphonium Iodide (9):

Freshly prepared iodomethyl methyl ether (**1c**; 7.5 g, 43.5 mmol) is added via syringe to a stirring solution of triphenylphosphine (**8**; 11.4 g, 43.5 mmol) in benzene (60 ml) in a 100 ml round-bottom flask at 25° under a nitrogen atmosphere. A white precipitate forms immediately upon addition. The mixture is stirred for 30 min, the solid is then isolated by filtration, and recrystallized from tetrachloromethane/dichloromethane; yield: 14.7 g (78%); colorless crystals, m.p. 178–180°.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 7.8$ (m, 15H); 5.73 (d, 2H, $J = 4$ Hz); 3.73 ppm (s, 3H).

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* Author to whom correspondence should be addressed.
** Undergraduate research participants.

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