



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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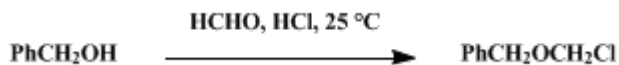
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 6, p.101 (1988); Vol. 52, p.16 (1972).

BENZYL CHLOROMETHYL ETHER

[Benzene, (chloromethoxy)methyl-]



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1. Procedure

Caution! Benzyl chloromethyl ether is a powerful alkylating agent and a potential carcinogen. Furthermore, it is a mild lachrymator and reacts with water and alcohols, forming hydrogen chloride. The procedure should be conducted in a hood, and inhalation and skin contact should be avoided.

A 1-l, three-necked flask equipped with an overhead mechanical stirrer with a Teflon paddle, gas-inlet tube, thermometer, and a calcium chloride drying tube (Note 1) is charged with 216 g. (2.00 moles) of benzyl alcohol (Note 2) and 66 g. (2.20 moles as CH₂O) of paraformaldehyde (Note 3). The resulting mixture is maintained at 20–25° with a water bath during addition of anhydrous hydrogen chloride (Note 4) at a moderate rate, with stirring (Note 5). After approximately 2 hours the reaction is complete, as judged by the appearance of two clear homogeneous phases (Note 6). The layers are separated, and the upper layer is diluted with 800 ml. of pentane and dried over anhydrous magnesium sulfate for 3 hours at 0°, with stirring. The drying agent is removed by filtration, 2–3 g. of anhydrous calcium chloride is added to the filtrate, and the solution is concentrated on a rotary evaporator (Note 7). The residual liquid, which is nearly pure benzyl chloromethyl ether, is decanted, affording 260 g. (83%) of crude product (Note 8). This crude benzyl chloromethyl ether, which is suitable for use in some applications, is stored over anhydrous calcium chloride at 0° under an inert atmosphere (Note 9) and (Note 10).

If further purification is desired, just prior to use the crude material (40 g.) may be distilled at approximately 3 mm from anhydrous calcium chloride (Note 11), affording very pure benzyl chloromethyl ether (35 g.), b.p. 70–71° (3 mm.) (Note 12) and (Note 13).

2. Notes

1. A Claisen adapter is utilized to accommodate both the thermometer and calcium chloride drying tube.
2. Fisher Scientific reagent grade benzyl alcohol was freshly distilled prior to use.
3. Fisher Scientific reagent grade paraformaldehyde was used.
4. Anhydrous hydrogen chloride was obtained from Matheson Gas Products and dried by passing it through concentrated sulfuric acid.
5. The gas-inlet tube utilized was a Pasteur pipet; however, a fritted glass gas-dispersion tube could be utilized. Hydrogen chloride is introduced as a stream of fine bubbles; the rate of addition controls the reaction temperature.
6. To judge whether the reaction is complete, stirring is stopped and the phases are permitted to separate. ¹H NMR analysis of the upper phase (CDCl₃) showed that the reaction is complete and devoid of major side-products.
7. Decomposition was noted during concentration and distillation in the absence of anhydrous calcium chloride.
8. The checkers obtained 316.3–316.6 g. (101%).
9. The crude material is satisfactory for the C-alkylation of an ester enolate; little difference was noted when the crude material was substituted for distilled material.

10. The crude product exhibits singlets in the ^1H NMR (CCl_4) at δ 4.68 (2H), 5.41 (2H), and 7.29 (5H). Both ^1H NMR and GC analyses indicate a purity of greater than 90%. GC analysis was carried out at 155° with a 2 m. \times 0.7 cm. column packed with silicone fluid No. 710 suspended on 60–80 mesh finebrick. The major impurities appear to be varying amounts of [benzyl chloride](#) and [dibenzyl formal](#), by ^1H NMR analysis.

11. Complete decomposition occurs if distillation is attempted at atmospheric pressure. Minor to occasionally major decomposition occurs upon attempted distillation at reduced pressure in the absence of anhydrous [calcium chloride](#), which retards the decomposition significantly.

12. The product gave satisfactory microanalytical data after one distillation. The reported physical constants for [benzyl chloromethyl ether](#) are b.p. $96\text{--}98^\circ$ (9.5 mm.), n_D^{20} 1.5264–1.5292.^{8,9}

13. The checkers used a procedure identical to that described above at one-eighth scale to prepare [bromomethyl ether](#), using [hydrogen bromide](#). A quantitative yield of crude material was obtained and distilled, giving a 97% yield of pure [benzyl bromomethyl ether](#), b.p. $55\text{--}57^\circ$ (1 mm.), n_D^{20} 1.5547: ^1H NMR (CDCl_3): δ 4.67 (s, 2H), 5.66 (s, 2H), 7.30 (s, 5H). Analysis calculated for $\text{C}_8\text{H}_9\text{BrO}$ (201.09): C, 47.79; H, 4.51; Br, 39.74. Found: C, 48.05; H, 4.68; Br, 40.05. This was found to be a superior alkylating agent.

3. Discussion

[Benzyl chloromethyl ether](#) is useful for introduction of a potential hydroxymethyl group in alkylation reactions. Hill and Keach¹⁰ first used this method and found it convenient in barbiturate syntheses. Graham and McQuillin,¹¹ and Graham, McQuillin, and Simpson¹² have extended the scope of the alkylation reaction to various ketone derivatives. They also have investigated the conditions for obtaining maximum C-alkylation and the stereochemistry of alkylation in various octalone systems.¹¹ Alkylation of ketones followed by [sodium borohydride](#) reduction and catalytic hydrogenolysis represents a convenient method for obtaining 1,3-diols.¹¹ Similarly, Wolff-Kishner reduction and catalytic hydrogenolysis give primary alcohols.¹¹ A procedure of this type has been used for obtaining bridgehead methanol derivatives of bicyclic compounds.¹³ Alkylation of ester enolates, generated by [lithium diisopropylamide](#), has been reported.¹⁴

Several other alkylations with [benzyl chloromethyl ether](#) using phosphorus compounds as nucleophiles have been reported.⁸ Hydrolysis and alcoholysis reactions of the reagent¹⁵ have been investigated, along with the addition of the [chloroether](#) to [propylene](#) in the presence of [zinc chloride](#).¹⁶ Alkylation of enamines with [benzyl bromomethyl ether](#) has been reported.¹⁷

[Benzyl chloromethyl ether](#) has been prepared from [benzyl alcohol](#), aqueous [formaldehyde](#) solution, and [hydrogen chloride](#).^{9,10,18} Gaseous [formaldehyde](#)⁹ and [1,3,5-trioxane](#)¹⁹ have also been used. This [chloromethyl ether](#) has also been prepared by the chlorination of [benzyl methyl ether](#).¹⁶ The present procedure is based on the first method, but avoids the use of a large excess of [formaldehyde](#) and provides a considerably simplified isolation procedure.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

Benzene, (chloromethoxy)methyl-

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

formaldehyde (50-00-0)

propylene (115-07-1)

hydrogen bromide (10035-10-6)

benzyl chloride (100-44-7)

Benzyl alcohol (100-51-6)

zinc chloride (7646-85-7)

Pentane (109-66-0)

chloromethyl ether (542-88-1)

magnesium sulfate (7487-88-9)

benzyl methyl ether (538-86-3)

sodium borohydride (16940-66-2)

chloroether (7791-21-1)

Benzyl chloromethyl ether (3587-60-8)

dibenzyl formal

bromomethyl ether

benzyl bromomethyl ether

lithium diisopropylamide (4111-54-0)

1,3,5-trioxane (110-88-3)

paraformaldehyde (30525-89-4)