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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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.

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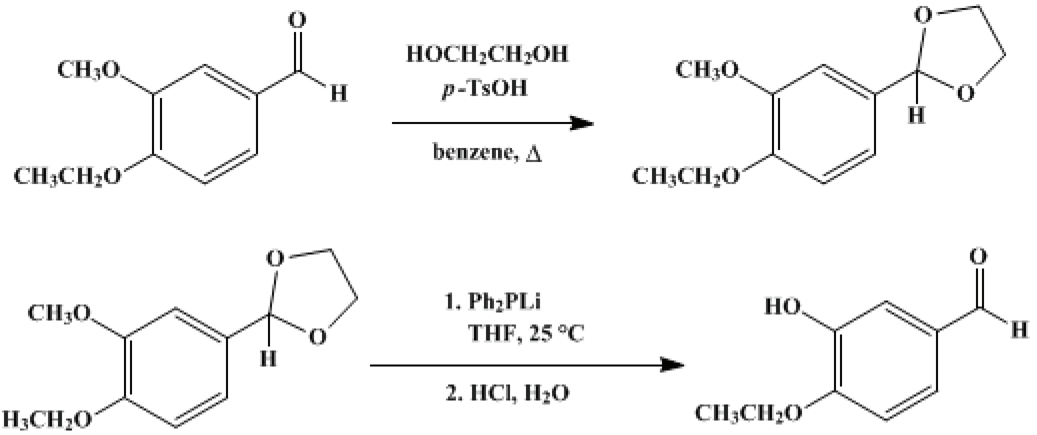
DEMETHYLATION OF METHYL ARYL ETHERS: 4-ETHOXY-3-HYDROXYBENZALDEHYDE

[Benzaldehyde, 4-ethoxy-3-hydroxy-]



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1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. 4-*Ethoxy*-3-*methoxybenzaldehyde ethylene acetal.* A 500-ml., three-necked flask with vertical necks is fitted with a magnetic stirring bar and a 30-ml. water separator, to which is attached a condenser topped with an argon inlet. The flask is charged with 300 mg. (0.00158 mole) of *p*-toluenesulfonic acid monohydrate, 270 ml. of benzene (Note 1), 33 g. (30 ml., 0.53 mole) of ethylene glycol, and 5.0 g. (0.028 mole) of 4-ethoxy-3-methoxybenzaldehyde (Note 2), then placed under a positive pressure of argon, which is maintained throughout the reaction. Vigorous stirring is begun, and the solution is brought to reflux with an oil bath at 110°.

After 20 hours at reflux, the mixture is cooled to room temperature with a water bath and poured with vigorous stirring into 500 ml. of 10% aqueous potassium carbonate contained in a 1-l. separatory funnel. The benzene layer is washed successively with two 250-ml. portions of 10% aqueous potassium carbonate and 250 ml. of brine containing potassium carbonate (Note 3), dried over sodium sulfate for 10 minutes, and filtered. Removal of the solvent on a rotary evaporator with a 25–35° water bath provides a solid yellow residue, which is dried under vacuum.

To obtain a crystalline product, a solution of the residue in 30 ml. of benzene containing a few drops of triethylamine (Note 4) is placed in a 250-ml. Erlenmeyer flask, heated gently on a steam bath, and diluted with 150 ml. of hexane. Heating is continued for about 5 minutes (Note 5), after which the solution is allowed to cool to room temperature, seeded, and put in a freezer at −15° for at least 5 hours. The resulting solid is collected by suction filtration, washed with cold hexane, and vacuum dried, giving 5.8 g. (94%) of light cream-colored crystals, m.p. 75–77°.

B. 4-*Ethoxy*-3-*hydroxybenzaldehyde.* A 100-ml., three-necked flask containing a magnetic stirring bar and fitted with an argon inlet, a rubber septum, and a ground-glass stopper in the center neck is evacuated, flame-dried, and allowed to cool under a positive pressure of argon, which is maintained throughout the following sequence. Using a syringe, 30 ml. of dry tetrahydrofuran (Note 6) and 5.0 ml. (0.029 mole) of diphenylphosphine (Note 7) are added through the septum. The resulting solution is stirred and cooled with an ice bath, and 15 ml. (0.032 mole) of cold 2.1 *M* *n*-butyllithium–hexane solution (Note 8) is added by syringe over *ca.* 3 minutes. Stirring is continued as the red solution is allowed to warm to room temperature over about 30 minutes before 5.0 g. (0.022 mole) of 4-ethoxy-3-methoxybenzaldehyde ethylene acetal is added through the center neck. The flask is stoppered, and the mixture is stirred at room temperature for 2 hours.

The reaction mixture is then poured into a 500-ml. Erlenmeyer flask containing 200 ml. of vigorously stirred water, 10 ml. of 10% aqueous sodium hydroxide is added, and the mixture is transferred to a 500-ml. separatory funnel. The reaction vessel and Erlenmeyer flask are rinsed with water, and the rinsings are also poured into the funnel. Alkali-insoluble impurities are removed by washing the basic aqueous phase with four 100-ml. portions of diethyl ether, which are combined and backextracted with two 50-ml. portions of 10% aqueous sodium hydroxide. The combined aqueous layers are then put into a 1-l. Erlenmeyer flask, cooled in an ice bath, and acidified with concentrated hydrochloric acid to a Congo red end point. During acidification the clear yellow basic solution becomes cloudy white. This milky suspension is stirred without cooling for 3 minutes then extracted with 200 ml. of ether and two 100-ml. portions of ether. The combined ether layers are washed successively with 100 ml. of water and 100 ml. of saturated aqueous sodium chloride, dried over magnesium sulfate, and filtered. Removal of solvent with a rotary evaporator provides a residue that is vacuum dried, yielding 3.58–3.60 g. (97–98%) of a slightly yellow solid, m.p. 121.5–126°. One recrystallization from 20 ml. of benzene gives almost white crystals which are vacuum dried, affording 3.21–3.29 g. (87–88%) of 4-hydroxy-3-ethoxybenzaldehyde, m.p. 125.5–127° (Note 9) and (Note 10).

2. Notes

1. Reagent grade benzene was used without further purification.
2. Practical grade 4-ethoxy-3-methoxybenzaldehyde was obtained by the submitters from MC and B Manufacturing Chemists and by the checkers from Aldrich Chemical Company, Inc. This material was purified by distillation (b. p. 125–135°/0.1 mm.), followed by one recrystallization from cyclohexane (100 ml./10 g. crude solid). Colorless crystals, m.p. 60–62°, were obtained after filtration and vacuum drying. Purification of 20 g. of the commercial material gave about 15 g. of recrystallized product.
3. This solution is prepared by dilution of 25 ml. of 10% aqueous potassium carbonate to 250 ml. with saturated aqueous sodium chloride.
4. Triethylamine was distilled from calcium hydride prior to use and added to the benzene to protect the sensitive acetal from hydrolysis.
5. It is not necessary to boil the solution. This heating merely prevents crystals from coming out of solution too fast on addition of the hexane.
6. Tetrahydrofuran was purified and dried according to the procedure described in *Org. Synth.*, **Coll. Vol. 5**, 976 (1973).
7. Commercial diphenylphosphine obtained from Orgmet, Inc., may be used without further purification. Alternatively, the material may be prepared from triphenylphosphine as follows. A 2-l., three-necked flask containing a magnetic stirring bar and fitted with an argon inlet is charged with 120 g. (0.458 mole) of triphenylphosphine and 1 l. of dry tetrahydrofuran ((Note 6)). To the stirred solution is added 18.42 g. (2.670 g.-atoms, 542 cm. of 0.32 cm.-diameter wire) of lithium wire, which has been washed with hexane and dried carefully with a paper towel. *(Caution! If the towel is rubbed against the lithium too fast, a fire will result.)* Lithium is added by cutting 3–5-mm. segments directly into the center neck of the flask with scissors. A slow argon flow is maintained throughout the addition, which requires about 20 minutes. The flask is stoppered, and the red solution is stirred for 2.5 hours under argon.

The solution is then filtered through a piece of glass wool (fitted loosely in a funnel) into a 2-l. beaker containing 600 g. of crushed ice. A glass rod is used to stir the mixture, and the reaction vessel and filter are rinsed with ether. The resulting two clear phases are transferred to a 2-l. separatory funnel and extracted with four 200-ml. portions of ether. The combined ether layers are washed with 250 ml. of 5% hydrochloric acid, 250 ml. of water, and two 250-ml. portions of saturated aqueous sodium chloride, then dried over magnesium sulfate for ½ hour. Since diphenylphosphine is susceptible to air oxidation, especially in dilute ether solution, the extractions should be carried out as quickly as possible. After gravity filtration, the ether solution is concentrated on a rotary evaporator, and the residue is vacuum dried, yielding 83.7 g. (99%) of crude product. Pure material is then obtained by distillation. The submitters used a small (14/20 joints, 15 cm. long) Vigreux column and observed b.p. 90–103° (0.06 mm.). Using a 20-cm. Vigreux column, the checkers observed b.p. 95–115° (0.06 mm.). In either case, the yield of clear liquid was 62 g. (74%). If the product is stored under argon in a bottle sealed with a rubber serum cap, it is stable for months at room temperature. *Caution! Care should be taken not to get any diphenylphosphine on a paper towel, as it may ignite spontaneously.*

8. *n*-Butyllithium in hexane was obtained from Ventron Corporation and stored in a refrigerator under argon. The solution was titrated with 2-butanol in xylene, using 1,10-phenanthroline as indicator.

9. The literature m.p. for the colorless crystals is 127–128°.[3]

10. IR ($CHCl_3$) cm.$^{-1}$: 3550 (OH), 1680 (C=O), 1610, 1580, 1510, 1470; ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons): 1.47 (t, *J* = 7,

3. Discussion

4-Ethoxy-3-hydroxybenzaldehyde (isobourbonal) has been prepared in good yield

The present procedure illustrates the facile demethylation of methyl aryl ethers with lithium diphenylphosphide.[4] This reaction is specific for methyl ethers and may be carried out in the presence of ethyl ethers in high yield.[5] Use of excess reagent allows cleavage in the presence of enolizable ketones.[6] In the present case, the cleavage may be performed without protection of the aldehyde, but two equivalents of reagent are required, and the yield is reduced to *ca.* 60%.

The exact time and temperature required for complete reaction must be determined for each individual compound. It has been observed that nucleophilic demethylation of methyl *o*-alkoxyaryl ethers is accelerated relative to anisole,[7] and this reaction is no exception. Lithium diphenylphosphide cleavage of anisole is complete in about 4 hours in refluxing tetrahydrofuran, whereas the present reaction is complete within 2 hours at 25°.

References and Notes

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

brine

4-Ethoxy-3-hydroxybenzaldehyde (isobourbonal)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether,
diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

Anisole (100-66-3)

cyclohexane (110-82-7)

ethylene glycol (107-21-1)

xylene (106-42-3)

lithium,
Lithium wire (7439-93-2)

magnesium sulfate (7487-88-9)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

triethylamine (121-44-8)

argon (7440-37-1)

calcium hydride (7789-78-8)

triphenylphosphine (603-35-0)

2-Butanol (78-92-2)

1,10-phenanthroline (66-71-7)

4-Ethoxy-3-hydroxybenzaldehyde,
Benzaldehyde, 4-ethoxy-3-hydroxy- (2539-53-9)

4-ethoxy-3-methoxybenzaldehyde (120-25-2)

diphenylphosphine (829-85-6)

4-Ethoxy-3-methoxybenzaldehyde ethylene acetal (52987-93-6)

4-hydroxy-3-ethoxybenzaldehyde (121-32-4) lithium diphenylphosphide

p-toluenesulfonic acid monohydrate (6192-52-5)