Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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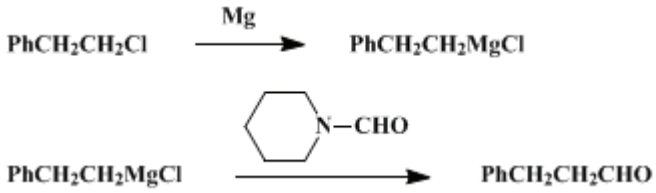
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.064.0114

Organic Syntheses, Coll. Vol. 7, p.451 (1990); Vol. 64, p.114 (1986).

FORMYL TRANSFER TO GRIGNARD REAGENTS WITH *N*-FORMYLPIPERIDINE: 3-PHENYLPROPIONALDEHYDE



Submitted by George A. Olah and Massoud Arvanaghi[1].
Checked by David Heiler and Martin F. Semmelhack.

1. Procedure

Magnesium (2.88 g, 0.12 mol), 300 mL of anhydrous tetrahydrofuran (Note 1), and 10 mg of iodine are placed in a 1-L, three-necked, round-bottomed flask fitted with a stirrer, dropping funnel with a pressure-equalizing tube, and a reflux condenser connected to a nitrogen flow line. Nitrogen is passed through the solvent for 15 min and a constant flow of nitrogen is maintained throughout the reaction. A solution of 14.06 g (0.1 mol) of (2-chloroethyl)benzene (Note 2) in 50 mL of tetrahydrofuran is placed in the dropping funnel. About 2 mL of this solution is added to the reaction mixture and the reaction is initiated by gently heating the flask (with a heat gun). Once the reaction has started, as evidenced by the disappearance of iodine color, the rest of the (2-chloroethyl)benzene solution is added dropwise at such a rate that a gentle reflux is maintained throughout the addition. The resulting solution is stirred for an additional 1 hr at 23°C, followed by heating at reflux for 8 hr. The reaction vessel is cooled to 0°C and a solution of 13.56 g (0.12 mol) of *N*-formylpiperidine (Note 3) in 50 mL of dry tetrahydrofuran is added dropwise (Note 4). The mixture is brought to 23°C and stirred for another 15 min.

The reaction mixture is quenched by the addition of 25 mL of ice water and slowly acidified to pH 2 with 75 mL of 3 *N* hydrochloric acid. The organic layer is separated and the aqueous layer is extracted with three 75-mL portions of ether. The extracts are combined with the original ether layer, washed successively with 50 mL of water, two 50-mL portions of aqueous 10% sodium bicarbonate, and 50 mL of saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. After the magnesium sulfate is removed by filtration, the solvent is removed at aspirator vacuum on a rotary evaporator and the residue is distilled through a short column to give 8.8–10.2 g (66–76%) of 3-phenylpropionaldehyde, bp 87°C (1.0 mm) (Note 5),(Note 6),(Note 7).

2. Notes

1. Technical-grade tetrahydrofuran was predried for a few days over sodium hydroxide. It was then heated under reflux over sodium wire with benzophenone until a permanent blue color developed and distilled with exclusion of atmospheric moisture. *(Caution: See p. 976 of Org. Synth., Coll. Vol. V for a warning regarding purification of tetrahydrofuran.)*
2. The (2-chloroethyl)benzene was purchased from Eastman Organic Chemicals and used without further purification.
3. *N*-Formylpiperidine was obtained from Reilly Tar and Chemicals or from Aldrich Chemical Company and used without further purification.
4. Too rapid addition of *N*-formylpiperidine should be avoided as it can result in a cake-like solid that hinders mixing of the reaction mixture. Efficient stirring is crucial to optimum yields.
5. The reported[2] boiling point for 3-phenylpropionaldehyde is 104–105°C (13 mm).
6. The spectral properties of the product are as follows: ^{13}C NMR ($CDCl_3$) δ: 27.9 (t, -CH_2-CH_2-CHO), 45.1 (t, -CH_2-CHO), 126.1 (d, *para*), 128.2 (d, *ortho*), 128.5 (d, *meta*), 140.2 (s, *ipso*), 201.4 (d, -CHO); ^{1}H NMR ($CDCl_3$) δ: 2.77 (m, -CH_2-CHO); 2.95 (m, -CH_2-CH_2-CHO), 7.16–7.33 (m, aromatic), 9.80 (t, -CHO); IR cm^{-1}: 2700, 1710.
7. (2-Bromoethyl)benzene can be used instead of (2-chloroethyl)benzene; anhydrous diethyl ether is

used as the solvent instead of tetrahydrofuran.

3. Discussion

The procedure described here is a one-step conversion of (2-chloroethyl)benzene to 3-phenylpropionaldehyde. The method is general and characterized by good yields, mild conditions, and easy preparation of 3-phenylpropionaldehyde in pure form from readily available starting materials. Several methods are described in the literature for the preparation of 3-phenylpropionaldehyde, including dry distillation of calcium formate with calcium hydrocinnamate,[3] sodium amalgam reduction, and deprotection of cinnamaldehyde dimethyl acetal,[4] or formation from heterocyclic system.[5,6] The present method has been shown[7] to be applicable to a wide variety of organolithium and Grignard reagents.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 328
- Org. Syn. Coll. Vol. 9, 707

References and Notes

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

hydrochloric acid (7647-01-0)

ether,
diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

iodine (7553-56-2)

Benzophenone (119-61-9)

sodium wire (13966-32-0)

(2-chloroethyl)benzene (622-24-2)

magnesium sulfate (7487-88-9)

(2-bromoethyl)benzene (103-63-9)

calcium formate (544-17-2)

Tetrahydrofuran (109-99-9)

N-FORMYLPIPERIDINE (2591-86-8)

3-Phenylpropionaldehyde (104-53-0)

cinnamaldehyde dimethyl acetal

calcium hydrocinnamate