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.

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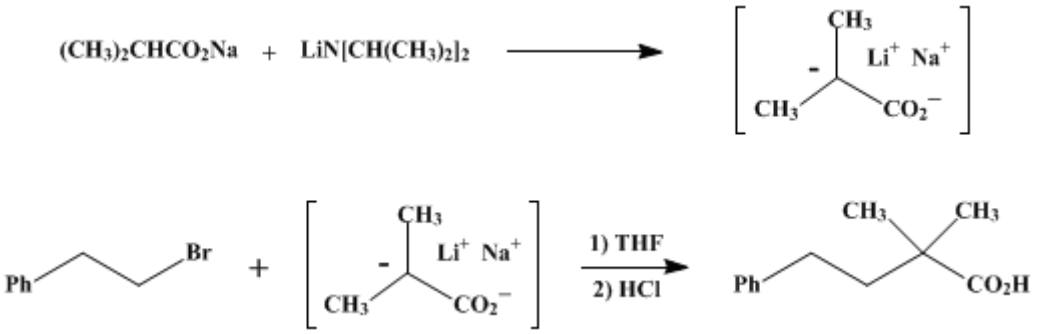
2,2-DIMETHYL-4-PHENYLBUTYRIC ACID

[Benzenebutanoic acid, α,α-dimethyl-]



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1. Procedure

A 500-ml., three-necked flask is equipped with a mechanical stirrer and a two-necked adapter carrying a Friedrich condenser, and a thermometer which contacts the flask contents. The third neck of the flask carries a pressure-equalizing dropping funnel which is exchanged for a serum stopper as required. The condenser is attached to a suitable source of nitrogen. The reaction flask is placed in a heating mantle and charged with 7.75 g. (0.0767 mole) of diisopropylamine (Note 1), 3.68 g. (0.082 mole) of 54% sodium hydride in mineral oil (Note 2), and 75 ml. of tetrahydrofuran (Note 3). From the dropping funnel, 6.6 g. (0.075 mole) of isobutyric acid (Note 4) is added to the stirred mixture over 5 minutes. The internal temperature rises to 50–60° and hydrogen evolution is completed by heating the mixture to reflux for 15 minutes. After cooling to 0° with an externally applied ice–salt bath (Note 5), 52 ml. of a standard solution of *n*-butyllithium in heptane (1.45 mmole/ml.; 0.075 mole) (Note 6) is added through the stopper by injection (Note 7) at a temperature below 10°. The ice bath is retained for 15 minutes before the mixture is heated to 30–35° for 30 minutes to complete the metalation. The resulting turbid solution is cooled, and 13.9 g. (0.0751 mole) of (2-bromoethyl)benzene (Note 8) is added from the dropping funnel over 20 minutes at 0°. A colorless precipitate of sodium bromide begins to separate almost immediately. The ice bath is retained for 30 minutes, after which the mixture is heated to 30–35° for 1 hour.

At the conclusion of the reaction period, 100 ml. of water is added at a temperature below 15° (Note 9). The aqueous layer is separated and the reaction flask and organic layer are washed with a mixture of 50 ml. of water and 75 ml. of diethyl ether. The aqueous layers are combined, back-extracted with 50 ml. of ether, and acidified to Congo red with 6 *N* hydrochloric acid. The product is extracted with two 75-ml. portions of ether, washed with 50 ml. of saturated sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent is evaporated. The remaining traces of solvent may be removed in a rotary evaporator, yielding 12–12.8 g. (83–90%) of crude 2,2-dimethyl-4-phenylbutyric acid, m.p. 89–94°, which is suitable for many purposes. Recrystallization from 75 ml. of hexane at room temperature followed by refrigeration yields 8.4–9.7 g. (58–67%) of product as colorless needles, m.p. 98–99.5° (Note 10). Recrystallization of the filtrate residue from 20 ml. of hexane yields a small second crop, 1.2–1.6 g. (8–11%), m.p. 95–97°. The combined yield totals 10–11 g. (70–76%) (Note 11).

2. Notes

1. Diisopropylamine supplied by Matheson, Coleman and Bell was distilled from calcium hydride, b.p. 83–85°.
2. Sodium hydride supplied by Ventron Corp., is satisfactory. It is unnecessary to remove the mineral oil.

3. Tetrahydrofuran was obtained in drum quantities from E. I. duPont de Nemours Co., and transferred under nitrogen pressure to 1-gallon containers for stock. This material could be used without special treatment. The quality of the tetrahydrofuran should be determined [*Org. Synth.*, **Coll. Vol. 5**, 976 (1973)] if there is no assurance of the absence of gross contamination. A small excess of sodium hydride was used in the reaction to remove traces of moisture which may have been introduced during measurement.
4. Isobutyric acid supplied by Matheson, Coleman and Bell is satisfactory.
5. A brisk nitrogen flow is required to exclude air when cooling.
6. *n*-Butyllithium in 1-mole serum cap bottles from Foote Mineral Co., was used. The less volatile hexane or heptane solutions were preferred.
7. The *n*-butyllithium solution was forced into a 100-ml. syringe through a 1½-in., 19 gauge hypodermic needle by slightly pressurizing (½ to 1½ p.s.i.) the storage bottle with nitrogen. Nitrogen was admitted through a second, 2-in., 20 gauge needle inserted at an upward angle through the stopper into the void space of the inclined bottle. The pressure in the bottle should be released and the bottle should be returned to an upright position before the syringe is withdrawn. This operation should be conducted behind a safety shield.
8. (2-Bromoethyl)benzene was used as supplied by Matheson, Coleman and Bell.
9. At the beginning, water should be added cautiously since a small quantity of unreacted sodium hydride is present.
10. The literature[2,3,4,5,6,7] reports m.p. 97–98°.
11. NMR analysis of the filtrate residue indicates that it is *ca.* 90% product. The submitters carried out the procedure on four times this scale, with mechanical stirring.

3. Discussion

2,2-Dimethyl-4-phenylbutyric acid has been prepared by Clemmensen reduction[2,3,4,5,6] or by hydriodic acid-phosphorus reduction[7] of 3-benzoyl-2,2-dimethylpropionic acid, and by catalytic reduction[6] of 2,2-dimethyl-4-phenyl-3-butenoic acid.

The preparation of 2,2-dimethyl-4-phenylbutyric acid is a specific example of a generally applicable procedure for alkylating dialkylacetic acids. The present procedure represents an improvement on one described earlier[8] in that one equivalent of *n*-butyllithium is required. Sufficient experience has been accumulated by the submitter over several years to recommend the present method as a possible alternative to the multistep Haller-Bauer sequence.[9] The procedure offers the obvious advantages of being short, avoiding use of blocking groups for the carboxyl group which must be removed later, and affording ease of workup while still providing preparative yields of product. The scale of the reaction can be increased to 1–2 moles with only a moderate increase in the size of the equipment.

The same procedure has been used to monoalkylate alkylacetic acids[10] and may be used to selectively monoalkylate methylated benzoic acids.[11] The metalated intermediates generated from alkylacetic acids are generally less soluble in the reaction medium specified, and heterogeneous mixtures result. The physical state of the reaction mixture has no apparent effect on the success of the subsequent alkylation[10] so long as metalation is complete. Homogeneous solutions may be obtained at the expense of operational convenience by suitable changes in the cation used,[11,12] or by use of hexamethylphosphoric triamide as co-solvent.[12,13] For warning concerning hexamethylphosphoric triamide, see *Science*, **190**, 422 (1975).

Metalated carboxylic acids have been employed as intermediates in a broad range of synthetic applications. The early literature has been summarized,[14] contrasting prior experience with the present method for generating carboxylic acid dianions. Likewise, more recent applications have been reviewed.[15,16]

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)

hydrogen (1333-74-0)

sodium chloride (7647-14-5)

sodium bromide (7647-15-6)

nitrogen (7727-37-9)

magnesium sulfate (7487-88-9)

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

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

heptane (142-82-5)

sodium hydride (7646-69-7)

isobutyric acid (79-31-2)

hexane (110-54-3)

calcium hydride (7789-78-8)

hexamethylphosphoric triamide (680-31-9)

diisopropylamine (108-18-9)

2,2-Dimethyl-4-phenylbutyric acid,
Benzenebutanoic acid, α,α-dimethyl- (4374-44-1)

hydriodic acid-phosphorus

3-benzoyl-2,2-dimethylpropionic acid

2,2-dimethyl-4-phenyl-3-butenoic acid