Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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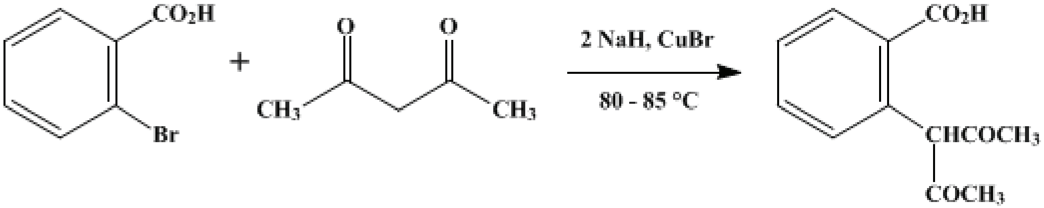
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.058.0052

Organic Syntheses, Coll. Vol. 6, p.36 (1988); Vol. 58, p.52 (1978).

COPPER CATALYZED ARYLATION OF β-DICARBONYL COMPOUNDS: 2-(1-ACETYL-2-OXOPROPYL)BENZOIC ACID

[Benzoic acid, 2-(1-acetyl-2-oxopropyl)-]



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Checked by Sadao Hayashi and Wataru Nagata.

1. Procedure

A 250-ml., three-necked, round-bottomed flask equipped with a sealed-mechanical stirrer, a Claisen adapter fitted with a thermometer and a gas-inlet adapter, and a calcium chloride drying tube (Note 1) is charged with 150 ml. of acetylacetone (Note 2) and (Note 3), 25 g. (0.12 mole) of 2-bromobenzoic acid (Note 4), and 1.0 g. of copper(I) bromide (Note 5). The mixture is thoroughly purged with dry nitrogen and stirred rapidly while 9.0 g. (0.47 mole) of an 80% dispersion of sodium hydride in mineral oil (Note 6) is slowly added portionwise through the inlet protected by the calcium chloride drying tube. Addition of the first portions of the sodium hydride results in an immediate exothermic reaction, and the temperature of the mixture rises rapidly to 50–55°. The remainder of the sodium hydride is added at such a rate that the temperature remains within the 50–55° range; external cooling with a cold-water bath may be necessary (Note 7). After addition of the sodium hydride is complete (30–35 minutes), the flask is placed in a hot-water bath heated to 80–85°, and the reaction mixture is stirred and heated for 5 hours, during which time a slow stream of dry nitrogen is passed through the apparatus.

When the reaction mixture has cooled, the contents of the flask are poured into a 1-l. Erlenmeyer flask containing 400 ml. of distilled water. The reaction flask and stirrer are thoroughly washed with an additional 100 ml. of distilled water, with the washings added to the bulk of the reaction mixture. The aqueous mixture is allowed to stand at room temperature for 15 minutes to ensure completion of hydrolysis and precipitation of inorganic salts. After the salts are removed by filtration under reduced pressure (Note 8) and discarded, the filtrate is transferred to a 1-l. separatory funnel, and the excess acetylacetone is separated (Note 9). The aqueous phase is washed with five 100-ml. portions of diethyl ether (Note 9) and transferred to a 1-l. conical flask. Nitrogen is blown through the solution for 15 minutes to remove traces of ether (Note 10). The aqueous solution is then acidified to pH 3 with concentrated hydrochloric acid, with the flask being constantly swirled during addition of the acid, and the mixture is allowed to stand at room temperature for 30 minutes to ensure complete precipitation of the product. The crude material is collected by filtration under reduced pressure, washed with 25 ml. of distilled water, and dried under reduced pressure over phosphorus pentoxide, giving 21–22 g. (76–80%) of crude product, m.p. 138–145° (Note 11). Recrystallization from a mixture of 50 ml. of methanol and 100 ml. of water gives 19.5–21 g. (71–76%) of pure material (Note 12) as colorless prisms, m.p. 142–144.5° (Note 11).

2. Notes

1. The checkers inserted a condenser between the flask and the drying tube to prevent acetylacetone from being carried away by the nitrogen stream.
2. The acetylacetone was washed with aqueous sodium hydrogen carbonate solution, dried over sodium sulfate, and distilled prior to use. The checkers used acetylacetone with a purity greater than 95%, purchased from Wako Pure Chemical Industries, Ltd., Japan, and purified by distillation prior to use.

3. The use of a large amount of acetylacetone as both reagent and solvent is essential to prevent precipitation of the sodium salts of acetylacetone and 2-bromobenzoic acid. If this happens, the whole reaction mixture rapidly solidifies, resulting in incomplete mixing and poor, irreproducible yields of the product.
4. Commercial 2-bromobenzoic acid, purchased from Aldrich Chemical Company, Inc., is a gray powder, m.p. 144–147°, and was purified as follows: the crude acid was dissolved in warm 2 *N* sodium hydroxide solution; the mixture was heated to reflux, treated with activated carbon, filtered, and cooled, and the filtrate was acidified with concentrated hydrochloric acid. The colorless solid that precipitated was collected by filtration under reduced pressure and recrystallized from aqueous methanol, giving pure 2-bromobenzoic acid as colorless needles, m.p. 148–150°. The checkers used 2-bromobenzoic acid of m.p. 151–151.5°, obtained from Wako Pure Chemical Industries, Ltd., Japan, without further purification. Their results were comparable to those of the submitters.
5. Copper(I) bromide was prepared according to *Org. Synth.*, **Coll. Vol. 3**, 186 (1955); the salt was dried under reduced pressure over phosphorus pentoxide prior to use. The checkers observed that good results could be realized by using a commercially available copper(I) bromide with a purity greater than 95% from Wako Pure Chemical Industries, Ltd., Japan, without purification.
6. The checkers used a 50% dispersion of sodium hydride in mineral oil, available from Wako Pure Chemical Industries, Ltd., Japan, and obtained results comparable to those of the submitters.
7. Cooling is normally required. It is important, however, to ensure that the temperature of the reaction mixture does not fall below 50°; otherwise efficient stirring becomes impossible.
8. The inorganic salts that precipitate at this stage are generally in a very finely divided form. A medium-sized Büchner funnel (11–15 cm.) or a small Büchner funnel (5–7.5 cm.) fitted with a Celite pad should be used to avoid slow filtration.
9. Acetylacetone can readily be recovered and recycled. The bulk of it, which is obtained at the separation step, is combined with the ether washings and dried over anhydrous sodium sulfate. The solvent is then removed by evaporation under reduced pressure and the residual crude acetylacetone is purified by distillation, giving 85–95 g. of pure acetylacetone.
10. Acidification without prior removal of the small amount of ether present in the aqueous solution results in precipitation of the product as an oily, semisolid mass that is difficult to filter.
11. Evolution of water is noticeable from *ca.* 130° upward; this is a result of lactone formation between the enolic hydroxyl group of the β-dicarbonyl unit and the aromatic carboxylic acid group.
12. The product, which exists entirely in the enolic form, has the following spectral data: UV (CH_3OH) nm. max. (ε): 227 (7760) and 287 (8190); IR (Nujol) cm^{-1}: 3300–2400, 1700–1690, 1305, 1270, 810, 770, 720, and 700; ^1H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.82 (sharp s, 6H, $2CH_3$), 7.2–8.2 (complex m, 4H, C_6H_4), 10.1 (broad s, 1H, COO*H*), and 16.3 (broad s, 1H, enolic O*H*).

3. Discussion

2-(1-Acetyl-2-oxopropyl)benzoic acid has been prepared by the copper-catalyzed arylation of acetylacetone with 2-bromobenzoic acid. Facile condensation of β-dicarbonyl compounds with 2-bromobenzoic acid was first demonstrated by Hurtley in 1929,[2] and reactions of this type have occasionally been employed with limited success in a number of natural product syntheses.[3] The reaction conditions originally employed for these condensations and subsequently adopted by all other workers involve the use of sodium ethoxide as base, ethanol as solvent, and copper powder as catalyst. Under these conditions, however, 2-ethoxybenzoic acid is obtained as a by-product in substantial amounts (25–35%), together with smaller amounts of unchanged 2-bromobenzoic acid (5–10%); furthermore, separation and purification of the desired α-(2-carboxyphenyl)-β-dicarbonyl product is often difficult and tedious.

The present method of preparation, described by Bruggink and McKillop,[4] has the particular advantages of high yield and manipulative simplicity, and avoids the problem inherent in Hurtley's procedure of separation of mixtures of carboxylic acids by fractional crystallization or column chromatography. The method has wide applicability with respect to both the β-dicarbonyl compound and the 2-bromobenzoic acid. The synthetic scope and limitations of this procedure for the direct arylation of β-dicarbonyl compounds have been fully defined with respect to a wide range of substituted 2-bromobenzoic acids and to certain other bromoaromatic and heteroaromatic carboxylic acids.[4]

References and Notes

1. School of Chemical Sciences, University of East Anglia, Norwich, England.
2. W. R. H. Hurtley, *J. Chem. Soc.*, 1870 (1929).
3. K. A. Cirigottis, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.*, **27**, 2209 (1974).
4. A. Bruggink and A. McKillop, *Tetrahedron*, **31**, 2607 (1975).

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

sodium salts of acetylacetone and 2-bromobenzoic acid

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

copper (7440-50-8)

carbon (7782-42-5)

sodium ethoxide (141-52-6)

2-bromobenzoic acid (88-65-3)

copper(I) bromide (7787-70-4)

Acetylacetone (123-54-6)

sodium hydride (7646-69-7)

2-(1-Acetyl-2-oxopropyl)benzoic acid,
Benzoic acid, 2-(1-acetyl-2-oxopropyl)- (52962-26-2)

2-ethoxybenzoic acid (134-11-2)

phosphorus pentoxide (1314-56-3)