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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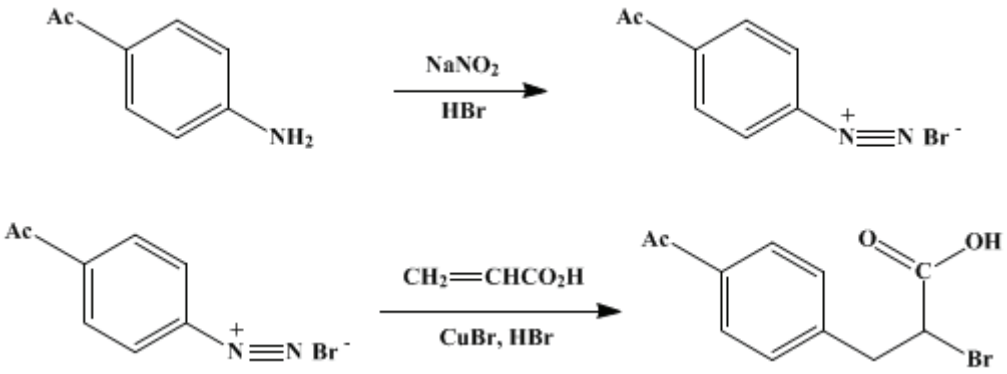
p-ACETYL-α-BROMOHYDROCINNAMIC ACID

[Benzenepropanoic acid, 4-acetyl-α-bromo-]



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1. Procedure

Caution! Since bromoacetone, a powerful lachrymator, is produced as a by-product in this preparation, the reaction should be performed in a hood.

A tared, 500-ml., two-necked, round-bottomed flask is equipped with a magnetic stirring bar, a thermometer, and an ice-filled cooling bath. A solution of 13.5 g. (0.100 mole) of 4-aminoacetophenone (Note 1) in 200 ml. of acetone is placed in the flask and stirred while 32 ml. (about 0.3 mole) of aqueous 48% hydrobromic acid is added. After the resulting solution has been cooled to 5–7°, it is stirred continuously while 20 ml. of an aqueous solution containing 6.90 g. (0.100 mole) of sodium nitrite is added rapidly (30 seconds) beneath the surface of the reaction solution with a hypodermic syringe or a long-stemmed dropping funnel. Stirring and cooling are continued until the exothermic reaction subsides (Note 2) and the reaction solution has cooled to 14–15°. After 106 g. (100 ml., 1.47 moles) of acrylic acid (Note 3) is added, the solution is again cooled to 14–15°, with stirring, before 0.10–0.11 g. (0.00069–0.00077 mole) of copper(I) bromide (Note 4) is added. Stirring is continued, during which time the solution darkens, and nitrogen evolution is observed; the temperature of the reaction mixture is kept below 33° by use of the external cooling bath. As soon as the evolution of nitrogen has ceased (usually 20 minutes is sufficient), the reaction solution is concentrated with a rotary evaporator, giving a mixture weighing about 120–130 g. The residual brown suspension is mixed with 5 g. of decolorizing charcoal and 200 ml. of water, and the resulting mixture is boiled for 3 minutes, and filtered while hot through a Büchner funnel containing Celite filter aid. The residue on the filter is washed with 100 ml. of boiling water, and the combined filtrates are diluted with 300 ml. of water. The resulting aqueous solution, from which the product begins to crystallize, is cooled in a water bath and then allowed to stand in a refrigerator (0–3°) for 24 hours to complete the crystallization of the crude product. The crystalline solid is collected on a filter, washed with two 100-ml. portions of cold water, and dried in the air. The crude product, a pale yellow solid (19.1–22.2 g.), is recrystallized from 40 ml. of a 2:3 (v/v) formic acid-water mixture. The resulting crystals are collected on a filter, washed with 20 ml. of 2:3 (v/v) cold formic acid-water, and dried in the air, yielding 16.6–18.2 g. (61–67%) of white needles, m.p. 158–160°, which are sufficiently pure for most purposes. Three additional crystallizations from 20-ml. portions of 2:3 (v/v) formic acid-water give 15.2–16.0 g. (56–59%) (Note 5) of the pure *p*-acetyl-α-bromohydrocinnamic acid, m.p. 159–161° (Note 6).

2. Notes

1. Commercial grades of acetone and 4-aminoacetophenone (Matheson, Coleman and Bell or Aldrich Chemical Company, Inc.) were used without further purification.
2. The temperature of the reaction mixture rises to about 30° and then falls to 15° as stirring and cooling are continued. If this preparation were performed on a larger scale, it would probably be necessary to add the sodium nitrite solution over a longer period of time in order to control the temperature.
3. A freshly opened bottle of acrylic acid, obtained from Eastman Organic Chemicals, was used without further purification. The checkers encountered difficulty in attempting to use samples of acrylic acid that had been stored in partially filled bottles for long periods of time.
4. A reagent grade of copper(I) bromide, obtained from Fisher Scientific Company, was washed with acetone until the washings were colorless and then dried.
5. The combined filtrates from these recrystallizations can be concentrated to obtain an additional 1–2 g. of product.
6. The product has IR absorption (KBr) at 1735, 1645, and 1607 $cm.^{-1}$ with a UV maximum (95% C_2H_5OH solution) at 252.5 nm (ε 17,000). The sample has ^1H NMR peaks (CF_3CO_2H) at δ 2.78 (s, 3H, CH_3CO), 3.2–3.9 (m, 2H, benzylic CH_2), 4.60 (t, J = 7.5 Hz., 1H, CHBr), 7.47 (d, J = 9 Hz., 2H, aryl CH), and 8.10 (d, J = 9 Hz., 2H, aryl CH). The mass spectrum has weak molecular peaks at *m/e* 270 and 272 with the following relatively abundant fragment peaks: *m/e* (rel. int.), 191 (73), 175 (100), 131 (52), 103 (40), 77 (55), and 51 (43). The product gives a deep red color when treated with sodium nitroprusside and aqueous base; this color changes to dark blue upon acidification with acetic acid.

3. Discussion

This procedure has been used to prepare a variety of substituted α-bromohydrocinnamic acids;[2] *p*-acetyl-α-bromohydrocinnamic acid was prepared for the first time by this method. The method illustrates a typical application of the Meerwein reaction for the arylation of unsaturated substrates.[3] In this reaction a catalytic amount of a copper(I) salt is used to reduce an aryl diazonium salt forming an aryl radical and a copper(II) halide. Addition of the aryl radical to an unsaturated substrate forms an alkyl radical that is reoxidized by the copper(II) halide present forming an alkyl halide and regenerating the copper(I) salt catalyst. In this preparation, the product, an α-bromo acid, is formed in an acidic reaction mixture and dehydrohalogenation does not occur. However, dehydrohalogenation of the intermediate halide is often observed in analogous reactions performed under neutral or basic reaction conditions.[3] The use of the Meerwein reaction to form ultimately 1-(4-nitrophenyl)-1,3-butadiene by the addition of an intermediate aryl radical to 1,3-butadiene followed by dehydrohalogenation of the initially formed alkyl halide is illustrated in *Organic Syntheses*.[4]

References and Notes

1. Department of Chemistry, Occidental College, Los Angeles, California 90041.
2. G. H. Cleland, *J. Org. Chem.*, **26**, 3362 (1961); *J. Org. Chem.*, **34**, 744 (1969).
3. C. S. Rondestvedt, Jr., *Org. React.*, **11**, 189 (1960); *Org. React.*, **24**, 225 (1976).
4. G. A. Ropp and E. C. Coyner, *Org. Synth.*, **Coll. Vol. 4**, 727 (1963).

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

4-aminoacetophenone

sodium nitroprusside

acetic acid (64-19-7)

HYDROBROMIC ACID (10035-10-6)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

acetone (67-64-1)

Acrylic acid (9003-01-4)

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

Bromoacetone (598-31-2)

1,3-Butadiene (106-99-0)

Benzenepropanoic acid, 4-acetyl-α-bromo-,
p-Acetyl-α-bromohydrocinnamic acid (18910-19-5)

1-(4-nitrophenyl)-1,3-butadiene (20264-89-5)