Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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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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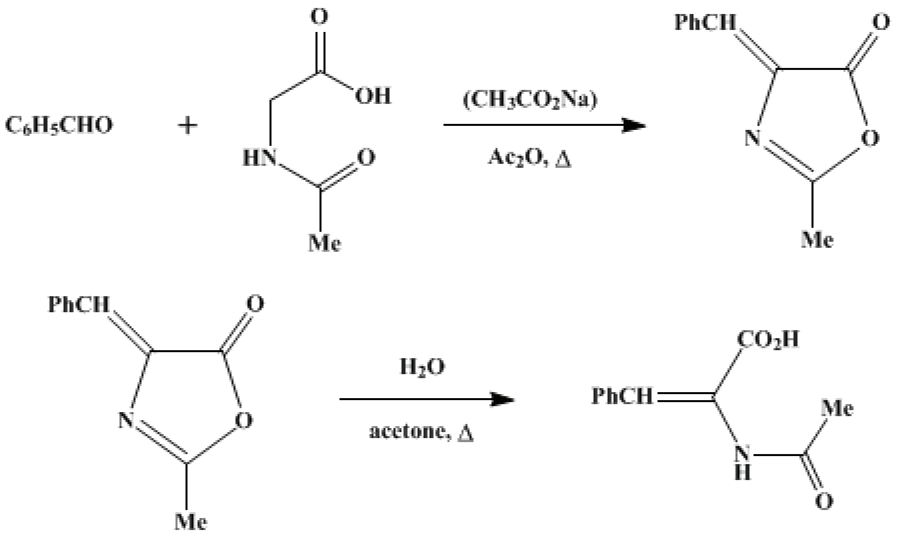
Organic Syntheses, Coll. Vol. 2, p.1 (1943); Vol. 19, p.1 (1939).

α-ACETAMINOCINNAMIC ACID

[Cinnamic acid, α-acetamido-]



Submitted by R. M. Herbst and D. Shemin.
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

A mixture of 58.5 g. (0.5 mole) of acetylglycine (p. 11) (Note 1), 30 g. (0.37 mole) of anhydrous sodium acetate, 79 g. (0.74 mole) of freshly distilled benzaldehyde, and 134 g. (1.25 moles) of 95 per cent acetic anhydride in a loosely corked 1-l. Erlenmeyer flask is warmed on the steam bath with occasional stirring until solution is complete (ten to twenty minutes). The resulting solution is boiled for one hour under reflux, cooled, and placed in a refrigerator overnight. The solid mass of yellow crystals is treated with 125 cc. of cold water and broken up with a stirring rod. The crystals are then transferred to a Büchner funnel and washed thoroughly with cold water (Note 2). After being dried in a vacuum desiccator over phosphorus pentoxide and potassium hydroxide, the crude azlactone weighs 69–72 g. (74–77 per cent of the theoretical amount). The product melts at 148–150°, and is sufficiently pure for preparative purposes (Note 3).

In a 1-l. round-bottomed, short-necked flask 47 g. (0.25 mole) of the crude azlactone of α-acetaminocinnamic acid is dissolved by boiling with a mixture of 450 cc. of acetone and 175 cc. of water. Hydrolysis is completed by boiling under reflux for four hours. Most of the acetone is then removed by distillation at ordinary pressure on a steam bath. The residual solution is diluted with 400 cc. of water, heated to boiling for five minutes to ensure complete solution of the acetamino acid, and filtered (Note 4) and (Note 5). A small amount of undissolved material (0.2–0.5 g.) which remains on the filter is washed with 50–75 cc. of boiling water. Any crystals which separate from the filtrate are redissolved by heating, after which the solution is boiled for five minutes with 10 g. of Norite and filtered with the aid of gentle suction while still almost at the boiling point (Note 5). The Norite is washed thoroughly on the funnel with two to four 50-cc. portions of boiling water to remove the crystals which separate during the filtration, and the washings are added to the main filtrate. After standing in a refrigerator overnight the colorless, crystalline needles are collected on a Büchner funnel (Note 6), washed with 150–200 cc. of ice-cold water, and dried for several hours at 90–100°. The yield is 41–46 g. (80–90 per cent of the theoretical amount) of practically pure material, m.p. 191–192° (Note 7).

2. Notes

1. The azlactone of α-acetaminocinnamic acid may also be prepared by substituting the equivalent amount of glycine for acetylglycine and increasing the amount of acetic anhydride to three molecular proportions, but the yield is only about 45–50 per cent of the theoretical amount.
2. If the excess benzaldehyde is not almost completely removed by repeated washing with water, a final wash with 50–75 cc. of ether may be advantageous, although this causes some loss of azlactone owing to its solubility in ether.
3. The azlactone can be recrystallized from alcohol, from carbon tetrachloride, or from ethyl acetate with addition of petroleum ether. Aqueous solvents should be avoided, since the azlactone ring is easily opened by water. When alcohol is used for recrystallization, there is some danger of opening the azlactone ring with the formation of an ester, particularly on prolonged heating of the solution.
4. The solution may be filtered by gravity through a large folded filter (preferably in a steam-jacketed funnel), or through a Büchner funnel with gentle suction.
5. The solubility of α-acetaminocinnamic acid in water decreases very rapidly on cooling below the boiling point of the solution. Since the solution is very nearly saturated with the product, a large share of the acid will crystallize in the funnel during filtration if the solution is allowed to cool too much. This property of the product makes it inadvisable to work with larger quantities.
6. Occasionally after treatment with Norite the solution is green owing to traces of iron and phenylpyruvic acid. If the crystals are still yellow at this point, the treatment with Norite should be repeated before the product is collected on a filter.
7. If further purification is desired, the product may be recrystallized from 600 cc. of boiling water, with a loss of about 5 per cent. The loss is due in part to hydrolysis of the product with the formation of phenylpyruvic acid.

3. Discussion

The azlactone of α-acetaminocinnamic acid has been prepared by heating a mixture of glycine, benzaldehyde, acetic anhydride, and anhydrous sodium acetate;[1], [2] and from *N*-chloroacetylphenylalanine by treatment with acetic anhydride.[2]

α-Acetaminocinnamic acid has been prepared from the corresponding azlactone by hydrolysis with either aqueous sodium hydroxide[1] or with boiling water alone.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 489
- Org. Syn. Coll. Vol. 2, 519

References and Notes

1. Erlenmeyer, Jr., and Früstück, Ann. **284**, 48 (1895).
2. Bergmann and Stern, ibid. **448**, 26 (1926).

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

petroleum ether

Azlactone of α-Acetaminocinnamic acid

alcohol (64-17-5)

ethyl acetate (141-78-6)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

carbon tetrachloride (56-23-5)

benzaldehyde (100-52-7)

acetone (67-64-1)

Norite (7782-42-5)

potassium hydroxide (1310-58-3)

Glycine (513-29-1)

α-Acetaminocinnamic acid,
Cinnamic acid, α-acetamido- (5469-45-4)

Acetylglycine (543-24-8)

Phenylpyruvic acid (156-06-9)

phosphorus pentoxide (1314-56-3)

N-chloroacetylphenylalanine (721-65-3)