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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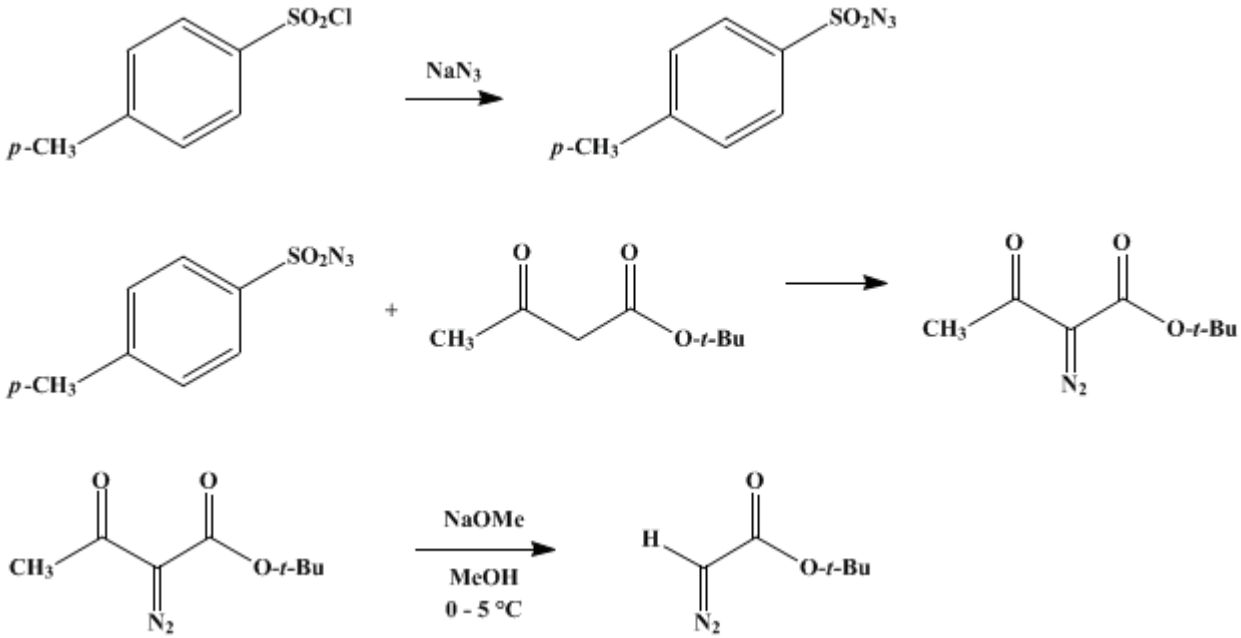
t-BUTYL DIAZOACETATE

[Acetic acid, diazo-, *tert*-butyl ester]



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Checked by C. John Blankley and Herbert O. House.

1. Procedure

Caution! Diazoacetic esters are toxic and potentially explosive and must be handled with caution. This preparation should be carried out in a hood, and the distillation of t-butyl diazoacetate should be conducted behind a safety shield.

A. *p-Toluenesulfonyl azide*.[2,3] A solution of 71.5 g. (1.10 moles) of sodium azide (Note 1) in 200 ml. of water is placed in a 2-l. Erlenmeyer flask and diluted with 400 ml. of 90% aqueous ethanol (Note 2). To this solution is added with stirring a warm (45°) solution of 190.5 g. (1.00 mole) of *p*-toluenesulfonyl chloride (Note 3) in 1 l. of 99% ethanol (Note 2). During this addition, sodium chloride separates, and the reaction mixture has been stirred at room temperature for 2.5 hours, most of the solvent is removed at 35° (15 mm.) with a rotary evaporator (Note 4). The residue is mixed with 1.2 l. of water in a separatory funnel, and the oily *p*-toluenesulfonyl azide is separated. This oil is washed with two 100-ml. portions of water and dried over anhydrous sodium sulfate. Filtration with suction gives 160–170 g. (81–86%, based on *p*-toluenesulfonyl chloride) of pure, colorless *p*-toluenesulfonyl azide which completely crystallizes on standing at 5°.

B. *t-Butyl α-diazoacetoacetate*. In a 2-l., wide-mouthed, Erlenmeyer flask are placed 118.5 g. (0.75 mole) of *t*-butyl acetoacetate (Note 5), 1 l. of anhydrous acetonitrile, and 75.8 g. (0.75 mole) of previously distilled triethylamine (b.p. 88.5–90.5°). The temperature of the mixture is adjusted to 20°, and 148 g. (0.75 mole) of *p*-toluenesulfonyl azide is added dropwise with vigorous stirring over 10–15 minutes. The addition causes the reaction mixture to warm to 38–40° and assume a yellow color. After the mixture has been stirred at room temperature for 2.5 hours, the solvent is evaporated at 35° (12 mm.). The partially crystalline residue is triturated with 1 l. of ether, and the mixture, including the insoluble residue, is placed in a 2-l. separatory funnel. The mixture is washed successively with a solution of 45 g. of potassium hydroxide in 500 ml. of water, a solution of 7.5 g. of potassium hydroxide

in 250 ml. of water, and 250 ml. of water (Note 6). The yellow-orange ethereal phase is dried over anhydrous sodium sulfate, and the solvent is evaporated at 35° (15 mm.) until the residue has attained a constant weight. The yellow-orange diazo ester weighs 130–135 g. (94–98%) (Note 7).

C. *t-Butyl diazoacetate*. Into a 1-l. three-necked flask fitted with a stirrer, a dropping funnel, and a thermometer is placed a solution of 92.6 (0.50 mole) of *t*-butyl α-diazoacetoacetate in 150 ml. of methanol. After this solution has been cooled to 2–3° in an ice bath, a solution of sodium methoxide, prepared from 11.5 g. (0.50 g. atom) of sodium and 150 ml. of methanol, is added dropwise with stirring at such a rate that the reaction mixture remains within the temperature range 0–5° (about 30 minutes is required for the addition). After the addition is completed, the mixture is stirred in the ice bath for an additional 30 minutes. The red reaction solution is poured into 1 l. of ice water, and the resulting mixture is extracted with 500 ml. of ether. The aqueous phase is saturated with sodium chloride and extracted with two 500-ml. portions of ether (Note 8). The combined ethereal extracts are washed with 500 ml. of water and dried over anhydrous sodium sulfate. After the mixture has been filtered and the residue has been washed with ether, the bulk of the solvent is removed from the combined ethereal filtrates at 30° and water aspirator pressure with a rotary evaporator (Note 9). The remaining ether is removed by distillation under slightly reduced pressure while the stillpot is heated with a water bath at 50°. The residual red oil is distilled. (*Caution! See above.*) (Note 10). After a small forerun the diazo ester distills during which time the temperature of the water bath is raised from 60° to 75°. The yield is 48–50 g. (68–70%) of yellow-orange liquid, b.p. 51–53° (12 mm.), n^{20}D 1.4551, R_f = 0.56 (chloroform) (Note 11).

2. Notes

1. The submitters used sodium azide obtained from Dr. F. Raschig, GmbH, 67 Ludwigshafen, Rhein, Germany. The checkers used material from Eastman Organic Chemicals.
2. The checkers found 95% ethanol denatured with methanol to be a satisfactory substitute.
3. The submitters used *p*-toluenesulfonyl chloride obtained from Badische Anilin- und Soda-Fabrik, 67 Ludwigshafen, Rhein, Germany. Very impure *p*-toluenesulfonyl chloride can be purified by recrystallization from ether. The checkers used material from Matheson, Coleman and Bell without further purification.
4. In order to prevent foaming, the concentration is begun with the water bath at *ca.* 10°, and the bath is warmed slowly to 35°.
5. *t*-Butyl acetoacetate may be prepared from *t*-butyl alcohol and diketene.[4] The checkers obtained this material from Eastman Chemical Products, Inc.
6. Acidification of the aqueous potassium hydroxide phase with 6*N* hydrochloric acid gives *p*-toluenesulfonamide. After being dried at 85° (50 mm.) the sample weighs 110–120 g. (86–94%) and melts at 132–134°.
7. If desired, the α-diazo β-keto ester can be purified by a low-temperature crystallization. The diazo ester (10 g.) is cooled to −70° to −75° in a dry ice-acetone bath, and crystallization is initiated by rubbing. *(Caution! The rubbing should not be continued after crystallization has been initiated.)* This material is treated with 5 ml. of anhydrous ether which has been previously cooled, and the mixture is filtered with suction. The residue from the filtration is placed in a flask, and the residual ether is removed by evaporation at 35° (15 mm.) to give 5–6 g. of the yellow diazo ester.[5]
8. If the ethereal phase contains a small amount of insoluble material, the mixture should be filtered to avoid difficulty in separating the phases.
9. The distillate is light yellow and contains some *t*-butyl diazoacetate.
10. This distillation has been conducted with the usual precaution (safety glasses, safety shield) with no explosions up to the present time.
11. The thin-layer chromatogram was obtained on "DC-Fertiplatte Merck Kieselgel F_{254}" purchased from E. Merck A. G., 61 Darmstadt, Germany, Employing an Eastman Chromatoplate K301R1 (silica without indicator) with chloroform as eluent, the checkers found an R_f value of 0.72.

3. Discussion

t-Butyl diazoacetate has been prepared by the present method, by alkaline decomposition of *t*-butyl N-nitroso-N-acetylglycinate,[6] and by diazotization of *t*-butyl glycinate.[7]

4. Merits of the Preparation

The transformation of an active CH compound into the corresponding diazo derivative with *p*-toluenesulfonyl azide has been designated a "diazo transfer reaction"[8] and possesses a variety of preparative uses. The method has been useful for the syntheses of diazo derivatives of cyclopentadiene,[3,9] 1,3-dicarbonyl compounds,[5,10,11] 1,3-disulfonyl compounds,[12] 1,3-ketosulfonyl compounds,[13,14,15] 1,3-ketophosphono compounds,[16] 1,3-ketophosphinyl compounds,[17] ketones,[18,19,20,21] carboxylic acid esters[18,21] and β-keto imines.[22] Further reaction of these diazo intermediates can lead to zao compounds,[11,13] 1,2,3-triazoles,[22,23] 1,2,3-thiadiazoles,[24] and pyrazolinones.[25] This and related diazo transfer reactions have been reviewed.[26]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 258
- Org. Syn. Coll. Vol. 6, 389
- Org. Syn. Coll. Vol. 6, 414
- Org. Syn. Coll. Vol. 7, 438
- Org. Syn. Coll. Vol. 9, 400
- Org. Syn. Coll. Vol. 9, 422

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

acetonitrile (75-05-8)

chloroform (67-66-3)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

diketene (674-82-8)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

sodium azide (26628-22-8)

triethylamine (121-44-8)

CYCLOPENTADIENE (542-92-7)

t-butyl alcohol (75-65-0)

t-butyl diazoacetate,
Acetic acid, diazo-, tert-butyl ester (35059-50-8)

p-Toluenesulfonyl chloride (98-59-9)

p-toluenesulfonyl azide (941-55-9)

t-BUTYL ACETOACETATE (1694-31-1)

t-butyl α-diazoacetoacetate (13298-76-5)

t-butyl glycinate (6456-74-2)

p-toluenesulfonamide (70-55-3)

t-butyl N-nitroso-N-acetylglycinate