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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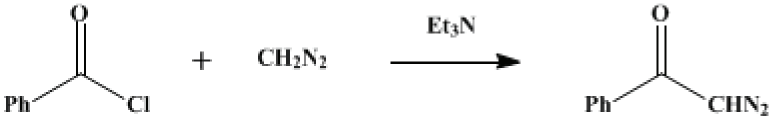
Organic Syntheses, Coll. Vol. 6, p.386 (1988); Vol. 53, p.35 (1973).

DIAZOACETOPHENONE

[Ethanone, 2-diazo-1-phenyl-]



Submitted by John N. Bridson and John Hooz[1].
Checked by Dennis R. Murayama and Ronald Breslow.

1. Procedure

Caution! All operations should be conducted in an efficient fume hood. Diazomethane is hazardous; directions for safe handling are given in Org. Synth., ***Coll. Vol. 4****, 250 (1963);* ***Coll. Vol. 5****, 351 (1973). Diazoacetophenone is a skin irritant and direct contact should be avoided.*

A solution of 0.375 mole of diazomethane in 1 l. of diethyl ether (Note 1) is placed in a 2-l. flask fitted with a large magnetic stirring bar, a two-necked adapter, equipped with a drying tube (containing potassium hydroxide pellets), and a pressure-equalizing dropping funnel. Triethylamine (37.9 g., 52.1 ml., 0.375 mole) (Note 2) is added, and the flask contents are cooled to *ca.* −10° to −5°. A solution of 52.75 g. (43.56 ml., 0.3754 mole) of benzoyl chloride (Note 3) in 300 ml. of dry ether is added to the stirred mixture over a period of 0.5 hour (Note 4). An additional 50 ml. of ether is rinsed through the dropping funnel. Stirring is continued for one hour at approximately 0°, then overnight at room temperature.

The resulting triethylamine hydrochloride precipitate (41.4 g., 81%) is filtered and washed with 100 ml. of dry ether. The solvent is removed from the combined filtrate by rotary evaporation, and the semi-solid residue crystallizes to an orange-red solid after refrigeration for several hours at *ca.* 5°. Crystallization from a mixture of 150 ml. of pentane and 120 ml. of dry ether affords 38.8 g. of diazoacetophenone as yellow square plates, m.p. 44–48°. Concentration of the mother liquor and extraction of the residue with boiling pentane yields an additional 7.8 g. of pale yellow rods, m.p. 47.5–48.5°, bringing the total yield to 46.6 g. (85%) (Note 5) and (Note 6).

2. Notes

1. Diazomethane was prepared by the method in *Org. Synth:*, **Coll. Vol. 5**, 351 (1973), using 10% extra 2-(2-ethoxyethoxy)ethanol and an extra 100 ml. of water over that recommended, to prevent stirring difficulties in the later stages of the distillation. The ethereal diazomethane solution was dried at 0° over potassium hydroxide pellets, and the concentration was determined by reaction of an aliquot with benzoic acid and analyzing the resulting methyl benzoate by GC.
2. Triethylamine, purchased from J. T. Baker Chemical Company, was refluxed over calcium hydride, then fractionally distilled through a 40-cm. Vigreux column, b.p. 81–82° (700 mm.); b.p. 89.5–90° (760 mm.).
3. Benzoyl chloride, obtained from British Drug House (Canada) Ltd., was purified, as described in *Org. Synth.*, **Coll. Vol. 3**, 112 (1955), by washing a benzene solution with 5% aqueous sodium hydrogen carbonate, drying over calcium chloride, and fractional distillation through a 40-cm. Vigreux column, b.p. 69–71° (12 mm.). The checkers used a fresh bottle, from Matheson, Coleman and Bell, without purification.
4. In the later stages of the addition a cake of crystals forms, preventing adequate stirring. This difficulty is overcome by temporarily interrupting the addition and swirling the flask manually—stirring then continues normally.
5. The submitters obtained a similar yield on twice the scale reported here.

6. Although crystallization from pentane gives better crystals, with an improved melting point range, recrystallization of the whole batch would require approximately 3 l. of solvent. Samples obtained from both ether-pentane and pentane evolve the theoretical amount of nitrogen on titration with 3 *N* hydrochloric acid.

3. Discussion

Apart from the reaction of diazomethane with benzoyl chloride,[2,3,4] diazoacetophenone has been prepared by the reaction of 2-aminoacetophenone hydrochloride with sodium nitrite,[5] from the mixed anhydride of benzoic acid and ethyl carbonate with diazomethane,[6] from benzoyl chloride and potassium methyldiazotate,[7] by treating the enamine formed from 2-formylacetophenone and *N*-methylaniline with *p*-toluenesulfonyl azide,[8] and from the reaction of the sodium enolate of 2-formylacetophenone with *p*-toluenesulfonyl azide.[9]

The reaction of an acid chloride with diazomethane illustrates a general method of preparing diazoketones. The acid chloride is slowly added to at least two equivalents of diazomethane; the hydrogen chloride liberated (Eq. 1) is then consumed according to Eq. 2. When the order of addition is reversed (*e.g.*, acid chloride is in excess) and only 1 mole of diazomethane is employed, the diazoketone reacts with hydrogen chloride, forming the α-chloroketone (Eq. 3).

$$RCOCl + CH_2N_2 \longrightarrow RCOCHN_2 + HCl$$

$$CH_2N_2 + HCl \longrightarrow CH_3Cl + N_2$$

$$RCOCHN_2 + HCl \longrightarrow RCOCH_2Cl + N_2$$

The method described here, discovered independently by Newman and Beal,[3] and Berenbom and Fones,[4] employs triethylamine (1 equivalent) to react with the hydrogen chloride; thus, only one equivalent of diazomethane is necessary. This modification was originally restricted to the use of either aromatic- or aliphatic acid chlorides lacking α-hydrogen atoms. Acid chlorides bearing α-hydrogens produce a mixture of products, presumably due to competing ketene formation and subsequent side reactions.

More recently it has been shown that, by operating at lower temperatures (−78°C), even simple aliphatic acid chlorides may also be successfully employed.[10] Some examples are the preparation of $C_6H_5CH_2CH_2COCHN_2$ (96%), *cyclo*-$C_6H_{11}COCHN_2$ (96%), $CH_3(CH_2)_7COCHN_2$ (96%), and $(CH_3)_2CHCOCHN_2$ (96%). However, this low temperature procedure is inapplicable to substrates with especially acidic α-hydrogens, such as phenylacetyl chloride, presumably due to competing ketene formation.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 919
- Org. Syn. Coll. Vol. 7, 438

References and Notes

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

potassium methyldiazotate

sodium enolate of 2-formylacetophenone

calcium chloride (10043-52-4)

hydrogen chloride,
hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether,
diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

Benzoic acid (65-85-0)

benzoyl chloride (98-88-4)

potassium hydroxide (1310-58-3)

methyl benzoate (93-58-3)

Triethylamine hydrochloride (554-68-7)

Pentane (109-66-0)

Ketene (463-51-4)

phenylacetyl chloride (103-80-0)

Diazomethane (334-88-3)

ethyl carbonate

N-Methylaniline (100-61-8)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

Diazoacetophenone,
Ethanone, 2-diazo-1-phenyl- (3282-32-4)

2-(2-ethoxyethoxy)ethanol (111-90-0)

2-aminoacetophenone hydrochloride (5468-37-1)

2-formylacetophenone

p-toluenesulfonyl azide (941-55-9)