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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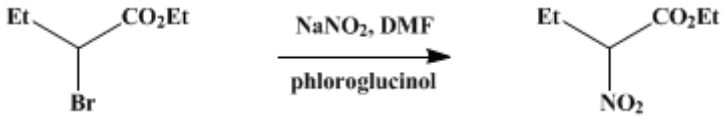
ETHYL α-NITROBUTYRATE

[Butyric acid, 2-nitro-, ethyl ester]



Submitted by Nathan Kornblum and Robert K. Blackwood[1].
Checked by James Cason, Joanne Facaros, and William G. Dauben.

1. Procedure

Ethyl α-bromobutyrate (58.5 g., 0.30 mole) (Note 1) is poured into a stirred mixture of 600 ml. of N,N-dimethylformamide (DMF) (Note 1), 36 g. of sodium nitrite (0.52 mole) (Note 1), and 40 g. of anhydrous phloroglucinol (0.32 mole) (Note 2) contained in a 1-l. three-necked flask equipped with a sealed stirrer. The flask is closed, except for a tube containing calcium chloride, and immersed in a water bath maintained at room temperature (Note 3). Stirring is continued for 2.5 hours (Note 4); then the reaction mixture is poured into 1.2 l. of ice water layered over with 300 ml. of ether (Note 5). After separation of the upper layer, the aqueous phase is extracted with four 100-ml. portions of ether. The combined extracts are washed with four 100-ml. portions of water and then dried over anhydrous magnesium sulfate. The magnesium sulfate is removed by suction filtration and washed with four 25-ml. portions of ether which are combined with the filtered extract.

The ether is distilled through a small column (Note 6), under reduced pressure, from a 1-l. flask which is heated by a bath whose temperature is gradually raised to about 60°. The residual yellow liquid is transferred, with the aid of a little anhydrous ether, to a 100-ml. flask, and the remaining solvent is distilled through the column under reduced pressure. Rectification of the residue yields 2–3 g. of fore-run boiling in the range 33–71°/1 mm. which is followed by 33–36 g. (68–75%) of colorless ethyl α-nitrobutyrate, b.p. 71°/1 mm., n_D^{20} 1.4233 (Note 7), (Note 8), and (Note 9).

2. Notes

1. The ethyl α-bromobutyrate employed was redistilled Eastman Kodak white label grade material, b.p. 64°/15 mm., n_D 1.4479. Technical DMF (du Pont) was used, and the sodium nitrite was an analytical grade.
Subsequent to the checking of this preparation, the submitters reported that DMSO (dimethyl sulfoxide) may be a somewhat better solvent for this preparation than is DMF. Since sodium nitrite is more soluble in DMSO, only 250 ml. of this solvent is required for the preparation. The more concentrated solution permits a reduction in reaction time to about 1.5 hours.
2. Ringwood Chemical Corporation technical grade phloroglucinol dihydrate was rendered anhydrous by heating for 3 hours at 110°. By reacting rapidly with any ethyl α-nitritobutyrate formed, it prevents nitrosation of the α-nitro ester. In the absence of phloroglucinol all the ethyl α-nitrobutyrate is destroyed.[2,3]
3. The reaction mixture becomes homogeneous and turns deep redbrown shortly after the addition of the α-bromo ester. The deep color is, presumably, due to nitrosated phloroglucinol; however, this in no way interferes with subsequent isolation of product.
4. Two hours allows more than sufficient time for complete reaction. Since the yield is not critically dependent on this factor, no attempt was made to establish the minimum reaction time. Even after a 17-hour reaction time there is no decrease in yield.
5. Approximately 200 ml. of this ether is required to saturate the aqueous DMF layer.
6. A 60 × 1 cm. externally heated column, packed with 1/8-in. glass helices and equipped with a total reflux variable take-off head, was used by the submitters.
7. Toward the end of the rectification the jacket of the column is heated to 90–95° in order to obtain the

last few grams of product.
8. The ethyl α-nitrobutyrate dissolves rapidly in 10% aqueous sodium hydroxide and dissolves completely in saturated aqueous sodium carbonate on shaking for 2–3 minutes.
9. This procedure has been applied successfully to the synthesis of other α-nitro esters from α-bromo esters,[3] as listed below; ethyl bromoacetate is exceptional in that it fails to give ethyl nitroacetate.

SYNTHESIS OF α-NITRO ESTERS FROM α-BROMO ESTERS

α-Nitro Ester	Reaction Time, hr.	Yield, %
Ethyl α-nitropropionate	2	62
Ethyl α-nitrocaproate	5	74
Ethyl α-nitroisobutyrate[a]	44	78
Ethyl α-nitroisovalerate	150	67
Ethyl α-phenyl-α-nitroacetate	2.5	70

[a] No phloroglucinol employed.

3. Discussion

Ethyl α-nitrobutyrate may be prepared in 75% yield by the reaction of silver nitrite with ethyl α-iodobutyrate,[4] in 82% yield by the reaction of sodium nitrite with ethyl α-bromobutyrate in dimethyl sulfoxide,[5] and in 51% and 46% yields from the appropriately substituted malonic or acetoacetic ester by nitration with acetone cyanohydrin nitrate, followed by cleavage of the nitrated esters by means of sodium hydride.[6] It also has been prepared in 18% yield by direct nitration and subsequent decarboxylation of diethyl ethylmalonate.[7] The present method offers the advantage of using sodium nitrite.

References and Notes

1. Purdue University, West Lafayette, Indiana. This research was supported, in part, by grants from the Explosives Department of E. I. du Pont de Nemours & Company and, in part, by the United States Air Force under contract No. AF 18 (600)-310 monitored by the Office of Scientific Research, Air Research and Development Command.
2. Kornblum, Blackwood, and Mooberry, *J. Am. Chem. Soc.*, **78**, 1501 (1956).
3. Kornblum, Blackwood, and Powers, *J. Am. Chem. Soc.*, **79**, 2507 (1957).
4. Kornblum, Chalmers, and Daniels, *J. Am. Chem. Soc.*, **77**, 6654 (1955).
5. Kornblum and Powers (to Purdue Research Foundation), U. S. pat. 2,816,909 [*C. A.*, **52**, 11896 (1958)].
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7. Kornblum and Eicher, *J. Am. Chem. Soc.*, **78**, 1494 (1956); Ulpiani, *Atti. reale accad. Lincei*, [5] **13**, II, 346 (1904).

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

ethyl α-nitritobutyrate

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

sodium nitrite (7632-00-0)

diethyl ethylmalonate (133-13-1)

Phloroglucinol (108-73-6)

phloroglucinol dihydrate (6099-90-7)

magnesium sulfate (7487-88-9)

silver nitrite (7783-99-5)

Ethyl bromoacetate (105-36-2)

N,N-dimethylformamide,
DMF (68-12-2)

sodium hydride (7646-69-7)

dimethyl sulfoxide,
DMSO (67-68-5)

Ethyl α-nitrobutyrate,
Butyric acid, 2-nitro-, ethyl ester (2531-81-9)

Ethyl α-bromobutyrate (533-68-6)

ethyl nitroacetate (626-35-7)

Ethyl α-nitropropionate (2531-80-8)

Ethyl α-nitrocaproate

Ethyl α-nitroisovalerate

Ethyl α-phenyl-α-nitroacetate

ethyl α-iodobutyrate

Acetone cyanohydrin nitrate (40561-27-1)

Ethyl α-nitroisobutyrate