



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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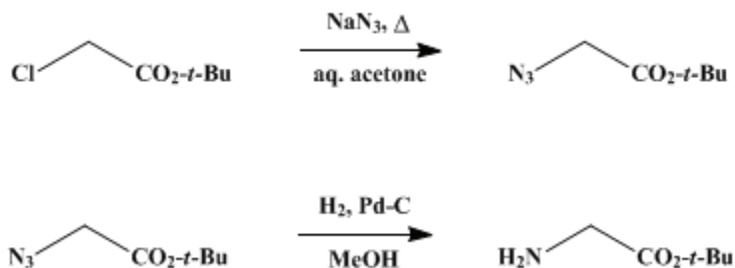
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 5, p.586 (1973); Vol. 45, p.47 (1965).

GLYCINE *t*-BUTYL ESTER



Submitted by A. T. Moore and H. N. Rydon¹.

Checked by William G. Dauben and John A. Hennings.

1. Procedure

A. *t*-Butyl azidoacetate. In a 300-ml. round-bottomed flask fitted with a reflux condenser are placed 30 g. (0.2 mole) of *t*-butyl chloroacetate (Note 1), 24 g. (0.37 mole) of sodium azide, and 90 ml. of 60% (v./v.) acetone-water. The heterogeneous mixture (two liquid phases and a solid phase) is heated under reflux on a steam bath for 18 hours, the acetone distilled, and 15 ml. of water added (Note 2). The mixture is transferred to a separatory funnel, the layers separated, and the lower aqueous layer extracted twice with 25-ml. portions of ether. The ethereal extracts are added to the original upper layer, and the solution is dried over anhydrous sodium sulfate. The ether is distilled, and the residual oil is fractionated under reduced pressure (Note 3), the fraction boiling from 33–41° (1 mm.) being collected; yield 29 g. (92%), n_D^{20} 1.4356 (Note 4).

B. *Glycine t*-butyl ester. In the center neck of a 500-ml. suction filtration flask is placed a gas-inlet tube which is connected to a nitrogen cylinder, and on the side arm of the flask there is attached an exit tube leading to a suitable ventilation duct. The flask is placed on a magnetic stirrer, and a solution of 28.9 g. (0.18 mole) of *t*-butyl azidoacetate in 150 ml. of methanol and 0.7 g. of 5% palladium-on-charcoal catalyst is added to the flask. A stream of nitrogen is swept over the surface of the stirred suspension for 5 minutes, the nitrogen cylinder is replaced by a hydrogen cylinder, and hydrogen is passed over the magnetically stirred mixture for 10 hours. The hydrogen is displaced from the flask by a sweeping with nitrogen, the catalyst is removed by filtration and is washed with 5 ml. of methanol. The filtrate is transferred to a 500-ml. Erlenmeyer flask, 15 g. (0.18 mole) of phosphorous acid is added, and the mixture is warmed gently to dissolve the phosphorous acid. The solution is cooled to room temperature (Note 5), 150 ml. of ether is added slowly, and the solution is cooled at 0° for 12 hours. The precipitated *glycine t*-butyl ester phosphite is filtered, washed with ether, and dried in a vacuum oven at 70°, yield 29–32 g. (75–82%), m.p. 144–147° (dec.) (Note 6) and (Note 7).

To 50 ml. of a well-cooled 6*N* sodium hydroxide solution is added, with stirring, 32 g. (0.15 mole) of the phosphite salt. The stirring is continued until all the solid has dissolved. The solution is transferred to a 125-ml. separatory funnel, extracted with three 20-ml. portions of ether, and the combined extracts dried over anhydrous sodium sulfate. The drying agent is removed by filtration, the solvent removed under reduced pressure, and the *glycine t*-butyl ester distilled, b.p. 65–67° (20 mm.), n_D^{20} 1.4237, yield 14 g. (72%, based on phosphite salt). The overall yield from *t*-butyl chloroacetate is 50–55%.

2. Notes

1. The *t*-butyl chloroacetate was prepared from chloroacetyl chloride and *t*-butanol following the procedure of Baker.²
2. The water is added to dissolve any inorganic salts which are still not in solution.
3. Owing to the possibly explosive nature of the ester, the distillation was conducted behind a safety screen, using a water bath for the heat source and keeping the pressure as low as convenient.

4. The submitters reported a boiling point of 63–64° (5–6 mm.), n^{20}_D 1.4348. The literature values are b.p. 72–73° (13 mm.) and n^{25}_D 1.4332.³ The submitters also report that the reaction has been run safely on a 200-g. scale.
5. If the mixture sets solid upon cooling, the lumps of phosphite salt should be broken up during the addition of the ether.
6. The crystallization of the crude product from methanol-isopropyl ether gave pure phosphite salt, m.p. 154–157° (dec.).
7. Some *t*-butyl azidoacetate can be recovered by evaporation of the mother liquor. After removal of the methanol from the filtrate, the residual oil is dissolved in ether, washed with distilled water, the ether removed, and the residue fractionally distilled under reduced pressure (using proper precautions).

3. Discussion

This method is a modification of that developed by Vollmar and Dunn.³ Glycine *t*-butyl ester also has been prepared by the acid-catalyzed addition of *N*-benzyloxycarbonylglycine to isobutene, followed by catalytic hydrogenolysis of the resulting *N*-benzyloxycarbonylglycine *t*-butyl ester.⁴ The esters of other amino acids have been prepared directly by the isobutene method.⁵

4. Merits of the Preparation

Glycine *t*-butyl ester is a valuable intermediate for the preparation of peptides of glycine, since the labile *t*-butyl group can readily be removed by acid under conditions which do not affect the blocked amino grouping. The present method using *t*-butyl chloroacetate is superior to that using the bromo derivative,³ since chloride is cheaper to prepare, less lachrymatory and more easily separated, by fractional distillation, from the *t*-butyl azidoacetate. The method is also less cumbersome than the procedure using isobutene.

References and Notes

1. Department of Chemistry, University of Exeter, Exeter, England.
2. R. H. Baker, *Org. Syntheses*, **24**, 21 (1944); Coll. Vol. **3**, 144 (1955).
3. A. Vollmar and M. S. Dunn, *J. Org. Chem.*, **25**, 387 (1960).
4. G. W. Anderson and F. M. Callahan, *J. Am. Chem. Soc.*, **82**, 3359 (1960).
5. R. W. Roeske, *Chem. Ind.* (London), 1121 (1959).

Appendix

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

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

palladium (7440-05-3)

chloroacetyl chloride (79-04-9)

Glycine (513-29-1)

sodium azide (26628-22-8)

phosphorous acid (13598-36-2)

isobutene (9003-27-4)

N-benzyloxycarbonylglycine (1138-80-3)

t-butanol (75-65-0)

methanol-isopropyl ether (598-53-8)

GLYCINE t-BUTYL ESTER (6456-74-2)

t-butyl chloroacetate (107-59-5)

t-butyl azidoacetate (6367-36-8)

glycine t-butyl ester phosphite

N-benzyloxycarbonylglycine t-butyl ester