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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

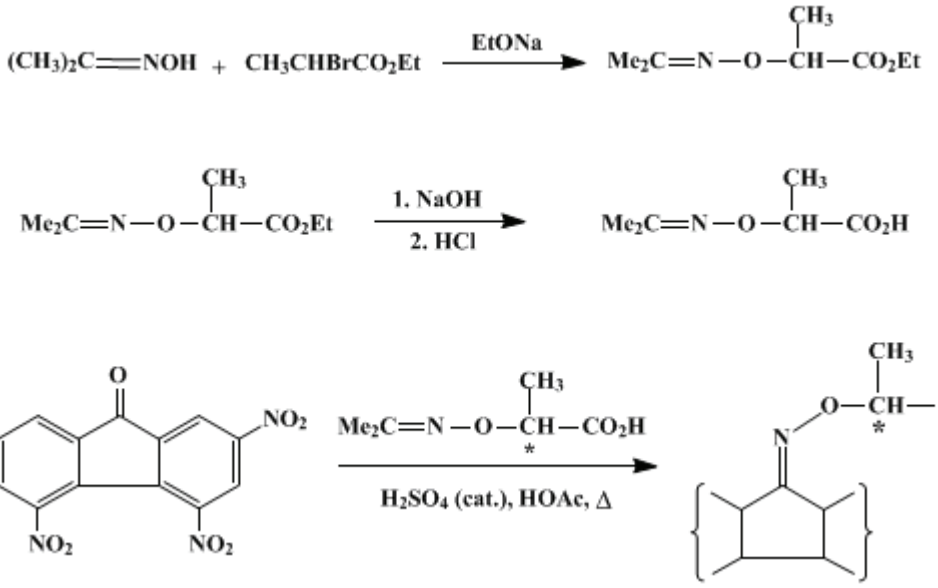
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.048.0120

Organic Syntheses, Coll. Vol. 5, p.1031 (1973); Vol. 48, p.120 (1968).

(+)- AND (−)-α-(2,4,5,7-TETRANITRO-9-FLUORENYLIDENEAMINOOXY)PROPIONIC ACID

[Propionic acid, 2-(2,4,5,7-tetranitrofluoren-9-ylideneaminooxy)-, (+)- and (−)-]



Submitted by Paul Block Jr[1] and Melvin S. Newman[2].
Checked by William G. Dauben, Milton E. Lorber, Carroll S. Montgomery, and Gary W. Shaffer.

1. Procedure

A. *Ethyl α-(isopropylideneaminooxy)propionate*. A 1-l. three-necked flask is equipped with a mechanical stirrer, a dropping funnel, and a thermometer that can be immersed in the contents of the flask. There is added to the flask 500 ml. of commercial absolute ethanol (Note 1) followed by 17.5 g. (0.76 g. atom) of sodium, which is added carefully in small portions. When a clear solution has been obtained, 55.0 g. (0.75 mole) of acetone oxime is added (Note 2). The flask is cooled in a water bath held at 5–10°, the stirrer is started, and 136 g. (0.75 mole) of ethyl α-bromopropionate (Note 3) is added during 20–30 minutes at a rate such that the temperature does not rise above 20°. The cooling bath is removed, and the stirring is continued until the contents of the flask reach room temperature.

After standing for 12 hours, the reaction mixture is filtered by gravity into a 1-l. round-bottomed flask, and the solid sodium bromide is washed with 50 ml. of ethanol. The combined filtrate and washings are concentrated to a volume of about 400 ml., and 250 ml. of water is added to the cooled concentrate. The mixture is extracted with 50 ml. of a 1:1 mixture of ether and benzene, and the aqueous layer is reextracted with 100 ml. of the same solvent mixture. The organic extracts are combined, washed with 100 ml. of water and 50 ml. of saturated aqueous sodium chloride, and filtered through a few grams of anhydrous magnesium sulfate. The solvent is removed on a rotary evaporator, and the residue is distilled to yield 71–77 g. (55–59%) of ethyl α-(isopropylideneaminooxy)propionate, b.p. 62–64° (4 mm.).

B. *d,l-α-(Isopropylideneaminooxy)propionic acid*. In a 1-l. three-necked flask fitted with a stirrer and a thermometer that can be immersed in the contents of the flask is placed 300 ml. of 5% aqueous sodium hydroxide (0.37 mole). The flask is heated on a water bath until the temperature of the solution reaches 70°, and 52 g. (0.30 mole) of ethyl α-(isopropylideneaminooxy)propionate is added. The mixture is stirred rapidly while the temperature is held at 70°; the stirring is continued for 20 minutes beyond the time necessary for the contents of the flask to become homogeneous (Note 4). The solution is cooled and acidified to Congo red paper with 5*N* hydrochloric acid, and 175 g. of ammonium sulfate

is added. The mixture is extracted three times with a total of 300 ml. of a 1:1 mixture of ether and benzene. The combined extracts are dried rapidly over 5 g. of anhydrous magnesium sulfate and filtered (Note 5). The solvent is removed by distillation, and 160 ml. of petroleum ether (b.p. 30–60°) is added to the cooled residue. The resulting solution is placed in a refrigerator for several hours. The crystals that separate are removed by suction filtration and washed with a small volume of cold petroleum ether. The yield of colorless product is 35–37 g. (80–85%); m.p. 59–60.5° (Note 6).

C. (+)- and (−)-*α-(Isopropylideneaminooxy)propionic acid-(−)-ephedrine salts*. A solution of 36.6 g. (0.200 mole) of (−)-ephedrine monohydrate (Note 7) in 800 ml. of ethyl acetate containing 6% of ethanol (Note 8) is placed in a 2-l. beaker. *d,l-α*-(Isopropylideneaminooxy)propionic acid (29.0 g., 0.200 mole) is dissolved in this solution by stirring (Note 9). The beaker is covered securely with a rubber dam, cooled for a short period in an ice bath, placed in a refrigerator at 0–5°, and allowed to remain undisturbed for 8–16 hours after crystallization has begun (Note 10). The solid mass of crystals is filtered by suction, and the funnel is covered with a rubber dam to remove most of the solvent. The solid product is placed in a 500-ml. beaker, 250 ml. of ethyl acetate is added (Note 11), and the mixture is heated until all the solid has dissolved. The solution is cooled, placed in a refrigerator for several hours, and filtered; the crystalline precipitate is dried in air. The yield of the (−)-ephedrine-(+)-α-(isopropylideneaminooxy)propionic acid salt is 22–25 g. (71–81%); m.p. 115–119° (Note 12) and (Note 13); $[\alpha]^{20}D$ −4.2° (*c* 1.5, chloroform).

The combined filtrates are diluted with an equal volume of petroleum ether (b.p. 30–60°), placed in a refrigerator for 8–16 hours, and filtered. The solid product is recrystallized from ethyl acetate (10 ml. per gram of the salt). The yield of the monohydrate of the (−)-ephedrine-(−)-α-(isopropylideneaminooxy)propionic acid salt is 19–26 g. (58–79%); m.p. 88–90°; $[\alpha]^{20}D$ −57° (*c* 1.5, chloroform) (Note 13) and (Note 14).

D. (+)- *and (−)-α-(Isopropylideneaminooxy)propionic acid*. To a solution of 20 g. (0.064 mole) of the (−)-base-(+)-acid salt in 60 ml. of water is added 14 ml. (0.070 mole) of 5*N* hydrochloric acid. The solution is filtered to remove a slight insoluble residue and extracted with four 25-ml. portions of a 1:1 mixture of ether and benzene. The combined extracts are dried rapidly over 1–2 g. of anhydrous magnesium sulfate and filtered. The organic solvents are removed by distillation from a steam bath, the residue is dissolved in 75 ml. of petroleum ether (b.p. 30–60°), and the solution is allowed to stand in a refrigerator for 12 hours. The crystalline product (7.0–7.5 g.; m.p. 75–81°) is collected and dissolved in hot acetone (0.5 ml. per gram), and the solution is diluted with hexane (5 ml. per gram). The solution is placed in a refrigerator for 8–16 hours, and the crystalline (+)-α-(isopropylideneaminooxy)propionic acid (5.5–6.5 g.; 59–70%) that separates is collected; m.p. 83–85°; $[\alpha]^{20}D$ +32° (*c.* 1.6, water).

In a similar manner, from 20 g. (0.061 mole) of the monohydrate of the (−)-base-(−)-acid salt, there is obtained 6.4–6.7 g. (73–76%) of the (−)-acid, m.p. 83–85°, $[\alpha]^{20}D$ −29° (*c* 1.44, water), directly from the crystallization from petroleum ether. Subsequent recrystallization from acetone-hexane is normally not required.

E. (+)- *and (−)-α-(2,4,5,7-Tetranitro-9-fluorenylideneaminooxy)propionic acid (TAPA)*. To a solution of 5.5 g. (0.038 mole) of either optical antipode of α-(isopropylideneaminooxy)propionic acid in 85 ml. of 96% acetic acid in a 250-ml. round-bottomed flask are added 9.0 g. (0.025 mole) of 2,4,5,7-tetranitrofluorenone,[3] 0.30–0.35 ml. of concentrated sulfuric acid, and a few boiling chips. The flask is fitted with an air condenser (Note 15), and the contents are heated under reflux so that the condensing liquid nearly reaches the top of the condenser (Note 16). After 2 hours, 18 ml. of water is added to the hot solution, and crystallization is allowed to take place slowly, first at room temperature and finally for 12 hours in a refrigerator. The yellow crystalline acid is filtered and dissolved in 70 ml. of hot acetic acid. The solution is diluted while hot with 60 ml. of water, cooled rapidly with stirring, and kept at 0° for several hours. The optically active TAPA is filtered and air-dried away from direct sunlight until the odor of acetic acid is negligible. The crystals are then dried in an oven at 110° (Note 17) and protected from light by storage in a suitable container; yield 7.8–10.0 g. (70–90%). The TAPA from the (−)-acid has $[\alpha]^{25}D$ +97° and that from the (+)-acid $[\alpha]^{25}D$ −97° (Note 18).

2. Notes

1. Pure anhydrous ethanol[4] offers no advantage over commercial absolute ethanol.
2. "Eastman grade" acetone oxime was used as obtained from Eastman Organic Chemicals.
3. "Eastman grade" ethyl α-bromopropionate was used as obtained from Eastman Organic Chemicals.
4. Usually 10–20 minutes are required to obtain complete reaction.
5. If the solution is not entirely colorless, it should be shaken with a small amount of activated carbon and filtered before distillation.
6. The checkers found 53–56°; m.p. 57–61° has been reported.[5]
7. "Ephedrine alkaloid hydrous," Merck, was used. If anhydrous ephedrine is employed, only 33 g. should be used, and 3.6 g. (0.20 mole) of water should be added. Anhydrous conditions lead to incomplete resolution.
8. Commercial absolute ethanol (48 ml.) is pipetted into a 1-l. graduated cylinder and diluted with 800 ml. of ethyl acetate ("Eastman grade").
9. Both components are soluble in ethyl acetate at room temperature; the resulting salt is not. By dissolving the components sequentially, precipitation of the salt is generally avoided. Should the salt form, however, it must be dissolved by gentle heating.
10. Prolonged standing must be avoided as the deposition of the (−)-ephedrine-(−)-acid salt can occur.
11. Ethanol is not added to the ethyl acetate at this point.
12. Highly purified samples have m.p. 124.0–124.5°.
13. The two diastereoisomeric salts can be readily distinguished from each other. The (−)-ephedrine-(+)-acid salt is formed as cottony crystals that grow in the solution and eventually become a solid, white opaque mass. The monohydrate of the (−)-ephedrine-(−)-acid salt consists of clear, chunky crystals that grow from, and adhere to, the bottom and sides of the flask.
14. The water of hydration is lost on standing in a desiccator over phosphorus pentoxide; the melting point eventually reached is 109–110°.[6]
15. A 250 × 15-mm. glass tube is satisfactory.
16. The suspended tetranitrofluorenone dissolves completely in about 25 minutes; the vigorous heating is required to bring about the solution and reaction.
17. One mole of acetic acid of solvation is lost only slowly at room temperature; the solvated product has m.p. *ca.* 123°.[5] The submitters found that the air-dried material, on being dried at 110°, yielded essentially solvent-free compound, m.p. 201–203° (dec. with prior darkening). The checkers found that at 110° the air-dried material melted, turned brown, and then resolidified. They also found that the material, on being dried at 70–80° (1 mm.) over potassium hydroxide pellets for several days, remained yellow but melted over a range 110–125°, resolidified, and remelted at 190–195°.
18. The checkers used material dried at 70–80° for their determination of the rotation and obtained values in agreement with those reported by the submitters.

3. Discussion

TAPA has been prepared only as described in this procedure.[5] α-(isopropylideneaminooxy) propionic acid has been prepared and resolved by the present procedure[6] and has been prepared directly from α-bromopropionic acid and resolved as the (−)-ephedrine salt by crystallization from hydrocarbon mixtures.[5]

4. Merits of the Preparation

The use of ethyl α-bromopropionate simplifies the preparation of α-(isopropylideneaminooxy) propionic acid. Resolution in ethyl acetate solution has proved less erratic than in the hydrocarbon solvents previously recommended,[5] and the isolation of both diastereoisomeric salts formed is facilitated. TAPA has found use in the resolution of polycyclic aromatic compounds that do not possess functional groups that would permit resolution by other methods.[5,7,8]

References and Notes

1. Department of Chemistry, University of Toledo, Toledo, Ohio.
2. Department of Chemistry, The Ohio State University, Columbus, Ohio 43210.

3. M. S. Newman and H. Boden, this volume, p. 1029.
4. R. H. Manske, *Org. Syntheses*, Coll. Vol. **2**, 154 (1943).
5. M. S. Newman and W. B. Lutz, *J. Am. Chem. Soc.*, **78**, 2469 (1956).
6. P. Block, Jr., *J. Org. Chem.*, **30**, 1307 (1965).
7. M. S. Newman, R. G. Mentzer, and G. Slomp, *J. Am. Chem. Soc.*, **85**, 4018 (1963).
8. M. S. Newman, R. W. Wotring, Jr., A. Pandit, and P. M. Chakrabarti, *J. Org. Chem.*, **31**, 4293 (1966).

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

petroleum ether

(+)- and (-)-α-(2,4,5,7-Tetranitro-9-fluorenylideneaminooxy)propionic acid

Propionic acid, 2-(2,4,5,7-tetranitrofluoren-9-ylideneaminooxy)-, (+)- and (−)-

(+)- and (−)-α-(Isopropylideneaminooxy)propionic acid-(−)-ephedrine salts

(−)-ephedrine monohydrate

(+)- and (−)-α-(Isopropylideneaminooxy)propionic acid

(+)- and (−)-α-(2,4,5,7-Tetranitro-9-fluorenylideneaminooxy)propionic acid (TAPA)

(−)-ephedrine

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium chloride (7647-14-5)

α-bromopropionic acid (598-72-1)

sodium bromide (7647-15-6)

acetone (67-64-1)

carbon (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

ammonium sulfate (7783-20-2)

magnesium sulfate (7487-88-9)

monohydrate (7732-18-5)

ethyl α-bromopropionate (535-11-5)

hexane (110-54-3)

acetone-hexane (821-55-6)

2,4,5,7-Tetranitrofluorenone (746-53-2)

Tetranitrofluorenone

acetone oxime (127-06-0)

ethyl α-(isopropylideneaminooxy)propionate (54716-29-9)

d,l-α-(Isopropylideneaminooxy)propionic acid,
α-(isopropylideneaminooxy)propionic acid,
(+)-α-(isopropylideneaminooxy)propionic acid (5001-36-5)

Ephedrine (90-82-4)

phosphorus pentoxide (1314-56-3)