Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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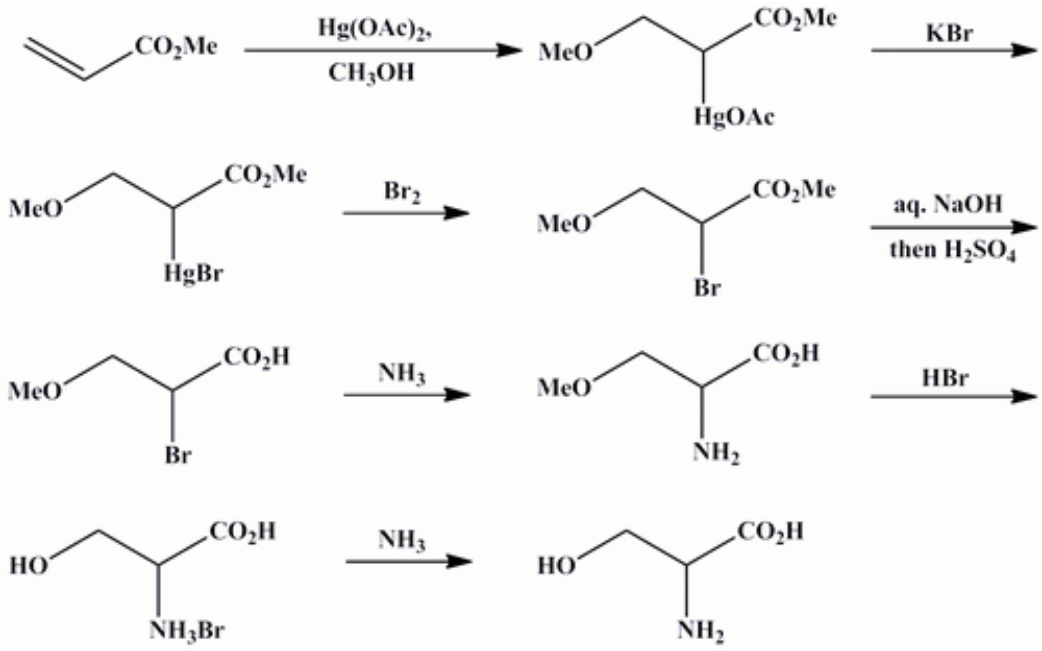
dl-SERINE



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1. Procedure

A. *Methyl α-bromo-β-methoxypropionate*. In a 5-l. flask is placed 450 g. of a 60% solution of methyl acrylate in methanol (Note 1) containing 3.1 moles of methyl acrylate (Note 2). To this solution are added 180 g. of methanol and 960 g. (3 moles) of mercuric acetate (Note 3). The mixture is allowed to stand at room temperature for 3 days with occasional shaking (Note 4). The flask is cooled in an ice bath, and a solution of 360 g. (3 moles) of potassium bromide in 1.2 l. of water is added with stirring during 15 minutes. The heavy oil that separates is extracted with 2.4 l. of chloroform (Note 5), and the aqueous layer is again extracted with 600 ml. of chloroform. The chloroform solutions are combined, washed three times with water, and carefully dried over anhydrous magnesium sulfate (Note 6).

The solution, filtered to remove the drying agent, is placed in a 4-l. beaker and warmed to 50°. The beaker is then exposed to direct sunlight (Note 7), and 450 g. (2.81 moles) of bromine is added with stirring (Note 8) as fast as it is used. The reaction starts slowly but accelerates rapidly, and considerable heat is evolved. The temperature of the solution should be kept below 55° (Note 9). The bromination usually requires 20–30 minutes. At the conclusion of the reaction, the flask is cooled for 15 minutes in an ice-salt bath, and the mercuric bromide is separated by filtration. The chloroform is removed by distillation under reduced pressure through a 20-in. column, and the residue is fractionally distilled under reduced pressure from a modified Claisen flask. The yield is 480–510 g. (81–86% based on the mercuric acetate) of a product boiling at 70–80° at 6 mm. This material contains 5–10% of methyl α,β-dibromopropionate, which is not readily removed. Since the impurity causes no trouble in the synthesis of serine, the crude bromo ester is used in succeeding steps (Note 10).

B. *α-Bromo-β-methoxypropionic acid*. Eight hundred grams of the bromo ester and 1 l. of 0.5 *N* sodium hydroxide are placed in a 5 l. three-necked flask equipped with an efficient stirrer and a separatory funnel, and cooled with running tap water. The stirrer is started, and 800 ml. of 5 *N* sodium hydroxide is added during the course of 2 hours. After the addition is complete, the solution is stirred for 1 hour and then neutralized with an equivalent quantity of sulfuric acid (Note 11). The neutralized solution is extracted once with a 1-l. portion, and three times with 500-ml. portions, of ether. The ether

extracts are combined, washed once with a cold saturated solution of sodium sulfate, and dried over anhydrous sodium sulfate; the ether is removed by distillation (Note 12). There remains 700–750 g. of crude bromo acid which is used without purification in the preparation of serine (Note 13).

C. *dl-Serine*. One-half (350–375 g.) of the crude bromomethoxypropionic acid prepared from the saponification of 800 g. of methyl α-bromo-β-methoxypropionate is heated with 3.5 l. of concentrated ammonium hydroxide in a glass-lined autoclave (Note 14) for 10–15 hours at 90–100°, and the solution from the bomb is concentrated to a thick syrup under reduced pressure (Note 15). Two liters of water is added, and the solution is concentrated to dryness. The cake is dissolved in 1.5 l. of 48% hydrobromic acid and refluxed for 2.5 hours. The resulting dark solution is concentrated to a volume of about 500 ml. and then cooled under the tap. The precipitated ammonium bromide is removed by filtration, and the filtrate is concentrated to a thick syrup (Note 16). One liter of water is added, and the solution is again concentrated to a thick syrup. The syrupy residue is dissolved in 375 ml. of warm water, and ammonium hydroxide is added carefully until a faint odor of ammonia persists after vigorous shaking. One and one-half liters of absolute ethanol is then added slowly (Note 17), and the mixture is allowed to stand overnight. The crude serine is filtered and the filtrate discarded. The precipitate is dissolved in 500 ml. of boiling water (Note 18), heated on the steam cone for 10 minutes with 10–15 g. of Darco (Note 19), and then filtered. Five hundred milliliters of absolute ethanol is added to the filtrate slowly with stirring. The mixture is cooled to 0° and is kept at this temperature for 1 hour with occasional stirring to ensure formation of a finely divided precipitate (Note 20). The serine is filtered, washed with ethanol and ether, and air-dried. The precipitates from several runs may be combined and recrystallized as above from 50% ethanol until a white product is obtained (one or two recrystallizations).

All the filtrates should be combined and evaporated to dryness under reduced pressure, and the residue should be recrystallized as above. The last concentrates (including filter paper and Darco washings), if quite dark, may be precipitated from 70% ethanol before recrystallizing. By this process a nearly quantitative recovery may be effected.

The over-all yield is 30 to 40% of the theoretical amount based on the mercuric acetate (Note 21).

2. Notes

1. The solution of methyl acrylate in methanol was obtained from Rohm and Haas Company.
2. If the methyl acrylate solution has stood for some time, it is advisable to use a 10% excess, since the solution slowly deteriorates. A low yield of bromo ester is usually caused by insufficient methyl acrylate.
3. Six hundred and forty-eight grams (3 moles) of mercuric oxide and 345 ml. (360 g., 6 moles) of acetic acid may be used just as satisfactorily as mercuric acetate. The solution of these substances should be cooled in an ice bath and vigorously shaken for several minutes after the reagents have been mixed, since the reaction of mercuric oxide with acetic acid produces considerable heat.
4. At this time there is still a small amount of undissolved mercuric acetate (and mercuric oxide, if used). Longer standing does not improve the yield.
5. All solutions of the mercury compounds should be handled with care, as they are extremely vesicant to some individuals.
6. The brominations proceed more smoothly if the chloroform solution is washed free of methanol and dried.
7. The bromination may be carried out just as satisfactorily with the light from two No. 2 Photoflood lamps. These lamps should be mounted in suitable reflectors as near the surface of the solution as possible. The time required may be slightly longer.
8. An efficient mechanical stirrer is required. Near the end of the bromination the precipitate of mercuric bromide becomes quite heavy.
9. The temperature may be controlled by passing tap water through an 8-mm. glass cooling coil mounted in the beaker. The bromination proceeds rapidly at 45–55°, rather slowly at 35–40°, and practically ceases below 30°.
10. The crude ester may be used directly in the preparation of serine. However, greater ease of purification and slightly better yields make it advantageous to prepare the free acid. Pure methyl α-bromo-β-methoxypropionate is obtained by fractionally distilling the crude material under reduced pressure through a Widmer column. From 100 g. of crude material there is obtained 80–90 g. of pure

ester, b.p. 73–75°/6 mm., n_D^{20} 1.4586.
11. It is advisable to keep the temperature below 30° during both the hydrolysis and neutralization.
12. The acid should not be heated for long periods. The last traces of ether should be removed under reduced pressure.
13. The crude bromo acid on standing 2–3 days may deposit an amorphous solid which is probably a polymerization product of α-bromoacrylic acid. If this is removed before the bromo acid is aminated, the subsequent purification of serine is much easier.
14. The checkers employed a simple autoclave, constructed as follows: A piece of 10-in. steam pipe 11 in. long and threaded at both ends was closed at one end by a standard pipe cap. A standard flange was screwed to the other end, and a blank companion flange seating on an "ammonia gasket" provided the closure for the top of the autoclave. A Pyrex battery jar 10 in. high and 8.5 in. in diameter fitted loosely in the pipe and was protected from breakage due to contact with the sides and bottom of the pressure vessel by rings made of rubber tubing. The battery jar was covered with a loosely fitting germinating dish to prevent condensate from the top from dripping into the reaction mixture. After the bromo acid had been introduced into the battery jar, concentrated ammonia was poured into the annular space between the jar and the pipe to provide better heat transfer. The autoclave was heated in a wash tub containing water which was kept boiling by a steam coil.
15. All the concentrations under reduced pressure required in this preparation were carried out with the aid of an efficient water pump.
16. The distillate may be redistilled at atmospheric pressure to recover the hydrobromic acid.
17. Absolute ethanol (200 ml.) is added to the warm (60–70°) solution, and the sides of the flask are scratched to induce crystallization; the remainder of the ethanol is then added in large portions with stirring over a period of 1 hour.
18. Pure *dl*-serine is soluble in water to the extent of 50 g. per liter at 25°, 200 g. at 80°, and approximately 30 g. at 5–10°. The presence of impurities, however, will increase its solubility greatly.
19. Norit is not so satisfactory as Darco.
20. Slow precipitation tends to give large crystals with resulting inclusion of colored impurities.
21. The yield is directly dependent upon the quality of the methyl acrylate used.

3. Discussion

Serine has been prepared by the Strecker method from glycol aldehyde[1] and from ethoxyacetaldehyde[2,3,4] by the condensation of ethyl formate with ethyl hippurate followed by reduction and hydrolysis,[5,6] from the reaction product of chloromethyl ether with ethyl sodium phthalimidomalonate,[7] by amination of α-bromo-β-methoxypropionic acid with subsequent demethylation,[8] by hydrolysis of 5-(methoxymethyl) hydantoin,[9] by hydrolysis of ethyl α-acetamido-β-hydroxypropionate,[10] by hydrogenolysis of N-benzylserine,[11] and by reduction of the 2,4-dinitrophenylhydrazone of hydroxypyruvic acid.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 813

References and Notes

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

Darco

2,4-dinitrophenylhydrazone of hydroxypyruvic acid

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

ammonium bromide (12124-97-9)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

mercuric acetate (1600-27-7)

mercuric oxide (21908-53-2)

Norit (7782-42-5)

potassium bromide (7758-02-3)

ammonium hydroxide (1336-21-6)

ethyl formate (109-94-4)

chloromethyl ether (542-88-1)

methyl acrylate (96-33-3)

magnesium sulfate (7487-88-9)

Ethyl Sodium Phthalimidomalonate

mercuric bromide (7789-47-1)

methyl α,β-dibromopropionate (1729-67-5)

serine (56-45-1)

bromomethoxypropionic acid

Methyl α-bromo-β-methoxypropionate (27704-96-7)

α-bromoacrylic acid (10443-65-9)

glycol aldehyde (141-46-8)

ethoxyacetaldehyde

ethyl hippurate

α-Bromo-β-methoxypropionic acid (65090-78-0)

5-(methoxymethyl) hydantoin

ethyl α-acetamido-β-hydroxypropionate

N-benzylserine

DL-Serine (25821-52-7)