



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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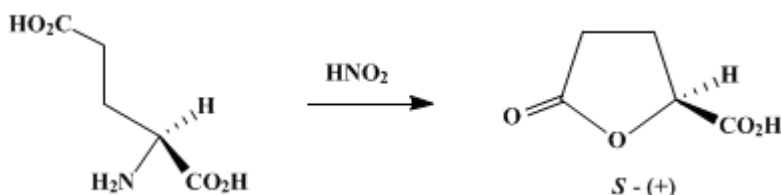
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 7, p.99 (1990); Vol. 63, p.121 (1985).

(S)-(+)- γ -BUTYROLACTONE- γ -CARBOXYLIC ACID

[2-Furancarboxylic acid, tetrahydro-5-oxo-, (S)-]



Submitted by Olivier H. Gringore and Francis P. Rouessac¹.

Checked by Matthew F. Schlecht, Howard Drossman, and Clayton H. Heathcock.

1. Procedure

Caution! This procedure should be conducted in a well-ventilated hood to avoid inhalation of poisonous NO₂ vapors. To protect the operator the distillation must be carried out with the usual precautions associated with vacuum distillation.

A 6-L Erlenmeyer flask which contains a large magnetic stirring bar is charged with 294 g (2 mol) of L-glutamic acid (Note 1) and 2 L of distilled water. The suspension is stirred vigorously while solutions of 168 g (2.4 mol) of sodium nitrite in 1.2 L of water and 1.2 L of aqueous 2 N sulfuric acid are added simultaneously from separatory funnels (Note 2). After the addition is complete (Note 3), the solution is stirred at room temperature for an additional 15 hr. The water is then removed by heating below 50°C under reduced pressure with a rotary evaporator (Note 4). The resulting pasty solid is triturated with 500 mL of boiling acetone and the hot solution is filtered and set aside to cool. This operation is repeated four times (Note 5) and (Note 6). Removal of solvent with a rotary evaporator affords 312 g of crude (+)- γ -butyrolactone- γ -carboxylic acid as a slightly yellow oil (Note 7) and (Note 8).

A 250-mL, round-bottomed flask is equipped with a magnetic stirring bar and charged with 100 g of the foregoing crude lactone acid (Note 9). The flask is fitted with a Claisen distillation apparatus and connected to a vacuum pump (Note 10) and (Note 11). The flask is gradually heated with an oil bath (160°C) until gas evolution ceases (Note 12). At this point the oil bath is removed and the black, viscous oil is distilled with the use of a flame (Note 13). The product, 58 g (70%), is collected as a colorless oil at 146–154°C (0.03 mm). The distillate crystallizes in the receiver, mp 66–68°C (Note 14) and (Note 15).

2. Notes

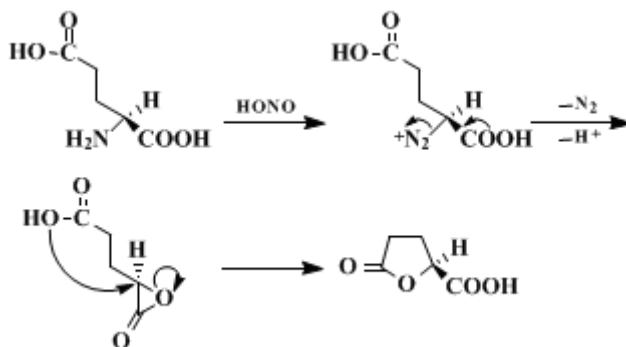
1. This material was purchased from the Aldrich Chemical Company Inc., $[\alpha]_D^{23} +29^\circ$ (6 N HCl, c 1).
2. The addition requires about 30 min. During addition the reaction mixture should warm to 30–35°C and smooth evolution of NO₂ and N₂ should occur. If the solutions of NaNO₂ and H₂SO₄ are added too rapidly, more gas appears to be generated and a reduction in yield occurs.
3. At this point the reaction mixture is clear and colorless. Residual brown gas usually remains in the flask.
4. If a conventional aspirator pump is employed, concentration can require several days. The checkers employed a rotary evaporator that was evacuated to approximately 3 mm by a vacuum pump. Two traps, one cooled in an ice–salt bath and the other in an acetone–dry-ice bath, were inserted between the rotary evaporator and the vacuum pump. In this way, the reaction mixture can be concentrated to a paste in about 16–20 hr.
5. Repetitive extraction may also be performed in a flask heated with a water bath to 65°C; acetone is removed by decantation. Ethyl acetate has also been used for the extraction.²

6. The checkers found that a higher recovery is obtained if the pasty solid is vigorously agitated during trituration with five 750-mL portions of boiling acetone.
 7. The crude yield reported is in excess of the theoretical yield (260 g). The checkers obtained crude yields of 243–259 g, probably because water was more efficiently removed in the concentration step.
 8. Although this material is sufficiently pure for some applications, it is advisable to purify it further before use. Distillation² and crystallization³ have been described. The submitters recommend purification by the distillation procedure given. By direct crystallization of 101 g of crude lactone acid from ether–petroleum ether, the checkers obtained 36.5 g (35%) of material, mp 72–74°C.
 9. If the distillation is carried out on a larger scale, the yield is lower.
 10. The submitters recommend a short-path distillation apparatus with large sections (i.e., wide bore) since the distillate partially crystallizes in the condenser during the distillation. It is important that the distillation apparatus have a Claisen head because the viscous material tends to bump.
 11. The vacuum pump should be protected by a soda–lime trap.
 12. During this heating period the system pressure should rise from 0.03 to 0.5 mm and the crude lactone acid should become black. When gas evolution ceases, the pressure decreases to its initial value.
 13. Distillation should be carried out briskly. If a simple bunsen burner with a low flame is used, distillation requires several hours. The checkers used a hot flame, about 13 cm in length, from a gas–air torch. In this way, the distillation requires only about 15 min. Distillation is discontinued when colored vapors appear.
 14. The checkers distilled crude lactone acid obtained in approximately quantitative yield (259 g). When this material was used, distillation of 100-g portions gave 64.3–66.4 g (65–66% yield).
 15. The submitters report that recrystallization from ethyl acetate–petroleum ether raises the melting point to 73°C. The product obtained is analytically pure, $[\alpha]_D^{21} + 16^\circ$ (EtOH, *c* 2). When the checkers used ethyl acetate–petroleum ether they often obtained an oily product.
- The spectrum of the lactone acid is as follows: ¹H NMR (CD₃COCD₃) δ: 2.1–2.9 (m, 4 H), 4.85–5.15 (m, 1 H), 5.1 (s, 1 H, COOH).

3. Discussion

The (*S*)-(+)- γ -butyrolactone- γ -carboxylic acid is a useful intermediate for the synthesis of pheromones,⁴ natural lignans,⁵ and other derivatives.⁶ In the same manner, but starting with *D*-glutamic acid, the (*R*)-(-)-lactone acid may be prepared.⁷ Lactonization occurs with full retention of configuration at the chiral center.^{8,9} Recently, authors have described an efficient method that allows the formation of derivatives of the (*R*)-(-)-lactone from the more available (*S*)-(+)-counterpart.¹⁰

The procedure is a detailed description of the Austin–Howard preparation.² The mechanism presumably involves anchimeric assistance of the carboxy group in decomposition of an intermediate diazonium ion, leading to a labile α -lactone:⁴



The title compound has also been prepared¹¹ using hydrochloric acid instead of sulfuric acid, and ethyl acetate instead of acetone. In the hands of the submitters, this procedure gave a lower yield.

References and Notes

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

petroleum ether

sulfuric acid (7664-93-9)

hydrochloric acid,
HCl (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium nitrite (7632-00-0)

acetone (67-64-1)

Glutamic Acid (56-86-0)

(+)- γ -butyrolactone- γ -carboxylic acid (21461-84-7)

D-Glutamic acid (617-65-2)

(S)-(+)- γ -Butyrolactone- γ -carboxylic acid,
2-Furancarboxylic acid, tetrahydro-5-oxo-, (S)- (53558-93-3)