A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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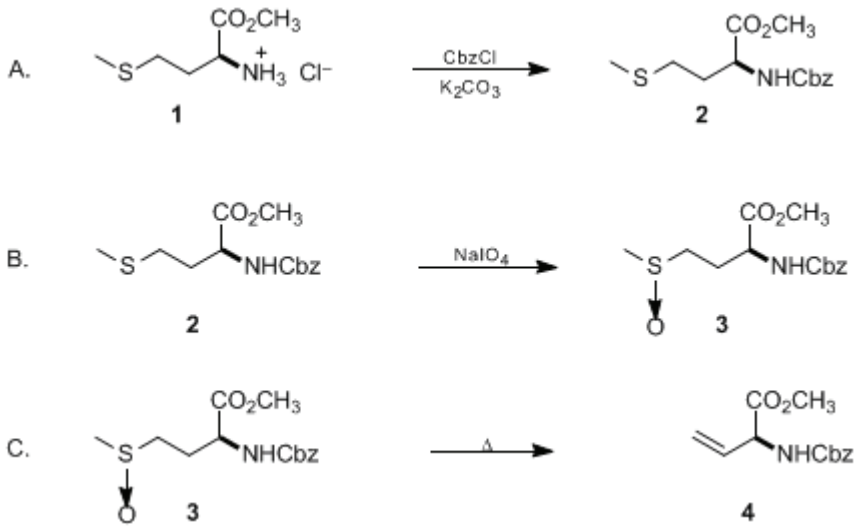
N-(BENZYLOXYCARBONYL)-L-VINYLGLYCINE METHYL ESTER

[3-Butenoic acid, 2-[[(phenylmethoxy)carbonyl]amino]-, methyl ester, (S)-]



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Checked by Antje Grützmann and Ekkehard Winterfeldt.

1. Procedure

A. *N-(Benzyloxycarbonyl)-L-methionine methyl ester* **(2)**. A 3-L, three-necked, Morton flask equipped with an efficient mechanical stirrer, thermometer, and a dropping funnel is charged with L-methionine methyl ester hydrochloride (117.6 g, 0.56 mol) (Note 1), potassium bicarbonate (282.3 g, 2.82 mol, 500 mol %), water (750 mL), and ether (750 mL), and the solution is cooled to 0°C. Benzyl chloroformate (105 g, 88.6 mL, 0.62 mol, 110 mol %, Aldrich Chemical Company, Inc.) is added dropwise over 1 hr, the cooling bath is removed, and the solution is stirred for 5 hr. Glycine (8.5 g, 0.11 mol, 20 mol %, Aldrich Chemical Company, Inc.) is added (to scavenge excess chloroformate) and the solution is stirred for an additional 18 hr. The organic layer is separated, and the aqueous layer is extracted with ether (2 × 200 mL). The combined organic layers are washed with 0.01 M hydrochloric acid (2 × 500 mL), water (2 × 500 mL), and saturated brine (500 mL), and then dried (Na_2SO_4), filtered, and evaporated on a rotary evaporator. The resulting oil is further dried in a Kugelrohr oven (50°C, 0.1 mm, 12 hr) to leave product **2** as a clear oil that solidifies upon cooling: 165–166 g (98–99%), mp 42–43°C.

B. *Methyl L-2-(benzyloxycarbonylamino)-4-(methylsulfinyl)butanoate* **(3)**. A 5-L, three-necked, Morton flask equipped with an efficient mechanical stirrer, thermometer, and dropping funnel is charged with **2** (166.0 g, 0.56 mol) and methanol (1.5 L), and the solution is cooled to 0°C. A solution of sodium periodate ($NaIO_4$) (131.4 g, 0.61 mol, 110 mol %) in water (2 L) is added dropwise over a period of 1.5 hr. The cooling bath is removed and the mixture is stirred for 18 hr. The product is vacuum-filtered through Celite and divided into two portions. Each portion is extracted with chloroform (6 × 200 mL), washed with water (300 mL) and brine (300 mL), dried (Na_2SO_4), filtered, and evaporated by rotary evaporation (bath temperature <30°C). The resulting oils are combined and further dried in a Kugelrohr oven (30°C, 0.1 mm, 12 hr), yielding the product as a waxy solid: 173.2 g, 99%.

C. *N-(Benzyloxycarbonyl)-L-vinylglycine methyl ester* **(4)**. Sulfoxide **3** (35.0 g, 0.11 mol) and Pyrex helices (35 g) are placed in a 1-L, round-bottomed flask, thoroughly mixed by shaking, and distilled from a preheated rocking Kugelrohr apparatus (195–200°C, 0.1–0.3 mm, 1 hr) into a chilled receiving

flask cooled in powdered dry ice to afford a yellow oil (Note 2) and (Note 3). Low pressure chromatography (LPC) of the crude oil gives the N-protected vinylglycine methyl ester **4** (17.4 g, 62%) of 95% purity (Note 4) and (Note 5). Medium pressure liquid chromatography (MPLC) of the crude oil provides pure **4** in 60% yield from **3** (Note 6). L-Vinylglycine hydrochloride can be obtained from **4** in almost quantitative yield by refluxing in 6 N hydrochloric acid for 1 hr.[2]

2. Notes

1. L-Methionine methyl ester hydrochloride is commercially available (Aldrich Chemical Company, Inc.); however, it is prepared easily as follows: A 3-L, three-necked, Morton flask is equipped with an efficient mechanical stirrer. The flask is charged with L-methionine (100.0 g, 0.67 mol) and methanol (0.7 L), the solution is cooled to 0°C, and hydrogen chloride gas is bubbled through the mixture for 15 min (in about 2 min the solution becomes homogeneous). The cooling bath is removed, the solution is stirred for 18 hr, and the solvent is evaporated. Further drying under reduced pressure gives L-methionine methyl ester hydrochloride as a white solid (132.5 g, 99%), that is suitable for most purposes. It can be recrystallized by dissolving in hot methanol (500 mL) and precipitating with ether (1 L) to give the pure hydrochloride: 117.6 g, 88%, mp 152–153°C.
2. *Caution: Stench. The entire reaction apparatus—Kugelrohr oven, vacuum pump, and subsequent chromatography—should be kept in an efficient fume hood.*
3. TLC of the distillate shows **4** (2/1, hexanes/ethyl acetate; visualization by staining with 5% ethanolic molybdophosphoric acid and charring) as the major product (R_f 0.37) along with minor amounts of the (E)- and (Z)-α,β-unsaturated isomer (R_f 0.40 and 0.30).
4. LPC conditions are as follows: 9-cm diameter column; 800 mL of 230–400 mesh EM Science silica gel; 4/1, hexanes/ethyl acetate (1.8 L) to 2/1, hexanes/ethyl acetate.
5. The ^{1}H NMR spectrum of **4** is as follows: ($CDCl_3$) δ: 3.77 (s, 3 H, CO_2CH_3), 4.94 (m, 1 H, α-H), 5.13 (s, 2 H, CH_2PH), 5.28 (dd, 1 H, J = 1.2, 10.3, H_{cis}), 5.36 (dd, 1 H, J = 1.4, 17.1, H_{trans}), 5.47 (bd, 1 H, NH), 5.91 (m, 1 H, H_{vinyl}), 7.35 (s, 5 H, ArH).
6. MPLC conditions are as follows: 40 cm × 6-cm column; 230–400 mesh EM Science silica gel; flow rate 18 mL/min; model 153 Altex UV Detector; retention time ca. 100 min; 4/1, hexanes/ethyl acetate. The distillate was chromatographed in 2.5-g batches. The checkers experienced significant losses in this step, which may be highly sensitive to the type of silica and the apparatus used. In any case the material obtained after the first chromatography will be acceptable for most purposes.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Vinylglycine is a natural amino acid found in mushrooms.[3] It is an inhibitor of pyridoxal-linked aspartate aminotransferase,[4] [5] and has also been postulated as an intermediate in the enzymatic conversion of homoserine to threonine[6] and α-ketobutyrate.[7] Protected vinylglycine is also a versatile asymmetric starting material for synthesis.[8] Variants have been prepared in racemic,[9,10,11,12,13,14] optically active,[15] optically pure,[2,16,17,18] and isotopically labeled form.[5,19,20,21] This procedure is derived from our earlier publication[2] and contains improvements in procedure and scale-up.

References and Notes

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

silica

hexanes

brine

hydrogen chloride,
hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

Glycine (513-29-1)

L-Methionine (63-68-3)

benzyl chloroformate (501-53-1)

threonine (72-19-5)

potassium bicarbonate (298-14-6)

Sodium periodate (7790-28-5)

Molybdophosphoric acid (51429-74-4)

N-(Benzyloxycarbonyl)-L-vinylglycine methyl ester

3-Butenoic acid, 2-[[(phenylmethoxy)carbonyl]amino]-, methyl ester, (S)- (75266-40-9)

N-(Benzyloxycarbonyl)-L-methionine methyl ester (56762-93-7)

L-methionine methyl ester hydrochloride (2491-18-1)

Methyl L-2-(benzyloxycarbonylamino)-4-(methylsulfinyl)butanoate

L-Vinylglycine hydrochloride

Vinylglycine

homoserine (672-15-1)

α-ketobutyrate