A Facile Synthesis of (*S*)-Isoserine from (*S*)-Malic Acid

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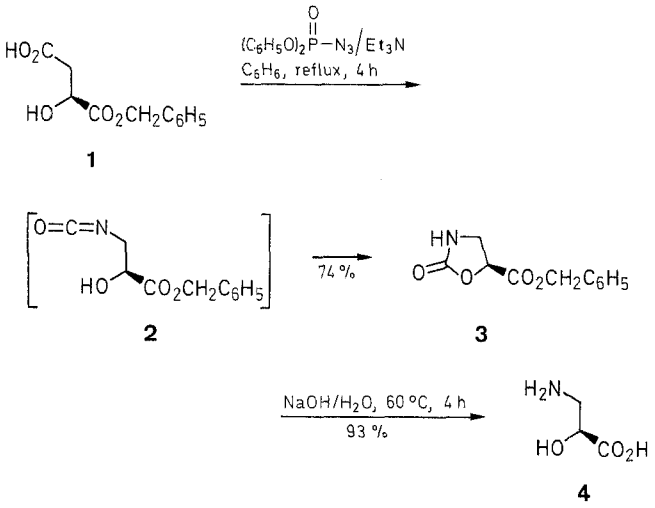
Reaction of (*S*)-malic acid 1-monobenzyl ester with diphenoxyphosphoryl azide in the presence of triethylamine gives benzyl (*S*)-2-oxooxazolidine-5-carboxylate, which is readily converted into (*S*)-isoserine by alkaline hydrolysis.

(*S*)-Isoserine [**4**; (*S*)-3-amino-2-hydroxypropanoic acid] is important and valuable not only as a constituent amino acid of biologically active peptides such as edeines[1] and tatumine,[2] but also as a useful component for the synthesis of β-lactam systems.[3] Several preparations of optically pure isoserine have been reported; they use chemical conversions from glucoses,[4] amino sugars,[5] or L-β-malamidic acid[6,7] as starting materials. We now report a new facile synthesis of (*S*)-isoserine (**4**) using easily available (*S*)-malic acid.

(*S*)-Malic acid 1-monobenzylester (**1**)[8] was treated with diphenoxyphosphoryl azide (DPPA) and triethylamine in boiling benzene to give benzyl (*S*)-2-oxooxazolidine-5-carboxylate (**3**) in 74% yield. In the first step of this reaction, compound **1** reacts with DPPA to afford the corresponding azide followed by a Curtius rearrangement[9] to give the isocyanate **2**, which undergoes spontaneous conversion into a cyclic carbamate **3** via intramolecular attack of the hydroxy group. The carbamate **3** can be hydrolyzed with aqueous sodium hydroxide to afford (*S*)-isoserine (**4**) without racemization and in high yield, whereas hydrolysis of **3** with hydrochloric acid does not give the desired result.



All melting points were measured with a Yamato MP-21 melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 243 polarimeter. IR spectra were determined on a Shimadzu IR-420 spectrophotometer. ^{1}H-NMR spectra were recorded on a Hitachi R-40 (90 MHz) spectrometer.

Benzyl (*S*)-2-Oxooxazolidine-5-carboxylate (3):

A solution of (*S*)-malic acid 1-monobenzyl ester[8] (**1**; 39.8 g, 0.179 mol) diphenoxyphosphoryl azide (53.9 g, 0.196 mol), and Et_3N (20.7 g, 0.205 mol) in dry benzene (600 mL) is heated under reflux for 4 h. The volatile materials are then removed under reduced pressure, H_2O (200 mL) is added to the residue, and this mixture is extracted with EtOAc (3 × 100 mL). The combined extracts are washed with saturated $NaHCO_3$ solution (2 × 70 mL) and dried ($MgSO_4$). The solvent is removed under reduced pressure and the residual solid is triturated with *i*-Pr_2O/MeOH (4:1). The crude product is collected by suction and recrystallized from EtOAc/*i*-Pr_2O; yield: 29.0 g (74%); mp 128–130 °C; $[\alpha]_D^{20}$ +3.6° (*c* = 1.0, DMF).

$C_{11}H_{11}NO_4$	calc.	C 59.72	H 5.01	N 6.33
(221.2)	found	59.73	4.80	6.35

IR (Nujol): ν = 3280, 1750, 1725 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ = 3.42 (dd, 1 H, *J* = 9, 6 Hz, H-4); 3.72 (t, 1 H, *J* = 9 Hz, H-4); 5.0–5.3 (m, 1 H, H-5); 5.10 (s, 2 H, $C_6H_5CH_2$); 7.22 (s, 5 H_{arom}); 7.63 (br, 1 H, NH).

(*S*)-Isoserine (4):

A solution of ester **3** (1.52 g, 6.9 mmol) in 3 *N* aqueous NaOH (20 mL) + MeOH (5 mL) is stirred at 60 °C for 4 h. Then, MeOH is evaporated under reduced pressure. The residual aqueous solution is charged on a column of Dowex 50W-X8 (H^+, 60 mL) and the column is washed with H_2O (200 mL). Elution with 5% aqueous NH_3 affords a fraction containing (*S*)-isoserine. This fraction is evaporated under reduced pressure and the residual solid is recrystallized from MeOH/H_2O (4:1) to afford **4**; yield: 0.67 g (93%); mp 194–196 °C; $[\alpha]_D^{20}$ −33.5° (*c* = 1.0, H_2O) [Lit.[7] mp 188–190 °C; $[\alpha]_D^{20}$ −32.2° (*c* = 1.0, H_2O)].

$C_3H_7NO_3$	calc.	C 34.28	H 6.72	N 13.33
(105.1)	found	34.21	6.82	13.18

IR (KBr): ν = 3400, 3050, 1620 cm^{-1}.

^{1}H-NMR (D_2O): δ = 2.97 (dd, 1 H, *J* = 14, 9 Hz, H-3); 3.23 (dd, 1 H, *J* = 14, 5 Hz, H-2); 4.30 (dd, 1 H, *J* = 9, 5 Hz), H-2).

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