O-Benzyl-N-*t*-butyloxycarbonyl-L-serine[1]

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In solid-phase peptide synthesis, it is desirable to incorporate both serine and threonine as their O-benzyl-N-acyloxycarbonyl derivatives.[3] Recently, a simple method for preparing O-benzyl-N-*t*-butyloxycarbonyl-L-threonine was reported.[4] On the other hand, methods for preparing O-benzyl-N-*t*-butyloxycarbonyl-L-serine are very laborious.[5,6] The present study reports a simple two-step synthesis of O-benzyl-N-*t*-butyloxycarbonyl-L-serine from L-serine.

O-Benzyl-N-*t*-butyloxycarbonyl-L-serine was obtained directly from the readily available N-*t*-butyloxycarbonyl-L-serine[7] by treatment of the latter compound, in anhydrous liquid ammonia, first with sodium metal and then with benzyl bromide. No detectable racemization was observed. By use of column chromatography for purification, it was possible to recover optically pure N-*t*-butyloxycarbonyl-L-serine for subsequent preparations. No ester was detected in the reaction mixture.

When the same procedure was applied to the synthesis of O-benzyl-N-*t*-butyloxycarbonyl-L-threonine, the maximum yield of this substance from N-*t*-butyloxycarbonyl-L-threonine was 6%.

Experimental Section[8]

O-Benzyl-N-*t*-butyloxycarbonyl-L-serine.—Freshly cut sodium metal (920 mg, 40 mg-atoms) was added to freshly distilled anhydrous ammonia (120 ml) at −70°, and N-*t*-butyloxycarbonyl-L-serine[7] (4.2 g, 20 mmol) was added with stirring under nitrogen. The mixture was vigorously stirred until colorless and then sodium metal (*ca.* 5 mmol) was added, followed by benzyl bromide (3.72 ml, 31 mmol). The turbid solution was stirred for 30–60 min at −50 to −30° to give a clear solution. The ammonia was then removed by slow evaporation and lyophilized. The residue was dissolved in distilled water (20 ml), and the solution was extracted with ether (two 20-ml portions). The aqueous phase was chilled, acidified to pH 3.5 with solid citric acid, saturated with sodium chloride, and extracted with ethyl acetate (four 100-ml portions). The combined organic layers were washed with saturated sodium chloride solution (three 35-ml portions) and dried over anhydrous sodium sulfate. The ethyl acetate was removed *in vacuo* at room temperature to give a colorless oil. The oil was dissolved in chloroform (8 ml), placed on a 3 × 45 cm column of silicic acid (150 g, Baker Analyzed), and eluted with chloroform (800 ml). The chloroform was evaporated *in vacuo* to give O-benzyl-N-*t*-butyloxycarbonyl-L-serine as a clear oil (2.7 g, 45%). Further elutions with methanol yielded 2.7 g of a mixture of N-*t*-butyloxycarbonyl-L-serine and traces of O-benzyl-N-*t*-butyloxycarbonyl-L-serine as an oil. Thin layer chromatography of the oils on silica gel plates in solvent system A against standard reference samples indicated the above structural assignments. An analytical sample of the O-benzyl-N-*t*-butyloxycarbonyl-L-serine was prepared by crystallization of the oil from ether–petroleum ether (bp 30–60°) and a recrystallization from the same solvent mixture: mp 56–58°; $[\alpha]^{25}D$ +19.8° (*c* 2.0, 80% EtOH) [lit.[9] mp 54–63°; $[\alpha]^{25}D$ +20.3° (*c* 2, 80% EtOH)].

Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.12; H, 7.19; N, 4.70.

Recrystallization of the oil from the methanol elution yielded optically pure starting material: mp 86–90°; $[\alpha]^{25}D$ −7.3° (*c* 2.29, 8% EtOH) [lit. mp 84°;[7] $[\alpha]^{25}D$ −7.7°[9] (*c* 2, 8% EtOH)].

Demonstration of Steric Purity.—An aliquot of O-benzyl-N-*t*-butyloxycarbonyl-L-serine prepared by the above procedure was dissolved in 5.4 *N* HBr–HOAc (2 ml). After 1 hr at room temperature, the reaction mixture was evaporated under water aspirator pressure at 20° to yield a residue which was then diluted to 5 ml with 1 *N* HCl for optical rotation determination. This sample showed the same optical rotation as a sample of L-serine similarly treated, $[\alpha]^{25}D$ +14° (*c* 2.1, 1 *N* HCl).

Registry No.—O-Benzyl-N-*t*-butyloxycarbonyl-L-serine, 23578-14-5.

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Preparation of 2-Acetamido-2-deoxy-α-glycopyranosides. II[1]

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Notwithstanding the marked influence of temperature on the anomeric equilibrium of glycosides of glucosamine and galactosamine,[2] a single product, phenyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-mannopyranoside (**1**),[3] is found to predominate in condensation of mannosamine pentaacetate with phenol, at 150 or 125° with catalysis by zinc chloride, or at 100° with *p*-toluenesulfonic acid. The β anomer (**2**), not reported previously, is isolable in small amount from all three reaction mixtures. A similar preference for formation of the α glycoside has been observed in analogous reactions of mannose derivatives.[4] Formulation of **1** as the α pyranoside[3] was confirmed by nmr studies.[5] The present formulation of **1** and **2** and the derived phenyl 2-acetamido-2-deoxy-α- and -β-D-mannopyranosides (**3** and **4**) as anomeric pairs of pyranosides is supported by their optical-rotation data and by their resistance to acid hydrolysis. For the glycosides **3** and **4**, the value of 2*A* ($\Delta[M]D$) is 43,800; for their tri-O-acetyl esters **1** and **2**, 2*A* is 60,500. For comparison, 2*A* is 47,400 for the phenyl α- and -β-D-mannopyranosides and 58,000 for their tetraacetyl esters.[4] A parallel correspondence has been noted for the glycosides of

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