A Facile Synthesis of N^2-Protected L-2,3-Diaminopropanoic Acid

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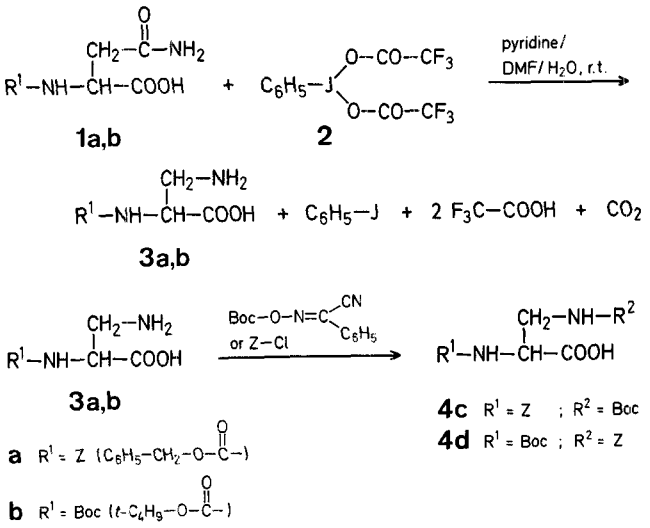
L-2,3-Diaminopropanoic acid (L-A_2pr) is a constituent amino acid of some peptide antibiotics: edeines[1], tuberactinomycins[2], and clinically useful bleomycins[3]. For the synthesis of these antibiotics or peptides containing L-2,3-diaminopropanoic acid, N^2-protected L-A_2pr **(3)**, N^3-protected L-A_2pr, and $N^{2,3}$-protected L-A_2pr **(4)** are important building blocks. Among them, N^2-benzyloxycarbonyl-L-A_2pr **(3a)**, N^2-benzyloxycarbonyl-N^3-*t*-butoxycarbonyl-L-A_2pr **(4c)** and N^2-*t*-butoxycarbonyl-N^3-benzyloxycarbonyl-L-A_2pr **(4d)** have been most widely used[4-7]. However, the syntheses of **3** and **4** are tedious compared with the easy accessibility of *N*-protected derivatives of other higher diamino acids such as L-2,4-diaminobutanoic acid, L-ornithine, and L-lysine. For example, compound **3a** has been prepared from L-serine methyl ester[4], compound **4c** from N^2-tosyl-L-asparagine via Hofmann rearrangement[4], and compound **4d** from L-aspartic acid via Schmidt reaction[6], each by a four-step sequence. Recently, the direct conversion of amides to amines with bis[trifluoroacetoxy]-phenyliodine **(2)** has been reported[8]. We describe here a convenient one-step synthesis of **3** from commercially available compounds **1**, e.g., from N^2-benzyloxycarbonyl- **(1a)** or N^2-*t*-butoxycarbonyl-L-asparagine **(1b)**, using **2** under mild conditions, and the subsequent preparation of **4**. The benzyloxycarbonyl and *t*-butoxycarbonyl groups were selected for *N*-protection in **3** and **4**.



The effect of some solvents on the reaction **(1a→3a)** at room temperature was studied (Table 1). Use of a mixture of dimethylformamide and water (1/1, by volume) gave the best yield of **3a**. We also found that the addition of pyridine may accelerate the reaction (Table 1).

Convenient standard conditions for the reaction **1→3** are described in the procedure for the synthesis of **3a**. Compounds **3** were thus obtained in good yields (Table 2). Treatment of **3a** with 2-(*t*-butoxycarbonyloxyimino)-2-phenylacetonitrile[9], and of **3b** with benzyloxycarbonyl chloride[4] in the usual manner gave the diprotected diamino acids **4c** and **4d**, respectively (Table 2). Crystalline dicyclohexylammonium salts of **4a** and **4b** were also prepared.

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Table 1. Effect of Solvent in the Preparation of N^2-Benzyloxycarbonyl-L-A_2pr (**3a**)[a]

Solvent (v/v)	Reaction time [h]	Yield[b] [%]
Dioxane/H_2O 1:1	24	42
DMF/acetonitrile/H_2O 1:1:1	24	57
DMF/H_2O 1:1	24	62
DMF/H_2O 1:1[c]	2	63

[a] Molar ratio of starting **1a** and **2** was 1:1.5.
[b] Yield was based on product isolated after batchwise treatment with Dowex 50 × 8 ($H^{\oplus}$ form) and one recrystallization from water/ethanol.
[c] Pyridine (2 equiv for **1a**) was added.

In a similar manner, N^2-*t*-butoxycarbonyl-L-2,3-diaminopropanoic acid (**3b**) is prepared from N^2-*t*-butoxycarbonyl-L-asparagine (**1b**) (see Table 2).

N^2-Benzyloxycarbonyl-N^3-*t*-butoxycarbonyl-L-2,3-diaminopropanoic Acid (4c):

Crude **3a** obtained above is directly treated with 2-(*t*-butoxycarbonyloxyimino)-2-phenylacetonitrile in dioxane/water (1:1 v/v) in the presence of triethylamine according to the published procedure[9]. Crystallization from ethyl acetate/ether/petroleum ether affords **4c**; yield: 87%; m.p. 144–146 °C.

Compound **4c** is converted to the *dicyclohexylammonium salt* by the addition of dicyclohexylamine (1.2 equiv) to its solution in ethanol. After evaporation of the solvent, the salt is crystallized from ethanol/ether/petroleum ether; yield: 76%; m.p. 191–192 °C.

Table 2. Preparation of N^2-Protected L-A_2pr (**3**) and $N^{2,3}$-Protected L-A_2pr (**4**)

Product	Yield[a] [%]	R_f[b]	m.p. [°C] found	m.p. [°C] reported or Molecular formula	$[\alpha]_D^{20}$	$[\alpha]_D^{22-25}$ reported
3a	84	0.59	228–230° (dec)	240–241° (dec)[10]	−7.8° (*c* 0.4, 1 normal NaOH)	−7.4 (*c* 0.4, 1 normal NaOH)[10]
3b	60	0.60	198–200° (dec)	$C_8H_{16}N_2O_4$[c] (204.2)	−2.7° (*c* 1, AcOH)	—
4c[d]	87	0.76	144–146°	145–148°[4]	−9.3° (*c* 1, methanol)	−9.5° (*c* 1, methanol)[4]
4d[d]	42	0.76	oil	oil[6]	—	—
4c·DCHA[e]	76	0.82	191–192°	194–195°[11]	+7.1° (*c* 1, methanol)	+0.5° (*c* 4, methanol)[11]
4d·DCHA[e,f]	38	0.82	177–178°	$C_{28}H_{45}N_3O_6$[c] (519.7)	+9.8° (*c* 1, methanol)	—

[a] Yield of isolated products based on **1**.
[b] T.L.C. was run on silica gel G (Merck) plates using butanol/AcOH/pyridine/H_2O (4:1:1:2 v/v) as eluent.
[c] The products gave satisfactory microanalyses: C, ±0.05; H, ±0.05, N, ±0.12.
[d] The product was obtained by direct N^3-acylation of crude **3**.
[e] Dicyclohexyammonium salts.
[f] The product was prepared from L-aspartic acid by the known method[6]; m.p. 176–178 °C; $[\alpha]_D^{20}$: +9.7° (*c* 1, methanol).

No racemization takes place during the reaction **1**→**3**, as verified by comparing the $[\alpha]_D$ value of the isolated hydrochloride of A_2pr after deprotection of **3a** or **3b** with the reported value for the hydrochloride of L-A_2pr[12].

The advantages of the procedure described here over currently used methods are the ready availability of starting materials, the avoidance of dangerous reagents and tedious reaction steps[4,6], and the convenience in product work-up. The *N*-protected L-A_2pr **3** and **4** thus obtained may serve as valuable intermediates for the synthesis not only of antibiotics containing A_2pr but also of an A_2pr-containing peptide which may serve as a precursor for the preparation of interesting dehydroalanine peptides[13].

Optical rotation was measured with a Union high-sensitivity polarimeter PM-71. N^2-Benzyloxycarbonyl-L-asparagine (**1a**) and N^2-*t*-butoxycarbonyl-L-asparagine (**1b**) were obtained from Protein Research Foundation, Osaka, Japan. Bis[trifluoroacetoxy]-phenyliodine (**2**) was prepared according to the procedure reported[8]. Melting points are uncorrected.

N^2-Benzyloxycarbonyl-L-2,3-diaminopropanoic Acid (3a):

To a stirred solution of bis[trifluoroacetoxy]-phenyliodine (**2**; 645 mg, 1.5 mmol) in dimethylformamide/water (8 ml; 1:1 v/v), N^2-benzyloxycarbonyl-L-asparagine (**1a**; 266 mg, 1 mmol) is added at room temperature. After 15 min, pyridine (0.16 ml, 2 mmol) is added, and stirring is continued for 3 h. The solvent is evaporated in vacuo and the residue dissolved in water (10 ml). The solution is washed extensively with ether and concentrated in vacuo to afford crude **3a** which is crystallized from ethanol/ether to give pure **3a**; yield: 201 mg (84%); m.p. 228–230° (dec); $[\alpha]_D^{20}$: −7.8° (*c* 0.4, 1 normal sodium hydroxide).

N^2-*t*-Butoxycarbonyl-N^3-benzyloxycarbonyl-L-2,3-diaminopropanoic Acid (4d):

Crude **3b** is treated with benzyloxycarbonyl chloride in water in the presence of sodium hydrogen carbonate according to the published procedure[4] to give **4d** as an oil; yield: 42%.

Compound **4d** is converted to its *dicyclohexylammonium salt* as described above; yield: 38%; m.p. 177–178 °C.

L-2,3-Diaminopropanoic Acid Hydrochloride:

From **3a**: A solution of **3a** (119 mg, 0.5 mmol) in acetic acid/water (3 ml; 1:1 v/v) is hydrogenated for 3 h in the presence of palladium black. The filtrate is evaporated, the residue dissolved in water containing 1 normal hydrochloric acid (0.5 ml), and the pH of the solution adjusted to 7 with triethylamine. After evaporation of the solvent, the product is crystallized from water/ethanol; yield: 65 mg (93%); m.p. 235–236 °C (dec); $[\alpha]_D^{20}$: +25.1° (*c* 2, 0.5 normal hydrochloric acid); Ref.[12], m.p. 236–237 °C; $[\alpha]_D^{27}$: +25.2° (*c* 2, 0.5 normal hydrochloric acid).

From **3b**: A suspension of **3b** (102 mg, 0.5 mmol) in 3.8 normal hydrogen chloride in dioxane (2 ml) is stirred for 1 h at room temperature, and the solvent is removed in vacuo. The residue is treated as described above to afford the product; yield: 58 mg (83%); m.p. 236–237° (dec); $[\alpha]_D^{20}$: +25.3° (*c* 2, 0.5 normal hydrochloric acid).

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