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Facile Way to Synthesize N^{α}-Boc-N^{β}-Cbz-2,3-Diaminopropionic Acid Derivatives via 5-Oxazolidinone

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Abstract: An economical and facile synthesis of N^{α}-Boc-N^{β}-Cbz-2,3-diaminopropionic acid derivatives is reported. The key aspect of this method is employment of N-Boc-5-oxazolidinone moiety to simultaneously provide proper protection of α-amido and α-carboxyl functional groups and affords the desired isocyanate **5** successfully by a Curtius rearrangement. The obtained intermediate **6** can be readily converted to various derivatives of N^{α}-Boc-N^{β}-Cbz-2,3-diaminopropionic acid by conventional procedure.

Keywords: Curtius rearrangement, 2,3-diaminopropionic acid, isocyanate, 5-oxazolidinone

L-2,3-Diaminopropanoic acid (Dap), a nonproteinogenic amino acid occuring in nature both in its free form and as a constituent of peptides,[1] has been widely used in the construction of medicinally important entities.[2] Thus, much effort has been directed toward the synthesis of it and its derivatives in recent years, and several new synthetic methodologies have been developed.[3]

The most common synthesis of Dap involves Hoffman[4] or modified Curtius[5] rearrangements of asparagines derivatives and various N-protecting groups (such as Cbz, Ts, Boc) are used. However, these methods, in

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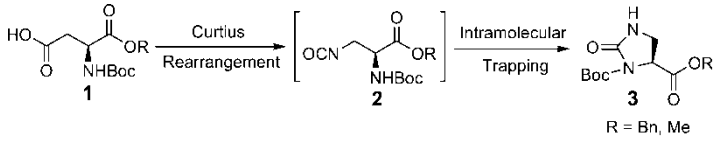
preparation of the derivatives of N^{α}-Boc-Dap, often suffer from low yields[6] or require expensive reagents such as bis-[trifluoroacetoxy]-iodo benzene[5,6] or diphenyl phosphorazidate (DPPA).[7a]

Here, we report an economical and facile way to synthesize the derivatives of N^{α}-Boc-Dap from Boc-L-aspartic acid. Synthetic analysis suggests that the isocyanate **2** from the L-aspartic acid derivative would provide efficient access to N^{α}-Boc-β-aminoalanine alkyl ester. But Boc-Asp-OR cannot afford the expected isocyanate **2**; it directly gives cyclic urea after a Curtius rearrangement (Scheme 1).[7]

To prevent the intermolecular trapping of the isocyanate after the Curtius rearrangement, the strategy of dual Boc-protection of the reactive nitrogen has been put forward, and the desired isocyanate was obtained successfully. This approach, without using bis-[trifluoroacetoxy]-iodo benzene or DPPA, provides a promising synthesis of the N^{β}-Cbz, N^{α}-Boc-Dap.[7b] However, it involves tedious protection and deprotection steps both in the α-carboxyl and α-amino groups. We thought that employment of N-Boc-5-oxazolidinone moiety could provide not only the protection of the α-carboxyl functional group but also the complete protection of the α-amino group. This protection strategy would also avoid the intermolecular trapping and afford the desired isocyanate. Moreover, it would shorten the route greatly.

Starting with Boc-L-aspartic acid, the 5-oxazolidinone **4** was prepared in good yield in benzene by a modification of the literature procedure.[8] We found that if toluene was used a very lower yield was obtained. The procedure for the preparation of compound 4 is as follows: Boc-L-aspartic acid (25 mmol) was dissolved in EtOAc (10 mL); benzene (200 mL) was added. The powder paraformaldehyde (50 mmol) and *p*-TsOH (1.5 mmol) were added slowly at about 60°C. Then the mixture was refluxed 2 h with removal of water by a Dean–Stark trap. EtOAc (100 mL) was added; the solution was washed with 0.3 M K_2CO_3 (2.5 mL) and brine (2 × 10 mL) and dried with Na_2SO_4. The solvent was evaporated to give a light yellow solid (4.4 g) in 72% yield. Recrystallization from anhydrous ether provided a sample for analytical characterization. Mp = 132–134°C; $[\alpha]_D^{20}$ +153.1 (c = 1, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.49 (s, 9H), 3.03–3.27 (m, 2H), 4.31 (s, 1H), 5.24 (d, 2H, J = 3), 5.45 (br, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 28.59, 34.70, 51.68, 78.84, 82.92, 152.24, 172.12, 175.26. MS: m/z = 284 $[M + K]^+$. Anal. calcd. for $C_{10}H_{15}NO_6$: C, 48.98; H, 6.17; N, 5.71. Found: C, 49.14; H, 6.39; N, 5.48.

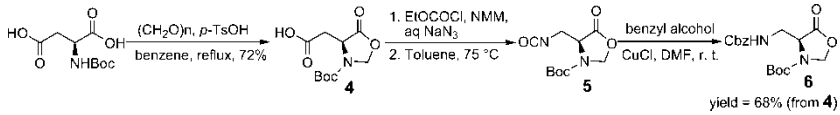


Scheme 1.

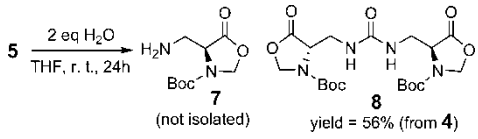
The 4-carboxylic acid was activated with ethyl chloroformate and N-methylmorpholine (NMM) in dry THF, followed by addition of aqueous sodium azide to afford the acyl azide (strong absorption at 2145 cm^{-1} in IR). Then the acyl azide was converted to isocyanate **5** (strong absorption at 2223–2255 cm^{-1} in IR) successfully in toluene at 75°C.[9] The procedure for the preparation of isocyanate 5:is as follows: 4 (10 mmol) was dissolved in dry THF (30 mL) and cooled to −15°C. After addition of EtOCOCl (11 mmol) and NMM (12 mmol), the mixture was stirred for 20 min. A solution of NaN_3 (25 mmol) in H_2O (5 mL) was added, and stirring continued for 1 h at −10°C. The solution was then diluted with water and extracted with EtOAc (150 mL). The organic layers were washed with brine (2 × 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give crude acyl azide. This crude acyl azide can be further purified by a flash-column chromatography (petroleum ether/EtOAc, 2:1, $R_f = 0.7$). Purified acyl azide was dissolved in toluene (30 mL), and the resulting solution was heated to 75°C under stirring. After the gas evolution had stopped, the toluene was removed under reduced pressure to afford isocyanate **5** as clear oil.

This isocyanate **5** was directly used in the next step without further purification. This isocyanate reacted with benzyl alcohol in the presence of CuCl in dry DMF to lead to the important intermediate **6**[10] (Scheme 2). The procedure for the preparation of compound 6. To a stirred green mixture of benzyl alcohol (9 mmol) CuCl (9 mmol), is as follows: and dry DMF (6 mL) at room temperature, a solution of isocyanate **5** in dry DMF (4 mL) was added. The solution was diluted with 1 N HCl (20 mL) after stirring for 3 h, then it was extracted with EtOAc (4 × 40 mL), washed with brine (3 × 20 mL), dried (Na_2SO_4), concentrated, and purified by column chromatography (petroleum ether/EtOAc, 4:1, $R_f = 0.3$) to afford a white solid (2.4 g) in 68% yield from compound **4**. Mp = 83–84°C; $[\alpha]_D^{20}$ +92.2 (c = 1, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.57$ (s, 9H), 3.75–3.88 (m, 2H), 4.31 (s, 1H), 5.11–5.21 (m, 4H), 5.42 (br, 1H), 7.39 (s, 5H). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 29.10$, 41.94, 55.98, 67.60, 78.73, 83.01, 128.23, 128.56, 136.19, 151.80, 156.13, 170.93. MS: m/z = 350 [M^+]. Anal. calcd. for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33; N, 8.00. Found: C, 58.46; H, 6.59; N, 8.24.

Directly reacting **5** with water in THF at room temperature did not give free β-amino **7**; ^1H NMR and electrospary MS indicated the isolated product was a symmetrical urea **8** (Scheme 3).



Scheme 2.



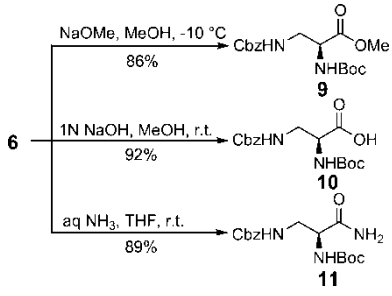
Scheme 3.

Compound **6**, containing the 5-oxazolidinone moiety, can undergo a ring-opening reaction in different alkaline conditions to afford corresponding N^{α}-Boc-N^{β}-Cbz-Dap derivatives in high yields. For example, when it was treated with NaOMe in MeOH at $-10^{\circ}C$,[8a] methyl ester **9** was obtained in 86% yield. Direct saponification of it with 1 N NaOH in MeOH at room temperature[11] afforded carboxylic acid **10**; opening the ring by aqueous ammonia[12] in THF provided carboxamide **11** (Scheme 4).

The procedure for the preparation of compound 9 is as follows: Na (80 mg) was added to anhydrous MeOH (32 mL) at $-10^{\circ}C$ with stirring. Compounds **6** (1.5 mmol) was added when Na was disappeared. After stirring for 1.5 h at this temperature, the solution was diluted with EtOAc (80 mL), 1 N HCl (5 mL), and brine (20 mL). The organic layer was washed with brine (2×10 mL), dried (Na_2SO_4), concentrated, and purified by column chromatography (petroleum ether/EtOAc, 2 : 1, $R_f = 0.4$) to afford a clear oil (0.45 g) in 86% yield. $[\alpha]_D^{20}$ -9.0 (c = 1, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.41$ (s, 9H), 3.52–3.58 (m, 2H), 3.69 (s, 3H), 4.34 (s, 1H), 5.05 (s, 2H), 5.43 (br, 1H), 5.60 (br, 1H), 7.29 (s, 5H). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 29.13$, 43.45, 53.21, 54.74, 67.39, 80.50, 128.09, 128.47, 136.26, 155.36, 156.66, 171.00. MS: $m/z = 352$ [M^+]. Anal. calcd. for $C_{17}H_{24}N_2O_6$: C, 57.94; H, 6.86; N, 7.95. Found: C, 57.71; H, 7.02; N, 8.07.

Selective removal of Cbz-protecting group of compounds 9–11 via hydrogenolysis (H_2-Pd/C) can afford the corresponding free β-amino in quantitative yield.[4,7b]

In conclusion, we have developed an economical and facile way to prepare the derivatives of N^{α}-Boc-Dap. The key aspect of this method is



Scheme 4.

employment of N-Boc-5-oxazolidinone moiety to provide a proper protection of the α-amino group and successfully affords the desired isocyanate by a Curtius rearrangement. The advantages over previous approaches are a shorter route by choosing the proper protection strategy, no costly reagents, a conventional procedure, and of good yields.

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