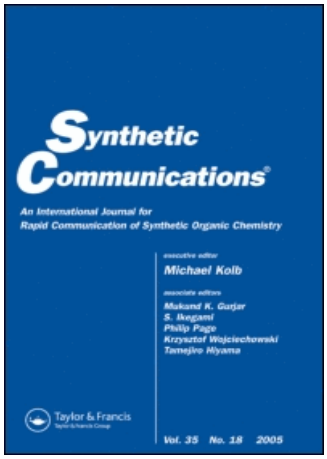

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Selective Mono-BOC Protection of Diamines

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Abstract: A facile route for mono-BOC protection of symmetrical and unsymmetrical diamines was developed by sequential additions of 1 mol of HCl and 1 mol of $(BOC)_2O$ followed by neutralization.

Keywords: diamine, mono-BOC, protection

Monofunctionalization of symmetrical or unsymmetrical diamines is an essential step for the synthesis of biologically important pharmacores and materials.[1–7] Recent progress on chemical and biological chip production requires monofunctionalized diamines to hold functional molecules at the one end while the other end is free to be attached on the solid surface.[8–10] Therefore, a facile and large-scale synthetic method is urgent for the preparation of monoprotected diamine.[11–22] Among the various amine protecting groups, BOC is the most popular, and its protected form is normally in a good physical state to be handled for the next reaction.[19] Herein we report a facile route for mono-BOC protection of symmetrical and unsymmetrical diamines whose procedure is cost-efficient and applicable to a multigram scale.

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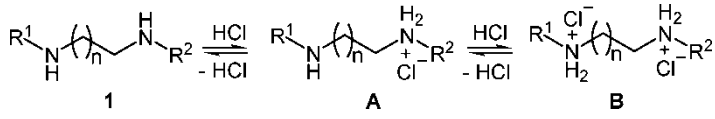


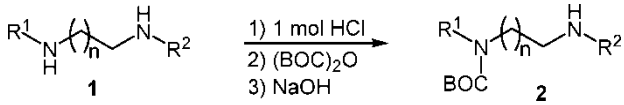
Scheme 1.

Two amine groups are differentiated as an acid salt and a free base, which is ready for further functionalization. One mole of hydrogen chloride was added to one molecule of a diamine bearing two basic amino groups in 50% aqueous methanol. The solution was stirred for 30 min to reach full equilibrium. Three different species would possibly exist including starting diamine **1** with two free amines, **A** as one free amine and one HCl salt, and **B** with two amine salts in aqueous methanol. Among them, **A** would be dominant in the solution after complete equilibrium (Scheme 1).

Addition of 1 mol of $(BOC)_2O$ into this solution would lead to the reaction of the free amine in the dominant species **A** to yield mono-BOC-protected diamine. This procedure was proven to be highly efficient with good yields compared to the conventional method that requires tight control of the substrate concentration and very slow addition of the $(BOC)_2O$ solution for a long time to prevent di-BOC formation.[14,20–22] After the reaction was completed, MeOH was evaporated and diethyl ether was added to remove unreacted diamine. Then NaOH solution was added to let one HCl amine salt free. The reaction product was extracted by organic solvent. This procedure is applicable to various diamines **1** to give mono-BOC-protected diamines **2** without tedious chromatographic procedure in high yield (Scheme 2).

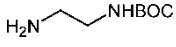
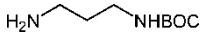
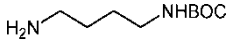
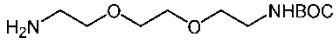
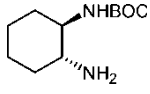
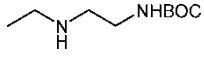
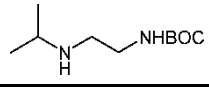
We have found that this was good for producing mono-BOC-protected diamines on a scale of several hundred grams, which is exemplified in Table 1. Acyclic symmetric diamines **1a**–**1d** yielded the expected products **2a**–**2d** in 65–87% yields. This worked for the cyclic diamine **1e** to provide the mono-BOC product **2e** in 80% yield. This procedure was also good for unsymmetric diamine substrates, **1f** and **1g**, to yield mon-BOC products, **2f** and **2g**, in 72 and 95% yields, respectively.

In conclusion, we developed a facile route for mono-BOC protection of symmetrical and unsymmetrical diamines by sequential additions of 1 mol of HCl and 1 mol of $(BOC)_2O$ followed by neutralization.



Scheme 2.

Table 1. Mono-BOC protection of diamines

Diamines	Products	Yield (%) [a,b]
1a		87 [12,14]
1b		75 [12,14]
1c		65 [12,14]
1d		74 [9]
1e		80
1f		72
1g		95

[a]All products characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry.
[b]Isolated yields after neutralization.

EXPERIMENTAL

General Procedure (for 2a)

To the solution of 150 mL of MeOH with cooling at 0°C, HCl gas (17 g) was added with stirring for 15 min. The mixture was stirred for 15 min at rt and was carefully added to ethylenediamine (28 g, 0.466 mol) at 0°C. The mixture was stirred for 15 min at room temperature before adding 50 mL of H_2O and stirring for another 0.5 h. To the solution $(BOC)_2O$ (101 g, 0.466 mol) in 200 mL of MeOH was added at room temperature for 10 min, and the resultant solution was stirred for 1 h. (A little better yield would be obtained by adding 1.5 mol equivalents of $(BOC)_2O$.) The mixture was concentrated in vacuo. Unreacted diamine was removed by diethyl ether (300 mL × 2). The residue was treated with 2 N NaOH (500 mL) solution. The product in the organic layer was extracted with CH_2Cl_2 (300 mL × 3). The combined extracts were washed with 300 mL of brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to yield 64.6 g (87%) of mono-BOC product as a colorless oil with more than 97% purity by HPLC.

Data

2a. Oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.92 (br s, 2H), 2.80 (t, $J = 6.0$ Hz, 2H), 3.14–3.19 (q, $J = 6.0$ Hz, 2H), 5.13 (br s, 1H). ^{13}C

NMR ($CDCl_3$, 50.3 MHz) δ 28.5, 41.8, 43.2, 79.2, 156.3. MS (FAB): $m/z = 161.1$ (MH^+).

2b. Oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.57–1.69 (m, 2H), 2.65 (br s, 2H), 2.73 (br s, 2H), 3.14–3.24 (m, 2H), 5.15 (br s, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 28.4, 32.6, 38.2, 39.3, 78.7, 156.2. MS (FAB): $m/z = 175.1$ (MH^+).

2c. Oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.36–1.49 (m, 4H), 2.12 (br s, 2H), 2.65–2.69 (m, 2H), 2.97–3.08 (m, 2H), 4.87 (br s, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 27.4, 28.3, 30.2, 40.5, 41.7, 78.8, 156.1. MS (FAB): $m/z = 189.1$ (MH^+).

2d. Oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.93 (br s, 2H), 2.60 (br s, 2H), 2.94–3.11 (m, 2H), 3.20–3.41 (m, 8H), 5.40 (br s, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 28.3, 40.2, 41.4, 70.7, 73.0, 78.7, 156.0. MS (FAB): $m/z = 248.2$ (MH^+).

2e. Oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.03–1.54 (m, 5H), 1.43 (s, 9H), 1.60–1.69 (m, 2H), 1.85–1.96 (m, 2H), 2.30 (t, $J = 10$ Hz, 1H), 3.00 (t, $J = 9.8$ Hz, 1H), 3.07–3.14 (m, 1H), 4.06 (d, $J = 3.4$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 25.2, 25.3, 28.5, 33.0, 35.2, 55.7, 57.7, 79.3, 156.2. MS (FAB): $m/z = 215.1$ (MH^+).

2f. Oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97–1.08 (m, 3H), 1.38 (s, 9H), 2.51–2.73 (m, 4H), 3.12–3.18 (m, 2H), 5.01 (broad s, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 15.0, 28.2, 40.0, 43.5, 48.9, 78.6, 156.1. MS (FAB): $m/z =$ 189.1 (MH^+).

2g. Oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.01 (d, $J = 6.7$ Hz, 6H), 1.37 (s, 9H), 2.61 (t, J = 6.6 Hz, 2H), 2.78 (sept, $J = 6.0$ Hz, 1H), 2.93 (t, $J = 6.6$ Hz, 2H), 5.62 (broad s, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 22.5, 28.3, 44.5, 48.7, 53.4, 78.5, 156.2. MS (FAB): $m/z = 203.1$ (MH^+).

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