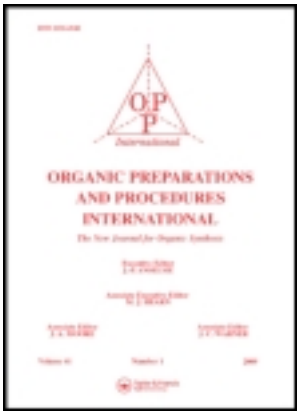

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Preparation of Mono Boc-Protected Unsymmetrical Diamines

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Preparation of Mono *Boc*-Protected Unsymmetrical Diamines

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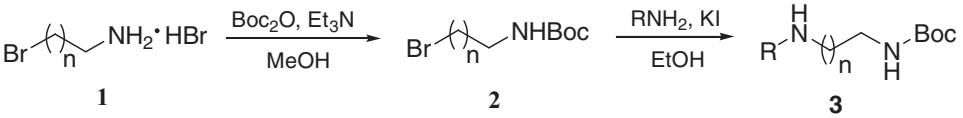
Monofunctionalized unsymmetrical diamines have been frequently used as starting materials in the synthesis of biological active agents and pharmacophores.[1–6] There have been some reports that chemical and biological chip production requires monofunctionalized diamines to hold functional molecules at the one end while the other end is free to be attached on the solid surface,[1,7–9] thus requiring a simple and efficient procedure for the preparation of mono-protected unsymmetrical diamines. Among the large number of protective groups for amino functions, the *tert*-butoxycarbonyl (Boc) group is among the most important,[10] because it can readily be removed with anhydrous hydrogen chloride gas or trifluoroacetic acid. Herein we report a facile synthetic route for preparation of mono-Boc-protected mixed primary-secondary amines by a procedure, which is cost-effective and applicable on a multigram scale (*Schemes 1* and *2*).



1 **2** **3**

n = 1 a) R = CH_3; b) R = CH_2CH_3; c) R = $CH(CH_3)_2$; d) R = $CH_2C_6H_5$
n = 2 e) R = CH_3

Scheme 1

The synthesis of N^1-alkyl-N^2-(Boc)-protected diamines **3a**–**3e** is outlined in *Scheme 1*. Treatment of 2-bromoethylamine hydrobromide (**1a**) or 3-bromopropylamine hydrobromide (**1e**) with Boc_2O and Et_3N in MeOH led to satisfactory yields of the *N*-(Boc)-2-bromo-ethylamine **2a** and *N*-(Boc)-3-bromopropylamine **2e** (85–95%), which were thus treated with excess aliphatic amines to afford **3a**–**3e** (75–82%) in high purity as shown by ^{1}H NMR analysis.

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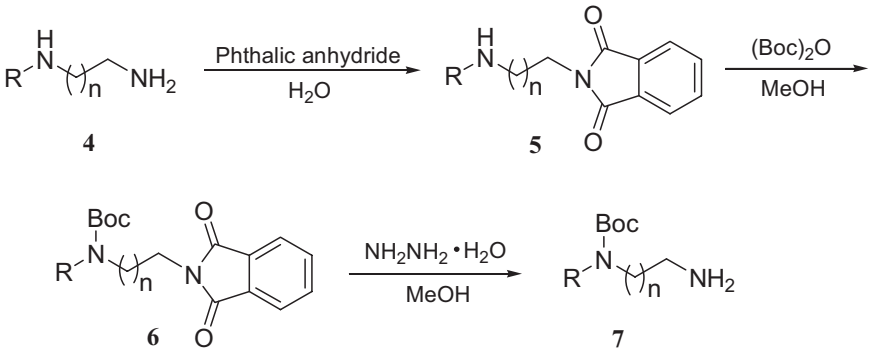

Scheme 2

The synthesis of N^1-alkyl-N^1-(Boc)-protected diamines **7a**–**7e** is outlined in *Scheme 2*. Treatment of *N*-alkyl-1,2-ethanediamines **4a**–**4d** or *N*-methyl-1,3-propanediamine **4e** with phthalic anhydride in H_2O led to good yields of phthalimido derivatives **5a**–**5d** or **5e** (70–80%). Reaction of these compounds with $(Boc)_2O$ in MeOH afforded the *N*-(Boc)-phthalimido derivatives **6a**-**6e** (58–68%). The conversion of **6** to the desired *N*-(Boc)-diamines **7a**–**7e** (81–87%) was accomplished by treatment with hydrazine hydrate in MeOH at room temperature. The products obtained were quite pure as shown by ^{1}H NMR analysis.

Experimental Section

Mps were determined on a Yanaco MP-500 micro-melting point apparatus and are uncorrected. IR spectra were recorded neat or as KBr pellets on a Nicolet-1705X IR spectrometer. ^{1}H NMR spectra were acquired on a Bruker AC-200MHz in $CDCl_3$ using Me_4Si as internal standard. Mass spectra were obtained on a Finnigan MAT 4510 spectrometer. Elemental analyses were determined on a Carlo Erbo-1160 elemental analyzer. Silica gel (200–300 mesh, Qingdao, China) was used for flash column chromatographies. All of the reagents and solvents were obtained commercially and used without further purification.

N-tert-Butoxycarbonyl-2-bromoethylamine (2a). Representative Procedure.

A solution of $(Boc)_2O$ (20.5 g, 94 mmol) in MeOH (60 mL) was added over a period of 0.5 h to a solution of 2-bromoethylamine hydrobromide (**1a**, 12.3 g, 60 mmol), Et_3N (10.1 g, 100 mmol) in MeOH (60 mL). The mixture was stirred for 18 h at room temperature. Then the reaction mixture was concentrated to dryness *in vacuo* to give a residue, which was added water (100 mL), extracted with CH_2Cl_2 (3 × 30 mL). The combined extract was dried ($MgSO_4$) and concentrated to dryness. Column chromatography (silica gel, hexane/EtOAc, 8:1) to afford **2a** (11.9 g, 89%) as a colorless oil. ^{1}H NMR: δ 1.43 [s, 9H, $C(CH_3)_3$], 3.45–3.57 (m, 4H, CH_2-CH_2), 4.97(br. s, 1H, NH); IR (neat): 3312, 2973, 1675, 1250, 735 cm^{-1}; MS (m/z): 224(M^+).

Anal. Calcd for $C_7H_{14}BrNO_2$: C, 37.52; H, 6.30; N, 6.25. Found: C, 37.49; H, 6.23; N, 6.34.

***N*-*tert*-Butoxycarbonyl-3-bromopropylamine** (**2e**), mp. 38–40°C, *lit*.[11] mp. 38–39°C, was obtained as a colorless oil in 95% yield from 3-bromopropylamine hydrobromide (**1e**) using a method similar to that for **2a**; ^{1}H NMR: δ 1.44 [s, 9H, $C(CH_3)_3$], 2.09(m, 2H, CH_2-CH_2-CH_2), 3.24(m, 2H, CH_2-NH), 3.46 (t, 2H, $BrCH_2$), 4.59 (br. s, 1H, NH); IR (neat): 3350, 2982, 1670, 1255, 728 cm^{-1}; MS (m/z): 238(M^+).

Anal. Calcd for $C_8H_{16}BrNO_2$: C, 40.33; H, 6.77; N, 5.88. Found: C, 40.53; H, 6.59; N, 5.73.

***N*^{1}-*tert*-Butoxycarbonyl-N^2-*methyl*-1,2-ethanediamine (3a). Representative Procedure.**

To a solution of **2a** (18.6 g, 83 mmol) in EtOH (100 mL), methylamine (16 mL, 40% w/v, 187 mmol) and KI (0.3 g, 1.8 mmol) as catalyst were added. Then the mixture was heated to 50°C till **2a** was completely consumed. The solution was concentrated *in vacuo* and then extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was dried ($MgSO_4$) and removal of the solvent gave **3a** (11.7 g, 81%) as a colorless oil. ^{1}H NMR: δ 1.46 [s, 9H, $C(CH_3)_3$], 2.40 (s, 3H,CH_3-NH), 2.78 (t, 2H, NH-CH_2), 3.23 (t, 2H, CH_2-NHBoc), 4.97 (br. s, 1H, NH); IR (neat): 3400, 2960, 1660, 1250, 739 cm^{-1}; MS (m/z): 174(M^+).

Anal. Calcd for $C_8H_{18}N_2O_2$: C, 55.15; H, 10.41; N, 16.08. Found: C, 55.25; H, 10.61; N, 16.17.

In the case of **3b**–**3d**, methylamine was replaced by ethylamine, *iso*-propylamine and benzylamine respectively. Compound **3e** was prepared from the reaction of methylamine with **2e**.

***N*^{1}-*tert*-Butoxycarbonyl-*N*^{2}-ethyl-1,2-ethanediamine (3b)**, mp. 54–56°C, *lit*. [12] mp. 54–55°C, recrystallized from pentane with cooling in a freezer to give a colorless solid (80%). ^{1}H NMR: δ 1.07 (t, 3H, CH_3-CH_2), 1.39 [s, 9H, $C(CH_3)_3$], 2.50–2.76 (m, 4H, CH_2-NH-CH_2), 3.17 (m, 2H, CH_2-NHBoc), 5.02 (br. s, 1H, NH); IR (neat): 3380, 2950, 1660, 1250, 735 cm^{-1}; MS (m/z): 188(M^+).

Anal. Calcd for $C_9H_{20}N_2O_2$: C, 57.42; H, 10.71; N, 14.88. Found; C, 57.32; H, 10.77; N, 14.91.

***N*^{1}-*tert*-Butoxycarbonyl-*N*^{2}-*iso*-propyl-1,2-ethanediamine (3c)**, 78% yield as a colorless oil; ^{1}H NMR: δ 1.04 [d, 6H, $(CH_3)_2$CH], 1.39 [s, 9H, $C(CH_3)_3$], 2.65 (t, 2H, NH-CH_2), 2.82 [spet, 1H, $(CH_3)_2CH$], 3.12 (t, 2H, CH_2-NHBoc), 5.67 (br. s, 1H, NH); IR (neat): 3370, 2960, 1670, 1245, 743 cm^{-1}; MS (m/z): 206(M^+).

Anal. Calcd for $C_{10}H_{22}N_2O_2$. C, 58.22; H, 10.75; N, 13.58. Found: C, 58.29; H, 10.87; N, 13.45.

***N*^{1}-*tert*-Butoxycarbonyl-*N*^{2}-benzyl-1,2-ethanediamine (3d)**, 75% yield as a colorless oil; ^{1}H NMR: δ1.40 [s, 9H, $C(CH_3)_3$], 2.81–3.08 (m, 4H, CH_2-CH_2), 3.93 (s, 2H, Ph-CH_2), 7.24–7.26 (m, 5H, Ph-H), 6.02 (br s, 1H, NH); IR (neat): 3370, 3010, 2930, 1656, 1613, 1576, 1508, 1255, 745 cm^{-1}; MS (m/z): 250(M^+).

Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found; C, 67.37; H, 8.96; N, 11.09.

***N*^{1}-*tert*-Butoxycarbonyl-*N*^{2}-methyl-1,3-propanediamine (3e)**, 82% yield as a colorless oil; ^{1}H NMR: δ 1.40 [s, 9H, $C(CH_3)_3$], 1.67 (m, 2H, CH_2-CH_2-CH_2), 2.47 (s, 3H,

CH_3-NH), 2.81 (t, 2H, NH-CH_2), 3.29 (t, 2H, CH_2-NHBoc), 4.95 (br. s, 1H, NH); IR (neat): 3400, 2963, 1661, 1250, 728 cm^{-1}; MS (m/z): 188(M^+).

Anal. Calcd for $C_9H_{20}N_2O_2$: C, 57.42; H, 10.71; N, 14.88. Found: C, 57.52; H, 10.53; N, 14.94.

N^1-Methyl-N^2-phthalyl-1,2-ethanediamine (5a). Representative Procedure.

Phthalic anhydride (12.0 g, 81 mmol) was added to a solution of *N*-methyl-1,2-ethanediamine **4a** (5.8 g, 78 mmol) in water (80 mL). The mixture was stirred at 100°C for 3 h. The solvent was distilled off *in vacuo* and acetone (60 mL) was added to the resulting residue. The insoluble solid was removed by filtration and the filtrate was concentrated to dryness. The residue was recrystallized from isopropanol and dried to yield **5a** (12.8 g, 80%) as a white solid. mp. 187–189°C, *lit*. [13] mp. 187.5–189°C; ^{1}H NMR: δ 1.92 (br. s, 1H, NH), 2.66 (s, 3H, CH_3), 3.33 (m, 2H, NH-CH_2), 3.86 (m, 2H, NH-CH_2-CH_2), 7.70–7.85 (m, 4H, Ar-H); IR (KBr): 3400, 3017, 2950, 1662, 1600, 1580, 1520, 743 cm^{-1}; MS (m/z): 204(M^+).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.81; H, 6.12; N, 13.54.

Compounds **5b**–**5e** were prepared and purified as in the procedure for **5a**.

N^1-Ethyl-N^2-phthalyl-1,2-ethanediamine (5b), 74% yield as a white solid, mp. 232–235°C, *lit*.[14] mp. 232–234°C; ^{1}H NMR: δ 1.67 (s, 3H, CH_3), 1.95 (br. s, 1H, NH), 2.53–2.74 (m, 4H, CH_2-NH-CH_2), 3.47 (t, 2H, NH-CH_2-CH_2), 7.65–7.80 (m, 4H, Ar-H); IR (KBr): 3420, 3020, 2970, 1665, 1603, 1585, 1510, 752 cm^{-1}; MS (m/z): 218(M^+).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.14; H, 6.57; N, 12.66.

N^1-*iso*-Propyl-N^2-phthalyl-1,2-ethanediamine (5c), 79% yield as a white solid, mp. 192–193°C, *lit*. [14] mp. 192–193°C; ^{1}H NMR: δ 1.12 [d, 6H, $(CH_3)_2$CH], 1.89 (br. s, 1H, NH), 2.64 (m, 2H, NH-CH_2), 2.78 [spet, 1H, $(CH_3)_2CH$], 3.83 (m, 2H, NH-CH_2-CH_2),, 7.70–7.82 (m, 4H, Ar-H); IR (KBr): 3425, 3033, 2950, 1666, 1606, 1576, 1500, 745 cm^{-1}; MS (m/z): 232(M^+).

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.34; H, 6.88; N, 12.22.

N^1-Benzyl-N^2-phthalyl-1,2-ethanediamine (5d), 70% yield as a white solid, mp. 245–247°C; ^{1}H NMR: δ 1.99 (br. s, 1H, NH), 2.75 (m, 2H, NH-CH_2), 3.86 (m, 2H, NH-CH_2-CH_2), 4.01 (s, 2H, Ph-CH_2), 7.16–7.30 (m, 5H, Ph-H), 7.69–7.85 (m, 4H, Ar-H); IR (KBr): 3440, 3035, 2941, 1665,,1603, 1585, 1507, 761 cm^{-1}; MS (m/z): 280(M^+).

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.71; H, 5.79; N, 9.89.

N^1-Methyl-N^2-phthalyl-1,3-propanediamine (5e), 72% yield as a white solid, mp. 204–206°C, *lit*. [15] mp. 204–207°C; ^{1}H NMR: δ 1.25 (br. s, 1H, NH), 1.69 (m, 2H, CH_2-CH_2-CH_2), 2.60 (s, 3H, CH_3-NH), 2.75 (m, 2H, NH-CH_2), 3.91 (m, 2H, CH_2-CH_2-N), 7.68–7.85 (m, 4H, Ar-*H*); IR (KBr): 3430, 3028, 2930, 1658, 1600, 1570, 1520, 730 cm^{-1}; MS (m/z): 218(M^+).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.14; H, 6.41; N, 12.75.

N*^{1}*-tert-Butoxycarbonyl-*N^1*-methyl-*N^2*-phthalyl-1,2-ethanediamine (6a). Representative Procedure.

A solution of $(Boc)_2O$ (11.8 g, 54 mmol) in MeOH (30 mL) was added dropwise over 1 h to a solution of **5a** (5.5 g, 27 mmol) in MeOH (20 mL). The mixture was stirred at 45°C for 36 h, then concentrated to dryness. The solid obtained was washed with MeOH (20 mL) and warm (50°C) water (2 × 15 mL), dissolved in acetone, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was recrystallized from acetone/water to give **6a** (5.6 g, 68%) as a white solid. mp. 94–96°C, *lit*. [12] mp. 94–95°; ^{1}H NMR: δ 1.23 [s, 9H, $C(CH_3)_3$], 2.84 (s, 3H, CH_3-NBoc), 3.47 (m, 2H, NBoc-CH_2), 3.80 (m, 2H, CH_2-CH_2-N), 7.70–7.88 (m, 4H, Ar-H); IR (KBr): 3080, 2970, 1654, 1600, 1578, 1500, 741cm^{-1}; MS (m/z): 304(M^+).

Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.21; H, 6.63; N, 9.21. Found: C, 63.14; H, 6.74; N, 9.11.

The analogues **6b–6e** were prepared and purified as in the procedure given for **6a**.

***N*^{1}*-tert-*Butoxycarbonyl-*N^1*-ethyl-*N^2*-phthalyl-1,2-ethanediamine (6b),** 65% yield as a white solid, mp. 50–52°C, *lit*. [12] mp. 50–52°C; ^{1}H NMR: δ 1.00 (m, 3H, CH_3-CH_2), 1.26 [s, 9H, $C(CH_3)_3$], 3.21 (m, 2H, CH_3-CH_2), 3.43 (m, 2H, NBoc-CH_2), 3.72 (t, 2H, CH_2-CH_2-N), 7.63–7.81 (m, 4H, Ar-H); IR (KBr): 3075, 2974, 1647, 1604, 1582, 1509, 752 cm^{-1}; MS (m/z): 318(M^+).

Anal. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.27; H, 6.75; N, 8.91.

***N*^{1}*-tert-*Butoxycarbonyl-*N^1*-iso-*propyl-*N^2*-phthalyl-1,2-ethanediamine (6c)**, 61% yield as a white solid, mp. 82–83°C; ^{1}H NMR: δ 1.01 [d, 6H, $(CH_3)_2CH$], 1.27[s, 9H, $C(CH_3)_3$], 2.67 [spet, 1H, $(CH_3)_2CH$], 3.20 (m, 2H, NBoc-CH_2), 3.82 (m, 2H, CH_2-CH_2-N), 7.70–7.82 (m, 4H, Ar-H); IR (KBr): 3030, 2944, 1646, 1601, 1577, 1504, 745 cm^{-1}; MS (m/z): 332(M^+).

Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.24; H, 7.04; N, 8.56.

***N*^{1}*-tert-*Butoxycarbonyl-*N^1*-benzyl-*N^2*-phthalyl-1,2-ethanediamine (6d)**, 58% yield as a white solid, mp. 111–112°C, *lit*. [12] mp. 111–113°C; ^{1}H NMR: δ 1.34 [s, 9H, $C(CH_3)_3$], 3.54 (m, 2H, NBoc-CH_2), 3.75 (m, 2H, CH_2-CH_2-N), 4.39 (t, 2H, Ph-CH_2), 7.16–7.26 (m, 5H, Ph-H), 7.69–7.82 (m, 4H, Ar-H); IR (KBr): 3025, 2932, 1636, 1611, 1580, 1500, 748 cm^{-1}; MS (m/z): 380(M^+).

Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.57; H, 6.28; N, 7.25.

***N*^{1}*-tert-*Butoxycarbonyl-*N^1*-methyl-*N^2*-phthalyl-1,3-propanediamine (6e)**, 64% yield as a white solid, mp. 74–76°C; ^{1}H NMR: δ 1.24 [s, 9H, $C(CH_3)_3$], 1.86 (m, 2H, CH_2-CH_2-CH_2), 3.14 (s, 3H, CH_3-NBoc), 3.36 (m, 2H, NHBoc-CH_2), 3.74 (m, 2H, CH_2-CH_2-N), 7.73–7.89 (m, 4H, Ar-H); IR (KBr): 3018, 2976, 1635, 1607, 1569, 1511, 727 cm^{-1}; MS (m/z): 318(M^+).

Anal. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.23; H, 6.90; N, 8.70.

N*^{1}*-tert-Butoxycarbonyl-N^1-methyl-1,2-ethanediamine (7a). Representative Procedure.

Hydrazine hydrate (9.2 g, 80% w/w, 150 mmol) was added dropwise to a solution of **6a** (23.6 g, 78 mmol) in MeOH (100 mL) at 60°C for 0.5 h. Then the mixture was stirred at

reflux for 4 h. After cooling to 25°C, the solution was filtered to remove insoluble materials and the filtrate was concentrated to dryness *in vacuo* to give an oily residue, to which was added water (30 mL), and then extracted with CH_2Cl_2 (3 × 30 mL). The combined extract was dried (Na_2SO_4) and concentrated to dryness. Column chromatography (silica gel, MeOH/CH_2Cl_2, 1:8) to afford **7a** (11.5 g, 85%) as a colorless oil. ^{1}H NMR: δ 1.26 (br. s, 2H, NH_2), 1.48 [s, 9H, $C(CH_3)_3$], 2.76 (t, 2H, CH_2-NH_2), 2.85 (s, 3H, CH_3-NBoc), 3.29 (t, 2H, NBoc-CH_2); IR (neat): 2970, 1655, 1260, 735 cm^{-1}; MS (m/z): 174(M^+).

Anal. Calcd for $C_8H_{18}N_2O_2$: C, 55.15; H, 10.41; N, 16.08. Found: C, 55.27; H, 10.48; N, 16.01.

Compounds **7b**–**7e** were prepared *via* similar procedure given for **7a**.

***N*^{1}-*tert*-Butoxycarbonyl-*N*^{1}-ethyl-1,2-ethanediamine (7b)**, 85% yield as a colorless oil; ^{1}H NMR: δ 1.10 (t, 3H, CH_3-CH_2), 1.21 (br s, 2H, NH_2), 1.42 [s, 9H, $C(CH_3)_3$], 2.83 (t, 2H, CH_2-NH_2), 3.27 (m, 4H, CH_2-NBoc-CH_2,); IR (neat): 2957, 1646, 1255, 734 cm^{-1}; MS (m/z): 188(M^+).

Anal. Calcd for $C_9H_{20}N_2O_2$: C, 57.42; H, 10.71; N, 14.88. Found; C, 57.30; H, 10.82; N, 14.96.

***N*^{1}-*tert*-Butoxycarbonyl-*N*^{1}-isopropyl-1,2-ethanediamine (7c)**, 83% yield as a colorless oil; ^{1}H NMR: δ 1.15 [d, 6H, $(CH_3)_2CH$], 1.30 (br. s, 2H, NH_2), 1.44 [s, 9H, $C(CH_3)_3$], 2.70 (t, 2H, CH_2-NH_2), 2.80 [spet, 1H, $(CH_3)_2CH$], 3.25 (t, 2H, NBoc-CH_2); IR (neat): 2950, 1645, 1257, 734 cm^{-1}; MS (m/z): 206(M^+).

Anal. Calcd for $C_{10}H_{22}N_2O_2$: C, 58.22; H, 10.75; N, 13.58. Found: C, 58.03; H, 10.62; N, 13.69.

***N*^{1}-*tert*-Butoxycarbonyl-*N*^{1}-benzyl-1,2-ethanediamine (7d)**, 81% yield as a colorless oil; ^{1}H NMR: δ 1.36 (br. s, 2H, NH_2), 1.44 [s, 9H, $C(CH_3)_3$], 2.71 (m, 2H, CH_2-NH_2), 3.29 (m, 2H, CH_2-NH_2), 4.52 (s, 2H, Ph-CH_2), 7.24–7.29 (m, 5H, Ph-H); IR (neat): 3020, 2943, 1640, 1603, 1575, 1490, 1240, 738 cm^{-1}; MS (m/z): 250(M^+).

Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found; C, 67.10; H, 8.74; N, 11.35.

***N*^{1}-*tert*-Butoxycarbonyl-*N*^{1}-methyl-1,3-propanediamine (7e),** 87% yield as a colorless oil; ^{1}H NMR: δ 1.25 (br. s, 2H, NH_2), 1.45 [s, 9H, $C(CH_3)_3$], 1.51–1.65 (m, 2H, CH_2-CH_2-CH_2), 2.76 (t, 2H, CH_2-NH_2), 2.90 (s, 3H, CH_3-NBoc), 3.15 (t, 2H, NBoc-CH_2); IR (neat): 2973, 1658, 1243, 726 cm^{-1}; MS (m/z): 188(M^+).

Anal. Calcd for $C_9H_{20}N_2O_2$: C, 57.42; H, 10.71; N, 14.88. Found: C, 57.53; H, 10.60; N, 14.76.

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