Electronic supplementary materials *Mendeleev Commun.*, 2023, **33**, 14–16

Selective Fmoc and Cbz protection of aromatic amino group in the presence of similar aliphatic function in liquid CO_2

**Dmitry A. Guk, Roman O. Burlutskiy, Dmitriy A. Lemenovskiy
and Elena K. Beloglazkina**

Experimental

General information:

All reagents were obtained from Sigma Aldrich and used without further purification. NMR measurements were carried out on Brucker-Avance 400 MHz spectrometer in $CDCl_3$ and DMSO-d_6 using TMS as an internal reference.

Silica gel 60 for column chromatography from Merck was used to separate mixtures where noted.

Electrospray ionization high-resolution mass spectra were recorded in positive ion mode on a TripleTOF 5600+ quadrupole time-of-flight mass spectrometer (ABSciex, Concord, Canada) equipped with DuoSpray ion source. The following MS parameters were applied: capillary voltage 5.5 kV; nebulizing and curtain gas pressure – 15 and 25 psi, respectively; ion source temperature – ambient; declustering potential 20 V; *m/z* range 100–1200. Elemental compositions of the detected ions were determined based on accurate masses and isotopic distributions using Formula Finder software (ABSciex, Concord, Canada). The maximum allowed deviation of the experimental molecular mass from calculated one was 5 ppm.

(A) General procedure of carrying out the reactions in liquid CO_2: Diamine (2.5 mmol) and DMF (1 ml) were placed into the reactor, and the reactor was filled with liquid CO_2 (50 ml) at a pressure of 50–55 bar. CbzCl or FmocCl (2.5 mmol) was placed into the injector, and the injector was filled with liquid CO_2 at the same pressure. The reactor was cooled in an ice water bath until the pressure was reduced to 40 bar, after which the acylating agent was transferred due to the pressure difference that appeared in the system. The cooling bath was removed and stirring was continued for 24 hours. After the excess CO_2 pressure was released, the reaction mixture was washed from the reactor with water, brought to pH 8 with 1M NaOH solution, and extracted with diethyl ether. The extract was washed with water, brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure.

All reactions in liquid carbon dioxide were carried out in the high-pressure experimental setup shown in Figure 1. Stirring was carried out using a laboratory magnetic stirrer.

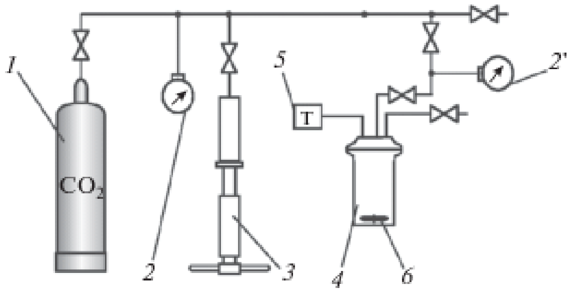

Figure S1. Installation for high pressure: (1) CO_2 cylinder, (2, 2 ') manometers, (3) hand screw press, (4) reactor, (5) thermocouple, (6) magnetic stir bar anchor.

(B) General procedure of carrying out the reactions without CO_2: Diamine (2.5 mmol) was placed in a 50 ml round bottom flask and dissolved in THF (5 ml). Water (10 ml) was added to the resulting solution with stirring, and then a solution of acylating agent (2.5 mmol) in THF (5 ml) was slowly added dropwise. The reaction mixture was stirred at room temperature for 24 hours, after which it was poured into a separating funnel. The mixture was diluted with water, brought to pH 8 with 1M NaOH solution and extracted with diethyl ether. The extract was washed with water, brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The separation of the obtained products was carried out by column chromatography on silica gel in the DCM/MeOH 30:1 eluent.

Characterization of the obtained products

Benzyl [4-(aminomethyl)phenyl]carbamate (1a). From 4-aminobenzylamine (305 mg, 2.5 mmol) and CbzCl (416 mg, 2.5 mmol) compound **1a** was obtained as a white solid. Yield: 100% (Method A). ^{1}H NMR (400 MHz, $CDCl_3$ δ, ppm): 7.31 - 7.44 (m, 7H, Ph-, Ar-), 7.24 (d, *J*=8.45 Hz, 2H, Ar-), 6.94 (br. s., 1H, NH), 5.20 (s, 2H, -CO-$\underline{CH_2}$-), 3.82 (s, 2H, -$\underline{CH_2}$-NH_2), 1.47 (br. s., 2H, -CH_2-$\underline{NH_2}$). HRMS: $(M+H)^+$ calc. 257.1284, found. 257.1281.

Benzyl 4-aminobenzylcarbamate (2a). From 4-aminobenzylamine (305 mg, 2.5 mmol) and CbzCl (416 mg, 2.5 mmol) compound **1b** was obtained as a white solid. Yield: 8% (Method B). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.29 - 7.41 (m, 5H, Ph-), 7.09 (d, *J*=8.11 Hz, 2H, Ar-), 6.65 (d, *J*=8.33 Hz, 2H, Ar-), 5.09 - 5.22 (m, 2H, -CO-$\underline{CH_2}$-), 5.00 (br. s., 1H, -CH_2-$\underline{NH}$-), 4.27 (d, *J*=5.70 Hz, 2H, -$\underline{CH_2}$-NH-), 3.67 (br. s., 2H, Ar-$\underline{NH_2}$). HRMS: $(M+H)^+$ calc. 257.1284, found. 257.1278

Benzyl (4-{[(benzyloxy)carbonyl]amino}benzyl)carbamate (3a). From 4-aminobenzylamine (305 mg, 2.5 mmol) and CbzCl (416 mg, 2.5 mmol) compound **3a** was obtained as a white solid. Yield: 82% (Method B). ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 7.32 - 7.44 (m, 13H, 2xPh-, Ar-), 7.26 - 7.19 (m, 2H, Ar-), 6.74 (br. s., 1H, NH), 5.20 (s, 2H, -CO-$\underline{CH_2}$-), 5.13 (s, 2H, -CO-$\underline{CH_2}$-), 5.06 (br. s., 1H, NH), 4.33 (br. s., 2H, -$\underline{CH_2}$-NH-). HRMS: $(M+H)^+$ calc. 391.1652, found. 391.1652.

Benzyl [3-(aminomethyl)phenyl]carbamate (1b). From 3-aminobenzylamine (305 mg, 2.5 mmol) and CbzCl (416 mg, 2.5 mmol) compound **1b** was obtained as a white solid. Yield: 85% (Method A). ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 9.78 (br. s., 1H,), 7.32 - 7.51 (m, 8H, Ph-, Ar-), 7.21 (t, *J*=7.81 Hz, 1H, Ar-), 6.99 (d, *J*=7.51 Hz, 1H, NH), 5.16 (s, 2H, -CO-$\underline{CH_2}$-), 3.68 (s, 2H, -$\underline{CH_2}$-NH_2), 1.97 (br. s., 2H, -CH_2-$\underline{NH_2}$). HRMS: $(M+H)^+$ calc. 257.1284, found. 257.1279.

Benzyl 3-aminobenzylcarbamate (2b). From 3-aminobenzylamine (305 mg, 2.5 mmol) and CbzCl (416 mg, 2.5 mmol) compound **2b** was obtained as a white solid. Yield: 58% (Method B). ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 7.71 (s, 1H, NH), 7.30 - 7.43 (m, 5H, Ph-), 6.94 (t, *J*=7.68 Hz, 1H, Ar-), 6.47 (s, 1H, Ar-), 6.37 - 6.45 (m, 2H, Ar-), 5.04 (s, 2H, -CO-$\underline{CH_2}$-), 5.02 (s, 2H, Ar-$\underline{NH_2}$), 4.06 (d, *J*=6.19 Hz, 2H, -$\underline{CH_2}$-NH_2). HRMS: $(M+H)^+$ calc. 257.1284, found. 257.1283.

Benzyl (3-{[(benzyloxy)carbonyl]amino}benzyl)carbamate (3b). From 3-aminobenzylamine (305 mg, 2.5 mmol) and CbzCl (416 mg, 2.5 mmol) compound **3b** was obtained as a white solid. Yield: 21% (Method B). ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 7.70 (s, 1H, NH), 7.24 - 7.45 (m, 10H, 2xPh-), 6.96 (t, *J*=7.77 Hz, 1H, Ar-), 6.52 (s, 1H, Ar-), 6.41 (d, *J*=7.85 Hz, 2H, Ar-), 6.24 (br. s., 1H, NH), 5.03 (s, 2H, -CO-$\underline{CH_2}$-), 4.23 (s, 2H, -CO-$\underline{CH_2}$-), 4.06 (d, *J*=6.19 Hz, 2H, -$\underline{CH_2}$-NH-) . HRMS: $(M+H)^+$ calc. 391.1652, found. 391.1647.

Benzyl [2-(aminomethyl)phenyl]carbamate (1c). From 2-aminobenzylamine (305 mg, 2.5 mmol) and CbzCl (416 mg, 2.5 mmol) compound **1c** was obtained as a white solid. Yield: 80% (Method A). ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 9.07 (br. s., 1H, NH), 7.29 - 7.36 (m, 5H, Ph-), 7.22 (t, *J*=5.78 Hz, 2H, Ar-), 7.04 - 7.13 (m, 1H, Ar-), 6.78 - 6.88 (m, 1H, Ar-), 4.52 (s, 2H, -CO-$\underline{CH_2}$-), 4.32 (s, 2H, -NH_2), 3.75 - 3.86 (m, 2H, -$\underline{CH_2}$-NH-). HRMS: $(M+H)^+$ calc. 257.1284, found. 257.1276.

Benzyl 2-aminobenzylcarbamate (2c). From 2-aminobenzylamine (305 mg, 2.5 mmol) and CbzCl (416 mg, 2.5 mmol) compound **2c** was obtained as a white solid. Yield: 95% (Method B). ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 7.66 (br. s., 1H, NH), 7.24 - 7.42 (m, 5H, Ph-), 6.88 -

7.00 (m, 2H, Ar-), 6.61 (d, *J*=7.46 Hz, 1H, Ar-), 6.45 - 6.53 (m, 1H, Ar-), 5.04 (s, 2H, -CO-$\underline{CH_2}$-), 4.98 (s, 2H, Ar-$\underline{NH_2}$), 4.04 (d, *J*=6.17 Hz, 2H, -$\underline{CH_2}$-NH-). HRMS: $(M+H)^+$ calc. 257.1284, found. 257.1283.

Benzyl (2-{[(benzyloxy)carbonyl]amino}benzyl)carbamate (3c) was not detected in both types of reaction (Method A or B).

Benzyl [4-(2-aminoethyl)phenyl]carbamate (1d). From 2-(4-aminophenyl)ethylamine (340 mg, 2.5 mmol) and CbzCl (416 mg, 2.5 mmol) compound **1d** was obtained as a white solid. Yield: 90% (Method A). ^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm): 9.40 (br. s., 1H, NH), 7.23 - 7.40 (m, 7H, Ph-, Ar-), 7.01 (d, *J*=8.28 Hz, 2H, Ar-), 5.09 (s, 2H, -CO-$\underline{CH_2}$-), 2.78 (t, *J*=6.90 Hz, 2H, -CH_2-$\underline{CH_2}$-NH_2), 2.58 (t, *J*=6.91 Hz, 2H, -$\underline{CH_2}$-CH_2-NH_2). HRMS: $(M+H)^+$ calc. 271.1441, found. 271.1439.

Benzyl 4-aminophenethylcarbamate (2d). From 2-(4-aminophenyl)ethylamine (340 mg, 2.5 mmol) and CbzCl (416 mg, 2.5 mmol) compound **2d** was obtained as a white solid. Yield: 21% (Method B). ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 7.25 - 7.41 (m, 6H, NH, Ph-), 6.84 (d, *J*=8.17 Hz, 2H, Ar-), 6.50 (d, *J*=8.22 Hz, 2H, Ar-), 5.01 (s, 2H, -CO-$\underline{CH_2}$-), 4.87 (s, 2H, Ar-$\underline{NH_2}$), 3.05 - 3.21 (m, 2H, -CH_2-$\underline{CH_2}$-NH_2), 2.54 (t, *J*=7.59 Hz, 2H, -$\underline{CH_2}$-CH_2-NH_2). HRMS: $(M+H)^+$ calc. 270.1368, found. 270.1362.

benzyl [4-(2-{[(benzyloxy)carbonyl]amino}ethyl)phenyl]carbamate (3d). From 2-(4-aminophenyl)ethylamine (340 mg, 2.5 mmol) and CbzCl (416 mg, 2.5 mmol) compound **3d** was obtained as a white solid. Yield: 47% (Method B). ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 9.70 (br. s., 1H, NH), 7.24 - 7.46 (m, 13H, NH, 2xPh-, Ar-), 7.09 (d, *J*=8.44 Hz, 2H, Ar-), 5.14 (s, 2H, -CO-$\underline{CH_2}$-), 5.00 (s, 2H, -CO-$\underline{CH_2}$-), 3.14 - 3.21 (m, 2H, -$\underline{CH_2}$-CH_2-NH-), 2.64 (m, 2H, -CH_2-$\underline{CH_2}$-NH-). HRMS: $(M+H)^+$ calc. 404.1736, found. 404.1735.

(9*H*-Fluoren-9-yl)methyl [4-(aminomethyl)phenyl]carbamate hydrochloride (1e·HCl**).** From 4-aminobenzylamine (305 mg, 2.5 mmol) and FmocCl (620 mg, 2.5 mmol) compound **1e**·HCl was obtained as a white solid. Yield: 95% (Method A). Stored and characterized as hydrochloride due to low stability of free amine **1e**. ^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm): 9.88 (br. s., 1H, NH), 8.52 (br. s., 3H, CH_2-$\underline{NH_3}^+$), 7.91 (d, *J*=7.40 Hz, 2H, Ar-), 7.76 (d, *J*=7.24 Hz, 2H, Ar-), 7.31 - 7.55 (m, 8H, Fluorenyl), 4.48 (br. s., 2H, -CO-$\underline{CH_2}$-), 4.31 (br. s., 1H, Fluorenyl-), 3.92 (s, 2H, -$\underline{CH_2}$-NH_3^+). HRMS: $(M+H)^+$ calc. 345.1597, found. 345.1595.

(9*H*-Fluoren-9-yl)methyl 4-aminobenzylcarbamate (2e). From 4-aminobenzylamine (305 mg, 2.5 mmol) and FmocCl (620 mg, 2.5 mmol) compound **2e** was obtained as a white solid.

Yield: 90% (Method B). ^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm): 7.89 (d, *J*=7.47 Hz, 2H, Fluorenyl-), 7.63 - 7.73 (m, 2H, Fluorenyl-), 7.41 (t, *J*=7.40 Hz, 2H, Fluorenyl-), 7.32 (t, *J*=7.38 Hz, 2H, Fluorenyl-), 6.90 (m, *J*=8.19 Hz, 2H, Ar-), 6.51 (m, *J*=8.19 Hz, 2H, Ar-), 4.95 (s, 2H, Ar-$\underline{NH_2}$), 4.31 (d, *J*=6.96 Hz, 2H, -CO-$\underline{CH_2}$-), 4.22 (d, *J*=6.74 Hz, 1H, Fluorenyl-), 4.01 (d, *J*=5.97 Hz, 2H, -$\underline{CH_2}$-NH-). HRMS: $(M+H)^+$ calc. 345.1597, found. 345.1594.

***tert*-Butyl [4-(aminomethyl)phenyl]carbamate (1f).** From 4-aminobenzylamine (305 mg, 2.5 mmol) and Boc$_2$O (524 mg, 2.5 mmol) compound **6a** was obtained as a white solid. Yield: 60% (Method A). ^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm): 9.25 (br. s., 1H, NH), 7.36 (d, *J*=8.35 Hz, 2H, Ar-), 7.18 (d, *J*=8.32 Hz, 2H, Ar-), 3.62 (s, 2H, -$\underline{CH_2}$-NH$_2$), 2.16 (br. s., 2H, -CH$_2$-$\underline{NH_2}$), 1.46 (s, 9H, 3xCH$_3$). HRMS: $(M+H)^+$ calc. 223.1441, found. 223.1438.

***tert*-Butyl 4-aminobenzylcarbamate (2f).** From 4-aminobenzylamine (305 mg, 2.5 mmol) and Boc$_2$O (524 mg, 2.5 mmol) compound **2f** was obtained as a white solid. Yield: 50% (Method B). ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 9.29 (br. s., 1H, NH), 7.37 (d, *J*=8.24 Hz, 2H, Ar-), 7.10 (d, *J*=8.24 Hz, 2H, Ar-), 4.03 (s, 2H, -$\underline{CH_2}$-NH-), 1.46 (s, 9H, 3xCH$_3$). HRMS: $(M+H)^+$ calc. 223.1441, found. 223.1433.

***tert*-Butyl {4-[(*tert*-butoxycarbonyl)amino]benzyl}carbamate (3f).** From 4-aminobenzylamine (305 mg, 2.5 mmol) and Boc$_2$O (524 mg, 2.5 mmol) compound **3f** was obtained as a white solid. Yield: 25% (Method A or B). ^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm): 7.31 (m, 3H, Ar-, NH-), 6.88 (d, *J*=8.15 Hz, 2H, Ar-), 6.48 (m, 1H, NH), 3.92 (s, 2H, -$\underline{CH_2}$-NH-), 1.38 (s, 18H, 6xCH$_3$). HRMS: $(M+H)^+$ calc. 323.1965, found. 323.1960.

Typical NMR for compounds of all structure types

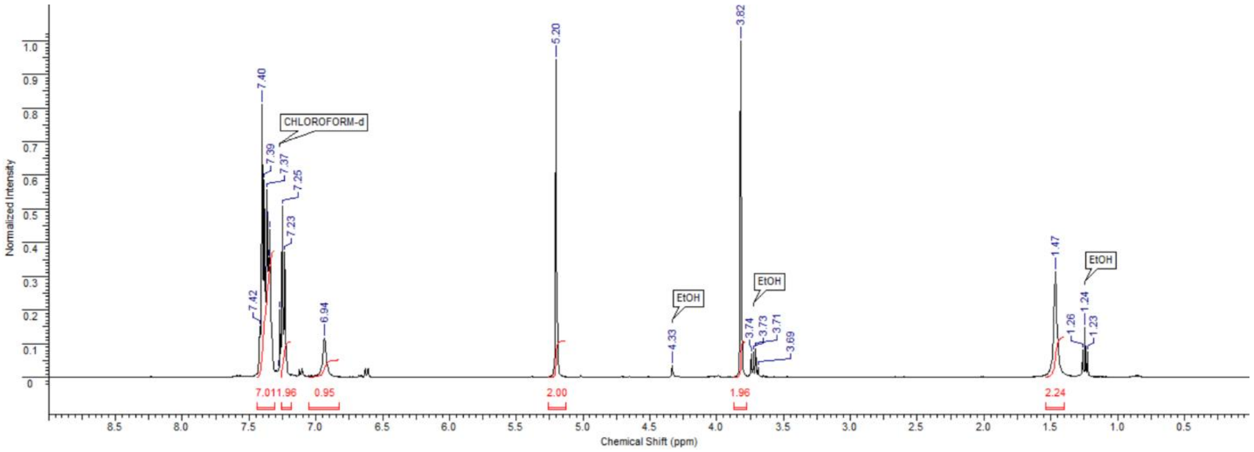

Figure S2. ^{1}H NMR for compound **1a**.

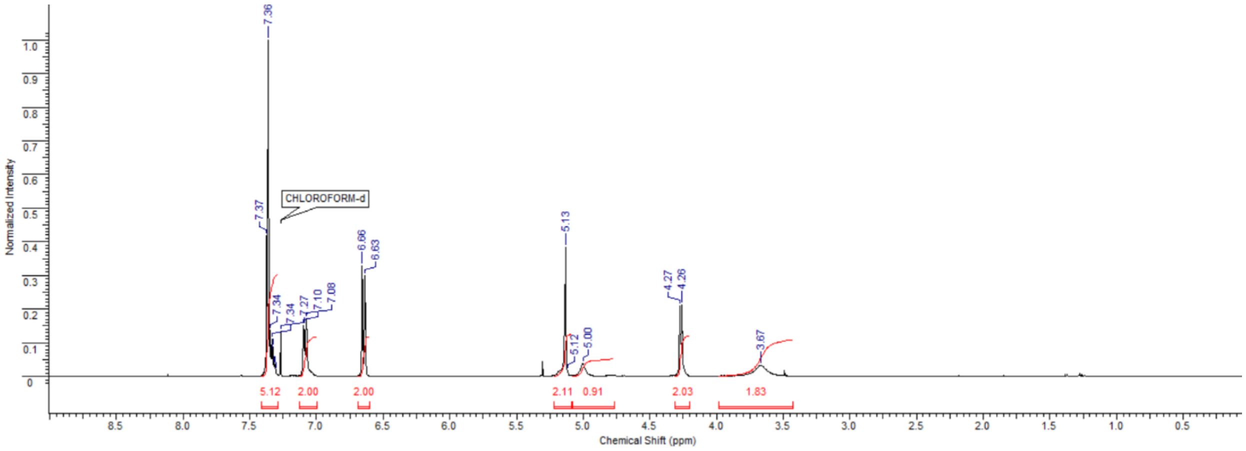

Figure S3. ^{1}H NMR for compound **2a**.

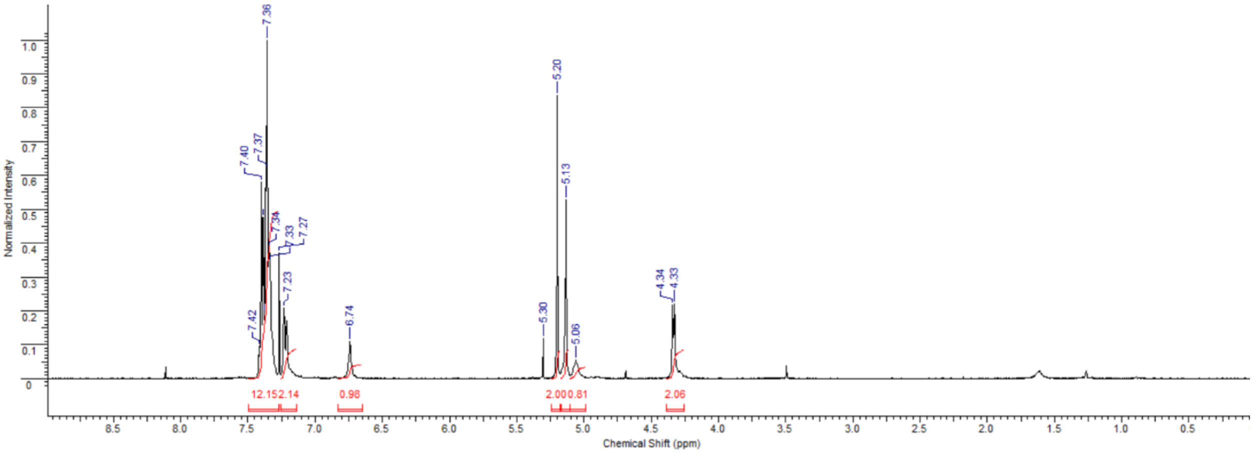

Figure S4. ^{1}H NMR for compound **3a**.