Supporting Information Section

Title: "**Synthesis of Methyl Carbamates from Primary Aliphatic Amines and Dimethyl Carbonate in Supercritical CO_2: Effects of Pressure and co-Solvents, and Chemoselectivity**."

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General. GLC and GC/MS (70 eV) analyses were run using HP5 and HP5/MS capillary columns (30 m), respectively. ^{1}H and NMR spectra were recorded on a 300 MHz spectrometer, using $CDCl_3$ or CD_3OD as solvents with TMS as the internal standard.

Amines **2a-g** and DMC were ACS grade and were employed without further purification. CO_2 was SFC/SFE grade with a purity of 99.998%.

o- and *p*-Hydroxybenzylamines (**2h** and **2i**) were prepared through the catalytic hydrogenation of the corresponding nitriles. [i] Accordingly, the nitrile (1 g, 8.4 mmol), Raney-Ni (~0.3 g wet of MeOH), and a 2M solution of NH_3 in MeOH (20 mL) were made to react at 100 °C and for 1.5 h, in a stainless steel autoclave pressurized with H_2 at 90 bar. Amines **2h** and **2i** were purified by flash chromatography (FCC) and they were isolated in 73 and 35% yields, respectively. Their physical and spectroscopic data were in agreement with those reported in the literature (**2h**, [ii] and **2i**, [iii]).

Synthesis, isolation and characterisation of methyl carbamates.

Methyl N-benzyl carbamate 5a. Purification and characterization data of **5a** are detailed in the experimental section. Spectroscopic and physical properties were in agreement with data of literature. [iv]

Methyl N-phenethyl carbamate 5b. According to procedure described in the experimental section, compound **5b** was obtained from the reaction of phenethylamine and methyl chloroformate. The crude product was isolated as a pale-yellow solid (mp 135-6 °C) in a 83% yield, and characterised as such. **GC-MS** m/z: 179 (M^+, 22%), 164 ($[M\text{-}Me]^+$, 5), 147 ($[M\text{-}OMe\text{-}H]^+$, 10), 104 ($[M\text{-}NHCO_2Me\text{-}H]^+$, 53), 91 ($[C_7H_7]^+$, 63), 88 ($[MeOC(O)N^+(H)=CH_2]$, 100%), 77 ($[C_6H_5]^+$, 8), 65 (14), 44 (21). Spectroscopic and physical properties were in agreement with data of literature. [v]

Methyl N-cyclohexyl carbamate 5c. According to procedure described in the experimental section, compound **5c** was obtained from the reaction of cyclohexylamine and methyl chloroformate. The crude product was isolated as a white solid (mp 76-78 °C) in a 69% yield, and characterised as such. **GC-MS** m/z: 113 (M^+, 26%), 84 (6), 70 ($[MeN^+(H)CHCH=CH_2]$, 100), 57 ($C_4H_9^+$, 24). Spectroscopic and physical properties were in agreement with data of literature. [vi]

Methyl N-(2-amino)benzyl carbamate 5d. Purification and characterization data of **5d** are detailed in the experimental section.

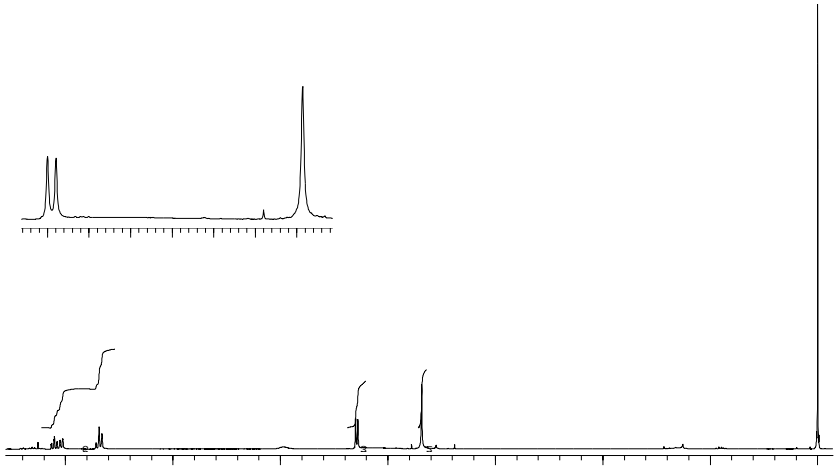


Figure 1a: ^{1}H NMR of **5d**.

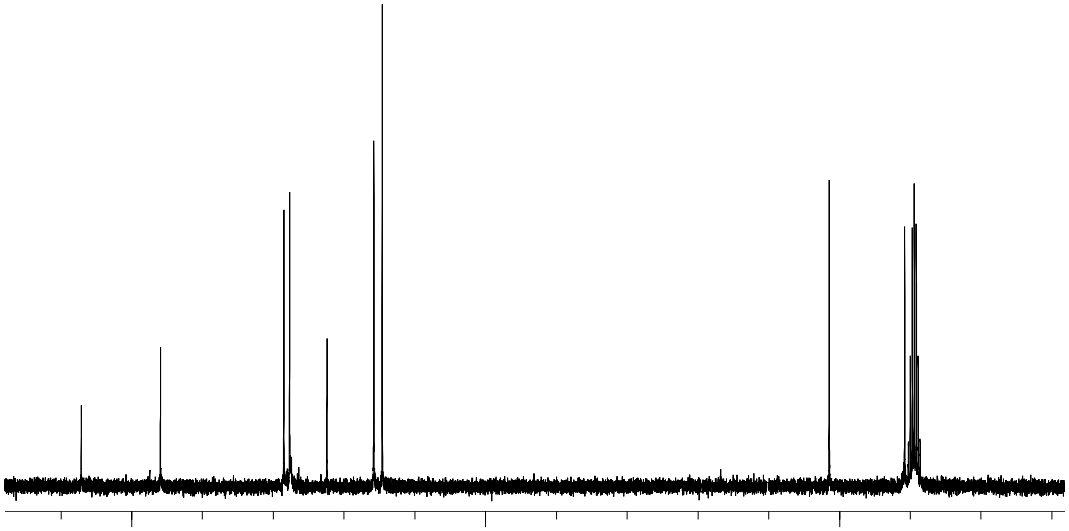


Figure 1b: ^{13}C NMR of **5d**.

Methyl N-(4-amino)benzyl carbamate 5e. [vii] Under the conditions of entry 7 in Table 3 (130 °C, 90 bar of CO_2), **5d** was obtained in a 84% amount by GC (conversion 100%). It was then purified by FCC on Al_2O_3 (Macheray-Nagel; eluant: CH_2Cl_2, MeOH, aq. NH_3 in a 9:1:0.1 v/v; R_f = 0.35), and isolated as a yellow-brown solid (mp 84-86°C) in a 49% yield.

GC-MS m/z: 180 (M^+, 93), 165 ($[M-Me]^+$, 80), 147 ($[M-OMe-2H]^+$, 16) 121 ($[M-COOMe]^+$, 33), 106 ($[M-NHCOOMe]^+$, 100), 94 (44), 77 (20), 65 (15). **^{1}H NMR** ($CDCl_3$, figure 2a) δ: 3.67 (3H, s), 4.23 (2H, d, J = 5.7 Hz), 4.88 (1H, s broad), 6.63 (2H, d, J = 8.46 Hz), 7.06 (2H, d, J = 8.21 Hz). **^{13}C NMR** (DMSO-d_6, figure 2b) δ: 157.6, 148.3, 128.9, 127.6, 114.5, 52.1, 44.4. **IR** (cm^{-1}) (KBr): 3346 (NH, stretching), 1703 (CO, stretching), 1614, 1517, 1402, 1263, 1138.

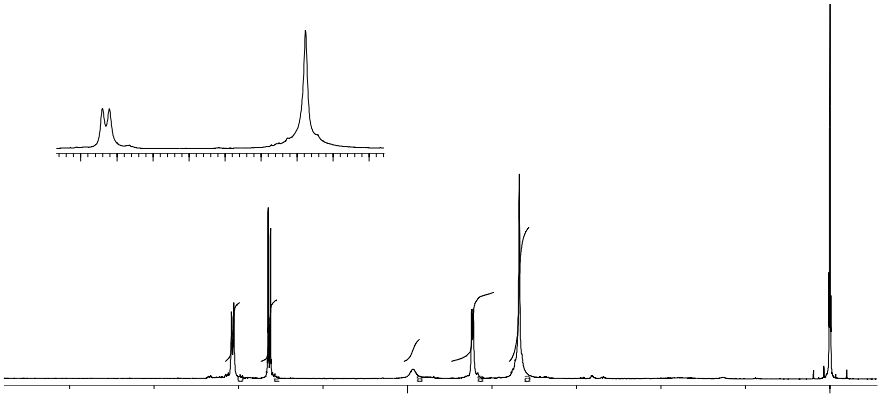


Figure 2a: ^{1}H NMR of **5e**.

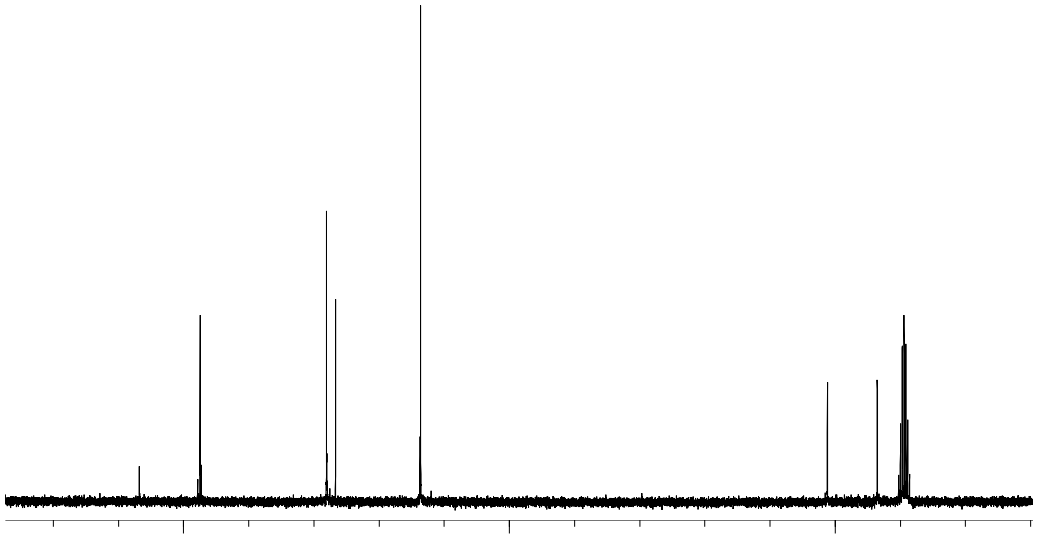


Figure 2b: ^{13}C NMR of **5e**.

Methyl N-(4-amino)phenethyl carbamate 5f. [viii] Under the conditions of entry 10 in Table 3 (130 °C, 90 bar of CO_2), **5f** was obtained in a 85% amount by GC (conversion 100%). It was then

purified by FCC on Al_2O_3 (Macheray-Nagel; eluant: CH_2Cl_2, MeOH, aq. NH_3 in a 9:1:0.1 v/v; R_f = 0.65), and isolated as a viscous brown oil, in a 45% yield.

GC-MS (70 eV), m/z: 194 (M^+, 16), 119 ($[M\text{-}NHCO_2Me\text{-}H]^+$, 38), 106 ($[NH_2PhCH_2]^+$, 100), 77 (7). **^{1}H NMR** ($CDCl_3$, Figure 3a) δ: 2.68 (2H, t, J = 6.90 Hz), 3.38 (2H, dd, J_1 = 6.6, J_2 = 13 Hz), 3.64 (3H, s), 4.68 (1H, s broad), 6.63 (2H, d, J = 8.39 Hz), 6.97 (2H, d, J = 8.29 Hz). **^{13}C NMR** ($CDCl_3$, Figure 3b) δ: 156.9, 144.8, 129.6, 128.5, 115.3, 51.9, 42.4, 35.2. **IR** (cm^{-1}) (KBr): 3346 (NH, stretching), 2943, 1705 (CO, stretching), 1630, 1510, 1261.

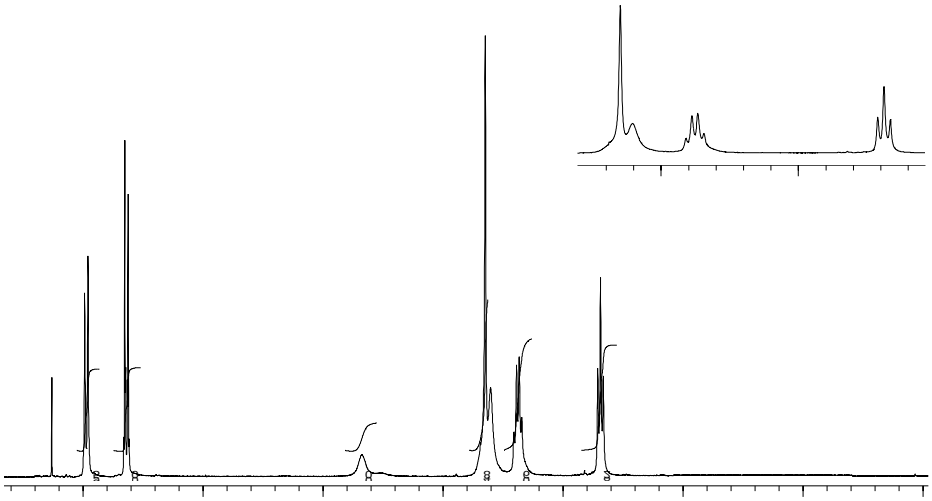


Figure 3a: ^{1}H NMR of **5f**.

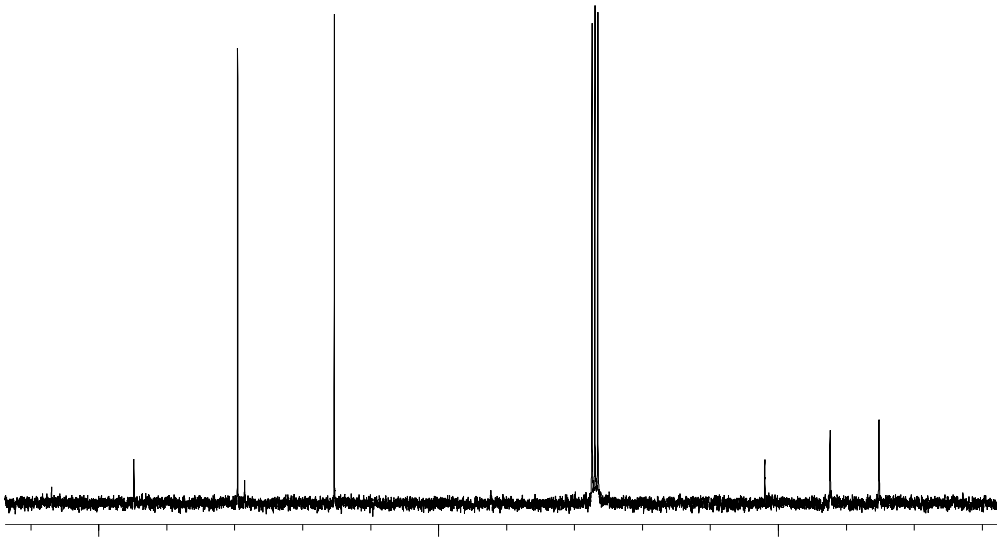


Figure 3b: ^{13}C NMR of **5f**.

Methyl N-(2-phenyl,2-hydroxy)ethyl carbamate 5g. [ix]Under the conditions of entry 11 in Table 3 (130 °C, 90 bar of CO_2), **5f** was obtained. It was then purified by FCC on Al_2O_3 (Macheray-Nagel; eluant: CH_2Cl_2, MeOH, aq. NH_3 in a 9:1:0.1 v/v; R_f = 0.5), and as a white solid (mp 88-90 °C) isolated in a 65% yield.

^{1}H NMR ($CDCl_3$, Figure 4a) δ: 2.68-2.78 (1H, s broad), 3.24-3.40 (1H, m), 3.48-3.65 (1H, m), 3.68 (3H, s), 4.80-4.89 (1H, m), 5.00-5.18 (1H, s broad), 7.30-7.39 (5H, m). **^{13}C NMR** (DMSO-d_6, Figure 4b) δ: 156.7, 127.9, 127.9, 126.9, 125.9, 71.3, 51.1, 41.8. **IR** (cm^{-1}) (KBr): 3377 (NH, stretching), 3275, 1689, 1550, 1284.

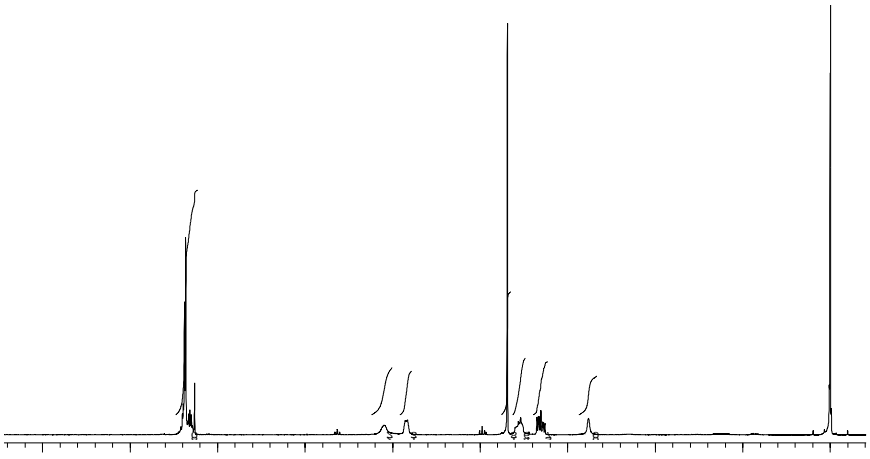


Figure 4a: ^{1}H NMR of **5g**.

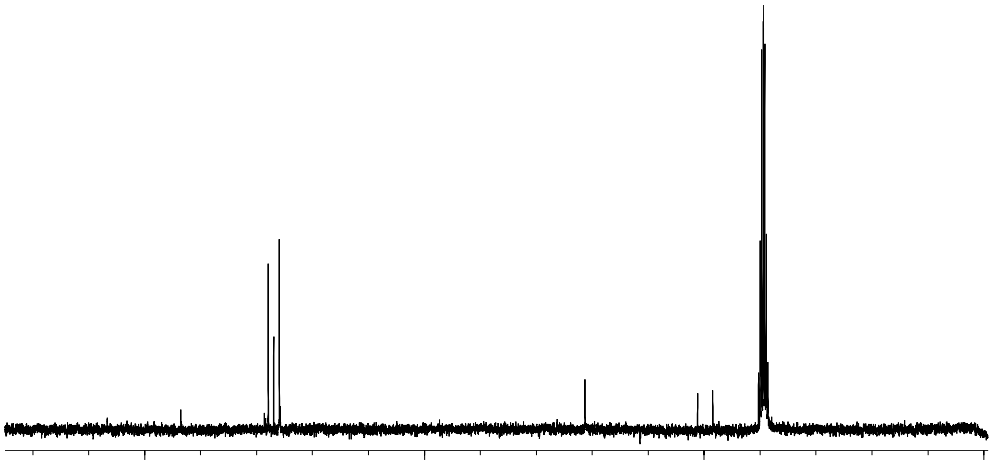


Figure 4b: ^{13}C NMR of **5g**.

Methyl N-(2-hydroxy)benzyl carbamate 5h. Under the conditions of entry 12 in Table 3 (130 °C, 90 bar of CO_2), **5g** was obtained in a 64% amount by GC (conversion 90%). It was then purified by FCC on Al_2O_3 (Macheray-Nagel; eluant: CH_2Cl_2, MeOH, aq. NH_3 in a 9:1:0.1 v/v; R_f = 0.35), and isolated as a pale-yellow solid (mp 142-144°C) in a 39% yield.

^{1}H NMR ($CDCl_3$, Figure 5a) δ: 3.62 (3H, s), 4.20 (2H, d, J = 6.63 Hz), 6.72-7.22 (m, 4H). **^{13}C NMR** ($CDCl_3$, Figure 5b) δ: 155.3, 130.5, 129.8, 128.9, 124.6, 121.9, 120.1, 52.9, 41.4.

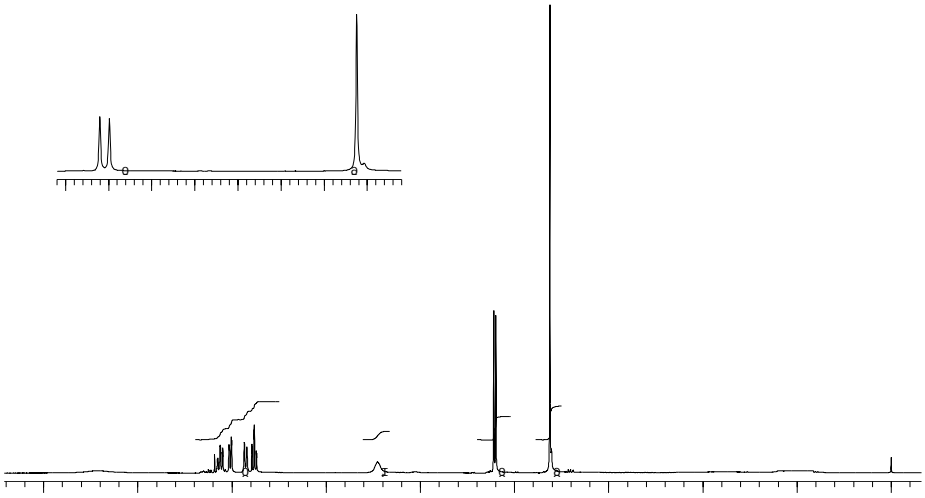


Figure 5a: ^{1}H NMR of **5h**.

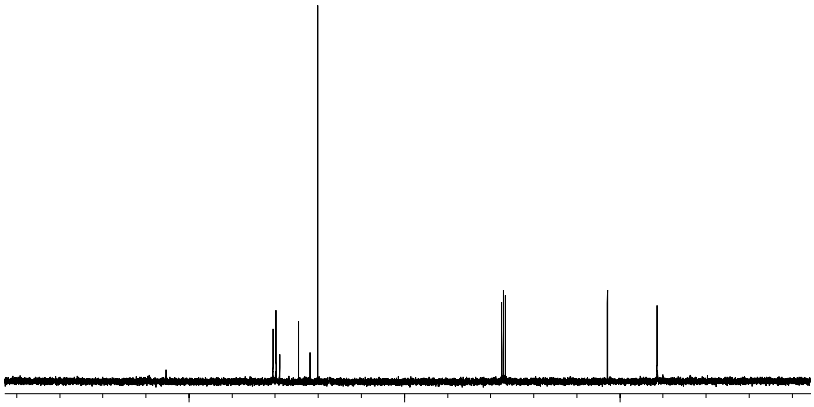
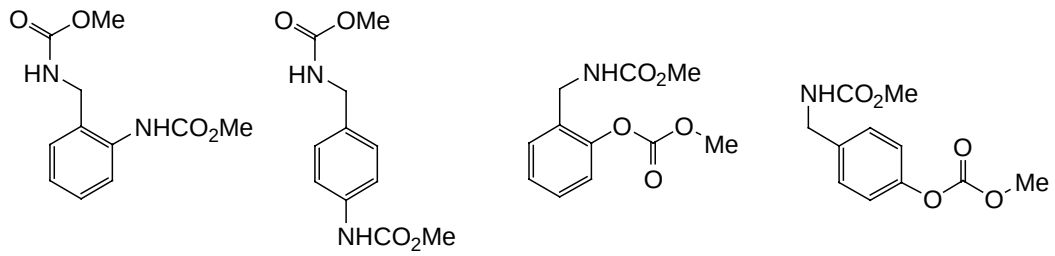


Figure 5b: ^{13}C NMR of **5h**.

According to procedure described in the experimental section, methyl carbamates **5l-m** and **9a-b** (Scheme 1) were obtained from the reaction of methyl chloroformate with *o*- and *p*-aminobenzyl

amines (**2d** and **2e**) and *o*- and *p*-hydroxybenzylamines (**2h** and **2i**). The crude compounds **5l-m** and **9a-b** were characterised as such.



5l **5m** **9a** **9b**

Scheme 1

Methyl 2-[(methoxycarbonyl)amino]benzyl carbamate 5l. Compound **5l** was isolated as a white solid (mp 98-100 °C). **GC-MS** (70 eV), m/z: 238 (M^+, 10%), 206 ($[M\text{-}OMe\text{-}H]^+$, 15), 179 ($[M\text{-}COOMe]^+$, 36), 147 ($[M\text{-}NHCOOMe\text{-}Me\text{-}2H]^+$, 100), 132 ($[M\text{-}NHCOOMe\text{-}OMe\text{-}H]^+$, 34), 104 (13), 77 (14). **^{1}H NMR** ($CDCl_3$, Figure 6) δ: 3.69 (3H, s), 3.79 (3H, s), 4.28 (2H, d, J = 6.40 Hz), 5.40 (1H, s broad), 7.01-7.35 (m, 3H), 7.85 (m, 1H).

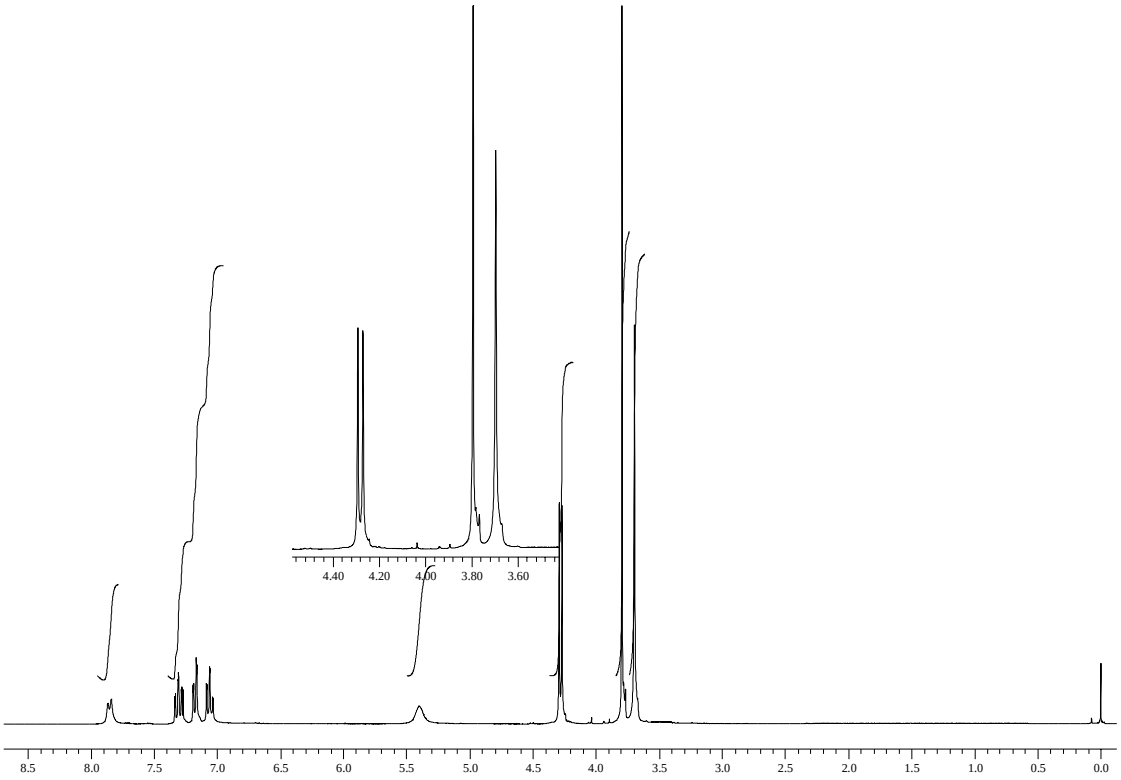


Figure 6. ^{1}H NMR of **5l**

Methyl 4-[(methoxycarbonyl)amino]benzyl carbamate 5m. Compound **5m** was isolated as a brown solid (mp 167-172 °C). **GC-MS** (70 eV), m/z: 238 (M^+, 8%), 223 ([M-Me]$^+$, 11), 206 ([M-OMe-H]$^+$, 24), 164 ([M-NHCOOMe]$^+$, 24), 147 ([M-NHCOOMe-Me-2H]$^+$, 38), 132 ([M-NHCOOMe-OMe-H]$^+$, 100), 90 (17), 77 (28). **^{1}H NMR** ($CDCl_3$, Figure 7) δ: 3.69 (3H, s), 3.76 (3H, s), 4.31 (2H, d, J = 5.5 Hz), 4.98 (1H, s broad), 7.21 (2H, d, J = 8.21 Hz), 7.33 (2H, s, J = 8.21 Hz).

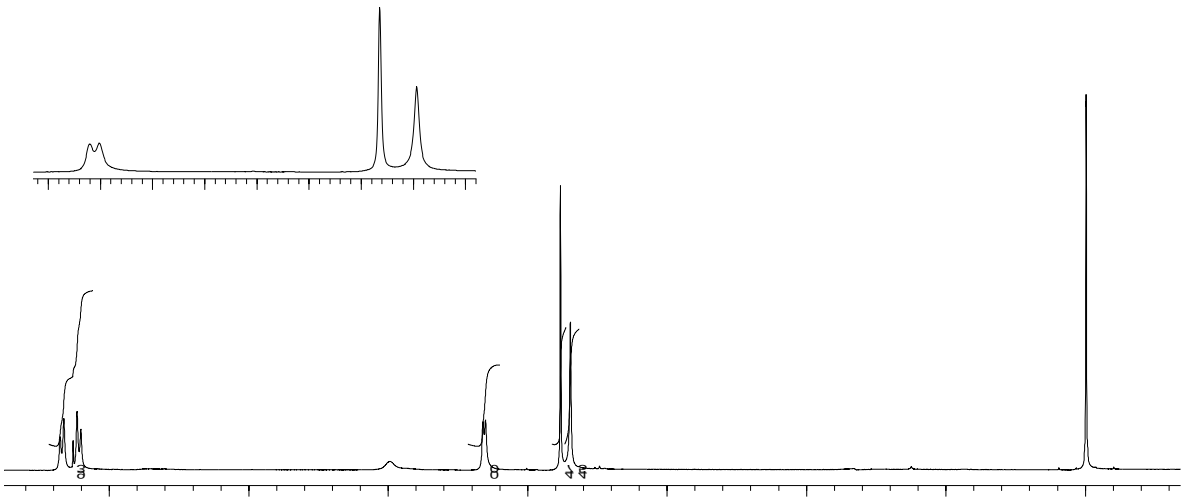


Figure 7. ^{1}H NMR of **5m**

***o*-[(N-methoxycarbonyl)]aminomethylphenyl methyl carbonate, 9a**. Compound **9a** was isolated as a white solid (mp 101-102 °C). **GC-MS** (70 eV), m/z: 239 (M^+, 1%), 207 ([M-OMe-H]$^+$, 11), 180 ([M-COOMe]$^+$, 100), 164 ([M-OCOOMe]$^+$, 16), 148 ([M-OCOOMe-Me-H]$^+$, 21) 121 ([M-(COOMe)$_2$]$^+$, 33), 106 (47), 78 (79). **^{1}H NMR** ($CDCl_3$, Figure 8) δ: 3.69 (3H, s), 3.79 (3H, s), 4.29 (2H, d, J = 6.65 Hz), 5.29 (1H, s broad), 7.01-7.35 (m, 3H), 7.86 (m, 1H).

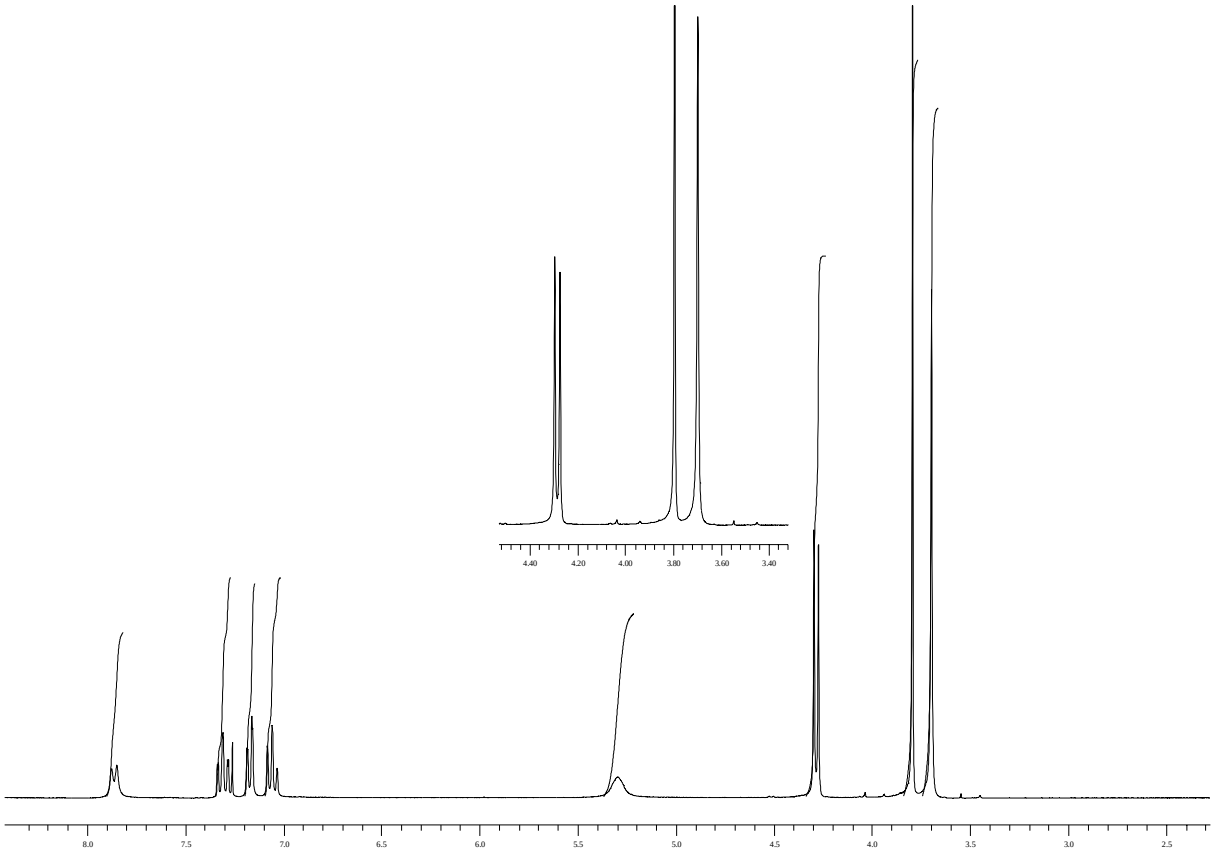


Figure 8. ^{1}H NMR of **9a**

***p*-[(N-methoxycarbonyl)]aminomethylphenyl methyl carbonate, 9b**. Compound **9b** was isolated as a highly viscous oil. **GC-MS** (70 eV), m/z: 239 (M^+, 13%), 224 ([M-Me]$^+$, 14%), 207 ([M-OMe-H]$^+$, 12), 180 ([M-COOMe]$^+$, 13), 163 ([M-OCOOMe-H]$^+$, 61), 121 ([M-$(COOMe)_2$]$^+$, 100), 109 (28), 77 (26).). **^{1}H NMR** ($CDCl_3$, Figure 9) δ: 3.68 (3H, s), 3.90 (3H, s), 4.26 (2H, d, J = 5.9 Hz), 5.18 (1H, s broad), 6.76 (2H, d, J = 8.45 Hz,), 7.10 (2H, s, J = 8.44 Hz).

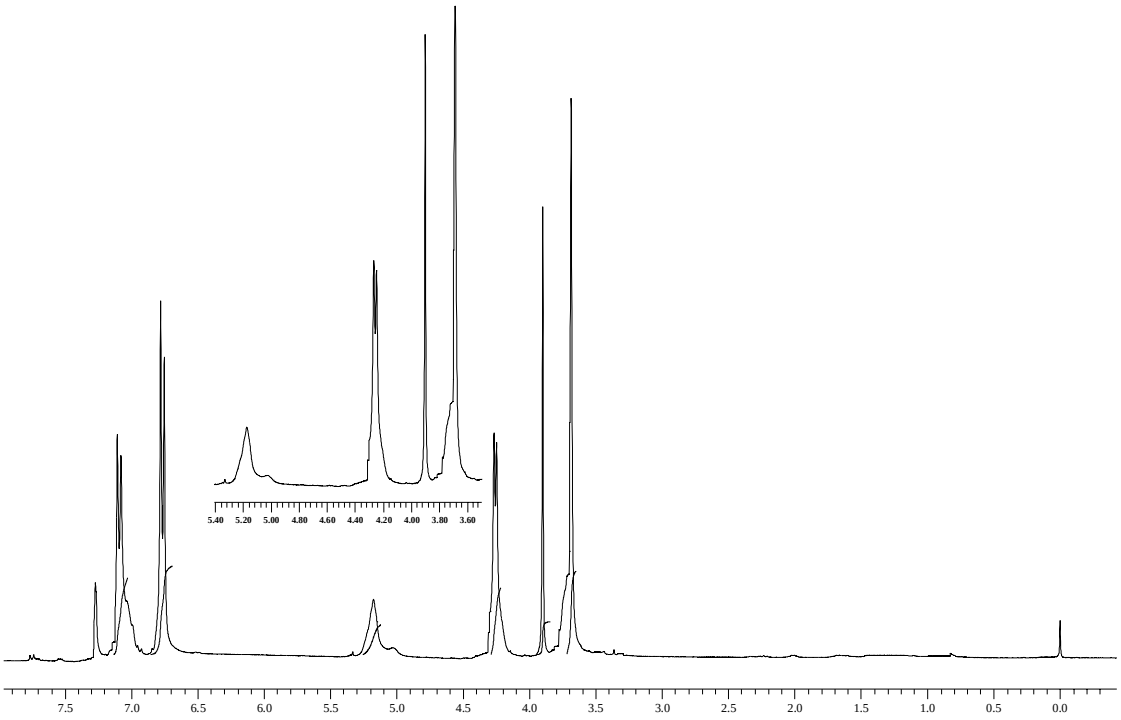


Figure 9. ^{1}H NMR of **9b**

Table 1. GC/MS spectra of N-methyl and N,N-dimethyl derivatives of amines **2b, 2d-e**, and **2f**

Product	**GC/MS (70 eV), m/z**
$C_6H_5(CH_2)_2NHMe$	135 (M^+, 3%), 105 ($[M-NHMe]^+$, 4), 91 ($[C_7H_7]^+$, 12), 77 ($[C_6H_5]^+$, 5), 44 ($[MeN^+(H)=CH_2]$, 100)
$C_6H_5(CH_2)_2NMe_2$	149 (M^+, 1%), 133 ($[M-Me]^+$, 1), 105 ($[M-NMe_2]^+$, 3), 91 ($[C_7H_7]^+$, 4), 77 ($[C_6H_6]^+$, 4), 58 ($Me_2N^+=CH_2$, 100)
$4NH_2C_6H_4CH_2NHMe$	136 (M^+, 43%), 135 ($[M-H-NH_2]^+$, 42), 119 ($[M-2H-Me]^+$, 7), 106 ($[M-NHMe]^+$, 100), 94 (16), 77 (12), 44 ($[MeN^+(H)=CH_2]$, 5)
$4NH_2C_6H_4CH_2NMe_2$	150 (M^+, 27%), 133 ($[M-NH_2-H]^+$, 3), 106 ($[M-NMe_2]^+$, 100), 77 (6), 58 ($Me_2N^+=CH_2$, 4)
$2NH_2C_6H_4CH_2NHMe$	136 (M^+, 82%), 121 ($[M-Me]^+$, 100), 106 ($[M-NHMe]^+$, 96), 94 (31), 77 (26), 44 ($[CH_3N^+(H)=CH_2]$, 12)
$2NH_2C_6H_4CH_2NMe_2$	150 (M^+, 48%), 135 ($[M-Me]^+$, 46), 118 ($[M-Me_2]^+$, 3), 106 ($[M-CH_2NMe_2]^+$, 100), 77 (15), 58 ($Me_2N^+=CH_2$, 13), 44 (21)
$4NH_2C_6H_4(CH_2)_2NHMe$	150 (M^+, 2%), 107 (100), 106 ($[M-CH_2NHMe]^+$, 54), 77 (10), 44 ($[MeN^+(H)=CH_2]$, 57)
$4NH_2C_6H_4(CH_2)_2NMe_2$	164 (M^+, 6), 106 ($[M-CH_2NMe_2]^+$, 8), 77 (4), 58 ($Me_2N^+=CH_2$, 100)

References

[i] Nystrom R. F. *J. Am. Chem. Soc.* **1955**, *77*, 2544-2545

[ii] Ludeman, S.M.; Zon, G. *J. Med. Chem.* **1975**, *18*, 1251-1253

[iii] Soledade, M.; Pedras, C.; Khan, A.Q.; Smith, K.C.; Stettner, S.L. *Can. J. Chem.* **1997**, *75*, 825-828.

[iv] Kost, D.; Zeichner, A.; Sprecher, M. *J. Chem. Soc., Perkin Trans. 2*, **1980**, 317

[v] Kita, Y.; Haruta, J.; Tagawa, H.; Tamura,Y. *J. Org. Chem.* **1980**, *45*, 4519.

[vi] Selva, M.; Tundo, P.; Perosa, A. *Tetrahedron Lett.* **2002** (43), 1217-1219.

[vii] Shriner, R. L.; Cross, J. M. *J. Am. Chem. Soc.* **1938**, *60*, 2338-40.

[viii] Prugh, J. D.; Birchenough, L. A., Egbertson, M. S. *Synth. Commun.* **1992**, 2357-60.

[ix] Matsumura, Y.; Ohishi, T.; Sonoda, C.; Maki, T.; Watanabe, M. *Tetrahedron* **1997**, *53*, 4579-4592.