Supporting Information

Hofmann Rearrangement of Carboxamides Mediated by Hypervalent Iodine Species Generated in situ from Iodobenzene and Oxone: Reaction Scope and Limitation

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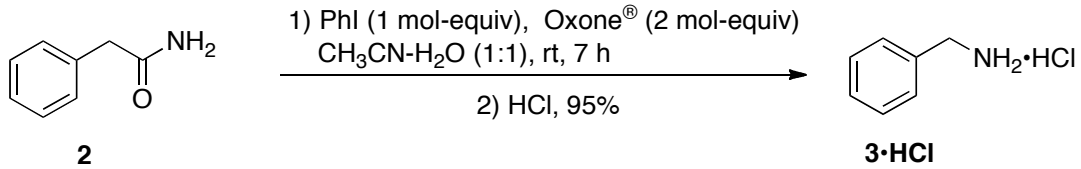
Contents: Page

General. All commercial reagents were ACS reagent grade and used without further purification. NMR spectra were recorded at 300 and 500 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR). Chemical shifts (δ) are reported in parts per million. GC-MS analysis was carried out with a HP 5890A Gas Chromatograph using a 5970 Series mass selective detector.

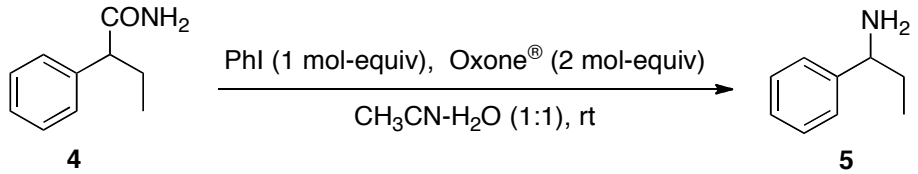
Preparation of benzylamine hydrochloride 3•HCl from 2-phenylacetamide 2 via Hofmann rearrangement.



2 **3•HCl**

To a mixture of Oxone® (1.23 g, 2 mmol) and *iodobenzene* (0.204 g, 1 mmol) in CH_3CN/H_2O (6 mL, 1:1, v/v), 2-phenylacetamide **2** (0.135 g, 1 mmol) was added under stirring at room temperature. The reaction mixture was stirred at room temperature for 7 h (the reaction was monitored by GC-MS). After completion of the reaction, the reaction mixture was filtered under reduced pressure. The insoluble residue (mainly containing inorganic salts) was washed with CH_3CN (5 mL) and discarded. The combined filtrate was mixed with HCl (15 mL, 20% aqueous solution), and the mixture was washed with ether (10 mL) to remove all non-polar impurities. The aqueous layer was concentrated at reduced pressure to give a sticky solid, which was thoroughly dried in vacuum. Crystallization from ethanol-ether afforded 0.136 g (95%) of benzylamine hydrochloride **3•HCl** as a slightly yellow crystalline solid, mp 253-255 °C (lit.[1], mp 258-260 °C). ^{1}H NMR 300 MHz (CD_3OD): δ 4.12 (br s, 2H, -C<u>H</u>$_2$-), 7.40 -7.48 (m, 5H, Ph).

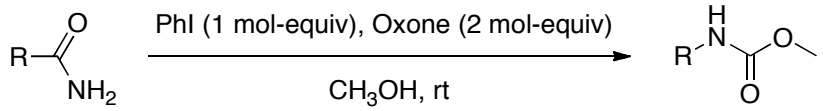
Preparation of (±)-α-phenylpropylamine 5 from 2-phenylbutyramide 4



4 **5**

To the mixture of Oxone® (1.23 g, 2 mmol) and iodobenzene (0.204 g, 1 mmol) in CH_3CN/H_2O (6 mL, 1:1, v/v), 2-phenylbutyramide **4** (0.163 g, 1 mmol) was added under stirring at room temperature. The reaction mixture was stirred at room temperature for 7 h (the reaction was monitored by GC-MS). After completion of the reaction, the reaction mixture was diluted with H_2O (10 mL), and extracted with $CHCl_3$ (3x10 mL). The organic phase was separated, and dried over Na_2SO_4 (anhydrous). Evaporation of $CHCl_3$ under reduced pressure afforded 0.115 g (85%) of (±)-α-phenylpropylamine **5** as a pale yellow oil. ^{1}H NMR 300 MHz ($CDCl_3$): δ 0.87 (t, *J*=7.5 Hz, 3H, -CH_2C<u>H</u>$_3$), 1.61 (br s, 2H, N<u>H</u>$_2$), 1.67-1.72 (m, 2H, -C<u>H</u>$_2$$CH_3$), 3.80 (t, *J*=6.9 Hz, 1H, -C<u>H</u>-), 7.31-7.33 (m, 5H, Ph). The product was identical to a commercially available sample (Aldrich) according to NMR and GC-MS data.

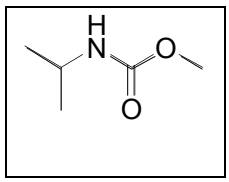
General procedure for preparation of carbamates 7a-k from amides 6a-k via Hofmann rearrangement.



6a-k **7a-k**

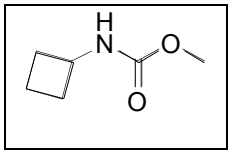
To the mixture of Oxone® (2 mol-equiv) and iodobenzene (1 mol-equiv) in MeOH (5 mL), an appropriate amide **6a-k** (1 mmol) was added under stirring at room temperature. The reaction mixture was stirred at room temperature for 7-12 h (the reaction was monitored by GC-MS). After completion of the reaction, the solvent was evaporated under vacuum. The resulting residue was diluted with H_2O (10 mL), and extracted with EtOAc (3x10 mL). The organic phase was separated, and dried over $MgSO_4$ (anhydrous). Evaporation of EtOAc under reduced pressure afforded a final product which in case of crystalline products was additionally purified by recrystallization from $CHCl_3$/hexane.

Methyl N-isopropylcarbamate 7c.



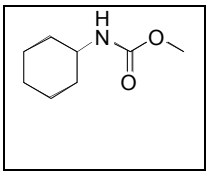
Reaction of isobutyramide **6c** (0.087 g, 1 mmol) according to the general procedure afforded 0.111 g (95%) of product **7c**, isolated as an oil. ^{1}H NMR 500 MHz ($CDCl_3$): δ 1.15 (d, *J*=6.3 Hz, 6H, 2C<u>H</u>$_3$), 3.65 (s, 3H, COOC<u>H</u>$_3$), 3.81 (br s, 1H, C<u>H</u>), 4.55 (br s, 1H, N<u>H</u>). EI-MS *m/z* (relative intensity, %): 117 $[M]^+$ (<5), 102 $[M\text{-}CH_3]^+$(100), 86 $[M\text{-}CH_3O]^+$(5), 70 $[C_3H_4NO]^+$ (6), 59 $[C_2H_3O_2]^+$ (26), 58 $[C_3H_8N]^+$ (50).

Methyl N-cyclobutylcarbamate 7d.



Reaction of cyclobutanecarboxamide **6d** (0.099 g, 1 mmol) according to the general procedure afforded 0.119 g (92%) of product **7d**, isolated as an oil. ^{1}H NMR 300 MHz ($CDCl_3$): δ 1.62-1.71 (m, 2H), 1.81-1.88 (m, 2H), 2.27-2.32 (m, 2H), 3.64 (s, 3H, COOC<u>H</u>$_3$), 4.13-4.18 (m, 1H, C<u>H</u>), 4.89 (br s, 1H, N<u>H</u>). EI-MS *m/z* (relative intensity, %): 128 $[M\text{-}1]^+$ 10), 110 (16), 95 $[C_5H_5NO]^+$(100), 81 $[C_5H_7N]^+$ (13), 69 $[C_4H_7N]^+$ (43), 55$[C_4H_7]^+$ (32).

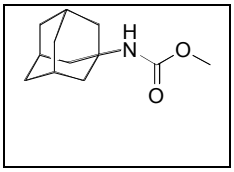
Methyl N-cyclohexylcarbamate 7e.



Reaction of cyclohexanecarboxamide **6e** (0.127 g, 1 mmol) according to the general procedure afforded 0.140 g (89%) of product **7e**, isolated as a slightly yellow microcrystalline solid, mp 73.5-74.5 °C (lit.[2], mp 72-75 °C). ^{1}H NMR 500 MHz

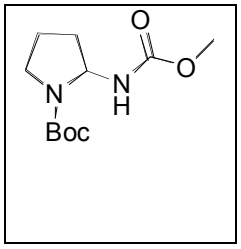
($CDCl_3$): δ 1.09-1.20 (m, 3H), 1.31-1.38 (m, 2H), 1.58-1. 62 (m, 1H), 1.67-1.72 (m, 2H), 1.92-1.94 (m, 2H), 3.48 (br s, 1H, C<u>H</u>), 3.65 (s, 3H, COOC<u>H</u>$_3$), 4.56 (br s, 1H, N<u>H</u>).

Methyl *N*-(1-adamantanyl)carbamate 7f.



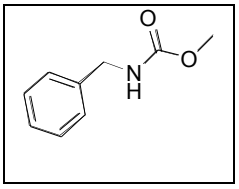
Reaction of 1-adamantanecarboxamide **6f** (0.179 g, 1 mmol) according to the general procedure afforded 0.188 g (90%) of product, isolated as a microcrystalline solid, mp 118-120 °C (lit.[3], mp 120 °C). ^{1}H NMR 300 MHz ($CDCl_3$): δ 1.67 (s, 6H), 1.93 (s, 6H), 2.07 (s, 3H), 3.60 (s, 3H, COOC<u>H</u>$_3$), 4.54 (br s, 1H, N<u>H</u>).

Methyl (1-Boc-pyrrolidin-2-yl)carbamate 7g.



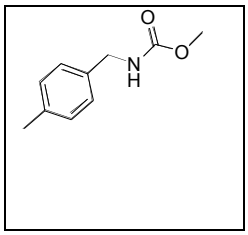
Reaction of 1-Boc-L-prolinamide **6g** (0.214 g, 1 mmol) according to the general procedure afforded 0.183 g (75%) of product **7g**, isolated as an oil. ^{1}H NMR 300 MHz ($CDCl_3$): δ 1.44 (s, 9H, COOC(C<u>H</u>$_3$)$_3$), 1.81-1.84 (m, 2H), 2.34-2.38 (m, 2H), 3.16 (br s, 2H), 3.68 (s, 3H, COOC<u>H</u>$_3$), 4.63 (br s, 2H, N<u>H</u> and C<u>H</u>). ^{13}C NMR 75 MHz ($CDCl_3$): δ 21.02, 28.62 (COOC(<u>C</u>H$_3$)$_3$), 33.21, 46.74, 51.88 (COO<u>C</u>H$_3$), 79.43, 83.04, 174.02, 179.51.

Methyl N-benzylcarbamate 7h.



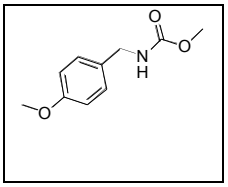
Reaction of 2-phenylacetamide **6h** (0.135 g, 1 mmol) according to the general procedure afforded 0.160 g (97%) of product **7h**, isolated as a microcrystalline solid, mp 63-65 °C (lit.[4], mp 64-65 °C). ^{1}H NMR 300 MHz ($CDCl_3$): δ 3.69 (s, 3H, COOC<u>H</u>$_3$), 4.36 (s, 2H, -C<u>H</u>$_2$-), 5.09 (br s, 1H, N<u>H</u>), 7.28-7.34 (m, 5H, Ph).

Methyl N-(4-methylbenzyl)carbamate 7i.



Reaction of 2-(*p*-tolyl)acetamide **6i** (0.149 g, 1 mmol) according to the general procedure afforded 0.166 g (93%) of product **7i**, isolated as a white microcrystalline solid, mp 68-70 °C. ^{1}H NMR 300 MHz ($CDCl_3$): δ 2.33 (s, 3H, -C<u>H</u>$_3$), 3.69 (s, 3H, COOC<u>H</u>$_3$), 4.32 (s, 2H, -C<u>H</u>$_2$-), 4.98 (br s, 1H, N<u>H</u>), 7.12-7.19 (m, 4H$_{arom.}$).

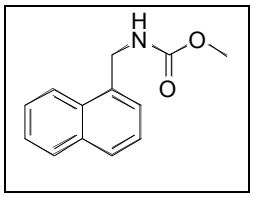
Methyl N-(*p*-methoxylbenzyl)carbamate 7j.



Reaction of 2-(4-methoxyphenyl)acetamide **6j** (0.165 g, 1 mmol) according to the general procedure afforded 0.185 g (95%) of product **7j**, isolated as a white microcrystalline solid, mp 73-74 °C (lit.[5], mp 73-74 °C). ^{1}H NMR 300 MHz ($CDCl_3$): δ 3.68 (s, 3H, COOC<u>H</u>$_3$), 3.78 (s, 3H, -OC<u>H</u>$_3$), 4.28 (br s, 2H, -C<u>H</u>$_2$-), 4.97

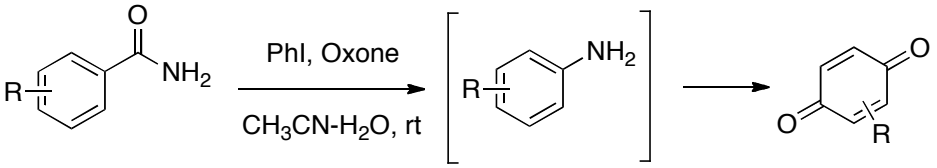
(br s, 1H, NH), 6.84-6.90 (m, $2H_{arom.}$), 7.19-7.24 (m, $2H_{arom.}$).

Methyl *N*-[(1-naphthyl)methyl]carbamate 7k.



Reaction of 1-naphthaleneacetamide **6k** (0.185 g, 1 mmol) according to the general procedure afforded 0.200 g (93%) of product, isolated as pale yellow microcrystalline solid, mp 84-86 °C (lit.[6], mp 84-88 °C). ^{1}H NMR 300 MHz ($CDCl_3$): δ 3.68 (s, 3H, $COOCH_3$), 4.79 (br s, 2H, $-CH_2-$), 5.09 (br s, 1H, NH), 7.39-7.41 (m, 2H, ArH), 7.46-7.52 (m, 2H, ArH), 7.77-7.78 (m, 1H, ArH), 7.84-7.86 (m, 1H, ArH), 7.96-8.01 (m, 1H, ArH).

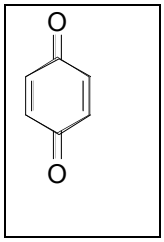
General procedure for preparation of 1,4-benzoquinones 10a-e from amides 8a-e.



8a-e **10a-d**

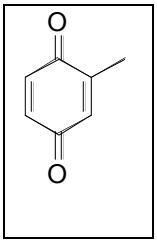
To the mixture of Oxone® (2 mol-equiv) and iodobenzene (1 mol-equiv) in CH_3CN/H_2O (6 mL, 1:1, v/v), an appropriate amide **8a-e** (1 mmol) was added under stirring at room temperature. The reaction mixture was stirred at room temperature for 7-12 h (the reaction was monitored by GC-MS). After completion of the reaction, the reaction mixture was diluted with H_2O (10 mL), and extracted with $CHCl_3$ (3x10 mL). The organic phase was separated, and dried over Na_2SO_4 (anhydrous). Evaporation of $CHCl_3$ under reduced pressure afforded a pure product **10**.

1,4-Benzoquinone 10a.



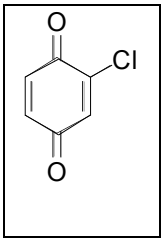
Reaction of benzamide **8a** (0.121 g, 1 mmol) according to the general procedure afforded 0.106 g (98%) of product **10a**, isolated as an orange microcrystalline solid, mp 115-116 °C (lit.[7], mp 116 °C). ^{1}H NMR 300 MHz ($CDCl_3$): δ 6.78 (s, 4H). The same product was obtained in reaction with 4-methoxybenzamide **8e** (0.102 g, 94%).

2-Methyl-1,4-benzoquinone 10b.



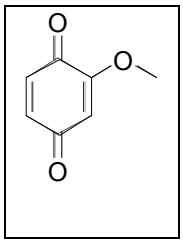
Reaction of *o*-toluamide **8b** (0.135 g, 1 mmol) according to the general procedure afforded 0.122 g (100%) of product **10b**, isolated as a yellow microcrystalline solid, mp 68-69 °C (lit.[7], mp 69 °C). ^{1}H NMR 300 MHz ($CDCl_3$): δ 2.03 (s, 3H, -C$\underline{H}_3$), 6.59 (s, 1H), 6.65-6.76 (m, 2H).

2-Chloro-1,4-benzoquinone 10c.



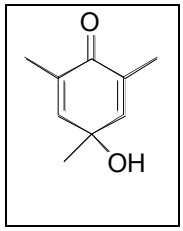
Reaction of 2-chlorobenzamide **8c** (0.155 g, 1 mmol) according to the general procedure afforded 0.135 g (95%) of product **10c**, isolated as a yellowish microcrystalline solid, mp 54-56 °C (lit.[7], mp 55-56 °C). ^{1}H NMR 300 MHz ($CDCl_3$): δ 6.80 (d, *J*=9.8 Hz, 1H), 6.91 (d, *J*=9.8 Hz, 1H), 6.99 (s, 1H).

2-Methoxy-1,4-benzoquinone 10d.



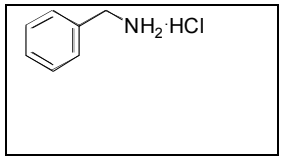
Reaction of 3-methoxybenzamide **8d** (0.151 g, 1 mmol) according to the general procedure afforded 0.134 g (97%) of product **10d**, isolated as a slightly brown microcrystalline solid, mp 142-144 °C (lit.[7], mp 144 °C). ^{1}H NMR 300 MHz ($CDCl_3$): δ 3.83 (s, 3H, -OC$\underline{H}_3$), 5.95 (br s, 1H), 6.72 (br s, 2H).

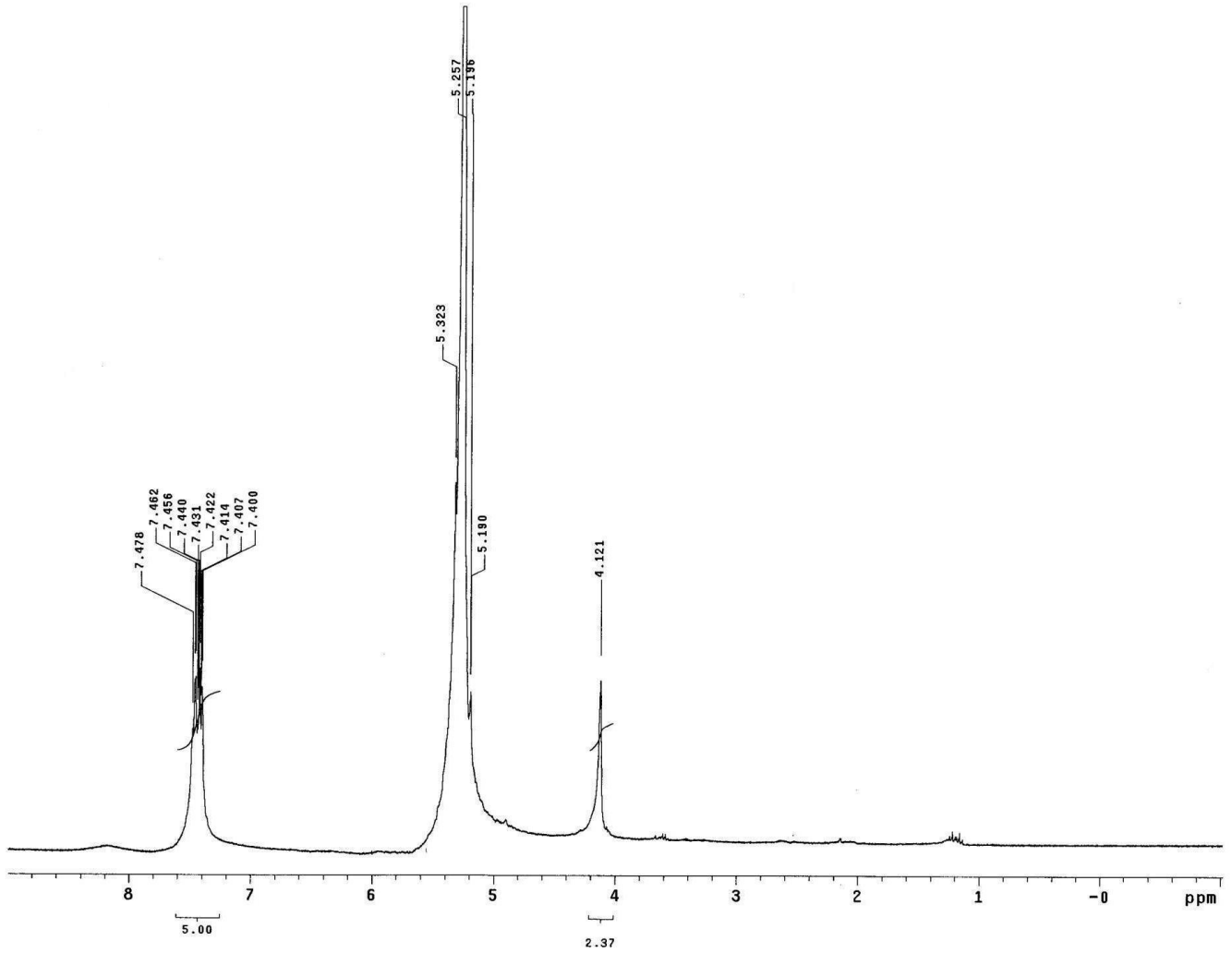
4-Hydroxy-2,4,6-trimethylcyclohexa-2,5-dienone 10e.

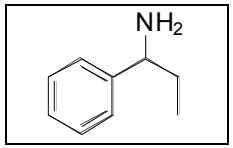


Reaction of 2,4,6-trimethylbenzamide **8f** (0.163 g, 1 mmol) according to the general procedure afforded product **10e**, isolated as a semisolid mass which on recrystallization from EtOH/water yields pure crystalline product 0.144 g (95%), mp 44.5-45.5 °C (lit.[8], mp 45-46 °C). ^{1}H NMR 300 MHz ($CDCl_3$): δ 1.43 (s, 3H, 4-C$\underline{H}_3$), 1.86 (s, 6H, 2,6-C$\underline{H}_3$), 6.62 (br s, 2H).

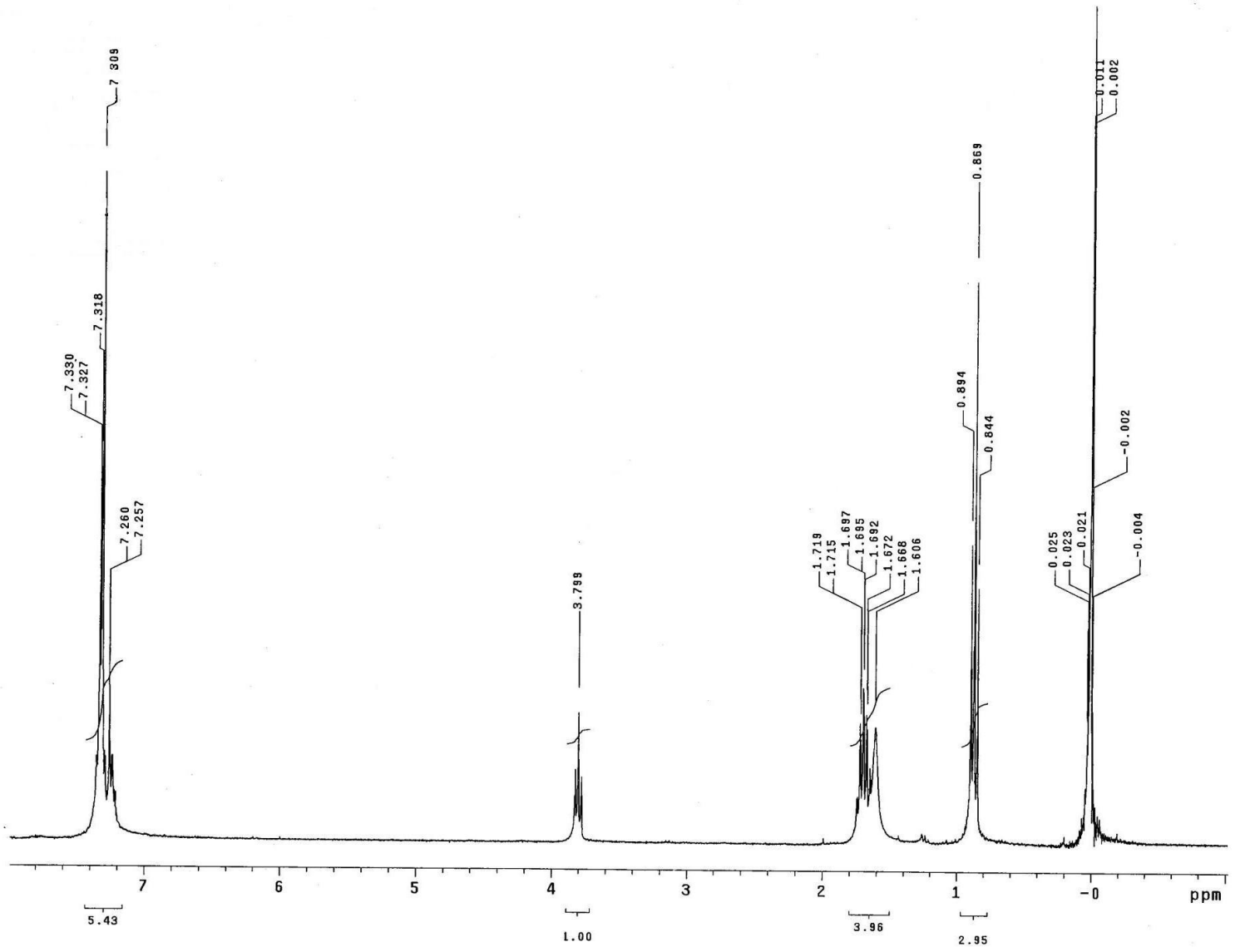
3. Copies of ^{1}H and ^{13}C NMR spectra
Benzylamine hydrochloride 3•HCl (300 MHz, $CDCl_3$)



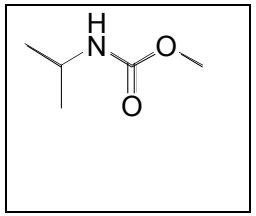


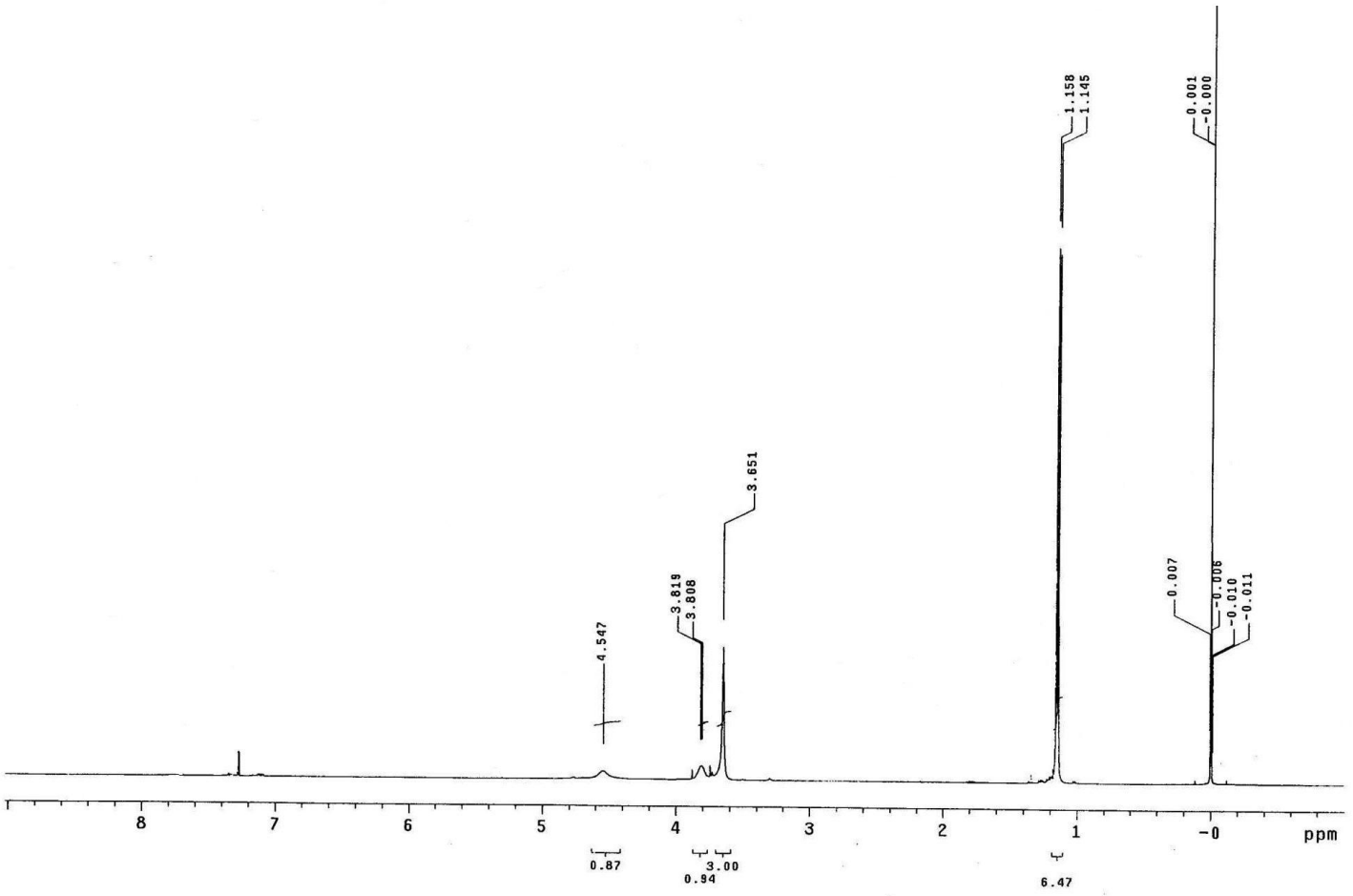


(±)-α-Phenylpropylamine 5 (300 MHz, $CDCl_3$)

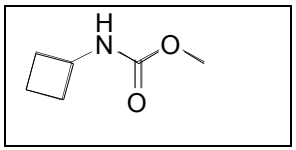


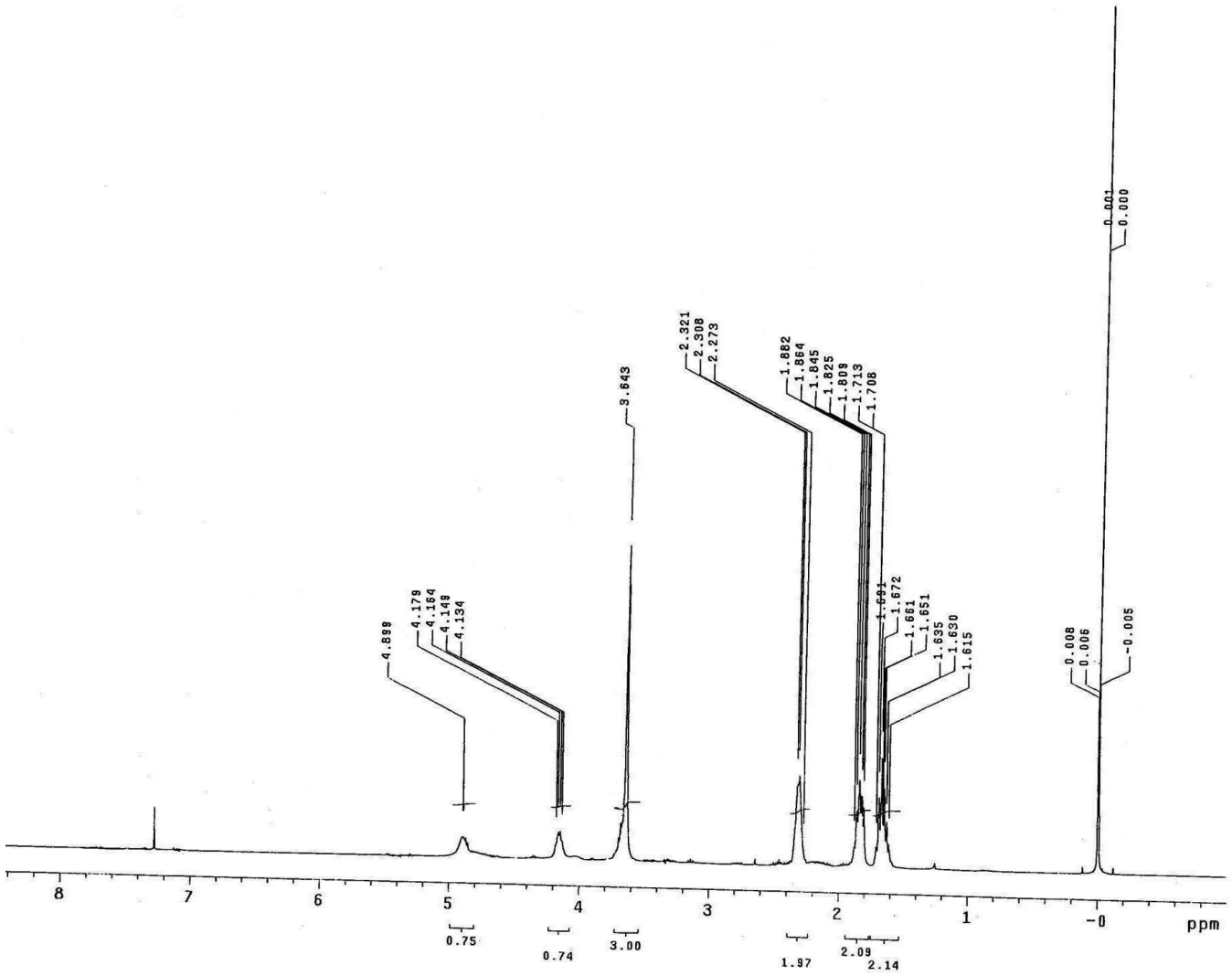
Methyl N-isopropylcarbamate 7c (500 MHz, $CDCl_3$)



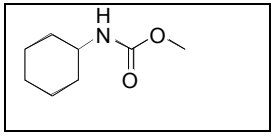


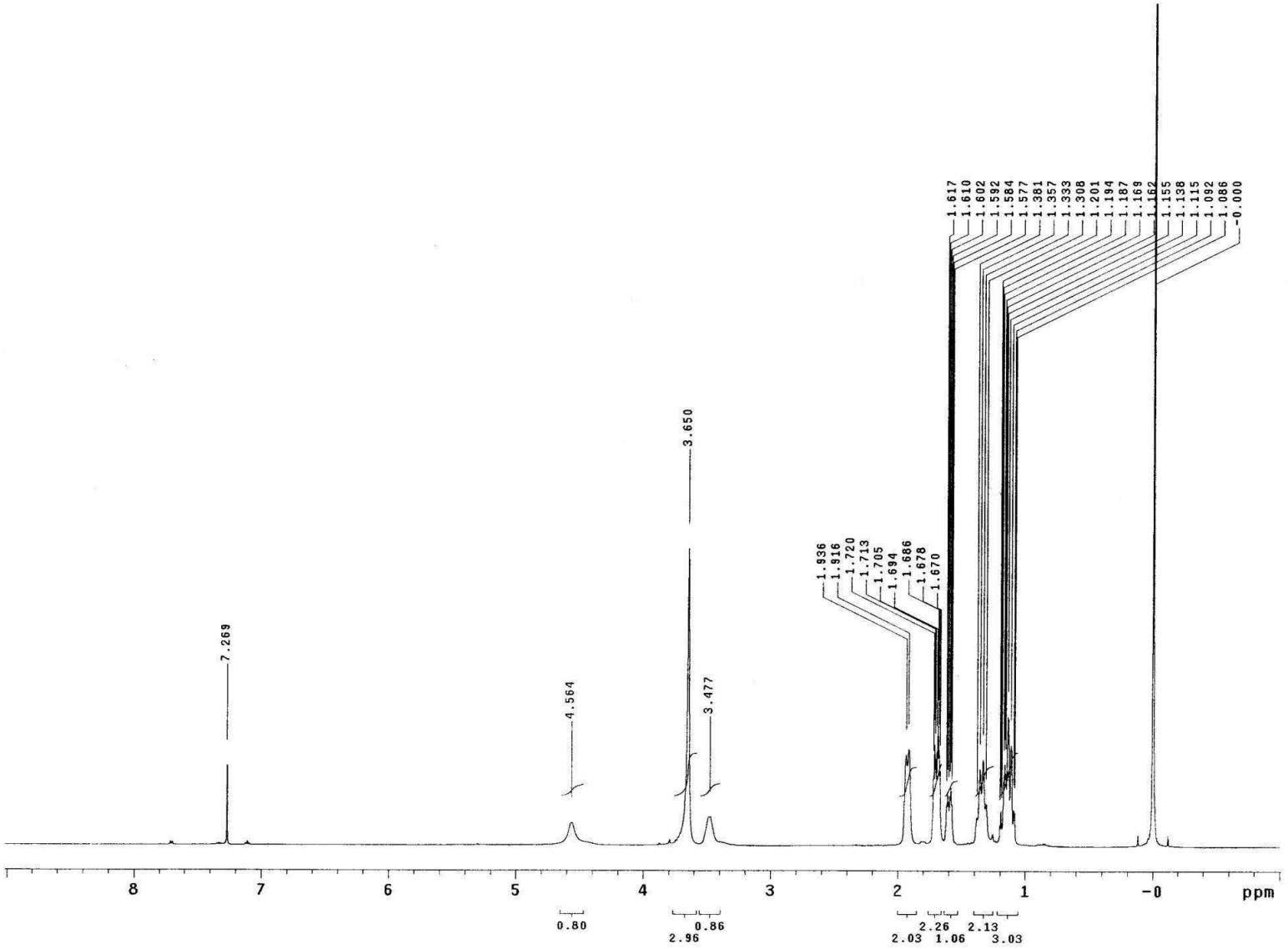
Methyl N-cyclobutylcarbamate 7d (300 MHz, $CDCl_3$)

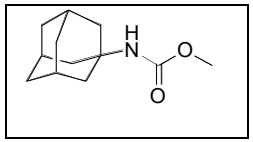




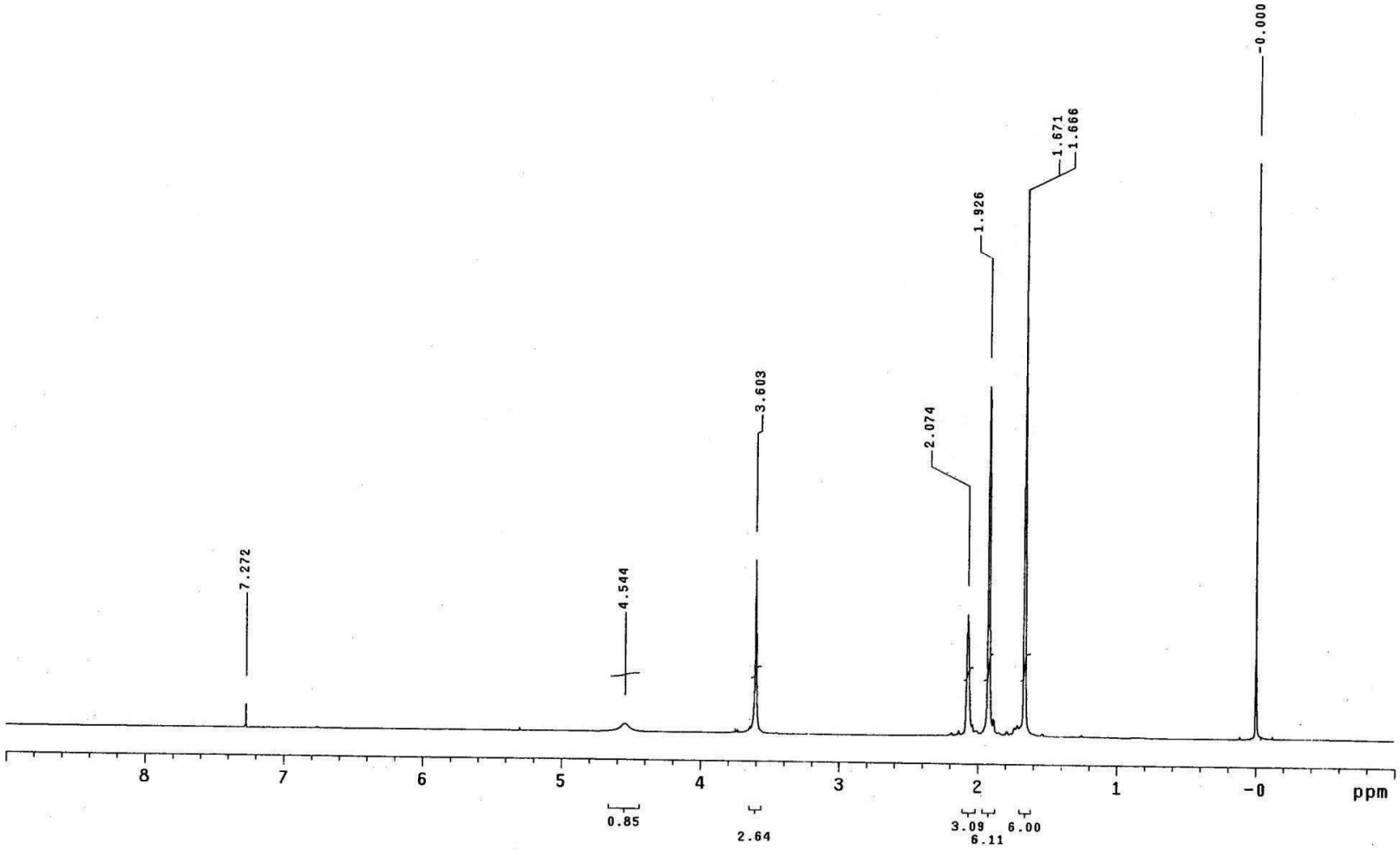
Methyl N-cyclohexylcarbamate 7e (500 MHz, $CDCl_3$)



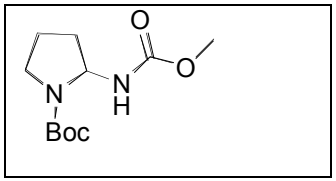


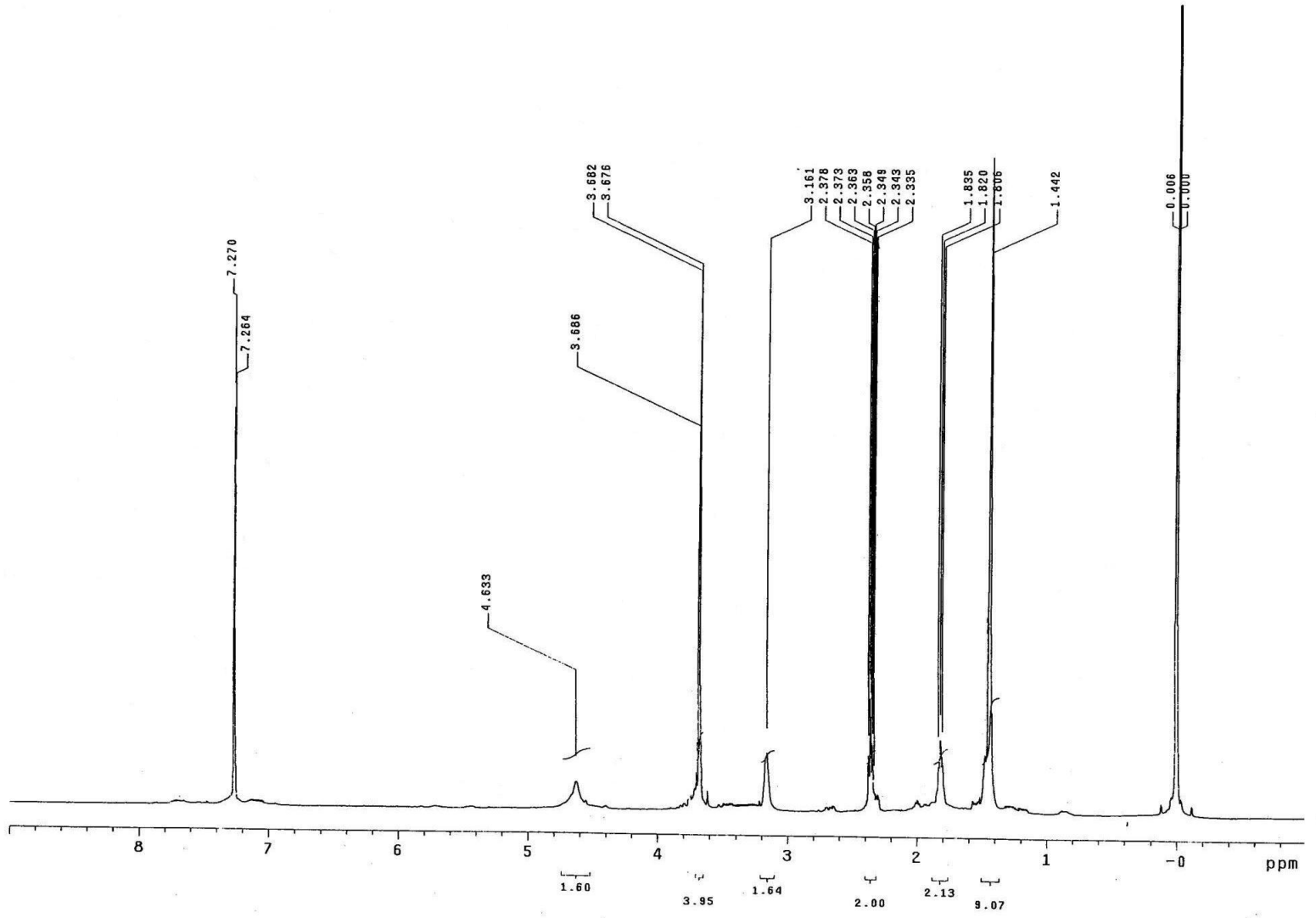


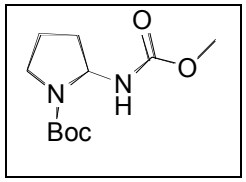
Methyl N-(1-adamantanyl)carbamate 7f (300 MHz, $CDCl_3$)



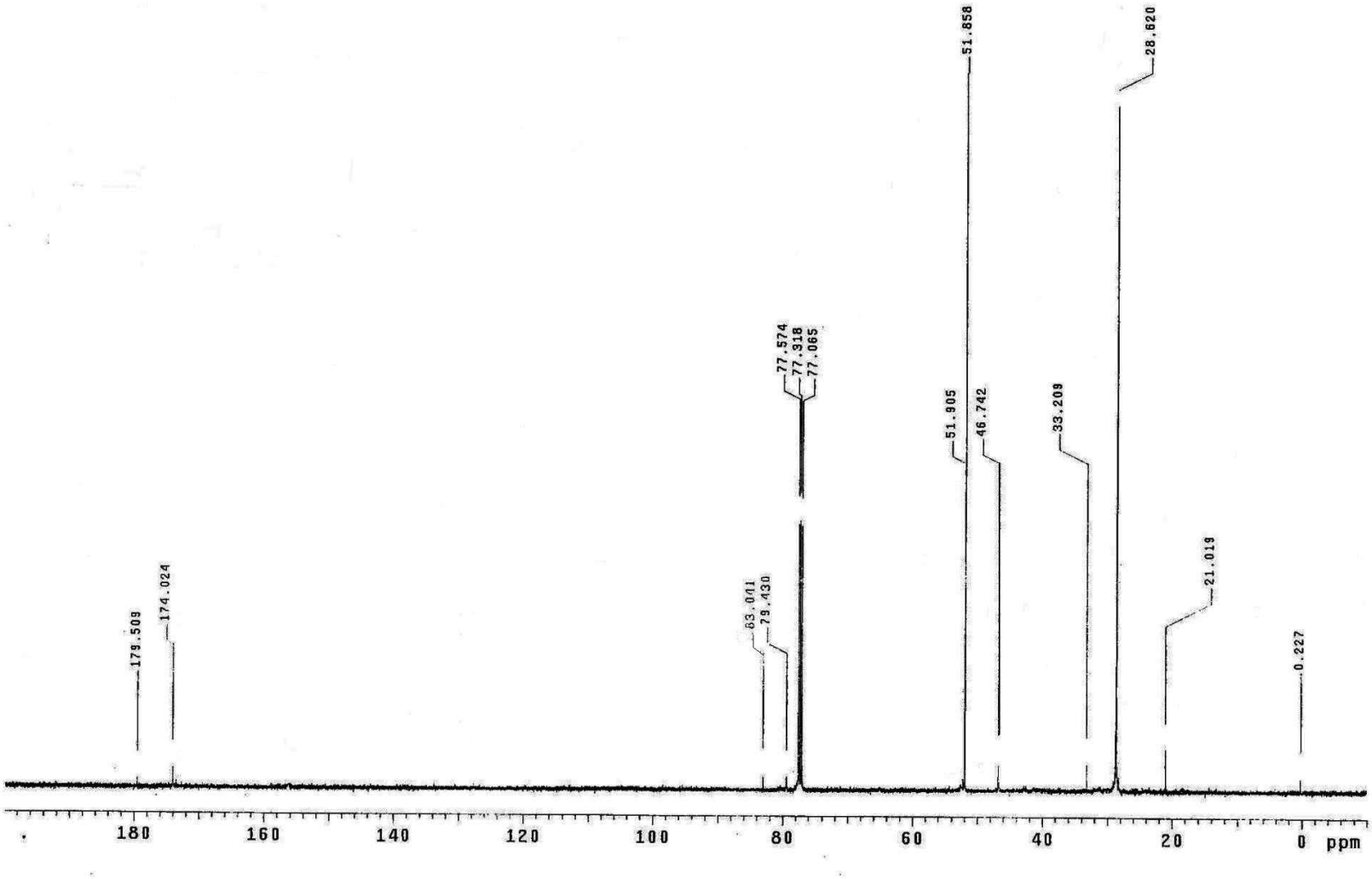
Methyl (1-Boc-pyrrolidin-2-yl)carbamate 7g (300 MHz, $CDCl_3$)

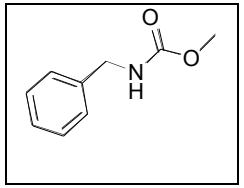




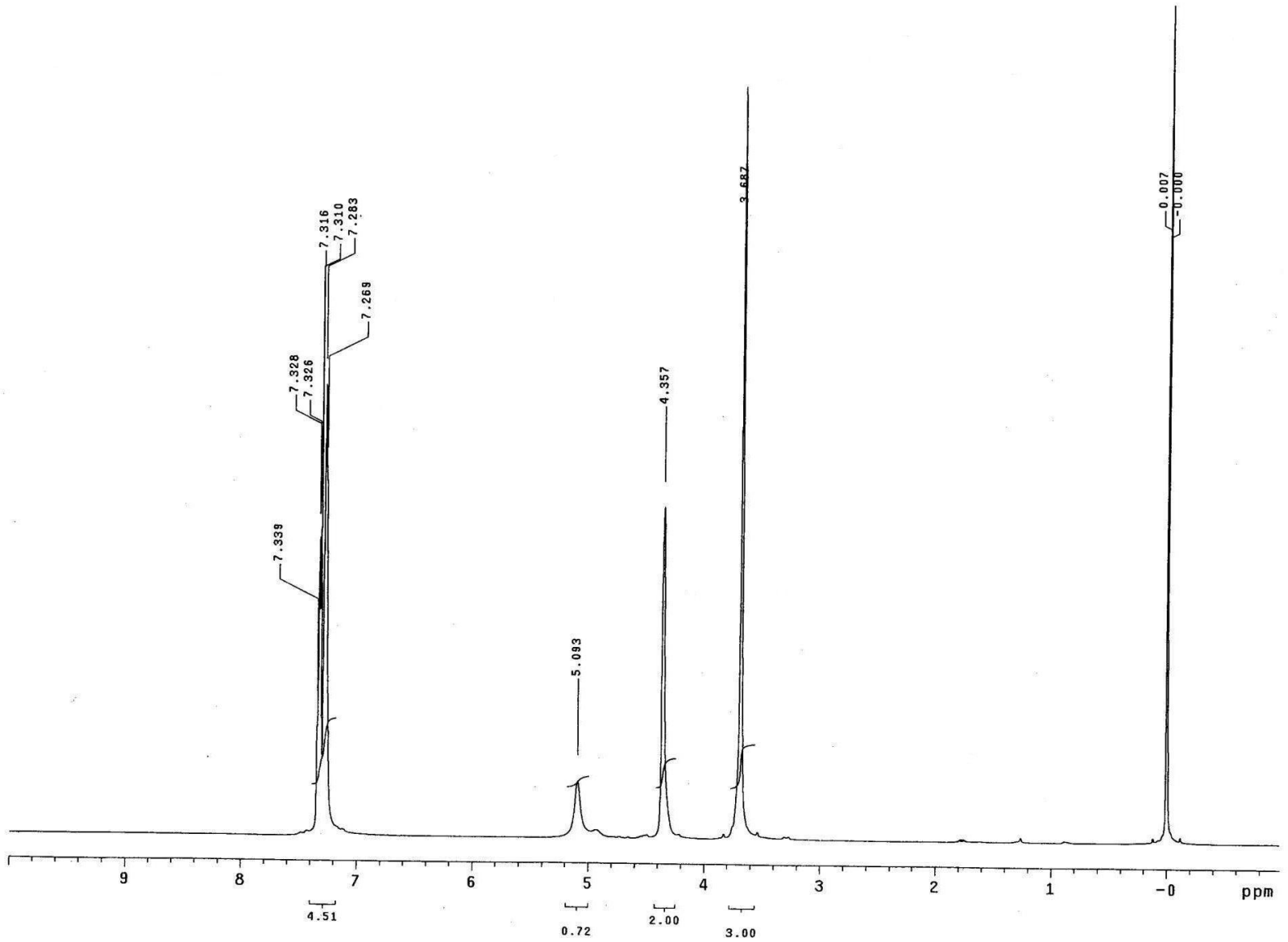


Methyl (1-Boc-pyrrolidin-2-yl)carbamate 7g (75 MHz, $CDCl_3$)

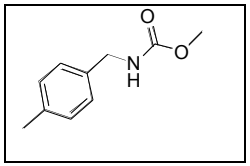


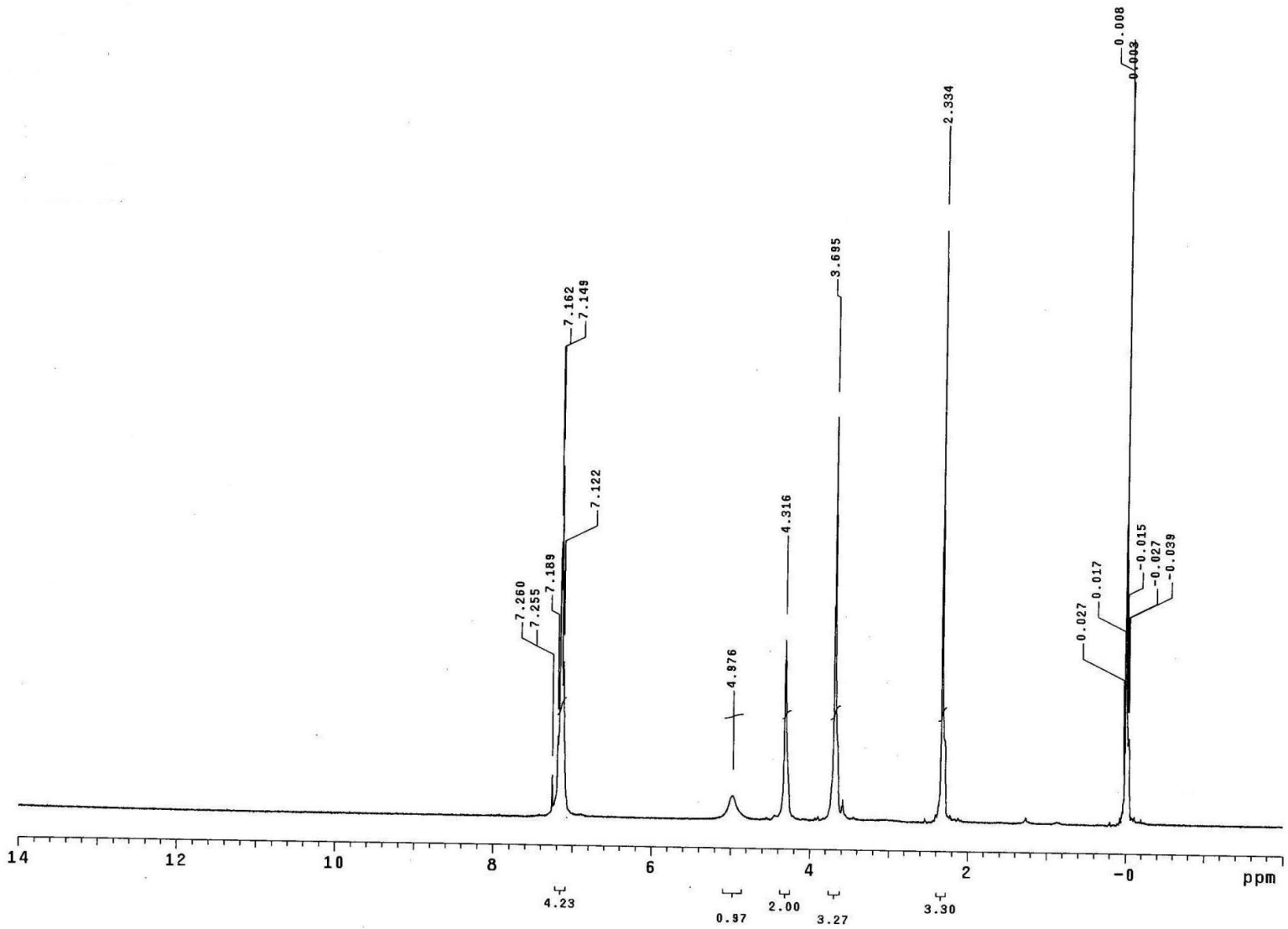


Methyl N-benzylcarbamate 7h (300 MHz, $CDCl_3$)

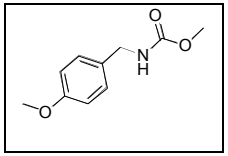


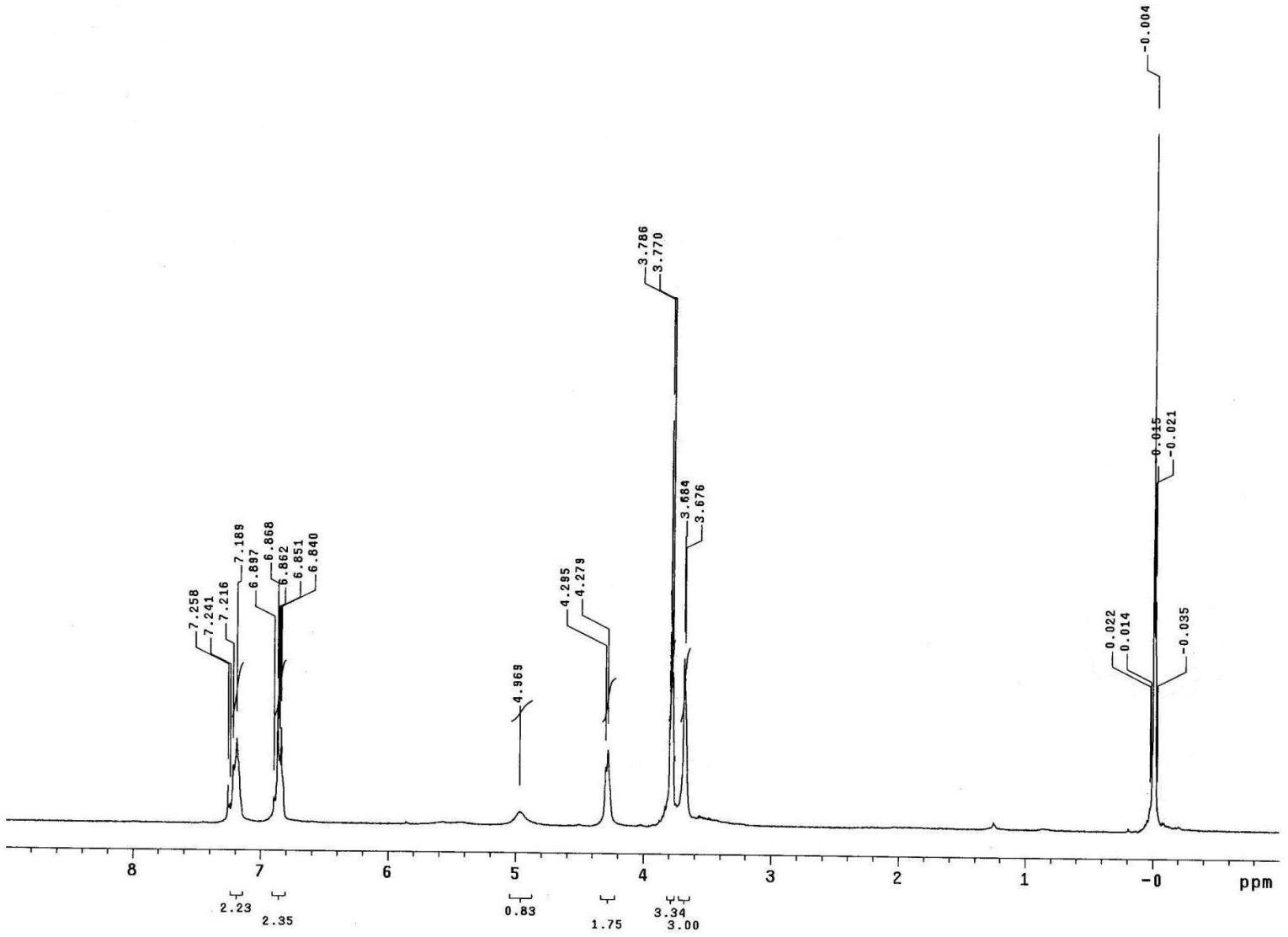
Methyl N-(4-methylbenzyl)carbamate 7i (300 MHz, $CDCl_3$).

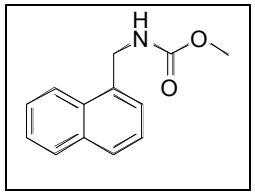




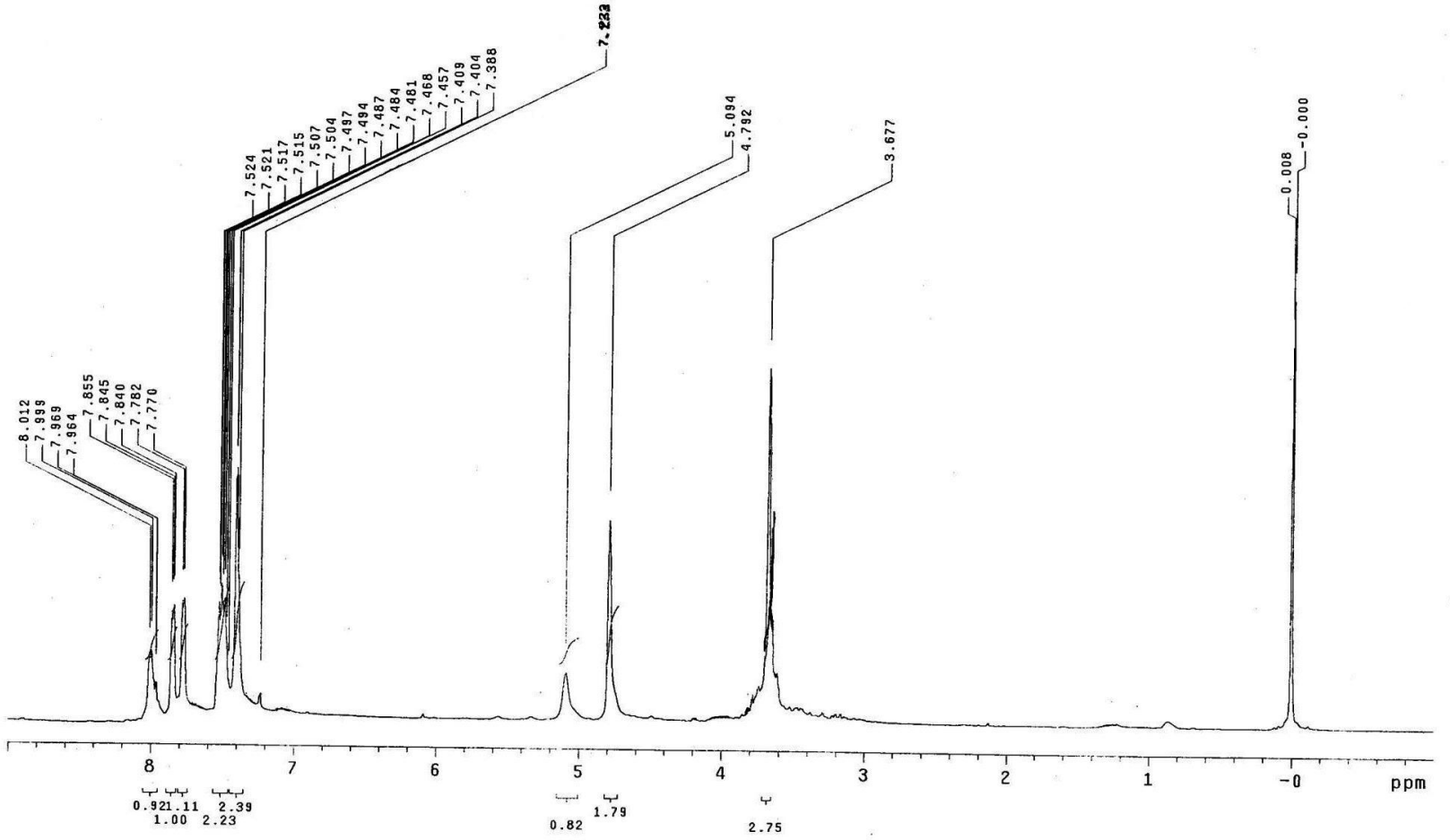
Methyl N-(*p*-methoxylbenzyl)carbamate 7j (300 MHz, $CDCl_3$)



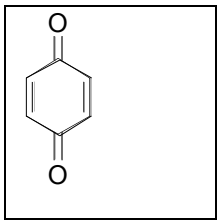


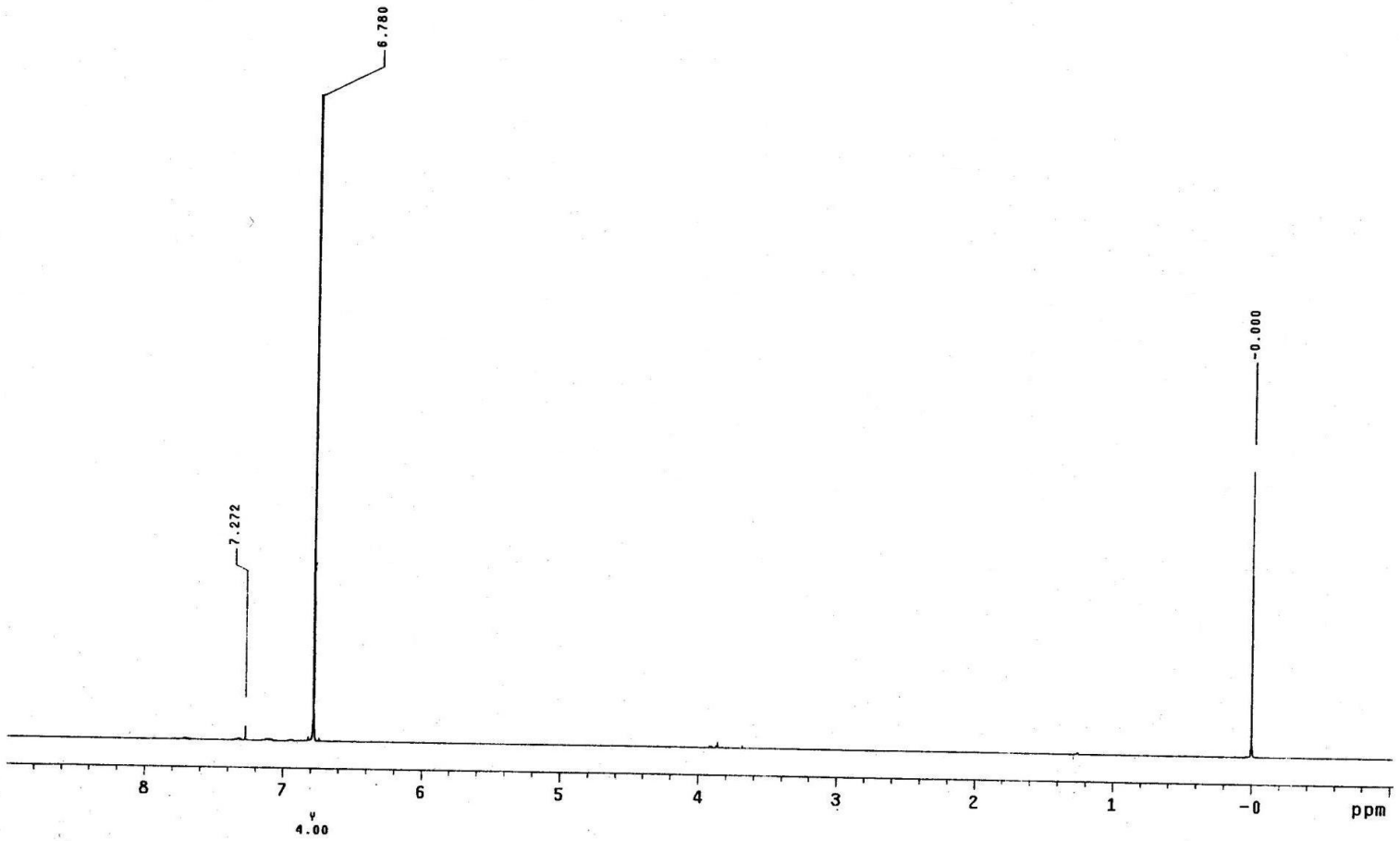


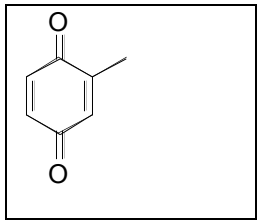
Methyl *N*-[(1-naphthyl)methyl]carbamate 7k (300 MHz, $CDCl_3$).



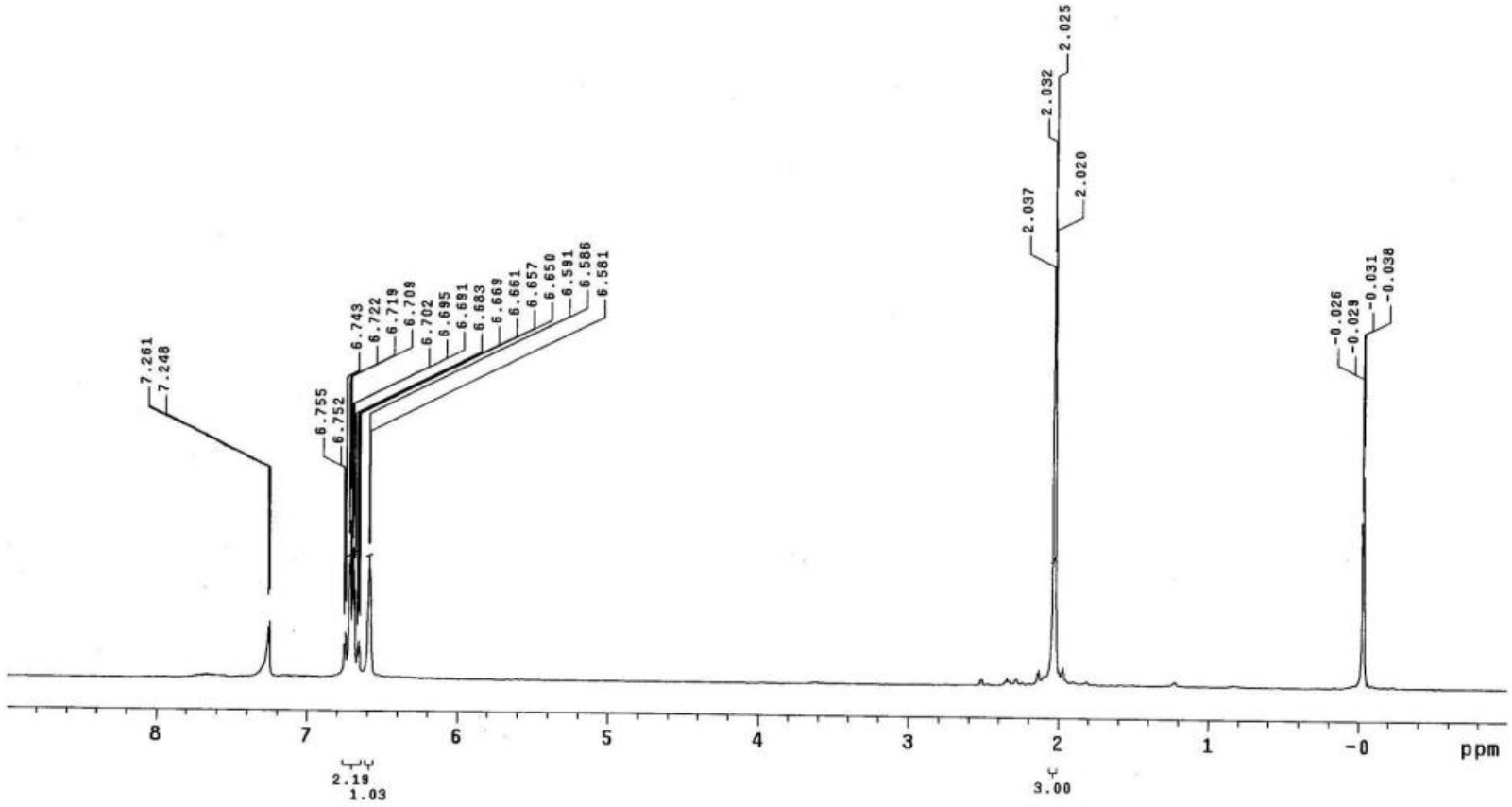
1,4-Benzoquinone 10a (300 MHz, $CDCl_3$)

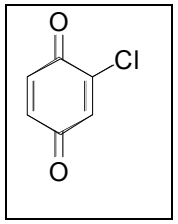




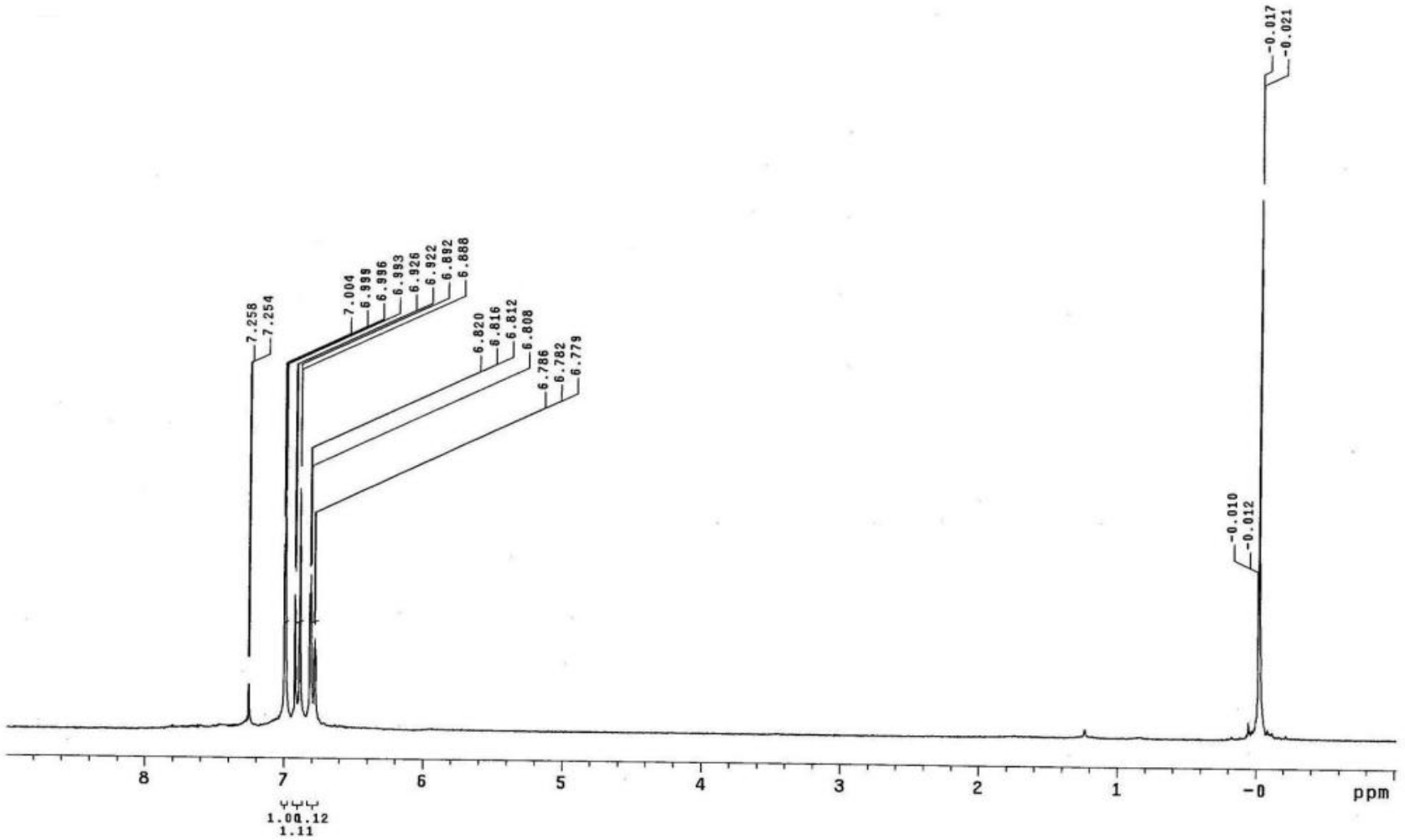


2-Methyl-1,4-benzoquinone 10b (300 MHz, $CDCl_3$)

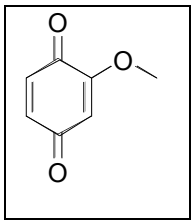


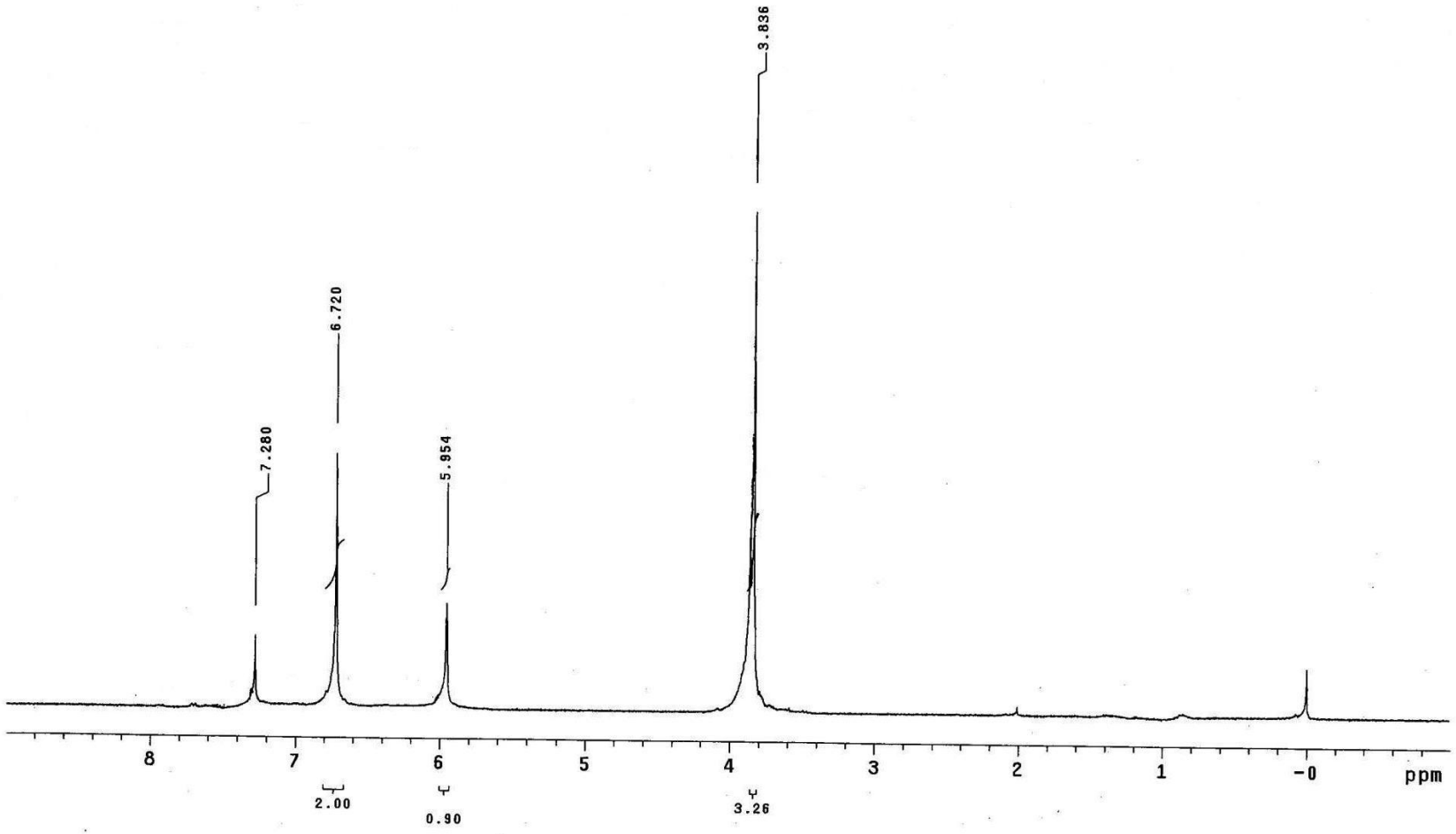


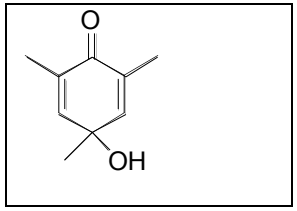
2-Chloro-1,4-benzoquinone 10c (300 MHz, $CDCl_3$)



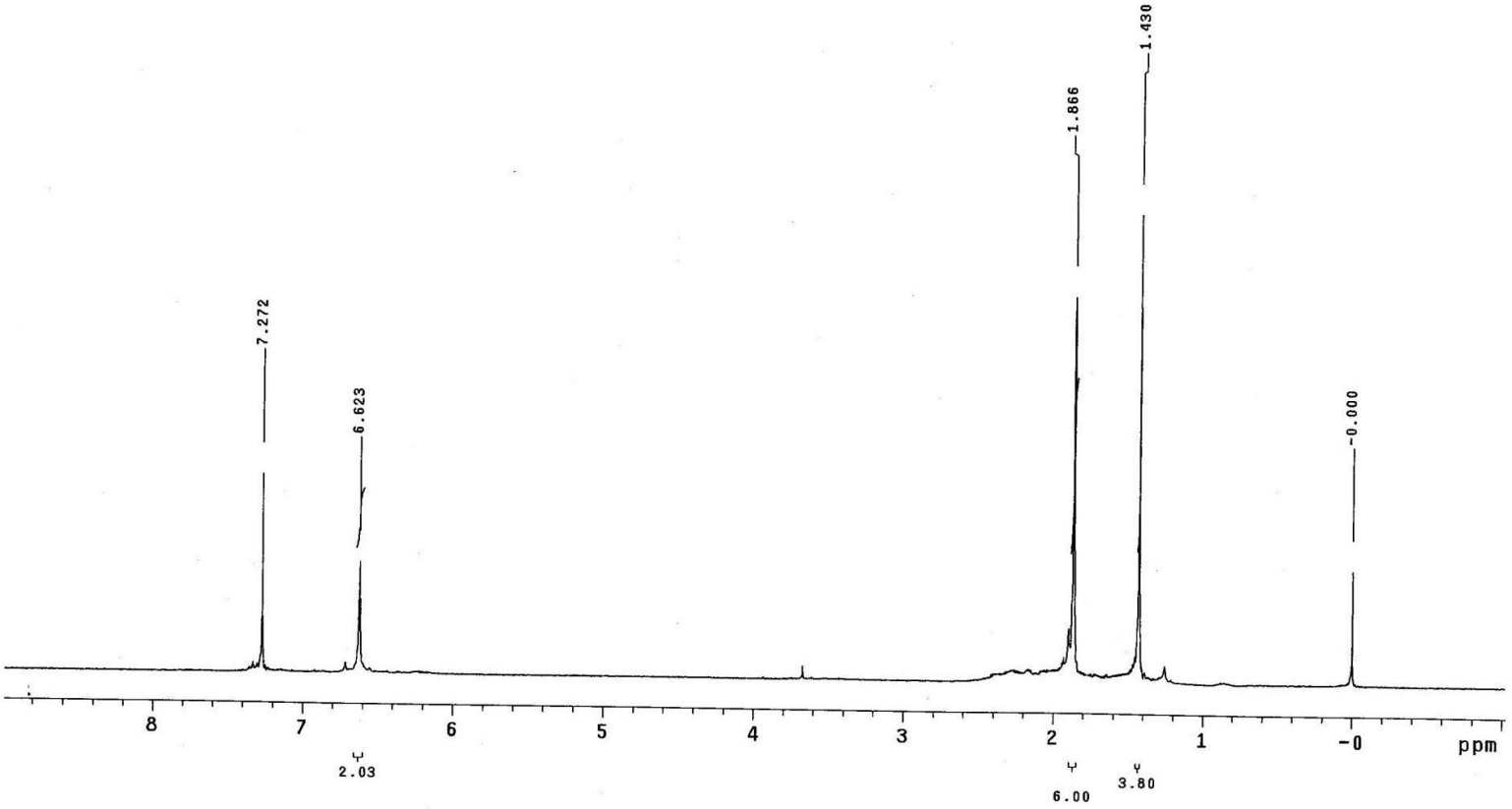
2-Methoxy-1,4-benzoquinone 10d (300 MHz, $CDCl_3$).







4-Hydroxy-2,4,6-trimethylcyclohexa-2,5-dienone 10e (300 MHz, $CDCl_3$)



References

1. Davies, S. G.; Mortimer, D. A. B.; Mulvaney, A. W.; Russell, A. J.; Skarphedinsson, H.; Smith, A. D.; Vickers, R. J. *Org. Biomol. Chem.* **2006**, *6*, 1625.
2. Radlick, P.; Brown, L. R. *Synthesis* **1974**, 290.
3. Stetter, H.; Wulff, K. *Chem. Ber.* **1962**, *95*, 2302.
4. Huang, X.; Seid, M.; Keillor, J. W. *Tetrahedron Lett.* **1997**, *38*, 313.
5. Chong, J. M.; Park, S. B. *J. Org. Chem.* **1993**, *58*, 7300.
6. Ito, Y.; Ushitora, H. *Tetrahedron* **2006**, *62*, 226.
7. Fischer, A. *Synthesis* **1985**, 641.
8. Nilson, A.; Ronlan, A.; Parker, V. D. *J. Chem. Soc., Perkin Trans. I* **1973**, 2336.