

Supplementary Information

Copper catalyzed coupling of aryl chlorides, bromides and iodides with amines and amides

Hanhui Xu and Christian Wolf*

Department of Chemistry, Georgetown University, Washington DC, 20057

cw27@georgetown.edu

Experimental Procedures

General Procedures. All chemicals used were of reagent grade and all reactions were carried out under nitrogen. Flash chromatography was performed on Kieselgel 60, particle size 0.032-0.063 mm. NMR spectra were obtained at 400 MHz (^1H NMR) and 100 MHz (^{13}C NMR) using CDCl_3 as solvent unless noted otherwise. Chemical shifts are reported in ppm relative to TMS.

General procedure for the Cu-catalyzed amination of aryl halides

A 10 mL reaction vessel was charged with Cu_2O (14.3 mg, 0.10 mmol), aryl halide (2.0 mmol), amine (4.0 mmol), 2.0 mL of *N*-methyl pyrrolidone (NMP) and a magnetic stir bar. The vessel was sealed with a Teflon screw cap, immersed in a preheated oil bath and the reaction mixture was stirred at the desired temperature. Upon completion, the reaction mixture was cooled to 25 °C, quenched with water, extracted with diethyl ether and dried over anhydrous MgSO_4 . The solvents were removed under vacuum and the residue was purified by flash chromatography on silica gel as described below.

***N*-Propylaniline.**¹ Purification by flash chromatography (hexanes:ethyl acetate=10:1) gave 256.9 mg of a colorless oil (1.90 mmol, 95%). ^1H NMR: δ 1.11 (t, J = 7.2 Hz, 3H), 1.69-1.79 (m, 2H), 3.18 (t, J = 7.2 Hz, 2H), 3.66 (s, br, 1H), 6.71-6.73 (m, 2H), 6.82-6.84 (m, 1H), 7.28-7.32 (m, 2H). ^{13}C NMR: δ 11.8, 22.8, 45.9, 112.8, 117.2, 129.3, 148.6.

***N*-Propyl-2-aminonaphthalene.**² Purification by flash chromatography (hexanes:ethyl acetate=10:1) gave 348.3 mg of a colorless oil (1.88 mmol, 94%). ^1H NMR: δ 1.23 (t, J = 7.2 Hz, 3H), 1.78-1.85 (m, 2H), 3.30 (t, J = 7.2 Hz, 2H), 3.79 (s, br, 1H), 6.99-7.02 (m, 2H), 7.46-7.50 (m, 1H), 7.64-7.68 (m, 1H), 7.84-7.96 (m, 3H).

^{13}C NMR: δ 12.0, 22.8, 46.0, 104.4, 118.4, 122.0, 126.2, 126.6, 127.7, 128.0, 129.1, 135.7, 146.5.

***N,N*-Diethylaniline.**³ Purification by flash chromatography (hexanes:ethyl acetate=10:1) gave 250.7 mg of white crystals (1.68 mmol, 84%). ^1H NMR: δ 1.13 (t, J = 7.2 Hz, 6H), 3.32 (q, J = 7.2 Hz, 4H), 6.60-6.67 (m, 3H), 7.17-7.21 (m, 2H). ^{13}C NMR: δ 12.7, 44.4, 112.0, 115.5, 129.3, 147.9.

Diphenylamine.⁴ Purification by flash chromatography (hexanes:ethyl acetate=10:1) gave 267.4 mg of white crystals (1.58 mmol, 79%). ^1H NMR: δ 5.58 (s, br, 1H), 6.87-6.91 (m, 2H), 7.00-7.03 (m, 4H), 7.20-7.24 (m, 4H). ^{13}C NMR: δ 117.9, 121.1, 129.5, 143.2.

Triphenylamine.⁵ Purification by flash chromatography (hexanes:ethyl acetate=10:1) gave 407.2 mg of white crystals (1.66 mmol, 83%). ^1H NMR: δ 6.97-6.99 (m, 3H), 7.00-7.09 (m, 6H), 7.20-7.25 (m, 6H). ^{13}C NMR: δ 122.7, 124.2, 129.2, 147.9.

3-Methyl-*N*-propylaniline.⁶ Purification by flash chromatography (hexanes:ethyl acetate=10:1) gave 259.7 mg of a colorless oil (1.74 mmol, 87%). ^1H NMR: δ 0.97 (t, J = 7.2 Hz, 3H), 1.55-1.64 (m, 2H), 2.25 (s, 3H), 3.06 (s, br, 2H), 3.45 (s, br, 1H), 6.30-6.40 (m, 2H), 6.49 (d, J = 7.2 Hz, 1H), 7.04 (t, J = 7.2 Hz, 1H). ^{13}C NMR: δ 11.7, 21.7, 22.9, 45.8, 110.0, 113.6, 118.1, 129.1, 138.9.

***N*-Cyclohexylaniline.**⁷ Purification by flash chromatography (hexanes:ethyl acetate=10:1) gave 241.9 mg of a colorless oil (1.38 mmol, 69%). ^1H NMR: δ 1.06-1.39 (m, 5H), 1.60-1.65 (m, 1H), 1.70-1.76 (m, 2H), 2.00-2.05 (m, 2H), 3.18-3.25 (m, 1H), 3.41 (s, br, 1H), 6.55 (d, J = 7.6 Hz, 2H), 6.32 (t, J = 7.2 Hz, 1H), 7.13 (t, J = 7.2 Hz, 2H). ^{13}C NMR: δ 25.1, 26.1, 33.6, 51.7, 113.2, 116.9, 129.3, 147.5.

***N*-Benzylaniline.**⁸ Purification by flash chromatography (hexanes:ethyl acetate=10:1) gave 263.9 mg of a colorless oil (1.44 mmol, 72%). ^1H NMR: δ 3.84 (s, br, 1H), 4.21 (s, 2H), 6.54 (d, J = 8.0 Hz, 2H), 6.67 (t, J = 7.2 Hz, 1H), 7.11 (t, J = 7.2 Hz, 2H), 7.20-7.30 (m, 5H). ^{13}C NMR: δ 48.4, 113.1, 117.7, 127.4, 127.7, 128.8, 129.5, 139.7, 148.3.

3-Nitro-*N*-propylaniline.⁹ Purification by flash chromatography (hexanes:ethyl acetate=8:2) gave 317.2 mg of a yellow oil (1.76 mmol, 88%). ^1H NMR: δ 1.01 (t, J = 7.2 Hz, 3H), 1.61-1.70 (m, 2H), 3.11 (t, J = 7.2 Hz, 2H), 4.10 (s, br, 1H), 6.85 (dd, J = 8.0, 2.4 Hz, 1H), 7.22-7.27 (m, 1H), 7.36 (t, J = 2.4 Hz, 1H), 7.45-7.48 (m, 1H). ^{13}C NMR: δ 11.5, 22.3, 45.5, 105.9, 111.4, 118.6, 129.6, 149.2.

3-Propylaminoaniline.¹⁰ Purification by flash chromatography (hexanes: ethyl acetate=9:1) gave 279.4 mg of a slight yellow oil (1.86 mmol, 93%). ^1H NMR: δ 0.96 (t, J = 7.2 Hz, 3H), 1.55-1.61 (m, 2H), 3.00 (t, J = 7.2 Hz, 2H), 3.52 (s, br, 3H), 5.89 (s, 1H), 6.02 (dd, J = 6.0, 2.4 Hz, 2H), 6.92 (t, J = 8.0 Hz, 1H). ^{13}C NMR: δ 11.7, 22.8, 45.8, 99.5, 103.9, 104.7, 130.0, 147.6, 149.8.

Ethyl 3-propylaminobenzoate.¹¹ Purification by flash chromatography (hexanes:ethyl acetate=9:1) gave 377.2 mg of a colorless oil (1.82 mmol, 91%). ^1H NMR: δ 0.96 (t, J = 7.2 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.56-1.62 (m, 2H), 3.05 (t, J = 7.2 Hz, 2H), 3.90 (s, br, 1H), 4.33 (q, J = 7.2 Hz, 2H), 6.71-6.74 (m, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.26 (t, J = 2.4 Hz, 1H), 7.34-7.36 (m, 1H). ^{13}C NMR: δ 11.5, 14.3, 22.5, 45.6, 60.7, 113.1, 117.0, 117.9, 129.0, 131.3, 148.6, 167.1.

4-Methoxy-*N*-propylaniline.¹² Purification by flash chromatography (hexanes:ethyl acetate=10:1) gave 267.7 mg of a yellow oil (1.62 mmol, 81%). ¹H NMR: δ 0.97 (t, J = 7.2 Hz, 3H), 1.57-1.63 (m, 2H), 3.01 (t, J = 7.2 Hz, 2H), 3.72 (s, br, 4H), 6.56 (dd, J = 6.8, 2.4 Hz, 2H), 6.77 (dd, J = 6.8, 2.4 Hz, 2H). ¹³C NMR: δ 11.7, 22.8, 46.9, 55.8, 114.2, 114.9, 142.8, 152.0.

4-Methylthio-*N*-propylaniline. Purification by flash chromatography (hexanes:ethyl acetate=10:1) gave 275.6 mg of a yellow oil (1.52 mmol, 76%). ¹H NMR: δ 0.96 (t, J = 7.2 Hz, 3H), 1.56-1.62 (m, 2H), 2.42 (s, 3H), 3.02 (t, J = 7.2 Hz, 2H), 3.64 (s, br, 1H), 6.54 (dd, J = 6.8, 2.4 Hz, 2H), 7.19 (dd, J = 6.8, 2.4 Hz, 2H). ¹³C NMR: δ 11.7, 15.8, 22.7, 45.8, 113.3, 129.6, 131.7, 148.9. Anal. calcd. for C₁₀H₁₅NS: C, 66.25; H, 8.34; N, 7.73. Found: C, 66.01; H, 8.27; N, 7.78.

***N*-Phenylleucine methyl ester.** Purification by flash chromatography (hexanes:ethyl acetate=9:1) gave 318.7 mg of a slight yellow oil (1.44 mmol, 72%). ¹H NMR: δ 0.95 (dd, J = 18.0, 6.8 Hz, 6H), 1.59-1.65 (m, 2H), 1.74-1.82 (m, 1H), 3.66 (s, 3H), 4.02 (s, br, 1H), 4.09 (t, J = 7.2 Hz, 1H), 6.59 (d, J = 8.0 Hz, 2H), 6.71 (t, J = 7.2 Hz, 1H), 7.04-7.19 (m, 2H). ¹³C NMR: δ 22.2, 22.8, 24.9, 42.4, 52.0, 55.1, 113.4, 118.3, 129.3, 147.1, 175.2. Anal. calcd. for C₁₃H₁₉NO₂: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.13; H, 8.74; N, 6.48.

HPLC enantioseparation: Column: (*S,S*)-Whelk-O-1, mobile phase: hexane:IPA (9:1), flow rate: 1.0 mL/min, detection wavelength: 240 nm, retention times: t_1 =5.51 min, t_2 =9.00 min, selectivity factor, α : 3.49.

***N*-Phenylalanine.**¹³ Purification by flash chromatography (CH₂Cl₂:ethyl acetate=6:4) gave 251.1 mg of white crystals (1.52 mmol, 76%). ¹H NMR (in CD₃OD): δ 1.43 (d, J = 7.2 Hz, 3H), 4.02 (q, J = 7.2 Hz, 1H), 5.16 (s, br, 2H), 6.61-6.67 (m, 3H), 7.07-7.112 (m, 2H). ¹³C NMR: δ 17.5, 52.0, 113.3, 117.7, 128.7, 147.2, 177.2.

HPLC enantioseparation: Column: (*S,S*)-Whelk-O-1, mobile phase: hexane:IPA:HOAc (90:10:1), flow rate: 1.0 mL/min, detection wavelength: 240 nm, retention times: t_1 =6.11 min, t_2 =7.27 min, selectivity factor, α : 1.58.

General procedure for the Cu-catalyzed amidation of aryl halides

A 10 mL reaction vessel was charged with Cu₂O (14.3 mg, 0.10 mmol), aryl halide (2.0 mmol), amide (4.0 mmol), base (4.0 mmol), 3.0 mL of *N*-methylpyrrolidone (NMP) and a magnetic stir bar. The vessel was sealed with a Teflon screw cap, immersed in a preheated oil bath and the reaction mixture was stirred at the desired temperature. Upon completion, the reaction mixture was cooled to 25 °C, quenched with water, extracted with diethyl ether and dried over anhydrous MgSO₄. The solvents were removed under vacuum and the residue was purified by flash chromatography on silica gel as described below.

***N*-Phenylbenzamide.**¹⁴ Purification by flash chromatography (hexanes:ethyl acetate=9:1) gave 382.6 mg of white crystals (1.94 mmol, 97%). ¹H NMR: δ 7.14 (t, J = 7.2 Hz, 1H), 7.25-7.53 (m, 5H), 7.64 (d, J = 7.6 Hz, 2H), 7.85 (d, J = 7.2 Hz, 2H),

7.97 (s, br, 1H). ^{13}C NMR: δ 120.3, 124.5, 127.0, 128.7, 129.1, 131.8, 135.0, 137.9, 165.8.

N-(3,5-Dimethylphenyl)benzamide.¹⁵ Purification by flash chromatography (hexanes:ethyl acetate=9:1) gave 441.6 mg of white crystals (1.96 mmol, 98%). ^1H NMR: δ 2.22 (s, 6H), 6.73 (s, 1H), 7.25 (s, 2H), 7.32-7.36 (m, 2H), 7.41-7.46 (m, 1H), 7.80 (dd, J = 7.2, 1.6 Hz, 2H), 8.27 (s, br, 1H). ^{13}C NMR: δ 120.3, 124.5, 127.0, 128.7, 129.1, 131.8, 135.0, 137.9, 165.8.

N-(3-Methoxyphenyl)benzamide.¹⁶ Purification by flash chromatography (hexanes:ethyl acetate=8:2) gave 418.2 mg of white crystals (1.84 mmol, 92%). ^1H NMR: δ 3.73 (s, 3H), 6.65-6.68 (m, 1H), 7.11-7.21 (m, 2H), 7.34-7.48 (m, 4H), 7.80 (dd, J = 7.2, 1.6 Hz, 2H), 8.30 (s, br, 1H). ^{13}C NMR: δ 55.2, 106.0, 110.5, 112.6, 127.1, 128.6, 129.7, 131.8, 134.9, 139.3, 160.1, 166.1.

N-(2-Methoxyphenyl)benzamide.¹⁷ Purification by flash chromatography (hexanes:ethyl acetate=8:2) gave 381.8 mg of white crystals (1.68 mmol, 84%). ^1H NMR: δ 3.84 (s, 3H), 6.84-6.87 (m, 1H), 6.96-7.06 (m, 2H), 7.41-7.49 (m, 3H), 7.86 (dd, J = 7.2, 1.6 Hz, 2H), 8.52-8.53 (m, 1H), 8.54 (s, br, 1H). ^{13}C NMR: δ 55.8, 110.0, 119.8, 121.1, 123.9, 127.0, 127.8, 128.8, 131.7, 135.2, 148.2, 165.2.

N-Phenylacetamide.¹⁸ Purification by flash chromatography (hexanes:ethyl acetate=8:2) gave 237.9 mg of white crystals (1.76 mmol, 88%). ^1H NMR: δ 2.12 (s, 3H), 7.07 (t, J = 7.2 Hz, 1H), 7.26 (t, J = 7.6 Hz, 2H), 7.51 (d, J = 7.6 Hz, 2H), 8.37 (s, br, 1H). ^{13}C NMR: δ 24.3, 120.2, 124.3, 128.9, 138.1, 169.2.

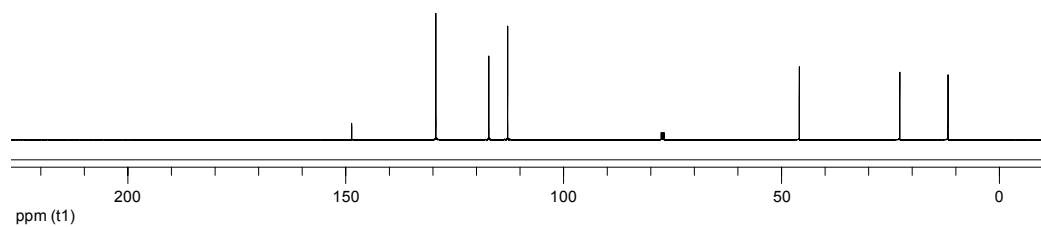
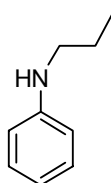
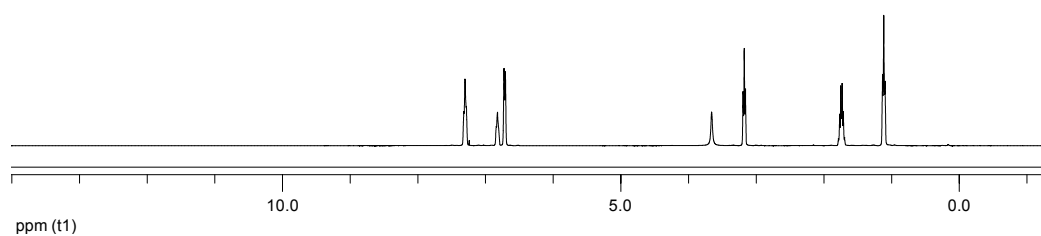
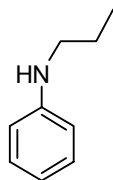
N-Methyl-N-phenylacetamide.¹⁸ Purification by flash chromatography (hexanes:ethyl acetate=7:3) gave 241.7 mg of white crystals (1.62 mmol, 81%). ^1H NMR: δ 1.87 (s, 3H), 3.26 (s, 3H), 7.20 (d, J = 7.2 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H). ^{13}C NMR: δ 22.2, 36.9, 126.9, 127.6, 129.6, 144.4, 170.2.

References

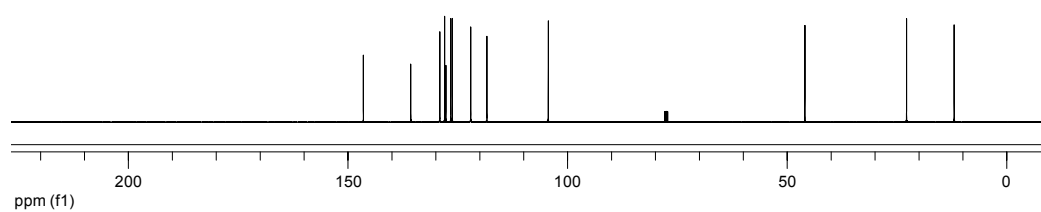
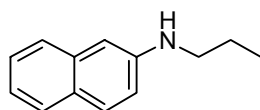
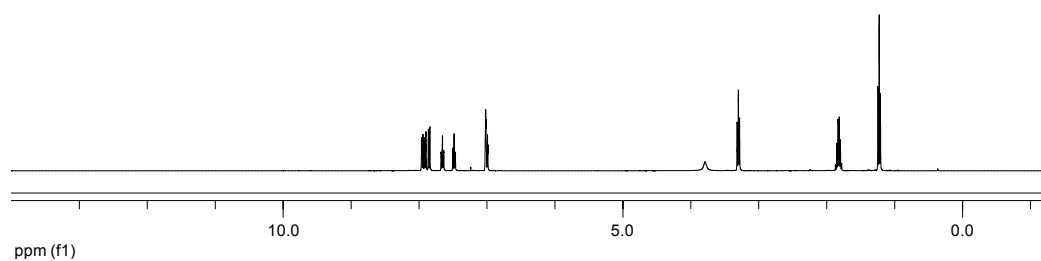
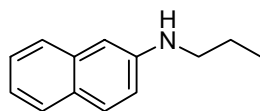
1. Byun, E.; Hong, B.; De Castro, K. A.; Lim, M.; Rhee, H. *J. Org. Chem.* **2007**, *72*, 9815-9817.
2. Povstyanoi, M. V.; Kochergin, P. M. *Khim Geterotsikl.* **1971**, *7*, 1115-1120.
3. Bigdeli, M. A.; Rahmati, A.; Abbasi-Ghadim, H.; Mahdavinia, G. H. *Tetrahedron Lett.* **2007**, *48*, 4575-4578.
4. Liu, Y.; Bai, Y.; Zhang, J.; Li, Y.; Jiao, J.; Qi, X. *Eur. J. Org. Chem.* **2007**, 6084-6088.
5. Chen, C.; Li, Y.; Yang, L. *J. Mol. Catal. A: Chem.* **2007**, *269*, 158-162.
6. Nacario, R.; Kotakonda, S.; Fouchard, D. M. D.; Tillekeratne, L. M. V.; Hudson, R. A. *Org. Lett.* **2005**, *7*, 471-474.
7. Fujita, K.; Enoki, Y.; Yamaguchi, R. *Tetrahedron* **2008**, *64*, 1943-1954.
8. Li, D.; Zhang, Y.; Zhou, G.; Guo, W. *Synlett* **2008**, 225-228.
9. Verardo, G.; Giumanini, A. G.; Strazzolini, P.; Poiana, M. *Synthesis* **1993**, 121-125.
10. Agafonov, N. E.; Dudin, A. V.; Preobrazhenskii, A. A.; Zhulin, V. M. *Russ. Chem. Bull.* **2003**, *52*, 273-275.
11. Ohishi, T.; Sugi, R.; Yokoyama, A.; Yokozawa, T. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 4990-5003.

12. Zhu, X.; Ma, Y.; Su, L.; Song, H.; Chen, G.; Liang, D.; Wan, Y. *Synthesis* **2006**, 3955-3962.
13. Lu, Z.; Twieg, R. J. *Tetrahedron Lett.* **2005**, 46, 2997-3001.
14. Betti, C.; Landini, D.; Maia, A.; Pasi, M. *Synlett* **2008**, 908-910.
15. Tietcheu, C.; Garcia, C.; Gardette, D.; Dugat, D.; Gramain, J. *J. Heterocycl. Chem.* **2002**, 39, 965-973.
16. Suresh Babu, V. V.; Vasanthakumar, G.; Tantry, S. J. *Tetrahedron Lett.* **2005**, 46, 4099-4102.
17. Kakarla, R.; Li, G.; Gerritz, S. W. *J. Comb. Chem.* **2007**, 9, 745-747.
18. Joseph, J. K.; Jain, S. L.; Sain, B. *J. Mol. Catal. A: Chem.* **2007**, 267, 108-111.

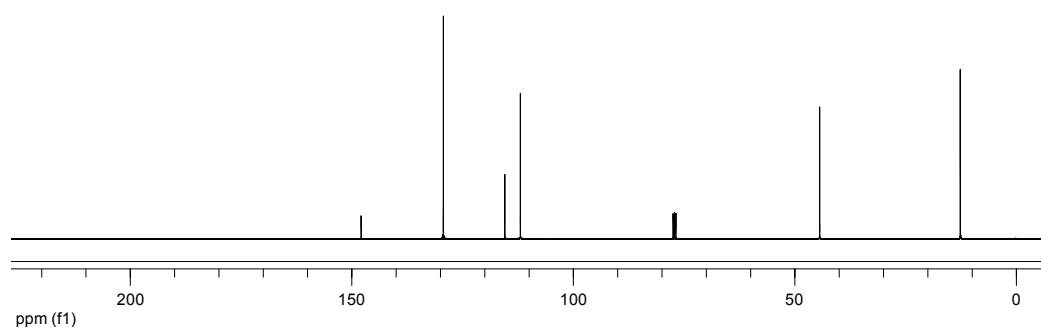
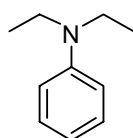
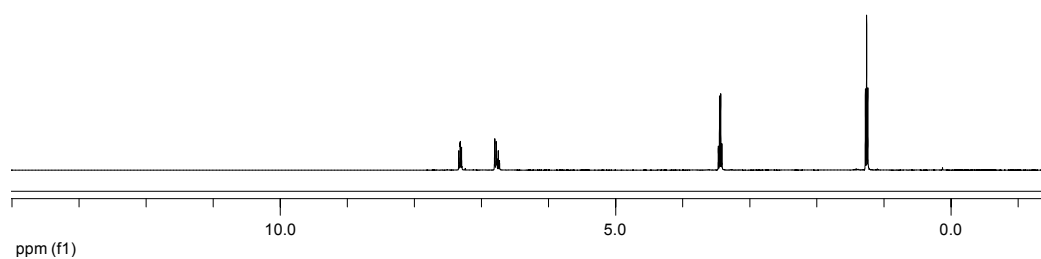
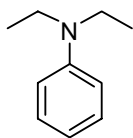
^1H NMR and ^{13}C NMR spectra of *N*-propylaniline in CDCl_3 :



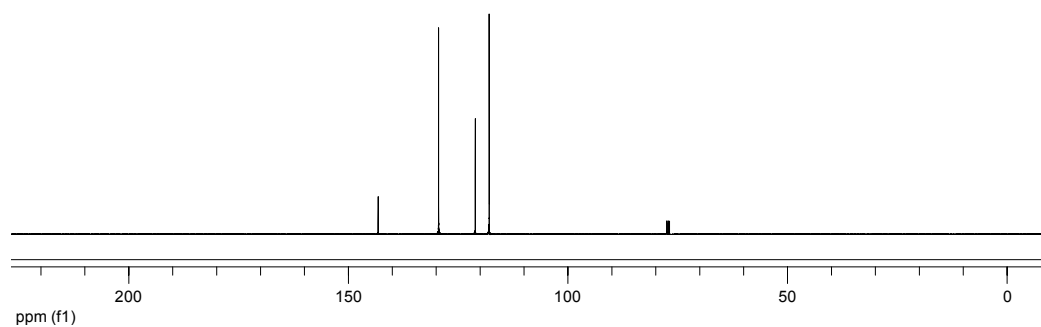
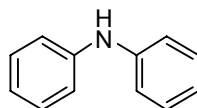
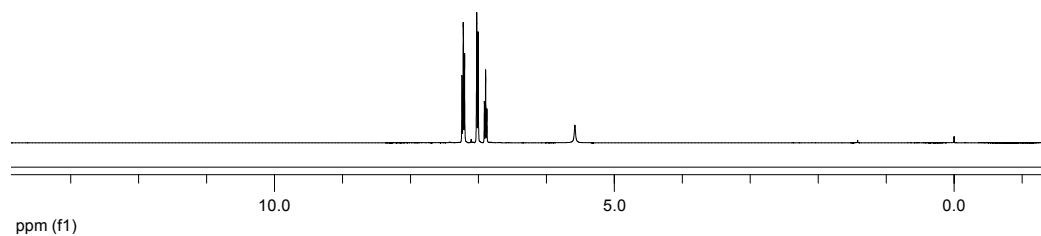
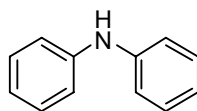
^1H NMR and ^{13}C NMR spectra of *N*-propyl-2-aminonaphthalene in CDCl_3 :



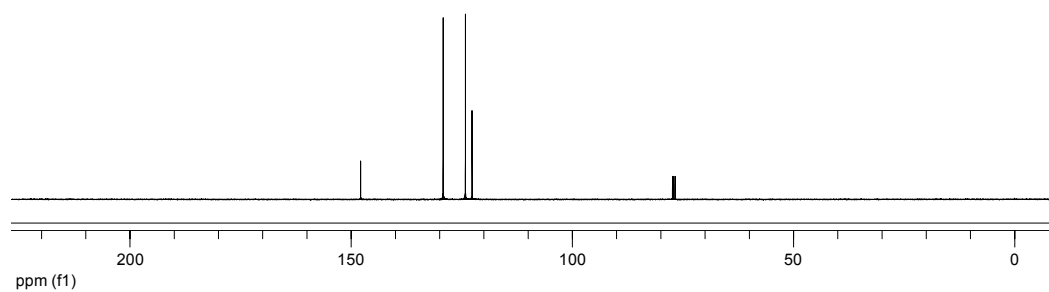
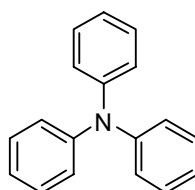
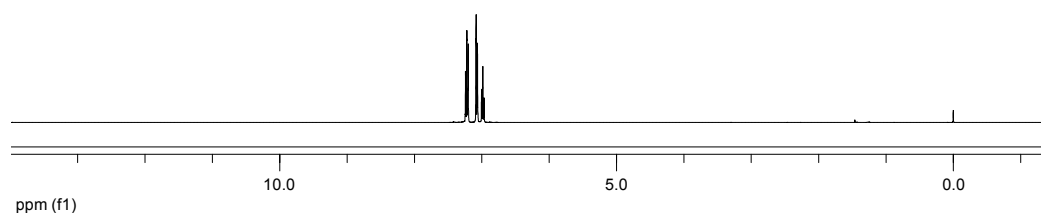
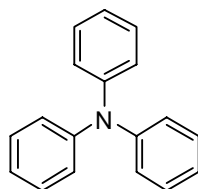
^1H NMR and ^{13}C NMR spectra of *N,N*-diethylaniline in CDCl_3 :



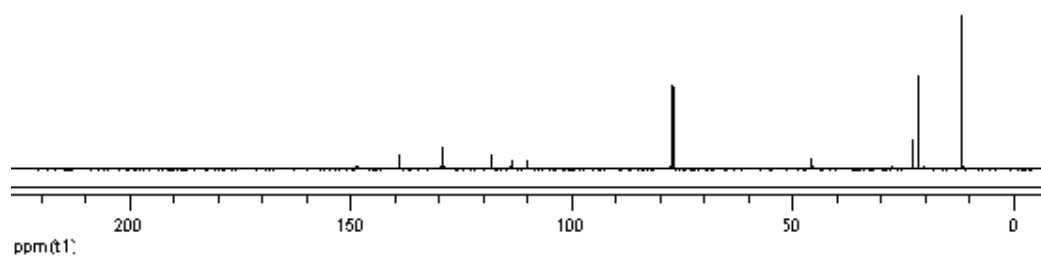
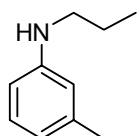
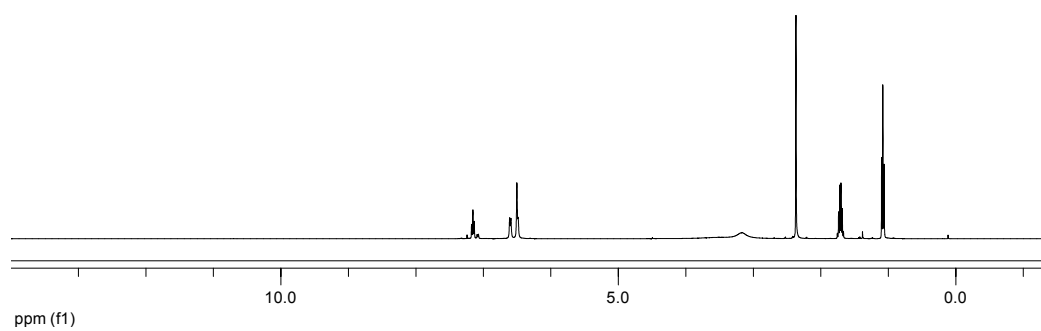
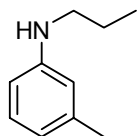
^1H NMR and ^{13}C NMR spectra of diphenylamine in CDCl_3 :



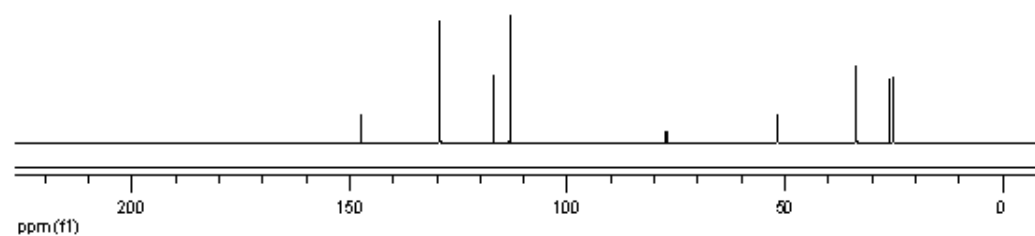
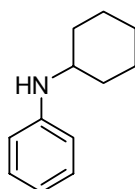
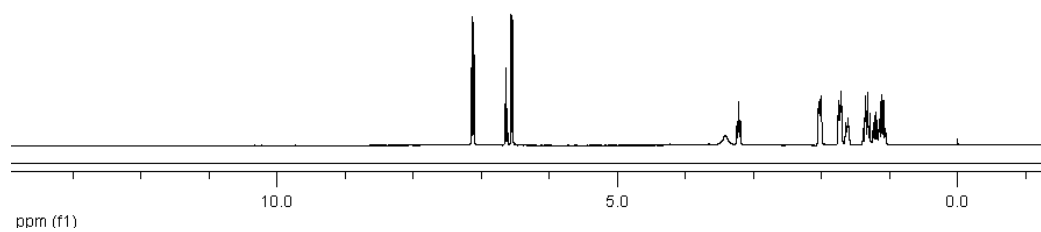
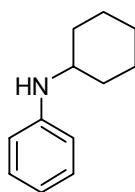
^1H NMR and ^{13}C NMR spectra of triphenylamine in CDCl_3 :



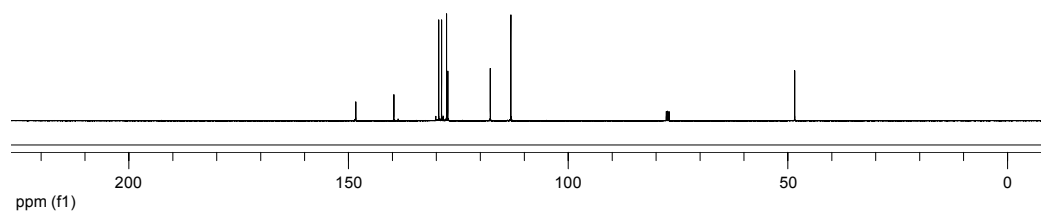
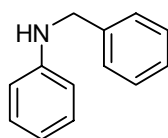
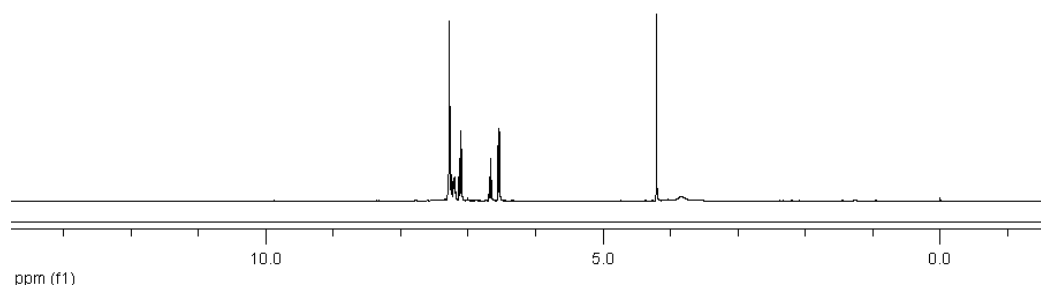
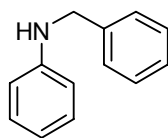
^1H NMR and ^{13}C NMR spectra of 3-methyl-*N*-propylaniline in CDCl_3 :



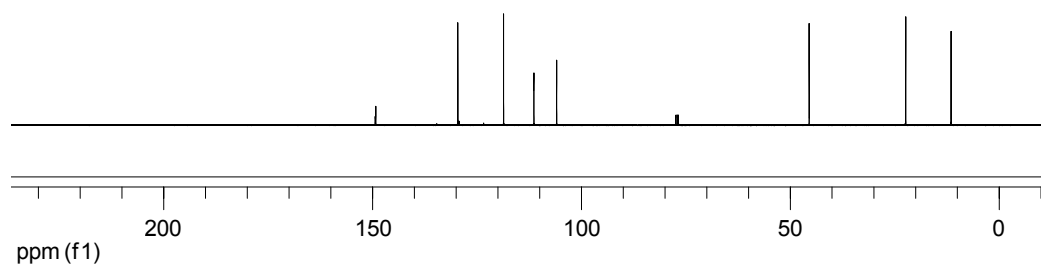
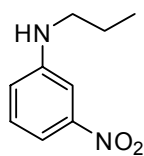
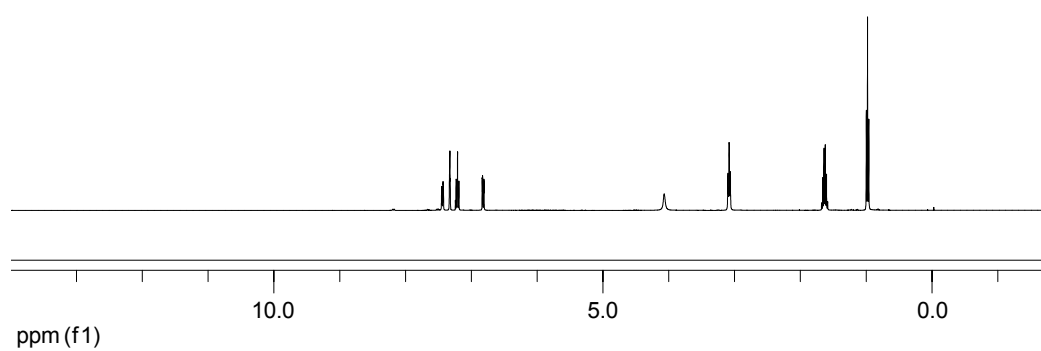
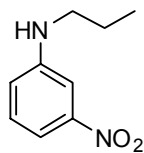
^1H NMR and ^{13}C NMR spectra of *N*-cyclohexylaniline in CDCl_3 :



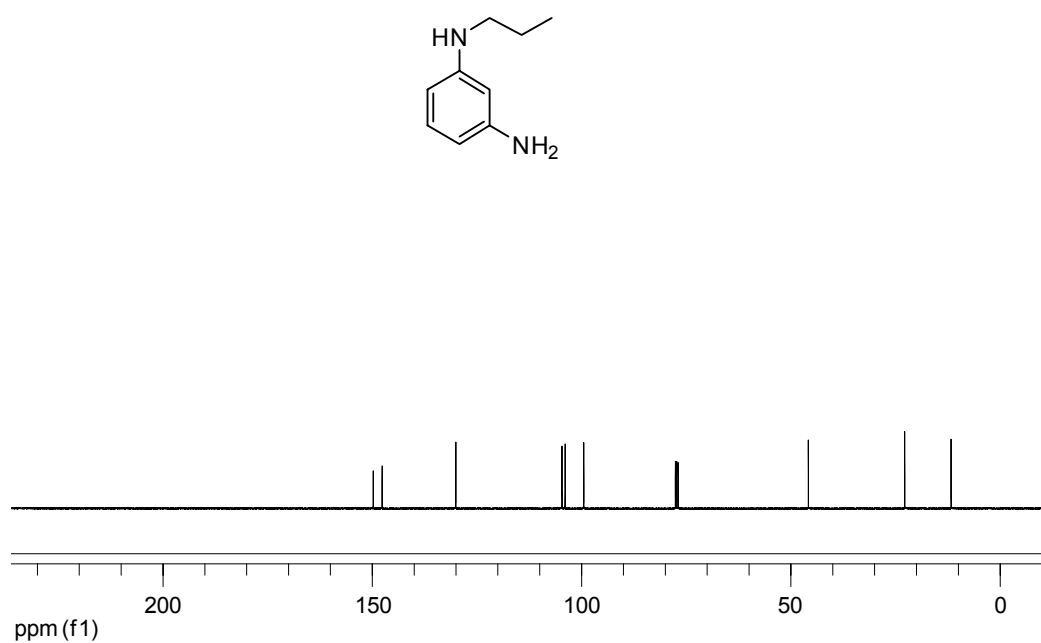
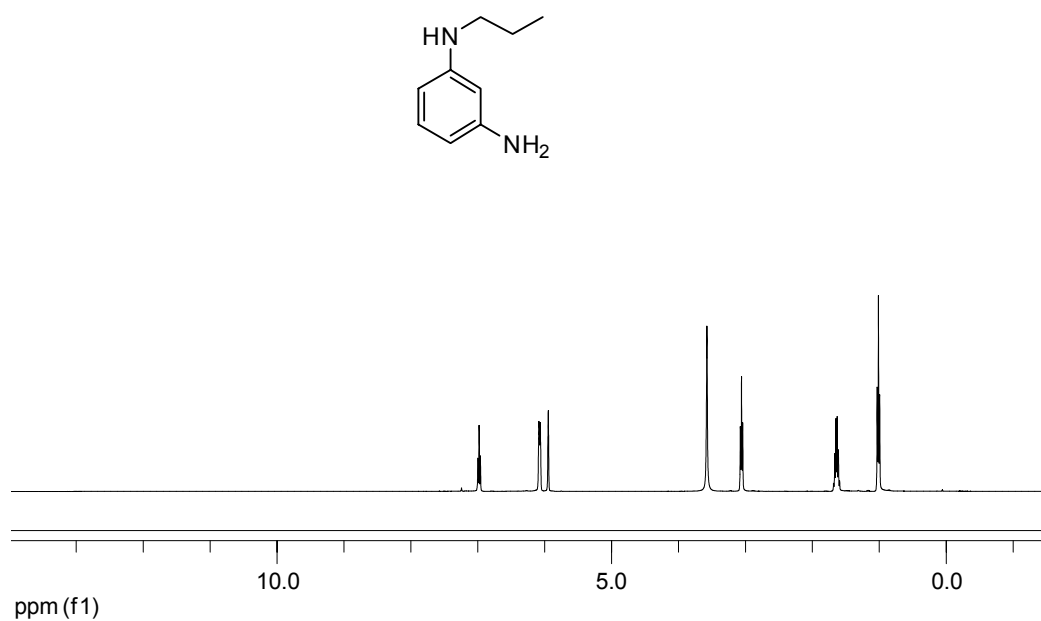
^1H NMR and ^{13}C NMR spectra of *N*-benzylaniline in CDCl_3 :



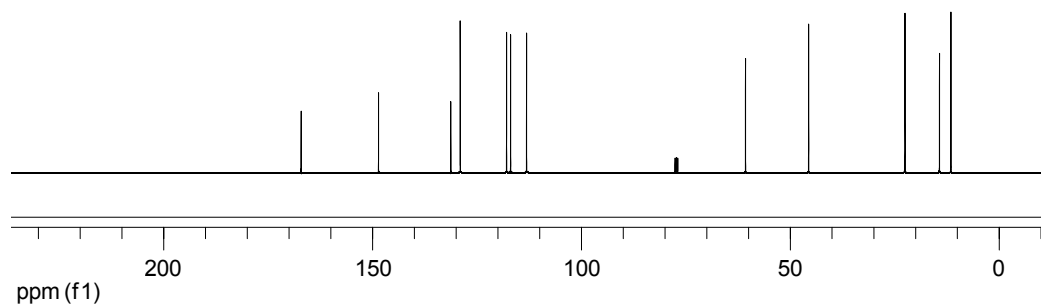
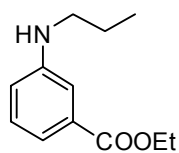
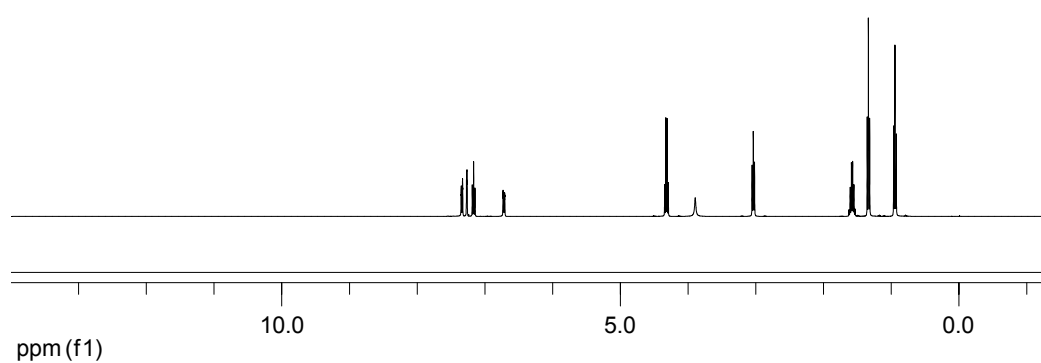
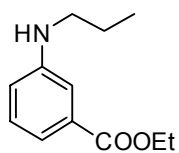
^1H NMR and ^{13}C NMR spectra of 3-nitro-*N*-propylaniline in CDCl_3 :



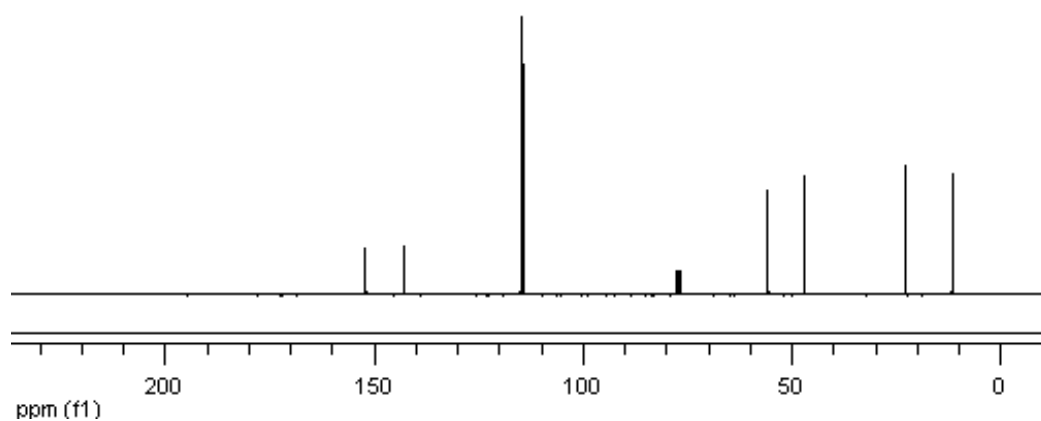
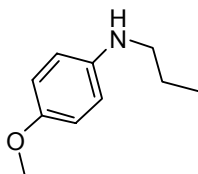
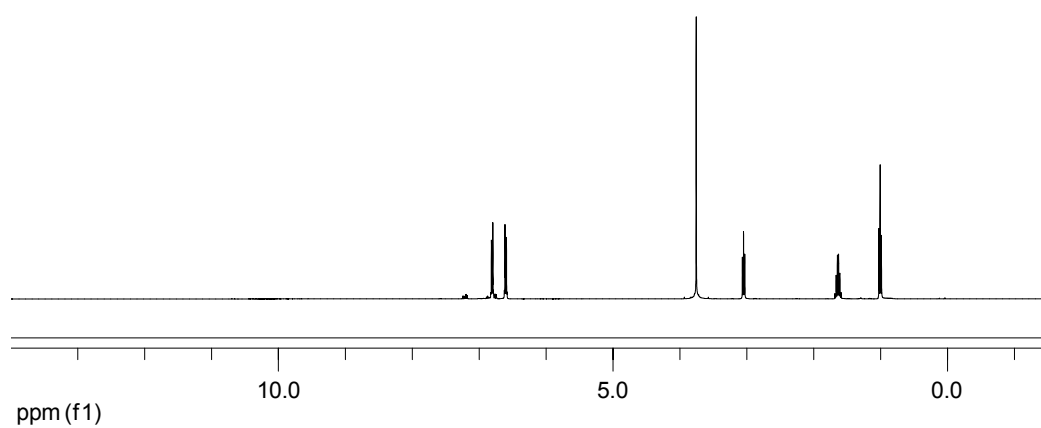
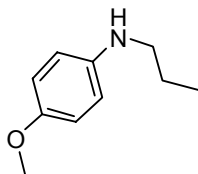
^1H NMR and ^{13}C NMR spectra of 3-propylaminoaniline in CDCl_3 :



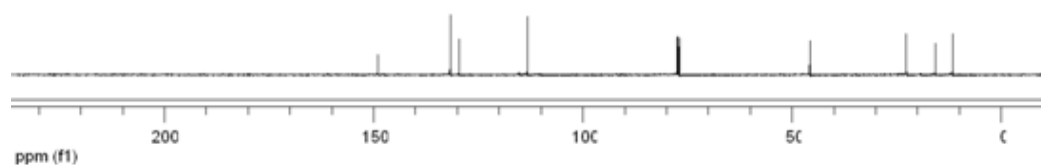
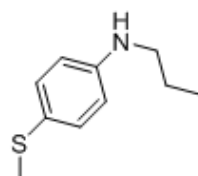
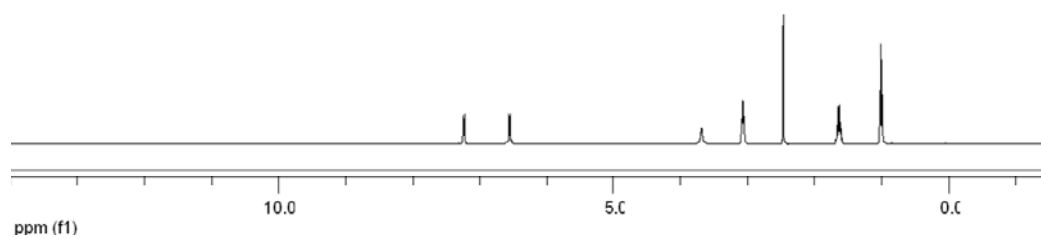
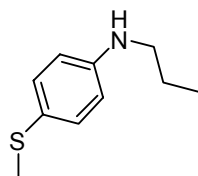
^1H NMR and ^{13}C NMR spectra of ethyl 3-propylaminobenzoate in CDCl_3 :



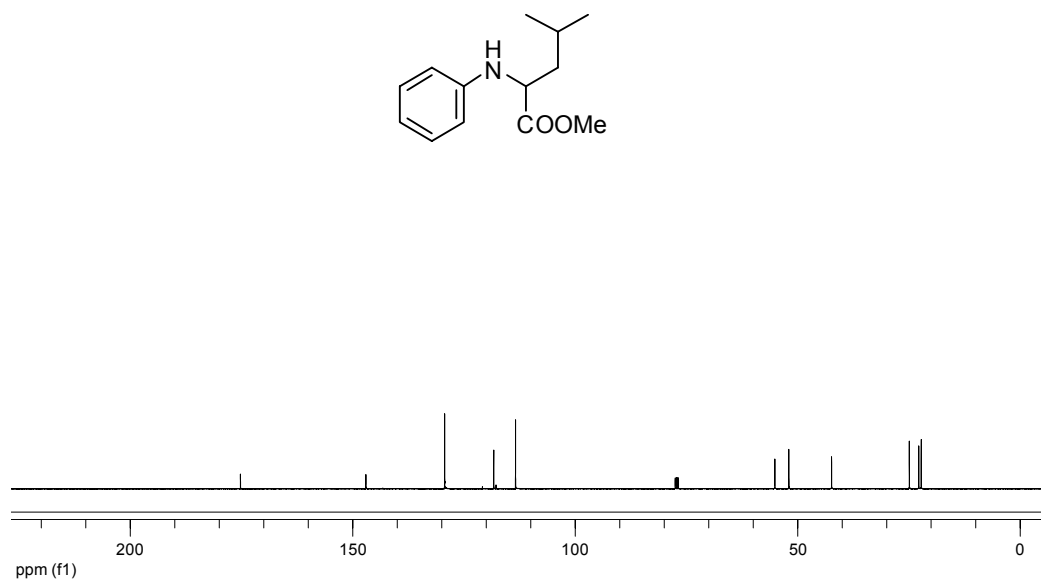
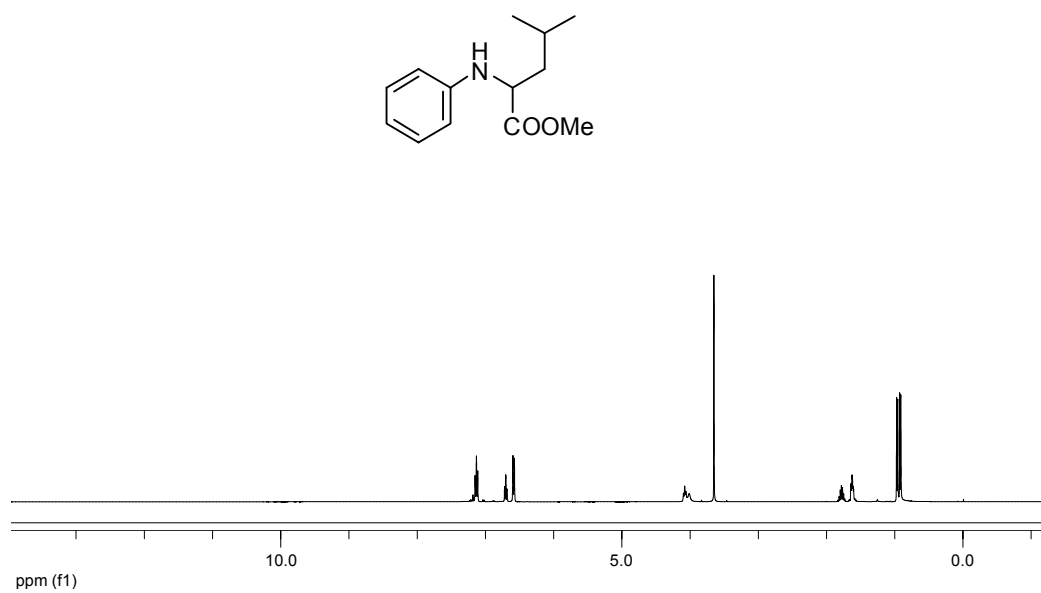
¹H NMR and ¹³C NMR spectra of 4-methoxy-*N*-propylaniline in CDCl₃:



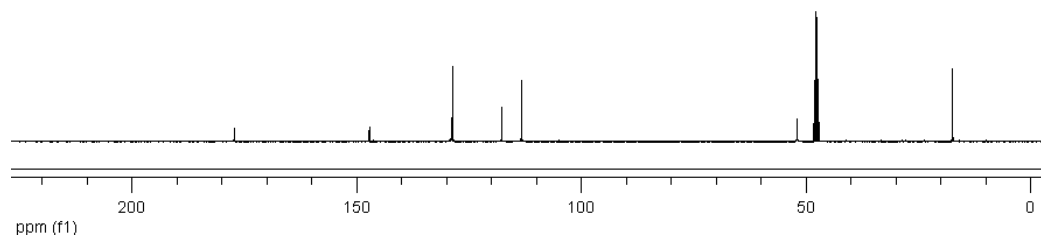
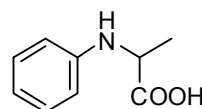
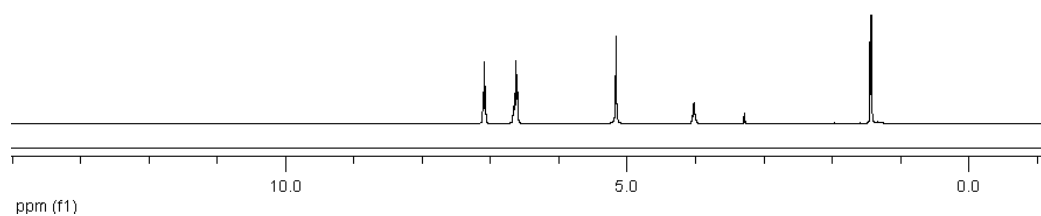
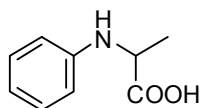
^1H NMR and ^{13}C NMR spectra of 4-methylthio-*N*-propylaniline in CDCl_3 :



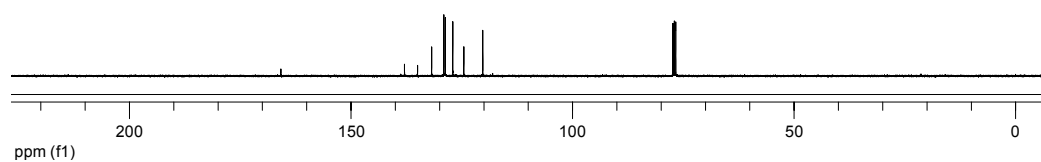
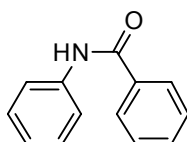
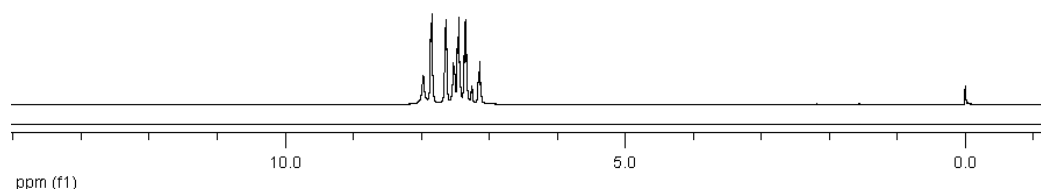
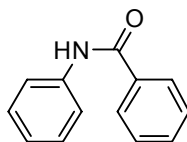
^1H NMR and ^{13}C NMR spectra of *N*-phenylllysine methyl ester in CDCl_3 :



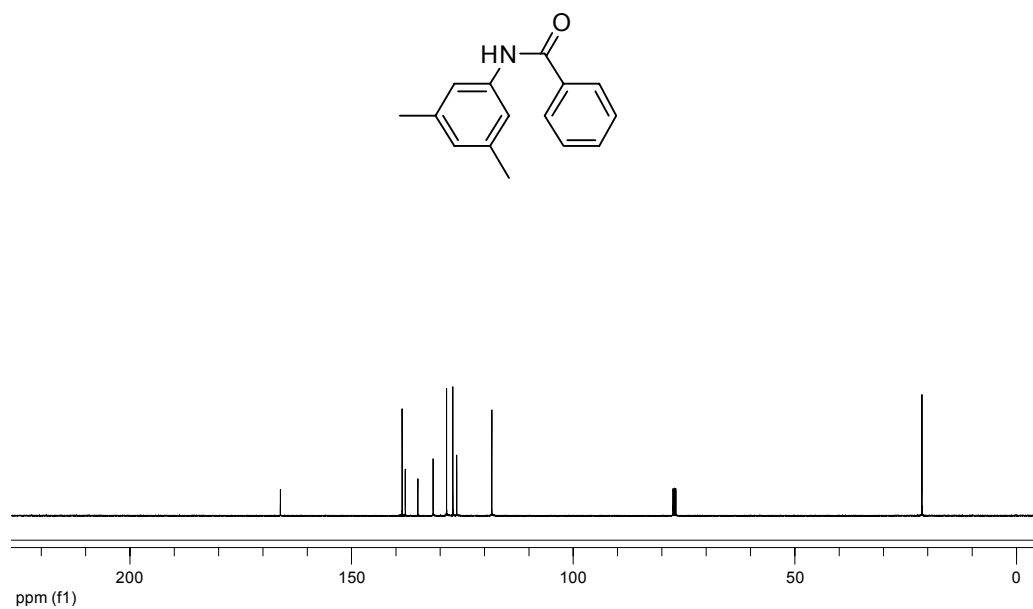
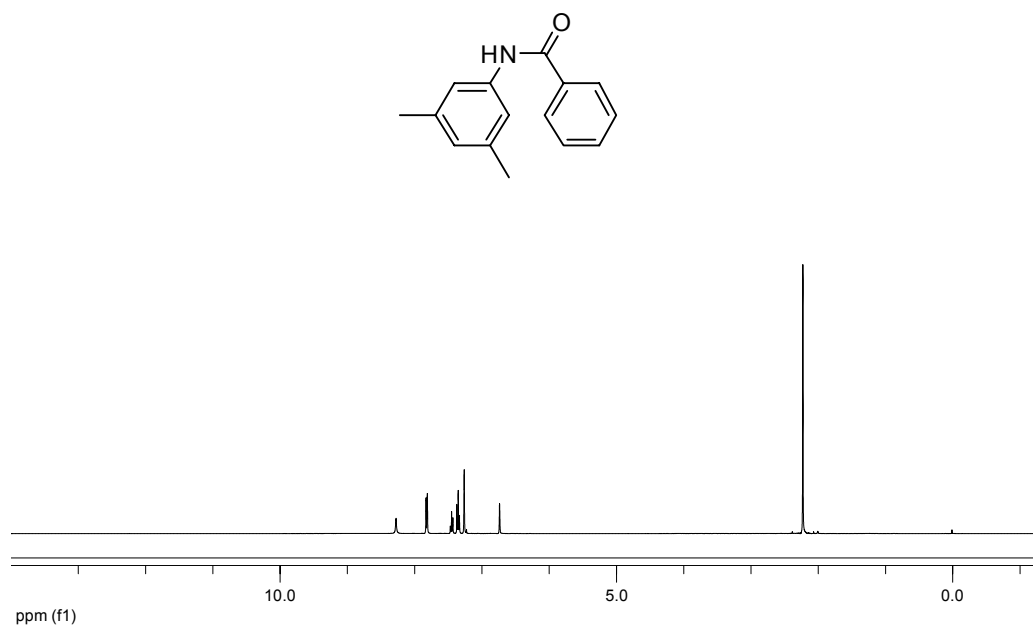
^1H NMR and ^{13}C NMR spectra of *N*-phenylalanine in CD_3OD :



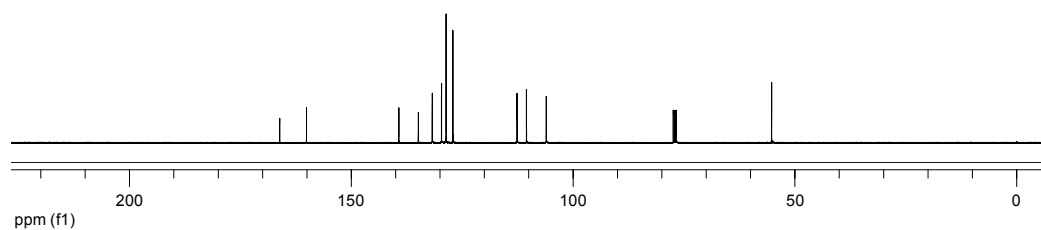
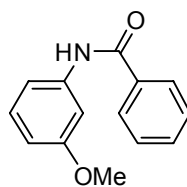
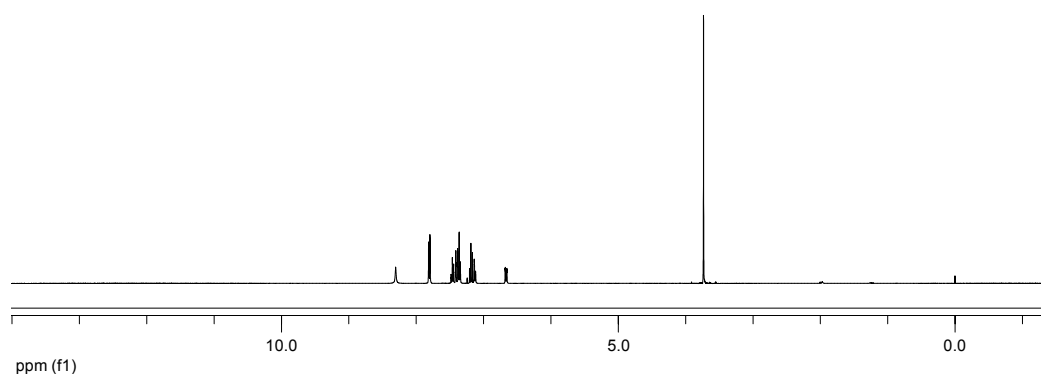
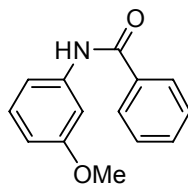
^1H NMR and ^{13}C NMR spectra of *N*-phenylbenzamide in CDCl_3 :



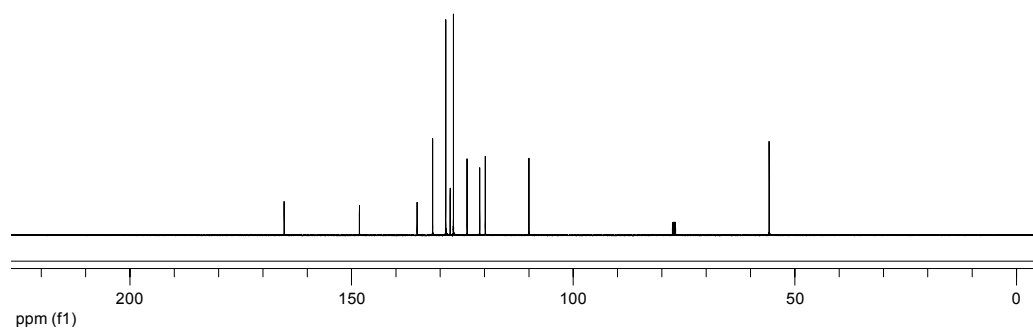
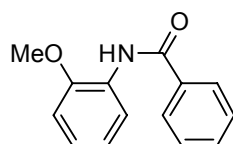
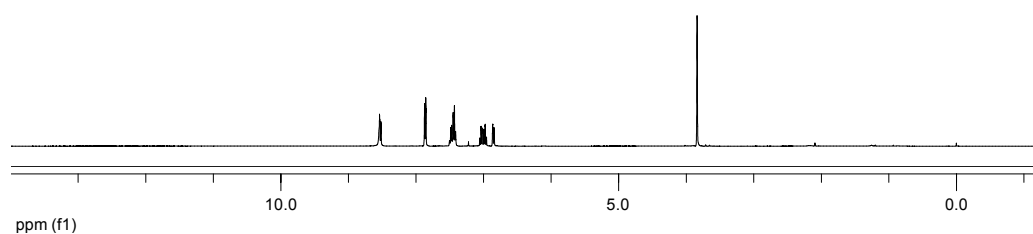
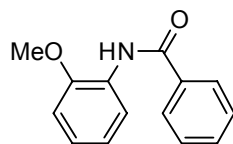
^1H NMR and ^{13}C NMR spectra of *N*-(3, 5-dimethylphenyl) benzamide in CDCl_3 :



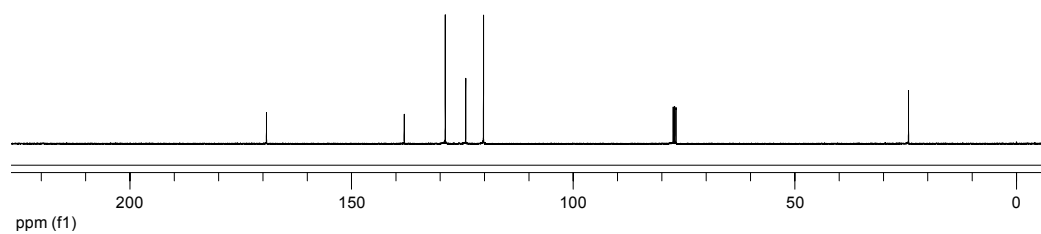
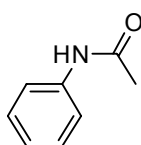
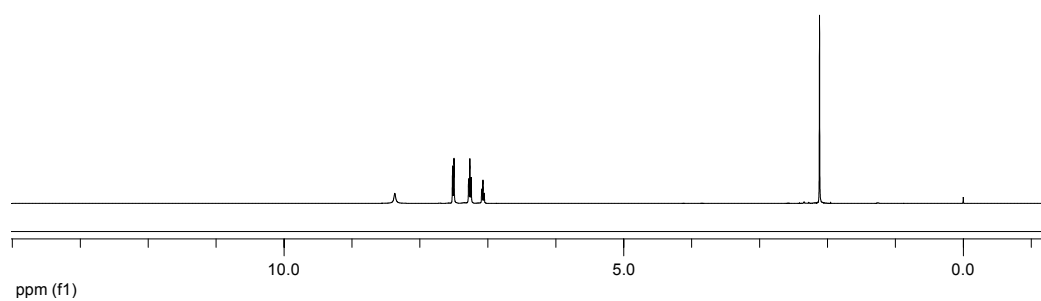
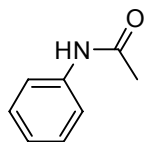
^1H NMR and ^{13}C NMR spectra of *N*-(3-methoxyphenyl) benzamide in CDCl_3 :



^1H NMR and ^{13}C NMR spectra of *N*-(2-methoxyphenyl)benzamide in CDCl_3 :



^1H NMR and ^{13}C NMR spectra of *N*-phenylacetamide in CDCl_3 :



^1H NMR and ^{13}C NMR spectra of *N*-methyl-*N*-phenylacetamide in CDCl_3 :

