Supporting Information

Development of Pd/C-Catalyzed Cyanation of Aryl Halides

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Table of Contents:

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1. General

All reactions were carried out under nitrogen atmosphere with a nitrogen inlet. HPLC solution yields are the average of two runs, isolated yields are one run. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz instrument with chemical shifts reported relative to residual deuterated solvent peaks or tetramethylsilane internal standard. Gas chromatographic analysis was performed with an FID detector and a J&W DB-1 30 m × 0.25 mm i.d. × 1.0 µm column under the following conditions: flow, 1 mL/min; temperature gradient, 60 °C to 280 °C at 1 °C/min, hold at 280 °C for 2 min. HPLC was performed using a Zorbax SB-C18 column (1.8 µm, 4.6 mm × 50 mm) using the following conditions: eluents, 0.1% aqueous TFA and 0.1% TFA in acetonitrile; eluent gradient, 95:5 0.1% aqueous TFA/0.1% TFA in acetonitrile to 15:85 0.1% aqueous TFA/0.1% TFA in acetonitrile from 1 to 12 min; flow, 1.5 mL/min; detector, 200 nm.

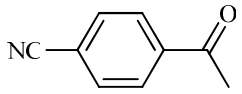
2. Representative experimental procedure

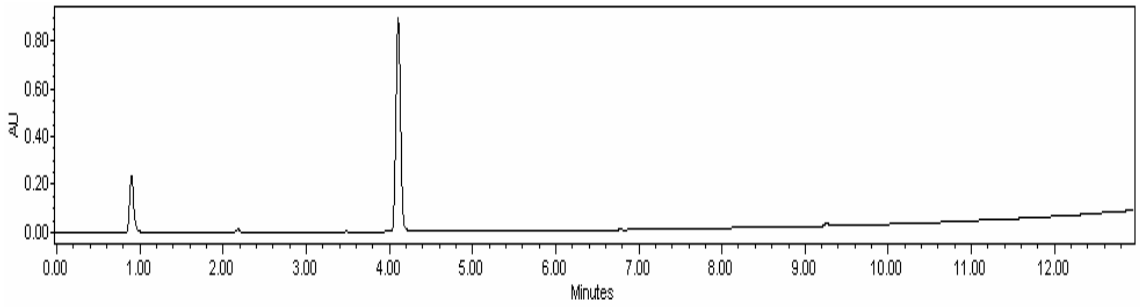
To a round bottom flask was added aryl halide (2.9 mmol), zinc cyanide (0.21 g; 1.74 mmol; 0.6 equiv) (CAUTION: HIGHLY TOXIC[1]), 10 wt % Pd/C[2] (0.13 g; 0.058 mmol; 2 mol %), 1, 1'-bis (diphenylphosphino)ferrocene (dppf) (66 mg; 0.116 mmol; 4 mol %) and DMAC (5 mL). The resulting slurry was sparged with sub-surface nitrogen for 10 min, and zinc formate dihydrate (46 mg; 0.29 mmol; 10 mol %) was added to the reaction mixture. The reaction mixture was again sparged with sub-surface nitrogen for 10 min, and was heated under nitrogen to 100-120 °C[3]. Reaction conversion was monitored by HPLC. For workup procedures used to obtain isolated yields, please refer to Section 4.

3. In-process HPLC/GC spectra versus commercially available markers

Included are copies of HPLC/GC spectra for all products in Tables 2 and Table 3. For all entries, the first spectrum shown is the spectra of the reaction mixture and the second spectrum is the authentic sample of the reaction product. All entries were analyzed using HPLC except Table 3, entry 2, where a GC was used.

Table 2, entry 1: 4-acetylbenzonitrile





Note: The 0.88 min peak is DMAC.

Authentic 4-acetylbenzonitrile (Aldrich)

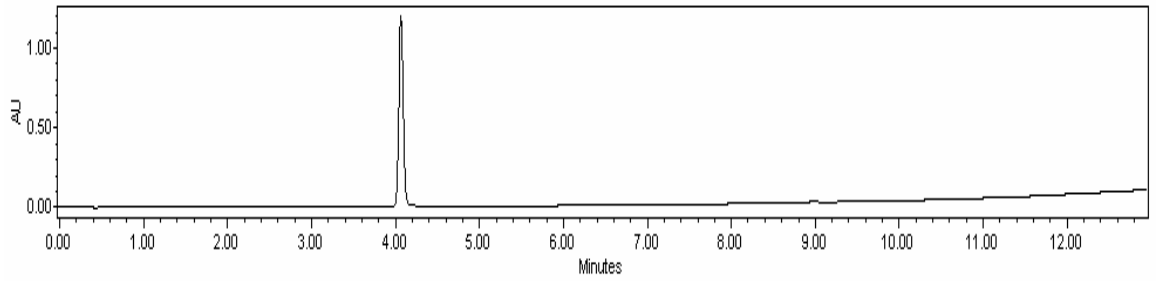
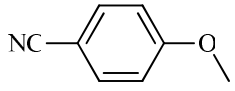
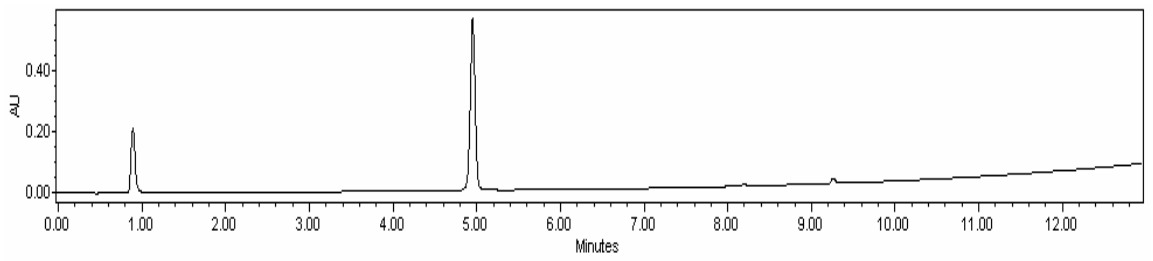


Table 2, entry 2: 4-methoxybenzonitrile





Authentic 4-methoxybenzonitrile (Aldrich)

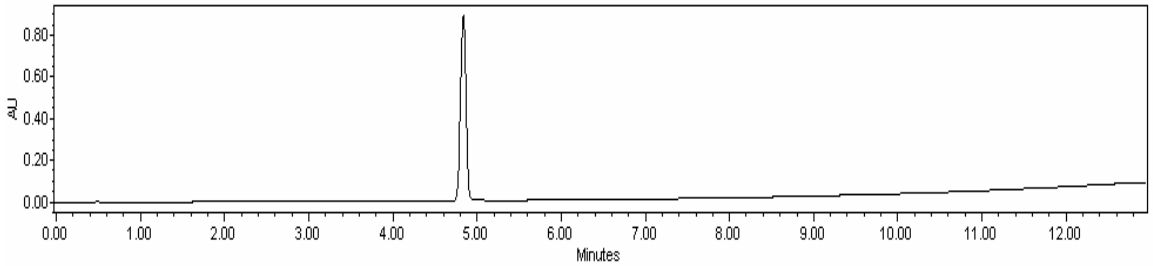
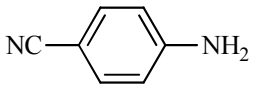
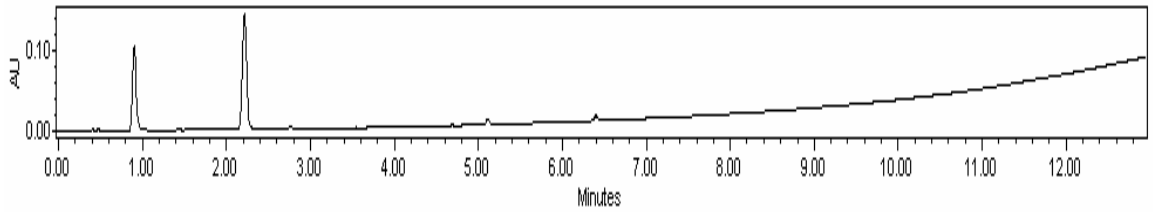


Table 2, entry 3: 4-Aminobenzonitrile





Authentic 4-aminobenzonitrile (Aldrich)

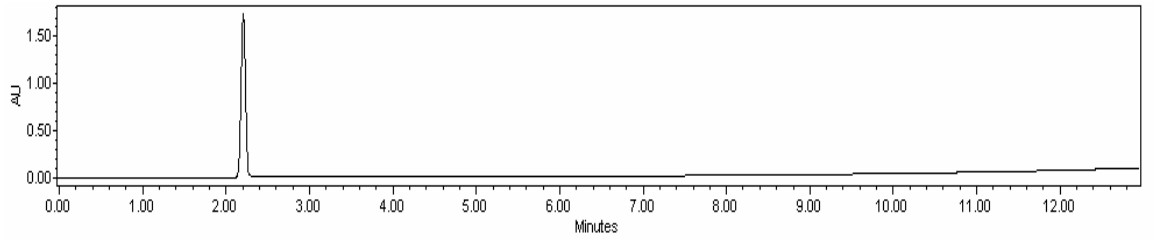
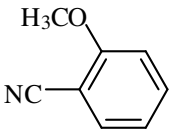
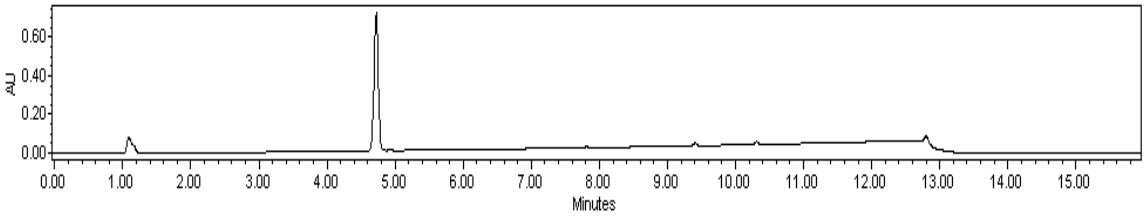


Table 2, entry 4: 2-methoxybenzonitrile





Authentic 2-methoxybenzonitrile

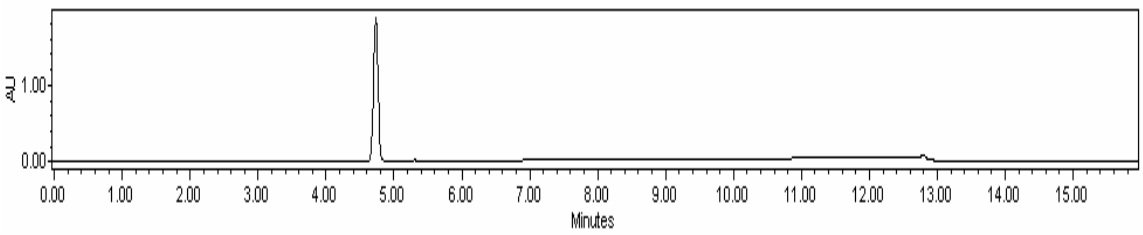
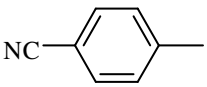
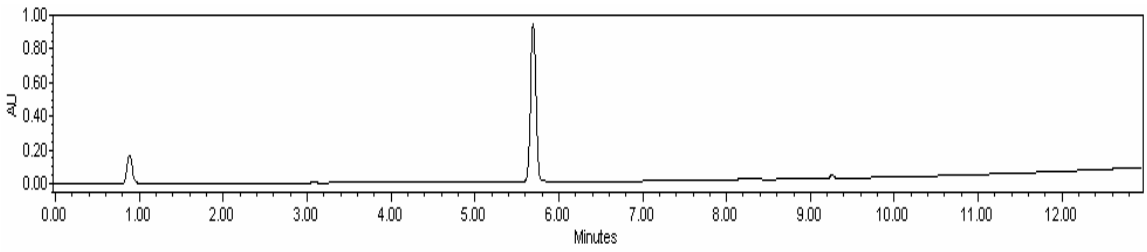


Table 2, entry 5: 4-methylbenzonitrile





Authentic 4-methylbenzonitrile

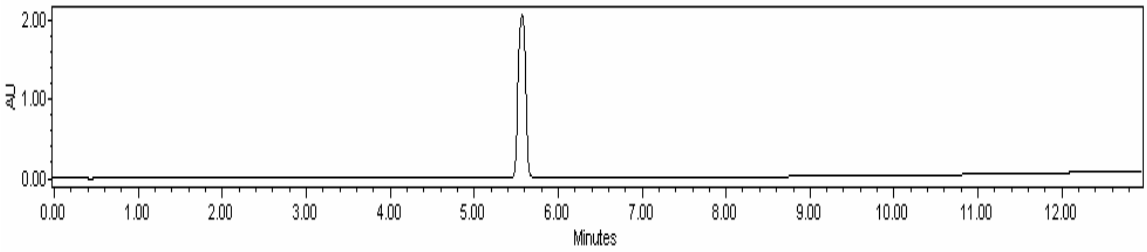
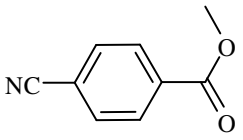
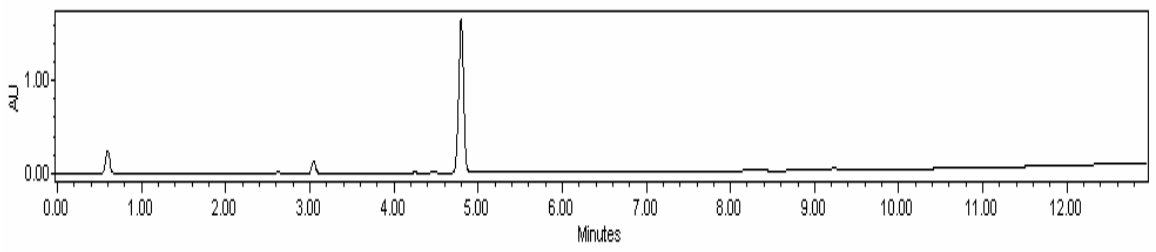


Table 2, entry 6: methyl-4-cyanobenzoate





Authentic methyl-4-cyanobenzoate (Aldrich)

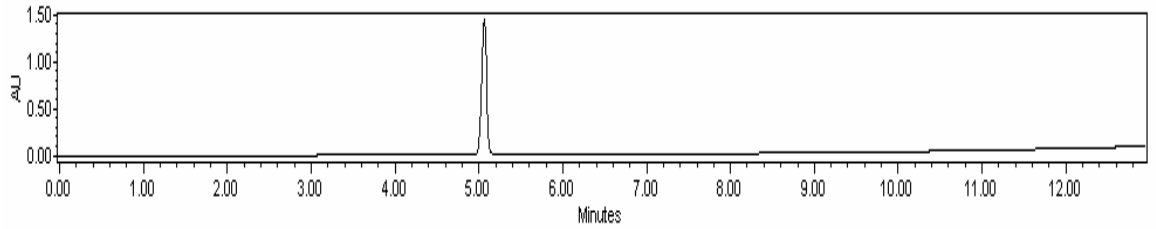
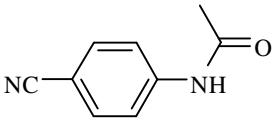
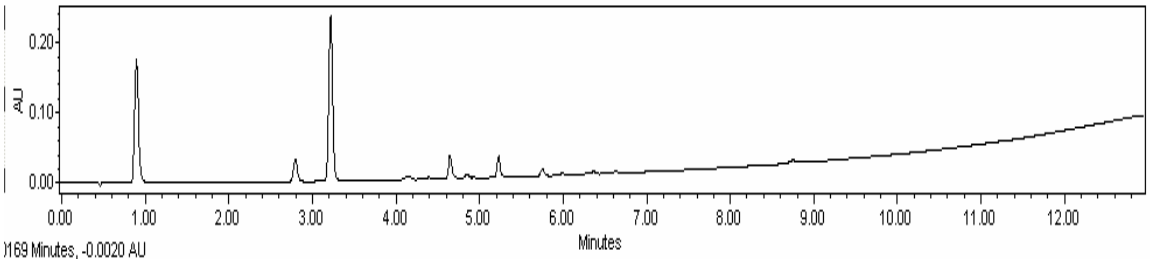


Table 2, entry 7: *N*-(4-cyanophenyl)acetamide





Authentic *N*-(4-cyanophenyl)acetamide

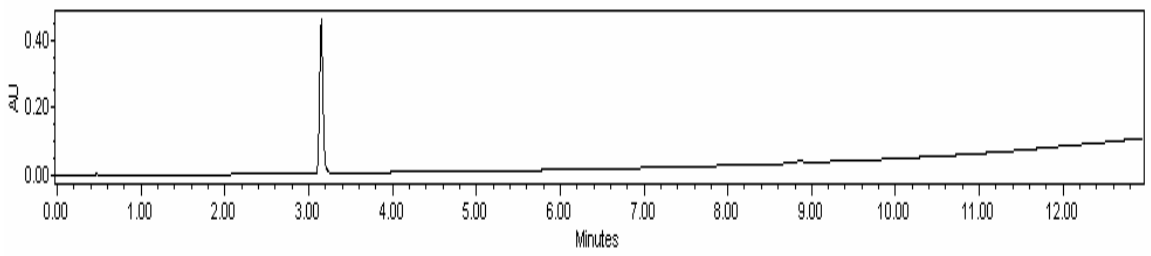
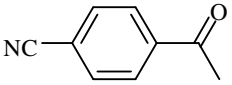
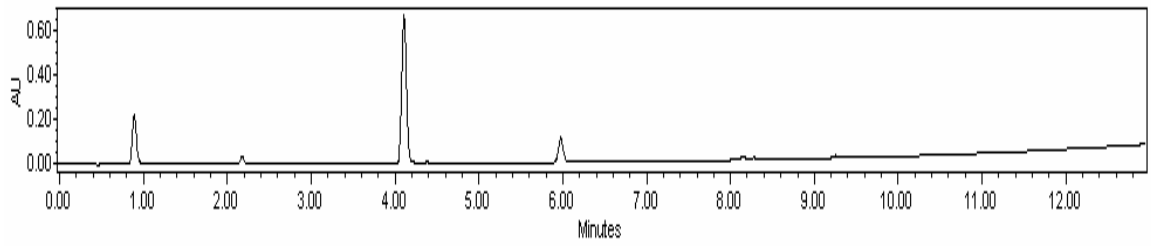


Table 2, entry 8: 4-acetylbenzonitrile





Authentic 4-acetylbenzonitrile

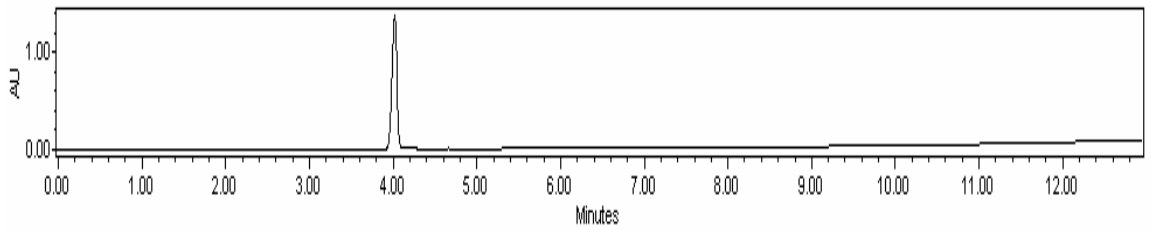
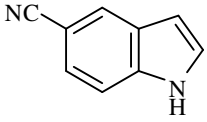
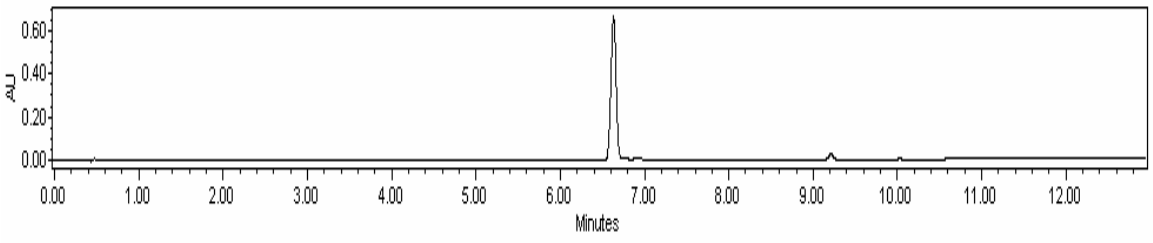


Table 3, entry 1: 1*H*-indole-5-carbonitrile





Authentic 1*H*-indole-5-carbonitrile

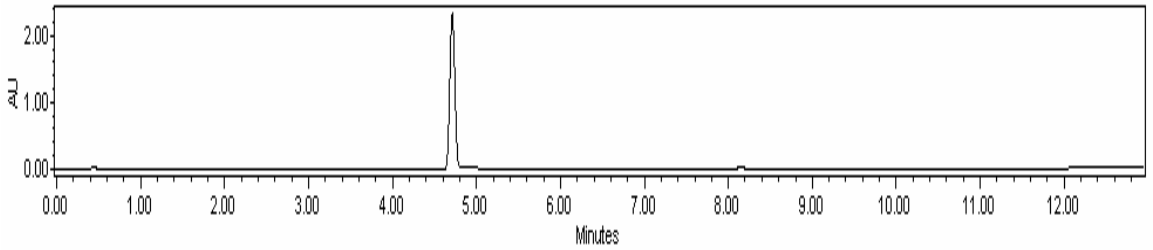
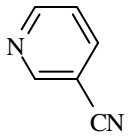
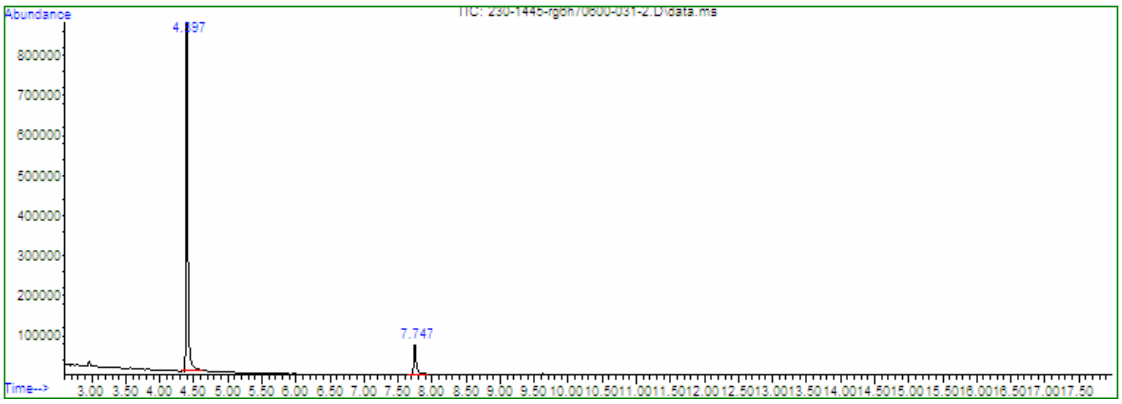


Table 3, entry 2: pyridine-3-carbonitrile





Note: The 4.5 min peak is DMAC.

Authentic pyridine-3-carbonitrile (Aldrich)

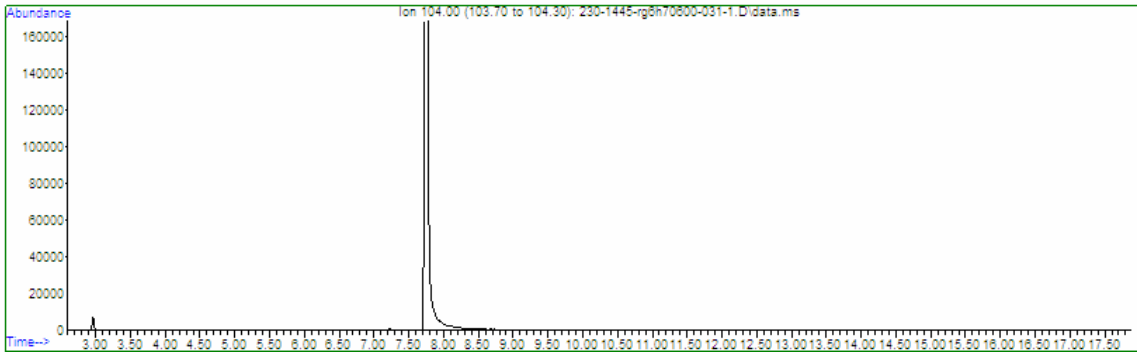
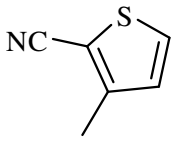
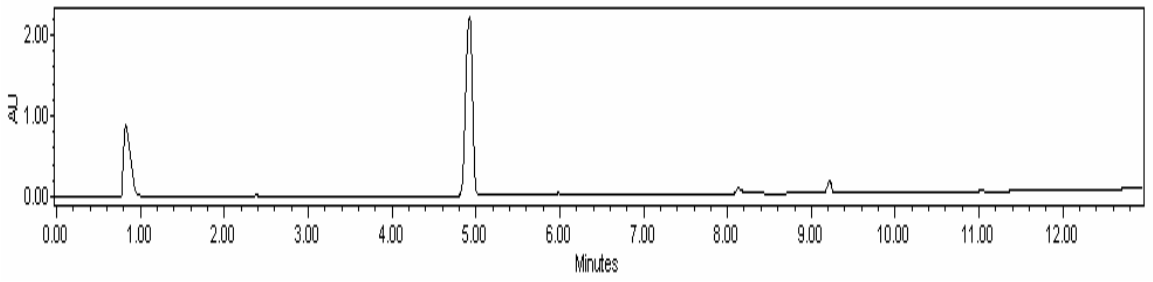


Table 3, entry 3: 3-methylthiophene-2-carbonitrile





Authentic 3-methylthiophene-2-carbonitrile

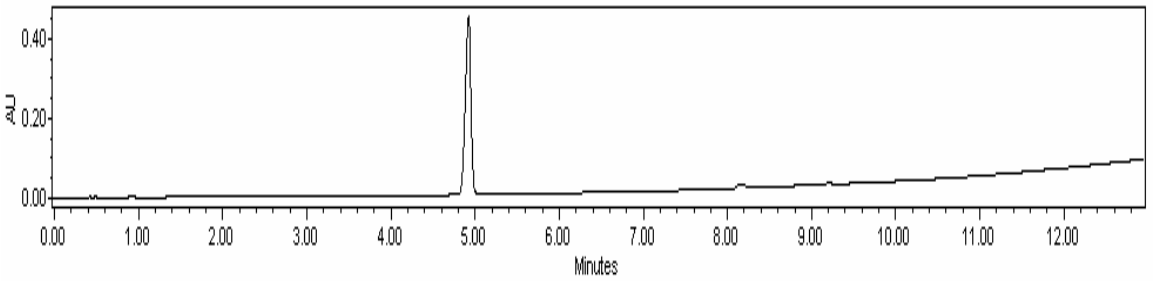
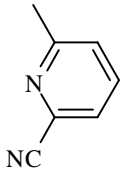
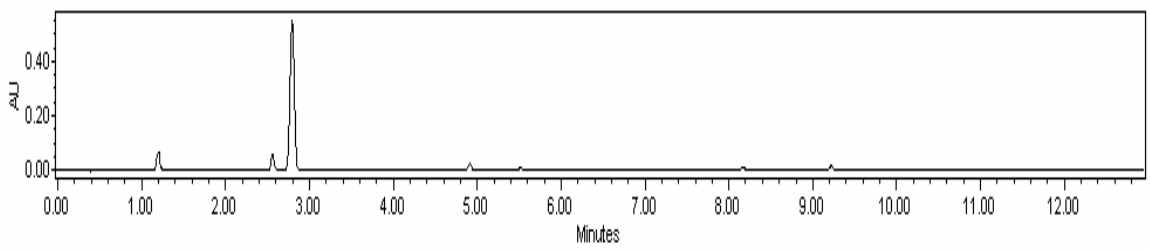


Table 3, entry 4: 6-methylpyridine-2-carbonitrile





Authentic 6-methylpyridine-2-carbonitrile

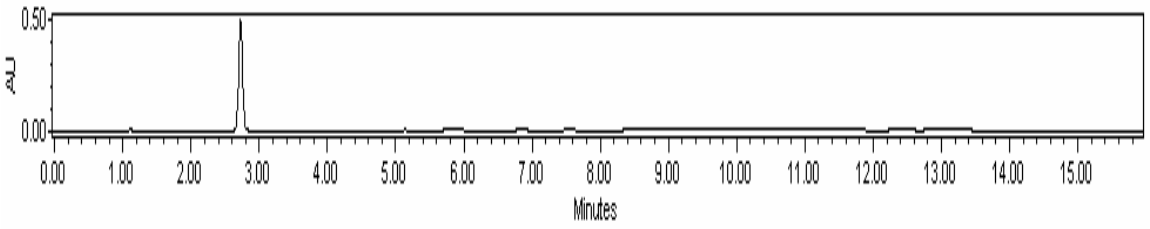
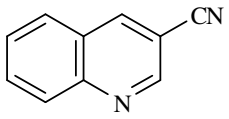
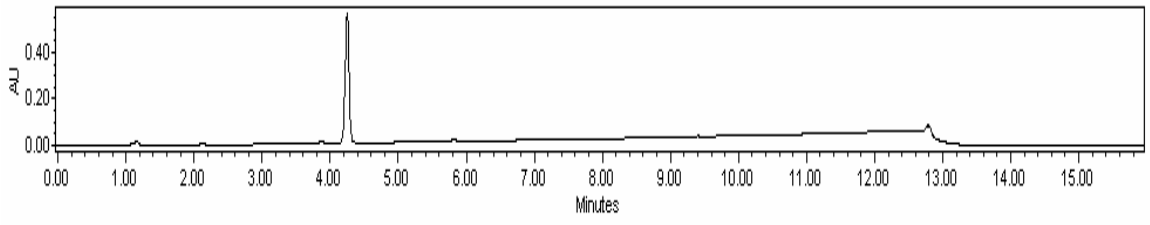


Table 3, entry 5: quinoline-3-carbonitrile





Authentic quinoline-3-carbonitrile

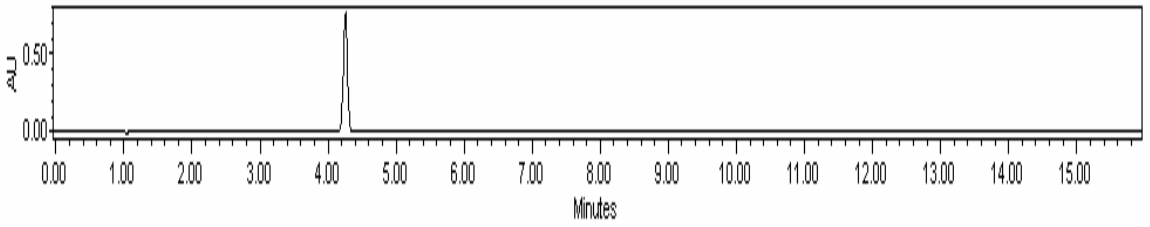
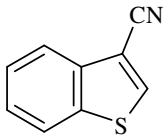
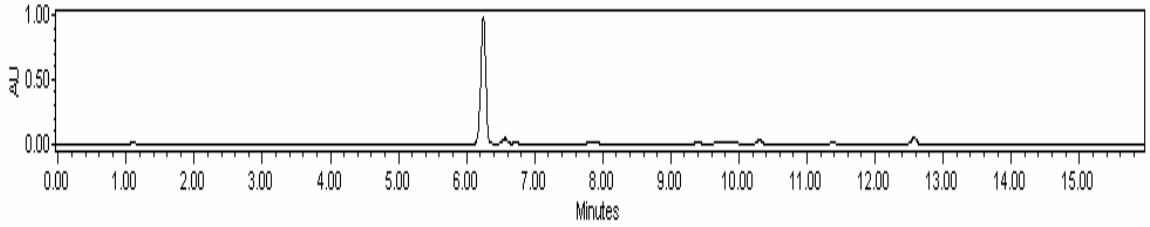


Table 3, entry 6: benzothiophene-3-carbonitrile





Authentic benzothiophene-3-carbonitrile

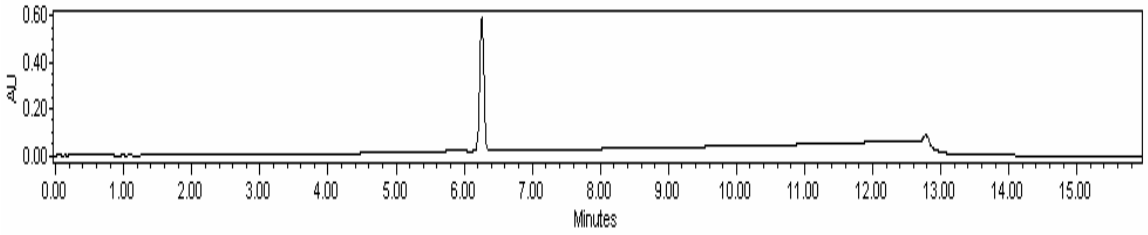
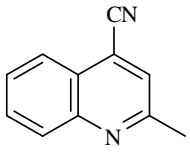
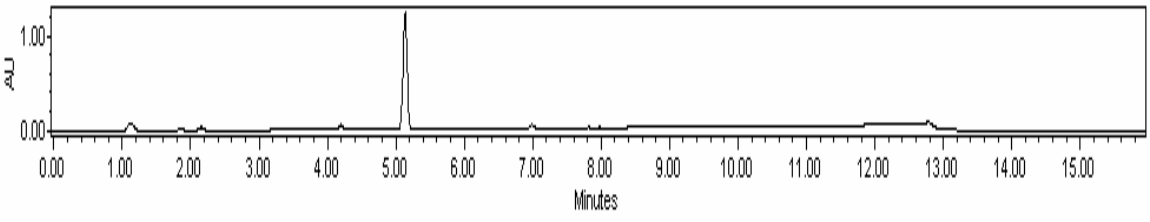


Table 3, entry 7: 2-methylquinoline-4-carbonitrile





Authentic 2-methylquinoline-4-carbonitrile

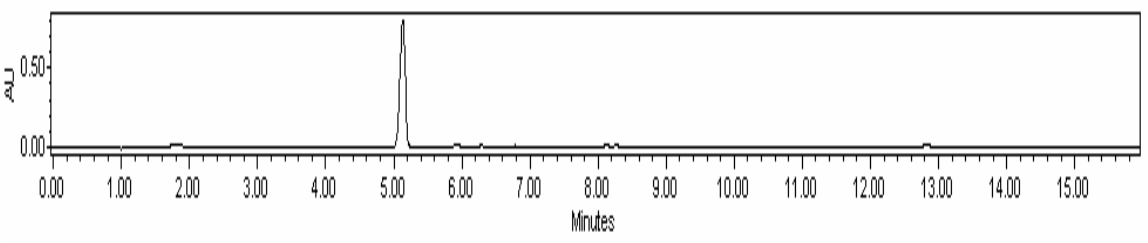
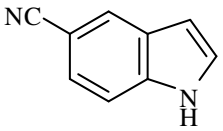
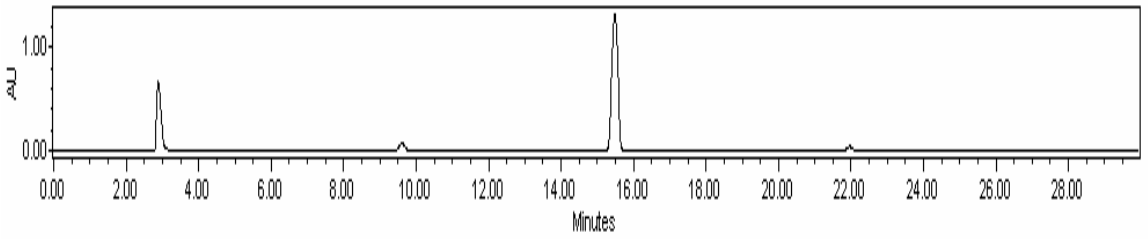
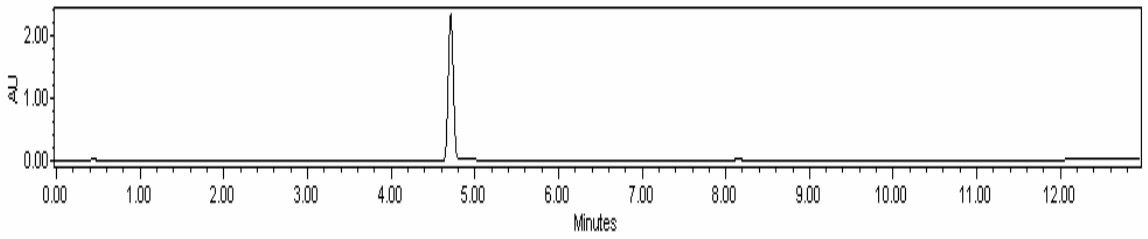


Table 3, entry 8: 1*H*-indole-5-carbonitrile





Authentic 1*H*-indole-5-carbonitrile



4. Work-up procedures and isolated yields

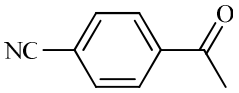
Upon completion of the reaction, the reaction mixtures were allowed to cool down to room temperature and worked up according to one of the two methods which will be referenced to as method A or B in the yield and spectral data summary of each compound.

Method A: The reaction mixture was diluted with 10 mL of EtOAc. The resulting slurry was filtered and the cake was rinsed with EtOAc (2 mL). The product was isolated

by washing the filtrate with water (2 × 10 mL) and 5% NH_4OH (1 × 10 mL). The organic layer was dried with Na_2SO_4. The volatile was removed in vacuo to give a residue, which was further purified by silica gel chromatography (EtOAc/heptanes) to provide the product.

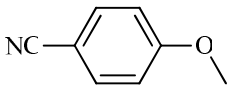
Method B[3]**:** The solids were removed by filtration. The DMAC filtrate was cooled to 10-15 °C and quenched slowly with 3 N aqueous ammonia until pH 10.5 – 11.0. The resulting slurry was further diluted with water and the mixture was stirred for 2 h at room temperature. The solid was collected by filtration. The cake was rinsed several times with water and air-dried with vacuum suction for 1 h. The cake was washed three times with heptanes and dried in a vacuum oven until constant weight.

Table 2, entry 1: 4-acetylbenzonitrile



Isolated with Method A. Input 4'-bromoacetophenone: 1.0 g (theoretical output 729 mg); output: 649 mg (89% yield). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 8.05 (1 H, d, *J* = 8.4 Hz), 7.79 (1 H, d, *J* = 8.4 Hz), 2.66 (3 H, s). ^{13}C NMR (400 MHz, *CDCl*$_3$) δ ppm 196.5, 139.9, 132.5, 128.7, 117.9, 116.4, 26.8.

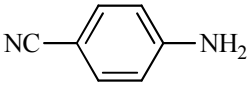
Table 2, entry 2: 4-methoxybenzonitrile



Isolated with Method A. Input 4-bromoanisole: 2.5 g (theoretical output 1.78 g); output: 1.55 g (87% yield). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 7.59 (2 H, m), 6.95 (2 H, m), 3.86

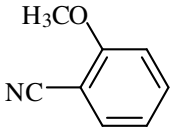
(3 H, s). ^{13}C NMR (400 MHz, *CDCl$_3$*) δ ppm 162.9, 134.0, 119.2, 114.8, 104.0, 55.6. HRMS (ES+) exact mass calcd for C_8H_7NONa 156.0425, found 156.0420.

Table 2, entry 3: 4-Aminobenzonitrile



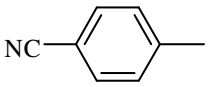
Isolated with Method B. Input 4-bromoaniline: 1.0 g (theoretical output 687 mg); output: 620 mg (90% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 7.40 - 7.44 (2 H, m), 6.64 - 6.68 (2 H, m), 4.21 (2 H, bs). ^{13}C NMR (400 MHz, *CDCl$_3$*) δ ppm 150.5, 133.8, 120.2, 114.5, 100.1.

Table 2, entry 4: 2-methoxybenzonitrile



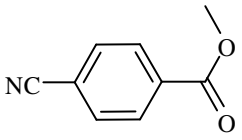
Isolated with Method A. Input 1-bromo-2-methoxybenzene: 1.0 g (theoretical output 712 mg); output: 648 mg (91% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 7.54 - 7.58 (2 H, m), 6.98 - 7.04 (2 H, m), 3.95 (3 H, s). ^{13}C NMR (400 MHz, *CDCl$_3$*) δ ppm 161.3, 134.4, 133.8, 120.8, 116.5, 111.3, 101.8, 56.0.

Table 2, entry 5: 4-methylbenzonitrile



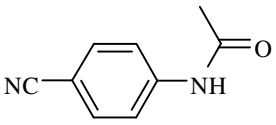
Isolated with Method A. Input 4-bromotoluene: 2.84 g (theoretical output 1.95 g); output: 1.85 g (95% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 7.54 (2 H, m), 7.28 (2 H, m), 2.43 (3 H, s). ^{13}C NMR (400 MHz, *CDCl$_3$*) δ ppm 143.7, 132.0, 129.9, 119.2, 109.3, 21.8. HRMS (ES+) exact mass calcd for C_8H_7NNa 140.0476, found 140.0471.

Table 2, entry 6: methyl-4-cyanobenzoate



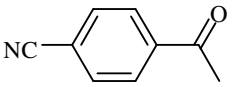
Isolated with Method A. Input methyl-4-bromobenzoate: 400 mg (theoretical output 298 mg); output: 259 mg (87% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.15 (2 H, d, J = 8.0 Hz), 7.76 (2 H, d, J = 7.6 Hz), 3.97 (3 H, s). ^{13}C NMR (400 MHz, *CDCl$_3$*) δ ppm 165.4, 133.9, 132.3, 130.1, 118.0, 116.4, 52.8.

Table 2, entry 7: *N*-(4-cyanophenyl)acetamide



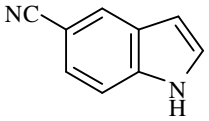
Isolated with Method B. Input 4-bromoacetanilide: 1.0 g (theoretical output 748 mg); output: 688 mg (92% yield). ^{1}H NMR (400 MHz, *DMSO-d6*) δ ppm 10.39 (1 H, s), 7.76 (4 H, s), 2.10 (3 H, s). ^{13}C NMR (400 MHz, *DMSO-d6*) δ ppm 169.1, 143.4, 133.2, 119.1, 118.9, 104.6, 24.2.

Table 2, entry 8: 4-acetylbenzonitrile



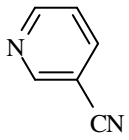
Isolated with Method A. Input 4-chloroacetophenone: 1.0 g (theoretical output 939 mg); output: 657 mg (70% yield). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 8.10 (2 H, d, J = 7.6 Hz), 8.02 (2 H, d, J = 8.0 Hz), 2.64 (3 H, s). ^{13}C NMR (400 MHz, DMSO-*d6*) δ ppm 197.3, 139.8, 132.7, 128.7, 118.1, 115.1, 27.0.

Table 3, entry 1: 1*H*-indole-5-carbonitrile



Isolated with Method A. Input 5-bromoindole: 1.0 g (theoretical output 725 mg); output: 653 mg (90% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.81 (1 H, bs), 8.02 (1 H, s), 7.28 – 7.51 (3 H, m), 6.65 (1 H, m). ^{13}C NMR (400 MHz, *CDCl$_3$*) δ ppm 137.6, 127.7, 126.6, 126.6, 124.8, 121.0, 112.1, 103.4, 102.7. HRMS (ES+) exact mass calcd for $C_9H_6N_2$ 141.0047, found, 141.0457.

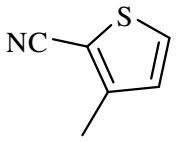
Table 3, entry 2: pyridine-3-carbonitrile



Isolated with Method A with control of distillation temperature/pressure to avoid loss of product. Input 3-bromopyridine: 2.0 g (theoretical output 1.32 g); output: 1.16 g (88% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.92 (1 H, s), 8.84 (1 H, d, J = 4.8 Hz), 8.00 (1 H, d, J = 8.0 Hz), 7.47 (1 H, dd, J = 8.0 Hz, J = 5.2 Hz). ^{13}C NMR (400 MHz, *CDCl$_3$*) δ

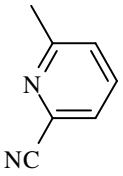
ppm 153.0, 152.5, 139.3, 123.7, 116.5, 110.1. Anal. calcd for $C_6H_4N_2$ C, 69.22, H, 3.87, N, 26.91, found C, 69.36, H, 3.88, N, 26.82.

Table 3, entry 3: 3-methylthiophene-2-carbonitrile



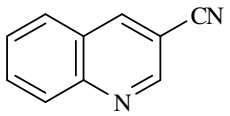
Isolated with Method A. Input 2-bromo-3-methylthiophene: 1.0 g (theoretical output 696 mg); output: 591 mg (85% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 7.48 (1 H, d, *J* = 5.2 Hz), 6.96 (1 H, d, *J* = 4.8 Hz), 2.45 (3 H, s). ^{13}C NMR (400 MHz, *CDCl$_3$*) δ ppm 149.5, 131.6, 129.5, 114.3, 105.9, 15.3. Anal. calcd for C_6H_5NS C, 58.51, H, 4.09, N, 11.37, S, 26.03, found C, 58.49, H, 4.13, N, 11.34, S, 26.05.

Table 3, entry 4: 6-methylpyridine-2-carbonitrile



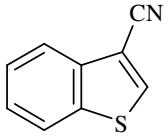
Isolated with Method A. Input 2-chloro-6-methylpyridine: 2.0 g (theoretical output 1.85 g); output: 1.78 g (96% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 7.73 (1 H, t, *J* = 7.6 Hz), 7.52 (1 H, d, *J* = 7.6 Hz), 7.39 (1 H, d, *J* = 8.0 Hz), 2.62 (3 H, s). ^{13}C NMR (400 MHz, *CDCl$_3$*) δ ppm 160.7, 137.1, 133.2, 126.9, 125.7, 117.4, 24.4.

Table 3, entry 5: quinoline-3-carbonitrile



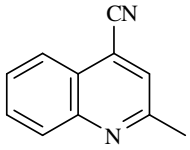
Isolated with Method A. Input 3-bromoquinoline: 1.0 g (theoretical output 741 mg); output: 637 mg (86% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.04 (1 H, d, *J* = 2.0 Hz), 8.55 (1 H, d, *J* = 2.4 Hz), 8.18 (1 H, m), 7.91 (2 H, m), 7.70 (1 H, m). ^{13}C NMR (400 MHz, *CDCl$_3$*) δ ppm 149.7, 148.8, 141.5, 132.8, 128.9, 128.5, 128.3, 126.2, 117.1, 106.6.

Table 3, entry 6: benzothiophene-3-carbonitrile



Isolated with Method A. Input 3-bromobenzothiophene: 1.0 g (theoretical output 747 mg); output: 613 mg (82% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.14 (1 H, s), 8.02 (1 H, d, *J* = 8.0 Hz), 7.93 (1 H, d, *J* = 8.0 Hz), 7.49 - 7.58 (2 H, m). ^{13}C NMR (400 MHz, *CDCl$_3$*) δ ppm 138.5, 137.6, 137.3, 126.2, 126.0, 122.6, 122.6, 114.4, 107.2.

Table 3, entry 7: 2-methylquinoline-4-carbonitrile

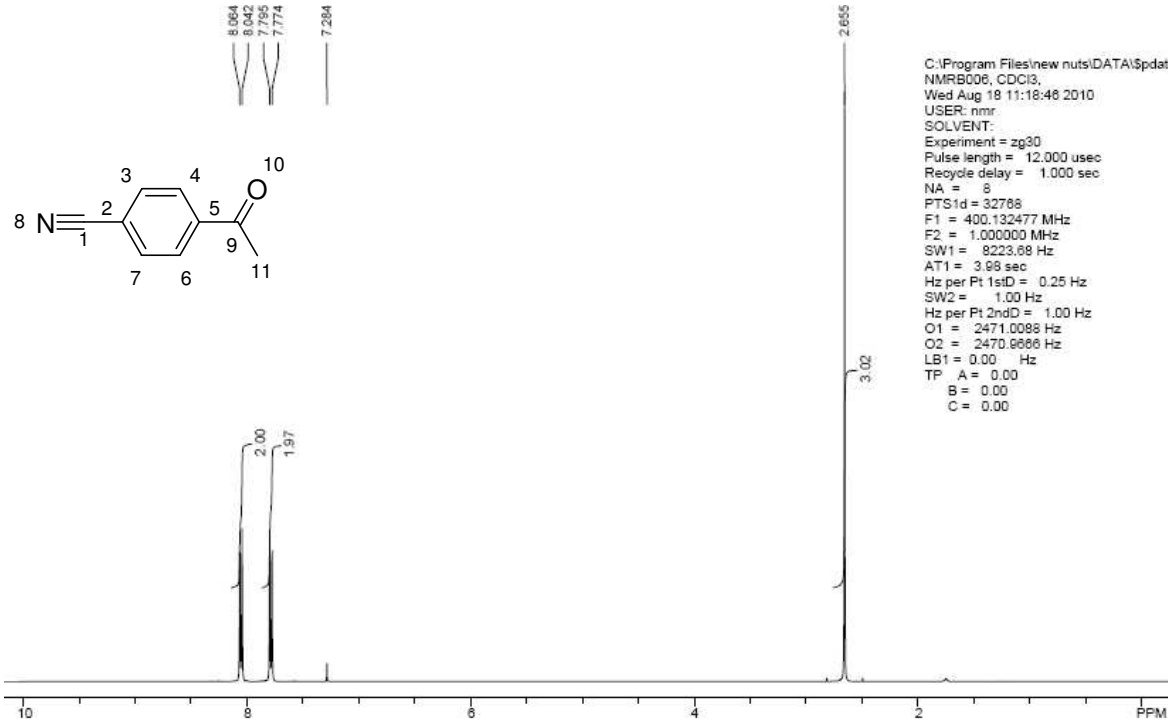


Isolated with Method A. Input 4-chloroquinaldine: 1.0 g (theoretical output 947 mg); output: 729 mg (77% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.01 – 8.06 (2 H, m), 7.74 (1 H, t, *J* = 7.6 Hz), 7.60 (1 H, t, *J* = 7.6 Hz), 7.54 (1 H, s), 2.72 (3 H, s). ^{13}C NMR

(400 MHz, $CDCl_3$) δ ppm 158.4, 147.8, 131.2, 129.5, 128.2, 125.9, 124.7, 124.0, 118.9, 115.7, 25.2.

5. Copies of ^{1}H and ^{13}C NMR of isolated products

Table 2, entry 1: 4-acetylbenzonitrile



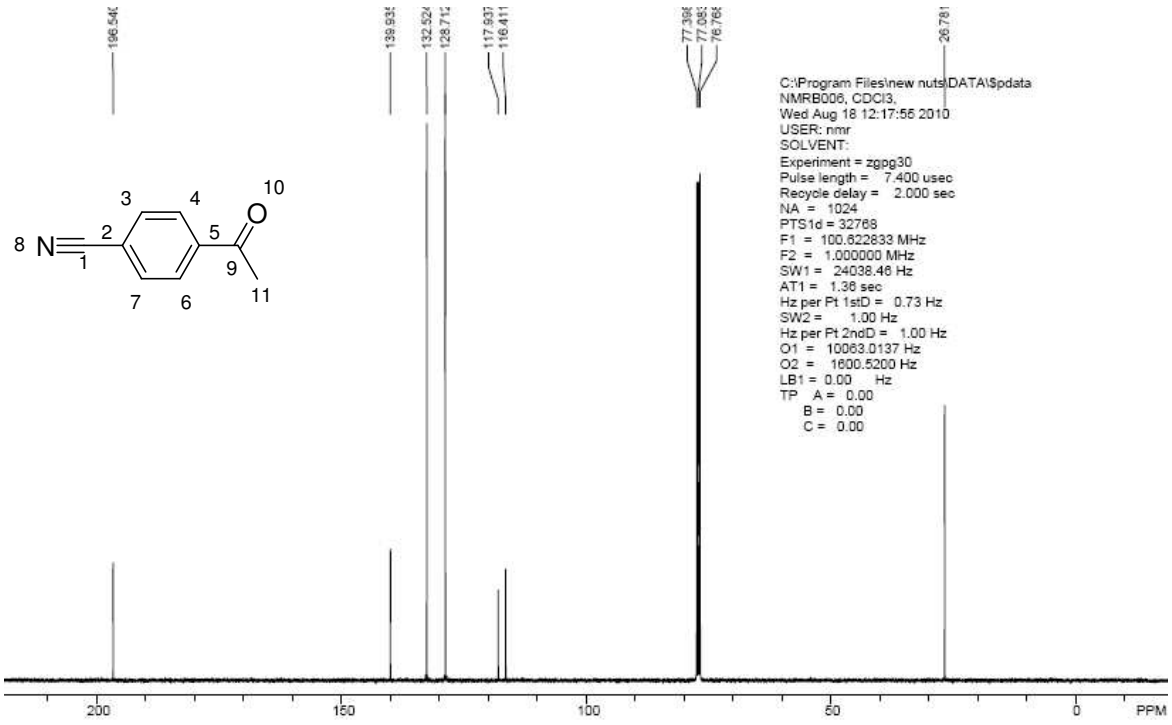
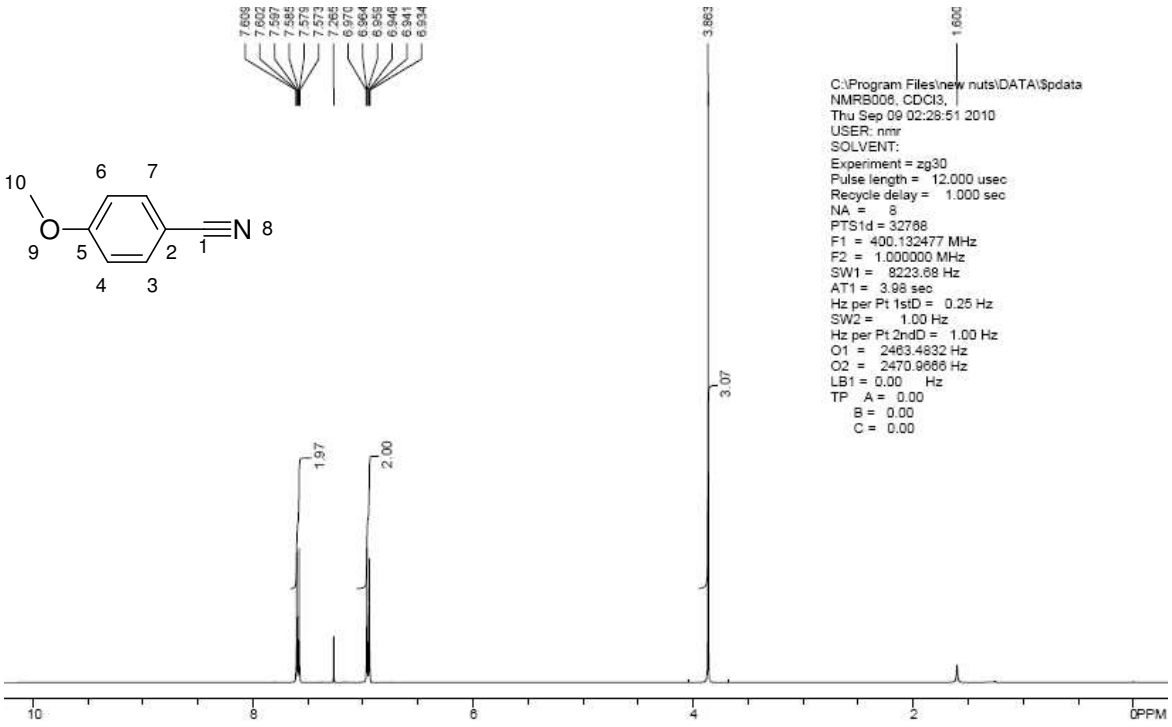


Table 2, entry 2: 4-methoxybenzonitrile



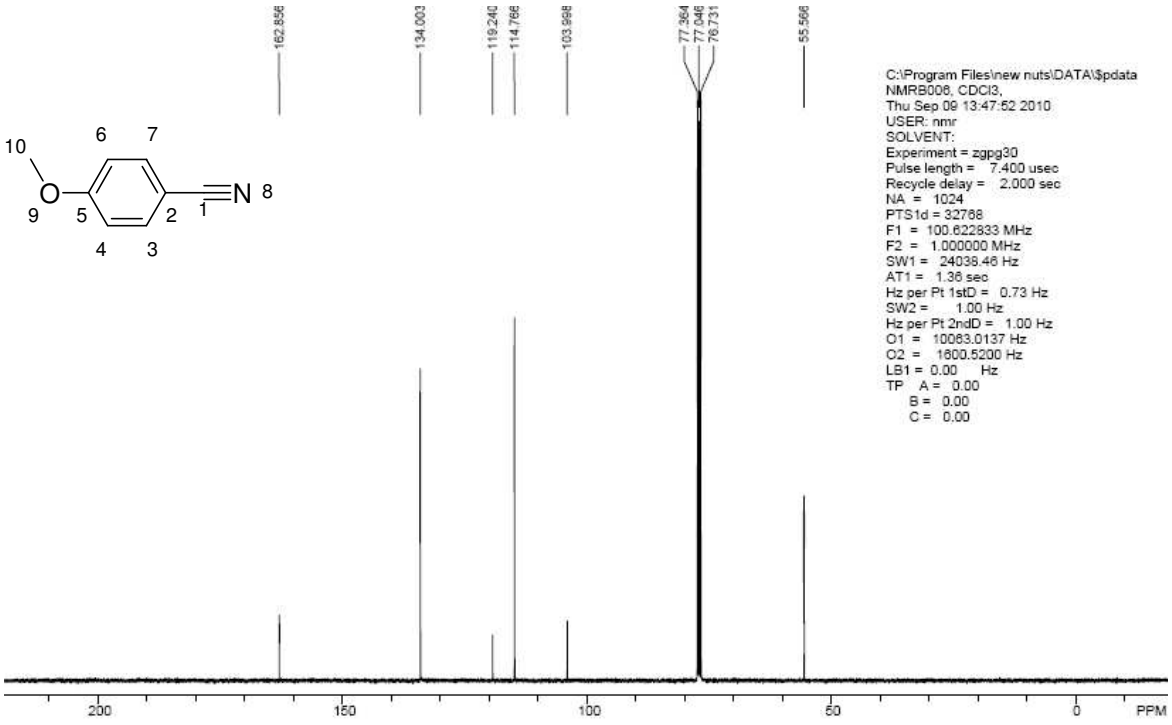
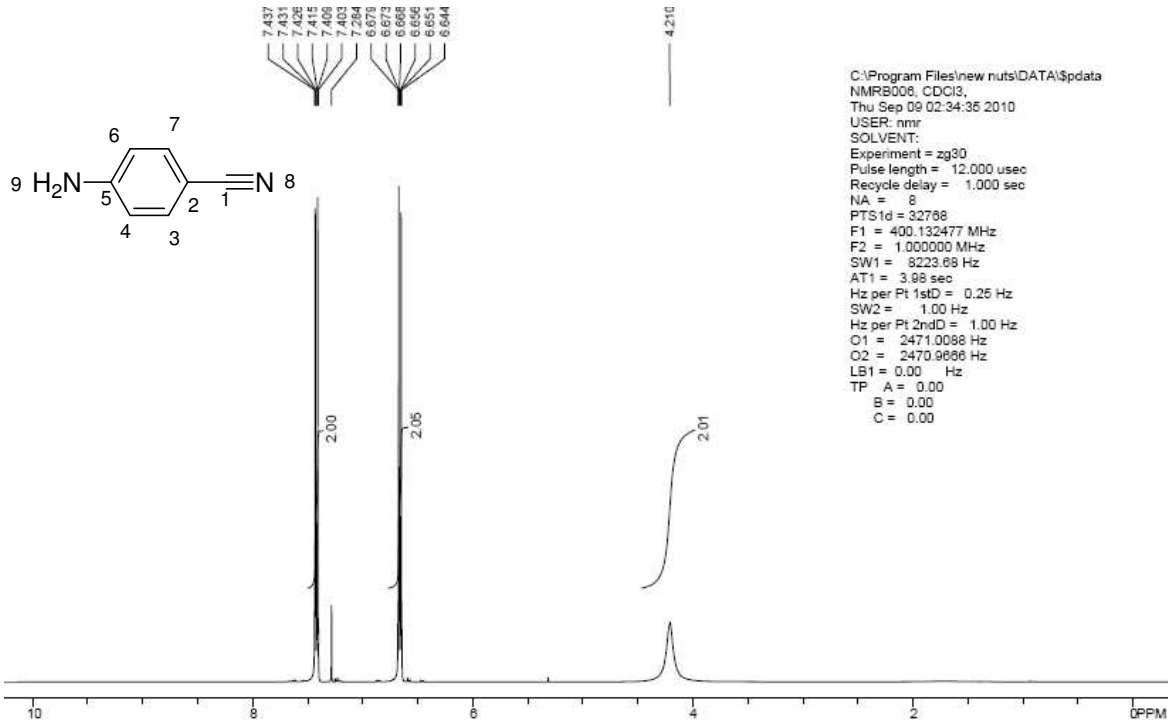


Table 2, entry 3: 4-Aminobenzonitrile



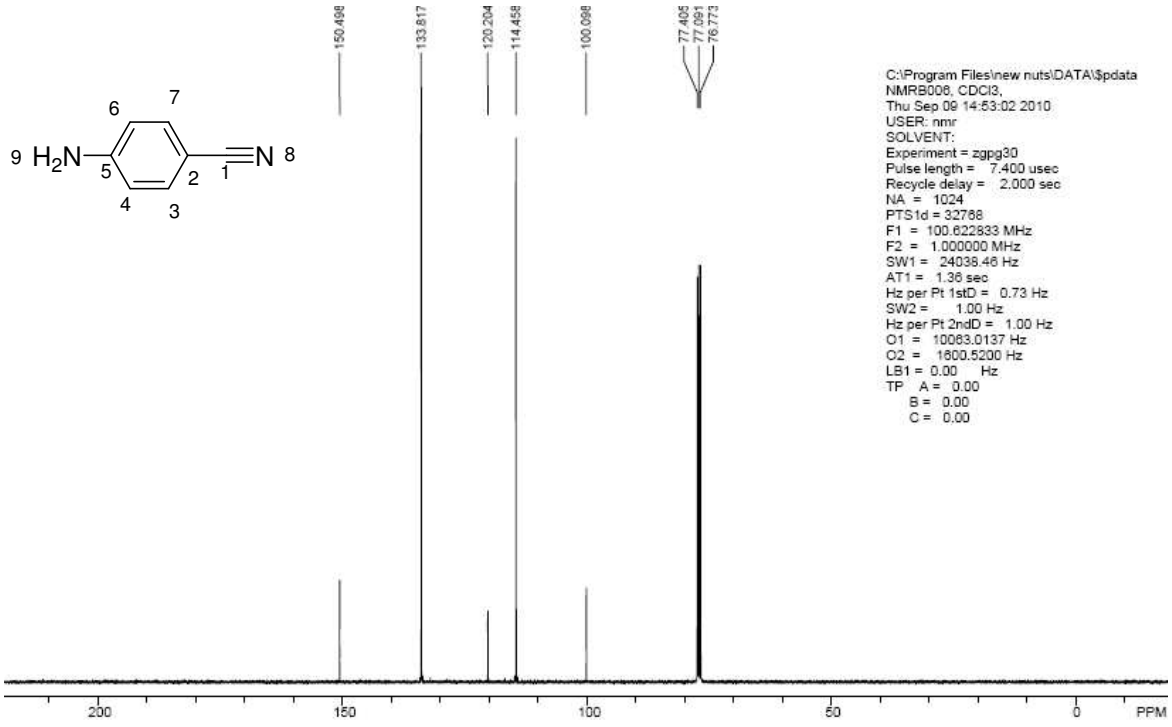
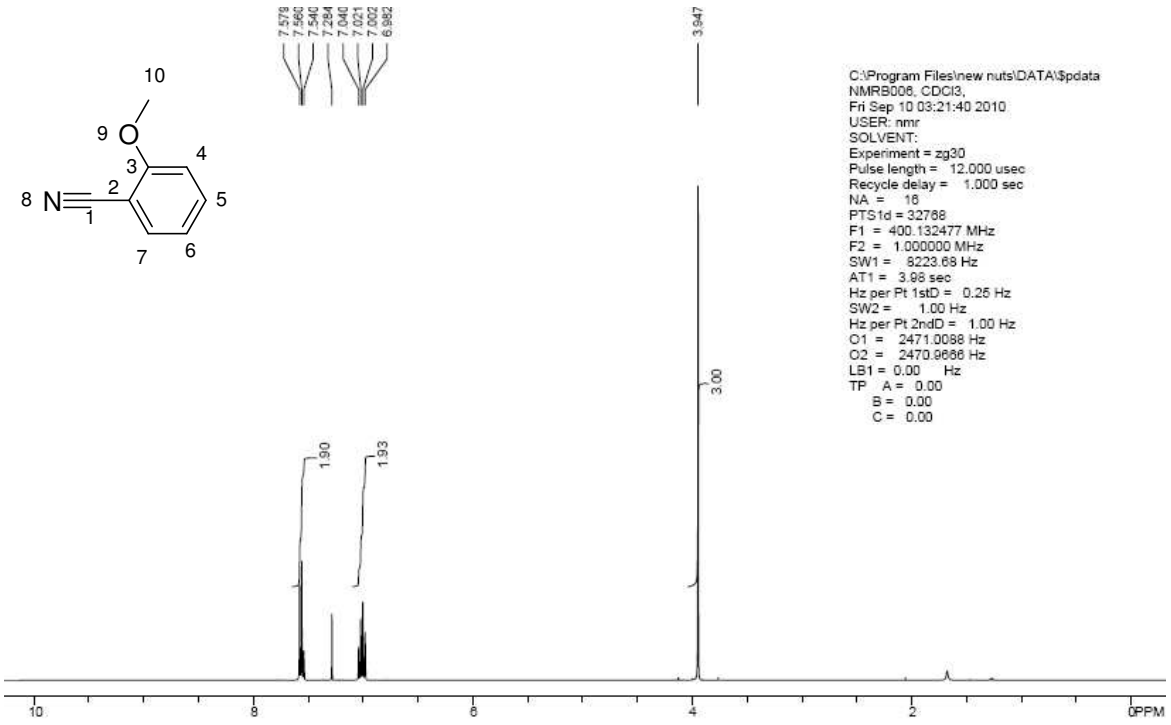


Table 2, entry 4: 2-methoxybenzonitrile



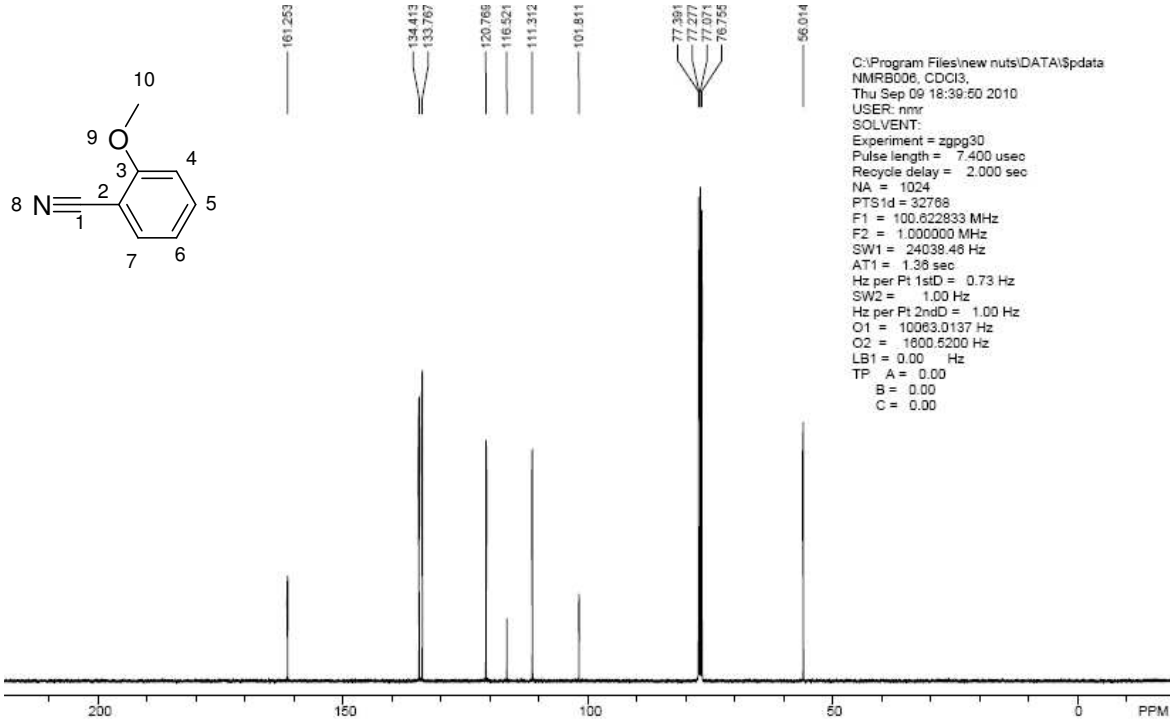
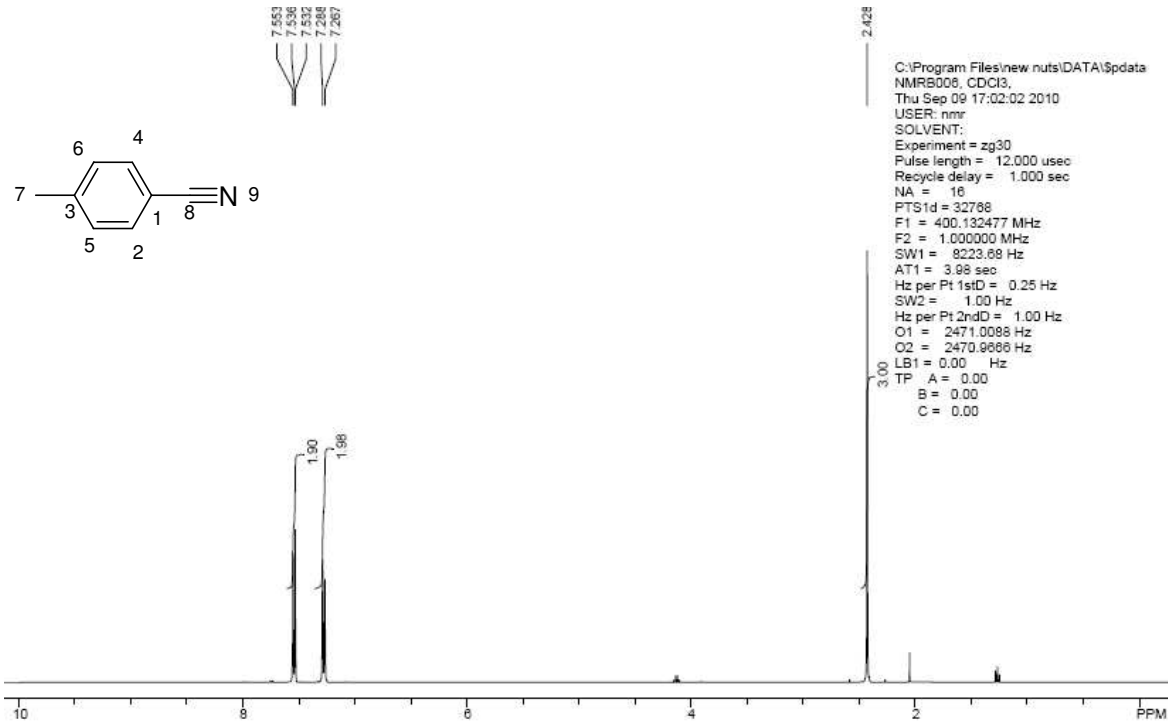


Table 2, entry 5: 4-methylbenzonitrile



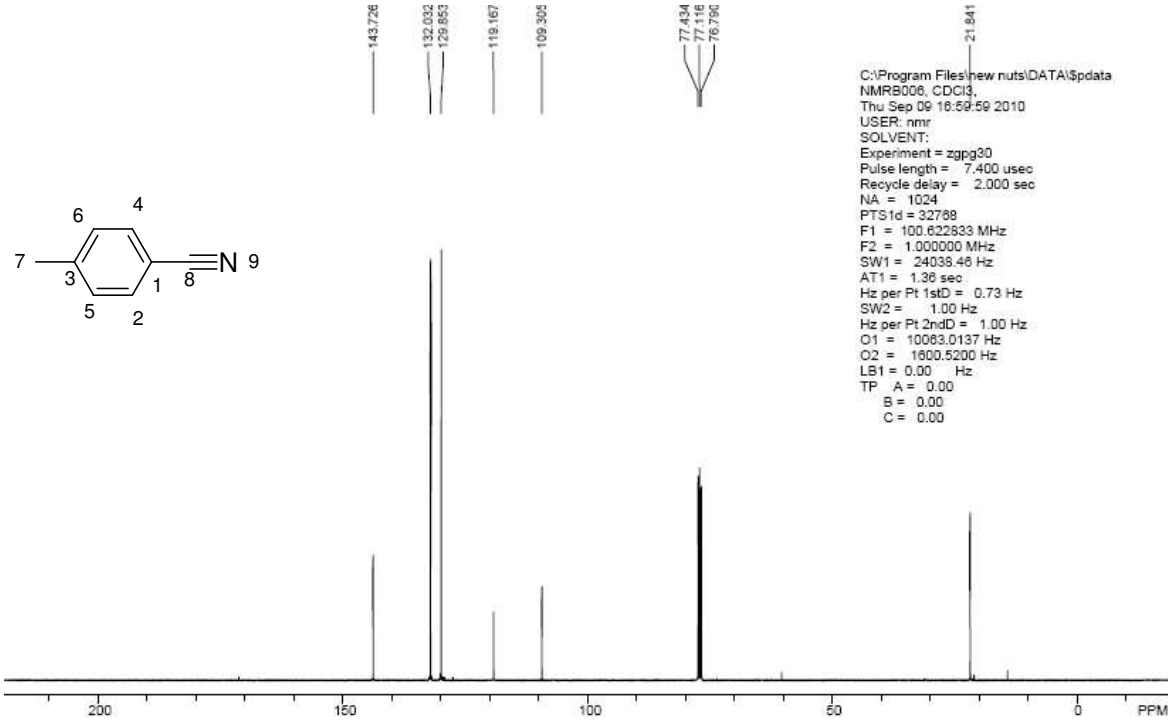
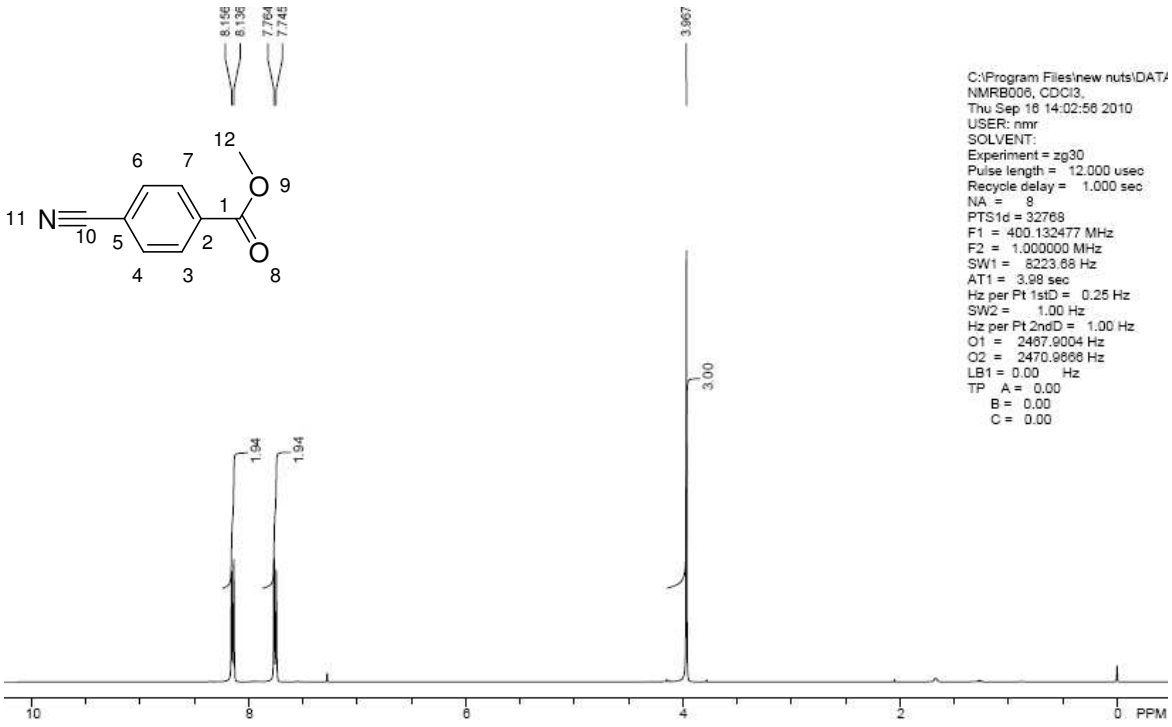


Table 2, entry 6: methyl-4-cyanobenzoate



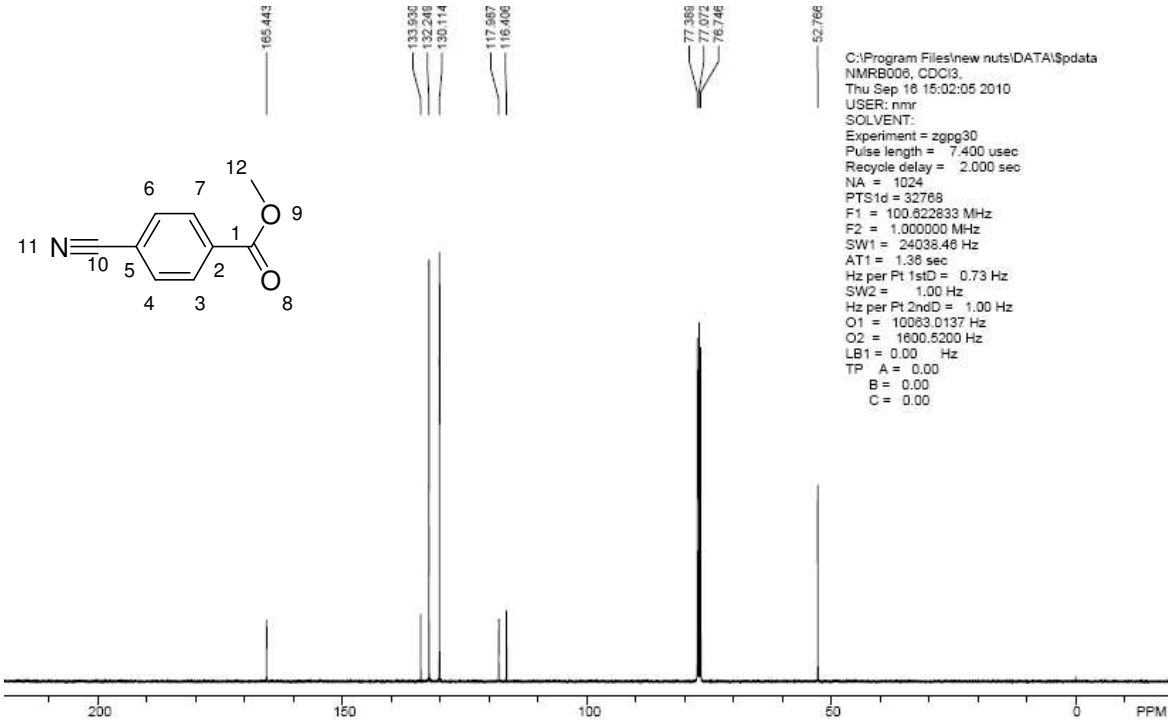
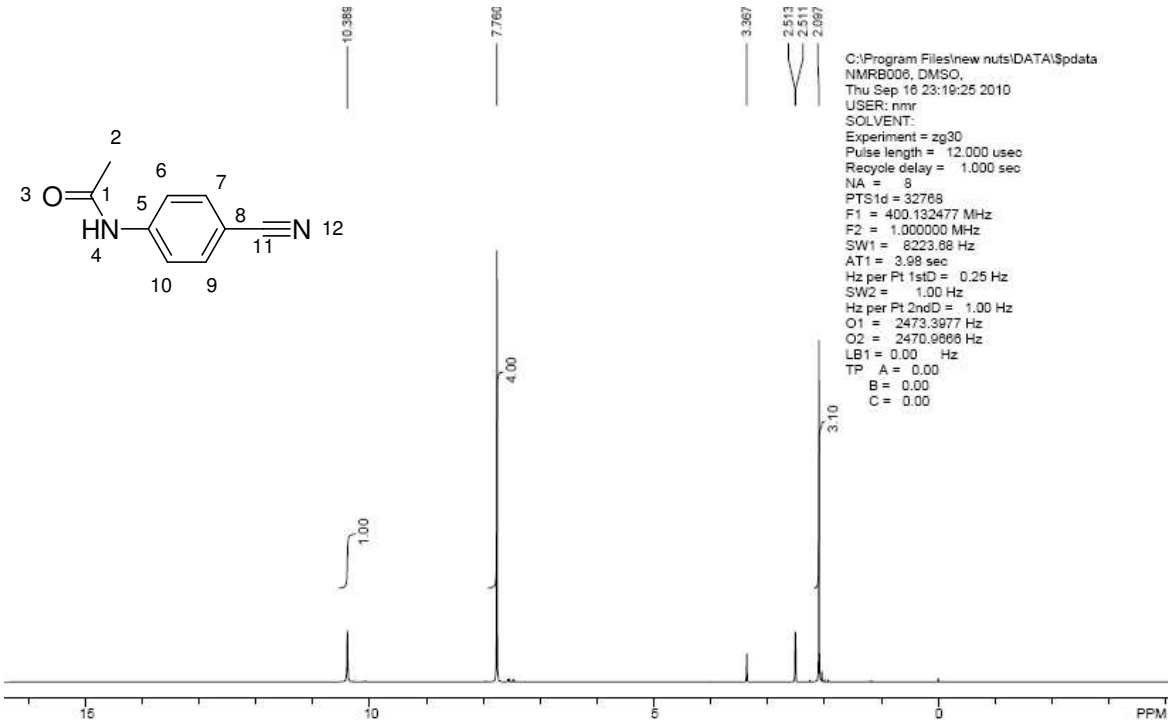


Table 2, entry 7: *N*-(4-cyanophenyl)acetamide



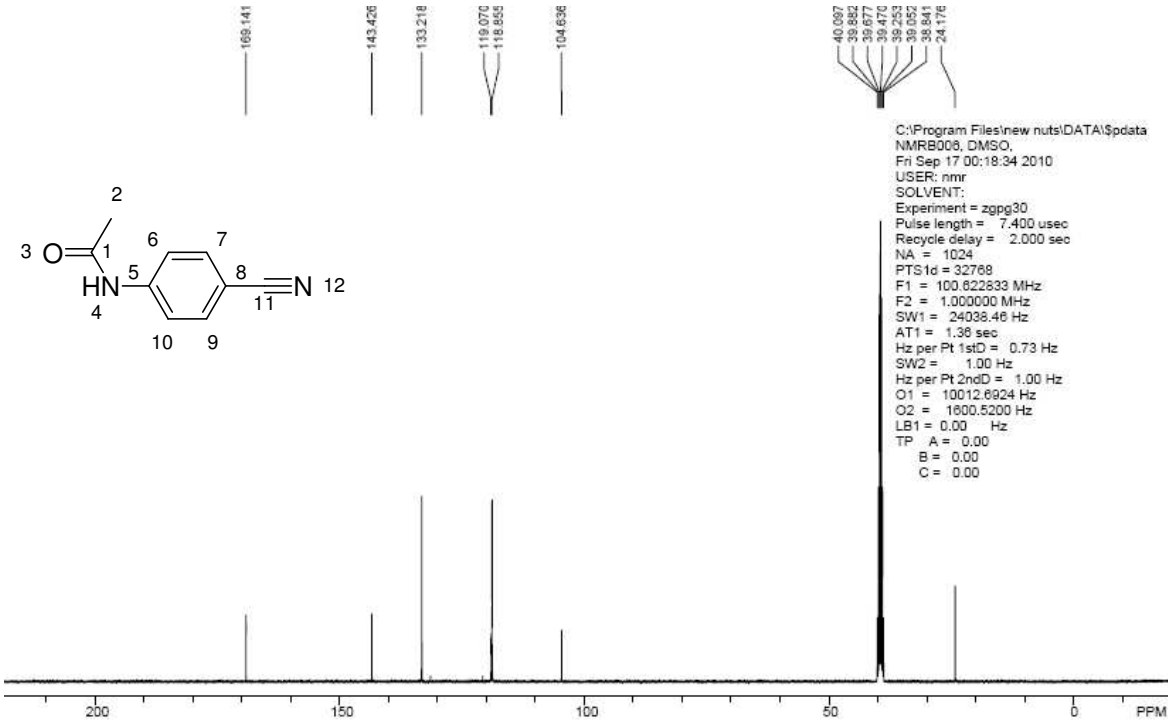
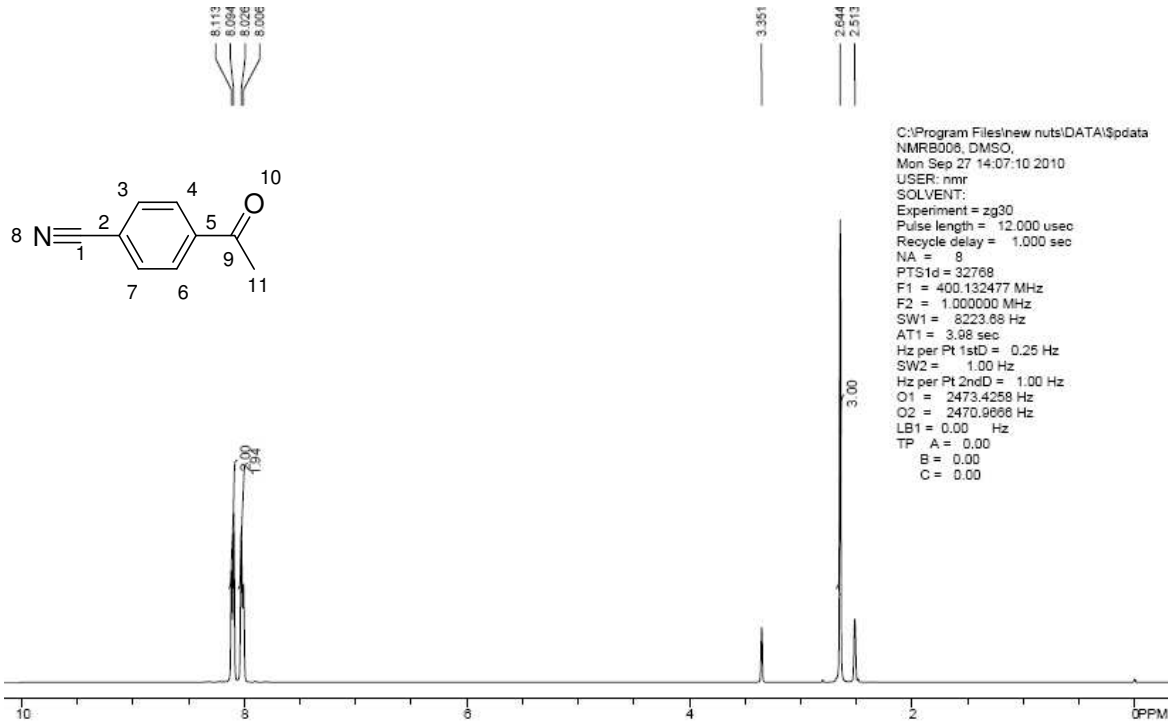


Table 2, entry 8: 4-acetylbenzonitrile



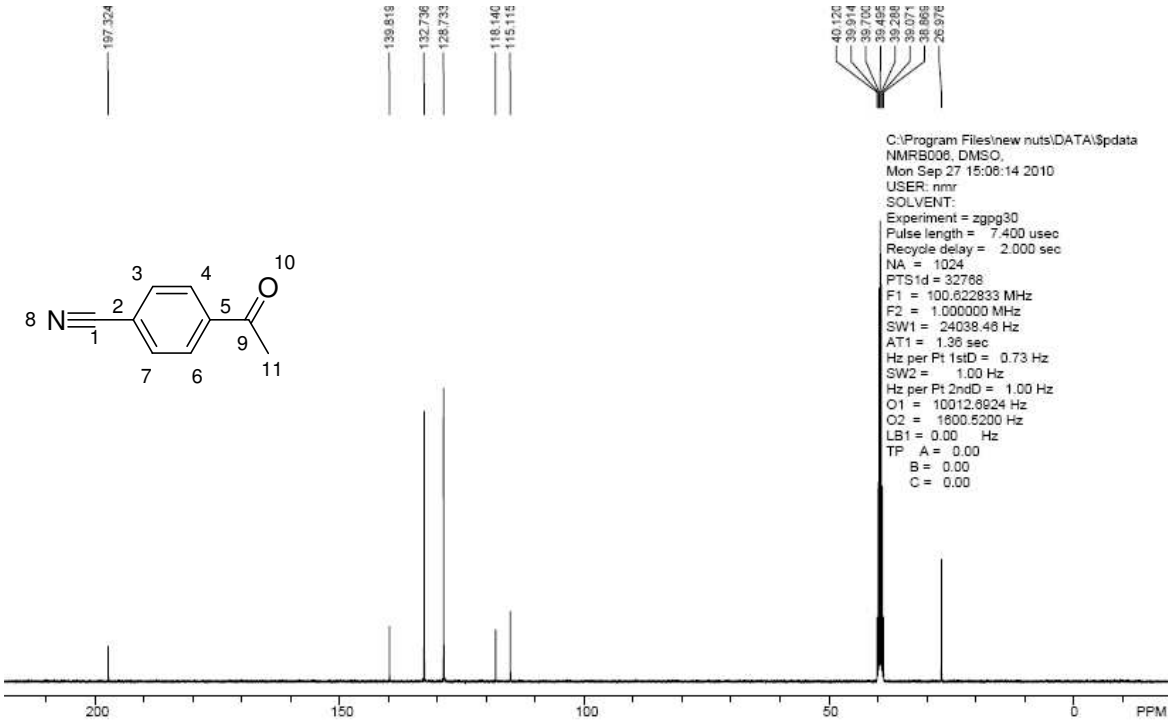
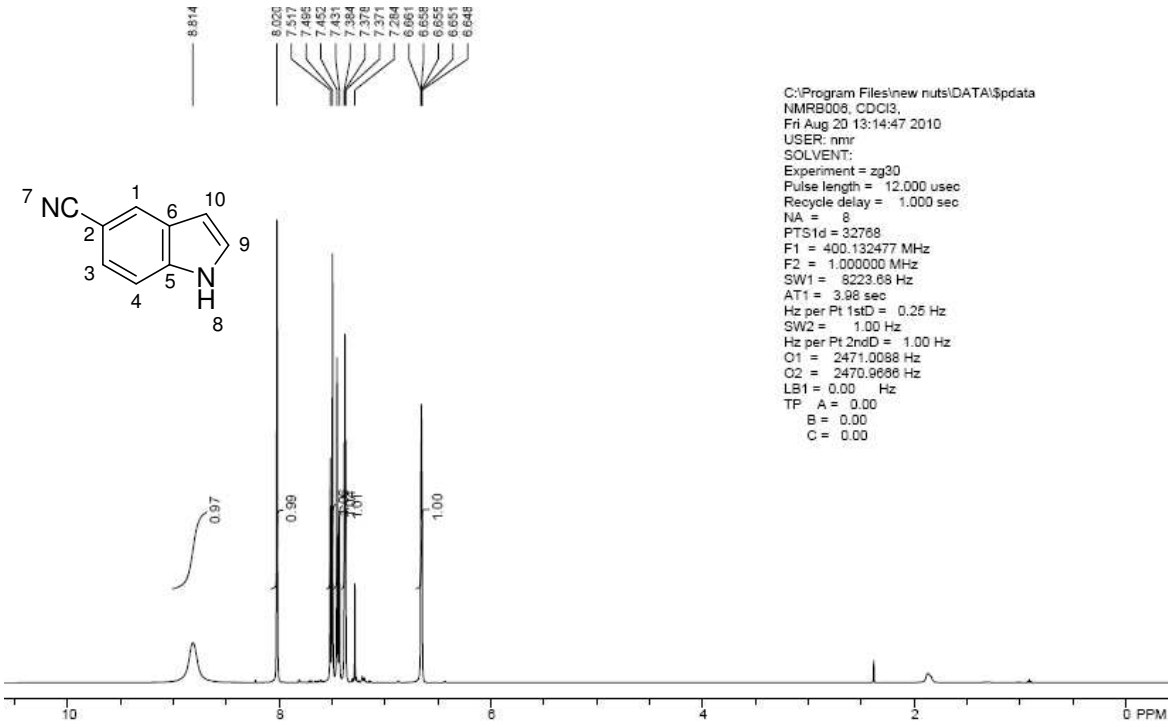


Table 3, entry 1: 1*H*-indole-5-carbonitrile



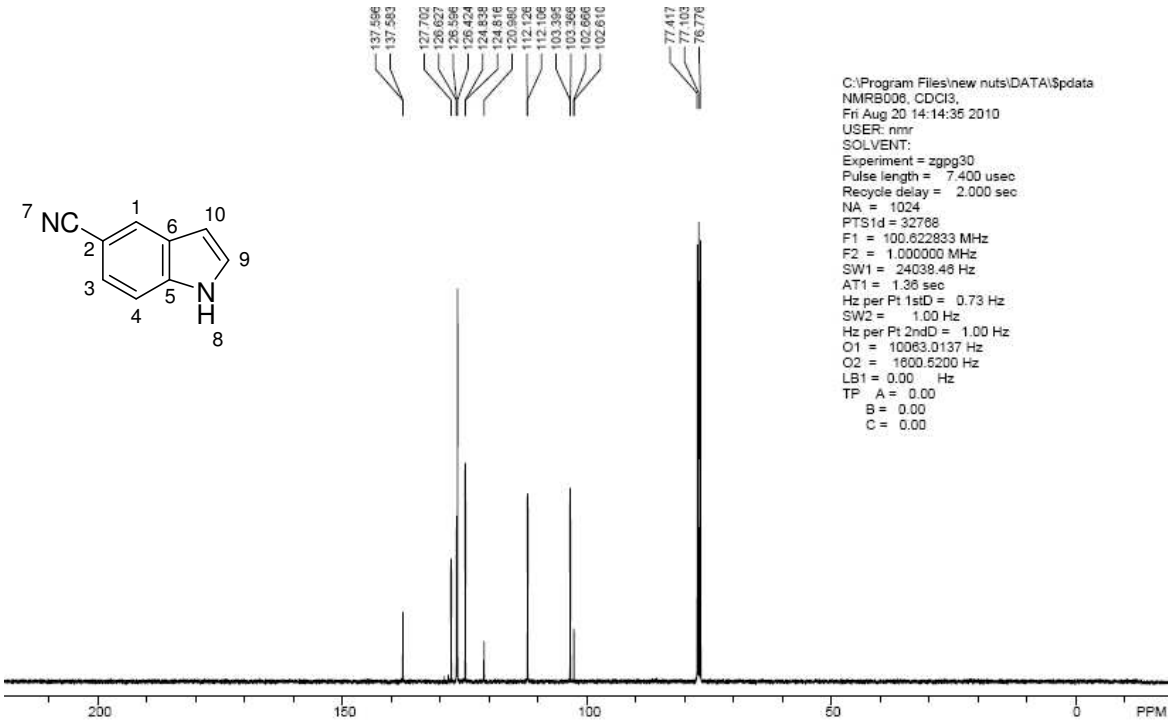
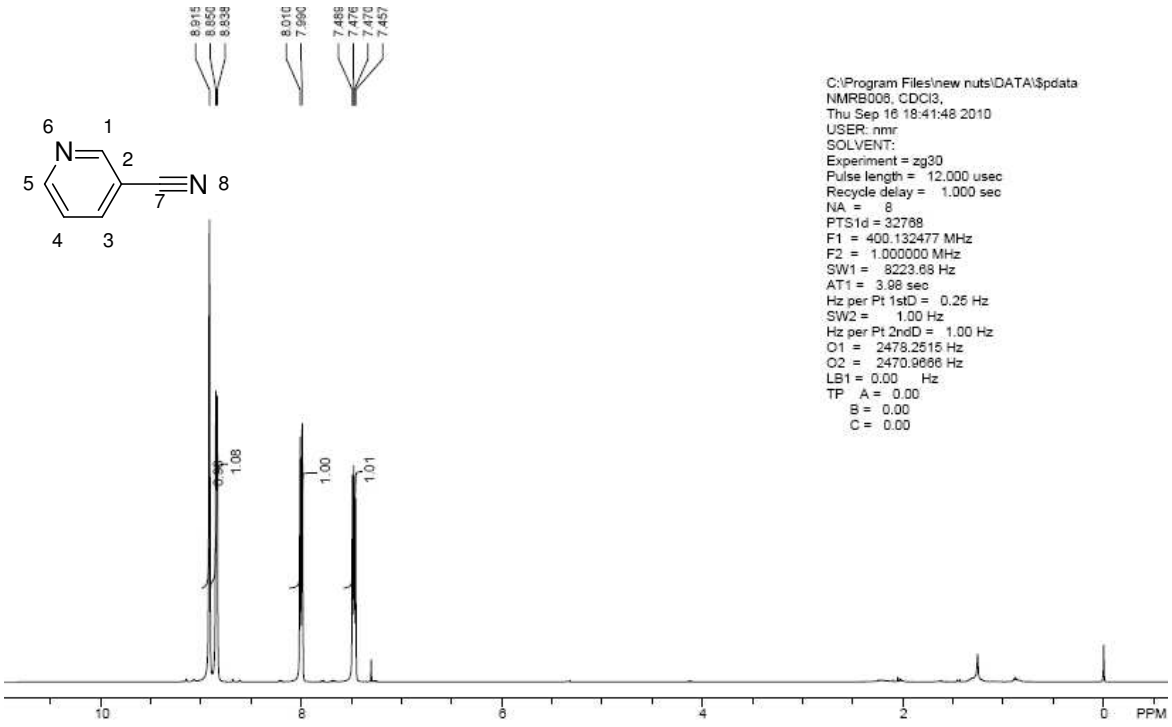


Table 3, entry 2: pyridine-3-carbonitrile



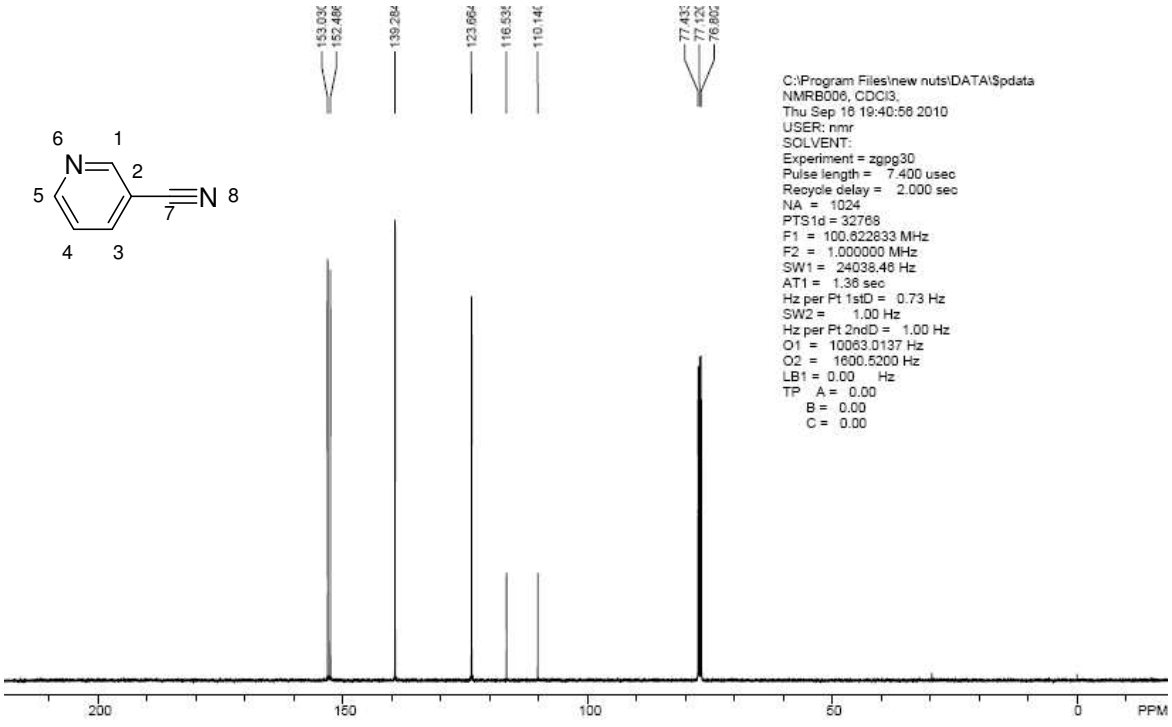
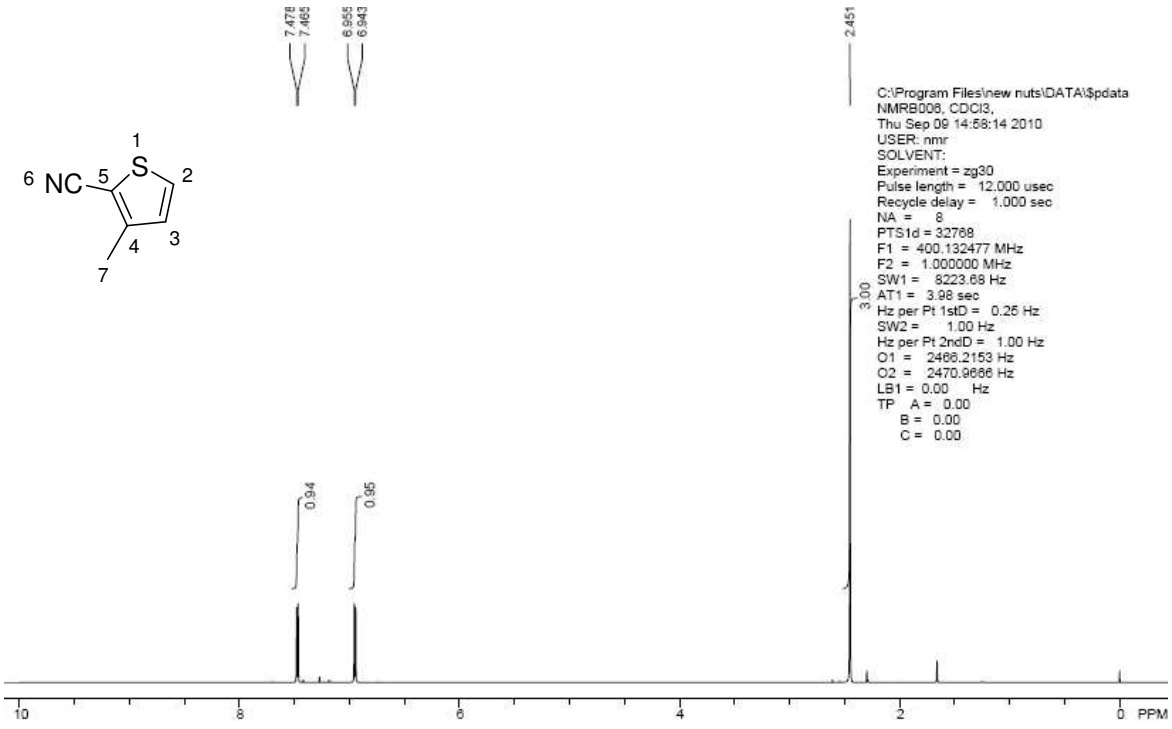


Table 3, entry 3: 3-methylthiophene-2-carbonitrile



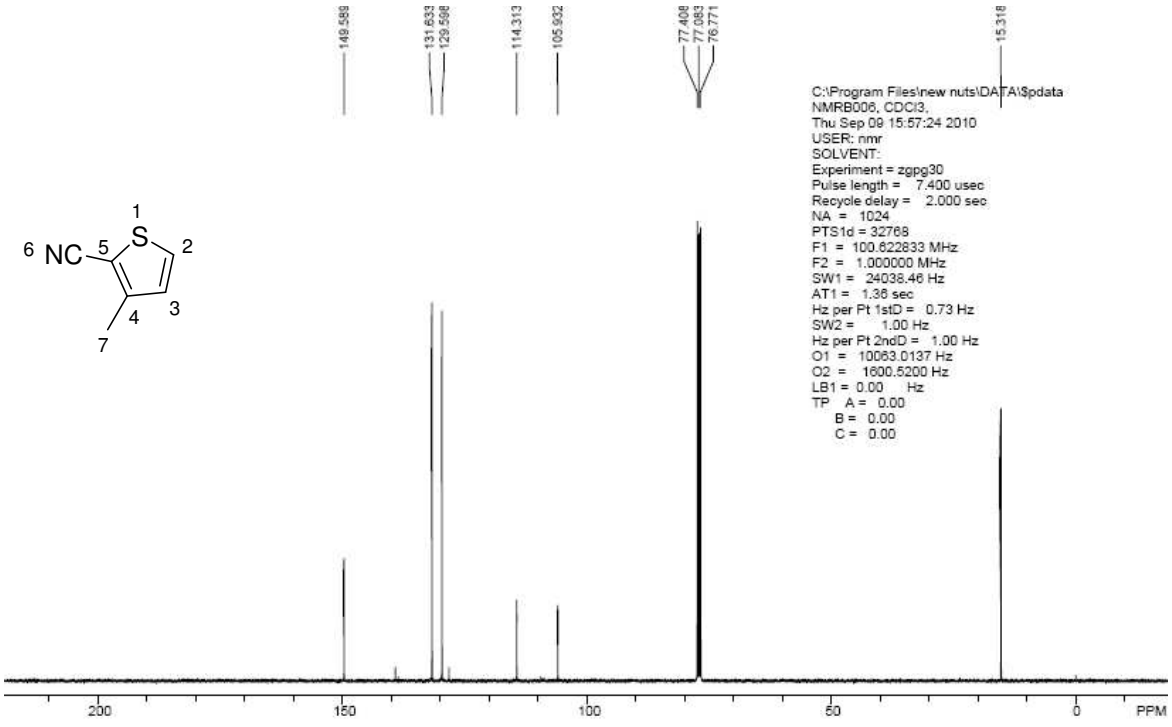
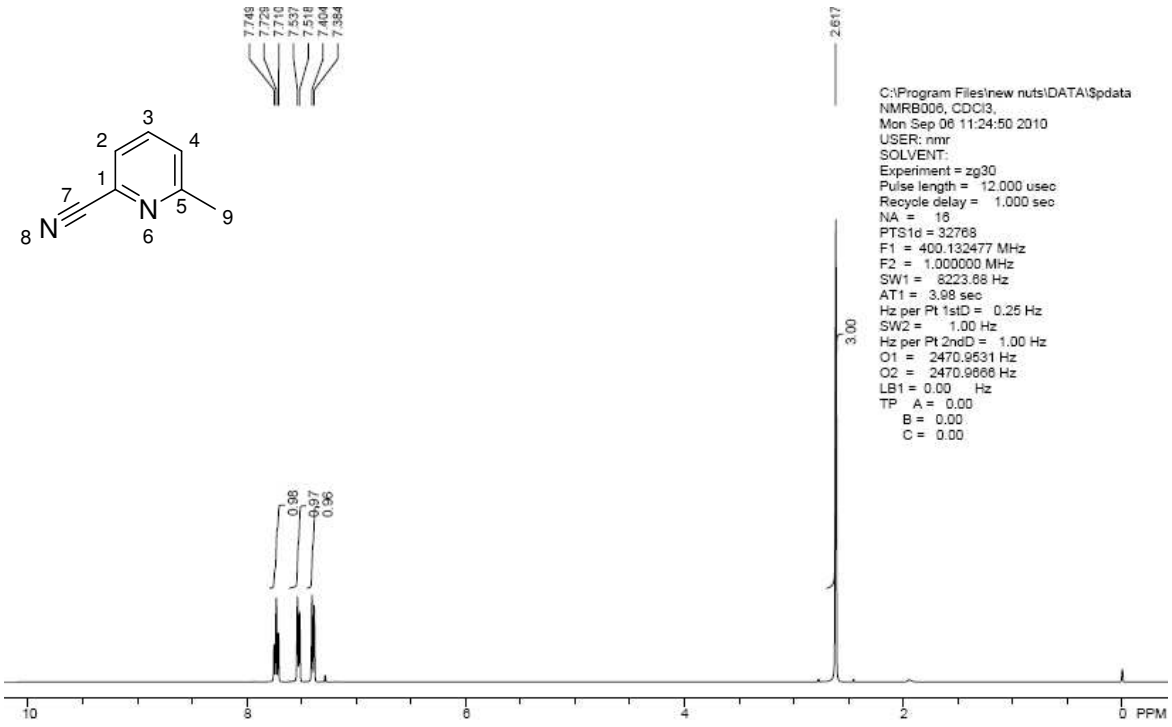


Table 3, entry 4: 6-methylpyridine-2-carbonitrile



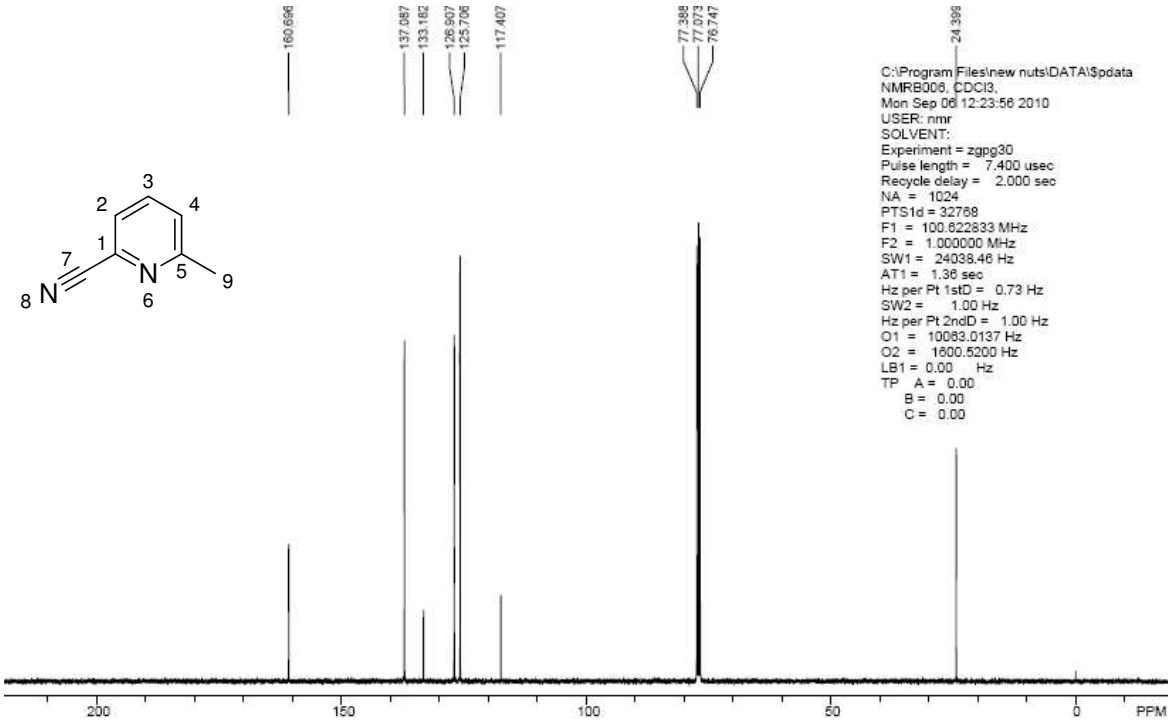
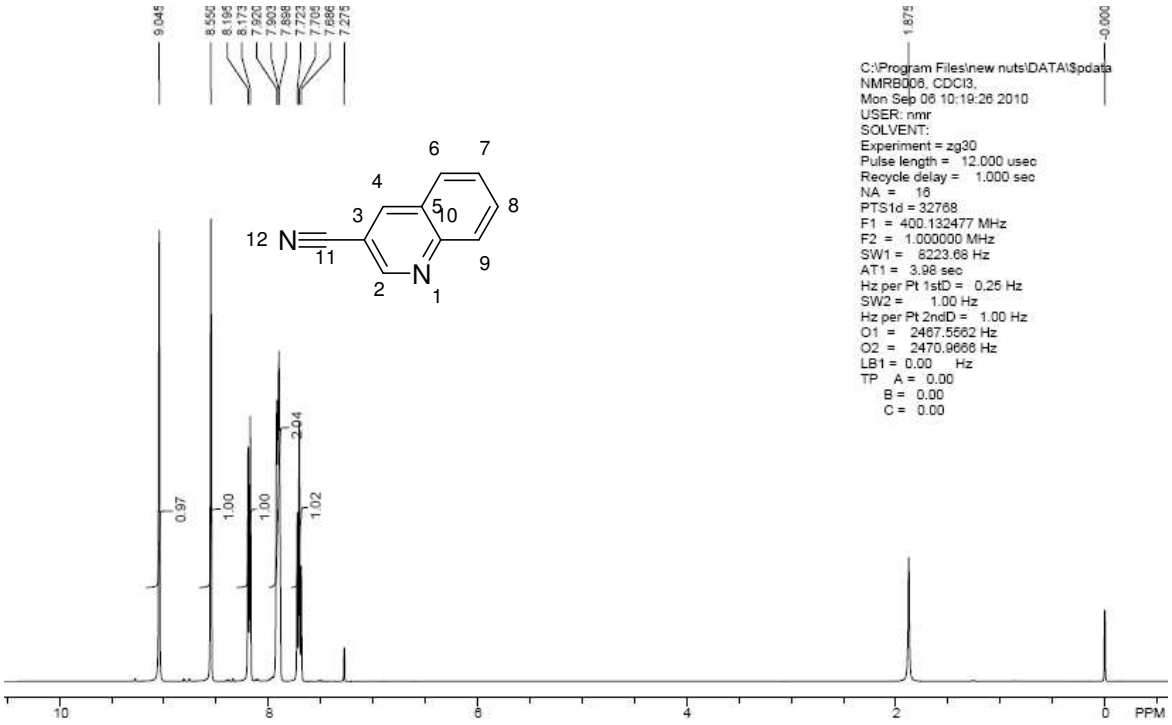


Table 3, entry 5: quinoline-3-carbonitrile



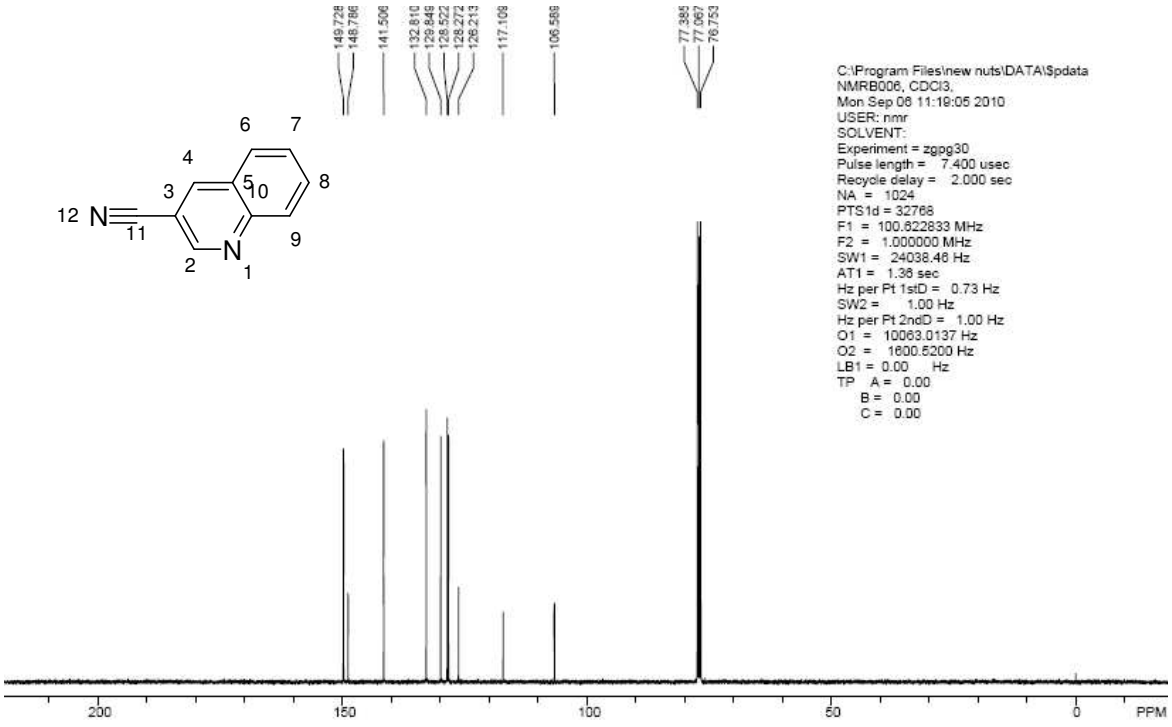
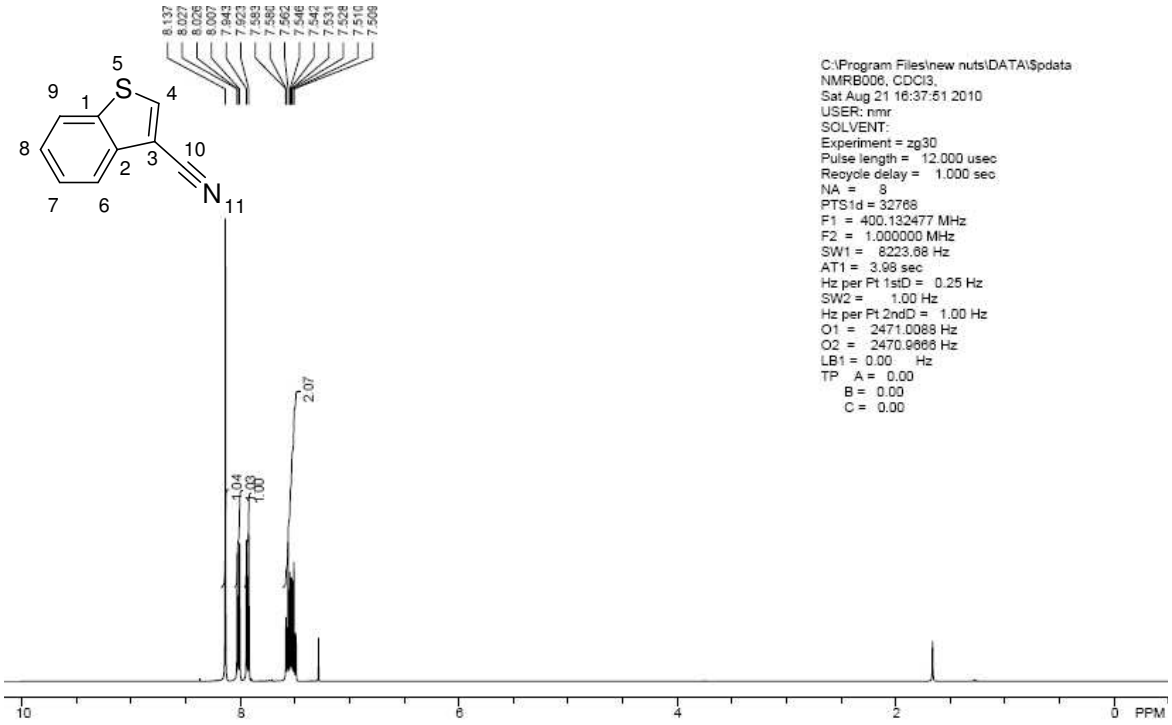


Table 3, entry 6: benzothiophene-3-carbonitrile



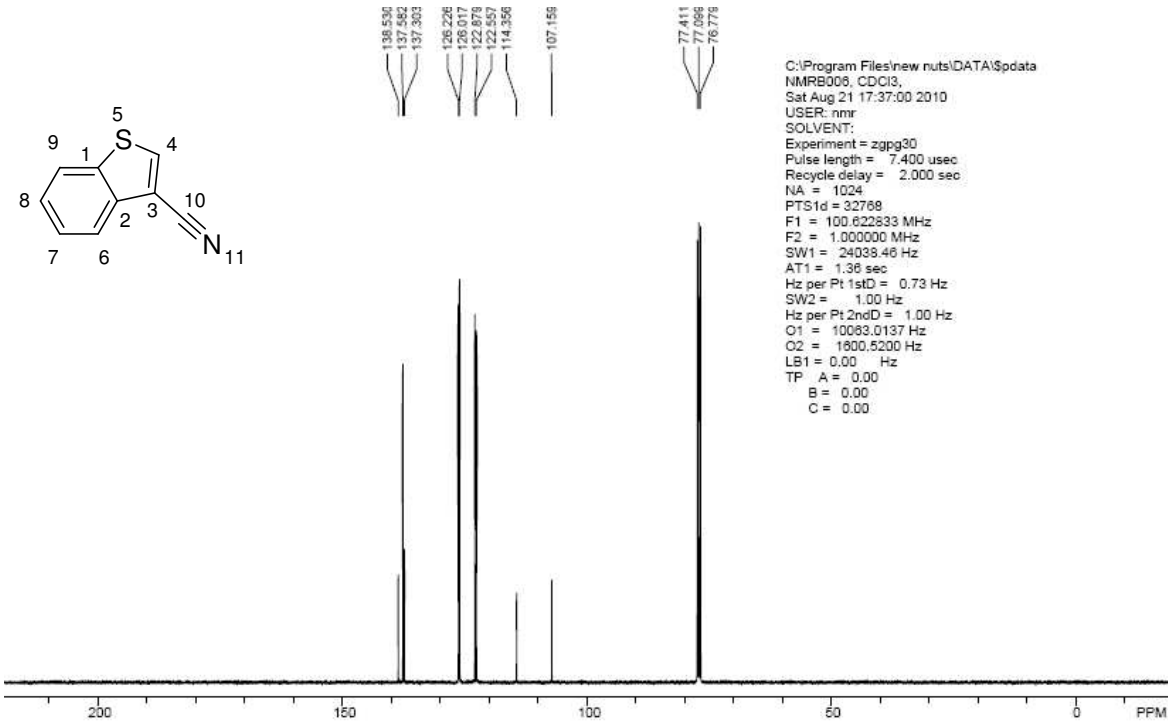
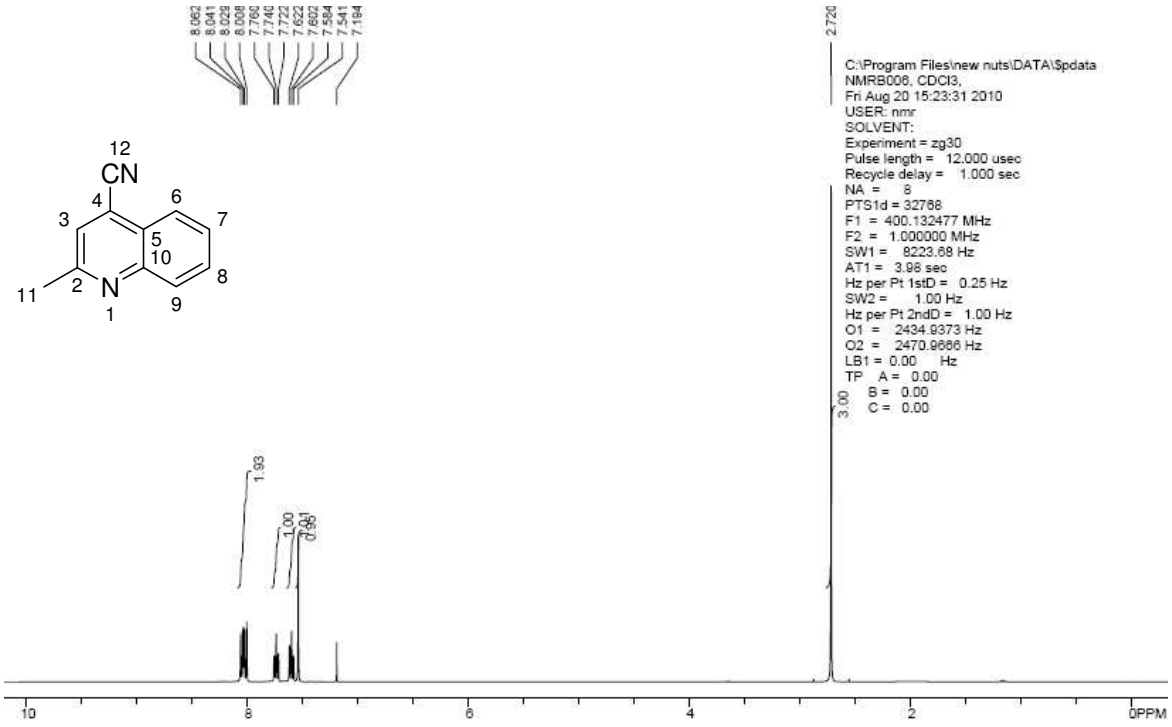
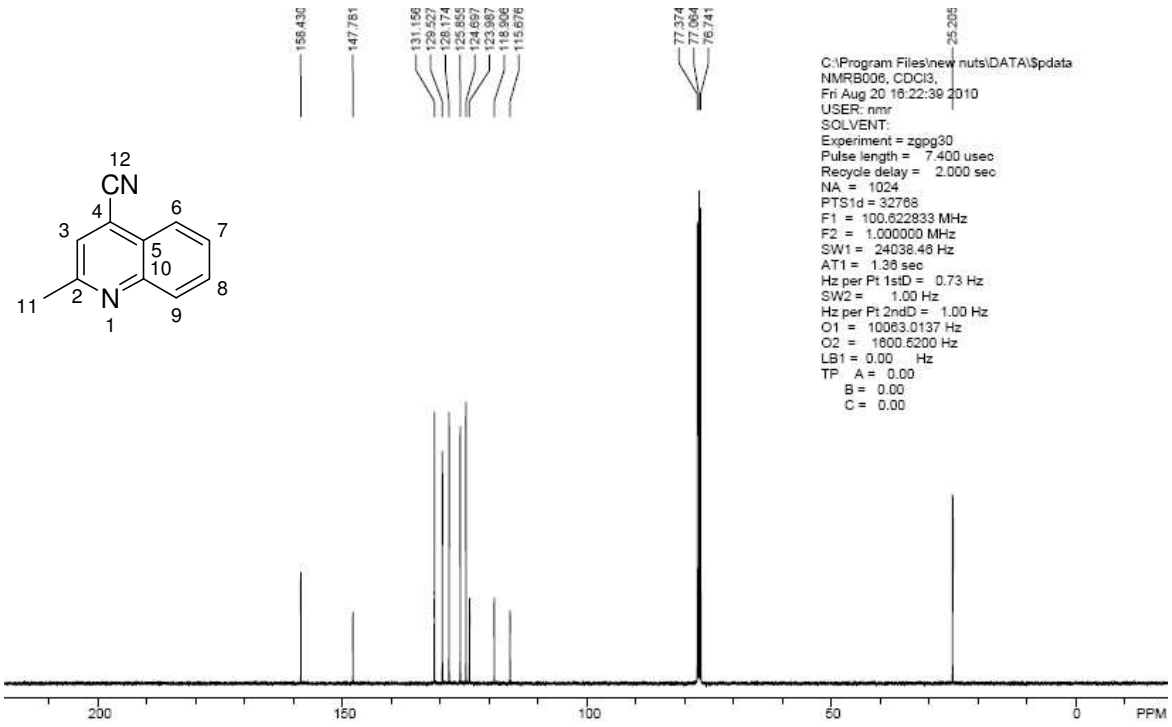


Table 3, entry 7: 2-methylquinoline-4-carbonitrile





References and Notes:

1. The reaction should be scrubbed with an aqueous NaOH solution. Cyanide containing waste should be decontaminated using a solution of NaOCl in water (CLOROX bleach). See: Lunn, G.; Sansone, E. B. *Destruction of Hazardous Chemicals in the Laboratory*, 2nd ed., Wiley & Sons: New York, 1994; pp 133-138.
2. Reproducible results were obtained with all lots of Pd/C tested. Most of the reactions were run using 10 wt. % Pd/C purchased from Aldrich (wet, Degussa type E101 NE/W).
3. See Table 2 and Table 3 for actual reaction temperature for each substrate.
4. Littke, A.; Soumeillant, M.; Kaltenback, R. F., III; Cherney, R. J.; Tarby, C. M.; Kiau, S. *Org. Lett.* **2007**, *9*, 1711.