Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supplementary Information

Towards Aryl C-N bond formation in dynamic thin films

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General Experimental

The design and operation of the vortex fluidic device (VFD) used herein is detailed elsewhere.[1]

All starting materials were obtained commercially and used without further purification unless otherwise stated. 2-Chloropyrazine, morpholine, piperidine and tryptamine hydrochloride were obtained from Alfa Aesar, Unilab, Fluka and The British Drug Houses, respectively, and all other starting materials were obtained from Sigma-Aldrich. Thin layer chromatography (TLC) was conducted on Merck Kieselgel 60 F_{254} plates and products were visualised under shortwave UV light (254 nm). Infrared spectra for novel compounds were recorded using a PerkinElmer Spectrum One Fourier transform infrared spectrometer fitted with an attenuated total reflectance (ATR) attachment. ^{1}H- and ^{13}C-nuclear magnetic resonance spectra were obtained using a Bruker ARX-500 spectrometer (500 MHz for ^{1}H or 125 MHz for ^{13}C). Each sample was dissolved in chloroform-*d* and each spectrum was calibrated using the residual solvent peak (δ 7.26 for ^{1}H and δ 77.0 for ^{13}C). Mass spectra were recorded with a Waters LCT Premier XE spectrometer, run in positive ionisation W-mode, using the electrospray ionisation technique.

Optimisation of reaction conditions for the coupling of 2-chloropyrazine and morpholine

Base and reaction time

A 10 mm NMR tube was charged with 2-chloropyrazine (143 μL, 1.60 mmol), morpholine (139 μL, 1.60 mmol), a base (3.20 mmol, omitted for no base control) and water (900 μL). The tube was capped tightly then rotated in the VFD at 7000 rpm with a tilt angle of 45° and heated at 100 °C for either 6 or 12 h. After this time the reaction mixture was allowed to cool, diluted with EtOAc (30 mL) then washed with 0.1 M aqueous K_2CO_3 (40 mL). The aqueous layer was separated and extracted with additional EtOAc (30 mL). The organic layers were then combined, dried with $MgSO_4$, filtered and evaporated. Starting materials were removed from the sample by placing the residue under high vacuum until the sample remained a constant weight.

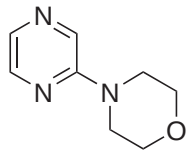
Tilt angle and rotation speed

Using the optimum base (K_3PO_4) and reaction time (12 h), a 10 mm NMR tube was charged with 2-chloropyrazine (143 μL, 1.60 mmol), morpholine (139 μL, 1.60 mmol), K_3PO_4 (679 mg, 3.20 mmol) and water (900 μL). The tube was capped tightly then rotated in the VFD at 2000, 3500, 5000 or 7000 rpm

with a tilt angle of 30, 45 or 60° and heated at 100 °C for 12 h. After this time the reaction mixture was allowed to cool, diluted with EtOAc (30 mL) then washed with 0.1 M aqueous K_2CO_3 (40 mL). The aqueous layer was separated and extracted with additional EtOAc (30 mL). The organic layers were then combined, dried with $MgSO_4$, filtered and evaporated. Starting materials were removed from the sample by placing the residue under high vacuum until the sample remained a constant weight.

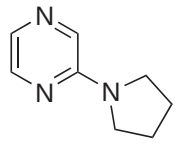
General procedure for the coupling of 2-chloropyrazine to various amines

2-Chloropyrazine (1.60 mmol, 143 μL) and the appropriate amine (1.60 mmol) were added to a solution of K_3PO_4 (3.20 mmol, 580 mg) and water (900 μL) in a 10 mm NMR tube. The tube was capped tightly then rotated in the VFD at 3500 rpm with a tilt angle of 45° and heated at 100 °C for 12 h. The reaction mixture was allowed to cool, diluted with EtOAc (30 mL) then washed with 0.1 M aqueous K_2CO_3 (40 mL). The aqueous layer was separated and extracted with additional EtOAc (30 mL). The organic layers were then combined, dried with $MgSO_4$, filtered and evaporated. If necessary, the crude product was purified by flash chromatography using eluent specified. All reactions were conducted in triplicate with the average shown. Errors obtained were within ± 3%.



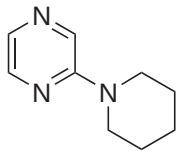
4-(Pyrazin-2-yl)morpholine (Table 1, entry 1)

The reaction was conducted using morpholine as per the general procedure to obtain the title compound as a yellow crystalline material (202 mg, 76%). ^{1}H NMR and ^{13}C NMR were consistent with literature values.[2] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, *J* = 1.5 Hz, 1H, H3), 7.94 (dd, *J* = 2.5, 1.5 Hz, 1H, H5), 7.76 (d, *J* = 2.5 Hz, 1H, H6), 3.71–3.67 (m, 4H), 3.44–3.40 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 141.4, 133.2, 130.6, 66.1, 44.4.



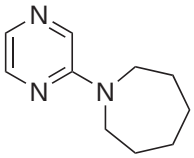
2-(Pyrrolidin-1-yl)pyrazine (Table 1, entry 2)

The reaction was conducted using pyrrolidine as per the general procedure to obtain the title compound as a yellow crystalline material (217 mg, 91%). ^{1}H NMR and ^{13}C NMR were consistent with literature values.[2] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (dd, *J* = 2.5, 1.5 Hz, 1H, H5), 7.86 (d, *J* = 1.5 Hz, 1H, H3), 7.74 (d, *J* = 2.5 Hz, 1H, H6), 3.51–3.44 (m, 4H, H2'+H5'), 2.07–1.99 (m, 4H, H3'+H4'). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.0, 142.7, 131.2, 130.8, 46.3, 25.4.



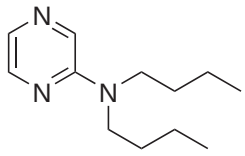
2-(Piperidin-1-yl)pyrazine (Table 1, entry 3)

The reaction was conducted using piperidine as per the general procedure to obtain the title compound as a yellow crystalline solid (218 mg, 78%). The ^{1}H NMR spectrum was consistent with that found in the literature.[3] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, *J* = 1.5 Hz, 1H, H3), 8.02 (dd, *J* = 2.5, 1.5 Hz, 1H, H5), 7.76 (d, *J* = 2.5 Hz, 1H, H6), 3.62–3.54 (m, 4H), 1.73–1.61 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.1, 141.7, 132.0, 131.1, 45.6, 25.3, 24.5.



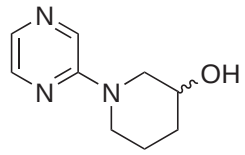
1-(Pyrazin-2-yl)azepane (Table 1, entry 4)

The reaction was conducted using azepane as per the general procedure and the crude material was purified using flash chromatography (3:7 EtOAc/hexanes) to obtain the title compound as a tan oil (231 mg, 82%). ^{1}H NMR and ^{13}C NMR were consistent with literature values.[2] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97–7.95 (m, 1H, H5), 7.95–7.93 (m, 1H, H3), 7.68 (d, *J* = 3.0 Hz, 1H, H6), 3.61–3.56 (m [app t], 4H, H2' and H') 1.78–1.72 (m, 4H, H3' and H6') 1.55–1.49 (m, 4H, H4' and H5'). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.9, 141.8, 130.9, 129.6, 47.0, 27.4, 27.0.



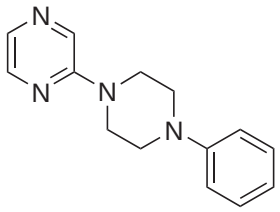
***N*,*N*-Dibutylpyrazin-2-amine (Table 1, entry 5)**

The reaction was conducted using dibutylamine as per the general procedure and the crude material was purified using flash chromatography (1:4 EtOAc/hexanes) to obtain the title compound as a yellow oil (29 mg, 9%): IR (ATR) $\bar{\nu}_{max}$ (cm^{-1}): 1574 (s). ^1H NMR (500 MHz, $CDCl_3$): δ 7.99–7.96 (m, 1H, H5), 7.92–7.90 (m, 1H, H3), 7.68 (d, *J* = 2.5 Hz, 1H, H6), 3.45–3.39 (m [app t], 4H, H1'), 1.62–1.53 (m, 4H, H2'), 1.49–1.40 (m [app sextet], 4H, H3'), 0.98–0.91 (m [app t], 6H, H4'). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.8, 141.9, 130.7, 129.8, 48.1, 29.6, 20.2, 13.9. HRMS–ESI (*m/z*): $[M+H]^+$ calcd for $C_{12}H_{22}N_3$, 208.1814; found, 208.1816.



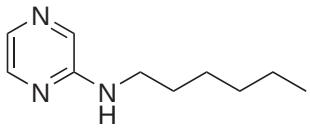
1-(Pyrazin-2-yl)piperidin-3-ol (Table 1, entry 6)

The reaction was conducted using 3-hydroxypiperidine as per the general procedure to obtain the title compound as a brown solid (212 mg, 74%). IR (ATR) $\bar{\nu}_{max}$ (cm^{-1}): 3231 (m, N–H + O–H), 1583 (s). ^1H NMR (500 MHz, $CDCl_3$): δ 8.08 (d, *J* = 1.0 Hz, 1H, H3), 7.98–7.95 (m, 1H, H5), 7.72 (d, *J* = 2.5 Hz, 1H, H6), 3.91 (dd, *J* = 13.0, 3.5 Hz, 1H, H2'a), 3.83–3.76 (m [app septet], 1H), 3.72 (ddd, *J* = 13.0, 6.0, 4.0 Hz, 1H, H6'a), 3.68 (br s, 1H, OH), 3.29–3.22 (m, 2H), 1.98–1.91 (m, 1H), 1.87–1.80 (m, 1H), 1.63–1.48 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.1, 141.6, 131.9, 131.0, 65.8, 51.4, 44.8, 32.6, 22.0. HRMS–ESI (*m/z*): $[M+H]^+$ calcd for $C_9H_{14}N_3O$, 180.1137; found, 180.1144.



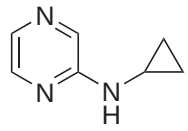
2-(4-Phenylpiperazin-1-yl)pyrazine (Table 1, entry 7)

The reaction was conducted using *N*-phenylpiperazine as per the general procedure and the crude material was purified using flash chromatography (2:3 EtOAc/hexanes) to obtain the title compound as an off white powder (276 mg, 81%). ^{1}H NMR and ^{13}C NMR were consistent with literature values.[2] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, *J* = 1.5 Hz, 1H, H3), 8.10–8.08 (m [app t], 1H, H5), 7.88 (d, *J* = 3.0 Hz, 1H, H6), 7.33–7.27 (m, 2H, H3' and H5'), 7.00–6.96 (m [app d], 2H, H2' and H6'), 6.93–6.89 (m [app t], 1H, H4'), 3.78–3.74 (m, 4H), 3.34–3.29 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.9, 151.0, 141.7, 133.2, 131.1, 129.2, 120.3, 116.4, 49.0, 44.5.



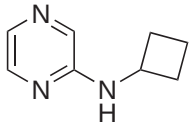
***N*-hexylpyrazin-2-amine (Table 1, entry 8)**

The reaction was conducted using hexylamine as per the general procedure and the crude material was purified using flash chromatography (Et_2O) to obtain the title compound as a yellow oil (158 mg, 55%): IR (ATR) $\bar{\nu}_{max}$ (cm^{-1}): 3287 (m, N–H), 1592 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (dd, *J* = 2.5, 1.5 Hz, 1H, H5), 7.86 (d, *J* = 1.5 Hz, 1H, H3), 7.77 (d, *J* = 2.5 Hz, 1H, H6), 4.61 (br s, 1H, NH), 3.35–3.29 (m [app dt], 2H, H1'), 1.66–1.58 (m, 2H, H2'), 1.43–1.27 (m, 6H, H3'+H4'+H5'), 0.92–0.85 (m, 3H, H6'). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 142.0, 132.6, 131.7, 41.6, 31.5, 29.4, 26.6, 22.5, 14.0. HRMS–ESI (*m/z*): $[M+H]^+$ calcd for $C_{10}H_{18}N_3$, 180.1501; found, 180.1504.



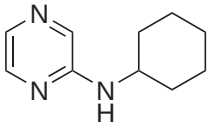
_N_-Cyclopropylpyrazin-2-amine (Table 1, entry 9)

The reaction was conducted using cyclopropylamine as per the general procedure and the crude material was purified using flash chromatography (Et_2O) to obtain the title compound as a brown solid (26 mg, 12%): IR (ATR) $\bar{\nu}_{max}$ (cm^{-1}): 3189 (m, N–H), 1584 (m). ^1H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, J = 1.5 Hz, 1H, H3), 7.95 (dd, J = 2.5, 1.5 Hz, 1H, H5), 7.86 (d, J = 2.5 Hz, 1H, H6), 5.43 (s, 1H, NH), 2.58–2.52 (m, 1H, H1'), 0.88–0.76 (m, 2H), 0.61–0.51 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 142.0, 133.8, 130.7, 23.5, 7.6. HRMS–ESI (*m/z*): $[M+H]^+$ calcd for $C_7H_{10}N_3$, 136.0875; found, 136.0871.



_N_-Cyclobutylpyrazin-2-amine (Table 1, entry 10)

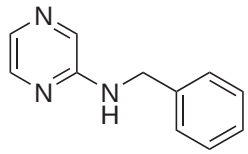
The reaction was conducted using cyclobutylamine as per the general procedure and the crude material was purified using flash chromatography (1:1 EtOAc/hexanes) to obtain the title compound as a pale yellow solid (68 mg, 29%). ^1H NMR and ^{13}C NMR were consistent with literature values.[3] ^1H NMR (500 MHz, $CDCl_3$): δ 7.95 (dd, J = 2.5, 1.5 Hz, 1H, H5), 7.80 (d, J = 1.5 Hz, 1H, H3), 7.79 (d, J = 2.5 Hz, 1H, H6), 4.86 (br s, 1H), 4.27–4.18 (m, 1H), 2.48–2.40 (m, 2H), 1.94–1.72 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.9, 132.4, 131.3, 46.5, 31.0, 15.0.



_N_-Cyclohexylpyrazin-2-amine (Table 1, entry 11)

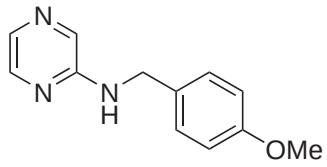
The reaction was conducted using cyclohexylamine as per the general procedure and the crude material was purified using flash chromatography (2:3 EtOAc/hexanes) to obtain the title compound as a white powder (56 mg, 20%). ^1H NMR and ^{13}C NMR were consistent with literature values.[2] ^1H NMR (500 MHz, $CDCl_3$): δ 7.92 (dd, J = 2.5, 1.5 Hz, 1H, H5), 7.81 (d, J = 1.5 Hz, 1H, H3), 7.72 (d, J = 2.5 Hz,

1H, H6), 4.60 (br s, 1H, NH), 3.70–3.60 (m, 1H), 2.07–1.98 (m, 2H), 1.79–1.70 (m, 2H), 1.68–1.59 (m, 1H), 1.45–1.33 (m, 2H), 1.27–1.14 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0, 142.0, 132.2, 132.0, 49.6, 33.1, 25.6, 24.8.



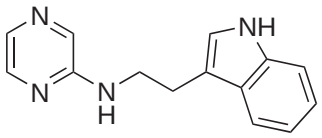
***N*-Benzylpyrazin-2-amine (Table 1, entry 12)**

The reaction was conducted using benzylamine as per the general procedure and the crude material was purified using flash chromatography (3:2 EtOAc/hexanes) to obtain the title compound as a white crystalline solid (96 mg, 32%). ^{1}H NMR and ^{13}C NMR were consistent with literature values.[4] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (dd, *J* = 2.5, 1.5 Hz, 1H, H5), 7.91 (d, *J* = 1.5 Hz, 1H, H3), 7.84 (d, *J* = 2.5 Hz, 1H, H6), 7.40–7.28 (m, 5H, H2'–H6'), 5.06 (br s, 1H, NH), 4.73–4.43 (m [AB quartet], 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.4, 141.9, 138.4, 133.1, 132.1, 128.7, 127.54, 127.51, 45.5.



***N*-(4-Methoxybenzyl)pyrazin-2-amine (Table 1, entry 13)**

The reaction was conducted using 4-methoxybenzylamine as per the general procedure and the crude material was purified using flash chromatography (1:1 EtOAc/hexanes) to obtain the title compound as a pale yellow powder (129 mg, 38%). ^{1}H NMR and ^{13}C NMR were consistent with literature values.[2] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (dd, *J* = 3.0, 1.5 Hz, 1H, H5), 7.89 (d, *J* = 1.5 Hz, 1H, H3), 7.83 (d, *J* = 3.0 Hz, 1H, H6), 7.31–7.27 (m, 2H, H2'' and H6''), 6.92–6.88 (m, 2H, H3'' and H5''), 5.00 (br s, 1H, NH), 4.51–4.48 (m [app d], 2H, H1'), 3.82 (s, 3H, OMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 154.4, 141.9, 133.0, 132.1, 130.4, 128.9, 114.1, 55.3, 45.0.

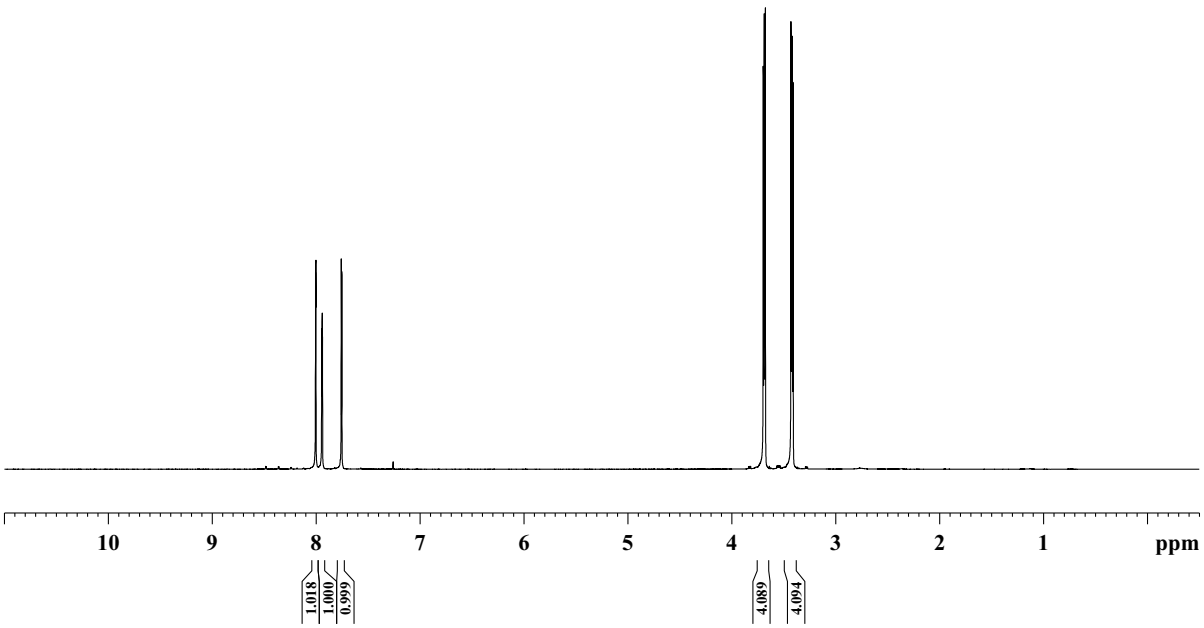


_N_-(2-(1_H_-Indol-3-yl)ethyl)pyrazin-2-amine (Table 1, entry 14)

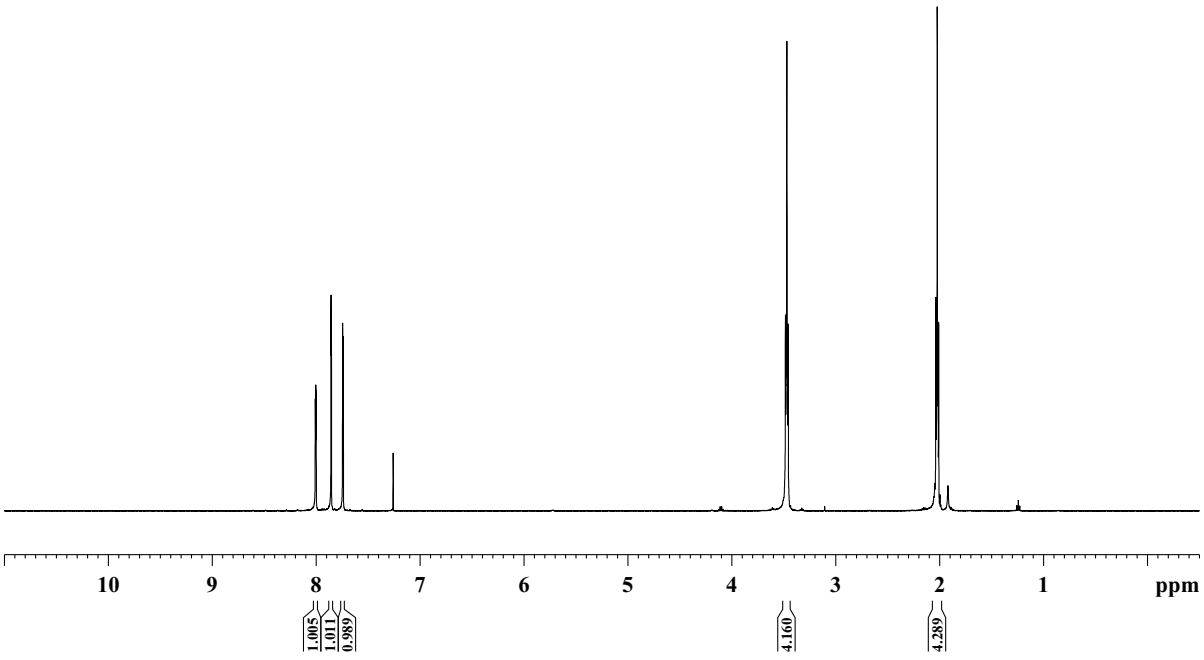
Tryptamine was prepared by shaking tryptamine hydrochloride (1.60 mmol) with 1 M NaOH (50 mL) solution followed by extraction with Et_2O (3 × 50 mL) and removal of the solvent *in vacuo*. The reaction was conducted using freshly prepared tryptamine as per the general procedure and the crude material was purified using flash chromatography (7:3 EtOAc/hexanes) to obtain the title compound as a tan powder (210 mg, 55%). ^{1}H NMR and ^{13}C NMR were consistent with literature values.[2] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (br s, 1H), 7.99 (dd, *J* = 3.0, 1.5 Hz, 1H, H4), 7.80 (d, *J* = 1.5 Hz, 1H, H3), 7.79 (d, *J* = 3.0 Hz, 1H, H6), 7.64–7.61 (m [app dq], 1H), 7.37 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H), 7.22 (ddd. *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.14 (ddd. *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.05–7.02 (m, 1H), 4.68 (br t, 1H), 3.73–3.68 (m [app q], 2H), 3.13–3.08 (m [app d], 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.6, 142.0, 136.4, 132.6, 132.2, 127.3, 122.24, 122.15, 119.5, 118.7, 112.9, 111.3, 41.5, 25.1.

^{1}H-NMR spectra for known adducts

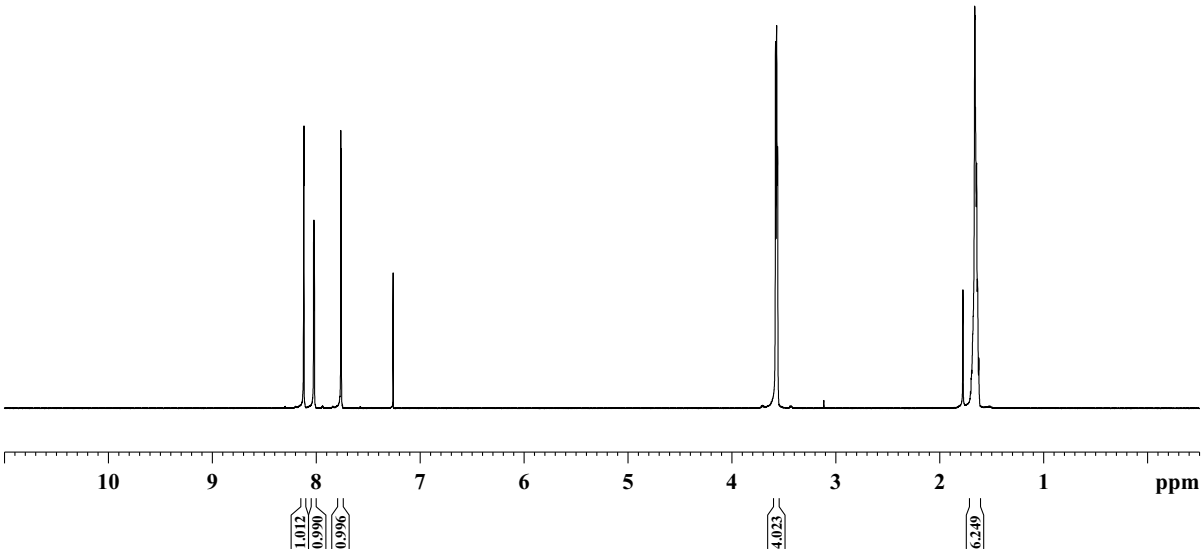
^{1}H NMR for Table 1, entry 1



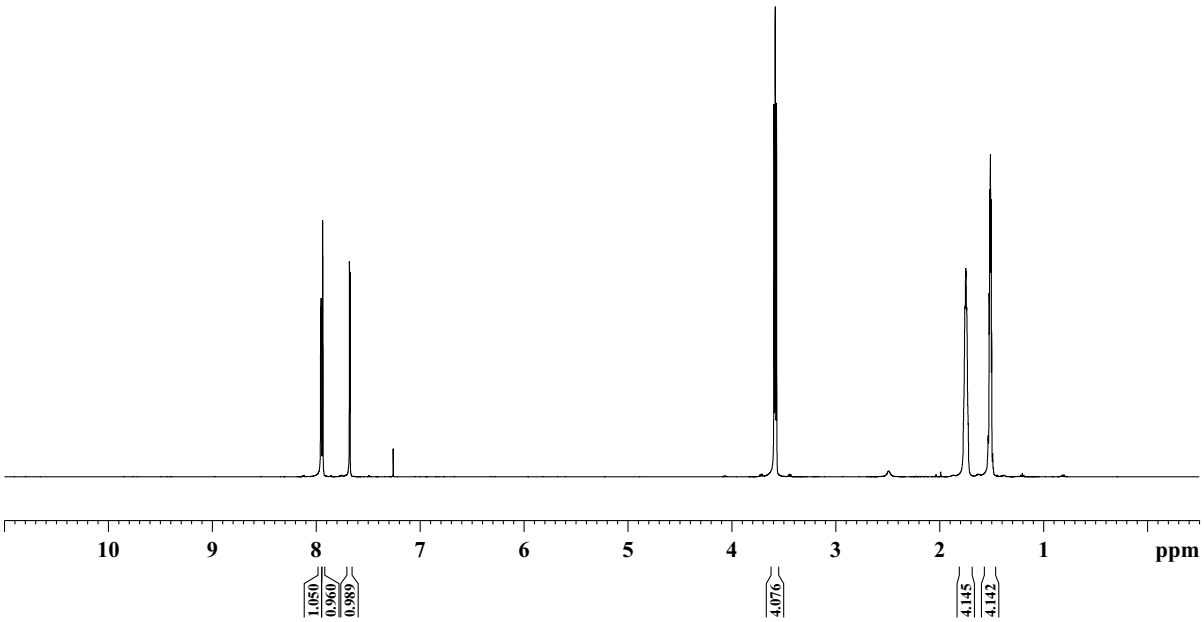
^{1}H NMR for Table 1, entry 2



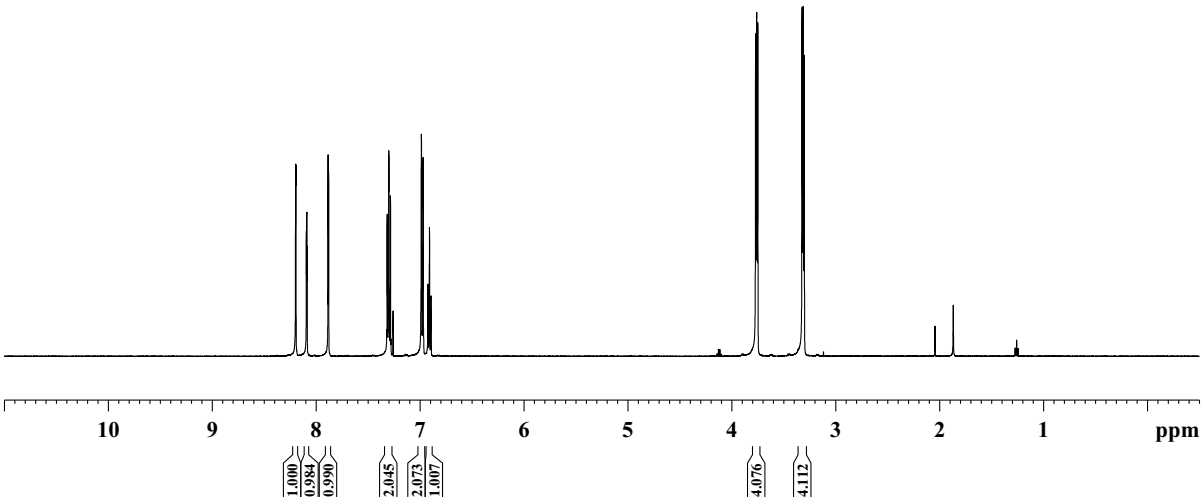
^{1}H NMR for Table 1, entry 3



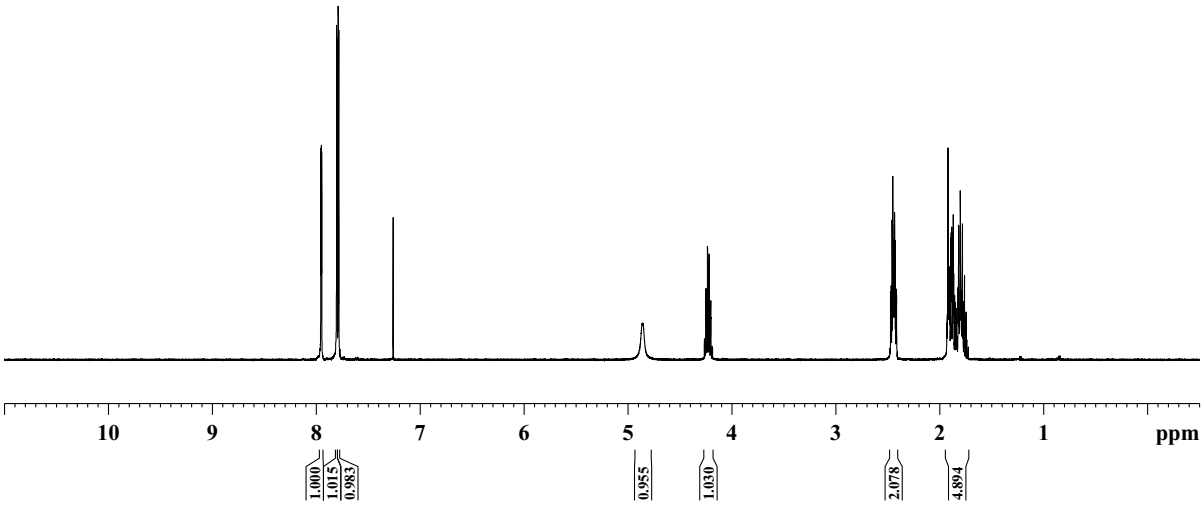
^{1}H NMR for Table 1, entry 4



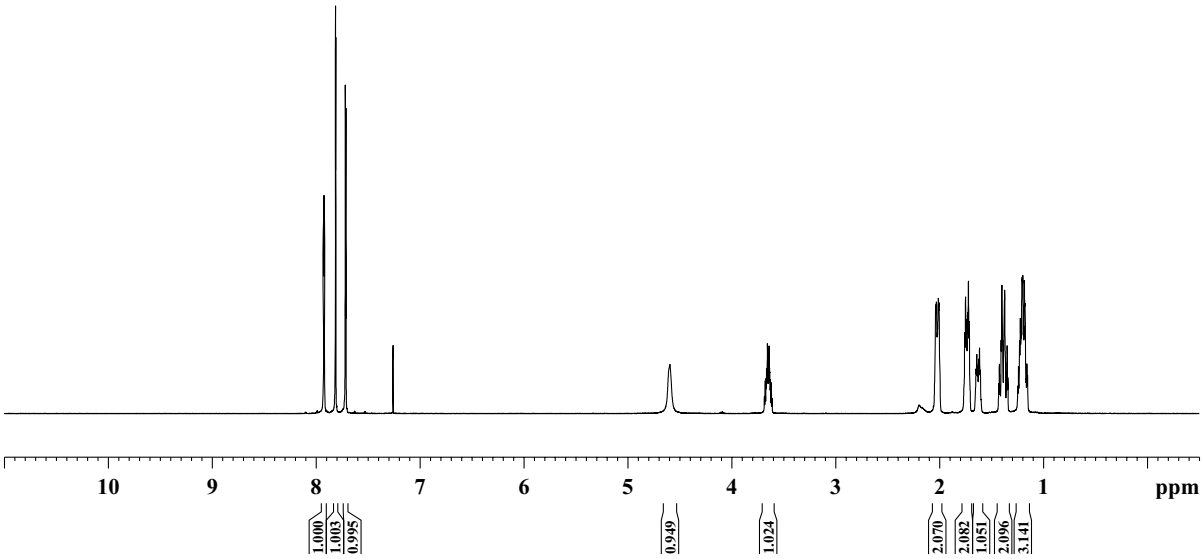
^{1}H NMR for Table 1, entry 7



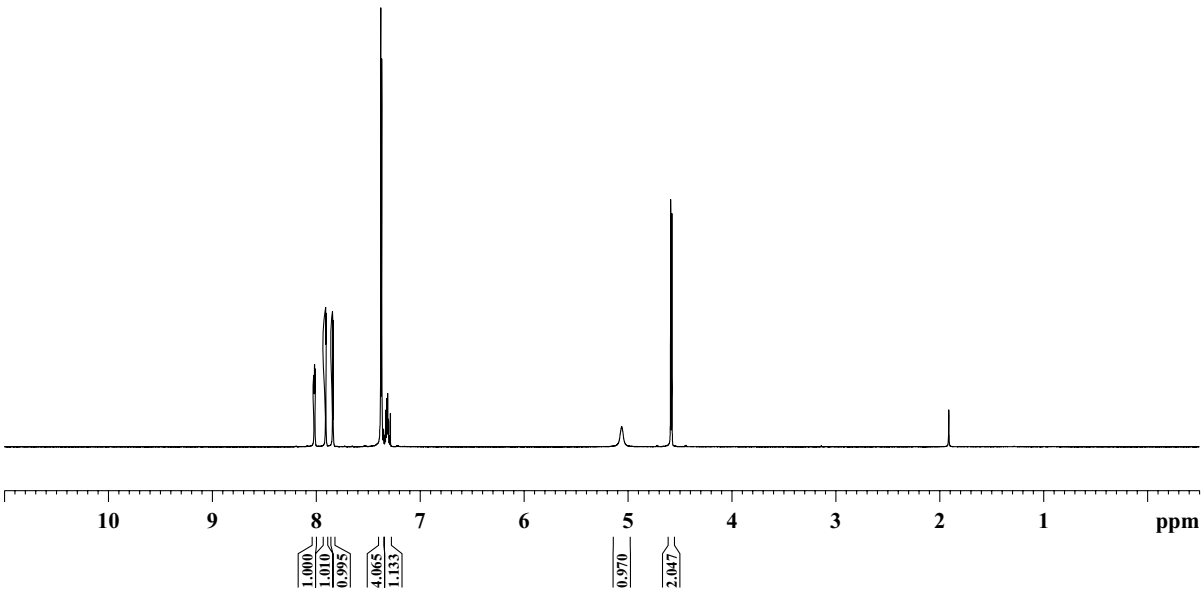
^{1}H NMR for Table 1, entry 10



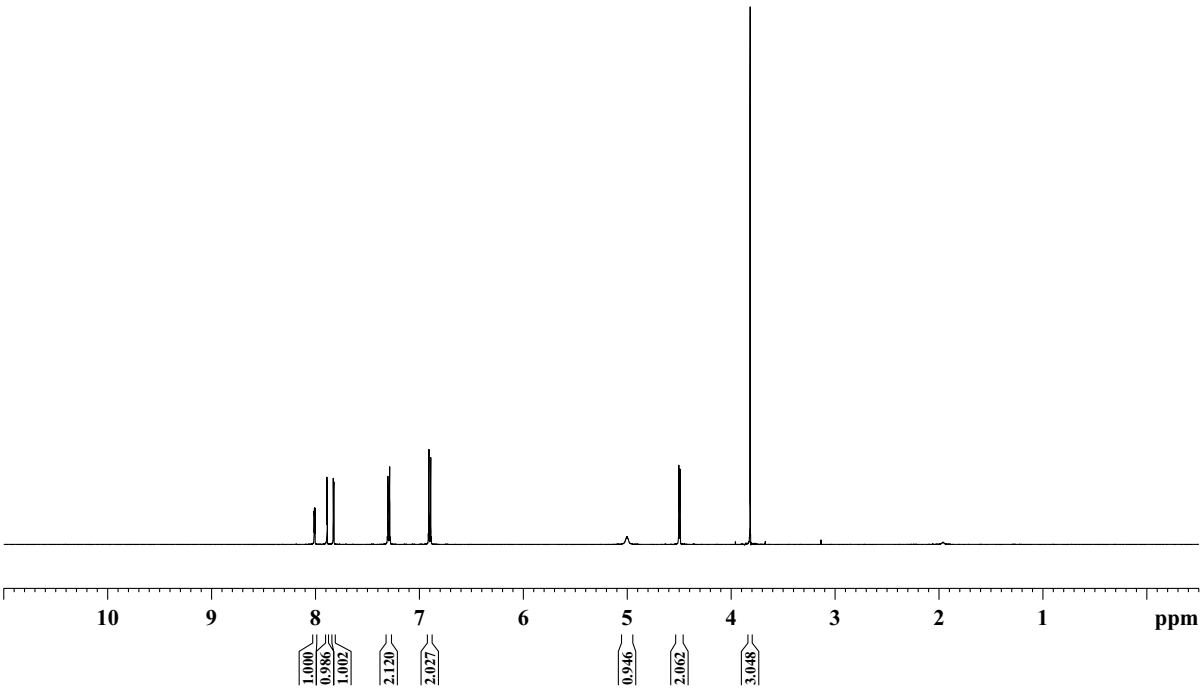
^{1}H NMR for Table 1, entry 11



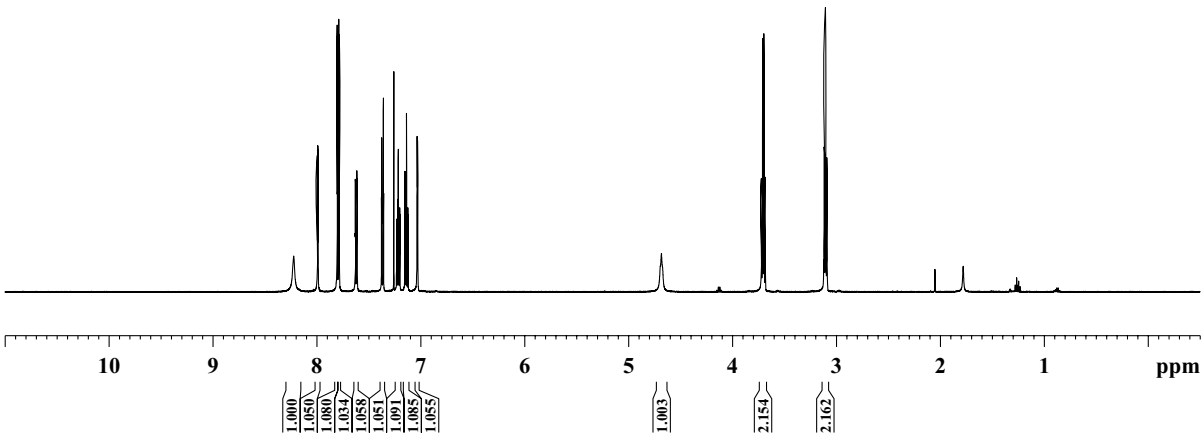
^{1}H NMR for Table 1, entry 12



^{1}H NMR for Table 1, entry 13

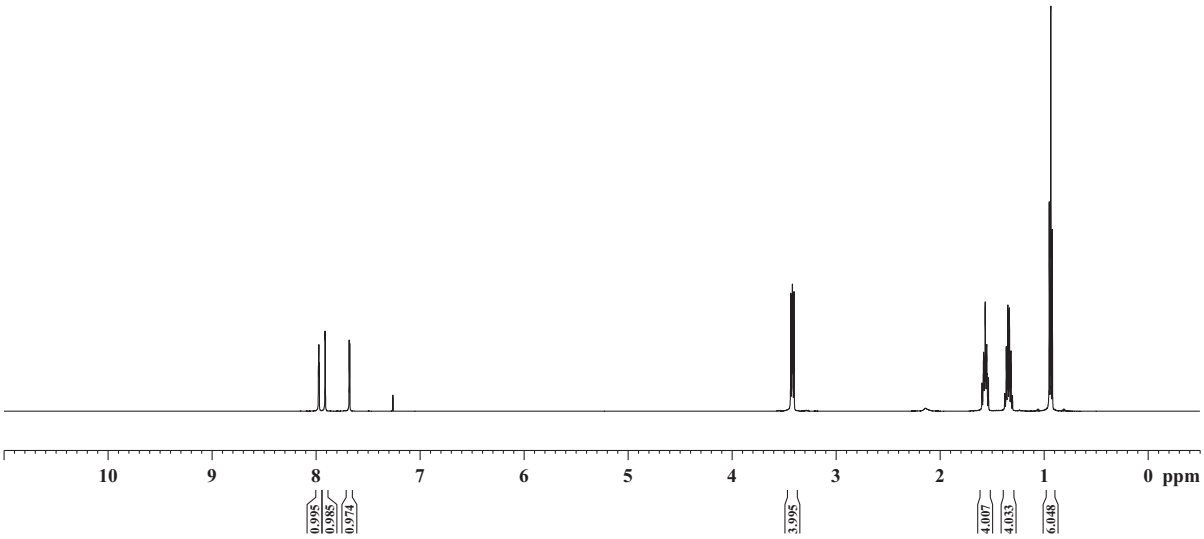


^{1}H NMR for Table 1, entry 14

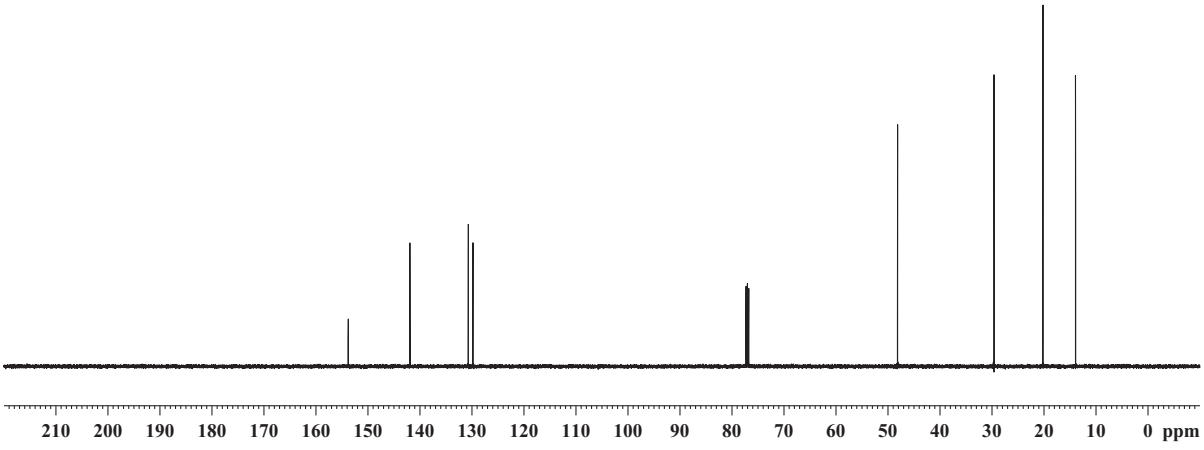


^{1}H- and ^{13}C-NMR spectra for novel adducts

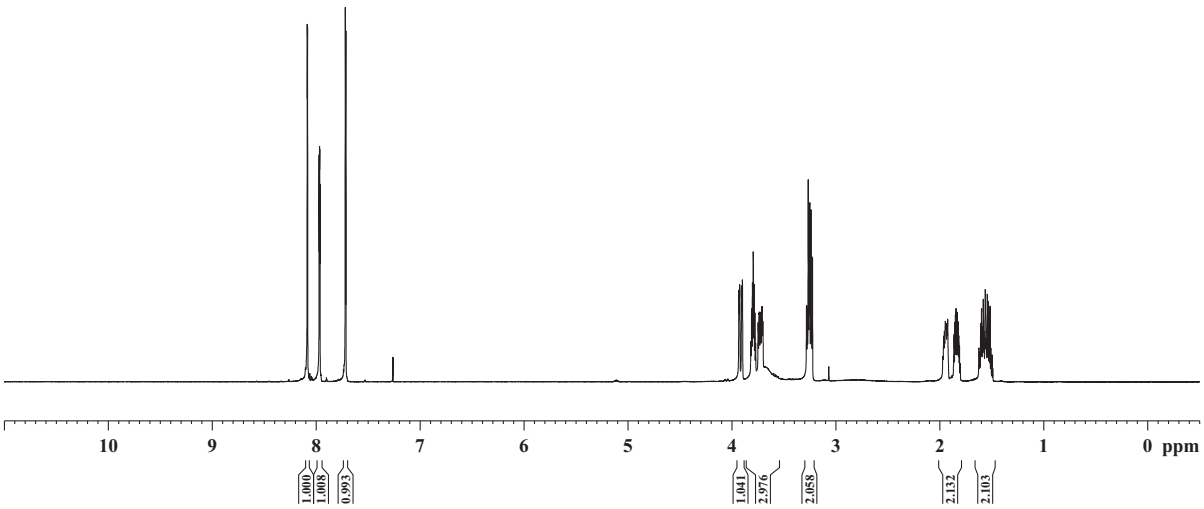
^{1}H NMR for Table 1, entry 5



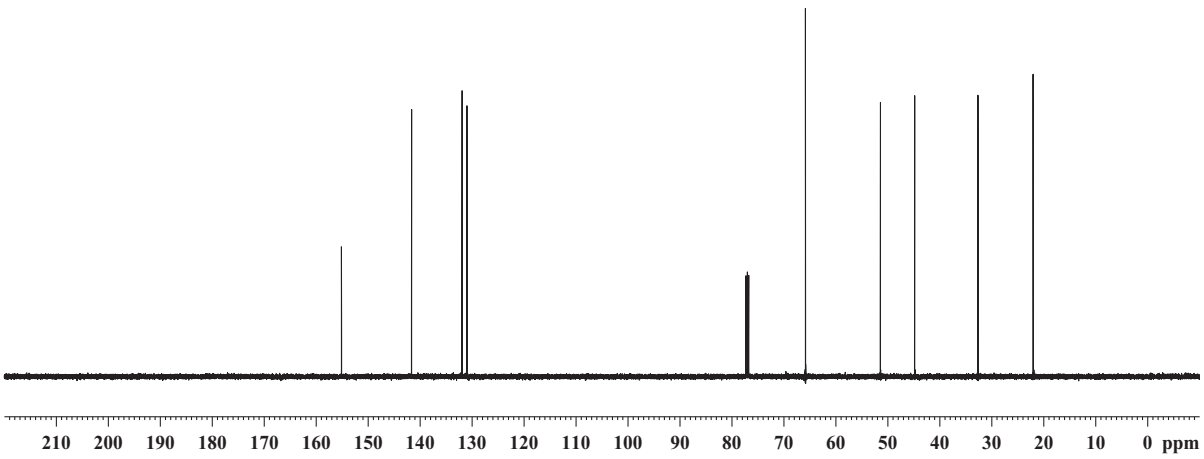
^{13}C NMR for Table 1, entry 5



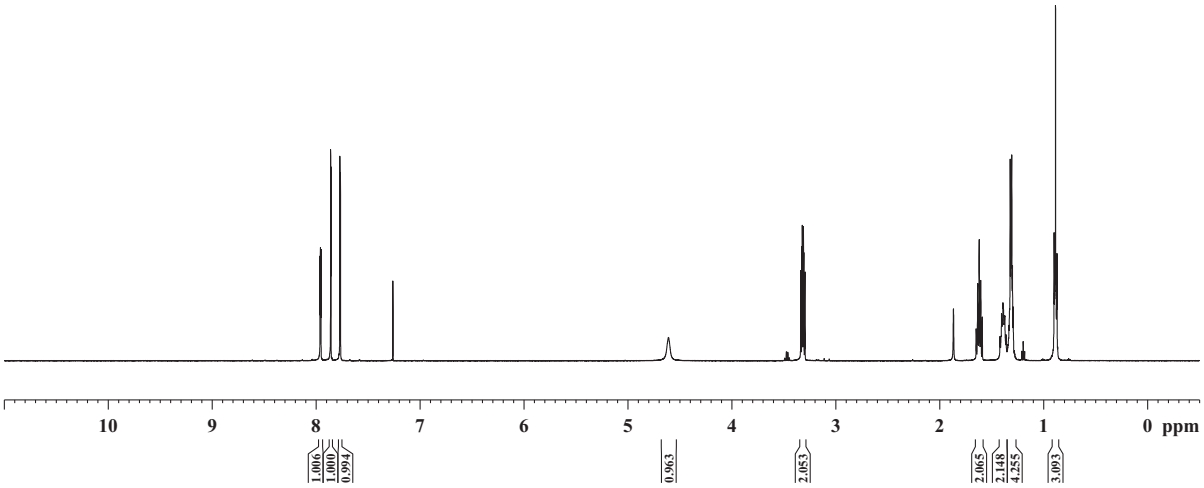
^{1}H NMR for Table 1, entry 6



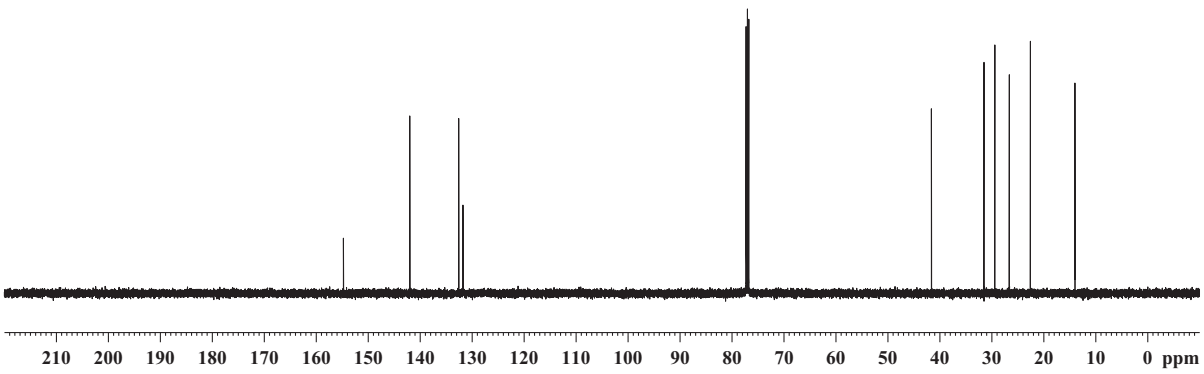
^{13}C NMR for Table 1, entry 6



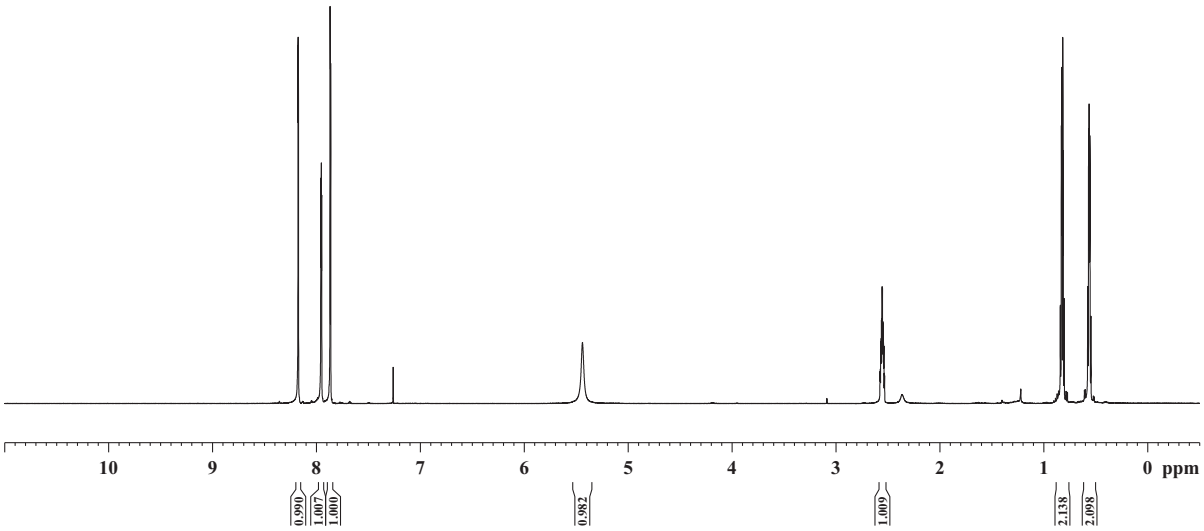
^{1}H NMR for Table 1, entry 8



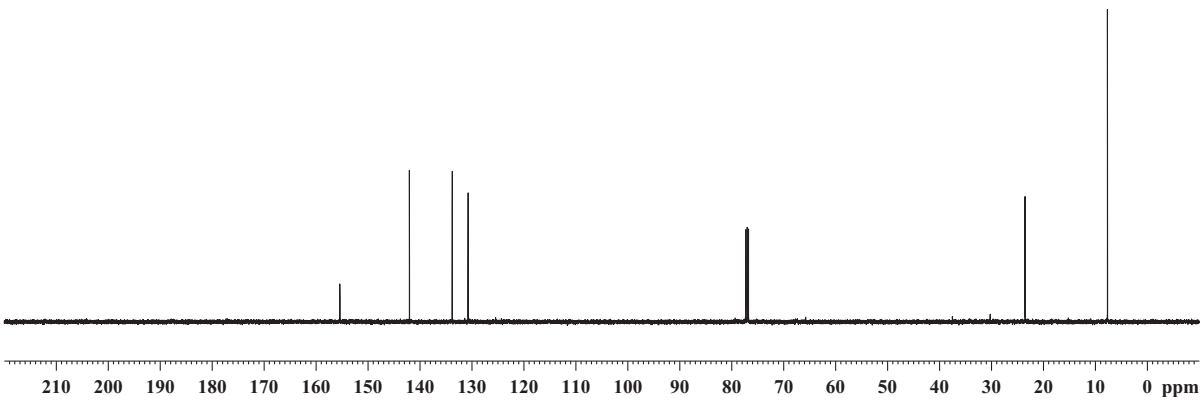
^{13}C NMR for Table 1, entry 8



^{1}H NMR for Table 1, entry 9



^{13}C NMR for Table 1, entry 9



References

[1] L. Yasmin, X. Chen, K. A. Stubbs and C. L. Raston, *Sci. Rep.*, 2013, **3**, 2282.

[2] K. Walsh, H. F. Sneddon and C. J. Moody, *ChemSusChem*, 2013, **6**, 1455–1460.

[3] D. E. Jones and M. S. South, *Tetrahedron*, 2010, **66**, 2570–2581.

[4] P. Jeanjot, F. Bruyneel, A. Arrault, S. Gharbi, J.-F. Cavalier, A. Abels, C. Marchand, R. Touillaux, J.-F. Rees and J. Marchand-Brynaert, *Synthesis*, 2003, **2003**, 513–522.