An Efficient, Inexpensive and Shelf-Stable Diazotransfer Reagent: Imidazole-1-sulfonyl Azide Hydrochloride

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SUPPORTING INFORMATION

Experimental Section

General experimental procedures have been given previously.[1]

Other General Procedures

Procedure A – Preparation of azides (with a subsequent acetylation)

Imidazole-1-sulfonyl azide hydrochloride **1.HCl** (0.25 g, 1.2 mmol) was added to the amine or ammonium salt substrate (1.0 mmol), K_2CO_3 (n + 0.5 mmol)[2] and $CuSO_4.5H_2O$ (2.5 mg, 10 μmol) in MeOH (5 mL) and the mixture stirred at room temperature for the specified time (Table 1).[3] The mixture was concentrated and co-evaporated with PhMe (2 × 10 mL). Acetic anhydride (0.76 mL, 8.0 mmol) was added to the residue in C_5H_5N (5 mL) and the mixture stirred (3 h.). The mixture was concentrated, diluted with H_2O (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Flash chromatography gave the azide.

Procedure B – Preparation of azides

Imidazole-1-sulfonyl azide hydrochloride **1.HCl** (0.25 g, 1.2 mmol) was added to the amine or ammonium salt substrate (1.0 mmol), K_2CO_3 (n + 0.5 mmol)[2] and $CuSO_4.5H_2O$ (2.5 mg, 10 μmol) in MeOH (5 mL) and the mixture stirred at room temperature for the specified time (Table 1).[3] The mixture was concentrated, diluted with H_2O (15 mL), acidified with conc. HCl and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Flash chromatography gave the azide.

Procedure C – Preparation of diazo compounds

Imidazole-1-sulfonyl azide hydrochloride **1.HCl** (0.25 g, 1.2 mmol) was added to the substrate (1.0 mmol) and the specified base (5.0 mmol) in MeCN (5 mL) and the mixture stirred at 40˚C for the specified time (Table 2).[3] The mixture was diluted with EtOAc (15 mL), washed with hydrochloric acid (2 × 15 mL, 1 M), H_2O (15 mL), dried ($MgSO_4$), filtered and concentrated. Flash chromatography gave the diazo compound.

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(1) Scaffidi, A.; Skelton, B. W.; Stick, R. V.; White, A. H. *Aust. J. Chem.* **2006**, *59*, 426–433.
(2) Where 'n' is the number of mols of acid in the system. For example: the reaction of **1.HCl** (1.2 mmol) and the amino acid L-valine (1.0 mmol) requires n = 2.2 mmol.
(3) Please refer to the Tables held within the paper.

***Imidazole-1-sulfonyl Azide* 1**

Sulfuryl chloride (0.40 mL, 5.0 mmol) was added drop-wise to an ice-cooled suspension of NaN_3 (0.32 g, 5.0 mmol) in MeCN (5 mL) and the mixture stirred overnight at room temperature. Imidazole (0.68 g, 10 mmol) was added to the ice-cooled mixture and the resulting slurry stirred for 3 h. at room temperature. The mixture was diluted with EtOAc (10 mL) and H_2O (10 mL) and the aqueous layer separated and discarded. The organic layer was washed with H_2O (10 mL) then saturated aqueous $NaHCO_3$ (2 × 15 mL), dried over $MgSO_4$ and filtered. Concentration of the filtrate and flash chromatography (EtOAc/petrol, 1:3) gave **1** as a colourless liquid (0.62 g, 72%). IR $\nu_{max.}$ (film) 2171, 1387 and 1172 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.17 (dd, 1 H, J = 0.8, 1.7 Hz, H-4), 7.35 (dd, 1 H, J = 1.4, 1.7 Hz, H-5), 7.96 (dd, 1 H, J = 0.8, 1.4 Hz, H-2); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ = 117.7 (C-5), 131.9 (C-4), 136.7 (C-2). HRMS (EI): m/z = 173.0013; $[M]^{+\bullet}$ requires 173.0010. Anal. Calcd. For $C_3H_3N_5O_2S$: C, 20.81; H, 1.75; N, 40.45. Found: C, 20.93; H, 1.79; N, 40.22.

***Imidazole-1-sulfonyl Azide Hydrochloride* 1.HCl**

Sulfuryl chloride (16.1 mL, 200 mol) was added drop-wise to an ice-cooled suspension of NaN_3 (13.0 g, 200 mmol) in MeCN (200 mL) and the mixture stirred overnight at room temperature. Imidazole (25.9 g, 380 mmol) was added portion-wise to the ice-cooled mixture and the resulting slurry stirred for 3 h. at room temperature. The mixture was diluted with EtOAc (400 mL), washed with H_2O (2 × 400 mL) then saturated aqueous $NaHCO_3$ (2 × 400 mL), dried over $MgSO_4$ and filtered. A solution of HCl in EtOH [obtained by the drop-wise addition of AcCl (21.3 mL, 300 mmol) to ice-cooled dry ethanol (75 mL)] was added drop-wise to the filtrate with stirring, the mixture chilled in an ice-bath, filtered and the filter cake washed with EtOAc (3 × 100 mL) to give **1.HCl** as colourless needles (26.4 g, 63%), m.p. 100–102°C.[4] IR $\nu_{max.}$ (KBr) 2173, 1384 and 1161 cm^{-1}. ^1H NMR (600 MHz, D_2O) δ = 7.68 (dd, 1 H, J = 1.3, 2.2 Hz, H-4), 8.09 (dd, 1 H, J = 1.6, 2.2 Hz, H-5), 9.53 (dd, 1 H, J = 1.3, 1.6 Hz, H-2); ^{13}C NMR (150.9 MHz, D_2O) δ = 120.8, 123.4, 138.3. HRMS (FAB): m/z = 174.0072; $[M - Cl]^+$ requires 174.0081. Anal. Calcd. For $C_3H_4ClN_5O_2S$: C, 17.19; H, 1.92; N, 33.41. Found: C, 17.30; H, 1.99; N, 33.13.

***1,3,4,6-Tetra*-O-*acetyl*-2-azido-2-deoxy-D-glucose**

1) D-Glucosamine hydrochloride (216 mg, 1.00 mmol) was treated according to Procedure A, with the use of **1** (1.20 mmol) instead of **1.HCl** [flash chromatography (EtOAc/petrol, 1:3)], to give 1,3,4,6-tetra-*O*-acetyl-2-azido-2-deoxy-D-glucose as a colourless gum (343 mg, 92%). The IR, ^1H and ^{13}C NMR spectroscopic data were in agreement with those published.[5] Anal. Calcd. For $C_{14}H_{19}N_3O_9$: C, 45.04; H, 5.13; N, 11.26. Found: C, 45.19; H, 5.04; N, 11.07.

2) D-Glucosamine hydrochloride (10.8 g, 50.0 mmol) was treated according to Procedure A [flash chromatography (EtOAc/petrol, 1:3)] to give 1,3,4,6-tetra-*O*-acetyl-2-azido-2-deoxy-D-glucose as a colourless gum (17.2 g, 92%).

(4) The evolution of gas from the melt of **1.HCl** suggests decomposition upon melting – see the DSC trace on page six. Please note that DSC on an identical sample suggests a melting point of 94°C, different to the 100–102°C obtained on a hot stage melting apparatus.

(5) Vasella, A.; Witzig, C.; Chiara, J.-L.; Martin-Lomas, M. *Helv. Chim. Acta* **1991**, *74*, 2073–2077.

***1,3,4,6-Tetra*-O-*acetyl*-2-azido-2-deoxy-D-galactose**

D-Galactosamine hydrochloride (108 mg, 0.500 mmol) was treated according to Procedure A [flash chromatography (EtOAc/petrol, 1:3)] to give 1,3,4,6-tetra-*O*-acetyl-2-azido-2-deoxy-D-galactose as a colourless gum (162 mg, 87%).The IR, ^{1}H and ^{13}C NMR spectroscopic data were in agreement with those published.[5] Anal. Calcd. For $C_{14}H_{19}N_3O_9$: C, 45.04; H, 5.13; N, 11.26. Found: C, 45.28; H, 5.28; N, 11.11.

***(2S)*-2-Azido-3-methylbutanoic acid**

L-Valine (117 mg, 1.00 mmol) was treated according to Procedure B [flash chromatography (EtOAc/petrol/AcOH, 20:79:1)] to give (2*S*)-2-azido-3-methylbutanoic acid as a pale yellow oil (120mg, 84%). $[\alpha]_D = -46.5$ (c = 1.0 in $CHCl_3$, lit.[6] $[\alpha]_D = -47.8$). The ^{1}H and ^{13}C NMR spectroscopic data were in agreement with those published.[6]

***(2S)*-2-Azido-4-methylpentanoic acid**

L-Leucine (131 mg, 1.00 mmol) was treated according to Procedure B [flash chromatography (EtOAc/petrol/AcOH, 15:84:1)] to give (2*S*)-2-azido-4-methylpentanoic acid as a pale yellow oil (134 mg, 85%). $[\alpha]_D = -13.8$ (c = 1.0 in $CHCl_3$, lit.[6] $[\alpha]_D = -13.0$). The ^{1}H and ^{13}C NMR spectroscopic data were in agreement with those published.[6]

***(2S)*-2-Azido-3-phenylpropanoic Acid**

L-Phenylalanine (165 mg, 1.00 mmol) was treated according to Procedure B [flash chromatography (EtOAc/petrol/AcOH, 10:89:1)] to give (2*S*)-2-azido-3-phenylpropanoic acid as a pale yellow oil (143 mg, 75%). $[\alpha]_D = -72.1$ (c = 1.0 in $CHCl_3$, lit.[6] $[\alpha]_D = -74.2$). The ^{1}H and ^{13}C NMR spectroscopic data were in agreement with those published.[6] Anal. Calcd. For $C_9H_9N_3O_2$: C, 56.54; H, 4.74; N, 21.98. Found: C, 56.45; H, 4.92; N, 21.74.

***(2S)*-2,6-Diazidohexanoic Acid**

L-Lysine hydrochloride (183 mg, 1.00 mmol) was treated according to Procedure B, with the addition of H_2O (5 mL) as a co-solvent [flash chromatography (EtOAc/petrol/AcOH, 10:89:1)], to give (2*S*)-2,6-diazidohexanoic acid as a pale yellow oil (131 mg, 66%). $[\alpha]_D = -49.3$. IR $\nu_{max.}$ (film) 2178, 1683 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.50–1.68 (m, 4 H, H-4,5), 1.78–1.95 (m, 2 H, H-3), 3.30–3.33 (m, 2 H, H-6), 3.95 (dd, 1 H, J = 5.1, 8.4 Hz, H-2); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ = 23.1 (C-4), 28.5 (C-5), 31.0 (C-3), 51.2 (C6), 61.7 (C2), 175.2 (C-1). HRMS (EI): m/z = 198.0883; $[M]^{+\bullet}$ requires 198.0871. Anal. Calcd. For $C_6H_{10}N_6O_2$: C, 36.36; H, 5.09; N, 42.41. Found: C, 36.21; H, 5.28; N, 42.30.

(6) Lundquist, IV, J. T.; Pelletier, J. C. *Org. Lett.* **2001**, *3*, 781–783.

4-Azidobutanoic Acid

4-Aminobutanoic acid (103 mg, 1.00 mmol) was treated according to Procedure B [flash chromatography (EtOAc/petrol/AcOH, 5:94:1)] to give 4-azidobutanoic acid as a pale yellow oil (93 mg, 72%). The IR, ^{1}H and ^{13}C NMR spectroscopic data were in agreement with those published.[7]

Methyl (2S)-2-Azido-3-(4-hydroxyphenyl)propanoate

L-Tyrosine methyl ester hydrochloride (232 mg, 1.00 mmol) was treated according to Procedure B [flash chromatography (EtOAc/petrol, 1:3)] to give methyl (2*S*)-2-azido-3-(4-hydroxyphenyl)propanoate as a pale yellow oil (199 mg, 90%), $[\alpha]_D = -10.3$. IR $\nu_{max.}$ (film) 2172, 1691 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 2.95$ (dd, 1 H, $J = 8.5, 14.1$ Hz, H-3), 3.10 (dd, 1 H, $J = 5.4, 14.1$ Hz, H-3), 3.77 (s, 3 H, OCH_3), 4.02 (dd, 1 H, $J = 5.4, 8.5$ Hz, H-2), 4.88 (s, 1 H, OH), 6.77–6.80 (m, 2 H, ArH), 7.09–7.11 (m, 2 H, ArH); ^{13}C NMR (150.9 MHz, $CDCl_3$) $\delta = 37.0$ (C-3), 52.8 (OCH_3), 63.6 (C-2), 115.7-155.0 (Ar), 170.6 (C-1). HRMS (FAB): m/z = 222.0901; $[M + H]^+$ requires 222.0888. Anal. Calcd. For $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.35; H, 5.18; N, 18.79.

Methyl (2S)-2-Azido-3-hydroxypropanoate

L-Serine methyl ester hydrochloride (156 mg, 1.00 mmol) was treated according to Procedure B [flash chromatography (EtOAc/petrol, 2:3)] to give methyl (2*S*)-2-azido-3-hydroxypropanoate as a pale yellow oil (120 mg, 83%), $[\alpha]_D = -93.4$ (c = 1.0 in $CHCl_3$, lit.[8] $[\alpha]_D = -92.2$). The ^{1}H and ^{13}C NMR spectroscopic data were in agreement with those published.[8] Anal. Calcd. For $C_4H_7N_3O_3$: C, 33.11; H, 4.86; N, 28.96. Found: C, 32.90; H, 4.89; N, 28.82.

(1S,2S)-2-Azido-1-phenyl-1,3-propanediol

(1*S*,2*S*)-2-Amino-1-phenyl-1,3-propanediol (167 mg, 1.00 mmol) was treated according to Procedure B [flash chromatography (EtOAc/petrol, 1:3)] to give (1*S*,2*S*)-2-azido-1-phenyl-1,3-propanediol as a pale yellow oil (176 mg, 91%), $[\alpha]_D = -72.0$ (c = 1.0 in $CHCl_3$, lit.[9] $[\alpha]_D = -76.26$). The IR, ^{1}H and ^{13}C NMR spectroscopic data were in agreement with those published.[9]

4-Azido-1-methoxybenzene

4-Anisidine (123 mg, 1.00 mmol) was treated according to Procedure B [flash chromatography (EtOAc/petrol, 1:3)] to give 4-azido-1-methoxybenzene as a yellow oil (116 mg, 78%). The IR, ^{1}H and ^{13}C NMR spectroscopic data were in agreement with those published.[10]

(7) van der Peet, P.; Gannon, C. T.; Walker, I.; Dinev, Z.; Angelin, M.; Tam, S.; Ralton, J. E.; McConville, M. J.; Williams, S. J. *ChemBioChem* **2006**, *7*, 1384–1391.
(8) Manabe, S.; Sakamoto, K.; Nakahara, Y.; Sisido, M.; Hohsaka, T.; Ito, Y. *Bioorg. Med. Chem.* **2002**, *10*, 573–581.
(9) Hajura, S; Karmakar, A.; Maji, T.; Medda, A. K. *Tetrahedron* **2006**, *62*, 8959–1965.
(10) Liu, Q.; Tor, Y. *Org. Lett.* **2003**, *5*, 2571–2572.

4-Azidobenzoic acid

4-Aminobenzoic acid (137 mg, 1.00 mmol) was treated according to Procedure B [flash chromatography (EtOAc/petrol/AcOH, 25:72:3)] to give 4-azidobenzoic acid as pale yellow crystals (139, 85%), m.p. 188.5–190˚C (lit.[11] m.p. 188–191 ˚C). The IR, ^{1}H and ^{13}C NMR spectroscopic data were in agreement with those published.[10]

2-Azidobenzoic acid

2-Aminobenzoic acid (137 mg, 1.00 mmol) was treated according to Procedure B [flash chromatography (EtOAc/petrol/AcOH, 25:72:3)] to give 2-azidobenzoic acid as pale yellow crystals (135 mg, 83%), m.p. 147–148.5˚C (lit.[11] m.p. 146–148˚C). The IR and ^{1}H NMR spectroscopic data were in agreement with those published.[11]

Diethyl Diazomalonate

Diethyl malonate (0.15 mL, 1.0 mmol) was treated according to Procedure C, using K_2CO_3 (0.69 g, 5.0 mmol) as base [flash chromatography (EtOAc/petrol, 1:19)], to give diethyl diazomalonate as a yellow oil (0.12 g, 65%). The IR and ^{1}H NMR spectroscopic data were in agreement with those published.[12] HRMS (FAB): m/z = 187.0714; $[M + H]^+$ requires 187.0719. Anal. Calcd. For $C_7H_{10}N_2O_4$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.42; H, 5.23; N, 14.93.

Ethyl 2-Diazoacetoacetate

Ethyl acetoacetate (0.13 mL, 1.0 mmol) was treated according to Procedure C, using K_2CO_3 (0.69 g, 5.0 mmol) as base [flash chromatography (EtOAc/petrol, 1:19)], to give ethyl 2-diazoacetoacetate as a yellow oil (92 mg, 59%). The IR and ^{1}H spectroscopic data were in agreement with those published.[12] HRMS (FAB): m/z = 157.0617; $[M + H]^+$ requires 157.0613. Anal. Calcd. For $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.46; H, 5.28; N, 18.07.

Ethyl Cyanodiazoacetate

Ethyl cyanoacetate (0.11 mL, 1.0 mmol) was treated according to Procedure C, using pyridine (0.40 mL, 5.0 mmol) as base [flash chromatography (EtOAc/petrol, 1:19)], to give ethyl cyanodiazoacetate as a yellow oil (85 mg, 61%). The IR, ^{1}H and ^{13}C NMR spectroscopic data were in agreement with those published.[13] HRMS (FAB): m/z = 140.0463; $[M + H]^+$ requires 140.0460. Anal. Calcd. For $C_5H_5N_3O_2$: C, 43.17; H, 3.62; N, 30.20. Found: C, 43.15; H, 3.78; N, 30.16.

(11) Xiong, Y.; Bernardi, D.; Bratton, S.; Ward, M. D.; Battaglia, E.; Finel, M.; Drake, R. R.; Radominska-Pandya, A. *Biochemistry* **2006**, *45*, 2322-2332.
(12) Rianelli, R. de S.; de Souza, M. C. B. V.; Ferreira, V. F. *Synth. Commun.* **2004**, *34*, 951–959.
(13) Wurz, R. P.; Lin, W.; Charette, A. B. *Tetrahedron Lett.* **2003**, *44*, 8845–8848.

Sample: ImSO2N3HCl
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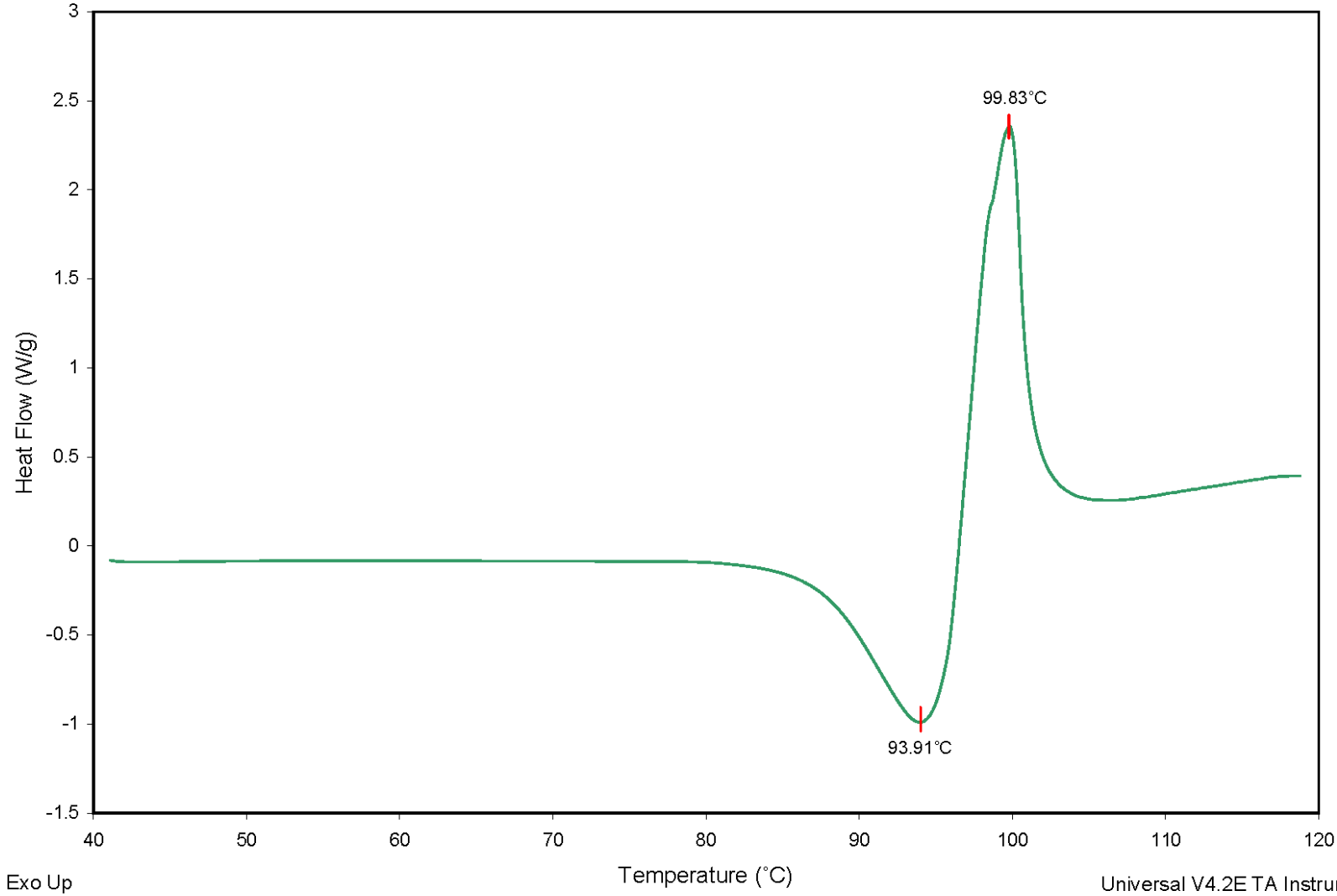
Method: Ramp, 5˚C/min

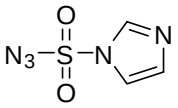
DSC

Run Date: 29-Jul-2007
Instrument: DSC Q10 V9.4 Build 287



Universal V4.2E TA Instruments

***Imidazole-1-sulfonyl Azide* 1**



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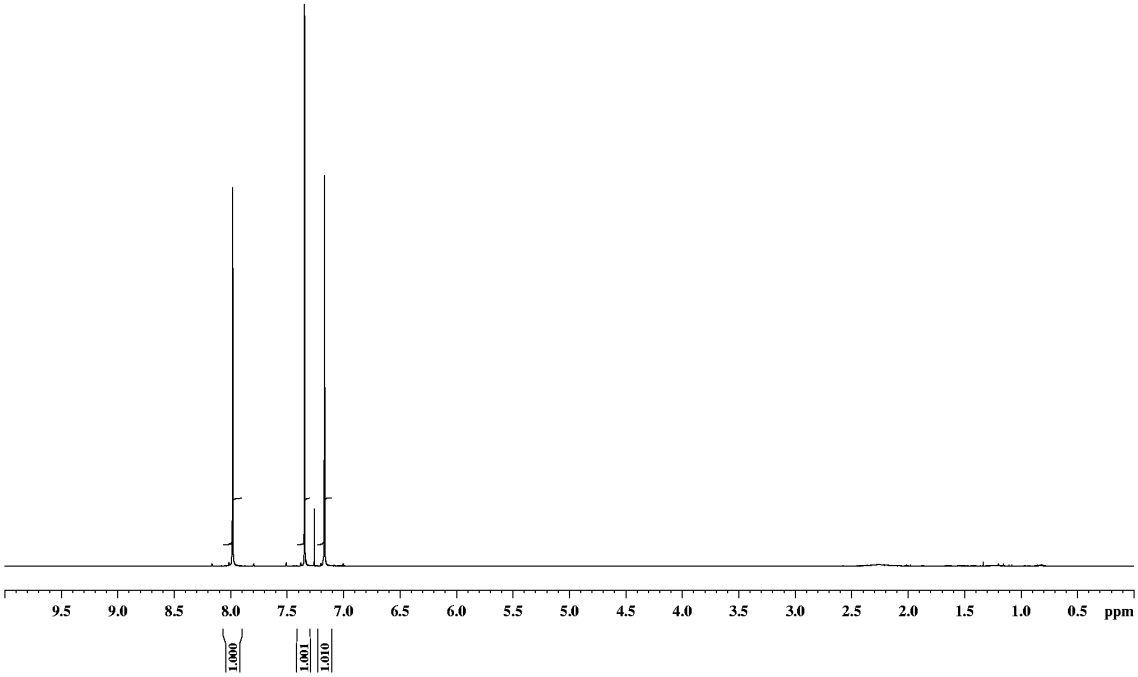

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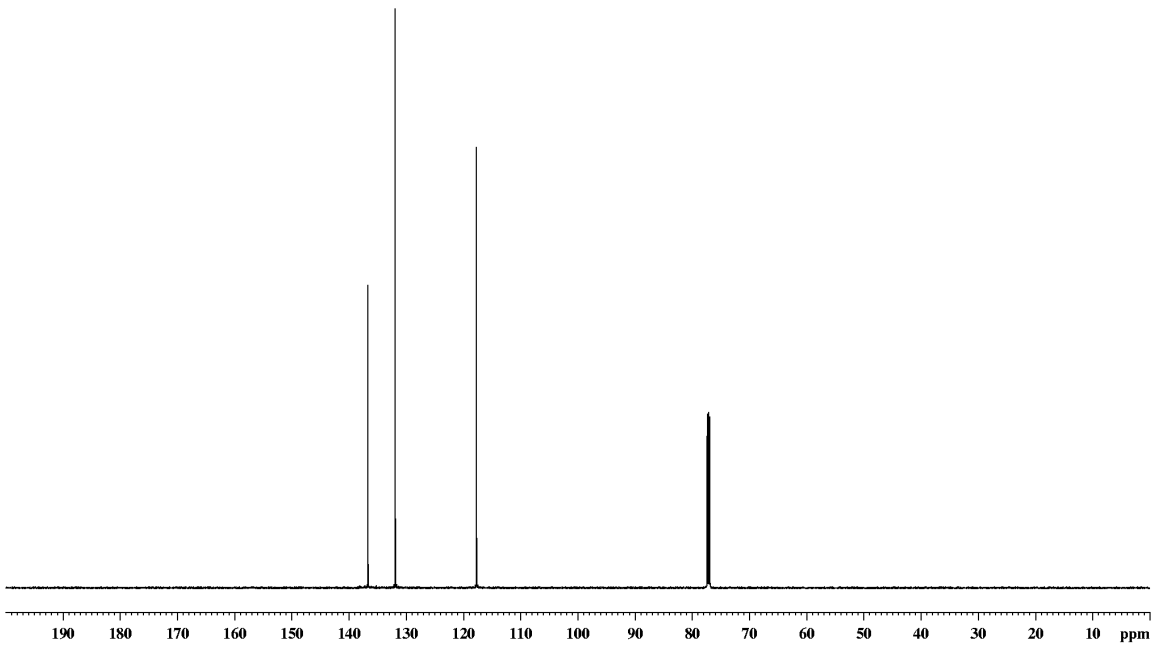
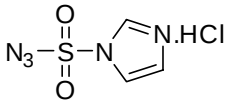
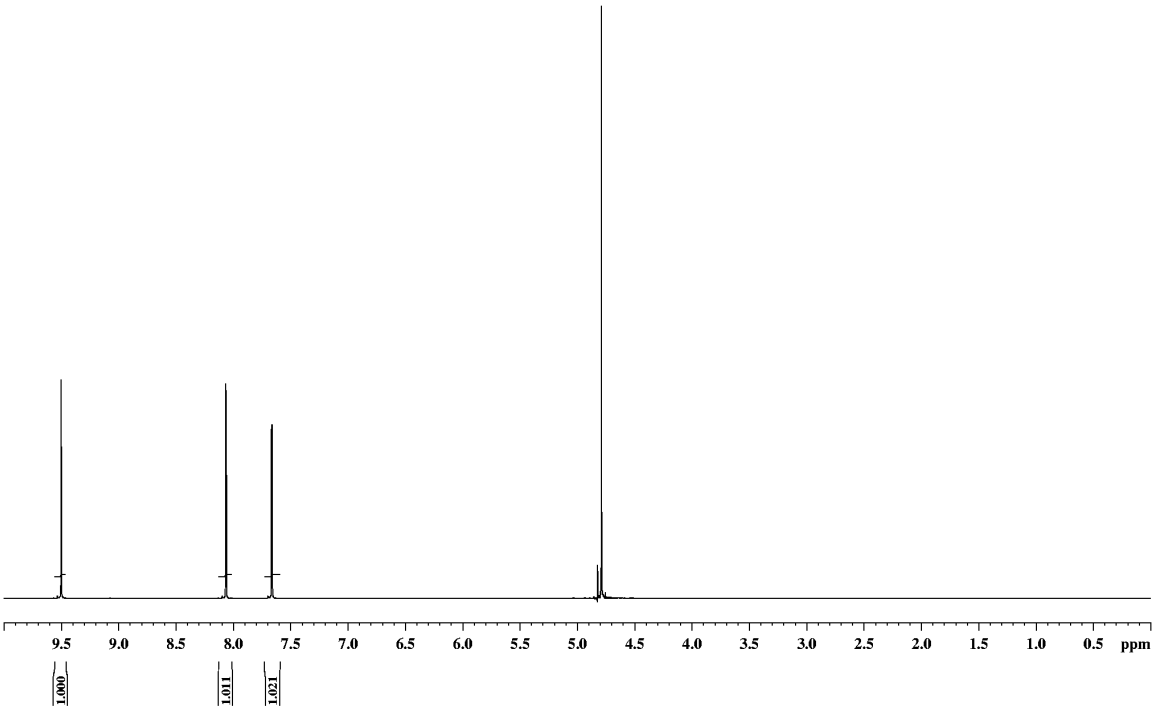


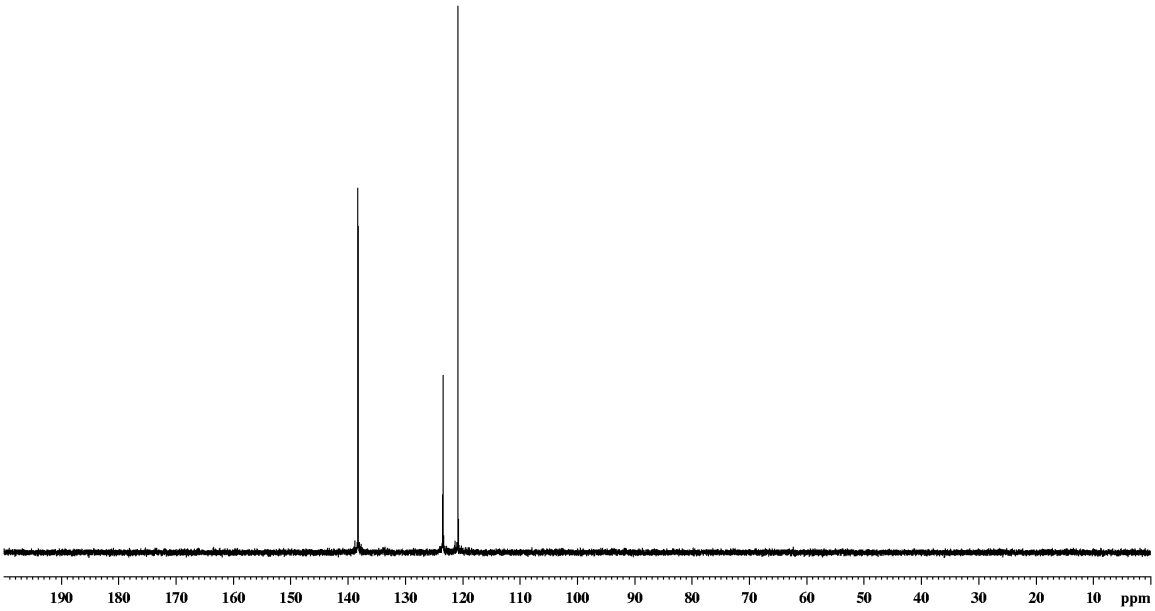
***Imidazole-1-sulfonyl Azide Hydrochloride* 1.HCl**



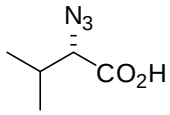
^{1}H NMR (600 MHz, D_2O)



^{13}C NMR (150.9 MHz, D_2O)



(2S)-2-Azido-3-methylbutanoic acid



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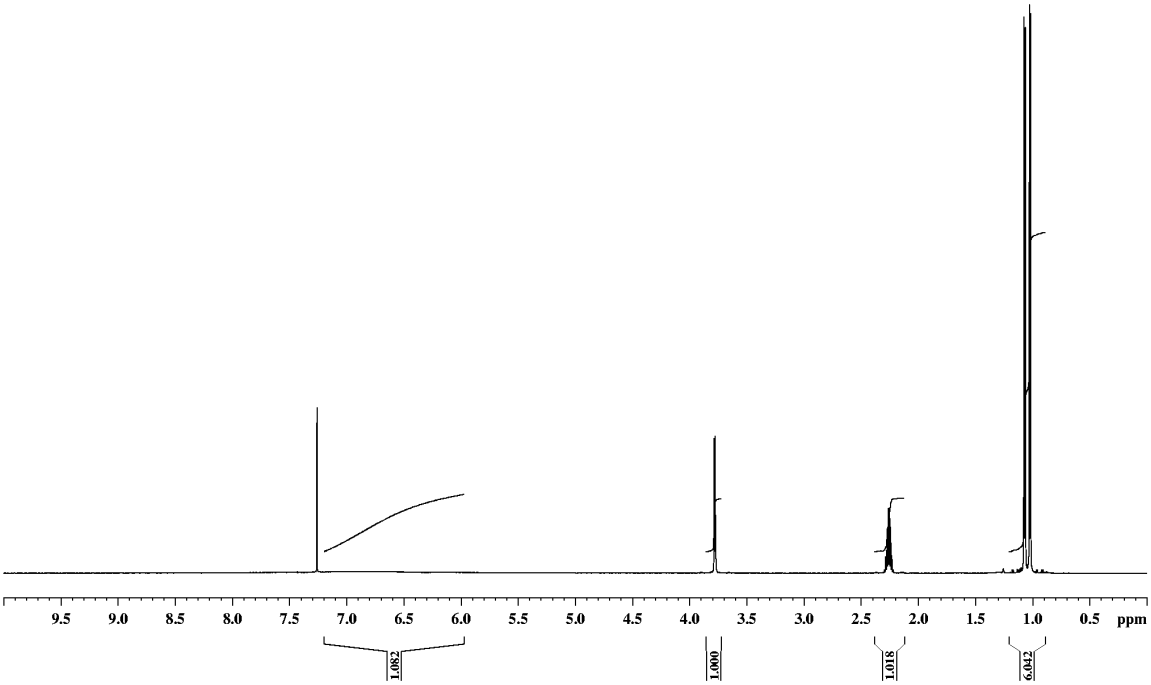
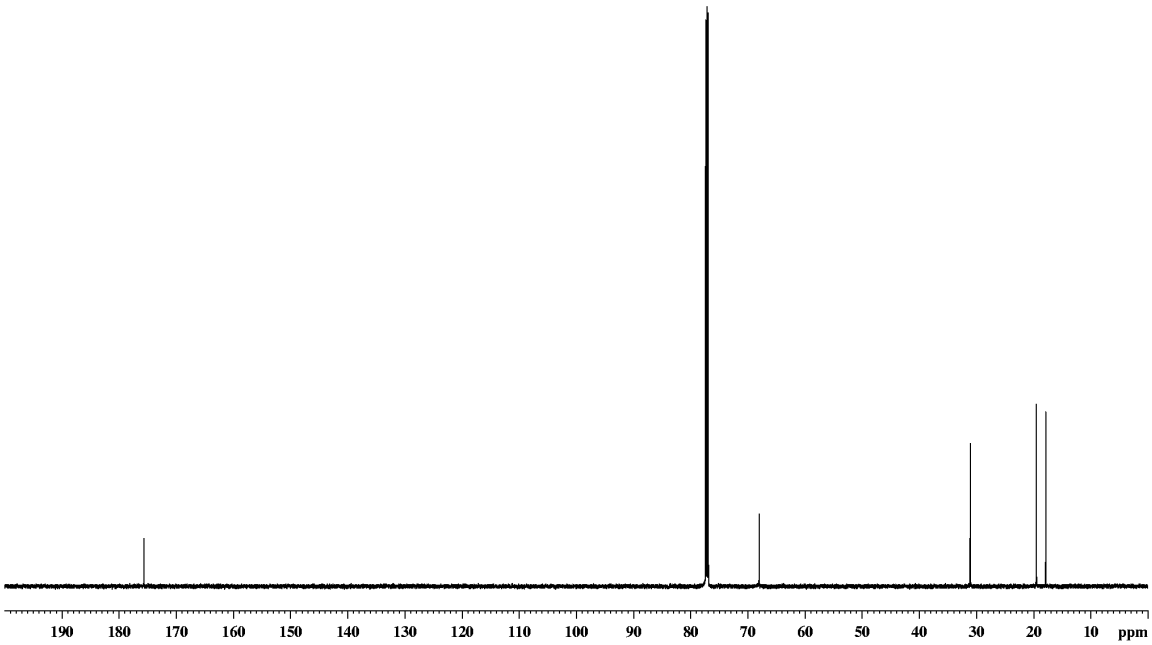
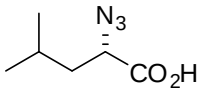


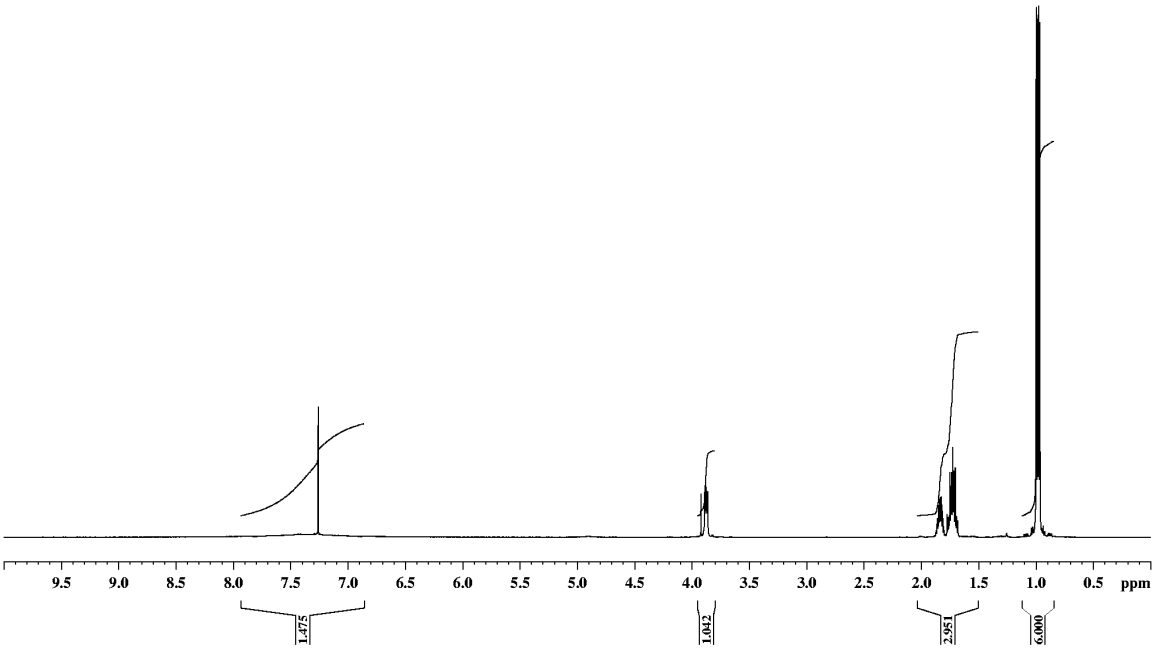
^{13}C NMR (150.9 MHz, $CDCl_3$)



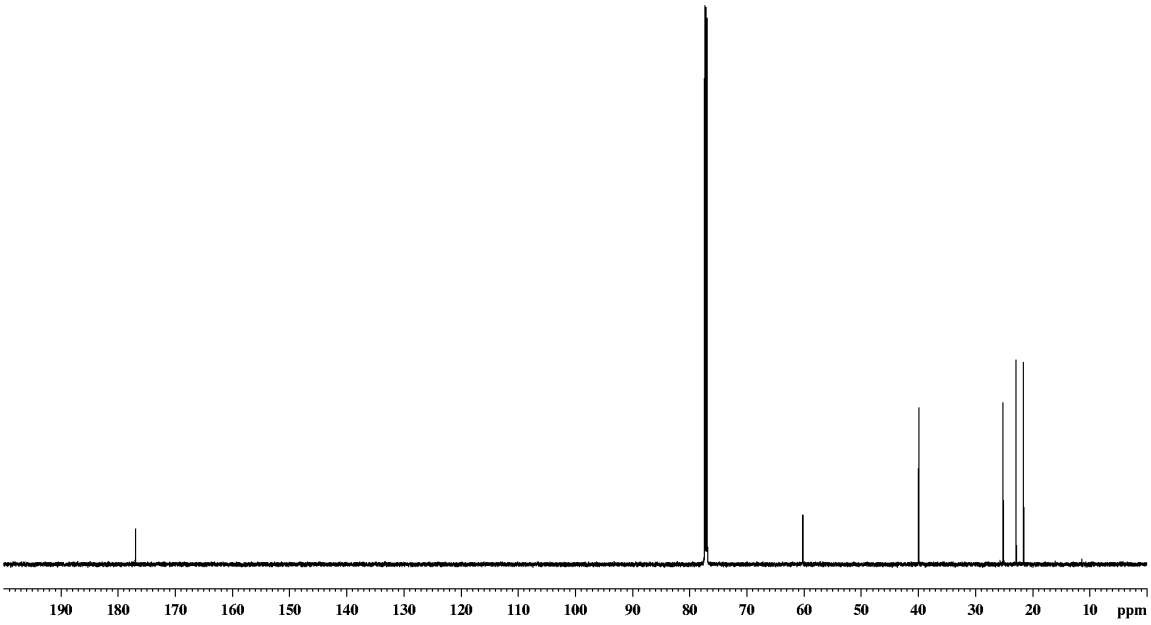
(2S)-2-Azido-4-methylpentanoic acid



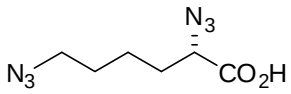
^{1}H NMR (600 MHz, $CDCl_3$)



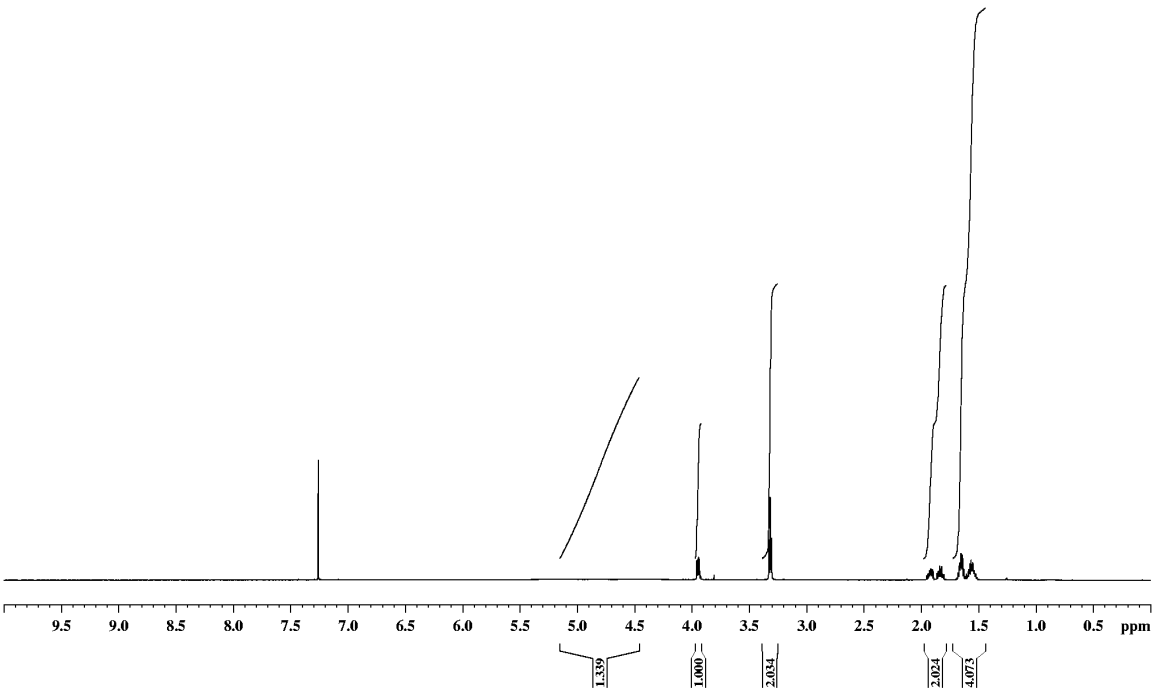
^{13}C NMR (150.9 MHz, $CDCl_3$)



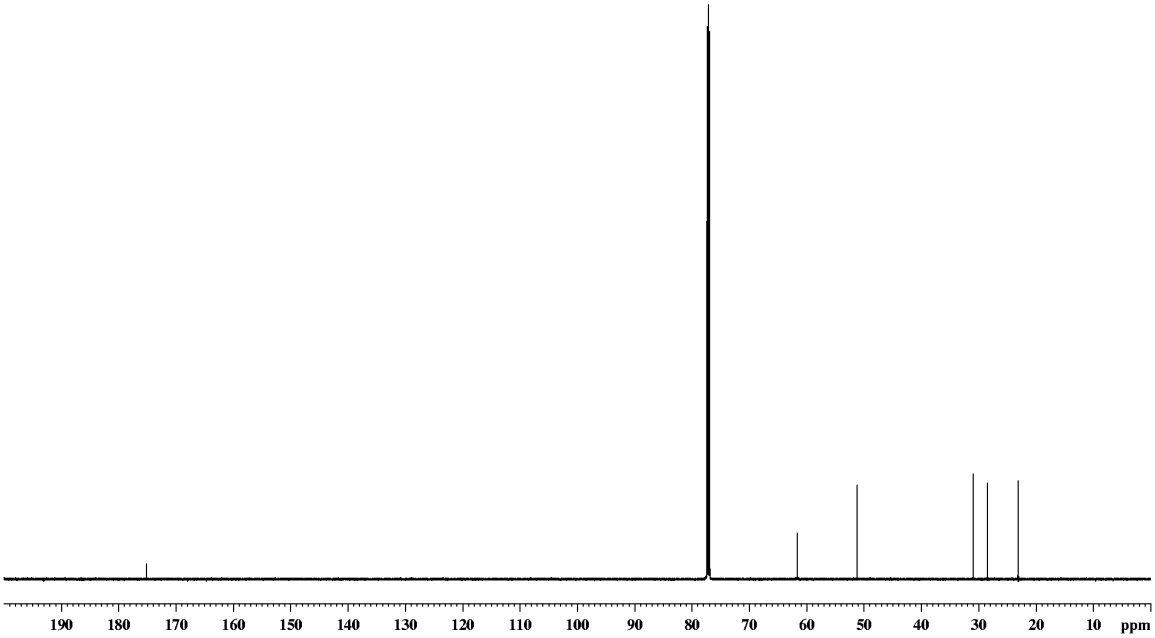
(2S)-2,6-Diazidohexanoic Acid



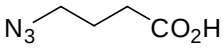
^{1}H NMR (600 MHz, $CDCl_3$)



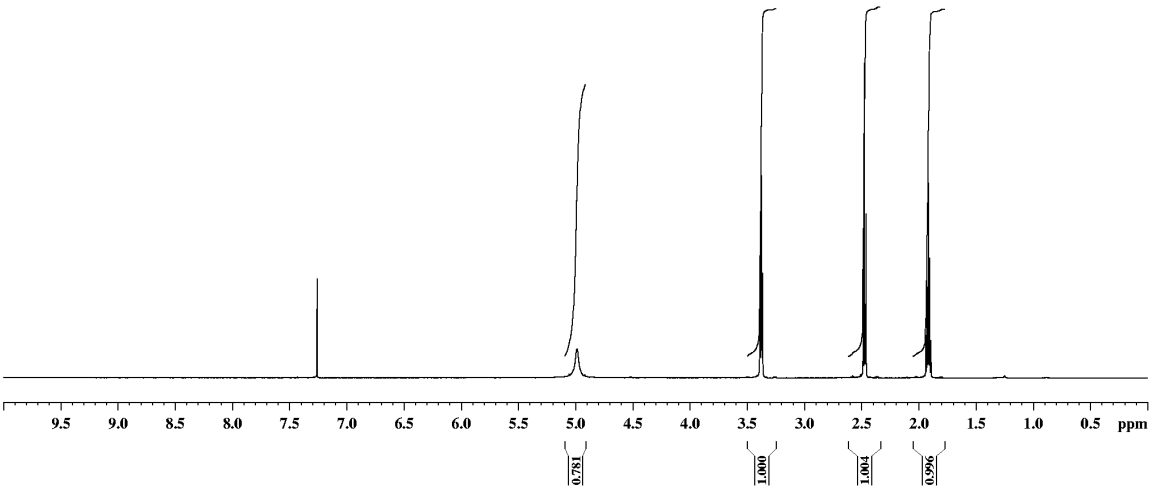
^{13}C NMR (150.9 MHz, $CDCl_3$)



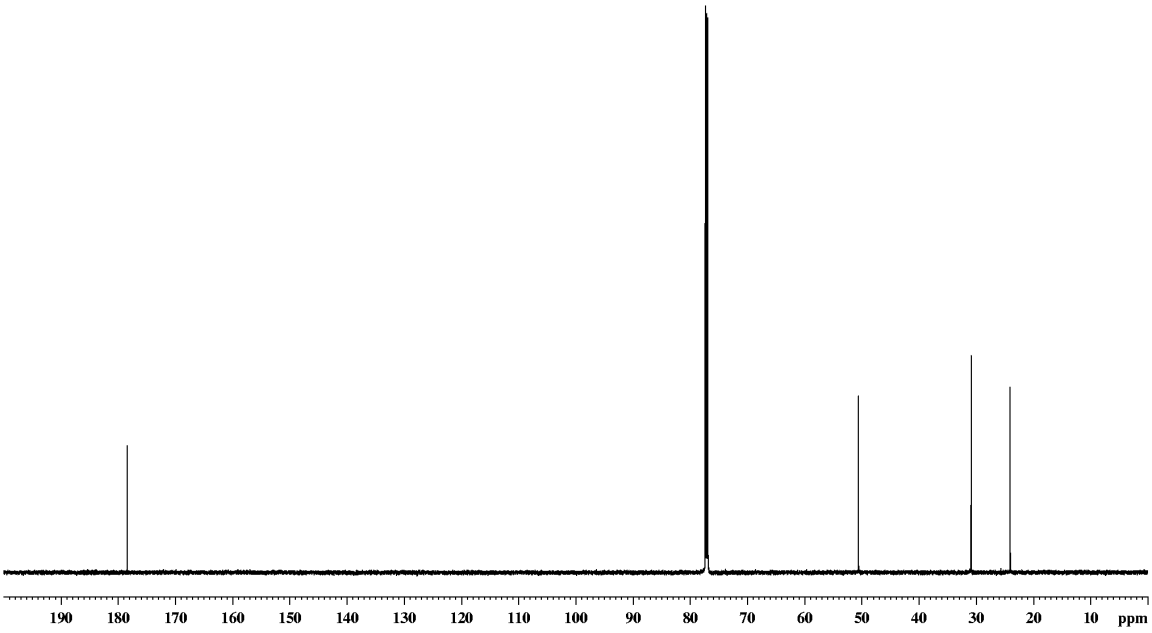
4-Azidobutanoic Acid



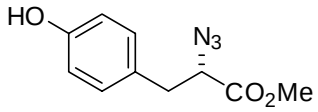
^{1}H NMR (600 MHz, $CDCl_3$)



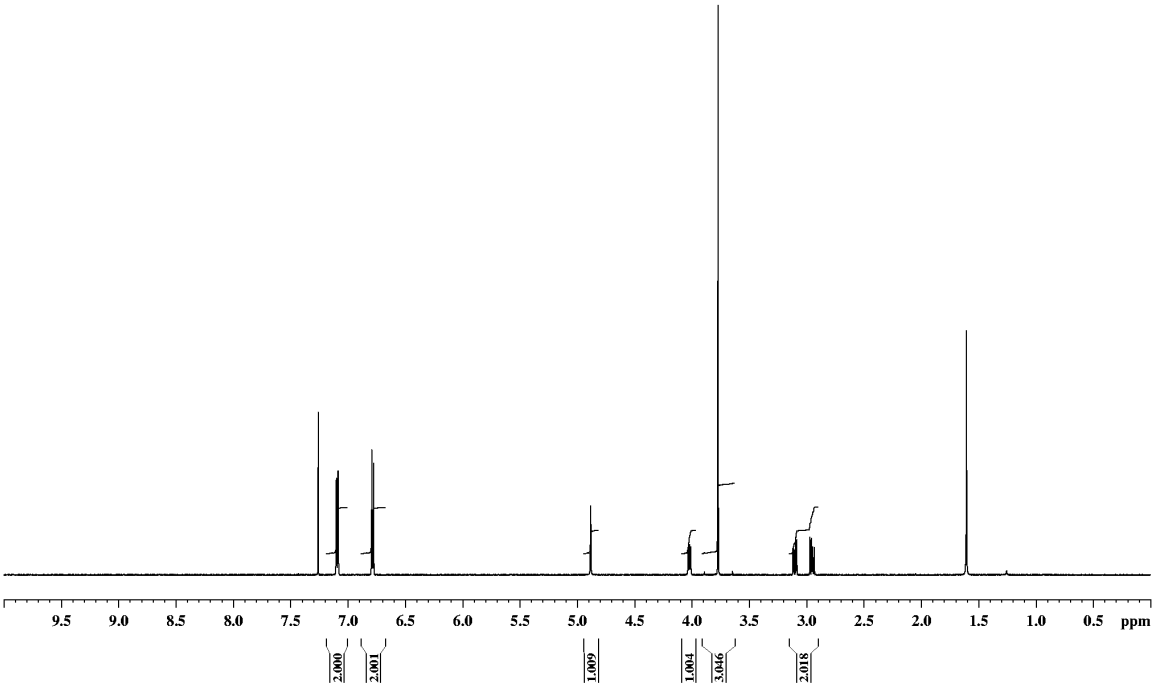
^{13}C NMR (150.9 MHz, $CDCl_3$)



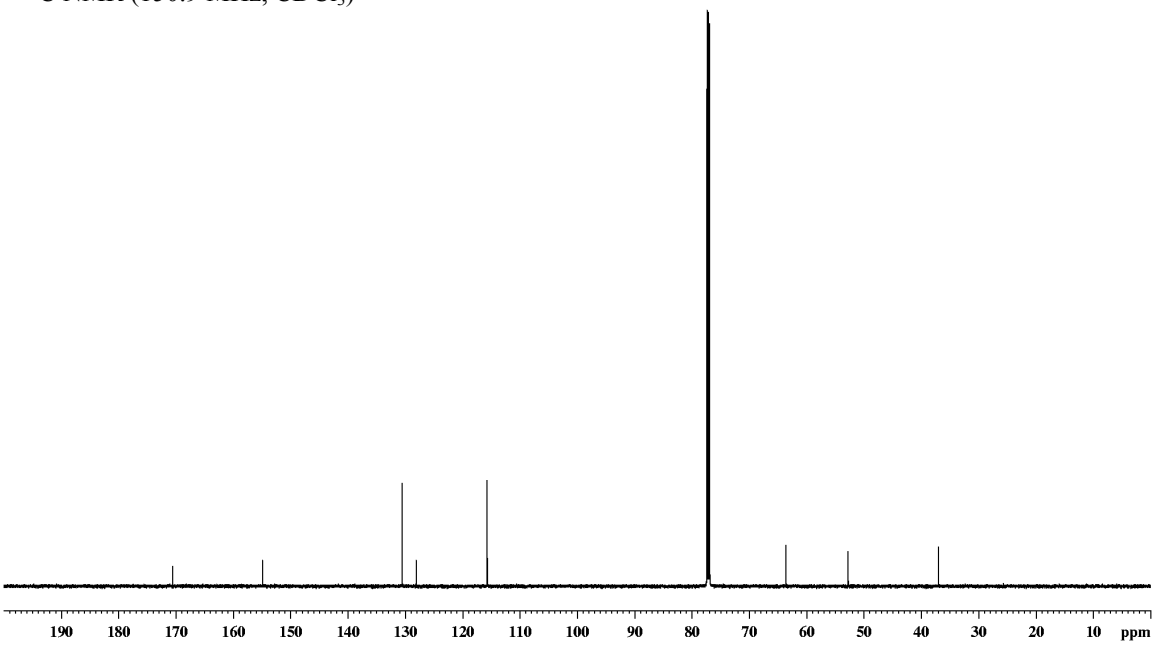
Methyl (2S)-2-Azido-3-(4-hydroxyphenyl)propanoate



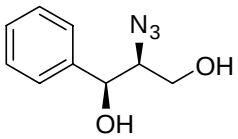
^{1}H NMR (600 MHz, $CDCl_3$)



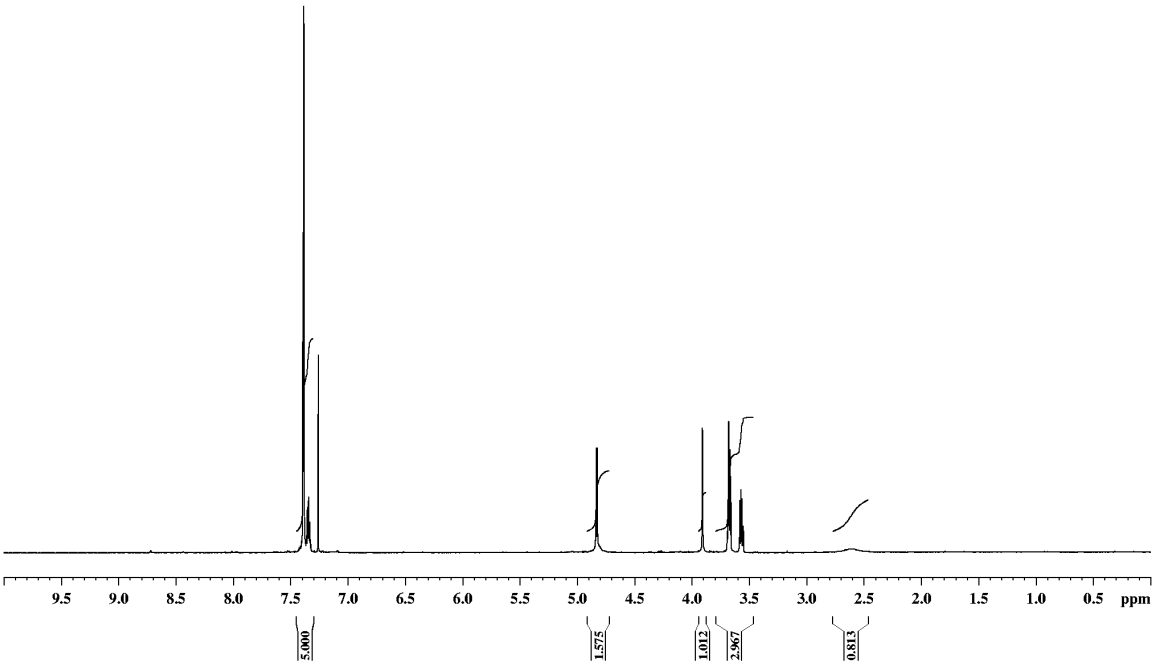
^{13}C NMR (150.9 MHz, $CDCl_3$)



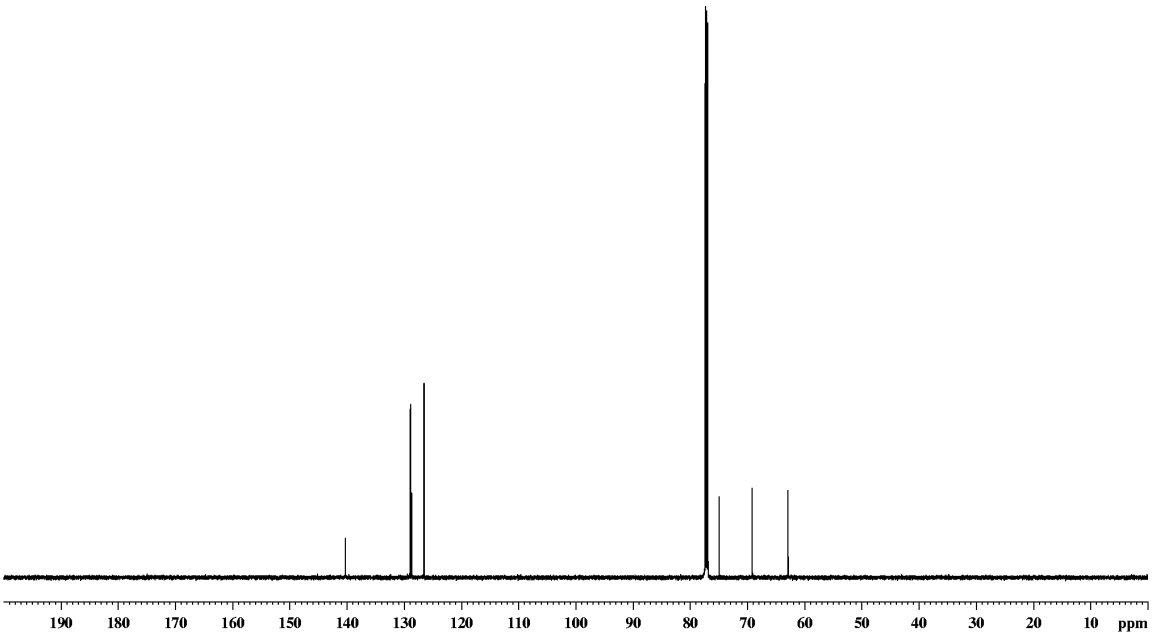
(1S,2S)-2-Azido-1-phenyl-1,3-propanediol



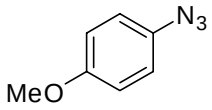
^{1}H NMR (600 MHz, $CDCl_3$)



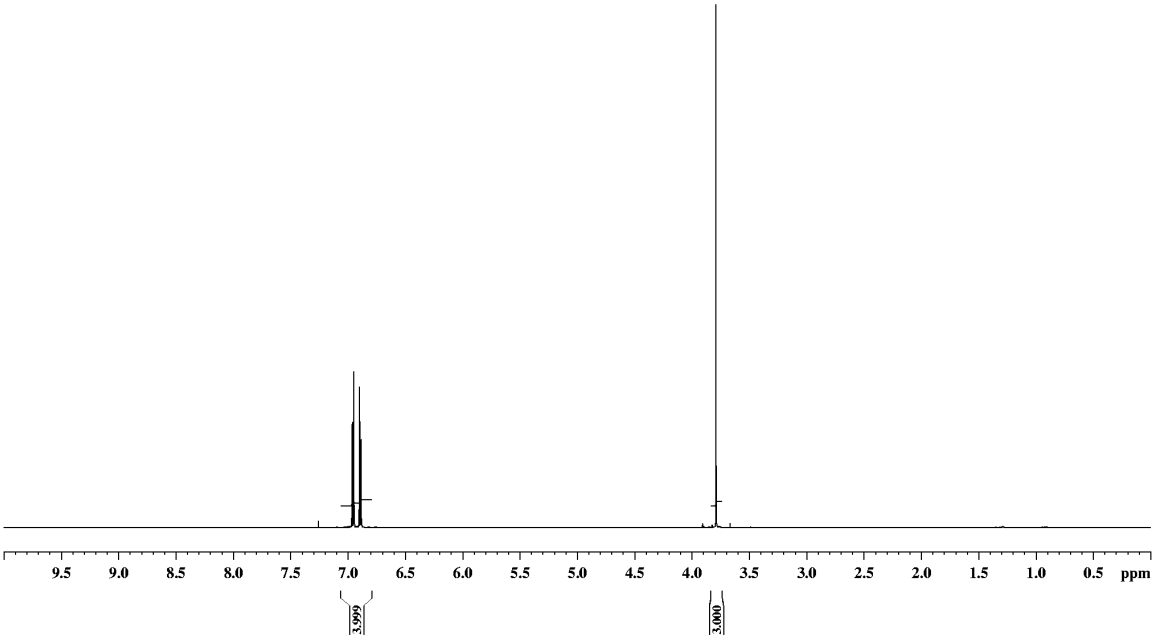
^{13}C NMR (150.9 MHz, $CDCl_3$)



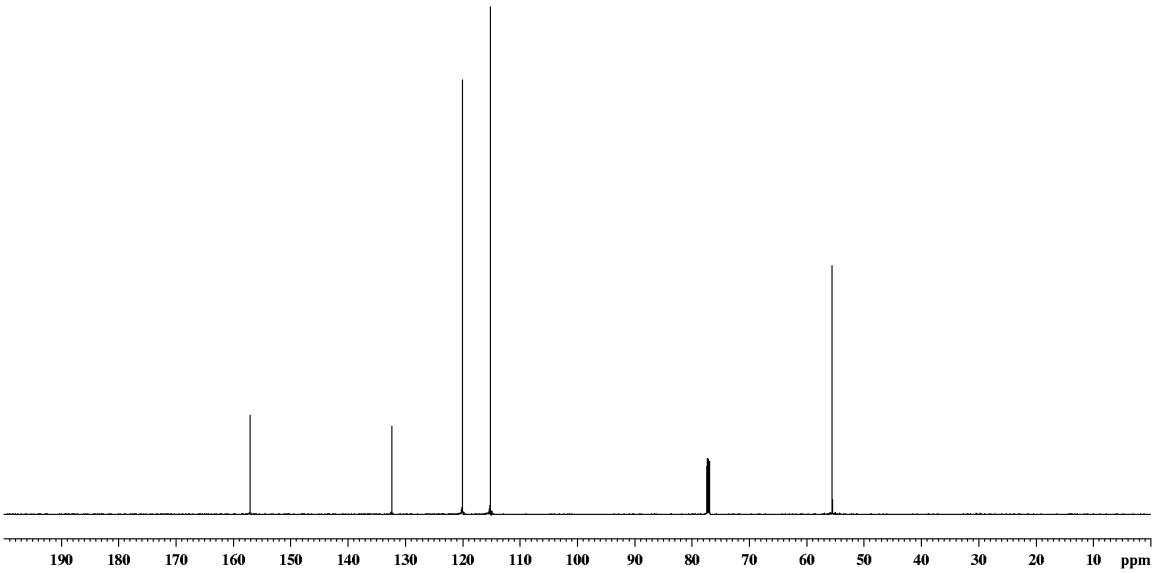
4-Azido-1-methoxybenzene



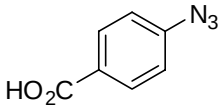
^{1}H NMR (600 MHz, $CDCl_3$)



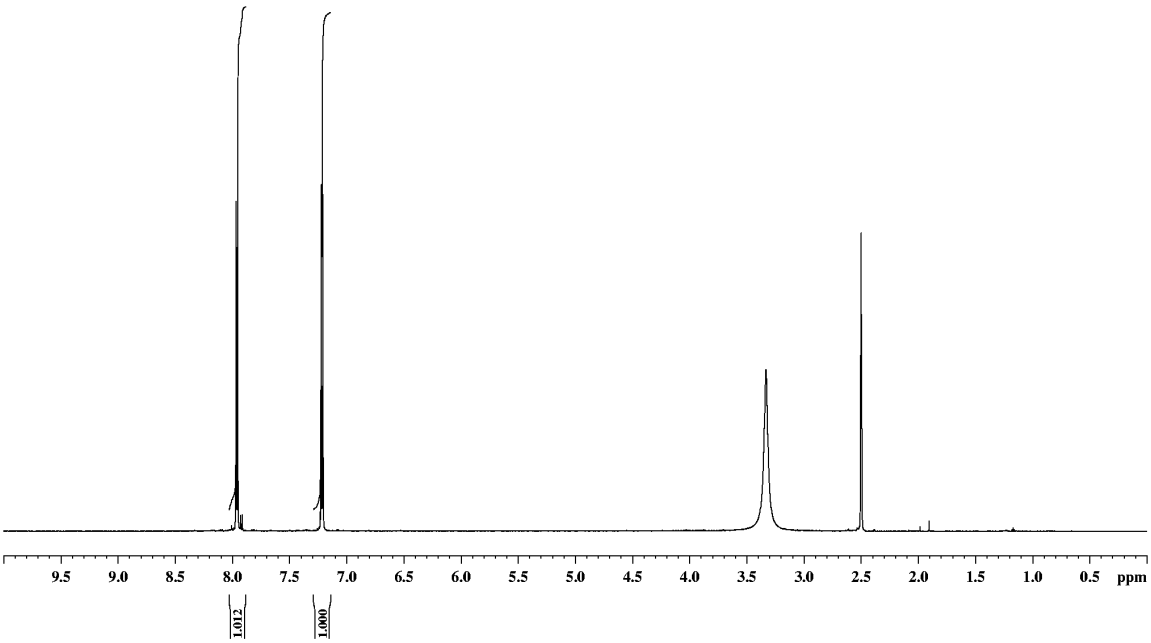
^{13}C NMR (150.9 MHz, $CDCl_3$)



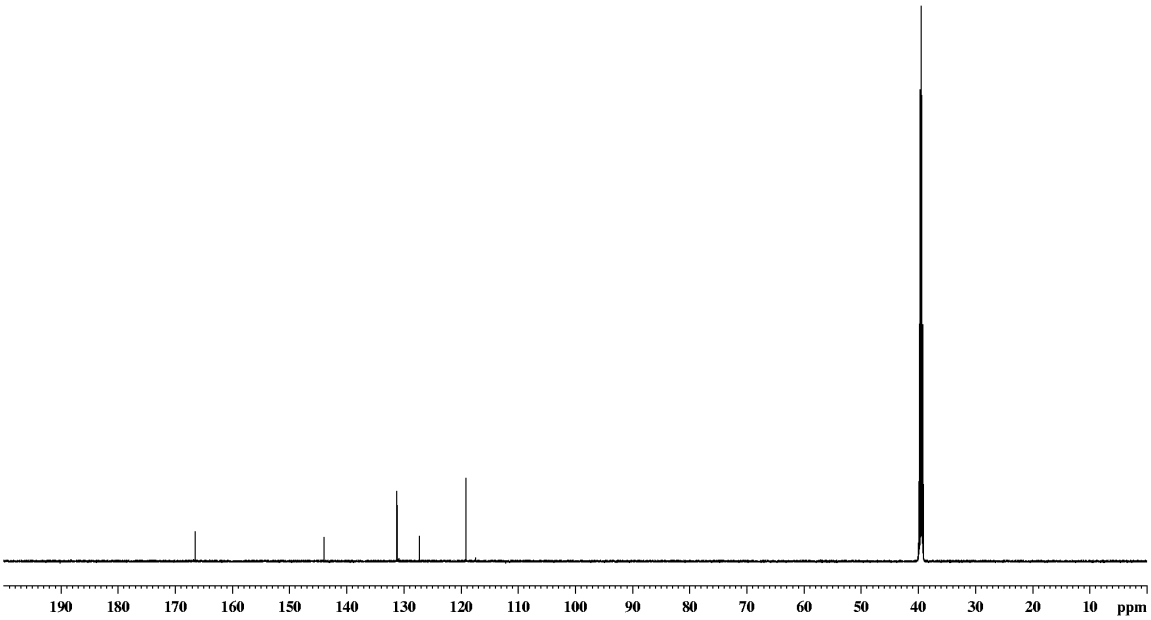
4-Azidobenzoic acid



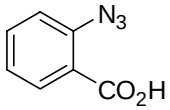
^{1}H NMR (600 MHz, $(CD_3)_2SO$)



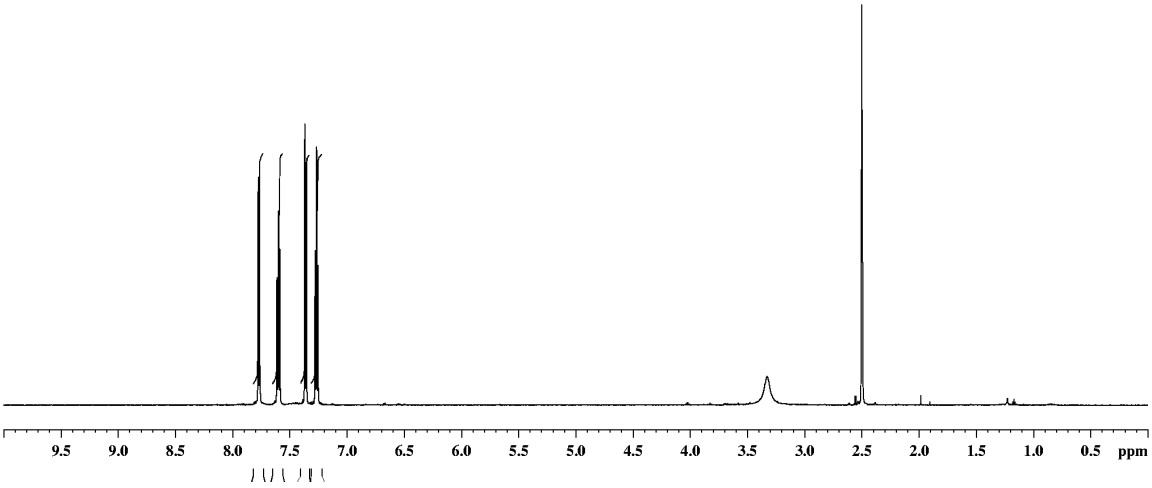
^{13}C NMR (150.9 MHz, $(CD_3)_2SO$)



2-Azidobenzoic acid



^{1}H NMR (600 MHz, $CDCl_3$)



^{13}C NMR (150.9 MHz, $CDCl_3$)