Electronic supporting information

Development of safely handleable synthetic equivalent of cyanonitrile oxide –1,3-dipolar cycloaddition of nitroacetonitrile–

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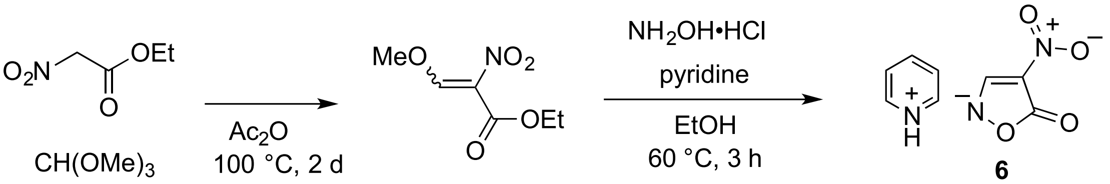
1. General

The melting points were determined on SRS-Optimelt Automated Melting Point System, and were uncorrected. All the dipolarophiles and solvents were commercially available and used as received. The ^{1}H NMR spectra were measured on a Bruker Ascend-400 at 400 MHz with tetramethylsilane as an internal standard. The ^{13}C NMR spectra were measured on a Bruker Ascend-400 at 100 MHz, and assignments of ^{13}C NMR spectra were performed by DEPT experiments. The high-resolution mass spectra were measured on an AB SCIEX Triple TOF 4600. The IR spectra were recorded on a JASCO FT/IR-4200 spectrometer.

2. Experimental procedure and spectral data

Synthesis of pyridinium salt 6[1]

Pyridinium salt **6** was synthesized by 2 steps reactions from commercially available ethyl nitroacetate *via* methyl 3-methoxy-2-nitropropenoate.[2]



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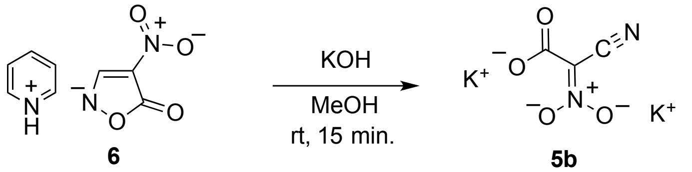
To a solution of methyl 3-methoxy-2-nitropropenoate (16.1 g, 100 mmol) in ethanol (160 mL), were added $NH_2OH•HCl$ (7.73 g, 120 mmol) and pyridine (20.2 mL, 250 mmol). The resultant mixture was heated at 60 °C for 3 h. After cooling, precipitated pale yellow needles were collected by filtration to afford pyridinium salt **6** (14.8 g, 71 mmol, 71%).

Synthesis of dipotassium salt 5b[1]

Pyridinium salt **6** (2.09 g, 10 mmol) was dissolved in 0.5 M MeOH solution of KOH (40 mL, 20 mmol), and stirred at room temperature for 15 min. A pale-yellow precipitate was observed during the stirring. The solid was collected by filtration to afford dipotassium cyano-*aci*-nitroacetate **5b** (2.01 g, 9.76 mmol, 98%).



Typical procedure for synthesis of 3-cyanoisoxazoles 8 and 11

In a screw capped test tube, dipotassium salt **5b** (41.2 mg, 0.2 mmol) was dissolved into a mixed solvent of MeCN/H_2O (*v*/*v* = 1/1, 2 mL). After adding ethynylbenzene **7a** (110 μL, 1mmol) and 1 M HCl (3 mL, 3 mmol), the resultant mixture was heated at 100 °C for 12 h in a sealed tube. The solvent was removed under reduced pressure, and MeCN (10 mL) was added to the residue. After filtration to remove the insoluble material, the filtrate was concentrated to afford 3-cyano-5-phenylisoxazole **8a**[3] (163 mg, 0.96 mmol, 96%) as a brown solid. Mp 84–88 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60–7.63 (m, 3H), 7.79 (s, 1H), 7.92–7.97 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 103.2 (C), 110.4 (C), 125.1 (C), 126.0 (CH), 129.5 (CH), 131.7 (CH), 140.1 (C), 172.0 (C); IR (ATR / cm^{-1}) 2253.

When other dipolarophiles were used, the experiments were conducted in a same way.

3-Cyano-5-(4-trifluoromethylphenyl)isoxazole (8b)[3]

Mp 92–95 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 1H), 8.05 (d, *J* = 8.2 Hz, 2H), 8.23 (d, *J* = 8.2 8.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 105.0 (CH), 110.2 (C), 123.7 (C, q, *J* = 271 Hz), 126.4 (CH, d, *J* = 3.5 Hz), 126.9 (CH), 128.7 (C), 131.3 (C, q, *J* = 32.1 Hz), 140.3 (C), 170.3 (C); IR (ATR / cm^{-1}) 2261, 1570, 1400, 1319; HRMS (ESI/TOF) calcd. for (M+H$^+$) $C_{11}H_6F_3N_2O$: 239.0427, found: 239.0428.

3-Cyano-5-(4-methylphenyl)isoxazole (8c)[4]

White solid, mp 95-98 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.40 (s, 3H), 7.42 (d, J = 8.0 Hz, 2H), 7.71 (s, 1H), 7.83 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (CH_3), 102.6 (C), 110.5 (C), 122.4 (C), 126.0 (CH), 130.0 (CH), 140.0 (CH), 141.2 (C), 172.2 (C); IR (ATR / cm^{-1}) 2257, 1504, 1400; HRMS (ESI/TOF) calcd. for (M+H$^+$) $C_{11}H_9N_2O$: 185.0715, found: 185.0714.

3-Cyano-5-(4-methoxyphenyl)isoxazole (8d)[4]

White solid, mp 104-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 6.69 (s, 1H), 7.01 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5 (CH_3), 100.0 (CH), 110.2 (C), 114.8 (CH), 118.2 (C), 127.9 (CH), 140.0 (C), 162.2 (C), 172.6 (C); IR (ATR / cm^{-1}) 2252, 1568, 1458; HRMS (ESI/TOF) calcd. for (M+H$^+$) $C_{11}H_9N_2O_2$: 201.0658, found: 201.0649.

***trans*-3-Cyano-4,5-diphenyl-2-isoxazoline (11e)**

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (d, J = 7.6 Hz, 1H), 5.69 (d, J = 7.6 Hz, 1H), 7.20–7.27 (m, 3H), 7.40–7.46 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.5 (CH), 92.9 (CH), 109.4 (C), 124.4 (CH), 126.5 (CH), 128.2 (CH), 128.2 (CH), 128.3 (CH), 128.8 (CH), 134.1 (C), 136.6 (C), 136.7 (C); IR (ATR / cm^{-1}) 2237, 1558, 1497, 1454; HRMS (ESI/TOF) calcd. for (M+H$^+$) $C_{16}H_{13}N_2O$: 248.1022, found: 248.1027.

3-Cyano-2-isoxazoline-5-carboxylic acid (11g)[4]

Yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.58 (dd, J = 7.6, 17.6 Hz, 1H), 3.72 (dd, J = 12.4, 17.6 Hz, 1H), 5.45 (dd, J = 7.6, 12.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 38.4 (C), 57.0 (CH), 80.1 (CH_2), 111.0 (C), 135.9 (C), 169.6 (C); IR (ATR / cm^{-1}) 2990, 2245, 1724, 1570, 1415; HRMS (ESI/TOF) calcd. for (M+Na$^+$) $C_5H_3N_2O_3Na$: 163.0114, found: 163.0121.

3-Cyano-5-methyl-2-isoxazoline-5-carboxylic acid (11i)

Yellow solid, mp 73-105 °C (dec.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.70 (s, 3H), 3.05 (d, J = 17.7 Hz, 1H), 3.68 (d, J = 17.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.9 (CH_3), 43.5 (CH_2), 87.8 (C), 109.0 (C), 133.4 (C), 172.9 (C); IR (ATR / cm^{-1}) 2940, 2241, 1701, 1431; HRMS (ESI/TOF) calcd. for (M+Na$^+$) $C_6H_5N_2O_3Na$: 177.0271, found: 177.0274.

References

1 N. Nishiwaki, Y. Takada, Y. Inoue, Y. Tohda and M. Ariga, *J. Heterocycl. Chem.*, 1995, **32**, 473.

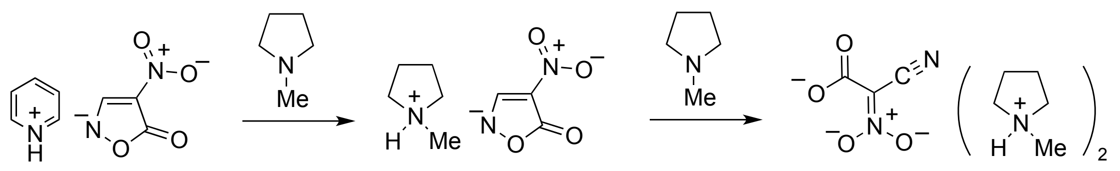
2 M. J. Kamlet, *J. Org. Chem.*, 1959, **24**, 714.

3 N. A. Bumagin, A. V. Kletskov, S. K. Petkevich, I. A. Kolesnik, A. S. Lyakhov, L. S. Ivashkevich, A. V. Baranovsky, P. V. Kurman and V. I. Potkin, *Chem. Heterocycl. Compd.*, 2014, **49**, 1515.

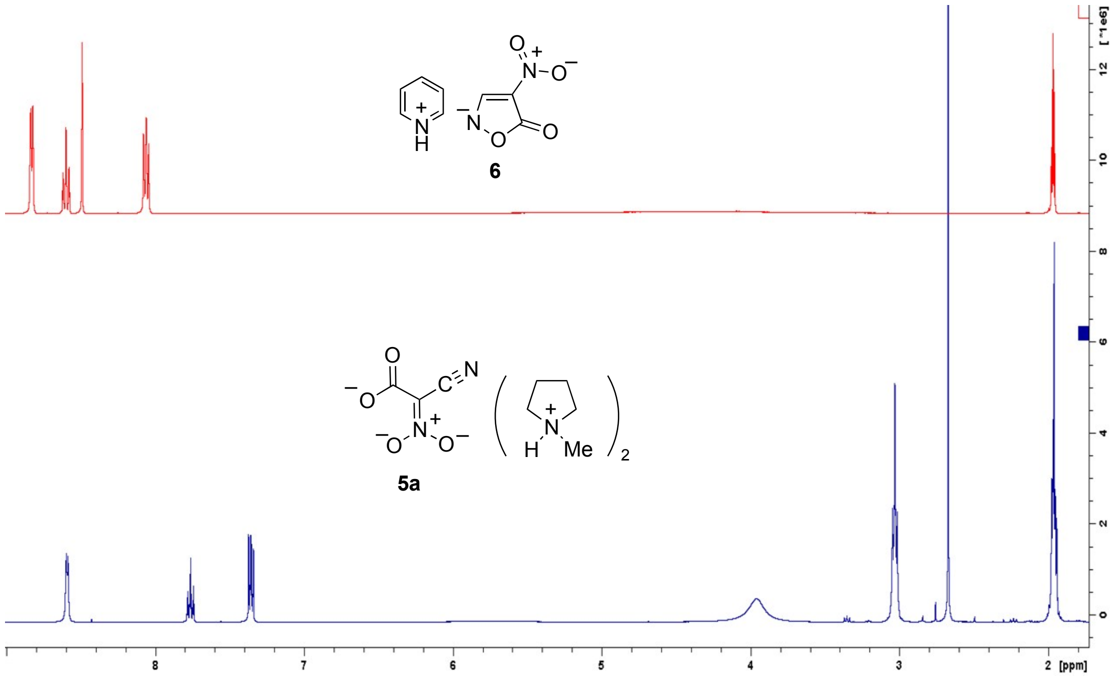
4 This compound is not found in the literature, but is commercially available.

3. Monitoring of the structural changes by ^{1}H NMR (in CD_3CN)

a) From pyridinium salt of nitroisoxazolone 6 to cyano-*aci*-nitroacetate 5a

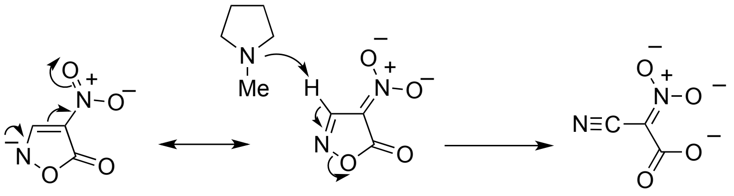


6 **6'** **5a**

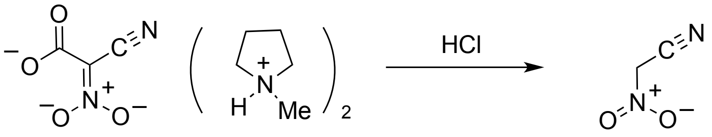


When 1 equiv. *N*-methylpyrrolidine was added to a solution of pyridinium salt **6**, signals of the pyridine ring shifted to the higher field, and signals of pyrrolidine shifted to the lower field. This change indicates that the counter cation of **6** exchanged from pyridinium ion to pyrrolidinium ion to afford **6'**.

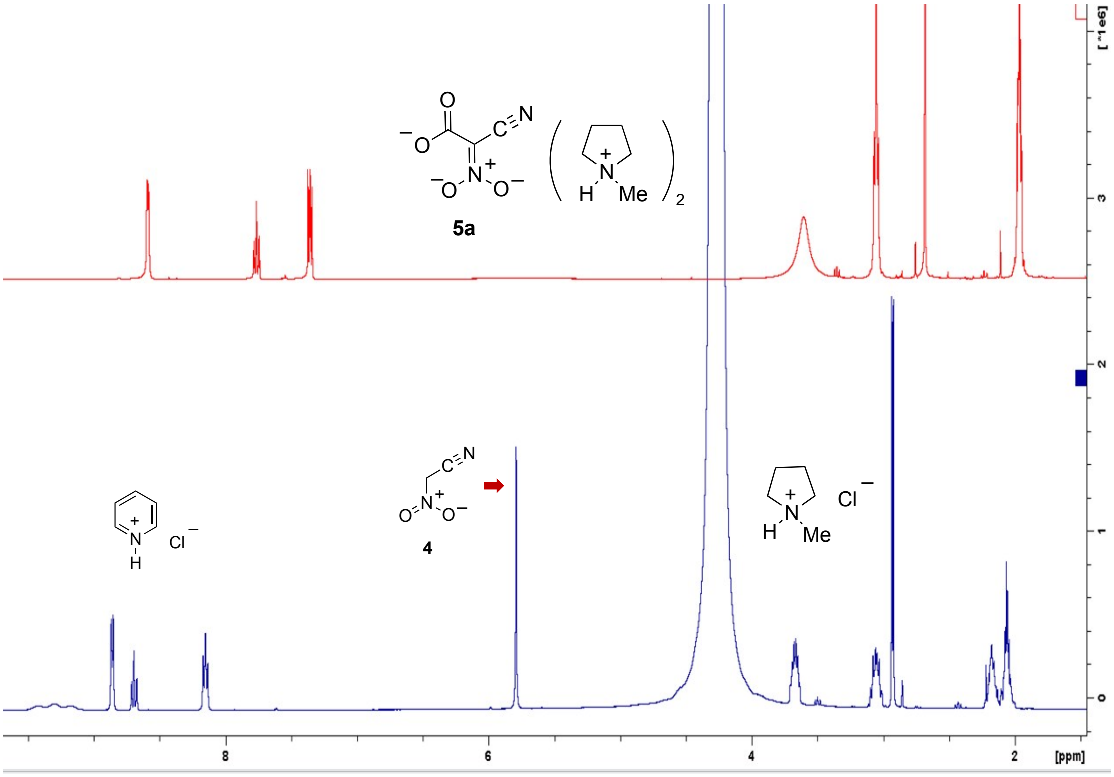
The singlet signal at 8.3 ppm disappeared when further 1 equiv. *N*-methylpyrrolidine was added. This spectral change means that deprotonation of the isoxazolone ring occurred at the 3-position, which causes the ring opening reaction to furnish cyano-*aci*-nitroacetate **5a**.



b) Acidification of cyano-*aci*-nitroacetate 5a

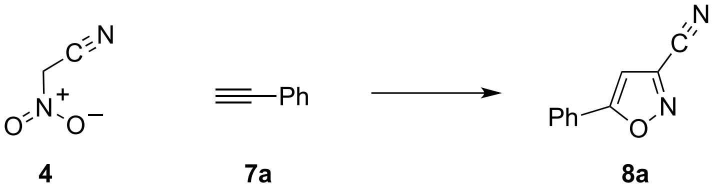


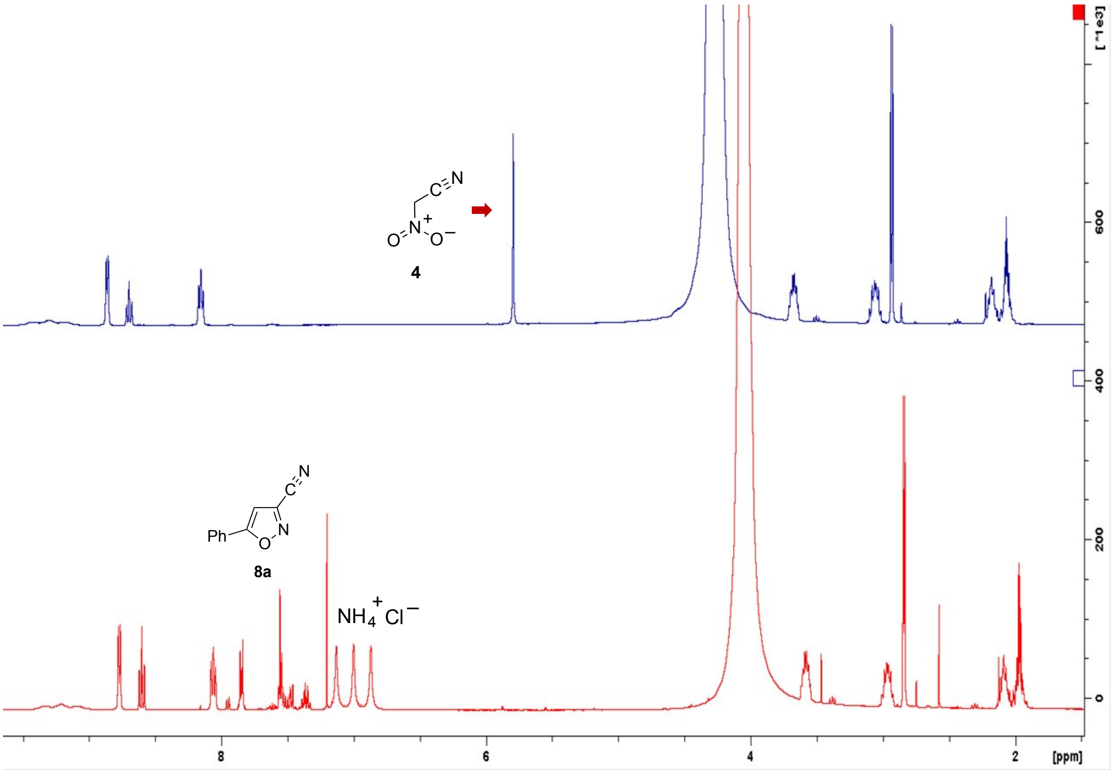
5a **4**



When 3 equiv. HCl were added to a solution of cyano-*aci*-nitroacetate **5a** in CD_3CN, a new singlet signal was observed at 5.8 ppm which was assigned to nitroacetonitrile **4**.

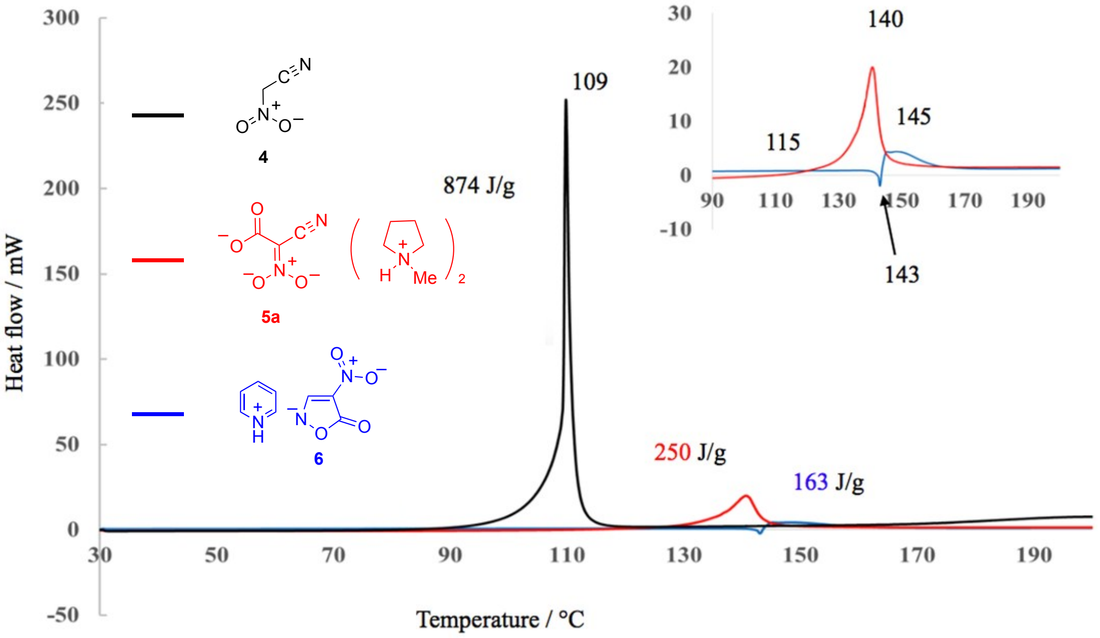
c) Cycloaddition of nitroacetonitrile 4 with ethynylbenzene 7a.





To a solution of nitroacetonitrile **4** in CD_3CN, ethynylbenzene **7a** was added, and the resultant solution was heated at 100 °C for 1 d. While the signal of **4** disappeared, signals of 3-cyanoisoxazole **8a** were newly observed. In addition, signals of ammonium chloride was also observed, which is presumably formed by acid hydrolysis of acetonitrile.

4. Differential scanning calorimetry (DSC) measurements



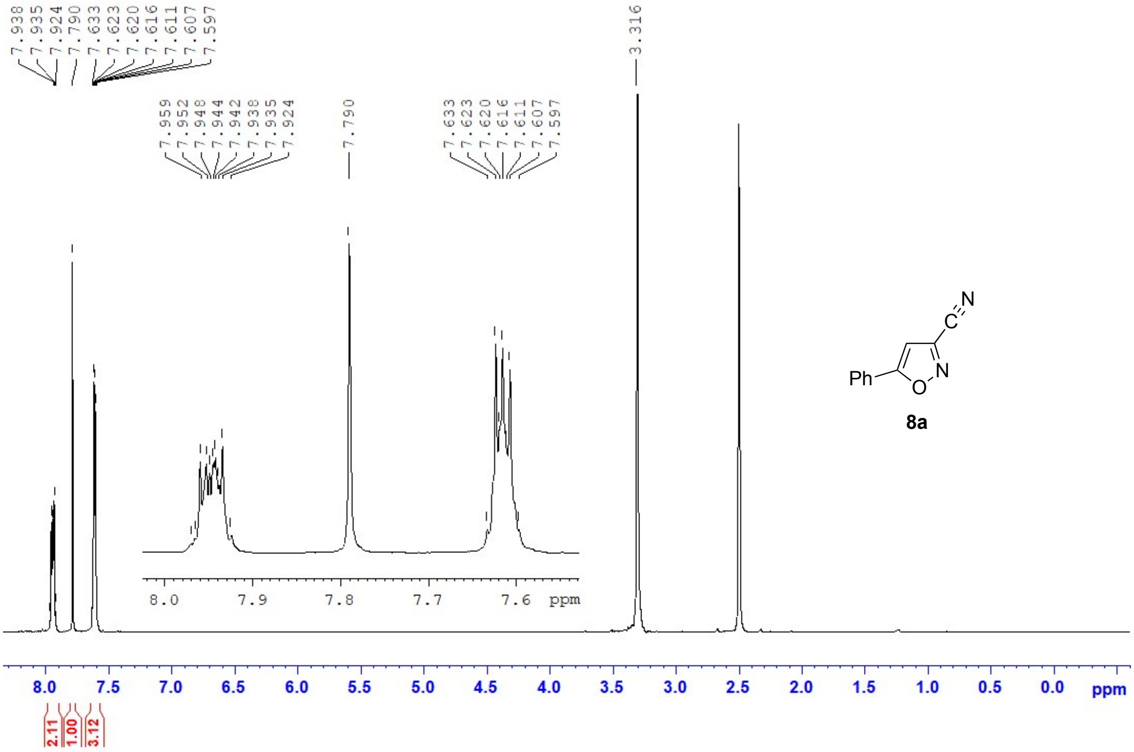
Nitroacetonitrile **4** rapidly decomposed in air at 109 °C, releasing 874 J/gof energy. This classifies it as an explosive material according to UN Orange Book.[5] Conversely, cyano-*aci*-nitroacetate **5a** and pyridinium salt **6** were stable even at 140 °C, and smaller energies (250 and 163 J/g, respectively) were released, indicating that both compounds are safely handleable reagents under air.

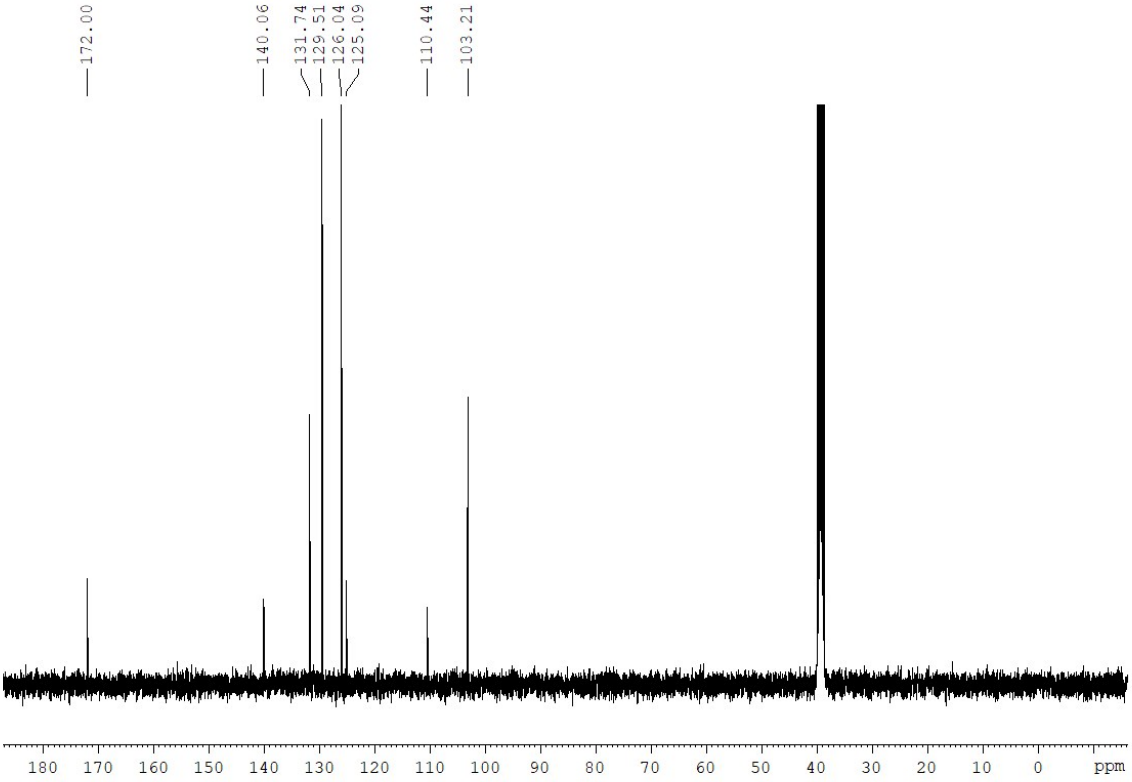
Reference

5 United Nations. *Recommendations on the Transport of Dangerous Goods Manual of Tests and Criteria*, 5th ed., New York, 2009; p 29.

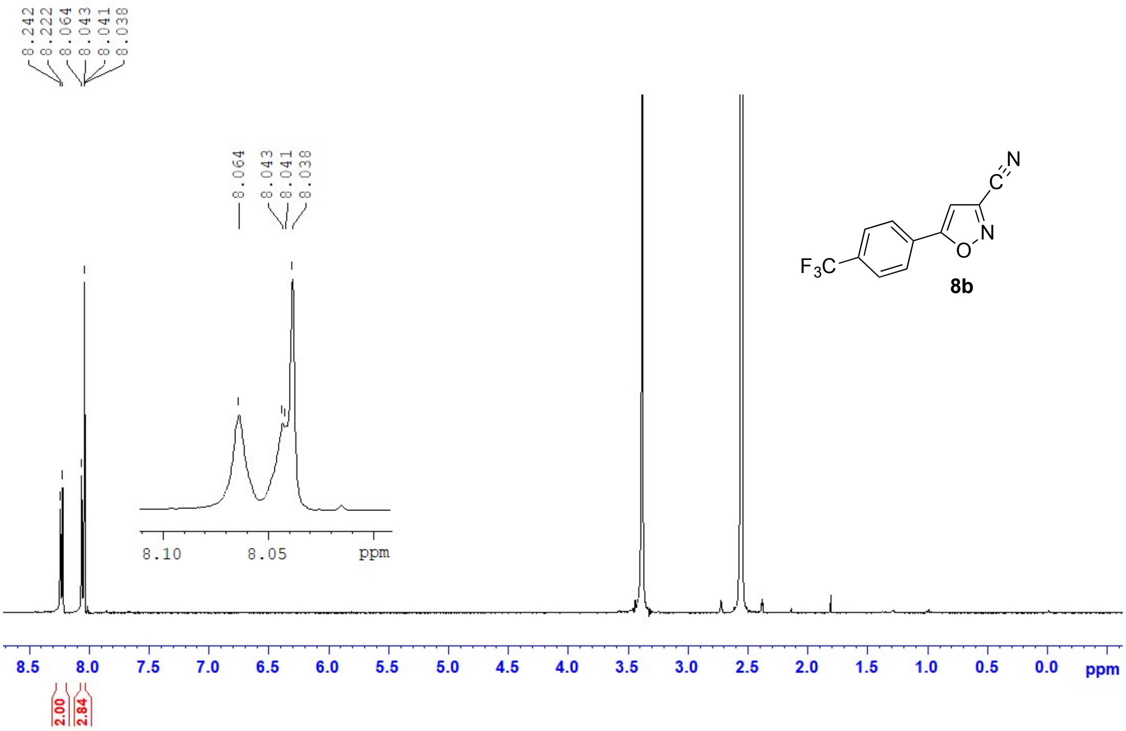
5. Copies of NMR spectra

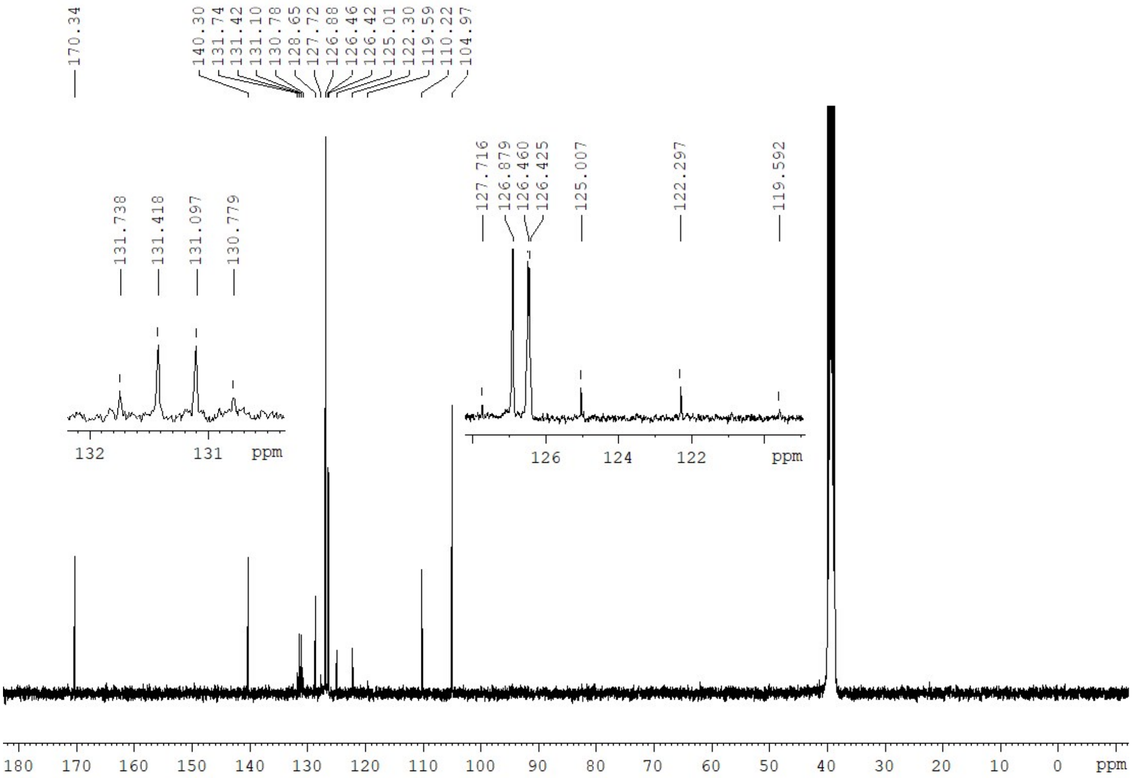
3-cyano-5-phenylisoxazole (8a) in DMSO-d_6



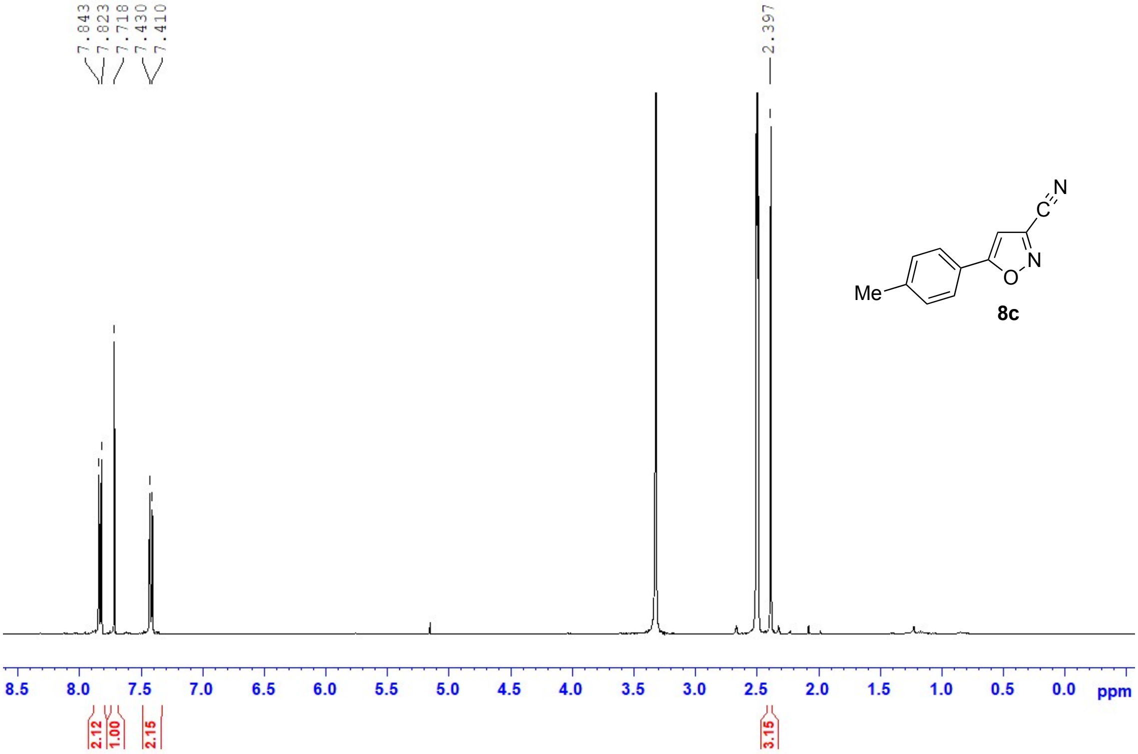


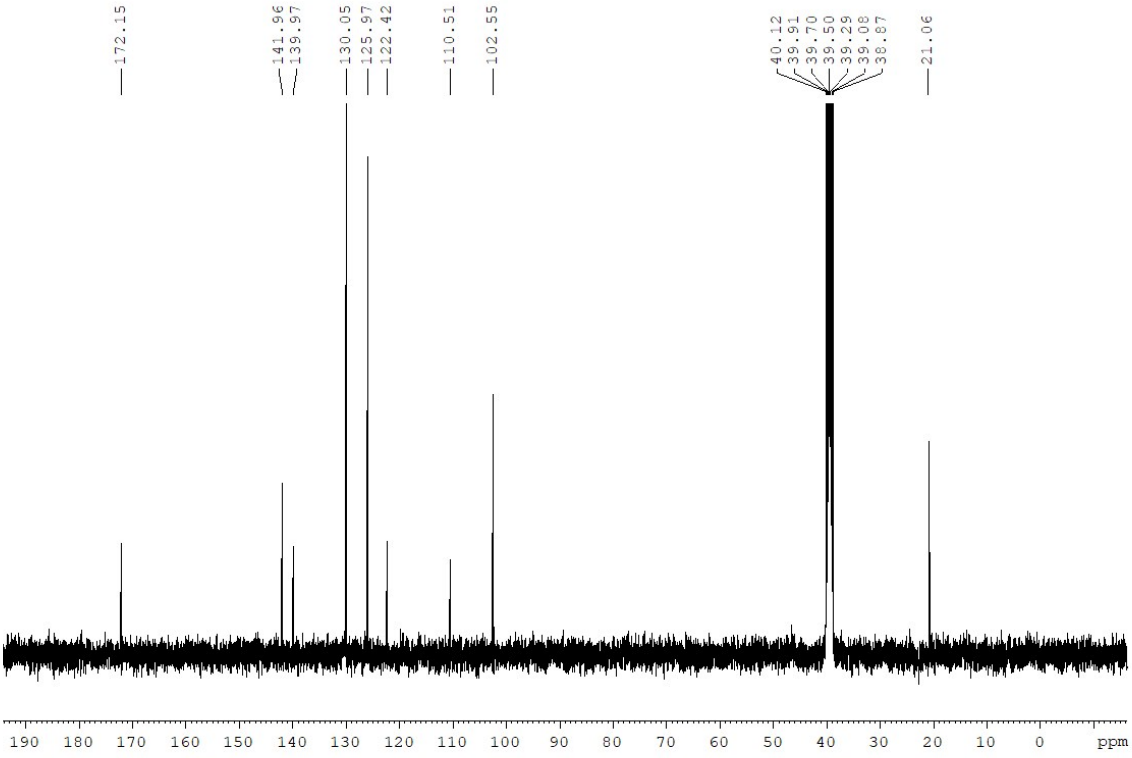
3-Cyano-5-(4-trifluoromethylphenyl)isoxazole (8b) in DMSO-d_6



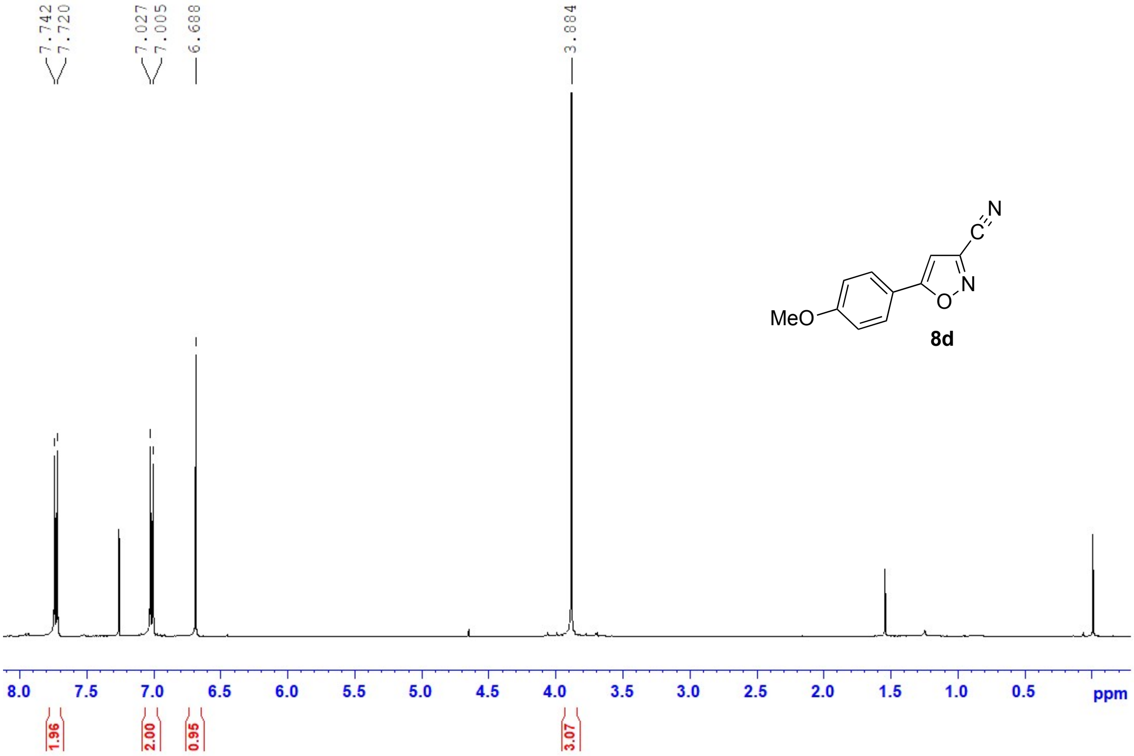


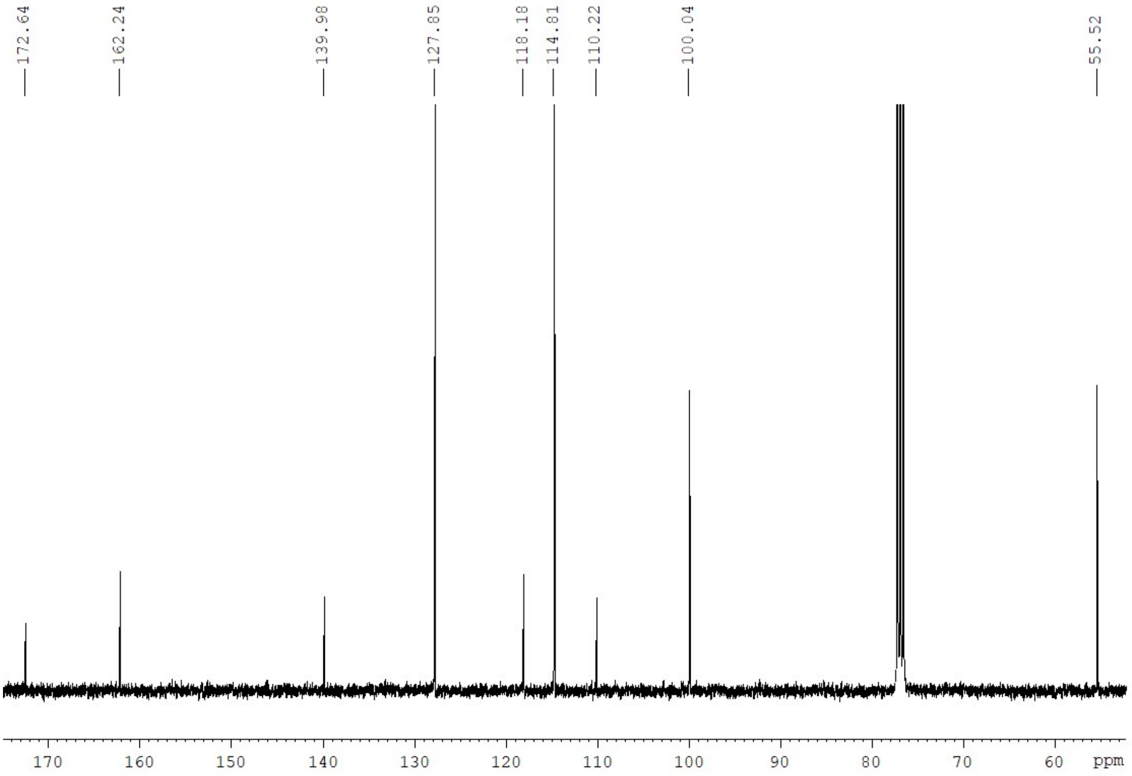
3-Cyano-5-(4-methylphenyl)isoxazole (8c) in DMSO-d_6



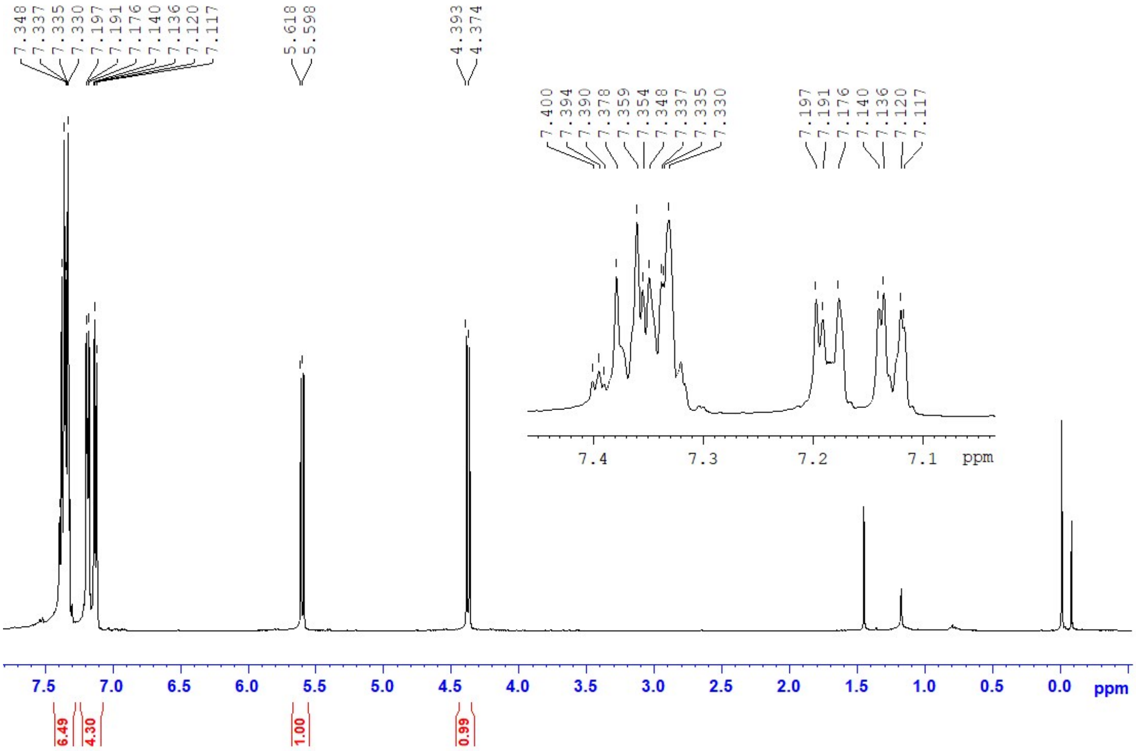


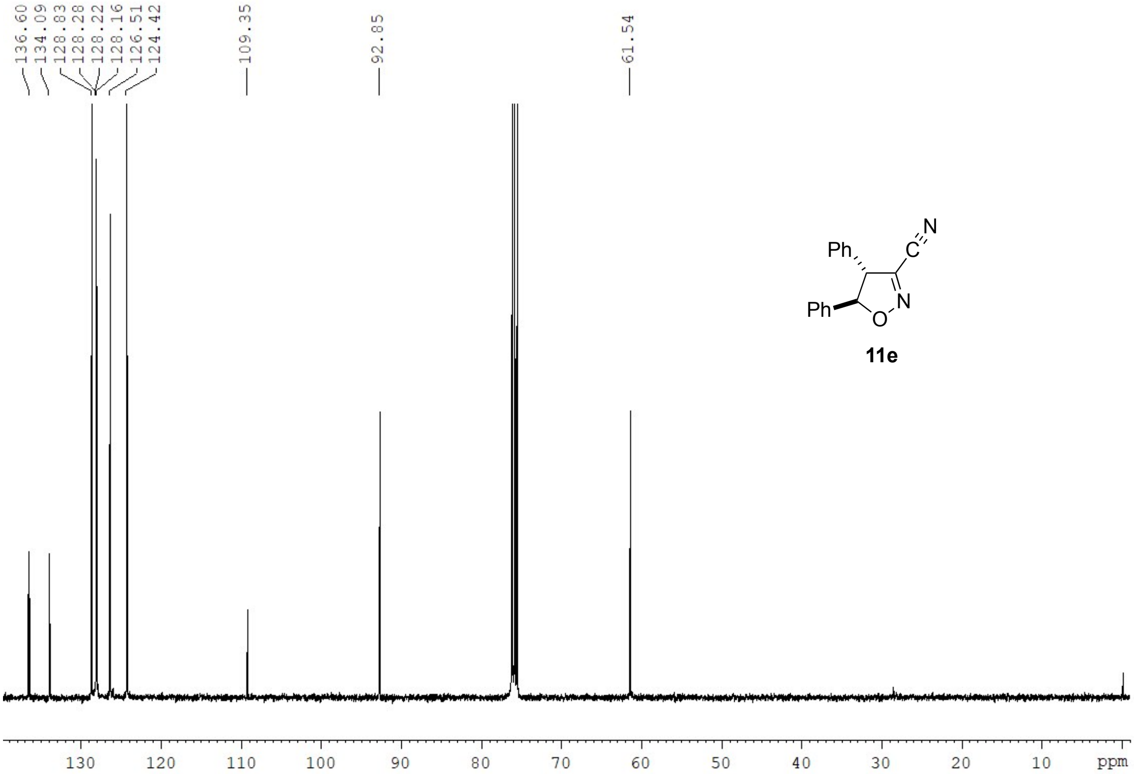
3-Cyano-5-(4-methoxyphenyl)isoxazole (8d) in $CDCl_3$



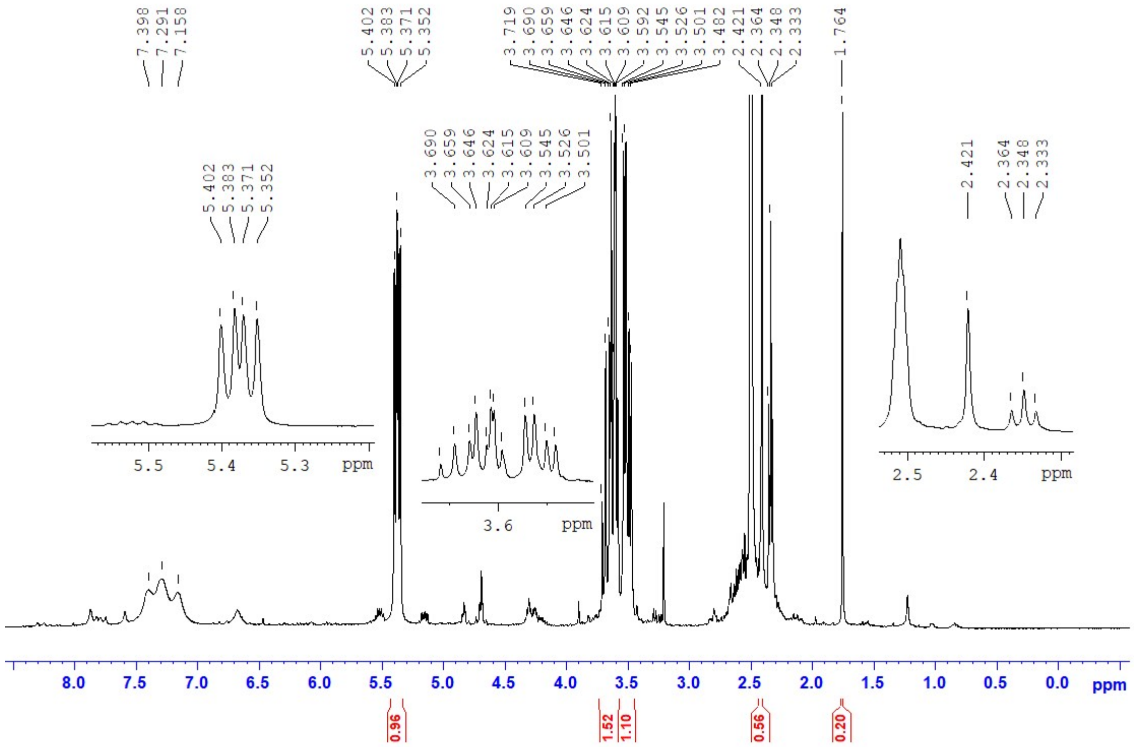


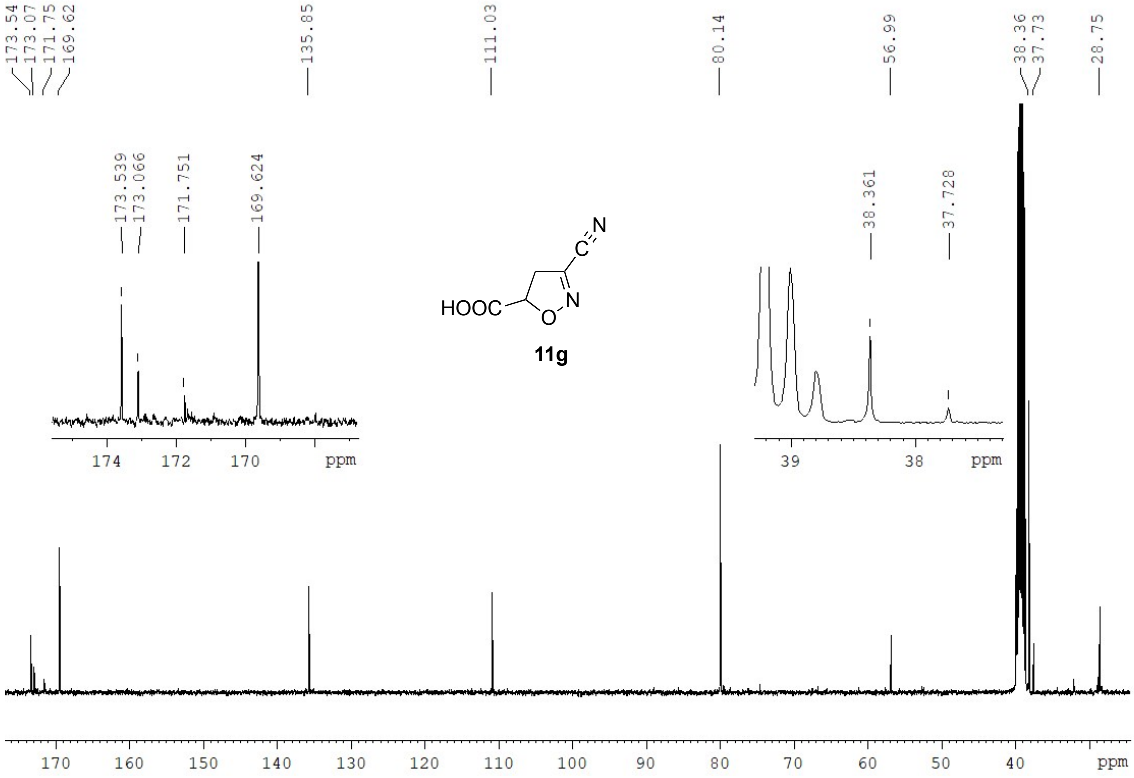
trans-3-Cyano-4,5-diphenyl-2-isoxazoline (11e) in CDCl$_3$





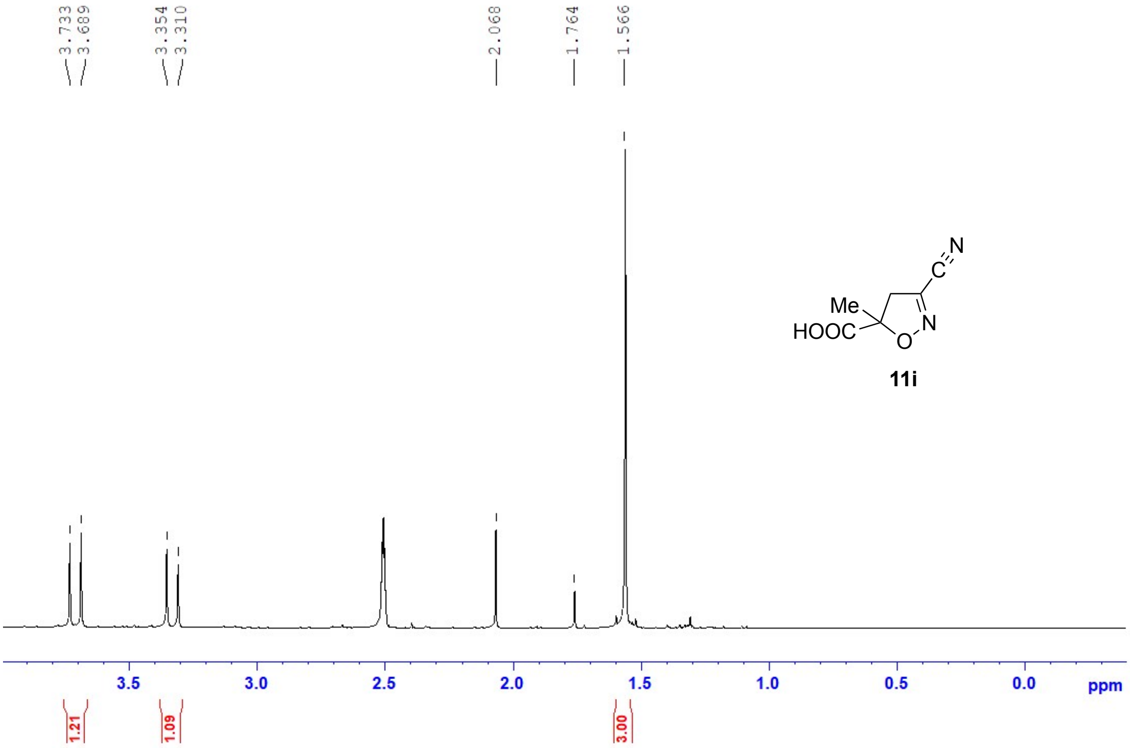
3-Cyano-2-isoxazoline-5-carboxylic acid (11g) in DMSO-d_6





11g

3-Cyano-5-methyl-2-isoxazoline-5-carboxylic acid (11i) in DMSO-d_6



11i