

Solvent-Free synthesis of 3,5-Isoxazoles via 1,3-Dipolar Cycloaddition of Terminal Alkynes and Hydroxyimidoyl chlorides over Cu/Al₂O₃ Surface under Ball-Milling Conditions.

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Supporting Information

This supporting Information contains a total of 62 pages

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General Considerations, Materials, and Instrumentations

General Considerations: Solids were directly weighed open-air and added directly into the reaction vial. Liquids were directly transferred from the vial containing the reagent using an automatic pipette with a plastic tip of appropriate size or a plastic syringe with a stainless-steel needle. Flash chromatography was carried out using 40-63 μ m silica gel (Silicycle).

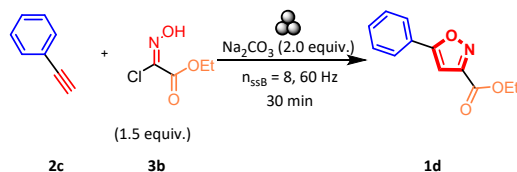
Materials: Distilled water was obtained from an in-house water distillery. All other reagents and chemicals were purchased from Sigma-Aldrich or AK Scientifics and used without further purification.

Instrumentation: ^1H (500MHz) and ^{13}C (125MHz) NMR spectra were recorded in CDCl_3 or $\text{DMSO-}d^6$ using a Varian Inova 500MHz spectrometer. Spectra were referenced to the residual solvent signal or the TMS signal. Spectral features are tabulated in the following order (Note: Spectral features are reported in the following format): chemical shift (δ , ppm); multiplicity (s-singlet, d-doublet, t-triplet, q-quartet, dd-doublet of doublets, m-multiplet), dt-double of triplets, ddd-doublet of doublets of doublets; coupling constants (J, Hz); number of protons. High resolution mass spectra (HRMS) were obtained using a LTQ Orbitrap Velos ETD (positive and negative mode) mass spectrometer. Liquid Chromatography-Inductively Coupled Plasma Mass Spectrometry (LC-ICP-MS) was obtained using an Agilent 7500ce with a MicroMist glass concentric nebulizer and a Quadrupole MS with a sensitivity range of 10^{-12} - 10^{-3} g/mL. The reactions were performed using a Fritsch Planetary Micro Mill model "Pulverisette 7" housing two stainless-steel (SS) cups containing eight stainless-steel (SS) balls each and sealed by a stainless-steel (SS) lid fitted with a Teflon gasket. The reported melting points are uncorrected and were measured using a Stuart SMP3 melting point apparatus. Fourier transform infrared (FT-IR) were acquired using a Thermo ScientificTM NicoletTM iS5 FTIR Spectrometer, ranging from 4000 to 400 cm^{-1} . Spectra were collected using 64 scans, and the data was processed using the Spectrum One software. X-ray photoelectron microscopy (XPS) measurements were carried out at the McGill Institute for Advance Materials with a Thermo-Scientific K-Alpha equipped with a 180° double focusing hemispherical analyzer with a 128-channel detector. MALDITOF-MS was obtained using an Autoflex III Smart Beam (from BRUKER) equipped with a laser Nd-YAG UV at 355 nm and an acceleration voltage at 20 KV

Abbreviations: Hexanes (Hex), Ethyl Acetate (EtOAc), Dichloromethane (DCM), 1,3,5-trimethoxybenzene (TMB), Dimethylsulfoxide (DMSO), Stainless Steel (SS), Melting point (MP), Ratio to front (R_f).

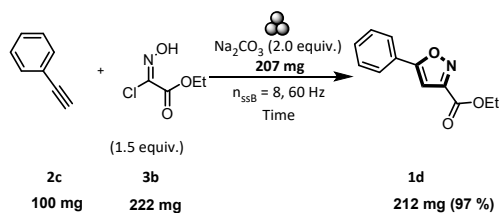
Procedure S1 (PS1): Solvent-Free and catalyst-free synthesis of 3,5-isoxazoles *via* 1,3-dipolar cycloaddition from terminal alkynes and hydroxyimidoil chlorides under ball-milling conditions.

Procedure Example:



Synthesis of ethyl 5-phenylisoxazole-3-carboxylate (1d): To a clean and dried stainless-steel (SS) planetary milling jar (approximately 50 mL capacity) with 8 SS balls (10 mm of diameter), it was weighed **3b** (0.222 g, 1.47 mmol, 1.5 equivalents.) and Na₂CO₃ (0.207 g, 1.95 mmol, 2.0 equivalents.). Then, phenylacetylene (**2c**) (108 μL, 0.979 mmol, 1.0 equivalents.) was added *via* micropipette. Once all reagents were introduced on the planetary milling jar, the milling jar was tightly sealed, and the mixture was milled for 30 minutes at 60 Hz. After 30 min, the jar was cooled at room temperature, and the reaction mixture was carefully transferred to a separatory funnel, washed with EtOAc (2x10mL) and a saturated aqueous solution of NaCl (2x10mL). The organic layer was collected, dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. **1d** was isolated from the crude mixture in a silica column using Hex: EtOAc (9:1) as eluent. Compound **1d** was isolated in 97 % yield (207.2 mg) as a white solid. **MP:** 54-57 °C, **R_f:** 0.38 **¹H NMR** (500 MHz, DMSO-*d*⁶) δ 7.99 – 7.95 (m, 1H), 7.59 – 7.54 (m, 1H), 7.50 (s, 1H), 4.40 (q, *J* = 7.11 Hz, 1H), 1.35 (t, *J* = 7.12 Hz, 2H). **¹³C NMR** (125 MHz, DMSO-*d*⁶) δ 171.5, 159.8, 157.3, 131.5, 129.8, 126.5, 126.3, 101.2, 62.4, 14.4. **HRMS:** *m/z* calculated for C₁₂H₁₁NO₃ [M+H]⁺: 218.0817 found 218.0813.

Atom Economy and E-Factor Calculations for the synthesis of 3,5-isoxazole **1d**:



E-Factor

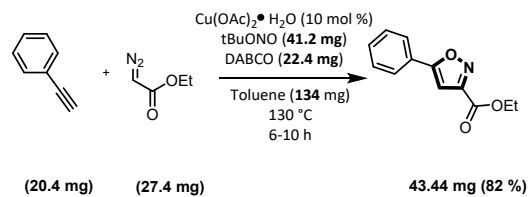
Total mass of reactants: 100 mg + 222 mg + 207 mg = 529 mg

Product mass: 212 mg

Waste: 529 mg – 212 mg = 317 mg

E-Factor = *Waste / Product mass* = 317 mg / 212 mg = **1.49**

E-factor calculation for previous report: X. Di Wang, L. H. Zhu, P. Liu, X. Y. Wang, H. Y. Yuan and Y. L. Zhao, *J. Org. Chem.*, 2019, **84**, 16214.



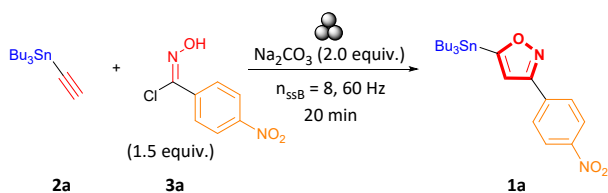
E-Factor

Total mass of reactants: 20.4 mg + 27.4 mg + 41.2 mg + 22.4 mg + 134 mg = 245.4 mg (Assuming 90 % recovery of toluene from distillation).

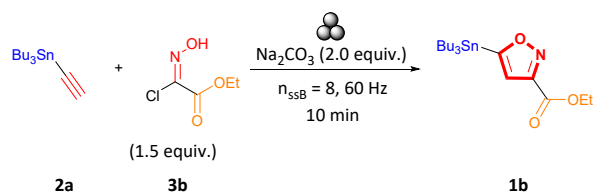
Product mass: 43.44 mg

Waste: 245.4 mg – 43.44 mg = 201.96 mg

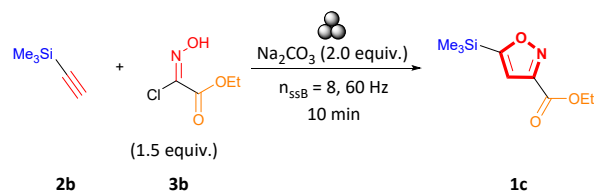
E-Factor = $\text{Waste} / \text{Product mass} = 201.96 \text{ mg} / 43.44 \text{ mg} = 4.65$



Synthesis of 3-(4-nitrophenyl)-5-(tributylstannyl)isoxazole (1a): Isoxazole **1a** was synthesized according to procedure (PS1), but the reagents were milled for 20 minutes rather than 60 minutes: Compound **1a** was isolated in a silica column using CHCl₃:Hexanes (9:1) as eluent. **1a** was isolated in 57 % yield (86.55 mg) as a colourless oil. **R_f**: 0.72 **¹H NMR** (500 MHz, CDCl₃) δ 8.30 (d, *J* = 8.82 Hz, 2H), 8.01 (d, *J* = 8.83 Hz, 2H), 6.75 (s, 1H), 1.65 – 1.54 (m, 6H), 1.36 (sextet, *J* = 7.33 Hz, 6H), 1.25 – 1.19 (m, 5H), 0.91 (t, *J* = 7.33 Hz, 9H). **¹³C NMR** (125 MHz, CDCl₃) δ 181.9, 158.5, 148.4, 135.9, 127.9, 124.1, 112.0, 28.8, 27.1, 13.6, 10.6. **HRMS:** *m/z* calculated for C₂₁H₃₂N₂O₃Sn [M+H]⁺: 481.1513 found 481.1509.



Synthesis of ethyl 5-(tributylstannyl)isoxazole-3-carboxylate (1b): Isoxazole **1b** was synthesized according to procedure (PS1), but the reagents were milled for 10 minutes rather than 60 minutes: Compound **1b** was isolated in a silica column using Hex:EtOAc (9:1) as eluent. **1b** was isolated in 72 % yield (98.18 mg) as a colourless oil. **R_f**: 0.40 **¹H NMR** (500 MHz, CDCl₃) δ 6.80 (s, 1H), 4.44 (q, *J* = 7.14 Hz, 2H), 1.60 – 1.52 (m, 6H), 1.42 (t, *J* = 7.15 Hz, 3H), 1.33 (sextet, 7.3 Hz, 6H), 1.22 – 1.15 (m, 6H), 0.89 (t, *J* = 7.33 Hz, 9H). **¹³C NMR** (125 MHz, CDCl₃) δ 182.4, 160.9, 154.4, 114.9, 61.9, 28.7, 27.1, 14.1, 13.5, 10.6. **HRMS:** *m/z* calculated for C₁₈H₃₃NO₃Sn [M+H]⁺: 432.1561 found 432.1564.

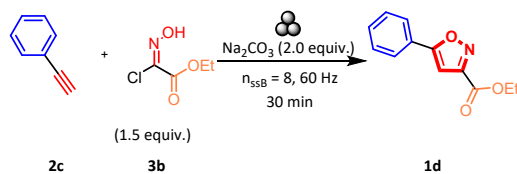


Synthesis of ethyl 5-(trimethylsilyl)isoxazole-3-carboxylate (1c): Isoxazole **1c** was synthesized according to procedure (PS1), but the reagents were milled for 10 minutes rather than 60 minutes: Compound **1c** was isolated in a silica column using Hex:EtOAc (9:1) as eluent. **1c** was isolated in 57 % (121.6 mg) yield as a white solid. **R_f**: 0.56 **¹H NMR** (500 MHz, DMSO-*d*⁶) δ 7.12 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.34 (s, 9H). **¹³C NMR** (125 MHz, DMSO-*d*⁶) δ 180.9, 160.1, 155.1, 113.9, 62.1, 14.4, -1.9. **HRMS:** *m/z* calculated for C₉H₁₅NO₃Si [M+H]⁺: 214.0899 found 214.0896.

Milling Time Optimization: Solvent-Free and catalyst-free synthesis of 3,5-isoxazoles via 1,3-dipolar cycloaddition from terminal alkynes and hydroxyimidoil chlorides under ball-milling conditions.

Prior to isolation of 3,5-isoxazoles (**1a-d**) the reactions between the corresponding terminal alkyne (**2a-c**) and hydroxyimidoil chloride (**3a-b**) were optimized in a 20 mg scale reaction to determine the proper milling time. The yield of the 3,5-isoxazoles was quantified by ¹H NMR and using TMB as an internal standard.

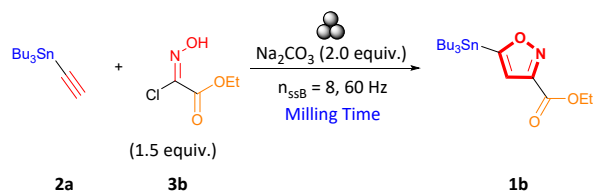
Procedure example for yield determination:



Milling time optimization for the synthesis of ethyl 5-phenylisoxazole-3-carboxylate (1d**):** To a clean and dried stainless-steel (**SS**) planetary milling jar (approximately 50 mL capacity) with 8 **SS** balls (10 mm of diameter), it was weighed **3b** (0.050 g, 0.330 mmol, 1.5 equivalents.) and Na₂CO₃ (0.047 g, 0.440 mmol, 2.0 equivalents.). Then, ethynylbenzene (**2c**) (24 μL, 0.220 mmol, 1.0 equivalents.) was added *via* an automated pipette. Once all reagents were introduced on the planetary milling jar, the mixture was milled at a corresponding time at 60 Hz. After the reaction time was accomplished, the jar was cooled at room temperature, and it was added 10-12 mg of TMB to the reaction crude. The reaction mixture was carefully transferred to a separatory funnel, washed with EtOAc (2x10mL) and a saturated aqueous solution of NaCl (2x10mL). The organic layer was collected, dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. The yield of **1d** was obtained by ¹H NMR.

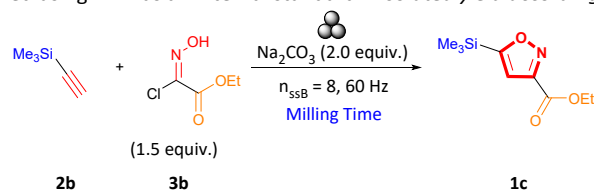
Time (min)	Yield (%) ^a
10	82
20	89
30	95 97 ^b
40	79
50	84
60	37
70	25

^a¹H NMR Yields. ^bIsolated yield according to **PS1**



Milling Time (min)	Yield (%) ^a
10	95 72 ^b
15	81
20	73

Reaction Conditions: 0.166 mmol of **2a**, 0.250 mmol of **3b**, 0.332 mmol of Na_2CO_3 , SS beaker (50 mL capacity), 8 x SS milling balls (10 mm diameter), milling at 60 Hz. ^a $^1\text{H-NMR}$ yields were measured using TMB as an internal standard. ^b Isolated yield according to **PS1**



Milling Time (min)	Yield (%) ^a
10	66 57 ^b
20	65
30	50

Reaction Conditions: 0.204 mmol of **2b**, 0.306 mmol of **3b**, 0.408 mmol of Na_2CO_3 , SS beaker (50 mL capacity), 8 x SS milling balls (10 mm diameter), milling at 60 Hz. ^a $^1\text{H-NMR}$ yields were measured using TMB as an internal standard. ^b Isolated yield according to **PS1**

Procedure S2 (PS2): Preparation of Cu/Al₂O₃ nanocomposites catalyst.

Cu/Al₂O₃ nanocomposite catalyst was synthesized according to the method described by Mukherjee *et al.*¹ with a slight modification. Briefly, in a 1 L round bottom flask equipped with a magnetic stir bar, it was weighted 15 g of neutral alumina and 1 g of CuSO₄ •5H₂O. The reagents were suspended in 30 mL of H₂O, and the mixture was stirred overnight at room temperature. Then, excess water was removed under reduced pressure, and the obtained solid was further dried in a vacuum oven at 100 °C overnight to obtain a light blue solid. ICP-MS analysis determined that the concentration of copper present in the alumina is 21.91 mg/g

Recycled Cu/Al₂O₃ nanocomposites catalyst.

ICP-MS analysis determined that the concentration of copper present in the alumina is 17.75 mg/g (first recycled), 9.02 mg/g (second recycled), and 3.38 mg/g (third recycled).

XPS analysis of Cu/Al₂O₃

XPS results agree with those reported by Mukherjee *et al.*¹ Below is portrayed the XPS analysis obtained for Cu/Al₂O₃.

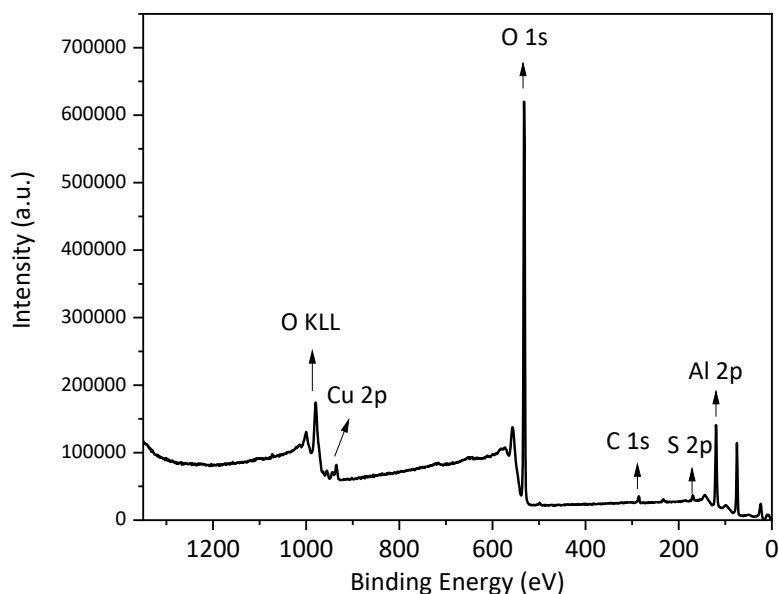


Figure S1: XPS survey spectrum of Cu/Al₂O₃ nanocomposite.

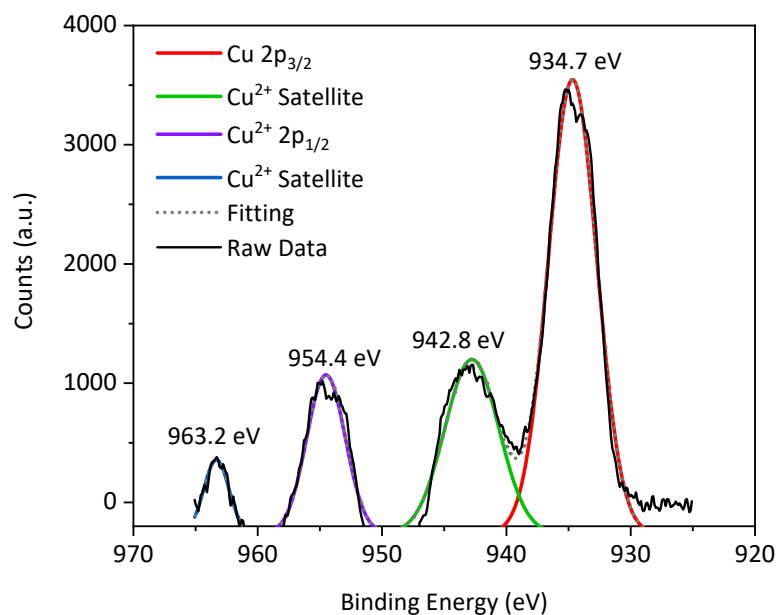


Figure S2: XPS pattern for a fresh sample of Cu/Al₂O₃ catalyst¹

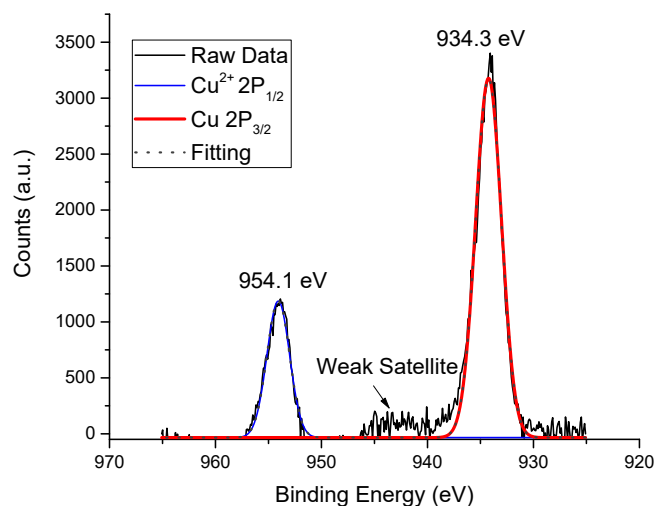


Figure S3: XPS pattern for first recycled of Cu/Al₂O₃ catalyst

¹ N. Mukherjee, S. Ahammed, S. Bhadra and B. C. Ranu, *Green Chem.*, 2013, **15**, 389–397.

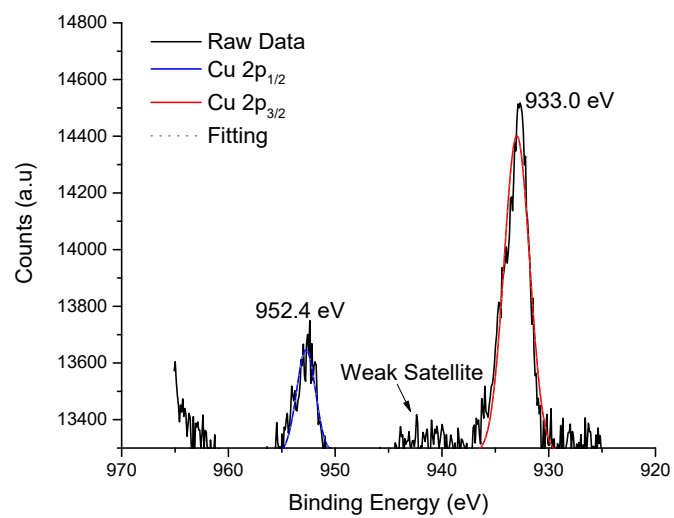
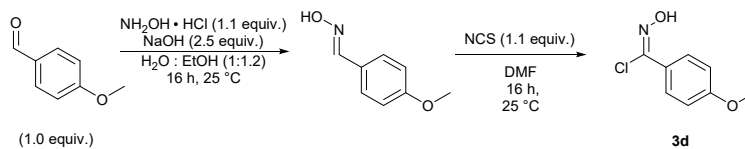


Figure S4: XPS pattern for second recycled of Cu/Al₂O₃ catalyst

Synthesis of (E,Z)-N-hydroxy-4-methoxybenzimidoyl chloride (18d)



Hydroxyimidoyl chloride **3d** was synthesized according to the procedure outline by F. Himo *et al.*² **3d** was obtained in 74 % yield (10.0 g) as a pale yellow solid. ¹H NMR (500 MHz, CDCl₃) δ 8.30 (br s, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 1H), 3.85 (s, 1H).²

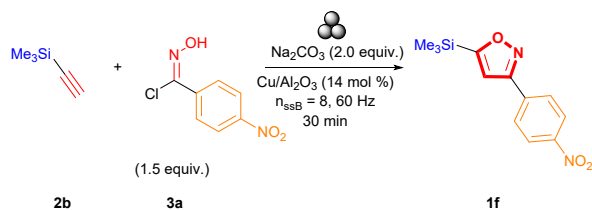
The reported analytical data is in agreement with the reported by E. Azzali *et al.*³

² F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless and V. V. Fokin, *J. Am. Chem. Soc.*, 2005, **127**, 210–216.

3 E. Azzali, D. Machado, A. Kaushik, F. Vacondio, S. Flisi, C. S. Cabassi, G. Lamichhane, M. Viveiros, G. Costantino and M. Pieroni, *J. Med. Chem.*, 2017, **60**, 7108–7122.

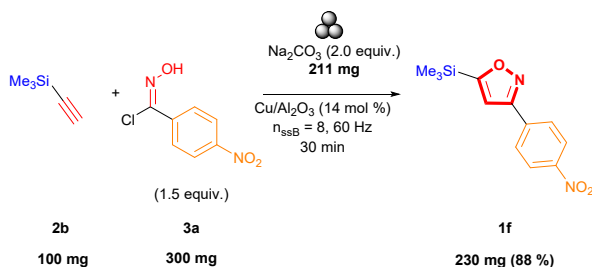
Procedure S3 (PS3): Solvent-Free synthesis of 3,5-isoxazoles via 1,3-dipolar cycloaddition from terminal alkynes and hydroxyimidoil chlorides under Cu/Al₂O₃ surface under ball-milling conditions.

Example:



Synthesis of 3-(4-nitrophenyl)-5-(trimethylsilyl)isoxazole (1f**):** To a clean and dried stainless-steel (**SS**) planetary milling jar (approximately 50 mL capacity) with 8 **SS** balls (10 mm of diameter), it was weighed **3a** (0.300 g, 1.5 mmol, 1.5 equivalents.), Na₂CO₃ (0.211 g, 2.0 mmol, 2.0 equivalents.), and Cu/Al₂O₃ (0.405 g, 0.14 mmol, 14 mol %) . Then, ethynyltrimethylsilane (**2b**) (141 μL, 1.0 mmol, 1.0 equivalents.) was added via an automated pipette. Once all reagents were introduced on the planetary milling jar, the mixture was milled for 30 minutes at 60 Hz. After 30 min, the milling jar was cooled to room temperature, and the Cu/Al₂O₃ was filtered through a sintered funnel and washed with EtOH³. The filtrate was collected, and the excess EtOH was removed under reduced pressure. Compound **1f** was isolated in a silica column using CHCl₃:Hex (99:1) as eluent. Compound **1f** was obtained in 88 % yield (231.2 mg) as a white solid. **MP**: 158-161 °C, **R_f**: 0.86 **¹H NMR** (500 MHz, DMSO-*d*⁶) δ 8.36 (d, *J* = 8.9 Hz, 2H), 8.18 (d, *J* = 8.9 Hz, 2H), 7.50 (s, 1H), 0.38 (s, 9H). **¹³C NMR** (125 MHz, DMSO-*d*⁶) δ 180.1, 159.4, 148.8, 135.2, 128.5, 124.8, 112.5, -1.6. **HRMS**: *m/z* calculated for C₁₂H₁₄N₂O₃Si [M+H]⁺: 263.0852 found 263.0848.

Atom Economy and E-Factor Calculations for the synthesis of 3,5-isoxazole **1f**:



E-Factor

Total mass of reactants: 100 mg + 300 mg + 211 mg = 611 mg (Cu/Al₂O₃ mass is not included in the calculations as the nanocomposite was recycled).

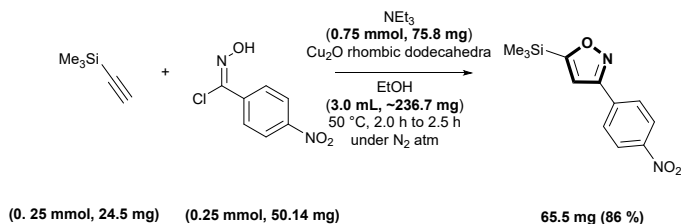
Product mass: 230 mg

Waste: 611 mg – 230 mg = 381 mg

³ **Cu/Al₂O₃ recycling:** The green coloured solid filter (Cu/Al₂O₃) can be recycled by washing with another 20mL portion of EtOH and let to dry under vacuum. The solid is collected and dried in high vacuum at room temperature for another 16 hours.

E-Factor = $Waste / Product\ mass = 381\ mg / 230\ mg = 1.65$

E-factor calculation for previous report: K. Chanda, S. Rej and M. H. Huang, *Nanoscale*, 2013, 5, 12494–12501.



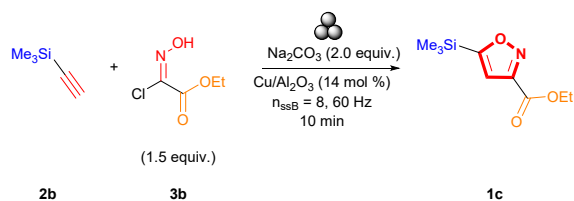
E-Factor

Total mass of reactants: 24.5 mg + 50.14 mg + 75.8 mg + 236.7 mg = 387.14 mg (Assuming 90 % recovery of EtOH from distillation, and Cu₂O mass was not included in the calculations as this was recycled).

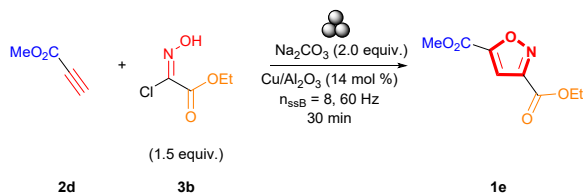
Product mass: 65.5 mg

Waste: 387.14 mg – 65.5 mg = 321.64 mg

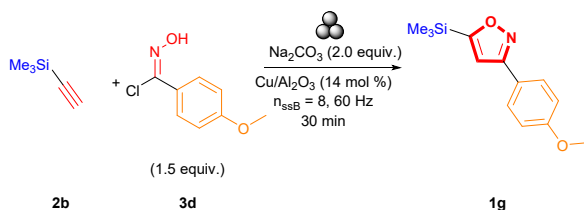
E-Factor = $Waste / Product\ mass = 321.64\ mg / 65.5\ mg = 4.91$



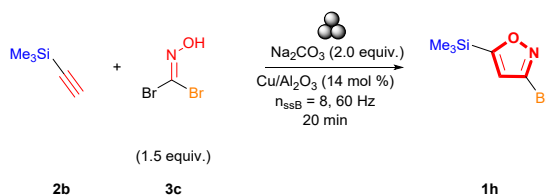
Synthesis of ethyl 5-(trimethylsilyl)isoxazole-3-carboxylate (19i): Isoxazole **19i** was synthesized according to procedure (PS3), but the reagents were milled for 10 minutes rather than 30 minutes. Compound **19i** was isolated in a silica column using Hex:EtOAc (9:1) as eluent. **19i** was isolated in 68 % yield (145.9 mg) as a colourless oil. **R_f**: 0.56 **¹H NMR** (500 MHz, DMSO-*d*⁶) δ 7.12 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.34 (s, 9H). **¹³C NMR** (126 MHz, DMSO-*d*⁶) δ 180.9, 160.1, 155.1, 113.9, 62.1, 14.4, -1.9. **HRMS:** *m/z* calculated for C₉H₁₅NO₃Si [M+H]⁺: 214.0899 found 214.0896.



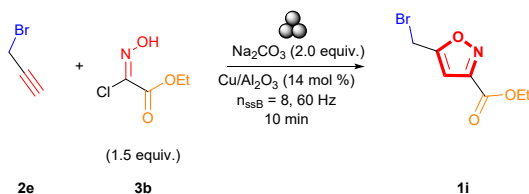
Synthesis of 3-ethyl 5-methyl isoxazole-3,5-dicarboxylate (1e): Isoxazole **1e** was synthesized according to procedure (PS3). Compound **1e** was isolated in a silica column using Hex: EtOAc:DCM (7:2:1) as eluent. **1e** was isolated in 56 % yield (132.4 mg) as a white solid. **MP:** 55-59 °C, **R_f:** 0.54, **¹H NMR** (500 MHz, DMSO-*d*⁶) δ 7.57 (s, 1H), 4.39 (q, *J* = 7.07 Hz, 2H), 3.92 (s, 3H), 1.33 (t, *J* = 7.12 Hz, 3H). **¹³C NMR** (126 MHz, DMSO-*d*⁶) δ 161.8, 158.9, 157.4, 156.5, 109.9, 62.7, 53.6, 14.3. **HRMS:** *m/z* calculated for C₈H₉NO₅ [M+H]⁺: 200.0559 found 200.0555.



Synthesis of 3-(4-methoxyphenyl)-5-(trimethylsilyl)isoxazole (1g): Isoxazole **1g** was synthesized according to procedure (PS3), but the reagents were milled for 10 minutes rather than 30 minutes. Compound **1g** was isolated in a silica column using Hex:EtOAc: Tol (8:1.6:0.4) as eluent. **1g** was isolated in 51 % yield (127 mg) as a colourless oil. **R_f:** 0.51 **¹H NMR** (500 MHz, DMSO-*d*⁶) δ 7.12 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.34 (s, 9H). **¹³C NMR** (125 MHz, DMSO-*d*⁶) δ 178.4, 160.7, 160.4, 128.4, 121.7, 114.2, 110.5, 55.3, -1.8. **HRMS:** *m/z* calculated for C₁₃H₁₇NO₂Si [M+H]⁺: 248.1101 found 248.1101.

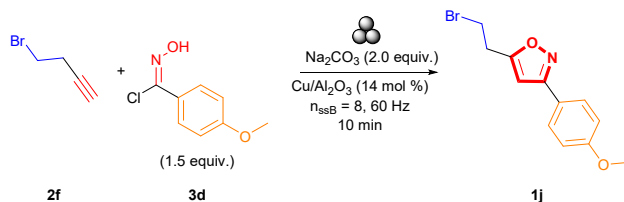


Synthesis of 3-bromo-5-(trimethylsilyl)isoxazole (1h): Isoxazole **1h** was synthesized according to procedure (PS3), but the reagents were milled for 20 minutes rather than 30 minutes. Compound **1h** was isolated in a silica column using Hex: EtOAc (100% Hexanes to 100% EtOAc) as eluent. **1h** was isolated in 70 % yield (149.7 mg) as a yellow solid. **R_f:** 0.37 **¹H NMR** (500 MHz, CDCl₃) δ 6.47 (s, 1H), 0.33 (s, 9H). **¹³C NMR** (125 MHz, CDCl₃) δ 180.9, 139.1 115.9, -2.2. **HRMS:** *m/z* calculated for C₆H₁₀BrNOSi [M+H]⁺: 219.9788 found 219.9792.

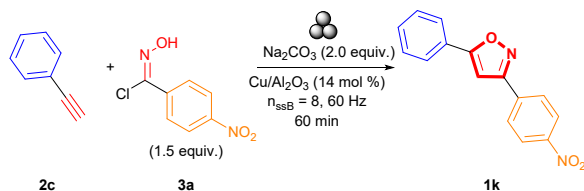


Synthesis of ethyl 5-(bromomethyl)isoxazole-3-carboxylate (1i): Isoxazole **1i** was synthesized according to procedure (PS3), but the reagents were milled for 10 minutes rather than 30 minutes. Compound **1i** was isolated in a silica column using Hex:DCM:EtOAc:Acetone (7:2:0.8:0.2) as eluent. **1i** was isolated in 71 % yield (139.6 mg) as a yellow solid. **MP:** 106-108 °C, **R_f:** 0.55 **¹H NMR** (500 MHz, DMSO-*d*⁶) δ 6.97 (s, 1H),

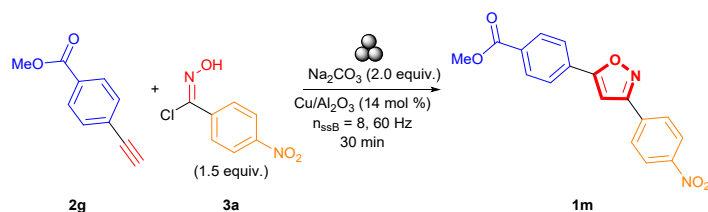
4.87 (s, 1H), 4.35 (q, $J = 7.11$ Hz, 1H), 1.29 (t, $J = 7.11$ Hz, 1H). $^{13}\text{C NMR}$ (125 MHz, $\text{DMSO-}d^6$) δ 170.6, 159.4, 156.9, 104.9, 62.4, 19.7, 14.4. **HRMS:** m/z calculated for $\text{C}_7\text{H}_8\text{BrNO}_3$ $[\text{M}+\text{H}]^+$: 233.976 found 233.9762.



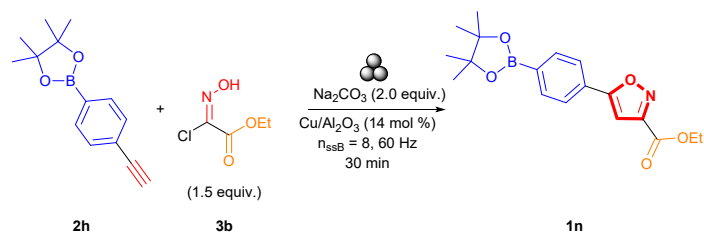
Synthesis of 5-(2-bromoethyl)-3-(4-methoxyphenyl)isoxazole (1j): Isoxazole **1j** was synthesized according to procedure (PS3), but the reagents were milled for 10 minutes rather than 30 minutes. Compound **1j** was isolated in a silica column using Hex:Et₂O:tol (8:1.6:0.4) as eluent. **1j** was isolated in 80 % yield (169 mg) as a white solid. **MP:** 75.2-76.4 °C, **R_f:** 0.150 $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.73 (d, $J = 8.9$ Hz, 2H), 6.97 (d, $J = 8.9$ Hz, 2H), 6.41 (s, 1H), 3.85 (s, 2H), 3.67 (t, $J = 7.0$ Hz, 2H), 3.37 (t, $J = 7.0$ Hz, 2H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 169.71, 162.09, 160.98, 128.16, 121.47, 114.28, 100.16, 55.34, 30.40, 27.93 **HRMS:** m/z calculated for $\text{C}_{12}\text{H}_{12}\text{BrNO}_2$ $[\text{M}+\text{H}]^+$: 282.0124 found 282.0127.



Synthesis of 3-(4-nitrophenyl)-5-phenylisoxazole (1k): Isoxazole **1k** was synthesized according to procedure (PS3), but the reagents were milled for 60 minutes rather than 30 minutes. Compound **1k** was isolated by recrystallizing the reaction crude in EtOH. **1k** was isolated in 38 % yield (98.6 mg) as a yellow solid. **MP:** 218-220 °C, **R_f:** 0.93 $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d^6$) δ 8.40 (d, $J = 8.77$ Hz, 2H), 8.20 (d, $J = 8.78$ Hz, 2H), 7.96 – 7.89 (m, 2H), 7.79 (s, 1H), 7.61 – 7.54 (m, 3H). $^{13}\text{C NMR}$ (125 MHz, $\text{DMSO-}d^6$) δ 170.9, 161.7, 148.9, 135.0, 131.3, 129.9, 128.3, 126.9, 126.1, 124.9, 99.6. **HRMS:** m/z calculated for $\text{C}_{15}\text{H}_{10}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 267.0770 found 267.0765.

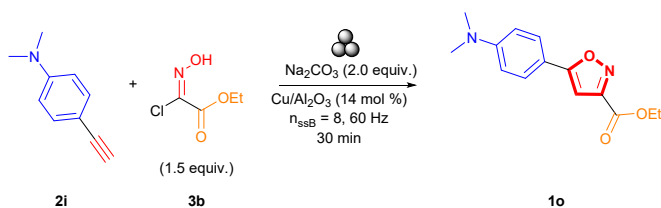


Synthesis of methyl 4-(3-(4-nitrophenyl)isoxazol-5-yl)benzoate (1m): Isoxazole **1m** was synthesized according to procedure (PS3). Compound **1m** was isolated in a silica column using DCM:Hex (9:1) as eluent. **1m** was isolated in 41 % yield (83.2 mg) as a white solid. **MP:** 229-230 °C, **R_f:** 0.93 $^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d^6$) δ 8.42 (d, $J = 8.92$ Hz, 1H), 8.22 (d, $J = 8.92$ Hz, 1H), 8.15 (d, $J = 8.55$ Hz, 1H), 8.09 (d, $J = 8.59$ Hz, 1H), 7.98 (s, 1H), 3.90 (s, 1H). $^{13}\text{C NMR}$ (125 MHz, $\text{DMSO-}d^6$) δ 169.8, 165.9, 161.9, 148.9, 134.8, 131.6, 130.8, 130.6, 128.4, 126.3, 124.9, 101.3, 52.9. **HRMS:** m/z calculated for $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 325.0824 found 325.0819.



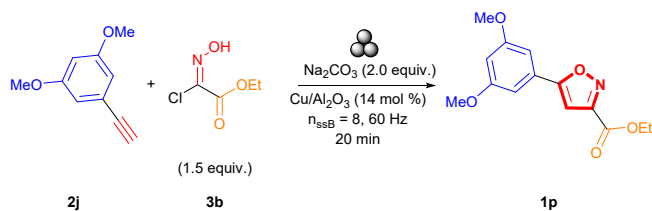
Synthesis of 3-(4-nitrophenyl)-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoxazole (1n):

Isoxazole **1n** was synthesized according to procedure (PS3). Compound **1n** was isolated in a by recrystallizing the reaction crude in Hexanes. **1n** was isolated in 70 % yield (107.6 mg) as a yellow solid. **MP:** 116-118 °C, **R_f:** 0.57 **¹H NMR** (500 MHz, CDCl₃) δ 7.91 (d, *J* = 7.90 Hz, 2H), 7.80 (d, *J* = 7.75 Hz, 2H), 6.97 (s, 1H), 4.47 (q, *J* = 7.13 Hz, 2H), 1.44 (t, *J* = 7.15 Hz, 3H), 1.36 (s, 12H). **¹³C NMR** (125 MHz, CDCl₃) δ 171.6, 159.9, 156.9, 135.4, 128.7, 124.9, 100.5, 84.2, 62.2, 24.9, 14.2. **HRMS:** *m/z* calculated for C₁₈H₂₂BNO₅ [M+H]⁺: 343.1700 found 343.1705.



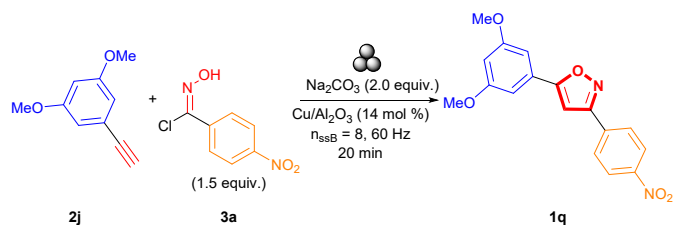
Synthesis of ethyl 5-(4-(dimethylamino)phenyl)isoxazole-3-carboxylate (1o):

Isoxazole **1o** was synthesized according to procedure (PS3). Compound **1o** was isolated in a silica column using Hex: EtOAc: DCM (7:2:1) as eluent. **1o** was isolated in 45 % yield (81.4 mg) as a brown solid. **MP:** 108-111 °C, **R_f:** 0.91 **¹H-NMR** (500 MHz, CDCl₃) δ 7.65 (d, *J* = 8.85 Hz, 2H), 6.72 (d, *J* = 8.87 Hz, 2H), 6.69 (s, 1H), 4.45 (q, *J* = 7.12 Hz, 2H), 3.03 (s, 6H), 1.43 (t, *J* = 7.13 Hz, 3H). **¹³C NMR** (125 MHz, CDCl₃) δ 172.5, 160.4, 156.7, 151.6, 127.2, 114.5, 111.9, 97.0, 62.0, 40.1, 14.1. **HRMS:** *m/z* calculated for C₁₁H₁₀N₂O₃ [M+H]⁺: 219.0764 found 219.0768.

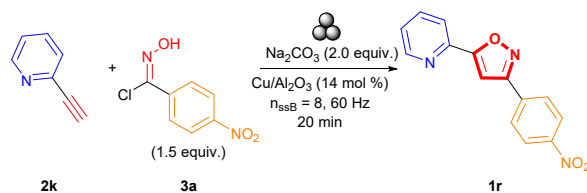


Synthesis of ethyl 5-(3,5-dimethoxyphenyl)isoxazole-3-carboxylate (1p):

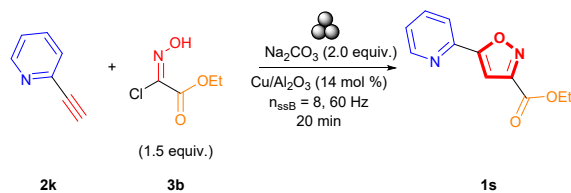
Isoxazole **1p** was synthesized according to procedure (PS3), but the reagents were milled for 20 minutes rather than 30 minutes. Compound **1p** was isolated by recrystallizing the reaction crude in Hexanes. **1p** was isolated in 71 % (121 mg) yield as a yellow solid. **MP:** 95.4-96.8 °C, **R_f:** 0.15 **¹H NMR** (500 MHz, DMSO-*d*⁶) δ 7.56 (s, 1H), 7.09 (d, *J* = 2.3 Hz, 2H), 6.64 (t, *J* = 2.2 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 6H), 1.33 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (125 MHz, DMSO-*d*⁶) δ 171.4, 161.5, 159.8, 157.3, 128.1, 104.1, 103.6, 101.8, 62.35, 56.05, 14.4. **HRMS:** *m/z* calculated for C₁₄H₁₅NO₅ [M+H]⁺: 278.1023 found 278.1024.



Synthesis of 5-(3,5-dimethoxyphenyl)-3-(4-nitrophenyl)isoxazole (1q): Isoxazole **1q** was synthesized according to procedure (PS3), but the reagents were milled for 20 minutes rather than 30 minutes. Compound **1q** was isolated by recrystallizing the reaction crude in Acetone:H₂O. **1q** was isolated in 76 % (152 mg) yield as a white solid. **MP:** 191-194 °C, **R_f:** 0.86 **¹H NMR** (500 MHz, DMSO-*d*⁶) δ 8.40 (d, *J* = 8.84 Hz, 2H), 8.17 (d, *J* = 8.87 Hz, 2H), 7.82 (s, 1H), 7.06 (d, *J* = 2.23 Hz, 2H), 6.66 (t, *J* = 2.21 Hz, 1H), 3.83 (s, 6H). **¹³C NMR** (125 MHz, DMSO-*d*⁶) δ 170.8, 161.6, 161.5, 148.9, 135.0, 128.6, 128.3, 124.9, 104.0, 103.2, 100.1, 56.0. **HRMS:** *m/z* calculated for C₁₇H₁₄N₂O₅ [M+H]⁺: 327.0975 found 327.0975.



Synthesis of 3-(4-nitrophenyl)-5-(pyridin-2-yl)isoxazole (1r): Isoxazole **1r** was synthesized according to procedure (PS3), but the reagents were milled for 20 minutes rather than 30 minutes. Compound **1r** was isolated in a silica column using CHCl₃ as eluent. **1r** was isolated in 16 % yield (43.8 mg) as a yellow solid. **MP:** 225-228 °C, **R_f:** 0.34 **¹H NMR** (500 MHz, DMSO-*d*⁶) δ 8.78 – 8.75 (m, 1H), 8.39 (d, *J* = 8.89 Hz, 2H), 8.27 (d, *J* = 8.89 Hz, 2H), 8.06 – 7.99 (m, 2H), 7.88 (s, 1H), 7.58 – 7.53 (m, 1H). **¹³C NMR** (125 MHz, DMSO-*d*⁶) δ 170.6, 161.8, 150.8, 149.0, 145.8, 138., 134.8, 128.5, 125.9, 124.8, 121.6, 101.8. **HRMS:** *m/z* calculated for C₁₄H₉N₃O₃ [M+H]⁺: 268.0722 found 268.0719.

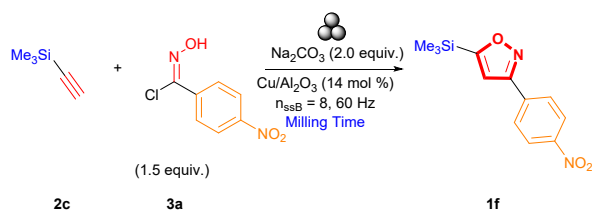


Synthesis of ethyl 5-(pyridin-2-yl)isoxazole-3-carboxylate (1s): Isoxazole **1s** was synthesized according to procedure (PS3), but the reagents were milled for 20 minutes rather than 30 minutes. Compound **1s** was isolated in silica column using EtOAc:DCM:Hex (5:2:1) as eluent. **1s** was isolated in 42 % yield (88.3 mg) as a brown oil. **R_f:** 0.82 **¹H NMR** (500 MHz, DMSO-*d*⁶) δ 8.75 (d, *J* = 4.7 Hz, 1H), 8.08 (d, *J* = 7.9 Hz, 1H), 8.03 (td, *J* = 7.7, 1.7 Hz, 1H), 7.56 (ddd, *J* = 7.4, 4.8, 1.1 Hz, 1H), 7.47 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (125 MHz, DMSO-*d*⁶) δ 170.9, 159.6, 157.3, 150.8, 145.3, 138.3, 126.0, 122.0, 103.2, 62.5, 14.4. **HRMS:** *m/z* calculated for C₁₄H₁₆N₂O₃ [M+H]⁺: 261.1234 found 261.1233.

Milling Time Optimization for the Solvent-Free synthesis of 3,5-isoxazoles *via* 1,3-dipolar cycloaddition from terminal alkynes and hydroxyimidoil chlorides under Cu/Al₂O₃ surface under ball-milling conditions.

Before isolation of 3,5-isoxazoles (**1c,1e-s**), the corresponding terminal alkyne and hydroxyimidoil chloride reactions were optimized in a 20 mg scale reaction to determine the proper milling time. The yield of the 3,5-isoxazoles was quantified by ¹H NMR and using TMB as an internal standard.

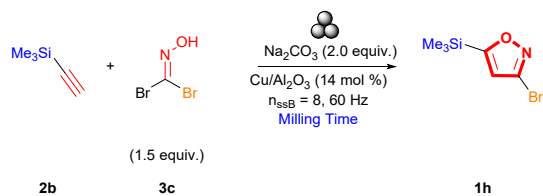
Example:



Milling time optimization for the synthesis of 3-(4-nitrophenyl)-5-(trimethylsilyl)isoxazole (1f**):** To a clean and dried stainless-steel (**SS**) planetary milling jar (approximately 50 mL capacity) with 8 **SS** balls (10 mm of diameter), it was weighed **3a** (0.050 g, 0.330 mmol, 1.5 equivalents.), Na₂CO₃ (0.047 g, 0.440 mmol, 2.0 equivalents.), and Cu/Al₂O₃ (89.1 mg, 0.031 mmol, 14 mol %). Then, ethynylbenzene (**2c**) (24 μL, 0.220 mmol, 1.0 equivalents.) was added *via* micropipette. Once all reagents were introduced on the planetary milling jar, the mixture was milled at a corresponding time at 60 Hz. After the reaction time was accomplished, the jar was cooled at room temperature, and it was added 10-12 mg of TMB to the reaction crude. Then the Cu/Al₂O₃ was filtered through a sintered funnel and washed with EtOH. The filtrate was collected, and the excess EtOH was removed under reduced pressure. The yield of **1f** was calculated by ¹H NMR using the signal at 7.50 ppm as a reference signal.

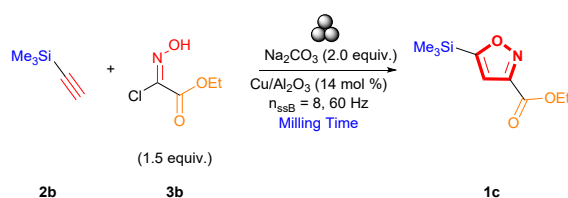
Milling Time (min)	Yield (%) ^a
10	38
20	32
30	92 88 ^b

^a¹H NMR Yields, ^b Isolated yield according to **PS3**



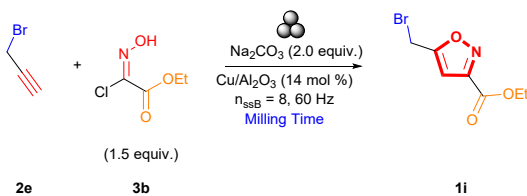
Milling Time (min)	Yield (%) ^a
20	20
30	73 70 ^b

Reaction Conditions: 0.204 mmol of **2b**, 0.305 mmol of **3c**, 0.406 mmol of Na₂CO₃, 0.0285 mmol of Cu/Al₂O₃, SS beaker (50 mL capacity), 8 x SS milling balls (10 mm diameter), and milling at 60 Hz. ^a ¹H-NMR yields were measured using TMB as an internal standard. ^b Isolated yield according to **PS3**



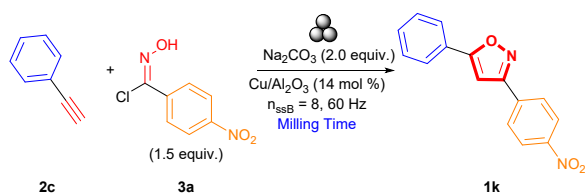
Milling Time (min)	Yield (%) ^a
10	70 68 ^b
20	60
30	59

Reaction Conditions: 0.204 mmol of **2b**, 0.306 mmol of **3b**, 0.408 mmol of Na₂CO₃, 0.029 mmol of Cu/Al₂O₃, SS beaker (50 mL capacity), 8 x SS milling balls (10 mm diameter), milling at 60 Hz. ^a ¹H-NMR yields were measured using TMB as an internal standard. ^b Isolated yield according to **PS3**



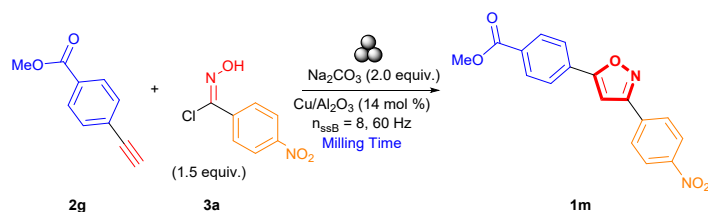
Time (min)	Yield (%) ^a
10	81 71 ^b
20	70
30	70
40	65

Reaction Conditions: 0.168 mmol of **2e**, 0.252 mmol of **3b**, 0.336 mmol of Na₂CO₃, 0.024 mmol of Cu/Al₂O₃, SS beaker (50 mL capacity), 8 x SS milling balls (10 mm diameter), milling at 60 Hz. ^a ¹H-NMR yields were measured using TMB as an internal standard. ^b Isolated yield according to **PS3**



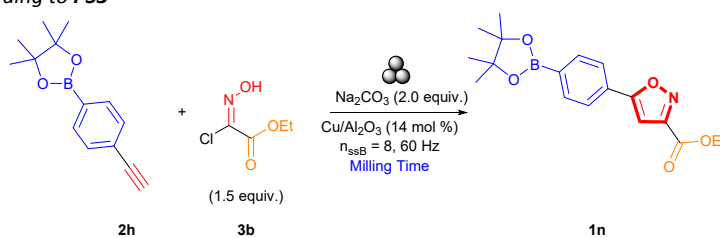
Milling Time (min)	Yield (%) ^a
10	N.R.
20	17
30	15
40	13
50	25
60	36 38 ^b

Reaction Conditions: 0.220 mmol of **2c**, 0.330 mmol of **3a**, 0.440 mmol of Na_2CO_3 , 0.031 mmol of $\text{Cu}/\text{Al}_2\text{O}_3$, SS beaker (50 mL capacity), 8 x SS milling balls (10 mm diameter), milling at 60 Hz. ^a ¹H-NMR yields were measured using TMB as an internal standard. ^b Isolated yield according to **PS3**



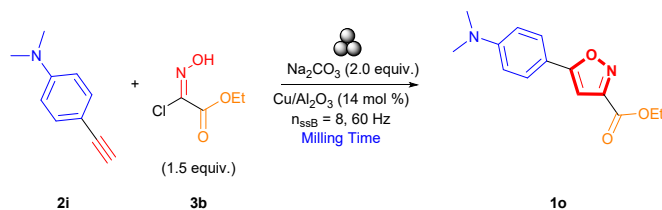
Milling Time (min)	Yield (%) ^a
10	33
20	24
30	45 41 ^b
40	13

Reaction Conditions: 0.166 mmol of **2g**, 0.249 mmol of **3a**, 0.332 mmol of Na_2CO_3 , 0.023 mmol of $\text{Cu}/\text{Al}_2\text{O}_3$, SS beaker (50 mL capacity), 8 x SS milling balls (10 mm diameter), milling at 60 Hz. ^a ¹H-NMR yields were measured using TMB as an internal standard. ^b Isolated yield according to **PS3**



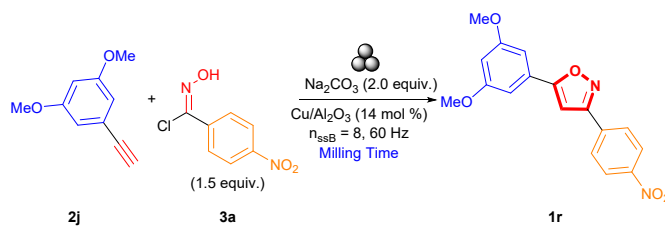
Milling Time (min)	Yield (%) ^a
20	50
30	75 70 ^b
40	52

Reaction Conditions: 0.088 mmol of **2h**, 0.123 mmol of **3b**, 0.176 mmol of Na_2CO_3 , 0.012 mmol of $\text{Cu}/\text{Al}_2\text{O}_3$, SS beaker (50 mL capacity), 8 x SS milling balls (10 mm diameter), milling at 60 Hz. ^a ¹H-NMR yields were measured using TMB as an internal standard. ^b Isolated yield according to **PS3**



Milling Time (min)	Yield (%) ^a
20	61
30	70 45 ^b

Reaction Conditions: 0.140 mmol of **2i**, 0.210 mmol of **3b**, 0.280 mmol of Na₂CO₃, 0.020 mmol of Cu/Al₂O₃, SS beaker (50 mL capacity), 8 x SS milling balls (10 mm diameter), milling at 60 Hz. ^a ¹H-NMR yields were measured using TMB as an internal standard. ^b Isolated yield according to **PS3**



Milling Time (min)	Yield (%) ^a
20	50
30	75 70 ^b
40	52

Reaction Conditions: 0.123 mmol of **2j**, 0.185 mmol of **2a**, 0.246 mmol of Na₂CO₃, 0.017 mmol of Cu/Al₂O₃, SS beaker (50 mL capacity), 8 x SS milling balls (10 mm diameter), milling at 60 Hz. ^a ¹H-NMR yields were measured using TMB as an internal standard. ^b Isolated yield according to **PS3**

^1H NMR and ^{13}C spectra

3-(4-nitrophenyl)-5-(tributylstannyl)isoxazole (1a)

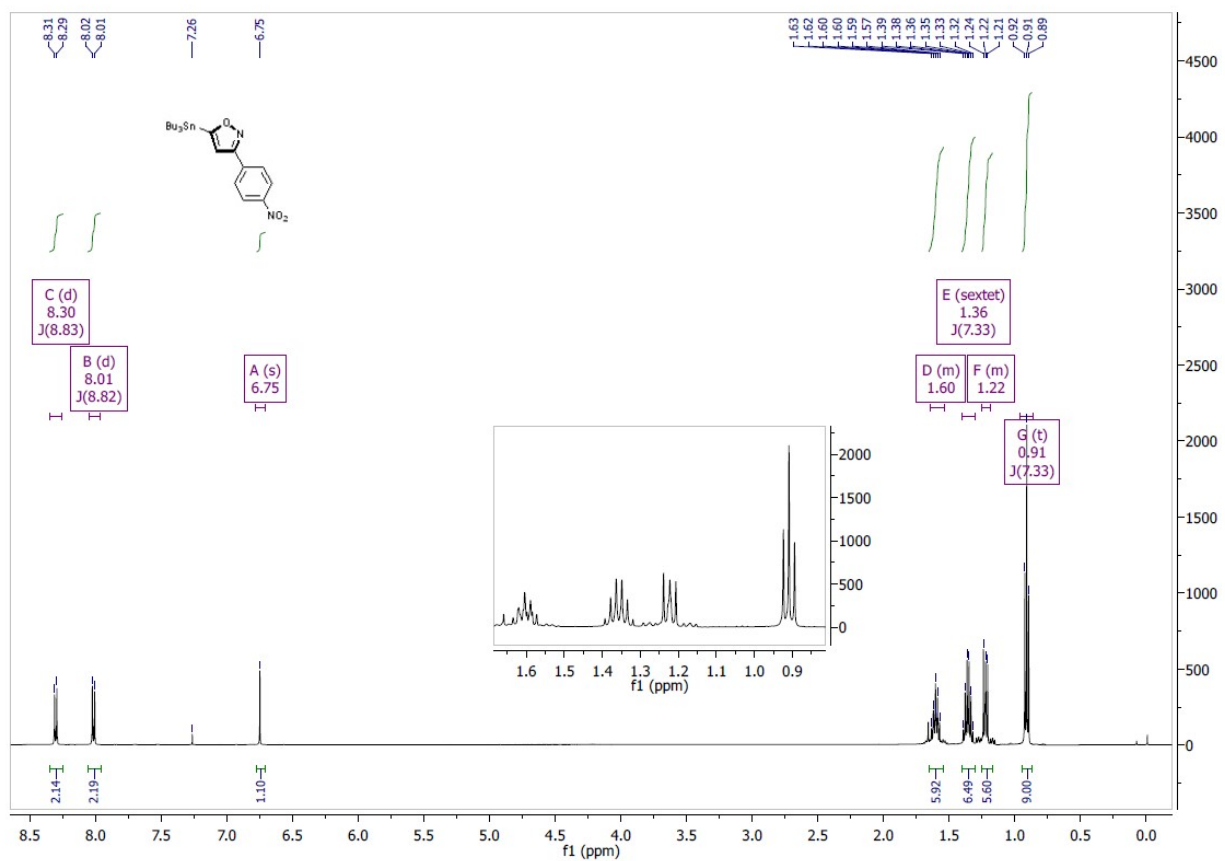


Figure S5: ^1H NMR spectrum of 3,5-isoxazole 1a

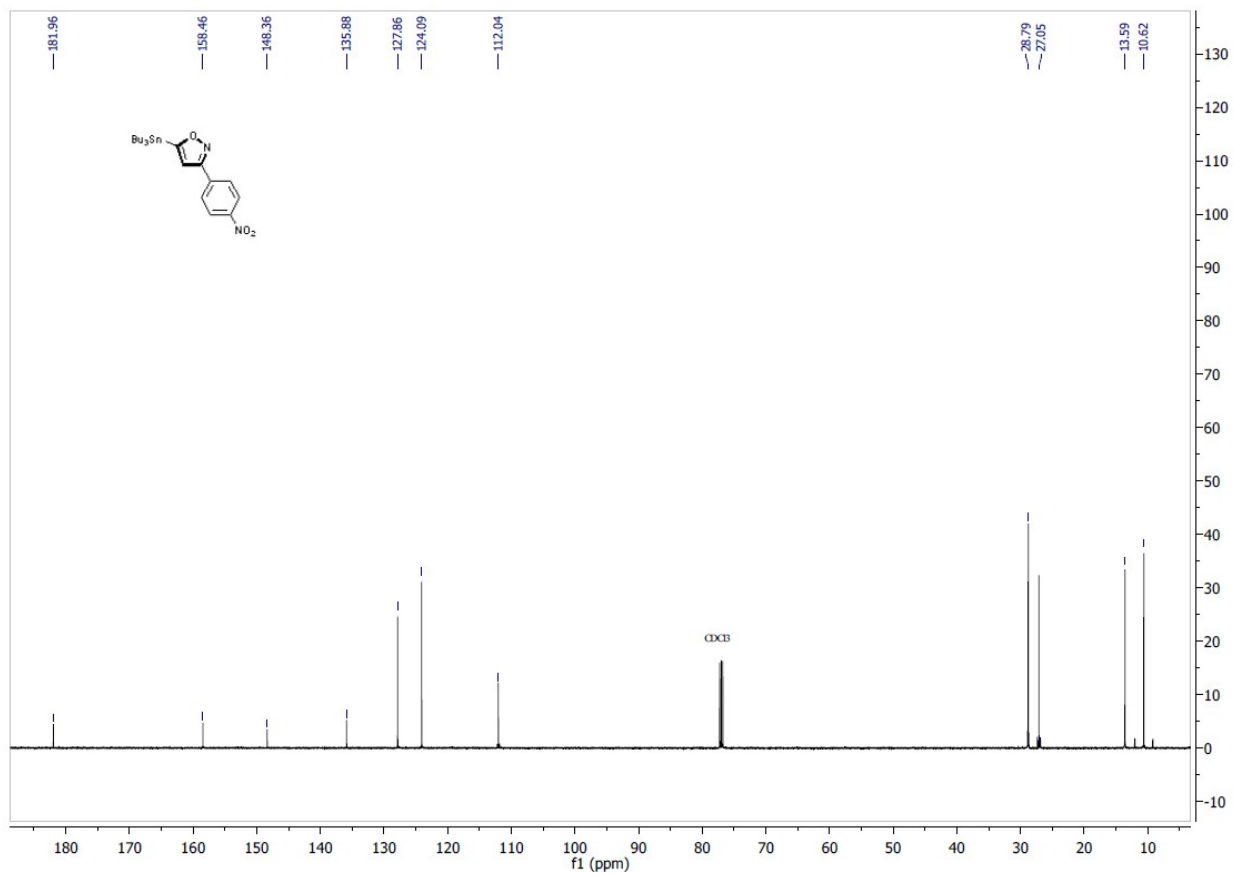


Figure S6: ¹³C NMR spectrum of 3,5-isoxazole 1a

Ethyl 5-(tributylstannyl)isoxazole-3-carboxylate (1b):

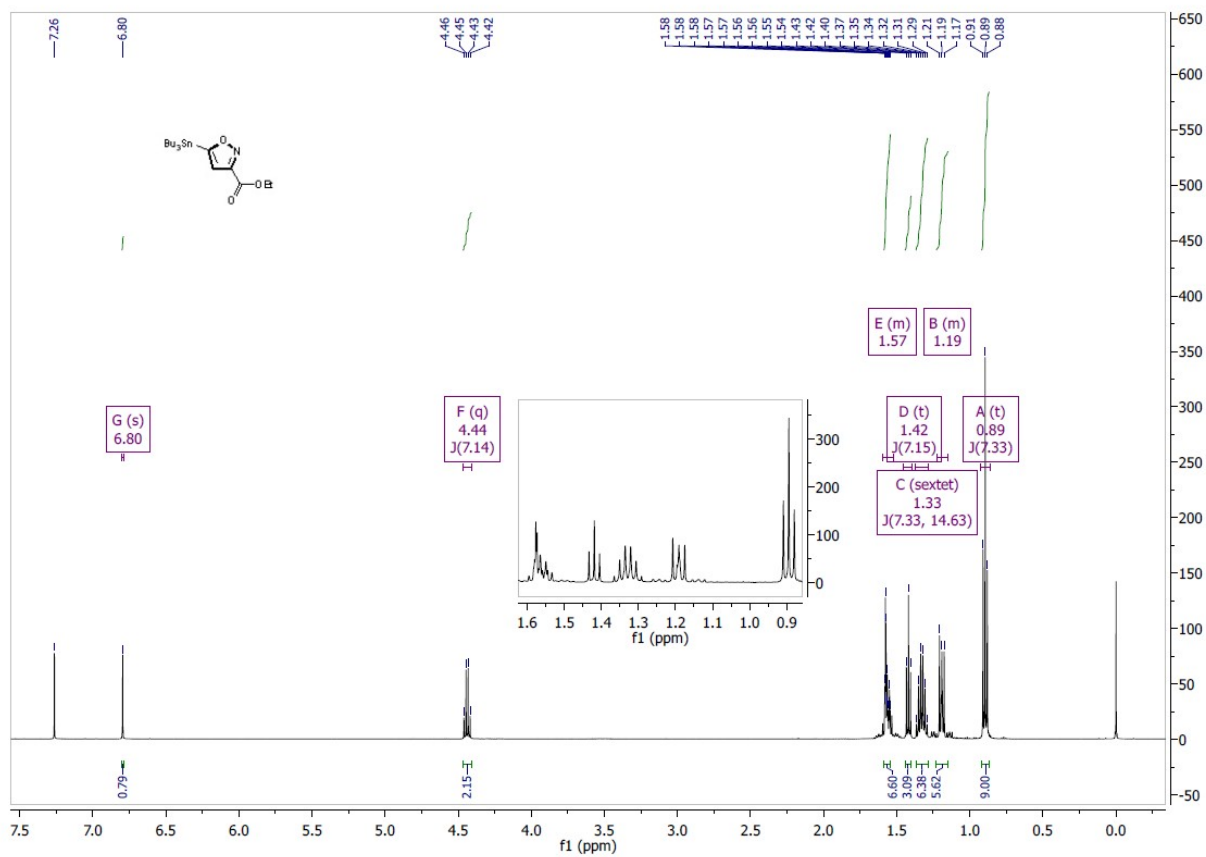


Figure S7: ¹H NMR spectrum of 3,5-isoxazole 1b

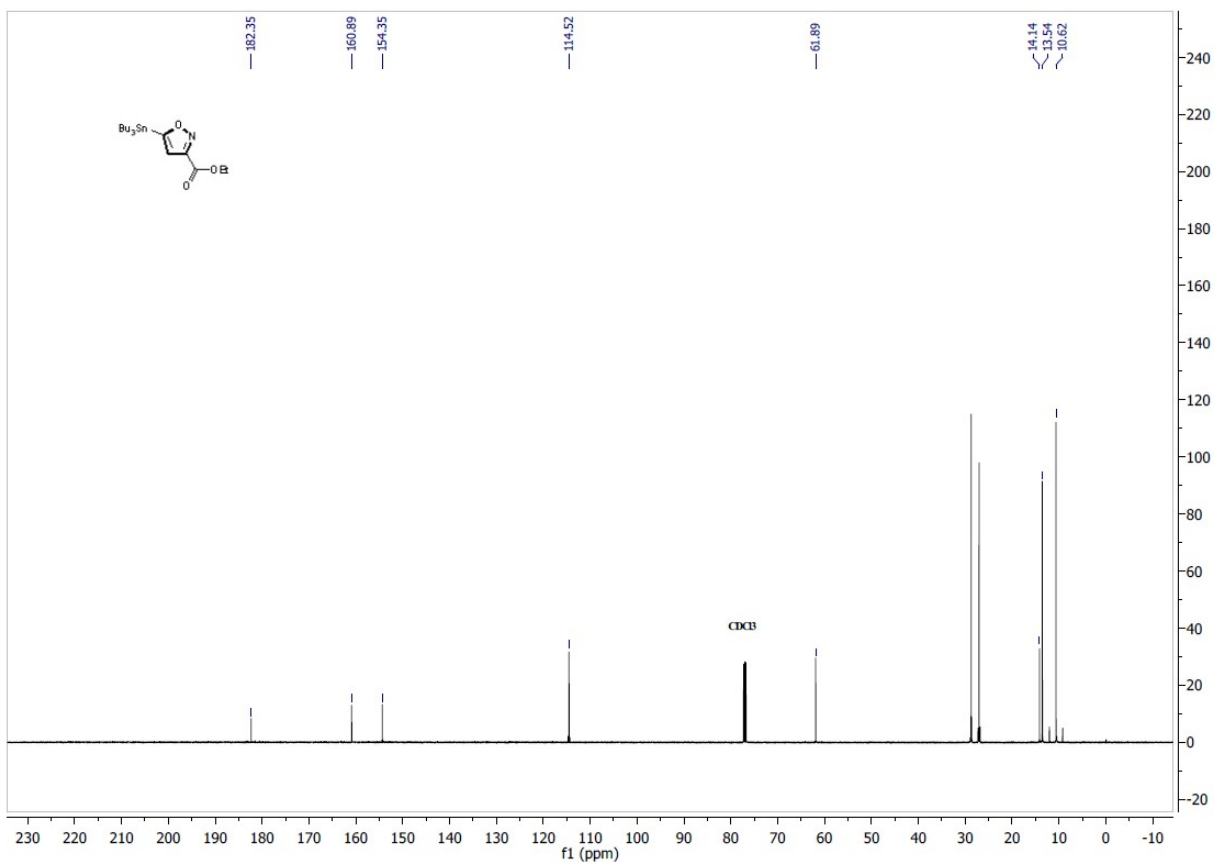


Figure S8: ¹³C NMR spectrum of 3,5-isoxazole **1b**

Ethyl 5-(trimethylsilyl)isoxazole-3-carboxylate (1c)

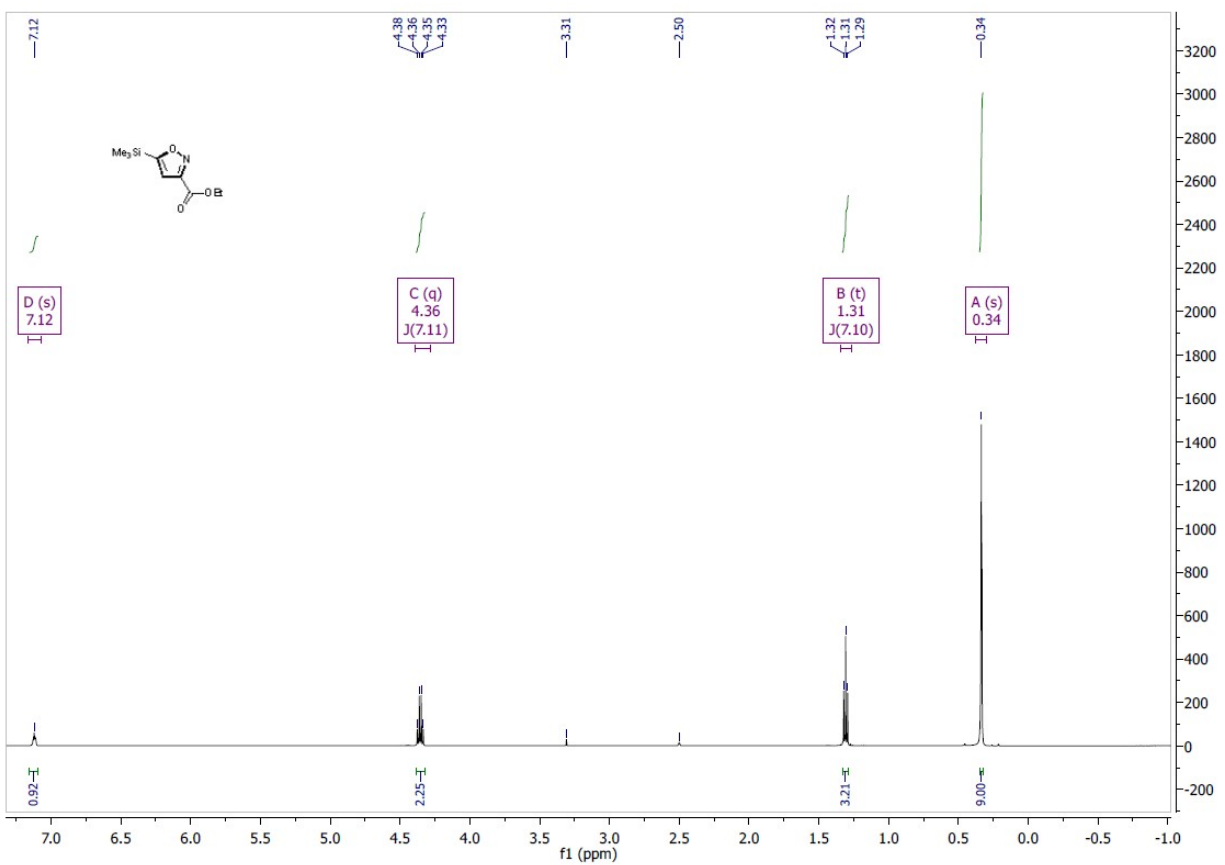


Figure S9: ¹H NMR spectrum of 3,5-isoxazole 1c

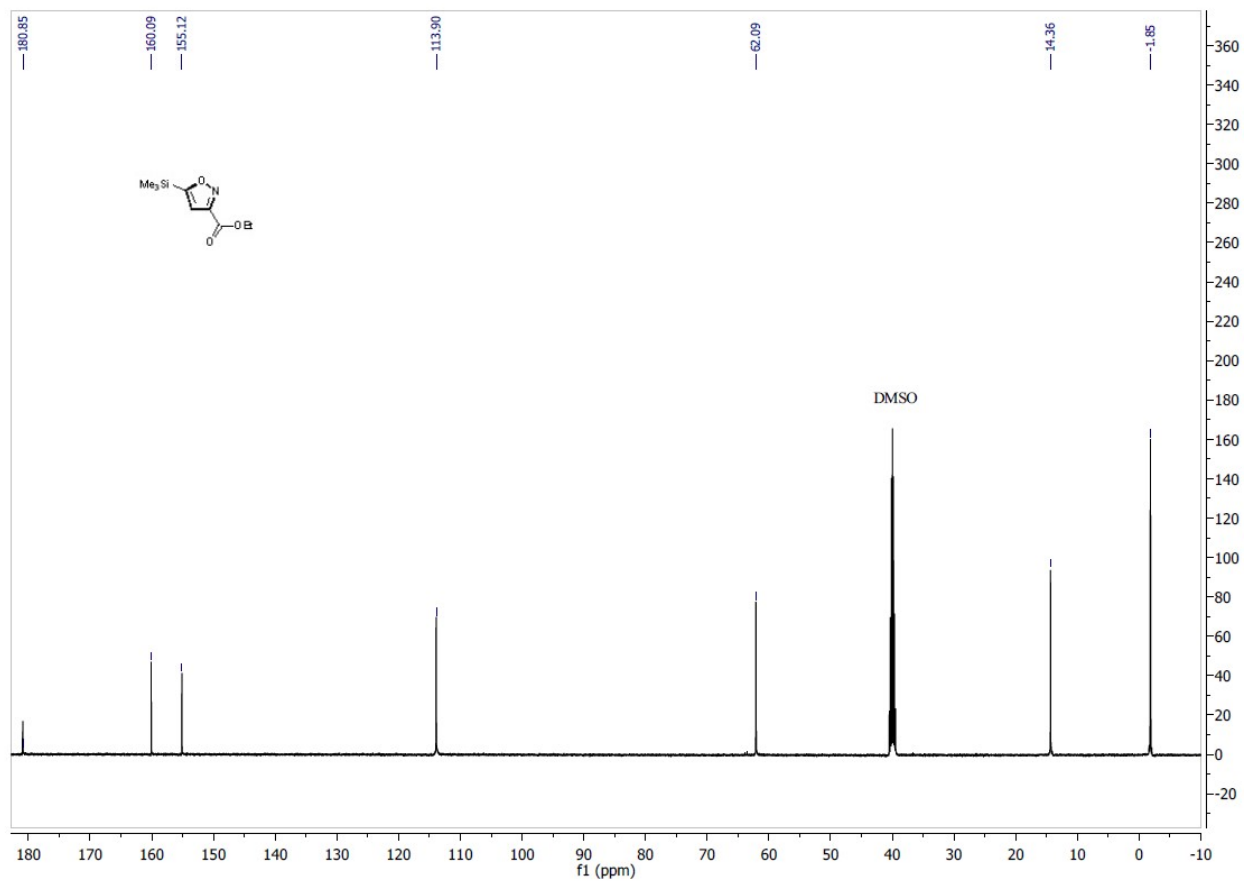


Figure S10: ^{13}C NMR spectrum of 3,5-isoxazole **1c**

Ethyl 5-phenylisoxazole-3-carboxylate (1d)

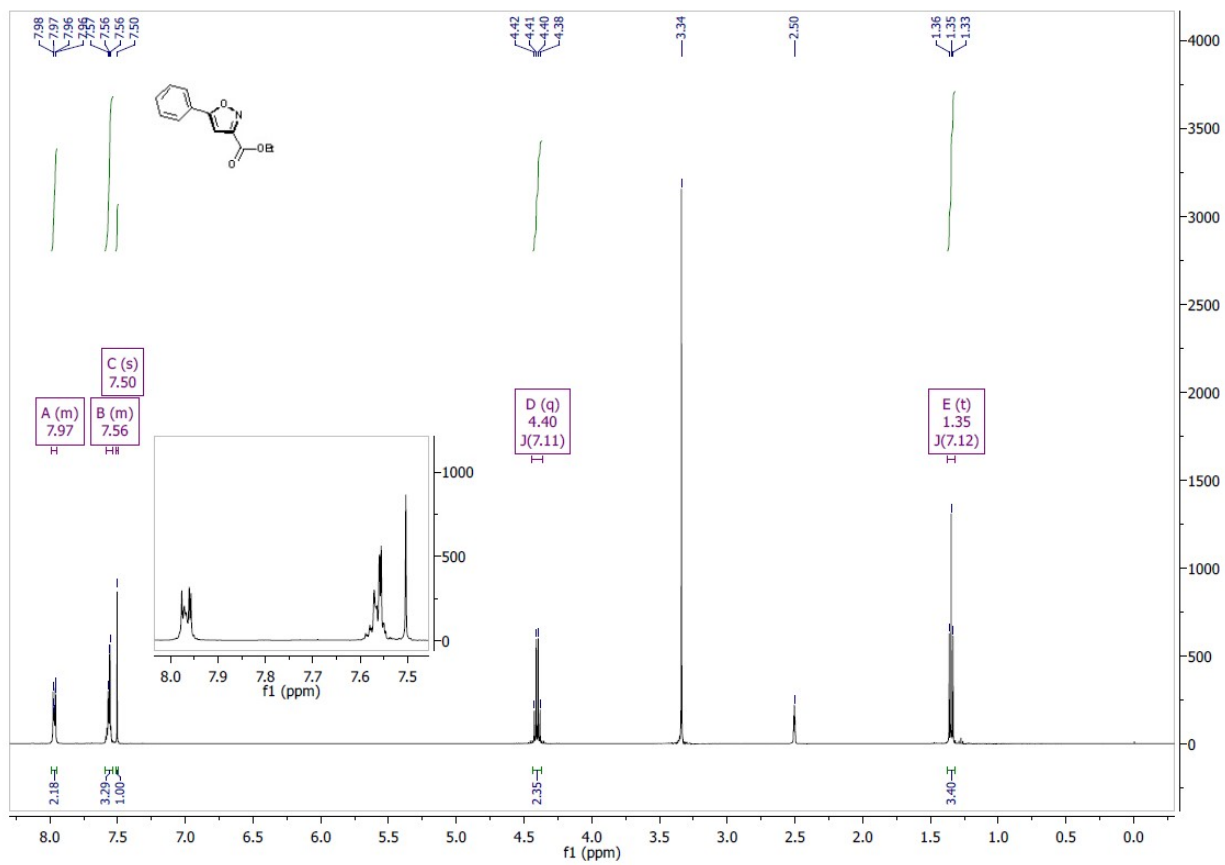


Figure S11: ¹H NMR spectrum of 3,5-isoxazole 1d

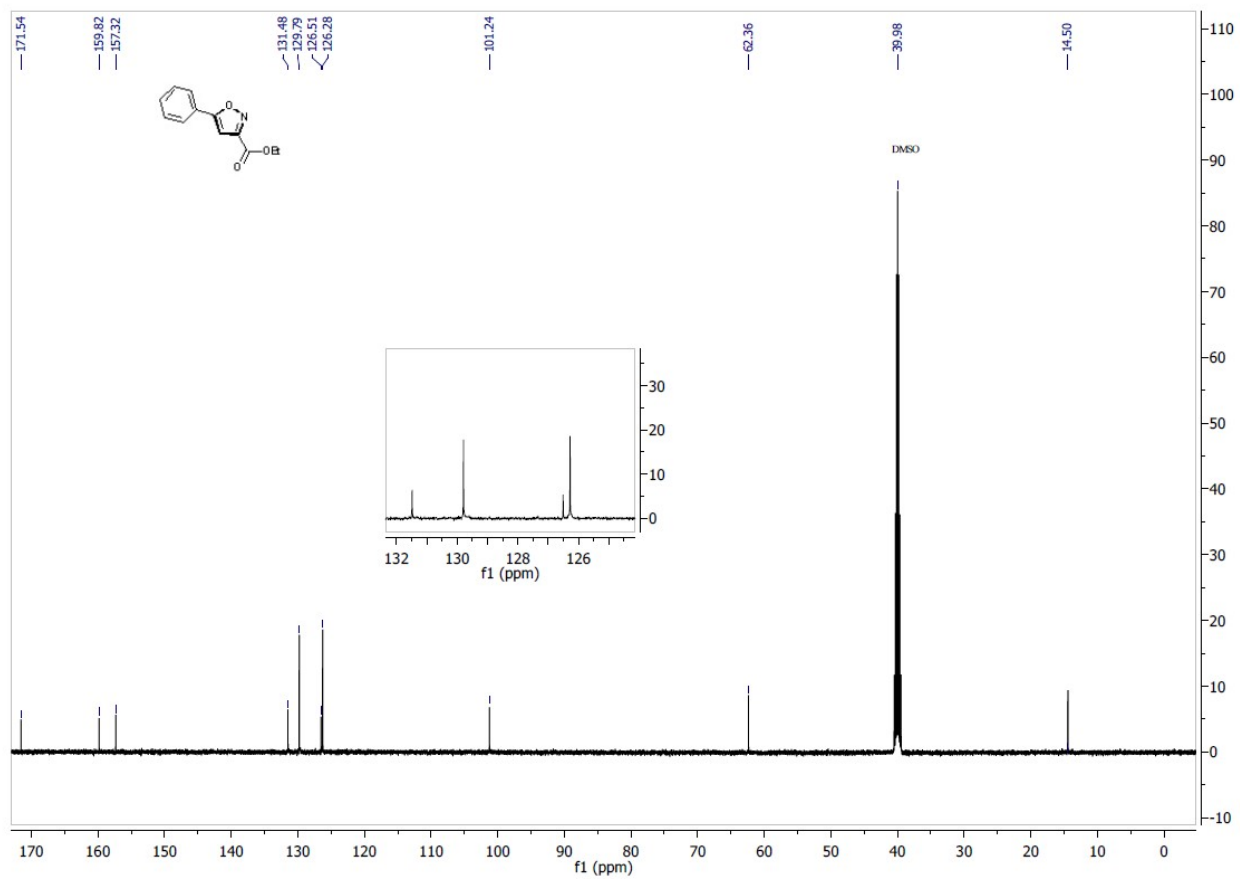


Figure S12: ^{13}C NMR spectrum of 3,5-isoxazole **1d**

3-ethyl 5-methyl isoxazole-3,5-dicarboxylate (1e)

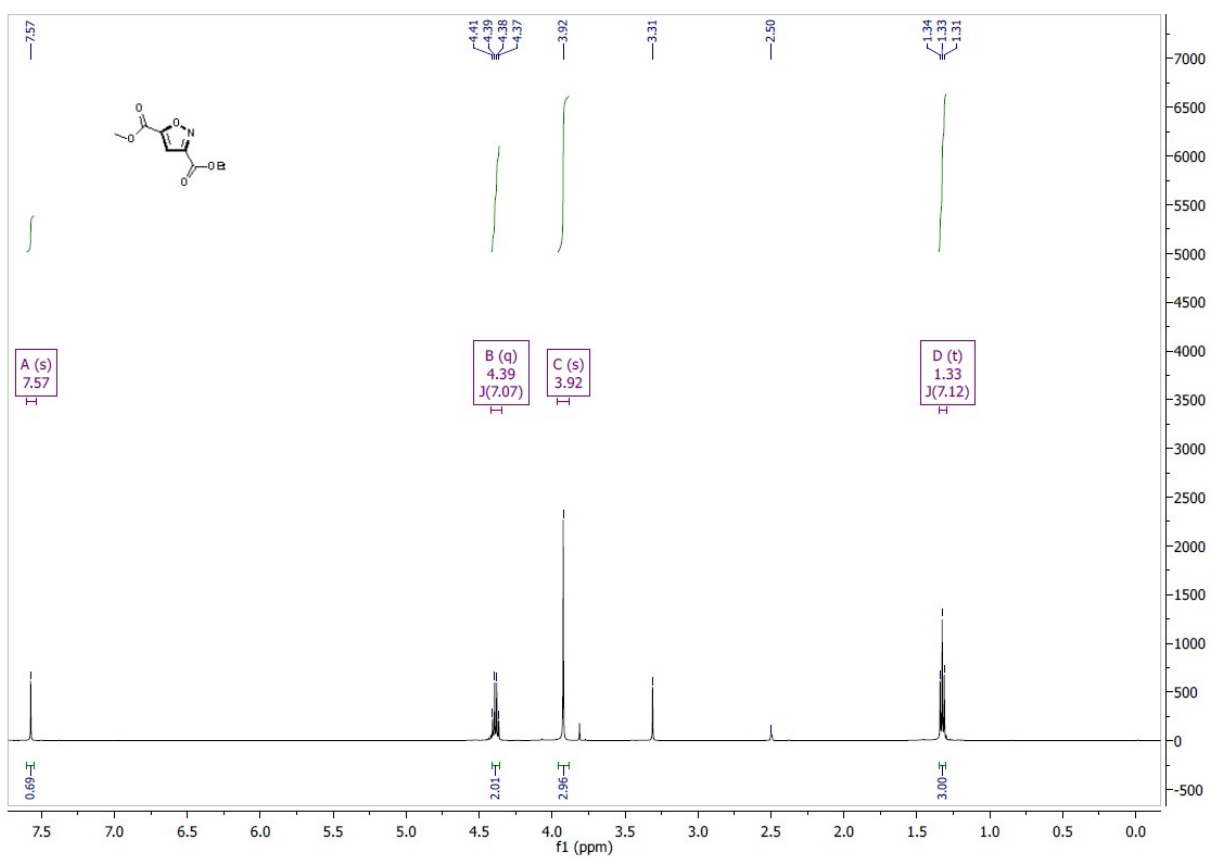


Figure S13: ¹H NMR spectrum of 3,5-isoxazole 1e

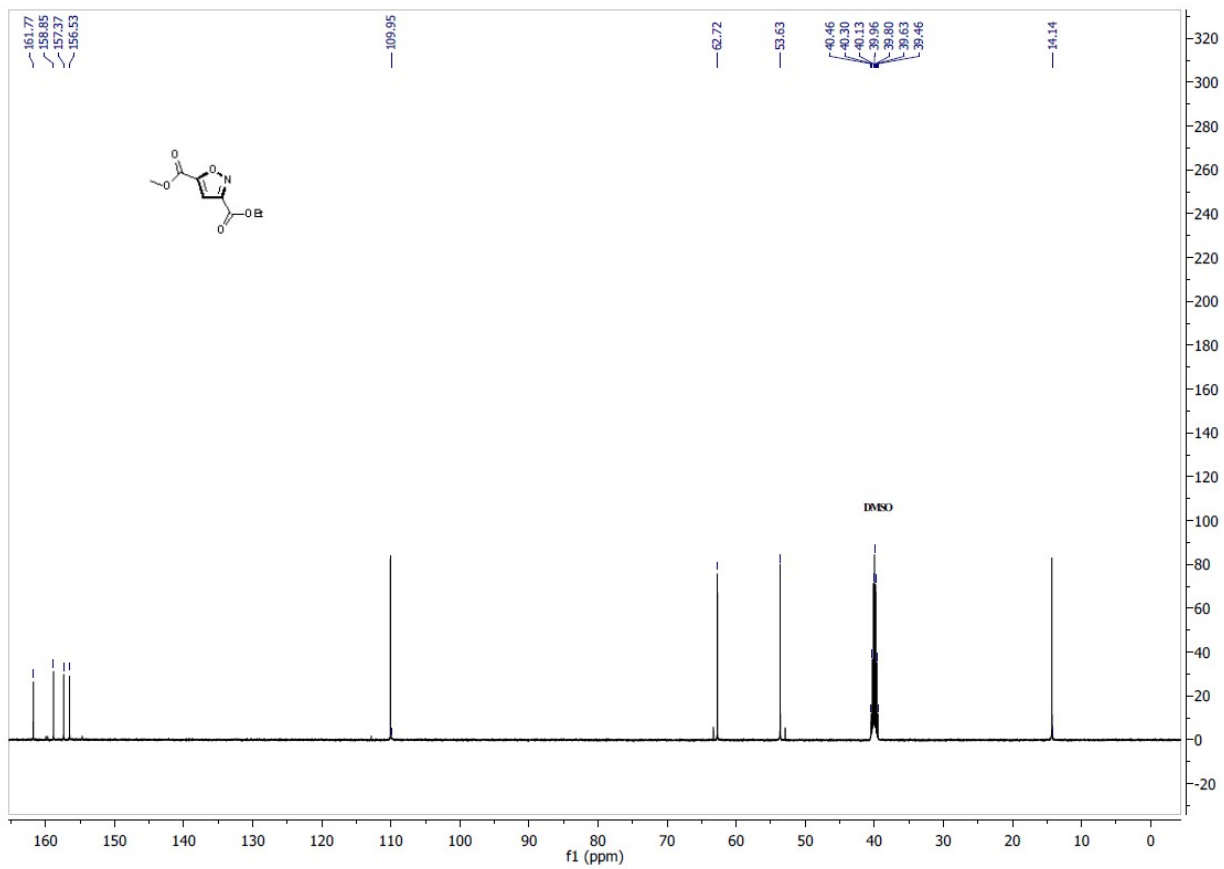


Figure S14: ^{13}C NMR spectrum of 3,5-isoxazole **1e**

3-(4-nitrophenyl)-5-(trimethylsilyl)isoxazole (1f)

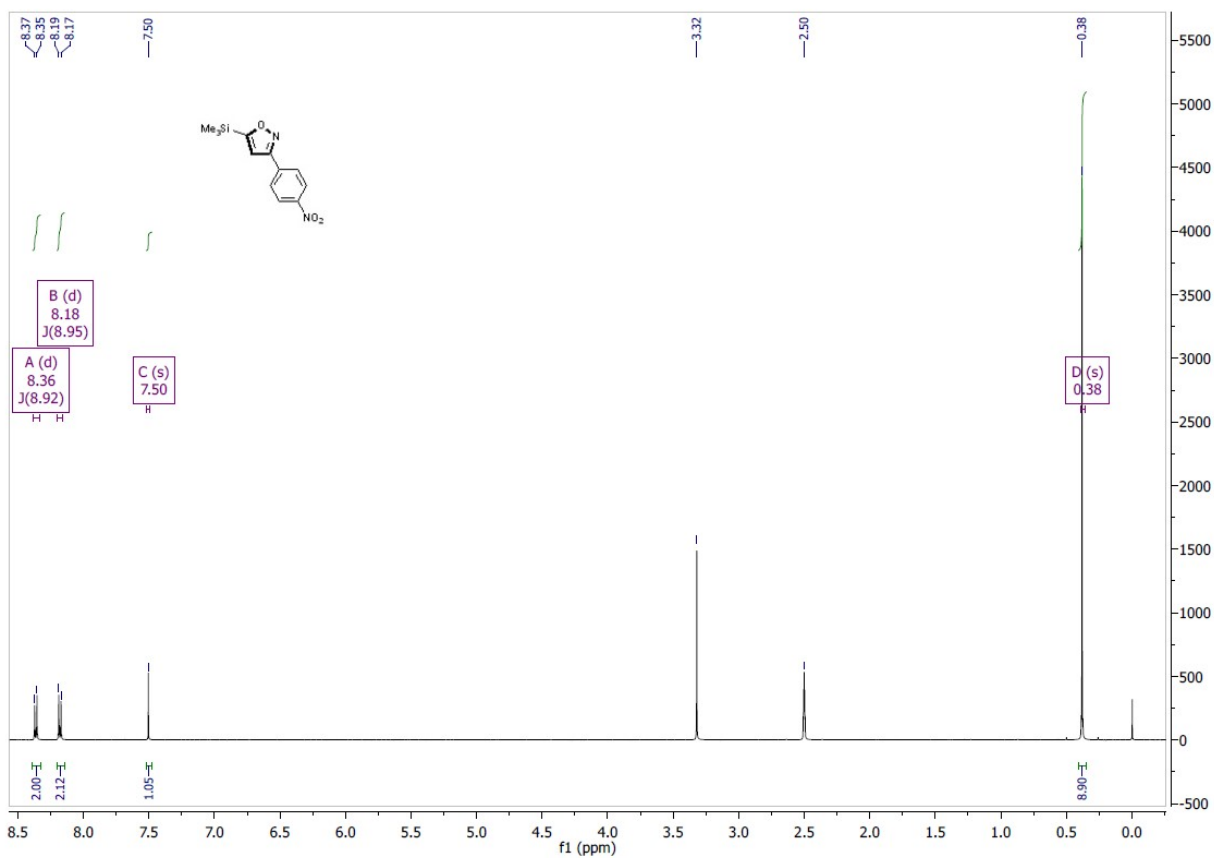


Figure S15: ¹H NMR spectrum of 3,5-isoxazole 1f

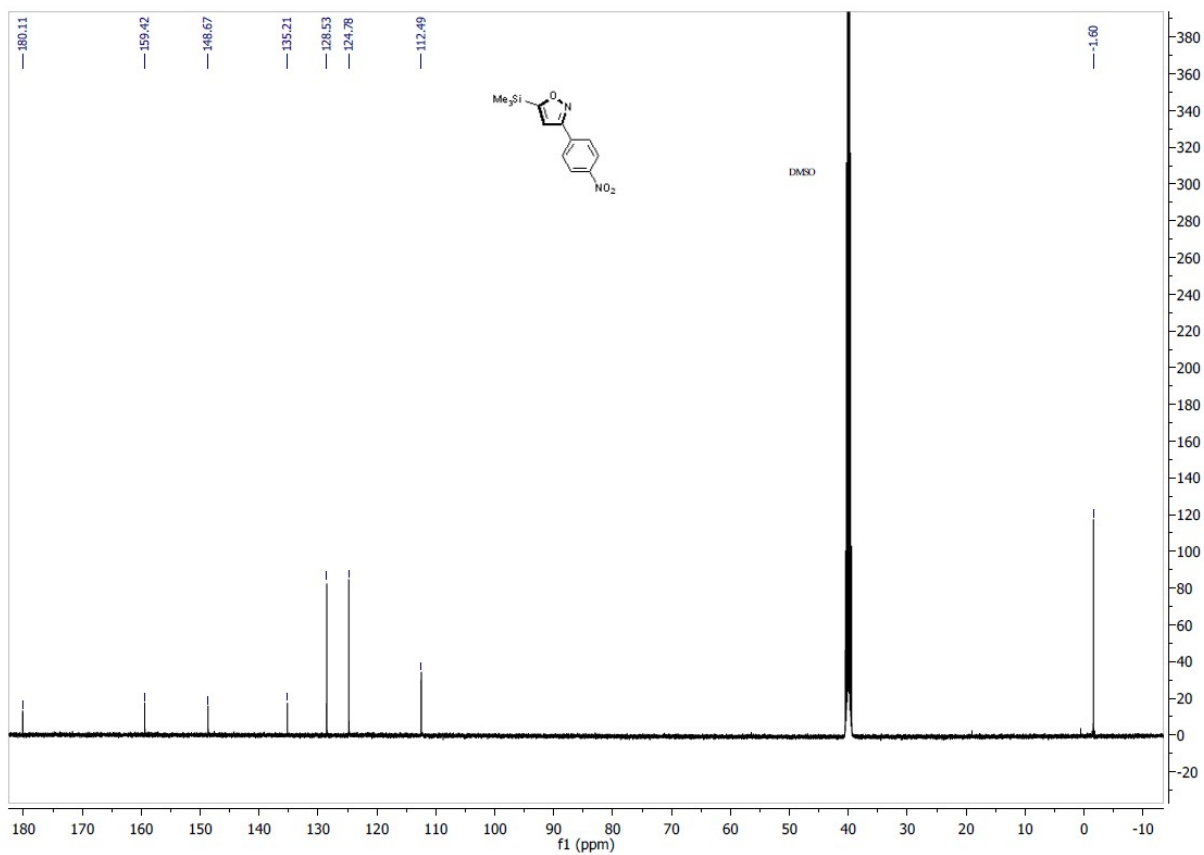


Figure S16: ^{13}C NMR spectrum of 3,5-isoxazole **1f**

3-(4-methoxyphenyl)-5-(trimethylsilyl)isoxazole (**1g**)

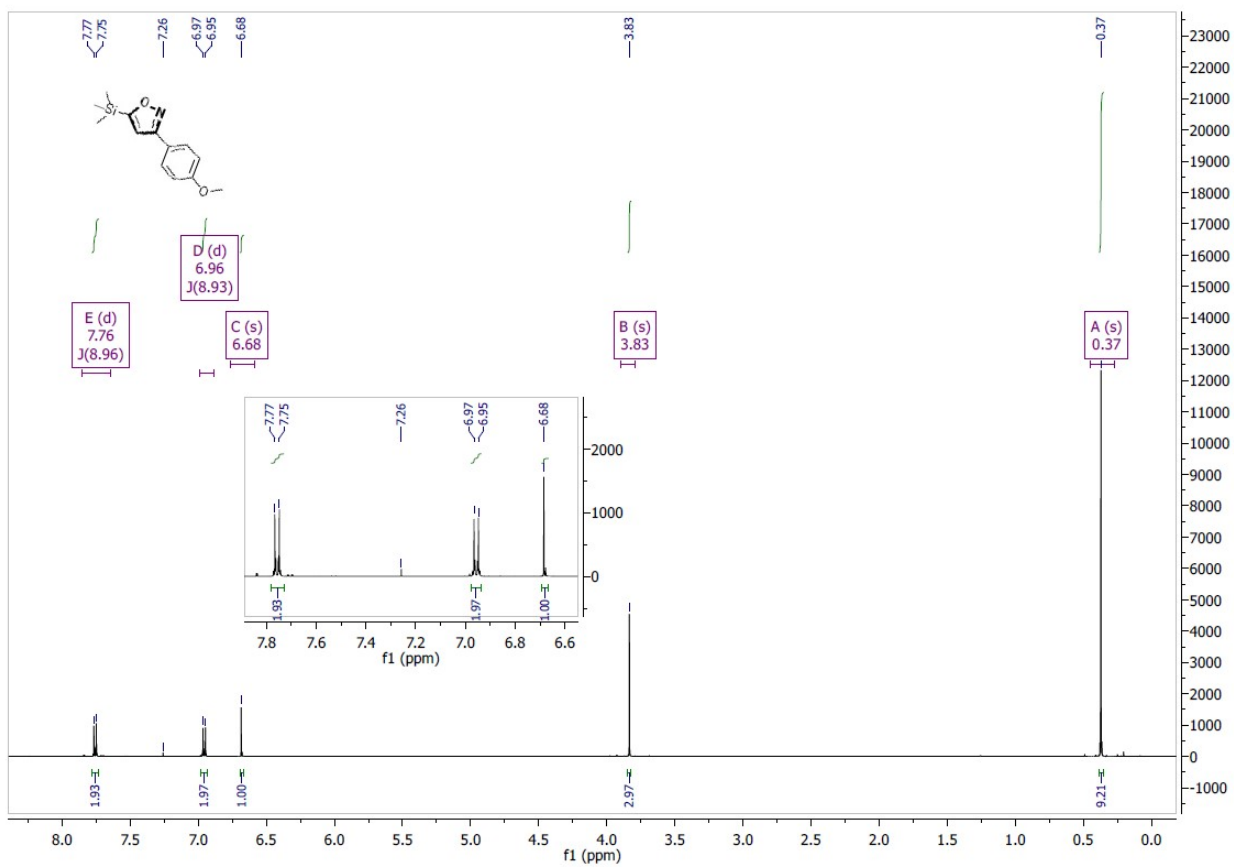


Figure S17: ¹H NMR spectrum of 3,5-isoxazole **1g**

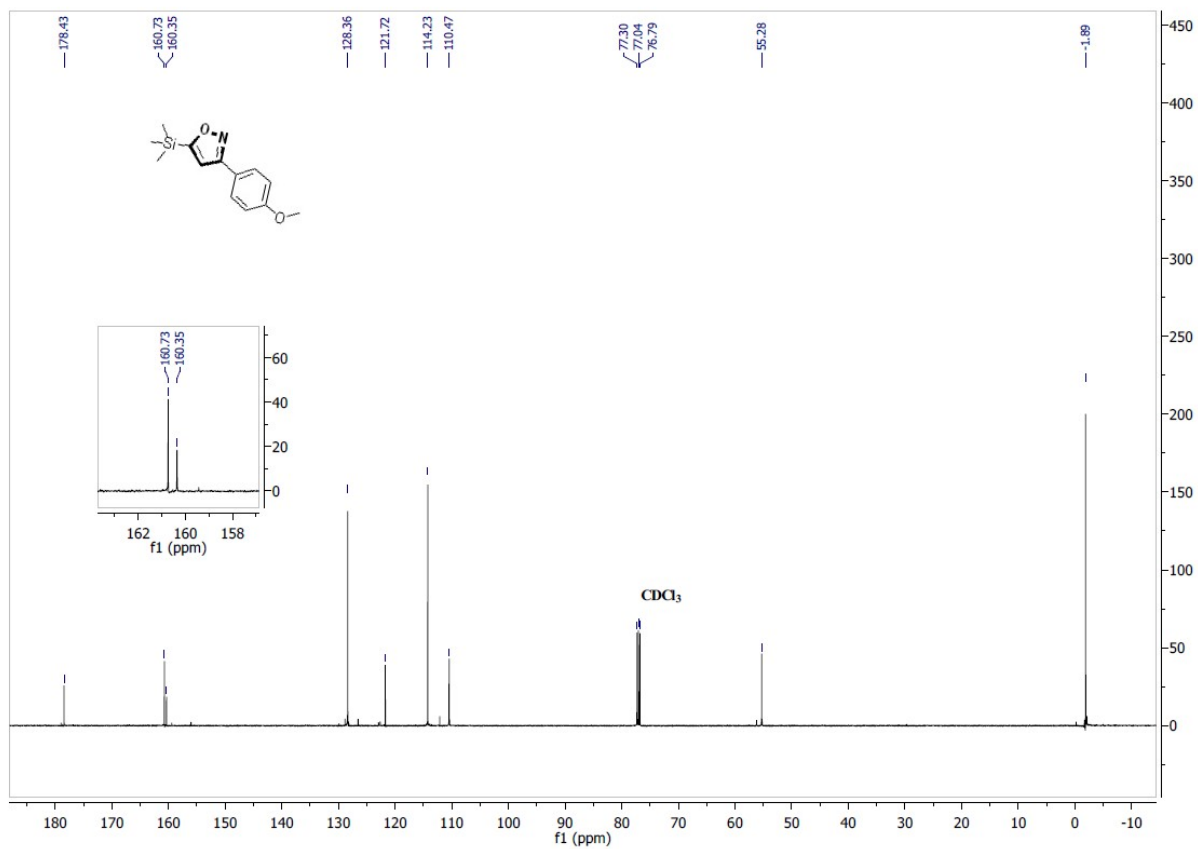


Figure S18: ^{13}C NMR spectrum of 3,5-isoxazole **1g**

3-bromo-5-(trimethylsilyl)isoxazole (1h)

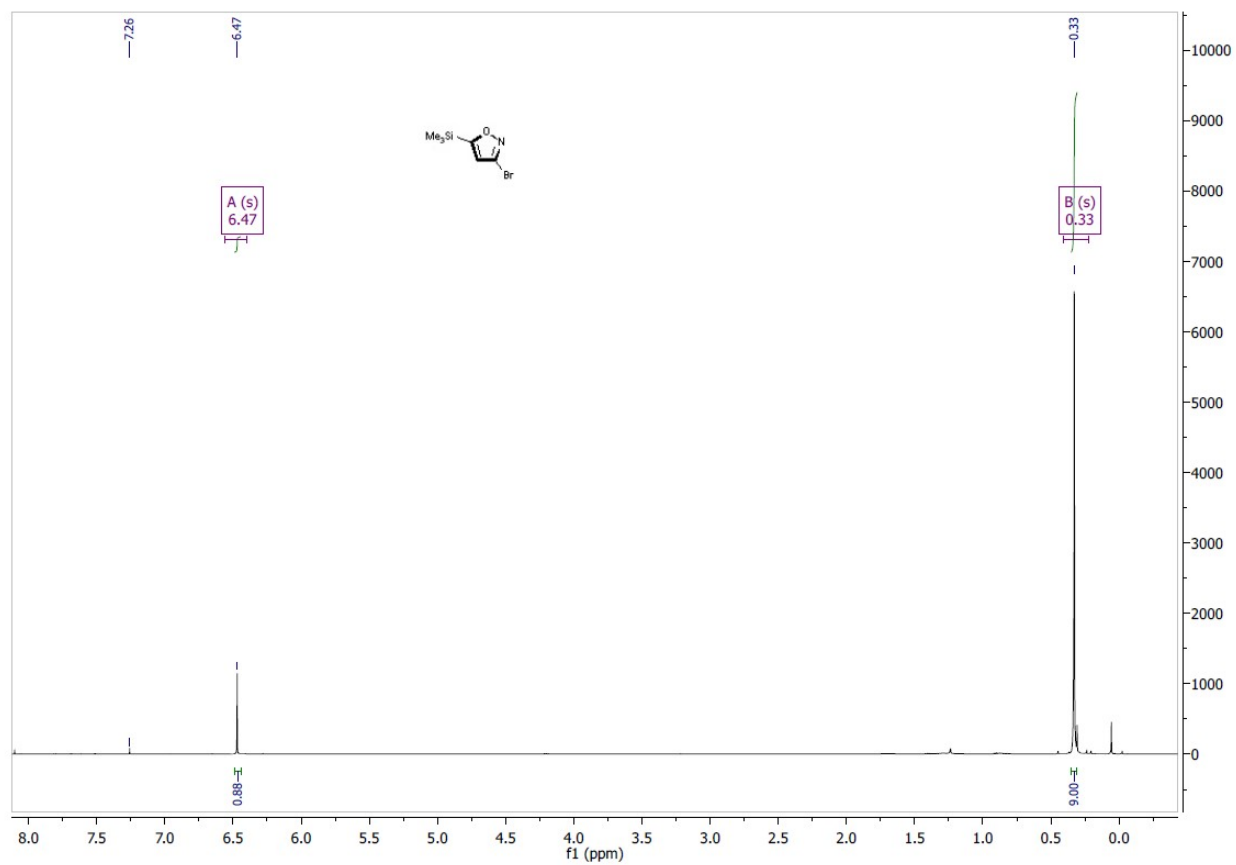


Figure S19: ¹H NMR spectrum of 3,5-isoxazole 1h

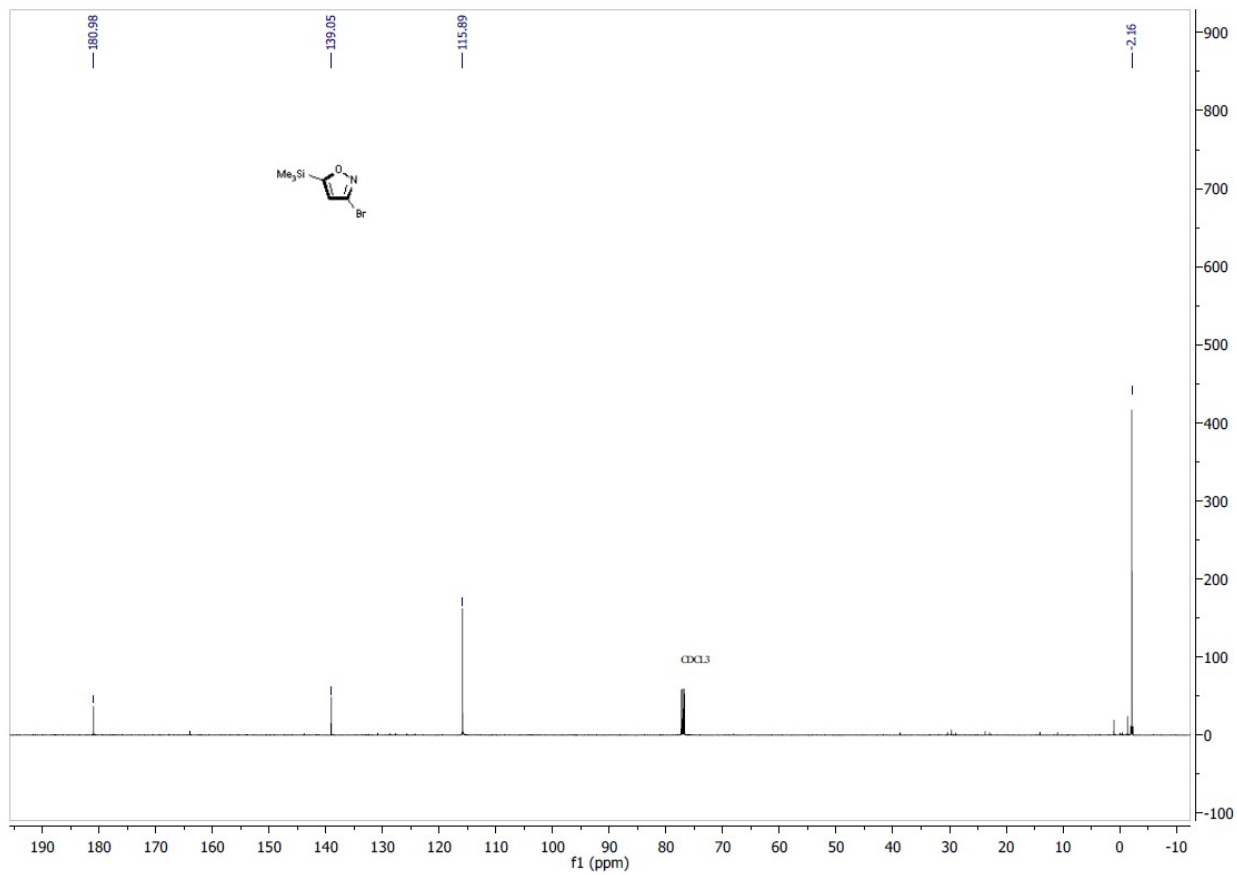


Figure S20: ¹³C NMR spectrum of 3,5-isoxazole **1h**

ethyl 5-(bromomethyl)isoxazole-3-carboxylate (1i)

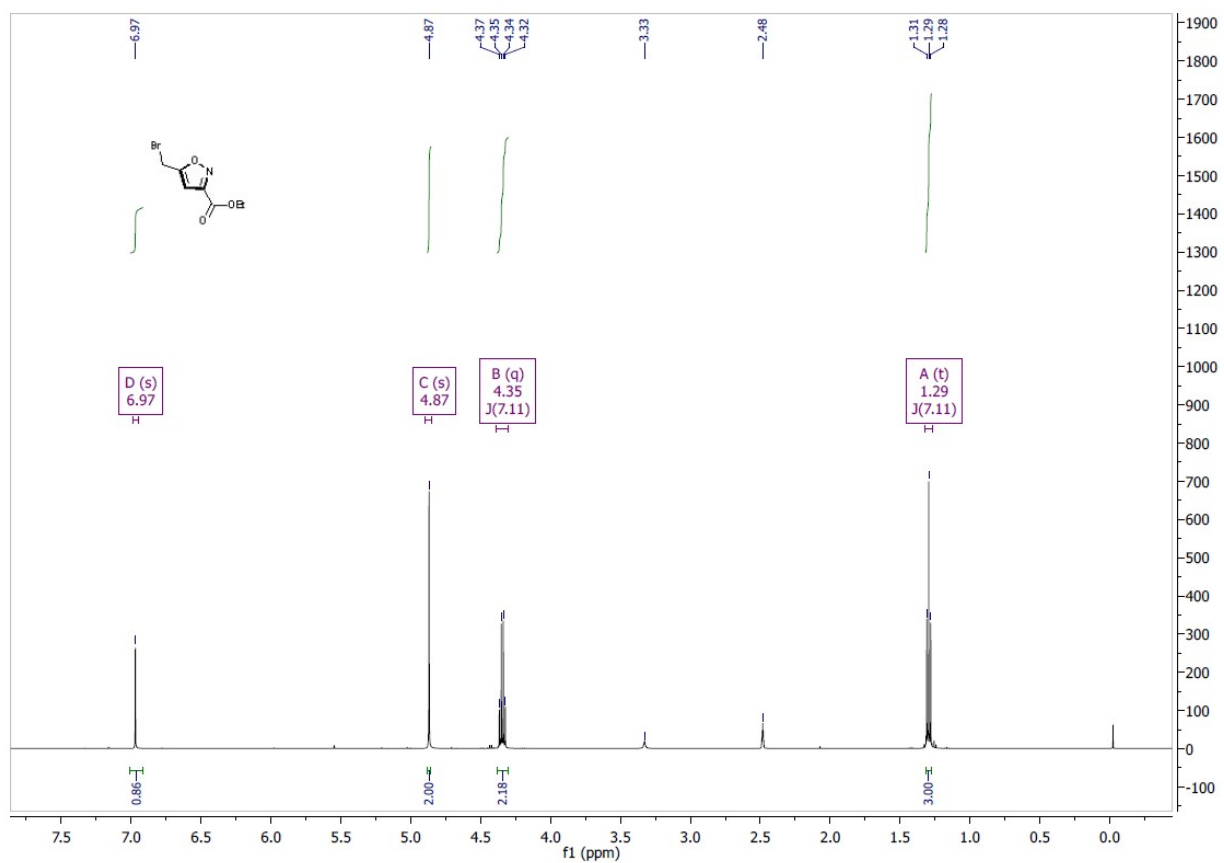


Figure S22: ^1H NMR spectrum of 3,5-isoxazole 1i

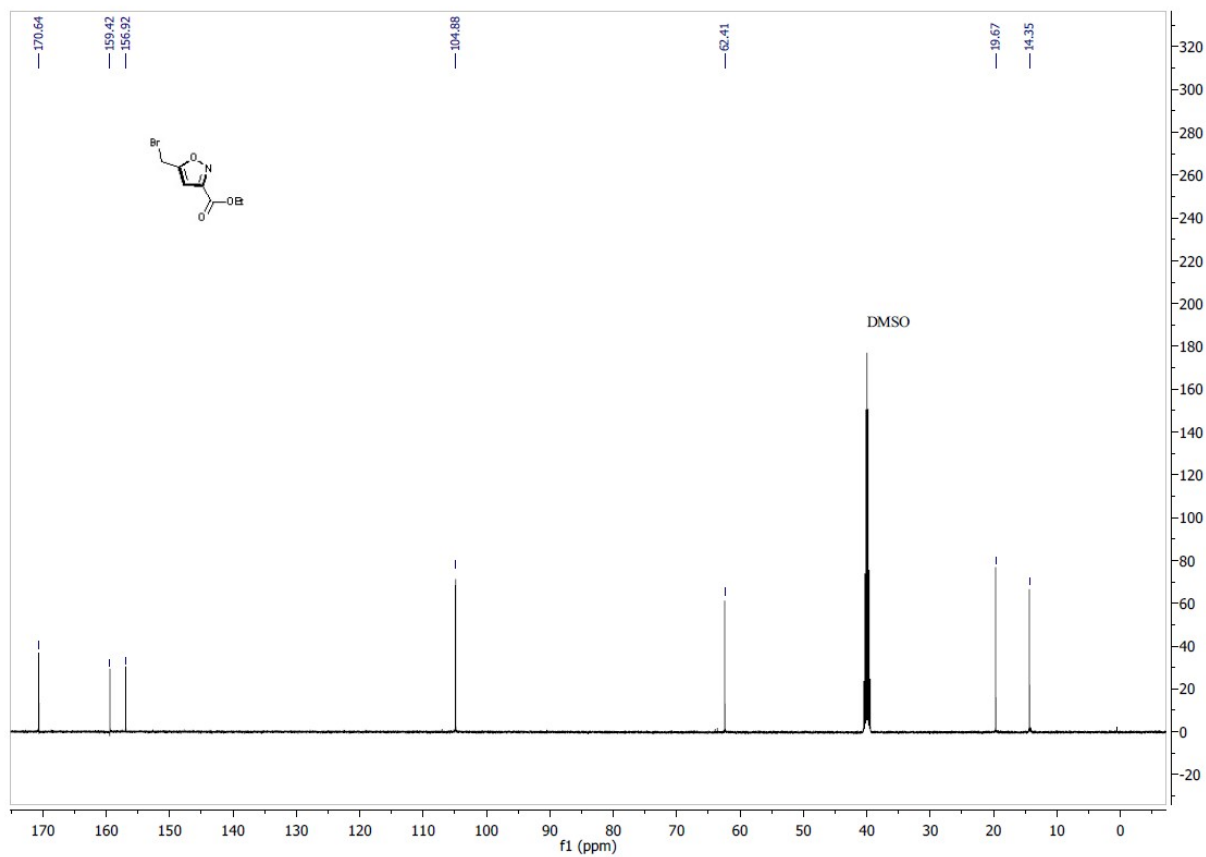


Figure S23: ^{13}C NMR spectrum of 3,5-isoxazole **1i**

5-(2-bromoethyl)-3-(4-methoxyphenyl)isoxazole (1j)

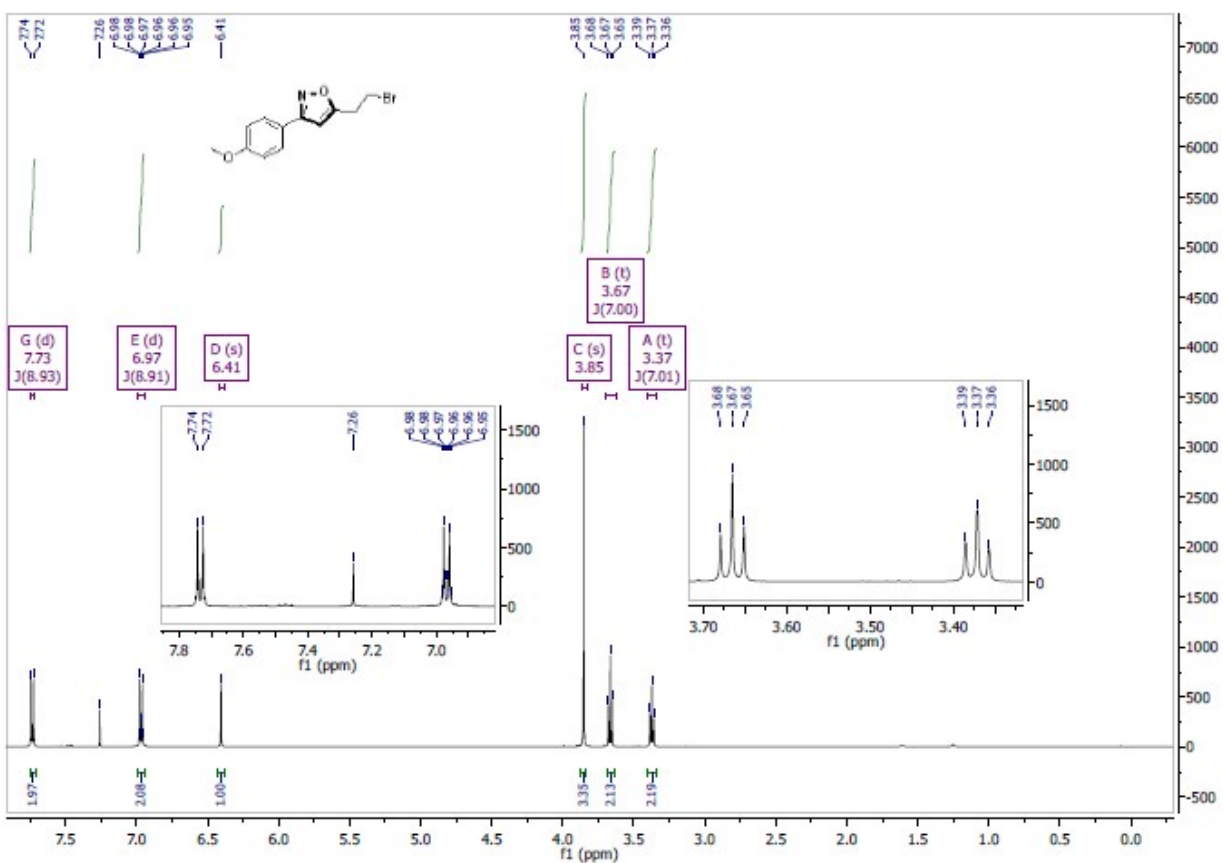


Figure S24: ¹H NMR spectrum of 3,5-isoxazole 1j

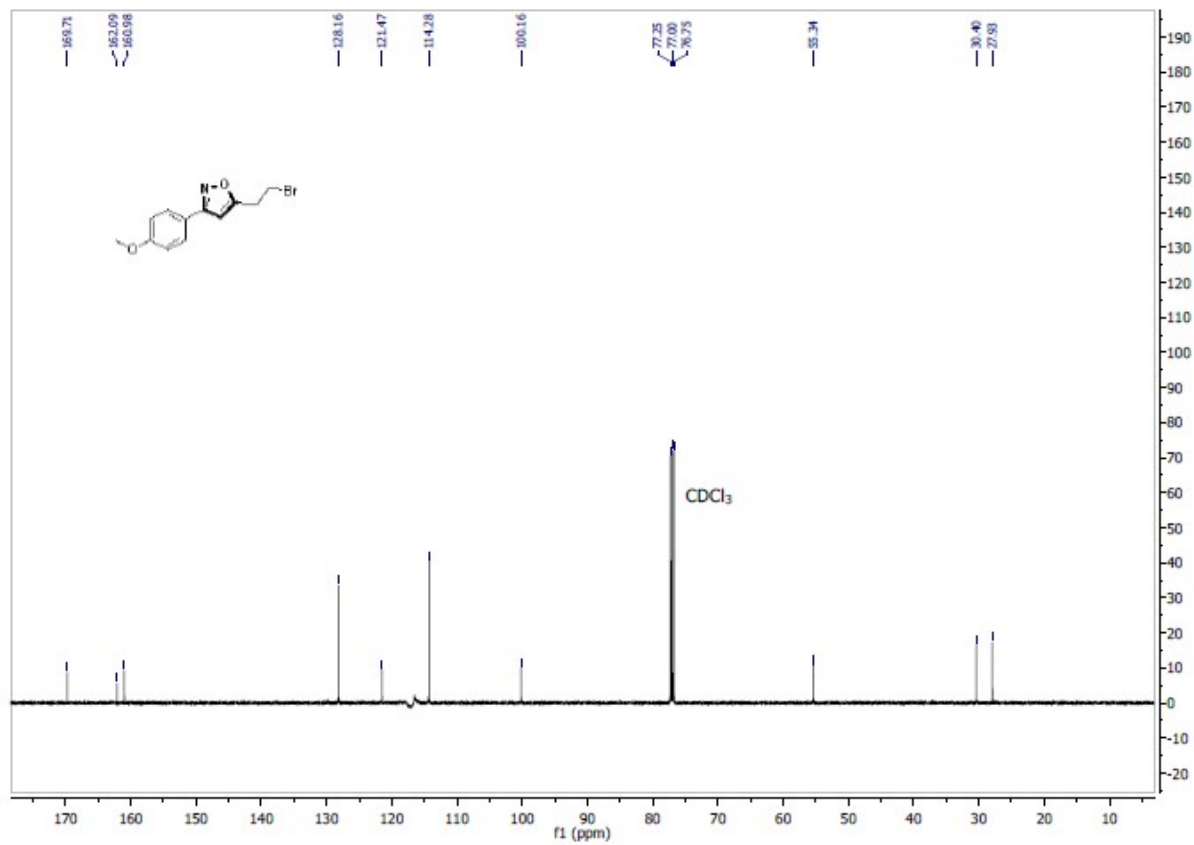


Figure S25: ^{13}C NMR spectrum of 3,5-isoxazole **1j**

3-(4-nitrophenyl)-5-phenylisoxazole (1k)

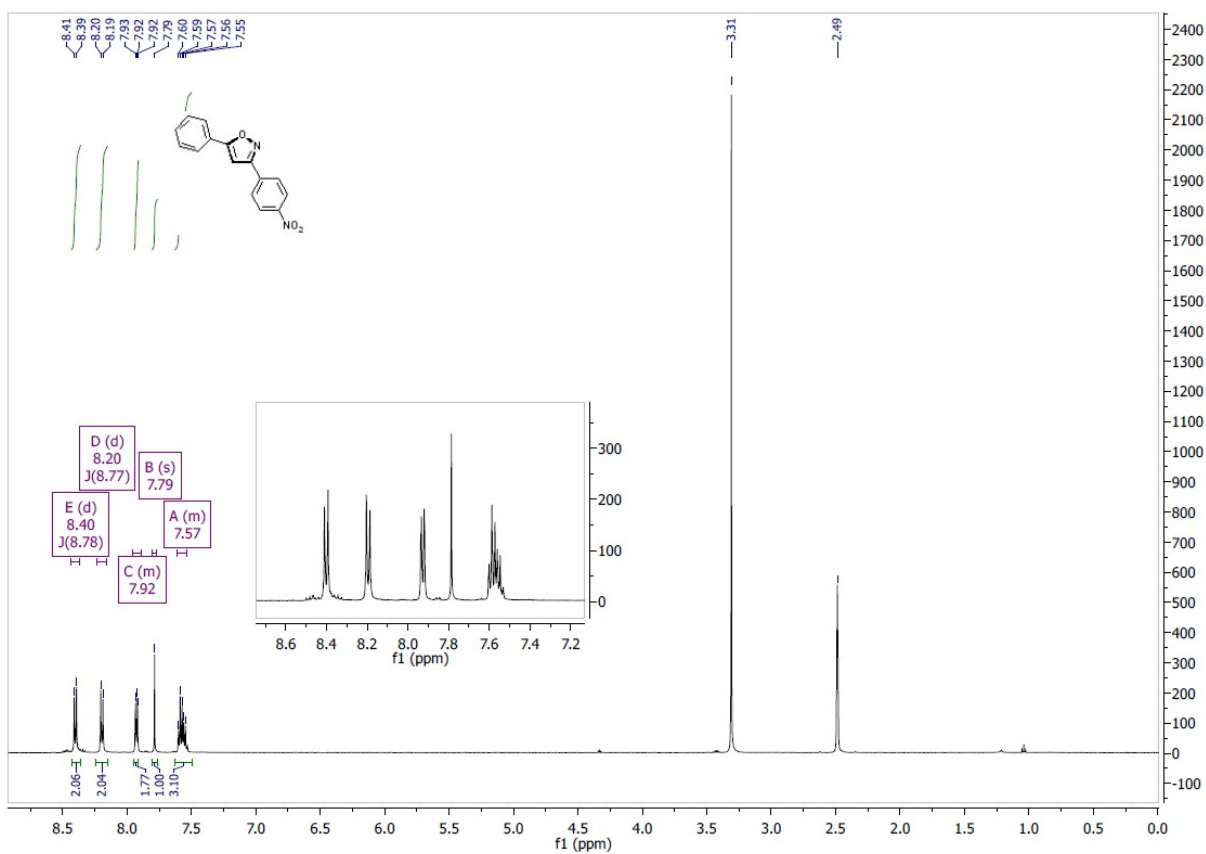


Figure S26: ^1H NMR spectrum of 3,5-isoxazole 1k

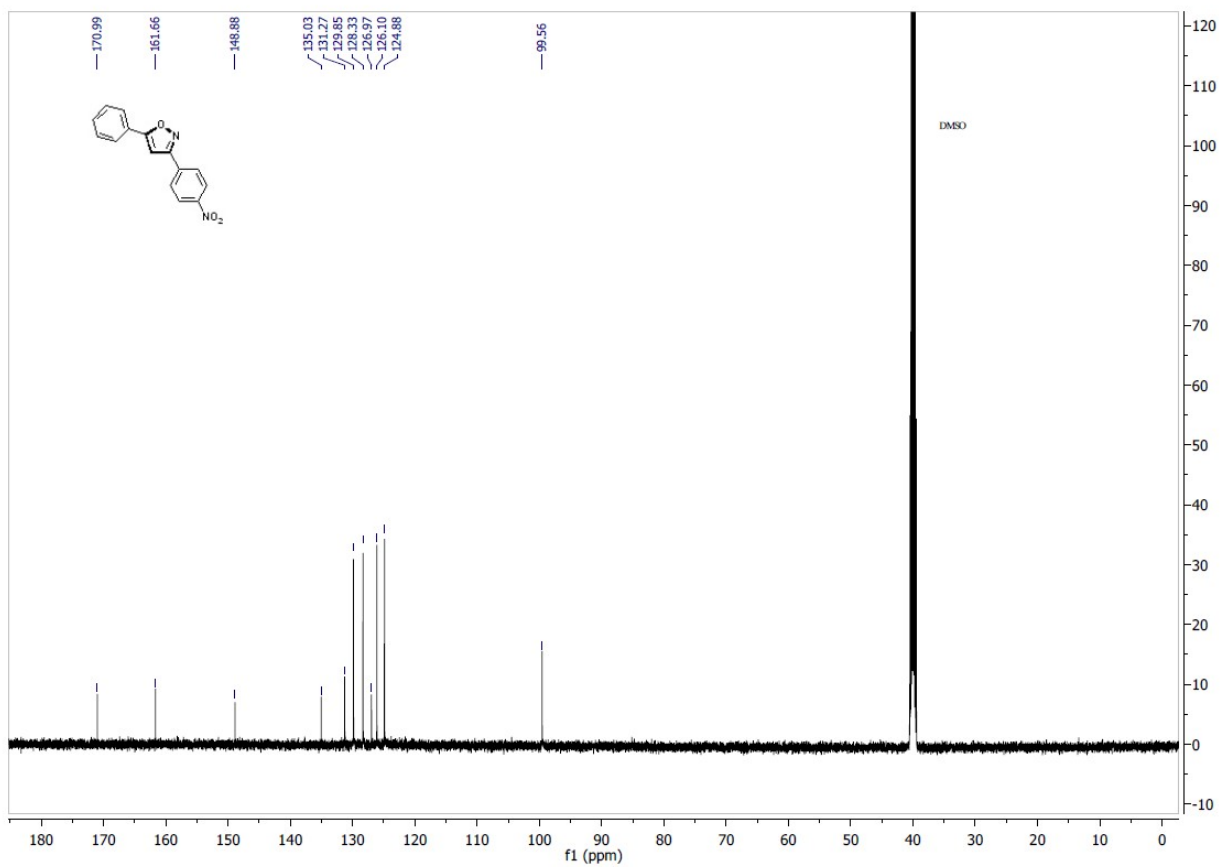


Figure S27: ^{13}C NMR spectrum of 3,5-isoxazole **1k**

Methyl 4-(3-(4-nitrophenyl)isoxazol-5-yl)benzoate (1m)

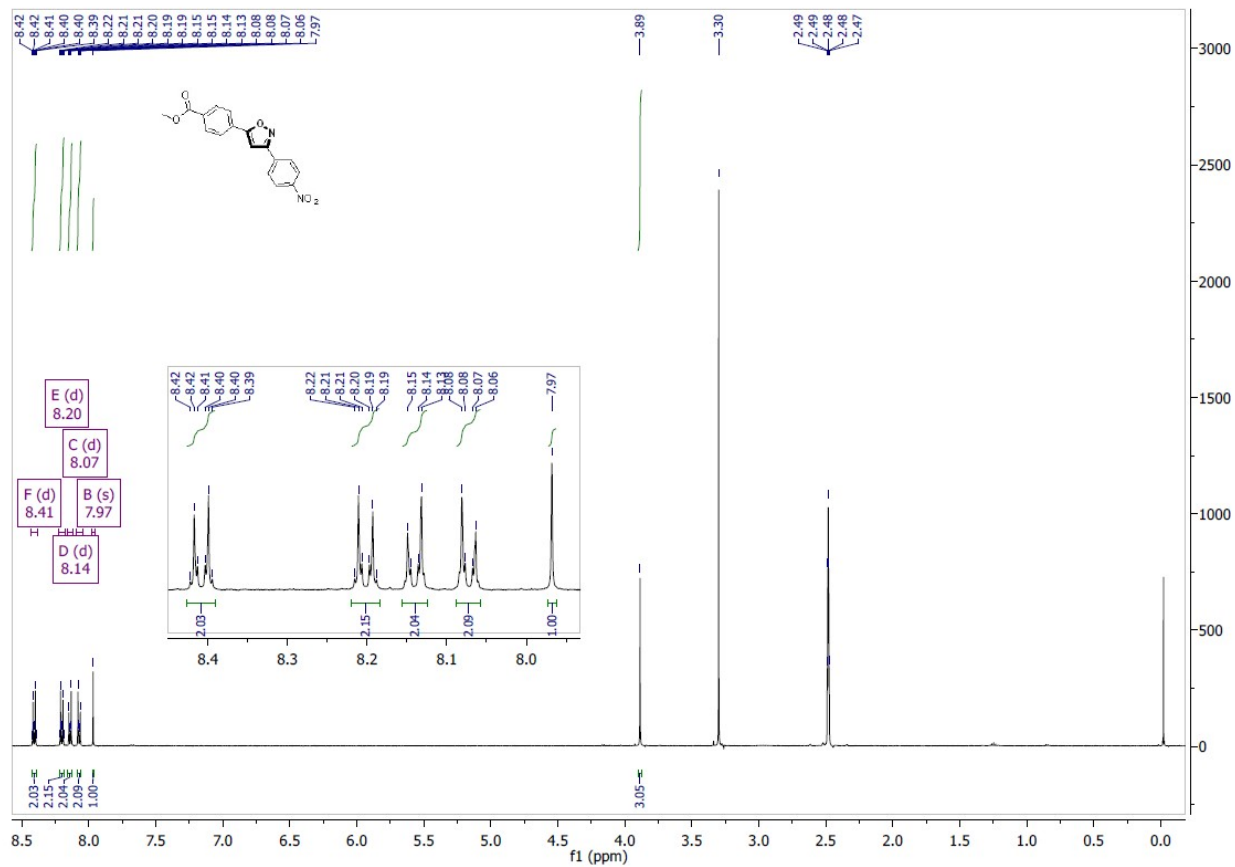


Figure S28: ¹H NMR spectrum of 3,5-isoxazole 1m

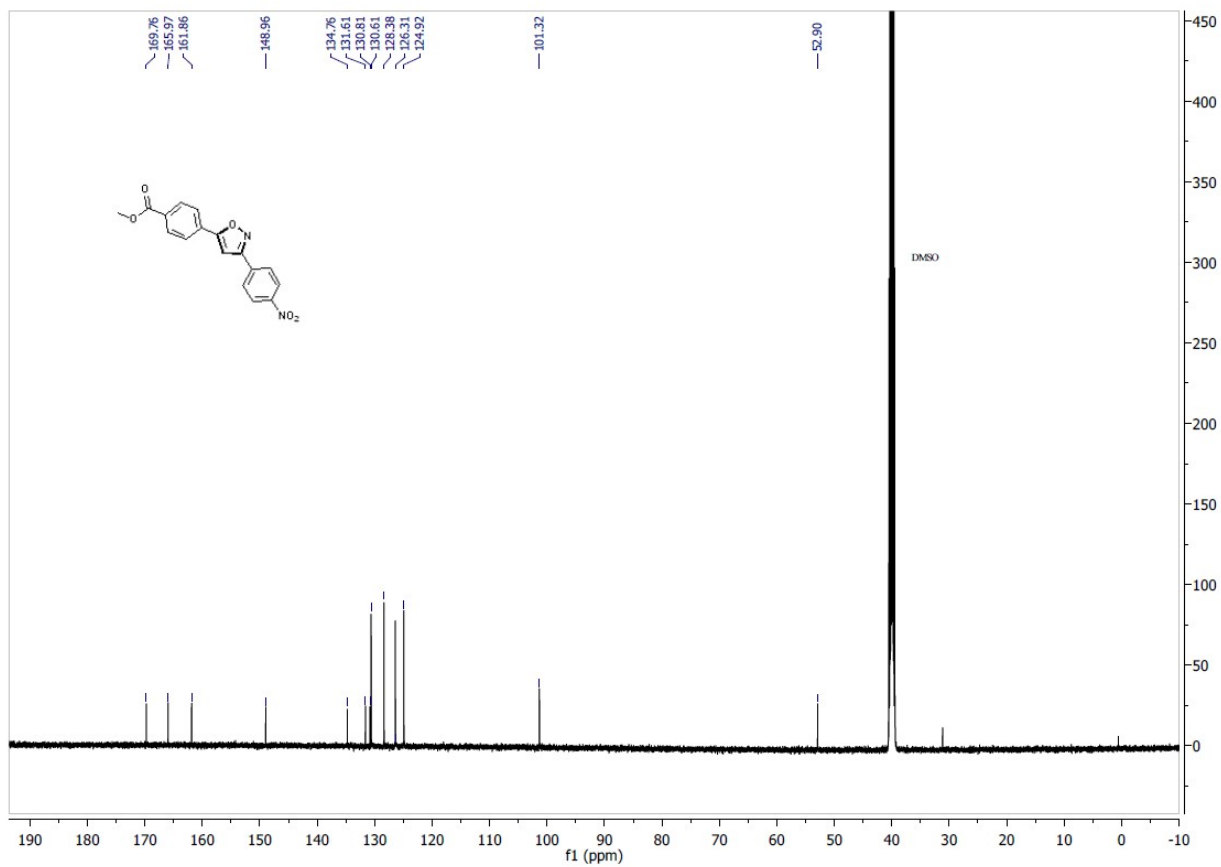


Figure S29: ^{13}C NMR spectrum of 3,5-isoxazole 1m

3-(4-nitrophenyl)-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoxazole (1n)

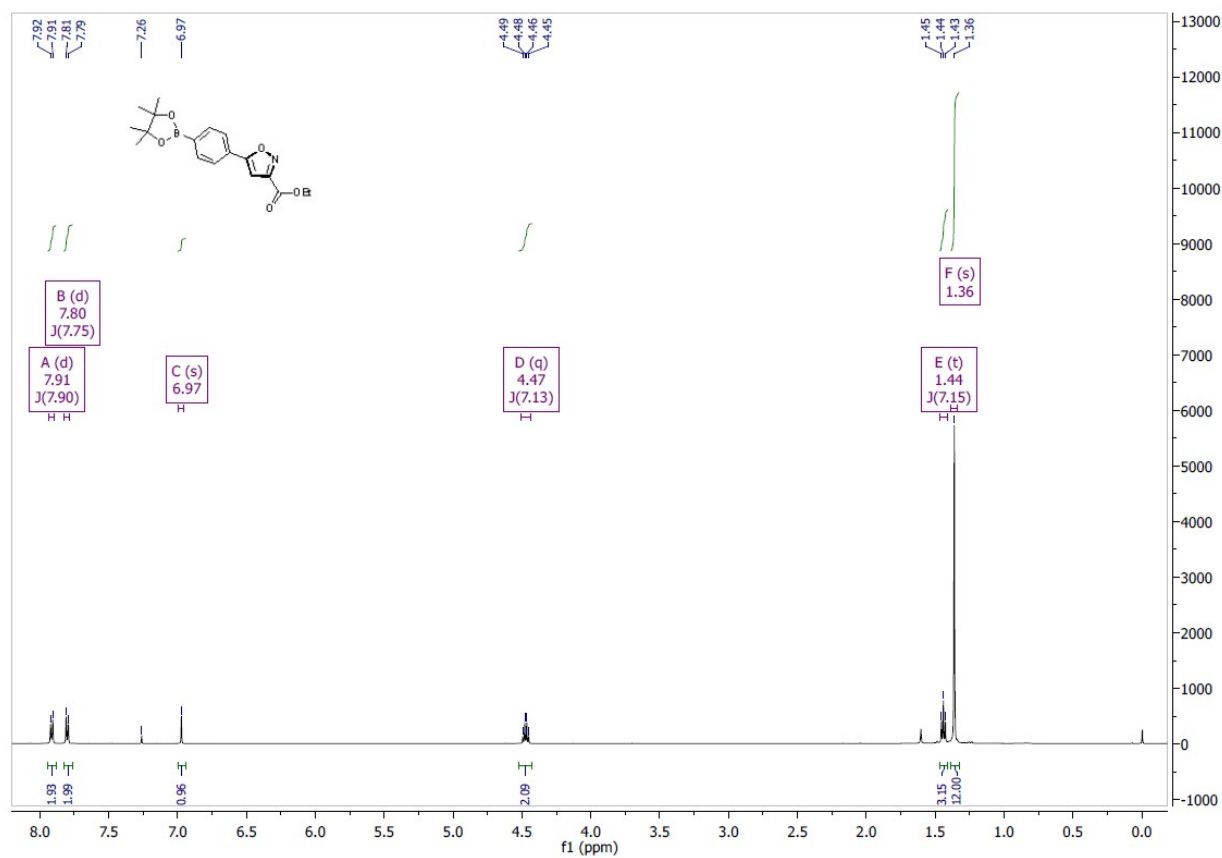


Figure S30: ¹H NMR spectrum of 3,5-isoxazole 1n

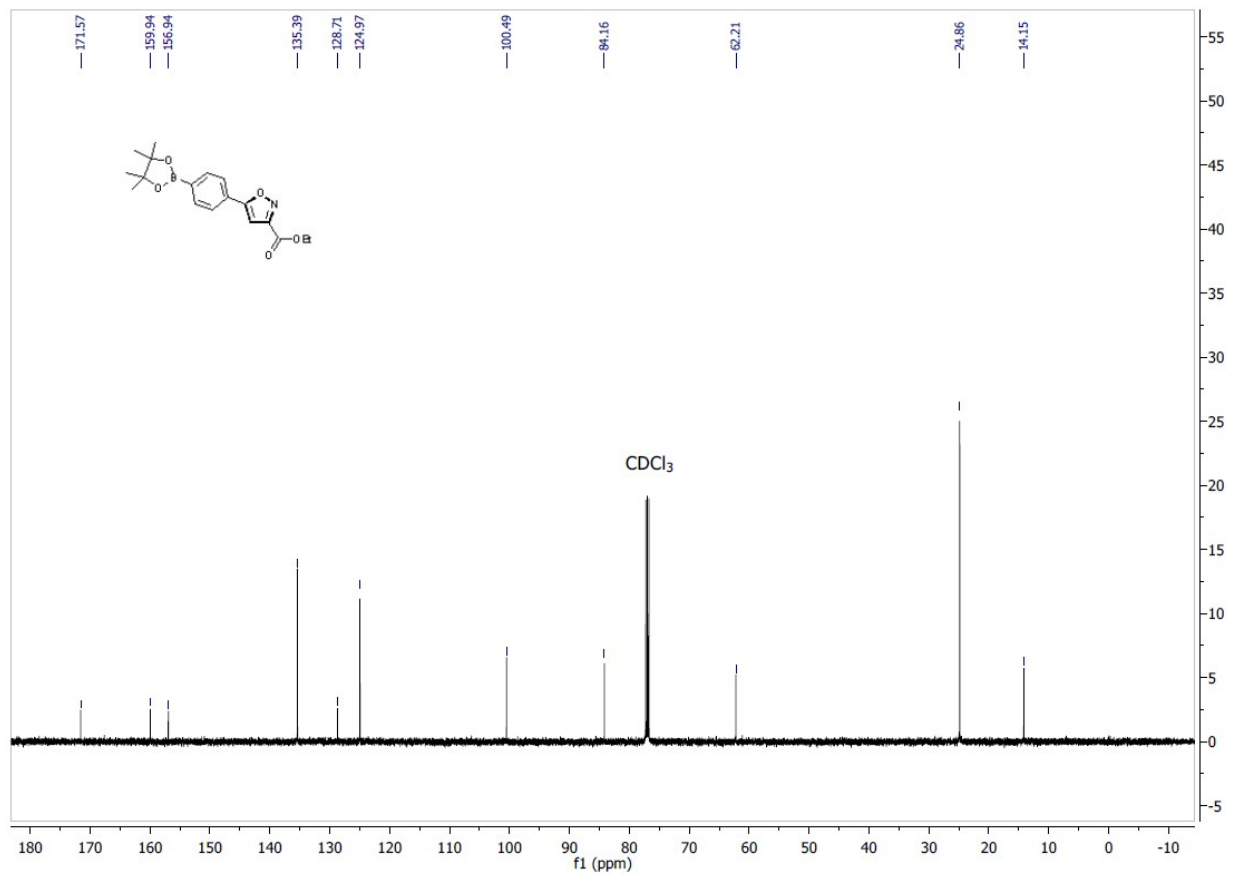


Figure S31: ¹³C NMR spectrum of 3,5-isoxazole 1n

Ethyl 5-(4-(dimethylamino)phenyl)isoxazole-3-carboxylate (1o)

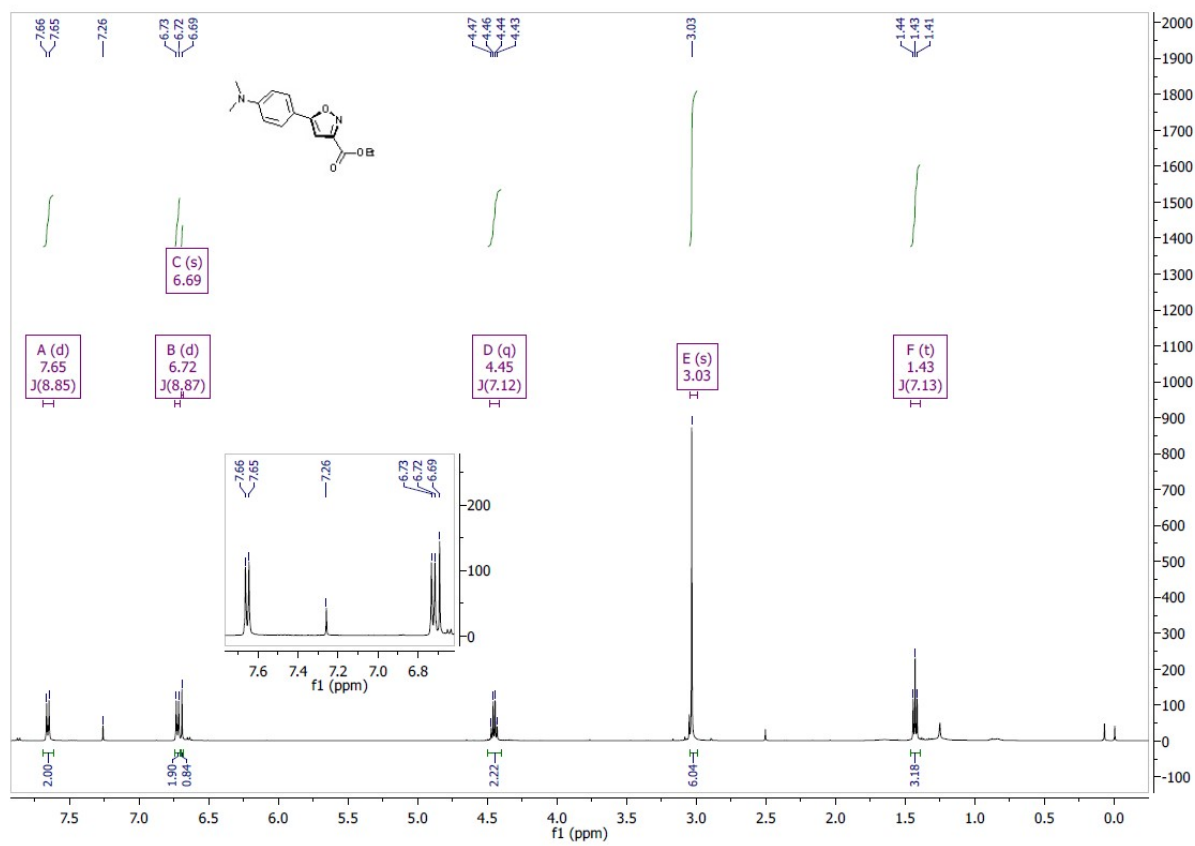


Figure S32: ¹H NMR spectrum of 3,5-isoxazole 1o

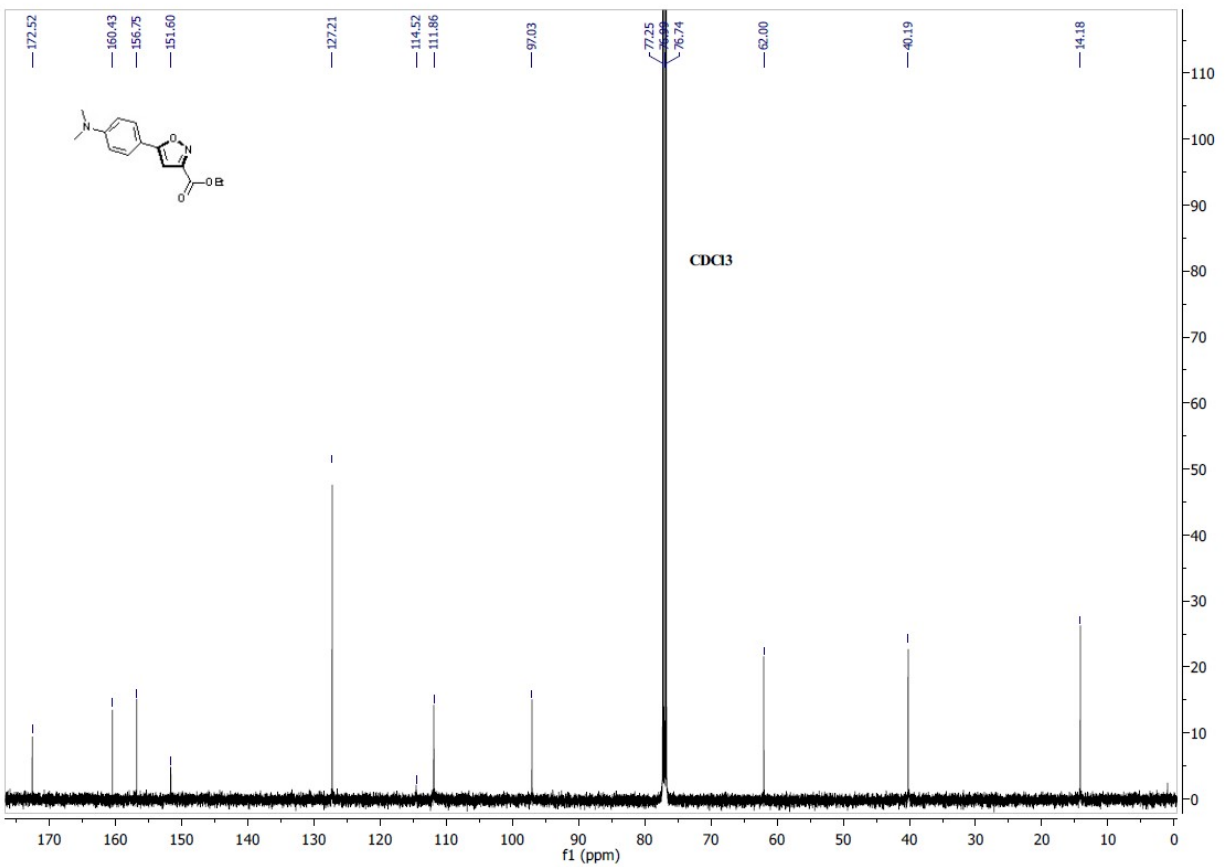


Figure S33: ^{13}C NMR spectrum of 3,5-isoxazole **1o**

ethyl 5-(3,5-dimethoxyphenyl)isoxazole-3-carboxylate (1p)

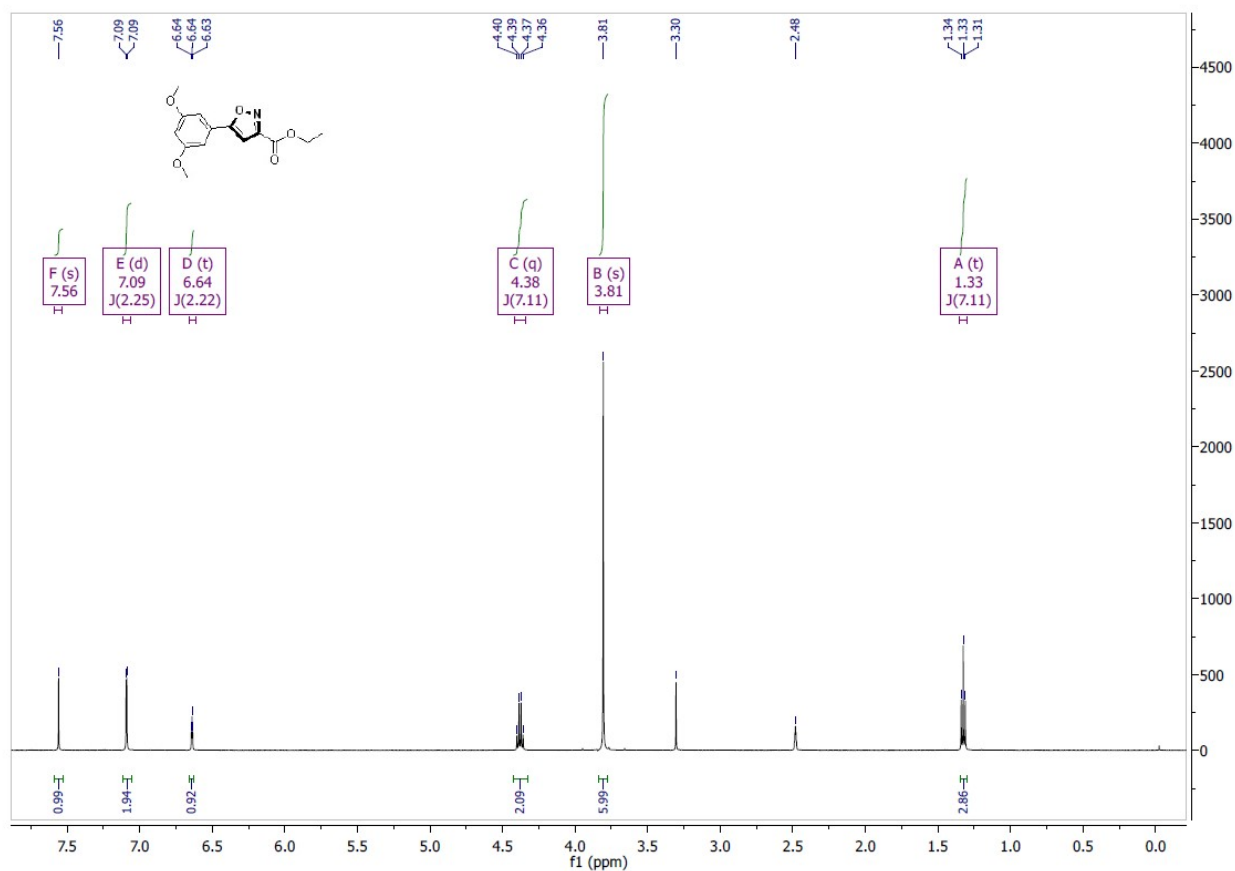


Figure S34: ¹H NMR spectrum of 3,5-isoxazole 1p

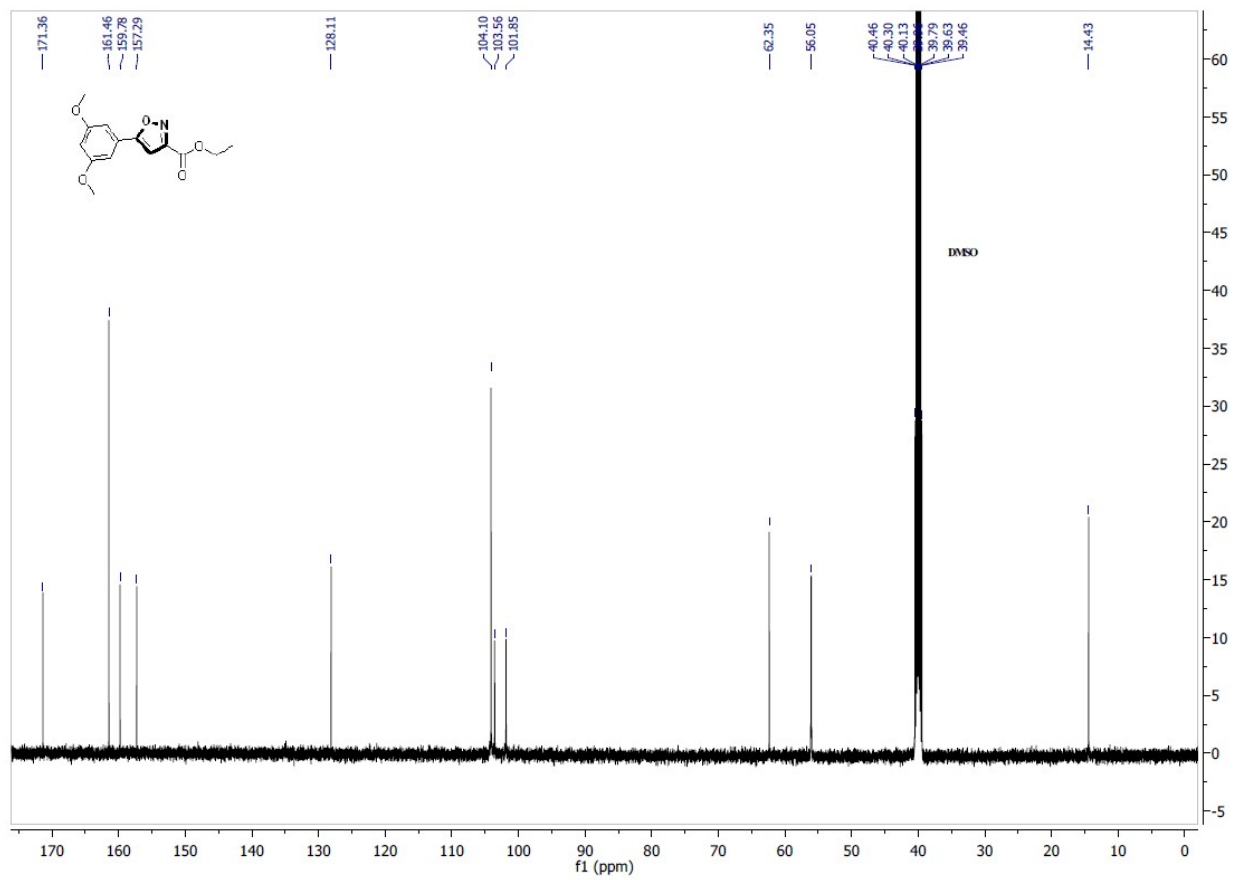


Figure S35: ^{13}C NMR spectrum of 3,5-isoxazole **1p**

5-(3,5-dimethoxyphenyl)-3-(4-nitrophenyl)isoxazole (1q)

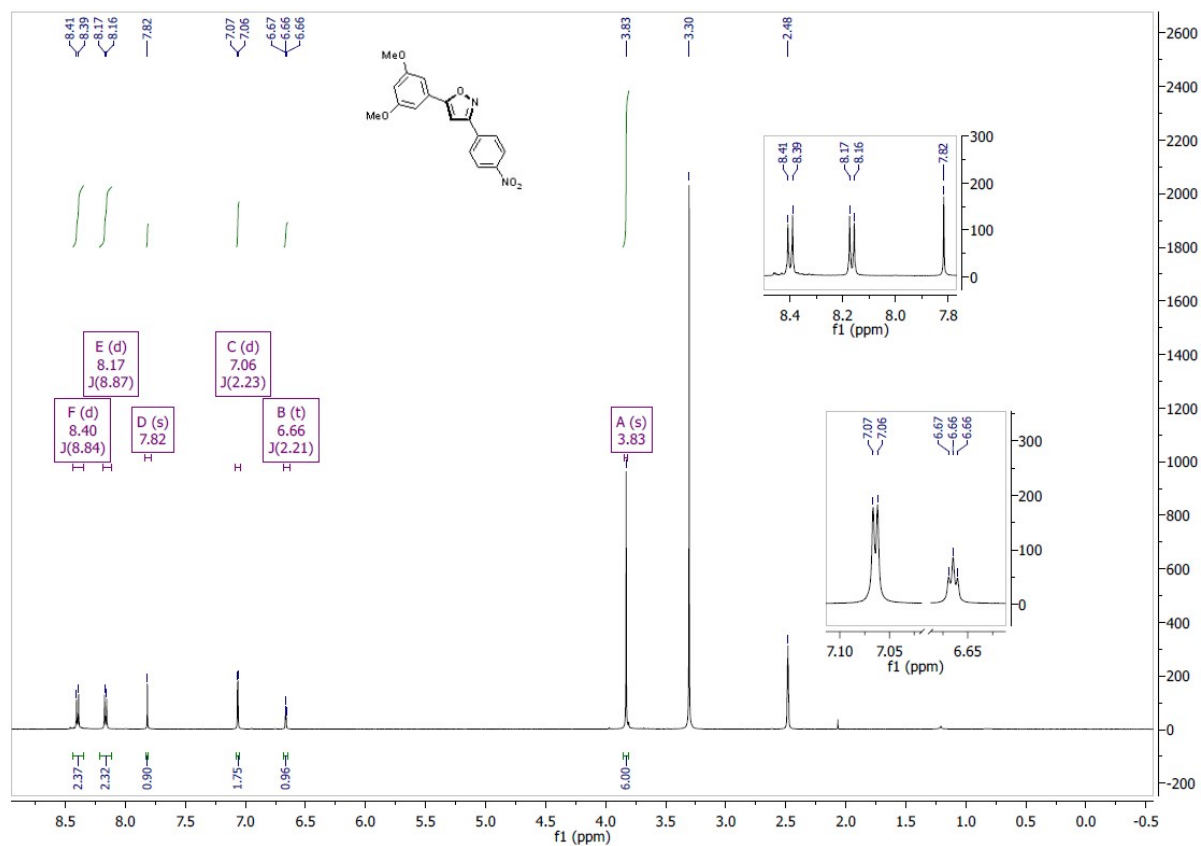


Figure S36: ¹H NMR spectrum of 3,5-isoxazole 1q

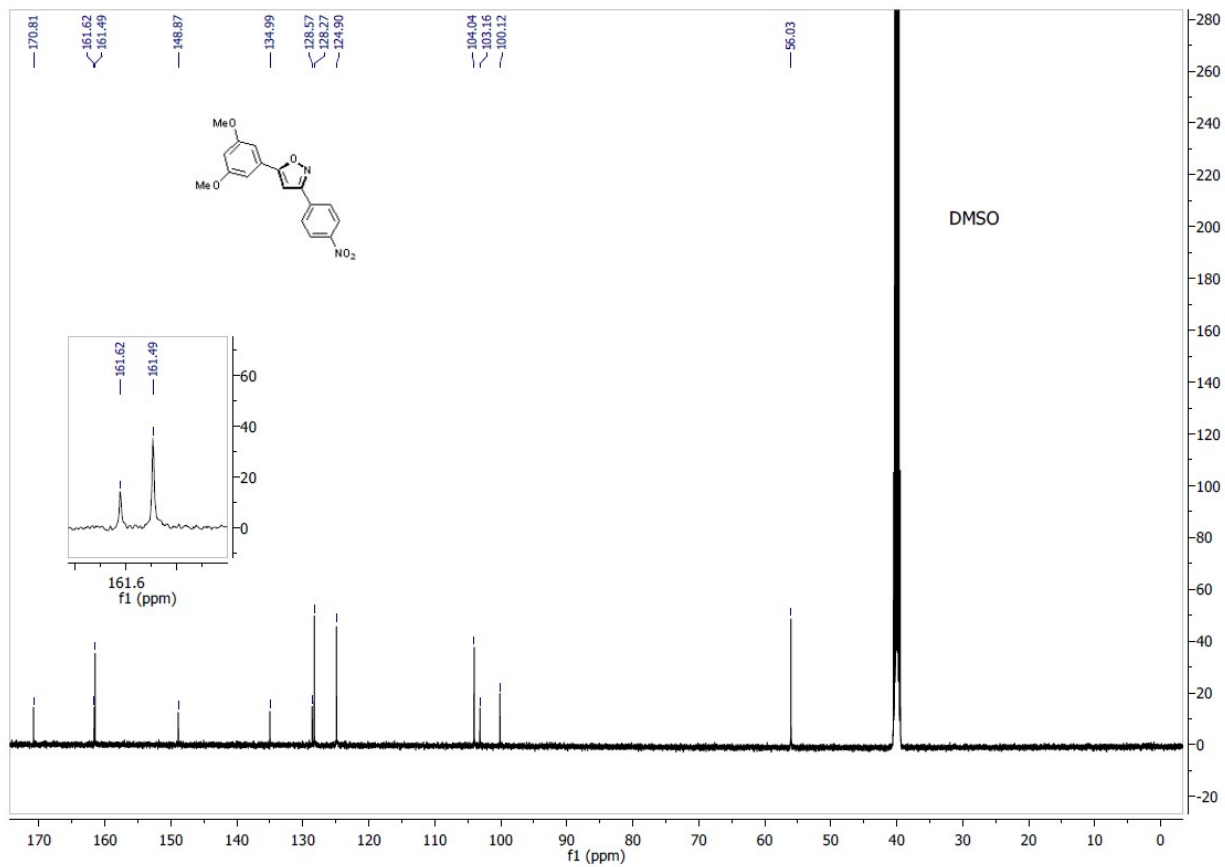


Figure S37: ¹³C NMR spectrum of 3,5-isoxazole **1q**

3-(4-nitrophenyl)-5-(pyridin-2-yl)isoxazole (1r)

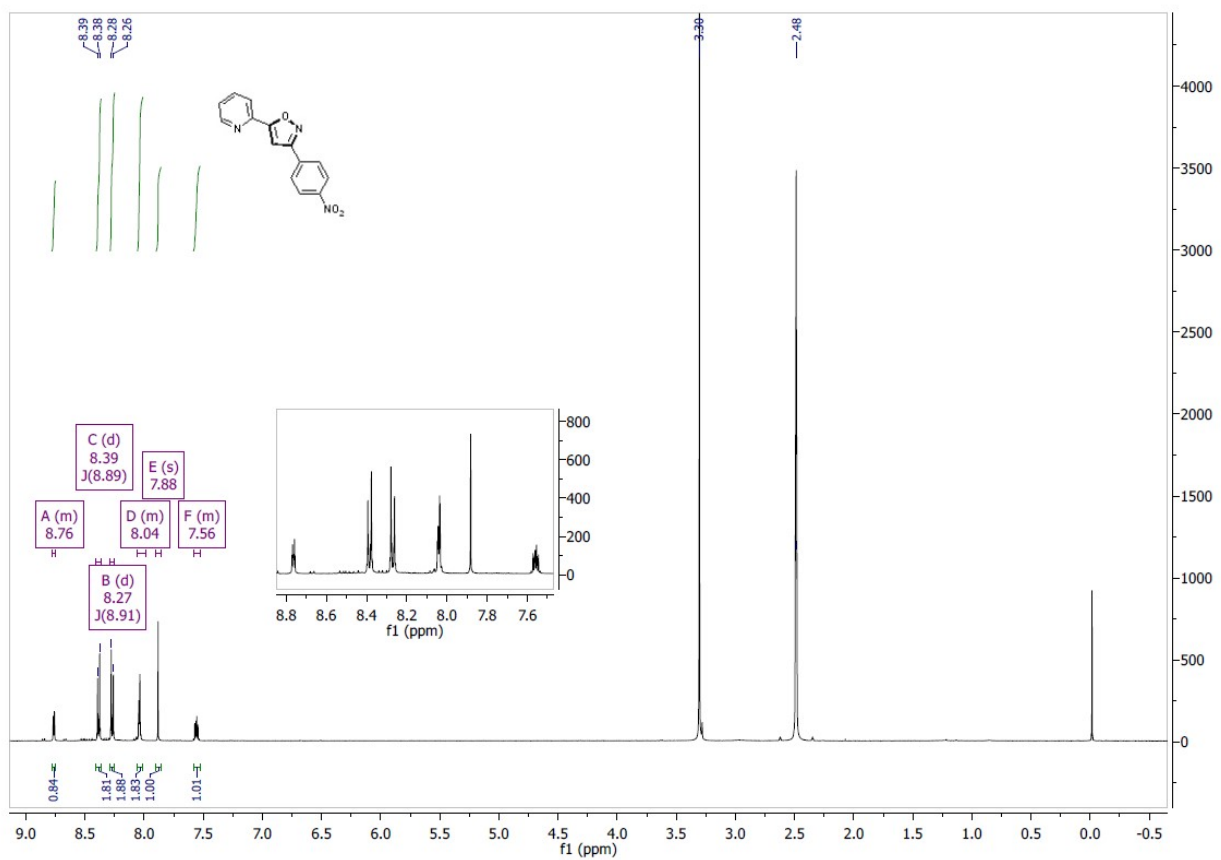


Figure S38: ¹H NMR spectrum of 3,5-isoxazole 1r

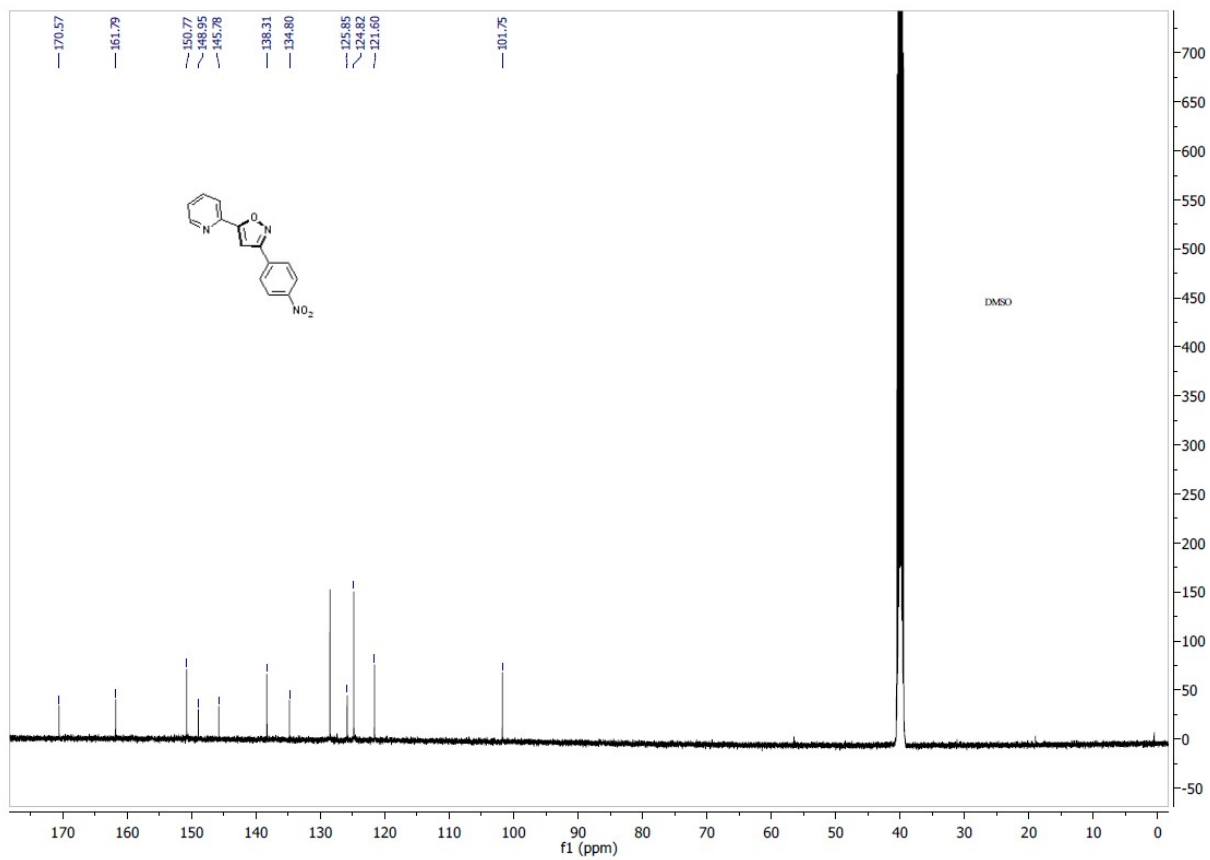


Figure S39: ^{13}C NMR spectrum of 3,5-isoxazole **1r**

Ethyl 5-(pyridin-2-yl)isoxazole-3-carboxylate (1s)

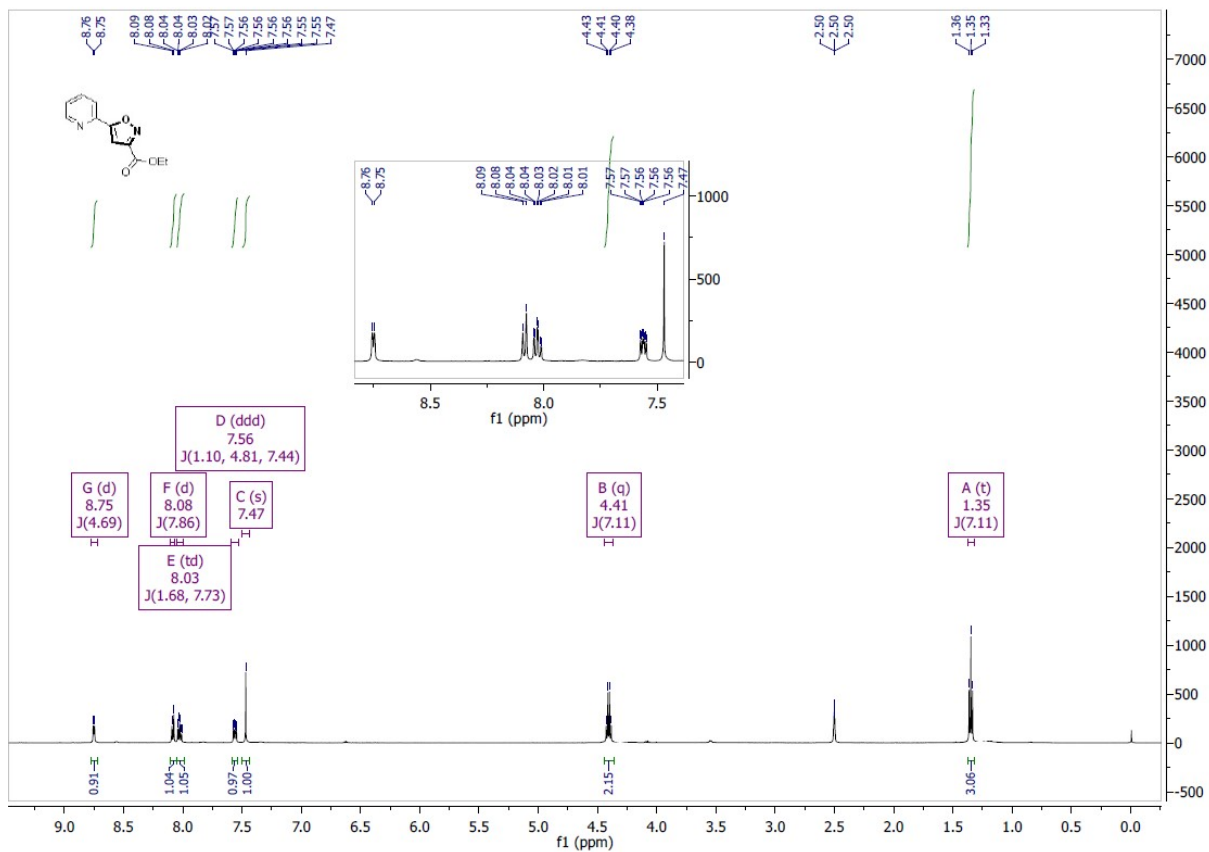


Figure S40: ¹H NMR spectrum of 3,5-isoxazole 1s

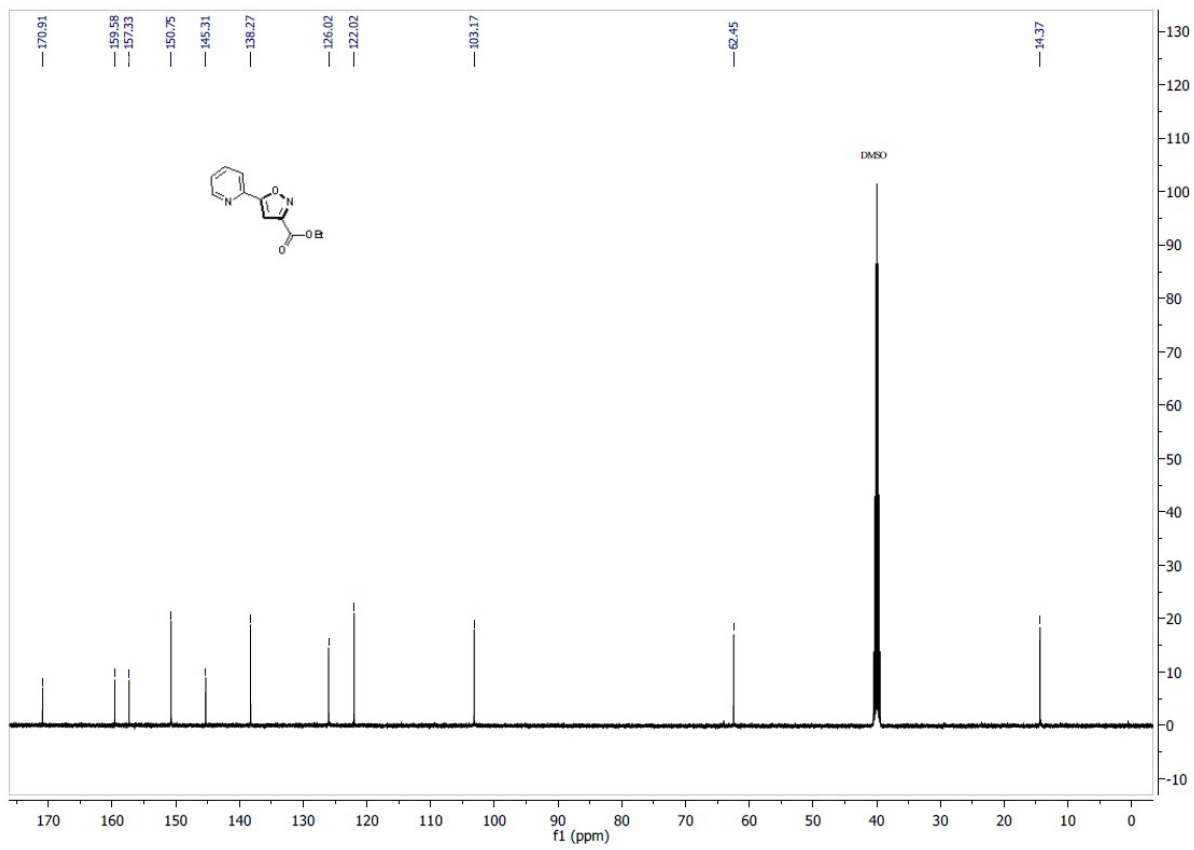
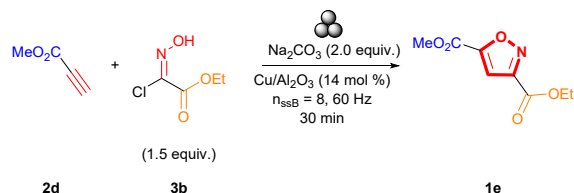


Figure S41: ^{13}C NMR spectrum of 3,5-isoxazole **1s**

Solid-state characterization of the reaction crude:



The solid crude for the synthesis of 3,5-isoxazole **1e** was analysed by FT-IR spectroscopy and MALDI-TOF MS to determine that **1e** was synthesized by the effect of mechanical energy. As a result, 3,5-isoxazole **1e** was synthesized according to **PS3**, but no isolation was attempted and the solid crude was analysed by FT-IR and MALDI-TOF MS with no addition of solvent.

FT-IR Spectra comparison.

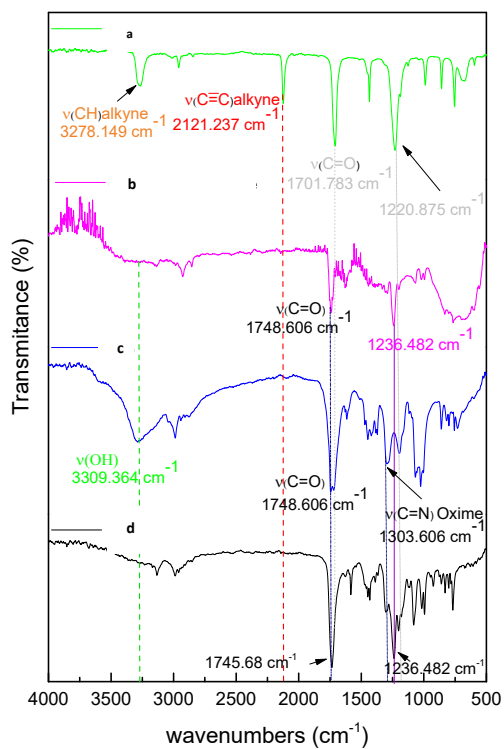
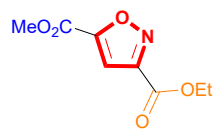


Figure S42: FT-IR spectra of the 3,5-isoxazole **1e** crude. From top to bottom a) Methyl propiolate **2d**. b) **1e** crude isoxazole sample. c) (E,Z)-2-chloro-2-(hydroxyimino)acetate (**3b**) d) Isolates sample of isoxazole **1e**

MOLDI-TOF MS



1e

Calculated m/z for (C₈H₉O₅N). m/z=199.048 found 199.051

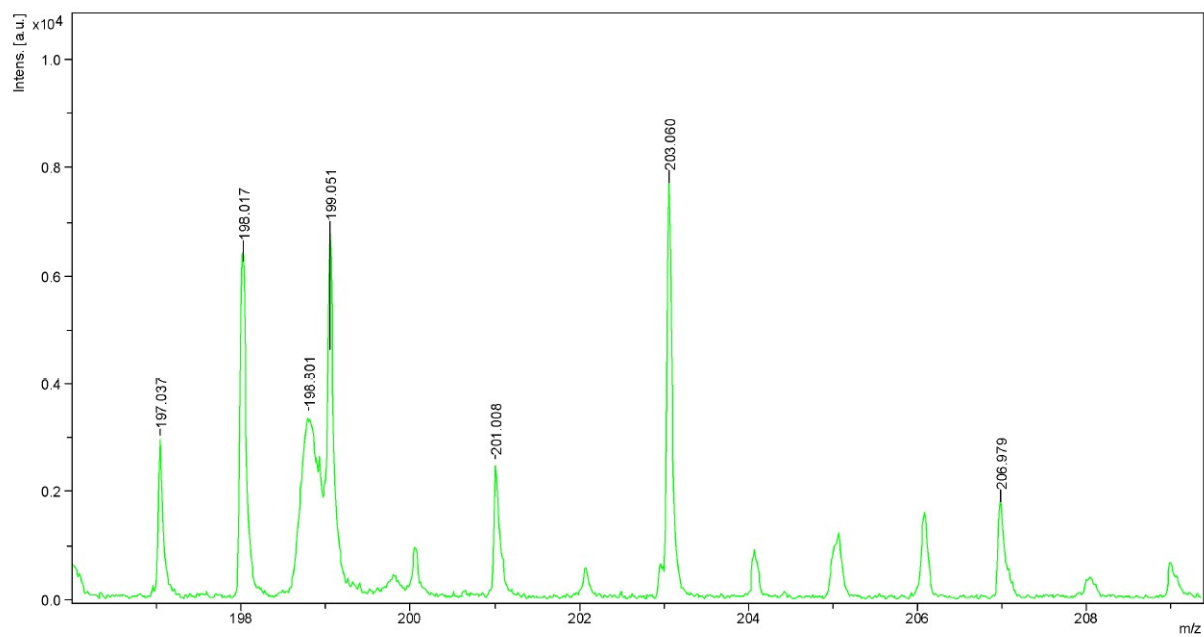


Figure S41: MALDI-TOF MS spectra of solid crude product 18e