Supporting Information

Comparative Photochemical Flow Synthesis of Ketenimines via Hg-Lamp and UV-C LED Irradiation

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1. Materials and Methods

1.1 General materials and methods

Unless otherwise stated, all solvents were purchased from Fisher Scientific and used without further purification. Also, unless otherwise stated, all substrates and reagents were purchased from Fluorochem or Sigma-Aldrich and used as received.

^{1}H NMR spectra were recorded on 400 and 500 MHz instruments and are reported relative to the residual solvent: $CDCl_3$ (δ 7.26 ppm) or DMSO-d_6 (δ 2.50 ppm). $^{13}C\{^{1}H\}$ NMR spectra were recorded on the same instruments (100 and 125 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm) or DMSO-d_6 (δ 39.52 ppm). ^{19}F NMR were recorded at 376 MHz. Data for ^{1}H NMR are reported as follows: chemical shift (δ/ ppm) (integration, multiplicity, coupling constant (Hz)). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br s = broad singlet, app = apparent. Data for $^{13}C\{^{1}H\}$ NMR are reported in terms of chemical shift (δ/ppm) and multiplicity (C, CH, CH_2, or CH_3). COSY and HSQC experiments were used in the structural assignment.

IR spectra were obtained by use of a Bruker Platinum spectrometer (neat, ATR sampling) with the intensities of the characteristic signals being reported as weak (w, 71% of the tallest signal).

High-resolution mass spectrometry was performed using the indicated techniques on a micromass LCT orthogonal time-of-flight mass spectrometer with leucine-enkephalin (Tyr-Gly-Phe-Leu) as an internal lock mass. GC–MS was performed on a Waters GCT Premier Agilent 7898 system (column Macherey–Nagel; Optima 5 MS, length 15 m, diameter 0.25 mm).

Continuous flow experiments were performed on a Vapourtec E-series system equipped with peristaltic pumps and a dynamic BPR achieved through utilisation of a peristaltic pump in a reverse direction (1-9 bar, Vapourtec). For photochemical experiments the under Hg-irradiation a UV150 module was used in combination with a medium pressure Hg-lamp equipped with a Vapourtec low pass UV filter #2 and cooled to 10-25 °C by passing a stream of compressed air cooled with a dry-ice dewar. The reactor volume for Hg-irradiation was 10 mL. For irradiation utilising the low-

wavelength LEDs a 3D printed reactor frame was paired with a coiled PTFE tubing system supported giving a reactor volume of 1.6 mL, the LED light source was secured 15 mm from the outside of the coiled tubing and a reflective polished aluminium plate placed behind the coiled reactor tubing. The low wavelength light sources were operated at maximum capacity with a total power usage of 33W. Reactor coils were made of PTFE tubing (i.d. 1/16 inch).

UV−vis measurements were performed with a Shimadzu UV-1800 UV spectrophotometer.

TLC was performed on Merck pre-coated Silica gel 60 F254 aluminium plates with realisation by UV irradiation at 254 nm, $KMnO_4$ and vanillin stain. Flash chromatography was performed using Macherey-Nagel silica gel 60 M, with a particle range of 0.04 - 0.063 mm.

1.2 Construction of low-wavelength LED reactor.

The frame for reactor v2 was designed and rendered using Blender™. The object was saved as a blend file and exported for printing on a Bambu Lab A1 3D printer. Polylactic acid (PLA) filament was used as the printing material. Printing was performed with a nozzle temperature of 220 °C and a heated bed temperature of 65 °C. The print parameters were: 0.2 mm layer height, 25% gyroid infill, and a 60° support overhang angle with a support density of 20%. A copy of the 3D print file is freely available at [https://www.thingiverse.com/thing:7128534].

With the reactor frame in hand two aluminium support rods were installed as can be seen in the image below (**Fig S1**) with 18 mm between the insides of the aluminium rods. The aluminium rods had a diameter of 3 mm and were 80 mm long. To protect the PLA, aluminium foil was wrapped around the entirety of the reactor frame. A reflective polished aluminium plate supplied by Signify was then placed on the back of the reactor frame, with the intention of reflecting transmitted light onto the backside of the coiled PTFE tubing. To prepare the coiled reactor tubing a glass vial with diameter of 30 mm was used a template for which the PTFE was tightly wound around. Once wound to the desired height which matched the UV-LED light source height, one side

of the tubing was secured with tape, whilst an aluminium rod was placed on the opposite end. Careful removal of the tape and placement of a second aluminium rod in its place whilst ensuring tension is kept on the coiled tubing afforded the reactor. Following the coiling, polyether ketone (PEEK) fittings were installed at the ends of the tubes secured using ferrules and stainless-steel rings. The reactor volume was measured my filling it completely via Luer lock syringes and recording the volume in triplicate until 3 readings agreed by 0.05 mL, measured using a 1 mL graduated cylinder. The reactor frame was mounted using m8 bolts and nuts with an irradiation distance of 15 mm between the tubing and the LED source.

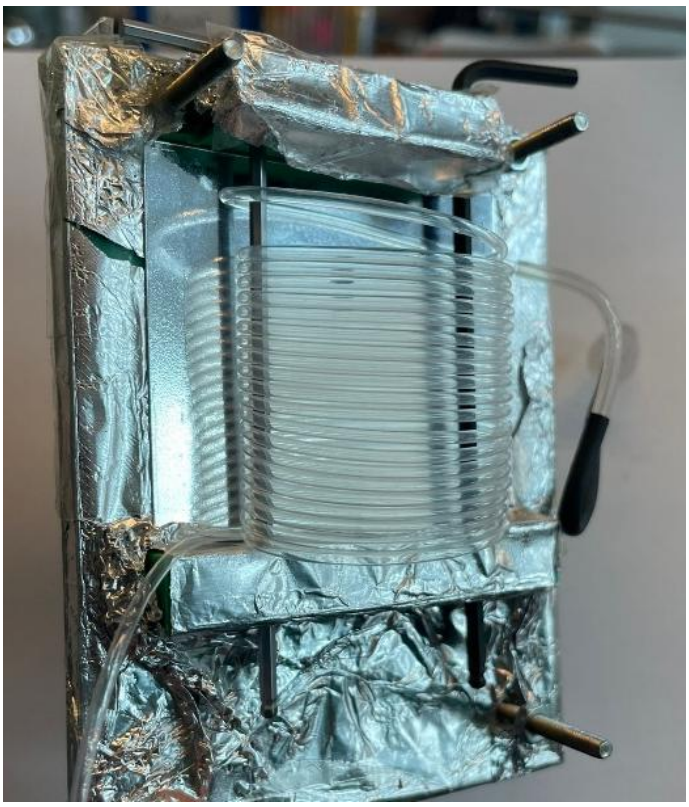


***Figure S1**: Image of the low-wavelength reactor*

The UV-emission spectra of the LEDs can also be seen below (Figure S2).

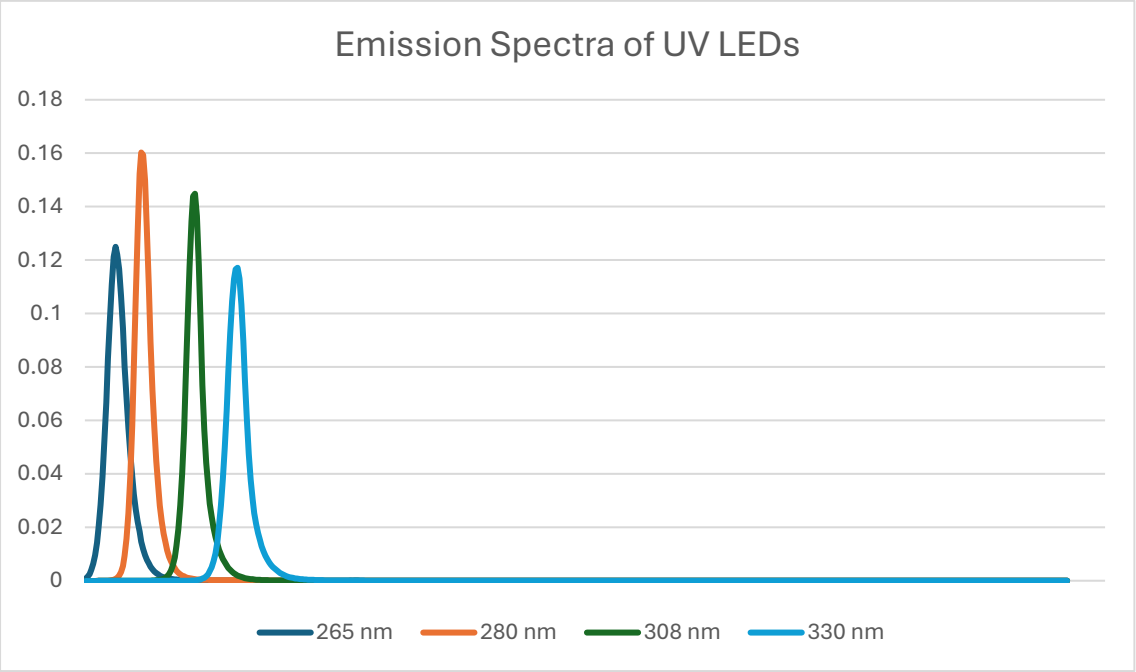


Figure S2: *UV-emission spectra of low-wavelength LEDs.*

1.3 DoE code

To carry out the design of experiments (DoE), Python was used in conjunction with Microsoft Copilot and Visual Studio Code to develop the necessary scripts. These scripts are freely accessible via the following GitHub repository:

https://github.com/ACUCD/AC_P5_DoE.git

2. Experimental Procedures

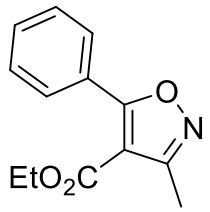
2.1 Synthesis of isoxazole **1a**

The following procedure was adapted from the previously described by Bracken *et al*. [C. Bracken and M. Baumann, *Org. Lett.*, 2023, **25**, 6593.].

To a solution of ethyl acetoacetate (9.72 mL, 77 mmol, 1 equiv.) in cyclohexane (17 mL, 4.5 M) was added aq. NaOH (3.5 mL, 33% w/w), and the mixture was stirred for 30 min at 0 ℃. Benzoyl chloride (11.4 mL, 98.1 mmol, 1.27 equiv.) and aq. NaOH (18 mL, 33% w/w), respectively, were then added dropwise. The mixture was stirred for 1 hr at 0 ℃, then heated to 40 ℃ and stirred for 1 hr. The reaction mixture was cooled to room temperature and stirred overnight. A yellow precipitate which formed was filtered, washed with Et2O and cyclohexane, before being dried under suction. Aqueous HCl (1 M, 78 mL, 78 mmol, 1.0 equiv.) was then added, and the solution was stirred before being diluted in EtOAc and washed with water. The organic layer was then further washed with sat. $NaHCO_3$ (75 mL) and brine (75 mL) before the organic layer was dried over anhydrous Na_2SO_4. The organic solvent was then evaporated to afford ethyl 2-benzoyl-3-oxobutanoate as a yellow oil 14.3 g (61 mmol, yield 81%) that was of sufficient purity to be used directly in the next step.

To a stirred solution of ethyl 2-benzoyl-3-oxobutanoate (14 g, 59.7 mmol) in EtOH (100 mL, 0.6 M) was added $H_2NOH.HCl$ (15.8 g, 228 mmol, 3.82 equiv.) in water (90 mL) dropwise under stirring. Using a DrySyn heating mantle, the reaction mixture was heated to 90 ℃ overnight and allowed to cool before then being diluted in EtOAc (100 mL). The organic layer was washed with water (100 mL) and then brine (100 mL). The organic layer was then dried over anhydrous Na_2SO_4 before being concentrated under vacuum to afford the crude product which was subsequently purified by column chromatography over silica gel (5% EtOAc/C-Hex) to afford pure compound **1a** as a colourless oil which crystallized upon standing to give a white solid (49.5 mmol, 11.4 g, 83%).

Ethyl 3-methyl-5-phenylisoxazole-4-carboxylate, 1a:



Chemical Formula: $C_{13}H_{13}NO_3$
Molecular Weight: 231.25

Yield = 49.5 mmol, 11.4 g, 83%, Appearance: white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.87 (m, 2H), 7.54-7.46 (m, 3H), 4.32 (q, *J* = 7.4 Hz, 2H), 2.52 (s, 3H), 1.31 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0 (C), 162.2 (C), 160.8 (C), 131.2 (CH), 129.2 (2CH), 128.2 (2CH), 127.1 (C), 108.2 (C), 60.9 (CH_2), 14.0 (CH_3), 12.3 (CH_3). IR (neat) v/cm^{-1}: 2994 (w), 1710 (s), 1608 (w), 1442 (m), 1442 (m), 1307 (m), 1099 (s), 758 (s), 698 (s). HR-MS (TOF-ES+) calc for $C_{13}H_{13}NO_3$ 232.0974 (M+H); found 232.0975 (M+H). UV-vis (λ_{max} MeCN) = 265 nm, ε = 11732 L mol^{-1} cm^{-1}.

2.2 Synthesis of isoxazoles **1b** and **1c.**

The following procedure was adapted from the previously described by Bracken *et al*. [C. Bracken and M. Baumann, *Org. Lett.*, 2023, **25**, 6593.].

The corresponding benzoic acid (10 mmol) was suspended in DCM (40 mL, 0.25 M) at room temperature. $SOCl_2$ (4 mL, 55.2 mmol, 5.5 equiv.) was then added dropwise along with a few drops of DMF (cat.). The suspension was heated at reflux (12 h, using a DrySyn heating mantle) while being monitored by TLC. Following total consumption of the starting material the reaction was ceased and the flask allowed to cool. The solvent was evaporated under reduced pressure before being flushed with N_2. The corresponding benzoyl chloride product was used directly in the next step without further purification.

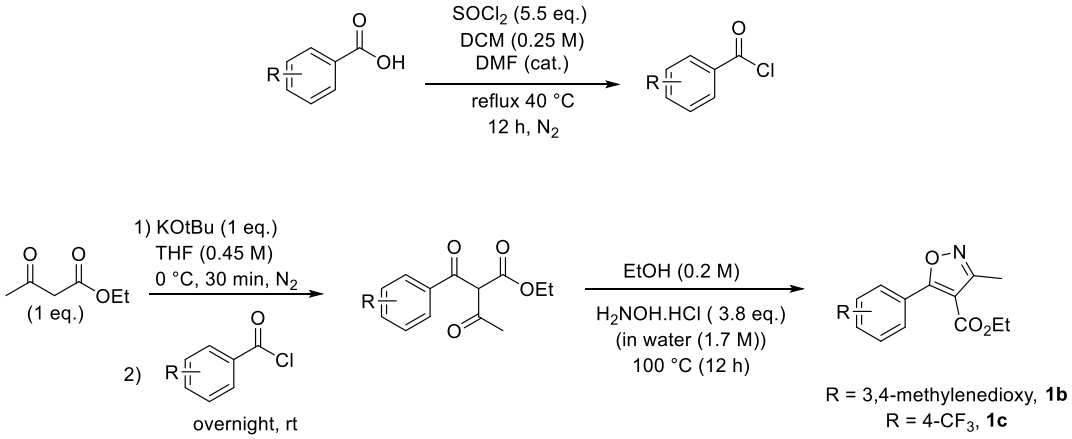
A pre-dried flask that had been flushed with N_2 was charged with a stir bar and KO^{t}Bu (10 mmol, 1.12 g, 1.0 equiv.) and left under N_2 for 15 mins. Dry THF (22 mL, 0.45 M) was then added, and the solution was stirred at 0 °C for 30 mins. Ethyl acetoacetate (10 mmol, 1.3 g, 1.28 mL, 1.0 equiv.) was then added and the solution was stirred for a further hour at 0 °C. To the now colourless solution, the appropriate benzoyl chloride reagent (10 mmol, 1.0 equiv.) was added dropwise (or dissolved in minimum volume

of dry THF and added dropwise). A precipitate formed in the flask, and the reaction was gradually warmed to room temperature before being left to stir overnight under N_2. The solution was then diluted in EtOAc (50 mL) before aqueous HCl (1 M, 1.0 equiv., 10 mL) was added. The solution was washed with water, followed by aqueous $NaHCO_3$ and brine (2 x 75 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 before the solvent was evaporated to provide the crude adduct as an orange oil which was used directly in the next step without further purification.

To a stirred solution of the freshly prepared adduct (7.5 mmol, 1.0 equiv.) in EtOH (38 mL, 0.2 M) was added $H_2NOH.HCl$ (1.98 g, 28.5 mmol, 3.8 equiv.) in water (16 mL, 1.7 M) dropwise under stirring. Using a DrySyn heating mantle, the reaction mixture was then heated to reflux overnight and allowed to cool before then being diluted in EtOAc (50 mL). The organic layer was washed with water (50 mL) and then brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4 before being concentrated under vacuum to afford the crude product which was subsequently purified by column chromatography using silica gel (5/10% EtOAc/c-Hex) to afford the pure isoxazole target compound as an oil, which often crystallised over time.

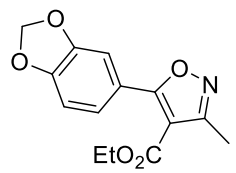
Alternatively, for isoxazoles known to crystallise, crude products that appeared semi-crystalline following aqueous extraction were recrystallised from a minimal volume of hot EtOH. Although this approach typically resulted in yields approximately 10–20% lower, it consistently afforded highly pure isoxazole products without the need for column chromatography.

An overview of this process can be seen below (**Scheme S1**).



Scheme S1: *General schematic for synthesis of isoxazoles* ***1b*** *and* ***1c*****.**

Ethyl 5-(benzo[d][1,3]dioxol-5-yl)-3-methylisoxazole-4-carboxylate, 1b:



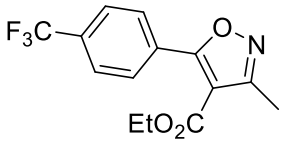
Chemical Formula: $C_{14}H_{13}NO_5$
Molecular Weight: 275.26

Yield = 4.2 mmol, 1.15 g, 42%, appearance: white solid - purified by column chromatography. Yield = 3.8 mmol, 1.05 g, 38%, appearance: white crystal - purified by crystallisation.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8 Hz, 1H), 7.46 (d, *J* = 1 Hz, 1H), 6.92 (d, *J* = 8 Hz, 1H), 6.07 (s, 2H), 4.34 (q, *J* = 7.5 Hz, 2H), 2.51 (s, 3H), 1.37 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.5 (C), 162.3 (C), 160.8 (C), 150.1 (C), 147.6 (C), 124.4 (C), 120.7 (CH_2), 109.4 (CH), 108.3 (CH), 107.5 (CH), 101.2 (C), 60.9 (CH_2), 14.2 (CH_3), 12.5 (CH_3). IR (neat) v/cm^{-1}: 2954 (w), 2915 (w), 1718 (s), 1623 (m), 1481 (s), 1448 (s), 1247 (s), 1093 (s), 1025 (s), 812 (m), 778 (m). HR-MS (TOF-ES+) calc for $C_{14}H_{13}NO_5$ 276.0872 (M+H); found 276.0872 (M+H). UV-vis (λ_{max} MeCN) = 265 nm, ε = 9798 L mol^{-1} cm^{-1}.

This data is consistent with published work [C. Bracken, M. Baumann. **2023**, *Org. Lett.* 25, 35, 6593-6597].

Ethyl 3-methyl-5-(4-(trifluoromethyl)phenyl)isoxazole-4-carboxylate, 1c:



Chemical Formula: $C_{14}H_{12}F_3NO_3$
Molecular Weight: 299.25

Yield = 4.5 mmol, 1.34 g, 45%, Appearance: white solid – purified by column chromatography. Yield = 3.9 mmol, 1.15 g, 39% - purified by crystallisation, appearance: white crystal.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 4.31 (q, *J* = 7.0 Hz, 2H), 2.51 (s, 3H), 1.31 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (C), 161.9 (C), 161.0 (C), 132.8 (q, $J_{C\text{-}F}$ = 33 Hz, C), 130.4 (C), 129.7 (2CH), 125.3 (q, $J_{C\text{-}F}$ = 4 Hz, 2CH), 123.6 (q, $J_{C\text{-}F}$ = 266 Hz, CF_3), 109.4 (C), 61.2 (CH_2), 14.0 (CH_3), 12.3 (CH_3). ^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$) δ -63.1 (3F). IR (neat) v/cm^{-1}: 3035 (w), 1721 (s), 1598 (m), 1415 (m), 1322 (s), 1167 (s), 1128 (s), 1021 (s), 856 (m), 779 (m). HR-MS (TOF-ES+) calc for $C_{14}H_{12}F_3NO_3$ 300.0848 (M+H); found 300.0849 (M+H). UV-vis (λ_{max} MeCN) = 265 nm, ε = 11703 L mol^{-1} cm^{-1}. This data is consistent with published work [C. Bracken, M. Baumann. **2023**, *Org. Lett.* 25, 35, 6593-6597].

2.3 Flow procedure for the formation of ketenimines

The isoxazole was dissolved in MeCN to the desired concentration, in some instances sonication was required to obtain a homogeneous solution.

In the case of Hg-lamp irradiation the resultant reactant solution was pumped using an Vapourtec V-3 peristaltic pump into a pre-charged UV-150 Vapourtec photochemical reactor equipped with a 10 mL PTFE coiled tube with an internal diameter of 1/32”, cooled by compressed air passed through a dry-ice filled dewar. A medium-pressure Hg-lamp was used fitted with a Vapourtec low pass filter #9, the lamp was operated at 130 W. The UV-150 photochemical reactor was conditioned by passing 15 mL total volume of solvent (MeCN) prior to the reaction and a flow rate of 0.8 mL min^{-1} was used to afford a reaction time of 12.5 minutes in the 10 mL reactor coil. The resultantly crude solution was collected in a flask, dried *in vacuo* and the crude ketenimine was quantified promptly using q-NMR with 1,3,5-trimethoxybenzne or 1,2-dichloroethene used as an internal standard, which are added via a stock solution of *d*-$CDCl_3$.

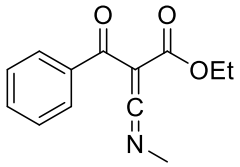
In the case of the UV-LEDs, the reactor frame was mounted 15 mm from the irradiation source and the loop conditioned with MeCN using a Vapourtec V-3 peristaltic pump for two full reactor volumes operating at 0.128 mL min^{-1}. The reaction solution was introduced via a Vapourtec V-3 peristaltic pump under the same flow rate to afford a reaction time of 12.5 minutes. Similarly, the resultant crude reaction solution containing ketenimine was collected in a flask and dried *in vacuo* and quickly prepared for q-NMR using the same stock solution of 1,3,5-trimethoxybenzne or 1,2-dichloroethene as for Hg-lamp irradiation.

In both instances a pale to dark yellow colour was observed upon exiting the photochemical reactor and was indicative of the degree of decomposition within the crude reaction mixture with paler to colourless solutions having cleaner conversion to ketenimine whilst darker solutions typically observed extensive decomposition.

In both instances a relaxation delay of 25 seconds was employed for the q-NMR analysis.

Isolation of the ketenimine species was not feasible due to their inherent instability and rapid decomposition. Previous studies confirmed their formation through crude NMR analysis and by reduction to the corresponding imine, which was subsequently characterised. Furthermore, later results in this work will demonstrate successful functionalisation of the ketenimine intermediates. For these reasons, extensive characterisation of the ketenimines themselves was not repeated. Instead, their presence in solution was validated by comparison of ^{1}H-NMR and ^{13}C-NMR spectra obtained from crude reaction mixtures. Only the corresponding peaks for the ketenimine species will be listed in the below characterisations but copies of the spectra are available in the appendix.

Ethyl 2-benzoyl-3-(methylimino)acrylate, 2a:



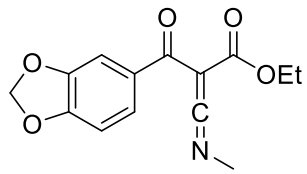
Chemical Formula: $C_{13}H_{13}NO_3$
Molecular Weight: 231.25

The target ketenimine **2a** observed a q-NMR yield of 47% when irradiated with the 265 nm LED at a concentration of 0.6 M and reaction time of 13 minutes in the reactor prototype v2. Listed characterisation peaks are taken form crude NMR and matched with previously reported NMR data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.57 (m, 2H), 7.48 - 7.35 (m, 3H), 4.17 (d, *J* = 7.1 Hz, 2H), 3.65 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0 (C), 165.9 (C), 143.0 (C, weak), 140.4 (C), 131.3 (CH), 128.9 (2CH), 128.6 (2CH), 69.0 (C), 60.2 (CH2), 33.0 (CH3), 14.5 (CH3).

This data is consistent with published work [C. Bracken, M. Baumann. **2023**, *Org. Lett.* 25, 35, 6593-6597].

Ethyl 2-(benzo[d][1,3]dioxole-5-carbonyl)-3-(methylimino)acrylate, 2b:



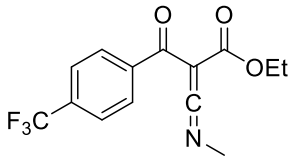
Chemical Formula: $C_{14}H_{13}NO_5$
Molecular Weight: 275.26

The target ketenimine **2b** observed a q-NMR yield of 68% when irradiated with the 308 nm LED at a concentration of 0.6 M and reaction time of 13 minutes in the reactor prototype v2.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8 Hz, 1H), 7.17 (s, 1H), 7.10 (d, *J* = 8 Hz, 1H), 5.97 (s, 2H), 4.15 (q, *J* = 7 Hz, 2H), 3.65 (s, 3H), 1.22 (t, *J* = 7 Hz, 3H).

This data is consistent with published work [C. Bracken, M. Baumann. **2023**, *Org. Lett.* 25, 35, 6593-6597].

Ethyl 3-(methylimino)-2-(4-(trifluoromethyl)benzoyl)acrylate, 2c:



Chemical Formula: $C_{14}H_{12}F_3NO_3$
Molecular Weight: 299.25

The target ketenimine **2c** observed a q-NMR yield of 38% when irradiated with the 265 nm LED at a concentration of 0.6 M and reaction time of 13 minutes in the reactor prototype v2. Listed characterisation peaks are taken form crude NMR and matched with previously reported NMR data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8 Hz, 2H), 7.69 (d, *J* = 8 Hz, 2H), 4.14 (q, *J* = 7 Hz, 2H), 3.76 (s, 3H), 1.19 (t, *J* = 7 Hz, 3H).

This data is consistent with published work [C. Bracken, M. Baumann. **2023**, *Org. Lett.* 25, 35, 6593-6597].

2.4 Calculation of external quantum yield and photoirradiation costs

External quantum yield is broadly defined in the IUPAC gold book as 'relating to the whole device or the overall process involved'. In this instance the 'whole device' will be all equipment required to produce the desired photo-irradiation. In this context the metric to compare external quantum yield will be the quantity of material converted (moles) per unit of energy (joules) and can be calculated as shown below (**Equation S1**). To measure the total electrical input required in joules the power usage of the irradiation device was measured using a socket-power meter to determine its wattage, which can be converted to joules by multiplying the time required in seconds to consume 1 mole of material (equation S2).

$$\phi_{ext} = \frac{moles\ converted}{total\ electrical\ input\ (J)}$$

Equation S1: *Calculation of external quantum yield (Φext) from the moles of compound converted per unit of total electrical energy input (J).*

$$Total\ electrical\ input\ (J) = Power\ (Watt)\ x\ time\ (seconds)$$

Equation S2: *Calculation of total energy usage.*

The cost of energy for the necessary irradiation to produce one mole of product can also be calculated by understanding the external quantum yield (mol J^{-1}) and the unit price of electricity (KWh) as shown in an example below (Equation S3).

$$\phi_{ext} = 1.21x10^{-9}\ mol\ J^{-1}$$

$$1\ kWh = 3.6\ x\ 10^{6}\ J$$

1 *kWh* costs € 0.3463

$$Energy\ required\ per\ mole = \frac{1}{\phi_{ext}}$$

$$Energy\ required\ per\ mole = \frac{1}{1.21x10^{-9}\ mol\ J^{-1}} = 8.26\ x\ 10^{8}\ J\ mol^{-1}$$

$$kWh\ per\ mole = \frac{8.26\ x\ 10^{8}\ J\ mol^{-1}}{3.6\ x\ 10^{6}\ J\ kWh^{-1}} = 229.57\ kWh\ mol^{-1}$$

$$Cost\ per\ mole = 229.57\ kWh\ mol^{-1}\ x\ 0.3463\ €\ kWh^{-1} = €79.43\ per\ mole.$$

Equation S3: *Exemplary calculation for cost of energy cost to irradiate and convert one mole of material given external quantum yield and unit cost of energy.*

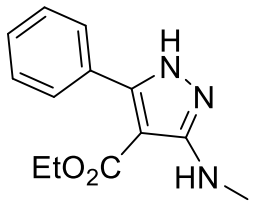
2.5 Procedure for the telescoped synthesis of pyrazole **3a**

Isoxazole **1a** (1.15g, 5 mmol) was dissolved in MeCN (8.3 mL, 0.6 M) requiring gentle stirring. The resulting solution was pumped through the photoreactor v2 described previously under the high throughput conditions with a flow rate of 0.128 mL min^{-1} achieving a residence time of 12.5 minutes. The resulting crude solution was passed into a T-piece mixer where it was mixed with a neat hydrazine (12.5 mmol) and catalytic quantity of Et_3N (0.5 mmol). The hydrazine reagent stream was pumped using a Luer lock syringe coupled with a Chemyx^{tm} syringe pump at a flow rate of 0.006 mL min^{-1} to achieve a ratio of 1:2.5 ketenimine to hydrazine. The reaction solution was passed through 10 cm of PTFE tubing before being collected into a round bottom flask under a N_2 atmosphere equipped with a magnetic stir bar and sealed with a septum. Once all the reaction solution had passed into the sealed round bottom flask the flow

input tube was removed from the septum of the round bottomed flask and the solution left stir overnight. A precipitate was observed after 30-minutes of stirring.

Following 12 h of stirring the reaction mixture was diluted in EtOAc (15 mL) and washed successively with aq. $NaHCO_3$ (25 mL) and brine (25 mL). The organic layer then dried over anhydrous Na_2SO_4 before being concentrated *in vacuo*, affording the crude product which was analysed by ^{1}H-NMR. The crude product was then purified by column chromatography on silica gel (1-10% EtOAc/c-Hex) affording the target product **3a** in a 43% yield over the two steps or a 96% for the final step, as an off-white solid.

Ethyl 3-(methylamino)-5-phenyl-1H-pyrazole-4-carboxylate, 3a:

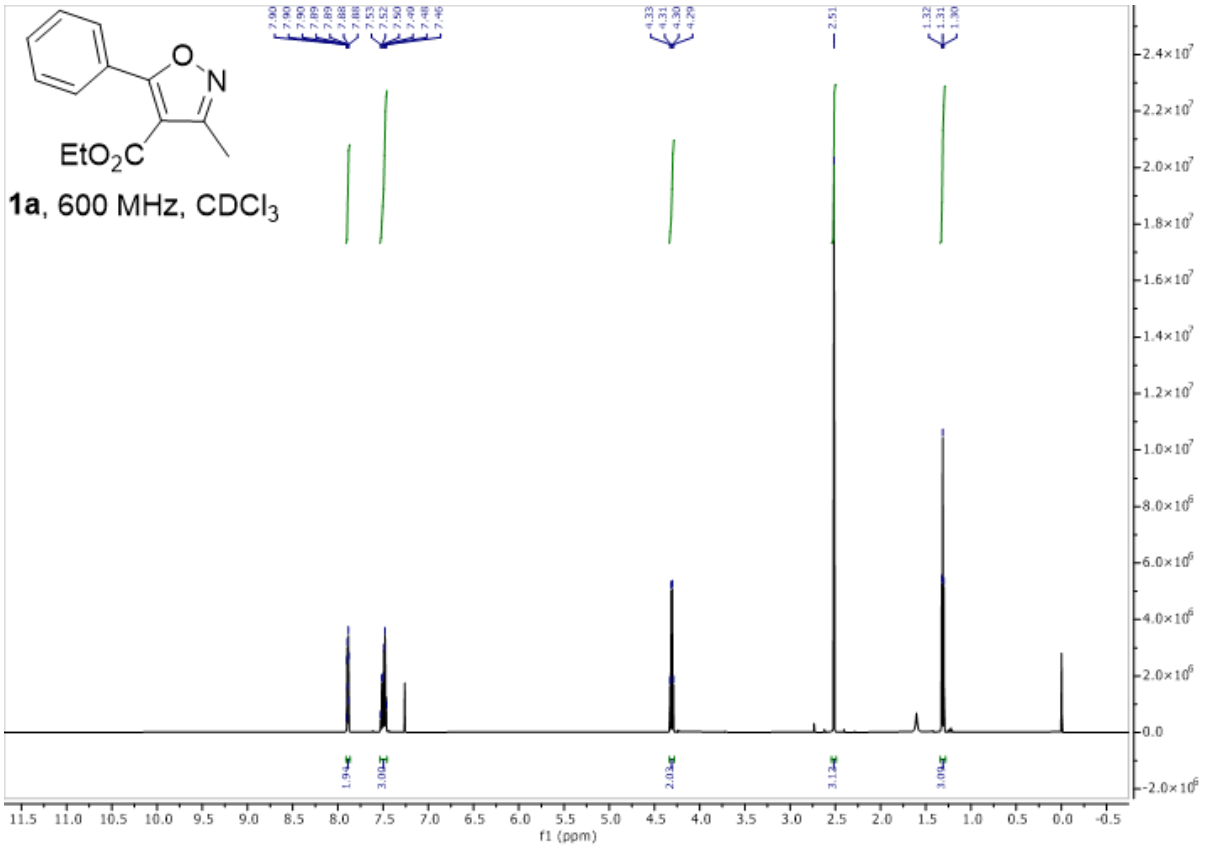


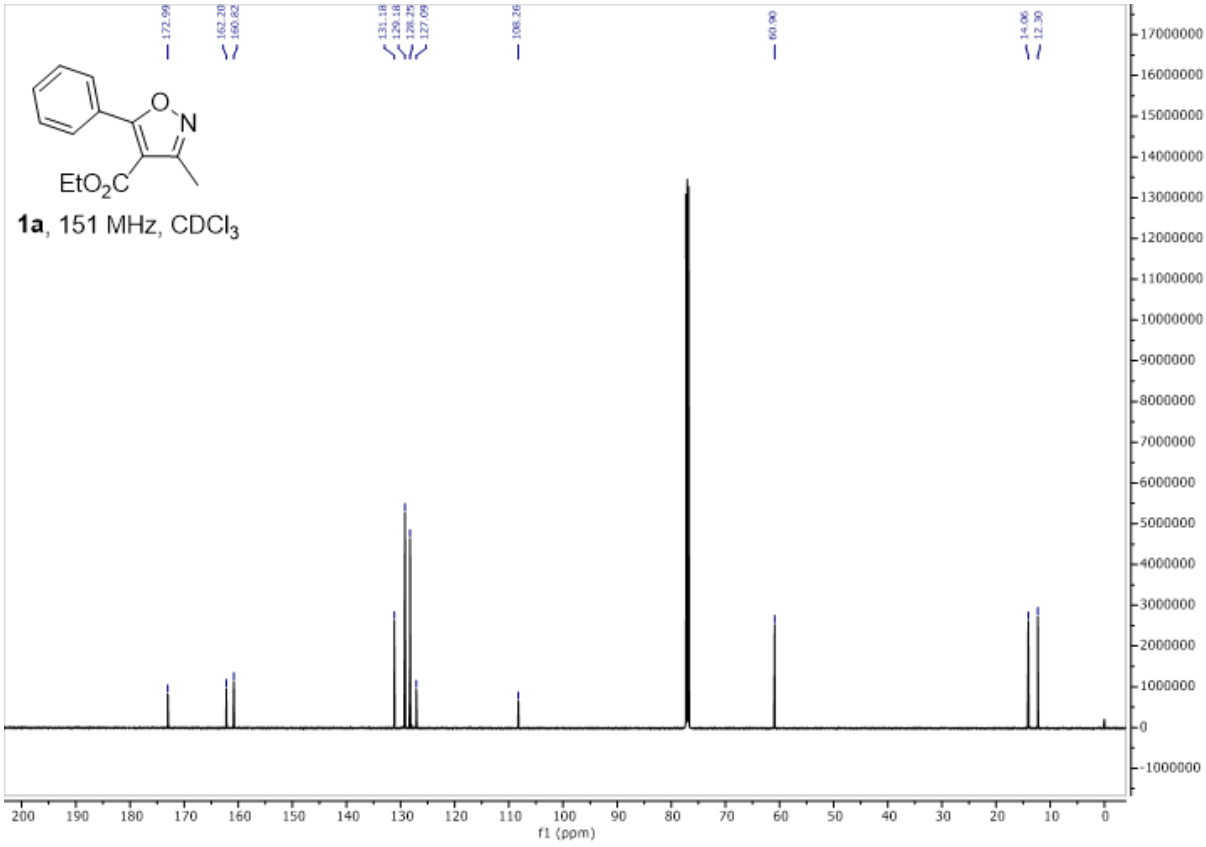
Chemical Formula: $C_{13}H_{15}N_3O_2$
Molecular Weight: 245.28

The target N-H pyrazole **3a** was isolated as an off-white powder with a 43% yield over the two steps described. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.53 (m, 2H), 7.40-7.35 (m, 3H), 5.81-5.87 (m, NH), 4.17 (q, *J* = 7.1 Hz, 2H), 2.92 (d, *J* = 4.8 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0 (C), 158.0 (C), 148.6 (C), 130.7 (C), 129.1 (2CH), 129.0 (CH), 127.9 (2CH), 110.0 (C), 59.5 (CH2), 29.6 (CH3), 14.1 (CH3). IR (neat) v/cm^{-1}: 3356 (w), 2926 (w), 1657 (s), 1516 9m), 1382 (m), 1282 (s), 1125 (m), 972 (m), SI-21766 (m), 699 (s). HR-MS (TOF-ES+) calc for $C_{13}H_{15}N_3O_2$ 245.1164 (M+H); found 245.1163 (M+H).

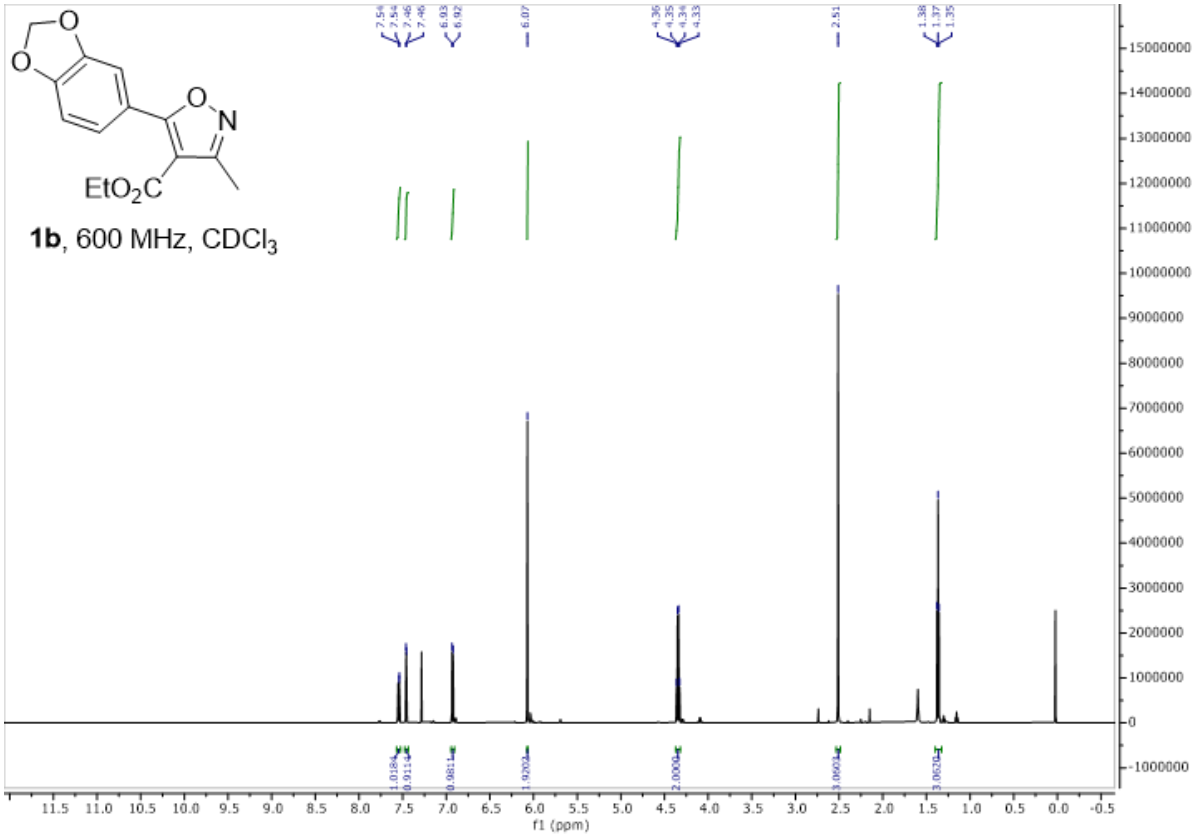
3. Copies of NMR Spectra

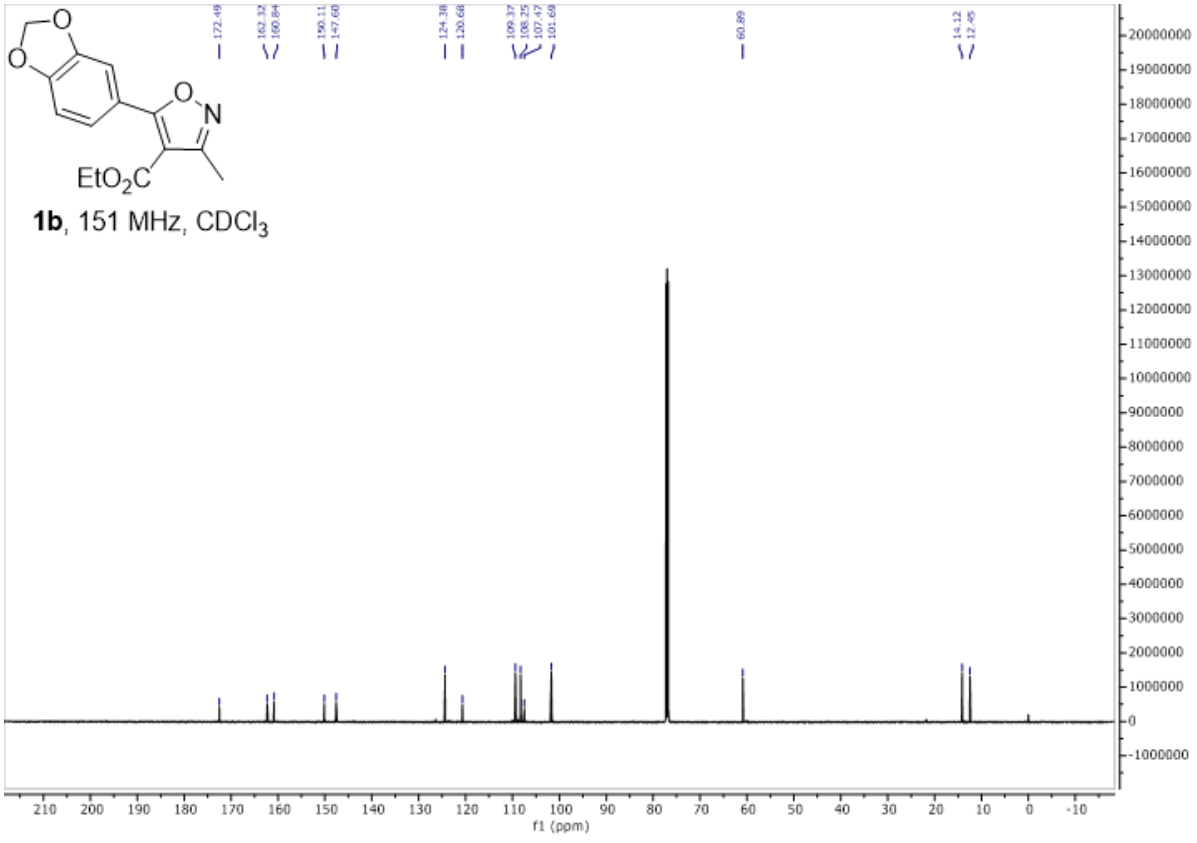
Ethyl 3-methyl-5-phenylisoxazole-4-carboxylate, 1a:



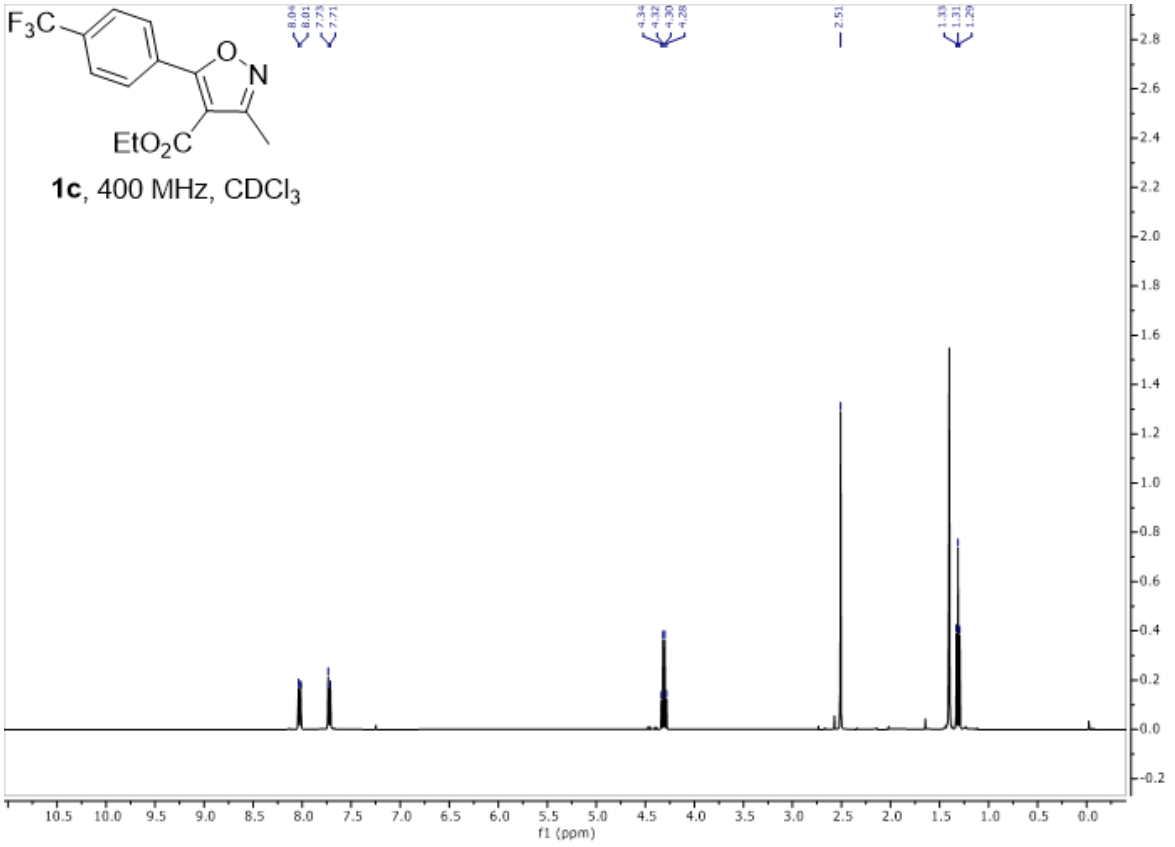


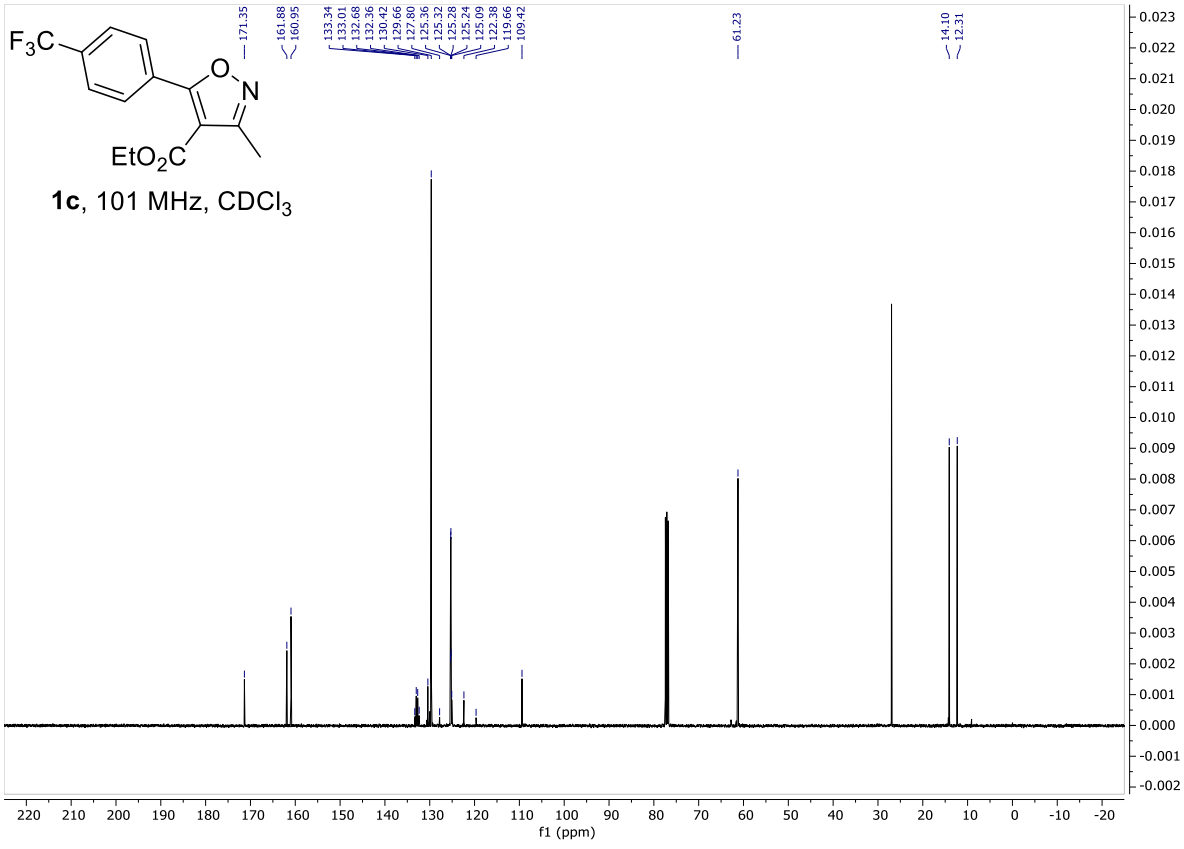
Ethyl 5-(benzo[d][1,3]dioxol-5-yl)-3-methylisoxazole-4-carboxylate, 1b:

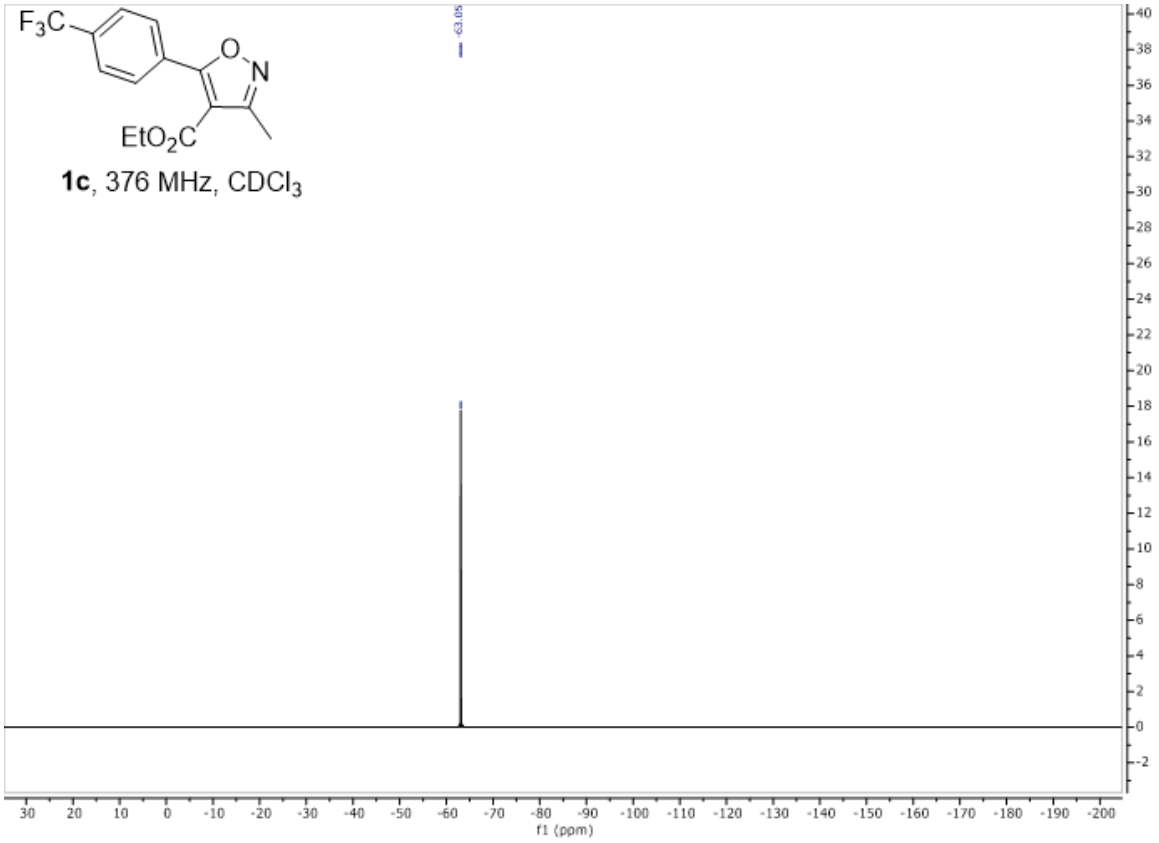




Ethyl 3-methyl-5-(4-(trifluoromethyl)phenyl)isoxazole-4-carboxylate, 1c:

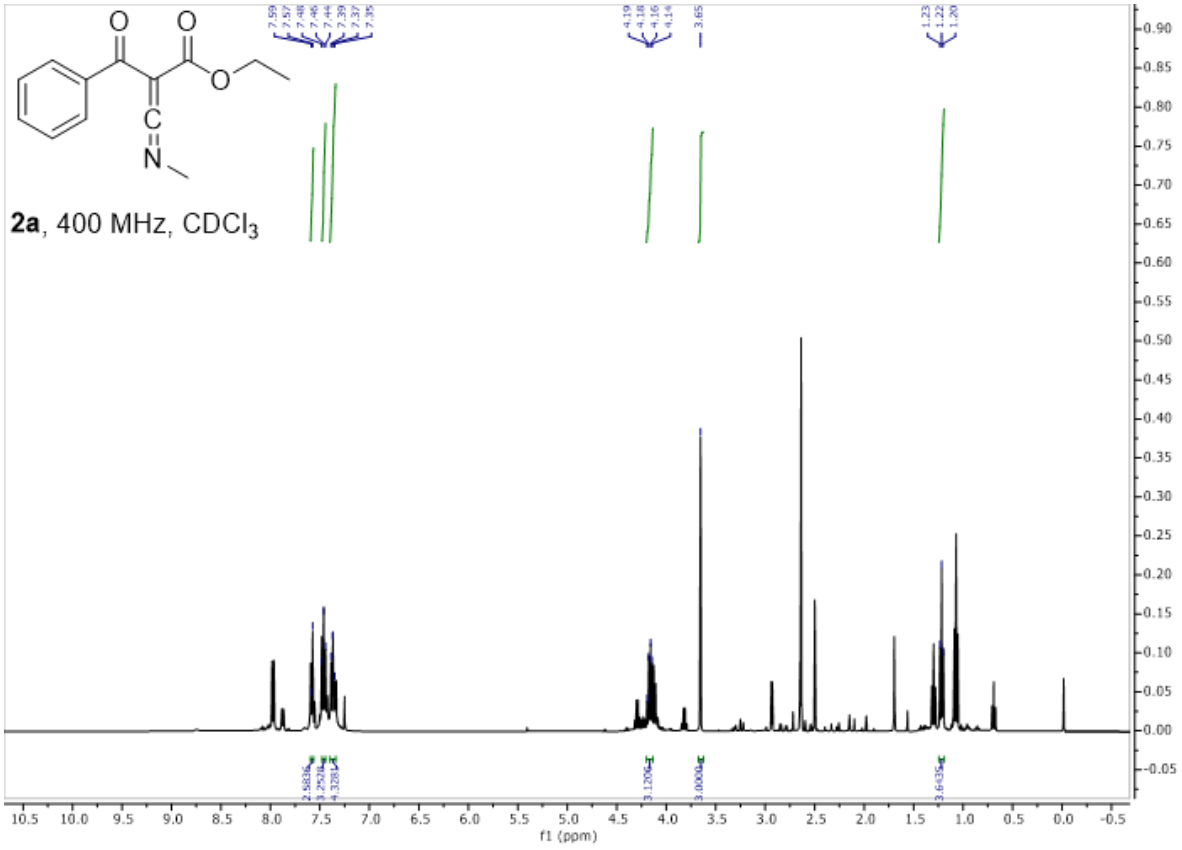


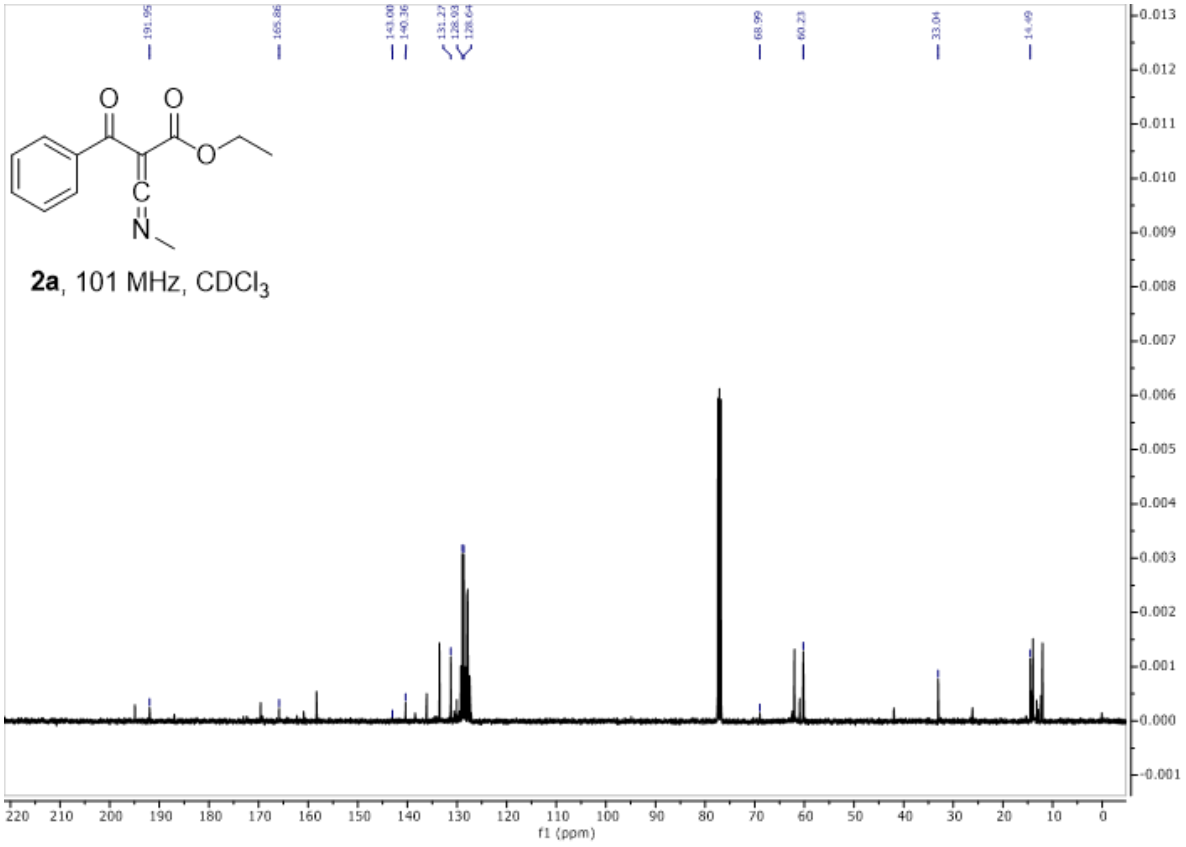




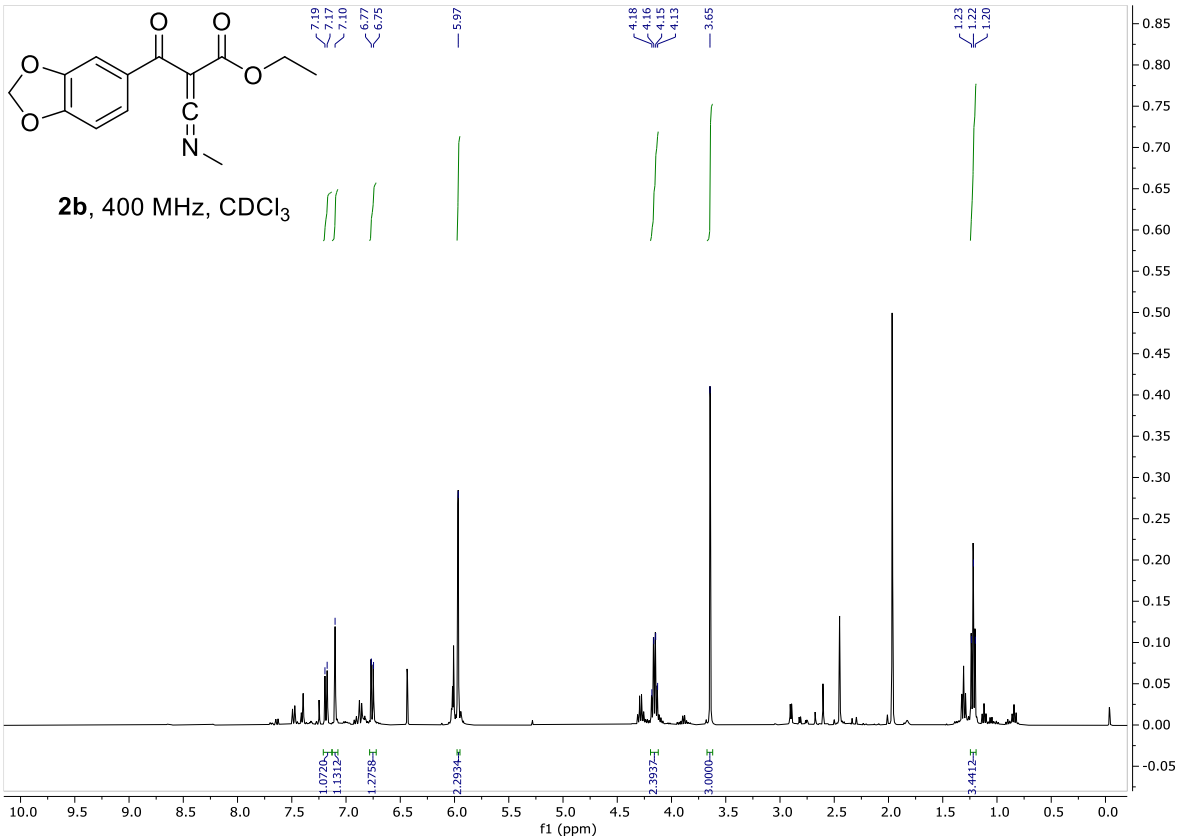
1c, 376 MHz, $CDCl_3$

Ethyl 2-benzoyl-3-(methylimino)acrylate, 2a:

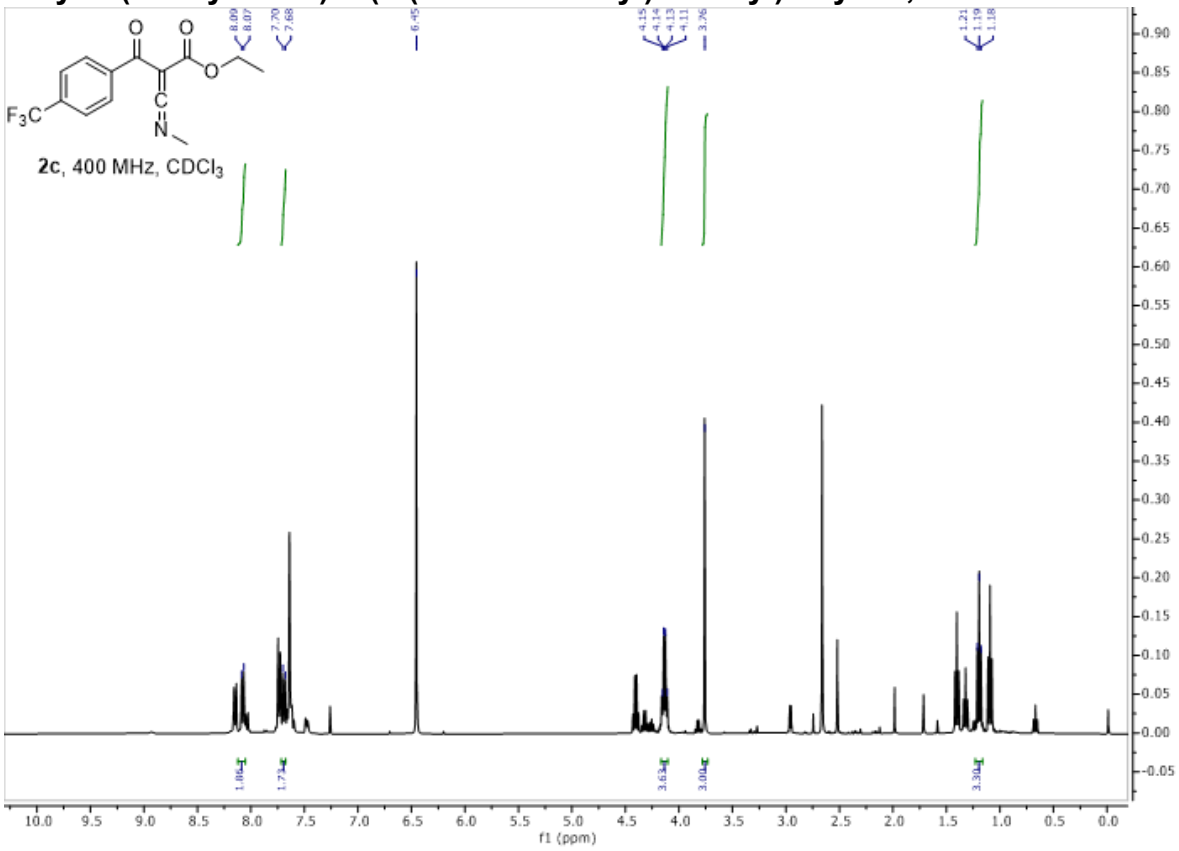




Ethyl 2-(benzo[d][1,3]dioxole-5-carbonyl)-3-(methylimino)acrylate, 2b:



Ethyl 3-(methylimino)-2-(4-(trifluoromethyl)benzoyl)acrylate, 2c:



Ethyl 3-(methylamino)-5-phenyl-1H-pyrazole-4-carboxylate, 3a: