



Combining C-H functionalisation and flow photochemical heterocyclic metamorphosis (FP-HM) for the synthesis of benzo[1,3]oxazepines

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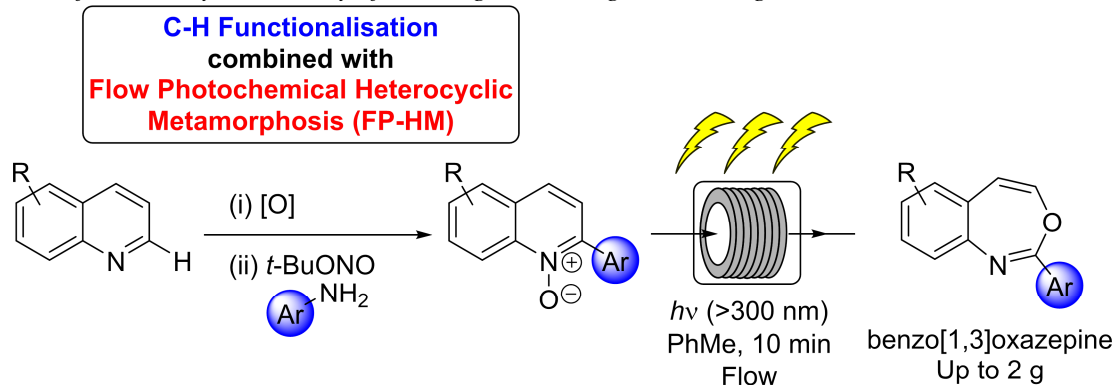
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Jasraj S. Babra,^a Andrew T. Russell,^a Christopher. D. Smith,^{a*} and Yuxiong Zhang^a^a Department of Chemistry, University of Reading, Whiteknights, Reading, RG6 6AD, UK

Combining C-H Functionalisation and Flow Photochemical Heterocyclic Metamorphosis (FP-HM) for the Synthesis of Benzo[1,3]oxazepines

Jasraj S. Babra,^a Andrew T. Russell,^a Christopher D. Smith,^{a*} and Yuxiong Zhang^a

* Corresponding Author: c.d.smith@reading.ac.uk (C. D. Smith)

^a Department of Chemistry, University of Reading, Whiteknights, Reading, RG6 6AD, UK

Keywords: Flow; Photochemistry; Heterocyclic metamorphosis; Quinoline *N*-oxide; Benzo[1,3]oxazepine.

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Abstract

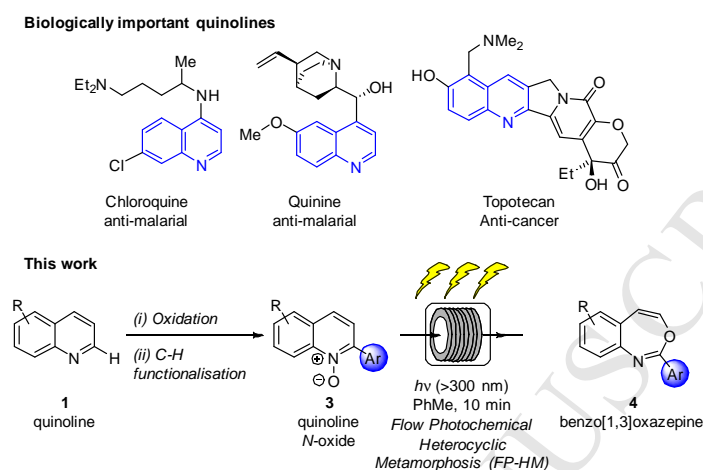
C-H Activation/functionalisation and Flow Photochemical Heterocyclic Metamorphosis (FP-HM) have been combined to synthesize a library of benzo[1,3]oxazepines, a rarely described heterocyclic family. This combined protocol allows a range of arylated products to be made from simple starting materials, and the cheap flow photochemical system has proven effective for rapid synthesis of gram-quantities of benzo[1,3]oxazepines.

Introduction

Within medicinal chemistry, the rapid generation of a library of products to investigate structure-activity relationships is vital for the synthesis of biologically-active molecules and investigation of a biological hypothesis.¹ Significant additional diversity may be obtained by the late-stage functionalisation of advanced intermediates or complex natural products by exploiting existing functionality, whilst avoiding linear sequences and duplicated synthetic efforts.² Two examples extensively used within medicinal chemistry include fluorination,³ to adjust a drug's metabolic profile and properties, and C-H functionalisation,⁴ to introduce further complexity or add functionality. There are, however, draw-backs to this approach such as a lack of generality, functionalisation of only one site or even the formation of intractable mixtures. An alternative less widely-investigated approach is exploitation of existing functionality by metamorphosing one heterocycle into another. Late-stage heterocyclic metamorphosis⁵ allows for significant transformation of a molecule's physical properties, for example by altering the basicity, the dipole moment, and any hydrogen-bond affinity, as well as the geometrical configuration.⁶ The new molecular scaffold generated, and the subsequent library of derivatives, can be screened for biological activity alongside the original heterocycle, allowing for rapid data generation. One important consideration of late-stage functionalisation is that the method should be mild and chemo-selective and we believe that the Flow Photochemical Heterocyclic Metamorphosis (FP-HM) protocol detailed herein fulfils these requirements.

We have directed our heterocyclic metamorphosis efforts towards transformations of the quinoline ring system, due to its importance in medicinal chemistry and as a privileged scaffold in the treatment of malaria (Scheme 1) and in anti-cancer drugs (Topotecan).⁷ Kaneko,⁸ Buchardt⁹ and Albini¹⁰ have observed that quinoline *N*-oxides (**3**) can be

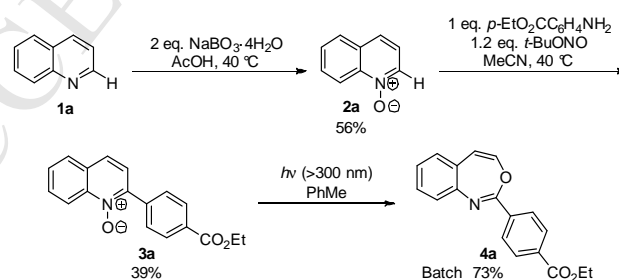
transformed into benzo[1,3]oxazepines (**4**), in variable yields when irradiated at >300 nm in non-hydrogen-bonding solvents. Benzo[1,3]oxazepines are an unusual heterocyclic system that have not been extensively reported¹¹ and although formally anti-aromatic, the 2-aryl derivatives are easily isolated and purified. Importantly, the seven-membered [1,3]-oxazepine ring leads to a slight geometrical distortion with respect to the quinoline ring system, and thus offers an interesting counterpoint to the parent quinoline for biological testing.



Scheme 1. Biologically important quinolines and the general scheme of this communication.

Results and Discussion

Commercially available quinoline (**1a**) was oxidised with sodium perborate in glacial AcOH (Scheme 2) to form the *N*-oxide derivative **2a**.¹² At this point we wished to develop a route to diversify this simple quinoline *N*-oxide by arylating the 2-position using C-H functionalisation. Whilst a range of methods for this transformation are known,¹³ we decided to use a slight variation of the Minisci-like radical arylation, reported by Horan, to form **3a**.^{13b} Horan's method uses diazonium salts derived *in situ* from anilines, and offers many benefits in terms of cost of materials, ready availability of aniline substrates, operational simplicity and facile purification. With a reliable route to the desired 2-aryl-quinoline *N*-oxide (**3a**) in hand, we investigated the photochemical rearrangement of the quinoline *N*-oxide to the corresponding benzo[1,3]oxazepine **4a**.



Scheme 2. Initial investigation towards benzo[1,3]oxazepine **4a**.

The UV-Vis spectrum of *N*-oxide **3a** shows a significant band λ_{\max} (PhMe) = 346 nm, ϵ = 14.3 M⁻¹cm⁻¹ (Figure 1, red), which maps onto the broad band with λ_{\max} = 335 nm of the commercially available 25 W Exo Terra UVB200 bulb (Figure 1, dotted blue). The use of such a 25 W bulb has many safety, cost and practical advantages over the powerful medium pressure mercury lamps that have been used in other systems^{10a,d} and permits facile scaling of the reactions when larger quantities of material are required due to its price and ready

availability. When a toluene solution of **3a** (1 mg/mL; 3.5 mM) in a Pyrex™ test tube (20 mL) was irradiated for 18 hrs with the 25 W Exo Terra UVB200 bulb full conversion to benzo[1,3]oxazepine **4a** was observed, along with some photochemical decomposition. Following flash column chromatography, 1,3-oxazepine **4a** was isolated in 73% yield.

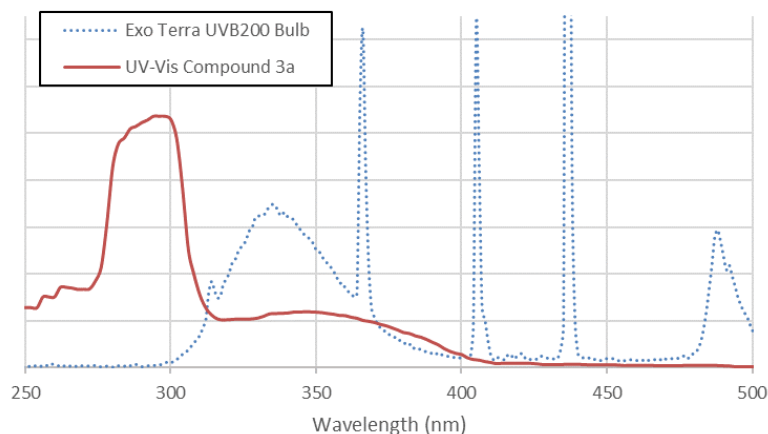
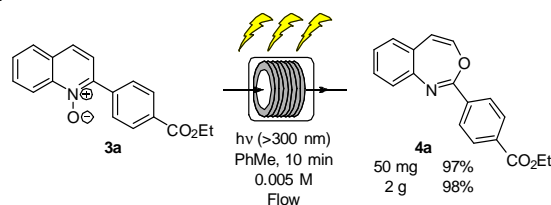


Figure 1. UV-Vis of compound **3a** overlaid with the output of the Exo Terra UVB200 bulb (toluene, unscaled).

On the basis of this promising result, we attempted the transformation in our photochemical flow reactor, similar to those previously described.¹⁴ Accordingly, *N*-oxide **3a** was dissolved in toluene (5 mM), and pumped using a Vapourtec E-Series peristaltic pump through a 10 mL reactor (PFA tubing: 1/16" OD, 0.5 mm ID) that was wrapped around a 25 W Exo Terra UVB200 lamp, and the solution irradiated. No degassing of the solution was performed. By ¹H-NMR we observed complete conversion into the desired benzo[1,3]oxazepine **4a** (Scheme 3) in only 6 min and compound **4a** was isolated in near quantitative yield. Following further experimentation, we extended the residence time in the reactor to 10 minutes to account for any operational or substrate variabilities. This significant improvement on the previous literature protocols in terms of yield, time and the continuous nature of the process makes scale-up facile. To prove the effectiveness of the procedure, we synthesized 1.9 g of **4a** within a 17 h period, providing the product in 98% yield and excellent purity. For comparison, in 18 h the batch-mode could only process milligram quantities of material in small 20 mL Pyrex test tubes due to the poor irradiation profile of classical laboratory glassware, additionally, the purity profile of the crude ¹H-NMR was significantly inferior.



Scheme 3. FP-HM performed on a gram-scale.

With conditions for conversion of the parent quinolone to the *N*-oxide, C-H functionalisation and heterocycle metamorphosis in hand, our attention turned to investigating the scope of the reaction. Commercially available quinolines **1a** and **1b** were converted to the corresponding *N*-oxides (**2a** and **2b**). C-H functionalisation was successful and provided

access to the requisite 2-arylquinoline *N*-oxides (**3a-k**), albeit in moderate yield. The main difficulties were found with sterically hindered anilines, for example in the case of **3f** where only trace quantities were isolated, and **3k** where the yield was 16% (Table 1). Pleasingly, when substrates **3a-k** were subjected to the flow photochemical heterocyclic metamorphosis (FP-HM) conditions the reaction was successful (Table 1, **4a-k**). In all cases the product was either prepared in analytically pure form, or, use of a short plug of silica was sufficient to remove base-line impurities. Esters, nitriles and halides all successfully underwent FP-HM in excellent yields (>90%). The only exceptions were the *ortho*-Me *N*-oxide (**4k**), which was isolated in 75% yield, and the *para*-nitro-substituted example (**4d**, 66% yield), which presented a slight difficulty because it was poorly soluble in toluene and was dissolved in a 1:1 solution of MeCN:PhMe. In this case, full conversion of this substrate was not achieved within the usual 10 minutes residence time and 15 min was chosen as a compromise; longer reaction times led to substantial photodegradation.

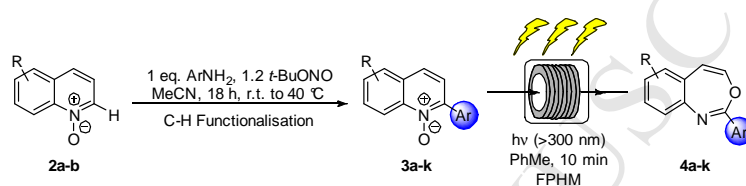
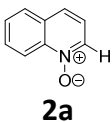
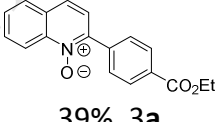
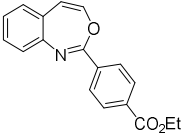
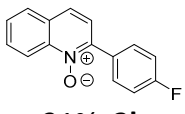
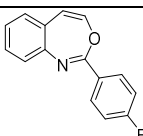
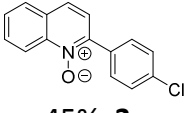
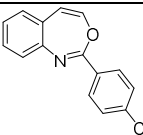
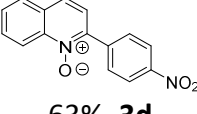
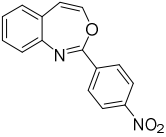
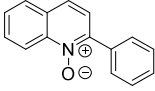
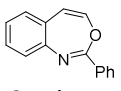
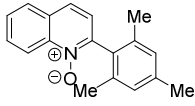
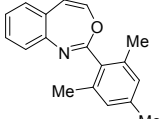
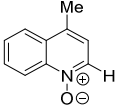
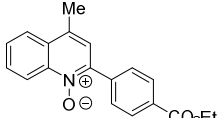
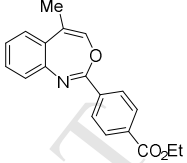
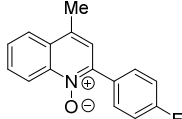
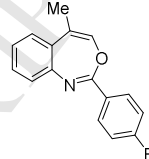
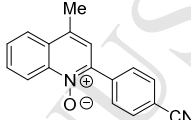
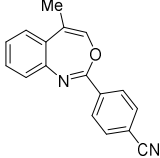
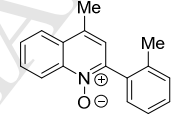
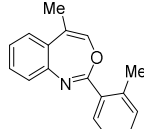


Table 1: Substrate scope of C-H Functionalisation and FP-HM.

Entry	Starting <i>N</i> -Oxide	C-H coupling partner – ArNH ₂	C-H Functionalisation ^a	FP-HM ^b
1	 2a	4-EtO ₂ CC ₆ H ₄ NH ₂	 39%, 3a	 97% (50 mg scale) 98% (2 g scale) 4a
2	2a	4-FC ₆ H ₄ NH ₂	 31%, 3b	 92%, 4b
3	2a	4-ClC ₆ H ₄ NH ₂	 45%, 3c	 95%, 4c
4	2a	4-O ₂ NC ₆ H ₄ NH ₂	 63%, 3d	 66%, 4d ^c
5	2a	PhNH ₂	 35%, 3e	 95%, 4e

6	2a	MesNH ₂	 Trace, 3f	 Not performed, 4f
7	 2b	4-EtO ₂ CC ₆ H ₄ NH ₂	 38%, 3g	 95%, 4g
8	2b	4-FC ₆ H ₄ NH ₂	 33%, 3h	 93%, 4h
9	2b	4-NCC ₆ H ₄ NH ₂	 29%, 3j	 98%, 4j
10	2b	2-MeC ₆ H ₄ NH ₂	 16%, 3k	 75%, 4k

a) C-H Functionalisation performed as per the general procedure A; b) FP-HM performed as per general procedure B; c) Solvent 1:1 MeCN:PhMe, residence time 15 min.

Conclusions

In conclusion, we have described an efficient method for the synthesis of a small library of unusual benzo[1,3]oxazepines in a rapid and cheap manner, starting from commercially-available quinolines. Molecular diversity was achieved through a very mild C-H functionalisation procedure, providing a route for substrate variability. This communication has utilised Flow Photochemical Heterocyclic Metamorphosis (FP-HM) to transform the well-known quinoline scaffold into benzo[1,3]oxazepines, resulting in changes to the molecule's basicity, geometry, dipole moment, hydrogen-bonding ability and size. Heterocyclic metamorphosis represents a different medicinal chemistry paradigm where the heterocycle is the function of change rather than a final diversification step. Due to the mild nature of FP-HM (10 min of irradiation) it is expected that valuable quinoline-based natural products, or late-stage intermediates, could be transformed into the corresponding benzo[1,3]oxazepines for additional biological testing, or subsequent additional manipulation. Finally, we have demonstrated the true scalability of FP-HM by the successful synthesis of 1.9 g of benzo[1,3]oxazepine **4a** in 17 hours. The continuous nature of the process means that further scale-up can be achieved simply by using multiple cheap photoreactors in series.

Acknowledgements

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Experimental

General

¹H-NMR spectra were recorded on Bruker DPX-400 (400 MHz) or Bruker Nanobay (400 MHz) spectrometers using tetramethylsilane (SiMe₄, $\delta_{\text{H}} = 0.00$ ppm); DCCl₃ (HCCl₃, $\delta_{\text{H}} = 7.26$ ppm) or the central resonance of D₃COD (D₃COD, $\delta_{\text{H}} = 2.50$ ppm) as internal reference. ¹³C-NMR spectra were recorded on Bruker DPX-400 (101 MHz) or Bruker Nanobay (101 MHz) spectrometers using the central resonance of CDCl₃ (CDCl₃, $\delta_{\text{C}} = 77.16$ ppm) or the central resonance of D₃COD (D₃COD, $\delta_{\text{C}} = 49.00$ ppm) as the internal reference. ¹⁹F-NMR spectra were measured relative to CFCl₃ $\delta_{\text{F}} = 0.00$ (external reference). Assignments were made using a range of NMR experiments (DEPT135, COSY, HMQC and HMBC). All chemical shifts are quoted in parts per million (ppm) down field from tetramethylsilane, measured from the centre of the signal except in the case of multiplets of more than one proton, which are quoted as a range. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin.), multiplet (m), (ap.) apparent, (br) broad and combinations thereof. Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer as a thin film. Letters in parentheses refer to relative absorbency of the main peak: w, weak, < 40%, m, medium, 41-74% of the main peak, s, strong >75%; and br, broad. Accurate mass data was recorded on a V.G. Micromass 70-70F machine under chemical ionisation (CI) or under electrospray conditions on a Thermo Scientific LTQ Orbitrap XL instrument. PE refers to the fraction of light petroleum ether boiling between 40 and 60 °C. All reagents were used as obtained from commercial sources, unless otherwise stated. Analytical thin layer chromatography (TLC) was performed using pre-coated Merck aluminum-backed silica gel plates (Silicagel 60 F₂₅₄). Visualization was by UV light and/or treatment with acidic potassium permanganate, ninhydrin or acidic ammonium molybdate(IV). UV-Vis spectrum was collected using a Jenway 6315 Spectrophotometer. The emission spectrum from the Exo Terra UVB200 bulb was measured using an Ocean Optics Red Tide USB650 fiber optic spectrometer.

General Procedure A – C-H Functionalisation (3a-k)

The quinoline *N*-oxide (3 mmol) and aromatic amine (3 mmol) were dissolved in MeCN (10 mL). *tert*-Butyl nitrite (3.6 mmol) was added in one portion and the reaction was stirred at ambient temperature for 15 mins, before warming to 40 °C overnight (typically 18 h). The mixture was dry loaded onto silica gel before purification by flash chromatography (typically 1:1 EtOAc:PE).

General Procedure B – Flow Photochemical Heterocyclic Metamorphosis (FP-HM) (4a-k)

A solution of substrate in PhMe (typically 50 mg in 30 mL; 5-10 mM) was pumped using a Vapourtec E-Scholar peristaltic pump system through a 10 mL reactor (PFA tubing: 1/16" OD, 0.5 mm ID) that was wrapped around a 25 W Exo Terra UVB200 lamp, and the solution irradiated. In general, the reaction requires a residence time of 6 min (1.67 mL/min); however, a residence time of 10 mins (1 mL/min) was typically used to account for experimental variabilities. The output from the reactor was concentrated *in vacuo* and, if necessary, was further purified by flash column chromatography (SiO₂; 1:2 EtOAc:PE).

Large-Scale Flow Photochemical Heterocyclic Metamorphosis (4a)

2-(4-(Ethoxycarbonyl)phenyl)quinoline 1-oxide (2 g, 6.8 mmol) was dissolved in PhMe (1 L, 6.8 mM) and pumped using a Vapourtec E-Scholar peristaltic pump system through a 10 mL reactor (PFA tubing: 1/16" OD, 0.5 mm ID) that was wrapped around a 25 W Exo Terra UVB200 lamp, and the solution irradiated. A residence time of 10 mins was used; the total reaction time was 17 hours. The output from the reactor was concentrated *in vacuo* to give ethyl 4-(benzo[d][1,3]oxazepin-2-yl)benzoate (**4a**) as a tan solid (1.935 g, 97%).

Batch Photochemical Heterocyclic Metamorphosis (4a)

Approximately 15 mg of *N*-oxide **3a** was dissolved in PhMe (15 mL) and placed in a Pyrex test-tube. The tube was sealed with a septum and placed next to the Exo Terra UVB200 lamp for 18 h. The reaction was concentrated *in vacuo* and purified by flash column chromatography (SiO₂; 1:2 EtOAc:PE) to give ethyl 4-(benzo[d][1,3]oxazepin-2-yl)benzoate (**4a**) a tan solid (11 mg, 73%).

Quinoline *N*-oxide¹⁵ (2a)

Quinoline (10 g, 77 mmol) was dissolved in AcOH (60 mL), then NaBO₃·4H₂O (15.7 g, 115.5 mmol) was added portion-wise to the solution over 10 mins. The reaction was heated at 40 °C overnight. Most of the AcOH was removed *in vacuo* and then the reaction partitioned with HCCl₃ (100 mL) and H₂O (300 mL), and the aqueous phase further extracted into HCCl₃ (2×100 mL). The combined organic phases were washed with aq. 2 M NaOH, dried with MgSO₄, filtered, then concentrated *in vacuo* to produce a dark brown deliquescent solid (6.23 g, 56%). IR (thin film) ν/cm^{-1} = 3397brw, 3063w, 2260w, 1656w, 1569w, 1510w, 1447w, 1392m, 1226m. ¹H-NMR (400 MHz, CDCl₃): δ/ppm = 8.76 (d, *J* = 8.5 Hz, 1H), 8.55 (d, *J* = 6.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.83 – 7.70 (m, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.31 (dd, *J* = 8.5, 6.0 Hz, 1H). ¹³C-NMR (101 MHz, DMSO-*d*₆): δ/ppm = 140.84 (C), 135.27 (CH), 130.32 (C), 130.32 (CH), 128.76 (CH), 128.66 (CH), 125.11 (CH), 121.94 (CH), 118.87 (CH). HRMS: (ESI⁺) [M+H]⁺ calculated for C₉H₈ON = 146.0606, found = 146.0600.

4-Methylquinoline 1-oxide¹⁶ (2b)

4-Methylquinoline (5.4 g, 38 mmol) was dissolved in AcOH (40 mL), then NaBO₃·4H₂O (8 g, 59 mmol) was added portion-wise to the solution over 10 mins. The reaction was heated at 40 °C overnight. Most of the AcOH was removed *in vacuo*, then the reaction partitioned with

HCCl₃ (50 mL) and H₂O (150 mL), and the aqueous phase further extracted into HCCl₃ (2×50 mL). The combined organic phases were washed with aq. 2 M NaOH, dried with MgSO₄, filtered, then concentrated *in vacuo* to produce an off-white deliquescent solid (2.7 g, 45%). IR (thin film) ν/cm^{-1} = 3283br w, 1571m, 1514w, 1394s, 1313m, 1277m, 1206m, 1145s, 1057m, 1040w, 969w, 826w, 791s, 702m. ¹H-NMR (400 MHz, D₃COD): δ/ppm = 8.67 (d, *J* = 8.5 Hz, 1H), 8.58 (d, *J* = 6.0 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.93 (t, *J* = 8.0 Hz, 1H), 7.82 (t, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 6.0 Hz, 1H), 2.75 (s, 3H). ¹³C-NMR (101 MHz, D₃COD): δ/ppm = 141.20 (C), 141.06 (C), 137.66 (CH), 132.49 (CH), 131.19 (C), 130.23 (CH), 126.55 (CH), 122.88 (CH), 120.26 (CH), 18.49 (CH₃). HRMS (ESI⁺) [M+H]⁺ calculated for C₁₀H₁₀ON = 160.0757, found = 160.0753.

2-(4-(Ethoxycarbonyl)phenyl)quinoline 1-oxide^{13b} (3a)

Off-white solid 341 mg, 39%. IR (thin film) ν/cm^{-1} = 1709s, 1561w, 1343m, 1273s, 1206w, 1102m, 1027w, 892w, 820m, 763m, 737m, 699w. ¹H-NMR (400 MHz, CDCl₃): δ/ppm = 8.82 (d, *J* = 8.5 Hz, 1H), 8.17 (app. d, *J* = 7.5 Hz, 2H), 8.05 (app. d, *J* = 7.5 Hz, 2H), 7.87 (m, 1H), 7.83 – 7.73 (m, 2H), 7.65 (t, *J* = 7.0 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 4.41 (q, *J* = 7.0 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H). ¹³C-NMR (101 MHz, CDCl₃): δ/ppm = 166.04 (CO), 143.99 (C), 142.20 (C), 137.66 (C), 131.08 (C), 130.76 (CH), 129.74 (C), 129.57 (CH), 129.38 (CH), 128.75 (CH), 128.08 (CH), 125.48 (CH), 123.02 (CH), 120.14 (CH), 61.17 (CH₂), 14.32 (CH₃). HRMS (ESI⁺) [M+H]⁺ calculated for C₁₈H₁₆O₃N = 294.1125, found = 294.1121. λ_{max} (PhMe) = 346 nm, ϵ = 14.3 M⁻¹cm⁻¹.

2-(4-Fluorophenyl)quinoline 1-oxide¹⁷ (3b)

Off-white solid 221 mg, 31%. IR (thin film) ν/cm^{-1} = 1600m, 1563m, 1501s, 1453w, 1326s, 1299m, 1232s, 1205w, 1162m, 1149w, 1096w, 1060w, 1017w, 889m, 805s, 802s, 769m, 737s, 606m. ¹H-NMR (400 MHz, CDCl₃): δ/ppm = 8.80 (d, *J* = 6.5 Hz, 1H), 8.04 – 7.93 (m, 2H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.79 – 7.67 (m, 2H), 7.61 (d, *J* = 7.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.22 – 7.08 (m, 2H). ¹³C-NMR (101 MHz, CDCl₃): δ/ppm = 163.17 (d, *J* = 250.5 Hz, CF), 144.14 (C), 142.13 (C), 131.81 (d, *J* = 8.5 Hz, CH), 130.76 (CH), 129.50 (C), 129.37 (d, *J* = 3.0 Hz, C), 128.51 (CH), 128.06 (CH), 125.75 (CH), 122.99 (CH), 120.07 (CH), 115.34 (d, *J* = 21.5 Hz, CH). ¹⁹F-NMR (376 MHz, CDCl₃): δ/ppm = -110.40. HRMS (ESI⁺) [M+H]⁺ calculated for C₁₅H₁₁ONF = 240.0819, found = 240.0825.

2-(4-Chlorophenyl)quinoline 1-oxide¹⁷ (3c)

Off-white solid 344 mg, 45%. IR (thin film) ν/cm^{-1} = 1688w, 1598w, 1561 w, 1487m, 1336s, 1324s, 1298m, 1278m, 1149m, 1093s, 1015m, 890m, 821s, 769m, 729m. ¹H-NMR (400 MHz, CDCl₃): δ/ppm 8.82 (d, *J* = 8.5 Hz, 1H), 7.94 (app. d, *J* = 8.5 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.82 – 7.72 (m, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.50 – 7.46 (m, 3H). ¹³C-NMR (101 MHz, CDCl₃): δ/ppm = 143.93 (C), 142.17 (C), 135.55 (C), 131.76 (C), 131.01 (CH), 130.81 (CH), 129.61 (C), 128.65 (CH), 128.54 (CH), 128.07 (CH), 125.66 (CH), 122.90 (CH), 120.13 (CH). HRMS (ESI⁺)

$[M+H]^+$ calculated for $C_{15}H_{11}ON^{35}Cl = 256.0524$, found = 256.0525; $C_{15}H_{11}ON^{37}Cl = 258.0494$, found = 258.0496.

2-(4-Nitrophenyl)quinoline 1-oxide¹⁷ (3d)

Yellow solid 502 mg, 63%. IR (thin film) $\nu/cm^{-1} = 1591m, 1511s, 1324s, 1247w, 1103w, 892w, 843m, 810s, 755s, 734s, 694m$. 1H -NMR (400 MHz, $CDCl_3$): $\delta/ppm = 8.82$ (d, $J = 8.5$ Hz, 1H), 8.35 (app. d, $J = 8.0$ Hz, 2H), 8.18 (app. d, $J = 8.0$ Hz, 2H), 7.92 (d, $J = 8.0$ Hz, 1H), 7.84 (t, $J = 7.0$ Hz, 2H), 7.71 (t, $J = 7.5$ Hz, 1H), 7.53 (d, $J = 8.5$ Hz, 1H). ^{13}C -NMR (101 MHz, $CDCl_3$): $\delta/ppm = 147.95$ (C), 142.77 (C), 142.30 (C), 139.70 (C), 131.11 (CH), 130.71 (CH), 130.00 (C), 129.22 (CH), 128.21 (CH), 125.70 (CH), 123.44 (CH), 122.65 (CH), 120.19 (CH). HRMS (ESI⁺) $[M+H]^+$ calculated for $C_{15}H_{11}O_3N_2 = 267.0764$, found = 267.0767.

2-Phenylquinoline 1-oxide¹⁸ (3e)

Off-white solid 232 mg, 35%. IR (thin film) $\nu/cm^{-1} = 1560m, 1491m, 1449w, 1348m, 1323m, 1283w, 1203w, 1133m, 1109m, 1061w, 888m, 761s, 733s, 695s, 609m, 567m, 540w$. 1H -NMR (400 MHz, $CDCl_3$): $\delta/ppm = 8.86$ (d, $J = 8.5$ Hz, 1H), 7.97 (d, $J = 7.0$ Hz, 1H), 7.88 (d, $J = 8.0$ Hz, 1H), 7.83 – 7.74 (m, 2H), 7.67 (m, 1H), 7.56 – 7.44 (m, 5H). ^{13}C -NMR (101 MHz, $CDCl_3$): $\delta/ppm = 145.24$ (C), 142.40 (C), 133.60 (C), 130.77 (CH), 129.73 (CH), 129.70 (CH), 128.59 (CH), 128.45 (CH), 128.38 (C), 128.11 (CH), 125.52 (CH), 123.47 (CH), 120.43 (CH). HRMS (ESI⁺) $[M+H]^+$ calculated for $C_{15}H_{12}ON = 222.0913$, found = 222.0912.

2-(4-(Ethoxycarbonyl)phenyl)-4-methylquinoline 1-oxide – novel (3g)

Off-white solid 349 mg, 38%. IR (thin film) $\nu/cm^{-1} = 2980w, 1714s, 1607w, 1560w, 1385w, 1366w, 1339m, 1291s, 1210w, 1104m, 1020w, 765m$. 1H -NMR (400 MHz, $CDCl_3$): $\delta/ppm = 8.91$ (d, $J = 7.0$ Hz, 1H), 8.18 (app. d, $J = 7.5$ Hz, 2H), 8.06 (app. d, $J = 7.5$ Hz, 2H), 7.99 (d, $J = 8.0$ Hz, 1H), 7.82 (m, 1H), 7.70 (t, $J = 7.5$ Hz, 1H), 7.35 (br s, 1H), 4.41 (q, $J = 7.0$ Hz, 2H), 2.71 (s, 3H), 1.43 (t, $J = 7.0$ Hz, 3H). ^{13}C -NMR (101 MHz, $CDCl_3$): $\delta/ppm = 166.13$ (CO), 141.72 (C), 137.74 (C), 134.00 (C), 131.04 (C), 130.50 (CH), 129.64 (CH), 129.49 (C), 129.37 (CH), 129.27 (C), 128.51 (CH), 124.69 (CH), 123.4 (CH), 120.74 (CH), 61.18 (CH_2), 18.36 (CH_3), 14.33 (CH_3). HRMS (ESI⁺) $[M+H]^+$ calculated for $C_{19}H_{18}O_3N = 308.1281$, found = 308.1282.

2-(4-Fluorophenyl)-4-methylquinoline 1-oxide – novel (3h)

Pale brown solid 253 mg, 33%. IR (thin film) $\nu/cm^{-1} = 1603m, 1510s, 1504s, 1398w, 1384w, 1338s, 1234s, 1208m, 1160m, 1150m, 1061w, 871w, 838s, 811w, 795w, 761m$. 1H -NMR (400 MHz, $CDCl_3$): $\delta/ppm = 8.90$ (d, $J = 8.5$ Hz, 1H), 8.10-7.80 (m, 3H), 7.80 (m, 1H), 7.68 (m, 1H), 7.33 (m, 1H), 7.20 (m, 2H), 2.69 (s, 3H). ^{13}C -NMR (101 MHz, $CDCl_3$): $\delta/ppm = 163.18$ (d, $J = 250.5$ Hz, CF), 143.49 (C), 141.67 (C), 134.02 (C), 131.82 (d, $J = 8.5$ Hz, CH), 130.46 (CH), 129.48 (d, $J = 3.5$ Hz, C), 129.08 (C), 128.29 (CH), 124.63 (CH), 123.48 (CH), 120.73 (CH), 115.33 (d, $J = 21.5$ Hz, CH), 18.37 (CH_3). ^{19}F -NMR (376 MHz, $CDCl_3$): $\delta/ppm = -110.66$. HRMS (ESI⁺) $[M+H]^+$ calculated for $C_{16}H_{13}ONF = 254.0976$, found = 254.0977.

2-(4-Cyanophenyl)-4-methylquinoline 1-oxide – novel (3j)

Tan solid 226 mg, 29%. IR (thin film) ν/cm^{-1} = 3054w, 2226s, 1605m, 1565w, 1501m, 1383s, 1369w, 1339s, 1306w, 1234w, 1209m, 1151m, 869w, 840m, 759s, 731m, 559s. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ/ppm = 8.87 (d, J = 8.5 Hz, 1H), 8.10 (app. d, J = 8.0 Hz, 2H), 8.01 (d, J = 8.5 Hz, 1H), 7.86 – 7.76 (m, 3H), 7.72 (t, J = 7.5 Hz, 1H), 7.32 (s, 1H), 2.71 (s, 3H, CH_3). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ/ppm = 145.48 (C), 141.80 (C), 138.10 (C), 134.28 (C), 132.11 (CH), 130.83 (CH), 130.48 (CH), 129.58 (C), 128.98 (CH), 124.90 (CH), 123.15 (CH), 120.86 (CH), 118.67 (C), 112.99 (C), 18.56 (CH_3). HRMS (ESI^+) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{17}\text{H}_{13}\text{ON}_2$ = 261.1022, found = 261.1020.

4-Methyl-2-(*o*-tolyl)quinoline 1-oxide – novel (3k)

Dark brown amorphous solid 120 mg, 16%. IR (thin film) ν/cm^{-1} = 2924w, 1600w, 1561w, 1494w, 1457w, 1387m, 1368w, 1338s, 1282w, 1234m, 1209m, 1150m, 1060w, 910w, 871w, 758s, 729s. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ/ppm = 8.90 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.80 (t, J = 7.5 Hz, 1H), 7.70 (t, J = 7.5 Hz, 1H), 7.41 – 7.28 (m, 4H), 7.20 (s, 1H), 2.69 (s, 3H), 2.26 (s, 3H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ/ppm = 146.34 (C), 141.53 (C), 137.77 (C), 134.00 (C), 133.51 (C), 130.34 (CH), 130.20 (CH), 129.44 (C), 129.36 (CH), 129.17 (CH), 128.35 (CH), 125.97 (CH), 124.79 (CH), 124.32 (CH), 120.91 (CH), 19.79 (CH_3), 18.42 (CH_3). HRMS (ESI^+) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{17}\text{H}_{16}\text{ON}$ = 250.1226, found = 250.1221.

Flow Photochemical Heterocyclic Metamorphosis**Ethyl 4-(benzo[*d*][1,3]oxazepin-2-yl)benzoate – novel (4a)**

Tan solid 49 mg, 98%; large scale 1.935 g, 97%.

IR (thin film) ν/cm^{-1} = 1715s, 1661w, 1596w, 1407w, 1366s, 1207m, 1103m, 1034m, 761m. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ/ppm = 8.16 (app. d, J = 8.5 Hz, 2H), 8.09 (app. d, J = 8.5 Hz, 2H), 7.30 – 7.24 (m, 2H), 7.13 (m, 1H), 7.08 (d, J = 7.5 Hz, 1H), 6.28 (d, J = 5.5 Hz, 1H), 6.00 (d, J = 5.5 Hz, 1H), 4.41 (q, J = 7.0 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ/ppm = 166.06 (CO), 152.75 (C), 144.82 (C), 144.50 (CH), 136.74 (C), 132.80 (C), 130.07 (C), 129.53 (CH), 129.26 (CH), 129.06 (CH), 128.64 (CH), 128.25 (CH), 126.18 (CH), 117.50 (CH), 61.29 (CH_2), 14.32 (CH_3). HRMS (ESI^+) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{18}\text{H}_{16}\text{O}_3\text{N}$ = 294.1125, found = 294.1128.

2-(4-Fluorophenyl)benzo[*d*][1,3]oxazepine – novel (4b)

Tan solid 46 mg, 92%. IR (thin film) ν/cm^{-1} = 1662m, 1634m, 1595m, 1504s, 1484w, 1444w, 1261m, 1207s, 1193s, 1151m, 1113m, 1098m, 843w, 761s. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ/ppm = 8.12 (app. dd, J = 8.5, 5.5 Hz, 2H), 7.27 – 7.23 (m, 2H), 7.15 – 7.06 (m, 4H), 6.28 (d, J = 5.5 Hz, 1H), 6.00 (d, J = 5.5 Hz, 1H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ/ppm = 165.06 (d, J = 252.5 Hz, CF), 152.97 (C), 145.17 (C), 144.63 (CH), 131.62 (d, J = 9.0 Hz, CH), 130.05 (C), 129.34 (CH), 129.11 (d, J = 3.0 Hz, C), (C), 128.50 (CH), 128.32 (CH), 125.89 (CH), 117.71 (CH),

115.60 (d, $J = 22.0$ Hz, CH). ^{19}F -NMR (376 MHz, CDCl_3): $\delta/\text{ppm} = -108.1$. HRMS (ESI^+) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{15}\text{H}_{11}\text{ONF} = 240.0819$, found = 240.0827.

2-(4-Chlorophenyl)benzo[*d*][1,3]oxazepine – reported but with no NMR^{9c} (4c)

Off-white solid 47 mg, 95%. IR (thin film) $\nu/\text{cm}^{-1} = 1661\text{m}, 1633\text{w}, 1592\text{s}, 1571\text{w}, 1488\text{w}, 1445\text{w}, 1401\text{w}, 1285\text{m}, 1259\text{m}, 1207\text{w}, 1183\text{w}, 1113, 1090\text{s}, 1032\text{w}, 761\text{s}, 523\text{w}$. ^1H -NMR (400 MHz, CDCl_3): $\delta/\text{ppm} = 8.04$ (app. d, $J = 8.5$ Hz, 2H), 7.40 (app. d, $J = 8.5$ Hz, 2H), 7.28 – 7.22 (m, 2H), 7.16 – 7.04 (m, 2H), 6.27 (d, $J = 5.5$ Hz, 1H), 5.99 (d, $J = 5.5$ Hz, 1H). ^{13}C -NMR (101 MHz, CDCl_3): $\delta/\text{ppm} = 145.04$ (C), 144.61 (CH), 137.87 (C), 131.43 (C), 130.65 (CH), 130.10 (C), 129.36 (CH), 129.18 (CH), 128.80 (C), 128.58 (CH), 128.35 (CH), 126.05 (CH), 117.68 (CH). HRMS (ESI^+) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{15}\text{H}_{11}\text{NO}^{35}\text{Cl} = 256.0524$, found = 256.0530; $\text{C}_{15}\text{H}_{11}\text{NO}^{37}\text{Cl} = 258.0494$, found = 258.0501.

2-(4-Nitrophenyl)benzo[*d*][1,3]oxazepine – novel (4d)

Due to solubility difficulties this transformation required a 1:1 MeCN:PhMe solvent system. A residence time of 15 min was used as a compromise between conversion and photodecomposition. Orange solid 33 mg, 66%. IR (thin film) $\nu/\text{cm}^{-1} = 1660\text{w}, 1598\text{m}, 1519\text{s}, 1482\text{w}, 1360\text{s}, 1261\text{w}, 1208\text{w}, 111\text{w}, 1036\text{w}, 1012\text{w}, 854\text{m}, 756\text{m}, 712\text{w}$. ^1H -NMR (400 MHz, CDCl_3): $\delta/\text{ppm} = 8.26$ (app. s, 4H), 7.29 – 7.25 (m, 2H), 7.16 (m, 1H), 7.08 (d, $J = 7.5$ Hz, 1H), 6.26 (d, $J = 6.0$ Hz, 1H), 5.98 (d, $J = 6.0$ Hz, 1H). ^{13}C -NMR (101 MHz, CDCl_3): $\delta/\text{ppm} = 151.54$ (C), 149.58 (C), 144.53 (C), 144.40 (CH), 138.77 (C), 130.21 (C), 130.14 (CH), 129.54 (CH), 129.06 (CH), 128.63 (CH), 126.90 (CH), 123.68 (CH), 117.57 (CH). HRMS (ESI^+) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{15}\text{H}_{11}\text{O}_3\text{N}_2 = 267.0764$, found = 267.0767.

2-Phenylbenzo[*d*][1,3]oxazepine^{11,19} (4e)

Off-white solid 46 mg, 95%. IR (thin film) $\nu/\text{cm}^{-1} = 3059\text{w}, 1651\text{s}, 1631\text{m}, 1448\text{w}, 1208\text{m}, 1197\text{m}, 1113\text{w}, 1037\text{w}, 1020\text{w}, 758\text{m}, 691\text{w}$. ^1H -NMR (400 MHz, CDCl_3): $\delta/\text{ppm} = 8.14$ – 8.10 (m, 2H), 7.51 – 7.39 (m, 3H), 7.31 – 7.23 (m, 2H), 7.15 – 7.06 (m, 2H), 6.30 (d, $J = 5.5$ Hz, 1H), 6.02 (d, $J = 5.5$ Hz, 1H). ^{13}C -NMR (101 MHz, CDCl_3): $\delta/\text{ppm} = 153.95$ (C), 145.31 (C), 144.79 (CH), 132.87 (C), 131.64 (CH), 130.12 (C), 129.35 (CH), 129.28 (CH), 128.53 (CH), 128.49 (CH), 128.22 (CH), 125.79 (CH), 117.76 (CH). HRMS (ESI^+) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{15}\text{H}_{12}\text{ON} = 222.0913$, found = 22.0916.

Ethyl 4-(5-methylbenzo[*d*][1,3]oxazepin-2-yl)benzoate – novel (4g)

Off-white solid 47 mg, 95%. IR (thin film) $\nu/\text{cm}^{-1} = 1716\text{s}, 1655\text{w}, 1634\text{w}, 1367\text{w}, 1301\text{s}, 1202\text{w}, 110\text{s}, 1011\text{m}, 761\text{w}$. ^1H -NMR (400 MHz, CDCl_3): $\delta/\text{ppm} = 8.19$ (app. d, $J = 8.5$ Hz, 2H), 8.10 (app. d, $J = 8.5$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.36 – 7.30 (m, 2H), 7.22 (m, 1H), 6.33 (q, $J = 1.0$ Hz, 1H), 4.41 (q, $J = 7.0$ Hz, 2H), 2.02 (d, $J = 1.0$ Hz, 3H), 1.42 (t, $J = 7.0$ Hz, 3H). ^{13}C -NMR (101 MHz, CDCl_3): $\delta/\text{ppm} = 166.19$ (CO), 154.62 (C), 144.81 (C), 140.66 (CH), 136.58 (C), 132.95 (C), 132.12 (C), 129.73 (CH), 129.07 (CH), 128.16 (CH), 128.00 (CH), 126.70 (CH),

125.69 (CH), 125.28 (C), 61.41 (CH₂), 15.35 (CH₃), 14.43 (CH₃). HRMS (ESI⁺) [M+H]⁺ calculated for C₁₉H₁₈O₃N = 308.1281, found = 308.1282.

2-(4-Fluorophenyl)-5-methylbenzo[d][1,3]oxazepine – novel (4h)

Off-white solid 47 mg, 98%. IR (thin film) ν/cm^{-1} = 1655m, 1597s, 1503s, 1480m, 1441w, 1410w, 1284m, 1258m, 1225m, 1202m, 1153m, 1095m, 1010w, 841w, 763m. ¹H-NMR (400 MHz, CDCl₃): δ/ppm = 8.19 – 8.10 (m, 2H), 7.39 (d, J = 8.5 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.20 (m, 1H), 7.17 – 7.08 (m, 2H), 6.33 (s, 1H), 2.03 (s, 3H). ¹³C-NMR (101 MHz, CDCl₃): δ/ppm = 164.96 (d, J = 252.5 Hz, CF), 154.61 (C), 144.90 (C), 140.59 (CH), 131.90 (C), 131.39 (d, J = 9.0 Hz, CH), 128.75 (C), 128.01 (CH), 127.70 (CH), 126.56 (CH), 125.21 (CH), 125.17 (C), 115.58 (d, J = 22.0 Hz, CH), 15.26 (s, CH₃). ¹⁹F-NMR (376 MHz, CDCl₃): δ/ppm = 108.0. HRMS (ESI⁺) [M+H]⁺ calculated for C₁₆H₁₃ONF = 254.0976, found = 254.0982.

4-(5-Methylbenzo[d][1,3]oxazepin-2-yl)benzonitrile – novel (4j)

Off-white solid 49 mg, 98%. IR (thin film) ν/cm^{-1} = 3063w, 2228m, 1659m, 1634w, 1596w, 1564w, 1500w, 1483w, 1441w, 1407w, 1283w, 1259m, 1203s, 1093s, 1073m, 1026w, 1012s, 863w, 843w, 762s. ¹H-NMR (400 MHz, CDCl₃): δ/ppm = 8.23 (app. d, J = 8.5 Hz, 2H), 7.73 (app. d, J = 8.5 Hz, 2H), 7.42 – 7.13 (m, 4H), 6.30 (s, 1H), 2.03 (s, 3H). ¹³C-NMR (101 MHz, CDCl₃): δ/ppm = 153.61 (C), 144.49 (C), 140.46 (CH), 136.82 (C), 132.36 (CH), 132.11 (C), 129.59 (CH), 128.34 (CH), 128.13 (CH), 126.82 (CH), 126.08 (CH), 125.39 (C), 118.55 (C), 114.75 (C), 15.40 (CH₃). HRMS (ESI⁺) [M+H]⁺ calculated for C₁₇H₁₃ON₂ = 261.1022, found = 261.1026.

5-Methyl-2-(*o*-tolyl)benzo[d][1,3]oxazepine – novel (4k)

Off-white solid 38 mg, 75%. IR (thin film) ν/cm^{-1} = 2956w, 2923w, 1652m, 1633w, 1597w, 1570w, 1483m, 1454w, 1440w, 1254m, 1193s, 1095s, 1071w, 1002s, 981w, 758s, 726m. ¹H-NMR (400 MHz, CDCl₃): δ/ppm = 7.92 (d, J = 7.0 Hz, 1H), 7.43 – 7.24 (m, 6H), 7.21 (m, 1H), 6.33 (q, J = 1.0 Hz, 1H), 2.69 (s, 3H), 2.04 (d, J = 1.0 Hz, 3H). ¹³C-NMR (101 MHz, CDCl₃): δ/ppm = 156.12 (C), 145.21 (C), 140.67 (CH), 139.83 (C), 134.43 (C), 132.03 (C), 131.82 (CH), 130.78 (CH), 130.59 (CH), 127.99 (CH), 127.86 (CH), 126.62 (CH), 125.89 (CH), 125.26 (CH), 125.04 (C), 22.75 (CH₃), 15.34 (CH₃). HRMS (ESI⁺) [M+H]⁺ calculated for C₁₇H₁₆ON = 250.1226, found = 250.1227.

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