Supporting information for

A Novel Route to 2-Arylquinolines: Reductive-Cleavage of 2’-nitroaryl-Δ²-Isoxazolines

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1. **General information**

All the reactions were monitored by TLC analysis. $^1$H and $^{13}$C NMR spectra were recorded without any internal standard. $^1$H NMR spectra & $^{13}$C NMR spectra were recorded on 400 MHz and 101 MHz (Bruker) AVANCE II/AVANCE III instruments respectively. Chemical shifts are reported in ppm and calibrated for CDCl$_3$ ($\delta = 7.27$ ppm) for $^1$H NMR and ($\delta = 77.0$ ppm) for $^{13}$C NMR spectroscopy. Coupling constants were measured in Hz. High Resolution Mass Spectroscopy data of the products were acquired using Agilent 6520 Q-TOF instruments with Mass hunter software. Column chromatographic purifications were performed on a CombiFlash Rf (Teledyne Isco) with silica gel (230-400 mesh particle size) using cyclohexane and ethylacetate as the mobile phase. Melting points were determined with a SRS-OptiMelt digital melting point apparatus and are uncorrected. DFT calculations were carried out with B3LYP/6-31G** level of theory with full geometry optimization. Gas phase energies for the four molecules (Scheme 3) were calculated using the Jaguar software, available in Schrodinger’s Maestro modelling suite (version 9.9.013).

2. **Optimization of reaction conditions with transition metal reagents:**

![Scheme 1](image)

Scheme 1: The optimisation of conversion of 1a to 3a using various reducing agents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reducing Agent [equiv.]</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Distribution (1a:2a:3a) [isolated % yield]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fe/NH$_4$Cl [4]</td>
<td>EtOH:H$_2$O (1:1)</td>
<td>RT</td>
<td>6</td>
<td>100:0:0</td>
</tr>
<tr>
<td>2</td>
<td>Fe/NH$_4$Cl [4]</td>
<td>EtOH:H$_2$O (1:1)</td>
<td>50</td>
<td>6</td>
<td>0:100:0</td>
</tr>
</tbody>
</table>
3. Optimization of reaction conditions with Sodium dithionite:

Table 2: Screening conditions using sodium dithionite for optimisation of the 1a to 3a conversion.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reducing Agent [eq.]</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Distribution (1a:2a:3a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sodium Dithionite [4]</td>
<td>EtOH</td>
<td>80</td>
<td>6</td>
<td>100:0:0</td>
</tr>
<tr>
<td>6</td>
<td>Sodium Dithionite-K₂CO₃[6]</td>
<td>DMSO</td>
<td>100</td>
<td>3</td>
<td>0:0:100</td>
</tr>
<tr>
<td>7</td>
<td>Sodium Dithionite [4]</td>
<td>DMSO</td>
<td>100</td>
<td>3</td>
<td>0:0:100</td>
</tr>
</tbody>
</table>
4. Study of hydrogen bonding by $^1$H NMR

![Scheme 2: Equilibrium between the two forms of 2a](image)

Table 3: Solvent polarity parameter $^3$ study of 2a and effect of $E^{N/T}$ on NH$_2$ ppm shift in $^1$H NMR.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$E^{N/T}$</th>
<th>$\delta$ ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>chloroform</td>
<td>0.259</td>
<td>3.98</td>
</tr>
<tr>
<td>Toluene</td>
<td>0.099</td>
<td>3.46</td>
</tr>
<tr>
<td>acetone</td>
<td>0.355</td>
<td>4.6</td>
</tr>
<tr>
<td>DMSO</td>
<td>0.444</td>
<td>5.01</td>
</tr>
</tbody>
</table>

![Figure 1 NH$_2$ chemical shift in 2a [0.2 M] with change in solvent (increasing solvent polarity parameter $E^{N/T}$)](image)

5. Details of DFT study:
Theoretical calculations were carried out with DFT calculations (B3LYP/6-31G** level of theory) with full geometry optimization (Figure 2) of 2a as well as 2n (a molecule with p-amino group).
Assuming, that the first step in the reductive cleavage is addition of an electron to the $\Delta^2$-isoxazoline ring to form a radical anion, the difference in the energy changes ($\Delta\Delta E$, equation 1) for the two processes ($2a^1\Delta 2a^1^-$ versus $2n\Delta 2n^-$) reflects the extent to which the ortho-amino group stabilizes (or destabilizes) the radical anion.

$$\Delta\Delta E = [E (2a^1^-) - E (2a^1)] - [E (2n^-) - E (2n)]$$  

Equation 1

Gas phase energies for the four molecules (Scheme 3) were calculated using the Jaguar software, available in Schrodinger’s Maestro modelling suite (version 9.9.013). These energies as shown in Scheme 3 were used to calculate the stability of the radical anions, with respect to their neutral counterparts.

The gas phase energy in Scheme 3 indicates that the ortho-amino group stabilized the formation of the radical anion by $\Delta\Delta E$ of -0.006567 Ha (or -17.2 kJ/mol,) compared to the non-hydrogen bonded form. This was further reinforced by an elongated O-N bond in the radical anion of $2a^1$ (1.47462 Å) compared to that in the radical anion of $2n$ (1.46062 Å).

Figure 1: Gas phase optimised geometries of $2a^1$ (a) and $2n$ (b) Using B3LYP/6-31G** level of theory.

The extent to which this stabilization might speed up the reductive cleavage reaction can be estimated using the Arrhenius equation (equation 2), assuming that the radical anion is the transition state for the reaction.

$$k = Ae^{-\frac{Ea}{RT}}$$  

Equation 2

It can be speculated from the above calculations that the ortho-amino-group stabilizes the radical anion and lowers the activation energy (Ea) by 17.2 kJ/mol. From the Arrhenius equation, this equates to an
acceleration in the rate of reaction by 1000-fold, which is consistent with the experimental observation,
that the ortho-amino group is required for the reductive cleavage of the $\Delta^2$-isoxazoline ring.

Scheme 3: Gas phase energies (Hartrees) and bond lengths (Å) based on DFT calculations.
6. Experimental procedure and characterization of compounds (3a-m)

Scheme 4: One pot conversion of 1a to 3a using a) method-1: iron with additives as reducing agent and b) method-2: metal free dithionite as reducing agent in DMSO.

**Method 1**: To a solution of Δ²-isoxazoline derivative 1a-m (1.00 mmol, 1.0 equiv.) in ethanol (7.0 ml) at 25 °C was added iron powder (8.00 mmol, 8.0 equiv.), ammonium chloride (8.00 mmol, 8.0 equiv.) and water (7.0 ml). The resulting suspension was stirred at 80 °C for 6 h and monitored by TLC and LC-MS. The reaction mixture was allowed to cool to 25 °C, and filtered through a bed of celite. The filtrate was distilled under reduced pressure and the resulting aqueous phase was extracted with ethyl acetate (3 x 5.0 ml). The combined organic layer was washed with water (5.0 ml) followed by brine (5.0 ml each), dried over sodium sulfate (anhyd.), filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography using silica gel with ethyl acetate and cyclohexane as the mobile phase to yield the desired product 3a-m.

**Method 2**: To a solution of 2'-nitroaryl-Δ²-isoxazoline 1 (1.00 mmol, 1.0 equiv.) in DMSO (7.0 ml) was added sodium dithionite (6.00 mmol, 6.0 equiv.) at 25 °C. The suspension was warmed to 100 °C and stirred for 3-5 h. The reaction was monitored by TLC and LC-MS and after complete conversion the reaction mixture was cooled to 25 °C. The reaction mass was poured into an ice cold solution of sodium hydroxide and stirred for 10 min. The aqueous phase was extracted with diethyl ether (3 x 10.0 ml) and the combined organic layer was washed with water (10.0 ml) followed by brine solution (10.0 ml each), dried over sodium sulfate (anhyd.), filtered and the filtrate was concentrated under reduced pressure to isolate the crude product. The product was purified by flash chromatography using silica gel with ethyl acetate and cyclohexane as the mobile phase.
2-phenylquinoline (3a):

![Chemical structure of 2-phenylquinoline (3a)](image)

The product 3a was isolated using method 1: 152 mg, Yield 74%, method 2: 143 mg, Yield 70%, white solid, MP=86-87 °C,(lit\(^2\) 86 °C). \(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) ppm = 8.26-8.16 (m, 4H), 7.90 (d, \(J = 8.7\) Hz, 1H), 7.85 (d, \(J = 8.3\) Hz, 1H), 7.75 (t, \(J = 7.6\) Hz, 1H), 7.57-7.46 (m, 4H), 7.27 (s, 1H).

\(^{13}\)C NMR (CDCl\(_3\), 101MHz): \(\delta\) ppm = 157.0, 136.5, 129.4, 129.3, 129.0, 128.5, 127.2, 127.1, 126.8, 126.0, 118.7. HRMS (ESI-TOF+): m/z calcd for \(\text{C}_{15}\text{H}_{11}\text{N} [(M + H)^+]: 205.0891, \text{Found}: 205.0891.

2-(4-bromophenyl)quinoline (3b):

![Chemical structure of 2-(4-bromophenyl)quinoline (3b)](image)

The product 3b was isolated using method 1: 226 mg, Yield 80%, white solid, MP=119-120 °C,(lit\(^3\) 119-120 °C). \(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) ppm = 8.31 (br s, 2H), 8.09 (d, \(J = 7.8\) Hz, 2H), 7.87 (d, \(J = 7.8\) Hz, 3H), 7.68 (d, \(J = 7.3\) Hz, 3H), 7.58 (s, \(J = 6.9, 6.9\) Hz, 1H). \(^{13}\)C NMR (CDCl\(_3\), 101MHz): \(\delta\) ppm = 155.8, 147.1, 138.3, 137.3, 132.2, 130.6, 129.7, 128.8, 127.6, 127.3, 127.0, 124.6, 119.2. HRMS (ESI-TOF+): m/z calcd for \(\text{C}_{15}\text{H}_{10}\text{BrN} [(M + H)^+]: 282.9997, \text{Found}: 282.9997.

2-(4-chloro-2-fluoro-phenyl)quinoline (3c):

![Chemical structure of 2-(4-chloro-2-fluoro-phenyl)quinoline (3c)](image)

The product 3c was isolated using method 1: 206 mg, Yield 80%, white solid, MP=85-86 °C. \(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) ppm = 8.26 (s, 2H), 8.20-8.25 (m, 7H), 8.15 (s, 1H), 8.13 (s, 2H), 8.11 (s, 1H), 7.86-7.90 (m, 9H), 7.77 (ddd, \(J = 8.5, 7.0, 1.4\) Hz, 5H), 7.59 (ddd, \(J = 8.1, 7.0, 1.3\) Hz, 5H), 7.32-7.35 (m, 5H), 7.27 (s, 6H), 7.24 (d, \(J = 2.0\) Hz, 2H). \(^{13}\)C NMR (CDCl\(_3\), 101MHz): \(\delta\) ppm = 132.5, 130.0, 129.5, 128.5, 127.5, 127.3,
127.0, 125.2, 124.3, 122.2, 122.1, 121.5, 117.2, 116.9; HRMS (ESI-TOF+): m/z calcd for C_{15}H_{9}ClFN [(M + H)^+]: 257.0407, Found: 257.0401.

2-(4-methoxyphenyl)quinoline (3d):

The product 3d was isolated using method 1: 188 mg, Yield 80% and method 2: 135 mg, Yield 55%, white solid, MP=125-126 °C, (lit\(^4\) 125-126 °C). \(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) ppm = 8.09-8.28 (m, 4H), 7.80-7.88 (m, 2H), 7.73 (t, \(J = 7.2\) Hz, 1H), 7.49-7.55 (m, 1H), 7.07 (d, \(J = 7.9\) Hz, 2H), 3.90 (s, 3H. \(^1\)C NMR (CDCl\(_3\), 101MHz): \(\delta\) ppm = 129.3, 127.7, 127.2, 118.9, 114.6, 55.7. HRMS (ESI-TOF+): m/z calcd for C_{16}H_{13}NO: [(M + H)^+]: 235.0997, Found: 235.0997.

2-(2-thienyl)quinoline (3e):

The product 3e was isolated using method 1: 162 mg, Yield 77%, cream colour solid, MP=132-133 °C, (lit\(^5\) 132 °C). \(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) ppm = 8.17 (d, \(J = 8.8\) Hz, 1H), 8.13 (d, \(J = 9.0\) Hz, 1H), 8.06 (dd, \(J = 3.0, 1.3\) Hz, 1H), 7.89 (dd, \(J = 5.0, 1.3\) Hz, 1H), 7.70-7.83 (m, 3H), 7.43-7.55 (m, 2H), 7.36 (s, 1H), 1.88 (br s, 1H), 1.27 (d, \(J = 6.3\) Hz, 1H). \(^1\)C NMR (CDCl\(_3\), 101MHz): \(\delta\) ppm = 153.3, 148.3, 142.7, 136.8, 129.7, 129.5, 127.5, 127.2, 126.9, 126.4, 126.1, 124.7, 119.1. HRMS (ESI-TOF+): m/z calcd for C_{16}H_{12}NS [(M + H)^+]: 211.0455, Found: 211.0448.

2-(6-bromo-2-pyridyl)quinoline (3f):

The product 3f was isolated using method 1: 221 mg, Yield 78% and method 2: 195 mg, Yield 69%, white solid, MP=158 °C.\(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) ppm = 8.66 (d, \(J = 7.6\) Hz, 1H), 8.57 (d, \(J = 8.5\) Hz, 1H), 8.29
(d, J = 8.7 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.87 (dd, J = 8.0, 1.5 Hz, 1H), 7.71-7.77 (m, 2H), 7.53-7.60 (m, 2H). 13C NMR (CDCl3, 101MHz): δ ppm = 157.5, 154.5, 147.9, 139.3, 137.0, 129.8, 129.7, 128.5, 128.4, 127.7, 127.1, 120.5, 119.1. HRMS (ESI-TOF+): m/z calcd for C14H9BrN2 [(M + H)⁺]: 283.9949, Found: 283.9945.

2-(2-quinolyl)aniline (3g):

![2-(2-quinolyl)aniline](image)

The product 3g was isolated using method 1: 158 mg, Yield 72% and method 2: 145 mg, Yield 66%, brown solid, MP=159-160 °C, (lit6 153 °C). 1H NMR (CDCl3, 400MHz): δ ppm = 8.22 (s, 1H), 8.20 (s, 2H), 8.08 (s, 1H), 8.05 (s, 2H), 7.86 (s, 2H), 7.82-7.84 (m, 5H), 7.80 (s, 2H), 7.69-7.72 (m, 11H), 7.52 (s, 1H), 7.26 (s, 4H), 6.84 (s, 6H), 6.82 ppm (s, 3H). 13C NMR (CDCl3, 101MHz): δ ppm = 159.2, 147.2, 146.8, 136.8, 130.4, 129.9, 129.7, 128.8, 127.5, 126.3, 126.2, 121.6, 120.5, 117.7, 117.5. HRMS (ESI-TOF+): m/z calcd for C15H12N2 [(M + H)⁺]: 220.1000, Found: 220.0998.

tert-buty1 2-methyl-4-(2-quinolyl)benzoate (3h):

![tert-butyl 2-methyl-4-(2-quinolyl)benzoate](image)

The product 3h was isolated using method 1: 261 mg, Yield 82%, white solid, MP=73-74 °C, (lit 125-126 °C). 1H NMR (CDCl3, 400MHz): δ ppm = 8.33 (d, J = 14.1 Hz, 2H), 8.01 (br s, 3H), 7.90-8.16 (m, 4H), 7.88 (d, J = 8.0 Hz, 2H), 7.79 (t, J = 6.9 Hz, 1H), 7.79 (d, J = 15.1 Hz, 1H), 7.59 (t, J = 6.8 Hz, 1H), 2.72 (s, 3H), 1.64 (s, 9H). 13C NMR (CDCl3, 101MHz): δ ppm = 166.7, 155.8, 139.9, 133.0, 131.2, 131.0, 130.8, 127.5, 127.3, 127.2, 125.3, 119.7, 81.3, 28.2, 22.0. HRMS (ESI-TOF+): m/z calcd for C21H21NO2 [(M + H)⁺]: 319.1572, Found: 319.1573.

3-chloro-4-(2-quinolyl)aniline (3i):
The product 3i was isolated using method 1: 188 mg, Yield 74%, off white gum. \( ^{1} \text{H NMR (CDCl}_3, 400 \text{MHz):} \) 
\[ \delta \text{ ppm = 8.18-8.23 (m, } J = 8.5 \text{ Hz, 2H)}, 7.86 (dd, } J = 8.0, 1.3 \text{ Hz, 1H}), 7.69-7.78 (m, 2H), 7.57 (ddd, } J = 8.2, 7.0, 1.1 \text{ Hz, 1H}), 7.20-7.28 (m, 1H), 7.02 (d, } J = 3.0 \text{ Hz, 1H}), 6.68 \text{ ppm (dd, } J = 8.5, 2.8 \text{ Hz, 1H}). \] 
\( ^{13} \text{C NMR (CDCl}_3, 101 \text{MHz):} \) \[ \delta \text{ ppm = 157.5, 147.6, 145.6, 139.6, 136.0, 129.9, 129.3, 127.6, 127.2, 126.9, 123.0, 121.2, 118.0, 116.9.} \] HRMS (ESI-TOF+): m/z calcd for C\(_{15}\)H\(_{11}\)ClN\(_2\) [(M + H)\(^+\)]: 254.0610, Found: 254.0611.

2-(3-pyridyl)quinoline (3j):

The product 3j was isolated using method 1: 148 mg, Yield 72%, and method 2: 134 mg, Yield 65%, white solid, MP=66-67 °C, (lit\(^7\) 66.5 °C). \( ^{1} \text{H NMR (CDCl}_3, 400 \text{MHz):} \) \[ \delta \text{ ppm = 9.34 (br s, 1H), 8.68 (br s, 1H), 8.45-8.50 (m, 1H), 8.18-8.22 (m, 1H), 8.15 (d, } J = 8.2 \text{ Hz, 1H}), 7.78-7.84 (m, 2H), 7.72 (t, } J = 7.0 \text{ Hz, 1H}), 7.49-7.55 (m, 1H), 7.39-7.45 ppm (m, 1H). \] 
\( ^{13} \text{C NMR (CDCl}_3, 101 \text{MHz):} \) \[ \delta \text{ ppm = 154.5, 150.0, 148.6, 148.3, 137.2, 135.2, 135.1, 130.0, 129.7, 127.6, 127.4, 126.8, 123.8, 118.5.} \] HRMS (ESI-TOF+): m/z calcd for C\(_{14}\)H\(_{10}\)N\(_2\) [(M + H)\(^+\)]: 206.0843, Found: 206.0835.

2-(2-bromo-4-chloro-phenyl)quinoline (3k)

The product 3k was isolated using method 1: 260 mg, Yield 82%, off white solid, MP=163-164 °C, (lit\(^8\) 160 °C). \( ^{1} \text{H NMR (CDCl}_3, 400 \text{MHz):} \) \[ \delta \text{ ppm = 8.17 (dd, } J = 1.3 \text{ and 8.3 Hz, 1H}), 7.87 (dd, } J = 1.0 \text{ and 8.0 Hz, 1H}), 7.63-7.76 (m, 1H), 7.44-7.59 (m, 3H), 7.20-7.31 (m, 1H), 6.39 (d, } J = 6.5 \text{ Hz, 1H}). \] 
\( ^{13} \text{C NMR (CDCl}_3,} \)
$^{101}$MHz): $\delta$ ppm = 157.4, 136.1, 134.4, 133.9, 131.6, 130.1, 130.1, 129.6, 127.6, 127.3, 127.2, 122.4, 119.8, 83.0. HRMS (ESI-TOF+): m/z calcd for $\text{C}_{15}\text{H}_9\text{BrClN}$ $[(\text{M} + \text{H})^+]$: 316.9606, Found: 316.9600.

2-(2,4,6-trifluorophenyl)quinoline (3l)

The product 3l was isolated using method 1: 210 mg, Yield 81%, and method 2: 137 mg, Yield 53%, white solid, MP=98 ºC. $^1$H NMR (CDCl$_3$, 400MHz): $\delta$ ppm = 8.26 (d, $J = 8.2$ Hz, 1H), 8.19 (d, $J = 8.2$ Hz, 1H), 7.88 (d, $J = 8.3$ Hz, 1H), 7.77 (ddd, $J = 8.5$, 7.0, 1.4 Hz, 1H), 7.60 (t, $J = 7.5$ Hz, 1H), 7.54 (d, $J = 8.5$ Hz, 1H), 6.83 ppm (t, $J = 8.0$ Hz, 2H). $^{13}$C NMR (CDCl$_3$, 101MHz): $\delta$ ppm = 164.1-159.5 (m, 3C), 149.1, 148.2, 136.5, 130.0, 129.7, 127.6, 127.3, 127.1, 123.2, 101.0-100.4(m, 2C). HRMS (ESI-TOF+): m/z calcd for $\text{C}_{15}\text{H}_8\text{F}_3\text{N}$ $[(\text{M} + \text{H})^+]$: 259.0608, Found: 259.0608.

2-(2-fluorophenyl)quinoline (3m)

The product 3m was isolated using method 1: 180 mg, Yield 81%, and method 2: 170 mg, Yield 76%, white solid, MP=93-94 ºC, (lit$^9$ 93 ºC). $^1$H NMR (CDCl$_3$, 400MHz): $\delta$ ppm = 8.14-8.25 (m, 4H), 7.84 (d, $J = 8.3$ Hz, 2H), 7.74 (ddd, $J = 8.5$, 7.0, 1.5 Hz, 1H), 7.54 (ddd, $J = 8.2$, 6.9, 1.0 Hz, 1H), 7.18-7.26 (m, 2H). $^{13}$C NMR (CDCl$_3$, 101MHz): $\delta$ ppm = 165.1-162.6 (d, $J=252.5$ Hz, 1C), 156.2, 148.1, 137.1, 135.7, 129.9, 129.6, 129.5, 129.5, 127.5, 127.1, 126.4, 118.7, 115.9, 115.7. HRMS (ESI-TOF+): m/z calcd for $\text{C}_{15}\text{H}_{10}\text{FN}$ $[(\text{M} + \text{H})^+]$: 223.0797, Found: 223.0796.
7. Experimental procedure and characterization of compounds (1a-m)

Scheme 5: Synthesis of 2'-nitroaryl-Δ²-isoxazolines 1a-m via the 3+2 cycloaddition

To a solution of oxime (1.00 mmol, 1.0 equiv.) in DMF (2.0 ml) at room temperature was added N-chlorosuccinimide (1.10 mmol, 1.10 equiv.) and stirred for 60 min. To the reaction mixture was added alkene in one portion (1.10 mmol, 1.1 equiv.) followed by a solution of triethylamine (1.00 mmol, 1.00 equiv.) in DMF (1.0 ml). After complete addition the reaction mixture was stirred at 23-25 °C till complete conversion of the chloro-oxime intermediate formed (reaction was monitored by TLC). After complete conversion the reaction mass was poured into an ice-water mixture (1:1 mixture, 10 vol. w.r.t DMF,) and stirred for 10 min. The aqueous phase was extracted with ethyl acetate (3 × 20.0 ml). The combined organic layer was washed with brine solution, dried over sodium sulfate (anhyd.), filtered and concentrated under reduced pressure to yield the crude product. Pure product was obtained by flash chromatography of the crude using silica gel as stationary phase and ethyl acetate : cyclohexane as the mobile phase.

5-(2-nitrophenyl)-3-phenyl-4,5-dihydroisoxazole (1a):

The product 1a (217 mg) was isolated using general procedure, Yield 81%, white solid, MP= 119-120 °C.

\(^1\)H NMR (CDCl₃, 400MHz): \(\delta\) ppm = 8.16 (d, \(J = 8.2\) Hz, 1H), 7.87 (d, \(J = 7.9\) Hz, 1H), 7.73-7.65 (m, 3H), 7.54-7.46 (m, 1H), 7.52-7.38 (m, 2H), 7.46-7.37 (m, 1H), 6.33 (dd, \(J = 6.6, 11.1\) Hz, 1H), 4.16 (dd, \(J = 11.2, 17.2\) Hz, 1H), 3.27 (dd, \(J = 6.6, 17.4\) Hz, 1H). \(^{13}\)C NMR (CDCl₃, 101MHz): \(\delta\) ppm = 156.2, 146.4, 137.9,
134.4, 130.4, 128.9, 128.7, 128.7, 127.6, 126.8, 125.1, 79.0, 44.1. HRMS (ESI-TOF+): m/z calcd for C_{15}H_{12}N_{2}O_{3} [(M + H)^+]: 268.0847, Found: 268.0847.

3-(4-bromophenyl)-5-(2-nitrophenyl)-4,5-dihydroisoxazole (1b):

![Structure of 1b](image)

The product 1b (303 mg) was isolated using general procedure, Yield 88%, off white solid, MP=170-172 °C. $^1$H NMR (CDCl$_3$, 400MHz): δ ppm = 8.17 (dd, $J = 8.3$, 1.3 Hz, 1H), 7.85 (d, $J = 8.1$ Hz, 1H), 7.71 (td, $J = 7.7$, 1.5 Hz, 1H), 7.53-7.56 (m, 5H), 6.34 (dd, $J = 11.3$, 6.8 Hz, 1H), 4.13 (dd, $J = 17.3$, 11.3 Hz, 1H), 3.24 (dd, $J = 17.3$, 6.8 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 101MHz): δ ppm = 154.5, 136.7, 133.5, 131.0, 127.2, 124.2, 123.8, 113.1, 184, 42.9. HRMS (ESI-TOF+): m/z calcd for C$_{15}$H$_{11}$BrN$_2$O$_3$ [(M + H)$^+$]: 345.9953, Found: 345.9919.

3-(4-chloro-2-fluoro-phenyl)-5-(2-nitrophenyl)-4,5-dihydroisoxazole (1c):

![Structure of 1c](image)

The product 1c (268 mg) was isolated using general procedure, Yield 84%, off white solid, MP=125-127 °C. $^1$H NMR (CDCl$_3$, 400MHz): δ ppm = 8.16 (d, $J = 7.9$ Hz, 1H), 7.80-7.85 (m, 2H), 7.70 (t, $J = 7.6$ Hz, 1H), 7.50 (t, $J = 7.8$ Hz, 1H), 7.26 (s, 2H), 7.10-7.21 (m, 2H), 6.33 (dd, $J = 11.3$, 7.0 Hz, 1H), 4.18 (ddd, $J = 17.9$, 11.3, 2.4 Hz, 1H), 3.31 ppm (ddd, $J = 18.1$, 7.0, 2.8 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 101MHz): δ ppm = 161.6, 152.6, 149.0, 137.9, 134.7, 130.0, 129.2, 128.9, 127.8, 125.5, 125.4, 117.7, 117.4, 79.7, 45.6. HRMS (ESI-TOF+): m/z calcd for C$_{15}$H$_{10}$ClFN$_2$O$_3$ [(M + H)$^+$]: 320.0363, Found: 320.0360.

3-(4-methoxyphenyl)-5-(2-nitrophenyl)-4,5-dihydroisoxazole (1d):

![Structure of 1d](image)
The product 1d (234 mg) was isolated using general procedure, Yield 79%, off white solid, MP=120-122 °C. Isolated as mixture of 2 regioisomer and used as such without separation.\(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) ppm = 8.14-8.18 (m, 2H), 7.83-7.90 (m, 2H), 7.60-7.74 (m, 6H), 7.47-7.56 (m, 3H), 6.90-6.96 (m, 3H), 6.32 (d, \(J = 6.5\) Hz, 1H), 6.29 (d, \(J = 7.0\) Hz, 1H), 4.07-4.17 (m, 2H), 3.94 (s, 2H), 3.84 (s, 4H), 3.19-3.27 (m, 2H). \(^{13}\)C NMR (CDCl\(_3\), 101MHz): \(\delta\) ppm = 133.5, 133.4, 127.8, 127.7, 127.4, 126.7, 126.6, 125.5, 124.2, 124.1, 120.5, 113.2, 110.9, 77.8, 55.3, 43.4. HRMS (ESI-TOF+): m/z calcd for C\(_{16}\)H\(_{14}\)N\(_2\)O\(_4\) [(M + H)\(^+\)]: 298.0953, Found: 298.0952.

5-(2-nitrophenyl)-3-(2-thienyl)-4,5-dihydroisoxazole(1e):

\[
\text{N} \quad \text{O} \\
| \text{N} \quad \text{O} \\
| \text{N} \quad \text{O}
\]

The product 1e (191 mg) was isolated using general procedure, Yield 70%, pale yellow solid, MP=137-138 °C. Isolated as mixture of 2 regioisomer and used as such without separation.\(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) ppm = 8.13-8.18 (m, 1H), 7.76-7.92 (m, 1H), 7.62-7.75 (m, 1H), 7.43-7.54 (m, 3H), 7.34-7.40 (m, 1H), 7.26 (s, 1H), 7.12 (d, \(J = 5.7\) Hz, 1H), 6.26-6.34 (m, 1H), 4.25-4.29 (m, 1H), 4.12 (dd, \(J = 17.1, 11.3\) Hz, 1H), 3.41 (dd, \(J = 17.8, 6.8\) Hz, 1H), 3.22 ppm (dd, \(J = 17.2, 6.4\) Hz, 1H). \(^{13}\)C NMR (CDCl\(_3\), 101MHz): \(\delta\) ppm = 152.4, 137.9, 134.5, 130.7, 128.8, 127.7, 127.0, 126.0, 125.6, 125.1, 78.7, 44.8. HRMS (ESI-TOF+): m/z calcd for C\(_{13}\)H\(_{10}\)N\(_2\)O\(_3\)S [(M + H)\(^+\)]: 274.0412, Found: 274.0410.

3-(6-bromo-2-pyridyl)-5-(2-nitrophenyl)-4,5-dihydroisoxazole (1f):

\[
\text{N} \quad \text{O} \\
| \text{N} \quad \text{O} \\
| \text{N} \quad \text{O}
\]

The product 1f (314 mg) was isolated using general procedure, Yield 90%, off white solid, MP=120-122 °C. \(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) ppm = 8.18 (dd, \(J = 8.2, 1.4\) Hz, 1H), 8.02 (d, \(J = 7.6\) Hz, 1H), 7.80 (d, \(J = 8.0\) Hz, 1H), 7.69 (t, \(J = 7.5\) Hz, 1H), 7.61 (t, \(J = 7.8\) Hz, 1H), 7.45-7.56 (m, 2H), 6.40 (dd, \(J = 11.4, 6.9\) Hz, 1H), 4.21 (dd, \(J = 18.3, 11.5\) Hz, 1H), 3.46 (dd, \(J = 18.4, 6.9\) Hz, 1H). \(^{13}\)C NMR (CDCl\(_3\), 101MHz): \(\delta\) ppm = 157.3, 149.8, 141.7, 138.6, 137.5, 134.4, 128.9, 128.8, 127.3, 127.0, 126.1, 121.6, 120.5, 80.1, 43.5. HRMS (ESI-TOF+): m/z calcd for C\(_{14}\)H\(_{10}\)BrN\(_3\)O\(_3\) [(M + H)\(^+\)]: 346.9905, Found: 349.9913.
3,5-bis(2-nitrophenyl)-4,5-dihydroisoxazole (1g):

![Structure of 3,5-bis(2-nitrophenyl)-4,5-dihydroisoxazole (1g)](image)

The product 1g (241 mg) was isolated using general procedure, Yield 77%, off white solid, MP=120-121 °C. $^1$H NMR (CDCl$_3$, 400MHz): δ ppm = 8.18 (dd, $J = 8.3$, 1.3 Hz, 2H), 8.07 (dd, $J = 8.0$, 1.3 Hz, 2H), 7.91 (dd, $J = 7.9$, 1.4 Hz, 2H), 7.69-7.80 (m, 4H), 7.52-7.65 (m, 6H), 6.42 (d, $J = 6.3$ Hz, 1H), 6.39 (d, $J = 6.3$ Hz, 1H), 4.04 (d, $J = 6.0$ Hz, 1H), 3.27 (d, $J = 6.3$ Hz, 1H), 3.22 (d, $J = 6.3$ Hz, 1H). $^{13}$C NMR (CDCl$_3$, 101MHz): δ ppm = 154.1, 145.4, 142.2, 136.3, 133.5, 132.6, 130.0, 129.9, 128.0, 127.0, 124.1, 124.0, 123.9, 78.7, 45.2. HRMS (ESI-TOF+): m/z calcd for C$_{15}$H$_{11}$N$_3$O$_5$ [(M + H)$^+$]: 313.0698, Found: 313.0698.

tert-butyl 2-methyl-4-[5-(2-nitrophenyl)-4,5-dihydroisoxazol-3-yl]benzoate (1h):

The product 1h (313 mg) was isolated using general procedure, Yield 82%, white solid, MP=167-168 °C. $^1$H NMR (CDCl$_3$, 400MHz): δ ppm = 8.18 (dd, $J = 8.3$, 1.3 Hz, 1H), 7.83-7.87 (m, 2H), 7.71 (t, $J = 7.6$ Hz, 1H), 7.49-7.54 (m, 3H), 4.15 (dd, $J = 17.3$, 11.3 Hz, 1H), 3.26 (dd, $J = 17.3$, 6.8 Hz, 1H), 2.58 (s, 3H), 1.57-1.62 ppm (s, 9H). $^{13}$C NMR (CDCl$_3$, 101MHz): δ ppm = 166.5, 155.7, 139.8, 137.7, 134.5, 133.4, 131.4, 130.7, 129.7, 128.8, 127.6, 125.2, 123.9, 81.6, 79.3, 43.9, 28.2, 21.7. HRMS (ESI-TOF+): m/z calcd for C$_{21}$H$_{22}$N$_2$O$_5$ [(M + H)$^+$]: 382.1528. Found: 382.1525.

3-(2-chloro-4-nitro-phenyl)-5-(2-nitrophenyl)-4,5-dihydroisoxazole (1i):

The product 1i (294 mg) was isolated using general procedure, Yield 85%, off white solid, MP=108-109 °C. $^1$H NMR (CDCl$_3$, 400MHz): δ ppm = 8.57 (d, $J = 2.8$ Hz, 1H), 8.18-8.23 (m, 2H), 7.87 (d, $J = 7.7$ Hz, 1H),
7.76 (t, J = 7.4 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 6.44 (dd, J = 11.2, 6.9 Hz, 1H), 4.34 (dd, J = 17.7, 11.2 Hz, 1H), 3.42 (dd, J = 17.7, 6.9 Hz, 1H). 13C NMR (CDCl3, 101MHz): δ ppm = 154.7, 147.9, 139.5, 137.0, 134.7, 131.9, 130.1, 129.2, 127.5, 125.6, 125.4, 80.4, 45.8. HRMS (ESI-TOF+): m/z calcd for C15H10ClN3O5 [(M + H)+]: 347.0308, Found: 347.0388.

5-(2-nitrophenyl)-3-(3-pyridyl)-4,5-dihydroisoxazole(1j):

![Chemical structure image]

The product 1j (188 mg) was isolated using general procedure, Yield 70%, off white solid, MP=115-116 °C. 1H NMR (CDCl3, 400MHz): δ ppm = 8.87 (br s, 1H), 8.19 (dd, J = 8.3, 1.3 Hz, 1H), 8.09 (dt, J = 8.0, 1.9 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 6.2 Hz, 1H), 6.39 (dd, J = 11.3, 6.8 Hz, 1H), 4.18 (dd, J = 17.3, 11.3 Hz, 1H), 3.29 (dd, J = 17.4, 6.9 Hz, 1H). HRMS (ESI-TOF+): m/z calcd for C14H11N3O3 [(M + H)+]: 269.0800, Found: 269.0800.

3-(2-bromo-4-chloro-phenyl)-5-(2-nitrophenyl)-4,5-dihydroisoxazole(1k):

![Chemical structure image]

The product 1k (310 mg) was isolated using general procedure, Yield 82%, MP=85-86 °C. 1H NMR (CDCl3, 400MHz): δ ppm = 8.18 (dd, J = 8.3, 1.3 Hz, 1H), 7.88 (d, J = 7.7 Hz, 1H), 7.74 (t, J = 7.5 Hz, 1H), 7.47-7.60 (m, 3H), 7.21-7.32 (m, 2H), 6.38 (dd, J = 11.3, 6.5 Hz, 1H), 4.25 (dd, J = 17.7, 11.2 Hz, 1H), 3.39 (dd, J = 17.6, 6.5 Hz, 1H). 13C NMR (CDCl3, 101MHz): δ ppm = 156.4, 146.5, 137.3, 134.9, 134.6, 133.8, 132.1, 132.0, 131.2, 130.7, 129.0, 125.3, 119.8, 79.9, 46.1. HRMS (ESI-TOF+): m/z calcd for C19H10BrClN2O3 [(M + H)+]: 379.9563, Found: 379.9564.

5-(2-nitrophenyl)-3-(2,4,6-trifluorophenyl)-4,5-dihydroisoxazole(1l):

![Chemical structure image]
The product **1l** (288 mg) was isolated using general procedure, Yield 90%, MP=75-76 °C. $^1$H NMR (CDCl$_3$, 400MHz): $\delta$ ppm = 8.16 (dd, $J$ = 8.0, 1.3 Hz, 1H), 7.85 (d, $J$=7.6 Hz, 1H), 7.72 (t, $J$ = 7.4 Hz, 1H), 7.51 (td, $J$ = 7.8, 1.5 Hz, 1H), 6.69-6.82 (m, 2H), 6.32 (dd, $J$ = 11.3, 6.8 Hz, 1H), 4.18 (ddt, 1H), 3.26 ppm (ddt, 1H). $^{13}$C NMR (CDCl$_3$, 101MHz): $\delta$ ppm = 164.5-162.6 (m, 3C), 148.2, 146.5, 137.4, 134.6, 129.0, 127.6, 125.3, 101.5-101.1(m, 2C), 79.1, 46.8. HRMS (ESI-TOF+): m/z calcd for C$_{15}$H$_9$F$_3$N$_2$O$_3$ [(M + H)$^+$]: 322.0565, Found: 322.0555.

3-(2-fluorophenyl)-5-(2-nitrophenyl)-4,5-dihydroisoxazole(1m):

![Chemical Structure](image)

The product **1m** (254 mg) was isolated using general procedure, Yield 89%, MP=136-137° C. $^1$H NMR (CDCl$_3$, 400MHz): $\delta$ ppm = 8.17 (dd, $J$ = 8.2, 1.4 Hz, 1H), 7.86 (dd, $J$ = 7.9, 1.1 Hz, 1H), 7.65-7.73 (m, 3H), 7.51 (t, $J$ = 7.8 Hz, 1H), 7.11 (t, $J$ = 8.1 Hz, 2H), 6.33 (dd, $J$ = 11.3, 6.8 Hz, 1H), 4.14 (dd, $J$ = 17.3, 11.3 Hz, 1H), 3.24 (dd, $J$ = 17.2, 6.7 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 101MHz): $\delta$ ppm = 165.2-162.7 (d, $J$ = 252.5 Hz, 1C), 155.3, 146.5, 137.8, 134.5, 128.9, 128.9, 128.8, 127.6, 125.3, 125.2, 116.1, 115.9, 79.2, 44.2. HRMS (ESI-TOF+): m/z calcd for C$_{15}$H$_{11}$FN$_2$O$_3$ [(M + H)$^+$]: 286.07537, Found: 286.07538.

8. $^1$H and $^{13}$C NMR spectra of compounds
9. References