Copper nitrate-mediated synthesis of 3-aryl isoxazolines and isoxazoles from olefinic azlactones

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General Information

All reagents were obtained from commercial sources without further purification, and commercially available solvents were purified before use. All new compounds were fully characterized. All melting points were taken on a WRS-1A or a WRS-1B Digital Melting Point Apparatus without correction. Infrared spectra were obtained using an AVATAR 370 FT-IR spectrometer. $^1$H, $^{13}$C and $^{19}$F NMR spectra were recorded with a Bruker AV-500 spectrometer operating at 500 MHz, 125 MHz and 470 MHz, respectively, with chemical shift values being reported in ppm relative to chloroform ($\delta = 7.26$ ppm), dimethyl sulfoxide ($\delta = 2.50$ ppm) or TMS ($\delta = 0.00$ ppm) for $^1$H NMR; with chloroform ($\delta = 77.16$ ppm), dimethyl sulfoxide ($\delta = 39.52$ ppm) for $^{13}$C NMR; with C$_6$F$_6$ ($\delta = -164.9$ ppm) for $^{19}$F NMR. Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded with an Agilent 5975C or Thermo Fisher Scientific LTQ FTICR-MS using an Electron impact (EI) or Electrospray ionization (ESI) techniques. The crystal structure was recorded on SMART APEXII X-ray diffraction spectrometer. Silica gel plate GF254 were used for thin layer chromatography (TLC) and silica gel H or 300–400 mesh were used for flash column chromatography. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise indicated. N-Alkylmaleimides 2a–2g and 2j–2n are all purchased from commercial sources.
2. Synthesis and Characterization of Substrates

2.1 Synthesis of Olefinic Azlactones

(Z)-4-Benzylidene-2-phenyloxazol-5(4H)-one (1a):\(^1\) Hippuric acid (1.80 g, 10 mmol), benzaldehyde (1.27 g, 12.0 mmol), NaOAc (0.25 g, 3.0 mmol) and Ac\(_2\)O (4.0 mL, 40.0 mmol) in THF (30 mL) was reflux for 3 h. Upon completion, the reaction mixture was cooled down to room temperature. A saturated aqueous solution of Na\(_2\)CO\(_3\) was added. The mixture was extracted with CH\(_2\)Cl\(_2\), dried with Na\(_2\)SO\(_4\), filtered, and the solvent was removed under vacuum. The given residue was purified by recrystallization from EtOH to give 1a as a yellow solid (1.30 g, 52%). M.p. 169-171 °C; IR (KBr, cm\(^{-1}\)): 3056, 1794, 1652, 1589, 1549, 1325, 1293, 1160, 982, 861, 764, 689; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 8.20-8.16 (m, 4H), 7.61 (m, 1H), 7.54-7.43 (m, 5H), 7.23 (s, 1H); 13C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 167.6, 163.5, 133.5, 133.4, 133.4, 133.3, 132.5, 131.8, 131.2, 129.0, 128.9, 128.4, 125.6.

(Z)-4-Benzylidene-2-methyloxazol-5(4H)-one (1b):\(^1\) N-Acetylglycine (3.42 g, 29.2 mmol), benzaldehyde (2.4 mL, 24.0 mmol), NaOAc (9.99 g, 122.0 mmol) in Ac\(_2\)O (70 mL) was reflux for 7 h. Upon completion, the reaction mixture was cooled down to room temperature. After being maintained 4 °C overnight. The solid was filtered and washed with water and a little EtOH. The desired product 1b was obtained as a light yellow solid (2.10 g, 47%). M.p. 152-153 °C; IR (KBr, cm\(^{-1}\)): 3058, 1774, 1653, 1595, 1261, 1165, 898, 766, 688; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 8.08-8.06 (m, 2H), 7.45-7.43 (m, 3H), 7.14 (s, 1H), 2.40 (s, 3H); 13C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 167.6, 163.5, 133.5, 133.4, 133.3, 132.5, 131.8, 131.2, 129.0, 128.9, 128.4, 125.6.

(Z)-4-Benzylidene-2-(4-methoxyphenyl)oxazol-5(4H)-one (1c):\(^2\) Following the general procedure as for 1b, (4-methoxybenzoyl)glycine (836.0 mg, 4.0 mmol), benzaldehyde (808.0 µL, 8.0 mmol), NaOAc (328 mg, 4 mmol) in Ac\(_2\)O (2.5 mL) was
reflux for 1 h. The solid was filtered and washed with water and a little EtOH. The desired product \(1c\) was obtained as a light yellow solid (248.0 mg, 28\%). M.p. 212-214 °C; IR (KBr, cm\(^{-1}\)): 3000, 2980, 1777, 1648, 1601, 1550, 1503, 1304, 1260, 1165, 981, 876, 840, 764, 685; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 8.19 (d, \(J = 7.2\) Hz, 2H), 8.14 (d, \(J = 8.9\) Hz, 2H), 7.49-7.42 (m, 3H), 7.19 (s, 1H), 7.03 (d, \(J = 8.9\) Hz, 2H), 3.91 (s, 3H); \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 168.0, 163.9, 163.4, 133.8, 133.6, 132.3, 130.9, 130.5, 130.2, 128.9, 117.9, 114.5, 55.6. EI-MS m/z: 279 [M\(^+\)].

\[(Z)-4-Benzylidene-2-(4-nitrophenyl)oxazol-5(4H)-one (1d)\]:\(^3\) Following the general procedure as for \(1b\), (4-nitrobenzoyl)glycine (336.0 mg, 1.5 mmol), benzaldehyde (303.0 \(\mu\)L, 3.0 mmol), NaOAc (615.0 mg, 7.5 mmol) in Ac\(_2\)O (4 mL) was reflux for 1 h. The solid was filtered to give the desired product \(1d\) as a light yellow solid (441 mg, 49\%). M.p. 230-232 °C; IR (KBr, cm\(^{-1}\)): 3063, 1788, 1651, 1519, 1344, 1318, 1161, 892, 856, 767, 696; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 8.40-8.35 (m, 4H), 8.23-8.21 (m, 2H), 7.52-7.51 (m, 3H), 7.39 (s, 1H); \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 166.8, 161.5, 150.4, 134.6, 133.1, 132.9, 132.6, 132.0, 131.2, 129.2, 129.1, 124.2. EI-MS m/z: 294 [M\(^+\)].

\[(Z)-4-Benzylidene-2-(tert-butyl)oxazol-5(4H)-one (1e)\]:\(^4\) Following the general procedure as for \(1b\), pivaloylglycine (286.0 mg, 1.8 mmol), benzaldehyde (152.0 \(\mu\)L, 1.5 mmol), NaOAc (615.0 mg, 7.5 mmol) in Ac\(_2\)O (3 mL) was reflux for 1 h. The solid was filtered and washed with water and a little EtOH. The desired product \(1e\) was obtained as a light yellow solid (75.4 mg, 22\%). M.p. 88-90 °C; IR (KBr, cm\(^{-1}\)): 3055, 2970, 2871, 1796, 1654, 1590, 1294, 1146, 1017, 859, 765, 692; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 8.12 (dd, \(J = 7.8, 2.5\) Hz, 2H), 7.52-7.51 (m, 3H), 7.39 (s, 1H); \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 174.8, 168.3, 133.3, 133.0, 132.3, 131.5, 131.0, 128.8, 34.4, 27.0; EI-MS m/z: 229 [M\(^+\)].

\[(Z)-4-(4-Bromobenzylidene)-2-phenyloxazol-5(4H)-one (1f)\]:\(^1\) Following the general procedure as for \(1a\), hippuric acid (358.5 mg, 2.0 mmol), 4-bromo-
benzaldehyde (444.0 mg, 2.4 mmol), NaOAc (49.2 mg, 0.6 mmol), Ac₂O (0.8 mL, 8.0 mmol) in THF (8 mL) was reflux for 3 h. The given residue was purified by recrystallization from ethyl acetate/DCM to give 1f as a light yellow solid (435.0 mg, 66%). M.p. 207-208 °C; IR (KBr, cm⁻¹): 3054, 1794, 1650, 1554, 1482, 1158, 1067, 983, 893, 824, 694; ¹H NMR (CDCl₃, 500 MHz): δ 8.18 (d, J = 7.4 Hz, 2H), 8.07 (d, J = 8.5 Hz, 2H), 7.65-7.60 (m, 3H), 7.54 (t, J = 7.8 Hz, 2H), 7.16 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 167.4, 164.0, 133.8, 133.7, 133.6, 132.4, 132.2, 130.1, 129.0, 128.5, 125.9, 125.4.

(Z)-4-(4-Nitrobenzylidene)-2-phenyloxazol-5(4H)-one (1g): Following the general procedure as for 1a, hippuric acid (358.5 mg, 2.0 mmol), 4-nitrobenzaldehyde (362.6 mg, 2.4 mmol), NaOAc (49.2 mg, 0.6 mmol), Ac₂O (0.8 mL, 8 mmol) in THF (8 mL) was reflux for 3 h. The solid was filtered and washed with water and a little ethyl acetate. The desired product 1g was obtained as a light yellow solid (335.7 mg, 57%). M.p. 238-240 °C; IR (KBr, cm⁻¹): 3100, 2900, 1796, 1651, 1552, 1517, 1336, 1295, 1160, 976, 858, 688; ¹H NMR (DMSO-d₆, 500 MHz): δ 8.55 (d, J = 8.8 Hz, 2H), 8.35 (d, J = 8.9 Hz, 2H), 8.19-8.18 (m, 2H), 7.77 (t, J = 7.5 Hz, 1H), 7.67 (t, J = 8.0 Hz, 2H), 7.48 (s, 1H); ¹³C NMR (DMSO-d₆, 125 MHz): δ 166.9, 165.3, 148.3, 140.1, 136.7, 134.8, 133.4, 129.9, 128.9, 127.4, 125.3, 124.4.

(Z)-4-(4-Methylbenzylidene)-2-phenyloxazol-5(4H)-one (1h): Following the general procedure as for 1a, hippuric acid (537.6 mg, 3.0 mmol), 4-methylbenzaldehyde (425.0 μL, 3.6 mmol), NaOAc (73.8 mg, 0.9 mmol), Ac₂O (1.2 mL, 12 mmol) in THF (10 mL) was reflux for 3 h. The given residue was purified by recrystallization from EtOH/DCM to give 1h as a yellow solid (412 mg, 52%). M.p. 144-145 °C; IR (KBr, cm⁻¹): 1795, 1649, 1551, 1324, 1157, 859, 816, 692; ¹H NMR (CDCl₃, 500 MHz): δ 8.17 (d, J = 7.4 Hz, 2H), 8.10 (d, J = 8.1 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.23 (s, 1H), 2.43 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 167.8, 163.0, 142.1, 133.2, 132.6, 132.4, 132.1, 130.9, 129.7, 128.9, 128.3, 125.7, 21.8.

(Z)-4-(Naphthalen-2-ylmethylene)-2-phenyloxazol-5(4H)-one (1i): Following the
general procedure as for 1a, hippuric acid (537.6 mg, 3.0 mmol), 2-naphthaldehyde (562.2 mg, 3.2 mmol), NaOAc (73.8 mg, 0.9 mmol), Ac₂O (1.2 mL, 12.0 mmol) in THF (10 mL) was reflux for 3 h. The given residue was purified by recrystallization from EtOH/ethyl acetate to give 1i as a yellow solid (408.5 mg, 45%). M.p. 150-152 °C; IR (KBr, cm⁻¹): 3054, 1793, 1650, 1557, 1330, 1161, 912, 879, 692; ¹H NMR (CDCl₃, 500 MHz): δ 8.52 (d, J = 8.5 Hz, 1H), 8.46 (s, 1H), 8.21 (d, J = 7.3 Hz, 1H), 7.94-7.90 (m, 2H), 7.85 (d, J = 7.8 Hz, 1H), 7.62 (t, J = 7.3 Hz, 1H), 7.58-7.52 (m, 4H), 7.39 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 167.7, 163.4, 134.5, 134.1, 133.3, 133.2, 131.9, 131.3, 129.2, 129.0, 128.7, 128.4, 128.1, 127.9, 127.8, 126.7, 125.7.

(Z)-4-(3-Cyanobenzylidene)-2-phenyloxazol-5(4H)-one (1j): Following the general procedure as for 1a, hippuric acid (268.5 mg, 1.5 mmol), 3-formylbenzonitrile (236.0 mg, 1.8 mmol), NaOAc (36.9 mg, 0.45 mmol), Ac₂O (0.6 mL, 6.0 mmol) in THF (8 mL) was reflux for 3 h. The given residue was purified by recrystallization from EtOH to give 1j as a light yellow solid (268.1 mg, 65%). M.p. 209-211 °C; IR (KBr, cm⁻¹): 3080, 2223, 1800, 1653, 1553, 1289, 1166, 989, 922, 879, 688; ¹H NMR (CDCl₃, 500 MHz): δ 8.67 (s, 1H), 8.27 (d, J = 7.9 Hz, 1H), 8.21-8.20 (m, 2H), 7.71 (dt, J = 7.8, 1.3 Hz, 1H), 7.68-7.65 (m, 1H), 7.61-7.56 (m, 3H), 7.17 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 166.8, 165.1, 136.1, 135.3 (two overlapped peaks), 134.6, 134.1, 133.6, 129.7, 129.1, 128.8, 127.9, 125.0, 118.4, 113.4; EI-MS m/z: 274 [M⁺].

(Z)-4-(2-Ethoxybenzylidene)-2-phenyloxazol-5(4H)-one (1k): Following the general procedure as for 1a, hippuric acid (537.6 mg, 3.0 mmol), 2-ethoxybenzaldehyde (424.0 µL, 3.6 mmol), NaOAc (73.8 mg, 0.9 mmol), Ac₂O (1.2 mL, 12.0 mmol) in THF (10 mL) was reflux for 3 h. The given residue was purified by recrystallization to give 1k as a light yellow solid (451.7 mg, 51%). M.p. 180-182 °C; IR (KBr, cm⁻¹): 3064, 2984, 2884, 1785, 1644, 1586, 1558, 1446, 1246, 1161, 1037, 980, 859, 754, 689; ¹H NMR (CDCl₃, 500 MHz): δ 8.88 (dd, J = 7.9, 1.7 Hz, 1H), 8.19-8.17 (m, 2H), 7.89 (s, 1H), 7.60 (t, J = 7.3 Hz, 1H), 7.54 (t, J = 7.8, 2H), 7.42-7.39 (m, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 4.13 (q, J = 7.0 Hz, 2H), 1.50 (t, J = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 167.9, 162.9, 158.8, 133.1, 133.0 (two overlapped peaks), 132.4, 128.9, 128.3, 126.3, 125.8, 122.7, 120.8, 111.7, 64.2, 14.8; EI-MS m/z: 293 [M⁺].
(Z)-4-(2-Fluorobenzylidene)-2-phenyloxazol-5(4H)-one (1l): Following the general procedure as for 1a, hippuric acid (537.6 mg, 3.0 mmol), 2-fluorobenzaldehyde (446.8 mg, 3.6 mmol), NaOAc (73.8 mg, 0.9 mmol), Ac₂O (1.2 mL, 12.0 mmol) in THF (10 mL) was reflux for 3 h. The given residue was purified by recrystallization to give 1l as a yellow solid (548.8 mg, 68%). M.p. 172-174 °C; IR (KBr, cm⁻¹): 3061, 3001, 1796, 1651, 1601, 1558, 1444, 1327, 1292, 1203, 985, 871, 761, 690; ¹H NMR (CDCl₃, 500 MHz): δ 8.89 (t, J = 7.4 Hz, 1H), 8.19 (d, J = 7.5 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.58 (s, 1H), 7.54 (t, J = 7.8 Hz, 2H), 7.46-7.42 (m, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 9.5 Hz, 1H); ¹⁹F NMR (CDCl₃, 470 MHz): δ -114.0 (m, Ar-F); ¹³C NMR (CDCl₃, 125 MHz): δ 167.1, 164.2, 162.0 (d, J_C-F = 256.7 Hz), 134.2, 133.6, 132.9 (d, J_C-F = 8.8 Hz), 132.7, 129.0, 128.5, 125.4, 124.6 (d, J_C-F = 3.6 Hz), 122.3 (d, J_C-F = 7.5 Hz), 121.8 (d, J_C-F = 10.7 Hz), 115.6 (d, J_C-F = 21.9 Hz); LC-MS (ESI) m/z: 268 [M+H]⁺.

2.2. Synthesis of N-Alkylisothiazol-3(2H)-one 1,1-dioxides

N-Alkylisothiazol-3(2H)-one 1,1-dioxides 2h–2i are prepared as follows:

2-Octylisothiazol-3(2H)-one 1,1-dioxide (2h): To a solution of 2-octylisothiazol-3(2H)-one (410.0 µL, 2.0 mmol) in DCM (10 mL) at 25 °C is added m-CPBA (85%, 803.0 mg, 4.6 mmol) and the resulting mixture is stirred at room temperature for 15 h. The mixture was filtered through a pad of silica gel and washed with DCM. A saturated aqueous solution of NaHCO₃ was added, the organics were extracted with DCM, dried with Na₂SO₄, filtered and the solvent was removed under vacuum. The given residue was purified by recrystallization from hexane/DCM to give 2h (380 mg, 78%) as a colorless liquid. IR (KBr, cm⁻¹): 3092, 2927, 2859, 1735, 1320, 918, 856, 790, 671; ¹H NMR (CDCl₃, 500 MHz): δ 7.37 (d, J = 7.2 Hz, 1H ), 6.77 (d, J = 7.2 Hz, 1H), 3.64 (t, J = 7.5 Hz, 2H), 1.80-1.73 (m, 2H), 1.36-1.20 (m, 10H), 0.88 (t, J = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 159.2, 138.4, 129.2, 39.8, 31.7, 29.1, 28.9, 28.1, 26.7, 22.6, 14.1; LC-MS (DART Positive) m/z: 246 [M+H]⁺; HRMS (DART, Positive) calcd for C₁₁H₂₃O₃N₂S [M+NH₄]⁺ 263.1424, found 263.1422.
2-Methylisothiazol-3(2H)-one 1,1-dioxide (2i): To a solution of 2-methylisothiazol-3(2H)-one (203.3 mg, 2.0 mmol) in DCM (10 mL) at 25 °C is added m-CPBA (85%, 803.0 mg, 4.6 mmol) and the resulting mixture is stirred at room temperature for 15 h. The mixture was filtered through a pad of silica gel and washed with DCM. A saturated aqueous solution of NaHCO₃ was added, the organics were extracted with DCM, dried with Na₂SO₄, filtered and the solvent was removed under vacuum. The given residue was purified by recrystallization from hexane/DCM to give 2i (205.2 mg, 85%) as a white solid. M.p. 106-108 °C; IR (KBr, cm⁻¹): 3173, 3094, 1741, 1332, 1300, 1163, 915, 856, 785, 668; ¹H NMR (CDCl₃, 500 MHz): δ 7.42 (d, J = 7.4 Hz, 1H), 6.80 (d, J = 7.4 Hz, 1H), 3.15 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 158.8, 138.4, 129.4, 23.5; LC-MS (DART Positive) m/z: 148 [M+H]; HRMS (ESI) m/z: calcld for C₄H₆NO₃S [M+H]+ 148.0063, found 148.0062.

3. Synthesis and Characterization of Products

General Procedure: To a test tube were added 1 (0.3 mmol), 2 (0.45 mmol), Cu(NO₃)₂·3H₂O (0.6 mmol), KI (0.3 mmol) in dioxane (1.5 mL). The mixture was stirred at 80 °C for 4 h under an air atmosphere as monitored by TLC. Upon completion, the reaction mixture was cooled down to room temperature and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give product 3.

3,5-Diphenyl-3a,6a-dihydro-4H-pyrrolo[3,4-d]isoxazole-4,6(5H)-dione (3a): Following the general procedure, the reaction mixture of 1a (74.7 mg, 0.3 mmol), 2a (78.1 mg, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 4 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3a (63.6 mg, 73%). M.p. 176-177 °C; IR (KBr, cm⁻¹): 3065, 1791, 1719, 1595, 1491, 1448, 1386, 1199; ¹H NMR (CDCl₃, 500 MHz): δ 8.03 (dd, J = 7.6, 1.5 Hz, 2H), 7.49-7.39 (m, 6H), 7.28-7.26 (m, 2H), 5.66 (d, J = 9.7 Hz, 1H), 4.97 (d, J = 9.7 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 170.8, 169.8, 152.8, 131.3, 130.8, 129.3, 129.2, 128.9, 128.1, 126.7, 126.2, 80.4, 54.9; EI-MS m/z: 292 [M⁺]; HRMS (EI) m/z: calcld for C₁₇H₁₂N₂O₃ [M⁺] 292.0848, found 292.0844.
5-(4-Chlorophenyl)-3-phenyl-3a,6a-dihydro-4H-pyrrolo[3,4-d]isoxazole-4,6(5H)-dione (3b): Following the general procedure, the reaction mixture of 1a (74.7 mg, 0.3 mmol), 1-(4-chlorophenyl)-1H-pyrrrole-2,5-dione 2b (93.6 mg, 0.45 mmol), Cu(NO$_3$)$_2$·3H$_2$O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 4 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3b (65.7 mg, 67%). M.p. 197-199 °C; IR (KBr, cm$^{-1}$): 3000, 2900, 1723, 1497, 1391, 1193, 894, 830, 759; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.95-7.93 (m, 2H), 7.56 (d, $J$ = 8.8 Hz, 2H), 7.51-7.50 (m, 3H), 7.33 (d, $J$ = 8.7 Hz, 2H), 5.74 (d, $J$ = 9.7 Hz, 1H), 5.41 (d, $J$ = 9.7 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 172.3, 171.2, 153.8, 133.8, 133.8, 131.3, 131.0, 129.6, 129.3, 129.2, 128.4, 127.6, 81.8, 55.8; EI-MS m/z: 326 [M$^+$]; HRMS (EI) m/z: calcd for C$_{17}$H$_{11}$ClN$_2$O$_3$ [M$^+$] 326.0458, found 326.0457.

3-Phenyl-3a,6a-dihydro-4H-pyrrolo[3,4-d]isoxazole-4,6(5H)-dione (3c): Following the general procedure, the reaction mixture of 1a (74.7 mg, 0.3 mmol), 1H-pyrrole-2,5-dione 2c (43.7 mg, 0.45 mmol), Cu(NO$_3$)$_2$·3H$_2$O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 2 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/DCM/ethyl acetate = 5/25/3) afforded 3c (43.7 mg, 67%). M.p. 220-221 °C; IR (KBr, cm$^{-1}$): 3198, 3094, 1793, 1729, 1563, 1336, 1180, 771; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.89 (s, 1H), 7.90-7.88 (m, 2H), 7.51-7.48 (m, 3H), 5.52 (d, $J$ = 9.4 Hz, 1H), 5.15 (d, $J$ = 9.4 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 174.8, 173.7, 154.0, 131.2, 129.2, 128.3, 127.6, 82.8, 56.6; EI-MS m/z: 216 [M$^+$]; HRMS (EI) m/z: calcd for C$_{11}$H$_8$N$_2$O$_3$ [M$^+$] 216.0535, found 216.0541.

5-Butyl-3-phenyl-3a,6a-dihydro-4H-pyrrolo[3,4-d]isoxazole-4,6(5H)-dione (3d): Following the general procedure, the reaction mixture of 1a (74.8 mg, 0.3 mmol), 1-butyl-1H-pyrrole-2,5-dione 2d (69.2 mg, 0.45 mmol), Cu(NO$_3$)$_2$·3H$_2$O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 4.5 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3d (66.7 mg, 82%). M.p. 82-84 °C; IR (KBr, cm$^{-1}$): 3064, 2952, 1783, 1709, 1444, 1402, 1333; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.97-7.95 (m, 2H), 7.47-7.41 (m, 3H), 5.49 (d, $J$ = 9.6 Hz, 1H), 4.81 (d, $J$ = 9.6 Hz, 1H), 3.54-3.45 (m, 2H), 1.54-1.47
(m, 2H), 1.28-1.20 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 172.0, 170.9, 152.8, 131.1, 128.8, 128.0, 126.8, 80.4, 54.9, 39.5, 29.4, 19.9, 13.5; EI-MS m/z: 272 [M\(^+\)]; HRMS (EI) m/z: calcd for C\(_{15}\)H\(_{16}\)N\(_2\)O\(_3\) [M\(^+\)] 272.1161, found 272.1159.

5-Benzyl-3-phenyl-3a,6a-dihydro-4\(H\)-pyrrolo[3,4-\(d\)]isoxazole-4,6(5\(H\))-dione (3e): Following the general procedure, the reaction mixture of 1a (74.8 mg, 0.3 mmol), 1-benzyl-1\(H\)-pyrrole-2,5-dione 2e (84.3 mg, 0.45 mmol), Cu(NO\(_3\))\(_2\)·3H\(_2\)O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 4.5 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3e (65.1 mg, 71%) as a white solid. M.p. 82-84 °C; IR (KBr, cm\(^{-1}\)): 3064, 2952, 1783, 1709, 1444, 1402, 1333; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.98 (dd, \(J\) = 7.7, 1.6 Hz, 2H), 7.48-7.43 (m, 3H), 7.36-7.27 (m, 5H), 5.48 (d, \(J\) = 9.6 Hz, 1H), 4.79 (d, \(J\) = 14.1 Hz, 1H), 4.70 (d, \(J\) = 14.1 Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 171.5, 170.6, 152.7, 134.6, 131.2, 128.9, 128.8, 128.4, 128.0, 126.8, 80.5, 54.9, 43.3; EI-MS m/z: 306 [M\(^+\)]; HRMS (EI) m/z: calcd for C\(_{18}\)H\(_{14}\)N\(_2\)O\(_3\) [M\(^+\)] 306.1004, found 306.1006.

3-Phenyl-5-(prop-2-yn-1-yl)-3a,6a-dihydro-4\(H\)-pyrrolo[3,4-\(d\)]isoxazole-4,6(5\(H\))-dione (3f): Following the general procedure, the reaction mixture of 1a (74.7 mg, 0.3 mmol), 1-(prop-2-yn-1-yl)-1\(H\)-pyrrole-2,5-dione 2f (61.0 mg, 0.45 mmol), Cu(NO\(_3\))\(_2\)·3H\(_2\)O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 2.5 h at 60 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3f (31.8 mg, 42%) as a colorless liquid. IR (KBr, cm\(^{-1}\)): 3285, 3063, 2974, 1795, 1725, 1425, 1389, 1338, 1180, 1043, 903, 759, 689, 628; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.98 (dd, \(J\) = 7.8, 1.4 Hz, 2H), 7.50-7.44 (m, 3H), 5.56 (d, \(J\) = 9.7 Hz, 1H), 4.88 (d, \(J\) = 9.7 Hz, 1H), 4.33-4.23 (m, 2H), 2.22 (t, \(J\) = 2.5 Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 170.3, 169.4, 152.4, 131.3, 128.9, 128.8, 128.4, 128.0, 126.8, 80.5, 54.9, 43.3; LC-MS (DART Positive) m/z: 255 [M+H\(^+\)]; HRMS (DART Positive) m/z: calcd for C\(_{13}\)H\(_{11}\)N\(_3\)O\(_2\) [M+H\(^+\)] 255.0764, found 255.0761.

3-(4-Bromophenyl)-5-phenyl-3a,6a-dihydro-4\(H\)-pyrrolo[3,4-\(d\)]isoxazole-4,6(5\(H\))-dione (3g): Following the general procedure, the reaction mixture of 1f (98.5 mg, 0.3
mmol), 1-phenyl-1H-pyrrole-2,5-dione 2a (77.9 mg, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 4 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3g (89.6 mg, 80%). M.p. 204-206 °C; IR (KBr, cm⁻¹): 2923, 1722, 1496, 1399, 832, 691, 619; ¹H NMR (CDCl₃, 500 MHz): δ 7.91 (d, J = 6.2 Hz, 2H), 7.59 (d, J = 6.9 Hz, 2H), 7.47-7.42 (m, 3H), 7.27-7.26 (m, 2H), 5.68 (d, J = 9.4 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 170.6, 169.7, 152.1, 132.2, 130.7, 129.5, 129.3 (two overlapped peaks), 126.1, 125.9, 125.7, 80.6, 54.7; EI-MS m/z: 370 [M⁺ (⁷⁹Br)], 372 [M⁺ (⁸¹Br)]; HRMS (EI) m/z: calcd for C₁₇H₁₁BrN₂O₃ [M⁺] 369.9953, found 369.9955.

3-(4-Nitrophenyl)-5-phenyl-3a,6a-dihydro-4H-pyrrolo[3,4-d]isoxazole-4,6(5H)-dione (3h): Following the general procedure, the reaction mixture of 1g (88.5 mg, 0.3 mmol), 2a (77.9 mg, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 4 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3h (69.4 mg, 69%). M.p. 251-252 °C; IR (KBr, cm⁻¹): 3068, 2956, 1791, 1723, 1518, 1386, 1205, 910, 856, 744, 688, 624; ¹H NMR (DMSO-d₆, 500 MHz): δ 8.36 (d, J = 8.8 Hz, 2H), 8.20 (d, J = 8.8 Hz, 2H), 7.50-7.42 (m, 3H), 7.29 (d, J = 7.4 Hz, 2H), 5.84 (d, J = 9.8 Hz, 1H), 5.49 (d, J = 9.8 Hz, 1H); ¹³C NMR (DMSO-d₆, 125 MHz): δ 172.2, 171.3, 153.1, 149.0, 133.8, 132.1, 129.7, 129.5, 129.4, 127.5, 124.4, 82.7, 55.4; EI-MS m/z: 337 [M⁺]; HRMS (EI) m/z: calcd for C₁₇H₁₁N₃O₅ [M⁺] 337.0699, found 337.0695.

5-Phenyl-3-(p-tolyl)-3a,6a-dihydro-4H-pyrrolo[3,4-d]isoxazole-4,6(5H)-dione (3i): Following the general procedure, the reaction mixture of 1h (79.1 mg, 0.3 mmol), 2a (78.0 mg, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 4 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3i (62.2 mg, 68%). M.p. 179-180 °C; IR (KBr, cm⁻¹): 3054, 2963, 1724, 1499, 1385, 1193, 892, 854, 695; ¹H NMR (CDCl₃, 500 MHz): δ 7.93 (d, J = 8.2 Hz, 2H), 7.48-7.40 (m, 3H), 7.28 (d, J = 7.3 Hz, 4H), 5.65 (d, J = 9.7 Hz, 1H), 4.96 (d, J = 9.7 Hz, 1H), 2.42 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 171.1, 170.0, 152.8, 141.8, 130.9, 129.6, 129.3, 129.2, 128.0, 126.2, 123.9, 80.3, 55.0, 21.6; EI-MS m/z: 306 [M⁺]; HRMS (EI) m/z: calcd for C₁₉H₁₄N₂O₃ [M⁺] 306.1004, found 306.1010.
3-(Naphthalen-2-yl)-5-phenyl-3a,6a-dihydro-4H-pyrrolo[3,4-d]isoxazole-4,6(5H)-dione (3j): Following the general procedure, the reaction mixture of 1i (89.9 mg, 0.3 mmol), 2a (77.9 mg, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 4 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3j (73.7 mg, 72%). M.p. 203-204 °C; IR (KBr, cm⁻¹): 3059, 1794, 1723, 1594, 1495, 1379, 1193, 899, 745; ¹H NMR (CDCl₃, 500 MHz): δ 8.53 (s, 1H), 8.08 (d, J = 8.7 Hz, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.86 (t, J = 9 Hz, 2H), 7.58-7.38 (m, 5H), 7.28 (d, J = 7.6 Hz, 2H), 5.71 (d, J = 9.7 Hz, 1H), 5.07 (d, J = 9.7 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 170.8, 170.0, 152.9, 134.4, 132.8, 130.8, 129.6, 129.3, 129.2, 129.0, 128.8, 127.9, 127.8, 126.9, 126.2, 124.2, 123.8, 80.6, 55.0; EI-MS m/z: 342 [M⁺]; HRMS (EI) m/z: calcd for C₂₁H₁₄N₂O₃ [M⁺] 342.1004, found 342.1001.

3-Phenylnaphtho[2,3-d]isoxazole-4,9-dione (3k): Following the general procedure, the reaction mixture of 1a (74.9 mg, 0.3 mmol), naphthalene-1,4-dione 2g (71.1 mg, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 2 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3k (55.9 mg, 68%). M.p. 137-138 °C; IR (KBr, cm⁻¹): 3072, 1685, 1433, 1340, 1261, 1204, 1167, 919, 716; ¹H NMR (CDCl₃, 500 MHz): δ 8.30-8.26 (m, 2H), 8.16 (dd, J = 7.6, 1.4 Hz, 2H), 7.89-7.82 (m, 2H), 7.59-7.53 (m, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 178.7, 173.4, 166.3, 161.0, 135.3, 134.3, 133.8, 133.8, 131.8, 131.3, 129.4, 128.7, 127.8, 127.3, 126.2, 119.6; EI-MS m/z: 275 [M⁺]; HRMS (EI) m/z: calcd for C₁₇H₉NO₃ [M⁺] 275.0582, found 275.0587.

3-(4,9-Dioxo-4,9-dihydronaphtho[2,3-d]isoxazol-3-yl)benzonitrile (3l): Following the general procedure, the reaction mixture of 1j (82.3 mg, 0.3 mmol), naphthalene-1,4-dione 2g (71.1 mg, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 4 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3l (68.9 mg, 76%). M.p. 203-205 °C; IR (KBr, cm⁻¹): 3080, 2231, 1688, 1581, 1461, 1427, 1336, 1204, 929, 804, 721; ¹H NMR (CDCl₃, 500 MHz): δ 8.58 (s, 1H), 8.47 (d, J = 8.0 Hz, 1H), 8.31-8.28 (m, 2H), 7.95-7.82 (m, 3H), 7.69 (t, J = 7.8 Hz, 1H); ¹³C
NMR (CDCl₃, 125 MHz): δ 178.6, 173.0, 166.6, 159.3, 135.6, 134.7, 134.6, 133.5, 133.4, 133.0, 131.8, 127.9, 127.7, 127.5, 119.4, 118.0, 113.3; LC-MS (DART Positive) m/z: 301 [M+H]+; HRMS (DART Positive) m/z: calcd for C₁₈H₉N₂O₃ [M+H]+ 301.0608, found 301.0605.

3-(2-Ethoxyphenyl)naphtho[2,3-d]isoxazole-4,9-dione (3m): Following the general procedure, the reaction mixture of 1k (88.1 mg, 0.3 mmol), naphthalene-1,4-dione 2g (71.1 mg, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 4 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3m (63.6 mg, 66%). M.p. 193-195 °C; IR (KBr, cm⁻¹): 3071, 2981, 2939, 2891, 1687, 1594, 1453, 1336, 1255, 1199, 1037, 918, 762, 721; ¹H NMR (CDCl₃, 500 MHz): δ 8.30-8.28 (m, 1H), 8.21-8.17 (m, 1H), 7.85-7.80 (m, 2H), 7.54-7.50 (m, 2H), 7.09-7.04 (m, 2H), 4.09 (q, J = 7.0 Hz, 2H), 1.18 (t, J = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz): 178.1, 173.6, 165.0, 158.7, 157.5, 135.1, 134.0, 133.8, 132.4, 132.1, 130.6, 127.4, 127.2, 121.5, 120.4, 115.5, 111.9, 63.9, 14.6; LC-MS (DART Positive) m/z: 320 [M+H]+; HRMS (DART Positive) m/z: calcd for C₁₉H₁₄NO₄ [M+H]+ 320.0917, found 320.0914.

3-(2-Fluorophenyl)naphtho[2,3-d]isoxazole-4,9-dione (3n): Following the general procedure, the reaction mixture of 1l (80.3 mg, 0.3 mmol), 2g (71.1 mg, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 4 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3n (58.6 mg, 67%). M.p. 192-194 °C; IR (KBr, cm⁻¹): 3077, 1686, 1584, 1514, 1465, 1336, 1197, 918, 758, 716; ¹H NMR (CDCl₃, 500 MHz): δ 8.31-8.29 (m, 1H), 8.23-8.21 (m, 1H), 7.87-7.82 (m, 2H), 7.62-7.57 (m, 2H), 7.35-7.27 (m, 2H); ¹⁹F NMR (CDCl₃, 470 MHz): δ -111.2 (m, Ar-F); ¹³C NMR (CDCl₃, 125 MHz): δ 178.1, 173.2, 165.0, 158.7, 157.5, 135.1, 134.0, 133.8, 132.4, 132.1, 130.6, 127.4, 127.2, 121.5, 120.4, 115.5, 111.9, 63.9, 14.6; EI-MS m/z: 293 [M+]; HRMS (EI) m/z: calcd for C₁₇H₁₄FNO₃ [M+] 293.0488, found 293.0497.
3-(4-Bromophenyl)naphtho[2,3-d]isoxazole-4,9-dione (3o): Following the general procedure, the reaction mixture of 1f (98.6 mg, 0.3 mmol), 2g (71.1 mg, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 4 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3o (64.9 mg, 61%). M.p. 178-180 °C; IR (KBr, cm⁻¹): 3082, 2924, 1686, 1588, 1443, 1335, 1261, 1195, 1001, 911, 821, 721; ¹H NMR (DMSO-d₆, 500 MHz): δ 8.19-8.15 (m, 2H), 8.04 (d, J = 8.5 Hz, 2H), 7.98-7.94 (m, 2H), 7.83 (d, J = 8.5 Hz, 2H); ¹³C NMR (DMSO-d₆, 500 MHz): δ 179.1, 173.6, 167.1, 159.9, 135.8, 135.0, 134.0, 132.3, 131.5, 127.5, 127.1, 125.8, 125.5, 119.4; EI-MS m/z: 352 [M⁺ (⁷⁹Br)], 353 [M⁺ (⁸¹Br)]; HRMS (EI) m/z: calcd for C₁₇H₈BrNO₃ [M⁺] 352.9688, found 352.9685.

5-Octyl-3-phenyl-3a,6a-dihydroisothiazolo[5,4-d]isoxazol-6(5H)-one 4,4-dioxide (3p): Following the general procedure, the reaction mixture of 1a (74.8 mg, 0.3 mmol), 2h (110.4 mg, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 4 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3p (55.2 mg, 50%). M.p. 81-83 °C; IR (KBr, cm⁻¹): 2924, 2856, 1738, 1458, 1348, 1156, 1077, 772, 689, 554; ¹H NMR (CDCl₃, 500 MHz): δ 7.78-7.76 (m, 2H), 7.54-7.46 (m, 3H), 5.72 (d, J = 10.4 Hz, 1H), 5.52 (d, J = 10.4 Hz, 1H), 3.68-3.58 (m, 2H), 1.77-1.71 (m, 2H), 1.31-1.25 (m, 10H), 0.87 (t, J = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 160.1, 151.1, 131.7, 129.3, 127.3, 126.5, 82.7, 69.6, 41.2, 31.7, 29.0, 28.9, 28.0, 26.6, 22.6, 14.1; EI-MS m/z: 364 [M⁺]; HRMS (EI) m/z: calcd for C₁₈H₂₄N₂O₄S [M⁺] 364.1457, found 364.1458.

5-Methyl-3-(naphthalen-2-yl)-5,6a-dihydroisothiazolo[5,4-d]isoxazol-6(3aH)-one 4,4-dioxide (3q): Following the general procedure, the reaction mixture of 1i (89.8 mg, 0.3 mmol), 2i (66.4 mg, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 4 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3q (46.3 mg, 49%). M.p. 198-200 °C; IR (KBr, cm⁻¹): 2952, 2923, 1734, 1462, 1340, 1218, 1149, 917, 804, 745, 612; ¹H NMR (CDCl₃, 500 MHz): δ 8.07 (d, J = 1.0 Hz, 1H), 7.98-7.86 (m, 4H), 7.62-7.56 (m, 2H), 5.80 (d, J = 10.4 Hz, 1H), 5.68 (d, J = 10.4 Hz, 1H), 3.18 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 159.9, 151.2, 134.6, 132.8, 129.4, 128.9, 128.2 (two overlapped peaks), 128.0, 127.3, 124.0, 123.2, 83.1, 69.6, 25.0; HRMS (ESI) m/z: calcd for C₁₅H₁₃N₂O₄S [M⁺H] 317.0596, found 317.0582.
5-Methyl-3-(4-nitrophenyl)-5,6a-dihydroisothiazolo[5,4-d]isoxazol-6(3aH)-one 4,4-dioxide (3r): Following the general procedure, the reaction mixture of 1g (88.5 mg, 0.3 mmol), 2i (66.3 mg, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol), KI (49.8 mg, 0.3 mmol) in dioxane (1.5 mL). After 4 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3r (19.7 mg, 21%). M.p. 260-261 °C; IR (KBr, cm⁻¹): 3086, 2963, 1720, 1520, 1419, 1346, 1263, 1153, 1099, 1025, 925, 803, 740, 690; ¹H NMR (DMSO-d₆, 500 MHz): δ 8.40 (d, J = 8.9 Hz, 2H), 8.04 (d, J = 8.9 Hz, 2H), 6.60 (d, J = 10.3 Hz, 1H), 6.12 (d, J = 10.3 Hz, 1H), 3.04 (s, 3H); ¹³C NMR (DMSO-d₆, 125 MHz): δ 161.1, 151.6, 149.3, 133.3, 128.9, 124.9, 85.2, 69.3, 24.8; EI-MS m/z: 312 [M+H]⁺; HRMS (EI) m/z: calcd for C₁₁H₁₀N₃O₆S [M+H]⁺ 312.0285, found 312.0283.

3-Phenyl-4,5-dihydroisoxazole-5-carbonitrile (3s): Following the general procedure, the reaction mixture of 1a (74.7 mg, 0.3 mmol), acrylonitrile (60.0 μL, 0.9 mmol), Cu(NO₃)₂·3H₂O (290.0 mg, 1.2 mmol), KI (99.6 mg, 0.6 mmol) in CH₃CN (1.5 mL). After 4.5 h at 50 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3s (29.1 mg, 56%). M.p. 63-66 °C; IR (KBr, cm⁻¹): 2990, 2429, 1564, 1444, 1352, 925, 870, 759, 685; ¹H NMR (CDCl₃, 500 MHz): δ 7.68-7.66 (m, 2H), 7.51-7.43 (m, 3H), 5.38 (dd, J = 10.5, 6.3 Hz, 1H), 3.81-3.71 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz): δ 156.3, 131.3, 129.1, 127.4, 127.1, 117.1, 66.6, 41.2; HRMS (ESI) m/z calcd for C₁₀H₉N₂O [M +H]⁺ 173.0715, found 173.0721.

Butyl 3-phenyl-4,5-dihydroisoxazole-5-carboxylate (3t): Following the general procedure, the reaction mixture of 1a (74.7 mg, 0.3 mmol), n-butyl acrylate (66.0 μL, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol), KI (49.7 mg, 0.3 mmol) in CH₃CN (1.5 mL). After 4 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3t (42.9 mg, 58%) as a yellow liquid; IR (KBr, cm⁻¹): 3061, 2961, 2873, 1742, 1454, 1352, 1205, 892, 760; ¹H NMR (CDCl₃, 500 MHz): δ 7.68-7.66 (m, 2H), 7.43-7.39 (m, 3H), 5.16 (dd, J = 10.5, 7.8 Hz, 1H), 4.20 (t, J = 6.8 Hz, 1H), 3.64-3.62 (m, 2H), 1.70-1.63 (m, 2H), 1.43-1.35 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 170.3, 156.0, 130.6, 128.8, 128.6, 126.9, 78.1, 65.9, 38.9, 30.5, 19.0, 13.7; EI-MS m/z: 247 [M⁺]; HRMS (EI) m/z: calcd for C₁₄H₁₇NO₃ [M⁺] 247.1208, found 247.1215.
**Benzyl 3-phenyl-4,5-dihydroisoxazole-5-carboxylate (3u):** Following the general procedure, the reaction mixture of 1a (74.7 mg, 0.3 mmol), benzyl acrylate (68 µL, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol), KI (49.7 mg, 0.3 mmol) in CH₃CN (1.5 mL). After 4.5 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3u (50.7 mg, 60%). M.p. 53-55 °C; IR (KBr, cm⁻¹): 3063, 2928, 1749, 1450, 1347, 1197, 1018, 886, 758, 696; ¹H NMR (CDCl₃, 500 MHz): δ 7.67 (dd, J = 7.6, 1.6 Hz, 2H), 7.45-7.33 (m, 8H), 5.27-5.19 (m, 3H), 3.69-3.59 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz): δ 170.0, 156.0, 135.1, 130.6, 128.8, 128.7, 128.6, 128.5, 128.4, 127.0, 78.1, 67.6, 38.9; EI-MS m/z: 281 [M⁺]; HRMS (EI) m/z: calcd for C₁₇H₁₅NO₃ [M⁺] 281.1052, found 281.1053.

**Dimethyl 3-phenylisoxazole-4,5-dicarboxylate (3v):** Following the general procedure, the reaction mixture of 1a (74.7 mg, 0.3 mmol), dimethyl acetylenedicarboxylate (54.0 µL, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol), KI (49.7 mg, 0.3 mmol) in CH₃CN (1.5 mL). After 4 h at 80 °C, purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3v (43.4 mg, 55%). M.p. 62-64 °C; IR (KBr, cm⁻¹): 3457, 2955, 2923, 1716, 1429, 1222, 1066, 918, 794, 686; ¹H NMR (CDCl₃, 500 MHz): δ 7.70-7.68 (m, 2H), 7.53-7.46 (m, 3H), 4.02 (s, 3H), 3.90 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 161.8, 161.3, 159.4, 156.5, 130.7, 128.9, 128.2, 126.9, 116.1, 100.0, 53.4, 53.2; EI-MS m/z: 261 [M⁺]; HRMS (EI) m/z: calcd for C₁₃H₁₁NO₅ [M⁺] 261.0637, found 261.0633.

**4. X-Ray Crystallographic Analysis for Compound 3r**

Crystallographic data for 3r: C₁₁H₉N₃O₆S, M = 311.27, orthorhombic, Pbcn (No. 61), a = 6.495 (3) Å, b = 17.713 (8) Å, c = 21.586 (10) Å, V = 2483 (2) Å³, Z = 8, Crystal size: 0.25x0.20x0.15 mm, T = 293 K, ρcalc = 1.665 g·cm⁻³, R₁ = 0.0374 (I>4σ(I)), wR₂ = 0.111 (all data), GOF = 1.031, reflections collected/unique: 14604 / 2926 (Rint = 0.0289), Data: 2306, restraints: 0, parameters: 198. CCDC 1884631 (3r) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
5. Mechanistic Studies

To a test tube were added 1a (74.7 mg, 0.3 mmol), 2a (77.9 mg, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol), KI (49.8, 0.3 mmol) and 1,4-dinitrobenzene (101.0 mg, 0.6 mmol) in dioxane (1.5 mL). The mixture was stirred at 80 °C for 4 h under an air atmosphere. Upon completion of the reaction, the solution was cooled down to room temperature and the solvent was removed under reduced pressure. The residue was purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3a (65 mg, 74%).

To a test tube were added 1c (83.7 mg, 0.3 mmol), 2a (77.9 mg, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol) and KI (49.8, 0.3 mmol) in dioxane (1.5 mL). The mixture was stirred at 80 °C for 4 h under an air atmosphere. Upon completion of the reaction, the solution was cooled down to room temperature and the solvent was removed under reduced pressure. The residue was purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3a (56.3 mg, 64%) and 4-methoxybenzoic acid (26.0 mg, 57%) as a white solid. No observable 4-methoxylbenzamide was isolated.

Characterization of 4-methoxybenzoic acid: ¹H NMR (CDCl₃, 500 MHz): δ 8.09 (d, J = 8.9 Hz, 2H), 6.98 (d, J = 8.9 Hz, 2H), 3.91 (s, 3H).

To a test tube were added 1d (88.3 mg, 0.3 mmol), 2a (77.9 mg, 0.45 mmol), Cu(NO₃)₂·3H₂O (145.0 mg, 0.6 mmol) and KI (49.8, 0.3 mmol) in dioxane (1.5 mL). The mixture was stirred at 80 °C for 4 h under an air atmosphere. Upon completion of
the reaction, the solution was cooled down to room temperature and the solvent was removed under reduced pressure. The residue was purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3a (55.0 mg, 63%), 4-nitrobenzamide (20.0 mg, 40%) and 4-nitrobenzoic acid (5.6 mg, 11%).

Characterization of 4-nitrobenzamide: \(^\text{16}\) \(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \(\delta\) 8.30-8.28 (m, 3H), 8.09 (d, \(J = 8.7\) Hz, 2H), 7.73 (s, 1H).

Characterization of 4-nitrobenzoic acid: \(^\text{17}\) \(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \(\delta\) 13.65 (s, 1H), 8.32 (d, \(J = 8.7\) Hz, 2H), 8.17 (d, \(J = 8.7\) Hz, 2H).

![Chemical Structure](image)

To a test tube were added (nitromethyl)benzene\(^\text{18}\) (41 mg, 0.3 mmol), 2a (77.9 mg, 0.45 mmol), Cu(NO\(_3\))\(_2\)·3H\(_2\)O (145.0 mg, 0.6 mmol) and KI (49.8, 0.3 mmol) in dioxane (1.5 mL). The mixture was stirred at 80 °C for 4 h under an air atmosphere. Upon completion of the reaction, the solution was cooled down to room temperature and the solvent was removed under reduced pressure. The residue was purification by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded 3a (<5%) and (nitromethyl)benzene (with 95% recovery).

6. Reference


$^{1}$H NMR (CDCl$_3$, 500 MHz)
DMSO-\textit{d}_6, 125 MHz
11
CDCl₃, 500 MHz
Figure 1: 1H NMR spectrum of compound II (CDCl₃, 125 MHz).
$2h$

CDCl$_3$, 500 MHz
$2i$

CDCl$_3$, 500 MHz

f$_1$ (ppm)
S53
CDCl\textsubscript{3}, 125 MHz
$^{3f}$

CDCl$_3$, 500 MHz
$3g$

CDCl$_3$, 500 MHz
$3K$

CDCl$_3$, 500 MHz
$\text{CDCl}_3$, 125 MHz
$3n$

CDCl$_3$, 500 MHz

(f1 in ppm)

0.0  0.5  1.0  1.5  2.0  2.5  3.0  3.5  4.0  4.5  5.0  5.5  6.0  6.5  7.0  7.5  8.0  8.5  9.0  9.5  10.0

8.3  8.2  8.1  8.0  7.9  7.8  7.7  7.6  7.5  7.4  7.3  7.2  7.1  7.0  6.9  6.8  6.7  6.6  6.5  6.4  6.3  6.2  6.1  6.0  5.9  5.8  5.7  5.6  5.5  5.4  5.3  5.2  5.1  5.0  4.9  4.8  4.7  4.6  4.5  4.4  4.3  4.2  4.1  4.0  3.9  3.8  3.7  3.6  3.5  3.4  3.3  3.2  3.1  3.0  2.9  2.8  2.7  2.6  2.5  2.4  2.3  2.2  2.1  2.0  1.9  1.8  1.7  1.6  1.5  1.4  1.3  1.2  1.1  1.0  0.9  0.8  0.7  0.6  0.5  0.4  0.3  0.2  0.1  0.0
$^{35}$S

CDCl$_3$, 125 MHz