Supporting Information for
One-Pot Copper(I)-Catalyzed Synthesis of 3,5-Disubstituted Isoxazoles

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General Experimental Procedures

Unless noted otherwise, all reagents and solvents were used as purchased without further purification. Melting points are uncorrected. Analytical TLC was performed using silica gel 60 F₂₅₄ glass plates (Merck). Flash column chromatography was performed on silica gel 60 (35–75 μ m, EM Science). Coupling constants (*J*) are reported in Hertz, and chemical shifts are reported in parts per million (δ) relative to CHCl₃ (7.26 for ¹H and 77.2 for ¹³C) or DMSO (2.50 for ¹H and 39.5 for ¹³C as internal reference).

Typical experimental procedure for synthesis of 3,5-disubstituted isoxazoles (20 mmol scale). *trans*-Cinnamaldehyde (2.6 g, 20 mmol) was added to the solution of hydroxylamine hydrochloride (1.46 g, 21 mmol) in 80 mL of 1:1 *t*-BuOH:H₂O. To this was added NaOH (0.84

g, 21 mmol), and after stirring for 30 min at ambient temperature, TLC analysis indicated that oxime formation was complete. Chloramine-T trihydrate (5.9 g, 21 mmol) was added in small portions over 5 min, followed by $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.15 g, 0.6 mmol) and copper turnings (*ca* 50 mg). 1-Ethynylcyclohexene (2.23 g, 21 mmol) was added, pH was adjusted to *ca.* 6 by addition of a few drops of 1M NaOH, and stirring was continued for another 6 hrs. The reaction mixture was poured into ice/water (150 mL), and 10 mL of dilute NH_4OH was added to remove all copper salts. Isoxazole (**1**) was collected by filtration, redissolved, and passed through a short plug of silica gel (ethyl acetate:hexanes 1:6, R_F = 0.6) affording 3.6 g (72%) of 5-cyclohex-1-enyl-3-styrylisoxazole as an off-white solid. M.p. 138-139 °C. ^1H -NMR (CDCl_3 , 600 MHz): δ = 7.52 (d, J = 7.4 Hz, 2H), 7.38 (m, 2H), 7.32 (m, 1H), 7.14 (d, J = 6.2 Hz, 2H), 6.64 (s, 1H), 6.31 (s, 1H), 2.36 (d, J = 1.8 Hz, 2H), 2.25 (d, J = 3.5 Hz, 2H), 1.78 (m, 2H), 1.69 (m, 2H). ^{13}C -NMR (CDCl_3 , 150 MHz): δ = 171.2, 136.2, 135.5, 130.4, 129.0, 127.2, 125.4, 116.7, 95.3, 25.6, 25.4, 22.3, 21.9. HRMS: calcd. for (MH^+) : 252.1383, found: 252.1381.

Typical experimental procedure for synthesis of 3,5-disubstituted isoxazoles (1 mmol scale) as exemplified by the reaction of benzaldehyde and phenyl acetylene. Hydroxylamine hydrochloride 73 mg (1.05 mmol) and benzaldehyde (122 mg, 1 mmol) were dissolved in 4 ml of *t*-BuOH:H₂O (1:1). After addition of NaOH (1.05 ml, 1M), the mixture was stirred for 30 min before Chloramine-T·3H₂O (295 mg, 1.05 mmol) was added in several portions. The mixture was stirred for another 5 min, after which time $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (7.5 mg, 3 mol%) and copper wire (*ca* 10 mg) were added, followed by phenylacetylene (102 mg, 1 mmol). pH was adjusted to *ca.* 6 by addition of a few drops of 0.1M NaOH, and stirring was continued for another 4 hrs. Ice-water (10 mL) was added to the mixture, followed by dilute NH_4OH (0.1 mL). The off-white product (**8**) was collected by filtration and recrystallized from *t*-BuOH:H₂O (1:2) to give 3,5-diphenylisoxazole as off-white solid in 72% yield. M.p. 139-140 °C. ^1H -NMR (CDCl_3 , 600MHz): δ = 7.84 (m, 4H), 7.47 (m, 6H), 6.84 (s, 1H); ^{13}C -NMR (CDCl_3 , 150MHz): δ = 169.5, 162.2, 130.1, 129.3, 129.0, 128.9, 126.8, 125.8, 97.4. HRMS calcd for (MH^+) : 222.0913, found: 222.0910.

Control experiment: non-catalyzed, thermal reaction of benzaldehyde and phenyl acetylene: Hydroxylamine hydrochloride (73 mg, 1.05 mmol) and benzaldehyde (122 mg, 1

mmol) were dissolved in 4 ml of *t*-BuOH:H₂O (1:1). After addition of 1.05 ml of NaOH (1M), the resulting mixture was stirred for 30 min before the slow addition of Chloramine-T trihydrate (295 mg, 1.05 mmol). The reaction was then heated in a sealed tube at 80 °C for 12 hrs. After extraction with EtOAc (2× 20ml), the organic solvent was then evaporated, and the crude mixture was analyzed by ¹H NMR to determine ratio of regioisomers, which was 3:1 in favor of the 3,5-diphenyl isoxazole. Virtually no reaction was observed after 12 hrs at ambient temperature.

Compound Characterization Data

3-Ethyl-5-phenylisoxazole (2)

Yield: 73% as white solid. M.p.: 27-28 °C. ¹H-NMR (CDCl₃, 500 MHz): δ = 7.40-7.70 (m 5H), 6.35 (s, 1H), 2.74 (q, 2H, *J* = 7.3 Hz), 1.38 (t, *J* = 7.3 Hz); ¹³C-NMR (CDCl₃, 125MHz): δ = 169.4, 165.8, 129.7, 128.8, 127.4, 125.5, 98.7, 19.5, 12.5. ESI-MS: 174.2 (MH⁺)

3-butyl-5-phenylisoxazole (3)

Yield: 70% as yellow crystals. M.p.: 27-28 °C. ¹H-NMR (CDCl₃, 500 MHz): δ = 7.75 (m, 2H), 7.40 (m, 3H), 6.34 (s, 1H), 2.66 (t, *J* = 7.4 Hz, 2H), 1.66-1.68 (m, 2H), 1.38-1.42 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H); ¹³C-NMR (CDCl₃, 125 MHz): δ = 169.3, 164.6, 129.8, 128.8, 127.5, 125.6, 99.0, 30.3, 25.7, 22.2, 13.6. ESI-MS: 202.3 (MH⁺).

3-Butyl-5-pentylisoxazole (4)

Yield: 70% as pale yellow oil. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ = 5.82 (s, 1H), 2.68 (t, J = 7.6 Hz, 2H), 2.26 (m, 2H), 1.68 (p, J = 7.5 Hz, 2H), 1.31-1.40 (m, 8H), 0.92 (t, J = 7.6 Hz, 3H); 0.88 (t, J = 7.2 Hz, 3H); $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ = 173.3, 159.3, 101.2, 31.4, 28.9, 28.7, 28.5, 28.4, 26.4, 22.4, 13.8, 11.2. ESI-MS: 195.3 (MH^+).

3-Cyclohexyl-5-phenylisoxazole (5)

Yield: 73% as white solid. M.p.: 33-34 °C. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ = 7.82 (m, 2H), 7.51 (m, 3H), 6.48 (s, 1H), 2.84 (m, 1H), 1.23-2.04 (m, 10H); $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ = 179.3, 169.3, 129.7, 128.7, 127.5, 125.6, 97.8, 35.7, 32.0, 29.4, 25.7; LC-MS 228.3 (MH^+)

5-((4-Methoxyphenoxy)methyl)-3-*tert*-butylisoxazole (6)

Yield: 57% as white solid. M. p. 52-54 °C. $^1\text{H-NMR}$ (CDCl_3 , 600 MHz): δ = 6.89 (dd, J = 7.0, 2.6 Hz, 2H), 6.83 (dd, J = 6.5, 2.2 Hz, 2H), 6.22 (s, 1H), 5.03 (s, 2H), 3.75 (s, 3H), 1.33 (s, 9H) .

^{13}C -NMR (CDCl_3 , 150 MHz): δ = 172.0, 167.5, 154.5, 152.0, 115.9, 114.6, 101.0, 62.2, 55.6, 32.0, 29.4 . HRMS calcd for (MH^+): 262.1438, found: 262.1434.

1-(4-((3-Benzhydrylisoxazol-5-yl)methoxy)phenyl)ethanone (7)

Yield: 61%, as white solid. M.p.: 99-101 °C. ^1H -NMR (CDCl_3 , 600 MHz): δ = 7.94 (d, J = 8.8 Hz, 2H), 7.32 (m, 4H), 7.26 (m, 2H), 7.21 (m, 4H), 6.98 (d, J = 8.8 Hz, 2H), 6.22 (s, 1H), 5.60 (s, 1H), 5.17 (s, 2H), 2.56 (s, 3H). ^{13}C -NMR (CDCl_3 , 150 MHz): δ = 196.6, 167.0, 165.8, 161.4, 140.7, 131.2, 130.6, 128.7, 128.5, 127.1, 114.4, 104.0, 61.5, 48.9, 26.6 . HRMS calcd for (MH^+): 384.1594, found: 384.1589.

(*E*)-3-(3-phenylisoxazole-5-yl)but-2-en-1-ol (9)

Yield: 76%, as white solid. M.p.: 91-93 °C. ^1H -NMR (CDCl_3 , 600 MHz): δ = 7.80 (m, 2H), 7.45 (m, 3H), 6.58 (m, 1H), 6.49 (s, 1H), 4.42 (d, J = 6.6 Hz, 2H), 2.06 (s, 3H). ^{13}C -NMR (CDCl_3 , 150 MHz): δ = 171.6, 162.8, 131.2, 130.2, 129.2, 129.1, 126.9, 124.5, 98.4, 59.4, 14.1 . HRMS calcd for (MH^+): 216.1019, found: 216.1021.

1-{4-[3-(4-Fluoro-phenyl)isoxazol-5-ylmethoxy]-phenyl}-ethanone (10)

Yield: 76% as white solid; M.p.: 114-115 °C; $^1\text{H-NMR}$ (CDCl_3 , 500MHz): δ = 7.96 (dd, J = 7.2, 1.7 Hz, 2H), 7.78 (dd, J = 6.9, 2.1 Hz, 2H), 7.15 (dd, J = 6.9, 2.1 Hz, 2H), 6.86 (dd, J = 7.2, 1.7 Hz, 2H), 6.82 (s, 1H), 5.27 (s, 2H), 2.56(s, 3H); $^{13}\text{C-NMR}$ (CDCl_3 , 125MHz): δ = 196.6, 167.8, 164.9, 162.9, 161.6, 131.4, 130.7, 128.8, 124.8, 116.2, 114.4, 101.5, 61.3, 26.4; HRMS calcd for (M H^+): 312.103, found: 312.1033.

3-(2-Bromophenyl)-5-phenylisoxazole (11)

Yield: 72% as white solid; M.p.: 74-76 °C. $^1\text{H-NMR}$ (CDCl_3 , 600MHz): δ = 7.85 (m, 2H), 7.71(m, 2H), 7.48 (m, 4H), 7.33 (m, 1H), 6.96 (s, 1H); $^{13}\text{C-NMR}$ (CDCl_3 , 150MHz): δ = 169.8, 163.2, 133.8, 131.6, 131.2, 130.8, 130.5, 129.2, 127.9, 127.6, 126.1, 122.5, 101.1. HRMS calcd for (MH^+): 300.0018, found: 300.0014.

3-Pentafluorophenyl-5-phenylisoxazole (12)

Yield: 68% pale yellow solid. M.p.: 133-134 °C; $^1\text{H-NMR}$ (CDCl_3 , 500MHz): δ = 7.82-7.85 (m, 2H), 7.50-7.55 (m, 3H), 6.84 (s, 1H); $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ = 171.0, 153.0, 141.0, 139.2, 137.1, 130.7, 129.1, 129.0, 125.8, 125.6, 100.2; ESI-MS: 312.2 (MH^+).

(3-(Pentafluorophenyl)isoxazol-5-yl)methanol (13)

Yield: 64% yellow solid. M.p.: 63-64 °C. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ = 6.60 (s, 1H) 4.85 (s, 2H); $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ = 172.4, 151.3, 143.1, 141.0, 136.4, 104.8, 103.5, 56.3; ESI-MS: 266.1 (MH^+).

5-((4-Methoxyphenoxy)methyl)-3-(4-nitrophenyl)isoxazole (14)

Yield: 69% as white solid. M.p. 138-140 °C. $^1\text{H-NMR}$ (CDCl_3 , 600 MHz): δ = 8.32 (dd, J = 7.0, 1.7 Hz, 2H), 7.99 (dd, J = 7.0, 1.7 Hz, 2H), 6.93 (dd, J = 6.6, 2.2 Hz, 2H), 6.86 (dd, J = 7.0, 2.6

Hz, 2H), 6.71 (s, 1H), 5.19 (s, 2H), 3.78 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ -NMR (CDCl_3 , 150 MHz): δ = 170.2, 160.9, 155.0, 151.9, 149.0, 135.1, 128.0, 124.4, 116.2, 115.0, 101.6, 62.4, 55.9. ESI-MS: 266.3 (MH^+).

3-(4-Methoxy-phenyl)-5-(4-*tert*-butyl-phenoxy)methyl)isoxazole (15)

Yield: 74 % as white solid; M.p. 120-122 °C . ^1H -NMR (CDCl_3 , 400 MHz): δ = 7.75 (dd, J = 6.8, 1.8 Hz, 2H), 7.33 (dd, J = 6.7, 2.0 Hz, 2H), 6.98 (dd, J = 7.0, 2.0 Hz, 2H), 6.92 (dd, J = 6.7, 2.0 Hz, 2H), 6.59 (s, 1H), 5.18 (s, 2H), 3.85 (s, 3H), 1.30 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ -NMR (CDCl_3 , 125 MHz): δ = 168.7, 162.3, 161.3, 155.8, 144.8, 128.5, 126.7, 121.5, 114.5, 114.4, 101.3, 61.8, 55.6, 34.3, 31.7 . HRMS calcd for (M H^+): 338.1751, found: 338.1747.

3-(4-Methoxy-phenyl)isoxazole-5-carboxylic acid (16)

Yield: 61% as white solid. M.p.: 137-140°C; ^1H -NMR (d^6 -DMSO, 500 MHz): δ = 7.87 (d, J = 8.8Hz, 2H), 7.70 (s, 1H), 7.05 (d, J = 8.8Hz, 2H), 3.82 (s, 3H); ^{13}C -NMR (d^6 -DMSO, 125 MHz): δ = 174.8, 162.3, 161.0, 157.6, 128.2, 120.0, 115.1, 107.2, 55.2; ESI-MS: 220.2 (MH^+).

[3-(4-Methoxy-phenyl)isoxazol-5-yl]-methanol (17)

Yield: 68% as white solid. M.p.: 88-90°C; $^1\text{H-NMR}$ (CDCl_3 , 500MHz): δ = 7.66 (d, J = 8.9Hz, 2H), 6.94 (d, J = 8.9Hz, 2H), 6.47 (s, 1H), 4.74 (s, 2H), 3.84 (s, 3H); $^{13}\text{C-NMR}$ (CDCl_3 , 125MHz): δ =171.9; 162.1, 161.0, 128.1, 121.2, 114.2, 99.7, 56.8, 55.3; ESI-MS: 205.2 (MH^+).

17-[3-(4-Methoxy-phenyl)isoxazol-5-yl]-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthrene-3,17-diol (18)

Yield: 66% as white solid. M.p.: 190-193°C; $^1\text{H-NMR}$ (CDCl_3 , 500MHz): δ = 7.80 (d, J = 9.1 Hz, 2H), 7.04 (d, J = 9.1 Hz, 1H), 6.95 (s, 1H), 6.45 (m, 2H), 3.79 (s, 3H), 2.70-2.72 (m, 2H), 2.13-2.15 (m, 1H), 1.95-1.97 (m, 1H),), 1.15-1.95 (m, 10H), 0.95 (s, 3H), 0.75 (m, 1H); $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ = 178.8, 160.5, 155.0, 137.1, 130.2, 128.1, 121.3, 114.92, 114.38, 112.7, 100.2, 82.2, 55.3, 48.4, 47.8, 43.1, 36.9, 33.0, 30.6, 29.2, 27.2, 26.1, 23.2, 14.1; HRMS calcd for (MH^+): 446.2326, found: 446.2329.

1-(4-((3-(furan-2-yl)isoxazol-5-yl)methoxy)phenyl)ethanone (19)

Yield: 68% as white solid. M.p.: 135-136 °C; $^1\text{H-NMR}$ (CDCl_3 , 500MHz): δ = 7.95 (d, J = 8.5 Hz, 2H), 7.84 (s, 1H), 7.50 (t, J = 2.2 Hz, 1H), 7.01 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 2.2 Hz, 1H), 6.47 (s, 1H), 5.23 (s, 2H), 2.55 (s, 3H); $^{13}\text{C-NMR}$ (CDCl_3 , 125MHz): δ = 196.5, 167.2, 161.3, 155.9, 144.1, 141.6, 131.3, 130.6, 115.3, 114.3, 108.5, 101.7, 61.1, 26.3; HRMS: calcd for (MH^+): 284.0917, found: 284.0916.

1 (unknown compound)

2 (KNOWN COMPOUND)

Basel, Yochai; Hassner, Alfred. **An improved method for preparation of nitrile oxides from nitro alkanes for in-situ dipolar cycloadditions.** Synthesis (1997), (3), 309-312.

3 (KNOWN COMPOUND)

Casnati, Giuseppe; Ricca, Aldo. **Aliphatic chloro oximes and their applications in the synthesis of isoxazole and β -furanone systems.** Tetrahedron Letters (1967), (4), 327-30

4 (unknown compound)

5 (unknown compound)

(modified after loading)
 VVF's
 LCMS Positive 10 min 2.5 min postrun
 500uL/min 10-100% CH3CN/Water w/TFA

6 (unknown compound)

8 (known compound)

Sheng, Shou-ri; Liu, Xiao-ling; Xu, Qu; Song, Cai-sheng. **One-pot synthesis of 3-substituted isoxazoles from phenyl vinyl selenide.** Synthesis (2003), (18), 2763-2764.

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 VVF's
 LCMS Positive 10 min 2.5 min postrun
 500uL/min 10-100% CH3CN/Water w/TFA

9 (unknown compound)

10 (unknown compound)

11 (known compound)

Dijcks, Fredericus Antonius; Grove, Simon James Anthony; Carlyle, Ian Craig; Thorn, Simon Nicholas; Rae, Duncan Robertson; Ruigt, Gerardus Stephanus Franciscus; Leysen, Dirk. **Preparation of heterocyclic benzenemethanamine derivatives as 1h ion channel modulators for use in psychotherapeutics.** PCT Int. Appl. (1999), 50 pp. CODEN: PIXXD2 WO 9918941 A2 19990422

12 (known compound)

Wakefield, Basil J.; Wright, D. J. **Polyhaloaromatic compounds. XII. Synthesis and cycloaddition reactions of pentafluoro- and pentachlorobenzonitrile N-oxide.** Journal of the Chemical Society [Section] C: Organic (1970), (9), 1165-8.

VVF's
LCMS Positive 10 min 2.5 min postrun
500uL/min 10-100% CH3CN/Water w/TFA

13 (unknown compound)

(modified after loading)
VVF's
LCMS Positive 10 min 2.5 min postrun
500uL/min 10-100% CH3CN/Water w/TFA

14 (unknown compound)

15 (unknown compound)

16 (KNOWN FROM SCIFINDER BUT NO REFERENCES GIVEN)

(modified after loading)
 VVF's
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17 (known compound)

Shang, Yong-Jia; Wang, Yan-Guang. **Synthesis of isoxazolines and isoxazoles using poly(ethylene glycol) as support.** Synthesis (2002), (12), 1663-1668.

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VVF's
LCMS Positive 10 min 2.5 min postrun
500uL/min 10-100% CH3CN/Water w/TFA

18 (unknown compound)

19 (unknown compound)