Synthesis of Isoxazoles via Electrophilic Cyclization

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SUPPORTING INFORMATION

General. The ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. All reagents were used directly as obtained commercially unless otherwise noted. The following starting materials were made according to literature procedures: 1,3-diphenylprop-2-yn-1-one,¹ 1-phenyl-2-butyne-1-one,² 4,4-dimethyl-1-phenylpent-1-yn-3-one,¹ *N*-methyl-3-indolecarboxaldehyde,³ 1-phenylnon-1-yn-3-one.⁴

General procedure for the preparation of alkynones from acyl chlorides. To a flask were added CuI (0.05 mmol), PdCl₂(PPh₃)₂ (0.01 mmol) and triethylamine (5 mL). The flask was flushed with argon and the terminal acetylene (2.5 mmol) was added to the stirred suspension, followed by immediate dropwise addition of benzoyl chloride (3.25 mmol, 1.3 equiv). The resulting mixture was allowed to stir at room temperature overnight, water (5 mL) was added, and the aqueous layer was extracted with hexanes. The organic layers were combined, dried and concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel to afford the desired alkynone.

3-(Cyclohex-1-enyl)-1-phenylprop-2-yn-1-one. Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 462 mg (88%) of the product as a yellow oil with spectral properties identical to those previously reported.⁵

1-Phenyl-3-(triisopropylsilyl)prop-2-yn-1-one. Purification by flash chromatography (10:1 hexanes/EtOAc) afforded 535 mg (82%) of the product as a yellow oil with spectral properties identical to those previously reported.⁶

4,4-Dimethyl-1-phenyl-2-pentyn-1-one. Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 428 mg (92%) of the product as a pale yellow oil with spectral properties identical to those previously reported.⁷

1-(1-Methylindol-3-yl)-3-phenylprop-2-yn-1-one. To a three-neck flask equipped with a stir bar was added phenyl acetylene (11.2 mmol, 1.14 g) and THF (7 mL). The stirred solution was cooled to 0 °C and flushed with argon. To the stirred solution, *n*-BuLi (2.5 M in hexanes, 4.5 mL, 11.2 mmol) was added dropwise. The resulting mixture was allowed to stir for 30 min at 0 °C. *N*-Methyl-3-indolecarboxaldehyde (9.3 mmol, 1.48 g) in THF (5 mL) was added dropwise and allowed to stir for 1 h at 0 °C. The solution was quenched with satd NH₄Cl solution and extracted with ether. The organic layers were combined, dried and concentrated under reduced pressure. The residue was dissolved in chloroform (20 mL) and MnO₂ (27.9 mmol, 2.43 g) was added to the solution. The suspension was refluxed for 1 h, the solution was cooled and filtered through a pad of celite, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel to afford 1.25 g (53%) of the product as a pale yellow solid: mp 112-114 °C; ¹H NMR (CDCl₃) δ 3.81 (s, 3H), 7.29-7.43 (m, 6H), 7.61-7.64 (d, *J* = 7.2 Hz, 2H), 7.89 (s, 1H), 8.39-8.42 (m, 1H); ¹³C NMR δ 33.8, 87.8, 88.0, 110.1, 118.5, 120.9, 122.5, 123.2, 124.0, 125.9, 128.7, 130.2, 132.8, 137.9, 139.1, 171.3; IR (neat, cm⁻¹) 3057, 1605; HRMS Calcd for C₁₈H₁₃NO: 259.0997. Found 259.1000.

General procedure for preparation of the *O*-methyl oximes. The alkynone (3.5 mmol), methoxylamine hydrochloride (7.0 mmol, 579 mg), Na₂SO₄ (7.0 mmol, 994 mg) and pyridine (1 mL) in methanol (10 mL) were stirred at room temperature. The reaction was monitored by TLC until the reaction was complete. The mixture was diluted with water (25 mL) and extracted with EtOAc (3 x 5 mL). The organic layer was

washed with brine, dried and evaporated. The residue was then purified by column chromatography on silica gel to afford the desired *O*-methyl oxime.

(*Z*)-1,3-Diphenylprop-2-yn-1-one *O*-methyl oxime (1). Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 617 mg (75%) of the product as an off white solid: mp 40-42 °C; ^1H NMR (CDCl_3) δ 4.14 (s, 3H), 7.37-7.40 (m, 6H), 7.60-7.63 (m, 2H), 7.90-7.93 (m, 2H); ^{13}C NMR (CDCl_3) δ 63.4, 79.7, 101.4, 122.0, 126.8, 128.6, 128.7, 129.8, 129.9, 132.4, 133.8, 140.2; IR (neat, cm^{-1}) 3052, 2935, 1598; HRMS Calcd for $\text{C}_{16}\text{H}_{13}\text{NO}$: 235.0997. Found: 235.1000.

(*Z*)-3-(Cyclohex-1-enyl)-1-phenylprop-2-yn-1-one *O*-methyl oxime (2). Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 678 mg (81%) of the product as a brown oil: ^1H NMR (CDCl_3) δ 1.61-1.70 (m, 4H), 2.15-2.18 (m, 2H), 2.25-2.30 (m, 2H), 4.09 (s, 3H), 6.37-6.42 (m, 1H), 7.34-7.39 (m, 3H), 7.81-7.86 (m, 2H); ^{13}C NMR (CDCl_3) δ 21.6, 22.4, 26.1, 29.0, 63.2, 76.6, 103.7, 120.2, 126.7, 128.5, 129.7, 134.0, 138.8, 140.3; IR (neat, cm^{-1}) 3063, 2936, 1640; HRMS Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}$: 239.1310. Found: 239.1313.

(*Z*)-1-Phenylbut-2-yn-1-one *O*-methyl oxime (3). Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 557 mg (92%) of the product as a pale yellow oil: ^1H NMR (CDCl_3) δ 2.19 (s, 3H), 4.09 (s, 3H), 7.35-7.37 (m, 3H), 7.82-7.85 (m, 2H); ^{13}C NMR (CDCl_3) δ 5.1, 63.2, 71.0, 99.7, 126.7, 128.5, 129.8, 134.0, 140.4; IR (neat, cm^{-1}) 3061, 2968, 1588; HRMS Calcd for $\text{C}_{11}\text{H}_{11}\text{NO}$: 173.0841. Found: 173.0846.

(*Z*)-4,4-Dimethyl-1-phenyl-2-pentyn-1-one *O*-methyl oxime (4). Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 640 mg (85%) of the product as a pale yellow oil: ^1H NMR (CDCl_3) δ 1.37 (s, 9H), 4.07 (s, 3H), 7.35 (d, $J = 6.6$ Hz, 3H), 7.81-7.84 (m, 2H); ^{13}C NMR (CDCl_3) δ 28.8, 30.9, 63.1, 70.2, 111.8, 126.7, 128.5, 129.6, 134.3, 140.3; IR (neat, cm^{-1}) 3060, 2970, 1950, 1586; HRMS Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}$: 173.0841. Found: 173.0848.

(Z)-1-Phenyl-3-(triisopropylsilyl)prop-2-yn-1-one O-methyl oxime (5).

Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 904 mg (82%) of the product as a colorless oil: ^1H NMR (CDCl_3) δ 1.15 (s, 21H), 4.07 (s, 3H), 7.34-7.37 (m, 3H), 7.84-7.88 (m, 2H); ^{13}C NMR (CDCl_3) δ 11.4, 18.9, 63.2, 96.1, 105.6, 126.6, 128.6, 129.7, 133.8, 140.1; IR (neat, cm^{-1}) 3062, 2941, 1537; HRMS Calcd for $\text{C}_{19}\text{H}_{29}\text{NOSi}$: 315.2018. Found: 315.2023.

(Z)-3-Phenylpropionaldehyde O-methyl oxime (6).

Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 145 mg (26%) of the product as a colorless oil: ^1H NMR (CDCl_3) δ 3.97 (s, 3H), 7.30-7.37 (m, 3H), 7.48-7.52 (dd, $J = 7.4$, 2.0 Hz, 2H), 7.53 (s, 1H); ^{13}C NMR (CDCl_3) δ 62.8, 81.7, 94.5, 121.9, 128.6, 129.5, 132.1, 133.5; IR (neat, cm^{-1}) 3058, 2973, 1598; HRMS Calcd for $\text{C}_{10}\text{H}_9\text{NO}$: 159.0684. Found: 159.0687.

(Z)-1-Phenylnon-1-yn-3-one O-methyl oxime (7).

Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 332 mg (39%) of the product as a pale yellow oil: ^1H NMR (CDCl_3) δ 0.89 (t, $J = 6.7$ Hz, 3H), 1.28-1.37 (m, 6H), 1.62-1.69 (m, 2H), 2.39 (t, $J = 7.4$ Hz, 2H), 3.97 (s, 1H), 7.29-7.37 (m, 3H), 7.48-7.55 (m, 2H); ^{13}C NMR (CDCl_3) δ 14.3, 22.8, 27.3, 28.8, 31.8, 34.6, 62.5, 80.6, 99.8, 122.1, 128.6, 129.6, 132.3, 142.3; IR (neat, cm^{-1}) 3065, 2929, 1672; HRMS Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}$: 243.1623. Found: 243.1627.

(Z)-4,4-Dimethyl-1-phenylpent-1-yn-3-one O-methyl oxime (8).

Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 535 mg (71%) of the product as an orange oil: ^1H NMR (CDCl_3) δ 1.26 (s, 9H), 3.97 (s, 3H), 7.30-7.35 (m, 3H), 7.51-7.54 (s, 2H); ^{13}C NMR (CDCl_3) δ 28.4, 37.2, 79.6, 100.6, 122.3, 128.6, 129.4, 132.2, 149.3; IR (neat, cm^{-1}) 3057, 2967, 1747, 1599; HRMS Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}$: 215.1310. Found: 215.1314.

(Z)-1-(1-Methylindol-3-yl)-3-phenylprop-2-yn-1-one O-methyl oxime (9).

Purification by flash chromatography (chloroform) afforded 716 mg (71%) of the product

as a colorless solid: mp 96-98 °C; ^1H NMR (CDCl_3) δ 3.78 (s, 3H), 4.15 (s, 3H), 7.28-7.38 (m, 6H), 7.49 (s, 1H), 7.61 (m, 2H), 8.30 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 33.3, 63.1, 80.3, 97.6, 109.6, 111.0, 121.2, 122.3, 123.0, 123.1, 125.1, 128.6, 129.5, 131.5, 132.3, 136.8, 138.0; IR (neat, cm^{-1}) 3052, 2934, 1614; HRMS Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}$: 288.1263. Found: 288.1268.

Procedure for iodocyclization using I_2 . To a stirred solution of the *O*-methyl oxime (0.25 mmol) in CH_2Cl_2 (2.5 mL) was added I_2 (0.75 mmol, 191 mg) and the solution was allowed to stir at room temperature for 1 h. The excess I_2 was removed by washing with a satd aq soln of $\text{Na}_2\text{S}_2\text{O}_3$. The aqueous solution was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anhydrous MgSO_4 and concentrated under reduced pressure to yield the crude product. Purification by flash chromatography afforded the product.

3,5-Diphenyl-4-iodoisoxazole (10). The product was obtained as a colorless solid: mp 176-178 °C (lit.⁸ mp 176.5-177.5 °C). The spectral properties were identical to those previously reported.⁸

General procedure for iodocyclization using ICl . To a stirred solution of the appropriate *O*-methyl oxime (0.25 mmol) in CH_2Cl_2 (2.5 mL) was added ICl (1M in CH_2Cl_2 , 1.2 equiv) dropwise and the solution was allowed to stir at room temperature. The reaction was monitored by TLC to establish completion. The excess ICl was removed by washing with a satd aq soln of $\text{Na}_2\text{S}_2\text{O}_3$. The aqueous solution was then extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anhydrous MgSO_4 and concentrated under a vacuum to yield the crude product, which was purified by flash chromatography on silica gel using EtOAc/hexanes as the eluent.

3,5-Diphenyl-4-iodoisoxazole (10). The product was obtained as a colorless solid: mp 176-178 °C (lit.⁸ mp 176.5-177.5 °C). The spectral properties were identical to those previously reported.⁸

5-(Cyclohex-1-enyl)-4-iodo-3-phenylisoxazole (14). The product was obtained as an off white solid: mp 80-82 °C; ^1H NMR (CDCl_3) δ 1.65-1.83 (m, 4H) 2.28-2.32 (m, 2H), 2.53-2.56 (m, 2H), 6.89 (s, 1H), 7.45-7.49 (m, 3H), 7.70-7.73 (m, 2H); ^{13}C NMR (CDCl_3) δ 21.6, 22.4, 25.8, 26.1, 54.2, 126.4, 128.6, 129.1, 129.2, 130.0, 134.5, 164.5, 170.6; IR (neat, cm^{-1}) 3061, 2932, 1639, 1546; HRMS for $\text{C}_{15}\text{H}_{14}\text{INO}$: 351.0120. Found: 351.0126.

5-Methyl-4-iodo-3-phenylisoxazole (15). The product was obtained as a colorless solid: mp 103-105 °C; ^1H NMR (CDCl_3) δ 2.54 (s, 3H), 7.45-7.49 (m, 3H), 7.77-7.80 (m, 2H); ^{13}C NMR (CDCl_3) δ 13.1, 58.0, 128.6, 128.7, 128.9, 130.2, 163.0, 171.6; IR (neat, cm^{-1}) 3062, 2926, 1571, 1460; HRMS for $\text{C}_{10}\text{H}_8\text{INO}$: 284.9651. Found: 284.9655.

5-tert-Butyl-4-iodo-3-phenylisoxazole (16). The product was obtained as a colorless solid: mp 92-93 °C; ^1H NMR (CDCl_3) δ 1.55 (s, 9H), 7.16-7.49 (m, 3H), 7.66-7.69 (m, 2H); ^{13}C NMR (CDCl_3) δ 28.5, 34.6, 128.6, 129.2, 129.3, 130.0, 165.0, 178.1; IR (neat, cm^{-1}) 3064, 2978, 1547; HRMS for $\text{C}_{13}\text{H}_{14}\text{INO}$: 327.0120. Found: 327.0124.

4-Iodo-3-phenyl-5-(triisopropylsilyl)isoxazole (17). The product was obtained as a colorless solid: mp 61-63 °C; ^1H NMR (CDCl_3) δ 1.17-1.19 (d, $J = 7.4$ Hz, 18H), 1.61-1.76 (m, 3H), 7.45-7.50 (m, 3H), 7.74-7.78 (m, 2H); ^{13}C NMR (CDCl_3) δ 11.7, 18.8, 70.2, 128.6, 128.8, 129.4, 129.9, 162.7, 178.2; IR (neat, cm^{-1}) 3058, 2944, 1462; HRMS for $\text{C}_{18}\text{H}_{26}\text{INO}$: 427.0825. Found: 427.0833.

4-Iodo-5-phenylisoxazole (18). The product was obtained as a yellow oil: ^1H NMR (CDCl_3) δ 7.49-7.51 (m, 3H), 8.03-8.06 (m, 2H), 8.29 (s, 1H); ^{13}C NMR (CDCl_3) δ 52.2, 126.9, 127.6, 129.0, 130.9, 157.1, 167.4; IR (neat, cm^{-1}) 3104, 3060, 1609, 1563; HRMS for $\text{C}_9\text{H}_6\text{INO}$: 270.9494. Found: 270.9500.

3-Hexyl-4-iodo-5-phenylisoxazole (19). The product was obtained as a yellow oil: ^1H NMR (CDCl_3) δ 0.90 (t, J = 6.9 Hz, 3H), 1.25-1.46 (m, 6H), 1.71-1.81 (m, 2H), 2.69 (t, J = 7.7 Hz, 2H), 7.48-7.51 (m, 3H), 8.00-8.04 (m, 2H); IR (neat, cm^{-1}) 3063, 2952, 1609, 1567; HRMS for $\text{C}_{15}\text{H}_{18}\text{INO}$: 355.0433. Found: 355.0437.

3-*tert*-Butyl-4-iodo-5-phenylisoxazole (20). The product was obtained as a colorless solid: mp 80-82 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.53 (s, 9H), 7.47-7.49 (dd, J = 5.1, 1.8 Hz, 3H), 7.90-7.94 (m, 2H); ^{13}C NMR (CDCl_3) δ 28.5, 33.8, 53.4, 127.8, 128.4, 128.8, 130.6, 169.4, 169.5; IR (neat, cm^{-1}) 3054, 2999, 1714; HRMS for $\text{C}_{13}\text{H}_{14}\text{INO}$: 327.0120. Found: 327.0126.

3-(4-Iodo-5-phenylisoxazol-3-yl)-1-methylindole (21). The product was obtained as a colorless solid: mp 217-219 $^{\circ}\text{C}$ (turned black); ^1H NMR (CDCl_3) δ 3.89 (s, 3H), 7.27-7.40 (m, 3H), 7.51-7.55 (m, 3H), 8.06-8.10 (m, 3H), 8.24-8.27 (d, J = 8.3 Hz, 1H); IR (neat, cm^{-1}) 3053, 2927, 1650; HRMS for $\text{C}_{18}\text{H}_{13}\text{IN}_2\text{O}$: 400.0073. Found: 400.0080.

Procedure for bromocyclization using Br_2 . To a stirred solution of the *O*-methyl oxime (0.25 mmol) in CH_2Cl_2 (2.5 mL) was added Br_2 (0.625 mmol, 100 mg) and the solution was allowed to stir at room temperature for 24 h. The excess Br_2 was removed by washing with a satd aq soln of $\text{Na}_2\text{S}_2\text{O}_3$. The aqueous solution was then extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anhydrous MgSO_4 and concentrated under reduced pressure to yield the crude product, which was further purified by flash chromatography to afford the product.

4-Bromo-3,5-diphenylisoxazole (11). The product was obtained as a colorless solid: mp 133-135 $^{\circ}\text{C}$ (lit.⁸ mp 132-134 $^{\circ}\text{C}$). The spectral properties were identical to those previously reported.⁸

General procedure for selenocyclization. To a stirred solution of the appropriate *O*-methyl oxime (0.25 mmol) in CH_2Cl_2 (2.5 mL) was added PhSeBr (3.0

equiv) and the solution was allowed to stir at room temperature for 24 h. A solution of satd aq $\text{Na}_2\text{S}_2\text{O}_3$ was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anhydrous MgSO_4 and concentrated under reduced pressure to yield the crude product, which was purified by flash chromatography on silica gel using EtOAc/hexanes as the eluent.

3,5-Diphenyl-4-(phenylselenyl)isoxazole (12). The product was obtained as a colorless solid: mp 101-103 °C; ^1H NMR (CDCl_3) δ 7.06-7.10 (m, 5H), 7.27-7.37 (m, 6H), 7.65-7.68 (dd, $J = 7.2, 2.2$ Hz, 2H), 7.99-8.03 (dd, $J = 6.1, 2.2$ Hz, 2H); ^{13}C NMR (CDCl_3) δ 96.6, 126.9, 127.6, 128.1, 128.7, 128.96, 128.98, 129.0, 129.1, 129.8, 130.1, 131.1, 131.9, 166.0, 172.7; IR (neat, cm^{-1}) 3058, 1553; HRMS for $\text{C}_{21}\text{H}_{15}\text{NOSe}$: 377.0319. Found: 377.0326.

5-(Cyclohex-1-enyl)-3-phenyl-4-(phenylselenyl)isoxazole (13). The product was obtained as a yellow oil: ^1H NMR (CDCl_3) δ 1.62-1.74 (m, 4H), 2.20-2.23 (m, 2H), 2.55-2.57 (m, 2H), 6.82 (m, 1H), 7.13-7.20 (m, 5H), 7.33-7.39 (m, 3H), 7.66-7.69 (m, 2H); ^{13}C NMR (CDCl_3) δ 21.7, 22.4, 25.9, 26.0, 94.9, 126.6, 128.5, 128.9, 129.0, 129.2, 129.6, 129.9, 132.4, 135.2, 165.6, 174.4 (one sp^2 carbon missing due to overlap); IR (neat, cm^{-1}) 3058, 2933, 1636, 1536; HRMS for $\text{C}_{21}\text{H}_{19}\text{NOSe}$: 381.0632. Found: 381.0638.

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