Supporting Information

Efficient Conversion of Aromatic Amines into Azides: A One-Pot Synthesis of Triazole Linkages.

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Materials and Methods

All Chemicals were purchased from either Sigma-Aldrich or Across, and were used without further purification. Flash Chromatography was employed MerckTM silica gel [Kieselgel 60 (0.040-0.063 mm)]. Analytical TLC was performed on 0.2 mm Silica-coated aluminium sheets from Merck [Kieselgel 60 F₂₅₄], and visualized with UV Light. Infra Red measurements were carried out on a Perkin Elmer, FT-IR Spectrometer: Spectrum 1000 with a SpecacTM golden gate. ¹H and ¹³C NMR spectra were recorded on a BrukerTM Avance400 spectrometer (400MHz for ¹H and 100MHz for ¹³C spectra) or BrukerTM Avance500 spectrometer (500MHz for ¹H and 125MHz for ¹³C spectra). Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; sept, septuplet; m, multiplet. LCMS was performed on a Waters Micromass 2Q coupled to a Waters Alliance 2695 HPLC (Phenomenex onyx monolithic C18 (50x4.6mm) column) and a Waters 2996 PDA. High Resolution Mass Spectroscopy was carried out on a MicromassTM Q-TOF Ultima Global Tandem Mass Spectrometer. All samples were run under Electrospray ionization mode using 50% Acetonitrile in Water and 0.1% Formic acid as solvent. Elemental analyses (EA) were performed using the Carlo-Erba Elemental Analyser 1108.

SAFETY WARNING

TMS-azide is volatile, latex-permeable and absorbed by the skin.

TMS-azide is known to be hydrolytically unstable, resulting in the release of hydrazoic acid, an unstable and very toxic compound.

see: http://www.osha.gov/dts/chemicalsampling/data/CH_245950.html

A potential hazard in the copper catalyzed procedure should be considered. Hydrazoic acid readily reacts with copper salts to form copper azide. Copper azides are extremely shock sensitive when dry, and they can be entrained in the product after precipitation. In the event of large scale reactions, we recommend precipitation of the product with basic ammonium citrate instead of methanol, or washing with a solution of ammonium hydroxide in order to remove traces of copper.

Amine to Azide conversion

1-Azidobenzene (**1**)¹

Aniline (200 mg, 2.14 mmol) was dissolved in CH_3CN (4 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added $t\text{-BuONO}$ (331 mg, 380 μL , 3.21 mmol) followed by TMSN_3 (300 mg, 340 μL , 2.56 mmol) dropwise. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum and the crude product was purified by silica gel chromatography (hexane) to give the product, **1**, as a pale yellow oil (236 mg, 93%). IR (film) 3062.99, 2124.35, 2093.43, 1593.63, 1491.52, 1294.58 cm^{-1} . ^1H NMR (CDCl_3 , 400MHz) δ : 6.96 (dd, $J = 7.6$ and 0.7 Hz, 2H), 7.06 (td, $J = 7.6$ and 0.7 Hz, 1H), 7.27 (t, $J = 7.6$ Hz, 2H). ^{13}C NMR (CDCl_3 , 100MHz) δ : 119.0, 124.9, 129.8, 140.0. EA calcd. for $\text{C}_6\text{H}_5\text{N}_3$: C, 60.50; H, 4.23; N, 35.27. Found: C, 60.48; H, 4.27; N, 35.25.

1-Azido-4-isopropylbenzene (**2**)²

4-Isopropylaniline (200 mg, 1.48 mmol) was dissolved in CH_3CN (2 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added $t\text{-BuONO}$ (230 mg, 263 μL , 2.22 mmol) followed by TMSN_3 (203 mg, 235 μL , 1.77 mmol) dropwise. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum and the crude product was purified by silica gel chromatography (hexane) to give the product, **2**, as a pale yellow oil (228 mg, 96%). IR (film) 2962.87, 2094.68, 1506.81, 1294.80 cm^{-1} . ^1H NMR (CDCl_3 , 400MHz) δ : 1.43 (d, $J = 6.8$ Hz, 6H), 2.78 (sept, $J = 6.8$ Hz, 1H), 6.85 (d, $J = 8.3$ Hz, 2H), 7.10 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR (CDCl_3 , 100MHz) δ : 24.0, 33.6, 118.9, 127.8, 137.5, 145.8. EA calcd. for $\text{C}_9\text{H}_{11}\text{N}_3$: C, 67.06; H, 6.88; N, 26.07. Found: C, 67.21; H, 6.81; N, 26.10.

1-Azido-2,6-diethylbenzene (**3**)²

2,6-Diethylaniline (200 mg, 1.34 mmol) was dissolved in CH₃CN (2 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (207 mg, 238 μL, 2.01 mmol) followed by TMSN₃ (185 mg, 213 μL, 1.61 mmol) dropwise. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum and the crude product was purified by silica gel chromatography (hexane) to give the product, **3**, as a colourless oil (220 mg, 95%). IR (film) 2968.77, 2093.35, 1446.61, 1296.68 cm⁻¹. ¹H NMR (CDCl₃, 400MHz) δ: 1.31 (t, *J* = 7.5 Hz, 6H), 2.80 (q, *J* = 7.5 Hz, 4H), 7.11 (m, 3H). ¹³C NMR (CDCl₃, 100MHz) δ: 14.7, 25.0, 126.3, 127.2, 136.1, 138.4. EA calcd. for C₁₀H₁₃N₃: C, 68.54; H, 7.48; N, 23.99. Found: C, 68.64; H, 7.46; N, 24.01.

1-Azido-3-ethynylbenzene (**4**)³

3-Aminophenylacetylene (200 mg, 1.70 mmol) was dissolved in CH₃CN (4 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (264 mg, 305 μL, 2.56 mmol) followed by TMSN₃ (236 mg, 270 μL, 2.05 mmol) dropwise. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum and the crude product was purified by silica gel chromatography (hexane) to give the product, **4**, as a yellow oil (205 mg, 84%). IR (film) 3292.80, 2108.34, 1597.76, 1574.71, 1483.78 cm⁻¹. ¹H NMR (CDCl₃, 400MHz) δ: 3.14 (s, 1H), 7.04 (dt, *J* = 7.6 and 1.8 Hz, 1H), 7.17 (t, *J* = 1.8 Hz, 1H), 7.34-7.27 (m, 2H). ¹³C NMR (CDCl₃, 100MHz) δ: 78.2, 82.6, 119.6, 122.4, 123.8, 128.6, 129.7, 140.3. EA calcd. for C₈H₅N₃: C, 67.13; H, 3.45; N, 29.40. Found: C, 67.22; H, 3.48; N, 29.50.

1-Azido-3-methoxybenzene (**5**)⁴

m-Anisidine (200 mg, 1.62 mmol) was dissolved in CH₃CN (2 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (250 mg, 290 μL, 2.44 mmol) followed by TMSN₃ (224 mg, 260 μL, 1.95 mmol) dropwise. The resulting solution was stirred at 4°C for 1 h. The reaction mixture was concentrated under vacuum and the crude product was purified by silica gel chromatography (hexane/ethyl acetate, 8:2) to give the product, **5**, as a yellow oil (213 mg, 88%). HPLC purity > 99%. IR (film) 2101.13, 1599.33,

1450.69, 1295.51, 1226.26 cm^{-1} . ^1H NMR (CDCl_3 , 400MHz) δ : 3.69 (s, 3H), 6.45 (t, $J = 2.3$ Hz, 1H), 6.55 (dd, $J = 8.3$ and 2.3 Hz, 1H), 6.60 (dd, $J = 8.3$ and 2.3 Hz, 1H), 7.15 (t, $J = 8.3$ Hz, 1H). ^{13}C NMR (CDCl_3 , 100MHz) δ : 55.3, 105.0, 110.7, 111.3, 130.4, 141.3, 160.9.

1-Azido-4-methoxybenzene (**6**)⁵

p-Anisidine (200 mg, 1.62 mmol) was dissolved in CH_3CN (2 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (250 mg, 290 μL , 2.44 mmol) followed by TMSN_3 (224 mg, 260 μL , 1.95 mmol) dropwise. The resulting solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum and the crude product was purified by silica gel chromatography (hexane/ethyl acetate, 8:2) to give the product, **6**, as a yellow oil (202 mg, 83%). HPLC purity > 99%. IR (film) 2097.14, 1501.10, 1284.49, 1241.12 cm^{-1} . ^1H NMR (CDCl_3 , 400MHz) δ : 3.70 (s, 3H), 6.81 (d, $J = 8.8$ Hz, 2H), 6.88 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (CDCl_3 , 100MHz) δ : 55.6, 115.2, 120.0, 132.4, 157.0.

1-Azido-4-nitrobenzene (**7**)⁶

4-Nitroaniline (100 mg, 0.72 mmol) was dissolved in CH_3CN (2 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (111 mg, 128 μL , 1.08 mmol) followed by TMSN_3 (100 mg, 115 μL , 0.86 mmol) dropwise. The resulting solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum and the crude product was purified by silica gel chromatography (0-5% MeOH/ DCM) to give the product, **7**, as an orange solid (90 mg, 76%). IR (film) 3111.77, 2121.20, 1589.32, 1511.28, 1487.23, 1338.33, 1285.15 cm^{-1} . ^1H NMR (CDCl_3 , 400MHz) δ : 7.80 (d, $J = 8.8$ Hz, 2H), 8.18 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (CDCl_3 , 100MHz) δ : 119.4, 125.6, 144.7, 146.9. EA calcd. for $\text{C}_6\text{H}_4\text{N}_4\text{O}_2$: C, 43.90; H, 2.44; N, 34.15. Found: C, 44.10; H, 2.56; N, 33.99.

1-Azido-4-iodobenzene (**8**)⁷

4-Iodoaniline (200 mg, 0.91 mmol) was dissolved in CH_3CN (2 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (141 mg, 162 μL , 1.36 mmol) followed by TMSN_3 (125 mg, 145 μL , 1.09 mmol) dropwise. The resulting

solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum and the crude product was purified by silica gel chromatography (0-5% MeOH/ DCM) to give the product, **8**, as a brown solid (200 mg, 90%). IR (film) 3244.78, 2116.30, 2080.26, 1569.58, 1475.18, 1285.20 cm^{-1} . ^1H NMR (CDCl_3 , 400MHz) δ : 6.72 (dd, $J = 8.8$ and 1.0 Hz, 2H), 7.58 (dd, $J = 8.8$ and 1.0 Hz, 2H). ^{13}C NMR (CDCl_3 , 100MHz) δ : 88.2, 121.1, 138.7, 140.00. EA calcd. for $\text{C}_6\text{H}_4\text{IN}_3$: C, 29.39; H, 1.63; N, 17.14. Found: C, 29.41; H, 1.61; N, 17.10.

1-Azidoacetophenone (**9**)⁸

4-Aminoacetophenone (200 mg, 1.48 mmol) was dissolved in CH_3CN (4 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (228 mg, 263 μL , 2.22 mmol) followed by TMSN_3 (204 mg, 235 μL , 1.77 mmol) dropwise. The resulting solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum. The resulting precipitate was washed with cold hexane, and dried under reduced pressure to give the product, **9**, as pure orange crystals (227 mg, 95%). IR (film) 3042.88, 2124.42, 2089.34, 1669.25, 1594.28, 1271.27 cm^{-1} . ^1H NMR (CDCl_3 , 400MHz) δ : 2.60 (s, 3H), 7.12 (d, $J = 8.3$ Hz, 2H), 7.99 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR (CDCl_3 , 100MHz) δ : 26.5, 119.0, 130.3, 133.8, 144.9, 196.6. EA calcd. for $\text{C}_8\text{H}_7\text{N}_3\text{O}$: C, 59.63; H, 4.35; N, 26.08. Found: C, 59.61; H, 4.38; N, 26.07.

1-Azidobenzonitrile (**10**)⁸

4-Aminobenzonitrile (200 mg, 1.69 mmol) was dissolved in CH_3CN (4 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (261 mg, 300 μL , 2.54 mmol) followed by TMSN_3 (234 mg, 270 μL , 2.03 mmol) dropwise. The resulting solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum. The resulting precipitate was washed with cold hexane, and dried under reduced pressure to give the product, **10**, as pure orange crystals (233 mg, 96%). IR (film) 3094.82, 2220.58, 2152.55, 2109.98, 1620.29, 1597.43, 1503.45 cm^{-1} . ^1H NMR (CDCl_3 , 400MHz) δ : 7.05 (d, $J = 8.3$ Hz, 2H), 7.59 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR (CDCl_3 , 100MHz) δ : 108.3, 118.4, 119.7, 133.9, 144.9. EA calcd. for $\text{C}_7\text{H}_4\text{N}_4$: C, 58.33; H, 2.77; N, 38.88. Found: C, 58.32; H, 2.78; N, 38.68.

2-Azido-5-nitrophenol (**11**)⁹

2-Amino-5-nitrophenol (500 mg, 3.24 mmol) was dissolved in CH₃CN (10 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (501 mg, 577 μL, 4.86 mmol) followed by TMSN₃ (448 mg, 516 μL, 3.89 mmol) dropwise. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum and the crude product was purified by silica gel chromatography (0-5% MeOH/ DCM) to give the product, **11**, as a yellow solid (434 mg, 74%). IR (film) 3370.77, 3106.88, 2125.56, 2098.56, 1600.73, 1498.43 cm⁻¹. ¹H NMR (CD₃OD, 400MHz) δ: 6.96 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 2.5 Hz, 1H), 7.59 (dd, *J* = 8.8 and 2.5 Hz, 1H). ¹³C NMR (CD₃OD, 100MHz) δ: 109.9, 114.7, 119.7, 133.4, 144.5, 149.9. MS [ES⁻]: 179 (M-1H)⁻, 359 (2M-1H)⁻. EA calcd. for C₆H₄N₄O₃: C, 40.00; H, 2.22; N, 31.11. Found: C, 40.28; H, 2.13; N, 31.01.

2-Azido-benzoic acid (**12**)¹⁰

Anthranilic acid (200 mg, 1.46 mmol) was dissolved in CH₃CN (4 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (226 mg, 260 μL, 2.18 mmol) followed by TMSN₃ (200 mg, 230 μL, 1.75 mmol) dropwise. The resulting solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum. The resulting precipitate was washed with water and hexane, and dried over phosphorus pentoxide under reduced pressure to give the product, **12**, as a pure beige solid (192 mg, 81%). IR (film) 2823.77, 2645.77, 2105.51, 1685.45, 1574.54, 1485.55, 1265.41 cm⁻¹. ¹H NMR (CDCl₃, 400MHz) δ: 7.22-7.16 (m, 2H), 7.56 (td, *J* = 8.0 and 1.5 Hz, 1H), 8.05 (dd, *J* = 7.8 and 1.5 Hz, 1H), 10.13 (bs, 1H). ¹³C NMR (CDCl₃, 100MHz) δ: 119.5, 120.9, 124.9, 133.3, 134.4, 140.2, 168.4. HRMS [ES⁻] calcd for C₇H₅N₃O₂ 162.0303 [M-H]⁻, found 162.0298. EA calcd. for C₇H₅N₃O₂: C, 51.54; H, 3.09; N, 25.76. Found: C, 51.47; H, 3.00; N, 25.48.

2-Azido-6-methylbenzoic acid (**13**)

2-Amino-6-methylbenzoic acid (100 mg, 0.66 mmol) was dissolved in CH₃CN (2 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (102 mg, 117 μL, 0.99 mmol) followed by TMSN₃ (91 mg, 105 μL, 0.79 mmol) dropwise. The resulting solution was stirred at room temperature for 2 h. The reaction mixture was

concentrated under vacuum. The resulting precipitate was washed with water and hexane, and dried over phosphorus pentoxide under reduced pressure to give the product, **13**, as a pure yellow solid (97 mg, 83%). IR (film) 2901.82, 2129.49, 1693.35, 1598.71, 1459.60, 1287.28 cm^{-1} . ^1H NMR (CDCl_3 , 400MHz) δ : 2.36 (s, 3H), 6.96 (d, $J = 7.8$ Hz, 1H), 7.00 (d, $J = 8.0$ Hz, 1H), 7.31 (t, $J = 7.8$ Hz, 1H), 10.45 (bs, 1H). ^{13}C NMR (CDCl_3 , 100MHz) δ : 19.8, 115.9, 124.5, 126.8, 131.0, 137.7, 137.7, 172.8. HRMS [ES^-] calcd for $\text{C}_8\text{H}_7\text{N}_3\text{O}_2$ 176.0460 [M-H^-], found 176.0461. EA calcd. for $\text{C}_8\text{H}_7\text{N}_3\text{O}_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 54.21; H, 4.11; N, 23.45.

2-Azido-6-chlorobenzoic acid (**14**)

2-Amino-6-chlorobenzoic acid (100 mg, 0.58 mmol) was dissolved in CH_3CN (2 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added $t\text{-BuONO}$ (90 mg, 103 μL , 0.87 mmol) followed by TMSN_3 (80 mg, 92 μL , 0.70 mmol) dropwise. The resulting solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum. The resulting precipitate was washed with water and hexane, and dried over phosphorus pentoxide under reduced pressure to give the product, **14**, as a pure yellow solid (89 mg, 78%). IR (film) 3029.83, 2115.49, 1701.40, 1575.58, 1444.51, 1292.47, 1266.44 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$, 400MHz) δ : 7.28 (d, $J = 8.0$ Hz, 1H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.45 (t, $J = 8.0$ Hz, 1H), 13.78 (bs, 1H). ^{13}C NMR ($\text{DMSO}-d_6$, 100MHz) δ : 118.0, 125.4, 127.0, 129.9, 131.2, 137.6, 165.4. HRMS [ES^-] calcd for $\text{C}_7\text{H}_4\text{ClN}_3\text{O}_2$ 195.9914 [M-H^-], found 195.9904. EA calcd. for $\text{C}_7\text{H}_4\text{ClN}_3\text{O}_2$: C, 42.65; H, 2.05; N, 21.32. Found: C, 42.70; H, 2.10; N, 21.21.

2-Azido-5-iodobenzoic acid (**15**)¹¹

2-Amino-5-iodobenzoic acid (100 mg, 0.38 mmol) was dissolved in CH_3CN (2 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added $t\text{-BuONO}$ (59 mg, 68 μL , 0.57 mmol) followed by TMSN_3 (52 mg, 60 μL , 0.46 mmol) dropwise. The resulting solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum. The resulting precipitate was washed with water and hexane, and dried over phosphorus pentoxide under reduced pressure to give the product, **15**, as a pure brown solid (74 mg, 67%). IR (film) 2800.71, 2114.40, 1688.44, 1556.51, 1475.49, 1298.39 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$, 400MHz) δ : 7.13 (d, $J = 8.6$ Hz, 1H), 7.85 (dd, $J = 8.6$ and 2.0 Hz, 1H), 7.97 (d, $J = 2.0$ Hz, 1H), 13.33 (bs, 1H). ^{13}C NMR ($\text{DMSO}-d_6$, 100MHz) δ : 88.6, 123.1, 125.8, 138.6, 139.0, 141.2, 165.0.

HRMS [ES⁻] calcd for C₇H₄IN₃O₂ 287.9270 [M-H]⁻, found 287.9256. EA calcd. for C₇H₄IN₃O₂: C, 29.08; H, 1.39; N, 14.54. Found: C, 29.10; H, 1.35; N, 14.56.

2-Azido-4-fluorobenzoic acid (16)

2-Amino-4-fluorobenzoic acid (100 mg, 0.64 mmol) was dissolved in CH₃CN (2 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (100 mg, 114 μL, 0.97 mmol) followed by TMSN₃ (84 mg, 97 μL, 0.77 mmol) dropwise. The resulting solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum. The resulting precipitate was washed with water and hexane, and dried over phosphorus pentoxide under reduced pressure to give the product, **16**, as a pure white solid (76 mg, 65%). IR (film) 2815.71, 2126.43, 1668.31, 1587.35, 1498.39, 1261.39 cm⁻¹. ¹H NMR (DMSO-*d*₆, 400MHz) δ: 7.08 (dd, *J* = 8.6 and 6.6 Hz, 1H), 7.24 (dd, *J* = 9.8 and 2.0 Hz, 1H), 7.82 (dd, *J* = 8.6 and 2.3 Hz, 1H), 13.15 (bs, 1H). ¹³C NMR (DMSO-*d*₆, 100MHz) δ: 108.6 (d, *J*_{CF} = 24.8 Hz), 112.1 (d, *J*_{CF} = 22.0 Hz), 120.3 (d, *J*_{CF} = 2.9 Hz), 133.7 (d, *J*_{CF} = 10.2 Hz), 141.6 (d, *J*_{CF} = 9.5 Hz), 162.9, 165.5 (d, *J*_{CF} = 6.6 Hz). HRMS [ES⁻] calcd for C₇H₄FN₃O₂ 180.0209 [M-H]⁻, found 180.0206. EA calcd. for C₇H₄FN₃O₂: C, 46.42; H, 2.23; N, 23.20. Found: C, 46.40; H, 2.20; N, 22.31.

2-Azido-4,5-dimethoxybenzoic acid (17)¹²

2-Amino-4,5-dimethoxybenzoic acid (100 mg, 0.51 mmol) was dissolved in CH₃CN (2 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (70 mg, 80 μL, 0.76 mmol) followed by TMSN₃ (78 mg, 90 μL, 0.61 mmol) dropwise. The resulting solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum. The resulting precipitate was washed with water and hexane, and dried over phosphorus pentoxide under reduced pressure to give the product, **17**, as a pure grey solid (88 mg, 78%). IR (film) 2520.85, 2132.69, 1680.61, 1518.60, 1251.42 cm⁻¹. ¹H NMR (CDCl₃, 400MHz) δ: 3.85 (s, 3H), 3.92 (s, 3H), 6.60 (s, 1H), 7.54 (s, 1H). ¹³C NMR (CDCl₃, 100MHz) δ: 56.3, 56.4, 102.2, 112.5, 114.7, 133.9, 146.5, 154.1, 167.2. HRMS [ES⁻] calcd for C₉H₉N₃O₄ 222.0515 [M-H]⁻, found 222.0527. EA calcd. for C₉H₉N₃O₄: C, 48.43; H, 4.06; N, 18.83. Found: C, 48.52; H, 4.23; N, 18.60.

2-Azido-4-nitrobenzoic acid (**18**)¹³

2-Amino-5-nitrobenzoic acid (100 mg, 0.55 mmol) was dissolved in CH₃CN (2 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (84 mg, 98 μL, 0.82 mmol) followed by TMSN₃ (76 mg, 87 μL, 0.66 mmol) dropwise. The resulting solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum. The resulting precipitate was washed with water and hexane, and dried over phosphorus pentoxide under reduced pressure to give the product, **18**, as a pure orange solid (102 mg, 90%). IR (film) 3304.59, 3122.75, 2124.42, 1710.47, 1580.59, 1341.30 cm⁻¹. ¹H NMR (DMSO-*d*₆, 400MHz) δ: 7.57 (d, *J* = 8.8 Hz, 1H), 8.34 (dd, *J* = 8.8 and 2.8 Hz, 1H), 8.45 (d, *J* = 2.8 Hz, 1H), 13.74 (bs, 1H). ¹³C NMR (DMSO-*d*₆, 100MHz) δ: 122.3, 124.0, 126.2, 127.4, 143.3, 145.6, 164.7. HRMS [ES⁻] calcd for C₇H₄N₄O₄ 207.0154 [M-H]⁻, found 207.0163. EA calcd. for C₇H₄N₄O₄: C, 40.39; H, 1.94; N, 26.92. Found: C, 40.59; H, 2.16; N, 26.68.

One-pot 'click reaction'

1,4-Diphenyl-1,2,3-triazole (**19**)¹⁴

Aniline (50 mg, 0.54 mmol) was dissolved in CH₃CN (2 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (83 mg, 96 μL, 0.81 mmol) followed by TMSN₃ (75 mg, 86 μL, 0.65 mmol) dropwise. The resulting solution was stirred at room temperature for 2 h. Phenylacetylene (59 mg, 63 μL, 0.54 mmol), aq. solution (0.2 mL) of CuSO₄·5H₂O (9 mg, 0.036 mmol) and sodium ascorbate (21 mg, 0.108 mmol) were then added and the reaction was stirred overnight at room temperature. Most of the solvent was evaporated and the product was then precipitated with methanol to give the product, **19**, as an off white solid (104 mg, 88%). IR (film) 3121.95, 3059.95, 2372.93, 1597.92, 1502.89, 1480.90 cm⁻¹. ¹H NMR (CDCl₃, 400MHz) δ: 7.30 (m, 1H), 7.39 (m, 3H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.85 (d, *J* = 7.9 Hz, 2H), 8.12 (s, 1H). ¹³C NMR (CDCl₃, 100MHz) δ: 117.6, 120.6, 125.9, 128.6, 128.8, 128.9, 129.8, 130.3, 137.1, 148.5. HRMS [ES⁺] calcd for C₁₄H₁₁N₃ 222.1031 [M+H]⁺, found 222.1029. EA calcd. for C₁₄H₁₁N₃: C, 76.00; H, 5.01; N, 18.99. Found: C, 75.82; H, 4.91; N, 18.72.

1-(4-Iodophenyl)-4-phenyl-1,2,3-triazole (20)

4-Iodoaniline (200 mg, 0.91 mmol) was dissolved in CH₃CN (2 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (141 mg, 162 µL, 1.37 mmol) followed by TMSN₃ (126 mg, 145 µL, 1.10 mmol) dropwise. The resulting solution was stirred at room temperature for 2 h. Phenylacetylene (140 mg, 150 µL, 1.37 mmol), aq. solution (2 mL) of CuSO₄·5H₂O (23 mg, 0.091 mmol) and sodium ascorbate (91 mg, 0.46 mmol) were then added and the reaction vessel was sealed, and the mixture was stirred overnight at room temperature. Reaction mixture was then cooled to 0°C, then filtered and washed with water and hexane to give the product, **20**, as a white solid (248 mg, 79%). IR (film) 3121.11, 3090.11, 1494.88, 1477.86, 1398.91 cm⁻¹. ¹H NMR (DMSO-*d*₆, 400MHz) δ: 7.33 (t, *J* = 7.4 Hz, 1H), 7.45 (m, 2H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.88 (d, *J* = 7.2 Hz, 2H), 7.94 (d, *J* = 8.6 Hz, 2H), 9.26 (s, 1H). ¹³C NMR (DMSO-*d*₆, 100MHz) δ: 94.3, 119.5, 121.8, 125.3, 128.3, 129.0, 130.1, 136.3, 138.6, 147.4. HRMS [ES⁺] calcd for C₁₄H₁₀N₃I 347.9992 [M+H]⁺, found 347.9980. EA calcd. for C₁₄H₁₀N₃I: C, 48.44; H, 2.90; N, 12.10. Found: C, 48.37; H, 2.86; N, 12.13.

1-(4-(4-Phenyl-1,2,3-triazol-1-yl)phenyl)ethanone (21)

4-Aminoacetophenone (123 mg, 0.91 mmol) was dissolved in CH₃CN (2 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (141 mg, 162 µL, 1.37 mmol) followed by TMSN₃ (126 mg, 145 µL, 1.10 mmol) dropwise. The resulting solution was stirred at room temperature for 2 h. Phenylacetylene (140 mg, 150 µL, 1.37 mmol), aq. Solution (2 mL) of CuSO₄·5H₂O (23 mg, 0.091 mmol) and sodium ascorbate (91 mg, 0.46 mmol) were then added and the reaction vessel was sealed, and the mixture was stirred overnight at room temperature. Reaction mixture was then cooled to 0°C, diluted with 10 mL H₂O then filtered and washed with water and ether to give the product, **21**, as a yellow solid (207 mg, 81%). IR (film) 3129.10, 3100.11, 1675.67, 1603.78, 1407.71, 1229.62 cm⁻¹. ¹H NMR (DMSO-*d*₆, 400MHz) δ: 2.44 (s, 3H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.46 (m, 2H), 7.91 (d, *J* = 7.9 Hz, 2H), 8.08 (d, *J* = 8.7 Hz, 2H), 8.15 (d, *J* = 8.7 Hz, 2H), 9.39 (s, 1H). ¹³C NMR (DMSO-*d*₆, 100MHz) δ: 26.8, 119.7, 119.7, 125.4, 128.4, 129.0, 130.0, 130.1, 136.4, 139.6, 147.6, 196.9. HRMS [ES⁺] calcd for C₁₆H₁₃ON₃ 264.1131 [M+H]⁺, found 264.1144. EA calcd. for C₁₆H₁₃ON₃: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.80; H, 4.84; N, 15.93.

1-(4-Nitrophenyl)-4-phenyl-1,2,3-triazole (**22**)¹⁵

4-Nitroaniline (202 mg, 1.46 mmol) was dissolved in CH₃CN (3 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (358 mg, 413 μL, 2.19 mmol) followed by TMSN₃ (202 mg, 233 μL, 1.75 mmol) dropwise. The resulting solution was stirred at room temperature for 2 h. Phenylacetylene (224 mg, 241 μL, 2.19 mmol), aq. Solution (3 ml) of CuSO₄·5H₂O (36 mg, 0.146 mmol) and sodium ascorbate (144 mg, 0.729 mmol) were then added and the reaction vessel was sealed, and the mixture was stirred overnight at room temperature. The CH₃CN was evaporated and the product was then precipitated with ether to give the product, **22**, as a tan solid (320 mg, 82%). IR (film) 3121.90, 3095.89, 1596.77, 1518.60, 1345.61 cm⁻¹. ¹H NMR (DMSO-*d*₆, 400MHz) δ: 7.43 (m, 1H), 7.54 (m, 2H), 7.98 (d, *J* = 7.8 Hz, 2H), 8.30 (d, *J* = 9.0 Hz, 2H), 8.53 (d, *J* = 9.0 Hz, 2H), 9.54 (s, 1H). ¹³C NMR (DMSO-*d*₆, 100MHz) δ: 120.0, 120.5, 125.4, 125.7, 128.6, 129.1, 129.8, 140.9, 146.7, 147.8. HRMS [ES⁺] calcd for C₁₄H₁₀N₄O₂ 267.0876 [M+H]⁺, found 267.0887. EA calcd. for C₁₄H₁₀N₄O₂: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.23; H, 3.77; N, 20.99.

2-(4-Phenyl-1,2,3-triazol-1-yl)benzoic acid (**23**)

Anthranilic acid (125, 0.91 mmol) was dissolved in CH₃CN (2 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (141 mg, 162 μL, 1.37 mmol) followed by TMSN₃ (126 mg, 145 μL, 1.10 mmol) dropwise. The resulting solution was stirred at room temperature for 40 min. Phenylacetylene (140 mg, 150 μL, 1.37 mmol), aq. solution (0.2 ml) of CuSO₄·5H₂O (23 mg, 0.091 mmol) and sodium ascorbate (91 mg, 0.46 mmol) were then added and the reaction was stirred overnight at room temperature. The reaction mixture was diluted with 10ml Et₂O and cooled to 0°C. The mixture was then filtered and the solid washed with Et₂O and H₂O to obtain the product, **23**, as a white solid (211 mg, 87%). IR (film) 3142.84, 2733.84, 1709.58, 1601.74, 1204.42 cm⁻¹. ¹H NMR (DMSO-*d*₆, 500MHz) δ: 7.38 (t, *J* = 7.4 Hz, 1H), 7.50 (m, 2H), 7.73 (m, 2H), 7.80 (m, 1H), 7.96 (m, 3H), 9.00 (s, 1H), 13.20 (bs, 1H). ¹³C NMR (DMSO-*d*₆, 125MHz) δ: 123.0, 125.2, 126.5, 128.1, 128.7, 129.0, 130.0, 130.5, 130.5, 132.5, 135.4, 146.4, 166.5. HRMS [ES⁺] calcd for C₁₅H₁₁N₃O₂ 266.0924 [M+H]⁺, found 266.0938. EA calcd. for C₁₅H₁₁N₃O₂: C, 67.92; H, 4.18; N, 15.84. Found: C, 67.63; H, 4.20; N, 15.64.

References:

- 1-Brown, H. C.; Midland, M. M.; Levy, A. B. *J. Am. Chem. Soc.* **1973**, *95*, 2394-2396.
- 2-Das, J.; Patil, S. N.; Awasthi, R.; Narasimhulu, C. P.; Trehan, S. *Synthesis* **2005**, *11*, 1801-1806.
- 3-Tomioka, H.; Sawai, S. *Org. & Biomol. Chemistry* **2003**, *1*, 4441-4450.
- 4-Roof, A. A. M.; Winter, W. J.; Bartlett, P. D. *J. Org. Chem.* **1985**, *50*, 4093-4098.
- 5-Meijer, E. W.; Nijhuis, S.; Van Vroonhoven, F. C. B. M. *J. Am. Chem. Soc.* **1988**, *110*, 7209-7210.
- 6-Nishiyama, K.; Anselme, J-P. *J. Org. Chem.* **1977**, *42*, 2636-2637.
- 7-Huang, Y.; Zhang, Y.; Wang, Y. *Tetrahedron Lett.* **1997**, *38*, 1065-1066.
- 8-Liu, Q.; Tor, Y. *Org. Lett.* **2003**, *5*, 2571-2572.
- 9-Kamal, A.; Prasad, B. R.; Ramana, A. V.; Babu, A. H.; Reddy, K. S. *Tetrahedron Lett.* **2004**, *45*, 3507-3509.
- 10- Takeuchi, H.; Hagiwara, S.; Eguchi, S. *Tetrahedron* **1989**, *45*, 6375-6386.
- 11- Perrier, H.; Prasit, P.; Wang, Z. *Tetrahedron Lett.* **1994**, *35*, 1501-1502.
- 12- Eguchi, S.; Matsushita, Y.; Takeuchi, H. *J. Org. Chem.* **1992**, *57*, 6975-6979.
- 13- Kutner, A.; Link, R. P.; Schnoes, H. K.; DeLuca, H. F. *Bioorg. Chem.* **1986**, *14*, 134-147.
- 14- Ito, S.; Kakehi, A.; Okada, K.; Goto, S.; Kawaguchi, H. *Heterocycles* **1997**, *45*, 889-896.
- 15- Zhao, Y-B.; Yan, Z-Y.; Liang, Y-M. *Tetrahedron Lett.* **2006**, *47*, 1545-1549.

Spectral data for new compounds **13**, **14**, **16**, **20**, **21** and **23**.

Compound **13**

Compound **14**

Chemical structure: N=[N+]=[N-]c1cc(F)ccc1C(=O)O

¹H NMR spectrum (DMSO-d₆) showing peaks at 12.0 ppm (broad, 1H), 8.0 ppm (multiplet, 2H), 7.8 ppm (doublet, 2H), and 4.8 ppm (singlet, 1H). Integration values are 1.00, 1.00, 2.00, and 1.00 respectively.

Chemical structure: Ic1ccc(cc1)-c2nnnc3ccccc23

¹H NMR spectrum (CDCl₃) showing peaks at 7.7 (s, 1H), 7.5 (d, 2H), 7.4 (d, 2H), 7.3 (d, 2H), and 7.2 (s, 1H). The inset shows the aromatic region with integration values: 1.00, 1.00, 1.00, 1.00, 1.00, 1.00, 1.00, 1.00, 1.00, 1.00.

Compound **21**

Compound **23**

HPLC traces for compounds 5 and 6.

Mobile Phase: (A) Water (formic acid 0.15%) and (B) acetonitrile (formic acid 0.15%).

Gradient: Initial composition 5% (B) to 95% (B) over 4 minutes.

Flow Rate: 1.5mL/min.