Isonitrile Alkylations: A Rapid Route to Imidazo[1,5-a]pyridine

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General procedure for the synthesis of imidazoles (General procedure 3)
General experimental conditions:

Tetrahydrofuran (THF) was freshly distilled from Na/benzophenone ketyl prior to use. Dichloromethane (CH$_2$Cl$_2$) was dried by passing through an alumina and molecular sieve drying train, marketed by Innovative Technology Inc. (Model: PS-MD-7). Other reagents were purchased at analytical or ACS grade, and used without further purification unless otherwise stated. Thin layer chromatography (TLC) was performed with UV active (w/ F-254) glass backed silica gel plates (Dynamic Adsorbents Inc.). TLC plates were visualized by exposure to short wavelength UV light (254 nm). Flash chromatography was performed using SiliaFlash® silica gel P60 (30-400 mesh) purchased from Silicycle, Florisil® (100-200 mesh) purchased from Alfa Aesar. Radial chromatography was performed on a Harrison Research Chromatotron™ using glass rotors covered with SiO$_2$ and leveled to 1, 2, and 4 mm thickness. $^1$H NMR and $^{13}$C NMR high resolution nuclear magnetic resonance spectra were obtained on a Bruker Avance 400 or a Bruker Avance 500 spectrometer.$^1$H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, m = multiplet, br = broad resonance, etc.), integration, and coupling constants (Hz). $^{13}$C NMR data are reported in parts per million (ppm) on the δ scale. High resolution mass spectra (HRMS) were recorded on a Thermo-Finnegan LTQ-FTMS in APCI mode. Infrared spectra were recorded on a Perkin Elmer Frontier FT-IR spectrometer with a universal ATR sampling accessory.

General procedure for isocyanide formation from a primary amine (General procedure 1).$^1$ Neat amine was added to methyl formate (0.2 M) at rt and then the reaction was monitored by TLC. After the reaction was complete (~ 2 days), the solution was concentrated by rotary evaporation. The resulting crude formamide (1.0 equiv.) was dissolved in dry
CH₂Cl₂ (0.2 M), and then i-Pr₂NH (3 equiv.) was added. The solution was cooled to -30 °C, and then phosphorous oxychloride (1.1 equiv.) was added dropwise. After 2 h, the reaction mixture was poured into a saturated, aqueous solution of sodium carbonate. The organic layer was separated and then the aqueous phase was extracted with CH₂Cl₂. The combined organic fractions were washed with water, brine, dried (Na₂SO₄), filtered, and concentrated. The crude isonitrile was purified by flash column chromatography on a short pad of silica gel (1.0 x 5.0 cm column for approximately 500 mg of the crude reaction mixture) to afford pure isonitrile.

4-(Isocyanomethyl)-1,1'-biphenyl (6b): Following general procedure 1, isonitrile 6b was prepared from 4-phenylbenzylamine (0.500 g, 2.73 mmol) as a white solid (0.417 g, 2.16 mmol) in 79% yield: IR (ATR) 3034, 2153 cm⁻¹; ¹H NMR (400 MHz, Chloroform-d) δ 7.65-7.55 (m, 4H), 7.47-7.33 (m, 5H), 4.66 (s, 2H); ¹³C NMR (100 MHz, Chloroform-d) δ 157.82 (br), 141.49, 140.28, 131.33, 128.94, 127.72, 127.15, 45.34 (t, J = 7.1 Hz); HRMS calculated for C₁₄H₁₂N⁺ 194.09643, found 194.09641 (M+H)⁺.

1-(Isocyanomethyl)-4-(trifluoromethoxy)benzene (6c): Following general procedure 1, isonitrile 6c was prepared from 4-trifluoromethoxybenzylamine (0.500 g, 2.62 mmol) as a yellow liquid (0.421g, 2.09 mmol) in 80% yield: ²IR (ATR) 2151 cm⁻¹; ¹H NMR (500 MHz, Chloroform-d) δ 7.38 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 4.63 (s, 2H); ¹³C NMR (126 MHz, Chloroform-d) δ 157.82 (br), 141.49, 140.28, 131.33, 128.94, 127.72, 127.15, 45.34 (t, J = 7.1 Hz); HRMS calculated for C₁₄H₁₂N⁺ 194.09643, found 194.09641 (M+H)⁺.

2-(Isocyanomethyl)furan (6d): Following general procedure 1, isonitrile 6d was
prepared from furfurylamine (0.500 g, 5.15 mmol) as a yellow liquid (0.403 g, 3.76 mmol) in 73% yield, that exhibited spectral data consistent with that already published.  

\[ \text{2-(Isocyanomethyl)-5-methylfuran (6e): Following general procedure 1, isonitrile 6e was prepared from (5-methyl-2-furyl)methylamine (0.500 g, 4.50 mmol) as a yellow liquid (0.441 g, 3.65 mmol) in 81% yield: IR (ATR) 2926, 2147 cm}^{-1}; {^1}H NMR (500 MHz, Chloroform-\text{d}) \delta 6.19 (d, \text{ } J = 2.1 \text{ Hz, 1H}), 5.92 (d, \text{ } J = 2.1 \text{ Hz, 1H}), 4.47 (s, 2H), 2.24 (s, 3H); {^{13}}C NMR (126 MHz, Chloroform-\text{d}) \delta 157.33 (t, \text{ } J = 4.1 \text{ Hz}), 153.17, 143.67, 109.90, 106.61, 38.81 (t, \text{ } J = 6.9 \text{ Hz}), 13.38; HRMS calculated for \text{C}_{7}\text{H}_{8}\text{ON}^+ 122.06004, found 122.06008 (M+H)^+. \]

\[ \text{(E)-(3-Isocyanoprop-1-en-1-yl)benzene (6f): Following general procedure 1, isonitrile 6f was prepared from cinnamylamine (0.500 g, 3.76 mmol) as a white solid (0.366 g, 2.56 mmol) in 68% yield: IR (ATR) 3028, 2149 cm}^{-1}; {^1}H NMR (400 MHz, Chloroform-\text{d}) \delta 7.43 – 7.24 (m, 5H), 6.72 (d, \text{ } J = 15.8 \text{ Hz, 1H}), 6.18-6.07 (m, 1H), 4.27 – 4.17 (m, 2H); {^{13}}C NMR (100 MHz, Chloroform-\text{d}) \delta 157.64 (t, \text{ } J = 5.6 \text{ Hz}), 135.50, 133.11, 128.75, 128.38, 126.65, 119.42, 43.59 (t, \text{ } J = 7.1 \text{ Hz}); \text{C}_{10}\text{H}_{10}\text{N}^+ 144.08078, found 144.08076 (M+H)^+. \]

**General procedure for the synthesis of imidazo[1,5-a]pyridines (General procedure 2).**

A hexanes solution of BuLi (1.1 equiv. 2.5 M) or a THF solution of KHMDS (1.3 equiv. 1.0 M) was added to a -78 °C THF solution (0.1 M) of the isonitrile (1.0 equiv.). After 5 min, a THF (0.5 M) solution of the 2-halopyridine was added. After 30 min, the reaction mixture was allowed to warm to rt and after 30 min, water was added and then the aqueous layer was extracted with EtOAc. The combined organic fractions were washed sequentially with water and brine, dried (Na$_2$SO$_4$), filtered, and then concentrated. The crude material was then purified by radial chromatography to afford pure product.
1-Phenylimidazo[1,5-a]pyridine (8a): Following general procedure 2 with benzylisonitrile (0.078 g, 0.67 mmol), 2-chloropyridine (0.075 g, 0.67 mmol) and KHMDMS (0.87 mL, 0.87 mmol), afforded imidazo[1,5-a]pyridine 8a (0.068 g, 0.35 mmol) in 53% yield: IR (ATR) 3042, 1601, 1517, 1457 cm\(^{-1}\); \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 8.13 (s, 1H), 7.90 - 7.86 (m, 3H), 7.78 (d, \(J = 9.3\) Hz, 1H), 7.47 - 7.41 (m, 2H), 7.30 – 7.24 (m, 1H), 6.74 (dd, \(J = 9.1, 6.5\) Hz, 1H), 6.53 (t, \(J = 6.7\) Hz, 1H); \(^{13}\)C NMR (126 MHz, Chloroform-\(d\)) \(\delta\) 135.10, 131.42, 128.77, 127.49, 126.48, 126.42, 122.58, 119.98, 118.88, 112.95; HRMS calculated for C\(_{13}\)H\(_{11}\)N\(_2\)\(^+\) 195.0917, found 195.0916 (M+H\(^+\)).

5-Methyl-1-phenylimidazo[1,5-a]pyridine (8b): Following general procedure 2 with benzylisonitrile (0.054 g, 0.46 mmol), 2-chloro-6-methylpyridine (0.059 g, 0.46 mmol) and BuLi (0.20 mL, 0.51 mmol), afforded imidazo[1,5-a]pyridine 8b (0.069 g, 0.33 mmol) in 72% yield: IR (ATR) 3052, 1639, 1600, 1538 cm\(^{-1}\); \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 8.01 (s, 1H), 7.91 - 7.86 (m, 2H), 7.67 (d, \(J = 9.3\) Hz, 1H), 7.47 - 7.40 (m, 2H), 7.25 (t, \(J = 7.4\) Hz, 1H), 6.68 (dd, \(J = 9.3, 6.5\) Hz, 1H), 6.30 (d, \(J = 6.5\) Hz, 1H), 2.45 (s, 3H); \(^{13}\)C NMR (100 MHz, Chloroform-\(d\)) \(\delta\) 135.35, 131.91, 131.37, 128.73, 127.00, 126.47, 126.31, 124.99, 120.34, 116.18, 111.86, 18.14; HRMS calculated for C\(_{14}\)H\(_{12}\)N\(_2\)Na\(^+\) 231.0893, found 231.0893 (M+Na\(^+\)).

5,7-Dimethyl-1-phenylimidazo[1,5-a]pyridine (8c): Following general procedure 2 with benzylisonitrile (0.054 g, 0.46 mmol), 2-chloro-4,6-dimethylpyridine (0.065 g, 0.46 mmol) and BuLi (0.20 mL, 0.51 mmol), afforded imidazo[1,5-a]pyridine 8c (0.079 g, 0.35 mmol) in 77% yield: IR (ATR) 3051, 2912, 1650, 1603 cm\(^{-1}\); \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 7.99 (s, 1H), 7.88 (d, \(J = 7.3\) Hz, 2H), 7.48 - 7.40 (m, 3H), 7.25 (t, \(J = 7.4\) Hz, 1H), 6.23 (s, 1H), 2.49 (s, 3H), 2.27 (s, 3H); \(^{13}\)C NMR (126 MHz, Chloroform-\(d\)) \(\delta\) 135.53, 130.78, 130.32, 128.66, 127.44, 126.33, 126.01, 124.50,
114.91, 113.97, 21.30, 17.98; HRMS calculated for C_{15}H_{14}N_{2}Na\(^{+}\) 245.1049, found 245.1049 (M+Na)\(^{+}\).

**7-Methyl-1-phenylimidazo[1,5-a]pyridine (8d):** Following general procedure 2 with benzylisonitrile (0.083 g, 0.71 mmol), 2-chloro-4-methylpyridine (0.090 g, 0.71 mmol) and KHMD (0.92 mL, 0.92 mmol), afforded imidazo[1,5-a]pyridine 8d (0.081 g, 0.39 mmol) in 55% yield: IR (ATR) 3055, 2910, 1644, 1610 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.09 (s, 1H), 7.89 – 7.87 (m, 2H), 7.83 (d, \(J = 7.2\) Hz, 1H), 7.55 (s, 1H), 7.48 – 7.42 (m, 2H), 7.28 – 7.24 (m, 1H), 6.42 (dd, \(J = 7.2, 1.5\) Hz, 1H), 2.32 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 135.26, 130.54, 129.65, 128.71, 126.98, 126.85, 126.24, 126.12, 122.03, 116.37, 115.94, 21.39; HRMS calculated for C_{14}H_{13}N_{2}Na\(^{+}\) 209.10732, found 209.10733 (M+Na)\(^{+}\).

**6-Bromo-5-methyl-1-phenylimidazo[1,5-a]pyridine (8e):** Following general procedure 2 with benzylisonitrile (0.054 g, 0.46 mmol), 5-bromo-2-chloro-6-methylpyridine (0.095 g, 0.46 mmol) and KHMD (0.74 mL, 0.74 mmol), afforded imidazo[1,5-a]pyridine 8e (0.100 g, 0.35 mmol) in 77% yield: IR (ATR) 3118, 1621, 1601, 1530 cm\(^{-1}\); \(^1\)H NMR (500 MHz, Chloroform-d) \(\delta\) 8.09 (s, 1H), 7.85 (d, \(J = 7.2\) Hz, 2H), 7.59 (d, \(J = 9.6\) Hz, 1H), 7.46 (t, \(J = 7.8\) Hz, 2H), 7.30 (t, \(J = 7.4\) Hz, 1H), 6.92 (d, \(J = 9.6\) Hz, 1H), 2.71 (s, 3H); \(^{13}\)C NMR (126 MHz, Chloroform-d) \(\delta\) 134.58, 133.42, 129.65, 128.62, 128.80, 126.85, 126.67, 126.15, 125.86, 124.33, 116.89, 108.81, 17.56; HRMS calculated for C_{14}H_{11}BrN_{2}Na\(^{+}\) 308.99978, found 308.99984 (M+Na)\(^{+}\).

**8-Bromo-1-phenylimidazo[1,5-a]pyridine (8f):** Following general procedure 2 with benzylisonitrile (0.073 g, 0.62 mmol), 3-bromo-2-chloropyridine (0.120 g, 0.62 mmol) and KHMD (0.81 mL, 0.81 mmol), afforded imidazo[1,5-a]pyridine 8f (0.099 g, 0.37 mmol) in 59% yield: IR (ATR) 3120, 1618, 1598, 1527 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.19 (s, 1H), 7.92 (d, \(J = 7.0\) Hz, 1H), 7.63 (dd, \(J = 7.7, 1.3\) Hz, 2H), 7.50 – 7.34 (m, S8
6-Fluoro-5-methyl-1-phenylimidazo[1,5-a]pyridine (8g) and 6-
Chloro-3-(isocyano(phenyl)methyl)-2-methylpyridine (8g’):
Following general procedure 2 with benzylisonitrile (0.054 g, 0.46 mmol), 2-chloro-5-fluoro-
6-methylpyridine (0.067 g, 0.46 mmol) and KHMDS (0.74 mL, 0.74 mmol), afforded imidazo[1,5-a]pyridine 8g (0.039 g, 0.175 mmol) in 38% yield and pyridine 8g’ (0.033 g, 0.14 mmol) in 30% yield. For 8g: IR (ATR) 3057, 2919, 1661, 1603 cm\(^{-1}\); \(^1\)H NMR (400 MHz, Chloroform-d) \(\delta\) 8.06 (s, 1H), 7.89 – 7.80 (m, 2H), 7.71 (dd, \(J = 9.9, 5.0\) Hz, 1H), 7.46 (t, \(J = 7.7\) Hz, 2H), 7.34 – 7.27 (m, 1H), 6.78 (dd, \(J = 9.8, 8.2\) Hz, 1H), 2.55 (d, \(J = 2.9\) Hz, 3H); \(^13\)C NMR (100 MHz, Chloroform-d) \(\delta\) 150.28 (d, \(J = 234.7\) Hz), 134.08 (d, \(J = 133.2\) Hz), 128.81, 126.80, 126.63, 125.87 (d, \(J = 3.5\) Hz), 125.11, 117.38, 117.02 (d, \(J = 9.9\) Hz), 112.90 (d, \(J = 28.3\) Hz), 10.56 (d, \(J = 1.4\) Hz); HRMS calculated for C\(_{14}\)H\(_{12}\)FN\(_2\)\(^+\) 227.0979, found 227.0980 (M+H\(^+\)). For 8g’: IR (ATR) 3068, 2135, 1582, 1563 cm\(^{-1}\); \(^1\)H NMR (400 MHz, Chloroform-d) \(\delta\) 7.66 (d, \(J = 8.2\) Hz, 1H), 7.43 – 7.34 (m, 3H), 7.30 – 7.25 (m, 3H), 6.05 (s, 1H), 2.50 (s, 3H); \(^13\)C NMR (100 MHz, Chloroform-d) \(\delta\) 159.54, 156.66, 150.61, 137.86, 135.13, 130.16, 129.30, 129.18, 126.72, 122.35, 58.26, 22.18; HRMS calculated for C\(_{14}\)H\(_{12}\)ClN\(_2\)\(^+\) 243.0684, found 243.0684 (M+H\(^+\)).

1-([1,1’-Biphenyl]-4-yl)-5-methylimidazo[1,5-a]pyridine (8h): Following general procedure 2 with 4-phenylbenzylisonitrile (0.052 g, 0.27 mmol), 2-
chloro-6-methylpyridine (0.034 g, 0.27 mmol) and KHMDS (0.35 mL, 0.35 mmol), afforded imidazo[1,5-a]pyridine 8h (0.069 g, 0.24 mmol) in 90% yield: IR (ATR) 3110, 3054, 1608, 1536 cm\(^{-1}\); \(^1\)H NMR (400 MHz, Chloroform-d) \(\delta\) 8.08 (d, \(J = 0.8\) Hz, 1H), 7.98 (d, \(J = 8.4\) Hz, 3H), 6.99 (d, \(J = 6.9\) Hz, 1H), 6.44 (t, \(J = 7.0\) Hz, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 134.74, 134.64, 131.54, 127.87, 127.43, 127.26, 124.40, 123.64, 121.68, 112.65; HRMS calculated for C\(_{13}\)H\(_{10}\)BrN\(_2\)\(^+\) 273.00219, found 273.00213 (M+H\(^+\)).
2H), 7.76 (d, J = 9.2 Hz, 1H), 7.73 – 7.61 (m, 4H), 7.44 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 6.77 (dd, J = 9.2, 6.5 Hz, 1H), 6.39 (d, J = 6.5 Hz, 1H), 2.54 (s, 3H); \(^{13}\)C NMR (100 MHz, Chloroform-\(d\)) \(\delta\) 140.93, 138.92, 134.39, 131.63, 131.49, 128.80, 127.41, 127.20, 127.14, 126.94, 126.77, 125.15, 120.49, 116.37, 112.00, 18.24; HRMS calculated for C\(_{20}\)H\(_{17}\)N\(_2\)\(^+\) 285.1385, found 285.1386 (M+H\(^+\)).

5-Methyl-1-(4-(trifluoromethoxy)phenyl)imidazo[1,5-a]pyridine (8i):

Following general procedure 2 with 4-trifluoromethoxybenzylisonitrile (0.066 g, 0.33 mmol), 2-chloro-6-methylpyridine (0.42 g, 0.33 mmol) and KHMS (0.43 mL, 0.43 mmol), afforded imidazo[1,5-a]pyridine 8i (0.081 g, 0.28 mmol) in 84% yield: IR (ATR) 3114, 1638, 1537, 1503 cm\(^{-1}\); \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 8.08 (s, 1H), 7.90 (d, \(J = 8.8\) Hz, 2H), 7.69 (d, \(J = 9.2\) Hz, 1H), 7.30 (d, \(J = 8.8\) Hz, 2H), 6.81 (dd, \(J = 9.2, 6.6\) Hz, 1H), 6.44 (d, \(J = 6.6\) Hz, 1H), 2.57 (s, 3H); \(^{13}\)C NMR (100 MHz, Chloroform-\(d\)) \(\delta\) 147.58 (q, \(J = 1.7\) Hz), 134.15, 131.58, 130.64, 127.56, 127.20, 125.18, 121.32, 120.86, 120.59 (q, \(J = 256.8\) Hz), 115.90, 112.04, 18.19; HRMS calculated for C\(_{15}\)H\(_{12}\)OF3N\(_2\)\(^+\) 293.0895, found 293.0896 (M+H\(^+\)).

1-(Furan-2-yl)-5-methylimidazo[1,5-a]pyridine (8j):

Following general procedure 2 with 2-isocyanomethylfuran (0.044 g, 0.41 mmol), 2-chloro-6-methylpyridine (0.052 g, 0.41 mmol) and KHMS (0.53 mL, 0.53 mmol), afforded imidazo[1,5-a]pyridine 8j (0.051 g, 0.26 mmol) in 63% yield: IR (ATR) 3123, 1643, 1612, 1539 cm\(^{-1}\); \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 8.00 (s, 1H), 7.87 (d, \(J = 9.2\) Hz, 1H), 7.49 (br d, \(J = 1.0\) Hz, 1H), 6.82- 6.75 (m, 1H), 6.75 (d, \(J = 3.3\) Hz, 1H), 6.52 (dd, \(J = 3.3, 1.8\) Hz, 1H), 6.41 (d, \(J = 6.5\) Hz, 1H), 2.55 (s, 3H); \(^{13}\)C NMR (100 MHz, Chloroform-\(d\)) \(\delta\) 151.17, 140.85, 131.12, 126.75, 125.06, 124.70, 120.40, 116.97, 112.28, 111.36, 103.93, 18.14; HRMS calculated for C\(_{12}\)H\(_{11}\)ON\(_2\)\(^+\) 199.0866, found 199.0866 (M+H\(^+\)).
5-Methyl-1-(5-methylfuran-2-yl)imidazo[1,5-a]pyridine (8k): Following general procedure 2 with 2-isocyanomethyl-5-methylfuran (0.047 g, 0.39 mmol), 2-chloro-6-methylpyridine (0.050 g, 0.39 mmol) and KHMDS (0.51 mL, 0.51 mmol), afforded imidazo[1,5-a]pyridine 8k (0.046 g, 0.22 mmol) in 56% yield: IR (ATR) 3108, 2920, 1618, 1643, 1584 cm⁻¹; ¹H NMR (400 MHz, Chloroform-d) δ 8.00 (s, 1H), 7.83 (d, J = 9.2 Hz, 1H), 6.77 (dd, J = 9.2, 6.5 Hz, 1H), 6.62 (d, J = 3.1 Hz, 1H), 6.41 (d, J = 6.5 Hz, 1H), 6.09 (br d, J = 3.1 Hz, 1H), 2.56 (s, 3H), 2.41 (s, 3H); ¹³C NMR (100 MHz, Chloroform-d) δ 150.71, 149.22, 131.02, 126.23, 125.00, 124.89, 119.93, 117.09, 112.19, 107.24, 104.90, 18.15, 13.78; HRMS calculated for C₁₃H₁₃ON₂⁺ 213.1022, found 213.1022 (M+H)⁺.

General procedure for the synthesis of imidazoles (General procedure 3). A hexanes solution of BuLi (1.1 equiv. 2.5 M) or a THF solution of KHMDS (1.3 equiv. 1.0 M) was added to a -78 °C THF solution (0.1 M) of the isonitrile (1.0 equiv.). After 5 min, a THF (0.5 M) solution of the imidoyl chloride was added. After 30 min, the reaction mixture was allowed to warm to rt. After 30 min, water was added and then the aqueous layer was extracted with EtOAc. The combined organic fractions were washed sequentially with water and brine, dried (Na₂SO₄), filtered, and then concentrated. The crude product was then purified by radial chromatography to afford pure imidazole.

1-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (9a): Following general procedure 3 with benzylisonitrile (0.054 g, 0.46 mmol), N-(4-chlorophenyl)benzimidoyl chloride (0.115 g, 0.46 mmol) and BuLi (0.20 mL, 0.51 mmol), afforded imidazole 9a (0.077 g, 0.23 mmol) in 50% yield: IR (ATR) 3049, 1601, 1498 cm⁻¹; ¹H NMR (400 MHz, Chloroform-d) δ 7.76 (s, 1H), 7.53 (d, J = 7.1 Hz, 2H), 7.35 – 7.18 (m, 8H), 7.18-7.12 (m, 2H), 7.05 (d, J = 8.6 Hz, 2H); ¹³C NMR (100 MHz, Chloroform-d) δ
139.18, 137.20, 134.95, 134.19, 133.86, 130.77, 129.80, 129.47, 128.77, 128.54, 128.35, 128.22, 127.22, 126.92, 126.81; HRMS calculated for C_{21}H_{16}ClN_2^+ 331.0997, found 331.0996 (M+H)^+.

1-Benzyl-4,5-diphenyl-1H-imidazole (9b): Following general procedure 3 with benzylisonitrile (0.054 g, 0.46 mmol), N-benzylbenzimidoyl chloride (0.106 g, 0.46 mmol) and BuLi (0.20 mL, 0.51 mmol), afforded imidazole 9b (0.087 g, 0.28 mmol) in 61% yield;^6 IR (ATR) 3062, 1603, 1506 cm⁻¹; ^1H NMR (400 MHz, Chloroform-d) δ 7.64 (s, 1H), 7.52 – 7.47 (m, 2H), 7.42 – 7.33 (m, 3H), 7.30 – 7.24 (m, 3H), 7.23 – 7.16 (m, 4H), 7.16 – 7.09 (m, 1H), 6.97 – 6.94 (m, 2H), 4.96 (s, 2H); ^13C NMR (100 MHz, Chloroform-d) δ 138.30, 137.14, 136.61, 134.54, 130.96, 130.55, 128.94, 128.83, 128.80, 128.73, 128.15, 127.92, 126.93, 126.52, 126.35, 48.77; HRMS calculated for C_{22}H_{19}N_2+ 311.1542, found 311.1543 (M+H)^+.

4-([1,1'-Biphenyl]-4-yl)-1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-imidazole (9c): Following general procedure 3 with 4-phenylbenzylisonitrile (0.052 g, 0.27 mmol), N-(4-chlorophenyl)-2,2,2-trifluoroacetimidoyl chloride (0.065 g, 0.27 mmol) and KHMDS (0.35 mL, 0.35 mmol), afforded imidazole 9c (0.064 g, 0.16 mmol) in 60% yield: IR (ATR) 3091, 1512, 1500 cm⁻¹; ^1H NMR (400 MHz, CDCl_3) δ 7.80 – 7.76 (m, 2H), 7.75 – 7.65 (m, 5H), 7.56 – 7.44 (m, 4H), 7.44 – 7.38 (m, 3H); ^13C NMR (100 MHz, CDCl_3) δ 145.08, 141.42, 140.59, 140.07, 135.83, 134.18, 131.51, 129.82, 129.41, 128.85, 127.54, 127.16, 126.99, 121.02 (t, J = 269.7 Hz), 117.66 (t, J = 38.4 Hz); HRMS calculated for C_{22}H_{19}N_2ClF_3^+ 399.0869, found 399.0870 (M+H)^+.

(E)-1-(4-Chlorophenyl)-5-phenyl-4-styryl-1H-imidazole (9d): Following general procedure 3 with (E)-(3-isocyanoprop-1-en-1-yl)benzene (0.051 g, 0.36 mmol), N-(4-chlorophenyl)-benzimidoyl chloride (0.089 g, 0.36
mmol) and KHMDS (0.46 mL, 0.46 mmol), afforded imidazole 9d (0.072 g, 0.21 mmol) in 57% yield: IR (ATR) 3039, 1598, 1494 cm⁻¹; ¹H NMR (500 MHz, Chloroform-d) δ 7.72 (s, 1H), 7.50 (d, J = 16.0 Hz, 1H), 7.46 (d, J = 7.3 Hz, 2H), 7.38 – 7.33 (m, 3H), 7.32-7.27 (m, 4H), 7.21 (br t, J = 7.3 Hz, 1H), 7.18-7.14 (m, 2H), 7.07 – 6.97 (m, 3H); ¹³C NMR (126 MHz, Chloroform-d) δ 138.38, 137.93, 137.66, 134.86, 133.82, 130.22, 130.07, 129.64, 128.71, 128.65, 128.58, 128.18, 127.25, 126.47, 126.44, 118.88; HRMS calculated for C₂₃H₁₈N₂Cl⁺ 357.11530, found 357.11546 (M+H)⁺.

5-Methyl-3-phenylimidazo[1,5-a]quinoline (10a): Following general procedure 2 with benzylisonitrile (0.054 g, 0.46 mmol), 2-chloro-4-methylquinoline (0.082 g, 0.46 mmol) and BuLi (0.20 mL, 0.51 mmol), afforded imidazo[1,5-a]quinoline 10a (0.098 g, 0.38 mmol) in 82% yield: IR (ATR) 3057, 1601, 1478 cm⁻¹; ¹H NMR (400 MHz, Chloroform-d) δ 8.54 (s, 1H), 7.90 – 7.84 (m, 3H), 7.70 (d, J = 8.0 Hz, 1H), 7.51 – 7.45 (m, 3H), 7.44 – 7.36 (m, 2H), 7.30 (br t, J = 7.4 Hz, 1H), 2.44 (s, 3H); ¹³C NMR (100 MHz, Chloroform-d) δ 135.02, 133.00, 131.00, 128.73, 128.49, 128.17, 127.12, 126.70, 126.58, 125.41, 125.38, 124.75, 124.55, 116.05, 114.52, 19.42; HRMS calculated for C₁₈H₁₄N₂Na⁺ 281.1049, found 281.1049 (M+Na)⁺.

8-([1,1'-Biphenyl]-4-yl)-2,4-dimethylimidazo[1,5-a]pyrimidine (11a): Following general procedure 2 with 4-phenylbenzylisonitrile (0.030 g, 0.16 mmol), 2-chloro-4,6-dimethyl pyrimidine (0.022 g, 0.16 mmol) and KHMDS (0.20 mL, 0.2 mmol), afforded imidazo[1,5-a]pyrimidine 11a (0.035 g, 0.12 mmol) in 76% yield: IR (ATR) 3049, 1557, 1499 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.49 (d, J = 8.2 Hz, 2H), 7.95 (s, 1H), 7.71-7.68 (m, 4H), 7.47-7.42 (m, 2H), 7.33 (t, J = 7.3 Hz, 1H), 6.33 (s, 1H), 2.56 (s, 3H), 2.55 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 155.85, 141.24, 138.98, 138.66, 135.24, 133.51,
128.75, 127.60, 127.12, 126.97, 126.92, 126.23, 121.61, 109.25, 25.02, 17.56; HRMS calculated for C_{20}H_{18}N_{3}^+ 300.1495, found 300.1495 (M+H)^+.

**Deuteo-5-methyl-1-phenylimidazo[1,5-a]pyridine (d-8b):** Following general procedure 3 with d_{2}-benzylisonitrile\(^7\) (10 mg, 0.085 mmol), 2-chloro-6-methylpyridine (11 mg, 0.085 mmol) and BuLi (0.04 mL, 0.094 mmol), afforded deuterated imidazo[1,5-a]pyridine (d-8b) (0.011g, 0.054 mmol) in 63% yield (\(^1\)H NMR integration indicated 22% deuteration at the imidazole carbon and 17% deuteration at the methyl group); IR (ATR) 3040, 1603, 1517, 1457 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.10 (s, 0.78H), 7.90 (d, \(J = 7.3\) Hz, 2H), 7.75 (d, \(J = 9.2\) Hz, 1H), 7.49 - 7.41 (m, 2H), 7.28 (t, \(J = 7.4\) Hz, 1H), 6.79 (dd, \(J = 9.2, 6.5\) Hz, 1H), 6.43 (d, \(J = 6.5\) Hz, 1H), 2.60 – 2.55 (m, 2.5H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 135.25 (br), 132.06, 131.41, 128.73, 127.07, 126.57, 126.38, 125.03, 120.33, 116.37, 111.95, 18.25, 18.00 (t, \(J = 19.7\) Hz); HRMS calculated for C\(_{14}\)H\(_{13}\)N\(_2\)\(^+\) 209.1073, found 209.1073 (M+H)^+; for C\(_{14}\)H\(_{12}\)D\(_2\)N\(_2\)\(^+\) 210.1136, found 210.1136 (M+H)^+; for C\(_{14}\)H\(_{10}\)D\(_3\)N\(_2\)\(^+\) 212.1262, found 212.1261 (M+H)^+.
HRMS spectra for deuteo-5-methyl-1-phenylimidazo[1,5-a]pyridine (d-8b)
Figure S1. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for 4-(Isocyanomethyl)-1,1'-biphenyl (6b)

Figure S2. $^{13}$C NMR spectrum (CDCl$_3$, 100 MHz) for 4-(Isocyanomethyl)-1,1'-biphenyl (6b)
Figure S3. $^1$H NMR spectrum (CDCl$_3$, 500 MHz) for 1-(Isocyanomethyl)-4-(trifluoromethoxy)benzene (6c)

Figure S4. $^{13}$C NMR spectrum (CDCl$_3$, 126 MHz) for 1-(Isocyanomethyl)-4-(trifluoromethoxy)benzene (6c)
Figure S5. $^1$H NMR spectrum (CDCl$_3$, 500 MHz) for 2-(Isocyanomethyl)furan (6d)
Figure S6. $^1$H NMR spectrum (CDCl$_3$, 500 MHz) for 2-(Isocyanomethyl)-5-methylfuran (6e)

Figure S7. $^{13}$C NMR spectrum (CDCl$_3$, 126 MHz) for 2-(Isocyanomethyl)-5-methylfuran (6e)
Figure S8. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for \((E)-(3$-isocyanoprop-1-en-1-yl)benzene\) (6f).

Figure S9. $^{13}$C NMR spectrum (CDCl$_3$, 100 MHz) for \((E)-(3$-isocyanoprop-1-en-1-yl)benzene\) (6f).
Figure S10. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for 1-Phenylimidazo[1,5-a]pyridine (8a)

Figure S11. $^{13}$C NMR spectrum (CDCl$_3$, 126 MHz) for 1-Phenylimidazo[1,5-a]pyridine (8a)
Figure S12. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for 5-Methyl-1-phenylimidazo[1,5-a]pyridine (8b)

Figure S13. $^{13}$C NMR spectrum (CDCl$_3$, 100 MHz) for 5-Methyl-1-phenylimidazo[1,5-a]pyridine (8b)
Figure S14. $^1$H NMR spectrum (CDCl$_3$, 500 MHz) for 5,7-Dimethyl-1-phenylimidazo[1,5-a]pyridine (8c)

Figure S15. $^{13}$C NMR spectrum (CDCl$_3$, 126 MHz) for 5,7-Dimethyl-1-phenylimidazo[1,5-a]pyridine (8c)
Figure S16. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for 7-Methyl-1-phenylimidazo[1,5-a]pyridine (8d)

Figure S17. $^{13}$C NMR spectrum (CDCl$_3$, 100 MHz) for 7-Methyl-1-phenylimidazo[1,5-a]pyridine (8d)
Figure S18. $^1$H NMR spectrum (CDCl$_3$, 500 MHz) for 6-Bromo-5-methyl-1-phenylimidazo[1,5-a]pyridine (8e)

Figure S19. $^{13}$C NMR spectrum (CDCl$_3$, 126 MHz) for 6-Bromo-5-methyl-1-phenylimidazo[1,5-a]pyridine (8e)
Figure S20. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for 8-Bromo-1-phenylimidazo[1,5-a]pyridine (8f)

Figure S21. $^{13}$C NMR spectrum (CDCl$_3$, 100 MHz) for 8-Bromo-1-phenylimidazo[1,5-a]pyridine (8f)
Figure S22. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for 6-Fluoro-5-methyl-1-phenylimidazo[1,5-a]pyridine (8g)

Figure S23. $^{13}$C NMR spectrum (CDCl$_3$, 100 MHz) for 6-Fluoro-5-methyl-1-phenylimidazo[1,5-a]pyridine (8g)
Figure S24. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for 6-Chloro-3-(isocyano(phenyl)methyl)-2-methylpyridine ($8g'$)

Figure S25. $^{13}$C NMR spectrum (CDCl$_3$, 100 MHz) for 6-Chloro-3-(isocyano(phenyl)methyl)-2-methylpyridine ($8g'$)
Figure S26. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for 1-([1,1'-Biphenyl]-4-yl)-5-methylimidazo[1,5-a]pyridine (8h)

Figure S27. $^{13}$C NMR spectrum (CDCl$_3$, 100 MHz) for 1-([1,1'-Biphenyl]-4-yl)-5-methylimidazo[1,5-a]pyridine (8h)
Figure S28. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for 5-Methyl-1-(4-(trifluoromethoxy)phenyl)imidazo[1,5-a]pyridine (8i).

Figure S29. $^{13}$C NMR spectrum (CDCl$_3$, 100 MHz) for 5-Methyl-1-(4-(trifluoromethoxy)phenyl)imidazo[1,5-a]pyridine (8i).
Figure S30. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for 1-(Furan-2-yl)-5-methylimidazo[1,5-a]pyridine (8j).

Figure S31. $^{13}$C NMR spectrum (CDCl$_3$, 100 MHz) for 1-(Furan-2-yl)-5-methylimidazo[1,5-a]pyridine (8j).
Figure S3. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for 5-Methyl-1-(5-methylfuran-2-yl)imidazo[1,5-a]pyridine (8k)

Figure S33. $^{13}$C NMR spectrum (CDCl$_3$, 100 MHz) for 5-Methyl-1-(5-methylfuran-2-yl)imidazo[1,5-a]pyridine (8k)
Figure S34. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for 1-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (9a)

Figure S35. $^{13}$C NMR spectrum (CDCl$_3$, 100 MHz) for 1-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (9a)
Figure S36. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for 1-Benzyl-4,5-diphenyl-1H-imidazole (9b)

Figure S37. $^{13}$C NMR spectrum (CDCl$_3$, 100 MHz) for 1-Benzyl-4,5-diphenyl-1H-imidazole (9b)
Figure S38. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for 4-([1,1'-Biphenyl]-4-yl)-1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-imidazole (9c)

Figure S39. $^{13}$C NMR spectrum (CDCl$_3$, 100 MHz) for 4-([1,1'-Biphenyl]-4-yl)-1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-imidazole (9c)
Figure S40. $^1$H NMR spectrum (CDCl$_3$, 500 MHz) for (E)-1-(4-Chlorophenyl)-5-phenyl-4-styryl-1H-imidazole (9d)

Figure S41. $^{13}$C NMR spectrum (CDCl$_3$, 126 MHz) for (E)-1-(4-Chlorophenyl)-5-phenyl-4-styryl-1H-imidazole (9d)
Figure S4. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for 5-Methyl-3-phenylimidazo[1,5-a]quinolone (10a)

Figure S3. $^{13}$C NMR spectrum (CDCl$_3$, 100 MHz) for 5-Methyl-3-phenylimidazo[1,5-a]quinolone (10a)
Figure S4. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for 8-([1,1'-Biphenyl]-4-yl)-2,4-dimethylimidazo[1,5-a]pyrimidine (11a)

Figure S4. $^{13}$C NMR spectrum (CDCl$_3$, 100 MHz) for 8-([1,1'-Biphenyl]-4-yl)-2,4-dimethylimidazo[1,5-a]pyrimidine (11a)
Figure S46. $^1$H NMR spectrum (CDCl$_3$, 400 MHz) for deuterated 1-Phenylimidazo[1,5-a]pyridine (d-8b)

Figure S47. $^{13}$C NMR spectrum (CDCl$_3$, 100 MHz) for deuterated 1-Phenylimidazo[1,5-a]pyridine (d-8b)


5 The data is similar to that previously reported: M.-S. Yu, W.-C. Lee, Chih-Hao Chen, F.-Y. Tsai, T.-G. Ong. Org. Lett. 2014, 16, 4826–4829.
