A Convenient Preparation of a Novel Class of Imidazo[1,5-a]pyridines: Decisive Role by Ammonium Acetate in Chemoselectivity

Jie Wang,[†] Richard Mason,[†] Donald VanDerveer,[‡] Ke Feng,[†] Xiu R. Bu^{†*}

Experimental Section

General. All the reactions were manipulated in nitrogen atmosphere. All chemicals were used as received. Thin-layer chromatography was carried out on 250 μ m silica gel plates containing a fluorescent indicator. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were recorded using TMS as reference, and reported as ppm for chemical shifts. The combustion analysis was performed in Atlantic Microlab, Norcross, Georgia. MS spectra were obtained in an EI mode. IR spectra were obtained on KBr pellets. Melting points were uncorrected. The x-ray structural determination used 1K CCD diffractometer with graphite-monochromated Mo-K α at 298 K.

2-(4-ethyl)-4,5-di(2-pyridyl)imidazole (2c), recrystallized from EtOAc/hexane (5:1, v/v). Yellow crystal, mp. 154-155 °C. IR (KBr) $\nu_{\max}$ 3394.5 (N-H) cm⁻¹. ¹H NMR (CDCl₃) δ 11.19 (br, 1H), 8.68 (br, 2H), 8.52 (br, 1H), 8.16 (br, 1H), 7.94 (d, 2H, J = 7.9 Hz), 7.80 (br, 1H), 7.66 (br, 1H), 7.27 (d, 2H, J = 7.9 Hz), 7.22 (m, 1H), 7.14 (br, 1H), 2.69 (q, 2H, J = 7.5 Hz), 1.26 (t, 3H, 7.5 Hz). ¹³C NMR(CDCl₃): δ 155.0, 148.6, 148.4, 146.2, 145.3, 140.0, 136.7, 136.5, 128.4, 128.2, 127.0, 125.7, 125.5, 123.4, 122.0, 28.6, 15.2. MS (EI): 326 (M⁺). Anal. Calcd for C₂₁H₁₈N₄: C, 77.28; H, 5.56; N, 17.16. Found: C, 77.05; H, 5.53; N, 17.13.

2-(4-isopropyl)-4,5-di(2-pyridyl)imidazole (2d), recrystallized from benzene/hexane (5/1, v/v). Yellow crystal, mp. 152-153 °C. IR (KBr) $\nu_{\max}$ 3356.1 (N-H) cm⁻¹. ¹H NMR (CDCl₃) δ 11.17 (br, 1H), 8.68 (br, 2H), 8.53 (br, 1H), 8.16 (br, 1H), 7.92 (d, 2H, J = 8.2 Hz), 7.80 (br, 1H), 7.67 (br, 1H), 7.30 (d, 2H, J = 8.2 Hz), 7.25 (m, 1H), 7.14 (br, 1H), 2.95 (septet, 1H, J = 6.9 Hz), 1.28 (d, 6H, J = 6.9 Hz). ¹³C NMR(CDCl₃): δ 155.0, 149.9, 148.6, 148.4, 146.2, 139.7, 136.5, 130.0, 127.1, 127.0,

125.7, 125.5, 123.5, 122.4, 121.9, 33.9, 23.9. MS (EI): 340 (M^+). Anal. Calcd for $C_{22}H_{20}N_4$: C, 77.63; H, 5.92; N, 16.45. Found: C, 77.50; H, 5.86; N, 16.47.

2-(4-chloro)-4,5-di(2-pyridyl)imidazole (2f), recrystallized from EtOAc.

Yellow crystal, mp. 178-179 °C. IR (KBr) $\nu_{\max}$ 3338.0 (N-H) cm^{-1} . ^1H NMR (CDCl_3) δ 11.55 (s, 1H), 8.64 (br. 2H), 8.48 (br, 1H), 8.12 (br., 1H), 7.91 (dd, 2H, $J = 7.2$ Hz, $J' = 1.7$ Hz), 7.79 (br, 1H), 7.57 (br, 1H), 7.38 (dd, 2H, $J = 7.2$ Hz, $J' = 1.7$ Hz), 7.37 (m, 1H), 7.16 (br, 1H); ^{13}C NMR 154.18, 148.30, 145.169, 139.90, 136.61, 134.76, 129.65, 129.13, 128.94, 128.67, 128.08, 126.92, 126.72, 123.26, 122.83, 122.36, 122.16. MS (EI): 332 (M^+). Anal. Calcd for $C_{19}H_{13}\text{ClN}_4$: C, 68.58; H, 3.94; N, 16.83. Found: C, 68.31; H, 3.97; N, 16.80.

Fig. S1 The molecular structure of **1a**.

Table S1. Crystal and experimental data

Formula: C₁₉ H₁₃ N₃ O
Formula weight: 299.32
Crystal size: 0.61 × 0.24 × 0.20 mm
Crystal system: Orthorhombic
Space group: *Pbca* Z=8
a = 12.2550(6) Å
b = 7.6660(4) $\alpha=\beta=\gamma=90^\circ$
c = 31.2543(16) *T* = 303(2) K
V = 2936.2(3) Å³
D_x = 1.354 g/cm³
R(*F*) = 0.0419, *wR*(*F*²) = 0.1216
Goodness of fit: 1.051
(Δ/σ)_{max} = 0.043
($\Delta\rho$)_{max} = 0.218 eÅ³
($\Delta\rho$)_{min} = -0.170 eÅ³
No. of reflections used: total, 3578 (unique, 2580)
Measurements: Bruker 1K CCD diffractometer
Radiation type: Mo-K α
Program system: SHELX-Plus
Structure determination: direct methods (SHELX97)
Refinement: full-matrix least-squares (SHELXL-97)

Table S2. Atomic Coordinates and Temperature Factors

<i>atom</i>	<i>X</i>	<i>Y</i>	<i>Z</i>	<i>U</i> _{eq}
C1	0.42451(10)	-0.08062(17)	0.59238(4)	0.0372(3)
N2	0.45833(8)	-0.01415(14)	0.63100(3)	0.0394(3)
C3	0.37016(10)	0.02923(17)	0.65243(4)	0.0378(3)
N4	0.27656(8)	-0.00588(14)	0.62853(3)	0.0365(3)
C5	0.16717(11)	0.02764(18)	0.63639(5)	0.0439(3)
C6	0.09245(11)	-0.0188(2)	0.60694(5)	0.0507(4)
C7	0.12419(11)	-0.1007(2)	0.56828(5)	0.0518(4)
C8	0.23153(11)	-0.12821(18)	0.55967(4)	0.0438(3)
C9	0.31089(10)	-0.07729(16)	0.58990(4)	0.0359(3)
C10	0.49730(11)	-0.14878(18)	0.55977(4)	0.0404(3)
O11	0.46389(8)	-0.18858(17)	0.52405(3)	0.0620(3)
C12	0.61681(10)	-0.17183(17)	0.56940(4)	0.0374(3)
C13	0.69217(11)	-0.1182(2)	0.53905(4)	0.0449(3)
C14	0.80171(12)	-0.1447(2)	0.54720(5)	0.0517(4)
C15	0.83114(11)	-0.2267(2)	0.58442(5)	0.0508(4)
C16	0.75072(12)	-0.2774(2)	0.61237(5)	0.0519(4)
N17	0.64403(9)	-0.25025(16)	0.60600(4)	0.0464(3)
C18	0.37091(11)	0.09850(17)	0.69614(4)	0.0410(3)
C19	0.45710(12)	0.2050(2)	0.70866(5)	0.0514(4)
C20	0.46568(15)	0.2604(2)	0.75040(6)	0.0645(5)
C21	0.38946(16)	0.2125(3)	0.78053(6)	0.0706(5)
C22	0.30382(15)	0.1074(3)	0.76858(5)	0.0680(5)
C23	0.29425(12)	0.0496(2)	0.72669(5)	0.0529(4)
H5	0.1450	0.0832	0.6625	0.047(4)
H6	0.0166	0.0040	0.6122	0.056(4)
H7	0.0697	-0.1370	0.5481	0.068(5)
H8	0.2532	-0.1818	0.5332	0.053(4)
H13	0.6688	-0.0639	0.5129	0.052(4)
H14	0.8561	-0.1065	0.5272	0.061(5)
H15	0.9066	-0.2482	0.5908	0.059(4)
H16	0.7724	-0.3361	0.6381	0.069(5)
H19	0.5109	0.2401	0.6881	0.054(4)
H20	0.5257	0.3335	0.7586	0.078(6)
H21	0.3960	0.2520	0.8096	0.094(6)
H22	0.2502	0.0737	0.7894	0.088(6)
H23	0.2344	-0.0244	0.7187	0.064(5)

Table S3. Bond Distances (Å)

C1-N2 1.3744(16)	C12-N17 1.3347(17)
C1-C9 1.3948(17)	C12-C13 1.3863(18)
C1-C10 1.4517(18)	C13-C14 1.3814(19)
N2-C3 1.3140(16)	C14-C15 1.370(2)
C3-N4 1.3951(16)	C15-C16 1.373(2)
C3-C18 1.4657(19)	C16-N17 1.3389(18)
N4-C5 1.3870(17)	C18-C23 1.391(2)
N4-C9 1.3906(16)	C18-C19 1.3914(19)
C5-C6 1.346(2)	C19-C20 1.376(2)
C6-C7 1.416(2)	C20-C21 1.376(3)
C7-C8 1.359(2)	C22-C23 1.387(2)
C8-C9 1.4109(18)	C21-C22 1.375(3)
C10-O11 1.2275(16)	C10-C12 1.5056(18)

Table S4. Bond Angles (°)

N2 C1 C9	110.06(11)	O11 C10 C12	118.49(12)
N2 C1 C10	124.39(11)	C1 C10 C12	119.98(11)
C9 C1 C10	125.53(12)	N17 C12 C13	123.61(12)
C3 N2 C1	107.06(10)	N17 C12 C10	117.86(11)
N2 C3 N4	110.76(11)	C13 C12 C10	118.46(12)
N2 C3 C18	124.16(11)	C14 C13 C12	118.52(14)
N4 C3 C18	125.04(11)	C15 C14 C13	118.68(13)
C5 N4 C9	121.28(11)	C14 C15 C16	118.74(13)
C5 N4 C3	131.61(12)	N17 C16 C15	124.21(14)
C9 N4 C3	106.98(10)	C12 N17 C16	116.21(12)
C6 C5 N4	119.16(14)	C23 C18 C19	118.53(13)
C5 C6 C7	120.92(13)	C23 C18 C3	122.55(12)
C8 C7 C6	120.23(13)	C19 C18 C3	118.66(12)
C7 C8 C9	119.45(14)	C20 C19 C18	120.39(15)
N4 C9 C1	105.13(10)	C19 C20 C21	120.97(16)
N4 C9 C8	118.79(11)	C22 C21 C20	119.25(16)
C1 C9 C8	136.07(12)	C21 C22 C23	120.53(16)
O11 C10 C1	121.53(12)	C22 C23 C18	120.33(15)