Oxidative Aromatization of 1,3,5-Trisubstituted Pyrazolines and Hantzsch 1,4-Dihydropyridines by Pd/C in Acetic Acid

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Supporting Information

General methods. All melting points were measured on a Yanaco MP-500D and uncorrected. ^1H and ^{13}C NMR spectra (400 and 100.6 MHz, respectively), were recorded on a Varian UNITY INOVA 400 or a JEOL JNM-LA 400 using Me_4Si as the internal standard in CDCl_3 . IR spectra were measured on a Horiba FT-710 or a Perkin-Elmer Spectrum 1000. Elemental analyses were performed on a Yanaco CHN Corder MT-5. Mass spectra were measured on a Shimadzu GCMS-QP 2000A. Preparative-column chromatography was carried out on Fuji–Devision BW-820. Thin-layer chromatography (TLC) was carried out on foil plates, Silica Gel 60 F₂₅₄ (E. Merck; layer thickness 0.2 mm).

Typical procedure is as follows (entry 1 in Table 1): The 200 mL flask was charged with 1,3,5-triphenylpyrazoline (**1**) 1.02 g (3.42 mmol), acetic acid (15 mL), and the 200 mg (20 weight%) of 10% Pd/C. The whole was warmed to 80 °C and stirred for 6.5 h at this temperature. After confirmation of the consumption by TLC analysis, Pd/C was filtered off using Celite. The filtrate was then poured into satd. NaHCO_3 and extracted with ethyl acetate (40 mL x 3). After usual work-up, the obtained residue was column chromatographed on silica-gel to afford 1,3,5-triphenylpyrazole (**7**) 0.87 g (86%) as a pale yellow solid. mp 141–142 °C (lit.⁸ 138–139 °C).

1,3,5-triphenylpyrazole (**7**)

R_f 0.28 (30:1 hexane–ethyl acetate); mp 141–142 °C; IR (KBr): ν_{max} (cm^{-1}) 3119, 3060, 1624, 1596, 1546, 1496, 1482, 1456, 1434, 1415, 1362, 1311, 1284, 1214, 1173, 1066, 1020, 1000, 972, 957; ^1H NMR (400 MHz, CDCl_3): δ 6.83 (s, 1H, H_4), 7.3–7.5 (m, 13H, Ar-H), 7.93 (d, 2H, $J = 7.7$ Hz, H_7 , H_{11}); ^{13}C NMR (100.6 MHz, CDCl_3): δ 105.1 (C-4), 125.2, 125.7, 127.3, 127.9, 128.2, 128.4, 128.6, 128.7, 128.8, 130.5, 133.0, 140.0, 144.3, 151.9. MS m/z (relative intensity): 297 (21.8%), 296 (100%), 295 (61.5%), 77 (48.5%), 51 (27.1%). Anal. Calcd for $\text{C}_{21}\text{H}_{16}\text{N}_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 85.41; H, 5.50; N, 9.20.

1,3-diphenyl-5-(4-methoxyphenyl)pyrazole (8)

8

R_f 0.28 (10:1 hexane–ethyl acetate); mp 79–80 °C; IR (KBr): $\nu_{\max}$ (cm⁻¹) 2835, 1613, 1596, 1519, 1496, 1457, 1362, 1295, 1251, 1175, 1111, 1074, 1030, 971, 913, 835, 798, 767, 693, 593; ¹H NMR (400 MHz, CDCl₃): δ 3.81 (s, 3H, CH₃O), 6.77 (s, 1H, H₄), 6.85 (d, 2H, J = 8.5 Hz, H₂₀, H₂₂), 7.2–7.4 (m, 10H, Ar-H), 7.92 (d, 2H, J = 7.7 Hz, H₇, H₁₁); ¹³C NMR (100.6 MHz, CDCl₃): δ 55.2 (CH₃O), 104.7 (C-4), 113.9, 122.9, 125.3, 125.7, 127.3, 127.9, 128.6, 128.9, 130.0, 133.1, 140.2, 144.2, 151.8, 159.5. MS m/z (relative intensity): 327 (22.4%), 326 (100%), 325 (23.9%), 311 (18.0%), 77 (33.8%). Anal. Calcd for C₂₂H₁₈N₂O: C, 80.96; H, 5.56; N, 8.58. Found: C, 81.02; H, 5.56; N, 8.53.

5-(4-chlorophenyl)-1,3-diphenylpyrazole (9)

9

R_f 0.35 (15:1 hexane–ethyl acetate); mp 114–115 °C; IR (KBr): $\nu_{\max}$ (cm⁻¹) 3052, 1595, 1497, 1484, 1424, 1391, 1360, 1211, 1175, 1092, 1014, 970, 917, 830, 806, 767, 691, 596, 537, 502; ¹H NMR (400 MHz, CDCl₃): δ 6.82 (s, 1H, H₄), 7.2–7.5 (m, 12H, Ar-H), 7.91 (d, 2H, J = 7.7 Hz, H₇, H₁₁); ¹³C NMR (100.6 MHz, CDCl₃): δ 105.2 (C-4), 125.3, 125.8, 127.6, 128.1, 128.6, 128.7, 128.9, 129.0, 129.9, 132.8, 134.3, 139.8, 143.1, 152.0. MS m/z (relative intensity): 332 (34.6%), 331 (39.6%), 330 (100%), 329 (53.3%), 77 (67.1%), 51 (38.9%). Anal. Calcd for C₂₁H₁₅ClN₂: C, 76.24; H, 4.57; N, 8.47. Found: C, 76.21; H, 4.57; N, 8.46.

1,3-diphenyl-5-(4-nitrophenyl)pyrazole (10)

10

R_f 0.31 (8:1 hexane–ethyl acetate); mp 142–144 °C; IR (KBr): $\nu_{\max}$ (cm⁻¹) 3062, 1596, 1548, 1496, 1457, 1427, 1339, 1290, 1262, 1176, 1108, 972, 853, 809, 769, 753, 695, 671, 596, 491; ¹H NMR (400 MHz, CDCl₃): δ 6.94 (s, 1H, H₄), 7.3–7.5 (m, 10H, Ar-H), 7.92 (d, 2H, J = 7.7 Hz, H₇, H₁₁), 8.18 (d, 2H, J = 8.5 Hz, H₂₀, H₂₂); ¹³C NMR (100.6 MHz, CDCl₃): δ 106.1 (C-4), 123.7, 125.3, 125.7, 128.1, 128.2, 128.6, 129.1, 129.2, 132.3, 136.5, 139.4, 141.8, 147.1, 152.2. MS m/z (relative intensity): 341 (100%), 340 (32.8%), 294 (30.1%), 77 (36.9%), 51 (21.8%). Anal. Calcd for C₂₁H₁₅N₃O₂: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.64; H, 4.42; N, 12.15.

5-(2-furyl)-3-(4-methylphenyl)-1-phenylpyrazole (**11**)

11

R_f 0.30 (15:1 hexane–ethyl acetate); mp 96–98 °C; IR (KBr): $\nu_{\max}$ (cm⁻¹) 2918, 2387, 2349, 1596, 1503, 1474, 1450, 1352, 1179, 1152, 1114, 1064, 1015, 989, 957, 895, 845, 819, 781; ¹H NMR (400 MHz, CDCl₃): δ 2.38 (s, 3H, CH₃), 5.97 (d, 1H, $J_{\text{H19-20}}$ = 3.4 Hz, H₁₉), 6.33 (dd, 1H, $J_{\text{H19-20}}$ = 3.4 Hz, $J_{\text{H20-21}}$ = 3.4 Hz, H₂₀), 6.95 (s, 1H, H₄), 7.23 (d, 2H, J = 8.5 Hz, H₁₄, H₁₆), 7.4–7.5 (m, 4H, Ar-H), 7.79 (d, 2H, J = 8.1 Hz, H₇, H₁₁); ¹³C NMR (100.6 MHz, CDCl₃): δ 21.3 (CH₃), 103.1 (C-4), 108.8 (C-19), 111.2 (C-20), 125.7, 128.4, 129.1, 129.9, 135.6, 137.8, 140.2, 142.5, 144.5, 152.0. MS m/z (relative intensity): 301 (22.6%), 300 (100%), 299 (20.2%), 77 (38.8%), 51 (22.4%). Anal. Calcd for C₂₀H₁₆N₂O: C, 79.98; H, 5.37; N, 9.33. Found: C, 80.02; H, 5.47; N, 9.21.

3-(4-chlorophenyl)-1-phenyl-5-(2-thienyl)pyrazole (**12**)

12

R_f 0.28 (30:1 hexane–ethyl acetate); mp 134–135 °C; IR (KBr): $\nu_{\max}$ (cm⁻¹) 3095, 3070, 3052, 1951, 1810, 1753, 1677, 1597, 1561, 1520, 1494, 1437, 1402, 1351, 1292, 1225, 1206, 1155, 1091, 1065; ¹H NMR (400 MHz, CDCl₃): δ 6.81 (s, H, H₄), 7.2–7.5 (m, 10H, Ar-H), 7.91 (d, 2H, J = 7.7 Hz, H₇, H₁₁); ¹³C NMR (100.6 MHz, CDCl₃): δ 105.2 (C-4), 125.3, 125.3, 125.8, 127.6, 128.1, 128.7, 128.8, 129.9, 132.8, 134.3, 139.8, 143.1, 152.0. MS m/z (relative intensity): 337 (33.6%), 336 (100%), 335 (33.1%), 77 (44.9%), 51 (25.1%). Anal. Calcd for C₁₉H₁₃ClN₂S: C, 67.75; H, 3.89; N, 8.32. Found: C, 67.78; H, 3.92; N, 8.32.

diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate (**19**)

19

R_f 0.35 (8:1 hexane–ethyl acetate); mp 71–72 °C; IR (KBr): $\nu_{\max}$ (cm⁻¹) 2986, 2978, 2930, 2912, 1718, 1591, 1555, 1548, 1444, 1380, 1368, 1297, 1254, 1223, 1205, 1123, 1109, 1044, 1025, 771; ¹H NMR (400 MHz, CDCl₃): δ 1.41 (t, 6H, $J_{\text{H9-H10}}$ = 7.3 Hz, H₁₀), 2.84 (s, 6H, H₇), 4.40 (q, 4H, $J_{\text{H9-H10}}$ = 7.3 Hz, H₉), 8.67 (s, 1H, H₄); ¹³C NMR (100.6 MHz, CDCl₃): δ 14.3 (C-10), 25.0 (C-7), 61.4 (C-9), 123.0 (C-3 and C-5), 140.9 (C-4), 162.2 (C-2 and C-6), 165.9 (C-8). MS m/z (relative intensity): 251 (39.8%), 206 (100%), 195 (19.6%), 178 (53.8%), 150 (29.0%), 106 (21.6%). Anal. Calcd for C₁₃H₁₇NO₄: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.04; H, 6.92; N, 5.54.

diethyl 2,4,6-trimethyl-3,5-pyridinedicarboxylate (**20**)

R_f 0.24 (6:1 hexane–ethyl acetate); IR (KBr): $\nu_{\max}$ (cm^{-1}) 2982, 2936, 2907, 2875, 1723, 1571, 1447, 1411, 1378, 1285, 1241, 1221, 1173, 1107, 1042, 938, 858, 837, 778, 569; ^1H NMR (400 MHz, CDCl_3): δ 1.39 (t, 6H, $J_{\text{H}_9-\text{H}_{10}} = 7.3$ Hz, H_{10}), 2.27 (s, 3H, H_{11}), 2.52 (s, 6H, H_7), 4.41 (q, 4H, $J_{\text{H}_9-\text{H}_{10}} = 7.3$ Hz, H_9); ^{13}C NMR (100.6 MHz, CDCl_3): 14.0 (C-10), 16.8 (C-11), 22.8 (C-7), 61.4 (C-9), 127.4 (C-3 and C-5), 141.9 (C-4), 154.7 (C-2 and C-6), 168.2 (C-8). MS m/z (relative intensity): 265 (31.4%), 236 (45.9%), 220 (100%), 208 (43.2%), 192 (25.9%), 77 (34.5%). Anal. Calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.21; H, 7.33; N, 5.19.

diethyl 4-phenyl-2,6-dimethyl-3,5-pyridinedicarboxylate (**21**)

R_f 0.24 (6:1 hexane–ethyl acetate); mp 60–61°C; IR (KBr): $\nu_{\max}$ (cm^{-1}) 3000, 2980, 2953, 2933, 1732, 1713, 1557, 1466, 1377, 1299, 1227, 1211, 1172, 1099, 1042, 861, 771, 755, 705; ^1H NMR (400 MHz, CDCl_3): δ 0.90 (t, 6H, $J_{\text{H}_9-\text{H}_{10}} = 7.3$ Hz, H_{10}), 2.60 (s, 6H, H_7), 4.00 (q, 4H, $J_{\text{H}_9-\text{H}_{10}} = 7.3$ Hz, H_9), 7.2–7.4 (m, 5H, H_{12} , H_{13} and H_{14}); ^{13}C NMR (100.6 MHz, CDCl_3): 13.4 (C-10), 22.8 (C-7), 61.2 (C-9), 126.8, 127.9, 128.0, 128.3, 136.4, 146.0 (C-3, C-5, C-4, C-11, C-12, C-13 and C-14), 155.3 (C-2 and C-6), 167.7 (C-8). MS m/z (relative intensity): 327 (71.2%), 282 (48.1%), 254 (42.4%), 236 (100%), 209 (29.4%), 139 (33.8%). Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.56; H, 6.49; N, 4.33.

diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**22**)

R_f 0.26 (2:1 hexane–ethyl acetate); mp 174–176 °C; IR (KBr): $\nu_{\max}$ (cm^{-1}) 3454, 2985, 2927, 2349, 1741, 1720, 1613, 1588, 1572, 1558, 1514, 1442, 1334, 1299, 1281, 1239, 1215, 1166, 1110, 1101; ^1H NMR (400 MHz, CDCl_3): δ 1.00 (t, 6H, $J_{\text{H}_9-\text{H}_{10}} = 7.2$ Hz, H_{10}), 2.63 (s, 6H, H_7), 4.06 (q, 4H, $J_{\text{H}_9-\text{H}_{10}} = 7.2$ Hz, H_9), 5.89 (br s, 1H, OH), 7.1–7.3 (m, 4H, H_{12} and H_{13}); ^{13}C NMR (100.6 MHz, CDCl_3): 13.7 (C-10), 22.6 (C-7), 61.5 (C-9), 115.2 (C-12), 127.4, 128.0, 129.5 (C-3, C-5, C-11 and C-13), 146.0 (C-4), 155.1, 156.5 (C-2, C-6 and C-14), 168.2 (C-8). MS m/z (relative intensity): 343 (100%), 297 (17.9%), 269 (56.6%), 252 (87.0%), 225 (21.8%), 121 (21.1%). Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.61; H, 6.19; N, 4.16.

diethyl 4-(4-nitrophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**23**)

R_f 0.25 (5:1 hexane–ethyl acetate); mp 115–116 °C; IR (KBr): $\nu_{\max}$ (cm⁻¹) 3113, 2979, 2928, 1722, 1602, 1558, 1518, 1350, 1315, 1229, 1216, 1118, 1107, 1045, 865, 843, 800, 748, 703, 663; ¹H NMR (400 MHz, CDCl₃): δ 0.98 (t, 6H, J_{H9-H10} = 7.3 Hz, H₁₀), 2.63 (s, 6H, H₇), 4.03 (q, 4H, J_{H9-H10} = 7.3 Hz, H₉), 7.4–7.5 (m, 2H, H₁₂), 8.2–8.3 (m, 2H, H₁₃); ¹³C NMR (100.6 MHz, CDCl₃): 13.7 (C-10), 23.1 (C-7), 61.7 (C-9), 123.2, 126.1, 129.3 (C-3, C-5, C-12 and C-13), 143.3, 143.9, 147.7 (C-4, C-11 and C-14), 156.1 (C-2 and C-6), 167.1 (C-8). MS m/z (relative intensity): 372 (48.8%), 355 (29.5%), 327 (100%), 299 (39.5%), 281 (32.5%), 139 (23.2%). Anal. Calcd for C₁₉H₂₀N₂O₆: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.43; H, 5.46; N, 7.55.