New one-pot synthesis of 4-arylpyrazolo[3,4-b]pyridin-6-ones based on 5-aminopyrazoles and azlactones

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General information

$^1$H and $^{13}$C NMR spectra were acquired on a Bruker DRX-400 spectrometer (working frequencies 400 and 100 MHz, respectively) in CDCl$_3$ or DMSO-$d_6$, with the residual solvent signals (CDCl$_3$: 7.26 ppm for $^1$H nuclei and 77.0 ppm for $^{13}$C nuclei; DMSO-$d_6$: 2.50 ppm for $^1$H nuclei and 39.5 ppm for $^{13}$C nuclei) serving as internal standards. All chemical shifts ($\delta$) are reported in ppm and coupling constants ($J$) in Hz. Absorption spectra were recorded on a PerkinElmer Lambda 750 diode array spectrophotometer, photoluminescence spectra were recorded on a Cary Eclipse fluorescence spectrophotometer. In both cases, the test compounds were dissolved in EtOH so that the concentration of the resulting solutions was lower than $10^{-5}$ mol/dm$^3$. The molar light absorption coefficient was determined according to the described method [1, 2]. The quantum yield was determined relative to quinine sulfate in 0.5 M H$_2$SO$_4$ ($\Phi_0$ 0.546) using the comparison method [3, 4]. Infra-red spectra were recorded on an Infralum FT-801 spectrometer for others in KBr pellets. The elemental analyses were carried out on a Carlo Erba 1106 CHN analyzer. The melting points were determined on a Reach devices RD-MP. Monitoring of the reaction progress and assessment of the purity of synthesized compounds were done by TLC on Silufol UV-254 plates, eluents CHCl$_3$–EtOAc, 10:1. Visualization of plates was done under UV light. Silica gel 60 (0.063–0.200 mm, Macherey-Nagel) was used for column chromatography.

The starting compounds 1 [5], 2a-i [6-10] were prepared following the reported methods.
Compounds characterization and analytical data

\[ N-(3\text{-methyl}-6\text{-oxo}-1,4\text{-diphenyl}-4,5,6,7\text{-tetrahydro}-1H\text{-pyrazolo}[3,4-b]\text{-pyridin-5-yl})\text{benzamide (3a).} \]

A mixture of 3-methyl-1-phenyl-1\text{-}H-pyrrozol-5-amine 1 (346 mg, 2 mmol) and 4-benzylidene-2-phenyl-oxazol-5(4\text{H})-one 2a (498 mg, 2 mmol) was heated at 150°C for 40 min, after cooling to room temperature, the product was purified by column chromatography on silica gel (eluent, CHCl$_3$–EtOAc, 10:1). Yield: 523 mg (62%) colorless crystals, m.p. >250°C (i-PrOH) (m.p. 268–270 (EtOH) [11]). IR (KBr): 3295, 3194, 3062, 3032, 2911, 1698, 1693, 1642, 1601, 1582, 1547, 1496, 1457, 1374, 1357, 1335, 1267, 1255, 1184, 1113, 1075, 1054, 1026, 1002, 916, 819, 819, 800, 754, 694, 660 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.46 (s, 3H), 4.40 (d, $J = 11.9$ Hz, 1H), 5.05 (dd, $J = 11.9, 9.0$ Hz, 1H), 7.20-7.26 (m, 1H), 7.31-7.39 (m, 5H), 7.40-7.45 (m, 2H), 7.48-7.53 (m, 3H), 7.55-7.59 (m, 2H), 7.71-7.74 (m, 2H), 8.68 (d, $J = 9.0$ Hz, 1H), 10.79 (s, 1H), $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 12.5, 41.4, 56.0, 102.3, 122.9, 126.8, 127.1, 127.2, 128.2, 128.3, 128.5, 129.2, 131.3, 134.1, 137.3, 137.9, 140.1, 145.5, 166.4, 168.5. Anal. Calcd for C$_{26}$H$_{22}$N$_4$O$_2$: C 73.92, H 5.25, N 13.26. Found: 73.80, H 5.30, N 13.15.

**General procedure for the synthesis of 3-methyl-1-phenyl-1,7-dihydro-6\text{-}H\text{-pyrazolo}[3,4-b]\text{-pyridin-6-one (4a-i).}** A mixture of 3-methyl-1-phenyl-1\text{-}H-pyrrozol-5-amine 1 (346 mg, 2 mmol) and azlactones 2a-i (2 mmol) was heated at 150°C for 40 min. Then the mixture was cooled and DMSO (4 mL) and t-BuOK (336 mg, 3 mmol) was added, after which the resulting mixture was heated at 150°C for 1.5 h. The reaction mixture was cooled, poured into H$_2$O (30 mL), and 10% HCl was added on cooling to pH ~ 3. The precipitate formed was filtered off, dried, and purified by column chromatography on silica gel (eluent, CHCl$_3$–EtOAc, 10:1).
3-Methyl-1,4-diphenyl-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin-6-one (4a). Yield: 439 mg (73%), colorless crystals, m.p. 194-195°C (m.p. 193-194°C [12]). IR (KBr): 3295, 3194, 3062, 3032, 2911, 1698, 1693, 1642, 1601, 1582, 1496, 1457, 1374, 1357, 1335, 1267, 1255, 1184, 1113, 1075, 1054, 1026, 1002, 916, 819, 819, 800, 754, 694, 660 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ: 1.46 (s, 3H), 4.40 (d, J = 11.9 Hz, 1H), 5.05 (dd, J = 11.9, 9.0 Hz, 1H), 7.20-7.26 (m, 1H), 7.31-7.39 (m, 5H), 7.40-7.45 (m, 2H), 7.48-7.53 (m, 3H), 7.55-7.59 (m, 2H), 7.71-7.74 (m, 2H), 8.68 (d, J = 9.0 Hz, 1H), 10.79 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 12.5, 41.4, 56.0, 102.3, 122.9, 126.8, 127.1, 127.2, 128.2, 128.3, 128.5, 129.2, 131.3, 134.1, 137.3, 137.9, 140.1, 145.5, 166.4, 168.5. Anal. Calcd for C₁₉H₁₅N₃O: C 75.73, H 5.02, N 13.94. Found: C 75.88, H 5.14, N 13.80.

4-(4-Chlorophenyl)-3-methyl-1-phenyl-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin-6-one (4b). Yield: 470 mg (70%), colorless crystals, m.p. 228-229°C. IR (KBr): 3056, 1647, 1642, 1595, 1576, 1503, 1429, 1383, 1348, 1281, 1262, 1159, 1121, 1090, 1015, 988, 887, 862, 830, 760, 731, 714, 691, 675 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ: 2.10 (s, 3H), 6.30 (s, 1H), 7.16-7.21 (m, 1H), 7.29-7.34 (m, 2H), 7.36-7.41 (m, 2H), 7.46-7.52 (m, 2H), 7.60-7.65 (m, 2H), 10.84 (br.s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 14.8, 107.0, 110.3, 122.2, 127.0, 128.7, 129.1, 129.7, 135.2, 135.5, 137.4, 143.8, 143.9, 149.2, 163.4. Anal. Calcd for C₁₉H₁₄ClN₃O: C 67.96, H, 4.20, N 12.51. Found: C 67.82, H, 4.11, N 12.34.

4-(4-Methoxyphenyl)-3-methyl-1-phenyl-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin-6-one (4c). Yield: 384 mg (58%), colorless crystals, m.p. 188-189°C. IR (KBr): 3063, 1632, 1597, 1586, 1574, 1503, 1387, 1356, 1252, 1211, 1159, 1090, 1015, 980, 889, 858, 835, 764, 733, 696 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ: 2.15 (s, 3H), 3.88 (s, 3H), 6.30 (s, 1H), 6.99-7.04 (m, 2H), 7.11-7.17 (m, 1H), 7.26-
7.31 (m, 2H), 7.37-7.41 (m, 2H), 7.59-7.64 (m, 2H), 10.85 (br.s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 15.0, 55.3, 107.3, 110.1, 113.8, 122.2, 126.9, 129.0, 129.4, 129.7, 137.5, 143.8, 144.1, 150.5, 160.3, 163.6. Anal. Calcd for C$_{20}$H$_{17}$N$_3$O$_2$: C 72.49, H 5.17, N 12.68. Found: C 72.34, H 5.13, N 12.79.

4-(3,4-Dimethoxyphenyl)-3-methyl-1-phenyl-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin-6-one (4d). Yield: 397 mg (55%), colorless crystals, m.p. 243-244°C. IR (KBr): 3069, 1634, 1607, 1599, 1582, 1429, 1356, 1221, 1159, 1115, 1015, 980, 862, 839, 799, 733, 698 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 2.19 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 6.47 (s, 1H), 7.04-7.11 (m, 2H), 7.13 (s, 1H), 7.25-7.30 (m, 1H), 7.49-7.54 (m, 2H), 8.20 (s, 2H), 11.39 (br.s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 15.3, 55.5, 55.6, 106.0, 109.2, 111.4, 112.5, 120.5, 121.3, 125.2, 128.9, 129.4, 139.3, 142.3, 148.3, 148.4, 149.3, 150.0, 163.4. Anal. Calcd for C$_{21}$H$_{19}$N$_3$O$_3$: C 69.79, H 5.30, N 11.63. Found: C 69.60, H 5.19, N 11.48.

3-Methyl-1-phenyl-4-(3,4,5-trimethoxyphenyl)-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin-6-one (4e). Yield: 438 mg (56%), colorless crystals, m.p. 184-185°C. IR (KBr): 3061, 3001, 2928, 2835, 1644, 1582, 1574, 1509, 1468, 1455, 1410, 1356, 1325, 1237, 1179, 1131, 1003, 828, 760, 731, 693 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 2.19 (s, 3H), 3.89 (s, 6H), 3.92 (s, 3H), 6.34 (s, 1H), 6.66 (s, 2H), 7.18-7.23 (m, 1H), 7.31-7.36 (m, 2H), 7.65-7.68 (m, 2H), 10.70 (br.s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 15.0, 56.2, 61.0, 105.8, 107.2, 110.1, 122.2, 127.0, 129.2, 132.5, 137.5, 138.7, 143.9, 144.0, 150.5, 153.1, 163.4. Anal. Calcd for C$_{22}$H$_{21}$N$_3$O$_4$: C 67.51, H 5.41, N 10.74. Found: C 67.66, H 5.19, N 10.83.
4-(4-Fluorophenyl)-3-methyl-1-phenyl-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin-6-one (4f).

Yield: 427 mg (67%), colorless crystals, m.p. 239-240°C. IR (KBr): 3075, 1632, 1582, 1429, 1389, 1356, 1266, 1252, 1221, 1157, 1115, 1015, 780, 924, 899, 862, 857, 839, 799, 764, 731, 696, 675, 569 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ: 2.10 (s, 3H), 6.31 (s, 1H), 7.16-7.24 (m, 3H), 7.31-7.37 (m, 2H), 7.39-7.45 (m, 2H), 7.63-7.67 (m, 2H), 10.50 (br.s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 14.8, 107.2, 110.3, 115.5 (d, J = 21.6 Hz), 122.3, 127.0, 129.2, 130.2 (d, J = 7.8 Hz), 133.1 (d, J = 3.5 Hz), 137.5, 143.8, 144.0, 149.5, 163.2 (d, J = 248.8 Hz), 163.2 (d, J = 248.8 Hz), 163.2. Anal. Calcd for C₁₉H₁₄FN₃O: C 71.46, H 4.42, N 13.16. Found: C 71.32, H 4.54, N 12.99.

3-Methyl-1-phenyl-4-(p-tolyl)-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin-6-one (4g). Yield: 441 mg (70%), colorless crystals, m.p. 217-218°C. IR (KBr): 3060, 1642, 1584, 1516, 1497, 1428, 1383, 1348, 1266, 1210, 1183, 1159, 1119, 1011, 1984, 851, 824, 762, 729, 693 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ: 2.12 (s, 3H), 2.45 (s, 3H), 6.31 (s, 1H), 7.12-7.17 (m, 1H), 7.26-7.36 (m, 6H), 7.59-7.63 (m, 2H), 10.90 (br.s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 14.9, 21.3, 107.2, 110.2, 122.2, 126.9, 128.3, 129.0 (3C), 134.2, 137.4, 139.0, 143.8, 144.1, 150.8, 163.6. Anal. Calcd for C₂₀H₁₇N₃O: C 76.17, H 5.43, N 13.32. Found: C 76.54, H 5.53, N 13.12.

4-(Furan-2-yl)-3-methyl-1-phenyl-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin-6-one (4h).

Yield: 338 mg (58%), colorless crystals, m.p. 188-189°C. IR (KBr): 3048, 1597, 1580, 1557, 1511, 1493, 1418, 1387, 1343, 1277, 1267, 1204, 1175, 1157, 1140, 1038, 1015, 957, 858, 820, 776, 764, 752, 727, 696, 658, 658, 598 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ: 2.57 (s, 3H), 6.57 (m, 2H), 6.92 (d, J = 3.3 Hz, 1H), 7.09-7.15 (m, 1H), 7.22-7.27 (m, 2H), 7.57-7.61 (m, 2H), 7.65-7.67 (m, 1H), 10.54 (br.s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 16.0, 105.2, 106.4, 111.8, 112.2, 122.2,
126.9, 128.9, 137.3, 137.7, 144.0, 144.1, 145.1, 150.4, 163.4. Anal. Calcd for C$_{17}$H$_{13}$N$_3$O$_2$: C 70.09, H 4.50, N 14.42. Found: C 70.19, H 4.41, N 14.28.

3-Methyl-1-phenyl-4-(thiophen-2-yl)-1,7-dihydro-6$H$-pyrazolo[3,4-$b$]pyridin-6-one (4i).

Yield: 368 mg (60%), colorless crystals, m.p. 190-191°C. IR (KBr): 3069, 1642, 1597, 1572, 1511, 1497, 1439, 1385, 1354, 1333, 1219, 1213, 1183, 1138, 1080, 1038, 1026, 1013, 976, 909, 849, 806, 799, 758, 727, 712, 694, 666 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 2.32 (s, 3H), 6.54 (s, 1H), 7.23-7.31 (m, 2H), 7.45-7.54 (m, 3H), 7.76-7.79 (m, 1H), 8.15-8.19 (m, 2H), 11.36 (br.s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 15.3, 106.6, 108.6, 120.7, 125.5, 127.9, 128.2, 128.9, 129.2, 137.2, 139.1, 140.6, 142.1, 150.1, 163.4. Anal. Calcd for C$_{17}$H$_{13}$N$_3$OS: C 66.43, H 4.26, N 13.67. Found: C 66.33, H 4.38, N 13.53.
References


Figure S1: $^1$H NMR spectrum of compound 3a (DMSO-$d_6$).
Figure S2: $^{13}$C NMR spectrum of compound 3a (DMSO-$d_6$).
Figure S3: $^1$H NMR spectrum of compound 4a (CDCl$_3$).
Figure S4: $^{13}$C NMR spectrum of compound 4a (CDCl$_3$).
Figure S5: $^1$H NMR spectrum of compound 4b (CDCl$_3$).
Figure S6: $^{13}$C NMR spectrum of compound 4b (CDCl$_3$).
Figure S7: $^1$H NMR spectrum of compound 4c (CDCl$_3$).
Figure S8: $^{13}$C NMR spectrum of compound 4c (CDCl$_3$).
Figure S9: $^1$H NMR spectrum of compound 4d (DMSO-$d_6$).
Figure S10: $^{13}$C NMR spectrum of compound 4d (DMSO-$d_6$).
Figure S11: $^1$H NMR spectrum of compound 4e (CDCl$_3$).
Figure S12: $^{13}$C NMR spectrum of compound 4e (CDCl$_3$).
Figure S13: $^1$H NMR spectrum of compound 4f (CDCl$_3$).
Figure S14: $^{13}$C NMR spectrum of compound 4f (CDCl$_3$).
Figure S15: $^1$H NMR spectrum of compound 4g (CDCl$_3$).
Figure S16: $^{13}$C NMR spectrum of compound 4g (CDCl$_3$).
Figure S17: $^1$H NMR spectrum of compound 4h (CDCl$_3$).
**Figure S18**: $^{13}$C NMR spectrum of compound 4h (CDCl$_3$).
Figure S19: $^{13}$C NMR spectrum of compound 4i (DMSO-$d_6$).
**Figure S20:** $^{13}$C NMR spectrum of compound 4i (DMSO-$d_6$).