Supporting Information

for

A convenient four-component one-pot strategy toward the synthesis of pyrazolo[3,4-d]pyrimidines

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Experimental section and copies of $^1$H and $^{13}$C NMR spectra of compounds
Experimental

Materials and methods

The starting materials are commercially available. Melting points were determined on XT4 microscope melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrophotometer with KBr pellets. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker 400 spectrometer with TMS as the internal standard. Mass spectra were recorded on a Bruker APEX IV using ESI ionization.

General procedure for the synthesis of compound 5. Hydrazine 1 (1.2 mmol), methylenemalononitrile 2 (1.0 mmol) were mixed in alcohol (15 mL), then aldehyde (3, 1.2 mmol) and sodium alkoxide (1.2 mmol) were added and the mixture was warmed to 60 °C. The completion of the reaction was monitored by TLC. The reaction solution was cooled to room temperature and diluted with water. The solid was filtered and the filtrate was extracted with acetic ether (3 × 20 mL). Then the organic layer was evaporated under reduced pressure. The solid was combined with filter cake and purified by crystallization from ethanol.

4-Ethoxy-1,6-diphenyl-1H-pyrazolo[3,4-d]pyrimidine (5a): Yellow solid; m.p. 147-148 °C; IR (KBr, ν, cm$^{-1}$): 3119, 2980, 1593; $^1$H NMR (400 MHz, DMSO-d6) (δ, ppm): 8.50-8.48 (m, 2H), 8.45 (s, 1H), 8.31-8.28 (m, 2H), 7.65-7.61 (m, 2H), 7.57-7.56 (m, 3H), 7.43-7.40 (m, 1H), 4.76 (q, $J = 8.0$ Hz, 2H), 1.50 (t, $J = 8.0$ Hz, 3H); $^{13}$C NMR (100 MHz, DMSO-d6) (δ, ppm): 163.7, 161.9, 155.8, 139.1, 137.3, 133.7, 131.7, 129.9, 129.8, 129.2, 128.9, 127.1, 121.3, 102.8, 100.0, 63.6, 14.8; HRMS (ESI): calcd. For C$_{19}$H$_{16}$N$_4$OH [M+H]$^+$ 317.1397; Found 317.1394.
4-Ethoxy-6-(4-methoxyphenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (5b): White solid; m.p. 152-154 °C; IR (KBr, ν, cm⁻¹): 3102, 2990, 1591; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 8.46-8.43 (m, 3H), 8.31-8.29 (m, 2H), 7.65-7.61 (m, 2H), 7.43-7.39 (m, 1H), 7.12-7.10 (m, 2H), 4.75 (q, J = 8.0 Hz, 2H), 3.86 (s, 3H), 1.49 (t, J = 8.0 Hz, 3H); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 163.5, 162.4, 161.9, 155.9, 139.2, 133.7, 130.6, 129.8, 7.12, 126.9, 121.1, 114.5, 102.3, 63.4, 55.8, 14.8; HRMS (ESI): calcd. For C₂₀H₁₈N₄O₂H [M+H]^+ 347.1503; Found 347.1500.

4-Ethoxy-1-phenyl-6-(p-tolyl)-1H-pyrazolo[3,4-d]pyrimidine (5c): White solid; m.p. 118-120 °C; IR (KBr, ν, cm⁻¹): 3064, 2976, 1595; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 8.37 (s, 1H), 8.32-8.25 (m, 4H), 7.63-7.59 (m, 2H), 7.41-7.37 (m, 1H), 7.31-7.29 (m, 2H), 4.69 (q, J = 8.0 Hz, 2H), 2.37 (s, 3H), 1.47 (t, J = 8.0 Hz, 3H); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 163.5, 162.0, 155.8, 141.6, 139.2, 134.6, 133.6, 129.8, 126.9, 121.2, 102.6, 63.4, 21.6, 14.8; HRMS (ESI): calcd. For C₂₀H₁₈N₄OH [M+H]^+ 331.1553; Found 331.1550.

4-Ethoxy-1-phenyl-6-(3,4,5-trimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine (5d): White solid; m.p. 176-178 °C; IR (KBr, ν, cm⁻¹): 3101, 2946, 1589; ¹H NMR (400 MHz, CDCl₃) (δ, ppm): 8.37 (d, J = 8.0 Hz, 2H), 8.20 (s, 1H), 7.88 (s, 1H), 7.58-7.54 (m, 2H), 7.31-7.35 (m, 1H), 4.79 (q, J = 8.0 Hz, 2H), 4.02 (s, 6H), 3.97 (s, 3H), 1.59 (t, J = 8.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) (δ, ppm): 163.4, 161.7, 155.8, 153.1, 140.9, 139.3, 133.0, 132.8, 129.0, 126.3, 121.2, 106.1, 102.6, 62.9, 61.0, 56.1, 14.5; HRMS (ESI): calcd. For C₂₂H₂₂N₄O₄H [M+H]^+ 407.1714; Found 407.1714.

6-(5-Bromo-2-methoxyphenyl)-4-ethoxy-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (5e): Yellow solid; m.p. 150-152 °C; IR (KBr, ν, cm⁻¹): 3070, 2982, 1589; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 8.47 (s, 1H), 8.28 (d, J = 8.0 Hz, 2H), 7.96 (s, 1H), 7.65 (d, J = 8.0
Hz, 1H), 7.60-7.56 (m, 2H), 7.39-7.36 (m, 1H), 7.18 (d, J = 8.0 Hz, 1H), 4.66 (q, J = 8.0 Hz, 2H), 3.87 (s, 3H), 1.46 (t, J = 8.0 Hz, 3H); 13C NMR (100 MHz, DMSO-d6) (δ, ppm): 163.2, 161.1, 157.8, 155.3, 139.1, 134.2, 133.9, 133.6, 129.8, 127.1, 121.2, 115.7, 112.1, 102.4, 63.7, 56.8, 14.7; HRMS (ESI): calcd. For C20H17BrN4O2[M+H]+ 425.0608; Found 425.0601.

4-Ethoxy-6-(3-nitrophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (5f): Pale yellow solid; m.p. 158-160 °C; IR (KBr, ν, cm⁻¹): 3076, 2980, 1594; 1H NMR (400 MHz, DMSO-d6) (δ, ppm): 9.08-9.07 (m, 1H), 8.81-8.79 (m, 1H), 8.47 (s, 1H), 8.38-8.35 (m, 1H), 8.23-8.21 (m, 2H), 7.84-7.80 (m, 1H), 7.65-7.61 (m, 2H), 7.45-7.41 (m, 1H), 4.74 (q, J = 8.0 Hz, 2H), 1.51 (t, J = 8.0 Hz, 3H); 13C NMR (100 MHz, DMSO-d6) (δ, ppm): 163.8, 159.5, 155.4, 148.7, 138.9, 134.7, 133.8, 130.9, 129.8, 127.3, 126.1, 122.9, 121.4, 103.2, 63.9, 14.7; HRMS (ESI): calcd. For C19H15N4O3H [M+H]+ 362.1248; Found 362.1247.

4-Ethoxy-6-(2-nitrophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (5g): Brown solid; m.p. 124-126 °C; IR (KBr, ν, cm⁻¹): 3069, 2990, 1593; 1H NMR (400 MHz, DMSO-d6) (δ, ppm): 8.50-8.47 (m, 3H), 8.34-8.32 (m, 2H), 7.98-7.96 (m, 1H), 7.88-7.84 (m, 1H), 7.81-7.76 (m, 1H), 7.62-7.59 (m, 2H), 7.44-7.41 (m, 1H), 4.64 (q, J = 8.0 Hz, 2H), 1.46 (t, J = 8.0 Hz, 3H); 13C NMR (100 MHz, DMSO-d6) (δ, ppm): 163.6, 159.6, 155.0, 150.6, 138.7, 133.9, 132.7, 132.1, 132.0, 131.3, 129.8, 127.4, 124.3, 121.4, 102.8, 64.0, 14.7; HRMS (ESI): calcd. For C19H15N5O3H [M+H]+ 362.1248; Found 362.1247.

1-(4-Chlorophenyl)-4-ethoxy-6-phenyl-1H-pyrazolo[3,4-d]pyrimidine (5h): Yellow solid; m.p. 160-162 °C; IR (KBr, ν, cm⁻¹): 3108, 2984, 1591; 1H NMR (400 MHz, DMSO-d6) (δ, ppm): 8.50-8.47 (m, 3H), 8.34-8.32 (m, 2H), 7.69-7.67 (m, 2H), 7.57-7.56 (m, 3H), 4.76 (q, J = 8.0 Hz, 2H), 1.50 (t, J = 8.0 Hz, 3H); 13C NMR (100 MHz, DMSO-d6) (δ, ppm):
163.6, 162.0, 155.9, 138.0, 137.2, 134.0, 131.8, 131.1, 129.8, 129.1, 128.9, 122.6, 102.8, 63.6, 14.8; HRMS (ESI): calcd. For C_{19}H_{15}ClN_{4}OH [M+H]^+ 351.1007; Found 351.1006.

1-(3,5-Dimethylphenyl)-4-ethoxy-6-phenyl-1H-pyrazolo[3,4-d]pyrimidine (5i): Yellow solid; m.p. 156-158 °C; IR (KBr, ν, cm⁻¹): 3107, 2980, 1596; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 8.49-8.46 (m, 2H), 8.43 (s, 1H), 7.91 (s, 2H), 7.58-7.56 (m, 3H), 7.05 (s, 1H), 4.77 (q, J = 8.0 Hz, 2H), 2.42 (s, 6H), 1.50 (t, J = 8.0 Hz, 3H); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 163.6, 161.8, 139.0, 137.4, 136.3, 133.4, 131.7, 129.3, 129.2, 128.8, 128.6, 119.9, 119.1, 102.7, 63.5, 21.7, 21.6, 14.8; HRMS (ESI): calcd. For C_{21}H_{20}N_{4}OH [M+H]^+ 345.1710; Found 345.1707.

4-Ethoxy-1-methyl-6-phenyl-1H-pyrazolo[3,4-d]pyrimidine (5j): Yellow solid; m.p. 214-216 °C; IR (KBr, ν, cm⁻¹): 3092, 2984, 1617; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 8.60 (s, 1H), 8.47-8.44 (m, 2H), 7.53-7.51 (m, 3H), 4.72 (q, J = 8.0 Hz, 2H), 4.15 (s, 3H), 1.47 (t, J = 8.0 Hz, 3H); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 164.6, 162.8, 160.4, 138.4, 130.9, 128.9, 128.5, 125.8, 101.7, 62.9, 41.0, 14.8; HRMS (ESI): calcd. For C_{14}H_{14}N_{4}OH [M+H]^+ 255.1240; Found 255.1240.

4-Ethoxy-1,3-dimethyl-6-phenyl-1H-pyrazolo[3,4-d]pyrimidine (5k): Yellow solid; m.p. 136-138 °C; IR (KBr, ν, cm⁻¹): 2984, 1598; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 8.50-8.47 (m, 2H), 7.55-7.54 (m, 3H), 4.71 (q, J = 8.0 Hz, 2H), 3.97 (s, 3H), 2.09 (s, 3H), 1.47 (t, J = 8.0 Hz, 3H); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 164.0, 161.0, 156.5, 140.8, 137.6, 131.3, 129.0, 128.7, 100.0, 62.9, 33.8, 14.8, 14.1; HRMS (ESI): calcd. For C_{15}H_{16}N_{4}OH [M+H]^+ 269.1397; Found 269.1393.

4-Methoxy-6-(4-methoxyphenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (5l): White solid; m.p. 142-144 °C; IR (KBr, ν, cm⁻¹): 3097, 2956, 1595; ¹H NMR (400 MHz, DMSO-d₆)
(δ, ppm): 8.47-8.45 (m, 3H), 8.31-8.29 (m, 2H), 7.65-7.61 (m, 2H), 7.43-7.39 (m, 1H), 7.12-7.10 (m, 2H), 4.24 (s, 3H), 3.86 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 163.8, 162.4, 161.9, 155.9, 139.2, 133.6, 130.6, 129.8, 127.0, 121.2, 114.5, 102.3, 55.9, 54.5; HRMS (ESI): calcd. For C₁₉H₁₆N₄O₂H [M+H]^+ 333.1346; Found 333.1342.

4-Methoxy-6-(3-nitrophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (5m): White solid; m.p. 175-177 °C; IR (KBr, ν, cm⁻¹): 3113, 2935, 1595; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 8.92 (m, 1H), 8.67-8.65 (m, 1H), 8.35 (s, 1H), 8.29-8.26 (m, 1H), 8.14-8.12 (m, 2H), 7.74-7.70 (m, 1H), 7.58-7.54 (m, 2H), 7.41-7.37 (m, 1H), 4.15 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 164.2, 159.7, 155.4, 148.7, 138.9, 134.9, 133.8, 131.0, 129.9, 127.4, 126.2, 123.0, 121.6, 103.2, 55.0; HRMS (ESI): calcd. For C₁₉H₁₆N₄O₂H [M+H]^+ 348.1091; Found 348.1091.

4-Butoxy-1,6-diphenyl-1H-pyrazolo[3,4-d]pyrimidine (5n): White solid; m.p. 99-101 °C; IR (KBr, ν, cm⁻¹): 3065, 2956, 1594; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 8.49-8.47 (m, 2H), 8.45 (s, 1H), 8.30-8.28 (m, 2H), 7.65-7.61 (m, 2H), 7.57-7.55 (m, 3H), 7.43-7.39 (m, 1H), 4.70 (t, J = 8.0 Hz, 2H), 1.89-1.82 (m, 2H), 1.56-1.47 (m, 2H), 0.99 (t, J = 8.0 Hz, 3H); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 163.7, 161.9, 155.8, 139.1, 137.3, 133.6, 131.7, 129.8, 128.8, 127.0, 121.1, 102.7, 67.1, 30.8, 19.2, 14.2; HRMS (ESI): calcd. For C₂₁H₂₀N₄O₂H [M+H]^+ 345.1710; Found 345.1708.

1,6-Diphenyl-4-propoxy-1H-pyrazolo[3,4-d]pyrimidine (5o): White solid; m.p. 128-129 °C; IR (KBr, ν, cm⁻¹): 3066, 2966, 1293; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 8.49-8.47 (m, 2H), 8.46 (s, 1H), 8.31-8.28 (m, 2H), 7.65-7.61 (m, 2H), 7.57-7.55 (m, 3H), 7.43-7.39 (m, 1H), 4.66 (t, J = 8.0 Hz, 2H), 1.95-1.86 (m, 2H), 1.07 (t, J = 8.0 Hz, 3H); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 163.8, 161.9, 155.8, 139.1, 137.3, 133.6, 131.7, 129.8, 129.1,
128.8, 127.0, 121.2, 102.7, 68.9, 22.2, 10.8; HRMS (ESI): calcd. For C₂₀H₁₈N₄OH [M+H]+ 331.1553; Found 331.1551.

4-Isopropoxy-1,6-diphenyl-1H-pyrazolo[3,4-d]pyrimidine (5p): White solid; m.p. 192-194 °C; IR (KBr, ν, cm⁻¹): 3064, 2977, 1595; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 8.53-8.51 (m, 2H), 8.48 (s, 1H), 8.33-8.31 (m, 2H), 7.67-7.63 (m, 2H), 7.60-7.58 (m, 3H), 7.45-7.41 (m, 1H), 5.87-5.81 (m, 1H), 1.52 (d, J = 8 Hz, 6H); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 163.6, 162.0, 155.9, 139.2, 137.5, 133.7, 131.2, 130.7, 129.9, 129.6, 129.2, 128.8, 127.1, 121.3, 100.0, 78.2, 22.2; HRMS (ESI): calcd. For C₂₀H₁₈N₄OH [M+H]+ 331.1553; Found 331.1549.
$^1$H and $^{13}$C NMR spectra of 5

5a

S8
S15
HRMS spectra of 5
Peking University Mass Spectrometry Sample Analysis Report

Analysis Info
Analysis Name  15050836_20150521_000005.d
Sample        Lmx-052-8
Comment       ESI Positive

Acquisition Date  5/21/2015 11:04:15 AM
Instrument      Bruker Apex IV FTMS
Operator        Peking University

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Peking University Mass Spectrometry Sample Analysis Report

Analysis Info
Analysis Name  15050836_20150521_000006.d
Sample        Lmx-052-4
Comment       ESI Positive

Acquisition Date  5/21/2015 11:05:49 AM
Instrument      Bruker Apex IV FTMS
Operator        Peking University

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S25