Supporting Information

One-Pot Tandem Synthesis of Tetrasubstituted Pyrazoles via 1,3-dipolar Cycloaddition between Aryl hydrazones and ethyl but-2-ynoate

Srikantamurthy Ningaiah^a, Shridevi D. Doddaramappa^b, Chandra^b, Mahendra Madegowda^b,
Shubakara Keshavamurthy^a, Umesha K. Bhadraiah^{a,*}

^a Department of Chemistry, Yuvaraja's College, University of Mysore, Mysore-570005,

^b Department of Studies in Chemistry, Manasagangotri, University of Mysore, Mysore-570006,

^c Department of Physics, Manasagangotri, University of Mysore, Mysore-570 006. India

kbu68umesha@rediffmail.com.

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* Corresponding author Tel.: +91 0821-2420398 E-mail address: kbu68umesha@rediffmail.com (U.K.B).

1. General information:

All chemicals were obtained from commercial suppliers and used without further purification. Melting points were determined in open capillaries on a Buchi oil melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on aluminum sheets precoated with silica gel 60 F₂₅₄ (0.2 mm, Merck). Chromatographic spots were visualized by UV light and/or with iodine. For column chromatography, silica gel of 100-200 mesh size was used. ¹H NMR spectra were acquired on a Bruker Avance 400 MHz instrument in DMSO-d₆ or CDCl₃ and TMS was used as an internal reference. ¹³C NMR spectra were recorded on a Bruker AMX-400 (100.6 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference (CDCl₃: δ 77.0 ppm). All novel compounds were characterized by LC-MS, and gave satisfactory results in agreement with the proposed structure. LC-MS data were obtained using electrospray ionization (positive mode) on a C-18 column at a flow rate 0.2 mL/ min using MeOH/water (90:10) as eluent. LC-MS M+H signals were consistent with expected molecular weight for all reported products. X-ray diffraction measurements were made on a Bruker APEX-II¹ CCD area detector with graphite monochromated radiation (Mo Kα). Raw data was processed and reduced by using APEX-II and SAINT. The structure was solved by direct methods using SHELXS.²

2. Experimental procedure for the synthesis of 6a:

To a stirred solution of benzaldehyde (0.106 g, 1.00 mmol) in EtOH (5 mL) was added phenyl hydrazine (0.119 g, 1.00 mmol, 1.1 equiv). After stirring at room temperature for 15 min, the benzaldehyde phenyl hydrazone was formed based on TLC analysis. Hg(OAc)₂ (0.478g, 1.5 mmol, 1.5 equiv) in 5ml EtOH and Ethyl but-2-ynoate (0.224g, 2.00 mmol, 2.0 equiv) were added simultaneously to the reaction mixture from two separate droppers. The contents were then allowed to stir at room temperature for 30 min (1.0 hr total). On completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was washed with 1M KBr solution (in order to remove mercury salts), with brine, dried over anhydrous Na₂SO₄ and then concentrated under reduced pressure. The crude product was

(1) Bruker, **2009**. APEX2 and SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.

(2) Sheldrick, G. M. *Acta Cryst.*, **2008**, A64, 112-122.

purified by column chromatography (*n*-hexane / EtOAc 95/05) two fractions which on evaporation, **6a** obtained as white solids 0.277g (96%) and **8a** as off white solids 0.057g (2%).

3. Physical and spectral data of compound **6** (a-l) and **8a**

6a: White solid; mp 102-104 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.15 (t, *J* = 7.2 Hz, 3H), 2.41 (s, 3H), 4.13 (q, *J* = 7.2 Hz, 2H), 7.29-7.36 (m, 4H), 7.41-7.45 (m, 4H), 7.49-7.57 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 12.75, 14.10, 60.10, 110.63, 125.85, 127.65, 128.23, 128.68, 129.25, 129.48, 133.18, 138.84, 144.79, 153.62, 164.21; LC-MS *m/z* 307.6 (M+H)⁺; Anal. Calcd for C₁₉H₁₈N₂O₂: C, 74.50; H, 5.90; N, 9.14; Found: C, 74.56; H, 5.91; N, 9.10.

6b: White solid; mp 88-90 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.14 (t, *J* = 7.2 Hz, 3H), 2.34 (s, 3H), 4.05 (q, *J* = 6.8 Hz, 2H), 7.37-7.42 (m, 2H), 7.43-7.45 (m, 1H), 7.49-7.54 (m, 4H), 7.79-7.78 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 12.75, 14.10, 60.10, 110.62, 125.85, 127.65, 128.23, 129.50, 129.53, 130.58, 136.60, 138.82, 144.80, 153.00, 164.22; LC-MS *m/z* 341.6 (M+H)⁺; Anal. Calcd for C₁₉H₁₇ClN₂O₂: C, 66.96; H, 5.03; N, 8.22; Found: C, 66.94; H, 5.00; Cl, 10.38; N, 8.16.

6c: White solid; mp 155-157 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.18(t, *J* = 7.2 Hz, 3H), 2.41 (s, 3H), 3.75 (s, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 6.94-6.98 (m, 2H), 7.37-7.42 (m, 1H), 7.48-7.55 (m, 4H), 7.79-7.82 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 12.75, 14.10, 55.81, 60.10, 110.62, 114.80, 125.18, 125.85, 127.65, 128.41, 129.44, 138.82, 144.80, 153.22, 160.52, 164.21; LC-MS *m/z* 337.5 (M+H)⁺; Anal. Calcd for C₂₀H₂₀N₂O₃: C, 71.41; H, 5.99; N, 8.33; Found: C, 71.38; H, 6.01; N, 8.30.

6d: Orange color thick paste; ¹H NMR (400 MHz, CDCl₃) δ 1.14(t, *J* = 7.2 Hz, 3H), 2.42 (s, 3H), 4.12 (q, *J* = 7.2 Hz, 2H), 7.49-7.56 (m, 5H), 7.97-7.99 (d, *J* = 8.8 Hz, 2H), 8.23-8.32 (d, *J* = 8.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 12.74, 14.10, 60.00, 110.63, 123.40, 125.16, 125.87, 127.66, 128.90, 138.83, 139.47, 144.79, 147.60, 150.58, 164.22; LC-MS *m/z* 352.4 (M+H)⁺; Anal. Calcd for C₁₉H₁₇N₃O₄: C, 64.94; H, 4.85; N, 11.99; Found: C, 64.92; H, 4.87; N, 11.92.

6e: Yellow color amorphous solid; ^1H NMR (400 MHz, CDCl_3) δ 1.03 (t, $J = 7.2$ Hz, 3H), 2.41 (s, 3H), 4.11 (q, $J = 7.2$ Hz, 2H), 7.33-7.42 (m, 2H), 7.43-7.45 (m, 1H), 7.49-7.54 (m, 4H), 7.83-7.85 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 12.75, 14.11, 60.10, 110.62, 125.14, 125.83, 127.65, 128.86, 129.53, 130.92, 133.23, 138.80, 144.80, 153.13, 164.21; LC-MS m/z 386.1 ($\text{M}+\text{H}$) $^+$; Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{BrN}_2\text{O}_2$: C, 59.23; H, 4.45; N, 7.27; Found: C, 59.20; H, 4.41; N, 7.25.

6f: Orange viscous liquid; ^1H NMR (400 MHz, CDCl_3) δ 1.07 (t, $J = 7.2$ Hz, 3H), 2.43 (s, 3H), 4.13 (q, $J = 7.2$ Hz, 2H), 7.23-7.31 (m, 3H), 7.58-7.62 (t, $J = 8$ Hz, 1H), 7.68-7.66 (d, $J = 8.4$ Hz, 2H), 8.16-8.27 (m, 2H), 8.75 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 12.75, 14.10, 60.03, 110.60, 122.62, 123.49, 125.87, 127.66, 129.40, 131.51, 134.20, 135.01, 138.82, 144.77, 148.02, 155.36, 164.20; LC-MS m/z 352.5 ($\text{M}+\text{H}$) $^+$; Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_4$: C, 64.95; H, 4.88; N, 11.96; Found: C, 64.93; H, 4.89; N, 11.99.

6g: White solids; mp 98-101 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 1.10 (t, $J = 7.2$ Hz, 3H), 2.41 (s, 3H), 4.11 (q, $J = 7.2$ Hz, 2H), 7.02-7.21 (m, 4H), 7.31-7.37 (m, 1H), 7.52-7.67 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 12.75, 14.10, 60.03, 110.60, 125.87, 126.82, 127.66, 128.83, 129.41, 129.58, 129.64, 133.41, 136.20, 138.82, 144.77, 153.80, 164.20; LC-MS m/z 341.6 ($\text{M}+\text{H}$) $^+$; Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{ClN}_2\text{O}_2$: C, 66.96; H, 5.03; N, 8.22; Found: C, 66.92; H, 5.06; N, 8.20.

6h: Off white amorphous solids; ^1H NMR (400 MHz, CDCl_3) δ 1.15 (t, $J = 7.2$ Hz, 3H), 2.42 (s, 3H), 4.14 (q, $J = 7.2$ Hz, 2H), 7.37-7.42 (m, 2H), 7.43-7.45 (m, 1H), 7.49-7.54 (m, 4H), 7.79-7.78 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 12.75, 14.11, 60.01, 110.60, 117.14, 120.47, 122.00, 125.86, 127.65, 129.41, 129.62, 130.07, 138.85, 144.75, 154.96, 156.07, 164.19; LC-MS m/z 323.6 ($\text{M}+\text{H}$) $^+$; Anal. Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_3$: C, 70.79; H, 5.63; N, 8.69; Found: C, 70.81; H, 5.60; N, 8.70.

6i: White solids; mp 72-74 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 1.15 (t, $J = 7.2$ Hz, 3H), 2.40 (s, 3H), 2.42 (s, 3H), 4.16 (q, $J = 7.2$ Hz, 2H), 7.25-7.31 (m, 2H), 7.38-7.47 (m, 2H), 7.65-7.68 (m, 2H), 7.41-7.83 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 12.75, 14.10, 20.09, 60.10, 110.63, 127.60, 128.23, 128.68, 129.25, 130.38, 133.18, 134.65, 136.03, 144.80, 153.62, 164.21;

LC-MS m/z 321.3 (M+H)⁺; Anal. Calcd for C₂₀H₂₀N₂O₂: C, 74.98; H, 6.29; N, 8.74; Found: C, 74.99; H, 6.30; N, 8.71.

6j: Off white solids; mp 86-88 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.10 (t, J = 7.2 Hz, 3H), 1.86 (s, 3H), 2.24 (s, 3H), 2.32 (s, 3H), 4.22 (q, J = 7.2 Hz, 2H), 6.90-6.96 (m, 2H), 7.07-7.12 (m, 3H), 7.43-7.46 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 12.77, 14.13, 17.09, 21.60, 59.98, 110.63, 126.25, 128.23, 128.68, 129.25, 130.95, 132.18, 133.17, 135.27, 137.62, 141.10, 144.80, 153.63, 164.21; LC-MS m/z 335.2 (M+H)⁺; Anal. Calcd for C₂₁H₂₂N₂O₂: C, 75.42; H, 6.63; N, 8.38; Found: C, 75.40; H, 6.64; N, 8.34.

6k: Yellow solids; mp 70-72 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.23 (t, J = 7.2 Hz, 3H), 2.40 (s, 3H), 4.05 (q, J = 7.2 Hz, 2H), 7.40-7.47 (m, 4H), 7.70-7.74 (m, 2H), 7.84-7.87 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 12.73, 14.09, 60.02, 110.62, 128.22, 128.67, 128.95, 129.25, 129.90, 132.05, 133.18, 136.63, 144.80, 153.60, 164.22; LC-MS m/z 341.5 (M+H)⁺; Anal. Calcd for C₁₉H₁₇ClN₂O₂: C, 66.96; H, 5.03; N, 8.22; Found: C, 66.99; H, 5.00; N, 8.24.

6l: Light yellow color solids; mp 122-124 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.33(t, J =7.2Hz, 3H), 2.40 (s, 3H), 4.20 (q, J = 6.85Hz, 2H), 7.25-7.35 (m, 3H), 7.38-7.40 (m, 2H), 7.49-7.50 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 12.78, 14.29, 60.11, 76.78, 77.03, 77.29, 110.62, 127.38, 128.14, 129.50, 129.54, 130.25, 130.90, 132.45, 135.48, 136.52, 139.20, 144.75, 153.11, 164.31; LC-MS m/z 410.8 (M+H)⁺; Anal. Calcd for C₁₉H₁₅Cl₃N₂O₂: C, 55.70; H, 3.69; N, 6.84; Found: C, 55.68; H, 3.71; N, 6.80.

8a: White solid; mp 100-102 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.14 (t, J = 7.2 Hz, 3H), 2.51 (s, 3H), 4.13-4.19 (q, J = 7.0 Hz, 2H), 7.38-7.42 (m, 3H), 7.49-7.53 (m, 1H), 7.55-7.61 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 11.40, 14.30, 61.10, 110.01, 124.35, 126.70, 127.53, 127.80, 128.20, 129.00, 132.48, 141.10, 141.20, 149.50, 163.10; LC-MS m/z 307.1 (M+H)⁺; Anal. Calcd for C₁₉H₁₈N₂O₂: C, 74.42; H, 5.88; N, 9.20; Found: C, 74.45; H, 5.90; N, 9.15.

4. Copy of ^1H and ^{13}C NMR spectra for **6 (a-l)** and **8a**

S-3(13C IN CDCL₃)