

Electronic Supplementary Information

Mechanically activated synthesis of 1,3,5-triaryl-2-pyrazolines by high speed ball milling

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Experimental

Materials and methods

Chalcones were prepared by earlier reported procedures. Other reagents were from commercial sources. The HSBM experiments were conducted in a planetary-centrifugal mill AGO-2 (acceleration: 60 g; volume of one drum: 35mL³; diameter of steel balls: 5 mm; weight of balls: 75 g). Melting points (mp) were recorded on a WRS-1B digital melting point apparatus and uncorrected. Infrared spectra were recorded on a Thermo Nicolet Avatar 370 spectrophotometer. ¹H NMR and ¹³C NMR spectra were obtained on a Varian Mercury plus-400 spectrometer using CDCl₃ as the solvent with TMS as the internal standard. Mass spectra were measured with a Finnigan Trace DSQ spectrometer.

Characterisation data for compounds

3a: Mp: 134 °C (Lit.,^{S1} 134 – 135 °C). IR (KBr): 3129, 1490, 1400 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 7.76 – 6.71 (m, 15 H, ArH), 5.48 (dd, *J* = 5.2, 9.6 Hz 1H, ArCHN), 3.93 (dd, *J* = 9.6, 14.0 Hz 1H, CH₂C=N), 3.11 (dd, *J* = 5.2, 14.0 Hz 1H, CH₂C=N). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 147.13, 144.22, 142.52, 132.23, 128.94, 128.81, 128.59, 127.35, 125.80, 125.64, 118.56, 112.91, 63.12, 42.95. m/z (EI) 298 (M⁺, 100), 221 (38), 206 (5), 194 (11), 91 (14).

3b: Mp: 160 – 161 °C (Lit.,^{S2} 162 °C). IR (KBr): 3132, 1489, 1398 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 7.77 – 6.97 (m, 14 H, ArH), 5.50 (dd, *J* = 5.6, 12.0 Hz 1H, ArCHN), 3.94 (dd, *J* = 12.0, 17.6 Hz 1H, CH₂C=N), 3.14 (dd, *J* = 6.0, 17.6 Hz 1H, CH₂C=N). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 148.05, 142.97, 141.99, 131.98, 129.00, 128.86, 128.61, 127.47, 125.77, 122.10, 114.29, 63.00, 43.06. m/z (EI) 332 (M⁺, 100), 255 (31), 125 (22).

3c: Mp: 129 – 132 °C (Lit.,^{S1} 129 – 131 °C). IR (KBr): 3133, 1492, 1395 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 7.76 – 6.71 (m, 14 H, ArH), 5.52 (dd, *J* = 6.0, 12.0 Hz 1H, ArCHN), 3.92 (dd, *J* = 12.0, 17.6 Hz 1H, CH₂C=N), 3.12 (dd, *J* = 7.2, 17.2 Hz 1H, CH₂C=N). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 147.27, 144.03, 141.42, 132.12, 131.86, 128.93, 128.88, 128.73, 128.60, 127.83, 125.69, 118.73, 112.94, 62.37, 42.71. m/z (EI) 332 (M⁺, 100), 221 (21), 194 (12), 91 (14).

3d: Mp: 139 – 140 °C (Lit.,^{S3} 140 °C). IR (KBr): 3134, 1490, 1400 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 7.77 – 6.67 (m, 13 H, ArH), 5.54 (dd, *J* = 6.4, 12.2 Hz 1H, ArCHN), 3.92 (dd, *J* = 12.0, 17.8 Hz 1H, CH₂C=N), 3.14 (dd, *J* = 6.4, 17.8 Hz 1H, CH₂C=N). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 148.15, 142.79, 140.86, 131.98, 131.86, 128.96, 128.65, 128.59, 127.78, 125.79, 122.26, 114.32, 62.26, 42.81. m/z (EI) 366 (M⁺, 72), 255 (37), 125 (100), 90 (100), 90 (34).

3e: Mp: 150 – 152 °C (Lit.,^{S4} 150 – 151 °C). IR (KBr): 3154, 1491, 1386 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 7.77 – 6.71 (m, 14 H, ArH), 5.50 (dd, *J* = 6.4, 12.0 Hz 1H, ArCHN), 3.91 (dd, *J* = 12.8, 17.6 Hz 1H, CH₂C=N), 3.13 (dd, *J* = 6.4, 17.2 Hz 1H, CH₂C=N). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 146.10, 144.03, 142.36, 133.05, 131.18, 128.93, 128.84, 128.66, 127.42, 127.29, 125.82, 118.81, 113.03, 63.33, 42.80. m/z (EI) 332 (M⁺, 100), 255 (41), 91 (14), 59 (11).

3f: Mp: 154 – 155 °C (Lit.,^{S5} 154 – 156 °C). IR (KBr): 3133, 1488, 1385 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 6.97 – 7.78 (m, 13 H, ArH), 5.52 (dd, *J* = 6.4, 12.4 Hz 1H, ArCHN), 3.92 (dd, *J* = 12.4, 17.6 Hz 1H, CH₂C=N), 3.13 (dd, *J* = 6.4, 18.0 Hz 1H, CH₂C=N). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 146.98, 142.76, 141.83, 133.28, 130.90, 129.01, 128.62, 127.52, 127.41, 125.77, 122.34, 114.38, 63.17, 42.89. m/z (EI) 366 (M⁺, 100), 289 (31), 125 (23).

3g: Mp: 148 – 149 °C (Lit.,^{S5} 149 – 150 °C). IR (KBr): 3159, 1635, 1400 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 7.76 – 6.72 (m, 13 H, ArH), 5.54 (dd, *J* = 6.0, 8.2 Hz 1H, ArCHN), 3.90 (dd, *J* = 12.0, 13.6 Hz 1H, CH₂C=N), 3.12 (dd, *J* = 6.4, 17.6 Hz 1H, CH₂C=N). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 146.19, 143.81, 141.21, 133.11, 131.92, 131.03, 128.91, 128.86, 128.62, 127.78, 127.29, 118.93, 113.01, 62.56, 42.53. m/z (EI) 366 (M⁺, 77), 255 (52), 91 (100), 77 (50), 64 (23).

3h: Mp: 146 – 147 °C (Lit.,^{S3} 148 °C). IR (KBr): 3145, 1488, 1405 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 7.77 – 6.68 (m, 12 H, ArH), 5.69 (dd, *J* = 6.0, 12.2 Hz 1H, ArCHN), 3.92 (dd, *J* = 12.0, 17.8 Hz 1H, CH₂C=N), 3.14 (dd, *J* = 6.0, 17.6 Hz 1H, CH₂C=N). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 147.12, 142.63, 140.74, 133.42, 132.11, 130.82, 129.02, 128.70, 127.81, 127.47, 122.57, 114.46, 62.51, 42.71. m/z (EI) 400 (M⁺, 73), 289 (26), 127 (31), 125 (100), 90 (26), 75 (17).

3i: Mp: 154 – 155 °C (Lit.,^{S5} 154 – 156 °C). IR (KBr): 3128, 1491, 1383 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 7.76 – 6.70 (m, 13 H, ArH), 5.45 (dd, *J* = 6.4, 12.4 Hz 1H, ArCHN), 3.87 (dd, *J* = 12.4, 17.6 Hz 1H, CH₂C=N), 3.71 (s, 3 H, CH₃), 3.08 (dd, *J* = 6.0, 17.2 Hz 1H, CH₂C=N). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 158.47, 146.06, 144.01, 134.24, 132.94, 131.27, 128.79, 128.65, 127.25, 127.06, 118.71, 114.32, 113.06, 62.80, 54.99, 42.78. *m/z* (EI) 362 (M⁺, 100), 255 (16), 228 (10), 91 (15).

3j: Mp: 134 – 135 °C (Lit.,^{S6} 135 – 137 °C). IR (KBr): 3135, 1498, 1386 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 7.70 – 6.67 (m, 14 H, ArH), 5.41 (dd, *J* = 6.4, 12.0 Hz 1H, ArCHN), 3.89 (dd, *J* = 12.0, 17.6 Hz 1H, CH₂C=N), 3.79 (s, 3 H, CH₃), 3.07 (dd, *J* = 6.0, 17.6 Hz 1H, CH₂C=N). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 159.80, 147.20, 144.55, 142.68, 128.92, 128.77, 127.30, 127.23, 125.82, 124.86, 118.21, 114.10, 112.75, 63.07, 55.21, 43.22. *m/z* (EI) 328 (M⁺, 100), 251 (31), 91 (6).

3k: Mp: 141 – 142 °C (Lit.,^{S7} 142 °C). IR (KBr): 3131, 1499, 1399 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 7.70 – 6.67 (m, 13 H, ArH), 5.36 (dd, *J* = 6.4, 12.0 Hz 1H, ArCHN), 3.85 (dd, *J* = 12.4, 17.6 Hz 1H, CH₂C=N), 3.79 (s, 3 H, CH₃), 3.71 (s, 3 H, CH₃), 3.04 (dd, *J* = 6.4, 17.2 Hz 1H, CH₂C=N). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 159.76, 158.39, 147.14, 144.58, 134.52, 128.68, 127.15, 127.00, 124.95, 118.14, 114.25, 114.07, 112.82, 62.61, 55.17, 54.95, 43.21. *m/z* (EI) 358 (M⁺, 100), 251 (21), 224 (19), 179 (17), 121 (19), 91 (61), 77 (18), 64 (14).

3l: Mp: 130 – 132 °C (Lit.,^{S8} 130 °C). IR (KBr): 3132, 1501, 1400 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 8.24 – 6.78 (m, 14 H, ArH), 5.78 (dd, *J* = 6.4, 12.8 Hz 1H, ArCHN), 4.03 (dd, *J* = 12.8, 17.6 Hz 1H, CH₂C=N), 3.25 (dd, *J* = 6.0, 17.6 Hz 1H, CH₂C=N). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 148.14, 147.54, 144.64, 143.94, 132.62, 131.97, 130.67, 129.02, 128.89, 128.63, 125.80, 122.46, 120.84, 119.00, 112.98, 62.24, 42.62. *m/z* (EI) 343 (M⁺, 20), 313 (100), 221 (61), 194 (9), 91 (15).

3m: Mp: 118 – 119 °C (Lit.,^{S9} 118 – 120 °C). IR (KBr): 3139, 1501, 1395 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 8.27 – 6.77 (m, 14 H, ArH), 5.62 (dd, *J* = 6.4, 12.8 Hz 1H, ArCHN), 3.98 (dd, *J* = 12.4, 17.2 Hz 1H, CH₂C=N), 3.19 (dd, *J* = 6.4, 17.6 Hz 1H, CH₂C=N). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 146.48, 145.00, 143.16, 141.94, 138.62, 129.00, 128.91, 127.53, 126.21, 125.77, 123.88, 119.61, 113.41, 63.59, 42.24. *m/z* (EI) 343 (M⁺, 100), 226 (47), 220 (17), 91 (70), 77 (46), 64 (31).

3n: Mp: 201 – 202 °C (Lit.,^{S10} 203 – 204 °C). IR (KBr): 3350, 3058, 1575, 1343 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 8.03 (s, 1 H, NH₂), 7.90 (s, 1 H, NH₂), 7.89 – 7.13 (m, 10 H, ArH), 5.93 (dd, *J* = 3.2, 11.2 Hz 1H, ArCHN), 3.91 (dd, *J* = 11.6, 18.2 Hz 1H, CH₂C=N), 3.14 (dd, *J* = 3.6, 18.0 Hz 1H, CH₂C=N). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 176.13, 154.91, 142.96, 130.86, 130.54, 128.66, 128.48, 127.09, 126.90, 125.26, 62.83, 42.38. *m/z* (EI) 281 (M⁺, 92), 248 (85), 177 (100), 145 (93), 104 (93), 77 (63).

3o: Mp: 125 °C (Lit.,^{S11} 125 – 126 °C). IR (KBr): 3114, 1502, 1370, 1133 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 7.81 – 6.61 (m, 13 H, furan H and ArH), 5.44 – 5.48 (m, 1H, ArCHN), 3.85 (dd, *J* = 12.0, 17.6 Hz 1H, CH₂C=N), 3.01 (dd, *J* = 6.4, 17.2 Hz 1H, CH₂C=N). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 147.41, 144.22, 144.06, 142.13, 139.20, 128.98, 128.84, 127.43, 125.79, 118.61, 112.91, 111.94, 110.75, 62.52, 42.90. *m/z* (EI) 288 (M⁺, 100), 211 (25), 91 (22), 77 (12).

3p: Mp: 111 – 113 °C (Lit.,^{S2} 112 °C). IR (KBr): 3446, 1598, 1504, 1402 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 7.35 – 6.61 (m, 10 H, ArH), 5.12 (dd, *J* = 7.2, 12.0 Hz 1H, ArCHN), 3.50 (dd, *J* = 12.0, 17.6 Hz 1H, CH₂C=N), 2.64 (dd, *J* = 7.2, 17.6 Hz 1H, CH₂C=N), 2.01 (s, 3H, CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 149.76, 146.24, 143.79, 129.53, 129.35, 127.83, 126.50, 118.45, 113.16, 63.94, 16.18. *m/z* (EI) 236 (M⁺, 100), 159 (62), 91 (54), 77 (14).

References

- S1 M. Kidwai, S. Kukreja and R. Thakur, *Lett. Org. Chem.*, 2006, **3**, 135.
- S2 K. W. Klupfel, O. Sus, W. Neugebauer and H. Behmenburg, *US Pat.*, 3180729, 1965.
- S4 V. G. Tishchenko, *Metody Polu. Khim. Reak. i Prep.*, 1964, 97.
- S5 O. Tsuge, H. Watanabe and Y. Kiryu, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 3654.
- S6 D. C. Reames, C. E. Harris, L. W. Dasher, R. M. Sandifer, W. M. Hollinger and C. F. Beam, *J. Heterocycl. Chem.*, 1975, **12**, 779.
- S7 D. Azarifar and B. Maleki, *J. Heterocycl. Chem.*, 2005, **42**, 157.
- S8 G. H. Sayed and H. Kjoesen, *J. Prakt. Chem. (Leipzig)*, 1980, **322**, 716.
- S9 J. N. Shah and C. K. Shah, *J. Org. Chem.*, 1978, **43**, 1266.
- S10 E. Jedlovska, L. Fisera and T. Liptaj, *Chem. Pap.*, 2005, **59**, 354.
- S11 S. Rathinasamy, S. S. Karki, S. Bhattacharya, L. Manikandan, S. G. Prabakaran, M. Gupta and U. K. Mazumder, *J. Enzym. Inhib. Med. Chem.*, 2006, **21**, 501.
- S12 Z. Oezdemir, H. B. Kandilci, B. Guemuesel, U. Calis, A. A. Bilgin, *Eur. J. Med. Chem.*, 2007, **42**, 373.