Condensation of *ortho*-phenylenediamines and phenylhydrazines with ethyl 4-chloro-3-oxobutanoate: A facile approach for the synthesis of substituted 1*H*-benzimidazoles, pyrazolones and pyrazoles

Dayakar Cherupally, Jyothi Dondra, Suman Pathi, China Raju Bhimapaka*

Natural Products Chemistry Division, CSIR-Indian Institute of Chemical Technology,

Hyderabad-500 007, India (phone: +914027161725; fax: +91402716512).

e-mail: chinaraju@iict.res.in

Experimental protocol

Ortho-phenylenediamines and ethyl 4-chloro-3-oxobutanoate were obtained from Sigma-Aldrich, phenylhydrazine hydrochlorides and solvents were commercially available. Column Chromatography (CC): silica gel (SiO₂; 60-120 mesh). Mp: Mettler-Temp apparatus; uncorrected. IR Spectra: Perkin-Elmer-1600 FT-IR spectrometer; in KBr; ν in cm⁻¹. ¹H- and ¹³C-NMR spectra: Bruker-Avance-300 spectrometers; solvent CDCl₃; chemical shifts δ in ppm rel. to Me₄Si as internal standard, *J* in Hz. MS-ESI: 7070 *H* spectrometer with a direct inlet system; in *m/z* (rel. %). ESI-HR-MS: Agilent 6510 Q-TOF LC/MS instrument.

Experimental Data

2-(Chloromethyl)-1*H*-benzo[*d*]imidazole (**3a**)

Pale yellow solid; Yield: 82%; Mp 152-154 °C; ¹H NMR (300 MHz, CDCl₃): δ = 4.85 (s, 2H, CH₂Cl), 7.19-7.28 (m, 2H, Ar-H), 7.55-7.62 (m, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃) δ = 37.4, 114.6, 121.7, 137.9, 148.7.; MS (ESI⁺) *m/z* = 167 (M+H)⁺.

2-(Chloromethyl)-5-nitro-1*H*-benzo[*d*]imidazole (**3b**)

Pale yellow solid; Yield: 75%; Mp 178-180 °C; ¹H NMR (300 MHz, CDCl₃): δ = 4.87 (s, 2H, CH₂Cl), 7.54-7.82 (m, 1H, Ar-H), 8.17 (s, 1H, Ar-H), 8.38-8.62 (m, 1H, Ar-H); MS (ESI⁺) *m/z* = 212 (M+H)⁺.

5-Chloro-2-(chloromethyl)-1*H*-benzo[*d*]imidazole (**3c**)

Pale yellow solid; Yield: 72%; Mp 128-130 °C; ¹H NMR (300 MHz, CDCl₃): δ = 4.82 (s, 2H, CH₂Cl), 7.18-7.22 (m, 1H, Ar-H), 7.41-7.53 (m, 1H, Ar-H), 7.57 (s, 1H, Ar-H); MS (ESI⁺) *m/z* = 201 (M+H)⁺.

(2-(Chloromethyl)-1*H*-benzo[*d*]imidazol-5-yl)(phenyl)methanone (**3d**)

Pale yellow solid; Yield: 60%; Mp 179-181 °C; ¹H NMR (300 MHz, CDCl₃): δ = 4.88 (s, 2H, CH₂Cl), 7.44-7.51 (m, 2H, Ar-H), 7.56-7.68 (m, 2H, Ar-H), 7.78-7.84 (m, 2H, Ar-H), 8.08 (s, 1H, Ar-H); MS (ESI⁺) *m/z* = 271 (M+H)⁺.

2-(Chloromethyl)-5-methyl-1*H*-benzo[*d*]imidazole (**3e**)

Pale yellow solid; Yield: 65%; Mp 148-150 °C; ¹H NMR (300 MHz, CDCl₃): δ = 2.57 (s, 3H, CH₃), 4.85 (s, 2H, CH₂Cl), 7.0-7.21 (m, 2H, Ar-H), 7.40 (s, 1H, Ar-H); MS (ESI⁺) *m/z* = 181 (M+H)⁺.

2-(Chloromethyl)-5,6-dimethyl-1*H*-benzo[*d*]imidazole (**3f**)

Pale yellow solid; Yield: 62%; Mp 153-155 °C; ¹H NMR (300 MHz, CDCl₃): δ = 2.36 (s, 6H, 2 CH₃), 4.82 (s, 2H, CH₂Cl), 7.33 (s, 1H, Ar-H); MS (ESI⁺) *m/z* = 195 (M+H)⁺.

3-(Chloromethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**5a**)

Pale yellow solid; Yield: 62%; Mp 117-119 °C; IR (KBr) 2795, 1759, 1558, 1407, 1259, 1155, 1032, 761, 696 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 3.62 (s, 2H, CH₂), 4.39 (s, 2H, CH₂Cl), 7.21 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.40 (t, *J* = 7.3 Hz, 2H, Ar-H), 7.82 (d, *J* = 8.3 Hz, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ = 39.6, 40.1, 118.9, 125.5, 128.8, 137.5, 154.5, 170.0.; MS (ESI⁺) *m/z* = 209 (M+H)⁺; HRMS (ESI⁺) calcd for C₁₀H₁₀ClN₂O (M+H)⁺ 209.0474, found 209.0476.

3-(Chloromethyl)-1-(3-nitrophenyl)-1*H*-pyrazol-5(4*H*)-one (**5b**)

Pale yellow solid; Yield: 52%; Mp 84-86 °C; IR (KBr) 2924, 2854, 1736, 1532, 1352, 1139, 1024, 739, 673 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 3.71 (s, 2H, CH₂), 4.44 (s, 2H,

CH₂Cl), 7.55 (t, J = 8.1, 1H, Ar-H), 8.02 (dd, J = 0.9, 8.1 Hz, 1H, Ar-H), 8.27 (dd, J = 0.9, 8.3 Hz, 1H, Ar-H), 8.68 (s, 1H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ = 40.3, 58.8, 69.5, 116.5, 118.6, 125.0, 129.8, 134.5, 138.8, 156.9, 170.3.; MS (ESI⁺) m/z = 254 (M+H)⁺; HRMS (ESI⁺) calcd for C₁₀H₉ClN₃O₃ (M+H)⁺ 254.0327, found 254.0325.

3-(Chloromethyl)-5-ethoxy-1-phenyl-1H-pyrazole (6a)

Yellow liquid; Yield: 5%; IR (KBr) 2928, 1561, 1262, 1140, 1044, 758, 690 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.45 (t, J = 7.0 Hz, 3H, CH₃), 4.18 (q, J = 7.0 Hz, 2H, OCH₂), 4.57 (s, 2H, CH₂), 5.75 (s, 1H, CH), 7.27 (tt, J = 1.1, 7.5 Hz, 1H, Ar-H), 7.41 (t, J = 7.5 Hz, 2H, Ar-H), 7.69 (dd, J = 1.0, 8.5 Hz, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ = 4.5, 39.8, 68.0, 85.6, 122.1, 126.3, 128.7, 138.3, 148.5, 155.0.; MS (ESI⁺) m/z = 236 (M+H)⁺; HRMS (ESI⁺) calcd for C₁₂H₁₃ClN₂ONa (M+Na)⁺ 259.0608, found 259.0614.

3-(Chloromethyl)-5-ethoxy-1-(3-nitrophenyl)-1H-pyrazole (6b)

Yellow liquid; Yield: 10%; IR (KBr) 2986, 1527, 1351, 1263, 1008, 735, 681 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.52 (t, J = 7.0 Hz, 3H, CH₃), 4.26 (q, J = 7.0 Hz, 2H, OCH₂), 4.56 (s, 2H, CH₂Cl), 5.79 (s, 1H, CH), 7.59 (t, J = 8.3 Hz, 1H, Ar-H), 8.13 (ddd, J = 0.9, 2.0 and 8.3 Hz, 2H, Ar-H), 8.69 (t, J = 2.0, 1H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ = 14.5, 39.4, 68.6, 86.2, 116.2, 120.4, 126.7, 129.6, 139.4, 148.5, 149.8, 155.5.; MS (ESI⁺) m/z = 282 (M+H)⁺; HRMS (ESI⁺) calcd for C₁₂H₁₃ClN₃O₃ (M+H)⁺ 282.0640, found 282.0643.

3-(Chloromethyl)-5-ethoxy-1-(4-fluorophenyl)-1H-pyrazole (6c)

Yellow liquid; Yield: 18%; IR (KBr) 2923, 1515, 1224, 1095, 837, 771 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.52 (t, J = 7.0 Hz, 3H, CH₃), 4.26 (t, J = 7.0 Hz, 2H, OCH₂), 4.56 (s, 2H, CH₂Cl), 5.76 (s, 1H, CH), 7.58 (t, J = 2.1 Hz, 1H, Ar-H), 8.13 (ddd, J = 8.2, 2.1 and 0.7, 2H, Ar-H), 8.69 (t, J = 2.1 Hz 1H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ = 14.5, 39.7, 68.13, 85.6, 115.5, 115.6, 123.9, 123.9, 148.6, 154.8.; MS (ESI⁺) m/z = 255 (M+H)⁺; HRMS (ESI⁺) calcd for C₁₂H₁₃ClFN₂O (M+H)⁺ 255.0615, found 255.0700.

3-(Chloromethyl)-5-ethoxy-1-p-tolyl-1H-pyrazole (6d)

Yellow liquid; Yield: 20%; IR (KBr) 2926, 2854, 1663, 1525, 1323, 1216, 1112, 1033, 777 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 1.43 (t, J = 7.0 Hz, 3H, CH_3), 3.26 (s, 2H, CH_3), 4.16 (q, J = 7.0 Hz, 2H, OCH_2), 4.56 (s, 2H, CH_2Cl), 5.76 (s, 1H, CH), 7.21 (d, J = 8.8 Hz, 2H, Ar-H), 7.55 (d, J = 8.8 Hz, 2H, Ar-H); MS (ESI^+) m/z = 251 ($\text{M}+\text{H}$) $^+$; HRMS (ESI^+) calcd for $\text{C}_{13}\text{H}_{17}\text{ClN}_2\text{O}$ ($\text{M}+\text{H}$) $^+$ 251.0945, found 251.0944.

3-(Chloromethyl)-5-ethoxy-1-(4-nitrophenyl)-1H-pyrazole (6e)

Colorless liquid; Yield: 22%; IR (KBr) 2983, 1597, 1508, 1335, 1112, 1038, 849, 750 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 1.52 (t, J = 6.9 Hz, 3H, CH_3), 4.25 (q, J = 6.9 Hz, 2H, OCH_2), 4.55 (s, 2H, CH_2Cl), 5.80 (s, 1H, CH), 8.01 (d, J = 9.2 Hz, 2H, Ar-H), 8.29 (d, J = 9.2 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, CDCl_3): δ = 14.5, 39.3, 68.7, 86.6, 120.8, 124.6, 143.5, 144.9, 150.4, 155.9.; MS (ESI^+) m/z = 282 ($\text{M}+\text{H}$) $^+$.

3-(Methoxymethyl)-1-phenyl-1H-pyrazol-5(4H)-one (7a)

Pale yellow solid; Yield: 52%; Mp 122-124 $^{\circ}\text{C}$; IR (KBr) 2925, 2821, 1737, 1553, 1396, 1111, 1029, 755, 686 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 3.42 (s, 3H, OCH_3), 3.54 (s, 2H, CH_2), 4.28 (s, 2H, OCH_2), 7.19 (t, J = 7.4 Hz, 1H, Ar-H), 7.40 (t, J = 7.7 Hz, 2H, Ar-H), 7.85 (d, J = 7.7 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, CDCl_3): δ = 40.3, 58.8, 69.6, 118.9, 125.2, 128.8, 137.8.; MS (ESI^+) m/z = 205 ($\text{M}+\text{H}$) $^+$; HRMS (ESI^+) calcd for $\text{C}_{11}\text{H}_{13}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 205.0970, found 205.0971.

3-(Ethoxymethyl)-1-phenyl-1H-pyrazol-5(4H)-one (7b)

Yellow liquid; Yield: 45%; IR (KBr) 2923, 2820, 1729, 1559, 1406, 1311, 1156, 1096, 1027, 950, 812, 768, 641 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 1.25 (t, J = 6.8 Hz, 3H, CH_3), 3.55 (s, 2H, CH_2), 3.58 (q, J = 6.8 Hz, 2H, OCH_2), 4.32 (s, 2H, OCH_2), 7.19 (t, J = 7.5, 1H, Ar-H), 7.39 (t, J = 7.5 Hz, 2H, Ar-H), 7.85 (t, J = 7.5 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz,

CDCl₃): δ = 15.0, 40.4, 66.6, 67.7, 118.9, 125.2, 128.8, 137.8, 156.9, 170.5.; MS (ESI⁺) m/z = 219 (M+H)⁺; HRMS (ESI⁺) calcd for C₁₂H₁₅N₂O₂ (M+H)⁺ 219.1128, found 219.1131.

3-(Isopropoxymethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (7c)

Pale yellow solid; Yield: 39%; Mp 123-125 °C; IR (KBr) 2923, 2821, 1734, 1559, 1407, 1245, 1156, 1095, 951, 812 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.20 (s, 3H, CH₃), 1.23 (s, 3H, CH₃), 3.55 (s, 2H, CH₂), 3.65-3.74 (m, 1H CH), 4.32 (s, 2H, CH₂), 7.19 (t, J = 7.5 Hz, 1H, Ar-H), 7.34 (t, J = 7.5 Hz, 2H, Ar-H), 7.84 (d, J = 7.7 Hz, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ = 21.9, 40.4, 65.4, 72.2, 118.9, 125.2, 128.8, 137.8, 157.4, 170.5.; MS (ESI⁺) m/z = 233 (M+H)⁺; HRMS (ESI⁺) calcd for C₁₃H₁₇N₂O₂ (M+H)⁺ 233.1284, found 233.1287.

3-(Isobutoxymethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (7d)

Pale yellow solid; Yield: 36%; Mp 78-90 °C; IR (KBr) 2959, 2873, 1727, 1551, 1258, 1090, 755, 682 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.92 (s, 3H, CH₃), 0.94 (s, 3H, CH₃), 1.85-1.93 (m, 1H, CH); 3.27 (d, J = 6.6 Hz, 2H, CH₂), 3.55 (s, 2H, CH₂), 4.31 (s, 2H, OCH₂), 7.19 (t, J = 7.3 Hz, 1H, Ar-H), 7.40 (t, J = 7.5 Hz, 2H, Ar-H), 7.85 (d, J = 8.6 Hz, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ = 19.2, 28.4, 40.4, 68.1, 78.0, 118.9, 125.2, 128.7, 137.8, 157.1, 170.1.; MS (ESI⁺) m/z = 247 (M+H)⁺; HRMS (ESI⁺) calcd for C₁₄H₁₉N₂O₂ (M+H)⁺ 247.1441, found 247.1443.

3-(Butoxymethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (7e)

Pale yellow solid; Yield: 35%; Mp 76-78 °C; IR (KBr) 2957, 2872, 1746, 1527, 1351, 1169, 1096, 758, 696 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.93 (t, J = 7.3, 3H, CH₃), 1.35-1.42 (m, 2H, CH₂), 1.56-1.62 (m, 2H, CH₂), 3.50 (t, J = 6.6 Hz, 2H, CH₂), 3.54 (s, 2H, CH₂), 4.31 (s, 2H, OCH₂), 7.19 (t, J = 7.3 Hz, 1H, Ar-H), 7.39 (t, J = 8.2 Hz, 2H, Ar-H), 7.62 (d, J = 7.6 Hz, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ = 13.8, 19.2, 31.5, 40.4, 67.9, 71.1, 118.9,

125.2, 128.7, 137.8, 157.0, 170.5; MS (ESI⁺) m/z = 247 (M+H)⁺; HRMS (ESI⁺) calcd for C₁₄H₁₉N₂O₂ (M+H)⁺ 247.1441, found 247.1444.

1-(4-Fluorophenyl)-3-(methoxymethyl)-1*H*-pyrazol-5(4*H*)-one (**7f**)

Colorless solid; Yield: 56%; Mp 110-112 °C; IR (KBr) 2915, 1743, 1565, 1244, 1028, 836, 761, 647 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 3.43 (s, 3H, OCH₃), 3.54 (s, 2H, CH₂), 4.27 (s, 2H, CH₂), 7.08 (t, J = 8.5 Hz, 2H, Ar-H), 7.79-7.85 (m, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ = 40.2, 58.9, 69.6, 115.4, 115.7, 120.7, 156.7, 158.4, 170.3.; MS (ESI⁺) m/z = 223 (M+H)⁺; HRMS (ESI⁺) calcd for C₁₁H₁₂FN₂O₂ (M+H)⁺ 223.0877, found 223.0876.

1-(4-Bromophenyl)-3-(methoxymethyl)-1*H*-pyrazol-5(4*H*)-one (**7g**)

Pale yellow solid; Yield: 54%; Mp 115-117 °C; IR (KBr) 2923, 2820, 1729, 1559, 1406, 1245, 1096, 812, 768 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 3.43 (s, 3H, OCH₃), 3.54 (s, 2H, CH₂), 4.27 (s, 2H, CH₂), 7.50 (d, J = 8.8 Hz, 2H, Ar-H), 7.78 (d, J = 8.8, 2H, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ = 40.3, 58.9, 69.5, 118.0, 120.2, 131.8, 136.9, 156.9, 170.3.; MS (ESI⁺) m/z = 283 (M+H)⁺; HRMS (ESI⁺) calcd for C₁₁H₁₂BrN₂O₂ (M+H)⁺ 283.0076, found 283.0074.

3-(Methoxymethyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5(4*H*)-one (**7h**)

Pale yellow solid; Yield: 50%; Mp 120-122 °C; IR (KBr) 2957, 1738, 1561, 1405, 1250, 1034, 822, 764, 644 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 3.42 (s, 3H, OCH₃), 3.52 (s, 2H, CH₂), 3.81 (s, 3H, OCH₃), 4.27 (s, 2H, CH₂), 6.92 (d, J = 9.2 Hz, 2H, Ar-H), 7.71 (d, J = 9.2 Hz, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ = 40.1, 55.4, 58.8, 69.6, 113.9, 120.9, 131.1, 156.3, 157.1, 170.2.; MS (ESI⁺) m/z = 235 (M+H)⁺; HRMS (ESI⁺) calcd for C₁₂H₁₅N₂O₃ (M+H)⁺ 235.1075, found 235.1077.

3-(Methoxymethyl)-1-*p*-tolyl-1*H*-pyrazol-5(4*H*)-one (**7i**)

Colorless solid; Yield: 51%; Mp 112-114 °C; IR (KBr) 2925, 2818, 1741, 1534, 1403, 1273, 1093, 817, 770 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 2.34 (s, 3H, CH₃), 3.42 (s, 3H, OCH₃)

3.52 (s, 2H, CH₂) 4.27 (s, 2H, CH₂) 7.20 (d, *J* = 8.2 Hz, 2H, Ar-H) 7.70 (d, *J* = 8.5 Hz, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ = 40.2, 53.4, 58.8, 69.6, 115.4, 115.6, 120.7, 120.7, 156.6, 170.2.; MS (ESI⁺) *m/z* = 219 (M+H)⁺.

1-(3-Chlorophenyl)-3-(methoxymethyl)-1*H*-pyrazol-5(4*H*)-one (**7j**)

Pale yellow solid; Yield: 55%; Mp 113-115 °C; IR (KBr) 2914, 1741, 1591, 1401, 1244, 1097, 787, 682 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 3.43 (s, 3H, OCH₃), 3.55 (s, 2H, CH₂), 4.28 (s, 2H, CH₂), 7.16 (ddd, *J* = 0.9, 1.1, and 8.9 Hz, 1H, Ar-H), 7.31 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.82 (ddd, *J* = 0.9, 1.1, and 8.2 Hz, 1H, Ar-H), 7.91 (t, *J* = 1.1 Hz, 1H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ = 40.3, 58.8, 69.5, 116.5, 118.6, 125.0, 129.8, 134.5, 138.8, 156.9, 170.3.; MS (ESI⁺) *m/z* = 239 (M+H)⁺; HRMS (ESI⁺) calcd for C₁₁H₁₂ClN₂O₂ (M+H)⁺ 239.0580, found 239.0581.

3-(Methoxymethyl)-1-(3-nitrophenyl)-1*H*-pyrazol-5(4*H*)-one (**7k**)

Pale yellow solid; Yield: 58%; Mp 96-98 °C; IR (KBr) 2924, 1621, 1530, 1350, 1273, 1097, 894, 737 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 3.45 (s, 3H, OCH₃), 3.61 (s, 2H, CH₂), 4.32 (s, 2H, CH₂), 7.56 (t, *J* = 8.2 Hz, 1H, Ar-H), 8.04 (ddd, *J* = 0.9, 2.1 and 8.2 Hz, 1H, Ar-H), 8.34 (dd, *J* = 1.0, 8.2, 1H, Ar-H), 8.74 (t, *J* = 2.1, 1H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ = 40.4, 58.9, 69.4, 113.2, 116.6, 119.4, 123.7, 127.1, 129.7, 157.6, 170.5.; MS (ESI⁺) *m/z* = 272 (M+Na)⁺; HRMS (ESI⁺) calcd for C₁₁H₁₁ClN₃O₄Na (M+Na)⁺ 272.0641, found 272.0642.

3-(Ethoxymethyl)-1-*p*-tolyl-1*H*-pyrazol-5(4*H*)-one (**7l**)

Yellow liquid; Yield: 45%; IR (KBr) 2925, 2861, 1719, 1517, 1104, 1022, 818, 764 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.25 (t, *J* = 7.0, 3H, CH₃), 2.34 (s, 3H, CH₃) 3.53 (s, 2H, CH₂), 3.57 (q, *J* = 7.0 Hz, 2H, OCH₂), 4.30 (s, 2H, CH₂), 7.19 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.70 (d, *J* = 8.5 Hz, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ = 15.0, 20.9, 40.3, 66.6, 67.7, 119.0, 129.3, 134.9, 135.3, 156.7, 170.4.; MS (ESI⁺) *m/z* = 233 (M+H)⁺; HRMS (ESI⁺) calcd for C₁₃H₁₇N₂O₂ (M+H)⁺ 233.1284, found 233.1281.

1-(3-Chlorophenyl)-3-(ethoxymethyl)-1*H*-pyrazol-5(4*H*)-one (**7m**)

Yellow liquid; Yield: 39%; IR (KBr) 2926, 1737, 1593, 1347, 1255, 1098, 875, 779 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 1.25 (t, J = 7.0 Hz, 3H, CH_3), 3.56 (s, 2H, CH_2), 3.59 (q, J = 7.0 Hz, 2H, OCH_2), 4.32 (s, 2H, CH_2), 7.16 (ddd, J = 0.9, 1.1 and 7.9 Hz, 1H, Ar-H), 7.31 (t, J = 8.1 Hz, 1H, Ar-H), 7.82 (ddd, J = 0.9, 1.1 and 8.2 Hz, 1H, Ar-H), 7.91 (t, J = 1.1 Hz, 1H, Ar-H); ^{13}C NMR (75 MHz, CDCl_3): δ = 15.0, 40.4, 66.8, 67.7, 116.5, 118.7, 125.1, 129.8, 134.5, 138.9, 157.3, 170.4.; MS (ESI^+) m/z = 253 ($\text{M}+\text{Na}$) $^+$; HRMS (ESI^+) calcd for $\text{C}_{12}\text{H}_{13}\text{ClN}_2\text{O}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 253.0738, found 253.0741.

3-(Ethoxymethyl)-1-(3-nitrophenyl)-1*H*-pyrazol-5(4*H*)-one (**7n**)

Yellow liquid; Yield: 51%; IR (KBr) 2925, 1726, 1531, 1349, 1250, 1154, 1096, 834, 737 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 1.24 (t, J = 7.0 Hz, 3H, CH_3), 3.54 (s, 2H, CH_2), 3.58 (q, J = 7.0 Hz, 2H, CH_2), 4.31 (s, 2H, CH_2), 7.19 (t, J = 7.5, 1H, Ar-H), 7.39 (t, J = 7.5 Hz, 2H, Ar-H), 7.84 (dd, J = 0.9, 8.5 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, CDCl_3): δ = 15.0, 17.0, 43.1, 66.8, 67.5, 113.1, 119.1, 119.4, 123.6, 129.6, 138.9, 148.4, 157.2, 170.6.; MS (ESI^+) m/z = 264 ($\text{M}+\text{H}$) $^+$; HRMS (ESI^+) calcd for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_4$ ($\text{M}+\text{H}$) $^+$ 264.0988, found 264.0979.

1-(3-Chlorophenyl)-3-(isopropoxymethyl)-1*H*-pyrazol-5(4*H*)-one (**7o**)

Yellow solid; Yield: 45%; Mp 102-104 $^{\circ}\text{C}$; ^1H NMR (300 MHz, CDCl_3): δ = 1.21 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 3.56 (s, 2H, CH_2), 3.66-3.74 (m, 1H, CH), 4.32 (s, 2H, CH_2), 7.16 (ddd, J = 0.8, 1.1 and 7.9 Hz, 1H, Ar-H), 7.31 (t, J = 8.0 Hz, 1H, Ar-H), 7.82 (ddd, J = 0.8, 1.1 and 8.2, 1H, Ar-H), 7.91 (t, J = 1.1 Hz, 1H, Ar-H); ^{13}C NMR (75 MHz, CDCl_3): δ = 21.9, 39.7, 40.0, 40.5, 65.3, 72.3, 116.5, 116.5, 118.7, 125.0, 129.8, 157.8, 170.5.; MS (ESI^+) m/z = 266 ($\text{M}+\text{H}$) $^+$; HRMS (ESI^+) calcd for $\text{C}_{13}\text{H}_{15}\text{ClN}_2\text{O}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 289.0714, found 289.0712.

5-Ethoxy-3-(methoxymethyl)-1-phenyl-1*H*-pyrazole (**8a**)

Yellow liquid; Yield: 15%; IR (KBr) 2925, 2854, 1509, 1456, 1266, 1096, 759, 693 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 1.45 (t, J = 7.0 Hz, 3H, CH_3), 4.18 (q, J = 7.0 Hz, 2H, OCH_2),

4.57 (s, 2H, CH₂), 5.75 (s, 1H, CH), 7.27 (t, $J = 7.4$ Hz, 1H, Ar-H), 7.41 (t, $J = 7.4$ Hz, 2H, Ar-H), 7.69 (d, $J = 8.5$ Hz, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): $\delta = 14.5, 58.1, 67.8, 69.0, 85.3, 122.0, 126.0, 128.6, 138.5, 149.4, 154.8$; MS (ESI⁺) $m/z = 233$ (M+H)⁺; HRMS (ESI⁺) calcd for C₁₃H₁₇N₂O₂ (M+H)⁺ 233.1284, found 233.1289.

5-Ethoxy-3-(ethoxymethyl)-1-phenyl-1H-pyrazole (8b).

Yellow liquid; Yield: 18%; ¹H NMR (300 MHz, CDCl₃): $\delta = 1.25$ (t, $J = 7.0$ Hz, 1H, CH₃), 1.43 (t, $J = 7.0$ Hz, 3H, CH₃), 3.60 (q, $J = 7.0$ Hz, 2H, OCH₂), 4.17 (q, $J = 7.0$ Hz, 2H, OCH₂), 4.48 (s, 2H, CH₂), 5.72 (s, 1H, CH), 7.24 (t, $J = 7.4$ Hz, 1H, Ar-H), 7.40 (t, $J = 7.4$ Hz, 2H, Ar-H), 7.70 (dd, $J = 8.8, 0.7$ Hz, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): $\delta = 14.5, 15.1, 65.8, 67.1, 67.1, 67.8, 85.4, 122.0, 126.0, 128.6, 138.6, 149.8, 154.9$; MS (ESI⁺) $m/z = 247$ (M+H)⁺.

5-Ethoxy-1-(4-fluorophenyl)-3-(methoxymethyl)-1H-pyrazole (8c)

Yellow liquid; Yield: 14%; IR (KBr) 2923, 2852, 1515, 1466, 1230, 1043, 836, 727 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): $\delta = 1.43$ (t, $J = 7.0$ Hz, 3H, CH₃), 3.42 (s, 3H, CH₃), 4.16 (q, $J = 7.0$ Hz, 2H, OCH₂), 4.42 (s, 2H, CH₂), 5.70 (s, 1H, CH), 7.09 (t, $J = 8.8$ Hz, 2H, Ar-H), 7.65-7.68 (m, 2H, Ar-H); MS (ESI⁺) $m/z = 251$ (M+H)⁺; HRMS (ESI⁺) calcd for C₁₃H₁₅FN₂O₂Na [M+Na]⁺ 273.1009, found 273.1010.

1-(4-Bromophenyl)-5-ethoxy-3-(methoxymethyl)-1H-pyrazole (8d)

Yellow liquid; Yield: 18%; IR (KBr) 2924, 2853, 1505, 1263, 1096, 827, 754 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): $\delta = 1.44$ (dt, $J = 1.5, 7.0$ Hz, 3H, CH₃), 3.42 (s, 3H, OCH₃), 4.14 (dq, $J = 1.5, 7.0$ Hz, 2H, OCH₂), 4.42 (s, 2H, CH₂), 5.70 (s, 1H, CH), 7.52 (dd, $J = 1.0, 8.8$ Hz, 2H, Ar-H), 7.63 (d, $J = 8.8$ Hz, 2H, Ar-H); MS (ESI⁺) $m/z = 333$ (M+Na)⁺; HRMS (ESI⁺) calcd for C₁₃H₁₅BrN₂O₂Na (M+Na)⁺ 333.0209, found 333.0205.

3-(Chloromethyl)-5-ethoxy-1-*p*-tolyl-1*H*-pyrazole (**8e**)

Yellow liquid; Yield: 12%; IR (KBr) 2923, 1519, 1467, 1265, 1093, 818, 753 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.44 (dt, *J* = 1.5, 7.0 Hz, 3H, CH₃), 3.42 (s, 3H, CH₃), 4.14 (dq, *J* = 7.0, 1.5 Hz, 2H, OCH₂), 4.42 (s, 2H, CH₂), 5.70 (s, 1H, CH), 7.52 (dd, *J* = 8.8, 1.0 Hz, 2H, Ar-H), 7.63 (td, *J* = 8.8, 2.8 Hz, 2H, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ = 14.5, 20.9, 39.9, 67.9, 85.4, 122.1, 129.3, 135.9, 136.2, 148.2, 154.8.; MS (ESI⁺) *m/z* = 247 (M+H)⁺; HRMS (ESI⁺) calcd for C₁₄H₁₉N₂O₂ (M+H)⁺ 247.1441, found 247.1440.

1-(3-Chlorophenyl)-5-ethoxy-3-(methoxymethyl)-1*H*-pyrazole (**8f**)

Yellow liquid; Yield: 15%; IR (KBr) 2925, 1594, 1504, 1439, 1246, 1096, 778, 682 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.46 (t, *J* = 7.0, 3H, CH₃), 3.42 (s, 3H, OCH₃), 4.19 (q, *J* = 7.0, 2H, OCH₂), 4.42 (s, 2H, CH₂), 5.70 (s, 1H, CH), 7.21 (dq, *J* = 8.0, 1.0 Hz, 1H, Ar-H), 7.32 (t, *J* = 8.2 Hz, 1H, Ar-H), 7.66 (dq, *J* = 8.2, 1.0 Hz, 1H, Ar-H), 7.79 (t, *J* = 1.1 Hz, 1H, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ = 14.5, 58.2, 68.1, 68.9, 85.6, 119.5, 129.8, 125.9, 129.7, 134.4, 139.6, 150.0, 155.1.; MS (ESI⁺) *m/z* = 267 (M+H)⁺; HRMS (ESI⁺) calcd for C₁₃H₁₅ClN₂O₂Na (M+Na)⁺ 289.0714, found 289.0716.

5-Ethoxy-3-(methoxymethyl)-1-(3-nitrophenyl)-1*H*-pyrazole (**8g**)

Yellow liquid; Yield: 10%; IR (KBr) 2924, 1527, 1350, 1262, 1035, 732, 678 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.44 (dt, *J* = 1.5, 7.0 Hz, 3H, CH₃), 3.42 (s, 3H, CH₃), 4.14 (dq, *J* = 1.5, 7.0 Hz, 2H, OCH₂), 4.42 (s, 2H, CH₂), 5.70 (s, 1H, CH), 7.52 (dd, *J* = 1.1, 8.8 Hz, 2H, Ar-H), 7.63 (td, *J* = 2.9, 2H, Ar-H); MS (ESI⁺) *m/z* = 278 (M+H)⁺.

5-Ethoxy-3-(ethoxymethyl)-1-*p*-tolyl-1*H*-pyrazole (**8h**)

Yellow liquid; Yield: 15%; IR (KBr) 2925, 2854, 1663, 1520, 1216, 1110, 1047, 819, 747 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.24 (t, *J* = 7.0 Hz, 3H, CH₃), 1.42 (t, *J* = 7.0 Hz, 3H, CH₃), 2.34 (s, 3H, CH₃), 3.59 (q, *J* = 7.0 Hz, 2H, OCH₂), 4.15 (q, *J* = 7.0 Hz, 2H, OCH₂), 4.47 (s, 2H, CH₂), 5.71 (s, 1H, CH), 7.20 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.56 (d, *J* = 8.3 Hz, 2H,

Ar-H). ^{13}C NMR (75 MHz, CDCl_3): δ = 14.6, 15.2, 20.9, 65.8, 67.2, 67.7, 85.3, 122.1, 129.1, 135.9, 136.1, 149.5, 154.8.; MS (ESI^+) m/z = 261 ($\text{M}+\text{H}$) $^+$; HRMS (ESI^+) calcd for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 261.1597, found 261.1598.

1-(3-Chlorophenyl)-5-ethoxy-3-(ethoxymethyl)-1*H*-pyrazole (**8i**)

Yellow liquid; Yield: 16%; ^1H NMR (300 MHz, CDCl_3): δ = 1.25 (t, J = 7.0 Hz, 3H, CH_3), 1.46 (t, J = 7.0 Hz, 3H, CH_3), 3.60 (q, J = 7.0 Hz, 2H, OCH_2), 4.19 (q, J = 7.0 Hz, 2H, OCH_2), 4.47 (s, 2H, CH_2), 5.72 (s, 1H, CH), 7.21 (ddd, J = 8.0, 1.9 and 0.9 Hz, 1H, Ar-H), 7.32 (t, J = 8.0 Hz, 1H, Ar-H), 7.65 (ddd, J = 8.2, 1.9 and 0.9 Hz, 1H, Ar-H), 7.78 (t, J = 1.9 Hz, 1H, Ar-H); MS (ESI^+) m/z = 281 ($\text{M}+\text{H}$) $^+$; HRMS (ESI^+) calcd for $\text{C}_{14}\text{H}_{17}\text{ClN}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 303.0870, found 303.0872.

Ethoxy-3-(ethoxymethyl)-1-(3-nitrophenyl)-1*H*-pyrazole (**8j**)

Yellow liquid; Yield: 11%; IR (KBr) 2985, 2936, 1531, 1350, 1257, 1028, 736, 684 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 1.27 (t, J = 6.7 Hz, 3H, CH_3), 1.5 (t, J = 6.9 Hz, 3H, CH_3), 3.61 (q, J = 6.7, 2H, OCH_2), 4.24 (q, J = 6.7 Hz, 2H, OCH_2), 4.49 (s, 2H, CH_2), 5.77 (s, 1H, CH), 7.58 (t, J = 8.3 Hz, 1H, Ar-H), 8.06 (m, 2H, Ar-H), 8.71 (s, 1H, Ar-H); MS (ESI^+) m/z = 292 ($\text{M}+\text{H}$) $^+$.

^1H NMR of compound 3d

^1H NMR of compound 3e

^1H NMR of compound 3f

HRMS of compound 5a

¹H NMR of compound 5b

¹³C NMR of compound 5b

HRMS of compound 5b

HRMS of compound 6a

HRMS of compound 6b

HRMS of compound 6c

HRMS of compound 6d

¹H NMR of compound 7b

¹³C NMR of compound 7b

HRMS of compound 7b

HRMS of compound 7c

HRMS of compound 7d

HRMS of compound 7e

HRMS of compound 7f

HRMS of compound 7g

HRMS of compound 7h

HRMS of compound 7k

HRMS of compound 7l

HRMS of compound 7m

HRMS of compound 7n

HRMS of compound 7o

HRMS of compound 8a

HRMS of compound 8c

HRMS of compound 8d

HRMS of compound 8e

HRMS of compound 8f

HRMS of compound 8h

HRMS of compound 8i