**Four component synthesis of highly fuctionalized pyrano[2,3-*c*]pyrazoles from benzyl halides.**

**.**

Mallappa Beerappa and Kalegowda Shivashankar\*

*P.G. Department of Chemistry, Central College Campus, Bangalore University, Bangalore - 560 001, Karnataka, India.*

**\***Corresponding author. Tel: +91-80-22961249, *E-mail addresses*: [shivashankark@gmail.com](mailto:shivashankark@gmail.com) (K. Shivashankar)

**SUPPORTING INFORMATION**

**Typical procedure for the synthesis of ethyl 6-amino-5-cyano-4-(2,6-dichlorophenyl)-2,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylate (5a)**

***N*-methylmorpholine *N*-oxide** (110 mg, 1.0 mmol) was added to a stirred solution of 2,6-dichloro benzyl bromide (200 mg, 0.84 mmol), malanonitrile (50 mg, 0.84 mmol) and silver oxide (230 mg, 1.0 mmol) in dry ethanol (10 mL) taken in a round-bottomed flask fitted with a reflux condenser and a guard tube. The resulting reaction mixture was heated at reflux condition. After half an hour, hydrazine hydrate (40 mg, 0.84 mmol) and diethyl acetylenedicarboxylate (160 mg, 0.8 mmol) were added. The mixture was stirred with a bar magnet until completion of the reaction as indicated by TLC. After cooling, the solid precipitated from the reaction mixture was filtered, washed with cold ethanol and recrystallised from ethanol.

**Ethyl 6-amino-5-cyano-4-(2,6-dichlorophenyl)-2,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylate (5a)**

White solid; mp 231-232 oC; IR (ATR, cm-1): 3396 (NH2), 3233 (NH), 2201 (CN), 1698 (C=O); 1H NMR (400 MHz, DMSO-*d6*): *δ =* 1.12 (t, *J* = 8 Hz, 3H, CH3), 3.83 (m, *J* = 4 Hz, 2H, CH2), 4.94 (s, 1H, C-H), 7.16–7.86 (m, 5H, 3ArH and NH2), 11.96 (s, 1H, NH) ppm; 13C NMR (100 MHz, DMSO-*d6*): *δ* = 14.0, 37.0, 53.3, 59.0, 99.5, 114.5, 126.3, 129.5, 129.7, 130.3, 135.0, 135.2, 142.7, 153.0, 158.4, 161.3 ppm; LCMS (M+H) = m/z 379.0; Anal. Calcd for C16H12Cl2N4O3: C, 50.68; H, 3.19; N, 14.78 found: C, 50.62; H, 3.11; N, 14.72%.

**Ethyl 6-amino-5-cyano-4-(3,4-dimethoxyphenyl)-2,4-dihydropyrano[2,3-*c*] pyrazole-3-carboxylate (5b)**

White solid; m.p. 201-203 oC; IR (ATR, cm-1): 3456 (NH2), 3242 (NH), 2210 (CN), 1694 (C=O); 1H NMR (400 MHz, DMSO-*d*6): *δ =* 1.06 (t, *J* = 8 Hz, 3H, CH3), 3.54 (s, 3H, OCH3), 3.76 (s, 3H, OCH3), 4.08 (m, *J* = 4 Hz, 2H, CH2), 4.91 (s, 1H, C-H), 6.58–6.98 (m, 5H, 3ArH and NH2), 13.51 (s, 1H, NH) ppm; 13C NMR (100 MHz, DMSO-*d6*): *δ* = 13.3, 37.0, 53.3, 59.5, 60.0, 60.2, 99.5, 111.3, 113.1, 114.5, 121.3, 129.1, 135.0, 137.2, 147.9, 153.1, 155.4, 160.3 ppm; Anal. Calcd for C18H18N4O5: C, 58.37; H, 4.90; N, 15.13 found: C, 58.35; H, 4.88; N, 15.12%.

**Ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5c)**

White solid; m.p. 233–235 oC (lit.3 m.p. 236–239 oC); IR (ATR, cm-1): 3441 (NH2), 3238 (NH), 2209 (CN), 1693 (C=O); 1H NMR (400 MHz, DMSO-*d*6): *δ =* 1.08 (t, *J* = 8 Hz, 3H, CH3), 3.96 (m, *J* = 4 Hz, 2H, CH2), 4.82 (s, 1H, C-H), 7.22–7.38(m, 4H, Ar-H), 7.72 (s, 2H, NH2)13.21 (s, 1H, NH) ppm; Anal. Calcd for C16H13ClN4O3: C, 55.74; H, 3.80; N, 16.25 found: C, 55.71; H, 3.79; N, 16.21 %.

**Ethyl 6-amino-5-cyano-4-(4-fluorophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5d)**

White solid; m.p. 215–217 oC (lit.3 m.p. 223–226 oC); IR (ATR, cm-1): 3452(NH2), 3228 (NH), 2219 (CN), 1690 (C=O); 1H NMR (400 MHz, DMSO-*d*6): *δ =* 1.13 (t, *J* = 8 Hz, 3H, CH3), 3.99 (m, *J* = 4 Hz, 2H, CH2), 5.14 (s, 1H, C-H), 7.18–7.36(m, 6H, 4Ar-H and NH2),13.32 (s, 1H, NH) ppm; Anal. Calcd for C16H13FN4O3: C, 58.54; H, 3.99; N, 17.07 found: C, 58.55; H, 3.95; N, 17.10 %.

**Ethyl 6-amino-5-cyano-4-(4-methoxyphenyl)-2,4-dihydropyrano[2,3-c] pyrazole-3-carboxylate (5e)**

Yellow solid; m.p. 200–202 oC (lit.3 m.p. 203–205 oC); IR (ATR, cm-1): 3448 (NH2), 3228 (NH), 2220 (CN), 1696 (C=O); 1H NMR (400 MHz, DMSO-*d*6): *δ =* 1.03 (t, *J* = 4 Hz, 3H, CH3), 3.77 (s, 3H, OCH3), 3.91(m, *J* = 8 Hz, 2H, CH2), 5.42 (s, 1H, C-H), 6.93–7.11(m, 4H, Ar-H), 7.34 (s, 2H, NH2) 13.34 (s, 1H, NH) ppm; Anal. Calcd for C17H16N4O4: C, 59.99; H, 4.74; N, 16.46 found: C, 59.97; H, 4.73; N, 16.41 %.

**Ethyl 6-amino-5-cyano-4-(4-nitrophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5f)**

Yellow solid; m.p. 210–212 oC (lit.3 m.p. 210–212 oC); IR (ATR, cm-1): 3449 (NH2), 3231(NH), 2197 (CN), 1689 (C=O); 1H NMR (400 MHz, DMSO-*d*6): *δ =* 1.08 (t, *J* = 8 Hz, 3H, CH3), 3.97 (m, *J* = 4 Hz, 2H, CH2), 5.26 (s, 1H, C-H), 7.50 (t, *J* = 4 Hz, 2H, Ar-H), 7.85 (s, 2H, NH2), 8.18–8.20 (q, *J* = 4 Hz, 2H, Ar-H), 13.44 (s, 1H, NH) ppm; Anal. Calcd for C16H13N5O5: C, 54.09; H, 3.69; N, 19.69 found: C, 54.10; H, 3.68; N, 19.71 %.

**Ethyl 6-amino-5-cyano-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5g)**

White solid; m.p. 208–210oC (lit.3 m.p. 208–210 oC); IR (ATR, cm-1): 3444 (NH2), 3231 (NH), 2198 (CN), 1690 (C=O); 1H NMR (400 MHz, DMSO-*d*6): *δ =* 1.04 (t, *J* = 4 Hz, 3H, CH3), 4.08 (m, *J* = 4 Hz, 2H, CH2), 4.74 (s, 1H, C-H), 7.02–7.30(m, 7H, 5Ar-H and NH2), 11.73 (s, 1H, NH) ppm; Anal. Calcd for C16H14N4O3: C, 61.93; H, 4.55; N, 18.06 found: C, 61.92; H, 4.53; N, 18.01 %.

**Ethyl 6-amino-4-(2-chlorophenyl)-5-cyano-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5h)**

White solid; m.p. 221–223 oC (lit.3 m.p. 218–220 oC); IR (ATR, cm-1): 3440 (NH2), 3233 (NH), 2202 (CN), 1688 (C=O); 1H NMR (400 MHz, DMSO-*d*6): *δ =* 1.11 (t, *J* = 8 Hz, 3H, CH3), 3.87 (m, *J* = 4 Hz, 2H, CH2), 4.72 (s, 1H, C-H), 7.23–7.64 (m, 6H, 4Ar-H and NH2), 13.32 (s, 1H, NH) ppm; Anal. Calcd for C16H13ClN4O3: C, 55.74; H, 3.80; N, 16.25 found: C, 55.71; H, 3.79; N, 16.23 %.

**Diethyl 6-amino-4-(2,6-dichlorophenyl)-2,4-dihydropyrano[2,3-*c*]pyrazole-3,5-dicarboxylate (5i)**

White solid; m.p. 243-245oC; IR (ATR, cm-1): 3466 (NH2), 3252 (NH), 1699 (C=O), 1694 (C=O); 1H NMR (400 MHz, DMSO-*d6*): *δ =* 0.94 (t, *J* = 8 Hz, 3H, CH3), 1.07 (m, *J* = 4 Hz, 3H, CH3), 3.88 (m, *J* = 4 Hz, 2H, CH2), 4.11 (m, *J* = 4 Hz, 2H, CH2), 5.84 (s, 1H, C-H), 7.08–7.96 (m, 5H, 3Ar-H and NH2), 13.31 (s, 1H, NH) ppm; 13C NMR (100 MHz, DMSO-*d6*): *δ* = 13.9, 14.0, 31.8, 58.4, 59.8, 73.0, 127.9, 128.1, 129.0, 129.2, 129.7 135.1, 135.3, 137.3, 137.3, 150.8, 159.1, 160.9, 168.4 ppm; Anal. Calcd for C18H17Cl2N3O5: C, 50.72; H, 4.02; N, 9.86 found: C, 50.68; H, 3.99; N, 9.80%.

**6-Amino-3-methyl-4-(2,4,6-trimethoxyphenyl)-2,4-dihydropyrano[2,3-*c*] pyrazole-5-carbonitrile (5j)**

Yellow solid; m.p. 214-216 oC ; IR (ATR, cm-1): 3459 (NH2), 3248 (NH), 2199 (CN), 1697 (C=O); 1H NMR (400 MHz, DMSO-*d6*): 1.86 (s, 3H, CH3), 3.63 (s, 3H, -OCH3), 3.70 (s, 6H, 2OCH3), 4.56 (s, 1H, C-H), 6.45 (s, 2H, ArH), 6.82 (s, 2H, NH2), 12.05 (s, 1H, NH) ppm; 13C NMR (100 MHz, DMSO-*d6*): *δ* = 9.8(CH3), 36.4(CH), 56.9(3-OCH3), 59.9(CN-C), 97.2, 104.6, 120.7(CN), 135.6, 136.2, 140.0, 152.7, 154.6, 160.4 ppm; Anal. Calcd for C17H18N4O4: C, 59.64; H, 5.30; N, 16.37 found: C, 59.60; H, 5.25; N, 16.31%.

**6-Amino-4-(4-hydroxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5k)**

Yellow solid; m.p. 223–224oC (lit.42 m.p. 222–223oC); IR (ATR, cm-1): 3450 (NH2), 3221 (NH), 2198 (CN), 1699 (C=O); 1H NMR (400 MHz, DMSO-*d*6): *δ =* 1.83 (s, 3H, CH3), 4.49 (s, 1H, C-H), 6.49–7.10 (m, 6H, 4Ar-H and NH2), 12.04 (s, 1H, NH) ppm; Anal. Calcd for C14H12N4O2: C, 62.68; H, 4.51; N, 20.88 found: C, 62.66; H, 4.51; N, 20.86 %.

**6-Amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5l)**

White solid; m.p. 245–246 oC (lit.42 m.p. 245–246 oC); IR (ATR, cm-1): 3433 (NH2), 3121 (NH), 2202 (CN), 1689 (C=O); 1H NMR (400 MHz, DMSO-*d*6): *δ =* 1.84 (s, 3H, CH3), 4.73 (s, 1H, C-H), 6.92-7.34 (m, 7H, 5Ar-H and NH2), 13.69 (s, 1H, NH) ppm; Anal. Calcd for C14H12N4O: C, 66.65; H, 4.79; N, 22.21found: C, 66.62; H, 4.76; N, 22.19 %.

**Ethyl 6-amino-4-(2,6-dichlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-*c*] pyrazole-5-carboxylate (5m)**

White solid; m.p. 212-214 oC; IR (ATR, cm-1): 3380 (NH2), 3265 (NH), 2209 (CN), 1691 (C=O); 1H NMR (400 MHz, DMSO-*d6*): *δ =* 0.96 (t, *J* = 8 Hz, 3H, CH3), 1.85 (s, 3H, CH3), 3.87 (m, *J* = 4 Hz, 2H, CH2), 4.56 (s, 1H, C-H), 7.12–7.58 (m, 5H, 3ArH and NH2), 13.39 (s, 1H, NH) ppm; 13C NMR (100 MHz, DMSO-*d6*): *δ* = 9.4, 13.7, 31.4, 58.3, 73.2, 96.2, 127.8, 128.1, 130.3, 134.1, 135.0 (2C), 135.0, 138.9, 155.3, 161.7, 165.5 ppm; Anal. Calcd for C16H15Cl2N3O3: C, 52.19; H, 4.11; N, 11.41 found: C, 52.15; H, 4.08; N, 11.40%.

**Ethyl 6-amino-4-(4-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole -5-carboxylate(5n)**

White solid; m.p. 239–241 oC (lit.42 m.p. 234–235 oC); IR (ATR, cm-1): 3439 (NH2), 3120 (NH), 2190 (CN), 1699 (C=O); 1H NMR (400 MHz, DMSO-*d*6): *δ =* 1.01(t, *J* = 8 Hz, 3H, CH3), 1.84 (s, 3H, CH3), 3.90 (q, *J* = 8 Hz, 2H, CH2) 4.59 (s, 1H, CH) 7.09-7.64 (m, 6H, 4Ar-H and NH2) ppm; Anal. Calcd for C16H16ClN3O3: C, 57.58; H, 4.83; N, 12.59 found: C, C, 57.56; H, 4.80; N, 12.52 %.

|  |  |  |
| --- | --- | --- |
| Entry | Compounds | Spectra |
| S7 | 5a | 1H |
| S8 | 5a | 13C |
| S9 | 5a | LC-mass spectrum |
| S10 | 5a | LC-mass spectrum |
| S11 | 5b | 1H |
| S12 | 5b | 13C |
| S13 | 5c | 1H |
| S14 | 5d | 1H |
| S15 | 5e | 1H |
| S16 | 5f | 1H |
| S17 | 5g | 1H |
| S18 | 5h | 1H |
| S19 | 5i | 1H |
| S20 | 5i | 13C |
| S21 | 5j | 1H |
| S22 | 5j | 13C |
| S23 | 5k | 1H |
| S24 | 5l | 1H |
| S25 | 5m | 1H |
| S26 | 5m | 13C |
| S27 | 5n | 1H |





































