Synthesis of 3-methyl-6-amino-5-cyano-4-aryl-1-phenyl-1,4-dihydropyrano [2,3-c]pyrazole catalysed by KF-montmorillonite

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The reaction of substituted arylidenemalononitriles and 3-methyl-1-phenyl-2-pyrazolin- 5-one in DMF in the presence of KF-montmorillonite provides a rapid synthesis of 3-methyl-6-amino-5-cyano-4-aryl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole derivatives.

Keywords: 1,4-dihydropyrano[2,3-c]pyrazole, KF-montmorillonite, synthesis, 4H-pyran

4H-Pyran derivatives are important building blocks for many natural compounds[1-4] with anti-allergic[5] and anti-cancer[6,7] activities. Substituted pyrazole and fused pyrazole derivatives are also important pharmaceutical products and biodegradable agrochemicals.[8] Consequently the synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivatives has an attractive research field.

KF-montmorillonite is a catalyst possessing a high proportion of large interlamellar spacing with some discrete spacings. Because of its stability, selectivity and ease of separation, KF-montmorillonite has found widespread acceptance in a variety of heterogeneous reactions, such as substitution,[9] addition,[10] oxidation,[11] rearrangement[12-14] and reductation[15,16] reactions. Montmorillonite clays have been used as acidic catalysts for many reactions. For example, we have reported its use as an alkaline catalyst in the synthesis of 3-aryl-3-cyclohexeneyl propanoic ester and biscoumarins.[17,18] Here, we describe the first example of the application of the KF-montmorillonite solid system as the basic system for the synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivatives in DMF.

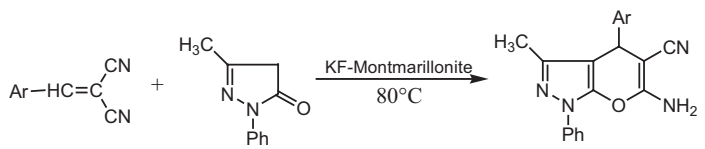
When substituted arylidenemalononitriles (**1**) and 3-methyl-1-phenyl-2-pyrazolin- 5-one (**2**) were stirred at 80°C for 4–6 h in DMF catalysed by KF-montmorillonite, 3-methyl-6-amino-5-cyano-4-aryl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole derivatives (**3**) were obtained in good to excellent yields. The results are shown in Table 1. All the products were fully characterised by their IR, ^{1}H NMR and MS. The probable mechanism for this reaction is also shown in Scheme 2.

Table 1 The synthesis of 1,4-dihydropyrano[*2,3-c*]pyrazole in aqueous media

Entry	Ar	Yield/%	m.p./°C[ref]
3a	4-$CH_3OC_6H_4$	90	174–176[19]
3b	3-$NO_2C_6H_4$	80	199–200[19]
3c	4-BrC_6H_4	88	191–192
3d	3,4-$(CH_3O)_2C_6H_3$	80	193–194[20]
3e	4-FC_6H_4	87	170–172[20]
3f	2-ClC_6H_4	80	207–208
3g	2,4-$Cl_2C_6H_3$	75	185–186[20]
3h	4-$NO_2C_6H_3$	83	196–197[19]
3i	4-$CH_3C_6H_4$	80	179–181[20]
3j	4-ClC_6H_4	92	180–181[19]

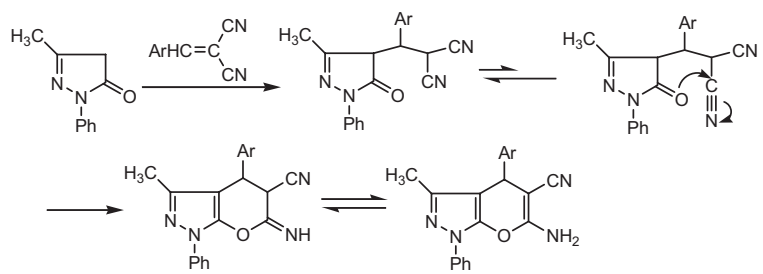
Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a FT IR-8101 spectrometer in KBr with absorptions in cm^{-1}. ^{1}H NMR was measured on a Bruker 400 MHz spectrometer in DMSO-d_6 with TMS as internal standard. Elemental analysis were determined using Perkin Elmer 2400



1 2 3

Scheme 1



Scheme 2

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elemental analyser. KF-montmorillonite was prepared according to the literature.[21]

Typical procedure for the synthesis of compound **3**

A dry 50-ml flask was charged with KF-montmorillonite clay (250 mg), arylidenemalononitrile (**1**) (2 mmol), 3-methyl-1-phenyl-2- pyrazolin-5-one (**2**) (2 mmol) and DMF (15 ml). The mixture was stirred at 80ºC for 4–6 h. The solid material was filtered off. The filtrate was poured into 200 ml water. The white solid was filtered off, then washed with water. The crude solid was purified by recrystallisation from 95% EtOH to give pure compound (**3**).

Spectroscopic data

3-Methyl-6-amino-5-cyano-4-(4-methoxyphenyl)-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3a**): M.p. 174–176°C (Lit.[19]: 173–175°C); ^{1}H NMR (DMSO-d_6, δ, ppm): 1.78 (3H, s, CH_3), 3.74 (3H, s, CH_3O), 4.63 (1H, s, C^4-H), 6.90 (2H, d, J = 8.4 Hz, ArH), 7.16–7.17 (4H, m, NH_2 + ArH), 7.30–7.34 (1H, m, ArH), 7.47–7.51 (2H, m, ArH), 7.78 (2H, d, J = 8.8 Hz, ArH); IR (KBr, ν, cm^{-1}): 3391, 3322, 2192, 1660, 1596, 1514, 1456, 1394, 1250, 1173, 1128, 1073, 1027, 813, 759, 692; Anal. Calcd for $C_{21}H_{18}N_4O_2$: C 70.38, H 5.06, N 15.63; found C 70.46, H 4.90, N 15.43.

3-Methyl-6-amino-5-cyano-4-(3-nitrophenyl)-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3b**): M.p. 199–200°C (Lit.[19]:198–201°C); ^{1}H NMR (DMSO-d_6, δ, ppm): 1.81 (3H, s, CH_3), 4.98 (1H, s, C^4-H), 7.32–7.52 (5H, m, NH_2 + ArH), 7.66–7.70 (1H, m, ArH), 7.77–7.81 (3H, m, ArH), 8.15 (2H, d, J = 4.0 Hz, ArH); IR (KBr, ν, cm^{-1}): 3460, 3350, 2194, 1665, 1640, 1591, 1580, 1495, 1452, 1387, 1354, 839, 820, 776, 746; Anal. Calcd for $C_{20}H_{15}N_5O_3$: C 64.34, H 4.05, N 18.76; found C 64.50, H 3.89, N 18.68.

3-Methyl-6-amino-5-cyano-4-(4-bromophenyl)-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3c**): M.p. 191–192°C; ^{1}H NMR (DMSO-d_6, δ, ppm): 1.79 (3H, s, CH_3), 4.73 (1H, s, C^4-H), 7.15–7.20 (2H, m, ArH), 7.22 (2H, s, NH_2), 7.29–7.35 (3H, m, ArH), 7.48–7.52(2H, m, ArH), 7.77–7.80(2H, m, ArH); IR (KBr, ν, cm^{-1}): 3454, 3329, 2203, 1665, 1596, 1518, 1494, 1444, 1390, 1264, 1226, 1126, 1068, 1027, 812, 753, 685; Anal. Calcd for $C_{20}H_{15}BrN_4O$: C 58.98, H 3.71, N 13.76; found C 58.63, H 3.86, N 13.80.

3-Methyl-6-amino-5-cyano-4-(3,4-dimethoxyphenyl)-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3d**): M.p. 193–194°C(Lit.[20]: 193–195°C); ^{1}H NMR (DMSO-d_6, δ, ppm): 1.83 (3H, s, CH_3), 3.73 (6H, s, 2 × CH_3), 4.64 (1H, s, C^4-H), 6.75–6.93 (3H, m, ArH), 7.15 (2H, s, NH_2), 7.31–7.33 (1H, m, ArH), 7.47–7.51 (2H, m, ArH), 7.80 (2H, d, J = 8.0 Hz, ArH); IR (KBr, ν, cm^{-1}): 3450, 3320, 3200, 2965, 2200, 1660, 1598, 1510, 1450, 1390, 1261, 1150, 1135, 1035, 810, 795, 760; Anal. Calcd for $C_{22}H_{20}N_4O_3$: C 68.03, H 5.19, N 14.62; found C 68.25, H 5.03, N 14.74.

3-Methyl-6-amino-5-cyano-4-(4-fluorophenyl)-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3e**): M.p. 170–172°C (Lit.[20]: 167–168°C); ^{1}H NMR(DMSO-d_6) δ: 1.78(s, 3H, CH_3), 4.72(s, 1H, C^4-H), 7.15–7.19(m, 2H, ArH), 7.22(s, 2H, NH_2), 7.29–7.34(m, 3H, ArH), 7.47–7.51(m, 2H, ArH), 7.78(d, J = 8 Hz, 2H, ArH); IR(KBr) ν: 3454, 3329, 2203, 1666, 1597, 1519, 1445, 1390, 1264, 1226, 1158, 1126, 1096, 1068, 1027, 812, 753, 685 cm^{-1}; Anal. Calcd for $C_{20}H_{15}FN_4O$: C 69.35, H 4.37, N 16.18; found C 69.49, H 4.13, N 16.05.

3-Methyl-6-amino-5-cyano-4-(2-chlorophenyl)-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3f**): M.p. 207–208°C; ^{1}H NMR (DMSO-d_6, δ, ppm): 1.80 (3H, s, CH_3), 4.72 (1H, s, C^4-H), 7.23–7.25 (4H, m, NH_2 + ArH), 7.31–7.35 (1H, m, ArH), 7.48–7.56 (4H, m, ArH), 7.78–7.80 (2H, m, ArH); IR (KBr, ν, cm^{-1}): 3450, 3324, 2199, 1660, 1594, 1518, 1488, 1391, 1127, 1126, 1070, 1010, 752, Anal. Calcd for $C_{20}H_{14}Cl_2N_4O$: C 66.21, H 4.17, N 15.44; found C 66.30, H 4.23, N 15.51.

3-Methyl-6-amino-5-cyano-4-(2,4-dichlorophenyl)-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3g**): M.p. 185–186°C (Lit.[20]: 182–184°C); ^{1}H NMR (DMSO-d_6, δ, ppm): 1.78 (3H, s, CH_3), 5.16 (1H, s, C^4-H), 7.31–7.44 (5H, m, NH_2 + ArH), 7.48–7.52 (2H, m, ArH), 7.62 (1H, s, ArH), 7.78 (2H, d, J = 8.0 Hz, ArH); IR (KBr, ν, cm^{-1}): 3458, 3325, 2198, 1660, 1583, 1560, 1520, 1493, 1470, 1457, 1392, 1269, 1182, 1126, 1102, 1072, 906, 836, 815, 758, 691; Anal. Calcd for $C_{20}H_{14}Cl_2N_4O$: C 60.47, H 3.55, N 14.10; found C 60.62, H 3.43, N 14.28.

3-Methyl-6-amino-5-cyano-4-(4-nitrophenyl)-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3h**): M.p. 196–197°C (Lit.[19] 194–196°C); ^{1}H NMR (DMSO-d_6, δ, ppm): 1.79 (3H, s, CH_3), 4.93 (1H, s, C^4-H), 7.32–7.35 (1H, m, ArH), 7.38 (2H, s, NH_2), 7.48–7.52 (2H, m, ArH), 7.58 (2H, d, J = 8.8 Hz, ArH), 7.79 (2H, d, J = 7.2 Hz, ArH), 8.23 (2H, d, J = 8.4 Hz, ArH); IR (KBr, ν, cm^{-1}): 3431, 3348, 2189, 1665, 1595, 1517, 1394, 1352, 1126, 1054, 831, 753; Anal. Calcd for $C_{20}H_{15}N_5O_3$: C 64.34, H 4.05, N 18.76; found C 64.25, H 4.09, N 18.92.

3-Methyl-6-amino-5-cyano-4-(4-methyphenyl)-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3i**): M.p. 179–181°C (Lit.[20]: 176–178°C); ^{1}H NMR (DMSO-d_6, δ, ppm): 1.78 (3H, s, CH_3), 2.28 (3H, s, CH_3), 4.62 (1H, s, C^4-H), 7.14–7.16 (6H, m, NH_2 + ArH), 7.31–7.33 (1H, m, ArH), 7.46–7.50 (2H, m, ArH), 7.78 (2H, d, J = 8.0 Hz, ArH); IR (KBr, ν, cm^{-1}): 3467, 3345, 2185, 1649, 1589, 1516, 1488, 1444, 1388, 1263, 1181, 1126, 1072, 1024, 839, 796, 759, 692, 666; Anal. Calcd for $C_{21}H_{18}N_4O$: C 73.67, H 5.30, N 16.36; found C 73.81, H 5.07, N 16.54.

3-Methyl-6-amino-5-cyano-4-(4-chlorophenyl)-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**3j**): M.p. 180–181°C (Lit.[19] 177–178°C); ^{1}H NMR (DMSO-d_6, δ, ppm): 1.79 (3H, s, CH_3), 4.73 (1H, s, C^4-H), 7.25 (2H, s, NH_2), 7.29–7.34 (3H, m, ArH), 7.41 (2H, d, J = 8.0 Hz, ArH), 7.47–7.51(2H, m, ArH), 7.78(2H, d, J = 8.0 Hz, ArH); IR (KBr, ν, cm^{-1}): 3459, 3325, 2202, 1661, 1594, 1518, 1491, 1444, 1391, 1262, 1127, 1089, 1066, 1015, 831, 804, 751, 686; Anal. Calcd for $C_{20}H_{15}ClN_4O$: C 66.21, H 4.17, N 15.44; found C 66.29, H 3.96, N 15.62.

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