

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

Nan Wu^{*a}, Xinnian Li^a, Yumei Wang^a and Daqing Shi^{*b}

^aDepartment of Aviation Oil and Material, Xuzhou Airforce College, Xuzhou 221000, Jiangsu, China

^bKey Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry and Chemical Engineering, Suzhou (Soochow) University, Suzhou, China

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 compounds¹⁻⁴ with anti-allergic⁵ 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 rearrangement¹²⁻¹⁴ and reduction^{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-cyclohexenyl 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

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

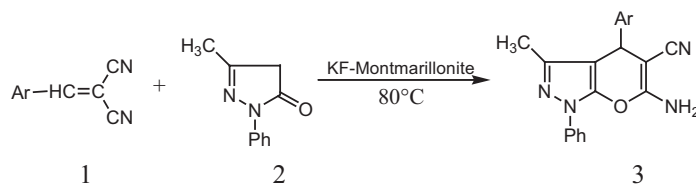
Entry	Ar	Yield/%	m.p./°C ^{ref}
3a	4-CH ₃ OC ₆ H ₄	90	174–176 ¹⁹
3b	3-NO ₂ C ₆ H ₄	80	199–200 ¹⁹
3c	4-BrC ₆ H ₄	88	191–192
3d	3,4-(CH ₃ O) ₂ C ₆ H ₃	80	193–194 ²⁰
3e	4-FC ₆ H ₄	87	170–172 ²⁰
3f	2-ClC ₆ H ₄	80	207–208
3g	2,4-Cl ₂ C ₆ H ₃	75	185–186 ²⁰
3h	4-NO ₂ C ₆ H ₃	83	196–197 ¹⁹
3i	4-CH ₃ C ₆ H ₄	80	179–181 ²⁰
3j	4-ClC ₆ H ₄	92	180–181 ¹⁹

characterised by their IR, ¹H NMR and MS. The probable mechanism for this reaction is also shown in Scheme 2.

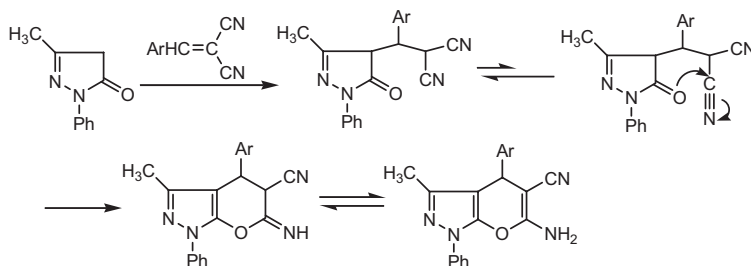
In conclusion, we have developed a mild and efficient method for the synthesis of 3-methyl-6-amino-5-cyano-4-aryl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole derivatives from substituted arylidenemalononitriles and 3-methyl-1-phenyl-2-pyrazolin-5-one in DMF.

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. ¹H 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



Scheme 1



Scheme 2

* Correspondent. E-mail: wunan_china@163.com

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 80°C 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-dihydropyran[2,3-c]pyrazole (3a): M.p. 174–176°C (Lit.¹⁹: 173–175°C); ¹H NMR (DMSO-*d*₆, δ, ppm): 1.78 (3H, s, CH₃), 3.74 (3H, s, CH₃O), 4.63 (1H, s, C⁴-H), 6.90 (2H, d, *J* = 8.4 Hz, ArH), 7.16–7.17 (4H, m, NH₂ + 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 C₂₁H₁₈N₄O₂: 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-dihydropyran[2,3-c]pyrazole (3b): M.p. 199–200°C (Lit.¹⁹: 198–201°C); ¹H NMR (DMSO-*d*₆, δ, ppm): 1.81 (3H, s, CH₃), 4.98 (1H, s, C⁴-H), 7.32–7.52 (5H, m, NH₂ + 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 C₂₀H₁₅N₅O₃: 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-dihydropyran[2,3-c]pyrazole (3c): M.p. 191–192°C; ¹H NMR (DMSO-*d*₆, δ, ppm): 1.79 (3H, s, CH₃), 4.73 (1H, s, C⁴-H), 7.15–7.20 (2H, m, ArH), 7.22 (2H, s, NH₂), 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 C₂₀H₁₅BrN₄O: 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-dihydropyran[2,3-c]pyrazole (3d): M.p. 193–194°C (Lit.²⁰: 193–195°C); ¹H NMR (DMSO-*d*₆, δ, ppm): 1.83 (3H, s, CH₃), 3.73 (6H, s, 2 × CH₃), 4.64 (1H, s, C⁴-H), 6.75–6.93 (3H, m, ArH), 7.15 (2H, s, NH₂), 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 C₂₂H₂₀N₄O₃: 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-dihydropyran[2,3-c]pyrazole (3e): M.p. 170–172°C (Lit.²⁰: 167–168°C); ¹H NMR (DMSO-*d*₆, δ, ppm): 1.78 (s, 3H, CH₃), 4.72 (s, 1H, C⁴-H), 7.15–7.19 (m, 2H, ArH), 7.22 (s, 2H, NH₂), 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, cm⁻¹): 3454, 3329, 2203, 1666, 1597, 1519, 1445, 1390, 1264, 1226, 1158, 1126, 1096, 1068, 1027, 812, 753, 685 cm⁻¹; Anal. Calcd for C₂₀H₁₅FN₄O: 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-dihydropyran[2,3-c]pyrazole (3f): M.p. 207–208°C; ¹H NMR (DMSO-*d*₆, δ, ppm): 1.80 (3H, s, CH₃), 4.72 (1H, s, C⁴-H), 7.23–7.25 (4H, m, NH₂ + 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 C₂₀H₁₄Cl₂N₄O: 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-dihydropyran[2,3-c]pyrazole (3g): M.p. 185–186°C (Lit.²⁰: 182–184°C); ¹H NMR (DMSO-*d*₆, δ, ppm): 1.78 (3H, s, CH₃), 5.16 (1H, s, C⁴-H), 7.31–7.44 (5H, m, NH₂ + 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 C₂₀H₁₄Cl₂N₄O: 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-dihydropyran[2,3-c]pyrazole (3h): M.p. 196–197°C (Lit.¹⁹: 194–196°C); ¹H NMR (DMSO-*d*₆, δ, ppm): 1.79 (3H, s, CH₃), 4.93 (1H, s, C⁴-H), 7.32–7.35 (1H, m, ArH), 7.38 (2H, s, NH₂), 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 C₂₀H₁₅N₅O₃: 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-methoxyphenyl)-1-phenyl-1,4-dihydropyran[2,3-c]pyrazole (3i): M.p. 179–181°C (Lit.²⁰: 176–178°C); ¹H NMR (DMSO-*d*₆, δ, ppm): 1.78 (3H, s, CH₃), 2.28 (3H, s, CH₃), 4.62 (1H, s, C⁴-H), 7.14–7.16 (6H, m, NH₂ + 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 C₂₁H₁₈N₄O: 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-dihydropyran[2,3-c]pyrazole (3j): M.p. 180–181°C (Lit.¹⁹: 177–178°C); ¹H NMR (DMSO-*d*₆, δ, ppm): 1.79 (3H, s, CH₃), 4.73 (1H, s, C⁴-H), 7.25 (2H, s, NH₂), 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 C₂₀H₁₅ClN₄O: C 66.21, H 4.17, N 15.44; found C 66.29, H 3.96, N 15.62.

Received 1 January 2008; accepted 14 January 2008

Paper 08/5015 doi: 10.3184/030823408X282695

References

- S. Hatokeyama, N. Ochi, H. Numata and S. Takano, *J. Chem. Soc., Chem. Commun.*, 1988, **17**, 1202.
- J. Bloxham, C.P. Dell and C.W. Smith, *Heterocycles*, 1994, **38**, 399.
- G.A.M. Nawwar, F.M. Abdelrazek and R.H. Swellam, *Arch. Pharm.*, 1991, **342**, 875.
- J. Zamocka, E. Misikova and J. Durinda, *Pharmazie*, 1991, **46**, 610.
- E.C. Witte, P. Neubert and A. Roesoh, *Ger Offen DE3427985*, 1986. [*Chem. Abstr.* 1986, 104:224915f].
- T. Hyama and H. Saimoto, *Jpn. Kokai Tokkyo Koho*, JP 62181276, 1987. [*Chem. Abstr.* 1988, 108:37645p].
- J.L. Wang, D. Liu, Z.J. Zhang, S. Shan, X. Han, S.M. Srinivasula, C.M. Croce, E.S. Alnemri and Z. Huang, *Proc. Natl. Acad. Sci. USA*, 2000, **97**, 7124.
- Y.A. Monamed, M.A. Zahran, M.M. Ali, A.M. El-Agrody and U.H. El-Said, *J. Chem. Res.(s)*, 1995, 32.
- A. Cornelis, C. Dony, P. Laszlo and K.M. Nsunda, *Tetrahedron Lett.*, 1991, **32**, 1423.
- M.E.F. Braibante, H.S. Braibante, L. Missio and A. Andricopulo, *Synthesis*, 1994, 898.
- A. Cornelis and P. Laszlo, *Synthesis*, 1980, 849.
- V. Hauke, J.M. Trendel and P. Albrecht, *Tetrahedron Lett.*, 1994, **35**, 2227.
- S. Chalais, P. Laszlo and A. Mathy, *Tetrahedron Lett.*, 1986, **27**, 2627.
- W.G. Dauben, J.M. Cogen and V. Behar, *Tetrahedron Lett.*, 1990, **31**, 3241.
- K. Mukkanti, Y.V.S. Rao and B.M. Choudary, *Tetrahedron Lett.*, 1989, **30**, 251.
- B.M. Choudary and K.K. Rao, *Tetrahedron Lett.*, 1992, **33**, 121.
- D.Q. Shi, Q.Y. Zhuang, L.C. Rong, J.X. Wang and X.S. Wang, *J. Xuzhou Normal University (Natural Science Edition)*, 2003, **21**, 37.
- N. Wu, X.N. Li, X. Xu and D.Q. Shi, *J. Chem. Res.(S)*, 2007, 561.
- J.F. Zhou, S.J. Tu, Y. Gao and M. Ji, *Chin. J. Org. Chem.*, 2001, **21**, 742.
- D.-Q. Shi, J. Mou, Q.-Y. Zhuang, L.H. Niu, N. Wu and X.S. Wang, *Syn. Comm.*, 2004, **34**, 1.
- D.Q. Shi, X.S. Wang, C.S. Yao and L.C. Rong, *J. Chem. Res.(S)*, 2002, 344.