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Daqing Shi [a b], Jie Mou [a], Qiya Zhuang [a b], Lihui Niu [a], Nan Wu [a] & Xiangshan Wang [a b]

[a] Department of Chemistry, Xuzhou Normal University, Xuzhou, 221116, P.R. China

[b] The Key Laboratory of Biotechnology on Medical Plant of Jiangsu Province, Xuzhou, P.R. China

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Three-Component One-Pot Synthesis of 1,4-Dihydropyrano[2,3-*c*]pyrazole Derivatives in Aqueous Media

Daqing Shi,[1,2,*] Jie Mou,[1] Qiya Zhuang,[1,2] Lihui Niu,[1] Nan Wu,[1] and Xiangshan Wang[1,2]

[1]Department of Chemistry, Xuzhou Normal University, Xuzhou, P.R. China
[2]The Key Laboratory of Biotechnology on Medical Plant of Jiangsu Province, Xuzhou, P.R. China

ABSTRACT

6-Amino-5-cyano-4-aryl-1,4-dihydropyrano[2,3-*c*]pyrazoles were synthesized by three-component reaction of aromatic aldehydes, malononitrile, and 3-methyl-1-phenyl-2-pyrazolin-5-one using triethylbenzylammonium chloride (TEBA) as catalyst in aqueous media. The reaction has the advantages of good yield, less pollution, ease of separation, and of being environment friendly.

Key Words: Aqueous media; 1,4-dihydropyrano[2,3-*c*]pyrazoles; One-pot synthesis; Three component.

*Correspondence: Daqing Shi, Department of Chemistry, Xuzhou Normal University, Xuzhou 221116, P.R. China; E-mail: dqshi@263.net.

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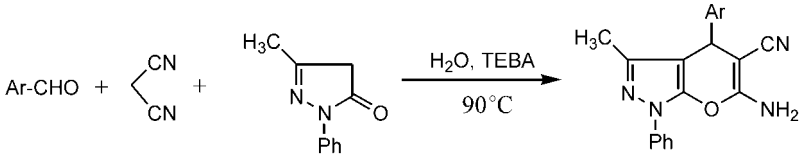
In recent years, the synthesis of 4*H*-pyran has attracted considerable interest as an important intermediate of many heterocycles.[1–3] This type of compound exhibits attractive pharmacological and biological properties as antiallergic[4] and antitumor agents.[5,6] 2-Amino-3-cyano-4*H*-pyrans possesses photochemical activity.[1] Polyfunctionalized 4*H*-pyrans are a common structural unit in a number of natural products.[7] The 4*H*-pyran ring can be transformed to pyridine systems, which relate to pharmacologically important calcium antagonists of the DHP type.[2,8,9] 4*H*-pyran derivatives are generally prepared by reaction of substituted cinnamicnitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one in organic solvent (i.e., ethanol or DMF) using piperidine or triethylamine as catalyst,[10] but most of them are toxic.

The need to reduce the amount of toxic waste and by-products arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods. One of the most promising approaches is using water as reaction media. Breslow, Bovy, and Hersch,[11] who showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic chemistry in the 1980's. Previously, the scant solubility of the reactants was the main reason that ruled out this solvent from studies. Further reasons that make water unique among solvents are that it is cheap, not inflammable, and more importantly, it is not toxic. Recently, there has been increasing recognition that water is an attractive medium for many organic reactions.[12] Based on our previous studies on the use of water as a solvent for carrying out carbon-carbon forming reactions under phase transmitting catalyst,[13] here we would like to report one-pot synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives by three-component reaction in aqueous media.

When aromatic aldehydes (**1**), malononitrile (**2**), 3-methyl-1-phenyl-2-pyrazolin-5-one (**3**), and triethylbenzylammonium chloride (TEBA) were stirred at 90°C for 6–10 h in water, the products (**4**) were obtained in good yields (Sch. 1) and the results are shown in Table 1.



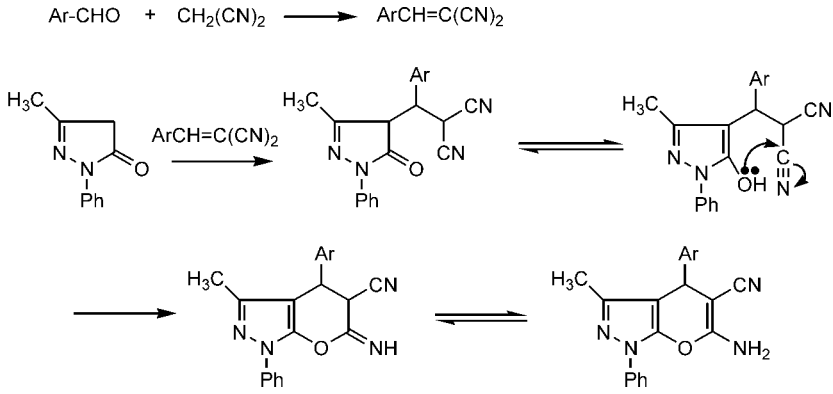
Scheme 1.

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

Entry	Ar	Time (h)	Yield (%)
4a	C_6H_5	6	99
4b	4-$CH_3C_6H_4$	6	99
4c	4-ClC_6H_4	6	99
4d	4-FC_6H_4	6	98
4e	4-$CH_3OC_6H_4$	6	96
4f	4-$NO_2C_6H_4$	10	89
4g	3,4-$OCH_2OC_6H_3$	6	98
4h	2,4-$Cl_2C_6H_3$	6	99
4i	3,4-$(CH_3O)_2C_6H_3$	8	87
4j	3-$NO_2C_6H_4$	10	90

According to our results, we can propose the reaction mechanism shown in Sch. 2.

In summary, the three-component reaction of aromatic aldehydes, malononitrile, and 3-methyl-1-phenyl-2-pyrazolin-5-one to 6-amino-5-cyano-4-aryl-1,4-dihydropyrano[2,3-*c*]pyrazoles has been efficiently performed in aqueous media. The easy purification of products by simple crystallization, and the use of water as solvent combined with the exploitation of the multicomponent strategy open to this process suggest good prospects for its industrial applicability.



Scheme 2.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on an FTIR-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 analyses were determined using Perkin-Elmer 2400 II elemental analyzer.

General Procedure

A mixture of the aromatic aldehydes **1** (2 mmol), malononitrile **2** (2 mmol), 3-methyl-1-phenyl-2-pyrazolin-5-one **3** (2 mmol), and TEBA (0.15 g) in H_2O (10 mL) was refluxed for 6–10 h at 90°C, then cooled to room temperature. The crystalline powder formed was collected by filtration, washed with water, and recrystallized from ethanol to give pure **(4)**.

4a: M.p. 168–170°C (Lit.[14] 168–170°C); ^1H NMR (DMSO-d_6, δ, ppm): 1.78 (3H, s, CH_3), 4.68 (1H, s, C^4-H), 7.20 (2H, s, NH_2), 7.25–7.37 (6H, m, ArH), 7.48–7.51 (2H, m, ArH), 7.79 (2H, d, $J = 8.8$ Hz, ArH); IR (KBr, ν, cm^{-1}): 3471, 3324, 2198, 1658, 1592, 1516, 1491, 1457, 1444, 1386, 1264, 1125, 1065, 1027, 753, 702, 685; Anal. Calcd. for $C_{20}H_{16}N_4O$: C 73.15, H 4.91, N 17.06; found C 73.27, H 5.03, N 17.31.

4b: M.p. 176–178°C; ^1H 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.

4c: M.p. 177–178°C (Lit.[14] 174–175°C); ^1H 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.

4d: M.p. 167–168°C; ^1H NMR (DMSO-d_6, δ, ppm): 1.78 (3H, s, CH_3), 4.72 (1H, s, C^4-H), 7.15–7.19 (2H, m, ArH), 7.22 (2H, s, NH_2), 7.29–7.34 (3H, m, ArH), 7.47–7.51 (2H, m, ArH), 7.78 (2H, d, $J = 8.0$ Hz, ArH); IR (KBr, ν, cm^{-1}): 3454, 3329, 2203, 1666, 1597, 1519, 1445, 1390, 1264, 1226, 1158, 1126, 1096, 1068, 1027, 812, 753, 685; 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.

4e: M.p. 173–175°C (Lit.[14] 170–172°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 70.54, H 4.89, N 15.40.

4f: M.p. 192–194°C (Lit.[14] 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.

4g: M.p. 174–176°C; ^{1}H NMR (DMSO-d_6, δ, ppm): 1.79 (3H, s, CH_3), 5.11 (1H, s, C^4-H), 6.50 (2H, s, OCH_2O), 7.25–7.29 (2H, m, ArH), 7.37 (1H, d, $J = 8.0$ Hz, ArH), 7.66 (2H, s, NH_2), 7.80–7.83 (1H, m, ArH), 7.97–8.00 (2H, m, ArH), 8.28 (2H, d, $J = 8.0$ Hz, ArH); IR (KBr, ν, cm^{-1}): 3404, 3323, 2196, 1661, 1595, 1521, 1486, 1445, 1393, 1254, 1235, 1129, 1072, 1037, 926, 841, 802, 789, 759, 691; Anal. Calcd. for $C_{21}H_{18}N_4O_3$: C 67.73, H 4.33, N 15.05; found C 67.94, H 4.05, N 14.93.

4h: M.p. 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.

4i: M.p. 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), 7.78–7.81 (2H, m, 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.

4j: M.p. 188–190°C (Lit.[14] 188–190°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 64.52, H 3.87, N 18.63.

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