One-pot synthesis of pyrano[3,2-*c*]pyran derivatives catalyzed by KF/Al_2O_3

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Abstract
A series of pyrano[3,2-*c*]pyran derivatives have been synthesized by the reaction of aromatic aldehyde, malononitrile or cyanoacetate and 4-hydroxy-5-methylpyran-2-one in EtOH at room temperature catalyzed by KF/Al_2O_3. The structures of the products were characterized by IR, ^1H NMR and elemental analysis, and 4a was further confirmed by X-ray diffraction analysis.

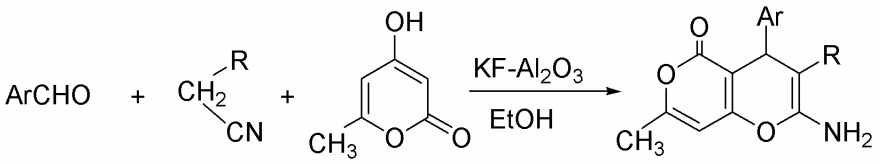
Keywords: Pyrano[3,2-*c*]pyran, KF/Al_2O_3, synthesis

Introduction

It is known that many pyran derivatives exhibit a wide spectrum of pharmacological activities and biological activities at melanocortin receptors being used in the design of peptidomimetics relating to a tripeptide structure,[1] such as fungicidal, insecticidal and acaricidal activity,[2] antiviral activity,[3] miticidal activity,[4] stimulant activity,[5] and anticonvulsant activity.[6] These promoted us to synthesis these compounds via a new way. Particularly, we focused our attention on the use of KF-alumina as catalyst, because the utility of fluoride salts as potential base in a variety of synthetic reactions has been recognized in recent years,[7] resulting in their higher selectivity, milder reaction conditions and easier work-up. Especially alumina coated with potassium fluoride (KF-alumina) has been a versatile solid-supported reagent developed by Ando *et al*. for alkylation.[8] Over the years the reagent has been found application in a large number of organic reactions.[9] In order to further enlarge the application of the reagent of KF-alumina, in this paper, we would like to report one pot synthesis these potential active pyrano[3,2-*c*]pyran derivatives by the reaction of aromatic aldehyde, malononitrile or cyanoacetate and 4-hydroxy-6-methylpyran-2-one catalyzed by KF-alumina at room temperature.

Results and Discussion

When aromatic aldehyde (**1**), malononitrile, or cyanoacetate (**2**) and 4-hydroxy-6-methylpyran-2-one (**3**) were treated with KF-Al_2O_3 in ethyl alcohol at room temperature, 2-amino-4-aryl-4*H*, 5*H*-pyrano[3,2-*c*]pyran-5-one derivatives (**4**) were obtained in slightly high yields (75-98%) (Scheme 1).



Scheme 1

Table 1. The reaction time and the yields of the products 4

Entry	Ar	R	Time(h)	Yields (%)
4a	3-$NO_2C_6H_4$	CN	6	75
4b	4-BrC_6H_4	CN	8	94
4c	2-ClC_6H_4	CN	8	98
4d	4-ClC_6H_4	CN	8	76
4e	4-Cl-2-$NO_2C_6H_3$	CN	5	84
4f	3,4-$Cl_2C_6H_3$	CN	5	83
4g	2,4-$Cl_2C_6H_3$	CN	5	86
4h	3-ClC_6H_4	CN	8	94
4i	3,4-$Cl_2C_6H_3$	CO_2Et	8	93
4j	2,4-$Cl_2C_6H_3$	CO_2Et	8	87
4k	3-ClC_6H_4	CO_2Et	10	82
4l	2-ClC_6H_4	CO_2Et	10	81
4m	4-ClC_6H_4	CO_2Et	10	94
4n	3,4-$Cl_2C_6H_3$	CO_2Me	8	88

In order to demonstrate the efficiency and the applicability of the present method, we performed the reaction of a variety of aromatic aldehyde with malononitrile or cyanoacetate and **3** in EtOH at room temperature and in the presence of KF-Al_2O_3. As shown in Table 1, we can see a series of **1** reacted with **2** and **3** to give the corresponding products **4** in good yields under same reaction conditions.

The isolated pyrano[3,2-*c*]pyran derivatives **4** were completely characterized by IR, ^{1}H NMR and elemental analyses. The analyses were in agreement with their structures. The melting

points of known compounds were conformed to those of the references reported. The IR spectra for **4a** exhibited sharp bands at 3400, 3327 cm^{-1} (NH_2), 2199 cm^{-1} (CN), 1716 cm^{-1} (C=O). The ^1H NMR spectrum of **4a** exhibited a singlet identified as methyl (2.24), two singlets exhibited at 4.57 and 6.32 ppm identified as two methines (CH and CH=), respectively, and along with multiplets (7.64–8.14) for aromatic protons. The NH proton resonance at 7.35 disappeared after addition of D_2O to the DMSO-d_6 solution of **4a**. In order to further confirm the structure of the product, the X-ray analysis[10] of **4a** was carried out. The crystal structure of **4a** was shown in Figure 1.

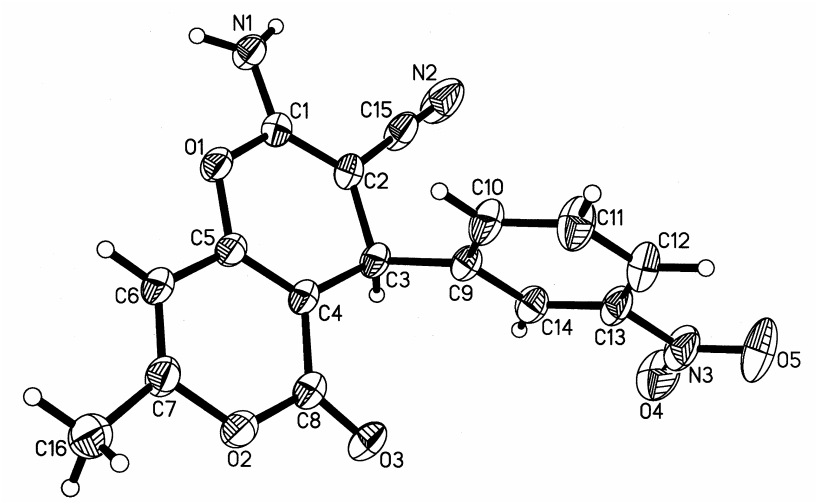
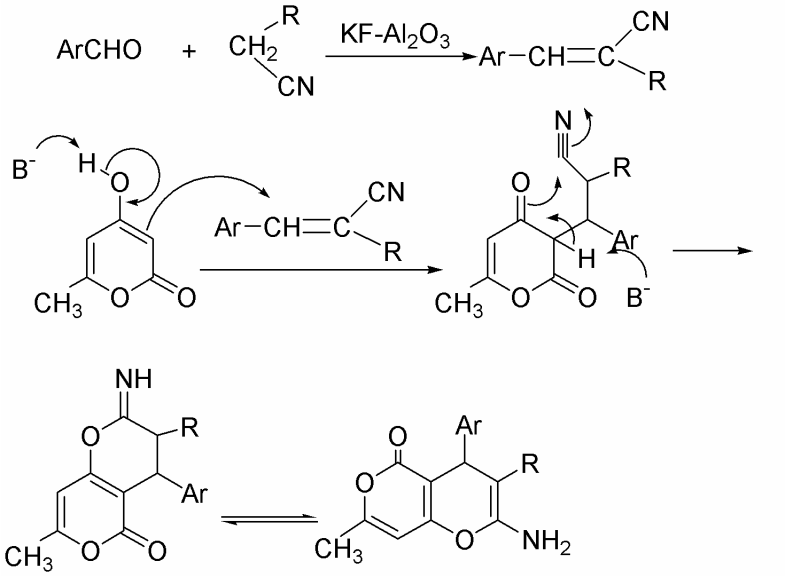


Figure 1. The crystal structure of **4a.**

Although the detailed mechanism of the above reaction has not been clarified yet, the formation of **4** can be explained by the possible mechanism presented in Scheme 2.



Scheme 2

In conclusion, we find a novel one-pot method available for the synthesis of pyrano[3,2-*c*]pyran derivatives. Meanwhile, the new method also further expands the application of the catalyst of KF-Al_2O_3 in organic synthesis. Compared with other methods,[11] this method has the advantage of one-step, easy work-up, milder reaction conditions and good yields in synthesis these potential active compounds.

Experimental Section

General Procedures. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a TENSOR 27 spectrometer in KBr. ^{1}H NMR spectra were obtained for solutions in DMSO-d_6 with Me_4Si as internal standard using a Bruker-400 spectrometer. Elemental analyses were carried out using Carlo Erba 1110 analyzer. X-ray diffraction was measured on a Siemens P4 diffractometer.

General procedure for pyrano[3,2-*c*]pyran derivatives (4). A dry 50 mL flask was charged with aromatic aldehyde **1** (2 mmol), malononitrile or cyanoacetate **2** (2.5 mmol) and 4-hydroxy-6-methylpyran-2-one **3** (2 mmol), KF-Al_2O_3 (100 mg) and ethyl alcohol (10 mL), the mixture was stirred at room temperature for 5-10 h. The mixture was poured into 200 mL water, the solid filtered off, and washed with water. The crude product was purified by recrystallization from DMF and water to give **4**.

2-Amino-3-cyano-4-(3-nitrophenyl)-4*H*,5*H*-pyrano[3,2-*c*]pyran-5-one (4a). Pale yellow crystals; m.p. 238-240 °C (lit. [11] 234-235 °C). ^{1}H NMR (DMSO-d_6, δ, ppm) δ: 2.24 (s, 3H, CH_3), 4.57 (s, 1H, CH), 6.32 (s, 1H, =CH), 7.35(s, 2H, NH_2), 7.64 (t, J = 8.0 Hz, 1H, ArH), 7.73(tt, J = 8.0 Hz, J' = 1.2 Hz, 1H, ArH), 8.05 (t, J = 2.0 Hz, 1H, ArH), 8.13(dd, dd, J = 8.0 Hz, J' = 2.0 Hz, J'' = 1.2 Hz, 1H, ArH). IR (KBr, cm^{-1}): 3400, 3327, 2199, 1716, 1615, 1526, 1448, 1383, 1263, 1200, 1143, 1024, 977, 817, 759, 733 cm^{-1}.

2-Amino-3-cyano-4-(4-bromophenyl)-4*H*,5*H*-pyrano[3,2-*c*]pyran-5-one (4b). Pale yellow crystals; m.p. 223-225 °C (lit. [11] 223-224 °C). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.23 (s, 3H, CH_3), 4.31 (s, 1H, CH), 6.29 (s, 1H, =CH), 7.17 (d, 2H, J = 8.4 Hz, ArH), 7.26 (s, 2H, NH_2), 7.51 (d, 2H, J = 8.4 Hz, ArH). IR (KBr, cm^{-1}): 3388, 3324, 2201, 1707, 1644, 1589, 1486, 1445, 1408, 1314, 1261, 1196, 1176, 1142, 1012, 982, 854, 829, 776.

2-Amino-3-cyano-4-(2-chlorophenyl)-4*H*,5*H*-pyrano[3,2-*c*]pyran-5-one (4c). Pale yellow crystals; m.p. 270-271 °C (lit. [11] 267-268 °C). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.24 (s, 3H, CH_3), 4.79 (s, 1H, CH), 6.29 (s, 1H, =CH), 7.21-7.32 (m, 5H, ArH + NH_2), 7.39 (dd, 1H, J = 7.6 Hz, J' = 1.2 Hz, ArH). IR (KBr, cm^{-1}): 3471, 3344, 3104, 2192, 1700, 1638, 1579, 1473, 1443, 1377, 1263, 1197, 1180, 1139, 1043, 964, 820, 762.

2-Amino-3-cyano-4-(4-chlorophenyl)-4*H*,5*H*-pyrano[3,2-*c*]pyran-5-one (4d). Pale yellow crystals; m.p. 231-232 °C (lit. [11] 230-231 °C). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.23 (s, 3H, CH_3), 4.32 (s, 1H, CH), 6.29 (s, 1H, =CH), 7.23 (d, 2H, J = 8.4 Hz, ArH), 7.26 (s, 2H, NH_2), 7.37 (d,

2H, *J* = 8.4 Hz, ArH). IR (KBr, cm^{-1}): 3382, 3324, 2202, 1711, 1645, 1590, 1488, 1445, 1414, 1385, 1314, 1261, 1196, 1092, 1015, 981, 854, 830, 807, 777.

2-Amino-3-cyano-4-(4-chloro-2-nitrophenyl)-4*H*,5*H*-pyrano[3,2-*c*]pyran-5-one (4e). Pale yellow crystals; m.p. 247-249 °C. ^{1}H NMR (DMSO-d_6, δ, ppm): 2.09 (s, 3H, CH_3), 5.08 (s, 1H, CH), 6.30 (s, 1H, =CH), 7.44 (s, 2H, NH_2), 7.54 (d, 1H, *J* = 2.0 Hz, ArH), 7.59 (dd, 1H, *J* = 8.8 Hz, *J*' = 2.0 Hz, ArH), 7.93 (d, 1H, *J* = 8.8 Hz, ArH). IR (KBr, cm^{-1}): 3419, 3332, 2195, 1703, 1644, 1588, 1522, 1449, 1382, 1338, 1260, 1198, 1145, 1040, 977, 900, 849, 199, 774. Anal. calcd for $C_{16}H_{10}ClN_3O_5$: C 53.42, H 2.80, N 11.68. Found: C 53.29, H 2.91, N 11.52.

2-Amino-3-cyano-4-(3,4-dichlorophenyl)-4*H*,5*H*-pyrano[3,2-*c*]pyran-5-one (4f). Pale yellow crystals; m.p. 239-241 °C. ^{1}H NMR (DMSO-d_6, δ, ppm): 2.23 (s, 3H, CH_3), 4.39 (s, 1H, CH), 6.29 (s, 1H, =CH), 7.22 (dd, 1H, *J* = 8.0 Hz, *J*' = 2.0 Hz, ArH), 7.32 (s, 2H, NH_2), 7.49 (d, 1H, *J* = 2.0 Hz, ArH), 7.58 (d, 1H, *J* = 8.0 Hz, ArH). IR (KBr, cm^{-1}): 3391, 3326, 2200, 1715, 1645, 1590, 1465, 1445, 1381, 1298, 1261, 1185, 1141, 1031, 983, 969, 898, 810, 786, 770. Anal. calcd for $C_{16}H_{10}Cl_2N_2O_3$: C 55.04, H 2.89, N 8.02. Found: C 54.90, H 2.99, N 8.00.

2-Amino-3-cyano-4-(2,4-dichlorophenyl)-4*H*,5*H*-pyrano[3,2-*c*]pyran-5-one (4g). Pale yellow crystals; m.p. 234-235 °C (lit. [11] 230-231 °C). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.24 (s, 3H, CH_3), 4.79 (s, 1H, CH), 6.30 (s, 1H, =CH), 7.29 (d, 1H, *J* = 8.0 Hz, ArH), 7.30 (s, 2H, NH_2), 7.38 (dd, 1H, *J* = 8.0 Hz, *J*' = 2.0 Hz, ArH), 7.57 (d, 1H, *J* = 2.0 Hz, ArH). IR (KBr, cm^{-1}): 3408, 3348, 2196, 1706, 1642, 1583, 1472, 1444, 1376, 1265, 1198, 1137, 1105, 1047, 966, 857, 828, 738.

2-Amino-3-cyano-4-(3-chlorophenyl)-4*H*,5*H*-pyrano[3,2-*c*]pyran-5-one (4h). Pale yellow crystals; m.p. 255-257 °C. ^{1}H NMR (DMSO-d_6, δ ppm): 2.24 (s, 3H, CH_3), 4.35 (s, 1H, CH), 6.29 (s, 1H, =CH), 7.17 (d, 1H, *J* = 7.6 Hz, ArH), 7.25-7.38 (m, 5H, ArH + NH_2). IR (KBr, ν, cm^{-1}): 3396, 3323, 2198, 1707, 1644, 1590, 1473, 1442, 1430, 1383, 1303, 1259, 1179, 1140, 1041, 980, 833, 803, 770. Anal. calcd for $C_{16}H_{11}ClN_2O_3$: C 61.06, H 3.52, N 8.90. Found: C 61.04, H 3.70, N 8.77.

Ethyl 2-amino-3-cyano-4-(3,4-dichlorophenyl)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]pyran-3- carboxylate (4i). Pale yellow crystals; m.p. 179-181 °C. IR (KBr, ν, cm^{-1}):3447, 3320, 1983, 1717, 1690, 1622, 1513, 1468, 1448, 1378, 1286, 1257, 1211, 1174, 1138, 1086, 1030, 976, 814, 787; ^{1}H NMR (DMSO-d_6, δ, ppm): 1.08 (t, 3H, *J* = 6.8 Hz, CH_3), 2.10 (s, 3H, CH_3), 3.97 (q, 2H, *J* = 6.8 Hz, CH_3), 4.52 (s, 1H, CH), 6.32 (s, 1H, =CH), 7.15 (dd, 1H, *J* = 8.8 Hz, *J*' = 2.0 Hz, ArH), 7.38 (d, 1H, *J* = 2.0 Hz, ArH), 7.52 (d, 1H, *J* = 8.8 Hz, ArH) 7.82 (s, 2H, NH_2). Anal. calcd for $C_{18}H_{12}Cl_2NO_5$: C 54.56, H 3.82, N 3.54. Found: C 54.48, H 3.93, N 3.50.

Ethyl 2-amino-3-cyano-4-(2,4-dichlorophenyl)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]pyran-3- carboxylate (4j). Pale yellow crystals; m.p. 206-208 °C (lit. [11] 204-205 °C). ^{1}H NMR (DMSO-d_6, δ, ppm): 1.04 (t, 3H, *J* = 7.2 Hz, CH_3), 2.10 (s, 3H, CH_3), 3.92 (q, 2H, *J* = 7.2 Hz, CH_3), 4.88 (s, 1H, CH), 6.29 (s, 1H, =CH), 7.26 (d, 1H, *J* = 8.4 Hz, ArH), 7.32 (dd, 1H, *J* = 8.4 Hz, J' = 2.4 Hz, ArH), 7.43 (d, 1H, *J* = 2.4 Hz, ArH), 7.85 (s, 2H, NH_2). IR (KBr, cm^{-1}): 3435, 3298, 2957, 1712, 1689, 1615, 1584, 1505, 1471, 1380, 1290, 1250, 1174, 1139, 1080, 1046, 957, 849, 817.

Ethyl 2-amino-3-cyano-4-(3-chlorophenyl)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]pyran-3-carboxylate (4k). Pale yellow crystals; m.p. 180-182 °C. ^{1}H NMR (DMSO-d_6, δ, ppm): 1.08 (t, 3H, *J* = 6.8

Hz, CH_3), 2.10 (s, 3H, CH_3), 3.96 (q, 2H, *J* = 6.8 Hz, CH_3), 4.52 (s, 1H, CH), 6.32 (s, 1H, =CH), 7.17 (d, 1H, *J* = 7.6 Hz, ArH), 7.11-7.31 (m, 4H, ArH), 7.79 (s, 2H, NH_2). IR (KBr, cm^{-1}): 3426, 3294, 2979, 1710, 1687, 1619, 1506, 1475, 1442, 1378, 1286, 1252, 1212, 1174, 1140, 1073, 1041, 958, 816, 782, 750. Anal. calcd for $C_{18}H_{16}ClNO_5$: C 59.76, H 4.46, N 3.87. Found: C 59.76, H 4.57, N 3.72.

Ethyl 2-amino-3-cyano-4-(2-chlorophenyl)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]pyran-3-carboxylate (4l). Pale yellow crystals; m.p. 203-204 °C (lit. [11] 203-205 °C). ^{1}H NMR (DMSO-d_6, δ, ppm): 1.03 (t, 3H, *J* = 7.2 Hz, CH_3), 2.22 (s, 3H, CH_3), 3.92 (q, 2H, *J* = 7.2 Hz, CH_3), 4.90 (s, 1H, CH), 6.29 (s, 1H, =CH), 7.14-7.24 (m, 3H, ArH), 7.29 (d, 1H, *J* = 8.0 Hz, ArH), 7.81 (s, 2H, NH_2). IR (KBr, cm^{-1}): 3421, 3295, 2988, 1715, 1688, 1621, 1509, 1440, 1379, 1287, 1176, 1077, 980, 956, 815, 773, 756.

Ethyl 2-amino-3-cyano-4-(4-chlorophenyl)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]pyran-3-carboxylate (4m). Pale yellow crystals; m.p. 160-161 °C (lit. [11] 156-157 °C). ^{1}H NMR (DMSO-d_6, δ, ppm): 1.07 (t, 3H, *J* = 6.8 Hz, CH_3), 2.22 (s, 3H, CH_3), 3.95 (q, 2H, *J* = 6.8 Hz, CH_3), 4.52 (s, 1H, CH), 6.31 (s, 1H, =CH), 7.19 (d, 2H, *J* = 8.4 Hz, ArH), 7.30 (d, 2H, *J* = 8.4 Hz, ArH), 7.77 (s, 2H, NH_2). IR (KBr, cm^{-1}): 3431, 3306, 2980, 1715, 1678, 1618, 1490, 1443, 1378, 1291, 1215, 1172, 1140, 1076, 1014, 981, 955, 841, 818.

Methyl 2-amino-3-cyano-4-(3,4-dichlorophenyl)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]pyran-3-carboxylate (4n). Pale yellow crystals; m.p. 193-197 °C. ^{1}H NMR (DMSO-d_6, δ, ppm): 2.10 (s, 3H, CH_3), 3.52 (s, 3H, CH_3O), 4.53 (s, 1H, CH), 6.32 (s, 1H, =CH), 7.17 (dd, 1H, *J* = 8.4 Hz, *J'* = 2.0 Hz, ArH), 7.36 (d, 1H, *J* = 2.0 Hz, ArH), 7.52 (d, 1H, *J* = 8.4 Hz, ArH), 7.83 (s, 2H, NH_2). IR (KBr, cm^{-1}): 3426, 3304, 2955, 1712, 1687, 1619, 1514, 1468, 1439, 1380, 1296, 1254, 1219, 1176, 1141, 1085, 1033, 973, 941, 810, 774, 746. Anal. calcd for $C_{17}H_{13}Cl_2NO_5$: C 53.42, H 3.43, N 3.66. Found: C 53.29, H 3.50, N 3.51.

Supplementary Information Available

Crystallographic data for the structure **4a** reported in this paper has been deposited at the Cambridge Crystallographic Data Centre as supplementary publication with No. CCDC-605772. Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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References and Footnotes

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10. X-ray crystallography for **4a**: Empirical formula $C_{16}H_{11}N_3O_5$, F_W = 325.28, T = 289(2) K, Monoclinic, space group P2(1)/c, a = 5.709(1) Å, b = 14.616(2) Å, c = 18.228(3) Å, β = 94.219 (2) °, V = 1516.8(8) Å^3, Z = 4, Dc = 1.424 Mg/m^3, $\lambda(MoK\alpha)$= 0.71073Å, μ = 0.109 mm^{-1}, F(000) = 672. 1.79°<θ<25.49°, R = 0.0423, wR = 0.0961. S = 0.952, Largest diff. Peak and hole: 0.153 and –0.181 e·Å^{-3}
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