A convenient synthesis of 2-amino-3-cyano-4-aryl-9,10-dihydrobenzo[*f*]chromene derivatives catalysed by KF/Al_2O_3

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A series of 2-amino-3-cyano-4-aryl-9,10-dihydrobenzo[*f*]chromene derivatives were synthesised from arylaldehyde, malononitrile with 7-methoxyl-1,2,3,4-tetrahydronaphthalene-2-one in ethyl alcohol at refluxing temperature catalysed by KF-Al_2O_3. The structure of the product was confirmed by X-ray analysis.

Keywords: benzo[*f*]chromene, arylaldehyde, malononitrile, naphthalene-2-one, synthesis

2-Aminochromene is a compound, which is found to possess antiestrogenic activity. It is devoid of any agonistic activity,[1] has been evaluated for potassium channel opening and hypotensive activies,[2] vasodilator and antihypertensive activies,[3] β-adrenolytic activity,[4] antimicrobial activity[5] and biological activity as a high-affinity retinoic acid receptor antagonist.[6] The utility of fluoride salts as potential bases in variety of synthetic reactions has been recognized in recent years. Especially potassium fluoride coated with alumina (KF-alumina) has been a versatile, solid-supported reagent used for Knoevenagel reaction,[7] Henry reaction,[8] Darzens reaction, [9] Wittig reaction,[10] alkylation,[11] elimination[9] and many other reactions.[12] Herein we report the synthesis of 2-amino-3-cyano-4-aryl-9,10-dihydrobenzo[*f*]chromene derivatives catalysed by KF–Al_2O_3.

When arylaldehyde (1), malononitrile (2) and 7-methoxyl-1,2,3,4-tetrahydro-naphthalene-2-one (3) were treated with KF-Al_2O_3 in ethyl alcohol at refluxing temperature, the 2-amino-3-cyano-4-aryl-9,10-dihydrobenzo[*f*]chromene derivatives (4) were obtained in good yields (79–92%) (Table 1) (Scheme 1)

The structures of products are all identified by IR, ^{1}H NMR and Elemental analysis. The structure of **4g** was further confirmed by X-ray analysis,[13] and the crystal structure of **4g** was shown in Fig.1 (turns molecules per unit cell).

In conclusion, we find a novel method available for the synthesis of benzo[*f*]chromene derivatives. Meanwhile, the new method also further expands the application of the catalyst KF–Al_2O_3 in organic synthesis. This new method has the advantages of an easy work-up, milder reaction conditions and high yields in synthesis of these potential biologically active compounds.

Experimental

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 solution in $CDCl_3$ with Me_4Si as internal standard using an Inova-400 spectrometer. Elemental analyses were carried out using Carlo Erba 1110 analyzer. X-ray diffraction was measured on a Siemens P4 diffractometer.

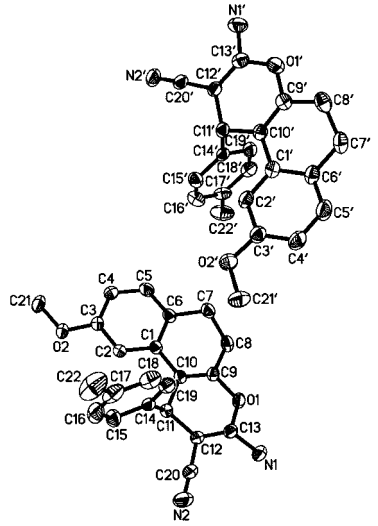


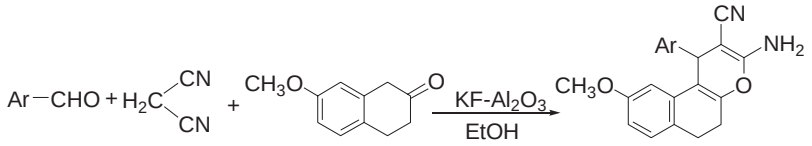
Fig. 1 Structure of the compound **4g**.

7-Methoxyl-1,2,3,4-tetrahydro-naphthalene-2-one was purchased from Nantong Baisheng Chemical Co. Ltd. of China. The other chemicals were of analytical reagent grade and were used directly without further purification.

General preparation of KF-alumina: To a solution of KF (58 g) in water (100 ml) was added Al_2O_3 (100 g) with stirring. The mixture was stirred for 3 h at 80 °C, then the solvent was evaporated and the solid was dried for 4 h at 120 °C to give KF-alumina.

Table 1 The synthetic data of the products

Entry	Ar	Time/h	M.p/°C	Yield/%
4a	3-$NO_2C_6H_4$	2	211–213	92
4b	4-ClC_6H_4	3	175–177	82
4c	2-ClC_6H_4	3	229–230	85
4d	3,4-$OCH_2OC_6H_3$	5	240–241	88
4e	4-$CH_3OC_6H_4$	5	200–201	79
4f	3,4-$Cl_2C_6H_3$	2.5	230–232	86
4g	4-$CH_3C_6H_4$	4	182–184	81
4h	4-BrC_6H_4	3	186–187	92
4i	3,4-$(CH_3O)_2C_6H_3$	5	175–177	83



Scheme 1

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*General procedure for the synthesis of 2-Amino-3-cyano-4-aryl-9,10-dihydrobenzo[f]chromene derivatives **(4)***: A dry 50 ml flask was charged with arylaldehyde **(1)** (4 mmol), malononitrile **(2)** (4 mmol), 7-methoxyl-1,2,3,4-tetrahydro-naphthalene-2-one **3** (5 mmol), KF-alumina (250 mg) and ethyl alcohol (10 ml). The mixture was stirred at reflux temperature for 2–5 h. The mixture was poured into 200 ml water; the solid was filtered off and washed with water. The crude product was purified by recrystallisation from 95% EtOH to give **4**.

4a: 92%, m.p. 211–213 °C; ^{1}H NMR ($CDCl_3$) δ: 2.62–2.65 (m, 2H, CH_2), 2.86–2.98 (m, 2H, CH_2), 3.64 (s, 3H, OCH_3), 4.54 (s, 2H, NH_2), 4.67 (s, 1H, CH), 6.45 (s, 1H, ArH), 6.58 (d, *J* = 8.0 Hz, 1H, ArH), 7.02 (d, *J* = 8.0 Hz, 1H, ArH), 7.48–7.52 (m, 1H, ArH), 7.71 (d, *J* = 7.2 Hz, 1H, ArH), 8.08 (d, *J* = 8.4 Hz, 1H, ArH), 8.12 (s, 1H, ArH); IR (KBr, ν, cm^{-1}): 3428, 3320, 2929, 2835, 2191, 1692, 1641, 1590, 1524, 1415, 1231, 1153, 1037, 853, 814, 720cm^{-1}. Anal.calcd for $C_{21}H_{17}N_3O_4$: C 67.19, H 4.56, N 11.19; found C 66.98, H 4.71, N 11.02.

4b: 82%, m.p. 175–177 °C; ^{1}H NMR ($CDCl_3$) δ: 2.58–2.63 (m, 2H, CH_2), 2.85–2.94 (m, 2H, CH_2), 3.64 (s, 3H, OCH_3), 4.45 (s, 2H, NH_2), 4.50 (s, 1H, CH), 6.48 (s, 1H, ArH), 6.57 (d, *J* = 8.0 Hz, 1H, ArH), 7.01 (d, *J* = 8.0 Hz, 1H, ArH), 7.23(s, 4H, ArH); IR (KBr, ν, cm^{-1}): 3405, 3296, 2937, 2886, 2827, 2184, 1692, 1641, 1598, 1575, 1497, 1407, 1230, 1196, 1153, 1087, 1037, 1005, 861, 763cm^{-1}. Anal.calcd for $C_{21}H_{17}ClN_2O_2$: C 69.14, H 4.70, N 7.68; found C 69.03, H 4.62, N 7.77.

4c: 85%, m.p. 229–230 °C; ^{1}H NMR ($CDCl_3$) δ: 2.52–2.64 (m, 2H, CH_2), 2.84–2.95 (m, 2H, CH_2), 3.64 (s, 3H, OCH_3), 4.45 (s, 2H, NH_2), 5.22 (s, 1H, CH), 6.57 (s, 1H, ArH), 6.58 (d, *J* = 6.4 Hz, 1H, ArH), 6.97 (d, *J* = 8.4 Hz, 1H, ArH), 7.10–7.19 (m, 2H, ArH), 7.27 (d, *J* = 7.6 Hz, 1H, ArH), 7.36 (d, *J* = 7.6 Hz, 1H, ArH); IR (KBr, ν, cm^{-1}): 3448, 3331, 2936, 2886, 2835, 2191, 1699, 1641, 1606, 1582, 1497, 1399, 1239, 1153, 1056, 873, 814, 763cm^{-1}. Anal.calcd for $C_{21}H_{17}ClN_2O_2$: C 69.14, H 4.70, N 7.68; found C 69.09, H 4.82, N 7.53.

4d: 88%, m.p. 240–241 °C; ^{1}H NMR ($CDCl_3$) δ: 2.55–2.62 (m, 2H, CH_2), 2.87–2.92 (m, 2H, CH_2), 3.65 (s, 3H, OCH_3), 4.40 (s, 2H, NH_2), 4.44 (s, 1H, CH), 5.90(d, *J* = 8.8Hz, 2H, OCH_2O), 6.57 (s, 1H, ArH), 6.58 (d, *J* = 6.4 Hz, 1H, ArH), 6.73(d, *J* = 6.4 Hz, 1H, ArH), 6.74(s, 1H, ArH), 6.83 (d, *J* = 7.6 Hz, 1H, ArH), 6.99 (d, *J* = 7.6 Hz, 1H, ArH); IR (KBr, ν, cm^{-1}): 3413, 3304, 2937, 2878, 2184, 1680, 1649, 1591, 1497, 1415, 1231, 1037, 931, 845, 814, 763cm^{-1}. Anal.calcd for $C_{22}H_{18}N_2O_4$: C 70.58, H 4.85, N 7.48; found C 70.62, H 4.93, N 7.26.

4e: 79%, m.p. 200–201 °C; ^{1}H NMR ($CDCl_3$) δ: 2.55–2.59 (m, 2H, CH_2), 2.87–2.94 (m, 2H, CH_2), 3.63 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.39 (s, 2H, NH_2), 4.48 (s, 1H, CH), 6.55 (s, 1H, ArH), 6.56 (d, *J* = 8.0 Hz, 1H, ArH), 6.82 (d, *J* = 8.4 Hz, 2H, ArH), 6.98 (d, *J* = 7.2 Hz, 1H, ArH), 7.22 (d, *J* = 8.4 Hz, 2H, ArH); IR (KBr, ν, cm^{-1}): 3397, 3304, 3202, 3936, 2828, 2200, 1680, 1641, 1598, 1505, 1415, 1254, 1172, 1021, 845, 814, 771cm^{-1}. Anal.calcd for $C_{22}H_{20}N_2O_3$: C 73.32, H 5.59, N 7.77; found C 73.12, H 5.64, N 7.59.

4f: 86%, m.p. 230–232 °C, ^{1}H NMR ($CDCl_3$) δ: 2.51–2.63 (m, 2H, CH_2), 2.83–2.94 (m, 2H, CH_2), 3.67 (s, 3H, OCH_3), 4.48 (s, 2H, NH_2), 5.17 (s, 1H, CH), 6.52 (s, 1H, ArH), 6.59 (d, *J* = 7.6 Hz, 1H, ArH), 6.98 (d, *J* = 7.6 Hz, 1H, ArH), 7.15 (d, *J* = 8.0 Hz, 1H, ArH), 7.21 (d, *J* = 8.0 Hz, 1H, ArH), 7.38(s, 1H, ArH); IR (KBr, ν, cm^{-1}): 3456, 3331, 2929, 2828, 2191, 1692, 1641, 1591, 1407, 1231, 1056, 873, 837, 771 cm^{-1}, Anal.calcd for $C_{21}H_{16}Cl_2N_2O_2$: C 63.17, H 4.04, N 7.02; found C 63.34, H 4.21, N 6.95.

4g: 81%, m.p. 182–184°C, ^{1}H NMR ($CDCl_3$) δ: 2.28 (s, 3H, CH_3), 2.56–2.63 (m, 2H, CH_2), 2.85–2.96 (m, 2H, CH_2), 3.62 (s, 3H, OCH_3), 4.39 (s, 2H, NH_2), 4.48 (s, 1H, CH), 6.55 (s, 2H, ArH), 6.98 (d, *J* = 7.2 Hz, 1H, ArH), 7.09 (d, *J* = 7.2 Hz, 2H, ArH), 7.19 (d, J = 7.2 Hz, 2H, ArH); IR (KBr, ν, cm^{-1}): 3413, 3331, 2936, 2827, 2191, 1699, 1651, 1606, 1575, 1497, 1407, 1282, 1239, 1153, 1056, 997, 880, 837, 763 cm^{-1}. Anal.calcd for $C_{22}H_{20}N_2O_2$: C 76.72, H 5.85, N 8.13; found C 76.60, H 6.03, N 7.87

4h: 92%, m.p. 186–187°C, ^{1}H NMR ($CDCl_3$) δ: 2.55–2.60 (m, 2H, CH_2), 2.87–2.92 (m, 2H, CH_2), 3.63 (s, 3H, OCH_3), 4.45 (s, 2H, NH_2), 4.48 (s, 1H, CH), 6.46 (s, 1H, ArH), 6.57 (d, *J* = 8.0 Hz, 1H, ArH), 6.99 (d, *J* = 7.2 Hz, 1H, ArH), 7.17–7.19(m, 2H, ArH), 7.39–7.42(m, 2H, ArH); IR (KBr, ν, cm^{-1}): 3409, 3303, 2937, 2827, 2191, 1680, 1641, 1598, 1575, 1497, 1407, 1239, 1204, 1145, 1056, 1013, 873, 837, 814cm^{-1}. Anal.calcd for $C_{21}H_{17}BrN_2O_2$: C 61.63, H 4.19, N 6.84; found C 61.43, H 4.32, N 6.77.

4i: 83%, m.p. 175–177°C, ^{1}H NMR ($CDCl_3$) δ: 2.56–2.60 (m, 2H, CH_2), 2.84–2.95 (m, 2H, CH_2), 3.63 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.40 (s, 2H, NH_2), 4.46 (s, 1H, CH), 6.56 (s, 1H, ArH), 6.58 (s 1H, ArH), 6.78 (d, *J* = 8.0 Hz, 1H, ArH), 6.81–6.85(m, 2H, ArH), 6.99(d, *J* = 8.0 Hz, 1H, ArH); IR (KBr, ν, cm^{-1}): 3413, 3304, 2937, 2878, 2184, 1680, 1649, 1591, 1497, 1415, 1231, 1037, 932, 845, 815, 764 cm^{-1}. Anal.calcd for $C_{23}H_{22}N_2O_4$: C 70.75, H 5.68, N 7.17; found C 70.59, H 5.71, N 7.08.

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13 X-ray crystallography for **4**g: A single crystal **4**g with dimensions of 0.56 mm λ 0.42 mm λ 0.42 mm was mounted on a Siemens P4 diffractometer. The data were collected at the temperature of 296(2) K with graphite monochromated Mo*K*α (λ = 0.71073 Å) radiation, using the ω scan technique. 6289 independent reflections were collected, of which 3775 reflections with $I>2\sigma(I)$ were considered to be observed. The structure was solved by direct method using SHELXTL program and expanded using Fourier technique. The non-hydrogen atoms were refined anisotropically, the hydrogen atoms were positioned geometrically and refined as riding [C–H = 0.93–0.98Å, N–H = 0.86 Å and $U_{iso}(H) = 1.2U_{eq}(C)$]. A full-matrix least-squares refinement gave final $R = 0.0376$ and $wR = 0.0843$ with $w = 1/[\sigma^2 (F_o^2) + (0.0485P)^2 + 0.2685P]$, where $P = (F_o^2 + 2F_c^2)/3$. Empirical formula $C_{22}H_{20}N_2O_2$, F_W = 344.40, T = 296(2) K, Triclinic, space group P–1, a = 10.120(1) Å, b = 13.127(1) Å, c = 15.203(2) Å, α = 67.841(9)°, β = 80.81(1) °, γ = 77.58(1)°, V = 1819.7(4) Å^3, Z = 4, Dc = 1.257 Mg/m^3, λ*(MoK*α*)* = 0.71073Å, μ = 0.081 mm^{-1}, F(000) = 728. 1.45°<θ<25.00, S = 0.859, Largest