Synthesis of 2-amino-3-ethoxycarbonyl-4-aryl-*4H,5H*-pyrano-[3,2-*c*]benzopyran-5-one

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A series of 2-amino-3-ethoxycarbonyl-4-aryl-4*H*,5*H*-pyrano-[3,2-*c*]benzopyran-5-ones have been were synthesised by the reaction of 4-hydroxycoumarin, an aromatic aldehyde and ethyl cyanoacetate under microwave irradiation with short times and high yields.

Keywords: 2-amino-3-ethoxycarbonyl-4-aryl-4*H*, 5*H*-pyrano-[3,2-*c*]benzopyran-5-one

Coumarins constitute an important class of bioactive natural products.[1] They have been found to possess diverse biological properties including antimicrobial, insecticidal, estrogenic, anticoagulant and antithrombotic activities. Compounds containing 4-hydroxycoumarin, such as 3-substituted-4-hydroxycoumarins and tricoumarol have been identified as active nonpeptidic HIV protease inhibitors.[2-4] Recently reported examples include: coumarin-7-xylosides as oral antithrombotic agents;[5] khellactone derivatives as potential HIV-1 inhibitors;[6] dihydrofurocoumarin derivatives as anticoagulants, insecticidals, anthelminthics, hypnotics, antifungals, phytoalexins and HIV protease inhibitors;[7] Phenprocoumon[8] and Warfarin as first generation HIV—PR inhibitors;[9-10] Warfarin,[11-12] Acenocoumarol[13] and Coumachlor[14-16] as anticoagulant and rodenticidal agents. More recently, the sulfonamides containing 4-hydroxy-2-pyrones have been identified as second generation HIV-PR inhibitors[17] and studied as protease inhibitory templates.[18] These important applications have generated considerable interest in this ring system and heterocycles fused at 3,4-position of coumarin also draw special attention.[19] Condensation of 4-hydroxycoumarin and α-ethoxycarbonylcinnamonitriles was previously described by Kudo, Masubuchi, EI-Agrody, Grocharenko, Abdel Hafiz and Mahran.[20] However the reported reactions involve two steps and the reaction time (the second step) is up to 3-10 hours. Microwave irradiation is a very useful technique in organic synthesis.[21- 24] It is a simple, timesaving, high-yielding, and environmentally friendly process.[25-26] We have already reported the synthesis of heterocyclic compounds under microwave irradiation. Herein we report an efficient one-pot synthesis of 2-amino-3-ethoxycarbonyl-4-phenyl-*4H,5H*-pyrano-[3,2-*c*]benzopyran-5-one by the reaction of 4-hydroxycoumarin with aromatic aldehyde and ethyl cyanoacetate in ethanolic piperidine under microwave irradiation. The reaction was completed in 10–16min with good yields (50–92%). The product structures were established on the basis of spectroscopic data and confirmed by X-ray diffraction studies on a monocrystal of **4c**.[27] The results obtained are shown in Table 1. We also have studied the condensation of 4-hydroxycoumarin and α-ethoxycarbonylcinnamonitriles under traditional heating conditions in ethanolic piperidine at 70 ˚C. The results are shown in Table 2. The synthetic route is shown in Scheme 1.

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on an FT IR-8101 spectrometer in KBr. ^{1}H NMR spectra were obtained for solutions in $CDCl_3$ or DMSO-d_6 with Me_4Si as internal standard using a DPX 300 MHz spectrometer. Elemental analyses was determined by using a

* Correspondence.

Table 1 Yields of the products under microwave irradiation

Entry	Ar	Time/min	Yield/%
4a	2-ClC_6H_4	14	90
4b	4-BrC_6H_4	15	80
4c	4-ClC_6H_4	10	92
4d	4-$CH_3C_6H_4$	14	82
4e	4-$CH_3OC_6H_4$	12	88
4f	4-$N(CH_3)_2C_6H_4$	12	72
4g	3-CH_3O-4-HOC_6H_3	16	50
4h	4-$NO_2C_6H_4$	14	60
4i	3-$NO_2C_6H_4$	14	68

Table 2 Yields of the products under traditional conditions

Entry	Ar	Time/h	Yield/%
4a	2-ClC_6H_4	8	30
4b	4-BrC_6H_4	6.5	45
4c	4-ClC_6H_4	4	37
4d	4-$CH_3C_6H_4$	8	35
4e	4-$CH_3OC_6H_4$	7.	25
4f	4-$N(CH_3)_2C_6H_4$	7	28
4g	3-CH_3O-4-HOC_6H_3	6.5	29
4h	4-$NO_2C_6H_4$	14	22
4i	3-$NO_2C_6H_4$	10	26

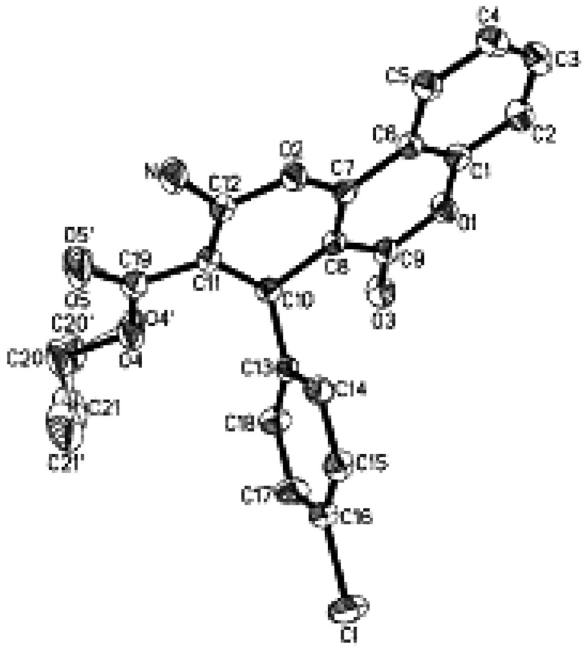
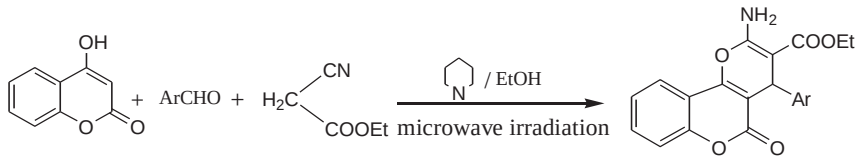


Fig. 1 X-ray crystal structure of **4c**.



1 **2** **3** **4**

Scheme 1

Perkin-Elmer 240c elemental analysis instrument. X-ray diffraction was measured on a Siemens P4 diffractometer. Microwave irradiation was carried out with a modified commercial microwave oven (2450 MHz, 650W) under atmospheric pressure

General procedure for synthesis of 2-amino-3-ethoxycarbonyl-4-phenyl-4H,5H-pyrano-[3,2-c]benzopyran-5-one **4**: A dry flask was charged with 4-hydroxycoumarin, an aromatic aldehyde and ethyl cyanoacetate in ethanolic piperidine. The flask was then connected to refluxing equipment. After microwave irradiation for 10–16 min., the reaction mixture was cooled and poured into water; the solid product was filtered off and washed with water. The crude solid was purified by recrystallisation from 95% EtOH to give title compound (**4**).

2-Amino-3-ethoxycarbonyl-4-(2-chorophenyl)-4H,5H-pyrano-[3,2-c]benzopyran-5-one, **4a**: M.p. 221–223 °C, IR(KBr, ν): 3398, 3283(NH_2), 1716(C=O), 1689(C=O), 1649(C=C) cm^{-1}; ^1H NMR (DMSO-d_6, δ): 1.05(t, 3H, CH_3, *J*=7.1 Hz), 3.95(q, 2H, CH_2, *J*=7.1 Hz), 5.08(s, 1H, CH), 7.16–7.99(m, 8H, ArH), 7.91(s, 2H, NH_2). Anal. calcd for $C_{21}H_{16}ClNO_5$: C 63.40, H 4.05, N 3.52, found C 63.58, H 4.15, N 3.32.

2-Amino-3-ethoxycarbonyl-4-(4-bromophenyl)-4H,5H-pyrano-[3,2-c]benzopyran-5-one, **4b**: M.p. >300 °C, IR(KBr, ν): 3408, 3272(NH_2), 1723(C=O), 1668(C=O), 1606(C=C)cm^{-1}; ^1H NMR (DMSO-d_6, δ): 1.31(t, 3H, CH_3, *J*=7.1 H_Z), 4.33(q, 2H, CH_2, *J*=7.1 H_Z), 6.24(s, 1H, CH), 7.83(s, 2H, NH_2), 7.06–8.00(m, 8H, ArH). Anal. calcd for $C_{21}H_{16}BrNO_5$: C 57.03, H 3.65, N 3.17, found C 57.23, H 3.74, N 3.05.

2-Amino-3-ethoxycarbonyl-4-(4-chorophenyl)-4H,5H-pyrano-[3,2-c]benzopyran-5-one, **4c**: M.p. 208–209 °C (207–208)[20a], IR(KBr, ν): 3400, 3300(NH_2), 1710(C=O), 1685(C=O), 1655(C=C) cm^{-1}; ^1H NMR (DMSO-d_6, δ): 1.10 (t, 3H, CH_3, *J*=6.8 H_Z), 3.99 (q, 2H, CH_2, *J*=6.8 HZ), 4.68(s, 1H, CH), 7.87(s, 2H, NH_2), 7.24–7.98(m, 8H, ArH).

2-Amino-3-ethoxycarbonyl-4-(4-methylphenyl)-4H,5H-pyrano-[3,2-c]benzopyran-5-one, **4d**: M.p. 199–201 °C(190)[20b] IR(KBr, ν): 3394, 3282(NH_2), 1700(C=O), 1680(C=O), 1650(C=C) cm^{-1}; ^1H NMR ($CDCl_3$, δ): 1.20(t, 3H, CH_3, *J*=7.2 H_Z), 2.27(s, 3H, CH_3), 4.08(q, 2H, CH_2, *J*=7.2 H_Z), 4.91(s, 1H, CH), 6.40(s, 2H, NH_2), 7.04–7.84(m, 8H, ArH).

2-Amino-3-ethoxycarbonyl-4-(4-methoxyphenyl)-4H,5H-pyrano-[3,2-c]benzopyran-5-one, **4e**: M.p. 178–179 °C (177–179)[20a], IR(KBr, ν): 3398, 3286(NH_2), 1698(C=O), 1656(C=O), 1610 (C=C) cm^{-1}; ^1H NMR($CDCl_3$, δ): 1.19(t, 3H, CH_3, *J*=7.2 H_Z), 3.75(s, 3H, OCH_3), 4.07(q, 2H, CH_2, *J*=7.2 H_Z), 4.89(s, 1H, CH), 6.39(s, 2H, NH_2), 6.77–7.84(m, 8H, ArH).

2-Amino-3-ethoxycarbonyl-4-(4-dimethylaminophenyl)-4H,5H-pyrano-[3,2-c]benzopyran-5-one, **4f**: M.p. 233–234 °C, IR(KBr, ν): 3401, 3283(NH_2), 1716(C=O), 1690(C=O), 1648(C=C) cm^{-1}; ^1H NMR(DMSO-d_6, δ): 1.59(t, 3H, CH_3, *J*=7.1 H_Z), 3.11(s, 6H, $N(CH_3)_2$), 4.51(q, 2H, CH_2, *J*=7.1 H_Z), 5.68(s, 1H, CH), 7.88(s, 2H, NH_2), 7.64–8.45(m, 8H, ArH). Anal. calcd for $C_{23}H_{22}N_2O_5$: C 67.97, H 5.46, N 6.89, found C 68.14, H 5.52, N 6.73.

2-Amino-3-ethoxycarbonyl-4-(4-hydroxy-3-methoxyphenyl)-4H,5H-pyrano-[3,2-c]benzopyran-5-one, **4g**: M.p. 231–232 °C, IR(KBr, ν): 3650(OH), 3400, 3300(NH_2), 1700(C=O), 1698(C=O), 1650(C=C) cm^{-1}; ^1H NMR(DMSO-d_6, δ): 1.16(t, 3H, CH_3, *J*=7.2 H_Z), 3.71(s, 3H, OCH_3), 4.02(q, 2H, CH_2, *J*=7.2 H_Z), 4.62(s, 1H, CH), 7.78(s, 2H, NH_2), 6.53–7.97(m, 7H, ArH) , 8.92(s, 1H, OH). Anal. calcd for $C_{22}H_{19}NO_7$: C 64.54, H 4.68, N 3.42, found C 64.73, H 4.54, N 3.29.

2-Amino-3-ethoxycarbonyl-4-(3-nitrophenyl)-4H,5H-pyrano-[3,2-c]benzopyran-5-one, **4h**: M.p. 228–230°C, IR(KBr, ν): 3421, 3325 (NH_2), 1720(C=O), 1670(C=O), 1608(C=C), 1521, 1347(N=O)cm^{-1}; ^1H NMR(DMSO-d_6, δ): 1.064(t, 3H, CH_3, *J*=6.8 H_Z), 3.45(q, 2H, CH_2, *J*=6.8 H_Z), 4.35(s, 1H, CH), 6.37(s, 2H, NH_2), 7.23–8.01(m, 8H, ArH). Anal. calcd for $C_{21}H_{16}N_2O_7$: C 61.77, H 3.95, N 6.86, found C 61.64, H 3.78, N 6.74.

2-Amino-3-ethoxycarbonyl-4-(4-nitrophenyl)-4H,5H-pyrano-[3,2-c]benzopyran-5-one, **4i**: M.p. 232–234°C, IR(KBr, ν): 3436, 3324(NH_2), 1721(C=O), 1685(C=O), 1603(C=C), 1521, 1342(N=O)cm^{-1}; ^1H NMR (DMSO-d_6, δ): 1.105(t, 3H, CH_3, *J*=7.2 H_Z), 3.99(q, 2H, CH_2, *J*=7.2 H_Z), 4.83(s, 1H, CH), 6.35(s, 2H, NH_2), 7.25–8.15(m, 8H, ArH), Anal. calcd for $C_{21}H_{16}N_2O_7$: C 61.77, H 3.95, N 6.86, found C 61.61, H 3.69, N 6.65.

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27 X-ray crystallography for **4c**: Empirical formula $C_{21}H_{16}NO_5$, F_W=397.80, T=296(2)K, triclinic, space group P-1, *a*=5.756(1)Å, *b*=10.099(1)Å, *c*=17.106(2)Å, α=80.49(1)°, β=83.13 (1)°, γ=80.07(1)° *V*=961.8 (3)Å^3, *Z*=2, *Dc*=1.374 Mg/m^3, λ*(MoK*α*)*= 0.71073Å, μ= 0.231 mm^{-1}, *F(000)*=412, 1.21°<θ<25.25°, *R*=0.0369, *wR*=0.0947. *S*=1.029, Largest diff. Peak and hole: 0.213 and –0.264e. ≈$^{-3}$. The ethyl group of the ester side chain is disordered. Hydrogen bonding occurs between the NH_2 group and the carbonyl of the ethoxycarbonyl at reasonable distances, Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 226407. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax(+44) 1223-3366-033; e-mail:deposit@ccdc.cam.ac.uk).