Unexpected ring-opening of a 2-pyrone ring in the synthesis of 3-[(*Z*)-1-hydroxy-3-oxobut-1-enyl]-2*H*-chromen-2-one derivatives catalysed by KF-alumina

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A series of 3-[(*Z*)-1-hydroxy-3-oxobutenyl]-2*H*-chromen-2-one derivatives were synthesised by an unexpected ring-opening of a 2-pyrone ring reaction of substituted salicylaldehydes, and 4-hydroxy-6-methyl-pyran-2-one in ethyl alcohol at room temperature catalysed by KF-Al_2O_3. The enol structure of the product not ketone was characterised by ^{1}H NMR, IR and elemental analysis, and enol and (*Z*)-structure further confirmed by X-ray diffraction analysis.

Keywords: coumarins, enol structure, KF-Al_2O_3, synthesis

Chromenes and their derivatives are important compounds, which are found to possess antiestrogenic activity and are devoid of any agonistic activity,[1] are evaluated for potassium channel opening and hypotensive activies,[2] vasodilator and antihypertensive activies,[3] β-adrenolytic activity,[4] antimicrobial activity[5] and biological activity of high-affinity retinoic acid receptor antagonist.[6] These promoted us to investigate these compounds through a simple route. 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 recognised in recent years.[7] However, low solubility of fluoride salts in ordinary solvents hampers their wide applications in organic synthesis. On the other hand, there has been increasing use of inorganic solid supports as catalysts for many years, resulting in 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 found application in a large number of organic reactions such as Knoevenagel reaction,[9] Henry reaction,[10] Darzens reaction,[11] Wittig reaction,[12] elimination[11] and many other reactions.[13] In order to further expand the application of this reagent, recently we selected the substituted salicylaldehydes and 4-hydroxy-6-methyl-pyran-2-one as substrates (Scheme 1), an unexpected ring-opening of a 2-pyrone ring reaction took place, with chromenes derivatives being obtained, not simple Knoevenagel condensation product. Here we report an efficient method for synthesis of 3-[(*Z*)-1-hydroxy-3-oxobut-1-enyl]-2*H*-chromen-2-one derivatives catalysed by KF–Al_2O_3.

The structure of **3a** was based on the spectroscopic data and elemental analysis. It should be noted that the IR spectra exhibited broad band at 3255 cm^{-1} (OH), 1737 cm^{-1} (C=O), and the NMR spectra showed the absence of the methylene group, instead a singlet at 15.95 ppm (OH) and a singlet at 7.06 ppm (CH). In order to further confirm the structure of the products, the X-ray diffraction analysis[14] of **3a** was carried out. The crystal structure of the product **3a** was shown in Fig. 1. From Fig. 1, we can see clearly that it was an enol form, not a ketone structure, perhaps the large conjugative system stable the enol moiety. Furthermore the original 2-pyranone ring was opened unexpectedly; perhaps a sequential reaction of the Knoevenagel condensation, intramolecular cyclisation followed by opening the ring may take place during the formation of the product. A plausible mechanism for the formation of **3** is outline in Scheme 2 (Table 1).

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 from solution in DMSO-d_6 or $CDCl_3$ with Me_4Si as internal standard using an Inova-400

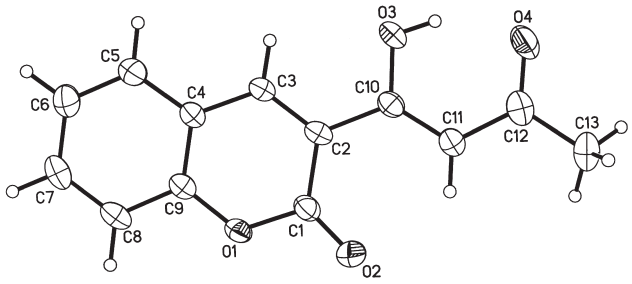
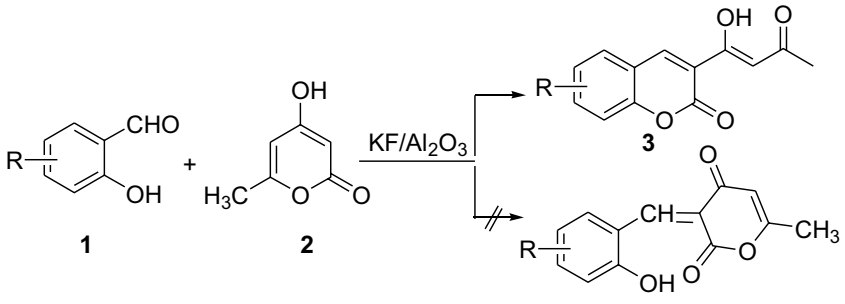


Fig. 1 The crystal structure of **3a** with 1.325(2) Å for C10-O3, 1.372(3) Å for C10-C11, 1.430(3) Å for C11-C12, 1.325(2) Å for C12-O4, 1.257(3) Å.



Scheme 1

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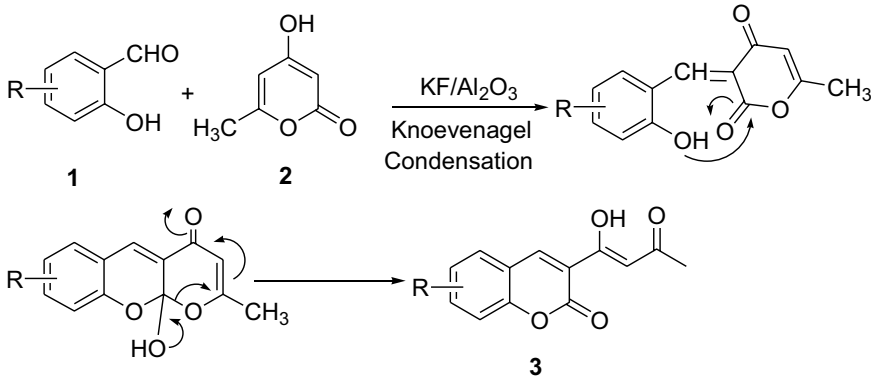

Scheme 2

Table 1 The reaction times and yields of the products **3**

Entry	R	Time/h	Yields/%
3a	H	8	93
3b	6-Br	8	91
3c	6-Cl	10	88
3d	6,8-Cl_2	10	86
3e	6-CH_3	12	87
3f	6,8-Br_2	12	92
3g	5,6-C_6H_4	10	82
3h	7-CH_3O	12	83

spectrometer. Elemental analyses were carried out using Carlo Erba 1110 analyser. X-ray diffraction was measured on a Rigaku Mercury diffractometer.

Typical experimental procedure

A dry 50 ml flask was charged with substituted salicylaldehydes (2 mmol), 4-hydroxy-6-methyl-pyran-2-one (2 mmol), KF-alumina (250 mg) and ethyl alcohol (10 ml). The mixture was stirred at room temperature for 8–12 h, the solid material was filtered off and washed with water, and the crude product was purified by recrystallisation from DMF and water to give **3**.

3-[(Z)-1-Hydroxy-3-oxobut-1-enyl]-2H-chromen-2-one (**3a**): Yellow solid. m.p. 148–150 °C. (Lit.[15] 148–150 °C). IR (KBr), *v*: 3255, 3059, 2939, 1737, 1580, 1474 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.37 (s, 3H, CH_3), 7.06 (s, 1H, CH), 7.36–7.41 (m, 2H, ArH), 7.63–7.69 (m, 2H, ArH), 8.70 (s, 1H, CH), 15.89 (s, 1H, OH).

3-[(Z)-1-Hydroxy-3-oxobut-1-enyl]-6-bromo-2H-chromen-2-one (**3b**): Yellow solid. m.p. 211–212 °C. (Lit.[15] 213–214 °C), IR (KBr), *v*: 3130, 3055, 1736, 1670, 1581, 1521, 1373, 1404 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.29 (s, 3H, CH_3), 7.01 (s, 1H, CH), 7.26 (d, J = 8.8 Hz, 1H, ArH), 7.72 (dd, J = 8.8 Hz, J' = 2.0 Hz, 1H, ArH), 7.78 (d, J = 2.0 Hz, 1H, ArH), 8.57 (s, 1H, CH), 15.96 (s, 1H, OH).

3-[(Z)-1-Hydroxy-3-oxobut-1-enyl]-6-chloro-2H-chromen-2-one (**3c**): Yellow solid. m.p. 197–199°C. IR (KBr), *v*: 3129, 3055, 1739, 1655, 1612, 1555, 1475, 1408 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.27 (s, 3H, CH_3), 4.18 (s, 1H, OH), 6.91 (s, 1H, CH), 7.52 (d, J = 8.8 Hz, 1H, ArH), 7.79 (dd, J = 8.8 Hz, J' = 2.4 Hz, 1H, ArH), 8.13 (d, J = 2.4 Hz, 1H, ArH), 8.81 (s, 1H, CH). Anal. Calcd for $C_{13}H_9ClO_4$: C 59.00, H 3.43; found C 58.87, H 3.45.

3-[(Z)-1-Hydroxy-3-oxobut-1-enyl]-6,8-dichloro-2H-chromen-2-one (**3d**): Yellow solid. m.p. 200–202 °C. IR (KBr), *v*: 3115, 3065, 1747, 1611, 1577, 1417 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.28 (s, 3H, CH_3), 4.18 (s, 1H, OH), 6.89 (s, 1H, CH), 8.10 (d, J = 2.0 Hz, 1H, ArH), 8.12 (d, J = 2.0 Hz, 1H, ArH), 8.80 (s, 1H, CH). Anal. Calcd for $C_{13}H_8Cl_2O_4$: C 52.20, H 2.70; found C 52.05, H 2.88.

3-[(Z)-1-Hydroxy-3-oxobut-1-enyl]-6-methyl-2H-chromen-2-one (**3e**): Yellow solid. m.p. 179–180 °C. IR (KBr), *v*: 3135, 3054, 2925, 1710, 1668, 1613, 1572, 1489, 1412 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.25 (s, 3H, CH_3), 2.39(s, 3H, CH_3), 4.16 (s, 1H, OH), 6.92 (s, 1H, CH), 7.39 (d, J = 8.4 Hz, 1H, ArH), 7.58 (d, J = 8.4 Hz, 1H, ArH), 7.76 (s, 1H, ArH), 8.77 (s, 1H, CH). Anal. Calcd for $C_{14}H_{12}O_4$: C 68.85, H 4.95; found C 68.80, H 4.98.

3-[(Z)-1-Hydroxy-3-oxobut-1-enyl]-6,8-dibromo-2H-chromen-2-one (**3f**): Yellow solid. m.p. 188–190 °C. IR (KBr), *v*: 3127, 3058, 1758, 1679, 1603, 1575, 1447, 1400 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.28 (s, 3H, CH_3), 4.18 (s, 1H, OH), 6.89 (s, 1H, CH), 8.28 (s, 2H, ArH), 8.77 (s, 1H, CH). Anal. Calcd for $C_{13}H_8Br_2O_4$: C 40.24, H 2.08; found C 40.10, H 2.32.

3-[(Z)-1-Hydroxy-3-oxobut-1-enyl]-2H-benzo[f]chromen-2-one (**3g**): Yellow solid. m.p. 218–220 °C. IR (Lit.[16] 218–220 °C). (KBr), *v*: 3128, 3057, 1720, 1667, 1606, 1559, 1465, 1437 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.27 (s, 3H, CH_3), 4.24 (s, 1H, OH), 6.98 (s, 1H, CH), 7.61–7.70 (m, 2H, ArH), 7.79–7.83 (m, 1H, ArH), 8.11 (d, J = 8.4 Hz, 1H, ArH), 8.35 (d, J = 8.8 Hz, 1H, ArH), 8.62 (d, J = 8.4 Hz, 1H, ArH), 9.45 (s, 1H, CH).

3-[(Z)-1-Hydroxy-3-oxobut-1-enyl]-7-methoxyl-2H-chromen-2-one (**3h**): Yellow solid. m.p. 175–177 °C. (Lit.[16] 174–175 °C)IR (KBr), *v*: 3132, 3043, 1727, 1680, 1608, 1502, 1427 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.23 (s, 3H, CH_3), 3.91 (s, 3H, CH_3O), 4.14 (s, 1H, OH), 6.90 (s, 1H, CH), 7.05 (dd, J = 8.8 Hz, J' = 2.4 Hz, 1H, ArH), 7.09 (d, J = 2.4 Hz, 1H, ArH), 7.91 (d, J = 8.8 Hz, 1H, ArH), 8.81 (s, 1H, CH).

In conclusion, we find a simple method available for the synthesis of 3-[(Z)-1-hydroxy-3-oxobut-1-enyl]-2*H*-chromen-2-one 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,[15,16] this method has the advantage of an easy work-up, milder reaction conditions and good yields in synthesis of these potential biologically active compounds.

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14 X-ray crystallography for **3a**: Crystallographic data for the structure **3a** reported in this paper has been deposited at the Cambridge Crystallographic Data Centre as supplementary publication with No. CCDC-282532. 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). Empirical formula $C_{13}H_{10}O_4$, F_W = 230.21, T = 193(2) K, triclinic, space group P-1, a = 6.7577 (19) Å, b = 8.799 (3) Å, c = 9.890 (4) Å, α = 83.17(4), β = 76.17(3), γ = 71.10(3) °, V = 539.7(3) Å^3, Z = 2, Dc = 1.417 Mg/m^3, λ(MoKα) = 0.71070Å, μ = 0.106 mm^{-1}, F(000) = 240, 3.17°<θ<25.35°, R = 0.0583, wR = 0.1526. S = 1.078, Largest diff. Peak and hole: 0.39 and -0.23 e·Å^{-3}. The non-hydrogen atoms were refined anisotropically, the hydrogen atoms were positioned geometrically and refined as riding.

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