Green synthesis of aurones and related compounds under solvent-free conditions

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3-Coumaranones were condensed with aldehydes on alumina or alumina–potassium fluoride without solvent under microwave irradiation or classical heating. Novel aurones and analogues bearing ferrocenyl, benzodioxole or benzodioxane groups were obtained in good yields without use of heavy metal reagents.

Keywords: aurone, ferrocene, solventless reaction, microwave

Aurones (2-benzylidene-1-benzofuran-3(2*H*)-ones) are natural compounds occurring as yellow dyes in plants and constitute a small part of a larger family of natural products known as flavonoids.[1] The class of flavonoids includes flavones, isoflavones, chalcones and aurones, and are mainly secondary metabolites of plants found in fruits and flowers. Aurones are structural isomers of flavones. They are less studied probably due to their low content in plants. Aurones are known for displaying a wide variety of biological activities:[2] they are described as enzyme inhibitors (tyrosinase, iodothyronine deiodinase, acetylcholinesterase, hepatitis C virus RNA-dependent RNA polymerase), and also as anticancer, antibacterial, antifungal, antioxidant, antiparasite (*Plasmodium falciparum*) and insect antifeedant agents.

Two types of synthesis of aurones have been generally reported. The first is the condensation of 3-coumaranones with aldehydes. The reaction is catalysed by alumina,[3] alumina–potassium fluoride,[4] barium oxide,[5] or eutectic choline chloride–urea.[6] The second methodology, analogous to the biosynthesis of aurones, is the oxidative rearrangement of chalcones in the presence of toxic metal salts such as thallium,[7] mercury,[8] or gold oxidants.[9]

The use of heavy metal salts (Ba, Tl, Hg, Au) has been recently described;[5,7–10] however, the use of heavy metals can be problematic for the preparation of drugs because traces of heavy metals can influence the results of biological tests. To achieve synthesis of new aurones under green conditions without the use of heavy metals, we have extended the scope of our work on the 3-coumaranone condensation.[4] We were interested in the synthesis of novel aurones carrying 2,3-dihydro-1,4-benzodioxin, 1,3-benzodioxol and ferrocenyl groups. 2,3-dihydro-1,4-benzodioxine and 1,3-benzodioxole are known for their biological properties,[11] but aurone derivatives of 2,3-dihydro-1,4-benzodioxine and 1,3-benzodioxole have not been reported. Ferrocenyl aurones were introduced recently by Jaouen and co-workers[12–14] for inducing morphological modifications of endothelial cells and as cytotoxic compounds against B16 murine melanoma cells.

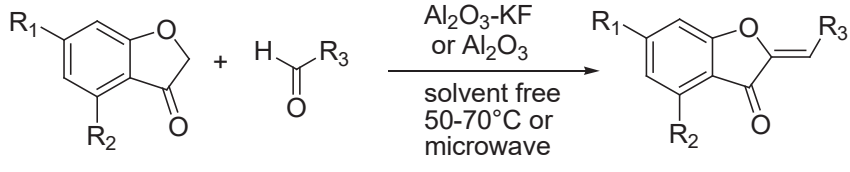
In this work, we decided to prepare aurones using a green approach, with a minimum of solvent. For this reason, we used solvent-free synthesis of aurones on alumina or alumina–potassium fluoride according to Scheme 1.

Alumina–potassium fluoride is a much more basic catalyst than alumina[15] and conducive to better yields than alumina; however, alumina was preferred in the case of function-free phenol. In fact, in the presence of potassium fluoride on alumina with coumaran-3-ones bearing a hydroxyl group, a phenate potassium salt was formed, which led to difficulties in aurone desorption, so in this case alumina was preferable as support. Furthermore, the reactions without solvent were accelerated by microwave heating.[16] Yields obtained were found to be similar under microwave irradiation and classical heating (Table 1).

All the reactions were stereospecific and the stereochemistry obtained for all the compounds was Z, this configuration corresponding to the configuration of natural aurones. The aurones **1a**, **1b**, **3b** and **3d** have already been reported.[10,17] To our knowledge, all other aurones described herein in the experimental part have never been reported. The biological properties of these new aurones are under study.

Conclusion

Condensation under solvent-free conditions of 3-coumaranones with aldehydes on classical heating or under microwave irradiation in the presence of alumina or alumina–potassium fluoride allowed the synthesis of new potentially biological aurones containing benzodioxane, benzodioxole, or ferrocenyl groups without the use of heavy metal reagents.



1 R_1 = OH, R_2 = H; **2** R_1 = OMe, R_2 = H; **3** R_1 = OH, R_2 = OH; **4** R_1 = OMe, R_2 = OMe; **5** naphthofuran-3(2*H*)-one.
a Ferrocene carboxaldehyde; **b** 1,3-benzodioxole-5-carboxaldehyde (piperonal); **c** 1,4-benzodioxane-6-carboxaldehyde; **d** 3,4,5-trimethoxybenzaldehyde.

Scheme 1 Condensation of 3-coumaranones **1–5** with aldehydes **a–d**.

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Table 1 Dry condensation of 3-coumaranones (**1–5**) with aldehydes (**a–d**)

3-Coumaranone	Aldehyde	Catalyst	Product	Yield/%[a]
1	**a**	Al_2O_3	**1a**	75
1	**c**	Al_2O_3	**1c**	86
2	**a**	Al_2O_3–KF	**2a**	88
2	**c**	Al_2O_3–KF	**2c**	86
2	**d**	Al_2O_3–KF	**2d**	91, 90[b]
3	**b**	Al_2O_3	**3b**	53, 55[b]
3	**c**	Al_2O_3	**3c**	86
3	**d**	Al_2O_3	**3d**	58, 57[b]
4	**c**	Al_2O_3–KF	**4c**	88
5	**a**	Al_2O_3–KF	**5a**	53
5	**b**	Al_2O_3–KF	**5b**	75, 74[b]

[a]Yields under classical heating.

[b]Yields under microwave heating.

Experimental

IR spectra were performed on solid samples using a Fourier transform Perkin Elmer Spectrum with ATR accessory. Only significant absorptions are listed. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC 400 spectrometers at 400 MHz. Samples were recorded in DMSO-d-6 solutions using TMS as an internal standard. The chemical shifts are expressed in δ units (ppm) and quoted downfield from TMS. The multiplicities are reported as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet (for details see ESI file) recorded on Waters mass spectrometers: QTOF Micro (ESI), Xevo G2-XS QTof (ESI) or Autospec (EI). Microwave irradiations were performed at 2450 MHz with an Anton Paar monowave 300.

6-hydroxybenzofuran-3(2*H*)-one (**1**),[18] 6-methoxybenzofuran-3(2*H*)-one (**2**),[19,20] 4,6-dihydroxybenzofuran-3(2*H*)-one (**3**),[21,22] 4,6-dimethoxybenzofuran-3(2*H*)-one (**4**),[23,24] and naphthofuran-3(2*H*)-one (**5**) were prepared according to the literature.[4] Aldehydes were commercial products (Alfa Aesar). Potassium fluoride on alumina was prepared according to the literature.[25]

Synthesis of aurone derivatives; general procedure

Classical heating procedure A: 1g of Al_2O_3–KF was added to the benzofuranone derivative (0.6 mmol) and the aldehyde (1.0–1.5 eq) dissolved in acetonitrile (1–2 mL). The mixture was evaporated under vacuum and the resulting solid was heated at 70 °C until TLC showed disappearance of the starting material (3–8 h). The mixture was extracted with ethanol and Al_2O_3–KF was removed by filtration. The filtrate was evaporated under reduced pressure to afford the corresponding crude aurone.

Classical heating procedure B: The same as procedure A but with Al_2O_3 instead of Al_2O_3–KF.

Microwave heating: Procedures A or B were used. The classical heating was substituted by microwave irradiation performed at 150 °C for 10 min.

*(Z)-2-[(ferrocenyl)methylidene]-6-hydroxy-1-benzofuran-3(2*H*)-one, $C_{19}H_{14}FeO_3$* (**1a**)

Compound **1a** was obtained by condensation of 6-hydroxybenzofuran-3(2*H*)-one (100 mg, 0.66 mmol) and ferrocenecarboxaldehyde (142 mg, 0.66 mmol), according to procedure B, to afford the product as: Pure violet solid; yield 171 mg (75%); m.p. >230 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.07 (d, 1H, *J* = 8.0 Hz), 6.13 (s, 1H), 5.90 (d, 1H, *J* = 8.0 Hz), 5.72 (s, 1H), 4.72 (s, 2H), 4.39 (s, 2H), 4.13 (s, 5H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.3, 167.3, 165.9, 146.5, 126.4, 114.5, 113.4, 111.9, 96.3, 74.1, 71.2, 71.1, 69.9; IR (cm^{-1}): 3295 (OH), 1666 (C=O), 1622–1500 (C=C), 1223 (C–O–C); HRMS (EI) calcd for $C_{19}H_{14}FeO_3$: 346.0292; found: 346.0296 (M^+).

*(Z)-2-[2,3-dihydro-1,4-benzodioxin-2-yl)methylidene]-6-hydroxy-1-benzofuran-3(2*H*)-one, $C_{17}H_{12}O_5$* (**1c**)

According to procedure B, with classical heating, compound **1c** was prepared by condensation of 6-hydroxybenzofuran-3(2*H*)-one (100 mg, 0.66 mmol) and 1,4-benzodioxane-2-carboxaldehyde (169 mg, 1.03 mol) to afford the product as: Pure yellow solid; yield 168 mg (86%); m.p. 230 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34 (s, 1H), 7.28 (d, 1H, *J* = 8.4 Hz), 7.07 (d, 1H, *J* = 8.8 Hz), 6.89 (d, 1H, *J* = 8.4 Hz), 6.17 (s, 1H), 5.86 (d, 1H, *J* = 8.8 Hz), 5.68 (brs, 1H), 4.27 (s, 4H); ^{13}C NMR (400 MHz, DMSO-d_6): 182.5, 176.3, 170.1, 150.3, 144.8, 143.7, 127.6, 124.7, 123.9, 120.6, 118.5, 117.8, 104.2, 103.2, 98.6, 64.8, 64.5; IR (cm^{-1}): 3290 (OH), 1667 (C=O), 1489–1620 (C=C), 1221 (C–O–C). MS (ES+) *m/z* (% relative abundance): 319 (M + Na, 100), 615 (2M + Na, 40); MS (ES–) *m/z* (% relative abundance): 295 (M – H, 100); HRMS (ESI) calcd for $C_{17}H_{13}O_5$: 297.0763; found: 297.0762 ($M + H^+$).

*(Z)-2-[(ferrocenyl)methylidene]-6-methoxy-1-benzofuran-3(2*H*)-one, $C_{20}H_{16}FeO_3$* (**2a**)

Compound **2a** was obtained by condensation of 6-methoxybenzofuran-3(2H)-one (108 mg, 0.66 mmol) and ferrocenecarboxaldehyde (141 mg, 0.66 mmol), according to classical heating procedure B to afford the product as: Pure violet solid; yield 209 mg (88%); m.p. 142 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.66 (d, 1H, *J* = 8.4 Hz), 7.13 (d, 1H), 6.83 (dd, 1H), 6.78 (s, 1H), 4.92 (s, 2H), 4.61 (s, 2H), 4.21 (s, 5H), 3.93 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 180.7, 168.9, 164.0, 146.5, 126.4, 115.4, 114.5, 111.8, 96.3, 73.8, 71.7, 71.1, 69.9, 55.7; IR (cm^{-1}): 1684 (C=O), 1635–1495 (C=C), 1222 (C–O–C); HRMS (EI) calcd for $C_{20}H_{16}FeO_3$: 360.0449; found: 360.0462 (M^+).

*(Z)-2-[(2,3-dihydro-1,4-benzodioxin-2-yl)methylidene]-6-methoxy-1-benzofuran-3(2*H*)-one, $C_{18}H_{14}O_5$* (**2c**)

According to procedure A, using classical heating, compound **2c** was prepared by condensation of 6-methoxybenzofuran-3(2*H*)-one (108 mg, 0.66 mmol) and 1,4-benzodioxane-2-carboxaldehyde (129 mg, 0.79 mol.). The crude product was recrystallised from methanol to afford the product as: Pure yellow solid; yield 176 mg (86%); m.p. 183 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.68 (d, 1H), 7.55 (d, 1H), 7.48 (dd, 1H), 7.18 (d, 1H), 6.98 (d, 1H), 6.85 (dd, 1H), 6.78 (s, 1H), 4.35–4.27 (m, 4H), 3.92 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.9, 168.2, 167.7, 146.8, 145.8, 144.0, 125.8, 125.76, 125.70, 120.1, 118.1, 114.5, 113.2, 111.7, 97.6, 64.9, 64.4, 56.9. IR (cm^{-1}): 1685 (C=O), 1637–1496 (C=C), 1221 (C–O–C). MS *m/z* (% relative abundance): 333 (M + Na, 75), 643 (2M + Na, 100); HRMS (EI) calcd for $C_{18}H_{14}O_5$: 310.08413; found: 310.0108 (M^+).

*(Z)-6-methoxy-2-[(3,4,5-trimethoxyphenyl)methylidene]-1-benzofuran-3(2*H*)-one, $C_{19}H_{18}O_6$* (**2d**)

According to procedure A, under both classical and microwave heating, compound **2d** was prepared by condensation of 6-methoxybenzofuran-3(2*H*)-one (108 mg, 0.66 mmol) and 3,4,5-trimethoxybenzaldehyde (194 mg, 0.99 mmol). The crude product was recrystallised from ethanol to afford the product as: Pure yellow solid; yield 206 mg (91%) under classical heating, 204 mg (90%) under microwave heating; m.p. = 175 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.68 (d, 1H), 7.34 (s, 2H), 7.18 (d, 1H), 6.86 (dd, 1H), 6.81 (s, 1H), 3.93 (s, 3H), 3.86 (s, 6H), 3.73 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 186.6, 165.3, 164.9, 152.0, 146.1, 138.7, 125.5, 116.0, 113.5, 111.6, 106.0, 96.0, 60.6, 56.8, 56.7, 56.1; IR (cm^{-1}): 1700 (C=O), 1602–1458 (C=C), 1230 (C–O–C). MS *m/z* (% relative abundance): 365 (M + Na, 70), 707 (2M + Na, 100); HRMS (ESI) calcd for $C_{19}H_{19}O_6$: 343.1182; found: 343.1181 ($M + H^+$).

*(Z)-4,6-dihydroxy-2-[(1,3-benzodioxol-5-yl)methylidene]-1-benzofuran-3(2*H*)-one, $C_{16}H_{10}O_6$* (**3b**)

The product was obtained by condensation of 4,6-dihydroxy-benzofuran-3(2*H*)-one (109 mg, 0.66 mmol) and piperonal (99 mg, 0.66 mol) according to procedure A under both classical and microwave heating as: Pure yellow solid; yield 104 mg (53%) under classical heating, 108 mg (55%) under microwave heating; m.p. 276 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.52–7.39 (m, 2H), 7.04 (s, 1H), 6.56 (s, 1H), 6.19 (s, 1H), 6.09 (s, 2H), 6.04 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 183.0, 166.0, 164.0, 160.7, 147.6, 147.0, 147.0, 146.5, 111.7, 113.0, 110.1, 102.2, 99.6, 97.3; HRMS (EI) calcd for $C_{16}H_{10}O_6$: 298.0477; found: 298.0502 (M^+).

*(Z)-4,6-dihydroxy-2-[(2,3-dihydro-1,4-benzodioxin-2-yl)methylidene]-1-benzofuran-3(2*H*)-one,* $C_{17}H_{12}O_6$ (**3c**)

According to the procedure B, with classical heating, compound **3c** was prepared by condensation of 4,6-dihydroxybenzofuran-3(2*H*)-one (128 mg, 0.66 mmol) and 1,4-benzodioxane-6-carboxaldehyde (128 mg, 0.78 mol), to afford the product as: Pure orange solid; yield 177 mg (86%); m.p. 260 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.45–7.35 (m, 2H), 6.95 (d, 1H), 6.45 (s, 1H), 5.75 (s, 2H), 4.28 (s, 4H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 182.4, 168.5, 164.1, 160.3, 158.0, 147.1, 123.9, 124.2, 117.9, 112.9, 103.0, 96.6, 95.6, 75.3. IR (cm^{-1}): 3287 (OH), 1664 (C=O), 1500–1622 (C=C), 1222 (C–O–C); MS (ES+) *m/z* (% relative abundance): 313 (M + H, 50), 335 (M + Na, 100), 647 (2M + Na, 30); MS (ES) *m/z* (% relative abundance): 311 (M – H, 100); HRMS (EI) calcd for $C_{17}H_{12}O_6$: 312.0634; found: 312.0600 (M$^+$).

*(Z)-4,6-dihydroxy-2-[(3,4,5-trimethoxyphenyl)methylidene]-1-benzofuran-3(2*H*)-one,* $C_{18}H_{16}O_7$ (**3d**)

According to procedure B, under both classical and microwave heating, compound **3d** was obtained by condensation of 4,6-dihydroxybenzofuran-3(2*H*)-one (109 mg, 0.66 mmol) and 3,4,5-trimethoxybenzaldehyde (194 mg, 0.99 mol), and was purified by column chromatography, to afford the product as: Orange solid; yield 132 mg (58%) under classical heating, 130 mg (57%) under microwave heating; m.p. 266 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.09 (s, 1H), 10.96 (s, 1H), 7.26 (s, 2H), 6.57 (s, 1H), 6.26 (s, 1H), 6.13 (s, 1H), 3.84 (s, 6H), 3.71 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.8, 165.0, 163.9, 160.0, 153.0, 145.7, 138.7, 110.2, 106.0, 100.2, 99.1, 92.0, 56.8, 56.1, 60.6; HRMS (EI) calcd for $C_{18}H_{16}O_7$: 344.0896; found: 344.0878 (M$^+$).

*(Z)-4,6-dimethoxy-2-[(2,3-dihydro-1,4-benzodioxin-2-yl)methylidene]-1-benzofuran-3(2*H*)-one,* $C_{19}H_{16}O_6$ (**4c**)

According to procedure A, with classical heating (**4c**) was prepared by condensation of 4,6-dimethoxybenzofuran-3(2*H*)-one (100 mg, 0.51 mmol) and 1,4-benzodioxane-2-carboxaldehyde (108 mg). The crude product was recrystallised from methanol to afford the product as: Pure yellow solid; 153 mg (88%); m.p. 173 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.50 (d, 1H), 7.43 (dd, 1H), 6.96 (d, 1H), 6.73 (d, 1H), 6.63 (s, 1H), 6.34 (d, 1H), 4.33–4.25 (m, 4H,), 3.91 (s, 3H), 3.88 (s, 3H); ^{13}C NMR 400 MHz, DMSO-d_6): δ 181.9, 168.2, 167.7, 146.8, 145.8, 144.0, 125.81, 125.76, 125.7, 120.0, 118.0, 114.5, 113.2, 111.8, 97.6, 64.9, 64.4, 56.9; IR (cm^{-1}): 1685 (C=O), 1637 (C=C); ES *m/z* (% relative abundance): 363 (M + Na, 50), 703 (2M + Na, 100); HRMS (ESI) calcd for $C_{19}H_{17}O_6$: 341.1025; found: 341.1037 (M + H$^+$).

*(Z)-2-[(ferrocenyl)methylidene]naphthofuran-3(2*H*)-one,* $C_{23}H_{16}FeO_2$ (**5a**)

Compound **5a** was obtained by condensation of naphthofuran-3(2*H*)-one (121 mg, 0.66 mmol) and ferrocene carboxaldehyde (141 mg, 0.66 mmol), according to procedure A, with classical heating, and was purified by flash chromatography on silica gel (eluent cyclohexane 9/ethyl acetate 1) to afford the product as: Violet solid; yield 133 mg (53%); m.p. 205 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.72 (d, 1H), 8.37 (d, 1H), 8.09 (d, 1H), 7.76–7.73 (m), 7.58 (d, 1H), 6.97 (s, 1H), 4.98 (s, 2H), 4.66 (s, 2H), 4.22 (s, 5H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 184.2, 160.0, 148.0, 133.0, 130.4, 129.4, 129.0, 128.0, 125.8, 122.0, 115.0, 113.0, 110.0, 76.1, 71.8, 71.5, 69.9; IR (cm^{-1}): 1685 (C=O), 1626–1488 (C=C), 1220 (C–O–C); HRMS (EI) calcd for $C_{23}H_{16}FeO_2$: 380.0500; found: 380.0506 (M$^+$).

*(Z)-2-[(1,3-benzodioxol-5-yl)methylidene]naphthofuran-3(2*H*)-one,* $C_{20}H_{12}O_4$ (**5b**)

According to procedure A under both classical and microwave heating, compound **5b** was prepared by condensation of naphthofuran-3(2*H*)-one (121 mg, 0.66 mmol) and piperonal (126 mg, 0.84 mol) to afford the product as: Pure green solid; yield 154 mg (74%) under classical heating, 156 mg (75%) under microwave heating; m.p. 218 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.72 (d, 1H), 8.41 (d, 1H), 8.12 (d, 1H), 7.82–7.77 (m, 2H), 7.69 (d, 1H), 7.64–7.58 (m, 2H), 7.11 (d, 1H), 7.02 (s, 1H), 6.15 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 180.4, 160.0, 148.4, 148.2, 147.2, 135.0, 134.4, 130.0, 128.4, 127.8, 127.7, 125.6, 124.4, 123.2, 115.0, 113.0, 111.2, 109.3, 108.9, 96.3. IR (cm^{-1}): 1682 (C=O), 1636–1482 (C=C), 1223 (C–O–C); HRMS (EI) calcd for $C_{20}H_{12}O_4$: 316.0736; found: 316.0706 (M$^+$).

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Electronic Supplementary Information

The ESI is available through:
stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

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