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One pot synthesis of aryl substituted aurones

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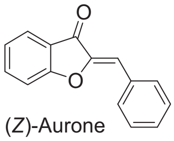
ABSTRACT

An efficient one-pot synthesis of new 4-hydroxy-2-(diarylmethylene)benzofuran-3(2*H*)-ones dyes (aryl substituted aurones) from 2′,6′-dihydroxyacetophenone, potassium *tert*-butoxide and aromatic ketones under thermal conditions is described.

1. Introduction

Aurones (2-benzylidenebenzofuran-3(2H)-ones) are natural occurring yellow dyes found especially in plants and in some marine organisms, usually in a hydroxylated form. Both *E* and Z isomers can be found in nature, although the latter is thermodynamically more stable and thus much more abundant. Besides their contribution to the pigmentation of flowers and fruits [1] aurones exhibit a wide variety of biological activities: they have been described as antifungal agents [2–4], antibacterial agents [5–9], insect antifeedant agents [10], antioxidants [11–14], as inhibitors of tyrosinase [15], iodothyronine-deiodinase [16], acetylcholinesterase [17], anticancer [18–20] and as possessing anti-inflammatory properties [10]. These compounds are usually prepared by three main methods: condensation between benzofuranones and benzaldehydes [10,15,17,18,21,22], oxidative cyclisation of 2′-hydroxychalcones [11] or by catalysed cyclisation of *ortho*-(1-hydroxyprop-2-ynyl)phenols or *ortho*-hydroxyaryl arylethynyl ketones [23–25]. In this paper we describe a fast and easy one-pot synthesis of new aryl substituted aurones starting from commercially available materials under thermal conditions.



(*Z*)-Aurone

2. Results and discussion

2′-Hydroxychalcones can be easily prepared, under mild conditions, by aldol condensation between 2′-hydroxyacetophenone and different benzaldehydes in the presence of base. This reaction is very general and these compounds are valuable intermediates in the synthesis of flavones [26–28] and aurones [11] (Scheme 1).

The reaction of 2′-hydroxyacetophenone with benzophenone in the presence of *t*-BuOK in toluene at reflux, gives the expected aryl substituted 2′-hydroxychalcone an useful compound that can be converted in acid medium to the 2,2-diphenylchroman-1-one, an important precursor for the synthesis photochromic chromenes [29,30]. In an attempt to prepare 2′,6′-dihydroxy-3-phenylchalcone we tried the reaction of 2′,6′-dihydroxyacetophenone with benzophenone in the presence of *t*-BuOK and using toluene as solvent, but no reaction was detected after 8 h at reflux. Changing the solvent to xylene led to the same result while when the reaction was performed in high boiling point solvents like DMSO, ethyleneglycol or nitrobenzene only degradation products were observed (Scheme 2).

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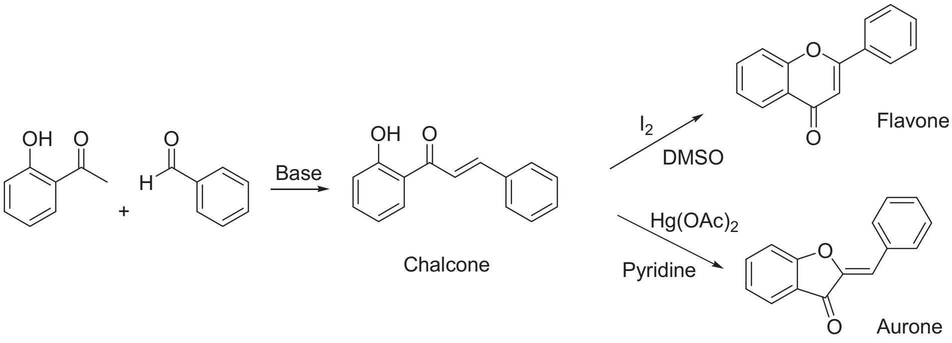
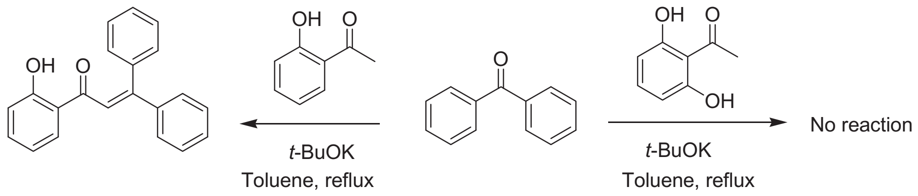


Scheme 1. Synthesis of flavones and aurones from 2′-hydroxychalcones.



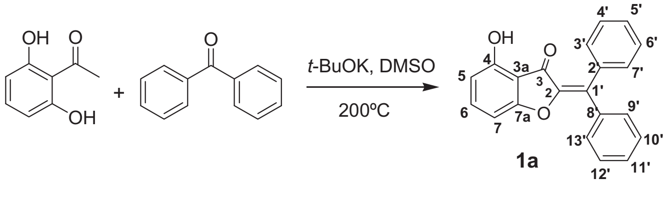
Scheme 2. Reaction of 2′-hydroxyacetophenone and 2′,6′-dihydroxyacetophenone with benzophenone.

However, heating a mixture of 2′,6′-dihydroxyacetophenone, potassium *tert*-butoxide and benzophenone in the presence of a very small amount of DMSO at 200 °C for 2 min affords a red mass that upon acid hydrolysis originated a deep yellow dye.

The ^{1}H NMR spectrum of this compound showed the expected aromatic signals but the absence of any signal that could be attributed to ethylenic protons, and the presence of only one phenolic proton pointed to a different structure. Mass spectrometry confirmed the molecular formula of the product as $C_{21}H_{14}O_3$ which indicates a difference of two hydrogen atoms from the predicted chalcone structure.

The structure of this new yellow dye was unambiguously established using 2D NMR experiments as being an aurone derivative (Scheme 3). ^{1}H–^{1}H scalar correlations were measured in COSY experiment (Fig. 1) from H-5 at 6.60 ppm up to H-7 at 6.76 ppm via H-6 at 7.51 ppm and for the two phenyl groups between H-3′/7′ at 7.60 ppm and H-4′/6′ at 7.44 ppm, and between H-9′/13′ at 7.37 ppm and H-10′/12′ at 7.50 ppm.

The HMBC spectrum (Fig. 2) evidences long-range C–H correlations between carbon C–4 at 156.9 ppm and aromatic protons H-5, H-6 and H-7, and the phenolic function at 8.06 ppm. The furanone quaternary carbons C-7a and C-3 were evidenced at 163.8 ppm and 184.8 ppm, respectively. Carbon C-7a is long-range correlated with H-5, H-6 and H-7, while carbon C-3 is correlated with H-5 and H-7. The carbon C-1′ at 133.0 ppm is long-range correlated with H-3′/7′ and H-9′/13′.



Scheme 3. Synthesis of 4-hydroxy-2-(diphenylmethylene)benzofuran-3(2H)-one dye **1a**.

The dye **1a** was obtained in 10% yield after column chromatography. Heating the reaction mixture for more than 2 min, or at higher temperature leads to more degradation while heating at lower temperature, leaves too much unreactive material. The reaction also works using *t*-butanol or DMF as solvent but with lower yields (7 and 8%, respectively) and the amount of solvent must be very low. If several mL are used only degradation products are detected. The best results were obtained using 60 mg of DMSO for 0.5 mmol of 2′,6′-dihydroxyacetophenone. Heating the reagents in an inert atmosphere (N_2) gave the same result.

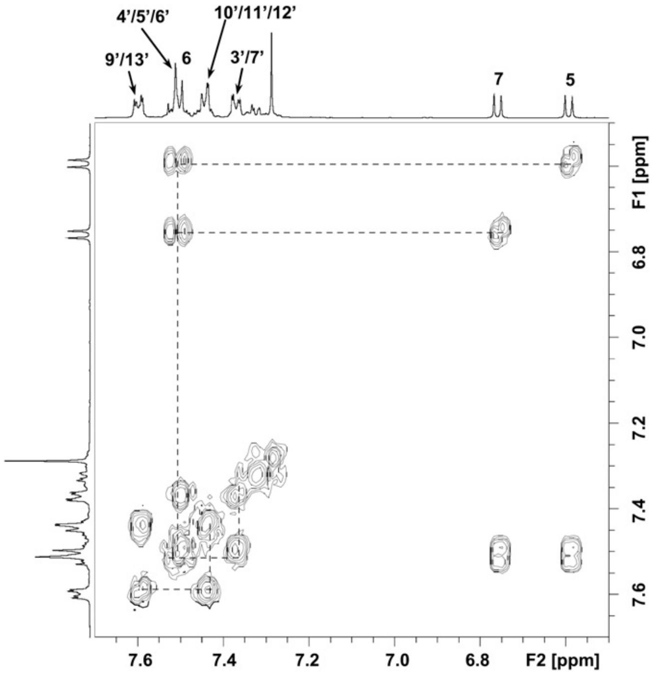


Fig. 1. ^{1}H–^{1}H COSY of **1a** in $CDCl_3$.

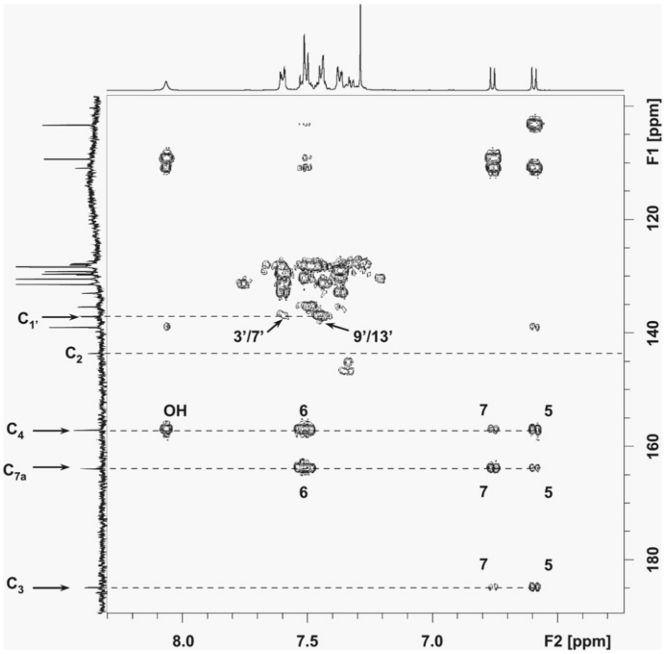


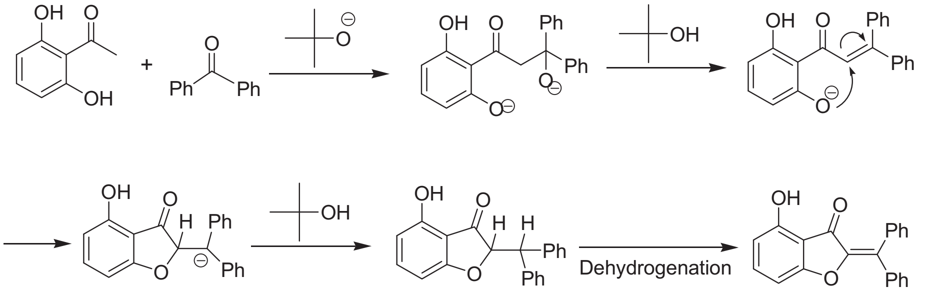
Fig. 2. ^{1}H–^{13}C HMBC of **1a** in CDCl$_3$.

The mechanism of this reaction may involve the intermediate formation of the chalcone by aldol condensation followed by intramolecular nucleophilic addition to the conjugated double bond leading to a carbanion stabilised by the two aromatic substituents, and finally dehydrogenation under thermal conditions leading to the conjugated aurone **1a** (Scheme 4).

Starting from fluorenone or 2-hydroxyfluorenone we obtained new 4-hydroxy-2-(diarylmethylene)benzofuran-3(2H)-ones dyes (aryl substituted aurones) **1b** and **1c** in 9 and 8% yield, respectively (Table 1). Although the yields of this transformation are rather low (8-10%), this reaction gives rise in one-pot to rather complex molecules that are not easy to prepare by other methods. To our knowledge there is only one report concerning the synthesis of 2-(diarylmethylene)-3-benzofuranones, in 4 steps from commercially available compounds [24].

The complete assignments of all proton and carbon resonances for dyes **1a**–**c** is reported in Table 2. For aurone **1c** the higher chemical shift of proton H-3′ (8.89 ppm), relative to proton H-13′ (8.36 ppm), suggests the position of the former near the carbonyl group. To unambiguously establish the configuration of the double bond of this compound, a 1D-NOESY experiment was performed (Fig. 3). Since a strong dipolar correlation between H-13′ at 8.36 ppm and H-7 at 6.98 ppm and H-12′ at 7.15 ppm was observed, proton H-13′ must be on the same side of H-7 and therefore the double bond has an *E* configuration.

These dyes show a broad absorption band in the UV–Vis spectrum with a maximum between 398–435 nm and molar absorption coefficients (ϵ) of 0.9×10^4 to 1.5×10^4 M^{-1} cm^{-1} in CH$_2$Cl$_2$



Scheme 4. Proposed mechanism for the formation of 4-hydroxy-2-(diphenylmethylene)benzofuran-3(2H)-one dye **1a**.

Table 1
Synthesis of 4-hydroxy-2-(diarylmethylene)benzofuran-3(2H)-ones dyes.

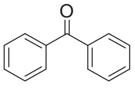
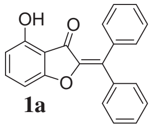
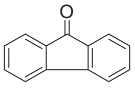
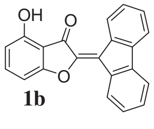
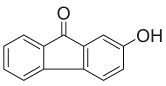
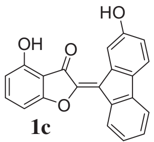
Ketone	Product	Yield (%)	λmax (nm) (ε)	λmax in basic medium (nm)
	 **1a**	10	398 (9 x 10^3)	462
	 **1b**	9	435 (1.5 x 10^4)	519
	 **1c**	8	433 (4.6 x 10^4)	500

Table 2
NMR spectral data for dyes **1a–c**.

	Dye **1a** ($CDCl_3$)		**1b** in $CDCl_3$		**1c** in DMSO-d_6	
	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
2	–	143.6	–	146.3	–	147.0
3	–	184.8	–	186.3	–	182.2
3a	–	110.8	–	110.4	–	110.6
4	–	156.9	–	157.3	–	157.9
5	6.60	109.3	6.69	109.9	6.69	111.1
6	7.51	139.0	7.59	139.4	7.61	139.3
7	6.76	103.2	6.88	103.3	6.98	102.8
7a	–	163.8	–	163.7	–	165.0
1′	–	133.0	–	129.4	–	125.6
2′	–	137.1	–	135.3	–	136.5
3′	7.60	131.4	9.33	128.0	8.89	115.5
4′	7.44	128.3	7.37	128.0	–	158.5
5′	7.44	129.6	7.44	130.8	6.86	117.5
6′	7.44	128.3	7.68	119.9	7.65	121.5
7′	7.60	131.4	–	141.3	–	132.5
8′	–	135.4	–	137.0	–	136.7
9′	7.37	130.5	–	142.2	–	142.0
10′	7.50	128.3	7.68	119.9	7.69	119.6
11′	7.50	129.1	7.44	130.8	7.41	130.9
12′	7.50	128.3	7.37	128.0	7.29	127.0
13′	7.37	130.5	8.46	129.5	8.36	129.0
OH	8.06	–	8.32	–	11.26 (C-4) 9.71 (C-4′)	–
	J in Hz		J in Hz		J in Hz	
3′–4′	7.8		7.6			
4′–5′			7.4			
5′–6′			7.2		8.6	
6′–7′	7.8					
9′–10′	7.8					
10′–11′			7.2		7.4	
11′–12′			7.4		7.7	
12′–13′	7.8		8.1		7.8	
5–6	8.0		8.3		8.2	
6–7	8.0		8.2		8.2	
3′–5′					2.2	

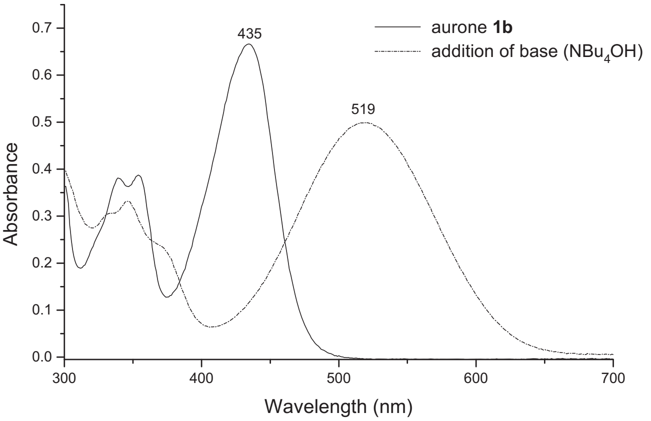


Fig. 4. UV/Vis spectra of compound **1b** (4.3×10^{-5} M, CH_2Cl_2) before and after the addition of base (Bu_4NOH).

which are in the range of those reported in the literature for aurones [31]. Since these aurones have phenolic groups their absorption spectra is pH dependent. The addition of base (Bu_4NOH) leads, as expected, to a strong bathochromic shift of the λ_{max} (64–84 nm) due to the formation of the phenolate anion (Fig. 4).

3. Experimental

The reactions were monitored by thin-layer chromatography on aluminum plates precoated with Merck silica gel 60 F254 (0.25 mm). Melting point were determined in capillary tubes and are uncorrected. The new compounds were determined to be >95% pure by ^1H NMR spectroscopy. UV–Vis spectra were recorded on a CARY 50 Varian spectrophotometer. IR spectra were obtained on a Perkin–Elmer FTIR 1600 spectrometer using KBr disks (wavenumbers in cm^{-1}). Electronic impact mass spectra were measured

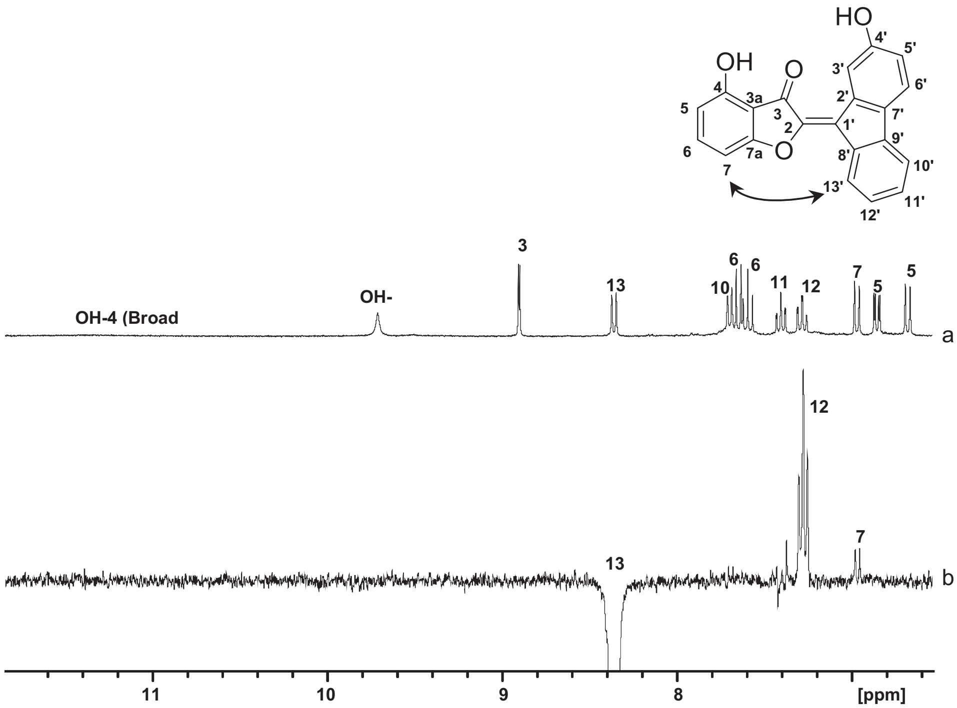


Fig. 3. a) ^1H NMR spectrum of **1c** and b) 1D NOESY spectrum with an irradiation of H-13′ to observe dipolar correlation.

on a AutoSpecE spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded at 298 K in $CDCl_3$ or DMSO using a Bruker Avance-500 spectrometer. Chemical shifts (δ) were reported in ppm and coupling constants (*J*) in Hz. Heteronuclear ^{1}H–^{13}C HSQC and HMBC experiments were carried out using standard procedures.

3.1. *4-Hydroxy-2-(diphenylmethylene)benzofuran-3(2H)-one **1a***

2′,6′-dihydroxyacetophenone (76 mg, 0.5 mmol), potassium *tert*-butoxide (168 mg, 1.5 mmol), benzophenone (182 mg, 1.0 mmol) and DMSO (60 mg) were mixed to get an homogeneous mass and heated in an oil bath at 200 °C for 2 min. The red-dark mass was hydrolysed with HCl (30 mL, 5%) and the mixture extracted with diethyl ether (3×20 mL). The yellow-orange organic phase was extracted with NaOH (10%, 20 mL) and the aqueous phase discarded. 20 mL of HCl (10%) were added and the mixture shaken vigorously. Finally the organic phase was separated, dried over anhydrous sodium sulphate and evaporated to give an yellow oil that was purified by column chromatography on SiO_2 (2–5% EtOAc/Petroleum ether) to afford dye **1a** as an yellow solid (16 mg, 10% yield). mp 117–119 °C. IR: 3157, 3064, 1674, 1614, 1580, 1458, 1300, 1184, 1048. For ^{1}H NMR and ^{13}C NMR data see Table 1. MS: *m*/*z* (%): 314 (M^+, 62), 313 (100), 237 (5), 165 (15). Exact mass for $C_{21}H_{14}O_3$: 314.0947; Found 314.0943.

3.2. *2-(9H-Fluoren-9-ylidene)-4-hydroxybenzofuran-3(2H)-one **1b***

Prepared from 9-fluorenone using the same procedure. The compound **1b** was isolated as a yellow solid (14 mg, 9% yield). mp 245-246. IR: 3337, 3106, 3050, 1680, 1636, 1610, 1585, 1467, 1448, 1347, 1318, 1140, 1045. For ^{1}H NMR and ^{13}C NMR data see Table 1. MS: *m*/*z* (%): 312 (M^+, 6.3), 311 (9), 256 (9), 213 (13), 98 (100). Exact mass for $C_{21}H_{12}O_3$: 312.0786; Found 312.0780.

3.3. *(E)-4-Hydroxy-2-(2-hydroxy-9H-fluoren-9-ylidene) benzofuran-3(2H)-one **1c***

Prepared from 2-hydroxyfluorenone using 2.5 mmol of potassium *tert*-butoxide (5 eq). The compound **1c** was isolated as an orange solid (15 mg, 8% yield). mp 220–222. IR: 3470, 3060, 1674, 1639, 1617, 1581, 1453, 1443, 1302, 1263, 1135, 1048. For ^{1}H NMR and ^{13}C NMR data see Table 1. MS: *m*/*z* (%): Exact mass for $C_{21}H_{12}O_4$: 328.0736; Found 328.0726.

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Appendix. Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.dyepig.2011.05.026.

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