Res Chem Intermed
DOI 10.1007/s11164-013-1031-5

Microwave-assisted, methanesulfonic acid-catalyzed synthesis of 3,3′-(arylmethylene)bis(4-hydroxy-2*H*-chromen-2-ones)

Xan Qi · Meng-Wei Xue · Xiao-Jun Sun · Yin Zhi · Jian-Feng Zhou

Received: 18 July 2012 / Accepted: 8 January 2013

Abstract Efficient synthesis of 3,3′-(arylmethylene)bis(4-hydroxy-2*H*-chromen-2-ones) has been achieved by methanesulfonic acid-catalyzed, microwave-assisted reaction of 4-hydroxycoumarin and aromatic aldehydes in ethanol. The procedure has the advantages of high yield, short reaction time, low energy consumption, and convenient work-up. Compound structures were confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and by elemental analysis.

Keywords 3,3′-(Arylmethylene)bis(4-hydroxy-2*H*-chromen-2-ones) · 4-Hydroxycoumarin · Methanesulfonic acid · Microwave irradiation

Introduction

Coumarin derivatives are widespread in nature and have a variety of biological activity, for example anticoagulant, insecticidal, antihelminthic, hypnotic, antifungal, phytoalexin, and HIV protease inhibition [1–3]. It has been found that the minimum active pharmacophore comprises a coumarin dimer containing an aryl substituent on the central linker methylene [3, 4]. Addition of 4 and 7-hydroxy substituents to the coumarin rings improves the potency of the compounds. Among the systems studied, 3,3′-(arylmethylene)bis(4-hydroxy-2*H*-chromen-2-ones) have been tested as a HIV integrase inhibitors, and have significant activity [3]. The compound is a 4-hydroxycoumarin (4-hc) dimer, consisting of two monomeric building blocks of 4-hc and a phenyl ring on the central methylene linker [5].

X. Qi · X.-J. Sun · Y. Zhi · J.-F. Zhou (✉)
Jiangsu Key Laboratory for Chemistry of Low-Dimensional Materials, School of Chemistry and Chemical Engineering, Huaiyin Normal University, Huaian 223300, China
e-mail: jfchow@sohu.com

M.-W. Xue
Department of Chemistry, Nanjing Xiaozhuang University, Nanjing 211171, China

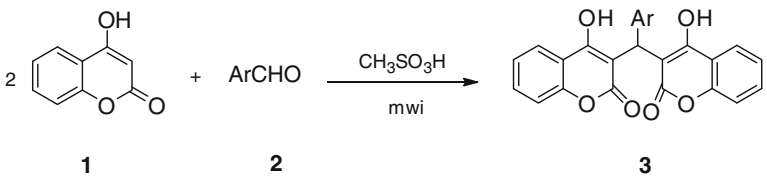
Published online: 29 January 2013

However, 3,3′-(arylmethylene)bis(4-hydroxy-2*H*-chromen-2-ones) are usually prepared by condensation of carbonyl compounds with 4-hydroxycoumarin in organic solvents [3, 6–9], which uses large amounts of hazardous and toxic solvents associated with such catalysts as piperidine [10], ethylene diammonium diacetate [11], glacial acetic acid, and acetic anhydride [6].

Recently, several methods using 4-hydroxycoumarin for preparation of 3,3′-(arylmethylene)bis(4-hydroxy-2*H*-chromen-2-ones) in aqueous media have been reported. Although these methods are effective and ecofriendly, usually they not only need TEBA [10] or I_2 [11] as catalyst, but also reaction time is long. Thus, the introduction of efficient new methods based on green methodology is still in great demand. Methanesulfonic acid (CH_3SO_3H) has been widely used for the catalysis of a variety of syntheses [12–16], because of the high purity of the product, rapid reaction, no byproducts, and low molecular weight, and, therefore, low cost per acid functionality. However, use of CH_3SO_3H as a catalyst in the synthesis of 3,3′-(arylmethylene)bis(4-hydroxy-2*H*-chromen-2-ones) has not yet been reported. As part of our group's continuing interest in microwave-assisted synthesis of organic compounds [17–22], in this paper, we report a general and practical method for microwave-assisted synthesis of 3,3′-(arylmethylene)bis(4-hydroxy-2*H*-chromen-2-ones), **3**, from 4-hydroxycoumarin, **1**, and aromatic aldehydes, **2**, with CH_3SO_3H as catalyst, in ethanol (Scheme 1). The reactions were completed in short reaction times of 6–9 min with high yields of 80–90 %, low energy consumption, and convenient work-up.

Experimental

Melting points were determined with a WRS-1B digital melting-point apparatus and are uncorrected. IR spectra were recorded on a Nicolet Avatar 360 FT-IR instrument. ^{1}H NMR spectra were measured on a Bruker 400-MHz spectrometer, in $CDCl_3$ or DMSO-d_6 as solvent, with TMS as internal standard. Elemental analysis was performed with a Perkin–Elmer 240 C elemental analyzer. Microwave-assisted reactions were performed in a CEM Discover monomode microwave reactor. All the reagents are commercially available.



Ar: a: C_6H_5 b: 4-$CH_3C_6H_4$ c: 4-ClC_6H_4 d: 4-$O_2NC_6H_5$ e: 4-$CH_3OC_6H_4$ f: 3,4-$(CH_3O)_2C_6H_3$ g: 4-$(CH_3)_2NC_6H_4$ h: 3,4-$OCH_2OC_6H_3$

Scheme 1 Synthesis of 3,3′-(arylmethylene)bis(4-hydroxy-2*H*-chromen-2-ones)

General procedure for preparation of 3,3′-(arylmethylene)bis(4-hydroxy-2*H*-chromen-2-ones) (**3a**–**h**)

4-Hydroxycoumarin, **1**, (2 mmol) and aromatic aldehyde, **2**, (1 mmol) were mixed with 3 mL ethanol. Methanesulfonic acid (0.05 g) was added and the reaction vial was sealed with a cap containing a septum. The loaded vial was then placed in the cavity of the microwave reactor and heated at 120 W and 120 °C for 6–9 min. After completion of the reaction (as indicated by thin-layer chromatography, TLC), the reaction mixture was left to cool to room temperature, resulting in precipitation of the solid product. The product was isolated by filtration, then washed with water and ethanol. The products were dried and recrystallized from a mixture of $CHCl_3$ and EtOH to afford the pure products **3a–h.**

3,3′-(Phenylmethylene)bis(4-hydroxy-2*H*-chromen-2-one) (**3a**)

^{1}H NMR ($CDCl_3$) δ: 6.12 (s, 1H, CH), 7.24–8.10 (m, 13H, 13 × CH), 11.33 (s, 1H, OH), 11.56 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 36.21,105.68, 116.64, 124.41, 124.87, 126.49, 126.88, 128.64, 132.84, 135.22, 152.54; IR (KBr) *v*: 3427, 3035, 1675, 1611, 1562, 1493, 1445, 1349, 759 cm^{-1}. Anal. calcd. for $C_{25}H_{16}O_6$: C 72.81, H 3.91; found C 72.61, H 3.79 %.

3,3′-((4-Chlorophenyl)methylene)bis(4-hydroxy-2*H*-chromen-2-one) (**3b**)

^{1}H NMR ($CDCl_3$) δ: 2.36 (s, 3H, CH_3), 6.09 (s, 1H, CH), 7.11–8.08 (m, 12H, 12 × CH), 11.32 (s, 1H, OH), 11.55 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 20.96, 35.90, 104.15, 116.62, 124.39, 124.83, 126.38, 129.34, 132.77, 136.42, 152.31; IR (KBr) *v*: 3450, 3075, 1670, 1614, 1563, 1510, 1413, 1350, 1308, 764 cm^{-1}. Anal. calcd. for $C_{26}H_{18}O_6$: C 73.23, H 4.25; found C 73.15, H 4.43 %.

3,3′-((4-Nitrophenyl)methylene)bis(4-hydroxy-2*H*-chromen-2-one) (**3c**)

^{1}H NMR ($CDCl_3$) δ: 6.14 (s, 1H, CH), 7.28–8.22 (m, 12H, 12 × CH), 11.40 (s, 1H, OH), 11.59 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 36.55, 103.30, 104.80, 116.26, 123.87, 124.52, 125.15, 127.58, 133.35, 143.36, 146.93, 152.40, 164.84, 166.42, 169.10; IR (KBr) *v*: 3450, 3078, 1657, 1611, 1560, 14517, 1465, 1345, 761 cm^{-1}. Anal. calcd. for $C_{25}H_{15}NO_8$: C 65.65, H 3.31, N 3.06; found C 65.73, H 3.24, N 2.89 %.

3,3′-(*p*-Tolylmethylene)bis(4-hydroxy-2*H*-chromen-2-one) (**3d**)

^{1}H NMR ($CDCl_3$) δ: 6.06 (s, 1H, CH), 7.17–8.10 (m, 12H, 12 × CH), 11.34 (s, 1H, OH), 11.56 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 35.85, 103.74, 105.30, 116.64, 124.42, 124.97, 127.98, 128.77, 132.75, 133.90, 152.57, 164.62, 166.84, 169.19; IR (KBr) *v*: 3427, 3075, 1675, 1615, 1561, 1492, 1444, 1349, 1270, 1212 cm^{-1}. Anal. calcd. for $C_{25}H_{15}ClO_6$: C 67.20, H 3.38; found C 66.98, H 3.27 %.

3,3′-((4-Methoxyphenyl)methylene)bis(4-hydroxy-2*H*-chromen-2-one) (**3e**)

^{1}H NMR ($CDCl_3$) δ: 3.82 (s, 3H, CH_3O), 6.07(s, 1H, CH), 6.87–8.08 (m, 12H, 12 × CH), 11.32(s, 1H, OH), 11.54 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 35.54, 55.27, 114.05, 116.62, 124.38, 124.84, 126.96, 127.63, 132.79, 158.46. IR (KBr) *v*: 3452, 3073, 1671, 1611, 1562, 1507, 1452, 1351, 1306, 1257, 768 cm^{-1}. Anal. calcd. for $C_{26}H_{18}O_7$: C 70.58, H 4.10; found C 70.82, H 3.94 %.

3,3′-((3,4-Dimethoxyphenyl)methylene)bis(4-hydroxy-2*H*-chromen-2-one) (**3f**)

^{1}H NMR ($CDCl_3$) δ: 3.76 (s, 3H, CH_3O), 3.89 (s, 3H, CH_3O), 6.10 (s, 1H, CH), 6.73–8.09 (m, 11H, 11 × CH), 11.32 (s, 1H, OH), 11.55(s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 35.78, 55.90, 56.13, 110.48, 111.32, 116.64, 118.95, 124.36, 124.89, 127.57, 132.83, 148.10, 149.17, 152.41; IR (KBr) *v*: 3435, 3073, 1670, 1614, 1562, 1512, 1451, 1351, 1308, 1259, 765 cm^{-1}. Anal. calcd. for $C_{27}H_{20}O_8$: C 68.43, H 4.25; found C 68.21, H 4.12 %.

3,3′-(Benzo[*d*][1, 3]dioxol-5-ylmethylene)bis(4-hydroxy-2*H*-chromen-2-one) (**3g**)

^{1}H NMR (DMSO-d_6) δ: 3.2 (s, 6H, $2CH_3$), 6.31 (s, 1H, CH),7.23–7.84 (m, 12H, 12 × CH); ^{13}C NMR (DMSO-d_6) δ: 36.45, 103.56, 116.05, 120.10, 123.49, 124.58, 128.68, 131.62, 141.21, 153.00, 164.94, 168.00; IR (KBr) *v*: 3428, 3083, 1662, 1610, 1563, 1523, 1448, 1349, 1309, 765 cm^{-1}. Anal. calcd. for $C_{27}H_{21}NO_8$: C 66.53, H 4.34, N 2.87; found C 65.29, H 3.24, N 2.98 %.

3,3′-((4-(Dimethylamino)phenyl)methylene)bis(4-hydroxy-2*H*-chromen-2-one) (**3h**)

^{1}H NMR ($CDCl_3$) δ: 5.97 (s, 2H, OCH_2O), 6.04 (s, 1H, CH), 6.69–8.07(m, 11H, 11 × CH), 11.29(s, 1H, OH), 11.62 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 35.93, 101.18, 107.22, 108.23, 116.62, 119.61, 124.40, 124.87, 128.97, 132.86, 146.86, 148.09; IR (KBr) *v*: 3425, 3078, 1670, 1563, 1494, 1440, 1343, 1308, 1234, 763 cm^{-1}. Anal. calcd. for $C_{26}H_{16}O_8$: C 68.25, H 3.77; found C 68.48, H 3.68 %.

Results and discussion

To determine the optimum reaction conditions, 4-chlorobenzaldehyde and 4-hydroxycoumarin were chosen as starting substrates. We investigated the effect of different microwave power and reaction temperature on the yield of product **3c** when reaction time was fixed. It was observed that irradiation at 120 W and reaction at 120 °C gave the best result (Table 1, entry 3).

Under these optimized reaction conditions, a series of 3,3′-(arylmethylene)bis (4-hydroxy-2*H*-chromen-2-ones) **3a–h** were synthesized; the results are summarized in Table 2. As shown in Table 2, when mixtures of 4-hydroxycoumarin and an

Table 1 Effect of microwave power and reaction temperature on the yield of product **3c**

Entry	Microwave power (W)	Reaction temperature (°C)	Reaction time (min)	Yield (%)[a]
1	100	100	8	65
2	100	120	8	78
3	120	120	8	89
4	120	150	8	85
5	150	120	8	80
6	150	150	8	62

[a] Yields of the isolated products

Table 2 Microwave-assisted synthesis of 3,3′-(arylmethylene)bis(4-hydroxy-2*H*-chromen-2-ones) **3a–h** catalyzed by methanesulfonic acid

Product	Ar	Time (min)[a]	Yield (%)[b]	Mp (°C) (lit. mp)
3a	C_6H_5	8	86	232–233 (228–230) [23]
3b	4-$CH_3C_6H_4$	8	90	270–271 (271–272) [24]
3c	4-$NO_2C_6H_4$	6	85	236–237 (232–234) [23]
3d	4-ClC_6H_4	8	89	259–260 (259–261) [24]
3e	4-$CH_3OC_6H_4$	8	88	248–249 (245–247) [24]
3f	3,4-$(CH_3O)_2C_6H_3$	8	87	267–268 (265–267) [24]
3g	4-$(CH_3)_2NC_6H_4$	9	89	217–218 (216–217) [21]
3h	3,4-$(OCH_2O)C_6H_3$	9	80	254–255 (255–257) [24]

[a] Microwave power, 120 W; reaction temperature, 120 °C

[b] Yields of the isolated products

aromatic aldehyde in ethanol, with methanesulfonic acid as catalyst, were irradiated at 120 W and 120 °C, the reactions were almost complete in 6–9 min. After completion of the reaction, the reaction mixture was left to cool to room temperature, resulting in precipitation of the solid product. The crude solids were purified by recrystallization from $CHCl_3$–ethanol to afford the products in 80–90 % yield. The structures of all the synthesized compounds were established on the basis of their spectroscopic data and elemental analysis.

Conclusions

We have developed a novel, efficient method for microwave-assisted synthesis of 3,3′-arylmethylene-)bis(4-hydroxy-2*H*-chromen-2-ones), using CH_3SO_3H as catalyst, in ethanol. Short reaction times, good yields, low energy consumption, and convenient work-up are advantages of this method.

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