Synthesis of functionalized furo[3,2-c]coumarins via a one-pot oxidative pseudo three-component reaction in poly(ethylene glycol)


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ABSTRACT

An efficient and straightforward synthesis of functionalized furo[3,2-c]coumarins via a one-pot oxidative pseudo three-component condensation of aldehydes and 4-hydroxycoumarin (2 equiv) in poly(ethylene glycol) (PEG) as solvent is described. A mixture of I2 and K2S2O8 in the presence of Na2CO3 was used as an oxidative reagent. The structure of the furo[3,2-c]coumarins was established by X-ray single crystal structure analysis.

1. Introduction

Multicomponent reactions (MCRs) have emerged as a highly efficient tool in modern synthetic organic chemistry due to features such as atom economy, straightforward reaction design, and the opportunity to construct target organic molecules by the introduction of several diverse elements. Typically, purification of products resulting from MCRs is also fairly simple since all the reactants employed are consumed and are incorporated into the target compound.1 MCRs leading to interesting heterocyclic compounds are particularly important for the preparation of diverse chemical libraries of 'drug-like' molecules.1

The use of an obviously benign and inexpensive solvent like water and poly(ethylene glycol) (PEG) could yield significant 'green chemistry' benefits. Ionic liquid solvents are also the most popular solvents but they are very expensive, and their toxicity and environmental effect are for the most part unknown.2 PEG is a thermally stable, inexpensive, recoverable, and non-toxic hydrophilic polymer, which can replace with volatile and hazardous organic solvents and complete toxicity profiles are available for a range of PEG molecular weights; some of them are already approved for internal consumption by the US FDA. The high solubility of PEGs in water and several organic solvents including alcohol, acetone, dichloromethane, and toluene instead of insolubility of them in less polar solvents such as hexane, cyclohexane, or diethyl ether cause to easy recovery and high performance of them in organic reactions.2,3

Furocoumarins are found in many natural products and exhibit potent biological activity. They are inherently photosensitive and found to have therapeutic applications.4 The photo chemotherapeutic effects rely on their ability to intercalate with the pyrimidine bases of microorganism DNA.5 Neo-tanshinlactone is known as a furo[3,2-c]coumarin that isolated from the rhizome of Salvia miltiorrhiza Bunge, which is an anti-breast cancer agent.6 The range of biological activities of furocoumarins such as insecticidal, antitumor, antioxidant, anticoagulant, antimicrobial, and antifungal has stimulated interest in the synthetic methods for the construction of them.4,6 There are several methods for the preparation of furocoumarins with most involving a Claisen rearrangement and a tandem alkylation/intramolecular aldolization reaction.7 Nair and co-worker reported preparation of furan annulated coumarin involving a [4+1] cycloaddition with various in situ generated...
heterocyclic coumarin methides and isocyanides. Also, Pd-catalyzed heteroannulation of 3-alkynyl-4-methoxycoumarins with aryl halides resulted in the formation of 3-aryl[furo[3,2-c]coumarins. Most synthetic routes have focused on coumestrol, which is the combination of the benzofuran and coumarin skeletons. Only a few reports have been described for the synthesis of substituted furo[3,2-c]coumarins. As our continuous endeavor dealing with the design and preparation of interesting organic structures, especially coumarin derivatives, we wish to describe herein a simple, inexpensive, and fairly efficient synthesis of functionalized furo[3,2-c]coumarins via the one-pot oxidative pseudo three-component condensation of aldehydes and 4-hydroxycoumarin (2 equiv) in PEG.

2. Results and discussion

Our research originated from an unexpected observation made during simple preparation of biscoumarins 3 according to a previously reported procedure. In refluxing water, the addition of 4-hydroxycoumarin 1 to formaldehyde 2a in the presence of iodine yield the expected biscoumarins 3a, in addition to small amount of unknown side product 4a (5%) (Scheme 1).

Compound 4a was separated and fully characterized by IR, 1H and 13C NMR spectra, and MS. The mass spectrum of 4a displayed a molecular ion signal at m/z 306 and an ion signal at m/z 186 indicating the loss of the 2-hydroxybenzoyl group. In the 1H NMR spectrum of compound 4a, in addition to the aromatic protons of coumarin ring and those assigned to the benzoyl ring (δ=7.0–8.1 ppm), a sharp singlet due to hydrogen in the furan ring, which fused to coumarin moiety (7.82 ppm) was observed. Also a broad singlet at 11.6 ppm due to exchangeable proton of hydroxyl group was assigned. The most important absorption band of the IR spectrum is detected at 1763 and 1630 cm⁻¹ distributed to the two carbonyl stretching frequency. Absorption bands at 3367 cm⁻¹ are associated with the hydroxyl group. The decoupled 13C NMR spectrum of 4a showed 18 distinct signals. In this spectrum, the methine of the furan moiety resonated at δ=111.6 ppm and the signal for the two carbonyls was observed at δ=163.3 and 184.5 ppm. In addition, eight methines and seven quaternary carbons, all in the aromatic region were in agreement with the proposed structure. Finally, the structure of compound 4a was confirmed by single crystal X-ray diffraction (Fig. 1).

The exclusive formation of the unexpected derivatives 4 prompted our interest in developing a general route to access this valuable class of compounds. It was noted that a ring opening and dehydrogenation process were performed under the reaction. Therefore, our attention turned toward several catalysts and dehydrogenative reagents to allow for a more efficient and selective formation of furoucoumarin from their corresponding biscoumarin. We therefore began our work by preparing the requisite catalytic amounts of iodine and sodium carbonate (entry 11, Table 1). The yields of the reaction under other conditions, such as different oxidants (entries 1–8 and 16–18, Table 1) as well as other solvents (entries 13–15, Table 1) were all inferior. The presence of iodine was the pivotal factor for the reaction to proceed and no reaction occurred without iodine (entries 16–18 in comparison with entries 5–7, Table 1). In addition, sodium carbonate (Na2CO3) as a base, gave optimum yield and it was much more efficient than 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (entry 11 in comparison to entries 9 and 10, Table 1).

The best result was obtained with 2 equiv of potassium persulfate, 10 mol % of iodine and 50 mol % of sodium carbonate with respect to the biscoumarin, in PEG300 at 120 °C in 10 h (entry 11, Table 1, yield 75%). No improvements were observed upon changing the reaction time or temperature. When the reaction was performed in the presence of ethanol or water as solvent, yields were 56% and 62%, respectively (entries 13 and 14, Table 1). The yields were not improved by extending reaction times and formation of unidentified side products was observed.

To examine the efficiency of this reaction, a series of biscoumarins (3a–j) derived from various aldehydes were employed. As summarized in Table 2, aldehydes with electron-donating substituents (entries 5 and 7, Table 2) and electron-withdrawing substituents (entry 4, Table 2) were well tolerated in the reaction. Also, this protocol can be applied not only to aliphatic and aromatic aldehydes with different substitution, but also to heterocyclic aldehydes (entries 7–9, Table 2).
In the next step, we looked into the possibility of condensation of 2 equiv of 4-hydroxycoumarin and aldehydes followed by furocoumarin ring formation, under the one-pot oxidative pseudo three-component condensation. Therefore, 4-hydroxycoumarin 1 was first treated with benzaldehydes 2 in the presence of iodine (25 mol%) in PEG300 at 80 °C for 0.5–5 h, to generate the corresponding biscoumarins 3, which was then allowed to react with potassium persulfate and sodium carbonate under optimum conditions. Under this condition, we obtained the corresponding furocoumarins without significant loss of yield in comparison with previous method (Scheme 2).

A plausible mechanism for this reaction is summarized in Scheme 3. Compounds 4 could be synthesized via sequential condensation, addition, cyclization, and oxidation. It is conceivable that initially the condensations between 2 equiv of 4-hydroxycoumarin 1 with aldehydes 2 could give intermediate 3. This generated biscoumarin could provide compound 5 via lactone ring opening by nucleophilic attack of water, which then undergoes a decarboxylation. Similar lactone ring opening and decarboxylation were previously reported. In the next step, the addition of enolate anion 6 to iodine yields compound 7. In this reaction potassium persulfate can oxidize iodide ion to iodine and recycle it in the process. Finally, intramolecular nucleophilic substitution of hydroxyl group to C–I bond in compound 7 gives compound 8, which was oxidized to afford the fully aromatized product 4. This type of dehydrogenation is well preceded.

### 3. Conclusions

In this work we have reported a facile one-pot synthesis of furan annulated coumarins via in situ generated biscoumarins, which offer a convenient and straightforward route to the synthesis of multisubstituted furocoumarin using PEG as a recyclable solvent. The notable features of this procedure are the application of an environmentally benign solvent, the cheap oxidant, its simplicity, and good yields. Also, we have studied the reusability of the oxidant as well as the solvent, which showed reusability for a number of cycles (three times) without significant loss of activity.

### 4. Experimental section

#### 4.1. General method

All commercially available reagents were used without further purification. Column chromatography was carried out on silica gel (70–230 mesh). TLC was conducted on silica gel 250 μm, F254 plates. Melting points were measured on a Kofler hot stage apparatus and are uncorrected. The IR spectra were taken using Nicolet FT-IR Magna 550 spectrographs (KBr disks). The mass spectra were run on a Finnigan Mat TSQ-70 spectrometer at 70 eV. 1H NMR spectra were recorded on a Bruker 400 or 500 MHz NMR instruments. The numbers of the target compounds used for 1H NMR data are depicted in Scheme 2. The chemical shifts (δ) and coupling constants (J) are expressed in parts per million and hertz, respectively. Elemental analyses were carried out with a Perkin–Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4% of the calculated values.

#### 4.2. General procedure for the synthesis of compound 4

To a mixture of 4-hydroxycoumarin (2 mmol) and aldehyde (1 mmol) in PEG (3 mL), catalytic amount of iodine (25 mol%) was added in ambient temperature. Reaction mixture was heated to 80 °C for several hours (0.5–5 h), after completion of the reaction (monitored by TLC) and formation of corresponding biscoumarin, the mixture was cooled and then potassium persulfate (2 equiv) and sodium carbonate (50 mol%) were added to the reaction mixture. The mixture was heated to 120 °C until the biscoumarin disappeared. After completion of the reaction, the mixture was cooled to room temperature, diluted with ethyl acetate (5 mL),...
and stirred for 20 min. This process was repeated twice. The combined ethyl acetate phase was removed under reduced pressure and the resulting crude product was purified by flash chromatography (20% ethyl acetate/petroleum ether) to give corresponding furocoumarins (4a–4j). The mother liquor (PEG/oxidants/base) was kept aside for further runs and was reused for a number of cycles (three times) without significant loss of its activity.

4.2.1. 2-(2-Hydroxybenzoyl)-4H-furo[3,2-c]chromen-4-one (4a). Yield (0.23 g, 75%) as yellow solid, mp 154–156°C; [Found: C, 70.23; H, 3.44. C18H10O5 requires C, 70.59; H, 3.29%]; νmax (KBr) 3367 (OH), 1763 (C=O), 1629 (C=O) cm⁻¹; δH (400 MHz, CDCl3) 7.00 (1H, td, J=8.4, 1.2 Hz, H5), 7.10 (1H, dd, J=8.4, 1.2 Hz, H3), 7.50 (1H, t, J=8.0 Hz, H8), 7.52 (1H, d, J=8.0 Hz, H6), 7.57 (1H, t, J=8.4 Hz, H4), 7.65 (1H, t, J=8.0 Hz, H2), 7.82 (1H, s, H7), 8.07 (1H, dd, J=8.4, 1.2 Hz, H6), 8.14 (1H, d, J=8.0 Hz, H9), 11.6 (1H, s, OH); δC (100.6 MHz, CDCl3) 111.6 (C10), 111.8 (C10), 117.7 (C3), 118.2 (C3'), 118.4 (C13), 118.9 (C6), 119.5 (C5'), 122.1 (C9), 125.1 (C8), 130.8 (C6'), 132.8 (C7), 137.1 (C4'), 151.9 (C4), 153.8 (C11), 157.2 (C2), 159.8 (C2'), 163.3 (C12), 184.5 (C=O benzoyl); m/z (EI) 306 [M⁺, 36], 246 (12), 186 (92), 121 (100), 101 (40), 92 (57), 75 (44), 65 (56%).

4.3. Crystal data and structure refinement details of compound 4a

Single crystals of 4a were prepared by using the branch tube method in n-hexane/ethyl acetate (10:1) at 45°C during one week. The yellow crystals were filtered off, washed with cold n-hexane, and dried at rt. C18H10O5, M=306.26, yellowish platelike block, crystal dimensions: 0.34 × 0.30 × 0.06 mm³; orthorhombic, space group Pbca; a=7.876(2), b=14.414(3), c=23.428(5) Å; V=2659.7(10) Å³; T=100(2) K; Z=8; ρcalcd=1.530 g cm⁻³; μ=0.11 mm⁻¹ (for Mo Kα, λ=0.71073 Å); R(000)=1264; reflections collected=33,860; reflections independent=5769 [Rint=0.034]; reflections observed=4066 [l>2σ(I)]; θ range 2.83–35.09°; h, k, l range: −12≤h≤11, −20≤k≤20, −32≤l≤32.
4.3.1. 2-(2-Hydroxybenzoyl)-3-methyl-4H-furo[3,2-c]chromen-4-one (4b). Yield (0.16 g, 56%) as yellow solid, mp 216–218 °C; [Found: C, 71.52; H, 3.97. C12H10O5 requires C, 71.25; H, 3.78%]; δmax (KBr) 3431 (OH), 1744 (C=O benzoyl).

4.3.2. 2-(2-Hydroxybenzoyl)-2-(2-hydroxybenzoyl)-3-(phenyl)-4H-furo[3,2-c]chromen-4-one (4c). Yield (0.19 g, 50%) as yellow solid, mp 203–205 °C; [Found: C, 75.12; H, 3.41. C12H10O5 requires C, 75.39; H, 3.69%]; δmax (KBr) 2922 (OH), 1742 (C=O benzoyl).

4.3.3. 2-(2-Hydroxybenzoyl)-3-(2,5-dihydroxyphenyl)-4H-furo[3,2-c]chromen-4-one (4d). Yield (0.22 g, 51%) as yellow solid, mp 80–82 °C; [Found: C, 76.12; H, 3.32; N, 3.51. C22H16O11 requires C, 76.45; H, 3.07; N, 3.28%]; δmax (KBr) 3557 (OH), 1764 (C=O benzoyl).

4.3.4. 2-(2-Hydroxybenzoyl)-3-(5-chlorofuran-2-yl)-4H-furo[3,2-c]chromen-4-one (4e). Yield (0.21 g, 47%) as yellow solid, mp 181 °C; [Found: C, 64.96; H, 2.55. C22H15ClO4 requires C, 64.69; H, 2.73%]; δmax (KBr) 3438 (OH), 1737 (C=O benzoyl).

4.3.5. 2-(2-Hydroxybenzoyl)-3-(3-nitro-2-methoxyphenyl)-4H-furo[3,2-c]chromen-4-one (4f). Yield (0.28 g, 62%) as yellow solid, mp 180–180 °C; [Found: C, 65.31; H, 3.12; N, 3.32. C22H14ClO5 requires C, 65.65; H, 3.31; N, 3.06%]; δmax (KBr) 3417 (OH), 1744 (C=O benzoyl).

4.3.6. 2-(2-Hydroxybenzoyl)-3-(3-bromo-4,5-dimethoxyphenyl)-4H-furo[3,2-c]chromen-4-one (4g). Yield (0.22 g, 42%) as yellow solid, mp 181–183 °C; [Found: C, 59.72; H, 3.53. C22H15BrO5 requires C, 59.50; H, 3.29%]; δmax (KBr) 3883 (OH), 1760 (C=O benzoyl).

4.3.7. 2-(2-Hydroxybenzoyl)-3-(thiophen-2-yl)-4H-furo[3,2-c]chromen-4-one (4h). Yield (0.22 g, 49%) as yellow solid, mp 154–156 °C; [Found: C, 68.36; H, 3.47. C22H14O2S requires C, 68.03; H, 3.11%]; δmax (KBr) 3414 (OH), 1739 (C=O benzoyl).

4.3.8. 2-(2-Hydroxybenzoyl)-3-(5-chlorofuran-2-yl)-4H-furo[3,2-c]chromen-4-one (4i). Yield (0.20 g, 49%) as yellow solid, mp 184–186 °C; [Found: C, 64.69; H, 2.55. C22H15ClO4 requires C, 64.96; H, 2.73%]; δmax (KBr) 3438 (OH), 1737 (C=O benzoyl).

4.3.9. 2-(2-Hydroxybenzoyl)-3-(3-nitro-2-methoxyphenyl)-4H-furo[3,2-c]chromen-4-one (4j). Yield (0.24 g, 58%) as yellow solid, mp 221–223 °C;
Corrections were applied to the data with the use of CRYSALIS RED. The crystallographic measurement was performed on a four-circle diffractometer with graphite-monochromatized Mo Kα radiation (ω and φ scans). Data were corrected for Lorentz and polarization effects. Data collection, cell refinement, and data reduction and analysis were carried out with the XcALIBUR PX software, CRYSTALS CCD and CRYSTALS RED, resp. (Oxford Diffraction Ltd., Abingdon, England, 2009). Empirical absorption correction was applied to the data with the use of CRYSTALS RED. The structure was solved by direct methods with the SHELX-97 program, and refined using SHELXL-97 with anisotropic thermal parameters for non-H atoms. All H atoms were found in difference Fourier maps. In the final refinement cycles, all C-bonded H atoms were treated as riding atoms in geometrically optimized positions, with C–H = 0.95 Å, and with Uiso(H) = 1.2 Ueq(C). O-bonded H atom was refined isotropically. The figure was made using DIAMOND program [ver. 3.0d. K. Brandenburg, Crystal Impact GbR, Bonn, Germany, 2005].

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4.4. X-ray—experimental details

The crystallographic measurement was performed on a κ-geometry XcALIBUR PX four-circle diffractometer with graphite-monochromatized Mo Kα radiation (ω and φ scans). Data were corrected for Lorentz and polarization effects. Data collection, cell refinement, and data reduction and analysis were carried out with the XcALIBUR PX software, CRYSTALS CCD and CRYSTALS RED, resp. (Oxford Diffraction Ltd., Abingdon, England, 2009). Empirical absorption correction was applied to the data with the use of CRYSTALS RED. The structure was solved by direct methods with the SHELX-97 program, and refined using SHELXL-97 with anisotropic thermal parameters for non-H atoms. All H atoms were found in difference Fourier maps. In the final refinement cycles, all C-bonded H atoms were treated as riding atoms in geometrically optimized positions, with C–H = 0.95 Å, and with Uiso(H) = 1.2 Ueq(C). O-bonded H atom was refined isotropically. The figure was made using DIAMOND program [ver. 3.0d. K. Brandenburg, Crystal Impact GbR, Bonn, Germany, 2005].

Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.05.112.

References and notes


