Hydroxylated Polyfunctionalized Benzo[*c*]coumarins by an Organocatalyzed Tandem 1,4-Conjugate Addition, Decarboxylation and Aromatization Reaction

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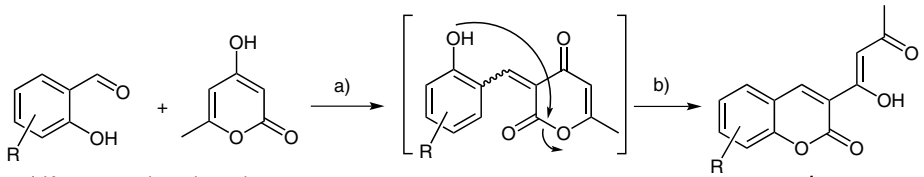
Abstract: Novel hydroxylated polyfunctionalized benzo[*c*]coumarins were synthesized by a new one-pot reaction of an unprotected monohydroxy-3-(acetoacetyl)coumarin as an active methylene Michael donor with 4-oxo-4*H*-chromene-3-carboxylic acid as a Michael acceptor in the presence of a catalytic amount of 4-pyrrolidin-1-ylpyridine. An organobase-catalyzed tandem 1,4-conjugate addition, decarboxylation and aromatization reaction mechanism is proposed.

Key words: heterocycles, polycycles, ketones, tandem reactions, addition reactions, catalysis

Coumarins (2*H*-benzopyran-2-ones) are an interesting class of oxygen-containing heterocycles and they are recognized as an outstanding category of polyphenolic compounds with valuable biological activities. They are a common and important family of natural products and, to date, more than one thousand coumarin derivatives have been described, most of which were isolated from over 800 plant species.[1] Coumarin derivatives exhibit useful pharmaceutical properties,[2] including antioxidant,[3] antiinflammatory,[4] anticancer,[5] and molluscicidal activities.[6] There is particular interest in the benzo[*c*]coumarin scaffold, because several of its hydroxylated derivatives and analogues have shown considerable medicinal benefits, the most interesting of which are a significant lipid-lowering potential and antioxidant activities.[7a] Other benzo[*c*]coumarin structures have been described as potent and selective antagonists of estrogen receptor subtype β.[7b]

Because of the natural occurrence and range of biological activities associated with coumarin scaffolds, various methods have been developed for their synthesis, of which the Pechmann reaction is among the most widely used.[8] Benzo[*c*]coumarins, however, constitute a subclass that have received less attention as synthetic targets. Several challenges remain in synthesizing these compounds in optimal yields and by short reactions sequences, particularly those derivatives bearing free hydroxy and other functional groups that are most likely to have biological effects.[7b–d] A good example of such a synthesis is the total synthesis of the fungal product graphislactone G (a natural benzo[*c*]coumarin) in a global yield of 22% from 5-methylbenzene-1,3-diol (orcinol) and 2,4,6-trihydroxybenzoic acid (phloroglucinic acid) in 13 steps, most of which involve protection–deprotection procedures.[7c] Lubbe and co-workers[7d] synthesized 7-hydroxy-2-(2-hydroxybenzoyl)-6*H*-benzo[*c*]chromen-6-ones by sequential domino reactions of 1,3-bis(silylenol) ethers with benzopyrylium triflates. Recently, a conjugate addition approach with electron-deficient C-2 chromones has been applied in the preparation of a wide range of oxygen-containing heterocyclic systems, such as functionalized 2-hydroxybenzophenones, 6*H*-benzo[*c*]chromenes, and benzo[*c*]coumarins. Despite its reliability, this method is strongly dependent on the nature of the substituents at the 3-position of the chromone starting material (the Michael acceptor), and is not free from the need for additional protecting steps.[8b]

Our group has long been involved in studying the synthesis of coumarins as well as their reactivities and related photophysical properties.[9] A particular focus has been on the synthesis of 3-(acetoacetyl)coumarins, which are ob-



Scheme 1 Synthesis of 3-(acetoacetyl)coumarins **1**

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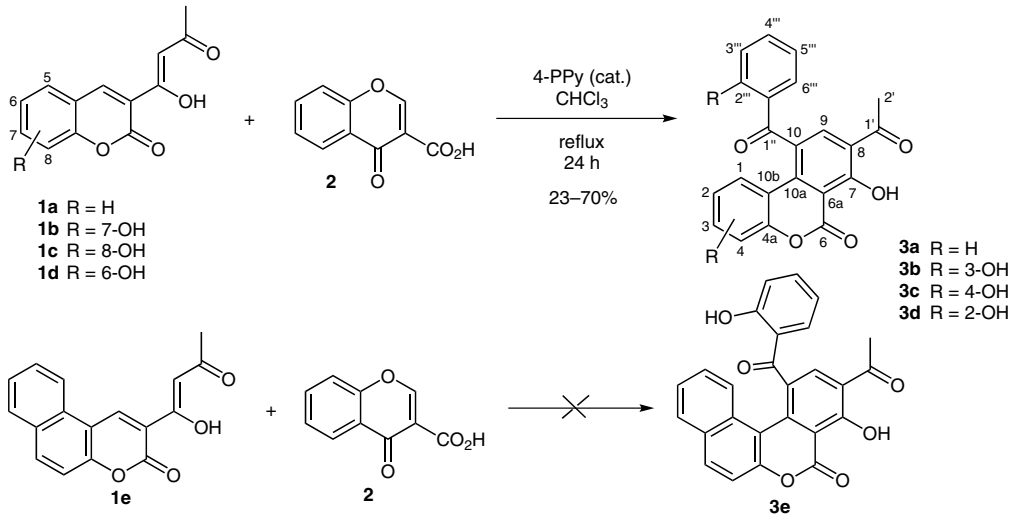
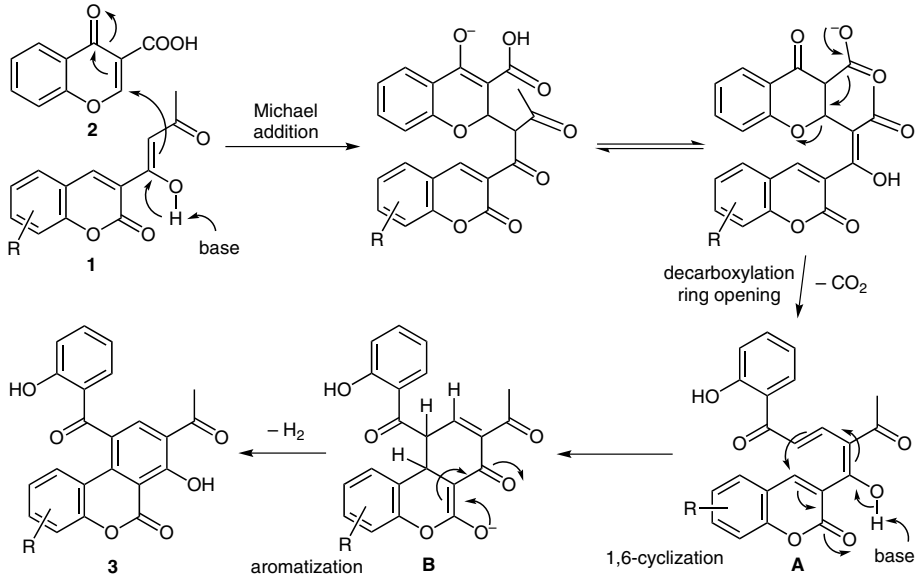


Scheme 2 Synthesis of benzo[*c*]coumarins **3a**–**d**

tained from substituted salicylaldehydes and 4-hydroxy-6-methyl-2*H*-pyran-2-one (triacetic acid lactone) through a tandem microwave-assisted Knoevenagel condensation and intramolecular translactonization process in an organobasic medium (Scheme 1).[10]

The resulting 3-acetoacetylcoumarins **1a**–**e** are strategic starting materials, as they contain a coumarin nucleus as well as the active methylene group of the acetoacetyl moiety, which is poised to undergo further useful chemical transformations. In a continuation of our studies on the establishment of new synthetic routes to biologically active coumarins, we developed an efficient one-pot synthesis of hydroxylated polyfunctionalized benzo[*c*]coumarins **3a**–**d**.

The first part of our synthetic strategy involved covalently connecting a chromone (benzopyran-4-one) ring with a coumarin (benzopyran-2-one) to form a bridged dyad. For this purpose, we selected electron-deficient 4-oxo-4*H*-chromene-3-carboxylic acid (**2**) because of its strong Michael-acceptor character, and we examined its reaction with the 1,3-dicarbonyl branch of 3-acetoacetylcoumarins **1a**–**e** in refluxing chloroform containing a catalytic amount of 4-pyrrolidin-1-ylpyridine (4-PPy); the reaction was performed without protecting the free hydroxy groups of coumarins **1b**–**d**. Monitoring by thin-layer chromatography indicated incomplete consumption of the starting reagents (**1a**–**e** and **2**) after 24 hours of reaction. The reactions were therefore worked up after the formation of substantial amounts of product had been observed in all cases except that of derivative **1e**, which contains a 5,6-benzo[*f*] group. The products were isolated by column chromatography. We expected the reaction to give the corresponding Michael adducts, but ^{1}H NMR spectroscopic analysis of the products indicated that, instead, the hydroxylated polyfunctionalized benzo[*c*]coumarins **3a**–



Scheme 3 Proposed mechanism for the formation of benzo[*c*]coumarins **3a**–**d**

d had been formed in moderate to good yields (23–70%) by a tandem pathway involving 1,4-conjugate addition, decarboxylation and aromatization (Scheme 2).[11–15]

This unexpected tandem pathway presumably involves an initial organobase-catalyzed 1,4-conjugate addition of the nucleophilic 1,3-dicarbonyl reagent **1** to the electron-deficient carboxylic acid **2** to give the intermediate **A** after cleavage of the chromone ring and decarboxylation. Intermediate **A** then undergoes a base-promoted intramolecular 1,6-cyclization to give intermediate **B**. The final step of the tandem process is oxidative aromatization of **B** to give the corresponding benzo[*c*]coumarin **3**, functionalized with both acetyl and 2-hydroxybenzoyl groups (Scheme 3).

Attempts to apply the same strategy with the unsubstituted chromone as a Michael acceptor for the acid **2** were unsuccessful, demonstrating the importance of the 3-carboxy functionality. This carboxylic group therefore promotes the conjugate addition, but can subsequently be readily eliminated by decarboxylation under mild conditions.

The structures of benzo[*c*]coumarins **3a**–**d** was established by means of extensive 2-dimensional NMR analyses (HSQC, HMBC, and NOESY; see the Supporting Information). The connectivities found in the HMBC spectra allowed us to assign the quaternary carbon resonances and to confirm the assignments of some of the proton-bearing carbons (Figure 1). Moreover, the NOESY experiment led us to conclude that there is free rotation of the 2-hydroxybenzoyl substituents, as evidenced by the NOE effects between the signals for the H-6‴ and H-5‴ atoms and those of the H-1 and H-9 atoms of the benzo[*c*]coumarin (Figure 1). This free rotation would not be possible if bulky substituents were present at positions C-1 and/or C-9 of the benzo[*c*]coumarin skeleton, which goes some way toward explaining why derivative **3e**, possessing a fused 1,2-benzo[*f*] group (Scheme 2), was not formed, and indicates a limitation of this new methodology.

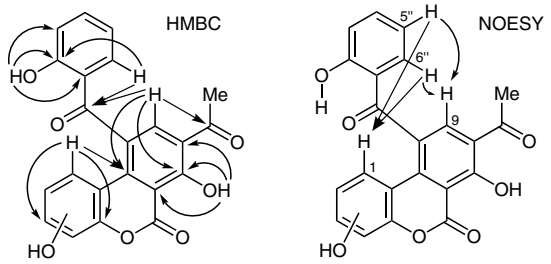


Figure 1 Main HMBC and NOESY correlations for benzo[*c*]coumarins **3a**–**d**

In conclusion, we have established a new and convenient route to hydroxylated polyfunctionalized benzo[*c*]coumarins in acceptable yields by a one-pot reaction of electron-deficient 4-oxo-4*H*-chromene-3-carboxylic acid with unprotected monohydroxy-3-(acetoacetyl)coumarins, avoiding the need to protect free hydroxy groups in the starting materials. We have therefore replaced the multistep reaction methods reported in the literature by a two-step process that proceeds under mild conditions in the presence of an organobase catalyst.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) **8-Acetyl-7-hydroxy-10-(2-hydroxybenzoyl)-6*H*-benzo[*c*]chromen-6-ones (3a–d)**
Carboxylic acid **2** (1.0 g, 5.26 mmol) was added to a soln of the appropriate 3-(acetoacetyl)coumarin **1a**–**d** (5.26 mmol) in $CHCl_3$ (20 mL). A catalytic amount of 4-PPy (0.26 mmol, 0.04 g) was added dropwise, and the mixture was refluxed with stirring for 24 h. Incomplete consumption of the starting materials was observed (TLC), even after an extended reaction time. The solvent was evaporated and the resulting gummy solid was directly purified by column chromatography [silica gel, PE–CH_2Cl_2 (gradient 3:1 to 2:1 to 1:1 to 0:1)]. Pure fractions were combined and precipitated in PE.

(12) **8-Acetyl-7-hydroxy-10-(2-hydroxybenzoyl)-6*H*-benzo[*c*]chromen-6-one (3a)**
White powder; yield: 1.371 g (70%); mp 197–198 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.79 (s, 3 H, H-2′), 6.79 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1 H, H-5‴), 7.20–7.10 (m, 2 H, H-2 and H-3‴), 7.28 (dd, *J* = 8.2, 1.4 Hz, 1 H, H-6‴), 7.42 (dd, *J* = 8.3, 1.1 Hz, 1 H, H-4), 7.58–7.49 (m, 2 H, H-3 and H-4‴), 7.65 (dd, *J* = 8.3, 1.3 Hz, 1 H, H-1), 8.19 (s, 1 H, H-9), 11.99 (s, 1 H, 2‴-O*H*), 13.24 (s, 1 H, 7-O*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 31.9 (C-2′), 108.0 (C-6a), 116.2 (C-10b), 118.0 (C-4), 118.8 (C-3‴), 119.3 (C-1‴), 119.6 (C-5‴), 124.2 (C-8), 125.4 (C-2), 125.7 (C-10), 127.5 (C-1), 132.4 (C-3), 132.8 (C-6‴), 137.7 (C-10a), 137.9 (C-4‴), 138.3 (C-9), 151.0 (C-4a), 163.6 (C-2‴), 163.8 (C-7), 165.3 (C-6), 196.2 (C-1′), 202.3 (C-1″). HRMS (ESI$^+$): *m/z* calcd for $[C_{22}H_{14}O_6 + Na]^+$: 397.0688; found: 397.0688.

(13) **8-Acetyl-3,7-dihydroxy-10-(2-hydroxybenzoyl)-6*H*-benzo[*c*]chromen-6-one (3b)**
White-yellowish powder; yield: 0.920 g (45%); mp 279–280 °C. ^{1}H NMR [300.13 MHz, DMSO-d_6–$CDCl_3$ (1:2)]: δ = 2.72 (s, 3 H, H-2′), 6.64 (dd, *J* = 9.0, 2.5 Hz, 1 H, H-2), 6.76–6.85 (m, 2 H, H-4 and H-5‴), 7.07 (dd, *J* = 8.5, 1.0 Hz, 1 H, H-3‴), 7.32 (dd, *J* = 8.0, 1.7 Hz, 1 H, H-6‴), 7.39 (d, *J* = 9.0 Hz, 1 H, H-1), 7.55 (ddd, *J* = 8.5, 7.2, 1.7 Hz, 1 H, H-4‴), 8.05 (s, 1 H, H-9), 10.34 (s, 1 H, 3-O*H*), 11.98 (s, 1 H, 2‴-O*H*), 13.30 (s, 1 H, 7-O*H*). ^{13}C NMR [75.47 MHz, DMSO-d_6–$CDCl_3$ (1:2)]: δ = 31.2 (C-2′), 103.1 (C-4), 106.0 (C-6a), 107.3 (C-10b), 113.8 (C-2), 117.9 (C-3‴), 119.1 (C-5‴), 119.5 (C-1‴), 121.7 (C-8), 124.6 (C-10), 128.3 (C-1), 132.4 (C-6‴), 137.0 and 137.3 (C-4‴ and C-9), 138.1 (C-10a), 152.3 (C-4a), 161.3 (C-3), 162.2 (C-2‴), 163.3 (C-7), 164.8 (C-6), 195.4 (C-1′), 201.4 (C-1″). HRMS (ESI$^+$): *m/z* calcd for $[C_{22}H_{14}O_7 + Na]^+$: 413.0637; found: 413.0622.

(14) **8-Acetyl-4,7-dihydroxy-10-(2-hydroxybenzoyl)-6*H*-benzo[*c*]chromen-6-one (3c)**
White-yellowish powder; yield: 1.091 g (53%); mp 272–273 °C. ^{1}H NMR [300.13 MHz, DMSO-d_6–$CDCl_3$ (1:2)]: δ = 2.74 (s, 3 H, H-2′), 6.80 (ddd, *J* = 8.1, 7.3, 1.1 Hz, 1 H, H-5‴), 6.93–7.12 (m, 4 H, H-1, H-2, H-3 and H-3‴), 7.32 (dd, *J* = 8.1, 1.7 Hz, 1 H, H-6‴), 7.54 (ddd, *J* = 8.7, 7.3, 1.7 Hz, 1 H, H-4‴), 8.07 (s, 1 H, H-9), 10.28 (s, 1 H, 4-O*H*), 11.68 (s, 1 H, 2‴-O*H*), 13.33 (s, 1 H, 7-O*H*). ^{13}C NMR [75.47 MHz, DMSO-d_6–$CDCl_3$ (1:2)]: δ = 31.3 (C-2′), 107.7 (C-6a), 116.7 (C-10b), 116.9 (C-1), 117.9 (C-3‴), 118.3 (C-3), 119.2 (C-5‴), 119.6 (C-1‴), 123.3 (C-8), 124.5 (C-2), 126.1 (C-10), 132.5 (C-6‴), 137.0 (C-4‴), 137.6 (C-9), 139.5 (C-10a), 145.64 (C-4 and C-4a), 162.0 (C-2‴), 162.9 (C-7), 164.5 (C-6), 195.5 (C-1′), 201.1 (C-1″). HRMS (ESI$^+$): *m/z* calcd for $[C_{22}H_{14}O_7 + Na]^+$: 413.0637; found: 413.0617.

(15) **8-Acetyl-2,7-dihydroxy-10-(2-hydroxybenzoyl)-6*H*-benzo[*c*]chromen-6-one (3d)**
White-yellowish powder; yield: 0.474 g (23%); mp 134–135 °C. ^{1}H NMR [300.13 MHz, DMSO-d_6–$CDCl_3$ (1:2)]: δ = 2.72 (s, 3 H, H-2′), 6.84 (t, *J* = 7.8 Hz, 1 H, H-5‴), 7.02 (dd, *J* = 8.9, 2.7 Hz, 1 H, H-3), 7.06–7.10 (m, 2 H, H-1 and H-3‴), 7.30 (d, *J* = 8.9 Hz, 1 H, H-4), 7.36 (d, *J* = 7.8 Hz, 1 H, H-6‴), 7.53–7.61 (m, 1 H, H-4‴), 8.04 (s, 1 H, H-9), 9.78 (s, 1 H, 2-O*H*), 11.70 (s, 1 H, 2‴-O*H*), 13.33 (s, 1 H, 7-O*H*). ^{13}C NMR [75.47 MHz, DMSO-d_6–$CDCl_3$ (1:2)]: δ = 31.3 (C-2′), 107.7 (C-6a), 112.0 (C-1), 116.3 (C-10b), 117.9 (C-3‴), 118.3 (C-4), 119.1 (C-5‴), 120.0 (C-1‴), 120.3 (C-3), 123.3 (C-8), 126.2 (C-10), 132.6 (C-6‴), 136.9 and 137.0 (C-4‴ and C-9), 137.1 (C-10a), 143.6 (C-4a), 154.1 (C-2), 162.1 (C-2‴), 162.9 (C-7), 165.0 (C-6), 195.4 (C-1′), 200.6 (C-1″). HRMS (ESI$^+$): *m/z* calcd for $[C_{22}H_{14}O_7 + Na]^+$: 413.0637; found: 413.0627.

