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Regiodivergent Annulation | *Very Important Paper* |

Acid-Catalyzed Regiodivergent Annulation of 4-Hydroxycoumarins with Isoprene: Entry to Pyranocoumarins and Pyranochromones

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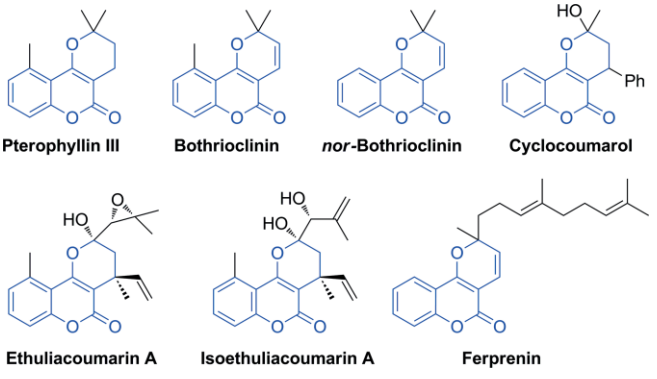
Abstract: An acid-catalyzed regiodivergent formal [3+3] annulation of 4-hydroxycoumarins with isoprene is developed. A variety of pyranocoumarins were obtained exclusively in the presence of strong Brønsted acid, while varying to Lewis acid delivered pyranochromones as main products. The protocol also features high atom-economy, wide substrate scope, easy scale-up, and good applications in natural product synthesis.

Pyranocoumarins are ubiquitous in nature, especially in various medicinal plants.[1] Cyclized prenylated coumarins such as pterophyllin III, bothrioclinin, and *nor*-bothrioclinin are the representatives that were primarily isolated from *Ekeberyia pterophylla* and *Bothriocline laxa* (Scheme 1).[2] Besides, the compounds with such framework often exhibit some intriguing biological activities. For instance, cyclocoumarol, a hemiketal form of anticoagulant drug warfarin, was recently proved to be a selective inhibitor of cyclooxygenase-2 (Scheme 1).[3] Ethuliacoumarin A and isoethuliacoumarin A, two active principles of the Egyptian plant *Ethulia conyzoides*, have been shown to possess significant molluscicidal activity (Scheme 1).[4] Ferprenin, derived from *Ferula communis*, could inhibit vitamin K epoxide reductase complex subunit 1 (VKORC1), a rate-limiting enzyme for vitamin K recycling (Scheme 1).[5] Therefore, considerable efforts have been devoted to the assembly of pyranocoumarins over the past decades.



Scheme 1. Representative natural products containing pyranocoumarin scaffold.

4-Hydroxycoumarin, which can be biosynthesized on a large-scale in *Escherichia coli*,[6] is generally served as starting material to prepare pyranocoumarins.[7] For example, this motif could be formed via two-step reactions of 4-hydroxycoumarin and prenyl bromide (Scheme 2a).[8] On the other hand, the annulation of 4-hydroxycoumarin with unsaturated precursors has recently emerged as a powerful means to access pyranocoumarin skeletons. Propargylic alcohols,[9] α,β-unsaturated ketones/aldehydes,[10] and nitroalkenes[11] were well explored in such transformations. 4-Hydroxycoumarin and prenal could undergo annulation to deliver pyranocoumarin (Scheme 2a).[10d,12] However, these approaches often generated stoichiometric by-products, and most of the precursors also required additional multistep synthesis. In this context, it is highly desirable to exploit an atom- and step-economical protocol to construct pyranocoumarins from low-cost reagents.[13]

Isoprene is an important C5 conjugated diene in industry that can be alternatively produced by fermentation of renewable feedstock.[14] Considering pterophyllin III, bothrioclinin, and *nor*-bothrioclinin also contain C5 motif, we envisaged that isoprene may serve as a precursor for the synthesis of such structures. However, both pyranocoumarins **3** and pyranochromones **4** are likely to be formed in the process.[15] Thus, how to tune the regioselectivity is a challenging issue.[16] Herein, an efficient acid-catalyzed formal [3+3] annulation of 4-hydroxycoumarin with isoprene is developed, and notably the regioselectivity can be manipulated through the choice of acid catalysts (Scheme 2b). When using strong Brønsted acid [2,4-$(NO_2)_2C_6H_3SO_3H$] as catalyst, the reaction exclusively furnished pyranocoumarins **3**. In comparison, the selectivity switched to

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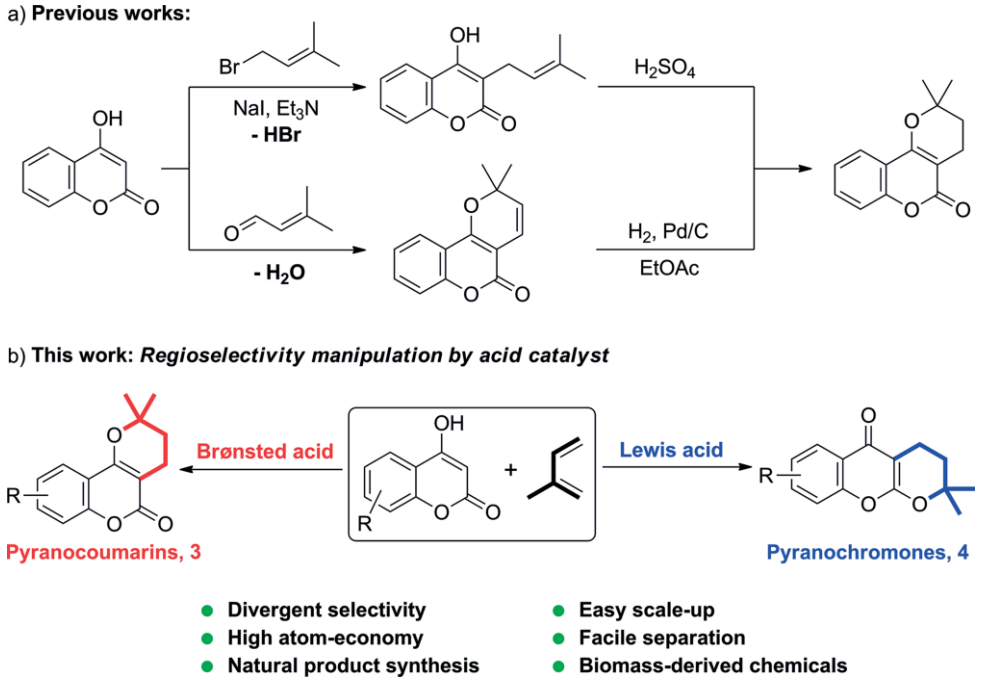


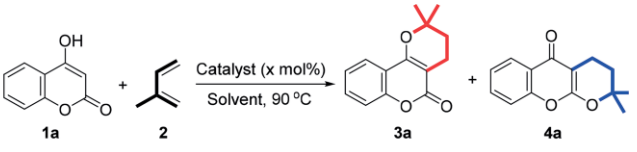
Scheme 2. The annulations of 4-hydroxycoumarin with diverse unsaturated precursors.

pyranochromones **4** by varying the catalyst to Lewis acid $Sm(OTf)_3$.

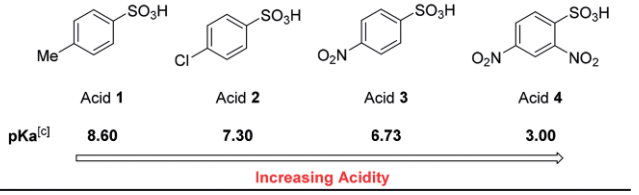
4-Hydroxycoumarin **1a** and isoprene **2** were selected as model substrates to test our initial hypothesis (Table 1). When the reaction was performed in DCE at 90 °C using *p*-toluenesulfonic acid (TsOH, acid **1**, 25 mol-%) as catalyst, both pyranocoumarin **3a** and pyranochromone **4a** were afforded with 1:1 *rr* (regioselectivity ratio) (Table 1, entry 1). Other aromatic sulfonic acids including 4-chlorobenzenesulfonic acid (acid **2**), 4-nitrobenzenesulfonic acid (acid **3**), and 2,4-dinitrobenzenesulfonic acid (acid **4**) were further screened (Table 1, entries 2–4). The pK_a values of acids **1**–**4** in acetonitrile are 8.60, 7.30, 6.73, and 3.00, respectively.[17] Increasing the catalyst acidity clearly led to an improvement in the regioselectivity of **3a**. The yield of **3a** reached up to 92 % and no **4a** was detected at all in the presence of 2,4-$(NO_2)_2C_6H_3SO_3H$ (acid **4**). An examination of the solvents showed that DMF completely suppressed the reaction, while dioxane gave the best result (Table 1, entries 5–7). Decreasing the amount of catalyst loading to 10 mol-% also exclusively furnished **3a** in a high yield (88 %) (Table 1, entry 8). To our surprise, when varying the catalyst to Lewis acid $Sm(OTf)_3$, the main product switched to pyranochromone **4a** albeit with a low regioselectivity (Table 1, entry 9). Gratifyingly, the utilization of DCE as solvent could increase the yield (52 %) and regioselectivity of **4a** (5:1) (Table 1, entry 10). However, other metal triflates such as $Zn(OTf)_2$, $Sc(OTf)_3$, and $Yb(OTf)_3$ all led to inferior results (Table 1, entries 11–13).

Subsequently, the optimized conditions were used to investigate the substrate scope for this divergent protocol (Table 2, Table 3). For Brønsted acid catalysis (Table 2), the desired pyranocoumarin 3a was isolated in 81 % yield after submitting 4-hydroxycoumarin **1a** and isoprene to the standard conditions. The electronic properties and positions of the substituents on

Table 1. Optimization of the reaction conditions.[a]



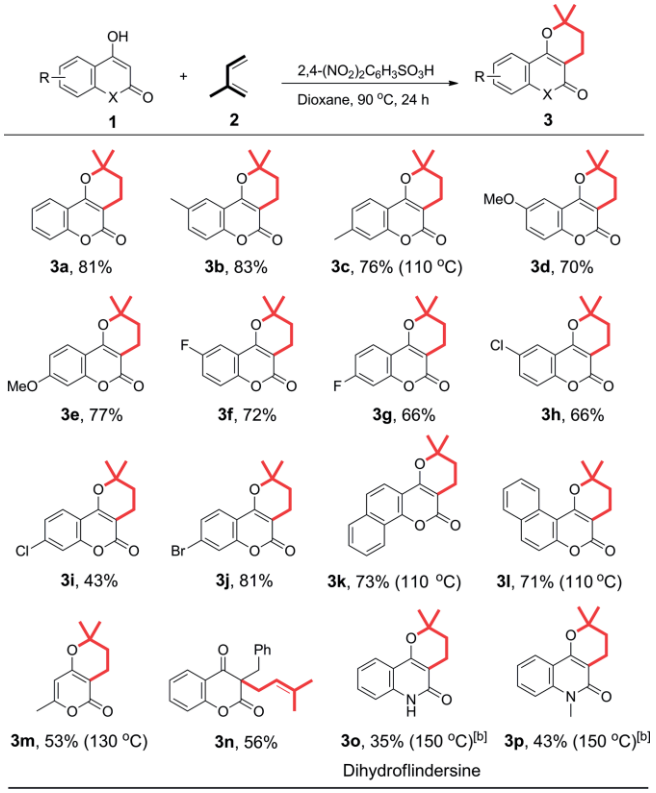
Entry	Catalyst (x mol%)	Solvent	Yield of **3a** (%)[b]	Yield of **4a** (%)[b]
1	Acid **1** (25)	DCE	36	36
2	Acid **2** (25)	DCE	67	8
3	Acid **3** (25)	DCE	84	6
4	Acid **4** (25)	DCE	92	-
5	Acid **4** (25)	DMF	N.R.	N.R.
6	Acid **4** (25)	Toluene	93	-
7	Acid **4** (25)	Dioxane	96	-
8	Acid **4** (10)	Dioxane	88	-
9	$Sm(OTf)_3$ (10)	Dioxane	12	30
10	$Sm(OTf)_3$ (10)	DCE	11	52
11	$Zn(OTf)_2$ (10)	DCE	26	39
12	$Sc(OTf)_3$ (10)	DCE	16	39
13	$Yb(OTf)_3$ (10)	DCE	12	50



[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), catalyst (*x* mol-%), solvent (0.5 mL), 90 °C, 24 h. [b] Yield was determined by HPLC using naphthalene as the internal standard. [c] pK_a values of acids in acetonitrile were given. N.R. = No reaction.

the phenyl ring had negligible influence on the reaction (**3b–j**). For example, electron-donating 6-OMe and 7-OMe hydroxycoumarins (**1d, 1e**) underwent the annulations smoothly to provide the corresponding products in 70 % and 77 % yield, respectively. Electron-withdrawing groups such as –F, –Cl, and –Br were compatible with the process as well (**3f–j**). A higher temperature (110 °C) was required to achieve good yields in the cases of benzocoumarins **1k** and **1l**. Notably, the annulation of hydroxypyranone **1m** with isoprene could take place at 130 °C, resulting in the formation of **3m** in 53 % yield. It is not surprising that prenylated diketone **3n** was afforded using 3-benzyl-4-hydroxycoumarin as substrate. More importantly, this transformation can be extended to 4-hydroxyquinolinones **1o** and **1p**. The resulting pyranoquinolinones **3o** and **3p** are the precursors of flindersine and *N*-methylflindersine.[18] It is noteworthy that no pyranochromone **4** was observed in all above case.

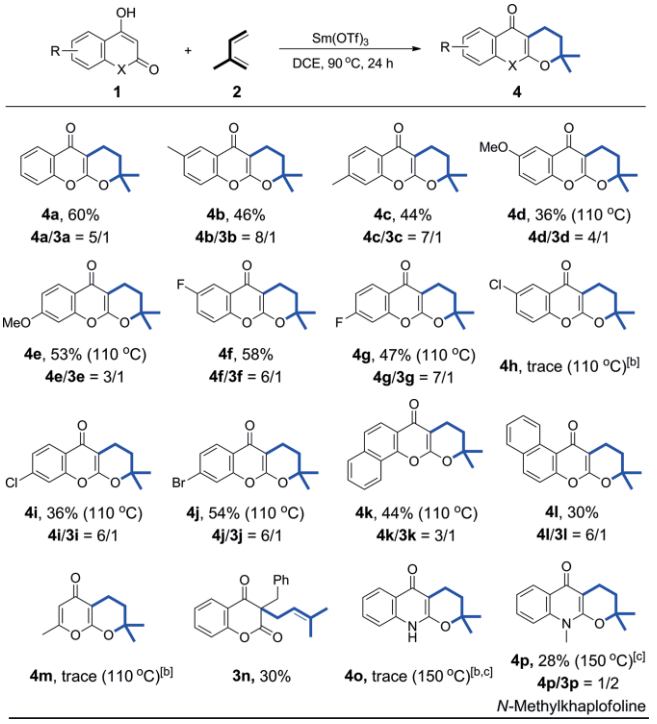
Table 2. Substrate scope for pyranocoumarins synthesis.[a]



[a] Reaction conditions: **1** (0.4 mmol), **2** (1.2 mmol), 2,4-$(NO_2)_2C_6H_3SO_3H$ (10 mol-%), dioxane (1.0 mL), 90 °C, 24 h. Only products **3** were observed and isolated yields were given. [b] 2,4-$(NO_2)_2C_6H_3SO_3H$ (1.0 equiv.).

For Lewis acid catalysis (Table 3), 4-hydroxycoumarin **1a** was converted to pyranochromone **4a** in 60 % yield with 5:1 *rr* under the optimized conditions. A range of substituents including –Me, –OMe, –F, –Cl, and –Br were all well-tolerated in the process, producing the desired pyranochromones in acceptable yields and regioselectivities. Benzocoumarins **1k** and **1l** were suitable substrates as well. It is noted that $Sm(OTf)_3$-catalyzed annulation of 6-Cl hydroxycoumarin **1h** with isoprene yielded pyranocoumarin **3h**, rather than the desired pyranochromone

Table 3. Substrate scope for pyranochromones synthesis.[a]

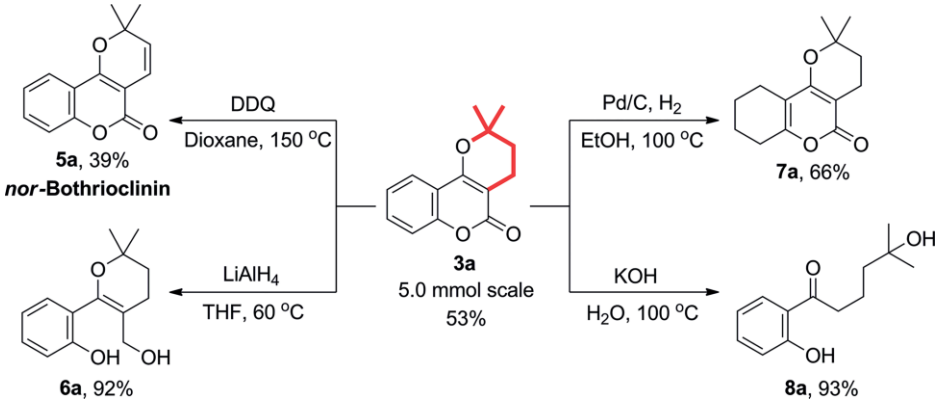


[a] Reaction conditions: **1** (0.4 mmol), **2** (1.2 mmol), $Sm(OTf)_3$ (10 mol-%), DCE (1.0 mL), 90 °C, 24 h. Isolated yields of **4** were given. The ratio was determined by ^1H NMR of crude reaction mixture. [b] Pyranocoumarins **3h** (53 %), **3m** (40 %) and pyranoquinolinone **3o** (53 %) were obtained. [c] $Sm(OTf)_3$ (1.0 equiv.).

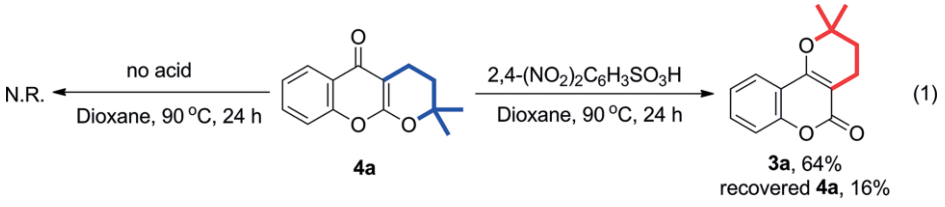
4h, as main product. This phenomenon was also observed in the reaction of hydroxypyranone **1m**. It is most likely because pyranochromones could be rapidly transformed into thermodynamically stable pyranocoumarins in both cases. The coupling of 3-benzyl-4-hydroxycoumarin **1n** with isoprene also occurred in the presence of $Sm(OTf)_3$, but the yield of **3n** (30 %) was lower than that in Brønsted acid catalysis (56 %). Naturally occurring alkaloid *N*-Me khaplofoline (**4p**) was successfully synthesized from 4-hydroxyquinolinone **1p** by this protocol, albeit with a slightly low yield.[19]

To demonstrate the synthetic utility of this methodology, diverse transformations of pyranocoumarin **3a** were studied (Scheme 3). The annulation of 4-hydroxycoumarin with isoprene could be easily scaled up to 5.0 mmol without protection from air or moisture, and a simple crystallization delivered **3a** in 53 % yield. The selective dehydrogenation of **3a** by DDQ furnished natural product *nor*-bothrioclinin **5a** in a moderate yield. The lactone motif of **3a** could be efficiently reduced by $LiAlH_4$ to afford diol **6a**. The benzene ring of **3a** was partially hydrogenated in the presence of Pd/C at 100 °C, leading to **7a** in 66 % yield.[20] Treatment of **3a** with KOH yielded ring-opening product **8a**.

To gain more insights into the competitive formation of pyranocoumarin **3a** and pyranochromone **4a**, some additional experiments were conducted at lower temperature within shorter time (12 h). As shown in Figure 1, pyranochromone **4a** was the main product below 70 °C, while pyranocoumarin **3a** became



Scheme 3. Synthetic transformations of pyranocoumarin **3a**.



predominant at higher temperature. With increasing the temperature (40–90 °C), the yield of pyranocoumarin **3a** dramatically increased from 1 % to 54 %. Meanwhile, the yield of pyranochromone **4a** gradually increased (18 % to 37 %) from 40 to 70 °C and obviously decreased by further raising the temperature. These findings indicated pyranochromone **4a** is a kinetic product, whereas pyranocoumarin **3a** is a thermodynamic product. Besides, pyranochromone **4a** could be readily transformed into pyranocoumarin **3a** under the standard conditions [Equation (1)].

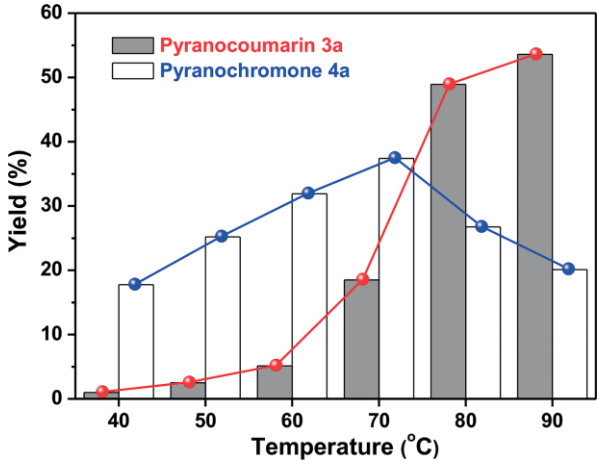
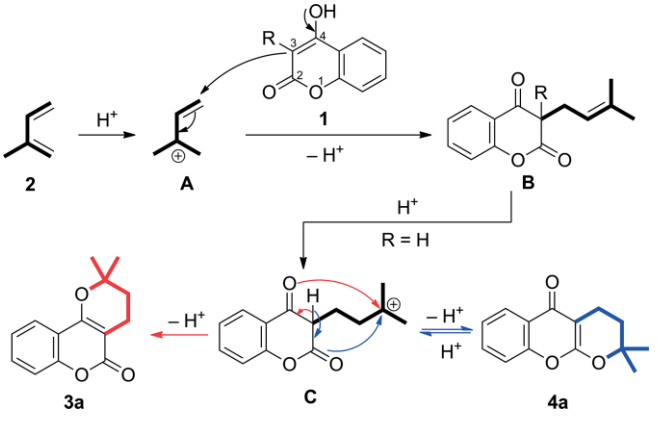


Figure 1. Temperature effect on the product distributions. Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), 2,4-$(NO_2)_2C_6H_3SO_3H$ (10 mol-%), dioxane (0.5 mL), *T*°C, 12 h. Yield was determined by HPLC using naphthalene as the internal standard.

On the basis of these experimental results, a plausible mechanism was proposed in Scheme 4. Isoprene **2** is initially protonated to form active isopentenyl cation **A**. The terminal C–C double bond of **A** is attacked by C3 of **1** to furnish prenylated diketone/coumarin **B**, followed by protonation to generate cation **C**. A final intramolecular cyclization affords pyranochromone **4a** or pyranocoumarin **3a**. It is worthwhile to mention that intermediate **C** to **4a** is a reversible pathway, while the route to **3a** is irreversible, which can account for the conversion of **4a** to **3a** in the presence of acid at high temperature.



Scheme 4. Proposed mechanism.

In conclusion, an acid-catalyzed regiodivergent annulation of biomass-derived 4-hydroxycoumarin and isoprene has been developed.[21] The strong Brønsted acid [2,4-$(NO_2)_2C_6H_3SO_3H$] exclusively resulted in pyranocoumarins, whereas the selectivity switched to pyranochromones in the presence of $Sm(OTf)_3$. The salient features of our protocol also include high atom-economy, wide substrate scope, easy scale-up, and good applications in natural product synthesis.

Acknowledgments

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Keywords: Regiodivergent annulation · Brønsted acid · Lewis acids · Isoprene · 4-Hydroxycoumarin

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[21] The reactions of 4-hydroxycoumarin with other conjugated dienes including 2,3-dimethylbutadiene, 1,3-cyclohexadiene, and 2-phenylbutadiene were also explored under both standard conditions, and details were given on page S7 of the supporting information.

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