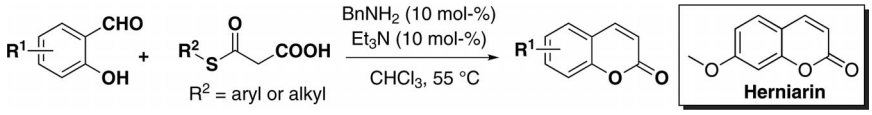
EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

Domino Reactions



We disclose an efficient route to synthesize 3,4-diunsubstituted coumarins through a cascade organocatalytic reaction. The reaction is catalyzed by using of a combination of benzylamine (10 mol-%) and triethylamine (10 mol-%). Various salicylaldehydes are tested, and the corresponding coumarin products are obtained in good to high yields under mild and metal-free reaction conditions.

Keywords: Natural products / Organocatalysis / Domino reactions / Decarboxylation / Amines

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Amine-Catalyzed Cascade Synthesis of 3,4-Diunsubstituted Coumarins

Jia Wei,[a] Pengcheng Wang,[b] Qianfa Jia,[a] Jiaoyao Huang,[b] Zhiyun Du,*[a] Kun Zhang,[a] and Jian Wang*[a,b]

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We disclose an efficient route to synthesize 3,4-diunsubstituted coumarins through a cascade organocatalytic reaction. The reaction is catalyzed by using of a combination of benzylamine (10 mol-%) and triethylamine (10 mol-%). Various salicylaldehydes were tested, and the corresponding coumarin products were obtained in good to high yields under mild and metal-free reaction conditions.

Introduction

As one of the prominent medicinal scaffolds, the coumarin is featured in numerous synthetic compounds and natural products that are used as drugs,[1] anticoagulants,[2a–2d] and pesticides.[2e] Coumarin and its derivatives have varied bioactivities including antimicrobial activity,[3a] antithrombotic activity,[3b] antipsoriasis activity,[3c] anticancer activity,[3d] anti-HIV activity,[3e] antiproliferative activity,[3f] inhibitory activity on viral proteases,[3g] estrogen-like effects,[3h] and central nervous system modulating activity.[3i] These important findings have attracted considerable attention to the functionalization of the coumarin skeleton. As exemplified in Figure 1, natural products **A**–**D** were reported to possess some biological properties. Herniarin (**A**) has been used as a sensitizer in German chamomile.[4] Marmin (**B**), a coumarin isolated from *Aegle marmelos* Correa, has shown antiallergic effects.[5] Aesculin (**C**) is used in microbiology laboratories to aid in the identification of bacterial species.[6] Aesculetin (**D**) is present in many toxic and medicinal plants, in the form of glycosides and caffeic acid conjugates, and can have an anticoagulant effect.[7] Thereby, the synthesis of this coumarin scaffold is of much interest.

Coumarins have been synthesized by several routes, including Pechmann synthesis,[8] Perkin synthesis,[9] Knoevenagel condensation,[10] the Reformatsky reaction,[11] the Wittig reaction,[12] and so on. Among these, the Pechmann reaction is the most widely used method, as the reaction involves the use of simple starting materials, such as phenols and β-keto esters, in the presence of acidic condensing agents. The use of various reagents such as H_2SO_4, $FeCl_3$, $ZnCl_2$, $POCl_3$, $AlCl_3$, HCl, phosphoric acid, trifluoroacetic acid, montmorillonite, and other clays are all well documented in the literature.[13] Most of these methods suffer from severe drawbacks including the use of a large amount of catalysts, long reaction times, and high temperatures. Some of the recent achievements in the efficient construction of this nucleus include the development of cation-exchange resins,[14a] solid acid catalysts and metal nitrates,[13] heteropolyacid-supported polyaniline catalysts,[14c,14d] microwave irradiation, ionic liquids as efficient catalysts,[14e] and very recently the Pt-catalyzed hydroarylation of propiolic acids with phenols.[14f] Consequently, there is ample room for further development of milder reaction conditions, increased variation in the substituents of both components, and better yields.

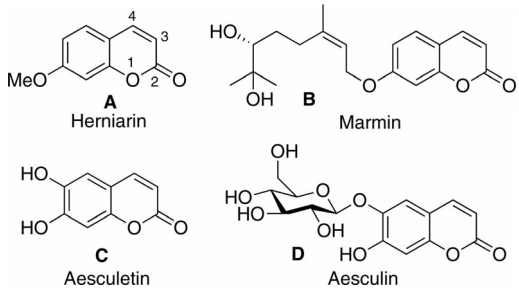

Figure 1. Representative examples of natural 3,4-diunsubstituted coumarins.

Recently, the scope of metal-free organocatalysts to promote cascade reactions has expanded.[15] It is noteworthy that a number of useful cascade reactions were reported.[16] Undoubtedly, the utilization of cascade reactions provides a useful synthetic tool for organic synthesis. It offers the possibility to form multiple chemical bonds in a one-pot process without isolating intermediates, changing reaction conditions, or adding reagents. Finally, this strategy reduces

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the synthetic costs and simplifies synthetic steps and processes. Inspired by the advantages and significances of this cascade strategy, we became interested in exploring a new cascade reaction for our targeted coumarins. Recently, our group reported the facile synthesis of 4-substituted 3,4-dihydrocoumarins and 3-hydroxyoxindoles through an organocatalytic decarboxylation process.[17] These reports revealed that the decarboxylative process[18] is a practical and efficient method for C–C bond formation. Herein, we report a cascade organocatalytic method for the facile synthesis of 3,4-diunsubstituted coumarins.

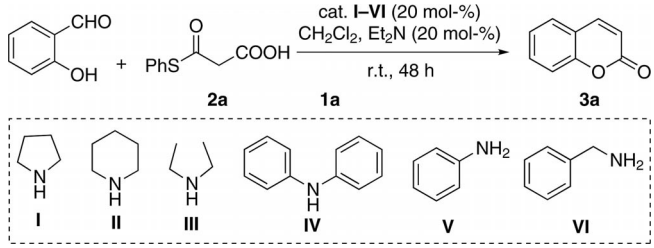
Results and Discussion

In an initial investigation, we conducted a model reaction between salicylaldehyde (**1a**) and malonic acid half-thioester **2a** by employing pyrrolidine **I** (20 mol-%) as an organocatalyst and Et_3N (20 mol-%) as a cocatalyst to afford desired product **3a** in 52% isolated yield (Table 1). To further improve the reaction yield, a series of commercially available, simple amines **II**–**VI** were examined. The yield slightly improved to 60% in the presence of primary benzylamine (**VI**; Table 1, entry 6), whereas all other tested amine catalysts resulted in low yields (Table 1, entries 2–5). In addition, base as the cocatalyst was found to have an important effect on the reaction yield (Table 2). A substantial decrease in the reaction yield was observed for stronger organic (Table 2, entry 3) and inorganic bases (17–51%; Table 2, entries 4–6). More importantly, the solvent was found to be a critical factor for changing reactivity (Table 3, entries 1–7). Among the solvents tested, $CHCl_3$ proved to be the best medium with respect to catalytic activity and yield (90%, 48 h, r.t.; Table 3, entry 2). Further changes in reaction temperature did have a significant effect on the reactivity (97%, 55 °C, 4 h; Table 3, entry 8). Notably, a catalyst loading of 5 mol-% provided the product in 95% yield in 10 h (Table 3, entry 10).

With the optimized reaction conditions in hand, the substrate scope of this transformation was examined by varying salicylaldehyde **1** (Table 4). Salicylaldehydes **1b**–**s** were successfully partook in the reaction, and corresponding adducts **3b**–**s** were obtained in good to excellent yields (80–96%, 3–12 h; Table 4, entries 2–18). Salicylaldehydes having both electron-donating and electron-withdrawing substituents can be efficiently catalyzed in this transformation. Thus, the substitution pattern of the arene had a limited influence on the reaction activity. Additionally, naphthyl-based salicylaldehyde also reacted in this process to form desired product **3s** (86%, 48 h; Table 4, entry 19). Lastly, we examined malonic half-thioesters **2b**–**d** (Table 5). Phenyl-substituted **2b** and **2c** and alkyl-substituted **2d** had limited influence on the reactivity (89–92% yield, 4 h; Table 5, entries 1–3). All these results indicate that the formation of the ester group by lactonization is not the rate-determining step.

Notably compound **3d**, named Herniarin (**A**), is a methoxy analogue of umbelliferone and can be found in natural

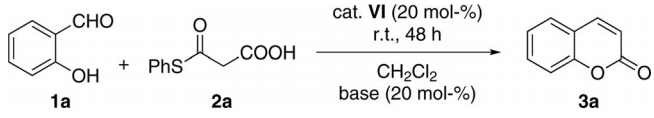
Table 1. Evaluation of organocatalysts.[a]



Entry	Catalyst	Yield [%][b]
1	**I**	52
2	**II**	42
3	**III**	40
4	**IV**	23
5	**V**	34
6	**VI**	60

[a] Reaction conditions: CH_2Cl_2 (0.4 mL), salicylaldehyde (**1a**; 0.1 mmol, 1.0 equiv.), malonic acid half-thioester **2a** (0.2 mmol, 2 equiv.), Et_3N (20 mol-%, 0.2 equiv.), and catalyst (20 mol-%) at room temperature for 48 h. [b] Yield of isolated product after column chromatography.

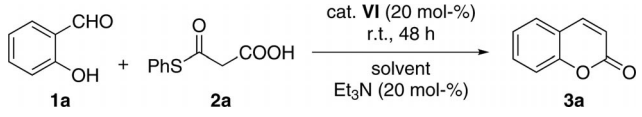
Table 2. Evaluation of bases.[a]



Entry	Base	Yield [%][b]
1	–[c]	31
2	2,6-lutidine	54
3	DBU[d]	48
4	LiOH	38
5	Na_2CO_3	17
6	Cs_2CO_3	51

[a] Unless specified, see the Exp. Section for reaction conditions. [b] Yield of isolated product after column chromatography. [c] No base. [d] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

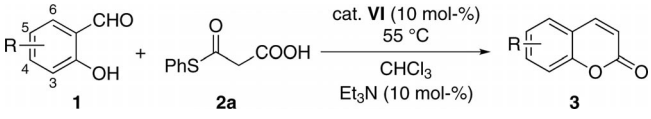
Table 3. Evaluation of solvents.[a]



Entry	Solvent	Yield [%][b]
1	CH_2Cl_2	60
2	$CHCl_3$	90
3	toluene	58
4	EtOAc	48
5	CH_3CN	52
6	Et_2O	60
7	DMSO	73
8[c]	$CHCl_3$	97
9[d]	$CHCl_3$	94
10[e]	$CHCl_3$	95

[a] Unless specified, see the Exp. Section for reaction conditions. [b] Yield of isolated product after column chromatography. [c] 55 °C, 4 h. [d] 10 mol-% of **IV**, 10 mol-% Et_3N, 55 °C, 6 h. [e] 5 mol-% of **IV**, 5 mol-% Et_3N, 55 °C, 10 h.

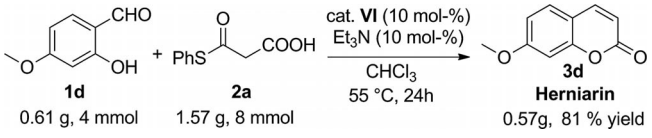
Table 4. Scope of substrates.[a]



Entry	R	Time [h]	Product	Yield [%][b]
1	H	6	**3a**	93
2	3-OMe	3	**3b**	90
3	3-OEt	3	**3c**	94
4	4-OMe	3	**3d**	92
5	4-OBn	9	**3e**	83
6	5-Me	9	**3f**	95
7	5-OMe	3	**3g**	95
8	5-*t*Bu	12	**3h**	86
9	3-OMe, 5-Br	3	**3i**	88
10	3-OMe, 5-NO_2	9	**3j**	87
11	5-F	9	**3k**	93
12	5-Cl	3	**3l**	90
13	5-Br	9	**3m**	91
14	5-NO_2	10	**3n**	96
15	3,5-Cl_2	3	**3o**	91
16	3,5-Br_2	12	**3p**	85
17	3-Br, 5-Cl	3	**3q**	89
18	3-Br, 5-NO_2	9	**3r**	80
19	2-naphthyl	48	**3s**	86

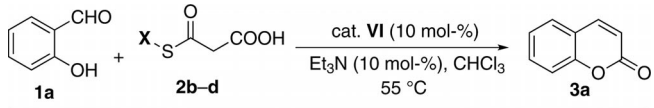
[a] Unless specified, see the Exp. Section for reaction conditions. [b] Yield of isolated product after column chromatography.

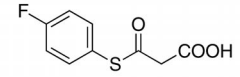
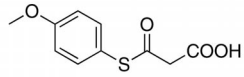
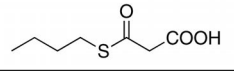
resources, such as *Herniaria glabra*, *Ayapana triplinervis*, and *Prunus*.[19] To show the potentially practical synthesis of our method, a half-gram scale synthesis was performed to assemble natural product Herniarin (**3d**, also **A**). By combination of **1d** and **2a** under standard conditions, desired product **3d** was rapidly produced [Equation (1), 81%, 24 h].



(1)

Table 5. Scope of malonic half-thioesters.[a]



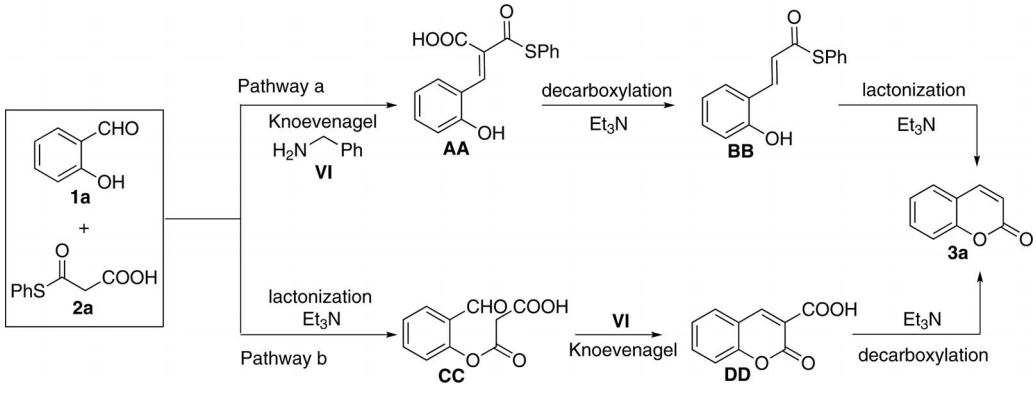
Entry	2		Time [h]	Yield [%]
1		**2b**	4	92
2		**2c**	4	89
3		**2d**	6	92

[a] Unless specified, see the Exp. Section for reaction conditions.

With regard to the reaction mechanism, two plausible pathways are proposed (Scheme 1). As shown in pathway a (Scheme 1), catalyst **VI** reacts with salicylaldehyde **1a** to form intermediate **AA** through a Knoevenagel reaction. Then, Et_3N triggers a decarboxylation elimination step to create intermediate **BB**. Finally, subsequent lactonization leads to target product **3a**. Without sufficient evidence in hand, the reaction can also be postulated to proceed through pathway b. Malonic acid half-thioester **2a** directly reacts with **1a** to generate intermediate **CC** in the presence of Et_3N. Subsequently, a Knoevenagel reaction affords construct intermediate **DD**. Finally, decarboxylation allows intermediate **DD** to be converted into coumarin **3a**.

Conclusions

In conclusion, we have documented an efficient route to synthesize 3,4-diunsubstituted coumarins through an organocatalytic cascade reaction. The reaction is catalyzed by using of a combination of benzylamine (10 mol-%) and triethylamine (10 mol-%). A number of salicylaldehydes were tested, and the corresponding coumarin products were obtained in good to high yields under mild and metal-free



Scheme 1. Proposed mechanism.

reaction conditions. Moreover, an amplified gram-scale synthesis indicates that our method has potential synthetic value. Further investigations on the applications of this organocatalytic decarboxylative cascade strategy to other biologically important molecules are underway in our laboratory.

Experimental Section

General Procedure: To a solution of salicylaldehyde (**1a**, 0.2 mmol) and benzylamine (0.02 mmol, 0.1 equiv.) in $CHCl_3$ (0.8 mL) was added **2b** (0.4 mmol) and Et_3N (0.02 mol, 0.1 equiv.). The reaction mixture was stirred at 55 °C for 6 h. The crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate) to afford desired product **3a** (93% yield).

Supporting Information (see footnote on the first page of this article): General experimental methods and characterization data.

Acknowledgments

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