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COMMUNICATION

Facile synthesis of 4-substituted 3,4-dihydrocoumarins *via* an organocatalytic double decarboxylation process†

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3,4-Dihydrocoumarins, considered to be valuable building blocks, have attracted considerable attention due to their various biological activities. Herein, we have documented an efficient and convenient double decarboxylation process for the synthesis of 4-substituted 3,4-dihydrocoumarin in moderate to excellent yields under mild reaction conditions (up to 98%).

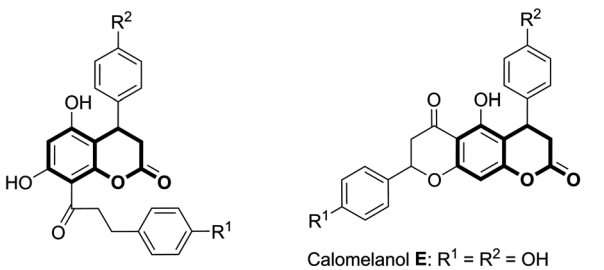
Introduction

Over the past few decades, natural products have proven to be useful small-molecule probes in medicinally community.[1] A rapid access to small molecules that are guided by natural products appears to be quintessential for the success of chemical genetics/genomics-based programs. The design and synthesis of novel scaffolds as chiral core structures for the library generation of natural product-like derivatives is an essential step in accessing a wide range of structural complexes in an efficient manner.[2]

3,4-Dihydrocoumarins, considered to be valuable building blocks, have attracted considerable attention due to their various biological activities,[3] such as aldose reductase inhibition,[4] protein kinases,[5] antiherpetic,[6] and flavoring agent to a diverse set of foods (soft drinks, yogurt, muffins).[7] In addition, the 3,4-dihydrocoumarin scaffold has been discovered in a number of important natural compounds as exemplified by Calomelanol **A–C**, **E–J** (Fig. 1).[8] In view of their wide biological applications, we wondered whether it would be possible to assemble a 3,4-dihydrocoumarin skeleton *via* an efficient process. In fact, several common methods have been reported, but most of these traditional approaches suffer from harsh reaction conditions, lack of substrate generality, the use a large excess of expensive transition metals, the use of a laborious multistep procedure, or corrosive organic acids, *etc*.[9] Surprisingly, despite the need for metal-free and environmentally benign methods, organocatalytic strategies for the synthesis of 3,4-dihydrocoumarins have been rarely reported. In 2007, Henry and Kwon discovered a tertiary phosphine catalyzed intramolecular [3 + 2] annulation strategy to construct cyclopentene-fused dihydrocoumarins in good to excellent to good yields (eqn (1)).[9w] Afterwards, Lectka's group documented an efficient [4 + 2] cycloaddition reaction of *ortho*-quinone methides with silyl ketene acetals to afford a variety of alkyl- and aryl-substituted 3,4-diydrocoumarins (eqn (2)).[9l] In 2009, Zeitler and Rose reported a one-pot, atom-economic *N*-heterocyclic carbine-catalyzed redox lactonization reaction of *o*-hydroxycinnamaldehydes in the presence of oxidants (eqn (3)).[9h] Most recently Hong *et al.* reported an amine-thiourea catalyzed Michael-acetalization process which could generate the 3,4-dihydrocoumarin scaffold in synthetic useful yields (eqn (4)).[9m] As part of a program geared toward the design and development of novel organocatalytic strategy for the efficient and mild synthesis of 3,4-dihydrocoumarins, here we document the first organocatalytic double decarboxylation strategy, thus leading to an efficient assembly of 4-substituted 3,4-dihydrocoumarins (eqn (5)).

Phosphine-catalyzed annulation (ref. 9*w*)

(1)



Calomelanol **A**: R^1 = OMe; R^2 = H
Calomelanol **B**: R^1 = OH; R^2 = H
Calomelanol **C**: R^1 = H; R^2 = OH

Calomelanol **E**: $R^1 = R^2$ = OH
Calomelanol **G**: R^1 = OMe; R^2 = OH
Calomelanol **H**: R^1 = OH; R^2 = H
Calomelanol **I**: R^1 = H; R^2 =OH
Calomelanol **J**: $R^1 = R^2$ = H

Fig. 1 Examples of 4-substituted 3,4-dihydrocoumarin scaffold based natural products.

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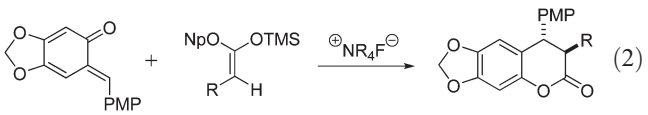
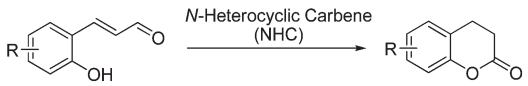
Cycloaddition of *o*-quinone methides (ref. 9*l*)



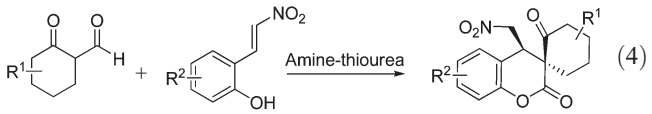
(2)

Carbene-catalyzed redox lactonization (ref. 9*h*)



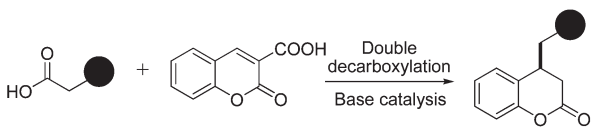
(3)

Cascade domino Michael-acetalization (ref. 9*m*)



(4)

This work: double decarboxylation



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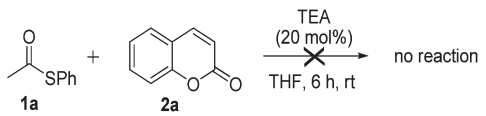

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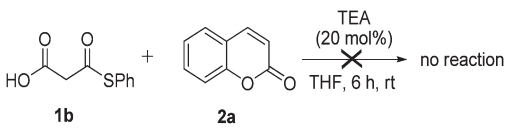

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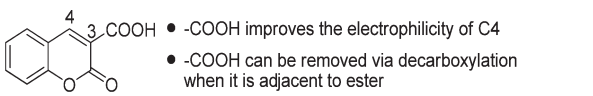
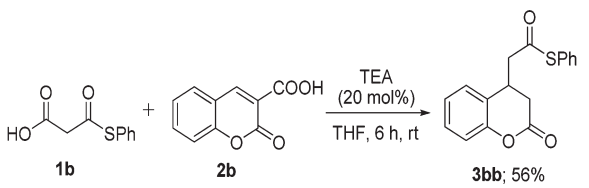
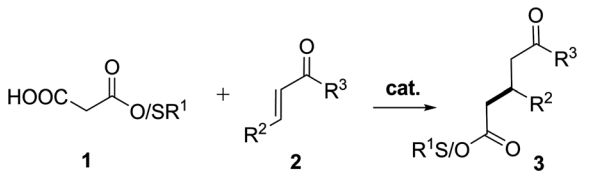




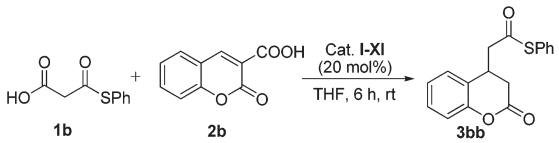
(8)

It is noteworthy that conjugate addition has represented a straightforward approach in the past few decades.[10] In general, in these processes activated methylenes such as malonates,[11] 1,3-ketoesters,[12] nitroalkanes,[13] bis-sulfones,[14] and active thioesters[15] as nuclephiles are commonly utilized. However, the direct introduction of a synthetically useful mono-ester or thioester (*e.g.* CH_2CO_2R or CH_2COSR) moiety is a challenging synthetic issue. The difficulty is due to the relatively high pK_a values of the α-protons of these carbonyl compounds.[16] We envision that a provisional "auxiliary" functional group, such as a carboxylic acid moiety,[17] can function as an ester or thioester synthon (Scheme 1). The introduction of a carboxylic acid group can activate the α-carbon of the ester or thioester and lead the expected nucleophilic conjugate addition. Moreover, the carboxylic acid moiety can be readily removed under mild conditions. This base-triggered double decarboxylation strategy



Scheme 1 Design of malonic acid half-esters or thioesters as nuclephiles for organocatalytic decarboxylation reactions of α,β-unsaturated carbonyls.

Table 1 Catalyst investigation[a]



Entry	Catalyst	Yield (%)[b]
1	i-Butylamine (**I**)	—
2	Pyrrolidine (**II**)	44
3	TEA (**III**)	56
4	DIPEA (**IV**)[c]	41
5	*N*-Methylmorpholine (**V**)	66
6	Pyridine (**VI**)	—
7	DMAP (**VII**)[d]	49
8	NaOAc (**VIII**)	—
9	Li_2CO_3 (**IX**)	—
10	Cs_2CO_3 (**X**)	—
11	NaOH (**XI**)	—

[a] Reaction conditions: **1b** (0.2 mmol, 1.0 equiv.), **2b** (0.24 mmol, 1.2 equiv.), catalyst (20 mol%), THF (0.4 mL), 6 h, room temperature. [b] Isolated yield after flash column purification. [c] *N*,*N*-Diisopropylethylamine. [d] 4-Dimethylaminopyridine.

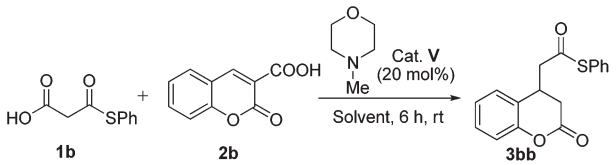
would be an ideal approach for greener and more atom-economic C–C bond formations.

Results and discussion

To test our hypothesis, two comparison experiments were initially carried out in the presence of a catalytic amount of triethylamine. Not surprisingly, thioester **1a** did not react with coumarin **2a** (eqn (6)). Unfortunately, our proposed malonic acid half thioester **1b** was also not reacted with coumarin **2a** to afford the desired product (eqn (7)). We deduce that the activity of coumarin **2a** might be a crucial issue. Towards this end, another controlled experiment was designed. As shown in eqn (8), coumarin-3-carboxylic acid **2b** was introduced to allow the reaction to afford the desired product **3bb** in a synthetically useful yield (eqn (8), 56%). In view of the structure of coumarin-3-carboxylic acid **2b**, the C3–COOH group may be helpful in improving the electrophilicity of C4 and prompting the conjugation addition to generate the featured compound **3bb**.

With this finding in hand, we then started to promote this reaction in a high efficiency fashion. In this context, we explored the reaction of malonic acid half thioester **1b** with coumarin-3-carboxylic acid **2b**, in the presence of primary amine, i-butylamine **I** and pyridine **VI**, we obtained none of the target 3,4-dihydrocoumarin **3bb** (Table 1, entries 1 and 6). Next, we examined the

Table 2 Optimization of other parameters[a]



Entry	Solvent	Yield (%)[b]
1	Et_2O	36
2	DCM	<5%
3	Toluene	<5%
4	EtOAc	<5%
5	Acetone	46
6	MeCN	<5%
7	THF	66
8	1,4-Dioxane	73
9	**DMF**	**82**
10[c]	DMF	76
11[d]	**DMF**	**90**
12[e]	DMF	90
13	EtOH	<5%
14	H_2O	<5%

[a] Reaction conditions: **1b** (0.2 mmol, 1.0 equiv.), **2b** (0.24 mmol, 1.2 equiv.), catalyst **V** (20 mol%), solvent (0.4 mL), 6 h, room temperature. [b] Isolated yield after flash column purification. [c] Cat. **V** (10 mol%), 12 h. [d] **1b** (0.24 mmol, 1.2 equiv.), **2b** (0.2 mmol, 1.2 equiv.), Cat. **V** (10 mol %), 12 h. [e] **1b** (0.3 mmol, 1.5 equiv.), **2b** (0.2 mmol, 1.2 equiv.), Cat. **V** (10 mol%), 12 h.

secondary amine, pyrrolidine **II**. Interestingly, pyrrolidine **II** afforded a 44% yield (Table 1, entry 2). Followed that, a series of tertiary amines, such as triethylamine **III**, *N*,*N*-diisopropylethylamine **IV**, *N*-methylmorpholine **V** and 4-dimethylaminopyridine **VII**, were investigated (Table 1, entries 3–5 and 7). It is noteworthy that *N*-methylmorpholine **V** was approved to be a more efficient catalyst (Table 1, entry 5, 66%, 6 h). In addition, several inorganic bases were applied to this reaction and finally demonstrated no catalytic activation (Table 1, entries 8–11).

In order to achieve a high chemical yield, we did further investigation on other parameters, such as solvent and ratio of components. Results showed that less polar solvents were poor reaction media (Table 2, entries 1–7, <5%–66%). Ethanol and water led to a sluggish reaction (Table 2, entries 13 and 14). Finally, a basic polar solvent was generally essential for a good chemical yield (Table 2, entry 9, 82%). In addition, if the ratio of **1b**/**2b** was adjusted from 1 : 1.2 to 1.2 : 1, a good chemical yield (90%) was finally obtained (Table 2, entry 11). Moreover, a lower catalyst loading caused a loss of reaction yield (Table 2, entry 10, 10 mol%, 76%).

Having established an efficient protocol for the reaction of **1b** and **2b**, we subsequently explored the substrate scope of this transformation. As shown in Table 3, a number of coumarin-3-carboxylic acids **2b–j** bearing electron donating and electron-withdrawing substituents were successfully applied to the double decarboxylation process. The corresponding adducts **3bb–bj** were isolated in moderate to excellent yields (60–96%). Furthermore, a diverse set of malonic acid half-thioesters were examined and demonstrated that the substitution pattern of the phenyl ring on thioester had limited influence on the catalytic activity of the reaction (Table 3, **3cb–fb**). Surprisingly, the alkyl substituted malonic acid half-thioesters **1g–h** also efficiently participated in the decarboxylation process to generate 4-alkyl thioester 3,4-dihydrocoumarin **3gb–hb** and provided 92% and 88% yields in 12 h. In addition to malonic acid half-thioester **1b–g**, several other α-functionalized carboxylic acids **1i–m**, which tolerated ester, amide, ketone, nitrile and aryl groups, were introduced to this process and the desired products **3ib–mb** were achieved in high to excellent yields (80–98%).

Conclusions

In summary, we have documented an efficient and convenient double decarboxylation process for the synthesis of 4-substituted 3,4-dihydrocoumarin in moderate to excellent yields (up to 98%). We hope that the catalytic system and strategy demonstrated here could be applied to efficiently assemble other synthetic useful chemical structures. Elaboration of above synthesized products and further applications of our proposed decarboxylation strategy are now ongoing in our group.

Acknowledgements

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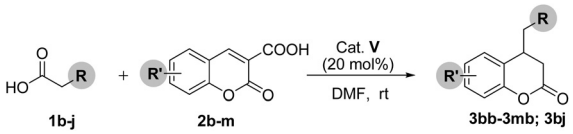
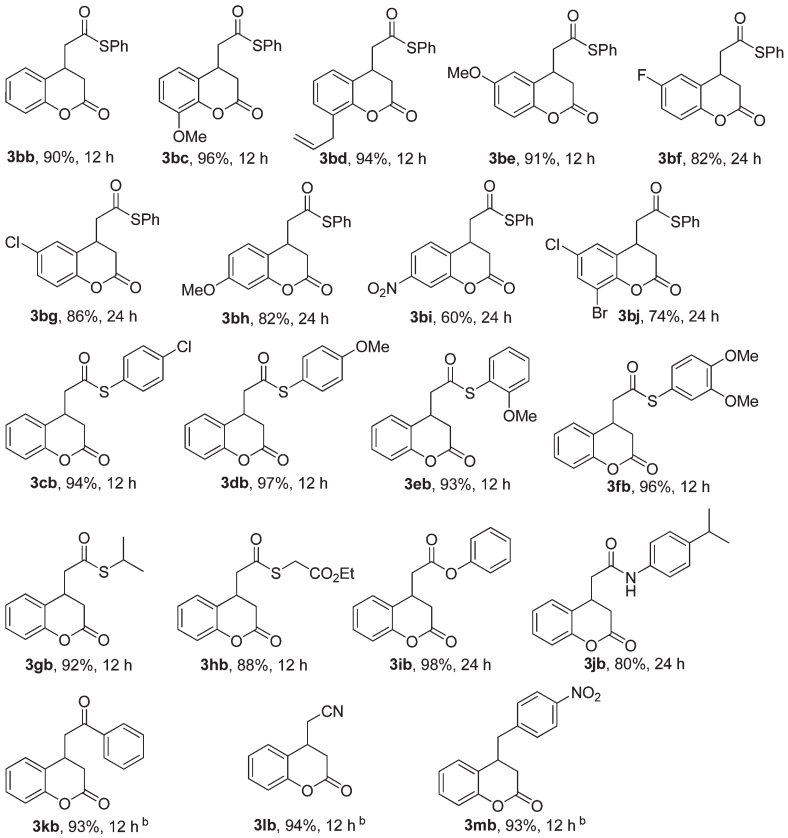
Table 3 Substrate scope[a]





[a] Reaction conditions: **1b–j** (0.2 mmol, 1.0 equiv.), **2b–m** (0.24 mmol, 1.2 equiv.), catalyst **V** (20 mol%), DMF (0.4 mL), room temperature. [b]70 °C.

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