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Modular access to furo[3,2-*c*]chromen-4-ones *via* Yb(OTf)$_3$-catalyzed [3 + 2] annulation of 4-hydroxycoumarins with β-nitroalkenes†

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A facile and efficient strategy for modular access to furo[3,2-*c*]chromen-4-ones using 4-hydroxycoumarin and β-nitroalkenes *via* Lewis acid-catalyzed formal [3 + 2] annulation protocol is described. This reaction proceeds *via* cascade Michael addition/nucleophilic addition/elimination in the presence of Yb(OTf)$_3$, which involves the formation of two new σ (C–C and C–O) bonds for the construction of a novel furan ring in a single operation. This protocol affords a variety of functional groups, thereby providing a practical and efficient method for the fabrication of a furo[3,2-*c*]chromen-4-one framework.

Introduction

Heterocycles featuring a chromen-4-one scaffold are abundantly found in natural products,[1] biologically active intermediates[2] and functional materials[3] with significant pharmaceutical and chemosensing properties. In particular, furan-fused chromen-4-ones display a range of activities in biological investigations and drug explorations,[4] for example, antiviral, anticancer, antifungal, antimicrobial, antioxidant, anticoagulant, anti-inflammatory, and Na^+ and K^+-ATPase inhibitory activities.[5] There are two typical regioisomers of furochromen-4-one with respect to the reciprocal orientation of fused furan, namely furo[3,2-*c*]chromen-4-one and furo[2,3-*c*]chromen-4-one (Fig. 1a). It was noted that the furo[3,2-*c*]chromen-4-one isomer expresses exclusive diverse biological properties, such as neo-tanshinlactone, which is a potent phospholipase inhibitor, and norpterophyllin and norisoerlengieafusicol possess anticoagulant and antifungal activities (Fig. 1b).[6] Apart from their medicinal properties, furan-fused chromen-4-ones also exhibit other important applications such as chemosensors, photosensitizers, and molecular probes.[7]

Considering the wide range of applications of furo[3,2-*c*]chromen-4-ones, over the years, various synthetic methods for their preparation have varied but were extensively integrated with 4-hydroxycoumarin as the starting material.[8] Employing aryl ketones as starting materials, Zhang and Phan reported a metal-free protocol for the synthesis of furo[3,2-*c*]chromen-4-ones (Scheme 1a).[9] Later, an improved formal [3 + 2] annulation of 4-hydroxycoumarins with oxime esters for constructing 2-aryl furo[3,2-*c*]chromen-4-ones was further developed (Scheme 1b).[10] Noland's group introduced an iron(III)-catalyzed three-component reaction of 4-hydroxycoumarins, 2-methylfuran, and aldehydes for the one-pot synthesis of functionalized furo[3,2-*c*]chromen-4-ones (Scheme 1c).[11] In 2022, Choudhury and co-workers disclosed a thiol-dependent reaction of arylglyoxal and 4-hydroxycoumarins in the presence of Sc(OTf)$_3$ for the easy access of 2-phenyl-4*H*-furo[3,2-*c*]chromen-4-ones (Scheme 1d).[12] Very recently, Yang and co-workers established a regioselective Lewis acid-catalyzed cascade annulation of *o*-hydroxyphenyl propargylamines with 4-hydroxycoumarins to give 2,3-disubstituted furo[3,2-*c*]chromen-4-ones (Scheme 1e).[13] β-Nitroalkenes have recently emerged as an adaptable C2-synthon in the synthesis of countless heterocycles.[14] For example, a furan

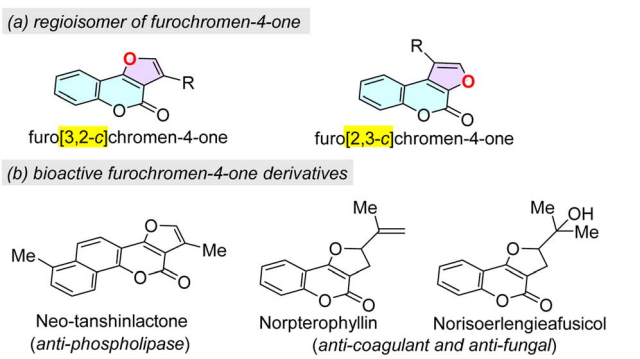

Fig. 1 Regioisomer of furochromen-4-one and the representative bioactive furo[3,2-*c*]chromen-4-one derivatives.

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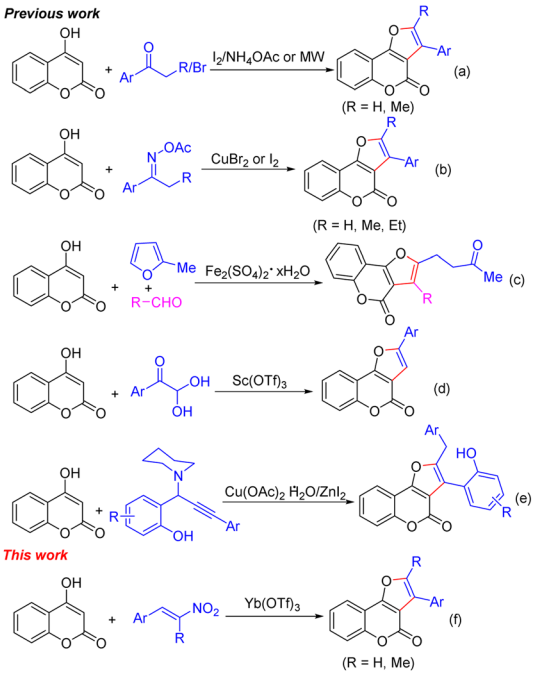


Scheme 1 Diverse strategies for the synthesis of furo[3,2-*c*]chromen-4-one derivatives.

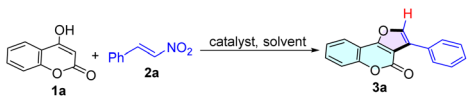
framework could be formed through the condensation reaction between 1,3-dicarbonyl equivalents and nitroalkenes.[15] In recent years, β-nitroalkenes have also been used to construct a furocoumarin scaffold with 4-hydroxycoumarins under various catalytic systems.[16] In continuation of our interest in investigating fused heterocyclic systems,[17] herein, we would like to report a facile strategy for modular access to furo[3,2-*c*]chromen-4-ones in moderate to good yields *via* the formal [3 + 2] annulations of 4-hydroxycoumarins with β-nitroalkenes in the presence of $Yb(OTf)_3$ as the Lewis acid (Scheme 1f).

Results and discussion

The reaction of 4-hydroxycoumarin **1a** and β-nitroalkene **2a** was selected as a model reaction for the optimization of reaction conditions (Table 1). Using 1,2-dichloroethane (1,2-DCE) as the solvent, four different rare-earth metal triflates were screened, and **3a** was generally obtained (Table 1, entries 2–5). $Yb(OTf)_3$ was found to be the most efficient catalyst for this reaction, providing the highest yield of the desired product **3a** (Table 1, entry 5). No reaction occurred in the absence of the catalyst or when the reaction was performed at room temperature (Table 1, entries 1 and 6). Changing the solvent to toluene, DMF, or THF gave inferior results (Table 1, entries 7–9). Further screening of the catalyst loading amount revealed that 10 mol% was optimal for the reaction, while lower (5 mol%) or higher (20 mol%) loadings all led to no improvement in the yield (Table 1, entries 10 and 11). It was worth mentioning that the reaction is tolerant of moisture and air and could be performed in commercial solvents under open air atmosphere.

With the optimized reaction conditions in hand, we then turned our attention to investigate the substrate scope (Table 2).

Table 1 Screening of the reaction conditions[a]



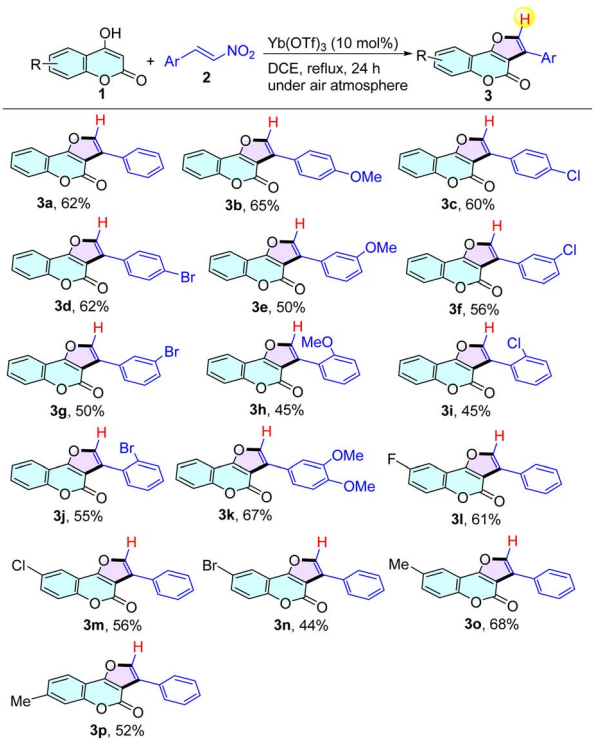
Entry	Catalyst (mol%)	Solvent	Temp. (°C)	Yield[b] (%)
1	No catalyst	1,2-DCE	84	0
2	$Sc(OTf)_3$ (10%)	1,2-DCE	84	55
3	$Y(OTf)_3$ (10%)	1,2-DCE	84	57
4	$La(OTf)_3$ (10%)	1,2-DCE	84	46
5	$Yb(OTf)_3$ (10%)	1,2-DCE	84	62
6	$Yb(OTf)_3$ (10%)	1,2-DCE	25	0
7	$Yb(OTf)_3$ (10%)	Toluene	90	46
8	$Yb(OTf)_3$ (10%)	DMF	90	0
9	$Yb(OTf)_3$ (10%)	THF	66	0
10	$Yb(OTf)_3$ (5%)	1,2-DCE	84	54
11	$Yb(OTf)_3$ (20%)	1,2-DCE	84	60
12	TfOH (20%)	1,2-DCE	84	20
13	TsOH (20%)	1,2-DCE	84	17

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), solvent (5 mL), reaction time (24 h), and the reaction was monitored using TLC. [b] Yield of the isolated product.

In general, the reaction proceeded smoothly with a broad spectrum of β-nitroalkenes **2**. Electron-rich (–OMe) and electron-deficient (–Cl, –Br) β-nitrostyrenes were well-tolerated, affording the corresponding 2-aryl furo[3,2-*c*]chromen-4-ones in 45–67% yields. Particularly, no significant effects were observed when altering the substituent to *meta*- or *ortho*-position (products **3e–3j**). It is notable to show that halogen groups, *e.g.*, –Cl and –Br, remained intact under these reaction conditions (products **3c**, **3d**, **3f**, **3g**, **3i**, and **3j**), which makes this transformation particularly attractive in terms of increasing the molecular complexity through transition metal-catalyzed crossing-coupling protocols. Encouragingly, disubstituted β-nitrostyrene was also successfully coupled with **1a** and generated the corresponding product **3k** in 67% yield. Subsequently, the suitability of 4-hydroxycoumarins was also tested under the standard conditions. Substituents including electron-withdrawing groups (*e.g.*, –F, –Cl, and –Br) and electron-donating groups (*e.g.*, –Me) at the 6-position of the phenyl ring were well tolerated, giving the corresponding products **3l–3o** in 44–68% yields. To our delight, the desired product **3p** was successfully obtained in 52% yield when altering the position of the methyl group.

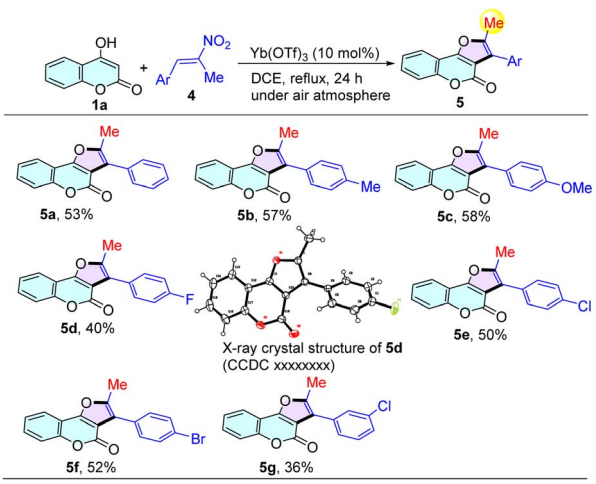
We next examined the structural diversity of various β-2-nitrophenylpropenes for the formation of 2,3-disubstituted furo[3,2-*c*]chromen-4-ones (Table 3). Substituents including electron-neutral (–Me), electron-rich (–OMe) and electron-deficient (–F, –Cl, –Br) β-2-nitrophenylpropenes at the *para*- and *meta*-positions of the benzene ring were well-tolerated, generating the desired products **5b–5g** in 36–58% yields. Moreover, the structure of the products **5d** (CCDC 2354856) was additionally confirmed by X-ray crystallographic analysis (see the ESI† for details).

Table 2 Substrate scope of 4-hydroxycoumarin with β-nitrostyrenes[a]



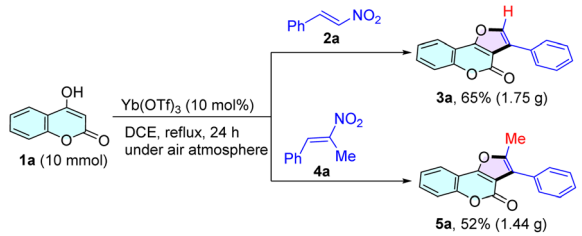
[a] Reaction conditions: 4-hydroxycoumarin **1** (0.5 mmol), β-nitrostyrenes **2** (0.5 mmol), and $Yb(OTf)_3$ (0.05 mmol) in 1,2-DCE (5 mL) at reflux under air atmosphere for 24 h. Isolated yields were reported.

Table 3 Substrate scope of 4-hydroxycoumarin with β-2-nitrophenylpropenes[a]

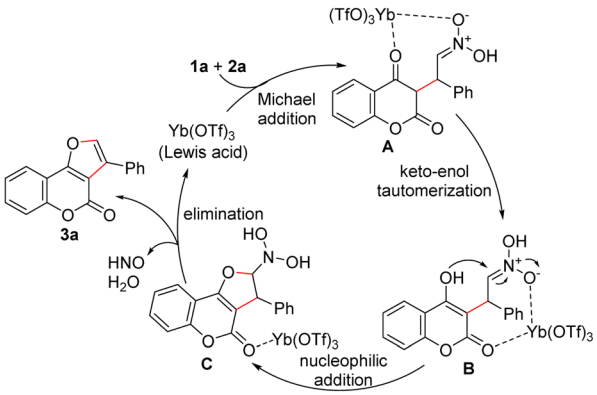


[a] Reaction conditions: 4-hydroxycoumarin **1** (0.5 mmol), β-2-nitrophenylpropenes **2** (0.5 mmol), and $Yb(OTf)_3$ (0.05 mmol) in 1,2-DCE (5 mL) at reflux under air atmosphere for 24 h. Isolated yields were reported.

To further explore the practical utility of this methodology as a synthetic tool, a scale-up synthesis of the products **3a** and **5a** was carried out under the standard conditions (Scheme 2).



Scheme 2 Scale-up synthesis of **3a** and **5a**.



Scheme 3 A possible mechanism for dehydrative annulations.

Encouragingly, this transformation could be scaled easily to 10.0 mmol to afford the desired products **3a** and **5a** without significantly compromising the yield, which showed promise for this synthetic strategy as a useful protocol in practical synthetic contexts.

Based on previous results obtained by other research groups,[18] a plausible mechanism for the $Yb(OTf)_3$-catalyzed cyclization reaction of 4-hydroxycoumarin with β-nitrostyrenes was proposed (Scheme 3). Initially, the intermediate **A** was generated from the Michael addition of 4-hydroxycoumarin **1a** to β-nitrostyrene **2a** in the presence of $Yb(OTf)_3$ and further underwent the keto–enol tautomerization to give the intermediate **B**. Subsequently, intramolecular nucleophilic addition of **B** would produce the intermediate **C**. Finally, the desired product **3a** was formed through the dehydration and elimination of hyponitrous acid (HNO).

Conclusions

In summary, we have successfully developed an $Yb(OTf)_3$-catalyzed formal [3 + 2] annulation of 4-hydroxycoumarins with β-nitroalkenes for modular access to furo[3,2-*c*]chromen-4-ones. Through this transformation, the furo[3,2-*c*]chromen-4-one framework was efficiently constructed, in which two new σ (C–C and C–O) bonds and a new furan ring were formed simultaneously in a single operation. This protocol features broad substrate scope, good functional groups, and without the need for inert atmosphere protection.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Conceptualization, H. Wang and X. He; methodology, H. Wang and Q. Ma; formal analysis, Y. Sun and S. Zhao; data curation, H. Wang and Y. Sun; writing – original draft preparation, H. Wang and Q. Ma; writing – review and editing, S. Wang and X. He; project administration, S. Wang and X. He; funding acquisition, S. Wang and X. He. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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