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KIO_3-catalyzed domino C(sp^2)-H bond sulfenylation and C-N bond oxygenation of enaminones toward the synthesis of 3-sulfenylated chromones

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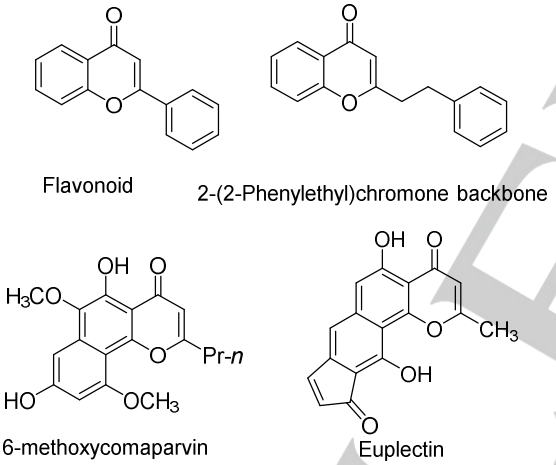
Abstract: Starting from 2-hydroxyphenyl functionalized enaminones and thiophenols, the facile synthesis of 3-sulfenylated chromones has been realized via KIO_3-catalyzed domino C-H bond sulfenylation and the subsequent C-N cleavage-based C-O bond formation in the bio-available green medium ethyl lactate (EL).

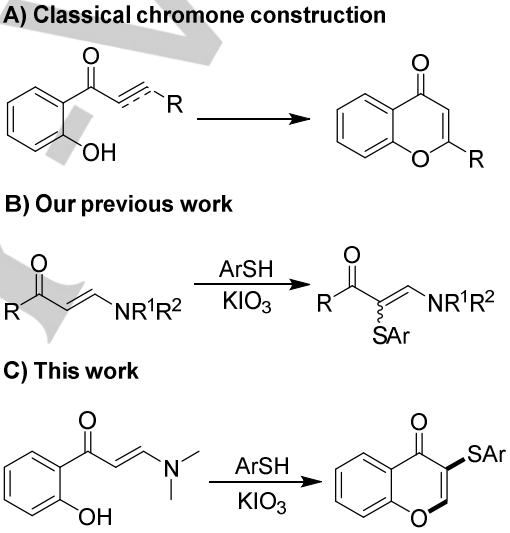
Introduction

Chromone heterocycle is a featured backbone in a huge number of valuable natural products and pharmaceuticals (Fig. 1).[1] This moiety is also crucial for the biological activities and functions of many complex molecules.[2] Moreover, the presence of the conjugate enone fragment and the reactive fused phenyl ring in the structure of chromones make them attractive as synthons in the generation of more structurally sophisticated organic



F igure 1 Several chromone-based natural products

products by means of various efficient organic transformations.[3] During the past decade, the synthesis of chromones has drawn extensive interest and won significant advances.[4] Presently, the available pathways toward the synthesis of chromone derivatives consist of two main prototypes: a) the direct elaboration of naturally or commercially available chromones;[5] b) domino reactions involving the construction of chromone ring and other bond transformation.[6] The former one, while theoretically simpler, suffers from the high cost and limited diversity of chromone substrates. On the other hand, as for the synthetic tactics involving the in situ chromone ring construction, the known reaction models are yet rather limited, especially in the synthesis of 3-substituted chromones since most known routes provide 2-substituted products (A, Scheme 1).[7]



Scheme 1 C(sp^2)-H sulfenylation and related chromone synthesis

Rather recently, we have successfully identified a novel transition metal-free catalytic protocol for the α-C(sp^2)-H sulfenylation reactions of β-enaminones for the synthesis of poly functionalized alknenes (B, Scheme 1),[8] which has also been gracefully complemented by other groups.[9] On the basis of our longstanding efforts in designing practical synthesis by making use of the combinatorial bond transformations of enaminones[10] as well as the elegant and versatile known synthesis based on the enaminone C-H functionalization,[11] we envision that combining the C(sp^2)-H sulfenylation and the C-N bond oxygenation with *o*-hydroxylphenyl functionalized enaminones would be a potentially applicable approach for the synthesis of 3-thiolated chromones. Herein, we report our work on this interesting new methodology toward 3-sulfenylated chromone synthesis under environmentally benign conditions consist of KIO_3 catalyst and green bio-based medium ethyl lactate (C, Scheme 1).[12]

Results and Discussion

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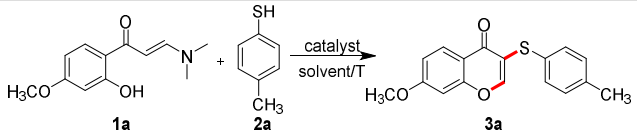
Originally, the reaction of enaminone **1a** and *p*-methyl thiophenol **2a** was conducted in the presence of different catalysts or catalyst-free condition in ethyl lactate (EL). The results showed that iodine-containing species, including KI, I_2, KIO_3 and $PhI(OAc)_2$ were capable of catalyzing the reaction to afford sulfenylated chromone **3a**, while blank entry and entry with TBHP didn't provide the product (entries 1-6, Table 1). In subsequent examination, reactions performed in different media such as DMF, toluene, MeCN, EtOH and water proved that none of these candidates was better than EL (entries 7-11, Table 1). Further investigation on the effect of catalyst loading and reaction temperature finally confirmed that 30 mol% KIO_3 and 60 °C were optimal reaction parameters, respectively (entries 12-16, Table 1).

Table 1 Optimization of reaction conditions.[a]



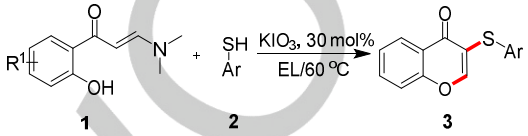
1a **2a** **3a**

Entry	Catalyst	Solvent	T (°C)	Yield (%)[b]
1	-	EL	90	nr
2	KI	EL	90	77
3	I_2	EL	90	71
4	KIO_3	EL	90	82
5	$PhI(OAc)_2$	EL	90	15
6	TBHP	EL	90	trace
7	KIO_3	DMF	90	80
8	KIO_3	toluene	90	12
9	KIO_3	MeCN	reflux	35
10	KIO_3	EtOH	reflux	22
11	KIO_3	H_2O	90	35
12[c]	KIO_3	EL	90	84
13[d]	KIO_3	EL	90	80
14[c]	KIO_3	EL	70	84
15[c]	KIO_3	EL	60	85
16[c]	KIO_3	EL	50	80

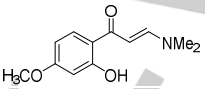
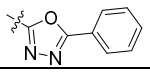
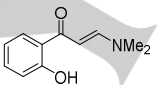
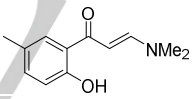
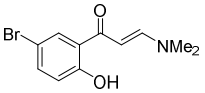
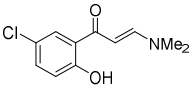
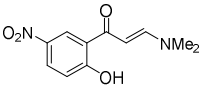
[a]General conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), catalyst (0.15 mmol) in 1.5mL solvent, stirred for 8 h. [b]Yield of isolated product. [c]Catalyst (0.09 mmol). [d]Catalyst (0.06 mmol).

In the section of scope examination, a broad array of thiophenols **2** as well as various enaminones **1** were employed, respectively, and afforded successfully diverse 3-thiolated chromone products **3** (Table 2). For the thiophenol component, similar yields of products were provided when different thiophenols was subjected to react with one same enaminone (see **3a**-**3g**, Table 1). Besides the generally good results employing conventional thiophenols, a notable point was that heteroaryl thiols also exhibited satisfactory tolerance to the synthetic protocol (**3f**, **3g**, Table 2). On the other hand, the strong electron withdrawing substitution on the enaminone was found to be negative by providing corresponding product with lower yield (**3z**, Table 2). No expect product was observed in the entry employing alkyl thiol such as propane-1-thiol.

Table 2 Scope of the transition metal-free domino reactions toward chromone synthesis.[a]



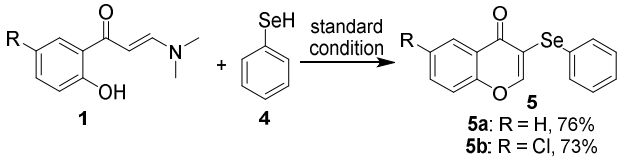
1 **2** **3**

Enaminone	Ar	Product	Yield (%)[b]
 **1a**	*p*-tolyl	**3a**	85
	p-i-PrC_6H_4	**3b**	85
	p-$MeOC_6H_4$	**3c**	83
	p-ClC_6H_4	**3d**	88
	o-tolyl	**3e**	80
	benzothiazole-2-yl	**3f**	81
		**3g**	80
 **1b**	Ph	**3h**	80(66)[c]
	p-tolyl	**3i**	83
	p-i-PrC_6H_4	**3j**	80
	p-$MeOC_6H_4$	**3k**	83
	p-ClC_6H_4	**3l**	86
	o-tolyl	**3m**	78
 **1c**	Ph	**3n**	84
	p-tolyl	**3o**	81
	p-i-PrC_6H_4	**3p**	82
	p-$MeOC_6H_4$	**3q**	85
	p-ClC_6H_4	**3r**	78
	p-BrC_6H_4	**3s**	80
 **1d**	Ph	**3t**	80
	p-tolyl	**3u**	77
	p-i-PrC_6H_4	**3v**	76
 **1e**	*p*-tolyl	**3w**	80
	p-i-PrC_6H_4	**3x**	79
	p-$MeOC_6H_4$	**3y**	82
 **1f**	*p*-tolyl	**3z**	76

[a]General conditions: enaminone **1** (0.3 mmol), thiol **2** (0.36 mmol) and KIO_3 (0.09 mmol) in 1.5 mL EL, stirred at 90 °C for 8 h; [b]Yield of isolated product based on **1**. [c]The yield in the parenthesis was acquired by employing 1,2-diphenyldisulfide as thio source at 80 °C.

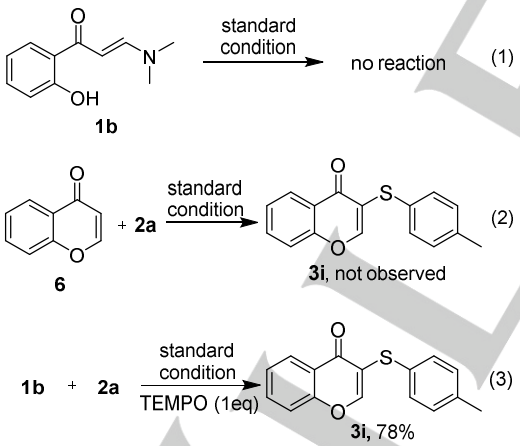
Notably, following the successful synthesis of 3-sulfenylated chromones via this domino reactions, the synthesis of equivalent

3-phenylselanylated chromones **5** were also found practical by simply employing benzeneselenol **4** as substrate under the standard reaction condition (Scheme 2)



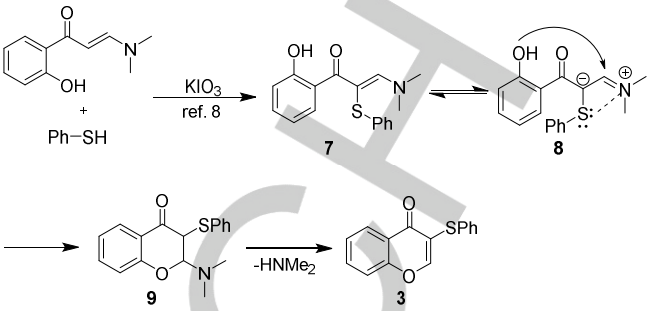
Scheme 2 Synthesis of 3-phenylselanylated chromones

To investigate the possible process of the reaction, several control experiments were designed. As outlined in Scheme 3, the first examination by subjecting only enaminone **1b** to the standard reaction condition afforded no reaction (Eq 1, Scheme 3), indicating that the C-N bond oxygenation was not practical in the absence of thiol component. In addition, the entry directly employing chromone **6** and thiophenol **2a** with standard reaction condition was found to be incapable of yielding target product **3i**, either (Eq 2, Scheme 3). The outcome also support that the annulation to chromone was not the initial step in the reaction. The attempts in isolating the sulfenylated acyclic product from the C-H sulfenylation of enaminone **1b** under the standard reaction conditions was not successful because of this intermediate may quickly undergo subsequent annulation to final product (see also Scheme 4). Additional experiment in the presence of TEMPO gave **3i** with 78% yield (Eq 3, Scheme 3), demonstrating that the reaction might not involve radical intermediates, which was in agreement with the case in previous work.[8]



Scheme 3 Control experiments

Based on the results from these control experiments, a concise reaction mechanism is proposed (Scheme 4). As mentioned in previous work,[8] the reaction between enaminone **1** and thiophenol first takes place to provide sulfenylated enaminone **7**. Consequently, the fast annulation based on the tautomeric intermediate **8** facilitates the formation of intermediate **9** via intramolecular addition of the hydroxyl to the imine fragment. The 3-thiolated chromone is finally generated via the elimination of dimethylamine on **9**.



Scheme 4 The proposed reaction mechanism

Conclusions

Conclusively, by employing a transition metal-free C(sp^2)-H sulfenylation as key transformation, we have designed a practical domino synthetic method towards the synthesis of 3-sulfenylated chromones. With only KIO_3 as catalyst, the reaction proceeds well in green solvent EL under mild heating to afford a broad array of 3-sulfenylated chromones. The features of sustainable green catalytic conditions as well as the easy availability of starting materials ensure the usefulness of the present method in the synthesis of these useful heterocyclic products.

Experimental Section

General procedure for the synthesis of **3** and **5**

To a round-bottom flask (10 ml) were added enaminone **1** (0.3 mmol), thiol **2**/benzeneselenol **4** (0.36 mmol), KIO_3 (0.09mmol) and ethyl lactate (1.5 mL). Then the resulting mixture was heated up to 60 ^oC, and stirred at the same temperature for 8 hours (TLC). After cooling down to room temperature, 5 mL of water was added, and the resulting mixture was extracted with ethyl acetate (3 × 8 mL). The organic phases were collected and washed with small amount of water for three times. After drying with anhydrous Na_2SO_4, the solid was filtered. The solvent was then removed under reduced pressure from the solution, and the resulting residue was subjected to flash silica gel column chromatography to provide pure products with the elution of mixed petroleum ether/ethyl acetate (v/v = 10:1).

Acknowledgements

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Keywords: Enaminone • domino • C-H sulfenylation • annulation • chromones

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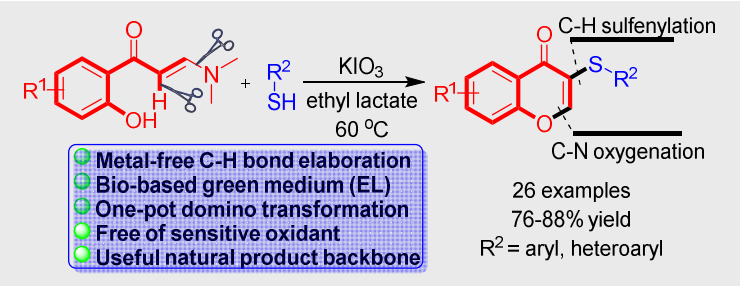

Chromone synthesis

*Shanshan Zhong, Yunyun Liu, Xiaoji Cao and Jie-Ping Wan**

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KIO_3-catalyzed domino C(sp^2)-H bond sulfenylation and C-N bond oxygenation of enaminones toward the synthesis of 3-sulfenylated chromones

The domino C-H sulfenylation and C-N cleavage-based annulation of enaminones lead to the concise construction of 3-sulfenylated chromones under transition metal-free condition.