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Iodine-mediated synthesis of sulfur-bridged enaminones and chromones via double C(sp^2)-H thiolation

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The reactions of various enaminones with elemental sulfur giving rise to both sulfur bridged enaminones and chromones have been realized via iodine promotion. All products were furnished by means of double C(sp^2)-H bond thiolation without using any metal catalyst or sensitive oxidant, providing a simple and efficient protocol for the synthesis of divergent sulfur derivatives of enaminones.

Introduction

Transition metal-catalyzed C-H activation reactions have won splendid success as powerful synthetic tactic during the last decade. It is inarguable that these catalytic transformations is now serving as indispensable tools in modern organic synthesis because of the inherent feature of step economy embedded in the direct transformation of naturally occurring C-H bonds.[1] On the other hand, in line with the transition metal-catalyzed models, the metal-free C-H bond cross coupling reactions have also emerged in recently years as highly significant strategy in the synthesis of numerous organic products.[2] Comparing with the transition metal-catalyzed C-H activation and other cross-coupling chemistry, the most notable features of the metal-free C-H bond elaboration are the low catalytic cost and free of trace metal contamination resulted from the metal catalysis, which is particularly crucial for the synthesis of biologically relevant organic compounds.[3] However, a major challenge in the metal-free C-H bond transformation is that most of the stable C-H bonds are hard to activate without the insertion of transition metal catalyst, which consequently restricts the designation of abundant applicable metal-free C-H elaboration approaches. In this context, developing more and greener methods allowing direct C-H transformation is currently highly demanding work.

Elemental sulfur is one of the most easily available raw chemicals with enriched storage in natural, and it is of high potential as "S" source in the synthesis of many sulfur-containing organic molecules.[4] Notably, elemental sulfur has in recent years found impressive application in the C-S bond formation reactions via various coupling protocols, by which a huge number of sulfur containing compounds have been synthesized. Interestingly, most of the known elemental sulfur-based C-S bond construction reactions are run with the catalysis of transition metal,[5] and transition metal-free methods enabling sulfur-based C-S bond formation are yet scarcely available.[6] Therefore, in order to further explore the potential of elemental sulfur in organic synthesis, developing practical coupling reactions forming C-S bonds without transition metal catalysis is of high significance.

Enaminones are synthons with ubiquitous application in organic synthesis, which enables synthesis of highly diverse types of organic products.[7] Accordingly, the synthesis of polyfunctionalized enaminones via the elaboration of simple enaminones has also attracted extensive research interest. One such elaboration route is the direct C-H functionalization of enaminones by employing either transition metal catalysis or transition metal-free tactic.[8] In 2016, our group has identified the first C-S bond forming reaction of enaminones via the catalysis of KIO_3 wherein thiophenols are used as the sulfenylating reagents,[9] and other groups later reported different catalytic approaches such as TBHP/TBAI catalysis [10] and palladium catalysis[11] for similar synthesis. Additionally, by making use of this featured transformation, we have recently accomplished the transition metal-free synthesis of 3-sulfenylated chromones via tandem C-H sulfenylation and intramolecular C-N bond oxygenation.[12] In continuous to our efforts in developing novel synthetic approaches based on the coupling transformation of the enaminone C-H bond,[13] we report herein the first elemental sulfur-based double C-H thiolation of enaminones with iodine promotion, which allows the facile and clean synthesis of various sulfur bridged enaminones and chromones.

Results and discussion

To start the investigation, the optimization on reaction conditions based on the model assembly of enaminone **1a**, *p*-methylaniline **2a** and sulfur powder **8**. The initial screening on various non-metal promoters, including TBHP, iodine, BPO and

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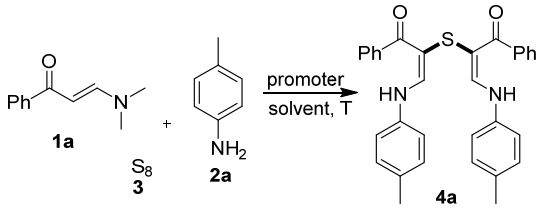
$PhI(AcO)_2$, proved that I_2 was the only applicable species enabling the expect double C-H thiolation to yield sulfur bridged enaminone product **4a** (entries 1-4, Table 1). The same reaction performed at different temperatures indicated that product **4a** was given with the optimal yield in the tested range (40-100 °C) at 90 °C (entries 5-8, Table 1). Subsequently, the entries in different reaction media such as DMSO, dioxane, elthyl lactate (EL) and toluene showed that each of these solvent could mediate the formation of **4a**, but all with inferior yield (entries 9-12, Table 1). In addition, the entries with either higher or lower loading of molecular iodine didn't lead to further increase in the product yield (entries 13-14, Table 1). Subsequently, the control entry conducted in the presence of 4 equiv. mole of TEMPO gave similarly high yield of **4a**, implying that the reaction did not involve free radical intermediate (entry 15, Table 1). And another entry performed under N_2 also gave similar **4a** with similar yield, suggesting that the presence of air did not impact the reaction (entry 16, Table 1).

Table 1 Optimization on reaction conditions[a]

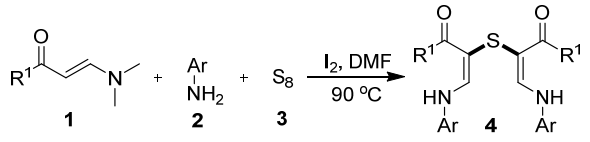


Entry	Promoter	Solvent	T (°C)	Yield[b] (%)
1	TBHP	DMF	60	trace
2	I_2	DMF	60	38
3	BPO	DMF	60	nr
4	$PhI(AcO)_2$	DMF	60	nr
5	I_2	DMF	40	31
6	I_2	DMF	80	56
7	I_2	DMF	90	67
8	I_2	DMF	100	65
9	I_2	DMSO	90	48
10	I_2	dioxane	90	51
11	I_2	EL	90	62
12	I_2	toluene	90	58
13[c]	I_2	DMF	90	63
14[d]	I_2	DMF	90	37
15[e]	I_2	DMF	90	64
16[f]	I_2	DMF	90	65

[a]General conditions: enaminone **1a** (0.2 mmol), amine **2a** (0.2 mmol), sulfur **3** (0.4 mmol) and promoter (0.1 mmol) in 2 mL solvent, stirred at 90 °C for 12 h. [b]Yield of isolated products base on **1a**. [c]The loading of I_2 was 0.2 mmol. [d]The loading of I_2 was 0.06 mmol. [e]Reaction in the presence of 0.8 mmol TEMPO. [f]Under N_2.

Following the work on reaction optimization, examination on the scope of this metal-free protocol toward the synthesis of sulfur bridged enaminones was carried out by subjecting different enaminones **1** and amines **2**. As shown in Table 2, when performed in 0.5 mmol substrate scale, the synthesis of sulfur bridged enaminones **4** was found with broad application scope. For the *N,N*-dimethyl enaminone **1**, the reactant with various substructures of functionalized phenyls, heteroaryl (**4i**, Table 2), alkyl (**4j**, Table 2) displayed general tolerance to the synthesis. On the other hand, the aryl primary amines, including those ones containing different types of substituents in *ortho*- *meta*- or *para*- site as well as heteroaryl amine (**4u**, Table 2) were also all applicable. However, alkyl amine was not able to provide corresponding *N*-alkyl product under the present condition. The products were mostly acquired with moderate to good yields, and relatively lower product yield occured in the entry using alkyl (R^1) functionalized enaminone (**4j**, Table 2).

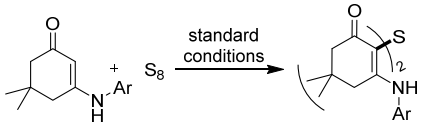
Table 2 The reaction of various enaminones and amines with sulfur powder[a]



R^1	Ar	Product	Yield[b] (%)
C_6H_5	4-MeC_6H_4	**4a**	69
4-MeC_6H_4	4-MeC_6H_4	**4b**	73
3-$MeOC_6H_4$	4-MeC_6H_4	**4c**	71
2-MeC_6H_4	4-MeC_6H_4	**4d**	65
4-ClC_6H_4	4-MeC_6H_4	**4e**	67
3,4-$MeO_2C_6H_3$	4-MeC_6H_4	**4f**	75
3,4-$Cl_2C_6H_3$	4-MeC_6H_4	**4g**	62
2-naphthyl	4-MeC_6H_4	**4h**	58
thiophen-2-yl	4-MeC_6H_4	**4i**	61
i-Butyl	4-MeC_6H_4	**4j**	52
C_6H_5	C_6H_5	**4k**	68
C_6H_5	2-MeC_6H_4	**4l**	64
C_6H_5	3-$MeOC_6H_4$	**4m**	70
C_6H_5	3-ClC_6H_4	**4n**	61
C_6H_5	3-$NO_2C_6H_4$	**4o**	57
C_6H_5	4-BrC_6H_4	**4p**	60
C_6H_5	4-FC_6H_4	**4q**	63
C_6H_5	4-IC_6H_4	**4r**	55
C_6H_5	4-$EtOCOC_6H_4$	**4s**	65
C_6H_5	2,4-$Me_2C_6H_3$	**4t**	74
C_6H_5	4-Mepyridin-2-yl	**4u**	56

[a]Conditions: enaminone **1** (0.5 mmol), amine **2** (0.5 mmol), sulfur **3** (1.0 mmol), I_2 (0.25 mmol) in 2 mL DMF, heating at 90 °C for 12 h. [b]Yield of isolated product based on enaminone **1**.

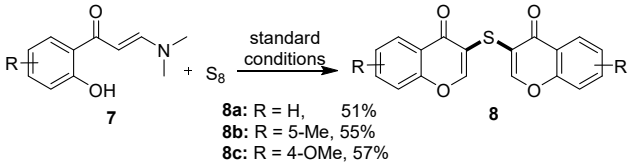
As the efforts in exploring the expanded application, some *NH*-enaminones **5** containing cyclohexenone structure were then employed to the standard catalytic conditions for the potential synthesis of sulfur bridged cyclic enaminones. While such products could only be accessed via copper-catalyzed enaminone C-H thiolation in known literature,[5i] we were delight to find that our metal-free catalytic approach was found to be practically applicable for the synthesis of target products **6** with fair yields (Scheme 1).



6a: Ar = Ph, 58%
6b: Ar = 4-ClC_6H_4, 53%

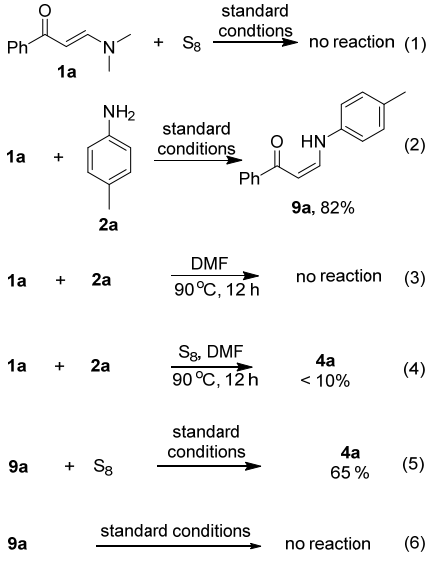
Scheme 1 The synthesis of sulfur bridged cyclohexenone-based enaminones

Interestingly, when *o*-hydroxylphenyl functionalized enaminones **7** was employed as the enaminone substrate, the standard catalytic condition enabled the formation of sulfur bridged chromones **8** as products (Scheme 2). Unlike the synthesis of **4** and **6**, the construction of **8** involved in the annulations based on the intramolecular C-N bond oxygenation and the double C-H thiolation. However, it should be noted that reaction giving **8** was sensitive to the functional group in the substrates **7**. The enaminone containing electron withdrawing group such as chlorine atom in the phenyl ring of **7**, for example, was not able undergo the reaction to yield corresponding sulfur bridged chromone product.



Scheme 2 Synthesis of sulfur bridged chromones

In order to gain some information in the possible reaction process, a series of control experiments were conducted. First, the N,N-dimethyl enaminone **1a** was found not reactive when subjected with sulfur powder under standard reaction conditions (Eq 1, Scheme 3). On the other hand, the reaction of **1a** and primary amine **2a** reacted smoothly to give *NH*-based enaminone **9a** with high yield (Eq 2, Scheme 3). No reaction took place between the two substrates without using iodine (Eq 3, Scheme 3). An additional entry of the model reaction without using iodine led to the formation of the target sulfur bridged enaminone **4a** with very low yield (Eq 4, Scheme 3), suggesting that iodine was crucial for the titled double C-H thiolation reaction. On the other hand, using directly the *NH*-enaminone **9a** and elemental sulfur gave target product **4a** with reasonable yield (Eq 5, Scheme 3), supporting that the transamination in Eq (2) was the initial



Scheme 3 Control experiments

step for the cascade reaction. Finally, running the reaction of **9a** with iodine by standard treatment gave no isolable iodinated species (Eq 6, Scheme 3), implying that iodine may act as Lewis acid and do not participate the redox transformation.

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Conclusions

In conclusion, by employing elemental sulfur as "S" source and iodine as promoter, we have successfully achieved the double C-H thiolation reaction of enaminones, which allowed the environmentally benign and economical synthesis of sulfur bridged enaminones and chromones. The metal- and sensitive oxidant-free conditions as well as the open air operation featured in this synthetic method ensure its high usefulness in the synthesis of these elaborated enaminones and chromones.

Experimental section

General procedure for the synthesis of sulfur bridged enaminones 4

To a 25 mL round-bottom flask were added enaminone **1** (0.5 mmol), amine **2** (0.5 mmol), sulfur powder **3** (1.0 mmol), I_2 (0.25 mmol) and DMF (2 mL). Then the mixture was heated up to 90 °C, and stirred at the same temperature for 12 hours under air atmosphere (TLC). After cooling down to room temperature, 5 mL of water was added, and the resulting mixture was extracted with ethyl acetate. The organic phases were collected and washed with small amount of water. After drying with anhydrous Na_2SO_4, the solid was filtered and the solvent was removed at reduced pressure. 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).

General procedure for the synthesis of sulfur bridged enaminones 6 and chromones 8

To a 25 mL round-bottom flask were added enaminone **5** or **7** (0.5 mmol), sulfur powder **3** (1.0 mmol), I_2 (0.25 mmol) and DMF (2 mL). Then the mixture was heated up to 90 °C, and stirred at the same temperature for 12 hours under air atmosphere (TLC). After cooling down to room temperature, 5 mL of water was added, and the resulting mixture was extracted with ethyl acetate. The organic phases were collected and washed with small amount of water. After drying with anhydrous Na_2SO_4, the solid was filtered and the solvent was removed at reduced pressure. 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).

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