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Metal-free oxidative carbonylation on enaminone C=C bond for the cascade synthesis of benzothiazole-containing vicinal diketones

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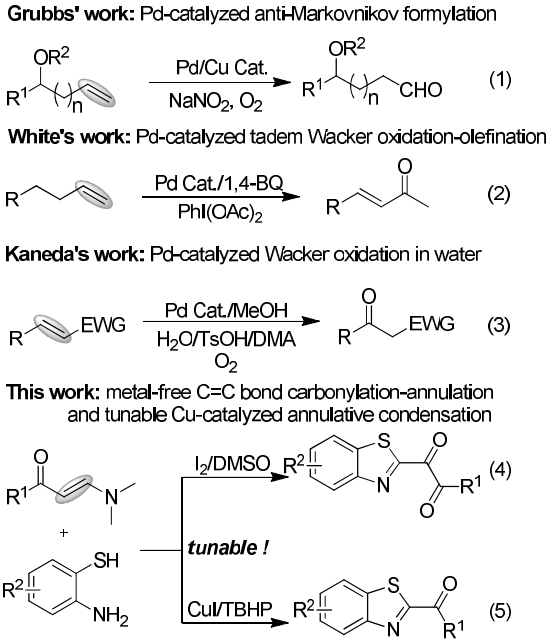
The cascade reactions between enaminones and *o*-aminothiophenols have been implemented to provide unprecedented vicinal diketones containing benzothiazole structure. The construction of the products have been realized under metal-free conditions via carbonylation on the C=C double bond of the enaminone. The tunable synthesis of 2-aroylbenzothiazoles has been achieved by using identical starting materials under modified reaction conditions.

Carbonylation is a fundamental and indispensable transformation in organic synthesis because of the numerous applications of the carbonyl functional group in organic synthesis. While the classical carbonylation tactics such as the coupling reactions using directly the CO sources (e.g. carbon monoxide), and the oxidative carbonylation on prior decorated functional groups have been dominantly employed in the synthesis of carbonyl products, the contemporary emphasis on chemical sustainability has stimulated the new trend in the carbonylation chemistry by the direct conversion of raw chemical bonds such as carbon-hydrogen and carbon-carbon bonds.[1] A readily available and practical carbonyl precursor of such kind is the C=C double bond. In conventional knowledge, the C=C double bonds usually undergo carbonylation in the form of full bond cleavage in the presence of potent oxidants such as ozone etc.[2] This oxidation model involves in the co-production of undesirable waste during the decomposition of the C=C bond, which results in urgent requirement on discovering alternative routes without fully cutting off the C=C bond. As the representative example of this kind, the Wacker–Tsuji oxidation provides a distinct option for the synthesis of carbonyl compounds by generating carbonyl without fragmentation of the C=C double bond.[3] This alkene-based carbonylation has recently exhibited fantastic application in a variety of practical organic synthesis. For example, Grubbs et al. have developed the aldehyde synthesis via the anti-Markovnikov reaction of alkenes by Pd-catalyzed olefin oxidation (Eq 1, Scheme 1).[4] White and Bigi reported the tandem Wacker oxidation/dehydrogenation reaction as a powerful tool for the synthesis of enones (Eq 2, Scheme 1).[5] Meanwhile, Kaneda et al have achieved a facile protocol for functionalized ketone synthesis via Pd-catalyzed Wacker oxidation on electron deficient alkenes (Eq 3, Scheme 1).[6]



Scheme 1 Typical organic synthesis based on alkene carbonylation

In light of the significant progress in the alkene-based oxidative carbonylation, tremendous interest has been inspired to the designation of carbonylation-based organic synthesis by employing alkenes as precursors. As a class of easily available and stable alkene derivatives, enaminones have displayed numerous applications in synthetic chemistry by participating the construction of various organic products.[7] However, in known literature, the majority of enaminone-based syntheses

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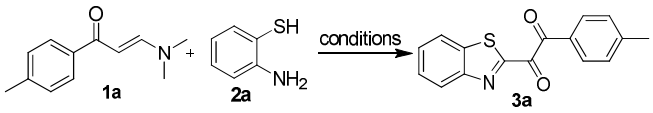
Electronic Supplementary Information (ESI) available: [General experimental information, experimental procedure for product synthesis, full characterization data, ^{1}H and ^{13}C NMR spectra of all products]. See DOI: 10.1039/x0xx00000x

take place via the conversion of C-H bond, C-N bond, C=O bond and/or the amino group,[8] and synthesis based on the activation of the C=C double bond of the enaminones has been barely explored. Although Wasserman and co-workers have reported the light induced enaminone C=C bond cleavage early in 1980s,[9] rare attention has been paid to the synthesis via the cleavage of enaminone C=C bond for a long period. It is in rather recent years that the invaluable application of tailoring the enaminone C=C bond in organic synthesis has been disclosed. In 2014, Li and Wu groups have discovered that the partial cleavage of enaminone C=C double bond permits the synthesis of useful α-amino esters by transition metal induced photocatalysis in the presence of alcohol, repectively.[10] Our group have previously realized different cascade reactions towards the synthesis of pyridines[11a] and quinoxalines[11b] initiated by the enaminone C=C double bond cleavage. In the process of our continuous exploration on the synthesis via the activation of enaminone C=C double bond, we report herein the first example on the metal-free cascade synthesis of 1,2-diketones containing benzothiazole backbone (Eq 4, Scheme 1) and the tunable copper-catalyzed synthesis of 2-aroyl benzothiazoles (Eq 5, Scheme 1) via selective partial and complete C=C bond cleavage, respectively.

Initially, the reaction of enaminone **1a** and o-aminothiophenol **2a** was tentatively conducted in the presence of different catalysts. These experiments disclosed that Lewis acid such as iron-, copper and palladium salts as well as Brønsted acid such as TsOH could both catalyze the cascade transformation to give diketone **3a**, however, molecular iodine displayed higher catalytic efficiency than any other candidate (entries 1-5, Table 1). Subsequent examination on the effect of reaction temperature proved that 110 °C was proper for the reaction (entries 6-7, Table 1). Further efforts in varying the reaction temperature as well as reaction medium of different polarity did not provide improved yield of the target product (entries 8-14, Table 1). It was notable that a control experiment performed under N_2 atmosphere could produce only trace amount of **3a**, suggesting the indispensable role of air (oxygen) as the oxidant in the reaction (entry 15, Table 1).

The scope of the method for the synthesis was investigated by using both structurally diverse enaminones and o-aminothiophenols. The typical results on the synthesis of benzothiazole containing vicinal diketones via this cascade process were shown in Table 2. Under the catalysis of molecular iodine, a broad array of benzothiazole-based vicinal ketones were acquired with fair to good yields. A tendency exhibited in these reactions was that enaminones containing electron withdrawing group usually gave lower yield of corresponding products (**3f** and **3g**, Table 2) probably because of the lower stability of related radical intermediates during the oxidation. In terms of the diversity, a notable fact was that the heteroaryl-based enaminone such as thiophen-2-yl

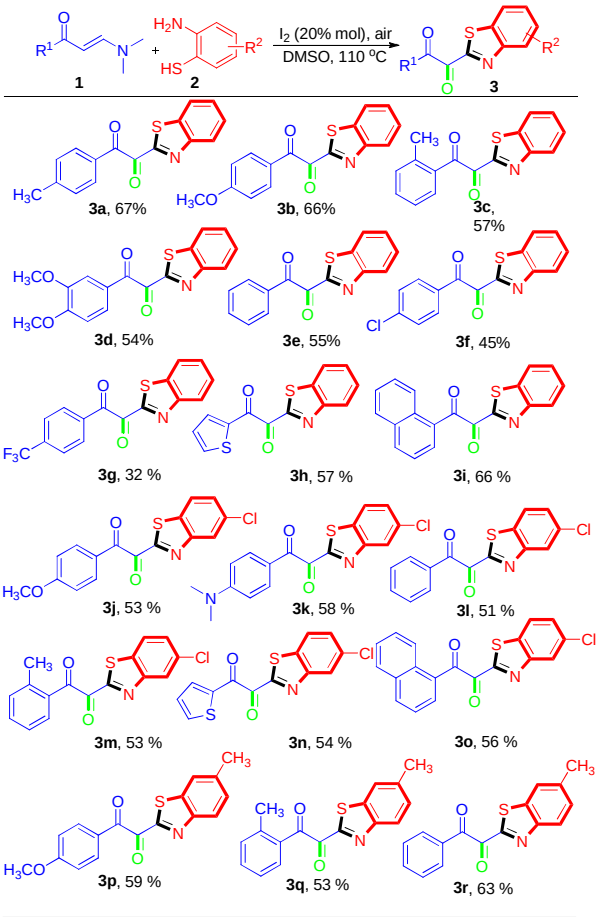
Table 1 Optimization on reaction conditions[a]



Entry	Catalyst	Solvent	T(°C)	Yield(%)[b]
1	$FeCl_3$	DMSO	120	51
2	CuI	DMSO	120	47
3	$Pd(AcO)_2$	DMSO	120	36
4	TsOH	DMSO	120	41
5	I_2	DMSO	120	55
6	**I_2**	**DMSO**	**110**	**67**
7	I_2	DMSO	100	29
8[c]	I_2	DMSO	110	50
9[d]	I_2	DMSO	110	54
10	I_2	DMF	110	trace
11	I_2	ethyl lactate	110	trace
12	I_2	toluene	110	16
13	I_2	dioxane	reflux	19
14	I_2	CH_3CN	reflux	trace
15[e]	I_2	DMSO	110	trace

[a]Unless otherwise specified, the reaction conditions are: **1a** (0.3 m mol), **2a** (0.3 m mol), catalyst (0.06 mmol) in 2 mL of solvent(s), stirred for 12 h at an air atmosphere. [b]Yield of isolated products based on A. [c]The I_2 was 0.03 mmol. [d]The I_2 was 0.09 mol. [e]The reaction was run under nitrogen atmosphere.

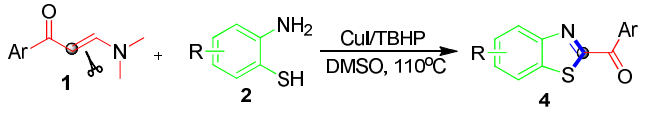
Table 2 Scope for of the metal-free cascade synthesis of vicinal diketones[a,b]



[a]Unless otherwise specified, the reaction conditions are: enaminone **1** (0.3 mmol), aminothiophenol **2** (0.3 mmol), I_2 (0.06mmol) and DMSO (2 mL) stirred at 110 °C for12 h at an air atmosphere. [b]Yield of isolated products based on enaminone.

functionalized enaminone exhibited tolerance to the synthesis (**3h** and **3n**, Table 2). Meanwhile, the application of alkyl-based enaminone was not achieved in the synthesis of corresponding diketones. Further attempts on using either *o*-aminophenol or *o*-phenylenediamine as the alternative substrate of *o*-aminothiophenol, however, failed to provide expect vicinal diketones probably because of the much weaker nucleophilicity of both hydroxyl and amino group than the thiol group. The structure of diketones was clearly assigned by abundant spectroscopic analysis and the X-ray single crystal analysis on **3i**.[12]

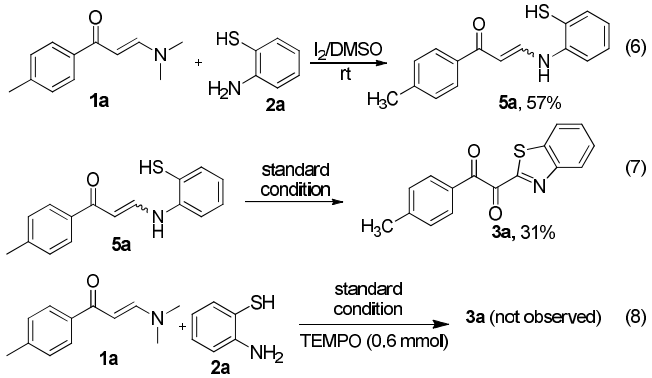
After demonstrating the general applicability of the metal-free diketone synthesis via the assembly of o-aminothiophenols and enaminones **1**, we subsequently forwarded our effort to explore the possible catalytic method for the synthesis of 2-aroyl benzothiazoles, which was expect to show distinct reactivity of these enaminones. After comprehensive endeavour in screening the reaction conditions (see supporting information), we were delighted to find that the catalytic system of CuI/TBPH/DMSO was able to promote the selective formation of various 2-aroyl benzothiazole via the C=C bond cleavage of enaminone. The extended investigation disclosed that the selective cascade reactions under the modified conditions enabled the synthesis on an array of 2-aroyl benzothiazoles **4**. Both carbon aryl and heteroaryl functionalized enaminones were successfully employed in this synthesis, providing corresponding products with generally moderate yields. on the other hand, the attempts in synthesizing similar 2-acylbenzothiazole by employing corresponding alkyl functionalized enaminone was not successful (Scheme 2).



4a, Ar = Ph, R = H, 54%;
4b, Ar = 4-$MeOC_6H_4$, R = H, 51%;
4c, Ar = 4-MeC_6H_4, R = H, 53%;
4d, Ar = 3,4-$(OCH_2O)C_6H_3$, R = H, 54%;
4e, Ar = 4-ClC_6H_4, R = H, 57%;
4f, Ar = 4-FC_6H_4, R = H, 61%
4g, Ar = 4-$CF_3C_6H_4$, R = H, 59%
4h, Ar = 4-$CF_3C_6H_4$, R = 4-Cl, 52%
4i, Ar = thiophen-2-yl, R = H, 48%
4j, Ar = naphth-1-yl, R = H, 52

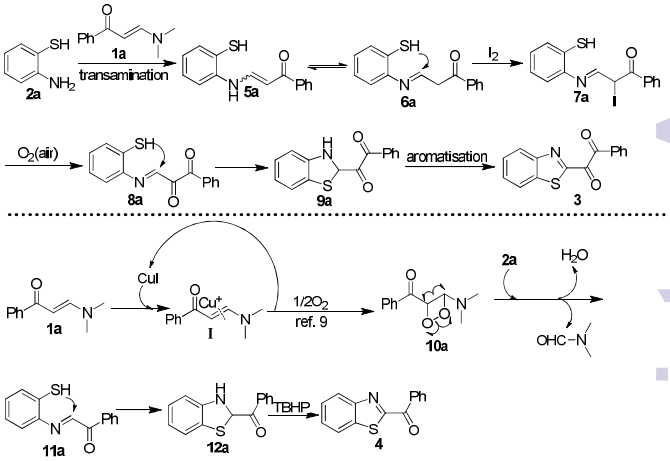
Scheme 2 Tunable synthesis of 2-arolbenzothiazoles

Following the successful discovery on the tunable synthesis of both benzothiazole functionalized vicinal diketones and 2-aroylbenzothiazoles, we designed some control experiments to explore the reaction mechanism. Firstly, we managed to prepare an intermediate of type **5a** by lowering the reaction



temperature to room temperature (Eq 6). Subsequently, the employment of **5a** to standard catalytic conditions smoothly provide target product **3a** with fair yield (Eq 7). Additionally, the control experiment in the presence of **2** equiv mole TEMPO was not able to provide **3a**, suggesting that the radical pathway was inhibited.

According to these results, we were able to propose the possible mechanism of the reactions as showing in Scheme 3. Taking the reaction of o-aminothiophenol **2a** and enaminone **1a** for example, in the synthesis of vicinal diketones, the reaction was initiated by the transamination between the amino group in **2a** and enaminone **1a** to provide intermediate **5a**[13] which presented partially in the form of isomeric **6a**. The methylene C-H bond in **6a** could be readily iodinated in the presence of molecular iodine, and the aerobic oxidation of the C-I bond in **7a** then led to the formation of diketone intermediate **8a**. Finally, the thiol addition to imine and the subsequent aromatization produced benzothiazole containin diketone **3a**. On the other hand, the copper-catalyzed tunable synthesis of 2-aroylbenzothiazoles begun from the transition state **I** which enabled the air oxidation on the C=C double bond to form cyclic peroxide intermediate **10a**. In the presence of aminothiophenol **2a**, the C-C bond cleavage on **10a** led to the production of iminoketone **11a** and released N,N-dimethylformamide. The synthesis of 2-aroylbenzithiazole **4** was realized in the presence TBHP via intramolecular annulations and oxidation.



Scheme 3 The postulated reaction mechanism

Conclusions

In conclusion, by employing simple enaminones and *o*-aminothiophenols as starting materials, the first example on the synthesis of benzothiazole-based vicinal diketones has been achieved via the cascade transformations involving the partial cleavage of enaminone C=C double bond under metal-free condition. Besides, the modification on reaction condition has been successfully accomplished to selectively yield 2-aroylbenzothiazoles via the full cleavage of the same C=C bond. The results represent not only new routes for the synthesis c these useful heterocyclic molecules, but more importantly

disclose the novel reactivity possessed by enaminones via the rarely noticed C=C bond activation.

Acknowledgments

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Metal-free oxidative carbonylation on enaminone C=C bond for the cascade synthesis of benzothiazole−containing vicinal diketones

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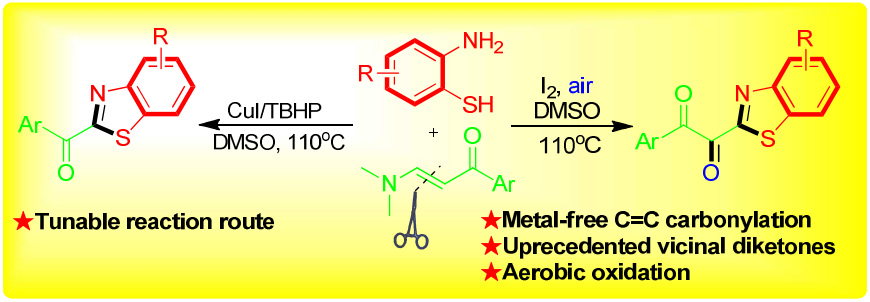

The tunable synthesis of benzothiazole functionalized vicinal diketones and 2-aroylbenzothiazoles have been realized by tailoring the enaminone C=C double bond.