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I_2-Catalyzed C−O Bond Formation and Dehydrogenation: Facile Synthesis of Oxazolines and Oxazoles Controlled by Bases

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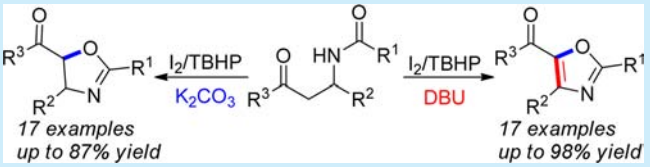
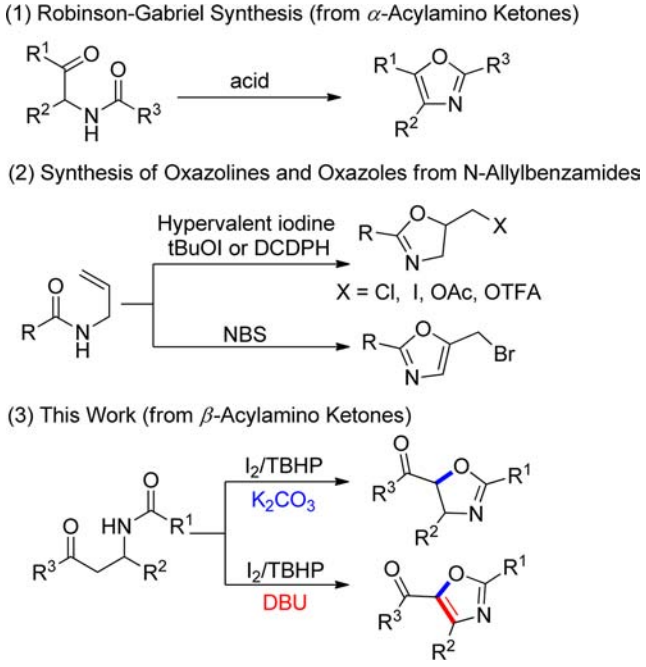
Supporting Information

ABSTRACT: A general method for the synthesis of oxazolines and oxazoles was developed through I_2-catalyzed C−O bond formation and dehydrogenation with the same oxidant, TBHP. By simply tuning reaction bases, either oxazolines or oxazoles were selectively produced from β-acylamino ketones.



Oxazole and oxazoline derivatives are ubiquitous heterocycles found in a wide range of natural products, pharmaceuticals, and agrochemicals, and enantiomerically pure oxazolines also serve as effective chiral sources or ligands for asymmetric transformations.[1] Their diverse biological activities and synthetic applications have stimulated substantial interest in the synthesis of these important heterocycles. Many synthetic strategies have been developed for the preparation of oxazoles and oxazolines,[2] with one of the most straightforward strategies being intramolecular cyclization of amide precursors.[3] Particularly, cyclodehydration of α-acylamino ketones promoted by Brønsted or Lewis acids, which is called the Robinson−Gabriel synthesis, is a classic method for the preparation of oxazoles (Scheme 1, (1)).[4] *N*-Allylbenzamides are common substrates for producing oxazoles and oxazolines via oxidative cyclization via different methods (Scheme 1, (2)). Thus, direct synthesis of oxazolines from *N*-allylbenzamides can be readily achieved using hypervalent iodine reagents, *t*BuOI or 1,3-dichloro-5,5-diphenylhydantoin.[5] In 2012, the first example of oxazole synthesis from *N*-allylbenzamides with NBS as the oxidant was reported.[6] Although oxazoles and oxazolines can be separately prepared from *N*-allylbenzamides using different methods, there has never been a general route to access both oxazoles and oxazolines from common substrates using the same oxidant. In addition, although oxazolines can be converted to oxazoles with various oxidants, such as activated MnO_2,[7] NiO_2,[8] $CBrCl_3$,[9] CuBr,[10] DDQ,[11] NBS,[12] etc.,[13] these methods often suffer from the use of metal or hazardous halo reagents,[7−10] excess amounts of oxidant,[11,12] or high reaction temperatures (>100 °C).[13] Therefore, conversion of oxazolines to oxazoles under mild and metal-free conditions is still in high demand.

Scheme 1. Synthetic Methods for Oxazolines and Oxazoles



Molecular iodine or iodide (TBAI) has recently emerged as a promising catalyst for C−O bond formation due to its "metal-like" character without the toxicity, supply, or cost issues of transition-metal salts.[14] In 2010, Ishihara and co-workers pioneered the intramolecular cycloetherification of ketones using the quaternary ammonium iodide/H_2O_2 system,[14a] and their asymmetric version was also applied to the enantioelective synthesis of tocopherols.[14b] Furthermore, the intra- and intermolecular α-oxyacylation of ketones involving iodide-catalyzed C−O bond formation can also be realized with TBHP or H_2O_2 as the co-oxidant.[14c] Inspired by these works, it occurred to us that if acylamino groups were located at the β-position of ketones, polysubstituted oxazolines might be constructed via iodine-catalyzed C−O bond formation. As a continuation of our work in iodine-mediated transformation,[15] herein, we report an intramolecular cyclization of ketones for the synthesis of oxazolines by I_2-catalyzed C−O bond formation with TBHP as the terminal oxidant in the presence of K_2CO_3. Furthermore, by tuning K_2CO_3 to DBU, the construction of oxazoles via I_2-catalyzed C−O bond formation and dehydrogen-

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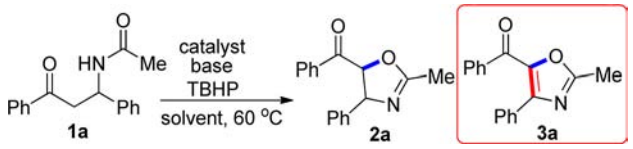
ation could also be achieved efficiently (Scheme 1, (3)). To the best of our knowledge, this is the first example of access to both oxazoles and oxazolines from common substrates using the same oxidant.

Initially, 3-acetylamino-1,3-diphenylpropan-1-one (**1a**) was chosen as a model substrate to explore the reaction conditions needed for oxazoline formation. Oxidative cyclization took place, and oxazoline **2a** was isolated in 22% yield in the presence of I_2 (10 mol %), KOH (2 equiv), and TBHP (3 equiv) in THF (Table 1, entry 1). Control experiments indicated that no cyclization occurred in the absence of iodine or any base (entries 2 and 3). A series of bases were then screened for this transformation (entries 4–8). We found that the yield of this model reaction could be increased to 82% when K_2CO_3 was used as the base (entry 6). Organic bases were also tried for this reaction, but **2a** was only obtained in 38% yield with the use of DABCO. However, when the base DBU was used, no oxazoline was detected, while oxazole **3a** was isolated as the sole product (95% yield), which indicated that further dehydrogenation catalyzed by iodine occurred in the present reaction system (entry 8).[16] Other commonly used solvents were also tested for this reaction (entries 9–11), but none of them gave a better result for C–O bond formation. Furthermore, an attempt to use other salts such as TBAB, TBAI, KI, NaI, or NIS as a catalyst also gave less effective results than iodine (entries 12–16). Notably, the present reaction could be effectively scaled up to gram scale with similar efficiency (1.06 g, with 80% yield for the model reaction) (entry 17), suggesting that the present oxidative cyclization could be employed as a practical method to access this kind of polysubstituted oxazoline.

Table 1. Optimization of the Reaction Conditions for the Synthesis of Oxazoline[a]



entry	catalyst	base	solvent	yield (%)[b]
1	I_2	KOH	THF	22
2	I_2		THF	0
3		KOH	THF	0
4	I_2	Cs_2CO_3	THF	39
5	I_2	Na_2CO_3	THF	70
6	I_2	K_2CO_3	THF	82
7	I_2	DABCO	THF	38
8[c]	I_2	DBU	THF	0
9	I_2	K_2CO_3	MeOH	trace
10	I_2	K_2CO_3	MeCN	62
11	I_2	K_2CO_3	EtOAc	71
12	TBAB	K_2CO_3	THF	10
13	TBAI	K_2CO_3	THF	66
14	KI	K_2CO_3	THF	74
15	NaI	K_2CO_3	THF	81
16	NIS	K_2CO_3	THF	80
17[d]	I_2	K_2CO_3	THF	80

[a]Reaction conditions: 0.3 mmol of **1a**, 0.03 mmol of catalyst, 0.6 mmol of base, 0.9 mmol of TBHP (70% in water), in 2 mL of solvent, at 60 °C for 2–4 h. [b]Isolated yield. [c]**3a** was isolated in 95% yield. [d]Reaction was run on a 5 mmol scale.

With the optimal reaction conditions in hand (Table 1, entries 6 and 8), the generality of base-induced switchable access to oxazolines and oxazoles was then investigated (Table 2). In all cases, oxazoline **2** and oxazole **3** were selectively produced from the corresponding β-acylamino ketones using different bases. First, the substituents on the aroyl moiety of β-acylamino ketones were examined, and products containing either electron-donating or electron-withdrawing substituents could be furnished in good to excellent yields (entries 1–5). Other aromatic rings such as naphthyl, furyl, and thienyl groups were all tolerated, and the desired products were obtained in good to high yields (entries 6–8). For the substituents on the aryl rings, the present transformations were also compatible for electron-donating, electron-withdrawing, and naphthyl groups (entries 9–13). Notably, the substrate bearing a *p*-nitrophenyl group only gave the desired products in moderate yields due to its strong electron-withdrawing ability (entry 10). When R^2 was replaced by a methyl group, the reaction also proceeded well and gave the desired products in moderate to good yield (46% for **2n** and 77% for **3n**) (entry 14). However, replacement of R^3 and R^2 with a methyl group failed to produce either oxazoles or oxazolines.[16] In addition, the present transformations also proceeded well when the acetyl group in the substrates was changed to the bulky aroyl groups, which made this methodology applicable to the synthesis of 2-aryl oxazolines and oxazoles (entries 15–17).

To gain insight into the reaction mechanism, a few control experiments were conducted.[16] The addition of radical scavengers such as TEMPO, BHT, and cyclohexadiene did not retard the oxidative cyclization of **1a** under standard conditions, which indicated that the cyclization might not proceed through a radical pathway. The oxidative cyclization also did not occur in the presence of a stoichiometric amount of I_2 under neutral conditions, which suggested that I_2 was not the actual oxidant species for the C–O bond formation. To elucidate the conversion of oxazolines to oxazoles, a one-pot reaction for the synthesis of **3a** was carried out (Scheme 2): after the reaction of **1a** under conditions A for 1 h, the addition of 2 equiv of DBU led to **3a** in 78% yield. This experiment strongly confirmed the formation of intermediate oxazoline for oxazole synthesis and that DBU played important roles in the conversion of oxazolines to oxazoles.

On the basis of the results of our control experiments and related work, a tentative mechanism is proposed in Scheme 3. According to Ishihara's studies,[14a–c] the oxidation of I_2 with TBHP might produce an active species, $[IO]^-$, which could be further oxidized by TBHP to the potential actual oxidant species, $[IO_2]^-$.[17] β-Acetylamino ketone **2a** could possibly react with $[IO_2]^-$ to give an intermediate **A**, which undergoes intramolecular cyclization to produce **2a** and the reductive form $[IO]^-$. When DBU is used as the base, an active iodoimine intermediate **B** could be generated via the disproportionation of I_2 in the presence of DBU,[18] followed by the reaction with **2a** to form the α-iodo intermediate **C**. Subsequent elimination of HI with DBU would provide the oxazole **3a** and release HI for the next cycle.

The present oxidative cyclization for the synthesis of polysubstituted oxazolines provides an easy access to other useful organic blocks (Scheme 4, eq 2). For example, the hydrolysis of **2a** with HCl (1.2 M) yielded the α-hydroxyl-β-amino ketone **4**, which has served as a versatile intermediate in various organic syntheses.[19] Furthermore, the present dehydrogenation was also suitable for other kinds of oxazoline: the treatment of oxazoline **5** with 10 mol % of I_2, 1 equiv of DBU, and

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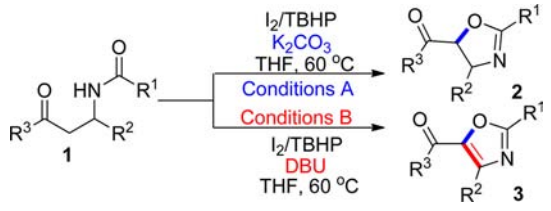
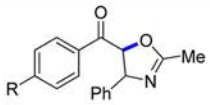
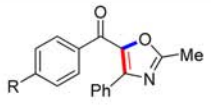
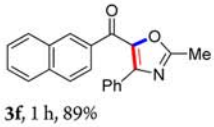
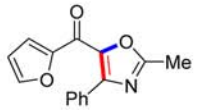
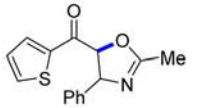
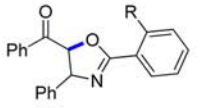
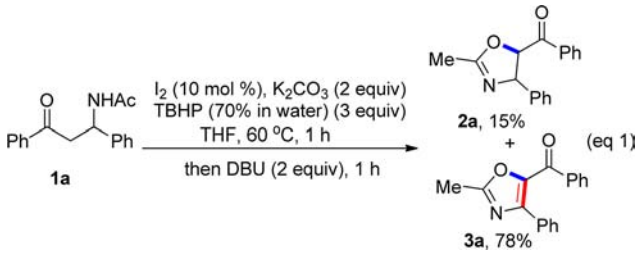
Table 2. Substrate Scope of Oxazoline and Oxazoline Construction[a]



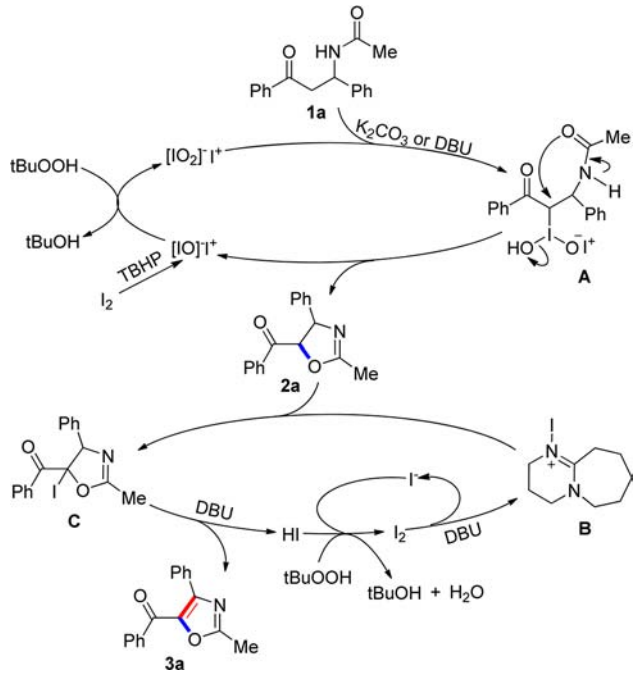
entry	2[b]	3[b]
1	 R = H, **2a**, 4 h, 82%	 R = H, **3a**, 4h, 95%
2	R = Cl, **2b**, 4 h, 85%	R = Cl, **3b**, 2 h, 82%
3	R = Br, **2c**, 4 h, 67%	R = Br, **3c**, 2 h, 76%
4	R = Me, **2d**, 4 h, 77%	R = Me, **3d**, 2 h, 85%
5	R = OMe, **2e**, 4 h, 78%	R = MeO, **3e**, 2 h, 98%
6	 **2f**, 5 h, 66%	 **3f**, 1 h, 89%
7	 **2g**, 4 h, 70%	 **3g**, 2 h, 80%
8	 **2h**, 4 h, 63%	 **3h**, 1 h, 74%
9	 R = 4-MeC$_6$H$_4$, **2i**, 4 h, 83%; **3i**, 2 h, 82%	
10	R = 4-NO$_2$C$_6$H$_4$, **2j**, 4 h, 67%; **3j**, 2 h, 57%	
11	R = 2-MeOC$_6$H$_4$, **2k**, 5 h, 83%; **3k**, 2 h, 88%[c]	
12	R = 2-ClC$_6$H$_4$, **2l**, 5 h, 87%; **3l**, 1 h, 86%	
13	R = 2-naphthyl, **2m**, 4 h, 78%; **3m**, 2 h, 77%	
14	R = Me, **2n**, 4 h, 46%;[d] **3n**, 2 h, 77%	
15	 R = H, **2o**, 4 h, 80%	 R = H, **3o**, 2 h, 90%
16	R = Cl, **2p**, 4 h, 81%	R = Cl, **3p**, 2 h, 94%
17	R = Me, **2q**, 4 h, 55%	R = Me, **3q**, 2 h, 81%

[a]Conditions A: 0.3 mmol of **1**, 0.03 mmol of I_2, 0.6 mmol of K_2CO_3, 0.9 mmol of TBHP (70% in water), in 2 mL of THF, stirred at 60 °C. Conditions B: 0.3 mmol of **1**, 0.03 mmol of I_2, 0.6 mmol of DBU, 0.9 mmol of TBHP (70% in water), in 2 mL of THF, stirred at 60 °C. [b]Reaction time and isolated yields of products are shown. [c]Reaction was run with 1.2 mmol of TBHP and 0.9 mmol of DBU. [d]Conversion: 57%.

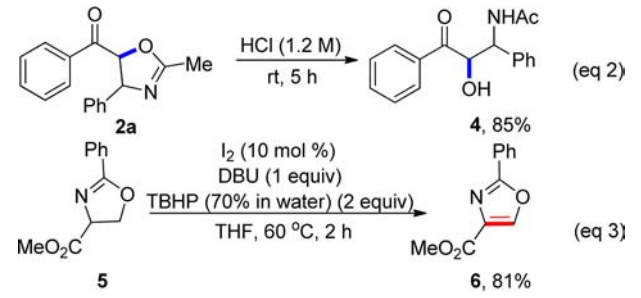
Scheme 2. One-Pot Synthesis of Oxazole 3a



Scheme 3. Tentative Mechanism



Scheme 4. Hydrolysis of 2a and Oxidation of 5



2 equiv of TBHP gave rise to the corresponding oxazole **6** in 81% yield (Scheme 4, eq 3), which demonstrated the potential of this method for the conversion of oxazolines to oxazoles.

In summary, we have developed a general method for the synthesis of oxazolines and oxazoles from *β*-acylamino ketones by I_2-catalyzed C−O bond formation and dehydrogenation. The selectivity of products was controlled using either K_2CO_3 or DBU as the base. This facile method has the advantage of broad substrate scope, mild reaction conditions, and high efficiency. Furthermore, the oxidative dehydrogenation catalyzed by I_2 has also provided a reliable alternative for oxazoline oxidation. Further work exploring the utility of this method and elucidation of the detailed mechanism is underway and will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01933.

Experimental procedures, optimization of reaction conditions, characterization data, copies of ^{1}H NMR and ^{13}C NMR of products (PDF)

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Notes

The authors declare no competing financial interest.

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