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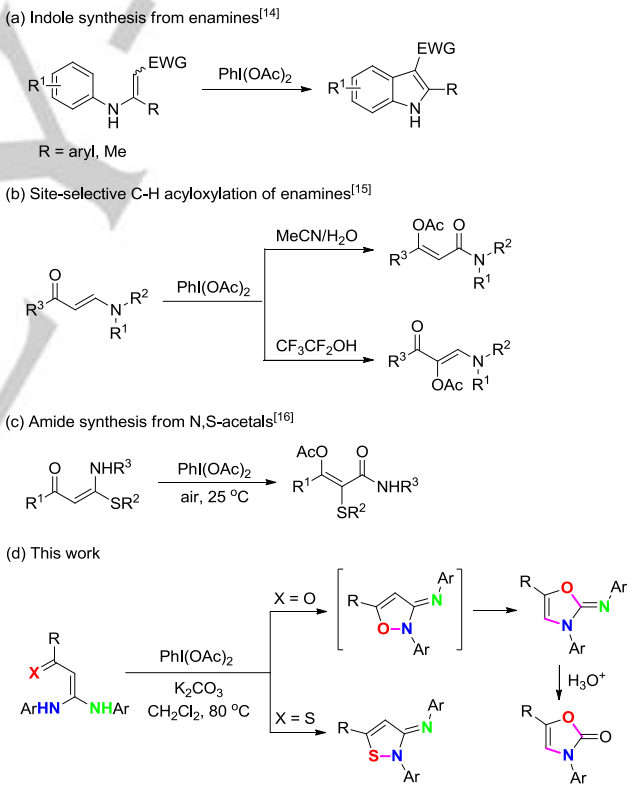
PIDA-Mediated Formal Olefinic C=C Bond Cleavage of α-Oxo Ketene N,N-Acetals toward Substituted Oxazolines

Tenglong Guo,[a] Fei Huang,[a] Quanbin Jiang,[a] and Zhengkun Yu*[a,b]

Abstract: Hypervalent iodine reagent $PhI(OAc)_2$ (PIDA) mediated formal oxidative C=C bond cleavage and subsequent cyclization of internal olefins, that is, α-oxo ketene N,N-acetals, affording substituted oxazolines. Isothiazoline derivatives were obtained from the reactions of α-thioxo ketene N,N-acetals with PIDA under the same conditions. Hydrolysis of the resultant oxazoline derivatives led to highly functionalized oxazolones. A plausible mechanism is proposed based upon the formation of isothiazoline-type intermediates.

Functionalization of olefins is an essential organic transformation in the fields of pharmaceuticals, agrochemicals, and materials science.[1] Among the diverse olefinic transformation methodologies, C=C bond cleavage occupies a particularly significant position in terms of building complex molecules from relatively simple raw materials.[2] For example, ring-closing metathesis (RCM) processes of olefins offer an efficient approach to cyclic hydrocarbons under transition-metal catalysis.[3] Various carbonyl-containing products were also accessed through the oxidative C=C bond cleavage.[4] Although significant progresses have been made in this area, the relevant synthesis of heterocyclic compounds has seldomly been documented under transition metal-free conditions. Substituted oxazolines are one of the common substructures in a wide variety of biologically active compounds, synthetic intermediates, and pharmaceuticals.[5] Consequently, various synthetic methods have been developed to access an oxazoline core.[6] However, there have been only a few scattered reports on the formation of 2-imino-1,3-oxazolines, which are regarded as the precursors of oxazolones widely existing in a number of natural products and pharmacological active compounds.[7] Condensation of α-haloketones and symmetrical diarylureas in the presence of bromine gives 2-aryl-imino-3-aryl-1,3-oxazolines.[8] Cathodic reduction of mono-imines with *N*-arylcarbonimidoyl dichlorides affords tetraaryl-iminooxazolines.[9] Reacting ketenimines with hydroxylamino derivatives to produce 2-imino-1,3-oxazolines.[10] Transition-metal-catalyzed reactions of alkyl diazoacetates with carbodi-imides or α-hydroxyketones can also be applied for the same purpose.[11,12] Unfortunately, these methods often encounter the issues such as low atom efficiency, high cost of toxic transition-metal catalysts, and lack of regioselectivity or structural diversity of the products.

Owing to the easiness of preparation and low toxicity as compared with transition-metal oxidants, hypervalent iodine reagents have been extensively used in modern organic synthesis.[13] Regarding iodo(III)-promoted oxidative transformations of amino-functionalized alkenes, Zhao, et al. developped a C–C bond formation strategy for indole synthesis *via* PIDA-mediated oxidization of *N*-aryl enamines (Scheme 1a).[14] Recently, Loh and Jiang group[15] reported highly site-selective C–H acyloxylation of enamines with PIDA, giving solvent-dependent α- and β-site-selective products (Scheme 1b). In a similar manner, synthesis of amides assisted by vicinal alkylthio migration of α-oxo ketene N,S-acetals was achieved by our group (Scheme 1c).[16]



Scheme 1. PIDA-Mediated Transformations of Functionalized Enamines.

During our ongoing investigation of functionalized internal olefins, that is, α-oxo ketene S,S-acetals[17] and N,S-acetals,[18] as versatile building blocks in organic synthesis,[16,19] we reasonably envisioned that their analogs α-oxo ketene N,N-acetals[20] might be utilized for the synthesis of functionalized heterocycles. Herein, we disclose PIDA-mediated olefinic C=C bond cleavage and cyclization of α-oxo ketene N,N-acetals for the synthesis of substituted oxazolines (Scheme 1d).

Initially, the reaction of α-benzoyl ketene N,N-acetal (**1a**) with PIDA was conducted to optimize the reaction conditions (Table 1). Treatment of **1a** with PIDA (1.2 equiv) in CH_2Cl_2 at ambient

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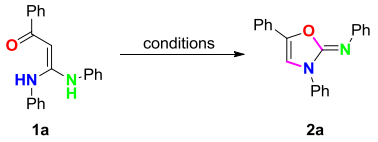
temperature afforded the target product **2a** in 32% yield (Table 1, entry 1). Elevating temperature obviously improved the reaction efficiency to form **2a** (64%) at 80 °C (Table 1, entries 1-3). CH_2Cl_2 acted as the most suitable solvent among those screened, i.e., DCE, dioxane, and DMF (Table 1, entries 4-6). Both $PhI(TFA)_2$ and $K_2S_2O_8$ could not initiate the reaction, and the reaction did not occur without PIDA (Table 1, entry 7). Variation of the amount of PIDA revealed that 1.2 equiv of PIDA was the suitable loading of the oxidant for the desired reaction (Table 1, entries 3, 8, and 9). A base was beneficial to the reaction, and **2a** was obtained in 74% yield in the presence of K_2CO_3 (Table 1, entries 10-12).

Table 1. Screening of reaction conditions.[a]



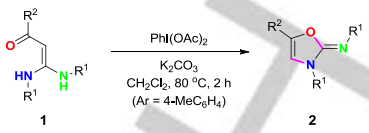
1a **2a**

Entry	Temp [°C]	Solvent	Oxidant	Base	Yield[b] [%]
1	25	CH_2Cl_2	$PhI(OAc)_2$		32
2	60	CH_2Cl_2	$PhI(OAc)_2$		42
3	80	CH_2Cl_2	$PhI(OAc)_2$		64
4	80	DCE	$PhI(OAc)_2$		48
5	80	dioxane	$PhI(OAc)_2$		50
6	80	DMF	$PhI(OAc)_2$		48
7	80	CH_2Cl_2			0
8[c]	80	CH_2Cl_2	$PhI(OAc)_2$		62
9[d]	80	CH_2Cl_2	$PhI(OAc)_2$		58
10	80	CH_2Cl_2	$PhI(OAc)_2$	Na_2CO_3	69
11	80	CH_2Cl_2	$PhI(OAc)_2$	K_2CO_3	74
12	80	CH_2Cl_2	$PhI(OAc)_2$	K_3PO_4	71

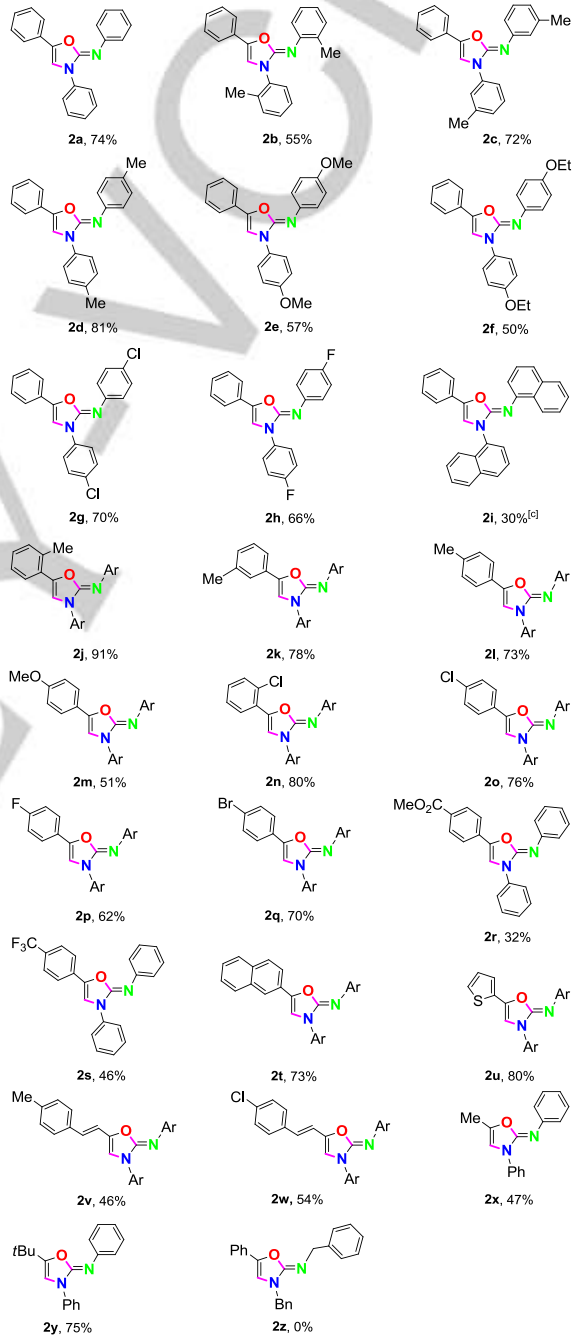
[a] Conditions: **1a** (0.2 mmol), oxidant (0.24 mmol), base (0.4 mmol), solvent (1.5 mL), in air, 2 h. The reaction was performed in a sealed 10-mL Pyrex glass screw-cap tube. [b] Isolated yield. [c] PIDA (0.2 mmol). [d] PIDA (0.3 mmol). PIDA = $PhI(OAc)_2$.

Next, the substrate scope of α-oxo ketene N,N-acetals (**1**) was explored under the optimized conditions (Table 2). A steric effect of methyl on the aryl moiety of the arylamino (NHAr) functionality was observed, leading to 2-, 3-, and 4-methyl-substituted products **2b** (55%), **2c** (72%), and **2d** (81%), respectively. The electronic effect from both electron-donating 4-OMe and 4-OEt groups was remarkable, which diminished the reaction efficiency in the formation of **2e** (57%) and **2f** (50%), while electron-withdrawing 4-Cl and 4-F-substituted aniline-derived N,N-acetals reacted well with PIDA to give **2g** (70%) and **2h** (66%) in good yields. 1-Naphthyl group exhibited an obvious steric effect on the yield of product **2i** which could only be obtained in 30% yield by extending the reaction time to 6 h. However, the methyl group on the aryl ring of the α-aroyl functionality in **1** exhibited an steric effect opposite to that on the NHAr moiety, facilitating the formation of **2j** (91%), **2k** (78%), and **2l** (73%). 4-OMe group in the aroyl moiety did not favor the reaction, resulting in **2m** in 51% yield. The 2-Cl and 4-Cl substi-

Table 2. Scope of α-Oxo Ketene N,N-Acetals **1**.[a,b]



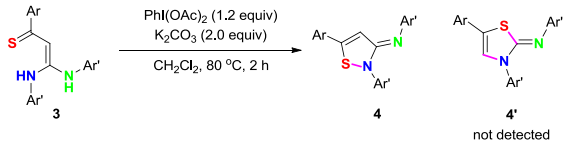
1 **2**

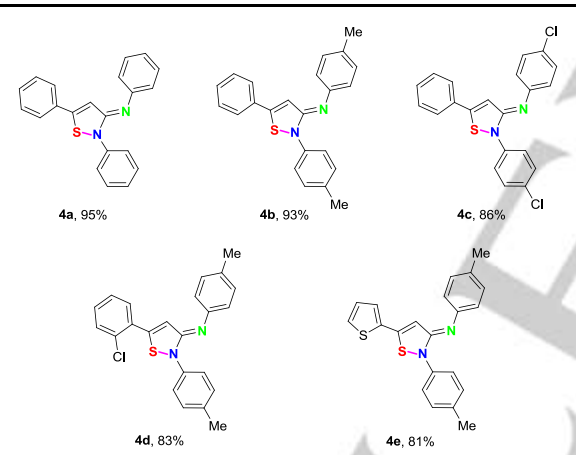


[a] Conditions: **1** (0.3 mmol), $PhI(OAc)_2$ (0.36 mmol), K_2CO_3 (0.6 mmol), CH_2Cl_2 (2.5 mL), 80 °C, air, 2 h. The reactions were performed in a sealed 10-mL Pyrex glass screw-cap tube. [b] Yields refer to the isolated products. [c] 6 h.

tuents promoted the formation of **2n** (80%) and **2o** (76%), while 4-Br and 4-F groups behaved less efficiently to render the production of **2p** and **2q** in 62-70% yields. However, the strong electron-withdrawing groups such as ester and trifluoromethyl on the aryl group diminished the formation of **2r** (32%) and **2s** (46%). 2-Naphthoyl did not exhibit a negative impact on the yield of **2t** (73%). To our delight, α-(2-thienoyl) N,N-acetal also efficiently reacted with PIDA to form **2u** (80%). However, as compared to the corresponding α-aroyl substrates **1l** and **1o**, α-alkenoyl N,N-acetals **1v** and **1w** only exhibited a lower reactivity to generate **2v** (46%) and **2w** (54%), respectively. Although α-acetyl N,N-acetal **1x** could not effectively react with PIDA to afford **2x** (47%), its α-pivaloyl analog **1y** demonstrated a good reactivity to form **2y** (75%). It should be noted that N-benzyl and other aliphatic amine-derived α-oxo ketene N,N-acetals did not undergo the same type of reactions.

Table 3. Synthesis of isothiozolines **4**.[a]





[a] Conditions: 3 (0.2 mmol), $PhI(OAc)_2$ (0.24 mmol), K_2CO_3 (0.4 mmol), CH_2Cl_2 (1.5 mL), 80 °C, air, 2 h. The reactions were performed in a sealed 10-mL Pyrex glass screw-cap tube. Yields refer to the isolated products.

To further demonstrate the synthetic application of the present protocol, α-thioxo N,N-acetals of type **3** were employed to react with PIDA under the same conditions (Table 3). Unexpectedly, isothiazoline derivatives **4a-4e** that are potentially biologically active and pharmaceutically useful[21] were obtained in 81-95% while the analogs of oxazolines **2**, that is, thiazolines **4'**, were not detected from the reaction mixtures of **3** with PIDA. It is noteworthy that the molecular structures of compounds **2** and **4** were further confirmed by the X-ray single crystal structural determinations of compounds **2d** and **4b** (Fig.s 1 and 2, see the Supplementary Information for details).

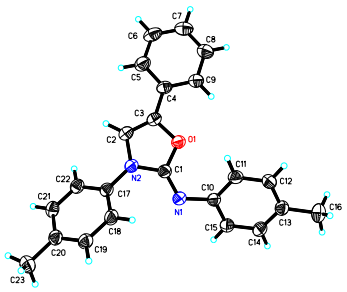


Figure 1. Molecular structure of compound **2d**.

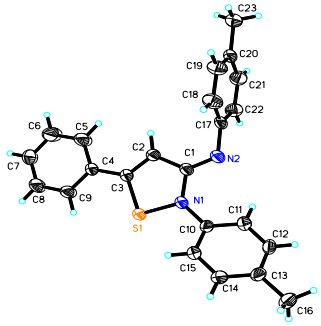
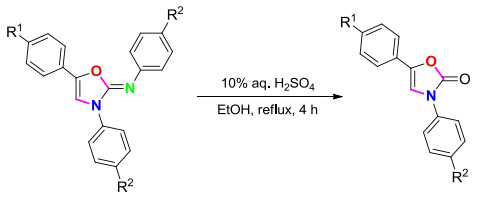
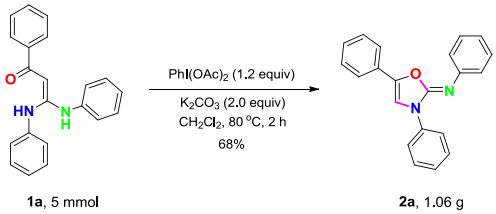


Figure 2. Molecular structure of compound **4b**.

2-Imino-functionalized oxazolines **2** were regarded as the precursors to oxazolones. Thus, compounds **2** were treated with 10% aqueous H_2SO_4 to be hydrolyzed [Eq. (1)], efficiently affording the corresponding oxazolone products **5a-5b** (80-85%) that are potentially useful building blocks in organic synthesis.[7] Such a transformation has been demonstrated that the present method is an alternative to access diverse oxazolone derivatives.



(1)

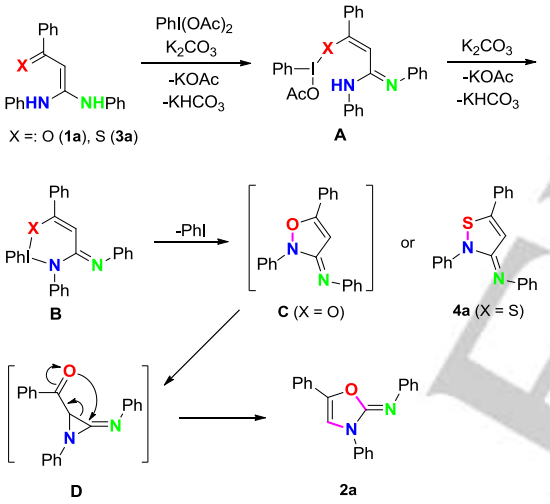


(2)

To further demonstrate the application potential of this synthetic strategy, a gram-scale reaction was conducted. The

reaction of **1a** (5 mmol, 1.56 g) proceeded smoothly under the standard conditions to afford **2a** (1.06 g) in 68% yield [Eq. (2)].

A plausible mechanism is proposed in Scheme 2. Initially, an amidine intermediate is formed upon enolization of the carbony or thiocarbonyl of substrate **1a** or **3a**, then interacts with PIDA to generate intermediate **A**[22] by loss of one molecule of acetic acid. Nucleophilic attack of the anilide nitrogen atom at the hypervalent iodo(III) center forms species **B**. The in situ generated HOAc was neutralized by K_2CO_3 base to prevent the intermediates and/or products **2a** or **4a** from decomposition under the acidic conditions. Subsequent reductive elimination of PhI yields iminoisoxazoline **C** or isothiazoline **4a**. Due to the instability of the N–O bond under the reaction conditions, intermediate **C** undergoes further Baldwin-rearrangement[23] to afford oxazoline **2a** through olefinic C=C bond cleavage/ cyclization of iminoacyl-aziridine species **D**. The formation of isothiazoline has suggested that the N-S bond in **4a** is stable under the stated conditions, whereas the N–O bond in isoxazoline **C** can not withstand the reaction conditions and thus undergoes further N–O cleavage reaction to form oxazoline **2a**.



Scheme 2. Proposed mechanism.

In summary, an efficient method has been developed to synthesize substituted oxazolines via PIDA-mediated olefinic C=C bond cleavage/cyclization of α-oxo ketene N,N-acetals. The methodology can also be applied to access isothiazolines from the corresponding α-thioxo ketene N,N-acetals. The high atom economy with use of cheap PIDA as the oxidant under transition metal-free conditions makes the synthetic protocol be environmentally benign.

Experimental Section

General procedure for the synthesis of 2

Synthesis of 2a: In a sealed 10-mL Pyrex glass screw-cap tube, a mixture of 1-phenyl-3,3-bis-(phenylamino)prop-2-en-1-one (**1a**) (94 mg, 0.3 mmol), $PhI(OAc)_2$ (116 mg, 0.36 mmol) and K_2CO_3 (83 mg, 0.6 mmol) in 2.5 mL CH_2Cl_2 was stirred at 80 °C under an air atmosphere for 2 h. After cooled to ambient temperature, 5 mL CH_2Cl_2 was added and the resultant mixture was filtered through a short pad of celite, followed by rinsing with 10 mL CH_2Cl_2. The combined filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60-90 °C)/EtOAc/ CH_2Cl_2 (15:1:1, v/v/v)) to afford **2a** as a white solid (69 mg, 74%).

Acknowledgements

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Keywords: PIDA • C=C Bond Cleavage • Internal Olefins • Oxazolines • Isothiazoline

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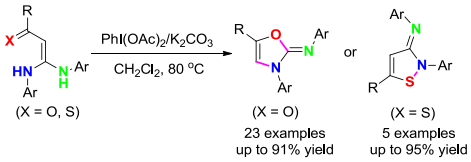

Formal Olefinic C=C Bond Cleavage! PIDA mediated oxidative formal C=C bond cleavage and subsequent cyclization of α-oxo ketene N,N-acetals, affording substituted oxazolines. Isothiazoline derivatives were obtained from the reactions of α-thioxo ketene N,N-acetals with PIDA under the same conditions. Hydrolysis of the resultant oxazoline derivatives led to highly functionalized oxazolone.

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PIDA-Mediated Formal Olefinic C=C Bond Cleavage of α-Oxo Ketene N,N-Acetals toward Substituted Oxazolines