Hypervalent Iodine

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

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Abstract: The hypervalent iodine reagent PhI(OAc)₂ (PIDA) mediated the formal oxidative C=C bond cleavage and subsequent cyclization of internal olefins, that is, α-oxo-ketene N,N-acetals, which afforded 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 was 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 progress has been made in this area, the relevant synthesis of heterocyclic compounds has seldom 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-iminoxazolines.[9] Reacting keteniminic with hydroxylamino derivatives produces 2-imino-1,3-oxazolines.[10] Transition-metal-catalyzed reactions of alkyl diazoacetates with carbodimides or α-hydroxyketones can also be applied for the same purpose.[11, 12] Unfortunately, these methods often encounter 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 and co-workers developed a C=C bond-forming strategy for indole synthesis through PIDA-mediated oxidation of N-aryl enamines (Scheme 1a).[14] Recently, Loh, Jiang and co-workers[15] reported highly site-selective C–H acylationlation of enamines with PIDA, giving solvent-dependent α- and β-site-selective products (Scheme 1b). In a similar manner, synthesis of amides assisted

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by vicinal alkylthio migration of α-oxo-ketene N,S-acetals was achieved by our group (Scheme 1c).

During our ongoing investigation of functionalized internal olefins, that is, α-oxo-ketene S,S-acetals and N,S-acetals, we reasonably envisioned that their analogs, α-oxo-ketene N,N-acetals, might be utilized for the synthesis of functionalized heterocycles. Here, 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$_2$Cl$_2$ at ambient 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$_2$Cl$_2$ acted as the most suitable solvent among those screened, for example 1,2-dichloroethane (DCE), 1,4-dioxane, and DMF (Table 1, entries 4–6). Both PhI(TFA)$_2$ (TFA = trifluoroacetate) and K$_2$S$_2$O$_8$ 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 for the reaction, and 2a was obtained in 74% yield in the presence of K$_2$CO$_3$ (Table 1, entries 10–12).

Next, the substrate scope of α-oxo-ketene N,N-acetals (1) was explored under the optimized conditions (Table 2). A steric effect of a methyl group on the aryl moiety of the arylamino (NHAr) functionality was observed, leading to 2b (55%), 2c (72%), and 2d (81%), respectively. The electronic effect from both electron-donating and electron-withdrawing groups on the aryl moiety was apparent in the steric effect for the formation of 2a (74%), 2b (78%), 2c (76%), and 2d (70%).
donating 4-OMe and 4-OEt groups was remarkable, which diminished the reaction efficiency in the formation of 2e (57%) and 2f (50%), whereas electron-withdrawing 4-Cl and 4-F-substituted N,N-acetals reacted well with PIDA to give 2g (70%) and 2h (66%) in good yields. The 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-aroylfuntionality in 1 exhibited a steric effect opposite to that on the NHAr moiety, facilitating the formation of 2j (91%), 2k (78%), and 2l (73%). A 4-OMe group in the α-aroyl moiety did not favor the reaction, resulting in 2m in 51% yield. The 2-Cl and 4-Cl substituents promoted the formation of 2n (80%) and 2o (76%), whereas 4-Br and 4-F groups behaved less efficiently to render the production of 2p and 2q in 62–70% yields. However, the strongly electron-withdrawing groups such as an ester or a trifluoromethyl moiety on the aryl group diminished the formation of 2r (32%) and 2s (46%). A 2-naphthyl moiety did not exhibit a negative impact on the yield of 2t (73%). To our delight, α-(2-thiencyl)-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 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.

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, which are potentially biologically active and pharmaceutically useful,[21] were obtained in 81–95% whereas the analogs of oxazolines 2, that is, thiazolines 4’, were not detected in the reactions 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 (Figures 1 and 2, see the Supporting Information for details).

2-Imino-functionalized oxazolines 2 were regarded as the precursors to oxazolones. Thus, compounds 2 were treated with 10% aqueous H$_2$SO$_4$ to undergo hydrolysis [Eq. (1)], which efficiently afforded the corresponding oxazolone products 5a–5b (80–85%) that are potentially useful building blocks in organic synthesis.[7] Such a transformation demonstrates that the present method is an alternative to access diverse oxazolone derivatives.
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 carbonyl or thiocarbonyl of substrate 1a or 3a. Then the amidine 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 is neutralized by K₂CO₃ base to prevent the intermediates and/or products 2a or 4a from decomposition under the acidic conditions. Subsequent reductive elimination of Ph 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 the iminocarbonyl-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 cannot withstand the reaction conditions and thus undergoes further N–O cleavage reaction to form oxazoline 2a.

In summary, an efficient method has been developed to synthesize substituted oxazolines through 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 the use of cheap PIDA as the oxidant under transition-metal-free conditions makes the synthetic protocol environmentally benign.

Experimental Section

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, 0.33 mmol), PIDA (116 mg, 0.36 mmol), and K₂CO₃ (83 mg, 0.60 mmol) in 2.5 mL CH₂Cl₂ was stirred at 80 °C under air for 2 h. After cooling to ambient temperature, CH₂Cl₂ (5 mL) was added and the resulting mixture was filtered through a short pad of Celite, followed by rinsing with CH₂Cl₂ (10 mL). 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/ CH₂Cl₂, (15:1:1, v/v/v)] to afford 2a as a white solid (69 mg, 74%).

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Conflict of interest

The authors declare no conflict of interest.

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