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ARTICLE

Preparation of oxazolines and oxazoles via a PhI(OAc)$_2$-promoted cyclization of *N*-propargylamides

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A metal-free cyclization of *N*-propargylamides for the synthesis of various oxazodines and oxazoles via a *5-exo-dig* process is presented. Using (diacetoxyiodo)benzene (PIDA) as the reaction promoter and lithium iodide (LiI) as the iodine source, intramolecular iodooxygenation of *N*-propargylamides proceeded readily, leading to the corresponding (*E*)-5-iodomethylene-2-oxazolines in good to excellent isolated yields. In addition, uisng PhI(OAc)$_2$/LiI system, *N*-propargylamides can be converted to the corresponding oxazole-5-carbaldehydes in the presence of oxygen under visible light irradiation. The resulting products can be further converted into various oxazoline and oxazole derivatives after simple derivatizations, and this method ultimately offers an efficient route to a variety of biologically active structures.

Introduction

Oxazolines and oxazoles are important structural motifs in many natural products[1] and biologically active molecules[2] (Figure 1). Moreover, these functional groups are also frequently employed in synthesis as versatile precursors,[3] protecting groups,[4] directing groups[5] and ligands/auxiliaries.[6] To this end, continuous efforts have been devoted to the development of novel methods for the synthesis of these compounds.[7]

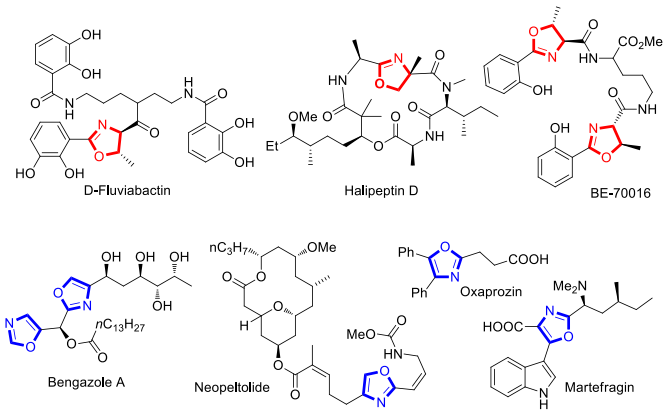
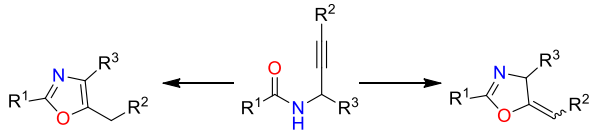


Figure 1. Oxazoline- and oxazole-containing compounds.

Among the various methods developed, cyclization of propargylic amides is one of the most attractive strategies for the synthesis of oxazolines and oxazoles due to the rapid assembly of structural complexity and good functional group compatibility as well as step economy of this method (Scheme 1).[8] Thus, substantial efforts have been devoted to these transformations, and a variety of efficient catalysts such as gold,[9] palladium,[10] copper,[11] silver,[12] iron,[13] zinc,[13b, 14] ruthenium,[15] tungsten,[16] mercury,[17] and Brønsted acids[18] as well as strong bases[19] have been developed.

In addition, a halogen-induced electrophilic cyclization of propargyl amides has also been demonstrated as an efficient means of accessing oxazoline or oxazole derivatives. For example, Caristi et al. reported the first electrophilic cyclization of propargylic amides into halomethyloxazolines, which are potential synthetic intermediates in the synthesis of functionalized oxazoles.[20] A variety of electrophiles such as iodine,[21] bromine,[22] and *N*-iodosuccinimide[23] could trigger this reaction. Finally, the cyclization of *N*-propargylamides could also be realized with hypervalent iodine reagents. For instance, Saito et al. demonstrated an iodine(III)-mediated oxidative cycloisomerization of propargylic amides into various functionalized oxazoles.[24]



Scheme 1. Synthetic approach to oxazolines and oxazoles.

Recently, we reported a (diacetoxyiodo)benzene (PIDA)-promoted intramolecular cyclization of *N*-allylamides into 5-halomethyloxazolines (Scheme 2a).[25] As a continuation of our studies on the cyclization of unsaturated (sulfon)amides,[26] we

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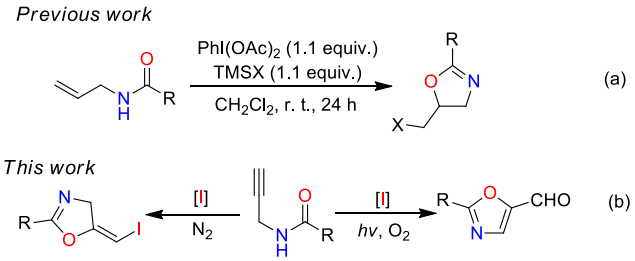
envisioned that a PIDA-mediated iodocyclization of *N*-propargylamides would be of great synthetic value since the resulting vinyl iodides can undergo other useful transformations, transition metal-catalyzed cross-couplings in particular, which provides opportunities for constructing more complex frameworks. Herein, we report the PIDA-promoted regioselective iodocyclization of *N*-propargylamides to provide various iodomethylenedihydrooxazoles through an intramolecular *5-exo-dig* process (Scheme 2b, left). In addition, we disclose that *N*-propargylamides can be converted to the corresponding oxazole-5-carbaldehydes in the presence of oxygen under visible light irradiation (Scheme 2b, right).

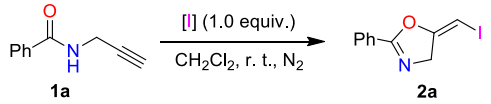


Scheme 2. PIDA-mediated functionalization of *N*-allyl or *N*-propynyl amide

Results and Discussion

We commenced our investigation with the optimization of the reaction conditions using *N*-(prop-2-yn-1-yl)benzamide (**1a**) as the model substrate, and the preliminary results are summarized in Table 1.

Table 1. Optimization of the reaction conditions.[a]



1a **2a**

entry	reagent	iodine source	solvent	isolated yield (%)
1	$PhI(OAc)_2$	TMSI	CH_2Cl_2	73
2	$PhI(OAc)_2$	NaI	CH_2Cl_2	88
3	$PhI(OAc)_2$	KI	CH_2Cl_2	83
4	$PhI(OAc)_2$	LiI	CH_2Cl_2	91
5	PhIO	LiI	CH_2Cl_2	60
6[b]	DMP	LiI	CH_2Cl_2	80
7[c]	IBX	LiI	CH_2Cl_2	72
8	*m*CPBA	LiI	CH_2Cl_2	78
9	$K_2S_2O_8$	LiI	CH_2Cl_2	NR[d]
10	Oxone	LiI	CH_2Cl_2	NR[d]
11	$(NH_4)_2SO_4$	LiI	CH_2Cl_2	NR[d]
12	$PhI(OAc)_2$	LiI	$Cl(CH_2)_2Cl$	85
13	$PhI(OAc)_2$	LiI	CCl_4	79
14	$PhI(OAc)_2$	LiI	$CHCl_3$	88
15	$PhI(OAc)_2$	LiI	DMF	6
16	$PhI(OAc)_2$	LiI	CH_3CN	20
17	$PhI(OAc)_2$	-	CH_2Cl_2	NR[d]
18	-	LiI	CH_2Cl_2	NR[d]

[a] All the reactions were run at 0.5 mmol scale in 2 mL of CH_2Cl_2 under N_2. [b] DMP=Dess-Martin periodinane. [c] IBX=2-Iodoxybenzoic acid [d] NR=No reaction,

To our delight, substrate **1a** underwent *5-exo-dig* cyclization in the presence of PIDA and TMSI under a nitrogen atmosphere giving (*E*)-5-(iodomethylene)-2-phenyl-4,5-dihydrooxazole (**2a**) in 73% yield (entry 1). The *E* configuration was determined by comparing the ^{1}H NMR data of this compound with those with known compounds.[27] Encouraged by these preliminary result, different iodine sources were tested to further improve the yield, and the investigation showed that LiI gave the best results (entries 1–4). Iodosobenzene, IBX or Dess-Martin periodinane in combination with LiI could also be used for cyclization of **1a**, but the yields were generally lower than PIDA-induced reactions (entries 5–7). Other oxidants, such as *m*CPBA, $K_2S_2O_8$, Oxone and $(NH_4)_2SO_4$, were also tested, but they were found to be less efficient than $PhI(OAc)_2$ (entries 8-11). The effect of the solvents on the course of the reaction was also noteworthy (entries 12–16), and CH_2Cl_2 was the most suitable solvent for the reaction. No product was obtained in the absence of an iodine source, indicating that the iodine atom in the product came from LiI rather than from the PIDA (entry 17). No reaction occurred in the absence of PIDA, indicating that PIDA played an important role in the reaction (entry 18). The three notable features of the present approach are (i) a 5-*exo-dig* ring closure to give an oxazoline without any indication of competing 6-*endo-dig* ring closure, (ii) no further isomerization to the oxazole due to the mild reaction conditions and (iii) no additional iodination of the phenyl ring.

Under the optimized reaction conditions, the scope of the formation of **2** from various *N*-propargyl amides **1** is summarized in Scheme 3. As these results showed, (*E*)-5-iodomethylene-2-oxazolines could be obtained in good to excellent isolated yields. Compared with known cyclization of *N*-propargylamides in which a strong Thorpe-Ingold effect was observed,[10d, 19b] the current reaction system was less dependent on the substituents at the propargylic position, and substrates without *gem*-disubstituents all gave good isolated yields. Electronic effects of the substituents on the aryl groups showed some effect on the reaction, and substrates with either electron-donating groups or halides on the aromatic rings could all be cyclized in good isolated yields (**2a**–**2i**). Phenyl rings bearing a nitro or a cyano moiety gave slightly lower yields probably due to the low reactivity of the substrate caused by the strong electron-withdrawing effects of the substituents (**2j** and **2k**). The reaction could also be scaled up to 10 mmol to give 2.60 g (87%) of product **2e**. The naphthalene-derived substrate worked well in the current reaction system, and the corresponding oxazoline was obtained in good yield (**2l**). Oxazoline-containing heterocycles have been used as important functional groups in antibacterial,[28] antituberculosis,[29] and antitumor agents.[30] Thus, structurally diverse heterocyclic oxazoline compounds were also prepared using the developed method. As shown in Scheme 3, thiophene-, furan-, pyrrole- and pyridine-containing

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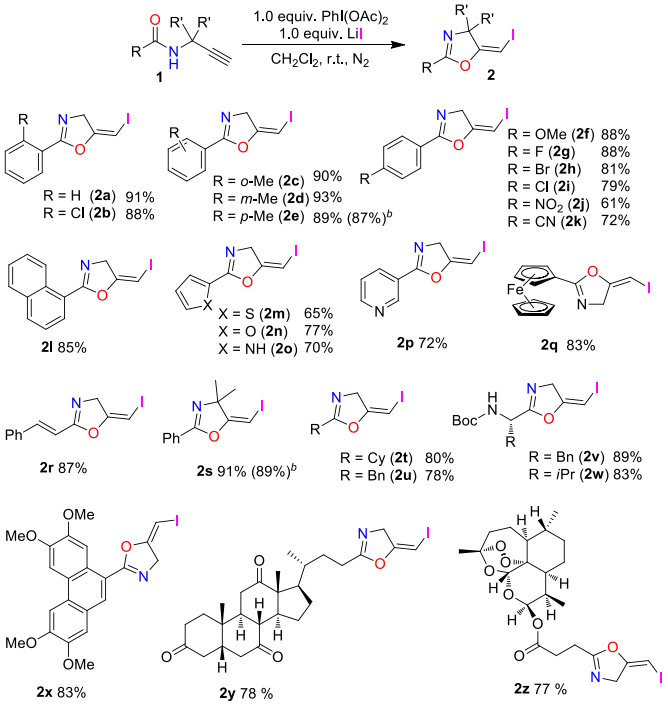
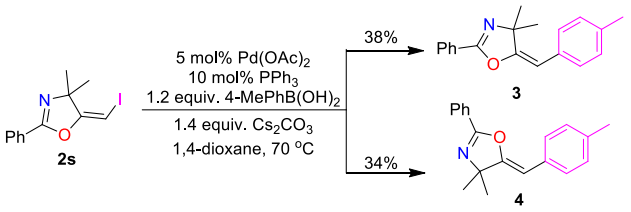
oxazoline compounds **2m**–**2p** could be obtained in satisfactory isolated yields. Ferrocene rings and styryl groups could also be tolerated in the current system (**2q** and **2r**). Substrates bearing a quaternary carbon center also reacted very well and provide the corresponding products in excellent yields (**2s**). Again, the reaction could be carried out on a 10 mmol without significant decreases in yield. Moreover, no additional iodination of the aromatic ring was observed in any case (**2a**-**2s**). Further, cyclization of *N*-propynyl amides of aliphatic carboxylic acids and natural α-amino acids were also tested and afforded the corresponding oxazoline products **2t**–**2w** in good isolated yields. To further evaluate the synthetic utility and generality of current procedure, more complex small molecules were then investigated. Gratifyingly, substrates bearing a phenanthrene group were compatible with the standard reaction conditions and provided desired oxazoline **2x** in 83% yield. Finally, dehydrocholic acid and artesunate derivatives were good candidates for this transformation (**2y** and **2z**), further highlighting the generality and great potential of the developed method.

Scheme 3. Synthesis of (*E*)-5-iodomethylene-2-oxazolines [a]



[a] Reaction conditions: 0.5 mmol of substrate, 0.5 mmol of $PhI(OAc)_2$, 0.5 mmol of LiI, 2 mL of CH_2Cl_2, 1 atm of N_2, 12 h. [b] 10 mmol scale.

The resulting iodomethylene-substituted cyclic compounds could be easily converted into trisubstituted alkenes via transition metal-catalyzed coupling reactions. For instance, almost an equimolar ratio of *E/Z*-isomers were obtained from the Suzuki coupling of (*E*)-alkene **2s** with *p*-tolylboronic acid in 1,4-dioxane (Scheme 4), which was not consistent with the observations made by Xu that the Suzuki coupling of **2s** and boronic acids produced a single geometric isomer.[11c] In addition, the structure of the product reported in Xu's work need to be revised since the NMR data are not in agreement with literature values.[12b, 31] (*E*)-Alkene **3** and (*Z*)-alkene **4** could be separated by flash column chromatography, and the structures of the compounds were established by NOE experiments. The geometric configuration of **4** was established by the strong NOESY correlation between the methyl protons and the vinylic proton, which were in agreement with the results reported by Strand and co-workers.[31]



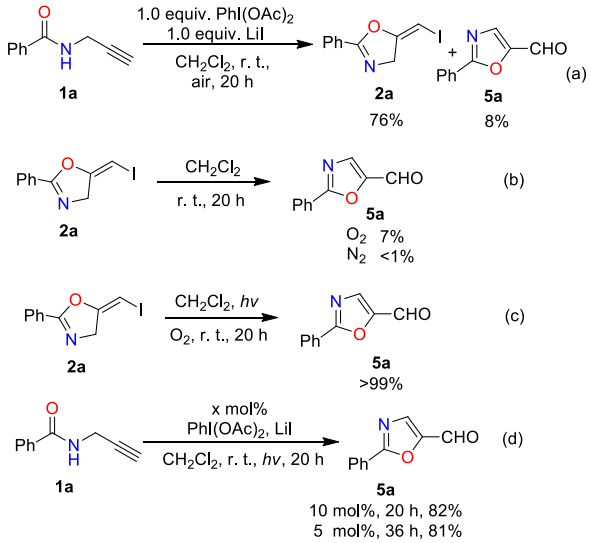
Scheme 4. Suzuki coupling of **2s** and *p*-tolylboronic acid

In the course of optimizing the reaction conditions, we found that when the reaction was carried out in the open air, oxazoline **2a** was obtained along with a small amount of oxazole-5-carbaldehyde **5a** (Scheme 5a); however, no **5a** was observed when the reaction was carried out under nitrogen (Table 1). These results indicated that the carbonyl oxygen atom in **5a** was from air.

Wang et al. recently discovered that the oxidative deiodination of **2a** to give **5a** can be achieved at 80 °C in the presence of dioxygen.[23a] Flynn and co-workers also showed that the deiodination of an analogous vinyl iodide can take place at elevated temperature and give the corresponding aldehydes in good yields.[32] Consistent with their reports, iodoalkene **2a** could be converted to **5a** under an oxygen atmosphere at ambient temperature, albeit at a lower yield (Scheme 5b). No transformation was observed when the reaction was carried out under nitrogen (Scheme 5b). Additionally, vinyl iodide **2a** could be stored for an extended period when it was kept in the dark under a nitrogen atmosphere. However, in the presence of air and light, **2a** gradually decomposed into aldehyde **5a** with a concomitant color change to red, owing to the generation of iodine. These results indicated that light and oxygen had a significant impact in deiodination step. Encouraged by the above results, we envisage that this process would proceed readily if the reaction was irradiated by visible light under an oxygen atmosphere. Therefore, **2a** was dissolved in CH_2Cl_2 under 1 atm of O_2 at ambient temperature, and the reaction mixture was irradiated by a standard 24 W household fluorescent bulb. As expected, **2a** could be nearly quantitatively converted to **5a** (Scheme 5c).

Given the importance of oxazole-5-carbaldehyde,[17b, 17c, 33] we then tried to combine the iodocyclization and oxidative deiodination into a one-pot procedure to prepare these compounds directly from propargylamides. During the preparation of this work, Wang et al. showed that propargylamides could be converted to the corresponding oxazole aldehydes using an I_2/visible light system.[34] Similarly,

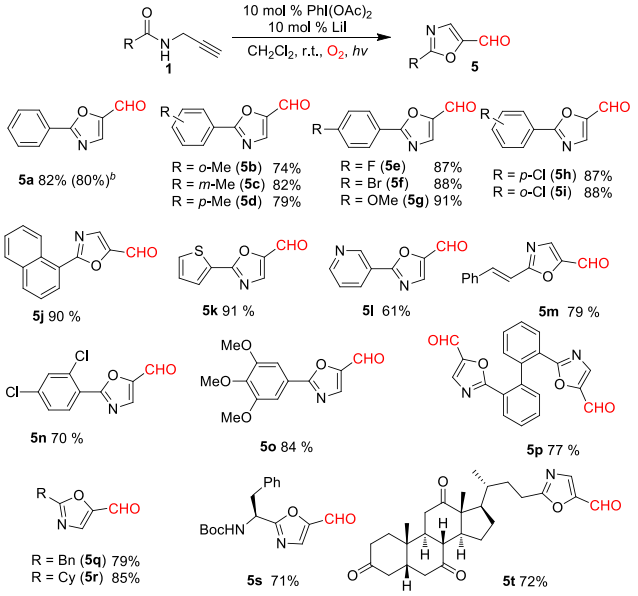
we found this transformation could also be accomplished using 10 mol % PIDA and LiI under visible light irradiation (Scheme 5d). Lowering the amount of PIDA and LiI to 5 mol % led to a slight drop of conversion, but this could be overcome by elongating the reaction time to 36 h.



Scheme 5. Synthesis of oxazole-5-carbaldehyde **5a**

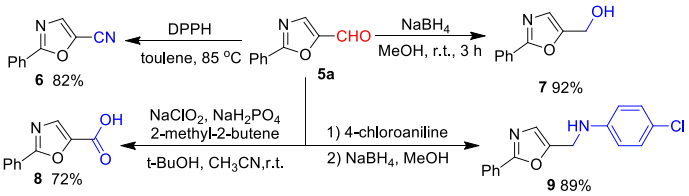
Given theirs low price, 10 mol % PIDA and 10 mol% LiI were finally chosen to test the scope of the reaction, and the results are summarized in Scheme 6. As shown in Scheme 6, propargylamides of aromatic, heteroaromatic, and aliphatic carboxyacids as well as those of natural α-amino acids all delivered the corresponding oxazole aldehydes in good yield. The cyclization could be run on more than a gram scale and provided the aldehyde in 80% isolated yield (**5a**).

Scheme 6. Synthesis of oxazole aldehydes [a]



[a] Reaction conditions: 0.5 mmol of substrate, 0.05 mmol of $PhI(OAc)_2$, 0.05 mmol of LiI, 2 mL of CH_2Cl_2, 1 atm of O_2, visible light, 24 h. [b] 10 mmol scale.

To demonstrate the synthetic value of the developed methodology, the aldehyde group in **5a** was converted to a variety of functional groups (Scheme 7). For example, using the procedure reported by Nantz,[35] aldehyde **5a** was smoothly transformed to corresponding nitrile **6** by heating with O-(diphenylphosphinyl)hydroxylamine (DPPH) in toluene. Sodium borohydride reduction of **5a** could generate alcohol **7**, a key intermediate in the synthesis of herbicides.[36] **5a** can be easily converted carboxylic acid **8**, a potential antibacterial agent,[37] under oxidative conditions. Insect growth regulator **9** can be easily prepared by the reductive amination of **5a** and 4-chloroaniline.[17b]



Scheme 7. Derivatizations of aldehyde **5a**.

A plausible mechanism, as outlined in Scheme 8, was proposed for the formation of oxazolines and oxazoles. First, PIDA promoted the oxidation of the iodide anion, producing iodoacetic acid (IOAc) as an intermediate,[38] which induced the electrophile-mediated cyclization of *N*-propargylamide to provide iodomethylenedihydrooxazole **2a**. The *E*-configuration of **2a** is generated by the *anti*-attack of the carbonyl group on the triple bond.[39] Radical intermediate **A** and an iodine radical are created by homolytic cleavage of the C-I bond under visible light irradiation.[40] Species **A** then quickly reacts with O_2 to give a peroxy-radical species **B**,[41] and the subsequently formed six-membered-ring transition state affords radical species **C**, which is a resonance structure of **D**.[23a] Species **D** releases a hydroxyl radical to yield aldehyde **5a**. The combination of iodine radicals and hydroxyl radicals results in the formation of HIO, which can decompose into iodine for the next catalytic cycle.

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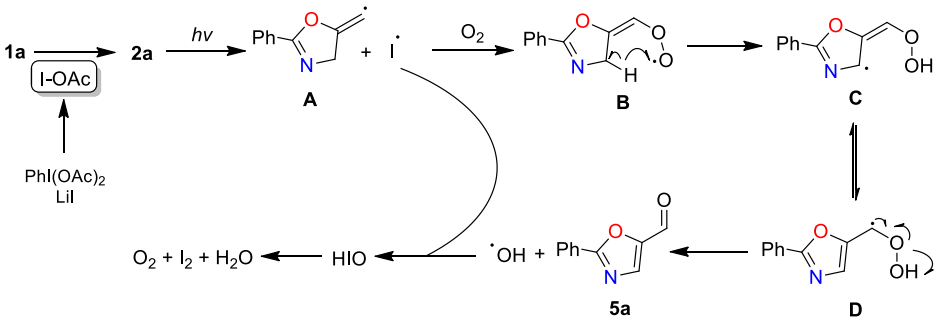

Scheme 8. Proposed mechanism

Conclusions

In summary, we have reported a simple, mild, and efficient method for the preparation of oxazolines and oxazoles. Using 1.0 equiv. of (diacetoxyiodo)benzene as the reaction promoter and 1.0 equiv. of LiI as the iodide source, (*E*)-5-(iodomethylene)-4,5-dihydrooxazole products could be obtained in good to excellent isolated yields. Moreover, *N*-propargylamides can be converted to the corresponding oxazole-5-carbaldehydes in the presence of oxygen under visible light irradiation. The resulting iodomethylenedihydrooxazole and oxazole-5-carbaldehyde compounds can be further converted into various oxazoline and oxazole derivatives after simple derivatizations, and this method ultimately offers an efficient route to a variety of biologically active structures. The good isolated yields, mild conditions, and operational simplicity make the current reaction an attractive method for the syntheses of a variety of medicinally and agrochemically relevant compounds.

Experimental section

General information

All reagents were used as received without further purification unless otherwise indicated. Solvents were dried and distilled prior to use. Reactions were monitored with thin layer chromatography using silica gel GF_{254} plates. Organic solutions were concentrated in vacuo with a rotavapor. Flash column chromatography was performed using silica gel (200–300 meshes). Petroleum ether used had a boiling point range of 60–90 °C. Melting points were measured on a digital melting point apparatus without correction of the thermometer. Nuclear magnetic resonance spectra were recorded at ambient temperature (unless otherwise stated) at 400 MHz (100 MHz for ^{13}C) in $CDCl_3$. Chemical shifts were reported in ppm (δ) using TMS as internal standard, and spin–spin coupling constants (J) were given in Hz. Infrared (IR) spectra were recorded with KBr pellet, and wavenumbers were given in cm^{-1}. High resolution mass spectrometry (HRMS) analyses were carried out on an FTICR HR-ESI-MS.

General procedure for the preparation of (*E*)-5-iodomethylene-2-oxazolines: A flame-dried Schlenk flask was charged with 0.5 mmol *N*-propargylamide, 0.5 mmol $PhI(OAc)_2$, 0.5 mmol LiI and 2 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature until complete disappearance of the starting material as shown by TLC (usually 12 h). CH_2Cl_2 (10 mL) was then added, and the mixture was washed with aqueous $Na_2S_2O_3$. The organic layer was dried over Na_2SO_4 and concentrated to give crude residue, which was purified by flash column chromatography to give the corresponding products.

(*E*)-5-(Iodomethylene)-2-phenyl-4,5-dihydrooxazole (**2a**). Compound **2a** was prepared according to the general procedure and isolated as a yellow solid (130 mg, 91% yield) after flash chromatography (petroleum ether/ethyl acetate = 30/1); mp = 107–108 °C (ref,[21b] mp = 104 °C). ^1H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.98 – 7.94 (m, 2H), 7.56 – 7.51 (m, 1H), 7.47 – 7.43 (m, 2H), 5.78 (t, *J* = 3.2 Hz, 1H), 4.62 (d, *J* = 3.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 162.9, 156.9, 131.1, 127.6, 127.0, 125.4, 60.2, 46.2. Spectral data are in agreement with literature values.[11c]

General procedure for the preparation of oxazole aldehydes: A solution of *N*-propargylamide (0.5 mmol, 1.0 equiv.), $PhI(OAc)_2$ (0.005 mmol, 0.1 equiv.), and LiI (0.005 mmol, 0.1 equiv.) in 2 mL of CH_2Cl_2 was irradiated under oxygen atmosphere with a 24 W fluorescent household bulb at room temperature. Upon completion (monitored by TLC，usually 24 h), CH_2Cl_2 (10 mL) was added, and the mixture was washed with aqueous $Na_2S_2O_3$. The organic layer was dried over Na_2SO_4 and concentrated to give crude residue, which was purified by flash column chromatography to give the corresponding products.

2-Phenyloxazole-5-carbaldehyde (5a). Compound **5a** was prepared according to the general procedure and isolated as a white solid (71 mg, 82% yield) after flash chromatography

(petroleum ether/ethyl acetate = 6/1); mp = 71–73 °C, (ref,[42] mp = 74–76 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 9.82 (s, 1H), 8.19 – 8.16 (m, 2H), 7.95 (s, 1H), 7.59 – 7.49 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 176.3, 165.5, 149.6, 139.1, 132.3, 129.1, 127.7, 125.9. Spectral data are in agreement with literature values.[34]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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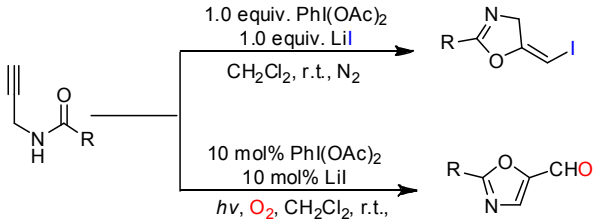

A metal-free cyclization of N-propargylamides for the synthesis of various oxazodines and oxazoles via a *5-exo-dig* process is reported herein.