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A Facile Microwave-Assisted Synthesis of Oxazoles and Diastereoselective Oxazolines Using Aryl-Aldehydes, *p*-Toluenesulfonylmethyl Isocyanide under Controlled Basic Conditions

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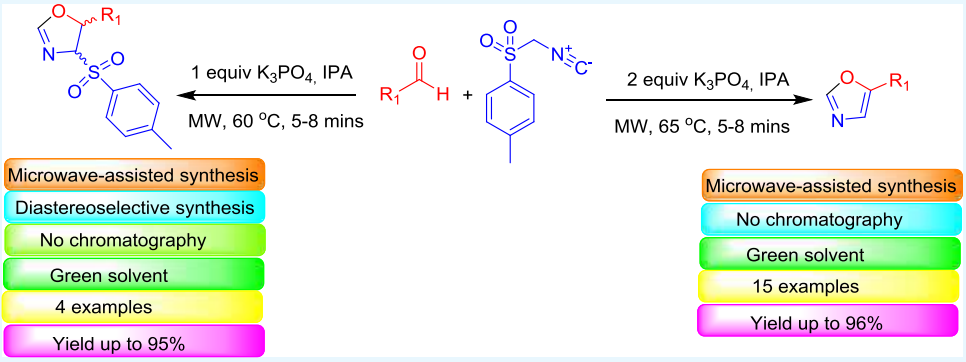

ABSTRACT: In this study, a highly efficient two-component [3 + 2] cycloaddition reaction of substituted aryl aldehydes with 4-toluenesulfonylmethyl isocyanide (TosMIC) in the presence of 2 equiv of potassium phosphate as a base to 5-substituted oxazoles were established in a isopropanol medium under microwave irradiation. However, using 1 equiv of K_3PO_4 as a base resulted in the diastereoselective synthesis of 4,5-disubstituted oxazolines under identical reaction conditions. The foremost benefits of these protocols are the moderate-to-excellent yields with good functional group compatibility, simple experimental procedure, inexpensive readily available starting materials, nonchromatographic purification, and high bond-forming efficiency. The synthetic manipulation reported herein represents a cleaner route to the sustainable preparation of 5-substituted oxazoles and diastereoselective 4,5-disubstituted oxazolines derivatives.

1. INTRODUCTION

Diverse heterocyclic small molecules are enormously used in biological systems as drug molecules to combat various diseases. Researchers in pharmaceutical industries and academia have a pronounced attention in the synthesis of small heterocyclic molecules, as they show innovative roles in all levels of biology including cell growth, sensing, and proliferation.[1] Heterocyclic small molecules are enormously significant for studying cell biology and the treatment of diverse diseases as they control the function of enzymes, receptors, and protein−protein interactions.[2,3] In this perspective, oxazoles and oxazolines are five-membered heterocyclic moieties containing nitrogen and oxygen as heteroatoms, which established an important class of drug candidates in organic chemistry. Predominantly, substituted oxazoles and oxazolines containing heterocycles could bind diverse enzymes and receptors via noncovalent interactions and in the biological system to display a wide variety of biological activities.[4−8] Numerous oxazole-containing drugs such as oxaprozin (**A**), a nonsteroidal anti-inflammatory drug (NSAID); pimprinin (**B**), an antimycobacterium agent; texalin (**C**), an antibacterial natural product; oxazole hydroxamate (**D**), a HDAC6 inhibitor; aleglitazar (**E**), an antidiabetic agent; siphonazole (**F**), an anticancer agent; and shahidine, an antimicrobial oxazoline drug (**G**), are extensively used in clinical exercises (Figure 1).[9−18] In view of their extensive bioactivities, several synthetic protocols have been developed by organic chemists.[19,20] In 1972, for the first time, Van Leusen and his group discovered a two-step [3 + 2] cycloaddition reaction from substituted aldehyde with 4-toluenesulfonylmethyl isocyanide (TosMIC) under a refluxing methanol solvent using K_2CO_3 as a base to 5-substituted oxazoles

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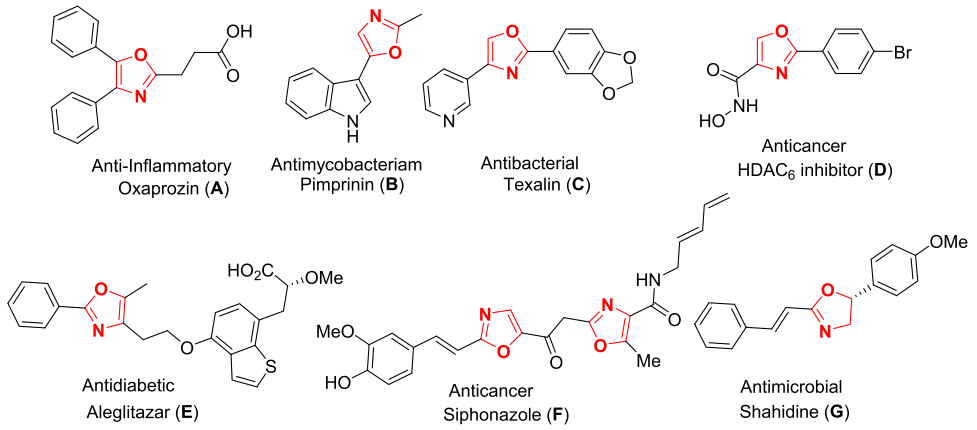
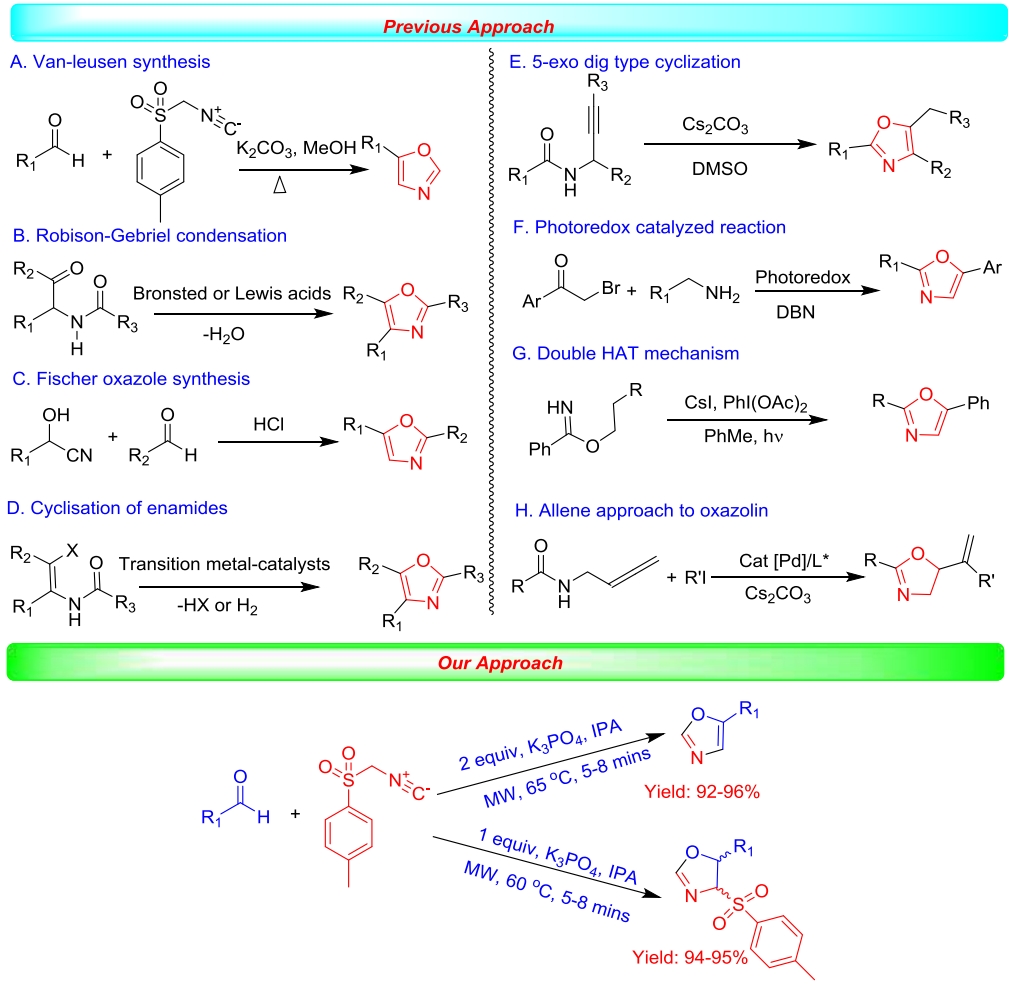


Figure 1. Selected biologically active oxazole and oxazoline derivatives.

Scheme 1. Oxazoles and Oxazolines Syntheses: Previous and Present Works



(Scheme 1A).[21] Subsequently, in 1999, Kulakarni and Ganesan modified the Van Leusen protocol for the oxazole synthesis using ambersep 900 OH^- as resin in a dimethoxyethane/MeOH-refluxing solvent (Table S1, entry 1).[22] In 2009, Ludivine et al. utilized the 1,8-diazabicyclo[5.4.0]undec-7-ene-polystyrnene as a mild base in an acetonitrile solvent at room temperature for oxazoline synthesis (Table S1, entry 2).[23] Very recently, Ramanathan et al. used imidazole as a base in a water medium for the diastereoselective synthesis of oxazolines and 5-substituted oxazoles (Table S1, entry 3).[24]

Other methods including the Robinson−Gabriel condensation of α-acyl amino ketone in the presence of dehydrating agents such as Bronstead or Lewis acid provided 2,4-disubstitutedoxazoles (Scheme 1B).[25] In 2018, Jiang et al. established a convenient copper-catalyzed [2 + 3] cyclization reaction of alpha-hydroxy ketones with arylacetonitriles to furnish 2,4,5-trisubstituted oxazoles (Scheme 1C).[26] Several other methods included the transition-metal-catalyzed cyclization of enamide with vinylic functionalization to the corresponding oxazoles (Scheme 1D).[27] In 2018, Chang et

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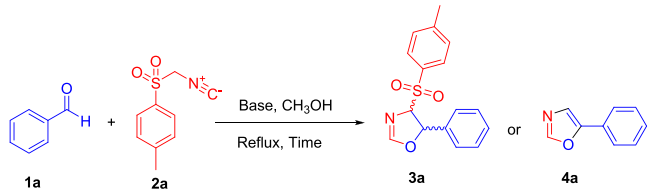
Table 1. Effect of Base for [3 + 2] Cycloaddition Reaction in CH_3OH Solvent[a]



entry	base	pK_a	equiv	time	oxazoline yield (%)[b] 3a	oxazole yield (%)[b] 4a
1				12 h	0	0
2	triethylamine	10.75	2	6 h	95	0
3	*N*,*N*-diisopropylethylamine	10.74	2	6 h	95	0
4	imidazole	6.9	2	6 h	92	0
5	*N*-methymorpholine	7.4	2	6 h	93	0
6	$NaHCO_3$	5.95	2	6 h	90	0
7	K_2CO_3	9.1	2	2 h	0	94
8	K_3PO_4	11.74	2	1.5 h	0	95

[a]Reaction was performed using **1a** (1.18 mmol), **2a** (1.18), and 2.36 mmol base. [b]Yield of the isolated product.

al. established a Cs_2CO_3-catalyzed halogen-free 5-*exo*-dig cyclization reaction for the amalgamation of oxazoles (Scheme 1E).[28] In 2019, Li et al. described tandem-oxidative cyclization reactions of α-bromo ketones and amines by a CO_2/photoredox co-catalyst for the preparation of substituted oxazoles (Scheme 1F).[29] In 2020, Nagib and his group have established a radical cascade strategy for the synthesis of oxazoles via the tandem hydrogen atom transfer (HAT) approach (Scheme 1G).[30] In 2018, Ma et al. described a highly effective enantioselective synthesis of asymmetric oxazoline derivatives via palladium-catalyzed reaction of aryl or 1-alkenyl iodides with *N*-(buta-2,3-dienyl) amides (Scheme 1H).[31]

However, all these methods suffer a few drawbacks such as the usage of toxic Lewis acid, transition-metal catalysts, longer reaction time, and toxic organic solvents such as CH_3OH, CH_3CN, and THF.[32−39] Henceforth, there is substantial attention in the improvement of alternate methodologies evading the usage of expensive base catalysts, toxic organic solvents, and transition-metal catalysts. Therefore, it is necessary to develop a novel protocol to build these diverse and functionalized oxazoles and oxazolines scaffolds for drug development. In the last decade, the combined application of microwave-assisted irradiation in green solvents has increased considerably owing to the generation of quick products in the nontoxic environment. In this respect, isopropanol is a very attractive nontoxic green polar solvent for several competent organic reactions that could solubilize numerous reactants at room or high temperatures.[40−42] Herein, we developed an expedient microwave-assisted simple protocol of 5-substituted oxazoles and diastereoselective 4,5-disubstituted oxazolines derivatives using K_3PO_4 as a base in an IPA reaction medium.[43]

2. RESULT AND DISCUSSION

At the beginning of this exploration, we have selected benzaldehyde **1a** and 4-toluenesulfonylmethyl isocyanide (TosMIC) **2a** as the model substrate. The reaction of benzaldehyde **1a** with 4-toluenesulfonylmethyl isocyanide (TosMIC) **2a** without a base in a refluxing methanol solvent for 12 h did not yield any 4,5-disubstituted oxazoline **3a** and 5-phenyl oxazole **4a** products (Table 1, entry 1). Interestingly, employing the 2 equiv of organic bases such as triethylamine, *N*,*N*-diisopropylethylamine, imidazole, *N*-methylmorpholine, and $NaHCO_3$ as inorganic mild bases for the same set of reactions under the refluxing methanol solvent for 6 h yielded 92−95% 4,5-disubstituted oxazolines **3a** (Table 1, entries 2−6). Surprisingly, using 2 equiv of K_2CO_3 or K_3PO_4 as a base, the same set of reaction yielded 5-phenyl oxazole **4a** in 94−95% in a reduced time (Table 1, entries 7 and 8). Because of a higher pK_a value of K_3PO_4 compared to K_2CO_3 or other organic bases, the [3 + 2] cycloaddition reaction resulted exclusively in 5-phenyl oxazole **4a** in a short time.[43,44]

Next, to improve the efficacy of this synthetic protocol, we have chosen 2 equiv of K_3PO_4 (pK_a = 11.74) as a suitable base for the [3 + 2] cycloaddition of 4-toluenesulfonylmethyl isocyanide (TosMIC) with benzaldehyde for various solvent optimization. Employing 2 equiv of the K_3PO_4 strong base, we screened several organic and green solvents for the same set of reactions at 60 °C. Using a polar aprotic solvent such as DMF and DMSO did not yield any cyclized product (Table 2, entries 1 and 2). However, using polar aprotic solvents such as THF and CH_3CN resulted in the 4,5-disubstituted oxazolines **3a** product with 95% yield in 6 h (Table 2, entries 3 and 4). Surprisingly, using 2 equiv of the K_3PO_4 base for the same set of reactions in a $CHCl_3$ solvent resulted in the formation of 4,5-disubstituted oxazolines **3a** and 5-phenyl oxazole **4a** in a 1:0.9 ratio (Table 2, entry 5). The use of H_2O-IPA as the reaction medium at 60 °C resulted in the formation 5-phenyl oxazole **4a** in greater proportion compared to 5-phenyl-4-tosyl-4,5-dihydrooxazole **3a** (Table 2, entry 6), whereas at room temperature condition, it obtained the exclusive formation of 5-phenyl-4-tosyl-4,5-dihydrooxazole **3a** (Table 2, entry 7). To avoid the toxic and high boiling solvents and shorten the reaction time, we performed the same set reaction in solvents such as EtOH and IPA and resulted in the formation of 5-phenyl oxazole **4a** in 92−95% yields (Table 2, entries 8 and 9).

However, the use of microwave irradiation at 65 °C and 350 W for 8 min in an IPA medium resulted in the formation of 5-phenyl oxazole **4a** in 96% yield (Table 2, entry 10). Next, we have chosen 2 equiv of the K_3PO_4 base for the synthesis of the 5-phenyl oxazole **4a** derivative with optimized microwave power and time. Additionally, by employing organic bases triethylamine, *N*,*N*-diisopropylethylamine, imidazole, and *N*-methylmorpholine as well as mild base $NaHCO_3$ for the same set of reactions at 60 °C in the IPA solvent for 6 h yielded only 92−95% of 4,5-disubstituted oxazoline **3a** (Table S1 and

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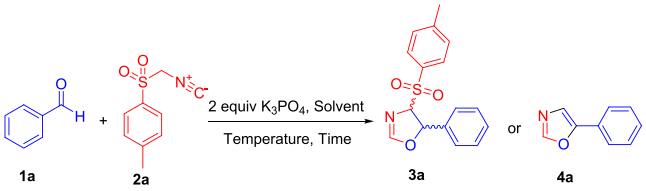
Table 2. Optimizations of Various Solvents for [3 + 2] Cycloaddition Reaction Using K_3PO_4 Base[a]

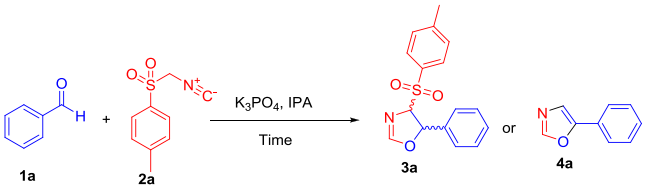


entry	solvent	temperature (°C)	time (h)	oxazoline yield (%)[c]	oxazole yield (%)[c]
1	DMF	60	6	0	0
2	DMSO	60	6	0	0
3	THF	60	6	95	0
4	CH_3CN	60	6	95	0
5	$CHCl_3$	60	6	50	40
6	IPA-H_2O	60	4	10	80
7	IPA	rt	6	94	0
8	EtOH	60	1.5	0	92
9	IPA	60	1	0	95
10	IPA	MW[b], 65	0.13	0	96

[a]Reaction was performed using **1a** (1.18 mmol), **2a** (1.18 mmol), and K_3PO_4 (2.36 mmol). [b]Microwave reactions were carried out in a microwave model no. CATA R (Catalyst Systems, Pune) at 65 °C using a power of 350 W. [c]Yield of the isolated product.

Figure S40). Hence, organic bases such as triethylamine, *N*,*N*-diisopropylethylamine, imidazole, and *N*-methylmorpholine, and mild base $NaHCO_3$ as well as room temperature of the reaction were not efficient to oxidize the 5-phenyl-4-tosyl-4,5-dihydrooxazole **3a** to the 5-phenyl oxazoles **4a**. Next, we focused our attention to the optimization of the reaction condition using K_3PO_4 as a base. The results are summarized in Table 3.

Table 3. Reaction Optimization Using K_3PO_4 Base Equivalents[a]



entry	base	equiv	temperature (°C)	time (h)	oxazoline yield (%)[b] 3a	oxazole yield (%)[b] 4a
1	K_3PO_4	0.3	60	12	70	0
2	K_3PO_4	0.5	60	12	85	0
3	K_3PO_4	1.0	60	12	90	0
4	K_3PO_4	1.5	60	12	65	30
5	K_3PO_4	1	MW[c], 60	0.13	94	0

[a]Reaction was performed using **1a** (1.18 mmol) and **2a** (1.18 mmol). [b]Yield of the isolated product. [c]Microwave reactions were carried out in a microwave model no. CATA R (Catalyst Systems, Pune) using a power of 280 W.

The optimal amounts of tripotassium phosphate bases were also evaluated in the same set of reactions. Using 0.3−1.0 equiv of K_3PO_4 as a base yielded exclusively the 5-phenyl-4-tosyl-4,5-dihydrooxazole **3a** in 70−90% yields (Table 3, entries 1−3). Using 1.5 equiv of K_3PO_4 for the same set of reaction resulted in the mixture of 5-phenyl-4-tosyl-4,5-dihydrooxazole **3a** and 5-phenyl oxazole **4a** in a 2:1 ratio (Table 3, entry 4). However, using 1 equiv of the K_3PO_4 base for the same set of reaction under microwave irradiation at 60 °C for 280 W in 8 min resulted in the formation of 5-phenyl-4-tosyl-4,5-dihydrooxazole **3a** in 94% yield (Table 3, entry 5). With the optimal reaction condition in hand, we have studied the substrate scope for the synthesis of substituted oxazoles and oxazolines using various substituted aldehyde (Scheme 2 and Tables 4 and 5). We also studied the kinetics of electron-donating and electron-withdrawing aldehydes for [3 + 2] cycloaddition reactions and are shown in Scheme 2. Diverse para-substituents on the aryl ring of aromatic aldehyde such as −Me, −OMe, −Cl, −CN, −Br, $-NO_2$, and −F are well tolerated for the [3 + 2] cycloaddition reactions, yielding the 5-substituted oxazole products **4** in high yields. Moreover, substitutents present on the *o*- or *m*-position of the aromatic ring such as −OH, $-NO_2$, −Cl, and heteroaryl aldehyde also yielded corresponding 5-substituted oxazoles products **4** in good yields (Table 4).

The formation of oxazoles and oxazolines was examined by the proton NMR spectroscopy. The representative compounds 5-(*p*-tolyl)-4-tosyl-4,5-dihydrooxazole **3b** and 5-(*p*-tolyl) oxazole **4b** product conversion were examined by proton NMR spectroscopy. It has been found that the characteristic vicinal protons H_a and H_b of the oxazoline ring appeared at 6.04 and 5.05 ppm, respectively, in spectra **A** in Figure 2. Subsequent formation of 5-(*p*-tolyl)oxazole confirmed by the disappearance of H_a and H_b protons and appearance of two-singlet proton at 8.42 and 7.63 ppm oxazole moieties and with the four aromatic proton of the tolyl moiety in spectra **B** in Figure 2.

From ^1H NMR spectra in spectra **A** in Figure 2, we observed that all the synthesized 4,5-disubstituted oxazoline derivatives **3a**−**3d** are diastereoselective. The ^1H NMR spectra of 4,5-disubstituted oxazoline **3b** show that the coupling constant value for vicinal $J_{Ha,Hb}$ are almost 6 Hz (Supporting Information). The previous literature report and coupling constant for all synthesized 4,5-disubstituted oxazoline derivatives of H_a and H_b confirmed that the synthesized oxazoline derivatives are trans (anti) geometrical formation.[45,46] In addition, to examine the limitations and scope of the [3 + 2] cycloaddition reactions, we have reacted aliphatic aldehyde such as butyraldehyde with 4-toluenesulfonylmethyl isocyanide (TosMIC) in the presence of 2 equiv of the potassium phosphate base in the IPA solvent at 60 °C heating for 6 h. However, we failed to obtain the desired oxazole or oxazoline derivatives.

Furthermore, we have established the potential synthetic utility of this synthetic procedure on the gram-scale synthesis using the model reaction. The reaction of 10 mmol **1a** with 10 mmol **2a** under microwave irradiation at 65 °C and 350 W for 8 min could afford a 1.4 g 5-phenyl oxazoles **4a** yield (96%).The present methodology represents the potential applications of the present synthetic protocol for a large-scale synthesis (Scheme 3).

Based on the experimental result of the reaction, a plausible mechanistic pathway for one-pot [3 + 2] cycloaddition reaction is outlined (Scheme 4). To synthesize diverse 5-substituted oxazoles derivatives, a minimum 2 equiv K_3PO_4 base was required in the IPA solvent. Mechanistically, we believe that the 1 equiv of the strong K_3PO_4 base abstracts protons from the acidic methylene position of 4-toluenesulfonylmethyl isocyanide (TosMIC) **2** provided the intermediate

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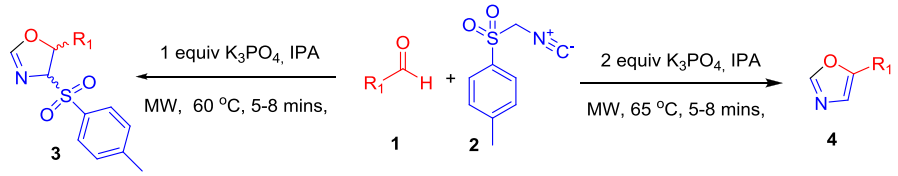
Scheme 2. One-Pot [3 + 2] Cycloaddition Reaction to 5-Substituted Oxazoles 4 and Diastereoselective 4,5-Disubstituted Oxazolines 3



2a′, which subsequently reacted with an arylaldehyde **1** to form intermediate **b′** and simultaneously undergone one-pot [3 + 2] cycloaddition reaction to form intermediate **c′** which under subsequent protonation from 4,5-disubstituted oxazoline derivatives **3d′**. In the presence of another 1 equiv of the K_3PO_4 strong base and heating condition, 4,5-disubstituted oxazoline derivatives **3d′** underwent elimination reaction by the formation of 5-substituted oxazoles **4e′**. Here, the tosyl group not only lower the pK_a value of TosMIC but also act as a leaving group in 4,5-disubstituted oxazolines that depend upon the solvent, nature of the bases, equivalent of bases, and temperature of the reaction. Hence selectively, we achieved 5-substituted oxazoles using 2 equiv of strong K_3PO_4 bases in the IPA solvent under microwave irradiation. Using 1 equiv of the strong K_3PO_4 base, 4,5-disubstituted oxazolines products **3d′** predominates under microwave irradiation for 5−8 mins at 60 °C. We achieved exclusively the synthesis of 4,5-disubstituted oxazolines and 5-substituted oxazoles in a short time using the K_3PO_4 strong base in the IPA solvent under appropriate microwave irradiation.

3. CONCLUSIONS

In summary, we have developed a one-pot microwave-assisted [3 + 2] cycloaddition reaction of a substituted arylaldehyde with 4-toluenesulfonylmethyl isocyanide (TosMIC) to diastereoselective 4,5-disubstituted oxazolines and 5-substituted oxazoles by controlling the amount of K_3PO_4 as the base. Moreover, using organic bases such as triethylamine, *N*,*N*-diisopropylethylamine, imidazole, and *N*-methylmorpholine in heating conditions resulted in 4,5-disubstituted oxazolines. The rapid, simple, one-pot microwave-assisted syntheses of 4,5-disubstituted oxazolines and 5-substituted oxazoles in the IPA solvent make the process environmentally benign and economical. The method is extremely efficient, took a very short time, and simple to perform under mild conditions. We trust that our process accompaniments with associated methodologies by providing an alternative for synthesizing 4,5-disubstituted oxazolines and 5-substituted oxazoles.

4. EXPERIMENTAL SECTION

4.1. General Methods. All the starting materials, substituted aryl aldehyde, 4-toluenesulfonylmethyl isocyanide (TosMIC), triethylamine, diisopropylethylamine, *N*-methylmorpholine, imidazole, sodium bicarbonate, potassium carbonate, potassium phosphate tribasic (anhydrous, reagent grade > 98%), and 2-propanol (anhydrous, 99.5%), were purchased from Sigma-Aldrich, and solvents were used from commercial suppliers without further purification. Analyses of ^{1}H NMR and ^{13}C NMR were performed by a Bruker DRX400 spectrometer (400 MHz). Chemical shifts are reported in parts per million (ppm) relative to the internal standard. Coupling constants (J) are given in hertz (Hz). Multiplicities of peaks are given as d (doublet), m (multiplet), s (singlet), and t (triplet). The removal of the solvent was carried out by a rotary evaporator under reduced pressure. IR spectra were recorded on a Bomen DA8 3 FTS spectrometer. GC−MS has been recorded using a Perkin Elmer Clarus 600C spectrometer. Microwave-assisted reactions were carried out in a catalyst scientific microwave oven system (model no: CATA R; Catalyst System, Pune) operating at 2450 MHz equipped with glass vial extension by a condenser used for performing the reaction. The microwave was equipped with a temperature control system (external probe).

4.2. Representative General Procedure for the Synthesis of 5-Phenyl Oxazoles 4a. In a 50 mL round-bottle flask, benzaldehyde **1a** (0.125 g, 1.18 mmol, 1.0 equiv), 4-toluenesulfonylmethyl isocyanide (TosMIC) **2** (0.230 g, 1.18 mmol, 1.0 equiv), and 10 mL IPA were added subsequently. Further, in the same round-bottle flask, K_3PO_4 was charged (0.500 g, 2.36 mmol, 2.0 equiv). The reaction mixture was irradiated in an open vessel fitted with a reflux condenser under 800 rpm stirring at 65 °C and 350 W for 8 min. After completion of the reaction as monitored by TLC, the reaction mixture was cooled to room temperature. The IPA solvent was removed under reduced pressure, and the crude product was diluted with water (15 mL) and extracted with ethyl acetate (15 mL). Further, the organic layer was washed with water (5 mL) and brine (5 mL). The crude product was washed with ice-cooled ether (15 mL) to provide pure products **4a** (without column chromatography) in 96% yield (0.16 g).

4.3. Representative General Procedure for the Synthesis of Diastereoselective 5-Phenyl Oxazoline 3a. In a 50 mL round-bottle flask, benzaldehyde **1a** (0.125 g, 1.18 mmol, 1.0 equiv), 4-toluenesulfonylmethyl isocyanide (TosMIC), **2** (0.230 g, 1.18 mmol, 1.0 equiv), and 10 mL IPA were added subsequently. In the same round-bottle flask, K_3PO_4 (0.381 g, 1.18 mmol, 1.0 equiv) was charged. The reaction mixture was irradiated in an open vessel under microwave at 60 °C and 280 W for 8 min. After completion of the reaction as monitored by TLC, the reaction mixture was cooled to room temperature. The IPA solvent was removed using reduced pressure, and the crude product was diluted with water (10 mL) and extracted with ethyl acetate. Further, the organic layer was washed with water (5 mL) and brine (5 mL). The crude product was washed with ice-cooled ether (15 mL) and hexane (10 mL) to provide pure products **3a** (without column chromatography) with 94% yield (0.34 g).

*4.3.1. 5-Phenyl Oxazole (**4a**).*[21−23] Brown liquid; R_f = 0.3 (20% EtOAc/*n*-hexane); yield: 0.164 g, 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.63−7.61 (m, 2H), 7.40−7.37 (m, 2H), 7.31 (d, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 150.5, 128.9, 128.7, 127.67, 124.3, 121.4. MS (*m*/*z*, EI$^+$) calcd for C_9H_7NO (+) 145.05, found 145.13.

*4.3.2. 5-(p-Tolyl) Oxazole (**4b**).*[22,37] Brown solid; R_f = 0.25 (20% EtOAc/*n*-hexane); yield: 0.156 g, 94%; mp 59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.63 (s, 1H), 7.61

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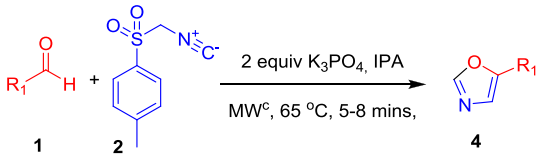
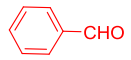
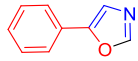
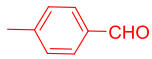
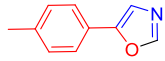
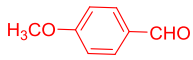
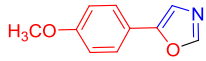
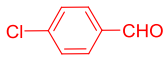
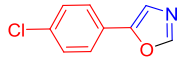
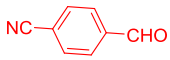
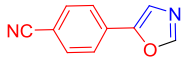
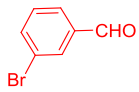
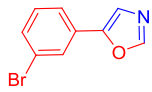
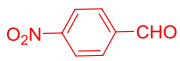
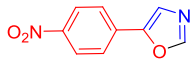
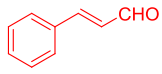
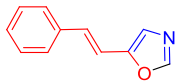
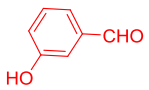
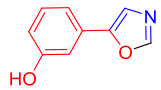
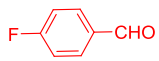
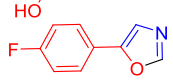
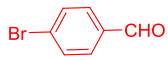
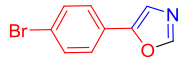
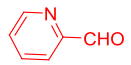
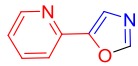
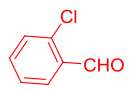
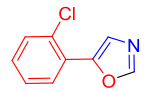
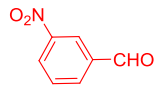
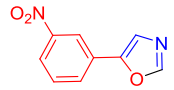
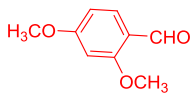
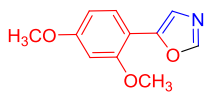
Table 4. Substrate Scope for 5-Substituted Oxazoles Derivatives 4[a]



1 2 4

Entry	R_1CHO	Product	Yield (%)[b]
4a			96
4b			94
4c			96
4d			94
4e			93
4f			94
4g			92
4h			94
4i			93
4j			90
4k			92
4l			90
4m			92
4n			90
4o			95

[a]The reactions were performed with aldehyde (3 mmol), tosmic (3 mmol), and K_3PO_4 (6 mmol) at 65 °C. [b]Isolated yield. [c]Microwave reactions were carried out in a microwave model no. CATA R (Catalyst Systems, Pune) using a power of 350 W.

(d, J = 8.4 Hz, 3H), 7.28 (d, J = 8.0 Hz, 2H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 150.1, 133.6, 130.1, 125.2, 124.5, 121.7, 21.3. MS (m/z, EI^+) calcd for $C_{10}H_9NO$ (+) 159.06, found 159.10.

*4.3.3. 5-(4-Methoxyphenyl) Oxazole (**4c**).*[22,37] Dark brown solid; R_f = 0.25 (20% EtOAc/*n*-hexane); yield: 0.154 g, 96%; mp 59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.23 (s, 1H), 6.95 (d, J = 8.4 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (100 MHZ, $CDCl_3$): δ 159.9, 151.6, 149.9, 125.9, 120.0, 114.4, 55.4. MS (m/z, EI^+) calcd for $C_{10}H_9NO_2$ (+) 175.06, found 175.13.

*4.3.4. 5-(4-Chlorophenyl) Oxazole (**4d**).*[22,37] Brown solid; R_f = 0.3 (20% EtOAc/*n*-hexane); yield: 0.15 g, 94%; mp 81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.34 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 150.5, 134.4, 129.2, 126.2, 125.6,

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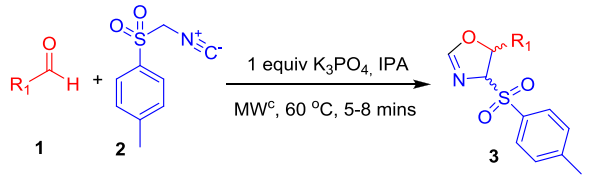
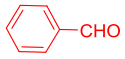
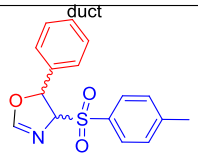
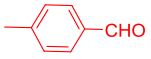
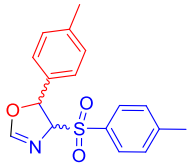
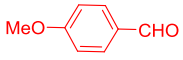
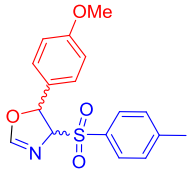
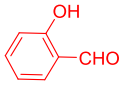
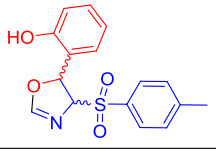
Table 5. Substrate Scope for the Diastereoselective 4,5-Disubstituted Oxazoline Derivatives 3[a]



Entry	R_1CHO	Product	Yield (%)[b]
3a			94
3b			95
3c			95
3d			94

[a]The reactions were performed with aldehyde (3 mmol), tosmic (3 mmol), and K_3PO_4 (3 mmol) at 60 °C. [b]Isolated yield. [c]Microwave reactions were carried out in a microwave model no. CATA R (Catalyst Systems, Pune) at 60 °C using a power of 280 W.

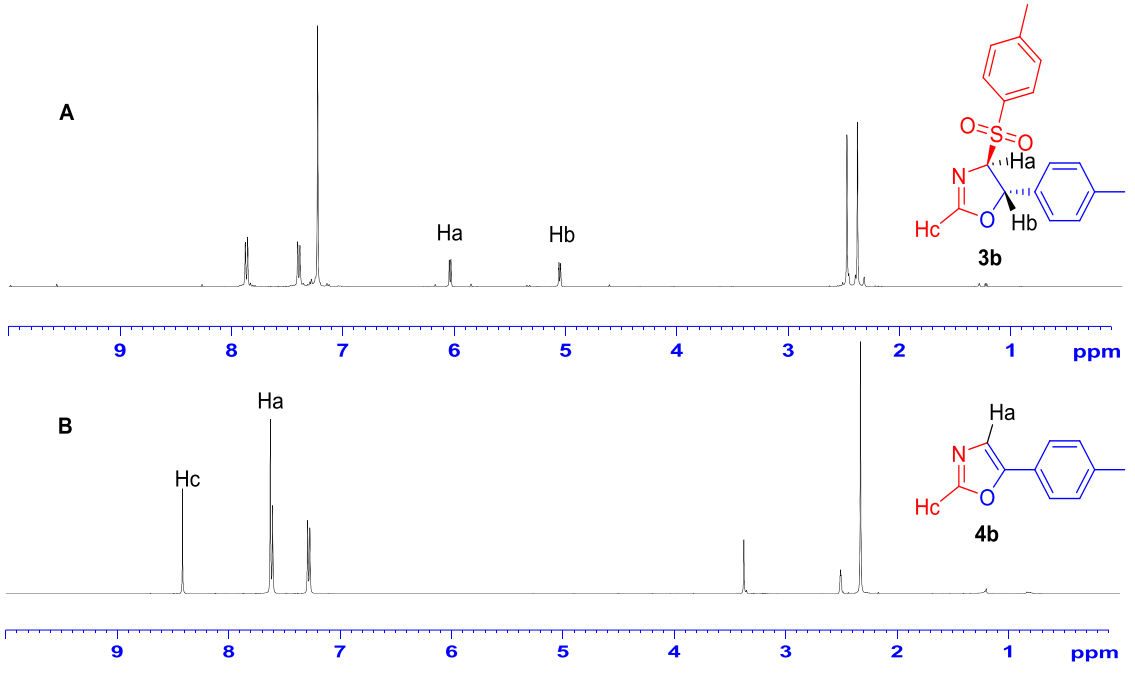


Figure 2. Representative stepwise monitoring 5-(*p*-tolyl)-4-tosyl-4,5-dihydrooxazole **3b** to 5-(*p*-tolyl)oxazole **4b** by ^{1}H NMR spectroscopy.

121.8. MS (*m*/*z*, EI$^+$) calcd for C_9H_6ClNO (+) 179.01, found 179.25.

*4.3.5. 4-(Oxazol-5-yl) Benzonitrile (**4e**).*[32] Brown solid; R_f = 0.3 (20% EtOAc/*n*-hexane); yield: 0.151 g, 93%; mp 71 °C;

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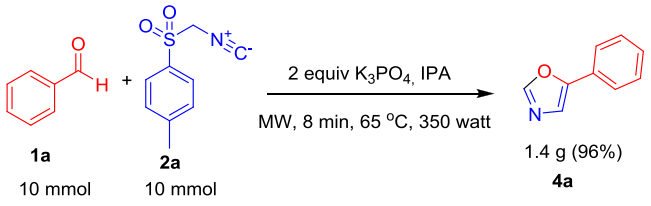
Scheme 3. Gram-Scale Synthesis of 5-Phenyl Oxazoles 4a



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.34 (s, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 150.5, 134.4, 129.2, 126.2, 125.6, 121.8. MS (m/z, EI$^+$) calcd for $C_{10}H_6N_2O$ (+) 170.04, found 170.06.

*4.3.6. 5-(3-Bromophenyl) Oxazole (**4f**).*[21,33,37] Yellow powder; R_f = 0.3 (20% EtOAc/*n*-hexane); yield: 0.142 g, 94%; mp 69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.79 (t, J = 1.7 Hz, 1H), 7.58−7.55 (m, 1H), 7.47−7.44 (m, 1H), 7.37 (s, 1H), 7.28 (d, J = 8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8, 150.1, 131.5, 130.5, 129.6, 127.3, 123.1, 122.9, 122.4. MS (m/z, EI$^+$) calcd for C_9H_6BrNO (+) 222.96, found 223.07.

*4.3.7. 5-(4-Nitrophenyl) Oxazole (**4g**).*[22,37] Brown solid; R_f = 0.3 (20% EtOAc/*n*-hexane); yield: 0.145 g, 92%; mp 103 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.66 (s, 1H), 8.38 (d, J = 8.8 Hz, 2H), 8.07 (s, 1H), 8.04 (d, J = 8.4 Hz, 2H), 8.04 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.9, 149.2, 147.3, 133.7, 126.1, 125.4, 125.0. MS (m/z, EI$^+$) calcd for $C_9H_6N_2O_3$ (+) 190.03, found 190.17.

*4.3.8. (E)-5-Styryloxazol (**4h**).*[21,35] Brown solid; R_f = 0.3 (20% EtOAc/*n*-hexane); yield: 0.154 g, 94%; mp 53 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 1.6 Hz, 2H), 7.21 (d, J = 7.2 Hz, 2H), 7.04 (s, 1H), 6.98 (d, J = 5.6 Hz, 2H), 6.82 (d, J = 16.0 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 150.4, 136.2, 130.3, 128.8, 128.4, 126.6, 124.2, 112.9. MS (m/z, EI$^+$) calcd for $C_{11}H_9NO$ (+) 171.06, found 171.17.

*4.3.9. 3-(Oxazol-5-yl) Phenol (**4i**).*[37] Brown solid; R_f = 0.4 (20% EtOAc/*n*-hexane); yield: 0.153 g, 93%; mp 113 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (brs, 1H), 7.92 (s, 1H), 7.17 (s, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 7.2 Hz, 2H), 6.74 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.9, 151.5, 150.6, 130.1, 128.7, 121.4, 117.0, 115.4, 111.3. MS (m/z, EI$^+$) calcd for $C_9H_7NO_2$ (+) 161.04, found 161.15.

*4.3.10. 5-(4-Fluorophenyl) Oxazole (**4j**).*[22,37] Brown liquid; R_f = 0.4 (20% EtOAc/*n*-hexane); yield: 0.148 g, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.56−7.53 (m, 2H), 7.22 (s, 1H), 7.04 (t, J = 8.4 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.04, 150.47, 126.37, 126.29, 124.06, 124.03, 121.03, 121.01, 116.21, 115. 99. MS (m/z, EI$^+$) calcd for C_9H_6FNO (+) 163.04, found 163.24.

*4.3.11. 5-(4-Bromophenyl) Oxazole (**4k**).*[33,37] Brown solid; R_f = 0.3 (20% EtOAc/*n*-hexane); yield: 0.14 g, 92%; mp 59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.46−7.40 (m, 4H), 7.27 (s, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 150.7, 150.6, 132.2, 126.7, 125.9, 122.6, 122.0. MS (m/z, EI$^+$) calcd for C_9H_6BrNO (+) 222.96, found 223.07.

*4.3.12. 5-(Pyridin-2-yl) Oxazole (**4l**).*[32] Black liquid; R_f = 0.4 (20% EtOAc/*n*-hexane); yield: 0.154 g, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 4.8 Hz, 1H), 7.90 (s, 1H), 7.71−7.66 (m, 1H), 7.63 (s, 1H), 7.58 (d, J = 8 Hz, 1H), 7.17 (dd, J = 4.8, 0.8 Hz 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 151.0, 149.9, 147.1, 136.9, 124.8, 123.1, 119.4. MS (m/z, EI$^+$) calcd for $C_8H_6N_2O$ (+) 146.05, found 146.18.

*4.3.13. 5-(2-Chlorophenyl) Oxazole (**4m**).*[22,37] Brown solid; R_f = 0.3 (20% EtOAc/*n*-hexane); yield: 0.145 g, 92%; mp 97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.70 (s, 2H), 7.36 (d, J = 8 Hz, 1H), 7.26 (d, J = 7.2 Hz, 1H), 7.20−7.19 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 148.2, 130.8, 130.7, 129.3, 127.9, 127.1, 126.5, 126.1. MS (m/z, EI$^+$) calcd for C_9H_6ClNO (+) 179.01, found 179.11.

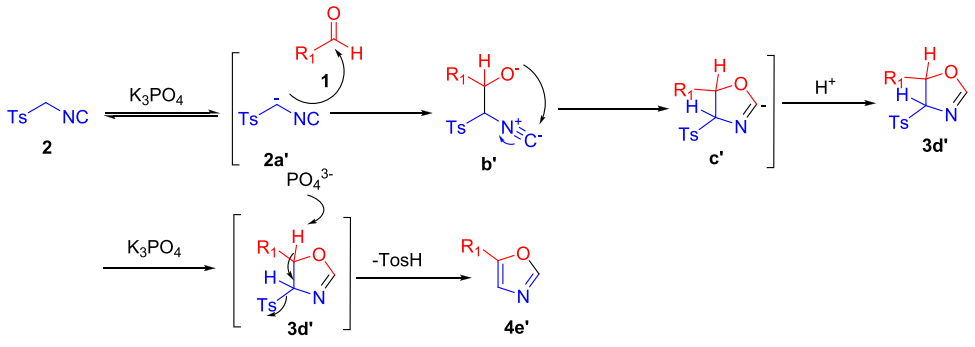
*4.3.14. 5-(3-Nitrophenyl) Oxazole (**4n**).* Pale brown solid; R_f = 0.3 (20% EtOAc/*n*-hexane); yield: 0.142 g, 90%; mp 79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (t, J = 1.6 Hz, 1H), 8.14−8.11 (m, 1H), 7.93 (s, 1H), 7.92−7.89 (m, 1H). 7.56 (t, J = 8.4 Hz, 1H), 7.45 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 149.4, 148.8, 130.1, 129.8, 129.4, 123.5, 123.1, 119.2. MS (m/z, EI$^+$) calcd for $C_9H_6N_2O_3$ (+) 190.03, found 190.17.

*4.3.15. 5-(2,4-Dimethoxyphenyl) Oxazole (**4o**).*[32] Yellow solid; R_f = 0.25 (20% EtOAc/*n*-hexane); yield: 0.146 g, 95%; mp 73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.16 (s, 1H), 7.13 (dd, J = 8.4, 2.0 Hz, 1H), 7.05 (d, J = 2.0 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 149.9, 149.5, 149.3, 120.7, 120.2, 117.3, 111.4, 107.6, 55.9. MS (m/z, EI$^+$) calcd for $C_{11}H_{11}NO_3$ (+) 205.07, found 205.20.

*4.3.16. 5-Phenyl-4-tosyl-4,5-dihydrooxazole (**3a**).*[35] White solid; R_f = 0.5 (20% EtOAc/*n*-hexane); yield: 0.335 g, 94%, mp 171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.4 Hz, 2H), 7.40 (t, J = 6.8 Hz, 4H), 7.33 (d, J = 6.8 Hz, 2H), 7.24 (s, 1H), 6.05 (d, J = 6.0 Hz, 1H), 5.05 (d, J = 6.0 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 145.7, 137.7, 133.1, 129.9, 129.6, 129.1, 92.6, 79.40, 21.8.

*4.3.17. 5-(p-Tolyl)-4-tosyl-4,5-dihydrooxazole (**3b**).*[23] White solid; R_f = 0.5 (20% EtOAc/*n*-hexane); yield: 0.313 g, 95%, mp 161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J =

Scheme 4. Plausible Reaction Mechanism to 5-Substituted Oxazoles 4



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8.0 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.23 (m, 5H), 6.03 (d, J = 6.0 Hz, 1H), 5.05 (dd, J = 6.0, 1.2 Hz, 1H), 2.47 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 145.7, 139.1, 134.8, 133.2, 129.9, 129.8, 129.6, 125.3, 92.5, 79.5, 21.8, 21.2. MS (m/z, EI$^+$) calcd for $C_{17}H_{17}NO_3S$ (+) 315.09, found 315.26.

*4.3.18. 5-(4-Methoxyphenyl)-4-tosyl-4,5-dihydrooxazole (**3c**).*[36] White solid; R_f = 0.5 (20% EtOAc/*n*-hexane); Yield = 0.289 g, 95%, mp 155 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.83 (d, J = 8.0 Hz, 1H), 7.67 (s, 1H), 7.48 (d, J = 8 Hz, 1H), 7.21 (d, J = 8 Hz, 1H), 7.21 (d, J = 8 Hz, 1H), 6.96 (d, J = 8 Hz, 1H), 5.86 (d, J = 5.6 Hz, 1H), 5.47 (d, J = 5.6 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 160.3, 145.7, 133.5, 130.2, 130.1, 129.9, 128.2, 114.7, 91.3, 79.3, 55.7, 21.6. MS (m/z, EI$^+$) calcd for $C_{17}H_{17}NO_4S$ (+) 331.08, found 331.19.

*4.3.19. 2-(4-Tosyl-4,5-dihydrooxazol-5-yl) Phenol (**3d**).* White solid; R_f = 0.6 (20% EtOAc/*n*-hexane); yield: 0.306 g, 94%; mp 109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79−7.72 (m, 2H), 7.30 (d, J = 8.8 Hz, 4H), 7.20 (d, J = 6.4 Hz, 2H), 7.14 (s, 1H), 5.95 (d, J = 6.0 Hz, 1H), 4.90 (d, J = 6.0 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 145.1, 136.2, 135.1, 133.0, 130.0, 129.6, 129.4, 128.8, 127.0, 126.6, 92.5, 78.7, 21.8. MS (m/z, EI$^+$) calcd for $C_{16}H_{15}NO_4S$ (+) 317.07, found 317.14.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c04130.

^{1}H NMR, ^{13}C NMR, and GCMS spectra of synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This article is dedicated to Prof. Chung Ming Sun for his enormous contribution in combinatorial chemistry.

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