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Facile, Selective, and Regiocontrolled Synthesis of Oxazolines and Oxazoles Mediated by ZnI_2 and $FeCl_3$

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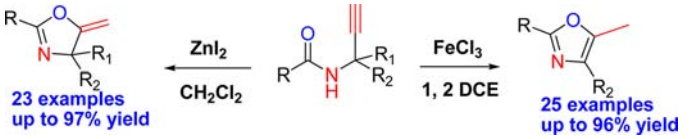
ABSTRACT



An expedient method for a direct approach to the selective and regiocontrolled synthesis of 2-oxazolines and 2-oxazoles mediated by ZnI_2 and $FeCl_3$ is described. A Lewis acid promoted cyclization of acetylenic amide with various functionalities was well tolerated to give 2-oxazolines and 2-oxazoles in good to excellent yields under mild reaction conditions.

Oxazolines and oxazoles have great importance due to their presence in a number of biologically active compounds,[1,2] such as antifungal, antiviral, antibacterial, and antiproliferative activities.[3] The potent biological activity and the prevalence of oxazoles in both natural products and pharmaceuticals has created significant interest in the synthesis of these heterocycles.[4]

Oxazolines and oxazoles are also utilized for other applications such as useful reagent/intermediates in organic synthesis.[5,6] In addition 2-oxazolines are excellent catalyst ligands[7] and protecting groups,[8] providing a continuing stimulus for the development of more common and versatile synthetic methodology to access these classes of compounds.

In recent years, the cyclization of acetylenic amides **1** to the corresponding methyleneoxazolines **2** and oxazoles **3** has been a focus of interest (Scheme 1). These transformations

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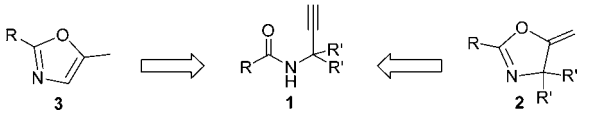
have been reported with transition metals[9a] such as Pd,[9] Cu,[10] Ag,[11] W,[12] Mo,[12] Au,[13] and Ru[13b] as well as with Ce,[16] Bronsted acids,[14] and strong bases.[15]

Scheme 1. Synthetic Approach to Oxazolines and Oxazoles



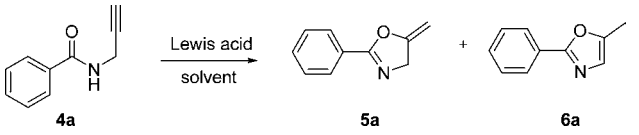
However, some of the above-reported methods suffer from one or more limitations such as low yield, poor regioselectivity, prolonged reaction time, and expensive catalysts in most cases. Therefore development of mild, economical, and complementary approaches to oxaza heterocycle derivatives is still highly desired due to their extreme significance.

In recent decades, Zn[17] and Fe[18] based catalysts have risen significantly in popularity to promote a broad range of organic transformations, owing to their abundance, affordability, and environmental friendliness. We herein report a novel ZnI_2 and $FeCl_3$ promoted cyclization via a C−O bond formation for selective synthesis of substituted oxazoline and oxazole heterocycles from acetylenic amide. It is important to note that this is an inexpensive, regioselective, alternative, and efficient approach in a 5-*exo*-*dig* cyclization mode.

The construction of oxaza heterocycles was initiated with *N*-Prop-2-ynyl-benzamide **4a** as the substrate. We first examined the ability of various Lewis acids to promote the formation of oxaza heterocycles. When **4a** was treated with stoichiometric CuI, $CuCl_2$, and $CuSO_4$ in CH_2Cl_2, there was no significant change in the reaction after 24 h at rt (Table 1, entries 1−3). To our delight, **4a** gave a dimerized product in quantitative yield using 10 mol % of CuI and DMF as a solvent (entry 4). Further reaction of **4a** with stoichiometric $ZnCl_2$ and $ZnBr_2$ produced the required compound **5a** in 75% and 72% yields respectively at rt after 12 h (entries 5 and 6). Interestingly, the best yield of **5a** was obtained when 1 equiv of ZnI_2 was used, and the reaction was complete within 4 h at rt to give a 93% yield (entry 7). Surprisingly, we found that **4a** on reaction with stoichiometric anhyd. $FeCl_3$ gave exclusively **6a** in 40% yield after 24 h at rt using CH_2Cl_2 (entry 8). Various solvents were screened to examine the feasibilty of the reaction with ZnI_2 (entries 7, 11−14), and we observed that the reaction proceeded well in CH_2Cl_2 as solvent (entry 7). We also examined the reaction with 0.5 and 0.3 equiv of ZnI_2 and observed that 0.5 equiv of ZnI_2 gave an 85% yield after 16 h (entries 15 and 16).

The promising result obtained from $FeCl_3$ (Table 1, entry 8) inspired us to further investigate the reaction conditions for a complete conversion of compound **4a**.

Table 1. Optimization of Lewis Acid Mediated Cyclization to Oxaza Heterocycles[a,b]



4a **5a** **6a**

entry	reagent	solvent	time (h)	temp (°C)	**5a** yield (%)	**6a** yield (%)
1	CuI	CH_2Cl_2	24	rt	–	–
2	$CuCl_2$	CH_2Cl_2	24	rt	–	–
3	$CuSO_4$	CH_2Cl_2	24	rt	–	–
4[c,d]	CuI	DMF	16	rt	–	–
5	$ZnCl_2$	CH_2Cl_2	12	rt	75	trace[h]
6	$ZnBr_2$	CH_2Cl_2	12	rt	72	trace[h]
7	ZnI_2	CH_2Cl_2	4	rt	93	–
8	$FeCl_3$	CH_2Cl_2	24	rt	–	40
9	–	toluene	24	130	traces	–
10	–	1,2-DCE	24	80	–	–
11	ZnI_2	1,2-DCE	16	rt	84	–
12	ZnI_2	CH_3CN	24	rt	traces	–
13	ZnI_2	toluene	16	rt	85	–
14	ZnI_2	THF	24	rt	68	–
15[e]	ZnI_2	CH_2Cl_2	16	rt	85	–
16[f]	ZnI_2	CH_2Cl_2	24	rt	68	–
17	$FeCl_3$	CH_2Cl_2	24	45	–	64
18	$FeCl_3$	1,2-DCE	2	80	–	90
19	$FeCl_3$	THF	2	65	–	–
20	$FeCl_3$	toluene	2	80	–	86
21	$FeCl_3$	CH_3CN	24	80	–	66
22	$FeCl_3$	1,2-DME	20	80	–	70
23[e]	$FeCl_3$	1,2-DCE	2	80	–	96
24[f]	$FeCl_3$	1,2-DCE	3	80	–	87
25[g]	$FeCl_3$	1,2-DCE	12	80	–	81
26[c]	$FeCl_3$	1,2-DCE	12	80	–	78

[a] All reactions were carried out in 1 mmol of **4a**, 1 equiv of reagent, and 2 mL of solvent unless otherwise noted. [b] For optimization, **4a** was isolated and studied. [c] 10 mol % of reagent. [d] Dimer of **4a**. [e] 50 mol % of reagent. [f] 30 mol % of reagent. [g] 20 mol % of reagent. [h] By ^{1}H NMR.

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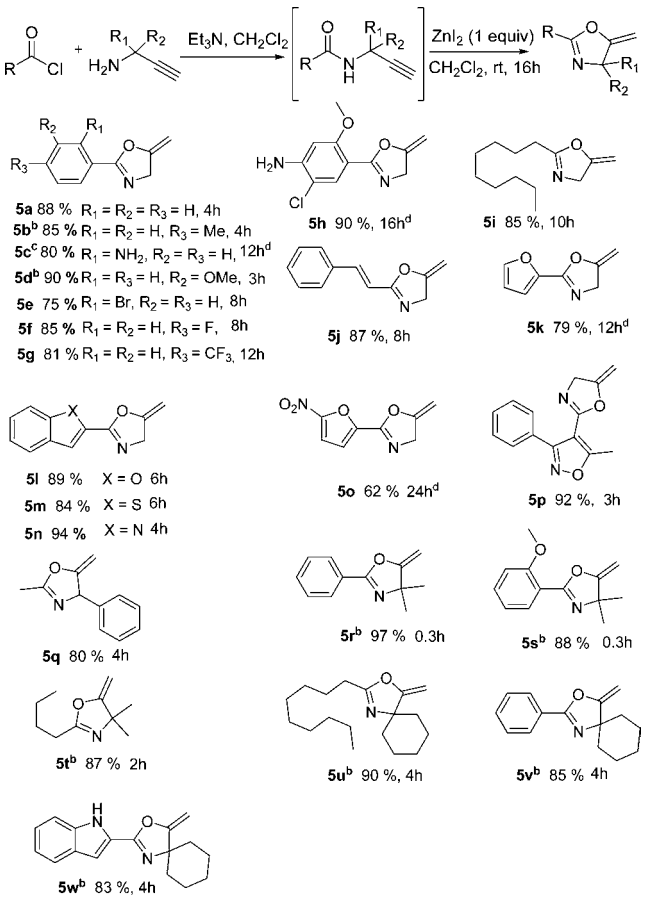
Scheme 2. ZnI_2 Promoted Cyclization Reaction of Propargyl Amides for the Synthesis of Oxazolines[a]

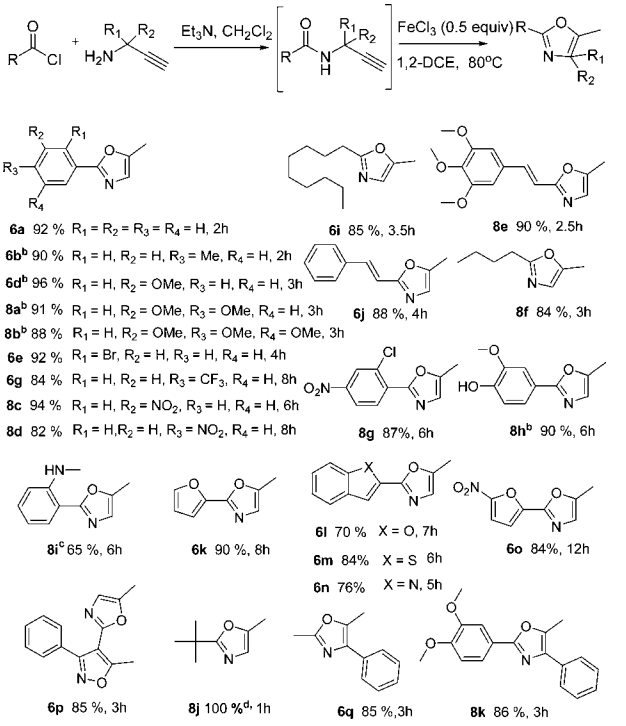


[a] All reactions were carried out in 1 mmol of acid chlorides, amine (1.2 equiv), Et_3N (2.0 equiv), and CH_2Cl_2 (5 mL), 2−12 h at rt, and then ZnI_2 (1 equiv) in CH_2Cl_2 (5 mL) unless otherwise noted. [b] Reactions were carried out using 50 mol % of ZnI_2. [c] Procedure for compound **5c** in the Supporting Information. [d] Reaction performed at 45 °C.

The reaction of **4a** with $FeCl_3$ under various solvent conditions such as CH_2Cl_2, 1,2-DCE, THF, toluene, acetonitrile, and 1,2-DME (entries 17−22) revealed 1,2-DCE to be the best solvent (entry 18). Then, the amount of $FeCl_3$ was varied (Table 1, entries 23−26). The results showed 0.5 equiv in 1,2-DCE at 80 °C (entry 23) to be the optimum conditions.

Under the optimized reaction conditions, the reaction scope of various propargyl amides with a variety of substituents were investigated for the formation of oxazolines. As shown in Scheme 2, a series of substituents on *N*-Prop-2-ynyl-benzamide including *p*-Me, *o*-NH_2, *m*-MeO, *o*-Br, *p*-F, and *p*-CF_3 were tolerated and the corresponding oxazolines were obtained in 81%−90% yields (Scheme 2, **5b**−**g**). Propargyl amides with an electron-donating group on the *ortho*-, *meta*-, or *para*-position (**5b**−**d**) gave slightly higher yields than those of an electron-withdrawing group on the corresponding positions (**5e**−**5g**). The reaction worked well with a multisubstituted alkynyl amide to give a 90% yield (**5h**). In contrast, a variety of aliphatic and heterocyclic derivatives of oxazolines were obtained in 62%−94% yields (Scheme 2, **5i**−**5p**) including derivatives such as furan, benzofuran, benzothiophene, indole, and isoxazoles. The reaction of mono- and di-α- substituted propargyl amides with 0.5 equiv of ZnI_2 afforded the corresponding multisubstituted oxazolines and spirocyclic compounds in 80%−97% yields (**5q**−**5w**). The structure of compound **5m** was confirmed by ORTEP (Figure 1).

Scheme 3. $FeCl_3$ Promoted Cyclization Reaction of Propargyl Amides for the Synthesis of Oxazoles[a]

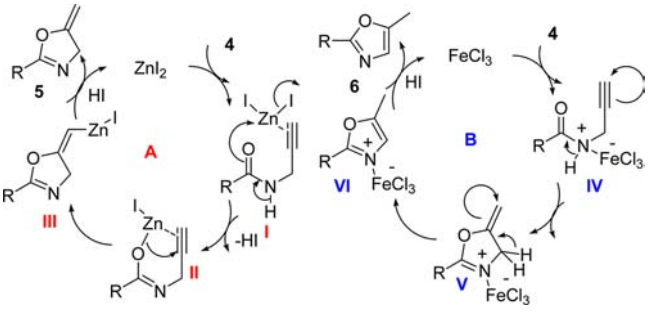


[a] All reactions were carried out in 1 mmol of acid chlorides, amine (1.2 equiv), Et_3N (2.0 equiv), and CH_2Cl_2 (5 mL), 2−12 h at rt, and then $FeCl_3$(50 mol %) in 1,2-DCE (5 mL) at 80 °C, 3−8 h, unless otherwise noted. [b] Reactions were carried out with 30 mol % of $FeCl_3$. [c] Procedure for compound **8i** in the Supporting Information. [d] Reaction conversion by GC.

From the optimized conditions for oxazole, the reaction scopes of various propargyl amides with a variety of substituents were investigated. As shown in Scheme 3, a series of substituents on *N*-Prop-2-ynyl-benzamide (**4a**) including *p*-Me, *o*-Br, and *p*-CF_3 were tolerated and corresponding oxazoles were obtained in excellent yields (Scheme 3, **6b**, **6e**, and **6g**). The reaction of a mono-, di-, and trimethoxy derivative gave the required compound in good yields (**6d**, **8a**, and **8b**). The presence of a nitro group at the *meta*- position gave a higher yield than at the *para*-position (**8c** and **8d**). The reaction of acryl amide derivatives gave the desired compounds **6j** and **8e** in 88% and 90% yields. Multisubstituents such as 2-Cl-4-NO_2 and 3-MeO-4-OH also produced the corresponding oxazole derivatives with good yields of 87% and 90% (**8g** and **8h**). The reaction of *o*-NHMe gave the required compound, albeit in low yield (**8i**). The reaction of aliphatic propargyl

amides underwent smooth conversion to produce oxazoles in excellent yields (Scheme 3, **6i**, **8f**, and **8j**). Attempts were made on various heterocyclic derivatives such as furan, benzofuran, benzothiophene, indole, and isoxazoles, which delightfully gave the desired compounds with good yields of 70%−90%. Finally, to explore the formation of a 2,4,5-trisubstituted oxazole derivative, α-substituted propargyl amides were employed under the standard conditions and the reaction gave the required oxazoles in good yields (Scheme 3, **6w**, **8k**). In general, the electron-donating and -withdrawing groups do not effect product formation under these conditions. The UV absorption of some oxazole compounds was in the 300−400 nm region depending on the conjugation ability. Compound **6j** in SI Table 1, entry 1 (see Supporting Information) showed a maximum absorption at 312 nm, excitation at 340 nm, and emission at 374 nm. The emission spectra of bis heterocyclic compounds (**6l**, **6m**, and **6n**) were in the 345−360 nm range. The structure of compound **6n** was confirmed by ORTEP[19] (Figure 1).

Scheme 4. A Plausible Reaction Mechanism for the Formation of Oxazoline (**A**) and Oxazoles (**B**)

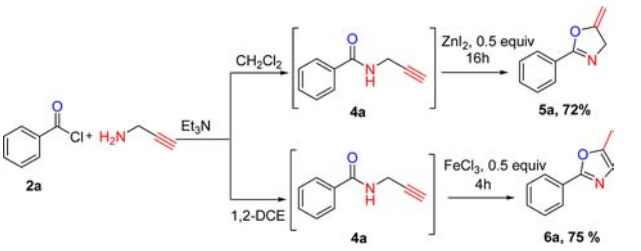


A plausible mechanism as outlined in Scheme 4 was proposed for the formation of oxazolines (**A**) and oxazoles (**B**) on the basis of the results obtained. Initial coordination of ZnI_2 to the triple bond of **4** enhances the electrophilicity of alkyne **I**. The amido-imido tautomerization of intermediate **I** followed by regioselective intramolecular 5-*exo-dig* cyclization via **II** gave the vinyl zinc intermediate **III** which, on hydrolysis with HI generated *in situ*, resulted in desired compound **5**. In mechanism **B**, presumably, iron acts as a Lewis acid that promotes the tautomerization of compound **4** via **IV** followed by 5-*exo-dig* cyclization to produce intermediate **V**. An internal proton transfer from intermediate **V** resulted in the formation of the required oxazole derivative **6**.

To check the feasibility of the reaction in a one pot sequential addition, we examined substrate **2a** with propargyl amine in CH_2Cl_2 and 1,2-DCE as the solvent with Et_3N as the base to obtain the intermediate **4a**, followed by

(19) CCDC number for compounds **5m**, **6n**, and **8b** are CCDC 890290, CCDC 890289, and CCDC 890288.

Scheme 5. One Pot Synthesis of Oxazolines and Oxazoles



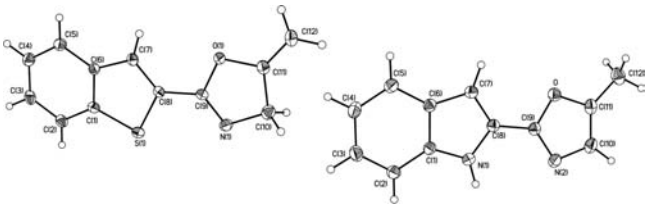


Figure 1. ORTEP for compounds **5m** and **6n**.

the addition of ZnI_2 and $FeCl_3$ producing the target compounds **5a** and **6a** in moderate yields (Scheme 5).

In conclusion, we have developed the first example of a ZnI_2 and $FeCl_3$ promoted cyclization of acetylenic amides to selectively achieve oxazolines and oxazoles via a C−O bond formation. The present Lewis acid promoted cyclization is a practical route for oxaza heterocycles. On the basis of the results obtained, several features should be noted: (1) an inexpensive, regioselective, alternative, and efficient approach in a 5-*exo-dig* cyclization mode is used; (2) the feasibility of reaction was studied with a wide range of functionality in good to excellent yields; (3) the feasibility of one pot synthesis via sequential addition gave the desired oxazolines and oxazoles in moderate yield; (4) no special precautions were required such as N_2 or argon to carry out the reaction, and this approach could find applicability in further cyclization leading to the formation of new heterocycles; and (5) the Lewis acid used here is abundant, affordable, and environmentally benign.

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Supporting Information Available. Experimental procedures, compound characterization, and crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.