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# Sequential Copper-Catalyzed Vinylation/ Cyclization: An Efficient Synthesis of Functionalized Oxazoles

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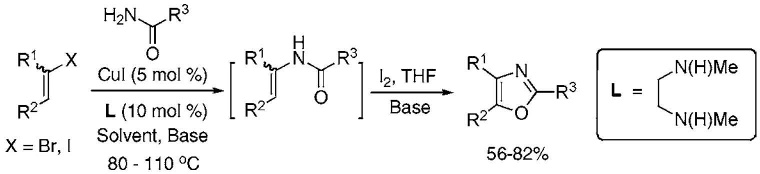
## ABSTRACT



**A modular and practical synthesis of highly substituted oxazoles has been developed. The transformation consists of a sequential copper-catalyzed amidation of vinyl halides followed by cyclization promoted by iodine. A wide variety of functionalized oxazoles and polyazoles can be obtained in a selective manner from simple and easily accessible precursors.**

The ubiquity of oxazoles in a wide variety of natural products[1] and their pivotal role as synthetic intermediates has attracted the attention of both industrial and academic communities for decades.[2] This interest arises from the fact that a significant number of complex molecules, such as Hennoxazoles, Diazonamide A, Micrococcin P1, Telomestatin, or Leucamide A, display significant biological activity as cytotoxic, antifungal, antibacterial, antitumor, and antiviral agents (Figure 1).[3] The discovery of their important pharmacological properties stimulated substantial interest in the chemistry and synthesis of these important heterocycles. Classical procedures for their preparation include, among others,[4] the Cornforth protocol,[5] decomposition of α-diazocarbonyl compounds in nitriles,[6] pyrolysis of *N*-acylisoxazolones,[7] oxidations of oxazolines,[8] or Robinson−Gabriel-type reactions.[9,10]

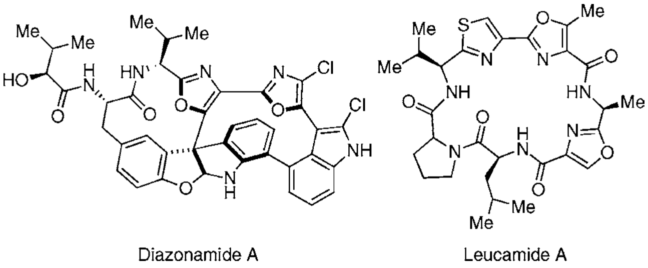


**Figure 1.** Linked polyazoles in natural products.

In recent years, novel strategies based on metal-catalyzed reactions[11] have overcome most of the disadvantages of the classic synthetic protocols, as harsh conditions are generally

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[1] For recent reviews: (a) Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464. (b) Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995.

[2] (a) Palmer, D. C.; Taylor, E. C. *Oxazoles: Synthesis, Reactions and Spectroscopy, Parts A & B, Chemistry of Heterocyclic Compounds*; JohnWiley & Sons: New York, 2004; Vol 60. (b) Maryanoff, C. A. In *Heterocyclic Compounds*; Turchi, I. J., Ed.; Wiley & Sons: New York, 1986; Vol. 45, Chapter 5.

[3] For a review on the occurrence of linked polyazoles in natural products, see: Riego, E.; Hernandez, D.; Albericio, F.; Alvarez, M. *Synthesis* **2005**, 1907.

[4] For selected methods for the preparation of oxazoles, see: (a) Herrera, A.; Martínez-Alvarez, R.; Ramiro, P.; Molero, D.; Almy, J. *J. Org. Chem.* **2006**, *71*, 3026. (b) Morwick, T.; Hrapchak, M.; De Turi, M.; Campbell, S. *Org. Lett.* **2002**, *4*, 2665. (c) Sisko, J.; Kassick, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A. *J. Org. Chem.* **2000**, *65*, 1516.

[5] (a)Yokohama, M.; Menjo, Y.; Watanabe, M.; Togo, H. *Synthesis* **1994**, 1467. (b) Cornforth, J. W.; Cornforth, R. H. *J. Chem. Soc.* **1947**, 96.

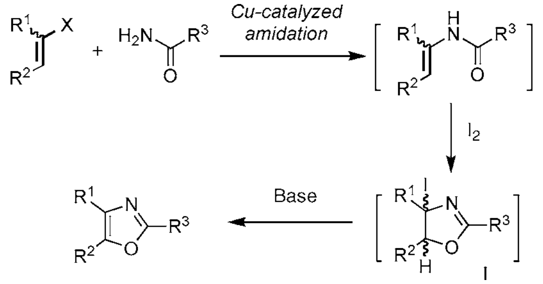
[6] Doyle, M. P.; Buhro, W. E.; Davidson, J. G.; Elliot, R. C.; Hoekstra, J. W.; Oppenhuizen, M. *J. Org. Chem.* **1980**, *45*, 3657.

10.1021/ol7024718 CCC: $37.00

avoided and readily available starting materials are utilized. Although considerable efforts have been made, the development of a milder and general route to access these nitrogen-containing heterocycles in the presence of other sensitive functional groups would be highly desirable. In this context, Cu-catalyzed transformations provide a promising alternative, mainly due to their high efficiency, mild reaction conditions, and low cost.[12,13]

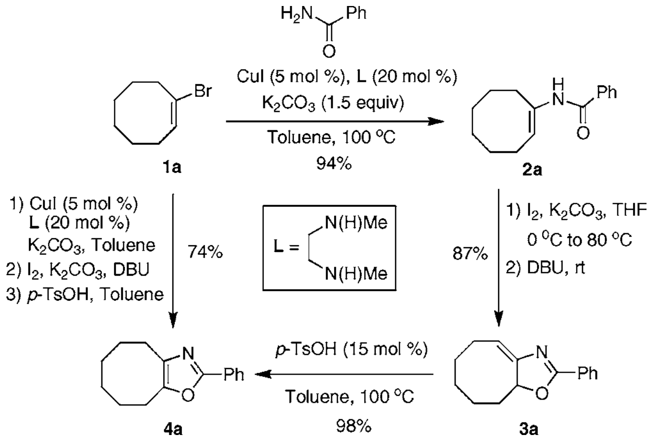
Recently, our research group has disclosed several sequential and cascade one-pot procedures for the synthesis of nitrogen-containing heterocycles based on Cu-catalyzed C−N bond-forming reactions.[14] Herein, we report our studies on the development of a general protocol for the synthesis of highly substituted oxazoles by a sequential Cu-catalyzed amidation of vinyl halides[15] followed by intramolecular cyclization promoted by iodine (Scheme 1).

**Scheme 1.** Synthesis of Oxazoles through a Sequential Cu-Catalyzed Vinylation/Cyclization



We started our work by examining the conversion of vinyl bromide **1a** to **2a** following the conditions we originally developed for the Cu-catalyzed amidation of vinyl bromides (Scheme 2).[14a] With no need for further optimization, **2a** was prepared in 94% yield. According to the general route depicted in Scheme 1, we next focused on the cyclization of substrate **2a** promoted by iodine, leading to intermediate type **I** (Scheme 1). Although some electrophilic iodine sources were also examined (ICl, NIS, and IPy$_2$•BF$_4$), the best results were obtained when using $I_2$ in THF at 80 °C.[16,17] In contrast, the use of $I_2$ in THF at room temperature resulted in a lower conversion of **2a**. The choice of the base played a crucial role; the use of 2 equiv of $K_2CO_3$ was found to be optimal, whereas reactions with $Cs_2CO_3$, $K_3PO_4$, NaO$^t$Bu, NaH, or NEt$_3$ were much slower or produced only decomposition products.[18] All attempts to isolate an intermediate of type **I** (Scheme 1) were unsuccessful. Instead, addition of DBU to the reaction mixture promoted the formation of **3a** in good overall yield. It is noteworthy that under these reaction conditions **4a** was not detected by $^1$H NMR spectroscopy of the crude reaction mixture. Subsequent acidic treatment was necessary to achieve isomerization, and oxazole **4a** was obtained in near quantitative yield. More importantly, oxazole **4a** could also be obtained from readily available vinyl halide **1a** without purification of the corresponding intermediates, in an overall yield similar to that achieved in the stepwise process.[19]

**Scheme 2.** Synthesis of Oxazoles through a Stepwise or a Sequential Protocol



Encouraged by these results, we sought to examine the scope and generality of the sequential method (Table 1). Although vinyl bromides afforded the corresponding oxazoles in good overall yields, the best results were accomplished by using vinyl iodides as coupling counterparts. In these cases, the Cu-catalyzed amidation was better

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(7) Prager, R. H.; Smith, J. A.; Weber, B.; Williams, C. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2665.

(8) For some selected examples, see: (a) Williams, D. R.; Lowder, P. D.; Gu, Y.-G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331. (b) Meyers, A. I.;Tavares, F. X. *J. Org. Chem.* **1996**, *61*, 8207.

(9) (a) Keni, M.; Tepe, J. J. *J. Org. Chem.* **2005**, *70*, 4211. (b) Pulici, M.; Quartieri, F.; Felder, E. R. *J. Comb. Chem.* **2005**, *7*, 463.

(10) (a) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165. (b) Brain, C. T.; Paul, J. M. *Synlett* **1999**, 1642. (c) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604.

(11) For selected references, see: (a) Kumar, M. P.; Liu, R.-S. *J. Org. Chem.* **2006**, *71*, 4951. (b) Davies, J. R.; Kane, P. D.; Moody, C. J. *J. Org. Chem.* **2005**, *70*, 7305. (c) Black, D. A.; Arndtsen, B. A. *Tetrahedron* **2005**, *61*, 11317. (d) Stephen, A.; Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *23*, 4391. (e) Milton, M. D.; Inada, Y.; Nishibayashi, Y.; Uemura, S. *Chem. Commun.* **2004**, *23*, 2712. (f) Lee, Y. R.; Yeon, S. H.; Seo, Y.; Kim, B. S. *Synthesis* **2004**, 2787. (g) Arcadi, A.; Cacchi, S.; Cascia, L.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2001**, *3*, 2501. (h) Lee, J. C.; Song, I.-G. *Tetrahedron Lett.* **2000**, *41*, 5891.

(12) For recent reviews on Cu-catalyzed C−N bond-forming reactions, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (c) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428.

(13) For a recent review on the synthesis of heterocycles by Cu-catalyzed reactions, see: Chemler, S. R.; Fuller, P. H. *Chem. Soc. Rev.* **2007**, *7*, 1153.

(14) (a) Jones, C. P.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 7968. (b) Martín, R.; Larsen, C. H.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 3379. (c) Rodríguez-Rivero, M.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 973. (d) Martín, R.; Rodríguez-Rivero, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079.

(15) (a) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (b) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809. (c) Shen, R.; Porco, J. A. *Org. Lett.* **2000**, *2*, 1333.

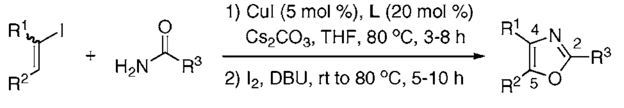
(16) For some selected related cyclizations promoted by iodine, see: (a) Hu, T.; Liu, K.; Shen, M.; Yuan, X.; Tang, Y.; Li, C. *J. Org. Chem.* **2007**, 72, 8555. (b) Davis, F. A.; Song, M.; Augustine, A. *J. Org. Chem.* **2006**, *71*, 2779. (c) Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, *7*, 5203. (d) Williams, D. R.; Osterhout, M. H.; Amato, G. S. *Heterocycles* **2004**, *64*, 45. (e) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459.

(17) The screening of the different reaction conditions was analyzed by $^1$H NMR spectroscopy of the crude reaction mixtures.

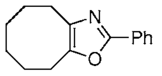
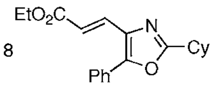
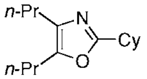
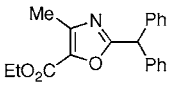
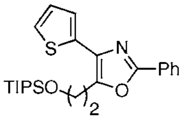
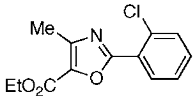
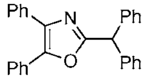
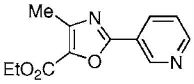
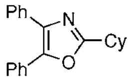
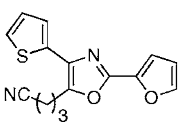
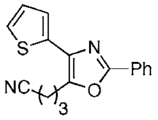
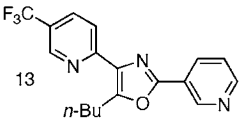
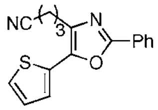
(18) The cyclization without base gave low conversions of **1a**.

(19) For experimental details, see Supporting Information.

**Table 1.** Scope of the Sequential One-Pot Cu-Catalyzed Amidation−Iodination Protocol[a]



**1 a-m** **4 a-m**

| entry | product | yield(%)[b] | entry | product | yield(%)[b] |
|---|---|---|---|---|---|
| 1 |  | 78, 74[c] (**4a**)[d] | 8 |  | 63 (**4h**) |
| 2 |  | 56 (**4b**)[d] | 9 |  | 82 (**4i**) |
| 3 |  | 72 (**4c**) | 10 |  | 77 (**4j**) |
| 4 |  | 79, 74[c] (**4d**) | 11 |  | 70 (**4k**) |
| 5 |  | 81 (**4e**) | 12 |  | 63 (**4l**) |
| 6 |  | 68 (**4f**) | 13 |  | 74 (**4m**) |
| 7 |  | 72 (**4g**) | | | |

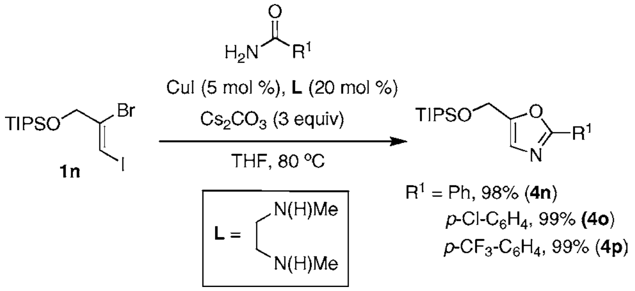
[a] Reaction conditions: (1) vinyl iodide (X = I, 1.0 equiv), amide (1.2 equiv), CuI (5 mol %), **L** (20 mol %), $Cs_2CO_3$ (1.5 equiv), THF (0.5 M) at 80 °C; 2) $I_2$ (1.1 equiv), $K_2CO_3$ (2 equiv), 3−5 h, and then, DBU (2 equiv). Cy = cyclohexyl, Ph = phenyl, TIPS = triisopropylsilyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, **L** = *N,N′*-dimethylethylenediamine. [b] Yields of the isolated products are the average of two runs. [c] Starting from vinyl bromide, using $K_2CO_3$ (2 equiv) and toluene (0.5 M) at 100 °C for the Cu-catalyzed amidation reaction. [d] ddition of *p*-TsOH·$H_2O$ (10 mol %) to the crude reaction mixture in toluene at 100 °C.

performed using $Cs_2CO_3$ and THF as the base and solvent, respectively.[15a] With regard to thearyl halide, both electron-rich and electron-deficient vinyl halides were equally efficient and could be combined both with aromatic or aliphatic amides. A variety of functional groups were tolerated in either substrate, including silyl groups (entry 3), nitriles (entries 6, 7, and 12), α,*β*-unsaturated moieties (entry 8), esters (entries 9−11), aryl halides (entry 10), $CF_3$ groups (entry 13), and heterocycles(entries 3, 6, 7, and 11−13). Polyazoles **4l** and **4m** (entries 12 and 13) could also be prepared in good yields by using our standard protocol.

Some important highlights of this transformation are (1) addition of *p*-TsOH·$H_2O$ to induce isomerization to the oxazole product was not necessary when aromatic or electron-withdrawing groups were present in position 4 and 5 of the oxazole ring. In this case, treatment with DBU gave rise directly to the corresponding aromatic heterocycle (entries 3−13); (2) the geometry of the starting vinyl halides **1b**−**m** did not affect the outcome of the sequential metal-catalyzed vinylation−cyclization, affording oxazoles **2b**−**m** with similar overall yield;[20] (3) selective iodination of the enamide leading to oxazoles **4** was observed when other olefinic double bonds or even electron-rich heterocycles were present (entries 3, 6−8, and 12); (4) although there have been several reports on the intramolecular haloetherifications of enamides,[21]using our protocol, however, no cyclic ether was detected in the crude reaction mixture leading to **4c** (entry 3).[22]

As the synthesis of mono- or disubstituted oxazoles afforded complex mixtures or in some instances, decomposition products, we decided to explore alternative routes for their synthesis. Given our success on recent cascade Cu-catalyzed reactions,[14b,d] we wondered whether it would be possible to effect a domino Cu-catalyzed C−N/C−O bond-forming reaction[23] employing a 1,2-dihaloalkene substrate as a means to access disubstituted oxazole (Scheme 3).[24]

**Scheme 3.** Synthesis of Disubstituted Oxazoles through a Domino Cu-Catalyzed C−N/C−O Bond-Forming Reaction



As shown in Scheme 3, disubstituted oxazoles bearing silyl groups, aryl chlorides, or $CF_3$ groups all could be prepared in quantitative yields from readily available 1,2-dihaloalkene **1n** by using essentially our standard protocol. The procedure allows easy and complete control over the installation of substitutents around the heterocyclic core, because the C−N

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(20) Cu-catalyzed amidation of isomerically pure *Z*-**1b** and *Z*-**1d** gave rise to mixtures of *E*- and *Z*-**2b-d** (~4:1), as shown by NMR spectroscopy of the crude reation mixtures. For similar isomerizations of enamides, see: (a) Reference 14b. (b) Wallace, D. J.; Klauber, D. J.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749.

(21) For some examples on halo-etherification and halo-lactonization of enamides, see: (a) Rudler, H.; Denise, B.; Xu, Y.; Parlier, A.; Vaissermann, J. *Eur. J. Org. Chem.* **2005**, 3724. (b) Rudler, H.; Denise, B.; Parlier, A.; Daranb, J. *Chem. Commun.* **2002**, *9*, 940. (c) Martín-López, M. J.; Bermejo-González, F. *Tetrahedron* **1998**, *54*, 12379. (d) Williams, R.; Milreis, G. F. *Tetrahedron Lett.* **1990**, *31*, 4297. (e) Shin, C.; Sato, Y.; Yoshimura, J. *Tetrahedron Lett.* **1981**, *22*, 2401.

(22) For a recent intramolecular halo-etherification using silyl ethers, see: Ko, C.; Hsung, R. P.; Al-Rashid, Z. F.; Feltenberger, T. L.; Yang, J.-H.; Wei, Y.; Zificsak, C. A. *Org. Lett.* **2007**, *9*, 4459.

(23) For related procedures using benzene derivatives, see: (a) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (b) Altenhoff, G.; Glorius, F. *Adv. Synth. Catal.* **2004**, *346*, 1661.

(24) During the preparation of this manuscript, a synthesis of oxazoles from1,2-dihaloalkene derivatives was published: Schuh, K.; Glorius, F. *Synthesis* **2007**, 2297.

bond-forming reaction takes place exclusively at the vinyl iodide moiety. A limitation of this method, however, is the lack of a general route for the synthesis of the requisite 1,2-dihaloalkene substrates.

In summary, a practical and mild new method for the synthesis of highly functionalized oxazoles and polyazoles has been developed. The readily availability of the precursors and the functional group tolerance should make this method attractive to synthetic chemists. Further investigations into the application of Cu-catalyzed vinylation processes for the synthesis of other heterocycles are currently underway in our laboratory.

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**Supporting Information Available:** Experimental procedures and spectral data for all compounds. This material isavailable free of charge via the Internet at http://pubs.acs.org.

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