doi:10.1246/cl.2012.636

Published on the web June 2, 2012

A Facile Access to 3,5-Disubstituted Oxazolones Featuring a Cu-catalyzed Cyclization of *N*-Alkynyl *tert*-Butyl Carbamates

Zenghui Lu,[1] Zhaozhen Yang,[1] Weijian Cui,[1] and Gangguo Zhu*[1,2]
[1]*Department of Chemistry, Zhejiang Normal University, 688 Yingbin Road, Jinhua 321004, P. R. China*
[2]*Key Laboratory of the Ministry of Education for Advanced Catalysis Materials, Zhejiang Normal University, Jinhua 321004, P. R. China*

(Received April 1, 2012; CL-120279; E-mail: gangguo@zjnu.cn)

Using cheap and readily accessible CuCl as the catalyst, an operationally simple and efficient method for the synthesis of 3,5-disubstituted oxazolones has been realized by the cyclization of *N*-alkynyl *tert*-butyl carbamates. The reaction proceeds under mild reaction conditions and shows good functional group compatibility.

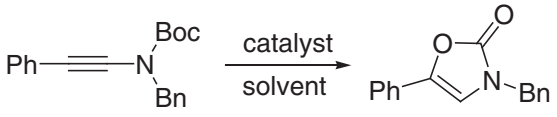
Oxazolones are a common structural motif that occurs in numerous natural products and pharmacological active molecules.[1] They are also found to be one of the most important building blocks in organic synthesis and have been widely utilized in a variety of organic reactions, including radical reactions,[2] [4 + 2] cycloaddition,[3] Pauson–Khand reaction,[4] and preparation of functionalized oxazolidinones and their derivatives.[5] Consequently, it is highly desirable to develop new methods allowing the efficient construction of oxazolones from readily available starting materials. Among these, oxazolones are often prepared by the Lewis acid- or base-catalyzed condensation of 1,2-aminoketones with carbonyl compounds.[6] However, the harsh conditions, such as strong acidic or basic additives, high temperature, or the utilization of toxic carbonylation reagents, limit the application of these methods.

Hashmi[7a] and Gagosz[7b] independently reported an elegant method for the synthesis of highly functionalized oxazolones using a Au-catalyzed cycloisomerization of *N*-alkynyl *tert*-butyl carbamates.[7,8] More recently, Lautens and co-workers disclosed a Pd-catalyzed efficient synthesis of 3,5-disubstituted oxazolones from β,β-dibromoenamides.[9] Despite these significant successes, the utilization of costly catalysts, such as gold or palladium complexes, has greatly diminished the synthetic utility of the aforementioned methods.

On the other hand, copper-catalyzed reactions have been dramatically increased over the past decade, and it proves to be one of the most powerful synthetic tools for the assembly of carbon–carbon and carbon–heteroatom bonds in organic chemistry.[10] Moreover, copper catalysts are usually low cost, readily accessible, and stable under a number of reaction conditions. Pursuing our interest in the development of transition-metal-catalyzed reactions from heteroatom-substituted acetylenes,[11] we wish to report here an efficient method for the synthesis of 3,5-disubstituted oxazolones via a Cu-catalyzed cyclization of *N*-alkynyl *tert*-butyl carbamates.

At the outset of this study, the reaction of *N*-alkynyl *tert*-butyl carbamates **1a** was chosen as a model reaction to evaluate the reaction parameters. As a result, the 3,5-disubstituted oxazolone **2a** was obtained in 72% isolated yield by treating **1a** with 10 mol % of $CuCl_2$ in toluene at 50 °C for 5 h (Table 1, Entry 1). The control experiment revealed that the metal catalyst is essential for the occurrence of this cyclization reaction (Entry 2). Encouraged by this promising result, we then examined other catalysts for this transformation.

Table 1. Screening of the reaction conditions[a]



1a **2a**

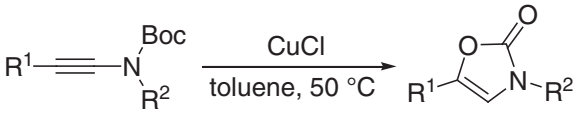
Entry	Catalyst	Solvent	Yield[b]/%
1	$CuCl_2$	toluene	72
2	—	toluene	NR[c]
3	$CuBr_2$	toluene	68
4	$Cu(OAc)_2$	toluene	38
5	$CuSO_4$	toluene	trace
6	CuBr	toluene	90
7	CuCl	toluene	91 (92)[d]
8	Cu_2O	toluene	trace
9	$FeCl_3$	toluene	messy
10	$ZnCl_2$	toluene	25
11	CuCl	CH_3CN	80
12	CuCl	DCE	84
13	CuCl	DMF	55
14	CuCl	DMSO	40
15	CuCl	THF	77
16	CuCl	dioxane	60
17	CuCl	EtOAc	80
18	CuCl	toluene	77[e]
19	CuCl	toluene	88[f,g]

[a]The reactions were carried out using **1a** (0.5 mmol) and Cu catalyst (0.05 mmol) in 2 mL of solvent at 50 °C for 5 h. [b]Isolated yields. [c]NR: no reaction. [d]Isolated yield on 10 mmol scale. [e]The reaction was run at room temperature for 24 h. [f]5 mol % of CuCl. [g]18 h.

Among the catalysts we tested, CuBr and CuCl turned out to be the best choices, giving rise to 3,5-disubstituted oxazolone **2a** in 90% and 91% yields, respectively (Entries 6 and 7). Other metal complexes, such as $FeCl_3$ and $ZnCl_2$, proved to be much less effective (Entries 9 and 10). Afterward, we decided to perform further optimization using CuCl as the catalyst.

A brief survey of the solvent indicated that toluene was the optimal solvent, although other solvents, such as CH_3CN, THF, and EtOAc, were also effective (Entries 11–17). Running the reaction at room temperature led to a decrease of the yield to 77% (Entry 18). In contrast, the decrease of amounts of CuCl from 10 to 5 mol % provided the desired product **2a** in 88%

Table 2. Synthesis of 3,5-disubstituted oxazolones **2**[a]



1 **2**

Entry	**1**	R^1	R^2	Yield[b]/%
1	**1a**	Ph	Bn	91 (**2a**)
2	**1b**	4-F-C_6H_4	Bn	76 (**2b**)
3	**1c**	4-Cl-C_6H_4	Bn	84 (**2c**)
4	**1d**	2-Cl-C_6H_4	Bn	83 (**2d**)
5	**1e**	4-Br-C_6H_4	Bn	86 (**2e**)
6	**1f**	3-Br-C_6H_4	Bn	85 (**2f**)
7	**1g**	4-Me-C_6H_4	Bn	81 (**2g**)
8	**1h**	4-*t*-Bu-C_6H_4	Bn	85 (**2h**)
9	**1i**	4-MeO-C_6H_4	Bn	82 (**2i**)
10	**1j**	3,4-$(MeO)_2$-C_6H_3	Bn	80 (**2j**)
11	**1k**	2-Naphthyl	Bn	72 (**2k**)
12	**1l**	*n*-C_8H_{17}	Bn	68 (**2l**)
13	**1m**	TBSO$(CH_2)_2$	Bn	83 (**2m**)
14	**1n**	TES	Bn	NR[c]
15	**1o**	Ph	Ph	80 (**2o**)
16	**1p**	Ph	*n*-Bu	75 (**2p**)
17	**1q**	Ph	Cy	73 (**2q**)

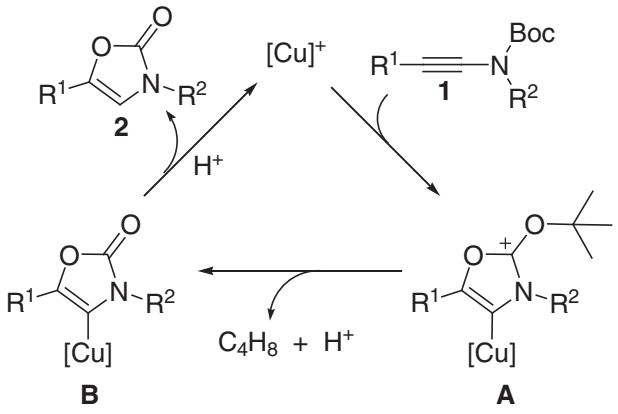
[a]The reactions were carried out using **1** (0.5 mmol) and CuCl (0.05 mmol) in 2 mL of toluene at 50 °C for 5–8 h. [b]Isolated yields. [c]The reaction was carried out at 80 °C for 8 h.

yield, albeit with a prolonged reaction time (18 h) (Entry 19). Therefore, we chose 10 mol % of CuCl as the catalyst, 50 °C as the reaction temperature, and toluene as the solvent for the optimal reaction conditions to access 3,5-disubstituted oxazolones.[12] Indeed, the reaction could be scaled up to 10 mmol to provide oxazolone **2a** in 92% isolated yield (Entry 7).

Having secured a reliable preparative protocol for the synthesis of 3,5-disubstituted oxazolones, we next focused on investigation of the scope and limitations of this reaction. As shown in Table 2, under the standard conditions, the cyclization of either aryl or alkyl *N*-alkynyl *tert*-butyl carbamates proceeded smoothly to furnish the desired 3,5-disubstituted oxazolones **2** in good to excellent yields. For example, substrate **1b** resulted in the formation of 3,5-disubstituted oxazolone **2b** in 76% yield (Entry 2). The *N*-alkynyl *tert*-butyl carbamates **1c** and **1d** afforded the corresponding 3,5-disubstituted oxazolones **2c** and **2d** in respective yields of 84% and 83%, implying that the steric hindrance on the benzene ring has little influence on this transformation (Entries 3 and 4).

The reaction of aliphatic ynamides **1l** and **1m** occurred uneventfully as well to give oxazolones **2l** and **2m** in good yields, while the formation of desired product from the silylated substrate **1n** did not take place, even at an elevated temperature (Entries 12–14). In addition, the effects of substituents on the nitrogen atom of starting materials **1** were briefly examined. Both *N*-phenyl substrate **1o** and *N*-Cy substrate **1q** successfully gave rise to the expected 3,5-disubstituted oxazolones **2o** and **2q** in good yields (Entries 15 and 17).

As such, we have developed an efficient and convenient method to assemble 3,5-disubstituted oxazolones via the Cu-catalyzed cyclization of *N*-alkynyl *tert*-butyl carbamates. Although the Au-catalyzed version has been previously reported by the groups of Hashmi[7a] and Gagosz,[7b] the utilization of inexpensive and readily accessible copper catalyst represents a practical alternative to access 3,5-disubstituted oxazolones.



Scheme 1. Proposed mechanism.

In view of the previous results,[7] a plausible mechanism is proposed in Scheme 1 to account for this Cu-catalyzed transformation of *N*-alkynyl *tert*-butyl carbamates. First, a cationic copper intermediate **A** is believed to be generated by the intramolecular attack of oxygen atom to the Cu-activated C–C triple bond. Then, the release of isobutylene and proton from species **A** leads to an oxazolone–copper intermediate **B**, followed by protodemetallation to produce 3,5-disubstituted oxazolones **2** with concurrent regeneration of the copper catalyst (Scheme 1).

In conclusion, a simple and practical method for the effective synthesis of 3,5-disubstituted oxazolones has been developed by a Cu-catalyzed cyclization of *N*-alkynyl *tert*-butyl carbamates. Using inexpensive and readily accessible CuCl catalyst, the reaction proceeds smoothly at mild reaction conditions, and it is operationally simple and practical for the synthetic community. Further investigations on synthetic applications of this protocol will be described in due course.[13]

This work has been supported by the National Natural Science Foundation of China (Nos. 20902084 and 21172199), Qianjiang Talents Project of the Science and Technology Office in Zhejiang Province (No. 2010R10016), and ZJNU GlycoDrug Research Centre.

References and Notes

1 For a recent review on oxazolones, see: S. Bala, M. Saini, S. Kamboj, *Int. J. ChemTech Res.* **2011**, *3*, 1102, and references therein.

2 a) Y. Yuasa, J. Ando, S. Shibuya, *J. Chem. Soc., Perkin Trans. 1* **1996**, 465. b) G. Butora, T. Hudlicky, S. P. Fearnley, A. G. Gum, M. R. Stabile, K. Abboud, *Tetrahedron Lett.* **1996**, *37*, 8155.

3 a) N. Hashimoto, T. Ishizuka, T. Kunieda, *Tetrahedron Lett.* **1994**, *35*, 721. b) S. V. D'Andrea, J. P. Freeman, J. Szmuszkovicz, *J. Org. Chem.* **1990**, *55*, 4356.

4 a) I. Nomura, C. Mukai, *Org. Lett.* **2002**, *4*, 4301. b) I. Nomura, C. Mukai, *J. Org. Chem.* **2004**, *69*, 1803.

5 a) Y. Yonezawa, C.-G. Shin, A. Ohtsu, J. Yoshimura, *Chem. Lett.* **1982**, 1171. b) T. Shono, Y. Matsumura, T. Kanazawa, *Tetrahedron Lett.* **1983**, *24*, 4577.

6 For selected reports on the synthesis of oxazolones, see: a) G. R. Lenz, C. Costanza, *J. Org. Chem.* **1988**, *53*, 1176. b) H. Aichaoui, J. H. Poupaert, D. Lesieur, J.-P. Hénichart, *Tetrahedron* **1991**, *47*, 6649. c) M. O. Hamad, P. K. Kiptoo, A. L. Stinchcomb, P. A. Crooks, *Bioorg. Med. Chem.* **2006**, *14*, 7051. d) K. Makino, N. Okamoto, O. Hara, Y. Hamada, *Tetrahedron: Asymmetry* **2001**, *12*, 1757. e) C. A. Marques, M. Selva, P. Tundo, F. Montanari, *J. Org. Chem.* **1993**, *58*, 5765. f) M. Yamashita, S.-H. Lee, G. Koch, J. Zimmermann, B. Clapham, K. D. Janda, *Tetrahedron Lett.* **2005**, *46*, 5495. g) H. Jiang, J. Zhao, A. Wang, *Synthesis* **2008**, 763.

7 a) A. S. K. Hashmi, R. Salathé, W. Frey, *Synlett* **2007**, 1763. b) F. M. Istrate, A. K. Buzas, I. D. Jurberg, Y. Odabachian, F. Gagosz, *Org. Lett.* **2008**, *10*, 925.

8 For the preparation of *N*-alkynyl *tert*-butyl carbamate substrates, see: a) Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz, E. L. Vera, *Org. Lett.* **2004**, *6*, 1151. b) X. Zhang, Y. Zhang, J. Huang, R. P. Hsung, K. C. M. Kurtz, J. Oppenheimer, M. E. Petersen, I. K. Sagamanova, L. Shen, M. R. Tracey, *J. Org. Chem.* **2006**, *71*, 4170. c) J. R. Dunetz, R. L. Danheiser, *J. Am. Chem. Soc.* **2005**, *127*, 5776. d) A. L. Kohnen, X. Y. Mak, T. Y. Lam, J. R. Dunetz, R. L. Danheiser, *Tetrahedron* **2006**, *62*, 3815. e) K. Villeneuve, N. Riddell, W. Tam, *Tetrahedron* **2006**, *62*, 3823.

9 D. I. Chai, L. Hoffmeister, M. Lautens, *Org. Lett.* **2011**, *13*, 106.

10 For recent reviews on copper catalysis, see: a) S. V. Ley, A. W. Thomas, *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. b) D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450. c) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054. d) F. Monnier, M. Taillefer, *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. e) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem., Int. Ed.* **2011**, *50*, 11062. f) Y. Liu, J.-P. Wan, *Org. Biomol. Chem.* **2011**, *9*, 6873.

11 a) X. Chen, W. Kong, H. Cai, L. Kong, G. Zhu, *Chem. Commun.* **2011**, *47*, 2164. b) D. Chen, Y. Cao, Z. Yuan, H. Cai, R. Zheng, L. Kong, G. Zhu, *J. Org. Chem.* **2011**, *76*, 4071. c) D. Chen, X. Chen, Z. Lu, H. Cai, J. Shen, G. Zhu, *Adv. Synth. Catal.* **2011**, *353*, 1474. d) H. Cai, Z. Yuan, W. Zhu, G. Zhu, *Chem. Commun.* **2011**, *47*, 8682. e) X. Chen, D. Chen, Z. Lu, L. Kong, G. Zhu, *J. Org. Chem.* **2011**, *76*, 6338. f) Z. Lu, W. Kong, Z. Yuan, X. Zhao, G. Zhu, *J. Org. Chem.* **2011**, *76*, 8524. g) G. Zhu, D. Chen, Y. Wang, R. Zheng, *Chem. Commun.* **2012**, *48*, 5796. h) Z. Lu, X. Xu, Z. Yang, L. Kong, G. Zhu, *Tetrahedron Lett.* **2012**, *53*, in press doi:10.1016/j.tetlet.2012.04.074.

12 Representative procedure for the Cu-catalyzed synthesis of 3,5-disubstituted oxazolones: To a solution of **1a** (154 mg, 0.5 mmol) in 2 mL of toluene was added CuCl (5.0 mg, 0.05 mmol) at 50 °C. After stirring for 5 h, the reaction mixture was concentrated and purified by column chromatography on silica gel (hexane/EtOAc = 6/1) to give 114 mg (yield: 91%) of **2a** as a white solid, mp: 148–150 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.79 (s, 2H), 6.64 (s, 1H), 7.21–7.50 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 47.9, 108.9, 122.9, 127.3, 128.0, 128.2, 128.5, 128.8, 129.1, 135.3, 139.3, 155.0; MS (EI, *m*/*z*): 251 (M^+, 95), 207 (2), 160 (8), 132 (20), 105 (100).

13 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

