ORGANIC LETTERS

2011
Vol. 13, No. 3
518−521

Copper(II)Chloride-Mediated Cyclization Reaction of *N*-Alkoxy-*ortho*-alkynylbenzamides

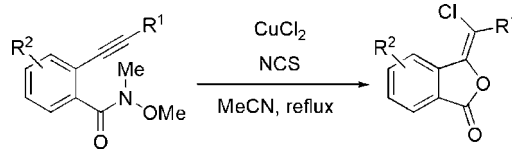
Manita Jithunsa, Masafumi Ueda, and Okiko Miyata*

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe, Hyogo 658-8558, Japan

miyata@kobepharma-u.ac.jp

Received December 1, 2010

ABSTRACT



A regioselective intramolecular cyclization/halogenation reaction of *N*-alkoxy-*o*-alkynylbenzamides with $CuCl_2$/NCS was developed. The corresponding 3-(chloromethylene)isobenzofuran-1-ones were exclusively obtained via *5-exo-dig* cyclization in moderate to excellent yields within 0.5−1 h. This approach has been successfully used to synthesize a biaryl compound by the Suzuki−Miyaura reaction.

Isobenzofuran-1-ones and isocoumarins are key components among several lactone natural products containing important biological activities[1] such as antifungal,[2] antimicrobial,[3] and acting as reactive intermediates[4] for target molecules. Consequently, numerous straightforward synthetic methods have been developed.[5−12]

Among these methods, the typical strategy for the synthesis of isobenzofuran-1-one is a transition metal,[10] organic base-catalyzed,[11] or halogen-mediated[12] cyclization of alkynes

(1) (a) Zhu, X. Z.; Li, X.-Y. *Eur. J. Pharmacol.* **2004**, *500*, 221. (b) Zamilpa, A.; Herrera-Ruiz, M.; del Olmo, E.; Lopez-Perez, J. L.; Tortoriello, J.; Feliciano, A. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3483.

(2) Holler, U.; Gloer, J. B.; Wicklow, D. T. *J. Nat. Prod.* **2002**, *65*, 876.

(3) (a) Chinworrungsee, M.; Kittakoop, P.; Isaka, M.; Chanpen, R.; Tanticharoen, M.; Thebtaranonth, Y. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2473. (b) Larsen, T. O.; Breinholt, J. *J. Nat. Prod.* **1999**, 1182. (c) Shim, S. H.; Swenson, D. C.; Gloer, J. B.; Dowd, P. E.; Wicklow, D. T. *Org. Lett.* **2006**, *8*, 1225. (d) Angawi, R. F.; Swenson, D. C.; Gloer, J. B.; Wicklow, D. T. *J. Nat. Prod.* **2003**, *66*, 1259. (e) Reategui, R. F.; Wicklow, D. T.; Gloer, J. B. *J. Nat. Prod.* **2006**, *69*, 113.

(4) (a) Patra, A.; Pahari, P.; Ray, S.; Mal, D. *J. Org. Chem.* **2005**, *70*, 9017. (b) Loughlin, W. A.; Jenkins, I. D.; Henderson, L. C.; Campitelli, M. R.; Healy, P. C. *J. Org. Chem.* **2008**, *73*, 3435. (c) Zhang, H.; Zhang, S.; Liu, L.; Luo, G.; Duan, W.; Wang, W. *J. Org. Chem.* **2010**, *75*, 368. (d) Hauser, F. M.; Gauuan, P. J. F. *Org. Lett.* **1999**, *1*, 671. (e) Fujimoto, T.; Imaeda, Y.; Konishi, N.; Hiroe, K.; Kawamura, M.; Textor, G. P.; Aertgeerts, K.; Kubo, K. *J. Med. Chem.* **2010**, *53*, 3517.

(5) For the synthesis of lactones via the reduction of anhydrides, see: (a) Bailey, D. M.; Johnson, R. E. *J. Org. Chem.* **1970**, *35*, 3574. (b) Schlessinger, R. H.; Ponticello, I. S. *J. Chem. Soc., Chem. Commun.* **1969**, 1013.

(6) For the synthesis of lactones from the oxidation of diols, see: (a) Sternberg, V. I.; Perkins, R. J. *J. Org. Chem.* **1963**, *28*, 323. (b) Fetizon, M.; Golfier, M.; Louis, J.-M. *Tetrahedron* **1975**, *31*, 171.

(7) For the synthesis of halosubstituted isocoumarins, see: (a) Roy, S.; Roy, S.; Neuenswander, B.; Hill, D.; Larock, R. C. *J. Comb. Chem.* **2009**, *11*, 1128. (b) Nagarajan, A.; Balasubramanian, T. R. *Indian J. Chem.* **1987**, *26B*, 917. (c) Nagarajan, A.; Balasubramanian, T. R. *Indian J. Chem.* **1988**, *27B*, 380. (d) Liang, Y.; Xie, Y.-X.; Li, J.-H. *Synthesis* **2007**, 400. (e) Peuchmaur, M.; Lisowski, V.; Gandreuil, C.; Maillard, L. T.; Martinez, J.; Hernandez, J.-F. *J. Org. Chem.* **2009**, *74*, 4158.

(8) (a) Bendall, V. I.; Dharamski, S. S. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2732. (b) Gutsche, C. D.; Jason, E. F.; Coffey, R. S.; Johnson, H. E. *J. Am. Chem. Soc.* **1958**, *80*, 5756. (c) Ziegert, R. E.; Torang, J.; Knepper, K.; Brase, S. *J. Comb. Chem.* **2005**, *7*, 147.

(9) For the synthesis of lactones via intramolecular Diel-Alder reactions, see: (a) Klemm, L. H.; Gopinath, K. W. *J. Heterocycl. Chem.* **1965**, *2*, 225. (b) Klemm, L. H.; Lee, L. H.; Gopinath, K. W.; Klopfenstein, C. E. *J. Org. Chem.* **1966**, *31*, 2376. (c) Klemm, L. H.; Gopinath, K. W. *Tetrahedron Lett.* **1963**, *4*, 1243. (d) Klemm, L. H.; Gopinath, K. W.; Lee, D. H.; Kelly, F. W.; Trod, E.; Mcquire, T. M. *Tetrahedron* **1966**, *22*, 1797.

(10) (a) Zhou, L.; Jiang, H.-F. *Tetrahedron Lett.* **2007**, *48*, 8449. (b) Bouyssi, D.; Balme, G. *Synlett* **2001**, 1191. (c) Kundu, N. G.; Pal, M. *J. Chem. Soc., Chem. Commun.* **1993**, 86. (d) Inack-Ngi, S.; Rahmani, R.; Commeiras, L.; Chouraqui, G.; Thibonnet, J.; Duchene, A.; Abarbri, M. *Adv. Synth. Catal.* **2009**, *351*, 779. (e) Doroh, B.; Sulikowski, G. A. *Org. Lett.* **2006**, *8*, 903. (f) Noriyuki, H. H.; Osaki, T.; Nakano, M.; Mori, H.; Katsumura, S. *J. Org. Chem.* **2004**, *69*, 7949. (g) Furuichi, N.; Hara, H.; Osaki, T.; Mori, H.; Katsumura, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1023.

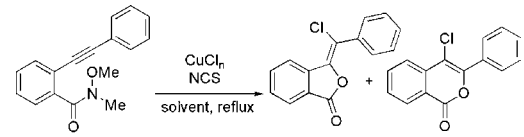
10.1021/ol1029035
Published on Web 12/28/2010

possessing a nucleophile. However, the synthesis often suffers from a lack of regioselectivity due to competitive cyclization through the *5-exo* or *6-endo* mode. Larock has succeeded in the synthesis of 4-iodoisocoumarins and 3-iodomethylisobenzofuranones by the regioselective electrophilic cyclization;[13] however, this selectivity was highly dependent on the bulkiness of the substituent. Thus, the development of a practical method for the synthesis of isobenzofuranones is highly desirable.

Although intramolecular annulation of carboxylic acids,[14] esters[15] and amides[16] to a variety of alkenes and alkynes for the synthesis of heterocycles have been reported, nothing is known about the cyclization of the Weinreb amide onto an alkyne. Therefore, we are interested in the potential of the Weinreb amide for the reaction with an alkyne moiety. In general, a carbonyl group of Weinreb amides is more electrophilic than that of regular amides.[17] However, there are few reports on a property of oxygen on carbonyl group in Weinreb amides. We anticipated that the enhancement of nucleophilicity of the carbonyl oxygen atom by an electron donation of the methoxy group (the alpha effect)[18] would lead to the chemoselective nucleophilic attack of the carbonyl oxygen over the other heteroatoms. Furthermore, it is thought that the coordination ability and partial C−N double bond character would influence the regioselectivity of cyclization. As a part of our program directed toward seeking the novel synthetic methodology of the substrate bearing N−O bond,[19] we report herein the $CuCl_2$-mediated chlorocyclization of *N*-alkoxy-*o*-alkynyl-benzamide for the selective synthesis of 3-(chloromethylene)isobenzofuran-1-ones.

We found that chlorobenzylidene isobenzofuran-1-one **2a** was exclusively obtained in 57% via regioselective cyclization, when *N*-methoxy-*o*-alkynylbenzamide **1a** was treated with 2.5 equivalents of $CuCl_2$ in MeCN at reflux for 0.5 h (Table 1, entry 1). Various additives and solvents have been screened to optimize the reaction conditions. The cyclization proceeded successfully in the presence of 2 equivalents of NCS to produce **2a** in 90% yield (entry 2). Interestingly,

Table 1. Optimized Conditions in the Cyclization of *N*-Alkoxy-*o*-alkynylbenzamide **1a**[a]



1a **2a** **3a**

entry	Cu salt (equiv)	additive (equiv)	solvent	*t* (h)	yield[b] (%)	
					2a	**3a**
1	$CuCl_2$ (2.5)	none	MeCN	0.5	57	–
2	**$CuCl_2$ (2.5)**	**NCS (2)**	**MeCN**	**0.5**	**90**	–
3	none	NCS (2)	MeCN	0.5	7	41
4	CuCl (2.5)	NCS (2)	MeCN	0.5	24	–
5	$CuCl_2$ (2)	NCS (1)	MeCN	0.5	64	–
6	$CuCl_2$ (2)	NCS (2)	MeCN	0.5	83	–
7	$CuCl_2$ (1)	NCS (2)	MeCN	0.5	61	–
8	$CuCl_2$ (0.5)	NCS (2)	MeCN	0.5	36	–
9	$CuCl_2$ (2.5)	NCS (2)	toluene	17	38	–
10	$CuCl_2$ (2.5)	NCS (2)	1,4-dioxane	16	57	8
11	$CuCl_2$ (2.5)	NCS (2)	DCE[c]	0.5	30	26
12	$CuCl_2$ (2.5)	NCS (2)	DMA	18	34	12
13	$CuCl_2$ (2.5)	NCS (2)	DMF[d]	3	36	31
14[e]	$CuCl_2$ (2.5)	NCS (2)	MeCN	0.5	80	–

[a] Conditions: **1a** (0.2 mmol), solvent (0.05 M) under Ar atmosphere. [b] Isolated yield. [c] Reaction was carried out at 90 °C. [d] Reaction was carried out at 130 °C. [e] The reaction was carried out with 1 g of **1a**.

only the *E*-isomer product **2a** was obtained. Using only NCS predominantly generated the six-membered-ring product **3a** in moderate yield (entry 3). These results indicated that $CuCl_2$ plays a pivotal role in a selective formation of five-membered-rings and the chlorocyclization was activated by NCS. It is also possible to use Cu(I)chloride as a chloride source; however, the efficiency to this reaction was low (entry 4). Reducing the amount of reagents led to a decrease in the chemical yields of **2a** (entries 5−8). Efficiency and selectivity of this reaction were strongly influenced by the reaction solvent. The use of nonpolar solvents and polar aprotic solvents except for MeCN afforded **2a** and/or **3a** in moderate yields (entries 9−13). Additionally, this reaction can be applied to a gram scale synthesis; thus, the chlorocyclization of **1a** (1 g) afforded **2a** in 80% yield (entry 14).

To confirm the priority of the Weinreb amide, other carbonyl derivatives as shown in Scheme 1 were tested. Chlorocyclization of primary, secondary and tertiary amides **1b**−**d** produced the mixture of products **2a** and **3a** in low to moderate yields. In contrast, exclusive formation of isocoumarin **3a** was observed when methyl ester **1e** was subjected to the cyclization reaction.[7d] These results indicate a necessary component of the Weinreb amide for the selective *5-exo-dig* cyclization. We anticipate that $CuCl_2$/NCS cyclization will provide direct access to the compounds isobenzofuran-1-one and isocoumarin by delivering **1a** and **1e** as a substrate, respectively.

With the optimal conditions in hand, we then explored the scope of substrates (Table 2). The reaction of various

(11) (a) Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5517. (b) Kanazawa, C.; Terada, M. *Tetrahedron Lett.* **2007**, *48*, 933. (c) Terada, M.; Kanazawa, C.; Yamanaka, M. *Heterocycles* **2007**, *74*, 819. (d) Biagetti, M.; Bellina, F.; Carpita, A.; Viel, S.; Mannina, L.; Rossi, R. *Eur. J. Org. Chem.* **2002**, 1063. (e) Ogliaruso, M. A.; Wolfe, J. F. In *Synthesis of lactones and lactams*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons Ltd.: England, 2003; p 3.

(12) (a) Biagetti, M.; Bellina, F.; Carpita, A.; Stabile, P.; Rossi, R. *Tetrahedron* **2002**, *58*, 5023. (b) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **2001**, *57*, 2857. (c) Sofia, M. J.; Katzenellenbogen, J. A. *J. Med. Chem.* **1986**, *29*, 230.

(13) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936.

(14) (a) Sashida, H.; Kawamukai, A. *Synthesis* **1999**, 1145. (b) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298. (c) Izumi, T.; Morishita, N. *J. Heterocyl.Chem.* **1994**, *31*, 145. (d) Korte, D. E.; Hegedus, L. S.; Wirth, R. K. *J. Org. Chem.* **1977**, *42*, 1329.

(15) (a) Woon, E. C. Y.; Dhami, A.; Mahon, M. F.; Threadgill, M. D. *Tetrahedron* **2006**, *62*, 4829. (b) Hellal, M.; Bourguignon, J.-J.; Bihel, F. J.-J. *Tetrahedron Lett.* **2008**, *49*, 62.

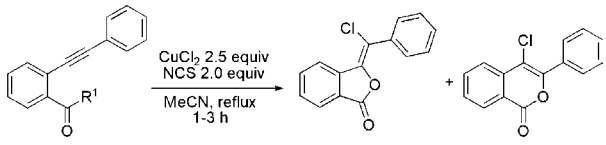
(16) (a) Bian, M.; Yao, W.; Ding, H.; Ma, C. *J. Org. Chem.* **2010**, *75*, 269. (b) Sakamoto, T.; An-naka, M.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1986**, *34*, 2754.

(17) Balasubramaniam, S.; Aidhen, I. S. *Synthesis* **2008**, *23*, 3707.

(18) Klopman, G. *Tetrahedron* **1970**, *26*, 4549.

(19) (a) Ueda, M.; Kawai, S.; Hayashi, M.; Naito, T.; Miyata, O. *J. Org. Chem.* **2010**, *75*, 914. (b) Ueda, M.; Sato, A.; Ikeda, Y.; Miyoshi, T.; Naito, T.; Miyata, O. *Org. Lett.* **2010**, *12*, 2594.

Scheme 1. Cyclization of Substrates **1** with Substituents on R^1



1	2a	3a
1a (R^1 = N(OMe)Me)	90%	-
1b (R^1 = NMe_2)	14%	trace
1c (R^1 = NHPh)	42%	trace
1d (R^1 = NH_2)	22%	7%
1e (R^1 = OMe)	-	88%

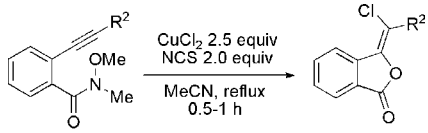
acetylenic substrates with $CuCl_2$/NCS displayed broad substrate capability and the reaction was tolerable toward a range of substituents on the acetylenic unit carrying a cyclic moiety or an acyclic moiety. An excellent chemical yield was observed in the reaction of TMS-substituted alkyne **1h** (entry 3), albeit a relatively lower yield was given by **1i** with *t*-butyl group (entry 4). Substrates bearing aliphatic substituents also worked well (entries 5−6). Alkyne **1l** with a silyloxymethyl group underwent chlorolactonization and then desilylation to yield the allylic alcohol **2l** in 64% yield (entry 7).

We next investigated the substitution variation of the benzamide moiety (Scheme 2). Particularly noteworthy is the tolerance of halogen groups. The manipulation of the benzamide bearing a halogen substituent such as a fluoro or chloro atom *para* or *meta* to the carbonyl group produced **2m**−**p** in very good yields (Scheme 2). Conversely, the substrate bearing an *ortho*-fluoro group to the carbonyl group afforded **2q** in lower yield. **1r** with an additional alkyne gave **2r** as a sole product without suppression of the desired reaction.

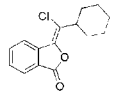
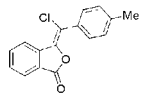
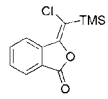
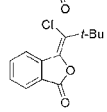
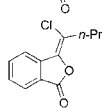
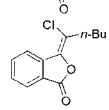
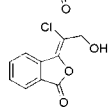
Alternatively, systems bearing electron-deficient or electron-rich substituents performed well (**2s**−**u**). Surprisingly, the cyclization worked well to give **2v** in 96% yield when the substrate contained a methoxy group *ortho* to the alkyne. Moreover, the naphthyl substrate was also demonstrated, affording **2w** in 64% yield.

Although the precise mechanism of this reaction could not be fully elucidated, a possible reaction pathway is shown in Scheme 3. The activation of an alkyne moiety of **1** by $CuCl_2$ is followed by the nucleophilic addition of the carbonyl oxygen to form an intermediate **B** via 5-*exo*-*dig* cyclization. The Cu(II) species are oxidized by another equivalent of

Table 2. $CuCl_2$-Mediated Chlorocyclization of *N*-Methoxy-*o*-alkynylbenzamide: the Effect of Substituents on Acetylenes[a]

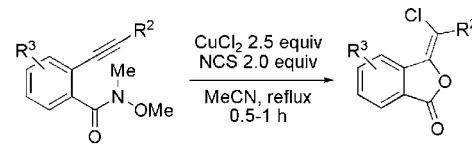


1f-l **2f-l**

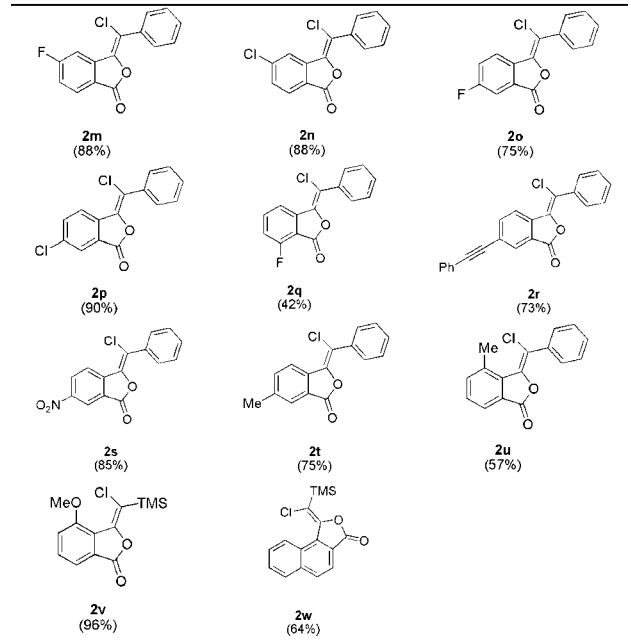
entry	substrate		product		yield[b] (%)
1	R^2 = cyclohexyl	**1f**		**2f**	79
2	R^2 = 4-MeC_6H_4	**1g**		**2g**	85
3	R^2 = TMS	**1h**		**2h**	99
4	R^2 = *t*-Bu	**1i**		**2i**	64
5	R^2 = *n*-Pr	**1j**		**2j**	68
6	R^2 = *n*-Bu	**1k**		**2k**	78
7	R^2 = CH_2OTBS	**1l**		**2l**	64

[a] Conditions: **1f-l** (0.2 mmol), $CuCl_2$ (2.5 equiv), NCS (2.0 equiv), MeCN (0.05 M) under Ar atmosphere. [b] Isolated yield.

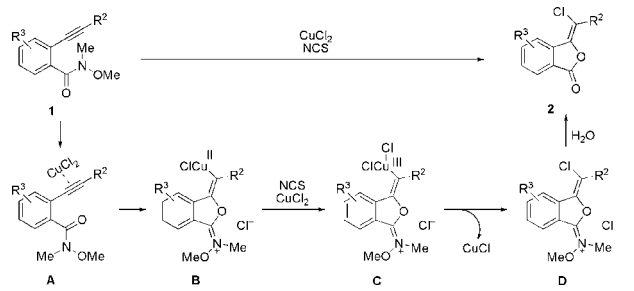
Scheme 2. $CuCl_2$-Mediated Cyclization of Substituted *N*-Alkoxy-*o*-alkynylbenzamides



1m-w **2m-w**



Scheme 3. Plausible Reaction Pathway



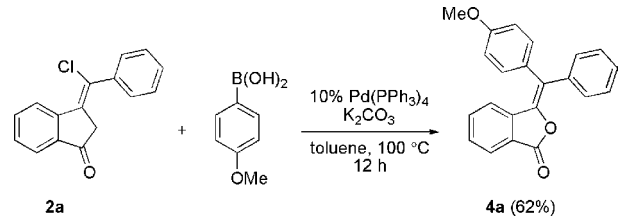
$CuCl_2$ to generate Cu(III) species **C**.[20] After chlorination at the copper atom by NCS, reductive elimination affords **D**. Finally, the work up process transforms the intermediate **D** to the product **2**.

The utilization of our products is challenging and provides a broad insight into chlorosubstitued iso-benzofuran-1-one. The Suzuki−Miyaura coupling of **2a** with *p*-methoxyphenylboronic acid yielded the biaryl product **4a** in 62% (Scheme 4).

In conclusion, we have developed a simple and rapid $CuCl_2$-mediated cyclization reaction of *N*-alkoxy-*o*-alkylbenzamides with a broad range of substitution and functionalization patterns for the synthesis of 3-(chloromethylene)-

(20) (a) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044. (b) Wu, H.; Hynes, J., Jr. *Org. Lett.* **2010**, *12*, 1192.

Scheme 4. Suzuki−Miyaura Coupling of **2a**



isobenzofuran-1-one derivatives. This work should open new perspectives in the chemistry of isobenzofuran-1-one and represents a useful tool for other reaction designs.

Acknowledgment. We thank the partial support by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and the Science Research Promotion Fund of the Japan Private School Promotion Foundation. M.U. is grateful for the Research Foundation for Pharmaceutical Science.

Supporting Information Available: Experimental details, characterization data, and copies of ^{1}H NMR, ^{13}C NMR spectra of all new compounds (compounds **1**−**4**). This material is available free of charge via the Internet at http://pubs.acs.org.

OL1029035