ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Catalyst-Free Intramolecular Oxidative Cyclization of *N*-Allylbenzamides: A New Route to 2,5-Substituted Oxazoles

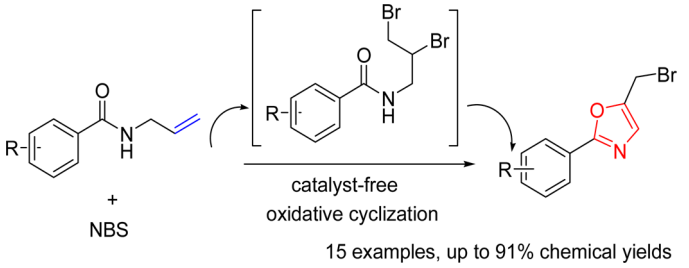
Wei Zhou, Chen Xie, Jianlin Han,* and Yi Pan*

School of Chemistry and Chemical Engineering, State Key Laboratory of Coordination, Nanjing University, Nanjing, 210093, China

hanjl@nju.edu.cn; yipan@nju.edu.cn

Received July 22, 2012

ABSTRACT



A catalyst-free intramolecular oxidative cyclization reaction of *N*-allylbenzamides has been developed to prepare 2,5-disubstituted oxazoles with good yields. This reaction gives an efficient synthetic strategy to form an oxazole nucleus directly from easily accessible substrates under temperate conditions.

The oxazole nucleus is an important structure in many natural products and compounds with biological or pharmaceutical activities.[1−4] 2,5-Substituted oxazoles also serve as useful building blocks in organic synthesis,[5] especially as intermediates for the formation of polysubstituted oxazoles.[6] There are many synthetic strategies available for the preparation of the oxazole nuclei,[7] and the use of *N*-propargylbenzamides as starting materials with Au,[8] Pd,[9] Ag,[10] Cu,[11] and Mo[12] catalysts is of great importance. However, there are still shortcomings, such as harsh reaction conditions and the use of expensive catalysts.

(1) For selected reviews, see: (a) Wipf, P. *Chem. Rev.* **1995**, *95*, 2125. (b) Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464. (c) Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995. (d) Riego, E.; Hernández, D.; Albericio, F.; Álvarez, M. *Synthesis* **2005**, 1907.

(2) (a) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303. (b) Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4765.

(3) Adamczeski, M.; Quinoa, E.; Crews, P. *J. Am. Chem. Soc.* **1988**, *110*, 1598.

(4) (a) Skepper, C. K.; Quach, T.; Molinski, T. F. *J. Am. Chem. Soc.* **2010**, *132*, 10286. (b) Wan, C.; Zhang, J.; Wang, S.; Fan, J.; Wang, Z. *Org. Lett.* **2010**, *12*, 2338.

(5) (a) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389. (b) Wasserman, H. H.; McCarthy, K. E.; Prowse, K. S. *Chem. Rev.* **1986**, *86*, 845. (c) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115. (d) Jin, Z. *Nat. Prod. Rep.* **2003**, *20*, 584. (e) Jin, Z. *Nat. Prod. Rep.* **2009**, *26*, 382.

(6) (a) Cano, I.; Álvarez, E.; Nicasio, M. C.; Pérez, P. J. *J. Am. Chem. Soc.* **2011**, *133*, 191. (b) He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482. (c) Wipf, P.; Aoyama, Y.; Benedum, T. E. *Org. Lett.* **2004**, *6*, 3593. (d) Badillo, J. J.; Arevalo, G. E.; Fettinger, J. C.; Franz, A. K. *Org. Lett.* **2011**, *13*, 418. (e) Wan, C. F.; Gao, L. F.; Wang, Q.; Zhang, J. T.; Wang, Z. Y. *Org. Lett.* **2010**, *12*, 3902.

(7) For selected examples, see: (a) Kumar, D.; Sundaree, S.; Patel, G.; Rao, V. S. *Tetrahedron Lett.* **2008**, *49*, 867. (b) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411. (c) Hashmi, A. S. K.; Rudolph, M.; Schymura, S.; Visus, J.; Frey, W. *Eur. J. Org. Chem.* **2006**, 4905. (d) Saito, A.; Matsumoto, A.; Hanzawa, Y. *Tetrahedron Lett.* **2010**, *51*, 2247.

(8) (a) Weyrauch, J. P.; Hashmi, A. S. K.; Schuster, A.; Hengst, T.; Schetter, S.; Littmann, A.; Rudolph, M.; Hamzic, M.; Visus, J.; Rominger, F.; Frey, W.; Bats, J. W. *Chem.—Eur. J.* **2010**, *16*, 956. (b) Doherty, S.; Knight, J. G.; Hashmi, A. S. K.; Smyth, C. H.; Ward, N. A. B.; Robson, K. J.; Tweedley, S.; Harrington, R. W.; Clegg, W. *Organometallics* **2010**, *29*, 4139. (c) Milton, M. D.; Inada, Y. Nishibayashi, Y.; Uemura, S. *Chem. Commun.* **2004**, 2712. (d) Hashmi, A. S. K.; Yu, Y.; Rominger, F. *Organometallics* **2012**, *31*, 895. (e) Egorova, O. A.; Seo, H.; Kim, Y.; Moon, D.; Rhee, Y. M.; Ahn, K. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 11446. (f) Paradise, C. L.; Sarkar, P. R.; Razzak, M.; De Brabander, J. K. *Org. Biomol. Chem.* **2011**, *9*, 4017.

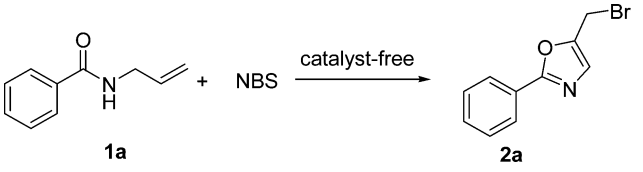
(9) (a) Arcadi, A.; Cacchi, S.; Cascia, L.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2001**, *3*, 2501. (b) Bacchi, A.; Costa, M.; Gabriele, B.; Pelizzi, G.; Salerno, G. *J. Org. Chem.* **2002**, *67*, 4450. (c) Beccalli, E. M.; Borsini, E.; Broggini, G.; Palmisano, G.; Sottocornola, S. *J. Org. Chem.* **2008**, *73*, 4746. (d) Saito, A.; Iimura, K.; Hanzawa, Y. *Tetrahedron Lett.* **2010**, *51*, 1471.

10.1021/ol302031z

Efficient, catalyst-free, synthetic methods for securing oxazoles remain of importance.

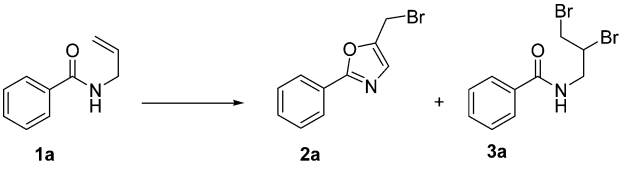
There have been some reports about the formation of oxazolines from *N*-allylbenzamides,[13] which needed an additional oxidant to form the oxazoles.[14] However, the direct synthesis of oxazoles from the readily available *N*-allylbenzamides still remains unexplored until now. So, we decided to explore an efficient tandem methodology for the preparation of 2,5-substituted oxazoles with *N*-allylbenzamides as starting materials. Herein, we wish to report a new route to 2,5-substituted oxazoles via intramolecular oxidative cyclization of *N*-allylbenzamides under temperate conditions without the use of any catalyst. Our studies on this reaction began by choosing **1a** as the model substrate, to test the possibility of cycloaddition under the oxidation of NBS (Scheme 1).

Scheme 1. NBS-Mediated Cyclization of *N*-Allylbenzamides



We were delighted to find the yield of this model reaction was good when the starting material **1a** was treated with NBS (3.0 equiv) in $ClCH_2CH_2Cl$ at 80 °C (Table 1, entry 1). This resulted in the 2,5-substituted oxazole **2a**, along with a 19% yield of the dibrominated product **3a**. No cyclization product was found when the reaction was decreased to 50 °C, and only **3a** was obtained in 43% yield (entry 3). No reaction took place when the temperature was further decreased to room temperature (entry 2). The best result was obtained when the reaction was kept at 100 °C. The highest yield was 88% (entry 4). The reaction time also had a great effect on the reaction, and a dramatic lower yield was found when the reaction was stopped at 12 h (entry 5). After investigation of the solvents, we found that the treatment of **1** in dioxane or CH_3CN gave only product **3a**, which was just the bromine addition product to the allyl group in **1** (entries 7 and 9). The use of other solvents did not improve this reaction (entries 8, 10, and 11). Furthermore, the addition of H_2O also inhibited it (entry 6). When NCS, NIS, or $PhI(OAc)_2$ was used instead of NBS, we did not get the expected cyclization products (entries 12, 13, and 14). When Br_2 or the combination of Br_2/K_2CO_3 was used in this reaction, the brominated product **3a** was obtained in high yield and only a trace amount of **2a** was detected (entries 15 and 16). Overall, $ClCH_2CH_2Cl$ was found to be the most effective solvent for this oxidative cyclization process using NBS as the oxidant at 100 °C.

Table 1. Optimization of the Oxidative Cyclization of *N*-Allylbenzamide[a]



entry	oxidative	solvent	temp (°C)	*t* (h)	**2a** (%)[b]	**3a** (%)[b]
1	NBS	DCE	80	24	72	19
2	NBS	DCE	rt	24	NR	
3	NBS	DCE	50	24	0	43
4	NBS	DCE	100	24	88	0
5	NBS	DCE	100	12	52	30
6	NBS	DCE	100	24	NR[c]	
7	NBS	CH_3CN	100	24	0	45
8	NBS	toluene	100	24	NR	
9	NBS	dioxane	100	24	0	80
10	NBS	DMF	100	24	NR	
11	NBS	HOAc	100	24	0	87
12	NCS	DCE	100	24	NR	
13	NIS	DCE	100	24	NR	
14	$PhI(OAc)_2$	DCE	100	24	NR	
15	Br_2	DCE	100	24	0	99
16	Br_2/K_2CO_3	DCE	100	24	<5	91

[a] All reactions were performed at 0.1 M with 3.0 equiv of oxidant in a sealed tube. [b] Isolated yields. [c] 2.0 equiv of water were added.

Under the optimized conditions, the scope of the *N*-allylbenzamide substrates was examined (Table 2). Because increased reaction times decreased the yield of this reaction, for each substrate this parameter was examined carefully. As shown in Table 2, the intramolecular cyclization can proceed smoothly for a wide range of substrates, resulting in moderate to excellent chemical yields. We found that the reaction of substrates with strong electron-withdrawing groups on the aromatic ring proceeded very rapidly. The reaction could complete within 2 h (entries 2, 9, and 10). Contrastingly, the existence of a strong electron-donating group on the aromatic ring inhibited this reaction, even prolonging the reaction time to 48 h (entry 16). It was also found that substrate **1o** with a 1-naphthyl group worked well in the system with a moderate yield (entry 15). Varying steric effects of the substrates had no dramatic effect on the reaction; these substrates still provided good yields (entries 2, 7, and 11–13). Notably, in the case of **1h**, the reaction gave the cyclization product, along with the methyl group on the *para*-position of the phenyl ring brominated by NBS (entry 8).

(10) Harmata, M.; Huang, C. *Synlett* **2008**, 1399.

(11) (a) Prior, A. M.; Robinson, R. S. *Tetrahedron Lett*. **2008**, *49*, 411. (b) Jin, C.; Burgess, J. P.; Kepler, J. A.; Cook, C. E. *Org. Lett*. **2007**, *9*, 1887. (c) Jin, C.; Manikumar, G.; Kepler, J. A.; Cook, C. E.; Allan, G. F.; Kiddoe, M.; Bhattacharjee, S.; Linton, O.; Lundeen, S. G.; Sui, Z. *Bioorg. Med. Chem. Lett*. **2007**, 5754.

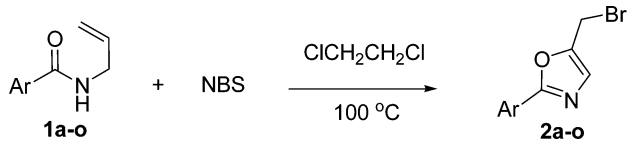
(12) Meng, X. J.; Kim, S. *Org. Biomol. Chem*. **2011**, *9*, 4429.

(13) (a) Jaganathan, A.; Garzan, A.; Whitehead, D. C.; Staples, R. J.; Borhan, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2593. (b) Minakata, S.; Morino, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett*. **2006**, *8*, 3335. (c) Morino, Y.; Hidaka, I.; Oderaotoshi, Y.; Komatsu, M.; Minakata, S. *Tetrahedron* **2006**, *62*, 12247.

(14) (a) Jiang, H. F.; Huang, H.; Cao, H.; Qi, C. *Org. Lett*. **2010**, *12*, 5561. (b) Murai, K.; Takahara, Y.; Matsushita, T.; Komatsu, H.; Fujioka, H. *Org. Lett*. **2010**, *12*, 3456.

The structure of **2d** was identified by single-crystal X-ray diffraction analysis (Figure 1).

Table 2. Synthesis of 2,5-Disubstituted Oxazoles from *N*-Allylbenzamide Substrates[a]



entry	Ar	product	t (h)	yield (%)[b]
1	C_6H_5	**2a**	24	88
2	2-ClC_6H_4	**2b**	1	70
3	3-ClC_6H_4	**2c**	12	69
4	4-ClC_6H_4	**2d**	12	88
5	4-FC_6H_4	**2e**	2	78
6	4-BrC_6H_4	**2f**	2	81
7	2-MeC_6H_4	**2g**	12	75
8	4-MeC_6H_4	**2h**	8	60[c]
9	4-$CF_3C_6H_4$	**2i**	1	60
10	4-$NO_2C_6H_4$	**2j**	1	77
11	2,3-diCl-C_6H_3	**2k**	12	62
12	2,4-diCl-C_6H_3	**2l**	2	72
13	2,6-diCl-C_6H_3	**2m**	2	91
14	3,4-diCl-C_6H_3	**2n**	2	76
15	1-naphthyl	**2o**	12	53
16	4-$MeOC_6H_4$	-	48	NR

[a] All the reactions were performed at 0.1 M with 3.0 equiv of NBS in $ClCH_2CH_2Cl$ at 100 °C in a sealed tube. [b] Isolated yields. [c] The *para*-methyl group of the phenyl ring was also substituted by NBS to be $BrCH_2C_6H_4$.

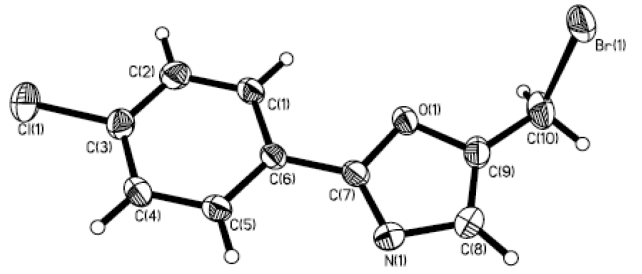
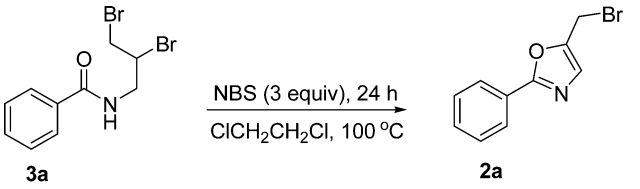


Figure 1. X-ray crystallography for **2d**.

To gain insight into the reaction mechanism, we tried to isolate the intermediate of this reaction. Decreasing the reaction temperature or reducing the reaction time led to the dibrominated product **3a**. After careful isolation of compound **3a**, we used it as starting material to perform the reaction under the same reaction conditions (Scheme 2). To our delight, **3a** could be converted into **2a** in high chemical yield under the same reaction conditions (89% yield). Thus, compound **3a** may be the intermediate or the captured intermediate of this oxidative cyclization procedure.

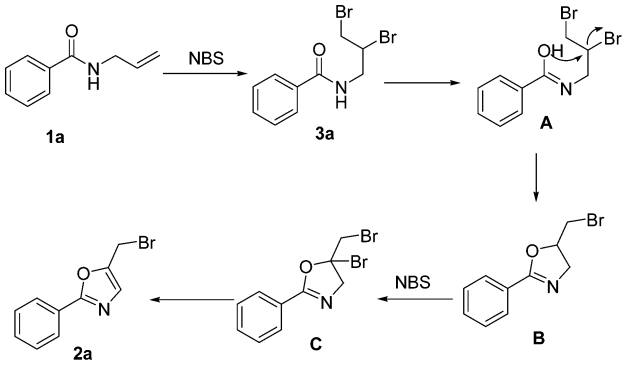
On the basis of the above experimental results, a plausible reaction mechanism for this intramolecular reaction is proposed in Scheme 3. It includes an oxidation/cyclization

Scheme 2. Insights into the Mechanism

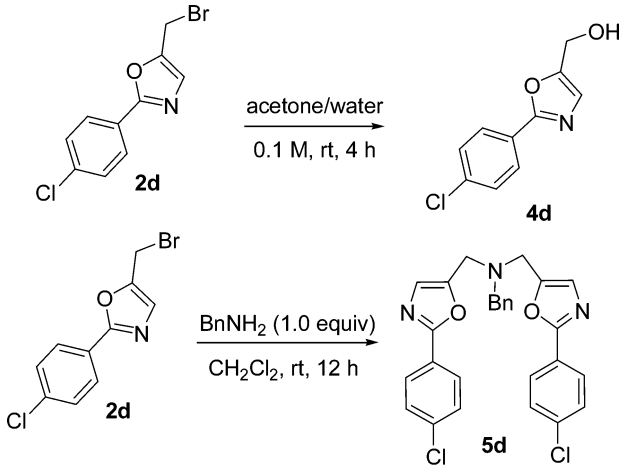


process. Initially, *N*-allylbenzamide **1a** reacts with NBS to form the dibrominated intermediate **3a**, which also exists as its imidic tautomer **A**. Intermediate **A** ungergoes intramolecular nucleophilic attack by the oxygen atom to form the cyclic intermediate **B**, along with loss of HBr. Intermediate **B** is then quickly brominated by NBS at 100 °C resulting in intermediate **C**, which proceeds through the elimination reaction to afford the target product **2a**.[8a,14b]

Scheme 3. Possible Mechanism



Scheme 4. Some Reactions of **2d**



The presence of the C−Br bond in the obtained 2,5-substituted oxazoles provided an easy access to other useful organic blocks (Scheme 4). When the product **2d**

was treated with acetone/water at room temperature for 4 h, **4d**[15] with an exocyclic hydroxyl group was quantitatively obtained. Product **2d** was also easily aminated by treatment with $BnNH_2$ in CH_2Cl_2 at room temperature to afford **5d** in 82% yield.

In conclusion, we have developed a facile catalyst-free pathway for the synthesis of 2,5-substituted oxazoles directly from *N*-allylbenzamides. This reaction involves readily available starting materials and tolerates a wide scope of substrates affording good yields. Subsequent research will focus on application of this methodology to access polysubstituted oxazoles.

(15) Compound **4d** could remain undecomposed at room temperature for at least 2 months.

Acknowledgment. We gratefully acknowledge the financial support from the National Natural Science Foundation of China (No. 21102071) and the Fundamental Research Funds for the Central Universities (Nos. 1107020522 and 1082020502). The Jiangsu 333 program (for Pan) and Changzhou Jin-Feng-Huang program (for Han) are also acknowledged.

Supporting Information Available. Experimental procedures, full spectroscopic data for new compounds, and single-crystal X-ray diffraction analysis of **2d**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.