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CuBr-Catalyzed Coupling of *N*-Tosylhydrazones and Terminal Alkynes: Synthesis of Benzofurans and Indoles

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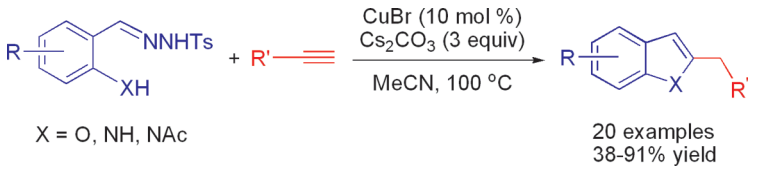
ABSTRACT



A new method for the synthesis of benzofurans or indoles *via* ligand-free CuBr-catalyzed coupling/cyclization of terminal alkynes with *N*-tosylhydrazones derived from *o*-hydroxy- or *o*-aminobenzaldehydes has been developed. A wide range of functional groups were found that are able to tolerate the reaction conditions.

Benzofuran and indole moieties are common structural units in natural products and exhibit interesting biological activities and potential pharmaceutical applications.[1] Among the methods to construct such structures, Pd-based cross-coupling reactions of *o*-iodophenols or *o*-iodoaniline with terminal alkynes with copper iodide as a cocatalyst (Sonagashira coupling), followed by 5-*endodig* cyclization, have been studied extensively in recent years.[2,3] However, a major drawback of this process for large-scale synthesis is the use of two metal catalysts, making recovery of the expensive palladium difficult.

Compared to noble-metal catalysts, copper-based methods have obvious economic attractiveness. Recently, several highly efficient copper-based Sonogashira coupling/cyclization sequences have emerged for the synthesis of furans and indoles.[4] For example, Venkataraman and co-workers have recently reported a protocol for the synthesis of benzofurans from *o*-iodophenols and terminal alkynes catalyzed by a well-defined $[Cu(phen)(Ph_3P)_2]NO_3$ catalyst.[4b] The synthesis of 2-substituted indoles was developed by Ma

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(3) For recent examples, see: (a) Kundu, N. G.; Pal, M.; Mahanty, J. S.; Dasgupta, S. K. *J. Chem. Soc., Chem. Commun.* **1992**, 41. (b) Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2815. (c) Khan, M. W.; Alam, M. J.; Rashid, M. A.; Chowdhury, R. *Bioorg. Med. Chem.* **2005**, *13*, 4796. (d) Sakai, H.; Tsutsumi, K.; Morimoto, T.; Kakiuchi, K. *Adv. Synth. Catal.* **2008**, *350*, 2498. (e) Zhang, H.-C.; Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanoff, B. E. *Org. Lett.* **2000**, *2*, 89. (f) Djakovitch, L.; Rollet, P. *Adv. Synth. Catal.* **2004**, *346*, 1782. (g) Leogane, O.; Lebel, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 350. (h) Pal, M.; Subramanian, V.; Yeleswarapu, K. R. *Tetrahedron Lett.* **2003**, *44*, 8221. (i) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017. (j) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3307. (k) Palimkar, S. S.; Kumar, P. H.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron* **2006**, *62*, 5109. (l) Pal, M.; Subramanian, V.; Batchu, V. R.; Dager, I. *Synlett* **2004**, *11*, 1965. (m) Bochicchio, A.; Chiummiento, L.; Funicello, M.; Lopardo, M. T.; Lupattelli, P. *Tetrahedron Lett.* **2010**, *51*, 2824.

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and co-workers using a CuI/L-proline system.[4f] We noted, however, in these cases ligands were essential for the success of the reactions. Considering the importance of benzofurans and indoles, it is highly desirable to develop alternative and novel methods for the synthesis of these structures.

In the past few years, *N*-tosylhydrazones have been proven as a new type of coupling partner for Pd-catalyzed cross-coupling reactions.[5] Moreover, palladium-based three-component coupling of *N*-tosylhydrazone, aryl bromide, and terminal alkyne with copper iodide as a cocatalyst has been reported by our group.[6] More recently, we have developed a method for the synthesis of substituted allenes *via* Cu(I)-catalyzed coupling of *N*-tosylhydrazones with terminal alkynes.[7] In this case, a bisoxazoline ligand was crucial for efficient allene formation. The mechanism for the allene formation is proposed as shown in Scheme 1. Cu carbene intermediate **A** is formed through dediazotization of the *in situ* generated diazo substrate. Subsequently, the alkynyl group of the Cu carbene **A** goes through a migratory insertion into the carbenic carbon to form intermediate **B**, which is followed by protonation to afford the allene product. We have conceived that if a suitable intramolecular nucleophile is introduced, the initially formed allene or intermediate **B** may undergo a cyclization to afford benzofuran or indole if the nucleophile is a hydroxy or an amino group, as shown by the transformation from **B** to **D** to **E**.[8] Herein we wish to report a method for the synthesis of benzofurans and indoles from *N*-tosylhydrazones derived from *o*-hydroxy- or *o*-aminobenzaldehydes and terminal alkynes based on a ligand-free CuBr-catalyzed coupling−allenylation−cyclization sequence.

Initially, the reaction conditions were optimized starting from *N*-tosylhydrazone **1a** and phenylacetylene (**2a**) in 1, 4-dioxane at 100 °C with various copper catalysts, as summarized in Table 1. It was observed that CuBr gave the best result (Table 1, entries 1−5). $Cu(OAc)_2$ and $CuBr_2$ were also effective, albeit affording the products with slightly

Scheme 1. Cu-Catalyzed Coupling of *N*-Tosylhydrazone and Terminal Alkyne

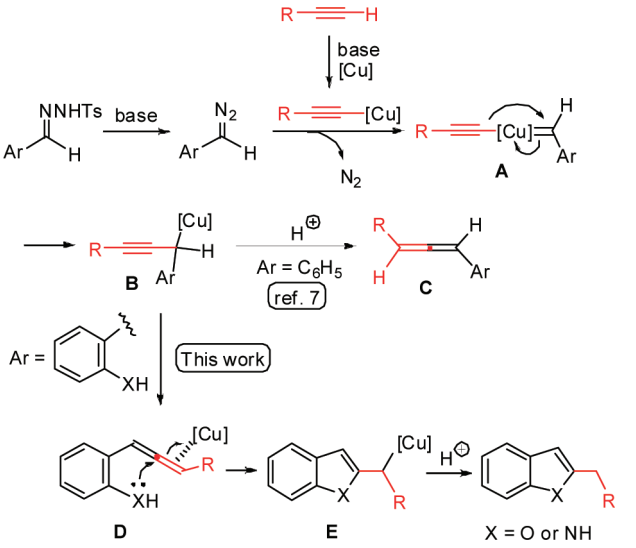
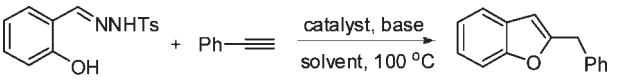


Table 1. Optimization of Reaction Conditions[a]



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

entry	catalyst	base	solvent	yield%[b]
1	CuI	Cs_2CO_3	dioxane	74
2	CuBr	Cs_2CO_3	dioxane	82
3	CuCl	Cs_2CO_3	dioxane	63
4	CuOTf	Cs_2CO_3	dioxane	69
5	$Cu(MeCN)_4PF_6$	Cs_2CO_3	dioxane	68
6	$Cu(OAc)_2$	Cs_2CO_3	dioxane	58
7	$CuBr_2$	Cs_2CO_3	dioxane	55
8	$FeCl_2$	Cs_2CO_3	dioxane	0
9	AgOTf	Cs_2CO_3	dioxane	trace
10	$AuCl_3$	Cs_2CO_3	dioxane	7
11	none	Cs_2CO_3	dioxane	0
12	**CuBr**	**Cs_2CO_3**	**MeCN**	**90**
13	CuBr	Cs_2CO_3	DMF	77
14	CuBr	Cs_2CO_3	DCE	70
15	CuBr	Cs_2CO_3	toluene	10
16	CuBr	K_2CO_3	MeCN	48
17	CuBr	^tBuOK	MeCN	51
18	CuBr	NaOMe	MeCN	11
19[c]	CuBr	Cs_2CO_3	MeCN	45

[a] All the reactions were carried out in sealed tubes using 0.4 mmol of tosylhydrazone **1a**, 0.5 mmol of phenylacetylene, 10 mol % of catalyst, and 3 equiv of base in the solvent at 100 °C for 4 h. [b] Yields were determined by GC using dodecane as internal standard. [c] The reaction was carried out at 80 °C.

diminished yields (entries 6 and 7). Other catalysts such as $FeCl_2$, AgOTf, and $AuCl_3$ were found to be essentially

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(6) Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2010**, *132*, 13591.

(7) Xiao, Q.; Xia, Y.; Li, H.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2011**, *50*, online, DOI: 10.1002/anie.201005741.

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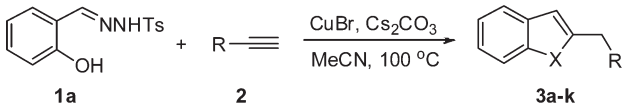
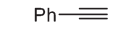
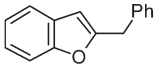
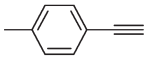
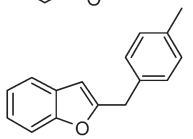
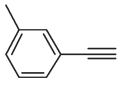
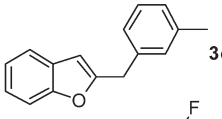
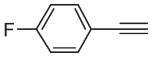
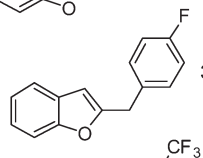
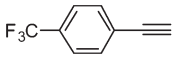
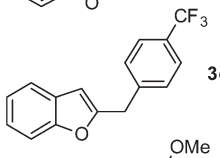
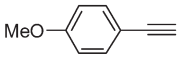
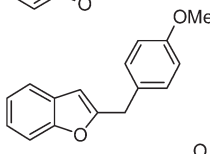
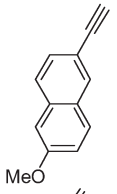
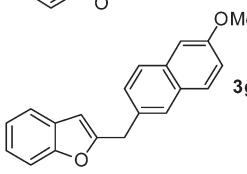
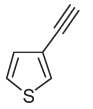
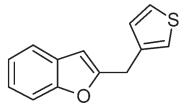
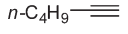
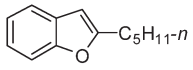
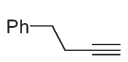
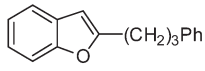
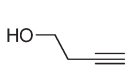
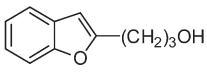
Table 2. Reaction of *N*-Tosylhydrazone **1a** with Various Terminal Alkynes Catalyzed by CuBr[a,8]



1a **2** **3a-k**

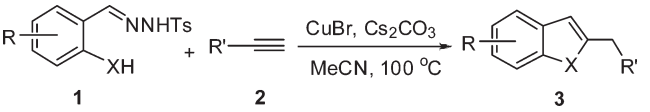
entry	alkyne	product	yield (%)[b]
1		 **3a**	85
2		 **3b**	85
3		 **3c**	83
4		 **3d**	70
5		 **3e**	86
6		 **3f**	74
7		 **3g**	57[c]
8		 **3h**	91
9		 **3i**	55
10		 **3j**	67
11		 **3k**	64

[a] Reaction conditions: *N*-tosylhydrazone **1a** (0.4 mmol), alkyne **2** (0.5 mmol), CuBr (10 mol %), Cs_2CO_3 (1.2 mmol), MeCN (5 mL), 100 °C, 4 h. [b] Isolated yield. [c] 31% yield of alkyne was recovered.

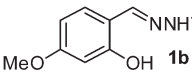
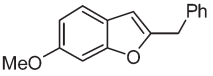
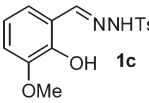
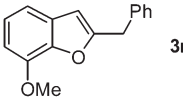
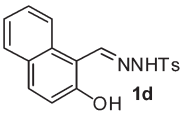
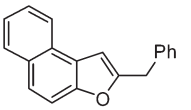
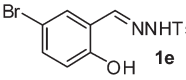
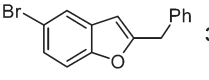
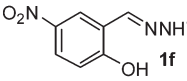
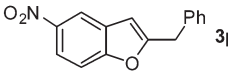
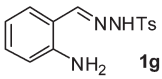
ineffective in this reactions (entries 8−10). A control experiment showed that no product could be detected in the absence of a copper catalyst (entry 11).

Further inspection of the reaction conditions revealed that this reaction proceeded more efficiently in polar solvents such as MeCN, DMF, and 1,2-dichloroethane (DCE)

Table 3. CuBr-Catalyzed Reaction of *N*-Tosylhydrazone with 1-Alkynes[a,8]



1 **2** **3**

entry	hydrazone	alkyne	product	yield (%)[b]
1	 **1b**		 **3l**	79
2	 **1c**		 **3m**	72
3	 **1d**		 **3n**	53
4	 **1e**		 **3o**	79
5	 **1f**		 **3p**	48
6	 **1g**		**3q**	74
7	**1g**		**3r**	72
8	**1g**		**3s**	41
9	**1h**		**3t**	38

[a] Reaction conditions: *N*-tosylhydrazone **1** (0.4 mmol), 1-alkyne **2** (0.5 mmol), CuBr (10 mol %), Cs_2CO_3 (1.2 mmol), MeCN (5 mL), 100 °C, 4 h. [b] Isolated yield.

(entries 12−14), whereas nonpolar solvent toluene was found to be unfavorable (entry 15). Then, a series of bases such as K_2CO_3, ^{t}BuOLi, and NaOMe were examined; however, they were all less efficient compared with Cs_2CO_3 (entries 16−18). Finally, we found that the yield of **3a** decreased sharply when the reaction was carried out at lower temperature (entry 19).

Having optimized the reaction conditions, we then explored the scope and limitation of the present CuBr-catalyzed tandem coupling−allenylation−cyclization method with a variety of terminal alkynes and *N*-tosylhydrazones.[9] As shown in Table 2, various functional groups including the

aryl, alkyl, naphthyl, and heterocycle present in alkynes **2** were tolerant of the reaction conditions. The reaction was found to be not significantly affected by the substituents on the aromatic ring of the terminal alkyne; both electron-rich (entries 2−3 and 6−7) and electron-deficient aryl substituted alkynes (entries 4 and 5) were effective. Treatment of 3-thienylacetylene with *N*-tosylhydrazone **1a** furnished the benzofuran **3h** in a yield of 91% (entry 8). Naphthyl and alkyl alkynes were also suitable for the reactions, albeit generating the corresponding products with moderately high yields (entries 7 and 9−10). We were pleased to find that the alkyne bearing a hydroxyl group reacted with *N*-tosylhydrazone **1a** under the optimized conditions to afford the desired benzofuran in 64% yield without the need of functional group protection (entry11).

To further expand the scope of the reaction, various substituted salicyl *N*-tosylhydrazones were employed as substrates to react with phenylacetylene. As shown in Table 3, hydrazones with a methoxy group at the *meta*- or *para*-position were both effective, affording the corresponding benzofurans **3l** and **3m** in yields of 79% and 72% respectively (entries 1 and 2). In another case, coupling of phenylacetylene with hydrazone bearing a naphthyl group (**1d**) led to the product **3n** in 53% yield (entry 3). It is noteworthy that a bromo substituent could survive in the reaction of **1e** and phenylacetylene (entry 4). Further examination of the scope of *N*-tosylhydrazone showed that the strong electron-withdrawing group on the aromatic ring hampered the formation of benzofurans. When *N*-tosylhydrazone **1f** was employed, the reaction with phenylacetylene yielded the benzofuran **3p** in only 48% (entry 5). Next, we checked the possibility of assembling 2-substituted indoles by our process and were pleased to observe that reaction of *N*-tosylhydrazone **1g** with phenylacetylene, 3-thienylacetylene, and 4-phenyl-1-butyne delivered the corresponding indole **3q**−**s** in yields of 74%, 72%, and 41% respectively (entries 6−8). As an additional example, it was found that using Ac protected *N*-tosylhydrazone **1h** also afforded the desired product in 38% yield (entry 9).

In summary, we have developed a new method for the synthesis of benzofuran and indole *via* CuBr-catalyzed coupling/allenylation/cyclization of terminal alkynes with *N*-tosylhydrazone derivatives. This method is based on salicyl *N*-tosylhydrazones, which are easily available from the coressponding aldehydes. A wide range of functional groups were found that are able to tolerate the reaction conditions. Moreover, this reaction uses inexpensive CuBr as a catalyst and is ligand-free, thus offering significant economic advantages over the many previous methods. Further application of this method is currently under investigation in our laboratory, and the results will be reported in due course.

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Supporting Information Available. Procedures for synthesis and characterization of products (^{1}H and ^{13}C NMR data). This material is available free of charge via the Internet at http://pubs.acs.org.

(9) **General procedure CuBr-catalyzed reaction of *N*-tosylhydrazone and alkyne:** CuBr (5.8 mg, 10 mol%), Cs_2CO_3 (1.2 mmol, 390 mg), and *N*-tosylhydrazone **1a**−**h** (0.4 mmol) were suspended in MeCN (5 mL) in a 10 mL Schlenk tube under nitrogen. Then terminal alkynes **2** (0.5 mmol) were added. The resulting solution was stirred at 100 °C for 4 h. After cooling to room temperature, the resulting mixture was filtered through a short path of silica gel, eluting with hexane and CH_2Cl_2. The volatile compounds were removed *in vacuo*, and the residue was purified by column chromatography (SiO_2, hexane).