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Synthesis of 3-Alkyl- or 3-Allenyl-2-amidobenzofurans via Electrophilic Cyclization of *o*-Anisole-Substituted Ynamides with Carbocations

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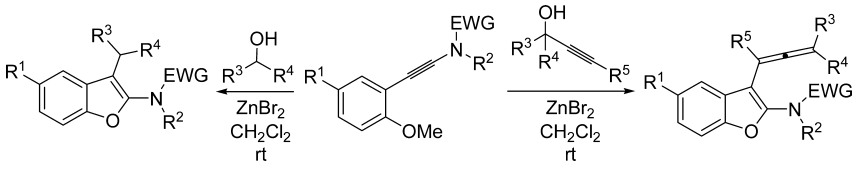
ABSTRACT



A facile carbocation-induced electrophilic cyclization reaction has been developed for the synthesis of 3-alkyl- or 3-allenyl-2-amidobenzofurans from *o*-anisole-substituted ynamides and diarylmethanol or 1,1-diarylprop-2-yn-1-ol.

Since new and more efficient methods for accessing ynamides were established,[1] ynamides have emerged as important synthons in modern organic synthesis.[2] A variety of important functional groups and cyclic systems such as enamides,[3] amidines,[4] indoles,[5] and pyridines[6] were successfully synthesized from ynamides. Benzofurans are the fundamental motif found in various natural products and the key structural units for pharmaceutical compounds.[7] As a special class of functionalized benzofurans, 2-amidobenzofurans are of considerable interest[8–11] and many methods have been established for their synthesis, such as

† These authors contributed equally.

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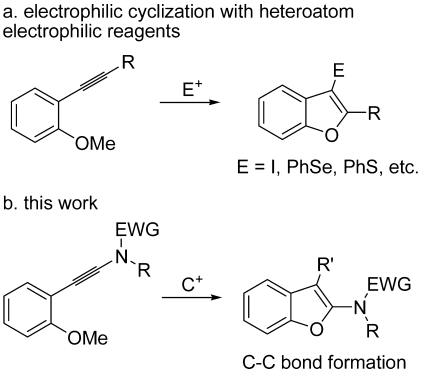
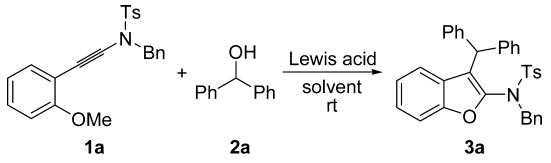
Beckmann rearrangement of aryl benzofuranyl oximes,[9] Curtius rearrangement of benzofuran-2-carboxylic acid,[10] and nitration/reduction/*N*-acylation of 2-trimethylstannyl benzofurans.[11] Recently, Hsung and co-workers developed an elegant synthesis of 2-amidobenzofurans from *O*-anisyl ynamides via a Rh(I)-catalyzed demethylation−cyclization reaction,[12] and the Skrydstrup group reported a Pd-catalyzed, one-pot, two-step synthesis of 2-amidobenzofurans from ynamides and *o*-iodophenol.[13] However, these methods could only afford 3-unsubstituted 2-amidobenzofurans. Electrophilic cyclization chemistry developed by Larock and co-workers provided access to various heterocyclic compounds including benzofurans.[14] Many electrophilic reagents (I, Br, PhSe, PhS, etc.) could induce the electrophilic cyclization of a carbon−carbon triple bond (Scheme 1a). To the best of our knowledge, carbocation-induced electrophilic cyclization of alkynes is still unreported. Considering that ynamides are more electron-rich than ordinary alkynes because of the donating ability of the nitrogen lone pair toward the alkynyl motif, we anticipate that ynamides would undergo electrophilic cyclization reactions with carbocations to form a C−C and C−O bond (Scheme 1, b). Herein, we wish to report the novel synthesis of 3-substituted 2-amidobenzofurans via electrophilic cyclization of *o*-anisole-substituted ynamides with carbocations.

Scheme 1



Initial studies focused on the reaction of *O*-anisyl ynamide **1a** with diphenylmethanol **2a**. $ZnCl_2$ was first chosen as the Lewis acid to generate the carbocation with diphenylmethanol in CH_2Cl_2. Fortunately, the expected 2-amidobenzofuran **3a** was obtained in 37% yield. Subsequent screening of Lewis acids showed that $ZnBr_2$ gave a better result than $ZnCl_2$ or ZnI_2 did (Table 1, entries 1−3), while other Lewis acids such as $AlCl_3$, $FeCl_3$, and $BF_3\cdot OEt_2$ were not effective (entries 4−6). Solvents were also important. Other common solvents such as toluene or THF did not give any expected product **3a** (entries 7−8). It should be noted that when a catalytic amount of $ZnBr_2$ was used, the yield was reduced dramatically (entry 9). Thus the following reaction conditions were chosen as optimum for all subsequent reactions: 0.5 mmol of **1**, 1.0 mmol of **2**, and 1.0 mmol of $ZnBr_2$ in CH_2Cl_2 were stirred at rt under N_2.

Table 1. Optimization of the Reaction Conditions[a]



entry	Lewis acid	solvent	time (h)	yield of **3a** (%)
1	$ZnCl_2$	CH_2Cl_2	4	37
2	$ZnBr_2$	CH_2Cl_2	3	72
3	ZnI_2	CH_2Cl_2	3	66
4	$AlCl_3$	CH_2Cl_2	14	0
5	$FeCl_3$	CH_2Cl_2	14	0
6	$BF_3\cdot OEt_2$	CH_2Cl_2	1	trace
7	$ZnBr_2$	toluene	1	0
8	$ZnBr_2$	THF	12	NR
9[b]	$ZnBr_2$	CH_2Cl_2	12	7

[a] Unless specified otherwise, the reaction was carried out using **1a** (0.5 mmol), **2a** (1.0 mmol), and a Lewis acid (1.0 mmol) in solvent (4 mL) at rt under N_2. [b] 0.05 mmol of $ZnBr_2$ was added.

Under the optimized conditions, the scope of this carbocation-induced electrophilic cyclization reaction was further investigated. The reaction was successful for various *O*-anisyl ynamides (Table 2, entries 1−5). It should be noted that when the amido group in **1** was replaced by an aryl or alkyl group, the corresponding 3-alkylbenzofuran was not detected. Substituted diarylmethanol, 1-arylprop-2-en-1-ol, and 1-arylprop-2-yn-1-ol worked well to afford the corresponding 3-alkyl, allyl, and propargyl 2-amidobenzofuran respectively (Table 2, entries 6−9), while simple phenylmethanol could not undergo this electrophilic cyclization reaction.

Interestingly, 3-allenyl-2-amidobenzofurans **5** were formed when 1,1-diarylprop-2-yn-1-ols **4** were used as the precursors of carbocations, and the corresponding 3-propargyl-2-amidobenzofurans were not found. As shown in Table 3, the reaction was successful for various *O*-anisyl ynamides (entries 1−4). The R^3 and R^4 groups of **4** can be a substituted

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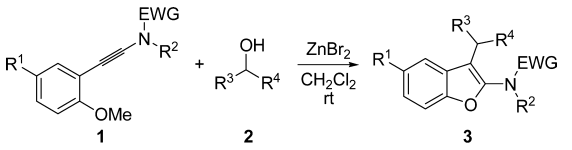
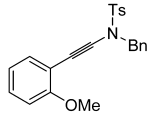
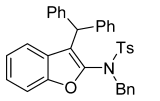
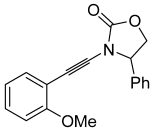
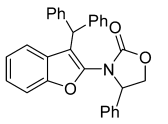
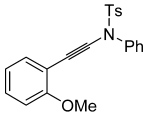
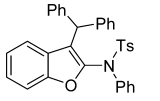
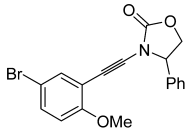
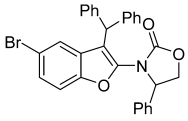
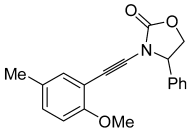
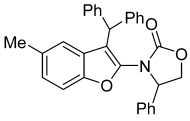
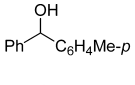
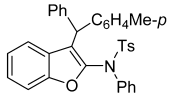
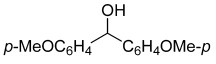
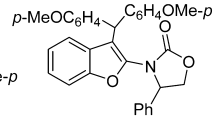
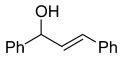
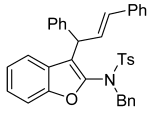
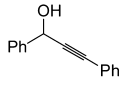
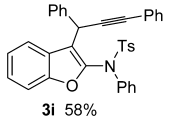
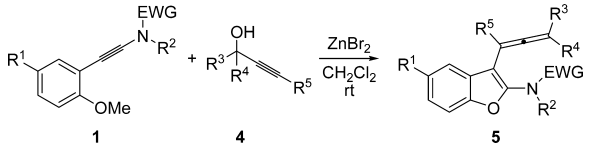
Table 2. Synthesis of 3-Alkyl-2-amidobenzofurans **3**[a]

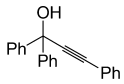
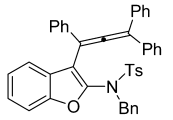
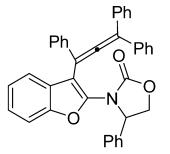
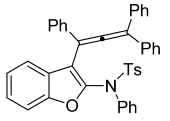
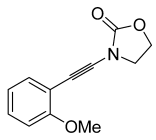
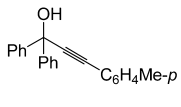
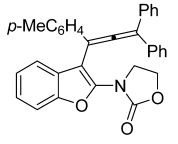
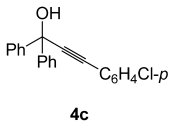
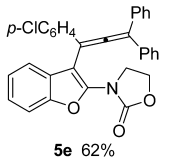
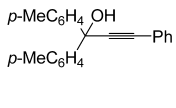
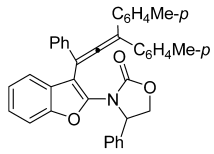
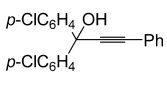
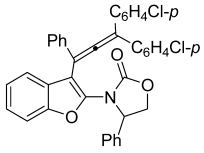
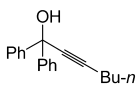
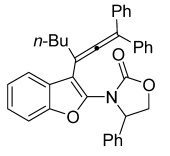


entry	1	2	yield of 3
1	 **1a**	 **2a**	 **3a** 72%
2	 **1b**	**2a**	 **3b** 84%
3	 **1c**	**2a**	 **3c** 54%
4	 **1d**	**2a**	 **3d** 69%
5	 **1e**	**2a**	 **3e** 76%
6	**1c**	 **2b**	 **3f** 60%
7	**1b**	 **2c**	 **3g** 54%
8	**1a**	 **2d**	 **3h** 71%
9	**1c**	 **2e**	 **3i** 58%

[a] The reaction was carried out using **1** (0.5 mmol), **2** (1.0 mmol), and $ZnBr_2$ (1.0 mmol) in CH_2Cl_2 (4 mL) at rt under N_2.

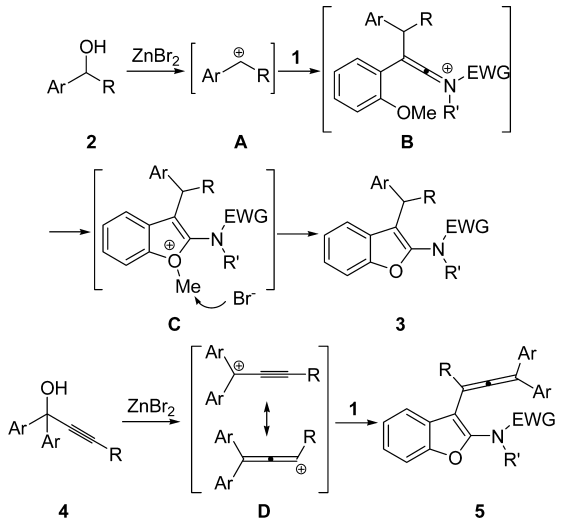
Table 3. Synthesis of 3-Allenyl-2-amidobenzofurans **5**[a]



entry	1	4	yield of 5
1	**1a**	 **4a**	 **5a** 65%
2	**1b**	**4a**	 **5b** 88%
3	**1c**	**4a**	 **5c** 75%
4	 **1f**	 **4b**	 **5d** 85%
5	**1f**	 **4c**	 **5e** 62%
6	**1b**	 **4d**	 **5f** 82%
7	**1b**	 **4e**	 **5g** 89%
8	**1b**	 **4f**	 **5h** 70%

[a] The reaction was carried out using **1** (0.5 mmol), **4** (1.0 mmol), and $ZnBr_2$ (1.0 mmol) in CH_2Cl_2 (4 mL) at rt under N_2.

Scheme 2



phenyl group with either an electron-donating or -withdrawing group (entries 6–7), while R^5 can be an aryl or alkyl group (entries 4, 5, 8). Thus this reaction provided access to benzofuran-substituted allenes which are important synthons in modern organic synthesis.[15]

The ESI-TOF MS analysis of the reaction mixture of **1b** and **2a** showed the existence of a diphenylmethyl cation, while the byproduct MeBr was obviously observed by GC-MS analysis of the gas composition of the reaction (see the Supporting Information for details). On the basis of the above experimental observations, a possible mechanism is given in Scheme 2. Initially, carbocation **A** would be formed from alcohol **2** with $ZnBr_2$. Electrophilic addition of the in situ generated carbocation with *O*-anisyl ynamide **1** gives the intermediate **B**.[16] Subsequent cyclization occurred to afford *O*-methyl benzofuran **C**, which is demethylated by a bromide anion to produce 2-amidobenzofuran **3**. In the case of alcohol **4**, propargylic carbocation/allenylic carbocation **D** formed from **4** and $ZnBr_2$ reacts with ynamide **1** to afford 3-allenyl-2-amidobenzofuran **5** selectively probably because of the steric hindrance of the two aryl groups.

In conclusion, we have described a novel carbocation-induced electrophilic cyclization reaction of *o*-anisole-substituted ynamides. 3-Alkyl, allyl, and propargyl 2-amidobenzofuran were provided respectively from various disubstituted alcohols. By utilization of 1,1-diarylprop-2-yn-1-ol, 3-allenyl-2-amidobenzofurans were afforded in high yield. Further investigation for the construction of other heterocyclic and carbocyclic systems via this carbocation-induced electrophilic cyclization reaction is ongoing in our laboratory.

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Supporting Information Available. Spectroscopic data for all new compounds. Detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.