Heterocycle Synthesis

DOI: 10.1002/ange.201408978

Metal-Free Radical 5-*exo*-dig Cyclizations of Phenol-Linked 1,6-Enynes for the Synthesis of Carbonylated Benzofurans**

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Abstract: *A new metal-free radical 5-exo-dig cyclization of phenol-linked 1,6-enynes with O_2, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), and tBuONO is described. With this general method, carbonylated benzofurans can be accessed through incorporation of two oxygen atoms into the product from O_2 and TEMPO through dioxygen activation and oxidative cleavage of the N–O bond, respectively.*

Benzofurans, including carbonylated benzofurans (Figure 1), are pervasive structural motifs found in natural products and pharmaceutical compounds with powerful biological properties.[1–2] For example, brazanquinones show selective inhibitory activity against a series of cancer cell lines.[2a–c] Balsaminones, which were isolated from the pericarp of the fruit *Impatiens balsamina* L., have significant antipruritic activity.[2d–f] Considerable efforts have thus been directed towards the discovery of efficient methods for their synthesis.[3–6] Despite remarkable advances in benzofuran synthesis, most of the traditional methods suffer from harsh conditions, limited functional group tolerability, and/or the cost of the catalytic system.[3–6] Furthermore, the assembly of carbonylated benzofuran scaffolds remains a great challenge.[3,4] Therefore, the development of mild and efficient routes and especially metal-free strategies towards carbonylated benzofurans is desirable.[6]

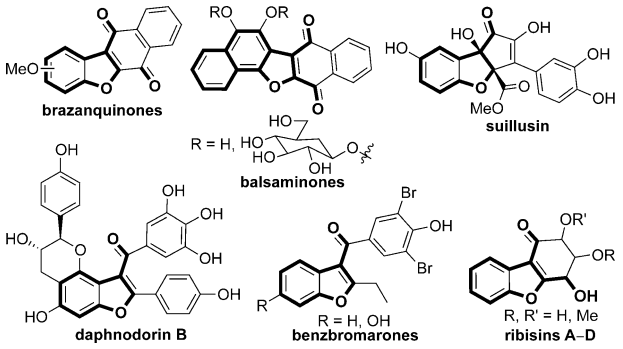
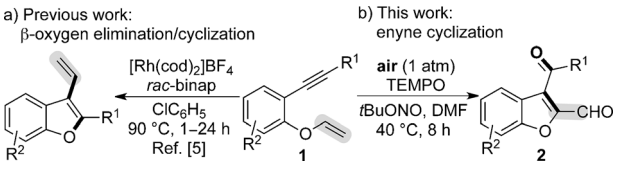


Figure 1. Examples of important carbonylated benzofurans.

The cyclization of 1,*n*-enynes has emerged as a powerful transformation that allows the rapid assembly of various complex ring systems in an atom- and step-economic manner.[7] Within the last years, many applications of the 1,*n*-enyne cyclization for the construction of various heterocycles, such as furans, pyrans, pyrroles, indoles, pyridines, quinolines, and other fused polyheterocycles, have been reported.[7,8] However, approaches using the real 1,*n*-enyne cyclization strategy to access benzofurans are lacking.[5] This is due to the fact that the intramolecular cyclization of phenol-linked 1,6-enynes in the presence of a rhodium catalyst leads to β-oxygen elimination/cyclization through cleavage and formation of the C(sp^2)–O bonds rather than direct enyne cyclization (Scheme 1 a).[5] We reasoned that direct cyclization reactions of phenol-linked 1,6-enynes might be realized under metal-free conditions. In the field of 1,*n*-enyne cyclization, radical strategies have played great roles and are now also shown to be useful for 1,*n*-enyne cyclizations.[7,8] However, the majority of radical cyclization reactions suffer from a requirement for precious and/or toxic metal complexes (often tin hydride reagents) and the difficult purification of the desired products from a large amount of unwanted side products and waste; therefore, they have received less attention over the past decade.[7,8] Herein, we report a novel metal-free radical 5-*exo*-dig cyclization of phenol-linked 1,6-enynes with air, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), and *t*BuONO[9] for the formation of carbonylated benzofuran scaffolds (Scheme 1 b). In this transformation, the addition of TEMPO across the C=C bond, oxidative elimination through cleavage of the N–O bond with *t*BuONO, cyclization with an alkyne, and radical dioxygen activation are achieved.[10] It should be noted that the two oxygen atoms that



Scheme 1. Cyclization of phenol-linked 1,6-enynes into benzofurans. binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, cod = cycloocta-1,5-diene.

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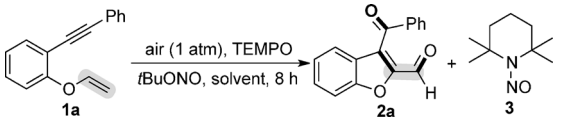
[**] We thank the NSFC (21172060), the Specialized Research Fund for the Doctoral Program of Higher Education (20120161110041), and the Hunan Provincial Natural Science Foundation of China (13JJ2018) for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201408978.

constitute the newly formed carbonyl groups of the benzofuran system originate from O_2 and TEMPO, respectively.

Our initial investigations began with the reaction of 1-(phenylethynyl)-2-(vinyloxy)benzene (**1a**) with air, TEMPO, and *t*BuONO for reaction optimization (Table 1). Treatment

Table 1: Optimization of the reaction conditions.[a]

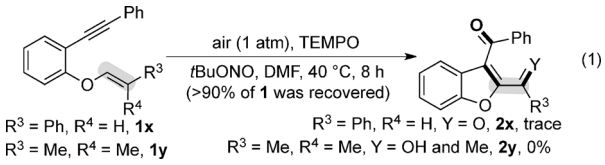


Entry	*t*BuONO [equiv]	TEMPO [equiv]	Solvent	*T* [°C]	Yield[b] [%]
1	3	3	DMF	RT	65
2	0	3	DMF	RT	0
3[c]	3	0	DMF	RT	0
4	3	3	MeCN	RT	48
5	3	3	EtOAc	RT	38
6	3	3	toluene	RT	18
7[d]	3	3	DMF	40	73
8	3	3	DMF	60	71
9[e]	3	3	DMF	40	73
10[f]	3	3	DMF	40	trace
11[g]	3	3	DMF	40	71

[a] Reaction conditions: **1a** (0.3 mmol), *t*BuONO, TEMPO, air (1 atm), solvent (2 mL), 8 h. [b] Yield of isolated product. [c] Another product, (2-(nitromethyl)benzofuran-3-yl)(phenyl)methanone (**4a**), was isolated in 23% yield together with > 50% yield of **1a**. [d] Product **3** was isolated in 70% yield based on the amount of TEMPO used. [e] Under O_2 atmosphere (1 atm). [f] Under argon atmosphere (1 atm) and in degassed solvent. [g] **1a** (1 g, 4.5 mmol), 24 h.

of 1,6-enyne **1a** with air, TEMP,O and *t*BuONO in DMF at room temperature for eight hours afforded the desired 3-benzoylbenzofuran-2-carbaldehyde (**2a**) in 65% yield (entry 1). However, in the absence of either TEMPO or *t*BuONO, the reaction did not result in the formation of detectable amounts of **2a** (entries 2 and 3). Without TEMPO, the nitration/cyclization product (2-(nitromethyl)benzofuran-3-yl)(phenyl)methanone (**4a**) was isolated in 23% yield (entry 3). Three other solvents, namely MeCN, EtOAc, and toluene, effected the reaction but were inferior to DMF (entries 4–6). Screening the effect of the reaction temperature revealed that higher temperatures were favorable, and 40 °C was found to be the preferred temperature (entries 1, 7, and 8). Notably, the reaction at 40 °C gave **2a** in 73% yield, while TEMPO was converted into 2,2,6,6-tetramethyl-1-nitrosopiperidine (**3**) in 70% yield (entry 7). When varying the amounts of TEMPO and *t*BuONO, we found that the reaction with three equivalents of TEMPO and *t*BuONO gave the best results (entry 7; see also the Supporting information, Table S1).[11] The yield under O_2 atmosphere was identical to that under air (entry 9), but the reaction was completely suppressed by using argon and degassed solvent (entry 10). The reaction with one gram of substrate **1a** gave the desired product in good yield (entry 11).

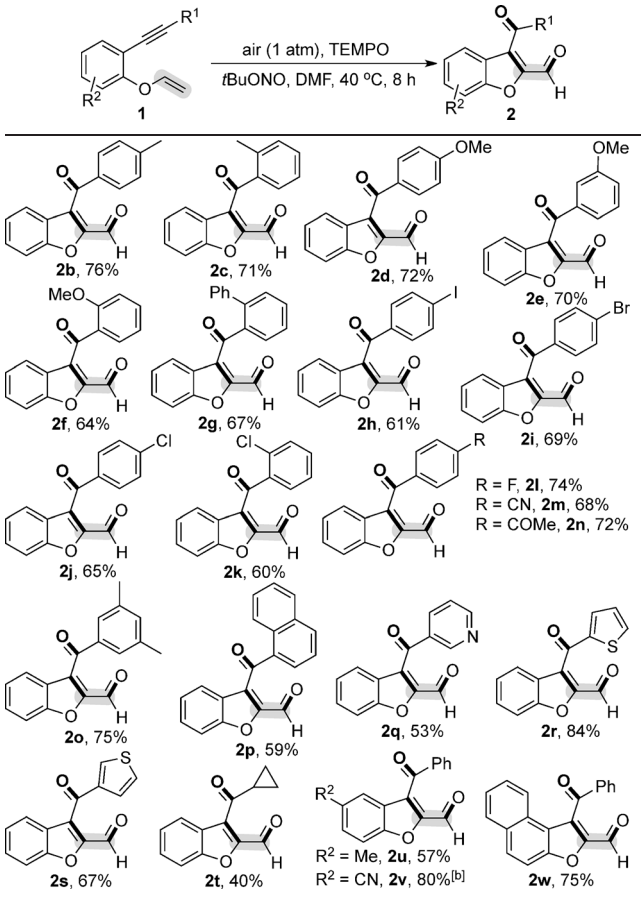
With the optimized reaction conditions in hand, we next investigated the generality of this metal-free cyclization reaction with respect to a range of 1-ethynyl-2-(vinyloxy)-benzenes **1** (Table 2). Gratifyingly, both electron-donating (**2b–g** and **2o**) and electron-withdrawing (**2h–n**) aromatic substituents were tolerated at the terminal alkyne. Moreover, even with bulky *ortho*-substituted aryl groups, the carbonylated benzofurans were furnished in good yields (**2c**, **2f**, **2g**, and **2k**), although these substrates were less reactive than their *para*- or *meta*-substituted counterparts. For example, whereas *para*-methyl-substituted 1,6-enyne **1b** afforded **2b** in 76% yield, *ortho*-methyl-substituted 1,6-enyne **1c** was converted into **2c** in 71% yield. For methoxy-substituted 1,6-enynes **1d–f**, the reactivity decreased from *para* to *meta* to *ortho* substitution (**2d–f**). Notably, substrates with strongly electron-withdrawing cyano and acetyl groups also delivered the carbonylated benzofurans **2m** and **2n** in good yields. Halide substituents (I, Br, Cl, and F) were well tolerated under these oxidative conditions (**2h–l**), and may serve as handles for further synthetic manipulations. 1,6-Enyne **1o**, which bears two methyl groups, and 1,6-enyne **1p**, which features a naphthalen-1-yl group, afforded benzofurans **2o** and **2p** in 75% and 59% yield, respectively. We were pleased to find that heteroaryl-substituted alkynes **1q–s** were also suitable substrates and allowed the formation of **2q–s** in moderate to high yields. Furthermore, the optimized reaction conditions were applicable to 1,6-enyne **1t**, which bears an alkyl group at the terminal alkyne (**2t**). Subsequently, representative 1,6-enynes were selected to illustrate the tolerance for substituents on the aryl ring of the 1-(vinyloxy)benzene moiety (**2u–w**). The substrate with an electron-donating methyl group afforded benzofuran **2u** in 57% yield, whereas with an electron-withdrawing CN substituent, benzofuran **2v** was obtained in 80% yield at 80 °C. We were pleased to find that **2w**, with a polycyclic ring system, was furnished in 75% yield.[2d,e] However, internal alkenes **1x** and **1y** did not react under the current cyclization conditions [Eq. (1)].



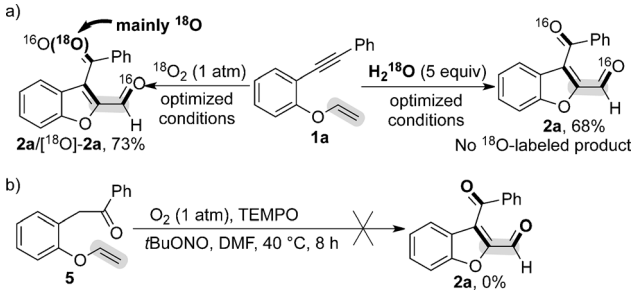
(1)

To elucidate the mechanism, some control experiments, including ^{18}O-labeling experiments, were conducted.[11] As expected, an ^{18}O atom was introduced into the ketonic carbonyl group under $^{18}O_2$ atmosphere (1 atm) as determined by GC-MS and ^{13}C NMR analysis (Scheme 2a). However, according to GC-MS and ^{13}C NMR analysis, ^{18}O atoms were not incorporated into the carbonyl groups in the presence of $H_2{}^{18}O$ (5 equiv) and anhydrous DMF (Scheme 2a). Notably, the results in Table 1 show that during the reaction, TEMPO is converted into 2,2,6,6-tetramethyl-1-nitrosopiperidine (**3**). These results imply that the oxygen atom of the aldehydic carbonyl group originates from TEMPO. Substrate **5** was subjected to the reaction with air, TEMPO, and *t*BuONO, but the desired product **2a** was not observed (Scheme 2b).

Table 2: Substrate scope.[a]



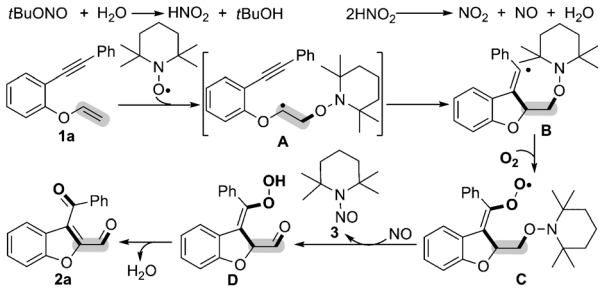
[a] Reaction conditions: **1** (0.3 mmol), *t*BuONO (3 equiv), TEMPO (3 equiv), air (1 atm), DMF (2 mL), 40 °C, 8 h. [b] At 80 °C.



Scheme 2. Control experiments.

The results of entries 1–3 in Table 1 suggest that the addition of TEMPO has precedence over the addition of NO_2 across the C=C bond in the presence of TEMPO and *t*BuONO. However, the desired product **2a** was not observed in the absence of *t*BuONO (entry 3). The results described above imply that one role of *t*BuONO is to trigger the current cyclization reaction by oxidative cleavage of the TEMPO N–O bond.

Consequently, the mechanism outlined in Scheme 3 was proposed for this enyne radical cyclization reaction. Generally, *t*BuONO readily decomposes into HNO_2 and *t*BuOH in the presence of H_2O, and HNO_2 is quickly converted into



Scheme 3. Possible mechanism.

NO_2, NO, and H_2O.[9,12] Initially, addition of TEMPO across the C=C bond of 1,6-enyne **1a** takes place to produce alkyl radical intermediate **A**, followed by a cyclization that affords vinyl radical intermediate **B**. Intermediate **B** is trapped by O_2 to afford superoxide radical **C**. Oxidative cleavage of the N–O bond in intermediate **C** with the aid of NO and single-electron transfer (SET)[10] occurs to form peroxyl intermediate **D** and 2,2,6,6-tetramethyl-1-nitrosopiperidine (**3**). Finally, O–O bond cleavage/isomerization of intermediate **D** delivers product **2a**.

In summary, we have developed the first metal-free 5-*exo*-dig cyclization of phenol-linked 1,6-enynes with O_2, TEMPO, and *t*BuONO through a radical process for the synthesis of carbonylated benzofurans. Importantly, this transformation incorporates two oxygen atoms from O_2 and TEMPO, respectively into the benzofuran system. Owing to its metal-free nature, this reaction satisfies the particular purity requirements of biological and medicinal chemistry. This simple radical strategy will renew our interest into applications of 1,*n*-enyne radical cyclizations, and related studies are currently underway in our laboratory.

Received: September 10, 2014
Revised: October 19, 2014
Published online: November 19, 2014

Keywords: benzofurans · cyclization · dioxygen activation · enynes · radical reactions

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