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Synthesis of Dihydrobenzofurans with Quaternary Carbon Center under Mild and Neutral Conditions

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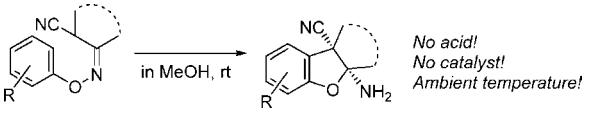
ABSTRACT



A new method has been developed for the construction of dihydrobenzofurans from *O*-aryloxime ethers bearing an α-cyano group using a sequential regioselective isomerization/[3,3]-sigmatropic rearrangement/cyclization reaction in MeOH without any catalysts under neutral conditions at ambient temperature. The current transformation provides environmentally benign and atom-economical access to a variety of dihydrobenzofurans containing a quaternary carbon from readily available cyclic and acyclic oxime ethers.

Dihydrobenzofuran derivatives are an important member of the benzofuran family,[1] and *cis*-dihydrobenzofurans bearing an all-carbon quaternary center, in particular, can be found in a variety of biologically important compounds, including galantamine-,[2] morphine-,[3] and lunarine-based[4] alkaloids, as well as marine natural products such as diazonamides.[5] In light of their interesting biological activities, a number of different synthetic strategies have been developed for the construction of dihydrobenzofurans, including strategies based on the phenolic oxidative coupling,[6] intramolecular Heck reaction,[7] Claisen rearrangement,[8] Birch–Cope sequence,[9] and intramolecular cyclization reaction.[10] Furthermore, the synthesis of dihydrobenzofurans bearing a quaternary carbon via the [3,3]-sigmatropic rearrangement of enehydroxylamines derived from oxime ethers is arguably one of the most straightforward

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synthetic methods currently available for the construction of these compounds.[11] Unfortunately, however, the application of this protocol has been severely limited because of its requirement for strongly acidic and high temperature conditions, which can lead to the decomposition of the substrates as well as other undesired side reactions.[12] Furthermore, it can be difficult to control the regiochemical outcome of the enamine formation under these conditions, with mixtures of the different regioisomers invariably being formed. When α-monosubstituted oxime ether was employed in this transformation, the isomerization of the imine led predominately to the least substituted enamine which underwent sequential [3,3]-sigmatropic rearrangement, cyclization, and elimination reactions to give the undesired benzofuran.[13,14] The synthesis of dihydrobenzofurans bearing a quaternary carbon center via a sequential regioselective isomerization and [3,3]-sigmatropic rearrangement pathway under neutral conditions therefore represents a highly desirable and challenging transformation in organic synthesis. With this in mind, it was envisaged that the regioselective formation of a more stable enamine through H-bonding would lead to the desired dihydrobenzofurans.

Hydrogen bonding has recently emerged as an important factor in the advancement of organic synthesis. Powerful organocatalysts and environmentally benign protic solvents, in particular, have been used to good effect as H-bond donors for the development of effective C−C bond forming reactions.[15] For example, Jorgensen[16] and Hillier[17] reported the occurrence of two H-bonds with water in the transition state of the Claisen rearrangement of an allyl vinyl ether that effectively accelerated the rate of the reaction (Figure 1). Similar H-bond promoted Claisen rearrangement reactions[18,19] encouraged us to investigate the possibility of developing an acid- and waste-free strategy for the synthesis of dihydrobenzofurans, with the key step being the regioselective isomerization of an oxime ether followed by a [3,3]-sigmatropic rearrangement sequence. It was envisaged that an oxime ether bearing an electron-withdrawing group (EWG), such as an ester or a nitrile, at the α-position of the imine moiety would give rise to the thermodynamically stable enamine and subsequently accelerate the [3,3]-sigmatropic rearrangement through H-bonding with water (Figure 1, **I→II→III**).

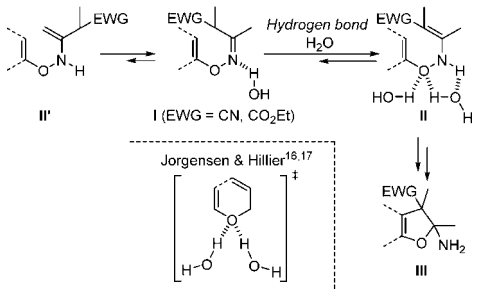

Figure 1. Proposed acceleration of the regioselective isomerization and subsequent [3,3]-sigmatropic rearrangement through H-bonding.

Oxime ethers of this particular type would then not only trigger the regioselective isomerization but also accelerate the subsequent sigmatropic rearrangement through H-bonding with a protic solvent. Herein, we present the first reported example of the regioselective isomerization−rearrangement−cyclization reaction sequence of oxime ethers promoted by a H-bonding effect. To the best of our knowledge, there have been no other reports in the literature concerning the efficient synthesis of valuable dihydrobenzofurans under mild and acid-free conditions.[20]

Oxime ether **1a** was selected as a model substrate for our initial evaluation of the regioselective isomerization and subsequent rearrangement, because it contained a cyano group which is both electron-withdrawing and provides minimal steric hindrance. The reaction of **1a** was initially screened against a range of different solvents that could perform as H-bond donors or acceptors (Table 1). When a suspension of **1a** was stirred in H_2O at ambient temperature for 72 h, none of the desired product was formed and only the starting material was recovered. The lack of reactivity in this case, however, was attributed to the poor solubility of **1a** in water (Table 1, entry 1).

Pleasingly, when the reaction was conducted in MeOH, the desired *cis*-dihydrobenzofuran **2a** was formed as the

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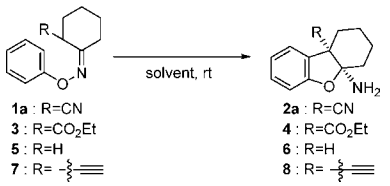
Table 1. Solvent and Substituent Effects



1a : R=CN
3 : R=CO_2Et
5 : R=H
7 : R= -≡

2a : R=CN
4 : R=CO_2Et
6 : R=H
8 : R= -≡

entry	substrate	solvent	t (h)	product	yield (%)[a,b]
1	**1a**	H_2O	72	**2a**	– (84)
2	**1a**	MeOH	24	**2a**	94
3	**1a**	EtOH	72	**2a**	81
4	**1a**	*i*-PrOH	120	**2a**	74
5	**1a**	CF_3CH_2OH	72	**2a**	47 (12)
6	**1a**	Et_2O	72	**2a**	– (99)
7	**1a**	CH_2Cl_2	120	**2a**	– (97)
8	**1a**	none	120	**2a**	– (99)
9	**3**	MeOH	48	**4**	– (99)
10	**5**	MeOH	48	**6**	– (99)
11	**7**	MeOH	48	**8**	– (99)

[a] Isolated yields. [b] Yields in parentheses are for the recovered starting materials.

sole product in high yield (Table 1, entry 2).[21] The application of other alcohols such as EtOH and *i*-PrOH led to lower yields of **2a** with longer reaction times also being required (Table 1, entries 3 and 4). Furthermore, the use of CF_3CH_2OH led to a significant reduction in the yield of **2a** (Table 1, entry 5). When the reaction was conducted in Et_2O or CH_2Cl_2 or under neat conditions, none of the desired product was formed, which indicated that protic solvents and hydrogen donors were critical to the success of the reaction (Table 1, entries 6–8).

To gain insight into the effect of the cyano group on this reaction, several other oxime ethers bearing a variety of other substituents were also subjected to the optimal reaction conditions. Interestingly, the MeOH-mediated reaction of **3** bearing the ethoxycarbonyl group did not take place. Given that the electron-withdrawing properties of the cyano group are similar to those of the ethoxycarbonyl group,[22] the corresponding enamine should have been formed (Figure 2). The transition state **B′** for the [3.3]-sigmatropic rearrangement, however, would have been conformationally disfavored because of steric repulsion, and the oxime ether **3** was subsequently recovered via the isomerization of the enamine (i.e., **A**→**3**). The acidity of the α-proton of the imine was also determined to be important to the success of this transformation, because the application of the optimal reaction conditions to the unsubstituted oxime ether **5** and the alkyne-substituted oxime ether **7** did not provide any of the desired products.

Having established the importance of the electron-withdrawing α-cyano group and the methanol solvent, we

(21) The stereostructure of **2a** was firmly established by the single-crystal X-ray analysis of the trifluoroacetamide **10** which was prepared by trifluoroacetylation of **2a** with TFAA (see Supporting Information).

(22) A value of the cyano and ethoxycarbonyl groups are 1.0 and 5.5 $kJ \cdot mol^{-1}$ respectively.

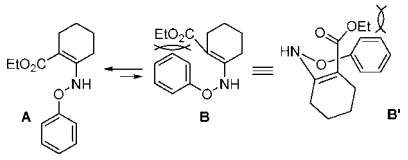


Figure 2. Different conformations of the enamines generated from **3**.

proceeded to investigate the application of the isomerization/rearrangement/cyclization reaction sequence to a variety of different oxime ethers **1b**–**h** (Table 2). The reactions of **1b** and **1c** with cycloheptane and cyclooctane rings, respectively, in MeOH proceeded smoothly to provide the corresponding dihydrobenzofurans **2b** and **2c** in high yields (Table 2, entries 1 and 2), although longer reaction times were required than that of **1a**. The reaction of **1d** bearing a macrocyclic ring in a mixture of MeOH and CH_2Cl_2 afforded the desired product **2d** in 84% yield (Table 2, entry 3).[23] We were also pleased to find that the reaction system could be successfully applied to the acyclic α-cyano oxime ethers. For example, the reactions of **1e**–**h** proceeded smoothly under the optimal conditions to give the corresponding dihydrobenzofurans **2e**–**h** in high yields as mixtures of diastereomers (Table 2, entries 4–7). Interestingly, the reaction of oxime ether **1i** bearing no alkyl group at the α-position gave the uncyclized product **9** in quantitative yield through the isomerization of the α-cyanoimine **E** to the stable β-enaminonitrile **9** following the [3,3]-sigmatropic rearrangement (Table 2, entry 8).

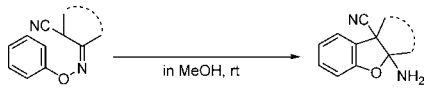
We then proceeded to examine the effect of different substituents on the benzene ring using a series of oxime ethers (Table 3). All of the oxime ethers studied were smoothly converted to the corresponding dihydrobenzofurans **2j**–**m** in good to high yields under the optimal conditions. Pleasingly, substrates **1l** and **1m** bearing a methyl or a trifluoromethyl group at the *o*-positions of their benzene ring, respectively, also worked well (Table 3, entries 3 and 4). The oxime ether **1n** bearing a *m*-methyl group on its benzene ring afforded the dihydrobenzofurans **2n** and **2n′** as a mixture of regioisomers in 73% yield (Table 3, entry 5).

To elucidate the mechanism of the transformation, the reaction was studied by ^1H NMR analysis. ^1H NMR spectra of a solution of **1a** in CD_3OD collected during the course of the reaction only revealed the consumption of **1a** and the generation of dihydrobenzofuran **2a**. After 24 h at ambient temperature, only **2a** could be detected by ^1H NMR as the sole product of the reaction. These results suggested that the [3,3]-sigmatropic rearrangement reaction of the *O*-aryl-*N*-vinylhydroxylamine and subsequent cyclization reaction must have occurred immediately after the isomerization of **1a** in the first step to form **2a**.

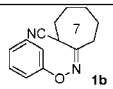
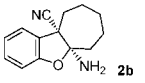
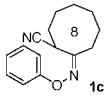
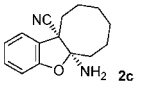
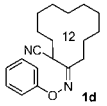
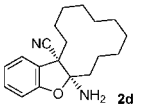
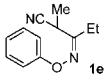
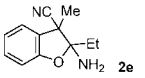
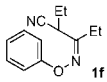
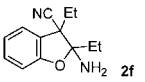
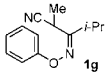
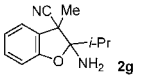
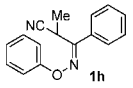
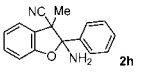
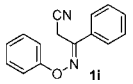
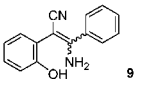
Based on the experimental observation from the current study, we have proposed a possible reaction pathway for the construction of dihydrobenzofuran **2** (Scheme 1).

(23) CH_2Cl_2 was used as a cosolvent.

Table 2. Reaction of Various Oxime Ethers



1 2

entry	substrate	product	t (h)	yield (%)[a,b]
1	 1b	 2b	34	91
2	 1c	 2c	116	95
3	 1d	 2d	204[c]	84
4	 1e	 2e	24	95[d]
5	 1f	 2f	66	85[d]
6	 1g	 2g	96	84[d]
7	 1h	 2h	168	87[e]
8	 1i	 9	40	99[f]

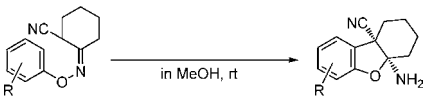
[a] Reaction conditions: Oxime ether **1** in MeOH at ambient temperature. [b] Isolated yields. [c] Reaction in a 5:2 (v/v) mixture of MeOH and CH_2Cl_2. [d] dr = 1:1. [e] dr = 4.5:1 [f] E/Z = 1:1.

Thus, the regioselective isomerization of oxime ether **1** activated by H-bonding would lead to the formation of the *O*-aryl-*N*-vinylhydroxylamine **D**. The subsequent sequential [3,3]-sigmatropic rearrangement and cyclization reaction would give rise to dihydrobenzofuran **2**. In the case of the unsubstituted oxime **1i** (R^1 = H, R^2 = Ph), the β-enaminonitrile **9** was presumably formed as a consequence of the rearomatization of **E**. The MeOH solvent was important for two reasons, including (i) promoting a shift in the imine-enamine equilibrium of **1** and (ii) accelerating the [3,3]-sigmatropic rearrangement of **D**.[24]

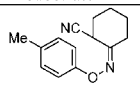
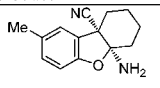
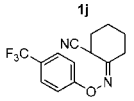
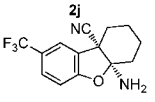
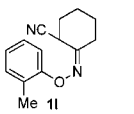
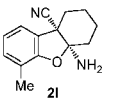
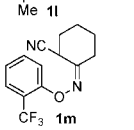
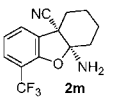
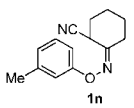
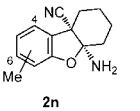
In summary, we established a highly efficient and general synthetic method for the construction of dihydrobenzofurans via the application of an isomerization/rearrangement/cyclization reaction sequence to α-cyano oxime ethers in MeOH. The MeOH-mediated reaction described herein presents several advantages over the existing methods, including the fact that the reaction proceeds under neutral conditions and does not require an extensive workup procedure. This new method therefore represents a much more operationally simple and practicable procedure.

(24) The possibility that MeOH is accerlating only the imine–enamine equibrium of **1a** cannot be excluded.

Table 3. Substituent Effects on the Benzene Ring

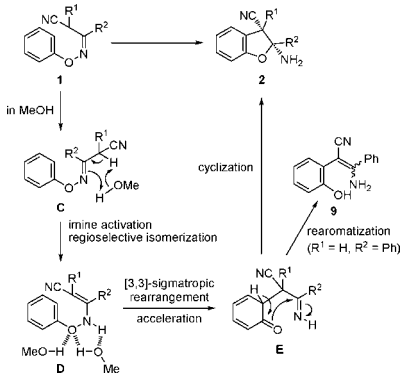


1j-n 2j-n

entry	substrate	product	t (h)	yield (%)[a,b]
1	 1j	 2j	53	85
2	 1k	 2k	17	70
3	 1l	 2l	28	65
4	 1m	 2m	21	79
5	 1n	 2n	30	73 (4-Me:6-Me = 1:1)

[a] Reaction conditions: Oxime ether **1** in MeOH at ambient temperature. [b] Isolated yields.

Scheme 1. Possible Reaction Pathway



1 2 C 9 D E

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Supporting Information Available. Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.