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Highly Effective Synthetic Methods for Substituted 2-Arylbenzofurans Using [3,3]-Sigmatropic Rearrangement: Short Syntheses of Stemofuran A and Eupomatenoid 6

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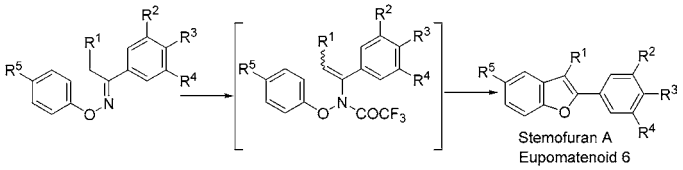
ABSTRACT



A new and efficient synthesis of 2-arylbenzofurans has been achieved via a route involving acylation and subsequent [3,3]-sigmatropic rearrangement of oxime ethers. Its synthetic utility is demonstrated by a short synthesis of stemofuran A and eupomatenoid 6 in which no procedure for protection of the phenolic hydroxyl groups is needed.

Benzo[*b*]furans carrying functional groups are attractive targets of organic synthesis because of their biological activity and their wide occurrence in nature.[1] As a consequence, there has been growing interest in developing general and versatile synthetic methods for benzofuran derivatives.[2] Some 2-arylbenzofurans are inhibitors of cell proliferation and platelet-activating factor, and some of them show good fungicidal, insecticidal, and cytotoxic activities.[1j−l] Therefore, 2-arylbenzofurans have been a new subject of synthetic studies for the development of biologically active compounds.[3]

We have now developed a new preparative route to 2-arylbenzofurans **1** using the successive reactions of oxime ethers. The route involves acylation, [3,3]-sigmatropic rearrangement, and intramolecular cyclization reactions.[4] Furthermore, this method was successively applied to the short synthesis of stemofuran A **2**[5] and eupomatenoid 6 **3**,[6] the latter of which has shown antifungal, insecticidal, and antioxidant activities (Figure 1).

We first investigated the substituent effects in the reaction of oxime ethers **4**, prepared by condensation of *O*-phenyl-

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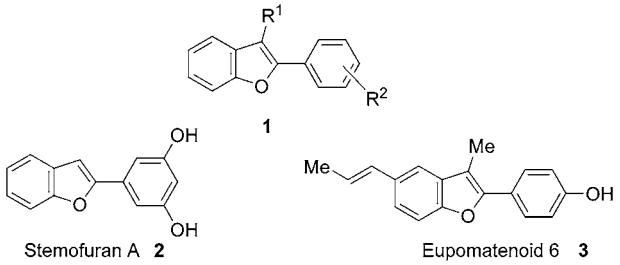
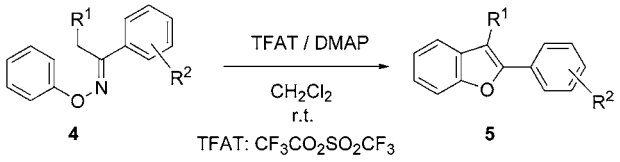


Figure 1. 2-Arylbenzofurans.

hydroxylamine and various acetophenones, with trifluoroacetyl triflate (TFAT),[7] which is a powerful acylating agent (Table 1).[8] When unsubstituted oxime ether **4a** was treated

Table 1. Conversion of Oxime Ethers into 2-Arylbenzofurans[a]



entry	4	R^1	R^2	time (h)	5	yield[b] (%)
1	**4a**	H	H	1	**5a**	99
2	**4b**	H	*p*-Br	1.5	**5b**	96
3	**4c**	H	*p*-NO_2	5	**5c**	85 (9)
4	**4d**	H	*p*-OH	2	**5d**	84
5	**4d**	H	*p*-OH	2	**5n**[c]	92
6	**4e**	H	*p*-OMe	2	**5e**	15 (12)
7	**4f**	Me	H	2	**5f**	82
8	**4g**	Me	*p*-Br	2	**5g**	91
9	**4h**	Me	*p*-OH	2	**5h**	86
10	**4i**	Me	*p*-OMe	2	**5i**	26 (13)
11	**4j**	H	*m*-Br	2	**5j**	94
12	**4k**	H	*m*-NO_2	5	**5k**	95
13	**4l**	H	*m*-OH	2	**5l**	86
14	**4m**	H	*m*-OMe	1.5	**5m**	93

[a] TFAT (5 equiv) and DMAP (3 equiv) were used. [b] Yields in parentheses are for the recovered starting material. [c] **5n** (R^2 = *p*-$OCOCF_3$).

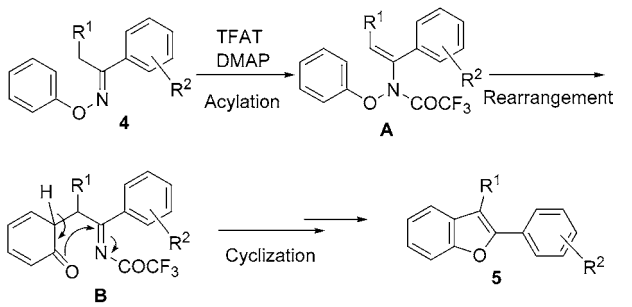
with TFAT (5 equiv) in the presence of (dimethylamino)-pyridine (DMAP) (3 equiv) at room temperature, the expected 2-phenylbenzofuran **5a** was obtained in quantitative yield (entry 1). Similarly, the reaction of oxime ethers **4b** and **4c** having the *p*-bromo- and *p*-nitrophenyl groups which are electron-withdrawing group proceeded smoothly to give 2-arylbenzofurans **5b** and **5c** in good yields, respectively (entries 2 and 3). Even when a phenolic hydroxyl group is present as an electron-donating group at the para position, the desired benzofuran **5d** was obtained in 84% yield after chromatograpy using silica gel (entry 4). Direct recrystallization of the crude product obtained from oxime ether **4d** gave benzofuran **5n** having a *p*-trifluoroacetoxy group (entry 5). However, the oxime ether **4e** with a *p*-methoxyl group gave the benzofuran **5e** only in low yield with a small amount of starting material **4e** (entry 6).

A similar trend was observed in the reaction of oxime ethers **4f**−**i**, prepared from propiophenones (entries 7−10). The oxime ethers **4f**−**h** were subjected to reaction with TFAT to give the 2-aryl-3-methylbenzofurans **5f**−**h** in good to excellent yields while the oxime ether **4i** having a *p*-methoxyl group gave corresponding benzofuran **5i** in 26% yield.

The next substrate of choice was oxime ethers **4j**−**m** with a meta-substituted phenyl group. Under similar reaction conditions, the oxime ethers **4j**−**l** were converted into the desired benzofurans **5j**−**l** in good yield (entries 11−13). The reaction of substrate **4m** with a *m*-methoxyl group also proceeded smoothly to afford the desired benzofuran **5m** in excellent yield (entry 14).

A plausible reaction pathway based on these results is shown in Scheme 1. As shown in our previous studies,[4] the

Scheme 1



oxime ethers **4** are acylated with TFAT to form the trifluoroacetylated compounds **A**. These would immediately rearrange to give the dienones **B,** which are converted into the 2-arylbenzofurans **5** via cyclization followed by elimination of trifluoroacetamide.

In the case of oxime ether **4d** with the hydroxyl group, the acylation proceeds at both the imine part and the hydroxyl group to form diacylated enehydroxylamine **C**, which can then rearrange to afford the acylated 2-arylbenzofuran **5n**. This labile benzofuran **5n** was readily hydrolyzed during column chromatograpy using silica gel to give the phenolic benzofuran **5d** (Scheme 2). Similarly, oxime ethers **4h** and **4l** would give the desired 2-arylbenzofurans **5h** and **5l** via the corresponding diacylated intermediates.

As mentioned above, the series of reactions leading to the formation of 2-arylbenzofurans proceeded smoothly except for oxime ethers having a *p*-methoxyl group (**4e** and **4i**). This

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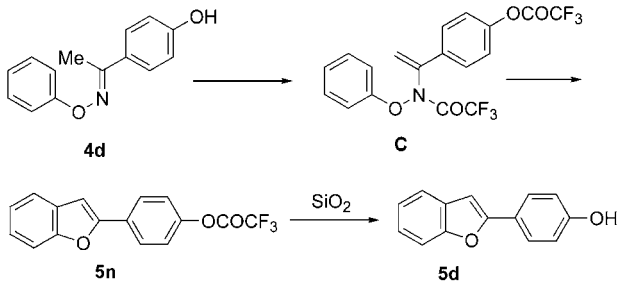
(8) When trifluoroacetic anhydride, which is the usual trifluoroacetyl agent, was used, the oxime ether could not give 2-arylbenzofuran.

Scheme 2

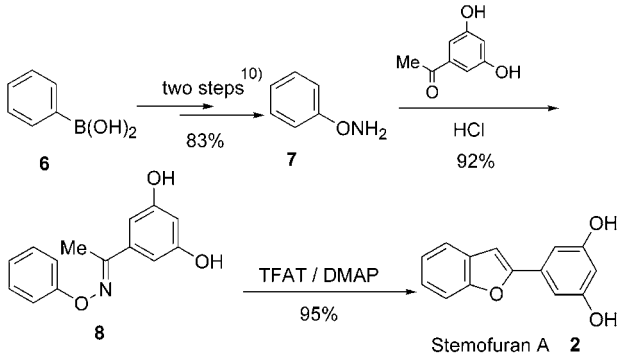


is due to the electron-donating ability of the *p*-methoxyl group. The electron-donating ability lowers the reactivity of the intermediates **B** formed from **4e** and **4i** toward nucleophilic attack of the carbonyl oxygen.

The high potential of this reaction for synthesis has been proved by the practical synthesis of natural 2-arylbenzofurans. We chose stemofuran A **2**[5] and eupomatenoid 6 **3**[6] as our targets which have a hydroxylphenyl group at the 2-position of the benzofuran skeleton. We succeeded in the total synthesis of these natural products without a step for protection of the phenolic hydroxyl groups.

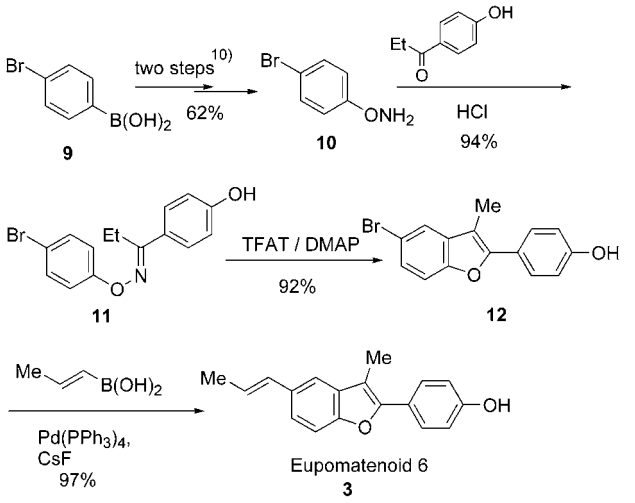
At first, we examined the preparation of stemofuran A **2**, recently isolated from *Stemona collinsae*[5] (Scheme 3). Al-

Scheme 3



though Pasturel et al.[9] synthesized stemofuran A **2** in 44% overall yield from 2-hydroxybenzaldehyde, the synthesis includes many transformations involving protection and deprotection of a hydroxyl group. *O*-Phenylhydroxyamine **7** was prepared from the phenylboronic acid **6** in two steps acccording to the literature procedures.[10] The condensation of **7** with dihydroxyacetophenone gave the oxime ether **8**, which was subjected to our reaction conditions to give stemofuran A **2** in 95% yield. The spectral data of this benzofuran **2** are identical with those reported in the literature.[5] Thus, we have succeeded in a four-step synthesis with 72% overall yield.

Scheme 4



Another target of our synthesis is eupomatenoid 6 **3**[6] (Scheme 4). Known syntheses of eupomatenoid 6 **3** reported by two groups[11,12] include the protection and deprotection reactions of the hydroxyl group.

The condensation of *O*-phenylhydroxylamine **10**,[10] prepared from boronic acid **9**, with propiophenone proceeded effectively to give the oxime ether **11** in excellent yield, which was then treated with TFAT to give the desired benzofuran **12** in 92% yield.

Finally, the introduction of a propenyl group was achieved by using Suzuki coupling with propenyl boronic acid to give eupomatenoid 6 **3** in 52% overall yield from **9** in five steps. Physical and spectral properties of **3** were identical with those of natural eupomatenoid 6 **3** reported in the literature.[6] Our synthesis is superior to those reported by both Bach's[12] and Stevenson's[11] groups in both yield and number of steps.

In conclusion, we have now established a novel and potential synthetic route to 2-arylbenzofurans. The reaction proceeds via sequential acylation, rearrangement, and cyclization of oxime ethers under the mild conditions. Furthermore, we have succeeded in the short synthesis of stemofuran A and eupomatenoid 6.

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

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