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Synthesis of a novel class of benzofurans via a three-component, regiospecific intramolecular heterocylization reaction

Bahador Karami *, Saeed Khodabakhshi, Fatemeh Hashemi

Department of Chemistry, Yasouj University, Yasouj 75918-74831, Iran

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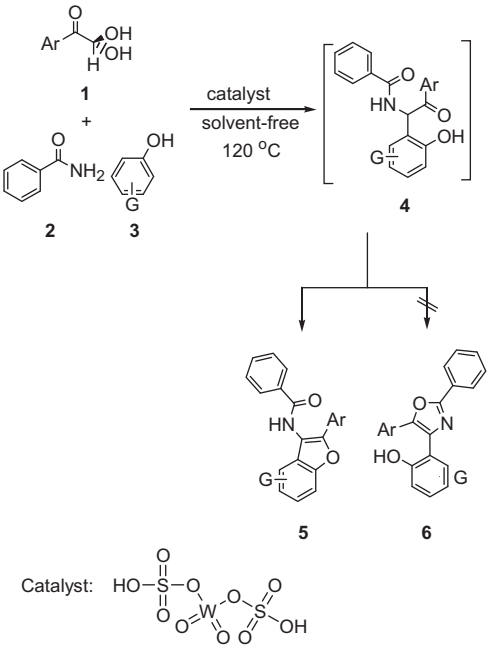
ABSTRACT

A new, convenient, and environmentally benign three-component synthesis of a novel class of benzofurans is developed by condensing different arylglyoxals, benzamide, and phenolic substrates under solvent-free conditions. These reactions are catalyzed by tungstate sulfuric acid (TSA) as a safe, clean, and recyclable solid acid. The method is operationally simple and provides access to a variety of 2-aryl-3-benzamido benzofurans in good to excellent yields.

Benzo-fused heterocycles play important roles in both drug discovery and chemical biology.[1] Among benzoheterocycles containing an oxygen atom, benzofurans are present in various biologically active molecules possessing, for example, antibacterial,[2] antifungal,[3] anti-inflammatory,[4] antidepressant,[5] and anticonvulsant[6] activity. For example, benzbromaron is a uricosuric agent used in the treatment of gout,[7] cloridarol is a vasodilator,[8] oxetorone is an antimigraine agent,[9] and amiodarone is an anti-arrhythmic agent used for various types of cardiac dysrhythmias, both ventricular and atrial.[10]

Several strategies for the synthesis of benzofurans are known. Almost all the reported methods can be classified into two categories: (1) intramolecular cyclization of benzene derivatives and (2) creation of an annellated carbocyclic ring.[11] The traditional methods for the synthesis of benzofuran derivatives involve the preparation, via *O*-alkylation of salicylaldehyde with chloroacetic acid, followed by dehydration of the resulting ether (category 1)[12] or via Perkin rearrangement in which a coumarin is reacted with a hydroxide (category 2).[13–15] New strategies have also been employed for the synthesis of benzofurans such as Claisen rearrangement and ring-closing metathesis,[16] condensation of benzil with phenols and aryl ethers mediated by $SnCl_2$,[17] a one-pot method for synthesizing 4-acetoxy-2-amino-3-arylbenzofurans,[18] and the synthesis of 2-imino-3-aminobenzofurans via multicomponent reactions from TosMIC.[19] It is important to mention that Wang et al. have reported a three-component process for the synthesis of 2-aryl-3-aminobenzofuran derivatives from phenols, arylglyoxal monohydrates, and *para*-toluenesulfonamide promoted by indium trichloride. Using this method, benzofurans were obtained in good



Scheme 1. Synthesis of 2-aryl-3-benzamido-benzofuran derivatives.

* Corresponding author. Tel.: +98 7412223048; fax: +98 7412242167.
E-mail address: karami@mail.yu.ac.ir (B. Karami).

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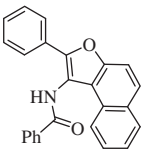
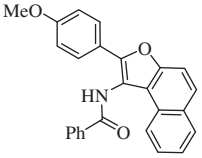
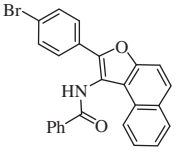
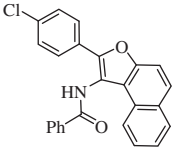
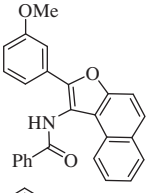
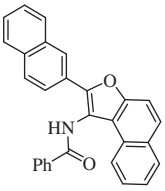
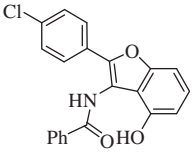
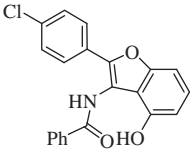
Table 1
Synthesis of novel benzofurans in the presence of TSA[30]

Entry	Product	Yield (%)[a]	Mp (°C)
5a		80	230–232
5b		75	239–241
5c		85	286–288
5d		80	270–272
5e		85	198–200
5f		75	220–222
5g		85	248–250
5h		75	225–227

[a] Isolated yield.

to excellent yields while the formation of diketones as by-products was effectively inhibited.[20]

Multicomponent reactions (MCRs) are powerful tools for the generation of chemical libraries and they have attracted significant attention due to their broad applications in medicinal chemistry for the production of various structural scaffolds, and in combinatorial synthesis.[21]

In continuation of our research on the development of novel techniques for the synthesis of heterocyclic compounds,[22–28] herein, we describe a new and green strategy for the preparation of novel benzofurans through a three-component reaction (category 1) similar to that reported earlier.[20]

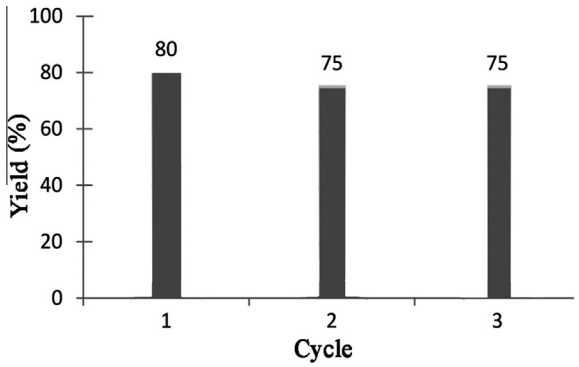
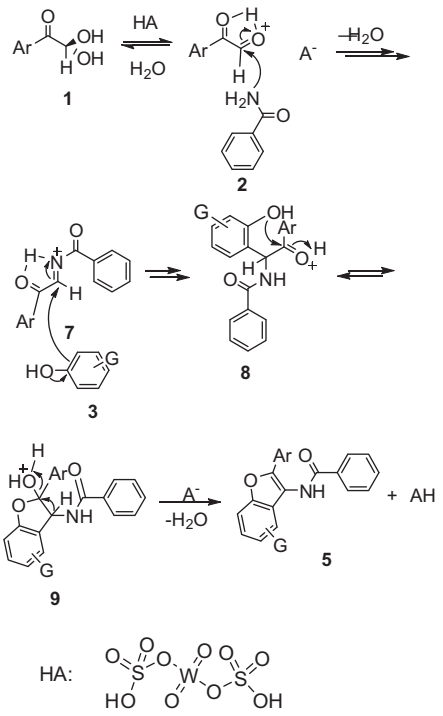


Figure 1. Recyclability of the TSA catalyst in the synthesis of **5a** over 3 runs.



Scheme 2. Suggested mechanism for the formation of 2-aryl-3-benzamido-benzofurans catalyzed by tungstate sulfuric acid.

According to previous reports on the synthesis of amidoalkyl naphthols,[29] we treated arylglyoxals **1** (obtained by selenium dioxide oxidation of the corresponding phenyl ketones) and benzamide (**2**) with phenolic substrates **3** in the presence of a catalytic amount of tungstate sulfuric acid (TSA) under solvent-free conditions (Scheme 1). Despite the low probability of intramolecular cyclization of intermediate **4**, we originally thought that the two isomers **5** and **6** would be formed. However, after characterization by IR and NMR spectroscopy, we found that only 2-aryl-3-benzamido-benzofurans **5** were actually formed.

The scope of this three-component reaction for the synthesis of 2-aryl-3-benzamido-benzofurans was studied and the results are summarized in Table 1. It should be mentioned that all the reactions proceeded by in situ generation of intermediate **4** and showed regiospecificity toward structural isomer **5** rather than oxazole **6**.

In these reactions, electron-rich and -deficient arylglyoxals, as well as various phenolic substrates worked well. Methods based on green chemistry principles have attracted growing interest from

the scientific community in recent years. The results in Table 1 indicate the feasibility of these three-component reactions under solvent-free conditions. All the products were synthesized in very good yields (75–85%) at 120 °C over 90–240 min. Moreover, the catalyst (TSA) is safe, separable, and can be reused several times. For example, the activity of the catalyst was tested in the synthesis of **5a** over three runs, during which little appreciable loss was observed in the catalytic activity (Fig. 1). Therefore, the efficiency of this strategy under environmentally friendly conditions is in accordance with green chemistry criteria.

A mechanistic rationale for the formation of compounds **5** is postulated in Scheme 2. The reaction is thought to take place in three steps. It is reasonable to assume that the initial event involves the generation of intermediate **7** via condensation of amide and arylglyoxal. In the next step, intramolecular cyclization of intermediate **8** gives **9** followed by dehydration to form the product **5**.

In summary, the reaction between arylglyoxals, benzamide, and phenol derivatives in the presence of a catalytic amount of tungstate sulfuric acid provides a simple one-pot entry for the synthesis of 2-aryl-3-benzamido-benzofurans of potential synthetic and pharmaceutical interest. This method has advantages such as the use of a safe and recyclable catalyst, avoidance of organic solvents, high yields of products, short reaction times, and a simple work-up procedure. It is worthwhile to note that the presence of transformable functionalities in the products makes them potentially valuable for further synthetic manipulations.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.124.

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30. General procedure for the synthesis of benzofurans **5**. A mixture of arylglyoxal **1** (1 mmol), benzamide (**2**) (1 mmol), and TSA (0.05 mmol) was stirred and heated at 120 °C in a preheated oil bath for 20 min. Next, the phenolic substrate **3** was added and the mixture was stirred for the appropriate amount of time (90–240 min). After completion of the reaction as indicated by TLC (EtOAc/hexane, 1:2), the mixture was added to hot EtOH and the catalyst was separated by filtration. The solvent was evaporated and the products **5** were purified by recrystallization from EtOH. Compound **5a**. ^{1}H NMR (DMSO-d_6, 400 MHz,): δ = 10.78 (s, 1H), 8.26 (d, 1H, J = 7.6 Hz), 8.21 (d, 2H, J = 7.2 Hz), 8.09 (d, 1H, J = 8.0 Hz), 8.04–7.90 (m, 4H), 7.74–7.65 (m, 3H), 7.57 (d, 2H, J = 7.6 Hz), 7.53 (d, 2H, J = 8.0 Hz), 7.43 (t, 1H, J = 7.6 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 167.21, 150.86, 149.10, 134.07, 132.72, 130.92, 129.83, 129.54, 129.47, 129.38, 129.25, 128.27, 127.66, 127.18, 126.87, 125.84, 125.41, 122.67, 121.40, 117.26, 113.05; IR (KBr) v: 3160, 3110, 2089, 1640, 1485, 1260, 1040, 800, 700 cm^{-1}. Anal. Calcd for $C_{25}H_{17}NO_2$: C, 82.63; H, 4.72; N, 3.85. Found: C, 82.90; H, 4.65; N, 3.77. Compound **5b**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.70 (s, 1H), 8.24 (d, 2H, J = 6.8 Hz), 8.22 (d, 1H, J = 8.0 Hz), 8.07 (d, 1H, J = 8.0 Hz), 7.89 (m, 4H), 7.74–7.64 (m, 3H), 7.56–7.50 (m, 2H), 3.81 (s, 3H), 7.11 (d, 2H, J = 9.2 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 167.20, 160.10, 150.46, 149.46, 134.11, 132.66, 130.89, 129.40, 129.35, 128.25, 127.58, 127.45, 126.99, 126.20, 125.28, 122.65, 122.36, 121.54, 115.05, 112.95, 55.77; IR (KBr) v: 3165, 3110, 2950, 1640, 1510, 1475, 1260, 1040, 800, 700 cm^{-1}. Anal. Calcd for $C_{26}H_{19}NO_3$: C, 79.37; H, 4.87; N, 3.56. Found: C, 79.51; H, 4.80; N, 3.45.