



# An efficient approach to construct 2-arylbenzo[*b*]furans from 2-methoxychalcone epoxides



Libo Ruan, Min Shi, Shiwei Mao, Lifang Yu, Fan Yang\*, Jie Tang\*

Institute of Drug Discovery and Development, Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, Shanghai 200062, China

## ARTICLE INFO

### Article history:

Received 4 November 2013  
Received in revised form 4 December 2013  
Accepted 17 December 2013  
Available online 22 December 2013

### Keywords:

2-Arylbenzo[*b*]furans  
2-Methoxychalcone epoxides  
Deformylation  
Cyclodehydration  
Stemofuran A

## ABSTRACT

An efficient and practical method for construction of 2-arylbenzo[*b*]furans from 2-methoxychalcone epoxides has been reported. Catalyzed by 2 mol % of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , 2-methoxychalcone epoxides went through the Meerwein rearrangement, followed by deformylation in one-pot to successfully afforded 2-methoxydeoxybenzoins. Afterward, 2-arylbenzo[*b*]furans were obtained in high yields (87%–100%) via intermolecular cyclodehydration of 2-methoxydeoxybenzoins with 48% HBr. By utilization of this approach, the natural product stemofuran A and the key intermediate of eupomatenoic 6 have been synthesized conveniently.

© 2013 Elsevier Ltd. All rights reserved.

## 1. Introduction

2-Arylbenzo[*b*]furans widely exist in natural products,<sup>1</sup> and many compounds including 2-arylbenzo[*b*]furan structural unit were found to possess attractive pharmacological activities, such as antitumor,<sup>2</sup> antiviral,<sup>3</sup> antioxidative,<sup>4</sup> and antifungal properties.<sup>5</sup> Their broad range of biological activities and significant pharmacological potentials have resulted in the development of many methods for their synthesis.<sup>6</sup> The palladium-catalyzed cross-coupling cyclization reaction from alkynes and *o*-halophenols was found to be efficient.<sup>7</sup> Other approaches for the synthesis of benzo[*b*]furans include cyclization of vinylic phenols through McMurry coupling reaction,<sup>8</sup> [3,3]-sigmatropic rearrangement of oxime ethers,<sup>9</sup> palladium-catalyzed enolate arylation.<sup>10</sup>

The relative ease of preparation chalcone epoxides makes them promising starting materials for preparation of a variety of heterocyclic compounds. Our group is interested in extent the application scope of these versatile molecules. Previously, we successfully used chalcone epoxides as a synthetic precursor for the preparation of 3-aryl quinolines.<sup>11</sup> Herein, we reported a new

practical synthetic route for the preparation of 2-arylbenzo[*b*]furans from 2-methoxychalcone epoxides.

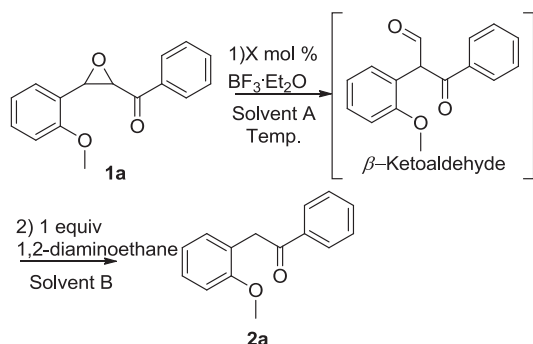
## 2. Results and discussion

Asokan co-workers observed that  $\beta$ -ketoaldehydes could react with 1,2-diaminoethane in THF to yield deoxybenzoins.<sup>12</sup> However, only 4-substitute substrates were tested. We considered that if the 2-alkyloxysubstituted chalcone epoxides were used in these reactions, 2-methoxydeoxybenzoins should be obtained conveniently, which could be further transformed to the corresponding 2-arylbenzo[*b*]furans via cyclodehydration.

We firstly focused on the optimization of the reaction conditions with 2,3-epoxy-3-(2-methoxy-phenyl)-1-phenylpropan-1-one (**1a**) as a model substrate (Table 1). Meerwein rearrangement of chalcone epoxides to form  $\beta$ -ketoaldehydes has been known for a long time,<sup>13</sup> and 2 equiv<sup>13</sup> or 1 equiv<sup>12</sup> of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  was used in the reaction. From the viewpoint of catalytic mechanism, we attempted to carry out the reaction with catalytic amount of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , and the results showed that the reduction of the amount of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  from 100 mol % to 2 mol % did not affect the yield (Table 1, entries 2–5). When the catalyst was further reduced to 0.5 mol % the yield of the product dropped to 21% due to an incomplete rearrangement reaction (Table 1, entry 6). Therefore, 2 mol % of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  was chosen as the optimal catalyst amount for the following rearrangement reactions. Change of the organic solvent of the rearrangement

\* Corresponding authors. Tel.: +86 21 62232764 (F.Y.); tel.: +86 21 62232100 (J.T.); e-mail addresses: [fyang@chem.ecnu.edu.cn](mailto:fyang@chem.ecnu.edu.cn) (F. Yang), [jtang@chem.ecnu.edu.cn](mailto:jtang@chem.ecnu.edu.cn) (J. Tang).

**Table 1**  
Optimization of reaction conditions for synthesis of 2-methoxydeoxybenzoin from 2-methoxychalcone epoxide



Entry <sup>a</sup>	BF <sub>3</sub> ·Et <sub>2</sub> O	Solvent A	Solvent B	Temp (°C)	Yield (%) <sup>b</sup>
1	100 mol %	DCM	THF	25	72
2	50 mol %	DCM	THF	25	71
3	10 mol %	DCM	THF	25	72
4	5 mol %	DCM	THF	25	77
5	2 mol %	DCM	THF	25	75
6	0.5 mol %	DCM <sup>c</sup>	THF	25	21 <sup>c</sup>
7	2 mol %	Toluene	THF	25	64
8	2 mol %	MeCN	THF	25	32
9	2 mol %	THF	THF	25	56
10	2 mol %	DCM <sup>c</sup>	THF	0	57
11	2 mol %	DCM	DCM	25	72

<sup>a</sup> Reaction conditions: 1 mmol of chalcone epoxides, 5 mL of solvent A, after the rearrangement reaction was complete, the solvent A was removed in vacuo, then added 5 mL solvent B, 1 equiv of 1,2-diaminoethane.

<sup>b</sup> Isolated yields.

<sup>c</sup> Reaction conducted for 4 h.

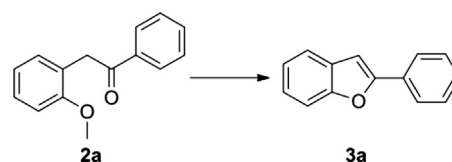
reaction indicated that the solvent played a paramount role in terms of rates and chemical yields, and DCM was still the best choice. The reaction finished in 5 min at 25 °C (Table 1, entry 5). The reactions were sluggish and gave lower yields in PhMe, MeCN, or THF due to the incomplete rearrangement (Table 1, entries 7–9). The influence of temperature on the rearrangement reaction was also preliminarily tested, and lower yield was obtained when decrease the temperature was decreased from 25 °C to 0 °C (Table 1, entry 10).

In addition, we found that the deformylation reaction of 2-methoxy- $\beta$ -ketoaldehyde could also be carried out in DCM instead of THF (Table 1, entry 11). Therefore the procedure was further simplified by successively performing the deformylation after the rearrangement of chalcone epoxides, and the two-step reaction proceeded in one-pot to afford the desired product **2a** in good yield.

To construct 2-arylbenzo[*b*]furan **3a**, **2a** was selected as a model substrate to examine its behavior under different demethylation conditions (Table 2). There are very few reports about the cyclodehydration of 2-alkoxydeoxybenzoin to afford benzo[*b*]furans, which was only carried out the reaction with BCl<sub>3</sub> at –78 °C,<sup>14a</sup> or with AlBr<sub>3</sub> in benzene.<sup>14c</sup> To our delight, treatment of **2a** with 48% HBr in AcOH, deoxybenzoin **2a** could be demethylated, and subsequently cyclodehydrated to give the desired benzo[*b*]furan **3a** in quantitative yield (Table 2, entry 5). Treatment of **2a** with BBr<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C gave **3a** in 43% yield due to side reaction (Table 2, entry 1), and only trace of **3a** was detected when AlCl<sub>3</sub>/Py or LiCl was used (Table 2, entries 2, 6). Although HI and TMSI/KI were competent reagents for this reaction (Table 2, entries 3, 4), from the standpoint of overall cost and for large scale reactions, 48% HBr was chosen as the demethylation reagent in the following reaction.

In order to examine the scope of this construction method for 2-arylbenzo[*b*]furans, a variety of 2-arylbenzo[*b*]furans were prepared through this two-step one-pot synthetic strategy, and the results were shown in Table 3. The variation of R<sub>1</sub> and R<sub>2</sub> groups had

**Table 2**  
Optimization of reaction conditions for conversion of 2-methoxydeoxybenzoin to benzo[*b*]furan<sup>a</sup>



Entry	Demethylation reagents	Solvent	Time	Temp (°C)	Yield (%) <sup>b</sup>
1	BBr <sub>3</sub>	DCM	0.5 h	0°	43
2	AlCl <sub>3</sub> /Py	DCM	6 h	rt	Trace
3	HI	H <sub>2</sub> O	6 h	Reflux	92
4	TMSI/KI	MeCN	6 h	Reflux	88
5	48% HBr	AcOH	6 h	Reflux	100
6	LiCl	DMF	12 h	110	Trace

<sup>a</sup> Reaction conditions: 1 mmol of **2a**, 4 equiv of demethylation reagents, the progress of the reaction was monitored by TLC.

<sup>b</sup> Isolated yields.

little influence on the reaction yields, and moderate to good overall yields were observed (Table 3, entries 1–11) regardless of the steric (*ortho*, *meta* and *para* positions) and electronic properties (both electronic rich and deficient). Importantly, heteroaromatic chalcone epoxide **1i** was a suitable substrate, giving the desired product **3i** in 87% yield (Table 3, entry 9). It is worth noting that the obtained halide products, such as bromide and iodide are very useful intermediates, which could be further functionalized to give a variety of derivatives (Table 3, entries 4–7, 10, 11).

To expand the utilization of the method, we attempted to construct a useful natural product stemofuran A and the key intermediate of natural product eupomatenoid 6,4-(5-bromo-3-methylbenzofuran-2-yl)phenol (**4m**). Stemofuran A was isolated from a methanolic extract of *Stemona collinsae* root, which was reported to have potential antifungal activity.<sup>2c</sup> Stemofuran A has been synthesized by several groups using different approaches.<sup>9,14a,b</sup> 4-(5-Bromo-3-methylbenzofuran-2-yl)phenol (**4m**) is an important synthetic intermediate used in the production of eupomatenoid 6,<sup>9</sup> which was first isolated in 1969 from the bark of *Eupomatia laurina* R. with a broad range of biological activities.<sup>14c–e</sup> **4m** was prepared by Naito and co-workers starting from oxime ethers through [3,3]-sigmatropic rearrangement reaction with 53% overall yield (4 steps).<sup>9</sup>

As illustrated in Scheme 1, stemofuran A was achieved with an overall yield of 71% began with 2-methoxychalcone epoxide (**11**), which was treated with 2 mol % of BF<sub>3</sub>·Et<sub>2</sub>O and then deformylated to afford the desired compound (**21**) in 76% yield. **21** underwent demethylation and cyclodehydration reactions in the presence of 48% HBr in acetic acid to give stemofuran A in excellent yield (94%). The spectral data of **31** are identical with those reported in the literature.<sup>14b</sup> Similarly, 4-(5-bromo-3-methylbenzofuran-2-yl)-phenol (**4m**) was synthesized in 64% overall yield. The readily available 2-methoxychalcone epoxide (**1m**) was converted into the corresponding deoxybenzoin (**2m**) by the sequence of Meerwein rearrangement, deformylation in 71% yield. The reaction of **2m** with methyl iodide in the presence of potassium *tert*-butoxide in THF gave the compound **3m** in 100% yield. Compound **3m** was then treated with 48% HBr in acetic acid under reflux to give 4-(5-bromo-3-methylbenzofuran-2-yl)-phenol (**4m**) in 90% yield. The procedure for synthesis of stemofuran A and **4m** is practical and convenient, and all the substrates and reagents are cheap and commercially available.

According to our experimental results and the reported literature,<sup>13,14</sup> a plausible reaction mechanism is proposed as shown in Scheme 2, which includes: i) The chalcone epoxides **A** undergoes smooth Meinwald rearrangement reaction with BF<sub>3</sub>·Et<sub>2</sub>O to give

Download English Version:

<https://daneshyari.com/en/article/5216949>

Download Persian Version:

<https://daneshyari.com/article/5216949>

[Daneshyari.com](https://daneshyari.com)