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Catalyst-free synthesis of 2,3-dihydrobenzofurans through [4+1] cycloaddition of *ortho*-hydroxyphenylsubstituted *para*-quinone methides and sulfur ylides

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ABSTRACT

An efficient [4+1] cycloaddition of *ortho*-hydroxyphenylsubstituted *para*-quinone methides and sulfur ylides was achieved under the catalyst-free condition. With this developed protocol, a series of *trans*-2,3-dihydrobenzofurans were obtained in excellent yields (up to 99%) with high diastereoselectivities (>20:1 dr). The usefulness of the protocol was also demonstrated by the versatile conversions of the 2,3-dihydrobenzofurans into other functionalized benzofurans.

1. Introduction

2,3-Dihydrobenzofuran framework is the structural motif frequently found in many biologically active molecules and natural products.[1] Particularly, *trans*-2,3-dihydrobenzofurans belong to an important class of heterocycles constitute the central skeleton of numerous pharmacologically important compounds, such as obtusafuran,[2] (±)-liliflol-B,[3] Conocarpan[4] and lithospemic acid[5] (Fig. 1). Inspired by these important motifs, intense efforts have been devoted to the synthesis of diverse 2,3-dihydrobenzofurans and a great number of efficient methods have been developed.[6] However, most of these methods need metal or catalysts and the strategies involved catalyst-free conditions were very limited. Despite these significant advances, given the profile between the potential bioactivities and molecular diversities, the development of new methods for the construction of 2,3-dihydrobenzofuran derivatives is still desirable and useful.

para-Quinone methides (*p*-QMs) are emerging as reactive intermediates in numerous chemical and biological process due to its aromatic zwitterionic resonances.[7] In 2016, Enders successfully introduced a hydroxyl group into the *p*-QMs to furnish new donor-Michael acceptor substrates and achieved the domino oxa-Michael/1,6-addition reaction of *ortho*-hydroxyphenyl-substituted *para*-quinone methides and isatin-derived enoates to 4-phenyl-substituted chromans bearing spiro-connected oxindole scaffolds.[8] On the other hand, sulfur ylides are one kind of valuable and versatile reagents, and have been extensively used as one-carbon units in cycloadditions to access cyclic compounds with structural diversity.[9] Based on this background, we envisioned that [4+1] cycloaddition of *ortho*-hydroxyphenyl-substituted *para*-quinone methides with sulfur ylides would be achieved under suitable conditions and furnish the 2,3-dihydrobenzofurans (Scheme 1). As part of our ongoing interest in the exploration of new methods for the construction of heterocyclic compounds,[10] herein we wish to describe the original results on this reaction.

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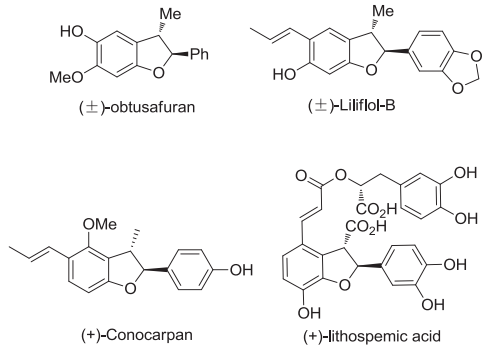
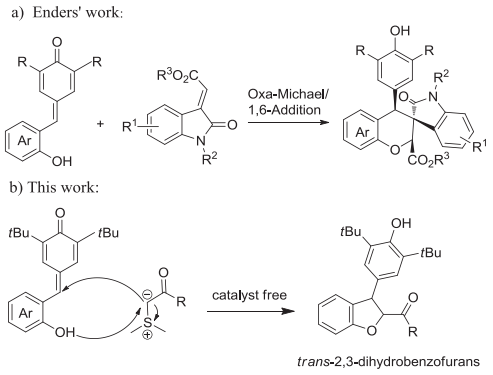


Fig. 1. Representative natural products containing 2,3-dihydrobenzofurans.



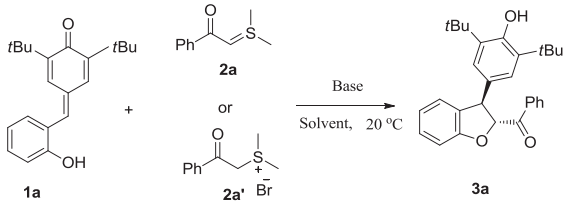
Scheme 1. Strategy for the synthesis of 2,3-dihydrobenzofurans.

2. Results and discussion

Initially, the investigation was conducted with *p*-QMs **1a** and benzoyl sulfur ylide **2a** as model substrates at 20 °C. To our delight, the reaction could proceed smoothly to completion within 20 h in DCM under catalyst free, furnishing the desired *trans*-2,3-dihydrobenzofuran product **3a** with excellent diastereoselectivity and yield (Table 1, entry 1, >20:1 dr and 98% yield). By contrast, sulfonium bromide **2a'** was also reacted with *p*-QMs **1a** with K_2CO_3 as a base in DCM at 20 °C and a decrease was observed in the yield with unchangeable diastereoselectivity (Table 1, entry 2, 86% yield and >20:1 dr). Subsequently, a series of solvents including toluene, THF, EtOAc, CH_3CN, acetone and MTBE were tested with the model reaction of *p*-QMs **1a** and benzoyl sulfur ylide **2a**. It was found that solvents have no significant effects on the diastereoselectivity and yield, and all the cases delivered excellent results (Table 1, entries 3–8). Among them, CH_3CN was chosen as the best reaction media in terms of reaction time. As conditions of choice, we utilized CH_3CN as the solvent at 20 °C with 1.5:1 of sulfur ylides to *p*-QMs.

With the optimized conditions in hand, the substrate scope of the *p*-QMs and sulfur ylides was tested. First, we focused on the examination of the hydroxyphenyl-substituted *p*-QMs **1** with benzoyl sulfur ylide **2a**. As summarized in Table 2, it was found that the positions and electronic natures of the substrates had slight effects on the yields and diastereoselctivities. A wide range of *p*-QMs bearing electron-donating or electron-withdrawing groups at the C4, C5 or C6 position of benezene ring were tolerated and furnished the corresponding products in high yields with excellent diastereoselectivities (Table 2, entries 1–8, 91–99% yield and >20:1 dr). Similarly, fused aromatic *p*-QMs **1j** also reacted efficiently with **2a**, giving the desired product **3j** in 96% yield with >20:1 dr (Table 1, entry 9). On the other hand, a survey of benzoyl sulfur ylide substrates was also conducted. We were pleased to find that, in general, the reactions of benzoyl sulfur ylides **2b-j** with *p*-QMs methide **1a** were able to proceed smoothly and afforded the corresponding products in 87–99% yield with >20:1 dr (Table 2, entries 10–18). This protocol was also expanded to fused aromatic and

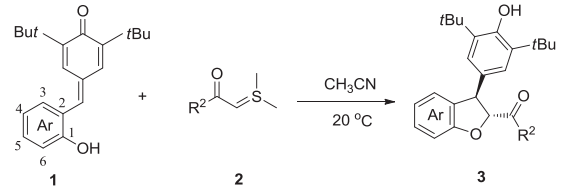
Table 1
Optimization of the Reaction Conditions.[a]



Entry	2	Solvent	Base	Time (h)	dr[b]	yield (%)[c]
1	**2a**	DCM	/	20	>20:1	98
2	**2a'**	DCM	K_2CO_3	120	>20:1	86
3	**2a**	Toluene	/	60	>20:1	99
4	**2a**	THF	/	21	>20:1	99
5	**2a**	EtOAc	/	15	>20:1	99
6	**2a**	CH_3CN	/	3	>20:1	99
7	**2a**	Acetone	/	11	>20:1	99
8	**2a**	MTBE	/	130	>20:1	99

MTBE = Methyl *tert*-butyl ether.
[a] Unless otherwise noted, all reactions were carried out with **1a** (0.2 mmol), **2a** or **2a'** (0.3 mmol), base (0.3 mmol), in 1 mL solvent at 20 °C.
[b] Determined by ^1H NMR analysis.
[c] Isolated yields.

Table 2
Substrate Scopes.[a]



Entry	Ar/**1**	R^2/**2**	Time (h)	dr[b]	**3**/yield (%)[c]
1	4-$CH_3C_6H_3$ (**1b**)	**2a**	2	>20:1	**3b**/99
2	4-$CH_3OC_6H_3$ (**1c**)	**2a**	2	>20:1	**3c**/91
3	5-$CH_3OC_6H_3$ (**1d**)	**2a**	2	>20:1	**3d**/99
4	6-$CH_3OC_6H_3$ (**1e**)	**2a**	2	>20:1	**3e**/99
5	6-$C_2H_5OC_6H_3$ (**1f**)	**2a**	2	>20:1	**3f**/99
6	5-FC_6H_3 (**1g**)	**2a**	2	>20:1	**3g**/92
7	5-ClC_6H_3 (**1h**)	**2a**	2	>20:1	**3h**/99
8	5-BrC_6H_3 (**1i**)	**2a**	2	>20:1	**3i**/99
9	2-Napthyl (**1j**)	**2a**	1	>20:1	**3j**/96
10	**1a**	3-$CH_3C_6H_4$ (**2b**)	2.5	>20:1	**3k**/97
11	**1a**	3-$CH_3OC_6H_4$ (**2c**)	2.5	>20:1	**3l**/99
12	**1a**	4-$CH_3C_6H_4$ (**2d**)	3	>20:1	**3m**/87
13	**1a**	4-$CH_3OC_6H_4$ (**2e**)	3	>20:1	**3n**/99
14	**1a**	4-$NO_2C_6H_4$ (**2f**)	3	>20:1	**3o**/94
15	**1a**	4-CNC_6H_4 (**2g**)	3	>20:1	**3p**/99
16	**1a**	4-ClC_6H_4 (**2h**)	2	>20:1	**3q**/99
17	**1a**	4-BrC_6H_4 (**2i**)	2	>20:1	**3r**/96
18	**1a**	4-$CF_3C_6H_4$ (**2j**)	2	>20:1	**3s**/99
19	**1a**	2-Napthyl (**2k**)	2	>20:1	**3t**/99
20	**1a**	2-Furyl (**2l**)	2	>20:1	**3u**/99
21	**1a**	2-Thiey (**2m**)	2	>20:1	**3v**/99

[a] Unless otherwise noted, all reactions were performed with **1** (0.2 mmol) and **2** (0.3 mmol) in CH_3CN (1 mL) at 20 °C.
[b] Determined by ^1H NMR analysis.
[c] Isolated yields.