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A mild method for generation of *o*-quinone methides under basic conditions. The facile synthesis of *trans*-2,3-dihydrobenzofurans†

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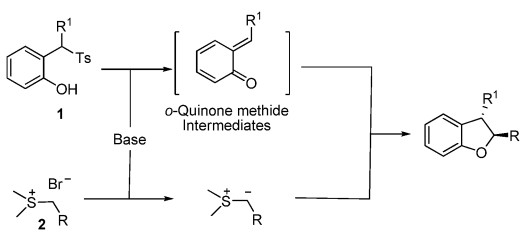
A novel and efficient method for the generation of *o*-quinone methide intermediates was developed from the readily available 2-tosylalkylphenols under the mild basic conditions, and their reactions with sulfur ylides were investigated for the stereoselective synthesis of *trans*-2,3-dihydrobenzofurans.

o-Quinone methides (*o*-QMs) are powerful intermediates in organic synthesis, drug chemistry and material chemistry.[1] Moreover, they have been implicated as the ultimate cytotoxins responsible for the functions of such agents as antitumor drugs, antibiotics, and DNA alkylators in biological chemistry.[2] As a consequence, some strategies have been successfully developed for generating *o*-QMs.[3] In the past decade, the most popular methods were photochemical initiation[4a–g] of *o*-(α-phenyl) substituted phenols or thermal[4h–j] initiation of various substituents on the benzene ring of *o*-methyl eneacetoxy-phenols. Lewis acid,[5a–c] base[5d–g] and chemical oxidants[5h] were also used to generate *o*-QMs. In 2003, Ohwada's group reported the retro-Diels–Alder reaction of 4*H*-1,2-benzoxazines to generate *o*-QMs.[6] Subsequently, the fluoride induced desilylation of silyl derivatives of *o*-hydroxybenzyl bromine (or iodide) and *o*-hydroxybenzyl nitrate was also described.[7] Very recently, Bharate and co-workers developed Knoevenagel-type condensation to furnish *o*-QMs.[8a] In addition, some efficient methods for generating *o*-QMs[8b,c] involving the use of transition-metal complexes were also successfully documented. Considering the importance of *o*-QMs as active intermediates and the instability of *o*-QMs due to dimerization as well as short lifetime,[9] developing a mild and efficient method for *o*-QMs generation from the commercially available starting materials would be very desirable in organic synthesis and drug research.

On the other hand, 2,3-dihydrobenzofuran derivatives are unique structural skeletons in many biologically active molecules and natural products.[10] They are present in molecules acting as potent inducers of the anticarcinogenic marker enzyme, quinone reductase,[10c] anti-multi drug resistant agents,[10e] insecticidal, antifungal, and anti-trypanosomal agents.[10f] Although some approaches for the synthesis of the 2,3-dihydrobenzofuran ring system have been described,[11] most of these methods have the drawbacks of poor chemo- and/or stereoselectivities, impeding their wider application. Thus, the development of an efficient, mild and convenient method for the preparation of these derivatives has important significance and still remains a great challenge.

Recently, as a good leaving group under basic conditions or with acidic reagents (Lewis type), an arylsulfonyl group has been used in organic synthesis.[12] We envisioned that the sulfonyl moiety at the benzylic position of 2-substituted phenol would also serve as a good leaving group, and the *o*-QM intermediates can be generated *in situ* under mild basic conditions. Ylides[13] act as a nucleophile under basic conditions, meanwhile, ylides could react with *o*-QMs to give the intermediate, followed by intramolecular nucleophilic attack of the oxygen anion on the carbon atom of ylides to furnish 2,3-dihydrobenzofuran derivatives (Scheme 1). In this process, a base has dual functions, generating both *o*-QM intermediates and ylides. Herein, we report an efficient approach for generation of *o*-QM intermediates under mild basic conditions which further underwent the reaction with sulfur ylides to synthesize *trans*-2,3-dihydrobenzofurans.



Scheme 1 General strategy for the mild generation of *o*-quinone methides and synthesis of *trans*-2,3-dihydrobenzofurans.

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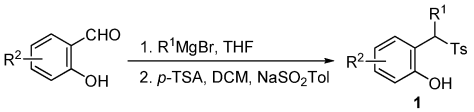
2-(1-Tosylalkyl)phenols can be conveniently synthesized from the commercially available 2-hydroxybenzaldehydes, Grignard reagents and the *p*-toluenesulfinic acid sodium salt (eqn (1)). Reactions of 2-hydroxybenzaldehydes with Grignard reagents gave the 2-hydroxyalkylphenols, followed by the acid-mediated substitution with the *p*-toluenesulfinic acid sodium salt to afford the desired 2-(1-tosylmethyl)phenols in moderate to excellent yields (35–86%).

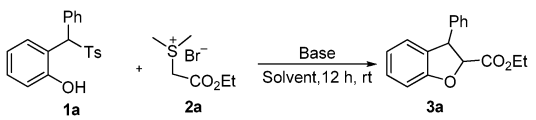


(1)

Yield: 35-86%

In our initial research, we performed the reaction between 2-(phenyl(tosyl)methyl)phenol **1a** and sulfonium salt **2a** (1.5 equiv.) at room temperature, using K_2CO_3 (4 equiv.) as the base and CH_2Cl_2 as the solvent, respectively. To our delight, 2,3-dihydrobenzofuran **3a** was isolated in 93% yield and excellent diastereoselectivity with the ratio of more than 20 : 1 (*trans*/*cis*) (entry 1, Table 1). The anionic base played a vital role in this reaction, that it not only assists elimination of arenesulfinic acid to form the *o*-QM intermediate, but also promote sulfur ylides to participate in the nucleophilic reaction subsequently (entries 2–6). KOH and KO^{t}Bu were not effective (entries 3 and 6), while K_3PO_4, NaOH and K_2CO_3 gave moderate to good yields (entries 1, 2 and 4), and Cs_2CO_3 gave the excellent yield and diastereoselectivity (entry 5). Then several common solvents such as CH_3CN, THF and toluene all led to the formation of the product **3a** in good yields and excellent diastereoselectivities except DMSO (entries 6–10), and CH_2Cl_2 gave the best result in terms of yield and *trans*/*cis* selectivity (98% yield and >20 : 1 dr) (entry 5). While decreasing the amounts of base to 2.5 equiv. and sulfonium salt to 1.1 equiv. did not affect the yield and the diastereoselectivity. Finally, we established the optimal reaction conditions for this reaction: using Cs_2CO_3 as the base and CH_2Cl_2 as the solvent to perform the reaction at room temperature. The structure and stereochemistry of **3** were well characterized by the combination of NMR, HRMS spectroscopy, and single-crystal X-ray analysis (see ESI†).

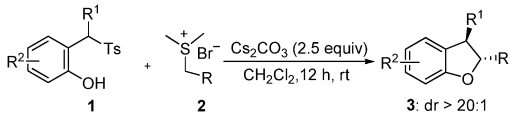
Table 1 Optimizing the conditions for the reaction of 2-(phenyl(tosyl)-methyl)-phenol **1a** with sulfonium salt **2a**[a]



Entry	Solvent	Base	Yield[b] (%)	dr[c]
1	CH_2Cl_2	K_2CO_3	93	>20 : 1
2	CH_2Cl_2	NaOH	81	>20 : 1
3	CH_2Cl_2	KOH	<5	n.d.
4	CH_2Cl_2	K_3PO_4	33	>20 : 1
5	CH_2Cl_2	Cs_2CO_3	98	>20 : 1
6	CH_2Cl_2	KO*t*Bu	<5	n.d.
7	CH3CN	Cs_2CO_3	85	>20 : 1
8	THF	Cs_2CO_3	94	>20 : 1
9	Toluene	Cs_2CO_3	94	>20 : 1
10	DMSO	Cs_2CO_3	10	12 : 1
11[d]	CH_2Cl_2	Cs_2CO_3	99	>20 : 1

[a] **1a** (0.2 mmol), **2a** (0.3 mmol), base (4.0 equiv.), solvents (3 mL), room temperature, 12 h. [b] Isolated yields. [c] Determined by ^{1}H NMR. [d] **2a** (0.24 mmol), base (2.5 equiv.).

Table 2 Substrate scope for the reaction of 2-(1-tosylalkyl)phenols **1** with sulfonium salt **2**[a]



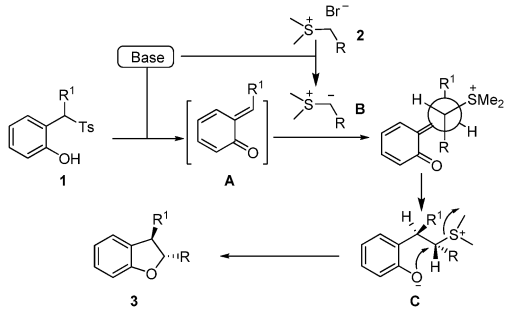
Entry	R^1	R^2	R	Yield[b] (%)
1	Ph	H	CO_2Et	99 (**3a**)
2	4-MeC_6H_4	H	CO_2Et	98 (**3b**)
3	3-MeC_6H_4	H	CO_2Et	91 (**3c**)
4	2-MeC_6H_4	H	CO_2Et	98 (**3d**)
5	4-MeOC_6H_4	H	CO_2Et	98 (**3e**)
6	4-$CF_3C_6H_4$	H	CO_2Et	91 (**3f**)
7	4-FC_6H_4	H	CO_2Et	93 (**3g**)
8	Ph	5-Br	CO_2Et	99 (**3h**)
9	Ph	5-OMe	CO_2Et	90 (**3i**)
10	CH_3	H	CO_2Et	80 (**3j**)
11	Et	H	CO_2Et	77 (**3k**)
12	Bu	H	CO_2Et	82 (**3l**)
13	Ph	H	CO_2Me	94 (**3m**)
14	Ph	H	CO_2Bn	67 (**3n**)
15	Ph	H	COPh	95 (**3o**)
16	Ph	H	$CONEt_2$	90 (**3p**)
17[c]	Ph	H	H	95 (**3q**)

[a] **1** (0.2 mmol), **2** (0.24 mmol), Cs_2CO_3 (2.5 equiv.), CH_2Cl_2 (3 mL), room temperature, 12 h. [b] Isolated yields and all of the dr >20 : 1. [c] Trimethylsulfoxonium iodide was used instead of sulfonium salts.

Under the optimized reaction conditions, a variety of 2-(1-tosylalkyl)phenols and sulfonium salts were explored to examine the generality of the reaction (Table 2). Various 2-(1-tosylalkyl)phenols underwent the reaction smoothly and gave the corresponding products with good to excellent yields and diastereoselectivities (>20 : 1). As to the substituents R^1, the aryl substituents showed better reactivity than alkyl substituents (entries 1–12). Although the steric and electronic nature of the aryl substituents had a little influence on the outcome of the reaction, generally high yields and diastereoselectivities were obtained (entries 1–7). The effect of substituents of the phenol did not inhibit the reaction (entries 8–9). Thereafter, various kinds of sulfur ylides were also tested; good yields and excellent diastereoselectivities were obtained (entries 13–16). Furthermore, the unstable ylide trimethylsulfoxonium iodide reacted well with **1a** to afford 3-phenyl-2,3-dihydrobenzofuran (**3q**) in 95% yield (entry 17). Subsequently, the synthesis of enantiomerically pure 2,3-dihydrobenzofuran was also tried. Using the known camphor derived chiral sulfonium salts developed by Dai and Tang[14,15] instead of sulfonium salt **2a**, only moderate enantioselectivity (37% ee) and 99% yield were obtained.

Based on the above experimental results and stereochemistry of the products, a plausible mechanism was proposed as illustrated in Scheme 2. Firstly, the reaction was initiated by the formation of the *o*-QM intermediate **A** in the presence of a base, then intermediate **A** reacts with sulfur ylides **B** to give the intermediate **C**, followed by *trans*-elimination–cyclization to afford the product *trans*-dihydrobenzofurans **3**.

In summary, we have successfully developed a novel and efficient method for generation of *o*-QM intermediates from the



Scheme 2 Plausible mechanism for the formation of *trans*-2,3-dihydrobenzofurans.

readily available 2-tosylalkylphenol under mild basic conditions, and their reactions with sulfur ylides for the stereoselective synthesis of 2,3-dihydrobenzofuran derivatives were investigated.[16] This methodology features cheap starting materials, mild reaction conditions, high yields and high stereoselectivity. Further studies on the application of *o*-QM intermediates in organic synthesis and the asymmetric version of the reactions are in progress.

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16 In the course of preparation of this manuscript, a paper on the generation of aza-*o*-quinodimethine intermediates from the *N*-(*ortho*-chloromethyl)aryl amides under mild basic conditions and their reactions with sulfur ylides for the synthesis of indoles was published, see: Q.-Q. Yang, C. Xiao, L.-Q. Lu, J. An, F. Tan, B.-J. Li and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 9137.

