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Synthesis of *trans*-disubstituted-2,3-dihydrobenzofurans by a formal [4 + 1] annulation between *para*-quinone methides and sulfonium salts†

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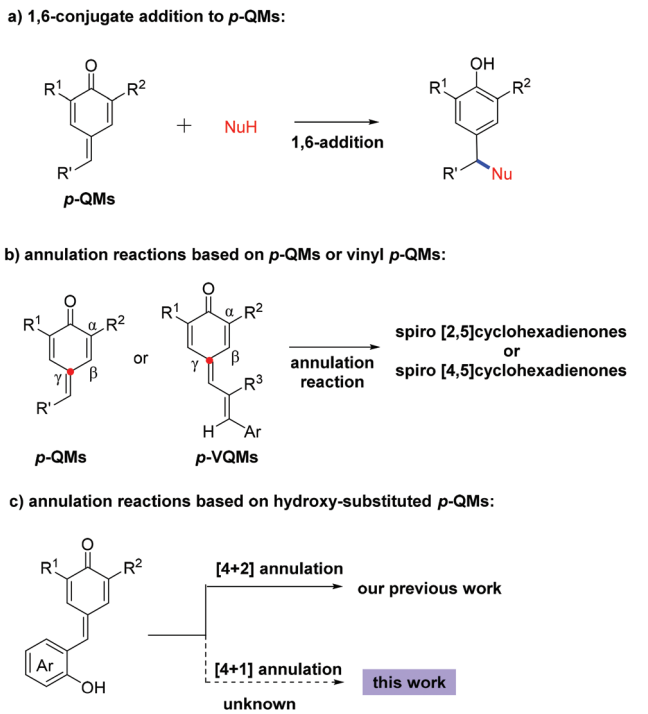
An efficient protocol for the synthesis of *trans*-disubstituted-2,3-dihydrobenzofurans through [4 + 1] annulation of *para*-quinone methides with sulfonium salts has been developed. Under very mild conditions this unprecedented reaction occurs in good to excellent yields (up to 99%), offering a straightforward access to a variety of 2,3-dihydrobenzofurans.

The 2,3-dihydrobenzofuran skeleton is an important structural unit that frequently appears not only in many synthetic bioactive molecules but also numerous natural products.[1] Thus, the development of methods to synthesize this kind of skeleton has attracted considerable attention in the synthetic community, and therefore numerous synthetic strategies have been reported to assemble 2,3-dihydrobenzofurans.[2] Among those strategies, the [4 + 1] annulation reaction has been shown to be very reliable for the construction of 2,3-dihydrobenzofuran frameworks.[3] However, the majority of the published [4 + 1] annulation reactions are based on the use of *o*-quinone methide intermediates.[4] Clearly, it is still very desirable to develop alternative methods to access this important skeleton.

On the other hand, due to their intrinsic reactivity *para*-quinone methides (*p*-QMs)[5] have been extensively explored during the past several years, and can react with a large number of nucleophiles in racemic[6] or enantioselective fashions (Scheme 1a).[7] Moreover, applications of *para*-quinone methides in annulation reactions have also been realized. The examples of use of *p*-QMs or vinyl *p*-QMs for annulation reactions to access spirocyclohexadienones were reported by the research groups of Yao, Fan, Zhao and Waser (Scheme 1b).[8] Among those reports the γ-carbon could serve as a potential nucleophilic site. Very recently, our group demonstrated that hydroxy-substituted *para*-quinone methides could be used as bifunctional substrates in an organocatalytic oxa-Michael/1,6-addition domino reaction, allowing the preparation of a series of 4-phenyl-substituted chromans in excellent stereoselectivities.[9] In 2017, the use of hydroxy-substituted *p*-QMs in the synthesis of spiro[chromane-2,1′-isochromene] derivatives and dihydrocounmarins have also been reported by the Tu/Jiang group[10] and Mei group,[11] respectively.



Scheme 1 Reported reactions based on *p*-QMs and our design.

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†Electronic supplementary information (ESI) available. CCDC 1814040. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8qo00008e

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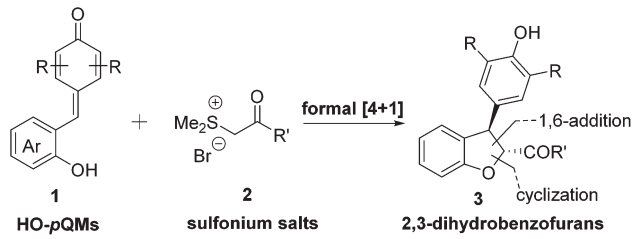
Despite those reports mentioned above, to the best of our knowledge the reaction of hydroxy-substituted *p*-QMs with other reaction partners, such as sulfonium salts, in a [4 + 1] annulation fashion is still unknown at the outset of this work (Scheme 1c).[12] In this context, we envisioned that a formal [4 + 1] reaction between hydroxy-substituted *p*-QMs **1** and sulfonium salts **2** might occur in the presence of an appropriate base. This expected annulation reaction could provide a general and straightforward method to access 2,3-dihydrobenzofurans **3**. Herein, we wish to present our preliminary results (Scheme 2).

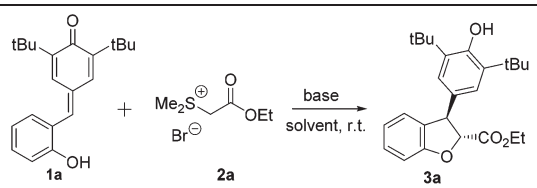
To test the feasibility of our reaction design, the *para*-quinone methide **1a** and ethyl dimethylsulfonium acetate bromide **2a** were selected as the model substrates to optimize the reaction conditions (Table 1). The initial experiment was conducted in which **1a** and **2a** were exposed to triethylamine (1.2 equiv.) in dichloromethane at room temperature. We were pleased to obtain the expected product **3a** in an acceptable yield of 50% (Table 1, entry 1). We found that the use of a suitable base is very critical for the success of this annulation reaction and thus an extensive screening of base was performed. The commonly used organic bases DABCO and DIPEA resulted in worse results, affording the desired product **3a** in 12% and 37% yield, respectively (entries 2 and 3). Further optimization revealed that inorganic bases had a positive influence on this transformation (entries 4–9). When cesium carbonate was used, the yield was improved to 90% (entry 9). Striving for higher efficiency, the effects of solvents in this model reaction were then examined (entries 10–16) and we found that acetonitrile as the reaction solvent delivered the best result (96% yield, entry 12).

With the optimum reaction conditions in hand, we sought to investigate the generality of this [4 + 1] aunulation process. First, the sulfonium salt component was evaluated. As shown in Table 2, a variety of sulfonium salts **2** underwent the formal [4 + 1] aunulation reaction to furnish **3a–3i** in 72–99% yield. In details, sulfonium salts containing ester groups (R^2 = EtO, MeO and *t*-BuO) readily reacted with **1a** to afford the desired annulation products in high yields. Besides the alkyl ester sulfonium salts, the ketone ones (R^2 = aryl group) proved to be



Scheme 2 Reaction design.

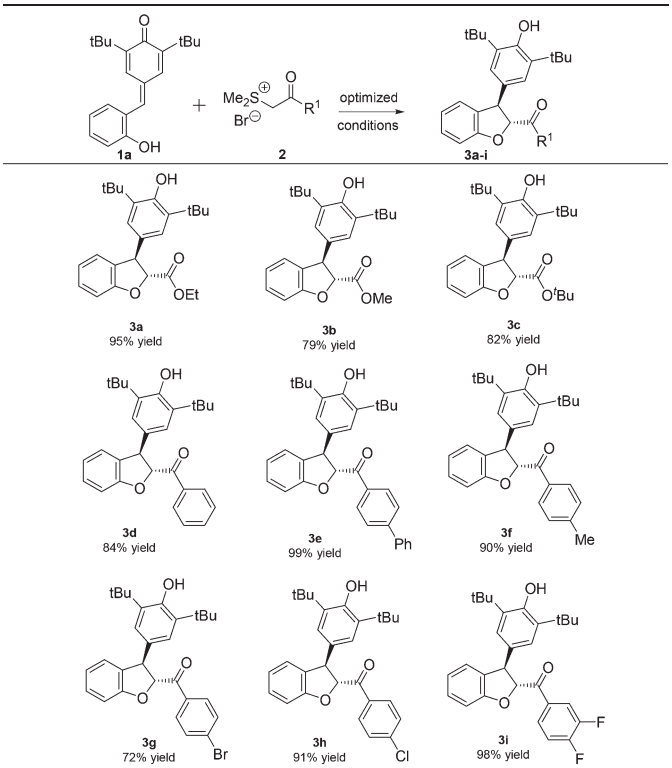
Table 1 Reaction condition optimization studies[a]



Entry	Base	Solvent	*t* (h)	Yield[b,c] (%)
1	Et_3N	CH_2Cl_2	48	50
2	DABCO	CH_2Cl_2	48	12
3	DIPEA	CH_2Cl_2	48	37
4	Na_2CO_3	CH_2Cl_2	48	43
5	K_2CO_3	CH_2Cl_2	4	87
6	K_3PO_4	CH_2Cl_2	4	84
7	NaOH	CH_2Cl_2	48	42
8	KOH	CH_2Cl_2	48	67
9	Cs_2CO_3	CH_2Cl_2	4	90
10	Cs_2CO_3	Toluene	2	93
11	Cs_2CO_3	THF	2	81
12	**Cs_2CO_3**	**CH_3CN**	**0.5**	**96**
13	Cs_2CO_3	EtOAc	4	85
14	Cs_2CO_3	$CHCl_3$	4	75
15	Cs_2CO_3	CCl_4	4	88
16	Cs_2CO_3	Et_2O	4	82

[a] All reactions were conducted with 0.2 mmol of **1a** (1.0 equiv.), 0.24 mmol of **2a** (1.2 equiv.), and 120 mol% of base in 2 mL of solvent at room temperature. [b] Yield of isolated compound **3a** after chromatography. [c] All diastereomeric ratios were higher than 20 : 1.

Table 2 Substrate scope of sulfonium bromides[a]



[a] Unless otherwise noted, the reactions were conducted with 0.40 mmol of **1** (1.0 equiv.), 0.48 mmol of **2** (1.2 equiv.) and 120 mol% of base in acetonitrile (4.0 mL) at room temperature. Yields are those of the isolated products **3a–3i** after column chromatography. The diastereomeric ratio was determined by ^{1}H NMR and all of them were higher than 20 : 1.

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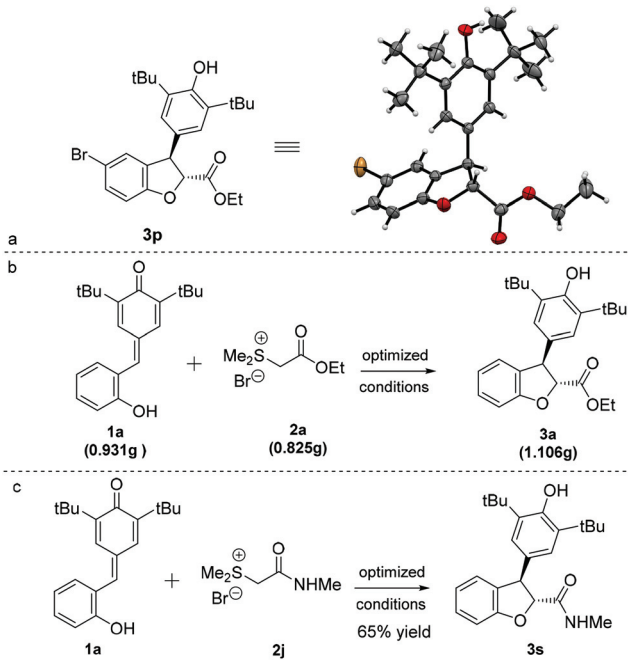
suitable substrates as well. Both electron-donating substituents (Ph, Me) and electron-withdrawing groups (Br, Cl) in the *para* position of the aryl ring of compounds **2** were well tolerated and the corresponding dihydrobenzofurans **3d–3h** could be obtained in very good to excellent yields (up to 99% yield). It is worth to mention that the 3,4-difluoro-substituted sulfonium salt also worked very well, delivering product **3i** in 98% yield.

Next, the substrate scope of this reaction was examined further by varying the reaction partner **1** (Table 3). We found that a wide range of hydroxy-substituted *p*-QMs were viable substrates and gave products **3j–3r** in 63–97% yield. Substrates bearing electron-donating (R^1 = Me, OMe), or electron-withdrawing groups (R^1 = Cl, Br) at the C4, C5, or C6 position of the phenyl ring of *p*-QMs **1** readily underwent this annulation process to furnish the corresponding 2,3-dihydrobenzofuran products in good to excellent efficiencies (**3j–3p**). Moreover, a naphthyl-substituted *p*-QMs smoothly reacted with the sulfonium salts, and the products **3q** and **3r** were obtained in 85% and 63% yield, respectively. Notably, the relative configuration of **3p** was unambiguously determined by X-ray crystallographic analysis (Scheme 3a).[13]

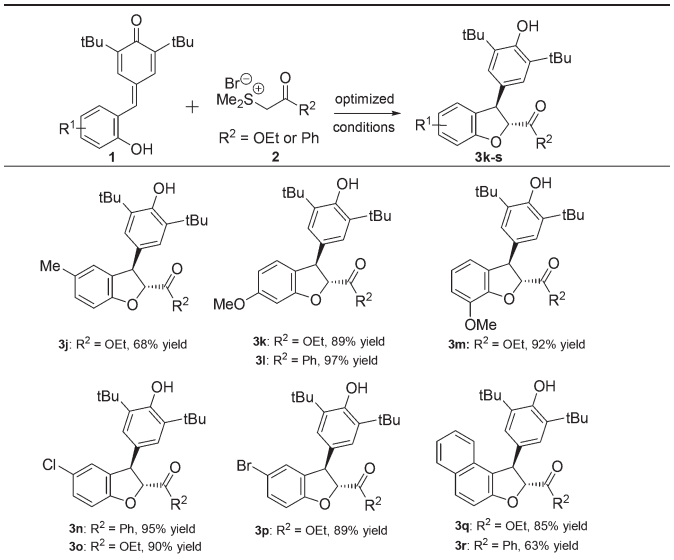
To show the general applicability and robustness of this novel [4 + 1] annulation reaction, we performed a gram scale reaction using **1a** and **2a** under the optimal conditions; the expected product **3a** could be isolated in 93% yield without erosion of the efficiency of this process (Scheme 3b). Furthermore, our protocol was also suitable for the amide-substituted sulfonium salt, affording the expected product **3s** in 65% yield (Scheme 3c).



Scheme 3 X-ray crystal structure of **3p**, gram-scale synthesis of **3a** and usage of the amide-substituted sulfonium salt.

In conclusion, we have developed a novel [4 + 1] annulation reaction between hydroxyphenyl-substituted *p*-QMs and sulfonium salts. This new protocol offers a facile and direct entry into a series of 2,3-dihydrobenzofurans. The procedure works under relatively mild and very simple experimental conditions and this is easily scalable to gram amounts.

Table 3 Substrate scope of the *p*-QMs[a]



[a] Unless otherwise noted, the reactions were conducted with 0.40 mmol of **1** (1.0 equiv.), 0.48 mmol of **2** (1.2 equiv.) and 120 mol% of base in acetonitrile (4.0 mL) at room temperature. Yields are those of the isolated products **3j–3r** after column chromatography. The diastereomeric ratio was determined by ^{1}H NMR and all of them were higher than 20 : 1.

Conflicts of interest

There are no conflicts to declare.

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