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Diastereoselective synthesis of CF_3-dihydrobenzofurans by [4+1] annulation of *in situ*-generated CF_3-*o*-quinone methides and sulfur ylides†

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An efficient and highly diastereoselective synthesis of CF_3-dihydrobenzofurans by the reaction of *in situ*-generated CF_3-*o*QMs in the presence of a base with sulphur ylides is put forward. The generality of the present developed method was well studied with diverse substrates to access the corresponding products in excellent yields. The highly reactive CF_3-*o*QM has been utilized first time for the annulation reaction.

Fluorine or fluoroalkyl group-containing organic molecules occupy a vital position in drug discovery due to the unique impact of fluorine atom in terms of lipophilicity, permeability, and protein-binding.[1] In the last two years, 45% of FDA-approved small molecule pharmaceuticals are fluorinated, which denotes the importance of synthesizing fluorinated molecules, with special emphasis on medicinal chemistry, for the identification of new scaffolds. Among the fluorinated functional groups, the trifluoromethyl group has emerged as one of the imperative fluoroalkyl groups to enhance the bio-efficacy and metabolic stability of the corresponding motifs, which is needed for the identification of lead compounds.[2] Thus, finding new methods for the inclusion of the CF_3 group into novel biological entities is always desirable and challenging.

In this context, *ortho*-quinone methides (*o*QMs) are powerful reactive intermediates in synthetic organic chemistry to construct complex medium sized rings.[3,4] Since *o*QM was first observed in 1907, it created a large impact in the synthesis of oxygen-containing benzannulated rings, which are of interest as photochromic materials and biologically active compounds.[3] However, the reactions of *o*QMs were restricted to electron-rich substrates due to their high electrophilic nature. However, annulation reactions of diversely substituted *o*QMs (substitution on the exocyclic double bond) were explored extensively for the construction of oxygen-containing complex heterocyclic structures;[3] however, it is quite surprising that annulation reactions involving trifluoromethyl-substituted *o*QM (CF_3-*o*QM) have not been reported yet, especially because CF_3-*o*QM is like a gold mine and could open the realm to construct versatile fluorinated oxygen architectures.

Kato *et al.* were the first to report the nucleophilic addition of Grignard reagents and amines to the *in situ*-generated trifluoromethyl-substituted *ortho*- and *para*-quinone methides

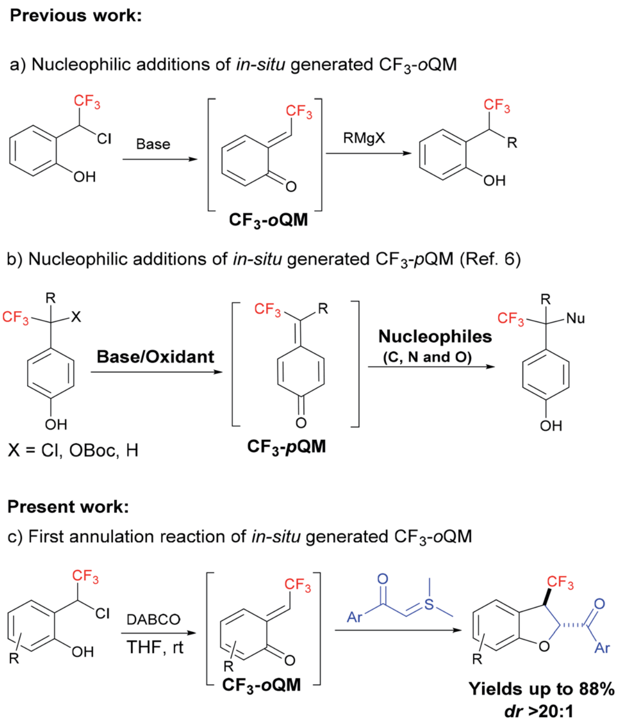

Fig. 1 Previous work *vs.* the present work.

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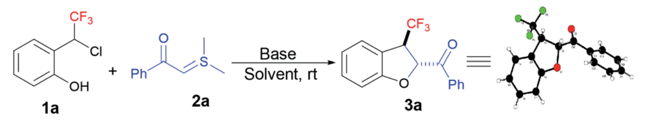
(Fig. 1a).[5] After that, there were no reports of this *in situ*-generated CF_3-*o*QM for any nucleophilic additions and annulations. In 2020, several papers were published on *in situ*-generated CF_3-*para*-quinone methides (CF_3-*p*QM) by quickly trapping them with different carbon and hetero atom-centered nucleophiles (Fig. 1b).[6] Notably, Waser *et al.* demonstrated that CF_3-*p*QM has higher electrophilicity parameter (*E*) when compared to other substituted *para*-quinone methides.[6d] Similarly, we hypothesized that CF_3-*o*QMs may also have higher "*E*" in comparison with the corresponding *o*QMs. Thus, the utilization of this highly reactive CF_3-*o*QM for annulation reactions is extremely challenging and equally desirable towards the synthesis of novel organofluorine molecules. In continuation of our research interest on *o*QM-based annulations and the development of new fluorinating methodologies,[7] herein, we report for the first [4 + 1] annulation of *in situ*-generated CF_3-*o*QM with sulphur ylide to access trifluoromethyl-substituted dihydrobenzofurans with high diastereoselectivity.

The study was initiated by exposing 2-(1-chloro-2,2,2-trifluoroethyl) phenol **1a** and sulphur ylide **2a** to 1.2 equiv. of Cs_2CO_3 at room temperature in THF. Delightedly, the *in situ*-generated CF_3-*o*QM was successfully trapped with sulphur ylide to afford the corresponding trifluoromethyl-substituted dihydrobenzofuran **3a** in 80% yield (Table 1, entry 1) with high diastereoselectivity. The investigation of a variety of solvents revealed that THF was the optimal solvent for the [4 + 1] annulation reaction (Table 1, entries 2–5). A quick survey was then conducted with different bases, and organic base DABCO was found to be the best to deliver **3a** in 93% yield (Table 1, entries 6–9). The control experiment showed that the reaction in the absence of a base failed to produce the [4 + 1] annulation product (Table 1, entry 10). The reaction conditions in entry 6 (Table 1) were optimal and gave the product in 93% yield with >20 : 1 dr. The configuration of the obtained product was confirmed as *trans* from the X-ray crystallographic structure of compound **3a** (CCDC 2023269).

Table 1 Optimization of reaction conditions[a]



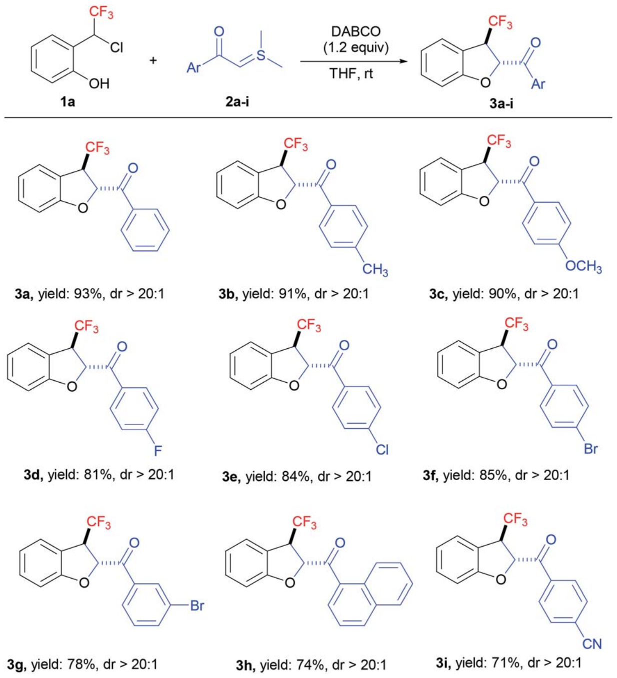
Entry	Base	Solvent	Yield[b]	dr[c]
1	Cs_2CO_3 (1.2 equiv.)	THF	80%	>20 : 1
2	Cs_2CO_3 (1.2 equiv.)	DCM	62%	>20 : 1
3	Cs_2CO_3 (1.2 equiv.)	CH_3CN	51%	>20 : 1
4	Cs_2CO_3 (1.2 equiv.)	Toluene	Trace	—
5	Cs_2CO_3 (1.2 equiv.)	MeOH	Trace	—
6	DABCO (1.2 equiv.)	THF	93%	>20 : 1
7	DBU (1.2 equiv.)	THF	65%	>20 : 1
8	Et_3N (1.2 equiv.)	THF	Trace	—
9	K_2CO_3 (1.2 equiv.)	THF	45%	>20 : 1
10	—	THF	NR	—

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), base (0.6 mmol) in solvent (2 mL) at rt. [b] Isolated yields. [c] dr was determined by ^{19}F NMR.

With the determination of optimized conditions, the substrate scope for the [4 + 1] annulation reaction was scrutinized by the reaction of compound **1a** with a broad array of sulphur ylides (Table 2). First, the reaction of electron-rich substrates **2b** (CH_3) and **2c** (OCH_3) afforded CF_3-dihydrobenzofurans **3b** (91%) and **3c** (90%) in very good yields, respectively. The halogen-containing sulphur ylides **2d**, **2e**, and **2f** (F, Cl, and Br) also proceeded smoothly to furnish the required products **3d–f** in excellent yield (up to 85%) and we observed a slight improvement in the yield from fluoro to bromo substrates. Further, the reaction of naphthalene-derived sulphur ylide **2h** also participated well in the reaction to deliver the required CF_3-dihydrobenzofuran **3h** in 74% yield. The electron-deficient substrate **2i** (CN) also underwent the [4 + 1] annulation reaction very well to give CF_3-dihydrobenzofuran **3i** in 71% yield. CF_3-*o*QM generated *in situ* from compound **1a**, was trapped with a wide range of sulphur ylides without any effect on the substituents to yield the required trifluoromethyl-substituted dihydrobenzofurans in good yields with high diastereoselectivity (dr > 20 : 1).

Next, we investigated the substrate scope with respect to *ortho*-hydroxy-CF_3-benzyl chlorides **1b–d** to delineate the generality of the present [4 + 1] annulation under the standard reaction conditions (Table 3). The reactions with CF_3-benzyl chlorides having electronically dissimilar groups as substituents, proceeded well to furnish the desired products in good yields. The reaction of methyl (**1b**)- and methoxy (**1c**)-substituted CF_3-benzyl chlorides with a variety of sulphur ylides delivered the corresponding CF_3-dihydrobenzofurans **3j–o** in

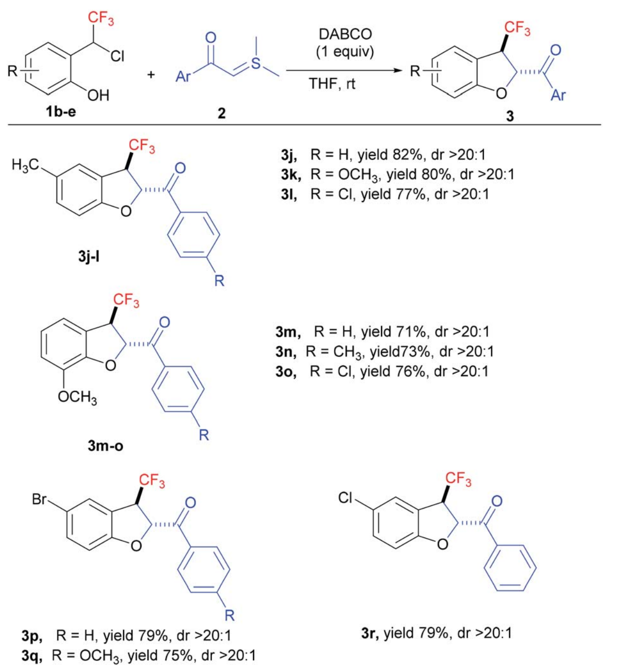
Table 2 The substrate scope of sulphur ylides (**2a–i**)[a]



3a, yield: 93%, dr > 20:1
3b, yield: 91%, dr > 20:1
3c, yield: 90%, dr > 20:1
3d, yield: 81%, dr > 20:1
3e, yield: 84%, dr > 20:1
3f, yield: 85%, dr > 20:1
3g, yield: 78%, dr > 20:1
3h, yield: 74%, dr > 20:1
3i, yield: 71%, dr > 20:1

[a] Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), DABCO (0.6 mmol), THF (2 mL). Isolated yield. dr was determined by ^{19}F NMR.

Table 3 The substrate scope of *ortho*-hydroxy CF_3-benzyl chloride (1b–e)

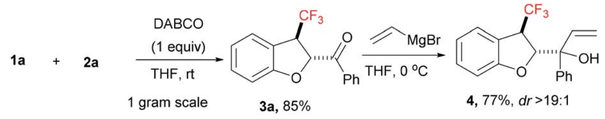


[a] Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), DABCO (0.6 mmol), THF (2 mL) at rt. Isolated yield. dr was determined by ^{19}F NMR.

excellent yields with good diastereoselectivity. Further, CF_3-*o*QMs generated from the bromo (**1d**)- and chloro (**1e**)-substituted CF_3-benzyl chlorides were also successfully trapped to deliver the desired products **3p–r** in good yields (up to 79% with >20 : 1 dr).

To determine the synthetic utility of the present transformation, we executed a gram scale [4 + 1] annulation reaction of compound **1a** with **2a** under applied reaction conditions, which gave CF_3-dihydrobenzofuran **3a** in 85% yield (Scheme 1). Later, we exposed compound **3a** to vinyl magnesium bromide at 0 °C in THF to furnish the corresponding alcohol **4** in good yield with excellent diastereoselectivity (dr > 19 : 1).

The plausible reaction mechanism for the base-catalyzed [4 + 1] annulation of *ortho*-hydroxy-CF_3-benzyl chloride **1a** with compound **2a** is depicted in Fig. 2. Initially, CF_3-*o*QM was generated in the presence of a stoichiometric amount of base.[5,8] This highly electrophilic CF_3-*o*QM undergoes nucleophilic addition with compound **2a** to form a new C–C bond in **TS I**; the diastereoselectivity in **TS I** arises due to the favourable steric repulsions between the trifluoromethyl group and sulphur ylide, resulting in the final compound with *trans* configuration. Finally, the intramolecular nucleophilic substitution in **TS I** by oxygen with a sulphonium moiety furnishes the desired CF_3-dihdrobenzofuran **3a** in good yield.



Scheme 1 The synthetic transformation of compound **3a**.

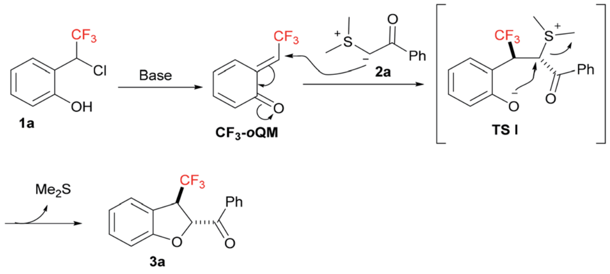


Fig. 2 The plausible reaction mechanism.

Conclusions

In conclusion, we demonstrated a novel method for the synthesis of CF_3-dihdrobenzofurans **3** *via* [4 + 1] annulation of *ortho*-hydroxy-CF_3-benzyl chlorides **1** with sulphur ylides **2** under basic conditions in good yields (up to 93%) and diastereoselectivities (>20 : 1). The highly reactive CF_3-*o*QM, due to the electron-withdrawing nature of the CF_3 group, was trapped successfully in the present [4 + 1] annulation. This annulation is the first example for the trapping of trifluoromethyl-substituted *o*QM. The core skeleton of dihydrobenzofuran obtained in the present protocol has received huge attention in literature,[9] and CF_3 present at a strategic position may improve the biological activities of molecules tremendously. Further, the expansion of annulation reactions *via in situ*-generated CF_3-*o*QMs is in progress in our laboratory to construct versatile trifluoromethyl-substituted oxygen-containing heterocycles.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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