RSC Advances



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PAPER



Cite this: RSC Adv., 2020, 10, 38588

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

Babli K. Jha,^{ab} Jaggaraju Prudhviraj,^a Prathama S. Mainkar, ^{Dab} Nagender Punna ^{*ab} and Srivari Chandrasekhar ^{*ab}

An efficient and highly diastereoselective synthesis of CF₃-dihydrobenzofurans by the reaction of in situ-

generated CF_3 -oQMs 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 -oQM has been utilized first time for the annulation

Received 26th August 2020 Accepted 29th September 2020

DOI: 10.1039/d0ra08289a

rsc.li/rsc-advances

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 CF₃ group into novel biological entities is always desirable and challenging.

reaction

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

^bAcademy of Scientific and Innovative Research (AcSIR), Ghaziabad, 201002, India

ic molecules structures;³ however, it is quite surprising that annulation the unique reactions involving trifluoromethyl-substituted aOM (CE aOM)

reactions involving trifluoromethyl-substituted *o*QM (CF₃-*o*QM) have not been reported yet, especially because CF₃-*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

Previous work:

a) Nucleophilic additions of in-situ generated CF3-oQM



b) Nucleophilic additions of *in-situ* generated CF₃-pQM (Ref. 6)

 $CF_{3} + X + CF_{3} + R + CF_$

Present work:

c) First annulation reaction of in-situ generated CF3-oQM



Fig. 1 Previous work vs. the present work.

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^aDepartment of Organic Synthesis and Process Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India. E-mail: srivaric@iict.res.in; nagenderpunna@iict.res.in

[†] Electronic supplementary information (ESI) available. CCDC 2023269. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ra08289a

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(Fig. 1a).⁵ After that, there were no reports of this in situgenerated CF₃-oOM for any nucleophilic additions and annulations. In 2020, several papers were published on in situgenerated CF₃-para-quinone methides (CF₃-pQM) by quickly trapping them with different carbon and hetero atom-centered nucleophiles (Fig. 1b).6 Notably, Waser et al. demonstrated that CF_3 -pQM has higher electrophilicity parameter (E) when compared to other substituted para-quinone methides.^{6d} Similarly, we hypothesized that CF₃-oQMs may also have higher "E" in comparison with the corresponding oQMs. Thus, the utilization of this highly reactive CF₃-oQM for annulation reactions is extremely challenging and equally desirable towards the synthesis of novel organofluorine molecules. In continuation of our research interest on oQM-based annulations and the development of new fluorinating methodologies,⁷ herein, we report for the first [4 + 1] annulation of *in situ*-generated CF₃oOM with sulphur vlide to access trifluoromethyl-substituted dihydrobenzofurans with high diastereoselectivity.

The study was initiated by exposing 2-(1-chloro-2,2,2trifluoroethyl) phenol 1a and sulphur ylide 2a to 1.2 equiv. of Cs₂CO₃ at room temperature in THF. Delightedly, the in situgenerated CF₃-oQM 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).



^{*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 ¹⁹F 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 (CH₃) and 2c (OCH₃) afforded CF₃-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 CF₃-dihydrobenzofuran 3h in 74% yield. The electron-deficient substrate 2i (CN) also underwent the [4 + 1]annulation reaction very well to give CF₃-dihydrobenzofuran 3i in 71% yield. CF₃-oQM 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 trifluoromethylsubstituted dihydrobenzofurans in good yields with high diastereoselectivity (dr > 20: 1).

Next, we investigated the substrate scope with respect to *ortho*-hydroxy-CF₃-benzyl chlorides **1b–d** to delineate the generality of the present [4 + 1] annulation under the standard reaction conditions (Table 3). The reactions with CF₃-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 CF₃-benzyl chlorides with a variety of sulphur ylides delivered the corresponding CF₃-dihydrobenzofurans **3j–o** in



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

Table 3 The substrate scope of ortho-hydroxy CF₃-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 ¹⁹F NMR.

excellent yields with good diastereoselectivity. Further, CF3oQMs generated from the bromo (1d)- and chloro (1e)substituted CF₃-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 CF₃-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-CF₃-benzyl chloride 1a with compound 2a is depicted in Fig. 2. Initially, CF3-oQM was generated in the presence of a stoichiometric amount of base.5,8 This highly electrophilic CF3-oQM 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



Scheme 1 The synthetic transformation of compound 3a.



Fig. 2 The plausible reaction mechanism.

oxygen with a sulphonium moiety furnishes the desired CF₃dihdrobenzofuran 3a in good vield.

Conclusions

In conclusion, we demonstrated a novel method for the synthesis of CF_3 -dihdrobenzofurans 3 via [4 + 1] annulation of ortho-hydroxy-CF3-benzyl chlorides 1 with sulphur ylides 2 under basic conditions in good yields (up to 93%) and diastereoselectivities (>20 : 1). The highly reactive CF₃-oQM, due to the electron-withdrawing nature of the CF₃ group, was trapped successfully in the present [4 + 1] annulation. This annulation is the first example for the trapping of trifluoromethyl-substituted oQM. The core skeleton of dihydrobenzofuran obtained in the present protocol has received huge attention in literature,9 and CF₃ present at a strategic position may improve the biological activities of molecules tremendously. Further, the expansion of annulation reactions via in situ-generated CF3-oQMs is in progress in our laboratory to construct versatile trifluoromethylsubstituted oxygen-containing heterocycles.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

The authors thank the Council of Scientific and Industrial Research (CSIR), Ministry of Science and Technology, Government of India for research facilities. B. J. thanks Department of Science & Technology (DST), Government of India for Inspire fellowship (IF170776). S. C. thanks the Science and Engineering Research Board, Government of India for J C Bose fellowship (SB/S2/JCB-002/2015). We gratefully acknowledge fruitful scientific discussions with Dr Balasubramanian Sridhar, Laboratory of X-ray Crystallography, CSIR-IICT, for X-ray analysis. CSIR-IICT manuscript communication no: IICT/Pubs./2020/ 243.

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