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# An efficient and simple one-pot synthesis of 2-perfluoroalkylated benzo[1,3] dioxole derivatives via double–Michael reaction of fluorinated alkynes

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ABSTRACT

An efficient, mild and very easy method for the synthesis of 2-fluoroalkylated 1,3-benzodioxole derivatives was developed through a double Michael-addition reaction on ethyl 4,4,4-trifluorobut-2-ynoate with corresponding catechols. The procedure does not require the use of expensive supplementary additives for the preparation of 2-fluoroalkylated benzo ketals.

## 1. Introduction

1,3-Benzodioxoles belong to the family of dioxoles which are oxygenated heterocyclic rings that are parents of dioxolanes (Fig. 1). They differ from the latter by the presence of unsaturation in the ring. The 1,3-Benzodioxole structure is commonly found in everyday life, for example in celery leaves contain apiole while black pepper has piperine and chavicine in its components [1]. 1,3-Benzodioxoles are also used in industry as fragrance ingredients [2].

In this paper, we focus on 1,3-benzodioxoles and specifically in 2-(trifluoromethyl)benzo[*d*][1,3]dioxole derivatives. The preparation of 1,3-benzodioxoles has generally been achieved through acetalization of the corresponding carbonyl compounds and catechol derivatives. The conditions are usually standard acid catalyst conditions with *p*-toluensulfonic acid [3], but also with the corresponding copper [4], trimethylsilyl trifluoromethanesulfonate [5] or pyridinium salt under reflux [6]. A second general route to 1,3-benzodioxole involves a β-elimination reaction [7] in the presence of $LiAlH_4$ and $TiCl_4$ [8] or other catalysts, such as phosphorus pentoxides [9]. Syntheses of 1,3-benzodioxoles using acetylenic esters have also been reported but require the use of catalysts [10] or limited to terminal alkynes [11]. In general, the known methods of synthesis of 1,3-benzodioxoles described in the literature use harsh conditions and the starting materials are not commonly available.

To the best of our knowledge, only a few publications deal with the synthesis of fluoroalkylated benzo [1,3]dioxoles [12]. This fact is somewhat surprising considering that it has been demonstrated that the incorporation of a trifluoromethyl group in organic compounds can play an important role in the search for new active pharmaceutical compounds [13]. The presence of a $CF_3$ moiety usually results in important changes in the biological properties of organic compounds [14]. The introduction of such a group on a heterocyclic pattern of biological interest is therefore likely to have a valuable effect and improve biological activity. This therefore remains a major challenge for many organic chemists.

For several years, our laboratory has been investigating fluorinated alkynes as the starting building blocks to synthesize new fluorinated heterocyclic compounds [15]. Recently, we reported the double conjugate addition of alcohols to ethyl perfluorinated propiolate using molecular sodium. The transformation provided easy regioselective access to perfluorinated ketals [16]. Herein, we wish to report the very latest results of our investigations on the synthesis of 1,3-benzodioxole derivatives using inter- and intramolecular double Michael addition of catechols to fluorinated alkynes **2**.

## 2. Results and discussion

We first examined the ketalization reaction between the fluorinated alkyne **2a** and benzo-1,2-diol (**1a)** in dichloromethane, in the presence of a base within 3 h reaction time. Several bases were tried at room temperature and the results are given in Table 1.

In general, the majority of the bases used led to average to good yields. Inorganic carbonate bases were found to be preferable to organic bases. The use of carbonate bases resulted in yields between 88–89%

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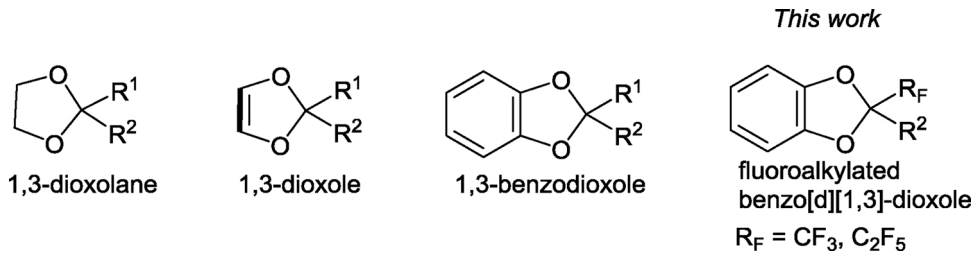
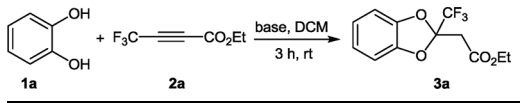



**Fig. 1.** Overview of the dioxole family.

**Table 1**
Base mediated Double-Michael reactions of catechol **1a** and alkyne **2a**.[a]




**1a** **2a** **3a**

| Entry | Base | x equiv | Yield (%)[b] |
|---|---|---|---|
| 1 | DABCO | 1 | 77 |
| 2 | | 0.5 | 49 |
| 3 | $Et_3N$ | 1 | 54 |
| 4 | | 0.5 | 26 |
| 5 | $Ph_3P$ | 1 | – |
| 6 | $Na_2CO_3$ | 1 | 88 |
| 7 | | 0.5 | 35 |
| 8 | $K_2CO_3$ | 1 | 89 |
| 9 | | 0.5 | 37 |
| 10 | NaH | 1 | 47 |
| 11 | | 2 | 25 |

[a] Conditions: 0.1 mmol of **1a**, 0.11 mmol (1.1 equiv) of **2a** and x equiv of base.
[b] Isolated yield of product **3a**.

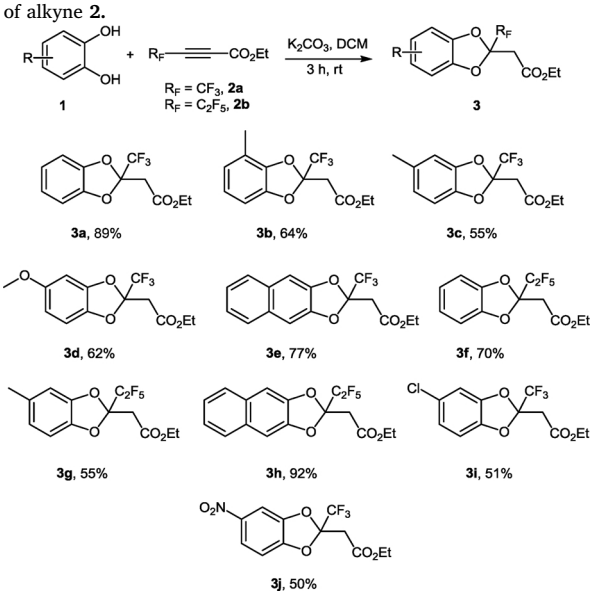
and $K_2CO_3$ proved to be the best base, giving 89% yield within 3 h reaction time (Table 1, entry 8). Lowering the amount of $K_2CO_3$ to 0.5 equiv and under the same conditions, the yield did not exceed 37% (Table 1, entry 9). Below 0.5 equiv of $K_2CO_3$, the reaction time was considerably longer and the yields were poor. The organic bases DABCO and triethylamine proceeded smoothly but yielded only average amounts of isolated product (Table 1, entries 1–4). In the absence of the base, no product was detected and only starting materials were recovered. This shows that a deprotonation step is mandatory to trigger the expected reaction. Triphenylphosphine, which is commonly employed in the traditional conjugate Michael addition reaction [17], did not give the desired cyclization product **3a**. This result was expected, because although triphenylphosphine is a good donor for Michael addition, it also has very weak basic properties that are unable to perform the deprotonation of catechol. The use of a stronger base such as NaH led to a moderate to poor yield (Table 1, entries 10 and 11), along with the presence of an unidentified side product.

A number of solvents were examined including ether, acetonitrile, DMF, toluene and dichloromethane, in the reaction of alkyne **2a** and benzo-1,2-diol in the presence of $K_2CO_3$. No significant difference in the yield of the cyclized product **3a** was observed. $CH_2Cl_2$ was chosen as the most suitable solvent for this ketalization reaction because of its simplicity of use and its easy removal from the mixture. When the reaction time was reduced to 2 h, the ketalization reaction was not complete. Finally the conditions used for the synthesis of fluorinated 1,3-benzodioxole **3a** were set at 1 equiv of $K_2CO_3$ in DCM, along with the corresponding reactants **1a** or **2a**.

To investigate the scope of the double-Michael addition reaction, catechols diversely substituted with methyl, methoxy, chloro or nitro groups were used to react with fluoroalkylated alkynes **2**. The results are summarized in Table 2.

As shown in Table 2, this reaction showed high regioselectivity.

**Table 2**
Synthesis of fluorinated 1,3-benzodioxoles **3a-j** by double-Michael annelation of alkyne **2.**




Indeed, in each case, only a five-membered ring was obtained, and no trace of the mono-addition product was detected. No seven-membered ring was formed resulting from the Michael and trans esterification reactions. No significant difference was observed in the yields obtained according to the nature of the fluorinated group. In addition, according to Jursic [18] a major drawback when synthesizing acetals starting from aliphatic aldehydes is the possible formation of 10 to 30% aldol byproducts. With the route we follow, this drawback is completely avoided. A methodology involving the addition of catechols over acetylene dicarboxylate derivatives in presence of a catalytic amount of DABCO was published in 2006 for the synthesis 1,3-benzodioxole dicarboxylates [19]. The authors suggested a mechanism involving a first attack by DABCO creating the key reactant of the reaction. As outlined in our proposed mechanism (Scheme 1), we suggest that the reaction operates by an initial deprotonation of the catechol into a catecholate which directly attacks the fluorinated alkyne **2** in a Michael addition route to afford the allenoate intermediate **4.** The latter is readily protonated by the second proton of phenol to yield intermediate **5**. A second subsequent intramolecular Michael addition followed by the protonation of the resulting alkylate by the conjugate acid of the base used affords the final product **3a**.

To increase the size of the oxygenated heterocycle, we next extended our methodology by using salicylic alcohol **6** under our reference conditions with alkyne **2a**. The reaction provided the corresponding fluorinated six-membered heterocycle **7** (Scheme 2). As shown with our assays using benzyl alcohol, $K_2CO_3$ is unable to deprotonate the benzyl alcohol to provide the corresponding addition compound. Therefore, the only explanation for the heterocycle **7** obtaining appears to be the formation of the benzyl alkoxide by an intramolecular deprotonation as described in our proposed mechanism.