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Water-Compatible Synthesis of 2-Trifluoromethyl-1,3-Dioxanes

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Abstract: A water-compatible method for the diastereoselective synthesis of 2-trifluormethyl-1,3-dioxanes is described. The reaction proceeds under mild reaction conditions using simple inorganic bases; it has a very good substrate scope and can be performed with different Michael acceptors. Additionally, the reaction products can be further functionalized, showing an excellent perspective for future applications.

Introduction

Fluorinated molecules are ever-present in different aspects of our daily life,^[1] especially in areas like agrochemistry,^[2] medicinal chemistry,^[3] and materials chemistry,^[4] among others. The trifluoromethyl group stands out as one of the most important in the chemistry of fluorinated molecules, and the number of drugs and drug candidates bearing this group is impressive.^[5] The methods for introducing the trifluoromethyl group in organic molecules can be divided in two main groups: direct trifluoromethylation,^[6] which is a field of a tremendous growth in recent years, and the use of small molecules bearing this group as reagents or starting materials. Consequently, new methods for installing the trifluoromethyl group in organic molecules are highly desirable.

Trifluoromethylation emerged as a preferred alternative mainly because the availability of trifluoromethylated small molecules is pretty limited. Among them fluoral (trifluoroacetaldehyde) can be considered as a suitable starting material because of its inherent reactivity compared with other aldehydes. Unfortunately, pure fluoral is an unstable gas, difficult to prepare and to use; however, its hydrate aqueous solution is commercially available and easy to handle. The difficulty to prepare fluorinated molecules in aqueous media has been the focus of many researches and reviewed recently;^[7] additionally the generation of stereogenic centers containing a fluorine atom or a trifluoromethyl group is also a very important field of investigation.^[8]

We recently described the preparation of trifluoromethylated 1,3dioxanes using trifluoroacetophenones with α , β -unsaturated- δ hydroxy Michael acceptors^[9] and we expanded the reaction scope to the use α , β -unsaturated α -amino- δ -hydroxycarboxylic acid esters (Scheme 1a).^[10] The method is based on the *in situ*

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generation of a hemiacetal anion that reacts in a Michael addition. This reaction, known since 1993,^[11] has been applied to the synthesis of many natural products -as a method to obtain protected syn 1,3-diols-,^[12] used with different Michael acceptors^[13] and reviewed very recently in the literature.^[14] Unfortunately, this reaction uses strong bases and requires anhydrous conditions. Inspired by our previous results and trying to generate a suitable and general method to synthesize 2trifluoromethyl-1,3-dioxanes, we decided to explore the reaction using aqueous fluoral hydrate and simple inorganic bases (Scheme 1b). Herein we describe our results in this field, offering a water-compatible method for the diastereoselective synthesis of fluorinated dioxanes and showing some subsequent functionalization of the obtained molecules.



Scheme 1. State of the art and proposed strategy.

Results and Discussion

The starting materials are easily prepared in two or three steps from commercially available aldehydes (the experimental details and the synthetic routes are described in the supporting information). We started our study using the same reaction conditions that are employed with benzaldehyde as the electrophilic reagent (Table 1, entry 1). Unfortunately, the desired dioxane 2a was obtained in only 7% yield, and 44% of the hemiacetal 3a was isolated. It has to be mentioned that the stereochemistry of the two isomers of the dioxane was determined by NOE experiments. The CF₃ group is always 1,3cis and the group in position 5 is cis in the major isomer and trans for the minor one; in consequence the diastereomeric ratio refers to 1,3-cis-1,5-cis and 1,3-cis-1,5-trans isomers. We decided to increase the amount of base in order to deprotonate the hemiacetal intermediate; after 12 hours we isolated 66% of dioxane and 26% of hemiacetal (entry 2). The reaction of tBuOK

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with water should produce KOH in solution, so we tried using directly KOH as base and increasing the reaction time. The yield for the dioxane did not improve, but the hemiacetal was not detected (entry 3); presumably the hemiacetal is not stable enough and it is degraded after long reaction times. As the reaction in under thermodynamic control, increasing the temperature allowed us to isolate the desired dioxane in very good yield and selectivity; we thus used the conditions of entry 4 to study the scope of our method.

 Table 1^[a]. Optimization of the reaction conditions



Entry	Conditions	3a ^[b]	2a ^[b]	d.r. ratio
1	(Fluoral 1.1 equiv; <i>t</i> BuOK 0.1 equiv) 3 additions, 7h, 0°C	44%	7%	91:9 ^[c]
2	(Fluoral 1.1 equiv; <i>t</i> BuOK 1.0 equiv) 5 additions, 12h, 0°C	26%	66%	77:23 ^[d] 75:25 ^[c]
3	(Fluoral 1.1 equiv; KOH 1.0 equiv) 5 additions, 24h, 0°C	traces	64%	87:13 ^[c]
4	(Fluoral 1.1 equiv; KOH 1.2 equiv) 4 additions, 12h, r.t.	N.D.	83%	89:11 ^[d] 90:10 ^[c]

[a] A complete table is presented in the supporting information. [b] Isolated yield. [c] Determined by ¹H NMR of purified product [d] Determined by ¹H NMR of crude reaction product.

Using KOH under the conditions described above, we applied the reaction to different substrates (Scheme 2). We started by changing the R group using another unbranched alkyl chain (product 2b), obtaining comparable results. The use of a cyclohexyl as a branched chain (product 2c) did not increase the selectivity, which is surprising since the increased steric hindrance should favor the cis, cis product. Fortunately, with an isopropyl group better yields and selectivities were observed, according to expectation (product 2d). The fused bicyclic dioxane 2e was obtained in acceptable yield and good selectivity, showing the usefulness of this method with additional alkyl groups γ to the Michael acceptor. Substrates with trisubstituted alkenyl groups afforded good yields and complete selectivity (see product 2f). Oxygenated groups have been described as problematic in this kind of reactions. In our case the conversion was low, but the selectivity was good (product 2g); increasing the reaction time did not improve the conversion. We then turned our attention to substrates with aromatic substituents, showing that substrates with simple aromatic groups (2h), slightly deactivated (2i) or activated (2i) groups lead to good yields and very good selectivities. Unfortunately, the more activated the ring, the poorer the conversion (compare products **2k** *vs* **2**I); however, in both cases the selectivity is good, and some starting material can be recovered. Heteroaromatic rings proved also problematic but better conversions, selectivities and yields were obtained comparing with strongly activated aromatics (see products **2m** and **2n**). Finally, α -substituted (with O and N) substrates were unreactive under these reaction conditions.



Scheme 2. Reaction Scope. ^adr of unpurified reaction mixture; ^bdr of purified product.

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Fortunately, other Michael acceptors proved suitable of this reaction and products **5** and **7** were obtained in good yields and selectivities from the corresponding sulfones **4** and Weinreb amides **6**, respectively, as shown in Scheme 3.



Scheme 3. Reaction with sulfones and Weinreb amides.

Acetals have been used as protecting groups for alcohols and diols for many years. The most commonly used for diols are aromatic (phenyl and *p*-methoxyphenyl) and aliphatic (acetonide); however, other groups coming from highly activated aldehydes have also been reported as alternative protecting groups for 1,3-diols, such as the 3,4-dinitrophenyl^[15] and trichloromethyl groups.^[16]. In consequence, the stability of acetals is well established particularly under basic conditions. However, acetals with strong electron-withdrawing groups (e.g. trichloromethyl) were easily cleaved under strongly basic and reductive conditions. As we were interested in the synthesis of trifluoromethylated dioxanes, it was important for us to demonstrate their stability and that they can be further functionalized, but also that they can resist typical and even stronger conditions used to deprotect other acetals.





The results shown in Scheme 4 illustrate reactions of the ester **2a** that do not affect the dioxane ring: with concentrated aqueous HCI, the acid **8** was isolated as the sole product; reduction under strong conditions furnished the free alcohol **9** also in good yield. The use DIBAL-H with a substrate without other oxidized functions (product **10**) led to the deprotection of the primary alcohol after long reaction times; otherwise **10** was recovered unchanged. It has to be mentioned that under the typical conditions used to cleave benzylidene acetals like $[H_2/Pd(C), H_2/Pd(OH)_2$ or even harder conditions employed to cleave acetals with strong electron withdrawing groups like (*n*BuLi, Na, or Zn/AcOH), the starting material was quantitatively recovered, proving the great stability of trifluoromethyl acetals and confirming their usefulness in late stage functionalization.

Conclusions

In summary, we have described a water-compatible and diastereoselective synthesis of 2-trifluoromethylated-1,3dioxanes; the use of aqueous fluoral hydrate is a good alternative to the use of toxic and dangerous gaseous fluoral. The Michael acceptor substrates are obtained by simple synthetic pathways and the reaction has a very good substrate scope. Furthermore, we demonstrated the excellent stability of trifluoromethylated acetals and the possibility to further functionalize them.

Experimental Section

To a solution of homoallylic alcohol (1 equiv.) in THF (0.2 M) at room temperature was added aqueous fluoral (75% in H_2O) (1.1 equiv.) followed by KOH (1.2 equiv.). The resulting mixture was stirred for 1 h at room temperature. A second portion of aqueous fluoral (75% in H_2O) (1.1 equiv.) and KOH (1.2 equiv.) was added. After 15 min, a third addition of fluoral and base was made, and 15 min later a fourth addition was performed under the same conditions. The resulting mixture was then stirred at room temperature for 12 -14 h and quenched with a saturated aqueous NH₄Cl solution. The aqueous phase was extracted with AcOEt (4 x 10mL) and the combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography.

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dioxanes using aqueous fluoral and KOH was developed. The products were obtained with high yields and selectivities, besides they proved to be stable enough to resist further functionalization. The reaction is easily performed and well tolerated with a broad range of substrates.

Diastereoselective Synthesis

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