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Journal of Fluorine Chemistry 101 (2000) 193–198

JOURNAL OF FLUORINE CHEMISTRY

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Convergent synthesis of fluoro and *gem*-difluoro compounds using trifluoromethyltrimethylsilane

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Received 9 May 1999; received in revised form 7 June 1999; accepted 7 June 1999

Abstract

Trifluorotrimethylsilane reacts with acylsilanes to give the corresponding difluoroenoxysilanes via the Brook rearrangement of the alcoholate adducts. The difluoroenoxysilane reacts in situ with various types of electrophilic substrates, leading to *gem*-difluoro functionalized derivatives in a one-pot methodology. This paper describes reactions with Michael acceptors, prenyl, benzyl and glycosyl donors leading to 2,2-difluoro-1,5-diketones, 4,4- or 6,6-difluorocyclohexenones, *o*- or *p*-fluorophenols, difluoro analogues of terpenes, and difluoro-*C*-glycosides.

Keywords: Trifluoromethyltrimethylsilane; Acylsilanes; Difluoro compounds; Fluorophenols; Terpenes; *C*-glycosides

1. Introduction

The selective synthesis of fluoro-substituted molecules strongly depends on the availability of fluorinated reagents and building blocks, and of course on the selectivity of the chemical transformations. If one can combine a convenient fluorinated reagent, its efficient conversion into a versatile building block, and its easy elaboration towards a target molecule, if, furthermore, the whole process may be carried out in the same pot, then the above requirements may be fulfilled at the same time. We propose such an approach in which the reagent is trifluoromethyltrimethylsilane (TFMTMS), the building block is a difluoroenoxysilane, and the key step for further elaboration is a Lewis acid activated reaction with an electrophilic substrate.

The historical background of this methodology is summarized in Scheme 1. When an acylsilane reacts with a perfluoroorganometallic reagent, an efficient and selective conversion into various organofluorosilicon derivatives occurs. The selectivity of these transformations depends on the experimental conditions [1]. The first step is a nucleophilic addition of an F-organomagnesium or an F-organolithium reagent, the adduct being trapped by water at low temperature or left to rearrange (Brook rearrangement) to give, after fluoride elimination, the enol silyl ether as a key intermediate which is isolated or reacted in situ for various applications.

This versatile reaction sequence prompted us to consider the possibility of applying a similar strategy for the synthesis of compounds bearing a difluoromethylene moiety [2] or even one fluorine atom in a definite position, via a difluoroenoxysilane. Several approaches to difluoroenoxysilanes have appeared in the literature since the first one reported by Ishihara who prepared them by silylation of a zinc difluoroenolate derived from a chlorodifluoromethyl ketone [3]. Other approaches, based on an intermediate trialkylsilyl trifluoromethyl carbinolate adduct similar to ours, used silyl lithium reagents either to prepare a needed trifluoroacetylsilane [4] or to add to a trifluoromethyl ketone [5]. A different method consists of the in situ silylation of a difluoroenolate obtained by electroreduction of a trifluoromethyl ketone [6]. Our strategy needed a trifluoromethyl organometallic reagent. The main group trifluoromethyl derivatives being less easily available [7], we were obviously attracted by the Ruppert discovery [8] and the further systematic investigation by Prakash's group [9] of TFMTMS as a convenient and effective nucleophilic trifluoromethyl donor. Our initial attempts using tetrabutylammonium fluoride as activator resulted in the formation of the aldol dimer of a difluoromethyl ketone, an unexpected but interesting result showing the probable intermediate of the desired enoxysilane. Using the less nucleophilic tetrabutylammonium difluorotriphenylstannate (DFTPS) [10] as activator

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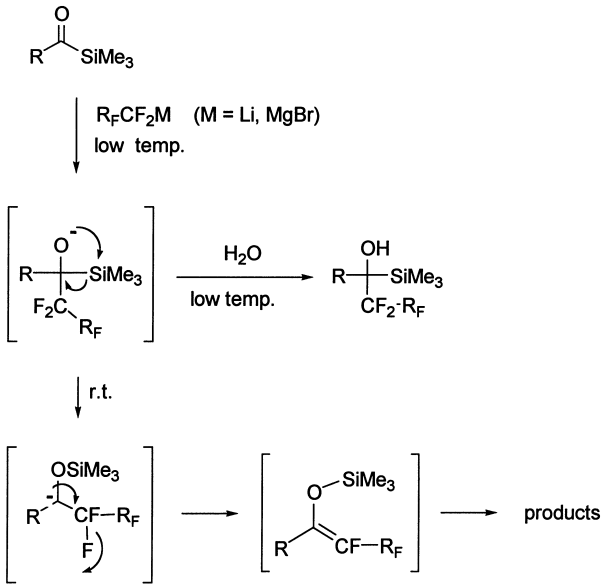
PII: S0022-1139(99)00158-X



Scheme 1.

allowed the reaction to stop at the right stage and to quantitatively convert the acylsilane into the corresponding difluoroenoxysilane (Scheme 2) [11]. The first advantage of this sequence is that the reaction was completed by using a catalytic amount of DFTPS, because of the fluoride elimination which follows the Brook rearrangement. The second one is the high efficiency of the reaction in various solvents, in particular in methylene chloride, a non-basic solvent ideal to perform Lewis acid catalyzed reactions in the same pot. Hence, we had in hand an overall process which starts with a chain reaction between the acylsilane and TFMTMS, initiated by a catalytic amount of fluoride, leading to the difluoroenoxysilane which reacts in situ with an electrophilic reagent to give an elaborated functionalized *gem*-difluoro compound.

From the investigations carried out so far, it appeared that each kind of electrophile needed a careful choice of the Lewis acid in order to obtain, if possible in catalytic conditions, interesting yields for the overall one-pot process. Although we have studied the Mukaiyama type aldol reaction [11,12], the remaining part of this report will be devoted to the applications of this methodology to Michael acceptors, prenyl and benzyl, or glycosyl donors as electrophilic substrates.

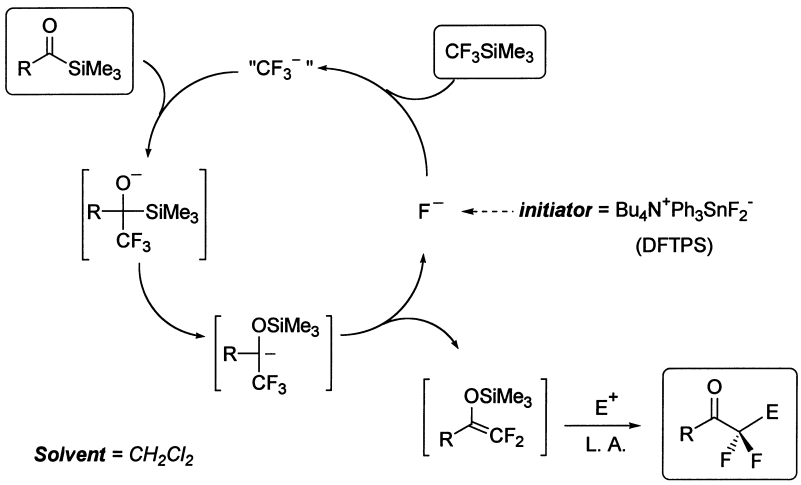
2. Synthesis of 2,2-difluoro-1,5-diketones, *gem*-difluorocyclohexenones, and fluorophenols

The reaction path leading to the title compounds is depicted in Scheme 3. Ytterbium triflate as Lewis acid gave the best results, working in catalytic amount. Overall yields from the starting acylsilanes were satisfactory for preparative purpose, with aliphatic and aromatic acylsilanes, and with unsubstituted (methyl vinyl ketone) as well as β-substituted (cyclohexenone) enones [13].

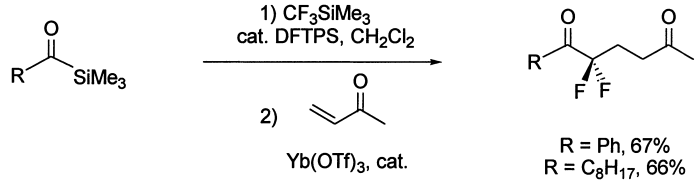
The 2,2-difluoro-1,5-diketones obtained were submitted to basic annulation conditions (Scheme 4). The regiochemistry of the cyclization of the diketone derived from benzoylsilane was not problematic, owing to a unique enolizable side in the molecule, and 4,4-difluoro-3-phenyl-cyclohex-2-enone was cleanly obtained by the catalytic basic treatment. Despite the presence of two enolizable sites, the diketone derived from an aliphatic acylsilane cyclized regiospecifically as well, but gave a 6,6-difluorocyclohex-2-enone. Therefore, an interesting feature of these α,α-difluorodiketones is the regiospecific formation of the enolate of the difluoroketone moiety [13].

Another interesting extension of this chemistry is the synthesis of fluoroaromatic compounds by a simple elimination of hydrogen fluoride, followed by the aromatization of the molecule. When the difluoro diketones were treated by an excess of methanolic potassium hydroxide, the corresponding *o*- or *p*-fluorophenol was directly obtained [13].

These examples show the feasibility of a methodology which allows, from TFMTMS, an acylsilane and an enone,



Scheme 2.



Scheme 3.

the regiospecific construction of multisubstituted difluorocyclohexenones and fluorophenols.

3. Synthesis of difluoroanalogues of terpenes

The introduction of fluorine in a terpene molecule can modify the physico–chemical properties of the molecule itself or of intermediates, most often carbocations, involved in their interactions with biological receptors [14]. Our methodology might contribute favorably to synthetic methods leading to terpene analogues selectively *gem*-difluoro substituted.

After several attempts, preparative conditions were found for the in situ prenylation of the difluoroenoxysilane. The reaction works with different types of acylsilanes [15], but the most interesting one is acetyltrimethylsilane which leads to the difluoro analogue of the key intermediate ketone towards the synthesis of monoterpenes. The best results were obtained with prenyl benzoate and trimethylsilyl triflate as the Lewis acid catalyst. Unfortunately, the reaction gave a difficult to separate 90/10 mixture of regioisomers, with the expected one as the major component (Scheme 5). One or two further steps carried out on the mixture led to simple *gem*-difluoro mono terpenes. Difluoro linalool was prepared as a pure compound by simple addition of vinyl magnesium bromide and chromatographic separation of the regioisomers. A Horner–Wadsworth–Emmons reaction followed by $LiAlH_4$ reduction led to an analogue of difluorogeraniol we have not yet managed to separate from its regioisomer [16].

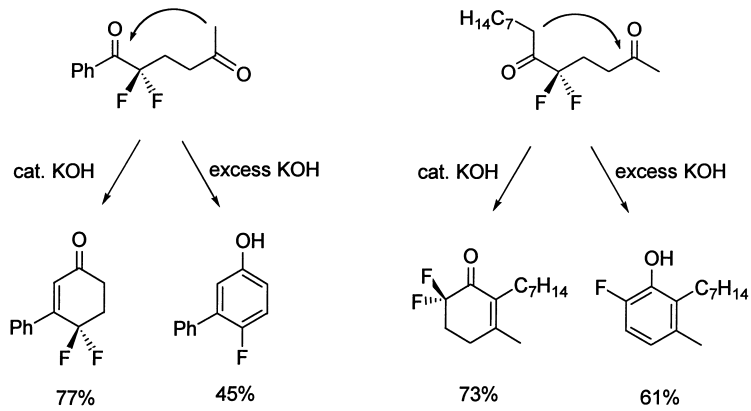
The results summarized in Scheme 6 show the versatility of the method for the synthesis of difluoro analogues of sesquiterpenes including an aryl moiety. In the synthesis of difluoro *ar*-turmerone, the aryl moiety comes from a benzylation of the difluoroenoxysilane derived from an acylsilane bringing the prenylic moiety. On the other hand, in the synthesis of difluorodihydro-*ar*-curcumene, an aroylsilane was converted into the corresponding difluoroenoxysilane which reacted with the prenyl donor [15].

An unexpected and interesting result was observed when we attempted to synthesize a difluoro analogue of farnesol by geranylation. Instead of the farnesol derivative, the only product obtained resulted from the rearranged cyclized intermediate carbocation (Scheme 7) [16]. Furthermore, a long cascade rearrangement was involved, leading to a compound which can be considered as a piperitol like derivative, rather than the terpineol like derivatives, compounds generally observed in such rearrangements [17].

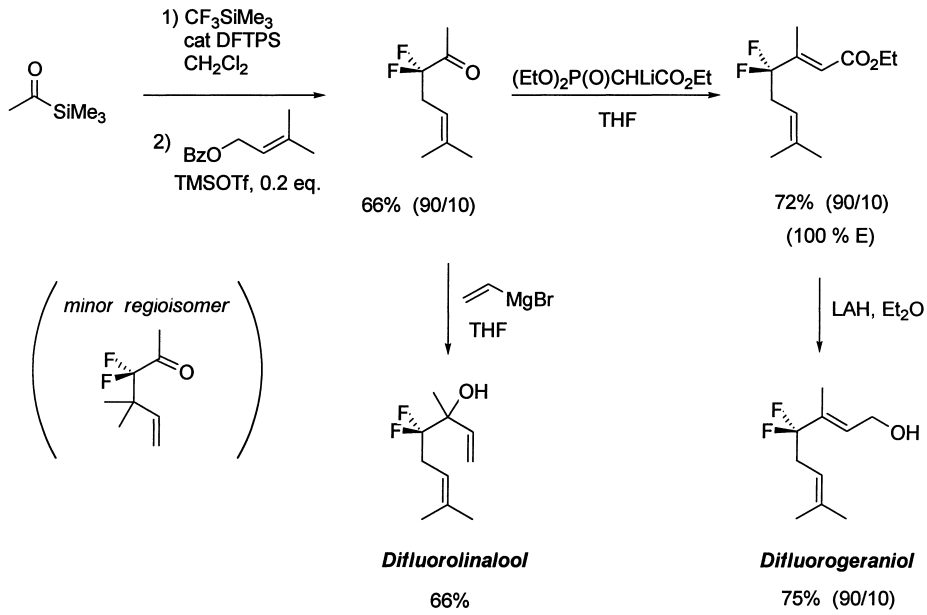
These examples demonstrate that the strategy using TFMTMS as fluorinated source is valuable in the synthesis of difluoro analogues of various types of terpene derivatives.

4. Synthesis of difluoro *C*-glycosides

A preliminary observation of reaction with acetals [11] prompted us to study the trapping of the difluoroenoxysilanes with glycosyl donors giving access to a difluoro *C*-glycoside as glycoside mimics. A completely different



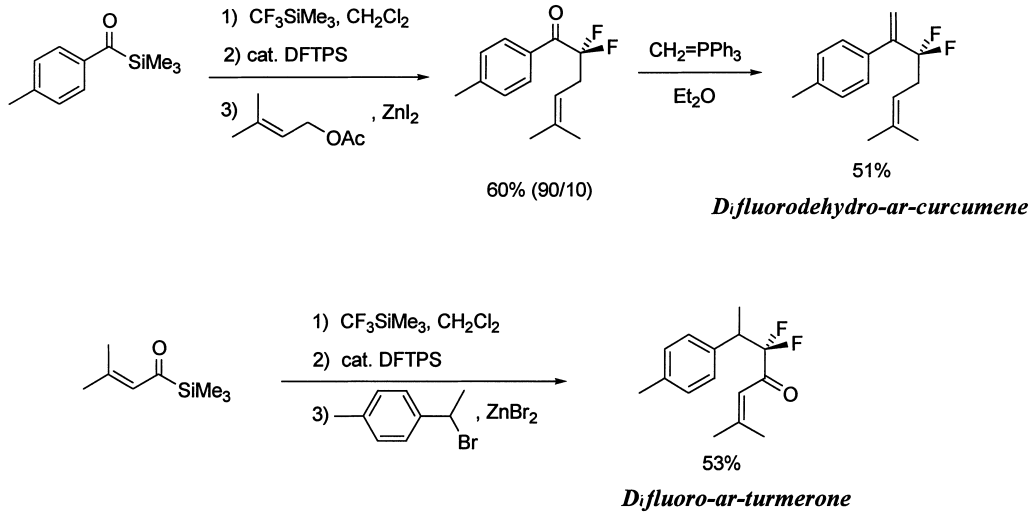
Scheme 4.



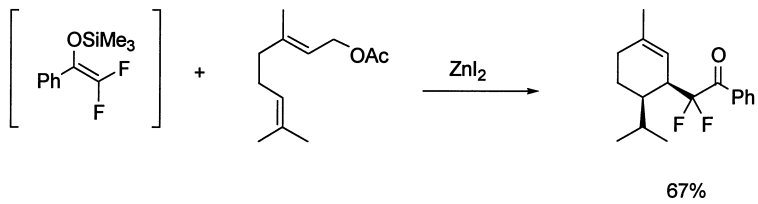
Scheme 5.

approach towards this type of compound was investigated by Motherwell's group [18–20]. Our first attempt with a glycosyl donor bearing an ester group at C-2 normally imposing a *C*-glycosylation via the β-face failed, leading to coupling with the non-anomeric ketal carbocation, whatever the nature (acetic or benzoic) of the ester (Scheme 8). Reaction with the anomeric carbon was restored as soon as the C-2 position was deoxygenated (Scheme 9) [21].

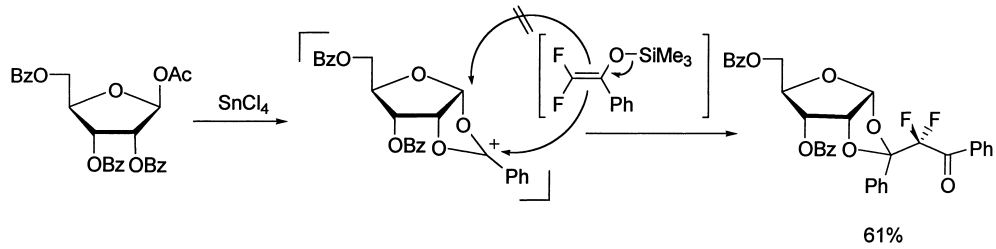
An effective coupling was obtained using tri-*o*-acetyl D-glucal as electrophilic substrate. Activation of the reaction by boron trifluoride etherate mildly gave the corresponding *C*-glycoside with a high overall yield (Scheme 10) [22]. The



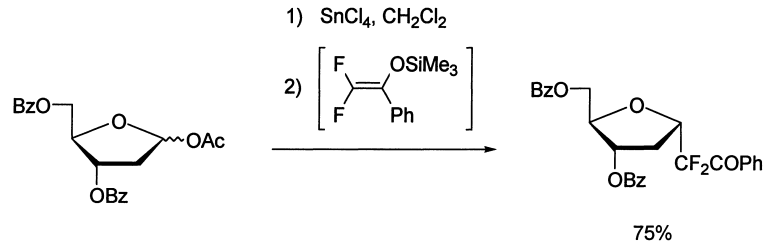
Scheme 6.



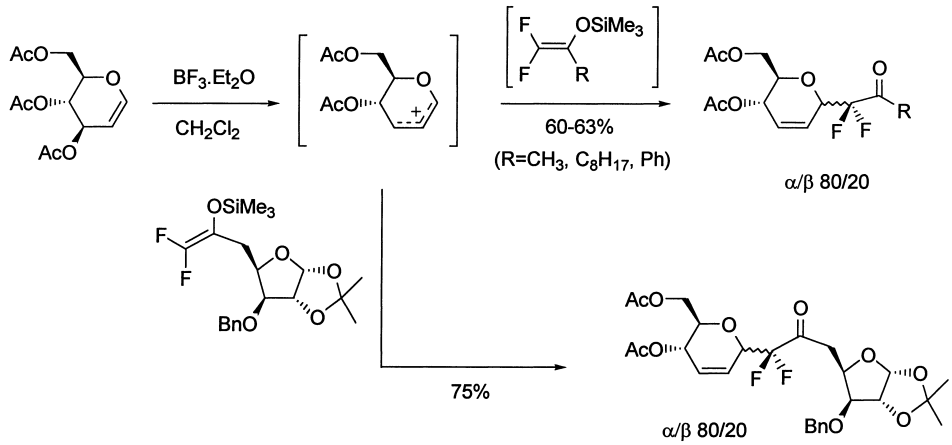
Scheme 7.



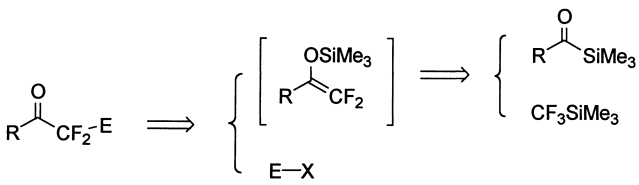
Scheme 8.



Scheme 9.



Scheme 10.



Scheme 11.

usefulness of the method for the synthesis of difluoro-*C*-disaccharides type products is also exemplified in Scheme 10: reaction of an acylsilane synthesized from D-xylose [23] with TFMTMS, according to our standard conditions, gave the corresponding sugar derived difluoroenoxysilane which was trapped by the boron trifluoride activated D-ribosyl donor [22]. The obtained product may be considered as a difluoro analogue of a disaccharide.

5. Conclusion

Trifluoromethyltrimethylsilane, a known convenient and effective reagent for nucleophilic trifluoromethylation of ketones, must also be considered as a reagent of choice for the synthesis of various functionalized fluoro and difluoro compounds. This method, based on the use of acylsilanes as starting materials and their ability to rearrange after trifluoromethylation, is advantageous owing to its one-pot and convergent character, as summarized in Scheme 11.

TFMTMS acts in these transformations as an equivalent of a difluoromethylene dianion. Furthermore, the method is very versatile owing to the various structure possibilities for acylsilanes and for electrophiles. We can expect various applications of the reactions reported here, as well as further extension of the methodology towards other types of electrophiles. Some of them are currently under investigation.

Acknowledgements

The authors thank the CNRS and the MENRT for their financial support.

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