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Nucleophilic difluoromethylation of aromatic aldehydes using trimethyl (trifluoromethyl)silane ($TMSCF_3$)

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Dedicated to the memory of Prof. George A. Olah.

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ABSTRACT

Reaction of the Ruppert–Prakash reagent (Me_3SiCF_3) with aromatic aldehydes in the presence of triphenylphosphine, lithium iodide and lithium tetrafluoroborate selectively furnishes *gem*-difluorinated phosphonium salts. Simple alkaline hydrolysis of these salts results in difluoromethylated products. Thus, one-pot nucleophilic difluoromethylation of aromatic aldehydes using Me_3SiCF_3 has been accomplished. The protocol tolerates electron withdrawing as well as electron donating substituents.

1. Introduction

Flouroalkylation has received significant interest in recent years among the synthetic community owing to the importance of selectively fluorinated organic compounds in drug discovery and development, pest control, agrochemicals and catalysis [1]. The difluoromethyl group has been considered a distinct fluoroalkyl moiety as it has been shown to be a lipophilic hydrogen bond donor. Consequently, it is considered in isostere based drug design approach and is already found in marketed medicines and agrochemicals [2].

Nucleophilic fluoroalkylation of electrophiles is a direct approach for the synthesis of fluorine containing compounds. Although nucleophilic perfluoroalkylation is well documented [3], the direct nucleophilc difluoromethylation has been challenging [4]. This can be attributed to lack of availability of versatile reagents that can transfer the difluoromethyl anion under mild conditions [5].

Unlike the non-fluorinated analogs, the preparation of trifluoromethyllithium and trifluoromethylmagnesium halides have been reported to be challenging and performed poorly for the nucleophilic trifluoromethylation of aldehydes [6]. Similarly, it is assumed that the preparation of the corresponding difluoromethyl compounds ($LiCF_2H$ and HF_2CMgX) would be significantly difficult barring their use in nucleophilic difluoromethylation. On the other hand, in general, the stability of transition metal based difluoromethyl compounds was found to be better than trifluoromethyl lithium and trifluoromethyl magnesium halides [7]. For instance, the following stability order, Zn > Cd > Cu, was observed for the corresponding difluoromethyl compounds [4]. Although these compounds were utilized for some synthetic applications, due to their less ionic nature of the C-M bond, they proved to be ineffective for difluoromethylation of carbonyl compounds such as aldehydes and ketones. On the contrary, the silicon regents have shown significant success in this area. The first report by Fuchikami announced that the nucleophilic difluoromethylation of aldehydes and ketones using (difluoromethyl)trimethylsilane (Me_3SiCF_2H) required elevated temperature (100 °C) in the presence of KF in DMF [8]. This indicated that the Si-CF_2H bond is difficult to cleave compared to the Si-CF_3 bond (eg. Me_3SiCF_3), demanding strongly basic conditions. This notion was later proven by Hu et al. using CsF or 18-crown-6 with KF for successful difluoromethylation of aromatic aldehydes and non-enolizable ketones (Scheme 1b) at room temperature and sulfinylamines at −78 °C using KO*t*-Bu [9]. Between the years of these two reports, alternative reagents of the anion $-CF_2Z$ (Z = SO_2Ph [10], $P(O)OEt_2$ [11], CF_2SPh [12], $SeCF_2Ph$ [13], CF_2SiMe_3 [14]) type with functional groups, which can be cleaved after transfer to obtain the desired CF_2H group or for further functionalization, have thrived. However, a versatile inexpensive reagent that employs mild conditions to transfer difluoromethyl anion is still in high demand. In this paper, the details of how the common, readily available nucleophilic trifluoromethylating reagent, Me_3SiCF_3, could be employed as a viable reagent for the direct difluoromethylation is discussed.

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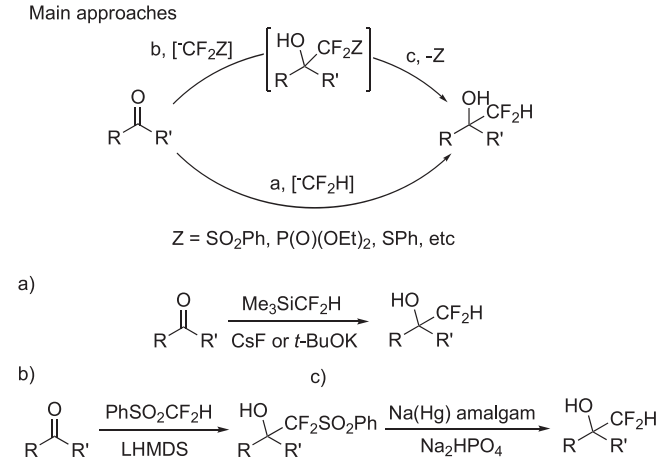


Scheme 1. Approaches for nucleophilic difluoromethylation of aldehydes and ketones.

2. Results and discussion

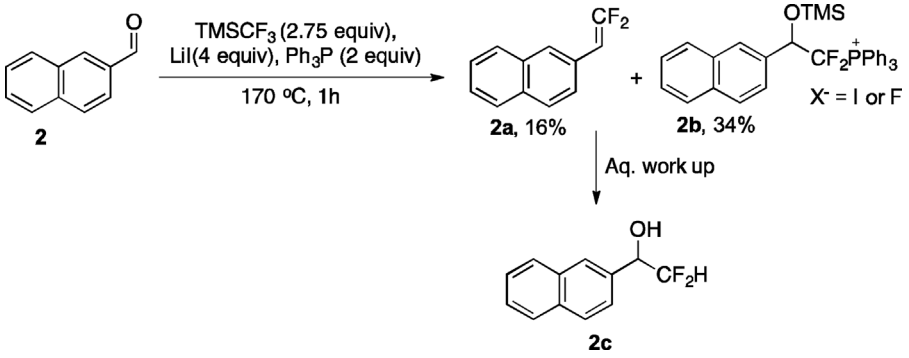
During our investigation of *gem*-difluoroolefination of carbonyl compounds using the Ruppert–Prakash reagent [15], **2b** was observed as a side product (Scheme 2). After an aqueous work up of the reaction mixture, we noticed the presence of difluoromethylated product (**2c**).

Upon examining the literature, Hu et al. in their attempt to *gem*-difluoroolefinate carbonyl compounds using Me_3SiCF_2Br/PPh_3 observed such an intermediate by NMR spectroscopy (Scheme 3a) [16]. Later, Dilman and co-workers reported that these intermediates could be hydrolyzed with a simple aqueous work up to provide difluoromethylated alcohols (Scheme 3b & c) [17].

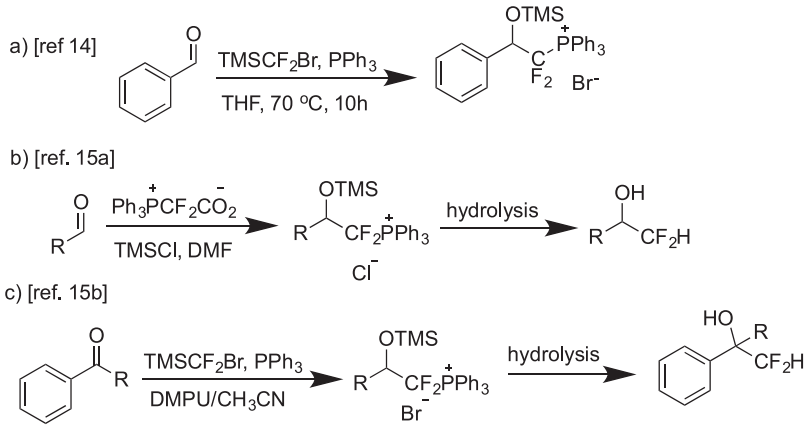
Based on these reports (Scheme 3) and our observations (Scheme 2), we debated the possibility of using the Ruppert–Prakash reagent as a facile nucleophilic difluoromethylating agent for carbonyl compounds. When the reagents used for such purposes were surveyed for their commercial accessibility and the cost, we found that the $TMSCF_3$ would be the cheapest reagent available in the market and can be procured for less than a USD per gram (See Supporting information).

Further, Me_3SiCF_3 is a primary source for easy access of the commonly used nucleophilic difluoromethylating reagents (Scheme 4), Me_3SiCF_2H and Me_3SiCF_2Br (*vide supra*). Thus, we were convinced that developing nucleophilic difluoromethylation process using Me_3SiCF_3 would be a more desirable approach as it will minimize the cost and the intermediate steps involved in the preparation of other reagents.

The optimization of the reaction was carried out with 2-napthaldehyde as a model substrate for convenient handling, as it is a free flowing solid. First, to reduce the reaction temperature from 170 °C, a mixed solvent approach was employed. The 1:1 mixture of diglyme/DMF at room temperature provided 1:1 mixture of **2a** and **2b** with total conversion of 42% (Table 1, Entry 1) and the Ruppert–Prakash reagent was completely consumed. To reduce the reactivity of iodide and prevent fast decomposition of $TMSCF_3$, the amount of DMF was reduced to 20%, and diglyme was replaced with THF for economical reasons. In this solvent system, the reaction observed to be slower at room temperature, therefore the reaction mixture was heated at 70 °C for 24 h, which led to only 10% of the desired product (Entry 2). When other solvent systems were examined under similar conditions, DMF/acetonitrile (Entry 4) was found to be better than DMF/benzene (Entry 3) or DMF/THF (Entry 2). Although total higher conversion was obtained in 20% DMF/acetonitrile, the ratio of **2a** and **2b** was observed to be 1:1. At this point, the amounts of PPh_3 and LiI on the reaction results were closely examined. It was found that less than an equivalent of PPh_3 reduced the total conversion, whereas the excess of PPh_3 had insignificant effect on the outcome of the reaction. However, when the amount of LiI was increased, the amount of expected product **2b** also increased (Entry 5 and 6). The improvement was only moderate even after addition of 6 equivalents of LiI. When DMPU was examined as a replacement for the DMF (Entry 7–10), 15% DMPU performed similar to



Scheme 2. Observation of α-difluoromethyl alcohol in the reaction of Me_3SiCF_3 with LiI/PPh_3 and 2-napthaldhyde.



Scheme 3. Difluoromethylene phosphonium intermediate.