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2-(Acetoxymethyl)-1,1-difluoro-3-(trimethylsilyl)propene: Preparation and Utility as a Novel Bifunctional Reagent Containing a CF_2 Group

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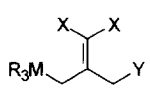
Abstract: The CF_2-containing reagent **2** has been conveniently prepared using CF_2Br_2 as the readily accessible starting material. The fluoride-mediated nucleophilic reactivity of **2** towards aromatic aldehydes has been demonstrated. Copyright © 1996 Elsevier Science Ltd

The incorporation of a difluoromethylene (CF_2) unit into substances for a diversity of biological applications is an important area of current organofluorine chemistry.[1] Recent work in this field has led to the discovery of a wide range of biologically interesting compounds such as the antitumor nucleoside Gemcitabine,[2] inhibitors[3] of renin, pepsin, elastase, HIV-1 protease, Interleukin-1β converting enzyme, and various α,α-difluoroalkylphosphanate-based mimics of natural phosphates.[4] A well-tried approach for the introduction of a CF_2 group involves the transformation of a ketonic carbonyl group or its equivalent using fluorinating agents such as DAST.[5] However, the practical applicability of this approach is often limited by the requirement to deploy a carbonyl group in the strategic position of a suitably protected precursor as well as by the hazardous and reactive nature of most fluorinating agents. An attractive alternative approach is to make use of easily accessible CF_2-containing building-blocks, *e.g.*, $BrCF_2CO_2R$, in the *de novo* construction of the target molecules. In this regard, the development of readily accessible and synthetically versatile CF_2-containing building blocks would be highly desirable. Encouraged by the synthetic success of some 1,3-bifunctional conjunctive reagents like **1** which possess both electrophilic and nucleophilic centers,[6] we have focused our efforts on the preparation of a fluorinated analog of these useful reagents. Herein, we present some preliminary results concerned with the preparation of the novel CF_2-containing reagent **2** and its fluoride-mediated nucleophilic addition to aldehydes.

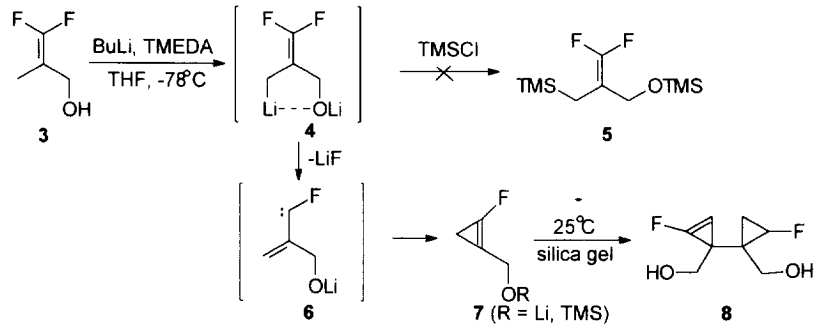


1: X = H
2: X = F, R_3M = TMS, Y = OAc

Although several methods are available for the preparation of the nonfluorinated counterpart[7] of **2**, the adaptation of these methods to the synthesis of the fluorinated reagent **2** was found to be not easy. In an attempt to prepare **2** using the metallation protocol developed for the preparation of the fluorine-free reagent,[7a] the fluorinated methallyl alcohol[8] **3** was treated with butyllithium and TMEDA in THF at low

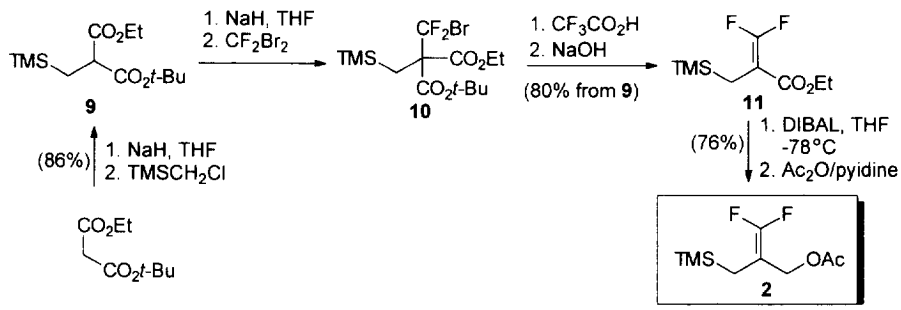
temperature. However, after quenching the reaction mixture with chlorotrimethylsilane, the only product that could be isolated from a complex mixture was the cyclopropene dimer **8,** which was believed to result from the elimination of lithium fluoride from the initially formed allyllithium intermediate **4**.[9] Previously, Seyferth has reported that simple *gem*-difluoroallyllithium was rather unstable even at low temperature.[10] As such, it can be concluded that the stability of **4** could not be significantly improved by the chelating effect exerted by the neighboring alkoxy group.

Scheme 1



After some further unsuccessful attempts, a convenient route was finally developed. It featured a formal alkylation reaction of a malonate anion with the readily accessible CF_2Br_2 (Scheme 2).[11] Thus, according to the procedure described by Purrington,[11b] the mixed malonate ester **9**, prepared by alkylation of *t*-butyl ethyl malonate with chloromethyltrimethylsilane, was treated succesively with sodium hydride and CF_2Br_2 to afford product **10**. The latter was directly subjected to decarboxylative-halide elimination[11a] to provide the difluoroacrylate **11** in 80% yield.[12, 13] Although previous reduction of a β,β-difluoroacrylate with DIBAL has been complicated by the concomitant 1,2- and 1,4-reductions[8], the reaction of **11** with the same reagent[14] proceeded admirably to the level of 1,2-reduction presumably due to the presence of the trimethylsilyl group in the allylic position. Subsequent acetylation of the resulting alcohol provided the desired fluorinated reagent **2** in 76% yield. The overall sequence required no chromatography for product separation and thus allowed a large scale preparation of the reagent **2**.

Scheme 2



The synthetic potential of **2** as a CF_2-containing bifunctional synthon has been briefly explored. Considering the successful cycloaddition chemistry of the corresponding fluorine-free reagent,[6a] our initial

effort was focused on the palladium catalyzed [3 + 2] reactions of **2** with Michael acceptors or aldehydes. Unfortunately, some exploratory experiments revealed a lack of reactivity for **2** in these reactions due to the presence of two fluorine atoms. The nucleophilic reactivity of **2** towards carbonyl compounds was next examined. Gratifyingly, it was found that **2** could be successfully used as an allylation reagent in its fluoride-mediated reactions with aromatic aldehydes[15] (Scheme 3). The results were summarized in the Table.

Scheme 3

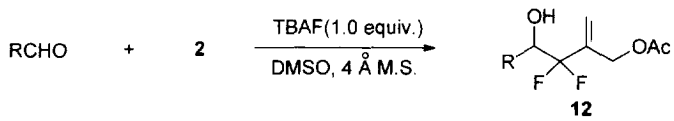
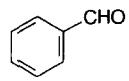
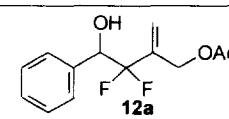
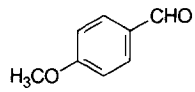
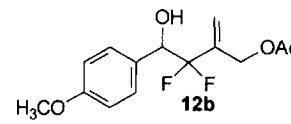
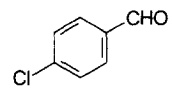
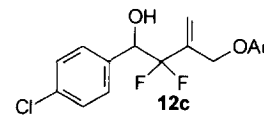
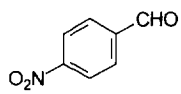
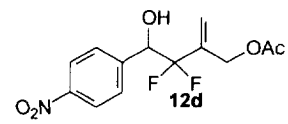
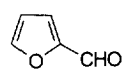
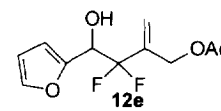


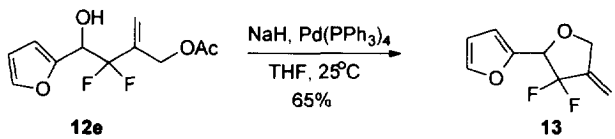
Table. Reaction of the CF_2-containing reagent 2 with aromatic aldehydes[a]

entry	aldehyde	product[b]	yield, %
1		 **12a**	78
2		 **12b**	85
3		 **12c**	75
4		 **12d**	80
5		 **12e**	81

[a] *General procedure*: At 0 °C, a solution of TBAF in THF (1.0 M, 1.0 mL) was added to a stirred mixture of **2** (1.0 mmol), the aldehyde (2.0 mmol) and 4 Å molecular sieve in DMSO (5 mL). The reaction was quenched with water after 30 min and the product was isolated by flash chromatography on silica gel. [b] All products were characterized by ^{1}H- and ^{19}F-NMR, MS and elemental analyses.

As can be seen from the Table, all products thus obtained were the ones in which the new carbon-carbon bond had been formed at the CF_2 terminus of the reagent. These multifunctional compounds are anticipated to be capable of further synthetic manipulations, among which the palladium-catalyzed intramolecular cyclization of **12e** to give the difluorinated tetrahydrofuran **13** has been demonstrated in Scheme 4.

Scheme 4



12e **13**

In conclusion, we have developed a convenient preparation of a novel CF_2-containing bifunctional reagent and briefly demonstrated its synthetic utility. Work continues in further exploring the use of **2** and related reagents in the construction of various functionalized CF_2-containing compounds.

Acknowledgment. This work was supported by grants from the National Natural Science Foundation of China and Shanghai Municipal Scientific Committee.

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13. **Procedure for the preparation of 11**. The procedure of Purrington[11a] was followed using **9** (11.0 g, 40 mmol) in the bromodifluoromethylation reaction (reaction time: 30 h) to obtain essentially pure **10** as judged by ^1H NMR. The latter was dissolved in trifluoroacetic acid (80 mL) and the solution was heated at 60 °C for 10 h. After removal of the volatile components under reduced pressure, the residue was taken up in THF (50 mL) and then stirred with 2 *N* aqueous NaOH (20 mL) for 30 min. The product was isolated by ether extraction and purified by distillation to give 7.1 g (80%) of **11**; bp 44-46 °C/4.5 mmHg. ^1H NMR ($CDCl_3$) δ 4.17 (q, J = 7.1 Hz, 2 H), 1.52 (t, J = 2.6 Hz, 2 H), 1.25 (t, J = 7.1 Hz, 3 H), - 0.02 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ (relative to CF_3CO_2H) -1.8 (1F), -5.6 (1F). Calcd for $C_9H_{16}F_2O_2Si$: C 48.65, H 7.21. Found: C 48.73, H 7.06.
14. Interstingly, when the reduction of **11** was performed with $LiAlH_4$, only the monofluorinated compound (*Z*)-$CFH{=}C(CH_2TMS)CH_2OH$ was obtained via a 1,4-reduction pathway.
15. Aliphatic aldehydes were found to be unreactive under the same reaction conditions.

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