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Review

1,4-Addition of the CF_3 group, perfluoroalkyl groups and functionalized difluoromethylated moieties: An overview

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ABSTRACT

Over the last years, the organofluorine chemistry field has known a very fast expansion offering to the scientific community a panel of efficient tools for the synthesis of fluorinated molecules. Despite these recent advances, the 1,4-addition of nucleophilic fluorinated groups onto Michael-type acceptors to construct R_f-containing $C(sp^3)$ center is underdeveloped and still constitutes a real synthetic challenge. This review aims at highlighting the key reports regarding such transformation involving the CF_3 group, perfluoroalkyl moieties and functionalized difluoromethylated nucleophilic species.

Contents

1. Introduction

Fluorinated molecules are key scaffolds in medicinal chemistry and agrochemical development [1]. The importance of the fluorinated molecules mainly results from the intrinsic properties of the fluorine atom [2]. Indeed, its unique features can strongly affect the physical and biological properties of a molecule. Therefore, a modification of the bioavailability, the lipophilicity and the acidity or the basicity of the neighboring functional groups is usually observed. As a matter of consequence, a significant increase of the demand for fluorinated molecules and particularly for versatile fluorinated building blocks has been recently witnessed. Hence, to access these fluorinated targets, the organic chemist community has devoted a lot of efforts to design innovative and straightforward methods [3]. While a phalanx of efficient transformations was recently developed to introduce fluorinated moieties onto molecules, a lack of attention has been paid to the venerable 1,4-addition of fluorinated moieties and particularly to the conjugate addition of the CF_3 group and the functionalized difluoromethylated residues. This statement contrasts with the high synthetic utility of this Michael reaction, which is recognized as one of the most common and powerful transformations in organic chemistry [4], taught in all universities

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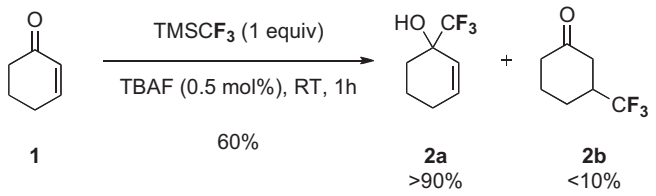
over the world and present in the most popular textbooks. Therefore, the 1,4-addition of fluorinated moieties onto readily available Michael acceptors constitutes an interesting alternative retrosynthetic disconnection to the use of fluorinated Michael acceptors [5]. From a synthetic point of view, this transformation represents a real challenge since the selective 1,4-addition should be favored over the competitive 1,2-addition reaction onto α,β-unsaturated carbonyl derivatives. Moreover, the 1,4-addition of fluorinated nucleophiles is particular due to the unique features of fluorinated carbanions as reactive species. Indeed, their reactivity strongly differs from the non-fluorinated analogs. In this review, we would like to describe an exhaustive state of the art of the 1,4-addition reactions of the trifluoromethyl group, the perfluoroalkyl groups and the functionalized difluoromethylated groups as nucleophiles. Note that herein, we will not focus on the addition reactions involving a radical pathway since these transformations cannot be really considered as a typical conjugate addition.

2. 1,4-Additions

2.1. 1,4-Addition of a CF_3 group or a C_nF_{2n+1} group

The first report of a 1,4-addition of the CF_3 group was reported in 1989 by Prakash, Olah and co-workers [6]. In the course to the development of a fluoride-induced trifluoromethylation reaction of carbonyl compounds, the authors observed the presence of the 1,4-adduct **2b** as trace (<10%) when cyclohexenone was used as a substrate (Scheme 1). This result, clearly highlighted the possibility to perform a 1,4-addition of the CF_3 group, however it also pointed out the difficulty to achieve selectively this transformation on simple Michael acceptors [7].

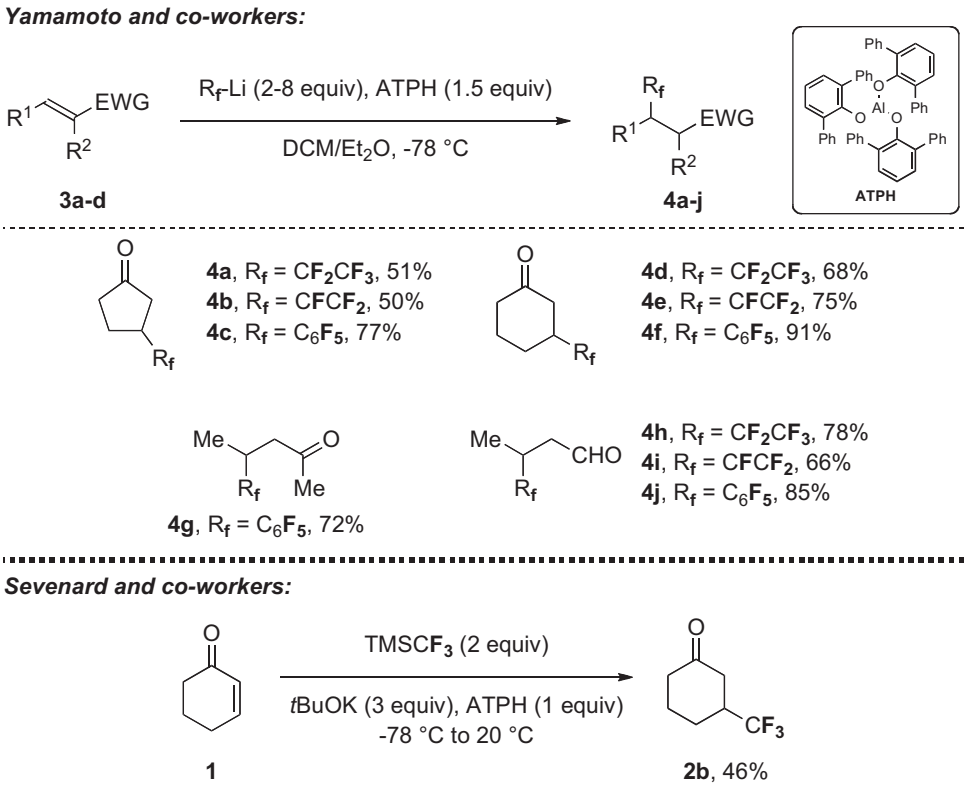
Later in 1994, Yamamoto and co-workers took benefit from the development of bulky Lewis acids to prevent the 1,2-addition reaction and to favor the conjugate addition [8]. Indeed, by using a



Scheme 1. First observation of the 1,4-addition of a CF_3 group.

stoichiometric amount of aluminum tris(2,6-diphenylphenoxide) (ATPH) as a sterically hindered Lewis acid, Yamamoto and co-workers successfully performed the 1,4-addition of perfluoroalkyl lithium onto unsaturated carbonyl derivatives. Remarkably, the use of α,β-unsaturated aldehydes as Michael acceptors was possible without formation of the 1,2-addition product. The corresponding Michael adducts **4a–j** were obtained in good to excellent yields and a broad range of perfluorinated nucleophiles was suitable. However, no introduction of the CF_3 group was realized due to the high instability of the corresponding lithiated species (Scheme 2). This limitation has been overcome by Sevenard in 2003, who astutely used the combination of $TMSCF_3$/*t*BuOK to generate the nucleophilic CF_3 species with ATPH [9]. With these reaction conditions, the cyclohexanone was converted onto the corresponding Michael adduct **2b** in 56% NMR yield and 46% isolated yield.

In 2000, Langlois and co-workers used a biased substrate to perform the 1,4-addition of the CF_3 group [10]. Indeed, by using *trans*-1-benzoyl-2-(dimethylamino)ethylene **5**, the authors obtained exclusively the 1,4-adduct **6** in 36% isolated yield. Note in that case, the nucleophilic source of CF_3 is generated from fluoroform (CHF_3) and $N(TMS)_3$ as a base (Scheme 3a). Nine years later, Dilman and co-workers applied a similar strategy to perform a formal 1,4-addition of the CF_3 group using the Ruppert-Prakash reagent along with a dual activation by means of fluoride anion and



Scheme 2. 1,4-Addition of the perfluoroalkyl and CF_3 groups onto enones and enals.