Journal of Fluorine Chemistry 161 (2014) 134–141

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Review

Nucleophilic non-metal assisted trifluoromethylation and perfluoroalkylation reactions of organic substrates

Sebastián Barata-Vallejo [a], M. Rosario Torviso [a], Beatriz Lantaño [a],
Sergio M. Bonesi [b], Al Postigo [a,*]

[a] Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 954, Buenos Aires CP 1113, Argentina
[b] CIHIDECAR – CONICET, Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Ciudad Universitaria, Pab. II, Buenos Aires CP 1428, Argentina

ARTICLE INFO

Article history:
Received 12 December 2013
Received in revised form 20 January 2014
Accepted 21 January 2014
Available online 31 January 2014

Keywords:
Nucleophilic trifluoromethylation
Fluoroform
Trimethylsilyltrifluoromethane
Fluorinated sulfones
Fluorinated sulfoxides
Fluorinated sulfides

ABSTRACT

Nucleophilic trifluoromethylation and perfluoroalkylation reactions have been the outstanding approach during the last few decades to effect fluoroalkyl group addition or substitution reactions. In most instances, perfluoroalkyl-metal species participate at the beginning of the reactions. In this account, however, the latest nucleophilic *non-metal* assisted or uncatalyzed trifluoromethylation and perfluoroalkylation reactions of substrates bearing biological relevance will be discussed.

Contents

1. Introduction

A recent review article by Wu, Beller and collaborators [1], and before that the seminal *in-depth* review article by Grushin and colleagues [2] appropriately summarize the nucleophilic trifluoromethylation and perfluoroalkylation reactions of organic substrates in the presence of metals. Thus numerous transformations regarding fluorination of both aliphatic and aromatic substrates either with or without formal leaving groups can be accomplished with the intervention of metals and transition metal complexes which aid in the coupling of the fluoroalkyl moieties that act as nucleophiles onto the organic electrophilic substrates.

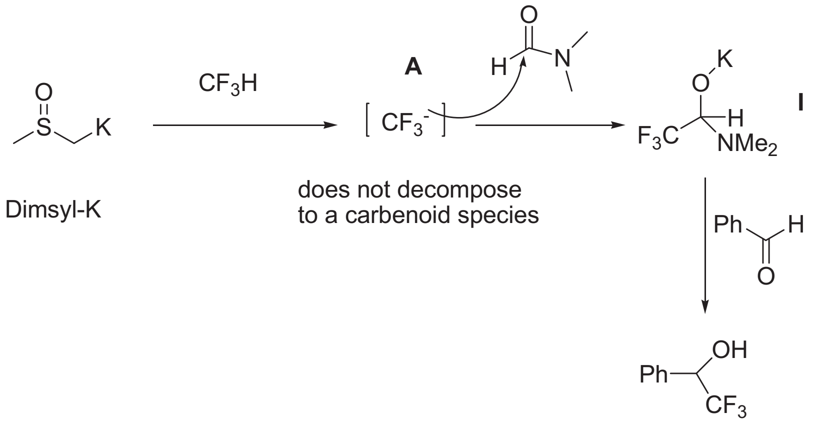
The nucleophilic trifluoromethylation has been extensively studied and reviewed [3]. However, the incorporation of CF_3 groups remains limited by the low stability of the CF_3 anion due to α-elimination to the difluorocarbene [4]. The following sections shall describe diverse sources of trifluoromethylating and perfluoroalkylating reagents such as fluoroform CF_3H, trimethylsilyltrifluoromethane (Me_3SiCF_3), fluorinated sulfones, sulfoxides, sulfides,

---

Abbreviations: BAIB, *bis*(acetoxy) iodobenzene; DMF, *N*,*N*-dimethylformamide; DFT, density functional theory; MF, metal fluoride; OPMB, 4-methoxybenzyloxy; R_f, perfluoroalkyl; TBAF, *tetra*butyl ammonium fluoride; TBAT, *tetra*butyl ammonium *tri*phenyldifluorosilicate; TEMPO, (2,2,6,6-tetramethyl-piperidin-1-yl)-oxyl); TFA, trifluoroacetic acid; THF, tetrahydrofuran; TMAF, *tetra*-methylammonium fluoride; TsOH, *p*-toluensulfonic acid.

[*] Corresponding author. Tel.: +54 011 4964 8200; fax.: +54 011 4964 8252.
E-mail addresses: apostigo@ffyb.uba.ar, alberto.postigo@ub.edu.ar (A. Postigo).

0022-1139/$ – see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jfluchem.2014.01.016



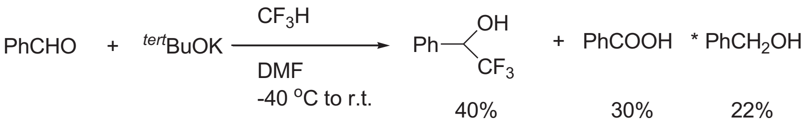
Scheme 1. Mechanism for the trifluoromethylation of benzaldehyde with CF_3H.

phosphorous-derived reagents, trifluoroacetate, hexafluoroacetone hydrate salts, and trifluoroacetaldehyde hydrates that can be employed as nucleophilic sources towards a variety of electrophiles, such as carbonyl compounds, thiocarbonyl compounds, halides, imines, hydrazones, nitrones, iminium salts, and azomethine imines.

2. The use of fluoroform (CF_3H) as nucleophilic trifluoromethylating agent

Fluoroform is a byproduct of Teflon manufacture, but if desired, it could be synthesized as a commodity chemical by fluorine/chlorine exchange of chloroform; a gas with a boiling point of −83 °C. However, until recently, it had attracted little interest as a synthetic fluorinated building block reagent, in spite of various reports by Shono, and Langlois since 1991 [5,6], which employed it for the nucleophilic trifluoromethylation of ketones. These earlier works set the stage for the recent series of important papers by Grushin, Prakash, and Shibata [7–9] where they have reported the use of fluoroform in a great variety of nucleophilic trifluoromethylation reactions with the intervention of metals or metalorganic species.

The reaction of fluoroform at room temperature with a deprotonating strong base, leads to rapid decomposition of the trifluoromethyl anion thus formed to a difluorocarbene intermediate. However, addition of 1 equiv. of CF_3H to ^{tert}BuOK in DMF in the presence of benzaldehyde (Barbier conditions) at −40 °C led to a mixture of the corresponding trifluoromethyl carbinol in 40% yield with 30% of benzoic acid, 22% of benzyl alcohol and 8% of remaining benzaldehyde as described in Eq. (1). When the same reaction was performed at room temperature as opposed to −40 °C, only the starting material was recovered [10].

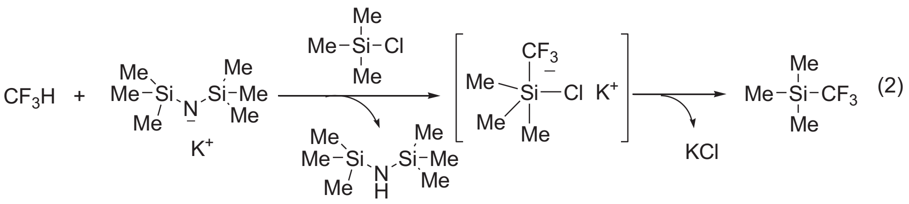


(1)

The reaction of fluoroform with metallated dimethyl sulfoxide (dimsyl-K) afforded 65% yield of the trifluoromethyl alcohol derived from benzaldehyde. The mechanism of the reaction could be explained by deprotonation of fluoroform by potassium dimsylate affording the trifluoromethyl anion which was trapped *in situ* by the carbonyl moiety of DMF solvent to form the *gem*-aminoalcoholate **1** (Scheme 1, step **A**). This intermediate is a *masked* and *stable* form of the trifluoromethyl anion at – 22 °C (a CF_3^- synthon), therefore avoiding the degradation of the carbenoid CF_3K [10].

The nucleophilic adduct between **A** (Scheme 1) and DMF (**1**, Scheme 1) reacts with benzaldehyde to afford the CF_3-alcohol.

Prakash and collaborators [8] have developed a protocol which generates and stabilises the CF_3^- anion to allow direct trifluoromethylation of a range of targets (Eq. (2)). The team initially showed that if CF_3H is dissolved in toluene with potassium hexamethyldisilazide as a stabilizing base, this allows the direct introduction of the CF_3 group into trimethylsilyl chloride (Eq. (2)). Building on this success, the researchers showed that careful optimization of solvent and reaction conditions enables CF_3H to trifluoromethylate a wide range of silicon, boron, sulfur and carbon-based compounds. Besides, the synthesis of the Ruppert reagent, Me_3SiCF_3 (*vide infra*), can easily be prepared from CF_3H as starting material (Eq. (2)) [8].



(2)

Luo and Qu have very recently uncovered [11] the origin of the remarkable effects of alkali metal salts of hexamethyldisilazane in the reaction of fluoroform with electrophiles. The detailed mechanism of trifluoromethylation of Si and C centers in the presence of $(Me_3Si)_2NK$ as a base has been studied using the DFT methods. The authors [11] found that the origin of the so pronounced an effect of the alkali metals is related to the stability