Tetrahedron 71 (2015) 7949–7976

Contents lists available at ScienceDirect

Tetrahedron

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

Tetrahedron report number 1091

An overview of reductive trifluoromethylation reactions using electrophilic ‘$^+CF_3$’ reagents

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A R T I C L E I N F O

Article history:
Received 20 April 2015
Available online 20 June 2015

Keywords:
Trifluoromethylation
Reduction
Single electron transfer
Radical
Electrophilic ‘$^+CF_3$’ reagents

Contents

1. Introduction

The era of fluorine chemistry began with the synthesis and successful isolation of elemental fluorine (F_2) by Henri Moissan in 1886.[1] Within more than a century’s development, especially in the past few decades, a large number of effective approaches for the introduction of fluorine atoms into widely used synthetic frameworks have been extensively exploited.[1,2] Fluorine has the strongest electronegativity (4.0 in Pauling scale) and a small atomic size (r_v=1.47 Å).[1] The C–F bond formed between fluorine and carbon is slightly longer than the C–H bond, but the bond energy of the former is much higher than that of the latter.[3] Fluorine is more similar to oxygen than to hydrogen in terms of electronic properties;[1,3] it can be used as a functional bioisostere of oxygen.[1a,4a] These unique ‘fluorine effects’ render enhanced biological activities of fluorinated bioactive molecules and fabulous physicochemical properties of fluorine-containing materials.[1]

Among fluorine-containing functional groups, the trifluoromethyl moiety (CF_3) is one of the most prevalent groups in

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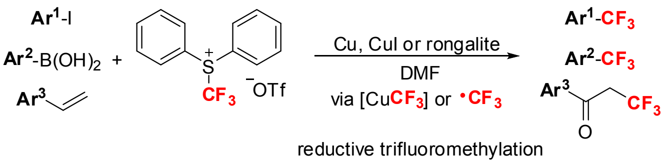
http://dx.doi.org/10.1016/j.tet.2015.06.056

design of new pharmaceuticals and agrochemicals because its incorporation into drug candidates can dramatically change their metabolic stability, lipophilicity, bioavailability, and the protein bind affinity.[1] The CF_3 group is an electron-withdrawing group and has a significant influence on the p*K*a values of the neighboring functional groups, such as alcohols, carboxylic acids, and amines, which result in 'special' properties.[1,4a] Despite fluorine is the most abundant halogen and ranks the 13th most abundant element in the earth's crust, there are no naturally occurring CF_3-substituted compounds and all the target CF_3-containing compounds are without exception artificially synthesized. Therefore, the development of efficient methods to introduce CF_3 group into organic scaffolds has become one of the hottest topics in organic synthesis today.[2,4,5]

The direct trifluoromethylation reactions have been confirmed to be the most important and promising methods to construct $C{-}CF_3$ bonds among the widely used approaches.[1,2,4,5] Traditionally, the direct trifluoromethylation includes the reactions of electrophiles with nucleophilic CF_3 reagents, nucleophiles with electrophilic CF_3 species, and radical acceptors with CF_3 radical precursors. It is remarkable that the direct trifluoromethylation of nucleophiles with nucleophilic CF_3 reagents and electrophiles with electrophilic CF_3 sources have also been accomplished. The reactions proceed through oxidative-trifluoromethylation mechanism[5g] and reductive-trifluoromethylation pathways,[6] respectively. The early examples of reductive trifluoromethylation showed that electrophiles, such as disulfides and aldehydes, can be readily trifluoromethylated by CF_3X (X=I, Br) or $PhSO_2CF_3$ in the presence of reductants like Na, Mg, Zn, and TDAE ([tetrakis(dimethylamino) ethylene]).[6] Although the nomenclature of reductive trifluoromethylation is known,[6] to our knowledge, its definition has never been made. To differentiate these transformations from other types of reactions, we tentatively propose a conceptual model of reductive trifluoromethylation in this report: electrophiles or nucleophiles are trifluoromethylated by CF_3 reagents in the presence of reductants, wherein the reactions start with the reduction of CF_3 sources.

The first metal-mediated reductive trifluoromethylation with electrophilic '$^+CF_3$' reagent was reported in 2011.[7] The reaction of aryl iodides (electrophiles) with electrophilic $[Ph_2SCF_3][OTf]$ salt in the presence of copper powder gave the corresponding trifluoromethylated products in almost quantitative yields; the $CuCF_3$ intermediate was determined in the reaction by ^{19}F NMR and mass spectrometric analysis of the reaction mixture.[7a] Later, Cu(I)-mediated reductive trifluoromethylation of arylboronic acids (nucleophiles) with $[Ph_2SCF_3][OTf]$ was performed, and the $CuCF_3$ species was observed similarly.[8a] The rongalite-initiated bifunctional trifluoromethylation of styrenes (nucleophiles) with $[Ph_2SCF_3][OTf]$ was harnessed, as well, and the CF_3 radical intermediate was captured by styrenes.[9] Since then, more trifluoromethylation reactions involving reductive transformation of electrophilic '$^+CF_3$' reagents have been reported.



In this review, we summarize the rapid progress of the reductive trifluoromethylation reactions with electrophilic '$^+CF_3$' reagents in the past few years, in which either electrophiles or nucleophiles are trifluoromethylated by '$^+CF_3$' sources in the presence of proper reductants. The reactions should involve CF_3 radicals, CF_3 anions or related intermediates, which are derived from the reduction of '$^+CF_3$' reagents by transition-metals, inorganic salts, photoredox catalysts or even substrates via single electron transfer processes. The reduction of '$^+CF_3$' sources is the initial step that triggers the entire reaction. Although numerous mechanistic discussions and debates have been commenced, the whole mechanisms of the reductive trifluoromethylation with '$^+CF_3$' reagents are still unclear (see Sections 2 and 3).

Our report will mainly focus on the transition-metal mediated/catalyzed trifluoromethylation of electrophiles/nucleophiles with electrophilic '$^+CF_3$' sources, which comprises CF_3 radicals or metal-CF_3 species, or undergoes other reductive transformation of '$^+CF_3$' reagents. The reactions of perfluoroalkyl halides ($R_{fn}X$, e.g., CF_3I) with reductants (such as $Na_2S_2O_4$ and Zn) and radical initiators (like Bz_2O_2 (benzoyl peroxide) and AIBN (azobisisobutyronitrile)), which give, respectively, the sulfinatodehalogenated products, the hydrodehalogenated products, the homo-coupling products, and the perfluoroalkylated products via radical or nucleophilic processes,[4b,10] represent a broader concept of reductive perfluoroalkylation reactions and will not be included in this report. We simply classify reductive trifluoromethylation reactions with electrophilic '$^+CF_3$' reagents, according to the type of CF_3 reagents, into two parts (see Sections 2 and 3). In each part, the debates related to the transformations are also described.

2. Reductive trifluoromethylation reactions with Umemoto's reagents and their analogs

2.1. Electrophilic Umemoto's reagents and their analogs

Because of the strong electronegativities of R_{fn} groups (e.g., CF_3: 3.45 in Pauling scale), $R_{fn}X$ (R_{fn}=perfluoroalkyl, X=I, Br, Cl) and even $R_{fn}OTf$ ($OTf{=}OSO_2CF_3$) do not undergo electrophilic perfluoroalkylation; the nucleophiles attack the halogen atoms (X) of $R_{fn}X$ or the sulfur center of OTf group rather than the R_{fn} groups.[11a-b] Significantly, in the 1970s and 1980s Yagupolskii and co-workers synthesized (perfluoroalkyl)-aryliodonium salts and (perfluoroalkyl)chalcogen salts (including '$^+CF_3$' salts), and found that these compounds can be used as electrophilic perfluoroalkylation reagents.[11c–e] Since this pioneering work, the design and synthesis of novel electrophilic '$^+CF_3$' reagents have been widely investigated (Scheme 1).[11a,b] *S*-(trifluoromethyl)dibenzothiophenium tetrafluoroborate and triflate (Umemoto's reagent, **1b**–**c**) and *S*-(Trifluoromethyl)diarylsulfonium triflate (Umemoto-Shreeve reagent, **1d**), developed by Umemoto, Shreeve, and so on, are the most widely used chalcogenium salts for effective electrophilic trifluoromethylation of a wide range of nucleophiles.[1,2,4,5,11,12] *S*-(Trifluoromethyl)thiophenium salts (expanded Yagupolskii-Umemoto-type reagents or Shibata's reagents, **1e**), prepared from triflic acid-catalyzed intramolecular cyclization of *o*-ethynylaryl-trifluoromethylsulfanes, have also demonstrated to be promising trifluoromethylation reagents for *β*-ketoesters and dicyanoalkylidenes.[13]

The Umemoto's reagent (**1b**) was initially described as a pure electrophilic '$^+CF_3$' source since it could form $CF_3SO_3CF_3$ (**2**) in high yield by pyrolysis (Scheme 2).[14] However, in the same article, the authors recognized that the reaction may occur via a bimolecular ionic substitution and/or a free radical chain mechanism, which is dependent upon the nature of the nucleophiles.[14] The kinetic study later disclosed that the cyclic Umemoto's reagent (**1b**) has higher reactivity than the non-cyclic Umemoto-Shreeve reagent (**1d**).[15] The critical difference in chemoselectivity of reactions between *S*-(methyl)dibenzothiophenium salt (**6**) and **1b** with aniline (N-methylation vs C-trifluoromethylation, Scheme 3) was indicative of a mechanism different from a classical S_N2 process, despite their respective CH_3 and CF_3 groups adopting similar orientations in the crystal structures.[15,16a] The Mulliken population analysis of *S*-(trifluoromethyl)dibenzothiophenium cation (**8**) indicated a positive