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Digest paper

Recent advance in radical fluoroalkylation with sulfinate salts

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ABSTRACT

In the last few years, the incorporation of a fluoroalkyl moiety into an organic molecule has been extensively studied. Especially, radical fluoroalkylation, involving the formation of C—C and C—heteroatom bonds, presents its valuable synthetic potential to achieve fluoroalkylated compounds. This digest paper highlights recent progress on fluoroalkylation with sulfinate salts, and focuses on radical tri-/di-/monofluoromethylation during the last five years.

Contents

Introduction

The incorporation of a fluorine atom or fluorinated group into a parent molecule has a profound effect on its biological, chemical, and physical properties.[1] As a result, >20% of the current approved drugs contain one or more fluorine atoms.[1] Despite the abundance of fluorine in the Earth's crust (13th most abundant element), natural fluorinated molecules are quite scarce. Until now, access to organofluorine compounds by chemical synthesis has become the dominant way though some natural and bioengineered enzymes have been identified for fluorine incorporation.[2,3] A series of comprehensive reviews on introduction of fluorine atoms or fluorine-containing groups have been published recently.[3]

In recent years, the development of efficient and practical protocols for direct introducing fluoroalkyl (R_f) moieties has turned

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into a considerable research focus for synthetic chemists.[3] Especially, many efforts have been focused on the radical fluoroalkylation for construction of C—C and C—heteroatom bonds.[3,4]

Sodium triflinate (CF_3SO_2Na), as an extensively used CF_3 radical precursor, was first developed by Langlois and co-workers in 1991.[5] Comparing with $TMSCF_3$ and Togni's reagent, CF_3SO_2Na (Langlois reagent) is more inexpensive and easily stored. A few years ago, zinc sulfinates $(R_fSO_2)_2Zn$, developed by Baran group,[6] were also used as the fluoroalkyl radical sources. Very recently, a practical and scalable protocol for preparation of sodium sulfinates R_fSO_2Na ($R_f = CF_2H$, CF_2Ph, and CH_2F) was developed by Hu's group,[7] providing the opportunity for further development of novel radical fluoroalkylation reactions. In this review, we summarize the recent advances on radical-mediated fluoroalkylation with sulfinate salts and wish to provide a synthetic perspective for organic chemists.

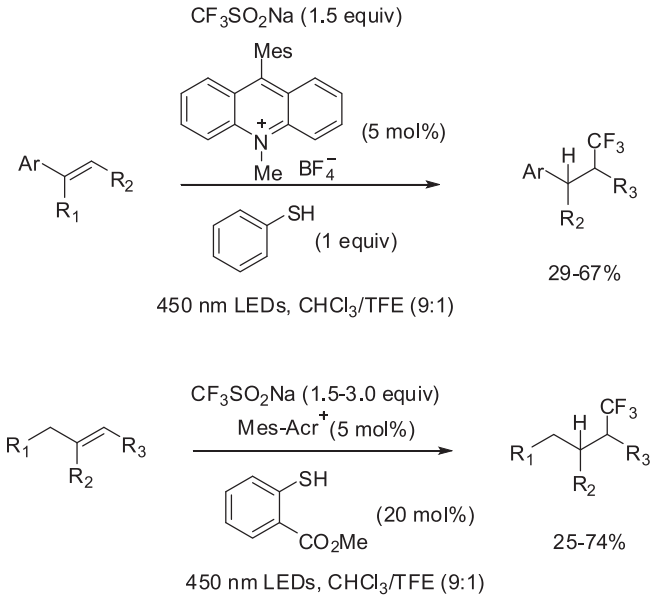
Fluoroalkylation via radical addition

Alkene/alkyne fluoroalkylation

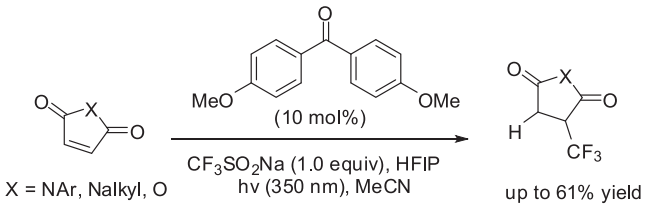
Hydrotrifluoromethylation

Pioneering study describing the hydrotrifluoromethylation of alkenes with CF_3SO_2K was reported by Tommasino et al. in 2002.[8] The work demonstrated that the trifluoromethylated aliphatic compounds could be obtained by electrochemical oxidation albeit with low chemoselectivity. Subsequently, a series of trifluoromethylation reactions involving unstable radical intermediate $CF_3SO_2^{\cdot}$ have been investigated. As a result, the direct single electron oxidation of the inexpensive Langlois reagent to generate a CF_3 radical could be an ideal strategy.

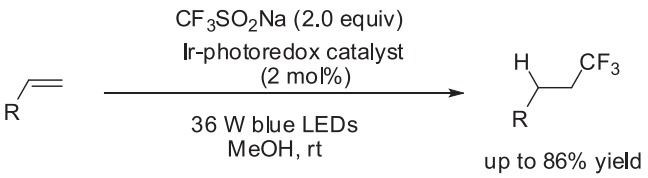
Photocatalytic radical fluoroalkylation provides a more sustainable and convenient alternative to the classical methods. The mild photoredox reaction conditions could tolerate a variety of functional groups, which shows the potential for late-stage modification of complex and bioactive molecules. In 2013, Nicewicz and co-workers reported a metal-free photoredox method for the hydrotrifluoromethylation of styrenes and unactivated aliphatic alkenes at room temperature (Scheme 1).[9] The commercially available and low cost Langlois reagent (CF_3SO_2Na) was used as a CF_3 radical source and *N*-methyl-9-mesityl acridinium (Mes-Acr$^+$) as a photoredox catalyst. Thiophenol was employed as a hydrogen atom donor for styrenes while methyl thiosalicylate seems to be more suitable for unactivated substrates. The transformation has a broad substrate scope, giving the anti-Markovnikov "fluoroform" addition products with high regioselectivity for all mono-, di- and trisubstituted alkenes.



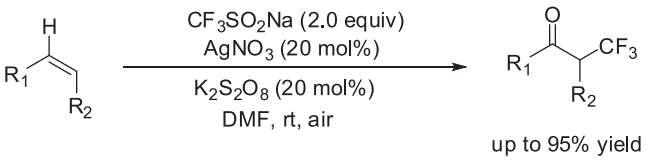
Scheme 1.



Scheme 2.



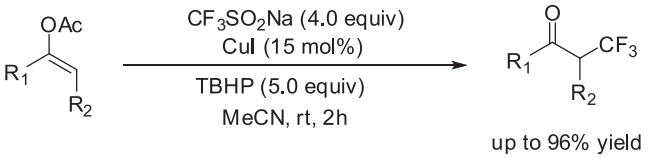
Scheme 3.



Scheme 4.

Although the CF_3 radical is widely accepted as electrophilic species, Rueping's hydrotrifluoromethylation of electron-poor olefins could be achieved using the Langlois reagent as CF_3 radical source and readily accessible benzophenone derivative as organic photocatalyst (Scheme 2).[10] The reactions were performed in a batch or flow process, providing the trifluoromethylated products in useful yields. The use of a photo-flow system resulted in much shorter reaction time, which shows the potential for rapid scale-up and in-line organic synthesis. In addition, the use of an iridium complex as photosensitizer was also able to initiate this radical reaction upon visible light irradiation. The mechanism studies showed that HFIP (hexafluoroisopropanol) acted as a proton donor and not as a hydrogen atom donor.

Zhu and co-workers developed an Ir-catalyzed photoredox process using methanol as a proton donor. The reaction was applied to various unactivated alkenes and Michael acceptors, providing corresponding hydrotrifluoromethylation products in good yields (Scheme 3).[11] This protocol is tolerant of a broad range of functional groups including ester, amide, ether, aldehyde, sulfone, ketone and aryl boronate, which displays potential for further application in medicinal and agrochemical research.



Scheme 5.