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A Study of Effects Unique Fluorine in Organic Reactions

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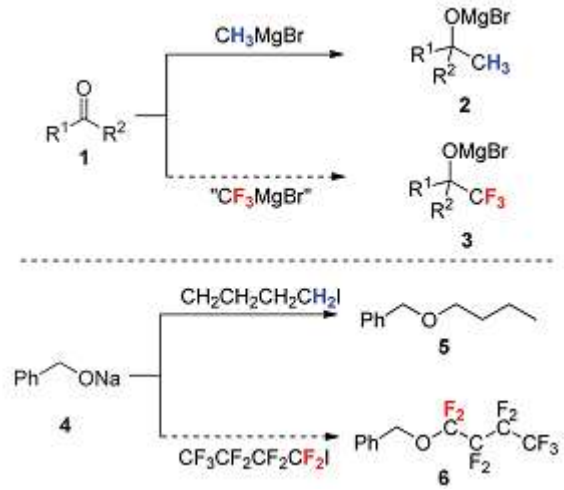
Abstract: *Fluor alkylation reaction, featuring the transfer of a fluoroalkyl group to a substrate, is a straightforward and efficient method for the synthesis of organ fluorine compounds. In fluoroalkylation reactions, fluorine substitution can dramatically influence the chemical outcome. On the one hand, the chemistry of alkylation with non-fluorinated reagents may not be applicable to fluoroalkylation, so it is necessary to tackle the fluorine effects to achieve efficient fluoroalkylation reactions. On the other hand, fluorine substitution may bring about new reactivity's and transformations that cannot be realized in alkylation with non-fluorinated reagents; thus, fluorine substitution can be used to explore new synthetic methods. This tutorial review provides a brief overview of the unique fluorine effects in recently developed nucleophilic, electrophilic, radical, and transition metal-mediated fluoroalkylation reactions by comparing with either their non-fluorinated counterparts or fluorinated counterparts with different numbers of fluorine substituents.*

Keywords: Fluor alkylation, reaction, influence, chemical, effects, fluorine, organic.

Introduction:

Nowadays, one of the major efforts of chemists in both academia and industry is the search for ‘‘special effect’’ chemicals with new structures and functions. In this context, fluorine is undoubtedly one of the elements that has attracted the highest recent research interest in several aspects of chemistry, since the judicious incorporation of the fluorine atom or the fluorinated moiety into organic compounds or polymers has become a powerful tool to discover new chemical entities possessing unique physical, chemical and/or biological properties. For instance, fluorinated materials have been widely used in liquid crystal displays of smart phones and in photovoltaic solar cells. 18F-labeled molecules are essential radiotracers for positron emission tomography (PET), which serves as a privileged diagnostic tool for cancers and other diseases. Polyfluorinated (fluorous) molecules are used in 19F magnetic resonance imaging (MRI) thanks to the high sensitivity of 19F nuclei in nuclear magnetic resonance (NMR) measurements. The highest impact of fluorine in life sciences is associated with the development of agrochemicals and pharmaceuticals. Recently, it has been estimated that about 30% of new approved drugs (excluding biopharmaceutical products) contained fluorine atoms or fluoroalkyl groups. The fact that fluorinated organic compounds and materials often show unusual physical, chemical, and/or biological properties and behaviour (in comparison with their non-fluorinated counterparts) is often called ‘‘fluorine effects’’ or ‘‘fluorine magic’’.

Review of literature: The profound effect of fluorine substitution on the chemical reactivity of organic compounds is an interesting research topic in organic chemistry. In this context, many fluoroalkylation reactions have been extensively studied over the past decade. Fluoroalkylation reactions, such as tri-, di-, and monofluoromethylations and other perfluoroalkylations and polyfluoroalkylations, represent one of the most straightforward and efficient methods for the incorporation of a fluoroalkyl group (such as CF3, CF2H, or CH2F group) into organic molecules. Traditionally, fluoroalkylation reactions can be divided into four categories: nucleophilic fluoroalkylation, electrophilic fluoroalkylation, radical fluoroalkylation, and transition metal-mediated fluoroalkylation. However, fluoroalkylation reactions are often surprisingly different from general alkylation reactions in organic chemistry, and the known knowledge of general alkylation chemistry cannot be simply used to predict the fluoroalkylation chemistry. Two typical examples are shown in Scheme 1. Firstly, Grignard reagent CH3MgBr can readily undergo nucleophilic addition to an aldehyde or ketone 1 to give product 2; however, a similar addition with CF3MgBr is very difficult, because CF3MgBr is highly unstable and readily decomposes to difluorocarbene (:CF2) and magnesium bromofluoride. Secondly, Williamson ether synthesis between sodium alkoxide 4 and n-butyl iodide gives ether product 5 through an SN2 reaction pathway; however, a similar SN2 reaction between 4 and perfluorobutyl iodide cannot proceed to give ether product 6. This is because the perfluorobutyl group in n-C4F9I is more electronegative than iodine, and the polarisation is thus reversed and nucleophile 4 attacks iodine rather than the carbon atom of the perfluorobutyl group.



Scheme 1 Unique features of fluoroalkylation compared to general alkylation reactions

Therefore, the understanding of the unique fluorine effects in fluoroalkylation reactions not only facilitates the prediction, design, and further development of fluoroalkylation chemistry, but also provides deeper insights into the unique features of fluorine and its related science. In this tutorial review, we wish to highlight some fluoroalkylation reactions that have been developed recently, and discuss the unique fluorine effects involved in these ‘‘surprising’’ reactions. The examples selected here merely help to interpret the concept of this review; for recent developments in fluoroalkylation reactions, one can refer to some comprehensive reviews.

The unique fluorine effects in nucleophilic fluoroalkylation reactions: Nucleophilic fluoroalkylation features the transfer of a fluoroalkyl group to an electrophile, in which either a free fluorocarbanion, an equivalent of a

fluorocarbanion (i.e., a species that has a similar reactivity character to a fluorocarbanion, such as pentacoordinate silicon species), or a fluoroalkyl metal species (RfM, M = main group metals in most cases) is involved. Fluorine substitution can influence the generation, the thermodynamic stability, and the kinetic reactivity (including the desired nucleophilic fluoroalkylation, competitive decomposition and protonation) of a fluorinated carbanion, thus distinguishing nucleophilic fluoroalkylations from non-fluorinated transformations and their counterparts with different number of fluorine substituents. In terms of the kinetic reactivity of fluorocarbanion, the competitive decomposition, which tends to occur more easily as the number of fluorine substituents increases, always has a negative (unfavourable) influence on the desired nucleophilic fluoroalkylation reaction. Nevertheless, in some cases, the fluorine substitution can play a positive (favorable) role in nucleophilic fluoroalkylation by facilitating the generation and stabilizing the reaction intermediates. In this section, we mainly explain the influence of fluorine substitution on the reactivity of a/b-fluorocarbanions and the methods for tuning their nucleophilic fluoroalkylation reactivity by changing the counteractions, the neighboring substituents, the catalysts, the solvents, and so on.

Fluoroalkylation of epoxides with fluoroalkyl sulfonic: In 2006, a study of nucleophilic ring-opening fluoroalkylation of epoxides conducted by us summarized the influence of a-fluorine substitution on the chemical reactivities of various carbanions. Reactions with di- and monofluoro (phenylsulfonyl) methyllithium showed that a-fluorine substitution on the carbanion dramatically decreases the carbanion's reactivity towards epoxides (Scheme 2). From the product yields, the reactivity of fluorinated carbanions (Nu) toward propylene oxide decreases in the following orders: (1) for different fluorinated anions: (PhSO2)2CF_4 $PhSO_2CHF_4$ $PhSO_2CF_2$; (2) for different halogen-substituted anions: $PhSO_2CC_{l2}$ $PhSO_2CF_2$. This unfavourable (negative) influence of fluorine substitution on the reaction of the carbanions was described as the ''negative fluorine effect (NFE)''.

The NFE in many nucleophilic fluoroalkylations, including but not restricted to the above mentioned fluoroalkylation of epoxides, can be attributed to the following two aspects: (1) the low thermal stability of the fluorine-substituted carbanion caused by its high tendency to undergo a-elimination of a fluoride ion (or another leaving group such as $PhSO_2$); (2) its intrinsic low nucleophilicity towards a certain electrophile such as the epoxide caused by factors such as the unmatched hard/ soft nature. Although the NFE could not be used to summarize all reactivity aspects of a-fluorocarbanions in nucleophilic fluoroalkylation reactions, it is at least helpful to better understand many nucleophilic fluoroalkylation reactions. The knowledge of the NFE can be used to tune and improve a nucleophilic fluoroalkylation reaction in the following manners: (1) slightly changing the neighboring groups; (2) changing the metal countercations; (3) enhancing the reactivity of the electrophiles. For a detailed discussion on the nucleophilic fluoroalkylation of various organic compounds by tackling the NFE, the

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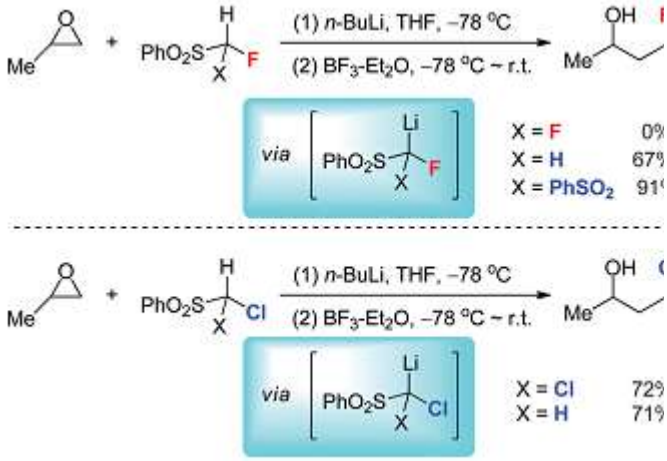
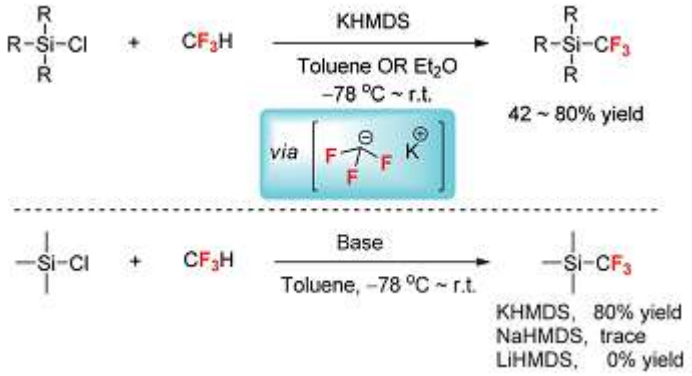
readers are recommended to refer to our previous reviews.



Scheme 2 Nucleophilic ring-opening fluoro- and chloromethylation of propylene oxide.

Direct trifluoromethylation with CF_3H: enhancing the reactivity by changing the metal–fluorine interaction: The metal–fluorine interaction can significantly influence the outcome of nucleophilic trifluoromethylation. Previously, fluoroform (CF_3H) was used for the trifluoromethylation of carbonyl compounds with a strong base in aprotic polar solvents. The in situ trapping of CF_3 by a solvent such as DMF to form an adduct is deemed to be important for stabilizing the labile trifluoromethyl anion, thus facilitating the nucleophilic trifluoromethylation. In 2012, Prakash et al. disclosed that the direct nucleophilic trifluoromethylation of silicon-, boron-, sulfur-, and carbon-centers with CF3H can be best performed in THF, ether, and toluene when potassium hexamethyldisilazide (KHMDS) was used as a base (Scheme 3). In this case, CF_3 generated from the deprotonation of CF3H undergoes nucleophilic trifluoromethylation rather than decomposition to the fluoride ion and singlet difluorocarbene. Indeed, CF3 with K+ /18-crown-6 as a countercation has been observed in a recent study.23 Control experiments demonstrated the importance of the countercation effect. Taking the reaction between CF3H and Me3SiCl in toluene for an example, the use of KHMDS gives Me3SiCF3 as a major product; in sharp contrast, sodium hexamethyldisilazide (NaHMDS) gives Me3SiCF3 as a minor product, whereas lithium hexamethyldisilazide (LiHMDS) cannot give the desired product. These observations show that the countercation K+ is important in stabilizing CF3 due to a weakened metal–fluorine interaction.



Scheme 3 Nucleophilic trifluoromethylation with CF_3H

The unique fluorine effects in electrophilic fluoroalkylation reactions: Despite the strong electron-withdrawing ability of fluorine atoms, the a-fluorine atom can stabilize carbocations through the interaction between the lone-pair electron of fluorine and the unoccupied p-orbital of the cationic carbon center. Studies have indicated that the stability of fluorinated carbocations decreases as follows: HCF2 + 4 CH_2F+4 CF_3+4 CH_3+. Although the fluorine effect is complex for CF_3+, this trend at least

shows that a-fluorine substitution is effective for stabilizing carbocations.4 However, in real electrophilic fluoroalkylation reactions, the fluoroalkylating agents are usually equivalents of fluorinated carbocations, rather than free fluorocarbocations. Thus, the electrophilic fluoroalkylations commence with the reaction of a nucleophilic centre (usually negatively charged) with an electrophilic fluorinated carbon centre, and conclude with the formation of a fluorinated sp3 -carbon centre. In this section, we will give a brief summary on the influence of fluorine substitution on the chemoselectivity and reaction mechanism of electrophilic fluoroalkylations.

The unique fluorine effects in radical fluoroalkylation reactions: Fluoroalkyl radicals, as very important reactive intermediates in organ fluorine chemistry, not only participate in fluoroalkyl addition to unsaturated systems, but also play roles in fluoroalkylation of nucleophiles (via single electron-transfer mechanism). A-Fluorination has a special effect on the structure and stabilization of methyl radicals. The trifluoromethyl radical is essentially tetrahedral, and difluoromethyl and monofluoromethyl radicals are pyramidal, while the methyl radical is planar.4 The kinetic analysis on the C–C bond homolytic cleavage of various fluorinated tert-butoxy radicals by Jiang et al. showed that the relative rate for the formation of methyl and fluoromethyl radicals decreases as follows: HCF2 (10.2) 4 CH2F (9.0) 4 CH3 (1.0) 4 CF3 (0.08).2,4 C–H bond dissociation energy calculations for fluorinated methanes also suggest that the thermodynamic stability of fluoromethyl radicals decreases in a similar order: CH2F4 HCF2 4 CH3 4 CF3. 2,4 These data indicate that both mono- and difluorination stabilize the methyl radical, whereas trifluorination destabilizes the radical. Calculations suggest that fluorine substitution destabilized the a-radicals inductively, but slightly stabilizes a-radicals through resonance; overall, the tetrahedral trifluoromethyl radical becomes the most unstable one among fluoromethyl radicals due to the diminished resonance stabilization. The reactivity of a fluoroalkyl radical can be divided into nucleophilicity and electrophilicity. On the one hand, due to the electron-donating resonance effect of lone-pair electrons on the a-fluoro substituent, all fluoromethyl radicals have lower ionization potential than CH3, with HCF2 being more nucleophilic than CH3; on the other hand, due to the strong inductive effect of the a-fluorine, CF3 is more electrophilic than CH3. 4,41 In radical fluoroalkylation with reagents of various forms, not only the stability and reactivity of the fluoroalkyl radicals, but also other factors such as the reduction potential and the stability of the fluoroalkyl radical precursors can influence the whole chemical outcome.

Conclusion: Incorporating fluorine atom(s) via fluoroalkylation has become a useful strategy in drug design and new functional material development. In fluoroalkylation reactions, the fluorine substitutions can dramatically influence the chemical outcome. As a result, the chemistry of alkylation with their non-fluorinated counterparts may not be applicable to fluoroalkylations. Therefore, tackling the unique fluorine effects is necessary to achieve desired fluoroalkylation reactions. On the other hand, the fluorine substitution can bring about new reactivity's and transformations that cannot be achieved in alkylation with non-fluorinated

reagents, thus fluorine substitution is also a tool to explore new synthetic methods. Fluorine effects are ubiquitous in fluoroalkylations, which are either negative or positive for the reactions. Understanding the unique fluorine effects in fluoroalkylation reactions not only facilitates the prediction, design, and further development of fluoroalkylation chemistry, but also provides deeper insights into unique features of fluorine and its related science. It is worthwhile to note that Cahard and Bizet12 also published a tutorial review on fluorine effects, concentrating on asymmetric synthesis using fluorinated substrates and fluorinated catalysts. Our Tutorial Review mainly discusses fluoroalkylation reactions, that is, the organic synthesis using fluorinated reagents. These two reviews complement each other, providing readers an opportunity to deeply understand the unique fluorine effects in organic chemistry.

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