Journal of Fluorine Chemistry 185 (2016) 1–16

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

Review

Aza-fluorocyclization of nitrogen-containing unsaturated compounds

Yurii A. Serguchev[a,*], Maxim V. Ponomarenko[b], Nikolai V. Ignat'ev[c,*]

[a] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 5 Murmanskaya, 04660 Kiev-94, Ukraine
[b] Life Sciences & Chemistry, Jacobs University Bremen gGmbH, Campus Ring 1, 28759 Bremen, Germany
[c] Dr. Ignatiev – Chemistry Consultancy, Duisburg, Germany

ARTICLE INFO

Article history:
Received 30 September 2015
Received in revised form 24 February 2016
Accepted 25 February 2016
Available online 27 February 2016

Keywords:
Aza-fluorocyclization
Electrophilic N–F reagents
Stereoselectivity

ABSTRACT

The aza-fluorocyclization of unsaturated nitrogen-containing compounds is reviewed. Syntheses of diverse fluorinated heterocycles by means of aza-fluorocyclization protocol are presented. The mechanism of the aza-fluorocyclization reactions, application of transition metals, and anionic phase-transfer catalysts are discussed. Advantages in the application of new strong electrophilic N–F reagents, including chiral $[N–F]^+$ compounds soluble in non-polar organic solvents, are presented. The reactivity of various N–F reagents is validated. The influence of the nature of transition metals catalysts, fluorinating reagents and solvents on the stereoselectivity of the fluorocyclization is discussed. The asymmetric fluorination by application of chiral organic oxidants and anionic phase-transfer catalysts is presented. Recent development dealing with the application of metal-catalysis in the syntheses of heterocyclic compounds by aza-fluorocyclization protocol is reviewed. The review covers the literature from 2011 to June 2015. References to some earlier publications are given to compare the results which are discussed.

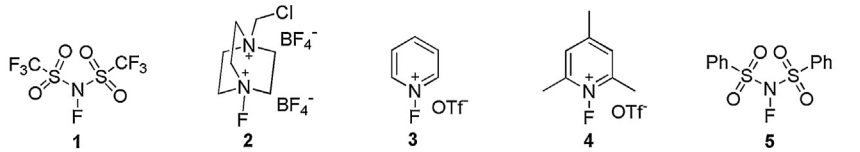
Contents

1. Introduction

The moiety of nitrogen-containing heterocycles can be found in the structure of many biologically and pharmacologically active compounds and in natural products [1]. The dominance of nitrogen containing pharmaceuticals relates to enhanced activity due to

* Corresponding authors.
E-mail addresses: serguch@gmail.com (Y.A. Serguchev), ignatiev@web.de, nikolai.ignatiev@external.merckgroup.com (N.V. Ignat'ev).

http://dx.doi.org/10.1016/j.jfluchem.2016.02.010
0022-1139/



Scheme 1. The redox potential as a measure of the relative reactivity in a series of N–F reagents.

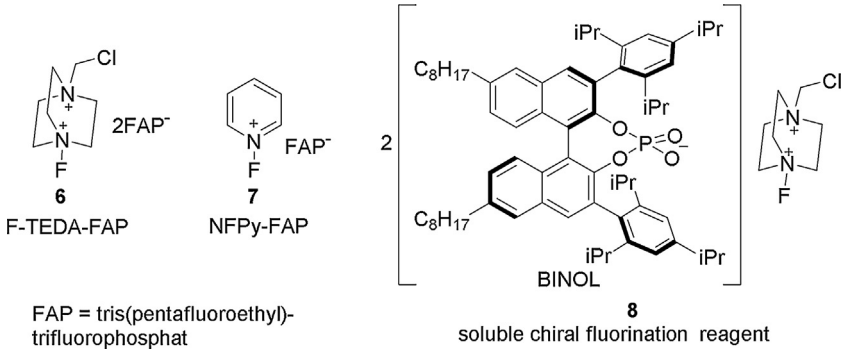
interaction with the biological target providing better bioavailability [2,3]. The replacement of hydrogen by fluorine in organic molecules frequently leads to dramatic changes in their properties, such as solubility, metabolic stability, and bioavailability [3,4]. The importance of fluoro-organic compounds is highlighted by statistic that about 35% of all modern agrochemicals and 20% pharmaceuticals incorporate at least one fluorine atom [4–6]. Known methods to access fluorinated nitrogen containing heterocycles are based on fluorination of heterocycles or via cyclization of fluorinated building blocks. Fluorocyclization of unsaturated nitrogen-containing compounds is another useful method towards fluorinated heterocycles. According to this protocol the fluorination and cyclization occur in one-pot procedure. This type of fluorocyclization is entitled as "aza-fluorocyclization" similar to well known aza-Prins [7], aza-Wacker [8] or aza-Nazarow [9] cyclizations. Recent progress in fluorocyclization methodology is stimulated by application of easy-to-handle electrophilic N–F reagents for selective syntheses of fluorinated carbocycles and heterocycles [10]. Contrary to electrophilic halocyclization [11,12], the aza-fluorocyclization of nitrogen-containing alkenes has some limitations. The common electrophilic N–F reagents exhibit low reactivity in aza-fluorocyclization reactions. Thus, only activated alkenes react under action of N–F reagents like 1-chlormethyl-4-fluor-1,4-diazoniabicyclo[2.2.2]octan-bistetrafluoroborate (F-TEDA-BF_4; trade name: Selectfluor®). However, Selectfluor® is able to fluorinate not only double bond but also reacts with primary and secondary amines affording —NF_2, —NHF, and >NF compounds [13]. Due to this reason, the fluorocyclization of unsaturated amines is complicated by competition in fluorination of the double bond and fluorination of amino group. To avoid this difficulties, the protection of amino group with electron-withdrawing substituents is required for effective aza-fluorocyclization of alkenes. Sulfonamides, carbamates, *N*-acylamides, etc., with enhanced N–H proton acidity, can be successfully involved into aza-fluorocyclization reactions. The aza-fluorocyclization of *N*-tosyl substituted aminoalkenes is the most-useful methodology to prepare fluorinated nitrogen-containing heterocycles. The problems and perspectives in catalytic asymmetric fluorination of organic compounds were highlighted in recent reviews by Yang et al. [14], asymmetric fluorocyclization of alkenes by Wolstenhulme and Gouverneur [15] and in mini-review written by Gulder and Gulder [16]. The actual review summarizes the recent progress in metal-free and metal-catalyzed aza-fluorocyclizations of alkenes and alkynes. The reactivity of diverse N–F reagents and transition metal catalysts promoting aza-fluorocyclizations of unsaturated compounds, as well as reaction mechanisms, are presented and discussed. Moreover, the review includes the enantionselective aza-fluorocyclization of alkenes under action of chiral cationic $[N–F]^+$ and $[N–F]^{2+}$ reagents and iodoarene difluorides.

2. Electrophilic fluorinating N–F reagents

Easy-to-handle electrophilic N–F compounds are extensively used as fluorinating reagents in various reactions [17], especially in fluorocyclization [10,15]. The reactivity of N–F reagents depends on their structure and correlates well with the electrochemical reduction potential (E_p^{red},*V*) [18] of these compounds (Scheme 1).

Various reaction's pathways by fluorination with N–F reagents are discussed in the literature. Electrophilic fluorocyclization of alkenes more likely proceeds via single-electron transfer (SET) mechanism. In the case of SET-mechanism the reduction potential (E_p^{red},*V*) of the N–F reagents is a good measure of their activity (Scheme 1).

Due to the limited solubility of cationic fluorinating $[N–F]^+$ and $[N–F]^{2+}$ reagents the reaction has to be carried out in polar solvents (acetonitrile, nitromethane, etc.) often at elevated temperatures. That is not favorable for the reaction's selectivity. Various N–F reagents have been used for the fluorination of activated alkenes. However, more potent N–F reagents or application of the catalysts are required to involve less reactive alkenes into fluorocylization reaction. Another possible way to increase the reactivity of $[N–F]^+$ reagents is improvement of their solubility in organic solvents. Several approaches have been proposed to develop the reagents possessing better solubility in common solvents. Shibata and co-workers [19,20] and Cahard et al. [21] reported chiral $[N–F]^+$ derivatives of *cinchona* alkaloids that are appreciably more reactive than neutral NFSI **5**. Due to better solubility in less polar media the



Scheme 2. Lipophilic $[N–F]^+$ reagents.