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A simple and efficient intramolecular 1,3-dipolar azidoalkyne cycloaddition: Synthesis of 6-perfluoroalkylated fused *exo*-bicyclic 1,2,3-triazolo-1,4-oxazines

Nejib Hussein Mekni[a,b,*]

[a] Department of Chemistry, Faculty of Science, Taibah University, P.O. Box 30002, Al-Madinah Al-Munawarah, Saudi Arabia
[b] Organic Structural Chemistry Laboratory, Synthesis and Physico-Chemical Studies, Chemistry Department, Faculty of Science of Tunis, University of Tunis El Manar, 2092 Tunis, Tunisia

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ABSTRACT

The synthesis of new 6-perfluoroalkylated 1,2,3-triazolo-1,4-oxazine ethers and thioethers as fused *exo*-heterobicyclic compounds was achieved from terminal perfluoroalkyl oxiranes by azide ion ring opening and propargylation reactions followed by a quick and spontaneous 1,3-dipolar intramolecular cycloaddition reaction.

1. Introduction

Organofluorinated compounds generally and fluoro-substituted heterocycles especially, are very interesting compounds [1,2]. They continue to play an increasingly important role in many areas as well as agrochemicals [3], surfactants [4], medical [5] and pharmaceutical products [6]. In particular, the perfluoroalkyl oxiranes are commodities in organic synthesis. They constitute the building block of some varieties of compounds having interesting applications as surfactants [7] and in polymer chemistry [8]. The development of efficient synthetic methods of perfluorinated heterocycles is of great importance because of their potential bioactive properties and commercial applications [9,10].

The 1,2,3-triazoles and 1,4-oxazines are heterocycles that are found in a large number of compounds [11,12]. Their applications have been reported in various areas [13]. Among them, the use of 1,2,3-triazoles as anti-HIV [14], anti-allergic [15], antibacterial [16], fungicides [17], herbicides [18], paints [19], corrosion inhibitors [20], pesticides [21] and agrochemical agents [22]. Oxazines derivatives have been the subject of great interest since the discovery of Efavirenz, a non-nucleoside inhibitor of reverse transcriptase used as selective anti-HIV drug [23].

The effectiveness and diversity of metal catalysts in the 1,3-dipolar azide-alkyne cycloaddition reaction [24], the most known one in the “click chemistry” [25], led to a large number of studies describing various applications of this reaction in organic synthesis [26], drug discovery [27], bioconjugation of polymer chemistry [28] and materials science field [26].

The intramolecular azide-alkyne reactions remain very limited compared to the intermolecular type [27,28]. The intramolecular reactions have focused on the synthesis of target molecules rather than a general systematic investigation of the potential and the applications in organic synthesis [27,29].

Observing the mechanism shown in Scheme 1, two possible bicyclic isomers can be formed depending on the number of bonds between the azide and alkyne groups. The azido-alkyne **I** can lead to either the *exo*-cyclic **II**, and/or the *endo*-cyclic **III** triazole or both of them [30]. The *exo*-cyclic isomer **II** is spontaneously more favored than the *endo*-cyclic isomer **III** due to geometrical constraints.

It is proven that the existence of a fluorine atom or fluoroalkyl group in an organic compound especially heterocyclic ones may have considerable effects on its physical, chemical and biological properties [31,32] compared to its hydrocarbon analog. Some perfluoroalkyl triazoles are synthesized via the intermolecular

* Corresponding author at: Department of Chemistry, Faculty of Science, Taibah University, P.O. Box 30002, Al-Madinah Al-Munawarah, Saudi Arabia.
E-mail address: n.mekni@gmail.com (N.H. Mekni).

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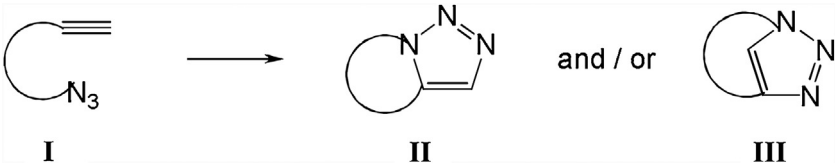


Scheme 1. *Exo*-cyclic and *endo*-cyclic products of the intramolecular azido-alkyne cycloaddition.

1,3-dipolar cycloaddition [33]. The compounds thus obtained have potential biological [34] and surface properties [35].

In a previous work, we have described the synthesis of a series of highly fluorinated heterocyclic compounds [36,37]. As continuation of this work, we decided to explore the synthesis of 6-perfluoroalkyl 1,2,3-triazolo-1,4-oxazines involving an intramolecular cycloaddition reaction. In this paper, we report on a simple synthetic route to polyfluoroalkylated fused heterobicycles, starting from perfluoroalkylated oxiranes [38] and proceeding via sequential regioselective epoxide opening by azide, *O*-propargylation and spontaneous 1,3-dipolar cycloaddition.

2. Results and discussion

The condensation of epichlorohydrin on perfluoroalkyl ethanols and perfluoroalkyl ethane thiols in the presence of tetrabutylammonium hydrogen sulfate as a phase transfer catalyst (PTC), provides access to corresponding fluoroalkyl terminal oxiranes **1** [38–40]. The regioselective nucleophilic oxirane ring opening is performed by azide ion action, yielding exclusively the perfluoroalkyl-azido-alcohols **2** (Scheme 2). Compounds **2** were prepared in satisfactory yields and the results are summarized in Table 1.

The following step consists in an *O*-propargylation by condensation of an excess of propargyl bromide on azido-alcohols **2**, using PTC in free-solvent conditions. The reaction produces the intermediate azido-alkyne ether **3** (Scheme 2). The latter cannot be isolated from the mixture, it undergoes an immediate transformation via a quick, spontaneous intramolecular 1,3-dipolar cycloaddition reaction, leading exclusively to the 6-perfluoroalkyl ether or thioethers 1,2,3-triazolo-1,4-oxazines fused *exo*-heterobicyclic compounds **4** in good yields (Table 1).

We have shown previously, that the presence of the perfluoroalkyl chain in organic molecules increases the reactivity of the azide group. They can react with n-butyl isocyanate, unreactive towards all other azides and lead to the 1-perfluoroalkyl-4-n-butyltetrazolin-5-ones [36].

Here, we found also that, the perfluoroalkyl chain have an increased effect on the rate of the intramolecular 1,3-dipolar cycloaddition reaction of the intermediates azido-alkyne ethers and thioethers **3** compared to their non fluorinated analogs [39]. Although the alkyne and azide groups are separated by the spacer CH_2-CH_2-Q-CH_2-CH- (Q = O, S) from fluorinated chain, its effect is remarkable, since the two successive reactions (condensation, then dipolar cycloaddition) are achieved in about one hour for ethers and in two hours for thioether compounds at moderate temperature (40 °C). This reaction time is almost the duration allowed to the condensation reaction of the propargyl bromide on non fluorinated alcohols and thiols [39,40]. We note also that the perfluoroalkyl-azido alkyne ethers are relatively more reactive than their homologous perfluoroalkyl-azido alkyne thioethers.

The flexibility of both azide and propargyl functional groups around their single bonds gives for the two reacting atomic orbitals a very great overlapping, which would facilitate the intramolecular cycloaddition, yielding the fused exo-heterobicyclic isomer composed of a stable six membered heterocyclic 1,4-oxazine ring, fused to the heteroaromatic 1,2,3-triazole five membered ring.

The formation of such compounds excluded all other possibilities of dimerization or polymerization, observed in the case of rigid azido-alkyne structures [41], even in the case of the cycloaddition in which the propargyl bromide was used in excess to azido alcohol.

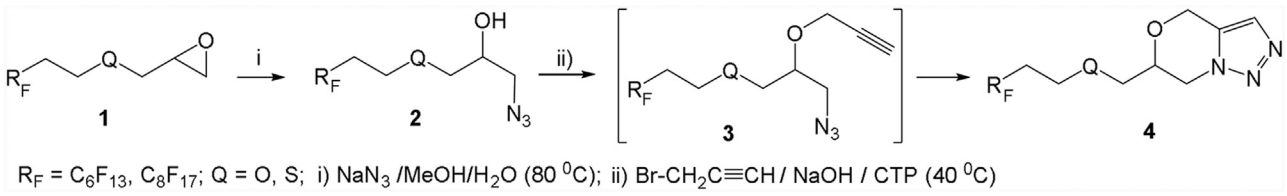
The identification of all compounds was carried out by IR and ^{1}H, ^{13}C and ^{19}F NMR, spectroscopy and confirmed by accurate measurement using HRMS. The ^{1}H NMR spectra of compounds **4a–d** are characterized by the presence of two deshielded signals, centered at 5.0 ppm and 4.3 ppm, attributed to *O*-CH_2-C=(*AB* system) and -CH_2-N (*AB* part of an *ABX* system) respectively, justifying the formation of the oxazine cycle with two non equivalent faces and having an asymmetric carbon atom (CH*,*X* part). The COSY proton NMR spectra of compounds **4a–d** show that the triazolic proton (7.50 ppm) interacts only with the two allylic protons (O-CH_2-C=) and confirms the formation of the *exo*-cyclic isomer **4** as the unique product [39].

3. Conclusion

The reaction reported herein is a contribution to the synthesis of organofluorinated compounds via intramolecular cycloaddition. The exclusive quick formation of the *exo*-cyclic 6-perfluoroalkyl-1,2,3-triazolo-1,4-oxazine isomers as azido-alkyne ethers and thioethers is in a nice agreement with the perfluoroalkyl chain effect on the reaction rate even it is relatively far from the functional groups. The new highly fluorinated fused *exo*-heterobicyclic compounds, synthesized in one step via a spontaneously and relatively quick intramolecular cycloaddition from simple reagents, may have interesting biological properties, since they represent a combination of three well-known biologically reactive groups (perfluoroalkyl chain [32], 1,2,3-triazole [13–22] and 1,4-oxazine [23]).

4. Experimental

IR spectra were recorded on PerkinElmer Paragon 1000 PC spectrometer. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a



Scheme 2. Synthesis of 6-perfluoroalkyl-1,2,3-triazolo-1,4-oxazines **4**.