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Reaction of imidazole derivatives with trifluoromethylated arylacetylenes

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ABSTRACT

The nucleophilic addition of imidazole derivatives to trifluoromethylated acetylenes was studied. Unpredictable regioselectivity of the reaction was observed to yield both β- and α-addition products. The reaction is 100% stereoselective to give the corresponding adducts as a *Z*-isomers only. The observed regioselectivity is discussed in terms of polarization of triple bond using experimental and calculated data.

1. Introduction

Imidazole is an important biological building block being presented in the amino acid histidine and possessing inherent catalyst and acid-base functionality. An imidazole ring is also a component of the biogenic amine histamine. It is interesting to note that the imidazole ring does not however appear in the most common H1 and H2 antagonists, presumably due to its metabolic vulnerability, with cimetidine (Tagamet®) being an exception. The use of such compounds has now been almost completely superseded by the prescription of alternative proton pump inhibitors such as esomeprazole (Nexium®) [1]. Benzimidazole is also a pharmacophore in medicinal chemistry. A lot of modern drugs have benzimidazole in the structure, Nexium is in top 10 drugs with sales in 2015 around USD 4.7 billion. On the other hand, *N*-vinylimidazole is important monomer for the preparation of various polymers having specific properties due to the presence of imidazole fragment (Scheme 1). Therefore, the search for new methods of functionalization of imidazole and benzimidazole, particularly *N*(1)-vinylation is considered as a challenge in organic synthesis.

First examples of addition of imidazole and benzimidazole to acetylene were published in 1969 [2]. The reaction demanded severe conditions (high pressure, activation with KOH (20–30%), heating at 160–180 °C) however, resulted in target *N*-vinyl imidazoles in high yields (77–86%). Allene can be also used for such vinylation (KOH-DMSO, 125–145 °C, 5–7 h) [3]. In similar conditions proceeds also the reaction of imidazoles with arylacetylenes, moreover the stereoselectivity can be controlled to give either *Z*- or *E*-isomers selectively in high yields (80–87%) [4]. Recently K_3PO_4-DMSO system (120 °C, 24 h) was proposed for *Z*-selective addition of imidazoles to arylacetylenes [5]. The addition of imidazoles to activated acetylenes proceeds much easier, prepared adducts can be used for subsequent synthesis of valuable condensed heterocycles [6].

On the other hand, organofluorine compounds are of a great importance for chemistry, biology, medicine, nanotechnology, and material science. Trifluoromethylated alkene fragment is a valuable structural unit, which is often presented in pharmaceuticals, agrochemicals, functionalized organic materials, etc. [7].

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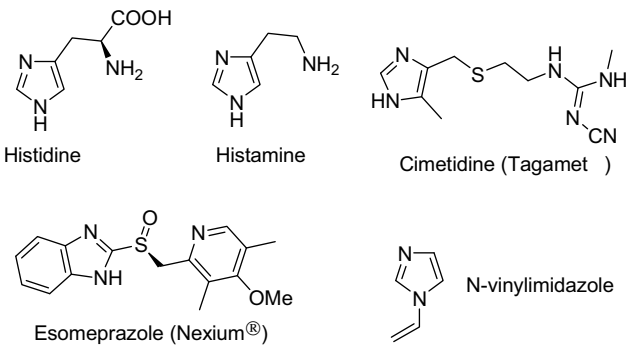

Scheme 1. Some practically important imidazole derivatives.

Therefore, nucleophilic addition of imidazole derivatives to trifluoromethylated acetylenes are of fundamental and practical interest. Very little is known about nucleophilic addition of imidazole derivatives to trifluoromethylated alkynes [8]. We have found in the literature that only two acetylenes bearing CF_3-group have been studied in this reaction. The addition of benzimidazole derivatives to symmetrical hexafluorobut-2-yne proceeds at room temperature without activator to form adducts with Z-selectivity (anti-addition) [9]. The same stereochemistry has been observed for the addition of imidazole to the trifluoromethylated acetylene having CH(Me)OCOMe [10] attached to the triple bond. The stereochemical result of the addition has been explained by the formation of thermodynamically favorable isomer [10].

2. Results and discussion

This work is devoted to the study of the reaction of some imidazoles and benzimidazoles **1** with trifluoromethylated arylacetylenes **2**. We found that imidazole (**1a**) (pKa in water 14.4 [11]) reacts with acetylenes **2** at room temperature in presence of 20 mol % KOH as a catalyst in acetonitrile during 24–72 h to give addition products in up to 86% yield (Tables 1). Surprisingly, we observed not only formation of expected β-adducts **3a–c**, in all cases products of α-addition of imidazole **4a–c** were also observed. Previously formation of similar α-products was observed by treatment of β-halo-β-trifluoromethylstyrenes with aliphatic secondary amines [12]. The ratio of these adducts depends on structure of starting acetylene to reach 95/5 ratio in the case of 4-methoxyphenyl substituted alkyne **2b**. Structures of prepared products were unambiguously determined using various spectroscopic NMR correlations (^{1}H, ^{13}C, ^{15}N, ^{19}F, 2D NOESY, COESY, HMBS, HSQC).

The reaction with more acidic benzimidazoles **1b**,**c** (benzimidazole pKa in water 12.8 [11]) demands heating (reflux in MeCN) during 14 h in the presence of KOH (20 mol% for **1b**, 30 mol% for **1c**) to form similarly two regioisomeric products **3d–h** and **4d–h** in up to 86% total yields (Table 1). Using DMSO as a solvent permits to perform the reaction under room temperature, however longer time is necessary to complete the reaction (24 h). For example, the reaction of benzimidazole **1b** with **2a** gives mixture of two regioisomeric products in 69% total yield (β:α ratio = 3:1). Most probably lower reactivity in this case can be explained by lower basicity and nucleophilicity of benzimidazole anion compared to deprotonated imidazole.

Very important is also the stereochemical result of the reaction. The reaction is 100% stereoselective and the corresponding alkenes (both α- and β-adducts) are isolated as *Z*-isomers only. Their structures were determined using 2D NOESY experiments. For example, characteristic cross-peaks between olefin proton and *ortho*-protons of aryl moiety were found. In the case of α-adducts **4,** additional cross-peaks with proton at C(2) of imidazole were observed. The observed stereochemistry for α- and β-adducts is in agreement with literature data [10].

The formation of α-adducts is very interesting from theoretical point of view because of CF_3-group is quite strong electron withdrawing group having 3.5 group electronegativity, therefore it is expected that triple bond in such acetylenes is polarized significantly. On the other hand steric effect can not be also underestimated. Conformation energies (A-values) of phenyl and trifluoromethyl are 3.0 and 2.1 kcal/mol respectively. Therefore, addition of nucleophile to adjacent to trifluoromethyl group position is more favorable from steric reason. Most probably unpredictable formation of adducts with attack of nucleophile to α-position of triple bond near trifluoromethyl group can be explained by interplay of electron and steric effects. Regioselectivity is higher in the case of acetylenes having most electron rich aryl group. To illustrate this observation we performed calculations of NPA charges (the natural population analysis) [13] at the DFT B3LYP/6-311G** level of theory (NBO 3.0 populations analysis have been carried out using Gaussian-09 package [14]) at the triple bond of acetylenes studied. It is known that calculated charges are often overestimated, however observed picture is in principle in agreement with experimental data. For all acetylenes Cβ-atom is positively charged. In the case of charge reaction control Cβ should be preferable place of attack of nucleophile. However, variation of charges at Cβ are not significant, these values do not correlate with observed regiochemistry.

The frontier-electron density theory of chemical reactivity by Fukui [15] explained the importance of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) in the chemical reactions. In a finite difference approximation, the f_k^+ values, governing for nucleophilic attack, for a system of *N* electrons are given by [16] as $f_k^+ = q_k(N+1) - q_k(N)$, where $q_k(N)$ is the total density on atom *k* for the system with *N* electrons. Based on the B3LYP/6-311G** NBO 3.0 populations analysis, the f_k^+ values obtained indicate that the Cα-atom is the most favorable center for the nucleophilic attack in all the series of trifluoromethylated acetylenes. Minimal $f_{C\alpha}^+$ in the case of methoxy group in the *para*-position and maximal ratio $f_{C\beta}^+/f_{C\alpha}^+$ are in good agreement with preferable formation of β-isomer. Nevertheless, there are no clear correlation between calculated Fukui indexes and observed regiochemistry. Most probably observed ratio of regioisomers is determined by interplay of all these factors.

Probably more important data can be obtained by comparison of observed chemical shifts of triple bond carbons in ^{13}C NMR. One can see that these data are in perfect agreement with observed selectivity and no very significant difference is observed for triple bond carbons chemical shifts of trifluoromethylated acetylenes (Table 2).

We calculated also thermodynamic characteristics of prepared products in CBS-QB3 approximation [17]. Possible reaction mechanism is given on Scheme 2. Most probably first step of the reaction (addition of azolyl anion to the triple bond) is equilibrium step. As a result only formation of *Z*-isomers is observed.

The calculated difference in Gibbs energies $\Delta G = 1.02$ kcal/mol predicts preferable formation of α-addition product in the case of the reaction of phenyl(trifluoromethyl)acetylenes with imidazole. However, if we compare Gibbs energies for carbanions intermediates in the same reaction, β-adduct will be more stable in the same reaction ($\Delta G = 1.87$ kcal/mol). Phenyl ring is conjugated with double bond in the case of β-attack carbanion (Fig. 1a). Contrary, in the case of α-addition of imidazole anion, both cycles have orthogonal arrangement to the plane Cα–Cβ–CF_3 (Fig. 1b).