Journal of Fluorine Chemistry 199 (2017) 77–91

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

Toward understanding regioselectivity and molecular mechanism in the synthesis of CF_2H-containing 2-pyrazolines: A molecular electron-density theory study

Saeedreza Emamian*

Chemistry Department, Shahrood Branch, Islamic Azad University, Shahrood, Iran

ARTICLE INFO

Keywords:
[3 + 2] cycloaddition reactions
Pyrazolines
Molecular electron density theory
Regioselectivity
Parr functions
ELF analysis

ABSTRACT

The domino process between a CF_2H-containing diazoalkane, **DAA 2**, and an electron-deficient alkene, **ANI 3**, in the presence of chloroform was theoretically studied at the DFT-MPWB1 K/6-311G(d,p) computational level. The initializing step in this domino process is associated with the C1 nucleophilic attack of **DAA 2** at the C4 carbon atom of **ANI 3** over the course of a polar *zw*-type 32CA reaction in an entirely C1-C4 regioselective manner to furnish corresponding 1-pyrazoline derivative **CA1n**. While a *stepwise* 1,3-H shift reaction assisted by an acetate anion and/or a thermal N_2 extrusion reaction can subsequently convert **CA1n** into corresponding 2-pyrazoline **PYZ 4** or cyclopropane **CP 5** derivatives, respectively, exploration of the relative Gibbs free energy profile evidently demonstrates that experimentally isolated **PYZ 4** is the only reachable product of the studied domino reaction. Analysis of the calculated nucleophilic and electrophilic Parr functions at the reactive sites of **DAA 2** and **ANI 3**, respectively, rationalizes the C1-C4 regioselectivity observed experimentally. An electron localization function (ELF) topological analysis of some selected points along the most favorable reactive channel involved in the initializing 32CA reaction allows establishing a non-concerted *two-stage one-step* molecular mechanism for the 32CA reaction of **DAA 2** toward **ANI 3**.

1. Introduction

Pyrazolines display diverse biological activities and play a key role in medicinal as well as agricultural chemistry. Due to extensive antimicrobial, anticancer, anti-tubercular, anti-inflammatory, antiviral, antitumor, and antiangiogenic functionalities, synthesis of pyrazolines has received much attention in recent years [1].

Incorporation of fluorinated substituents into bioactive molecules can noticeably affect their activities due to some distinctive properties of the fluorine atom [2]. For instance, fluorine atom as the most electronegative element can induce dramatic changes in acidity and basicity of neighboring functional groups. In addition, the replacement of a hydrogen atom by a fluorine atom alters the polarity of drug targets; *i.e.* the lipophilicity is decreased in the case of mono- and trifluoromethylation of alkanes while lipophilicity is increased in the case of aromatic fluorination and perfluorination. Moreover, fluorine can substantially affect the conformation of molecules due to inherent stereoelectronic preferences like the gauche effect [3].

Difluoromethyl group, $-CF_2H$, is widespread in agrochemistry and medicinal chemistry. This group exhibits unique physico-chemical properties. For example, since the C—F bond is metabolically stable, its introduction allows an isosteric replacement of metabolically sensitive C—H bonds to increase the stability of the drug candidate [3]. Furthermore, considering the high polarity of C—H bond, the $-CF_2H$ unit can be employed as a bioisostere of a carbinol moiety as well as a more lipophilic hydrogen bond donor [4]. Among fluoroalkyl-substituted pyrazolines some CF_2H-containing derivatives such as Deracoxib have received particular attention in the past years due to distinguishing biological activities [5].

One of the most well-known and powerful synthetic routes to construct fluoroalkyl-substituted pyrazolines in an atom-economic manner is to use [3 + 2] cycloaddition (32CA) reaction of *in situ* generated fluorinated diazoalkanes (DAAs) toward electron-deficient (ED) alkenes [6]. It is worthy to mention that the strong repulsion caused by lone-electron pairs of two adjacent sp^2 hybridized nitrogen atoms in 1-pyrazolines makes them generally unstable. Thus, either a 1,3-H shift reaction or a thermal N_2 extrusion process (depending on the reaction conditions and the nature of substituents present on DAA and ED-alkene skeletons) experienced at 1-pyrazolines leads to generation, respectively, the more stable 2-pyrazolines or cyclopropane derivatives (see Scheme 1) [7].

In a 32CA reaction, *as the main focus of current study*, a three-atom-

* Corresponding author.
E-mail addresses: s_emamian@iau-shahrood.ac.ir, saeedreza_em@yahoo.com.

http://dx.doi.org/10.1016/j.jfluchem.2017.05.004
Received 18 February 2017; Received in revised form 3 May 2017; Accepted 8 May 2017
Available online 09 May 2017
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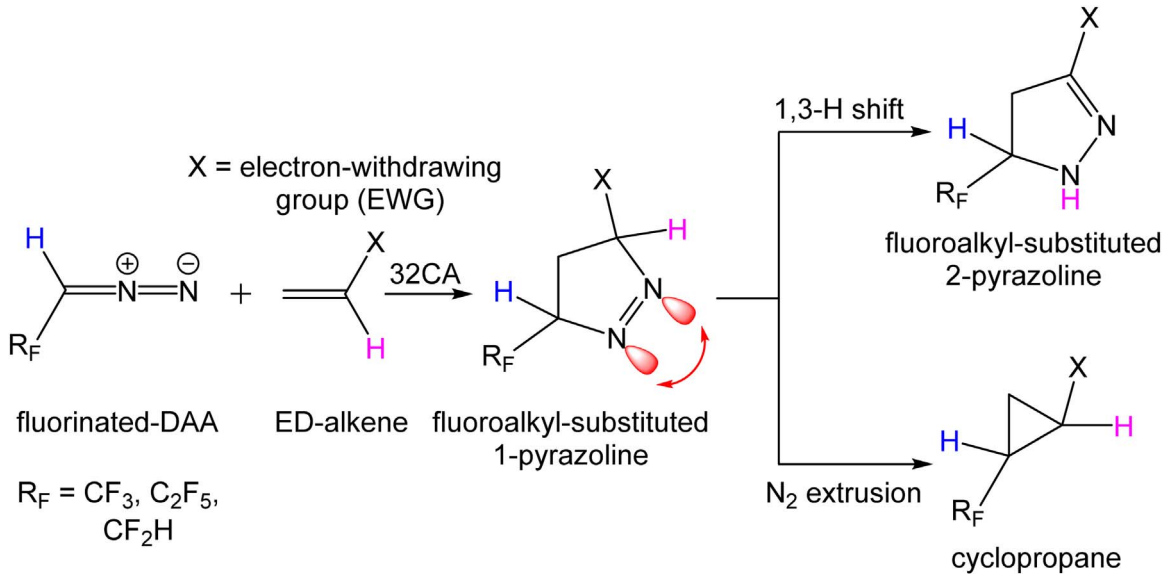
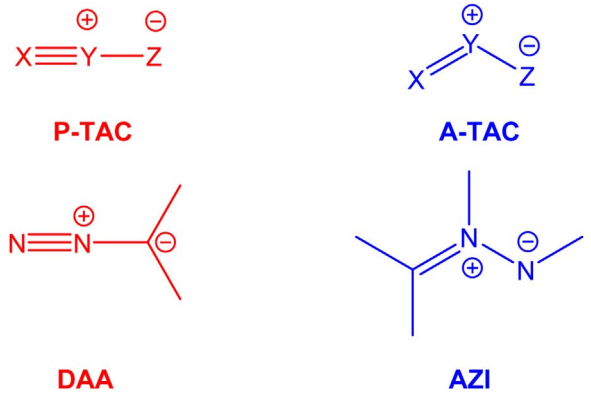


Scheme 1. Generation of fluoroalkyl-substituted 1-pyrazolines *via* 32CA reaction of a fluorinated DAA toward an ED-alkene and subsequent transformation to the corresponding 2-pyrazoline and cyclopropane derivatives through a 1,3-H shift and a thermal N_2 extrusion process, respectively.



Scheme 2. Geometrical representation of P-TACs (*e.g.* DAAs) and A-TACs (*e.g.* AZIs).

component (TAC) bearing 4π electrons delocalized over three continued atoms is attacked by an unsaturated bond to construct a five-membered heterocyclic compound in a highly selective fashion provided that both TAC and unsaturated bond frameworks to be electronically activated through substitution of proper functional groups [8]. It is worth mentioning that while most chemists traditionally prefer to use "13DC reaction" phrase to indicate participation of a "1,3-dipole" species in the reaction toward an unsaturated bond, the nature and electronic behavior of the involved species in this kind of cycloadditions can be portrayed in a more understandable and reasonable manner when "13DC reaction" and "1,3-dipole" phrases are replaced by [3 + 2] cycloaddition (32CA) reaction and three-atom-component (TAC), respectively [8][8b].Geometrically, TACs are classified as propargylic type (P-TAC), *e.g.* DAAs, and the allylic-type (A-TAC), *e.g.* azomethine imines (AZIs). As sketched in Scheme 2, P-TACs are characterized by a linear structure with an additional double bond between the X and Y atoms while A-TACs are bent with no mentioned additional bond [9].

Establishing a reliable relationship between the ground-state (GS) molecular electronic structures and reactivity is one of the most important and challenging issues in chemistry. Ess and Houk studied the reactivity of twelve TACs in 32CA reactions toward ethylene and acetylene through the distortion/interaction model (DIM) [10]. In the DIM, activation energy ($\Delta E^{\neq}$) is divided into two additive terms namely distortion energy ($\Delta E_d^{\neq}$) and interaction energy ($\Delta E_i^{\neq}$) resulting in a good linear correlation coefficient, R^2 = 0.97, between $\Delta E^{\neq}$ and $\Delta E_d^{\neq}$. It is worth noting that despite of such an acceptable correlation coefficient, the Ess and Houk's model should be revisited since it suffers from a conceptual defect. Indeed, taking density functional theory (DFT) into account, dividing the TS geometry into two separate fragments, as proposed by Ess and Houk, does not have any physical sense because the energy of a given system, such as a TS, not only is the functional of the electron-density distribution over the whole of the system but highly depends on the spatial position of nuclei. Consequently, the energy of the two separated fragments is not allowed to be correlated with the energy of the corresponding TS considering this very important fact that "*the external potential created by one fragment over the other one is lost when one of them is removed*" [11]. Thus, it is evident why the geometry dependence of activation energy cannot be rationalized *via* Ess and Houk's model [12].

A new reactivity model namely molecular electron-density theory (MEDT) has been proposed very recently by Domingo stating "*while the distribution of the electron-density is responsible for the molecular shape and physical properties, the capability for changes in electron-density and not the molecular orbital(MO) interactions is responsible for the reactivity*" [13]. Within MEDT, in addition to exploration and characterization of potential energy surface (PES) of the considered reaction, some very helpful theoretical approaches such as analysis of the conceptual density functional theory (CDFT) [14], quantum topological analysis of the electron localization function (ELF) [15], quantum theory of atoms in molecules (QTAIM) [16] analysis, and non-covalent interaction (NCI) [17] analysis are taken into account to rigorously study the molecular reactivity in organic reactions [18]. Several MEDT studies devoted to 32CA reactions have allowed to classify 32CA reactions in three different types considering the GS electronic nature of the involved TAC as: i) *pseudodiradical*-type (*pr*-type) [9]; ii) *carbenoid*-type (*cb*-type) [19]; and iii) *zwitterionic*-type [9] (*zw*-type) reactions. The *pr*-type 32CA reactions involve TACs with a high *pseudodiradical* character which easily take place *via* a very low polar and early transition state (TS) [9]. On the other hand, TACs with a carbenoid character contribute in *cb*-type 32CA reactions in which the nucleophilic character of carbenoid TAC together with the electrophilic character of unsaturated bond control the feasibility of reaction [19]. The *zw*-type 32CA reactions demand TACs with a high *zwitterionic* character in which, very similar to *cb*-type reactions, the electrophilic/nucleophilic interactions proceed the reaction [9]. Scheme 3 summarizes three types reactivity found in 32CA reactions in terms of the GS electronic structure of participating TACs derived from MEDT [13].