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## A theoretical study of the mechanism and selectivity of the intramolecular 1,3-dipolar cycloaddition reaction of the nitron–alkene derived from 2-allylthiobenzaldehyde for the synthesis of tricyclic isoxazolidines

Fouad Chafaa<sup>a</sup>, Djamila Hellel<sup>a</sup>, Abdelmalek Khorief Nacereddine<sup>a,b,\*</sup>, Abdelhafid Djerourou<sup>a</sup>

<sup>a</sup>Laboratoire de Synthèse et Biocatalyse Organique, Département de Chimie, Faculté des Sciences, Université Badji Mokhtar Annaba, BP 12, 23000 Annaba, Algeria

<sup>b</sup>Département de Physique et Chimie, Ecole Normale Supérieure d'Enseignement Technologique de Skikda, Cité des frères Boucetta, Azzaba, Skikda, Algeria

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### ABSTRACT

A computational study of the mechanism as well as the regio- and stereoselectivities of the intramolecular 1,3-dipolar cycloaddition (IMDC) of nitron–alkene **1**, derived from 2-allylthiobenzaldehyde, has been carried out using DFT methods at the MPWB1K/6-31G(d,p) level of theory. The four possible pathways, fused and bridged regioisomeric modes, and the two stereoisomeric approaches *endo* and *exo* for the IMDC reaction are analyzed and discussed. Analysis of the potential energy surface showed that this IMDC reaction kinetically favors formation of the isoxazolidine generated from the fused-endo pathway. The obtained results corroborate very well with the published experimental data. Analysis of TS geometries and bond order indicate that these IMDC reactions proceeded through a one-step synchronous mechanism for the fused modes and is asynchronous for the bridged modes.

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### Introduction

Over the past few decades, polyheterocyclic compounds have been extensively studied for their varied application in the fields of biology, material science, and supramolecular chemistry.<sup>1</sup> Many methods have been reported in the literature for the synthesis of these molecules, however short and efficient syntheses still remain a challenge for synthetic organic chemists. Existing methods require high dilution reaction conditions and long reaction times. The intramolecular 1,3-dipolar cycloaddition (IMDC) of nitron–alkene compounds is a versatile and efficient protocol for the stereo- and regioselective construction of complex heterocyclic architectures having both nitrogen and oxygen atoms in a five-membered unit.<sup>2</sup> The fused and bridged mode of the IMDC which afford fused or bridged isoxazolidines, respectively, are both key intermediates in the syntheses of natural products or analogues with biological importance.<sup>3</sup>

These reactions are characterized by high regioselectivity and stereoselectivity and are useful in organic synthesis. A tremendous amount of theoretical and experimental work devoted to the study

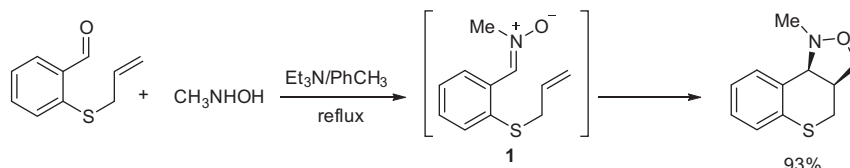
of the mechanism and selectivities of IMDC reactions can be found in the literature. Xiang theoretically studied,<sup>4</sup> through DFT methods, the regioselectivity of the IMDC reaction of various *N*-3-alkenyl nitrones and found that the position of the substituent played a major role in both the determination of selectivity and the reaction rate. Purushothaman et al.<sup>5</sup> have synthesized bicyclic pyrrolidine and pyrrolizidine grafted macrocycles through an IMDC reaction between azomethine ylides and dipolarophiles, of which the alkenyl-aldehydes derived from salicylaldehyde were reacted with secondary amino acids to generate azomethine ylides, which were trapped intramolecularly by suitable dipolarophiles to give the corresponding macrocycles in moderate yields.

Recently, Saubern et al.<sup>6</sup> reported the intramolecular cycloaddition of nitron–alkene **1**, generated in situ from the corresponding 2-(allylthio)benzaldehyde, for the synthesis of the corresponding tricyclic isoxazolidines. They found that this reaction exclusively gave a single cycloadduct originating from the fused-endo pathway (Scheme 1).

Our aim of the present letter was to undertake a computational investigation of the regio- and stereoselectivities observed experimentally by Saubern et al. in order to shed light on the factors that controlled the selectivity and influenced the mechanism of this IMDC reaction.

\* Corresponding author. Tel.: +213 778781313.

E-mail address: [malek\\_khorief@yahoo.com](mailto:malek_khorief@yahoo.com) (A.K. Nacereddine).



**Scheme 1.** Synthesis of tricyclic isoxazolidines from 2-(allylthio)benzaldehyde.

## Computational methods

DFT computations were carried out using the MPWB1K<sup>7</sup> exchange–correlation functional, together with the standard 6-31G(d,p) basis set.<sup>8</sup> The stationary points were characterized by frequency computations in order to verify that TSs only had one imaginary frequency (see ESI for details) Values of enthalpies, entropies and free energies in toluene were calculated using standard statistical thermodynamics at 383.15 K and 1 atm over the optimized gas phase structures<sup>9</sup> and have been scaled by 0.96.<sup>10</sup> The electronic structures of critical points were analyzed using the natural bond orbital (NBO) method.<sup>11</sup> Solvent effects of toluene were considered at the same level of theory by single-point calculations of the gas-phase structures using a self-consistent reaction field (SCRF)<sup>12</sup> based on the polarizable continuum model (PCM) reported by Tomasi.<sup>13</sup> All computations were carried out with the Gaussian 09 suite of programs.<sup>14</sup>

## Results and discussion

Previous theoretical studies have indicated that 1,3-dipolar cycloaddition reactions proceed through a concerted mechanism.<sup>15</sup> Therefore, in this letter we only considered the concerted mechanism for the IMDC reaction of nitronium–alkene **1**. Consequently, four TSs and the corresponding [3+2] cycloadducts (CAs) were located and characterized related to the possible regio- and stereoselective modes of cyclization. Thus, the studied IMDC reaction can take place via two regioisomeric pathways; the fused or bridged modes and two stereoisomeric approaches; *endo* or *exo* with respect to the nitrogen of the nitronium functional group. The *endo* approach corresponded to the cycloaddition of the (*E*)-nitronium, whereas, the *exo* approach corresponded to the (*Z*)-nitronium (see Scheme 2). Cartesian coordinates of the stationary points are summarized in the ESI.

Total and relative energies of the stationary points associated with the IMDC reaction of nitronium–alkene **1** are summarized in Table 1. The energy profiles of the four pathways corresponding

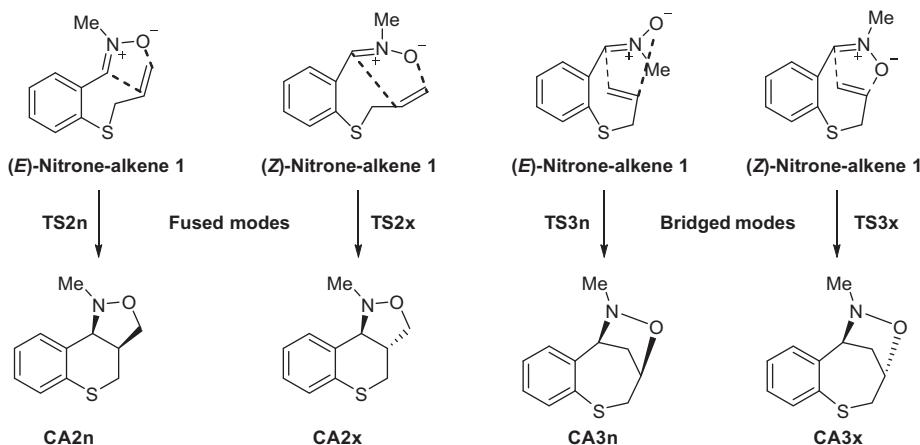
**Table 1**

Total energies (*E*, in a.u.) and relative energies<sup>a</sup> ( $\Delta E$ , in kcal/mol), in gas phase and in toluene, of the stationary points involved in the IMDC reaction of nitronium–alkene **1**

System	Gas phase		Toluene	
	<i>E</i>	$\Delta E$	<i>E</i>	$\Delta E$
( <i>E</i> )-nitronium–alkene <b>1</b>	–954.79862		–954.806899	
( <i>Z</i> )-nitronium–alkene <b>1</b>	–954.803103	–0.004		
<b>TS2n</b>	–954.77173	13.46	–954.781141	16.16
<b>TS2x</b>	–954.768171	19.11	–954.772813	21.39
<b>TS3n</b>	–954.74624	32.87	–954.750056	35.67
<b>TS3x</b>	–954.76557	20.74	–954.770499	22.84
<b>CA2n</b>	–954.86401	–41.03	–954.86742	–37.98
<b>CA2x</b>	–954.85826	–37.42	–954.862349	–34.79
<b>CA3n</b>	–954.85510	–35.44	–954.859069	–32.74
<b>CA3x</b>	–954.85508	–35.43	–954.859058	–32.73

<sup>a</sup> Relative to E(*E*)-nitronium–alkene.

to the fused/bridged regioisomeric paths and *endo/exo* stereoisomeric approaches are illustrated in Figure 1. The low difference between the energies of the (*Z*)-nitronium and that of the (*E*)-nitronium (0.004 kcal/mol) revealed that the condensation reaction of 2-(allylthio)benzaldehyde with *N*-methylhydroxylamine could lead to the formation of both geometric nitronium isomers. From Table 1, a comparison between the gas-phase activation energies associated with the four competitive reactive pathways of this IMDC reaction indicated that the fused modes (**TS2n** and **TS2x**) were more favorable than the bridged ones, while the fused-*endo* approach mode, giving **CA2n**, was more favorable than the fused-*exo* one by 5.65 kcal/mol, indicating that this IMDC reaction was completely *endo* stereoselective, allowing the formation of **CA2n** as the kinetically favored cycloadduct. These results were in clear agreement with the previous reported experimental data.<sup>6</sup> We also noted that the reaction was exothermic in the range between 35.43 and 41.03 kcal/mol. The exothermic character of this IMDC reaction makes the cycloaddition irreversible, therefore this IMDC reaction is only under kinetic control. On the other hand, the bridged regioisomeric pathways were less favored than the fused



**Scheme 2.** Possible IMDC pathways of nitronium–alkene **1**.

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