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Investigation on the effect of trifluoromethyl group on the [3+2] cycloadditions of thiocarbonyl S-methanides with α, β-unsaturated ketones: A theoretical study using DFT

Seyed Javad Hosseini*

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

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ABSTRACT

A [3+2] cycloaddition (32CA) reaction among a thiocarbonyl ylide (TCY 2) with (E)-4,4,4-trifluoro-4-phenylbut-3-en-2-one (TFB 4) as an electron-deficient enone in tetrahydrofuran (THF) were studied within the Molecular Electron Density Theory (MEDT), at the DFT-B3LYP/6-31G(d) computational level to analysis energetics, selectivities, and mechanistic aspects. The reaction can progress in four competitive 32CA reaction paths. An analysis of the density functional theory (DFT)-based reactivity indices shows that TCY 2 is a strong nucleophile and TFB 4 is a strong electrophile. Parr function analysis at the reactive sites of reagents demonstrates that the C1-C6 attack should be the more favorable regioselective channel in 32CA reaction of TCY 2 toward TFB 4. An exploration of computed relative Gibbs free energies implies that the studied 32CA reaction leads to thiolanes 4 as the unique cycloadduct, in complete agreement with the experimental outcomes. The global electron density transfer (GEDT) value at the energetically most preferred transition state TS 1 reveals that this *pseudoradical* type (*pdr-type*) 32CA reactions exhibits a notable polar character.

Keywords: Fluorinated enones; Thiocarbonyl ylides; Chemoselectivity; Regioselectivity; DFT study

1. INTRODUCTION

Heterocyclic compounds are found in large spectrum of biological active compounds including antifungal [1], anti-inflammatory [2], antibacterial [3], antioxidant [4], anticonvulsant [5], antiallergic [6], herbicidal activity [7] and anticancer activity [8]. Therefore, study on stereoselective synthesis approaches of heterocyclic compounds and their mechanistic aspects have been an interesting area of research for a long time. Among many reports in chemical literature, an efficient method for making five-membered heterocyclic compounds in a high stereoselective manner is [3+2] cycloaddition (32CA) reactions [9]. In a 32CA reaction a three-atom-component (TAC), counting four π-electrons

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*Corresponding author: javadhosseni@yahoo.com & jhosseini@iau-shahrood.ac.ir

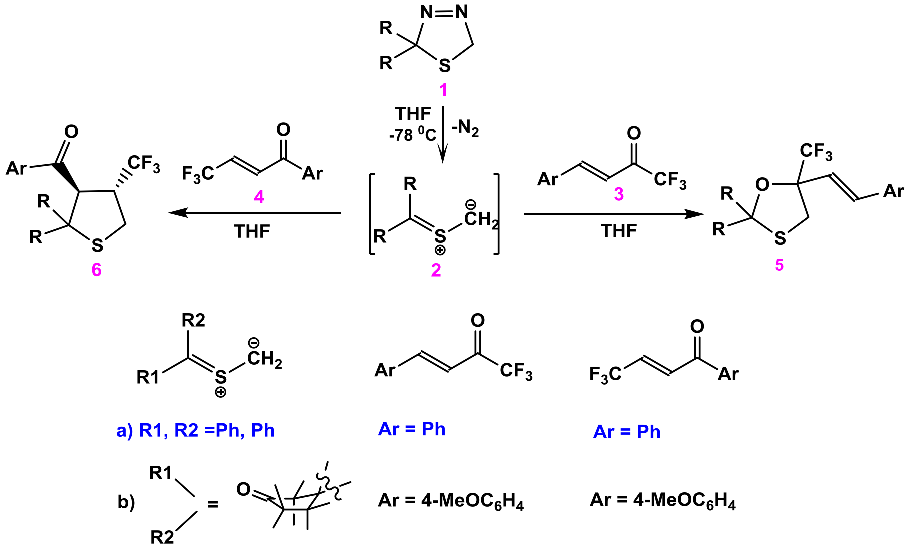
delocalized over three continued nuclei, interacts with an unsaturated bond to produce corresponding [3+2] cycloadduct [10].

Mloston and co-workers [11] have reported a chemoselective and regioselective 32CA reactions of thiocarbonyl S-methanides (2) with α, β-unsaturated ketones. as shown in Scheme 1, some fluoroalkylated enones (3 and 4) efficiently trap by *in situ* generated of 2 to form corresponding fluoroalkylated, 5-membered heterocycles (5 and 6) without formation of any side products. The CF3 group detemine regioselective of reaction so that linking CF3 group to each of the C=O framework or C=C framework, make it more reactive for interact with 2.

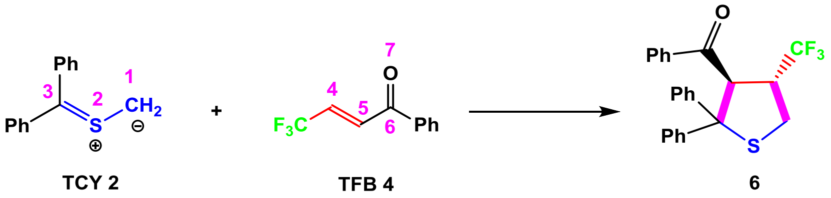
Very Recently [12], we theoretically investigated the reaction of diphenyl thiocarbonyl S-methanide as a thiocarbonyl ylide (TCY **2)** with enones **3**, providing corresponding experimentally isolated Heterocycles **5** (see Scheme 1). During this effort, the energetics, chemo- and regioselectivity and the mechanistic aspects of the reaction was studied based on a reactivity model namely molecular electron density theory (MEDT) [10] proposed by Domingo. Analysis of the conceptual density functional theory (CDFT) reactivity indices and consideration of barrier energy in competitive reaction paths approved formation of oxathiolanes **5** as the sole product, in excellent agreement with the experimental findings.

Detailed and comprehensive description on the meaning and concept of MEDT, and several theoretical tools using by MEDT to characterize the molecular mechanism of the studied reactions can be found in references 10, 12- 14.

In the present work, as displayed in Scheme 2, the reaction between TCY **2**, with (E)-4,4,4-trifluoro-4-phenylbut-3-en-2-one, TFB **4**, as another part of experimentally research reported by Mloston and co-workers [11] providing isolated thiolanes **6** (entry a in Scheme 1) is theoretically studied at the DFT-B3LYP/6-31G(d) computational level to probe the energetics, explanation of observed chemo- and regioselectivity as well as the mechanistic aspects.



Scheme 1. Synthetic route employed by Mloston and co-workers [11] to generate fluoroalkylated, **5** and **6** respectively, *via* a regioselective 32CA reaction of *in situ* generated **2** with fluoroalkylated enones **3** and **4** respectively.



Scheme 2. Computational model considered for the reaction of TCY **2**, with TFB **4**.

2. COMPUTATIONAL DETAILS

All the reactants, intermediates, the transition states and products was optimized at B3LYP DFT-functional [15] conjugated with 6-31G(d) basis set [16]. The effects of acetonitrile as solvent were simulated by means of the Marenich, Cramer, and Truhlar's SMD solvation model [17] in the basis of the self-consistent reaction field (SCRF) [18]. Using the second-order González-Schlegel integration method [19, 20], the intrinsic reaction coordinate (IRC) paths [21] were traced in both forward and reverse directions to confirm that located TSs truly connect two associated minima.

The electronic chemical potential, μ, and the chemical hardness, η, are calculated by the following expression, $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L - \varepsilon_H)$, respectively [22] based on the HOMO energies (ε_H) and LUMO energies (ε_L). The global electrophilicity index ω [23] is obtained by the expression $\omega = \mu^2/2\eta$. The global nucleophilicity index N [24], based on the HOMO energies taken from the Kohn-Sham scheme [25], is represented as $N = \varepsilon_H(\mathrm{Nu}) - \varepsilon_H(\mathrm{TCE})$, in which Nu denotes the given nucleophilic species. This relative nucleophilicity index refers to tetracyanoethylene (TCE) since it presents the lowest HOMO energy in a long series of molecules already studied in the context of polar organic reactions, thus handling an always positive nucleophilicity index. Nucleophilic P_k^- and electrophilic P_k^+ Parr functions [26] were obtained through the analysis of the Mulliken atomic spin density (MASD).The natural population analysis (NPA) within the natural bond orbital (NBO) calculations [27] was done to acquire natural atomic charges used within the evaluation of the global electron density transfer (GEDT) value [28] at the selected TSs as a measure of the polar character of the studied reaction. All calculations were performed using Gaussian16 software package [29]. The electron localization function (ELF) analyses were done with the TopMod program [30] and comprehensive description on the meaning and concept of ELF can be found in references 31 and 32.

3. RESULTS AND DISCUSSION

3.1. Analysis of the GS electronic structures of TCY 1 and 2.

Representation of ELF valence attractor positions together with corresponding populations, natural atomic charges, obtained through an NPA, ELF valence basins and proposed Lewis structures for TCYs **1** and **2** are shown in Fig. 1. As shown, the ELF topology of simplest TCY **1** shows that the C1–S2 and S2–C3 bonding regions are characterized with the presence of one V (C1, S2) and V (S2, C3) disynaptic basin, respectively, any of which with a population of 2.40e. This value, which is slightly greater than the anticipated value of 2e, portrays a single bond with a double character for the C1–S2 and S2–C3 interatomic regions. The existence of one V (S2) monosynaptic basin integrating 3.09e shows that there is a non-bonding region around S2 atom equivalent to one lone electron pair instead of the expected two lone electron pairs. Actually, one of lone-electron pairs of S2 is delocalized over two C1 and C3 terminal carbons which lead to creation two C1 and C3 *pseudoradical* centers and, also to shift C1-S2 and S2-C3 bonding character towards double one. Observations of two V (C1) and V' (C1) monosynaptic basins at the C1 carbon atom integrating 0.8e approve the *pseudoradical* nature of the C1 center. Likewise, an identical ELF pattern found over C3 carbon atom in TCY **1** characterizes C3 as another *pseudoradical* center. Similarly, the ELF topology of experimental TCY **2** permits characterizing the *pseudoradical* nature for the C1 and C3 centers. After establishing the bonding pattern of TCY **2**, the charge distribution was explored through an NPA. The atomic charges located over the nuclei involved in TCY **2** (C1, S2, and C3 atoms) are given in Fig. 1. While C1 with a charge of -0.80*e* and C3 with a charge of -0.32*e* are the most negative centers, respectively, the S2 atom displays the most positive charge of 0.70*e*. Such evidences indicate both S2-C1 and S2-C3 are polarized toward carbon atoms and, at the first glance, a commonly accepted 1,2-*zwitterionic* structure with a noticeable charge separation may be concluded for TCY **2**, as shown in scheme 4.

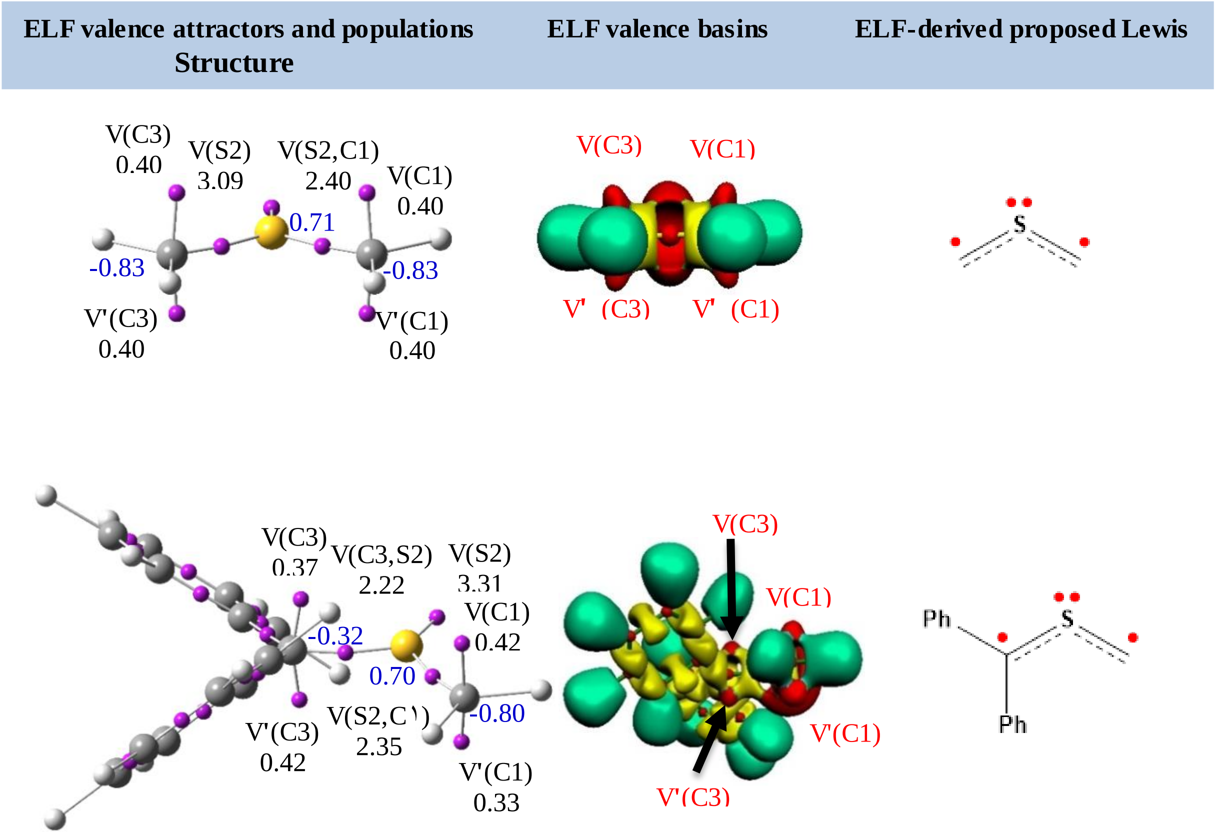


Fig. 1. Representation of ELF valence attractor positions together with corresponding populations (black values in *e*), natural atomic charges (blue values in *e*), and proposed Lewis structure for the GS electronic structure for simplest TCY **1** (top) and experimental TCY **2** (bottom).

It should be noted that "*within the DFT framework, the charge distribution distinguished by the NPA is the consequence of the asymmetric electron density distribution resulting from the presence of different nuclei in the molecule, rather than the consequence of the resonance Lewis structures*". So TCY **2** is as an *integrated* molecular system with the most negative center on C1 carbon atom and the 1,2- *zwitterionic* representation should be avoided for C=S=C framework in TCY **2**. In consequence, as shown by the Lewis structure in Fig. 1, based on ELF patterns, the experimental TCY **2** participates in a *pdr-type* 32CA reaction toward an unsaturated bond.

3.2. The global and local CDFT reactivity indices at the GS electronic TCY 2 and TFB 4.

The CDFT global reactivity indices are widely used as a highly useful tool to define the chemical reactivity in organic reactions [33, 34]. Therefore, the CDFT global reactivity indices for TCY **2** and TFB **4**, *i.e.* electronic chemical potential (μ), chemical hardness (η), global electrophilicity (ω), and global nucleophilicity (*N*) are computed at the B3LYP/631G (d) computational level and associated values are presented in Table 1.

The value of μ for TCY **2**, -3.18 eV, is greater than that of TFB **4**, -4.66 eV, respectively, indicating that along a polar 32CA reaction, the GEDT should take place from TCY **2** toward TFB **4** so that TCY **2** acts as a nucleophile and TFB **4** as an electrophile, respectively. TCY **2** and TFB **4** exhibit a high global electrophilicity indices 1.76, and 2.23 eV, respectively, which are classified as a strong electrophilic species within the electrophilicity scale [35]. On the other hand, TCY **2** with the high global nucleophilicity indices, 4.50 eV, is classified as a strong nucleophile within the nucleophilicity scale [36].

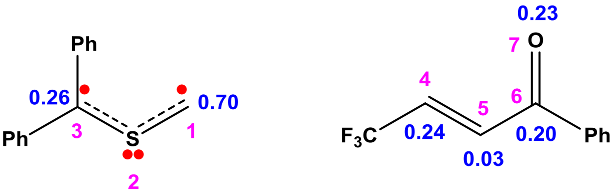
According to the high electrophilic character of TFB **4** arising from existence of highly electron-withdrawing CF_3 functional group and the high nucleophilic character of TCY **2**, this *pdr-type* 32CA reaction has a high polar character which progress with a low relative activation barrier. (see latter)

Table 1. B3LYP/6-31G(d) computed electronic chemical potential (μ) chemical hardness (η), global electrophilicity (ω), and global nucleophilicity (*N*), in eV, for TCY **2** and TFB **3**.

Species	**μ**	**η**	**ω**	***N***
TCY 2	-3.18	2.86	1.76	4.50
4TFB	-4.66	4.86	2.23	2.02

When an electrophile/nucleophile pair come close together, in case steric effects do not inhibit, the most electrophilic center of electrophile approaches the most nucleophilic center of nucleophile to proceed the reaction within energetically most preferred channel leading to generation major regioisomer through the lowest energy barrier pathway. A powerful tool in study of the local reactivity in *polar* processes are the electrophilic P_k^+ and nucleophilic P_k^- Parr functions [26]. Therefore, nucleophilic P_k^- Parr functions of TCY **2** and the electrophilic P_k^+ Parr functions of TFB **4** were analyzed in order to characterize the most electrophilic and nucleophilic centers of the species involved in mention 32CA reactions (Scheme 3).

Analysis of the nucleophilic P_k^- Parr functions of TCY **2** indicated that the C1 carbon is the most nucleophilic center of this molecules, $P_k^- = 0.70$, while the C3 carbon is a marginally activated nucleophilic center, P_k^- = 0.26.



Scheme 3. The B3LYP/6-31G(d) computed the nucleophilic P_k^- Parr functions of TCY **2** (left) and the electrophilic P_k^+ Parr functions of TFB **3** (right).

On the other hand, analysis of the electrophilic P_k^+ Parr functions of TFB **4** indicates that the C4 carbon is the most electrophilic centers of this molecules, P_k^+ = 0.24, while the C6 carbon is marginally activated as an electrophilic center, P_k^+ = 0.20. Note that the C5 carbon of TFB **4** possessing a low P_k^+ value of 0.03 is deactivated as an electrophilic center.

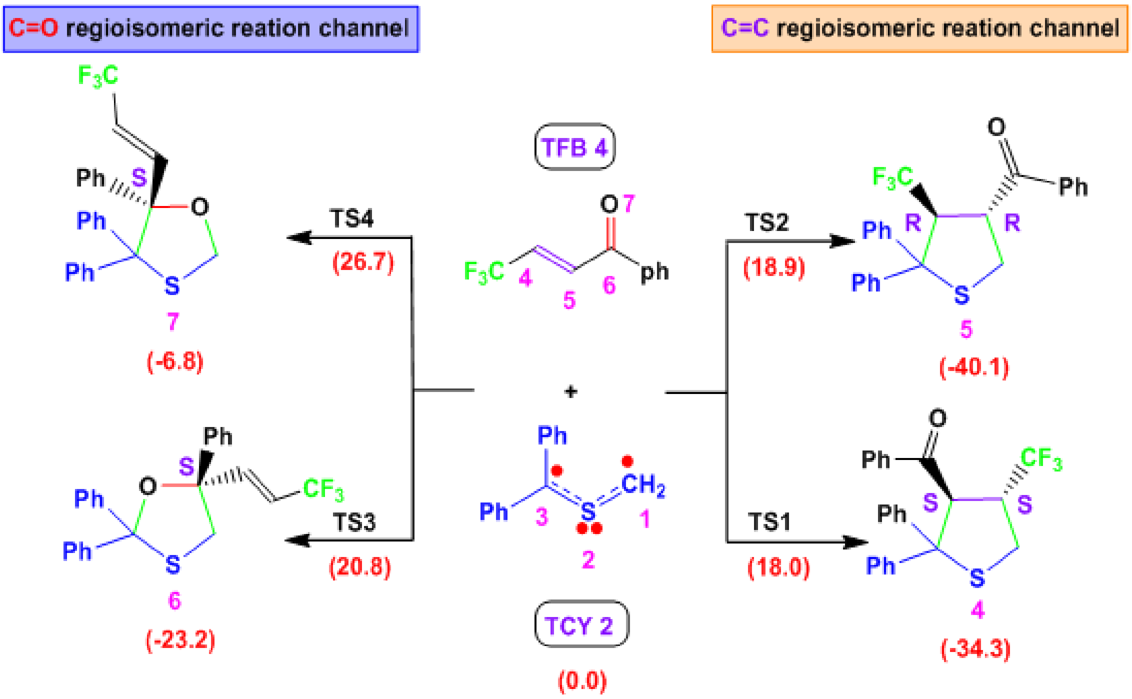
From the CDFT analysis performed in this section, we can conclude that high nucleophilic character of TCY **2** and the high electrophilic character of TFB **4** point to a polar character and, consequently, a moderate activation energy for the reaction of TCY **2** with TFB **4**. Also the great nucleophilic character of the C1 carbon in TCY **2** and high electrophilic character of C4 carbon in C=C frameworks of TFB **4** confirm the chemoselectivity and regioselectivity observed experimentally in formation C1-C4 bond on the interaction between TCY **2** and TFB **4**.

3.4. Exploration of the reaction paths involved in the interaction between TCY 2 and TFB 4

Upon *in situ* generation TCY **2** by introducing TFB **4** into the reaction mixture, as evidently illustrated in Scheme 4, the reaction can continue in two chemoselective channels (C=C involvement channel or C=O involvement channel). In C=C channel a pair stereoisomeric reaction paths associated with the formation of the C1–C4 single bond and also a pair stereoisomeric reaction paths associated with the formation of the C1–C5 single bond are anticipated. But, since similarity energy for their enantiomeric transition state structures (TSs), only one enantiomeric reaction paths associated with the formation of the C1–C4 single bond and C1–C5 single bond were considered. Also in C=O channel since similarity energy for their enantiomeric TSs, only one enantiomeric reaction paths associated with the formation of the C1–C6 single bond and C1–O7 single bond were considered.

Evaluation relative Gibbs free energies given in scheme 4 show that among located TSs, the **TS1** with an activation barrier of 18.0 kcal/mol, are the less energetic TSs. Note, however, that this activation barrier is consequence of the polar character of the *pdr-type* 32CA reaction (see section 3.2), and can be access able under experimentally working conditions leading to the creation stereoisomer **4.** These results, in excellent agreement with the experimental findings [11], explain why interaction between TCY **2** and TFB **4** leads to the formation of thiolanes **4** as the only isolable product over the course of a chemoselective (CF_3-C4=C5 involvement rather than Ph-C6=O7 one in TFB **3**) and regioselective (C1-C4 attack instead of C1-C5 one) 32CA reaction.

The B3LYP/6-31G(d) optimized structure of **TS1** through **TS4** involved in 32CA reactions of TCY **2** toward TFB **4** including some key geometrical distances as well as the unique imaginary frequency, in cm^{-1}, in THF is given in Fig. 2. Considering that the C1-C4, C1-C5, C1-C6 and C1-O7single bond formation takes place at different distances.



Scheme 4. Competitive reaction paths involved in the 32CA reaction of TCY **2** toward TFB **4**. The B3LYP/6-31G(d) computed relative Gibbs free energies (red values) in THF at 289.0 K and 1.0 atm are given in kcal/mol.

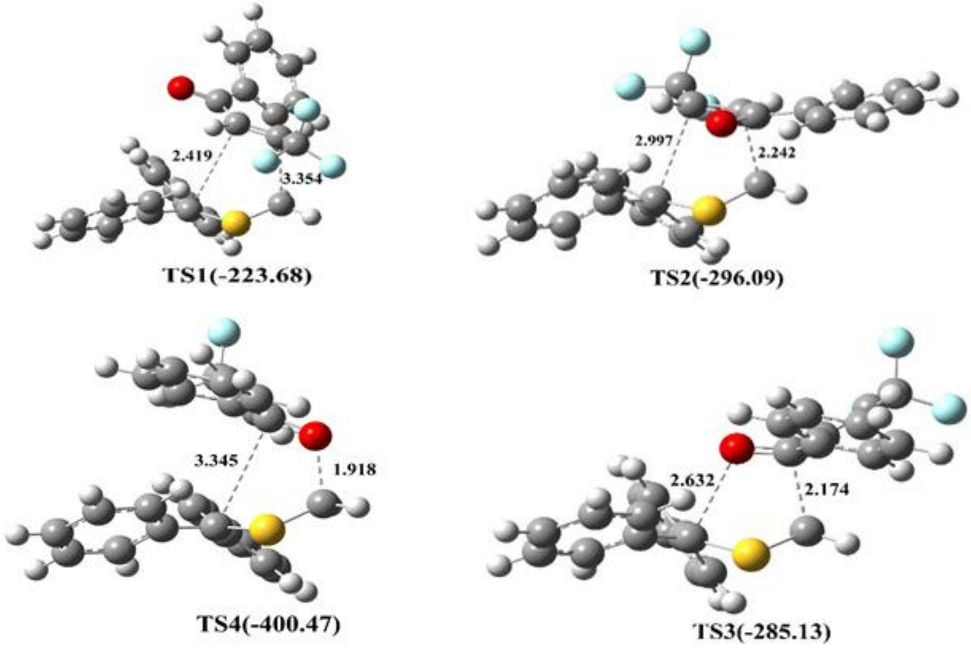


Fig. 2. B3LYP/6-31G (d) optimized structure of TSs involved in 32CA reactions of TCY **2** toward TFB **4** in THF. While some geometrical distances are given in Angstrom, the unique imaginary frequency given in the parenthesis is in cm^{-1}.

Several MEDT studies have shown a very good relationship between the polar character and the possibility of cycloaddition reactions. Therefore, the polar nature of this 32CA reaction was valued by computing the GEDT [25]at the corresponding TSs. Reactions with the GEDT values of 0.00e correspond to non-polar processes, while values higher than 0.20e correspond to polar processes. The B3LYP/6-31G (d) GEDT value, which fluxes from the TCY **2** to the C=C framework are 0.19 and 0.21e at **TS1** and **TS2**, respectively. Moreover, the GEDT value which fluxes from TCY **2** to the C=O framework is 0.33 and 0.24 at **TS3** and **TS4,** respectively. The GEDT values found at the energetically most preferred **TS1** indicates that this *pdr-type* 32CA reaction has a polar character.

4. CONCLUSIONS

The chemo- and regioselective [3+2] cycloaddition (32CA) reaction of *in situ* generated diphenyl thiocarbonyl S-methanide as a thiocarbonyl ylide, TCY **2** with (E)-4,4,4-trifluoro-1-phenylbut-2-en-1-one **(**TFB **4**) yielding thiolanes **4** experimentally described very recently by Mloston and co-workers [19], has been theoretically studied within the Molecular Electron Density Theory (MEDT) at the DFT-B3LYP/6-31G(d,) computational level.

Among the four types of reactivity provided for 32CA reactions, the 32CA reactions of TCY **2** with TFB **4** should be classified as *pdr-type* 32CA reaction, in which the high nucleophilic character of TCY **2** is responsible for the polar character displayed by the reaction.

An analysis of the density functional theory (DFT)-based reactivity indices shows that TCY **2** is a strong nucleophile at C1 carbon atom and TFB **4** is strong electrophiles at C4. While, within interaction between TCY **2** and TFB **4** formation C1-C4 is favorable, in excellent agreement with the experimental findings.

Consideration of the four competitive reaction paths for the reaction of TCY **2** with TFB **4** evidently indicates that the C=C framework of TFB **4** rather than its C=O one participates in this *pdr-type* 32CA reaction. Indeed, linking CF3 group to the C=C framework make it more reactive for the 32CA reaction with TCY **2**. Consequently, the 32CA reaction of TCY **2** toward TFB **4** yields thiolanes **4** as the sole product through a moderate activation barrier, in excellent agreement with the experimental findings.

CONFLICT OF INTEREST

The author declare that they have no conflict of interest.

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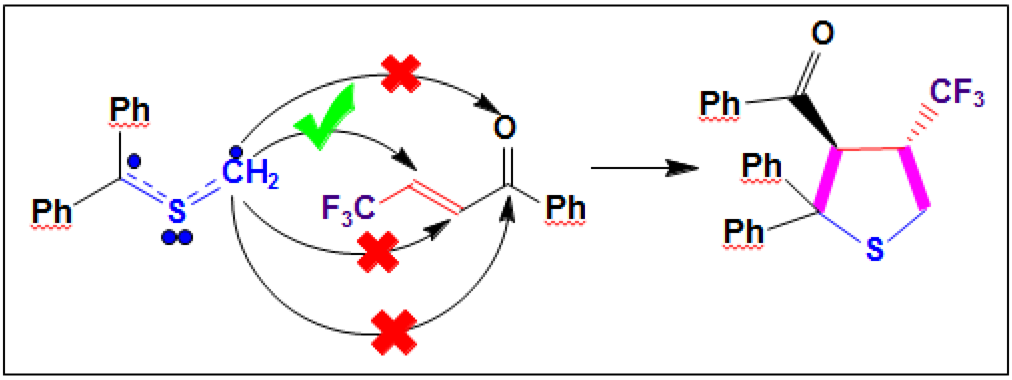

Graphical abstract