



[3 + 2] cycloaddition reaction between CF₃-substituted thiocarbonyl ylides and thioketones: Exploration of regioselectivity and mechanistic aspects using Molecular Electron Density Theory

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ABSTRACT

A CF₃-containing thiadiazole derivative, **TDA1**, participates in a domino process initialized with a thermal N₂ extrusion experienced at **TDA1** within a retro- [3 + 2] cycloaddition (32CA) reaction to yield CF₃-substituted thiocarbonyl ylide **TCY3**. Then, **TCY3** is trapped over the course of a subsequent 32CA reaction toward thioketone **TBP4** to generate dithiolane derivative **CA5**. This domino process was studied through Molecular Electron Density Theory (MEDT) at the B3LYP/6-31G(d) computational level. Exploration of the relative Gibbs free energies obviously indicates that this domino process needs to overcome high barriers justifying why the harsh conditions (100 °C for 24h in toluene) is experimentally requested. In excellent agreement with the experimental findings, an entirely C1–C5 regioselective, polar, and *pmr*-type 32CA reaction of *in situ* generated **TCY3** toward **TBP4** leads to the formation of cycloadduct **CA5** as the sole product along a quite *irreversible* pathway. While the high global electrophilicity ω index of **TBP4** together with the high global nucleophilicity N index of **TCY3** are responsible for the considerable polar character of the mentioned 32CA reaction, analysis of the electrophilic P_k^+ and nucleophilic P_k^- Parr functions at the reactive sites of reactants allows to rationalize C1–C5 regioselectivity observed experimentally. In terms of quantum topological analysis of the electron localization function (ELF) over some relevant points located along the IRC profile connecting separate **TCY3** and **TBP4** to **CA5**, a non-concerted *two-stage one-step* molecular mechanism is established for this polar *pmr*-type 32CA reaction. Such ELF analysis evidently shows that formation of the first C1–C5 and second C3–S4 single bonds is a direct consequence of coupling C1- to –C5 and C3- to –S4 *pseudoradical* centers, respectively.

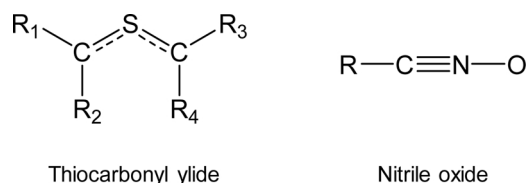
1. Introduction

Chemo-, regio-, and stereoselective construction of five-membered heterocycles can be feasible in an atom-economical fashion *via* [3 + 2] cycloaddition (32CA) reactions as one of the most powerful and versatile synthetic routes [1]. A five-membered heterocycle, commonly known as a formal [3 + 2] cycloadduct (CA), can effectively be achieved when a three-atom-component (TAC) and an unsaturated compound approach each other over the course of a 32CA reaction provided both of which are properly activated by functional groups [2]. In this sense, TAC denotes a neutral species involving an arrangement of three continued nuclei sharing a delocalized electron density [3]. From geometrical point of view, TACs are classified into allylic-type ((A-TAC)) TACs, *e.g.* thiocarbonyl ylides (as the main focus of current study), and propargylic-type ((P-TAC)) TACs, *e.g.* nitrile oxides (Scheme 1) [4].

It has been well documented that the reactivity of TACs in 32CA reactions can be correlated to the ground-state (GS) molecular electronic structure of such compounds. In this regards, Ess and Houk proposed a distortion/interaction model (DIM) in which activation energy, $\Delta E^\ddagger$, is divided into two additive terms namely distortion energy, $\Delta E_d^\ddagger$, and interaction energy, $\Delta E_i^\ddagger$ [5,6]. In DIM, distortion energy denotes the energy required to distort reactants (TAC as well as unsaturated species) on going from their GS molecular electronic structure to the corresponding molecular electronic structure in the transition state (TS). On the other hand, interaction energy indicates the energy released within interaction of distorted reactants in the TS. Considering an acceptable linear correlation coefficient ($R^2 = 0.97$) between B3LYP/6-31G(d) computed activation enthalpies and distortion energies, Ess and Houk concluded that distortion energy of reactants should be responsible for the origin of different reactivity displayed by

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Scheme 1. Geometrical representation of thiocarbonyl ylide as an A-TAC and nitrile oxide as a P-TAC.

considered TACs in the investigated 32CA reactions. It is worthy to mention that, despite such good correlation coefficient found by Ess and Houk, the geometry dependence of activation energy cannot be rationalized by DIM [7,8]. The DIM was later revisited by Braida and co-workers [9] to figure out why the distortion experienced by TACs should be the main factor of controlling reactivity of TACs in 32CA reactions. A detailed analysis allowed them to find that distortion results in a considerably increase of *singlet* diradical character of participating TACs on going from GS electronic structure towards the TS one and, hence, facilitates corresponding 32CA reaction. Indeed, if a given TAC displays a noticeable *singlet* diradical character in the GS electronic structure a significantly fewer distortion needs to be experienced and, thus, the barrier of 32CA reaction decreases [7].

Very recently, Domingo has proposed a new reactivity model namely Molecular Electron Density Theory (MEDT) to understand reactivity in organic reactions. MEDT states that “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” [10]. In addition to exploration reaction paths, MEDT takes analysis of the conceptual density functional theory (CDFT) [11], quantum topological analysis of the electron localization function (ELF) [12], quantum theory of atoms in molecules (QTAIM) [13] analysis, and non-covalent interaction (NCI) [14] analysis into consideration to study the molecular reactivity in organic reactions in a rigorous manner [15]. Several MEDT studies have been directed to 32CA reactions including different TACs resulting in a reasonable and straightforward classification for these types of cycloadditions as: i) *pseudo(di)radical*-type (*pdr*-type); ii) *pseudo(mono)radical*-type (*pmr*-type); iii) carbenoid-type (*cb*-type); and iv) zwitterionic-type (*zw*-type) 32CA reactions [16]. The *pdr*- and *pmr*-type 32CA reactions involve, respectively, TACs with a *pseudo(di)radical* and *pseudo(mono)radical* character while to have a *cb*- and *zw*-type 32CA reaction participating TACs should display a carbenoid and zwitterionic character, respectively. The reactivity trend

decreases in the order $pdr > pmr \geq \text{carbenoid} > \text{zwitterionic}$, i.e. while *pdr*-type 32CA reactions take place easily through early TSs even with a very low polar character, *zw*-type 32CA reactions highly need proper nucleophilic/electrophilic activations to proceed in an acceptable rate [16]. The relationship between the Lewis structures derived from ELF analysis of the TACs and their reactivity type in 32CA reactions is given in Scheme 2 [16].

Thiocarbonyl ylides (TCYs) belong to the sulphur-centered (A-TACs) (Scheme 1) whose participation in 32CA reactions towards C–C double bonds yields tetrahydrothiophene derivatives which have received particular attention due to occurrence as the ring system motifs in natural and non-natural products providing a widespread spectrum of biological activities [17]. TCYs can also be trapped by the highly reactive and polarized C–S double bond of thioketones over the course of 32CA reaction to generate 1,3-dithiolane derivatives. Trifluoromethyl-containing dithiolanes have been found considerable utilization in the agrochemical and pharmaceutical industries [18].

Very recently, Kowalski and co-workers have synthesized CF_3 -containing 1,3-dithiolane derivative (CA5) via a domino reaction [19]. As depicted in Scheme 3, their synthetic route comprises *in situ* generation of TCY3 through a thermal N_2 extrusion (a retro-32CA reaction) experienced by CF_3 -containing 2,5-dihydro-1,3,4-thiadiazole derivative (TDA1) and, then, trapping TCY3 by the employed thioketone (thio-benzophenone, TBP4) over the course of a regioselective 32CA reaction.

The highly electron-withdrawing CF_3 functional group substituted at TCY3 is expected to display distinguished effects on the reactivity of TCY3 and the molecular mechanistic aspects involved in the corresponding 32CA reaction. Due to our ongoing interest in the study of 32CA reactions, an MEDT study is performed to shed light on the energy, selectivities, and molecular mechanistic aspects of the domino reaction given in Scheme 3.

2. Details of calculations

All geometry optimizations were performed using the B3LYP functional [20] together with the standard 6-31G(d) basis set [21]. A subsequent frequency calculation at the same computational level allowed us to characterize the nature of optimized stationary points; that is, all reactants, intermediates, and products have not any imaginary frequency and TSs (the first-order saddle points) have one and only one true imaginary frequency. Employing the second order González-Schlegel integration method [22], the intrinsic reaction coordinate (IRC) paths [23] were traced in both forward and backward directions

Lewis structure of TAC	Name	Structure / reactivity in 32CA reaction
	Azomethine ylide	<i>Pseudo(di)radical</i> / <i>pdr</i> -type
	Azomethine imine	<i>Pseudo(mono)radical</i> / <i>pmr</i> -type
	Nitrile ylide	Carbenoid / <i>cb</i> -type
	Nitron	Zwitterionic / <i>zw</i> -type

Scheme 2. Relationship between Lewis structure of different TACs and their reactivity in 32CA reactions in terms of ELF analysis within the MEDT.

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