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Mechanistic studies on tandem cascade [4 + 2]/ [3 + 2] cycloaddition of 1,3,4-oxadiazoles with olefins

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ABSTRACT

The mechanism of the reaction of 1,3,4-oxadiazoles with alkenes (ethylene) and cycloalkenes (cyclobutene, cyclopentene, cyclohexene and cycloocene) have been studied computationally at the DFT M06−2X/6-311G* level. The reaction is found to proceed *via* a concerted [4 + 2] addition followed by nitrogen extrusion and then [3 + 2] addition in a tandem cascade fashion, which in the case of cycloalkenes leads to exo-fused or endo-fused subframes, the exo of which is kinetically and thermodynamically favored. The [4 + 2] step is the rate-determining step of the reaction. CF_3 as a substituent on the 1,3,4-oxadiazole decreases the activation barriers of the rate-determining step, while CO_2Me on the oxadiazole increases the activation barriers of the rate-determining step, markedly in the case of the reaction with cyclopentene and only marginally in the reactions with ethylene. Increasing temperature decreases the barrier of the rate-determining step and stability of the products but increases the rate of the nitrogen extrusion step. The low barriers of the second and third steps of the reaction compared to the first step means that the intermediates will not be isolated in the reaction, confirming the experimental observations of earlier workers. Based on calculated activation barriers, the reactivity of the various cycloalkenes considered in this study follows the order: cyclooctene > cyclopentene > cyclohexene > cyclobutene which is consistent with the trends in product yields obtained in earlier experimental studies.

1. Introduction

Tandem cascade reactions (sometimes referred as domino reactions) are chemical reactions involving at least two consecutive reactions in which each step of the sequence depends on the functionality formed directly in the previous step [1–4], without the need for isolation of intermediates, addition of regents or modification of reaction conditions before each subsequent reaction in the sequence [5–8]. Cascade reactions have several benefits notably atom economy i.e. several transformations in one synthetic operation (only a single reaction solvent, workup procedure, and purification step may be required to provide a product that have been made over the course of several individual steps).

Several experimental studies have been devoted to the study of the inter- and intramolecular tandem [4 + 2]/[3 + 2] cycloaddition reactions of nitroalkenes. Vasil'ev [9] reported polyfluorinated 1,3,4- oxadiazoles which undergo a tandem [4 + 2]/[3 + 2] cycloadditions with acyclic alkenes. It was reported that ethylene react in a sealed vessel at 200–220 C with 2,5-bis-trifluoromethyl-1,3,4-oxadiazole to produce 41% yield of 1,4-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]heptane. Recently, Opoku et al. have reported some theoretical studies on some selected tandem sequential cycloaddition reactions [10–12].

Thalhammer and co-workers [13] have reported a range of cycloalkenes which react with 2,5-bis-trifluoromethyl-1,3,4-oxadiazole **1(OD)** to form highly symmetrical coupled products **1** (n = 1,2,3,5) (Scheme 1), in which the rings were exo-fused to the 7-oxanorbornane subframe.

Vasil'ev and co-workers [9] proposed that the reaction proceeds via [4 + 2] addition, followed by nitrogen extrusion and then [3 + 2] addition in a tandem cascade fashion to afford oxabicyclo [2.2.1] heptane moiety. In other related works, Sears and his colleagues [14] have reported the utility of acyclic alkenes reaction with 1,3,4-oxadiazole derivatives in the tandem cascade [4 + 2]/[3 + 2] cycloaddition fashion.

In light of the above, this study seeks to theoretically investigate the tandem cascade [4 + 2]/[3 + 2] cycloaddition of 1,3,4-oxadiazole with alkenes. The geometries and relative energies of

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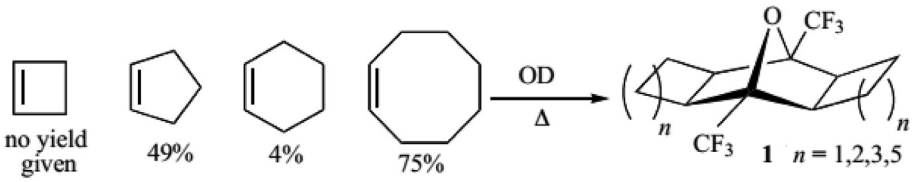


Scheme 1. Reaction of cycloalkenes with 2,5-bis-trifluoromethyl-1,3,4-oxadiazole [13].

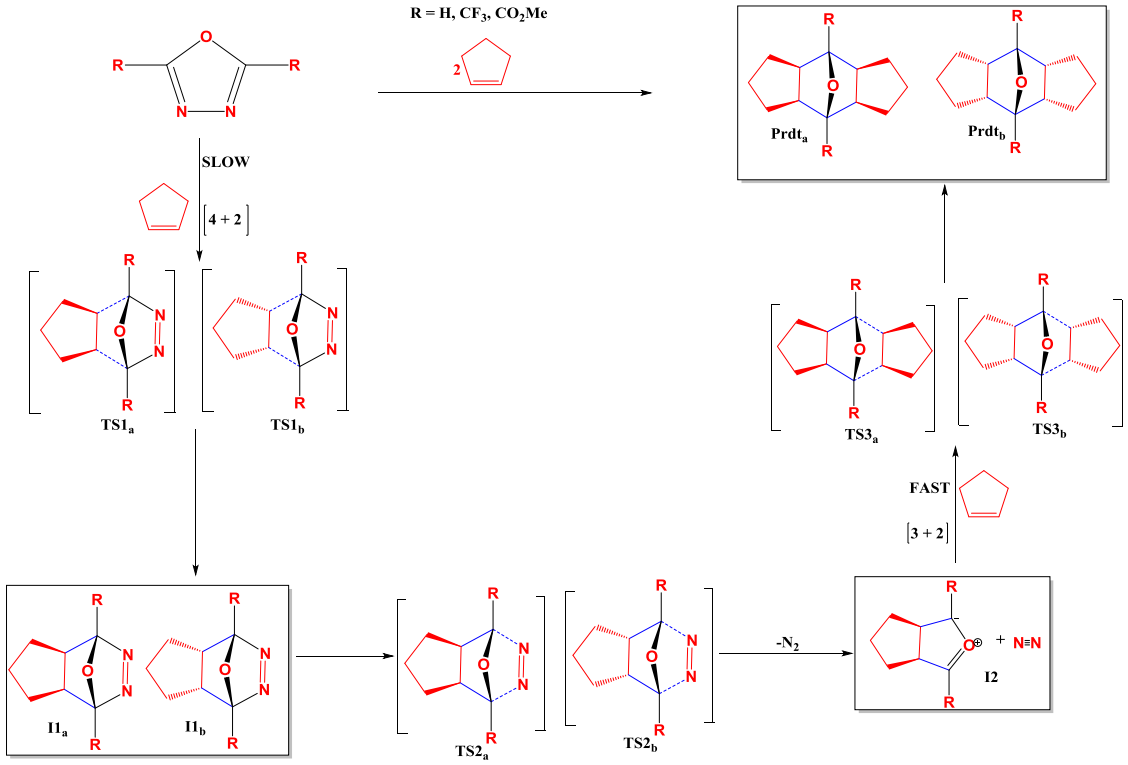
the reactants, transition states, relevant intermediates and products along our proposed reaction pathways (Schemes 2 and 3) are computed to provide mechanistic insights into the reaction. The effects of temperature and substituents on the energetics of the reaction are investigated. Global electrophilicity indices are also employed to rationalize the reactivity of the reacting species.

2. Computational details and methodology

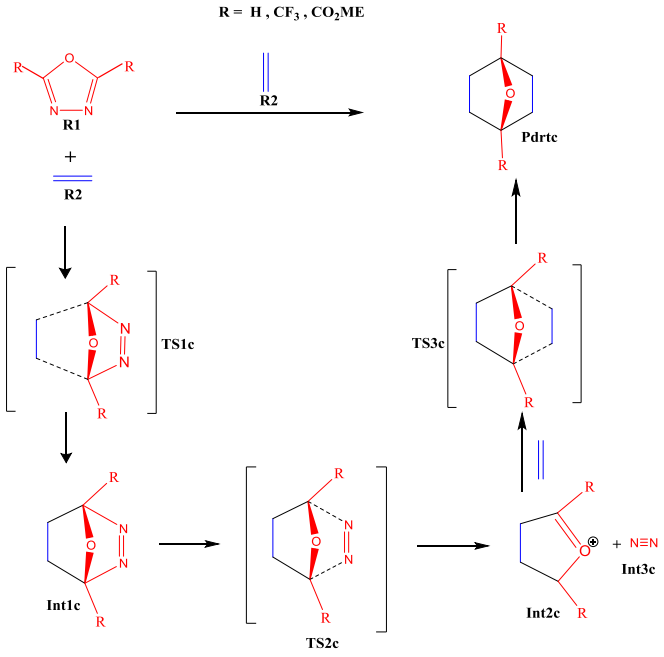
All calculations were carried out using Spartan '14 V1.1.8 [15] and Gaussian 09 [16] Molecular Modeling programs at the DFT M06−2X/6-311G* level of theory [17]. The M06−2X functional developed by Zhao and Truhlar [18] is a hybrid meta-generalized gradient approximation (meta-GGA) established to be effective at computing thermochemical and kinetic parameters, especially where nonlocal dispersion interactions play a role [19−21]. In chemical reactions where dominant changes in C−C bond breaking and formation occur, Houk and co-workers have established that M06−2X generally avoids systematic errors associated with energetic barrier heights present with, for instance, B3LYP [22]. Some recent studies have shown that, the M06−2X is the best performing functional in theoretical studies of tandem organic reactions [10−12].

The starting geometries of the molecular system were constructed using Spartan's graphical model builder and minimized interactively using the MMFF force field [23]. All geometries were fully optimized without any symmetry constraints. The optimized geometries were subjected to full frequency calculations to verify the nature of the stationary points. Equilibrium geometries were characterized by absence of imaginary frequencies. The transition-state structures (first-order saddle points on the PES) were located by performing a series of constrained geometry optimizations in which the forming and breaking bonds were fixed at various lengths whiles the remaining internal coordinate were optimized. The approximate stationary points located from such a procedure were then fully optimized using the Berny algorithm [24] within the standard transition-state optimization procedure in the Gaussian 09 computational chemistry software package. The default self-consistent field (SCF) convergence criteria (SCF=Tight) within the Gaussian 09 molecular modeling package was used [25,26]. All transition state structures were ensured to have a Hessian matrix with a single negative eigenvalue, characterized by an imaginary vibrational frequency along the reaction coordinate [27−29].

The global electrophilicities (ω) and maximum electronic charge (ΔN_{max}) of the reacting species were calculated using Equations (1) and (2) [30] and the results as shown in Tables 3 and 4 The electrophilicity index has been used as a parameter for the analysis of



Scheme 2. Proposed pathways for the reaction of 1,3,4-oxadiazoles with cycloalkene.



Scheme 3. Proposed pathways for the reaction of 1,3,4-oxadiazoles with ethylene.

the chemical reactivity of molecules. It is a measure of the ability of a reaction substrate to accept electrons [31] and is a function of the electronic chemical potential, $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and chemical hardness, $\eta = (\varepsilon_L - \varepsilon_H)$ as defined by Pearson's acid-base concept [32]. Species with large electrophilicity values are more reactive towards nucleophiles.

Equations (1) and (2) are based on Koopmans theory [30] which was originally developed for calculating ionization energies from closed-shell Hartree–Fock wavefunctions, but have since been adopted as acceptable approximations for computing electronic chemical potential and chemical hardness.

$$\omega = (\mu^2/2\eta) \quad (1)$$

$$\Delta N_{max} = -\mu/\eta \quad (2)$$

The ΔN_{max} parameter measures the maximum electronic charge that the electrophile may accept. Thus species with large ΔN_{max} values would be excellent electrophiles. The reported energies are Gibbs free energies with zero-point energy corrections.

3. Results and discussions

3.1. Tandem cascade [4 + 2]/[3 + 2] cycloadditions of unsubstituted 1,3,4-oxadiazoles with ethylene and cyclopentene

The optimized geometries of the reactants, transition states and products involved in the tandem cascade [4 + 2]/[3 + 2] cycloaddition of 1,3,4 oxadiazole with alkenes (ie. cyclopentene and ethylene) as well as the relative energies of the stationary points are shown in Figs. 1 and 2 respectively. In the reactions of the unsubstituted 1,3,4-oxadiazole (R1 = R2 = H) and cyclopentene, the results show that, in the first step of the coupling reaction, cyclopentene reacts with 1,3,4-oxadiazole *via* a [4 + 2] addition fashion through either the exo-transition state **TS1$_a$** with activation barrier of 34.9 kcal/mol to form intermediate **Int1$_a$** or through the endo-transition state (**TS1$_b$**) with activation barrier of 34.5 kcal/mol to form intermediate **Int1$_b$**. The barriers for the endo- and exo-pathways are practically equal, and thus the endo-exo selectivity of the intermediates is very low. Intermediates **Int1a** and **Int1b** are 2.5 and 5.6 kcal/mol less stable than the separated reactants. In **TS1$_a$** and **TS1$_b$**, the lengths of the C–C bond are 2.137 Å and C–C is 2.125 Å respectively. In going to intermediate **Int1** via transition state **TS1**, the bond length of the C–C decreases by 0.598 Å for *exo* and 0.579 Å for *endo* pathway, indicating bond formation of the C–C bond.

The intermediate **Int1$_a$ and Int1$_b$** undergo nitrogen extrusion through transition state **TS2$_a$** and **TS2$_b$** to form intermediate **Int2** with activation barrier of 19.0 kcal/mol and 21.5 kcal/mol respectively. In forming intermediate **Int2** via transition state **TS2**, the C–O bond length of the carbonyl ylide intermediate **Int2** increases by only 0.003 Å. The bond length of the C–N between **Int1** and **TS2** increase by 0.632 Å for exo and 0.636 Å for endo pathway, indicating breaking of the C–N bond.

The carbonyl ylide intermediate **Int2** then reacts with another cyclopentene molecule in a [3 + 2] addition fashion through *exo* and *endo* transition states **TS3a** and **TS3b** with barriers of 9.6 and 1.5 kcal/mol respectively. It is the [3 + 2] addition step that determines the stereochemistry of the final product and since the *exo* pathway has an activation barrier of 8.1 kcal/mol less than the *endo*, the kinetically preferred pathway is the *exo*.

The final product is exergonic with reaction energy of $-64.7 kcalmol^{-1}$ for exo and $-45.8 kcalmol^{-1}$ for endo with respect to the starting materials. Hence the exo-fused subframe product is thermodynamically favored over the endo-fused subframe product.

The reaction with ethylene initiates likewise *via* the [4 + 2] through **TS1c** with an activation barrier of 32.4 kcal/mol to form the first intermediate **Int1c** with reaction energy of 0.9 kcal/mol. Unlike in the case of the reaction with cyclopentene, the reaction with ethylene does not produce stereoisomers. The intermediate undergoes nitrogen extrusion through transition state **TS2c** to form the 1,3-diazole intermediate **Int2c** with activation barrier of 20.4 kcal/mol and reaction energy of 9.6 kcal/mol relative to the starting materials.

The 1,3-diazole intermediate undergoes [3 + 2] cycloaddition reaction with the second ethylene to afford the six membered bicyclic ring via activation barrier of 20.0 kcal/mol and with relative reaction energy of −69.4 kcal/mol.

As seen in both Figs. 1 and 2, the rate-determining step of the tandem cascade reaction is the [4 + 2] step. Surprisingly, the barriers of the reactions involving a strained molecule like cyclopentene and a linear one like ethylene are practically equal for this step. However, for the [3 + 2] step leading to the final product the barrier of the reaction involving the strained cyclopentene is markedly lower than that involving the ethylene. The results also show that the second and third steps (nitrogen extrusion and [3 + 2] addition steps) are faster than the first step i.e. the [4 + 2] step. This implies that the final product and not the intermediates will be isolated. This is in conformity with experimental observations of earlier workers.

3.2. Effect of temperature on tandem cascade [4 + 2]/[3 + 2] cycloadditions of parent 1,3,4-oxadiazoles with cyclopentene

This section explores the effect of temperature on the energetics of the reaction of 1,3,4-oxadiazoles with cyclopentene along the exo pathway. The results (Fig. 3) show that increasing temperature on the reaction affords a thermodynamically less stable adduct than at 298 K. It is observed that as temperature increases the intermediates that are formed are less stable than the adducts generated from 298 K. For the unsubstituted cycloadduct intermediate **Int1$_a$**, the molecule at 298.15 K is 5.1 kcal/mol lower in

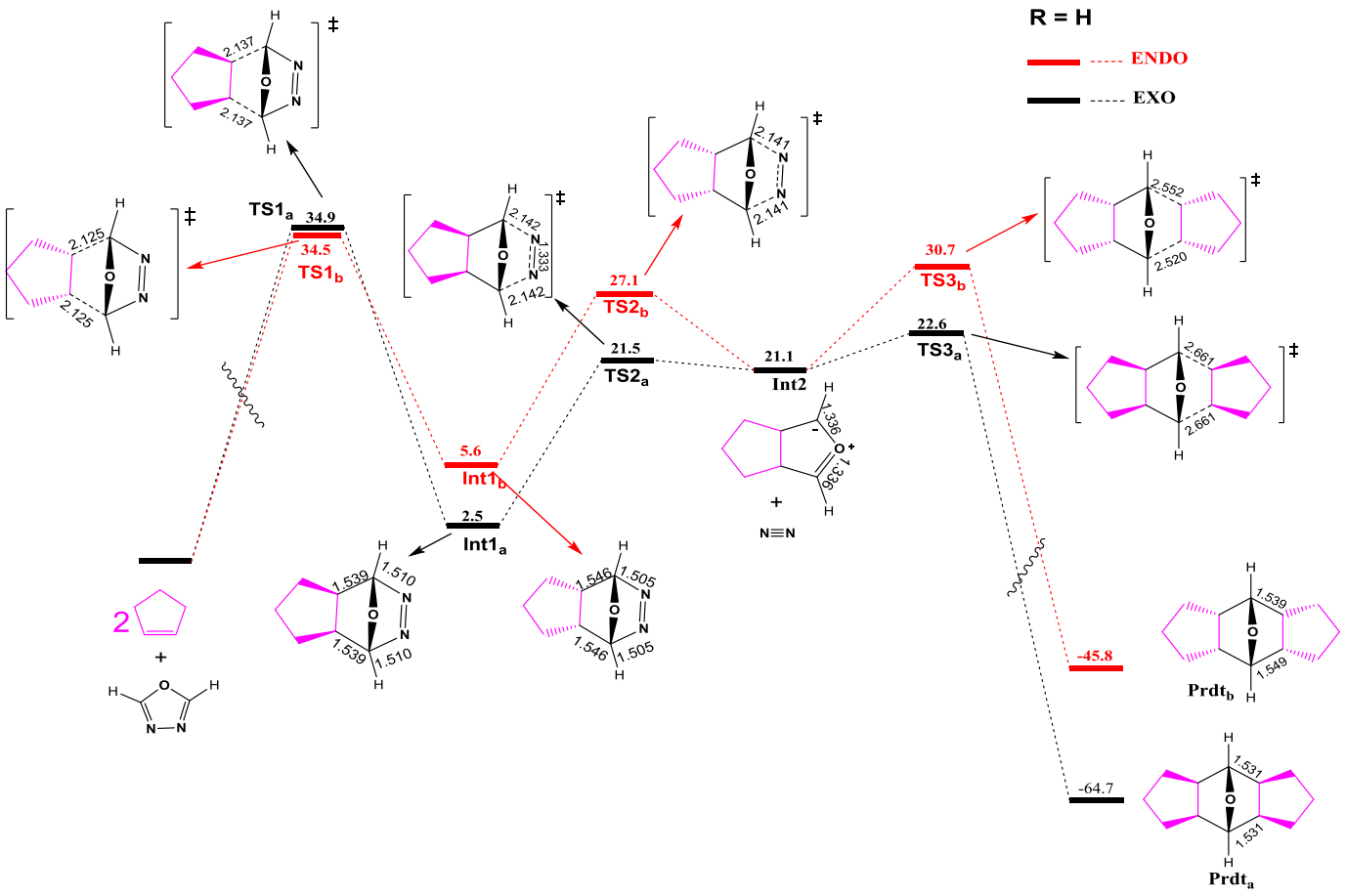


Fig. 1. Free energy profile for tandem cascade [4 + 2]/[3 + 2] cycloadditions of unsubstituted 1,3,4-oxadiazole with cyclopentene. Relative energies in kcal/mol. All bond distances are measured in Å.

energy than at 398.15 K and 10.3 kcal/mol lower in energy than at 498.15 K. For the rate-determining step of the parent reaction i.e. the [4 + 2] addition step, the activation barrier is 34.9 kcal/mol at 298.15 K, 39.8 kcalmol^{-1} at 398.15 K and 45.0 kcalmol^{-1} at 498.15 K. Thus, the reaction at 298.15 K is kinetically favored over 398.15 K and 498.15 K. However, the activation energy for the N_2 extrusion step (second step) decrease marginally from 19.0 to 18.6 and 18.3 kcal/mol as temperature increases from 298.15 K to 398.18 K and 498.15 K respectively. This implies that increasing temperature slightly increases the rate of nitrogen extrusion to form the dipolar intermediate **Int2$_a$** for the final step. Finally, the minimum barrier required for formation of the final products at 298.15 K, 398.15 K and 498.15 K are 1.5 kcal/mol, 6.7 kcal/mol and 12.2 kcal/mol respectively. The barriers at 298.15 K are lower than at 398.15 and 498.15 K. The energies for the formation of the final product from parent substrate at 298.15 K is −64.7 kcal/mol which makes it thermodynamically more stable compared with the adduct generated from the unsubstituted substrates with relative energy of −58.2 kcal/mol and −51.4 kcal/mol at 398.15 K and 498.15 K respectively.

3.3. Effect of −CF$_3$ and −CO$_2$Me substituents on the tandem cascade [4 + 2]/[3 + 2] cycloadditions of 1,3,4-oxadiazoles with cyclopentene and ethylene

This section explores the effect of CF_3 and CO_2Me substituents on 1,3,4-oxadiazole on the energetics of the reaction. It must be noted that in the case of cyclopentene reaction with the 1,3,4-oxadiazole, only the favourable pathway (exo pathway) is considered in this section. The results (Tables 1 and 2) show that the reaction with the CF_3 substituent on the 1,3,4-oxadiazole affords a more thermodynamically stable adduct than the parent substrate. Intermediates formed from the CF_3-substituted 1,3,4-oxadiazole for both alkenes (cyclopentene and ethylene) are generally more stable compared to the intermediates generated from the parent substrates. For the cycloadduct intermediate **Int1**, the CF_3-substituted 1,3,4-oxadiazole is 12.1 kcalmol^{-1} and 12.8 kcalmol^{-1} lower in energy for cyclopentene and ethylene respectively than their parent intermediate **Int1**. The activation energy for the rate-determining step (i.e. the [4 + 2] step) of the reaction of CF_3-substituted 1,3,4-oxadiazole with cyclopentene and ethylene is kinetically favored over the parent reactions by 7.5 and 7.0 kcal/mol respectively. This implies that CF_3-substituted 1,3,4-oxadiazole with the alkenes would require relatively lower energy for the formation of the corresponding products compared to the parent substrate. The reaction energies for the formation of the final product with the CF_3 substituents for both cyclopentene and ethylene substrates are −76.3 and −88.5 kcal/mol, making them thermodynamically more stable compared to the products generated from the parent substrates where the relative energies are −64.7 and 69.4 kcal/mol respectively.

On the contrary, reaction of CO_2Me-substituted 1,3,4-oxadiazole affords a less thermodynamically stable adduct as depicted in Table 2. The CO_2Me substituted intermediate **Int1** is 11.1 kcal/mol

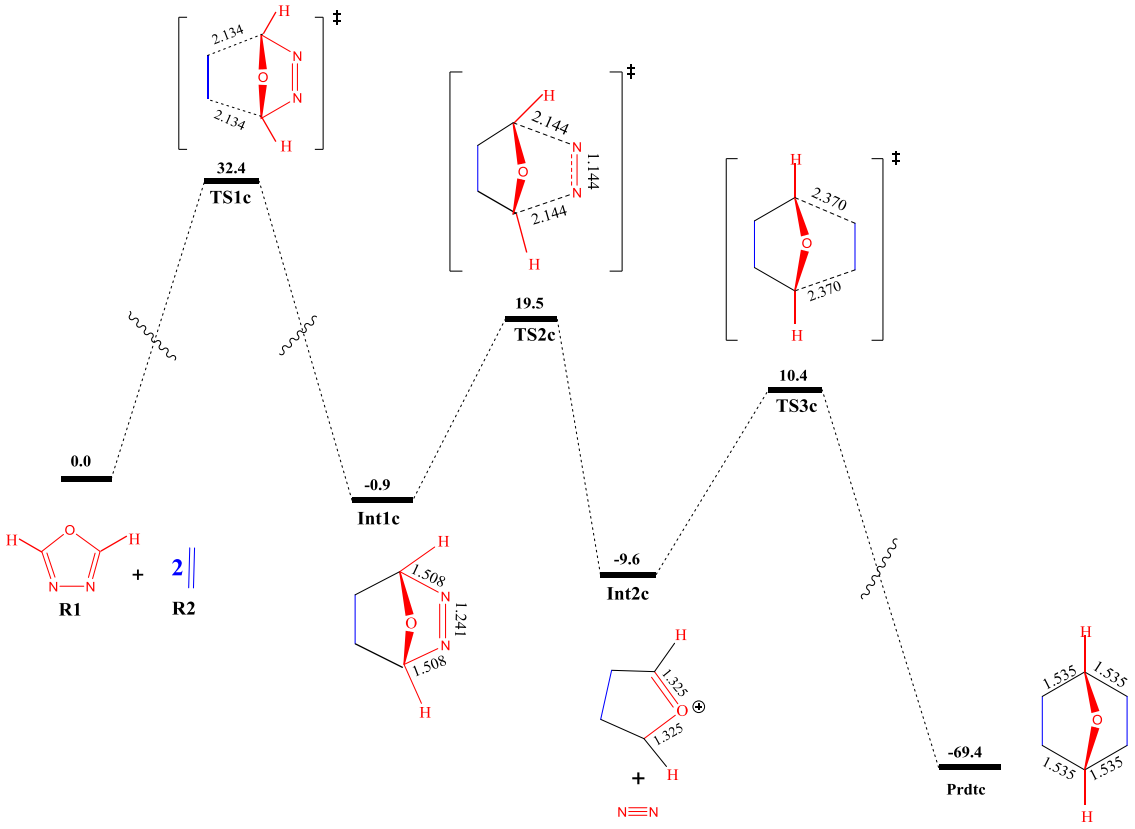


Fig. 2. Free energy profile for tandem cascade [4 + 2]/[3 + 2] cycloadditions of unsubstituted 1,3,4-oxadiazoles with ethylene. Relative energies in kcal/mol.

and 0.4 kcal/mol higher in energy for cyclopentene and ethylene respectively than the parent intermediate **Int1**. With regards to cyclopentene, the activation barrier of the [4 + 2] step involving the CO_2Me-substituted 1,3,4-oxadiazole is 51.2 kcal/mol compared to 34.9 kcal/mol for the parent reaction, and for ethylene the barrier for the CO_2Me-substituted 1,3,4-oxadiazole is 35.2 kcal/mol compared to 32.4 kcal/mol for parent substrate.

As in the parent reaction, the rate-determining step is the first step, which involves the [4 + 2] coupling of CO_2Me-substituted 1,3,4-oxadiazole with either alkenes. It is seen from the rate-determining steps that the reaction involving the CO_2Me-substituted substrate is kinetically less favored compared with parent substrate. Finally, the minimum barrier required to form the final products for the CO_2Me-substituted reaction involving for cyclopentene and ethylene are 6.2 kcal/mol and 7.5 kcal/mol respectively whilst those of the parent substrates are 1.5 kcal/mol and 20.0 $kcalmol^{-1}$ for cyclopentene and ethylene respectively. The energies for the formation of the CO_2Me substituted product for cyclopentene is −55.1 $kcalmol^{-1}$ which is thermodynamically less stable compared with the adduct generated from the parent substrates with relative energy of −64.7 kcal/mol. Also the CO_2Me-substituted product from ethylene is relatively lower in energy than the corresponding parent product by 7.9 $kcalmol^{-1}$. Both cases indicate that the CO_2Me-substituted products formed are thermodynamically less stable compared to the parent ones.

3.4. Tandem cascade [4 + 2]/[3 + 2] cycloaddition of CF_3 -substituted 1,3,4-oxadiazole with cyclobutene, cyclohexene and cyclooctene

In the study by Thalhammer et al. [13], it was reported that the reaction between a range of cycloalkenes with 2,5-bis-trifluoromethyl-1,3,4-oxadiazole form exo-fused stereoselective products in varied yields. Specifically, they observed that the 2,5-bis-trifluoromethyl-1,3,4-oxadiazole reacted with cyclobutene, cyclopentene, cyclohexene, and cyclooctene with 0%, 49%, 4% and 75% yields respectively. Having established the mechanistic channels of the reaction of the 2,5-bis-trifluoromethyl-1,3,4-oxadiazole with cyclopentene in the above sections, we devote this section to the other cycloakenes considered in their [13] work.

Fig. 4 shows the zero-point-corrected Gibbs free energy profile as well as the optimized transition states and equilibrium geometries located on the potential energy surface (PES) of the [4 + 2]/[3 + 2] cycloaddition of CF_3-substituted 1,3,4-oxadiazole with cyclobutene. As it can be seen from Fig. 4 the initial [4 + 2] addition occurs with activation barriers of 11.5 kcal/mol and 10.5 kcal/mol respectively for $\mathbf{TS1_a}$ and $\mathbf{TS1_b}$ respectively, suggesting a competitive step. This is followed by the formation of a very stable adduct with reaction energies of 28.4 kcal/mol and 24.0 kcal/mol respectively for the $\mathbf{Int_a}$ and $\mathbf{Int_b}$ respectively. Comparing the reaction energies of the intermediates ($\mathbf{Int_a}$ and $\mathbf{Int_b}$), it is obvious that $\mathbf{Int_a}$ is favored over the $\mathbf{Int_b}$. The N_2 extrusion step (TS2) will occur via the favourable $\mathbf{TS2_a}$ with an energy barrier of 16.9 kcal/mol leading to the formation of **Int2** with a reaction energy of 15 kcal/mol. The barrier for the second step is obviously higher than that of the first step. This observation coupled with the fact that several attempts to locate the $\mathbf{TS3_a}$ along the favourable pathway has been unsuccessful give credence that the reaction will most likely terminate at the Diels-Alder step. These trends are consistent with the 0% yield of the tandem adduct recorded by Thalhammer and co-workers [13] in their experimental work.

In Figs. 5 and 6, we report the optimized geometries as well as

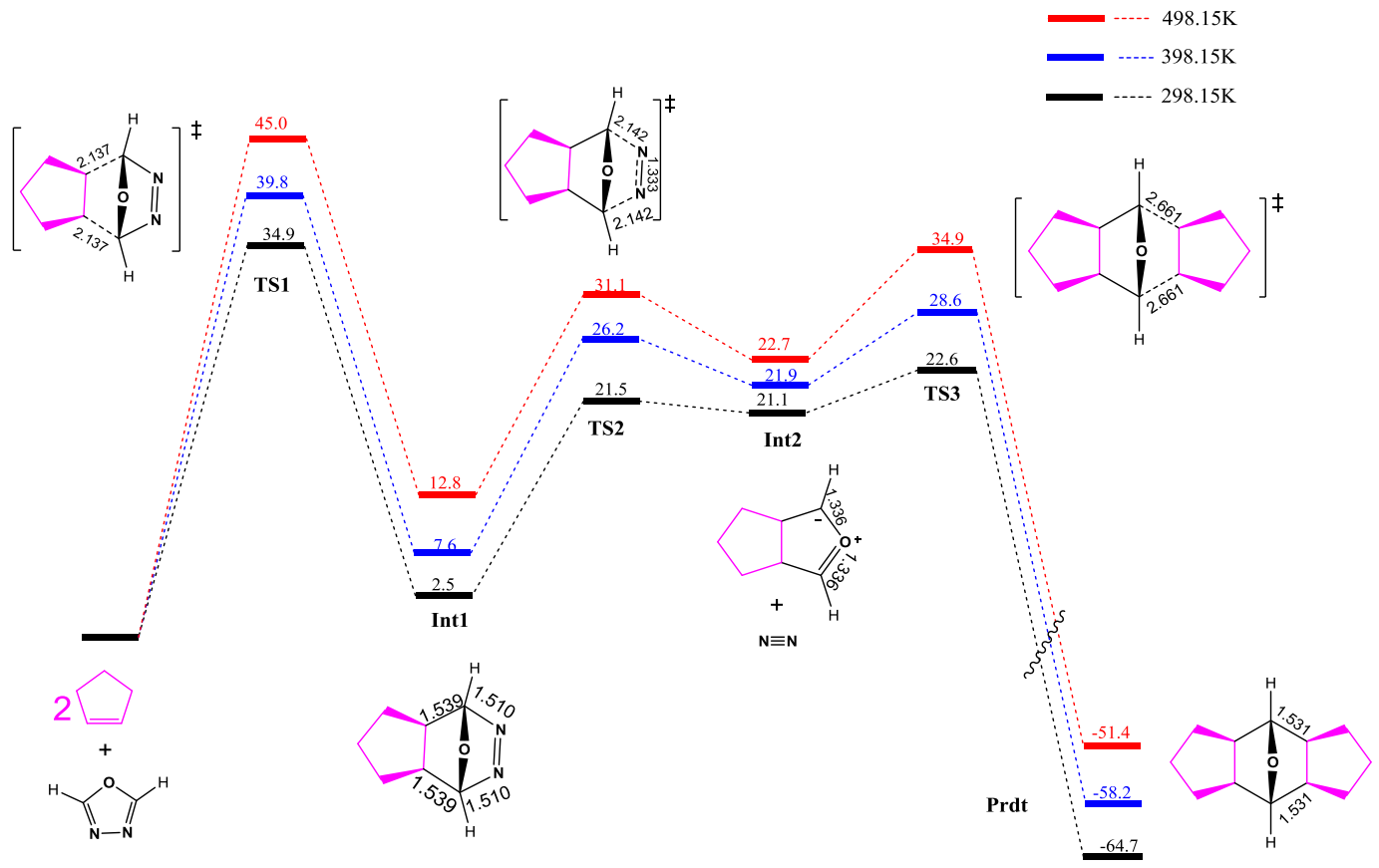


Fig. 3. Free energy profile for temperature effect on the tandem cascade [4 + 2]/[3 + 2] cycloadditions of unsubstituted 1,3,4-oxadiazoles with cyclopentene. Relative energies in kcal/mol.

Table 1
Effect of CF_3 substituent on 1,3,4-oxadiazole with alkenes (cyclopentene and ethylene). Relative energies in kcalmol^{-1}.

	1,3,4-oxadiazole with cyclopentene	CF_3-substituted 1,3,4-oxadiazole with cyclopentene	1,3,4-oxadiazole with ethylene	CF_3-substituted 1,3,4-oxadiazole with ethylene
TS1	34.9	27.4	32.4	25.4
Int1	2.5	−9.6	−0.9	−11.9
TS2	21.5	12.8	19.5	7.3
Int2	21.1	5.3	−9.6	−7.3
TS3	22.6	–	10.4	–
FINAL PRODUCT	−64.7	−76.3	−69.4	−88.5

Table 2
Effect of CO_2ME substituent on 1,3,4-oxadiazole with alkenes (cyclopentene and ethylene). Relative energies in kcalmol^{-1}.

	1,3,4-oxadiazole with cyclopentene	CO_2ME substituted oxadiazole with cyclopentene	1,3,4- oxadiazole with ethylene	CO_2ME-substituted oxadiazole with ethylene
TS1	34.9	51.2	32.4	35.2
Int1	2.5	13.6	−0.9	−0.4
TS2	21.5	17.7	19.5	9.9
Int2	21.1	4.7	−9.6	−4.2
TS3	22.6	10.9	10.4	3.3
FINAL PRODUCT	−64.7	−55.1	−69.4	−61.5

the relative energies of all the stationary points involved in the tandem cascade [4 + 2]/[3 + 2] cycloaddition of CF_3-substituted 1,3,4-oxadiazole with cyclohexene and cyclooctene respectively. In the cyclohexene reaction (Fig. 5), it is realized that **TS1$_b$** has the lowest activation energy (11.4 kcal/mol) leading to the formation of **Int$_b$** with a reaction energy of 19.7 kcal/mol. This is followed by **TS2$_b$** with an activation barrier of 20.2 kcal/mol to form **Int2** with a reaction energy of 7.3 kcal/mol. Considering the instability of **Int2**

Table 3
Global electophilicity indices for the various reacting species in eV.

	Parent reactants			CF_3-substituents on 1,3,4- oxadiazole			CO_2Me substituents on 1,3,4- oxadiazole		
	Oxadiazole	Cyclopentene	INT 2	Oxadiazole	Cyclopentene	INT 2	Oxadiazole	Cyclopentene	INT 2
E_{HOMO}	−8.18	−6.59	−4.84	−9.21	−6.59	−6.23	−8.42	−6.59	−5.94
E_{LUMO}	−0.34	1.09	−0.96	−1.84	1.09	−2.49	−2.31	1.09	−2.76
μ	−4.26	−2.75	−2.90	−5.53	−2.75	−4.36	−5.37	−2.75	−4.35
η	7.84	7.68	3.89	7.37	7.68	3.74	6.11	7.68	3.18
ω	1.16	0.49	1.08	2.07	0.49	2.54	2.36	0.49	2.98
ΔN_{max}	0.54	0.36	0.74	0.75	0.36	1.17	0.88	0.36	1.37

Table 4
Global electophilicity indices for the various reacting species in eV.

	Parent reactants			CF_3 substituents on 1,3,4- oxadiazole			CO_2Me substituents on 1,3,4- oxadiazole		
	Oxadiazole	Ethylene	INT 2	Oxadiazole	Ethylene	INT 2	Oxadiazole	Ethylene	INT 2
E_{HOMO}	−8.18	−7.55	−4.66	−9.21	−7.55	−6.13	−8.60	−7.55	−6.01
E_{LUMO}	−0.34	0.75	−0.89	−1.84	0.75	−2.50	−2.52	0.75	−2.92
μ	−4.26	−3.40	−2.78	−5.53	−3.40	−4.32	−5.37	−3.40	−4.47
H	7.84	8.30	3.77	7.37	8.30	3.63	6.11	8.30	3.09
Ω	1.16	0.70	1.02	2.07	0.70	2.56	2.36	0.70	3.23
ΔN_{max}	0.54	0.41	0.74	0.75	0.41	1.19	0.88	0.41	1.45

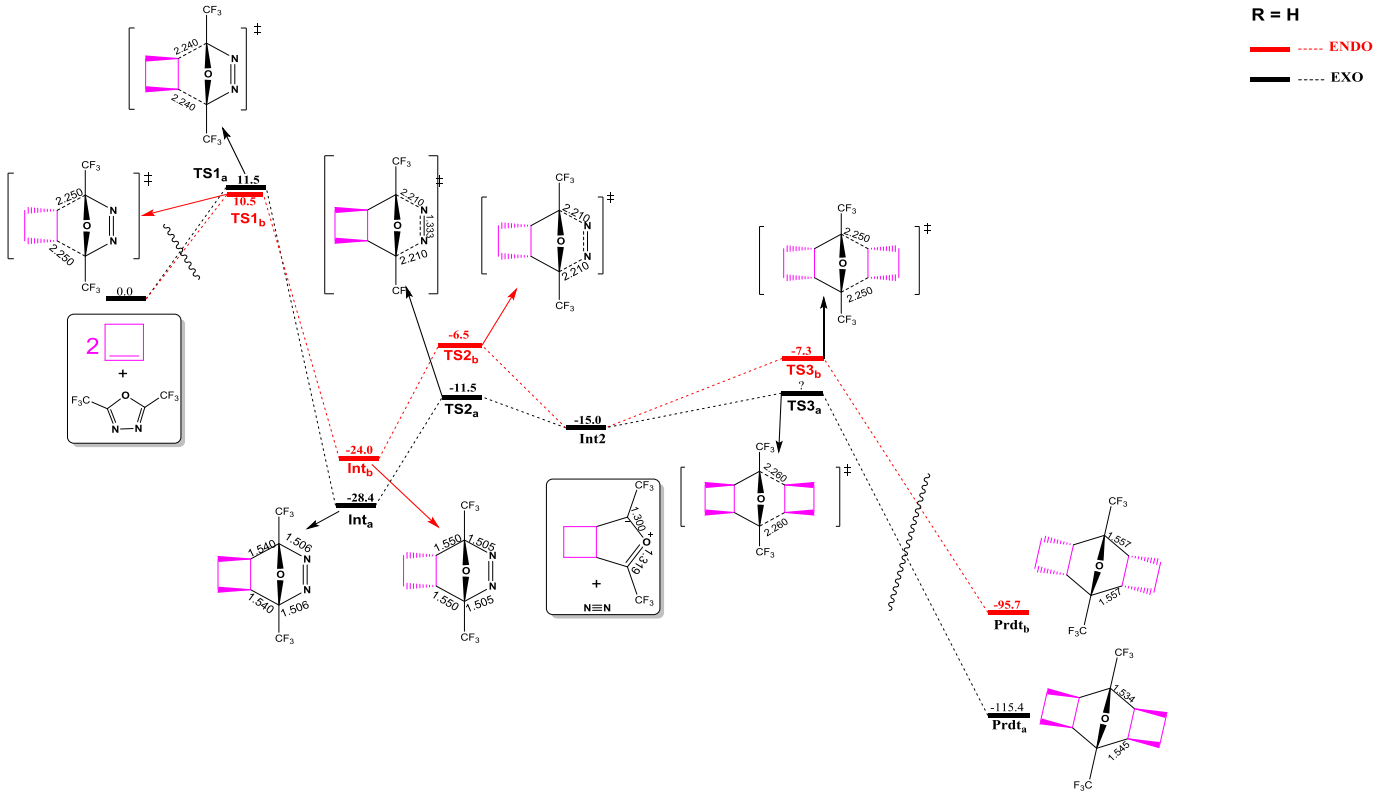


Fig. 4. Free energy profile for the tandem cascade [4 + 2]/[3 + 2] cycloadditions of CF_3-substituted 1,3,4-oxadiazole with cyclobutene. Relative energies in kcal/mol. All bond distances are measured in Å.

coupled with the higher activation barrier (11.6 kcal/mol for **TS3$_b$**) required to form the final products, it can be concluded that formation of the tandem adduct is highly disfavoured. This observation is consistent with experimentally obtained yield of 4%.

In the last instance, we consider the reaction of the cyclooctene with the CF_3-substituted 1,3,4-oxadiazole. In this case, the reaction is found to generally favour the endo pathway (path b). The Diels-Alder cycloaddition step along the favourable pathway (**TS1$_b$**) has an activation barrier of 6.6 kcal/mol to form **Int$_b$** with a reaction energy of 25.2 kcal/mol. The nitrogen extrusion proceeds with an energy barrier of 17.8 kcal/mol to form **Int2** with a reaction energy of 11.0 kcal/mol. In the tandem [3 + 2] addition step, an activation barrier of 2.5 kcal/mol along the **TS3$_b$** pathway is recorded leading to the formation of **Prdt$_b$** with a reaction energy of 79.7 kcal/mol. Based on the energetic trends, it is expected that the tandem [3 + 2] cycloaddition of **Int2** with the cyclooctene to form the tandem

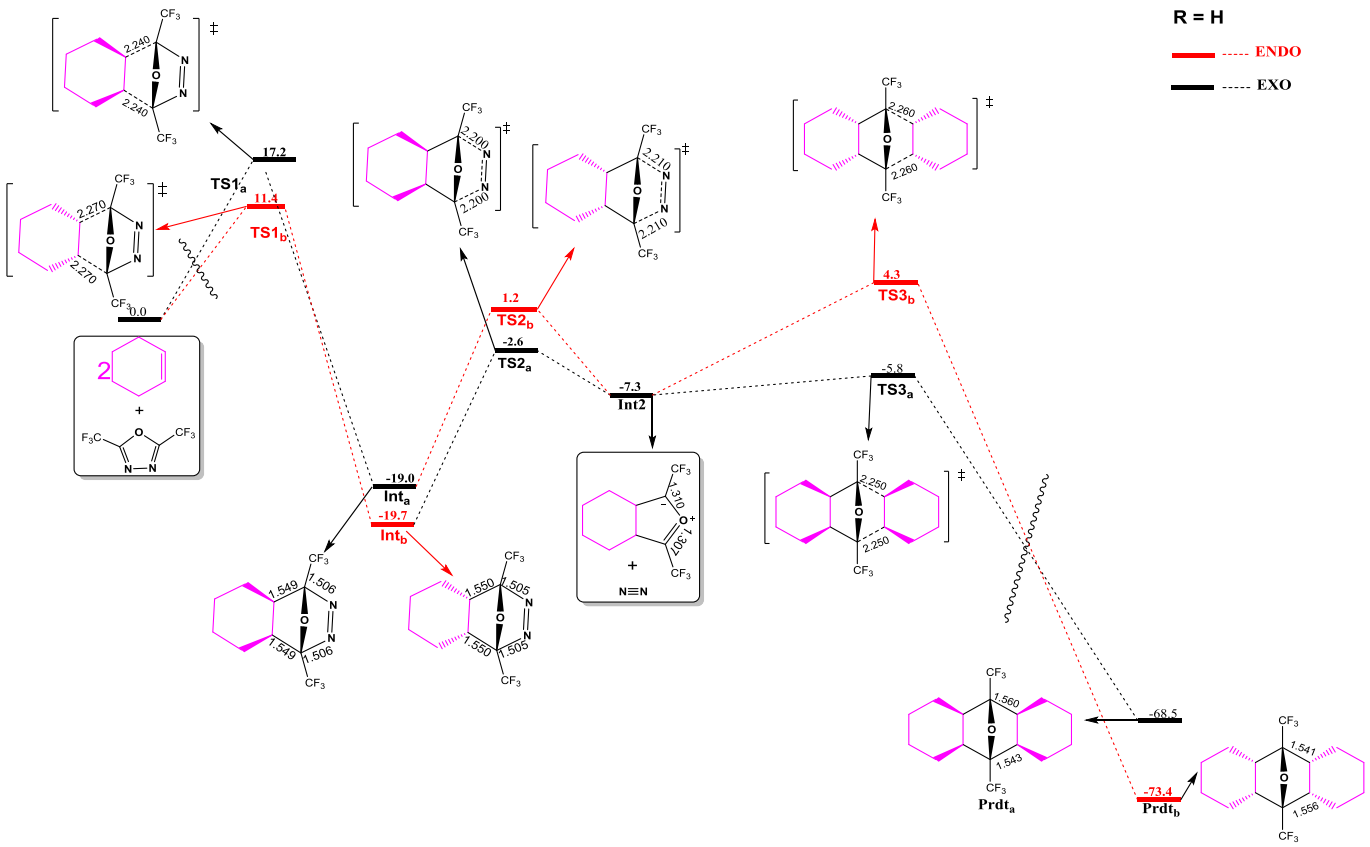


Fig. 5. Free energy profile for tandem the cascade [4 + 2]/[3 + 2] cycloadditions of CF_3-substituted 1,3,4-oxadiazole with cyclohexene. Relative energies in kcal/mol. All bond distances are measured in Å.

adduct will easily occur. This explains why a product yield of 79% was obtained in the experimental work [13] in contrast to cyclobutene and cyclohexene.

3.5. Global reactivity indices for the reacting species

The electrophilicity index, chemical potential and chemical hardness of the reactants for both alkenes are shown in Table 3 and Table 4**.** The parent 1,3,4-oxadiazole reactant has a low chemical potential and chemical hardness, as well as a low electrophilicity index compared to tthe alkene, indicating that the oxadiazole acts as the electrophile in the reaction whiles the alkenes acts as the nucleophile in both steps. The ΔN_{max} values also show that the oxadiazole will more readily accept electrons.

Introducing CF_3 as a substituent on the 1,3,4-oxadiazole lowers the electronic chemical potential (μ), chemical hardness (η) and electrophilicity index (ω) compared to the parent reactants. This account for the lowering in activation energies when CF_3 is introduced as a substituent on the 1,3,4- oxadiazole. The lowering in the electrophilicity indices indicate that the CF_3-substituted 1,3,4-oxadiazole is much more electron-deficient than the parent 1,3,4-oxadiazole. A similar trend is observed when th ester group CO_2Me is introduced as a substituent on the 1,3,4- oxadiazole. However, values recorded for CF_3 substituents are much lower than that of CO_2Me substituents indicating that CF_3 substituted 1,3,4- oxadiazole is more electron-deficient than CO_2Me substituted 1,3,4-oxadiazole. Order of electron deficient 1,3,4-oxadiazole: CF_3 substituted 1,3,4- oxadiazole > CO_2ME substituted 1,3,4- oxadiazole > Parent 1,3,4- oxadiazole.

4. Conclusion

The following conclusions are drawn from the results:

1. In the tandem cascade [4 + 2]/[3 + 2] reaction of 1,3,4-oxadiazole with alkenes, the [4 + 2] step is the rate-determining step for both substituted and unsubstituted 1,3,4-oxadiazoles reacting with the parent olefin whereas the [3 + 2] step is the step that determines the stereo-selectivity of the reaction (*exo* versus *endo* subframe).
2. Increasing temperature increases the activation barriers and reduces stability of the products. Moreover, increasing the temperature increases the rate of the nitrogen extrusion step of the reaction.
3. CF_3 as a substituent on the oxadiazole decreases the activation barriers and increases the stability of product whiles CO_2Me on the contrary increases the activation barriers and decreases stability of the product. Hence the reaction of the CF_3-substituted 1,3,4-oxadiazole is kinetically and thermodynamically favored over the CO_2Me-substituted 1,3,4-oxadiazole.
4. The low barriers of the second and third steps of the reaction mean that the intermediates will not be isolated in the reaction, confirming the experimental observations of earlier workers.
5. In the reaction of cyclobutene and the CF_3-substituted 1,3,4-oxadiazole, the reaction will most likely terminate at the [4 + 2] addition step as the subsequent steps are found to be unfavorable due to higher activation barriers.
6. In the case of cyclobutene reaction with CF_3-substituted 1,3,4-oxadiazole, the nitrogen extrusion and the [3 + 2] steps are found to occur with higher energy barriers, suggesting

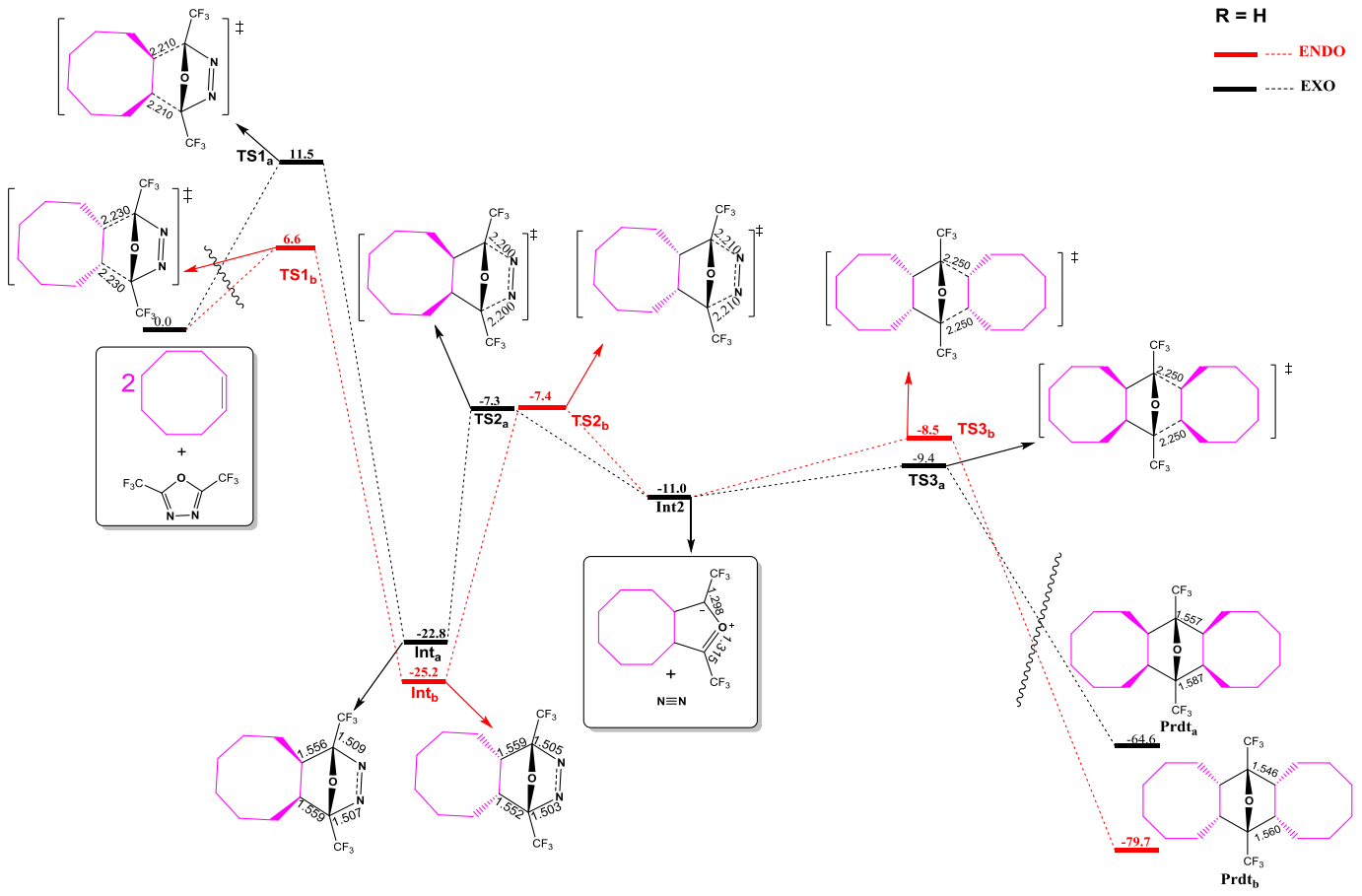


Fig. 6. Free energy profile for tandem cascade [4 + 2]/[3 + 2] cycloadditions of CF_3-substituted 1,3,4-oxadiazole with cyclooctene. Relative energies in kcal/mol. All bond distances are measured in Å.

unfavorable steps and hence the observation of very low reaction yields in prior experimental studies.

7. In cyclooctene reaction with CF_3-substituted 1,3,4-oxadiazole, the initial [4 + 2] addition step is found to be the rate-determining step whereas the subsequent steps generally occur with lower activation energies. This explains why higher yields in this particular instance were obtained in earlier experimental works.

Conflicts of interest

The authors declare that they have no conflict of interest whatsoever regarding this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmgm.2019.107452.

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