Investigation of the mechanism of formation of nitro-substituted nicotine analog via the (3 + 2) Cycloaddition reaction of (E)-substituted nitroethene derivatives and C, N-Disubstituted pyridinyl nitrones: A Density Functional Theory study

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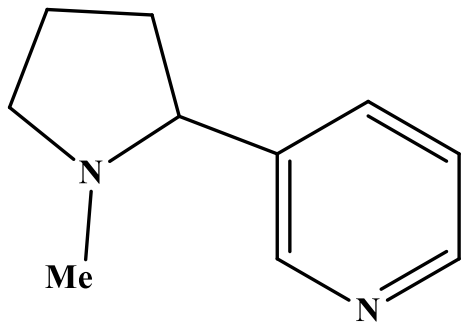
Outline

- Introduction and literature review
- Aims and objectives
- Justification
- Methodology
- Scheme
- Results and discussion
- Conclusion

Introduction and literature review

- Nicotine analog is one of the five-membered ring compound prepared from (3 + 2) Cycloaddition reaction.
- Nicotine is a major alkaloid found in tobacco plants **[1]**. Due to its biological activity, a lot of researchers have developed interest in it **[2]**.

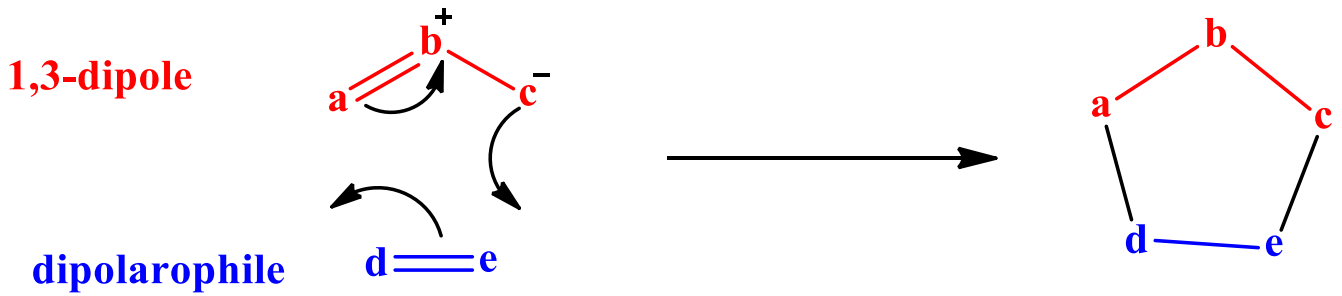


Nicotine

1. Sun, B., Tian, Y.X., Zhang, F., Chen, Q., Zhang, Y., Luo, Y., Wang, X.R., Lin, F.C., Yang, J. and Tang, H.R., 2018. Variations of alkaloid accumulation and gene transcription in Nicotiana tabacum. *Biomolecules*, *8*(4), p.114.
2. Powledge, T.M., 2004. Nicotine as therapy. *PLoS Biol*, *2*(11), p.e404.

Introduction and literature review

- (3 + 2) Cycloaddition reaction is a useful method for the synthesis of five-membered heterocycles**[1,2]**.
- It involves the reaction between a dipolarophile and a 1,3 dipole. This reaction was initially suggested by Smith in 1938, but was generalized by Huisgen in 1960's for worldwide application**[3,4]**. This reaction is the most efficient method for the preparation of five-membered heterocycles.

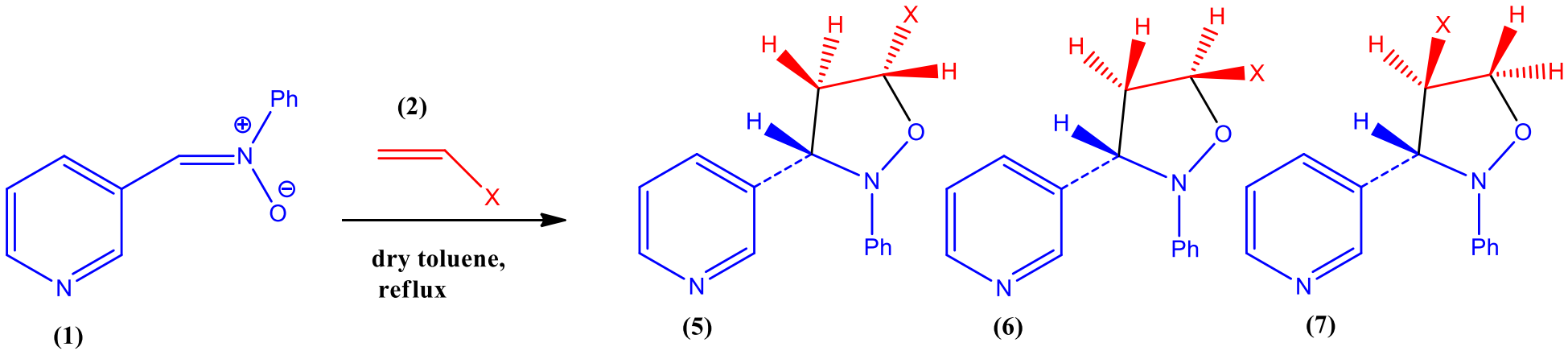


1. Huisgen, R., 2000. Adventures with heterocycles. *Chemical and pharmaceutical bulletin*, *48*(6), pp.757-765.
2. Padwa, A. and Pearson, W.H. eds., 2003. *Synthetic applications of 1, 3-dipolar cycloaddition chemistry toward heterocycles and natural products* (Vol. 59). John Wiley & Sons.
3. Smith, L.I., 1938. Aliphatic Diazo Compounds, Nitrones, and Structurally Analogous Compounds. Systems Capable of Undergoing 1, 3-Additions. *Chemical Reviews*, *23*(2), pp.193-285.
4. Huisgen, R., 1963. 1, 3-dipolar cycloadditions. Past and future. *Angewandte Chemie International Edition in English*, *2*(10), pp.565-598.

Introduction and literature review

- Singh et al in 2005 reported the development of an efficient route to novel nicotine analog by reacting α-(3-Pyridyl)-N-phenylnitrone with several dipolarophiles.

Scheme 1



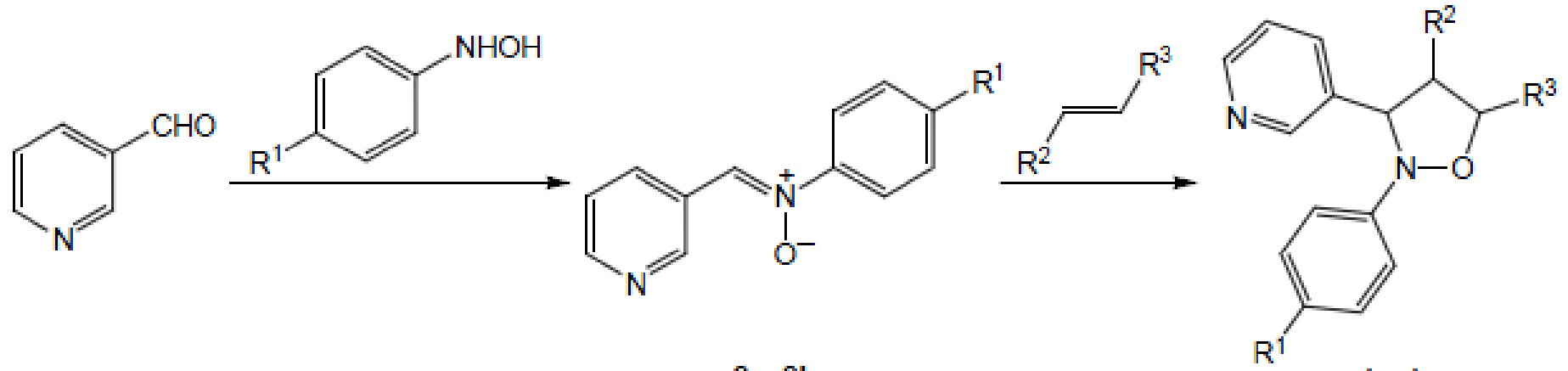
Singh, G., Ishar, M.P.S., Girdhar, N.K. and Singh, L., 2005. Investigations on regio-and stereoselectivities in cycloadditions involving α-(3-pyridyl)-N-phenylnitrone: Development of an efficient route to novel nicotine analogs. *Journal of heterocyclic chemistry*, *42*(6), pp.1047-1054.

Reaction Time and Yields (%) of the products (5-7)

Serial No.	X	Reaction time (h)	Yield (%) of various products 5:6:7		
1	**OEt**	30	**5a**(90)	**6a**(traces)	**7a**(--)
2	**OisoButyl**	12	**5b**(90)	**6b**(traces)	**7b**(--)
3	**Ph**	24	**5c**(90)	**6c**(<5)	**7c**(--)
4	**4-Pyridyl**	24	**5d**(87)	**6d**(--)	**7d**(--)
5	**$CH(OMe)_2$**	24	**5e**(75)	**6e**(--)	**7e**(--)
6	**CN**	18	**5f**(40)	**6f**(30)	**7f**(20)
7	**COMe**	10	**5g**(10)	**6g**(¬10)	**7g**(70)
8	**CO_2Me**	15	**5h**(15)	**6h**(15)	**7h**(60)

Introduction and literature review

- Kuzenkov et al in 2018 synthesized substituted 3-(1,2-oxazolidin-3-yl)pyridines by reacting N-(pyridin-3-ylmethylidene)-N-phenylaminoxide with ethyl acrylate, styrene and their derivatives.



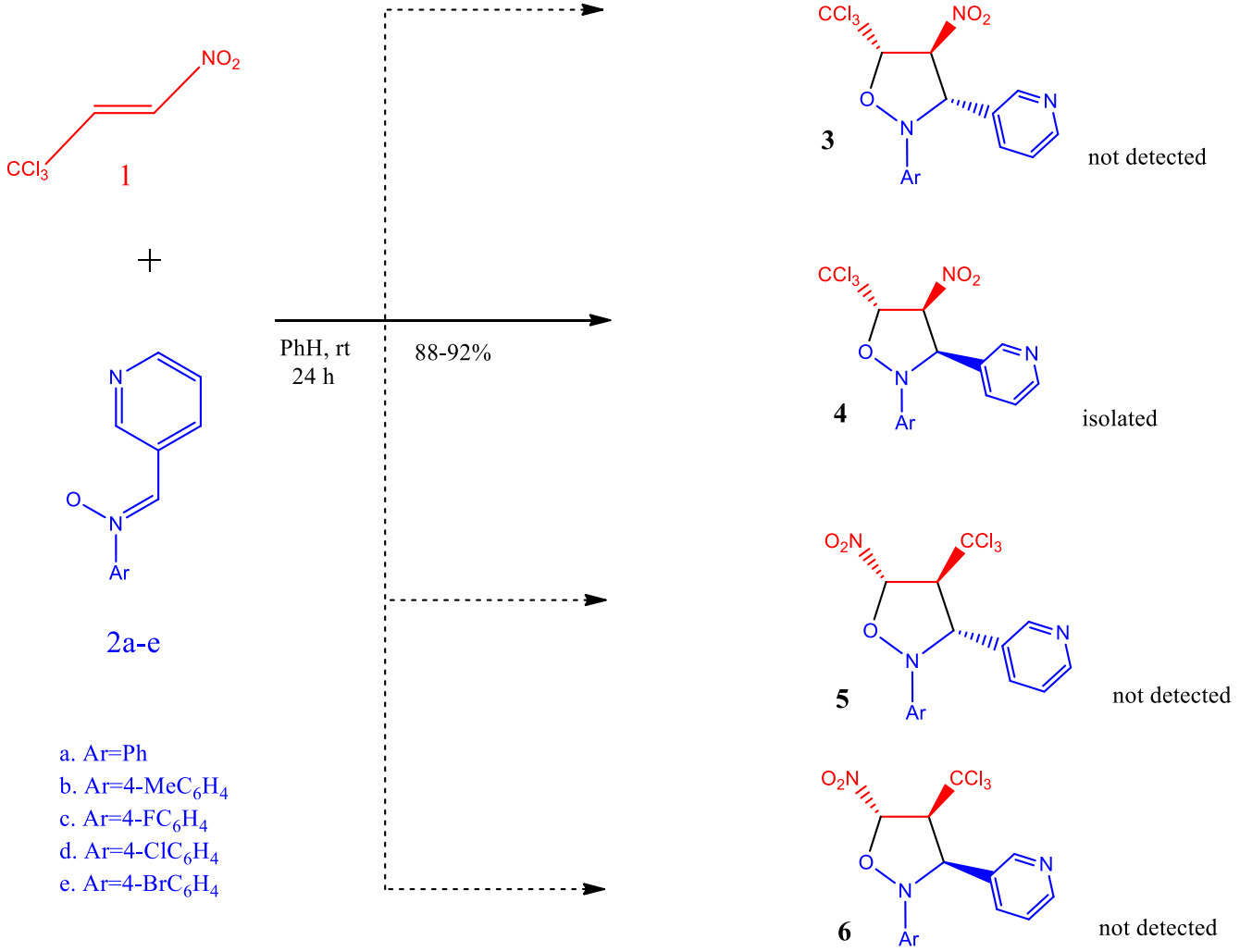
2a, 2b **1a–1e**

1, $R^1 = R^2 = H$, $R^3 = Ph$ (**a**); $R^1 = H$, $R^2 = COOEt$, $R^3 = C_6H_4F$-4 (**b**); $R^1 = Cl$, $R^2 = COOEt$, $R^3 = H$ (**c**); $R^1 = Cl$, $R^2 = H$, $R^3 = Ph$ (**d**); $R^1 = Cl$, $R^2 = H$, $R^3 = C_6H_4Br$-4 (**e**); **2**, $R^1 = H$ (**a**), Cl (**b**).

Kuzenkov, A.V., Zakharychev, V.V. and Volkova, A.N., 2018. Synthesis and Fungicidal Activity of Substituted 3-(1, 2-Oxazolidin-3-yl) pyridines. *Russian Journal of Organic Chemistry*, *54*(5), pp.763-765.

Introduction and literature review

- Fryźlewicz et al also reported on the reaction between (*E*)-3,3,3-Trichloro-1-nitroprop-1-ene and *N*-aryl(pyridin-3-yl) nitrones.



Fryźlewicz, A., Łapczuk-Krygier, A., Kula, K., Demchuk, O.M., Dresler, E. and Jasiński, R., 2020. Regio-and stereoselective synthesis of nitrofunctionalized 1, 2-oxazolidine analogs of nicotine. *Chemistry of Heterocyclic Compounds*, pp.1-3.

Aims and Objectives

- From the papers reviewed, a novel reaction route for synthesizing a nicotine analog has been developed by singh et al in 2005.
- This reaction route which possesses a high degree of regio- and stereo-selectivity has been used been worked on by other researchers such as Kuzenkov et al and Fryźlewicz et al.
- But through all their research, an explanation on the selectivity observed in the reaction has not been explored.
- My objective is to apply computational chemistry tools to explore the selectivity observed and also provide a mechanistic insight into the effects of substituents on the reaction.

Aims and objectives

- ❖To ascertain what is controlling the regio- and stereoselectivity.
- ✓The mechanistic effect of a wide range of substituents on both reactants with different electronic and steric effects.
- ❖To investigate the effect of solvent on the rate and selectivities of the reaction.

Justification

- This will help rationalize this unique reactivity pattern seen with the reaction of (E)-nitro-substituted alkene with nitrones for the formation of nicotine analogs.
- The study will provide a justification to the experimental result that was obtained.

Methodology

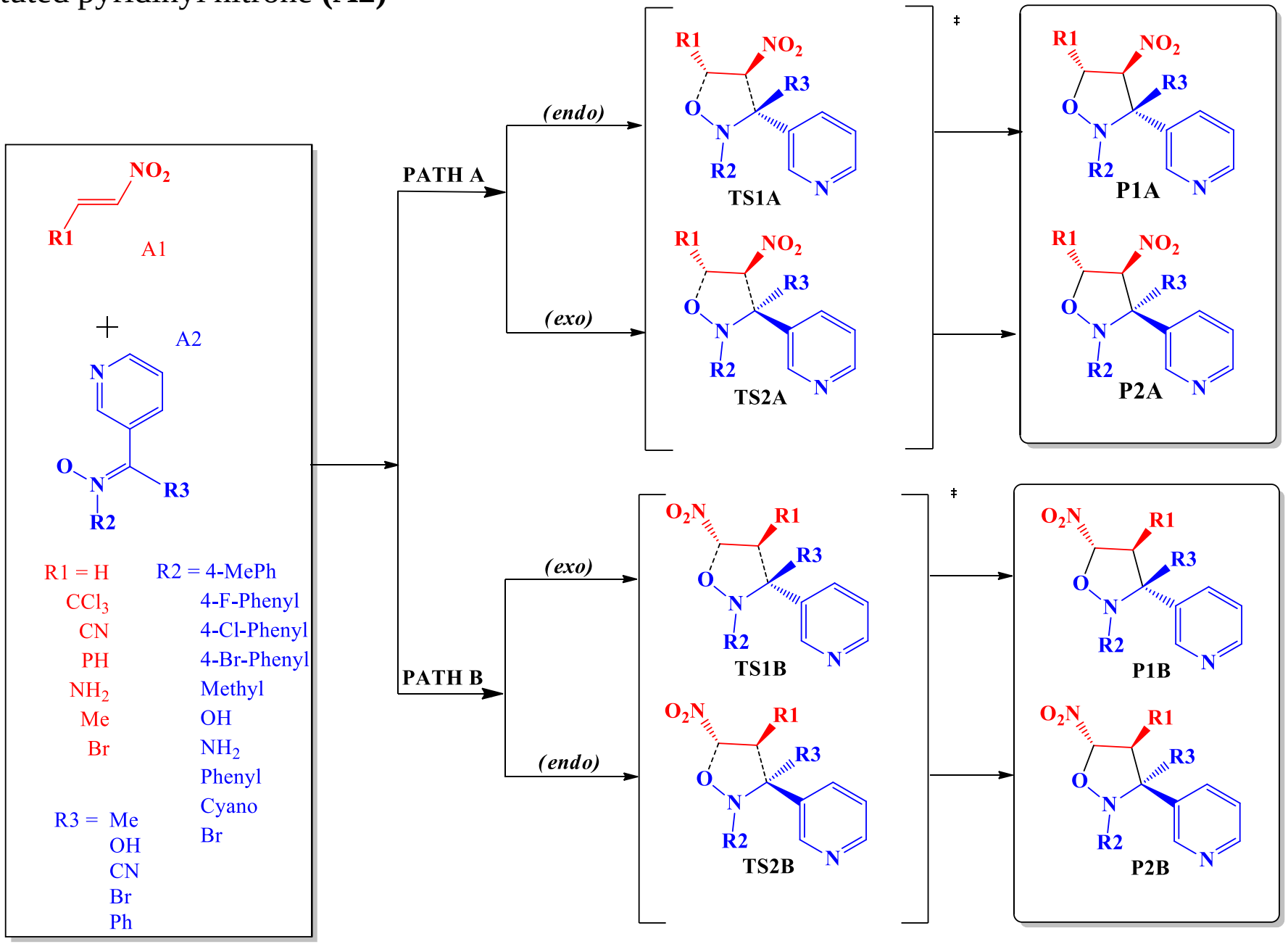
- The geometries of the molecular systems were constructed and minimized using "Spartan 10" model builder.
- Geometry and energy optimization of the stationary points (reactants, transition states structures and products) were carried out using B3LYP-D3 method with

  6-311G (d, p) basis sets using "Gaussian 09".
- The rate constants of the reaction at a 25ºC [k(T)] were calculated using equation: $K(T) = \frac{K_B\ T}{hc^\circ} e^{-\Delta^\ddagger G/RT}$, where K_B = 1.380662 × 10^{-23} J/K, T = 298.15 K, h = 6.62617 × 10^{-34} Js, R = 1.987 cal/mol, c = 1. $\Delta^\ddagger G^\circ$ is Gibbs free energy of activation.
- The global reactivity indices were calculated using: $\omega = \mu^2/2\eta$,

  $N = E_{HOMO(Nuc)} - E_{HOMO(TCE)}$, where $\mu = (E_{HOMO} + E_{LUMO})/2$ and

  $\eta = (E_{HOMO} - E_{LUMO})$.
- $E_{HOMO(TCE)}$ = -9.120689505 eV

Scheme 3: Proposed scheme for the reaction of (E)-substituted nitroethene derivative (**A1**) with *C*, *N*-disubstituted pyridinyl nitrone **(A2)**



RESULTS AND DISCUSSION

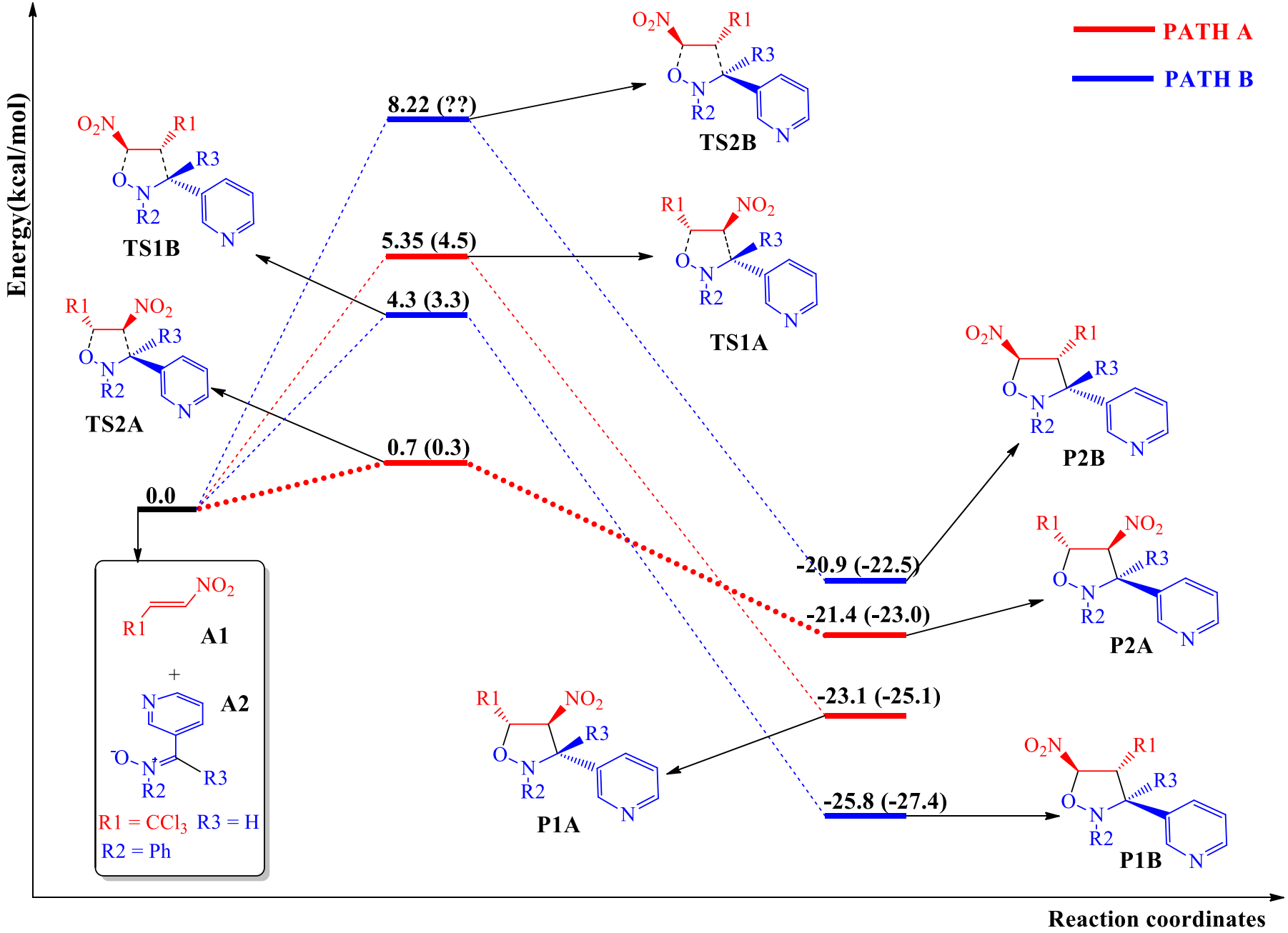


Figure 1: Gibbs free energy profile for the reaction of (E)-substituted-nitroethene with C, N-Disubstituted pyridinyl nitrone in both gas phase and solvent phase (benzene).

Table 1: Rate constants of the reaction (E)-substituted-nitroethene with N-Phenyl-C-pyridinyl-nitrone for the formation of the various cycloadducts computed in both gas phase and solvent phase (benzene) at room temperature. **R1** = CCl3, **R2** = Phenyl and **R3** = H

Products	**Rate constants[k(T)]/s^{-1}**	**Rate constants[k(T)]/s^{-1}**
	Gas phase	**Solvent phase (benzene)**
P1A	3.07×10^{9}	7.43×10^{8}
P2A	3.87×10^{12}	1.81×10^{12}
P1B	2.21×10^{10}	4.23×10^{9}
P2B	-	5.85×10^{6}

Solvent effect

Table 2: Activation energies and reaction energies of the various elementary steps in the reaction between (E)-substituted-nitroethene derivatives with *N*-substituted-*C*-pyridinyl-nitrones in different solvents.
R1 = CCl_3 , R2 = Phenyl and R3 = H

Solvent	TS1A	TS1B	TS2A	TS2B	P1A	P1B	P2A	P2B
Benzene	5.4	4.3	0.7	8.2	-23.1	-25.8	-21.4	-20.9
Toluene	5.4	4.4	0.8	8.3	-23.0	-25.7	-21.3	-20.8
Nitromethane	6.0	5.1	0.9	9.4	-21.1	-24.3	-19.9	-19.3

Table 3: Activation energies and reaction energies of the various elementary steps in the reaction between (E)-substituted-nitroethene derivatives with *C, N*-disubstituted pyridinyl nitrone at different level of theories. R1 = CCl_3 , R2 = Phenyl and R3 = H

Basis sets : 6-311G (d, p)

Level of theory	TS1A	TS2A	TS1B	TS2B	P1A	P2A	P1B	P2B
B3LYP	18.6	14.2	-	22.5	-11.4	-9.8	-13.1	-6.7
B3LYP-D3	5.4	0.7	4.3	8.2	-23.1	-21.4	-25.8	-20.9
M06	-5.7	-5.8	5.6	9.9	-29.3	-27.5	-32.7	-21.0
M06-2X	3.5	-2.5	2.9	5.7	-35.4	-34.7	-38.3	-33.4

Table 4: Activation energies and reaction energies (in kcal/mol) of the various elementary steps in the reaction of **(E)-substituted- nitroethene derivatives** and *N*-Phenyl-*C*-pyridinyl Nitrones.

R1	TS1A	TS2A	TS1B	TS2B	P1A	P2A	P1B	P2B
H	6.3	4.1	7.5	8.3	-19.2	-17.5	-22.4	-21.8
EDG								
Methyl	8.4	4.4	11.4	12.8	-17.7	-17.6	-19.9	-17.8
NH_2	12.9	9.9	21.1	20.3	-9.8	-10.3	-9.1	-2.5
EWG								
CN	5.1	4.3	4.7	5.6	-17.0	-14.1	-20.8	-19.3
Br	6.2	3.8	7.2	9.0	-24.6	-23.8	-23.1	-22.1
BG								
Phenyl	8.4	6.9	15.8	11.0	-16.8	-14.7	-17.8	-15.3

Table 5: Activation energies and reaction energies (in kcal/mol) of the various elementary steps in the reaction of (E)-substituted nitroethene (R1 = CCl_3) with ***C, N*-disubstituted pyridinyl nitrones derivatives**.

R2	R3	TS1A	TS2A	TS1B	TS2B	P1A	P2A	P1B	P2B
Methyl	**H**	6.4	3.3	10.0	11.4	-21.1	-19.6	-23.5	-18.4
NH_2	**H**	5.7	3.0	12.6	10.5	-22.6	-20.8	-25.1	-21.6
OH	**H**	11.6	7.7	13.1	13.7	-15.6	-14.3	-18.2	-13.8
CN	**H**	4.0	1.9	7.0	6.9	-29.6	-	-31.8	-27.5
Br	**H**	14.2	12.2	15.2	17.6	-13.5	-12.1	-15.2	-14.0
4-Me-Ph	**H**	6.5	1.9	-	9.4	-21.7	-19.8	-24.2	-18.8
4-F-Ph	**H**	5.6	0.9	4.7	8.5	-21.6	-19.7	-24.2	-18.8
4-Br-Ph	**H**	5.6	0.9	4.6	8.4	-23.5	-21.6	-26.1	-21.0
4-Cl-Ph	**H**	5.6	0.9	4.6	8.5	-21.7	-19.9	-24.3	-19.3
Ph	**Methyl**	3.8	-0.4	5.4	7.4	-24.7	-23.0	-22.9	-16.6
Ph	**OH**	-	-7.1	-2.4	-1.3	-26.3	-	-25.6	-20.0
Ph	**CN**	12.8	6.8	12.5	15.3	-16.1	-15.2	-16.5	-9.7
Ph	**Br**	8.1	3.1	7.8	11.3	-31.4	-30.9	-26.8	-30.6
Ph	**Phenyl**	7.6	-8.8	0.8	1.2	-24.8	-24.3	-20.4	-17.7

Fig 2: Graphical illustration of the highest occupied molecular orbital (HOMO) – lowest unoccupied molecular orbital (LUMO) interaction between **(E)-substituted-nitroethene (A1)** and ***N*-phenyl-*C*-pyridinyl-Nitrone (A2)** .
R1 = CCl_3 , R2 = Phenyl and **R3 = H**

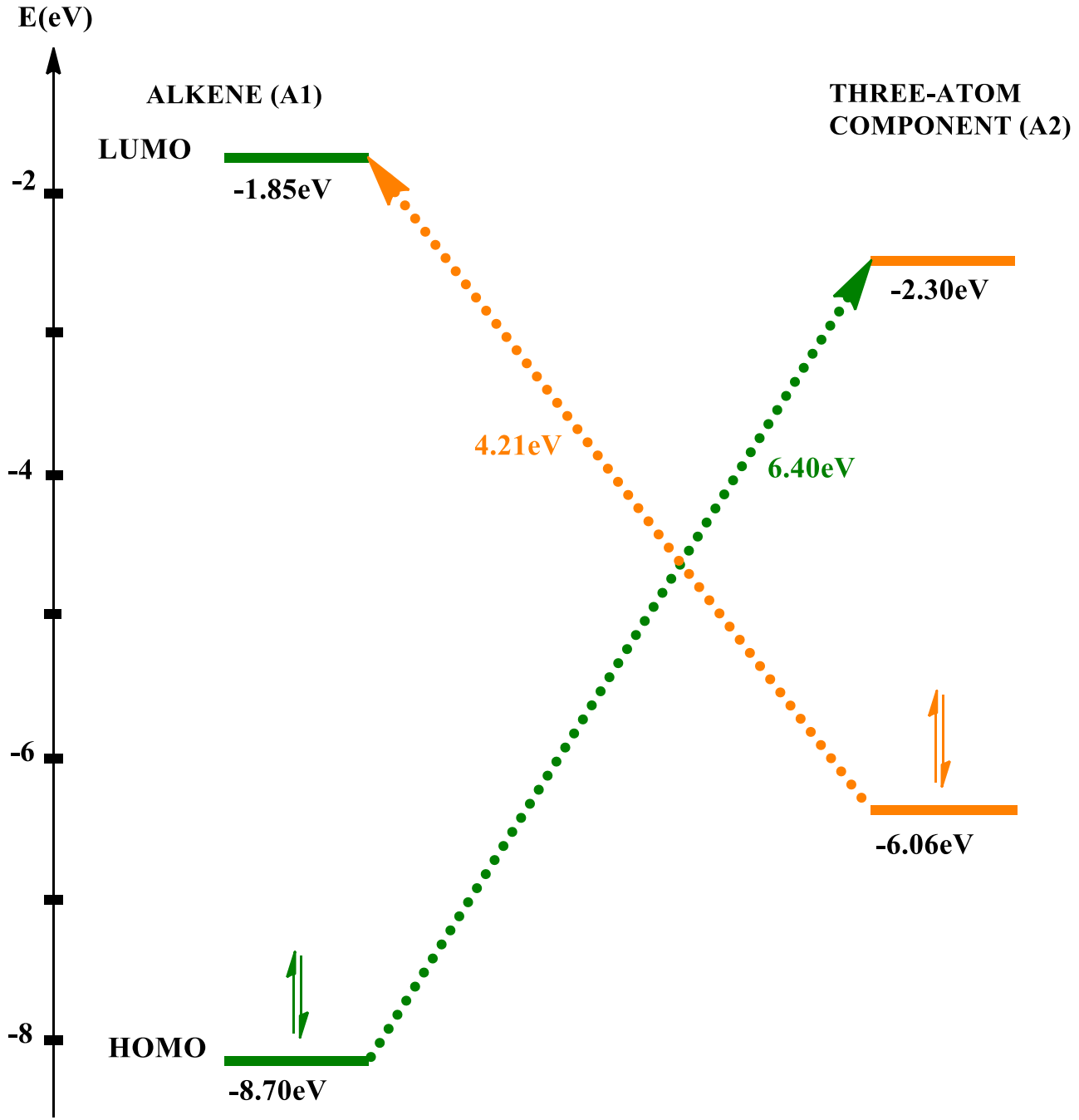


Table 6: Global reactivity indices for (E)-substituted-nitroethene, **A1** (alkene). HOMO, LUMO energies, electronic chemical potential (μ), chemical hardness (η), global electrophilicity (ω) and global nucleophilicity (N). All in eV.

R1	HOMO	LUMO	μ	η	ω	N
CCl_3	-8.70	-1.85	-5.27	6.84	2.03	0.43
H	-8.36	-2.80	-5.58	5.56	2.80	0.76
Methyl	-8.17	-2.57	-5.37	5.60	2.57	0.95
NH_2	-6.74	-1.91	-4.33	4.83	1.94	2.38
CN	-8.90	-3.74	-6.32	5.16	3.87	0.22
Br	-8.09	-3.01	-5.55	5.08	3.03	0.03
Phenyl	-7.09	-2.89	-4.99	4.20	2.96	2.03

Table 7: Global reactivity indices for *N*-Substituted-*C*-pyridinyl-nitrones, **A2** (three-atom components). HOMO, LUMO energies, electronic chemical potential (μ), chemical hardness (η), global electrophilicity (ω) and global nucleophilicity (N). All in eV.

R2	R3	HOMO	LUMO	μ	η	ω	N
Methyl	**H**	-6.09	-1.85	-3.97	4.24	1.86	3.03
NH_2	**H**	-6.25	-1.93	-4.09	4.32	1.94	2.87
OH	**H**	-6.34	-1.89	-4.12	4.45	1.91	2.78
CN	**H**	-6.81	-3.04	-4.93	3.77	3.22	2.31
Br	**H**	-6.21	-2.16	-4.19	4.05	2.17	2.91
Phenyl	**H**	-6.06	-2.30	-4.18	3.76	2.33	3.06
4-Me-Ph	**H**	-6.02	-2.12	-4.07	3.90	2.12	3.10
4-Cl-Ph	**H**	-6.16	-2.44	-4.30	3.72	2.49	2.96
4-F-Ph	**H**	-6.11	-2.35	-4.23	3.76	2.38	3.01
4-Br-Ph	**H**	-6.15	-2.45	-4.30	3.70	2.50	2.97
Ph	**Me**	-5.98	-1.86	-3.92	4.12	1.86	3.14
Ph	**OH**	-5.85	-2.03	-3.94	3.82	2.03	3.27
Ph	**CN**	-6.64	-2.81	-4.73	3.83	2.92	2.48
Ph	**Br**	-6.21	-2.16	-4.19	4.05	2.17	2.91
Ph	**Ph**	-6.00	-2.21	-4.11	3.79	2.23	3.12

Conclusion

- The 32CA reaction between (E)-substituted-nitroethene derivatives (**A1**, R1= CCl3) and C, N-disubstituted-pyridinyl nitrone derivatives (**A2**, R2= Phenyl and R3 = H) is fully regio- and stereoselective towards the formation of the exo 4-nitro substituted nicotine analog product (**P2A**).This reaction is kinetically controlled.
- Solvent show no significant effect on the energetic pattern.
- Electron-donating and withdrawing groups on both **A1** and **A2** increase the activation energies of the reaction relative to the parent reaction but reaction trend remains the same.
- EDGs substitution on the alkene is fully regioselective to path A whiles EWGs substitution is partially regioselective to both path A and B.
- The reactions are kinetically controlled due to the thermodynamic stability of all the considered isomeric products in all reactions studied.

THANK YOU