

Exploration of regioselectivity phenomenon in [2+3] cycloaddition reactions between arylnitrones and trans-substituted nitroethenes on the basis of the reactivity indices theory

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ABSTRACT

Analysis of global electrophilicity and nucleophilicity power of the addends indicate polar character of [2+3] cycloaddition reactions between arylnitrones and trans-substituted nitroethenes. The regioselectivity of these reactions is determined by nucleophilic attack of oxygen atom from nitrone on activated β -position of nitroalkene. Interaction of this type leads to 4-nitroisoxazolidines, which are the only reaction products.

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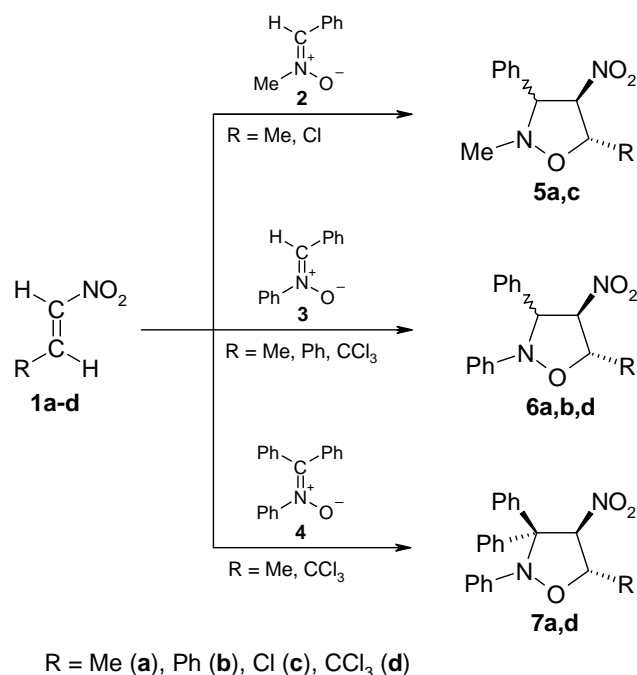
1. Introduction

[2+3] Cycloaddition reactions of nitrones with conjugated nitroalkenes are the most universal methods for preparation of nitroisoxazolidines, which are effective synthons in syntheses of aminoacids, alkaloids and β -lactams^{1,2}. It is interesting, that these reactions exhibit extremely high regioselectivity. [2+3] Cycloaddition of nitrones with simple α,β -disubstituted ethenes almost always leads to mixtures of regioisomeric adducts. On the other hand, [2+3] cycloaddition of arylnitrones with trans-substituted nitroethenes usually proceeds in a regioselective way (e.g., the reaction of arylnitrones with (E)-1-nitroprop-1-ene³⁻⁵, (E)- β -nitrostyrene⁶, (E)-2-chloro-1-nitroethene⁷ and (E)-3,3,3-trichloro-1-nitroprop-1-ene^{4,7}). All of these reactions occur with full regiocontrol and lead to the

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corresponding 4-nitroisoxazolidines as the only reaction products (**Scheme 1**, **Table 1**), regardless of the nature of substituent in β -position of the nitroethenyl moiety (**Table 2**). In the present work we decided to explain this phenomenon on the grounds of electrophilicity and nucleophilicity indices theory. Recently, similar approach was used successfully to explain the regiochemical aspects of nitrones [2+3] cycloaddition with several dipolarophiles^{8,9}.



Scheme 1. Regioselectivity of [2+3] cycloaddition reactions between nitroalkenes **1a-d** and nitrones **2-4**.

Table 1. Experimental conditions and yields for model reactions.

Addents		Conditions	Yields [%]	Regioisomer ratio [4-nitro]:[5-nitro]	Ref.
Nitroalkene	Nitrone				
1a	2	80°C, benzene, 3h	94	1:0	3
1a	3	25°C, toluene, 24h	97	1:0	4
1a	4	25°C, solvent free, 0,25h	96	1:0	5
1b	3	80°C, toluene, 24h	92	1:0	6
1c	2	25°C, benzene, 24h	41	1:0	7
1d	3	25°C, toluene, 24h	94	1:0	4
1d	4	25°C, toluene, 12h	98	1:0	6

2. Results and Discussion

The global (electronic potential μ , electrophilicity power ω , nucleophilicity N) and local (electrophilicity ω_k , nucleophilicity N_k) reactivity indices for example reactants (**1-2**) were estimated according to the equations recommended by *Parr*¹⁰ and *Domingo*⁸ (for details see next section). Electrophilicity scale was built and validated by *Domingo* group¹¹ based on the B3LYP/6-31g(d) calculations. This model was adopted for most reaction systems⁹. Therefore, the quantum chemical calculations were performed using B3LYP/6-31g(d) theoretical level¹². The results are collected in

Table 2. Global and local electronic properties of nitroalkenes **1a-d** and nitrones **2-4**

1	R	σ_R	Global properties			Local properties				
			μ (a.u.)	ω (eV)	N (eV)	ω_α (eV)	ω_β (eV)	N _C (eV)	N _O (eV)	
1a	Me	-0.17	-0.1867	2.36		0.05	0.25			
1b	Ph	-0,01	-0.1760	2.66		0.10	0.23			
1c	Cl	0.23	-0.2053	2.89		0.09	0.34			
1d	CCl ₃	0.45	-0.2147	3.27		0.15	0.34			
2	2	- 3	-	-0.1244	1.35	3.62			0.29	0.63
3	-	-	-	-0.1312	1.67	3.64			0.28	0.57
4	-	-	-	-0.1256	1.56	3.83			0.31	0.60

It has been found, that the nitrones **2-4** show weaker electrophilic character than the nitroethenes **1a-d**. Their electronic potential (μ) equals $-0.1244 \div -0.1256$ a.u., whereas that of the nitroalkenes **1a-d** is only $-0.1867 \div -0.2147$. This indicates, that in the reactions studied, the charge should be transferred from nitrone to nitroalkene. Analysis of global electrophilicity indices (ω) leads to similar conclusion.

In particular, global electrophilicity (ω) of 1-nitroprop-1-ene (**1a**) is equal 2.36 eV. Replacement of methyl group with phenyl ring increases ω value to 2.66 eV. Further increase of the nitroalkene electrophilicity takes place after introduction electron withdrawing substituents (e.g., Cl, CCl₃) into the β -position of nitrovinyl moiety. In consequence, 3,3,3-trichloro-1-nitroprop-1-ene ($\omega=3.27$ eV) is the strongest electrophile in this study.

Table 3. Electrophilicity difference ($\Delta\omega$) for the nitroalkene/nitrone pairs

Addents		$\Delta\omega$
Nitroalkene	Nitrone	[eV]
1a	2	1.01
1a	3	0.69
1a	4	0.80
1b	3	0.99
1c	2	1.54
1d	3	1.60
1d	4	1.71

For comparison, global electrophilicity (ω) of the nitrone (**2**) equals 1.35 eV. Hence in terms of the *Domingo* terminology⁸, **2** is a moderate electrophile. The ω values of the nitrones **3** and **4** are slightly higher (1.67 eV and 1.56 eV respectively), so they are stronger electrophiles. This is what we expected due to the nucleophilic character of $>C=N(O)-$ moiety, electrophilicity of the nitrones **2-4** are lower than those of the nitroalkenes **1a-d**. In the reactions studied they are nucleophiles (global nucleophilicity $N > 3.5$ eV).

The electrophilicity difference ($\Delta\omega$) of the analysed reagent pairs (**Scheme 1**) is in the range from 0.69 to 1.71 (**Table 3**). Therefore, the reactions can be considered as polar cycloadditions⁸. According to the *Domingo* concept^{8,13}, the regioselectivity of such reactions may be forecasted using local electrophilicity (ω_k) and nucleophilicity (N_k) indices. According to this approach, most favorable interaction takes place between most nucleophilic and most electrophilic centers.

The values of ω_k obtained for the nitroalkenes **1a-d** (**Table 2**) indicate, that β -position of the nitrovinyl moiety is the most electrophilic site, therefore, it should be the preferred position for

nucleophilic attack. In particular, for less electrophilic 1-nitroprop-1-ene (**1a**) $\omega_{\beta}=0.23$ eV, whereas for more electrophilic 3,3,3-trichloro-1-nitroprop-1-ene (**1d**) $\omega_{\beta}=0.34$ eV. On the other hand, the N_k indices indicate that in the nitrones **2-4**, the oxygen atom of $>C=N(O)-$ moiety is the most nucleophilic site ($N_O=0.57\div 0.63$ eV). Hence, the reaction course should be controlled by the attack of one of the nucleophilic sites in the nitrone on the electrophilic site localized on the atom C_{β} in nitrovinyl group of the corresponding nitroalkene. (**Scheme 1**). Interactions of this type lead to 4-nitroisoxazolidines.

3. Conclusions

Analysis of global electronic properties of the addends indicate polar character of [2+3] cycloaddition reactions between arylnitrones and trans-substituted nitroethenes. This is consistent with the kinetic studies^{3,7}. The regioselectivity of these reaction is determined by nucleophilic attack of the oxygen atom of $>C=N(O)-$ nitrone moiety on activated β -position of nitroalkene. Interaction of this type leads to 4-nitroisoxazolidines as the only reaction products³⁻⁷.

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Computational details

The quantum-chemical calculations were performed on a SGI-Altix-3700 computer in the Cracow Computing Center "CYFRONET". Hybrid B3LYP functional and 6-31G(d) basis set included within GAUSSIAN 2009 software¹² were applied. For structure optimization of the reactants FOPT procedure was applied. Calculations of all critical structures were performed for the temperature $T=298$ K and pressure $p=1$ atm. The global reactivity indexes were estimated according to equations recommended by *Parr* and *Yang*¹⁰ and *Domingo*⁸. In particular, the electronic chemical potentials (μ) and chemical hardness (η) of the reactants **1** and **2** were evaluated in terms of the one electron energies of FMO:

$$\mu=(E_{\text{HOMO}}+E_{\text{LUMO}})/2; \quad \eta=E_{\text{LUMO}}-E_{\text{HOMO}}$$

The values of μ and η were then used for calculation of the global electrophilicity (ω) according to the formula:

$$\omega=\mu^2/2\eta$$

The global nucleophilicity (N) of nitrones **1a-d** was calculated as the difference¹²:

$$N=E_{\text{HOMO}}(\text{nitrone})-E_{\text{HOMO}}(\text{tetracyanoethene})$$

The local electrophilicity (ω_k)⁸ condensed to atom k was calculated by projecting the index ω onto reaction centre k in the molecule by using *Fukui* function f_k^+ , whereas the local nucleophilicity (N_k)¹³ condensed to atom k was calculated using global nucleophilicity N and *Fukui* function f_k according to the formulas:

$$\omega_k=f_k^+\omega; \quad N_k=f_kN$$

According to Contreras observations¹⁴, Fukui f_k^+ is represented by the square of the suitable LUMO coefficient (C), whereas f_k^- by the square of the suitable HOMO coefficient:

$$f_k^+ = C_{\text{LUMO}}^2; \quad f_k^- = C_{\text{HOMO}}^2$$

The results are collected in Table 2.

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