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## Highlights

- SET mechanism has been suggested to describe the nucleophilic aromatic substitution reactions of 2-methoxy-3,5-dinitropyridine by secondary cyclic amines in acetonitrile solution.
- $E$  values of six anisoles have been predicted according to the  $E$  vs  $\omega$  correlation (Eq.I) demonstrated in this work and found to agree with those reported in the literature.
- $E = -93.41 + 23.73 \omega$  ( $R^2 = 0.9997$ ) (I)
- The expansion of the applicability of Mayr's equation (II) to these types of processes further demonstrates the generality of this relationship.
- $\log k (20\text{ }^\circ\text{C}) = s_N (E + N)$  (II)

Journal Pre-proof

# Electrophilicity, Mechanism and Structure-Reactivity Relationships of Cyclic Secondary Amines Addition to 2-Methoxy-3,5-dinitropyridine

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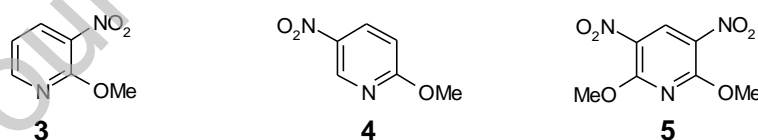
## ABSTRACT

The second-order rate constants ( $k$ ) for the nucleophilic aromatic substitution reactions of 2-methoxy-3,5-dinitropyridine **1** with secondary cyclic amines **2a-c** in acetonitrile solution at 20 °C are reported. The logarithms of these rate constants are particularly significant as possible measures of the electrophilicity parameters  $E$  for 2-methoxy-3,5-dinitropyridine **1** according to the linear free energy relationship  $\log k (20\text{ °C}) = s_N(N + E)$ . Additional kinetic data for reactions of 2-methoxy-3,5-dinitropyridine **1** with a series of nitroalkyl anions in DMSO solution are also measured and found to agree with those calculated by Mayr's approach from the known two solvent-dependent parameters  $N$  and  $s_N$  of nitroalkyl anions and the electrophilicity parameter  $E$  measured in this work. A Single Electron Transfer (SET) mechanism is proposed for the  $S_NAr$  reactions, on the basis of the linear Brønsted plot with the  $\beta_{\text{nuc}}$  value of 0.94. The validity of this mechanism is confirmed by the agreement between the rate constants,  $k$ , and the oxidation potentials  $E^\circ$  of these series of secondary cyclic amines. Also, reactivity descriptors such as the electronic chemical potential ( $\mu$ ), and the chemical hardness ( $\eta$ ) for a series of pyridine derivatives were calculated by Density Functional Theory (DFT), and it is shown that the global electrophilicity index ( $\omega = \mu^2/\eta$ ) correlate significantly with the electrophilicity parameters  $E$ .

**Keywords** : Substituted Pyridine Derivatives / Kinetics / Equation of Mayr / Electrophilicity / Single Electron Transfer Mechanism / DFT Analysis.

## 1. Introduction

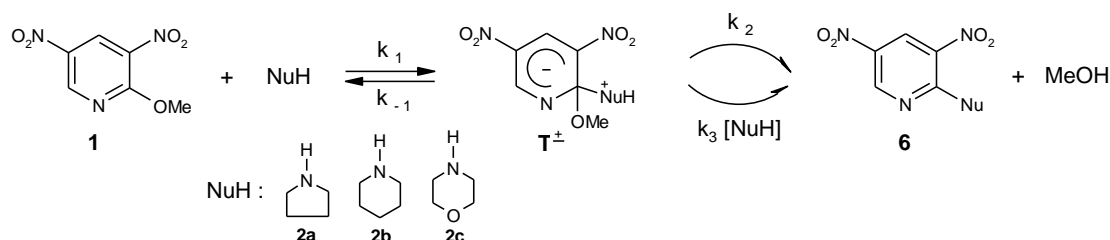
Pyridine derivatives have been widely investigated for their importance in biological and industrial processes and synthetic applications.[1-7] In terms of reactivity, it should be noted that isomeric addition at substituted and unsubstituted carbons of some pyridine derivatives has been the subject of extensive experimental and theoretical studies. [8-10] Reactions of 2-methoxy-3-nitropyridine **3** with a series of secondary cyclic amines have generally been understood to proceed through a polar  $S_NAr$  mechanism on the basis of the fact that Brønsted plot was found to be linear with  $\beta_{nuc} = 0.52$ . [11] Similar conclusion has also been drawn for the corresponding reactions with 2-methoxy-5-nitropyridine **4** ( $\beta_{nuc} = 0.55$ ). [11] While, Mahdhaoui and coworkers have recently reported that the reactions of 2,6-dimethoxy-3,5-dinitropyridine **5** with weakly basic 4-X-substituted phenoxide anions (e.g., X = Cl and CN) proceeds through a polar  $\sigma$ -complexation mechanism, while the corresponding reaction with strongly basic phenoxide anions (e.g., X = Me and OMe) proceeds through a single electron transfer mechanism (SET). [12] Such single electron transfer mechanism in  $\sigma$ -complexation reactions is considered to be the only time reported in literature but have been observed in some  $S_NAr$  reactions. [13-15]



To get more information on reactivity and mechanism, our kinetic study has been extended to reactions of 2-methoxy-3,5-dinitropyridine **1** with the secondary cyclic amines **2a-c** as reference nucleophiles in acetonitrile at 20 °C (Scheme 1). As will be seen, the effect of the nucleophile nature on reactivity and mechanism have been examined quantitatively and discussed on the basis of linear free-energy relationships (LFER). On the other hand, the second-order rate constants ( $k$ ) of these reactions have been described by Equation (1) (where  $N$  and  $s_N$  are nucleophile-specific parameters) [16] in order to evaluate the electrophilicity parameter  $E$  of the electrophile **1** and to include it into the comprehensive electrophilicity scale of Mayr.

$$\log k (20\text{ }^\circ\text{C}) = s_N (E + N) \quad (1)$$

In addition, theoretical study based on density functional theory has been performed at the B3LYP/6-311g(d,p) level [17] in order to establish a correlation between the calculated global electrophilicity index ( $\omega$ ) values for a series of pyridines and their electrophilicity parameter  $E$  measured using Mayr's approach.

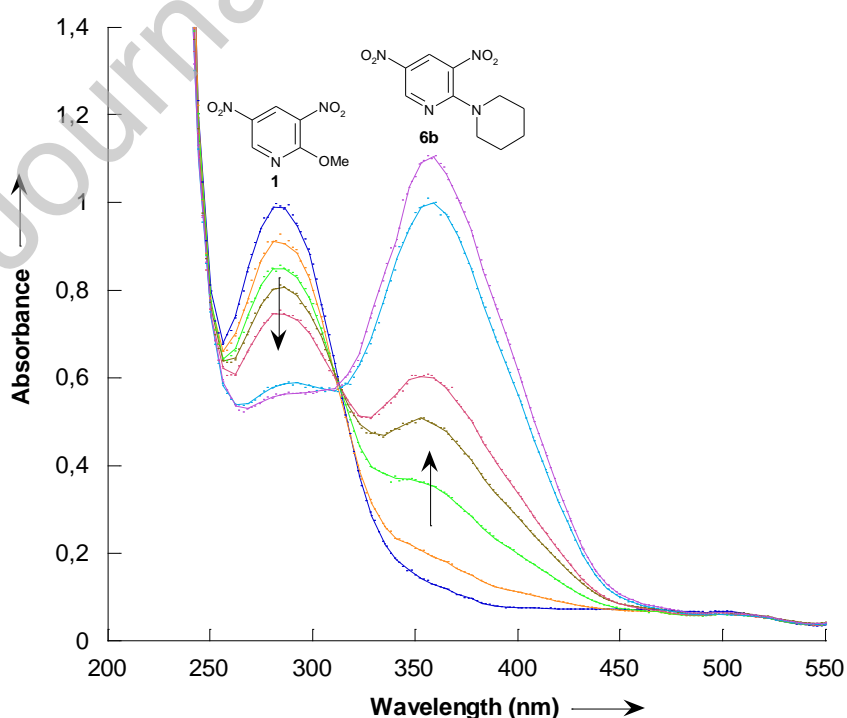


**Scheme 1.**  $S_NAr$  reactions of the 2-methoxy-3,5-dinitropyridine **1** with various secondary cyclic amines in  $CH_3CN$  at  $20\text{ }^\circ C$ .

## 2. Results and Discussion

### 2.1. Structural studies of the substitution products **6a-c**

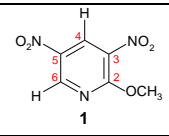
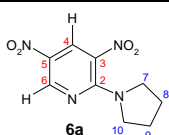
Addition of dilute solutions of amines **2a-c** to a colorless solution of 2-methoxy-3,5-dinitropyridine **1** in acetonitrile resulted in the formation of yellow species exhibiting intense absorption maxima at 356, 358 and 331 nm, respectively. These  $\lambda_{max}$  are characteristic for the formation of substitution products. Figure 3 illustrates the UV-vis absorption spectra describing the progressive conversion of the 2-methoxy-3,5-dinitropyridine **1** to the substitution product **6b**. A clear isosbestic point is observed at 312 nm, indicating the involvement of two species in an equilibrium.



**Figure 1.** Time dependence of the electronic absorption spectrum of 2-methoxy-3,5-dinitropyridine **1** ( $5 \times 10^{-5}\text{ mol L}^{-1}$ ) in the presence of piperidine **2b** ( $2 \times 10^{-2}\text{ mol L}^{-1}$ ) in  $CH_3CN$  solution at  $20\text{ }^\circ C$ .

It is interesting to note that pyridine **1** does not give  $\sigma$ -adduct of C-H attack with any of the investigated nucleophiles under the reaction conditions; only attack at C-OMe to afford the substitution products **6** is observed. Substitution products **6a-c** have also been characterized through analysis of  $^1\text{H}$  NMR spectra. In the case of substitution product **6a**, all the chemical shifts and coupling constants data are summarized in Table 1. Interestingly, we have succeeded in isolating **6a**. Dissolution of this compound in  $\text{CD}_3\text{CN}$  afforded NMR spectra which were identical to those recorded in the *in situ* generation of **6a** in this solvent.

**Table 1.**  $^1\text{H}$  NMR shifts values for 2-methoxy-3,5-dinitropyridine **1** and the substitution product (3,5-dinitro-2-(pyrrolidin-1-yl)pyridine) **6a** (300 MHz,  $\text{CD}_3\text{CN-d}_3$ ).

	$\delta$ (ppm)					Coupling constants (Hz)
	<b>H<sub>4</sub></b>	<b>H<sub>6</sub></b>	<b>CH<sub>3</sub></b>	<b>H<sub>7-10</sub></b>	<b>H<sub>8-9</sub></b>	
 <p><b>1</b></p>	9.27	8.99	4.20	–	–	$J_{4-6} = 2.6$
 <p><b>6a</b></p>	8.78 <sup>a</sup> (8.78) <sup>b</sup>	9.11 (9.11)	–	3.47 (3.49)	1.97 – 2.01 (1.97 – 2.01)	$J_{4-6} = 2.6$ ( $J_{4-6} = 2.4$ )

<sup>a</sup>Product *in situ*.

<sup>b</sup>Synthesized product.

## 2.2. Kinetics of the reactions of 2-methoxy-3,5-dinitropyridine **1** with secondary cyclic amines **2a-c**

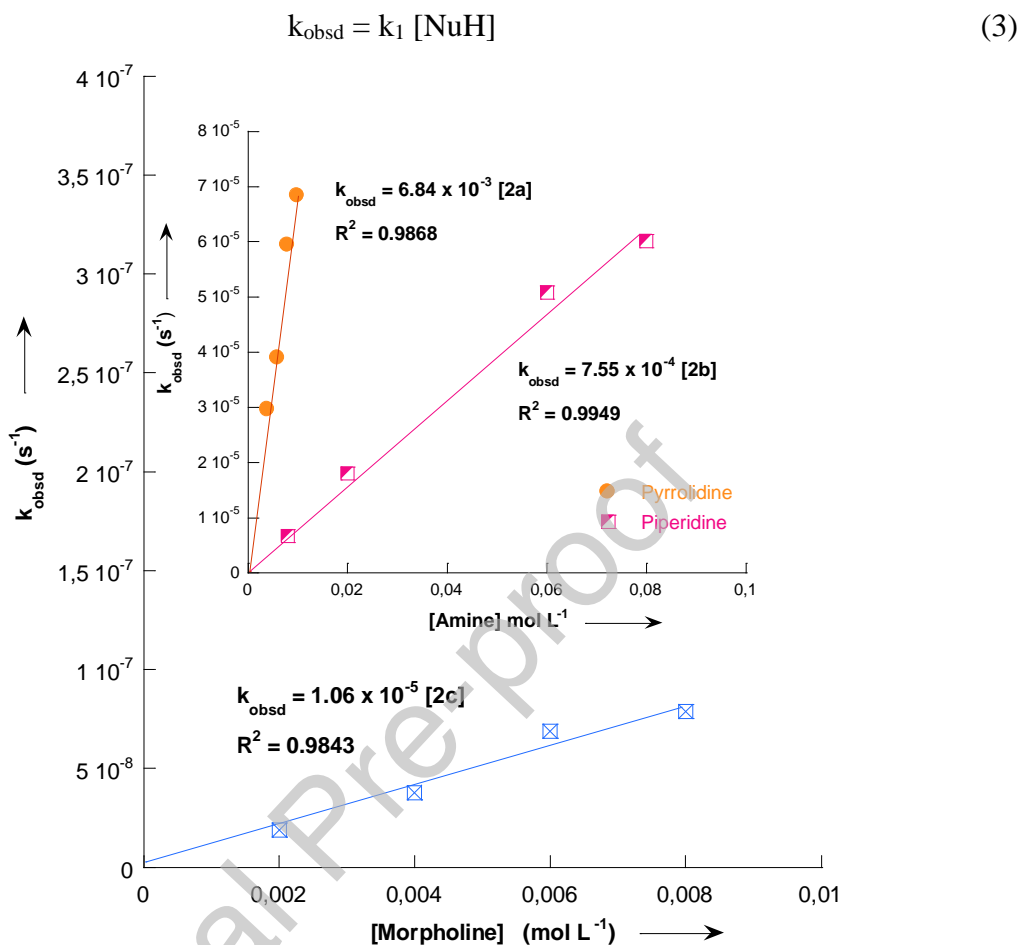
The kinetics of the reactions of 2-methoxy-3,5-dinitropyridine **1** with secondary amines **2a-c** in acetonitrile at 20 °C were monitored photometrically by following the appearance of the absorbances of substitution products **6a-c** at or close to their absorption maxima ( $330 \text{ nm} < \lambda_{\text{max}} < 360 \text{ nm}$ ).

Our results can be interpreted on the basis of Scheme 1, in which the nucleophilic attack by amine **2** is the rate-limiting step. Under these experimental conditions, the commonly accepted general expression for the observed first-order rate constants,  $k_{\text{obsd}}$ , pertaining to the process is given by Eq. (2).<sup>[18-22]</sup> All  $k_{\text{obsd}}$  values obtained are summarized in Supplementary Table S1 and displayed in Figure 2.

$$k_{\text{obsd}} = \frac{k_1(k_2 + k_3[\text{NuH}])}{k_{-1} + k_2 + k_3[\text{NuH}]}[\text{NuH}] \quad (2)$$

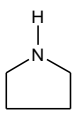
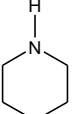
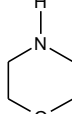
Figure 2 shows that in all cases the plots of  $k_{\text{obsd}}$  against the concentrations of the amine **2** were linear with negligible intercepts. This result confirmed the first-order of the reactions of **1** with **2a-c**, and indicated that the formation of the zwitterionic intermediate  $\text{T}^\ddagger$  is the rate-limiting step of the uncatalysed reaction and the pseudo-first-order rate constants ( $k_{\text{obsd}}$ ), for

all the reactions can be readily derived from Eq. (3) ( $k_{-1} \ll k_2 + k_3 [\text{NuH}]$ ). The values of the second-order rate constants,  $k_1$ , determined from the slopes of  $k_{\text{obsd}}$  vs.  $[\text{NuH}]$  plots are collected in Table 2.



**Figure 2.** Influence of the concentration of amine **2a-c** on the observed first-order rate constant ( $k_{\text{obsd}}$ ) for addition to 2-methoxy-3,5-dinitropyridine **1** in acetonitrile solution at 20 °C.

**Table 2.** Summary of second-order rate constants for addition reactions of secondary amines **2a-c** with 2-methoxy-3,5-dinitropyridine **1** in acetonitrile solution at 20 °C.

Amine			
	<b>2a</b>	<b>2b</b>	<b>2c</b>
$k_1^a$ ( $\text{M}^{-1} \text{s}^{-1}$ )	$6.84 \times 10^{-3}$	$7.55 \times 10^{-4}$	$1.06 \times 10^{-5}$
$\text{pK}_{\text{aH}}$	19.62 <sup>b</sup>	19.35 <sup>b</sup>	16.61 <sup>c</sup>
$N / s_N^d$	18.64 / 0.60	17.35 / 0.68	15.65 / 0.74
$E_p^{\text{ox}}$ (V vs NHE)	1.09 <sup>e</sup>	1.36 <sup>e</sup>	1.48 <sup>f</sup>

<sup>a</sup>Values of  $k_1$  are determined in this work from the slope of plots of  $k_{\text{obsd}}$  vs.  $[\text{Amine}]$ .

<sup>b</sup>pK<sub>aH</sub> values for conjugated acid of amines **2a** and **2b** in CH<sub>3</sub>CN solution taken from ref [23a].

<sup>c</sup>pK<sub>aH</sub> value for conjugated acid of amine **2c** in CH<sub>3</sub>CN solution taken from ref [23b].

<sup>d</sup>N and *S<sub>N</sub>* values in CH<sub>3</sub>CN solution were taken from ref [30].

<sup>e</sup>E<sub>p<sup>ox</sup></sub> values for amines **2a** and **2b** in CH<sub>3</sub>CN solution were taken from ref [28].

<sup>f</sup>E<sub>p<sup>ox</sup></sub> value for amine **2c** in CH<sub>3</sub>CN solution was taken from ref [29].

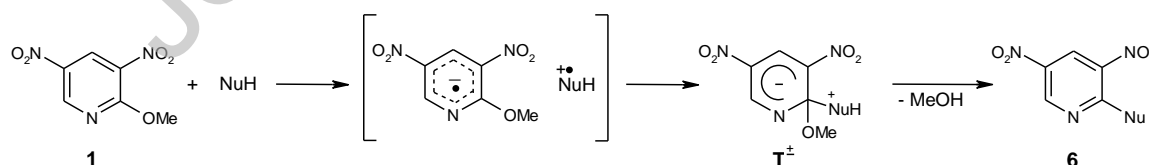
### 2.3. Effect of amine basicity and mechanism

The effect of amine basicity on reactivity is illustrated in Figure 3 for the reactions of 2-methoxy-3,5-dinitropyridine **1** with secondary amines **2a-c**. As seen from Figure 3, the Brønsted plot of log *k*<sub>1</sub> in function of the pK<sub>aH</sub> values of the conjugate acids of the amines **2a-c** in acetonitrile solution [23] listed in Table 2 is in good agreement and the corresponding relationship is the following

$$\log k_1 = -20.54 + 0.94 \text{ pK}_{\text{aH}} \quad (R^2 = 0.9958) \quad (2)$$

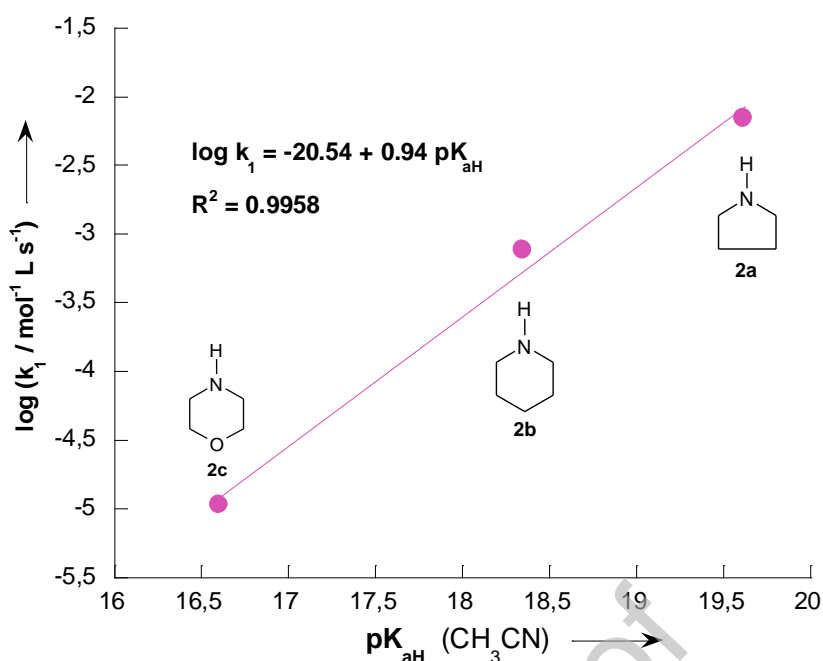
The β<sub>nuc</sub> value for the reactions of **1** (i.e., β<sub>nuc</sub> = 0.94) is much larger than that reported previously for the corresponding reactions of 2-methoxy-3-nitropyridine **4** (i.e., β<sub>nuc</sub> = 0.52) and 2-methoxy-5-nitropyridine **5** (i.e., β<sub>nuc</sub> = 0.55) performed in acetonitrile, which were proposed to proceed through a S<sub>N</sub>Ar mechanism.[11] Such a large β<sub>nuc</sub> value is typical for reactions reported previously to proceed through a single electron transfer (SET) process. [12-15, 24-27]

In our study, the fact that the log *k*<sub>1</sub> is linearly related to the oxidation peak potentials E<sub>p<sup>ox</sup></sub> (V vs NHE) values of the amine radical cations measured in acetonitrile [28, 29] (Figure 4) confirms the possibility that our S<sub>N</sub>Ar reactions proceed via electron transfer mechanism (Scheme 2) in which the formation of the substitution products **6a-c** will then proceed through initial (fast) electron-transfer from the amines **2a-c** to the 2-methoxy-3,5-dinitropyridine **1** and subsequent (slow) coupling of the resulting cation and anion radicals within the solvent cage via the transition state T<sup>±</sup>. [10]

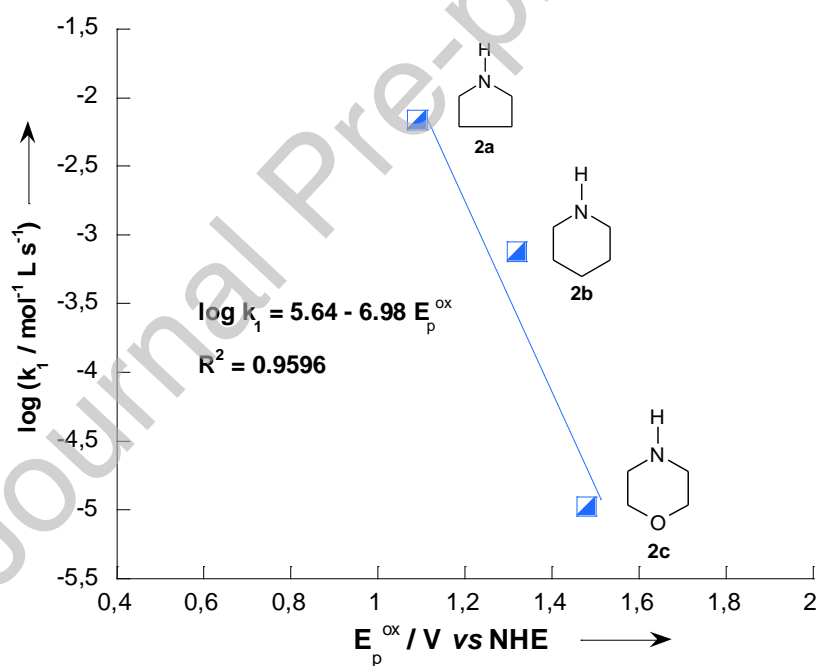


**Scheme 2.** Proposed mechanistic pathway for the reactions of 2-methoxy-3,5-dinitropyridine **1** with **2a-c** in acetonitrile at 20 °C.





**Figure 3.** Effect of the amine basicity on the rate of the reaction of 2-methoxy-3,5-dinitropyridine **1** with secondary amines **2a-c** in  $CH_3CN$  solution at 20 °C. The  $pK_{aH}$  values were taken from ref [23].

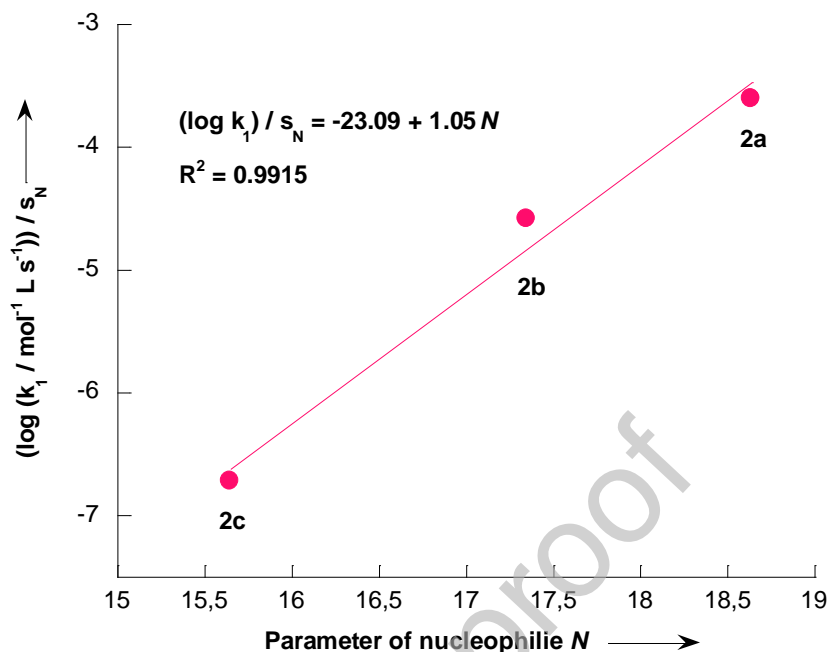


**Figure 4.** The influence of the oxidation peak potential  $E_p^{ox}$  of amines on the rate constants of reactions of 2-methoxy-3,5-dinitropyridine **1** with **2a-c** in acetonitrile at 20 °C. The identity of points is given in Table 2.

#### 2.4. Quantification of electrophilicity $E$ of 2-methoxy-3,5-dinitropyridine **1**

In order to measure the electrophilicity parameters  $E$  describing the reactivity at C-OME position of 2-methoxy-3,5-dinitropyridine **1**, we used the nucleophilicity parameters  $N$  and  $s_N$  for the three secondary amines **2a-c** determined by Kanzian and co-workers [30] in  $CH_3CN$  solution at 20 °C (Table 2). As required by Eq. (1), a linear plot of  $(\log k_1)/s_N$  versus

nucleophilicity parameters  $N$  was obtained with slope close to 1, indicating that Eq. (1) is applicable to these  $S_NAr$  reactions (Figure 5).[16, 31-36] From the intercept of this line with the ordinate axis, the reactivity of pyridine **1** is derived ( $E = -21.99$ ).

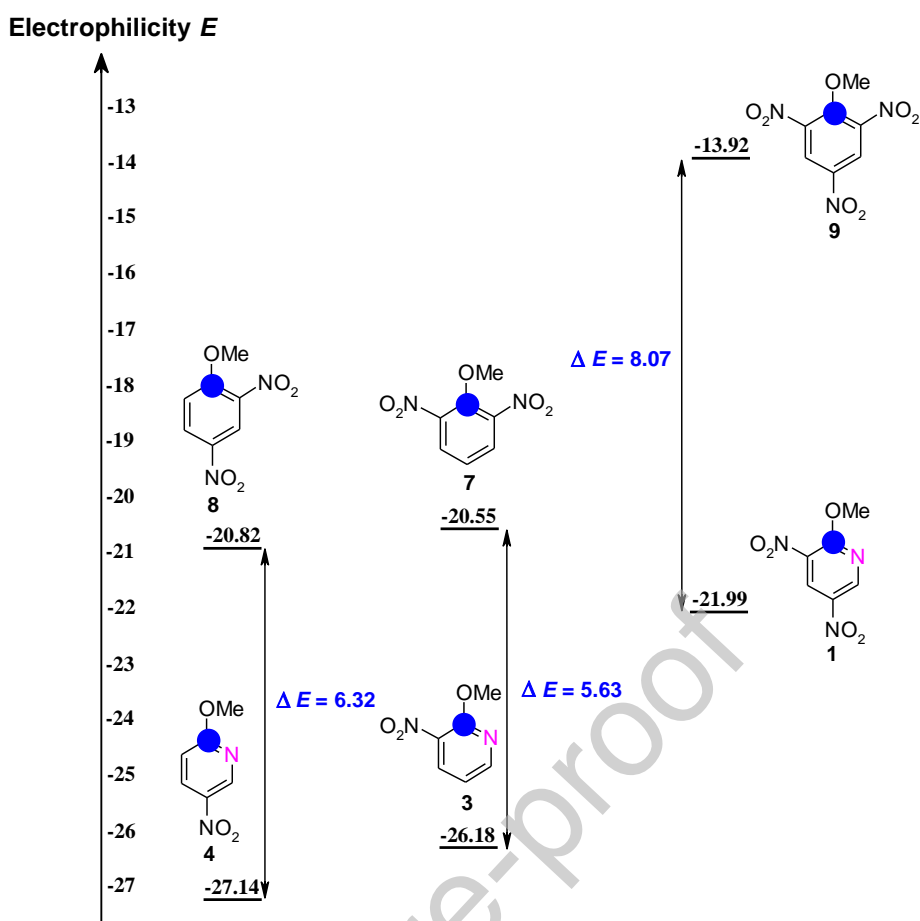


**Figure 5.** Plot of the rate constants  $(\log k_1)/s_N$  for the reaction of the 2-methoxy-3,5-dinitropyridine **1** with the reference nucleophiles **2a-c** versus their nucleophilicity parameters  $N$  in  $\text{CH}_3\text{CN}$  solution at  $20^\circ\text{C}$ .

Figure 6 compares the reactivity of the 2-methoxy-3,5-dinitropyridine **1** ( $E = -21.99$ ) with other pyridines, namely 2-methoxy-3-nitropyridine **3** ( $E = -26.18$ ), and 2-methoxy-5-nitropyridine **4** ( $E = -27.14$ ) recently reported by Mahdaoui and co-workers.[11] Also given for purposes of comparison are the  $E$  values reported for 2,6-dinitroanisole **7**, ( $E = -20.55$ ), 2,4-dinitroanisole **8** ( $E = -20.82$ ) and 2,4,6-trinitroanisole **9** ( $E = -13.92$ ).[11]

As can be seen in Figure 6, the electrophilicity parameter  $E$  remains essentially unchanged on going from **3** to **4**, while the difference in reactivity between 2-methoxy-3,5-dinitropyridine **1** and 2-methoxy-5-nitropyridine **4**, the weakest ones electrophiles known to date is approximately 5 units of  $E$ .

Also to be noted is that the electrophilicity  $E$  values measured for pyridines **3** and **4** are 5.50-6.50 orders of magnitude lower than those reported for anisoles **7** and **8**.[11] This important decreases is therefore of particular interest in the understanding of the factors affecting the reactivity of the aza group.



**Figure 6.** Comparison of the electrophilicities of pyridine **1** with those of a few pyridines and anisoles.

It is interesting to note that applicability of the electrophilicity parameter  $E$  of our 2-methoxy-3,5-dinitropyridine **1** for predicting the rate constants of their reactions with other types of nucleophiles has been confirmed. In fact, the kinetics data obtained for the reactions of 2-methoxy-3,5-dinitropyridine **1** with a series of nitroalkyl anions **10a-c** in DMSO solution at 20 °C (the detailed results are collected in Table 3) indicates that the predicted ( $k_1^{\text{calcd}}$ ) and experimental ( $k_1^{\text{exp}}$ ) rate constants differ only by a factor of 4-5. This result agrees within the confidence limit of Mayr's approach (factor 10-100) [38-40] with the predicted ( $k_1^{\text{calcd}}$ ) by Mayr's equation.

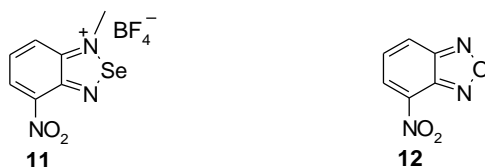
Most importantly, we demonstrated that the ( $\log k_1^{\text{exp}}$ ) values are linearly related to the calculated rate constants ( $\log k_1^{\text{calcd}}$ ) values (see Figure 7 and Eq. 3).

$$\log k_1^{\text{exp}} = 0.65 + 0.98 \log k_1^{\text{calcd}} \quad (R^2 = 0.9922) \quad (3)$$

The deviations between calculated rate constants from Eq. (3) and experimental rate constants have been observed by many authors.[41-45] Necibi and co-workers, for example, have observed a linear correlation between the experimental rate constants ( $\log k_1^{\text{exp}}$ ) and

calculated rate constants ( $\log k_1^{\text{calcd}}$ ) for reactions of benzoselenadiazolium cation **11** with the nitroalkyl anions **10a-c** in methanol ( $\log k_1^{\text{exp}} = -0.88 + 1.14 \log k_1^{\text{calcd}}$  ( $R^2 = 0.9875$ )).[45]

Raissi and co-workers have demonstrated that the ( $\log k_1^{\text{exp}}$ ) values for reactions of 4-nitrobenzofurazan **12** with a series of secondary cyclic amines in acetonitrile solution at 20 °C also correlate well with ( $\log k_1^{\text{calcd}}$ ) values ( $\log k_1^{\text{exp}} = -1.60 + 0.98 \log k_1^{\text{calcd}}$  ( $R^2 = 0.9860$ )).[41]



As discussed in a previous paper,[43] the reasons for such linear correlations are still not fully understood. Therefore, a more detailed examination of the results is necessary to confirm this approach.

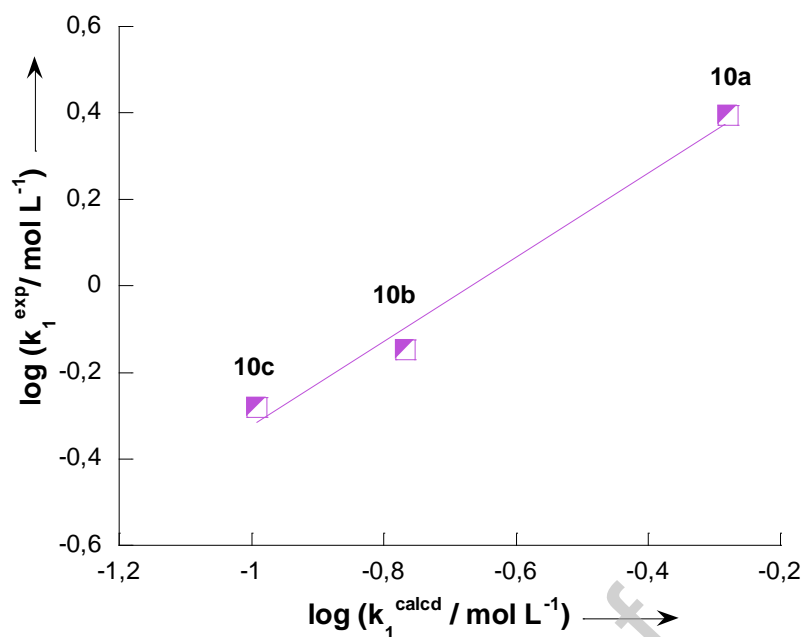
**Table 3.** Experimental and calculated second-order rate constants for the reactions of 2-methoxy-3,5-dinitropyridine **1** with a series of nitroalkyl anions **10a-c** in DMSO solution at 20 °C.

Electrophile	Nucleophile	$N/s_N$ <sup>a</sup>	$k_1^{\text{exp}}$ <sup>b</sup> (M <sup>-1</sup> s <sup>-1</sup> )	$k_1^{\text{calcd}}$ <sup>c</sup> (M <sup>-1</sup> s <sup>-1</sup> )	$k_1^{\text{exp}}/k_1^{\text{calcd}}$
<p><b>1</b> <math>E = -21.99</math></p>	<b>10a</b> MeCH=NO <sub>2</sub> <sup>-</sup>	21.54/0.62	2.48	5.26 x 10 <sup>-1</sup>	4.71
	<b>10b</b> C H <sub>2</sub> =NO <sub>2</sub> <sup>-</sup>	20.71/0.60	7.12 x 10 <sup>-1</sup>	1.71 x 10 <sup>-1</sup>	4.16
	<b>10c</b> Me <sub>2</sub> C=NO <sub>2</sub> <sup>-</sup>	20.61/0.69	5.23 x 10 <sup>-1</sup>	1.12 x 10 <sup>-1</sup>	4.67

<sup>a</sup> $N$  and  $s_N$  values in DMSO were taken from ref. [37].

<sup>b</sup>This work.

<sup>c</sup> $k_1^{\text{calcd}}$  calculated by Eq. (1) with the  $N$  and  $s_N$  parameters for the nitroalkyl anions in DMSO indicated in this Table and the electrophilicity parameter  $E$  for pyridine **1**.



**Figure 7.** Linear correlation between  $\log k_1^{\text{exp}}$  and  $\log k_1^{\text{calcd}}$  for the reactions of 2-methoxy-3,5 dinitropyridine **1** with a series of nitroalkyl anions **10a-c** in DMSO solution at 20 °C.

### 2.5. Correlation between electrophilicity parameter ( $E$ ) and global electrophilicity index ( $\omega$ )

In order to establish a relationship between the electrophilicity parameters  $E$  proposed by Mayr [16] and the global electrophilicity index ( $\omega$ ) well-known of Parr,[46] an theoretical study has been performed using density functional theory (DFT). In this context, electronic chemical potential ( $\mu$ ) and chemical hardness ( $\eta$ ) for the three nitropyridines **1**, **3** and **4** have been calculated at B3LYP/6-311g(d,P) basis set, in acetonitrile, as follow

$$\mu = (\epsilon_{\text{HOMO}} + \epsilon_{\text{LUMO}})/2 \quad (5)$$

$$\eta = (\epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}}) \quad (6)$$

where  $\epsilon_{\text{HOMO}}$  and  $\epsilon_{\text{LUMO}}$  are energies of the frontier molecular orbitals HOMO and LUMO, respectively.[46]

The obtained values of  $\mu$  and  $\eta$  were considered for the calculation of the global electrophilicity index ( $\omega$ ) for these series of electrophiles **1**, **3**, and **4** according to Eq. (7) developed by Parr and Yang.[46a] Table 4 reports the calculated quantum chemical parameters which are related to the molecular electronic structure of the molecules under consideration, including their experimentally measured electrophilicity parameters  $E$ .

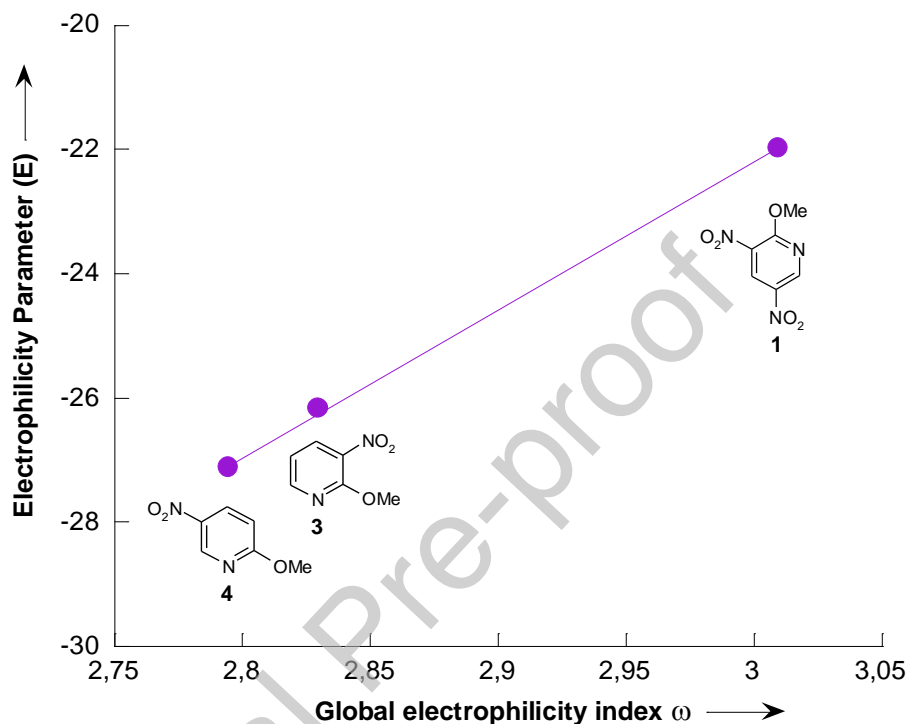
$$\omega = \mu^2/2\eta \quad (7)$$

Analysis of the data summarized in Table 4 revealed that the values of electrophilicity ( $E$ ) proposed by Mayr [16] are linearly related to the global electrophilicity index ( $\omega$ ) defined by Parr and Yang [46a] As can be seen in Figure 8, excellent straight line is obtained on plotting

the measured  $E$  values of these series of pyridines against their global electrophilicity  $\omega$  calculated in this work. The following equation (8) describes this linear dependence.

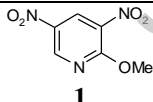
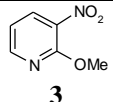
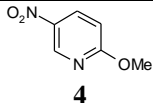
$$E = -93.41 + 23.73 \omega \quad (R^2 = 0.9997) \quad (8)$$

Relationships between parameters  $E$  and  $\omega$  have also been reported by many authors.[47-54] More recently, Rammah and co-workers have also observed a satisfactory correlation between  $E$  and  $\omega$  parameters of a series of benzotriazoles ( $E = -50.25 + 4.09 \omega$ ,  $R^2 = 0.9788$ ).[53]



**Figure 8.** Correlation between experimentally determined electrophilicities ( $E$ ) and global electrophilicity index ( $\omega$ ) calculated at B3LYP/6-311g(d,p) level for the pyridines **1**, **3** and **4** listed in Table 4.

**Table 4.** Global properties for the whole series of pyridines **1**, **3** and **4**.

Electrophile	$\epsilon_{\text{HOMO}}$ (AU)	$\epsilon_{\text{LUMO}}$ (AU)	$\mu$ (eV)	$\eta$ (eV)	$\omega$ (eV)	$E$
 <b>1</b>	-0.28318	-0.10838	-5.39	4.660	3.010	-21.99 <sup>b</sup>
 <b>3</b>	-0.26390	-0.10248	-4.985	4.390	2.830	-26.18 <sup>c</sup>
 <b>4</b>	-0.26393	-0.10133	-4.970	4.420	2.794	-27.14 <sup>c</sup>

<sup>a</sup>  $\epsilon_{\text{HOMO}}$ ,  $\epsilon_{\text{LUMO}}$ ,  $\mu$ ,  $\eta$  and  $\omega$  values determined in this work at the B3LYP/6-311g(d,p) level of theory.

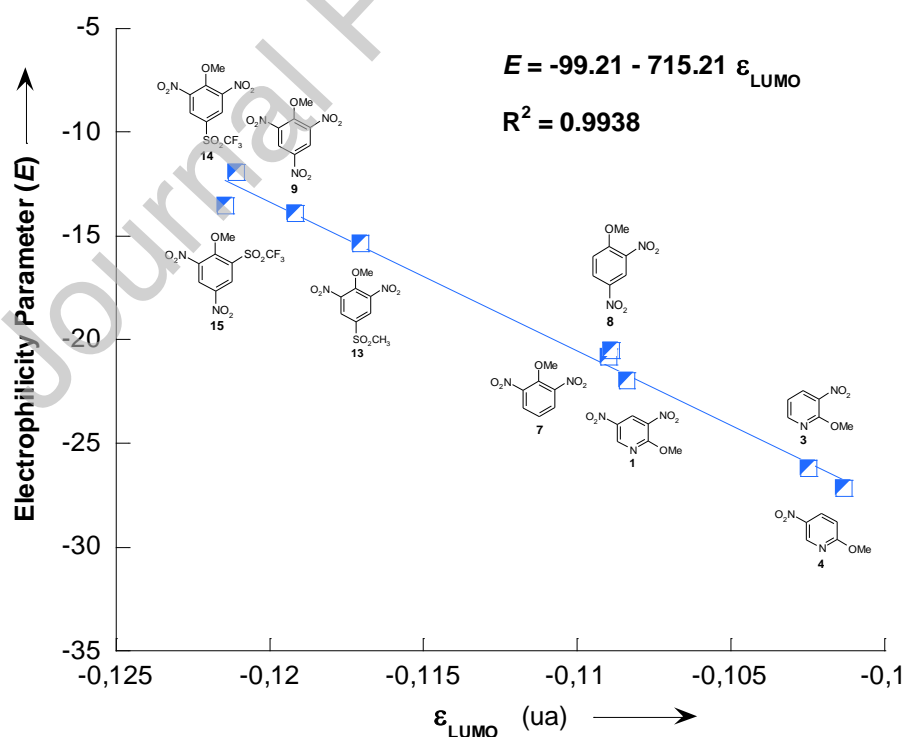
<sup>b</sup> This work.

<sup>c</sup> From ref [11].

Interestingly, correlation (8) can be used as a good model to predict the unknown electrophilicity parameters  $E$  at C-OMe position of several neutral electron-deficient structures. At this point, we decided to use Eq. 8 to recalculate the  $E$  values of six anisoles **7-9** and **13-15** whose experimental data are available.[11] In fact, using their global electrophilicity  $\omega$  determined in the present study by quantum chemical calculations at the B3LYP/6-311g(d,p) level of theory using Gaussian 09, we predict the electrophilicity parameters  $E'$  of these six anisoles. The results are compared in Table 5. It can be seen that these theoretical  $E'$  values vary significantly from -21.67 to -12.56. It is interestingly to note that these results from the Eq. (8) are in reasonable agreement with those reported by Mahdhaoui and coworkers.[11]

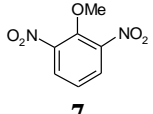
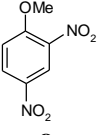
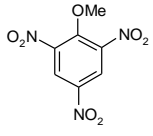
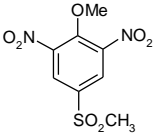
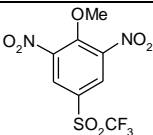
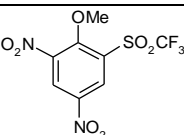
Plotting the electrophilicity parameters  $E$  of anisoles **7-9** and **13-15** and the three pyridines **1**, **3** and **4** against their  $\epsilon_{\text{LUMO}}$  calculated at B3LYP/6-311g(d,p) level listed in Tables 4 and 5, we obtained a nice correlation as shown in Figure 9. This behavior indicates that Equation (8) can successfully predict the values of this series of anisoles **7-9** and **13-15**.

The results from the present study should represent one of the first confirmation for the applicability of the reactivity parameters  $E$  reported in Table 5 for predicting rate constants with various types of nucleophiles.



**Figure 9.** Correlation between experimentally determined electrophilicities ( $E$ ) and lowest unoccupied molecular orbital energies ( $\epsilon_{\text{LUMO}}$ ) calculated at B3LYP/6-311g(d,p) level for the nine electrophiles listed in Tables 4 and 5.

**Table 5.** Global properties for the whole series of anisoles **7-9, 13-15**.

Electrophile	$\epsilon_{\text{HOMO}}$ (AU)	$\epsilon_{\text{LUMO}}$ (AU)	$\mu$ (eV)	$\eta$ (eV)	$\omega$ (eV)	$E'$ <sup>b</sup>	$E$ <sup>c</sup>
 <b>7</b>	-0.27067	-0.10896	-5.165	4.410	3.025	-21.63	-20.82
 <b>8</b>	-0.27145	-0.10889	-5.175	4.430	3.023	-21.67	-20.55
 <b>9</b>	-0.28675	-0.11916	-5.52	4.560	3.341	-14.13	-13.92
 <b>13</b>	-0.28418	-0.11703	-5.4550	4.550	3.270	-15.81	-15.34
 <b>14</b>	-0.29234	-0.12107	-5.6200	4.660	3.389	-12.99	-11.94
 <b>15</b>	-0.29468	-0.12146	-5.6650	4.710	3.407	-12.56	-13.56

<sup>a</sup> $\epsilon_{\text{HOMO}}$ ,  $\epsilon_{\text{LUMO}}$ ,  $\mu$ ,  $\eta$  and  $\omega$  values calculated in this work at the B3LYP/6-311g(d,p) level of theory.

<sup>b</sup> $E'$  values calculated in this work from Eq. (8).

<sup>c</sup> $E$  values taken from ref [11].

### 3. Conclusion

On the basis of the large Brønsted coefficients ( $\beta_{\text{nuc}} = 0.94$ ), a single electron transfer mechanism has been suggested to describe the nucleophilic aromatic substitution reactions of 2-methoxy-3,5-dinitropyridine by secondary cyclic amines in acetonitrile solution. The SET mechanism has also been supported by the satisfactory linear correlation obtained between ( $\log k_1$ ) and the oxidation potentials of amines ( $E^\circ$ ). Using Mayr's approach, the electrophilicity parameter  $E$  for the 2-methoxy-3,5-dinitropyridine has been determined ( $E = -21.99$ ) and integrated into a comprehensive electrophilicity scale of Mayr. From global electrophilicity  $\omega$  determined in the present study employing density functional (DFT) theory, the  $E$  values of six anisoles have been predicted according to the  $E$  vs  $\omega$  correlation (Eq.8) and found to agree with those reported in the literature.



## 4. Experimental Section

### 4.1. Materials

The 2-methoxy-3,5-dinitropyridine was prepared, as previously described.<sup>[8, 9]</sup> All the secondary cyclic amines **2** (morpholine, piperidine and pyrrolidine) were commercial products and were redistilled before use whenever necessary. Commercially available nitromethane (99%), nitroethane (98%), and 2-nitropropane (99%) were used as received. Acetonitrile (Aldrich, HPLC: 99.9%) was available of the highest quality and used without further purification.

All spectrophotometric measurements were carried out using a spectrophotometer (UV-1650 Shimadzu, Japan) equipped with a Peltier temperature controller (model TCC-240 A), which is able to keep to temperature within 0.1 K.

### 4.2. Kinetic Measurements

All kinetic investigations were performed in acetonitrile solution at 20 °C by following the disappearance of the UV/vis absorptions of the 2-methoxy-3,5-dinitropyridine **1** (284 nm) under pseudo-first-order conditions (2-methoxy-3,5-dinitropyridine concentration of approximately  $3 \times 10^{-5}$  mol L<sup>-1</sup> and nucleophile concentrations in the range  $2 \times 10^{-3}$  to  $8 \times 10^{-2}$  mol L<sup>-1</sup>).

The observed first-order rate constants,  $k_{\text{obsd}}$ , were evaluated from the correlation  $\text{Ln}(A_{\infty} - A_t)$  as a function of time, where  $A_{\infty}$  and  $A_t$  are the values of equilibrium absorbance and the absorbance after time  $t$ , respectively. Measured first-order rate constants values,  $k_{\text{obsd}}$ , together with detailed reaction conditions are summarized in Tables S1 and S2 in the Supporting Information.

### 4.3. Methods and Computational Aspects

The optimized geometries for the ground ( $S_0$ ) states of investigated compounds resulting from the  $S_NAr$  reactions of the 2-methoxy-3,5-dinitropyridine with various secondary cyclic amines were obtained using density functional theory (DFT) at the B3LYP/6-311g(d,p) level of theory,<sup>[55, 56]</sup> with the Gaussian 09 quantum software package developed by Frisch and coworkers.<sup>[57]</sup> Theoretical calculations were performed in polar acetonitrile (CH<sub>3</sub>CN) using the conductor-like polarizable continuum model (CPCM).<sup>[58]</sup> The Gaussian view 05 software<sup>[59]</sup> was used to read Gaussian output files and visualize the obtained results.

The extracted highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energy levels are used to calculate the electronic chemical potential ( $\mu$ ), chemical hardness ( $\eta$ ), as well as the global electrophilicity index ( $\omega$ ), as described in Equations 5-7.

### Supporting Information Available

Concentrations and the measured rate constants,  $k_{\text{obsd}}$ , for the individual kinetic experiments values for reactions the 2-methoxy-3,5-dinitropyridine **1** with secondary cyclic amines **2a-c** in  $\text{CH}_3\text{CN}$  solution (Table S1).

Concentrations and the measured rate constants,  $k_{\text{obsd}}$ , for the individual kinetic experiments values for reactions of the 2-methoxy-3,5-dinitropyridine **1** with nitroalkyl anions in DMSO (Table S2).

### Conflicts of interest statement

The authors hereby confirm they have no conflict of interest.

### Authors contribution

TS, OA and AH achieved her experimental works with the help of TB and J-CG. Theoretical calculations were conducted by SA. The manuscript was jointly written and arranged under TB, SA and JCG guidance.

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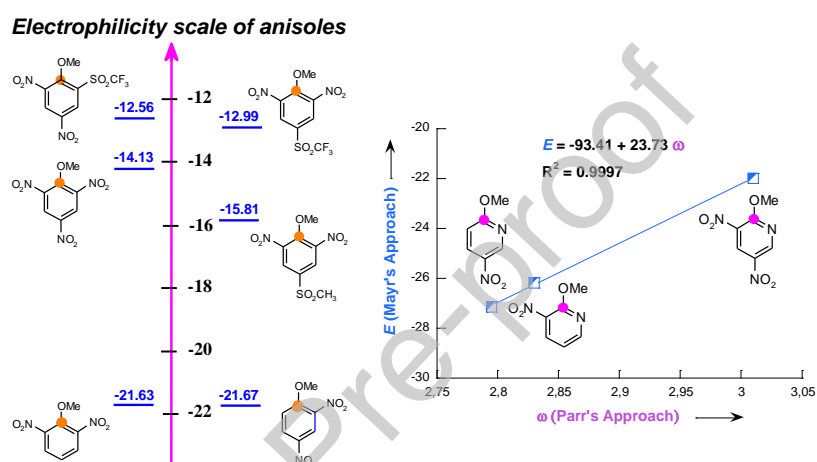
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## Graphical Abstract

The  $E$  parameters of various anisoles (see Figure) were derived from the correlation between experimentally measured electrophilicities ( $E$ ) and global electrophilicity index ( $\omega$ ) calculated at B3LYP/6-311g(d,p) level for a series of pyridines.



## AUTHORS CONTRIBUTION

TS, OA and AH achieved her experimental works with the help of TB and J-CG. Theoretical calculations were conducted by SA. The manuscript was jointly written and arranged under TB, SA and JCG guidance.

## DECLARATION-OF-COMPETING-INTERESTS

The authors hereby confirm they have no conflict of interest.