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## Reactivity of the ethyl oleate in the [3+2] cycloaddition to arylonitrile N-oxide: a reexamination

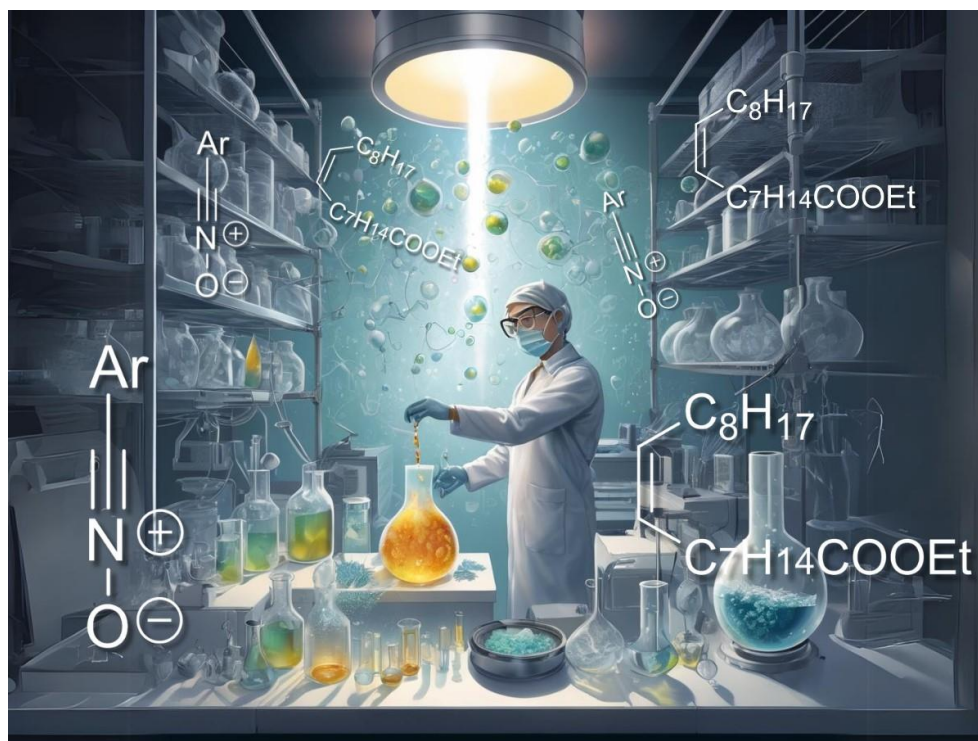
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**Abstract:** The course of the reactions between ethyl oleate and aromatic nitrile N-oxides was reexamined under the laboratory conditions. The reaction course was explained on the basis of the DFT quantumchemical calculations. It was found that independently of the reaction protocol, in any case the expected 2-isoxazolines are not formed. Instead of this, respective diarylfuroxanes were isolated from post-reaction mixtures.

**Keywords:** Nitrile N-oxides, 2-isoxazolines, furoxanes, DFT calculation, mechanism.

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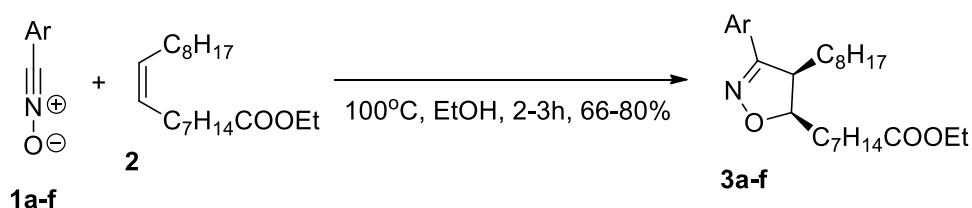
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## Introduction

2-Isoxazolines play an important role in medicinal chemistry. This group of compounds constitutes an important molecular segment of many biologically active products [1-3]. Derivatives containing isoxazole/isoxazoline fragments have biological effects such as: anticancer [4-12], anti-inflammatory [13-15], analgesic activity [16], anti-Alzheimer's disease [15,17,18], anti-asthmatic [19,20], antidiabetic [21-23], antituberculosis [24], as well as antithrombotic activity [10], antioxidant [16,25-27], antibacterial [28-31], antifungal [32-34] and anti-insecticidal [35]. Due to weak nitrogen-oxygen bonds and aromatic character, isoxazoles and isoxazolines are particularly valuable intermediates in many methods of synthesizing bioactive compounds, because such a ring system allows for quite easy modification of substituents in their ring structures [5]. Their unique structure allows them to bind with high affinity to separate receptors, which enables the development of innovative drugs with original therapeutic applications [36].

The most universal method for the preparation of the 2-isoxazoline molecular systems are the [3+2] cycloaddition reactions between nitrile N-oxides and alkenes [37-44].

Some years ago, Kumar and coworkers [45] described the protocol for the preparation of 2-isoxazolines via [3+2] cycloaddition scheme based on the ethyl oleate as the 2 $\pi$ -electron component and arylonitrile N-oxides as three atom components (TACs) (Scheme 1).



Ar = Ph (a), 4-MeO-C<sub>6</sub>H<sub>4</sub> (b), 3,4-(MeO)<sub>2</sub>-C<sub>6</sub>H<sub>3</sub> (c), 4-Me-C<sub>6</sub>H<sub>4</sub> (d), 4-F-C<sub>6</sub>H<sub>4</sub> (d), 4-Cl-C<sub>6</sub>H<sub>4</sub> (e), 4-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub> (f)

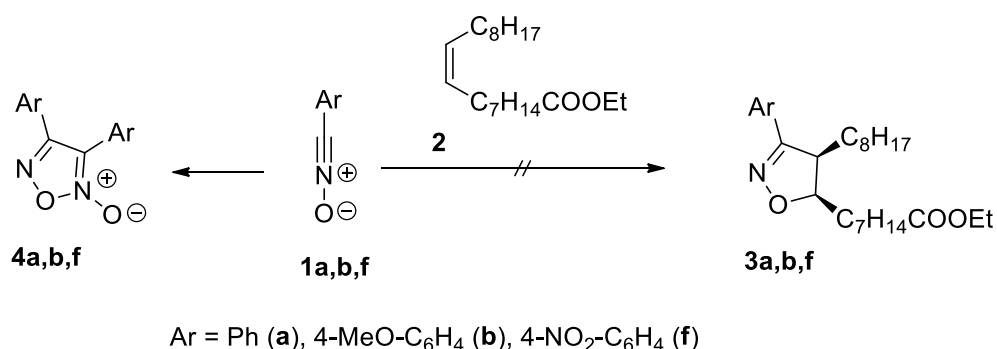
Scheme 1.

The described protocol exhibits however many doubts. First, the Authors specified, that the reaction is realized at 100°C in boiling ethanol (*sic!*) at normal pressure. Next,

according to the presented data, all reactions were completed after 2-3h. On the other hand, it is generally known, that aromatic nitrile N-oxides are generally moderately reactive. Even in the presence of the electrophilically activated alkenes they react rather slowly [46]. Finally, most benzonitrile N-oxide, [3+2] cycloadditions are realized not regioselectively, even in the case of electrophilic alkenes 2 $\pi$ -electron component. When non-activated alkenes are used as the 2 $\pi$ -electron component, the cycloaddition always proceeds with the low regiocontrol [46,47]. Thus, the presented procedure is not very reliable. Therefore, it was decided on the comprehensive reexamination of the title processes. We hope, that our study shed new light on the questions of the reactivity of the oleic acid esters in the [3+2] cycloaddition processes.

## Results and discussion

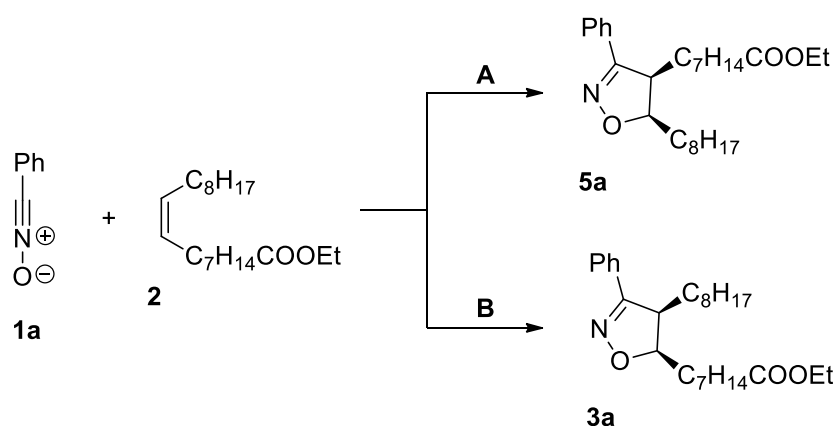
Within the first stage of our research, we repeated point by point the procedure described by Kumar and coworkers [45]. Of course, it was impossible to realize this protocol at 100°C in boiling ethanol, because its b.p. is equal 78°C. We examined the reaction with the participation of the benzonitrile N-oxide (**1a**) and its substituted methoxy and nitro analogues (**1b** and **1f** respectively). The reaction progress was monitored using HPLC technique. Unfortunately, in any cases, no cycloaddition product was detected. All examined reactions lead to respective nitrile oxime dimers (diarylfuroxanes) independently of the nature of the substituent in the aryl ring of the nitrile-oxide (Scheme 2).



Scheme 2.

Next, we performed attempts for the search of alternative protocol for these reactions, based on the other [3+2] cycloaddition procedures previously verified [48-50]. All attempts for the preparation of 2-isoxazoline analogs on this way were not successful. Only respective furoxane dimers were detected in the postreaction mixtures. So, the synthetic protocol published by Kumar and coworkers [45] includes fundamental errors and inaccuracies, and should be considered as completely non-repeatable.

For better understanding of the extremely low reactivity of the ethyl oleate (**2**) in the [3+2] cycloaddition to nitrile N-oxides, the full exploration of the energetic profiles of the process was performed. For this purpose, the results of the B3LYP/6-311G(d) quantumchemical calculations were applied. Within these calculations, the presence of the solvent in the reaction environment was simulated using PCM algorithm [51-56]. Both theoretically possible regioisomeric pathways (Scheme 3) of the [3+2] cycloaddition involving the parent benzonitrile N-oxide (**1a**) and the ethyl oleate (**2**) were considered in the ether and ethanol solutions.



Scheme 3.

Our DFT computational study shows clearly that the nature energy profiles for both considered pathways are similar, and typical for the one-step [3+2] cycloaddition. In particular, in the simulated ethereal solution, between valleys of reactants and products, two critical points were detected and verified: the pre-reaction molecular complex (**MCA** and **MCB** respectively) and the transition state (**TSA** and **TSB** respectively) (Figure 1). The one-step nature of analyzed cycloaddition was fully verified by the analysis of respective IRC trajectories.

In the initial phase of reaction, the interactions between starting molecules in the ethereal solution lead to the formation of the pre-reaction molecular complexes **MCA** and **MCB**. This process is barrierless and is accompanied with the reduction of the enthalpy of the reaction system about 1.2–18kcal/mol. The entropic factor determines however positive values of the Gibbs free energy of **1a+2→MCA** and **1a+2→MCB** transformations. This excludes the possibility of the existence of mentioned intermediates as structures stable from thermodynamical point of view. It should be underlined that no new s-bonds are formed within the MCs. In the framework of the pre-reaction complex, substructures of addends adopt orientations determined by further regiodirection of the intermolecular interactions. So, detected structures should be classified as orientation complexes. Next, no electron

density transfer can be observed within MCs. In the consequence, these intermediates should not be considered as charge-transfer (CT) complexes [57,58].

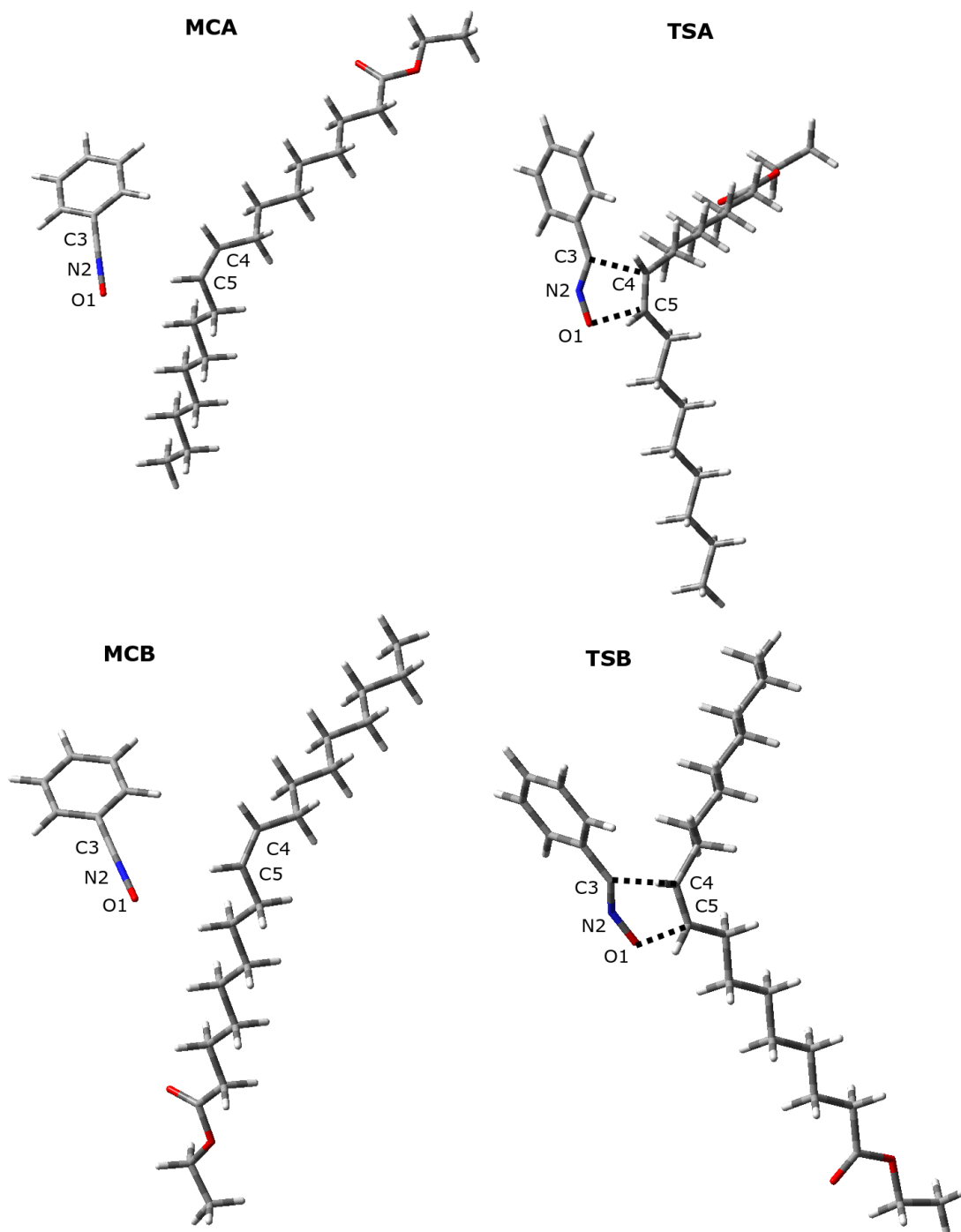


Fig. 1. Views of critical structures of the [3+2] cycloaddition reactions between benzonitrile N-oxide (**1a**) and the ethyl oleate (**2**) in the Et<sub>2</sub>O solution according to the B3LYP/6-311G(d) (PCM) calculations.

The next reaction phase is a transformation of the respective MC to TS. It is interesting that, in the contrast to the data reported by Kumar and coworkers [45], the

computed activation parameters suggest evidently low regioselectivity within this reaction, characterized by isoenthalpic nature of both possible activation barriers. Next, the observed Gibbs free energies of the activation are high, which suggest a preference for the formation of diarylfiruxane instead of expected cycloadducts (Table 2). Within **TSA** and competitive **TSB**, two new single bonds are formed – C3-C4 and C4-C5. The development of both new bonds is always very similar. So, both optimized transition states should be classified as rather synchronous. Very similar is the image of considered the model reaction in the more polar ethanolic solution.

Table 1. Energetical parameters for the [3+2] cycloaddition reactions between benzonitrile N-oxide (**1a**) and the ethyl oleate (**2**) in the Et<sub>2</sub>O and EtOH solutions according to the B3LYP/6-311G(d) (PCM) calculations ( $\Delta H$  and  $\Delta G$  are in kcal/mol;  $\Delta S$  are in cal/molK).

Solvent	Path	Transition	$\Delta H$	$\Delta G$	$\Delta S$
Et <sub>2</sub> O	<b>A</b>	<b>1a+2</b> → <b>MCA</b>	-1.8	7.2	-30.0
		<b>1a+2</b> → <b>TSA</b>	21.4	33.9	-42.1
		<b>1a+2</b> → <b>3a</b>	-30.9	-15.9	-50.6
	<b>B</b>	<b>1a+2</b> → <b>MCB</b>	-1.2	6.1	-24.4
		<b>1a+2</b> → <b>TSB</b>	21.4	34.4	-43.6
		<b>1a+2</b> → <b>4a</b>	-30.9	-15.0	-53.6
EtOH	<b>A</b>	<b>1a+2</b> → <b>MCA</b>	-1.1	5.3	-21.4
		<b>1a+2</b> → <b>TSA</b>	21.6	33.9	-41.1
		<b>1a+2</b> → <b>3a</b>	-31.2	-15.7	-52.0
	<b>B</b>	<b>1a+2</b> → <b>MCB</b>	-1.1	5.4	-21.6
		<b>1a+2</b> → <b>TSB</b>	21.6	34.1	-41.8
		<b>1a+2</b> → <b>4a</b>	-31.2	-15.4	-52.8

Table 2. Key parameters of critical structures for the [3+2] cycloaddition reactions between benzonitrile N-oxide (**1a**) and the ethyl oleate (**2**) in the Et<sub>2</sub>O and EtOH solutions according to the B3LYP/6-311G(d) (PCM) calculations ( $\Delta H$  and  $\Delta G$  are in kcal/mol;  $\Delta S$  are in cal/molK).

Solvent	Structure	Interatomic distances [ $\text{\AA}$ ]					GEDT [e]
		O1-N2	N2-C3	C3-C4	C4-C5	C5-O1	
Et <sub>2</sub> O	<b>1a</b>	1.214	1.162				
	<b>2</b>				1.337		
	<b>MCA</b>	1.216	1.161	4.970	1.337	3.728	0.00
	<b>TSA</b>	1.233	1.215	2.258	1.378	2.343	0.08
	<b>3a</b>	1.398	1.286	1.523	1.540	1.460	
	<b>MCB</b>	1.216	1.161	5.007	1.337	3.746	0.00
	<b>TSB</b>	1.233	1.215	2.259	1.378	2.342	0.08
	<b>4a</b>	1.398	1.286	1.523	1.540	1.460	
EtOH	<b>1a</b>	1.216	1.161				
	<b>2</b>				1.337		
	<b>MCA</b>	1.219	1.160	4.993	1.337	3.757	0.00
	<b>TSA</b>	1.236	1.214	2.257	1.377	2.359	0.09
	<b>3a</b>	1.401	1.286	1.522	1.540	1.463	
	<b>MCB</b>	1.219	1.160	5.072	1.337	3.756	0.00
	<b>TSB</b>	1.236	1.214	2.258	1.377	2.357	0.09
	<b>4a</b>	1.401	1.286	1.522	1.540	1.462	

## **Experimental Part**

### General

HPLC analyses were done using a Knauer device with a UV-VIS detector (LiChrospher 18-RP 10  $\mu\text{m}$  column, eluent: 80%v methanol). M.p. values were measured on the Boetius apparatus and are uncorrected.

### Reaction procedure A

A mixture of respective aromatic oxime **2** (2.2 mmol), ethyl oleate **1** (2.0 mmol) and chloramine-T trihydrate (3.0 mmol) in the solvent (EtOH, Et<sub>2</sub>O) (30 ml) was refluxed on a water bath for 3 hours. The progress of the reaction was monitored by TLC and HPLC. The post-reaction mixture was filtered and evaporated to dryness. The organic residue was washed by water, and recrystallized. The diarylfuroxanes obtained were identified via comparison of the mp's with respective parameters from the literature and using HPLC technique based on samples prepared according to the known procedures [50].

### Reaction procedure B

An erlenmeyer flask containing 10 ml of THF was placed in an ice bath. Then ethyl oleate **1** (2.0 mmol) and hydroxamoyl chloride (2.2 mmol) were added and stirred for 10 min. Then K<sub>2</sub>CO<sub>3</sub> (1 mmol) was dosed in small portions during 30 min period. After that time, the ice bath was removed. The mixture was left for 24 h with constant stirring. The solvent was evaporated and remaining solid was mixed with diethyl ether and filtered to remove insoluble side products. The ether was removed under vacuum, and the remaining crude product was washed with light petroleum ether and recrystallized. The diarylfuroxanes obtained were identified via comparison of the m.p. with respective parameters from the literature and using HPLC technique based on samples prepared according to the known procedures [50].

### DFT Computational details

All calculations reported in this paper were performed using the "Ares" infrastructure at the "Cyfronet" computational center in Cracow. The B3LYP functional with the 6-311G(d) basis set included in the GAUSSIAN package [59] was used. All optimized critical structures were verified by vibrational frequency analysis to determine whether they constitute minima or maxima on the potential energy surface (PES). All transition structures showed a single imaginary frequency ( $\nu$ ), whereas reactants, intermediates and products had none. The intrinsic reaction coordinate (IRC) path was traced in order to check the energy profiles

connecting each transition structure to associated minima of the proposed mechanism. The calculations were carried out for the simulated presence of benzene or diethyl ether as the reaction mediums (the PCM model [51] was used). All calculations were performed for 298 K and 1 atm pressure.

## Conclusions

Our comprehensive, experimental and quantumchemical studies on the [3+2] cycloaddition reactions of the ethyl oleate to arylonitrile N-oxide clearly show, that under protocols typical for nitrile oxide cycloadditions, the title reaction does not lead to the expected 2-isoxazoline analogs. In all cases, of the applied procedure, only respective diarylfuroxanes were detected in the postreaction mixtures. These results were rationalized based on the results from the DFT quantumchemical calculations. In particular, our DFT study clearly indicates very low reaction regioselectivity and a favored character of the formation of furoxanes as dimers of nitrile oxides instead of 2-isoxazolines.

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