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Unexpected Course of [2+3] Cycloaddition of 2-nitropropene to (*Z*)-*C,N*-diphenylnitrone*

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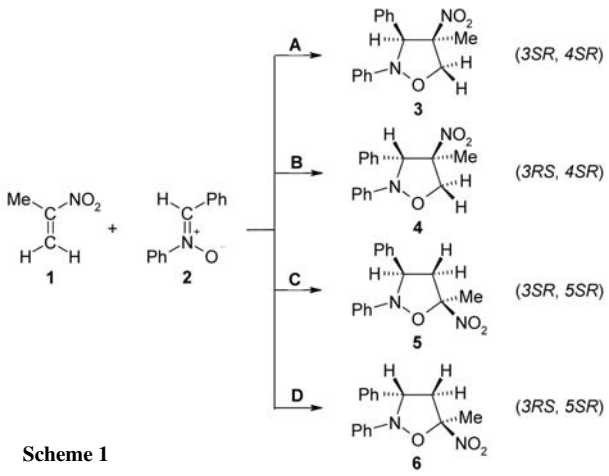
Abstract

The [2+3] cycloaddition of 2-nitropropene to (*Z*)-*C*,*N*-diphenylnitrone leads to 3,4-*trans*-2,3-diphenyl-4-nitro-4-methyl- and 3,5-*trans*-2,3-diphenyl-5-nitro-5-methylisoxazolidines as primary reaction products. This, however, is not the only pathway of 2-nitropropene conversion. In the reaction conditions, the nitroalkene also undergoes isomerisation and the resulting *trans*- and *cis*-1-nitropropenes yield respective stereoisomeric 2,3-diphenyl-4-nitro-5-methylisoxazolidines in the reaction with (*Z*)-*C,N*-diphenylnitrone.

Keywords: [2+3] Cycloaddition, nitrone, nitroalkene, nitroisoxazolidine

1. Introduction

This work is a continuation of our systematic study dealing with the reactivity of conjugated nitroalkenes in [2+4] π-electron cycloaddition reactions.[1–7] Previously,[3] the B3LYP/6-31G(d) simulation of competing 2-nitropropene (**1**) to (*Z*)-*C*,*N*-diphenylnitrone (**2**) [2+3] cycloaddition pathways has been presented (Scheme 1). We have found that they are all kinetically allowed. In polar solvents (acetone, nitromethane) the most favoured are pathways **B** and **D**, while **C** and **A** are least favoured. However, no literature data is available to confirm which pathways are actually followed.



Scheme 1

Therefore, the aim of this work has been to determine experimentally which of the pathways are really preferred. Our purpose was the compilation of quantumchemical calculations with experimental results in order to facilitate the understanding of the course of the [2+3] cycloaddition of 2-nitroalkenes to nitrones.

2. Experimental

2. 1. General

Melting points were determined on a Boetius apparatus and are not corrected. ^{1}H-NMR spectra were taken on a Bruker Avance AMX (300MHz) in $CDCl_3$. Chemical shifts are expressed in ppm downfield from TMS used as an internal standard. IR spectra were recorded on a Bio-

* Part 4 of the series 'Conjugated Nitroalkenes in Cycloaddition Reactions'; Part 3 see Ref. 1.

Rad 175 C spectrometer in KBr pellets or in film. Elemental analyses were determined on a Perkin-Elmer PE-2400 CHN apparatus. HPLC analyses were carried out using a Knauer apparatus coupled with a UV-VIS detector (λ = 254 nm). The following analytical systems were used: (a) Lichrospher 100-5 RP18 (250*4) column, eluent: methanol-water 75:25 v/v, eluent flow rate: 1.3 mL/min, (b) Nucleosil 100-10 Si (250*4) column, eluent: *n*-hexane-ethyl acetate (98:2 v/v), eluent flow rate: 1.3 mL/min, λ = 254 nm, t = 25 °C. The reaction mixture was separated by HPLC using semipreparative column Eurospher 100–10 Si (250*16) and hexane-ethyl acetate (98:2 v/v) as the eluent at flow rate 10 mL/min.

2. 2. Reagents

2-Nitropropene **1** was prepared[8] by pyrolysis of 2-nitropropyl phtalate. (*Z*)-C,N-diphenylnitrone **2** was prepared[9] by condensation of benzaldehyde with phenylhydroxylamine in ethanol.

Reaction of 2-nitropropene with Z-C,N-diphenylnitrone

A mixture of 2-nitropropene **1** (1740 mg, 20 mmol) and of (*Z*)-*C*,*N*-diphenylnitrone **2** (985 mg, 5 mmol) in 10 mL of anhydrous acetonitrile was stirred in dark at room temperature for 24 h. The solvent was evaporated *in vacuo* to dryness and the residue was separated by semipreparative HPLC. Evaporation of the eluent from the obtained fractions gave isoxazolidines **4**, **7–9, 11**. The products were recrystallized from anhydrous *n*-hexane.

Isomerisation of 3,4-*cis*-4,5-*trans*-2,3-diphenyl-4-nitro-5-methylisoxazolidine 8

To a solution of 3,4-*cis*-4,5-*trans*-2,3-diphenyl-4-nitro-5-methylisoxazolidine **8** (568 mg, 2 mmol) in 10 mL of anhydrous acetonitrile catalytic amounts of basic Al_2O_3 were added. The content was stirred at 25 °C. After 48 h, the mixture was filtered and the solvent was distilled off. The residue was resolved by semipreparative HPLC. Evaporation of the eluent from the obtained fractions gave isoxazolidine **11** and unreacted isoxazolidine **8**. Both products were recrystallized from anhydrous *n*-hexane.

3. Results and Discussion

The title [2+3] cycloaddition was carried out at room temperature, using a four-fold molar excess of 2-nitropropene and acetonitrile as the solvent. When the reaction was completed, the solvent together with excess of nitroalkene was removed under vacuum and the residue was analyzed HPLC. It was established that instead of the expected four products (Scheme 1) the reaction afforded five products (Figure 1).

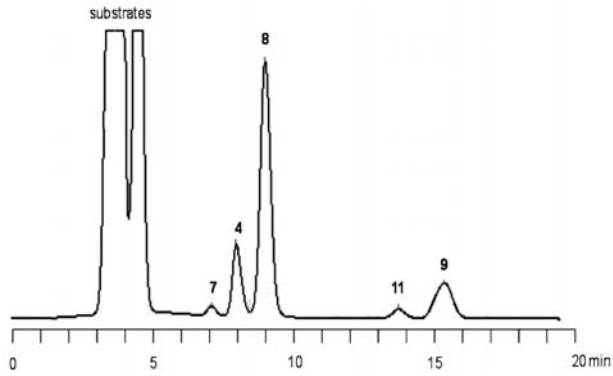


Figure 1. The chromatogram of reaction mixture of 2-nitropropene **1** with (*Z*)-*C*,*N*-diphenylnitrone **2** after 8h (Lichrospher 100-5 RP18 column was used).

The compounds were separated by semipreparative HPLC, which yielded individual compounds in the analytically pure form.

Based on elemental analysis and an MS spectrum (Table 1), the first compound to be separated (R_t = 7.1 min) was assigned with a molecular formula of $C_{16}H_{17}NO_2$. The molecular weight of its molecular ion (m/e = 255) was 29u lower than those of expected [2+3] cycloadducts. Bands typical for monosubstituted benzene ring,[10] isoxazolidine ring[11] as well as methyl and hydroxyl[10] group vibrations are seen in its IR spectrum. However, no bands from the nitro group[10] are observed. The protons of the heterocyclic ring in the ^{1}H-NMR spectrum (Table 2) form an ABX spin system. Therefore, a structure of 2,3-diphenyl-5-methyl-5-hydroxyisoxazolidine is assigned to the compound. The coupling constant values indicate that H3 and H4 protons are in *cis* configuration (J_{H3H4} = 10.4 Hz), while H3 and H4' ($J_{H3H4'}$ = 7.1 Hz) protons are in *trans*. However, in the NOESY spectrum (Table 2) of the compound, a strong off-diagonal correlation signal between the protons of the methyl group and the H4' proton and a relatively weaker signal between the protons of the same methyl group and the H4 proton were noted. Therefore, the methyl group and the H4 proton are located on the opposite sides of the virtual plane of the azolidine ring. In consequence, the compound with R_t = 7.1 min was assigned with a structure of 3,5-*trans*-2,3-diphenyl-5-hydroxy-5-methylisoxazolidine (**7**).

Based on elemental analysis and an MS spectrum, the second compound to be separated (R_t = 7.9 min) was assigned with a molecular formula of $C_{16}H_{16}N_2O_3$. The molecular weight of its molecular ion (m/z = 284) is exactly equal to the sum of molecular weights of substrates **1** and **2**. Owing to the presence of bands typical of isoxazolidine ring[11], nitro and methyl groups as well as monosubstituted benzene ring[10] vibrations in the IR spectrum, the structure of diphenylmethylnitroisoxazolidine was assigned. Information about its regioisomerism was provided by an ^{1}H-NMR spectrum (Table 2). In particular, the

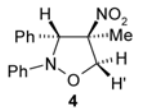
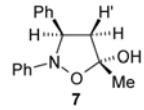
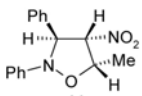
Table 1. Essential physical properties of isoxazolidines **4,7-9,11**.

Nr	R_T [min]	Yield [%]	t_t [°C] Found	Ref. 4	Brutto Formula	Found % Calculated % C	H	N	$M^{+\bullet}$ [m/z] (%)	IR [cm^{-1}]
4	7.9	15	84–86	–	$C_{16}H_{16}N_2O_3$	67.40 67.59	5.63 5.67	9.84 9.85	284 (72)	Isox. ring: 1183; Aryl. ring: 695, 755; CH_3: 1391, 1453; NO_2: 1362, 1545
7	7.1	2	104–105	–	$C_{16}H_{17}NO_2$	75.43 75.23	6.63 6.71	5.68 5.49	255 (14)	Isox. ring: 957, 1185; Aryl. ring: 698, 750; CH_3: 1399, 1452; OH: 3482
8	9.0	58	86–87	86–87	$C_{16}H_{16}N_2O_3$	66.90 67.59	5.57 5.67	9.68 9.85	284 (76)	Isox. ring: 959, 1179; Aryl. ring: 695, 749; CH_3: 1380, 1449; NO_2: 1369, 1546
9	15.3	13	Liquid	Liquid	$C_{16}H_{16}N_2O_3$	67.70 67.59	5.82 5.67	9.38 9.85	284 (100)	Isox. ring: 962, 1180; Aryl. ring: 697, 756; CH_3: 1453; NO_2: 1376, 1555
11	13.7	2	76–77	–	$C_{16}H_{16}N_2O_3$	67.10 67.59	5.68 5.67	9.76 9.85	284 (100)	Isox. ring: 960, 1182; Aryl. ring: 693, 701, 759; CH_3: 1385, 1454; NO_2: 1373, 1549

observed AX;M type spin system confirms the location of both nitro and methyl groups at the C4 position of the isoxazolidine ring. Unfortunately, the 1D spectrum did not permit us to determine its stereoisomerism. This problem was however successfully resolved by means of a NOESY experiment.

It appeared that in the NOESY spectrum (Table 2) the intensity of correlation signals between the protons of the methyl group and the H3 and H5' protons of the azolidine ring was similar. However the correlation signal between proton H5 and the protons of the methyl group was much stronger. This suggests that the H3 proton and the methyl group are located on the opposite sides of the virtual plane of the azolidine ring. Therefore, CHN analysis data and IR, MS and ^{1}H-NMR spectra prove that the compound with R_T = 7.9 min is the expected 3,4-*trans*-2,3-diphenyl-4-methyl-4-nitroisoxazolidine **4**. The optimisation of molecular geometry using the B3LYP/6-31g(d) al-

Table 2. ^{1}H-NMR[a] and NOESY[b] data for isoxazolidines **4**,**7**,**11**.

		C<u>H</u>$_3$	**H3**	**H5**	**H5'**	
 **4**	C<u>H</u>$_3$	**1.93** (s)				
	H3	M	**4.56** (s)			
	H5	S	M	**4.14** (d)	9.36	
	H5'	M	M		**5.09** (d)	
		O<u>H</u>	**C<u>H</u>$_3$**	**H3**	**H4**	**H4'**
 **7**	O<u>H</u>	**1.56** (s)				
	C<u>H</u>$_3$		**1.70** (s)			
	H3		VW	**4.92** (dd)	10.47.1	
	H4		M		**2.87** (dd)	12.2
	H4'		S			**2.31** (dd)
		C<u>H</u>$_3$	**H3**	**H4**	**H5**	
 **11**	C<u>H</u>$_3$	**1.33** (d)			6.3	
	H3	W	**5.14** (d)	3.5		
	H4	M		**5.19** (dd)	5.7	
	H5		W		**4.79** (m)	

[a] Chemical shifts and multiplicities (in parentheses) are placed diagonally and *J* (Hz) off-diagonally (upper); aryl protons are not included. [b] Placed off-diagonally (lower): VW – very weak, W – weak, M – medium, S – strong.

gorithm confirmed that the average distance between the methyl group protons and protons H3 and H5' is 3.8 Å and 3.9 Å, respectively, while for proton H5 only 2.9 Å in isoxazolidine **4**. This is consistent with the NOESY results.

Unexpectedly, were the products eluting et a 9.0 and 15.3 min respectively. Based on elemental analysis data and MS and IR spectra (Table 1), structures of 3,4-*cis*-4,5-*trans*-2,3-diphenyl-4-nitro-5-methylisoxazolidine (**8**) and 3,4-*trans*-4,5-*trans*-2,3-diphenyl-4-nitro-5-methylisoxazolidine (**9**) were assigned, respectively. The compounds were identical to the products of obtained of [2+3] cycloaddition of nitrone **2** with *trans*-1-nitropropene (**10**) described previously.[4]

Similarly to products **8** and **9**, the composition of the fourth product (R_t = 13.7min) corresponded to the sum of substrates. However, it was none of the cycloadducts shown in Scheme 1. Its IR spectrum proved to be very similar to those of isoxazolidines **8** and **9** (Table 1). The methyl group and azolidine ring protons in the ^{1}H-NMR (Table 2) spectrum form an A_3MXY spin system. Its parameters (Table 2) indicate that the compound's regioisomerism is analogous to that of isoxazolidines **8** and **9**. The coupling constants of the heterocyclic ring protons (J_{H3H4} = 3.5 Hz, J_{H4H5} = 5.7 Hz) indicate that H3 and H4 protons are in *trans* configuration, while H4 and H5 protons are in *cis*. The NOESY spectrum (Table 2) also indicates such stereoisomerism. This was further supported by a weak correlation signal between protons H3 and H5 and the medium-intensity correlation signal between the protons of the methyl group and the H4 proton.

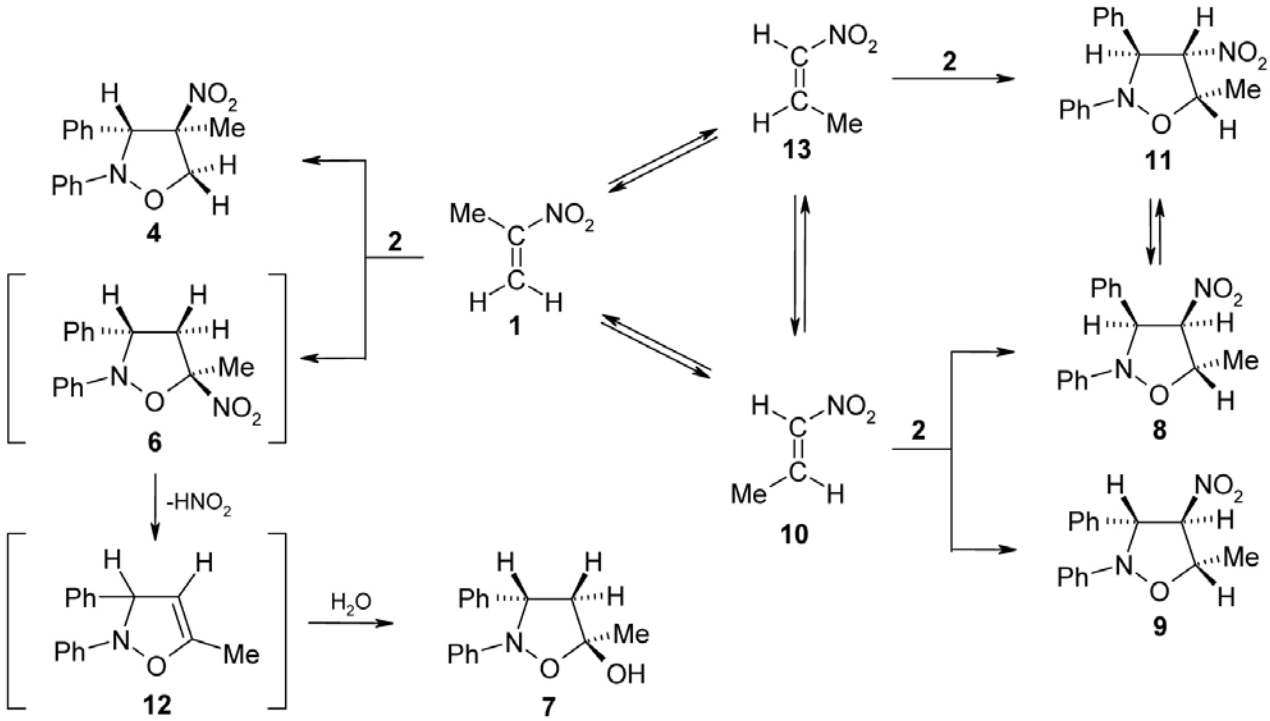
In order to conclusively confirm the structures, MS, IR and ^{1}H-NMR spectra and physicochemical constants (m.p. and R_T) were compared of the test compound and 3,4-*trans*-4,5-*cis*-2,3-diphenyl-4-nitro-5-methyl-isoxazolidine (**11**) that we alternativity synthesised by the catalytic isomerisation of 3,4-*cis*-4,5-*trans*-2,3-diphenyl-4-nitro-5-methylisoxazolidine (**8**) (see Experimental).

Quantitative HPLC analysis of the reaction mass proved that products **7**, **4**, **8**, **11**, **9** formed in a molar ratio of ~1:7:29:1:7.

Based on the current and our earlier investigation of nitroisoxazolidine[4,12] and nitroisoxazoline[13,14] chemistry, we propose the course of reaction between 2-nitropropene **1** and (*Z*)-*C*,*N*-diphenylnitrone **2** as shown in Scheme 2.

It seems that isoxazolidines **4** and **6** are the primary reaction products. This supported by the B3LYP/6-31G(d) calculations[3] according to which free activation enthalpies ($\Delta G^{\neq}$) for reactions on pathways **B** and **D** (Scheme 1) are 28.9 and 29.5 kcal/mol, respectively, while on pathways **A** and **C** 29.6 and 31.9 kcal/mol, respectively. Compound **4** is stable under reaction conditions. However, **6** is likely converted to 2,3-diphenyl-5-methyl-Δ^4-isoxazoline (**12**) due to the *syn*-elimination of an HNO_2 molecule, which yields hydroxymethylisoxazolidine **7** in reaction with water from HNO_2 decomposition. 5-Nitroisoxazolidine dehydronitration[15–17] and Δ^4-isoxazoline hydration[11] were reported some years ago. They easily proceed under mild conditions. This substantiates the **6**→**7** conversion as postulated.

The presence of nitromethylisoxazolidines **8**, **9**, **11** in the reaction mixture suggests that *trans* and *cis* 1-nitro-



Scheme 2

propenes (**10**, **13**) were also present in the reaction environment together with 2-nitropropene **1**. They compete in the reaction with nitrone **2** following the [2+3] cycloaddition mechanism. However, it cannot be ruled out that nitroisoxazolidine **11** was also formed as a consequence of the autocatalytic isomerisation of isoxazolidine **8**. Such reactions are known in nitroisoxazoline chemistry.[13]

We postulate nitropropenes **10** and **13** were formed in the reaction mixture by the isomerisation of nitropropene **1**. Similar reactions are catalysed by both inorganic and organic bases,[12,18–22] including cycloadducts, which form in the reaction tested. This was confirmed by the ^{1}H-NMR spectra of 2-nitropropene **1** in deuteroacetonitrile. When catalytic amounts of isoxazolidine **4** were added to the solution, signals from *trans*-1-nitropropene (**10**) protons were found after approx. 2 h apart from resonance signals from 2-nitropropene protons in the spectrum. After 18 h, *cis*-1-nitropropene **13** proton signals also appeared. B3LYP/6-31g(d) calculations confirm that the simultaneous presence of all three nitroalkenes suggested is possible in the reaction environment. However, nitropropene **10** is thermodynamically the most stable. Hence, its content in the equilibrium mixture is the largest (**1**:**10**:**13** ≈1:7:5.5). Consequently, it becomes evident that the **8** and **9** content in the product mixture is the highest.

4. Conclusion

The [2+3] cycloaddition reaction of 2-nitropropene to (*Z*)-*C*,*N*-diphenylnitrone leads to 3,4-*trans*-2,3-diphenyl-4-nitro-4-methyl- and 3,5-*trans*-2,3-diphenyl-5-nitro-5-methylisoxazolidines as primary reaction products. This, however, is not the only pathway of 2-nitropropene conversion. In the reaction conditions, the 2-nitropropene also undergoes isomerisation and the resulting *trans*- and *cis*-1-nitropropenes yield respective stereoisomeric 2,3-diphenyl-4-nitro-5-methylisoxazolidines in the reaction with (*Z*)-*C*,*N*-diphenylnitrone.

5. Acknowledgements

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Povzetek

Avtorji v prispevku poročajo o [2+3] cikloadiciji 2-nitropropena na (*Z*)-*C*,*N*-difenilnitron, ki vodi do nastanka 3,4-*trans*-2,3-difenil-4-nitro-4-metil- in 3,5-*trans*-2,3-difenil-5-nitro-5-metilizoksazolidinov kot glavnih reakcijskih produktov. Vendar to ni edina možna pretvorba 2-nitropropena, saj v danih reakcijskih pogojih nitroalken izomerizira. Nastali *trans*- oziroma *cis*-1-nitropropen daje pri reakciji z (*Z*)-*C*,*N*-difenilnitronom ustrezne stereoizomerne 2,3-difenil-4-nitro-5-metilizoksazolidine.