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[3+2] Cycloadditions of 1-halo-1-nitroethenes with (Z)-C-(3,4,5-trimethoxyphenyl)-N-methyl-nitrone as regio- and stereocontrolled source of novel bioactive compounds: preliminary studies

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Preliminary experiments shows, that [3+2] cycloadditions reactions proceeds with full regioselectivity and high stereoselectivity. In consequence, 3,4-trans-2-methyl-3-(3,4,5-trimethoxyphenyl)-4-halo-4-nitroisoxazolidines are forming as predominantly (or sole) products. Additionally, prognosis for the synthesized compounds to be potential ingredients of drugs is good.

1. Introduction

Isoxazolidines are an important class of bioactive compounds.[1-3] The presence of the nitro group in the molecule of these compounds stimulate extra forms of biological activity [4] and allows for a wide range of further functionalizations.[5-8] This justifies undertaken by us a few years ago a comprehensive study on the synthesis of nitro substituted isoxazolidines by [3+2] cycloaddition of nitroalkenes to nitrones. So far we have dealt mainly with reactions where 2-substituted nitroethenes [9-14] were participated. The accumulated research material makes it possible to formulate some general conclusions about regioselectivity, stereoselectivity and reaction mechanisms of this group. A little is currently known about similar reactions involving nitroethenes functionalized from a position 1 of the nitrovinyl fragment. This paper provides a summary of our recent, preliminary studies in this area. In particular, in the context of the whole study, we present a diagnosis for a course of two [3+2] cycloadditions of 1-chloro-1-nitroethene (**1a**) and 2-(trichloromethyl)-1-bromo-1-nitroethene (**1b**) with

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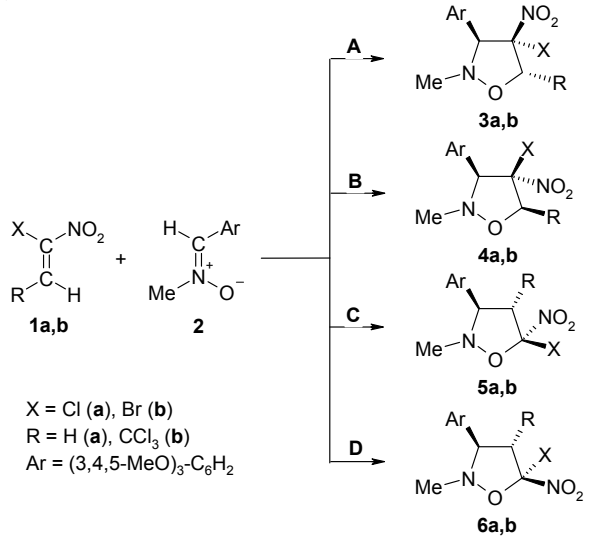
a strong nucleophile (Z)-C-(3,4,5-trimethoxyphenyl)-N-methyl-nitrone (**2**), which was previously tested in the reactions with 2-substituted nitroethenes.[12]

2. Results and Discussion

Assuming that the reaction takes place through a one-step mechanism, the cycloadditions of the test components could in theory be accomplished on four regio- and stereoisomeric paths, leading finally to nitroisoxazolidines **3-6a, b**.



Scheme 1. Theoretically possible paths of [3+2] cycloaddition between 1-halo-1-nitroethenes **1a,b** with (Z)-C-(3,4,5-trimethoxyphenyl)-N-methyl-nitrone **2**

In the first step of our studies we decided to determine which of the paths are actually proceed in reality. For this purpose, we performed a series of tests of varying the reaction time, temperature and solvent. We have found that both cycloadditions in methylene chloride (DCM) are easily progressing at room temperatures, at twice molar excess of nitroalkene. Under these conditions, the conversion of the nitrone is finished in 2 hours.

Both reaction mixtures were analyzed by HPLC. It has been found that the reaction of 1-chloro-1-nitroethene (**1a**) from (Z)-C-(3,4,5-trimethoxyphenyl)-N-methyl-nitrone (**2**) leads toward two products, which could be isolated with semi-preparative HPLC. Based on elemental analysis and spectral data we have established that these are stereoisomeric 3,4-trans- (**3a)** and 3,4-cis-2-methyl-3- (3,4,5-trimethoxyphenyl)-4-chloro-4-nitroisoxazolidines (**4a**). In turn, a similar reaction involving 2-(trichloromethyl)-1-bromo-1-nitroethene (**1b**) has produced only the product, which by elemental analysis and spectral data was assigned as 3,4-cis-2-methyl-3-(3,4,5-trimethoxyphenyl)-4-bromo-4-nitro-5-(trichloromethyl)-isoxazolidine (**3b**). We have decided to explain the observed regioselectivity on the basis of a recently intensively developed,[11,15-17] conceptual DFT study based on the analysis of the electrophilicity ω and nucleophilicity *N* indices. The necessary descriptors havebeen obtained from quantum-chemical calculations. So, the global electrophilicity (ω) of adducts[11] were determined on the basis of electronic values of chemical potentials (μ) and chemical hardness.

$$(\eta)\quad \omega=\mu^2/2\,\eta, \tag{1}$$

$$\mu\approx(E_{HOMO}+E_{LUMO})/2 \qquad \eta\approx E_{LUMO}-E_{HOMO}, \tag{2}$$

whereas the global nucleophilicity (N)[18] of nitrone can be expressed in terms of equation:

$$N=E_{HOMO\ (nitrone)} - E_{HOMO\ (tetracyanoethene)} \tag{3}$$

The local electrophilicity (ω_k)[19] condensed to atom k was calculated by projecting the index ω onto any reaction center k in the molecule by using Parr function P^+_k [20]:

$$\omega_k = P^+_k \cdot \omega \quad (4)$$

The local nucleophilicity (N_k)[21] condensed to atom *k* was calculated using global nucleophilicity N and *Paar* function P^-_k[20] according to the formula:

$$N_k = P^-_k \cdot N \quad (5)$$

Such obtained reactivity indexes are gathered in **Table 1**.

Table 1. Global and local electronic properties for 1-halo-1-nitroethenes **1a,b** and (Z)-C-(3,4,5-trimethoxyphenyl)-N-methyl-nitrone **2**

	Global properties			Local properties				
	μ (au)	η (au)	ω (eV)	N (eV)	N_C (eV)	N_O (eV)	ω_α (eV)	ω_β (eV)
1a	-0.2019	0.1927	2.88				0.02	1.29
1b	-0.2010	0.1879	2.93				0.00	0.17
2	-0.1191	0.1499	1.29	3.84	0.17	1.47		

From the collected data it can be shown that a stronger nucleophilic center for this reaction in the nitrone molecule is a carbon atom on the CNO fragment. In turn, a stronger electrophilic reaction center in the nitroalkene molecules is always β-carbon atom on the nitrovinyl fragment. An interaction of these centers controls flow of the reaction, directing the reaction along the pathways leading to adducts with a nitro group at C4 position of the isoxazolidine ring. Finally, we have decided to diagnose a potentially interesting bioactivity properties of the synthesized compounds. For this purpose we have used PASS simulation program, which has recently been successfully applied to a design of a number of medicines [22]. It has been found (**Table 2**), that the compound **1a** shows in five areas a high probability of an action in a manner similar to known drugs (Pa = 0.7 or more), at a relatively low coefficient of inactivity (Pi <0.05). Slightly less attractive from the application point of view seems to be the product **1b** (**Table 3**). In the near future the issue of bioactivity will be a subject of our detailed laboratory analysis.

Table 2. The PASS simulations for 2-methyl-3-(3,4,5-trimethoxyphenyl)-4-chloro-4-nitroisoxazolidines

Activity	The probability of activity (Pa)	The probability of non-occurrence of activity (Pi)
Ubiquinol-cytochrome-c reductase inhibitor	0.767	0.044
Membrane permeability inhibitor	0.706	0.036
Acrocylindropepsin inhibitor	0.700	0.044
Chymosin inhibitor	0.700	0.044
Saccharopepsin inhibitor	0.700	0.044
Antileukemic	0.603	0.009
Aspulvinone dimethylallyltransferase inhibitor	0.636	0.085
Polarisation stimulant	0.549	0.021
Phobic disorders treatment	0.620	0.113

Table 3. The PASS simulations for 2-methyl-3-(3,4,5-trimethoxyphenyl)-4-bromo-4-nitro-5-(trichloromethyl)-isoxazolidine

Activity	The probability of activity (Pa)	The probability of non-occurrence of activity (Pi)
Antileukemic	0.572	0.010
Antifungal	0.545	0.024
Ubiquinol-cytochrome-c reductase inhibitor	0.618	0.100
CYP2H substrate	0.544	0.096
Calcium regulator	0.419	0.035
Acrocylindropepsin inhibitor	0.476	0.123
Chymosin inhibitor	0.476	0.123
Saccharopepsin inhibitor	0.476	0.123
Antineoplastic (lung cancer)	0.378	0.026

3. Conclusions

Cycloaddition reactions involving 1-halo-substituted nitroalkenes are proceeding under mild conditions. There is an evident preference for one of the four theoretically possible configurations of the transition state. This makes the synthesis to be accomplished with regiospecificity and in a highly stereoselective manner. A prognosis for the synthesized compounds to be potential ingredients of drugs is good. Finally it should be noted, that due to unequivocal degree of substitution of reactions centers of addents, [3+2] cycloadditions involving 1-halo-1-nitroethenes may proceed via stepwise mechanisms. Some examples of these type mechanisms were described recently[23-26]. Due to this, mechanistic aspects of nitrone / 1-halo-1-nitroethene cycloadditions would be subject of further, comprehensive studies.

4. Experimental

4.1. Instruments

Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were determined on a Perkin-Elmer PE-2400 CHN apparatus. Mass spectra (EI, 70eV) were obtained using a Hewlett-Packards 5989B spectrometer. IR spectra were recorded on a Bio-Rad spectrophotometer. ^{1}H-NMR spectra were taken on a Bruker (500 MHz) spectrometer, using TMS as an internal standard, and $CDCl_3$ as a solvent. Liquid chromatography (HPLC) was done using a Knauer apparatus equipped with a UV-VIS detector. For monitoring of the reaction progress, LiChrospher 100-10-RP column (4x240 mm) and 75 % methanol as the eluent at flow rate 1.2 ml/min were used. The separation of the post-reaction mixtures was performed on the same Knauer apparatus, using a semipreparative column (LiChrospher 100-10-RP, 16x240 mm) and 70 % methanol as the eluent at flow rate 10 ml/min.

4.2. Reagents

3,3,3-trichloro-1-bromo-1-nitroethene **1b** and (Z)-C-(3,4,5-trimethoxyphenyl)-N-methyl-nitrone **2** was synthesized according to the procedures described in the literature: **1b**,[27] **2.**[28] For 1-chloro-1-nitroethene **1a** a new efficient synthetic procedure has been developed, which was a modification of a synthetic route developed in the early twentieth century.[29]

A Claisen flask was charged with P_2O_5 (42 g). The flask was heated to 150 °C, after which the pressure in the distillation assembly was reduced to 110 mmHg. Then it has been slowly added dropwise to the flask of 2-chloro-2-nitroethanol (38 g), which had been synthesized from 2-nitroethanol by a procedure described in detail in [30]. The resulting 1-chloronitroethene immediately distilled out and condensed in a receiver cooled to 0 °C. The crude product was dried with Na_2SO_4 and then distilled under a reduced pressure in an atmosphere of argon. On this way, 16g (52%) of 1-chloronitroethene **1a** was obtained. Its purity was confirmed by GC. B.p. 55-56 °C / 90 mmHg (Ref.[25]) 54 °C. / 14 mmHg); ^{1}H NMR: 6.85 ppm (1H, d, J = 3.92Hz), 6.04 ppm (1H, d, J = 3.92Hz); IR cm^{-1}: 1548, 1333 (NO_2), 1620 (C=C).

4.3 Experimental procedure and physical data

A mixture of a suitable nitroalkene (0.02mol) and nitrone (0.01mol) in 5cm^3 of DCM was stirred at room temperature for 2 hours. The solvent was evaporated *in vacuo* to dryness and the semiliquid residue was separated by semipreparative HPLC. Evaporation of the eluent from the obtained fractions gave the diarylnitroisoxazolidines **3** and **4**.

3,4-trans-2-methyl-3-(3,4,5-trimethoxyphenyl)-4-chloro-4-nitroisoxazolidine (**3a**)

Yield 75 %, colorless crystals, m.p. 134 (cyclohexane). R_T (min): 3.7. IR, ν, cm^{-1}: 1567, 1352 (NO_2), 1182 (-C-N-), 1235, 1051 (CH_3-O-Ar), 858 (Ar), 807 (C-Cl). NMR ^{1}H, ppm (*J*, Hz): 6.54 (2H, s, $C_6\underline{H}_2$), 5.25 (1H, d, *J*=10.24, H5), 4.45 (1H, d, *J*=10.24, H5'), 4.00 (1H, s, H3), 3.88 (3H, s, p-OC$\underline{H}_3$),

3.85 (6H, s, m-OC<u>H</u>$_3$), 2.74 (3H, s, N-C<u>H</u>$_3$). NMR ^{13}C, ppm: 139.2 138.4, 137.5, 106.2, 96.1, 78.3, 76.8, 62.6, 58.1, 45.3. Found, %: C 46.67; H 5,13; N 8,32. $C_{13}H_{17}N_2O_6Cl$. Calculated, %: C 46.90; H 5,11, N 8.42.

3,4-cis-2-methyl-3-(3,4,5-trimethoxyphenyl)-4-chloro-4-nitroisoxazolidine (**4a**)

Yield 18 %, oil. R_T (min): 5.4. IR, ν, cm^{-1}: 1574, 1349 (NO_2), 1182 (-C-N-), 1236, 1057 (CH_3-O-Ar), 867 (Ar), 797 (C-Cl). NMR ^{1}H, ppm (*J*, Hz): 6.62 (2H, s, C_6<u>H</u>$_2$), 5.13 (1H, d, *J*=10.96, H5), 4.30 (1H, d, *J*=10.96, H5'), 4.21 (1H, s, H3), 3.91 (3H, s, p-OC<u>H</u>$_3$), 3.88 (6H, s, m-OC<u>H</u>$_3$), 2.76 (3H, s, N-C<u>H</u>$_3$). NMR ^{13}C, ppm: 138.9 138.2, 137.6, 105.9, 96.0, 78.3, 77.1, 62.4, 59.3, 46.2. Found, %: C 46.92; H 5.10; N 8.37. $C_{13}H_{17}N_2O_6Cl$. Calculated, %: Calculated, %: C 46.90; H 5,11, N 8.42.

3,4-trans-2-methyl-3-(3,4,5-trimethoxyphenyl)-4-bromo-4-nitro-5-(trichloromethyl)-isoxazolidine (**3b**)

Yield 92 %, colorless crystals, m.p. 152 (ethanol-hexane 9:1 v/v). R_T (min): 5.4. IR, ν, cm^{-1}: 1573, 1352 (NO_2), 1186 (-C-N-), 1240, 1047 (CH_3-O-Ar), 859 (Ar), 788 (C-Cl), 698 (C-Br). NMR ^{1}H, ppm (*J*, Hz): 6.53 (2H, s, C_6<u>H</u>$_2$), 5.36 (1H, s, H5), 4.41 (1H, s, H3), 3.87 (3H, s, p-OC<u>H</u>$_3$), 3.85 (6H, s, m-OC<u>H</u>$_3$), 2.76 (3H, s, N-C<u>H</u>$_3$). NMR ^{13}C, ppm: 139.8, 138.5, 137.0, 106.7, 99.0, 79.6, 78.5, 62.3, 58.9, 47.2. 19.2. Found, %: C 34.05.92; H 3.25; N 5.70. $C_{14}H_{16}N_2O_6Cl_3Br$. Calculated, %: Calculated, %: C 34.00; H 3,26, N 5.66.

References

1 Romeo R., Navarra M. Giofrè S.V., Carnovale C., Cirmi S., Lanza G., Chiacchio M.A. **(2014)** Synthesis and biological activity of new arenediyne-linked isoxazolidines. *Bioorg. Med. Chem*., 22 (13) 3379-3385.

2 Malhotra S., Balwani S., Dhawan A., Raunak, Kumar Y., Singh B.K., Olsen C.E., Prasad A.K., Parmar V.S., Ghosh B. **(2012)** Design, synthesis and biological activity evaluation of regioisomeric spiro-(indoline-isoxazolidines) in the inhibition of TNF-α-induced ICAM-1 expression on human endothelial cells. *Med. Chem. Commun.*, 3 (12) 15361547.

3 Burton G., Clarke G.J., Douglas J.D., Eglington A.J., Frydrych C.H., Hinks J.D., Hird N.W. **(1996)** Novel C-2 substituted carbapenem derivatives. Part II. Synthesis and structure-activity relationships of isoxazolin-2-yl, isoxazolidin-2-yl and 2-pyrazolin-2-yl carbapenems generated using 1,3-dipolar cycloaddition chemistry. *J Antibiot*, 49 (12) 1266-1274.

4 Boguszewska-Czubara A, Łapczuk-Krygier A., Rykała K., Biernasiuk A., Wnorowski A, Popiołek Ł., Maziarka A., Hordyjewska A., Jasiński R. Novel synthesis scheme and in vitro antimicrobial evaluation of a panel of (E)-2-aryl-1-cyano-1-nitroethenes", *J. Enzyme Inhib. Med. Chem.*, Accepted Manuscript (DOI: 10.3109/14756366.2015.10702).

5 Ono N. **(2001)** *The nitro group in organic synthesis*, Wiley-VCH: Weinheim.

6 Ballini R., Petrini M. **(2004)** Recent synthetic developments in the nitro to carbonyl conversion (Nef reaction. *Tetrahedron*, 60 (5) 1017-1047.

7 Belenkii L.I. **(2007)** *Nitrile oxides, nitrone and nitronates in orgnanic synthesis*. Ed, Feuer H., Wiley.

8 Jasiński R. **(2015)** A new mechanistic insight on beta-lactam systems formation from 5-nitroisoxazolidines. *RSC Adv.*, 5 (62) 50070-50072.

9 Jasiński R. **(2009)** Regio- and stereoselectivity of [2+3]cycloaddition of nitroethene to (Z)- N-aryl-C-phenylnitrones. *Coll. Czech. Chem. Commun*., 74 (9) 1341-1349.

10 Jasiński R. **(2009)** The question of the regiodirection of the [2+3] cycloaddition reaction of triphenylnitrone to nitroethene. *Chem. Heterocyclic Compd*., 45 (6) 748-749.

11 Jasiński R. **(2012)** Exploration of regiospecificity phenomenon in [2+3] cycloaddition reactions between arylnitrones and trans-substituted nitroethenes on the basis of the reactivity indices theory. *Current Chem. Lett*., 1, 157-162

12 Jasiński R., Ziółkowska M., Demchuk O.M., Maziarka A. **(2014)** Regio- and stereoselectivity of polar [2+3] cycloaddition reactions between (Z)-C-(3,4,5-trimethoxyphenyl)-N-methylnitrone and selected (E)-2-substituted nitroethenes. *Central Eur. J. Chem*., 12 (5) 586-593.
13 Jasiński R., Mróz K., Kącka A. Experimental and theoretical DFT study on synthesis of sterically crowded 2,3,3,(4)5-tetrasubstituted-4-nitroisoxazolidines via 1,3-dipolar cycloaddition reactions between ketonitrones and conjugated nitroalkenes. *J. Heterocyclic Chem*. Accepted Manuscript (DOI: 10.1002/jhet.2442).
14 Jasiński R., Mróz K. **(2015)** Kinetic aspects of [3+2] cycloaddition reactions between (E)-3,3,3-trichloro-1-nitroprop-1-ene and ketonitrones, *React. Kinet. Mech. Catal*. 116 (1) 35-41.
15 (a) Parr R.G., von Szentpaly L., Liu L.S. **(1999)** Electrophilicity Index. *J. Am. Chem. Soc.* 121 (9) 1922; (b) Domingo L.R., Aurell M.J., Perez P., Contreras R. **(2002)** Quantitative characterization of the global electrophilicity power of common diene/dienophile pairs in Diels–Alder reactions. *Tetrahedron*, 58 (22) 4417-4423.
16 Kapłon K., Demchuk O.M., Wieczorek M., Pietrusiewicz K.M. **(2014)** Brönsted acid catalyzed direct oxidative arylation of 1,4-naphthoquinone. *Current Chem. Lett.*, 3(1) 23-36.
17 Chattaraj P.K., Giri G., Duley S. **(2011)** Update 2 of: Electrophilicity index. *Chem. Rev*., 111 (2) PR43-PR75.
18 Domingo L.R, Chamorro E., Perez P. **(2008)** An understanding of the electrophilic/nucleophilic behavior of electro-deficient 2,3-disubstituted 1,3-butadienes in polar diels-alder reactions. A density functional theory study. *J. Org. Chem*., 73(12) 4615-4624.
19 Domingo L.R., Aurell M.J., Perez P, Contreras R. **(2002)** Quantitative characterization of the local electrophilicity of organic molecules.Understanding the regioselectivity on Diels-Alder reactions. *J. Phys. Chem. A* 106 (29) 6871-6875.
20 Domingo L.R., Perez P., Saez J.A. **(2013)** Understanding the local reactivity in polar organic reactions through electrophilic and nucleophilic Parr functions. *RSC Adv*. 3 (5) 1486-1494.
21 Perez P., Domingo L.R., Duque-Noreña M., Chamorro E. **(2009)** A condensed-to-atom nucleophilicity index. An application to the director effects on the electrophilic aromatic substitutions. *J. Mol. Struct. (TheoChem)* 895 (1) 86-91.
22 Jaśkowska J., Kowalski P. **(2007)** Zastosowanie programu PASS w prognozowaniu aktywności farmakologicznej substancji organicznych. *Czasopismo Techn. PK. (Chemia)*, 1-Ch 37-45.
23 Siadati S.A. **(2016)** A Theoretical Study on Stepwise- and Concertedness of the Mechanism of 1,3-Dipolar Cycloaddition Reaction Between Tetra Amino Ethylene and Trifluoro Methyl Azide. *Comb. Chem. High Throughput Screen*, 19 (2) 170-175.
24 Siadati, SA. **(2015)** An example of a stepwise mechanism for the catalyst-free 1,3-dipolar cycloaddition between a nitrile oxide and an electron rich alkene. *Tetrahedron Lett*. 56 (34) 4857-4863.
25 Mloston G., Urbaniak K., Linden A., Heimgartner H **(2015)** Selenophen-2-yl-Substituted Thiocarbonyl Ylides – at the Borderline of Dipolar and Biradical Reactivity. *Helv. Chim. Acta.* 98 453-461.
26 Jasiński R **(2015)** A stepwise, zwitterionic mechanism for the 1,3-dipolar cycloaddition between (Z)-C-4-methoxyphenyl-N-phenylnitrone and gem-chloronitroethene catalysed by 1-butyl-3-methylimidazolium ionic liquid cations. *Tetrahedron Lett.* 56 (3) 532-535.
27 Durden J.A., Heywood D.L., Sousa A.A., Spurr H.W. **(1970)** Synthesis and Microbial Toxicity of Dinitrobutadienes and Related Compounds. *J. Agric. Food Chem*., 18 (1) 50-56.
28 Wagner G., Garlan T. **(2008)** Synthesis of 5-trichloromethyl-Δ^4-1,2,4-oxadiazolines and their rearrangement into formamidine derivatives**.** *Tetrahedron Lett*. 49 (22) 3596-3599.
29 Wilkendorf R., Trènel M. **(1924)** Zur Kenntnis aliphatischer Nitro-alkohole. *Chem. Ber.*, 57 (2) 306.
30 Jasiński R. **(2013)** *Preparatyka alifatycznych nitrozwiązków*. RTN, Radom.