Communication

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Unusual regioselectivity in [3+2] cycloaddition reactions between (E)-3-nitroacrylic acid derivatives and (Z)-C,N-diphenylimine N-oxide

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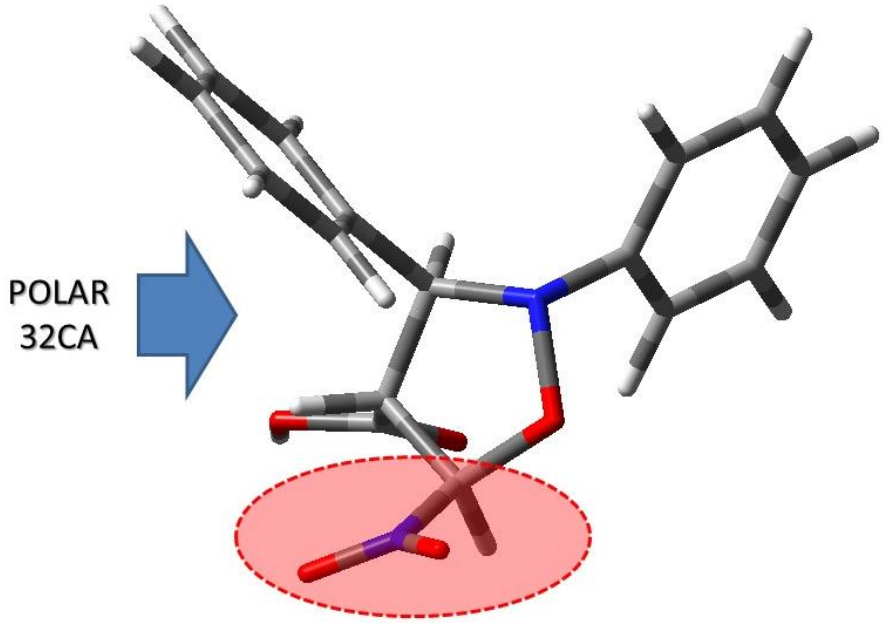

Abstract: [3+2] cycloaddition reactions of -COOMe and -CN trans-substituted nitroethenes with (Z)-C,N-diphenylimine N-oxide were tested. For the contrast to most known nitroalkene/nitrone cycloadditions, the reactions studied realized with the formation of 5-nitroisoxazolidines.

Keywords: [3+2] cycloaddition; nitroethenes, (Z)-C,N-diphenylimine N-oxide

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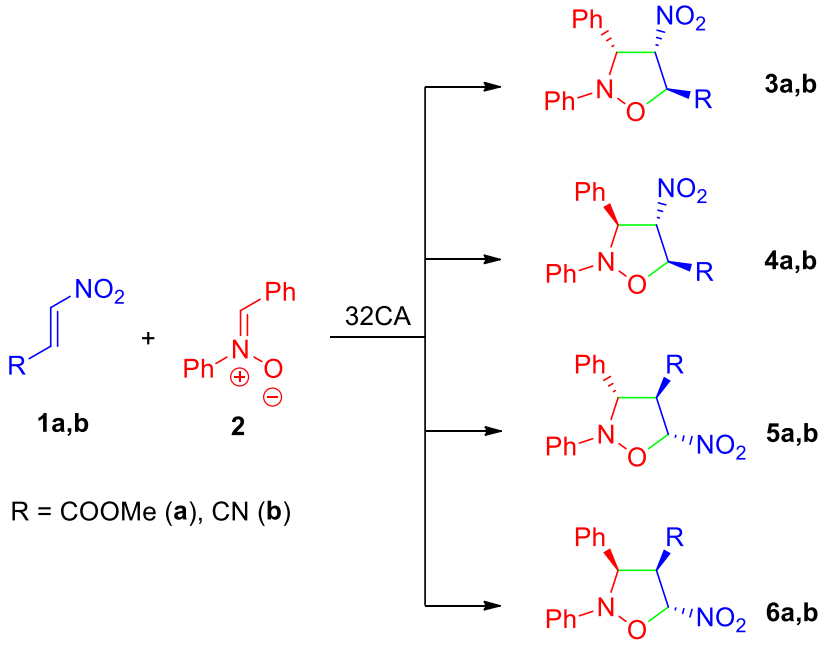
Isoxazolidines are an important class of heteoryclic compounds with potential biological and pharmaceutical activity [1- 4]. Additionally, the presence of the nitro group in these compounds stimulate extended wide spectrum of further functionalizations [5, 6]. Most universal strategy for synthesis of these compounds are [3+2] cycloaddition reactions [7] between nitrones and conjugated nitroalkenes. At this time, generally aryl [8, 9], alkyl [10, 11] as well as trihalomethyl [10, 12, 13] substituted nitroethene analogs were tested as components of this type cycloaddition. In all cases, only the mixtures of 3,4-cis and 3,4-trans-4-nitroisoxazolidines were always obtained as reaction products. In any reaction, regioisomeric 5-nitroisoxazolidines are not formed. Within this work, we decide to shed light on similar reactions involving 3-nitroacrylic acid derivatives. Products of these reactions, due to presence of carbonyl or nitrile group, should be susceptible to further functionalization directions, which makes them attractive for organic synthesis.

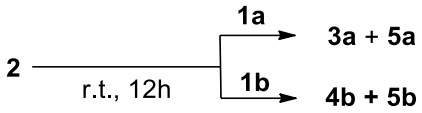
Assuming a one-step mechanism, between (E)-3-nitroacrylic acid derivatives **(1a,b)** and (Z)-C,N-diphenylimine N-oxide could in theory proceed on four regio- and stereoisomeric paths, leading to nitroisoxazolidines **3-6a,b** (Scheme 1):



Scheme 1. Theoretically possible channels of 32CAs of (E)-3-nitroacrylic acid derivatives (**1a,b**) with (Z)-C,N-diphenylimine N-oxide (2).

Assuming a both reactions were examined in the environment of the 1-butyl-3-methylimidazolium chloride and different temperatures and reaction times. Reaction progress was monitored by HPLC. It was found that both cycloaddition proceed rapidly at the r.t. and gave mixtures of isomeric nitroisoxazolidines. Reaction products we have isolated by means of semipreparative HPLC and identified using elemental analysis and spectral data.

Surprisingly we established, that in these reactions 5-nitrosubstituted isoxazolidines (**5a** or **5b** respectively) are formed, along to expected 4-nitro adducts (Scheme 2). Similar reactions selectivity was observed in the case of process realized in "conventional" solvents such as benzene, DCM and chloroform.



Scheme 2. Regio- and stereoselectivity of 32CAs of (E)-3-nitroacrylic acid derivatives (**1a,b**) with (Z)-C,N-diphenylimine N-oxide (2).

Experimental

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 80% 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 75% methanol as the eluent at flow rate 10 ml/min.

Reagents

Methyl 3-nitroacrylate **(1a)**, 3-nitroacrylonitrile **(1b)** and C,N-diphenylimine N-oxide **(2)** was synthesized according to the procedures described in the literature: **1a,b** [14, 15] **2** [16].

[3+2] cycloaddition between (E)-3-nitroacrylic acid derivatives and C,N-diphenylimine N-oxide – general procedure

A mixture of a suitable nitroalkene (0.03mol) and nitrone (0.01mol) in 3g of 1-butyl-3-methylimidazolium chloride was stirred at room temperature for 12 hours. The ionic liquid was filtered, and the solid residue was separated by semipreparative HPLC. Evaporation of the eluent from the obtained fractions gave the diphenylnitroisoxazolidines. Key physicochemical properties of these products are listed below:

3,4-cis-4,5-trans-2,3-diphenyl-4-nitro-5-carbomethoxyisoxazolidine

Colorless crystals; m.p.: 83-85 °C (cyclohexane); R_T [min]: 11.2; ^{1}H-NMR: 3.87 (s, 3H), 5.12 (d, 1H, J=8.4Hz), 5.63 (d, 1H, J=5.3Hz), 5.86 (dd, 1H, J=8.4Hz, J=5.3Hz), 7.04-7.08 (m, 3H), 7.22-7.25 (m, 2H), 7.36-7.37 (m, 3H), 7.44-7.46 (m, 2H); ^{13}C-NMR: 53.29, 71.95, 77.69, 93.13, 118.05, 124.49, 128.11, 128.83, 128.93, 129.52; IR ν [cm^{-1}]: 1551, 1368 (NO_2), 1184, 923 (isox. ring), 697, 757 (aryl); MS [m/e]: 328(M^+), 222, 197, 196, 194, 181, 180, 91; Brutto formula: $C_{17}H_{16}N_2O_5$; Elemental analysis: found 64.94%C, 8.53%H, 4.92%N, calculated 62.19%C, 8.53%H, 4.91%N.

3,4-cis-4,5-trans-2,3-diphenyl-4-carbomethoxy-5-nitro-isoxazolidine

Colorless crystals; m.p.: 129-131 °C (ethanol); R_T [min]: 15.4; ^{1}H-NMR: 3.40 (s, 3H), 4.61 (dd, 1H, J=8.0Hz, J=2.9Hz), 5.33 (d, 1H, J=8.0Hz), 6.32 (d, 1H, J=2,9Hz), 6.97-7.02 (m, 3H), 7.20-7.23 (m, 2H), 7.27-7.30 (m, 5H); ^{13}C-NMR: 52.69, 68.94, 77.17,104.36, 116.53, 123.28, 128.19, 128.61, 128.73, 128.79; IR ν [cm^{-1}]: 1575. 1360 (NO_2), 1182, 956, 917 (isox. ring), 692, 753 (aryl); MS [m/e]: 328(M^+), 282, 281, 254, 222, 181, 180; Brutto formula: $C_{17}H_{16}N_2O_5$; Elemental analysis: found: 62.34%C, 8.60%H. 4.89%N, calculated 62.19%C, 8.53%H, 4.91%N.

3,4-trans-4,5-trans-2,3-diphenyl-4-nitro-5-cyanoisoxazolidine

Colorless crystals; m.p.: 96-97 °C (ethanol); R_T [min]: 7.6; ^{1}H-NMR: 4.85 (d, 1H, J=5.1Hz), 5.47 (dd, 1H, J=5.1Hz, J=1.6Hz), 5.79 (d, 1H, J=1.6Hz), 7.04-7.06 (m, 2H), 7.26-7.29 (m, 3H), 7.45-7.50 (m, 3H), 7.61-7.63 (m, 2H); ^{13}C-NMR: 74.00, 119.36, 126.08, 127.73, 129.02, 129.76; IR ν [cm^{-1}]: 1563, 1366 (NO_2), 2257 (CN), 1218, 967, 923 (isox. ring), 697, 778 (aryl); MS [m/e]: 295(M^+), 249, 222, 181, 180, 142, 91; Brutto formula: $C_{16}H_{13}N_3O_3$; Elemental analysis: found: 64.91%C, 4.29%H, 14.31%N, calculated 65.06%C, 4.16%H, 14.23%N.

3,4-cis-4,5-trans-2,3-diphenyl-4-cyano-5-nitroisoxazolidine

Colorless crystals; m.p.: 90-92 °C (cyclohexane); R_T [min]: 9.4; ^{1}H-NMR: 4.42 (dd, 1H, J=2.8Hz, J=8.1Hz), 4.64 (d, 1H, J=8.1Hz), 5.27 (d, 1H, J=2.8Hz), 7.14-7.15 (m, 2H), 7.20-7.23 (m, 2H), 8.27-7.31 (m, 3H), 7.38-7.42 (m, 3H); ^{13}C-NMR: 74.16, 102.43, 117.37, 121.11, 125.96, 127.35, 129.03, 129.36, 129.75, 130.05; IR ν [cm^{-1}]: 1579, 1370 (NO_2), 1201, 917 (isox. ring), 694, 763; MS [m/e]: 295(M^+), 249, 222, 221, 181, 180, 91; Brutto

formula: $C_{16}H_{13}N_3O_3$; Elemental analysis: found: 64.09%C, 4.30%H, 14.48%N, calculated 65.06%C, 4.16%H, 14.23%N.

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