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SYNTHESIS AND PROPERTIES OF AZOLES AND THEIR DERIVATIVES. 45*. REGIO- AND STEREOSELECTIVITY OF THE [2+3]-CYCLOADDITION OF *E*-β-NITROSTYRENE TO *Z*-C-PHENYL-N-ARYLNITRONES

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It is shown using spectroscopic methods that the [2+3]-cycloaddition of Z-C-phenyl-N-arylnitrones to E-β-nitrostyrene is regiospecific and leads to a mixture of the corresponding (3SR,4SR,5SR)- and (3SR,4RS,5RS)-2-aryl-4-nitro-3,5-diphenylisoxazolidines. The regioselectivity of the reaction is explained in terms of hard and soft acid and base theory.

Keywords: [2+3]-cycloaddition, nitroalkenes, nitrones, nitroisoxazolidines, regioselectivity, stereoselectivity, reactivity indexes.

In the previous papers in this series [2,3] we have studied [2+3]-cycloaddition of *E*-β-nitrostyrene to *para*- and *meta*-substituted derivatives of benzonitrile N-oxide. It was established that the reactions were not regioselective and led to a mixture of the corresponding 3-aryl-4-nitro-5-phenyl- and 3-aryl-5-nitro-4-phenylisoxazolines.

The reactions of nitrones with unsaturated nitro compounds have not been thoroughly studied [4-9]. Data on relative influence of structural factors on the regio- and stereoselectivity of the process are practically non-existent in the literature. Considering this it seemed expedient to us to study the reaction of *E*-β-nitrostyrene (**1**) with a series of *Z*-C-phenyl-N-arylnitrones (**2a-f**) to elucidate how the regio- and stereochemistry of the end products depended on the nature of the substituents in the N-phenyl ring of the nitrone.

Assuming that the reaction occurred by the concerted mechanism, it might be expected that the products would be enantiomeric pairs of the regio- and stereoisomeric arylnitrodiphenylisoxazolidines **3-6**. These compounds may be of interest as promising intermediates for the synthesis of β-lactams [7, 10], Δ^4-isoxazolines [10, 11] and other compounds with practically valuable properties [12].

Cycloaddition was carried out in dry toluene at 75-80°C with a 1.5 to 2-fold molar excess of alkene. The reaction was monitored by HPLC. In these conditions conversion of nitrones reached 90-95% after heating for 20-24 h, and the resultant mass contained only two products with different retention times (R_t) apart from excess nitrostyrene and unreacted nitrone. These compounds were isolated in pure form by liquid chromatography using a semi-preparative column containing Lichrospher 100 RP-18 as sorbent, after which their structures were studied by standard physicochemical methods (Tables 1, 2).

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[*] For communication 44, see [1].

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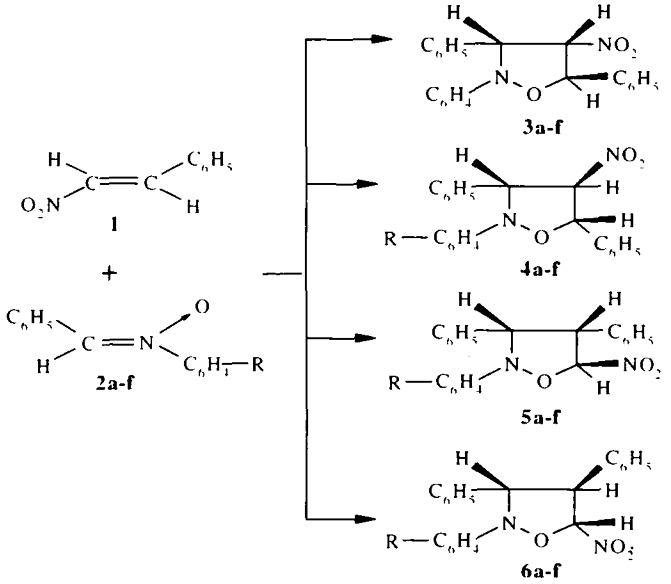

2-6 **a** R = *p*-NO_2; **b** R = *p*-$COOCH_3$; **c** R = *m*-Br; **d** R = *p*-Br; **e** R = *p*-Cl; **f** R = *p*-CH_3

According to the elemental analysis and mass spectra both isolated compounds in each case had the empirical formula corresponding to that of the expected nitroisoxazolidines **3-6**. Their IR spectra contained bands corresponding to the isoxazolidine ring [12], the nitro group, and mono- or disubstituted phenyl groups. However these bands did not differentiation of the regio- and stereoisomers. The UV spectra were also unsuitable for this purpose because they only contained intense bands characteristic of π→π* electron transitions in aromatic rings.

TABLE 1. Characteristics of the Synthesized 2-Aryl-4-nitro-3,5-diphenylisoxazolidinones **3a-f** and **4a-f**

Compound	R	Empirical formula	Found, % Calculated, % C	 H	 N	mp, °C	R_t, min	Yield, %
3a	*p*-NO_2	$C_{21}H_{17}N_3O_5$	64.19 64.45	4.08 4.35	11.03 10.74	132-134	5.66	22
3b	*p*-COOMe	$C_{23}H_{20}N_2O_5$	68.02 68.32	5.21 4.95	7.22 6.93	Liquid	6.39	18
3c	*m*-Br	$C_{21}H_{17}N_2O_3Br$	59.60 59.29	3.72 4.00	6.88 6.50	Liquid	10.48	12
3d	*p*-Br	$C_{21}H_{17}N_2O_3Br$	59.64 59.29	3.94 4.00	6.74 6.59	Liquid	10.90	15
3e	*p*-Cl	$C_{21}H_{17}N_2O_3Cl$	66.50 66.23	4.38 4.47	7.16 7.36	Liquid	9.73	16
3f	*p*-Me	$C_{22}H_{20}N_2O_3$	73.00 73.33	5.18 5.55	8.08 7.77	Liquid	7.61	15
4a	*p*-NO_2	$C_{21}H_{17}N_3O_5$	64.08 64.45	4.14 4.35	11.00 10.74	167-169	7.06	64
4b	*p*-COOMe	$C_{23}H_{20}N_2O_5$	68.30 68.32	4.82 4.95	6.93 7.20	134-136	8.26	68
4c	*m*-Br	$C_{21}H_{17}N_2O_3Br$	59.64 59.29	3.84 4.00	6.84 6.59	144-145	14.93	72
4d	*p*-Br	$C_{21}H_{17}N_2O_3Br$	59.51 59.29	3.82 4.00	6.74 6.59	132-133	14.59	68
4e	*p*-Cl	$C_{21}H_{17}N_2O_3Cl$	66.40 66.23	4.36 4.47	7.66 7.36	117-120	12.48	70
4f	*p*-Me	$C_{22}H_{20}N_2O_3$	73.01 73.33	5.80 5.55	8.12 7.77	106-108	14.93	68

TABLE 2. Spectroscopic Characteristics of the Compounds Synthesized

Compound	UV spectrum, λ, nm (log ε)	IR spectrum, cm^{-1}			^{1}H NMR spectrum					M$^+$, %
		ν_{NO_2}	ν_{isox}	ν_{arom}	δ_{H-3} (d)	δ_{H-4} (dd)	δ_{H-5} (d)	$J_{3,4}$	$J_{4,5}$	
3a		1335 1555	1265 1115	700 850	5.25	5.62	6.27	9.4	7.1	391 (100)
3b		1370 1555	1280 1110	700 850	5.12	5.51	6.07	9.5	7.4	404 (76)
3c	212 (4.55) 251 (4.04)	1375 1560	1280 1050	700 775	5.00	5.47	6.06	9.5	7.5	
3d	209 (4.51) 255 (4.19)	1370 1545	1260 1075	700 825	4.94	5.47	6.06	9.3	7.3	
3e	209 (4.39) 252 (4.03)	1370 1545	1265 1095	700 825	4.94	5.47	6.06	9.4	7.2	
3f	212 (4.44) 245 (4.09)	1370 1555	1260 1050	700 810	4.94	5.45	6.06	9.3	7.1	
4a	207 (4.39) 340 (4.10)	1335 1555	1275 1110	700 845	5.71	5.36	5.73	3.7	6.1	391 (100)
4b	208 (4.39) 270 (4.23)	1370 1555	1270 1105	700 850	5.73	5.33	5.74	3.8	6.2	404 (85)
4c	212 (4.60) 244 (4.08)	1360 1555	1285 1045	700 780	5.56	5.31	5.74	4.2	5.9	424 (95)
4d	208 (4.52) 248 (4.22)	1360 1555	1265 1055	700 830	5.52	5.31	5.72	4.2	5.9	424 (78)
4e	207 (4.46) 246 (4.19)	1360 1555	1265 1095	700 830	5.51	5.32	5.75	4.3	5.6	380 (57)
4f	207 (4.47) 241 (4.10)	1360 1555	1260 1055	700 810	5.53	5.30	5.78	4.3	5.5	360 (55)

The compounds obtained were successfully identified only *via* ^{1}H NMR spectroscopy. In particular, in the spectra of the substances with the smaller R_f values, there were three protons with an AMX spin system in addition to the benzene multiplets and the methyl singlets. Computer analysis of the spin-spin coupling constant using the PCMODEL-4 program indicated cycloadducts in which the nitro groups at C(4) and the phenyl group at C(3) were on the same side of the plane of the azolidine ring, which corresponds to the structures of the (3*SR*,4*SR*,5*SR*)-2-aryl-4-nitro-3,5-diphenylisoxazolidinones (**3a-f**). The protons of the isoxazolidine ring of the adducts with the greater R_f values form a similar spin system. However, analysis of the spin-spin coupling constant in this case indicates a structure in which the phenyl group at C(3) and the nitro group at C(4) are on opposite sides of the plane of the ring and this corresponds to the structures of the (3*SR*, 4*RS*, 5*RS*)-2-aryl-4-nitro-3,5-diphenylisoxazolidinones (**4a-f**).

Thus, in contrast to the reaction with substituted benzonitrile N-oxides, the reaction of *E*-β-nitrostyrene (**1**) with *Z*-C-phenyl-N-arylnitrones (**2a-f**) is completely regiospecific, but not stereospecific, no matter what the substituent in the N-phenyl ring. It should be noted that we obtained similar results for the reaction of *E*-β-nitrostyrene with *Z*-C-aryl-N-phenylnitrones containing various substituents in the C-phenyl ring [13].

Recently the hard and soft acid and base theory has been most commonly used [14] to explain regiochemical aspects of cycloaddition reactions and excellent agreement with experiment has been obtained [15- ;. We therefore used the same approach to explain the regioselectivity of the reactions we studied. In particular it became clear from analysis of the values of the ionization potentials (*IE*) and electron affinities (*EA*) calculated by the semiempirical AM1 method that the interaction of the HOMO of the 1,3-dipole with the LUMO of the dipolarophile was dominant since the energy gap between them was less than the energy gap between the HOMO of the dipolarophile and the LUMO of the 1,3-dipole (Table 3). The extent of these interactions may be estimated *via* the nucleophilic (s'_k) and electrophilic (s_k) local indexes of softness [14]:

$$s'_k = [q_k(N+1) - q_k(N)]/(IE - EA); \quad s_k = [q_k(N) - q_k(N-1)]/(IE - EA),$$

TABLE 3. Results of Quantum Chemical Calculations of the [2+3]-Cycloaddition Reaction of Nitrostyrene **1** to Nitrones **2a-f**

Compound	IE, eV	EA, eV	Atom k	$q_k[N-1]$, e	$q_k[N]$, e	$q_k[N+1]$, e	$10^3 \cdot s_k$	$10^3 \cdot s'_k$	$10^6 \cdot N^{(1)}_{\alpha\beta}$	$10^6 \cdot N^{(1)}_{\beta}$
1	9.56	1.65	C_α	-0.0753	-0.0106	-0.1424	-5.76	-11.73		
			C_β	-0.0144	-0.2184	-0.3201	-18.16	-9.05		
2a	8.36	2.15	C	-0.0833	-0.1834	-0.3132	-9.51	-12.99	134.9	76.2
			O	-0.2269	-0.4422	-0.4888	-20.45	-4.42		
2b	8.11	1.65	C	-0.0824	-0.1967	-0.3197	-11.66	-12.55	156.3	103.2
			O	-0.2317	-0.4427	-0.5000	21.55	-5.84		
2c	8.06	1.33	C	-0.0838	-0.2023	-0.3140	-12.56	-11.84	172.0	120.7
			O	-0.2333	-0.4422	-0.5200	-22.14	-8.25		
2d	8.08	1.43	C	-0.8140	-0.2006	-0.3184	-12.52	-12.37	150.4	103.4
			O	-0.2411	-0.4439	-0.5169	-21.29	-7.66		
2e	8.06	1.35	C	-0.0816	-0.2028	-0.3176	-12.85	-12.16	151.3	106.0
			O	-0.2434	-0.4443	-0.5200	-21.30	-8.02		
2f	7.92	1.10	C	-0.0813	-0.2106	-0.3144	-14.35	-11.52	173.8	132.9
			O	-0.2474	-0.4453	-0.5268	-21.97	-9.05		

where $q_k(N)$ denotes the charge on atom k of the molecule containing N electrons, while $q_k(N-1)$ and $q_k(N+1)$ are the charges on the same atom in the anion and the cation of the molecules. In the reactions studied nitrones **2a-f** have nucleophilic properties while nitrostyrene **1** has electrophilic properties. Hence the regioselectivity of the reaction should be determined by the indexes s'_k calculated for the α and β carbon atoms of the nitrovinyl residue of the alkene and the indexes s_k calculated for the carbon and oxygen atoms of the C=N→O fragment of the 1,3-dipole.

In the general case, if the atoms i and j of the nucleophilic reagent form σ bonds during the cycloaddition process with atoms k and l respectively of the electrophilic reagent then, according to Chandra's hypothesis [17], the measure of the regioselectivity of the process is the index in the form:

$$\Delta^{kl}_{ij} = (s_i - s'_k)^2 + (s_j - s'_l)^2$$

The reaction follows the path for which Δ is smaller. It is seen from Table 3 that $\Delta^{CO}_{\alpha\beta} > \Delta^{CO}_{\beta\alpha}$ for each pair of substrates. This means that the reaction should follow the path in which the β and α carbon atoms of the vinyl residue of styrene form σ bond with the C and O atoms respectively of the C=N→O unit of nitrones, i.e., to give isoxazolidines with the nitro groups at C(4) of the heterocycle. The same conclusion may be reached by examining the reaction in terms of frontier molecular orbital theory [18].

The fact that the reaction studied leads to a mixture of two stereoisomers may be explained by steric factors. It follows from the AM1 calculations of the transitions states for the reaction of *Z*-C,N-diphenylnitrone with *E*-β-nitrostyrene that the approach of the 1,3-dipole to the double bond of the dipolarophile in the case of formation of (3*SR*,4*SR*,5*SR*)-4-nitro-2,3,5-triphenylisoxazolidines is more sterically hindered than in the case of formation of the diastereomeric (3*SR*,4*RS*,5*RS*)-4-nitro-2,3,5-triphenylisoxazolidines [1]. It may be assumed that an analogous picture is observed in [2+3]-cycloadditions involving nitrones **2a-f**, so that the isomers **4** predominate in the reaction mixture.

EXPERIMENTAL

Melting points were determined on a Boetius heated stage. IR spectra of KBr disks or thin films were recorded with a Bio-Rad FTS 175C spectrometer. UV spectra of methanol solutions were recorded with a Specord spectrophotometer. ^{1}H NMR spectra of $CDCl_3$ solutions with TMS as internal standard were measured at room temperature with Tesla BS-487C (80 MHz) spectrometer. Elemental analyses for C, H, and N were carried out with a Perkin-Elmer instrument. HPLC analyses were carried with a Knauer apparatus using 4 × 240 mm steel column containing Lichrospher 100 RP-18 absorbent (10 μ) and an efficiency of not less than 11000 theoretical plates with respect to anthracene, with an ultraviolet detector set at 320 nm for the substrates and 254 nm for the products. The eluent was methanol–water (4:1 by volume) with a flow rate of 1 ml/min. Separation of the reaction mass was carried out on the same apparatus, but fitted with a semi-preparative steel column (250 × 16 mm) with Lichrospher 100 RP-18 (10 μ) absorbent. Rate of flow of the eluent (4:1 methanol–water) was 12.5 ml/min.

Calculations by the AM1 method from the MOPAC 93 suite of programs [19] were carried out on a CONVEX 3220 computer. Calculations using the PCMODEL-4 program were carried on a Pentium II computer (400 MHz). For calculations of the ionization potentials (*IE*) of the substrates calculated values of the heats of formation of the neutral molecules and their cations under standard conditions were used, and for calculations of the electron affinities (*EA*) the heats of formation of the neutral molecules and the corresponding anions under standard conditions were used. Charges on the reaction centers (q_k) were obtained by analysis of the electron density according to Mulliken [19].

Nitrostyrene **1** and nitrones **2a-f** were synthesized by literature methods [20, 21].

General Method for the [2+3]-Cycloaddition of *E*-β-Nitrostyrene (1) to *Z*-C-Phenyl-N-arylnitrones (2a-f). A solution of *E*-β-nitrostyrene (3.0 g, 0.02 mol) and the corresponding *Z*-C-phenyl-N-arylnitrone (0.01 mol) in dry toluene (25 ml) was heated at 75-80°C for 20-24 h. The solution was evaporated to dryness, the residue was analyzed by HPLC for its stereoisomer content, and the mixture then underwent separation by semi-preparative HPLC. The nitroisoxazolidines **3** and **4** were obtained after evaporation of the eluent in vacuum and were studied by spectroscopic methods. Their physicochemical constants are given in Table 2.

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REFERENCES

1. A. Baranski, M. Olszanska, and K. Baranska, *J. Phys. Org. Chem.*, (in press).
2. A. Baranski and E. Cholewka, *Polish J. Chem.*, **65**, 2061 (1991).
3. A. Baranski and E. Cholewka, *Polish J. Chem.*, **63**, 483 (1989).
4. A. Baranski and V. I. Kelarev, *Khim. Geterotsikl. Soedin.*, No. 4, 435 (1990).
5. A. Baranski, *Polish J. Chem.*, **73**, 1711 (1999).
6. P. Borrachero, F. Cabrera, M. J. Dianez, M. D. Estrada, M. G. Guillen, A. Castro, J. M. Moreno, J. L. Paz, and S. P. Garrida, *Tetrahedron: Asymmetry*, **10**, 77 (1999).
7. A. Ranaka, T. Mori, and K. Mitsuchashi, *Bull. Chem. Soc. Jpn.*, **66**, 263 (1993).
8. T. Yakura, T. Nakazawa, M. Takino, and M. Ikeda, *Chem. Pharm. Bull.*, **40**, 2014 (1992).
9. M. Burdisso, R. Gandolfi, and P. Grunanger, *Tetrahedron*, **45**, 5579 (1989).
10. A. Padwa, L. Fisera, K. F. Koehler, A. Rodriguez, and G. S. K. Wong, *J. Org. Chem.*, **49**, 276 (1984).
11. A. Padwa, K. F. Koehler, and A. Rodriguez, *J. Org. Chem.*, **49**, 282 (1984).
12. P. Grunanger and P. Vita-Finzi, *The Chemistry of Heterocyclic Compounds*, Ed. A. Padwa, Academic Press, New York (1992), Vol. **49**, part 1, p. 649.
13. A. Baranski, *Polish J. Chem.*, **74**, No. 6 (2000) (in press).
14. R. G. Pearson, *Chemical Hardness. Applications from Molecules to Solids*. Wiley-VCH, Weinheim etc. (1997).
15. D. Sengupta, A. K. Chandra, and M. T. Nguyen, *J.Org.Chem.*, **62**, 6004 (1997).
16. K. Chandra, T. Uchimaru, and M. T. Nguyen, *J. Chem. Soc., Perkin Trans. 2*, 2117 (1999).
17. A. K. Chandra and M. T. Nguyen, *J. Comput. Chem.*, **19**, 195 (1999).
18. I. Fleming, *Frontier Orbitals and Reactions in Organic Chemistry* [Czech translation], NTL, Praha (1983), p. 46.
19. J. J. P. Stewart, *MOPAC 93.00 Manual*. Fujitsu Ltd., Tokyo, 1993.
20. A. I. Vogel, *Preparative Organic Chemistry*. [Polish translation], PWN, Warsaw (1984), p. 680.
21. W. Rundel, *Houben-Weyl. Methoden der Organischen Chemie*. G. Thieme Verlag, Stuttgart (1968), **X**, Teil 4, p. 374.