Chemistry of Heterocyclic Compounds, Vol. 37, No. 12, 2001

SYNTHESIS AND PROPERTIES OF AZOLES AND THEIR DERIVATIVES.
47*. REGIOSELECTIVITY, STEREOSELECTIVITY AND KINETICS OF [2+3] CYCLOADDITION REACTION OF *Z*-C,N-DIPHENYLNITRONE WITH *E*-β-NITROSTYRENES*[2]

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The [2+3] cycloaddition of Z-C,N-diphenylnitrone with E-β-nitrostyrenes leads to (3SR, 4SR, 5SR)- and (3SR, 4RS, 5RS)-2,3-diphenyl-4-nitro-5-arylisoxazolidines as the only reaction products. The kinetics of the reaction was studied by using the HPLC method. It was found that total rate constants increase with increasing substituent Hammett σ-constants. The substituent effect is rationalized in terms of FMO theory.

Keywords: nitroalkenes, nitroisoxazolidines, nitrones, [2+3] cycloaddition, regioselectivity, stereoselectivity, substituent effect.

This contribution is intended as a continuation of our studies concerning the regio- and stereochemical aspects of the cycloadditions of nitroalkenes [2-8]. In previous papers of this series [6, 7] we stated that [2+3] cycloaddition of *E*-β-nitrostyrene to *Z*-C,N-diarylnitrones, independently on the substituent in the phenyl rings of the parent nitrone, show high regioselectivity leading to suitable 4-nitroisoxazolidines as the only reaction products. The results were successfully rationalized by application of FMO [9] and HSAB [10] theories. Extending the study, it was of interest to investigate the regio- and stereoselectivity of the [2+3] cycloaddition of *Z*-C,N-diphenylnitrone (**1**) to nitroalkenes with similar steric requirements but different electron distributions on the reaction sites. For this purpose *E*-β-nitrostyrenes **2a-g** were chosen as model dipolarophiles (Scheme, Table 1). Reaction of such reactants theoretically [11] should lead to mixtures of enantiomeric pairs of regio- and stereoisomeric nitroisoxazolidines **3a-g** – **6a-g**. The goal of the present study was: (i) to find out the true reaction regio- and stereoselectivity and (ii) to define the substituent effect on the reaction rates.

Similarly as was described for the [2+3] cycloadditions of a parent *E*-β-nitrostyrene with *Z*-C-phenyl-N-aryl- and *Z*-C-aryl-N-phenylnitrones [6, 7], the reaction of the studied compounds was carried out at 75-80°C, using a double stoichiometric quantity of alkene and toluene as a solvent. By means of independent experiments

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* Part 46 see [1].

*[2] This work we dedicate to Professor Edmunds Lukevics on the occasion of 65th birthday.

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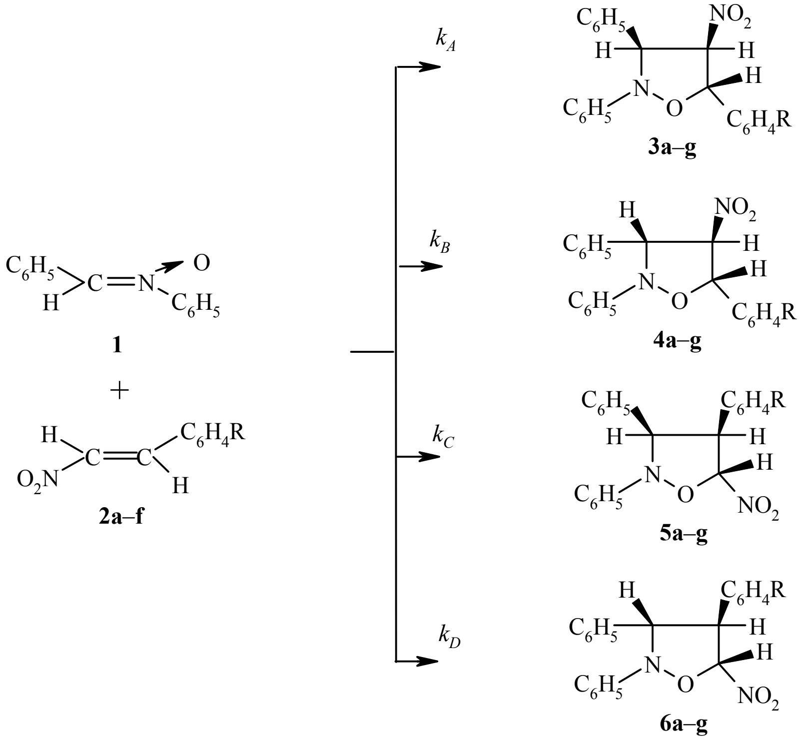
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1670-1677, December, 2001. Original article submitted July 30, 2001.



a R= *p*-Me$_2$N, **b** *p*-MeO, **c** *p*-Me, **d** *p*-Cl, **e** *p*-Br, **f** *m*-Cl, **g** *p*-COOMe

it was stated that reactants **1** and **2a-g** are stable compounds under the above-mentioned conditions. When the reaction was completed, the solvent was evaporated *in vacuo* and the crude post-reaction mass was tested by means of HPLC. It was found that in all cases the reaction leads to an oily substance, which always contained two new compounds in addition to some quantity of the corresponding substrates. Their retention times (R_T) differed among each other as well as from R_T of the substrates. Chromatography of this oily material by means of semipreparative HPLC furnished pure products, the spectral characteristics of which (Table 2) were very

TABLE 1. Selected Molecular Properties of *Z*-C,N-Diphenylnitrone **1** and *E*-β-Nitrostyrenes **2a-g** in the Gas Phase as Calculated by the AM1 Method, and the Overall Rate Constants for Their Cycloaddition in Toluene at 80°C*

Compound	σ(R)	μ, D	Charge [e] on the reaction sites:		*E*, eV		$k_{tot}\,10^4$	*r*	*n*	SD
			C/Cα	O/Cβ	HOMO	LUMO				
1	—	3.65	-0.200	-0.485	-8.39	-0.86	—	—	—	—
2a	-0.83	8.90	0.013	-0.245	-8.53	-1.02	0.63	0.999	9	0.01
2b	-0.27	6.96	0.001	-0.229	-9.37	-1.26	1.91	0.999	10	0.02
2c	-0.17	6.54	-0.006	-0.223	-9.64	-1.31	2.87	0.998	9	0.03
2d	0.23	4.81	-0.014	-0.214	-9.84	-1.53	6.64	0.999	10	0.02
2e	0.23	4.59	-0.017	-0.212	-9.89	-1.59	6.85	0.999	9	0.02
2f	0.37	5.48	-0.016	-0.211	-9.98	-1.50	8.75	0.998	9	0.03
2g	0.45	4.72	-0.024	-0.203	-10.22	-1.75	10.33	0.994	6	0.07

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* *r* – correlation coefficient, *n* – number of data in the set, SD – standard deviation.

close to those obtained recently for the cycloadducts prepared from *Z*-C,N-diarylnitrones and *E*-β-nitrostyrene [6, 7]. Thus, the IR spectra showed absorption bands attributable to an unconjugated nitro group, mono and disubstituted phenyl rings, as well as to an isoxazolidine ring. In the mass spectra each product displayed a parent peak having the expected formula and a characteristic C_6H_5NHO fragment [6, 12]. Furthermore, several fragments that could reasonably be assumed to result from simultaneous rupture of isoxazolidine ring bonds N–O and C(3)–C(4), O–C(5) and C(3)–C(4), and N–O and C(5)–C(4), as well as the exocyclic bond C–NO_2, were present. Especially helpful was the RC_6H_4CO fragment, which comes from the products **3** and **4** rather than their regioisomers **5** and **6**. Unfortunately, the obtained mass spectra did not allow us to differentiate stereoisomers **3** and **4**. (They will be the subject of a separate paper.) However, ^1H NMR spectral data and simulations of spin coupling constants with the PCMODEL-4 program allowed us to establish the precise structures. They unequivocally demonstrate that the cycloadducts with the shorter retention time should have the structures (3*SR*, 4*SR*, 5*SR*)-2,3-diphenyl-4-nitro-5-arylisoxazolidines **3a**-**g**, while the products with the longer retention time correspond to (3*SR*, 4*RS*, 5*RS*)-2,3-diphenyl-4-nitro-5-arylisoxazolidines **4a**-**g**.

Thus, [2+3] cycloaddition of **1** with *E*-β-nitrostyrenes **2a**-**g**, independently of the polarization of the latter, is regiospecific but not stereospecific. This conclusion is in good agreement with the results of our recent quantum-chemical calculations of the reaction by means of the AM1/COSMO method [8].

In order to gain a better insight into the mechanistic aspects of the reaction under study, kinetic investigations were undertaken. Their purpose was to determine the substituent effect on the reaction rate. The kinetic experiments were carried out at 80±0.2°C using 11.5-13.5 mole excess of alkene with respect to nitrone **1** and dry toluene as a solvent. They were followed by quantitative HPLC analysis of an area (*S*) of the peak at the R_T characteristic of nitrone **1**. The details of the kinetic procedure as well as the apparatus used are described in another publication [5]. The pseudo-first order rate constants, k^*, were calculated from a plot of ln*S* versus time *t* by a least squares method. The second-order rate constants, k_{tot}, which in fact are the sums of k_A and k_B (cf. Scheme), were calculated according to the standard method [13] from the quotient of k^* and the initial concentration of a suitable nitrostyrene. They are gathered in Table 1 along with the parameters of the regression analysis of the results from the experimental data. In the present investigation we used k_{tot} instead of k_A and k_B because the molar ratio [**3**]/[**4**] changes slightly with progress of the reaction, shifting to the value characteristic of thermodynamic equilibrium. Previously, a similar approach was successfully applied by us [1] in the kinetic study of [2+3] cycloaddition of C,N-diarylnitrones to the parent *E*-β-nitrostyrene.

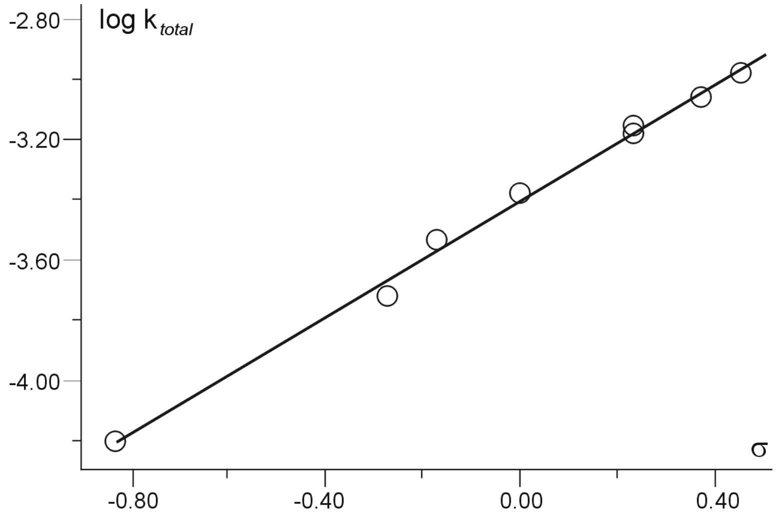


Fig. 1. Hammett plot for the [2+3] cycloaddition of diphenylnitrone **1** and nitrostyrenes **2a**-**g**. Data for *E*-β-nitrostyrene (σ = 0) are taken from ref. [5].

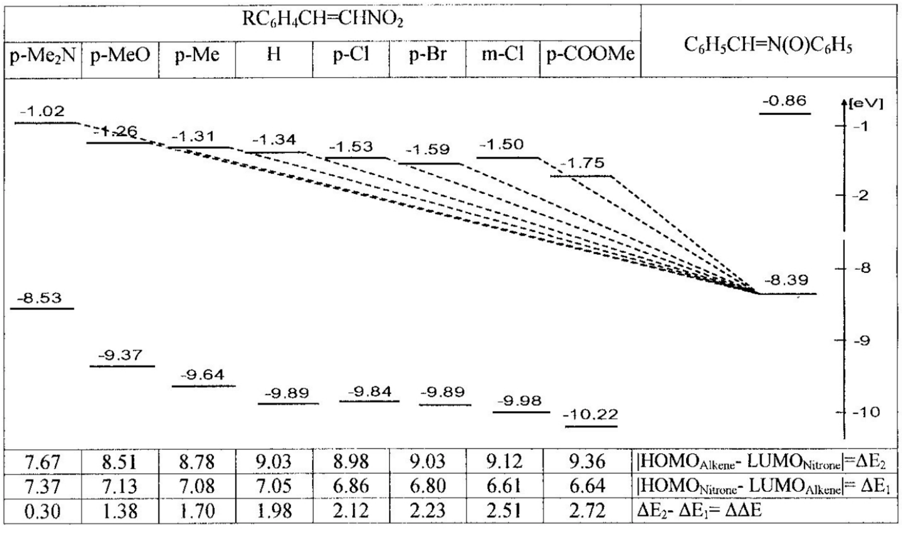
As can be seen from Table 1, the cycloaddition under study is influenced by the substituent in the phenyl ring of the parent *E*-β-nitrostyrene. In particular, on going from *p*-(N,N-dimethylamino)-*E*-β-nitrostyrene (**2a**) to *p*-methoxycarbonyl-*E*-β-nitrostyrene (**2g**), the rate constant k_{tot} increases by a factor of *ca.* 16. The substituent effect on the reaction rate was examined using σ, σ^+, σ^0, σ^-, σ^R and σ^I sets of Hammett constants [13, 14]. The best linear relationship was found when the values of log k_{tot} were plotted against the values of the σ constants (Fig. 1):

$$\log k_{tol} = 0.97\sigma - 3.40 \ (r = 0.99,\ s = 0.03)$$

The small value of the reaction constants (ρ = 0.97) precludes the possibility of a zwitterion intermediate and suggests at the same time a transition state of only small ionic character.

The substituent effect observed in this study is in good agreement with the perturbation interaction diagram (Fig. 2) elaborated by us on the basis of FMO energies for reactants **1** and **2a**-**g** (Table 1). From this diagram it is obvious that the energy gap between the LUMO of a dipolarophile and the HOMO of a 1,3-dipole (ΔE_1) is in all cases smaller than that (ΔE_2) between the HOMO of a dipolarophile and the LUMO of a 1,3-dipole. Moreover, ΔE_1 decreases with increase of the substituent σ-constants. Such an orbital arrangement is characteristic of a normal type reaction according to Sustmann's classification for cycloaddition [15]. Therefore, with regard to FMO theory [16, 17] a linear correlation between log k and $1/\Delta E_1$ should exist. Actually, by plotting the k_{tot} values on a log scale *versus* reciprocal ΔE_1 values, a straight line (Fig. 3) was obtained; however, the correlation parameters are rather poor (r = 0.95, s = 0.14).

At this point it is necessary to note that the cycloaddition of an extremely electron-deficient dipolarophile to an electron-rich 1,3-dipole may proceed *via* a zwitterionic intermediate [18, 19]. The results of the present study and our recent investigation [5] of Eyring parameters and the solvent effect suggest that, in spite of the highly polarized structures of nitrostyrenes **2a**-**g**, their reaction with nitrone **1** is a one-step concerted process. We hope that the results reported here would be helpful in evaluating the regioselectivity of [2+3] cycloaddition of nitrones with other conjugated nitroalkenes with the use of the PMO approach [20]. Work on this problem is in progress.



p-Me2N	p-MeO	p-Me	H	p-Cl	p-Br	m-Cl	p-COOMe	
7.67	8.51	8.78	9.03	8.98	9.03	9.12	9.36	$\lvert HOMO_{Alkene} - LUMO_{Nitrone}\rvert = \Delta E_2$
7.37	7.13	7.08	7.05	6.86	6.80	6.61	6.64	$\lvert HOMO_{Nitrone} - LUMO_{Alkene}\rvert = \Delta E_1$
0.30	1.38	1.70	1.98	2.12	2.23	2.51	2.72	$\Delta E_2 - \Delta E_1 = \Delta\Delta E$

Fig. 2. FMO interaction diagram for [2+3] cycloaddition of diphenylnitrone **1** with nitrostyrenes **2a**-**f**. Data for the diagram are taken from Table 1 and ref. [5].

TABLE 2. Yields and Physical Properties of 5-Aryl-4-nitro-2,3-diphenylisoxazolidines **3a-g** and **4a-g**

Com- pound	Yield, %	mp, °C	^{1}H NMR*					IR, ν, cm^{-1}			MS M$^{+?}$(%)	R$_T$, min	Found, % / Calculated, %		
			δ_{H-3}, d	δ_{H-4}, dd	δ_{H-5}, d	$J_{3,4}$	$J_{4,5}$	NO$_2$	isox	aryl			C	H	N
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
3a	15	148-151	4.95	5.41	6.10	9.2	7.3	1560 1370	1240 1040	700 820	389 (86)	8.9	$\frac{70.86}{70.95}$	$\frac{6.12}{5.91}$	$\frac{11.02}{10.80}$
3b	14	115-16	4.99	5.33	6.00	9.5	7.5	1560 1370	1250 1050	700 840	376 (89)	6.6	$\frac{70.06}{70.21}$	$\frac{5.46}{5.32}$	$\frac{7.68}{7.45}$
3c	16	117-19	4.95	5.30	6.00	9.5	7.3	1570 1370	1260 1040	690 810	360 (86)	8.7	$\frac{73.02}{73.33}$	$\frac{5.53}{5.55}$	$\frac{7.28}{7.78}$
3d	16	134-135	4.99	5.25	6.04	9.5	7.3	1570 1370	1270 1040	690 820	380 (72)	9.7	$\frac{66.02}{66.23}$	$\frac{4.44}{4.47}$	$\frac{7.28}{7.36}$
3e	17	139-140	4.99	5.28	6.03	9.5	7.1	1550 1370	1270 1070	700 820	424 (84)	11.0	$\frac{58.98}{59.29}$	$\frac{4.02}{4.00}$	$\frac{6.30}{6.59}$
3f	18	100-101	4.99	5.42	6.05	9.3	7.3	1550 1370	1260 1060	690 750	—	10.2	$\frac{66.52}{66.23}$	$\frac{4.32}{4.47}$	$\frac{7.16}{7.36}$

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
3g	17	131-133	5.01	5.44	6.14	9.5	7.3	1550 1370	1280 1080	700 830	—	7.0	$\frac{67.78}{68.32}$	$\frac{4.92}{4.95}$	$\frac{6.98}{6.93}$
4a	72	99-100	5.61	5.31	5.65	4.2	6.6	1550 1360	1190 1030	700 820	389 (75)	15.5	$\frac{80.00}{70.95}$	$\frac{5.86}{5.91}$	$\frac{10.82}{10.80}$
4b	70	92-93	5.63	5.25	5.70	4.4	6.4	1550 1350	1250 1030	700 830	—	9.9	$\frac{70.00}{70.21}$	$\frac{5.40}{5.32}$	$\frac{7.58}{7.45}$
4c	74	Liquid	5.58	5.27	5.70	4.2	6.1	1560 1370	1250 1030	700 820	360 (100)	14.8	$\frac{73.44}{73.33}$	$\frac{5.60}{5.55}$	$\frac{7.94}{7.78}$
4d	63	106-107	5.56	5.25	5.76	4.4	5.4	1550 1350	1250 1090	700 830	380 (96)	15.5	$\frac{66.09}{66.23}$	$\frac{4.50}{4.47}$	$\frac{7.23}{7.36}$
4e	66	103-105	5.56	5.25	5.75	4.2	5.4	1550 1350	1250 1070	690 820	—	17.7	$\frac{59.08}{59.29}$	$\frac{4.22}{4.00}$	$\frac{6.42}{6.59}$
4f	67	Liquid	5.54	5.28	5.77	4.4	5.4	1560 1370	1210 1080	700 760	—	15.0	$\frac{66.52}{66.23}$	$\frac{4.62}{4.47}$	$\frac{7.18}{7.36}$
4g	69	86-89	5.54	5.30	5.87	4.4	5.1	1560 1370	1280 1020	700 820	404 (80)	10.3	$\frac{68.09}{68.32}$	$\frac{5.01}{4.95}$	$\frac{7.07}{6.93}$

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* Only azolidine ring protons are included.

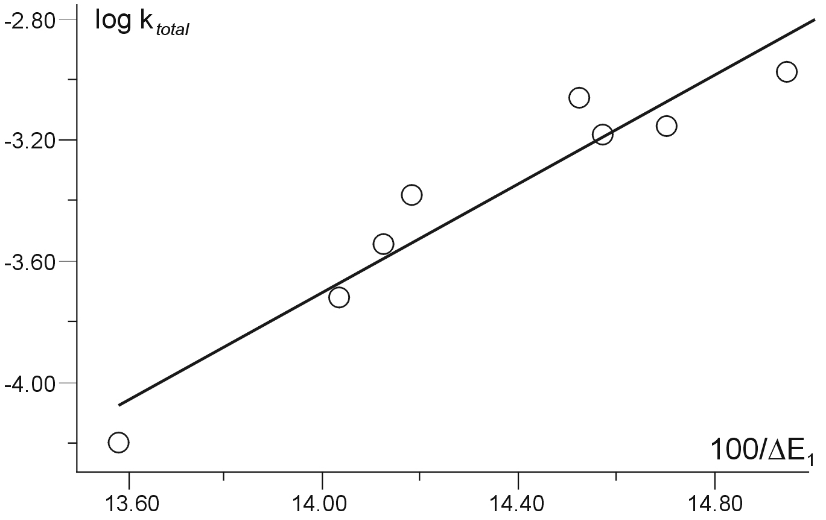

Fig. 3. Plot of log k_{tot} as a function of the reciprocal value of ΔE_1 gap.

EXPERIMENTAL

All melting points were determined on the Boethius apparatus and are not corrected. HPLC analyses and separation of the cycloadducts were carried out with the Knauer apparatus analogously as was recently reported [5, 6]. IR spectra were recorded on a Bio-Rad FTS 175C spectrometer in KBr discs. Mass spectra (70 eV) were measured with a MAT-311A spectrometer. ^{1}H NMR spectra were measured on a Tesla BS-567C (80 MHz) instrument in $CDCl_3$ with TMS as internal standard. Elemental analyses were determined on a Perkin-Elmer PE-2400 CHN apparatus.

Materials: *Z*-C,N-diphenylnitrone **1** and *E*-β-nitrostyrenes **2a-g** were prepared according to known procedures [21, 22].

General Procedure for the Cycloaddition of *Z*-C,N-Diphenylnitrone (1) with *E*-β-Nitrostyrenes 2a-g. Nitrone **1** (0.98 g, 5 mmol) was added to a solution of suitable *E*-β-nitro-styrene (10 mmol) in 20 ml of dry toluene and the mixture was heated at 75-80°C for 20-24 h in the dark and under an argon atmosphere. After cooling, the reaction mixture was concentrated under reduced pressure. The residue, after testing (HPLC), was separated by means of semipreparative HPLC using 70-80% methanol as an eluent. Evaporation of the eluent from the obtained fractions afforded suitable nitroisoxazolidines with purity adequate for CHN and spectral characterization (Table 2).

Acknowledgment

The authors are grateful to the Polish State Committee for Scientific Research for financial support of this work (Grants Nr C-2/324/DS/95 and C-2/332/BW/95). Thanks are also due to Mrs. Z. Schmidt for elemental analysis, to Mrs. E. Cholewka for measurement of IR and NMR spectra, and to Mr. M. Wisniowski for measurement of mass spectra.

REFERENCES

1. A. Baranski, *J. Phys. Org. Chem.*, in press.
2. A. Baranski, *Czasop. Technicze PK, Ser. chemia*, 13, and ref. therein (1992).
3. A. Baranski, *J. Mol. Struct.,* Theochem, **432**, 229 (1998).
4. A. Baranski, *J. Mol. Struct.*,Theochem, **499**, 185 (2000).
5. A. Baranski, *Polish J. Chem.*, **73**, 1711 (1999).
6. A. Baranski, *Polish J. Chem.*, **74**, 767 (2000).
7. A. Baranski, *Khim. Geterotsikl. Soedin.*, 840 (2000).
8. A. Baranski, M. Olszanska, and K. Baranska, *J. Phys. Org. Chem.*, **13**, 858 (2000).
9. I. Fleming, *Hranicni Orbitaly a Reakcie v Organickoi Chemii,* NTL, Praha, 1983.
10. R. G. Pearson, *Chemical Hardness. Application from Molecules to Solids*, Wiley-VCH, Weinheim, 1997.
11. M. Frederickson, *Tetrahedron*, **53**, 403 (1997).
12. Q. N. Porter, *Mass Spectrometry of Heterocyclic Compounds. 2. Ed.*, J. Wiley & Sons, New York, 1985.
13. K. Schwetlick, *Kinetische Methoden zur Untersuchung von Reactionsmechanismen*, VEB, Deutscher Verlag der Wissenschaften, Berlin, 1971.
14. J. Shorter, *Correlation Analysis in Organic Chemistry, An Introduction to Linear Free-energy Relationships*, Clarendon Press, Oxford, 1973.
15. R. Sustmann, *Pure Appl. Chem.*, **40**, 569 (1974).
16. R. Huisgen, in: A. Padwa (ed.), *1,3-Dipolar Cycloaddition Chemistry*, Vol. **1**, Wiley Interscience, New York (1984).
17. Ya. D. Samuilov and A. I. Konovalov, *Usp. Khim.*, **53**, 566 (1984).
18. K. Houk, *Acc. Chem. Res.*, **8**, 361 (1975).
19. R. Huisgen, G. Mloston, T. Oshima, and J. Rapp, *J. Heterocycl. Chem.*, *Suppl. Issue*, **24**, S-1 (1987).
20. G. Klopmann, in: G. Klopmann (ed.), *Chemical Reactivity and Reaction Paths*, New York (1974).
21. W. Rundel, in: *Houben-Weyl. Methoden der Organischen Chemie*, Vol. **10/4**, Thieme Verlag, Stuttgart (1968), 372.
22. J. Plenkiewicz, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.*, 627 (1961).