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1,3-DIPOLAR CYCLOADDITION OF DIAZOMETHANE TO β-ARYLACRYLYLOXIRANES

A. M. Zvonok, N. M. Kuz'menok, and L. S. Stanishevskii

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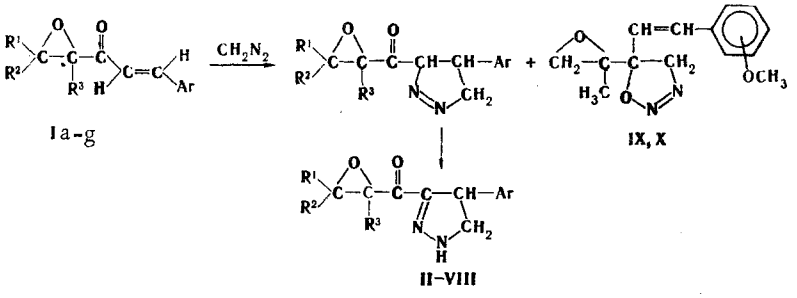
Diastereomeric 4-aryl-3-epoxypropionyl-2-pyrazolines were obtained by cycloaddition of diazomethane to β-arylacrylyloxiranes. It was established that, in addition to the formation of pyrazolines, competitive addition of diazomethane to the carbonyl group to give oxadiazolines occurs when electron-donor substituents are present in the aromatic ring in the 2 or 4 position. Some chemical properties of 4-aryl-3-epoxypropionyl-2-pyrazolines were studied.

In a continuation of our research on the reactivities of β-arylacrylyloxiranes in cycloaddition reactions [1] and in order to synthesize new α,β-epoxy ketones of the heterocyclic series, in the present research we studied the 1,3-dipolar cycloaddition of diazomethane to β-arylacrylyloxiranes.

We established that the reaction of β-arylacrylyloxiranes Ia-g with diazomethane leads to mixtures of two diastereomeric (A and B) 4-aryl-3-epoxypropionyl-2-pyrazolines II-VIII, which differ with respect to the configuration of the chiral center of the epoxy ring and are products of isomerization of the initially formed 1-pyrazolines. The indicated course of the reaction is confirmed by the isolation by chromatography on silica gel of the intermediate 4-phenyl-3-(2-methyl-2,3-epoxypropionyl)-1-pyrazoline when Ia is subjected to reaction with diazomethane at 0°C.



Ia-g IX, X II-VIII

Ia, II A, B $R^1=R^2=H$, $R^3=CH_3$, Ar=Ph; Ib, III A, B $R^1=R^3=CH_3$, $R^2=H$, Ar=Ph; Ic, IV A, B $R^1=R^2=CH_3$, $R^3=H$, Ar=Ph; Id, V A, B $R^1=R^2=H$, $R^3=CH_3$, Ar=4-BrC_6H_4; Ie, VII A, B $R^1=R^2=H$, $R^3=CH_3$, Ar=4-FC_6H_4; If VII A, B $R^1=R^2=H$, $R^3=CH_3$, Ar=4-$CH_3OC_6H_4$; Ig, VIII A, B $R^1=R^2=H$, $R^3=CH_3$, Ar=2-$CH_3OC_6H_4$

Bands of stretching vibrations of C=O and C=N bonds at 1660 and 1650 cm^{-1} and absorption of the NH group of a pyrazoline ring at 3420 cm^{-1}, which is characteristic for the investigated structures [2, 3], are present in the IR spectra of II-VIII. The IR spectrum of the intermediate 4-phenyl-3-(2-methyl-2,3-epoxypropionyl)-1-pyrazoline differs substantially from the IR spectrum of 2-pyrazoline II in that the characteristic absorption of the NH group of the pyrazoline ring is absent, while stretching vibrations of the C=O bond are ob-

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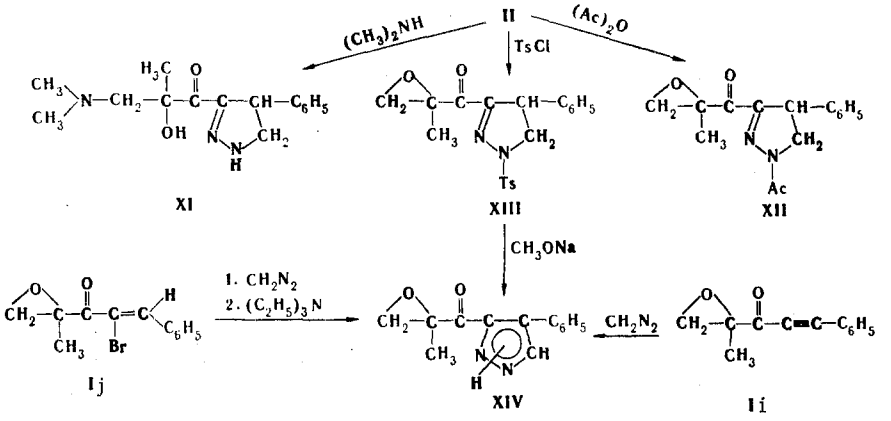
served at 1710 cm^{-1}. In the PMR spectra of II-VIII the protons of the pyrazoline ring form an ABCX spin system in which the AB part is made up of the protons of the methylene group, the C part is the hydrogen atom attached to the benzyl center, and X is the proton bonded to the nitrogen atom. The signals of the vicinal cisoid H_A and H_C protons are two quartets with J_{AC} = 5.0 Hz. The spin-spin coupling constant (SSCC) of the geminal H_A and H_B protons is 9.6 Hz. The absorption of the H_B nucleus appears in the form of a group of six lines in pairs and is the result of overlapping of two quartets, as can be judged from the distribution of the intensities of the signals and the SSCC, which are J_{BC} = 11.6 Hz and J_{BX} = 1.6 Hz.

A study of the dipolarophile activity of β-arylacrylyloxiranes Ia-g in the reaction with diazomethane showed that the yields and character of the reaction products depend on steric and electronic factors in the dipolarophile. The presence of electron-acceptor substituents in the benzene ring of β-arylacrylyloxiranes Id, e increases the dipolarophile activity of the indicated compounds, and this affects the yields of pyrazolines V and VI. Competitive addition of diazomethane to the carbonyl group to give 1,2,3-oxadiazolines IX and X occurs in addition to the formation of pyrazolines VII and VIII when there are electron-donor substituents in the aromatic ring of the dipolarophiles (If, g). In the case of unsaturated ketones we found only one instance of the formation of this sort of product in the reaction of diazomethane with 1,4-benzoquinone [4] in the literature.

The yield of oxadiazoline IX is low (3%) in the case of If; however, the yield of oxadiazoline X reaches 20% when there is a methoxy group in the ortho position, in which case, in addition to electronic factors, the substituent exerts appreciable steric hindrance leading to shielding of the double bond.

The IR spectra of oxadiazolines IX and X do not contain the characteristic absorption of a carbcnyl group and a pyrazoline ring NH bond, but stretching vibrations of the C=C bond are observed at 1605 cm^{-1}. In the PMR spectra of IX and X the geminal protons of the oxadiazoline and epoxide rings show up in the form of two AB systems with SSCC 5.0 Hz, and the signals of the protons attached to the double bond are observed in the form of multiplets at weak field.



The synthesized epoxyketopyrazolines II-VIII display the chemical properties that are characteristic for compounds that contain pyrazoline and epoxide rings. Thus the reaction of epoxyketopyrazoline II with dimethylamine in isopropyl alcohol leads to aminohydroxypyrazoline XI, which was obtained alternatively by cycloaddition of diazomethane to 1-dimethylamino-2-hydroxy-2-methyl-5-phenyl-4-penten-3-one (Ih) [5]. N-Acetyl- or N-tosylpyrazolines XII and XIII are formed in the reaction of pyrazoline II with acetic anhydride or p-toluenesulfonyl chloride in the presence of triethylamine. Treatment of N-tosylpyrazoline XIII with alkali leads to aromatization of the pyrazoline ring to give 4-phenyl-3(5)-(2-methyl-2,3-epoxypropionyl)pyrazole (XIV), which was obtained alternatively by cycloaddition of diazomethane to 2-methyl-5-phenyl-1,2-epoxy-4-pentyn-3-one (Ii) and the reaction of diazomethane with 4-bromo-2-methyl-5-phenyl-1,2-epoxy-4-penten-3-one (Ij) with subsequent dehydrobromination with triethylamine.

The application of known methods for the conversion of the pyrazoline ring to a pyrazole ring by means of $Pb(OAc)_4$, MnO_2, PbO_2, chloranil, and bromine was unsuitable for the oxidation of epoxyketopyrazoline II.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	R¹	R²	R³	Ar	mp, °C	R_f	Found, % C	Found, % H	Found, % N	Empricial formula	Calculated, % C	Calculated, % H	Calculated, % N	A/B	Yield, %
II^A_B	H	H	CH_3	C_6H_5	144—145 124—125	0,21 0,24	67,6 67,7	6,0 6,1	12,1 12,1	$C_{13}H_{14}N_2O_2$	67,8	6,1	12,2	2,3/1	75
III^A_B	CH_3	H	CH_3	C_6H_5	165—166 160—161	0,22 0,25	68,7 68,6	6,6 6,5	11,3 11,4	$C_{14}H_{16}N_2O_2$	68,8	6,6	11,4	2,5/1	72
IV^A_B	CH_3	CH_3	H	C_6H_5	181—182 163—164	0,24 0,24	68,5 68,7	6,4 6,6	11,3 11,2	$C_{14}H_{16}N_2O_2$	68,8	6,6	11,4	1/1	94
V^A_B	H	H	CH_3	4-BrC_6H_4	173—174 160—161	0,18 0,21	50,3 50,4	4,1 4,1	9,0 8,8	$C_{13}H_{13}BrN_2O_2$	50,5	4,2	9,0	3/1	99
VI^A_B	H	H	CH_3	4-FC_6H_4	154—155 142—143	0,19 0,21	62,8 62,9	5,0 5,1	11,0 11,1	$C_{13}H_{13}FN_2O_2$	62,9	5,3	11,2	2,5/1	79
VII^A_B	H	H	CH_3	4-$CH_3OC_6H_4$	Mixture, 145—148	0,16 0,22	64,4 64,6	6,0 6,1	10,7 10,5	$C_{14}H_{16}N_2O_3$	64,6	6,2	10,7	2,5/1	70
$VIII^A_B$	H	H	CH_3	2-$CH_3OC_6H_4$	160—162 144—145	0,18 0,24	64,6 64,5	6,0 6,0	10,7 10,6	$C_{14}H_{16}N_2O_3$	64,6	6,2	10,7	—	54
IX	H	H	CH_3	4-$CH_3OC_6H_4$	Oil	0,25	64,6	6,1	10,5	$C_{14}H_{16}N_2O_3$	64,6	6,2	10,7	—	3
X	H	H	CH_3	2-$CH_3OC_6H_4$	82—83	0,27	64,6	6,2	10,7	$C_{14}H_{16}N_2O_3$	64,6	6,2	10,7	—	20
XI	H	H	CH_3	C_6H_5	117—119	—	65,1	7,6	15,2	$C_{15}H_{21}N_3O_2$	65,4	7,7	15,2	—	72
XII	H	H	CH_3	C_6H_5	106—108	—	66,2	5,7	10,2	$C_{15}H_{16}N_2O_3$	66,2	5,9	10,2	—	76
XIII	H	H	CH_3	C_6H_5	189—190	—	62,1	5,1	7,1	$C_{20}H_{20}N_2O_4S$	62,5	5,3	7,3	—	92
XIV	H	H	CH_3	C_6H_5	176—179	—	68,1	5,0	12,1	$C_{13}H_{12}N_2O_2$	68,4	5,3	12,2	—	80

TABLE 2. Spectral Characteristics of the Compounds

Compound	Solvent	Chemical shift, δ, ppm: CH_3	pyrazole ring protons, ABCX system: 4-H—C	5-H—B	5-H—A	NH—X	epoxide ring protons, A′,B′ system: A′	B′	IR spectrum, cm^{-1}
II^A_B	d_6-Acetone	1,46	4,32	3,38	3,52	7,92	2,65 2,65	2,88 3,04	1660 (C=O); 1650 (C=N); 3420 (NH)
III^A_B	d_6-Acetone	1,18; 1,24; 1,40 1,23; 1,29; 1,44	4,30	3,96	3,50	7,85	—	—	1660 (C=O); 1650 (C=N); 3415 (NH)
IV^A_B	d_6-Acetone	1,33; 1,30 1,11; 1,08	4,35	4,00	3,58	7,93	—	—	1660 (C=O); 1650 (C=N); 3413 (NH)
XI^A_B	d_6-Acetone	1,30	4,32	3,96	3,50	7,90	2,28 2,28	3,15 3,33	1660 (C=O); 1650 (C=N); 3480 (OH)
XII^A_B	d_6-Acetone	1,48	4,56	4,20	3,72	—	2,64 2,64	2,90 3,24	1690 (C=O); 1660 (C=O); 1650 (C=C)
$XIII^A_B$	d_5-Pyridine	1,30	4,42	4,00	3,47	—	2,65 2,65	3,00 3,27	1695 (C=O); 1660 (C=O); 1650 (C=C)
XIV	d_5-Pyridine	1,53	—	—	—	7,83	2,80 2,80	3,10 3,30	1675 (C=O); 3400 (NH)
IX	CCl_4	1,22	2,45; 2,83	(CH_2 gem)	4,50; 5,00	(CH=CH)	2,26	2,60	1606 (C=C)
X	CCl_4	1,25	2,53; 2,96	(CH_2 gem)	4,40; 5,07	(CH=CH)	2,27	2,66	1605 (C=C)

EXPERIMENTAL

The IR spectra of 10^{-1} and 10^{-3} M solutions of the substances in chloroform and carbon tetrachloride were recorded with a Specord 75IR spectrometer. The PMR spectra of solutions of the compounds in d_6-acetone, d_5-pyridine, and CCl_4 were measured with Varian HA-100 D 15 and Varian XL-100 spectrometers with hexamethyldisiloxane as the internal standard. The characteristics of the synthesized compounds and their spectral data are presented in Tables 1 and 2.

4-Aryl-3-(1-R^1-2-R^2-3-R^3-2,3-epoxypropionyl)-2-pyrazolines (II-VIII) and 5-[2-(4(2)-Methoxyphenyl-vinyl]-5-(2-methyl-2,3-epoxypropionyl)-1,2,3-oxadiazolines (IX, X). A 100-ml sample of an ether solution of diazomethane obtained from 11 g of N-nitrosomethylurea was added at 15°C to a solution of 0.05 mole of Ia-g in 100 ml of ether, and the mixture was stirred for 2 h. 2-Pyrazolines II-VIII were removed by filtration, the ether was evaporated partially with a film evaporator, and the residual product was separated. Diastereomers A and B were separated by crystallization from methanol, ethanol, or isopropyl alcohol. Oxadiazoline IX was isolated by chromatography on silica gel [elution with petroleum ether–ether (1:1)]. Oxadiazoline X was separated by crystallization from isopropyl alcohol. Carrying out the reaction of Ia with diazomethane at 0°C made it possible to isolate 4-aryl-3-(2-methyl-2,3-epoxypropionyl)-1-pyrazoline by chromatography on silica gel [elution with hexane–ether (1:1)].

4-Phenyl-3-(3-dimethylamino-2-hydroxy-2-methylpropionyl)-2-pyrazoline (XI). A) A 0.15-mole sample of dimethylamine in isopropyl alcohol was added to 6.9 g (0.03 mole) of pyrazoline II in 20 ml of isopropyl alcohol. After 24 h, the solvent was removed with a film evaporator, and the residue was crystallized from ethanol–ether.

B) A 100-ml sample of an ether solution of diazomethane was added to 11.6 g (0.05 mole) of 1-dimethylamino-2-hydroxy-2-methyl-5-phenyl-4-penten-3-one (Ih) in 100 ml of ether. After 2 h, the ether was evaporated to give XI, which was identical to the product obtained by the method described above. The yield was 72%.

1-Acetyl-4-phenyl-3-(2-methyl-2,3-epoxypropionyl)-2-pyrazoline (XII). Acetic anhydride (10 ml) and 10 ml of triethylamine were added to 11.5 g (0.05 mole) of pyrazoline II in 50 ml of chloroform, and the reaction mixture was allowed to stand at 20°C for 12 h. The solvent was evaporated, and the residue was diluted with water. The aqueous mixture was extracted with ether, and the extract was dried with magnesium sulfate. The ether was evaporated, and the residue was crystallized from methanol–ether.

1-Tosyl-4-phenyl-3-(2-methyl-2,3-epoxypropionyl)-2-pyrazoline (XIII). A 7.6-g (0.04 mole) sample of freshly recrystallized p-toluenesulfonyl chloride and 5.5 ml of triethylamine were added to 4.6 g (0.02 mole) of pyrazoline II in dry tetrahydrofuran (THF), and the precipitate was removed by filtration, washed with water, dried, and recrystallized from THF–methanol.

4-Phenyl-3(5)-(2-methyl-2,3-epoxypropionyl)pyrazole (XIV). A) An equimolar amount of a methanol solution of sodium methoxide was added to 7.8 g (0.02 mole) of 1-tosylpyrazoline XIII in THF–methanol, and the reaction was carried out at 20°C for 12 h. The solvent was evaporated, and the residue was diluted with water. The aqueous mixture was neutralized with a dilute solution of hydrochloric acid, and the crystals were removed by filtration and crystallized from toluene.

B) A 20-ml sample of an ether solution of diazomethane was added to 1.9 g (0.01 mole) of 2-methyl-5-phenyl-1,2-epoxy-4-penten-3-one (Ii) in ether. After 10 min, 1.8 g of pyrazole XIV, which was identical to the compound obtained above, precipitated. The yield was 80%.

C) An excess amount of an ether solution of diazomethane was added to 5.3 g (0.02 mole) of 4-bromo-2-methyl-5-phenyl-1,2-epoxy-4-penten-3-one (Ij) in 150 ml of ether, and the mixture was allowed to stand at 20°C for 3 h. The ether was evaporated, and the oily product was dissolved in acetone and treated with 3 ml of triethylamine. The precipitated salt was removed by filtration, the acetone was evaporated, and 3.3 g of pyrazole XIV, which was identical to the product obtained above, was isolated. The yield was 72%.

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SYNTHESIS OF BENZIMIDAZOLE-2-CARBOXYLIC ACID AMIDES FROM o-PHENYLENEDIAMINE AND OXAMIC ACID ESTERS

P. A. Petyunin and Abdul Malek Choudry

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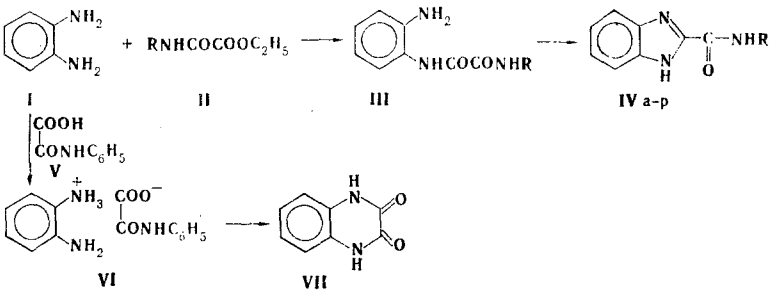
A method for the preparation of N–R amides of benzimidazole-2-carboxylic acid on the basis of the reaction between o-phenylenediamine and esters of N–R oxamic acids was developed.

Little study has been devoted to N-substituted amides of benzimidazole-2-carboxylic acid, and information regarding them is limited [1-3]. At the same time, they may be of interest as biologically active compounds.

We set out to develop a practicable method for the preparation of N–R amides (IV) of benzimidazole-2-carboxylic acid on the basis of the reaction between o-phenylenediamine I and oxamic acid esters II. This reaction is usually carried out in organic solvents [1] or in the fused state [4].

We found that amides IVa-p are formed in good (up to 90%) yields when the reaction is carried out in dimethylformamide (DMF) and that the stepwise mechanism of this transformation is described by the scheme



The possibility of the intermediate formation of amides III in the first step is in agreement with the data in [3].

Benzimidazoles IVa-p (Table 1) are crystalline substances that are soluble in aqueous alkalis; some of them are also soluble in mineral acids.

The structure of IV is confirmed by data from the IR spectra (Table 2), in which absorption bands at 1620-1650 cm^{-1} (amide C=O) and absorption at 3220-3280 cm^{-1}, which corresponds to the stretching vibrations of the NH groups, are present. In addition, the spectra contain absorption bands that are characteristic for the benzimidazole ring [5].

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