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ISOXAZOLIDINES WITH A CYCLOBUTANE LINK

N. A. Akmanova, Kh. F. Sagitdinova, A. I. Popenova, V. N. Domrachev, and E. S. Balenkova

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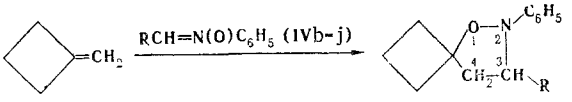
N-(Phenacylidene)- and N-(arylaminooxoethylidene)aniline N-oxides form 1:1 adducts with methylenecyclobutane. The addition of the nitrones proceeds specifically and leads to substituted isoxazolidines in high yields. In the case of N-(phenylaminooxoethylidene)aniline N-oxide it was shown that 1-methylcyclobutene and bicyclobutylidene also undergo cycloaddition to give isoxazolidines.

Unsaturated compounds of the cyclobutane series, inasmuch as they are strained systems, can serve as active dipolarophiles; however, not enough study has been devoted to their behavior in 1,3 cycloaddition [1, 2].

In the present research we studied the reaction of nitrones with methylenecyclobutane (I), 1-methylcyclobutene (II), and bicyclobutylidene (III). The N-oxides of N-(benzylidene)- (IVa), N-(phenacylidene)- (IVb), and N-(arylaminooxoethylidene)anilines (IVc-j) were used in the reaction with olefin I. The course of the reaction of the nitrones with the olefins was monitored by means of thin-layer chromatography (TLC) on aluminum oxide. It was established nitrone IVa does not undergo cycloaddition with olefin I at room temperature. The reaction of olefin I with nitrones IVb-j is complete after 2-3 days; according to the results of elementary analysis and the data from the PMR spectra, 1:1 adducts are formed with retention of the four-membered ring. The presence in the spectra of all adducts Vb-j of a quartet of a 3-H proton (1H) at 3.85-5.00 ppm constituted evidence for the direction of addition of nitrones IVb-j to olefin I. This signal is observed at weaker field (4.78-5.00 ppm) for Vb as compared with adducts Vc-j (3.78-4.25 ppm). The multiplicity of this signal is explained by the nonequivalence of the 4-H methylene protons of the heteroring. Thus an analysis of the PMR spectra makes it possible to conclude that the addition of nitrones Vb-j to olefin I leads to the formation of 3-substituted 2-phenyl-1-oxa-2-azaspiro[3,4]octanes and proceeds in such a way that the oxygen atom of the nitrone adds to the sterically more hindered atom of olefin I.



I Vb-j

IV, V b R=C_6H_5CO; c R=C_6H_5NHCO; d R=*o*-BrC_6H_4NHCO; e R=*m*-BrC_6H_4NHCO; f R=*m*-$CH_3C_6H_4NHCO$; g R=*p*-$CH_3C_6H_4NHCO$; h R=*p*-$CH_3OC_6H_4NHCO$; i R=*p*-$C_2H_5OC_6H_4NHCO$; j R=*p*-$CH_3COC_6H_4NHCO$

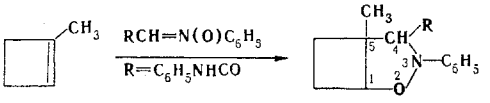
Bashkir State University, Ufa 450074. M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1316-1318, October, 1982. Original article submitted March 12, 1982.

TABLE 1. 2-Phenyl-3-R-1-oxa-2-azaspiro[3,4]octanes (Vb-j)

Compound	mp, °C (from ethanol)	R_f	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
Vb	97—99	0,75	77,5	6,2	4,4	$C_{19}H_{19}NO_2$	77,8	6,5	4,8
Vc	108—109	0,79	73,8	6,3	9,4	$C_{19}H_{20}N_2O_2$	74,0	6,5	9,1
Vd	83—84	0,78	59,2	4,7	7,5	$C_{19}H_{19}BrN_2O_2$	58,9	4,9	7,2
Ve	89—90	0,79	59,3	5,0	6,9	$C_{19}H_{19}BrN_2O_2$	58,9	4,9	7,2
Vf	62—64	0,84	74,3	6,7	8,4	$C_{20}H_{22}N_2O_2$	74,5	6,8	8,7
Vg	87—88	0,80	74,2	6,5	8,9	$C_{20}H_{22}N_2O_2$	74,5	6,8	8,7
Vh	123—124	0,84	70,8	6,3	8,0	$C_{20}H_{22}N_2O_3$	71,0	6,5	8,3
Vi	134—136	0,82	71,3	6,5	8,1	$C_{21}H_{24}N_2O_3$	71,6	6,8	8,0
Vj	144—145	0,81	72,2	6,1	7,8	$C_{21}H_{22}N_2O_3$	72,0	6,3	8,0

Additional information regarding the reaction of olefin I with nitrones IVb-j was obtained by monitoring its rate from the change in the relative intensity of the signals of the NH and CH protons in the PMR spectra in $CDCl_3$, respectively, for starting amido nitrones IVc-j and nitrone IVb and their reaction mixtures. In our case, just as previously noted in [3] nitrone IVb was found to be the most active compound, and 50% of it was converted after 40 min. Of the investigated amido nitrones, the most reactive are nitrones IVc, j, whereas o-substituted nitrone IVd has the lowest reactivity.

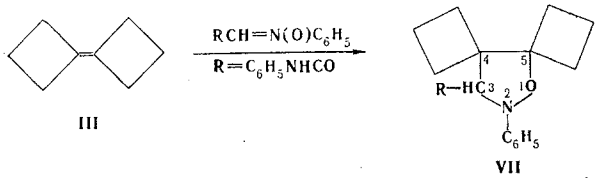
The cycloaddition of 1-methylcyclobutene (II) and bicyclobutylidene (III) was studied with the most active amido nitrone IVc. An unexpected result was obtained with olefin II. A multiplet of an isoxazolidine 1-H proton (1H) at 3.30-3.75 ppm and a singlet of a 4-H proton (1H) at 4.40 ppm were observed in the PMR spectrum of adduct VI. These data constitute evidence in favor of a 5-methyl-3-phenyl-4-phenylcarbamoyl-2-oxa-3-azabicyclo[3.2.0]heptane (VI) structure and excludes the alternative 1-methyl-3-phenyl-4-phenylcarbamoyl-2-oxa-3-azabicyclo[3.2.0]hepatane structure. The question as to whether adduct VI is produced in the form of two stereoisomeric forms with cis and trans orientations of the 4-H proton relative to the CH_3 group remains unanswered.



II VI

The addition of amido nitrone IVc to olefin II proceeds contrary to the rather widely accepted rule, according to which the oxygen atom of the nitrone adds to the most sterically hindered end of the olefin.

In bicyclobutylidene III the double bond is markedly shielded with respect to the approach of the nitrone, and adduct VII was therefore isolated only in the case of the prolonged action of nitrone IVc (43 days) on this olefin.



III VII

Thus unsaturated hydrocarbons of the cyclobutane series are quite active dipolarophiles in reactions with nitrones and form isoxazolidines.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded at 30°C with a Tesla spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard. Thin-layer chromatography (TLC) was carried out on Al_2O_3 (activity II) with benzene–ethanol (10:1) as the solvent. The starting methylenecyclobutane (I) had bp 42.0-43.3 C (755 mm) and n_D^{20} 1.4204 [bp 41.5-42.0°C (750 mm) and n_D^{20} 1.4206-1.4212 [4]]. 1-Methylcyclobutene (II) had bp 37.0-37.5°C (750 mm) and n_D^{20} 1.4086 [bp 37.3°C (760 mm) and n_D^{20} 1.4081 [5]]. Bicyclobutylidene (III) had bp 30°C (7 mm) and n_D^{19} 1.4845 (bp 144-145°C and n_D^{20} 1.4835 [6]).

Reaction of Olefins I-III with Nitrones Va-j. A solution of 2 mmole of the corresponding nitrone and 10 mmole ofolefin I-III in 2 ml of o-xylene was maintained at 20°C until the nitrone vanished completely (according to monitoring by TLC). The excess hydrocarbon and solvent were removed, ethanol was added to the residue, and the liberated crystals were removed by filtration and recrystallized from ethanol.

2-Phenyl-3-R-1-oxa-2-azaspiro[3,4]octanes (Vb-j) (Table 1). The yields were almost quantitative. The PMR signals of the cyclobutane link and the heteroring were observed at 1.38-2.63 (6H, m, cyclobutyl), 2.25-2.85 (2H, m, 4-H), and 3.85-5.0 ppm (1H, m, 3-H).

5-Methyl-3-phenyl-4-phenylcarbamoyl-2-oxa-3-aza[3.2.0]heptane (VI). This compound was obtained in 90% yield and had mp 75-78°C (from ethanol) and R_f 0.63 [benzene–ethanol (10:1)]. PMR spectrum: 1.38 (3H, s, 5-CH_3), 2.0 (4H, cyclobutyl), 3.30-3.75 (1H, m, 1-H), 4.40 (1H, s, 4-H), 6.50-8.00 (10H, m, 2C_6H_5), and 8.98 ppm (1H, s, NH). Found: C 73.8; H 6.6; N 8.7%. $C_{19}H_{20}N_2O_2$. Calculated: C 74.0; H 6.4; N 8.9%.

4,4,5,5-Di(trimethylene)-2-phenyl-3-phenylcarbamoylisoxazolidine (VII). This compound was obtained in 81% yield and had mp 150-152°C (from ethanol) and R_f 0.76 [benzene–ethanol (10:1)]. PMR spectrum: 1.08-3.00 (12H, m, cyclobutyl), 3.90 (1H, s, 3-H), 6.50-8.0 (10H, m, 2C_6H_5), and 8.98 ppm (1H, s, NH). Found: C 75.6; H 6.8; N 8.1%. $C_{22}H_{24}N_2O_2$. Calculated: C 75.8; H 6.8; N 8.0%.

The course of the reaction of nitrones IVb-j with olefin I was monitored from the change in the intensity of the signal of the NH group at 12.37 ppm for amido nitrones IVc-j and the change in the intensity of the signal of the proton of the CH group at 8.25 ppm for nitrone IVb and for the reaction mixtures. The initial concentrations of the nitrone and methylenecyclobutane in $CDCl_3$ were 0.5 mole/liter.

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