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SYNTHESIS OF HETEROCYCLES ON THE BASIS OF PRODUCTS OF ADDITION OF POLYHALOALKANES TO UNSATURATED SYSTEMS.

2.* OBTAINING ISOXAZOLE DERIVATIVES BY 1,3-DIPOLAR CYCLOADDITION WITH THE PARTICIPATION OF POLYHALO-SUBSTITUTED ALKENECARBONITRILE OXIDES

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Oximes of 3,3-dichloropropenal and 4,4,4-trifluoro-3-chloro-1-butenal were obtained on the basis of products of free-radical addition of CCl_4 and CF_3CCl_3 to vinyl butyl ether. Generation of the corresponding nitrile oxides from these oximes and reaction of the nitrile oxides in situ with vinyl butyl ether, phenylacetylene, and propargyl alcohol via the scheme of 1,3-dipolar cycloaddition are proposed as a method for the synthesis of isoxazoles containing β,β-dichlorovinyl and β-trifluoromethyl-β-chlorovinyl substituents in the 3 position.

The products of the addition of polyhaloalkanes to functionally substituted unsaturated systems are convenient starting compounds in the synthesis of various heterocycles. We have previously developed a new method for the synthesis of 1-aryl-5-chloropyrazoles by heterocyclization of arylhydrazones of 3,3-dichloro-2-propenal – an accessible unsaturated aldehyde obtained on the basis of products of addition of CCl_4 to vinyl ethers [1]. Later we subjected the production of addition of CCl_4 to methyl vinyl ketones – 3,5,5,5-tetrachloro-2-pentanone – to reactions that are characteristic for α-halo carbonyl compounds, which led to 2,2,2-trichloroethyl-substituted furans and thiazoles [2].

*See [1] for Communication 1.

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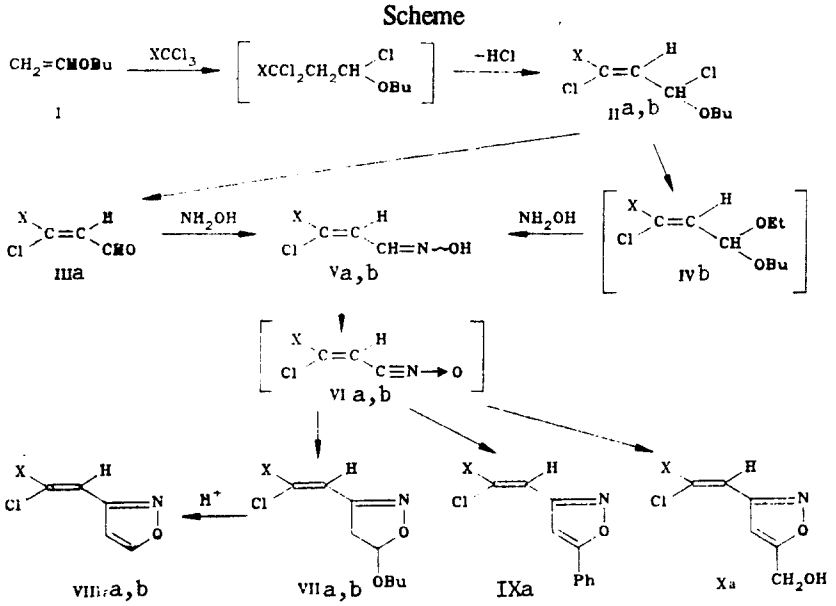
0009-3122/90/2609-1043$12.50

Scheme

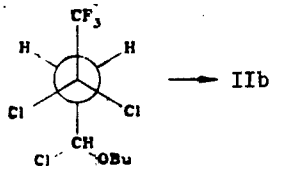


II, III, V—X a X=Cl; II, IV—VIII b X=CF_3

In the present paper we proposed a method for the synthesis of isoxazole derivatives on the basis of products of addition of CCl_4 and CF_3CCl_3 to vinyl butyl ether (I) using 1,3-dipolar cycloaddition. The method makes it possible to obtain isoxazoles that have ClXC=CH– substituents (X = Cl or CF_3) in the 3 position and free 4 and 5 positions, which is essential for the synthesis of physiologically active compounds of the series [3] and also expands the rather limited possibilities of the synthesis of fluorine-containing isoxazoles and simultaneously makes it possible to utilize unfavorable (in an ecological respect) freons. The synthesis of 3-(2,2-dichlorovinyl)-substituted and 3-(Z-3,3,3-trifluoro-2-chloro-2-propenyl)-substituted isoxazoles was carried out via the scheme presented above.

3,3-Dichloropropenal (IIIa) was obtained by a known method [4] from vinyl butyl ether and CCl_4 and was converted to oxime Va (a mixture of E and Z isomers in a ratio of ~60:40), from which nitrile oxide VIa was generated in the presence of dipolarophiles. The addition of nitrile oxide VIa to vinyl ether I gives isoxazoline VIIa which is converted in high yield to isoxazole VIIIa on treatment with concentrated sulfuric acid by a method similar to that in [5]. The use of phenylacetylene and propargyl alcohol as dipolarophiles leads to the formation of the corresponding isoxazoles IXa and Xa.

1,1,1-Trifluoro-2,2,2-trichloroethane was obtained by treatment of freon-113 (CF_2ClCCl_2F) with aluminum chloride [6]. The addition of CF_3CCl_3 to ether I was carried out in the presence of a mixture of benzoyl peroxide and azobisisobutyronitrile (the separate use of the indicated initiators decreases the yield of the addition product). The substance obtained was subjected, without prior purification, to heat treatment, as a result of which chloroacetal IIb was isolated. The Z configuration of IIb was confirmed by the ^{19}F NMR spectrum (singlet of a CF_3 group that is characteristic for Z isomers [7]). In addition, in this case any variant of splitting out of HCl that proceeds as trans elimination should lead to the formation of the Z isomer:



In contrast to chloroacetal IIa, its analog IIb does not split out BuCl on thermolysis, and it was therefore treated with alcohol, and the resulting acetal IVb was converted, without isolation, to oxime Vb, which is a mixture of E and Z isomers in a ratio of ~80:20. Oxime Vb was converted, without isolation, to nitrile oxide VIb in the presence of vinyl ether I, as a result of which isoxazoline VIIb was synthesized; as described above for isoxazoline VIIa, isoxazole VIIIb was then obtained from isoxazoline VIIb.

Attempts to obtain products of cycloaddition of nitrile oxides VIa, b to carboxylic acid nitriles were unsuccessful. Similar attempts to introduce a fluorine-containing nitrile oxide into 1,3-dipolar cycloaddition with nitriles were also unsuccessful [8].

We have already mentioned that oximes Va, b exist in solutions in the form of mixtures of E and Z isomers. For the quantitative evaluation of the isomer ratios we studied the ^1H, ^{15}N, and ^{13}C NMR spectra of the indicated compounds. It is apparent from the data presented in Tables 1 and 2 that, in all of the spectra, the signals related to the –CH=N– fragment are

TABLE 1. Spectral Characteristics of Oximes Va, b

Compound	PMR spectrum, δ, ppm (J, Hz)			^{15}N NMR spectrum, δ, ppm (J, Hz)	^{13}C NMR spectrum, δ, ppm (J, Hz)			
	CH=N	ClXC=CH	OH		CH=N d	ClXC=CH	=CXCl, q	CF_3, q
Z-Va	8,21 (d $^3J_{H,H}$=9,2)	8,00 (d $^3J_{H,H}$=9,2)	10,77	−29,6 (d ^2J_H=25,0)	142,22 ($^1J_{C,H}$=182)	116,94 (d $^1J_{C,H}$=171)	132,03	—
E-Va	8,81 (d $^3J_{H,H}$=9,6)	7,41 (d $^3J_{H,H}$=9,6)	10,77	−16,5 (d $^2J_{H,N}$=2,8; d $^3J_{H,N}$=2,1)*	146,88 ($^1J_{C,H}$=170)	122,57 (d $^1J_{C,H}$=166)	128,86	—
Z-Vb	7,60 (d $^3J_{H,H}$=9,0; q ^5J_H=0,7)	7,55 (d $^3J_{H,H}$=9,0; q $^4J_{H,F}$=0,7)	10,78	−11,5 (d $^2J_{H,N}$=16,0) [−15,4 (J=4,0)]**	141,48 ($^1J_{C,H}$=184)	117,67 q (d $^1J_{C,H}$=169; q $^3J_{C,F}$=4)	128,07 ($^2J_{C,F}$=39)	120,30 ($^1J_{C,F}$=272)
E-Vb	8,12 (d $^3J_{H,H}$=9,6; q $^5J_{H,F}$=0,9)	7,01 (d $^3J_{H,H}$=9,6; q $^4J_{H,F}$=0,9)	10,78	3,0 (d $^2J_{H,N}$=2,7; d $^3J_{H,N}$=1,9)* [−0,24 (J=1,8)]**	145,88 ($^1J_{C,H}$=172)	125,42 (d $^1J_{C,H}$=163; q $^3J_{C,F}$=5)	126,00 ($^2J_{C,F}$=39)	120,35 ($^1J_{C,F}$=272)

*Found in the region of selective decoupling (SPTCW).

**Measured at −20°C.

TABLE 2. PMR Spectra of Isoxazoline Derivatives VII and Isoxazole Derivatives VIII-X

Compound	Chemical shifts of the protons, δ, ppm (J, Hz)			
	heteroring protons		ClXC=CH, s	protons of the substituent in the 5 position
	4-H	5-H		
VIIa	3,18 ... 3,38 m (2H)	5,60 dd (J_{AX}=5,75; J_{BX}=3,00)	6,83	0,90 t (Me); 1,23 ... 1,44 m (CH_2); 1,46 ... 1,63 m (CH_2); 3,50 dt (1H, OCH_2, $^2J_{H,H}$=9,5; $^3J_{H,H}$=6,2); 3,81 dt (1H, OCH_2, $^2J_{H,H}$=9,5; $^3J_{H,H}$=6,2)
VIIb*	3,30 ... 3,45 m (2H)	5,70 dd (J_{AX}=5,50; J_{BX}=3,75)	7,29	0,93 t (Me); 1,20 ... 1,45 m (CH_2); 1,50 ... 1,65 m (CH_2); 3,55 dt (1H, OCH_2, $^2J_{H,H}$=10; $^3J_{H,H}$=6,5); 3,85 dt (1H, OCH_2, $^2J_{H,H}$=10; $^3J_{H,H}$=6,5)
VIIIa	6,86 d	8,43 d (J_{45}=2,0	7,02	—
VIIIb**	7,06 d	8,54 d (J_{45}=2,2	7,51	—
IXa	7,03 s	—	7,04	7,48 m (3H, m-and p-H 7,80 m (2H, s o-H)
Xb	6,75 s	—	6,89	4,32 m (OH); 4,73 s (CH_2)

*δ_{19_F} −8.40 ppm.

**δ_{19_F} −8.8 ppm.

represented "in a double set." The isomer ratios were evaluated from the integral curves in the PMR spectra. The mutual assignment of the ^1H, ^{13}C, and ^{15}N signals to one or the other isomer was determined from the results of $^{13}C-\{^1H\}$ and $^{15}N-\{^1H\}$ selective double heteronuclear resonance, while the configurations of the oximes were established from the $^2J_{15_{N,}1_H}$ and $^1J_{13_{N,}1_H}$ spin-spin coupling constants (SSCC).

According to the data in [9-12] for oximes, imines, and hydrazones, $^2J_{15_{N,}1_H} = -10$ to -20 Hz in the –CH=N– fragment if the H atom is cis-oriented relative to the unshared pair of electrons of the nitrogen atom (the Z isomer); however, in the case of the E isomers the absolute value of the constant is substantially lower, J = ±2-5 Hz. In this fragment the $^1J_{13_{C,}1_H}$ constant also depends on the stereochemistry: For the Z isomers its value is 12-19 Hz greater than for the E isomers [12, 13].

The $^2J_{15_{N,}1_H}$ constants of the isomers (the signs were not determined) differ substantially and correspond to the data in [9-12] for Z and E isomers (see Tables 1 and 2), which also makes it possible to make the assignments, while the $^1J_{13_{C,}1_H}$ values for the Z isomers are 12 Hz greater than for the E isomers (cf. [12, 13]). Let us note that the signals of the ^1H, ^{13}C, and ^{15}N nuclei for the –CH=N– fragment of the E isomer lie in the weaker-field region than in the case of the Z isomer.

The structures of the compounds synthesized for the first time (isoxazolines VIIa, b and isoxazoles VIIIa, b, IXa, and Xa) were confirmed by PMR and mass-spectral data (Table 2). The signals of the protons of the rings of isoxazolines, which form an ABX system, are represented by characteristic doublets of doublets of 5-H (H_X) protons and multiplets of protons in the 4 position (the H_A and H_B signals are superimposed). The butoxy groups of the isoxazolines show up in the spectra as triplets of CH_3 groups (~1 ppm), two multiplets of CH_2 groups (1.4-1.6 ppm), and two doublets of triplets of an OCH_2 group (3.5 and 3.8 ppm). No difficulty is encountered in interpreting the spectra of the isoxazoles.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a Bruker WM-250 radiospectrometer. The ^{19}F NMR spectra were obtained with a Perkin–Elmer R-32 spectrometer (86.4 MHz) with CF_3COOH as the external standard. The ^{15}N, ^{13}C, and ^1H NMR spectra of oximes Va, b were obtained with a Bruker AM-300 spectrometer for the protons; the ^{15}N chemical shifts (CS) were measured relative to CH_3NO_2 as the external standard, while the ^{13}C and ^1H CS were measured relative to the solvent (chloroform), the concentration of oxime Va was 3.1 g/3.5 ml, the concentration of oxime Vb was 3.4 g/2 ml, and the temperature was 25°C.

The mass spectra were obtained with a Varian MAT-CH-6 spectrometer at an ionization energy of 70 eV with direct introduction of the samples into the ion source. The melting (decomposition) points were determined with a Boetius microscope stage. Monitoring of the course of the reactions and the purity of the compounds was carried out by means of TLC on Silufol UV-254 plates in a hexane–ethyl acetate system (1:1).

The results of elementary analysis for all of the compounds described below were in agreement with the calculated values.

3,3-Dichloropropenal Oxime (Va, $C_3H_3Cl_2NO$). Alcohol (30 ml) was added to a solution of 7.50 g (108 mmoles) of $NH_2OH\cdot HCl$ and 8.66 g (131 mmoles) of AcONa in 35 ml of water, the mixture was cooled to 10°C, and a solution of 13.2 g (107 mmoles) of 3,3-dichloropropenal [4] in 35 ml of alcohol was added dropwise at this temperature. The resulting solution was refluxed for 4 h, after which it was cooled and poured into 250 ml of water. The aqueous mixture was extracted with ether (three 100-ml portions), and the combined extracts were washed successively with water, a saturated solution of $NaHCO_3$, and water and then dried with $MgSO_4$. The ether was removed in vacuo at room temperature to give 13.11 g (89%) of oxime Va with mp 39-42°C. A sample for analysis was additionally purified by chromatography with a column packed with silica gel by elution with hexane–ethyl acetate (2:1). Oxime Va should be stored at temperatures below 0°C, since instances of its spontaneous decomposition, which is possibly accelerated in the presence of traces of acid, were observed at room temperature.

3-(2,2-Dichlorovinyl)-5-phenylisoxazole (IXa, $C_{11}H_7Cl_2NO$). A solution of 10 g (56 mmoles) of N-bromosuccinimide in 60 ml of DMF was added at 0-5°C to a solution of 6.55 g (47 mmoles) of oxime Va in 75 ml of DMF, after which a solution of 8 ml (57 mmoles) of triethylamine and 9.57 g (93.8 mmoles) of phenylacetylene in 20 ml of DMF was added dropwise at 0-7°C in the course of 30 min. The mass was maintained at room temperature for 12 h, after which it was poured into 350 ml of cold water, and the aqueous mixture was extracted with ether (four 75-ml portions). The ether extract was washed thoroughly with water and dried with $MgSO_4$, and the ether was removed in vacuo. Crystallization of the residue from aqueous alcohol gave 9.24 g (82%) of isoxazole IXa with mp 63.0-63.5°C and M^+ 239 (for ^{35}Cl).

3-(2,2-Dichlorovinyl)-5-hydroxymethylisoxazole (Xa, $C_6H_5Cl_2NO_2$). This compound was obtained as in the case of isoxazole IXa, but 5.3 g (94 mmoles) of propargyl alcohol was used as the dipolarophile. Workup gave 4.31 g (48%) of isoxazole Xa with bp 153-157°C (0.6-1.0 mm), mp 56-59.5°C (crystallized on standing after distillation), and M^+ 193 (for ^{35}Cl).

5-Butoxy-3-(2,2-dichlorovinyl)-2-isoxazoline (VIIa, $C_9H_{13}Cl_2NO_2$). This compound was obtained from 4.6 g (33 mmoles) of oxime Va, 7.02 g (39 mmoles) of N-bromosuccinimide, 5.5 g (39 mmoles) of Et_3N, and 6.58 g (65.7 mmoles) of vinyl ether I under the conditions used for the synthesis of IXa. Workup gave 5.28 g (68%) of isoxazoline VIIa with bp 99-102.5°C (0.05 mm), n_D^{20} 1.5100, and M^+ 237.

3-(2,2-Dichlorovinyl)isoxazole (VIIIa, $C_5H_3Cl_2NO$). A solution of 3.57 g (15 mmoles) of isoxazoline VIIa in 5 ml of concentrated H_2SO_4 was stirred for 8 h at room temperature, after which it was poured into water, and the aqueous mixture was extracted with ether. The ether extract was washed successively with water, $NaHCO_3$ solution, and water and dried with $MgSO_4$. The ether was then removed by distillation, and the residue was fractionated to give 1.71 g (70%) of isoxazole VIIIa with bp 106-108°C (32-33 mm), n_D^{20} 1.5357, and M^+ 163.

Z-1-Butoxy-4-trifluoro-1,3-dichloro-2-butene (IIb, $C_8H_{11}Cl_2F_3O$). A mixture of 180 g [114 ml (0.96 mole)] of CF_3CCl_3 [6], 31.7 g [41 ml (316 mmoles)] of vinyl ether I, 1.31 g of benzoyl peroxide, and 0.25 g of azobisisobutyronitrile was stirred and refluxed for 12 h, after which the excess CF_3CCl_3 was removed by distillation at atmospheric pressure, and the residue was heated (at a bath temperature of 160-190°C) until hydrogen chloride evolution ceased. The residue was fractionated to give 67.9 g (86%) of IIb with bp 52-54.5°C (2-3 mm) and n_D^{20} 1.4122. PMR spectrum: 0.95 (t, CH_3), 1.33-1.50 (m, CH_2), 1.53-1.72 (m, CH_2), 3.58 (1H, d.t, OCH_2), 3.98 (1H, d.t, OCH_2), 6.32 (d, H_{vinyl}), 6.76 ppm (d, CHCl), J = 8 Hz. ^{19}F NMR spectrum: –8.03 ppm (s).

5-Butoxy-3-(3,3,3-trifluoro-2-chloro-2-propenyl)isoxazoline (VIIb, $C_{10}H_{14}ClF_3NO_2$). A solution of 20.22 g (80 mmoles) of chloroacetal IIb in 8 ml of CCl_4 and 10 ml (171 mmoles) of anhydrous ethanol was refluxed until HCl evolution ceased, after which the excess alcohol and CCl_4 were removed in vacuo, and the residue was dissolved in 50 ml of alcohol. A solution of 5.3 g (76 mmoles) of $NH_2OH \cdot HCl$ in 15 ml of water was added to this solution, and the mixture was refluxed for 4 h. The solvent was removed by distillation in vacuo, and 70 ml of DMF was added to the residue, which contained oxime Vb and a small amount of butanol. The resulting solution was cooled to 0-5°C and was then treated under the conditions described above for the synthesis of isoxazoline VIIa [16.8 g (93 mmoles) of N-bromosuccinimide, 14.86 g (148 mmoles) of vinyl ether I, and 12.7 ml (90 mmoles) of Et_3N]. Fractionation yielded 11.35 g (52% based on IIb) of isoxazoline VIIb with bp 84-88°C (0.05-0.06 mm), n_D^{20} 1.4493, and M^+ 271.

3-(3,3,3-Trifluoro-2-chloro-2-propenyl)isoxazole (VIIIb, $C_6H_3ClF_3NO$). The reaction of 4.78 g (17.6 mmoles) of isoxazoline VIIb under the conditions used for the synthesis of isoxazole VIIIa gave 2.48 g (71%) of isoxazole VIIIb with bp 82°C (35 mm), n_D^{20} 1.4432, and M^+ 197.

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