NUCLEOPHILIC SUBSTITUTION IN β-CHLOROACRYLIC ACIDS BY CYCLIC THIOAMIDES

L. V. Zav'yalova, N. K. Rozhkova,
and K. L. Seitanidi

UDC 547.78.6:547.634

The nucleophilic substitution of halogen in β-chloroacrylic acids by benzoxazoline-2-thione and benzimidazoline-2-thione was studied by PMR spectroscopy. It is shown that the reaction with benzimidazoline-2-thione proceeds with 100% retention of configuration, whereas only the trans isomer is isolated with benzoxazoline-2-thione because of prior isomerizaton of the starting acid.

The reaction of benzothiazoline-2-thione (I) with cis- and trans-β-chloroacrylic acids (II, III) proceeds basically stereospecifically as direct nucleophilic substitution through the sulfur atom [1]. Continuing our research we studied the behavior of benzoxazoline-2-thione (IV) and benzimidazoline-2-thione (V) in this reaction.

Under conditions identical to those previously described (refluxing in acetone), IV did not react, whereas V gave low yields of products (Table 1). An increase in the reaction temperature to 80-110°C makes it possible to raise the yields to 47-54%. Products of substitution at the sulfur atom – trans-β-(2-benzoxazolylthio)- and trans-β-(2-benzimidazolylthio)acrylic acids (VI, VII) – were isolated.

In the reaction of V with II, in addition to substitution one also observes intramolecular acylation to give benzimidazo[1,2-b]-1,3-thiazin-4-one (VIII).

In order to make a more thorough investigation of the stereospecificity of the reaction, we used PMR spectroscopy to study the isomeric composition of the crude reaction mixtures obtained in the reactions of I, IV, and V (Table 2).

trans-Acid III reacts with thioamides I, IV, and V, and cis-acid II reacts with benzimidazoline-2-thione to give products of unchanged configuration.

The product of the reaction of cis-acid II with benzoxazoline-2-thione is the trans isomer, whereas in the reaction with benzothioazoline-2-thione the isomeric composition depends on the reaction temperature: As the temperature is raised, the amount of trans isomer increases. However, the latter results cannot be considered to be a consequence of inversion of configuration at the instant the reaction occurs. We have observed the isomerization of cis-acid III to trans-acid III at 110°; this isomerization practically does not occur at lower temperatures but is accelerated in the presence of thioamides I and IV. This sort of cis–trans isomerization in the presence of thioamides has been previously noted [2]. At 56-80° thioamide V does not catalyze this process, and isomerization of the acids formed in the reaction to the corresponding trans acids does not occur.

The reaction of IV and V with propiolic acid IX gives only cis-β-(2-benzoxazolylthio)acrylic acid (X) and benzimidazo[1,2-b]-1,3-thiazin-4-one VIII, respectively; this makes it possible to exclude a mechanism for the reaction with β-chloroacrylic acids II and III through cleavage–addition. The previously proposed mechanism of synchronous addition–cleavage [1] is a general one for similar reactions of heterocyclic

---

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 47-49, January, 1975. Original article submitted October 24, 1973.

TABLE 1. Conditions and Products of the Reaction of Benzimidazoline-2-thione and Benzoxazoline-2-thione with cis- and trans-β-Chloroacrylic and Propiolic Acids

Thioamide	Acids	Reaction temp., °C	Reaction product	Yield, %
IV	II	110	VI	45,4
IV	III	110	VI	54,3
IV	II	80	VI	18,8
IV	III	80	VI	15,6
IV	IX	80	X	63,6
V	II	56	VIII	14,2
V	IX	76	VIII	80,9
V	II	80	VIII	47,6
V	III	56	VII	28,5
V	III	80	VII	57,0

TABLE 2. Isomeric Compositions of the Crude Products

Thioamide	Configuration of the starting acids	Reaction temp., °C	Isomeric composition, %	
			cis	trans
I	cis	56	70	30
	trans		0	100
I	cis	80	32	68
	trans		0	100
I	cis	110	10	90
	trans		0	100
IV	cis	110	0	100
	trans		0	100
V	cis	56	100	0
	trans		0	100
V	cis	80	100	0
	trans		0	100

thioamides and is explained by their ambifunctionality, owing to which a transition state with retention of the double bond is formed. The question of the one-step direct substitution of an activated double bond is discussed in the literature [3].

The structures of the isolated compounds were proved by data obtained from their IR, UV, and PMR spectra. On the basis of a comparison of the spin–spin coupling constants of X ($J = 7.1$ Hz), a cis configuration was assigned to it, whereas trans configurations were assigned to VI and VII ($J = 15$ Hz) [5]. The UV spectral data (λ_{max} 290 nm, log ε 4.39 and 4.41 for X and VI, and λ_{max} 295-297 nm, log ε 4.1 and 4.3 for VIII and VII) make it possible to assert that substitution in the IV and V molecules occurs at the sulfur atom [6].

The carboxyl group of VI and VII shows up in the IR spectra as a band at 1700-1710 cm^{-1}, whereas the carboxyl group of X appears in the IR spectrum as a band at 1680 cm^{-1}. In the spectrum of VIII the frequency of the amide carbonyl group appears at 1630 cm^{-1}. The molecular weight (202), determined by mass spectrometry, corresponds to the calculated value. In contrast to VII, an ester is not formed when VIII is treated with diazomethane.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer. The UV spectra of ethanol solutions were recorded with an EPS-3T spectrophotometer. The PMR spectra of trifluoroacetic acid solutions were recorded with a JNM 4H 100 spectrometer.

trans-β-(2-Benzoxazolylthio)acrylic Acid (VI). A 0.5-g (5 mmole) sample of trans-β-chloroacrylic acid was added to a solution of 0.75 g (5 mmole) of benzoxazoline-2-thione in 30 ml of toluene, and the mixture was refluxed for 10 h. It was then extracted with small portions of concentrated HCl, and the hydrochloric acid solution was diluted with water. The resulting precipitate was recrystallized from aqueous ethanol (1 : 1) to give a shiny white powder with mp 147-148°. Found: N 6.3%. $C_{10}H_7NO_3S$. Calculated: N 6.3%. The PMR spectrum contains doublets of protons of CH= groups at σ 6.12 and 7.75 ppm and a singlet of aromatic ring protons at σ 7.2 ppm. The same compound was similarly obtained from benzoxazoline-2-thione and cis-β-chloroacrylic acid.

cis-β-(2-Benzoxazolylthio)acrylic Acid (X). A 0.7-g (10 mmole) sample of propiolic acid was added to a solution of 1.5 g (10 mmole) of benzoxazoline-2-thione in 50 ml of benzene, and the mixture was refluxed for 1 h. The resulting precipitate was then separated and recrystallized from toluene–ethanol (2 : 1) to give white needles with mp 152-153°. Found: N 6.2%. $C_{10}H_7NO_3S$. Calculated: N 6.3%. PMR spectrum, δ, ppm: doublets of the protons of CH= groups at 6.17 and 7.6 ppm and a multiplet of aromatic ring protons at 7.3 ppm.

trans-β-(2-Benzimidazolylthio)acrylic Acid (VII). A 0.5-g (5 mmole) sample of trans-β-chloroacrylic acid was added to a solution of 0.75 g (5 mmole) of benzimidazoline-2-thione in 10 ml of ethanol and 40 ml of xylene, and the mixture was held at 80° for 10 h. The solvent was then removed, and the residue was washed with acetone. Recrystallization from acetic acid gave shiny white plates with mp 197-198°. Found: N 13.0%. $C_{10}H_8N_2O_2S$. Calculated: N 13.2%. PMR spectrum, δ, ppm: doublets of protons of CH= groups at 6.04 and 7.65, and singlet of aromatic ring protons at 7.32.

The same compound was obtained by refluxing benzimidazoline-2-thione with trans-β-chloroacrylic acid in acetone for 16 h.

Benzimidazo[1,2-b]-1,3-thiazin-4-one (VIII). A 0.5-g (5 mmole) sample of cis-β-chloroacrylic acid was added to a solution of 0.75 g (5 mmole) of benzimidazoline-2-thione in a mixture of 10 ml of ethanol and 40 ml of xylene, and the mixture was refluxed at 80° for 10 h. The solvent was removed, and the residue was washed with acetone and recrystallized from acetic acid to give white needles with mp 207-208°. Found: N 13.8%. $C_{10}H_6N_2OS$. Calculated: N 13.9%. PMR spectrum, δ, ppm: doublet of protons of a –CH= group at 6.06 and triplet of aromatic ring protons at 7.27 (J = 10 Hz). The same compound was obtained by reaction of benzimidazoline-2-thione with propiolic acid after the mixture had been refluxed for 1 h.

LITERATURE CITED

1. N. K. Rozhkova and L. V. Zav'yalova, Khim. Geterotsikl. Soedin., 934 (1973).
2. L. W. Howland and W. F. Brueksch, US Patent No. 2454385 (1948); Chem. Abstr., 43, 1798 (1949).
3. Y. Modena, Accounts of Chem. Res., 4, 73 (1971).
4. C. K. Ingold, Structure and Mechanisms in Organic Chemistry, Cornell Univ. (1969).
5. A. N. Kurtz, W. E. Billups, R. B. Greenleg, H. F. Hamil, and W. F. Pace, J. Org. Chem., 30, 3141 (1965).
6. K. V. Anan'eva and N. K. Rozhkova, Uzb. Khim. Zh., 5, 56 (1973).