SYNTHESIS OF 2-ALKYLTHIO-5-ACETYL-2-OXAZOLINES

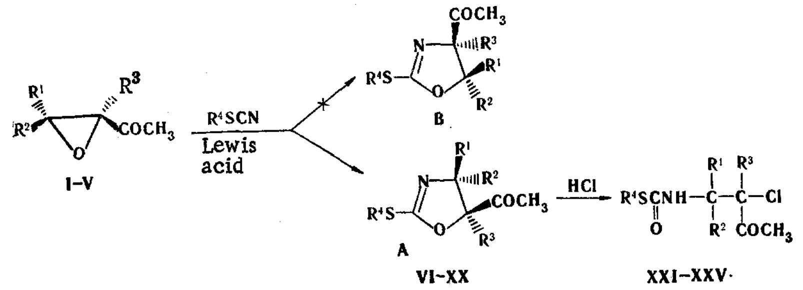
O. N. Bubel', I. G. Tishchenko, O. A. Grinkevich,
and A. F. Abramov

UDC 547.787.07

The reaction of 2-acetyloxiranes with alkyl thiocyanates in the presence of Lewis acids (BF_3, $AlCl_3$) has given 2-alkylthio-5-acetyl-2-oxazolines (yields 40-60%). It has been shown that the reaction of trans-2-acetyl-3-methyloxirane and of trans-2-acetyl-3-methyloxirane and of trans-2-acetyl-2,3-dimethyloxirane with alkyl thiocyanates takes place stereospecifically and leads to cis-2-alkylthio-5-acetyl-2-oxazolines.

By analogy with the reaction of alkyl thiocyantes with glycide ethers [1], taking place under the conditions of acid catalysis and leading to the formation of 2-alkylthio-5-ethoxycarbonyl-2-oxazolines, it could be assumed that 2-acetyloxiranes would also react with alkyl thiocyanates, being converted into the corresponding 2-alkylthio-2-oxazolines.

A study of the reaction of alkyl thiocyanates with the acetyloxiranes (I-V) in the presence of an equimolar amount of a Lewis acid (BF_3, $AlCl_3$) has shown that in all cases 2-alkylthio-5-acetyl-2-oxazolines (VI-XX, Table 1) are formed with yields of 40-60%.



I, VI—VIII, XXI $R^1=R^2=R^3=H$; II, IX—XI, XXII $R^1=R^2=H$, $R^3=CH_3$; III, XII—XIV, XXIII $R^1=R^2=CH_3$, $R^3=H$; IV, XV—XVII, XXIV $R^1=CH_3$, $R^2=R^3=H$; V, XVIII—XX, XXV $R^1=R^3=CH_3$, $R^2=H$; VI, IX, XII, XV, XVIII, XXI—XXV $R^4=CH_3$; VII, X, XIII, XVI, XIX $R^4=C_2H_5$; VIII, XI, XIV, XVII, XX $R^4=i\text{-}C_3H_7$

In the case of the oxirane (III), catalysis by boron trifluoride led to a complex mixture of products of the transformation of the oxirane, while the use of anhydrous aluminum chloride permitted the oxazolines (XII-XIV) to be obtained in satisfactory yields. In the case of the oxiranes (I, II, IV, and V) it proved to be desirable to use only boron trifluoride.

Analysis of the reaction mixtures by GLC showed that only the oxazolines (VI-XX), with some contamination by the products of the isomerization of the oxiranes, were formed, although in pyridine the formation of two structural isomers (A and B) or a mixture of them and, in the case of the trans-oxiranes (IV and V), a mixture of the individual cis, trans isomers might be expected.

The IR spectra of compounds (VI-XX) contained strong absorption bands of the stretching vibrations of C=N groups (1608-1625 cm^{-1}) and of C=O groups (1718-1725 cm^{-1}) and also of the vibrations of the C—O—C fragment (1110-1160 cm^{-1}) which, in combination with features of the PMR spectra (Table 2) and elementary analysis, permit these compounds to be regarded as 2-alkylthio-2-oxazolines.

V. I. Lenin Belorussian State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 468-471, April, 1980. Original article submitted April 12, 1979; after revision, October 1, 1979.

0009-3122/80/1604-0352$07.50

TABLE 1. 5-Alkylthio-5-acetyl-2-oxazolines (VI-XX) and S-Alkyl N-(2-Acetyl-2-chloroalkyl)thiocarbamates (XXI-XXV)

Compound	bp, °C (pressure)	mp, °C (from hexane)	n_D^{20}	d_4^{20}	Found, %		Empirical formula	Calculated, %		Yield, %
					C	H		C	H	
VI	66 (1)	—	1,5084	1,2066	45,5	5,6	$C_6H_9NO_2S$	45,3	5,7	41
VII	70 (1)	—	1,5022	1,1581	48,7	6,5	$C_7H_{11}NO_2S$	48,5	6,4	46
VIII	72 (1)	—	1,4945	1,1131	51,5	7,1	$C_8H_{13}NO_2S$	51,3	7,0	50
IX	46 (0,5)	—	1,4956	1,1459	48,7	6,4	$C_7H_{11}NO_2S$	48,5	6,4	54
X	50 (0,5)	—	1,4905	1,1007	51,5	7,2	$C_8H_{13}NO_2S$	51,3	7,0	62
XI	51 (0,5)	—	1,4834	1,0716	53,9	7,5	$C_9H_{15}NO_2S$	53,7	7,5	63
XII	50 (0,5)	—	1,4942	1,1124	51,5	7,1	$C_8H_{13}NO_2S$	51,3	7,0	51
XIII	56 (0,5)	—	1,4882	1,0828	53,8	7,5	$C_9H_{16}NO_2S$	53,7	7,5	50
XIV	58 (0,5)	—	1,4821	1,0489	55,9	8,0	$C_{10}H_{17}NO_2S$	55,8	8,0	49
XV	64 (0,8)	—	1,5050	1,1635	48,7	6,3	$C_7H_{11}NO_2S$	48,5	6,4	60
XVI	71 (0,8)	—	1,4972	1,1221	51,6	7,2	$C_8H_{13}NO_2S$	51,3	7,0	50
XVII	72 (0,8)	—	1,4908	1,0844	53,8	7,5	$C_9H_{15}NO_2S$	53,7	7,5	54
XVIII	65 (0,8)	—	1,4918	1,1134	51,4	7,0	$C_8H_{13}NO_2S$	51,3	7,0	44
XIX	73 (0,8)	—	1,4855	1,0773	53,9	7,6	$C_9H_{15}NO_2S$	53,7	7,5	48
XX	75 (0,8)	—	1,4798	1,0477	55,9	7,9	$C_{10}H_{17}NO_2S$	55,8	8,0	41
XXI	123 (1,2)	59—60	—	—	37,1	5,0	$C_6H_{10}ClNO_2S$	36,8	5,2	80
XXII	116 (1,0)	35—36	—	—	40,2	5,8	$C_7H_{12}ClNO_2S$	40,1	5,8	92
XXIII	107 (1,0)	—	1,5175	1,1989	43,1	6,4	$C_8H_{14}ClNO_2S$	42,9	6,3	85
XXIV	—	79—80	—	—	40,3	5,9	$C_7H_{12}ClNO_2S$	40,1	5,8	76
XXV	—	63—64	—	—	43,2	6,4	$C_8H_{14}ClNO_2S$	42,9	6,3	90

TABLE 2. PMR Spectra of the Oxazolines (VI-XX) and of the Thiocarbamates (XXI-XXV)

Compound	δ, ppm, J, Hz					
	R^1	R^2	R^3	R^4	CH_3CO	NH*
VI	3,87 dd (8,14)	4,14 dd (10, 14)	4,89 dd (8, 10)	2,49 s	2,23 s	—
VII	3,87 dd (8,14)	4,14 dd (10, 14)	4,86 dd (8, 10)	1,38 t, 3,04 q (7)	2,23s	—
VIII	3,87 dd (8,14)	4,14 dd (10, 14)	4,83 dd (8, 10)	1,41 d, 1,42 d, 3,68 m (7)	2,22s	—
IX	3,49 d (14)	3,86 d (14)	1,44 s	2,41s	2,16 s	—
X	3,35 d (14)	3,70 d (14)	1,37 s	1,30 t 2,81 q(7)	2,06 s	—
XI	3,51 d (14)	3,88 d(14)	1,44s	1,39 d 3,66 m(7)	2,16 s	—
XII	1,14 s	1,45s	4,45 s	2,49 s	2,23 s	—
XIII	1,12 s	1,43 s	4,40 s	1,38 t 3,02 q (7)	2,21s	—
XIV	1,12 s	1,42 s	4,38 s	1,40 d 3,67 m (7)	2,21 s	—
XV	1,14 d (7)	4,48 dq (7, 10)	4,88 d (10)	2,50 s	2,21s	—
XVI	1,14 d (7)	4,48 dq (7,10)	4,85 d (10)	1,39 t, 3,04 q (7)	2,21 s	—
XVII	1,14d (7)	4,48 dq (7,10)	4,82 d (10)	1,47 d, 3,70m (7)	2,21s	—
XVIII	1,10 d (7)	3,94 q (7)	1,48 s	2,47 s	2,21 s	—
XIX	1,10 d (7)	3,94 q (7)	1,48 s	1,38 t, 3,03 q(7)	2,23 s	—
XX	1,09 d (7)	3,94 q (7)	1,47 s	1,42 d, 3.67 m (7)	2,22 s	—
XXI	3,70 t (6)		4,43 t (6)	2,36 s	2,31s	6,42 t (6)
XXII	3,67 d (7)		1,68 s	2,34s	2,29s	5,94 t (7)
XXIII	1,48 s	1,52s	5,01 s	2,32 s	2,29 s	5,77 s
XXIV	1,34 d (7)	4,37—4,64 m	4,34 d (4)	2,32 s	2,30 s	5,90 d (7)
XXV	1,28 d (7)	4,40—4,70 m	1,64 s	2,35s	2,30 s	5,90 d (6)

---

*Signal broadened.

However, on the basis of these facts alone it is difficult to make a choice between structures A and B. Consequently, in order to establish the direction of the opening of the oxiranes (I-V), the oxazolines (VI, IX, XII, XV, and XVIII) obtained, respectively, from oxiranes (I-V) and methyl thiocyanate were converted into the thiocarbamates (XXI-XXV). In the IR spectra of the thiocarbamates (XXI-XXV), strong absorption bands of the stretching vibrations of thiocarbamate and acetyl carbonyl groups (1690 cm^{-1} and 1714-1727 cm^{-1}, respectively) and also the bands of associated and free vibrations of NH groups (3350 cm^{-1} and 3430-3445 cm^{-1}, respectively) are observed.

In the PMR spectra of compounds (XXI-XXV) (Table 2) the following multiplicities of the signals of the N–H protons are observed: triplets (6.42 ppm, J = 6 Hz; 5.94 ppm, J = 7 Hz) in the case of the thiocarbamates (XXI and XXII) [from the oxazolines (VI and IX)], a singlet (5.77 ppm) and a doublet (5.90 ppm, J = 6 Hz) for the thiocarbamates (XXIII and XXV) (from the oxazolines (XII and XVIII), respectively, and a doublet (5.90 ppm, J = 7 Hz) for the thiocarbamate (XXIV) [(from the oxazoline (XV)]. In the last case, a doublet (4.34 ppm, J =

4 Hz) and a multiplet (4.37-4.64 ppm) of the signals of methine protons were also observed. Such a multiplicity of the signal of the N–H proton and also the multiplicity of the methine protons in the case of the thiocarbamate (XXIV) show that the opening of the oxiranes (I-V) by alkyl thiocyanates under the conditions of catalysis by Lewis acids takes place from the side of the β-carbon atom, and the oxazolines obtained have the structures of 2-alkylthio-5-acetyl-2-oxazolines (A).

For compounds (XV-XVII) obtained from the trans-oxiranes (IV), the spin–spin constant of the coupling of the 4-H protons with the 5-H protons was 10 Hz, which is characteristic for cis-substituted 2-oxazolines [2] and, consequently, the oxazolines (XV-XVIII) have the cis configuration. In the case of the oxazolines (XVIII-XX), obtained from the 2r-acetyl-2,3t-dimethyloxiranes (V), the configuration was determined on the basis of the Overhauser effect. On irradiation with the resonance frequency of the 5-CH_3 group, an increase in the intensity of the quartet signal of the 4-H proton by approximately 30% was observed, which indicates its cisoid arrangement; consequently, the oxazolines (XVIII-XX) have the structure of 2-alkylthio-5r-acetyl-4c,5-dimethyl-2-oxazolines.

Since, according to GLC results, we observed the formation of only the oxazolines (XV-XX), it may be assumed that the oxiranes (IV and V) react with alkyl thiocyanates under conditions of catalysis by Lewis acids with inversion of the configuration of the C_3 atom by the mechanism proposed previously for the reaction of carbonyl compounds with oxiranes [3].

EXPERIMENTAL

The IR spectra of 0.1 M solutions of the substances in CCl_4 were taken on a UR-20 spectrophotometer. The PMR spectra were obtained on a Varian HA-100 spectrometer for 10% solutions in CCl_4 or $CHCl_3$, with HMDS as internal standard. The experiment on the nuclear Overhauser effect was performed on a JNM-PS-100 spectrometer. The samples were prepared and the measurements were carried out by a known method [4]. GLC was performed on a LKhM-7A chromatograph with a katharometer; column 2.0 m × 3 mm filled with 5% of silicone elastomer E-301 on the support Chromasorb W with particle dimensions of 80-100 mesh; rate of flow of helium 30 ml/min; column temperature 120-130°C.

The initial oxiranes (I-V) were obtained by the epoxidation of the corresponding unsaturated ketones with alkaline hydrogen peroxide. The alkyl thiocyanates were synthesized from alkyl iodides and potassium thiocyanate [5].

2-Alkylthio-5-acetyl-2-oxazolines (VI-IX, XV-XX, Table 1). With stirring, 0.1 mole of boron trifluoride was passed through a solution of 0.12 mole of an alkyl thiocyanate in 100 ml of methylene chloride, the temperature being kept between 0 and –5°C, after which the reaction mixture was cooled to –10°C and 0.1 mole of the appropriate oxirane was added dropwise over 1 h and 30 min. Then 1 mole of sodium bicarbonate and 20 ml of water were added and extraction with diethyl ether was performed (3 × 150 ml). The ethereal extracts were dried with sodium sulfate, the ether was distilled off in a rotary evaporator, and the residue was fractionated under reduced pressure.

2-Alkylthio-5-acetyl-2-oxazolines (XII-XIV, Table 1). Over 2 h at room temperature, 0.1 mole of the oxirane (III) in 30 ml of methylene chloride was added to a solution of 0.1 mole of anhydrous aluminum chloride in 30 ml of methylene chloride and 0.35 mole of an alkyl thiocyanate. Then the reaction mixture was treated with 1.5 mole of sodium bicarbonate and 5 mole of water and was extracted with ether (4 × 100 ml). The ethereal extracts were dried with sodium sulfate, the ether was distilled off on a rotary evaporator, and the residue was fractionated under reduced pressure.

S-Alkyl N-(2-Acetyl-2-chloroalkyl)thiocarbamates (XXI-XXV, Table 1). At room temperature, an excess of hydrogen chloride was passed through a solution of 0.01 mole of the appropriate 2-oxazoline in 20 ml of ether. Then the ether was distilled off and the residue was heated with 20 ml of toluene until it had dissolved completely. The toluene was distilled off under reduced pressure and the residue was crystallized or was distilled under reduced pressure.

LITERATURE CITED

1. O. N. Bubel', I. G. Tishchenko, and O. A. Grinkevich, Khim. Geterotsikl. Soedin., No. 4, 460 (1979).
2. U. Schollköpf, G. Fritz, J. Hoppe, R. Harms, K. Hantke, K. D. Scheunemann, E. Eilers, and E. Blume, Ann. Chem., No. 1, 183 (1976).
3. V. N. Yandovskii and T. I. Temnikova, Zh. Org. Khim., 4, 1758 (1968).
4. C. L. Van Antwerp, J. Chem. Educ., 50, 638 (1973).
5. P. Allen, J. Am. Chem. Soc., 57, 198 (1935).