EFFECT OF STEREOCHEMICAL AND ELECTRONIC FACTORS ON THE BREAKDOWN AND REARRANGEMENT OF 2-AZIDOVINYL KETONES

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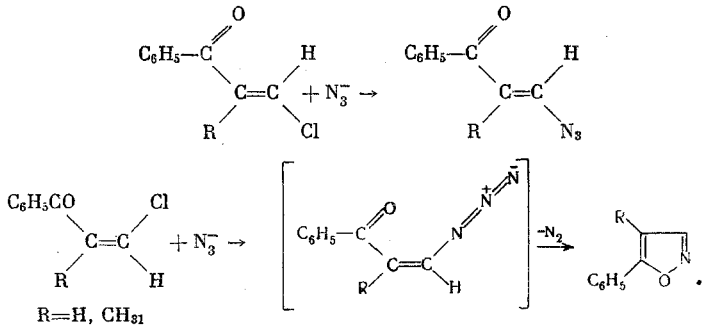
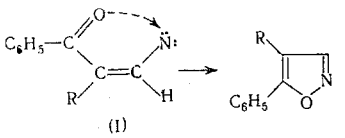
We have shown previously that the ketovinylation of the azide ion goes with preservation, in the main, of the original geometric configuration (Scheme 1), and from cis-2-chlorovinyl ketones, instead of the expected cis-2-azidovinyl ketones, the corresponding isoxazoles are isolated. We regard the formation of the latter as the result of the spontaneous breakdown of the intermediate cis-2-azidovinyl ketones [1].

Scheme 1



In such breakdown the formation may occur of the imidogen (I), the stabilization of which must be effected

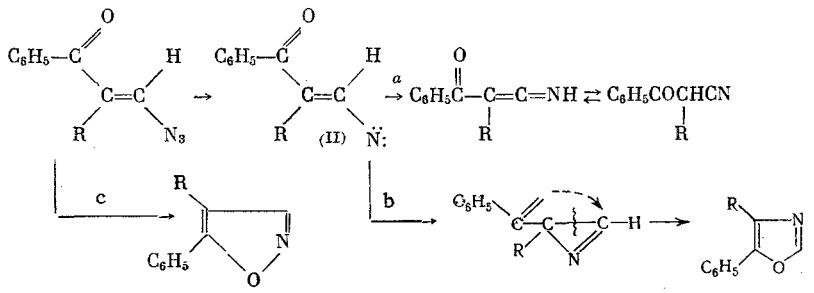


(I)

by reaction between the electrophilic imidogen nitrogen and the nucleophilic oxygen atom of the carbonyl group.*

Trans-2-azidovinyl ketones are considerably more stable than their cis-isomers. They decompose only when heated [2] or in a strongly acid medium [3]. It may be expected that the thermal breakdown of trans-2-azidovinyl ketones will lead to the imidogen (II), which unlike (I) should have the trans configuration. The stereochemical conditions should affect the way in which this species is stabilized, and it must be expected that products will be formed that are different from those given by cis-2-azidovinyl ketones. In fact, we have shown previously [2] that the thermolysis of trans-3-azidoacrylophenone leads mainly to the formation of benzoylacetonitrile by a route which can be represented by Scheme 2 (route *a*, in which R = H).

Scheme 2



* It is possible that the breakdown of the cis-2-azidovinyl ketone and the cyclization into an isoxazole may proceed synchronously.

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However, benzoylacetonitrile was accompanied by a small amount of a substance which was not identified at that time.

In the present work we have investigated the thermolysis of trans-2-azidovinyl ketones in greater detail with the use of a larger amount of trans-3-azidoacrylophenone and also for the case of trans-3-azido-2-methylacrylophenone. The thermolysis of the latter was studied with the use of butyl alcohol and dimethylformamide (DMFA) as media. In this case the expected 2-benzoylpropionitrile was obtained in very low yield, whereas the main product proved to be an isomeric nitrogen-containing substance which in spectral characteristics (IR and PMR spectra) and behavior in TLC differed also from the 4-methyl-5-phenylisoxazole which we had prepared previously [1], although it was highly reminiscent of the latter in its properties. It must be mentioned that 4-methyl-5-phenylisoxazole was also detected in the reaction, but only in traces (TLC data). Like 4-methyl-5-phenylisoxazole, the unknown compound obtained gave a complex with $CdCl_2$ which readily decomposed on steam distillation in presence of H_2SO_4. It also did not dissolve in aqueous alkalies, but, unlike the corresponding isoxazoles, it scarcely reacted at all with sodium ethoxide in alcohol. It should be noted that the PMR spectrum of this compound is very similar to that of 4-methyl-5-phenylisoxazole, but the signals from corresponding protons are somewhat shifted. Detailed investigation showed that the unknown substance was 4-methyl-5-phenyloxazole, which was confirmed by comparison with a known sample prepared by the method described in [4] (the IR and PMR spectra were identical, and a mixture of their picrates melted without depression).

We also detected benzoic acid in the reaction products, and we showed that hydrocyanic acid was liberated in the course of the thermolysis.* All this indicates that the breakdown and rearrangement of trans-3-azido-2-methylacrylophenone take more than one course. It is impossible to imagine the formation of an oxazole ring in the given concrete case with the rearrangement of the carbon skeleton of the original molecule. Such rearrangement with subsequent cyclization into a 4-methyl-5-phenyloxazole can be supposed to go through the intermediate formation of an aziridine ring, which is known to be formed readily in the thermolysis of some vinyl azides [7, 8]. Subsequent cleavage of the C–C bond (originally a double bond) with cyclization, as represented in Scheme 2 (route b), must lead to the corresponding oxazole. It should be noted that in the study of the photochemical rearrangement of isoxazoles acylaziridines were isolated as intermediate products, and these were readily converted further into oxazoles when heated or treated with sodium ethoxide [6, 9]. Similar intermediate products could probably be isolated also in our case, but the use of milder conditions would be necessary. A detailed investigation of the thermolysis of large amounts (about 24 g) of trans-3-azidoacrylophenone in DMFA also led to the conclusion that, apart from the main product, benzoylacetonitrile, a smaller amount of previously unidentified 5-phenyloxazole is formed and contains some admixture of 5-phenylisoxazole (about 70% of the former in the mixture of heterocycles).

Thus, for 2-methyl-substituted trans-3-azidoacrylophenone the extent of conversion into the oxazole ring is greater than for the unsubstituted compound, which is understandable, however, for the electrophilic imidogen nitrogen atom readily forms a three-membered ring with an ethylenic grouping of higher electron density. This suggests that, not only stereochemical factors, but also electronic effects can affect the result of the thermolysis of trans-2-azidovinyl ketones. We must mention that the thermolysis of the same compounds was studied in [10]. However, in that investigation no significance was attached to stereochemical factors, and chromatographic methods were not used, and it was therefore concluded that, apart from benzoylacetonitriles, only isoxazoles are formed. Thus, 4-methyl-5-phenyloxazole – the main product of the thermolysis of 3-azido-2-methylacrylophenone – was taken in [10] to be the corresponding isoxazole, whereas the formation of isoxazoles in the cases examined of trans-2-azidovinyl ketones, though occurring in principle (route c, Scheme 2), is made difficult by its probable dependence on the preliminary trans → cis isomerization of the original ethylenic compounds. Even if such isomerization does occur to a slight extent for 3-azidoacrylophenone, it can be practically neglected in the case of its 2-methyl derivative.

EXPERIMENTAL

Trans-2-azidovinyl ketones were prepared by the method described in [1]. IR-spectra were determined with a UR-10 instrument, and PMR spectra were determined with Hitachi H-60 (34°) and Perkin-Elmer R-12 (35°) instruments.

* We shall not discuss the sources of benzoic and hydrocyanic acids in the thermolysis here in detail, but it is most probable that they are formed from 2-benzoylpropionitrile, which, as reported by the authors who prepared it for the first time, gives benzoic and hydrocyanic acids on standing, which makes the isolation of an analytically pure sample of 2-benzoylpropionitrile difficult [5]. It is also possible that these products are formed in the partial oxidation of the oxazole [6].

Thermolysis of trans-3-Azidoacrylophenone in DMFA. With stirring and heating a solution of 24 g of trans-3-azidoacrylophenone in 200 ml of DMFA was added dropwise to 100 ml of DMFA heated to 50-55°. Heating and stirring were continued further for 3 h. On the next day solvent was removed in a vacuum through a high column. The residue was diluted with ether. The ethereal solution was extracted six times with 5% NaOH. The alkaline solution was acidified, and the crystals of benzoylacetonitrile which came down were filtered off, washed with water, and dried. Yield 17.1 g (85%), mp 80°; a mixture with a known sample [11] melted without depression.

The ethereal solution remaining after the alkali extraction was evaporated. The residue was an oil, which was extracted with pentane. After the evaporation of pentane we obtained 1.14 g of oil, which according to GLC (with tristearin as carrier) was a mixture of about 70% of 5-phenyloxazole and about 30% of 5-phenylisoxazole. The mixture obtained was treated with an alcoholic solution of sodium ethoxide. After 2 days alcohol was vacuum-evaporated down to one-half of its original volume. The residue was poured into water and extracted with ether. From the ethereal solution we obtained 5-phenyloxazole (purified further by passage through a small column of alumina in hexane), mp 38-40° [12]. The IR and PMR spectra coincided with those of a known sample [12]. In the PMR spectrum (ethyl ether, hexamethyldisiloxane) we found the following signals from protons: $\delta_{\underset{=C-H}{2}}$ = 7.41 ppm (singlet), $\delta_{\underset{=C-H}{4}}$ = 7.96 ppm (singlet), and $\delta_{C_6H_5}$, a multiplet in the range 7.11-7.72 ppm. For comparison we determined the PMR spectrum (ethyl ether, hexamethyldisiloxane) of the isomeric 5-phenylisoxazole [13] and found the following signals from protons: $\delta_{\underset{=C-H}{3}}$ = 6.49 ppm (doublet), $\delta_{\underset{=C-H}{4}}$ = 8.17 ppm (doublet) [$J_{\underset{H,H}{3\ 4}}$ = 1.7 Hz], $\delta_{C_6H_5}$, a multiplet in the range 7.13-7.78 ppm. The alkaline layer remaining after the sodium ethoxide treatment was acidified, and we isolated benzoylacetonitrile (mp 80°, undepressed in a mixture test) formed by the opening of the 5-phenylisoxazole ring [11].

Thermolysis of trans-3-Azido-2-methylacrylophenone – in Butyl Alcohol. A mixture of 7.48 g of trans-3-azido-2-methylacrylophenone and 120 ml of absolute butyl alcohol was boiled for 10 h with a reflux condenser connected to a Tishchenko vessel containing 10% NaOH.* In the course of the thermolysis a weak stream of nitrogen was passed through the reaction mixture. Butyl alcohol was removed in a vacuum. To the residue we added 100 ml of ether and 35 g of finely ground cadmium chloride. After 3 days the complex with cadmium chloride was filtered off and washed on the filter with dry ether. The residue was treated with 50 ml of 10% H_2SO_4 and steam-distilled. The yield of 4-methyl-5-phenyloxazole was 2.85 g; it contained about 5% of 4-methyl-5-phenylisoxazole as impurity. For the purification of 4-methyl-5-phenyloxazole see below.

The ethereal solution remaining after the separation of the cadmium chloride complex was evaporated. The residue was an oil containing 2-benzoylpropionitrile and benzoic acid. The latter (about 0.5 g) was isolated from the mixture by treatment with saturated sodium bicarbonate solution. 2-Benzoylpropionitrile (yield 1.66 g) is an oil, bp 127-130° (3 mm) [11]; decomposes on keeping with the liberation of benzoic acid. Found: C 74.64; H 5.75%. $C_{10}H_9ON$. Calculated: C 75.47; H 5.75%. IR-spectrum, ν, cm^{-1}: 1684 (C=O), 2257 (N≡C). PMR spectrum, ppm: δ_{CH} (quadruplet) = 4.74, δ_{CH_3} (doublet) = 1.43 [J_{CH_3-CH} = 7.54 Hz], C_6H_5, multiplet (about 7.09 ppm).

In Dimethylformamide. A mixture of 0.495 g of trans-3-azido-2-methylacrylophenone and 300 ml of dry DMFA was refluxed for 10 h in a stream of nitrogen. The out-going gases were passed through 10% NaOH in a Tishchenko vessel to trap HCN liberated. The reaction mixture was poured into water and extracted with ether. The ethereal solution was extracted with 5% NaOH. Ether was evaporated, and the residue (0.42 g) was 4-methyl-5-phenyloxazole containing traces of 4-methyl-5-phenylisoxazole (according to TLC on alumina with a 1:5 mixture of acetone and hexane as solvent). From the alkaline solution by acidification and extraction with ether we obtained about 0.06 g of a mixture of 2-benzoylpropionitrile and benzoic acid.

Purification of 4-Methyl-5-phenyloxazole. A solution of C_2H_5ONa in alcohol prepared from 0.3 g of sodium and 7 ml of absolute alcohol was added to 1.8 g of 4-methyl-5-phenyloxazole containing 4-methyl-5-phenylisoxazole as impurity. On the next day 30 ml of dry ether was added. The precipitate formed was filtered off and washed on the filter with dry ether. The treatment of the precipitate with dilute H_2SO_4 gave

* At the end of the reaction cyanide ions were detected in this solution.

0.07 g of benzoic acid, mp 118° (a mixture with a known sample melted without depression). The ethereal-alcoholic filterate was evaporated, and the residue was treated with 5% KOH. After the acidification of the alkaline solution we obtained 0.02 g of a nitrogen-containing oil (probably 2-benzoylpropionitrile) [its IR-spectrum contained bands at 1684 (C=O) and 2257 (C≡N) cm^{-1}]. The ethereal solution was washed with water, dried over Na_2SO_4, and evaporated. The residue (1.35 g) was pure 4-methyl-5-phenyloxazole, bp 124-125° (15 mm), mp 36-37°. In its PMR spectrum (solvent DMFA; hexamethyldisiloxane): $\delta_{=C-H}$ = 8.19 ppm, δ_{CH_3} = 2.41 ppm, $\delta_{C_6H_5}$, multiplet in the range 7.12-7.75 ppm. Found: C 75.49; H 5.85%. $C_{10}H_9ON$. Calculated: C 75.44; H 5.69%.

The picrate, prepared in the usual way in ether, had mp 122° (methanol). Found: C 49.48; H 3.11%. $C_{16}H_{12}N_4O_8$. Calculated: C 49.04; H 3.16%.

The IR and PMR spectra of the sample obtained coincide with those of known 4-methyl-5-phenyloxazole [4]; a mixture of the picrates melted without depression. For comparison we give the PMR spectrum of 4-methyl-5-phenylisoxazole: $\delta_{=C-H}$ = 8.37 ppm, δ_{CH_3} = 2.21 ppm, $\delta_{C_6H_5}$, multiplet in the range 7.26-7.71.

In conclusion we thank N. P. Gambaryan for his participation in the discussion of the possible scheme of the rearrangement into the oxazole ring, and also P. V. Petrovskii and B. V. Lokshin for determining the PMR and IR spectra.

CONCLUSIONS

1. An investigation was made of the thermal breakdown of trans-2-azidovinyl ketones, and it was shown that, in contrast with the breakdown of their cis-isomers, which give isoxazoles, the trans-azides form mainly benzoylacetonitriles and oxazoles, and the proportions of these in the mixture depend on the nature of the substituents at the double bond.

2. A scheme for the rearrangement of the trans-2-azidovinyl ketones into oxazoles is discussed.

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