SYNTHESIS OF PYRAZOLES BY CONDENSATION OF UNSYMMETRICAL DIALKYLHYDRAZINES WITH β-CHLOROVINYL KETONES

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1,3-Dialkylpyrazoles (in yields up to 70%), dialkylhydrazones of saturated ketones (CH₃COR), and salts of formic acid are obtained by the alkali-induced decomposition of the products of condensation of salts of unsymmetrical dialkylhydrazines with chlorovinyl ketones (ClCH = CHCOR). Schemes for the formation of these compounds are proposed.

It is well known that pyrazoles are formed by the reaction of hydrazine and monosubstituted hydrazines with β -chlorovinyl ketones [1,2]. It was of interest to introduce unsymmetrical dialkylhydrazines into this reaction. In analogy with the reaction of dialkylhydrazines and the simplest α , β -unsaturated carbonyl compounds [3], one could also expect here the formation of nitrogen heterocycles and, in particular, the unknown and apparently extremely unstable 1,1-dialkylpyrazolium salts or even the products of their profound disintegration. In fact, it was recently observed [4] that indazoles are formed when attempts are made to obtain dimethylhydrazones of the aromatic analogs of β -chlorovinyl ketones – o-haloacetophenones. The intermediate formation of quaternary 1,1-dimethylindazolinium salts, which are readily dealkylated on heating with excess unsymmetrical dimethylhydrazine, was proposed.*

It turned out that methyl and ethyl β -chlorovinyl ketones react with alcoholic solutions of the hydrochlorides of 1,1-dimethyl-, diethyl-, and di-n-butyl hydrazines to form low-melting, semicrystalline products that cannot be recrystallized and contain chlorine in the ionic or very readily ionized form (precipitated directly with silver nitrate), but are not pure compounds.

Subsequent treatment of these mixtures with 50% alkali at room temperature with subsequent distillation led to the isolation, as major products, of 1,3-dialkylpyrazoles (Table 1), of which only two have been previously described [5]. N,N-Dialkylhydrazones of acetone or methyl ethyl ketone (from methyl and ethyl β -chlorovinyl ketones, respectively, Table 2), were found along with the pyrazoles.

Formate salts were detected in the aqueous alkali layer from the decomposition; their yield, determined by the calomel method, was 36 mole % (in the experiment with dimethylhydrazine and methyl β -chlorovinyl ketone).

If, however, the condensation of methyl β -chlorovinyl ketone is carried out with excess dimethylhydrazine hydrochloride, a light-yellow, extremely hygroscopic salt, which, according to its composition and PMR spectrum, corresponds to trimethylhydrazinium chloride, and can be isolated from the crystalline mass formed. The yield of pyrazole also rises to 70%, and no side products of the alkaline decomposition are observed.

The following scheme can be proposed for the transformation on the basis of the experimental results:

$$\begin{array}{c} \text{CICH}=\text{CH}\\ \text{R} \end{array} \begin{array}{c} \text{C}=\text{O} + \text{H}_{2}\text{NNR}_{2}^{\prime} + \text{HCI} \longrightarrow \begin{bmatrix} \text{CICH}=\text{CH}\\ \text{R} \end{array} \end{array} \begin{array}{c} \text{C}=\text{N}-\text{N}R_{2}^{\prime} \end{bmatrix} \longrightarrow \begin{bmatrix} \text{HC}-\text{C}-\text{R}\\ \text{HC}+\text{N}\\ \text{R}^{\prime} \end{array} \\ \begin{array}{c} \text{HC}\\ \text{R}^{\prime} \end{array} \\ \begin{array}{c} \text{HC}\\ \text{R}^{\prime} \end{array} \end{array} \begin{array}{c} \text{HC}\\ \text{HC}\\ \text{HC} \end{array} \\ \begin{array}{c} \text{HC}\\ \text{HC} \end{array} \\ \end{array}$$
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*The reaction was carried out with 2-bromoacetophenone and 2-chloro-5-nitroacetophenone [4].

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TABLE 2. Yields of 1,3-Dialkylpyrazoles and Hydrazones (from equimolar amounts of chlorovinyl ketones and dialkylhydrazines) The initial products of the reaction of chlorovinyl ketones with the salts of unsymmetrical dialkylhydrazines are apparently the corresponding chlorohydrazones which, under the reaction conditions, are cyclized to the isomeric 1,1-dialkylpyrazole salts. Being extremely unstable, they immediately lose an alkyl radical, thereby quaternizing the hydrazine.

On heating with alkali the chlorohydrazones are cleaved at the C = C bond to formates and dialkyl-hydrazones of saturated ketones:

 $\frac{\text{CICH}=\text{CH}}{\text{R}} \xrightarrow{\text{CNNR}_2'} \frac{\text{KOH}}{\text{H}_2\text{O}} \frac{\text{CH}_3}{\text{R}} \xrightarrow{\text{C}=\text{NNR}_2'} + \text{HCOOK} + \tilde{\text{KCI}}$

The comparatively facile cleavage of α , β -unsaturated dialkylhydrazones at the C = C bond was previously noted in [6].

Since unsymmetrical dialkylhydrazines are considerably more accessible and cheaper than monosubstituted hydrazines, this reaction may be of interest for the preparation of alkyl-substituted pyrazoles.

EXPERIMENTAL

Methyl β -chlorovinyl ketone [bp 36° (16 mm)] and ethyl β -chlorovinyl ketone [49° (21 mm)] were obtained according to [1]. Diethylhydrazine was prepared by reduction of diethylnitrosamine with zinc amalgam by a somewhat modified method [7]. The reduction was carried out in a 2-liter, round-bottom flask with vigorous stirring instead of shaking in a separatory funnel. Alkalination and subsequent distillation were carried out in the same flask with stirring; this eliminated severe bumping during boiling of the reaction mixture with its precipitate of zinc hydroxide. The diethylhydrazine obtained in this manner (51%) had bp 99.5° (755 mm) and n_D^{20} 1.4212. Di-n-butyl hydrazine was obtained by reduction of the nitrosamine with lithium aluminum hydride [8] and had bp 80-81° (20 mm) and n_D^{20} 1.4346.

<u>Reaction of Alkyl β -Chlorovinyl Ketones with Dialkylhydrazines.</u> Hydrazine (0.5 mole) was neutralized with cooling and stirring with a solution of 42.5 ml of hydrochloric acid (sp. gr. 1.18) in 50 ml of ethanol. Chlorovinyl ketone (0.5 mole) was then added dropwise to the salt formed. Addition of ketone to the dimethylhydrazine is accompanied by appreciable heating and was therefore carried out with ice-bath cooling. The reaction with heavier hydrazines (R' = C_2H_5 and C_4H_9) proceeds sluggishly, so that the reaction mixtures were refluxed for 3 h. Viscous, semicrystalline residues were formed in quantitative yields after vacuum distillation of the solvents (to constant weight).

The products of condensation of methyl β -chlorovinyl ketone with dimethylhydrazine (a) and diethylhydrazine (b) were analyzed: a) Found %: Cl (Volhard) 24.26, 24.08; N 18.86, 18.92. C₆H₁₁N₂Cl.* Calculated %: Cl 24.20; N 19.11. b) Found %: Cl 22.97, 22.97 (Volhard); N 23.63, 23.67 (Schoniger); E† 150.8. C₆H₁₁N₂Cl.‡ Calculated %: Cl 24.20; M 146.5.

<u>Alkaline Decomposition of the Condensation Products.</u> This was carried out by treatment in the cold with 70 g of 50% KOH. An organic layer with the characteristic odor of pyrazole formed immediately. The distillate was distilled from a Würtz flask (to dryness), saturated with KOH, and the organic layer was removed, dried over alkali, and distilled through a column (15 theoretical plates). The chromatograms of the unfractionated organic layers in all cases contained two major peaks which were identified as dialkylhydrazones and pyrazole.

The corresponding N,N-dialkylhydrazones of acetone (from methyl β -chlorovinyl ketone) and methyl ethyl ketone (from ethyl β -chlorovinyl ketone) were contained in the low-boiling fractions; their formation was confirmed by gas-liquid chromatography (GLC) (comparison with standard samples). The dimethyl-hydrazones of acetone and methyl ethyl ketone were isolated preparatively (Table 2). The dimethylhydrazone of acetone had bp 94° (761 mm), d²⁰ 0.7956, n²⁰ 1.4230. The dimethylhydrazone of methyl ethyl ketone had bp 113-114° (753 mm), n²⁰ 1.4282. The characteristics of the authentic preparations of the dialkylhydrazones of the saturated ketones, prepared by condensation of the corresponding dialkylhydrazines with ketones, coincided with the characteristics of the dialkylhydrazones obtained.

^{*1,1,3-}Trimethylpyrazolium chloride.

[†] Equivalent weight determined by titration of alcoholic alkali with phenolphthalein as the indicator.

^{‡1-}Ethyl-3-methylpyrazole hydrochloride.



Fig. 1. IR spectra of the synthesized 1,3-dialkylpyrazoles (obtained with a UR-10 spectrophotometer, layer thickness 13 μ m: 1) 1,3-dimethylpyrazole; 2) 1-methyl-3-ethylpyrazole; 3) 1-ethyl-3-methylpyrazole; 4) 1,3-diethylpyrazole.

The high-boiling fractions were pure 1,3-dialkylpyrazoles, the purity of which was proved by GLC.

The pyrazoles obtained (Table 1) are greenish-yellow liquids that are quite soluble in organic solvents; the ethyl- and methyl-substituted pyrazoles are soluble in water.

The picrates of the pyrazoles were prepared by the addition of a saturated solution of picric acid in alcohol to a concentrated alcoholic solution of the pyrazole. Slow cooling of the boiling liquid precipitated yellow picrate crystals which, in two cases, were identified by comparison of the melting points with those reported in the literature (Table 1). Two other picrates were obtained for the first time.

Picrate of 1-methyl-3-ethylpyrazole. Found %: N 20.78, 20.46. C₁₂H₁₃N₅O₇. Calculated %: N 20.65. Picrate of 1,3-diethylpyrazole. Found %: N 19.97, 19.62. C₁₃H₁₅N₅O₇. Calculated %: N 19.83.

Condensation of Methyl β -Chlorovinyl Ketone with Excess Dimethylhydrazine. Methyl β -chlorovinyl ketone (0.4 mole) was added dropwise with cooling and stirring to 0.8 mole of dimethylhydrazine hydrochloride, prepared by the addition of hydrazine to a solution of 70 ml of hydrochloric acid (sp. gr. 1.18) in 70 ml of ethanol. The reaction mass was heated to 40° under the vacuum of a water vacuum pump to remove the solvents. The residue, which was brought up to a constant weight of 95 g (97% yield), was ayellow crystalline mass. A sample of 11 g of this mass was treated four times with 25 ml of chloroform. The insoluble oil was removed, evacuated at 100°, washed on the filter with chloroform, and the light-yellow hydroscopic crystals [(4.3 g (84%)]* were analyzed for chlorine (Volhard). Found %: Cl 32.11, 32.12. C₃H₁₁N₂Cl. Calculated %: Cl 32.13. The PMR spectrum of the aqueous solution of the salt contained one singlet (6.84 ppm). The chemical shifts of the methyl groups of the specially prepared trimethylhydrazinium iodide (from dimethylhydrazine and methyl iodide in n-heptane) were 6.51 ppm.

^{*}Based on starting ketone.

A 50-g sample of the crystalline mass was dissolved in the minimum amount of water and saturated with solid potassium hydroxide. The resulting organic layer was dried and distilled to give a single product -1,3-dimethylpyrazole [13.8 g (70%)]* with bp 138-139° (765 mm).

<u>UV Spectra of the Pyrazoles.</u>[†] These were obtained from n-hexane solutions with an SF-4 spectrophotometer. The layer thickness was 1 cm for solutions with concentrations of ~10⁻⁴ M and 0.05-0.1 cm for concentrations of ~10⁻³ M. All of the preparations had strong $\pi \to \pi$ transition bands at 220-222 nm, characteristic for pyrazoles [9, 10] (Table 1).

IR Spectra. The IR spectra of the synthesized pyrazoles (Fig. 1) are characterized by valence vibrational frequencies of the ring $(1523-1531 \text{ cm}^{-1}, \text{very strong}, \text{ and } 1482-1493 \text{ cm}^{-1}, \text{ strong})$ and of the hydrogen atoms $(3122-3128 \text{ cm}^{-1} \text{ and } 3107-3110 \text{ cm}^{-1})$. The weak, broad bands at ~1600 and 1685 cm^{-1} can apparently be considered to be analogous to the well-known groups of overtone and composite frequencies in the spectra of aromatic compounds which characterize the number and positions of the substituents.

There are three intense bands at 2975, 2935, and 2878 cm^{-1} in the region of C-H stretching vibrations and, in addition, for compounds substituted at the nitrogen with a methyl group, weak bands at 2812-2815 cm^{-1} .

In the "fingerprint" region one should first of all note the very strong [the most intense in all the investigated compounds and rather broad ($\Delta \nu_{1/2} \approx 40 \text{ cm}^{-1}$)] band at 755-759 cm⁻¹, which apparently can be assigned to the planar deformation vibrations of the ring [11].

The second intense band in this region, which is also extremely frequency-stable ($1208-1217 \text{ cm}^{-1}$), is probably associated with the planar deformation vibrations of the hydrogen atoms of the pyrazole ring.

<u>Gas-Liquid Chromatography.</u> GLC was carried out with a Tswett-1 chromatograph with a glass column 4 mm in diameter and 1.2 m long; the support was INZ-600 (0.3-0.5 mm), the liquid phase (15%) was polyethylene glycol 400 and triethanolamine (1:1), and the column temperature was 80°. Nitrogen and helium were used as gas carriers.

For quantitative analysis of the reaction mixtures, it was first established for control mixtures of pyrazoles and the corresponding hydrazones ($R = CH_3$, $R' = CH_3$, and C_2H_5) that the normalization coefficient for the hydrazone peak area is 1.5. The pyrazole and hydrazone content was calculated from the ratio of the peak areas using the normalization coefficient (Table 2).

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^{*}Of the theoretical yield according to the indicated reaction scheme.

[†]Obtained by L. M. Korzhikova in the Laboratory of Molecular Spectroscopy, Leningrad State University.