REACTION OF α-CHLOROACRYLONITRILE WITH HYDRAZINES

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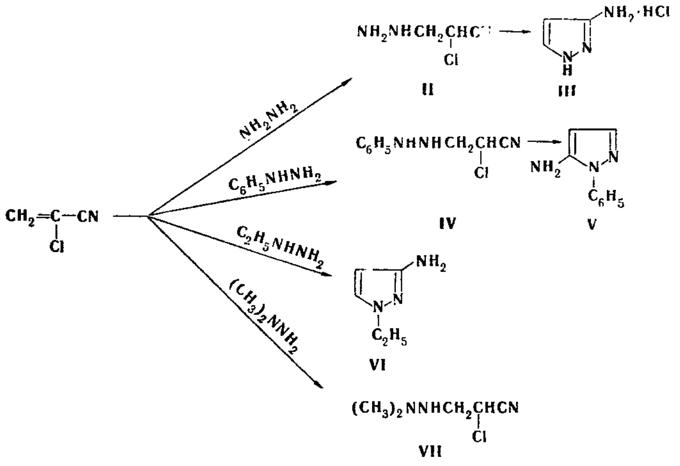
UDC 547.464.6'339.2'334'772,1:543.422.25

A method was developed for the synthesis of 3(5)-aminopyrazole, 1-phenyl-5-aminopyrazole, and 1-ethyl-3-aminopyrazole by reaction of α-chloroacrylonitrile with the appropriate hydrazines. The corresponding addition products – 3-(2,2-dimethylhydrazino)- and 3-(2-phenylhydrazino)-2-chloropropionitriles – were isolated in the case of 1,1-dimethylhydrazine and phenylhydrazine.

Reactions of α,β-dihalopropionitriles and α-haloacrylonitriles with amines give 1-substituted aziridines.

No information is available in the literature regarding the reaction of hydrazines with α-chloroacrylonitrile (I). It might have been assumed that the chief products of the reaction of hydrazine with α-chloroacrylonitrile would be 3-hydroazino-2-chloropropionitrile (II) or 3(5)-aminopyrazole hydrochloride (III). A PMR study showed that a mixture of II and III is formed in this case. The order of mixing the reagents has a substantial effect on their ratio. Thus when nitrile I was added to a solution of hydrazine in dimethyl sulfoxide (DMSO) the chief reaction product was pyrazole III. The yield of the latter increased when an excess amount of hydrazine was used or sodium methoxide was added. If equimolecular ratios of the starting components were mixed in the reverse order, the percentage of hydrazine II in the reaction mixture reached 60%. Temperature has little effect on the ratio of the reaction products. On the basis of these results a preparative method was worked out for the preparation of pyrazole III in 50-60% yield; the method is much more convenient than the method described in [2-5].



As one should have expected, in the case of phenylhydrazine the cyclization proceeded somewhat more slowly because of the reduced electron density on the substituted nitrogen atom. We were therefore also

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Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 246-249, February, 1975. Original article submitted November 27, 1973.

able to isolate an intermediate addition product — 3-(2-phenylhydrazino)-2-chloropropionitrile (IV). Hydrazinonitrile IV is extremely inclined to undergo cyclization to 1-phenyl-5-aminopyrazole (V) and also to undergo oxidation, and this hinders its isolation in pure form. The conclusion regarding the structure of IV is confirmed by the PMR data.

The reaction of ethylhydrazine with nitrile I gives 1-ethyl-3-aminopyrazole (VI). In this case, addition occurs at the substituted nitrogen atom of ethylhydrazine in connection with the donor effect of the ethyl group.

The structures of pyrazoles V and VI are confirmed by their PMR spectra. We found that $^3J_{HH} = 1.8$ + 0.1 Hz in the case of V, whereas $^3J_{4,5} = 2.5$ Hz was found for 1-phenyl-3-aminopyrazole in three solvents. The structure of VI was proved by comparison of its PMR spectrum with the known [6] spectra for 1-methyl-3-amino- and 1-methyl-5-aminopyrazoles. The J values for these aminopyrazoles differ substantially as a function of the position of the amino groups — $J_{3,4} = 1.9$ Hz for 5-aminopyrazole and $J_{4,5} = 2.2$ Hz for 3-aminopyrazole. We found that $^3J_{HH} = 2.2 \pm 0.1$ Hz for VI. The chemical shifts are also close to those in the spectrum of 1-methyl-3-aminopyrazole (VI).

Addition product VII, which has a very great tendency to undergo further transformations, was isolated in good yield in the reaction of nitrile I with 1,1-dimethylhydrazine. Thus addition product VII decomposes violently when it is heated above 60°. When hydrazinonitrile VII is stored in a sealed ampul at 0° its hydrochloride is formed, and the liquid layer gradually turns bright red.

EXPERIMENTAL

The PMR spectra of 10% solutions were obtained with an R-12A spectrometer (60 MHz). The internal standard for solutions in CCl_4 and DMSO was tetramethylsilane, and the internal standard for solutions in D_2O was sodium 3-(trimethylsilyl)propiosulfonate. The IR spectra of mineral oil and hexachlorobutadiene pastes or liquid films of the compounds were obtained with a UR-20 spectrometer.

Chromatographic analysis was accomplished with a Pye Unicam 105 apparatus. The detector was a flame-ionization device, the column was 60 m long and 8 mm in diameter, the support was Fluoropack-80 (0.25-0.315 mm), and the stationary phase was E-301 (6%). The thermostat temperature was 120-130°, the temperature gradient was 6 deg/min, and the carrier-gas (helium flow rate was 300 ml/min.

Reaction of α-Chloroacrylonitrile (I) with Hydrazine. An 8.75-g (0.1 mole) sample of nitrile I in 20 ml of DMSO was mixed at room temperature with 3.2 g of hydrazine in 25 ml of DMSO, and the mixture was held at room temperature for 20 h. It was then analyzed by PMR spectroscopy. PMR spectrum* of hydrochloride II: τ 6.47 (2H, d, J = 6.4 Hz, CH_2); 4.28 ppm (1H, t, J = 6.4 Hz, CH); pyrazole hydrochloride III: τ 2.26 [1H, d, J = 2.6 Hz, 3(5)-H], 4.11 (1H, d, J = 2.6 Hz, 4-H), and an overall broad singlet for NH protons at 1.4 ppm.

3(5)-Aminipyrazole (III). A 17.5-g (0.2 mole) sample of nitrile I was added with stirring and cooling to −20° to a solution of 6.4 g (0.2 mole) of hydrazine in 100 ml of a 2 N sodium methoxide solution in methanol. The temperature of the mixture was raised to room temperature, after which it was stirred for 4 h and filtered. The solvent was evaporated from the filtrate, and the residue was vacuum distilled at 85° (0.3 mm) to give 8.3-10.0 g (50-60%) of product. According to the data in [5], this compound has bp 116° (1.5 mm). The degree of purity was determined by means of gas—liquid chromatography (GLC). PMR spectrum (in D_6-DMSO): τ 2.80 [1H, d, J = 2.0 Hz, 3(5)-H], 4.61 (1H, d, 4-H), and 3.40 ppm (3H, s, NH_2, NH). Found: C 43.4; H 6.2; N 50.6%. $C_3H_5N_3$. Calculated: C 43.4; H 6.0; N 50.6%.

3-(2-Phenylhydrazino)-2-chloropropionitrile (IV). A mixture of 10.8 g (0.1 mole) of phenylhydrazine and 8.75 g (0.1 mole) of nitrile I was allowed to stand at room temperature for 24 h, after which it was filtered to give 1.0 g of phenylhydrazine hydrochloride. The filtrate was dissolved in 50 ml of ether, and the ether solution was washed thoroughly with water. Ether (50 ml) was added, and the mixture was dried with anhydrous sodium sulfate, passed through a column containing 50 g of aluminum oxide, and evaporated at reduced pressure. The yield of hydrazine IV, which was obtained as a reddish oil, was 16.0 g (85%). PMR spectrum (in CCl_4): τ 2.6-2.9 (5H, m, C_6H_5), 4.9 (1H, s, NH), 6.1 (1H, s, NH), 5.59 (1H, t, J = 6.7 Hz, CH), 7.0 ppm (2H, d, J = 6.7 Hz, CH_2). Found: C 55.2; H 5.0; N 21.7%. $C_9H_{10}ClN_3$. Calculated: C 55.2; H 5.1; N 21.5%.

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*The following abbreviations are used here and subsequently: m is multiplet, s is singlet, d is doublet, and t is triplet.

1-Phenyl-5-aminopyrazole (V). A) A 16.0-g sample of hydrazinonitrile IV was allowed to stand at room temperature for 1 week, after which the solidified mass was triturated with ether, and the yellow solid was treated with 42 ml of a 2 N solution of sodium methoxide in methanol. The mixture was filtered, the filtrate was evaporated, and the residue was vacuum distilled at 123-130° (0.02 mm) to give 4.0 g (30 %) of product. The degree of purity of pyrazole V and starting hydrazinonitrile IV was checked by thin-layer ion-exchange chromatography on Fixion-50 X8 with a methanol–water (3 : 1) system. PMR spectrum (in CCl_4): τ 2.5-2.9 (5H, m, C_6H_5), 2.93 (1H, d, J = 1.8 Hz, 3-H), 4.75 (1H, d, J = 1.8 Hz, 4-H), and 6.00 ppm (2H, s, NH_2). Found: C 67.3; H 5.4; N 26.9 %. $C_9H_9N_3$. Calculated: C 67.9; H 5.7; N 26.4 %.

B) An 8.75-g (0.1 mole) sample of nitrile I was added at 20° to a solution of 10.80 g (0.1 mole) of phenylhydrazine in 50 ml of a 2 N solution of sodium methoxide in methanol, after which the temperature of the mixture was raised to room temperature, and it was stirred for 12 h. It was then filtered, and the solvent was evaporated from the filtrate. The residue was then vacuum distilled at 123-130° (0.02 mm) [bp 136-139° (0.02 mm)] to give 8.4 g (53 %) of product.

1-Ethyl-3-aminopyrazole (VI). A) A solution of 8.75 g (0.1 mole) of nitrile I in 25 ml of absolute ether was added at −8° to 6.0 g (0.1 mole) of ethylhydrazine in 25 ml of absolute ether, after which the temperature of the mixture was raised gradually to room temperature in the course of 3 h, and the mixture was maintained at room temperature for 24 h. The resulting oil was washed with ether and treated with 100 ml of a 2 N solution of sodium methoxide in methanol. The resulting precipitate was removed by filtration, the filtrate was evaporated, and the residue was distilled at 50° (0.1 mm) to give 6.1 g (55 %) of product. PMR spectrum (in CCl_4): τ 3.10 (1H, d, J = 2.2 Hz, 5-H), 4.70 (1H, d, J = 2.2 Hz, and 4-H), 6.19 (2H, q, J = 7.1 Hz, CH_2), 8.66 (3H, t, J = 7.1 Hz, CH_3), 6.3 ppm (2H, s, NH_2). Found: C 54.3; H 8.0; N 37.7%. $C_5H_9N_3$. Calculated: C 54.0; H 8.1; N 37.8%.

B) An 8.75-g (0.1 mole) sample of nitrile I was added at −20° to a solution of 6.0 g (0.1 mole) of ethylhydrazine in 50 ml of a 2 N solution of sodium methoxide in methanol. The temperature of the mixture was then raised to room temperature, and it was stirred for 4 h. The solvent was then evaporated, and the residue was vacuum distilled at 50° (0.1 mm) to give 6.7 g (60 %) of product. The degree of purity was determined by GLC.

3-(2,2-Dimethylhydrazino)-2-chloropropionitrile (VII). A solution of 54.0 g (0.9 mole) of 1,1-dimethylhydrazine in 75 ml of absolute ether was added at 0° to 52.5 g (0.6 mole) of nitrile I, after which the temperature of the mixture was raised to room temperature, and it was held at this temperature for 24 h. The oily precipitate of dimethylhydrazine hydrochloride was separated and washed with ether, and the filtrates were combined and vacuum evaporated. The residue was distilled at 25° (0.01 mm) with cooling of the receiver with a dry ice–acetone mixture. The yield of light-yellow oil with n_D^{23} 1.4575 was 35.0-45.0 g (40-51 %). PMR spectrum (in CCl_4): τ 7.61 [6H, s, $N(CH_3)_2$], 6.83 (2H, d, J = 7.0 Hz, CH_2), 5.32 (1H, t, J = 7.0 Hz, CH), 7.2 ppm (1H, s, NH). IR spectrum: 2260 (C ≡N), 2790 and 2830 [$N(CH_3)_2$], 3260 and 1640 (NH), and 2860 and 2960 cm^{-1} (CH_2 and CH). Found: C 40.3; H 6.9; N 28.4 %. $C_5H_{10}ClN_3$. Calculated: C 40.7; H 6.8; N 28.5 %.

Hydrochloride of Hydrazinonitrile VII. A solution of 18.0 g (0.30 mole) of 1,1-dimethylhydrazine in 100 ml of absolute benzene was added dropwise with stirring at 0° to a solution of 24.0 g (0.28 mole) of nitrile I in 150 ml of absolute benzene. After 30 min, the temperature of the mixture was raised to room temperature and it was allowed to remain at this temperature for 24 h. The oily precipitate was separated, and the filtrate was evaporated at room temperature. The residue was dissolved in ether, and the ether solution was cooled and saturated with dry hydrogen chloride. The light-yellow precipitate was removed by filtration and recrystallized from absolute ethanol to give 18.0-23.0 g (34-40 %) of a product with mp 182-184°. PMR spectrum (in D_2O): τ 6.90 [6H, s, $N(CH_3)_2$], 6.38 (2H, d, J = 5.3 Hz, CH_2), 4.94 ppm (1H, t, J = 5.3 Hz, CH). IR spectrum: 2260 (C≡N), 3180, 1555 cm^{-1} (NH). Found: C 32.9; H 6.4; N 23.9 %. $C_5H_{10}ClN_3$ HCl. Calculated: C 32.6; H 6.0; N 22.8 %.

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