

REACTIONS OF HYDRAZINE DERIVATIVES

XLVIII.* SYNTHESIS OF 1-ARYLPYRAZOLIDINES

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Conditions were worked out for the synthesis of a number of 1-arylpirazolidines with alkyl groups in the 4 and 5 positions of the five-membered ring by reduction of the corresponding 3- or 5-pyrazolidones with lithium aluminum hydride.

We have previously described a new route for the synthesis of 1-(3-aminopropyl)indoles [3] starting from 1-arylpirazolidines, which, in turn, were obtained by the reduction of the corresponding oxo compounds. The literature contains data [4] regarding the preparation of 1-phenylpyrazolidines by the reduction of the corresponding 5-pyrazolidones, but Bouchet et al. obtained a mixture of pyrazolidine and the corresponding Δ^2 -pyrazoline in a ratio of 2:1.

In recent years, the isomeric 1-aryl-3-pyrazolidones have become accessible; these are formed by the reaction of the corresponding arylhydrazines with α,β -unsaturated acids or their derivatives (see, for example, [5]). The literature does not contain any data regarding the reduction of 1-aryl-3-pyrazolidones.

We have shown that the reduction of 1-aryl-3-pyrazolidones and the isomeric 1-aryl-5-pyrazolidones with lithium aluminum hydride in ether or tetrahydrofuran at a reagent molar ratio of 1:1.5-2 leads to 40 to 70% yields of 1-arylpirazolidines. The yield of 1,5-diphenylpyrazolidine falls to 25% only in the case of 1,5-diphenyl-3-pyrazolidone, probably due to its poor solubility in ether.

The nature of the substituent in the phenyl ring (alkyl or halogen) does not affect the yields of 1-arylpirazolidines. The 1-arylpirazolidines formed are very readily oxidized to the corresponding 1-aryl- Δ^2 -pyrazolines, traces of which are detected in the reaction products by means of thin-layer chromatography.

The percentage of 1-arylpirazolines in the reaction products varies markedly as a function of the subsequent treatment of the reaction mass after reduction. Thus the percentage of 1-aryl-2-acetylpyrazolidine reached 78-80% compared with 18-20% of the corresponding pyrazoline, according to gas-liquid chromatography, if the reaction mass was acetylated with acetic anhydride and distilled after decomposition of excess lithium aluminum hydride, extraction with ether or benzene, prolonged drying of the extract (12-24 h), and removal of solvent by distillation. If, however, the ether extract was treated with excess acetic anhydride immediately after separation, the percentage of 1-arylpirazolines in the mixture obtained does not exceed 3-8%, and, in a number of experiments, these compounds were not detected at all. Storage of the 1,5-diphenylpyrazolidine base for two weeks at 0° led to complete oxidation and quantitative formation of the corresponding Δ^2 -pyrazoline, which was identified by a mixed-melting-point determination with an authentic sample of 1,5-diphenyl- Δ^2 -pyrazoline and from the IR spectra. Attempts to distill 1-(p-tolyl)pyrazolidine in an air stream at 12 mm led to complete conversion to 1-(p-tolyl)- Δ^2 -pyrazoline; it can be distilled without appreciable change only under argon at 3-5 mm. This sort of dependence of the percentage of 1-arylpirazolines in the reaction mass on the time and method of treatment and storage makes it possible to as-

*See [1, 2] for communications XLVI and XLVII.

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TABLE 1. 1-Arylpyrazolidines

Pyrazolidine	Bp (mm) or mp	Empirical formula	Found, %		Calcu- lated, %		Iso- lation meth- od	Yield, %
			C	H	C	H		
1-Phenyl-2-acetyl*	152—156 (6)†	C ₁₁ H ₁₄ N ₂ O	—	—	—	—	B, C	54,0 (52)‡
1-Phenyl-4-methyl*	134—136 (8)	C ₁₀ H ₁₄ N ₂	74,01	8,29	74,04	8,65	A	70,0 (65)‡
1,5-Diphenyl	212—214 (15)	C ₁₅ H ₁₆ N ₂	80,43	7,16	80,40	7,15	A	25,0
1-(o-Tolyl)-2-acetyl	166—168 (7)	C ₁₂ H ₁₆ N ₂ O	70,94	7,36	70,58	7,84	C	48,0
1-(m-Tolyl)-2-acetyl	178—181 (9)	C ₁₂ H ₁₆ N ₂ O	70,64	8,02	70,58	7,84	C	53,0
1-(p-Tolyl)-2-acetyl	163—165 (6)	C ₁₂ H ₁₆ N ₂ O	70,63	7,73	70,58	7,84	B, C	51,0
1-(o-Chlorophenyl), hydrochloride	208—210	C ₉ H ₁₁ ClN ₂ · HCl	49,24	5,57	49,31	5,49	D	39,4
1-(m-Chlorophenyl)-2- acetyl	73—77	C ₁₁ H ₁₃ ClN ₂ O	58,82	5,94	58,96	5,82	C	43,0
1-(p-Chlorophenyl), hy- drochloride	217—219	C ₉ H ₁₁ ClN ₂ · HCl	49,37	5,22	49,31	5,49	D	49,5
1-(p-Chlorophenyl)-4- methyl, hydrochloride	205—206	C ₁₀ H ₁₃ ClN ₂ · HCl	51,51	6,06	51,50	6,02	D	62,0
1-(o-Bromophenyl)-4- methyl, hydrochloride	190—192	C ₉ H ₁₁ BrN ₂ · HCl	40,91	4,66	40,98	4,55	D	36,0
1-(o-Bromophenyl)-4- methyl, hydrochloride	187—189	C ₁₀ H ₁₃ BrN ₂ · HCl	42,67	5,17	42,97	5,05	D	39,0

*Commercial "Phenidone" and "Methylphenidone" preparations were used as the starting compounds.

†bp 231–232° (110 mm) [7].

‡The numbers in parentheses are the yields for the reduction of the corresponding 5-pyrazolidones.

sume that the formation of Δ^2 -pyrazolines is a secondary process associated with oxidation of the initially formed 1-arylpyrazolidines.

The reduction of 5-pyrazolidones proceeds without any substantial differences. For example, by reducing 1-phenyl-4-methyl-3-pyrazolidone and 1-phenyl-4-methyl-5-pyrazolidone under the same conditions and by treating the ether extract with excess acetic anhydride immediately after decomposition of the reaction mass we obtained the same yield (~70%) of 1-phenyl-2-acetyl-4-methylpyrazolidine. According to gas-liquid chromatography, the percentage of the corresponding pyrazoline in both samples was 4–6%. The low yields in several experiments are explained by the fact that starting oxo compounds which are slightly soluble in ether are therefore partially recovered unchanged from the reaction mixtures.

EXPERIMENTAL

The starting 1-arylpyrazolidones were obtained by the well-known methods in [4] starting from the corresponding arylhydrazines and esters of α,β -unsaturated acids. Sodium butoxide was used as the condensing agent.

1-(o-Bromophenyl)-3-pyrazolidone. o-Bromophenylhydrazine [18.7 g (0.1 mole)] was added to a solution of 3 g (0.13 mole) of sodium metal in 80 ml of absolute n-butanol, and 12.9 g (0.15 mole) of methyl acrylate was added dropwise with vigorous stirring. The reaction mixture was refluxed on an oil bath for 5 h, cooled rapidly to room temperature, and the reaction mixture was dissolved in 100 ml of water with stirring. It was neutralized with 50% acetic acid to pH 6. The organic layer was separated and washed with water. The resulting precipitate was filtered and washed with a small amount of ether. Recrystallization from aqueous alcohol gave 15.6 g (68%, based on the hydrazine) of 1-(o-bromophenyl)-3-pyrazolidone with mp 197–199°. Found %: C 44.68; H 3.87. C₉H₉BrN₂O. Calc. %: C 44.65; H 3.72.

4-Methyl-1-(o-bromophenyl)-3-pyrazolidone. This was similarly obtained in 53% yield from o-bromophenylhydrazine and methyl methacrylate and had mp 167–169° (from aqueous alcohol). Found %: C 47.08; H 4.61. C₁₀H₁₁BrN₂O. Calc. %: C 47.09; H 4.33.

TABLE 2. Percentage of 1-Arylpyrazolidines and 1-Arylpyrazolines in the Products of the Reduction of 1-Arylpyrazolidones According to Gas-Liquid Chromatography

Starting pyrazolidones	Pyrazolidines obtained	Workup method	Pyrazolidine, %	Pyrazoline, %
1-Phenyl-3-pyrazolidone	1-Phenyl-2-acetylpyrazolidine	B	85	15
		C	92.3	7.7
1-Phenyl-5-pyrazolidone		C	98	2
1-Phenyl-4-methyl-3-pyrazolidone	1-Phenyl-4-methyl-2-acetylpyrazolidine	C	96	4
1-Phenyl-4-methyl-5-pyrazolidone		C	100	0
1-(o-Tolyl)-3-pyrazolidone	1-(o-Tolyl)-2-acetylpyrazolidine	C	100	0
1-(m-Tolyl)-3-pyrazolidone	1-(m-Tolyl)-2-acetylpyrazolidine	C	100	0
1-(p-Tolyl)-3-pyrazolidone	1-(p-Tolyl)-2-acetylpyrazolidine	B	79	21
		C	93.5	6.5
1-(p-Chlorophenyl)-2-acetyl-3-pyrazolidone	1-(p-Chlorophenyl)-2-acetylpyrazolidine	B	77	23

Reduction of 1-Aryl-3-pyrazolidones. A suspension of 0.15 mole of lithium aluminum hydride in 100 ml of absolute ether was added gradually to 0.075 mole of 1-aryl-3-pyrazolidone in 150 ml of absolute ether or tetrahydrofuran. The mixture was heated for 2.5-3 h. The reaction mass was decomposed successively with 20 ml of ethyl acetate and 20 ml of water. The inorganic precipitate was filtered and washed thoroughly with ether. Various methods were used to work up the reaction mass.

A) The ether extract was dried with anhydrous sodium sulfate for 12-24 h, the ether was removed by distillation, and the residue was vacuum-distilled under argon.

B) After drying, the ether was removed by distillation, the residue was treated with excess acetic anhydride, and the mixture was refluxed for 2 h. Excess anhydride was removed by distillation, and the residue was vacuum-distilled.

C) A large excess of acetic anhydride was added carefully to the crude ether solution, the ether was removed by distillation, and the residual mass was refluxed for 2 h. The acetic anhydride was removed by distillation, and the residue was vacuum-distilled.

D) A stream of dry HCl was bubbled through the crude ether solution, and the resulting precipitate was filtered and washed with ether. The hydrochloride obtained was recrystallized from absolute alcohol.

A number of 1-aryl-5-pyrazolidones and 1-aryl-3-pyrazolidones with various substituents in the phenyl ring were reduced via the method presented above. The 1-arylpyrazolidines obtained by reduction were isolated in the form of acetyl derivatives [via methods (A), (B), and (C)] or hydrochlorides [via method (D)]. The hydrochlorides could be completely freed from traces of 1-arylpyrazolines by recrystallization. The acetyl derivatives of the 1-arylpyrazolidines were generally liquids which formed azeotropic mixtures on distillation with 1-arylpyrazolines. The R_f values of the 1-aryl-2-acetylpyrazolidines ranged from 0.15 to 0.35 during chromatography in a thin layer of aluminum oxide (activity II according to Brockmann) in a benzene-cyclohexane-methanol (25:25:1) system, while the 1-arylpyrazolines in the same systems had R_f values from 0.75 to 0.80; this made it possible to readily separate them preparatively in a column filled with aluminum oxide.

The yields and constants of the compounds obtained are presented in Table 1. The purity of the compounds obtained was monitored by chromatography and IR spectroscopy.

The IR spectra were obtained with a UR-20 spectrometer.

The percentage of acetylpyrazolidines in the reaction mixture was determined with an SKB-4 chromatograph with a flame-ionization detector and a column 2-m long and 3 mm in diameter with polypropylene glycol sebacate on Cellite-545 as the packing at a column temperature of 198° and a gas carrier (nitrogen) flow rate of ~ 5 liter/h.

The gas-liquid chromatography data for the percentage of 1-aryl-2-acetylpyrazolidines and 1-aryl-pyrazolines in the reaction mixture as a function of the workup methods are presented in Table 2.

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