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SYNTHESIS OF 1-ARYL-5-CHLOROPYRAZOLES

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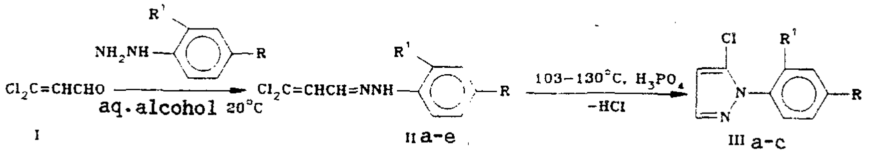
UDC 547.778.4'556.4'381.07

A method for obtaining 1-aryl-5-chloropyrazoles with vacant 3 and 4 positions by cyclization of 3,3-dichloro-2-propenal arylhydrazones is proposed.

1-Arylpyrazole derivatives are widely used as biologically active substances [1-3]. 1-Aryl-5-chloropyrazoles, the chlorine atom in which is capable of undergoing nucleophilic substitution [2, 4], while the vacant 4 position ensures the case of electrophilic substitution [3], are interesting intermediates for obtaining them.

1-Aryl-5-chloropyrazoles are usually obtained from other pyrazole derivatives. Thus 1-phenyl-5-chloropyrazole was obtained by decarboxylation of the corresponding 4-carboxylic acid or by treatment of 1-phenyl-5-pyrazolone with phosphorus oxychloride [5]. In [2, 4] 1-aryl-5-chloropyrazoles were obtained by nonaqueous diazotization of 5-amino-1-arylpyrazoles by means of butyl nitrite or nitrosyl chloride.

It seemed expedient to us to investigate the possibility of the synthesis of 1-aryl-5-chloropyrazoles with vacant 3 and 4 positions by cyclization of arylhydrazones of the accessible 3,3-dichloro-2-propenal (I) via the scheme



II III a $R=H$, b $R=Me$, c,d $R=NO_2$; a—c $R'=H$, d $R'=NO_2$, e $R'=COOH$

This sort of reaction has been realized only in the cyclization of 2,3,3-trichloro-2-propenal phenylhydrazone, as a result of which 1-phenyl-4,5-dichloropyrazole was obtained in 4.2% yield [6].

Aldehyde I was obtained by the method in [7] on the basis of the free-radical addition of CCl_4 to vinyl butyl ether. Hydrazones II (Table 1) were obtained in > 80% yields (the products darken under the influence of light and on contact with air oxygen).

The cyclization of hydrazones II to 1-aryl-5-chloropyrazoles (Table 1) was carried out in 85% phosphoric acid at 103-130°C, and the products were obtained in 22-39% yields. Xylene, DMSO, DMF, sulfolane, ethanol, aqueous ethanol (in pure form or with added acidic or basic catalysts such as potassium carbonate, sodium hydrocarbonate, and p-toluenesulfonic acid), acetic acid, a mixture of acetic anhydride with acetic acid, and 30% aqueous methane-

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TABLE 1. Characteristics of 3,3-Dichloro-2-propenal Arylhydrazones II and 1-Aryl-5-chloropyrazoles III

Compound	Empirical formula	mp,** °C [bp, °C (mm)]	M^+ (^{35}Cl)	PMR spectrum, ppm (SSCC, J, Hz)					Yield, %	
				pyrazole fragment		aryl fragment	aliphatic fragment		A	B
				H^3	H^4		C^1H	C^2H		
IIa	$C_9H_8Cl_2N_2$	89...91 (82...83 [14])	214	—	—	6,87...7,06; 7,22...7,34 (5H, m)	7,50 (d, $J=8,9$)	6,68	83	
IIb	$C_{10}H_{10}Cl_2N_2$	104,5...106,5	228	—	—	2,30 (Me, s); 6,93 (2H); 7,09 (2H) (d, $J=7,8$)	7,47 (d, $J=9,1$)	6,67	85	
IIc	$C_9H_7Cl_2N_3O_2$	206...210	259	—	—	7,0...7,1; 8,1...8,3 (4H, m)	7,65 (d, $J=9,1$)	6,69	87	
IId	$C_9H_6Cl_2N_4O_4$	165...170 (156 [13])	304	—	—	7,95 (1H, d, $J=9,7$); 8,35 (1H, dd, $J=9,7$ and 2,5); 9,13 (1H, d, $J=2,5$)	7,97 (d, $J=9,2$)	6,76	90	
IIe	$C_{10}H_8Cl_2N_2O_2$	199,5...201,0	—	—	—	6,80...6,90 (1H, m); 7,40...7,55 (2H, m); 7,80...7,95 (1H, m)	7,90 (d, $J=9,0$)	6,86	90	
IIIa	$C_9H_7ClN_2$	{105...106 (3); 60 (0,05) [15]}	178	7,67 (d, $J=2$)	6,39	7,35...7,60 (5H, m)	—		34	
IIIb	$C_{10}H_9ClN_2$	{122...124 (6)}	192	7,67 (d, $J=2$)	6,38	2,40 (Me, s); 7,28 (2H, d, $J=8$); 7,44 (2H, d, $J=8$)	—			38
IIIc	$C_9H_6ClN_3O_2$	111,5...112,5	223	7,74 (d, $J=2$)	6,48	7,82...7,92 (2H, m); 8,10...8,30 (2H, m)	—			23

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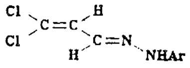
*Compound IIIa had n_D^{20} 1.5880; IIIb had n_D^{20} 1.5790.

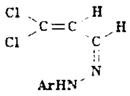
**The compounds were recrystallized: IIa, b from hexane, IIc from aqueous MeOH, and IIe and IIIc from aqueous EtOH.

sulfonic acid solution were also tested as reaction media. Attempts were made to accomplish the cyclization of the hydrazones in the fused state. In all of the enumerated cases pyrazoles III either were not formed or their yields were lower than when phosphoric acid was used.

The data in [8, 9] on the structures of N,N-dimethylhydrazones and 2,4-dinitrophenylhydrazones of unsaturated aldehydes provide evidence in favor of the s-trans,syn structure of these compounds, since in the PMR spectra the spin-spin coupling constants (SSCC) of the "aldehyde" and olefinic protons are ~ 10 Hz. Hydrazones IIa-d (SSCC ≈ 9 Hz) obtained by us evidently have the same structure.



S-trans-syn



S-cis,anti

Prior transition from the s-trans to the s-cis conformation and from the syn configuration to the anti configuration is evidently necessary for accomplishing the intramolecular condensation of hydrazones IIa-d. The first transition requires an energy expenditure on the order of 20 kJ/mole [10], while the second transition requires an expenditure on the order of 90-130 kJ/mole [11, 12] (the latter transition is catalyzed by acids [12]). In principle, transitions of this sort are not required for intermolecular condensation. The validity of the latter assumption is confirmed indirectly by the formation of large amounts of resinification products in the cyclization of hydrazones IIa-c. In the cyclization of hydrazones IId, e we did not detect the formation of the corresponding pyrazoles. In these cases cyclization is evidently additionally hindered by the existence of a hydrogen bond [13] between the NH proton and the ortho substituent of the aryl ring.

Thus the reasons for the moderate yields of pyrazoles III are the unfavorable geometry of hydrazones II and, possibly, the relatively low reactivity of the dichlorovinyl group.

EXPERIMENTAL*

The PMR spectra of solutions of the compounds in CDCl$_3$ were recorded with a Bruker WM-250 spectrometer (250 MHz). The mass spectra were obtained with a Varian MAT CH-6 spectrometer at an ionization energy of 70 eV with direct introduction of the samples into the ion source. The melting (decomposition) points were determined with a Boetius microscope stage. The course of the reaction and the purity of the compounds were monitored on Silufol UV-254 plates in a hexane–ethyl acetate system (volume ratio from 1:1 to 4:1).

The characteristics of the synthesized II and III are presented in Table 1. Satisfactory results of elementary analysis for the C, H, Cl, and N content were obtained for II and III.

3,3-Dichloro-2-propenal (I). This compound was obtained by the method in [7] and had bp 125-126°C and n_D^{20} 1.5070 (bp 124-125°C and n_D^{20} 1.5067 [7]). PMR spectrum: 6.41 (1H, d, 2-H, $^3J_{21}$ = 7.9 Hz), 9.84 ppm (1H, d, 1-H, $^3J_{12}$ = 7.9 Hz).

3,3-Dichloro-2-propenal Arylhydrazones (IIa-d). A solution of 0.12 mole (14.9 g) of 3,3-dichloro-2-propenal in 120 ml of ethanol was added dropwise with stirring at ~ 20°C to a solution of 0.12 mole (16.3 g) of AcONa·3H$_2$O and 0.12 mole of the arylhydrazine hydrochloride in a mixture of 130 ml of water and 130 ml of ethanol, after which the mass was stirred for 3 h (a precipitate formed ~ 1 h after the addition) and stored overnight in a refrigerator. The solid product was removed by filtration, washed with a small amount of aqueous ethanol, and dried.

1-Aryl-5-chloropyrazoles (IIIa-c). A) An 18.8-mmole sample of hydrazone II was dissolved in 60 ml of 85% phosphoric acid, and the solution was heated until hydrogen chloride evolution began (103-130°C). The mixture was maintained at this temperature until hydrogen chloride evolution ceased (from the absence of the starting hydrazone according to TLC), after which it was cooled and poured into 10% NaOH (pH 7-8), and the mixture was extracted with

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*With the participation of B. P. Fabrichnyi and E. A. Sgibneva.

ether. The extracts were dried with $MgSO_4$, the solvent was removed, and pyrazole III was isolated by chromatography of the residue with a column packed with SiO_2 [elution with acetone–heptane (1:4) or hexane–ethyl acetate (4:1)].

B) A 46.5-mmole sample of hydrazone II was added slowly with stirring to 64 ml of heated (to 60°C) 85% phosphoric acid, after which the temperature was raised to 130°C, and the mixture was maintained at this temperature for 1.5 h until hydrogen chloride evolution had ceased completely. It was then cooled and transferred to a flask for steam distillation, and 0.5-0.7 liter of distillate was removed by distillation and extracted with ether. The extracts were dried with $MgSO_4$, the ether was removed, and pyrazole III was isolated by fractionation (or crystallization) of the residue in vacuo.

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