NUCLEOPHILIC SUBSTITUTION REACTIONS IN 4-HALONITRO-PYRAZOLECARBOXYLIC ACIDS

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The reaction of 4-bromo-1-methyl-3-nitropyrazole-5- and 4-bromo-1-methyl-5-nitropyrazole-3-carboxylic acids with arylamines in aqueous solution in the presence of monovalent copper salts leads to the formation of 4-arylamino- and 4-hydroxy substituted nitropyrazolecarboxylic acids.

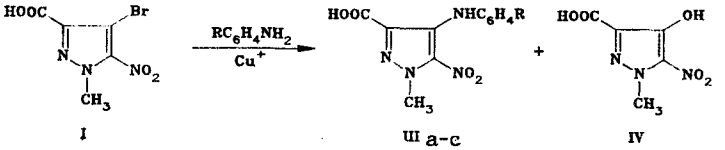
Nucleophilic substitution reactions in the 4-halopyrazole series has not been adequately studied. It is known that as a consequence of the high nucleophilicity of the 4 position of the heterocycle, 4-halopyrazoles are extremely inert in reactions of this sort [1]. Nucleophilic substitution of the halogen in these compounds is possible only if nitro groups are present in neighboring positions of the pyrazole ring [2, 3] or if copper compounds are used as a catalyst [4, 5].

The activating effect of a carboxyl group on the mobility of a halogen atom in 4-halopyrazolecarboxylic acids in the presence of a copper catalyst was noted in [6] but a systematic study of such reactions was not carried out.

We have established [7] that the reaction of 4-halo-1-methyl-pyrazole-3- and 5-carboxylic acids with aromatic amines in the presence of a copper catalyst leads to the formation of 4-arylamino substituted pyrazoles and is accompanied by reductive dehalogenation. In this paper, we consider nucleophilic substitution reactions in the 4-halo-1-methylnitropyrazolecarboxylic acid series.

The introduction of a nitro group in the 3 or 5 position of a molecule of 4-halo-1-methylpyrazole-3- or -5-carboxylic acid significantly increases the rate of substitution of the halogen atom in reactions of these compounds with aromatic amines. The reaction of 4-bromo-1-methyl-5-nitropyrazole-3-carboxylic acid (I) and of 4-bromo-1-methyl-3-nitropyrazole-5-carboxylic acid (II) with aniline takes place even at 60-70°C while the substitution of the halogen atom in 4-bromopyrazolecarboxylic acids which do not contain nitro groups requires prolonged heating at 100°C [7]. As in the case of 4-halopyrazolecarboxylic acids, nucleophilic substitution in compounds I and II occurs only in the presence of monovalent copper salts, but no reductive dehalogenation is observed in this case. Divalent copper salts do not posses any catalytic activity in this reaction.

In the reaction of compounds I and II with arylamines in aqueous solution, the replacement of the halogen with a hydroxyl group was observed along with the formation of the 4-arylamino substituted compound. This was not noted in the case of 4-halopyrazolecarboxylic acids [7].



I III a-c IV

III a R=H; b R=2-OCH3; c R=4-NO2

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TABLE 1. Substituted 1-Methylpyrazolecarboxylic Acids

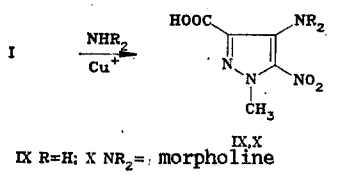
Compound	T_{mp},* °C	PMR spectrum, δ, ppm		Found, %			Empirical formula	Calculated, %			Yield, %
		CH_3	other protons	C	H	N		C	H	N	
IIIa	190—191	4,25	7,29 (5H, m, arom.)	49,8	4,2	20,9	$C_{11}H_{10}N_4O_4$	50,4	3,8	21,4	71
IIIb	227—228	4,20	3,76 (s, OCH_3), 6,62 (4H, m, arom.)	49,1	3,9	19,0	$C_{12}H_{12}N_4O_5$	49,3	4,1	19,2	80
IIIc	184—186	4,23	6,93 (2H, d, 2′-H and 6′-H), 7,96 (2H, d, 3′-H and 5′-H)	42,8	2,6	20,0	$C_{11}H_9N_5O_6$	43,0	2,9	19,8	56
IV	135—137	4,06	—	31,9	2,7	22,3	$C_5H_5N_3O_5$	32,0	2,7	22,5	69
V	143—145	4,14	7,12 (5H, m, arom.)	50,5	4,1	21,2	$C_{11}H_{10}N_4O_4$	50,4	3,8	21,4	65
VI	183—184	4,02	—	32,2	2,7	22,1	$C_5H_5N_3O_5$	32,0	2,7	22,5	50
IX	215—216	4,18	—	31,9	4,1	29,7	$C_5H_6N_4O_4$	32,4	3,7	30,1	84
X	156—158	4,21 (in $CDCl_3$)	3,17 (4H, m, CH_2), 3,80 (4H, m, CH_2)	41,6	4,6	22,2	$C_9H_{13}N_4O_5$	42,0	5,0	21,8	77

*Compound IIIb was crystallized from methanol, compound X from water.

The amount of 4-hydroxy derivative, IV, obtained is determined by the ratio of the rates of the two parallel reactions taking place and depends primarily on the basicity of the aromatic amine in the reaction (in the reaction of compound I with o-anisidine, the yield of compound IV was 8%, and with p-nitroaniline, 24%); in the absence of an arylamine, the reaction proceeds solely to the formation of the 4-hydroxy derivative.

The nonequivalency of the $C_{(4)}$—$C_{(5)}$ and $C_{(4)}$—$C_{(3)}$ bonds in the pyrazole ring [8] causes the activation effect of the nitro group to differ in the 3-nitro- and 5-nitro-4-halopyrazolecarboxylic acids in nucleophilic substitution reactions. This is most clearly shown in the different reactivities of 1-methyl-5-nitro-4-chloropyrazole-3-carboxylic acid (VII) and 1-methyl-3-nitro-4-chloropyrazole-5-carboxylic acid (VIII). Thus, compound VII on boiling with o-anisidine for 18 h gives 4-arylaminopyrazole IIIb in 67% yield while acid VIII under similar conditions does not react.

In distinction to the reactions of 4-halopyrazolecarboxylic acids with ammonia and aliphatic amines, which lead to unsatisfactory results because of the high sensitivity of the 4-amino derivatives being formed to atmospheric oxygen, when compound I reacts with ammonia or morpholine, the corresponding 4-aminonitrosubstituted IX and X are obtained in yields of 84% and 77%, respectively.



IX R=H; X NR_2= morpholine

EXPERIMENTAL

The PMR spectra were measured on a Tesla BS-497 instrument (100 MHz, HMDS internal standard) in DMSO-D_6. The mass spectra of compounds IV and VI were obtained on an MX-1309 instrument with an ionization potential of 70 eV and an ionization chamber temperature of 150°C.

The 4-halonitropyrazolecarboxylic acids I, II, VII, and VIII were obtained according to [9].

The characteristics of compounds IIIa-c, IV-VI, IX and X are given in Table 1.

4-Arylamino-1-methyl-5-nitropyrazole-3-carboxylic Acids (IIIa-c). A mixture of 2.5 g (0.01 mole) of acid I, 0.011 mole of the corresponding aniline, and 0.4 g CuBr are heated in

100 ml of a 5% soda solution for 4 h at 60-70°C. The reaction mixture is cooled and the precipitate of copper salt of compound IV filtered off. The filtrate is acidified with HCl and the precipitate filtered off and crystallized from 50% acetic acid. The 4-arylamino-1-methyl-5-nitropyrazolecarboxylic acids IIIa-c were obtained analogously.

1-Methyl-3-nitro-4-phenylaminopyrazole-5-carboxylic acid (V) is obtained in the manner described above from acid II and anoline at 70°C over a 6-h period. The product is purified by reprecipitation with subsequent crystallization from 1:1 aqueous ethanol.

1-Methyl-4-hydroxy-5-nitropyrazole-3-carboxylic acid (IV). 2.5 g (0.01 mole) of compound I and 0.4 g CuBr in 50 ml of 5% soda solution are heated at 80°C for 8 h, the mixture is cooled, and the precipitate filtered off and dissolved in water with heating. This solution is acidified to pH 4-5 by the addition of H_2SO_4 and the resulting precipitate is filtered off and crystallized from water. Yield, 1.3 g. M^+ 187.

1-Methyl-4-hydroxy-3-nitropyrazole-5-carboxylic Acid (VI) is obtained in an analogous way to compound IV.

4-Amino-1-methyl-5-nitropyrazole-3-carboxylic acid (IX). 2.5 g (0.01 mole) of acid I and 0.4 g CuBr are heated in aquous ammmonia 30 ml of 25% to 100°C in an autoclave and kept at this temperature for two hours, then cooled and evaporated down to a volume of 10 ml and acidified with acetic acid to pH 4-5. The precipitate is filtered off and recrystallized from acetic acid. Yield, 1.56 g.

1-Methyl-4-morpholino-5-nitropyrazolecarboxylic acid (X). 2.5 g (0.01 mole) of compound I and 0.4 g CuBr in 50 ml of 30% aqueous morpholine solution are heated for two hours at 70°C, cooled, acidified to pH 4-5 with acetic acid, and extracted with chloroform. After distilling off the solvent, 1.98 g of compound X are obtained.

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