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CONDITIONS FOR THE SELECTIVE CONVERSION OF QUATERNARY 3-ANILINO-1,5-DIMETHYLPYRAZOLIUM SALTS INTO 3-ANILINO-1,5-DIMETHYLPYRAZOLE

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The possibility has been studied of converting quaternary 3-anilino-1,5-dimethylpyrazolium salts into 3-anilino-1,5-dimethylpyrazole, the first representative of the 1-alkyl-3-arylaminopyrazoles. The dependence of the reaction direction on the nature of the substituent at position 2 has been clarified. The most effective result was obtained with a cyanoethyl substituent. On boiling the initial salt with aqueous ammonia the target product is isolated in quantitative yield. Syntheses of the initial salts are described. C-Sulfonation was detected on interacting 3-anilino-1-benzoyl-3-methylpyrazole and dimethyl sulfate, with the formation of p-(3-amino-1,2,5-trimethylpyrazolio)benzenesulfonate.

Keywords: hydrazines, pyrazoles, dehaloalkylation, quaternization, selectivity, C-sulfonation, cyanoethylation.

Arylamino-substituted pyrazoles have been known for more than a hundred years [1]. Up to the present time efficient pesticides [2], antipyretics [3], disperse dyestuffs [4], and anti-inflammatory [5] and hypotensive [6] agents have appeared among their derivatives. However 1-alkyl-3-arylaminopyrazoles have not been described until now. Their synthesis is expedient for the search for new substances of practical use, but problematical from a methodological point of view. In particular, according to the data of the Michaelis school [7-9], on thermal dehalogenalkylation of quaternary 3-arylaminopyrazolium salts the alkyl group bound to the ring nitrogen atom in position 1 is split off and 5-arylaminopyrazoles are formed. We assumed that this reaction may be converted into a method of synthesizing 3-arylaminopyrazoles. A necessary condition must probably be the presence of a readily leaving substituent in position 1 of the initial salts. Experimental verification of the hypothesis and selection of a suitable substituent has been carried out on quaternary 3-anilino-1,5-dimethylpyrazolium salts and is presented in this work.

First we contemplated synthesizing and testing quaternary pyrazolium salts containing such readily leaving groups as benzoyl in position 1. The interaction of acetothioacetanilide (**1**) and benzoylhydrazine (**2a**) with the formation of the initial 5-anilino-1-benzoylpyrazole (**3a**) has been described by us previously [10]. Quaternization of compound **3a** with dimethyl sulfate proceeds, as we found, ambiguously and did not stop at the stage of forming the expected quaternary salt **4a**. The subsequent conversion is probably effected through a series of intermediate compounds **5-7**. After treatment of the reaction mixture with aqueous ammonia a compound with a betaine structure **8** was obtained in low yield. The result indicates that the benzoyl group is

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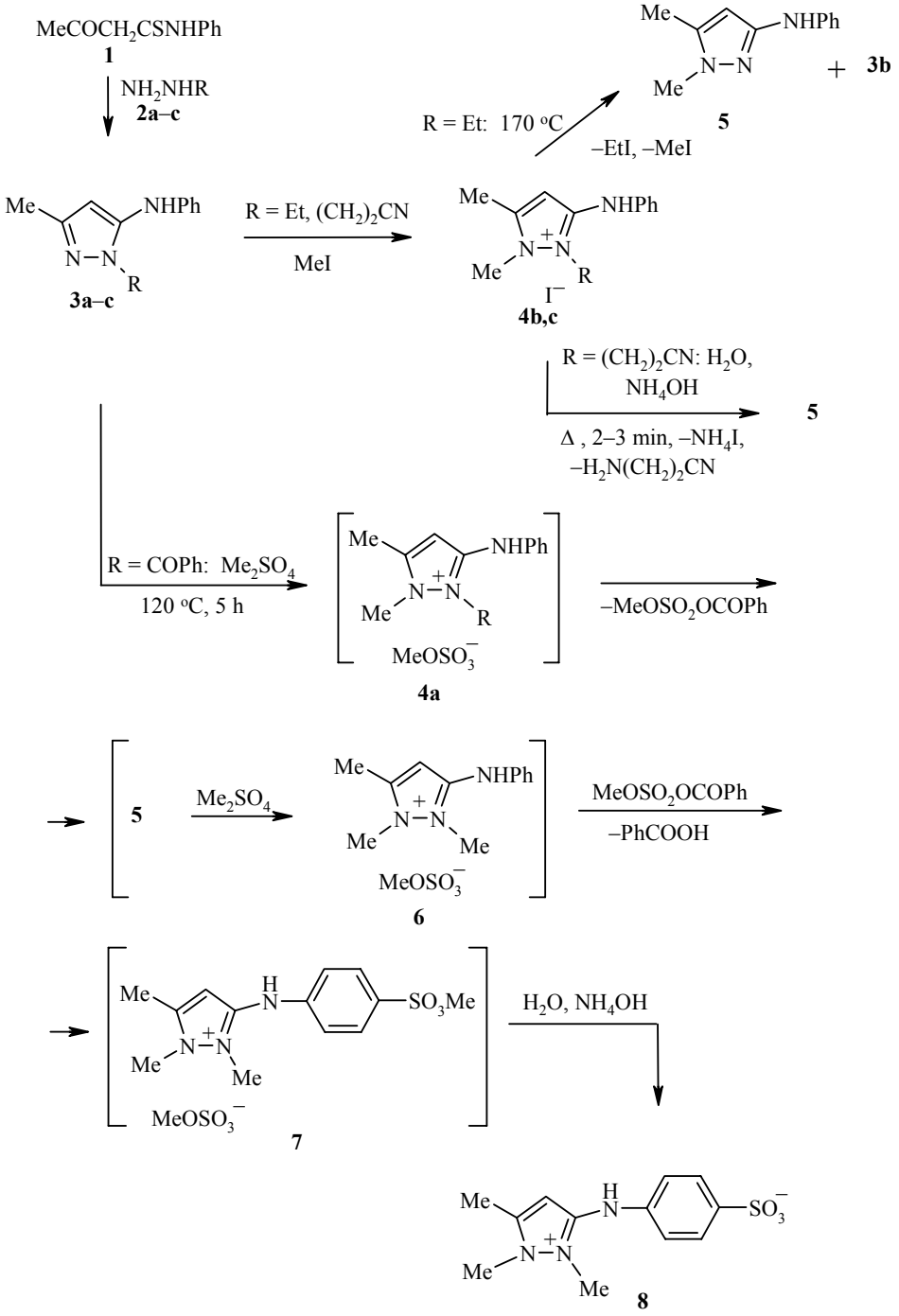
unsuitable for the solution of the problem being investigated. It leaves the nitrogen atom even under the conditions for obtaining the initial salt under the action of the nascent, low reactivity nucleophile, methylsulfate anion. Probably a mixed anhydride of methyl sulfate and benzoic acid is formed, which then sulfonates the aniline fragment at the *para* position. The possibility also appears of methylating the second ring nitrogen atom, which has been carried out.



2– 4 a R = COPh, **b** R = Et, **c** R = $(CH_2)_2CN$

Proceeding from the results presented it was necessary to test more stable substituents. Ethyl and cyanoethyl were tested. By interacting reactant **1** with ethyl- and cyanoethylhydrazines **2b,c** by the procedure of [11] we obtained the corresponding previously undescribed pyrazoles **3b,c**. These compounds were more nucleophilic than the N-benzoyl analog **3a** mentioned above. Quaternization took place under the action of an excess of methyl iodide on extended refluxing in acetone and gave the starting salts **4b,c** in high yield.

The ethyl-substituted salt **4b** underwent dehaloalkylation on refluxing in diglyme. However the process occurred nonselectively with fission of ethyl and methyl iodides. As was established by ^{1}H NMR, a mixture was formed of the desired compound **5** and the ethylpyrazole **3b** mentioned already in a molar ratio of 2:3. The mixture was not successfully separated either by crystallization or chromatographically (compounds **4c** and **5** have practically coincident R_f values).

As we revealed, the cyanoethyl group possesses optimal properties for an efficient solution to the problem being investigated. In difference to benzoyl it was retained on obtaining the quaternary salt, and, in difference to ethyl, was readily removed from the salt regioselectively. The reaction occurred on boiling salt **4c** in aqueous ammonia and was complete after 2-3 min. The conversion is probably fission of hydriodic acid and transcyanoethylation. Ammonium iodide and 3-aminopropionitrile, the formation of which must be expected, are soluble in water and do not impede the isolation of the desired product. Compound **5** crystallized from the reaction mixture in practically quantitative yield in an analytically pure state.

The compounds **3b,c**, **4b,c**, **5**, and **8** synthesized by us were colorless crystalline substances. Salts **4b,c** and **8** were soluble in hot water, poorly in cold, and in acetone. The remaining compounds were soluble in acetone, chloroform, and ethyl acetate, worse in alcohol (with the exception of product **5**), and insoluble in hexane and water. On extended storage iodides **4b,c** acquire a yellow color, but the remaining compounds were unchanged.

Pyrazoles **3b,c** and salts **4b,c** were obtained by us by standard methods and their structures were confirmed by the investigations carried out. The formation of betaine **8** was unexpected. This is the first example known to us of C-sulfonation on interaction with dimethyl sulfate. Nonetheless the structure of **8** followed readily from the data of ^{1}H NMR spectra. The chemical shifts of the H-4 proton, and of the protons of the methyl and amino groups linked to the heterocycle were extremely close in size to those detected for the quaternary salts **4b,c**. The appearance of the aromatic protons of the aniline fragment was typical for a 1,4-disubstituted benzene ring. Comparison of the ^{1}H NMR spectra of 3-arylaminopyrazole **5** and 5-arylamino-pyrazoles **3b,c** clearly indicates the energetically more favorable conjugation system between the nitrogen atom of the aniline fragment and the ring C=N bond in the first compound. This is caused by the fact that the conjugation system is one multiple bond shorter. As a result the electron density is increased at the heterocycle and reduced at the extracyclic amino group. The signal of the H-4 proton of compound **5** was displaced by 0.16-0.20 ppm towards high field, but the amino group proton was displaced by 0.29-0.47 ppm towards low field. The appearance of the aromatic protons of the aniline fragment was extremely noteworthy. In compounds **3b,c** and the quaternary salts **4b,c** the extracyclic nitrogen atom exerts an electron-donating influence on the phenyl fragment, and the signals of its protons appeared in the sequence *m*, *o*, and *p* from low to high field. For compound **5** the sequence of the *o*- and *p*-signals was different going towards high field and the signal of the *o*-protons was displaced (compared with compounds **3b,c**) by 0.40-0.50 ppm towards low field. The effect is probably caused by the deshielding effect of the lone pair of electrons of the pyrazole nitrogen atom. Deshielding of the aniline fragment is of course possible only for structure **5** as it exerts maximum effect on the spatially closely disposed *o*-protons.

The selective N-decyanoethylation of pyrazolium salts, shown by us, probably has a general character. In view of the availability of cyanoethylhydrazine [12] this reaction may be used for the directed synthesis of new 1-alkyl-3-arylaminopyrazoles. It is also expedient to study the N-decyanoethylation of a series of 1,2- and 1,3-diazolium salts as a method of synthesis of previously unknown or difficultly available compounds.

TABLE 1. Physicochemical and Spectral Characteristics of Compounds **3b,c**, **4b,c**, **5**, and **8**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	IR spectrum, ν, cm^{-1}	Yield %
		C	H	N			
3b	$C_{12}H_{15}N_3$	71.45 / 71.61	7.56 / 7.51	20.81 / 20.88	113-114	3210 (NH)	67
3c	$C_{13}H_{14}N_4$	69.16 / 69.00	6.14 / 6.24	24.60 / 24.76	121-121.5	2255 (C≡N), 3240 (NH)	75
4b	$C_{13}H_{18}IN_3$	45.55 / 45.49	5.27 / 5.29	12.18 / 12.24	135-136	3225 (NH)	98
4c	$C_{14}H_{17}IN_4$	45.61 / 45.66	4.58 / 4.65	15.18 / 15.22	201-202	2260 (C≡N), 3110 (NH)	97
5	$C_{11}H_{13}N_3$	70.39 / 70.56	7.07 / 7.00	22.40 / 22.44	101-103	3250 (NH)	97
8	$C_{12}H_{15}N_3O_3S$*[2]	51.29 / 51.23	5.45 / 5.37	14.79 / 14.94	345-347	3215, 3490 (NH)	38

* Compounds were crystallized from 2-propanol (**3c**, **4b**), water–2-propanol, 1:2 (**3b**, **4c**), hexane–ethyl acetate, 4:1 (**5**), water–acetic acid, 4:1 (**8**).

*[2] Found, %: S 11.49. Calculated, %: S 11.40.

TABLE 2. ^{1}H NMR Spectra of Compounds **3b,c**, **4b,c**, **5**, and **8**

Compound	Chemical shifts (DMSO-d_6), δ, ppm (*J*, Hz)
3b	1.24 (3H, t, *J* = 7.2, $\underline{CH_3}CH_2$); 2.11 (3H, s, CH_3Het); 3.89 (2H, q, *J* = 7.2, $\underline{CH_2}CH_3$); 5.76 (1H, s, H-4); 6.73 (1H, t, *J* = 7.2, *p*-ptoton C_6H_5); 6.79 (2H, d, *J* = 7.8, *o*-protons C_6H_5); 7.16 (2H, dd, J_1 = 7.2, J_2 = 7.8, *m*-protons C_6H_5); 7.78 (1H, s, NH)
3c	2.12 (3H, s, CH_3Het), 2.96 (2H, t, *J* = 6.3, CH_2CN), 4.15 (2H, t, *J* = 6.3, CH_2N), 5.81 (1H, s, H-4), 6.78 (1H, t, *J* = 7.5, *p*-ptoton C_6H_5), 6.88 (2H, d, *J* = 7.8, *o*-protons C_6H_5), 7.19 (2H, dd, J_1=7.2, J_2 = 7.8, *m*-protons C_6H_5), 7.96 (1H, s, NH)
4b	1.29 (3H, t, *J* = 6.9, $\underline{CH_3}CH_2$), 2.37 (3H, s, CH_3Het), 3.84 (3H, s, CH_3N), 4.42 (2H, q, *J* = 6.9, $\underline{CH_2}CH_3$), 6.25 (1H, s, H-4), 7.14 (1H, t, *J* = 6.9, *p*-ptoton C_6H_5), 7.26 (2H, d, *J* = 7.5, *o*-protons C_6H_5), 7.41 (2H, dd, J_1=6.9, J_2 = 7.5, *m*-protons C_6H_5), 9.26 (1H, s, NH)
4c	2.37 (3H, s, CH_3Het), 3.11 (2H, t, *J* = 6.9, CH_2CN), 3.84 (3H, s, CH_3N), 4.74 (2H, t, *J* = 6.9, CH_2N), 6.27 (1H, s, H-4), 7.15 (1H, t, *J* = 7.6, *p*-ptoton C_6H_5), 7.26 (2H, d, *J* = 7.8, *o*-protons C_6H_5), 7.43 (2H, dd, J_1 = 7.6, J_2 = 7.8, *m*-protons C_6H_5), 9.47 (1H, s, NH)
5	2.18 (3H, s, CH_3Het), 3.60 (3H, s, CH_3N), 5.60 (1H, s, H-4), 6.67 (1H, t, *J* = 7.2, *p*-ptoton C_6H_5), 7.14 (2H, dd, J_1 = 7.2, J_2 = 7.5, *m*-protons C_6H_5), 7.29 (2H, d, *J* = 7.5, *o*-protons C_6H_5), 8.25 (1H, s, NH)
8	2.36 (3H, s, CH_3Het), 3.79 (3H, s, CH_3N), 3.83 (3H, s, CH_3N), 6.30 (1H, s, H-4), 7.08, 7.60 (4H, dd, *J* = 8.4, *p*-C_6H_4), 9.31 (1H, s, NH)

EXPERIMENTAL

The IR spectra were recorded on a UR 20 instrument in KBr disks. The ^{1}H NMR spectra were recorded on a Varian VXR 300 (300 MHz) spectrometer, internal standard was TMS. A check on the progress of reactions and the homogeneity of the compounds synthesized was effected by TLC on Silufol UV 254 plates in the solvent system benzene–ethanol, 9:1 (visualization in UV light).

The characteristics of the synthesized compounds are given in Tables 1 and 2.

1-Substituted 5-Anilino-3-methylpyrazoles (3b,c). A solution of hydrazine **2b** or **2c** (12 mmol) in 2-propanol (2 ml) was added dropwise during 5 min to a boiling solution of compound **1** (1.93 g, 10 mmol) in 2-propanol (3 ml). Boiling was continued for a further 15 min to complete the reaction. The mixture was stirred until crystallization commenced (in the synthesis of compound **3b** the reaction mixture was first diluted with water (5 ml)), then maintained at 15-20°C for 2 h, and at -5°C for 1 h. The solid was filtered off, and washed with aqueous 2-propanol, 1:1.

2-Substituted 3-Anilino-1,5-dimethylpyrazolium Iodides (4b,c). Mixtures of pyrazole **3b** or **3c** (3 mmol), methyl iodide (4.43 g, 30 mmol), and acetone (1.5 ml) were refluxed for 9 or 45 h respectively. After cooling, the solid was filtered off, and washed with acetone. Compound **4b** was recrystallized from 2-propanol. Compound **4c** was obtained in an analytically pure state.

3-Anilino-1,5-dimethylpyrazole (5). A mixture of salt **4c** (0.74 g, 2 mmol) and 20% aqueous ammonia (2 ml) was stirred and refluxed for 2-3 min. Water (2 ml) was then added and the mixture stirred until the resulting oil crystallized. After cooling, the solid was pulverized, filtered off, washed with water, and dried at 80°C.

***p*-(3-Amino-1,2,5-trimethylpyrazolio)benzenesulfonate (8).** A mixture of pyrazole **3a** (1.38 g, 5 mmol) and freshly distilled dimethyl sulfate (1.51 g, 12 mmol) was maintained at 115-120°C for 5 h. After cooling, water (3 ml) and 20% aqueous ammonia (3 ml) were added. The mixture was stirred and refluxed for 2-3 min. After cooling, the solid was filtered off, washed with water, with 2-propanol, and with ether.

Dehaloalkylation of 3-Anilino-2-ethyl-1,5-dimethylpyrazolium Iodide. Compound **4b** (0.2 g) was refluxed in diglyme (1 ml) for 8 h. The solvent was evaporated in the vacuum of a water-jet pump with heating on a boiling water bath. The residue was dissolved in methylene chloride (5 ml) and passed through a column of Al_2O_3 (d = 1 cm, h = 4 cm), eluting with methylene chloride, and discarding eluate in front of the running colorless fraction. The solvent was evaporated. The residue was dried from traces of diglyme in a Fischer pistol at 115°C in a water-jet pump vacuum for 3 h. The oil obtained was dissolved in DMSO-d_6 (1.5 ml) and the ^{1}H NMR spectrum taken. The spectrum was interpreted by comparison with the spectra of compounds **3b** and **5**. The dehaloalkylation product obtained was mainly a mixture of compounds **3b** and **5** in a molar ratio of 3:2 (the composition was estimated from the integrated intensities of the C-methyl group signals).

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