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NEW METHOD FOR THE SULFONATION OF PYRAZOLES

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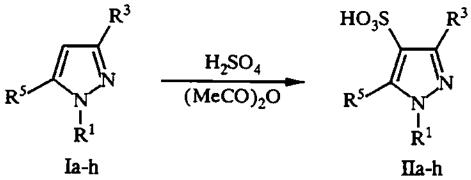
It has been found that pyrazoles are readily sulfonated in position 4 by concentrated sulfuric acid in acetic anhydride.

We had previously shown in [1] that pyrazoles with position 4 of the ring unoccupied can be acylated in this position by refluxing with anhydrides or acid chlorides and by the catalytic action of concentrated sulfuric acid (0.2 moles per mole of pyrazole). In an experiment in which we were attempting to reproduce this reaction with 1-phenyl-3,5-dimethylpyrazole (Ic) and acetic anhydride, we accidentally delayed the heating phase for 1 h, at which time we noted precipitation of a sediment that we first considered to be the sulfate of the pyrazole. However, when this substance was dissolved in water and the solution was made alkaline, it did not release pyrazole; hence it was obvious that the precipitate was a sulfonic acid. The question of the site of entry of the sulfo group was readily resolved by analysis of the PMR spectrum, which did not exhibit the signal of a proton in position 4 of the pyrazole ring at approximately 6 ppm [2] (Table 2). The multiplet of aromatic protons with an intensity amounting to 5 protons was characteristic for monosubstituted phenyl, not 1,4-disubstituted phenyl (see Table 2). In addition, the solubility and constants of the product, 1-phenyl-3,5-dimethylpyrazolesulfonic acid IIc did not coincide with the corresponding values for the known 1-(4-sulfophenyl)-3,5-dimethylpyrazole [3]. Indirect evidence that the sulfo group had entered specifically the pyrazole ring was found in the ready implantation of a sulfo group into the molecule of 1-p-nitrophenyl-3,5-dimethylpyrazole (Ig), since in this case there was no possibility of sulfonation in the phenyl ring.



The reaction proceeded readily with all of the other pyrazoles except the 1,3,5-triphenylpyrazole and 3-methyl-5-ethoxypyrazole. In these cases, no precipitate of sulfonic acid was formed. However, we believe that this simply reflects the good solubility of the corresponding sulfonic acids in the reaction mixture. In the case of 3,5-diphenylpyrazole, the precipitate proved to be the sulfate of 3,5-diphenylpyrazole with mp 225°C, which regenerated 3,5-diphenylpyrazole after treatment with ammonia. Even extended heating (6 h) at 140°C did not result in sulfonation. The role of the acetic anhydride in this reaction evidently comes down to removal of the water that is released upon sulfonation. In the interest of reliability in performing the reaction, we have recommended short-term heating in the general procedure; however, this step can be omitted if necessary.

This method of sulfonation has significant advantages over well-known methods that call for many hours of heating pyrazoles in oleum at temperatures above 100°C [4, 5, 6], followed by a complex procedure for isolation of the free sulfonic acid.

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TABLE 1. Yields and Constants of Sulfonic Acids of Pyrazole Series

Compound	R^1	R^3	R^5	Empirical formula	Found, % / Calculated, %		mp, °C	IR spectrum, ν, cm^{-1}	UV spectrum, λ, nm (log ε)	Yield, %
					C	H				
IIa	H	CH_3	CH_3	$C_5H_9N_2O_3S$	33,72 34,09	5,09 4,55	342...344	1563	214 (4,06)	60,2
IIb	CH_3	CH_3	CH_3	$C_6H_{11}N_2O_3S$	37,24 37,89	5,53 5,26	326...328	1565	216 (4,04)	66
IIc	C_6H_5	CH_3	CH_3	$C_{11}H_{13}N_2O_3S$	51,98 52,38	4,97 4,76	346...348 (decomp.)	1592	247 (4,24)	87
IId	$C_6H_5CH_2$	CH_3	CH_3	$C_{12}H_{15}N_2O_3S$	53,70 54,14	5,55 5,26	240...241	1575	202 (4,08)* 215 (3,28) 251 (2,26) 257 (2,32)	62
IIe	C_6H_5	CH_3	Cl	$C_{10}H_{10}ClN_2O_3S$	44,21 43,96	3,61 3,30	270...271	1555	207 (4,30) 241 (4,16)	93
IIf	C_6H_5†	CH_3	OC_2H_5	$C_{12}H_{15}N_2O_4S$	50,76 51,06	5,13 4,94	156...158	1553	242 (4,13)	79
IIg	n-$NO_2C_6H_4$	CH_3	Cl	$C_{10}H_9ClN_3O_5S$	37,29 37,74	2,88 2,52	313...315	1560	213 (4,28) 292 (4,19)	96
IIh	H	CH_3	Cl	$C_4H_6ClN_2O_3S$	23,90 24,36	2,97 2,54	269...270	1580	244 (4,08)	39

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*λ_{max} 202 — inflection.

†Reaction performed without heating.

TABLE 2. PMR Spectra of Sulfonic Acids of Pyrazole Series, δ, ppm

Compound	R^1	R^3, s	R^5, s
IIa	—	2,28	2,28
IIb	3,78 (s)	2,31	2,26
IIc	7,24...7,42 m	2,28	2,23
IId	CH_2 (s), 5,32 (2H, s), 7,21...7,47 (m)	2,45	2,31
IIe	7,35...7,47 (m)	2,27	—
IIf	7,51...7,71 (m)	2,36	1,26 (t, J = 6 Hz, 4,44 (q, J = 6Hz)
IIg	8,37, 7,88 (AB-syst., J = 7 Hz	2,37	—
IIh	—	2,48	—

EXPERIMENTAL

IR spectra were registered on a Perkin-Elmer 577 spectrometer, with KCl tablets. UV spectra were taken in alcohol in a Specord M-40 spectrophotometer. PMR spectra were registered in a Bruker WM-250 instrument in DMSO-d_6.

General Method for Sulfonation of Pyrazoles. To 0.15 mole of freshly distilled acetic anhydride, 0.1 mole of 96% H_2SO_4 is added while stirring. After this mixture has been cooled, a solution of 0.1 mole of pyrazole in 5 ml of glacial acetic acid is added dropwise while stirring. The reaction mass is left for three days without access of moisture, then refluxed on an oil bath for 0.5 h and left for one day in a refrigerator without access of moisture. The precipitated crystals are filtered off, washed with dry benzene, and dried in a vacuum desiccator over P_2O_5.

The yields and constants are listed in Table 1, and PMR data in Table 2.

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