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N-o-CHLOROPHENYLSULFONYLCARBAMOYL DERIVATIVES OF PYRAZOLES, PYRAZOLINES, AND IMIDAZOLE

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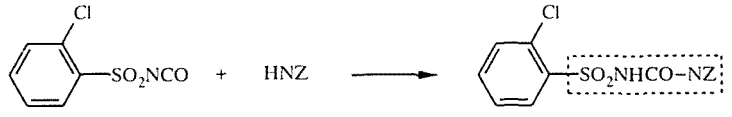
In the reaction of o-chlorosulfonyl isocyanate with imidazole, pyrazoles, and pyrazolines with a free NH group of the nucleus under mild conditions, N-acylation takes place with the formation of a heterocyclic containing, at the nitrogen atom of the nucleus, an o-Cl-$C_6H_4SO_2NHCO-$ group which hydrolyzes very easily in the case of pyrzoles.

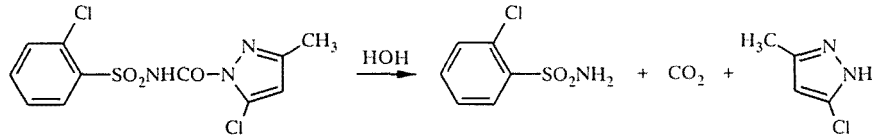
Continuing our studies in the area of sulfonyl ureas [1], we attempted to obtain sulfonyl ureas in which one nitrogen atom of urea belongs to a heterocyclic ring. For this purpose, pyrzoles, pyrazolines, and imidazole, unsubstituted at the nitrogen atom of the nucleus, were introduced into the reaction with o-chlorosulfonyl isocyanate. The reaction took place exothermically under mild conditions and formed N-o-chlorophenylsulfonyl-carbamoyl derivatives of the corresponding heterocyclics I-XI (see Table 1) in satisfactory yields.



I – XI

HNZ) I 3-methyl-5-chloropyrazole; II) pyrazole; III) 3,5-dimethylpyrazole; IV) 3,4,5-trimethylpyrazole; V) 3-methylpyrazole; VI) 3-methyl-5-ethoxypyrazole; VII) 3,5,5-trimethylpyrazoline; VIII) 3-ethyl-5-phenylpyrazoline; IX) 3-tert-butyl-5-phenyl-pyrazoline; X) imidazole; XI) 4,4′-bis(3,5-dimethylpyrazole)

Appreciable difficulties arose in the identification of the acyl pyrazole derivatives obtained because of their high hydrolyzability. Ordinary sulfonyl ureas $Ar-SO_2NHCO-Het$ also hydrolyze fairly readily, the time of half–hydrolysis at pH 6 being 8 to 1000 h in water [2, 3], but in our cases, the rate of hydrolysis was significantly higher; this is natural, since in the case of pyrazoles, the phenylsulfonylcarbamoyl derivatives are azolides [4]. For compound I, which has a particularly low basicity (see Table 1), the hydrolysis was already taking place when the sample was ground up with KCl for the purpose of recording the IR spectrum.



The hydrolysis took place with particular ease in the solvents used for recording NMR spectra (CD_3CN and CD_3SOCD_3) owing to the homogeneity of the medium and the traces of water present in these solvents. All our attempts at recording the NMR spectra of the pyrazole derivatives led to spectra of the hydrolysis products. The ease of hydrolysis of the arylsulfonylcarbamoyl derivatives in comparison with the acyl derivatives can be explained by the additional electron-acceptor action of the arylsulfonylamide group. At first glance the high hydrolytic stability of the imidazole derivative compared to the pyrazole derivative seems surprising, since in a number of ordinary acyl derivatives everything is different [4]. Apparently, because of the high basicity (see Table 1) of the imidazole nucleus, N-arylsulfonylcarbamoylimidazole exists in the form of a bipolar ion whose carbonyl carbon atom is less exposed to nucleophilic attack during hydrolysis.

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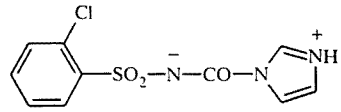
TABLE 1. Yields and Constants of N-(o-chlorophenylsulfonylcarbamoyl) Derivatives

Compound	Heterocyclic	Empirical formula	M.P., °C	IR spectrum, C=O, cm^{-1}	UV spectrum, λ_{max} (log ε)	pK_a of conj. acid in 50% alcohol, spectrophotometrically	Yield, %
I	3-Methyl-5-chloropyrazole	$C_{11}H_9Cl_2N_3O_3S$	187...189	–*	260 (3,90), 265 (3,98), 268 (3,93), 274 (4,02), 279 (3,87)	0,03	58
II	Pyrazole	$C_{10}H_8ClN_3O_3S$	138...140	1725	259 (2,80), 267 (3,08), 273 (3,26), 281 (3,20)	2,7	87
III	3,5-Dimethylpyrazole	$C_{12}H_{12}ClN_3O_3S$	183...184	1740	213 (4,20), 252 (2,38), 259 (2,66), 267 (2,94), 273 (3,11), 280 (3,05)	3,5	98
IV	3,4,5-Trimethylpyrazole	$C_{13}H_{14}ClN_3O_3S$	152...153	–	259 (2,17), 267 (2,95), 273 (3,12), 281 (3,05)	–	56
V	3-Methylpyrazole	$C_{11}H_{10}ClN_3O_3S$	151...153	1650, 1750	259 (2,51), 267 (2,76), 273 (2,93), 281 (2,87)	–	59
VI	3-Methyl-5-ethoxypyrazole	$C_{13}H_{14}ClN_3O_4S$	138...140	1735	259 (2,78), 267 (3,05), 273 (3,22), 281 (3,10), 299 (1,83)	2,4	85
VII	3,5,5-Trimethylpyrazoline	$C_{13}H_{16}ClN_3O_3S$	189...191	1675	224 (4,32), 236 (4,27), 272 (3,07), 281 (2,90)	4,1	83
VIII	3-Ethyl-5-phenylpyrazoline	$C_{18}H_{18}ClN_3O_3S$	153...154	1690	259 (2,78), 266 (3,01), 273 (3,17), 280 (3,10)	–	67
IX	3-tert-Butyl-5-phenylpyrazoline	$C_{20}H_{22}ClN_3O_3S$	202...204	1675	217 (4,40), 238 (4,20), 272 (3,09), 281 (3,24), 298 (1,99)	–	74
X	Imidazole	$C_{10}H_8ClN_3O_3S$	127...128	1675	260 (2,69), 267 (2,90), 273 (3,06), 280 (2,99)	7,0	73
XI	4,4′-bis(3,5-dimethylpyrazole)	$C_{24}H_{22}Cl_2N_6O_6S_2$	173...175	–	257 (3,15), 264 (3,33), 271 (3,50), 278 (3,51)	3,0 (pK_{a2} 1,9)	61

*A dash in the column means that in the region of C=O vibrations, absorption is absent due to hydrolysis and decarboxylation.

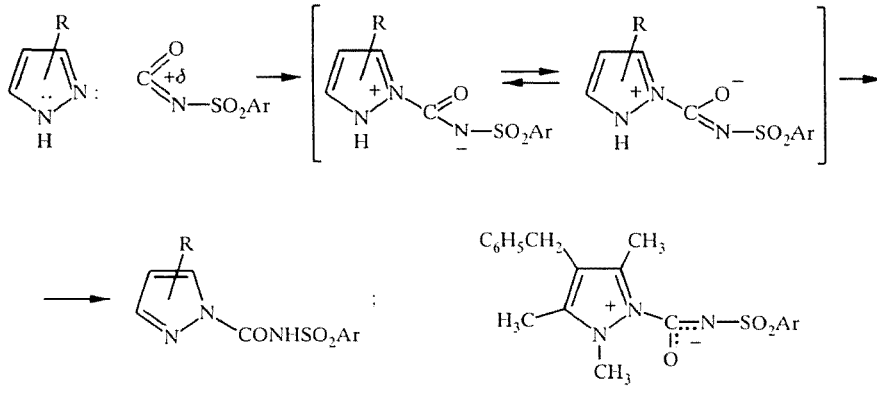


The presence of a negative charge on the nitrogen of the urea fragment is confirmed by a lower value of the vibration frequency of the carbonyl group (ν_{CO} 1675) in comparison with the pyrazole derivatives (ν_{CO} ~11730 cm^{-1}; see Table 1) [5].

For reasons which we are unable to explain, all 4-substituted pyrazoles hydrolyzed very readily.

Pyrazoline derivatives are fairly stable under ordinary conditions. Thus, in the PMR spectrum (CD_3CN) of the derivative of 3,5,5-trimethylpyrazoline there is a singlet of two equivalent 5-CH_3 groups at 1.28, a singlet of two equivalent protons in the 4 position at 2.81, and a singlet of the 3-CH_3 group at 1.99 ppm. The protons of the aromatic o-chloropyhenylsulfamide nucleus give a characteristics multiplet at 7.4-8.1 ppm. The spectra of derivatives of 3,5-dimethylpyrazole and 3-methyl-5-chloropyraozole during their recording in CD_3CN are convered to the spectra of the corresponding pyrazoles (for 3,5-dimethylpyrazole: a single of six protons of equivalent CH_3 groups at 2.10, and the signal of the 4-H proton at 5.78; for 3-methyl-5-chloropyrazole: a singlet of the CH_3 group at 2.17 and of the 4-H proton at 5.94) and o-chlorophenylsulfamide (a multiplet at 7.4-8.1 ppm).

To prove acylation at the nitrogen atom of 3,5-dimethylpyrazole, we recorded the ^{13}C NMR spectra of 3,5-dimethylpyrazole itself and its acyl derivative, both of which during the recording of the spectrum (DMSO-d_6) were hydrolyzed in accordance with the usual scheme. ^{13}C NMR spectrum of 3,5-dimethylpyrzole: signals of equivalent CH_3 groups 11.9, 103 ($C_{(4)}$), 142.5 ppm (equivalent $C_{(3)}$ and $C_{(5)}$); J_{CH3} = 127, $J_{C(4)H}$ = 170 Hz. The ^{13}C NMR spectrum of o-cholophenylsulfamide contains four singles of C−H groups at 126.9, 128.9, 131.2, and 132.8 ppm; J_{CH} 162-168 Hz and two singles of quaternary carbon at 130.7 (C−Cl) and 141.2 ppm (C−SO_2^-).



II III

We postulate that the first stage of the acylation process is an attack of the electrophilic fragment of arylsulfonyl isocyanate at the nitrogen atom of the pyrazole nucleus that has a electron pair. A redistribution of electron density with the formation of the end product of reaction II then takes place in the bipolar intermediate. In this connection, in the case of asymmetric pyrazoles (and also imidazoles), a mixture of isomers should be formed in which the isomer formed from the more basic pyrazole in accordance with the scheme given above predominates. Unfortunately, the low stability of acyl pyrazoles did not permit the solution of this problem. In the case of pyrazolines, in which the nitrogen atom in the 1 position is the main one, acylation takes place in the usual manner, as in the case of amines.

In the case of completely substituted pyrazoles (1,3,5-trimethyl-4-benzyl and 1-benzyl-3,4,5-trimethyl), the bipolar adduct III can be separated in the form of a thick oil that hydrolyzes readily in accordance with the usual scheme [6].

EXPERIMENTAL

The ^{13}C NMR spectra were recorded with a Bruker M-250 instrument, and the PMR spectra, with a Tesla Bs-497 instrument (100 MHz). The IR spectra were recorded in KCl pellets with a Perkin-Elmer 577 spectrometer; the electronic absorption spectra were recorded in acetonitrile with a Specord M-40 spectrophotometer.

Sulfonyl Ureas (General Procedure). To a solution of 0.02 mole of the corresponding heterocyclic compound in 10 ml of absolute benzene and 0.5 ml of absolute acetonitrile is added a solution of freshly vacuum-distilled 0.02 mole of o-chlorosulfonyl isocyanate in 10 ml of absolute benzene; one observed a heating of the reaction mixture, which is then heated to boiling for 1 h. Crystals usually precipitate during the heating or when cooling of the mixture begins. The precipitated crystals are filtered off, contact with air being avoided as much as possible, washed with absolute benzene, and dried in a vacuum over phosphorus pentoxide and paraffin. The yields and constants are listed in Table 1; all the compounds showed a satisfactory elemental analysis for C, H, N, and S.

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