Chemistry of Heterocyclic Compounds, Vol. 32, No. 2, 1996

C-ACYLATION OF π-RICH HETEROCYCLES BY *o*-CHLOROBENZENESULFONYLISOCYANATE

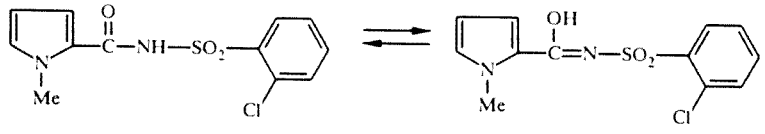
N. L. Nam, I. I. Grandberg, and V. I. Sorokin

Nitrogen-containing π-rich heterocycles under mild conditions are acylated by o-chlorobenzene-sulfonyl-isocyanate, forming C-arylsulfonylcarbamoyl derivatives; O- and S-containing heterocycles do not react under these conditions.

Earlier [1] we observed that *o*-chlorobenzenesulfonylisocyanate reacts with N-substituted pyrazoles with formation of C-sulfonylcarbamoyl derivatives according to an electrophilic substitution scheme. Literature data on reactions of sulfonylisocyanates with heterocycles are quite contradictory. Thus Barnett reported [2] that pyrrole reacts with chlorosulfonyl-isocyanate (I) at the 2 position, while with an excess of I it reacts at the 2,4 and 2,5 positions; at the same time, Seefelder writes [3] that pyrrole reacts with *p*-toluenesulfonylisocyanate in the 3 position. In a paper by Mehta [4], it is said that carbazole reacts with chlorosulfonylisocyanate at the nitrogen atom, while Seefelder [13] says that carbazole reacts with *p*-toluenesulfonylisocyanate at the 3 position; in the review by Ulrich [5] on the chemistry of sulfonylisocyanates, these contradictions are somewhat glossed over.

The reactivity in electrophilic substitution reactions increases in the isocyanate series presented below; and in the last, most active members of the series (sulfonylisocyanate), the chemical nature of R still has little effect on its reactivity, and all the sulfonylisocyanates have close reactivities: $Alk-N{=}C{=}O < Ar-N{=}C{=}O < Cl_3C-N{=}C{=}O < RCO-N{=}C{=}O < RSO_2-N{=}C{=}O$.

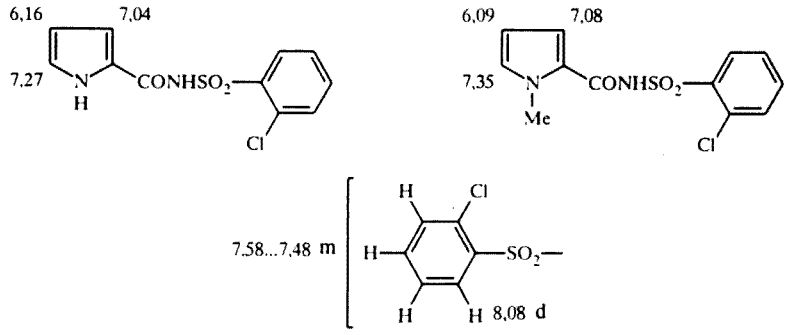
We used *o*-chlorobenzenesulfonylisocyanate in this reaction. In most of the studied cases, the reaction proceeded exothermically; it was only with the goal of increasing the yield that we used brief heating in chlorobenzene as the solvent. Pyrrole itself, N-methylpyrrole, and indoles reacted with good yields; the only problem was establishing the position where the sulfonylcarbamoyl group was introduced. However, we could not get thiophene, 2-methylfuran, 2,5-dimethylfuran, benzothiophene, benzofuran, and N-benzylimidazole to react even when heating for many hours in chlorobenzene. This is especially surprising since Graf [6] reported earlier that furan and thiophene, when reacted with chlorosulfonylisocyanate, form sulfonylcarbamoyl derivatives in the α position of the heterocycle. Of course, Graf [7] has noted that toluenesulfonylisocyanate does not react with these heterocycles. In order to prove the location of the sulfonylcarbamoyl residue in pyrrole and N-methylpyrrole, we used the PMR method. Thus in the spectrum for N-methylpyrrole, in addition to signals from protons of the *ortho*-disubstituted phenyl ring of the sulfonylcarbamoyl group (see below), we saw a narrow singlet from the $N-CH_3$ group at 3.19 ppm and poorly resolved but narrow multiplets at 6.09, 7.08, and 7.35 ppm. The poor resolution of the signals in this and all the remaining cases, it seems to us, is due to amido—imidol tautomerism in the sulfonylcarbamoyl residues.



Using the data in [8-10] on correlation of the chemical shifts for protons on the pyrrole ring when introducing electron-acceptor substituents, we can unambiguously determine that the sulfonylcarbamoyl substituent is introduced at the 2 position. Analogous conclusions may also be drawn for unsubstituted pyrrole (see Table 2).

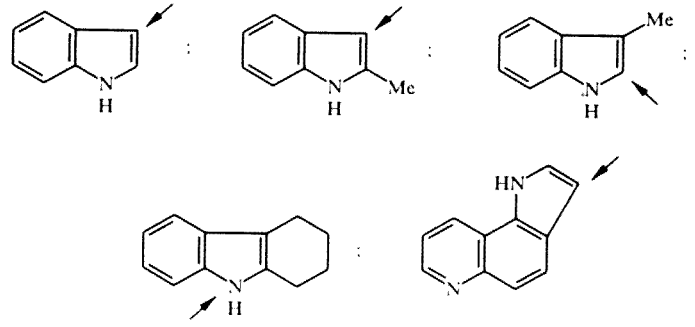
K. A. Timiryazev Moscow Agricultural Academy, Moscow 127650. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 205-209, February, 1996. Original article submitted December 13, 1995.

 0009-3122/96/3202-0180$15.00

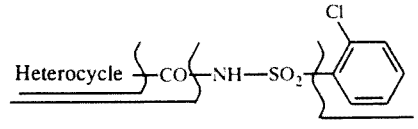


With the same approach to substitution on the indole ring, using the data in [11,12] we determined the position at which the substituent was introduced (indicated by the arrows) in indole, 2- and 3-methylindoles and tetrahydrocarbazole (see the tables). Based on this, we consider that also in pyrrolo[2,3-*e*]quinoline, substitution occurs at the 3 position, as indicated by the arrow.

Scheme 1



As in the case of pyrazole derivatives [1], none of the *o*-chlorobenzenesulfonylcarbamoyl derivatives obtained yield M^+ ions in the mass spectrum under conditions of direct injection into the source; only fragments of the following type are registered:



It was of interest to investigate the reactions of *o*-chlorobenzenesulfonylisocyanate with 2,6-dimethylpyrone, displaying aromatic properties to some degree. We know [13] that 2,6-diphenylpyrone reacts with chlorosulfonylisocyanate as an unenolized ketone with loss of CO_2.

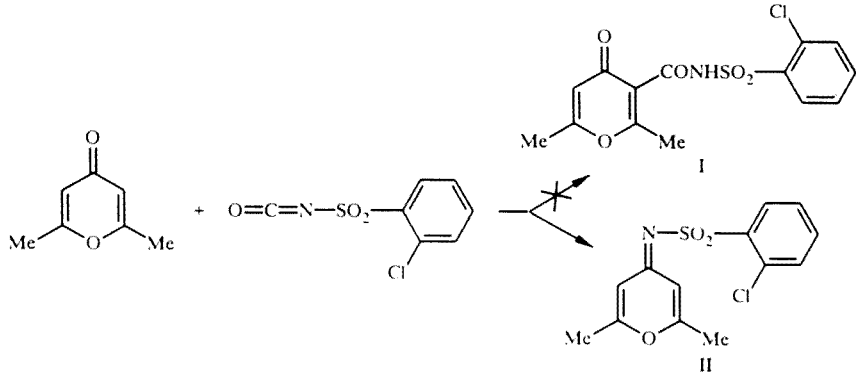


TABLE 1. Yields and Constants for *o*-Chlorobenzenesulfonylcarbamoyl Derivatives

Heterocycle	Empirical formula	mp, °C	IR spectrum, C=O, cm^{-1}	UV spectrum, λ_{max} (lgε), nm	Yield, %
1-Methylpyrrolyl-2	$C_{12}H_{11}ClN_2O_3S$	199...200	1625	220 (4,32), 277 (4,53), 282 (4,54)	80
3-Methylindolyl-2	$C_{16}H_{13}ClN_2O_3S$	183...185	1673	238 (4,74), 264 (4,22), 272 (4,20), 280 (4,13), 291 (4,23), 298 (4,30)	81
Pyrrolyl-2	$C_{11}H_9ClN_2O_3S$	241...243	1665	219 (4,12), 282 (4,30)	89
2-Methylindolyl-3	$C_{16}H_{13}ClN_2O_3S$	200...202	1660	244 (4,18), 279 (3,93)	89
Indolyl-3	$C_{15}H_{11}ClN_2O_3S$	230...232	1680	234 (4,20), 255 (4,03), 276 (4,06), 283 (4,13), 290 (4,15)	92
Pyrrolo[2,3-*e*]-quinolinyl-3	$C_{18}H_{11}ClN_3O_3S$	237...240	1682	214 (4,47), 228 (4,35), 240 (4,28), 267 (4,54), 322 (3,70)	66
N-Tetrahydrocarbazolyl	$C_{19}H_{17}ClN_2O_3S$	155...156	1685	226 (4,52), 272 (3,89), 280 (3,91), 290 (3,91)	31
o-Chlorophenylsulfonylimine 2,6-Dimethylpyrone	$C_{13}H_{12}ClNO_3S$	151...152	1663	223 (4,36), 292 (4,71)	72

TABLE 2. PMR Spectra of *o*-Chlorobenzenesulfonylcarbamoyl Derivatives, δ, ppm

Heterocycle	Position of H or substituting group								
	1	2	3	4	5	6	7	8	exchanged H (OH, NH)
1-Methylpyrrolyl-2	3,19 (CH_3, s)	–	7,08 (m)*	6,09 (m)*	7,35 (m)*				3,28 (br.s)
Pyrrolyl-2	–	–	7,04 (m)*	6,16 (m)*	7,27 (m)*				3,27 (s)
3-Methylindolyl-2	–	–	2,22 (CH_3, s)	8,06 (m)	7,60 (m)	7,60 (m)	7,23 (m)		4,38 (br.s)
2-Methylindolyl-3	–	2,59 (CH_3, s)	–	7,43 (m)	7,37 (m)	7,37 (m)	7,22 (m)		3,26 (br.s)
3-Indolyl	–	8,20 (d)	–	8,51 (m)	7,65 (m)	7,65 (m)	7,45 (m)		3,28 (s)
N-Tetrahydrocarbazolyl	2,69 (t)	1,81 (m)	1,81 (m)	2,51 (t)	6,9...7,6(m)	6,9...7,6(m)	6,9...7,6 (m),7-H, 8-H	6,9...7,6 (m)	
o-Chlorobenzenesulfonylimine of 2,6-dimethylpyrone	–	2,36 (CH_3, s)	6,78 (br.s)	–	6,78 (br.s)	2,36 CH_3, s			

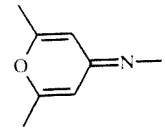
*Poorly resolved signal.

TABLE 3. Elemental Analysis Data

o-Chlorobenenesulfonyl carbamoyl derivative	Empirical formula	Found, % / Calculated, %	
		C	H
1-Methylpyrrolyl-2	$C_{12}H_{11}ClN_2O_3S$	47.8 48.2	3.4 3.7
3-Methylindolyl-2	$C_{16}H_{13}ClN_2O_3S$	55.5 55.0	3.9 3.7
Pyrrolyl-2	$C_{11}H_9ClN_2O_3S$	46.5 46.3	3.5 3.2
2-methylindolyl-3	$C_{16}H_{13}ClN_2O_3S$	55.7 55.0	4.1 3.7
Indolyl-3	$C_{15}H_{11}ClN_2O_3S$	53.5 53.7	3.8 3.3
o-Chlorobenzosulfonylimine of 2,6-dimethylpyrone	$C_{13}H_{12}ClNO_3S$	52.8 52.3	4.1 4.0
Pyrrolo[2,3-*e*]-quinolinyl-3	$C_{18}H_{11}ClN_3O_3S$	56.6 56.1	3.3 2.9
N-Tetrahydrocarbazolyl	$C_{19}H_{17}ClN_2O_3S$	57.9 58.6	4.2 4.4

In the PMR spectrum of the derivative obtained, there is a narrow singlet from protons of the methyl groups (intensity 6H) and a broad singlet (intensity 2H) from protons in the 3 and 5 position as a result of *syn-anti* tautomerism in the imine group, which determined the structure of the compound obtained as II. It is interesting to note that the effect of the *syn-anti* transition does not affect the width of the singlet from the CH_3 group: it remains narrow. One more proof of structure II is its insolubility in dilute base, while all the remaining sulfonylcarbamoyl derivatives are quite soluble in base.

In contrast to all the sulfonylcarbamoyl derivatives, the sulfonyliminopyrone II in the mass spectrum (under direct injection conditions) yields a molecular ion peak corresponding to mass 297, of moderate intensity (10%). We should note that the system of conjugated bonds



in the IR spectrum gives an intense band at 1663 cm^{-1}, which can be easily assumed as a C=O band (see Table 2).

The data we obtained on orientation agree well with the general conclusions on electrophilic substitution in five-membered heterocycles presented in the review [14].

EXPERIMENTAL

The UV spectra were taken in alcohol on a Specord M-40; the IR spectra were recorded on a Perkin-Elmer 577 in KBr pellets; the PMR spectra were recorded on an AM-300 Bruker in DMSO-D_6.

General Technique for Obtaining *o*-Chlorobenzenesulfonylcarbamoyl Derivatives. 6 ml dry chlorobenzene, 0.01 moles of the corresponding heterocycle, and 0.01 moles of freshly vacuum distilled *o*-chlorobenzenesulfonylisocyanate were placed with stirring into a 25 ml flask with a magnetic stirrer and reflux condenser fitted with a calcium chloride tube. The reaction mixture was stirred for 15 min, then heated with boiling for 20 min. After cooling, 10 ml of a 1:2 benzene—hexane mixture was added and it was heated again to boiling. After cooling, the residue was filtered off and heated again with 10 ml 50% methanol. After cooling, the residue was again filtered off, dried, and recrystallized from a benzene—hexane mixture with varying ratios of the components (depending on the solubility). The yields and constants of the compounds obtained are presented in the tables.

REFERENCES

1. N. L. Nam, I. I. Grandberg, and V. I. Sorokin, Khim. Geterotsikl. Soedin., No. 1, 46 (1994).
2. G. H. Barnett and H. J. Anderson, Canad. J. Chem., **58**, 409 (1980).
3. M. Seefelder, Chem. Ber., **96**, 3243 (1963).
4. G. Mehta and D. N. Dhas, Synthesis, No. 3, 374 (1978).
5. H. Ulrich, Chem. Rev., **65**, 369 (1965).
6. R. Graf, Lieb. Ann., No. 661, 111 (1963).
7. R. Graf, Chem Ber., **89**, 1071 (1956).
8. S. Gronowitz, A. Jornfeldt, B. Gestobbot, and R. Hoffman, Ark. Kemi, **18**, 133 (1961).
9. R. A. Jones, T. Mc. L. Spotswood, and A. Chenychit, Tetrahedron, **23**, 4469 (1967).
10. D. Barton and W. D. Ollis (eds.), Comprehensive Organic Chemistry [Russian translation], Khimiya, Moscow (1985), Vol. 8, p. 337.
11. D. Barton and W. D. Ollis (eds.), Comprehensive Organic Chemistry [Russian translation], Khimiya, Moscow (1985), Vol. 8, p. 494.
12. M. Jardine and C. Brown, Canad. J. Chem., **41**, 2067 (1963).
13. J. A. van Allen, J. Heterocyclic Chem., **2**, 195 (1974).