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ARYLSULFENYLATION OF HETEROCYCLIC COMPOUNDS WITH ARYLSULFENAMIDES IN THE PRESENCE OF PHOSPHORUS(V) OXOCHLORIDE*

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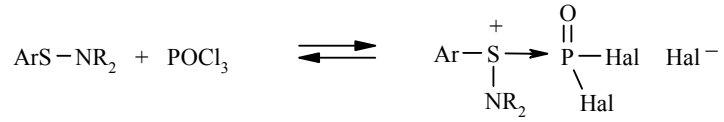
The electrophilic sulfenylation of a series of indoles and pyrroles with arylsulfenamides in the presence of phophorus(V) oxohalide has been studied. It has been shown that arylsulfenylation of indoles led to products with substitution at position 3, while in the case of pyrrole it occurred at position 2.

Keywords: indoles, pyrroles, electrophilic substitution, sulfenylation.

Sulfur-containing indoles are widely known compounds with a variety of biological activity. Indoles with substitutions in position 3 are effective in the treatment of a wide range of illnesses, such as obesity [1], oncological diseases [2], diseases of the heart and bacterial infections [3]. They are also starting materials in the synthesis of preparations with antiHiv activity [4], inhibitors of 5-lipoxygenases [5], and in addition they are used in the synthesis of organic compounds possessing nonlinear optical properties [6].

Arylsulfenyl halides are usually used for sulfenylation of five-membered aromatic heterocyclic compounds [7-12]. However the basic problem with their use is the instability of the arylsulfenyl halides starting materials.

We have shown previously that the reactions of arylsulfenamides with alkenes, alkynes, and dienes in the presence of phosphorus(V) and sulfur(IV) oxohalides leads to the formation of β-halosulfides in quantitative yields. The mechanism of the reaction includes preliminary coordination of the phosphorus atom to the sulfur atom of the sulfenamide starting material [13, 14]. In the present work we report a simple method for the sulfenylation of a series of indoles and pyrroles with arylsulfenamides **1-3** in the presence of a phosphorus(V) oxohalide.



1–3

A

1 Ar = Ph, NR_2 = NEt_2; **2** Ar = 2-$O_2NC_6H_4$, NR_2 = $N(CH_2CH_2)O$;
3 Ar = 4-$O_2NC_6H_4$, NR_2 = $N(CH_2CH_2)O$

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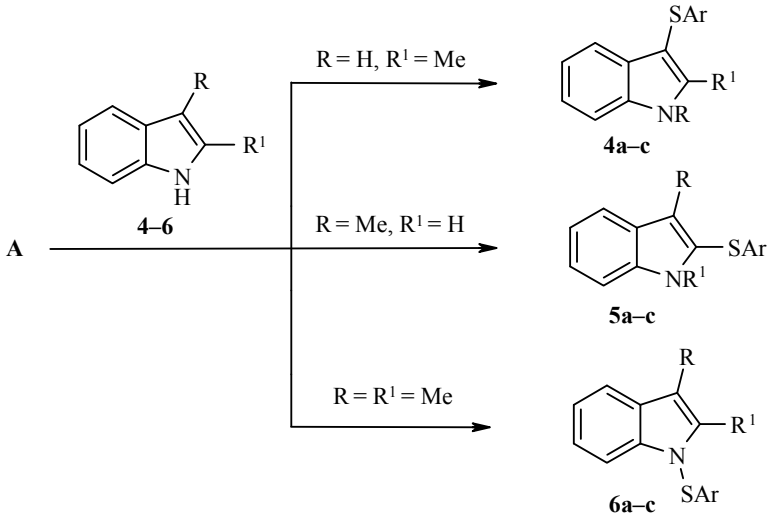
We have shown previously that the interaction of arylsulfenamides with phosphorus(V) or sulfur(IV) oxohalides led to the formation not of arylsulfenhalides but to the donor-acceptor complex **A** which is the immediate electrophilic reagent [14].

In the cases of interaction with indoles or pyrroles intermediate **A** may react to form the corresponding sulfides:



4–6 a Ar = Ph, **b** Ar = *o*-$O_2NC_6H_4$, **c** Ar = *p*-$O_2NC_6H_4$

As a result of the interaction of indoles and pyrroles with arylsulfenamides in the presence of phosphorus oxohalides a series of unsymmetrical sulfides were obtained. The results of the sulfenylation reactions are summarized in Table 1.

TABLE 1. Results of Sulfenylation of Indoles and Pyrroles with Arylsulfenamides in the Presence of Phosphorus(V) Oxohalide

Substrate	Sulfen-amide	Reaction product	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
				C	H	N		
4	**1**	**4a**	$C_{15}H_{13}NS$	75.02 / 75.31	5.46 / 5.46	5.65 / 5.86	147	61
	2	**4b**	$C_{15}H_{12}N_2O_2S$	63.19 / 63.38	4.33 / 4.23	9.80 / 9.86	153	86
	3	**4c**	$C_{15}H_{12}N_2O_2S$	63.30 / 63.38	4.28 / 4.23	9.77 / 9.86	133	97
5	**1**	**5a**	$C_{15}H_{13}NS$	75.00 / 75.31	5.47 / 5.46	5.77 / 5.86	98	96
	2	**5b**	$C_{15}H_{12}N_2O_2S$	63.40 / 63.38	4.23 / 4.23	9.86 / 9.86	125	95
	3	**5c**	$C_{15}H_{12}N_2O_2S$	63.20 / 63.38	4.16 / 4.23	9.78 / 9.86	113	99
6	**1**	**6a**	$C_6H_{15}NS$	—	—	—	—	81
	2	**6b**	$C_{16}H_{14}N_2O_2S$	—	—	—	165	78
	3	**6c**	$C_{16}H_{14}N_2O_2S$	—	—	—	—	79
7	**1**	**7a** +**7d**	$C_{11}H_{11}NS$	—	—	—	—	97
	2	**7b**	$C_{11}H_{10}N_2O_2S$	56.49 / 56.47	4.37 / 4.35	11.80 / 11.97	—	96
	3	**7c**	$C_{11}H_{10}N_2O_2S$	56.30 / 56.47	4.29 / 4.35	11.81 / 11.97	79	99

TABLE 2. ^{1}H NMR Spectra of the Products of Sulfenylation of Indoles

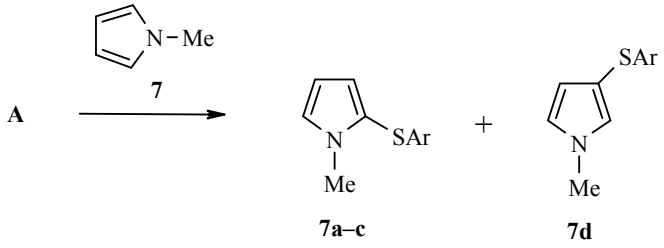
Compound	Chemical shifts, δ, ppm (*J*, Hz)							
	R (3H, s)	R^{1} (3H, s)	H-4 (1H)	H-5 (1H)	H-6 (1H)	H-7 (1H)	NH (1H, s)	Ar
4a	—	2.55	7.79 (d, *J* = 7.9)	6.89 (dd, *J* = 7.9, *J* = 7.1)	7.20 (dd, *J* = 8.0, *J* = 7.1)	7.31 (d, *J* = 7.9)	8.56	7.15-7.52 (5H, m)
4b	—	2.60	7.53 (d, *J* = 8.0)	6.89 (dd, *J* = 8.0, *J* = 7.0)	7.36 (dd, *J* = 8.0, *J* = 7.0)	7.41 (d, *J* = 8.0)	8.70	7.28-8.52 (4H, m)
4c	—	2.58	7.59 (d, *J* = 8.0)	6.95 (dd, *J* = 8.0, *J* = 7.0)	7.24 (dd, *J* = 8.0, *J* = 7.0)	7.45 (d, *J* = 8.0)	8.44	7.35 (2H, d, *J* = 9.0), 8.11 (2H, d, *J* = 9.0)
5a	2.43	—	7.69 (d, *J* = 8.0)	7.09 (dd, *J* = 8.0, *J* = 7.0)	7.28 (dd, *J* = 8.0, *J* = 7.0)	7.54 (d, *J* = 8.0)	7.99	7.15-7.50 (5H, m)
5b	2.45	—	7.50 (d, *J* = 8.1)	6.55 (dd, *J* = 8.1, *J* = 7.0)	7.15 (dd, *J* = 8.1, *J* = 7.0)	7.44 (d, *J* = 8.0)	8.05	7.34-8.42 (4H, m)
5c	2.41	—	7.39 (d, *J* = 8.0)	7.10 (dd, *J* = 8.0, *J* = 7.0)	7.22 (dd, *J* = 8.1, *J* = 7.0)	7.34 (d, *J* = 8.0)	8.10	7.68 (2H, d, *J* = 9.0), 8.25 (2H, d, *J* = 9.0)
6a	2.40	2.40	7.31 (m)	7.23 (m)	7.27 (m)	7.31(m)	–	7.20-7.55 (5H, m)
6b	2.38	2.38	7.31 (d, *J* = 8.1)	6.80 (dd, *J* = 8.2, *J* = 7.0)	7.22 (dd, *J* = 8.1, *J* = 7.0)	7.59 (d, *J* = 8.0)	–	7.12-7.88 (4H, m)
6c	2.30	2.30	7.24 (d, *J* = 8.0)	6.95 (dd, *J* = 8.0, *J* = 7.0)	7.17 (dd, *J* = 8.1, *J* = 7.0)	7.63 (d, *J* = 8.0)	–	7.27 (2H, d, *J* = 9.0), 8.15 (2H, d, *J* = 9.0)

As expected, interactions of complex **A** with indoles unsubstituted at position 3 gave compounds substituted at this position. At the same time indoles substituted at position 3 formed the corresponding 2-indolyl aryl sulfides [15-17]. The corresponding indolylaryl sulfides were obtained with yields from good to quantitative.

Reactions with 2,3-disubstituted indoles led to products of N-sulfenylation, which were formed in much smaller yields than in the case of 2- or 3-monosubstituted indoles.

Arylsulfenylation of N-methylpyrrole led to the formation of 2-arylthiopyrroles in quantitative yield. However in the case of the reaction of N-methylpyrrole with arylsulfenamide **1** a mixture of 2- and 3-substituted pyrroles **7a** and **7d** was obtained in a ratio of 2:3.

Thus the proposed method of sulfenylation of indoles and pyrroles with arylsulfenamides in the presence of phosphorus oxohalides is a suitable simple preparative method foe the preparation of the required compounds in high yields. In most cases sulfenylation led to the formation of just one regioisomer. In the course of investigating the reaction mixtures formation of by-products was not observed which makes possible the use of this method for the sulfenylation of a range of nitrogen-containing five-membered heterocyclic compounds.



7a–c **7d**

7 a,d Ar = Ph, **b** Ar = *o*-$O_2NC_6H_4$, **c** Ar = *p*-$O_2NC_6H_4$

TABLE 3. ^{1}H NMR Spectra of the Products of Sulfenylation of N-Methyl-pyrrole

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)					
	N–R (3H, s)	H-2	H-3 (1H, d, *J* = 2.8)	H-4 (1H)	H-5 (1H, d)	Ar
7a	3.64	—	6.12	6.10 (dd, *J* = 2.8, *J* = 3.1)	6.80 (*J* = 3.0)	7.10-7.52 (5H, m)
7d	3.64	6.05 (1H, d, s)	—	6.10 (d, *J* = 2.8)	6.84 (*J* = 2.8)	7.10-7.55 (5H, m)
7b	3.75	—	6.08	6.12 (dd, *J* = 2.8, *J* = 3.1)	6.90 (*J* = 3.1)	7.05-7.90 (4H, m)
7c	3.74	—	6.05	6.14 (dd, *J* = 2.8, *J* = 2.9)	6.87 (*J* = 2.9)	7.18 (2H, d, *J* = 9.0); 8.00 (2H, d, *J* = 9.0)

TABLE 4. ^{13}C NMR Spectra of Products of Sulfenylation of Indoles and N-Methylpyrrole

Compound	Chemical shifts, δ, ppm
4b	135.8, 133.2, 129.9, 125.8, 124.7, 123.0, 121.0, 119.7, 115.6, 110.0
4c	149.7, 124.9, 124.0, 122.8, 121.2, 118.5, 111.0, 37.0
5a	137.5, 137.0, 129.5, 129.0, 127.0, 126.0, 124.0, 121.5, 120.0, 111.0, 41.0
7c	134.0, 129.5, 127.5, 127.0, 126.5, 125.9, 125.0, 120.8, 109.0, 34.0

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE (400 and 100 MHz, respectively) in $CDCl_3$ as solvent and internal standard. Elemental analyzes of the synthesized compounds were carried on a Carlo-Erba CHN-analyzer.

General Method. To a solution of heterocyclic compound (2.5 mmol) in absolute methylene chloride (10 ml), a solution of arylsulfenamide **1-3** (2.5 mmol) in CH_2Cl_2 was added at room temperature. The mixture formed was stirred for 10 min and then a solution of phosphorus(V) oxochloride (2.5 mmol) in the same solvent (10 ml) was added and stirring was continued for 4 h. The solution was passed through a layer of silica gel (height 3 cm). After removing the solvent in vacuum, solid crystalline substances were obtained, the products of the electrophilic substitution.

NMR swpectroscopic data for the compounds synthesized are given in Tables 2-4.

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