Synthesis and some spectral properties of 5-substituted 2-anilino-1,3,4-thiadiazoles

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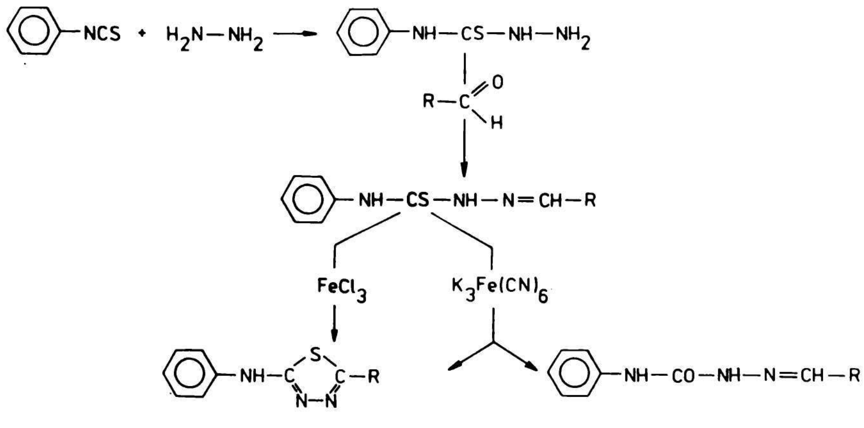
The preparation of 5-substituted 2-anilino-1,3,4-thiadiazoles by oxidation with $FeCl_3$ or $K_3Fe(CN)_6$ of the corresponding thiosemicarbazones is described. The structure of the synthesized substances was confirmed by i.r., u.v., and mass spectral evidence.

В работе приводится синтез 5-замещенных 2-анилино-1,3,4-тиадиазолов окислением соответствующих тиосемикарбазонов с $FeCl_3$ или $K_3Fe(CN)_6$. Структура синтезированных соединений была подтверждена на основании ИК, УФ и масс-спектров.

The derivatives of 1,3,4-thiadiazole have been extensively studied from the point of view of their synthesis and physicochemical properties [1—5]. Compounds of this class are important also because of their biological activity [5—8].

Our attention has been focused on the preparation of some derivatives of 2-anilino-1,3,4-thiadiazole by means of the oxidation of the corresponding thiosemicarbazones (Scheme 1). We have therefore been looking for a reagent capable of oxidizing thiosemicarbazones substituted with activating or deactivating



Scheme 1

Table 1

New 5-substituted 2-anilino-1,3,4-thiadiazoles*

Compound	R	Formula	*M*	Calculated/found		Yield	M.p.
				% N	% S	%	°C
I	$3\text{-}CH_3\text{—}C_6H_4$	$C_{15}H_{13}N_3S$	267.3	15.71	11.99	53	170—172
				15.72	12.18		
II	$3\text{-}CH_3O\text{—}C_6H_4$	$C_{15}H_{13}N_3OS$	283.3	14.82	11.31	50	166—167
				14.86	11.46		
III	$4\text{-}CH_3CONH\text{—}C_6H_4$	$C_{16}H_{14}N_4OS$	310.4	18.05	10.32	20	275—278
				17.93	10.49		
IV	$3,4\text{-}Cl_2C_6H_3$	$C_{14}H_9Cl_2N_3S$	322.2	13.00	9.93	80	242—243
				12.94	10.11		
V	$4\text{-}Br\text{—}C_6H_4$	$C_{14}H_{10}BrN_3S$	332.2	12.64	9.65	80	232—233
				12.69	9.75		
VI	C_4H_3O	$C_{12}H_9N_3OS$	243.3	17.25	13.17	39	174—176
				17.16	13.41		

* In order to test the method of oxidation with $FeCl_3$ and obtain substances for spectral measurements the following known compounds were also prepared (the physical constants agreed well with the data in the literature (see below) where also R and the yields are given):

VII (phenyl, [9], 72%); *VIII* (nitrophenyl, [13], 92%); *IX* (4-*N*,*N*-dimethylaminophenyl, [9], 24%); *X* (4-tolyl, [9], 65%); *XI* (4-methoxyphenyl, [9], 60%); *XII* (4-chlorophenyl, [9], 80%); *XIII* (5-nitro-2-furyl, [14], 85%); *XIV* (methyl, [15], 28%).

substituents and have tried $FeCl_3$ and $K_3Fe(CN)_6$ for this purpose similarly as in [9]. Of the tried reagents ferric chloride was the most successful one as it produced 1,3,4-thiadiazoles as the sole products.

We have found that the yields of the desired products (Table 1) largely depend

Table 2

Characteristic i.r. and u.v. spectral data for the studied 1,3,4-thiadiazoles

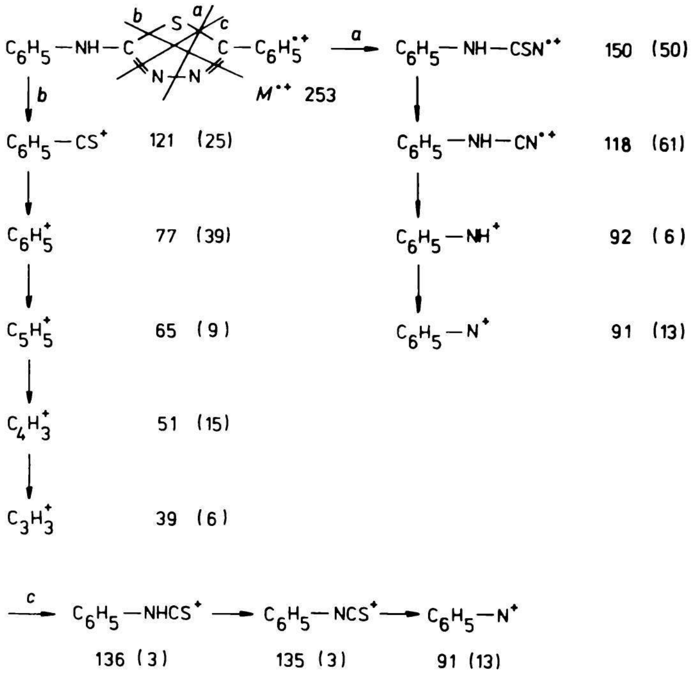
Compound	IR, cm^{-1}							UV	
	ν(NH)	ν(C=N)	ν(C=C)	ν_{skelet}				λ_{max}, nm	log ε
I	3250	1630	1610	1510	1460	1435	1310	254	4.03
	3200		1580	1235				328	4.32
II	3250	1625	1610	1510	1460	1430	1315	253	4.02
	3195		1580	1295	1215			331	4.32
III	3290	1625	1605	1685	1545	1510	1455	267	4.09
				1430	1410	1375		337	4.48
IV	3250	1620	1605	1510	1560	1460	1440	259	4.12
	3200		1500	1280	1230	1215		340	4.33
V	3240	1620	1605	1510	1455	1430	1395	257	4.16
	3195		1580	1350	1270	1300	1230	335	4.41
IV	3245	1625	1606	1505	1460	1430	1265	257	3.95
	3195		1570	1220				335	4.34
VII	3250	1625	1610	1510	1475	1460		253	4.11
	3200			1440	1270	1225	1205	328	4.38
VIII	3250	1630	1605	1525	1510	1465	1440	276	4.22
	3200		1580	1280	1225	1200		375	4.29
IX	3250	1620	1610	1545	1510	1460	1430	235	4.21
	3200							351	4.55
X	3255	1625	1610	1510	1450	1435	1320	254	4.10
	3200		1580	1225				329	4.39
XI	3240	1630	1610	1525	1510	1460	1430	259	4.03
	3190		1580	1310	1250			331	4.42
XII	3240	1620	1605	1510	1455	1435	1400	259	4.12
	3195		1580	1350	1300	1270	1225	340	4.36
XIII	3285	1615	1570	1540	1505	1450	1350	295	4.12
	3200			1260	1230			402	4.28
XIV	3250	1620	1565	1525	1500	1450	1325	243	3.75
	3195			1310	1250			285	4.21

upon the nature of the substituents at the position 5 of the aromatic thiadiazole ring. While substrates bearing an activating substituent give lower (20—60%) yields, the corresponding bromo and chloro derivatives give yields of 80%, and compounds having a nitro group at the position 4 and 5 on the benzene and furan ring give yields of 92 and 85%, respectively,

The reaction performed with $K_3Fe(CN)_6$ as the oxidizing reagent was not a simple process as it gave, in addition to unwanted by-products, only low yields of the desired thiadiazoles. Thus, the oxidation of 1-benzal-4-phenylthiosemicarbazone with $K_3Fe(CN)_6$ gave the corresponding thiadiazole and 1-benzal-4-phenylsemicarbazone in the yields of 10 and 40%, respectively.

Table 2 shows the i.r. spectral data for the prepared compounds *I—XIV*. The thiadiazoles show pronounced absorbance at 1650—1300 cm^{-1}. Since both C=C vibrations of the aromatic ring and the skeletal vibrations of the thiadiazole appear in this region, unambiguous band assignment was prevented.

The thiadiazoles show at 3300—3200 cm^{-1} a doublet of symmetrical absorption bands of equal intensity. It is known [10], that compounds containing a secondary amino group show a single absorption ν(NH) band, whereas solid, *N*-substituted



Scheme 2
Mass spectral fragmentation of *VII*

acid amides, as a result of the pronounced associations, show absorption at two distinct cm^{-1} values. Since the compounds under investigation contain the skeletal arrangement similar to that of acid amides the pair of the absorption bands referred to was assigned analogously, *i.e.* to the ν_{as}(NH) in the solid state. The correctness of this assignment was confirmed by measurements in chloroform in which case thiadiazoles produced spectra containing, instead of the above-mentioned doublet, a band at 3390 cm^{-1} of the free NH vibrations.

The u.v. spectral characteristics of thiadiazoles are given in Table 2. As can be seen, all compounds except the nitro derivatives, show absorption bands at 243—267 and 285—359 nm, the former being more intense. The nitro compounds show a bathochromic shift.

The structure of the synthesized thiadiazoles was confirmed also by mass spectrometry. As an example, Scheme 2 shows the deduced fragmentation pathway of *VII*. The appearance of the molecular ion and further fragment peaks makes it possible to confirm the expected structure.

Experimental

The i.r. spectra for compounds in KBr pellets (compound—KBr ratio 1 : 500) were measured with a double-beam UR-20 spectrophotometer (Zeiss, Jena). The measurements in the ν(NH) regions were done also for the solutions in chloroform at several concentrations. The instrument was calibrated against a polystyrene foil.

The u.v. spectra (200—800 nm) for the solutions in dioxan ($3—5 \times 10^{-5}$ M) were obtained with a specord UV VIS (Zeiss, Jena) instrument.

The mass spectra (70 eV) were recorded at an emission of 100 μA with an MS-902 spectrometer using the direct sample introduction technique. The temperature of the ionizing chamber was 145°C.

The thiosemicarbazones were prepared by treatment of commercial phenyl isothiocyanate with hydrazine hydrate. The produced phenyl thiosemicarbazide [11] was subsequently condensed with aldehydes to give the corresponding thiosemicarbazones [12].

Oxidation of thiosemicarbazones with $FeCl_3$

a) *2-Anilino-5-(4-nitrophenyl)-1,3,4-thiadiazole*

A solution of ferric chloride (4 g; 0.015 mol) in alcohol (30 ml) was added to a solution of 1-(4-nitro-benzal)-4-phenyl thiosemicarbazone (1.5 g; 0.005 mol) in alcohol (150 ml) and the mixture was heated under reflux for 30 min. The precipitate formed was collected, washed with alcohol and the crude product was crystallized from benzene. Yield 1.38 g (92%), m.p. 274—276°C.

b) *2-Anilino-5-furyl-1,3,4-thiadiazole*

A solution of ferric chloride (2.4 g; 0.009 mol) in alcohol (20 ml) was added to a solution of 1-furylaldehyde-4-phenyl thiosemicarbazone (0.7 g; 0.003 mol) in alcohol (50 ml) and the mixture was heated for 30 min. The brownish solution was concentrated and the crude product was precipitated by the addition of water. The solid was collected, dissolved in alcohol, treated with charcoal and again precipitated with water. Recrystallization from alcohol gave material (0.27 g; 39%), melting at 174—176°C.

c) *2-Anilino-5-phenyl-1,3,4-thiadiazole*

A solution of ferric chloride (4 g; 0.015 mol) in alcohol (30 ml) was added to a solution of 1-benzal-4-phenylthiosemicarbazone (1.3 g; 0.005 mol) in alcohol (50 ml) and the mixture was heated for 70 min. The formed precipitate was collected, washed with alcohol and recrystallized from the same solvent to give 0.8 g (62%) of the product melting at 199—200°C. Other 5-substituted 2-anilino-1,3,4-thiadiazoles were prepared in the same manner (Table 1).

Oxidation of thiosemicarbazones with $K_3Fe(CN)_6$

2-Anilino-5-phenyl-1,3,4-thiadiazole

To a solution of 1-benzal-4-phenyl thiosemicarbazone (1 g; 0.004 mol) in ethanol (50 ml) was added at 50°C and with stirring a solution of sodium hydroxide (2 g) in water (20 ml), followed by a solution of $K_3Fe(CN)_6$ (10 g) in water (90 ml). The precipitate was collected after 15 min and washed with several portions of hot water to remove the inorganic material. The crude product was dried and eluted (twice) from a column of silica gel (30 g) with chloroform—acetone (9 : 1) and then from a column of alumina (80 g) with chloroform—acetone (7 : 3). The following compounds were obtained, in addition to the starting material:

1-benzal-4-phenyl semicarbazone (0.4 g; 40%), m.p. 178—179°C (for $C_{14}H_{13}O$ (239.26) calculated: 70.28% C, 5.45% H, 17.58% N; found: 70.43% C, 5.32% H, 17.41% N);

2-anilino-5-phenyl-1,3,4-thiadiazole (6.1 g; 10%), m.p. 197—199°C.

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