A New Synthesis of Symmetrical 2,5-Diaryl-1,3,4-thiadiazoles

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Treatment of aromatic aldehydes with sulfur and hydrazine hydrate in the ratio 1:2:3, respectively, under the Willgerodt conditions affords the title compounds in excellent yields and in a good state of purity. Under the same conditions 2-chloro and 2,6-dichlorobenzaldehyde yield 3*H*-1,2-benzodithiole-3-thione and bis-(2,6-dichlorobenzyl)tetrasulfide, respectively.

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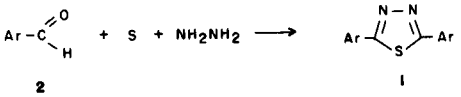
As a part of a program directed to obtain molecules with biological acitivity, containing 1,3,4-thiadiazole ring, in a previous paper, some of us, reported on the synthesis and pharmacological activity of a series of 2-amino-5-aryl-1,3,4-thiadiazoles [1]. In continuation the following is a report on an attractive method for the preparation of symmetrical 2,5-diaryl-1,3,4-thiadiazoles **1**.

Several publications and patents describe the synthesis of these heterocyclic compounds by treatment of mono- or 1,2-dibenzoylhydrazine with phosphorus pentasulfide or by oxidation of thiobenzoylhydrazones of aromatic aldehydes [2]. We obtained thiadiazoles **1a-r**, in an easier fashion by treatment of aromatic aldehydes **2a-r** with sulfur and hydrazine hydrate, in the ratio 1:2:3 respectively, under the Willgerodt conditions, in a steel autoclave at 150° for 12 hours (Scheme 1).

Scheme 1

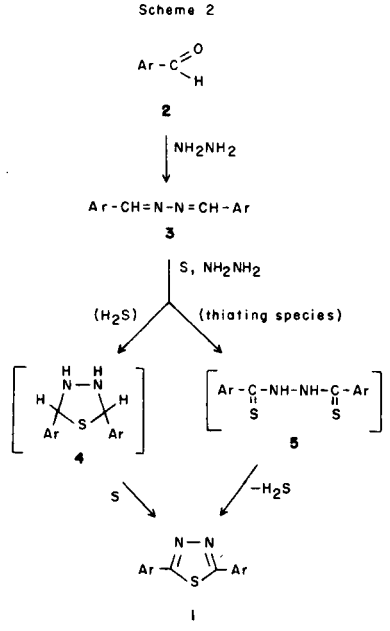


2 **1**

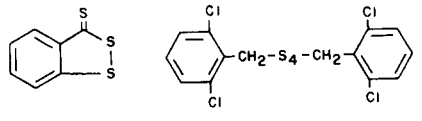
1,2a	Ar = C_6H_5	**1,2j**	Ar = 4-$CH_3C_6H_4$
b	Ar = 3-ClC_6H_4	**k**	Ar = 3-$CH_3OC_6H_4$
c	Ar = 4-ClC_6H_4	**l**	Ar = 4-$CH_3OC_6H_4$
d	Ar = 4-BrC_6H_4	**m**	Ar = 4-$(CH_3)_2NC_6H_4$
e	Ar = 3,4-$Cl_2C_6H_3$	**n**	Ar = 3,4-$(CH_3)_2C_6H_3$
f	Ar = 4-$O_2NC_6H_4$	**o**	Ar = 3,4,5-$(CH_3O)_3C_6H_2$
g	Ar = 2-HOC_6H_4	**p**	Ar = 3,4-$(OCH_2O)C_6H_3$
h	Ar = 4-HOC_6H_4	**q**	Ar = 2,4-$(CH_3O)_2C_6H_3$
i	Ar = 3-$CH_3C_6H_4$	**r**	Ar = 2,5-$(CH_3O)_2C_6H_3$

Our synthetic approach was based on the assumption that hydrazine could lead to benzalazines **3**. On the other hand hydrazine, because of its basic character, should be able to open the eight-membered ring of elemental sulfur and then to generate thiating species. Interaction of **3** with thiating species should yield intermediate thiadiazolidines **4** and/or 1,2-dithiobenzoylhydrazines **5**, which are known to afford 1,3,4-thiadiazoles **1**, under the adopted experimental conditions [2,3] (Scheme 2).

Scheme 2



With exception of 2-chloro- and 2,6-dichlorobenzaldehyde which lead to 3*H*-1,2-benzodithiole-3-thione **6** and bis(2,6-dichlorobenzyl)-tetrasulfide **7** respectively, in all the other cases, thiadiazoles **1a-r** were obtained in excellent yields (Table 1) and good state of purity.



6 **7**

In no reaction mixture could sulfurated intermediates **4** and **5** be isolated. On the other hand experiments carried out below 150° in a steel autoclave or by refluxing benzaldehyde, sulfur and hydrazine hydrate in the ratio 1:2:3 in ethanol, *N,N*-dimethylformamide, pyridine or dioxane, led only to the isolation of benzalazine.

The formation of trithione **6**, in the case of 2-chlorobenzaldehyde, can be ascribed to an easy 2-chlorine sub-

Table 1

2,5-Diaryl-1,3,4-thiadiazoles **1a-r**

Compound No.	Ar	Yield %	Crystallization Solvent	Mp °C	Lit Mp °C	References
1a	C_6H_5	86	Ethanol	143-144	143-144	[5]
1b	3-ClC_6H_4	92.3	Dioxane/Ethanol/Water (6:2:1)	155-156	153.5-155.5	[5]
1c	4-ClC_6H_4	92.2	Dioxane/Ethanol (5:1)	224-225	224.8-225.4	[5]
1d	4-BrC_6H_4	95	Dioxane/Ethanol/Water (8:1:1)	240-241	241.2-242.8	[5]
1e	3,4-$Cl_2C_6H_3$	95	Dioxane/Ethanol (4:1)	238-239	238-241	[5]
1f	4-$NO_2C_6H_4$	22	DMF	331	331	[6]
1g	2-OHC_6H_4	82	Ethanol	231-232	231-232	[7]
1h	4-OHC_6H_4	96.2	Ethanol	307-308	300	[7]
1i	3-$CH_3C_6H_4$	96.2	Ethanol/Water (5:2)	90-91	88.8-89.8	[5]
1j	4-$CH_3C_6H_4$	91	Ethanol/Water (1:1)	162-163	163.6-164.8	[5]
1k	3-$CH_3OC_6H_4$	91.2	Ethanol/Water (1:1)	89-90	89.5-90.5	[5]
1l	4-$CH_3OC_6H_4$	91.7	Ethanol	171-172	171-172	[5]
1m	4-$(CH_3)_2NC_6H_4$	72	DMF	290-292		
1n	3,4-$(CH_3)_2C_6H_3$	98.6	Dioxane/Ethanol/Water (8:10:1)	191-192	189.6-190.8	[5]
1o	3,4,5-$(CH_3O)_3C_6H_2$	84.2	Dioxane/Ethanol/Water (3:2:3)	188	187-188	[5]
1p	3,4-$(CH_2O)C_6H_3$	82	DMF	241-242		
1q	2,4-$(CH_3O)C_6H_3$	91.4	Dioxane	180-181	178.6-179.8	[5]
1r	2,5-$(CH_3O)C_6H_3$	92	Ethanol/Water (1:1)	148-150	149.2-150.2	[5]

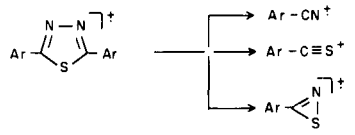
Table 2

Elemental Analyses of **1a-r**

Compound No.	Molecular Formula	Calcd. C	H	N	S	Found C	H	N	S
1a	$C_{14}H_{10}N_2S$	70.58	4.20	11.76	13.44	70.74	4.15	11.81	13.55
1b	$C_{14}H_{18}Cl_2N_2S$	54.73	2.60	9.12	10.42	54.56	2.71	9.16	10.51
1c	$C_{14}H_8Cl_2N_2S$	54.73	2.60	9.12	10.42	54.88	2.39	9.35	10.65
1d	$C_{14}H_8Br_2N_2S$	42.44	2.02	7.07	8.08	42.54	2.21	7.21	7.73
1e	$C_{14}H_6Cl_4N_2S$	44.70	1.59	7.45	8.51	44.84	1.62	7.62	8.74
1f	$C_{14}H_8N_4O_4S$	51.21	2.43	17.07	9.75	51.50	2.61	17.18	9.57
1g	$C_{14}H_{10}N_2O_2S$	62.22	3.70	10.37	11.85	62.06	3.50	10.18	11.63
1h	$C_{14}H_{10}N_2O_2S$	62.22	3.70	10.37	11.85	62.44	3.89	10.53	11.93
1i	$C_{15}H_{14}N_2S$	72.18	5.26	10.52	12.03	72.29	5.24	10.53	12.32
1j	$C_{15}H_{14}N_2S$	72.18	5.26	10.52	12.03	72.25	5.23	10.35	12.29
1k	$C_{15}H_{14}N_2O_2S$	64.42	4.69	9.39	10.73	64.69	4.83	9.60	10.94
1l	$C_{15}H_{14}N_2O_2S$	64.42	4.69	9.39	10.73	64.57	4.45	9.59	10.65
1m	$C_{18}H_{20}N_4S$	66.60	6.17	17.28	9.87	66.79	6.38	17.33	9.64
1n	$C_{18}H_{18}N_2S$	73.46	6.12	9.52	10.88	73.21	6.35	9.24	11.03
1o	$C_{20}H_{22}N_2O_6S$	57.41	5.26	6.69	7.65	57.19	5.31	6.34	7.75
1p	$C_{14}H_{10}N_2O_4S$	55.62	3.31	9.27	10.59	55.37	3.04	9.45	10.80
1q	$C_{18}H_{18}N_2O_4S$	60.33	5.02	7.82	8.93	60.47	4.84	7.98	9.12
1r	$C_{18}H_{18}N_2O_4S$	60.33	5.02	7.82	8.93	60.67	4.84	7.50	8.81

stitution of thiating agent. Similar cyclizations in related systems have been reported [4]. The intriguing formation of tetrasulfide **7** from 2,6-dichlorobenzaldehyde deserves further investigations.

Structures **1a-r** were consistent with elemental analyses and mass spectra. The melting points of the already known thiadiazoles agree well with those reported in the literature. Mass spectra exhibited prominent molecular ion (base peak) and three strong fragment ions arising from C-S bonds rupture.



Trithione structure **6** was supported by elemental analysis, mixed melting point and by comparison of ir and mass spectra with an authentic sample. Tetrasulfide structure **7** was identified on the basis of elemental analysis and pmr and mass spectra. The pmr spectrum showed a multiplet centered at δ 7.00 for aromatic protons and a singlet at δ 4.05 for methylene protons. Mass spectrum was dominated by dichlorotropilium ion, which furnished the base peak, molecular ion and fragment ions deriving by the subsequent loss of sulfur atoms from molecular ion.

Because of the ready availability of reactants and its experimental simplicity, the "one pot" approach here reported seems to be a convenient alternative synthetic method to prepare symmetrical 2,5-diaryl-1,3,4-thiadiazoles **1**.

In preliminary biological tests, compounds **1a,g,j,l,o,q** were found to exhibit an antimycotic activity higher than that of 2-amino-5-aryl-1,3,4-thiadiazoles [1] but a lower antibacterial one. Complete results of biological screening will be reported at a later date.

EXPERIMENTAL

Melting points were determined on an electrothermal apparatus and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 281 spectrophotometer. The pmr spectra were determined on a Varian A 60 spectrometer using tetramethylsilane as an internal standard. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. Mass spectra were obtained with an LKB 9000 S mass spectrometer. All starting materials were commercial products.

2,5-Diaryl-1,3,4-thiadiazoles **1a-r**.

A mixture of aromatic aldehyde **2a-r** (0.02 moles), sulfur (0.03 g-atom) and hydrazine hydrate (0.08 moles, 4 ml) in ethanol (20 ml) was heated at 150° in a steel autoclave for 12 hours. After cooling, the reaction mixture was diluted with a small amount of ethanol. Sulfur which separated was filtered off. The filtrate was evaporated under reduced pressure and the residue crystallized from an appropriate solvent. Yields, melting points, crystallization solvents and elemental analysis of thiadiazoles **1a-r**, are given in Tables 1 and 2.

In some cases thiadiazole separated together with sulfur from ethanol. The reaction mixture was then evaporated under reduced pressure and the residue dissolved in chloroform. The chloroform solution was shaken with a concentrated sodium sulfide solution (to remove most of the sulfur), with water, dried (magenesium sulfate), filtered and then evaporated under reduced pressure. The resulting residue was crystallized from an appropriate solvent.

3*H*-1,2-Benzodithiole-3-thione (**6**).

A mixture of 2-chlorobenzaldehyde (0.02 moles), sulfur (0.03 moles) and hydrazine hydrate (0.08 moles, 4 ml) in ethanol (20 ml) was heated at 150° in a steel autoclave for 12 hours. After cooling, the reaction mixture was evaporated under reduced pressure and the residue, which was mainly compound **6** and sulfur, was chromatographed on silica gel 60 (Merck), using cyclohexane as eluent. Elution gave sulfur as the first product and then **6** as orange needles (1.98 g, 54%), mp 95° (lit [8], mp 94-95°); ms: 184 (M^+).

Anal. Calcd. for C_7H_4S: C, 45.65; H, 2.17; S, 52.17. Found: C, 45.70; H, 2.24; S, 51.94.

Bis(2,6-dichlorobenzyl)tetrasulfide (**7**).

The conditions and work up employed for the preparation of compounds **1** were used. Starting from 3.5 g (0.02 mole) of 2,6-dichlorobenzaldehyde, 2.8 g (63%) of tetrasulfide **7** was obtained as white crystals, mp 172-173°; pmr (carbon disulfide): 4.05 (s, CH_2, 4H), 6.85-7.15 (m, aromatic, 6H); ms: 446 (M), 414 (M − 32), 382 (M − 64), 350 (M − 96), 159 (dichlorotropilium ion, base peak).

Anal. Calcd. for $C_{14}H_{10}Cl_4S_4$: C, 37.50; H, 2.23; S, 28.57. Found: C, 37.62; H, 2.18; S, 28.49.

Benzalazine (**3a**).

When a mixture of benzaldehyde, sulfur and hydrazine hydrate in ethanol in the ratio 1:2:3 was heated in a steel autoclave at 110-130° or refluxed in ethanol, *N,N*-dimethylformamide, pyridine or dioxane for 48 hours, benzalazine was isolated in nearly quantitative yield, mp 93° (lit [9], mp 92°), together with unreacted sulfur. Copious evolution of hydrogen sulfide was observed during refluxing.

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