Rapid Synthesis of 2,5-Disubtituted 1,3,4-Thiadiazoles under Microwave Irradiation

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The one pot, three-components condensation of aromatic aldehydes, hydrazine and sulfur in ethanol under microwave irradiation provided symmetrically 3,5-disubstituted 1,3,4-thiadiazoles in high yields and good purity. This reaction must be conducted under pressure of hydrogen sulfide produced *in-situ*. The structure of the compounds was confirmed by ^{1}H, ^{13}C NMR, MS and elemental analysis.

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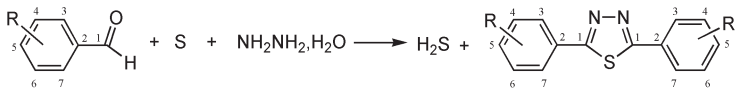
Introduction

As a part of a program directed to obtain heterocyclic molecules which can be used as corrosion inhibitors [1-4] and which can exhibit antimicotic and antibacterial activities [5,6], a number of symmetrically 2,5-disubstituted-1,3,4-thiadiazoles are quickly prepared by the reaction of aromatic aldehyde on hydrazine hydrate in presence of sulphur under microwave irradiation. Several publication and patents describe the synthesis of these heterocyclic compounds by treatment of mono or 1,2-dibenzoylhydrazine with phosphorous pentasulfide [7] and by treatment of aromatic aldehydes with sulphur and hydrazine hydrate in a steel autoclave at 150 °C for 12 hours [8]. Microwave assisted organic reaction constitute an emerging technology that make experimentally and industrially important organic syntheses more effective and more eco-friendly than conventional reactions [9,10]. This technique has been applied with success to a number of synthesis of heterocylic compounds proceeding with or without solvent such as 1,2,4-triazoles [11,12], 1,3,4-oxadiazoles [13] and 1,3,4-thiadiazoles [14].

Results and Discussion

The reaction of aromatic aldehydes with hydrazine hydrate and sulfur takes place in good yields and rapidly under microwave irradiation (Scheme and Table 1) and must be conducted under pressure of hydrogen sulfide. For this purpose we have used a microwave equipment designed for extraction, digestion, dissolution, hydrolysis or drying material. The primary purpose of this equipment is the rapid preparation of samples for a variety of analysis procedures, but we report here that it can be very efficient for organic syntheses, which must be carried out under a moderate controlled pressure. In each synthesis of thiadiazoles, the initial product is the yellow colored benzalazine, which can be isolated after 15 mn of reaction. After 1 h of microwave heating under pressure of hydrogen sulfide, the thiadiazoles can be obtained in excellent yields and good purity. Under classical heating, a good completion of this reaction required much longer times (12 h) and if the reaction is stopped after 1 hour of reaction as in microwave experiments, the thiadiazoles can be detected in very low quantities, the major products of the reaction being the corresponding azines. 2-Chlorobenzaldehyde yields 3*H*-1,2-benzodithiole-3-thione under the same experimental conditions, as it was reported by G. Mazzone et *al.* [8]. The elemental analysis (Table 2) and mass spectra are in accordance with the proposed structures. The melting points of the already known thiadiazoles agree will those reported in the literature (Table 2). The ^{1}H and ^{13}C nmr data are given in Table 3 and 4. A typical reaction procedure is as follows for the preparation compounds **2a-p**.

Scheme 1



1, 2a	Ar = 2-HOC_6H_4	**1, 2i**	Ar = 4-$(CH_3)_2NC_6H_4$
b	Ar = 3-HOC_6H_4	**j**	Ar = 4-$CH_3C_6H_4$
c	Ar = 4-HOC_6H_4	**k**	Ar = 4-ClC_6H_4
d	Ar = 3,4-HOC_6H_4	**l**	Ar = 2-pyridyl
e	Ar = C_6H_5	**m**	Ar =3-pyridyl
f	Ar = 2-$CH_3OC_6H_4$	**n**	Ar = 4-pyridyl
g	Ar = 3-$CH_3OC_6H_4$	**o**	Ar = 2-thienyl
h	Ar = 4-$CH_3OC_6H_4$	**p**	Ar = 3-thienyl

Table 1
2,5-Diaryl-1,3,4-thiadiazoles **2a-p**

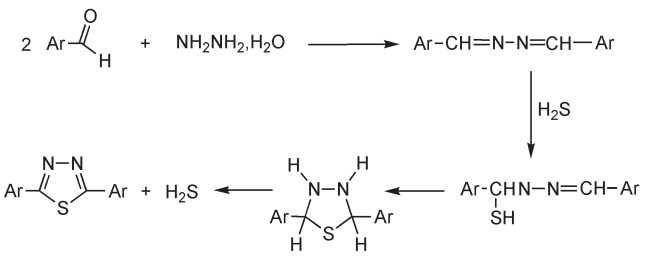
Compound No.	Ar	Yield (%)	Mp (°C)	Lit Mp (°C)	*m/z* (M +1)	References
2a	2-HOC_6H_4	83.7	230-231	231-232	271	[8]
2b	3-HOC_6H_4	97	273-274		271	
2c	4-HOC_6H_4	97.4	308-309	307-308	271	[8]
2d	3,4-HOC_6H_4	94	318 dec.		303	
2e	C_6H_5	89	143-144	143-144	239	[8]
2f	2-$CH_3OC_6H_4$	87	305 dec		299	
2g	3-$CH_3OC_6H_4$	94	90-91	89-90	299	[8]
2h	4-$CH_3OC_6H_4$	92	171.5-172	171-172	299	[8]
2i	4-$(CH_3)_2NC_6H_4$	76	289-290	290-292	325	[8]
2j	4-$CH_3C_6H_4$	94.2	163-164	162-163	267	[8]
2k	4-ClC_6H_4	94	224-225	224-225	308	[8]
2l	2-pyridyl	80	218-219		241	
2m	3-pyridyl	83	222-223		241	
2n	4-pyridyl	82	239-240		241	
2o	2-thienyl	75	158-159		251	
2p	3-thienyl	78	170.5-171		251	

Table 2
Elemental Analyses of **2a-p**

Compound No.	Molecular Formula	Calcd. C	H	N	S	Found C	H	N	S
2a	$C_{14}H_{10}N_2O_2S$	62.22	3.70	10.37	11.85	62.18	3.69	10.36	11.89
2b	$C_{14}H_{10}N_2O_2S$	62.22	3.70	10.37	11.85	62.25	3.71	10.34	11.81
2c	$C_{14}H_{10}N_2O_2S$	62.22	3.70	10.37	11.85	62.30	3.68	10.38	11.83
2d	$C_{14}H_{10}N_2O_4S$	55.62	3.31	9.27	10.59	55.71	3.35	9.24	10.61
2e	$C_{14}H_{10}N_2S$	70.58	4.20	11.76	13.44	70.72	4.18	11.80	13.50
2f	$C_{16}H_{14}N_2O_2S$	64.42	4.69	9.39	10.73	64.52	4.65	9.43	10.71
2g	$C_{16}H_{14}N_2O_2S$	64.42	4.69	9.39	10.73	64.61	4.72	9.42	10.68
2h	$C_{16}H_{14}N_2O_2S$	64.42	4.69	9.39	10.73	64.58	4.68	9.43	10.66
2i	$C_{18}H_{20}N_4S$	66.60	6.17	17.28	9.87	66.73	6.19	17.21	9.82
2j	$C_{16}H_{14}N_2S$	72.18	5.26	10.52	12.03	72.26	5.24	10.485	12.00
2k	$C_{14}H_8Cl_2N_2S$	54.73	2.60	9.12	10.42	54.82	2.42	9.31	10.46
2l	$C_{12}H_8N_4S$	60.00	3.33	23.33	13.33	60.13	3.32	23.41	13.27
2m	$C_{12}H_8N_4S$	60.00	3.33	23.33	13.33	60.09	3.30	23.45	13.31
2n	$C_{12}H_8N_4S$	60.00	3.33	23.33	13.33	60.12	3.37	23.38	13.27
2o	$C_{10}H_6N_2S_3$	48.00	2.40	11.20	38.40	48.11	2.38	11.16	38.36
2p	$C_{10}H_6N_2S_3$	48.00	2.40	11.20	38.40	48.08	2.41	11.17	38.39

It is well known that the aldehydes react very rapidly with hydrazine to give the corresponding azines. Subsequent reaction with hydrogen sulfide, first produced

Scheme 2



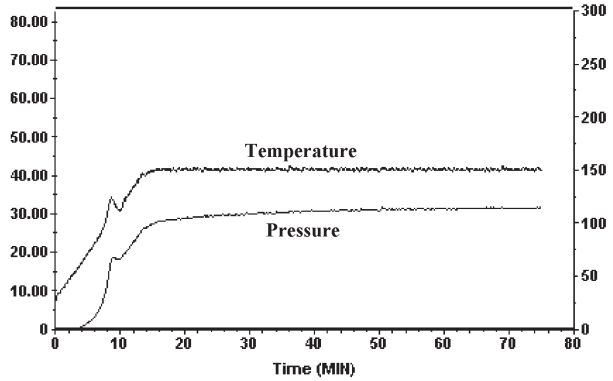


Figure. Evolution of temperature and pressure during the reaction.

Table 3

^{1}H nmr data (d values, dimethyl-d_6 sulfoxide) for 2,5-Diaryl-1,3,4-thiadiazoles **2a-p**

Compound No.	Aromatic signals	Substituent
2a	7.02 (t, J = 7.2 Hz, 2H); 7.09 (d, J = 8.06 Hz, 2H), 7.39 (t, J = 7.08 Hz, 2H); 8.25 (d, J = 7.33 Hz, 2H)	11.31 (s, 2H) OH
2b	6.96-7.00 (m, 2H); 7.41-7.42 (m, 6H)	9.97 (s, 2H) OH
2c	6.95 (d, J = 8.79 Hz, 4H); 7.81 (d, J = 8.54 Hz, 4H)	10.41 (s, 2H) OH
2d	6.88 (d, J = 8.06 Hz, 2H); 7.25 (d, J = 8.06 Hz, 2H); 7.41 (s, 2H)	9.60 (s, 4H) OH
2e	7.58-7.61 (m, 6H); 8.00-8.05 (m, 4H)	—
2f	6.91 (d, J = 7.32 Hz, 2H); 7.00 (t, J = 8.24 Hz, 2H); 7.16 (d, J = 7.33 Hz, 2H); 7.29 (t, J = 7.78 Hz, 2H)	3.78 (s, 6H) OCH_3
2g	7.16 (d, J = 7.63 Hz, 2H); 7.45-7.59 (m, 6H)	3.85 (s, 6H) OCH_3
2h	7.13 (d, J = 8.54 Hz, 4H); 7.94 (d, J = 8.54 Hz, 4H)	3.85 (s, 6H) OCH_3
2i	6.82 (d, J = 8.54 Hz, 4H); 7.76 (d, J = 8.54 Hz, 4H)	3.01 (s, 12H) CH_3
2j	7.32 (d, J = 7.94 Hz, 4H); 7.84 (d, J = 7.94 Hz, 4H)	2.37 (s, 6H) CH_3
2k	7.69 (d, J = 7.82 Hz, 4H); 8.05 (d, J = 7.82 Hz, 4H);	—
2l	7.62 (d, J = 6.1 Hz, 2H); 8.07 (d, J = 7.78 Hz, 2H) 8.34 (t, J = 7.92 Hz, 2H); 8.76 (t, J = 3.96 Hz, 2H)	—
2m	7.65 (t, J = 4.85 Hz, 2H); 8.44 (d, J = 7.82 Hz, 2H); 8.79 (d, J = 7.82 Hz, 2H); 9.22 (s, 2H)	—
2n	8.02 (d, J = 6.4 Hz, 4H); 8.84 (d, J = 6.4 Hz, 4H)	—
2o	7.27 (t, J = 4.42 Hz, 2H); 7.81 (d, J = 3.67 Hz, 2H); 7.88 (d, J = 4.88 Hz, 2H)	—
2p	7.68 (d, J = 5.19 Hz, 2H); 7.80 (d, J = 5.19 Hz, 2H); 8.33 (s, 2H)	—

Table 4

^{13}C nmr data (d values, dimethyl-d_6 sulfoxide) for 2,5-Diary-1,3,4-thiadiazoles **2a-p**
(Numerotation of C is given is Scheme 1)

Compound No.	C_1	C_2	C_3	C_4	C_5	C_6	C_7	Substituent
2a	163.12	116.49	154.74	116.80	131.87	119.66	127.65	—
2b	167.64	130.67	118.67	157.99	113.72	130.56	118.56	—
2c	166.55	120.63	129.20	116.18	160.28	116.18	129.20	—
2d	166.58	119.79	114.10	148.64	145.83	116.19	120.95	—
2e	167.72	131.45	127.64	129.46	129.51	129.46	127.64	—
2f	169.56	124.91	156.95	111.12	130.79	120.03	128.96	55.43
2g	167.63	130.64	130.73	159.73	117.35	112.28	120.15	55.40
2h	166.58	122.15	129.16	114.85	161.56	114.85	129.16	55.46
2i	168.52	127.54	126.09	114.15	151.85	114.15	126.09	39.68
2j	161.12	130.96	128.69	130.69	140.5	130.69	128.69	21.25
2k	166.91	129.59	128.20	129.35	136.15	129.35	128.20	—
2l	171.14	148.17	—	150.30	126.22	138.02	120.56	—
2m	171.12	126.20	148.16	—	150.29	120.54	137.99	—
2n	170.23	137.27	122.76	152.22	—	152.22	122.76	—
2o	160.89	131.10	—	130.69	128.67	130.94	—	—
2p	161.76	128.62	130.75	—	127.95	126.21	—	—

by the reaction of hydrazine with sulfur, leads to the formation of the tertrahydrothiadiazole ring, which is rapidly dehydrogenated by the sulfur (Scheme 2).

The first step, the azine formation, is expected to be faster than the second one, the addition of hydrogen sulfide, which must be present in excess as it can be seen on the figure. When the reaction is stopped just after the stabilization of the pressure (15 min), the yield in thiadiazoles is very poor and the azine can be isolated in good quantity.

Several new 1,3,4-thiadiazoles have been tested as corrosion inhibitors for steel in acidic media. These studies have shown that the thiadiazole derivatives are very efficient even at low concentration (10^{-4} *M*) [3,15].

EXPERIMENTAL

A mixture of aromatic aldehyde **1a-r** (0.02 moles), sulfur (0.03 g-atom) and hydrazine hydrate (0.08 moles) in ethanol (20 ml) was introduced into a fluoropolymere cylindrical flask placed in a MARS5 XP-1500 PLUS CEM multimode microwave reactor and irradiated for 1 h (300 W) at 150 °C under pressure (Figure). After cooling, the solvent was evaporated under reduced pressure.

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

The residue was treated with ethanol and filtered to remove the sulfur. The ethanolic solution was evaporated under reduced pressure and the residue was treated with 50 ml of an aqueous solution of sodium hydroxide (20 %) and filtered. Treatment of the filtrate with an aqueous hydrochloric acid solution (37 %) gives a yellowish precipitate, which is collected by filtration and washed with water and dried. Products were crystallized from ethanol.

2,5-Diaryl-1,3,4-thiadiazoles **2e-p**.

The residue was dissolved in chloroform. The chloroform solution was shaken with a concentrated sodium sulfide solution (to remove most of the sulfur), with water, dried (magnesium sulfate), filtered and then evaporated by rotary evaporation. The resulting residue was crystallized from ethanol.

Products **2a-p** was identified by ^{1}H and ^{13}C nmr and MS: data are in accordance with the proposed structures.

REFERENCES AND NOTES

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