2-Pyridyl-5-alkyloxyphenyl-1,3,4-thiadiazoles by the Action of Sulfur on Methylpyridines in the Presence of Alkyloxybenzoylhydrazines

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Title thiadiazoles were obtained by reaction of sulfur and methylpyridines in the presence of alkyloxybenzoylhydazines. Corresponding oxadiazoles together with symmetrical 2,5-dialkyloxyphenyl-1,3,4-thiadiazoles were also isolated as by-products. The formation of different reaction products is rationalized.

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In a previous paper we reported the synthesis and biological activity of several series of 2-amino- and 2-amino substituted-5-alkyloxyphenyl-1,3,4-thiadiazoles [1].

In order to extend our investigations on structure-activity relationships with regard to the nitrogen containing substituents, we prepared a series of 2-pyridyl-5-alkyloxyphenyl-1,3,4-thiadiazoles. These latter compounds could show a modified activity because of amino-2-group substitution by a pyridine nucleus.

Biological activity deriving from alkyloxyphenyl groups on 5-position was previously discussed [2,3].

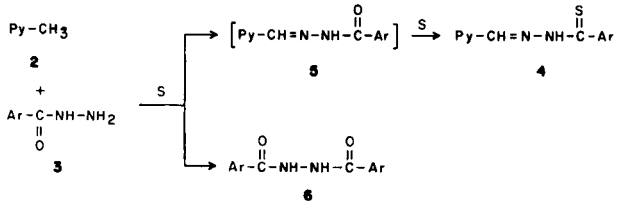
The following reports the proper conditions for the new synthesis of 2-pyridyl-5-alkyloxyphenyl-1,3,4-thiadiazoles **1a-h** based on the action of sulfur on alkylheterocycles **2a-d** in the presence of aroylhydrazines **3a,b**.

Oxidation of methylpyridines **2** by sulfur in the presence of aroyl and heteroaroylhydrazines **3** has been utilized for the preparation of pyridinaldehyde thioaroylhydrazones **4** [4].

Unisolable intermediates of the reaction were showed to be the pyridinaldehyde aroylhydrazones **5** and symmetrical diaroylhydrazines **6** were found as secondary products [4,5].

At higher temperatures, however, yields of **4** decrease because of their conversion into more stable unidentified compounds [5].

Scheme 1

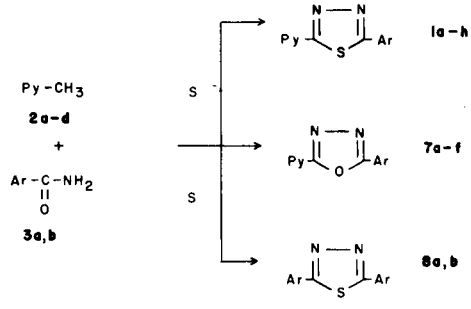


Py = 2-pyridyl, 4-pyridyl, 2-quinolyl; Ar = phenyl, substituted phenyl, 2-pyridyl, 4-pyridyl.

Because of the facile oxidizability of thioaroylhydrazones **4** [6] and the well known oxidizing ability of sulfur, transformation of the acyclic **4** into 2-pyridyl-5-aryl-1,3,4-thiadiazoles under the reaction conditions could be anticipated at higher temperatures than those used for the synthesis of **4**.

Indeed the reaction of sulfur, methylpyridines **2a-d** and alkyloxybenzoylhdyrazines **3a,b** in the ratio 2.0:1.5:1, respectively, at 180° (oil bath) for 12 hours, quenched by adding acetonitrile to the still warm solution, afforded the expected thiadiazoles **1a-h** in satisfactory yields, along with much minor amounts of the corresponding oxadiazoles **7a-f** and symmetrical 2,5-dialkyloxyphenyl-1,3,4-thiadiazoles **8a,b** as by-products. Thiadiazoles **1** could be obtained by repeated crystallizations of reaction crudes in

Scheme 2



2a Py = 2-pyridyl
2b Py = 4-pyridyl
2c Py = 2-quinolyl
2d Py = 4-quinolyl
3a Ar = 3,4-(OCH_2O)-C_6H_3
3b Ar = 3,4,5-(OCH_3)$_3$-C_6H_2
8a Ar = 3,4-(OCH_2O)-C_6H_3
8b Ar = 3,4,5-(OCH_3)$_3$-C_6H_2

1a Py = 2-pyridyl,	Ar = 3,4-(OCH_2O)-C_6H_3
1b Py = 4-pyridyl,	Ar = 3,4-(OCH_2O)-C_6H_3
1c Py = 2-quinolyl,	Ar = 3,4-(OCH_2O)-C_6H_3
1d Py = 4-quinolyl,	Ar = 3,4-(OCH_2O)-C_6H_3
1e Py = 2-pyridyl,	Ar = 3,4,5-(OCH_3)$_3$-C_6H_2
1f Py = 4-pyridyl,	Ar = 3,4,5-(OCH_3)$_3$-C_6H_2
1g Py = 2-quinolyl,	Ar = 3,4,5-(OCH_3)$_3$-C_6H_2
1h Py = 4-quinolyl,	Ar = 3,4,5-(OCH_3)$_3$-C_6H_2
7a Py = 2-pyridyl,	Ar = 3,4-(OCH_2O)-C_6H_3
7b Py = 4-pyridyl,	Ar = 3,4-(OCH_2O)-C_6H_3
7c Py = 2-quinolyl,	Ar = 3,4-(OCH_2O)-C_6H_3
7d Py = 2-pyridyl,	Ar = 3,4,5-(OCH_3)$_3$-C_6H_2
7e Py = 4-pyridyl,	Ar = 3,4,5-(OCH_3)$_3$-C_6H_2
7f Py = 2-quinolyl,	Ar = 3,4,5-(OCH_3)$_3$-C_6H_2

Table 1

2-Pyridyl-5-alkyloxyphenyl-1,3,4-thiadiazoles **1a-h**

Compound	Ar	Py	Yield %	Mp °C [a]	Molecular Formula	Analysis % C	H	Calcd./Found N	S
1a	3,4-(OCH_2O)-C_6H_3	2-pyridyl	37	212	$C_{14}H_9N_3O_2S$	59.36	3.18	14.84	11.30
						59.41	3.21	14.81	11.35
1b	3,4-(OCH_2O)-C_6H_3	4-pyridyl	45	203-204	$C_{14}H_9N_3O_2S$	59.36	3.18	14.84	11.30
						59.28	3.24	14.87	11.33
1c	3,4-(OCH_2O)-C_6H_3	2-quinolyl	48	221	$C_{18}H_{11}N_3O_2S$	64.86	3.30	12.61	9.60
						65.00	3.14	12.69	9.75
1d	3,4-(OCH_2O)-C_6H_3	4-quinolyl	32	185	$C_{18}H_{11}N_3O_2S$	64.86	3.30	12.61	9.60
						65.01	3.32	12.59	9.65
1e	3,4,5-(OCH_3)$_3$-C_6H_2	2-pyridyl	39	195-196	$C_{16}H_{15}N_3O_3S$	58.35	4.55	12.76	9.72
						58.45	4.58	12.80	9.75
1f	3,4,5-(OCH_3)$_3$-C_6H_2	4-pyridyl	47	186	$C_{16}H_{15}N_3O_3S$	58.35	4.55	12.76	9.72
						58.37	4.52	12.81	9.77
1g	3,4,5-(OCH_3)$_3$-C_6H_2	2-quinolyl	48	196-197	$C_{20}H_{17}N_3O_3S$	63.32	4.48	11.08	8.44
						63.45	4.51	10.85	8.48
1h	3,4,5-(OCH_3)$_3$-C_6H_2	4-quinolyl	36	214-215	$C_{20}H_{17}N_3O_3S$	63.32	4.48	11.08	8.44
						63.41	4.50	10.87	8.41

[a] Mp °C of the recrystallized products from DMF-EtOH (1:10).

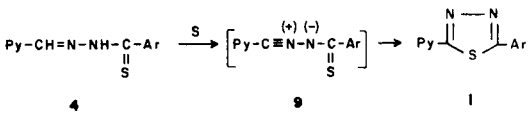
the yields stated in Table 1. Column chromatography of the mother liquors afforded by-products **7** and **8**.

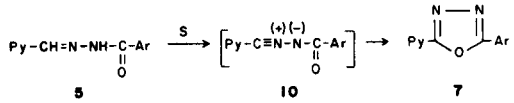
No formation of oxadiazoles was observed in reactions with lepidine **2d**. The lesser reactivity of lepidine is also showed by the lower yields of corresponding thiadiazoles **1g,h**. Because of the even lesser pyridine 3-group, attempts to prepare 2-(3-pyridyl)-derivatives were unsuccessful.

As it was verified independently for two terms of the series (see experimental), the formation of **1** and **7** under the new conditions is due to oxidation ability of sulfur upon **4** and **5** respectively.

The details of the oxidations with sulfur are unknown. Sulfur could however oxidize **4** and **5** to the corresponding nitrile imine intermediates **9** and **10**, which could cyclize intramolecularly by a 6π-electrocyclic process [7].

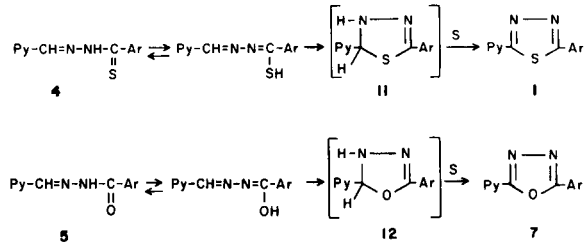
Scheme 3





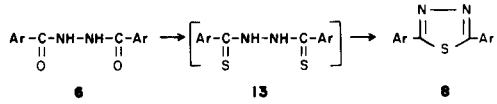
Sulfur could also conceivably oxidize **4** and **5** by oxidative aromatization of the ring tautomers **11** and **12** [8].

Scheme 4



The formation of symmetrical thiadiazoles **8** clearly accounts for the lack of diaroylhydrazines **6** among the secondary reaction products, since these latter undoubtedly are converted into **8** *via* dithioaroylhydrazines **13** which spontaneously split off hydrogen sulphide [6].

Scheme 5



The very low yield of **8** shows that the route leading to **4** is disfavoured under the new experimental conditions.

Structures of all new isolated thiadiazoles **1a-h** were consistent with elemental analysis, and ir, pmr and mass spectra. No absorption of NH and NHCS was observed in the ir spectra, but those of thiadiazole ring at 1600-1640 cm^{-1} (C=N) and 1080-1095 cm^{-1} (C-S-C) and those of pyridyl and substituted phenyl rings. The pmr spectra exhibited

Table 2

2-Pyridyl-5-alkoxyphenyl-1,3,4-oxadiazoles **7a-f**

Compound	Ar	Py	Mp °C [a]	Molecular Formula	Analysis % Calcd./Found C	H	N
7a	3,4-(OCH_2O)-C_6H_3	2-pyridyl	184-185	$C_{16}H_{15}N_3O_4$	62.92	3.37	15.73
					62.41	3.34	16.08
7b	3,4-(OCH_2O)-C_6H_3	4-pyridyl	194-195	$C_{16}H_{15}N_3O_4$	62.92	3.37	15.73
					63.05	3.31	15.69
7c	3,4-(OCH_2O)-C_6H_3	2-quinolyl	187	$C_{18}H_{11}N_3O_4$	68.13	3.47	13.24
					68.22	3.51	13.27
7d	3,4,5-(OCH_3)$_3$-C_6H_2	2-pyridyl	177-178	$C_{16}H_{15}N_3O_4$	61.34	4.79	13.41
					60.80	4.71	13.73
7e	3,4,5-(OCH_3)$_3$-C_6H_2	4-pyridyl	211-212	$C_{16}H_{15}N_3O_4$	61.34	4.79	13.41
					61.51	4.83	13.45
7f	3,4,5-(CH_3O)$_3$-C_6H_2	2-quinolyl	209-210	$C_{20}H_{17}N_3O_4$	66.11	4.68	11.57
					66.21	4.62	11.61

[a] Mp °C of the recrystallized products from ethanol.

signals of methylene and methoxy protons at δ 6.1 and 3.8 for derivatives **1a-d** and **1e-h** respectively, in addition to those of aromatic and heteroaromatic ones. Mass spectra showed molecular ions as base peaks and fragment ions deriving from C-S bonds rupture according to the reported thiadiazoles fragmentation upon electron impact [9].

The structure of new oxadiazoles **7a-f** (Table 2) followed from elemental analysis, ir and mass spectra. The ir spectra contained oxadiazole ring bands at 1580-1640 cm^{-1} for C=N bonds and 1025-1030 cm^{-1} for C-O-C bonds.

Mass spectra provided a fragmentation pattern in good agreement with that of 2,5-diaryl-1,3,4-oxadiazoles [10]. Base peaks corresponded to alkyloxybenzoyl ions and other relatively intense peaks corresponded to molecular, heteroaroyl, alkyloxybenzonitrile, phenyl and pyridyl ions.

Thiadiazoles **8a,b** were identified by mixture melting points and mass spectra comparison with authentic samples.

Although the procedure reported here for the synthesis of 2-pyridyl-5-aryl-1,3,4-thiadiazoles affords lower yields than those obtainable by oxidative cyclization of thioaroylhydrazones **4**, it appears a convenient "one step" route which involves simple manipulation and readily available reactants.

For the synthesized compounds **1a-h** the biological screenings are in progress and results will be reported at a later date.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. The ir spectra were recorded using a Perkin-Elmer 281 spectrophotometer for potassium bromide mulls. The pmr spectra were recorded with a Varian A 60 instrument for solutions in deuteriochloroform with tetramethylsilane as internal standard. Mass spectra were obtained with a LKB 9000 S spectrometer. Elemental analyses were performed on a Carlo Erba 1006 elemental analyzer. Silica gel used in column chromatography was a product of Merck (particle size 0.05-0.2 mm).

Alkyloxybenzoylhydrazines **3a,b** and corresponding 4-pyridinaldehyde hydrazones **5a,b** and thiohydrazones **4a,b** were prepared according to literature methods.

2-Pyridyl-5-alkyloxyphenyl-1,3,4-thiadiazoles, **1a-h**.

A mixture of sulfur (0.04 mole), methylpyridines **2a-d** (0.03 mole) and alkyloxybenzoylhydrazines **3a,b** (0.02 mole) was heated in an oil bath at 180° for 12 hours, during which time hydrogen sulphide continuously evolved. Acetonitrile (about 50 ml) was added to the still warm solution and the precipitate was filtered off after cooling. Concentration of mother liquors yielded a further crop of precipitate and unchanged methylpyridine. From combined precipitates pure thiadiazoles **1a-h** were obtained by repeated crystallization from dimethylformamide-ethanol (1:10).

See Table 1 for experimental details.

Thiadiazoles **1b,f** were also obtained in high yields by refluxing a pyridine solution of corresponding thiohydrazones **4a,b** (0.01 mole) and sulfur (0.01 mole) for 24 hours. Evaporation of pyridine under reduced pressure gave a solid which was recrystallized from dimethylformamide-ethanol (1:10):**1b** (72%) mp 203-204°; **1f** (76%) mp 186°.

2-Pyridyl-5-alkyloxyphenyl-1,3,4-oxadiazoles, **7a-f**.

Oxadiazoles **7a-f** were isolated in a pure state by subjecting evaporated crystallization mother liquors of thiadiazoles to column chromatography (ethylacetate-cyclohexane, 1:4).

See Table 2 for experimental details.

Oxadiazoles **7b,e** were also obtained in high yields by refluxing a pyridine solution of corresponding hydrazones **5a,b** (0.01 mole) and sulfur (0.01 mole) for 24 hours. Evaporation of pyridine under reduced pressure gave a solid which was recrystallized from ethanol:**7b** (76%) mp 194.8°; **7e** (78%) mp 211-212°.

Furthermore they were identical (mixed mp and superimposed ir spectra) with a specimen prepared by the Gibson oxidative cyclization [11] of corresponding hydrazones **5a,b**.

2,5-Dialkyloxyphenyl-1,3,4-thiadiazoles, **8a,b**.

Thiadiazoles **8a,b** were isolated in a pure state as first products by subjecting evaporated crystallization mother liquors of thiadiazoles to column chromatography (ethylacetate-cyclohexane, 1:4).

2,5-bis(3,4-Dioxymethylenphenyl)-1,3,4-thiadiazole (**8a**).

This compound had mp 242° (lit [9], mp 241-242°); ms: 326 (M^+).

Anal. Calcd. for $C_{16}H_{10}N_2O_4S$: C, 58.99; H, 3.06; N, 8.58; S, 9.81. Found: C, 58.92; H, 3.03; N, 9.01; S, 9.79.

2,5-bis(3,4,5-Trimethoxyphenyl)-1,3,4-thiadiazole (**8b**).

This compound had mp 188-189° (lit [9], mp 188°); ms: 418 (M^+).

Anal. Calcd. for $C_{20}H_{22}N_2O_6S$: C, 57.41; H, 5.26; N, 6.69; S, 7.65. Found: C, 57.21; H, 5.32; N, 6.38; S, 7.75.

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