Synthesis of Some New 2-(4-Halophenylamino)-5-(isomeric pyridyl)-1,3,4-thiadiazoles

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Summary: Twelve 2-(4-halophenylamino)-5-(isomeric pyridyl)-1,3,4-thiadiazoles (17-28) were prepared as pure crystalline solids, by the acid catalysed intramolecular dehydrative cyclization of the corresponding 4-(4-halophenyl)-1-(isomeric pyridoyl) thiosemicarbazides (5-16). The latter were prepared by reaction of 4-halophenyl isothiocyanate (3a-d) with each of the three isomeric pyridinecarboxylic acid hydrazides (4a-c). The effect of structure on reactivity with respect to the halogen atom and isomeric pyridyl group is discussed. A plausible mechanism for intramolecular cyclodehydration of the thiosemicarbazides to 1,2,4-thiadiazoles is also suggested. The purified new compound, were characterized on the basis of elemental analysis, IR and mass spectral data.

Introduction

1,3,4-Thiadiazoles constitute an important class of five membered nitrogen-sulfur heterocycles [1,2] exhibiting a wide variety of biological activities and have useful applications. Simple derivatives like 2-amino-1,3,4-thiadiazole show anti-tumor and neoplasma inhibitor activity and 5-amino-2-mercapto-1,3,4-thiadiazole has been used against liver disorders [3]. A survey of literature reveals that 1,3,4-thiadiazoles bearing amino and pyridyl substituents at 2- and 5-positions of the heterocyclic ring are significantly more active. Thus 2-(2-ethylphenylamino)-5-methyl-1,3,4-thiadiazole (1) possesses depressant and analgesic activity [4]. Also 5-(4-pyridyl)-2-(2-pyridylmethylthio)-1,3,4-thiadiazole [2] is an ulcer inhibitor [5] and 2-(4-chlorophenyl)-5-(3-pyridyl)-1,3,4-thiadiazole has potent insecticidal action [6] other derivatives of 1,3,4-thiadiazole have shown anti-convulsant, and anti-tubercular [7], anti-bacterial [8], anti-viral [9] fungicidal [8] and hydrogen-antagonistic [10] activities.

A literature survey reveals that no systematic work has been reported on the synthesis of isomeric pyridyl group bearing 2-(4-halophenylamino)-1,3,4-thiadiazoles. The present work aims at the synthesis of new 1,3,4-thiadiazoles bearing isomeric pyridyl substituents at 5-position and 4-halophenylamino groups at the 2-position of the heterocyclic ring.

An interesting aspect of the present work is that the intermediate in the synthesis of 1,3,4-thiadiazoles are substituted thiosemicarbazides. A number of substituted thiosemicarbazides have been reported to show a vast spectrum of biological activities such as anti-bacterial, fungicidal, herbicidal, anti-convulsant and hypoglycemic [11-17]. Some substituted thiosemicarbazides have also been reported as plant growth promoting agents [18].

Results and Discussion

The plan for the synthesis of title compounds is illustrated by Scheme-1. The required 4-halophenyl isothiocyanates (3a-d) were prepared by standard methods involving reaction of 4-haloanilines with carbon disulphide via the dithiocarbamate intermediates. The purified compounds were characterized on the basis of their infrared spectral data and a comparison of their melting points with the literature values. Table-1 shows that there is close agreement between the observed and reported melting points. The melting points of the four isothiocyanates increase smoothly with an increase in the size of the halogen atom whereas the yield decreases in this order. IR spectra (KBr-disc) showed the characteristic strong absorption of the -N=C=S group in the range of 2060-2090 cm^{-1} and the C-X absorption at 542-1065 cm^{-1}.

Direct condensation of each of the four 4-halophenyl isothiocyanates (3a-d) with each of the isomeric hydrazides (4a-c) in refluxing absolute ethanol afforded the twelve substituted thiosemicarbazides (5-16) in good yields. Except for three 4-iodophenyl substituted thiosemicarbazides (14-16) all other thiosemicarbazides were obtained in 68-80% yield (Table-1). In general, the rate of reaction was quite slow for the condensation of 3-pyridinecarboxylic acid hydrazide as compared to the 2- and 4-isomers which showed nearly similar behaviour. All the isolated thiosemicarbazides were recrystallized from 50% aqueous-ethanol. Only the 4-(4-chlorphenyl)-1-(4-pyridoyl) thiosemicarbazide (10) is already reported in the literature [18] while the other isolated thiosemicarbazides appear to be new compounds. The isolated thiosemicarbazides were characterized on the basis of their elemental analysis (Table-1), IR spectral data and mass spectral data (Table-2). The IR spectra of the isolated thiosemicarbazides (KBr-dics) showed the characteristic absorption at 1250-1270 cm^{-1} attributed to C=S of the thiourea residue. Other important absorption included the carbonyl stretchings at 1640-1662 cm^{-1}, and N-H stretchings in the region 3260-3300 cm^{-1} (Table-2). In addition C-F, C-Cl, C-Br and C-I stretchings were observed in the region of 1060-1065 cm^{-1}, 731-735 cm^{-1}, 638-644 cm^{-1} and 542-556 cm^{-1} respectively for the corresponding halogen compounds.

The mass spectra of all the isolated thiosemicarbazides (5-16) showed M^+ peak at the corresponding m/z. However in the case of the chlorine and bromine bearing thiosemicarbazides (8-10 and 11-13) M+2 peak was also observed (Table-2). The intensity of M^+ and M+2 peak was in the ratio of 3:1 for the chlorine bearing compounds and 1:1 for the bromine bearing compounds. It is interesting to note that the base peak in the mass spectra of each of the compounds (5-13) was observed at m/z 78. However, for compounds (14-16) the same was observed at 261 which corresponds to M-137.

The acid catalysed intramolecular dehydrative cyclization of the thiosemicarbazides (5-16) afforded the corresponding disubstitued

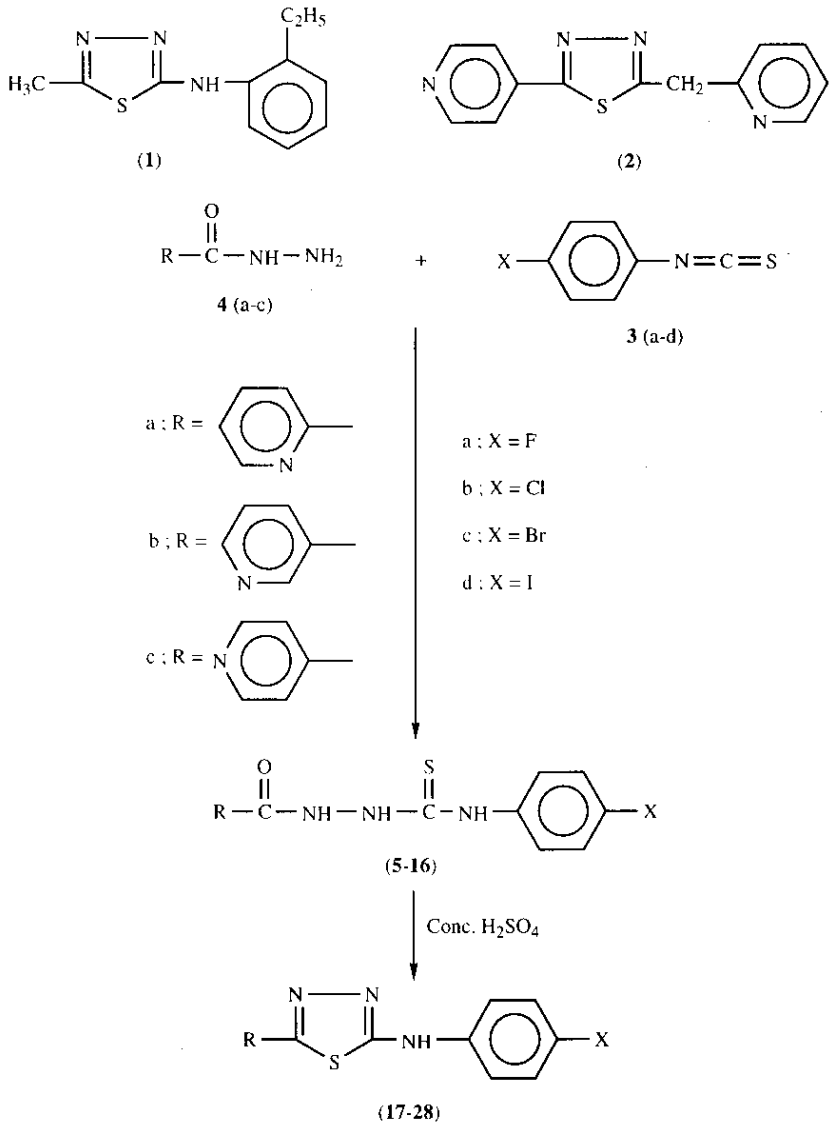
Table-1: Reaction Time and Physical Data of the Isolated Thiosemicarbazides (5-16)

Isolated Compound			Reflux	%	M.P.	R_f value*	Elemental Analysis % Calc. (% Found)			
No.	R	X	time(h)	Yield	(obs)°C		C	H	N	S
5	2-Pyridyl	F	5.0	80.1	181	0.88	53.79(53.58)	3.79(3.86)	19.31(19.24)	11.03(10.96)
6	3-Pyridyl	F	7.0	68.3	185	0.80	53.79 (53.59)	3.79(3.88)	19.31(19.27)	11.03(10.98)
7	4- Pyridyl	F	6.0	76.5	182	0.82	53.79(53.64)	3.79(3.84)	19.31(19.30)	11.03(11.05)
8	2- Pyridyl	Cl	4.0	75.5	180	0.64	50.90(50.82)	3.59(3.64)	18.27(18.25)	10.44(10.40)
9	3- Pyridyl	Cl	5.0	72.1	195	0.54	50.90(50.80)	3.59(3.64)	18.27(18.20)	10.44(10.46)
10	4- Pyridyl	Cl	4.5	74.2	175	0.56	50.90(50.81)	3.59(3.68)	18.27(8.20)	10.44(10.38)
11	2- Pyridyl	Br	9.0	73.2	185	0.64	44.44(44.38)	3.13(3.10)	15.95(15.88)	9.12(9.07)
12	3- Pyridyl	Br	11.0	69.1	196	0.54	44.44(44.40)	3.13(3.16)	15.95(15.90)	9.12(9.05)
13	4- Pyridyl	Br	10.0	70.3	185	0.52	44.44(44.38)	3.13(3.08)	15.95(15.89)	9.12(9.10)
14	2- Pyridyl	I	6.0	50.2	186	0.64	39.20(39.16)	2.76(2.81)	14.07(14.02)	8.04(8.00)
15	3- Pyridyl	I	8.0	46.5	210	0.62	39.20(39.14)	2.76(2.80)	14.07(13.98)	8.04(7.96)
16	4- Pyridyl	I	13.0	12.0	170	0.60	39.20(39.18)	2.76(2.78)	14.07(13.97)	8.04(8.03)

*methanol:chloroform (1:1)

Table-2: Spectral Data of the Isolated Thiosemicarbazides (5-16)

Isolated Compound			IR spectral data cm^{-1}				Mass spectral data (m/z)
No.	R	X	νC-X	νC=S	νC=O	νN-H	
5.	2-Pyridyl	F	1062	1263	1657	3260	290(M^+), 153, 137, 111, 106, 78
6.	3- Pyridyl	F	1065	1257	1656	3266	290(M^+), 153, 137, 111, 106, 78
7	4- Pyridyl	F	1060	1269	1650	3262	290(M^+), 153, 137, 111, 106, 78
8	2- Pyridyl	Cl	731	1266	1662	3298	308, 306 (M^+), 171, 169, 129, 127, 137, 106, 78
9	3- Pyridyl	Cl	735	1260	1655	3287	308, 306 (M^+), 171, 169, 129, 127, 137, 106, 78
10	4- Pyridyl	Cl	735	1264	1660	3280	308, 306 (M^+), 171, 169, 129, 127, 137, 106, 78
11	2- Pyridyl	Br	644	1269	1662	3298	353 351 (M^+), 216, 214, 174, 172, 137, 106, 78
12	3- Pyridyl	Br	638	1262	1649	3294	353, 351 (M^+), 216, 214, 174, 172, 137, 106, 78
13	4- Pyridyl	Br	642	1267	1650	3290	353, 351 (M^+), 216, 214, 174, 172, 137, 106, 78
14	2- Pyridyl	I	542	1269	1640	3286	398(M^+), 261, 219, 137, 106, 78
15	3- Pyridyl	I	548	1266	1640	3286	398(M^+), 261, 219, 137, 106, 78
16	4- Pyridyl	I	556	1260	1662	3280	398(M^+), 261, 219, 137, 106, 78



Scheme-1: Synthesis of 2,5-disubstituted-1,3,4-thiadiazoles.

1,3,4-thiadiazoles (17-28) in 71-85% yield (Table-3). The general trend of the yield in this series was also observed in the final products. Thus, the fluorine-bearing 1,3,4-thiadiazoles (17-19) were obtained in maximum yields (80-85%), whilst the iodine-bearing 1,3,4-thiadiazoles (26-28) were obtained in relatively low yield (70-72%). The isolated yields, in general, were higher for the 2- and 4-pyridyl substituted thiadiazoles as compared to 3-pyridyl compounds (18,21,24,27). Out of the twelve isolated 2,5-substituted-1,3,4-thiadiazoles only three compounds (22,23 and 25) are already known [13,19]. However, these were synthesized by methods different than applied in the present work.

The mechanism of intramolecular dehydrative cyclization of thiosemicarbazides (5-16) is illustrated in Scheme-2. The reaction is initiated by the nucleophilic attack of sulphur on the electrophilic carbon of the protonated carbonyl group (Scheme-2). This is followed by dehydration to the respective thiadiazole (17-28). The purity of the

Table-3: Physical Data of the Isolated Thiadiazoles (17-28)

Isolated Compound			Yield	M.P.	R_f value**	Elemental Analysis % Calc. (% Found)			
No.	R	X	%	(obs)°C		C	H	N	S
17	2-Pyridyl	F	81.5	218	0.91	57.35(57.30)	3.31(3.34)	20.59(20.51)	11.76(11.72)
18	3-Pyridyl	F	80.2	170	0.86	57.35(57.28)	3.31(3.37)	20.59(20.50)	11.76(11.72)
19	4- Pyridyl	F	85.5	231	0.84	57.35(57.28)	3.31(3.38)	20.59(20.55)	11.76(11.71)
20	2- Pyridyl	Cl	75.6	220	0.68	54.07(54.00)	3.12(3.24)	19.41(19.27)	11.09(11.15)
21	3- Pyridyl	Cl	74.7	260	0.66	54.07(53.98)	3.12(3.20)	19.41(19.32)	11.09(11.18)
22	4- Pyridyl	Cl	75.0	272	0.63	54.07(53.96)	3.12(3.20)	19.41(19.36)	11.09(11.14)
23	2- Pyridyl	Br	75.3	195	0.58	46.85(46.81)	2.70(2.69)	16.82(16.75)	9.61(9.59)
24	3- Pyridyl	Br	73.5	133	0.64	46.85(46.80)	2.70(2.74)	16.82(16.78)	9.61(9.61)
25	4- Pyridyl	Br	78.0	240*	0.58	46.85(46.78)	2.70(2.70)	16.82(16.75)	9.61(9.60)
26	2- Pyridyl	I	72.0	248	0.63	41.05(41.00)	2.37(2.41)	14.74(14.70)	8.42(8.38)
27	3- Pyridyl	I	70.5	152	0.69	41.05(40.96)	2.37(2.40)	14.74(14.68)	8.42(8.40)
28	4- Pyridyl	I	71.5	116	0.58	41.05(40.98)	2.37(2.42)	14.74(14.68)	8.42(8.38)

*Decomposed. ** Methanol-Chloroform (1:1)

Table-4: Spectral Data of the Isolated Thiadiazoles (17-28)

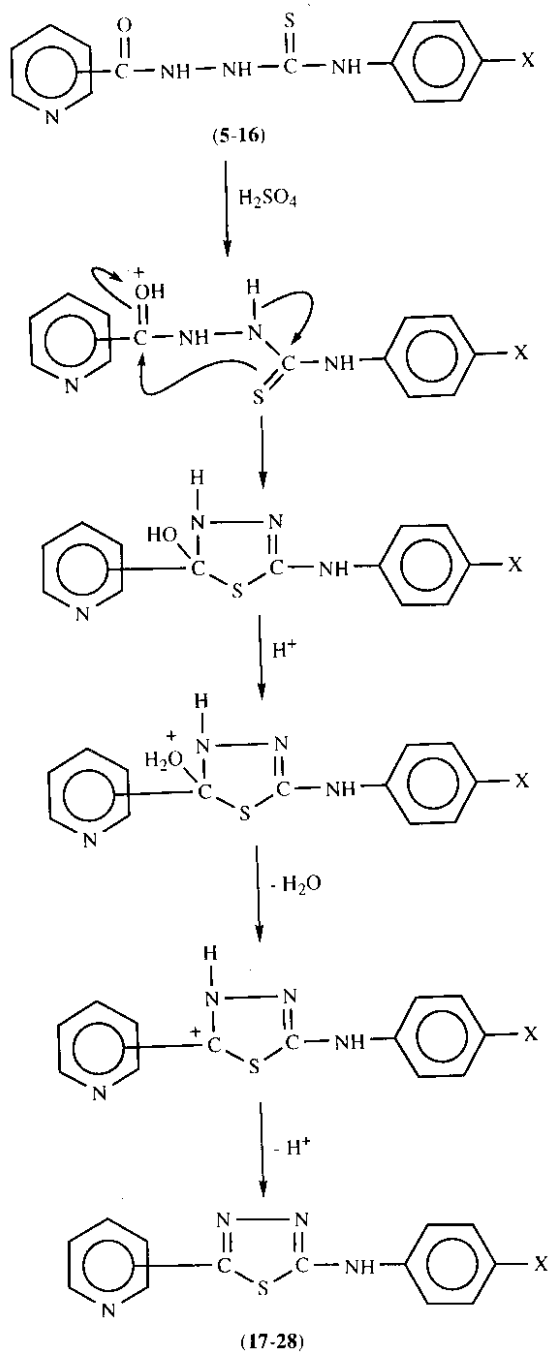
Isolated Compound			IR spectral data cm^{-1}				Mass spectral data (m/z)
No.	R	X	ν_{C-S}	ν_{C-X}	$\nu_{C=C/C=N}$	ν_{N-H}	
17	2-Pyridyl	F	681	1060	1587	3290	272(M^+), 168, 153, 136, 119, 104, 78
18	3- Pyridyl	F	672	1063	1557	3298	272(M^+), 168, 153, 136, 119, 104, 78
19	4- Pyridyl	F	669	1062	1590	3272	272(M^+), 168, 153, 136, 119, 104, 78
20	2- Pyridyl	Cl	670	734	1587	3280	290, 288 (M^+),187, 185,171, 169,136, 119,104,78
21	3- Pyridyl	Cl	669	738	1566	3280	290, 288 (M^+),187, 185,171, 169,136, 119,104,78
22	4- Pyridyl	Cl	681	735	1588	3252	290, 288 (M^+),187, 185,171, 169,136, 119,104,78
23	2- Pyridyl	Br	669	640	1570	3256	333,331 (M^+), 231,229,216,214,136,119,104,78
24	3- Pyridyl	Br	672	639	1557	3370	333,331 (M^+), 231,229,216,214,136,119,104,78
25	4- Pyridyl	Br	681	644	1567	3280	333,331 (M^+), 231,229,216,214,136,119,104,78
26	2- Pyridyl	I	669	543	1569	3256	380(M^+),276, 261, 136, 119, 104, 78
27	3- Pyridyl	I	670	547	1590	3232	380(M^+),276, 261, 136, 119, 104, 78
28	4- Pyridyl	I	679	555	1570	3250	380(M^+),276, 261, 136, 119, 104, 78

synthesized 2,5-disubstituted-1,3,4-thiadiazoles was established by thin layer chromatography on silica plate in methanol:chloroform (1:1),. The R_f values are listed in Table-3. Further evidence of the purity comes from the sharpness of their observed melting points which are also listed in the same Table.

The characterization of the synthesized 2,5-disubstituted 1,3,4-thiadiazoles (17-28) was based on the elemental analysis, infra-red and mass spectral data. A good agreement of the calculated and the found %age of C,H,N and S is illustrated in Table-3. Further evidence was obtained by recording their IR-spectra (KBr-disc). Apart from the usual aromatic C-H absorptions in the region of 3040-3010 cm^{-1} for the phenyl and the pyridyl groups, other important observed absorptions are summarized in Table-4. In contrast to $\nu_{C=S}$ of the thiosemicarbazides in the region of 1257-1269 cm^{-1}, ν_{C-S} in thiadiazoles was observed in the region of 669-681 cm^{-1}. In each case a prominent peak was observed for the ν_{C-X} at the appropriate frequency. The mass spectral data of the disubstituted 1,3,4-thiadiazoles (Table-4) provided further proof to the structure. In each case the molecular ion peak (M^+) was observed at the expected m/z. However, as observed in the mass spectra of chlorine- and bromine-bearing thiosemicarbazides, M+2 peak was also observed in the mass spectra of the corresponding chlorine and bromine bearing 1,3,4-thiadiazoles (20-25). Again, the intensity of M^+ and M+2 peak was in the ratio of 3:1 for the chlorine compounds and 1:1 for the bromine compounds. In each case common peaks at m/z 136, 119, 104 and 78 were observed. The above mass spectral data is in line with the mass spectral data of all other isolated 1,3,4-thiadiazoles.

Experimental

Melting points observed are uncorrected and were determined using a Gallenkamp digital apparatus. IR spectra in KBr were recorded on a Hitachi Model 270-50 spectrophotometer. The elemental analysis of the synthesized compound was carried out at the Micro-analytical laboratory, Institute of Organic Chemistry, University of Stuttgart, Germany.



Scheme-2: Mechanism of dehydrative cyclization.

Isomeric Pyridinecarboxylic acid hydrazides (4a-c)

Whereas 3-pyridinecarboxylic acid hydrazide (4b) and 4-pyridinecarboxylic acids hydrazide (4c) were commercially available; 2-pyridinecarboxylic acid hydrazide (4a) was prepared from 2-pyridinecarboxylic acid by an already reported method [20].

4-Halophenyl isothiocyanates (3a-d)

4-Halophenyl isothiocyanates (3a-d) were prepared from the respective 4-haloaniline using the same method as reported [21] for preparation of phenylisothiocyanate from aniline. In general, a mixture of 4-haloaniline (0.5 mol), carbon disulphide (0.78 mol) in methanol (95%, 90 ml) was cooled to 10°C before adding ammonia (33%, 0.63 mol). In each case this yielded a milky suspension. Occasional shaking resulted in a clear solution in which heavy crystals of intermediate dithiocarbomate separated out. The solid was filtered, washed with diethyl ether (2x50 ml) and dissolved in cold water (600 ml). An aqueous solution of lead nitrate (0.5 mol) was then slowly added to the dithiocarbomate solution. The mixture was thoroughly stirred for twenty minutes. It was then allowed to stand overnight and then subjected to steam distillation. The distillate was collected in a flask acidified with a drop of 2N sulphuric acid. 3b, 3c and 3d were obtained as crude solids in the distillate. They were thus filtered, washed with water and recrystallized from 50% aqueous ethanol. 4-Fluorophenyl isothiocyanate (3a), being a low melting solid, was extracted from the steam distillate using diethyl ether (3 x 150 ml). The ether-layer was separated and dried over anhydrous sodium sulphate. After filtration the solvent was removed using a rotary evaporator and the residual liquid was distilled under reduced pressure to yield 4-fluorophenyl isothiocyanate (3a). Table-5 shows the % yield, the m.p. (obs.), R_f values and the characteristic IR spectral data of the four isolated isothiocyanates (3a-d).

Table-5: Physical data of the Isolated 4-Halophenyl isothiocyanates (3a-d)

Compound	M.P. (°C)				IR spectral data (cm^{-1})		
No.	obs.	lit.	% Yield	R_f-value*	$\nu_{N=C=S}$	ν_{C-X}	$\nu_{1,4\text{-disubstituted aryl}}$
3a	-[a]	26-28[b]	45.0	0.65	2062	1090	834
3b	44	42-44[c]	40.0	0.51	2086	723	825
3c	58	60-61[d]	32.0	0.46	2090	645	820
3d	65	-[e]	35.0	0.43	2080	532	813

*methanol: chloroform (1:1). [a]isolated as a semisolid. [b]Reference 23. [c]Reference 24. [d]Reference 24. [d]Reference 21. [e]not found.

Preparation of 4-(4-Halophenyl)-1-(isomeric pyridoyl) thiosemicarbazides (5-16)

Respective 4-halophenyl isothiocyanates (3a-d; 0.01 mol) in absolute ethanol (50-120 ml) was added slowly to a stirred ethanolic solution of isomeric pyridinecarboxylic acid hydrazides (4a-c, 0.01 mol). The reaction mixture was refluxed for a certain period of time (Table-1). This was then cooled to room temperature to furnish a white solid in each case. The solid was filtered off and recrystallized from aqueous ethanol (50%). In Table-1 are summarized the reaction time and the physical data of the isolated thiosemicarbazides (5-16).

Preparation of 2-(4-Halophenylamino)-5-(isomeric pyridyl)-1,3,4-thiadiazoles (17-28)

The general procedure for preparation of (17-28) was a slight modification of a previously reported method [22]. Each thiosemicarbazide (5-16, 0.01 mol) was added in portions to 100 ml of conc. sulphuric acid at 0°C with continuous stirring. The reaction mixture was stirred further for 3 h at room temperature (18-20) and was allowed to stand overnight. Neutralization with dil. ammonium hydroxide precipitated a crude solid which was filtered, and washed with water. The crude product was then recrystallized from mixture of acetic acid and water (1:1 or 1:2) to furnish disubstituted 1,3,4-thiadiazoles (17-28). The observed melting points, % yields and other physical data of the isolated thiadiazoles are listed in Table-3.

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References

1. A.R. Katritzky and A.J. Boulton, Advances in Heterocyclic Chemistry, Academic Press, London, Vol. 9, p. 165 (1968).
2. S. Coffey and M.S. Ansell, 'Rodd's Chemistry of Carbon Compounds '2nd ed., Elsevier Science Publishers, Oxford Vol. IV, Part D, p. 150 (1986).
3. H. Iwamoto and K. Nishikiori, Kokai Tokkyo Koho Jp-62, 153,276 [87,153,276] (Cl.C07D 249/14), 1987; *Chem. Abstr.*, **107**, 236714q (1987).
4. P. Mishra and R.U. Madahava, *J. Inst. Chem.*, **61**, 31 (1989).
5. Y. Hasegawa, T. Yanagisawa and K. Hosaka, Jpn.-01, 233, 282 [89,233,282] (Cl.C07 D417/12), 1989; *Chem. Abstr.*, **112**, 358724 (1991).
6. S. Farooq, J. Ehrenfreund and R.U. R.Rudolf, Eur. Pat. Appl. EP-207, 004 (Cl. 607 D417/04) 1986; *Chem. Abstr.*, **106**, 84616y (1987).
7. M.R. Stillings, A.P. Wellsourn and D.S. Walter, *J. Med. Chem.*, **29**, 2280 (1986).
8. K.S. Srivastana, R.B. Pathak and S.C. Bahel, *J. Indian Chem.Soc.*, **66**, 210 (1989).
9. J.B. Rieder and A.W. Spitzer, Eur. Pat. Appl. EP-229, 501 (Cl. C12 N5/00) (1987).
10. R.A. Holstedi and P. Jessup, U.S. Pat. 4, 623, 474 (Cl. 252-475), (1986).
11. W. Rudnika, H. Foks, M. Janowiec and Z.K. Zwolska, *Acta. Pol. Pharm.*, **43**, 523 (1986).
12. R.S. Sharma and S.C. Bahel, *J. Indian Chem. Soc.*, **59**, 877 (1982).
13. Z. Zhang, K. Yang and F. Zeng, *Gaodeng Xuexiao Huaxu Xuebao*, **9**, 239 (1988).
14. N.G. Birendra and K.J.C. Sarmoh, *J. Heterocycl. Chem.*, **21**, 1225 (1984).
15. L.I. Vershchagin and I.N. Kuznetsova, *Khim. Geterotsikl. Soedin*, 932 (1986).
16. R.S. Sharma, *Indian J. Pharm.*, **32**, 91 (1970).
17. M.I. Hussain and A. Kumar, *Curr. Sci.*, **55**, 644 (1986).
18. Z. Zhang, K. Yang and F. Zeng, Z.Xu. Lanzhou Daxue Xuebao, *Ziran Kexueban*, **24**, 131 (1988).
19. B. Modzelewska and A. Maliszewska, *Ann. Univ. Marie Curie Sklodoska, Sect. AA: Chem.*, 39-40, 163 (1984-85).
20. R. Iqbal and F. Malik, *J. Chem. Soc. Pak.*, **6**, 43 (1984).
21. Gilman and Blatt, Organic Synthesis, Collective Volume I, 2nd ed., J. Wiley and Sons, New York p. 447 (1967).
22. E. Hoggarth, *J. Chem. Soc.*, 1963 (1949).
23. Aldrich Catalogue; Handbook of Fine Chemicals, Cat. No. 12840-6, p. 740 (1994-95).
24. Aldrich Catalogue, Handbook of Fine Chemicals, Cat. No. 25378-2, p. 360 (1994-95).