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Synthesis and Spectral Analysis of Some 4-Substituted-5,7-diarylpyridino[3,4-d]-1,2,3-thiadiazoles

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Some 3-substituted-2,6-diarylpiperidin-4-ones are converted into semicarbazones and then treated with thionyl chloride. After repeated column chromatography, the thiadiazoles **1-15** are separated and confirmed by elemental analysis, ^{1}H, ^{13}C NMR and IR spectral studies.

Key Words: 1,2,3-Thiadiazoles, Semicarbazones, IR and NMR, Piperidones.

INTROMDUCTION

In continuation of our studies on the synthesis and spectral analysis of 1,2,3-selenadiazoles, in this paper, the synthesis of another set of heterocycles 1,2,3-thiadiazoles is reported. It is well known that sulphur containing heterocycles[1,2], exhibit a wide variety of biological activities[3-5]. Besides possessing identical number of valence electrons, sulphur and selenium are approximate in size also. Hence, this pair of elements may be considered as isosteric. The medicinal implications of isosterism[6] were reviewed by Schatz[7]. The toxicity of sulphur and selenium compounds[8] is also almost equal.

EXPERIMENTAL

The C, H, N analysis was performed on a Heraeus-C,H,N rapid analyzer. ^{13}C NMR spectra were recorded on a DRX 500 and AMX 400 spectra operating at 125.7 and 100 MHz, respectively using 10 mm sample tubes. Solution for the measurement of spectra were prepared by dissolving 0.5 of the sample in 2.5 mL of chloroform-*d* containing 1 % TMS and acetone-*d*. All the chemical shift values are with reference to TMS. IR spectra were recorded in Jasco-700 infrared spectrometer using KBr pellets.

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Proton NMR spectra were recorded on a DRX 500 NMR and AMX 400 NMR spectrometer operating at 500 and 400 MHz, respectively. Samples were prepared by dissolving about 10 mg of sample in 0.5 mL of acetone and chloroform-*d* containing 1 % TMS. All the chemical shifts are with reference to TMS.

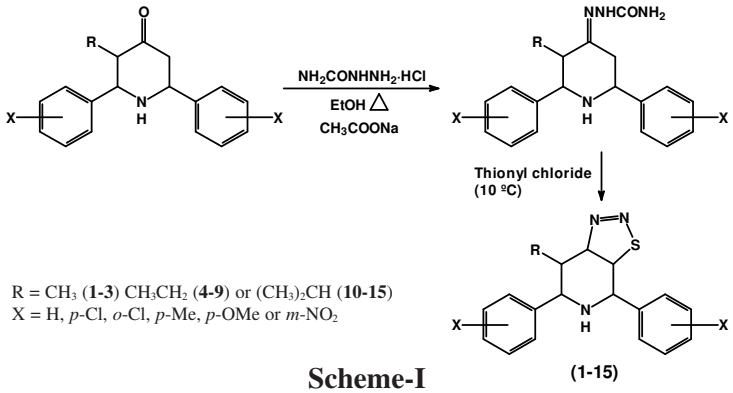
The column was packed with silica-gel (60-200 mesh) in *n*-hexane. The eluting solvents used are benzene, chloroform and chloroform-ethyl acetate. The separated compounds were checked with co-TLC. The compounds were found to be separated in chloroform:ethyl acetate (4:1).

Preparation of 3-substituted-2,6-diarylpiperidin-4-ones: The 2,6-diarylpiperidones were prepared following the procedure adopted by Noller and Baliah[9]. Ammonium acetate (100 mmol), benzaldehyde (200 mmol) and appropriate ketone (200 mmol) were dissolved in 95 % alcohol (80 mL). The solution was heated on a hot plate with gentle swirling until the colour of the mixture changed to orange. The mixture was cooled and poured into ether (100 mL) and concentrated hydrochloric acid (14 mL) was added. The precipitated 2,6-diarylpiperidin-4-one hydrochloride was collected by filtration and re-crystallization from ethanol-ether. The hydrochloride was dispersed in acetone and concentrated ammonia was added drop-wise until a clear solution was obtained. The clear solution was poured into cold water and the solid precipitated was collected and crystallized from ethanol. The observed melting points are in excellent agreement with those of the reported ones.

Preparation of semicarbazone: A mixture of respective 2,6-diarylpiperidin-4-one (1g, 0.0027 mol), semicarbazide hydrochloride (0.316, 0.0027 mol) and sodium acetate (0.750 g) in ethanol (40 mL) was refluxed for 2 h on a steam bath and cooled. The separated solid was filtered, washed with water and re-crystallized from ethanol.

Preparation of 5,7-diaryl-4-alkyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles (1-15): Appropriate 2,6-diphenylpiperidin-4-one semicarbazone (0.005 mol) was added portion-wise to thionyl chloride (2.5 mol) in an ice-bath and kept for an hour at room temperature. Chloroform (20 mL) was added to the reaction mixture and decomposed with ice-cold sodium carbonate solution. The organic layer was washed with 4-5 times each with 10 mL of water and dried over anhydrous sodium sulphate. After the evaporation of solvent, the obtained gummy mass was solidified by treatment with cyclohexane. The solid product obtained was subjected to column chromatography (**Scheme-I**). The analytical data of compounds **1-15** is given in Table-1.

The compounds show characteristic absorption for aromatic C-H stretching, aliphatic C-H stretching C=C ring stretching and C=C ring stretching. The IR spectral values of thiadiazoles are given in Table-2.



Scheme-I

TABLE-1
ANALYTICAL DATA OF 1,2,3-THIADIAZOLES DERIVATIVES (**1-15**)

Compd.	m.f. / (m.w.)	m.p. (ºC) / Yield (%)	R	X	Elemental analysis (%): Found (Calcd.)		
					C	H	N
1	$C_{18}H_{11}N_3SCl_2$ (372.27)	92-94 (49)	CH_3	*p*-Cl	57.30 (57.40)	3.89 (3.98)	11.09 (11.09)
2	$C_{18}H_{11}N_3SCl_2$ (372.27)	97-99 (47)	CH_3	*o*-Cl	57.32 (57.40)	3.89 (3.98)	11.11 (11.16)
3	$C_{18}H_{11}N_3O_4S$ (393.38)	110-111 (52)	CH_3	*m*-NO_2	54.25 (54.35)	3.70 (3.77)	17.55 (17.61)
4	$C_{19}H_{15}N_3S$ (317.41)	109-110 (55)	C_2H_5	H	70.80 (70.93)	5.83 (5.91)	13.01 (13.06)
5	$C_{19}H_{13}N_3SCl_2$ (386.30)	118-119 (47)	C_2H_5	*p*-Cl	58.14 (58.41)	4.30 (4.35)	10.67 (10.76)
6	$C_{19}H_{13}N_3SCl_2$ (386.30)	122-123 (49)	C_2H_5	*o*-Cl	58.14 (58.41)	4.20 (4.35)	10.50 (10.76)
7	$C_{21}H_{19}N_3S$ (345.46)	126-128 (49)	C_2H_5	*p*-Me	72.01 (72.10)	6.40 (6.58)	11.95 (12.01)
8	$C_{21}H_{19}N_3O_2S$ (377.46)	131-132 (50)	C_2H_5	*p*-OMe	66.01 (66.06)	5.95 (6.03)	10.97 (11.00)
9	$C_{19}H_{13}N_5O_4S$ (407.40)	140-141 (46)	C_2H_5	*m*-NO_2	55.43 (55.41)	4.15 (4.13)	17.05 (17.01)
10	$C_{20}H_{17}N_3S$ (331.44)	118-120 (38)	$(CH_3)_2CH$	H	71.55 (71.54)	6.27 (6.26)	12.52 (12.55)
11	$C_{20}H_{15}N_3SCl_2$ (400.32)	131-139 (35)	$(CH_3)_2CH$	*p*-Cl	59.25 (59.35)	4.61 (4.69)	10.35 (10.38)
12	$C_{20}H_{15}N_3SCl_2$ (400.32)	137-139 (34)	$(CH_3)_2CH$	*o*-Cl	59.30 (59.35)	4.66 (4.69)	10.35 (10.38)
13	$C_{22}H_{21}N_3S$ (359.49)	141-143 (30)	$(CH_3)_2CH$	*p*-Me	72.58 (72.62)	6.81 (6.87)	11.43 (11.55)
14	$C_{22}H_{21}N_3O_2S$ (391.49)	147-150 (35)	$(CH_3)_2CH$	*p*-OMe	66.67 (66.74)	6.28 (6.32)	10.55 (10.61)
15	$C_{20}H_{15}N_5O_4S$ (421.43)	152-153 (38)	$(CH_3)_2CH$	*m*-NO_2	56.41 (56.40)	4.47 (4.46)	16.47 (16.45)

TABLE-2
IR SPECTRAL DATA OF THE SYNTHESIZED 1,2,3-THIADIAZOLES (**1-15**)

Compd.	N–H *str.* (cm^{-1})	Aromatic C–H *str.* (cm^{-1})	Aliphatic C–H *str.* (cm^{-1})
01	3431	3027	2973
02	3426	3068	2978
03	3420	3045	2975
04	3432	3092	2960
05	3413	3037	2966
06	3410	3068	2964
07	3416	3027	2971
08	3405	3016	2962
09	3411	3057	2928
10	3454	3095	2964
11	3414	3062	2963
12	3425	3068	2968
13	3455	3026	2964
14	3410	3038	2960
15	3416	3040	2962

RESULTS AND DISCUSSION

Some 3-substituted-2,6-diarylpiperidin-4-ones are converted into semicarbazones and they are treated with thionyl chloride (**Scheme-I**). After repeated column chromatography, the thiadiazoles (**1-15**) are separated and confirmed by elemental analysis, ^{1}H, ^{13}C NMR and IR spectral studies.

5,7-Diaryl-4-methyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles (1-3): In compounds **1-3**, the signals are assigned for respective carbons by comparing[10,11] with that of parent compound. The ^{13}C signals between 162.00-164.09 ppm and between 153.12-156.25 ppm are assigned to C-9 and C-8, respectively. The C-4 carbon appears in the region of 44.90-45.36 ppm. The upfield signal in the region of 62.27-63.23 ppm is assigned to C-7 carbon. Then the remaining signal in the region of 59.17-59.76 ppm is assigned to C-5 carbon. The aromatic protons appear in the range of 126.44-130.57 ppm. The methyl carbon at C-4 appears in the range of 10.05-10.78 ppm. The two *ipso* carbons appear in the range of 142.95-143.76 and 139.91-140.18 ppm, respectively.

The singlet in the region of 5.53-5.98 ppm is conveniently assigned to H-7. The doublet appears in the region of 4.03-4.27 ppm is assigned to H-5. A multiplet, which appears in the region of 3.6 ppm, is due to the H-4 proton. The aromatic protons appear in the range of 7.19-8.37 ppm. The peak observed around 2.13-2.19 ppm is due to the N-H proton. The absorption in the region of 0.82-0.90 ppm is due to the methyl protons.

5,7-Diaryl-4-ethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles (4-9): In compounds **5-9**, the chemical shifts are assigned for respective carbons by comparing[11] with that of compound **4**. The ^{13}C signals in the following ranges of 63.22-63.88, 59.20-60.00, 44.00-44.98, 21.34-22.77, 10.42-14.52 ppm are conveniently assigned to C-7, C-5, C-4, CH_2 carbon of ethyl group and methyl carbon of ethyl group, respectively. The C-9 and C-8 carbons are found to appear in the region of 161.00-161.90 ppm and 151.60-152.92 ppm, respectively. The two *ipso* carbons appear between 142.96-143.66 and 140.11-142.26 ppm, respectively. The aromatic carbons of the two phenyl groups appear in the range of 126.30-130.69 ppm. The methyl carbons in the phenyl ring appear at 20.16 and 22.33 ppm for compound **7** and the methoxy carbons appear at 55.36 ppm for compound **8**.

A singlet in the region of 5.35-5.69 ppm, a doublet in the region of 4.0-4.22 ppm and a multiplet between 3.68-3.84 ppm are assigned to H-7, H-5 and H-4, respectively. The two methylene protons of CH_2CH_3 appear in the region of 2.23-2.64 and 1.66-1.9 ppm. The triplet for three protons of methyl appears between 0.7-0.9 ppm. The NH proton is observed in the region of 2.0-2.16 ppm. The aromatic protons appear in the region of 6.60-8.41 ppm. For compound **7**, the methyl protons appear at 2.37 and 2.44 ppm. For compound **8**, the methoxy protons appear at 3.83 and 3.85 ppm. This is due to the different orientation of the phenyl rings.

5,7-Diaryl-4-isopropyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles (9-15): In compounds **11-15**, the chemical shifts are assigned for respective carbons by comparing[11] with that of compound **10**. The C-4, C-7, C-5, C-8, C-9 carbons are assigned from the signals between 45.41-45.96, 65.37-65.90, 64.44-64.95, 155.00-156.96, 162.32-162.88 ppm, respectively. The *ipso* carbons appear in the range of 141.48-143.76 ppm and 139.43-140.17 ppm. The methyl carbons are predicted by the signals between 19.74-21.9 ppm. The signals for methine carbons in the phenyl rings are found in the range of 33.13-33.65 ppm. The aromatic carbons appear in the region of 125.66-130.95 ppm. For compound **13**, the signals of methyl carbons are observed at 20.35 and 20.69 ppm due to the two different orientations of the phenyl rings. But for the compound **14**, the signals of methoxy carbons are merged and obtained at 54.98 ppm.

The H-7 proton appears in the region of 5.61-5.89 ppm for compounds **11-15**. The H-5 proton obtained in the region of 3.65-3.85 ppm appears as a doublet. The H-4 proton appears in the range of 1.67-1.80 ppm as a multiplet. The methine protons appear in the region of 2.30-3.04 ppm as a multiplet. The NH proton appears in the range of 2.1-2.2 ppm. The two methyl protons appear in the range of 0.9-1.0 ppm and 1.13-1.4 ppm, respectively. The signals in the region of 6.60-8.43 ppm are due to the aromatic protons. For the compound **14**, the methyl protons in the phenyl rings appear at 2.37 ppm where as for **15**, the methoxy protons in the phenyl rings appear at 3.8 ppm.

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