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Research Paper

SYNTHESIS OF 2-SUBSTITUTEDGUANIDINO-4-SUBSTITUTED-IMINE-6-SUBSTITUTEDIMINO-1,3,5-THIADIAZINES

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Abstract

A novel series of 2-substitutedguanidino-4-substitutedimine-6-substitutedimino-1,3,5-thiadiazines **(IIIa[1]-e[5])** have been recently synthesized by refluxing N-methylformamidino-N'-phenyliminothiocarbamide also called as 1-(N-substitutedcarbamimidoyl)3-{N-(E)-substitutedmethylidinecarbamimidoyl}thiourea **(Ia-e)** with various isocyanodichloride **(II1-5)** in acetone-ethanol medium in 1:1 molar proportion. The structure of all the synthesized compounds was justified on the basis of chemical characteristics, elemental analysis and IR, NMR and mass spectral analysis.

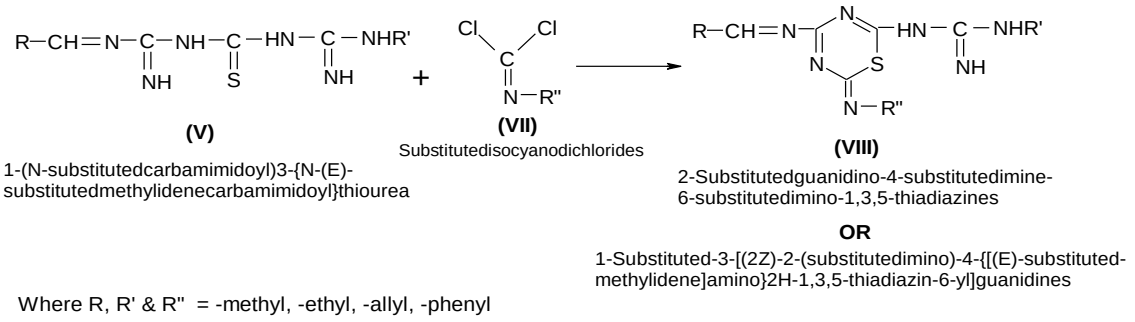
Key words: Guanidine, 1,3,5-thiadiazines, acetone, ethanol etc.

INTRODUCTION

The literature survey reveals that when the heterocyclic compounds containing 1,3,5-thiadiazine as a parent nucleus then that molecule will enhance medicinal, pharmaceutical, agricultural and industrial activities of that drug[1-9]. Hence, nowadays the drug containing 1,3,5-thiadiazine nucleus are widely used in pharmaceutical, medicinal, biochemical and biotechnological fields. It has been reported that thiadiazine nucleus and its analogous possess[10] antiviral, antifungal, antibacterial, anti-tuberculostatic and anti-helminthic properties. Several thiadiazines are widely used in the treatment of cancer[11] and anti-HIV[12-13] drugs. They are also used in agriculture[14] as like fungicidal[15], insecticidal[16]. These 1,3,5-thiadiazines are also effective against copper corrosion[17-18] and used in lubricating oil[19]. The important reactions of substituted isocyanodichlorides have been briefly investigated by some researchers[20-30]. In the view of utility and significances of these compounds in various fields and as a part of wider programme in the synthesis of nitrogen, nitrogen and sulphur containing heteroacycles and heterocycles to developed an alternative route for the synthesis of six member heterocycles in this laboratory, it is quite interesting to investigate the cyclisation of 1-(N-substitutedcarbamimidoyl)3-{N-(E)-substitutedmethylidinecarbamimidoyl}-thiourea **(Ia-f)** with N-substitutedisocyanodichlorides **(IIa-d)** in acetone-ethanol medium to synthesise 2-

substitutedguanidino-4-substitutedimine-6-substitutedimino-1,3,5-thiadiazines **(IIIa1-e5)**.

The tentative reaction and mechanism for the formation of product is depicted below **Scheme-I**.



Scheme-I

RESULT AND DISCUSSION

Synthesis of 2-phenylguanidino-4-methylimino-6-phenylimino-1,3,5-thia-diazine (IIIa^1):

A reaction mixture of N-methylformamidino-N'-phenylimino-thiocarbamide **(Ia)** with phenylisocyanodichloride **(II1)** in 1:1 molar ratio was refluxed on water bath in acetone-ethanol medium for 4 hours. During heating evolution of hydrochloride gas was clearly noticed. After distillation of excess of acetone-ethanol ivory coloured product was isolated this on basification with dilute ammonium hydroxide lemon yellow crystals were afforded, yield 82%, m.p. 128^{0}C. The probable mechanism of the formation of **(IIIa^1)** is depicted below **(Scheme-II)**.

Properties of (IIIa^1):

1) It was lemon yellow crystalline solid having m.p.128^{0}C.
2) It gave positive test for nitrogen and sulphur and negative test for chlorine.
3) It does not desulphurized when boiled with alkaline plumbite solution which clearly indicates that sulphur is not free and gets cyclised.
4) It was soluble in benzene, acetic acid, DMF and DMSO.
5) **Elemental analysis**: The result of elemental analysis is given in **Table No. 1.1**

Table No-1.1

Elements	Found (%)	Calculated (%)
Carbon	58.90	59.5041
Hydrogen	04.29	04.6832
Nitrogen	26.54	26.9972
Sulphur	08.78	08.8154

6) From the analytical data the molecular formula was found to be $C_{18}H_{17}N_7S_1$.
7) **IR Spectrum of compound**: IR spectrum of compound was carried out in KBr pellets and reproduce on **Plate No. PVR-8**, an important absorption are correlated as follows in **Table No.-1.2.**

Table No.-1.2.

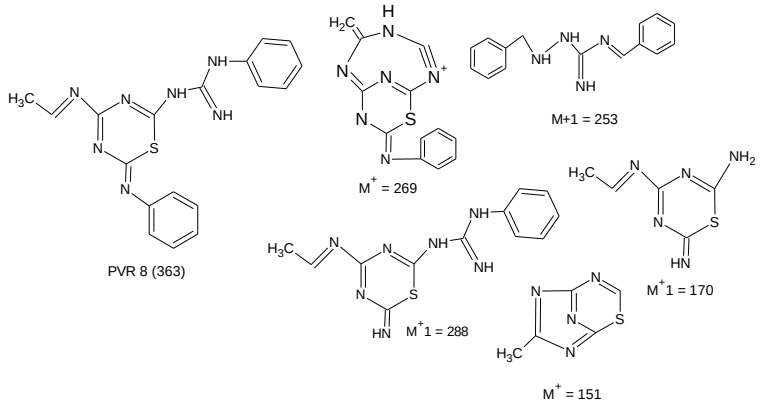
Absorption observed cm^{-1}	**Assignment**	**Absorption Expected cm^{-1}**
3185.10	ArC-H[32] stretching	3150-3000
1637.7	C=N[33] stretching	1750-1450
1254.30	C-N[34] stretching	1360-1000
725.37	C-S[34] stretching	800-600
668.34	Mono-substituted ph-ring	800-600
3376.8	NH Stretching	3500-3000
1507.18	Ar C=C stretching	1600-1450

8) **PMR-Spectrum:**

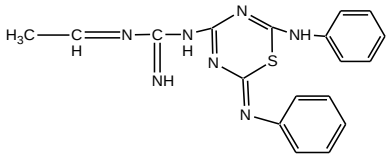
The PMR spectrum[24,36] of compound was carried out in $CDCl_3$ and DMSO-d_6 and reproduced on **PMR Plate No. PVR-8**. This spectrum distinctly displayed the signals due to Ar-protons at δ 6.6253-8.4541ppm, NH protons at δ 3.1786-4.8738 ppm, =NH protons at δ 3.1786-3.7665 ppm, -CH proton at δ 2.1345-2.6119 ppm and $-CH_3$ protons at δ 1.2024-1.5318 ppm.

9) **Mass spectrum**:-

The Mass analysis of the compound was carried out and reproduced on **Mass Plate No. PVR-8**. The fragmentation occurs during the analysis is given in **Mass Scheme-I.**



From the above properties and spectral analysis of the compound **(IIIa[1])** was assigned the structure as 2-methylguanidino-4-methylimine-6-phenylimino-1,3,5-thiadiazines **(IIIa[1]).**

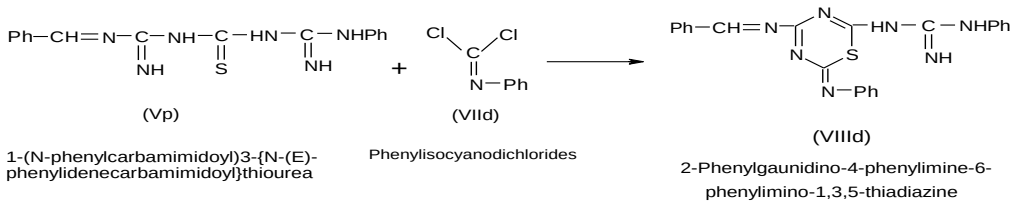


(VIIIa)

Synthesis of 2-phenylguanidino-4-phenylimine-6-phenylimino-1,3,5-thiadi-azine (IIIa[3]):

A reaction mixture of N-phenylformamidino-N'-phenylimino-thiocarbamide **(Ic)** with phenylisocyanodichloride **(IId)** in 1:1 molar ratio was refluxed acetone-ethanol medium for 2 hours. During heating evolution of hydrochloride gas was clearly noticed. After distillation of excess of acetone-ethanol dark brown colour product was

isolated this on basification with dilute ammonium hydroxide afforded lemon yellow crystals, yield 72%, m.p. 240^{0}C. The probable mechanism of the formation of **(IIIa^3)** is depicted below **(Scheme-II)**.



Where R, R' & R" = -methyl, -ethyl, -allyl, -phenyl

Scheme-II

Properties of (IIIa^3):

1) It was lemon yellow crystalline solid having m.p.240^{0}C**.**
2) It gave positive test for nitrogen and sulphur.
3) It does not desulphurized when boiled with alkaline plumbite solution which clearly indicate that sulphur is not free as in **(IIIa^3)** and gets cyclised.
4) It was soluble in benzene, acetic acid, DMF and DMSO.

10) **Elemental analysis**: The result of elemental analysis is given in **Table No.1.4**

Table 1.4

Elements	Found (%)	Calculated (%)
Carbon	66.98	67.3170
Hydrogen	03.51	04.3902
Nitrogen	19.75	20.4878
Sulphur	07.49	07.8

5) From the analytical data the molecular formula was found to be $C_{23}H_{19}N_7S_1$.
6) **IR Spectrum of compound**: IR spectrum of compound was carried out in KBr pellets and reproduce on Plate No. **PVR-7**, an important absorption are correlated as follows in **Table no-1.5.**

Table 1.5

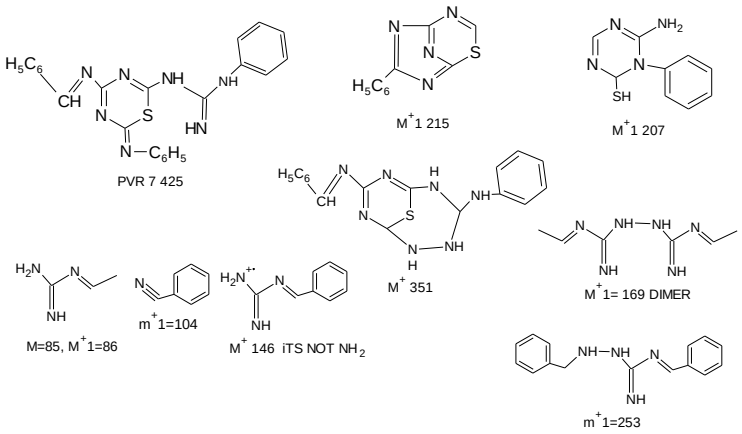
Absorption observed (cm^{-1})	Assignment	Absorption Expected (cm^{-1})
3176.0	ArC-H[32] stretching	3150-3000
1635.0	C=N[33] stretching	1750-1450
1254.30	C-N[34] stretching	1360-1000
723.14	C-S[34] stretching	800-600
668.12	Mono-substituted –ph ring	800-600
3376.8	NH Stretching	3500-3000
1504.1	Ar C=C stretching	1600-1450

7) **PMR-Spectrum:**

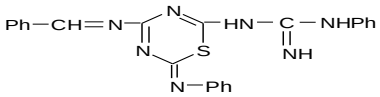
The PMR spectrum[24,36] of compound was carried out in $CDCl_3$ and DMSO-d_6 and reproduced on **PMR Plate No. PVR-7**. This spectrum distinctly displayed the signals due to Ar-protons at δ 6.647-8.1570 ppm, NH protons at δ 3.5515 ppm, =NH protons at δ 2.5627-2.5850 ppm, and -CH proton at δ 2.1134 ppm.

8) **Mass spectrum**:-

The Mass analysis of the compound was carried out and reproduced on **Mass Plate No. PVR-7**. The fragmentation occurs during the analysis is given in **Mass Scheme-II.**



From the above properties and spectral analysis of the compound **(IIIa^3)** was assigned the structure as 2-phenylguanidino-4-phenylimine-6-phenylimino-1,3,5-thiadiazine **(IIIa^3).**



(VIIId)

2-Phenylgaunidino-4-phenylimine-6-phenylimino-1,3,5-thiadiazine

Similarly, N-ethylformamidino-N'-phenyliminothiocarbamide **(Ib)**, N-3-nitrophenylformamidino-N'-phenyliminothiocarbamide **(Id)**, N-4-nitrophenylformamidino-N'-phenyliminothiocarbamide **(Ie)** and N-3-p-dimethylphenyl- formamidino-N'-phenyliminothiocarbamide **(If)** were interacted with phenylisocyanodichloride **(II2)** to isolate 2-phenylguanidino-4-ethylimino-6-phenylimino-1,3,5-thiadiazine **(IIIa^2),** 2-phenylguanidino- 4-(3-nitro)phenylimine-6-phenylimino-1,3,5-thiadiazine**(IIIa^4)**,2-phenylgua-nidino-4-(4-nitro)phenylimine-6-phenylimino-1,3,5-thiadiazine**(IIIa^5)** and 2-phenylguanidino-4-(3-p-dimethyl)phenylimine-6-phenylimino-1,3,5-thiadiazine **(IIIa^6)** respectively by above mentioned method in **Experiment No. 3-30** and enlisted in **Table No.-1.7**.

Table No.-1.7

Expt No	Comp No	Substitued isocyanodi-chloride	2-Phenylguanidino-4-**substituted**imine-6-**substituted**imino-1,3,5-thiadiazine	Yield %	M.P. ^{0}C
3	(Ib)	Phenyl.....	.....4-ethylimine-6phenyl.....	82	192
4	(Id)	Phenyl.....	.....4-(3-nitro)phenylimine-6-phenyl....	80	204
5	(Ie)	Phenyl.....	.....4-(4-nitro)phenylimine-6-phenyl.....	76	215
6	(If)	Phenyl.....	.....4-(3-p-dimethyl)phenylimine-6phenyl.....	75	189
7	(Ia)	Methyl.....	.....4-methylimine-6-methyl.....	85	178
8	(Ib)	Methyl.....	.....4-ethylimine-6-methyl.....	82	197
9	(Ic)	Methyl.....	.....4-phenylimine-6-methyl.....	80	210
10	(Id)	Methyl.....	.....4-(3-nitro)phenylimine-6-methyl.....	78	235
11	(Ie)	Methyl.....	.....4-(4-nitro)phenylimine-6-methyl.....	78	203
12	(If)	Methyl.....	.....4-(3-p-dimethyl)phenylimine-6-methyl.....	75	183
13	(Ia)	Ethyl.....	.....4-methylimine-6-ethyl.....	84	155
14	(Ib)	Ethyl.....	.....4-ethylimine-6-ethyl.....	82	168
15	(Ic)	Ethyl.....	.....4-phenylimine-6-ethyl.....	78	244
16	(Id)	Ethyl.....	.....4-(3-nitro)phenylimine-6-ethyl.....	75	276
17	(Ie)	Ethyl.....	.....4-(4-nitro)phenylimine-6-ethyl.....	76	279
18	(If)	Ethyl.....	.....4-(3-p-dimethyl)phenylimine-6-ethyl.....	74	230
19	(Ia)	t-butyl....	.....4-methylimine-6-t-butyl.....	75	256
20	(Ib)	t-butyl....	.....4-ethylimine-6-t-butyl.....	72	234
21	(Ic)	t-butyl....	.....4-phenylimine-6-t-butyl.....	72	278
22	(Id)	t-butyl....	.....4-(3-nitro)phenylimine-6-t-butyl....	68	145
23	(Ie)	t-butyl....	.....4-(4-nitro)phenylimine-6-t-butyl....	65	167
24	(If)	t-butyl....	.....4-(3-p-dimethyl)phenylimine-6-t-butyl.....	66	174
25	(Ia)	p-Cl-Ph...	.....4-methylimine-6-(p-Cl)-phenyl.....	68	234
26	(Ib)	p-Cl-Ph...	.....4-ethylimine-6-(p-Cl)-phenyl.....	65	201
27	(Ic)	p-Cl-Ph...	.....4-phenylimine-6-(p-Cl)-phenyl.....	64	185
28	(Id)	p-Cl-Ph...	.....4-(3-nitro)phenylimine-6-(p-Cl)phenyl...	63	214
29	(Ie)	p-Cl-Ph...	..4-(4-nitro)phenylimine-6-(p-Cl)-phenyl..	62	248
30	(If)	p-Cl-Ph...	..4-(3-p-dimethyl)phenylimine-6-(p-Cl)-phenyl..	62	199

EXPERIMENTAL

Experiment No. 1

Synthesis of 2-substitutedguanidino-4,6-susbstitutedlimino-1,3,5-thiadiazine(IIIa^1-e^5):

A reaction mixture of N-substitutedformamidino-N'susbtitutediminothio-carbamide **(Ia-e)** (0.1M) with substitutedisocyanodichloride **(II1-5)** (0.1M) in 1:1 molar ratio was refluxed on water bath in 50% acetone-ethanol (15 ml) medium for 2 hours. During heating evolution of hydrochloride gas was clearly noticed. After distillation of excess of acetone-ethanol dark brown colour product was isolated this on basification with dilute ammonium hydroxide lemon yellow crystals were afforded, yield, m.p. recorded.

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