IJCPS Vol. 5, No,-5,Sep-Oct 2016 ISSN:2319-6602
www.ijcps.org International Journal of Chemical and Physical Sciences

Synthesis of 1,3-Diformamidinothiocarbamide and 1-Formamidino-3-Substituted for Mamidinothiocarbamides

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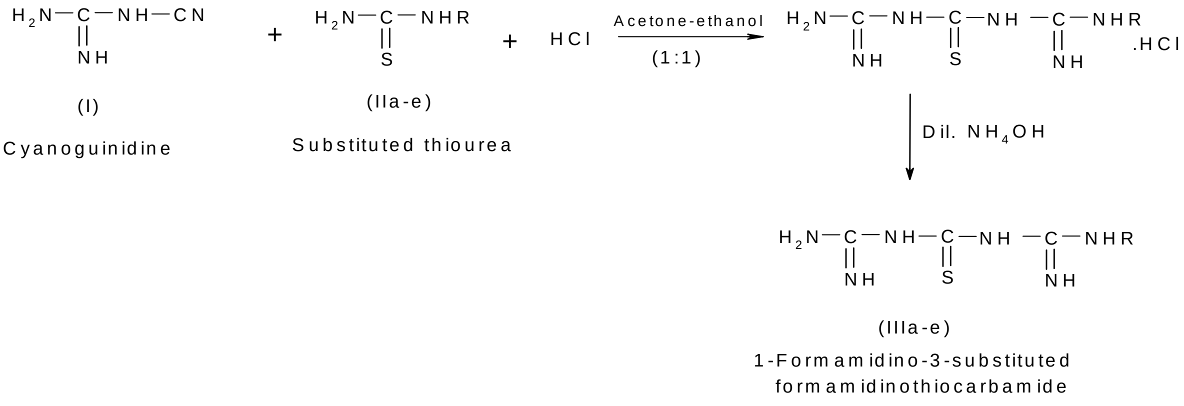
Abstract

A novel synthesis of a series of 1,3-diformamidinothiocarbamide (IIIa) and 1-formamidino-3-substitutedformamidinothiocarbamides (IIIb-e) were successfully synthesized in this laboratory. 1,3-Diformamidinothiocarbamide (IIIa) and 1-formamidino-3-substitutedformamidinothiocarbamides (IIIb-e) were synthesized by the reactions of dicyandiamide (I) with various thiocarbamides (IIa-e) and HCl in acetone-ethanol medium in 1:1 molar proportion. The structure of the synthesized compounds was justified on the basis of usual chemical characteristics and spectral study.

KEYWORDS:Dicyandiamide, various thioureas, HCl, acetone, ethanol, etc.

Introduction

Dicyanadiamide is an important organic compound for its pharmaceutical, medicinal, biological, agricultural and industrial applications[1-6]. It is a bifunctional molecule which possesses basic formamidino group at 3 positions and cyano/nitrilo group at 1 position. Therefore, this molecule produces varieties of interesting heteroacycles and heterocycles possesses their own identity and importance. In drug chemistry, these nucleus containing compounds enhance the potency and therapeutic value of that drug. Hence, there is a continuous evolution in drug, medicinal and pharmaceutical sciences and focus on the maintaining green chemistry. The tentative reaction for the formation of product is depicted as below.



$$H_2N-\underset{\underset{NH}{\|}}{C}-NH-CN + H_2N-\underset{\underset{S}{\|}}{C}-NHR + HCl \xrightarrow[(1:1)]{\text{Acetone-ethanol}} H_2N-\underset{\underset{NH}{\|}}{C}-NH-\underset{\underset{S}{\|}}{C}-NH-\underset{\underset{NH}{\|}}{C}-NHR\ .HCl \xrightarrow{\text{Dil. } NH_4OH} H_2N-\underset{\underset{NH}{\|}}{C}-NH-\underset{\underset{S}{\|}}{C}-NH-\underset{\underset{NH}{\|}}{C}-NHR$$

Where, R = -H, -methyl, -ethyl, -allyl, -phenyl.

As evident from the structure of dicyandiamide, it is much more interesting that this compound possesses formamidino and a cyano group.Therefore, it can be easily reacted with various thioureas in presence of various organic solvent. This reaction of cyanogaunidine and various thioureas in which 1,3-

diformamidinothiocarbamide and1-formamidino-3-substitutedformamidinothiocarbamide were isolated[7-10]. All these compounds showed remarkable pharmaceutical, medicinal, agricultural and industrial values.Hence, it appeared sufficiently interesting to reinvestigate the reactions of cyanoguanidine, various thiocarbamides and hydrochloric acid in acetone-ethanol (1:1) medium to isolate 1,3-diformamidinothiocarbamides and 1-formamidino-3-substitutedformamidinothiocarbamides. These compounds are the best intermediate in the synthesis of novel series of biurets, thiadiazoles and triazines. With the above aim and objectives, the interaction of cyanogaunidine and various thiocarbamides had been investigated.

Materials and Method:

The melting points of all the synthesized compounds were recorded using hot paraffin bath and are uncorrected. The carbon and hydrogen analysis was carried out on Carlo-Ebra-1106 analyzer; nitrogen estimation was carried out on Column-N-analyzer-29. IR spectra were recorded on Perkin-Elmer spectrophotometer in the range of 4000-400 cm^{-1} in KBr pellets. PMR spectra were recorded on Bruker AC-300F spectrometer with TDS as internal standard using $CDCl_3$ and DMSO-d_6 as a solvent. The purity of the compound was checked out by TLC on silica gel-G plates with the thickness of 0.3mm. All chemicals used were of AR grade.

Synthesis of 1,3-diformamidinothiocarbamide (IIIa):

1,3-Diformamidinothiocarbamide **(IIIa)** was synthesized by refluxing a mixture of cyanoguanidine **(I)** (0.1M), thiocarbamide **(IIa)** (0.1M) and hydrochloric acid in acetone-ethanol medium for 4 hours on water bath, during refluxing clear solution was obtained. After distillation of solvent, dark yellow crystals were separated out, which on basification with dilute ammonium hydroxide afforded crystals, which were washed with ether and recrystallized with aqueous ethanol.Yield 80%, m.p. 266^{0}C.

Synthesis of 1-formamidino-3-methylformamidinothiocarbamide:

1-Formamidino-3-methylformamidinothiocarbamide**(IIIb)**was synthesized by refluxing a mixture of cyanogaunidine **(I)** (0.1M),methylthiocarbamide **(IIb)** (0.1M) and hydrochloric acid in acetone-ethanol medium for 4 hours on water bath, during refluxing clear solution was obtained.After distillation of solvent, brownish crystals were separated out, which on basification with dilute ammonium hydroxide afforded crystals, which were washed with ether and recrystallized with aqueous ethanol. Yield55%, m.p. 123^{0}C.

Synthesis of 1-formamidino-3-ethylformamidinothiocarbamide:

1-Formamidino-3-ethylformamidinothiocarbamide **(IIIc)** was synthesized by refluxing a mixture of cyanoguanidine **(I)** (0.1M), ethylthiocarbamide **(IIc)** (0.1M) and hydrochloric acid in acetone-ethanol medium for 4 hours on water bath, during refluxing clear solution was obtained. After distillation of solvent, brownish crystals were separated out, which on basification with dilute ammonium hydroxide afforded crystals, which were washed with ether and recrystallized with aqueous ethanol. Yield 64%, m.p. 108^{0}C.

Synthesis of 1-formamidino-3-allylformamidinothiocarbamide:

1-Formamidino-3-allylformamidinothiocarbamide **(IIId)** was synthesized by refluxing a mixture of cyanogaunidine **(I)** (0.1M), allylthiocarbamide**(IId)** (0.1M) and hydrochloric acid in acetone-ethanol medium for 4 hours on water bath, during refluxing clear solution was obtained. After distillation of solvent, dark yellow crystals were separated out, which on basification with dilute ammonium hydroxide afforded crystals, which were washed with ether and recrystallized with aqueous ethanol.Yield 69%, m.p. 203^0C.

Synthesis of 1-formamidino-3-phenylformamidinothiocarbamide:

1-Formamidino-3-methylformamidinothiocarbamide **(IIIe)** was synthesized by refluxing a mixture of cyanoguanidine**(I)** (0.1M), phenylthiocarbamide **(IIe)** (0.1M) and hydrochloric acid in acetone-ethanol medium for 4 hours on water bath, during refluxing clear solution was obtained. After distillation of solvent, brownish crystals were separated out, which on basification with dilute ammonium hydroxide afforded crystals, which were washed with ether and recrystallized with aqueous ethanol. Yield 61%, m.p. 183^0C.

Results and Discussion

Synthesis of 1,3-Diformamidinothiocarbamide (IIIa):

1,3-diformamidinothiocarbamide **(IIIa)** was synthesized by refluxing a mixture of cyanogaunidine **(I),** thiocarbamide **(IIa)** and hydrochloric acid in acetone-ethanol medium for 4 hours on water bath. During boiling suspended cyanoguanidine **(I)** went into the solution which turned yellow colour. It was filtered in hot conditions and after distillation of solvent brownish crystals were isolated which on basification with dilute ammonium hydroxide afforded crystals, which were washed with several times of ether, yield 87%. It was crystallized with aqueous ethanol formed needle shaped dark yellow crystals, yield 63%, m.p. 266^0C.

Properties of (IIIa):

It was needle shaped dark yellow crystalline solid having m.p.266^0C.It gave positive test for nitrogen and sulphur.Desulphurized when boiled with alkaline plumbite solution.The benzene solution of compound when treated with pure and dry carbon disulphide a yellow colour was developed, which clearly indicated presence of basic imino (=NH) group[11].It was soluble in alcohol, acetone, dioxane and DMSO while insoluble in water.

Elemental Analysis:

The result of elemental analysis is given in Table No.-1

Table No.-1

Elements	Found (%)	Calculated (%)
Carbon	22.1	22.5
Hydrogen	4.8	5
Nitrogen	52.2	52.5
Sulphur	19.8	20

From the analytical data the molecular formula was found to be $C_3H_8N_6S$.IR Spectrum of compound:IR spectrum of compound was carried out in KBr pellets and reproduce on IR Plate No. PPB-1, an important absorption are correlated as follows,

PMR-Spectrum:

The PMR spectrum of compound[13,15-16] was carried out in $CDCl_3$ and DMSO-d_6 and reproduced on PMR Plate No. PPB-1. This spectrum distinctly displayed the signals –NH protons at δ 4.5588ppm, -NH_2 protons at δ 3.3722 and at δ 1.3606-1.3961 due to =NH protons.

Synthesis of 1-Formamidino-3-Phenylthiocarbamide (IIIe):

Interactions of cyanogaunidine (I) andphenylthiocarbamide (IIe)was carried out in presence of hydrogen chloride in acetone-ethanol medium for 4 hours on water bath. During boiling suspended cyanoguanidine **(I)** went into the solution which turned yellow colour. It was filtered in hot conditions and after distillation of solvent brownish crystals was isolated which on basification with dilute ammonium hydroxide afforded crystals, which were washed several times with ether. It was crystallized with aqueous ethanol formed dark yellow crystals, yield 68%, m.p. 127^0C.

Table No.-2

Absorption observed incm^{-1}	Assignment	Absorption expected incm^{-1}
3382.11	-OH[11]	3500-3000
3151.11	C-N[12-13]	3150-3000
1578.6	=C=N[14]	1750-1450
1506.8	C-N[12-13]	1789-1471
1253.14	N=C=S[12-13]	1340-1250

Properties of (IIIe):

It was dark yellow crystalline solid having m.p.127^0C.It contained nitrogen and sulphur.Desulphurized when boiled with alkaline plumbite solution.The benzene solution of compound when treated with pure and dry carbon disulphide a yellow colour was developed, which clearly indicated presence of basic imino (=NH) group[11].It was soluble in alcohol, acetone, dioxane and DMSO while insoluble in water.

Elemental analysis: The result of elemental analysis is given in Table No.-3

Table No.-3

Elements	Found (%)	Calculated (%)
Carbon	44.66	45.76
Hydrogen	4.26	5.08
Nitrogen	34.57	35.59
Sulphur	12.66	13.55

From the analytical data the molecular formula was found to be $C_9H_{12}N_6S$.

IR Spectrum of compound:

IR spectrum of compound was carried out in KBr pellets and reproduce on IR Plate No. PPB-2, an important absorption are correlated as follows,

Table No.-4

Absorption observed in cm^{-1}	**Assignment**	**Absorption Expected in cm^{-1}**
3185.11	Ar-H Stretching	3300-3000
3151.11	C-N Stretching[12-13]	3150-3000
1639.5	=C=N Stretching[14]	1750-1450
1506.8	C-N Stretching[12-13]	1789-1471
1253.14	N=C=S Stretching[12-13]	1340-1250

***PMR-Spectrum*:**

The PMR spectrum of compound[17,21]was carried out in $CDCl_3$ and DMSO-d_6 and reproduced on PMR Plate No. PPB-2. This spectrum distinctly displayed the signals Ar-NH protons at δ6.3602-9.9261 ppm, =NH protons at δ1.2489-2.5713ppm and –NH_2 protons at δ3.2773-3.4194.

Similarly,1,3-diformamidinothiocarbamide(IIIa),1-formami-dino-3-ethylformamidinothiocarbamide (IIIb), 1-formamidino-3-ethylformamidinothiocarbamide (IIIc)and 1-formamidino-3-allylformamidinothiocarbamide (IIId) were prepared by the interaction of cyanogaunidine (I) with methylthiocarbamide (IIb), ethylthiocarbamide (IIc) and allylthiocarbamide(IId) respectively by above mentioned method and enlisted in (Table No.-5).

Table No.-5

Sr.No.	1-Formamidino-3-**substituted**formamidinothiocarbamide	**Yield (%)**	**m.p.(^{0}C)**
1	**--1,3-diformamidino-**	80	266
2	---------3-**methyl-------**	55	123
3	---------3-**ethyl---------**	64	108
4	---------3-**allyl----------**	69	203

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