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Green Synthesis of 1-Substituted-3-(4-Pyridineimino)-Thiocarbamides

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ABSTRACT

Recently in this laboratory the economical, environmental, solvent free, mild and having simple work-up reaction condition was developed for the green synthesis of a novel series of 1-substituted-3-(4-pyridinoimino)thiocarbamides (IIIa-e) having high product yield and avoid treacherous byproducts. The interactions of 4-cyanopyridine (I), concentrated hydrochloric acid and various thiourea (IIa-e) were carried out in microwave oven to synthesize (IIIa-e). The green chemistry parameters were maintained. The synthesized compounds were recrystalised and the structure of synthesized compounds were justified and established on the basis of elemental analysis, chemical characteristics and spectral studies.

Introduction

In the recent years solvent free reaction conditions have been studied1. The solvent free reactions usually take shorter reaction time, simpler reactors more efficient work up to procedure, easier separation and purifications than conventional reaction conditions2-3.

These reactions are economical, environmental, mild and having simple work-up with high product yield and avoid treacherous byproducts. So the great task towards chemist is to develop non-hazardous synthetic methodology for the organic synthesis. The main target of these basic principles are to explore an alternative reaction conditions and reaction medium to achieve the preferred chemical transformations with minimum byproducts or waste generation as well as to eliminate the use of unadventurous organic solvent. It also gave strict legal restrictions on pollution exposures.

The literature surveys prove that some offshoot of 4-cyanopyridine showed astounding and conspicuous anti-HIV4, anti-tumor5, anti-cancer6-7, anti-depresant8, anti-hypertensive9, anti-diabetic10, anti-pyretic11-12, anti-fungal and anti-viral13 activities. 4-cyanopyridine and its imitative are highly active against the herpes virus14-15 and also showed anti-tubercular16, anti-histaminic17, anti-inflammatory, analgesic18, anti-bacterial19, anti-microbial20, while several plagiaristic of 4-cyanopyridine are used as cardiovascular, A2A adenosine receptor antagonists21. Derivatives of 4-cyanopyridine possesses 1 KK-B inhibitor22, anxiolytic23, hypnotic24, corticotropin-releasing factor (CRF) antagonist25-26, xanthine oxidase inhibitory27-28, and anti-arrhythmic29.

Cyanopyridine is also used as an intermediate in the synthesis of various nitrogen, sulphur, nitrogen and sulphur containing heteroacycles and heterocycles.

4-Cyanopyridine is very interesting heterocycle due to its momentous and adaptable nature having biological and pharmacological actions30-36. It is used as intermediate in the various syntheses in pharmaceutical industries for the isolation of nicotinamide, nicotinic acid and isonicotinic acid37-39. In the recent two decades the importance of 4-cyanopyridine in organic synthesis had been increased due to its most resourceful properties40-41. It is used for the manufacture of vitamin B-3, herbicides, pharmaceuticals and picolinate micronutrients42-49. 4-Cyanopyridine is the best preliminary material for invent of many agrochemicals, 4-DMAP and isoniazides. 4-Cyanopyridine is also used as an intermediate in the synthesis of orally bioavialable cannabinoid receptor-2 agonists' agents50. When we go through literature survey it was observed that synthesis of imines and Schiff bases have been done in adequate detail51-55.

Recently in this laboratory Tayade et al56-63 synthesized new series of thiadiazoles, thiadiazines and dithiazines by exploring the synthetic application of -amino, -cyano, -halo etc. groups successfully and also studied their antimicrobial, antifungal and physiochemical parameters. As 4-cyanopyridine, thiocarbamide and their derivatives showed pharmaceutical, medicinal, agricultural, biological and industrial significances and applications. Hence taking all these facts into consideration this research scheme was designed. During designing this scheme it was also planned to developed a new green synthesis route for the synthesis of 1-substituted-3-(4-pyridineimino)thiocarbamides (IIIa-e) by the interactions of 4-cyanopyridine (I), conc. HCl and various thioures (IIa-e) by making the use of microwave oven as a reaction chamber.

The main objective of the work is to synthesize a novel series of 1-substituted-3-(4-pyridineimino)thiocarbamides (IIIa-e) to set up new solvent free reaction condition and also to reduce the time span of such type of reactions and at the same time it was also thought to increase the yield of product by maintaining the purity. This work is useful to incoming researcher in organic chemistry in the synthesis of such types of compounds. The newly synthesized compounds will be expected to possess more practical utility and the new thiocarbamido substituent may enhance the potency of the compound and can also be used as drug.

Experimental

Experiment No. 1

Synthesis of 1-(4-pyridineimino)thiocarbamide (IIIa):

A mixture of 4-cyanopyridine (I) (0.1 M), thiourea (IIa) (0.1 M) and concentrated hydrochloric acid (1ml) is irradiate

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in microwave oven for 2 minutes and then allowed to cool. The yellow crystals of 1-(4-pyridineimino)thiocarbamide (IIIa) were obtained. It was washed several times with ether, recrystalised from ethanol and dried. Yield 94%, m.p. 148 0C.

Experiment No. 2

Synthesis of 1-methyl-3-(4-pyridineimino)thiocarbamide (IIIb)

A mixture of 4-cyanopyridine (I) (0.1 M), methylthiourea (IIb) (0.1 M) and concentrated hydrochloric acid (1ml) is irradiate in microwave oven for 2 minutes and then allowed to cool. The yellow crystals of 1-methyl-3-(4-pyridineimino)thiocarbamide (IIIb) were obtained. It was washed several times with ether, recrystalised from ethanol and dried. Yield 91%, m.p. 156 ^{0}C.

Experiment No. 3

Synthesis of 1-ethyl-3-(4-pyridineimino)thiocarbamide (IIIc):

1-Ethyl-3-(4-pyridineimino)thiocarbamide (IIIc) was synthesized by interacting 4-cyanopyridine (I), ethylthiourea (IIc) and hydrochloric acid in microwave oven for 2 minutes. Yellow crystals were obtained; these were washed several times with ether. Recrystalised from ethanol. Yield 96%, melting point 168^{0}C.

Experiment No. 4

Synthesis of 1-allyl-3-(4-pyridineimino)thiocarbamide (IIId):

A mixture of 4-cyanopyridine (I) (0.1 M), allylthiourea (IId) (0.1 M) and concentrated hydrochloric acid (1ml) is irradiate in microwave oven for 2 minutes and then allowed to cool. The yellow crystals of 1allyl-3-(4-pyridineimino) thiocarbamide (IIId) were obtained. It was washed several times with ether, recrystalised from ethanol and dried. Yield 88%, m.p. 162 ^{0}C.

Experiment No. 5

Synthesis of 1-phenyl-3-(4-pyridineimino)thiocarbamide (IIIe):

This compound was synthesized by interacting 4-cyanopyridine (I), phenylthiourea (IIe) and hydrochloric acid in microwave oven for 2 minutes. Lemon yellow crystals were obtained, which were collected by filtration and washed several times with ether. Recrystalised with ethanol. Yield 95%, melting point 147^{0}C.

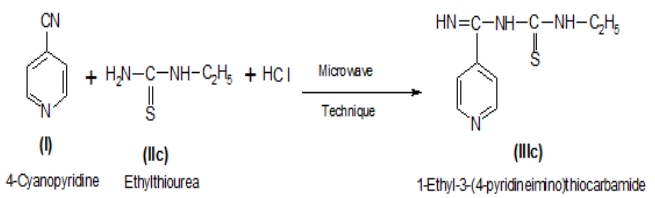
Result and Discussion

A)Synthesis of 1-ethyl-3-(4-pyridineimino)thiocarbamide (IIIc)

1-Ethyl-3-(4-pyridineimino)thiocarbamide (IIIc) was synthesized by interacting 4-cyanopyridine (I), ethylthiourea (IIc) and hydrochloric acid in microwave oven for 2 minutes. Yellow crystals were obtained; these were washed several times with ether. Recrystalised from ethanol. Yield 96%, melting point 168^{0}C.

The probable reaction for the formation of (IIIc) is depicted below,

Reaction



Properties of (IIIc)

1) It is yellow coloured crystalline solid having melting point 1680C.

2) It gave positive test for nitrogen and sulphur (negative test for chlorine which clearly indicate removal of chlorine)

3) It was desulphurised by alkaline plumbite solution which clearly indicate the presence of C=S group. It also gave positive test for imino group64.

4) It was soluble in water, ethanol, DMSO-d6 while insoluble in carbon tetra chloride, chloroform, benzene, dioxane, petroleum ether.

5) It formed picrate having melting point 181^{0}C.

6)Elemental Analysis: The result of elemental analysis is given in Table No. II-1

Table No. II-1

Sr. No.	Elements	Found	Calculated
1.	Carbon	51.32	51.92
2.	Hydrogen	05.62	05.76
3.	Nitrogen	26.36	26.92
4.	Sulphur	15.38	15.38

7) From the analytical data the molecular formula was found to be C9H12N4S.

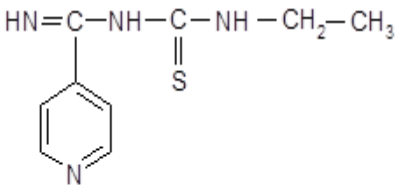
8) IR spectrum: IR spectrum of compound (IIIc) was carried out in KBr-pellets and is reproduced on IR Plate No. DTT-1. The important absorptions are correlated as follows and are depicted in Table No. II-2

Table No. II-2

Sr. No.	Absorption Observed(cm^{-1})	Assignment	Absorption
1.	3393.26	NH stretching	3500-3000
2.	2804.41	CH stretching	3000-2500[65]
3.	1611.48	=C=Sstretching	1750-1180[66]
4.	1594.74	C = NH (imino grouping)	1789-1471[56]
5.	1466.61	C = N stretching(Ring)	1600-1430[57]
6.	1415.43	NC=Sstretching	1550-1250[61]
7.	1083.61	C-N stretching	1200-1000

9) **PMR spectrum:** The PMR spectrum of compound was carried out in $CDCl_3$ and DMSO-d_6 and reproduced on **PMR Plate No. DTT-1.** This spectrum distinctly displayed the signals due to pyridino proton at δ7.0426-8.9799 ppm, NH proton at δ4.0573-4.9972 ppm, N-CH_2 proton at δ 2.0372-3.1515 ppm, CH_3 proton at δ1.3766-1.9085 ppm, imino (=NH) proton at δ1.1292-1.2135 ppm.

From the above chemical characteristics and spectral analysis the compound (IIIc) was assigned the structure as 1-ethyl-3-(4-pyridineimino)-thiocarbamide (IIIc**)**



(IIIc)

1-Ethyl-3-(4-pyridineimino)thiocarbamide

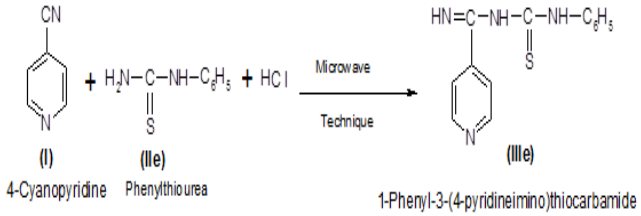
B)Synthesis of 1-phenyl-3-(4-pyridineimino)thiocarbamide (IIIe)

This compound was synthesized by interacting 4-cyanopyridine (I), phenylthiourea (IIe) and hydrochloric acid

in microwave oven for 2 minutes. Lemon yellow crystals were obtained, which were collected by filtration and washed several times with ether. Recrystalised with ethanol. Yield 95%, melting point 147^{0}C.

The probable reaction for the formation of (IIIe) is depicted below,

Reaction



Properties of (IIIe)

1) It is yellow colored crystalline solid having melting point 147^{0}C.

2) It gave positive test for nitrogen and sulphur (negative test for chlorine which clearly indicated removal of chlorine).

3) It was desulphurised by alkaline plumbite solution and it also gave positive test for imino group64 which clearly indicate the presence of C=S and C=NH group respectively.

4) It was soluble in water, ethanol, DMSO-d6 while insoluble in carbon tetra chloride, chloroform, benzene, dioxane, petroleum ether.

5) It formed picrate having melting point 160^{0}C.

6) **Elemental Analysis:** The result of elemental analysis is given in TableNo.II-3

Table No. II-3

Sr. No.	Elements	Found	Calculated
1.	Carbon	60.15	60.93
2.	Hydrogen	04.22	04.68
3.	Nitrogen	21.56	21.87
4.	Sulphur	12.50	12.50

7) From the analytical data the molecular formula was found to be C13H12N4S.

8) IR spectrum: IR spectrum of compound (IIIe) was carried out in KBr-pellets and is reproduced on IR Plate No. DDT-5. The important absorption is correlated as follows and is depicted in Table No. II-4

Table No. II-4

Sr. No.	Absorption Observed(cm^1)	Assignment	Absorption
1.	3328.26	NH stretching	3500-3000
2.	3028.01	Ar-CH stretching	3150-3000[65]
3.	1631.34	=C=S stretching	1750-1180[66]
4.	1554.79	C = NH (imino grouping)	1789-1471[56]
5.	1489.88	C = N stretching (Ring)	1600-1430[57]
6.	1297.24	N-C=S stretching	1550-1250[61]
7.	1123.86	C-N stretching	1200-1000
8.	721.62	Monosubstituted Benzene	750-700

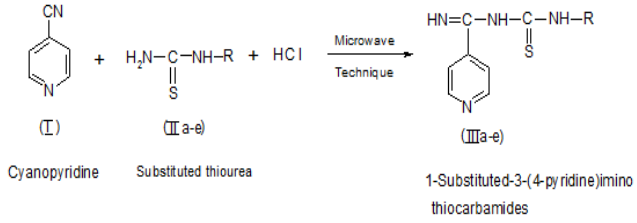
9) **PMR spectrum:** The PMR spectrum of compound was carried out in $CDCl_3$ and DMSO-d_6 and reproduced on **PMR plate No. DTT-5.** This spectrum distinctly displayed the signals due to pyridino proton at δ7.6681-8.8791 ppm, Ar-H proton at δ7.0284-7.5998 ppm, NH proton at δ4.5830 ppm, imino (=NH) proton at δ1.1103-1.2181 ppm.

From the above chemical characteristics and spectral analysis the compound **(IIIe)** was assigned the structure as 1-phenyl-3-(4-pyridineimino)-thiocarbamide

Table No. II-5

Sr. No.	Expt. No.	1-Substituted-3-(4-pyridineimino)-thiocarbamides (IIIa,b and d)	Yield (%)	M.P. ^{0}C
1.	1	1-H …….	94	148^{0}C
2.	2	1-Methyl…	91	156^{0}C
3.	4	1-Allyl……	88	162^{0}C

Scheme I



Where, R = -H, $-CH_3$, $-C_2H_5$, $-C_3H_5$, $-C_6H_5$

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