CYCLOTRIMERIZATION OF NITRILES WITH α-HETEROATOMS CATALYZED BY USING TUNGSTEN AND MOLYBDENUM BRONZES

By

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TABLE OF CONTENTS

Chapter Page

I. INTRODUCTION AND LITRATURE REVEIW.....1

INTRODUCTION 1
Cycloaddition Reaction.....3
Nucleophilic Aromatic Substitution of Cyanuric Chloride 4
Cyclotrimerization Reaction 6
Introduction to Tungsten and Molybdenum Bronze.....12

II. PREPARATION OF ALTRETAMINE BY TRIMERIZATION OF DIMETHYLCYANAMIDE USING A METAL BRONZE AS THE CATALYST... 16

INTRODUCTION 16
EXPERIMENTAL.....21
Preparation of Tungsten Bronze 21
Preparation of Molybdenum Bronze.....21
Reaction of Dimethycyanamide with Hydrogen Bonzes.....22
RESULTS AND DISCUSSION 23
CONCLUTION.....34

III. REACTION OF METHYLTHIOCYANATE WITH METAL BRONZE.....35

INTRODUCTION 35
EXPERIMENTAL.....36
RESULTS AND DISCUSSION.....21
CONCLUTION.....40

REFERENCES 41

Chapter Page

LIST OF TABLES

Table Page

1.1 Cyclotrimerization of Dialkylcyanamides 9

1.2 Cyclotrimerization of Nitrile.....11

2.1 Reaction of Dimetylcyanamide with Tungsten and Molybdenum Bronze in toluene at 150 o C 25

2.2 Reaction of Dimetylcyanamide with Hydrogen Bronzes in toluene/ Hexane at 150C... 26

2.3 Reaction of Dimethylcyanamide with Excess Tungsten and Molybdenum Bronze... 27

2.4 Reaction of Dimethylcyanamide with Hydrogen bronzes at higher Temperature 28

LIST OF FIGURES

Figure Page

1.1 Example of Biologically Active Compound Containing 1,3,5-Trazine 2

1.2 Cycloaddition Reactions to Form Trazine Derivatives.....3

1.3 Classic Pathway to Substituted.....4

1.4 Nucleophilic Substitution of Cyanuric Chloride.....5

1.5 Cyclotrimerization of Dimethylcyanamide with Tris(dimethylamide)aluminium..7

1.6 Propose Mechanism for Cyclotrimeriation of Dimethylcyanamide with Tris(dimethylamide)aluminium 7

1.7 Cyclotrimerization of Dialkylcyanamides 10

1.8 Cyclotrimerization of Nitrile.....11

1.9 Crystal Structure of WO_3 and $AxWO_3$ 13

1.10 Hydrogen Molybdenum Bronze Phases are formed by the Intercalation of Atomic Hydrogen (i.e. H+ + e-) into the Layered Structure of MoO3.....14

1.11 Hydrogen Intercalation Sites in MoO_3.....15

2.1 Ovarian Cancer Stage IIA, IIB, and IIC 17

2.2 Altretamine Activated Through Metabolic Oxidation to Intermediate Methylol Derivatives and Formaldehyde 18

2.3 Chemical Pathway for Formation of Altretamine Byproducts 19

2.4 Reduction of Hexamethylolmelamine Hexamethyl ether.....20

2.5 Reaction of Dimethylcyanamide with Tungsten Hydrogen Bronze 24

2.6 Reaction of Dimethylcyanamide with Molybdenum Bronze 24

2.7 Propose Mechanism for Cyclotrimerization of Dimethylcyanamide by Metal Bronzes (M=W or MO) 30

2.8 GC-MS Chromatogram of Tetramethylguanidine at 6.73 Retention Time 31

2.9 GC-MS chromatogram of Altretamine 32

2.10 GC-MS Spectra of Altretamine 32

2.11 ^{1}H-NMR Spectra of the Product from the Cyclotrimerization of Dimethylcyanamide 33

2.12 ^{13}C-NMR Spectra of the Product from the Cyclotrimerization of Dimethylcyanamide 34

2.13 The infrared spectrum of Altretamine.....35

3.1. Reaction of Methylthiocyanate with Tungsten and Molybdenum Bonzes 38

3.2 ^{1}H-NMR Spectra of the Product from the Cyclotrimerization of Dimethylcyanamide 39

3.3 GC-MS chromatogram 2, 4-Bis (methylthio)-1, 3, 5-Triazine.....40

3.4 GC-MS Spectra of 2, 4-Bis (methylthio)-1, 3, 5-Triazine.....40

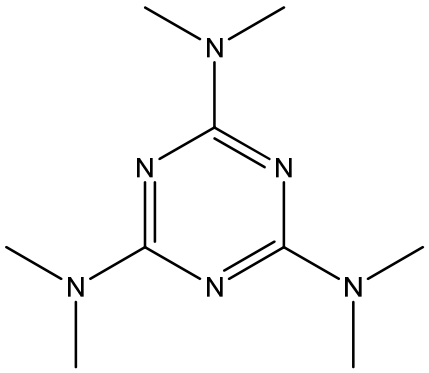
3.5 infrared spectrum of 2, 4-Bis (methylthio)-1, 3, 5-Triazine 41

CHAPTER I

INTRODUCTION AND LITRETURE REVEIW

INTRODUCTION

Cyclotrimerization of nitriles and cyanamides yields a variety of substituted S-triazine derivatives. In 1954, the first s-triazine was structurally determined. Due to the applications of s-triazine in different fields, numerous researches have been conducted to find other derivative of triazine. Several researchers have investigated the S-trazine nucleus in the search of potential therapeutic agents to treat diseases due to bacteria, cancer, antitumor and malaria.[1] For example as shown in figure 1.1, hexamethylmelamine (**1**) and 2-amino-4-morpholino-s-trazine (**2**) are used clinically to treat lung, breast, and ovarian cancer, respectively.[2] Hexamethylmelamine, is also known as altretamine. It consists of a symmetric six-member triazene ring with three attached dimethylamine group 1 and has the chemical name 2, 4, 6-tris (dimethylamine)-S-triazene. Recently, other related amine-substituted triazines, such as compound 3 in Figure 1.1 have shown antitumor activity in human cancer and murine leukemia cell lines.[2c]



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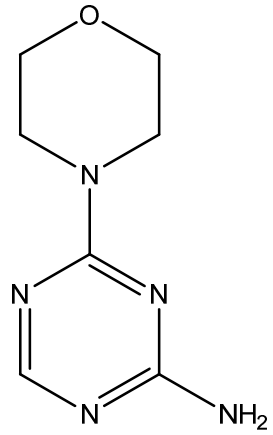

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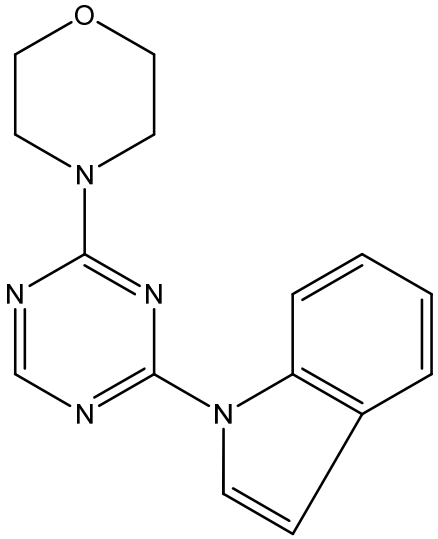


3

R= Dimethylamine, 2,6-dimethyl-morpholine

Figure 1.1: Example of Biologically Active Compound Containing 1,3,5-Trazine

Substituted s-triazine derivatives can be synthesized by several different routes. The most common methods are cycloaddition reactions to form the triazine ring (Figure1.2), nucleophilic aromatic substitution of cyanuric chloride (Figure 1.3), and cyclotrimerization of organic cyanamides and nitriles. Notably ,the direct trimerization of cyanamides and nitriles is both easy and effective and can yield the desired compounds in a single-step reaction.[3]

Cycloaddition Reaction

Cycloaddition reactions are the most frequently used methods for the production of rings. Cycloadditions can be carried out using heat, light or with a variety of catalysts. However, these reactions usually require high temperature and the presence of polar functional groups in the substrates. For example, treating a nitrile with a nitrile-substituted guanidine derivative in the presence of a base, typically sodium or potassium hydroxide, provides a synthetic route to trazine derivatives.[3a]

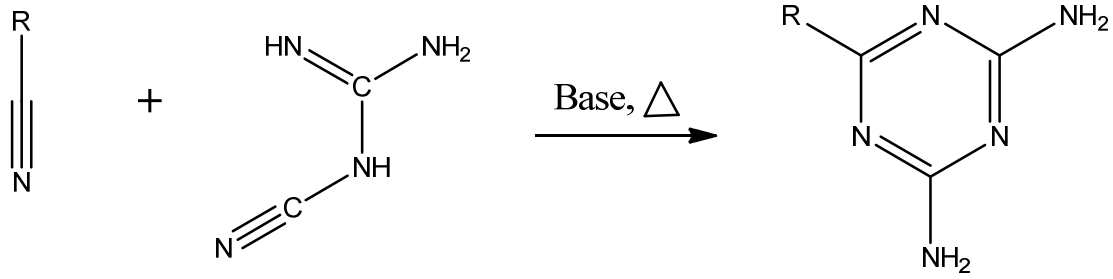


Figure 1.2 Cycloaddition Reactions to Form Trazine Derivatives

Transition metal catalysis plays an increasingly important role in the cycloaddition reactions. Such reactions have established their usefulness in the formation of complex molecules and rings. Recent reports in transition metal catalyzed, [4+4] cycloadditions of bis-dienes, [4+2] cycloadditions of diene-ynes (and allenes), [5+2] cycloadditions of vinylcyclopropanes (VCPs) and [6+2] cycloadditions of vinylcyclobutanones cycloaddition reactions [4, 5] have provided efficient methods for the construction of 5 to 8-membered rings.

Nucleophilic Aromatic Substitution of Cyanuric Chloride

Nucleophilic aromatic substitution of cyanuric chloride in a chemoselective fashion can be used to produce substituted s-trazine products with high chemical complexity (Figure1.3). However, these substitution reactions require long reaction times and generally achieve low yield.

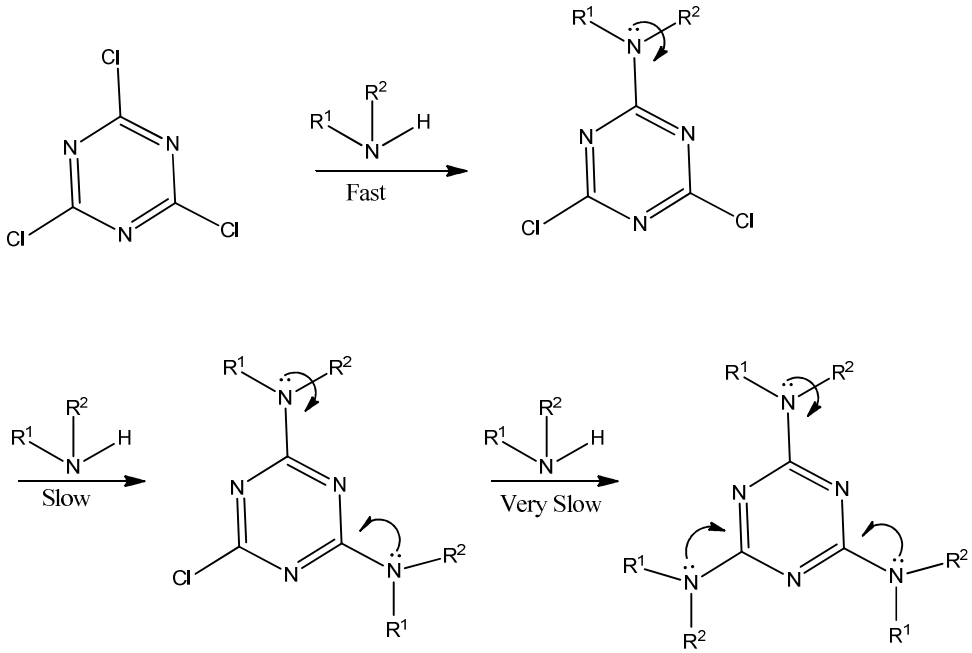


Figure 1.3: Classic Pathway to Substituted Trazine[6]

One of the earliest examples of the use of nucleophilic aromatic substitution to triazine groups was reported in 1996 and described the prepation from cyanuric chloride by treatment with ammonia, primary or secondary amines.[6] It is already well known that the accumulation of electron donating amine substituents gradually decreases the reactivity of the triazine ring. Therefore, each substitution proceeds steadily but less readily than the precede one (Figure1.4). Thus, the exhaustive substitution usually proceeds under harsh reaction condition. The substitution of chlorine can be controlled by temperature to run in a stepwise manner. An empirical rule, based upon observation, is that mono-substitution of chlorine occurs below or at 0 ^{o}C, di-substitution at room temperature and tri-substitution above 60 ^{o}C .[7]

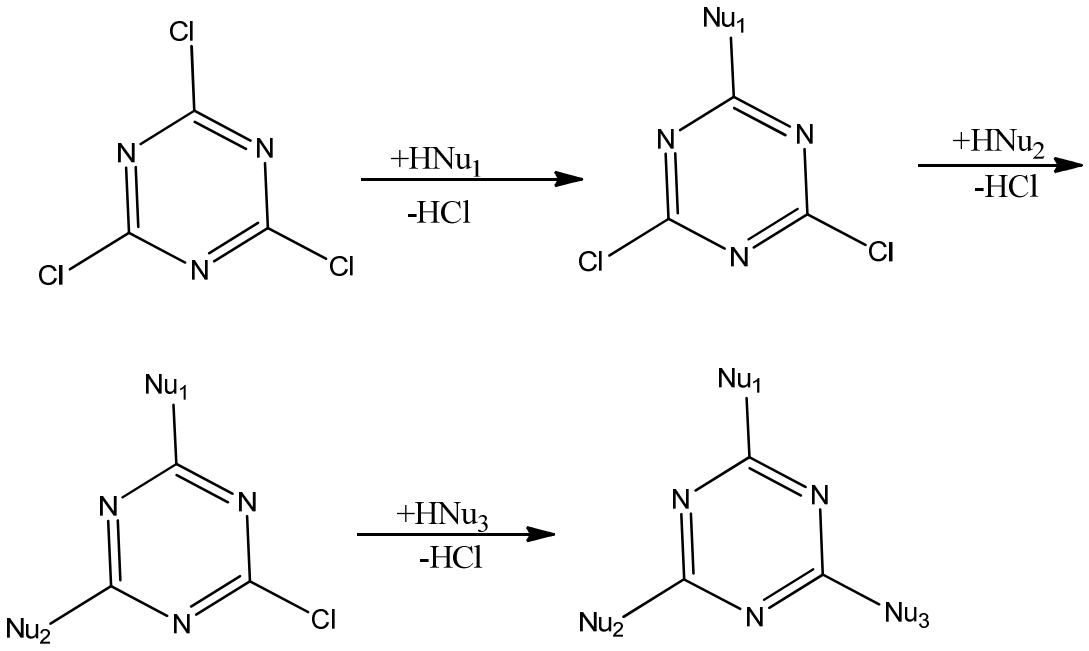


Figure 1.4: Nucleophilic Substitution of Cyanuric Chloride [8]

Kolerski and Kaminsk also demonstrated that each sequential displacement of chlorines on cyanuric chloride becomes slower and more difficult to perform. [8] For example when

displacement of chlorines by MeOH was performed, the first chlorine could be displaced at 0 °C; the second one was substituted at room temperature, while the third one required 100 °C.

Cyclotrimerization Reaction

There have been several investigations into the trimerization of nitriles[9] and cyanamides[10]. The first cyclotrimerization reaction introduced by Berthelot in 1866 by cyclization of acetylene to benzene. High temperatures were needed to perform this reaction. In 1948, Reppe discovered the first transition metal-catalyzed version of this reaction in which nickel was used, leading to the formation of substituted benzenes. [11] Since then, several strong reagents have been found to catalyze the trimerization of alkynes, alkenes, aldehydes and ketones, imines, isocyanates, isothiocyanates, dimethylcyanamide and nitriles with variable degrees of success. For example, a variety of Brønsted and Lewis acids and mixtures of them have been employed to promote cyclotrimerization of nitriles and cyanamides. [12] Under both acid and base conditions high pressure and temperature are required for this reaction. Lewis acids, such as $LaO_3SCF_3$and $SnCl_2$, are commonly used as catalysts for the cyclotrimerization of nitriles,[13] and neutral aluminum complexes are also used as Lewis acid catalysts in organic synthesis.[14] Aluminum amides are potential bifunctional catalysts, possessing a Lewis acidic Al (III) center and an activated nucleophilic amido group. Dornan and co-worker found that tris(dimethylamido)aluminum readily catalyzed the cyclotrimerization of dimethylcyanamide at room temperature.[15] The addition of 4-5 mol% tris(dimethylamido)aluminium to a solution of dimethylcyanamide in hexane led to the product hexamethylmelamine in good yield. Computational studies using the Density Functional Theory revealed the mechanistic details of the transformation.

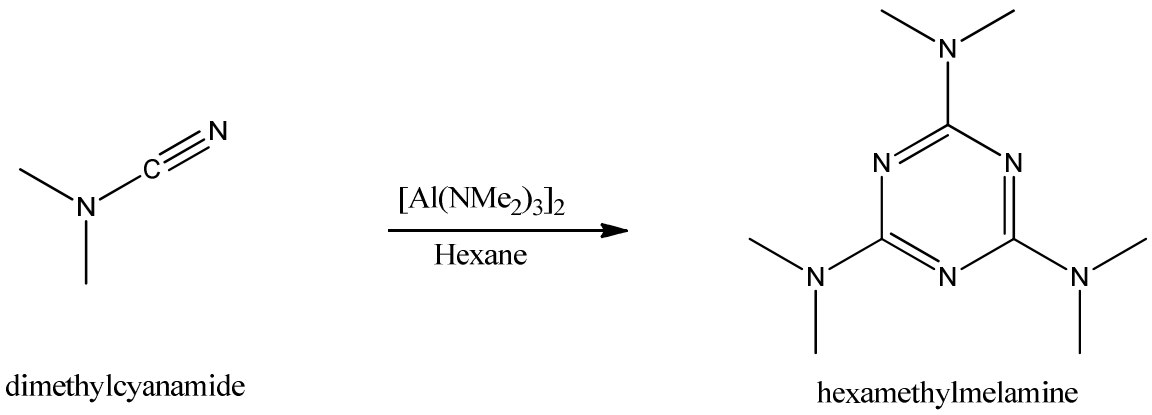


Figure 1.5 Cyclotrimerization of Dimethylcyanamide with Tris(dimethylamide)aluminium[15]

Based on the result, the proposed mechanism for the interaction dimethylcyanamide with tris(dimethylamide)aluminium is shown in Figure 1.6:

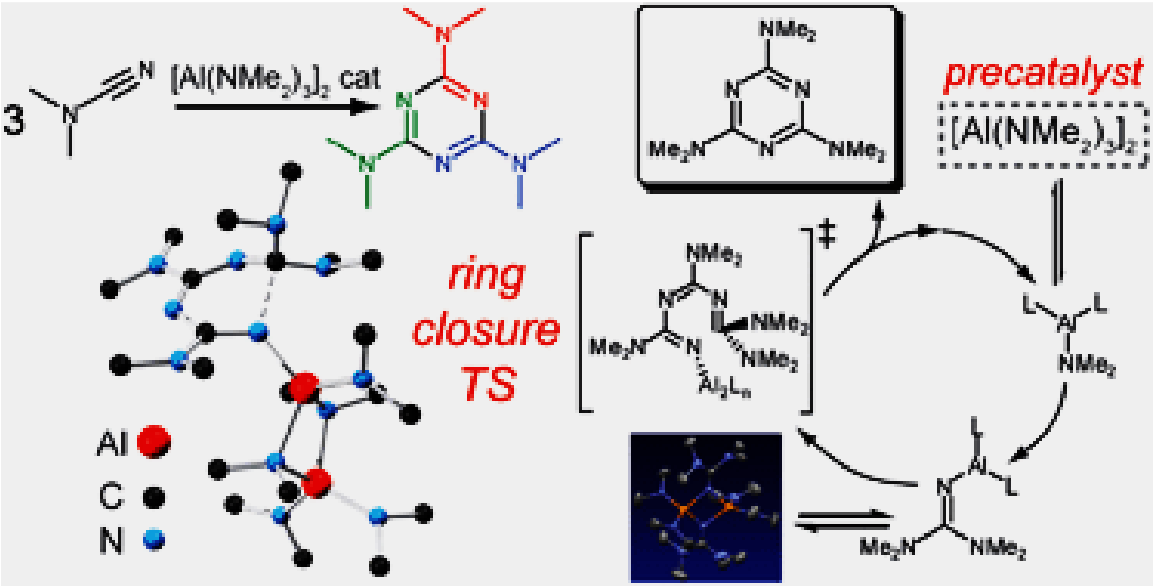


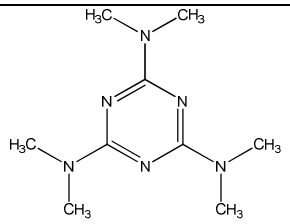
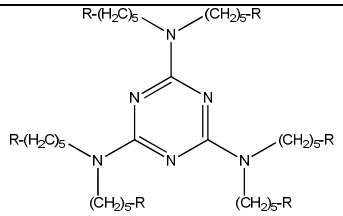
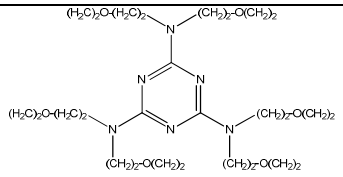
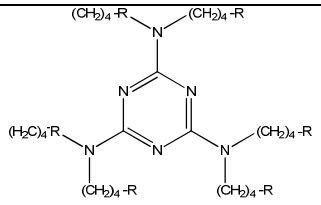
Figure 1.6: Propose Mechanism for Cyclotrimeriation of Dimethylcyanamide with Tris(dimethylamide)aluminium[15]

Experimental support for this step of mechanism is provided through the stoichiometric reaction of the $[Al(NMe_2)_3]_2$ pre-catalyst and dimethylcyanamide. The cyclotrimerization initiated by insertions of dimethylcyanamide into the aluminum amide bond. Two subsequent insertion of dimethylcyanamide, followed by nucleophilic ring closure and an aromatizing de-insertion, provide the product. From this reaction, the dimerization product was isolated and characterized[15].

Antonio and coworkers also develop an effective method, for the cyclotrimerization of cyanamides and nitriles[16] that utilized triflic anhydride in dichloromethane at room temperature. The results of their investigation are printed in table 1 .1.

Table 1.1

Cyclotrimerization of Dialkylcyanamides

Entry	R_1, R_2	Conditions	Product **3**	Yield (%)
1	CH_3	r.t./ 12h		67
2	$-(CH_2)_5$-R	r.t./12h		81
3	$-(CH_2)_2-O(CH_2)_2$	r.t./12h		89
4	$-(CH_2)_4$ -R	r.t /12h		73

The reaction is believed to involve the formation of a bistriflylisourea intermediate, which reacts quickly with two molecules of cyanamide to produce the trazine product Figure 1.7:

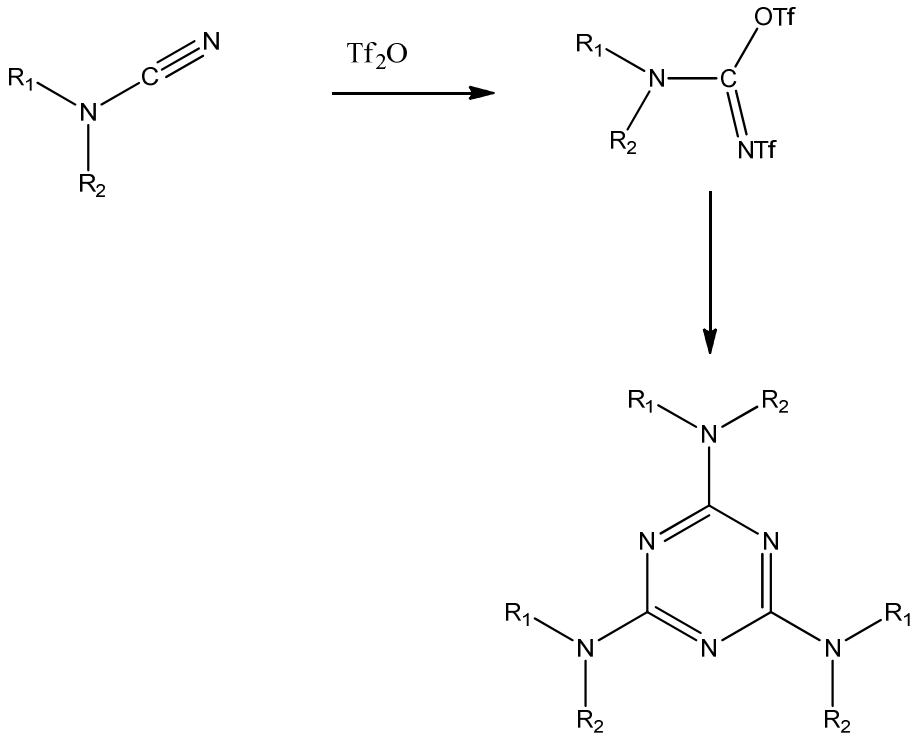
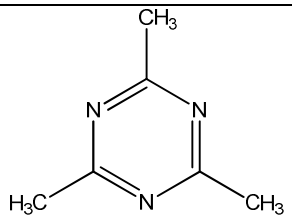
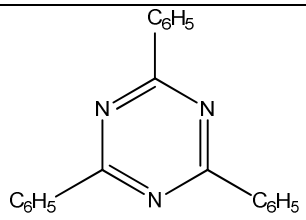
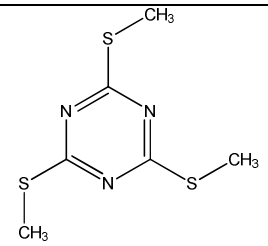


Figure 1.7: Cyclotrimerization of Dialkylcyanamides

The authors extended their work by using other classes of nitriles such us; acetonitrile, benzonitrile, and methylthiocyanate with triflic anhydride in dichloromethane at the same condition and found s-trazine product in excellent yield.

Table1. 2

Cyclotrimerization of Nitrile

Entry	**R**	Conditions	Product 5	Yield (%)
1	CH_3	r.t./ 12h		89
2	C_6H_5	r.t. /12h		91
3	CH_3-S	r.t./ 12h		88

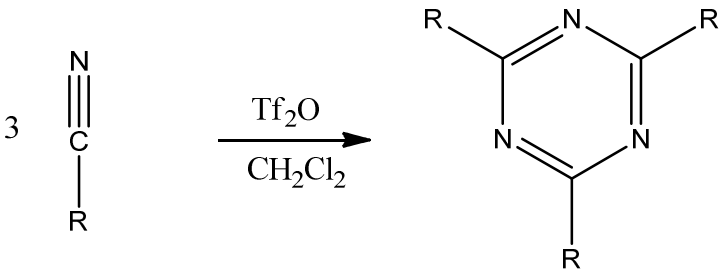


Figure 1.8: Cyclotrimerization of Nitrile

Numerous syntheses of trisubstituted -1,3,5-triazine derivatives are reported in the literature using several transition metals as catalysts, including both late transition metals, such as Ti, Mo, Cr, Fe, Zr, Nb and Ta. In this investigation, the cyclotrimerization of dialkylcyanamides was catalyzed by tungsten and molybdenum hydrogen bronzes. These hydrogen bronze are products obtained from hydrogen insertion into tungsten and molybdenum trioxides. The longest known oxide bronzes are those of tungsten but in the past few years molybdenum, vanadium, niobium, tantalum and titanium bronze have prepared and have shown similar properties. The rest of the chapter will focus on the chemical transformation by using tungsten and molybdenum hydrogen bronze.

Introduction to Tungsten and Molybdenum Bronze

Most early transition metals have their greatest stability in their highest oxidation states. This stability has made molybdenum and tungsten two of the most widely used metals as metathesis catalysts or catalyst precursors. These metals also have the ability to form bonds with carbon, nitrogen and oxygen. [17] Oxide bronzes are a group of well-defined, non-stoichiometric, insertion compounds having the general formula $A_xM_yO_{z.,}$ where M is a transition metal, A is H^+, alkali metal, alkaline earth metal, and lanthanide, or other metals. The hydrogen insertion compounds of MoO_3 and WO_3 have been studied previously[18]. It is well established that tungsten trioxide interacts at an ambient temperature with atomic hydrogen generated in the gas phase, in the aqueous phase, or by "Hydrogen spillover," to form hydrogen tungsten bronze. Hydrogen tungsten bronzes are non-stoichiometric materials with the chemical formula $H_xWO_{3.}$ The hydrogen content can vary from 0.1-0.6.[19] The yellow to blue color change associated with the

formation of the hydrogen tungsten bronze has long been used as a test for the presence of atomic hydrogen. Tungsten trioxide has a monoclinically distorted ReO_3 –like structure which is formed by corner shared WO_6 octahedra. [20]

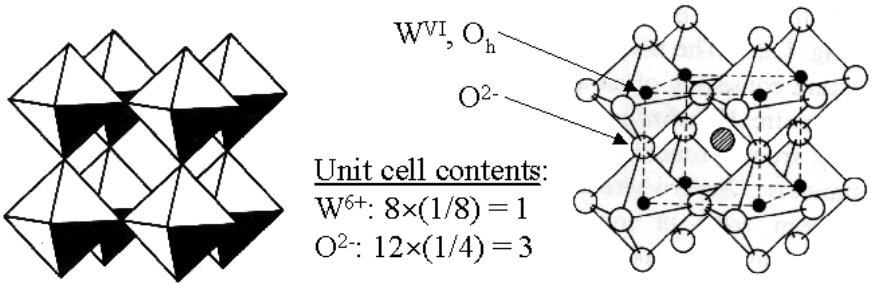


Figure 1.9: Crystal Structure of WO_3 and A_xWO_3 [21]

These materials adopt several crystallographic chemistry: such as orthorhombic bronzes with x = 0.1, tetragonal bronzes with x = 0.23 and 0.33, hexagonal bronzes with x = 0.24 and cubic bronzes with x = 0.53. All of these phases are strongly colored and metallic. The first method used to synthesize hydrogen bronzes was the reaction of tungsten (VI) oxide with nascent hydrogen and produced by a reaction of zinc with hydrochloric acid[22].

$$3\ WO_3 \xrightarrow{Zn/HCl} HW_3O_9 \qquad \text{(Eq. 1.1)}$$

The structure of the hydrogen tungsten bronze obtained by this synthesis pathway is tetragonal. Later, hexagonal hydrogen tungsten bronze was prepared by a reaction of Cu^+ with monoclinic WO_3 to form $CuWO_4$, This was then reduced under a hydrogen flow to form to $H_xWO_3{}^+Cu$, followed by elimination of copper by washing with concentrated nitric acid. [22]

Recently, a mechanochemical synthesis route has been successfully used for bronze formation, by milling WO_3 with liquid hydrocarbons (e.g. xylene) under air. In this case, the hydrocarbons are the source of hydrogen, and the tetragonal structure is obtained. [19]

In contrast, MoO_3 has an unusual layer structure in which infinite chains of vertex sharing MoO_6 octahedra are fused together by edge sharing to form corrugated layers. The layers are stacked parallel to one another and are separated by a van der Waals gap of -7 A. [23]

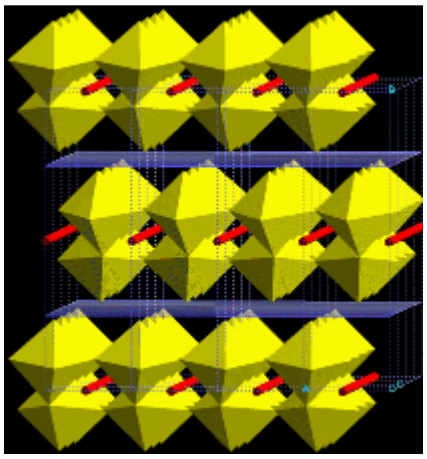


Figure 1.10: Hydrogen Molybdenum Bronze Phases are formed by the Intercalation of Atomic Hydrogen (i.e. $H^+ + e^-$) into the Layered Structure of MoO_3[24]

Molybdenum trioxide is capable of incorporating hydrogen, thus forming four phases of bronze H_xMoO_3, in the range $0 < x \leq 2$. Each MoO_6 octahedron has one singly, two doubly and three triply coordinated oxygen atoms. The hydrogen bronze phases H_xMoO_3 were first investigated by Glemser and co-workers. [25] The four distinct phases in the range $0 < x \leq 2$ are blue orthorhombic, $0.23 < x < 0.4$, blue monoclinic, $0.85 < x < 1.04$; and red monoclinic, $1.55 < X < 1.72$. The fourth phase of highest hydrogen content is the green monoclinic, $H_{2.0}MoO_3$.[26] In the case of the orthorhombic phase, hydrogen atoms are attached as -OH groups to the doubly bridging oxygen atoms in the intralayer sites.

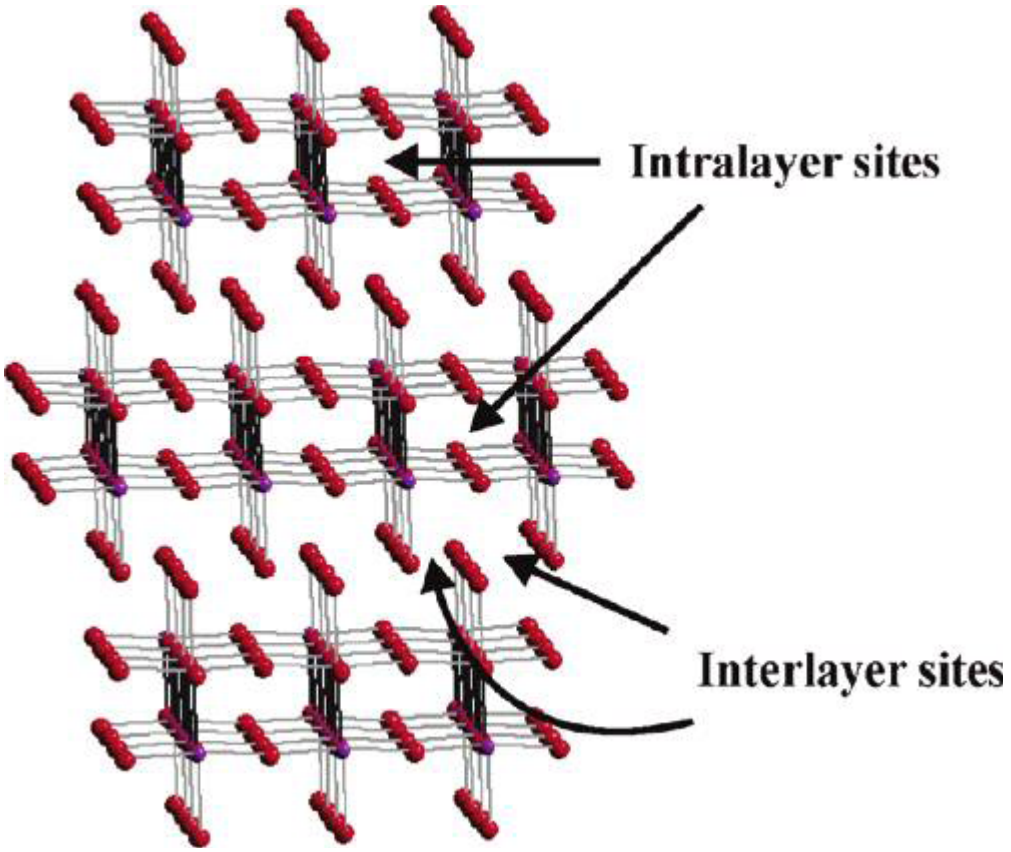


Figure1.11: Hydrogen Intercalation Sites in MoO_3[27]

These bronzes are usually prepared from single crystals or from powders of low surface area at room temperature by using atomic hydrogen which can be generated in different ways: reaction of HCl on Zn, cathodic reduction, hydrogen plasma, mercury photosensitization, and dissociative chemisorption on an appropriate metal supported on MoO_3. At a higher temperature, the action of gaseous methanol on MoO_3 of a high surface area, also results in the formation of molybdenum hydrogen bronze.

CHAPTER II

PREPARATION OF ALTRETAMINE BY TRIMERIZATION OF DIMETHYLCYANAMIDE USING A METAL BRONZE AS THE CATALYST

INTRODUCTION

The cyclotrimerization of nitriles is a useful method for the construction of three new bonds in a one-step process. Nitriles, such as dimethylcyanamide, may cyclotrimerize in the presence of various catalysts to produced altretamine (hexamethylmelamine). The latter compound is a synthetic antitumor agent primarily used in treating advanced ovarian cancer. It was originally developed by the National Cancer Institute and has been used in the treatment of ovarian cancer for over 30 years. Ovarian cancer is the fifth most common cancer among women, and it causes more deaths than any other type of cancer. Less than one-third of ovarian cancers are detected before they have spread outside of the ovaries. The risk for developing ovarian cancer appears to be affected by several factors. Certain gene defects (BRCA1 and BRCA2) are one of the causes of ovarian cancer and a personal history of breast cancer and/or a family history of breast or ovarian cancer are other cause of ovarian cancer.[28] There are four stages of ovarian cancer. Each stage identifies the size and location of the tumor. Stage 1 is growth limited to the ovaries, stage 2 involves pelvic extension, stage 3 may involve peritoneal implants outside the pelvis and stage 4 involves distant metastases. In the early stages, the disease is often asymptomatic although symptoms of nausea, dyspepsia, and vague lower abdominal discomfort may be present. Abdominal pain, distension, or vaginal bleeding usually indicates advanced disease.[29] The more advanced the ovarian cancer, the more difficult it is to treat.

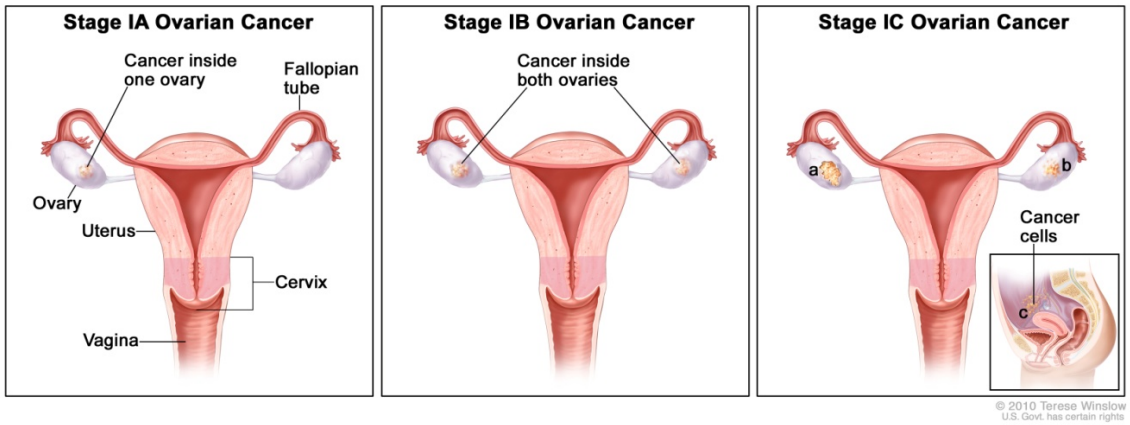


Figure 2.1: Ovarian Cancer Stage IIA, IIB, and IIC [24]

One of the most commonly used treatment methods for ovarian cancer is chemotherapy. Chemotherapy consists of antineoplastic drugs that target cancer cells and cause their destruction. Altretamine is one of the chemotherapy drugs classified as an alkylating agent. Alkylating agents are used to treat various forms of cancer and are so named because of their ability to add alkyl groups to many electronegative groups under conditions present in the cells. They stop tumor growth by cross-linking guanine bases in DNA double-helix strands, thus directly attacking DNA. This makes the strands unable to uncoil and separate. As this is necessary in DNA replication, the cells can no longer divide. In addition, these drugs add methyl or other alkyl groups onto molecules where they do not belong, which in turn inhibit their correct utilization by base pairing and cause a miscoding of DNA. Alkylating agents are cell cycle-nonspecific and work by three different mechanisms all of which achieve the same end result - disruption of DNA function and cell death. [30] Altretamine is activated through metabolic oxidation to intermediate methylol derivatives and formaldehyde (Figure 2.2). Metabolism of altretamine is a requirement of cytotoxicity. It is unclear which metabolite is the major species responsible for cytotoxicity or the

primary mechanism of cytotoxicity.

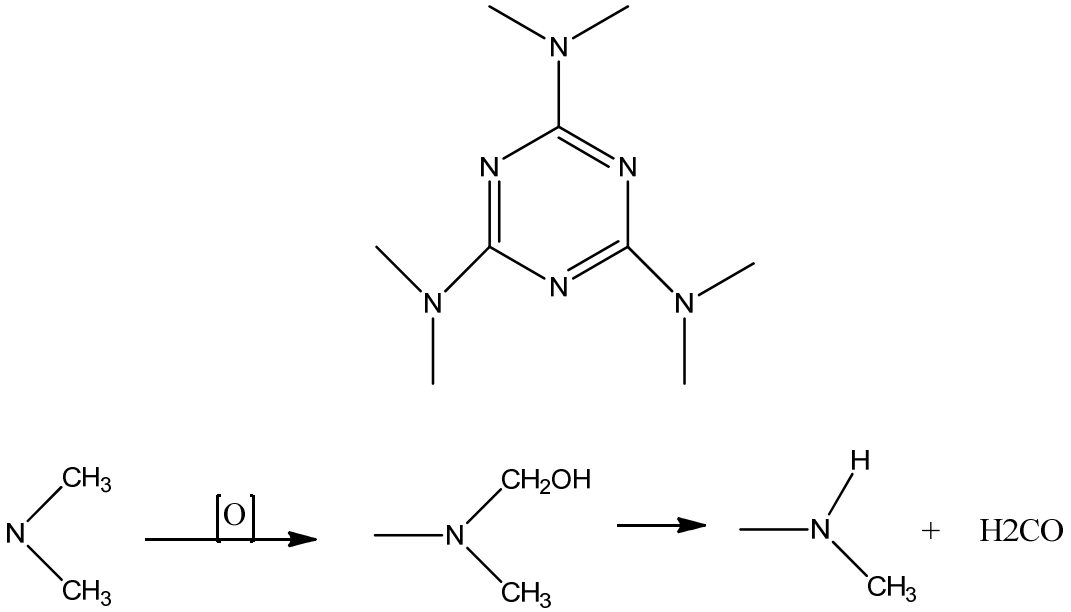


Figure 2.2: Altretamine Activated Through Metabolic Oxidation to Intermediate Methylol Derivatives and Formaldehyde

The anticancer agent altretamine has the formula $C_9 H_{18} N_6$ and a chemical name of 2, 4, 6-tri (dimethylamine)-S-triazine along with a relative molecular mass of about 210.3. Furthermore altretamine is a white crystalline powder that melts at 172°± 1°C. Altretamine can be synthesized by reacting dimethylamine and sodium hydroxide aqueous solutions with cyanuric acid in acetone .This synthesis was first reported by KAISER *et al*. [31]One of the limitations of this method is due to the high reactivity of cyanuric chloride, causing it to become partially or completely hydrolyzed in water, leading to several potential by-products that form during its synthesis. Therefore, the altretamine product can be contaminated with one or two impurities showed in Figure (2.3)

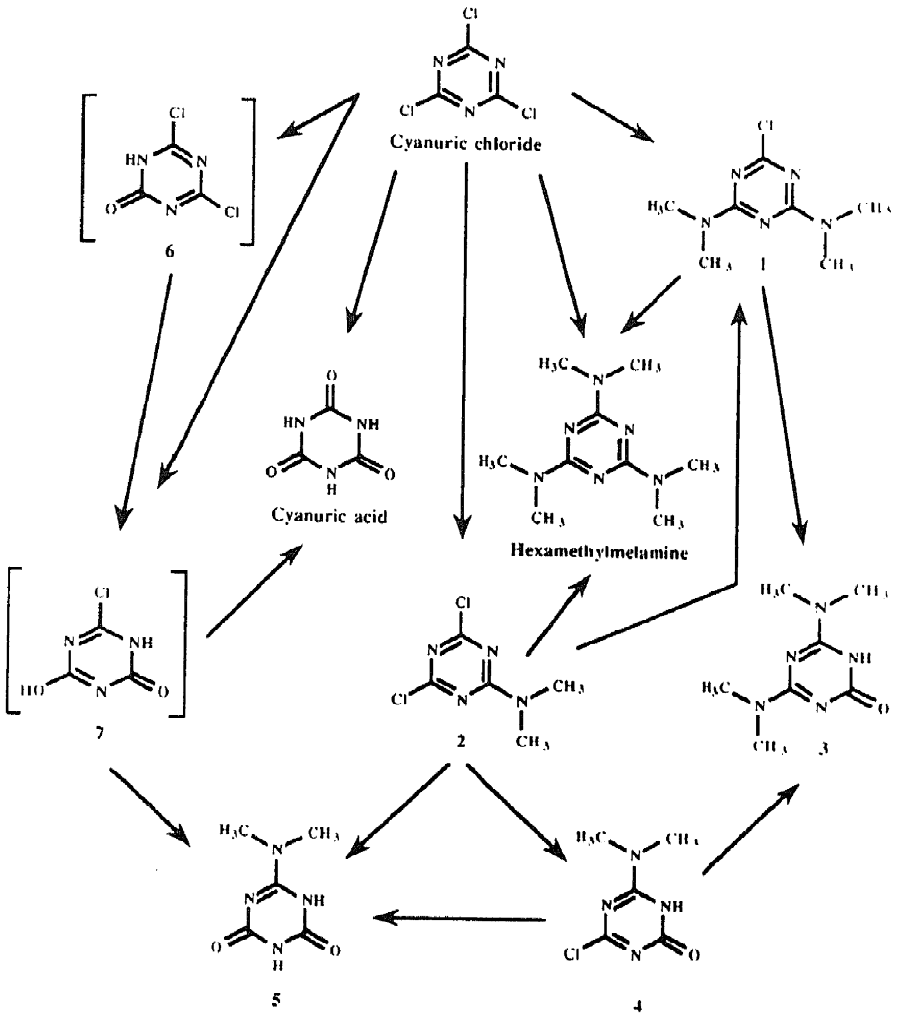


Figure 2.3: Chemical Pathway for Formation of Altretamine Byproducts [32]

The manufacturing process for altretamine since 1969 involves the reduction of hexamethylolmelamine-hexamethyl ether in the presence of methanol, at 90°-100°C, in the presence of Raney nickel as the catalyst[33]. The reaction produced a better yield than the previously reported method.

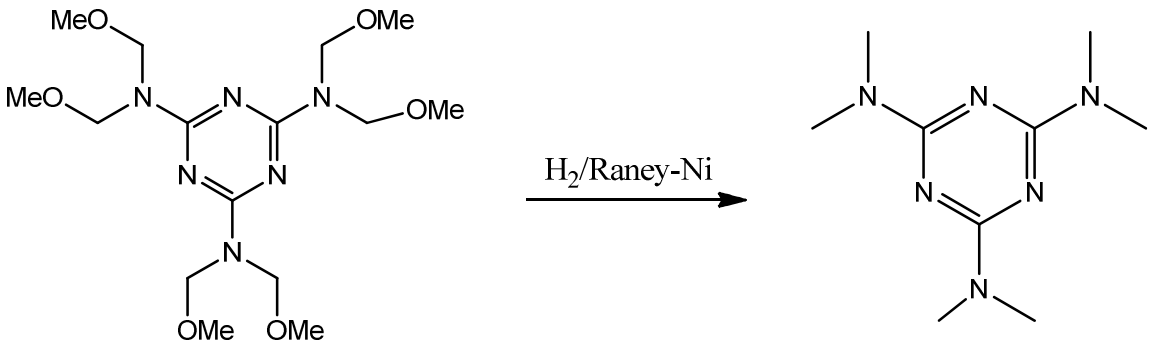


Figure 2.4: Reduction of Hexamethylolmelamine Hexamethyl ether [33]

Although altretamine can be synthesized by the nucleophilic aromatic substitution of cyanuric chloride and reduction of Hexamethylolmelamine-hexamethyl ether, a simpler and atom-economical synthesis can be envisaged through the cyclotrimerization of dimethylcyanamide. Several reagents has been found to catalyze the cyclotrimerization of dimethylcyanamide with variable degrees of success, including tris(dimethylamide)aluminium [15]and triflic anhydride. [16]

In the course of these investigations, it was found that tungsten and molybdenum bronze readily catalyzed the cyclotrimerization of dimethylcyanamide to produce altretamine.

Experimental

All reagents were commercial products, ACS Grade or better and were used without further purification.

Preparation of Tungsten Bronze

Tungsten bronze was prepared by using the dissolving metal reduction technique. First, 30 g of tungsten trioxide were placed in a 250 ml three-neck flask containing 56.80 g granular zinc metal and a large magnetic stirbar . Water is added to form slurry. After that, the first neck of the flask plugged by using a glass stopper. In the second neck, a dropping funnel containing 200 ml of concentrated hydrochloric acid was fitted, and on the third neck, a paraffin bubbler was attached. Then, the flask was placed in a water bath.

The hydrochloric acid was added dropwise at a rate of one drop per second to the magnetically-stirred reaction mixture. The reaction immediately turned from yellow to blue. The acid must be added to the reaction very slowly since it evolves hydrogen gas, which is explosive. After the addition of hydrochloric acid, the reaction mixture was filtered through a nylon membrane filter, and the solid was washed three times with 300 ml of water, and then dried in a vacuum oven. The yield of the dark blue hydrogen tungsten bronze was 29.01 g (96.70%).

Preparation of Molybdenum Bronze

The same procedure used in preparing tungsten hydrogen bronze was employed to synthesize molybdenum hydrogen bronze. Exactly 30 grams of molybdenum trioxide were placed in a 250 ml three-neck flask containing 56.80 g of granular zinc metal and a magnetic stir-bar. A certain amount 5 ml of water was added to form slurry. A funnel, which contains 200 ml of hydrochloric acid, was connected to the center neck of the flask that was placed in a water bath at

room temperature. One of the other necks was plugged with a glass stopper and on the third neck a paraffin bubbler was attached. Then, HCl was added drop-wise producing a magnetically-stirred reaction mixture. The reaction immediately turned from yellow color to purple and the hydrogen gas is removed through the bubbler. The acid must be added to the reaction very slowly since it evolves hydrogen gas, which is explosive. The initial color of the product was greenish-gold that slowly turned to a red violet color and finally to a dark blue color. In order for the reaction to be complete, it was allowed to react for overnight. Once the blue colored product was obtained, it was washed with water (3 times in 300 ml) and then dries it in a vacuum oven. The yield of the hydrogen molybdenum bronze was 28.77g, (95.58%).

Reaction of Dimethycyanamide with Hydrogen Bonzes

The reaction between the hydrogen bronze (0.5 g) and dimethylcyanamide (1g) were carried out in a sealed culture tubes at 150 □ C. The sealed glass tubes were placed in heat block at 150 □ C for 7 days. The amount of reactant and products in the reaction mixtures were determined by cooling the glass tube to room temperature and then, the white solid product was extract with methylene chloride .This extracted sample analyzed by GC/MS. Compounds were identified by comparison of their mass spectra to the NIST database .When the reaction temperature increased to 170^0C (Table 2.4). This reaction was performed in Teflon-lined, stainless steel bombs, and the sealed reactors were placed in digital controlled oven at 170 □ C and the products were characterized by using GC-MS, NMR and Infrared Spectroscopiy.

Gas chromatogram/ mass spectroscopic analyses: were performed on Hewlett Packard G1800A equipped with a 30m × 0.25 mmHP5 column. The temperature program used was initial hold of 5 min at 70^{o}C, a ramp of 5^{o}C/min to 170^{o}C. The helium flow rate was 1 ml/min.

Infrared Spectroscopic Data: was obtained via infrared spectral data which was obtained using KBr pellets recorded on a Jasco-RA spectrophotometer.

NMR Spectra: were recorded using a UNITY *INOVA* 400 NB NMR

Results and Discussion

In these investigations, the molybdenum hydrogen bronze and tungsten hydrogen bronze readily catalyzed the cyclotrimerization reaction of dimethylcyanamide. The additions of 5 mol% tungsten hydrogen bronze to a solution of dimethylcyanamide in hexane or toluene led to the formation of altretamine. Molybdenum hydrogen bronze reacted similarly but produced pentamethyl-1, 3, 5-triazine-2, 4, 6-triamine as the major product. This product resulted from cyclotrimerization of dimethylcyanamide followed by dealkylation. Loss of a CH_3-group from altretamine was also observed during mass spectral analysis. Loss of mass 15 (m/z) is a predominant process and results in the spectrums base peak. The general reaction of dimethylcyanamide and the hydrogen bronze are shows in Figure (2.5), and Figure (2.6). Results obtains from the various reaction condition are laid out in Table 2.1, 2.2, 2.3.

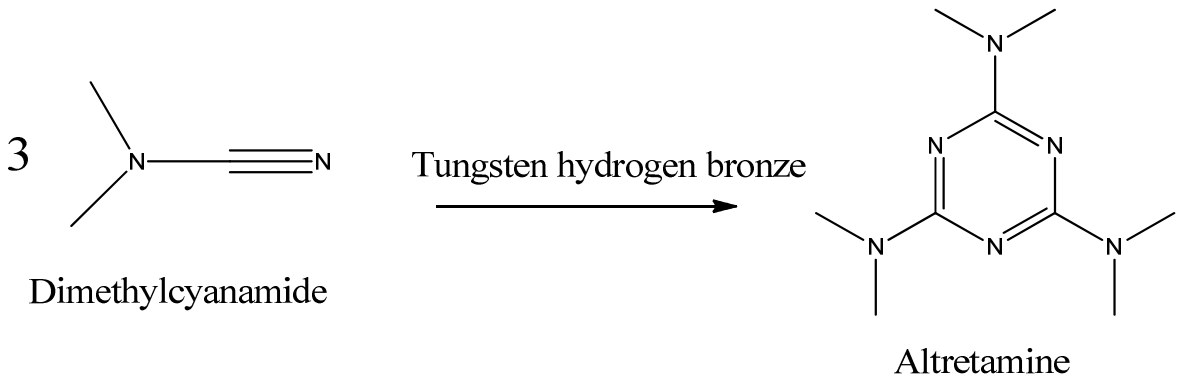


Figure 2.5: Reaction of Dimethylcyanamide with Tungsten Hydrogen Bronze

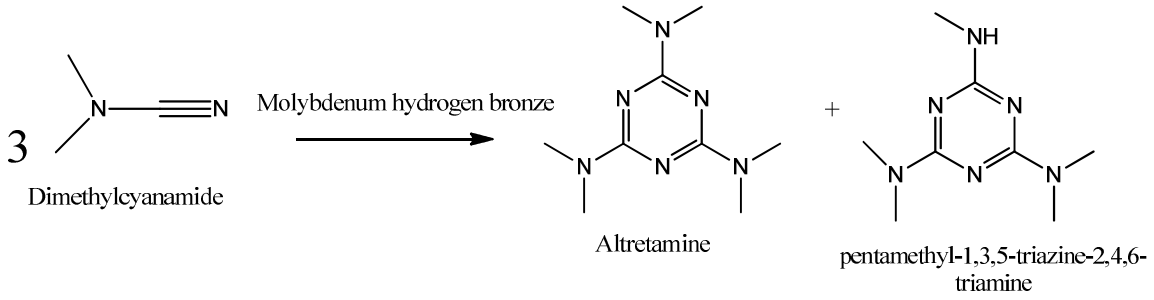


Figure 2.6: Reaction of Dimethylcyanamide with Molybdenum Bronze

Table 2.1 shows the results of reactions between dimethylcyanamide and both hydrogen bronzes. After six days reaction with molybdenum bronze tetramethylguanidine was completed. Under the same reaction conditions tungsten hydrogen bronze only produced altretamine as a minor product and yield pentamethyl-1, 3, 5-triazine-2, 4, 6-triamine as a major product.

Table 2.1

Reaction of Dimetylcyanamide with Tungsten and Molybdenum Bronze in Toluene at 150 ^{o}C

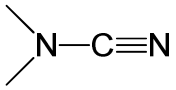
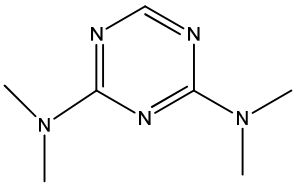
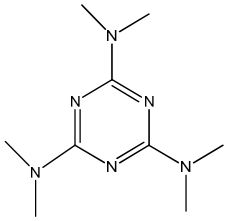
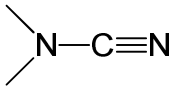
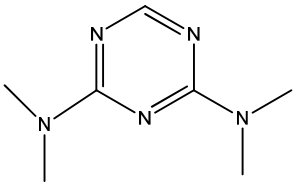
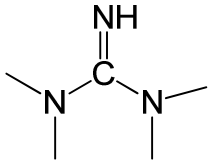
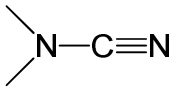
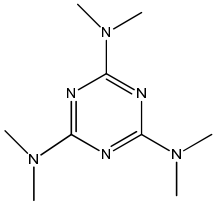
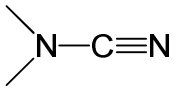
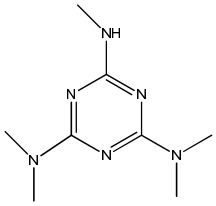
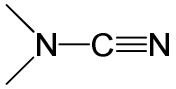
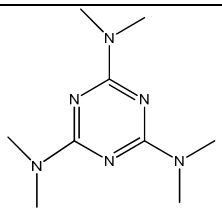
Entry	Substrate	Catalyst	Solvent	Condition	Major product	Minor product
1		TB	Toluene	150 ^{o}C, 7 days	 84%	 8%
2		MB	Toluene	150 ^{o}C, 6 days	 58.2%	 41.8%

Table 2.2

Reaction of Dimetylcyanamide with Hydrogen Bronzes in toluene/ Hexane at 150C

Entry	Substrate	Catalyst	Solvent	Condition	Major product	Minor product
1		TB	Toluene	150 °C, 30 days	 17.90%	0
2		MB	Toluene	150 °C, 30 days	 50.84%	0
3		TB	Hexane	150 °C, 7 days	 36%	0

Tungsten hydrogen bronze reacted with dimethylcyanamide in toluene to produced altretamine in a good yield. This was a pure product, and no side products were observed. As the results (Table 2.2) show, the reaction between dimethylcyanamide and molybdenum bronze in toluene gave pentamethyl-1, 3, 5-triazine-2, 4, 6-triamine as the major product (Entry 2).

pentamethyl-1, 3, 5-triazine-2, 4, 6-triamine(Pentamethylmelamine) is the monodemethylated correspondent of hexamethylmelamine and also has also antitumour activity[34]. Pentamethylmelamine is chosen on the basis of its greater chemical stability ,

furthermore 23 times more soluble than altretamine and has equivalent activity in a number of experimental tumour test systems[35].

The reaction time improved by replacing toluene with hexane and the percentage yield also improved by increasing the mole percentage of the catalyst from 10% to 20 % (Table 2.3). However, a different decomposition product was produced when the reaction temperature increased to 170 □ C (Table 2.4). This product was a singly deaminated version of altretamine.

Table 2.3

Reaction of Dimethylcyanamide with Excess Tungsten and Molybdenum Bronze

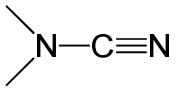
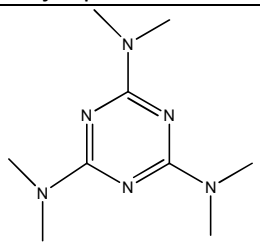
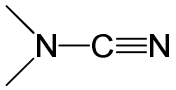
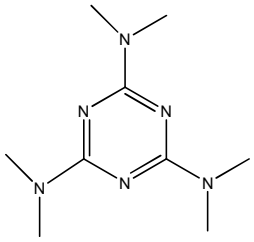
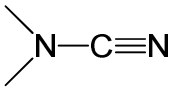
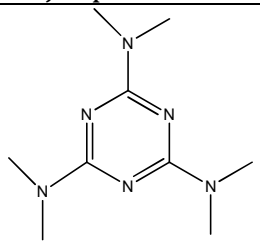
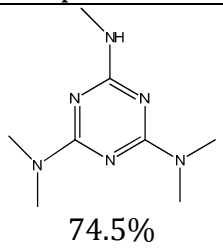
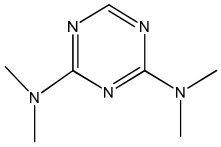
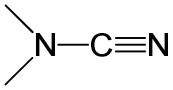
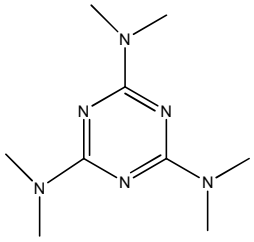
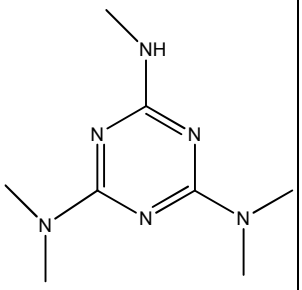
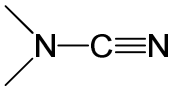
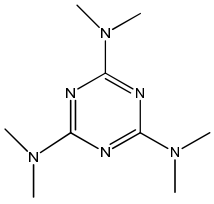
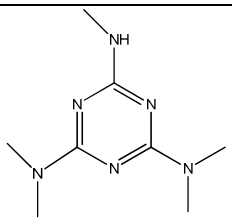
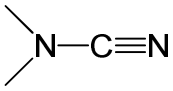
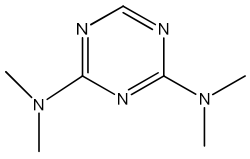
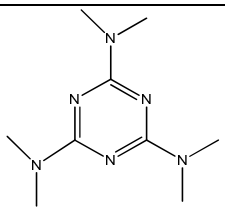
Entry	Substrate	Catalyst	Solvent	Condition	Major product	Minor product
1		TB	Toluene	150 °C, 7 days	 82%	0
2		TB	Hexane	150 °C, 7 days	 56.9	0

Table 2.4

Reaction of Dimethylcyanamide with Hydrogen bronzes at Higher Temperature

Entry	Substrate	Catalyst	Solvent	Condition	Major product	Minor product
1		TB	Toluene	170 ° C, 48 hr	 22.3 %	 74.5%  3.3 %
2		TB	Toluene	170 ° C, 72 hr	 57.3%	 42.6%
3		TB	Toluene	170 ° C, 96hr	 89.2 %	 10.8 %
4		MB	Toluene	170°C 48hr	 87.2%	 12.8%

Based on the results obtained, the proposed mechanism for the interaction of dimethylcyanamide with molybdenum and tungsten hydrogen bronzes is shown in Figure 2.7:

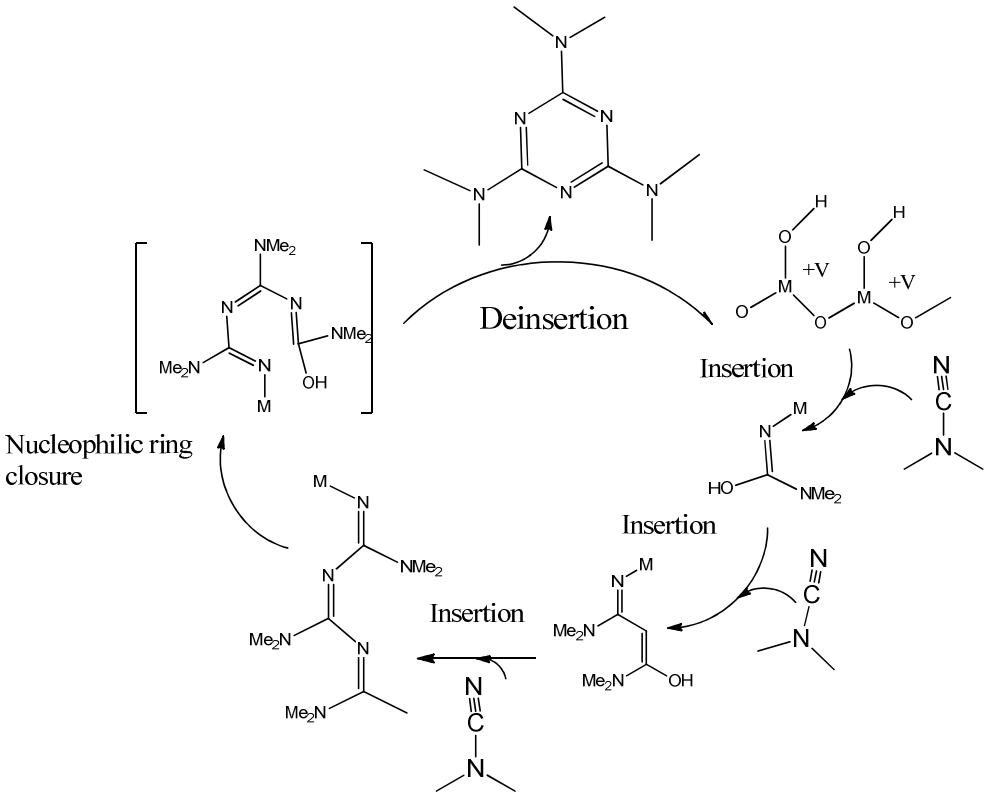


Figure 2.7: Propose Mechanism for Cyclotrimerization of Dimethylcyanamide by Metal Bronzes (M=W or MO).

The cyclotrimerzation was first initiated by insertion of dimethylcyanamide into the M-OH bond of the catalyst. Two subsequent insertions of cyanamide, followed by nucleophilic ring closure and an aromatizing de-insertion provided the altretamine product.

The GC-MS chromatogram of the methylene chloride extract of the product showed a single peak having mass 210 m/z Figure 2.. This extract was evaporated and the residue was dissolved in C_7D_8 and the carbon (^{13}C) and the proton (^{1}H) nuclear magnetic resonance spectra (NMR) were recorded in toluene-d_8. The proton spectrum (solvent C_7D_8) showed a singlet

resonance with a chemical shift of 2.99 ppm. This is to be expected for aromatic CH_3N-groups. The ^{13}C spectrum (solvent C_7D_8) exhibited resonances with 35.7 ppm, as expected for CH_3N-groups and I66 ppm belonging to the ring carbon atoms. The infrared spectrum of a KBr-pellet containing product, recorded on a Jasco-RA spectrophotometer, is shown in Figure 2.10. The absorptions at 2926, 807 and 2869 cm^{-1} are due the $(CH_3)_2N$-groups, while the peaks at 1541, 1388 and 1301$cm^{-1}$are characteristic for ring substituted s-triazines.

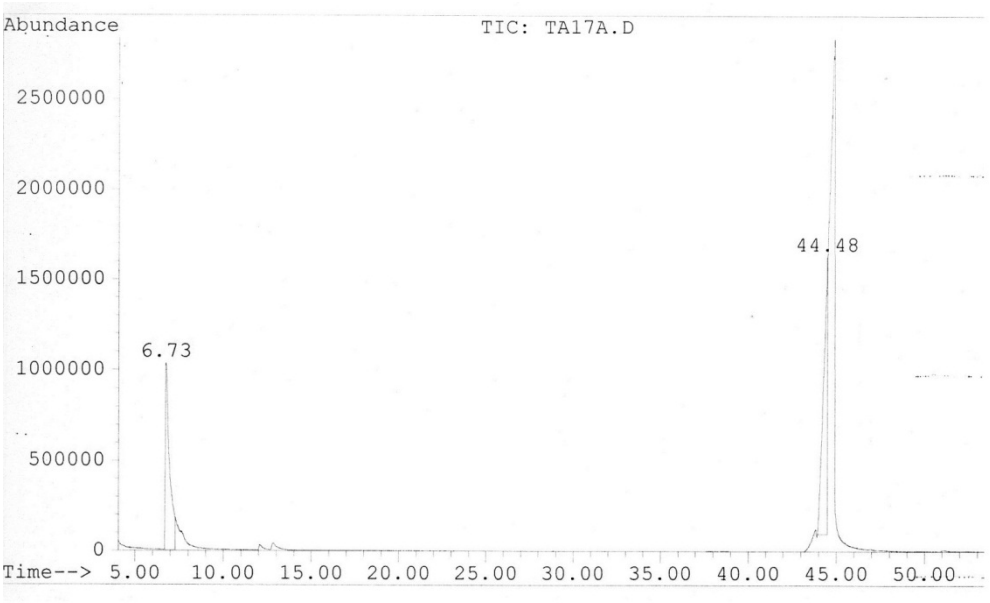


Figure 2.8: GC-MS Chromatogram of Tetramethylguanidine at 6.73 Retention Time

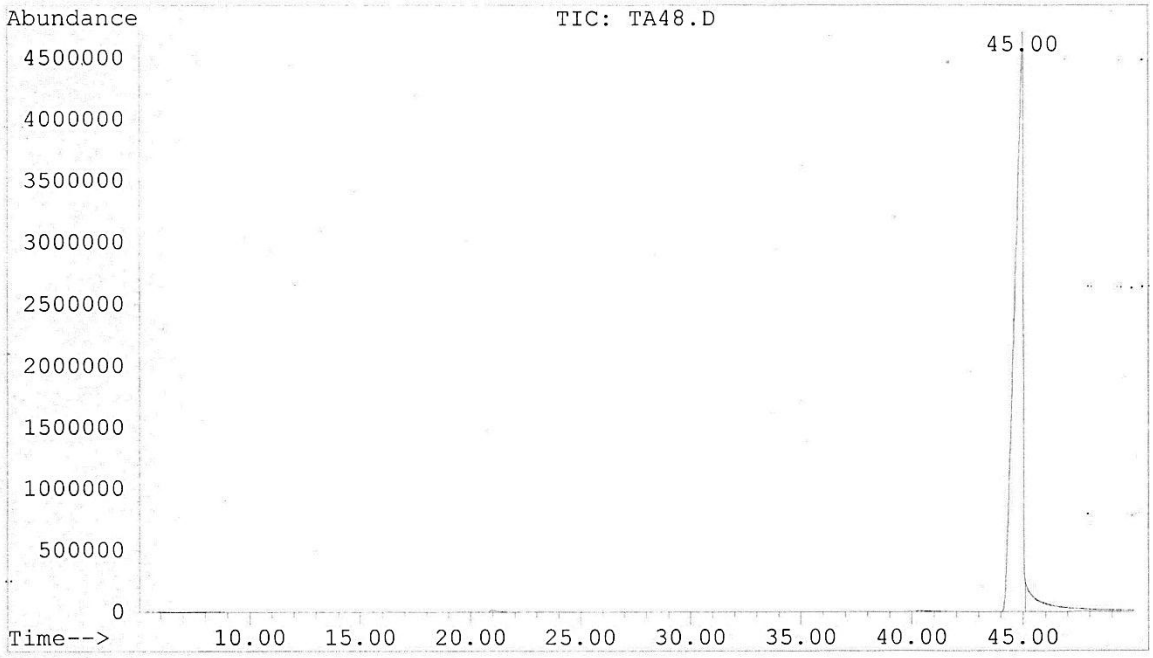


Figure 2.9: GC-MS chromatogram of Altretamine

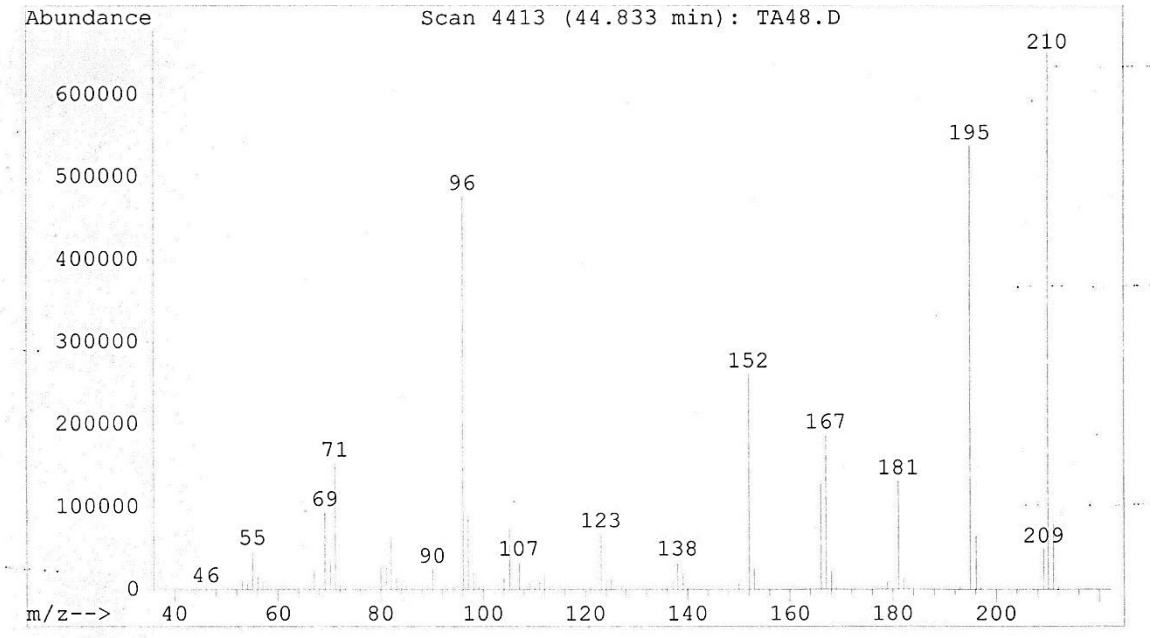


Figure 2.10: GC-MS Spectra of Altretamine

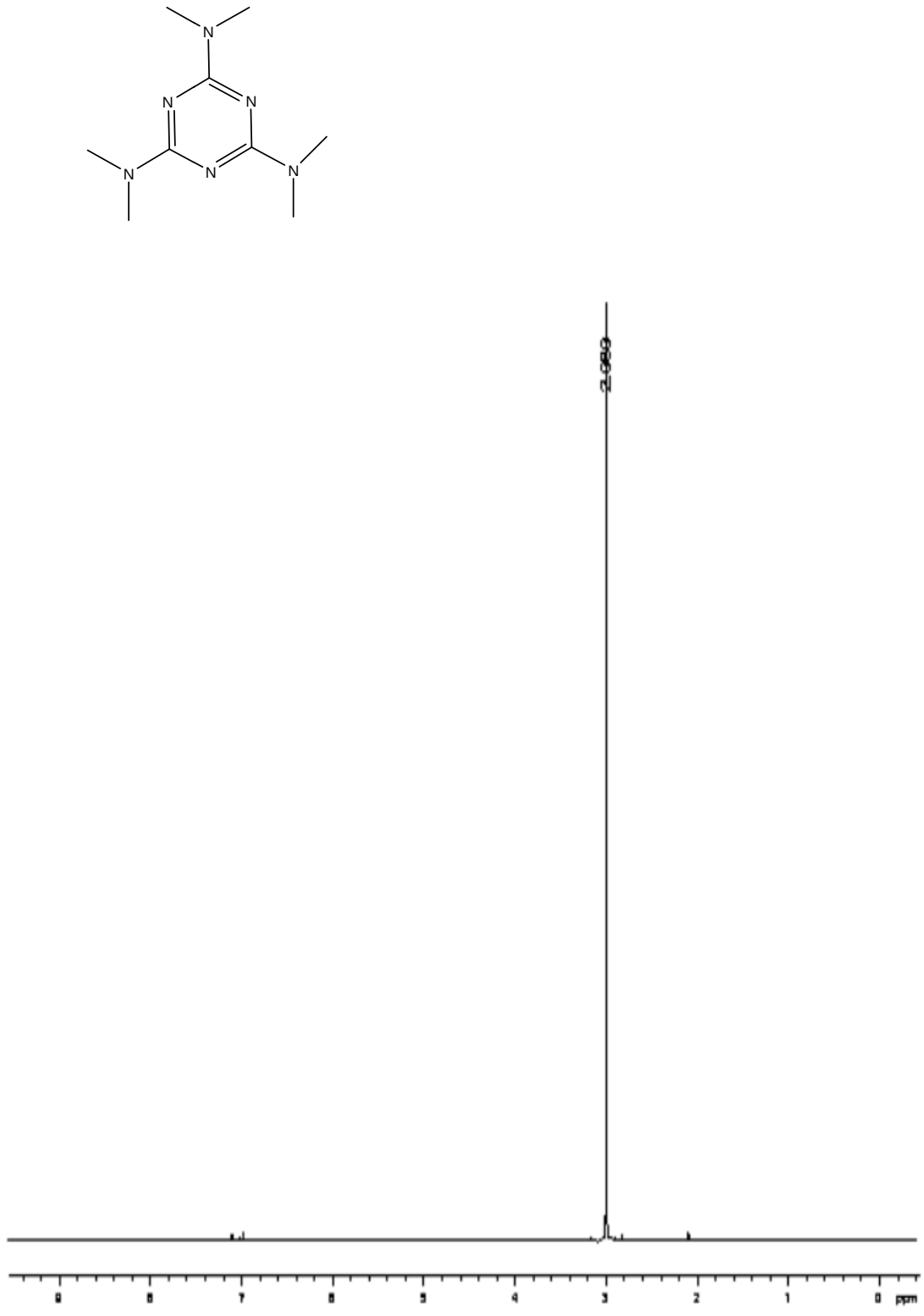


Figure 2.11 ^{1}H-NMR Spectra of the Product from the Cyclotrimerization of Dimethylcyanamide

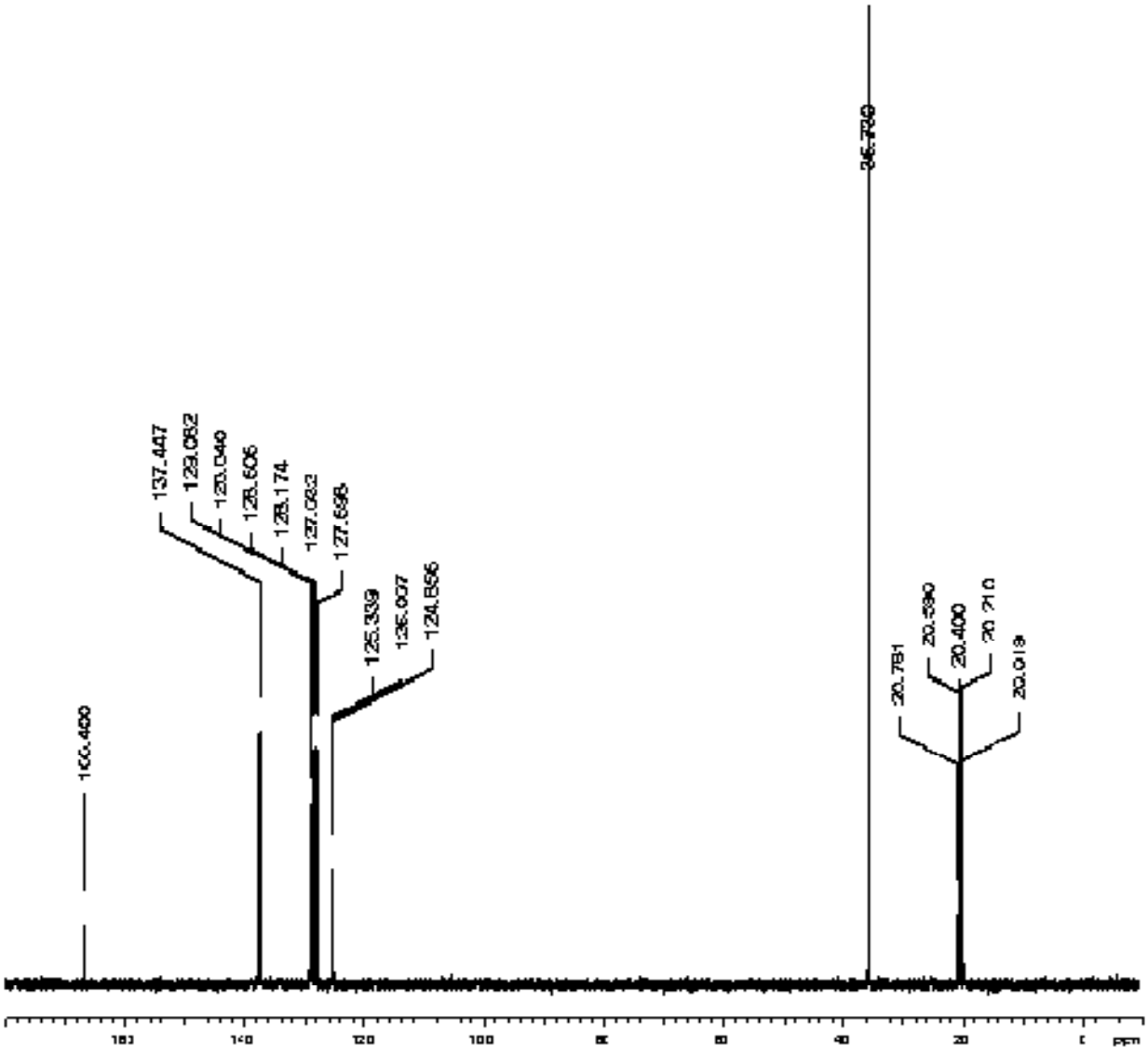


Figure 2.12: ^{13}C-NMR Spectra of the Product from the Cyclotrimerization of Dimethylcyanamide

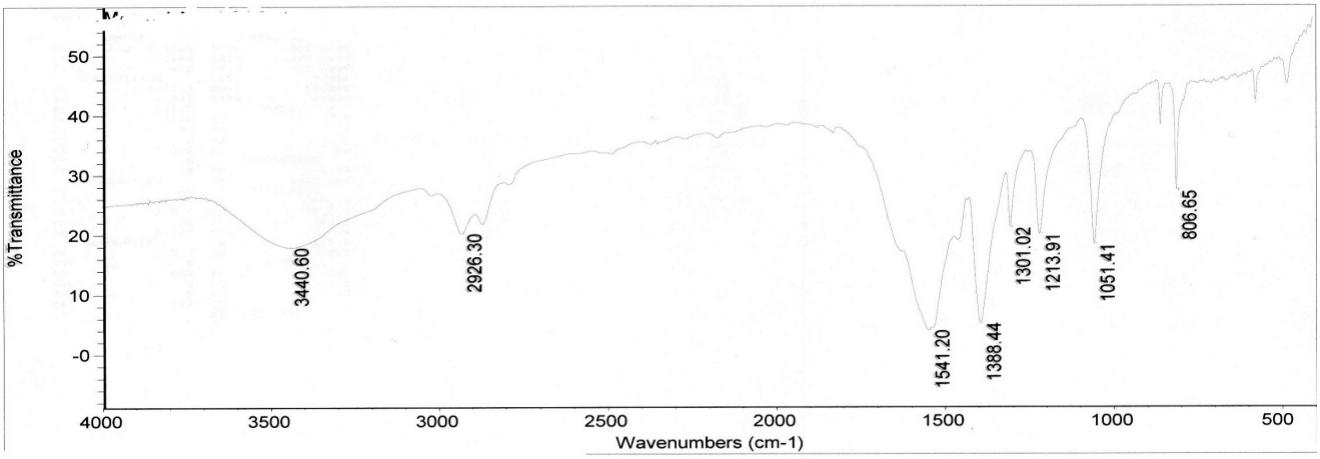


Figure 2.13: The infrared spectrum of Altretamine

Conclusion

A simple and one-pot synthetic procedure has been developed for the preparation of altretamine under a mild reaction conditions. The synthesis of altretamine has been performed by cyclotrimerization of dimethylcyanamide using tungsten and molybdenum hydrogen bronze as catalysts in hexane. Tungsten hydrogen bronze was seen to be more selective in the production of altretamine since no side product was observed. Pure altretamine was not synthesized by using molybdenum hydrogen bronze. Therefore, tungsten hydrogen bronze is a better reagent for cyclotrimerization of dimethylcyanamide.

CHAPTER III

REACTION OF METHYLTHIOCYANATE WITH METAL BRONZE

Triazines derivatives are interesting compounds with biologically important properties. They have found widespread applications in the pharmaceutical, plastic, pesticides, dyes, and textile industries. The chemistry of this group of compounds has been studied extensively and has been the subject of many reviews[36].

All of the s-triazine derivatives that have wide[37] practical applications are mono, di- or tri-substituted, symmetrical and nonsymmetrical compounds bearing different substituents. One of the common methods led to s-triazines is cyclotrimerization of nitriles. The possibility of substituting the nitriles in this reaction by other cyano compounds, such as organic cyanates, thiocyanates and substituted cyanamides, has been considered.

In the previous chapter cyclotrimerization of dimethylcyanamide was performed to synthesize altretamine using tungsten and molybdenum hydrogen bronzes as catalysts. In order to extend this synthetic procedure to other classes of nitriles, the reaction of methylthiocyanate with tungsten and molybdenum hydrogen bronze was investigated.

Experimental

Tungsten and molybdenum hydrogen bronzes were prepared by the procedure reported in Chapter 2. The reaction between the methylthiocyanate (1.00g) and the metal bronze (0.50 g) were carried out in sealed culture tubes at 150°C in toluene. The sealed glass tubes were placed in a heat block for 15 days. The amount of reactant and products in the reaction mixtures were determined by cooling the glass tube to room temperature then, the mixture filtered through 45 µm nylon membrane filter, the yellow solid product extract with methylene chloride and this extract sample analyzed by GC/MS. Compounds were identified by comparison of their mass spectra to the NIST database .

Results and Discussion

As previously reported, the preparation of the altretamine was carried out conveniently by heating a mixture of dimethylcyanamide and hydrogen bronze in a glass tube at 150 °C. In this chapter, methylthiocyanate was reacted with tungsten and molybdenum bronzes in toluene at 150^{o}C .Methylthiocyanate did not produce the trimerization product of methylthiocyanate, 2,4,6-tris(methylthio)-1,3,5-triazine but instead it gave 2,4-bis(methylthio)-1,3,5-triazine. This product resulted from the loss of the dimethylamine group because of the low stability of 2, 4, 6-tris (methylthio)-1, 3, 5-triazine, which decomposes with the formation of 2, 4-bis (methylthio)-1, 3, 5-triazine. The general reaction of methylthiocyanate and the hydrogen bronze is shown in (Figure 3.1)

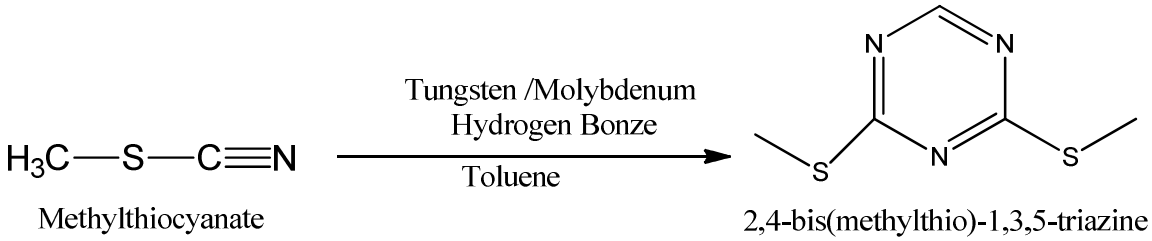


Figure: 3.1. Reaction of Methylthiocyanate with Tungsten and Molybdenum Bonzes

GC-MS analysis of the compound revealed the molecular mass of 173 g/mol, and the NMR spectra showed two signals for symmetrical structure.

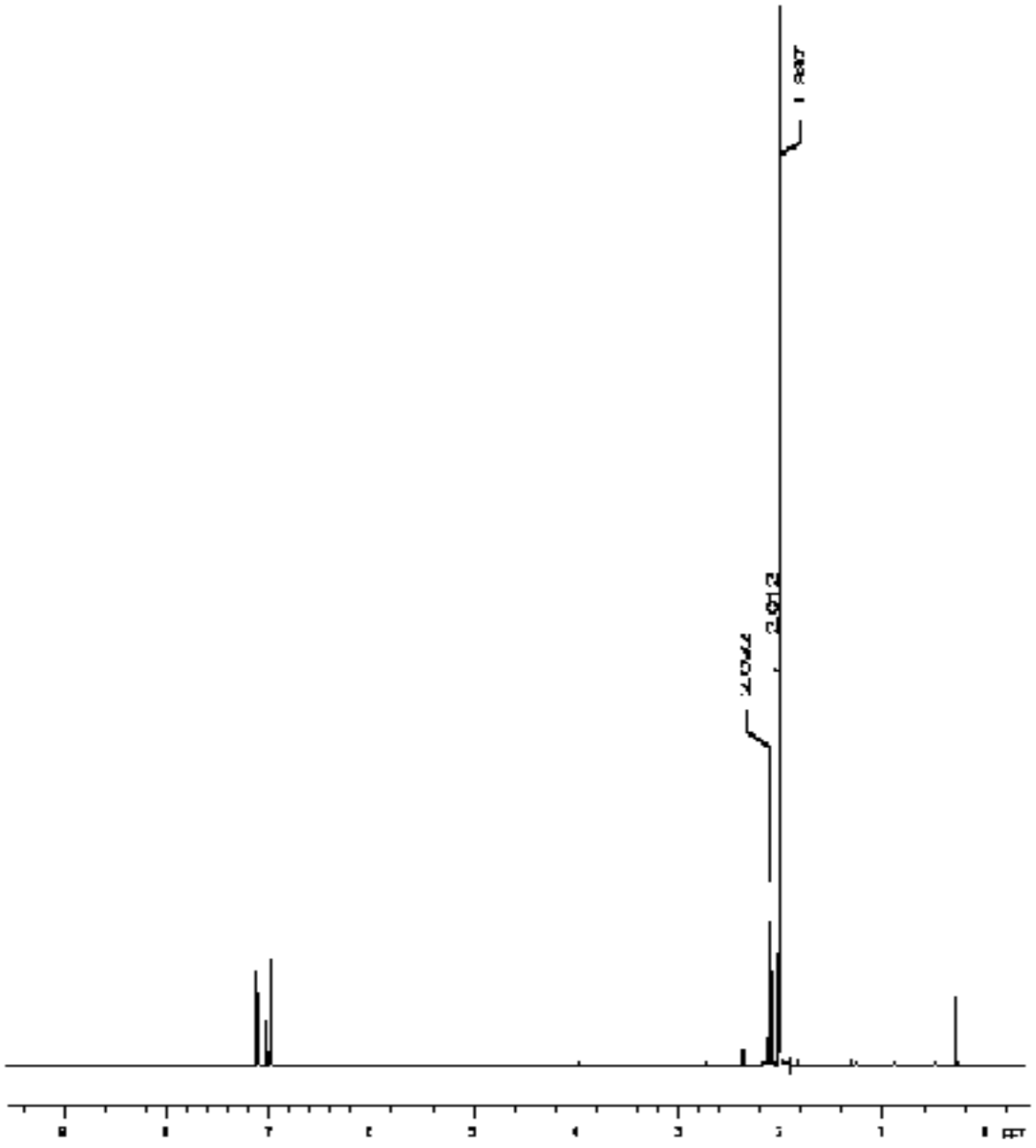


Figure: 3.2 ^{1}H-NMR Spectra of the Product from the Cyclotrimerization of Dimethylcyanamide

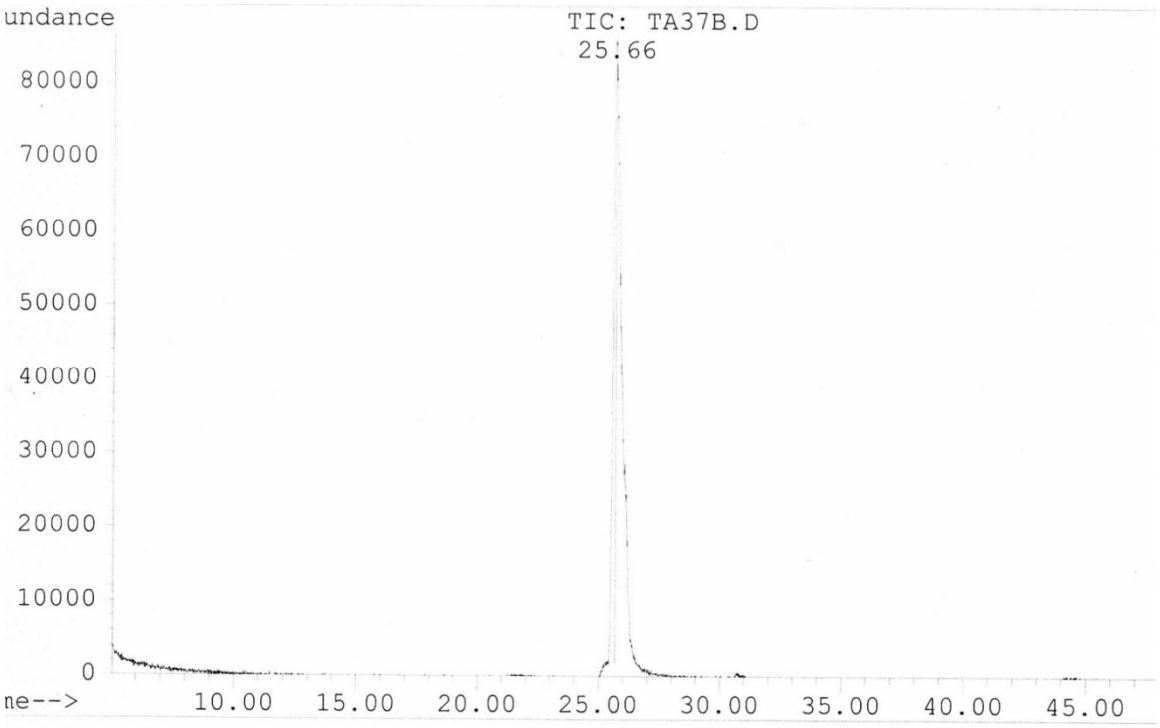


Figure 3.3: GC-MS chromatogram 2, 4-Bis (methylthio)-1, 3, 5-Triazine

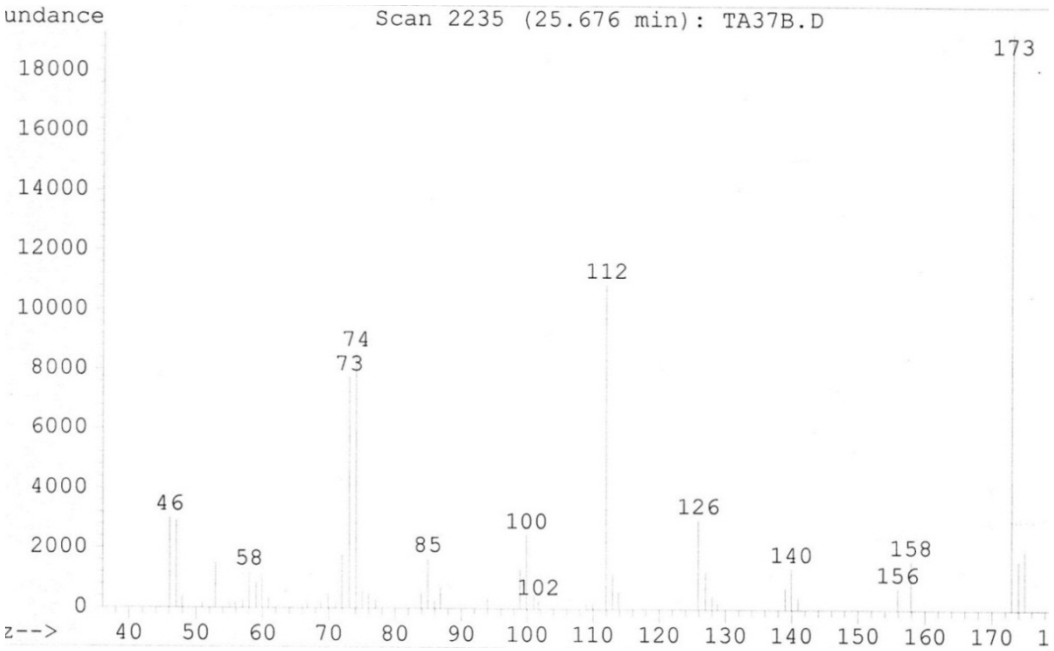


Figure 3.4 : GC-MS Spectra of 2, 4-Bis (methylthio)-1, 3, 5-Triazine

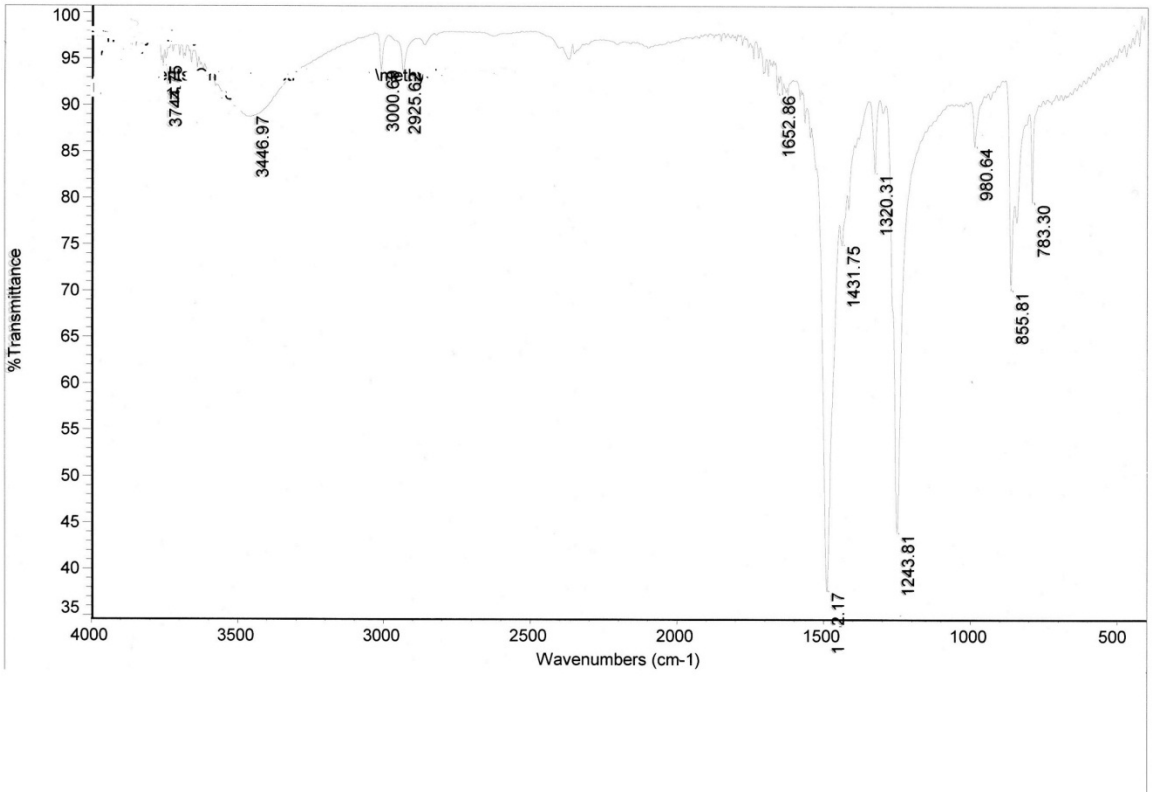


Figure 3.5: infrared spectrum of 2, 4-Bis (methylthio)-1, 3, 5-Triazine

Conclusion

Molybdenum and tungsten hydrogen bronzes were effective catalysts for synthesis of s-trazine products from methylthiocyanate. A practical synthesis of substituted s-triazines from readily available starting materials has been discovered under mild reaction conditions. In light of its simplicity and efficiency, this reliable method is expected to have a broad utility due to the scope of applications of the s-triazines.

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VITA

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Pages in Study: 47 Candidate for the Degree of Master of Science

Major Field: Chemistry

Findings and Conclusions:

Altretamine (hexamethylmelamine) is a chemotherapeutic agent used to treat advanced ovarian cancer. A simple one-pot synthesis procedure has been developed for the synthesis of altretamine under mild reaction condition. The preparation of atretamine has been performed by cyclotrimerization of dimethylcyanamide using tungsten and molybdenum hydrogen bronze as catalyst. These hydrogen bronzes are simply products obtained from hydrogen insertion into tungsten and molybdenum trioxides. The reaction was carried out in sealed culture tube at 150°C and the products were characterized by using nuclear magnetic resonance (NMR), gas chromatography/mass spectrometric analysis (GC-MS) and, infrared spectroscopy (IR). The same reaction can be applied to methylthiocyanate

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