

## Copyright Warning & Restrictions

The copyright law of the United States (Title 17, United States Code) governs the making of photocopies or other reproductions of copyrighted material.

Under certain conditions specified in the law, libraries and archives are authorized to furnish a photocopy or other reproduction. One of these specified conditions is that the photocopy or reproduction is not to be “used for any purpose other than private study, scholarship, or research.” If a user makes a request for, or later uses, a photocopy or reproduction for purposes in excess of “fair use” that user may be liable for copyright infringement,

This institution reserves the right to refuse to accept a copying order if, in its judgment, fulfillment of the order would involve violation of copyright law.

**Please Note: The author retains the copyright while the New Jersey Institute of Technology reserves the right to distribute this thesis or dissertation**

Printing note: If you do not wish to print this page, then select “Pages from: first page # to: last page #” on the print dialog screen

The Van Houten library has removed some of the personal information and all signatures from the approval page and biographical sketches of theses and dissertations in order to protect the identity of NJIT graduates and faculty.

## ABSTRACT

### NOVEL SYNTHESIS OF 2-METHYL-3,4,5-TRICHLOROPYRIMIDINE

by  
Daniel M. Goldman

A one-step synthesis of the heterocycle 2-methyl-3,4,5-trichloropyrimidine by the cycloaddition of hexachloropropene with acetamidine hydrochloride in methanolic NaOH was attempted. The product was dark amber oil. A by-product of this reaction was sodium chloride. The proposed reaction was expected to proceed via a  $S_N2$  nucleophilic displacement of three chlorine atoms on hexachloropropene by acetamidine, the nucleophile. The proposed driving force for this transformation is the lone pair of electrons on the amidine nitrogen along with the electron withdrawing ability of three chlorines on hexachloropropene which induces a partial positive charge on the carbon. It is proposed that the chlorine atoms became good leaving groups based upon literature precedent presented in the introduction. The chlorine atoms act as good leaving groups via  $S_N2$  nucleophilic displacement by the nitrogen atoms. This thesis discusses a synthetic strategy for the possible synthesis of 2-methyl-3,4,5-trichloropyrimidine and its analogs.

**NOVEL SYNTHESIS OF 2-METHYL-3,4,5-TRICHLOROPYRIMIDINE**

by  
**Daniel M. Goldman**

**A Thesis  
Submitted to the Faculty of  
New Jersey Institute of Technology  
in Partial Fulfillment of the Requirements for the Degree of  
Master of Science in Applied Chemistry**

**Department of Chemistry and Environmental Science**

**May 2002**

Blank Page

**APPROVAL PAGE**

**NOVEL SYNTHESIS OF 2-METHYL-3,4,5-TRICHLOROPYRIMIDINE**

**Daniel M. Goldman**

---

Dr. David Kristol, Thesis Advisor Date  
Professor of Biomedical Engineering  
Department of Biomedical Engineering  
NJIT

---

~~Dr. Barbara Kebbekus, Committee Member~~ Date  
~~Professor of Chemistry~~  
~~Department of Chemistry and Environmental Science~~  
~~NJIT~~

---

Dr. Tamara Gund, Committee Member Date  
Professor of Chemistry  
Department of Chemistry and Environmental Science  
NJIT

---

Dr. Louis Barash, Committee Member Date  
Adjunct Professor of Chemistry  
Department of Chemistry and Environmental Science  
NJIT

## BIOGRAPHICAL SKETCH

**Author:** Daniel M. Goldman  
**Degree:** Master of Science in Applied Chemistry  
**Date:** May 2002

### **Undergraduate Education and Graduate Education:**

- Master of Science in Applied Chemistry  
New Jersey Institute of Technology, Newark, NJ, 2002
- Bachelor of Science in Chemistry,  
Worcester Polytechnic Institute, Worcester, Massachusetts, 1976

**Major:** Applied Chemistry

This thesis is dedicated to the memory of my parents Irving and Beatrice Goldman and my dear friend Arthur R. Leckart.



## ACKNOWLEDGEMENT

I wish to express sincere gratitude to my wife Evonne and my children Renee' and David Goldman. The sacrifice made throughout this research and graduate education at NJIT in the form of personal and emotional support by them will never be forgotten.

A distinctive recognition to the silent advisors behind the scenes who provided technical support in the form of materials and knowledge: Mr. William Aronoff of Triad Scientific Inc. of Edison, New Jersey; Dr. Howard Perlmutter of NJIT; Dr. Vincent Venturella of Ventura Associates; Dr. Chandos Caldwell; Dr. Andrew Thompson of J-Star Research Inc.; Dr. Yao-Ming Cheng; Mr. Christopher Blank of Australian National University; Mr. Bruce Leisen of Biomira Inc.; Dr. Robin Martin of Advanced Chemistry Development Inc.; and Dr. Glenn Diegnan of Hurley Associates; and Mr. Erwin Weiser.

Further appreciation is extended to Mr. Bruce Slutsky of the NJIT library as well as Mr. Yogesh Gandhi and Mr. William Guzy of the Department of Chemical Engineering and Department of Chemistry and Environmental Science at NJIT.

Special thanks to Dr. Louis Barash for providing additional laboratory and thesis writing support throughout the course of my research and serving on the committee.

Final appreciation to my major advisor, Dr. David Kristol, and the other members of the committee, Dr. Barbara Kezbekus and Dr. Tamara Gund, whose guidance kept me on the straight path to completion.

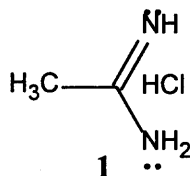
## TABLE OF CONTENTS

<b>Chapter</b>	<b>Page</b>
1 INTRODUCTION.....	1
2 RESULTS AND DISCUSSION .....	20
3 EXPERIMENTAL SECTION .....	25
4 CONCLUSIONS .....	27
REFERENCES .....	28

## CHAPTER 1

### INTRODUCTION

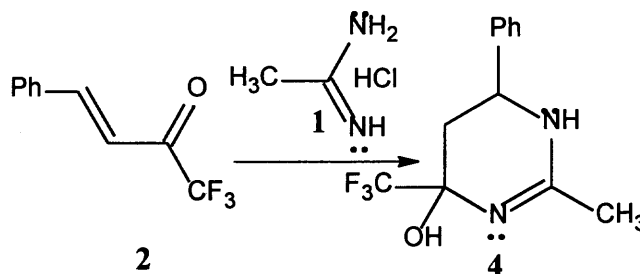
The purpose of this research is to examine the reaction of hexachloropropene with amidines, such as acetamidine to produce pyrimidines in one step. Acetamidine exhibits the following structural and physical properties; molecular weight of 94.55, and a melting point range of 164°C - 166°C. Amidines in general and acetamidines in particular are prepared by the Pinner reaction by passing HCl gas into a solution of a nitrile. When crystallized from alcohol, compound forms long white prisms, soluble in water and alcohol, but insoluble in acetone or ether. Compound (1) acetamidine, serves as a precursor in the synthesis of imidazoles, pyrimidines, and triazines. The free base of this compound has a UV maximum value of 224 nm ( $\epsilon$  4000) and a  $pK_a$  (25°C) of 12.1. As a free base the compound exhibits a strong alkaline reaction and will thermally decompose into ammonia and acetic acid.



Many synthetic applications utilizing acetamidine depend on the electronic nature of the lone pair of electrons found on the reacting nucleophilic nitrogen atom. This reactivity of the lone pair of electrons is enhanced by the electron donating ability of the nitrogen atom. During the presented reaction with hexachloropropene, the individual chlorine atoms become a good leaving group. Based upon the literature in this introduction, this occurred via nucleophilic displacement by the nitrogen atom.

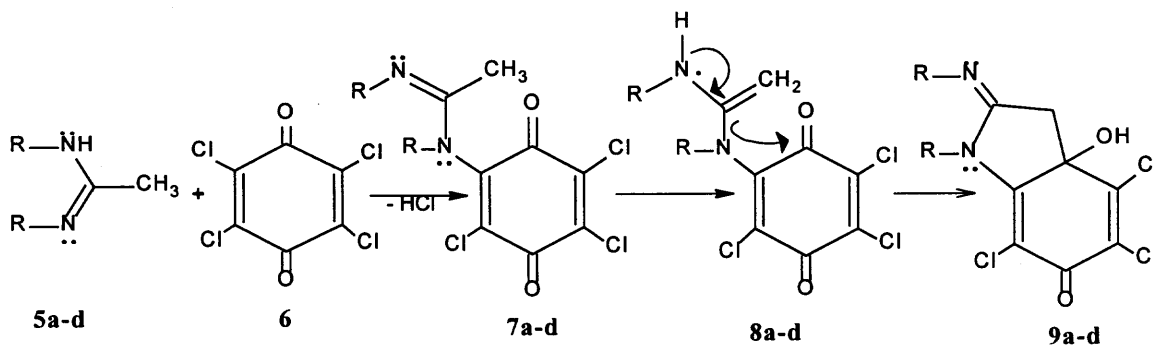
This introduction summarizes some of the reactions of amidines, which lends support to our goal to produce imidazoles, pyrimidines, and triazenes, etc.

Work by Nenajdenko, Sanin, Kuz'min, Balenkova<sup>1</sup> illustrates the reaction of acetamidine with a trifluoromethyl-containing ketone in Scheme 1. The yield of product (4) was 55%.



Scheme 1

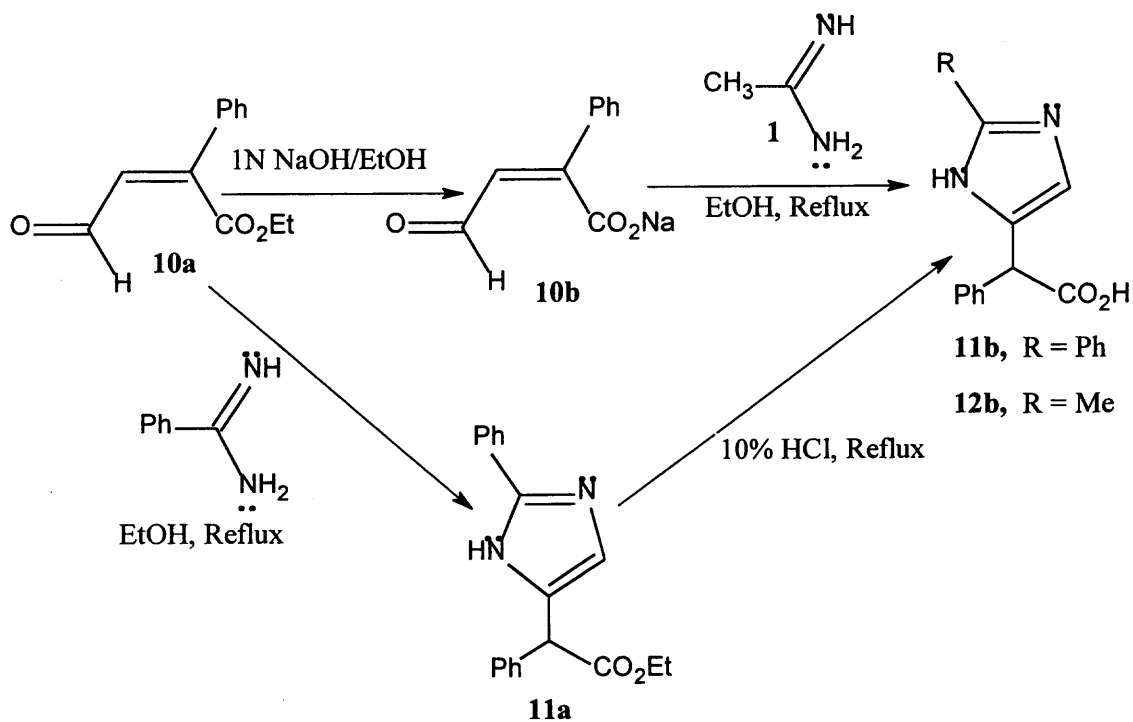
Work by Dopp, Gomaa, Henkel, and Nour El-Din<sup>2</sup> showed that two equivalents of an N<sup>1</sup>, N<sup>2</sup>-diarylacetamidine (5a-d) reacts with 2,3,5,6-tetrachlorobenzoquinone (6) in ethyl acetate at room temperature to form tetrahydroindolones (9a-d) as the major product. As shown in Scheme 2, the major product of tetrahydroindolones (9a-d) gave yields from 12% - 80%. The minor products of 2-arylamino-3,5,6-trichloro-1,4-benzoquinones (7a-d) gave yields from 5% - 6%.



- 5a-d
- a, R = 2-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>
- b, R = 4-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>
- c, R = 4-CH<sub>3</sub>O-C<sub>6</sub>H<sub>4</sub>
- d, R = 4-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>

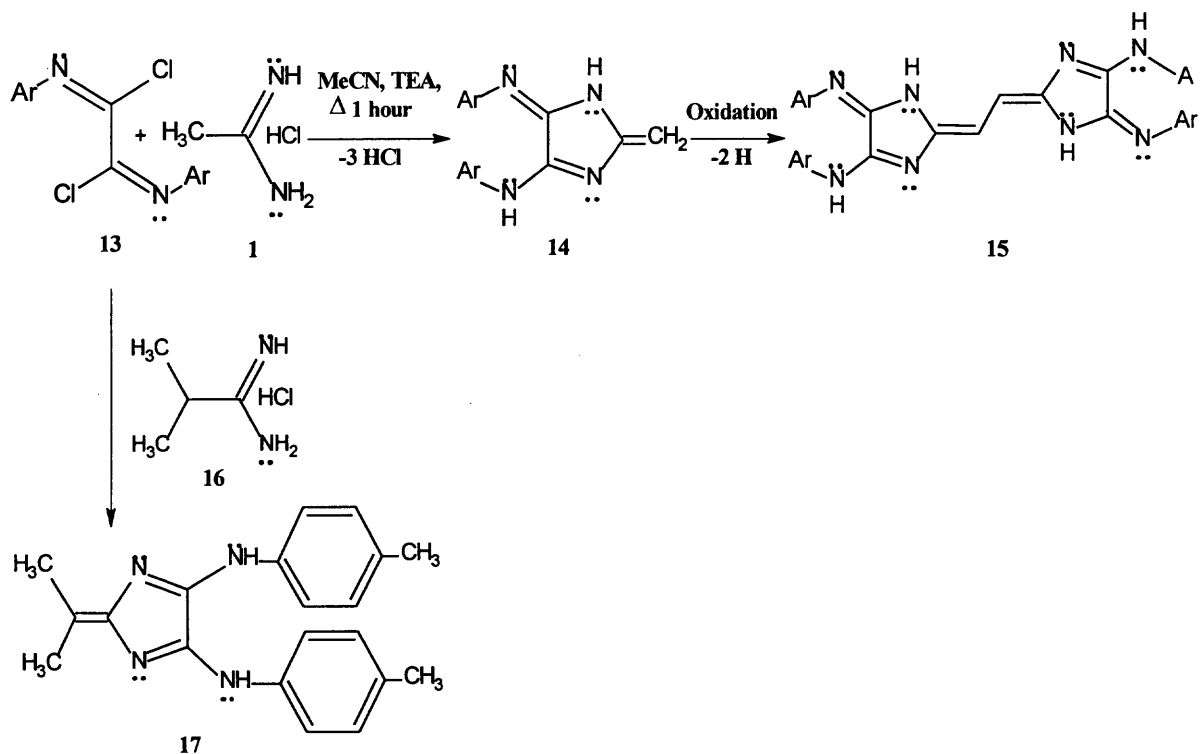
Scheme 2

The ethyl ester of  $\alpha$ -phenyl- $\beta$ -formylacrylic acid (**10a**) and its corresponding sodium salt (**10b**) behaved as Michael acceptors when reacting with the starting material, benzamidine hydrochloride as shown in Scheme 3. This reaction yielded (**11a**) 2-phenyl-5-( $\alpha$ -phenylethoxycarbonylmethyl)imidazole. Acid hydrolysis of the imidazole ester (**11a**) formed the corresponding acid (**11b**). The cyclocondensation of benzamidine with the sodium salt (**10b**) of phenyl- $\beta$ -formylacrylic acid yielded product (**11b**). Reaction of acetamidine hydrochloride with the sodium salt of  $\alpha$ -phenyl- $\beta$ -formylacrylate (**10b**) produced product (**12b**), the corresponding acid derivative<sup>3</sup>.



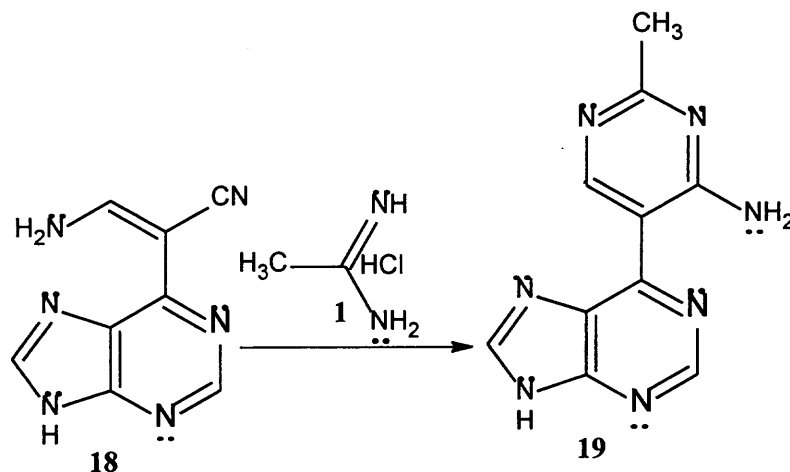
**Scheme 3**

Scheme 4 shows the cycloacylation of acetamidinium hydrochloride (1) with the bisimidoyl chloride (13) of oxalic acid yields a diazafulvene<sup>4</sup>. Reflux in acetonitrile with triethylamine and HCl formed a slightly yellow solution that eventually becomes deep red. The product dimer (15) was obtained by the continued addition of the bisimidoyl chlorides (13). The addition of concentrated HCl precipitated the dimeric compound (15) from the reaction mixture. The use of DMF gave crystals of compound (15) with a metallic-green luster. Isopropylamidinium hydrochloride (16) reacts with the bisimidoyl chlorides (13) to form compound (17) without concomitant formation of the corresponding dimer product.



Scheme 4

Work by Himamichi and Miyasaka<sup>5</sup> illustrated in Scheme 5 that  $\alpha$ -(aminomethylene)-6-purineacetonitrile (**18**) when reacted with acetamidine (**1**) in sodium n-propoxide in n-propyl alcohol yielded 6-(4-amino-2-methyl-5-pyrimidinyl)-purine (**19**) in a 63% yield.

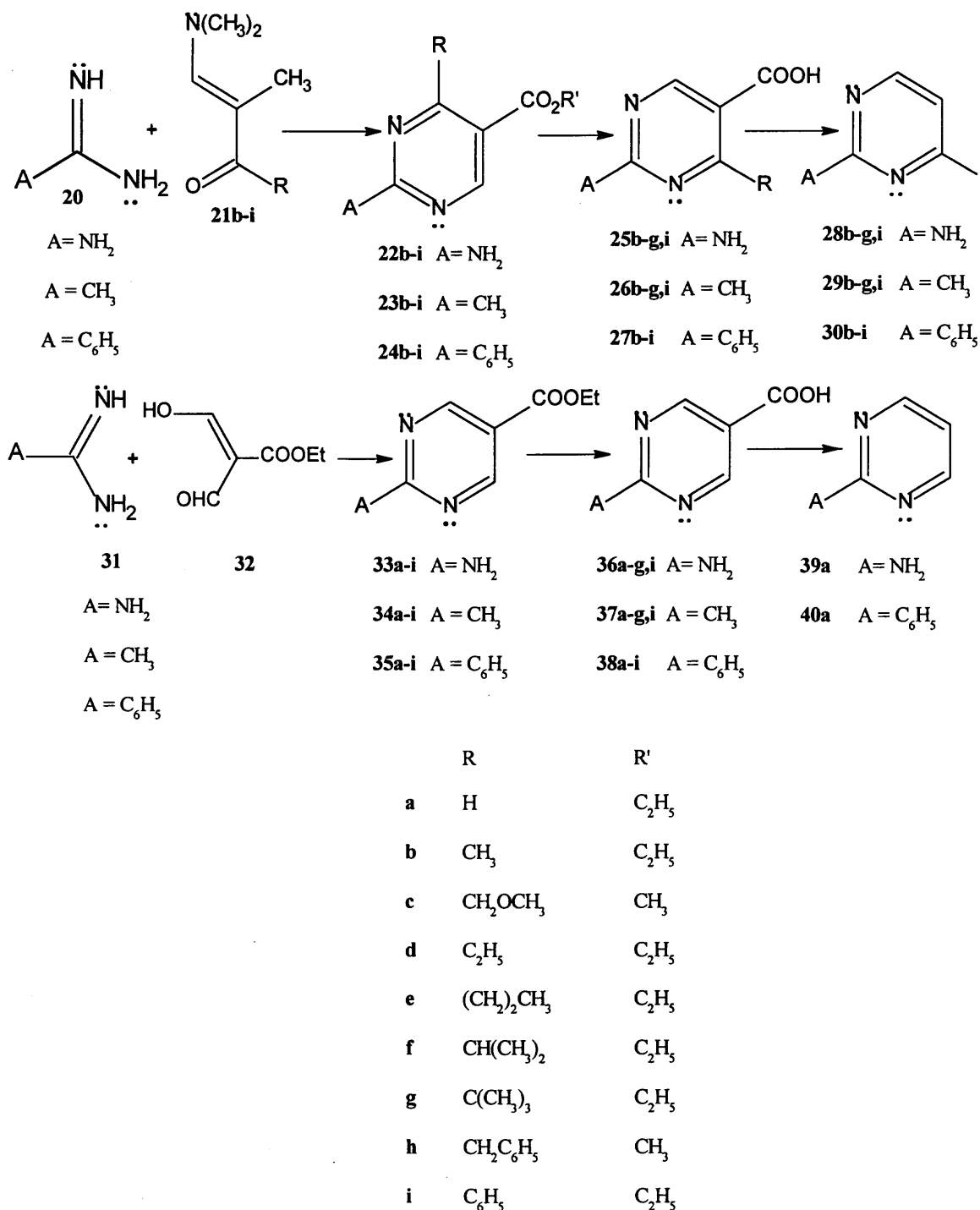


**Scheme 5**

Scheme 6 shows 2,4-disubstituted ethyl and methyl 5-pyrimidinecarboxylates (**22b-i**, **23b-i**, and **24b-i**) were synthesized using guanidine acetate, acetamidine hydrochloride, and benzamidine hydrochloride with ethyl or methyl 2-dimethylaminomethylene-3-oxoalkanoate.<sup>6</sup> These reactions were performed using sodium methoxide in refluxing alcohol. The results were yields of 60% to 88% of 4-substituted ethyl or methyl 2-amino-5-pyrimidinecarboxylates (**22b-i**), 2-methyl-5-pyrimidinecarboxylates (**23b-i**), and 2-phenyl-5-pyrimidinecarboxylates (**24b-i**).

Another reaction illustrated in Scheme 6 exhibits the products of 4-unsubstituted ethyl 2-amino, 2-methyl and 2-phenyl-5-pyrimidinecarboxylates (**30**) prepared by the reaction of ethyl 2,2-diformylacetate with guanidine, acetamidine, and benzamidine<sup>7</sup>. The esters of (**33a-i**, **34a-i**, **35a-i**) gave yields in the range of 61% to 99% for the corresponding 4-substituted 2-amino-pyrimidine-5-carboxylic acids (**36a-g, i**) and 2-phenyl-pyrimidine-5-

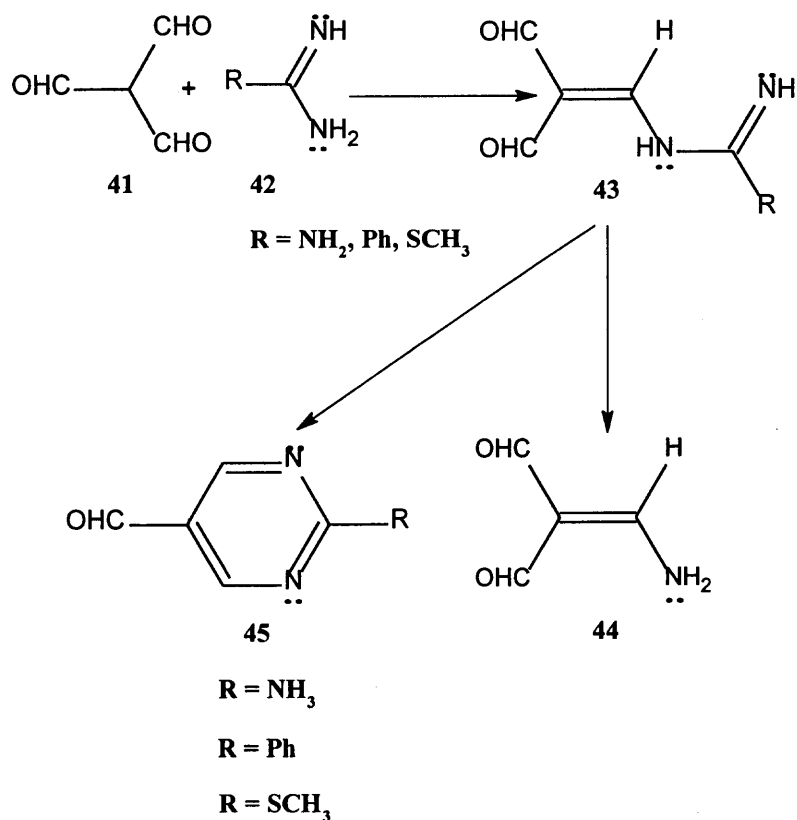
carboxylic acids (**38a-i**). These esterification reactions were performed with potassium hydroxide in boiling ethanol followed by acidification.



Scheme 6



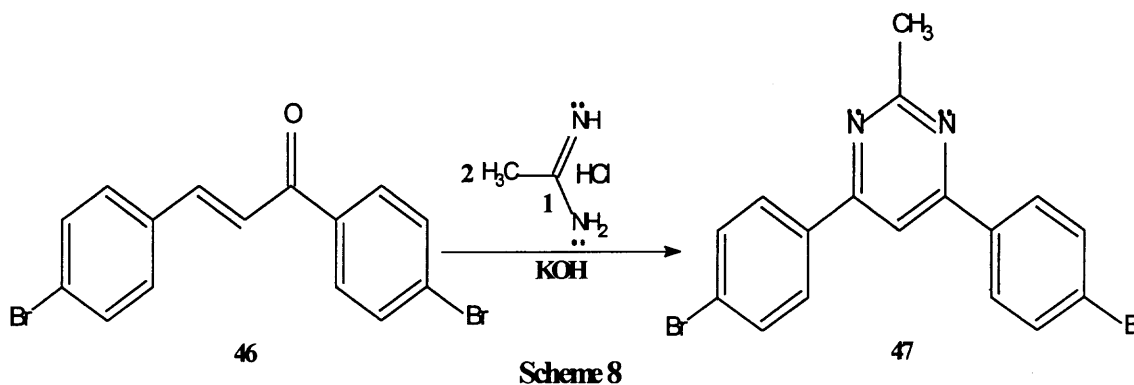
Scheme 7 shows triformylmethane (**41**) reacting with benzamidine, guanidine, and S-methylisothiurea to form 2-substituted pyrimidine-5-carboxaldehydes<sup>8</sup> (**45**). The exception here is that acetamidine did not yield the expected heterocyclic (**45**, R = CH<sub>3</sub>) pyrimidinecarboxaldehyde, but rather 1-aminoethylene-2,2-dicarboxaldehyde (**44**). The formation of substituted 1,1-diformylethylene (**43**) (R = NH<sub>2</sub>, Ph, or SCH<sub>3</sub>) intermediate(s) yields compound (**44**) via hydrolysis. The suggested intermediates (**43**) (R = NH<sub>2</sub>, Ph, and SCH<sub>3</sub>) cyclize to form 2-substituted pyrimidine-5-carboxaldehydes, (**45**).



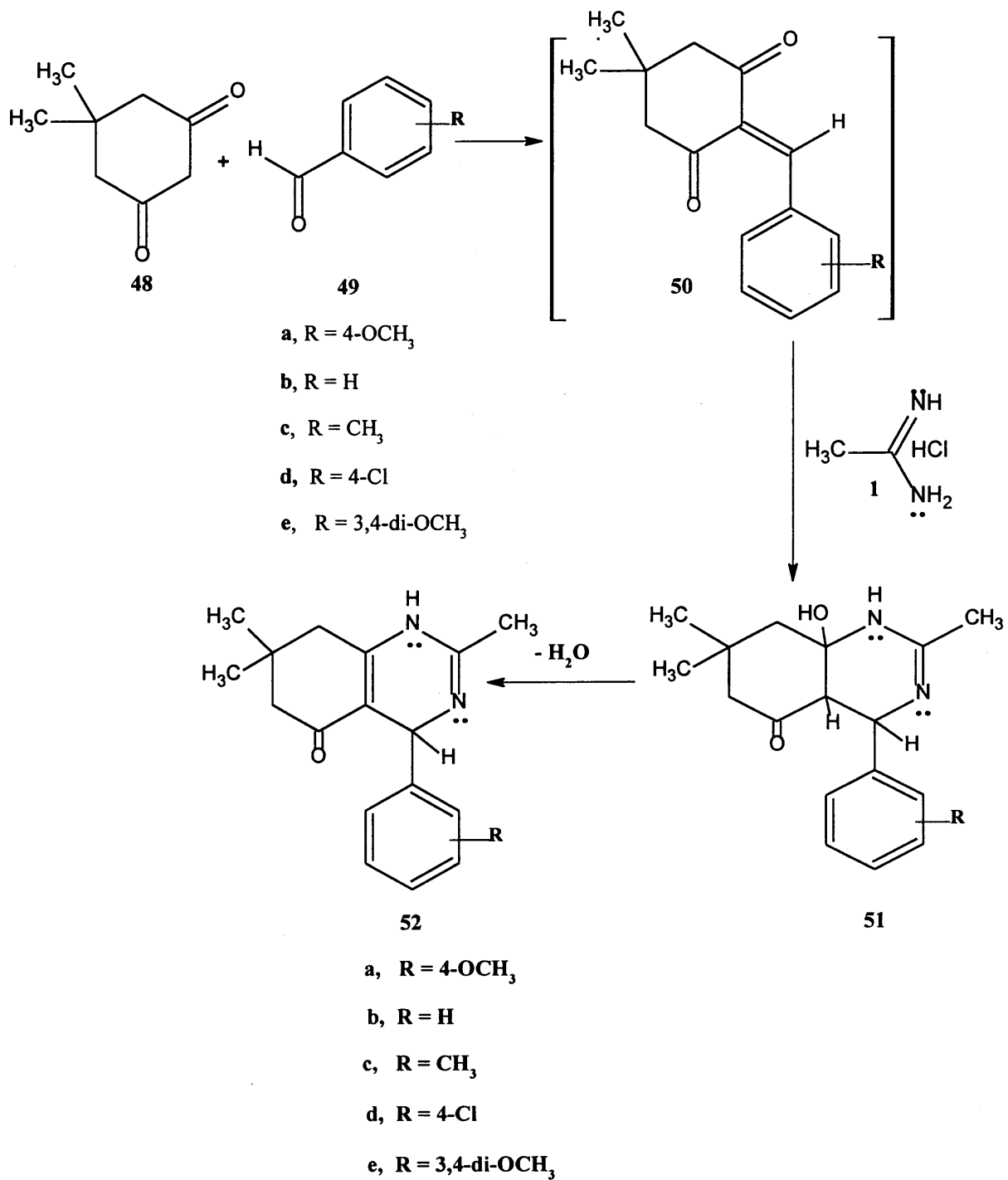
**Scheme 7**

In Scheme 8 the base promoted condensation between 1,3-di-(4-bromophenyl)propen-1-one (**46**) and acetamidine is another example of an acetamidine cycloaddition to an  $\alpha,\beta$ -unsaturated ketone<sup>9</sup>. Two moles of  $\alpha,\beta$ -unsaturated ketone are consumed during the reaction; with one mole being incorporated into the pyrimidine ring

while the other acted as an oxidizing agent to produce 4,6-bis-(4-bromophenyl)-2-methyl-pyrimidine (47).

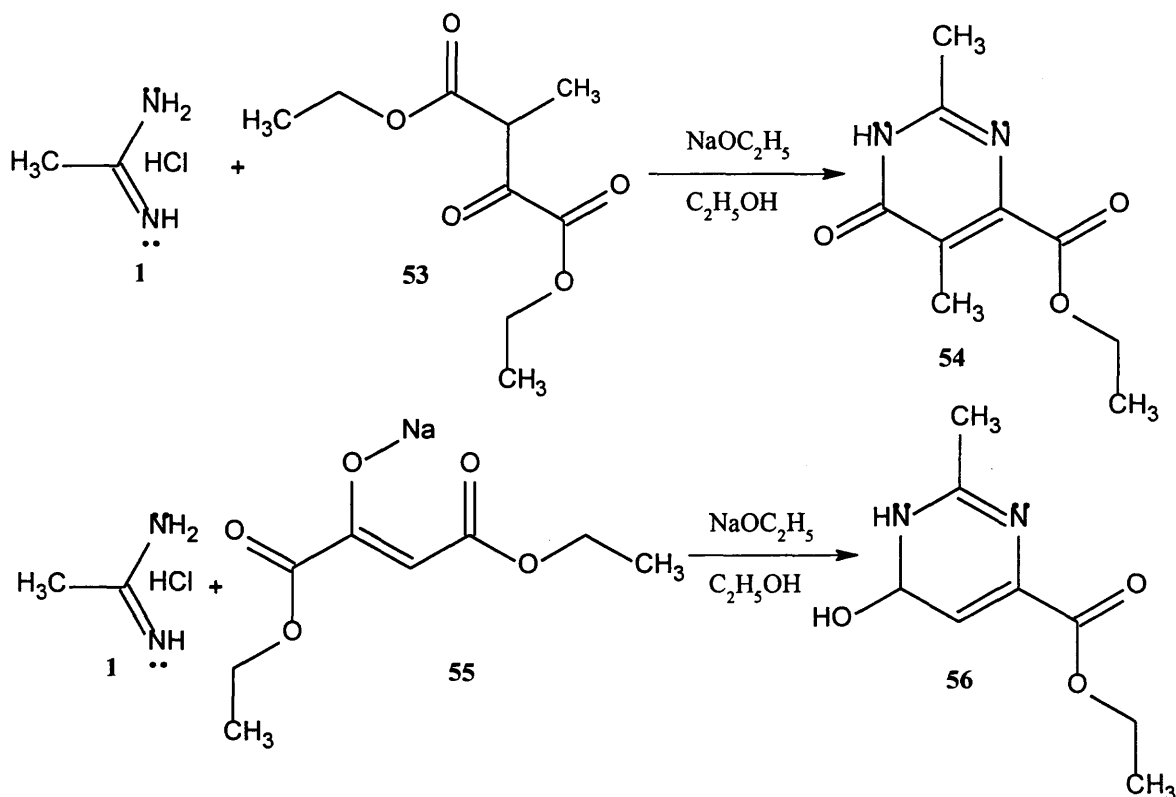


Scheme 9 is an example of the condensation of equal molar amounts of dimedone (48) and anisaldehyde (49a) in methanolic sodium methoxide at room temperature to form the intermediate,  $\alpha,\beta$ -ethylenic carbonyl (50), which reacts with acetamidine hydrochloride (1) to form the product 4-aryl-2,7,7-trimethyl-3,4,5,6,7,8-hexahydro-5-oxoquinazolines (52a-e)<sup>10</sup>. It is interesting to note that in contrast to the previous reaction, oxidation to form the corresponding phenyl pyrimidines did not occur.



Scheme 9

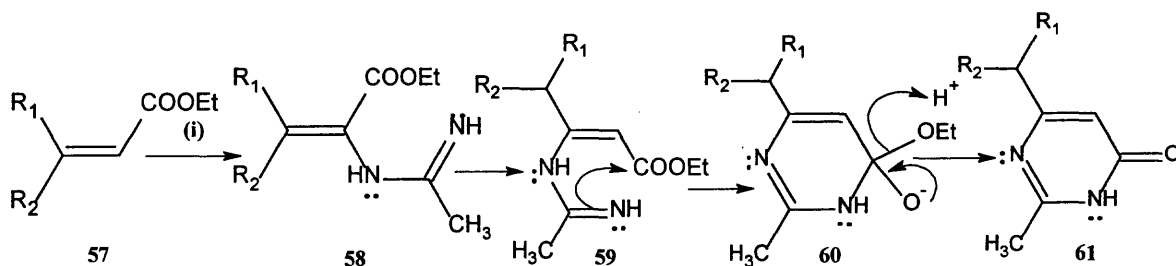
Scheme 10 shows that ethyl 2,5-dimethyl-4-oxypyrimidine-6-carboxylate (**54**) is formed by the reaction of acetamide hydrochloride (**1**) with the  $\beta$ -ketoester, diethyloxapropionate (**53**) in refluxing in ethanolic sodium ethoxide<sup>11</sup>. The yield obtained was 52%. A similar reaction using the sodium salt of diethyl oxalacetate (**55**) with acetamide hydrochloride (**1**) gave a 10% yield of ethyl 2-methyl-4-oxypyrimidine-6-carboxylate (**56**).



**Scheme 10**

The synthesis of 2-methylpyrimidin-4-(3H)-ones (**61**) via acetamide HCl and ethyl alka-2,3-dienoates (**57a,b**) in Scheme 11 is an example of a Michael addition to the unconjugated enaminic ester (**58**)<sup>12</sup>. The ester then begins to cyclize to form a conjugated adduct (**56**). At the ethoxycarbonyl group in (**58**), an intramolecular nucleophilic attack occurs leading to the formation of 2-methylpyrimidin-4(3H)-ones (**61**). A reaction

performed with equivalent amounts of acetamidine hydrochloride and ethyl 4-methylpenta-2,3-dienoate (**57a**) with potassium carbonate was heated at 50°C in tetrahydrofuran for seven hours resulted in formation of a 60% yield of the product 2-methyl-6-(1-methylethyl)pyrimidin-4-(3H)-one (**61a**).

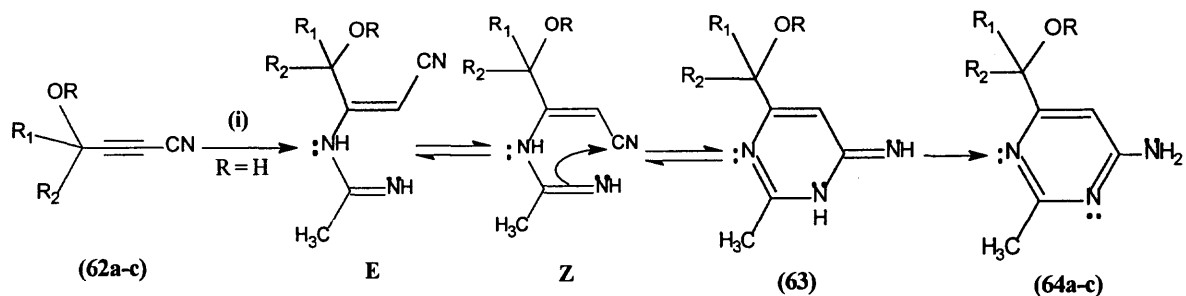


(i) Acetamidine HCl /  $K_2CO_3$  / reflux in THF

(a)  $R_1 = R_2 = Me$  (b)  $R_1 = Et$   $R_2 = Me$

**Scheme 11**

Scheme 12 illustrates a cycloaddition reaction using an equivalent amount of 4-hydroxynitrile (**62a**,  $R=H$ ) with acetamidine hydrochloride forming the intermediate adducts (*E,Z*)<sup>13</sup>. The formation of these acetamidino adducts indicates that there is an equilibrium involving competitive cyclization with compound (**61**). The 4-amino-6-(1-hydroxyalkyl)-2-methylpyrimidine (**64a**,  $R=H$ ) gave a very low yield. In an effort to increase the yields of pyrimidines (**64 a-c**) 4-substituted-tetrahydropyranloxyalk-2-ynenitrile (**62a-c**) were used. The reactions were carried out in refluxing THF with one equivalent of acetamidine hydrochloride and sodium bicarbonate. The resulting products were the 4-amino-2-methylpyrimidines (**64a-c**) in a 60 - 70% recrystallized yield.

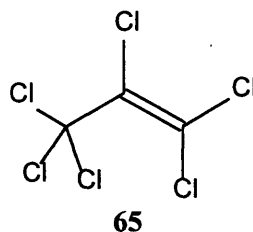


(i) Acetamidine.HCl / Na<sub>2</sub>CO<sub>3</sub> / reflux THF

(a) R<sub>1</sub> = Me, R<sub>2</sub> = Et; (b) R<sub>1</sub> = R<sub>2</sub> = Et; (c) R<sub>1</sub> = Me, R<sub>2</sub> = t-Bu

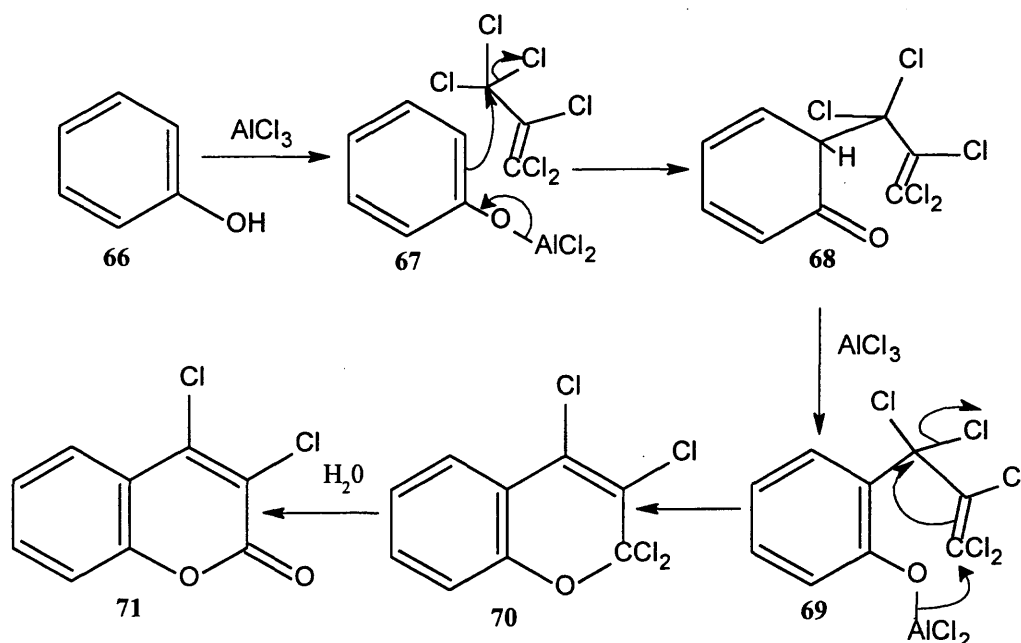
**Scheme 12**

The molecule of hexachloropropene (**65**) exhibits the following structural and physical properties: molecular weight of 248.75, boiling point range of 209°C - 210°C, density of 1.765; refractive index of 1.548; vapor density of 8.3 (air =1). It is soluble in diethyl ether and various chlorinated solvents and relatively insoluble in water and methanol. Many of the reactions of hexachloropropene can be rationalized on the basis of the presence of multiple chlorines, which can act as good leaving groups when reacted with nucleophiles. Compound (**65**) is a precursor in the synthesis of various forms of industrial freons. In addition, it is used as a chemical promoter for the production of ethylene/propylene copolymer rubber.



Scheme 13 illustrates the formation of 3,4-dichlorocoumarin (**71**) by an aluminum chloride catalyzed reaction of phenol (**66**) with hexachloropropene. The phenol reacts with one equivalent of aluminum chloride to yield the intermediate (**67**) in which the oxygen carbon bond subsequently undergoes an electron transfer from the oxygen aluminum bond

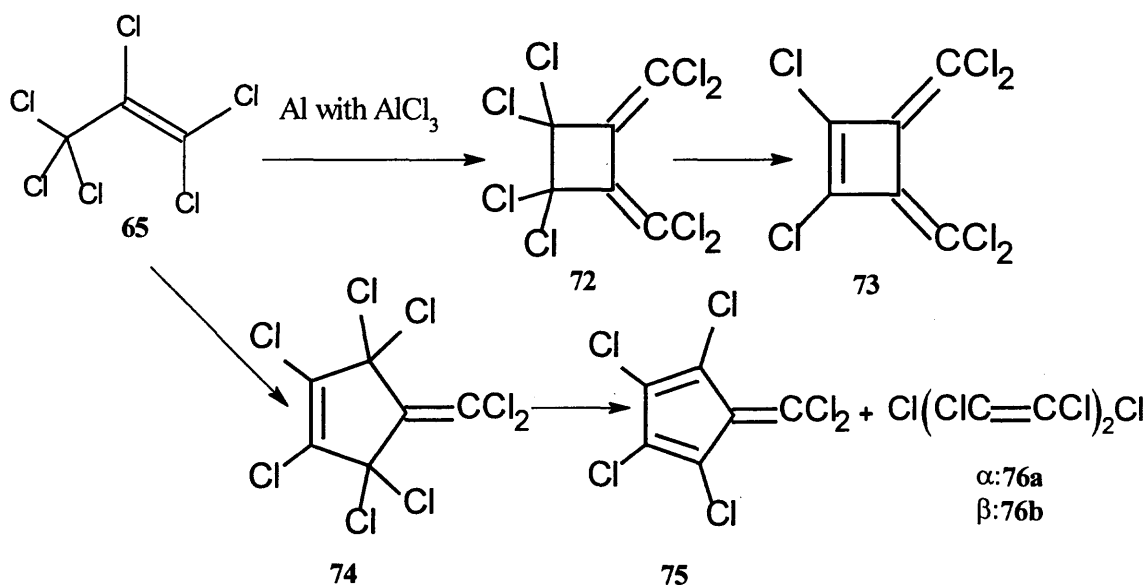
through the benzene ring resulting in an  $S_N2$  displacement at the electron deficient carbon of the trichloromethyl group in the hexachloropropene molecule<sup>14</sup>. Displacement at the ortho position of the aluminum-phenol complex (67) in a stepwise or in a concerted reaction leads to the formation of a cyclohexadienone (68). Further reaction of (69) with  $AlCl_3$  forms (69) which can cyclize to give (70). Hydrolysis produces the 3,4-dichlorocoumarin (71).



**Scheme 13**

Shown in Scheme 14 is the dechlorination and cyclization of hexachloropropene (65) using various forms of aluminum (chips, granules, or powdered aluminum metal combined with mercury).<sup>15</sup> This reaction resulted in the formation of perchloro-(3,4-dimethylenecyclobutene) (73) with a yield of 55%. This reaction mixture also contained perchloro-(3,4-dimethylenecyclobutane) (72) having a melting point of 93°C. Product (72) could further be dechlorinated to (73). To achieve the 55% yield of (73), the various form of aluminum metal had to have a purity of 99.99% when amalgamated with aluminum

chloride. This amalgamated combination also promotes the cyclization of hexachloropropene (65) to a four-member ring. Another dechlorination and cyclization of hexachloropropene (65) in Scheme 14 forms a five-member ring of perchloro-4-methylenecyclopentene (74), perchlorofulvene (75), and two perchlorobutdienes ( $\alpha$ : 76a,  $\beta$ : 76b).<sup>16</sup> These reaction products were obtained when granulated aluminum of a lower purity was used and amalgamated with  $\text{AlCl}_3$ . The presence of such trace metal impurities as copper, iron, and silicon can alter the reaction path by which hexachloropropene can cyclize or dimerize with itself along with dechlorination.

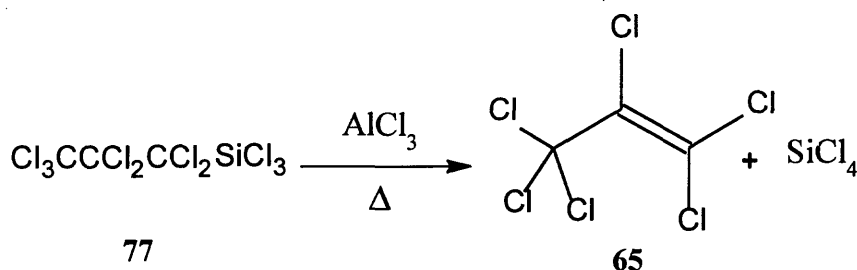


**Scheme 14**

Heating of trichloro(pentachloroallyl)silane (77) with  $\text{AlCl}_3$  at a temperature of  $160^\circ\text{C}$  to  $180^\circ\text{C}$  caused dechlorination with the formation of silicon tetrachloride and hexachloropropene (65) in 76% and 52% yield respectively, as shown in Scheme 15.<sup>17</sup> Reaction products which formed were silicon tetrachloride and hexachloropropene (65) in a yield of 52% for hexachloropropene and 76% for silicon tetrachloride. The IR spectrum of compound (75) displayed a strong absorption at approximately  $615\text{ cm}^{-1}$ . This vibration

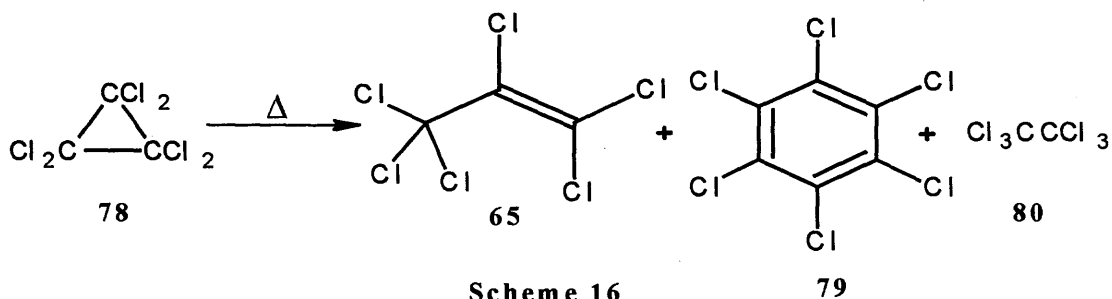


frequency represents the Si-Cl bond in the trichlorosilyl group. Absence of absorption bands in the 3000–2800  $\text{cm}^{-1}$  and 1500-1150  $\text{cm}^{-1}$  support a perchlorinated material (77). The IR spectrum of compound (75) is reported to exhibit a strong absorption at 620  $\text{cm}^{-1}$  (s) for the  $-\text{SiCl}_3$  group, as well as medium intensity absorption at 535-450  $\text{cm}^{-1}$ . The  $-\text{SiCl}$  vibration absorbs at 550-470  $\text{cm}^{-1}$ . The compound (65) displayed the characteristic absorption bands at 640-610  $\text{cm}^{-1}$  for the Si-Cl bond.

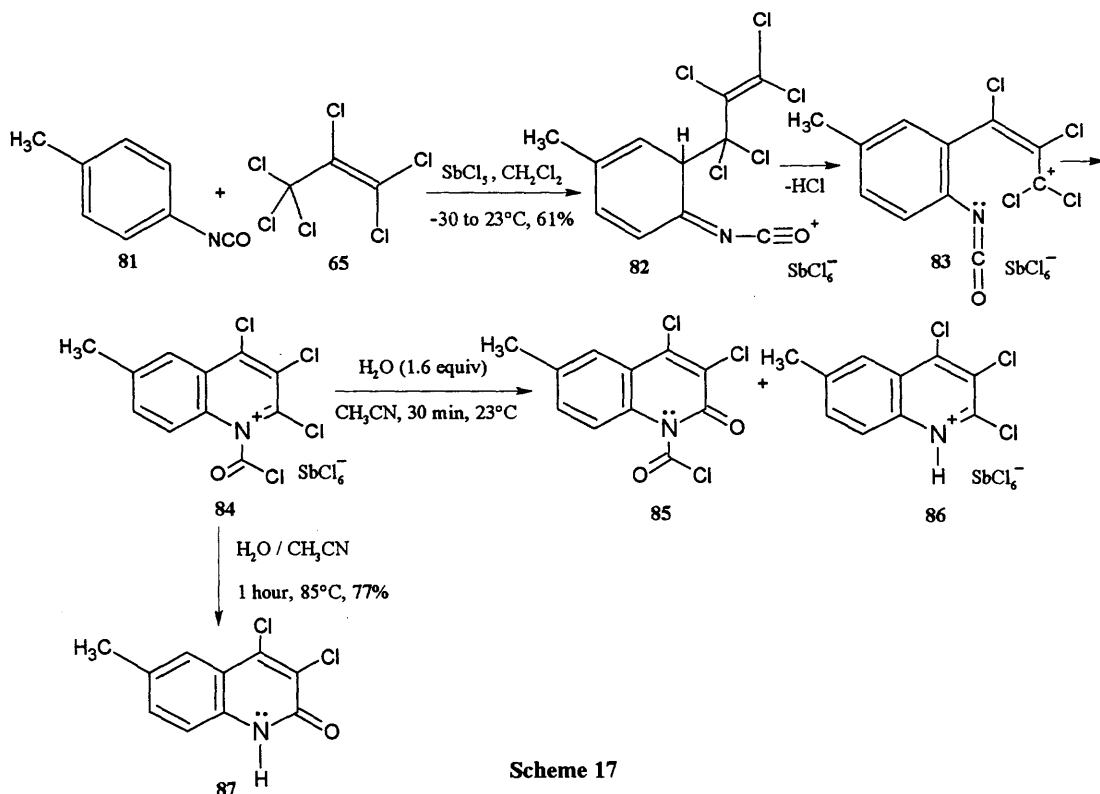


**Scheme 15**

Work by Hale<sup>18</sup> on the thermal isomerization of hexachlorocyclopropane using the Lewis acid, AlCl<sub>3</sub> is shown in Scheme 16. Vaporphase pyrolysis under reduced pressure of hexachloropropane results in the formation of three products shown in Scheme 16, (65) hexachloropropene, (79) 1,2,3,4,5,6 - hexachlorobenzene, and (80) hexachloroethane. A flow system utilizing argon as the carrier gas was passed sublimed (78) hexachloropropane through an unpacked Vycor tube. The reaction was carried out at various temperatures, e.g. at 200°C, no detectable decomposition products were formed. At 300°C an 80% yield of (65) resulted and at a temperature of 400°C at a 25% yield of (80) and 30% yield of (79). It is worth noting that no polymerization products were detected even up to ca. 500°C where complete thermal decomposition of (78) occurs. It was reported that an unresolved decomposition mixture displayed infrared absorptions characteristic of carbon tetrachloride and 1,1,2,2-tetrachloroethylene.

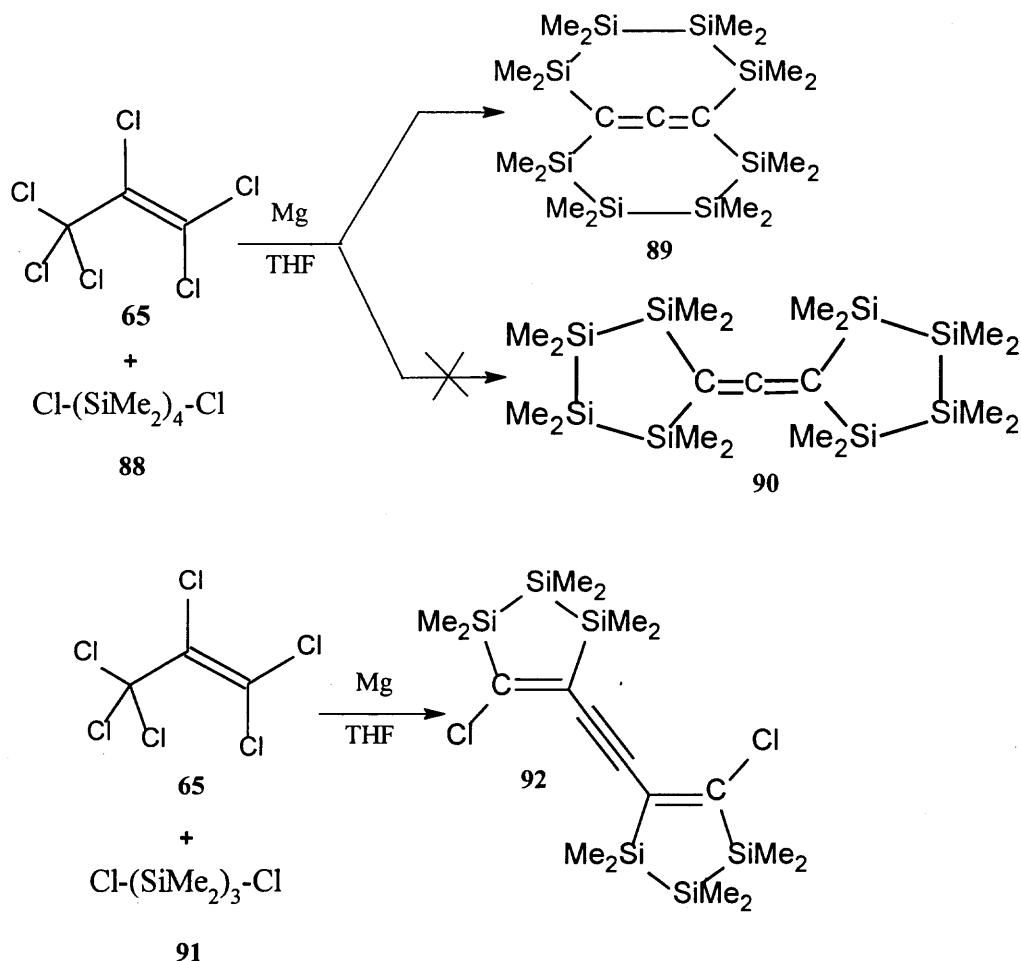


Work by J. Jochims, A. Hamed, M. Al-Talib<sup>19</sup> in Scheme 17 showed that compound (**84**) was formed by a Friedel-Crafts alkylation of hexachloropropene (**65**) with *p*-tolylisocyanate (**81**). To initiate this reaction, one equivalent of *p*-tolylisocyanate (**81**) was reacted with hexachloropropene (**65**). The aromatic ring of *p*-tolylisocyanate (**81**) is activated for electrophilic attack with hexachloropropene (**65**) at the ortho carbon by the methyl and isocyanate substituents. Small amounts of water caused the *N*-acyliminium (**84**) to hydrolyze to give a mixture of the quinolone (**85**), with a yield of 26%, and the quinolinium salt (**86**) with a yield 47%. A larger excess of water produced more quinolone (**87**).



A reaction illustrated in Scheme 18 shows hexachloropropene (**65**) reacting with 1,4-dichlorooctamethyltetrasilane in the presence of magnesium gave octasila[4,4]-betweenallene (**89**) in a 34% yield.<sup>20</sup> <sup>1</sup>H and <sup>13</sup>C NMR spectra of (**89**) shows the four equivalent methyl groups and characteristic allenic sp and sp<sup>2</sup> at 207.8 and 122.9 ppm, respectively. Another isomer (**90**), which was expected to be formed, but could not be obtained.

The examination of a similar reaction in Scheme 18 showing hexachloropropene (**65**) reacting with 1,3-dichlorohexamethyltrisilane was evaluated. The corresponding [3,3]-betweenallene could not be obtained.<sup>21</sup> An unexpected 2:2 adduct (**92**) was isolated as a volatile product with a yield of 16%. The reaction of the 1,3-dichloro-2,2-diphenyltetramethyltrisilane and hexachloropropene with magnesium does not produce hexasila [3,3]-betweenallene. X-ray crystallographic analysis of the structure (**89**) showed a dihedral geometry around the allenic structure with a symmetric conformation. The synthetic procedure to make structure (**89**), hexadecamethyl-2,3,4,5,6,7,8,9,10-octasilabicyclo[4,4,1]undeca-1-(11),6(11)-diene can be described in the following way. A 40 mmol suspension of magnesium powder in THF was added drop wise for one hour to another THF solution containing 2.00 mmol of hexachloropropene (**65**) and 5.00 mmol of 1,4-dichlorooctamethyltetrasilane. An exothermic reaction occurred resulting in the darkening. The THF solution was heated to 50°C for four hours after the addition was completed. THF was removed and hexane was added to the remaining residue. The excess magnesium and the precipitate was filtered and then concentrated. A 34% yield of compound (**89**) was separated from the reaction mixture by gel permeation chromatography. Recrystallization from hexane resulted in formation of colorless crystals with a prism shape and a melting point range of 146.5°C to 147.5°C.

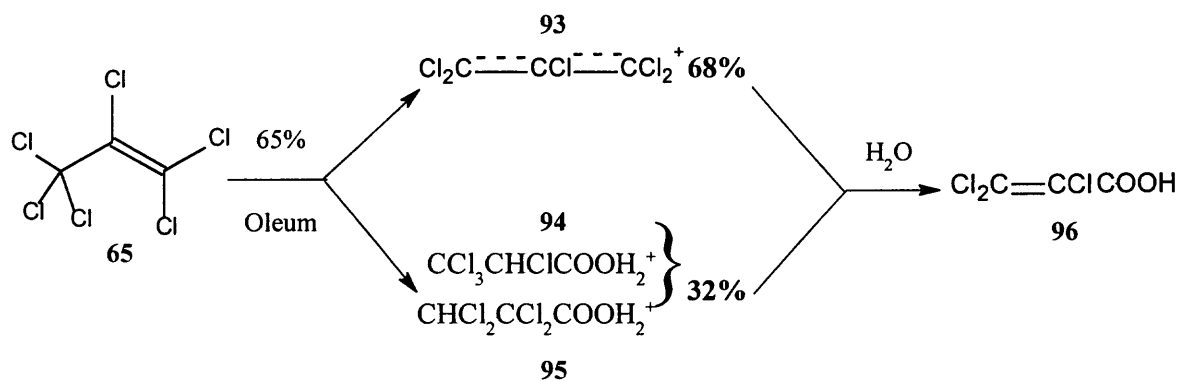


Scheme 18

Work by Deno, Holland, and Schulze<sup>22</sup> on the degradation pathway of hexachloropropene reacting with  $\text{AlCl}_3$  in sulfur trioxide-sulfuric acid is shown in Scheme 19.

Hexachloropropene added to 65% oleum produced two sharp  $^1\text{H}$  NMR bands at 4.40 ppm and 4.70 ppm at the initial time point, both with approximately the same intensity. At the second time point of one hour, the response ratio of the 4.40 ppm and 4.70 ppm changed to 75:25. The third time point taken two days later showed the ratio changing to 78:22. At all three time points the total response of the two peaks remained constant. The reaction with the oleum solution was quenched in ice water to produce trichloroacrylic acid with a yield of 97%. The loss of HCl occurred. An extinction coefficient of  $1.03 \times 10^4$  was calculated

for structures (94) and (95) at the wavelength of 420 m $\mu$  with the additional hexachloropropene. The  $^1\text{H-NMR}$  signal showed that the sum of the peak areas for components (94) and (95) were equivalent to 0.32 mole of hydrogen atom per mole hexachloropropene added. The  $^1\text{H-NMR}$  findings indicate that 68% of the added hexachloropropene reacted to form another component (93) not containing  $\text{H}^+$ . Component (93) was ruled out as hexachloropropene due to fact that it was soluble in the oleum mixture. Two possible structures to consider would be the protonated forms of trichloroacrylic acid and the pentachloroallyl cation. The absorption spectra clearly indicate that the major component (93) formed at 68% was the pentachloroallyl cation with an extinction coefficient of  $1.58 \times 10^4$  at 420 m $\mu$ . This ion (93) is not equilibrium with the other ions (94) and (95), since (94) and (95) change their ratios without changing their total amount. Further studies have shown that hexachloropropene reacts slower with 20% oleum, but were able to produce the  $^1\text{H-NMR}$  signals at 4.40 ppm and 4.70 ppm.

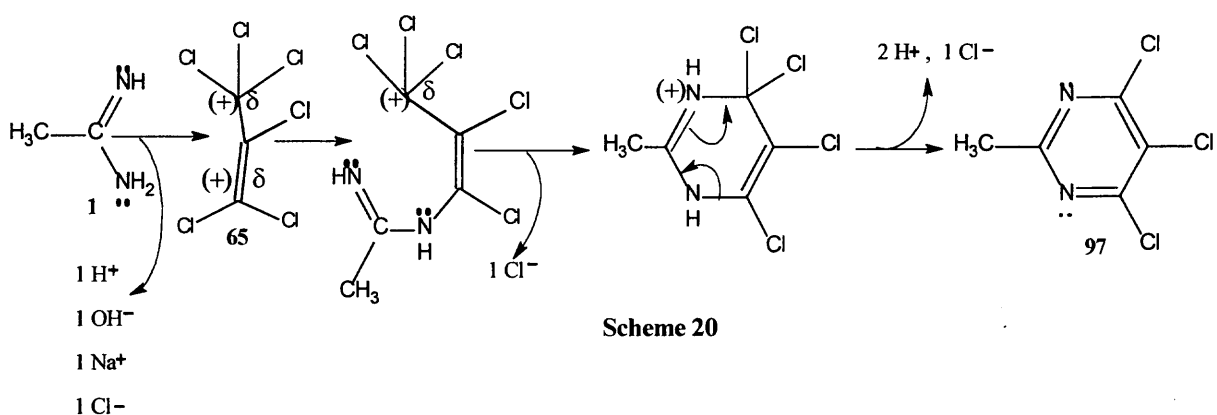


Scheme 19

## CHAPTER 2

### RESULTS AND DISCUSSION

The justification for attempting the prospective reaction of acetamidine hydrochloride (1) with hexachloropropene (65) was to form the compound 2-methyl-3,4,5-trichloropyrimidine (97) by cyclization. This reaction of hexachloropropene with acetamidine was expected to take place by the proposed  $S_N2$  nucleophilic mechanism illustrated in Scheme 20. The molecular formula of (97) is  $C_5H_3Cl_3N_2$  with a molecular



Scheme 20

weight of 197.45. The isolated product was light amber oil at room temperature. The theoretical values for the elemental composition are C (30.41%) H (1.53%) Cl (53.87%) N (14.19%). Experimentally measured values of the isolated oil yielded C (30.45%) H (3.59%) Cl (33.61%) N (9.05%). Serious disagreement between the theoretical and experimental values could be attributed to a low melting point solid that is very slow to crystallize at room temperature and therefore difficult to purify. The presence of a green flame via the flame test indicated the presence of a chlorinated compound. Additional discrepancies in the theoretical versus experimental elemental values can be explained in the following ways:

1. The proposed compound (**97**) could contain impurities that were present at the time of analysis that could not be resolved from the main band on the silica TLC plate.

Several different solvent systems including 100% chloroform, 10% methanol / 90 % hexane, 50% ethyl acetate / 50% hexane were tried with no success. The reason for this lack of band resolution may be attributed to the inability of silica gel to separate closely related basic organic compounds. As an alternative, another solid stationary support such as acid washed alumina might have been appropriate to resolve the base sensitive organic components in the mixture.

2. Another reason for the disagreement between the expected and the observed elemental analyses could be that the product contained the element oxygen originating from the methanolic NaOH. The formation of an oxygenated compound could have resulted during the course of the reaction.
3. Prolonged heating in methanolic NaOH may have promoted a forced degradation of the main product to an olefinic product, as has been frequently observed in bimolecular elimination reactions.

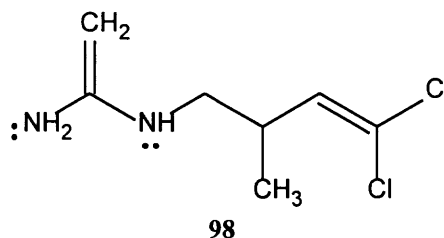
Fourier Transform Infrared Spectroscopy displayed the presence and absence of the following absorption bands. The N-H stretch (**3340  $\text{cm}^{-1}$** ), skeletal ring stretching vibration bands were absent (**1600  $\text{cm}^{-1}$**  and **1300  $\text{cm}^{-1}$** ). The -C=O stretch, N-H bending (**1640  $\text{cm}^{-1}$** ), C-N stretch (**1390  $\text{cm}^{-1}$** ), C-Cl stretch (**850  $\text{cm}^{-1}$**  and **910  $\text{cm}^{-1}$** ) were present. The heteroaromatic substitution bands (**810  $\text{cm}^{-1}$**  to **789  $\text{cm}^{-1}$** ) were absent. The bands for CH<sub>2</sub> rock and the out-of-plane N-H wagging (**720  $\text{cm}^{-1}$** ) were present.

<sup>1</sup>H NMR showed a shift assignment at approximate **2.0 ppm** relative to the TMS internal standard. This assignment could possibly be attributed to such structures as CH<sub>3</sub>-

CO-N-R or -CH-C-Cl. The  $^1\text{H}$  shift assignment of **2.8 ppm** for the methyl proton was absent.

Also, absent were the  $^{13}\text{C}$  NMR shift assignments at **117.59 ppm**, **162.86 ppm**, **170.57 ppm** that clearly indicated that the backbone pyrimidine ring is not present. The methyl carbon at **26.1 ppm** was also absent. Present were the  $^{13}\text{C}$  shift assignments for -C=O (**177.84 ppm**); -CO-NH-R (**168.44 ppm**); =CH- (**130.78 ppm**); =C(Cl)<sub>2</sub> (**120.98 ppm**); -CH<sub>2</sub>- (**23.48 ppm**).

The methyl proton signal at **2.8 ppm** in the  $^1\text{H}$  spectra is also absent. It can, therefore, be concluded that the proposed molecule 2-methyl-3,4,5-trichloropyrimidine (**95**) was not synthesized.

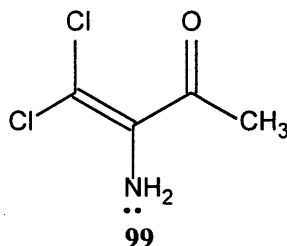


Compound (**98**) is in agreement with the following spectroscopic evidence; FTIR shows absorption bands C-N stretch (**1390 cm<sup>-1</sup>**), C-Cl stretch (**850 cm<sup>-1</sup>** and **910 cm<sup>-1</sup>**) C-N stretch (**1390 cm<sup>-1</sup>**), C-Cl stretch (**850 cm<sup>-1</sup>** and **910 cm<sup>-1</sup>**);  $^{13}\text{C}$  shift assignments at =CH-, (**130.78 ppm**); =C(Cl)<sub>2</sub> (**120.98 ppm**);  $^1\text{H}$  assignments at (**2.0 ppm**) attributed to such structures as -CH-C-Cl. The theoretical elemental values are C (43.10%) H (6.20%) Cl (36.35%) N (14.36%) for this prospective structure (**98**). The experimentally measured values are C (30.45%) H (3.59%) Cl (33.61%) N (9.05%). Unfortunately, the elemental analysis does not correspond well with structure (**98**). This spectroscopic evidence could possibly indicate that another reaction path could have led to formation of compound (**97**). Excessive heating for a prolonged period may have inadvertently cleaved the



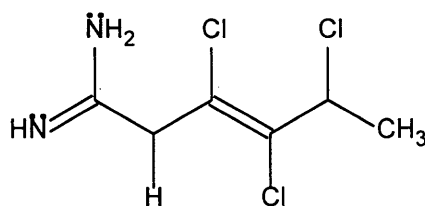
chloropyrimidine ring permitting oxygen from the methanolic NaOH to be incorporated into the reaction path.

FTIR evidence shows that -C=O stretch, N-H bending ( $1640\text{ cm}^{-1}$ ), C-N stretch ( $1390\text{ cm}^{-1}$ ), C-Cl stretch ( $850\text{ cm}^{-1}$  and  $910\text{ cm}^{-1}$ ) were present.  $^{13}\text{C}$  shift assignments were as



follows for -C=O ( $177.84\text{ ppm}$ ); -CO-NH-R ( $168.44\text{ ppm}$ ); =CH- ( $130.78\text{ ppm}$ ); =C(Cl)<sub>2</sub> ( $120.98\text{ ppm}$ ); -CH<sub>2</sub>- ( $23.48\text{ ppm}$ ). The  $^1\text{H}$  assignment of ( $2.0\text{ ppm}$ ) was attributed to both the structures of -CH-C-Cl and CH<sub>3</sub>-CO-N-R. The theoretical elemental values are C (31.20%) H (3.27%) Cl (46.04%) N (9.10%) O (13.38%) for this prospective structure. The experimentally measured values are C (30.45%) H (3.59%) Cl (33.61%) N (9.05%). The elemental analysis does not correspond well with structure (99), despite supporting NMR and FTIR spectroscopic evidence.

The spectroscopic evidence also supports the proposed structure of compound (100). FTIR shows absorption bands C-N stretch ( $1390\text{ cm}^{-1}$ ), C-Cl stretch ( $850\text{ cm}^{-1}$  and  $910\text{ cm}^{-1}$ ) C-N stretch ( $1390\text{ cm}^{-1}$ ), C-Cl stretch ( $850\text{ cm}^{-1}$  and  $910\text{ cm}^{-1}$ ), CH<sub>2</sub> rock, and the out-of-plane N-H wagging ( $720\text{ cm}^{-1}$ ) was present.



100

$^{13}\text{C}$  shift assignment attributed to  $=\text{CH}-$  was (130.78 ppm). A  $^1\text{H}$  assignment of (2.0 ppm) was attributed to  $-\text{CH}-\text{C}-\text{Cl}$ .

Since the oxygen atom was part of the original reaction mass and was not experimentally determined by elemental analysis, an attempt to quantitate its value from the experimentally measured values of C (30.45%) H (3.59%) Cl (33.61%) N (9.05%) was tried. This was done with the objective to propose a new chemical formula. A value of 23.30 percent oxygen was derived by difference from the total elemental composition. From the calculated elemental composition of C (30.45%) H (3.59%) Cl (33.61%) N (9.05%) O (23.30%), a formula of  $\text{C}_4\text{H}_6\text{NCl}_2\text{O}_2$  was postulated. A literature search of the formula index of Beilstein, Chemical Abstracts, and the CRC Handbook of Data on Organic Compounds, 2nd edition was unsuccessful in revealing any known compounds. This can be explained by the fact that the compound was not pure due to a melting point that was less than the room temperature of  $28^\circ\text{C}$ .

In summary, the three structures suggested are alternate compounds that are supported by the spectroscopic evidence as opposed to structure (97), although they are in disagreement with the observed experimental elemental analysis values and the proposed chemical formula of  $\text{C}_4\text{H}_6\text{NCl}_2\text{O}_2$ . Further evaluation of the spectroscopic evidence could yield other prospective structures with various reasons for their formation.

## CHAPTER 3

### EXPERIMENTAL SECTION

#### Synthesis of 2-Methyl-3,4,5-Trichloropyrimidine (95)

Using a 500 MHz Varian spectrometer, the  $^1\text{H}$  and  $^{13}\text{C}$  NMR (125 MHz) spectra were recorded, respectively in deuteromethanol. Chemical shifts are reported in ppm from tetramethylsilane, added as internal standard. The Fourier Transform Infrared spectrum was obtained on a Perkin Elmer Model 1600 spectrometer.

Compound (1), acetamidine HCl 23.3 grams (247.1 mmoles) was reacted with 40 mL of hexachloropropene (63) (283.8 mmoles) in methanolic sodium hydroxide. The methanolic sodium hydroxide was freshly prepared by dissolving 40.0 grams of sodium hydroxide in one hundred milliliters of water, then adding one hundred milliliters of methanol to a total volume of two hundred milliliters. The mixture was transferred to a two hundred fifty milliliter three neck flask while stirring magnetically. The bath temperature was maintained within a range of  $70^\circ\text{C}$  to  $75^\circ\text{C}$  during the initial stirring. The reaction mixture became cloudy and was maintained at  $72^\circ\text{C}$  for seven days resulting in the formation of a precipitate and was sodium chloride. The temperature of the reaction mixture latter equilibrated and remained constant at  $72^\circ\text{C}$  for seven days resulting in the precipitation of a solid. The filtrate was concentrated to approximately 10 mL, yielding a light amber oil. The oil was dissolved in 150 mL of chloroform and transferred to a 500 mL separatory funnel, washed with five 100 mL portions of water to remove any residual sodium chloride. TLC showed minute traces of organic components. The chloroform layer was dried with a  $3\text{\AA}$  molecular sieve overnight. The dried chloroform layer was concentrated to 10 mL to give a dark amber oil. A flame test

was positive for chlorine. The oily extract was dissolved in 10 mL of ethyl acetate and purified by column chromatography (Selecto Scientific 63-200 mesh silica) using a mobile phase consisting of 60% ethyl acetate and 40% hexane. This attempted purification was carried out without success.

The FTIR spectra,  $^{13}\text{C}$  and  $^1\text{H}$  NMR spectra, and elemental analysis were determined. The calculated value for the empirical formula of  $\text{C}_5\text{H}_3\text{N}_2\text{Cl}_3$  is C (30.41%) H (1.53%) Cl (53.87%) N (14.19%). Found were C (30.45%) H (3.59%) Cl (33.61%) N (9.05%). The following absorption bands were displayed: N–H stretch (**3340  $\text{cm}^{-1}$** ), skeletal ring stretching vibration bands (**1600  $\text{cm}^{-1}$  and 1300  $\text{cm}^{-1}$** ) -C=O stretch, N–H bending (**1640  $\text{cm}^{-1}$** ), C–N stretch (**1390  $\text{cm}^{-1}$** ), C–Cl stretch (**850  $\text{cm}^{-1}$  and 910  $\text{cm}^{-1}$** ),  $\text{CH}_2$  rock, out-of-plane N–H wagging (**720  $\text{cm}^{-1}$** ).

The  $^1\text{H}$  spectrum was obtained under decoupled conditions. The 2.0 ppm shift assignment relative to the TMS internal standard could possibly be attributed to such structures as  $\text{CH}_3\text{-CO-N-R}$  or  $\text{-CH-C-Cl}$ . Various  $^{13}\text{C}$  NMR shift assignments were present for –C=O (**177.84 ppm**), -CO-NH-R (**168.44 ppm**), =CH– (**130.78 ppm**), =C(Cl)<sub>2</sub> (**120.98 ppm**), –CH<sub>2</sub>– (**23.48 ppm**).

## CHAPTER 4

### CONCLUSIONS

The author attempted a novel synthesis of an analog of the chloropyrimidine molecule by ring closure via hexachloropropene and acetamidine HCl. It apparently did not succeed.

For future investigations into this synthesis, the author proposes the following.

1. Reduce the heating time from one hundred sixty-eight hours to a time not to exceed perhaps twenty-four hours.
2. The use of an aprotic solvent such as dimethyl sulfoxide or dimethyl formamide known to enhance the rates of nucleophilic substitution reactions.
3. Purification of the reaction mixture with acid washed alumina support as opposed to silica support to resolve the base sensitive organic components.
4. The use of a Kuglerohr distillation apparatus (Sigma Cat.No. Z40,113-7) to purify a low melting point solid that I was unable to crystallize by conventional means.

## REFERENCES

1. V. Nenajdenko, A. Sanin, V. Kuz'min, E. Balenkova; Russian Journal of Organic Chemistry, vol.32, 1996, pp.1529-1539.
2. D. Dopp, A. M. Gomaa, G. Henkel, and A.M. Nour El-Din; Journal of Heterocyclic Chemistry, 1995, vol.32, pp.603-610.
3. C. Saturnino, M. Abarghaz, M. Schmitt, C. Wermuth, and J. Bourguignon; Heterocycles, 1995, vol.41, pp.1491-1502.
4. J. Brandenburg, C. Kaepplinger, and R. Beckert; Synthesis, 1996, vol.11, pp.1302-1304.
5. N. Hamamichi and T. Miyasaka; Journal of Heterocyclic Chemistry, 1990, vol.27, pp.835-838.
6. P. Schenone, L. Sansebastiano, and L. Mosti; Journal of Heterocyclic Chemistry, 1990, vol.27, pp.295-305.
7. P. Schenone, L. Sansebastiano, and L. Mosti; *ibid.*
8. K. Takagi, A. Bajnati, and M. Hubert-Habart; Journal of Heterocyclic Chemistry, 1994, vol.31, pp.973-976.
9. D. Boykin, A. Kumar, M. Bajic, G. Xiao, and W. Wilson; European Journal of Chemistry and Therapeutics, 1997, vol.32, pp.965-972.
10. V. Ahluwalia, C. Gupta, and C. Khanduri; Indian Journal of Chemistry, 1992, vol.31B, pp.355-356.
11. J. Redd, J. Bradshaw, P. Huszthy, and R. Izatt; Journal of Heterocyclic Chemistry, 1994, vol.31, pp.1047-1052.
12. R. Roberts, S. Landor, and E. Bolessa; Tetrahedron Letters, 1994, vol.35, pp.3021-3024.
13. R. Roberts, S. Landor, and E. Bolessa; *ibid.*
14. M. Newman and S. Schiff; Journal of the American Chemical Society, 1959, vol.81, pp.2266-2270.
15. A. Fujino, Y. Nagata, and T. Sakan; Bulletin of the Chemical Society of Japan, 1965, vol.38, pp.295-301.
16. A. Fujino, Y. Nagata, and T. Sakan; *ibid.*

17. G. Motsarew, V. Inshakowa, A. Raskina, V. Rosenberg, and V. Kolbasov; *Journal of General Chemistry of the USSR*, **1990**, vol.334, pp.669-675.
18. W. Hale, *Canadian Journal of Chemistry*, **1966**, vol.44, pp.1100-1101.
19. J. Jochims, A. Hamed, and M. Al-Talib; *Journal of Practical Chemistry*, **1992**, vol.334, pp.669-675.
20. T. Shimizu, F. Hojo, and W. Ando; *Journal of the American Chemical Society*, **1993**, vol.115, pp.3111-3115.
21. T. Shimizu, F. Hojo, and W. Ando; *ibid.*
22. N. Deno, G. Holland, and T. Schulze; *Journal of Organic Chemistry*, **1966**, vol.32, pp.1496-1498.