TRIMETHYLSILYLBROMOKETENE AND REACTIONS OF α-HALOACID HALIDES WITH DIISOPROPYLCARBODIIMIDE

DISSERTATION

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By

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Trimethylsilylbromoketene was synthesized by the triethylamine dehydrohalogenation of trimethylsilylbromoacetyl bromide or chloride. This ketene was found not to undergo cycloaddition reactions with activated olefins, such as cyclopentadiene, ethyl vinyl ether and dihydropyran. The ketene cycloadded to tert-butylbenzylimine to yield 1-tert-butyl-3-bromo-4-phenyl-3-trimethylsilyl-2-azetidinone. in the absence of triethylamine the trimethylsilylbromoacetyl bromide reacted with two equivalents of the imine to yield the nonsilylated 3-bromo-1-tert-butyl-4-phenyl-2-azetidinone.

Attempts to effect cycloaddition of trimethylsilylbromoketene with diisopropylcarbodiimide were unsuccessful. In every instance the nonsilylated 3-bromo-1-isopropyl-4-isopropylimino-2-azetidinone was the product isolated. The best yield of this azetidinone was obtained when the acid chloride was allowed to react with the carbodiimide yielding 1-chloro-N-(trimethylsilylbromoacetyl)-N,N'-diisopropylformamidine which was dehydrohalogenated with triethylamine to yield the azetidinone.

The above procedure was applied to the chloroformamidines generated from the reactions of chloroacetyl chloride, 2-chloropropanoyl chloride and dichloroacetyl chloride with

diisopropylcarbodiimide. The triethylamine dehydrohalogenation of these chloroformamidines yielded the substituted 2-azetidinones. The yields of azetidinones by this method was a considerable improvement over previously reported methods.

The ring closure of the formamidines to the azetidinones is believed to proceed via an enolate anion. This enolate can undergo intramolecular displacement of a chloride ion to form the azetidinone or eliminate a chloride ion forming the halogenated ketene and the carbodiimide followed by subsequent cycloaddition to the azetidinone.

1-Chloro-N-(trimethylsilylbromoacetyl)-N,N'-diisopropylformamidine was hydrolyzed to N-(trimethylsilylbromoacetyl)-N,N'-diisopropylurea. This urea yielded 3-isopropyl-2-isopropylimino-5-oxazolidinone when heated slightly above its melting point for one hour. If the chloroformamidine was allowed to stand at room temperature a polymeric tar formed which was hydrolyzed to yield 3-isopropyl-2-isopropylimino-4-oxazolidinone.

The chloroformamidines from the reactions of chloroacetyl chloride, 2-chloropropanoyl chloride and 2-chloro-2-methylpropanoyl chloride with diisopropylcarbodimide were hydrolyzed to the respective acylureas. Heating these acylureas to slightly above their melting points yielded substituted 5-oxazolidinones. N-(Chloroacetyl)-N,N'-diisopropylformamidine was hydrolyzed in the presence of triethylamine to

yield 3-isopropyl-2-isopropylimino-4-oxazolidinone. The mechanism proposed for the ring closure of the acylureas to the 4- and 5-oxazolidinones is by the intramolecular nucleophilic displacement of the alpha-halogen on the acyl group.

3-Isopropyl-2-isopropylimino-5-oxazolidinone was treated with aqueous base to yield the rearrangement product 1,3-diisopropyl-1,3-diazolidine-2,4-dione. Air hydrolysis of 3-isopropyl-2-isopropylimino-4-methyl-5-oxazolidinone yielded the 1,3-diazolidine-2,4-dione along with 3-isopropyl-4-methyl-2,5-oxazolidinedione.

The alpha-halogen on the acyl group is necessary for the formation of the 2-azetidinones from chloroformamidines and of oxazolidinones from acylureas.

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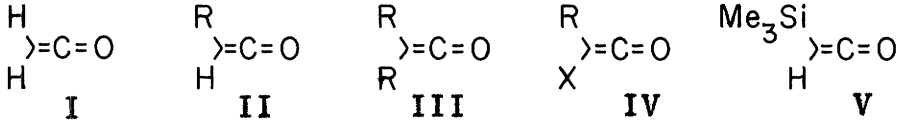
CHAPTER I

INTRODUCTION

Ketenes consist of the group of compounds containing carbon-carbon-oxygen cumulative double bonds. The first reported account of synthesizing a ketene was in 1905 by Staudinger.[1]

Ketenes are classified on the basis of the substituents on the ketene fuctionality. The simplest member of this group or class of compounds is referred to simply as ketene (I). An aldoketene (II) is a monosubstituted ketene, and a ketoketene (III), a disubstituted ketene. Halogenated ketenes (IV) are defined as ketenes which have a halogen atom directly bonded to the ketene functionality. Organometallic ketenes have a metal atom bonded to the ketene functionality, such as trimethylsilylketene (V).

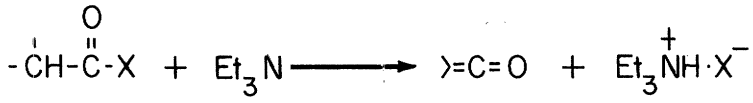


I II III IV V

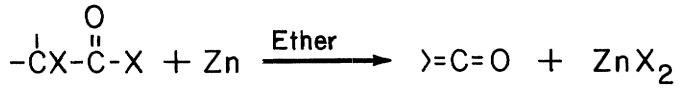
The reactivity of a ketene is dependent upon the substituent attached to the ketene functionality. Ketene is a gas and can be isolated but is quite suseptible to dimerization.[2] Aldoketenes are generally quite unstable and

exist in solution only short periods of time prior to dimerization.[3] Ketoketenes are considered the most stable ketenes and can generally be isolated and stored in the cold. Halogenated ketenes are extremely reactive and tend to polymerize readily. Therefore, reactions involving halogenated ketenes are in situ reactions; whereby, the ketenes are trapped in solution. Sterically hindered halogenated ketenes, such as tert-butylchloroketene, have been observed in solution.[4] Organometallic ketenes have been found to exhibit very unusual stability; for instance, trimethylsilylketene, an aldoketene, may be stored neat in a refrigerator for several weeks.[5]

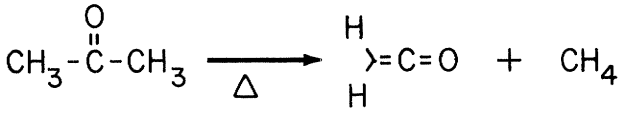
Ketenes may be synthesized by several general methods, but the most widely used method involves the triethylamine dehydrohalogenation of an appropriately substituted acid halide.[6] The dehydrohalogenations are usually accomplished in a hydrocarbon solvent and the amine salt precipitates resulting in a hydrocarbon solution of the ketene.

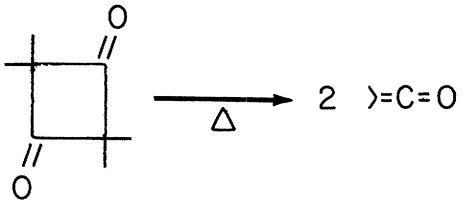


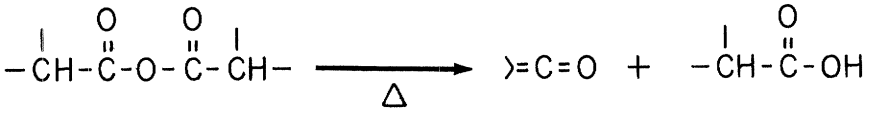
Another widely used method involves the zinc dehalogenation of an α-haloacid halide in an ether solution.

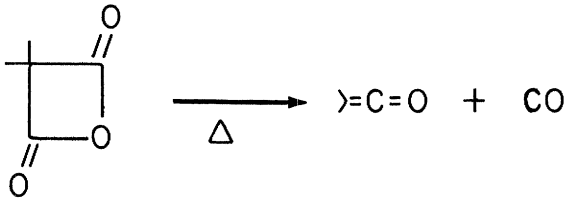


Pyrolysis of compounds which can eliminate a small molecule to yield a ketene is a method used for generating low molecular weight, stable ketenes.[7-10]

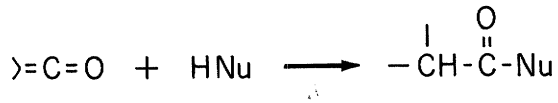




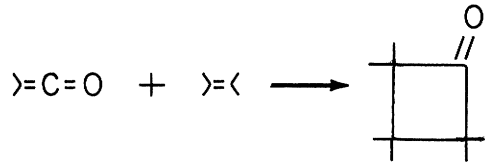




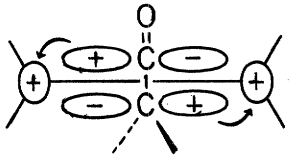
There are two principle types of reactions which ketenes undergo; these are nucleophilic addition and cycloaddition reactions. The nucleophilic addition of amines, alcohols, acids, water, etc., to ketenes is a common method of acylation.[11]



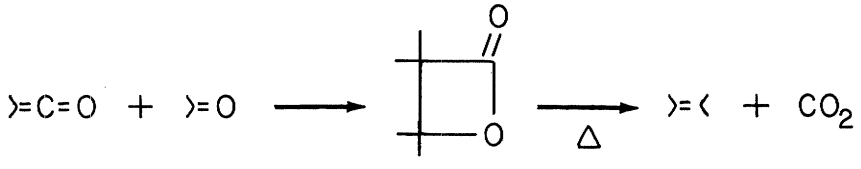
Ketenes undergo cycloaddition reactions with unsaturated compounds, such as olefins, carbonyl compounds, imines and carbodiimides. The cycloaddition of a ketene with an olefin yields a cyclobutanone.[12-15] The cyclobutanone arises from



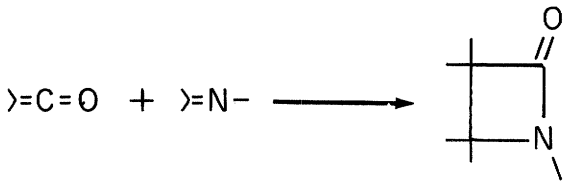
a (2+2) cycloaddition process exclusively, even with conjugated dienes. The mechanism has been described by Woodward and Hoffmann as a thermally [π2s+π2a] concerted process.[25] The conservation of orbital symmetry dictates that there must be an orthogonal approach in which the π system of the ketene acts in an antarafacial manner and the π system of the olefin, in a suprafacial manner.



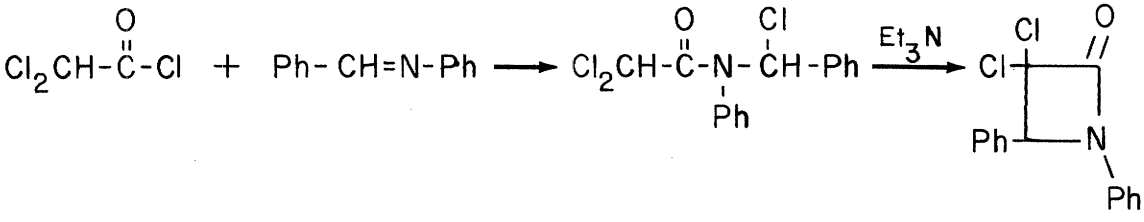
Ketenes undergo cycloaddition reactions with carbonyls to produce 2-oxetanones (β-lactones) which are susceptible to decarboxylation when heated.[16-18,26]



The cycloaddition of ketenes and imines to form 2-azetidinones (β-lactams) dates back to the early investigations of Staudinger.[19,20,27] Duran and Ghosez have reported the cycloaddition of chloro- and dichloroketene



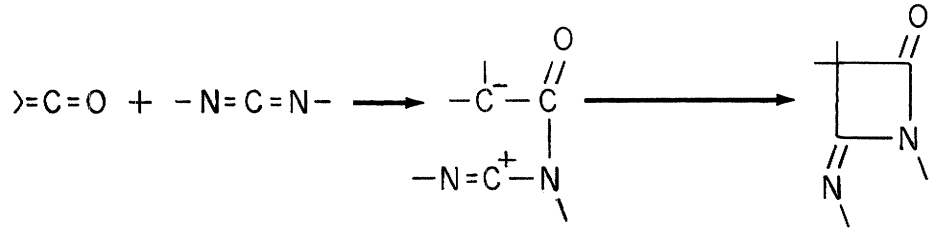
with various imines.[28] Dichloroacetyl chloride was reacted with an imine to produce the amide which is the addition product of the acid halide to the carbon-nitrogen double bond of the imine. Treatment of this amide with



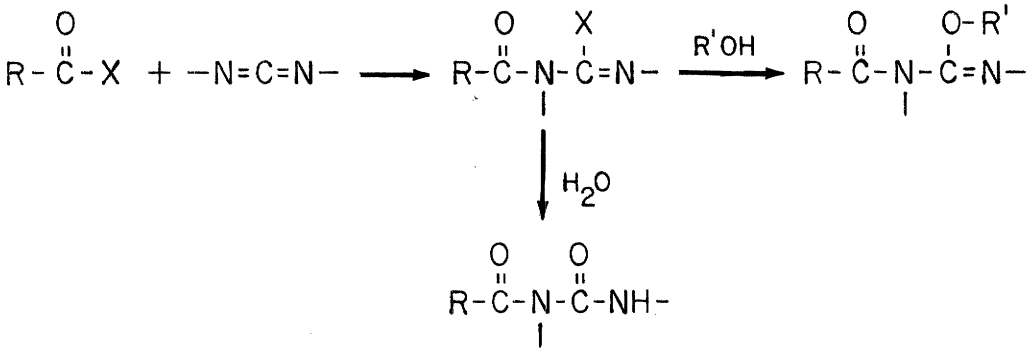
triethylamine gave a poor yield of the 2-azetidinone as compared to conditions where the dichloroketene was generated in the presence of the imine. Due to the drastic decrease in yield, the amide formation was not considered to be a major intermediate to 2-azetidinone formation.

The products of the reactions of ketenes and carbodiimides are 4-imino-2-azetidinones.[21-24] The reaction mechanism of the cycloaddition of ketenes to carbodiimide

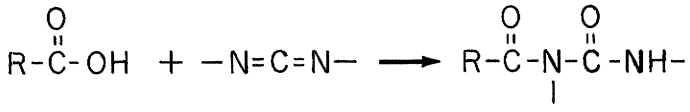
has been shown to be a two step process involving a 1,4-zwitterionic intermediate.[24]

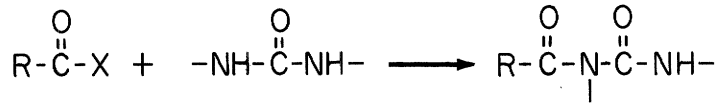


Acid halides react with carbodiimides to form N-acyl-chloroformamidines which react with alcohols to yield O-alkyl-N-acylisoureas and with water to yield N-acyl-ureas.[29,30] N-Acylureas may also be produced by the

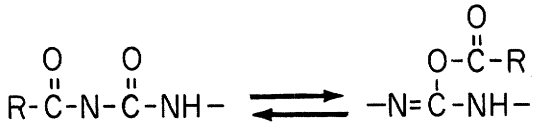


controlled reaction of acids with carbodiimides and by the reaction of an acid halide with an appropriately substituted urea.[31-38]

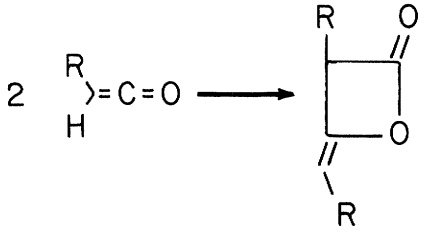


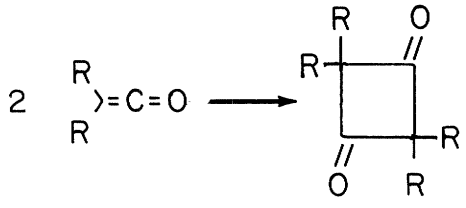


N-Acylureas readily rearrange to O-acylisoureas depending upon reaction conditions. The urea is favored under basic conditions.[32,33,37]



Ketenes react with themselves to form dimers and polymers. Aldoketenes generally undergo thermal dimerization to yield 2-oxetanones, and ketoketenes generally dimerize to 1,3-cyclobutanediones.[2,39,40] Halogenated ketenes do not





undergo homodimerization but some mixed dimers involving halogenated ketenes and dialkylketenes have recently been synthesized.[41] Halogenated ketenes are very susceptible to polymerization and in essentially all reactions involving haloketenes some oil and/or tar is produced.

Organometallic ketenes, which were first reported in 1965, are generally synthesized by the thermal decomposition of an ethoxyacetylene. This reaction applies to metal

$$EtO\text{-}C{\equiv}C\text{-}MR_3 \xrightarrow[\Delta]{} \begin{matrix} R_3M \\ H \end{matrix}\!\!>\!=C=O$$

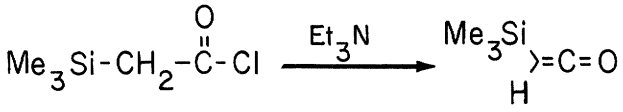
atoms, such as silicon, germanium and tin. The bis-substituted and mixed organometallic ketenes may be generated by performing the decomposition in the presence of a trialkylmetal halide, such as chlorotrimethylsilane and bromotrimethylgermanium.[5,42-44]

$$EtO\text{-}C{\equiv}C\text{-}MR_3 + R'_3M'\text{-}X \xrightarrow[\Delta]{} \begin{matrix} R_3M \\ R'_3M' \end{matrix}\!\!>\!=C=O$$

Trimethylsilylketene has been the most studied of the organometallic ketenes and is usually prepared by the ethoxyacetylene method.[5,43]

$$EtO\text{-}C{\equiv}C\text{-}H \xrightarrow[2.\ Me_3SiCl]{1.\ MeLi} EtO\text{-}C{\equiv}C\text{-}SiMe_3 \xrightarrow{120^\circ} \begin{matrix} Me_3Si \\ H \end{matrix}\!\!>\!=C=O$$

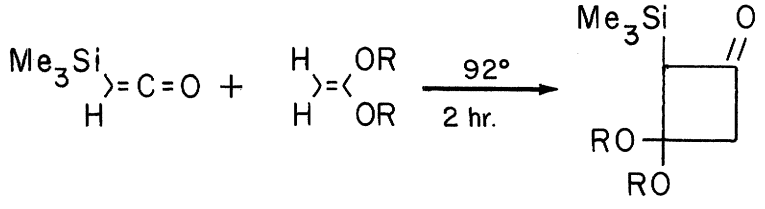
An alternate method for generating trimethylsilylketene is the dehydrohalogenation of trimethylsilylacetyl chloride



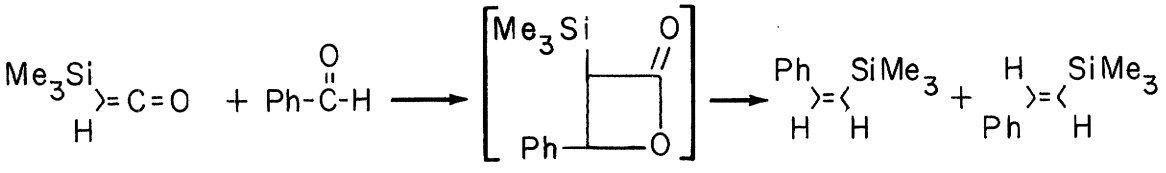
with triethylamine. The yield, however, is quite low.[45]

Trimethylsilylketene is unique among ketenes because of the extraordinary stability of this aldoketene. Trimethylsilylketene has been shown to be a powerful acylating agent for hindered amines and alcohols. Efforts to obtain cycloadditions with olefinic compounds such as cyclopentadiene, ethyl vinyl ether, cyclohexene, etc., have proved futile.[5]

The cycloaddition of trimethylsilylketene and ketene acetals has been reported to occur under rather vigorous conditions.[46] Also, the condensation of trimethylsilylketene

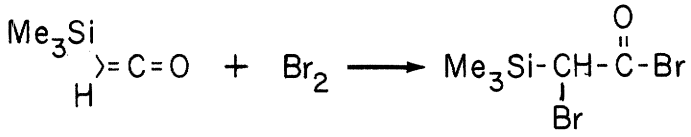


with benzaldehyde gave <u>cis</u>- and <u>trans</u>-trimethylsilylstyrene



which presumably involved cycloaddition to form the 2-oxetanone which decarboxylated to yield the olefins.[47]

Trimethylsilylketene adds bromine readily to the carbon-carbon double bond to produce trimethylsilylbromoacetyl bromide.[43]



The original objective of this investigation was to synthesize and study trimethylsilylhaloketenes in order to learn more about the novel effect of the trimethylsilyl group upon the ketene functionallity. During the course of some reactions of trimethylsilylbromoketene, some unexpected results were discovered in the reactions of diisopropylcarbodiimide and trimethylsilylbromoacetyl bromide. Consequently, the objective was modified to include an investigation into the reactions of α-haloacid halides and carbodiimides.

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CHAPTER II

EXPERIMENTAL

Infrared (ir) spectral data were obtained on Perkin-Elmer Model 237 and Beckman Model 33 grating infrared spectrometers. Spectra were obtained using neat samples, suspensions in potassium bromide discs or fluorolube oil, and in carbon tetrachloride solutions. Sodium chloride discs were used for neat samples and mulls, and fixed thickness sodium chloride cells of 0.1 mm thickness were used for the solution samples.

Nuclear magnetic resonance (nmr) spectra were recorded on Hitachi Perkin-Elmer R24B and JEOL PSM-100 spectrometers. Tetramethylsilane was used as an internal standard for all spectra except for the compounds with a trimethylsilyl group.

Vapor phase chromatography separations were achieved using a 10 ft. by 0.25 in. outside diameter glass column packed with 10% SE-30 on Chromosorb WAW, 60/80 mesh in a Varian 1525B Gas Chromatograph with a thermal conductivity detector.

Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-6E Double Focusing Mass Spectrometer.

Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Indiana.

Preparation of Reagents

Solvents were dried and purified by distillation from sodium-potassium alloy under nitrogen atmosphere prior to use. Commercially available triethylamine was dried over sodium metal and distilled prior to use.

N-tert-Butylbenzylimine was prepared from benzaldehyde and tert-butylamine according to standard procedures.[1] N,N'-Diisopropylcarbodiimide was commercially available and used without further purification. Cyclopentadiene was obtained by thermally cracking commercially available dicyclopentadiene at about 140° and used immediately. Ethyl vinyl ether and dihydropyran were commercially available and distilled just prior to use.

Acetyl chloride was commercially available and used without further purification. Chloroacetyl chloride, dichloroacetyl chloride and 2-chloropropanoyl chloride were prepared by reacting the appropriate commercially available acid with thionyl chloride.[2-4] 2-Bromo-2-methylpropanoyl chloride was prepared by the α-bromination of commercially available isobutyryl chloride with molecular bromine by standard procedures.[5] The structures of the resulting acid halides were confirmed by the nmr spectra and by agreement of the observed boiling points with those reported in the literature.

Preparations of Trimethylsilated Reagents

Trimethylsilated reagents which were not commercially available were prepared from available starting material as described below.

Trimethylsilylketene[6]

To 14 g (0.2 m) of ethoxyacetylene in 500 ml of dry ethyl ether at -78° under a nitrogen atmosphere was added 81 ml (0.2 m) of 2.25 M methyllithium. The reaction was allowed to stir for thirty minutes and then 22 g (0.2 m) of trimethylchlorosilane was added. The reaction was stirred for an additional eight hours and allowed to come to room temperature. The mixture was then allowed to set until the salt precipitate had settled. The solution was decanted very carefully and the ether evaporated on a rotary evaporator. The residue was then subjected to a 0.1 Torr vacuum and the ethoxy(trimethylsilyl)acetylene collected in the vacuum trap. This acetylene was then heated ot 120° and the trimethylsilylketene distilled. Redistillation gave 11.4 g of ninety per cent pure trimethylsilylketene (50% yield). Bp., 82°; ir, 2110 cm^{-1}; nmr (CCl_4), δ, 0.00 (s, 9 H), 1.46 (s, 1 H).

Trimethylsilylacetic Acid[7]

To 5 g (0.2 m) of magnesium in dry ether under nitrogen was added 12 g (0.1 m) of chloromethyltrimethylsilane. (Methylmagnesium bromide was often added to initiate the

reaction.) After four hours the reaction was poured onto crushed dry ice and allowed to warm to room temperature. Dilute hydrochloric acid was added until the water layer was acidic, then the ether layer was separated and dried over calcium chloride. The ether was evaporated and 12 g of acid obtained (91% yield). Mp., 42°; ir, 3020 and 1690 cm^{-1}; nmr (CCl_4), δ, 0.00 (s, 9 H), 1.70 (s, 2 H), 11.80 (s, 1 H).

Trimethylsilylbromoacetyl Bromide[8]

A carbon tetrachloride solution of bromine was added to trimethylsilylketene in carbon tetrachloride until the bromine color persisted indicating the complete formation of acid bromide. Ir, 1800 cm^{-1}; nmr, (CCl_4), δ, 0.00 (s, 9 H), 3.78 (s, 1 H).

Trimethylsilylchloroacetyl Chloride

A carbon tetrachloride solution of chlorine was added to trimethylsilylketene in carbon tetrachloride until the ketene band in the ir disappeared. The excess chlorine was removed by bubbling nitrogen through the solution. Ir, 1795 cm^{-1}.

Reactions of Trimethylsilylhaloacetyl Halides

Trimethylsilylhaloacetyl halides were found to react in the manner described in the following section.

Trimethylsilylbromoketene

A 1.4 ml (0.01 m) portion of triethylamine in 10 ml of hexane was added dropwise with stirring at room temperature to 0.01 m of trimethylsilylbromoacetyl bromide (prepared from 1.1 g (0.01 m) of trimethylsilylketene) in 50 ml of hexane. The formation of ketene was evidenced by an ir band at 2114 cm^{-1}.

Trimethylsilylchloroketene

A 1.4 ml (0.01 m) portion of triethylamine in 10 ml of hexane was added dropwise with stirring at room temperature to 0.01 m of trimethylsilylchloroacetyl chloride in 50 ml of hexane. The formation of ketene was evidenced by an ir band at 2105 cm^{-1}.

1-tert-Butyl-3-trimethylsilyl-3-bromo-4-phenyl-2-azetidinone

To a refluxing solution of 0.01 m of trimethylsilylbromoacetyl bromide in 60 ml of heptane was added 3.2 g (0.02 m) of N-tert-butylbenzylimine followed immediately by the dropwise addition of 1.4 ml (0.01 m) of triethylamine. After refluxing overnight, the amine salt was removed by filtration and the solvent removed on a rotary evaporator. The residue crystallized to give 2.0 g of azetidinone (56% yield) and purification was accomplished by sublimation. Mp., 169°; ir, 1733 cm^{-1}; nmr (CCl_4), δ, 0.00 (s, 9 H), 1.00 (s, 9 H), 4.45 (s, 1 H) and 7.03 (s, 5 H). Mass spectrum parent peak m/e 353 and 355.

Analysis: Calculated for $C_{16}H_{24}BrNOSi$: C, 54.23; H, 6.78; N, 3.95. Found: C, 54.14; H, 6.90; N, 3.90.

3-Bromo-1-tert-butyl-4-phenyl-2-azetidinone

To a refluxing solution of 0.01 m of trimethylsilyl-bromoacetyl bromide in heptane was added 3.2 g (0.02 m) of N-tert-butylbenzylimine. After refluxing overnight, the imine salt was removed by filtration and the solvent removed on a rotary evaporator. The residue crystallized to 2.3 g of azetidinone (80% yield) and purification was by sublimation. Mp., 124°; ir, 1745 cm^{-1}; nmr (CCl_4), δ, 1.25 (s, 9 H), 4.90 (s, 1 H), 4.95 (s, 1 H) and 7.30 (s, 5 H). Mass spectrum parent peak m/e 281 and 283.

Analysis: Calculated for $C_{13}H_{16}BrNO$: C, 55.33; H, 5.72; N, 4.96. Found: C, 55.16; H, 5.72; N, 4.69.

3-Bromo-1-isopropyl-4-isopropylimino-2-azetidinone

To a refluxing solution of 0.01 m of trimethylsilyl-bromoacetyl bromide in heptane was added 2.7 ml (0.15 m) of diisopropylcarbodiimide followed by the immediate dropwise addition of 1.4 ml (0.01 m) of triethylamine with stirring. After refluxing for three hours, the salt was removed by filtration and the solvent evaporated. The residue distilled at 72° at 0.25 Torr to give 2.2 g of azetidinone (90% yield). Ir, 1700 and 1850 cm^{-1}; nmr (CCl_4), δ, 1.11 and 1.16 (two d, 6 H), 1.38 (d, 6 H), 3.70 (m, 2 H) and 4.92 (s, 1 H).

Analysis: Calculated for $C_9H_{14}Br_2N_2O$: C, 33.16; H, 4.33; N, 8.59. Found: C, 33.46; H, 4.37; N, 8.56.

N-(Trimethylsilylbromoacetyl)-N,N'-diisopropylurea

To 0.01 m of trimethylsilylbromoacetyl chloride in 50 ml of ether was added 1.8 ml (0.01 m) of diisopropylcarbodiimide at room temperature with stirring. After thirty minutes, 1-chloro-N-(trimethylsilylbromoacetyl)-N,N'-diisopropylformamidine had formed as evidenced by the carbonyl and carbon-nitrogen double bond at 1709, 1695 and 1670 cm^{-1} in the ir spectrum of the reaction solution. A 10 ml portion of water was added and after fifteen minutes, the reaction mixture was filtered to remove the N,N'-diisopropylurea. The ether layer was separated, dried over calcium chloride and evaporated to give 2.5 g of acylurea (74% yield) which was purified by sublimation at room temperature in vacuuo. Mp., 67°; ir, 1705 and 1660 cm^{-1}; nmr (CCl_4), δ, 0.00 (s, 9 H), 1.05 (d, 6 H), 1.18 (d, 6 H), 3.43 (s, 1 H), 3.9 (m, 2 H) and 6.6 (broad s, 1 H).

Analysis: Calculated for $C_{12}H_{25}BrN_2O_2Si$: C, 42.73; H, 7.47; N, 8.30. Found: C, 42.54; H, 7.46; N, 8.48.

3-Isopropyl-2-isopropylimino-5-oxazolidinone

A 2.0 g (0.006 m) portion of N-(trimethylsilylbromoacetyl)-N,N'-diisopropylurea was heated to 70° for one hour to give 1.1 g of 5-oxazolidinone (100% yield). Infrared and nmr spectra were identical with an authentic sample.

3-Isopropyl-2-isopropylimino-4-oxazolidinone

To 0.01 m of trimethylsilylbromoacetyl bromide in hexane was added just enough diisopropylcarbodiimide to react with all of the acid bromide as evidenced by the loss of the acid halide carbonyl at 1800 cm^{-1}. The solvent was evaporated to leave a colorless viscous liquid which turned to a scarlet polymer-like material on standing at room temperature overnight. This material was insoluble in hexane, carbon tetrachloride, chloroform and ether. Triethylamine, also, had no effect. Upon adding water there was an immediate reaction. An oil formed on the top of the water and was extracted with ether. The ether was dried over calcium chloride and evaporated to give 1.0 g of 4-oxazolidinone (56% yield). Infrared and nmr spectra were identical with an authentic sample.

Attempted Cycloaddition of Trimethylsilylbromoketene with 1,3-Cyclopentadiene

To a refluxing solution of 0.01 m of trimethylsilylbromoacetyl bromide in heptane was added 2.6 g (0.04 m) of freshly prepared cyclopentadiene followed immediately by the addition of 1.4 ml (0.01 m) of triethylamine. Trimethylsilylbromoketene was formed as evidenced by ir and disappeared after refluxing overnight. No evidence for the formation of the cyclobutanone cycloadduct was observed. A polymeric tar remained after filtering the salt and evaporating the solvent.

Attempted Cycloaddition of Trimethylsilylbromoketene with Ethyl Vinyl Ether

To a refluxing solution of 0.01 m of trimethylsilylbromoacetyl bromide in heptane was added 1.4 g (0.02 m) of ethyl vinyl ether followed immediately by the addition of 1.4 ml (0.01 m) of triethylamine. Trimethylsilylbromoketene was formed as evidenced by ir and disappeared after refluxing overnight. No evidence for the formation of cyclobutanone cycloadduct was observed and a polymeric tar was obtained after filtering the salt and evaporating the solvent.

Attempted Cycloaddition of Trimethylsilylbromoketene with Dihydropyran

To a refluxing solution of 0.01 m of trimethylsilylbromoacetyl bromide in heptane was added 1.7 g (0.02 m) of dihydropyran followed immediately by the addition of 1.4 ml (0.01 m) of triethylamine. Trimethylsilylbromoketene was formed as evidenced by ir and disappeared after refluxing overnight. No evidence for the formation of cyclobutanone cycloadduct was observed and a polymeric tar was obtained after filtering the salt and evaporating the solvent.

Reactions of α-Haloacid Halides with N,N'-Diisopropylcarbodiimide

3-Chloro-1-isopropyl-4-isopropylimino-2-azetidinone

To 8.9 ml (0.05 m) of diisopropylcarbodiimide in 60 ml of tetrahydrofuran was added 2.0 ml (0.025 m) of chloroacetyl chloride with stirring at room temperature. An ir spectrum

of the reaction solution revealed the loss of the acid chloride carbonyl at 1760 cm^{-1} and the appearance of the 1-chloro-N-(chloroacetyl)-N,N'-diisopropylformamidine carbonyl and carbon-nitrogen double bond at 1695 and 1670 cm^{-1}, respectively. The solution was brought to reflux and 7.0 ml (0.05 m) of triethylamine added dropwise with stirring. After refluxing for three hours, the amine salt was removed by filtration and the solvent evaporated. The residue was dissolved in carbon tetrachloride and poured into dilute hydrochloric acid to hydrolyze the excess carbodiimide to the N,N'-diisopropylurea. The insoluble urea was filtered, the carbon tetrachloride solution evaporated and the residue distilled to give 3.3 g of azetidinone (65% yield). Bp., 65° at 0.01 Torr; ir, 1830 and 1710 cm^{-1}; nmr (CCl_4), δ, 1.16 and 1.18 (two d, 6 H), 1.38 (d, 6 H), 3.7 (m, 2 H) and 5.06 (s, 1 H). Mass spectrum parent peak m/e 202 and 204.

Analysis: Calculated for $C_9H_{15}ClN_2O$: C, 53.33; H, 7.46; N, 13.82. Found: C, 53.08; H, 7.20; N, 14.06.

3-Chloro-1-isopropyl-4-isopropylimino-3-methyl-2-azetidinone[9]

To 8.9 ml (0.05 m) of diisopropylcarbodiimide in 60 ml of tetrahydrofuran was added 2.6 ml (0.025 m) of 2-chloropropanoyl chloride with stirring at room temperature. An ir spectrum of the reaction solution revealed the loss of the acid chloride carbonyl at 1760 cm^{-1} and the appearance of the 1-chloro-N-(2-chloropropanoyl)-N,N'-diisopropylformamidine carbonyl and carbon-nitrogen double bond at

1695 and 1675 cm^{-1}, respectively. The solution was brought to reflux and 7.0 ml (0.05 m) of triethylamine added dropwise with stirring. After refluxing for three hours, the amine salt was removed by filtration and the solvent evaporated. The residue was dissolved in carbon tetrachloride and poured into dilute hydrochloric acid to hydrolyze the excess carbodiimide to the N,N'-diisopropylurea. The insoluble urea was filtered and the carbon tetrachloride solution dried over calcium chloride and evaporated. The residue crystallized to give 3.8 g of azetidinone (70% yield); purification was by sublimation. Mp., 47°; ir, 1815 and 1708 cm^{-1}; nmr (CCl_4), δ, 1.13 and 1.18 (two d, 6 H), 1.40 (d, 6 H), 1.82 (s, 3 H) and 3.8 (m, 3 H). Mass spectrum parent peak m/e 216 and 218.

Analysis: Calculated for $C_{10}H_{17}ClN_2O$: N, 12.93. Found: N, 12.71.

3,3-Dichloro-1-isopropyl-4-isopropylimino-2-azetidinone

To 8.9 ml (0.05 m) of diisopropylcarbodiimide in 60 ml of tetrahydrofuran was added 3.0 ml (0.025 m) of dichloroacetyl chloride with stirring at room temperature. An ir spectrum of the reaction solution revealed the loss of the acid chloride carbonyl at 1755 cm^{-1} and the appearance of the 1-chloro-N-(dichloroacetyl)-N,N'-diisopropylformamidine carbonyl and carbon-nitrogen double bond at 1710 and 1665 cm^{-1}, respectively. The solution was brought to reflux and 7 ml

(0,05 m) of triethylamine added dropwise with stirring. After refluxing for three hours, the amine salt was removed by filtration and the solvent evaporeted. The residue was dissolved in carbon tetrachloride and poured into dilute hydrochloric acid to hydrolyze the excess carbodiimide to the N,N'-diisopropylurea. The insoluble urea was filtered and the carbon tetrachloride solution dried over calcium chloride and evaporated. The residue crystallized and was sublimed to give 4.1 g of azetidinone (70% yield); purification was by gas chromatography. Mp., 55°; ir, 1830 and 1710 cm^{-1}; nmr (CCl_4), δ, 1.19 (d, 6 H), 1.42 (d, 6 H) and 4.0 (m, 2 H). Mass spectrum parent peak m/e 236, 238 and 240.

Analysis: Calculated for $C_9H_{14}Cl_2N_2O$: C, 45.59; H, 5.95; N, 11.81. Found: C, 44.35; H, 5.86; N, 11.15.

1-Chloro-N-(chloroacetyl)-N,N'-diisopropylformamidine

To 8.9 ml (0.05 m) of diisopropylcarbodiimide in 100 ml of carbon tetrachloride was added 4.0 ml (0.05 m) of chloroacetyl chloride. After thirty minutes the ir spectrum showed the loss of the acid halide carbonyl at 1760 cm^{-1} and the carbodiimide band at 2105 cm^{-1} and the formation of the formamidine which is unstable. Ir, 1695 and 1670 cm^{-1}; nmr (CCl_4), δ, 1.23 (d, 6 H), 1.35 (d, 6 H), 3.90 (h, 1 H), 4.15 (s, 2 H) and 4.46 (h, 1 H).

N-(Chloroacetyl)-N,N'-diisopropylurea

A 0.05 m portion of 1-chloro-N-(chloroacetyl)-N,N'-diisopropylformamidine (as prepared above) in 100 ml of hexane was poured into 25 ml of water with stirring and allowed to stir for thirty minutes. The hexane layer was separated, dried over calcium chloride and evaporated to leave a viscous oil which represented a quantitative yield of the acylurea as evidenced by ir and nmr. The product was unstable at room temperature. Ir, 3300, 1720 and 1670 cm^{-1}; nmr (CCl_4), δ, 1.15 (d, 6 H), 1.25 (d, 6 H), 4.0 (m, 2 H), 4.18 (s, 2 H) and 7.50 (broad d, 1 H).

3-Isopropyl-2-isopropylimino-5-oxazolidinone

A 1.0 g (0.004 m) portion of N-(chloroacetyl)-N,N'-diisopropylurea was allowed to stand at room temperature overnight during which time crystals formed. The crystals were filtered and washed with acetone to give 0.46 g of 5-oxazolidinone (77% yield) which was purified by sublimation. Mp., 192°; ir, 1795 and 1670 cm^{-1}; nmr (DMSO-d_6), δ, 1.35 (d, 6 H), 1.44 (d, 6 H), 4.10 (h, 1 H), 4.58 (h, 1 H) and 5.05 (s, 2 H). Mass spectrum parent peak m/e 184.

As an alternate synthesis, 9.4 g (0.1 m) of chloroacetic acid in 100 ml of ether was added with stirring to 17.8 ml (0.1 m) of diisopropylcarbodiimide in 300 ml of carbon tetrachloride at room temperature. After stirring overnight, 5.6 g (0.04 m) of the insoluble N,N'-diisopropylurea was

filtered from the reaction. The solvent was evaporated and 4.2 g. (0.02 m) of the 5-oxazolidinone (22% yield) crystallized out of the residue. The diisopropylurea and 5-oxazolidinone were identified by ir and nmr.

1,3-Diisopropyl-1,3-diazolidin-2,4-dione

A 1.0 g (0.005 m) portion of 3-isopropyl-2-isopropylimino-5-oxazolidinone was added to a mixture of 20 ml of 1 M potassium hydroxide and 20 ml of ether with stirring. After five minutes the ether layer was separated, dried over calcium chloride and evaporated to give 0.75 g of dione (75% yield). This dione is a viscous liquid and was collected from a gas chromatograph for analyses. Ir, 1700 cm^{-1}; nmr (CCl_4), δ, 1.05 (d, 6 H), 1.50 (d, 6 H), 3.8 (m, 2 H) and 4.35 (s, 2 H). Mass spectrum parent peak m/e 184.

Analysis: Calculated for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.20. Found: C, 58.55; H, 8.92; N, 15.21.

3-Isopropyl-2-isopropylimino-4-oxazolidinone

To 0.01 m of 1-chloro-N-(chloroacetyl)-N,N'-diisopropylformamidine (as prepared above) in 50 ml of hexane was added 1.4 ml (0.01 m) of triethylamine at room temperature followed immediately by the addition of excess water. After a few minutes the amine salt precipitated; the solution was filtered and the solvent evaporated to give 1.6 g of the 4-oxazolidinone (88% yield). Mp., 46-48°; ir, 1750 and 1690 cm^{-1}; nmr

(CCl_4), δ, 1.15 (d, 6 H), 1.35 (d, 6 H), 3.59 (s, 2 H) and 4.2 (m, 2 H). Mass spectrum parent peak m/e 184.

Analysis: Calculated for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.20. Found: C, 58.27; H, 8.48; N, 15.21.

1-Chloro-N-(2-chloropropanoyl)-N,N'-diisopropylformamidine

To 8.9 ml (0.05 m) of diisopropylcarbodiimide in 150 ml of hexane was added 5.1 ml (0.05 m) of 2-chloropropanoyl chloride at room temperature with stirring. After thirty minutes the solvent was evaporated to leave a quantitative amount of formamidine as evidenced by ir and nmr analysis. Bp., 34° at 0.025 Torr; ir, 1700 and 1665 cm^{-1}; nmr (CCl_4), δ, 1.23 (d, 6 H), 1.35 (d, 6 H), 1.58 (d, 3 H), 3.90 (h, 1 H), 4.45 (h, 1 H) and 4.67 (q, 1 H).

Analysis: Calculated for $C_{10}H_{19}Cl_2N_2O$: N, 11.06. Found: N, 11.39.

N-(2-Chloropropanoyl)-N,N'-diisopropylurea

A 5.3 g (0.02 m) portion of 1-chloro-N-(2-chloropropanoyl)-N,N'-diisopropylformamidine was dissolved in 20 ml of ether and then this solution was poured into 30 ml of water and stirred for two hours. The ether layer was separated, dried with calcium chloride, and evaporated to give 4.9 g of the acylurea (100% yield) which was recrystallized from petroleum ether. Mp., 92°; ir, 3260, 1740, 1695 and 1660 cm^{-1}; nmr (CCl_4), δ, 1.25 (d, 6 H), 1.35 (d, 6 H), 1.62 (d, 3 H), 4.2 (m, 2 H), 4.54 (q, 1 H) and 6.95 (s, 1 H).

Analysis: Calculated for $C_{10}H_{19}ClN_2O_2$: C, 51.17; H, 8.16; N, 11.93. Found: C, 51.37; H, 8.29; N, 12.07.

3-Isopropyl-2-isopropylimino-4-methyl-5-oxazolidinone

A 0.5 g (0.002 m) portion of N-(2-chloropropanoyl)-N,N'-diisopropylurea was heated to 100° for one hour to give 0.4 g of 5-oxazolidinone (98% yield). The 5-oxazolidinone melted at 110° but would not sublime in vacuuo. Attempted recrystallization left only an oil. Ir, 1790 and 1665 cm^{-1}; nmr (DMSO-d_6), δ, 1.35 (d, 6 H), 1.40 (d, 6 H), 1.55 (d, 3 H), 4.05 (h, 1 H), 4.93 (h, 1 H) and 5.27 (q, 1 H). Mass spectrum parent peak m/e 198.

1,3-Diisopropyl-5-methyl-1,3-diazolidine-2,4-dione and 3-Isopropyl-4-methyl-2,5-oxazolidinedione

A 0.8 g (0.004 m) portion of 3-isopropyl-2-isopropylimino-4-methyl-5-oxazolidinone was allowed to stand in air for two weeks. Gas chromatographic analysis showed the presence of two components which were collected and analyzed.

1,3-Diisopropyl-5-methyl-1,3-diazolidine-2,4-dione; liquid; ir, 1700 cm^{-1}; nmr (CCl_4), δ, 1.05 (d, 6 H), 1.40 (d, 6 H), 1.45 (d, 3 H), 3.8 (m, 2 H) and 4.36 (q, 1 H).

Analysis: Calculated for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.12. Found: C, 60.28; H, 9.06; N, 13.95.

3-Isopropyl-4-methyl-2,5-oxazolidinedione; liquid; ir, 1820 and 1745 cm^{-1}; nmr (CCl_4), δ, 1.35 (d, 6 H), 1.46 (d, 3 H), 4.01 (h, 1 H) and 4.43 (q, 1 H).

Analysis: Calculated for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.89; H, 7.27; N, 9.37.

N-(2-Bromo-2-methylpropanoyl)-N,N'-diisopropylurea

To 4.5 ml (0.025 m) of diisopropylcarbodiimide in 100 ml of cyclohexane was added 4.3 g (0.023 m) of 2-bromo-2-methylpropanoyl chloride at room temperature with stirring. After thirty minutes water was added and the reaction stirred for an additional fifteen minutes. A 10 ml portion of ether was added to aid in the solubility of the acylurea and then the reaction was filtered to remove the insoluble N,N'-diisopropylurea. The organic layer was separated, dried with calcium chloride and evaporated to give 5.0 g of the acylurea (74% yield) which was purified by recrystallization from petroleum ether. The acylurea decomposed slowly at room temperature. Mp., 87-89°; ir, 3300, 1700, 1675 and 1640 cm^{-1}; nmr (CCl_4), δ, 1.30 (d, 6 H), 1.45 (d, 6 H), 2.05 (s, 6 H), 4.02 (h, 1 H), 4.62 (h, 1 H) and 6.98 (broad d, 1 H).

4,4-Dimethyl-3-isopropyl-2-isopropylimino-5-oxazolidinone

A 4.0 g (0.014 m) portion of N-(2-bromo-2-methylpropanoyl)-N,N'-diisopropylurea was placed in a sublimation apparatus and heated to 95° for one hour. A vacuum was applied and 3.6 g of 5-oxazolidinone sublimed (90% yield). Mp., 185°; ir, 1785 and 1695 cm^{-1}; nmr (DMSO-d_6), δ, 1.35

(d, 6 H), 1.44 (d, 6 H), 1.62 (s, 6 H), 4.03 (h, 1 H) and 4.68 (h, 1 H). Mass spectrum parent peak m/e 212.

Trapping Chloroketene Generated from 1-Chloro-N-(chloroacetyl)-N,N'-diisopropylformamidine with Cyclopentadiene

To 4.5 m. (0.025 m) of diisopropylcarbodiimide in 75 ml of tetrahydrofuran was added 2.0 ml (0.025 m) of chloroacetyl chloride at room temperature with stirring. The reaction was brought to reflux and 2.7 g (0.041 m) of freshly prepared cyclopentadiene was added. Then 7 ml (0.050 m) of triethylamine was added dropwise with stirring and the reaction allowed to reflux for three hours. The salt was filtered and the solvent evaporated. Gas chromatographic analysis showed a 3:1 ratio of 3-chloro-1-isopropyl-4-isopropylimino-2-azetidinone to 7-chlorobicyclo[3.2.0]hept-2-en-6-one.[10] The two peaks were collected and analyzed. The ir and nmr spectra were identical with authentic samples.

Attempted Ring Closure of 1-Chloro-N-acetyl-N,N'-diisopropylformamidine

To 6.5 ml (0.037 m) of diisopropylcarbodiimide in 75 ml of tetrahydrofuran was added 1.8 ml (0.025 m) of acetyl chloride with stirring at room temperature. The reaction was brought to reflux and the ir spectrum of the solution showed the formation of 1-chloro-N-acetyl-N,N'-diisopropylformamidine as evidenced by the carbonyl and carbon-nitrogen double bond at 1695 and 1670 cm^{-1}, respectively.[11] Then 7 ml

(0.05 m) of triethylamine was added and the reaction allowed to reflux overnight. The ir spectrum of the solution showed no evidence for 1-isopropyl-4-isopropylimino-2-azetidinone.

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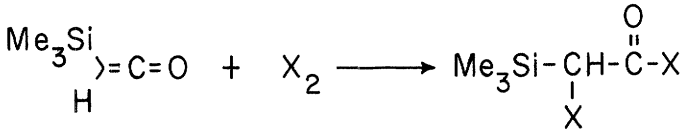
CHAPTER III

RESULTS AND DISCUSSION

This study of trimethylsilylbromoketene originated from interest in the opposite electronic effects of the bromo and trimethylsilyl substituents on the reactivity of the ketene functionality. Halogen substituents are known to have an activating influence on the ketene functionality via an electron withdrawing effect. The trimethylsilyl group has been found to have an extremely stabilizing effect on the ketene functionality through an electron donating effect.[1]

Trimethylsilylbromoacetyl bromide was synthesized by the addition of bromine to trimethylsilylketene.[2] The synthesis

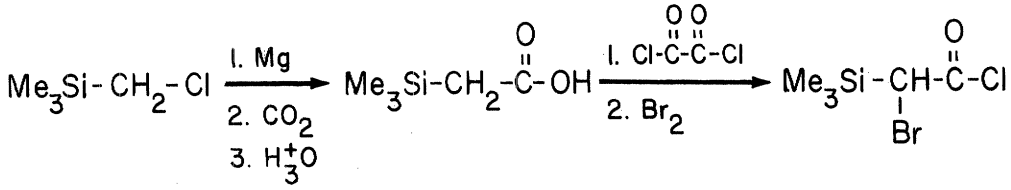


X = Br, Cl

of trimethylsilylketene gives, at best, a sixty per cent yield from the ethoxyacetylene which is prohibitively expensive for large scale reactions. In addition, an impurity, as evidenced by nmr, is often present which apparently inhibits the reactions of trimethylsilylbromoacetyl bromide.

Trimethylsilylchloroacetyl chloride was made by the chlorination of trimethylsilylketene with chlorine gas dissolved in carbon tetrachloride. The yields of products from the reactions with trimethylsilylchloroacetyl chloride were considerably less than for the trimethylsilylbromoacetyl bromide system; and, therefore, little work was done with the chloro system.

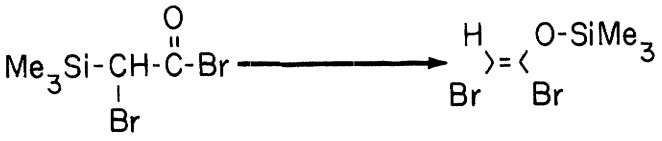
The synthesis of trimethylsilylbromoacetyl chloride was developed as an alternate route to trimethylsilylbromoketene. Chloromethyltrimethylsilane was converted to the



Grignard reagent with magnesium in ether. The Grignard was carbonated by pouring the solution over dry ice and acidifying to give trimethylsilylacetic acid. The trimethylsilylacetic acid was converted to the acid chloride with oxalyl chloride, and then brominated with molecular bromine to yield trimethylbromoacetyl chloride which had properties similar to the acid bromide.

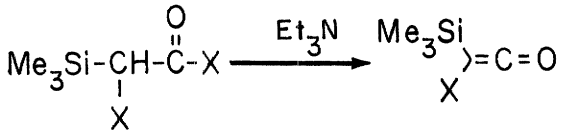
The trimethylsilylbromoacetyl halides could not be made in large quantities and stored due to tautomerization of the trimethylsilyl group to form the siloxyethylene as evidenced

by infrared. Decomposition occurred with loss of trimethyl-



bromosilane. Attempted vacuum distillation of the acid bromide gave only polymer and trimethylbromosilane. The yield of acid halide was assumed to be quantitative and the yields of product based upon the amount of trimethylsilyl-ketene or trimethylsilylacetic acid used. The acid halides were made just prior to use.

Trimethylsilylbromoketene was generated by the dehydrohalogenation of trimethylsilylbromoacetyl bromide with triethylamine in various solvents such as hexane, heptane,



X = Br, Cl

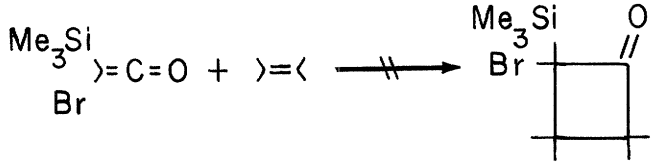
carbon tetrachloride, chloroform and ether. In each case the ketene band was observed in the infrared and the solution became a pale yellow which is indicative of ketene formation.

The trimethylsilylbromoketene was stable in solution for several days with no indication of dimerization. Attempts to isolate the ketene were unsuccessful, as the ketene band

in the infrared disappeared within twenty minutes upon filtering the amine salt from the reaction mixture. After evaporating the solvent, the residue was a tar-like substance which had no interpretable bands in the infrared. This behavior is not unusual for halogenated ketenes nor for trimethylsilylketene when generated by dehydrohalogenation.[3,4] The possibility of bromoketene being the ketene observed is not likely, since whenever bromoketene is generated by dehydrohalogenation of bromoacetyl bromide, the ketene polymerizes almost immediately.[5]

Trimethylsilylchloroketene was generated by the triethylamine dehydrohalogenation of trimethylsilylchloroacetyl chloride and had properties similar to trimethylsilylbromoketene.

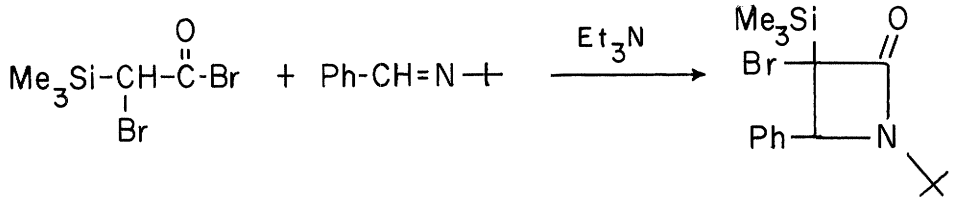
Trimethylsilylbromoketene did not yield cyclobutanones with activated olefins, such as cyclopentadiene, ethyl vinyl ether and dihydropyran. The order of addition of reagents



had no effect on the attempted cycloadditions, because in every case, the formation of ketene was observed in the infrared. Under mild conditions, such as room temperature

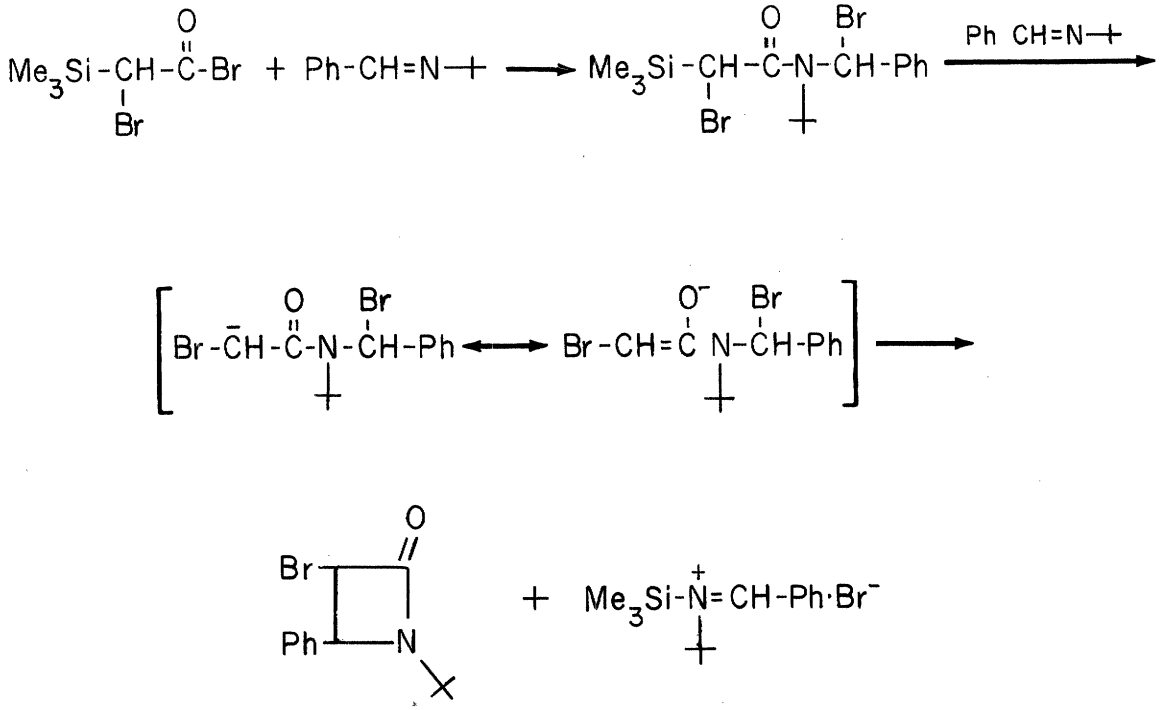
or in a dry ice-acetone bath, the ketene persisted for several days and no cycloadducts were observed.

The cycloaddition of trimethylsilylbromoketene and N-tert-butylbenzylimine yielded 1-tert-butyl-3-bromo-4-phenyl-3-trimethylsilyl-2-azetidinone. Trimethylsilylbromoacetyl



bromide was made by the bromination of trimethylsilylketene in heptane at room temperature. The infrared spectrum of the solution showed the complete conversion of the ketene to trimethylsilylbromoacetyl bromide. This solution was brought to reflux prior to adding the imine to avoid polymerization of the imine or any side reactions between the imine and the acid halide. The imine was added before the triethylamine to allow for complete mixing before any ketene was generated in order to minimize polymerization of the trimethylsilyl-bromoketene. Upon addition of the triethylamine, the ketene band was observed in the infrared and this band persisted for several hours. The reaction was allowed to reflux overnight and the silylated azetidinone cycloadduct was isolated.

With no triethylamine present, the reaction described above resulted in an eighty per cent yield of the non-silylated azetidinone. The imine served as the base, but

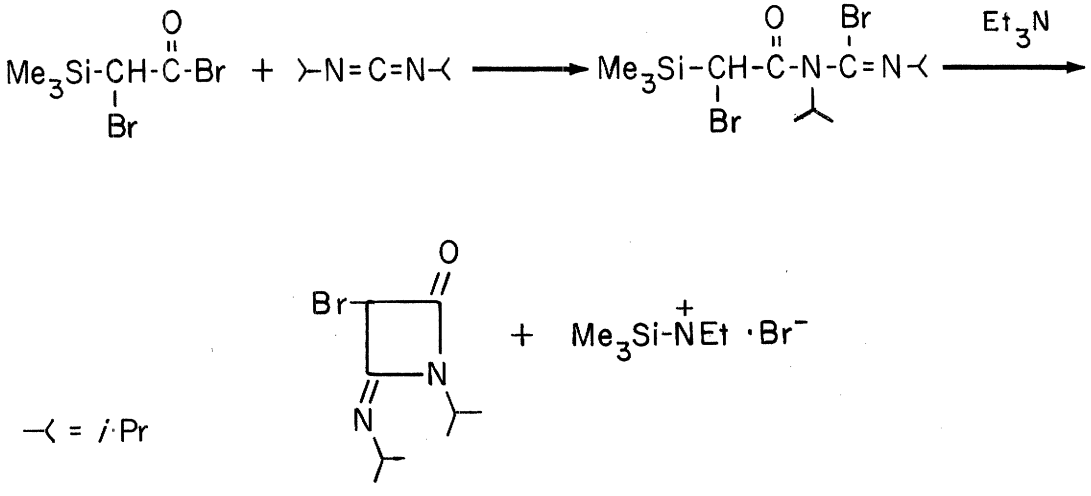


the basicity of the imine is apparently not sufficient to effect the dehydrobromination of trimethylsilylbromoacetyl bromide. No ketene band was observed in the infrared. The acid halide apparently added to the imine to give the amide as shown above. A second molecule of imine then could attack the trimethylsilyl group generating an anion which is resonance stabilized with the carbonyl and inductively stabilized by the bromo substituent. The anion would be expected to undergo an intramolecular nucleophilic

displacement yielding the azetidinone. The salt which was isolated from the reaction mixture was extremely hygroscopic and fumed in air which is indicative of a trimethylsilyl amine salt. Duran and Ghosez reported a similar reaction between dichloroacetyl chloride and N-benzylaniline.[6]

Carbodiimides are very reactive in ketene cycloadditions and, therefore, were selected to study with trimethylsilylbromoketene. Since alkyl carbodiimides form cycloadducts with ketenes far more readily than do aryl carbodiimides, diisopropylcarbodiimide was selected for study.[7] This carbodiimide is commercially available and is a liquid at room temperature.

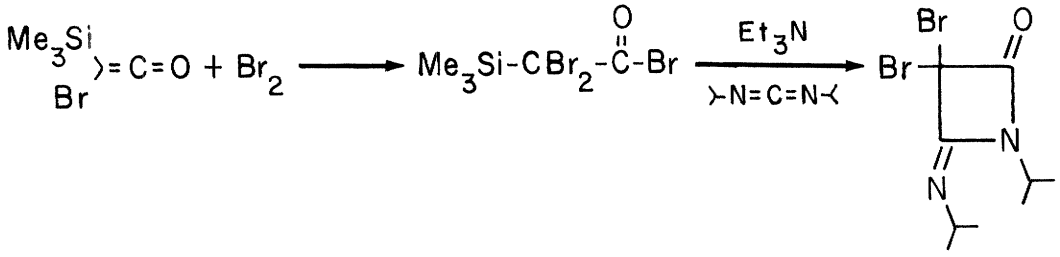
The cycloaddition of trimethylsilylbromoketene and diisopropylcarbodiimide was attempted in the same manner as described for the imine above. Upon addition of the triethylamine, salt formation was observed but there was no ketene band in the infrared. The product isolated from the



reaction mixture was the non-silylated 3-bromo-1-isopropyl-4-isopropylimino-2-azetidinone. The salt filtered from the reaction mixture was extremely hygroscopic and fumed in air which is indicative of a trimethylsilylammonium salt.

The reaction was repeated in which the triethylamine was added prior to the carbodiimide so that trimethylsilylbromoketene was generated as evidenced by infrared. No trimethylsilylbromoketene cycloadduct was obtained and the yield of the non-silylated azetidinone was greatly decreased. In another instance the trimethylsilylbromoketene solution was filtered into the carbodiimide. The ketene band in the infrared persisted in the solution for several hours and disappeared overnight on standing at room temperature. None of the silylated azetidinone was observed.

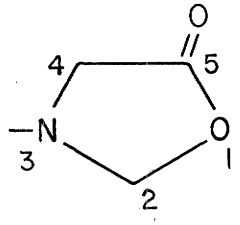
In the reactions of trimethylsilylbromoacetyl bromide and diisopropylcarbodiimide, a small amount of 3,3-dibromo-1-isopropyl-4-isopropylimino-2-azetidinone was observed and



isolated. In an effort to ascertain the origin of the dibromoazetidinone, trimethylsilylbromoketene was generated

and then a stoichiometric amount of bromine was added. The ketene band in the infrared disappeared and an acid halide carbonyl band appeared which was attributed to trimethylsilyldibromoacetyl bromide. The reaction mixture was brought to reflux and diisopropylcarbodiimide and triethylamine were added. The dibromoazetidinone was isolated from the reaction and the salt from the reaction was extremely hygroscopic and fumed in air. Consequently, the origin of the dibromoazetidinone is the result of the small amount of excess bromine added when making trimethylsilylbromoacetyl bromide adding to the trimethylsilylbromoketene, and the resultant acid halide undergoing azetidinone formation with the diisopropylcarbodiimide.

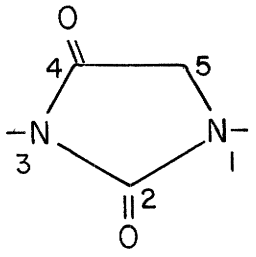
During the attempts to isolate an intermediate in the formation of the non-silylated 4-imino-2-azetidinones, substituted five member heterocyclic compounds were synthesized. 5-Oxazolidinones were isolated and identified by the

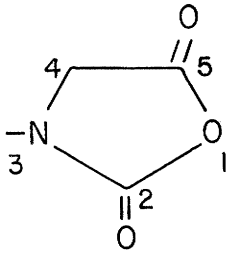


carbonyl at about 1790 cm^{-1} and the carbon-nitrogen double bond at about 1670 cm^{-1} in the infrared and by the ring protons about δ 5.0 in the nmr spectrum. The mass spectra

were consistent with the structures. The 5-oxazolidinones were sensitive to air hydrolysis and the elemental analyses were consistently low.

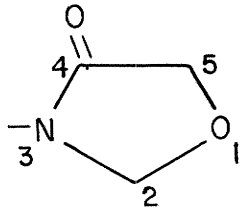
The hydrolysis products of the 5-oxazolidinones were fully characterized as substituted 1,3-diazolidine-2,4-diones and 2,5-oxazolidinediones. The 1,3-diazolidine-2,4-diones





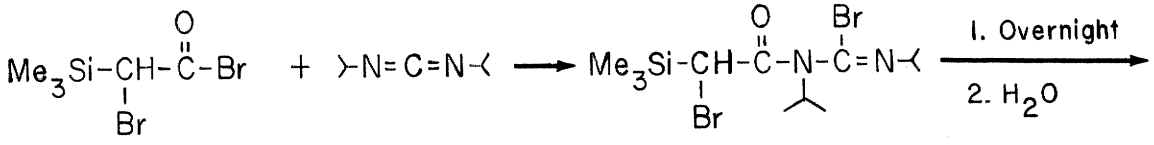
were identified by the carbonyl at 1700 cm^{-1} in the infrared and the ring protons at about δ 4.35 in the nmr spectrum. The 2,5-oxazolidinedione had carbonyls at about 1820 and 1745 cm^{-1} in the infrared and the ring protons at δ 4.43 in the nmr spectrum. The mass spectra were consistent with the structures.

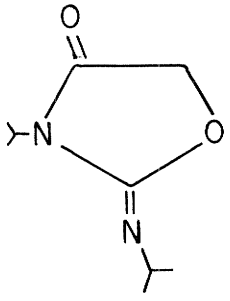
The 4-oxazolidinone was characterized by the carbonyl at 1750 cm^{-1} and the carbon-nitrogen double bond at 1690 cm^{-1}



in the infrared and by the ring protons at δ 3.60 in the nmr spectrum. The mass spectrum and elemental analysis were consistent with the structure.

Equimolar amounts of trimethylsilylbromoacetyl bromide and diisopropylcarbodiimide were reacted to yield the bromoformamidine as evidenced by the infrared spectrum. The

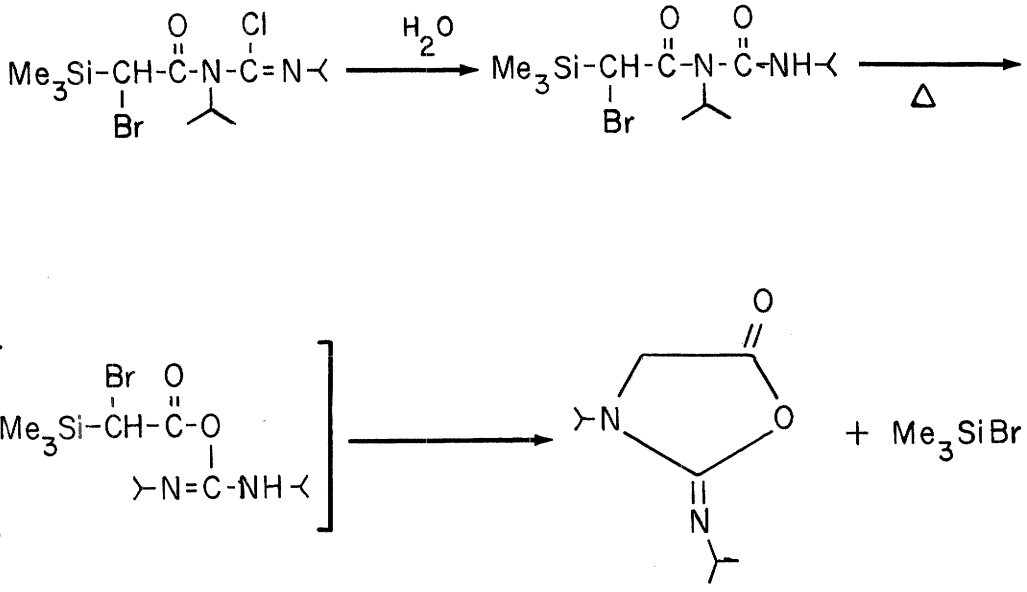




solvent was evaporated leaving a viscous oil which changed to a bright scarlet polymeric compound overnight. Attempts to dissolve this residue in organic solvents, such as hexane, carbon tetrachloride, chloroform and ether, were unsuccessful. The addition of triethylamine also had no effect. Upon adding water there was an immediate reaction and 3-isopropyl-2-isopropylimino-4-oxazolidinone was isolated.

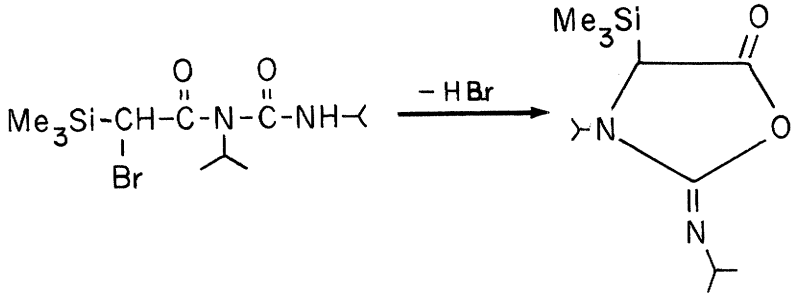
To determine if the 4-oxazolidinone was derived from N-(trimethylsilylbromoacetyl)-N,N'-diisopropylurea, the

hydrolysis product of the chloroformamidine, water was added to a solution of the chloroformamidine, and the acylurea was



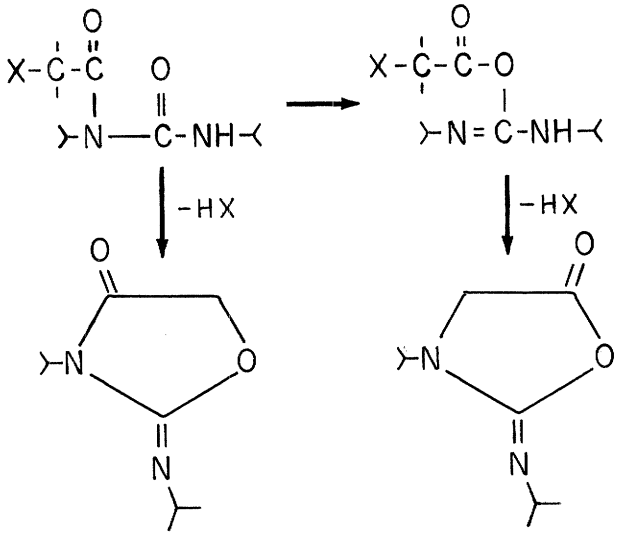
isolated. When the acylurea was heated slightly above the melting point for one hour, 3-isopropyl-2-isopropylimino-5-oxazolidinone was obtained. Trimethylsilylbromosilane was eliminated as evidenced by nmr.

The formation of the 4-trimethylsilyl-5-oxazolidinone was observed in carbon tetrachloride in an nmr tube. Attempts



to duplicate the reaction on a large scale were unsuccessful, as only the non-silylated 5-oxazolidinone could be obtained.

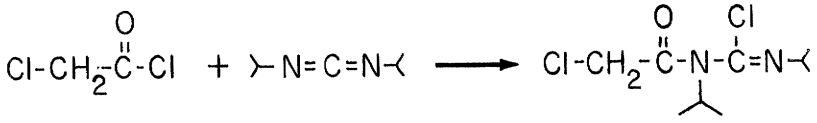
The N-(α-haloacyl)urea can yield the 4-oxazolidinone directly by the displacement of the α-halogen on the acyl substituent by the oxygen of the carbonyl group of the urea.



The formation of the 5-oxazolidinone necessitates the rearrangement of the N-acylurea to the O-acylisourea followed by the nucleophilic displacement of the α-halogen on the acyl group by the amino group of the isourea. In each case there is subsequent loss of a hydrogen halide.

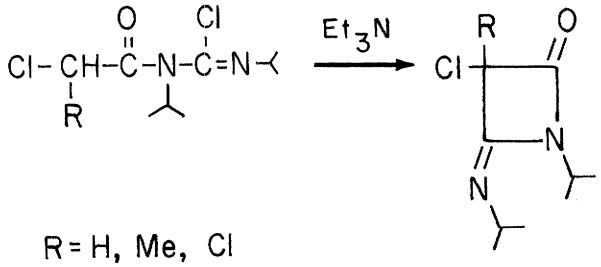
The loss of the trimethylsilyl group led to an investigation of a proton analog of the trimethylsilylbromoacetyl halides to determine if the reactions were characteristic of the trimethylsilylacid halides. Chloroacetyl chloride was chosen since it is readily available.

Chloroacetyl chloride reacted with diisopropylcarbodiimide to form the chloroformamidine. However, this chloro-



formamidine could not be isolated but polymerized upon attempted vacuum distillation. The infrared spectrum was consistent with that reported by Hartke for similar compounds, and the nmr spectrum was consistent with the chloroformamidine structure.[8] Due to the thermal instability of this compound, the mass spectrum was of little value, though some fragments could be explained.

3-Chloro-1-isopropyl-4-isopropylimino-2-azetidinone was obtained in good yield by the triethylamine dehydrohalogenation of the chloroformamidine obtained from the reaction



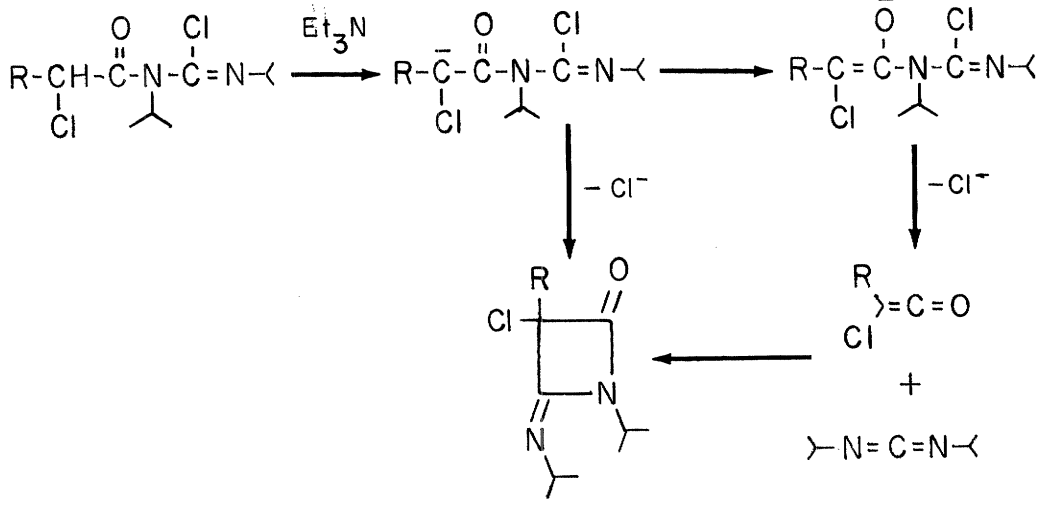
R = H, Me, Cl

of chloroacetyl chloride with diisopropylcarbodiimide. 3-Chloro-1-isopropyl-4-isopropylimino-3-methyl-2-azetidinone was prepared from 2-chloropropanoyl chloride and

3,3-dichloro-1-isopropyl-4-isopropylimino-2-azetidinone, from dichloroacetyl chloride in seventy per cent yields by the same procedure.

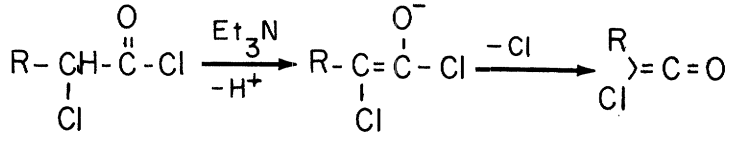
Previously, 3-halo-2-azetidinones had been prepared by the <u>in situ</u> cycloaddition of halogenated ketenes with carbodiimides, but the yields were poor except for the <u>in situ</u> cycloaddition of dichloroketene with dicyclohexylcarbodiimide reported by Hull.[4,9] This azetidinone is believed to have been generated from the chloroformamidine, although no mention was made of this intermediate. Hull's procedure involved the addition of triethylamine to a refluxing solution of dichloroacetyl chloride and dicyclohexylcarbodiimide in cyclohexane. This procedure was repeated and the chloroformamidine was observed in solution by infrared before the triethylamine was added.

There are two feasible routes to the 3-halo-2-azetidinones from the acylchloroformamidines. Reaction with

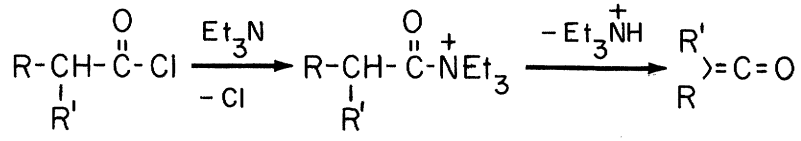


triethylamine could yield the enolate anion which can undergo an intramolecular nucleophilic displacement to the azetidinone, or elimination can occur from the enolate to yield the ketene which would subsequently undergo cycloaddition with the carbodiimide.

The formation of the enolate anion is supported by studies of the mechanism of the triethylamine dehydrohalogenation of α-haloacid halides. The <u>in situ</u> generation of haloketenes by the dehydrohalogenation of α-haloacid halides has been found to proceed through the enolate ion. The



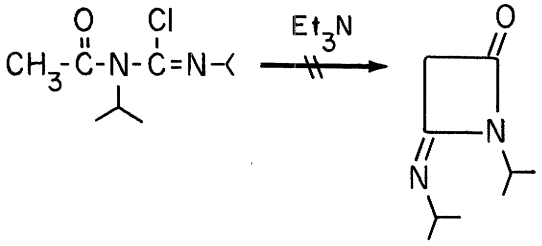
formation of non-halogenated ketenes by the dehydrohalogenation of an appropriate acid halide occurs through an acyl



ammonium intermediate.[10]

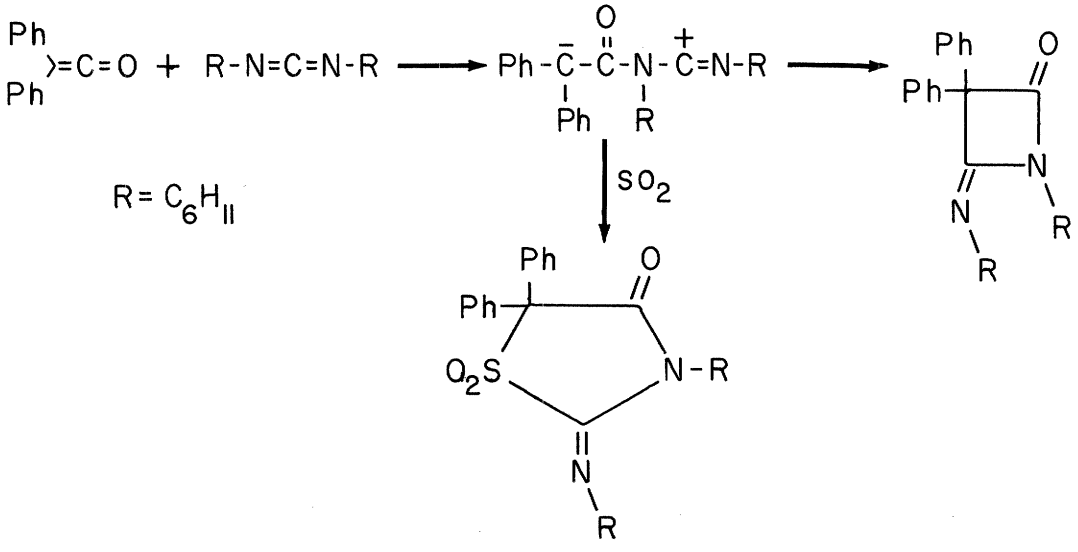
To test the necessity of the enolate in the formamidine ring closure, acetyl chloride was added to an equivalent amount of diisopropylcarbodiimide in tetrahydrofuran, and

the chloroformamidine was observed in the infrared. The solution was brought to reflux and after several hours and



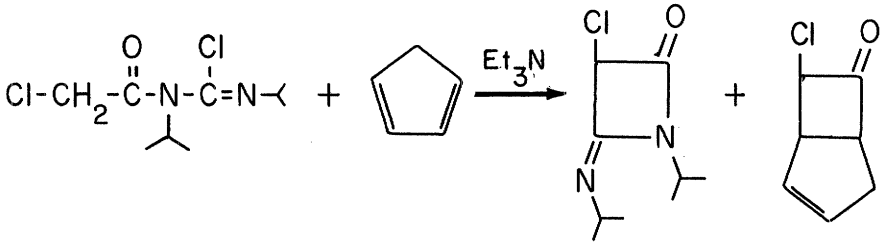
even overnight, no azetidinone was observed. Therefore, the enolate ion must be essential to the formation of the 2-azetidinones from acylchloroformamidines.

This enolate anion is similar to the zwitterionic intermediate proposed by Brady and Dorsey that was trapped with sulfur dioxide in the diphenylketene-dicyclohexylcarbodiimide cycloaddition.[11] The intramolecular displacement



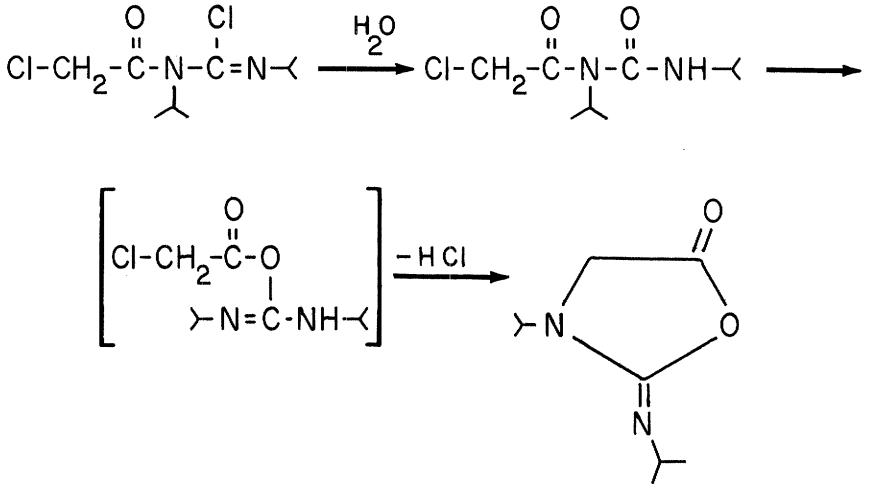
of the halogen of the formamidine to give the four member ring is expected to be quite facile.

However, when a four-fold excess of cyclopentadiene, an excellent ketene trapping agent, was added prior to the



addition of the triethylamine, the chloroketene cycloadduct with the cyclopentadiene was obtained in a 1:3 ratio to the azetidinone. When a stoichiometric amount of chloroacetyl chloride and diisopropylcarbodiimide was used, there was no appreciable decrease in the yield of azetidinone as would be expected if the major route to the azetidinone were through chloroketene. If chloroketene were produced in an appreciable amount, there would be a considerable amount of polymer. Consequently, both mechanistic pathways appear to be operable, but the intramolecular cyclization is apparently the principle route to the azetidinone.

1-Chloro-N-(chloroacetyl)-N,N'-diisopropylformamidine was generated in ether and then the solution poured into water to hydrolyze the formamidine to N-(chloroacetyl)-N,N'-diisopropylurea. The ether layer was separated, dried and evaporated to give the acylurea which was a clear,



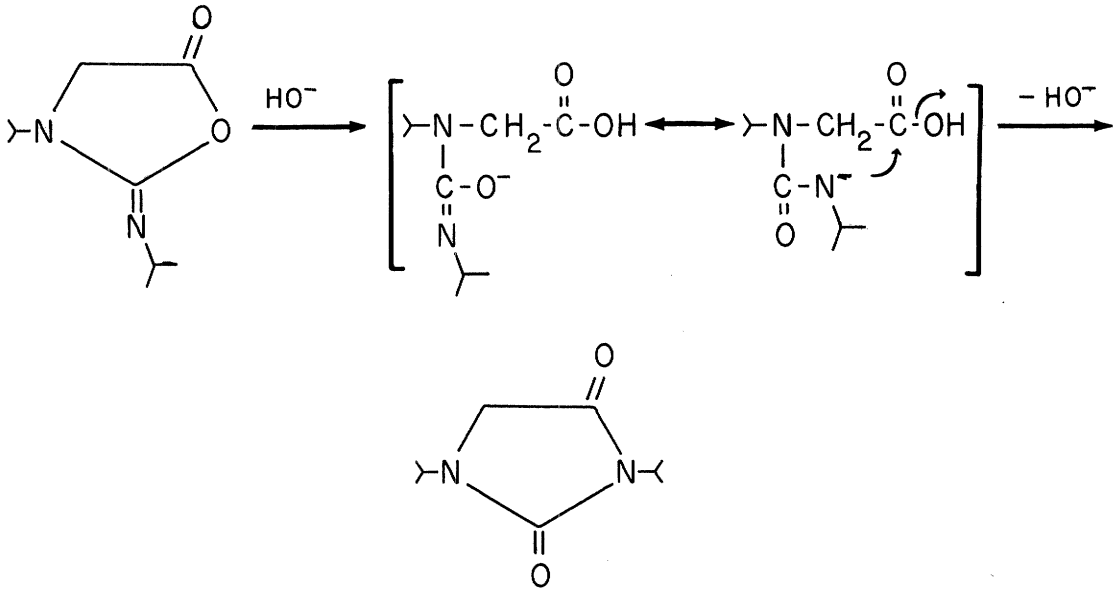
viscous liquid. On standing overnight at room temperature the acylurea underwent a rearrangement and condensation to 3-isopropyl-2-isopropylimino-5-oxazolidinone.

The acylurea was characterized by infrared and nmr, but the mass spectrum gave no parent peak. Several of the fragments were consistent with the acylurea and a parent peak for the 5-oxazolidinone was present. The inlet system temperature of the mass spectrometer was sufficient to effect oxazolidinone formation.

3-Isopropyl-2-isopropylimino-5-oxazolidinone crystallized from the acylurea and was insoluble in most organic solvents including acetone. Initial purification was by washing the filtrate with acetone to remove any by-products and unreacted acylurea. The 5-oxazolidinone was sensitive to moisture and undergoes rearrangement and hydrolysis on exposure to air.

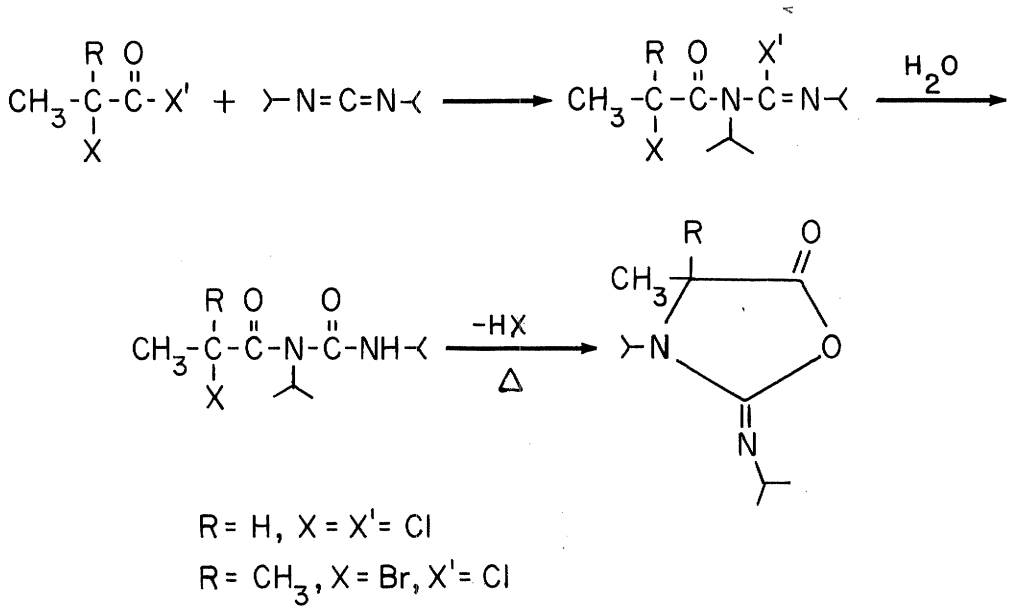
The 5-oxazolidinone was washed with an ether and 0.1 M potassium hydroxide suspension for five minutes and

1,3-diisopropyl-1,3-diazolidine-2,4-dione was recovered from the ether layer. This could occur from a nucleophilic attack



of a hydroxide at the carbonyl to open the ring forming an oxyanion that would be stabilized by the imine. A subsequent ring closure would give the diazolidinedione. When the reaction was allowed to proceed for more than five minutes the diazolidinedione was hydrolyzed further, in which case the products were not identified.

3-Isopropyl-2-isopropylimino-4-methyl-5-oxazolidinone was obtained from N-(2-chloropropanoyl)-N,N'-diisopropylurea and 4,4-dimethyl-3-isopropyl-2-isopropylimino-5-oxazolidinone was obtained from N-(2-bromo-2-methylpropanoyl)-N,N'-diisopropylurea. The two acylureas were obtained from the hydrolysis of the respective formamidines which were

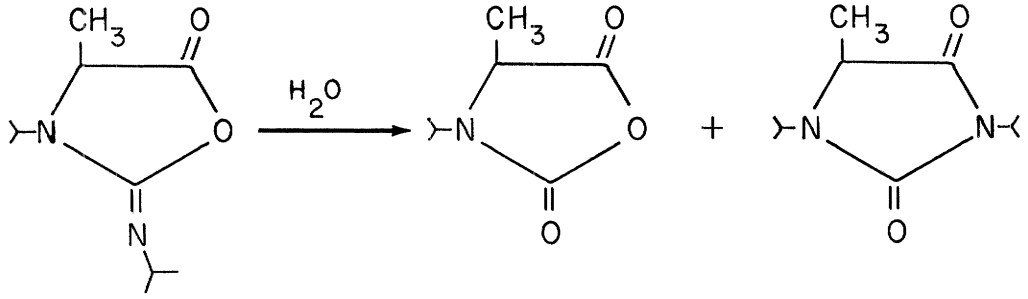


R= H, X = X'= Cl

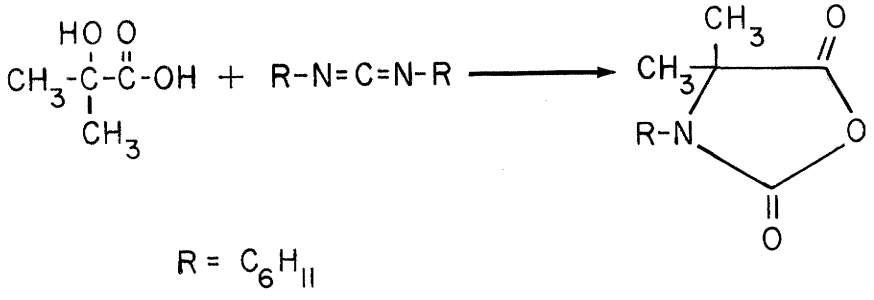
R= CH_3, X = Br, X'= Cl

made from the reaction of diisopropylcarbodiimide with 2-chloroprppanoyl chloride and 2-bromo-2-methylpropanoyl chloride, respectively. The solid acylureas did not spontaneously undergo oxazolidinone formation until molten which appears to be necessary for rapid oxazolidinone formation. If the acylureas were heated excessively, they sublimed before the ring formation could occur.

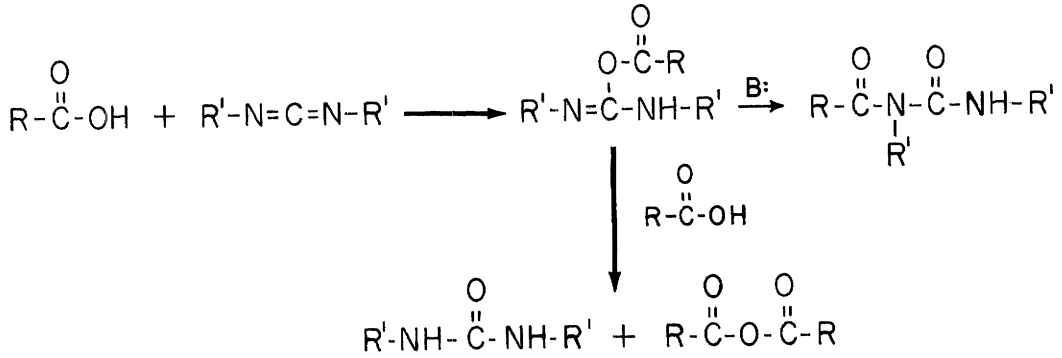
A sample of 3-isopropyl-2-isopropylimino-4-methyl-5-oxazolidinone was allowed to stand in air for two weeks.



The initially solid 5-oxazolidinone reacted with the moisture in the air and was converted to a viscous oil. This oil was dissolved in ether and analyzed by gas chromatography which showed two peaks of equal intensity. The peaks were collected and identified as 3-isopropyl-4-methyl-2,5-oxazolidinedione and 1,3-diisopropyl-5-methyl-1,3-diazolidine-2,4-dione as shown, respectively. The diazolidinedione is the rearrangement product and the oxazolidinedione is the result of hydrolysis of the carbon-nitrogen double bond of the 5-oxazolidinone. The similar 3-cyclohexyl-4,4-dimethyl-2,5-oxazolidinedione was obtained by Robba and Maume from the reaction of 2-hydroxy-2-methylpropanoic acid with dicyclohexylcarbodiimide.[12]

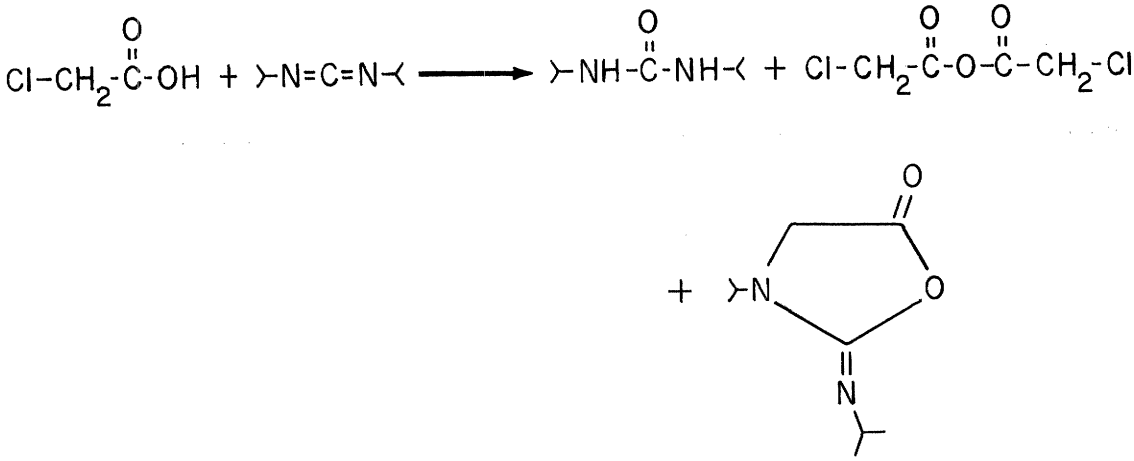


In reactions of organic acids with carbodiimides the main products are usually acid anhydrides and the disubstituted urea. The mechanism of the reaction is believed to proceed via the O-acylisourea which reacts with a second equivalent of acid to generate the anhydride and the urea.



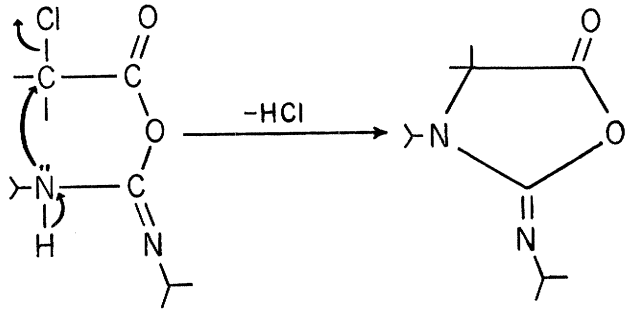
When equimolar amounts of acid and carbodiimide were used in the presence of a base, such as pyridine, the acylurea was reportedly isolated.[13]

In order to verify the intermediacy of the O-acylisourea in the formation of the 5-oxazolidinones, chloroacetic acid and diisopropylcarbodiimide were reacted in carbon tetrachloride. The 5-oxazolidinone was isolated along



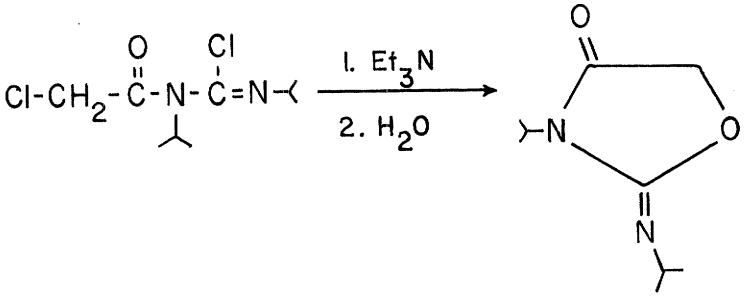
with some N,N'-diisopropylurea which is the result of chloroacetic anhydride formation.

Since hydrogen chloride is eliminated from the acylurea in oxazolidinone formation, the reaction conditions are acidic causing the N-acylurea to rearrange to the O-acyl-isourea. The 5-oxazolidinone formation from the O-acylisourea



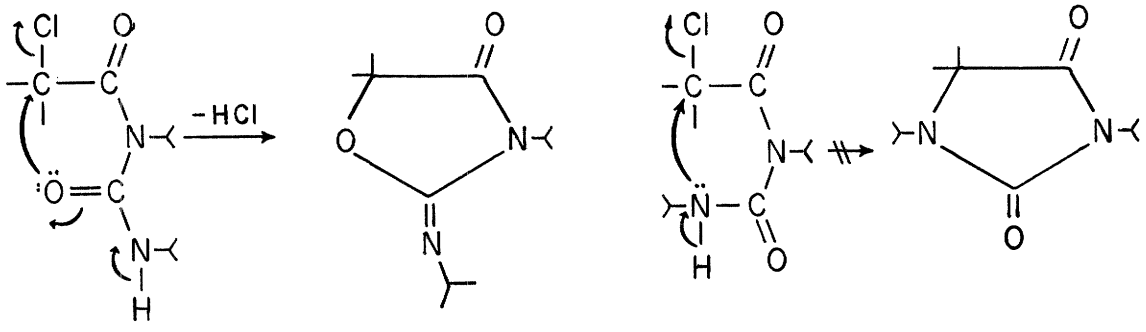
is the result of a nucleophilic displacement of the α-chloro substituent on the acyl group by the amino group of the isourea with the subsequent loss of hydrogen chloride.

The formation of 3-isopropyl-2-isopropylimino-4-oxazolidinone from the acylchloroformamidine was accomplished by adding triethylamine to the acylchloroformamidine in hexane



at room temperature followed immediately by the addition of water. The acylchloroformamidine will react slowly with the triethylamine at room temperature to give the 2-azetidinone so the addition of water is critical. The presence of the amine inhibits the formation of the O-acylisourea and scavenges the hydrogen chloride that is eliminated from both the hydrolysis of the chloroformamidine and the ring closure. Mironova and Dvorko have reported a similar reaction of chloroacetic anhydride or chloroacetyl chloride with N,N'-dicyclohexylurea in benzene in the presence of pyridine.[14]

The 4-oxazolidinone ring formation arises from the nucleophilic displacement of the α-chloro substituent on the acyl group by the oxygen of the carbonyl of the urea with subsequent loss of hydrogen chloride. There was no evidence



for the formation of the diazolidinedione which would arise from the nitrogen of the amino group of the urea displacing the chloride ion.

In conclusion, trimethylsilylbromoketene was generated by the dehydrohalogenation of trimethylsilylbromoacetyl halides with triethylamine and was stable in solution. The stabilizing effect of the trimethylsilyl group is somewhat countered by the bromo substituent, but the ketene failed to undergo cycloaddition with activated olefins. However the cycloaddition with an imine was accomplished. The loss of the trimethylsilyl group under the reaction conditions proved to be the greatest problem in obtaining the silylated cycloadducts with carbon-nitrogen double bonds.

The reactions of trimethylsilylbromoacetyl halides with carbodiimides led to some interesting reactions of non-silylated α-haloacid halides which proved not to be characteristic of the trimethylsilyl group but of the α-halogen. It was discovered that α-haloacylchloroformamidines when dehydrohalogenated with triethylamine would undergo ring closure to 3-halo-2-azetidinones in good yields. Hydrolysis of the α-haloacylchloroformamidines gave N-(α-haloacyl)-ureas which underwent ring closure to yield 4- or 5-oxazolidinones. The acidity of the reaction was the major factor as to whether the N-(α-haloacyl)ureas cyclized to a 4- or 5-oxazolidinone. The 5-oxazolidinone forms under acidic conditions and the 4-oxazolidinone, under basic conditions. The 5-oxazolidinones rearranged with aqueous base to 1,3-diazolidinediones or hydrolyzed to 5-oxazolidinediones.

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