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The Lewis Acid Catalyzed Aza-Claisen
Rearrangement of Allylenamines

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THE LEWIS ACID CATALYZED AZA-CLAISEN REARRANGEMENT OF ALLYLENAMINES

By

David Phillip Voss

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ABSTRACT

THE LEWIS ACID CATALYZED AZA-CLAISEN REARRANGEMENT OF ALLYLENAMINES

By

David Phillip Voss

The synthesis of N-alkylallylenamines from commercially available materials by several routes is demonstrated. The Lewis acid catalysis of the aza-Claisen rearrangement of aliphatic allylenamines by several Lewis acids is described. Titanium tetrachloride, trimethyl aluminum, and DIBAL-H all were used successfully to effect the aza-Claisen at 111° C. Bisphenoxy aluminum catalysts were found to be able to catalyze the rearrangement at 25° C. The rearrangement products, γ,δ-unsaturated imines, were reduced facilely to δ,ε-unsaturated amines by several different reducing agents. These δ,ε-unsaturated amines were then cyclized to the piperidine and pyrrolidine ring systems with elemental iodine. Chiral oxazolines were made, allylated and deprotonated to give *N,O*-ketene acetals, which were subjected to thermal aza-Claisen rearrangement at 185° C.

DEDICATION

This thesis is dedicated to my loving wife Lisa Ann. Without her love and support this thesis could not have completed.

ACKNOWLEDGEMENTS

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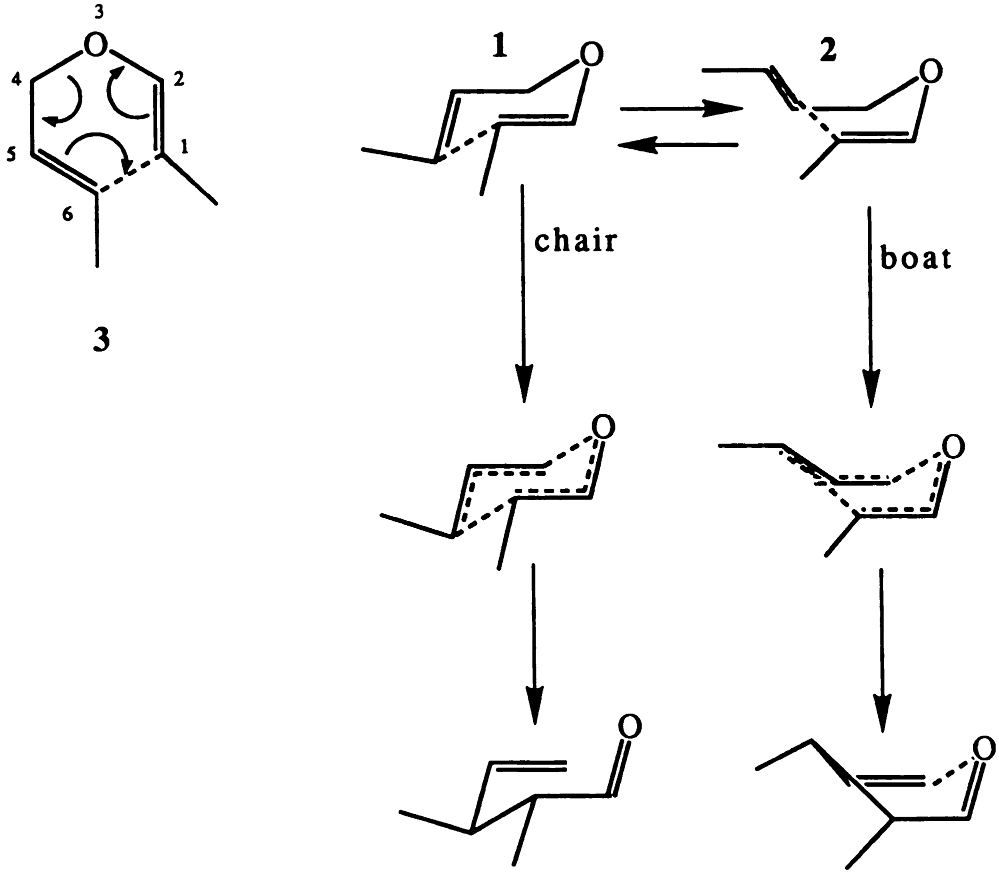
INTRODUCTION

The Aliphatic Oxa-Claisen Rearrangement

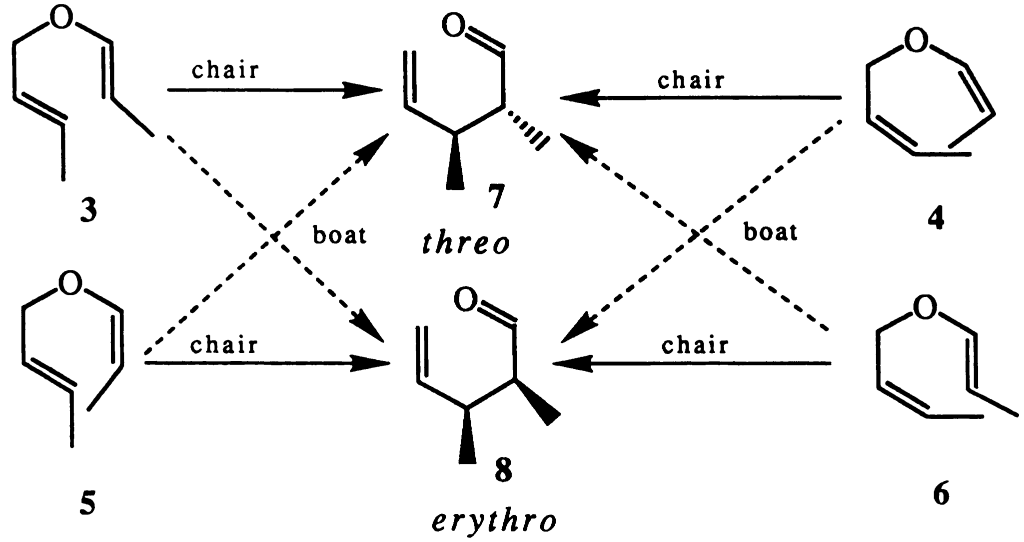
The Claisen rearrangement is one of the oldest and most commonly used reactions in organic synthesis. Each year, dozens of references to this ubiquitous reaction can be found in Chemical Abstracts. Along with its carbon analogue, the Cope rearrangement, the Claisen is the basic example of a 3,3 sigmatropic shift that goes through a structurally defined transition state.[1] The aliphatic Claisen rearrangement, in its basic form, is the conversion of an allyl vinyl ether to a γ,δ-unsaturated aldehyde or ketone. This process involves carbon-carbon bond formation between two relatively unfunctionalized carbons. The only requirement for the reaction to proceed is that the carbons be olefins of some sort. The driving force for the reaction, in the simplest case, is the formation of the carbonyl. The reaction enthalpy in the typical Claisen rearrangement is approximately 25 kcal/mol.[2]



Scheme I Chair and Boat Transition States

An important factor in making the Claisen rearrangement a synthetically useful reaction is that the reaction's transition states are well defined geometrically (Scheme I). There are two common transition state geometries for the Claisen rearrangement to proceed through: the chair and the boat. In most acyclic cases, the chair-like geometry is thermodynamically heavily favored, often accounting for 96% or more of the products.[3] The chair-like form minimizes diaxial interactions between substituents and also eliminates eclipsing interactions. The boat-like geometry accounts for the balance of the products in the typical Claisen rearrangement. However, some Claisen rearrangements, especially

Claisen rearrangements, especially certain cyclic systems, may be geometrically constrained such that the boat-like form is the only geometry that can be adopted.[4] In the case of 1,6 substituted allyl vinyl ethers, the products of the chair and boat geometries are diastereomers and thus can be separated and the chair to boat transition state geometry ratio can be measured. The 1,6 substitution also illustrates the second factor governing the relative stereochemistry of the Claisen rearrangements products: the geometry of the olefins.



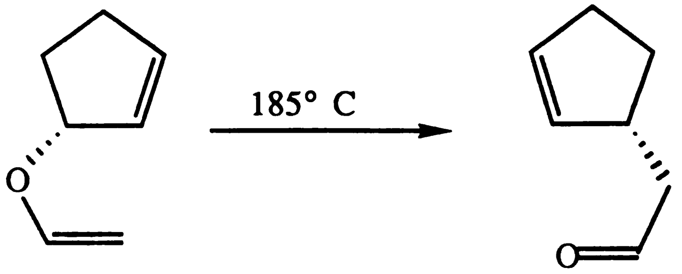
Scheme II Olefin Geometries Effects on Stereochemistry

The influences of both the olefins' configurations and chair *versus* boat transition state geometry on the final products are illustrated in Scheme II. The configuration of the double bonds, either *E* or *Z*, controls the relative stereochemistry of the newly formed chiral centers. In the chair transition state, if both double bonds are either *E* or *Z* , then the double bonds will be *threo* to one another in the product. If the olefin geometries are mixed, then the product. If the olefin geometries are mixed, then the *erythro* product will be formed. The stereochemistry of the rearrangement has actually been studied in some detail.[5] Schmid[6] has prepared all of the allyl vinyl ethers shown in Scheme II and rearranged them. As was expected, the major products, in each case, are those formed *via* a chair-like transition state. The *Z,Z* and *E,E* isomers both gave a product ratio of 2.2:97.8, *erythro:threo,* respectively. The *E,Z* and *Z,E* isomers gave almost exactly the opposite ratio; 97:3, *erythro:threo.* This extreme preference for the chair-like form would permit, if the appropriate crotyl propenyl ether can be prepared, the synthesis of *threo* or *erythro* products at will. If enantiomerically pure material was used, then a high degree of asymmetric induction might be expected.

In the typical Claisen rearrangement, a substituent on the 4 position tends to assume the *E* geometry in the product, when the chair-like transition state geometry predominates. From Scheme I, it can be seen that there is a steric interaction between substituents (including hydrogen) on the 2 and 4 positions in the chair geometry. When the substituent on the 2 position is hydrogen and the 4 position contains an ethyl group the *E* to *Z* ratio is 9:1. If the substituent on 4 is isopropyl then the ratio becomes 93:7. Finally, with the 4 substituent as an ethyl group and the 2 substituent being dimethylamino the *E* to *Z* ratio is 99.4:0.6. The Claisen rearrangement is then especially selective in the geometry of the product olefins.

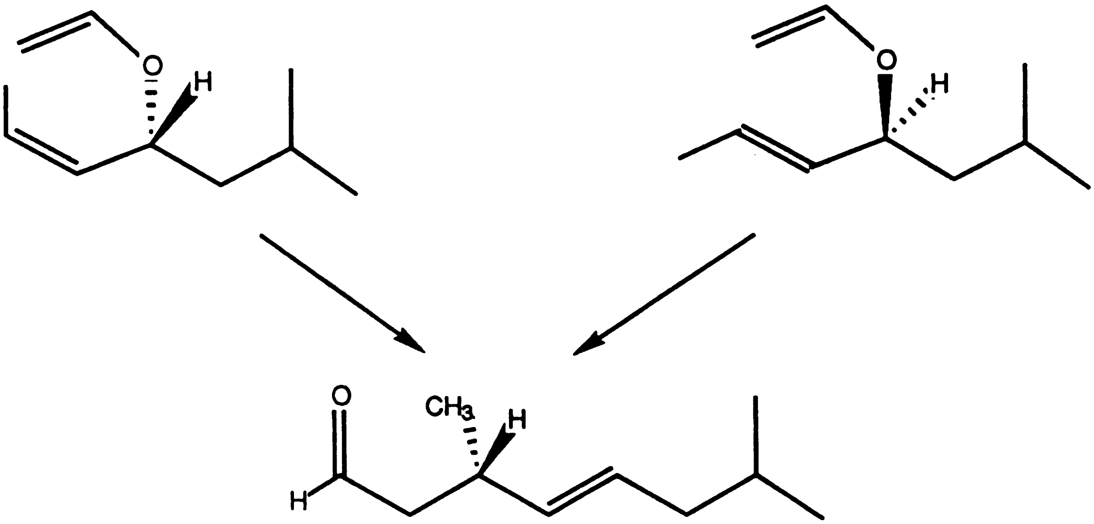
Chiral Oxa-Claisen Rearrangements

When the 4 position is made into a chiral center by attaching a substituent, then asymmetric induction will occur in the transition state to induce chirality into the new chiral center(s) on the 1 and 6 positions (if they have substituents).[5] The preparation of enantiomerically pure allyl vinyl ethers is very difficult, which has limited the utility of the Claisen rearrangement as an asymmetric synthetic method. However, when the starting material can be either made chirally or it can be resolved, then the Claisen shows a high degree of asymmetric induction.



(1)

In fact, several systems with chiral 1-allyl positions have been investigated. For example, Hill[1] has prepared chiral cyclo-2-penten-1-ol and converted it to the corresponding vinyl ether. Rearrangement of this ether at 185° C gave (-)-cyclopentene-3-acetaldehyde in 81% yield (eq 1). Because there is no substituent on the 1 position of this substrate, it cannot be shown whether the substrate passed through either a chair or boat transition state. The aldehyde was then oxidized to the corresponding acid, which was then compared to authentic samples of the acid. The optical activities of the product and the authentic sample were found to be in agreement.



(2)

Another example of the chiral Claisen rearrangement is shown in eq 2. In this work, Chan[2] showed that synthesis of both the (*S*)-*E* and (*R*)-*Z* isomers of the allyl vinyl ether would lead to the same Claisen rearrangement product. This is as expected for the required chair conformation. Because the (*R*)-*Z* isomer would need to have one substituent in a pseudo-axial position, while the (*S*)-*E* isomer can have both groups in pseudo-equatorial positions, it might be expected that the rearrangement of the (*S*)-*E* isomer would proceed faster. In fact, it does; rearrangement of the (*S*)-*E* isomer takes place in 74 hours at 80° C, whereas the (*R*)-*Z* isomer takes 120 hours. The degree of asymmetric induction is extremely high; 98.4% for the (*R*)-*Z* isomer and 98% for the (*S*)-*E* isomer.

The chirality transfer from the 4 position on the allyl moiety to the 2 and 3 positions of the product aldehyde occurs because the allyl substituent has to be in an equatorial position to minimize diaxial interactions. This requirement can only be met by one of the chair-like transition states in a chiral system. Thus the chirality of the allylic carbon is transferred to the two newly formed chiral centers. This also illustrates a disadvantage of the oxa-Claisen: it is self-immolative in the chirality of the initial chiral center.

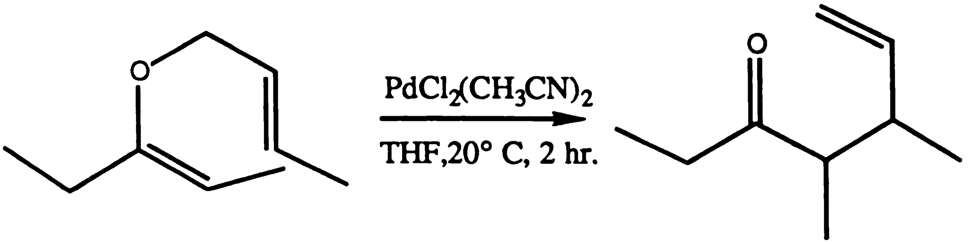
The most notable disadvantage of the Claisen rearrangement however, is the high initiation temperature required. The average Claisen rearrangements activation energy in approximately 30 kcal/mol.[3] This translates into reaction temperatures of 180-220° C. Such extreme temperatures preclude the use of almost all common solvents for the reaction and also prevent the use of many thermally labile organic moieties. Thus it is very desirable to promote the Claisen rearrangement at lower temperatures, using catalysts. There are two main groups of aliphatic Claisen rearrangement catalysts: Lewis acids, and transition metal compounds.[4]

Catalysis of the Oxa-Claisen Rearrangement

Lewis acids are the most common class of catalysts for the Claisen rearrangement. They function by reacting with the Lewis basic ether oxygen thereby inducing partial positive charge at that site. This positively charged oxygen then helps drive the rearrangement. The resulting carbonyl is less Lewis basic and the complex dissociates. Many different Lewis acids have been used to promote the Claisen rearrangement. However, not all catalysts for the aromatic Claisen rearrangement work on the aliphatic system. Although $TiCl_4$ is a useful Lewis-acid catalyst for the aromatic Claisen rearrangement[5] it fails to promote the rearrangement of crotyl vinyl ether.[6] Boron trifluoride is reported to give complex product mixtures and low yields.[7] The alkyl aluminum compounds have, however, been used successfully.

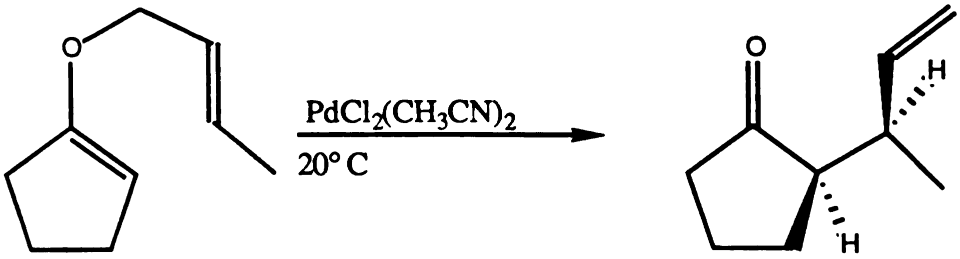
Simple trialkyl aluminum compounds, such as trimethyl aluminum and triethyl aluminum, will catalyze the rearrangement at 25° C,[13] but the end product is not the carbonyl but the alkylated alcohol. Some rearrangement hydrogenation products are seen with triethyl aluminum (15%) and hydrogenation is the only product seen with triisobutyl aluminum. If alkenyl or alkynyl substituents are attached to a simple dialkyl aluminum compound then addition of the alkenyl or alkynyl group to the carbonyl occurs.[13] The use of dialkyl aluminum hydrides results in hydrogenation products as would be expected.

Yamamoto has synthesized several interesting Lewis acid catalysts for the Claisen rearrangement.[8] These Lewis acids promote the oxa-Claisen rearrangement at -78° and do not reduce the product carbonyl compounds. They are bisphenoxy methyl aluminum compounds, derived from trimethyl aluminum and two equivalents of the appropriate phenol. Specifically, bis-(4-bromo-2,6-di-*tert*-butylphenoxy) methyl aluminum catalyzes the Claisen rearrangement at -78° C, but if the bromide substituent is absent, the catalyst fails. The most likely way for the bromine to affect the metal center is by induction. It is not clear, however, that this is the only factor involved. If induction is the pathway for activation of the catalyst then it follows that *ortho or para* halogen substituents on the phenoxy groups should increase the reactivity of the Lewis acid.



(4)

Palladium compounds are another class of catalysts that can be used successfully to promote the aliphatic Claisen rearrangement.[9,10,11,12,13] They can only be used if the substrate meets certain structural constraints. Palladium has a marked tendency to complex with the vinyl ether moiety rather than the allyl olefin of Claisen rearrangement substrates. For palladium to catalyze the Claisen rearrangement the metal must coordinate with the allyl olefin. Cleavage of the ether to allyl alcohol occurs when this happens. Van der Baan[14] has found that while C_1 substituted allyl vinyl ethers can be rearranged successfully (19% yield) at 25° C, using 0.5 equivalents $PdCl_2(CH_3CN)_2$ as the catalyst, unsubstituted ethers give only cleavage products. However, to obtain synthetically useful yields, there must be a C_2 substituent as well (eq 4). The allyl vinyl ether shown rearranged in 2 hours at 25° C to give the product ketone in 93% yield. The C_1 substituent helps prevent complexation of the metal to the vinyl ether moiety while the C_2 group serves to stabilize the positive charge positioned at C_2 during the metal complexation.[20]



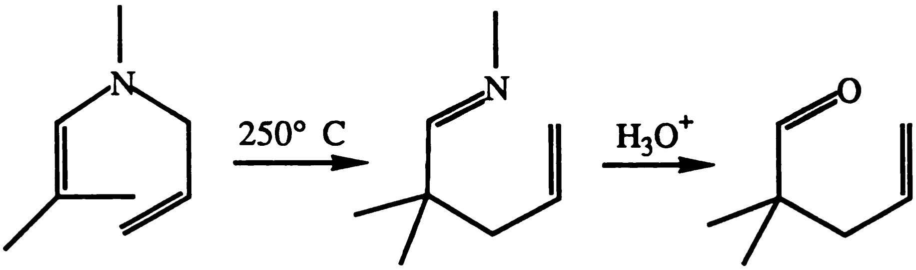
(5)

The $PdCl_2(CH_3CN)_2$ catalyzed rearrangement shown in equation 5 gives products that are consistent with the transition state being of boat geometry.[15] Mikami has rationalized this by suggesting that the metal coordinates, in a bridging fashion, to both olefins simultaneously. This substrate fits all of van der Baan's criteria required to prevent cleavage from being the major reaction,[20] although the boat geometry of the transition state is surprising as van der Baan believes the transition state for his rearrangements was the chair.

The Aliphaic Aza-Claisen Rearrangement

The aza-Claisen rearrangement shows the same proclivity as the oxa-Claisen towards the chair transition state geometry. In other respects as well, it behaves in the same fashion as the oxa-Claisen rearrangement. There are two important exceptions to this; the aza-Claisen requires even higher activation energies than the oxa-Claisen rearrangement, and nitrogen is of course trivalent. The typical aza-Claisen's activation energy is approximately 6 kcal/mol higher than the oxa-Claisen rearrangements,[16] which translates into reaction temperatures of 220-250° C. These elevated temperatures make promotion of the aza-Claisen even more necessary than for the oxa-

Claisen rearrangement. The trivalency of nitrogen requires an additional substituent that can be used to synthetic advantage.

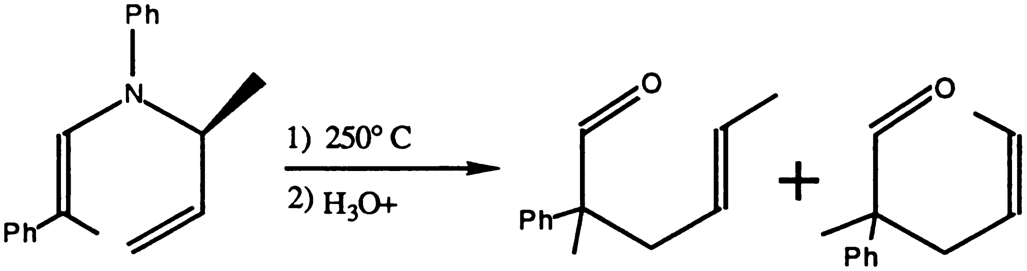


(6)

9

The purely aliphatic aza-Claisen rearrangement has been rarely reported in the literature and there are few reports of catalysis in this type of system.[8] In one of the few examples of the aliphatic aza-Claisen rearrangement, Hill[17] has rearranged enamine **9**,(eq 6) at 250° C, by heating it for one hour in a sealed tube. No yield was reported.

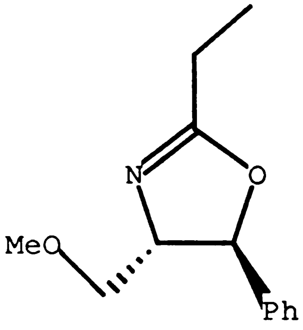
Chiral Aza-Claisen Rearrangements



(7)

The chiral aza-Claisen rearrangement has rarely been attempted. The most notable example of a chiral thermal aza-Claisen rearrangement has been done by Hill.[23] Equation 7 shows the rearrangement of the disubstituted enamine. Hill confirmed by NMR that the isomer shown was the only one present. Rearrangement (250° C) gave a 90:10 mixture of *E* and *Z* products, respectively. The calculated asymmetric induction was 69%.[23] The configurations of the stereocenters in *E* and *Z* are as would be predicted for the chair transition state.

Another way to control the stereochemistry of the aza-Claisen rearrangement is by the use of a chiral auxiliary, such as the chiral oxazolines **10**[18] and **11**.[19,20,21] Kurth alkylated **11** with *cis* and *trans* crotyl tosylates to produce the corresponding quaternary ammonium tosylate salts (Scheme III). Each salt was then deprotonated and the resulting *N,O*-ketene acetals were rearranged in refluxing decalin (185° C) in four hours. The products were then hydrolyzed to corresponding the pentenoic acids. Kurth obtained a product ratio of 85:15 from *trans* crotyl tosylate with the major diastereomer being the *threo* isomer.



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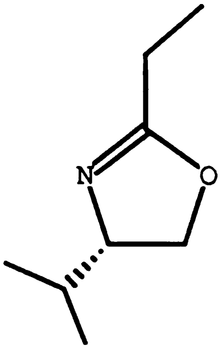
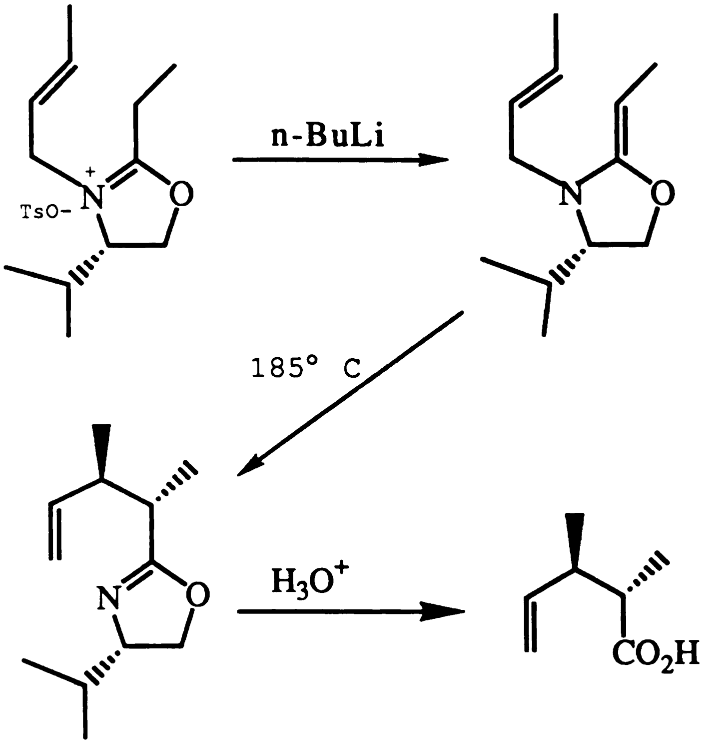


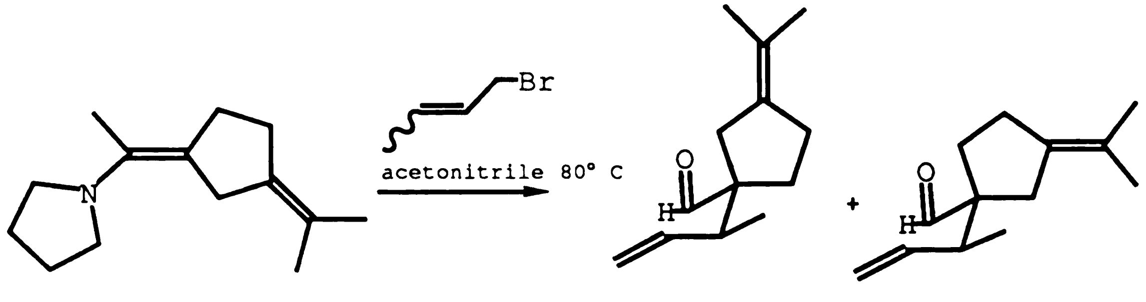
11



Scheme III Reactions of Oxazolines

These conditions are extreme and are an excellent example of why Claisen rearrangements need to be promoted at lower temperatures to be synthetically useful. Many types of useful functionality cannot survive temperatures this high. The aza-Claisen would be a much more useful reaction if some means could be used to lower the activation energy.

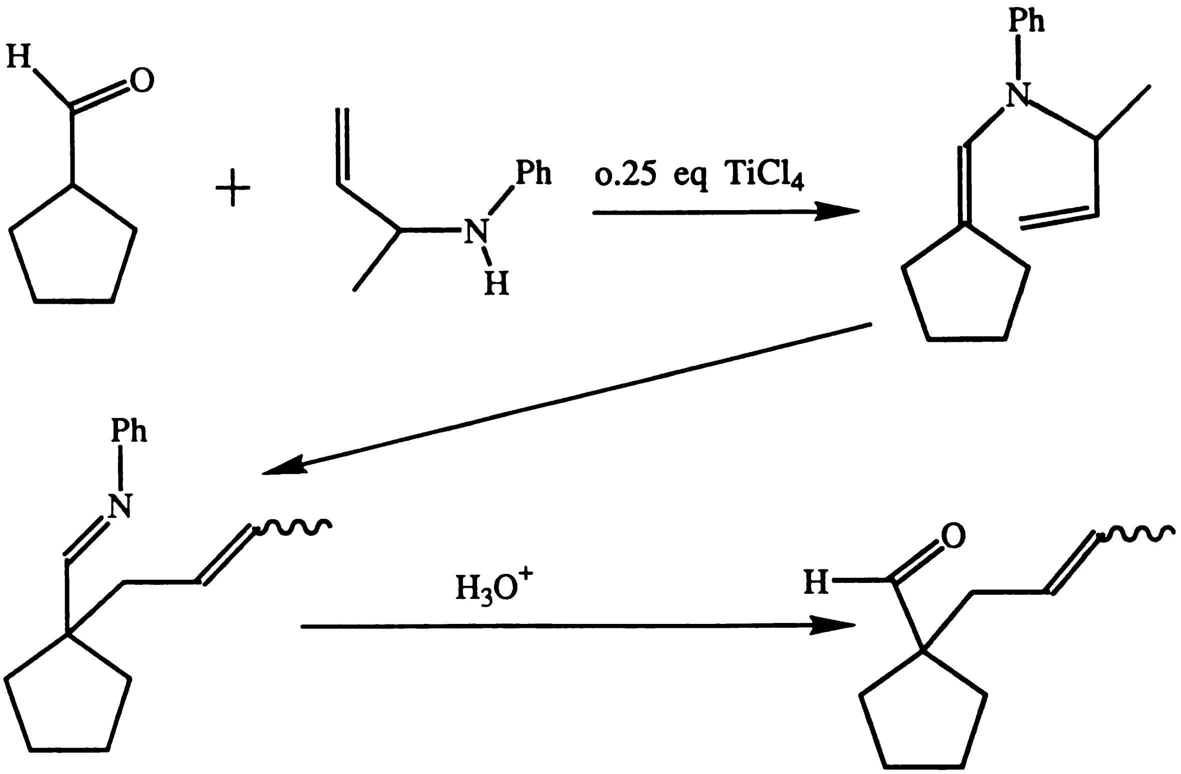
Catalysis of the Aza-Claisen Rearrangement



(7)

12 **13** **14**

The aza-Claisen rearrangement can be promoted by applying a positive charge to the nitrogen, in a similar fashion to the catalysis of the oxa-Claisen rearrangement. Alkylation with an allyl halide is one such route.[22,23,24,25,26,27] This route is essentially the Stork enamine reaction.[28] McCurry[29] has prepared enamine **12** and alkylated it with both pure *trans* and *cis* crotyl bromides in acetonitrile at 80° C (eq 7). The resulting quaternary salts then rearranged and were hydrolyzed to give aldehydes **13** and **14** in 75% yield. The ratio of **13** to **14** was 55:45 for alkylation with the *trans*-crotyl bromide. This ratio was reversed by using *cis*-crotyl bromide. Thus the charge-promoted aza-Claisen can be seen to be quite stereospecific.



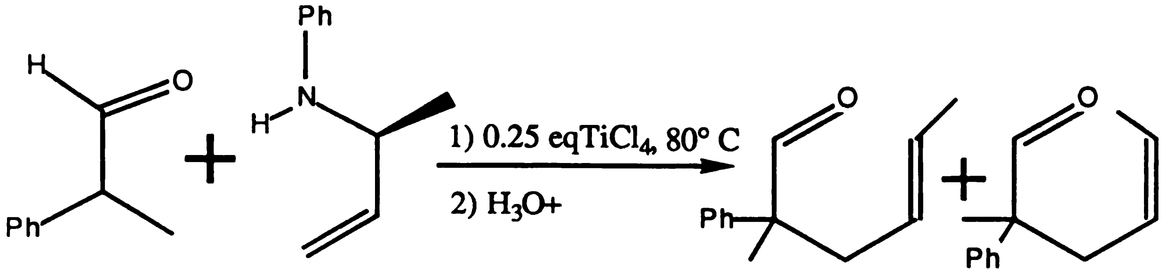
15

Scheme IV Hill's $TiCl_4$ Catalyzed Aza-Claisen Rearrangement

Hill reported in 1978 that the aza-Claisen could be catalyzed by TiCl4,[12] one of the most commonly used Lewis acids. Hill used TiCl4 to both catalyze the formation of enamines, from aldehydes and secondary amines, and to promote their rearrangement. The resulting imines were then hydrolyzed to their corresponding aldehydes. However, he recovered relatively low yields, 30-40%, of rearranged and hydrolyzed products. His best yield was 61%, for the synthesis of aldehyde **15** (Scheme IV).

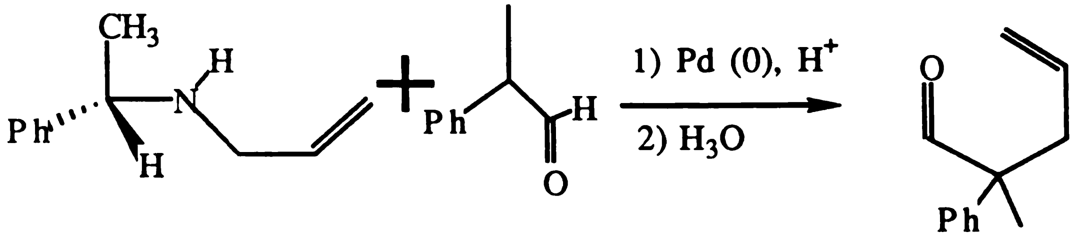
The allylenamines Hill made as intermediates were all N-vinyl-N-allyl substituted anilines. The products of these rearrangements are Schiff bases and are easily hydrolyzed to aldehydes but are not suitable precursors for many natural products. The two ketones he tried, cyclohexanone and acetophenone, failed to form enamines and thus could not rearrange.

Murahashi has promoted the aza-Claisen rearrangement of *N*-phenylallylenamines and *N*-methylallylenamines with a neutral palladium catalyst. The palladium catalyst, $Pd(PPh_3)_4$, was only effective when used with an equimolar amount of trifluoroacetic acid.[30] The use of 0.1 equivalents of each catalyst promoted the rearrangement at temperatures from 50-100° C in 20 hours.[31] The catalyst was also effective in promoting the formation of enamines in a fashion similar to Hill.[12] The secondary allylamine was reacted with a carbonyl and the palladium-protic acid catalyst at 80° C, to give both enamine formation and Claisen rearrangement in 20 hours.



(8)

The catalyzed, chiral aza-Claisen rearrangement is at least as rare as the uncatalyzed reaction. Hill has used his process of *in situ* $TiCl_4$ catalyzed enamine formation followed by aza-Claisen rearrangement, on the same substrate he used to perform the chiral thermal rearrangement (eq 8). Since the enamine is made *in situ* Hill could not be sure of the double bond geometry. However, the resulting rearrangement revealed an asymmetric induction of 67%.[12] Since this is virtually the same induction that occurred in the thermal case the enamine most likely was formed in the predicted fashion. The initial secondary amine was of only 45% e.e., thus, despite the relatively high degree of asymmetric induction the products enantiomeric excess was only 15%. The fact that the asymmetric inductions were similar suggests that the catalyzed aza-Claisen also predominantly proceeds through the chair transition state.



(9)

Murahashi[36] has attempted to use the trivalency of nitrogen to advantage in a chiral aza-Claisen rearrangement. Using the chiral amine shown in equation 9, he attempted to catalyze both enamine formation and the Claisen rearrangement *in situ*, with the $Pd(PPh_3)_4$-protic acid catalyst. Although enantiomerically pure starting material was used the enantiomeric excess in the product was only 12%. This could possibly be attributed to two factors; the remoteness of the chiral center to the rearrangement and the possibility of mixed enamine olefin geometry. Each of the two geometric isomers of the enamine leads to a different product. These two factors could be separated if the reaction were attempted on preformed enamine.

The aza-Claisen rearrangement proceeds through a structurally defined transition state, which can be used to accurately predict the products of the reaction. If a chiral starting material is used, new chiral centers are formed, in a specific fashion. However, the aza-Claisen rearrangement requires very high temperatures to proceed thermally and thus is unsuitable for use in syntheses containing thermally labile moieties. Catalysts that can lower the activation energy, and thus the reaction temperature, are very desirable. Several of the catalysts useful to promote the oxa-Claisen, especially Lewis acids, are directly applicable to the aza-Claisen.

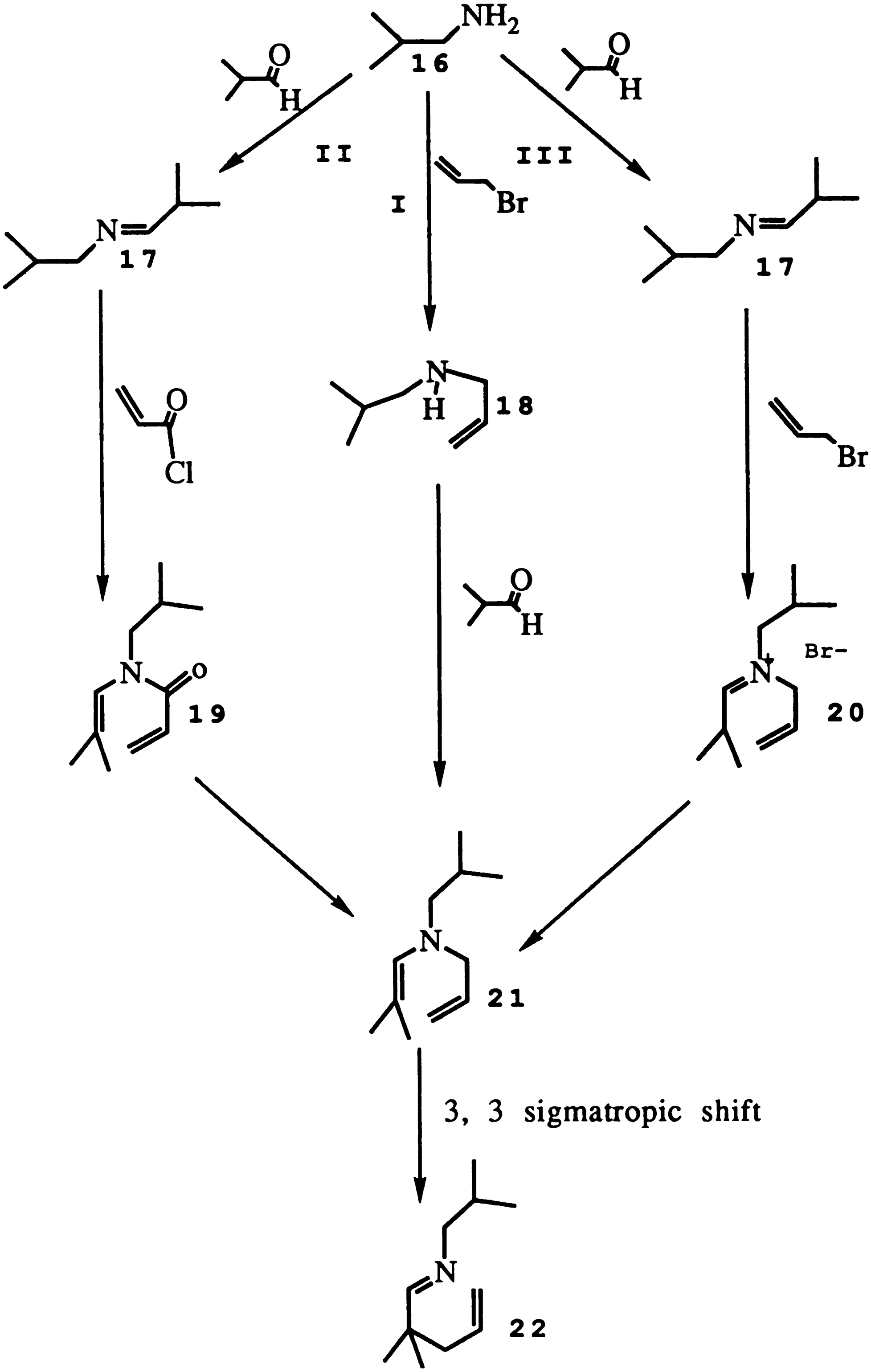
RESULTS AND DISCUSSION

At the start of this project it was found that allylenamines, the nitrogen analogues of allyl vinyl ethers, were not generally commercially available. There were also few direct routes in the literature to *N*-alkylallylenamines.[36] Therefore, any synthesis of aliphatic γ,δ-unsaturated imines *via* the aza-Claisen had to begin with the testing of routes for the synthesis of aliphatic allylenamines. Efficient catalysts, necessary for the promotion of the aza-Claisen rearrangement, had to be prepared and tested. Routes for the reduction of the resulting γ,δ–unsaturated imines to the corresponding amines had to be developed to preserve the synthetically useful nitrogen. Enantioselective forms of the aza-Claisen rearrangement, using chiral auxiliaries, needed to be explored. Finally, the δ,ε–unsaturated amines were to be cyclized to the pyrrolidine and piperidine ring systems, excellent starting points for the synthesis of many natural products.

Synthesis of Allylenamines

Allylenamines were synthesized *via* a number of different routes from the alkyl amine **16**. These pathways are summarized in Scheme V. The most direct method was the condensation of aldehyde with secondary allylamine **16** (pathway I). This route, however, required the synthesis of the appropriate secondary allylamine **18** which was not commercially available. An alternative route, (pathway II), was through the reduction of acryloyl enamide **19** to the allylenamine **21**. The required starting material for this route was the easily prepared imine, **17**, and acryloyl chloride. Because of the expense of acryloyl chloride, pathway II was favored only for valuable amines. A third route was the direct alkylation of imine **17** with an allyl halide (pathway III). This presumably generated the iminium salt, which was then deprotonated *in situ* to give the desired allylenamine.

Direct allylation of amines with one equivalent of allyl halide gave the diallylamine as a major product (pathway I). The diallylamine product was quite difficult to separate efficiently from the desired monoallylamine. However, when the reaction was run with a twelve-fold excess of amine it gave less than one percent diallylation.



Scheme V Synthetic Routes to Allylenamines

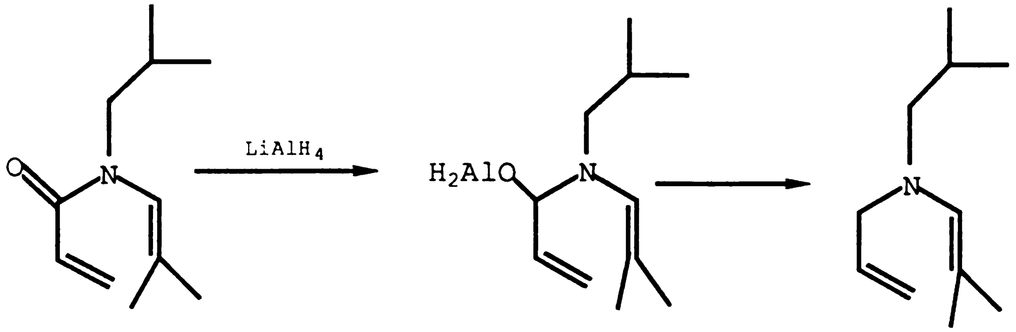
Alkylation of isobutylamine using this procedure gave a 73 % distilled yield of allylisobutylamine **18.** This route, however, was obviously unsuitable for valuable or rare amines, because of the quantity of amine required, even though the unreacted amine can be recovered almost quantitatively.

Reaction of allylisobutylamine **18** with isobutyraldehyde in refluxing benzene, in the presence of 0.025% of *p*-toluenesulfonic acid, was complete in 24 hours. Water was removed azeotropically. This reaction gave, after distillation, a 71 % yield of **21.** When heated for longer periods, a side product, that was not easily removed by distillation, was formed. This side product was not identified, because by increasing the amount of solvent and heating for only 24 hours the amount of side product formed was reduced to less than 1%, by GC. This side product is probably an aldol product from the reaction of the enamine product with more isobutyraldehyde. Interestingly, when toluene was used as the condensation solvent the additional heat, and the presence of the *p*-toluenesulfonic acid, was sufficient to drive the aza-Claisen rearrangement, albeit quite slowly, over a period of several days.

Another route to allylenamines was by the reduction of the appropriate acryloyl enamide. These were synthesized from the corresponding imine and acryloyl chloride. The imine, **17**, was easily made by the condensation of the corresponding primary amine, **16**, and isobutyraldehyde in the presence of molecular sieves to remove water. This reaction was quite exothermic, and was completed, at room temperature, in only a few hours. Distillation gave a 68% yield of imine, **17**. Because this reaction initially evolved a considerable amount of heat, care had to be taken as imines are reported to polymerize easily. Alternatively the condensation could be driven by the azeotropic removal of water, but this caused two problems: first, it increased the chances of polymerization, and second, the separation of benzene (toluene would be worse) from the product was most difficult.

The imine, **17**, could be acylated with acryloyl chloride in the presence of a base, such as triethylamine, to trap the byproduct, hydrogen chloride. Imine **17** was heated to reflux in tetrahydrofuran with a slight excess of acryloyl chloride, and produced an 88% isolated yield of the acryloyl enamide, **19**.

Reduction of the enamide, **19**, with LAH gave the enamine, **21**, (eq 10). Enamines are extremely sensitive to hydrolysis and care must be taken during workup so that the desired enamine is not hydrolyzed with the excess reducing agent and aluminum salts. When DIBAL-H was used, the enamine was only the first product; for it then rearranged to the imine which was reduced to the δ,ε-unsaturated amine by the DIBAL-H.



(10)

The third attempted route to allylenamines was through the generation and deprotonation of iminium salts, (pathway III). Imine **17** was added to an alkyl halide in an attempt to obtain salt **20**. This salt would then be deprotonated with a suitable base to yield the enamine, **21**. Imine **17**, was dissolved in benzene, treated with allyl bromide and heated to reflux. After three days, GC's of the reaction mixture showed mostly starting material and some of the enamine **21**. The salt has been isolated in the case of a cyclohexyl rather than an isobutyl alkyl group on the imine. This route has been reported to give aza-Claisen products in some cases.[28-33,35] The positive charge on the nitrogen served to promote the rearrangement in these cases.

Lewis-acid Catalyzed Aza-Claisen Rearrangements

The results of the catalyzed aza-Claisen rearrangements are summarized in Table 1. Titanium tetrachloride, having previously been reported to catalyze the aza-Claisen by Hill,[12] was the first catalyst tried on the allylenamine **21**. It was found that 0.5 equivalents of $TiCl_4$ would drive the rearrangement of **21** to **22** at 70° C; however, at this temperature, the reaction proceeded too slowly to be useful synthetically, completing the reaction only after several days. A temperature of 111° C, refluxing toluene, proved to be a satisfactory reaction temperature, completing the rearrangement in approximately 12 hrs. However, although conversion to **22** was the only product, by GC the yields, based on o-xylene as an internal standard, were only in the 20 percent range.

The catalyst loadings were reduced accordingly. Using 0.2 equivalents catalyst gave a GC yield of **22** of 85 percent while 0.1 equivalents gave a 99 percent yield. These reactions were also complete in the acceptable time of 24 hours.

Boron trifluoride etherate was also tried at the 0.5 equivalent level, but it proved to be a poorer catalyst than the titanium tetrachloride. Aluminum trichloride, a very commonly used Lewis acid, was also tested. It was found to completely destroy the starting materials with no product being detected.

Another common Lewis acid, trimethyl aluminum, was also examined. When used to catalyze the ordinary Claisen rearrangement, the addition of a methyl group to the newly formed carbonyl occurs.[13,32] A similar result was expected with the aza-Claisen. Trimethyl aluminum did not alkylate imine **22** in refluxing toluene. The trimethyl aluminum was initially used at a one equivalent level as alkylation was expected. The product formed, was imine **22**, which could be isolated by reduction to amine **23**. This rearrangement also occurred in a 99 percent GC yield (versus o-xylene internal standard).

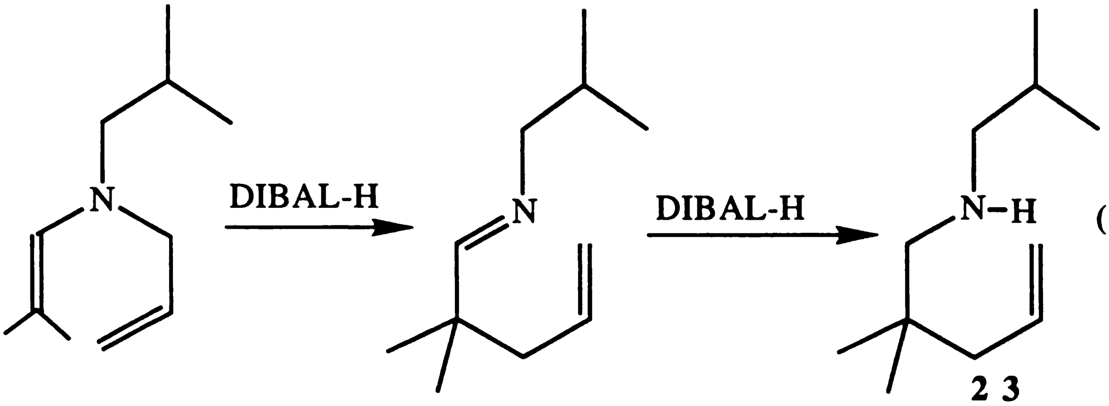
The rearrangement using one equivalent of trimethyl aluminum could be run at temperatures as low as 50° C, (see table) but the reaction was extremely slow. Catalyst levels as low as 0.1 equivalents did catalyze the reaction, in refluxing toluene, but they too, were quite slow. The optimum reaction conditions for trimethyl aluminum were found to be 1.2 equivalents of catalyst in refluxing toluene. This reaction was complete in six hours.

Table 1 Lewis-acid Catalyst Results

Catalyst	Equivalents	Time	Temperature	Conversion
$TiCl_4$	0.10	24hrs	111° C	100%
$TiCl_4$	0.50	<12hrs	111° C	100%
$TiCl_4$	0.50	<24hrs	50° C	10%
$Et_2O{:}BF_3$	0.50	slow	111° C	------
Cl_3Al	1.00	Destroys starting material		
Me_3Al	1.20	6hrs	111° C	100%
Me_3Al	0.20	24hrs	111° C	20%
Me_3Al	0.20	3 days	111° C	50%
$(PhO)_2AlMe$	1.00	12hrs	25° C	100%
$(ArO)_2AlMe$	5.00	<2hr	25° C	100%
DIBAL-H	2.00	36hrs	25° C	10%
DIBAL-H	2.00	3 hrs	111° C	60%
DIBAL-H	2.00	6 hrs	111° C	100%

The bisphenoxy methyl aluminum compounds catalyzed the oxa-Claisen at extremely low temperatures, -78° C.[15] It would be reasonable then, for these catalysts to effect the aza-Claisen at moderate temperatures. The simplest such compound, bisphenoxy methyl aluminum was tested as a catalyst for the aza-Claisen rearrangement and was found to be quite a good catalyst. One equivalent of this catalyst caused the rearrangement of **21** to **22** to occur within 12 hours at room temperature. As Yamamoto had found halogen substituents increase the catalysts reactivity, bis-(2,4,6-trichlorophenoxy) methyl aluminum was prepared and tested as a catalyst. Five equivalents of this catalyst caused the rearrangement of **21** to **22** to occur in two hours at room temperature. These bisphenoxy compounds were, thus, quite promising catalysts, having effected a 200° C drop in the rearrangement temperature.

DIBAL-H was both a good Lewis acid and an excellent reducing agent. Since the δ,ε-unsaturated amines were the desired products, instead of the imines, the reduction of the imine *in situ* was actually an advantage. The DIBAL-H produced the desired amine, **23**, from the enamine **21** in one pot, as shown in eq 11. DIBAL-H did effect the rearrangement, at temperatures as low as 25°. However, at this temperature the reaction was quite slow (3-4 days). Since the product was the δ,ε-unsaturated amine, two equivalents of DIBAL-H were used, so that the catalyst concentration did not ever go below one equivalent, ensuring a reasonable reaction time. When heated to reflux (toluene) the reaction went to over 50 percent completion in three hours. The reaction was complete, by GC in six hours.



23

(11)

All of the Lewis acids tried directly affected the reaction rate when their concentrations were varied. Therefore, the Lewis acid-enamine complex must be part of the rate determining step of the rearrangement. Thus, for a catalyst to be effective in what is normally considered a catalytic amount, approximately 0.1

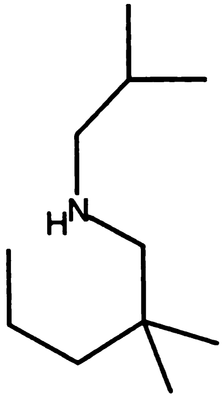
equivalents and lower, the catalyst must be extremely efficient in promoting the rearrangement.

Reduction of the γ,δ-Unsaturated Imine

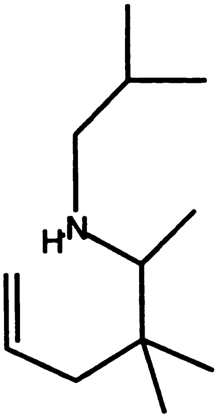
The imine, **22**, produced by the rearrangement, proved difficult to isolate with toluene as the solvent. Therefore, as imines are mainly desired only as intermediates, imine **22** was reduced ***in situ*** to amine **23** with lithium aluminum hydride. The amine was easily isolated from the toluene as its hydrochloride salt, which was then converted back to the free amine. An isolated yield of 71% of **23** was obtained for the titanium tetrachloride catalyzed rearrangement of **21**, followed by lithium aluminum hydride reduction. Using trimethyl aluminum as the catalyst, a considerably faster reaction, followed by LAH reduction, an isolated yield of 69% of **23** has been attained.

Interestingly, when titanium tetrachloride was the rearrangement catalyst, and the unsaturated amine **23** the desired product, then the reduction needed to be done at -78° C. When the reduction was done at room temperature an over-reduction occurred, which could be driven to be the sole product by heating. This over-reduction product was the fully saturated amine, **24**, and was the only product isolated. The yield of **24** was reasonable, 65%, considering the reaction was not optimized. This over-reduction only occurred in the presence of titanium tetrachloride and is thus presumably caused by an aluminum-titanium-hydride complex. When the reduction was done at -78° C over-reduction to **24** was minimal; less than two percent.

Mixtures of $TiCl_4$ and $LiAlH_4$ have been previously reported to cause facile reduction of terminal alkenes. Wilson[33] has found that equimolar mixtures of $TiCl_4$ and $LiAlH_4$ effectively reduce 1-octene to n-octane at 0° C in diethyl ether solvent. The alkane was obtained in 92% yield. Poor results were reported with disubstituted alkenes. However, Sato,[34] using 0.05 equivalents $TiCl_4$ to 1 equivalent of $LiAlH_4$, has found that although ether is usable as a solvent for the reduction of terminal alkenes it is an extremely poor solvent and it completely unsuitable for use with internal alkenes. Tetrahydrofuran was the best solvent for terminal alkenes, reduction of 1-hexene being essentially quantitative in 0.5 hours at room temperature. The use of diglyme as solvent permits the reduction of internal alkenes, including cyclohexene. The reaction of the disubstituted alkenes is quite slow; 2-hexene is reduced to n-hexane only after 80 hours at 20° C, but gives a 98% yield. Cyclohexene was reduced still more slowly requiring 150 hours at 20° C. The yield was also poor; only 46%. The $LiAlH_4$:$TiCl_4$ ratio used by ourselves, for the imine reduction, was almost identical to Sato's ratio.[41] The $LiAlH_4$ used for the imine reduction was in THF solvent. Since THF appears to be the best solvent for terminal alkene reduction, the overreduction found appears to be quite reasonable.



24

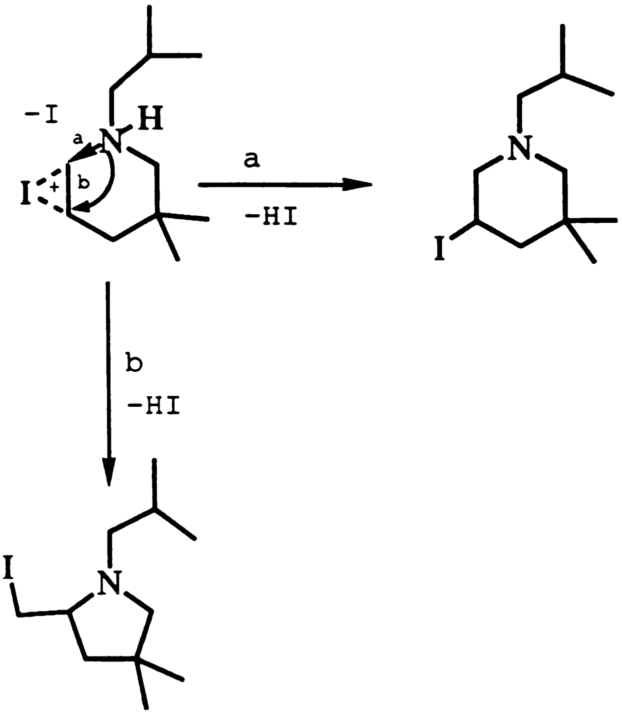


25

As imine **22** could not be isolated from toluene, a rearrangement was done in toluene ^{8}D and an NMR spectrum taken. This spectrum was compared to a sample of **22** made by condensing 2,2-dimethyl-4-pentenal with isobutylamine (81% isolated yield). The spectra were identical and the peak assignments were as would be expected for the δ,ε-unsaturated imine.

To confirm that the amine **23**, isolated after LAH reduction with trimethyl aluminum as the catalyst, was indeed not the methylated amine the methyl substituted amine **25** was prepared by reacting methyl magnesium iodide with the imine **22**. Imine **22** reacted quite facilely with methyl magnesium iodide. A 73 percent isolated yield was obtained of methylated amine, **25**. Comparison of NMR spectra confirm the identity of **25** and that it is different from **23**.

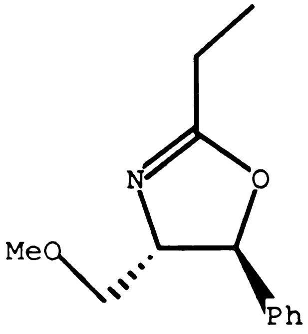
The isolated δ,ε−unsaturated amines could serve as a basis for the creation of cyclic amines. Several reports have been made of ways to cyclize unsaturated amines. Among them are; elemental iodine,[35] mercuric acetate,[42] and elemental bromine.[36] Iodine and bromine should react in a similar fashion, *via* a halonium ion transition state (see Scheme VI). If the nitrogen's lone pair attacked the tertiary side of the intermediate carbocation, a five-membered ring would result; attack at the terminal carbon would give a six-membered ring. The resulting amino iodide could then be reduced by lithium aluminum hydride to the cyclic amine. Alternatively, this iodide could be converted to several other kinds of functional groups. It is likely the mercuric acetate also goes through a similar transition state, involving the mercurium ion. The selectivity of these three cyclization reagents proved to be rather poor at room temperature. A ratio of 2:1 five-membered ring to six-membered ring was obtained with mercuric acetate, while a 3:1 ratio was obtained with



Scheme VI Iodine Mediated Cyclization

iodine. Bromine gave even worse results and also showed side product formation, by GC.

Chiral Aza-Claisen Rearrangements



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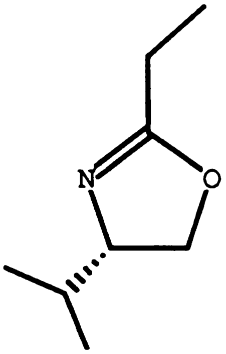
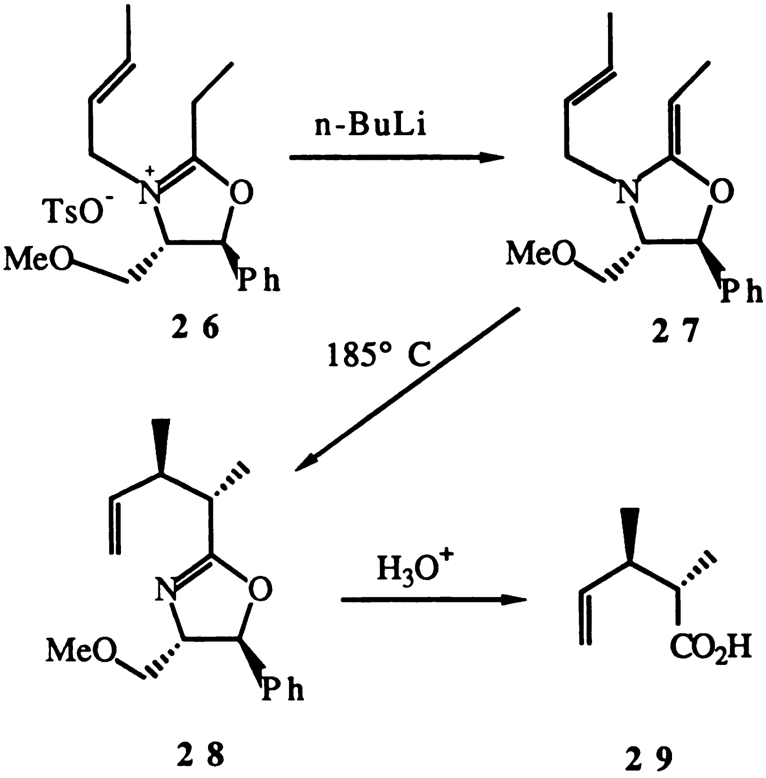


11

The use of a chiral auxiliary was one route to a stereoselective aza-Claisen rearrangement. Oxazolines have been used as chiral auxiliaries for the thermal aza-Claisen rearrangment by Kurth, but catalysis of the rearrangement of this system has not been attempted. The oxazoline **10**,[24] synthesized by Meyers, is quite similar to Kurth's oxazoline, **11**[25-27] but has the potential advantage of a Lewis basic oxygen on one of the chiral centers. This could possibly coordinate to a Lewis acid catalyst, along with the nitrogen, to increase the stereoselectivity of the rearrangment. Oxazoline **10,** however, had not been used for aza-Claisen rearrangements before. Therefore, the product ratios for this oxazoline's thermal rearrangement needed to be determined, so that they could be compared to the catalyzed rearrangements product ratios.



(12)

Cis-crotyl tosylate was used to alkylate **10** to give the tosylate salt **26** (eq 12). This salt was deprotonated with n-butyl lithium at -78° C to give the *N,O*-ketene acetal **27**, which was then thermally rearranged in refluxing decalin (185°) to give the rearrangement product **28**. Hydrolysis of **28** gave the unsaturated pentenoic acid **29** plus the initial chiral auxiliary used to make the starting oxazoline. The diastereomer of **28** shown was the major product. The ratio of diastereomers produced was determined by 250 MHz proton NMR, and found to be 80:20, allowing for the initial ratio *cis* to *trans* in the crotyl tosylate. However, 185° C is too high a temperature for many organic substituents to survive intact.

Summary

The use of Lewis acid catalysts to effect the aza-Claisen rearrangement could be seen to be a useful reaction. The substrate allyl enamines were easily prepared by a number of different routes. The δ,ε-unsaturated imines produced by the rearrangement could be reduced facilely and then cyclized into both the pyrrolidine and piperidine ring systems. The reaction can also be easily adapted to chiral substrates to create multiple chiral centers, which are common in natural products.

EXPERIMENTAL

General methods

All flasks used for water or oxygen sensitive reactions were subject to repetitive vacuum-argon purges, and heated while under vacuum (.01 mm Hg) to remove any remaining water. Other reactions were done under a nitrogen atmosphere. Toluene, benzene, tetrahydrofuran, and ether were all distilled from sodium-benzophenone ketyls. Methylene chloride, decalin and 1,2-dichloroethane were distilled from calcium hydride. The toluene ^{8}D` was vacuum transferred from a sodium-benzophenone ketyl. Other solvents and chemicals were used as provided by the manufacturer The NMR spectra were taken on either a Bruker WM-250, a Varian Gemini 300, or a Varian VXR 300S spectrometer as indicated with the spectroscopic data. Gas chromatograms were run isothermally, using a 50 meter OV-17 capillary column at 200° oven temperature, 220° injector temperature, and 250° detector (FID) temperature on a Perkin-Elmer 8500 gas chromatograph. Helium gas pressure was 15 psi with a flow rate of 2 ml/min. Infrared spectra were recorded on a Nicolet 42 FT-IR instrument.

Allylisobutylamine **18**

Allyl bromide (1 mole, 121 gm) was added dropwise to a stirred 2000 ml flask charged with isobutylamine **16** (12 moles, 876 gm). The solution was stirred and heated to reflux for two hours. The remaining isobutylamine was distilled off and the residue neutralized with a 40% NaOH solution. The aqueous base was extracted with ether; combined ether layers washed with saturated brine, and dried over anhydrous K_2CO_3 and then fractionally distilled. Yield 82.35 gm 72.9%: ^1H NMR (300 MHz, $CDCl_3$), δ 0.73 (d, J=3.35 Hz, 6 H), δ 1.15 (br. s, 1 H), δ 1.60 (m, 1 H), δ 2.23 (d, J=6.7 Hz, 2 H), δ 3.05 (d, J=5.03 Hz, 2 H), δ 4.90 (m, 1 H), δ 5.75 (m, 1 H); ^{13}C NMR (75.429 MHz, $CDCl_3$), δ 20.43, δ 28.17, δ 52.43, δ 57.28, δ 115.24, δ 136.97.

Synthesis of Enamine 21 by Condensation of 18 with Isobutyraldehyde

A 1000 ml flask under nitrogen was charged with 600 ml of benzene 175 mmol (19.75 gm) of allylisobutylamine, 175 mmol (12.6 gm) of isobutyraldehyde, and 0.25 mol% (83 mg) of *p*-toluenesulfonic acid. The flask was fitted with a Dean-Stark trap and condenser and heated to reflux for 24 hours. The reaction was monitored by GC. Workup was by distillation (74-75° C @ 20 mm Hg) of the resulting mixture which gave 112 mmol (18.68 gm) of enamine **10**, a 71% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J=6.42 Hz, 7 H), δ 1.58 (s, 3 H), δ 1.68 (s, 3 H), δ 2.27 (d, J=6.98 Hz, 2 H), δ 3.28 (d, J=6.14 Hz, 2 H), δ 5.11 (dd, J=6, 10 Hz, 2 H), δ 5.25 (s, 1 H), δ 5.84 (m, 1 H); ^{13}C NMR (75.429 MHz) δ 17.8, δ 20.5 (2), δ 22.0, δ 27.7, δ 59.5, δ 63.0, δ 116.0, δ 135.5, δ 136.5; IR (neat) 3200, 2925, 2900, 2800, 2750, 1600, 900 cm^{-1}; MS m/e 167 Daltons

Isobutylisobutylideneamine 17

A 500 ml round bottom flask, under nitrogen, was charged with 4Å molecular sieves, 150 ml diethyl ether and 100 mmol (7.3 gm) isobutylamine. Isobutyraldehyde (100 mmol, 7.2 gm) was added via syringe. The solution was stirred overnight at room temperature and then decanted away from the sieves. The solvent was evaporated under reduced pressure to leave a clear oil. Distillation (Kugelrohr) gave a yield of 8.61 gm, 67.8 % (50-65° C @ 40 mm Hg).: ^{1}H NMR (300 MHZ, $CDCl_3$),.δ 0.82 (d, J=8.1 Hz, 6 H),.δ 1.01 (d, J=8.09 Hz, 6 H),.δ 1.83 (m, 1 H),.δ 2.38 (m, 1 H),.δ 3.10 (d, J=9.49 Hz, 2 H),.δ 7.39 (d, J=6.42 Hz, 1 H); ^{13}C NMR (75.429 MHz, $CDCl_3$),δ 19.32, δ 20.31, δ 29.00, δ 33.83, δ 69.28, δ 169.40

N,N-Isobutylisobutenyl Acrylamide, 19

A 500 ml round bottom flask was charged with 300 ml THF, 100 mmol (12.7 gm) of imine **17**, and 1 equivalent (13.9 ml) triethylamine. The flask was cooled to 0° C in an ice bath and then 120 mmol (10.86 gm) of acryloyl chloride was added dropwise. The solution was heated to reflux for six hours, cooled to room temperature and then filtered away from the triethylamine hydrochloride. The solvent was removed at reduced pressure to leave a clear oil, which after distillation (kugelrohr) gave a yield of15.96 gm, 88.3%. bp. 78-83° C @ 5mm Hg, ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.86 (d, J=6.7 Hz, 6 H), δ 1.51 (d, J=1.4 Hz, 3 H), δ 1.72 (d, J=1.7 Hz, 3 H), δ 1.87 (m, 1 H), δ 3.27 (d, J=7.25 Hz, 2 H), δ 5.54 (dd, J=2.51,9.91 Hz,1 H), δ 5.79 (m, 1 H), δ 6.30 (dd, J=2.51,16.87 Hz, 1 H), δ 6.45 (dd, J=16.75,10.05 Hz, 1 H); ^{13}C NMR (75.429 MHz, $CDCl_3$), δ 17.73, δ 20.35, δ 21.98, δ 26.92, δ 54.71, δ 123.89, δ 126.91, δ 128.93, δ 135.7, δ 165.8

Titanium Tetrachloride Catalyzed Rearrangement and Reduction of 21 to 23

A 50 ml Schlenk tube was charged with a magnetic stirbar, 25 ml toluene, 10 mmol (1.67 gm) **21**, and 10 mmol (1.06 gm) o-xylene as a GC standard, all under argon. Cool the vessel to -78° C (dry ice-acetone) and add dropwise 10 mol% (110 µl) titanium tetrachloride. The vessel was heated to reflux and the reaction progress followed by GC. Complete at 24 hours cool to -78° C and add 150 mol% (15 ml

1M LAH in THF) of lithium aluminum hydride. Let stir six hours then hydrolyze with 0.6 ml water, 0.6 ml 15% sodium hydroxide, and then 1.8 ml water. Filter the resulting solution on a frit and remove solvent under reduced pressure to leave a clear oil. Distill (kugelrohr), 80° C 10 mm Hg, Yield 1.2 gm, 71 %: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.9 (s, 13 H), δ 1.7 (m, 1 H), δ 2.0 (d, J=7.54 Hz, 2 H), δ 2.30 (s, 2 H), δ 2.38 (d, J=6.7 Hz, 2 H), δ 4.9 (d, J=0.84 Hz, 1 H), δ 5.1 (s, 1 H), δ 5.8 (m, 1 H); ^{13}C NMR (75.429 MHz, $CDCl_3$) δ 20,δ 26, δ 28, δ 34, δ 44, δ 58, δ 60, δ 116, δ 136; IR (neat) 3950, bd 3800-3250, 3200, 2950, 2850, 2800, 2300, 2250, 1450, 1380, 1360, 1100, 1050, 1000, 900 cm^{-1}.

Trimethyl Aluminum Catalyzed Rearrangement of 21 to 22 Followed by Reduction to 23

A 100 ml Schlenk tube was charged with 25 ml toluene, 50 mmol (8.35 gm) of **21** and one equivalent *o*-xylene as a GC standard. A preliminary GC was taken. The vessel was cooled to -78° C under argon.and 1.2 equivalents of trimethyl aluminum added (30 ml of a 2M solution in toluene), and then heated to reflux for six hours. After six hours the vessel was cooled to room temperature and 1.2 equivalents (including trimethyl aluminum) of a 1M THF solution of LAH was added dropwise. The reaction was stirred overnight and hydrolyzed in the same fashion as done previously. The reaction mixture was filtered and the solvent removed under reduced pressure, to leave a clear oil. Distillation (kugelrohr) (50-60° C @ 5 mm Hg) yielded 5.89 gm (69.7 %) of product.: ^{1}H NMR (300 MHz, CDCl3) δ 0.9 (s, 13 H), δ 1.7 (m, 1 H), δ 2.0 (d, J=7.54 Hz, 2 H), δ 2.30 (s, 2 H), δ 2.38 (d, J=6.7 Hz, 2 H), δ 4.9 (d, J=0.84 Hz, 1 H), δ 5.1 (s, 1 H), δ 5.8 (m, 1 H); ^{13}C NMR (75.429 MHz, CDCl3) δ 20,δ 26, δ 28, δ 34, δ 44, δ 58, δ 60, δ 116, δ 136; IR (neat) 3950, bd 3800-3250, 3200, 2950, 2850, 2800, 2300, 2250, 1450, 1380, 1360, 1100, 1050, 1000, 900 cm^{-1}.

Bisphenoxymethyl Aluminum Catalyzed Rearrangement of 21 to 22

A Schlenk tube, charged with 1 mmol trimethyl aluminum in 5 ml toluene,was cooled to -78° C. To this stirred tube 2 mmol phenol (.17 gm) in 2 ml toluene were added. The vessel was warmed to room temperature and stirred one hour. Added dropwise was a solution of one equivalent (0.167 gm) of **21** cooled to -78° C in the same manner as for titanium tetrachloride. The reaction was warmed to room temperature and let stir 12 hours. The reaction was complete by GC (*o*-xylene internal standard)

Bis(2,4,6-trichlorophenoxy) Methyl Aluminum Catalyzed Rearrangement of Enamine 21 to Imine 22

A Schlenk tube, charged with 1 mmol trimethyl aluminum in 5 ml toluene,was cooled to -78° C, and 2 mmol 2,4,6-trichlorophenol was added. The tube was warmed to room temperature and stirred one hour. Added dropwise was a solution of 0.2 mmol (0.0334 gm) of **21** cooled to -78° C in the same manner as for titanium tetrachloride.

The tube was warmed to room temperature and the reaction monitored by GC. The reaction was complete by GC at 2 hours (*o*-xylene internal standard).

DIBAL-H Catalyzed Rearrangement and Reduction of Enamine 21 to Amine 23

A Schlenk tube was charged with 5 ml toluene and 1 mmol (0.167 gm) of **21** then cooled to 0° C. Two mmol of DIBAL-H in toluene was added dropwise. The tube was heated to reflux and the reactions progress was monitored by GC. The reaction was 50 % complete at 3 hours, and was complete at 6 hours (versus *o*-xylene internal standard).

Imine 22 by Condensation

To a 80 ml of benzene in a 250 ml round bottom flask, under argon, 20 mmol (2.48 gm) of 2,2-dimethyl-4-pentenal was added followed by 20 mmol (1.46 gm) of isobutyraldehyde. The flask was fitted with a Dean-Stark trap and a condenser and heated to reflux for 12 hours. After cooling the benzene was removed under reduced pressure to give an oil. Distillation of this oil (36-39° C @ 5mm Hg) yielded 2.96 gm of product (82.7%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J=3.35 Hz, 6 H), δ 1.04 (s, 6 H), δ 1.88 (m, 1 H), δ 2.15 (d, J=6.98 Hz, 2 H). δ 3.17 (d, J=6.7 Hz, 2 H), δ 4.95 (d, J=..Hz, 1 H), δ 5.05 (s, 1 H), δ 5.75 (m, 1 H), δ 7.25 (s, 1 H); ^{13}C NMR (75.429 MHz, $CDCl_3$) δ 20.43, δ

24.64, δ 29.12, δ 39.0, δ 44.7 δ 69.45, δ 117.21, δ 134.68, δ 170.99; IR (neat) 322, 2950, 2900, 2850, 2800, 2750, 1700, 1200, 1175, 1150, 900 cm-1

Reaction of Imine 22 with Methyl Magnesium Iodide

A solution of 20 mmol (1.67 gm) of imine **22** in 10 ml ether was added dropwise to a solution of 1.5 mmol of CH_3MgI in 30 ml ether, cooled to -78° C. The reaction was warmed to room temperature and let stir for 6 hours. The solution was hydrolyzed with 5 ml water, filtered, and the ether removed under reduced pressure to yield an oil. Distillation (kugelrohr) gave 7.3 mmol, 1.33 gm 73% (60-70° C @ 10 mm Hg)

Cyclization of Amine 23 with Iodine

A 500 ml flask was charged with 100 ml methylene chloride, 100 ml ether, and 20 mmol (3.38 gm) of amine **23**. Iodine, 1.2 equivalents (6.1 gm), was added in one batch and the flask stirred one hour. The flask was cooled to 0° C and 50 mmol of LAH in THF was added, then it was stirred 4 hours. The solution was hydrolyzed with 3 ml water, 3 ml 15% NaOH, followed by 9 ml water. The solution was then filtered and the solvents removed under reduced pressure to yield an oil. Distillation of this oil (kugelrohr) gave a yield of 14.2 mmol, 2.4 gm 71 %,(60-70° C @ 10 mm Hg).

Tosylation of Methyl Oxazoline 10 to give Salt 26

The methyl oxazoline **10**[24] and the *trans*-crotyl tosylate[26] were mixed, neat, in a flask with a magnetic stirrer, under argon. The mixture was stirred until the viscosity increase ceased, approximately 4 days. The solution was washed three times with petroleum ether to remove impurities. As **26** was a extremely viscous oil, it was dissolved directly in THF for rearrangement.

Deprotonation of Salt 26 to 27 Followed by Rearrangement to 28.

The tosylate salt, **26**, was dissolved in 20 ml THF and cooled to -78° C. Sufficient n-butyl lithium was added to bring the solution to a 1,10-phenanthroline endpoint. To the cooled vessel 50 ml of decalin was added. Additional n-butyl lithium was added to bring the solution back to the 1,10-phenanthroline endpoint. The THF was removed under reduced pressure to leave the *N,O*-ketene acetal in decalin solution. The vessel was then heated to 185° C for 4 hours to effect the rearrangement. The vessel was cooled to room temperature and the solution was extracted twice with 10% HCl and the aqueous layers washed with pet. ether. The solution was basified with 40% NaOH and extracted four times with 25 ml ether. The combined ether layers were washed with saturated brine and dried over sodium sulfate. The ether was then removed under reduced pressure to leave a red-brown oil. The yield was 61%.

BIBLIOGRAPHY

Bibliography

[1] Hill, R. K.; Edwards, A. G.,*Tetrahedron Lett.*, **1964**, 44, 3239

[2] Chan,K.; Cohen, N.; De Noble, J.P.; Specian, A. C.; Saucy, G. *J. Org. Chem.*, **1976**,41, 3497

[3] Review 1(b)

[4] Review 1 (a)

[5] Review 1 (a)

[6] Hill, R. K,; Khatri, H. N. *Tetrahedron Lett.* **1978**, 4337

[7] Takai, K.; Mori, I; Oshiwa, K; Nozaki, H. , *Tetrahedron Lett.*,**1981**, 22, 3985

[8] Yamamoto,H; Maruoka, K.; Nonoshita, K. ; Banno, H. , *J. Am. Chem. Soc.*,**1988**,110, 7922

[9] Balavoine, G.; Bram, G.; Guibe, F. *Nouv. J. Chim.* **1978**, 2, 207-209

[10] Tsuji, J.; Kobayshi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett,* **1980**, 1475-1478

[11] Rhoads, S. J.; Watson, J. M. *J. Am. Chem. Soc.*,**1971**, 93, 5813-5815

[12] Trost, B. M.: Runge, T. A. *J. Am. Chem. Soc.*, **1981**, 103, 2485-2487

[13] Bruce, J. M.; Roshan-Ali, Y. *J. Am. Chem. Soc*, **1981**, 103, 193

[14] van der Baan, J. L.; Bickelhaupt, F.,*Tetrahedron Lett.*, **1986**, 6287

[15] Mikami, K.; Takahashi, K.; Nakai, T. *Tetrahedron Lett.*, **1987**, 5879

[16] review 1(b)

[17] Hill, R.K.; Gilman, N. W.*Tetrahedron Lett.* **1967**, 1421

[18] Meyer, A. I.;Knaus, G. ; Kamata, K.; Ford, M. *J. Am. Chem. Soc.*,**1976**, 98, 567

[19] Kurth, M. J.; Decker, O. H. W., *J. Org. Chem.* **1985**, 51,1377

[20] Kurth, M. J.; Decker, O. H. W; Hope, H.;Yanuck, M. D.; *J. Am. Chem. Soc.*,**1985**, 107, 443-455

[21] Kurth, M. J.; Brown, E. G.: Decker, O. H. W.; *J. Org. Chem.*,**1985**, 50, 4984-4986

[22] Gilbert, J. C.; K. P. A.;*Tetrahedron Lett.*,**1984**, 25, 2303

[23] Brannock, K. C.; Burpitt, R .D.; *J. Org. Chem.*,**1961**, 26, 3576

[24] Houdewind, P; Pandit, U. K.; *Tetrahedron Lett.*,**1974**, 27, 2359

[25] Opitz, G; *Leibig. Ann. Chem.*,**1961**, 649, 26-37; 36-47; 47-57

[26] Opitz, G; Mildenberger, H.; *Leibig. Ann. Chem.*,**1961**, 650, 115-121, 122-132

[27] Opitz, G; Mildenberger, H.; *Angew. Chem.*, **1960**, 72, 169

[28] A. Gilbert Cook, *Enamines: Synthesis, Structure, and Reactions*, pp. 183-189, Marcel Dekker inc.1988

[29] McCurry, P. M,; Singh, R. K. ; *Tetrahedron Lett*, **1973**,35, 3325

[30] Murahashi, S.; Makabe, Y.; Kunita, K. *J. Org. Chem.* **1988**, 53, 4489

[31] Murahashi, S. I.; Makabe, Y., *Tetrahedron Lett.*, **1985**, 26, 5563

[32] Takai, K.; Mori, I; Oshiwa, K; Nozaki, H,. *Bull Chem. Soc. Jap*, **1984**, 57, 446

[33] Chum, P. W.; Wilson, S. E., *Tetrahedron Lett.*, **1976**, 15

[34] Sato, F.; Sato, S.; Kodama, H.; Sato, M, *J. Organometallic Chem.*, **1977**, 142, 71

[35] Wilson, S. R.; Sawacki, R. A *J. Org. Chem*, **1979**, 44, 287

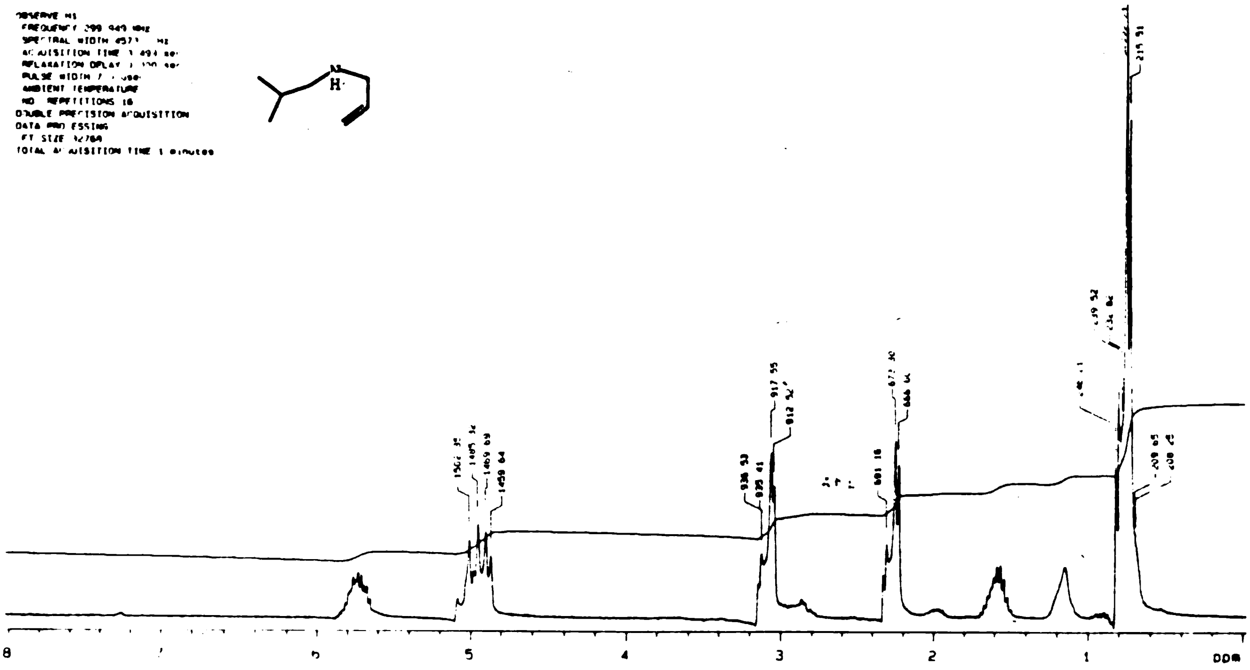
[36] Wilson, S. R.;Sawacki, R. A ; *J. C. S. Chem. Comm.*,**1977**,431

APPENDICES

APPENDIX A

APPENDIX A

^{1}H NMR SPECTRA



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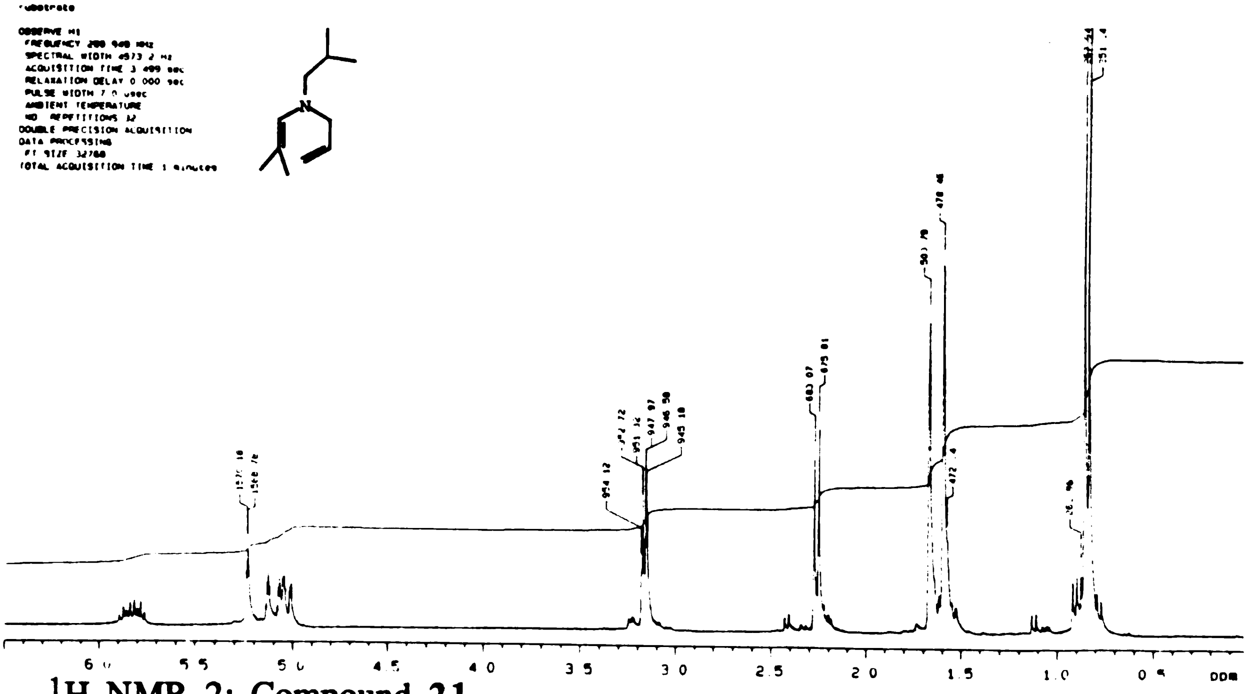

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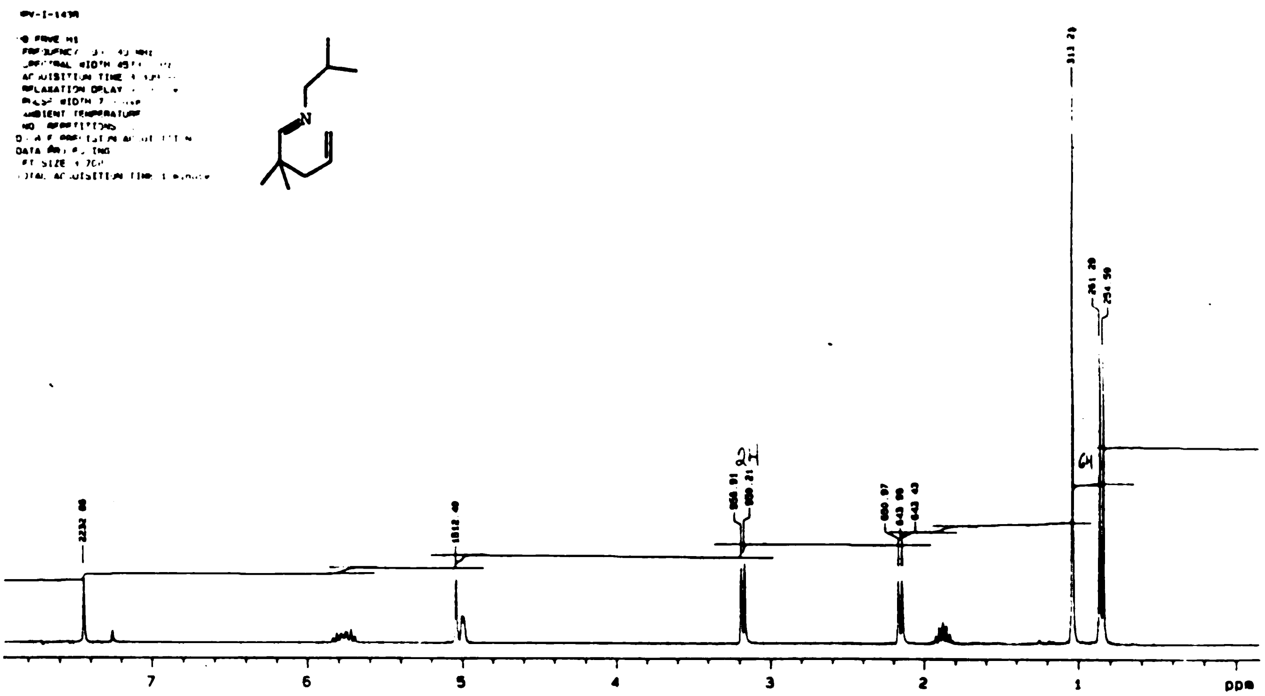

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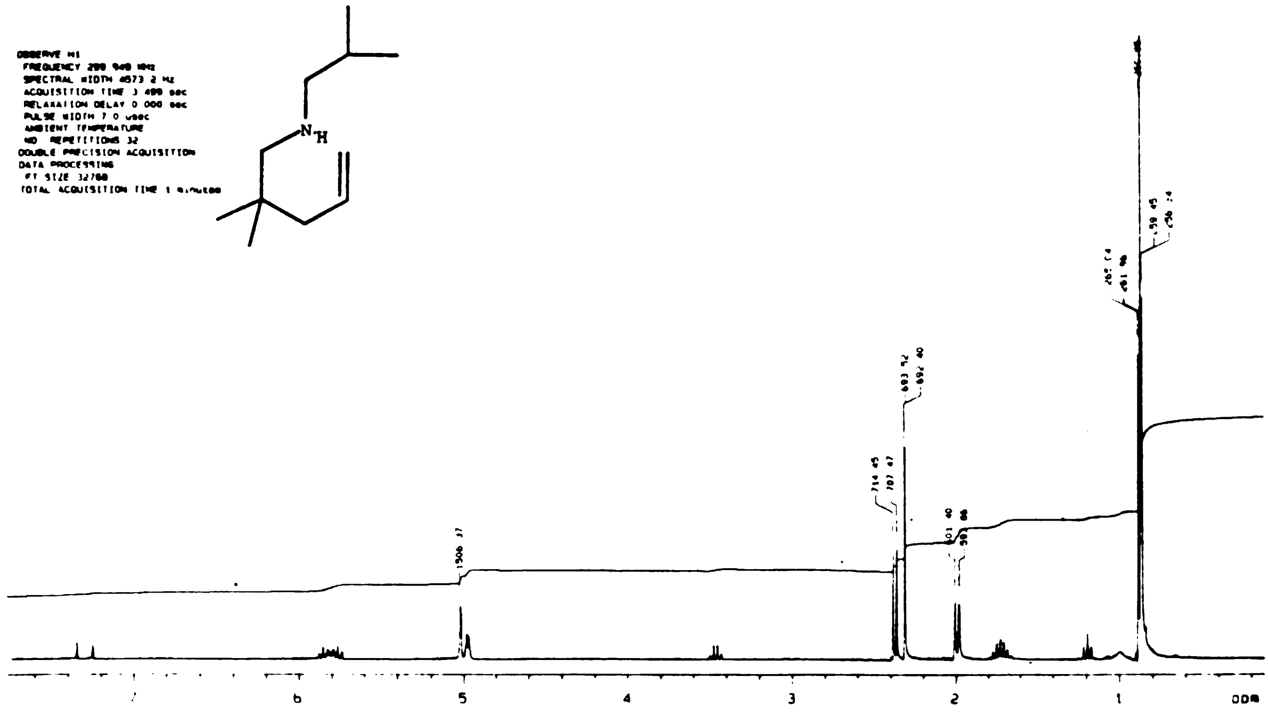

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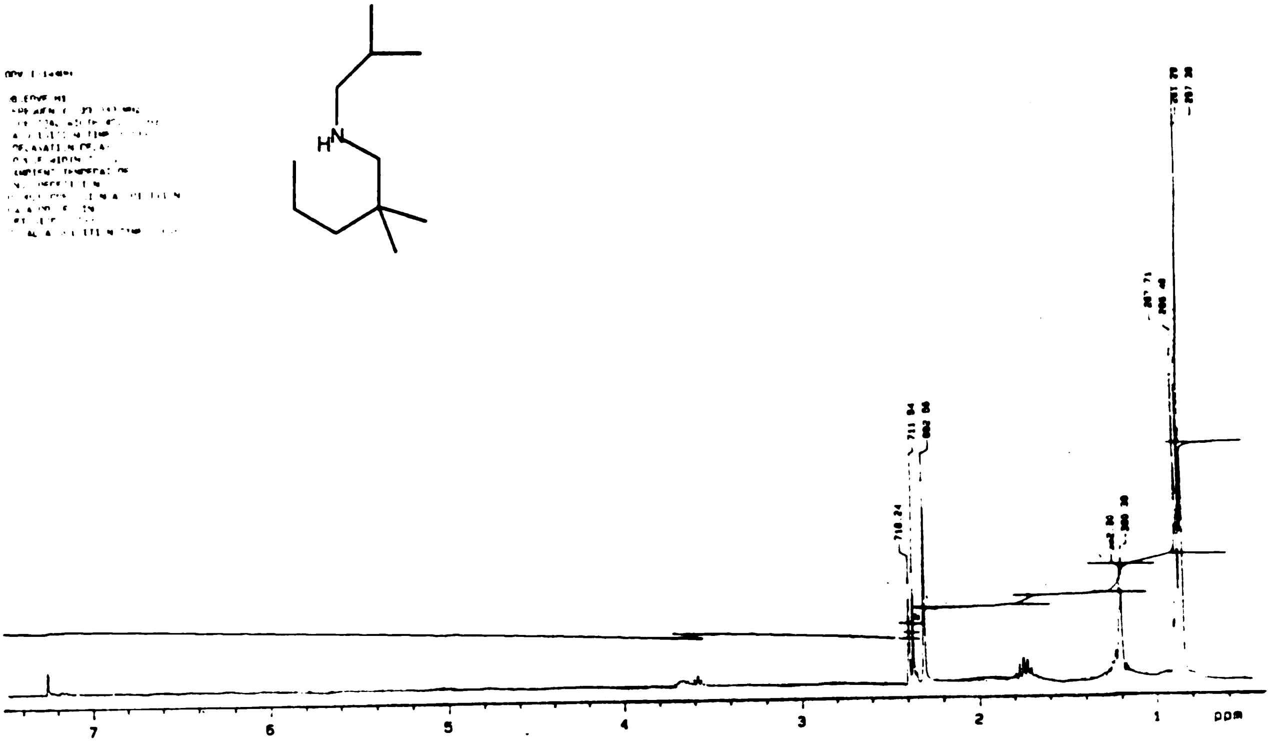

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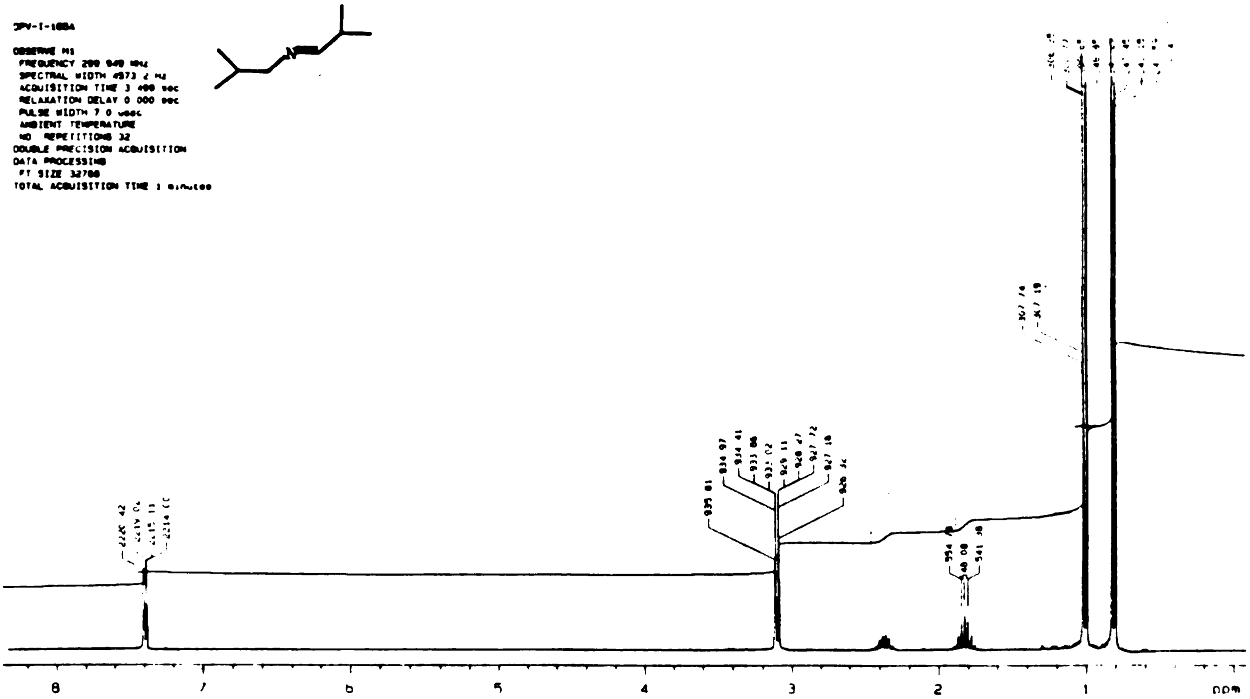

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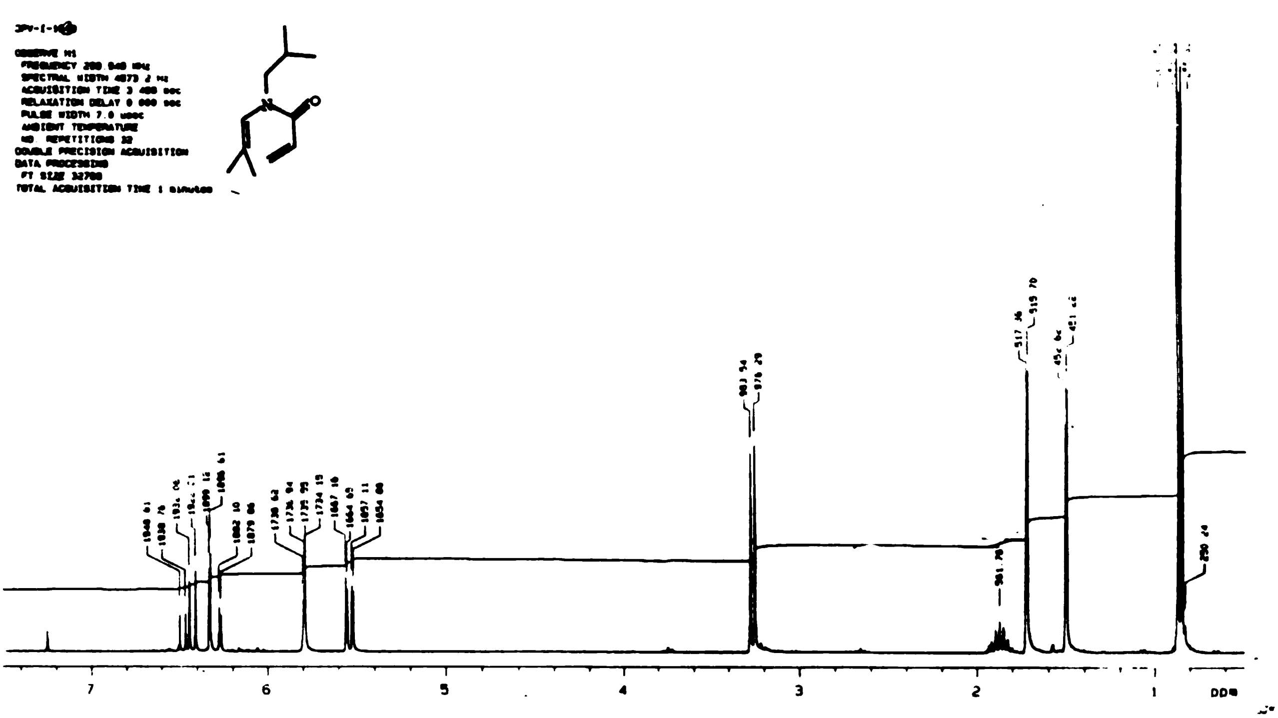

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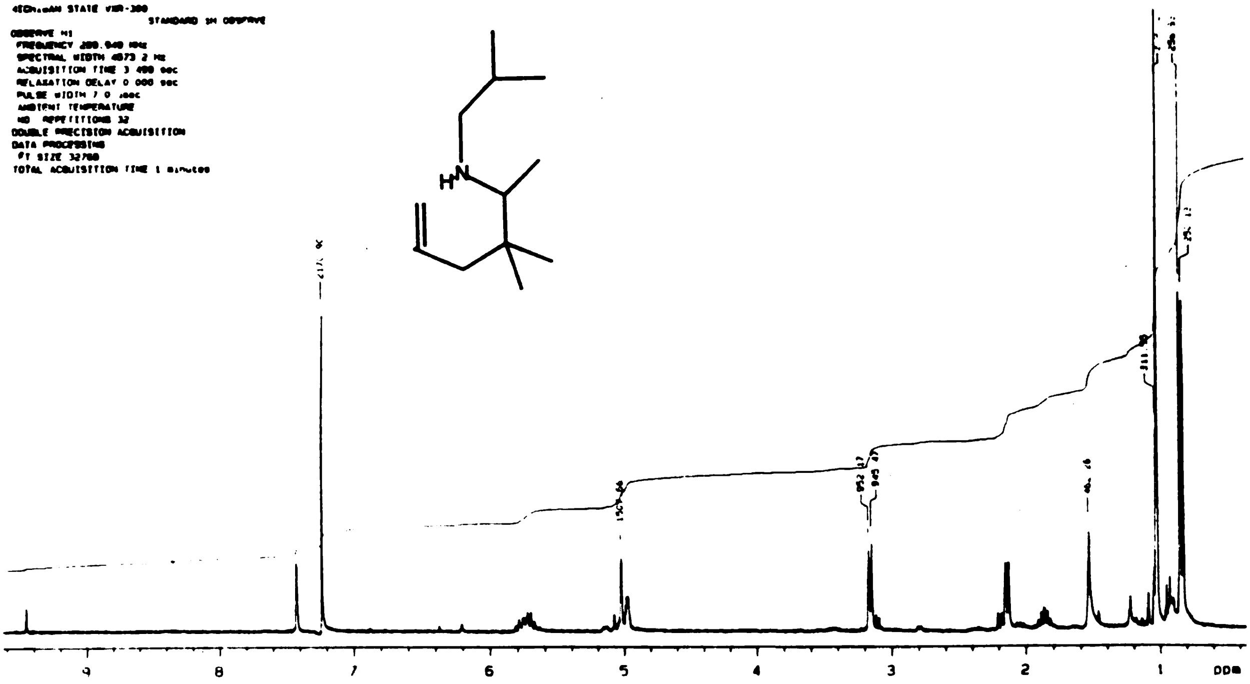
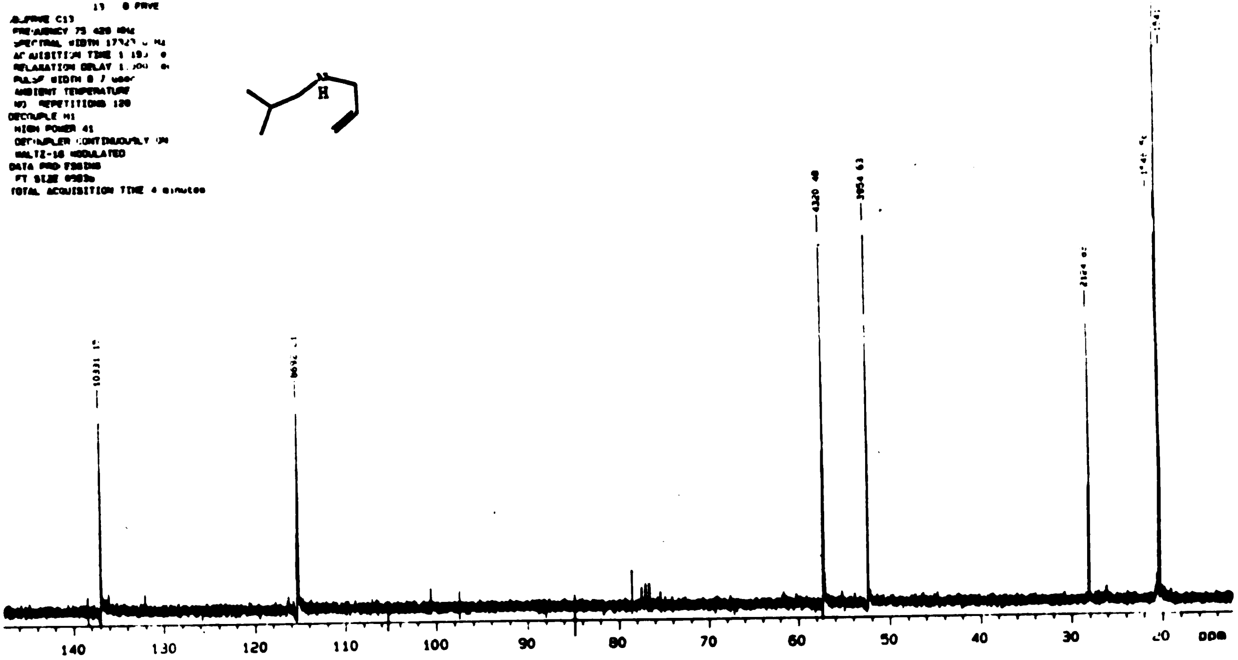


¹H NMR 8: Compound **25**

APPENDIX B

APPENDIX B

^{13}C NMR SPECTRA



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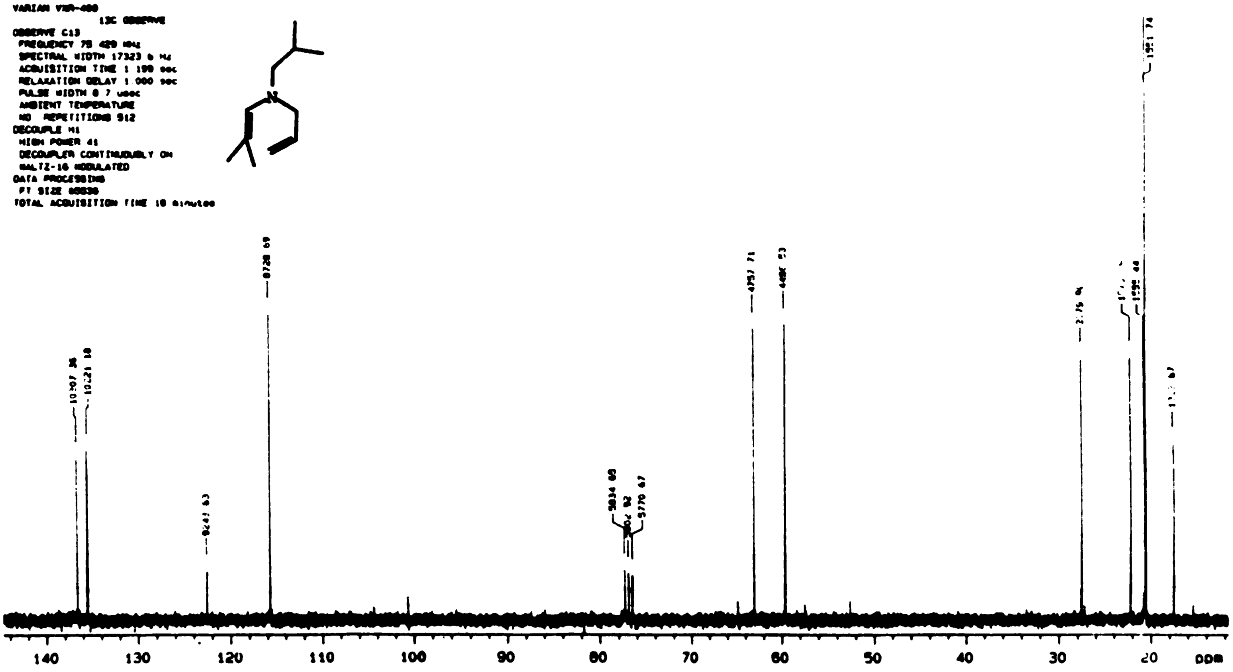

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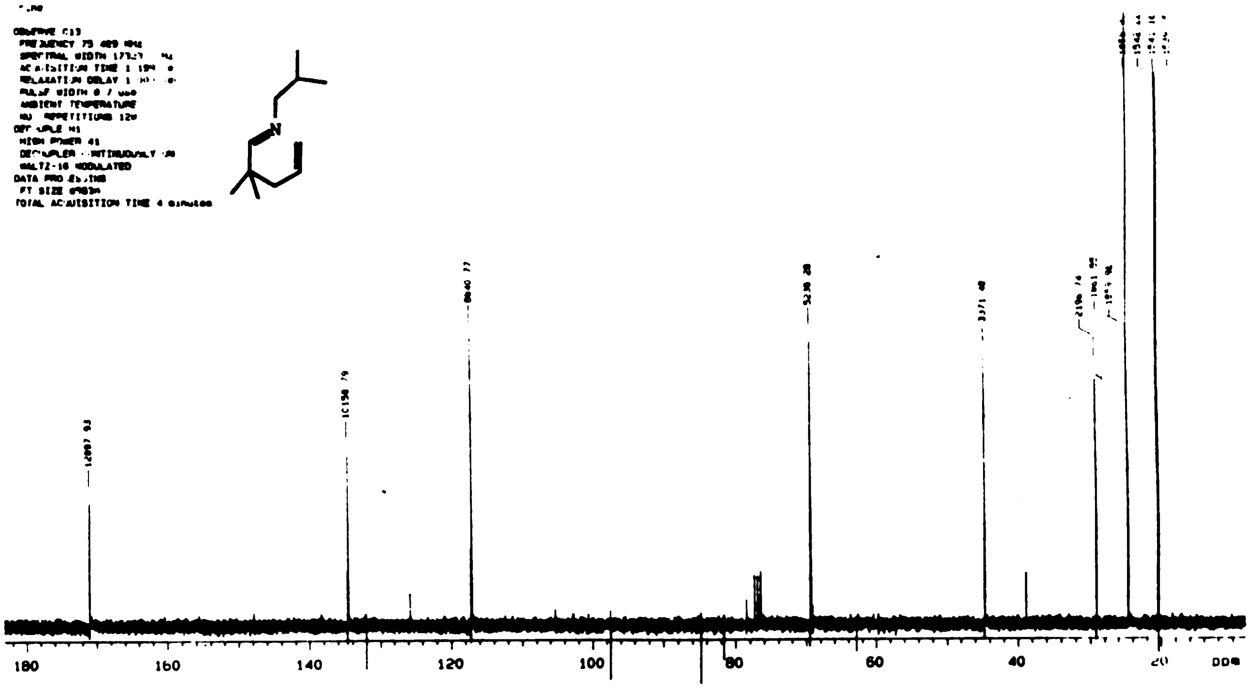

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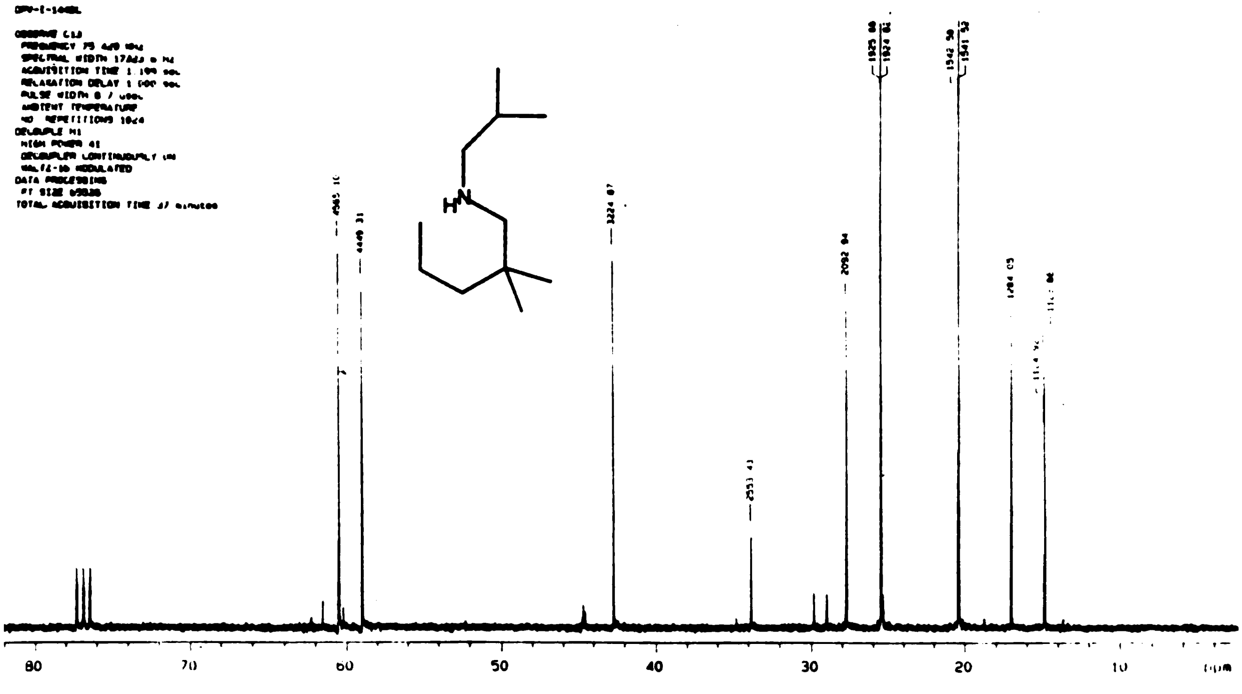

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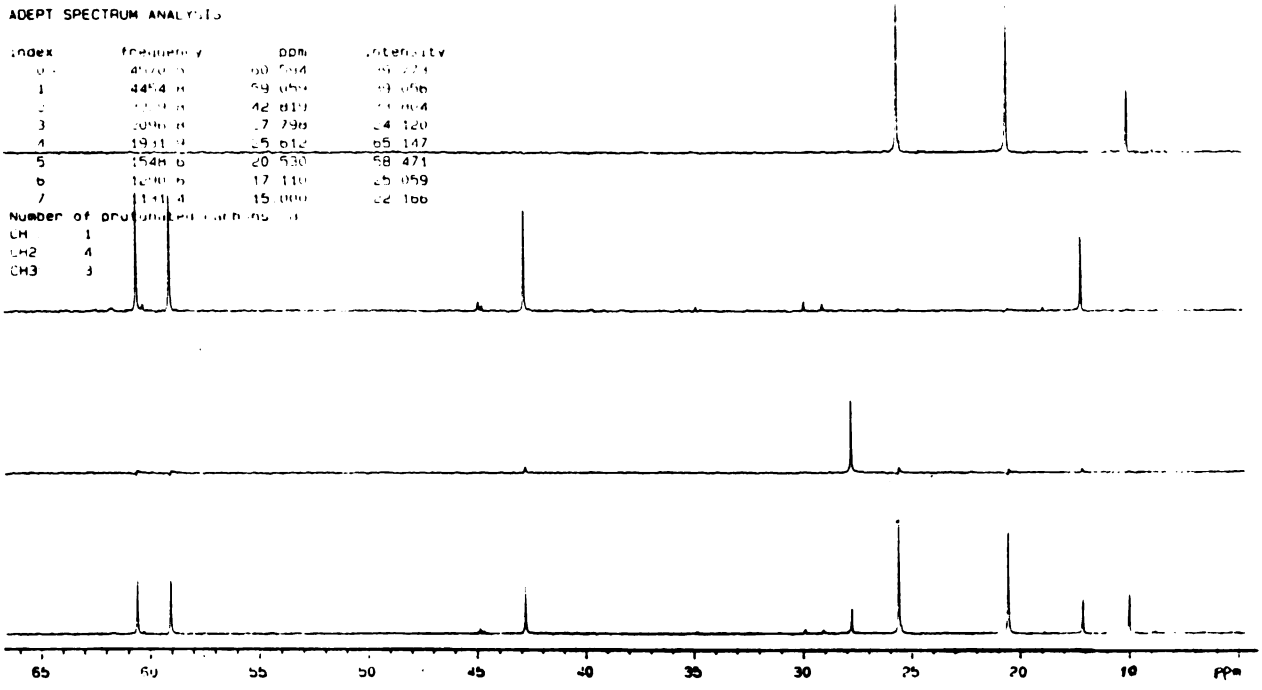

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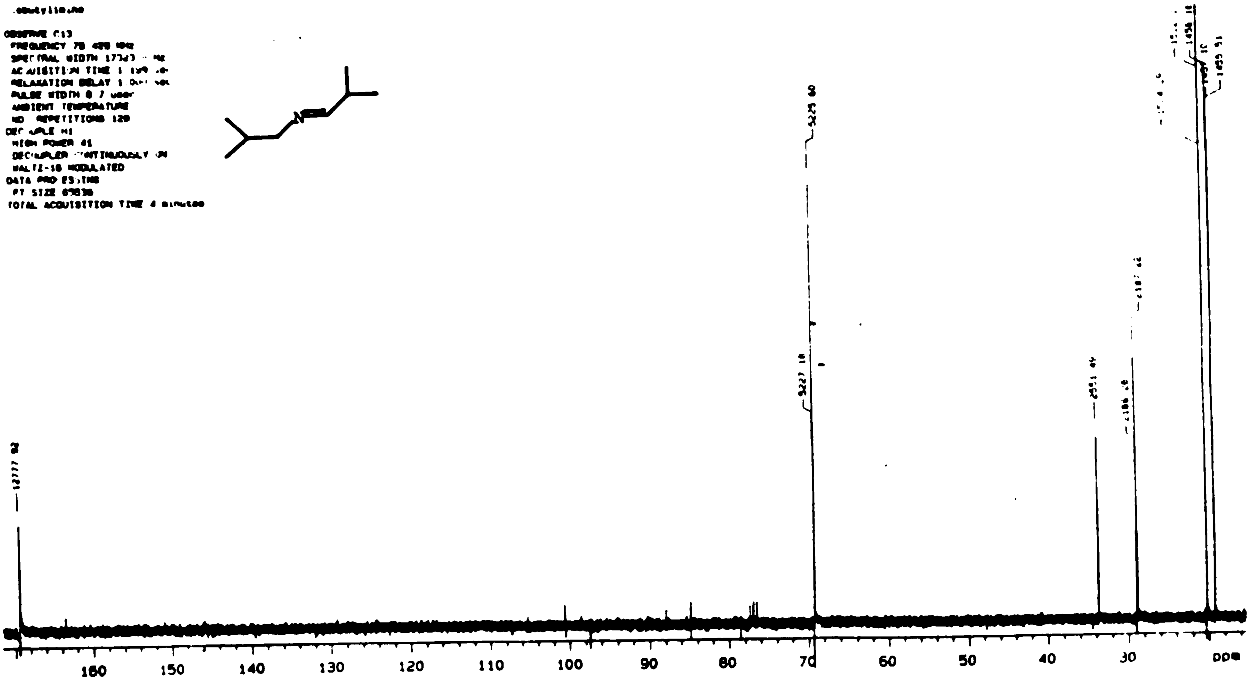
ADEPT SPECTRUM ANALYSIS

index      frequency        ppm        intensity
  0        [illegible]      60.[illegible]4   [illegible]
  1        44[illegible]4.[illegible]   59.[illegible]   [illegible]
  2        [illegible]      42.81[illegible]  [illegible]
  3        2096.[illegible] 27.79[illegible]  24.120
  4        19[illegible]1.[illegible] 25.612  65.147
  5        1548.6           20.530     58.471
  6        12[illegible].6  17.110     25.059
  7        11[illegible]1.4 15.000     22.166
Number of protonated carbons [illegible]
CH      1
CH2     4
CH3     3
```

¹³C NMR 6: Compound **24** DEPT Spectra



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.obutyl[illegible]

OBSERVE C13
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 SPECTRAL WIDTH 17343 - Hz
 ACQUISITION TIME 1.150 sec
 RELAXATION DELAY 1.000 sec
 PULSE WIDTH 8.7 usec
 AMBIENT TEMPERATURE
 NO. REPETITIONS 120
DECOUPLE H1
 HIGH POWER 41
 DECOUPLER CONTINUOUSLY ON
 WALTZ-16 MODULATED
DATA PROCESSING
 FT SIZE 65536
TOTAL ACQUISITION TIME 4 minutes
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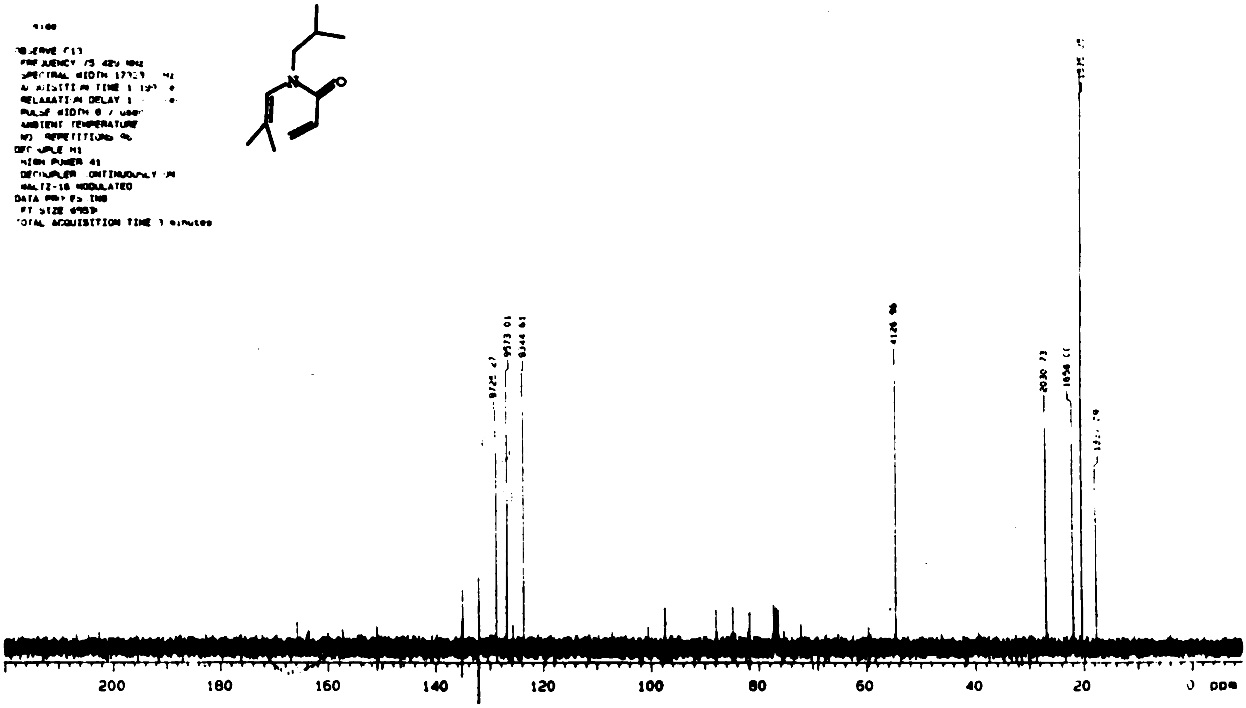
¹³C NMR 7: Compound **17**



^{13}C NMR 8: Compound **19**