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New Applications of Sigmatropic Rearrangements

to Amine Syntheses

Masa-aki Kakimoto

Contents

4. Synthesis of Pyrrolidine Derivatives. Directed 2-Aza-Cope Rearrangement.

1. Introduction

In the recent synthetic chemistry, the major objectives have been assumed as follows.

1) The overall yield should be high.

2) The reaction conditions should be mild (in the air atmosphere at room temperature, etc.).

3) The procedure should not be complicated (the usual equipment, easy separation of the products).

4) The reagents should be easily available and inexpensive.

5) The reaction should be regio- and stereo-selective.

Despite the discovery in 1912 (Claisen rearrangement),[1] the sigmatropic rearrangement has only since the mid 1960's become a useful tool to the synthetic organic chemist, this being due to the discovery of a series of new reagents of the points above. The sigmatropic rearrangement, particularly useful ones in the synthetic chemistry being [2,3] and [3,3]-sigmatropic rearrangement, is the one of the intramolecular rearrangement, and thus, it is considered as the powerful methodology of the carbon-carbon bond formation by the reorganization. The many elegant kinetic, stereochemical and theoretical studies[2] that have provided the insight into and

$$\overset{-}{Y} - X \quad \rightleftharpoons \quad Y - \overset{-}{X}$$

[2,3]-Sigmatropic rearrangement

$$X \overset{}{\underset{Y}{\diagdown}} \overset{Z}{\diagup} \quad \rightleftharpoons \quad X \overset{}{\underset{Y}{\diagup}} \overset{Z}{\diagdown}$$
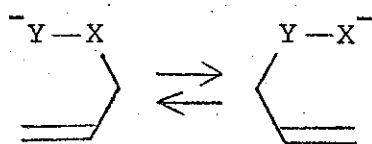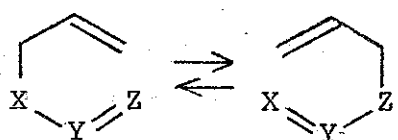
[3,3]-Sigmatropic rearrangement

appreciation for the sigmatropic rearrangement prompted many of the synthetic applications.

Many examples of [2,3]-sigmatropic rearrangement which are already used as the synthetic methodology have been reported.

$$\overset{\diagdown}{S}=O \quad \rightleftharpoons \quad -S-O \qquad \qquad (1)^{3)}$$

$$\overset{\diagdown}{\underset{+}{S}} - \overset{-}{\underset{}{C}} \overset{\diagup}{\diagdown} \quad \longrightarrow \quad -S-C \overset{\diagup}{\diagdown} - \qquad (2)^{4)}$$

$$X - \overset{-}{C} \overset{\diagdown}{\diagdown} \quad \longrightarrow \quad \overset{-}{X} - C \overset{\diagup}{\diagup} - \qquad X = O, \ S \qquad (3)^{5)}$$
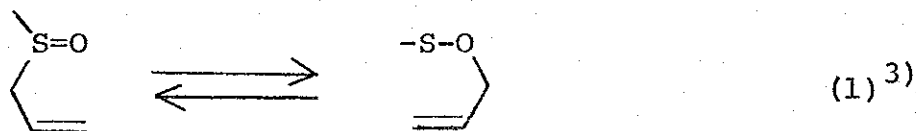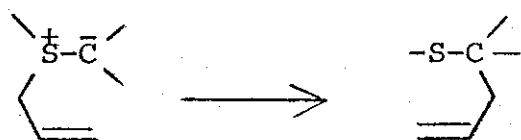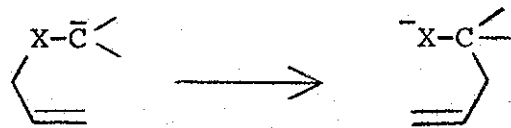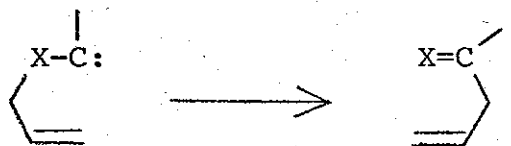
$$X - \overset{|}{C}\colon \quad \longrightarrow \quad X = C \overset{\diagup}{\diagup} \qquad X = O, \ S \qquad (4)^{6)}$$

In [2,3]-sigmatropic rearrangement of allylsulfoxide (eq.1),

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which was developed mainly by Evans,[7] it was demonstrat-
ed that the allylsulfoxide was the synthetic equivalent
of 1.[8] As shown in eq.5, by reversible sigmatropic
rearrangement S-allylsulfoxide is conveniently prepared
from the readily available O-allylsulfenate. The
alkylation of α-carbon and the following sigmatropic
reorganization affords γ-alkylated allylalcohol. Some
natural occuring products, nuciferal,[9] prostaglandines,[10]

(5)
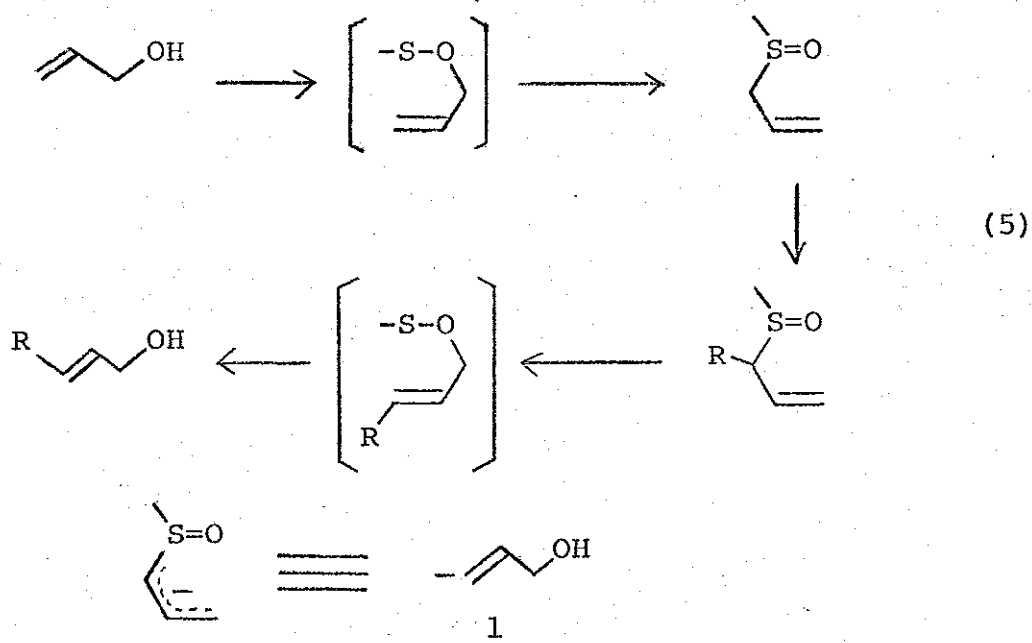
and cepharamine[11] were synthesized by this method.

   The most elegant synthesis using S-allyl S-C ylids
(eq.2) was demonstrated by Vedejs as the [2,3]-sigmatropic

(6)

3
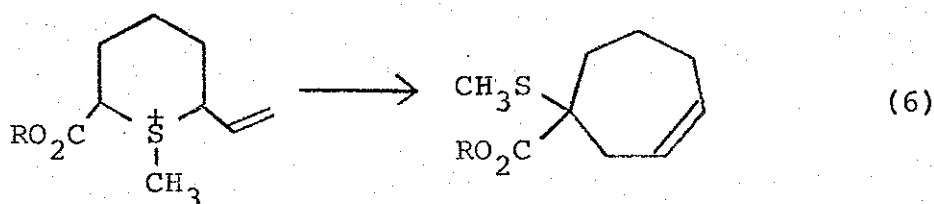
ring expansion reaction (eq.6).[12] Terpenoid syntheses[13] inclusing highly stereo-selective synthesis of bakkenolide-A,[14] were also achieved by this method.

Wittig rearrangement (eq.3)[15] and its carbene analog (eq.4)[16] have been studied in the same manner.

The typical [3,3]-sigmatropic rearrangements are Cope rearrangement[17] and Claisen rearrangement.[1] Traditionally, the Claisen rearrangement has involved the thermal sigmatropic reorganization of an allyl vinyl ether 2 into a homoallylic carbonyl compounds 3 by a concerted intramolecular process. This definition (a or d : oxygen) has been expanded to include any re-organization of type 4→5, in which at least a or d is

2   3

4   5
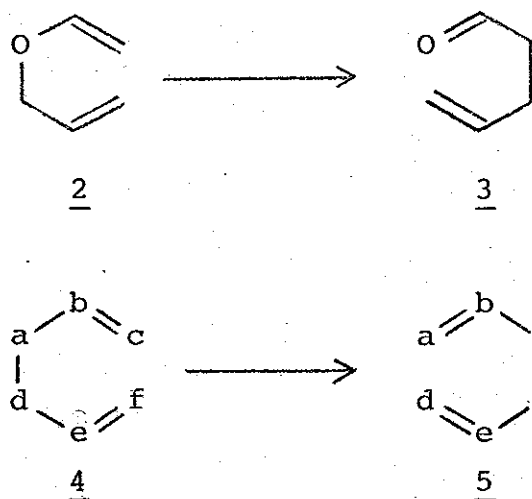
an atom other than carbon, the all carbon case being known as the Cope rearrangement. Since the applications reported about [3,3]-sigmatropic rearrangement have been more than the ones about [2,3]-sigmatropic rearrange-ment,[7],[13] many reviews for Claisen rearrangement and Cope rearrangement have been published.[18] These studies

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include the broad of stereospecific synthesis,[18d]
mechanistic studies[19] and so on.

Cope rearrangement has been utilized in the synthesis
and the structural determination of terpenoids. Thus,
sesquiterpenes, which have cyclodecadiene ring system
(Germacrene type terpenes) or which have divinylcyclo-
hexane ring system (Elemene type terpenes), can be
synthesized, and their stereo chemistry can be determined
by the stereospecificity of Cope rearrangement.[20]
Scheme I shows the simplified principle of this determina-
tion. Significant modification of Cope rearrangement is

Scheme I
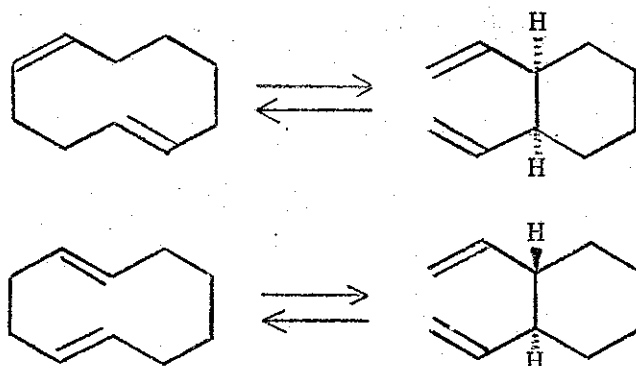
the oxy-Cope rearrangement,[21] especially its analogs of
siloxy-Cope rearrangement[22] and anionic oxy-Cope
rearrangement[23] which were developed to avoid the major
side reaction of usual oxy-Cope rearrangement such as
retro-ene elimination, and to improve the reaction condi-
tions. Although the details of anionic oxy-Cope
rearrangement will be discussed in Chapter 4, the author
assumes that the anionic oxy-Cope rearrangement will be
remarkably useful procedure in the synthetic chemistry
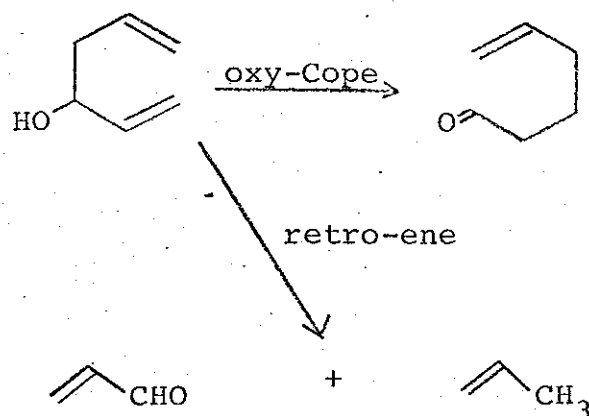
because of the mild conditions.

Claisen rearrangement may have the more spread applications than Cope rearrangement. The ready availability of allylic alcohols in organic chemistry, coupled with the generation of two functional groups of different chemospecificity such as carbonyl (electrophilic) and olefine (nucleophilic) allows for a diversity of selective transformations. Since the latent carbonyl residue (vinyl ether) is appended to the allylic alcohol, its oxidation level, functionality and substitution pattern can be conveniently altered by the judicious application of the appropriate carbonyl enol equivalent. The most common methods for preparing unsaturated carbonyl compounds, amides, esters, and carboxylic acids are illustrated in eq.(7)-(11). These methods are modification on the temperature of the rearrangement as well as the induction of the various functionalities.

$\xrightarrow{\sim 200°C}$ (7) [24]

$\xrightarrow{\sim 200°C}$ (8) [25]

$\xrightarrow{150°C}$ (9) [26]

$\xrightarrow{140°C}$ (10) [27]

$\xrightarrow{25°C}$ (11) [28]
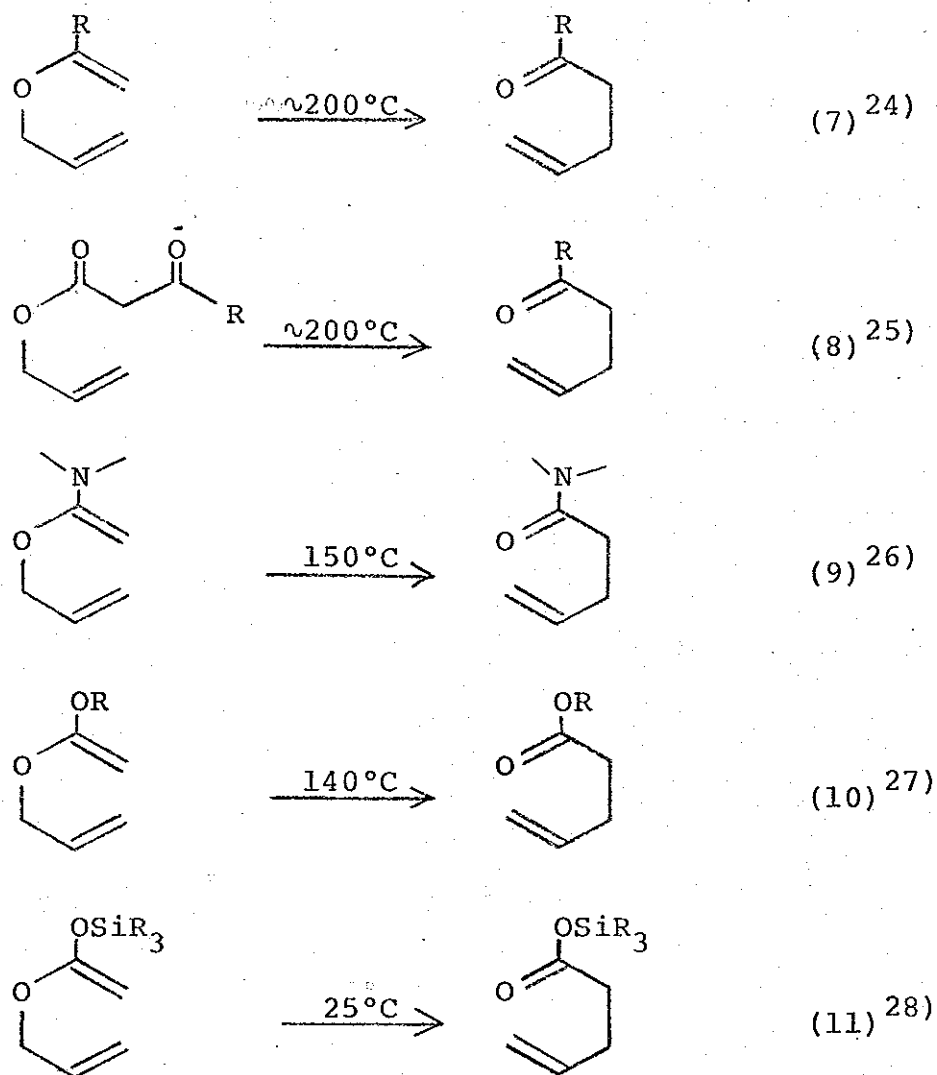
The high stereo-selectivity of the sigmatropic rearrangement is well explained by the conformation of the intermediates. In the case of [2,3]-sigmatropic rearrangement, it is known that the most stable intermediate is "exofolded envelope"[29] rather than its "endo" type (Scheme II). Similarly, [3,3]-sigmatropic rearrangement goes on via the most stable chair like transition state (Scheme III).[30]

Scheme II

Endo   (Minor)   (Major)   Exo

Z   E

Scheme III

Axial   (Minor)   (Major)   Equatorial

Z   E

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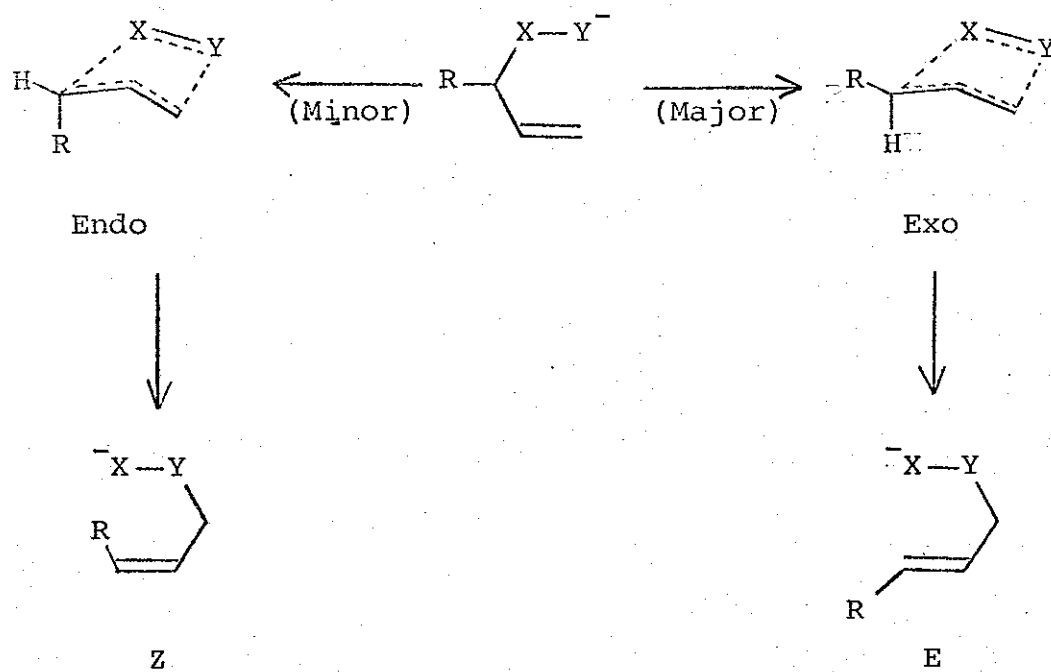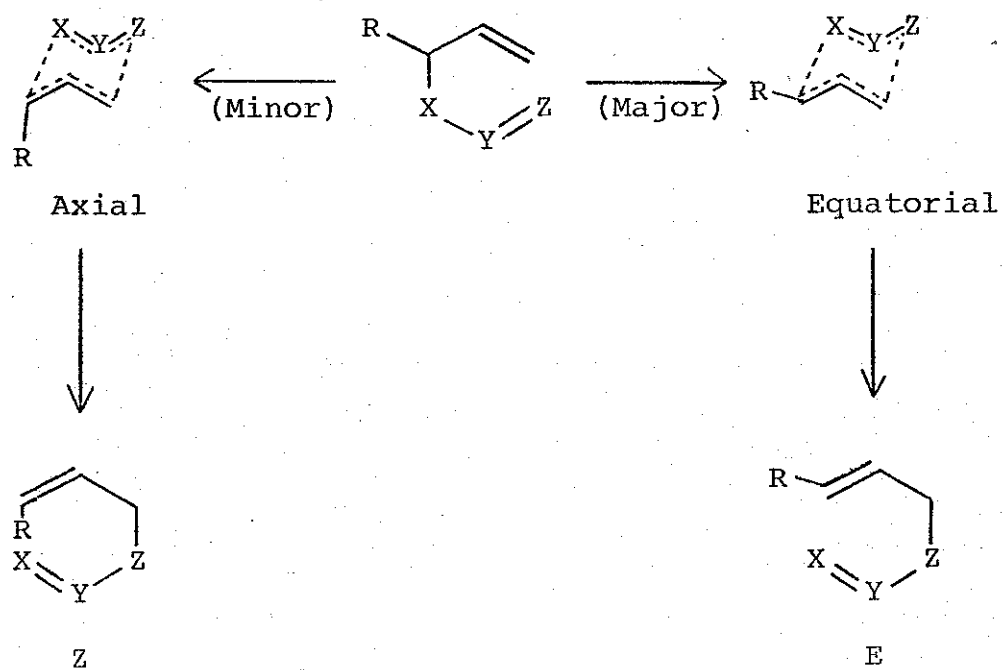
In the thesis, the auther has developed the new
synthetic methods using the sigmatropic rearrangement on
the points of view as follows;

1) The reaction condition should be remarkably mild.

2) The starting materials should be available and the
   products should be difficult to prepare by ordinary
   procedure.

3) The reaction should proceed in regio- and stereo-
   selective manner.

In Chapter 2, synthesis of allyltosylamides via
[2,3]-sigmatropic rearrangement of allylsulfilimines will
be described.
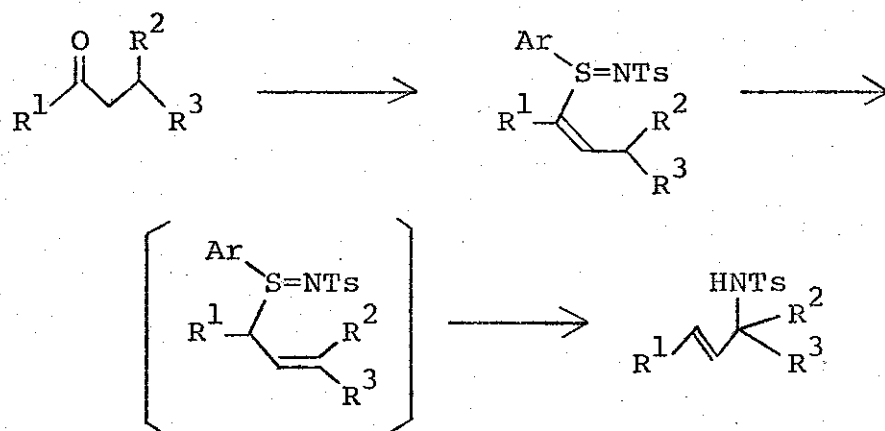
This method is convenient for the transformation of
carbonyl compounds to allyltosylamides. The characteris-
tic point of this method is that S-allylsulfilimines which
are not prepared conveniently are synthesized in situ from
readily available S-vinylsulfilimines. Allylamines, which
should be derived from allyltosylamides, are sometimes
difficult to be synthesized. Typically allylamines are
prepared as eq.12 by the classical methods.[31]

$$\text{(structure with } R^2, R^4, R^5, R^1, X, R^3 \text{)} \quad + \quad RNH_2 \quad \longrightarrow \quad \text{(structure with } R^2, R^4, R^5, R^1, NHR, R^3 \text{)} \qquad (12)$$
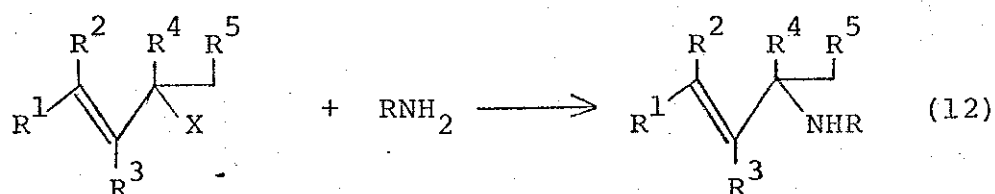
But this reaction possesses some problems such as diallyl-ation of amine (eq.13), elimination of HX (eq.14) and possibility of undesired S_N' reaction (eq.15). When the

$$\text{(structure with } R^1, R^2, R^4, R^5, N, R \text{)} \qquad (13)$$

$$\text{(structure with } R^2, R^4, R^5, R^1, X, R^3 \text{)} \quad + \quad RNH_2 \quad \longrightarrow$$

$$\text{(structure with } R^3, R^1, R^5, R^2, R^4 \text{)} \qquad (14)$$

$$\text{(structure with } R^1, R^2, R^4, R^5, RNH, R^3 \text{)} \qquad (15)$$
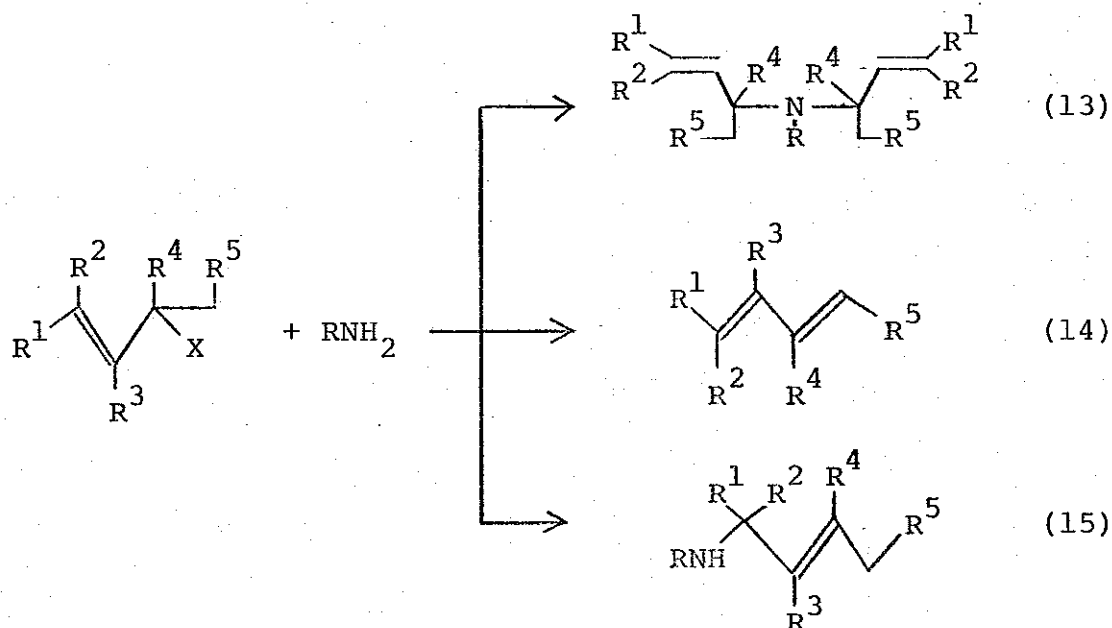
sigmatropic rearrangement is used for the synthesis of allylamines, these problems might be avoided because the reaction proceeds via the cyclic intermediate.[32]

The newly improved method of the transposition of allylalcohols to rearranged allylamines via [3,3]-sigmatropic rearrangement of allylcyanates will be described in Chapter 3. This transposition reaction is also the convenient method for the preparation of allylamines.

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Allylcyanates can be synthesized in situ by the simple
reaction between readily available allylalcohols and
cyanogenchloride. The stable rearranged allyisocyanates,
which are isolated in good yield, can be hydrolyzed by
alkali to afford allylamines. Compared with traditional

$$R^1R^2C=CRCR^3R^4 \text{ (OH)} \xrightarrow{\text{ClCN}} R^1R^2C=CRCR^3R^4 \text{ (N}\equiv\text{C-O)}$$

$$\xrightarrow{\quad} R^1R^2CCR=CR^3R^4 \text{ (N=C=O)} \xrightarrow{^-\text{OH}} R^1R^2CCR=CR^3R^4 \text{ (NH}_2)$$
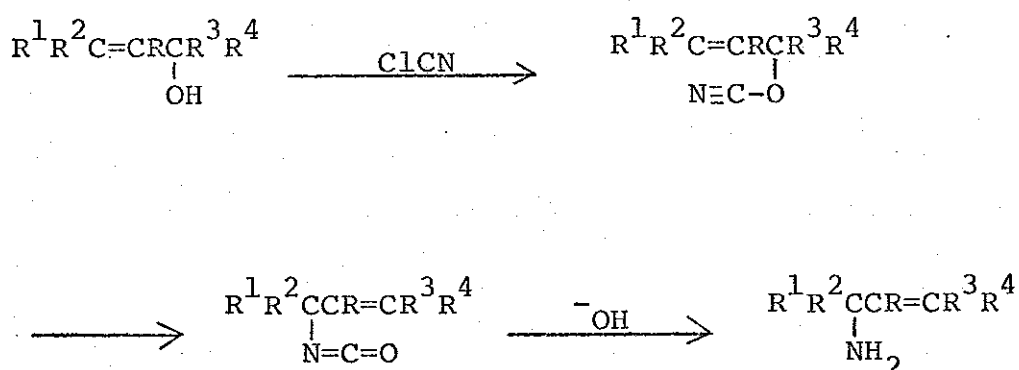
O-N functional transposition reaction,[32] the reaction
condition is remarkably improved (137°C $\rightarrow$ <25°C). The
significant improvement is that the highly hindered α-
trisubstituted allylamine, which was synthesized in only
20 % yield by the previous method, can be obtained in
ca. 50 % yield.

In Chapter 4, the new pyrrolidine synthesis through
2-aza-[3,3]-sigmatropic rearrangement will be discussed.
The pyrrolidine ring system constructs the various
alkaloids,[33] for instance, pyrrolidine alkaloids, indole
alkaloids, amaryllidaceae alkaloids, tropane alkaloids,
etc.. The pyrrolidines have been synthesized mainly by
the reduction of γ-lactam or the reduction of pyrrole
derivatives. Scheme IV shows some of the traditional

synthesis of pyrrolidines.[34]

Scheme IV
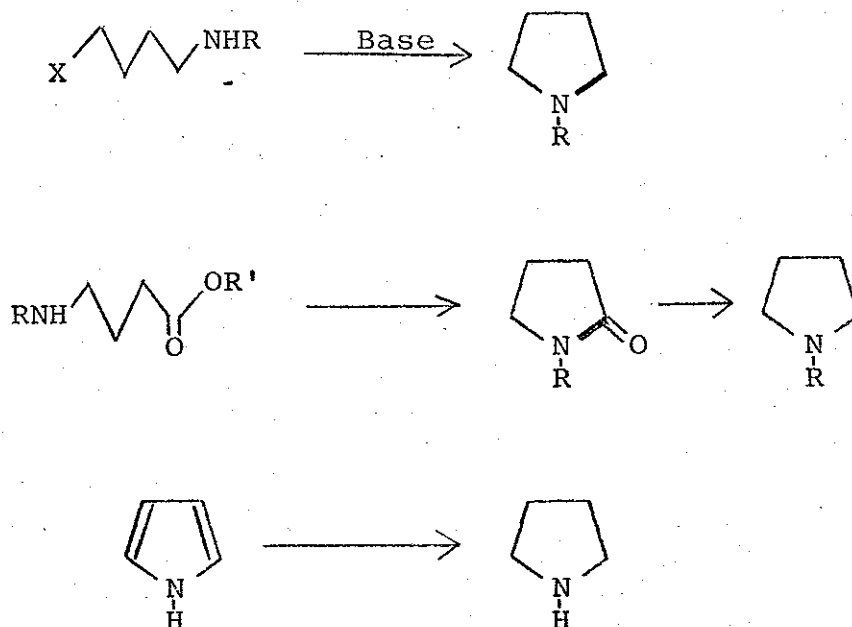
The author's strategy of the pyrrolidine synthesis
is, as shown in Scheme V, Mannich type cyclization[35] of
iminium salt $\underline{7}$. The key intermediate $\underline{7}$ can be synthesized
via 2-azonia-[3,3]-sigmatropic rearrangement[36] (quarteriz-
ed 2-aza-[3,3]-sigmatropic rearrangement in acid condition)
of iminium salt $\underline{8}$. While the problem faced on should be
how to control the equilibrium of the sigmatropic re-
arrangement ($\underline{8} \rightarrow \underline{7}$), the desired pyrrolidines $\underline{6}$ are syn-
thesized even from the thermodynamically less stable
sigmatropic isomer $\underline{7}$ (R=aromatic). It is found that the
starting sigmatropic isomer $\underline{8}$ can be prepared from carbonyl
compounds and ammonium salt $\underline{9}$ by the simple procedure, but
the limitation was that the carbonyl compounds should be
unhindered aldehydes. To improve the limitation, 5-

vinyloxazolidines <u>12</u>, which are obtainable conveniently

Scheme V
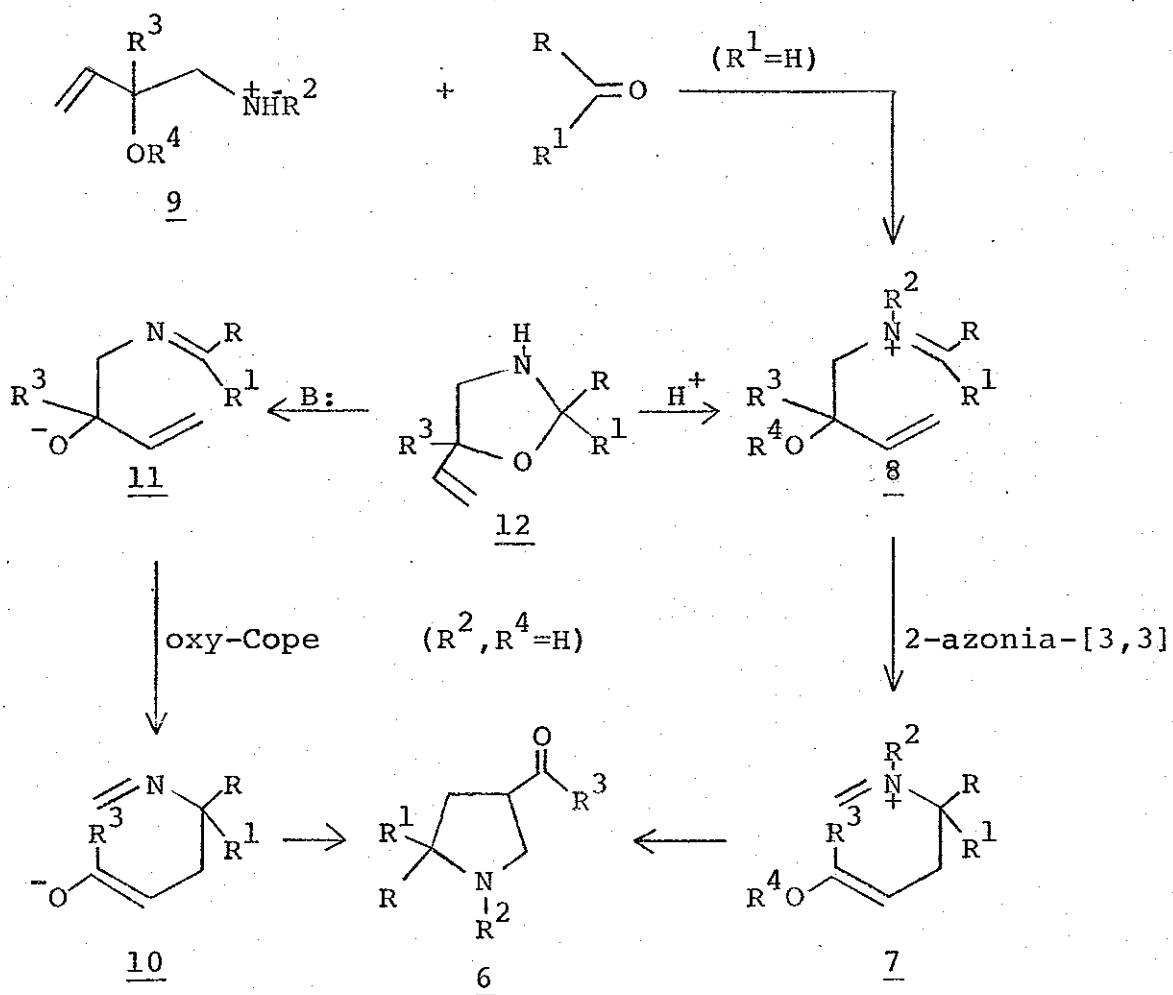
even from hindered aldehydes, are used as the precursor

of <u>6</u>, and the synthesis of <u>6</u> from <u>12</u> is examined under

both the acidic condition $(\underline{12} \rightarrow \underline{8} \rightarrow \underline{7} \rightarrow \underline{6})$ and the basic

condition $(\underline{12} \rightarrow \underline{11} \rightarrow \underline{10} \rightarrow \underline{6})$. Whereas 1-aza-spiro[4,5]decanes

<u>13</u> whose structure is difficult to construct can be syn-

thesized from <u>12</u> under the acidic condition, other pyrroli-

dines can be prepared in only low yields by acid catalyzed

2-azonia-[3,3]-sigmatropic rearrangement. On the other

hand, pyrrolidines <u>6</u> should be synthesized by the anionic

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cyclization reaction of enolate

anion 10. Furthermore, 10 should be

the sigmatropic isomer of alkoxide

11 which is clearly the starting

structure of anionic oxy-Cope re-

arrangement.[7] Thus, the pyrrolidine
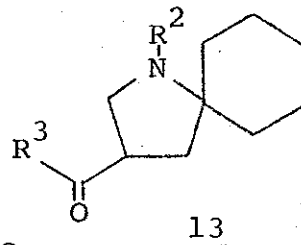
synthesis is remarkably improved by anionic 4-oxy-2-aza-

Cope rearrangement, and especially the pyrrolidines which

can not be prepared by acid catalyzed 2-azonia-[3,3]-

sigmatropic rearrangement were synthesized in good yields

under the remarkably mild conditions.

The control of the equilibrium may be one of the

problems in synthetic chemistry, which the author sometimes

have faced on through the work. In Chapter 2, the equilib-

rium of vinylsulfilimines 14 and allylsulfilimines 15

where the equilibrium should lie to 14 because of the

conjugation in $>$C=C$<$ and $>$S=N-, and the equilibrium between

15 and 16 which lies to 16[37] were successfully controlled.

Thermodynamically unstable 15 should rearrange to 16

smoothly, as 16 is cleaved when the thiophilic reagent

attacks 16 and the overall reaction which includes two

equilibrium processes (14⇄15, 15⇄16) affords allyltosyl-

14   15   16   17
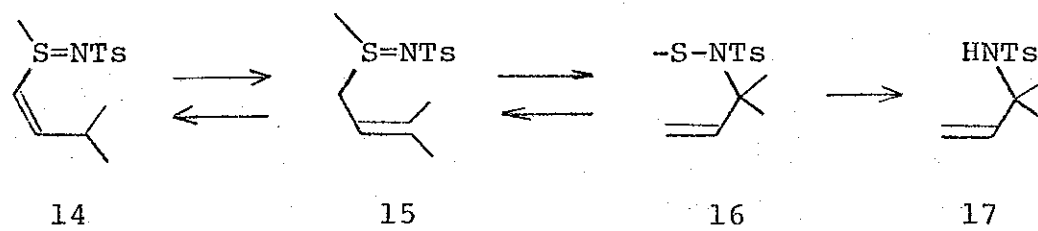
amides 17 conveniently because of the irreversible process
(16→17).

A similar control technic of the equilibrium is also
examined in Chapter 4. Thus, the pyrrolidines are
conveniently synthesized even from the less stable sigma-
tropic isomers by the simple incorporation of the irrevers-
ible processes (18→19, 20→21).
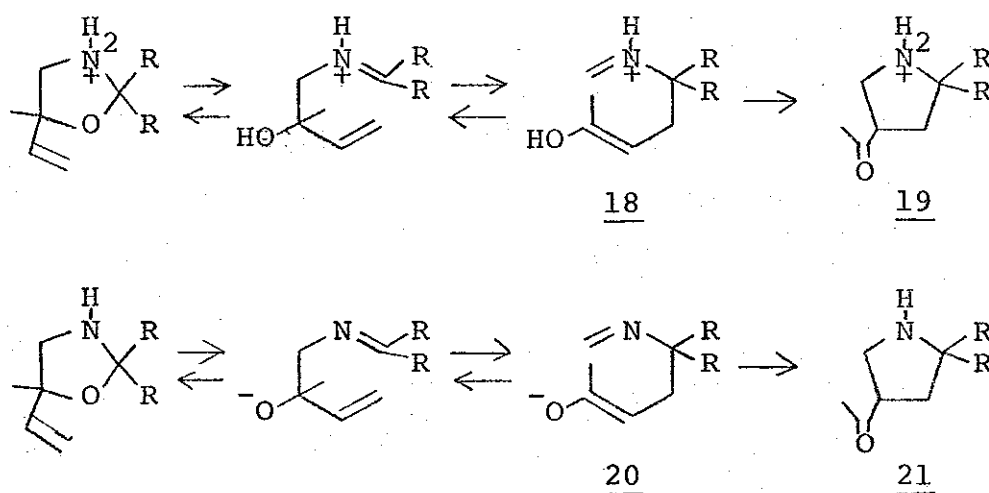
Thus, the author has developed some new synthetic
methods by means of the sigmatropic rearrangement. While
they are the simple and basic methods, they have their
own characteristics and have the abilities of the wide
applications.

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2. Synthesis of N-Allyltosylamides from Carbonyl Compounds. [2,3]-Sigmatropic Rearrangement of Allylsulfilimines.

2-1 Introduction

Yamamoto and his coworkers have studied the syntheses and the reactions of various sulfilimines.[1] N-Tosyl-sulfilimine moiety ($>$S=N-Ts)[2] has the electron with-drawing ability, and it is found that S-vinyl sulfilimines are the acceptors of Michael addition reaction. Thus, N-tosyl-S-vinylsulfilimine 1 reacted with various protic nucleophiles such as alcohols, thiols, amines and active methylene compounds, affording the corresponding Michael adducts 2 in high yields.[3] Olefinic products were
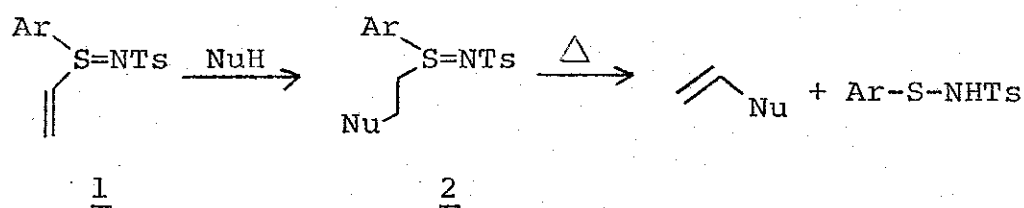
Nu : OR, SR, NR_2, etc.

produced quantitatively by the pyrolysis of these Michael adducts. The author investigated the reaction of S-vinyl-sulfilimines with Grignard reagents in the point of view of carbon-carbon bond formation.[4] In the reaction between S-vinylsulfilimines and Grignard reagents, β-

subsituted vinyl sulfides were obtained in 50-80% yield
(eg. 1). However, in the case of S-1-propenylsulfilimine,
unexpected N-allyltosylamide 3 was obtained in 10% yield
in addition to the desired vinylsulfide (21% yield)(eg.2).
This result suggests that 3 was formed via intramolecular
rearragement.

$$\text{(1)}$$

21%   10%   (2)
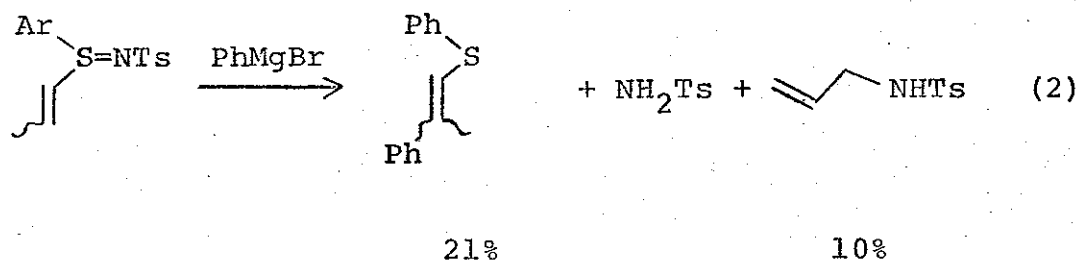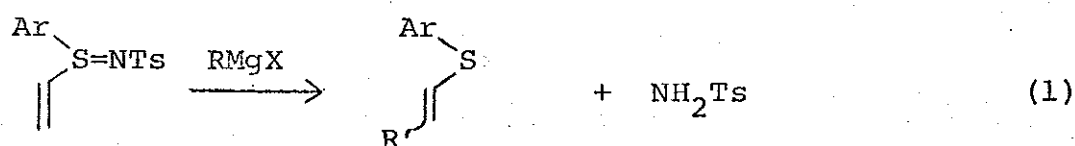
[2,3]-Sigmatropic rearrangements of allylsulfoxides[5]
and allylsulfilimines[6] are well known. Although the
trasformation from vinylsulfoxide to rearraged allylalcohol
was reported,[7] to the author's knowledge the synthesis of
N-allyltosylamides from S-vinylsulfilimines has not been
reported. The transformation[8] from S-(2-substituted vinyl)
sulfilimines 4 to N-allyltosylamides 7 must comprise the
novel isomerization of 4 to S-allyl-N-tosylsulfilimines
5 and following [2,3]-sigmatropic rearrangement to N-allyl-
sulfenamides 6, which are cleaved by the reaction with
thiophilic reagent. The result of the reaction 1-propenyl-
sulfilimine and phenylmagnesiumbromide suggests that the
isomerization 4 → 5 might be catalyzed by base. When S-

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vinylsulfilimines 4 were treated with sodium ethoxide in ethanol, corresponding N-allyltosylamides 7 were obtained in good yields.

Considering that S-(2-substituted vinyl) sulfilimines 4 are synthesized from carbonyl compounds via vinylsulfides 8,[9] this transformation to 7 is high potential methodology for synthesis of allylamines[10] from carbonyl compounds (allylamines should be prepared from allyltosylamides by the reduction[11] or the hydrolysis under acidic condition.[12]) Clearly vinylsulfides 8 are much easier to get than allyl-sulfides, and the chemistry of vinylsulfides has been developed recently.[9]
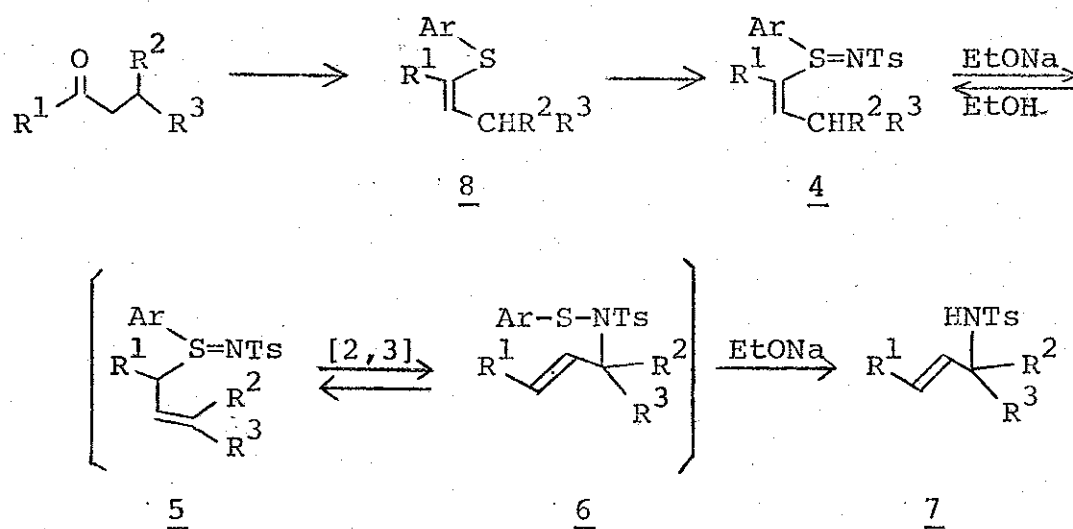
2-2 Preparation of S-(2-substituted vinyl) sulfilimines.

Synthesis of vinylsulfilimine has been well investigated[13] as Scheme I. In this project, the reaction between vinylsulfides and chloramine T was employed for the preparation of vinylsulfilimines.[14] Although vinyl-

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Scheme I
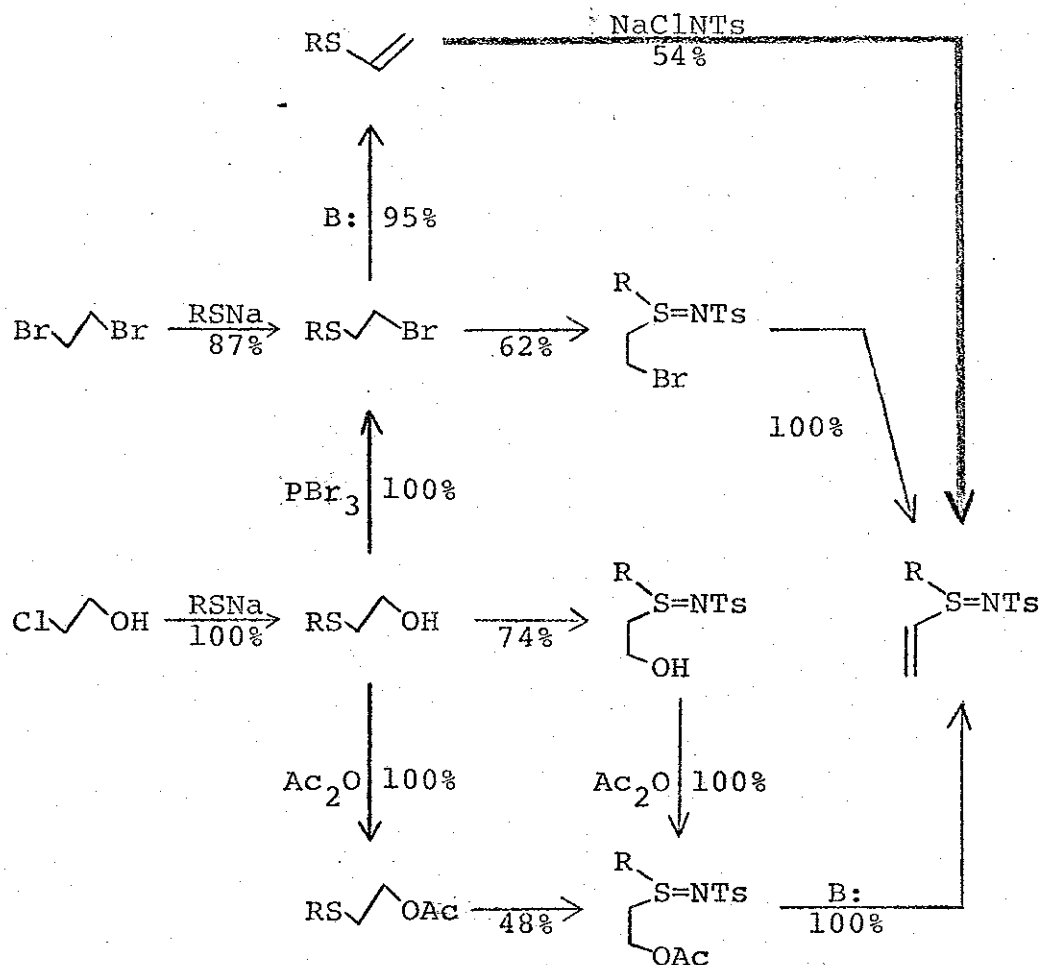
sulfilimines are not obtained in so good yield by this
method, the process has the benefit that S-(2-substituted
vinyl) sulfides 8 can be synthesized from available carbonyl
compounds with aryl thiols by easy procedures.[9]

Synthesis of S-(2-substituted vinyl) sulfides 8

The results of the preparation of S-(2-substituted
vinyl) sulfides 8 are summarized in Table 1. And the
spectral data of 8 are summarized in Table 2.

Phenyl-1-propenylsulfide 8a was synthesized from allyl-

phenylsulfide with sodium ethoxide in the manner of the description.[15]   Other S-(2-substituted vinyl) sulfides were prepared from carbonyl compounds. Thus, when carbonyl compounds were reacted with 2 equv. of arylthiol under the condition of azeotropic removal of water in toluene with catalytic amount of p-toluenesulfonic acid or simple stirring with excess phosphorus pentoxide in CH_2Cl_2 at 25°C, corresponding dithioacetals were obtained. Thermal
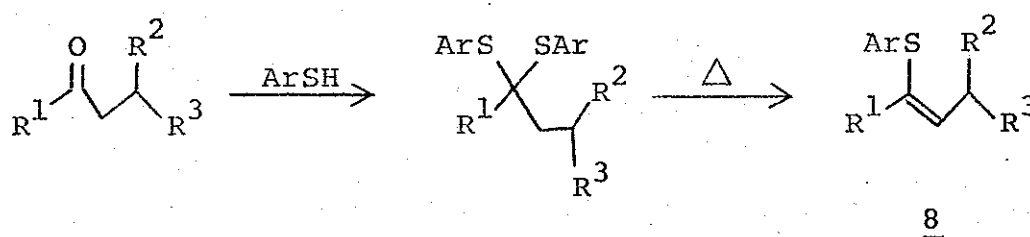
decomposition (∿200°C) of dithioacetals afforded S-(2-substituted vinyl) sulfides **8**.

NMR spectrum of **8b** showed **8b** was the mixture of E and Z isomers (ca. 2:1). Identification of the structure **8b** was as follows; two allylic methyl peaks were observed at 1.65 and 1.87 ppm, and the coupling constants of these doublets were 7.0 Hz and 6.0 Hz respectively. These values are the almost same as the ones in the literature (5.0-7.0 Hz for E, 6.0-8.0 Hz for Z).[16]

Synthesis of S-(2-substituted vinyl) sulfilimines 4

S-(2-substituted vinyl) sulfilimines **4** were prepared by the reaction between corresponding S-(2-substituted vinyl) sulfides and chloramine T in methanol.[14] The major problem of this reaction was the low yield. Generally

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Table 1. Preparation of S-(2-substituted vinyl)sulfides 8
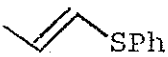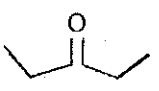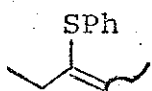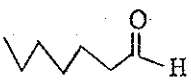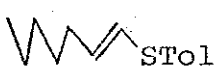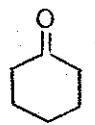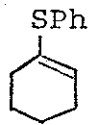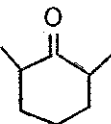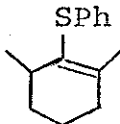
	Carbonyl	Vinylsulfide	B.p.(°C/mmHg)	Yield(%)
a	————	⌇SPh	61-69/1.5	92
b	(propanone)	SPh	83-84/2	68
c	(aldehyde)	STol	103-106/1	89
d	(cyclohexanone)	SPh	86-90/1	86
e	(2,6-dimethylcyclohexanone)	SPh	95-98/1	79

Table 2. Spectral data of 8

	IR(cm^{-1})	^{1}H NMR(δ, CDCl$_3$)
8a	3010, 1588, 1478 1447, 1023, 747	1.73(d,3H), 5.85(m,2H) 7.10(m,5H)
8b	2990, 1585, 1476 1439, 1021, 738	1.10(t,3H), 1.65,1.87(d,d,3H) 2.17(q,2H), 5.90(q,1H), 7.20(m,5H)
8c	2930, 1595, 1490 1453, 1011, 805	0.63-1.6(m,9H), 2.10(m,2H), 2.30 (s,3H), 5.83(m,2H), 7.10(m,4H)
8d	2940, 1583, 1475 1436, 1020, 740	1.60(m,4H), 2.27(m,4H) 6.00(m,1H), 7.23(m,5H)
8e	2870, 1584, 1475 1438, 1021, 735	1.10(d,3H), 1.26-2.47(m,10H) 7.13(m,5H)

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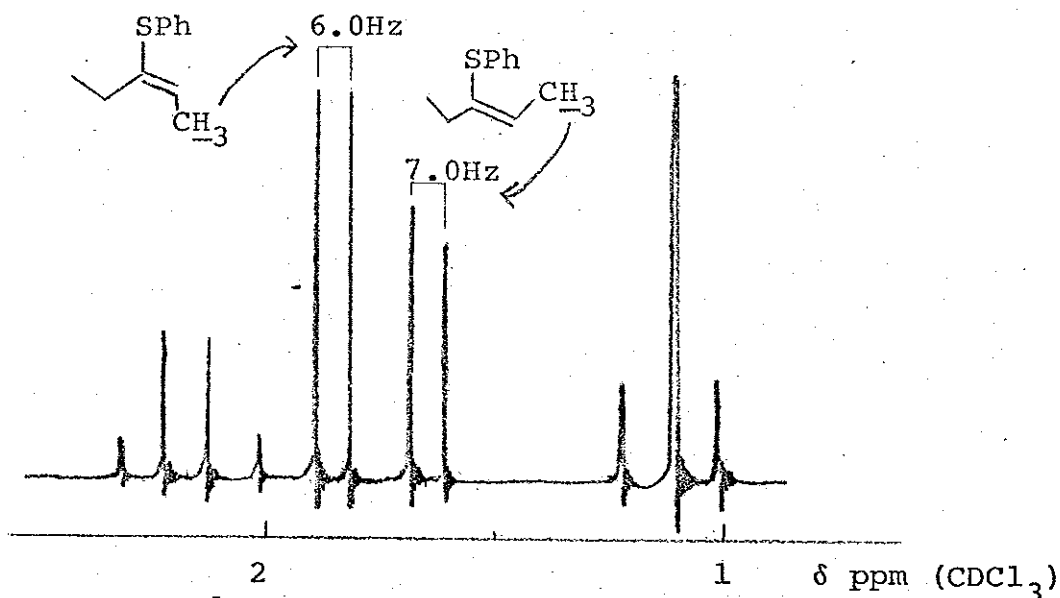
Fig. 1. ^{1}H NMR spectrum of 8b

in the reaction of chloramine T with sulfides which have

the electron withdrawing substitutions, sulfilimines are

obtained in poor yield.[2]

The results of the preparation of S-(2-substituted

vinyl) sulfilimines 4 are summarized in Table 3 and these

spectral data are shown in Table 4. In NMR spectrum of 4b,

the different chemical shifts (1.82 and 0.91 ppm) and the

different coupling constants (6.0 Hz and 8.0 Hz) of each

allylic methyls (E and Z) were observed as in the case of

sulfide 8b.

2-3   Synthesis of N-allyltosylamides from S-(2-substituted

      vinyl) sulfilimines.

Treatment S-(2-substituted vinyl) sulfilimines 4 with

sodium ethoxide in ethanol at 25∿50°C afforded rearranged

allyltosylamides 7 in good yield. The yield of 7 and the

spectral data are summarized in Table 5 and 6. As minor

products, S-2-ethoxy-alkyl sulfilimines 9 which should be

Table 3. Prepatation of S-(2-substituted vinyl)sulfilimines **4**
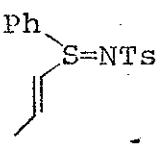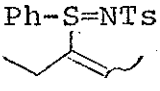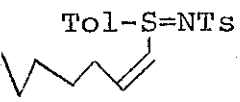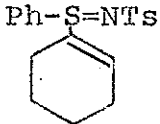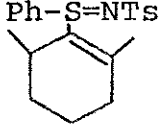
	Sulfilimines **4**	M.p.(°C)	Yield(%)
a	Ph S=NTs	96–100	45
b	Ph—S=NTs	111–112	50
c	Tol—S=NTs	128–130	67
d	Ph—S=NTs	101.5–102	78
e	Ph—S=NTs	110–112	63

Table 4. Spectral data of **4**

	IR(cm^{-1})	^{1}H NMR(δ, CDCl$_3$)
4a	1293, 1280, 1140 970, 808, 743	1.90, 2.02(d,d,3H), 2.36(s,3H) 6.19(m,2H), 7.24(m,9H)
4b	1278, 1136, 1086 985, 811, 760	0.75(t,3H), 1.82,1.91(d,d,3H) 2.20(m,2H), 2.36(s,3H), 6.54, 6.16(q,q,1H), 7.49(m,9H)
4c	1295, 1280, 1135 1075, 960, 810	0.75–1.60(m,9H), 2.38(s,3H) 2.40(s,3H), 6.12(m,1H) 6.65(m,1H), 7.50(m,8H)
4d	1285, 1139, 1085 960, 815, 750	1.53(m,4H), 2.17(m,4H), 2.40 (s,3H), 6.83(m,1H), 7.47(m,9H)
4e	1280, 1135, 1083 950, 812, 754	0.40(d,3H), 1.46(m,6H), 2.13 (m,6H), 2.37(s,3H), 7.48(m,9H)

Table 5.   Preparation of N-allyltosylamides 7
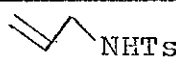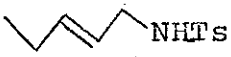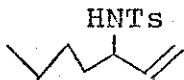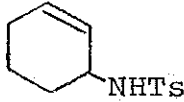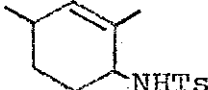
	7	M.p.(°C)	Yield(%) of 7	Yield(%) of 9
7a	⟋⟍NHTs	62-63	69	31
7b	⟍⟋⟍NHTs	oil	84	0
7c	(HNTs structure)	oil	57	39
7d	(cyclohexene NHTs structure)	95-97	83	7
7e	(dimethylcyclohexene NHTs structure)	105-107	80	0

Table 6.   Spectral data of 7

	IR(cm^{-1})	^{1}H NMR(δ, CDCl$_3$)
7a	3250, 1422, 1324 1160, 1090, 810	2.42(s,3H), 3.57(t,2H) 5.46(m,4H), 7.54(dd,4H)
7b	3280, 1425, 1322 1160, 1091, 810	0.84(t,3H), 1.92(m,2H), 2.40(s,3H) 3.54(t,2H), 5.50(m,4H), 7.58(dd,4H)
7c	3290, 1425, 1325 1155, 1090, 810	1.11(m,9H), 2.38(s,3H), 3.68(t,3H) 5.23(m,3H), 5.30(d,1H), 7.47(dd,4H)
7d	3290, 1420, 1321 1158, 1087, 808	1.89(m,6H), 2.44(s,3H), 3.82(m,1H) 5.19(d,1H), 5.58(m,2H), 7.52(dd,4H)
7e	3275, 1435, 1322 1159, 1090, 808	0.87(d,3H), 1.48(s,3H), 0.83-2.30 (m,5H), 2.37(s,3H), 3.60(m,1H), 4.75(d,1H), 5.33(m,2H), 7.50(dd,4H)

produced by the normal Michael addition reaction[4] were

obtained. To avoid the formation of undesired product 9,

7   9
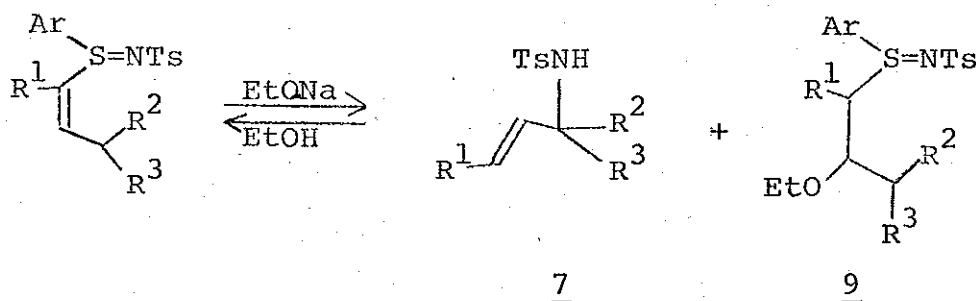
sodium t-butoxide which has little nucleophilicity was

employed as the base instead of sodium ethoxide. Thus,

when S-vinylsulfilimine 4e was treated with equal mole

of sodium t-butoxide in t-butanol at room temperature

for 24 hr, 4e was recovered in the yield of 50% and only

27% of N-allyltosylamide 7e was obtained.

While the mechanism of the transformation (4→7) was

outlined in 2-1, the mechanism of isomerization 4→5 are

supposed; 1) as depicted in Scheme Ⅱ, allyl anion formed

at γ-position of S-vinylsulfilimine 4 should be in equili-

brium with allyl anion at α-position, and S-allylsulfilimine

5 was produced by protonation.   2) S-2-ethoxyalkyl sulfili-

Scheme II

4   5

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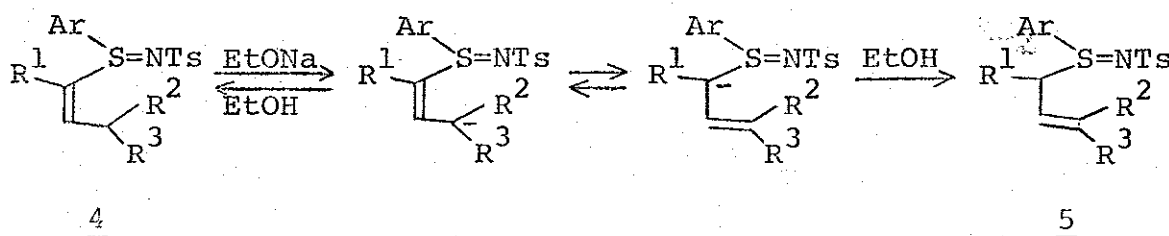
mines $\underline{9}$ might be produced by the normal Michael addition, and the elimination of ethanol might afford $\underline{5}$. In this mechanism, unacceptable points are that Michael adducts $\underline{9}$ should be very stable and the elimination should afford $\underline{4}$ but $\underline{5}$ predominantly.

Scheme III

$$\begin{array}{ccc} \underline{4} & \underline{9} & \underline{5} \end{array}$$
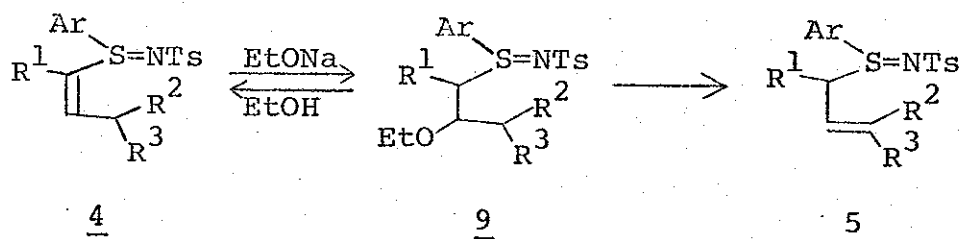
Through the reaction $(\underline{4} \rightarrow \underline{7})$, a few equilibrium steps seem to be contained (eg. 3). These equilibriums are

$$\begin{array}{cccc} \underline{4} & \underline{5} & \underline{6} & \underline{7} \end{array} \qquad (3)$$

+ Ar-S-OEt
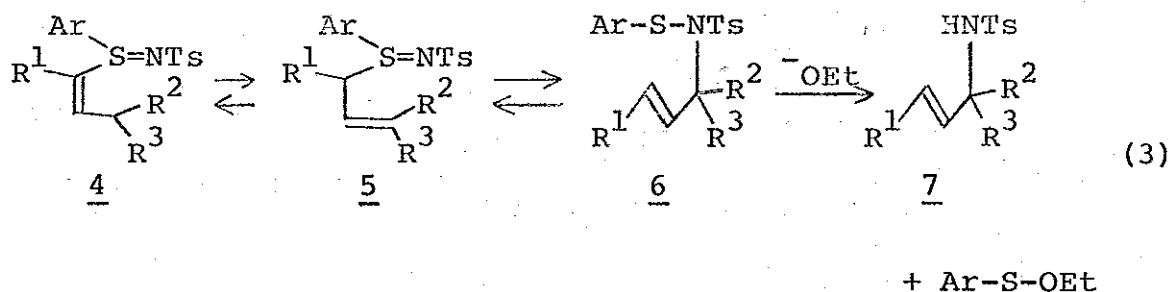
controlled by the final cleavage of N-allylsulfenamide $\underline{6}$ with thiophilic reagent (NaOEt). When sodium t-butoxide was used as the base in this reaction, $\underline{7}$ was obtained in low yield. It is why sodium t-butoxide has the far small thiophilicity compared with sodium ethoxide.

According to the NMR spectrum of $\underline{7b}$ using decoupling technique, double bond of $\underline{7b}$ was constructed by E comformer only. This result means that the rearrangement $\underline{4} \rightarrow \underline{7}$ proceeds

Scheme IV
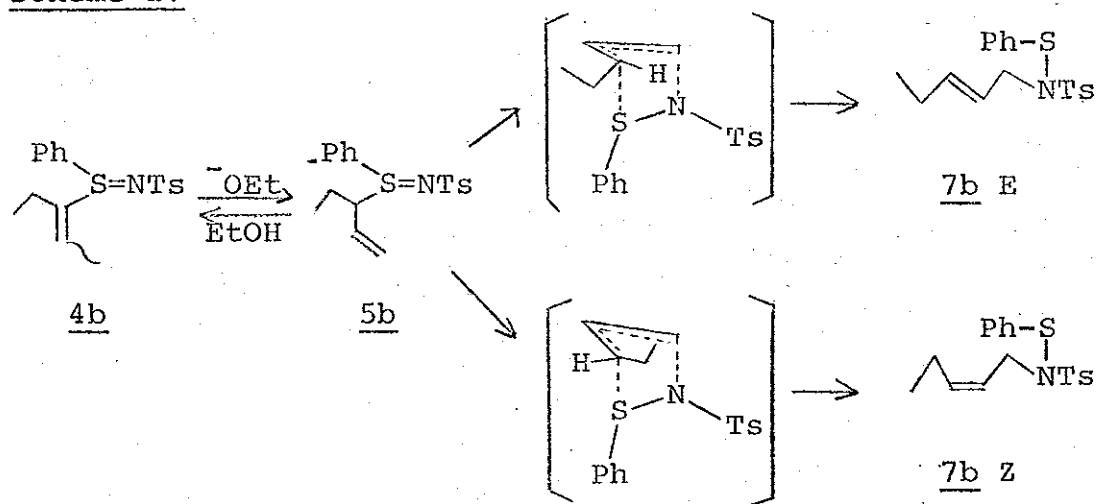
in very high stereoselective manner via "folded envelope" form intermediate.[17] In this theory, the configuration of α-position of sulfur atom decides the stereochemistry of producing olefine. As showen in Scheme IV, all the substitutions should be exo-position in the most stable intermediate. Considering that only E isomer was obtained in this reaction, the equilibrium exists between 4b and 5b and only one configuration at α-position can rearrange smoothly.

2-4 Experimental Section

Tetrahydrofuran (THF) was purified by distillation from lithium aluminum hydride. Toluene was purified by distillation from sodium. Ethanol was purified by distillation from sodium. Sodim hydride was previously washed by n-hexane.

^{1}H NMR spectra were determined with a Varian EM 360 spectrometer and JNM-PS-100 spectrometer. ^{1}H NMR shifts are reported δ-values in parts per million relative to internal tetramethylsilane. Abbreviations used are : s, singlet; d, doublet; t, triplet; q, quartet; and m, complex multiplet.

Infrared spectra (IR) were determines with a Hitachi Model API-S2 spectrophotometer. Absorption values are reported in cm^{-1}.

Melting points are not corrected.

Phenyl-1-propenylsulfide 8a

28 g (1 mol) of sodium hydroxide was dissolved in 500 ml of water in 1 L three necked flask fitted with dropping funnel and nitrogen inlet, which was well boiled and cooled down under nitrogen atmosphere. 110 g (1 mol) of thiophenol was added dropwise over 15 min. to the solution at 25°C under nitrogen. 121 g (1 mol) of allyl-bromide was added dropwise at 0°C over 30 min., and the solution was stirred for 6 hr at 25°C. After the aqeous layer was separated, extracted three times by 100 ml portion of ether. The combined extraction was dried

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over unhydrous sodium sulfate. The crude allylphenylsulfide
was obtained by the evaporation of the solvent in quantita-
tive yield. The crude sulfide was dissolved in 500 ml of
ethanol in 1 L flask, and 1 g of sodium hydride was added
carefully. The solution was refluxed for 6 hr, the solvent
was evaporated. The oily product was dissolved in 200 ml
of ether and washed with 50 ml of water. After the solution
was dried over unhydrous sodium sulfate, pure phenyl-1-
propenylsulfide was distilled at 61-69°C/1.5 mmHg in the
yield of 138 g (92 %).

IR(NaCl film) : 3010, 1588, 1478, 1447, 1023, 747

NMR(CDCl$_3$) : 1.73(d, 3H), 5.85(m, 2H), 7.10(m, 5H)

1-Ethyl-1-propenylphenylsulfide 8b

A) A solution of 17.2 g (0.2 mol) of 3-pentanone,
44 g (0.4 mol) of thiophenol, 500 mg of p-toluenesulfonic
acid and 100 ml of toluene was heated at reflux for 12 hr
with azeotropic removal of water. The solution was washed
with 50 ml of 10 % sodium hydroxide solution and 50 ml of
water. The solution was dried over unhydrous sodium sulfate
and the solvent was evaporated. The crude 3-pentanone
diphenylthioacetal (recrystalized product; m.p. 76-77°C)
was heated and the mixture of thiophenol and the product
was distilled at 150-200°C/5 mmHg. Thiophenol was distill-
ed from the mixture at 45°C/5 mmHg and pure 1-ethyl-1-
propenylphenylsulfide was distilled at 83-84°C/2 mmHg
in the yield of 22.2 g (63 %).

B)   3.5 g (41 mmol) of 3-pentanone, 8.96 g (82 mmol)
of thiophenol, and 6 g of phosphorouspentoxide in 30 ml
of methylenechloride was stirred for 24 hr at 25°C. The
precipitate was filtered and rinsed with 30 ml of methylene
chloride. 3-pentanone diphenylthioacetal was obtained
by the evaporation of the solvent. 1-Ethyl-1-propenylphenyl
sulfide was obtained by the thermal decomposition of 3-
pentanone diphenylthioacetal as described in method A).
IR(NaCl film) : 2990, 1585, 1476, 1439, 1021, 738
NMR(CDCl$_3$) : 1.10(t, 3H), 1.65 and 1.87(d,d, 3H), 2.17(q, 2H)
               5.90(q, 1H), 7.20(m, 5H)

1-Heptenyltolylsulfide 8c

     Hydrogen chloride gas was passed for 2 hr at 0°C
through a solution of 4.56 g (40 mmol) of heptanal, 9.92 g
(80 mmol) of p-thiocresol and 70 ml of methylene chloride.
The solution was stirred for 20 hr at 25°C. Crude heptanal
ditolylthioacetal was obtained by the evaporation of the
solvent. To the solution of 3.44 (10 mmol) of heptanal
ditolylthioacetal in 20 ml of ether, was added dropwise over
1 hr at 0°C the solution of 1.73 g (10 mmol) of m-chloro-
perbenzoic acid in 20 ml of ether. After the solution was
stirred for 30 min. at 0°C, the solution was washed three
times by 20 ml portion of sodium bicarbonate aqueous
solution and once by 20 ml of water.   The solution was
dried over unhydrous sodium sulfate. Heptanal ditolylthio-
acetal monooxide was obtained by the evaporation of the
solvent. Thermal decomposition (∿200°C/2 mmHg) afforded

crude 1-heptenyltolylsulfide and the pure product was

distilled at 103-106°C/1 mmHg in the yield of 1.96 g (89 %).

IR(NaCl film) : 2930, 1595, 1490, 1453, 1011, 805

NMR(CDCl$_3$) : 0.63-1.60(m, 9H), 2.10(m, 2H), 2.30(s, 3H),

            5.83(m, 2H), 7.10(m, 4H)

1-Cyclohexenylphenylsulfide 8d

    1.96 g (20 mmol) of cyclohexanone, 4.4 g (40 mmol)

of thiophenol and 3 g of phosphorouspentoxide in 30 ml

of benzene was stirred for 24 hr at 25°C. The precipitate

was filtered. Cyclohexanone diphenylthioacetal was

obtained by the evaporation of the solvent. 1-Cyclohexenyl-

phenylsulfide was obtained by the thermal decomposition

of cyclohexane diphenylthioacetal at ∿200°C/5 mmHg. The

pure product was distilled at 86-90°C/1 mmHg in the yield

of 3.27 g (86 %).

IR(NaCl film) : 2940, 1583, 1475, 1436, 1020, 740

NMR(CDCl$_3$) : 1.60(m, 4H), 2.27(m, 4H), 6.00(m, 1H),

            7.23(m, 5H)

2,6-Dimethyl-1-hexenylphenylsulfide 8e

    A solution of 3.78 g (30 mmol) of 2,6-dimethylcyclo-

hexanone, 6.6 g (60 mmol) of thiophenol, 50 mg of p-

toluenesulfonic acid and 30 ml of toluene was heated at

reflux for 12 hr with azeotropic removal of water. The

solution was washed with 10 ml of 5 % sodium hydroxide

solution and 10 ml of water. The solution was dried over

unhydrous sodium sulfate and the solvent was evaporated.

Thermal decomposition of obtained 2,6-dimethylcyclohexanone

diphenylthioacetal afforded 2,6-dimethylcyclohexenylphenyl

sulfide. The pure product was distilled at 95-98°C/1 mmHg

in the yield of 5.19 g (79 %).

IR(NaCl film) : 2870, 1584, 1475, 1438, 1021, 735

NMR(CDCl$_3$) : 1.10(d, 3H), 1.26-2.47(m, 10H), 7.13(m, 5H)

S-phenyl-S-1-propenyl-N-tosylsulfilimine 4a

　　　　To the solution of 13.5 g (48 mmol) of chloramine T

in 50 ml of methanol, was added 7.2 g (48 mmol) of phenyl-

1-propenylsulfide and 1 drop of acetic acid. The solution

was stirred for 24 hr at 25°C. The solvent was evaporated.

The residue was dissolved in 30 ml of methylene chloride

and 30 ml of water. The organic layer was washed twice

by 30 ml of water and dried over unhydrous sodium sulfate.

The solvent was evaporated. The crude oily product was

crystalized by the treatment of 50 ml of ether. Pure

S-phenyl-S-1-propenyl-N-tosylsulfilimine was obtained by

recrystalization from methylene chloride and ether.

M. p. was 96-100°C. The yield was 6.9 g (45 %).

IR(KBr) : 1293, 1280, 1140, 970, 808, 743

NMR(CDCl$_3$) : 1.90 and 2.02(d,d, 3H), 2.36(s, 3H), 6.19(m, 2H),

　　　　　　　7.24(m, 9H)

E. A. : Cal.　　: C; 60.15, H; 5.37, N; 4.39

　　　　Found　: C; 59.68, H; 5.31, N; 4.39

S-(1-ethyl)-1-propenyl-S-phenyl-N-tosylsulfilimine 4b

To the solution of 28.2 g (0.1 mol) of chloramine T
in 100 ml of methanol, was added 17.6 g (0.1 mol) of 1-
ethyl-1-propenylphenylsulfide and 1 drop of acetic acid.
The solution was stirred for 24 hr at 25°C. The solvent
was evaporated. The residue was dissolved in 50 ml of
methylene chloride and 50 ml of water. The organic layer
was washed twice by 30 ml of water and dried over unhydrous
sodium sulfate. The solvent was evaporated. The crude
oily product was crystalized by the treatment of 100 ml
of ether. Pure S-(1-ethyl)-1-propenyl-S-phenyl-N-tosyl-
sulfilimine was obtained by recrystalization from methylene
chloride and ether. M. p. was 111-111.5°C, the yield was
17.35 g (50 %).

IR(KBr) : 1278, 1136, 1086, 985, 811, 760

NMR(CDCl$_3$) : 0.75(t, 3H), 1.82 and 1.91(d,d, 3H),2.20(m, 2H)

2.36(s, 3H), 6.54 and 6.16(q,q, 1H), 7.49(m, 9H)

E. A. : Cal.   : C; 62.21, H; 6.10, N; 4.03

Found : C; 62.39, H; 6.27, N; 4.01

S-1-cyclohexenyl-S-phenyl-N-tosylsulfilimine 4d

To the solution of 8.46 g (30 mmol) of chloramine T
in 100 ml of ethanol, was added 5.7 g (30 mmol) of 1-
cyclohexenylphenylsulfide and 1 drop of acetic acid. The
solution was stirred for 24 hr at 25°C. The solvent was
evaporated. The residue was dissolved in 50 ml of methylene
chloride and 50 ml of water. The organic layer was washed
twice by 30 ml portion of water and dried over unhydrous

sodium sulfate. The solvent was evaporated. The crude

oily product was crystalized by the treatment of 100 ml of

ether. Pure S-1-cyclohexenyl-S-phenyl-N-tosylsulfilimine

was obtained by recrystalization from methylene chloride

and ether. M. p. was 101.5-102°C, and the yield was

8.428 g (78 %).

IR(KBr) : 1285, 1139, 1085, 960, 815, 750

NMR(CDCl$_3$) : 1.53(m, 4H), 2.17(m, 4H), 2.40(s, 3H),

6.83(m, 1H), 7.47(m, 9H)

E. A. : Cal. : C; 63.47, H; 5.90, N; 3.90

Found : C; 63.21, H; 5.84, N; 3.95

S-1-heptenyl-S-tolyl-N-tosylsulfilimine 4c

To the solution of 1.8 g (6.4 mmol) of chloramine T

in 30 ml of ethanol, was added 1.4 g (6.4 mmol) of 1-

heptenyltolylsulfide and 1 drop of acetic acid. The

solution was stirred for 24 hr at 25°C. The solvent was

evaporated. The residue was dissolved in 20 ml of methylene

chloride and 20 ml of water. The organic layer was washed

twice by 10 ml portion of water and dried over unhydrous

sodium sulfate. The solvent was evaporated. The crude

oily product was crystalized by the treatment of 30 ml of

ether. Pure S-1-heptenyl-S-tolyl-N-tosylsulfilimine was

obtained by recrystalization from methylene chloride and

ether. M. p. was 128-130°C, and the yield was 1.67 g (67 %).

IR(KBr) : 1295, 1280, 1135, 1075, 960, 810

NMR(CDCl$_3$) : 0.75-1.60(m, 9H), 2.38(s, 3H), 2.40(s, 3H)

6.12(m, 1H), 6,65(m, 1H), 7.50(m, 8H)

E. A. : Cal.   : C; 64.73, H; 7.00, N; 3.60
           Found : C; 64.85, H; 7.02, N; 3.45

S-2,6-dimethyl-1-cyclohexenyl-S-phenyl-N-tosylsulfilimine 4e

     To the solution of 6.49 g (23 mmol) of chloramine T

in 100 ml of methanol, was added 5 g (23 mmol) of 2,6-

dimethyl-1-cyclohexenylphenylsulfide and 1 drop of acetic

acid. The solution was stirred for 24 hr at 25°C. The

solvent was evaporated. The residue was dissolved in 50 ml

of methylene chloride and 50 ml of water. The organic

layer was washed twice by 30 ml of water and dried over

unhydrous sodium sulfate. The solvent was evaporated.

The crude oily product was crystalized by the treatment

of 100 ml of ether. Pure S-2,6-dimethyl-1-cyclohexenyl-

S-phenyl-N-tosylsulfilimine was obtained by recrystalization

from methylene chloride and ether. M. p. was 110-112°c

and the yield was 5.61 g (63 %).

IR(KBr) : 1280, 1135, 1083, 950, 812, 754

NMR(CDCl$_3$) : 0.40(d, 3H), 1.46(m, 6H), 2.13(m, 6H), 2.37

          (s, 3H), 7.48(m, 9H)

E. A. : Cal   : C; 65.07, H; 6.51, N; 3.61
          Found : C; 64.86, H; 6.35, N; 3.58

N-Allyltosylamide 7a

     72 mg (3 mmol) of sodium hydride was added to the

solution of 957 mg (3 mmol) of 4a in 20 ml of ethanol.

The solution was heated at 50°C for 3 hr. The solvent was

evaporated. The residue was dissolved in 20 ml of methylene

chloride and washed three times by 10 ml portion of 5 %
hydrochloric acid solution and 10 ml of water. The organic
layer was dried over unhydrous sodium sulfate. The solvent
was evaporated. 433 mg (69 %) of 7a and 360 mg (31 %) of
S-2-ethoxypropyl-S-phenyl-N-tosylsulfilimine 9a were
separated from the residue by column chromatography on
silica gel (ether). M. p. of 7a (purified by chromato-
graphy on alumina chloroform) was 62-63°C (Lit. 64-65°C).[18]
IR(KBr) : 3250, 1422, 1324, 1160, 1090, 810
NMR(CDCl$_3$) : 2.42(s, 3H), 3.57(t, 2H), 5.46(m, 4H),
                7.54(dd, 4H)

N-2-penpenyltosylamine 7b

96 mg (4 mmol) of sodium hydride was added to the
ethanol solution (20 ml) of 1.04 g (3 mmol) of 4b. The
solution was heated at 50°C for 3 hr. The solvent was
evaporated. The residue was dissolved in 20 ml of methylene
chloride and washed three times by 10 ml portion of 5 %
hydrochloric acid solution and 10 ml of water. The organic
layer was dried over sodium sulfate. The solvent was
evaporated. Column chromatography on silica gel (chloro-
form) afforded 604 mg (84 %) of 7b as the colorless oil.
IR(NaCl film) : 3280, 1425, 1322, 1160, 1091, 810
NMR(CDCl$_3$) : 0.84(t, 3H), 1.92(m, 2H), 2.40(s, 3H),
                3.54(t, 2H), 5.50(m, 4H), 7.58(dd, 4H)

N-1-allylpentyltosylamide 7c

48 mg (2 mmol) of sodium hydride was added to the
ethanol solution (20 ml) of 778 mg (2 mmol) of 4c. The
solution was heated at 50°C for 3 hr. The solvent was
evaporated. The residue was dissolved in 20 ml of methylene
chloride and washed three times by 10 ml portion of 5 %
hydrochloric acid solution and 10 ml of water. The organic
layer was dried over unhydrous sodium sulfate. The solvent
was evaporated. Column chlromatography on silca gel (
methylene chloride) afforded 306 mg (57 %) of 7c and
345 mg (39 %) of 9c.

IR(NaCl film) : 3290, 1425, 1325, 1155, 1090, 810

NMR(CDCl$_3$) : 1.11(m, 9H), 2.83(s, 3H), 3.68(t, 3H),
5.23(m, 3H), 5.30(d, 1H), 7.47(dd, 4H)

N-2-cyclohexenyltosylamide 7d

96 mg (4 mmol) of sodium hydride was added to the
ethanol solution (20 ml) of 1.08 g(3 mmol) of 4d. The
solution was stirred for 5 hr at 25°C. The solvent was
evaporated. The residue was dissolved in 20 ml of methylene
chloride and washed three times by 10 ml portion of 5 %
hydrochloric acid solution and 10 ml of water. The organic
layer was dried over unhydrous sodium sulfate. The residue
of the evaporation of the solvent was washed by 10 ml of
n-hexane and then 10 ml of ether. Obtained crystal was
9d (85 mg, 7 %). 620 mg (83 %) of 7d was obtained by
the evaporation of the solvent. M. p. was 95-97°C (
ether-n-hexane).

IR(KBr) :3290, 1420, 1321, 1158, 1087, 808

NMR(CDCl$_3$) : 1.89(m, 6H), 2.44(s, 3H), 3.82(m, 1H),

5.19(d, 1H), 5.58(m, 2H), 7.52(dd, 4H)

E. A. : Cal. : C; 62.11, H; 6.83, N; 5.57

Found : C; 62.05, H; 6.73, N; 5.59

N-2,4-dimethylcyclohexenyltosylamide 7e

72 mg (3 mmol) of sodium hydride was added to the
ethanol solution (20 ml) of 1.16 g (3 mmol) of 4e. The
solution was heated at 50°C for 5 hr. The solvent was
evaporated. The residue was dissolved in 20 ml of methylene
chloride and washed three times by 10 ml portion of 5 %
hydrochloric acid solution and 10 ml of water. The organic
layer was dried over unhydraous sodium sulfate. The
solvent was evaporated. Column chromatography on silica
gel (chlorofom) afforded 670 mg (80 %) of 7e. M. p. was
105-107°C (n-hexane).

IR(KBr) : 3275, 1435, 1322, 1159, 1090, 808

NMR(CDCl$_3$) : 0.87(d, 3H), 1.48(s, 3H), 0.83-2.30(m, 5H),

2.37(s, 3H), 3.60(m, 1H), 4.75(d, 1H),

5.33(m, 2H), 7.50(dd, 4H)

E. A. : Cal. :C; 64.47, H; 7.59, N; 5.01

Found :C; 64.69, H; 7.48, N; 5.38

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3. Synthesis of Rearranged Allylamines from Allylalcohols. [3,3]-Sigmatropic Rearrangement of Allylcyanates.

3-1 Introduction

Overman has demonstrated the superior method for 1,3 transposition of allylic alcohol and amine function.[1] Thus, if allylic trichloroacetimidates $\underline{1}$[1a)1b)] and allylic pseudoureas $\underline{2}$[1d)] were heated at 137°C (refluxing xylene), rearranged trichloroacetamides $\underline{3}$ and ureas $\underline{4}$ were obtained respectively.(Scheme I) The whole reaction was constructed

Scheme I

$$R^1R^2C=CRCR^3R^4 \quad \xrightarrow{\text{Y-CN}} \quad R^1R^2C=CRCR^3R^4 \quad \xrightarrow{137°C}$$

with OH on the first structure; on the second structure the substituent is $Y-\underset{\underset{NH}{\|}}{C}-O$

$$\underline{1,}\ \underline{2}$$

$$R^1R^2CCR=CR^3R^4 \quad \xrightarrow{^-OH} \quad R^1R^2CCR=CR^3R^4$$

with $HN-\underset{\underset{O}{\|}}{C}-Y$ on the first structure and NH_2 on the second structure

$$\underline{3,}\ \underline{4}$$

$$\underline{1,}\ \underline{3}\ :\ Y= -CCl_3 \qquad \underline{2,}\ \underline{4}\ :\ Y= -N\bigcirc$$
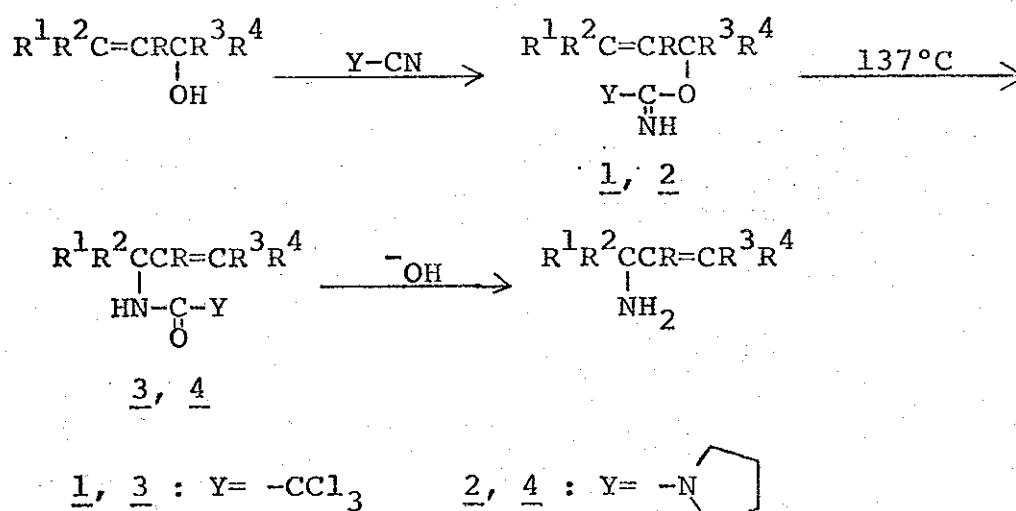
by the initial formation of $\underline{1}$ from allylalcohols, successive [3,3]-sigmatropic rearrangement from $\underline{1}$ to $\underline{3}$, and hydrolysis of $\underline{3}$ producing rearranged amines. Some of the important features of this sequence were as follows; a) the overall high yields, b) the relatively low temperatures

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required for the thermal rearrangement, c) the ability of mercury (II) to catalyze the rearrangement of imidate derivatives of 2-alken-1-ols, d) the total regiospecificity and high stereoselectivity of the process, e) the ease of removal of the trichloroacetyl proup. Finally this method for the preparation of amines would be particularly useful for the synthesis of tertiary carbinyl amines, for which there are few alternate synthetic methods.[2]

With a goal of developing similar methodology in which the thermal rearrangement could be accomplished at or below room temparature, the author was attracted to the procedure of Scheme II.[3] Attempts[4] to prepare allylic cyanic esters[5] have invariably led to the formation of allylic isocyanates, and such results have been interpreted to

Scheme II

$$R^1R^2C\text{=}CRCR^3R^4 \underset{OH}{|} \quad \xrightarrow{\quad ClCN \quad} \quad R^1R^2C\text{=}CRCR^3R^4 \underset{N\equiv C\text{-}O}{|}$$

$$\underline{5}$$

$$\xrightarrow{\qquad} \quad R^1R^2CCR\text{=}CR^3R^4 \underset{N\text{=}C\text{=}O}{|} \quad \xrightarrow{\quad {}^-OH \quad} \quad R^1R^2CCR\text{=}CR^3R^4 \underset{NH_2}{|}$$

$$\underline{6}$$
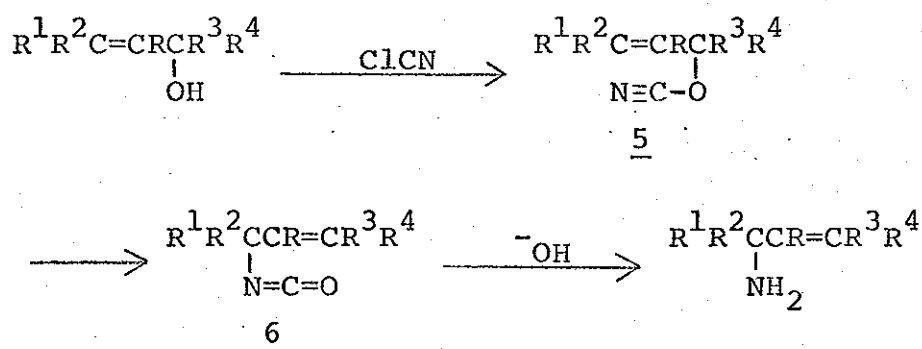
mean that the allyl cyanate to allyl isocyanate rearrangement ($\underline{5} \rightarrow \underline{6}$) occurs rapidly at room temperature. Especially this rearrangement is supported by [3,3]sigmatropic re- arrangement of allylic thiocyanates.[6] The direct synthe-sis of alkyl cyanates from the reaction of alkoxides and

cyanogen halides has been reported.[5)7)] However, good

yields have been obtained by this procedure with bridge-

head[7a)] and acidic alcohols[7b)7c)] only. Typically

encountered problems are further transformations of the

initially formed alkyl cyanates,[8)] leading to the formation

of iminocarbonates,[9)] isocyanates,[7a)10)] cyanate or iso-

cyanate trimers and alkenes. We anticipated that many

of these problems would be avoided in the reaction of

an allylic alkoxide with a cyanogen halide if the initially

formed allylic cyanate 5 underwent rapid rearrangement to

isocyanate 6. In this section the author reports what

to our knowledge is the first study of the reaction of

allylic and propargylic alcohols with cyanogen chloride.

As detailed below, the methodology of Scheme II was found

to be synthetically useful for the introduction of nitrogen

at highly hindered allylic positions.

3-2   The rearrangement of allylic cyanates to allylic

isocyanates

Sequential treatment of a tetrahydrofuran (THF)

solution of geraniol at 0°C with n-butyllithium (1 equiv)

and cyanogen chloride (1 equiv) and subsequent reaction

for 3 hr at room temperature afforded a mixture of linalyl

isocyanate 8 and the dimeric carbamate 9. Isocyanate 8

was isolated in 40% yield by direct distillation of the

crude reaction mixture at reduced pressure, and it was

characterized by reaction with pyrrolidine to afford the

known urea 10.[2d]   Carbamate 9 was isolated in 50% yield
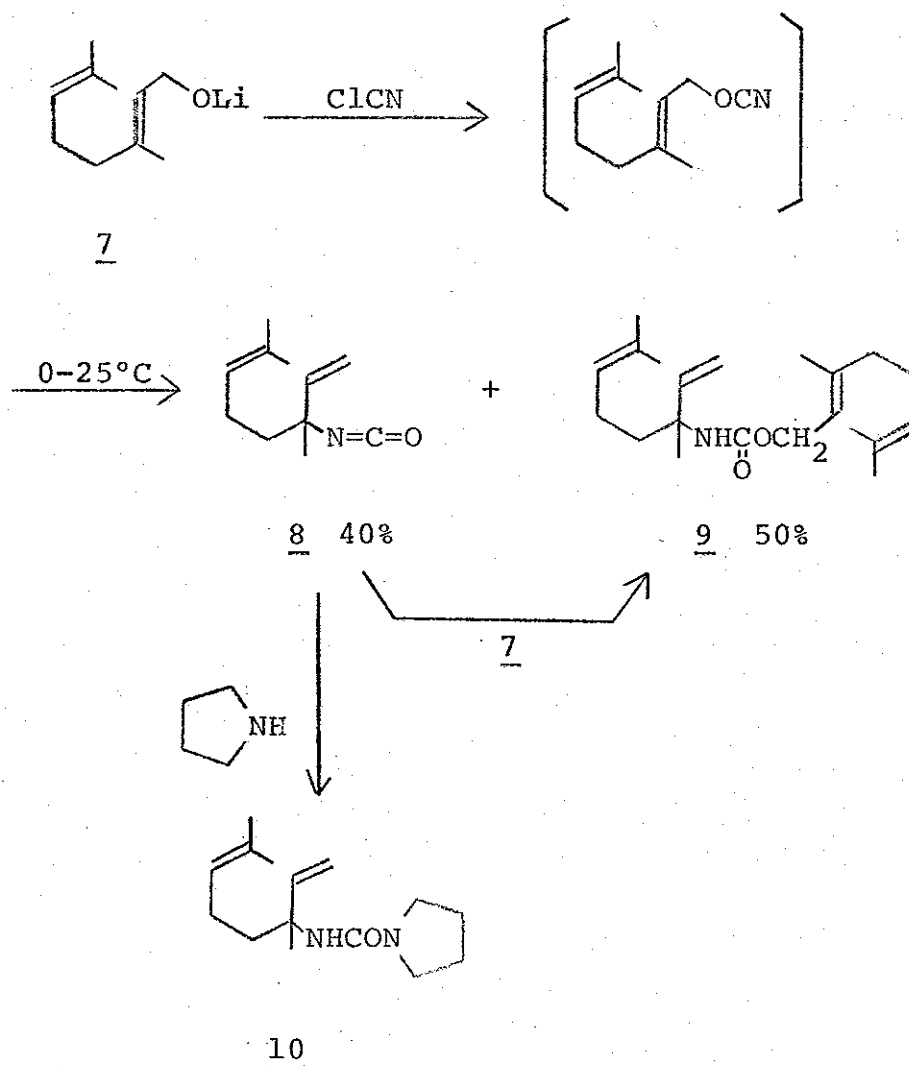
by a combination of chromatograghy and distillation. That 9 was likely formed from the reaction of isocyanate 8 with alkoxide 7 was confirmed by the quantitative conversion of 8→9 under identical conditions. A variety of experimental parameters (Table I) was examined in an attempt to optimize the formation of 8. As expected, the yield of 8 was improved when excess cyanogen chloride was employed, although the increase was not dramatic (8 formed in 68% yield) even when 10 equiv of cyanogen chloride was employed. The use of lower reaction temperatures and longer addition times had surprisingly little effect on the improvement of yield of 8.

Table I. Reaction of the lithium salt of geraniol 7 with cyanogen chloride in THF.

|	Reaction conditions		
ClCN (equiv)	Time of addin(min)	Temp (°C)	Isolated yield of 8 (%)
1.0	15	0	40
1.5	15	0	48
10	15	0	68
10	15	−78	65
13	600	25	34

Similar treatment of the lithium salts of 2-cyclohexen-1-ol with 20 equiv of cyanogen chloride followed by product isolation after the addition of pyrrolidine afforded a mixture of carbamate 13 (51%) and the known urea 14 (21%).[2d] The higher yield of carbamate produced in this case reflects the greater reactivity toward alkoxide of the less

sterically hindered isocyanate 12. The ability of un-
hindered isocyanates to compete with cyanogen bromide for
an alkoxide anion has been noted previously.[10] The ter-
tiary alcohol linalool was recovered unchanged from se-
quential treatment with n-butyllithium and cyanogen chloride.
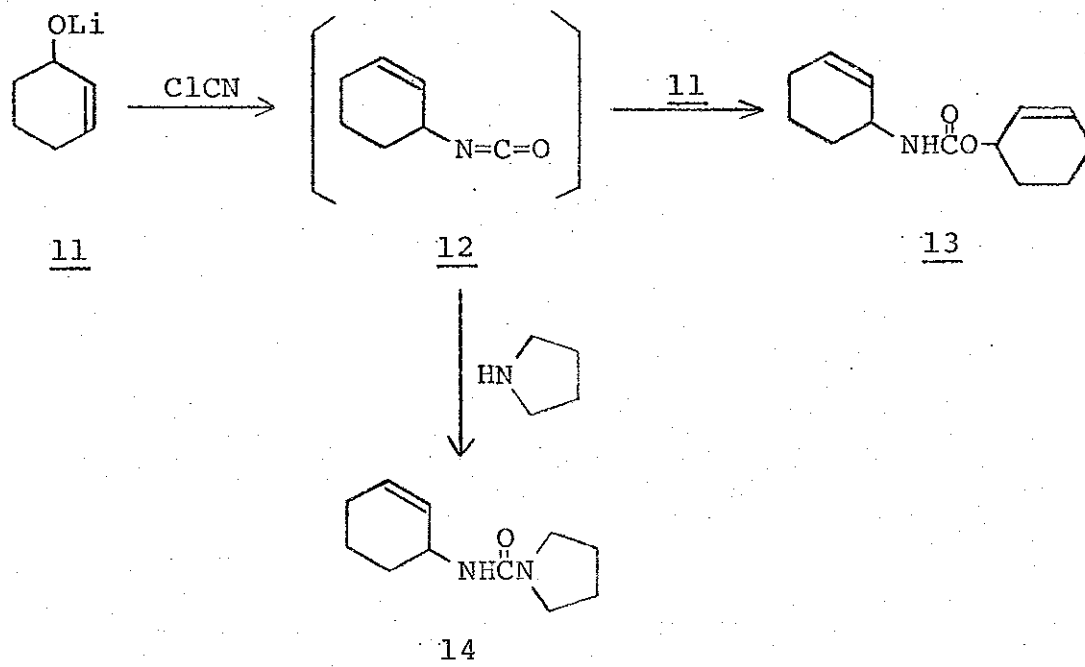
We next examined the application of the allyl cyanate
methodology for introducing nitrogen functionality at the
hindered 3 position of a 3-substituted 2-cyclohexenyl system,
e.g., 15→20. The inability to accomplish conversions of
this type in even moderate yield is the major limitation
of the allylic trichloroacetimidate method[2a)2b)] of trans-
posing alcohol and amine functions. This appeared at the
outset as a potentially attractive application of the allyl
cyanate methodology since the rearranged isocyanate would
be highly hindered, and the low temperature of the thermal
rearrangement might reduce complications from competing
elimination pathways.[2a)2b)] In the event, treatment of

the lithium salts of alcohol $15^{2c)}$ with 20 equiv of cyanogen

chloride afforded a mixture of the rearranged isocyanate

17 and the dimeric carbamate 18 in yields of ∿50 and 14%,

respectively. Isocyanate 17 was characterized by conver-

sion to the crystalline urea 19,[2d] which was produced

44% overall yield from alcohol 15. Significantly, the

allylic urea with an unrearranged carbon skeleton, which

was produced[2d] to a minor extent in the rearrangment of

the pyrrolidinecarboximidic ester of alcohol 15, was not

formed (<2%) in the cyanogen chloride reaction. The

regiospecific conversion of 15 to derivatives of the

rearranged amine 20 in overall yields of greater than 50%

represents a significant improvement over the existing

15 R^1=H
16 R^1=Li

R= $-(CH_2)_3-CH\overbrace{}^{O}_{O}$
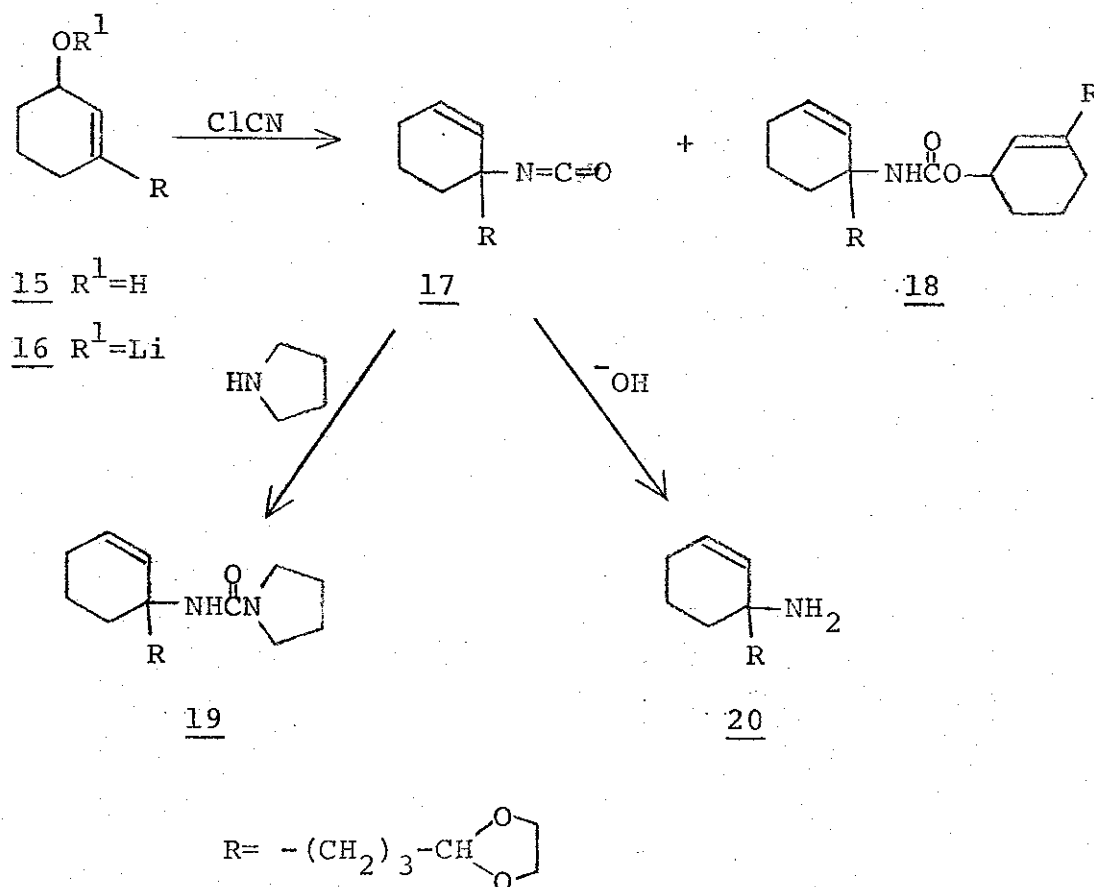
methodology.[2]   In a single experiment, the crude mixture

of 17 and 18 was directly hydrolyzed with ethanolic

potassium hydroxide to afford the allylically rearranged

amine 20 in 36% overall yield from alcohol 15.

In an attempt to generate allenyl isocyanate 21, 2-

octyn-l-ol was treated in a similar fashion with n-butyl-

lithium (1 equiv) and cyanogen chloride (10 equiv). No

isocyanate or allene products were detected, and the only

product isolated (in 70% yield) was the propargylic chloride

22. 1-Octanol was similarly converted to 1-chlorooctane

in 81% yield. Although the formation of alkyl chlorides

from the reaction of alkoxides and cyanogen chloride has

apparently not been noted previously,[5][7][8] it is not

surprising since alkyl cyanate are known to be converted

alkyl chlorides when treated with HCl[8a] and to alkyl

iodides when treated with potassium iodide.[8b]

$$
\begin{array}{c}
\left[
\begin{array}{c}
\text{n-C}_5\text{H}_{11} \\
\diagdown \\
\hspace{1.5em} \text{C=C=CH}_2 \\
\diagup \\
\text{O=C=N}
\end{array}
\right] \\
\underline{21}
\end{array}
$$

n-C$_5$H$_{11}$C≡CCH$_2$OH

n-C$_5$H$_{11}$C≡CCH$_2$Cl

22

51
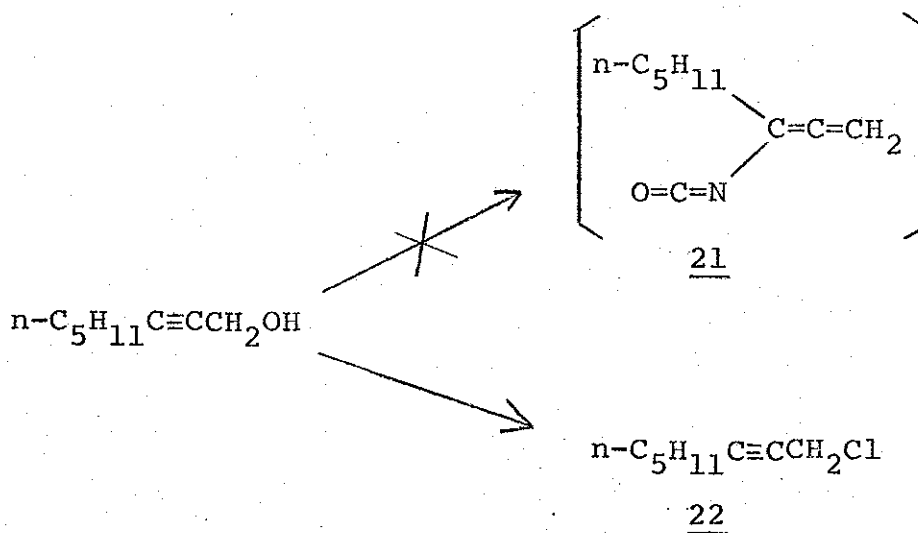
3-3 Experimental Section

Cyanogen chloride was dried by passage through a calcium chloride drying tower, condensed at 0°C in a rubber septum sealed graduated cylinder, and transfered under a nitrogen atmosphere by standard double-needle techniques. Tetrahydrofuran (THF) was purified by distillation from sodium and benzophenone.

^{1}H NMR spectra were determined with a Varian EM 360 spectrometer. ^{13}C NMR spectra were determined at 22.62 MHz with a Brucker WH-90 spectrometer. ^{1}H NMR and ^{13}C NMR shifts are reported as δ values in ppm relative to internal tetramethylsilane. Coupling constants (J) are reported in Hz and refer to apparent multiplicities, and not true coupling constants; abbreviations used are: s, singlet; d, doublet; t, triplet; m, complex multiplet.

Infrared spectra (IR) were determined with a Perkin Elmer Model 283 spectrophotometer.

Mass spectra were determined with a DuPont 21-498 double focussing spectrometer.

Reaction of geraniol with cyanogen chloride. Preparation of 3,7-dimethyl-1,6-octadien-3-yl isocyanate 8 and carbamate 9.

A stirred solution of cyanogen chloride (5 ml, 0.1 mol) and 30 ml of anhydrous THF was treated dropwise at 0°C over 15 min with a THF solution of alkoxide 7 (prepared from the reaction of 1.54 g (10 mmol) of geraniol with n-butyllithium (1.6 M in hexane, at 0°C in 10 ml of THF

using bipyridyl as an indicator). The cooling bath was removed and the reaction mixture was stirred for 3 hr at room tmperature. Excess cyanogen chloride and THF were removed at reduced pressure on a rotary evaporater, and the residue was dissolved in ethyl acetate and filtered through a short plug of silica gel. After concentration, the residue was distilled to afford 1.22 g (68 %) of pure isocyanate $\underline{8}$; b. p. 69-72°C/2.5 mmHg.

IR(NaCl film) : 2260(ν N=C=O), 1460, 1380, 980, 920 cm^{-1}

^{1}H NMR(CDCl$_3$) : 4.8-6.1(m, four vinylic hydrogens), 1.62
(s, C$\underline{H}_3$), 1.38(s, C$\underline{H}_3$)

^{13}C NMR(CDCl$_3$) : 142.2(C2), 132.2(C7), 123.4(C6),1.20.8(N=$\underline{C}$=O)
112.8(C1), 62.2(C3), 43.0(C4), 29.2($\underline{C}$H$_3$),
25.6($\underline{C}$H$_3$), 23.3(C5), 17.6($\underline{C}$H$_3$)

Mass(m/e) : 179.130(C$_{11}$H$_{17}$NO requires 179.131), 136, 121, 96

Treatment of a hexane solution of the distillation residue with activated chacoal, followed by bulb to bulb distillation (bath temp. 150°C/0.001 mmHg) afforded 422 mg (25 %, 90% pure by ^{1}H NMR) of carbamate $\underline{9}$ as a colorless liquid.

IR(NaCl film) ν : 3350(NH), 1720(C=O), 1505, 1240, 1065 cm^{-1}

^{1}H NMR(CDCl$_3$) : 5.96(dd, J=10, 18Hz, C$\underline{H}$=CH$_2$), 4.8-5.7(m,
five vinylic hydrogens), 4.70(broad s, N$\underline{H}$),
4.50(d, J=7Hz, C$\underline{H}_2$O), 1.65(s, C$\underline{H}_3$), 1.55
(s, C$\underline{H}_3$), 1.36(s, C$\underline{H}_3$)

E. A. : Cal. for C$_{21}$H$_{35}$NO$_2$: C; 75.61, H; 10.60, N; 4.20
Found   : C; 75.57, H; 11.09, N; 4.51

Preparation of urea 10

A solution of 540 mg (3 mmol) of isocyanate 8, 280 mg (4 mmol) of freshly distilled pyrrolidine, and 5 ml of THF was maintained at room temperature for 2 hr and concentrated to afford a solid residue. This residue was dissolved in n-hexane, treated with activated charcoal, and crystallized to afford 10, m. p. 48-50°C (Lit.[1d] 37-38°C) in essentially quantitative yield. This sample of 10 was idential (^{1}H NMR, IR) with a sample prepared from thermal rearrangement of geranyl 1-pyrrolidinecarboximidate.

Preparation of carbamate 9 from the reaction of alkoxide 7 and isocyanate 8

A solution of 720 mg (4 mmol) of 8 and 15 ml of THF was treated dropwise at 0°C with a THF solution of 7 (10 ml of a 0.40 M solution), and then stirred for 3 hr at room temperature. The solution was neutralized with acetic acid, concentrated, and the residue was purified by chromatography on silica gel (ethyl acetate) to afford 1.32 g (99 %) of 9, which was identical (^{1}H NMR, IR) with a sample prepared from geraniol.

Reaction of 2-cyclohexen-1-ol with cyanogen chloride. preparation of carbamate 13 and urea 14

A stirred solution of cyanogen chloride (10 ml, 0.19 mol) and 100 ml of anhydrous THF was treated dropwise at 0°C over a period of 10 hr with a 0.1 M THF solution of alkoxide 11 (100 ml, 10 mmol, prepared from 2-cyclohexen-1-ol as

described for 7, and added with a syringe pump). After
stirring for 12 hr at room temperature the reaction mixture
was concentrated, the residue was dissolved in 50 ml of
THF, and treated dropwise with 10 ml of freshly distilled
pyrrolidine. After stirring at room temperature for 1 day,
the reaction mixture was concentrated and purified by
chromatography on silica gel (5:1 hexane:ethyl acetate)
to afford 400 mg (21 %) of the known urea 14, m. p. 91-93°C
(lit.[1d] 92.5-93°C, identical by IR, ^{1}H NMR), and 567 mg
(51 %) of carbamate 13, m. p. 81-83°C (after sublimation)
IR(KBr) ν : 3320(NH), 1680(C=O), 1520, 1240, 1055, 1025 cm^{-1}
^{1}H NMR(CDCl$_3$) : 5.2-6.1(m, four vinylic hydrogens), 5.0

    (m, NH), 5.6(m, CHOR), 4.1(m, CHNH)

E. A. : Cal. for C$_{13}$H$_{19}$NO: C, 70.56; H, 8.65; N, 6.33

        Found   : C, 70.36; H, 8.71; N, 6.37

Reaction of 3-(4-ethylenedioxy-1-butyl)-2-cyclohexen-1-ol
with cyanogen chloride. Isolation of isocyanate 17,
carbamate 18, and urea 19.

    In a similar fashion, cyanogen chloride (5 ml, 0.10
mol, in 30 ml of THF) was treated dropwise at 0°C over
15 min with a 0.50 M THF solution of alkoxide 16 (10 ml,
5.0 mmol, prepared from 3-(4-ethylenedioxy-1-butyl)-2-
cyclohexen-1-ol[1c] as described for 7). After stirring
for 4 hr at 0°C, the reaction mixture was concentrated,
filtered through a short column of silica gel (ethyl acetate),
and distilled (90-120°C/0.05 mmHg) to afford 795 mg of a
∿70 % pure sample of isocyanate 17.

Purification of the distillation residue by chromatography

on silica gel (1:1 hexane:ethyl acetate) afforded 172 mg

(14 %) of carbamate 18.

IR(NaCl film) ν : 3350(NH), 1715(C=O), 1515, 1235, 1140,

945 cm^{-1}

^{1}H NMR(CDCl$_3$) : 5.81(apparent s, CH=CH), 5.50(broad s,

CH=CH), 5.10(broad s, NH), 4.82(broad t,

J=4, OCHO), 4.60(broad s, CO$_2$CH), 3.60-

4.00(m, OCH$_2$CH$_2$O)

A 237 mg portion of the crude isocyanate sample described

above was treated in THF for 12 hr at room temperature with

1 ml of pyrrolidine. Concentration, and purification of

the residue by chromatography on silica gel (7:3 hexane:

ethyl acetate) afforded 203 mg of the pure urea 19 (0.66

mmol, 44 % overall from alcohol 15), m. p. 74-75°C (hexane)

(lit.[1d] 62-64°C) which was identical (^{1}H NMR, IR) with

an authentic sample[1d]. An early chromatography fraction

yielded 90 mg of a mixture [1c] of the 1- and 2-(4-ethylene-

dioxy-1-butyl)-1,3-cyclohexadienes. The known[1c] urea with

an unrearranged carbon skeleton, 3-(4-ethylenedioxy-1-

butyl)-2-cyclohexen-1-yl 1-pyrrolidinecarboxamide, could

not be detected (TLC and ^{1}H NMR) in the crude reaction

mixture, or in any of the chromatography fractions.

1-(4-Ethylenedioxy-1-butyl)-2-cyclohexen-1-yl amine 20

In an identical fashion cyanogen chloride (100 mmol)

was treated with alkoxide 16 (5.0 mmol) to afford a mixture

of 17 and 18. This mixture was heated at reflux for 36 hr

under a nitrogen atmosphere with 15 ml of ethanol and 7.5 ml of a 40 % potassium hydroxide solution. The alkaline mixture was then acidified (pH ∿ 6) with 50 % acetic acid, extracted one time with 20 ml of ether, basified, and the amine product isolated by extraction with ether. Short-path distillation (85-90°C/0.02 mmHg) of the dried (Na_2SO_4) extract yielded 443 mg (42 %) of amine 20 (85 % pure, contaminated with diene). A pure sample of amine 20 was obtained by extraction with cold 10 % HCl, washing with ether, basification, and short-path distillation as a colorless loquid.

IR(NaCl film) ν : 3350, 3290(NH), 2930, 1440, 1140, 1035, 940, 730 cm^{-1}

^{1}H NMR(CDCl$_3$) : 5.4-5.7(m, CH=CH), 4.81(t, J=4, OCHO), 3.5-4.0(m, OCH$_2$CH$_2$O), 1.8(s, NH$_2$)

^{13}C NMR(CDCl$_3$) : 135.3(CH=), 127.0(CH=), 104.6(OCHO), 64.8(OCH$_2$), 50.8, 43.0, 36.4, 34.5, 25.2, 19.3, 18.3

Preparation of 1-chloro-2-octyne 22

A stirred solution of cyanogen chloride (4 ml 80 mmol) and 20 ml of THF was treated dropwise at 0°C over 15 min with a 0.5 M THF solution of lithium 2-octyn-1-oxide (8.0 mmol, prepared as described for 7). After stirring at room temperature for 3 hr, the reaction mixture was concentrated and bulb to bulb distilled (bath temp, 50-100°C/2 mmHg) to afford 807 mg (70 %) of the chloride 20, which was identical (IR, ^{1}H NMR, ^{13}C NMR) with an authentic sample

prepared by the reaction 2-octyn-1-ol with thionyl chloride.

IR(NaCl film) ν : 2930(CH), 2230(C$\equiv$C), 1468, 1262, 1150 cm^{-1}

^{1}H NMR(CDCl$_3$) : 4.13(t, J=2.5, C$\underline{H}_2$-Cl), 1.7-0.7(m)

^{13}C NMR(CDCl$_3$) : 87.8, 75.2, 31.23, 31.18, 28.4, 22.4, 19.0, 14.0

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# 4. Synthesis of Pyrrolidine Derivatives. Directed 2-Aza-Cope Rearrangements.

4-1 Introduction

When the sigmatropic rearrangement is carried out, the major problem often to be faced is that the final products are the mixture of the starting isomer and the rearranged isomer because of the equilibrium.[1] In the

Cope rearrangement

Claisen rearrangement
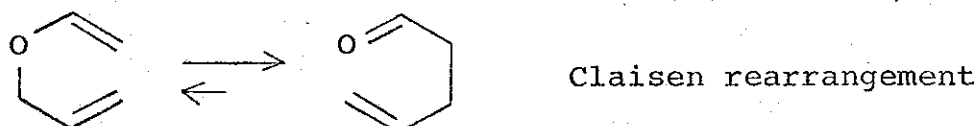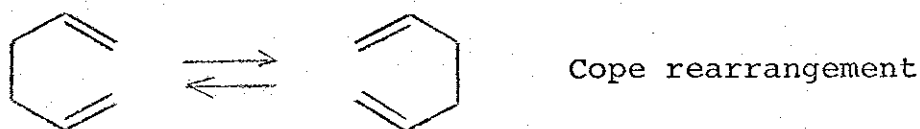
case of Claisen rearrangement[2] in which the hetero atom is introduced at 3-position of 1,5-hexadiene system, the equilibrium lies so far to the right (carbonyl, imine, etc.). But the mixture of two isomers is often obtained in usual Cope rearrangement,[1],[3] because in this case there is no driving force to shift the equilibrium.

2-Azonia-[3,3]-sigmatropic rearrangement[4] the author noted is considered to be similar to the case of Cope rearrangement. This rearrangement appears to be a particularly attractive vehicle for the elaboration of methodology

$$\underset{\underline{1}}{\overset{R^2}{\underset{R^4}{R^3-\overset{N^+}{\underset{|}{}}\diagdown R^1}}} \quad \underset{\longleftarrow}{\overset{\longrightarrow}{}} \quad \underset{\underline{2}}{\overset{R^2}{\underset{R^4}{R^3=\overset{N^+}{\underset{|}{}}\diagdown R^1}}}$$

2-azonia-[3,3]-

sigmatropic rearrangement
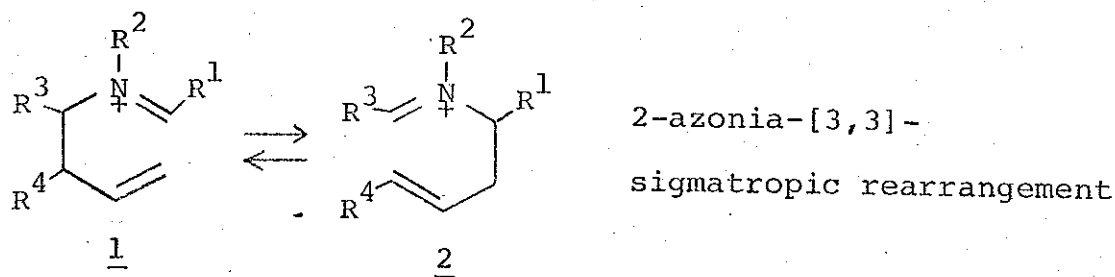
of carbon-carbon bond formation. The reversible reorgan-

ization occurs under remarkably mild conditions (typically

100-200°C below the corresponding Cope rearrangement),[4]

and a variety of methods are available for preparing the

starting iminium ion $\underline{1}$.[5] To be synthetically useful the

2-azonia-[3,3]-sigmatropic rearrangement must be irrevers-

ible in the desired direction, and to date essentially

all applications have been in benzoheterocyclic system,[4]

where the rearrangement is driven by aryl conjugation of

the product iminium ion (R^3= aryl). To direct this re-

arrangement the author planed an intramolecular trapping

procedure. The strategy is to incorporate a nucleophilic

substituent in such a fashion that it is latent in the

starting sigmatropic isomer, but upon rearrangement is

unleashed and irreversibly captures the desired product

iminium ion. For this purpose, oxygen functionality was

induced at 4-position of 2-aza-1,5-hexadiene system (R^4=

OR).

As shown in Scheme I, rearranged iminium ion isomer

could afford pyrrolidine by a ring closure of Mannich

type.[5],[6] In the beginning within this context the author

examined the reaction of aldehyde and salts of N-alkyl-

Scheme I
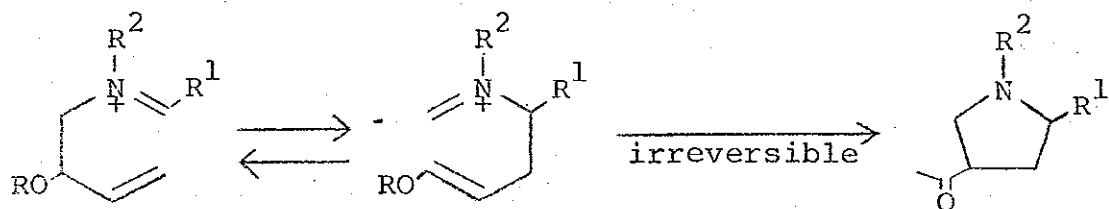
2-alkoxy-3-butenamines $\underline{3}$, and found that this reaction
afforded 3-acetylpyrrolidines $\underline{4}$ $(R^3 = Me)$ in a simple step,
and in excellent yield (eq.1). The major limitation of
this reaction is that the carbonyl component must be an

$$R^1CHO \quad + \qquad\qquad \xrightarrow{80°C} \qquad\qquad \tag{1}$$

$$\underline{3} \qquad\qquad\qquad\qquad \underline{4}$$
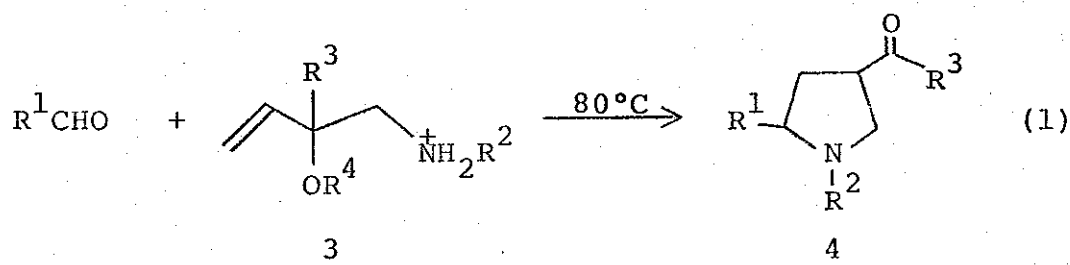
unhindered aldehyde. For example, pivaldehyde and ali-
phatic ketones were recovered unchanged when heated at
reflux in benzene with amine salt $\underline{3}$.

The limitation described above should be caused by
the steric hindrance around the carbonyl function or
starting ammonium salt $\underline{3}$. The reaction was successfully
extended to ketones when N-substituent of ammonium salt $\underline{3}$
was replaced by hydrogen. Thus, when 1-amino-2-methyl-3-
buten-2-ol $\underline{5}$ and cyclohexanone were treated with 0.9 equiv
of d-10-camphorsulfonic acid at 80°C, 45% of the correspond-
ing 3-acetylpyrrolidine was obtained. On the other hand,
it was found that various ketones afforded 5-vinyloxazoli-

45%

5   6
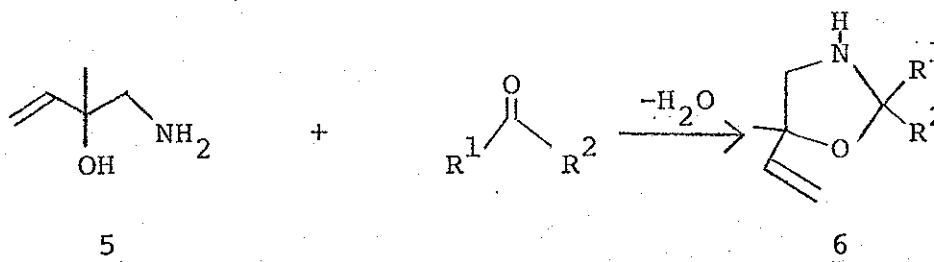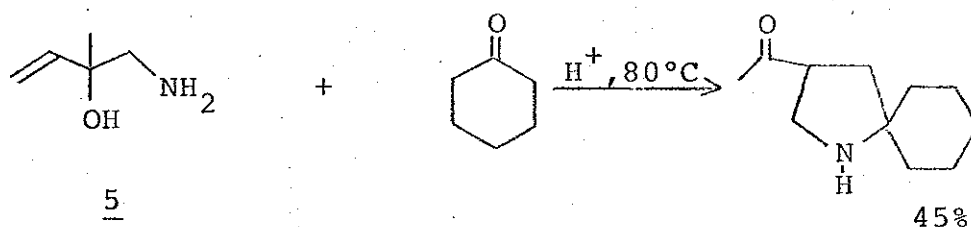
dines **6** by the reaction with **5** under the neutral conditions
in high yield.[7] It is significant that **6** also seems to
be the precursor of iminium ion **7** under the acidic condition.
As shown in Scheme II, 3-acetylpyrrolidine **8** would be
synthesized from **6** successively. This approach allows

Scheme II

7   8
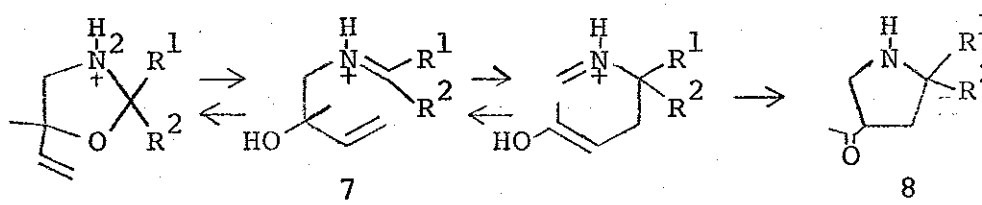
cycloalkanes to be utilized as the carbonyl components in
this pyrrolidine synthesis, and results in a convenient
construction of substituted 1-azaspiranes which are diffi-
cult to synthesize by other methods.[8] In this way the
1-azaspiro[4,5]decanes were prepared in isolated yields
of greater than 50% from their cyclohexanone precursors.
However, the use of ketones in this pyrrolidine synthesis
(Scheme II) may be limited to cyclohexanones, since re-

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arrangement of 5-vinyloxazolidines 6 derived from 3-pentan-
one and cyclopentanone afforded the corresponding pyrroli-
dines in only low yield.

As described, when the sigmatropic rearrangement is
incorporated in a synthetic methodology, it is the major
factor to control the equilibrium.[1] Oxy-Cope rearrange-
ment is one of the such examples.[9] By the introduction

oxy-Cope rearrangement
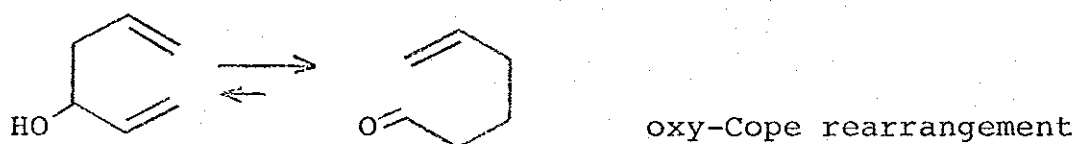
of hydroxy group at 3 position of 1,5-hexadiene, the
equilibrium successfully lies far to the right affording
carbonyl compounds. Furthermore Evans has developed this
rearrangement as a base accelerated oxy-Cope rearrangement.[10]
It is well known that [3,3]-sigmatropic rearrangement is
carried out faster when two olefines of 1,5-hexadiene have
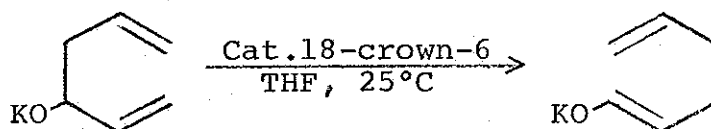
the different polarity.[5a] The 1,2-olefinic part in 3-oxy-
1,5-hexadiene would become more negative by the simple
improvement of alcohol to alkoxide. So the activation
energy in the rearrangement might depend on the negativity
of homoallylic alkoxide. It has been shown that, when

potassium cation is used as the counter cation of alkoxide together with a catalytic amount of 18-crown-6, the oxy-Cope rearrangement was accelerated surprisingly.[10] The author planed to incorporate oxy-Cope rearrangemnet into 2-aza-Cope rearrahgement system. 5-Vinyloxazolidines $\underline{6}$ might have the equilibrium as depicted in Scheme III.

Scheme III
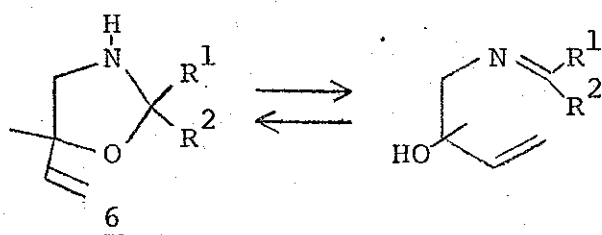
Actually, in the case of the conjugating system (R^1= Ph, R^2= H), hydroxy imine was isolated instead of the corresponding oxazolidines by the reaction of 1-amino-2-methyl-3-buten-2-ol $\underline{5}$ and benzaldehyde. Scheme IV shows the reaction pathway of the base accelerated 4-oxy-2-aza-[3,3]-sigmatropic rearrangement. Treatment of 5-vinyloxazolidines $\underline{6}$ with base should afford 4-alkoxy-2-aza-1,5-hexadiene $\underline{11}$

Scheme IV
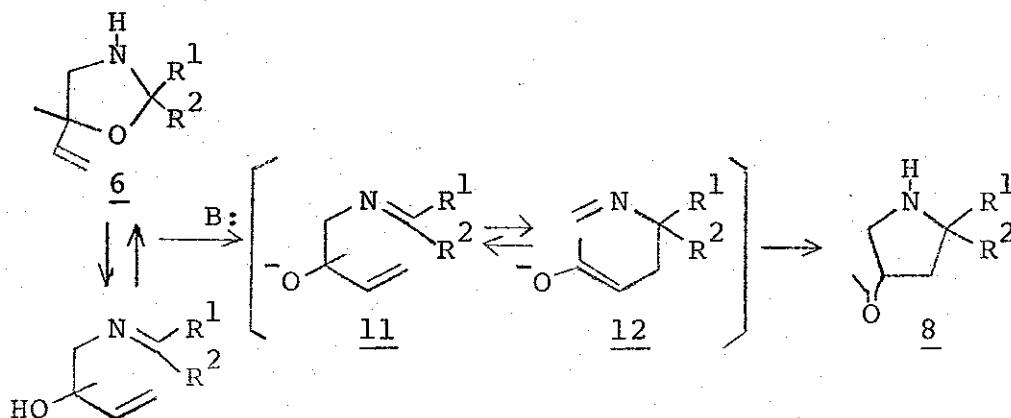
as intermediates. The successive ring closure to 3-acetyl-pyrrolidines $\underline{8}$ is induced by the intramolecular attack of the rearranged enolate anions $\underline{12}$ on the imine function endocyclicly.[11]

In this chapter, synthesis of 1-amino-3-buten-2-ol derivatives which are the versatile starting materials of pyrrolidine synthesis will be described in the beginning (4-2). In the following sections, the synthesis of 3-acetylpyrrolidines derived from various aldehydes (4-3), preparation of 5-vinyloxazolidines (4-4), 2-azonia-[3,3]-sigmatropic rearrangement starting from 5-vinyloxazolidines (4-5), 4-oxy-2-aza-Cope rearrangement (4-6) and finally the stereochemistry of these pyrrolidine syntheses (4-7) will be discussed.

4-2 Synthesis of 1-amino-3-buten-2-ol derivatives
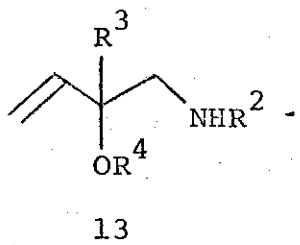
In this section 1-amino-3-buten-2-ols, the starting materials of the new pyrrolidine synthesis, was tried to be synthesized by a few methods.

The first attempt was the reduction of acrolein cyanohydrin (eq.2).[12),13)]

O-Protected cyanohydrin 14 was prepared from acrolein by the known methods in the yield of 80%.[14)] Although the

13

$$ \text{(eq. 2)} $$

27%
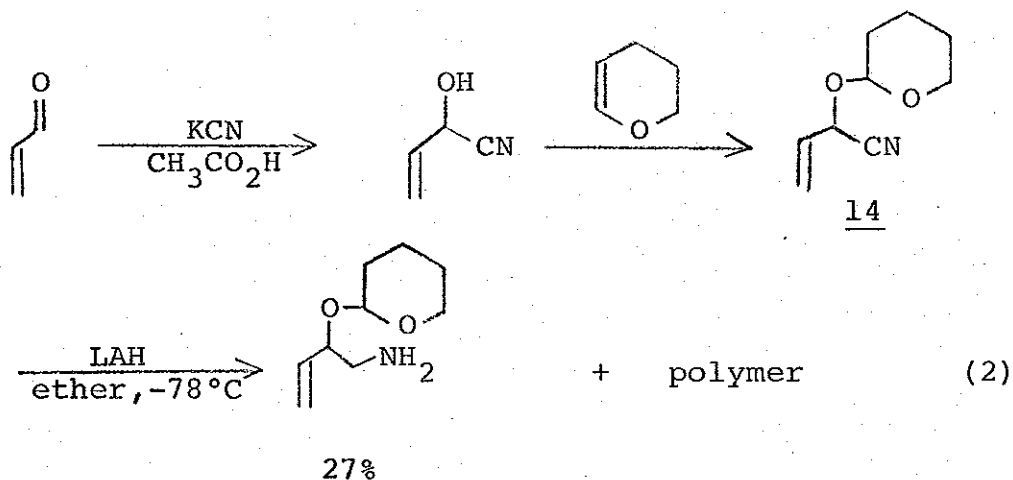
various attempts to reduce the nitril to amine were tried, only 27% of the desired amine was obtained together with considerably high molecular weight material when 1/4 equiv of lithium aluminum hydride was used in ether at -78°C.

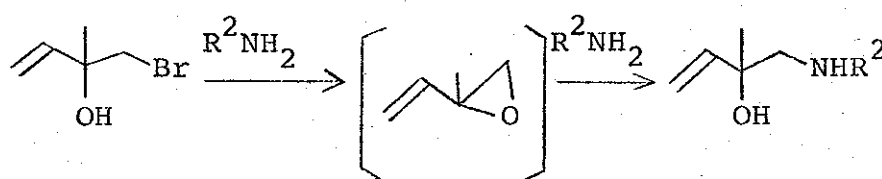The next attempt was the direct amination of 1-bromo-2-alkoxy-3-butenes 15 (eq.3). 15 was prepared from butadiene or isoprene by the O-alkylation of their bromohydrins in 70-80% yield[15)]. When 15b (R^3= H, R^4= 1-ethoxyethyl) was reacted with n-propylamine, 1-propylamino-2-(1-ethoxy)-ethoxy-3-butene 13B was obtained in good yield. 13b was deprotected to afford 1-propylamino-3-buten-2-ol 13a.

$$\text{(3)}$$

15b: R^3=H, R^4= $\sim$O$\sim$

15L: R^3=CH$_3$, R^4= $\sim$O$\sim$

15c: R^3=H
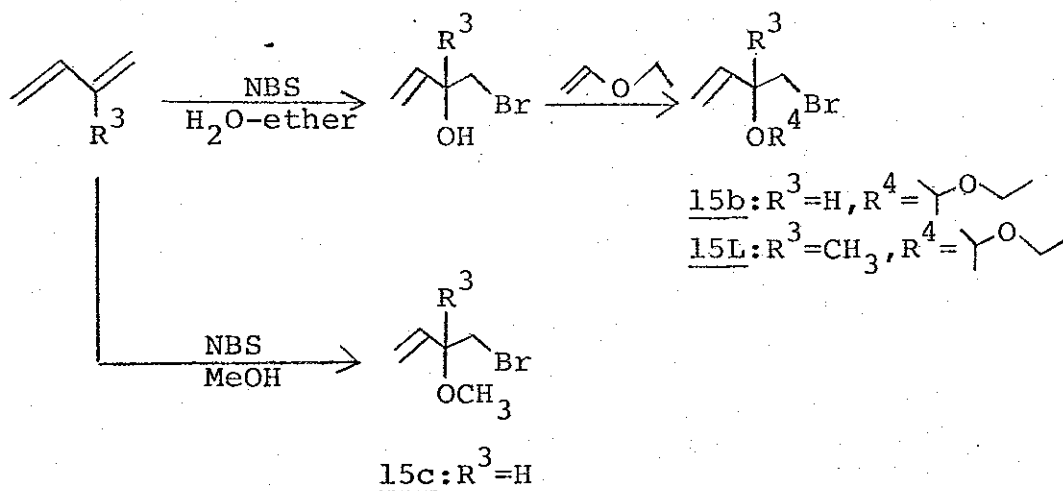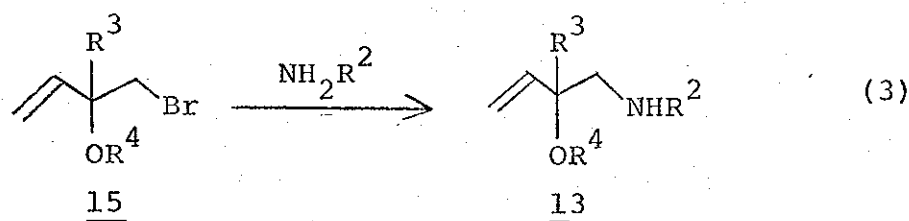
13c (R^4= methyl) was obtained by methylation of 13a, or alternative amination of 15c (R^4= methyl)[15b) directly. But the direct amination of 15L (R^3= methyl, R^4= 1-ethoxy-ethyl) by n-propylamine was not succeeded apparently because of the steric hindrance due to the neopentyl nature of the bromide.
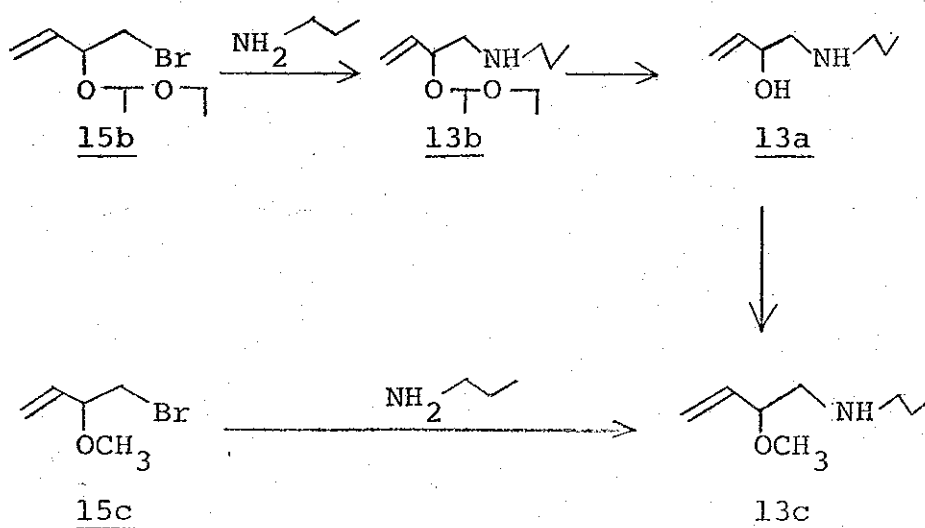
It has been known that 1-amino-2-ol component can be prepared by the reaction of epoxides and various amines.[15] In the next step, the reactions of 2-methyl-1,2-epoxy-3-butene with amines were examined. To simplify the procedure, 2-methyl-1,2-epoxy-3-butene was synthesized in situ by use of excess of amines and the corresponding amino-

alcohol was obtained in one pot process. Thus, when 1-bromo-2-methyl-3-buten-2-ol was treated with 10 equiv of n-propylamine, 1-propylamino-2-methyl-3-buten-2-ol 13d was obtained as colorless oil.[16a] In this reaction it might be possible that undesired isomer 16d is also obtained
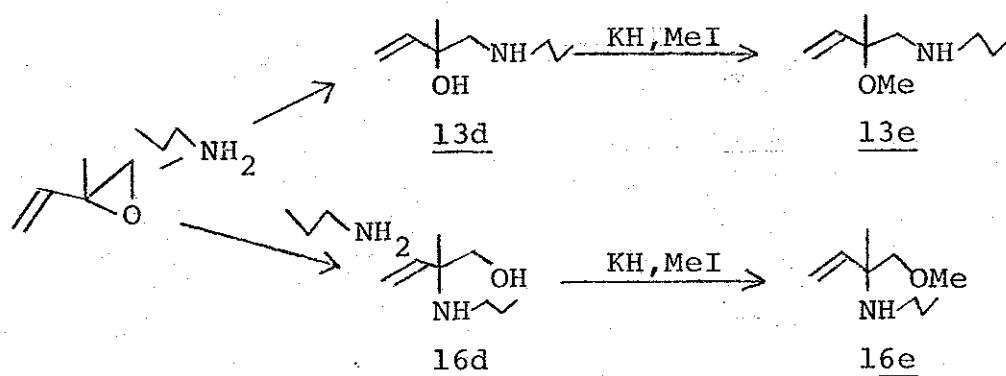
The unambiguous structure of methylated aminoalcohol 13e was determined as follows. 1) In G.C. analysis of 13e, only one peak was observed. 2) In ^{1}H NMR spectrum, four protons which attached to the α-carbons (marked C in 13e) of nitrogen atom were observed at 2.30 ppm, and no peaks

were observed from 3.30 ppm to 4.90

ppm. This observation strongly indicated

the sample did not have O-methylenes.

13e
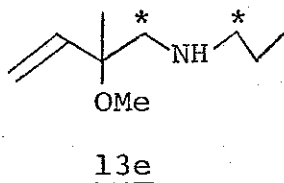
3) Finally, ^{1}H NMR spectrum of HBF$_4$

salt of 13e showed the marked methylenes

at 3.08 ppm as multiplet which were

considerably shifted to downfield, but other protons did

shift only 0.1 ppm. The great shift of these protons by

changing from amine to ammonium salt indicated that these

protons were attached to the α-carbons of nitrogen atom.

Still no peaks were observed at 3.30-4.90 ppm even in the

^{1}H NMR spectrum of the salt of 13e. Significantly, when

the smallest amine, ammonia, reacted with 1-bromo-2-methyl-

3-buten-2-ol, providing one isomer of 1-amino-2-methyl-

3-buten-2-ol 13k.[16b),16c] In the ^{1}H NMR spectrum of 13k

13k
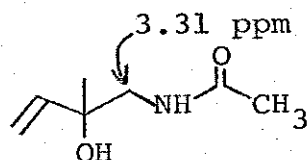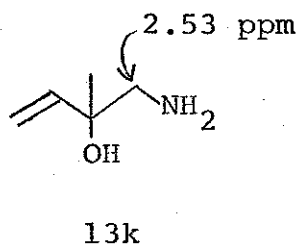
while the methylene protons were observed at 2.53 ppm as

singlet, no peaks were observed from 3.0 ppm to 4.9 ppm.

The methylene peaks were shifted to 3.31 ppm, doublet,

when the aminoalcohol 13k was acetylated. No peaks corre-

sponding to O-methylene were observed in this case, either.
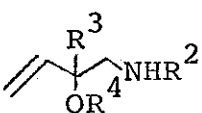
It was found that the reaction between 1-bromo-2-

methyl-3-buten-2-ol and excess amines afforded regioselec-

tively 1-amino-2-methyl-3-buten-2-ols by a very simple

procedure. In the same manner, 1-bromo-3-buten-2-ol 15a

was reacted with n-propylamine and following O-methylation

afforded 1-propylamino-2-methoxy-3-butene 13c. The product,

however, contained 28% of undesired isomer, 2-propylamino-

15a   13c   16c
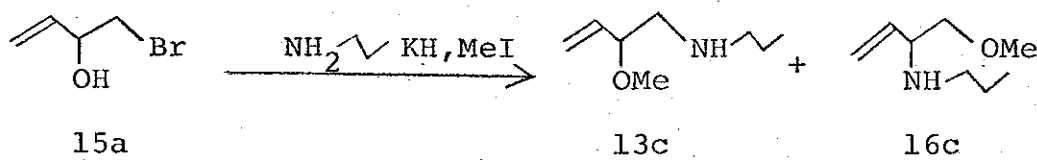
1-methoxy-3-butene 16c. The minor isomer could not be

separated by the careful distillation or column chromato-

graphy.

Table 1 shows the results of the preparation of 1-

amino-3-buten-2-ol derivatives 13. The spectral data of

these compounds are summarized in Table 2.

Table 1. Preparation of

$\underline{13}$

$\underline{13}$	R^2	R^3	R^4	b.p. (°C/mmHg)	Yield(%)
a	$n\text{-}C_3H_7$	H	H	84–87/12	88
b	$n\text{-}C_3H_7$	H		98–100/16	97
c	$n\text{-}C_3H_7$	H	Me	56–59/13	89
d	$n\text{-}C_3H_7$	Me	H	78–78.5/18	92
e	$n\text{-}C_3H_7$	Me	Me	69–70/14	86
f	$C_6H_5CH_2$	Me	H	109–110/2.5	83
g	$C_6H_5CH_2$	Me	Me	96–97/2	87
h	cyclohexyl	Me	H	103–107/10	58
i	cyclohexyl	Me	Me	102–104/8	87
j	CH_3	Me	H	68–70/18	67
k	H	Me	H	71–75/17	62

Table 2. Spectral data of 13

	IR(cm^{-1})	^{1}H NMR(δ, $CDCl_3$)
13a	3440, 2941, 1465 1120, 920	0.89(t,3H), 1.35(m,2H), 2.41 (m,4H), 3.67(m,1H), 5.48(m,3H)
13b	3340, 2938, 1465 1130, 1058, 930	0.60-1.20(m,11H), 2.43(m,4H) 3.40(m,2H), 3.98(m,1H), 4.57 (q,1H), 5.46(m,3H)
13c	3330, 2935, 1465 1105, 925	0.88(t,3H), 1.37(m,2H), 2.45(m,4H) 3.20(s,3H), 3.61(m,1H), 5.52(m,3H)
13d	3430, 2930, 1452 1370, 1123, 920	0.92(t,3H), 1.26(s,3H), 1.42 (m,2H), 2.60(m,4H), 5.50(m,3H)
13e	3330, 2940, 1450 1120, 1070, 921	0.90(t,3H), 1.24(s,3H), 1.44(m,2H) 2.57(m,4H), 3.05(s,3H), 5.42(m,3H)
13f	3430, 2970, 1454 1367, 1110, 920	1.10(s,3H), 2.50(dd,2H), 3.78 (s,2H), 5.40(m,3H), 7.19(s,5H)
13g	3328, 2930, 1451 1121, 1072, 920	1.23(s,3H), 2.50(s,2H), 3.01(s,3H) 3.70(s,2H), 5.50(m,3H), 7.20(s,5H)
13h	3440, 2930, 1451 1370, 1120, 922	1.13(s,3H), 0.70-2.20(m,11H) 2.55(dd,2H), 5.43(m,3H)
13i	3330, 2930, 1451 1130, 1072, 923	1.20(s,3H), 0.70-2.40(m,11H) 2.50(s,2H), 3.07(s,3H), 5.50(m,3H)
13j	3430, 2980, 1455 1370, 1120, 924	1.13(s,3H), 2.40(s,3H), 2.50(d,2H), 5.30(m,3H)
13k	3420, 2970, 1455 1370, 1238, 922	1.19(s,3H), 2.51(s,2H) 2.69(s,3H), 5.35(m,3H)

4-3   2-Azonia-[3,3]-sigmatropic rearrangement

   starting from aldehydes

   As described in 4-1, the starting iminium ion of 2-
azonia-[3,3]-sigmatropic rearrangement should be synthesized
by the dehydrative condensation of aldehydes with the
salts of 1-amino-3-buten-2-ol derivatives 13.[17]   When
benzaldehyde was reacted with 2-methoxy-2-methyl-N-propyl-
3-butenammonium tetrafluoroborate 17e with azeotropic
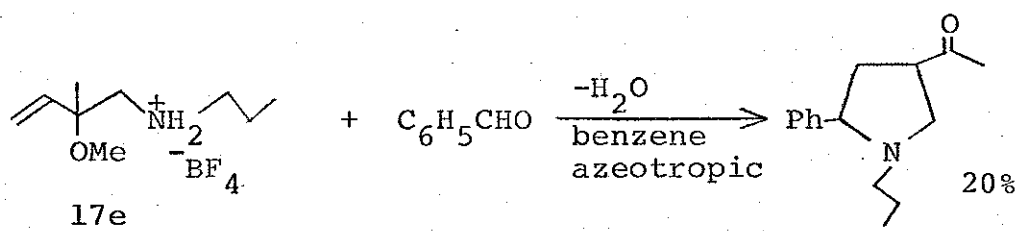
removal of water in refluxing benzene for 6 hr, only 20%
of 3-acetyl-5-phenyl-1-propylpyrrolidine was obtained.
In spite of the depression of this result, the simple
heating of the mixture of benzaldehyde and 17e in reflux-
ing benzene for 6 hr without removing water afforded the
desired pyrrolidine in remarkably higher yield (87%).[18]
Considering these results, a mechanistic rationale for the
pyrrolidine synthesis is provided in Scheme V. The de-
hydrative condensation of the starting aldehyde and sec-
ondary amine salt 17 gives iminium salt 18, which under-
goes [3,3]-sigmatropic rearrangement to 19 under these
mild conditions. Intramolecular ring closure of Mannich
type reaction results in the irreversible trapping of
the rearranged iminium ion isomer 19 to give the oxy
carbocation 20. Hydrolysis ($R^4 = CH_3$) or deprotonation

Scheme V
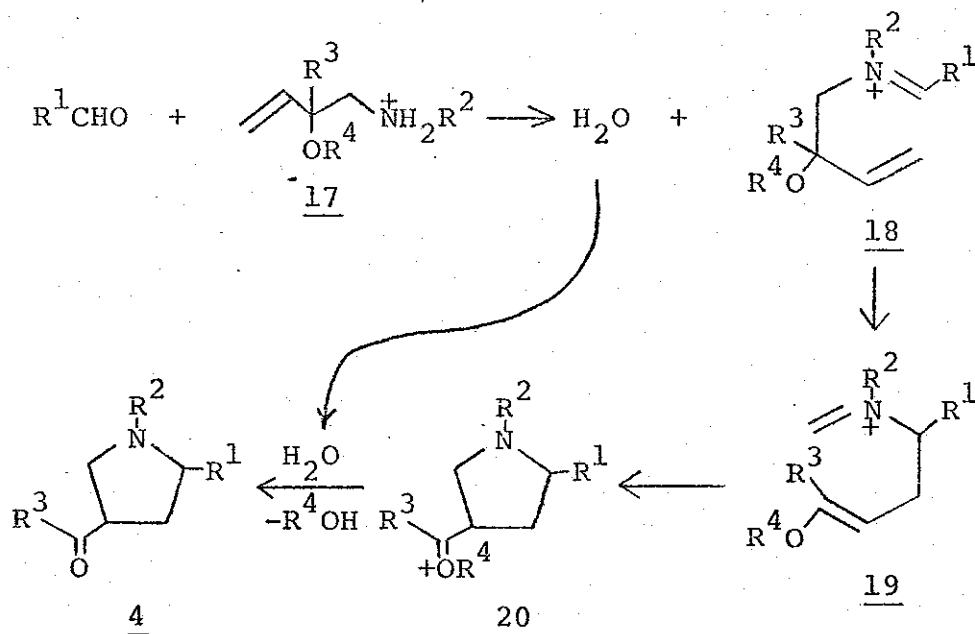
$(R^4 = H)$ of <u>20</u> by the water which is afforded by the initial

condensation yields the acetylpyrrolidine product <u>4</u>.

Table 3 summarized the results of the reaction

between various aldehydes and 1-amino-3-buten-2-ol derivatives.

In the procedure A, the crystalline tetrafluoroborate, and

in the procedure B, the free amine and 0.9 equiv of d-10-

camphorsulfonic acid were employed respectively. The

spectral data of the obtained 3-acetylpyrrolidines were

shown in Table 4 and Table 5.

The reaction succeeds with variety of aliphatic,

aromatic and heteroaromatic aldehydes and affords uniform-

ly excellent yields. Entry 5 demonstrates that the reaction

according to procedure B may be accomplished with catalytic

amount (0.1 equiv) of acid. The critical oxgen function

may be either a methoxy or hydroxyl group. In cases where

a direct comparison can be made (entries 9-13), the reaction

Table 3. Preparation of 3-acetylpyrrolidine <u>4</u>

$$R^1CHO \quad + \quad \overset{+}{N}H_2R^2 \xrightarrow[\text{PhH}]{80°}$$

Entry		R^1	R^2	OR^3		T(h)	Y(%)
<u>4a</u>	1	C_6H_5	$n\text{-}C_3H_7$	OMe	A	5	87
	2	C_6H_5	$n\text{-}C_3H_7$	OMe	B	24	85
<u>4b</u>	3	⬡–	$n\text{-}C_3H_7$	OMe	A	24	95
	4	⬡–	$n\text{-}C_3H_7$	OMe	B	24	84
	5	⬡–	$n\text{-}C_3H_7$	OMe	B*	24	90
<u>4c</u>	6	$n\text{-}C_6H_{13}$	$n\text{-}C_3H_7$	OMe	A	24	97
<u>4d</u>	7	⟍⟋⟍⟋	$n\text{-}C_3H_7$	OMe	A	24	90
<u>4e</u>	8	$n\text{-}C_6H_{13}$	⬡–	OMe	A	24	95
<u>4f</u>	9	C_6H_5	$C_6H_5CH_2$	OMe	B	24	54
	10	C_6H_5	$C_6H_5CH_2$	OMe	B	72	89
	11	C_6H_5	$C_6H_5CH_2$	OH	B	24	94
<u>4g</u>	12	furyl	$C_6H_5CH_2$	OMe	B	24	57
	13	furyl	$C_6H_5CH_2$	OH	B	24	95
<u>4h</u>	14	pyridyl	$C_6H_5CH_2$	OH	B	24	91
<u>4i</u>	15	pyridyl	CH_3	OH	B	24	84

*0.1 equiv of acid was used.

Table 4. Spectral data of 3-acetylpyrrolidines $\underline{4}$

	IR(cm^{-1})		^{1}H NMR(δ,CDCl$_3$) typical
$\underline{4a}$	2960, 2790, 1715		2.16, 2.17(acetyl)
	1363, 1172, 758		
$\underline{4b}$	2925, 2785, 1725		2.15, 2.17(acetyl)
	1450, 1355, 1175		
$\underline{4c}$	2940, 2800, 1723		2.17(s, acetyl)
	1475, 1368, 1178		
$\underline{4d}$	2959, 2790, 1722		2.18(s, acetyl)
	1446, 1375, 1175		
$\underline{4e}$	2930, 2838, 1725		2.12(s, acetyl)
	1450, 1355, 1160		
$\underline{4f}$	3030, 2795, 1725		2.11, 2.14(acetyl)
	1375, 1173, 755		7.25(aromatic)
$\underline{4g}$	2960, 2800, 1723		2.07, 2.12(acetyl)
	1356, 1150, 735		6.28, 7.30(aromatic)
$\underline{4h}$	3030, 2800, 1720		2.12, 2.15(acetyl)
	1425, 1363, 1170		7.30, 7.83, 8.70(aromatic)
$\underline{4i}$	2950, 2780, 1723		2.13, 2.18, 2.21, 2.26(acetyl
	1430, 1378, 1171		N-C$\underline{H}_3$), 7.15, 7.61, 8.56(aromatic)

Table 5. ^{13}C NMR (δ, ppm CDCl$_3$) of $\underline{4}$

$\underline{4a}$	208.2, 208.1, 143.2, 142.6, 128.3, 127.4, 127.3 127.1, 127.0, 70.3, 69.2, 55.8, 55.4, 55.3, 54.3 49.1, 38.0, 37.2, 28.9, 27.1, 21.6, 21.5, 11.7
$\underline{4b}$	209.2, 208.5, 69.4, 68.7, 56.4, 55.9, 55.7, 55.1 49.4, 48.6, 39.6, 38.8, 31.1, 30.8, 28.9, 28.2 27.1, 26.9, 26.8, 26.2, 26.0, 25.6, 21.5, 11.8
$\underline{4c}$	208.4, 208.0, 64.9, 64.3, 55.8, 55.6, 55.4, 54.7 48.7, 48.4, 33.7, 33.4, 33.0, 32.7, 31.6, 29.4 28.6, 27.0, 25.9, 22.3, 21.5, 21.4, 13.7, 11.7
$\underline{4e}$	208.5, 208.2, 59.1, 58.9, 57.9, 56.2, 49.6, 48.9 48.6, 47.9, 34.1, 33.3, 32.5, 32.4, 31.5, 29.2 28.5, 27.3, 26.0, 25.3, 24.5, 22.2, 13.7
$\underline{4f}$	208.2, 142.7, 142.2, 139.2, 139.1, 129.8, 129.4 128.5, 128.3, 128.2, 127.6, 127.5, 127.3, 126.8 69.4, 68.8, 57.7, 57.2, 55.3, 54.3, 48.9, 37.6, 37.1, 29.0, 27.3
$\underline{4g}$	207.6, 154.8, 154.7, 141.6, 138.5, 129.3, 128.4 128.2, 127.9, 126.6, 109.9, 109.8, 61.3, 60.9 57.3, 56.8, 54.5, 53.6, 48.5, 33.0, 32.5, 28.5, 27.0
$\underline{4h}$	207.2, 207.1, 149.0, 148.5, 148.3, 138.2, 138.1, 137.8, 137.4, 134.6, 134.4, 128.0, 127.8, 126.5, 123.2, 123.1, 66.2, 65.7, 57.2, 56.7, 54.9, 54.0 48.6, 36.5, 28.6, 27.0
$\underline{4i}$	207.6, 149.1, 149.0, 148.5, 148.4, 137.4, 137.1 134.7, 134.5, 123.3, 123.2, 68.4, 67.7, 58.3, 57.5 48.6, 48.5, 39.5, 36.9, 36.8, 28.8, 27.3

was slightly faster and in the case of furfural higher yielding, when the hydroxyl group was employed. Particularly significant are the absence of products resulting from diene cyclization[19] when citral (entry 7) was employed, the high yields obtained with acid sensitive furfural (entry 13) and the convenient preparation of 3-acetylnicotine (entry 15) by this procedure. It is particularly significant that, for many of the examples summarized in Table 3, R^1 was an aryl group, and thus the initially formed iminium ion isomer 18 was the more stable. The success of the reaction in these cases clearly illustrates the power of this approach for directing the 2-azonia-[3,3]-sigmatropic rearrangement, as it demonstrates that even the less stable sigmatropic isomer may be captured in high yield.

In extending this methodology to the preparation 3-formylpyrrolidines, the author examined the reaction of aldehydes and 2-methoxy-N-propyl-3-butenammonium fluoroborate 17c. When the ammonium salt 17c was allowed to react with heptanal for 24 hr in refluxing benzene, the dimethyl acetal 21 of formylpyrrolidine was isolated in 21% yield, together with considerably high molecular weight material. The desired formylpyrrolidine was not detected. The polymerization reaction might be carried out as Scheme VI. The dimethyl acetal 21 would be formed as a minor product by the reaction of oxycarbocation and methanol which is produced simultaneously with formylpyrrolidine. On the other hand, formylpyrrolidine would

80
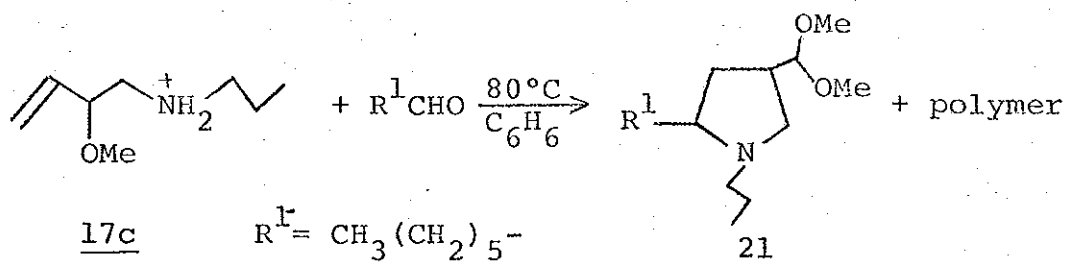
react with the starting ammonium salt 17c producing poly-

meric product. This polymerization reaction, however,

Scheme VI
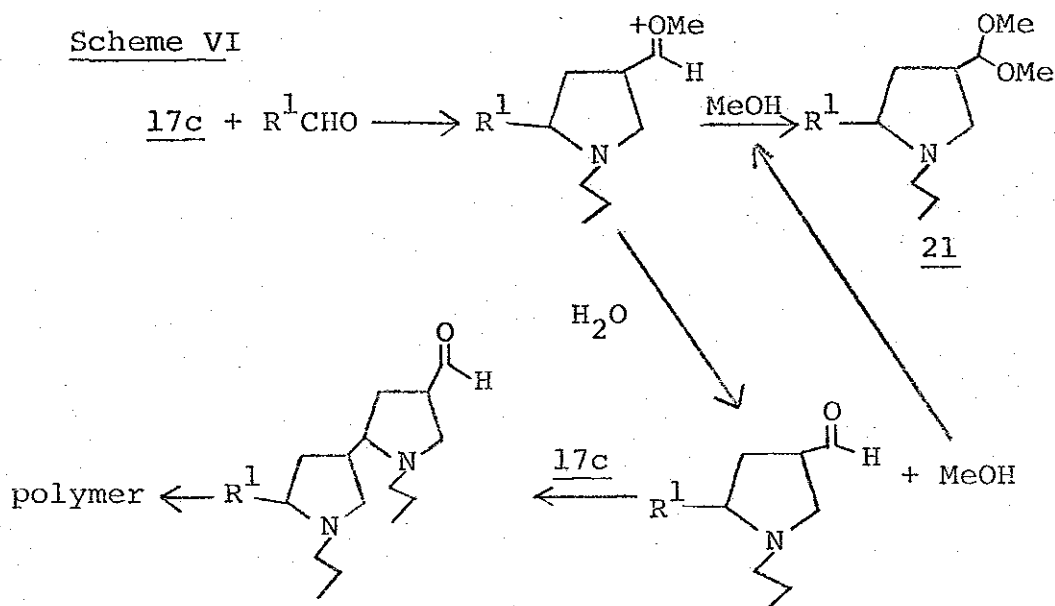
which is an obvious disadvantage in this case was almost

totally suppressed, when the identical reaction was carried

out under acetalizing condition (3-Å molecular sieves,

1 equiv of methanol) and afforded the dimethyl acetal of

formylpyrrolidine 21 in 81% (R^1= $CH_3(CH_2)_5$-) isolated

81
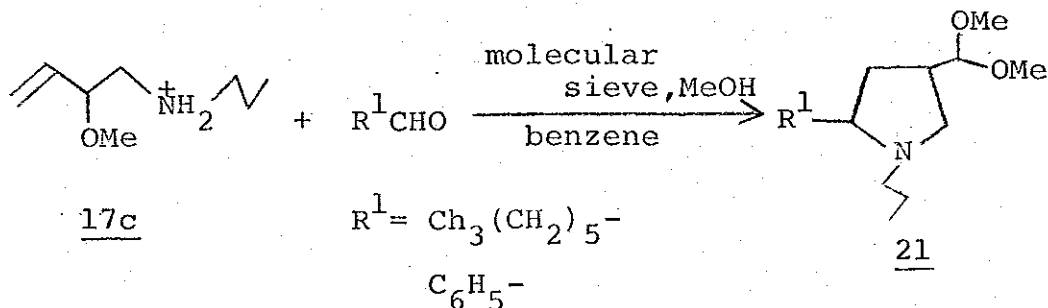
yield. Aromatic homolog such as benzaldehyde $(R^1 = C_6H_5)$ was similarly converted to 21 in 69% isolated yield.

4-4 Synthesis of 5-vinyloxazolidines

The major limitation of the new pyrrolidine synthesis described in 4-3 was that the carbonyl component must be an unhindered aldehyde. To extend this reaction to ketones, 1-amino-2-methyl-3-buten-2-ol as N-unsubstituted amine component was employed for the starting amine. The reaction between 1-propylamino-2-methyl-3-buten-2-ol **13d** and various carbonyl compounds, even aliphatic aldehyde, did not afford any remarkable products (eq. 4). On the other hand, surprisingly 5-vinyloxazolidines **6** were produced in high yields when 1-amino-2-methyl-3-buten-2-ol **5** was reacted with various carbonyl compounds under azeotropic reflux

$$\text{(4)}$$

13d

$$\text{(5)}$$

5   **6**
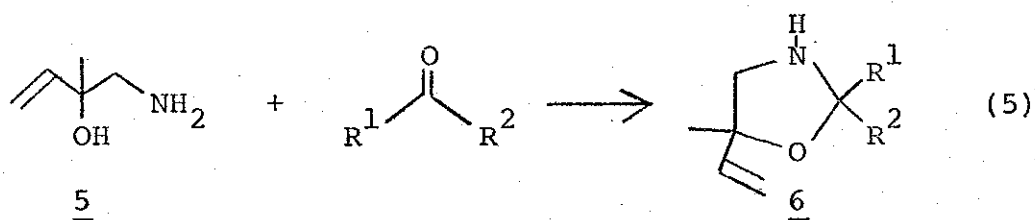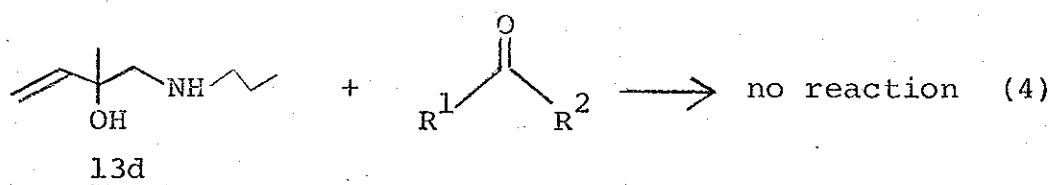
in benzene (Method A), or simple stirring in THF with anhydrous sodium sulfate (Method B) (eq. 5). 5-Vinyl-oxazolidines **6** obtained were considerably stable compounds, especially in the case of R^1, R^2 = alkyl. The boiling point and the yields of **6** were shown in Table 6, and the spectral data were summarized in Table 7.

Table 6. Preparation of 5-vinyloxazolidines 6

Oxazolidine		b.p.(°C/mmHg)*	Yield(%)	Method
6a		73-75/3	92	A
6b		140-145/3	91	A
6c		85/3	91	A
6d		120/3	58	A
6e		100-103/5	94	A
6f		100-106/6	83	B
6g		110/250	93	B
6h		120-130/0.05	92	A
6i		105-110/0.05	56	B
6j		120-125/6	95	B

*Bath temperature of bulb to bulb distillation.

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Table 7.   Spectral data of 5-vinyloxazolidines 6

	IR(cm^{-1})	^{1}H NMR(δ ppm CDCl$_3$)
6a	3300, 2960, 1445 1369, 1140, 1070	1.35(s,3H), 1.65(m,10H), 2.18 (s,1H), 3.01(s,2H), 5.48(m,3H)
6b	3275, 2980, 1464 1368, 1190, 1128	0.88(s,9H), 1.33(s,3H), 1.67(m,8H) 2.23(s,1H), 3.03(s,2H), 5.45(m,3H)
6c	3300, 2980, 1456 1368, 1160, 1055	0.97(m,3H), 1.34(d,3H), 1.57(m,9H) 2.27(s,1H), 3.05(s,2H), 5.45(m,3H)
6d	3330, 2940, 1458 1371, 1068, 1028	0.99(m,6H), 1.33(s,3H), 1.70(m,8H) 3.03(d,2H), 5.50(m,3H)
6e	3320, 1460, 1372 1155, 1104, 920	0.96(t,3H), 1.34(s,3H), 1.67(q,2H) 2.20(s,1H), 3.03(d,2H), 5.51(m,3H)
6f	3300, 2960, 1452 1338, 1097, 920	1.33(s,3H), 1.77(m,8H), 2.43(s,1H) 2.98(m,2H), 5.45(m,3H)
6g	3340, 2990, 1482 1370, 1095, 1030	0.96(d,9H), 1.30(d,3H), 2.31(s,1H) 2.90(s,2H), 5.50(m,3H)
6h	3300, 2940, 1470 1443, 1365, 1110	1.35(m,25H), 3.04(s,2H), 5.50(m,3H)
6i	3450, 2995, 1645 1374, 1115, 922	1.30(s,3H), 3.05(s,1H), 3.53(s,2H) 5.47(m,3H), 7.40(m,5H), 8.13(s,1H)
6j	3430, 2940, 1650 1619, 1446, 1380	1.30(s,3H), 1.61(s,3H), 1.70(s,3H) 1.88(m,3H), 2.20(m,4H), 2.85(m,2H) 3.48(s,1H), 5.50(m,5H), 8.22(d,1H)

The spectral data of 6 suggested the equilibrium between the imine form and the oxazolidine form, because the products which are figured as the oxazolidine form in the Tables have the small absorption at 1640 cm^{-1}

6
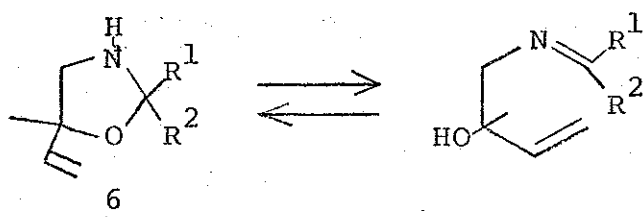
(ν C=N). It is worthwhile to mention that the products derived from the starting amine 5 and benzaldehyde or citral have the imine structure which was deduced by the strong absorption of ca. 1650 cm^{-1} in IR spectrum and ca. 8.20 ppm ($>$C=NH-) in ^{1}H NMR spectrum. In these cases, as imine component can be stabilized by the conjugation with aromatic system or olefin, the equilibrium might lie to the imine form exclusively.

4-5 Synthesis of pyrrolidines from 5-vinyloxazolidines

via acid catalyzed

2-azonia-[3,3]-sigmatropic rearrangement.
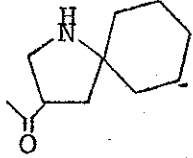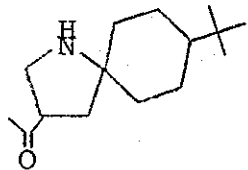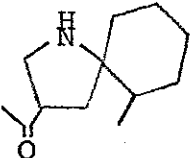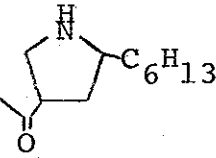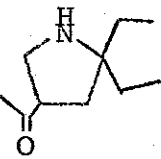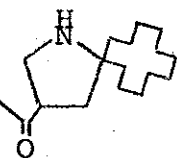
The spectral data suggested the presence of equilibrium between 4-vinylimine structure and 5-vinyloxazolidine structure as described in 4-4. This means the starting iminium ion of 2-azonia-[3,3]-sigmatropic rearrangement can be prepared directly from imine form and even from 5-vinyloxazolidine form by according to the equilibrium shown in Scheme VII.

Scheme VII
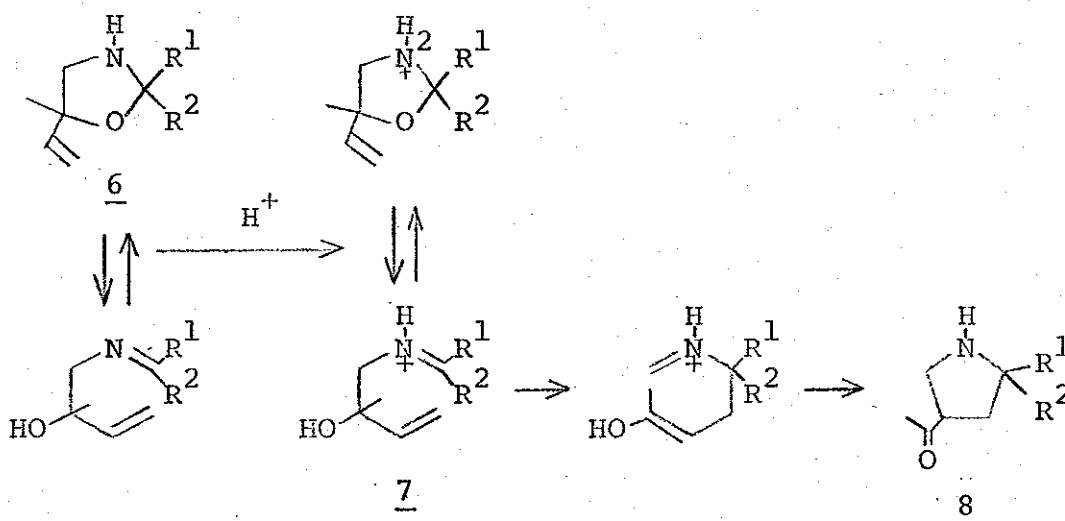
The results, when 5-vinyloxazolidines 6 are treated with 1 equiv. of d-10-camphorsulfonic acid at reflux in benzene for 24 hr, are summarized in Table 8.[20] 1-Azaspiro[4,5]decanes could be synthesized in isolated yields of greater than 50% from corresponding cyclohexanones successfully. Azaspirane 22 was produced in lower yield (45%) from the direct reaction of aminoalcohol 5 and cyclohexanone,[18] while it was not formed to a significant extent when the corresponding oxazolidine 6 (R^1, R^2=-$(CH_2)_5$-) was

Table 8. Preparation of 3-acetylpyrrolidine <u>8</u> by

2-azonia-[3,3]-sigmatropic rearrangement

3-acetylpyrrolidine		b.p.(°C/mmHg)*	yield(%)
<u>8a</u>		80-85/0.05	69
<u>8b</u>		100/0.05	70
<u>8c</u>		90-100/0.05	55
<u>8g</u>	C_6H_{13}	105-110/0.04	65
<u>8e</u>		80-85/0.05	9
<u>8k</u>		130-140/0.02	13

*Bath temperature of bulb to bulb distillation

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treated with 0.1 equiv. of the acid catalyst.[18)]
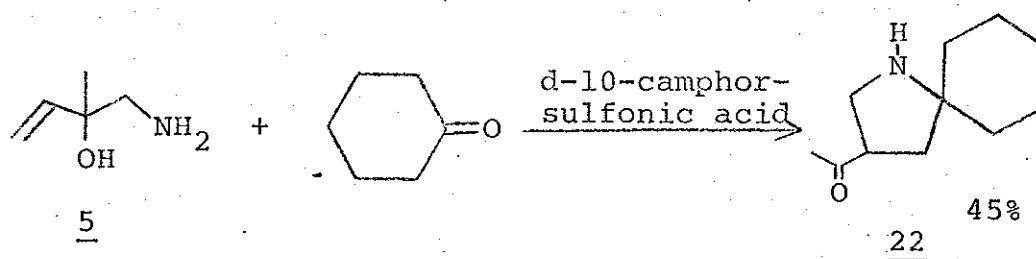
The imine 23 prepared from cyclohexanone and 2-methoxy-
2-methyl-3-butenamine also afforded azaspirane 22 in 57%
yield, when 23 was treated for 72 hr in refluxing benzene
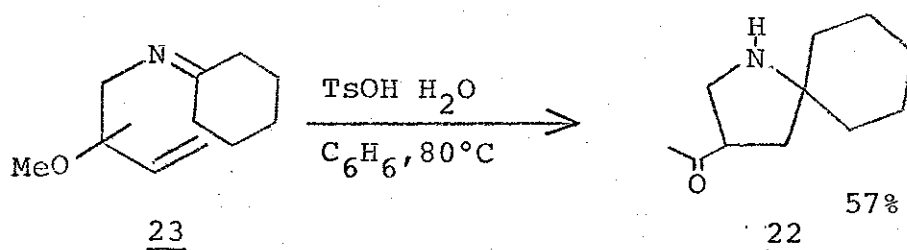
with 1.0 equiv. of p-toluenesulfonic acid monohydrate.

Preliminary indications are that the use of ketones
in this pyrrolidine sythesis may be limited to cyclo-
hexanones, since 3-acetyl-5,5-diethylpyrrolidine was
formed in only low yield from 3-pentanone precursor, and
rearrangement of the 5-vinyloxazolidine derived from cyclo-
pentanone afforded no recognizable 1-azaspiro[4,4]nonane
products. In the case of 5-vinyloxazolidine derived from
cyclododecanone, the desired 3-acetylpyrrolidine was obtained
in 13% yield and 80% of cyclododecanone was isolated. From
such results, it was deduced that the undesired decomposi-
tion reaction might occur as shown in Scheme VIII. The
starting ketones ($R^1R^2C=O$) may be produced directly or
by the hydrolysis of imine compounds. The epoxide or

aziridine which was expected from the Scheme might have
so low boiling point that they could not be isolated under
the condition. The undesirable side reaction seems to
occur depending on the bulkyness around the carbonyl function.
Because cyclohexanone would be stericly unhindered than
diethylketone, 1-azaspiro[4,5]decanes could be produced
successlully.
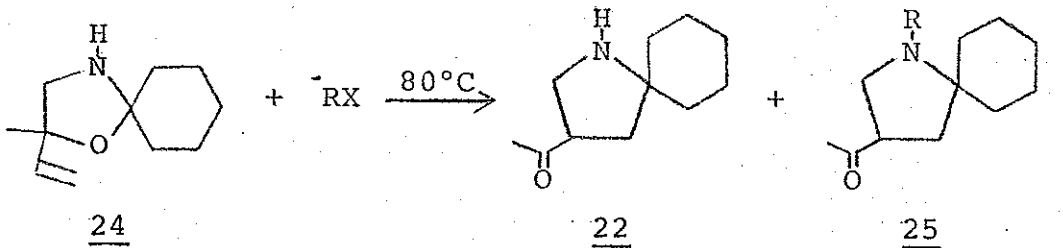
Scheme VIII
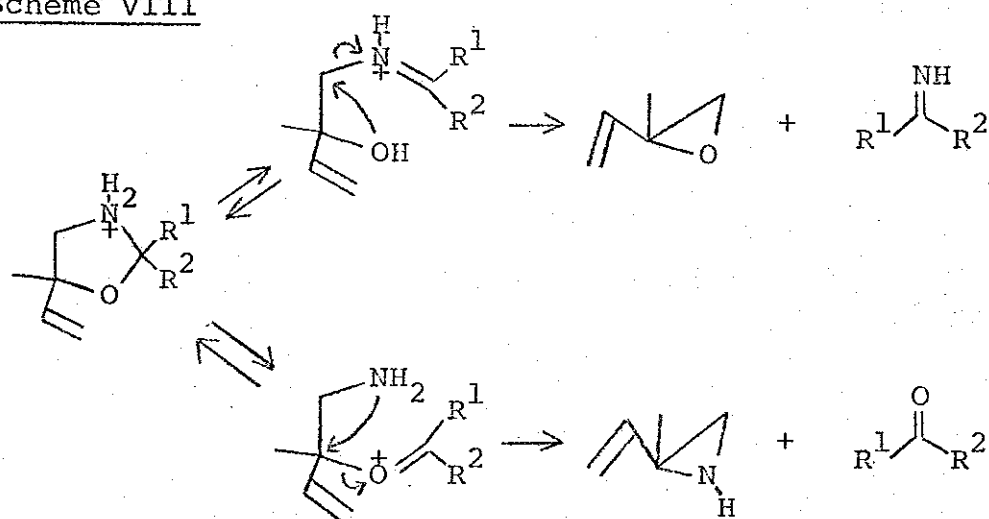
As the extention of the method to the synthesis of
N-alkylpyrrolidine derivatives treatment of oxazolidine
24 with alkylating agents (1.0 equiv.) at 80°C for 24 hr
afforded 1-alkyl-1-azaspiro[4,5]decanes, 25, in reasonable
yields, together with smaller amounts of the nonalkylated
azaspirane 22. Results are summarized in Table 9.

The formation of nonalkylated azaspirane may be
explained by the miglation of proton from alkylated 5-
vinyloxazolidine 26 or the produced salt of pyrrolidine
25, 22. Scheme IX shows the reaction pathway.

Table 9. Reaction of 24 with alkylating reagents

RX	Solvent	Yield of 25 (%)	Yield of 22 (%)
MeI	C_6H_6	54	17
MeOTs	C_6H_6	49	17
n-C_8H_{17}I	DMF	48	21
n-C_6H_{13}I	DMF	45	9

Scheme IX

91
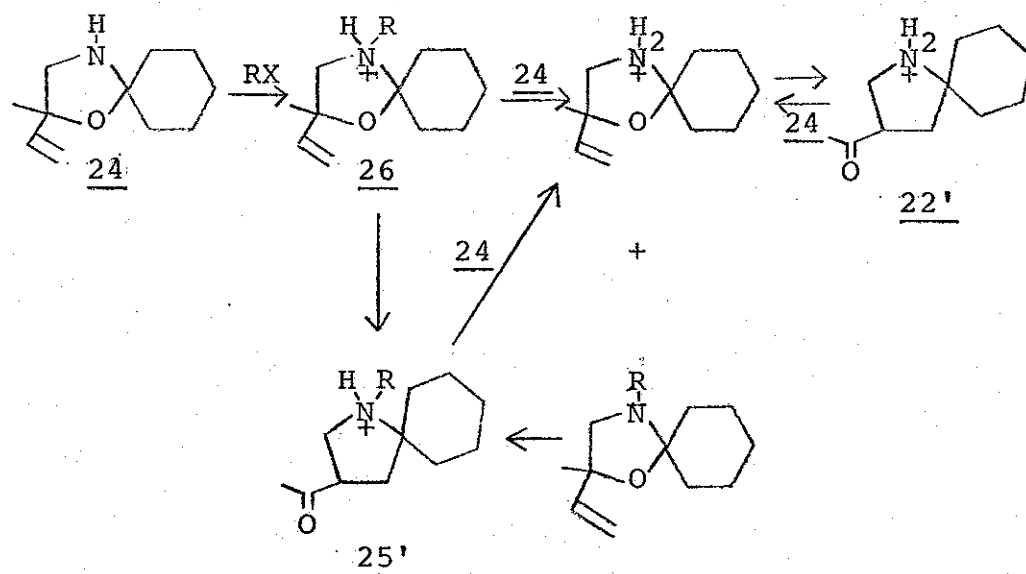
4-6 Base accelerated 4-oxy-2-aza-Cope rearrangement

5-Vinyloxazolidines derived from various carbonyl compounds would have the ability of the oxy-Cope rearrangement latently as described in 4-1. According to the description[10] this process might proceed under remarkably mild conditions compared with acid catalyzed 2-azonia-[3,3]-sigmatropic rearrangement. As provided in Table 10,[21]
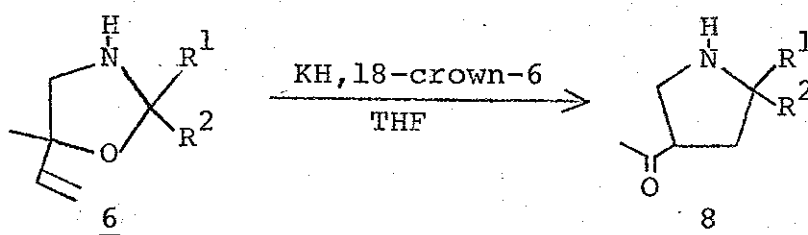
the pyrrolidine synthesis was surprisingly improved. The reaction was carried out by using 1.5 equiv. of potassium hydride and 0.1 equiv. of 18-Crown-6 in THF at 25°C for 24 hr.
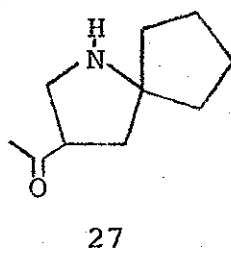
5-Vinyloxazolidines 6 derived from other ketones as well as cyclohexanones afforded 3-acetylpyrrolidines 8 in high yields. Especially, 1-azaspiro-[4,4]nonane 27, which could not be prepared by 2-azonia-[3,3]-sigmatropic rearrangement, was synthesized feasibly from cyclopentanone precurser.

The counter cation of the alkoxide should be potas-sium.[13] When sodium hydride or n-butyllithium was used as the base with 18-crown-6, 5-vinyloxazolidines 6 was recovered almost quantitatively even in refluxing THF. On the other hand, it is well known that 18-crown-6 catalyzes the oxy-Cope rearrangement when KH is used as the

base.[10]   4-oxy-2-aza-Cope rearrangement was also very

slow at 25°C without 18-crown-6 in THF.   It is significant

that HMPA effectively catalyzed the reaction instead of

18-crown-6.   Judging from these results, the reaction rate

should depend on the nature of alkoxide.   Thus, under the

condition that K^+ is chelated by 18-crown-6[22] or solvated

by HMPA, the alkoxide would have the high basicity (nucleo-

philicity) because of its nakedness.   4-oxy-2-aza-Cope

reaction also successfully proceeded in refluxing THF

without catalyst.

Table 10.   Preparation of 3-acetylpyrrolidines 8 by

4-oxy-2-aza-Cope rearrangement

	b.p. (°C/mmHg)*	Yield(%)
8a	80-85/0.05	79
8b	100/0.05	91
8d	75-80/0.03	82
8e	80-85/0.05	82
8f	80/0.1	66
8h	130-140/3	72
8i	130-135/0.07	91
8j	135-140/0.03	49
8k	130-140/0.02	84

*Bath temperature of bulb to bulb distillation
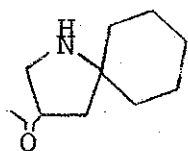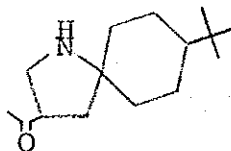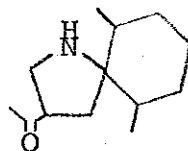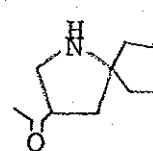
8a   8b   8d   8e
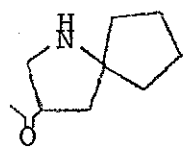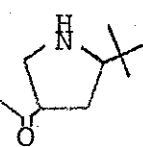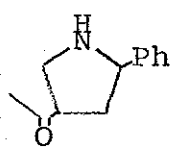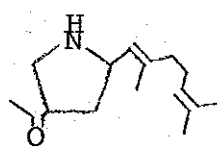
8f   8h   8i   8j
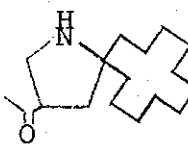
8k
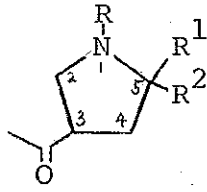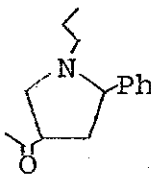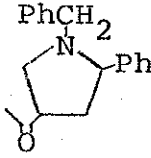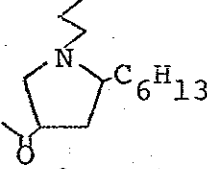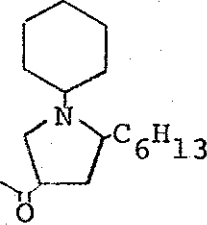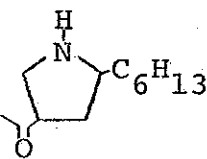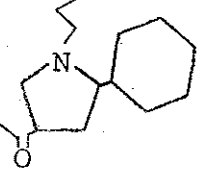
Table 11. Spectral data of 3-acetylpyrrolidine 8
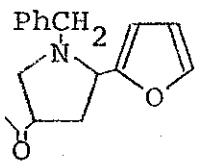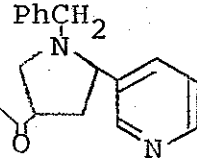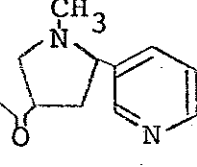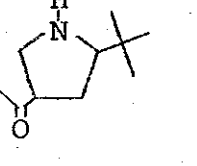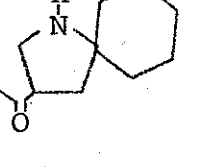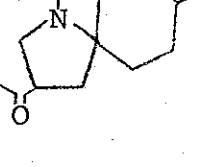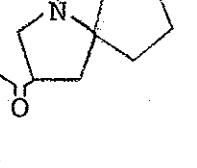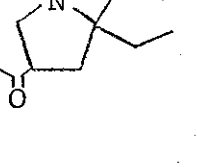
	IR(cm^{-1})			^{1}H NMR(δ ppm CDCl$_3$)
8a	3300,	1705,	1448	1.56(m,10H), 2.22(s,3H)
	1363,	1175,	918	3.18(m,3H)
8b	3330,	1705,	1440	0.84(s,9H), 1.48(m,11H)
	1363,	1170,	1092	2.19(s,3H), 3.16(m,3H)
8c	3350,	1705,	1445	0.95(d,3H), 1.55(m,9H)
	1363,	1170,	1050	2.10(s,3H), 3.16(m,3H)
8d	3350,	2940,	1705	0.88(m,6H), 2.12(s,3H)
	1460,	1365,	1170	
8e	3350,	2950,	1710	0.86(t,6H), 1.60(m,6H)
	1460,	1362,	1170	2.08(s,3H), 3.13(m,3H)
8f	3300,	2960,	1705	1.30-2.00(m,11H),
	1450,	1360,	1165	2.13(s,3H), 3.10(m,3H)
8g	3320,	2950,	1710	0.87(m,3H), 1.33(m,8H), 2.18
	1460,	1365,	1175	(s,3H), 2.00(s,1H), 3.10(m,4H)
8h	3350,	2920,	1710	0.91(d,9H), 1.80(m,3H)
	1450,	1320,	1145	2.21(s,3H), 3.00(m,4H)
8i	3350,	2900,	1710	2.09(s,3H), 7.18(m,5H)
	1455,	1360,	1120	
8j	3350,	2950,	1715	1.67(d,9H), 2.20(s,3H)
	1645,	1450,	1380	
8k	3360.	1710,	1470	1.40(m,24H), 2.19(s,3H)
	1445,	1363,	1172	3.18(m,3H)

Table 12. ^{13}C NMR(δ, ppm CDCl$_3$)of $\underline{8}$

$\underline{8a}$	209.1, 62.3, 52.9, 47.8, 39.7, 38.2, 37.3, 29.2 25.9, 23.9, 23.6
$\underline{8b}$	209.0, 62.0, 52.0, 48.3, 47.9, 42.9, 38.3, 37.2 32.3, 29.2, 27.6, 24.2, 23.6
$\underline{8e}$	209.2, 66.0, 52.8, 48.3, 38.9, 30.4, 29.4, 29.2 8.9, 8.7
$\underline{8f}$	208.8, 71.3, 52.7, 48.6, 40.8, 38.6, 29.1, 24.4 24.2
$\underline{8g}$	209.4, 208.9, 60.9, 59.3, 52.3, 52.0, 49.3, 49.2 36.2, 35.8, 35.5, 34.8, 31.9, 29.5, 29.1, 27.5 27.4, 22.7, 14.1
$\underline{8h}$	209.3, 71.4, 69.9, 68.0, 52.4, 52.3, 49.7, 47.0 45.1, 42.4, 33.2, 32.8, 30.4, 29.2, 29.1, 26.8 26.6, 26.4

	C$_2$	C$_3$	C$_4$	C$_5$	AcetylCH$_3$
	55.8	49.1	38.0	70.3	28.9
	55.4		37.2	69.2	27.1
	57.7	48.9	37.6	69.4	29.0
	57.2		37.1	68.8	27.3
	55.8	48.7	33.7	64.9	28.6
	55.6	48.4	33.4	64.3	27.0
	57.9	48.9	34.1	59.1	28.5
	56.2	48.6	33.3	58.9	27.3
	52.3	49.3	31.9	60.9	27.5
	52.0	49.2	29.5	59.3	27.4
	56.4	49.4	39.6	69.4	28.9
	55.9	48.6	38.8	68.7	28.2

	C_2	C_3	C_4	C_5	AcetylCH$_3$
(PhCH$_2$ furan)	57.3	48.5	33.0	61.3	28.5
	56.8		32.5	60.9	27.0
(PhCH$_2$ pyridine)	57.2	48.3	36.5	66.2	28.6
	56.7			65.7	27.0
(CH$_3$ pyridine)	58.3	48.6	36.9	68.4	28.8
	57.5	48.5	36.8	67.7	27.3
(H tert-butyl)	52.4	49.7	33.2	69.9	29.2
	52.3	49.5	32.8	68.0	29.1
(spirocyclohexane)	52.9	47.8	37.3	62.3	29.2
(tert-butyl spirocyclohexane)	52.0	47.9	37.2	62.0	29.2
(spirocyclopentane)	52.7	48.6	38.6	71.3	29.1
(diethyl)	52.8	48.3	38.9	66.0	29.2

98

4-7 The stereochemistry of the new pyrrolidine synthesis

3-Acetylpyrrolidines which were synthesized by the

reaction of aldehydes and the salts of 1-amino-3-buten-2-ol

derivatives contained two stereo isomers, cis and trans

in the ratio ca. ~1:1 by ^{13}C NMR analysis. The isomeriza-

tion from the one isomer to the other isomer did not proceed
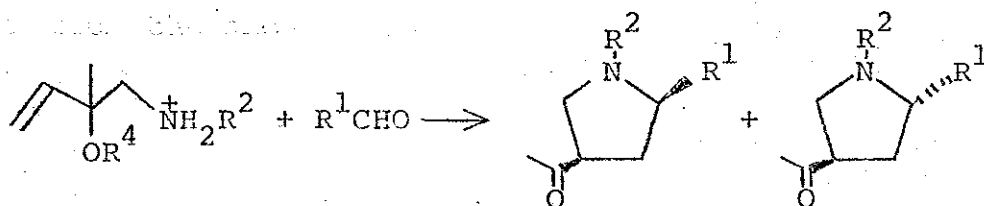
by the treatment with a base (Na_2CO_3).

The significant observation was that 3-acetyl-8-t-

butyl-1-azaspiro[4,5]decane 28 which was prepared by 2-

azonia-[3,3]-sigmatropic rearrangement from its 4-t-butyl-

cyclohexanone precurser (see 4-5) contained predominantly
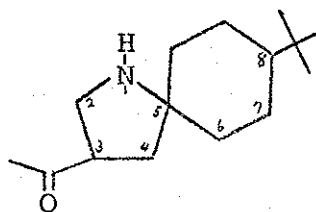
28

a single isomer (92%). However, when

28 was synthesized by 4-oxy-2-aza-Cope

rearrangement (4-6), 28 was the mixture

of two stereoisomers in the ratio 3:2.

The ratio of the isomers was calculated

by the integration of acetyl protons in ^1H NMR spectrum

using the shift reagent.[23] Thus, when Eu(fod)$_3$ was added

to the CDCl$_3$ solution of 28, the acetyl protons were shifted

to down field. Figure 1 shows the linear relation between

the ratio of Eu(fod)$_3$ and the observed shift ($\Delta\delta$). It was

found that the minor isomer shifted significantly more

than the major isomer.

The unambiguous comformation of these two isomers was determined from ^{1}H NMR spectrum of the N-benzylated derivatives. When the mixture of the two isomers (3:2) prepared by 4-oxy-2-aza-Cope rearrangement was treated by 0.3 equiv. of benzyl iodide and base, N-equatorial isomer 28b should

O:minor isomer

△:major isomer
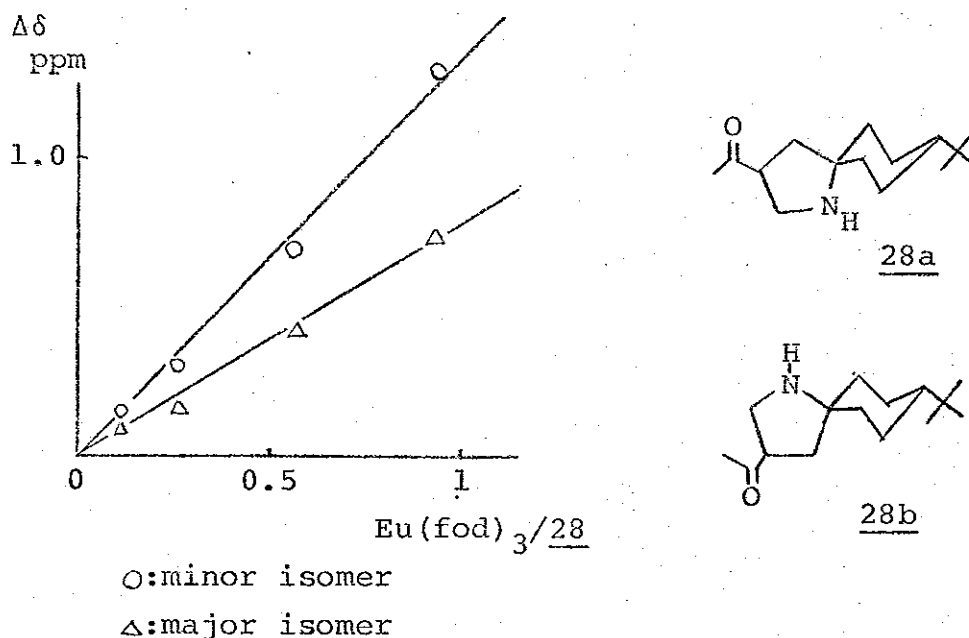
Fig. 1

be benzylated predominantly,[24] because the reaction rate is generally larger at the equatorial position than the axial position. On the other hand, by benzylation of the 92% pure isomer which was prepared by 2-azonia-[3,3]-sigmatropic rearrangement affords almost pure N-benzyl 28a or 28b. In ^{1}H NMR spectrum of benzylated 28b which was prepared tentatively by partial benzylation of the mixture, the sharp doublet of axial methylene (C_4) was observed at 1.29 ppm (J=12Hz). But N-benzylated 28 which was derived by benzylation of the 92% pure isomer did not show the remarkable signal around 1.30 ppm. This result

means that the latter sample has the equatorial methylene

which has the lower chemical shift and the broad shape.

From these observation it was concluded that the product

of 2-azonia-[3,3]-sigmatropic rearrangement was 28a in 92%

stereo selectivity, and the major isomer of 4-oxy-2-aza-

Cope rearrangement was also 28a.

It has been well studied that in the case of allyl-

sulfoxide 29 [2,3]-sigmatropic rearrangement occurs prefer-

entially across the equatorial face of exo-olefin in cyclo-

hexane ring system.[25] However, such a selectivity is not

29   8   :   92
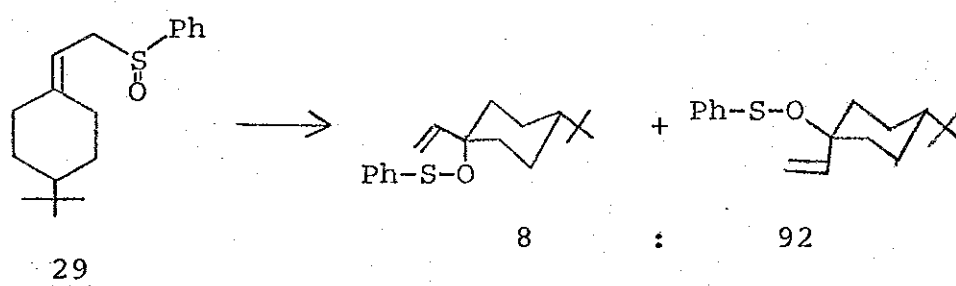
observed in [3,3]-sigmatropic rearrangement. Thus, Claisen

rearrangement of allylvinyl ether 30 affords the mixture

of the two stereo isomers in the ratio of 52:48.[26]

30   52   :   48
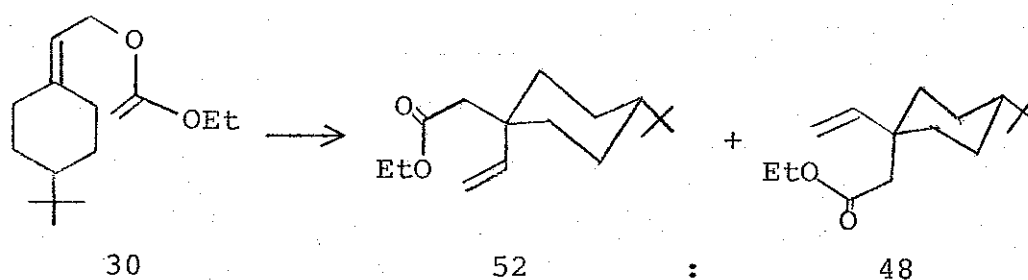
It is significant that in the present work 2-azonia-

[3,3]-sigmatropic rearrangement was proceeded in a highly

stereo-selective manner. The high stereo-selectivity in

2-azonia-[3,3]-sigmatropic rearrangement and the low stereo-

selectivity in 4-oxy-2-aza-Cope rearrangement could be

Scheme X
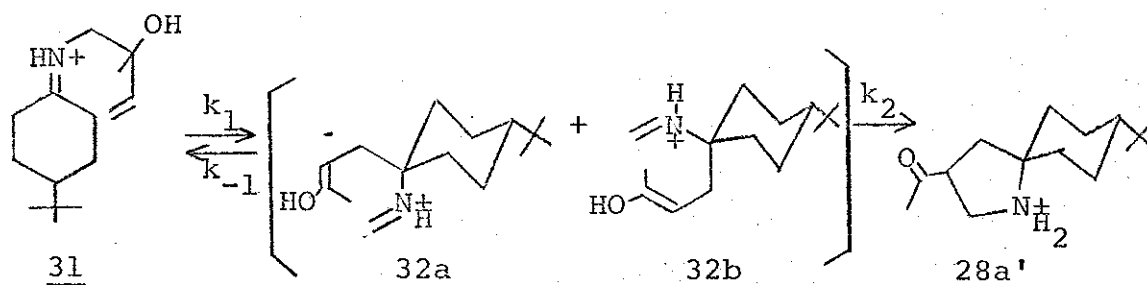
explained as follows. Scheme X shows the reaction pathway
in the case of 2-azonia-[3,3]-sigmatropic rearrangement.
Iminium ion 31 would rearrange with rate constant k_1 to
afford 32a and 32b, of which the former should be more
stable than the latter thermodynamically. If the rate
(k_2) of the cyclization from 32 to pyrrolidine salt 28'
is slower than the reverse rate (k_{-1}) from 32 to 31 ($k_{-1} >$
k_2), the stable intermediate 32a should be stored, so the
N-axial pyrrolidine 28a should be produced predominantly
as the final product.

To the contrary, in the case of 4-oxy-2-aza-Cope
rearrangement, the rate of the cyclization may be faster
than the reverse rearrangement ($k_{-1} \leqslant k_2$). Under such a
kinetically controlled reaction the mixture of 28a and 28b
may be produced.
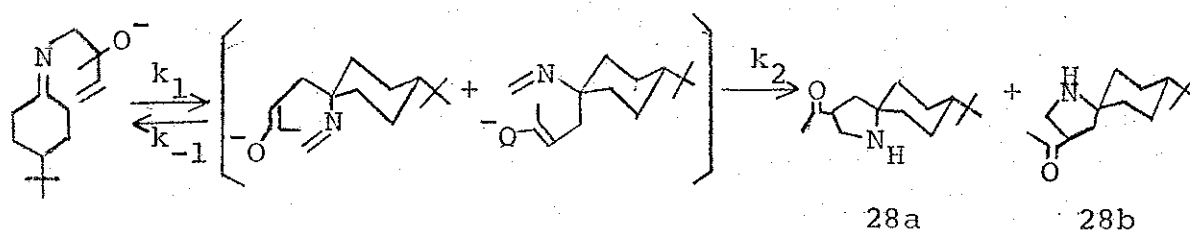
4-8 Experimental Section

Tetrahydrofuran (THF) was purified by distillation from sodium and benzophenone. Benzene was purified by distillation from sodium.

^{1}H NMR spectra were determined with a Varian EM 360 spectrometer. ^{13}C NMR spectra were determined at 22.62 MHz with a Brucker WH-90 spectrometer and at 25 MHz with JEOL-FX-100 spectrometer. In the experimental section, NMR means ^{1}H NMR spectrum and CMR means ^{13}C NMR spectrum respectively. ^{1}H NMR and ^{13}C NMR shifts are reported δ-values in parts per million relative to internal tetra-methylsilane. Abbreviations used are : s, singlet; d, doublet; t, triplet; q, quartet; and m, complex multiplet.

Infrared spectra (IR) were determined with a Perkin-Elmer Model 283 spectrophotometer and a Hitachi Model API-S2 spectrophotometer. Absorption values are reported in cm^{-1}.

Mass spectra were determined with a Dupont 21-498B double focusing spectrometer. m/e values are reported and parentheses after m/e values means the relative intensity.

Boiling points of bulb to bulb distillations are reported by bath temperatures. Melting points are not corrected.

1-Bromo-2-methyl-3-buten-2-ol 15d

   40.5g (0.6mol) of isoprene was dissolved in 140 ml of
ether and 100 ml of water in three necked flask equiped with
mechanical stirrer , condenser and thermometer.   106.8g (0.6
mol) of N. B. S. was added at 5°C on the ice bath.   After the
addition of N.B.S. was completed , the ice bath was removed.
The reaction began at about 25°C exothermicly, the temperature
of the solution was maintained at 30°C with the ice bath.   After
the crystal of N.B.S. was disappered, the solution was stirred
for 3 hr at 25°C.   100 ml of water was added. The organic layer
was separated, the aqueous layer was extracted three times
by 50 ml portion of ether.   The combained ether solution was
washed with 100 ml of water, dried over sodium sulfate.
After the solvent was evaporated, the pure isoprenebromohydrine
was distilled at 63-66°C/20 mmHg, yielding 69g (70%).
NMR (CDCl$_3$) 1.47(S,3H), 2.42(S,1H), 3,53(S,2H), 5.63(m,3H)

Butadienebromohydrine 15a

   125 ml(1.5 mol) of butadiene was dissolved in 350 ml
of ether and 150 ml of water in 1 L of three necked flask
equiped with mechanical stirrer, thermometer and dry ice
condenser at -10°C.   267g (1.5 mol) of NBS was added at the
temperature.   The bath was removed, and the solution was
allowed under the gently refluxing (cooled the flask if
necessary).   The solution was stirred for 4 hr.   200 ml of
water was added, the organic layer was separated.   Combained
ether extraction of aqueous layer (50mlX3) was dried over
sodium sulfate.   After the sol-vent was evaporated butadiene-

bromohydrine was distilled at 63-65°C/16mmHg., in the yield

of 177g (78 %).

NMR: 3.26(d, 2H), 4.68(m, 1H), 5.40(m, 3H)
  (CDCl$_3$)

Butadienebromohydrine 1-ethoxy-ethylether 15b

In 20 ml flask, 6.04g (0.04mol) of butadienebromohydrine

was added dropwise to 2.88g (0.04 mol) of ethylvinylether at

0°C. The mixture was stirred for 3 hr. Direct distillation

afforded 7.9g (89%) of butadienebromohydrine 1-ethoxy-ethyl-

ether at 80-87°C/15 mmHg.

NMR (CCl$_4$): 1.15(m, 6H), 3.25(d, 2H), 3.50(q, 2H), 4.16(q, 1H)
        4.70(m, 1H), 5.52(m, 3H)

2-(1-ethoxy)-ethyl-3-butenyl-n-propylamine 13b

In 20 ml flask, 1.12g (5 mmol) of butadienebromohydrine

1-ethoxy-ethylether was added dropwise to 5 ml of n-propyl-

amine at 0°C, the mixture was stirred for 24 hr. The excess

of n-propylamine was evaporated, the residue was dissolved

in 10 ml of 10% sodium hydroxide solution and 10 ml of ether.

Ether extraction (5 ml X 3) was dried over sodium sulfate,

and the solvent was evaporated. Pure 1-N-propylamino-2-(1-

ethoxy)-ethoxy-3-butene was distilled at 98-100°C/16mmHg in

the yield of 976 mg (97%).

NMR (CCl$_4$) : 0.60-1.20(m, 11H), 2.43(m, 4H), 3.40(m, 2H)
        3.98(m, 1H), 4.57(q, 1H), 5.46(m, 3H)

IR (NaCl film): 3340, 2938, 1465, 1130, 1097, 1058, 930

1-N-propylamino-3-buten-2-ol 13a

To 950 mg (4.7 mmol) of 1-N-propylamino-2-(1-ethoxy)-ethoxy-3-butene in 5 ml of methanol, 5-N hydrochloric acid solution was added dropwise to pH 3 at 0°C. The solution was stirred for 24 hr, the solvent was evaporated. The residue was dissolved in 5 ml of ether, 10% sodium hydroxide solution was added to pH 10. The ether extraction was dried over sodium sulfate, the solvent was evaporated, and distilled at 72-75°C/9 mmHg in the yield of 500 mg (80 %).

NMR (CDCl$_3$): 0.89(t, 3H), 1.35(m, 2H), 2.41(m, 4H), 3.67(m, 1H), 5.48(m, 3H)

IR (NaCl film): 3440, 2941, 1465, 1120, 920

Butadienebromohydrine methylether 15c

17.8g (0.1 mol) of NBS was dissolved in 50 ml of methanol 8.4 ml (0.1 mol) of butadiene was added to the solution at -50°C. The dry ice bath was removed. The solution was stirred for 6 hr at 25°C. After the solution was diluted with 70 ml of water, was extracted four times by 30 ml portion of ether. The ether extraction was dried over sodium sulfate, the solvent was evaporated. The pure product was distilled at 65-70°C/58 mmHg in the yield 9.24g (56%).

NMR (CDCl$_3$): 3.16(s, 3H), 3.30(d, 2H), 4.64(m, 1H), 5.47(m, 3H)

1-N-propylamino-2-methoxy-3-butene 13c

A) 800 mg of potassiumhydride (22.4% in oil) was
suspended in 50 ml of THF. 2.58g (20 mmol) of 1-N-propyl-
3-buten-2-ol was added dropwise at 0°C under nitrogen.
After the solution was stirred for 15 min. at the temperature,
2.84g (20 mmol) of methyliodide was added slowly. The solution
was stirred for 3 hr at 25 °C. The precipitate was filtered.
1-N-propylamino-2-methoxy-3-butene was distilled from the
residue of evaporation at 56-59°C/13 mmHg in the yield of
2.56g (89%).

B) To 100 ml of n-propylamine in 200ml flask, 23g
(0.14 mol) of butadienebromohydrine methylether was added
dropwise at 0°C. The solutionwas stirred for 12 hr. The
excess of amine was evaporated,80 ml of 15 % of sodium hydroxide
solution was added to the residue. The solution was extracted
three times by 50 ml portion of ether, dried over sodium
sulfate. The product was distilled in the yield of 14.4g
(72 %).

NMR(CDCl$_3$): 0.88(t, 3H), 1.37(m, 2H), 2.45(m, 4H), 3.20
(s, 3H), 3.61(m, 1H), 5.52(m, 3H)
IR(NaCl film): 3330, 2935, 1465, 1105, 925

1-N-prpylamino-2-methyl-3-buten-2-ol 13d

14.9g (90 mmol) of isoprenebromohydrine was added drop-
wise to 100 ml of n-propylamine at 0?C. The solution was
refluxed for 6 hr. The excess of n-prpylamine was evaporated.
The residue was dissolved in 30 ml of 15% of sodium hydroxide
solution and 50 ml of ether. The separated aqueous layer was

exracted three times by 20 ml portion of ether. The combained

ether extraction was dried over sodiumsulfate. The solvent was

evaporated, 1-N-propylamino-2-methyl-3-buten-2-ol was distilled

at 78-78.5°C/18 mmHg in the yield of 11.84g (92%).

NMR (CDCl$_3$):   0.92(t, 3H), 1.26(s, 3H), 1.42(m, 2H) 2,60(m, 4H)

5.50(m, 3H)

IR (NaCl film): 3430, 2930, 1452, 1370, 1123, 920

1-N-propylamino-2-methoxy-2-methyl-3-butene 13e

1.6g (40 mmol) of potassiumhydride (24% in oil) was

suspended in 100 ml of THF. 5.75g (40 mmol) of 1-N-prpylamino-

-2-methyl-3-buten-2-ol was added dropwise at 0°C under nitrogen.

After the solution was stirred for 15 min. at the temperature,

5.68g (40 mmol) of methyliodide was added. The solution was

stirred for 3 hr at 25 °C. The precipitate was filtered.

The solvent was evaporated, and 1-N-propylamino-2-methoxy-2-

methyl-3-butene was distilled at 69-70°C/14 mmHg in the

yield of 5.4g (86 %).

NMR (CDCl$_3$): 0.90(t, 3H), 1.24(s, 3H), 1.44(m, 2H), 2.57

(m, 4H), 3.05(s, 3H), 5.42(m, 3H)

IR (NaCl film): 3330, 2940, 1450, 1120, 1070, 921

2-methoxy-2-methyl-3-butenyl-n-propylammonium tetrafluoroborate 17e

2.28g (14.5 mmol) of 2-methoxy-2-methyl-3-butenyl-n-

propylamine dissolved in 30 ml of 95% ethylalcohol. 1.57ml

of tetrafluoroboric acid (previously titrated by 1N sodium

hydroxide solution, and known as 9.2 mmol/ml) was added at

0°C with stirring. (In this time, the solution should be

slightly basic.) The solvent was evaporated in vacuo, the
obtained white crystal was washed with ether. In the further
reaction the salt was used without recrystalization. The
salt could be recrystalized with the careful addition of
ether to the ethanolic solution of the salt. M.P. was 168-170°C.

NMR(CDCl$_3$): 0.99(t, 3H), 1.40(s, 3H), 1.78(m, 2H), 3.08(m, 4H)
3.24(s, 3H), 5.47(m, 3H)

IR (KBr) : 2970, 2800, 1040-1110,

E.A. : Cal. C:44.10, N:5.72, H:8.23.
Fou. C:44.19, N:5.67, H:8.12.

2-hydroxy-2-methyl-3-butenyl-benzylamine 13f

12.75g (77 mmol) of isoprenebromohydrine was added drop-
wise to 70 ml of benzylamine at 0°C. The solution was stirred
for 6 hr at 25°C and 3 hr at 110°C. The excess amine was
distilled away under reduced pressure, the residue was dissolved
in 50 ml of 15% sodiumhydroxide solution and 30 ml of ether.
The aqueous layer was extracted by three times 20 ml portion
of ether. The ether extraction was dried over sodium sulfate,
the solvent was evaporated. 2-Hydroxy-2-methyl-3-butenyl-
benzylamine was distilled at 109-110°C/2.5 mmHg in the yield
of 12.2g (83 %).

NMR(C Cl$_4$): 1.10(s, 3H), 2.50(dd, 2H), 3.78(s,2H), 5.40(m,
3H), 7.19(s, 5H)

IR(NaCl film): 3430, 2970, 1454, 1367, 1110, 920

2-methoxy-2-methyl-3-butenyl-benzylamine 13g

1.2g (30 mmol) of potassium hydride(24% in oil) was suspended in 100 ml of THF. 5.73g (30 mmol) of 2-hydroxy-2-methyl-3-butenyl-benzylamine was added dropwise at 0°C under nitrogen. After the solution was stirred for 15 min. at the tempareture, 4.26g (30 mmol) of methyliodide was added. The solution was stirred for 5 hr at 25°C. The precipitate was filtered. The solvent was evaporated, and 2-methoxy-2-methyl-3-butenyl-benzylamine was distilled at 96-97°C/2 mmHg in the yield of 5.33g (87 %).

NMR(C Cl$_4$): 1.23(s, 3H), 2.50(s, 2H), 3.01(s, 3H), 3.70(s,
2H), 5.50(m, 3H), 7.20(s, 5H)

IR(NaCl film): 3328, 2930, 1451, 1121, 1072, 920

2-hydroxy-2-methyl-3-butenyl-cyclohexylamine 13h

8.25g (50 mmol) of isoprenebromohydrine was added dropwise to 100 ml of cyclohexylamine in the sealed bottle at 0°C. The solution was stirred for 6 hr at 25°C, and heated for 3 hr at 110°C. The excess amine was distilled away under the reduced pressure, the residue was dissolved in 50 ml of 15% sodium hydroxide solution and 30 ml of ether. The aqueous layer was extracted three times by 20 ml portion of ether. The ether extraction was dried over sodiumsulfate, the solvent was evaporated. 2-Hydroxy-2-methyl-3-butenyl-cyclohexylamine was distilled at 103-107°C/10 mmHg in the yield of 5.29g (58 %).

NMR(C Cl$_4$) : 1.13(s, 3H), 0.7-2.20(m, 11H), 2.55(dd, 2H),
5.43(m, 3H)

IR(NaCl film): 3440, 2930, 1451, 1370, 1120, 922

2-methoxy-2-methyl-3-butenyl-cyclohexylamine 13i

1g (27 mmol) of potassium hydride(20.4% in oil) was suspended in 100 ml of THF. 5g (27 mmol) of 2-hydroxy-2-methyl-3-butenyl-cyclohexylamine was added dropwise at 0°C under nitrogen. After the solution was stirred for 15 min. at the temperature, 3.83g (27 mmol) of methyliodide was added. The solution was stirred for 6 hr at 25°C. The precipitate was filtered. The solvent was evaporated, and 2-methoxy-2-methyl-3-butenyl-cyclohexylamine was distilled at 102-104°C/8 mmHg in the yield of 4.65g (87 %).

NMR(C Cl$_4$) : 1.20(s, 3H), 0.7-2.40(m, 11H), 2.50(s, 2H),

3.07(s, 3H), 5.50(m, 3H)

IR(NaCl film): 3330, 2930, 1451, 1130, 1072, 923

2-methoxy-2-methyl-3-butenyl-cyclohexylammonium tetrafluoroborate 17i

4.4g (22 mmol) of 2-methoxy-2-methyl-3-butenyl-cyclohexylamine was dissolved in 30 ml of 95% ethylalcohol. 2.4 ml of tetrafluoroboric acid (9.2 mmol/ml) was added at 0°C with stirring. The solvent was evaporated, the obtained white crystal was washed with ether. The salt was recrystalized from ethanol-ether or benzene. M.p. was 238-240°C(decomposed).

NMR(CDCl$_3$): 1.40(s, 3H), 1.00-2.33(m, 11H), 3.05(d, 2H)

3.23(s, 3H), 5.68(m, 3H)

IR(KBr): 2990, 2800, 1035-1110

E.A.: Cal.   C:50.55, H:8.48, N:4.91

Found: C:50.48, H:8.46, N:4.87

2-hydroxy-2-methyl-3-butenyl-methylamine 13j

3g (18 mmol) of isoprenebromohydrine was added dropwise
to 30 ml of 40 % methylamine aqueous solution. The mixture
was stirred for 12 hr at 25°C. Potassiumhydroxide was added
to be saturated at 0°C. The solution was extracted four times
by 20 ml portion of ether, the etherextraction was dried over
sodiumsulfate. The solvent was evaporated. 2-hyroxy-2-methyl-
3-butenyl-methylamine was distilled at 68-70°C/18 mmHg in the
yield of 1.4g (67 %).
NMR(CCl$_4$) : 1.13(s, 3H), 2.40(s, 3H), 2.4(d, 2H), 5.30(m, 3H)
IR(NaCl film): 3430, 3330, 2980, 1455, 1370, 1120, 924

2-hydroxy-2-methyl-3-butenylamine 13k

11.5g (70 mmol) of isoprenebromohydrine was suspended in
50 ml of ammonia water (28 %) in 100 ml sealed tude. The
solution was heated at 60°C with stirring for 24 hr. Sodium
hydroxide was added to the solution to be saturated at the ice
bath. The solution was extracted four times by 20 ml portion
of ether, dried over sodiumsulfate. The solvent was evaporated
and 2-hydroxy-2-methyl-3-butenylamine was distilled at 72-75°C
/17 mmHg in the yield of 4.38g (62 %).
NMR(CDCl$_3$) :1.19(s, 3H), 2.51(s, 2H), 2.69(s, 3H), 5.35(m, 3H)
IR(NaCL film) : 3420, 2970, 1455, 1412, 1370, 1238, 922

2-methoxy-2-methyl-3-butenylamine 13L

1.2g (30 mmol) of potassium hydride(24 % in oil) was
suspended in 100 ml of THF. 3.03g (30 mmol) of 2-hydroxy-
2-methyl-3-butenylamine was added dropwise at 0°C under

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nitrogen. After the solution was stirred for 15 min. at the temperature, 4.26g (30 mmol) of methyliodide was added. The solution was stirred for 6 hr at 25°C. The precipitate was filtered. The solvent was evaporated, and 2-methoxy-2-methyl-3-butenylamine was distilled at 80- 84°C/20 mmHg in the yield of 2.14g (62 %).

NMR(CDCl$_3$) : 1.27(s, 5H), 2.70(s, 2H), 3.22(s, 3H), 5.50(m, 3H)

3-Acetyl-5-phenyl-1-propylpyrrolidine 4a

A) 735 mg (3 mmol) of 2-methoxy-2-methyl-3-butenyl-n-propyl ammonium tetrafluoroborate was suspended in 5 ml of benzene. 350 mg (3.3 mmol) of benzaldehyde was added, andheated at reflux for 5 hr. After the mixture was cooled down to 25°C, 3 ml of 1N sodiumhydroxide solution was added. The organic layer was separated, and the aqueous layer was extrcted three times by 5 ml portion of ether. The combained extraction was dried over sodiumsulfate, the solvent was evaporated. 3-acetyl 5-phenyl-1-propylpyrrolidine was distilled at 95°C/0.01 mmHg (bulb to bulb) in the yield of 599 mg (87 %).

B)   209 mg (0.9 mmol) of d-10-camphorsulfonic acid was added to 106 mg (1mmol) of benzaldehyde ᴀin 3 ml of benzene. The ⌐and 157 mg (1mmol) of 2-methoxy-2-methyl-3-butenylpropylamine⌐ solution was refluxed for 24 hr. After the solution was cooled down to 25°C, 1N sodiumhydroxide solution was added. The product was extracted by ether. The yield was 85%.

CMR(CDCl$_3$) : 208.2,208.1(C=O), 143.2, 142.6, 128.2, 127.4,

127.3, 127.1, 127.0, 70.3, 69.2, 55.8, 55.4,

55.3, 54.3, 49.1, 38.0, 37.2, 28.9, 27.1, 21.6,

21.5, 11.8

IR(NaCl film) :   2960, 2790, 1715, 1363, 1172, 758

Mass :   231.162(M$^+$, cal.231.162)(8), 202(100), 188(23), 154(12)

3-Acetyl-5-cycloheyl-1-propylpyrrolidine 4b

A)   382 mg (3.5 mmol) of cyclohexanecarboxaldehyde was added to 735 mg (3 mmol) of 2-methoxy-2-methyl-3-butenyl-n-propylammonium tetrafluoroborate in 5 ml of benzene. The mixture was heated at reflux for 24 hr. After the mixture

was cooled down to 25 °C, 3 ml of 1N sodiumhydroxide solution
was added. The organic layer was separated, and the aqueous
layer was extracted three times by 5 ml portion of ether.
The combained extraction was dried over sodium sulfate, the
solvent was evaporated. 3-Acetyl-5-cyclohexyl-1-propylpyrrolidine
was distilled at 90-95°C/5x10^{-3}mmHg in the yield of 678 mg
(95 %).

B) 696 mg (3 mmol) of d-10-camphorsulfonic acid was added
to 518 mg (3.3 mmol) of 2-methoxy-2-methyl-3-butenyl-n-propyl
amine in 5 ml of benzene. 392 mg (3.5 mmol) of cyclohexane-
carboxaldehyde was added to the solution. The solution was
heated at reflux for 24 hr. After the solution was cooled
down to 25 °C, 3 ml of 1N sodium hydroxide solution was added.
The product was extracted by ether. The yield was 660 mg
(84 %).

C) 76 mg (0.33 mmol) of d-10-camphorsulfonic acid was added
to 518 mg (3.3 mmol) of 2-methoxy-2-methyl-3-butenyl-n-propyl-
amine in 5 ml of benzene. 392 mg (3.5 mmol) of cyclohexane-
carboxaldehyde was added to the solution. The solution was
heated at reflux for 24 hr. After the solution was cooled
down to 25°C, 0.4 ml of 1N sodiumhydroxyde solution was added.
The product was extracted by ether. The yield was 708 mg
(90 %).

CMR(CDCl$_3$); 209.2, 208.5, 69.4, 68.7, 56.4, 55.9, 55.7, 55.1,
49.9, 48.6, 39.6, 38.8, 31.1, 30.8, 28.9, 28.2,
27.1, 26.9, 26.8, 26.2, 26.0, 25.6, 21.5, 11.8
IR(NaCl film); 2925, 2785, 1725, 1450, 1355, 1175

3-Acetyl-5-n-hexyl-1-propylpyrrolidine <u>4c</u>

A)   735 mg (3 mmol) of 2-methoxy-2-methyl-3-butenyl-n-propyl-
ammonium tetrafluoroborate was suspended in 5 ml of benzene.
399 mg (3.5 mmol) of heptanal was added, and heated at reflux for
24 hr. After the solution was cooled down to room temperature,
3 ml of 1N sodiumhydroxide solution was added. The organic
layer was separated, the aqueous layer was extracted three
times by 5 ml portion of ether. The combained extraction
was dried over sodiumsulfate. Distillation (bulb to bulb)
at 85-90°C/0.01mmHg afforded 3-acetyl-5-n-hexyl-1-propylpyrrolidine
in the yield of 698 mg (97 %).

B)   245 mg (1 mmol) of 2-methoxy-2-methyl-3-butenyl-n-propyl-
ammonium tetrafluoroborate was suspended in 5 ml of benzene
containing 2 drops of water. 207 mg (1.1 mmol) of heptanal
diethylacetal was added to the solution and refluxed for 24
hr. After the solution was cooled down to 25°C, 3 ml of 1N
sodiumhydroxide solution was added. The product was extracted
by ether. The yield was 227 mg (95 %).

CMR(CDCl$_3$) : 208.4, 208.0, 64.9, 64.3, 55.8, 55.6, 55.4, 54.7,
           48.7, 48.4, 33.7, 33.4, 33.0, 32.7, 31.6, 29.9,
           28.6, 27.0, 25.9, 22.3, 21.5, 21.4, 13.7, 11.7

IR(NaCl film) : 2940, 2800, 1723, 1475, 1368, 1178

Mass : 239.225(M$^+$,Cal.239.225)(6.0), 210(10.5), 164(14.3),
       154(100)

3-Acetyl-5-(3,7-dimethyl-2,6-octadienyl)-1-propylpyrrolidine 4d

490 mg (2 mmol) of 2-methoxy-2-methyl-3-butenyl-n-propyl-
ammonium tetrafluoroborate was suspended in 4 ml of benzene.
334 mg (2.2 mmol) of citral (the mixture of geranial and neral)
was added. The solution was heated at reflux for 24 hr.
After the solution was cooled down to the room temperature,
2 ml of 1N sodiumhydroxide solution was added. The organic
layer was separated, the aqueous layer was extracted   three
times by 5 ml portion of ether. The extraction was dried
over sodiumsulfate, and the solvent was evaporated. 3-Acetyl-
5-(3,7-dimethyl-2,6-octadienyl)-1-propylpyrrolidine was distilled
at 120-125°C/0.001 mmHg (bulb to bulb) in the yield of 497 mg
(90 %).
IR(NaCl film): 2959, 2790, 1722, 1446, 1375, 1175

3-Acetyl-5-n-hexyl-1-cyclohexypyrrolidine 4e

855 mg (3 mmol) of 2-methoxy-2-methyl-3-butenyl-cyclohexyl
ammonium tetrafluoroborate was suspended in 5 ml of benzene.
399 mg (3.5 mmol) of heptanal was added to the solution. The
mixture was heated at reflux for 24 hr. After the solution was
cooled down to the room temperature, 3 ml of 1N sodium hydroxide
solution was added. The organic layer was separated, and the
aqueous layer was extracted three times by 5 ml portion of ether.
The extraction was dried over sodiumsulfate, the solvent was
evaporated. 3-Acetyl-5-n-hexyl-1-cyclohexylpyrrolidine was
distilled at 105-110°C/0.001 mmHg in the yield of 829 mg (99%).
CMR($CDCl_3$) : 208.5, 208.2, 59.1, 58.9, 57.9, 56.2, 49.6, 48.9,
48.6, 47.9, 34.1, 33.3, 32.5, 32.4, 31.5, 29.2,

28.5, 27.3, 26.0, 25.3, 24.5, 22.2, 13.7

IR(NaCl film) : 2930, 2838, 1725, 1450, 1355, 1160

3-Acetyl-5-phenyl-1-benzylpyrrolidine 4f

A) 677 mg (3.3 mmol) of 2-methoxy-2-methyl-3-butenyl-benzyl-amine and 350 mg (3.3 mmol) of benzaldehyde was mixed up in 5 ml of benzene. 696 mg (3 mmol) of d-10-camphorsulfonic acid was added to the solution. The solution was refluxed for 24 hr. After the solution was cooled to 25°C, 3 ml of 1N sodiumhydroxide solution was added. The organic layer was separated, the aqueous layer was extracted by three times by 5 ml portion of ether. The extraction was dried over sodiumsulfate, the solvent was evaporated. 3-Acetyl-5-phenyl-1-benzylpyrrolidine was distilled at 130-140°C/0.001 mmHg (bulb to bulb) in the yield of 448 mg (54 %).

By the same procedure, when the reactiontime was expanded to 72 hr, the yield was 825 mg (98 %).

B) 630 mg (3.3 mmol) of 2-hydroxy-2-methyl-3-butenyl-benzyl-amine and 350 mg (3.3 mmol) of benzaldehyde was mixedup in 5 ml of benzene. 696 mg (3 mmol) of d-10-camphorsulfonic acid was added to the solution. The solution was heated at reflux for 24 hr. After the solution cooled down to 25°C, 3 ml of 1N sodiumhydroxide solution was added. The product was extracted by ether. The yield was 860 mg (94 %).

CMR(CDCl$_3$) ; 208.2, 142.7, 142.2, 139.2, 139.1, 129.8, 129.4, 128.5, 128.3, 128.2, 127.6, 127.5, 127.3, 126.8, 69.4, 68.8, 57.7, 57.2, 55.3, 54.3, 48.9, 37.6, 37.1, 29.0, 27.3

IR(NaCl film) : 3030, 2795, 1725, 1375, 1173, 755

3-Acetyl-5-furanyl-1-benzylpyrrolidine 4g

A) 677 mg (3.3 mmol) of 2-methoxy-2-methyl-3-butenyl-
benzylamine and 576 mg (6 mmol) of furfural was mixed up in
5 ml of benzene. 696 mg (3 mmol) of d-10-camphorsulfonic acid
was added to the solution. The mixture was heated at reflux
for 24 hr. After the solution was cooled down to the room
temperature, 3 ml of 1N sodiumhydroxide solution was added.
The organic layer was separated, the aqueous layer was extracted
three times by 5 ml portion of ether. The combained extraction
was dried over sodiumsulfate, the solvent was evaporated.
3-Acetyl-5-furanyl-1-benzylpyrrolidine was distilled at
130-135°C/0.01 mmHg in the yield of 511 mg (57 %).

B) 630 mg (3.3 mmol) of 2-hydroxy-2-methyl-3-butenyl-
benzylamine and 576 mg (6 mmol) of furfural was mixed up in
5 ml of benzene. 696 mg (3 mmol) of d-10-camphorsulfonic acid
was added to the solution. The mixture was heated at reflux
for 24 hr. After the solution was cooled down to 25°C, the
product was extracted by ether. The yield was 876mg (99%).
CMR(CDCl$_3$) : 207.6, 154.8, 154.7, 141.6, 138.5, 129.3, 128.4,
                128.2, 127.9, 126.6, 109.9, 109.8, 61.3, 60.9,
                57.3, 56.8, 54.5, 53.6, 48.5, 33.0, 32.5, 28.5,
                27.0
IR(NaCl film) :2960, 2800, 1723, 1356, 1150, 735

3-Acetyl-5-(3-pyridyl)-1-benzylpyrrolidine <u>4h</u>

630 mg (3.3 mmol) of 2-hydroxy-2-methyl-3-butenyl-benzylamine and 353 mg (3.3 mmol) of nicotinaldehyde was mixed up in 5 ml of benzene. 696 mg (3 mmol) of d-10-camphor-sulfonic acid was added to the solution. The mixture was heated at reflux for 24 hr. After the solution was cooled down to the room temperature, 3 ml of 1N sodiumhydroxide solution was added. The organic layer was separated, the aqueous layer was extracted three times by 5 ml portion of ether. The combained extraction was dried over sodiumsulfate, the solvent was evaporated. 3-Acetyl-5-(3-pyridyl)-1-benzylpyrrolidine was distilled at 135-150°C/0.01 mmHg (bulb to bulb) in the yield of (91 %).

CMR(CDCl$_3$) : 207.2, 207.1, 149.0, 148.5, 148.3, 138.2, 138.1,
137.8, 137.4, 134.6, 134.4, 128.0, 127.8, 126.5,
123.2, 123.1, 66.2, 65.7, 57.2, 56.7, 54.9, 54.0,
48.3, 36.5, 28.6, 27.0

IR(NaCl film) : 3030, 2800, 1720, 1425, 1363, 1170

3-Acetyl-5-(3-pyridyl)-1-methylpyrrolidine(3-Acetylnicotine) <u>4i</u>

379.5 mg (3.3 mmol) of 2-hydroxy-2-methyl-3-butenyl-methylamine and 353 mg (3.3 mmol) of nicotinaldehyde was mixted up in 5 ml of benzene. 696 mg (3 mmol) of d-10-camphor-sulfonic acid was added to the solution. The mixture was heated at reflux for 24 hr. After the solution cooled to 25°C, 3 ml of 1N sodiumhydroxide solution was added. The organic layer was separated, the aqueous layer was extracted three times by 5 ml portion of ether. The combained extraction was dried

over sodiumsulfate, the solvent was evaporated. 3-Acetylnicotine was distilled at 95-100°C/0.01 mmHg (bulb to bulb) in the yield of 565 mg (84 %).

CMR(CDCl$_3$) : 207.6, 149.1, 149.0, 148.5, 148.4, 137.4, 137.1,
134.7, 134.5, 123.3, 123.2, 68.4, 67.7, 58.3, 57.5,
48.6, 48.5, 39.5, 36.9, 36.8, 28.8, 27.3

IR(NaCl film) : 2950, 2780, 1723, 1430, 1378, 1171

3-Formyl-5-phenyl-1-propylpyrrolidine dimethylacetal 21a

462 mg (2 mmol) of 2-methoxy-3-butenyl-n-propylammonium tetrafluoroborate was added to 212 mg (2 mmol) of benzaldehyde and 96 mg (3 mmol) of methanol in 3 ml of benzene. 600 mg of 3-A molecular sieves was added to the solution, and heated at reflux for 24 hr. After the solution was cooled to 25°C, 2 ml of 1N sodiumhydroxide solution was added. The organic layer was separated, the aqueous layer was extracted three times by 5 ml portion of ether. The combained extraction was dried over sodiumsulfate, and the solvent was evaporated. 3-Formyl-5-phenyl-1-propylpyrrolidine dimethylacetal was distilled at 105-110°C/0.01 mmHg in the yield of 362 mg (69 %).

PMR(CDCl$_3$) : 3.12, 3.18(OC$\underline{H}_3$), 7.21(aromatic)

CMR(CDCl$_3$) : 143.7, 143.5, 128.3, 127.4, 126.9, 107.5, 107.2,
70.6, 69.7, 56.3, 56.0, 55.9, 54.9, 53.2, 52.8,
52.5, 38.6, 38.2, 37.3, 21.7, 11.9

IR(NaCl film) :2940, 2790, 1450, 1125, 1060, 755, 698

Mass: 263(75), 233(26), 231(100), 122(11)

3-Formyl-5-n-hexyl-1-propylpyrrolidine dimethylacetal 21b

693 mg (3 mmol) of 2-methoxy-3-butenyl-n-propylammonium tetrafluoroborate was added to 399 mg (3.5 mmol) of heptanal and 192 mg (6 mmol) of methanol in 3 ml of benzene. 600 mg of 3-A molecular sieves was added to the solution, and heated at reflux for 24 hr. After the solution was cooled to 25°C, 3 ml of 1N sodiumhydroxide solution was added. The organic layer was separated, the aqueous layer was extracted three times by 5 ml portion of ether. The combained extraction was dried over sodiumsulfate, and the solvent was evaporated. 3-Formyl-5-n-hexyl-1-propylpyrrolidine dimethylacetal was distilled at 95-100°C/0.005 mmHg (bulbto bulb) in the yield of 661 mg (81 %).

By the same procedure, without methanol and molecular sieves, the yield was 174 mg (21 %).

CMR(CDCl$_3$) : 107.2, 107.1, 65.2, 64.5, 56.3, 55.8, 55.3, 52.8, 52.5, 52.4, 37.9, 37.6, 33.9, 33.4, 32.7, 31.7, 29.5, 26.1, 22.4, 21.5, 13.8, 11.9

IR(NaCl film) : 2930, 2783, 1160, 1380, 1115, 1060

Mass : 271(45), 239(100), 185(59)

2-Methyl-2-vinyl-1-oxa-4-azaspiro[4,5]decane 6a

A solution of 2.94 g (30 mmol) of cyclohexanone and 3.03 g (30 mmol) of 1-amino2-methyl-3-buten-2-ol in 30 ml of benzene was heated at reflux for 2 hr with azeotropic removal of water. The solvent was evaporated, and 2-methyl-2-vinyl-1-oxa-4-azaspiro[4,5]decane was distilled at 73-75°C/3 mmHg in the yield of 5.0 g (92 %).

NMR(CDCl$_3$) : 1.35(s, 3H), 1.65(m, 10H), 2.18(s, 1H), 3.01(s, 2H), 5.48(m, 3H)

IR(NaCl film) : 3300, 2960, 1445, 1369, 1140, 1070, 920

8-t-Butyl-2-methyl-2-vinyl-1-oxa-4-azaspiro[4,5]decane 6b

A solution of 1.56 g (10 mmol) of 4-t-butylcyclohexanone and 1.01 g (10 mmol) of 1-amino-2-methyl-3-buten-2-ol in 20 ml of benzene was heated at reflux for 2 hr with azeotropic removal of water. The solvent was evaporated, and 8-t-butyl-2-methtyl-2-vinyl-1-oxa-4-azaspiro[4,5]decane was distilled at 140-145°C/3 mmHg (bulb to bulb) in the yield of 2.19 g (91 %).

NMR(CDCl$_3$) : 0.88(s, 9H), 1.33(s, 3H), 1.67(m, 8H), 2.23(s, 1H) 3.03(s, 2H), 5.45(m, 3H)

IR(NaCl film) : 3275, 2980, 1462, 1368, 1190, 1128, 949, 910

2,6-Dimethyl-2-vinyl-1-oxa-4-azaspiro[4,5]decane 6c

A solution of 1.12 g (10 mmol) of 2-methylcyclohexanone and 1.01 g (10 mmol) of 1-amino-2-methyl-3-buten-2-ol in 20 ml of benzene was heated at reflux for 3 hr. The solvent was evaporated, and 2,6-dimethyl-2-vinyl-1-oxa-4-azaspiro[4,5]decane

was distilled at 85°C/5 mmHg (bulb to bulb) in the yield of 1.
76 g (91 %).

NMR(CDCl$_3$) : 0.97(m, 3H), 1.34(d, 3H), 1.57(m, 9H), 2.27(s, 1H)
3.05(s, 2H), 5.45(m, 3H)

IR(NaCl film) : 3300, 2980, 1456, 1368, 1160, 1055, 920

2,6,10-Trimethyl-2-vinyl-1-oxa-4-azaspiro[4,5]decane 6d

A solution of 1.26 g (10 mmol) of 2,6-dimethylcyclohexanone,
1.01 g(10 mmol) of 1-amino-2-methyl-3-buten-2-ol and 10 mg of
p-toluenesulfonic acid in 2 ml of benzene was heated at reflux
with azeotropic removal of water. The solvent was evaporated,
2,6,10-trimethyl-2-vinyl-1-oxa-4-azaspiro[4,5]decane was
distilled at 120°C/3 mmHg (bulb to bulb) in the yield of 1.21 g
(58 %).

NMR (CDCl$_3$) : 0.99(m, 6H), 1.33(s, 3H), 1.70(m, 8H), 3.03(d,
2H), 5.50(m, 3H)

IR(NaCl film) ; 3330, 2940, 1458, 1371, 1068, 1028, 920

2,2-Diethyl-5-methyl-5-vinyloxazolidine 6e

A solution of 1.01 g (10 mmol) of 1-amino-2-methyl-3-
buten-2-ol, 860 mg (10 mmol) of 3-pentanone and 10 mg of
p-toluenesulfonic acid in 20 ml of benzene was heated at reflux
with azeotropic removal of water. The solvent was evaporated,
2,2-dimethyl-5-methyl-5-vinyloxazolidine was distilled at 100-
110°C/5 mmHg (bulb to bulb) in the yield of 1.56 g(94 %).

NMR(CDCl$_3$) :0.95(t, 6H), 1.34(s, 3H), 1.67(q, 4H), 2.20(s, 1H)
3.02(d, 2H), 5.51(m, 3H)

IR(NaCl film) : 3320, 1460, 1372, 1155, 1104, 920

2-Methyl-2-vinyl-1-oxa-4-azaspiro[4,4]nonane 6f

A solution of 505 mg (5 mmol) of 1-amino-2-methyl-3-buten-2-ol, 420 mg (5 mmol) of cyclopentanone,1 drop of $HClO_4$ solution (60%) and 2 g of sodiumsulfate in 20 ml of THF was stirred for 24 hr at 25°C. Sodiumsulfate was filtered. After the solvent was evaporated, 2-methyl-2-vinyl-1-oxa-4-azaspiro[4,4]nonane was distilled at 100-105°C/6 mmHg (bulb to bulb) in the yield of 693 mg (83 %).

NMR($CDCl_3$) : 1.33(s, 3H), 1.77(m, 8H), 2.43(s, 1H), 2.98(m, 2H)
          5.45(m, 3H)

IR(NaCl film) : 3300, 2960, 1452, 1338, 1097, 920

2-t-Butyl-5-methyl-5-vinyloxazolidine 6g

A solution of 860 mg (10 mmol) of trimethylacetaldehyde, 1.01 g (10 mmol) of 1-amino-2-methyl-3-buten-2-ol, 1 drop of 60% $HClO_4$ solution and 2 g of sodiumsulfate in 20 ml of THF was stirred for 24 hr at 25 °C. Sodiumsulfate was filterd. After the solvent was evaporated, 2-t-butyl-5-methyl-5-vinyloxazolidine was distilled at 110°C/200 mmHg (bulb to bulb) in the yield of 1.57 g (93 %).

NMR($CDCl_3$) : 0.96(d, 9H), 1.30(d, 3H), 2.31(s, 1H), 2.90(s, 2H)
          5.50(m, 3H)

IR(NaCl film) : 3340, 2990, 1482, 1370, 1095, 1030, 949, 920

Benzylidene 2-hydroxy-2-methyl-3-butenylamine <u>6j</u>

A solution of 1.06 g (10 mmol) of benzaldehyde , 1.01 g

(10 mmol) of 1-amino-2-methyl-3-buten-2-ol in 20 ml of benzene

was heated at reflux with azeotropic removal of water. The

solvent was evaporated, benzylidene 2-hydroxy-2-methyl-3-

butenylamine was distilled at 120-125 ℃/6 mmHg (bulb to bulb)

in the yield of 1.87 g (99 %).

NMR(CDCl$_3$) : 1.30(s, 3H), 3.05(s, 1H), 3.53(s, 2H), 5.47(m, 3H),

7.40(m, 5H), 8.13(s, 1H)

IR(NaCl film) : 3450, 2995, 1645, 1452, 1374, 1115, 922, 758

3,7-Dimethyl-2,6-octadienylidene 2-hydroxy-2-methyl-3-butenylamine <u>6i</u>

A solution of 1.52 g (10 mmol) of citral (the mixture of

geranial and neral), 1.01 g(10 mmol) of 1-amino-2-methyl-3-buten-

2-ol and 2 g of sodium sulfate in 20 ml of THF was stirred for 24

hr at 25°C. Sodium sulfate was filtered. After the solvent was.

evaporated, 3,7-dimethyl-2,6-octadienylidene 2-hydroxy-2-methyl-

3-butenylamine was distilled at 105-110°C/0.05 mmHg (bulb to bulb)

in the yield of 1.31 g (56 %).

NMR(CDCl$_3$) : 1.30(s, 3H), 1.61(s, 3H), 1.70(s, 3H), 1.88(m, 3H),

2.20(m, 4H), 2.85(m, 2H), 3.48(s, 1H), 5.50(m, 5H),

8.22(d, 1H)

IR(NaCl film) : 3430, 2940, 1650, 1619, 1446, 1380, 921

2-methyl-2-vinyl-1-oxa-4-azaspiro[4,11]hexadecane <u>6h</u>

A solution of 1.82 g (10 mmol) of cyclododecanone, 1.01 g

(10 mmol) of 1-amino-2-methyl-3-buten-2-ol and 50 mg of p-toluene

sulfonic acid in 20 ml of benzene was heated at reflux with

azeotropic removal of water for 3 hr. The solvent was evaporated,

and 2-methyl-2-vinyl-1-oxa-4-azaspiro[4,11]hexadecane was

distilled at 120-130°C/0.05 mmHg in the yield of 2.4 g(92 %).

NMR(CDCl$_3$) : 1.35(m, 25H), 3.04(s, 2H), 5.50(m, 3H)

IR(NaCl film) : 3300, 2940, 1470, 1443, 1365, 110, 920

3-Acetyl-1-azaspiro[4,5]decane <u>8a</u> (acid catalyzed reaction)

   A solution of 543 mg (3 mmol) of 2-methyl-2-vinyl-1-oxa-4-azaspiro[4,5]decane, 696 mg (3 mmol) of d-10-camphorsulfonic acid and 3 ml of benzene was heated at reflux under nitrogen for 24 hr. After the mixture was cooled to room temperature, 3 ml of 1N sodium hydroxide solution was added. The organic layer was separated, the aqeous layer was extracted three times by 5 ml portion of ether. The combained extraction was dried over sodium sulfate. The solvent was evaporated, and 3-acetyl-1-azaspiro[4,5]decane was distilled at 80-85°C/0.05mmHg (bulb to bulb) in the yield of 375 mg (69 %).

IR(NaCl film) : 3300, 1705, 1448, 1363, 1175, 918

CMR(CDCl$_3$) : 209.1, 62.3, 52.9, 47.8, 39.7, 38.2, 37.3, 29.2,

           25.9, 23.9, 23.6

Mass : 182(11.6), 181(M$^+$ 100), 165(1.3), 137(7.1)

3-Acetyl-8-t-butyl-1-azaspiro[4,5]decane <u>8b</u> (acid catalyzed reaction)

   A solution of 717 mg (3 mmol) of 8-t-butyl-2-methyl-2-vinyl-1-oxa-4-azaspiro[4,5]decane, 696 mg (3 mmol) of d-10-camphorsulfonic acid, and 3 ml of benzene was heated at reflux for 24 hr under nitrogen. After the solution was cooled to 25°C, 3 ml of 1N sodium hydroxide solution was added. The organic layer was separated, the aqueous layer was extracted three times by 5 ml portion of ether. The combained extraction was dried over sodium sulfate. The solvent was evaporated, 3-acetyl-8-t-butyl-1-azaspiro[4,5]decane was distilled at 100°C/0.05 mmHg (bulb to bulb) in the yield of 501 mg (71 %).

IR(NaCl film) : 3330, 1705, 1440, 1363, 1170, 1092

CMR(CDCl$_3$) : 209.0, 62.0, 52.0, 48.3, 47.9, 42.9, 38.3, 37.2,
32.3, 29.2, 27.6

Mass : 238(13.8), 237(M$^+$ 100), 137(10.3)

3-Acetyl-6-methyl-1-azaspiro[4,5]decane 8c (acid catalyzed reaction)

A solution of 585 mg (3 mmol) of 2,6-dimethyl-2-vinyl-1-oxa-4-azaspiro[4,5]decane, 696 mg (3 mmol) of d-10-camphorsulfonic acid, and 3 ml of benzene was heated at reflux for 24 hr under nitrogen. After the mixture was cooled to room temperature, 3 ml of 1N sodium hydroxide solution was added. The organic layer was separated, the aqueous layer was extracted three times by 5 ml portion of ether. The combained extraction was dried over sodium sulfate. The solvent was evaporated, 3-acetyl-6-methyl-1-azaspiro[4,5]decane was distilled at 70°C/0.05 mmHg (bulb to bulb) in the yield of 320 mg (55 %).

IR(NaCl film) : 3350, 1705, 1445, 1363, 1170, 1050

NMR(CDCl$_3$) : 0.95(d, 3H), 1.55(m, 9H), 2.10(s, 3H), 3.16(m, 3H)

Mass : 196(12.7), 195(M$^+$ 100), 181(4.46), 152(5.49), 137(3.1)

3-Acetyl-5-n-hexylpyrrolidine 8g acid catalyzed reaction)

A solution of 394 mg (2 mmol) of 2-n-hexyl-5-methyl-5-vinyloxazolidine, 464 mg (2 mmol) of d-10-camphorsulfonic acid 2 ml of benzene was heated at reflux under nitrogen for 24 hr. After the solution was cooled to room temperature, 2 ml of 1N sodium hydroxide solution was added. The organic layer was separated, the aqueous layer was extracted three times by 5 ml portion of ether. The combained ether extraction was dried

over sodium sulfate. The solvent was evaporated, 3-acetyl-5-
n-hexypyrrolidine was distilled at 120-130°C/0.15 mmHg (bulb to
bulb)in the yield of 255 mg (65 %).

IR(NaCl film) : 3320, 1705, 1460, 1360, 1170

CMR(CDCl$_3$) : 209.4, 208.9, 60.9, 59.3, 52.3, 52.0, 49.3, 49.2,
36.2, 35.8, 35.5, 34.8, 31.9, 29.5, 29.1, 27.5,
27.4, 22.7, 14.1

Mass : 199(10.8), 198(52.3), 197(M$^+$ 100), 181(1.7), 111(13.1)

3-Acetyl-5,5-diethylpyrrolidine 8e (acid catalyzed reaction)

A solution of 507 mg (3 mmol) of 2,2-diethyl-5-methyl-5-
vinyloxazolidine, 696 mg (3 mmol) of d-10-camphorsulfonic acid
and 3 ml of benzene was heated at reflux under nitrogen for
24 hr. After the solution was cooled to room temperature, 3 ml
of 1N sodium hydroxide solution was added. The organic layer
was separated, the aqueous layer was extracted three times by
5 ml portion of ether. The combained ether extraction was
dried over sodium sulfate. The solvent was evaporated, 3-acetyl-
5,5-diethylpyrrolidine was distilled at 80-85°C/0.05 mmHg in the
yield of 46 mg (9 %).

IR(NaCl film) ; 3350, 2960, 1710, 1460, 1362, 1170

CMR(CDCl$_3$) : 209.2, 66.0, 52.8, 48.5, 38.9, 30.4, 29.4, 29.2,
8.9, 8.7

Mass : 170(13.8), 169(M$^+$ 100), 153(1.6), 139(16.6)

3-Acetyl-1-azaspiro[4,11]hexadecane <u>8k</u> (acid catalyzed reaction)

A solution of 530 mg (2 mmol) of 2-methyl-2-vinyl-1-oxa-4-azaspiro[4,11]hexadecane, 464 mg (2 mmol) of d-10-camphorsulfonic acid and 2 ml of benzene was heated at reflux under nitrogen for 24 hr. After the solution was cooled to room temperature, 2 ml of 1N sodium hydroxide solution was added. The organic layer was separated, the aqueous layer was extracted three times by 5 ml portion of ether. The combained extraction was dried over sodium sulfate. The solvent was evaporated. G.C. analysis (SE-30, 150°C) of the obtained crude product (425 mg) showed two peakes at 3min and 22 min. These two peaks were identified as cyclododecanone and 3-acetyl-1-azaspiro[4,11]hexadecane respectively by the comparison of authentic samples. The retio of the two peaks was 83:17, and the yield of 3-acetyl-1-aza-spiro[4,11]hexadecane was 13 %.

3-Acetyl-1- azaspiro[4,5]decane <u>8a</u> (base catalyzed reaction)

362 mg (2 mmol) of 2-methyl-2-vinyl-1-oxa-4-azaspiro[4,5]-decane was added dropwise 120 mg (3 mmol) of prewashed potassium hydride suspended in 5 ml of THF at 0°C. After 52.8 mg (0.2mmol) of 18-Crown-6 was added, the solution was stirred for 24 hr at 25°C under nitrogen. 214 mg (4 mmol) of crystalline ammonium chloride and 2 g of crystalline sodium sulfate hydrate were added to the solution. The inorganic precipitate was filtered after the solution was stirred for 30 min. The solvent was evaporated, 3-acetyl-1-azaspiro[4,5]decane was distilled at 80-85°C/ 0.05 mmHg in the yield of 286 mg (79 %).

3-Acetyl-8-t-butyl-1-azaspiro[4,5]decane 8b (base catalyzed reaction)

717 mg (3 mmol) of 8-t-butyl-2-methyl-2-vinyl-1-oxa-4-azaspiro[4,5]decane was added dropwise 160 mg (4.5 mmol of pre-washed potassium hydride suspended in 5 ml of THF at 0°C. After 79.0 mg (0.3 mmol) of 18-Crown-6 was added, the solution was stirred for 24 hr at 25°C under nitrogen. 321 mg (6 mmol) of crystalline ammonium chloride and 2 g of crystalline sodium sulfate hydrate were added to the solution. The inorganic precipitate was filtered after the mixture was stirred for 30 min. The solvent was evaporated, 3-acetyl-8-t-butyl-1-azaspiro-[4,5]decane was distilled at 100°C/0.05 mmHg (bulb to bulb) in the yield of 666 mg (93 %).

3-Acetyl-6,10-dimethyl-1-azaspiro[4,5]decane 8d

836 mg (4 mmol) of 2,6,10-trimethyl-2-vinyl-1-oxa-4-azaspiro[4,5]decane was added dropwise to 240 mg (6 mmol) of potassium hydride suspended in 5 ml of THF at 0°C. After 106 mg (0.4 mmol) of 18-Crown-6 was added to the solution, the mixture was stirred for 24 hr at 25°C under nitrogen. 428 mg (8 mmol) of ammonium chloride and 2 g of crystalline sodium sulfate hydrate were added. The mixture was stirred for 30 min., and the inorganic precipitate was filtered. The solvent was evaporated, 3-acetyl-6,10-dimethyl-1-azaspiro[4,5]-decane was distilled at 75-80°C/0.03 mmHg (bulb to bulb) in the yield of 681 mg (82 %).

IR(NaCl film) : 3350, 2940, 1705, 1460, 1365, 1170

NMR(CDCl$_3$) : 2.12(s, 3H), 0.88(m, 6H)

3-Acetyl-5,5-diethylpyrrolidine 8e (base catalyzed reaction)

676 mg (4 mmol) of 2,2-diethyl-5-methyl-5-vinyloxazolidine was added dropwise to 240 mg (6 mmol) of potassium hydride suspended in 5 ml of THF at 0°C. After 106 mg (0.4 mmol) of 18-Crown-6 was added, the mixture was stirred for 24 hr at 25°C under nitrogen. 428 mg (8 mmol) of ammonium chloride and 2g of crystalline sodium sulfate hydrate were added. The mixture was stirred for 30 min., and the inorganic precipitate was filtered. The solvent was evaporated, 3-acetyl-5,5-diethylpyrrolidine was distilled at 80-85°C/0.05 mmHg (bulb to bulb) in the yield of 553 mg (82 %).

3-Acetyl-1-azaspiro[4,4]nonane 8f

835 mg (5 mmol) of 2-methyl-2-vinyl-1-oxa-4-azaspiro[4,4]-nonane was added to 280 mg (7 mmol) of potassium hydride suspended in 10 ml of THF at 0°C. After 132 mg (0.5 mmol) of 18-Crown-6 was added, the mixture was stirred for 24 hr at 25°C under nitrogen. 535 mg (10 mmol) of crystalline ammonium chloride and 2 g of crystalline sodium sulfate hydrate were added to the solution. The mixture was stirred for 30 min., and the inorganic precipitate was filtered. The solvent was evaporated, 3-acetyl-1-azaspiro[4,4]nonane was distilled at 80°C/0.1 mmHg (bulb to bulb) in the yield of 550 mg (66 %).

IR(NaCl film) : 3300, 2960, 1705, 1450, 1360, 1165

CMR(CDCl$_3$) : 208.8, 71.3, 52.7, 48.6, 40.8, 38.6, 29.1, 24.4, 24.2

Mass : 169(4.7), 168(34.0), 167(M$^+$ 100), 151(1.6), 138(3.4), 123(12.6)

3-Acetyl-5-t-butylpyrrolidine 8h

500 mg (2.9 mmol) of 2-t-butyl-5-methyl-5-vinyloxazolidine
was added dropwise to 160 mg (4.5 mmol) of prewashed potassium
hydride suspended in 5 ml of THF at 0°C. After 76 mg (0.29 mmol)
of 18-Crown-6 was added, the mixture was stirred for 24 hr at
25°C under nitrogen. 321 mg (6 mmol) of crystalline ammonium
chloride and 2 g of crystalline sodium sulfate hydrate were
added to the solution. The mixture was stirred for 30 min.,
fitering the inorganic precipitate. The solvent was evaporated,
3-acetyl-5-t-butylpyrrolidine was distilled at 130-140°C/2 mmHg
(bulb to bulb) in the yield of 360 mg (72 %).

IR(NaCl film) : 3350, 2920, 1710, 1450, 1320, 1145

CMR(CDCl$_3$) : 209.3, 71.4, 69.9, 68.0, 52.4, 52.3, 49.7, 49.5,
47.0, 45.1, 42.4, 33.2, 32.8, 30.4, 29.3, 29.1,
26.8, 26.6, 26.4

Mass : 170(10.3), 169(M$^+$ 100), 153(1.3), 139(2.5), 111(12.0)

3-Acetyl-5-phenylpyrrolidine 8i

945 mg (5 mmol) of bendylidene 2-hydroxy-2-methyl-3-butenyl
amine was added dropwise to 300 mg (7.5 mmol) of potassium
hydride suspended in 10 ml of THF at 0°C. After 132 mg (0.5
mmol) of 18-Crown-6 was added, the solution was stirred for
24 hr at 25°C under nitrogen. 5 ml of saturated ammonium
chloride aqeous solution was added to the solution at 0°C.
The solution was extracted four times by 5 ml portion of
ether. The extraction was dried over sodium sulfate, and
the solvent was evaporated. 3-acetyl-5-phenylpyrrolidine
was distilled at 130-135°C/0.07 mmHg (bulb to bulb) in the

yield of 859 mg (91 %).

IR(NaCl film) : 3350, 2900, 1710, 1455, 1360, 1120

NMR(CDCl$_3$) : 2.09(s, 3H), 7.18(m, 5H)

Mass : 191(2.9), 190(25.8), 189(M$^+$ 100), 160(3.2), 145(2.9)

3-Acetyl-5-(3,7-dimethyl-2,6-octadienyl)-pyrrolidine 8j

   705 mg (3 mmol) of 3,7-dimethyl-2,6-octadienylidene
2-hydroxy-2-methyl-3-butenylamine was added to 160 mg (4.5
mmol) of prewashed potassium hydride suspended in THF at 0°C.
After 79 mg (0.3 mmol) of 18-Crown-6 was added the solution
was stirred for 24 hr at 25°C under nitrogen.   321 mg of
crystalline ammonium chloride and 2 g of crystalline sodium
sulfate hydrate was added to the solution.   The mixture was
stirred for 30 min., filtering the inorganic precipitate.
The solvent was evaporated, 3-acetyl-5-(3,7-dimethyl-2,6-
octadienyl)pyrrolidine was distilled at 135-140°C/0.03 mmHg
(bulb to bulb) in the yield of 348 mg (49 %).

IR(NaCl film) : 3350, 2950, 1715, 1645, 1450, 1380, 1420

Mass : 236(8.7), 235(M$^+$ 100), 205(1.9), 191(2.8), 111(7.1)

3-Acetyl-1-azaspiro[4,11]hexadecane 8k (base catalyzed reaction)

   530 mg (2 mmol) of 2-methyl-2-vinyl-1-azaspiro[4,11]-
hexadecane was added to 120 mg (3 mmol) of prewashed potassium
hydride suspeded in THF.   After 53 mg (0.2 mmol) of 18-Crown-6
was added, the solurion was stirred for 24 hr at 25°C under
nitrogen.   214 mg of crystalline ammonium chloride and 2 g of
crystalline sodium sulfate hydrate were added to the solution.
The mixture was stirred for 30 min., filtering the inorganic

precipitate. The solvent was evaporated, 3-acetyl-1-azaspiro-
[4.11]hexadecane was distilled at130-140°C/0.02 mmHg (bulb to
bulb) in the yield of 447 mg (84 %).

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5. Conclusions-

The author has studied about applications of sigma-
tropic rearrangement to the syntheses of amine derivatives.
Through out the present work, the author stands on the
point of view as described in Introduction and believes
that the object has been achieved.

In Chapter 2, [2,3]-sigmatropic rearrangement of
S-allylsulfilimines has been applied to the synthesis of
N-allyltosylamides starting from S-vinylsulfilimines.
This study reveals that the transformation $\underline{1} \to \underline{2}$ can be
achieved in the case of X = N-function. This transforma-
tion is also one of the synthetic utility of the
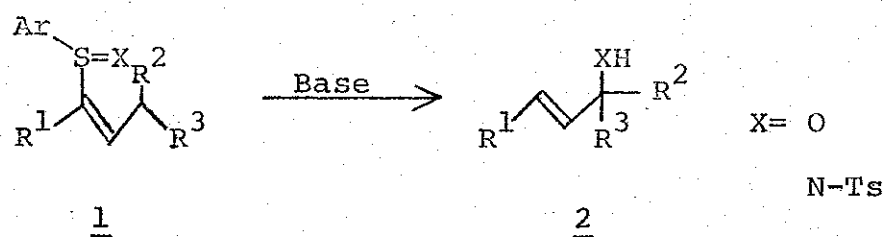
vinylsulfide whose applicaitons have not fully been
studied. The attractive point of this mehtodology is
that the starting S-vinylsulfilimines can be prepared
from easily available carbonyl compounds via vinylsulfide,
and thus N-allyltosyl amides can be synthesized from
carbonyl compounds by three step reactions (eq.1).

$$R^1 \underset{O}{\overset{}{\bigwedge}} \underset{R^3}{\overset{R^2}{}} \longrightarrow \underset{R^1}{\overset{Ar}{\underset{}{\bigwedge}}} \overset{S}{\underset{R^3}{\overset{}{\bigwedge}}} R^2 \longrightarrow \underset{R^1}{\overset{Ar}{\underset{}{\bigwedge}}} \overset{S=NTs}{\underset{R^3}{\overset{}{\bigwedge}}} R^2 \longrightarrow R^1 \overset{HNTs}{\underset{R^3}{\bigwedge}} R^2 \qquad (1)$$
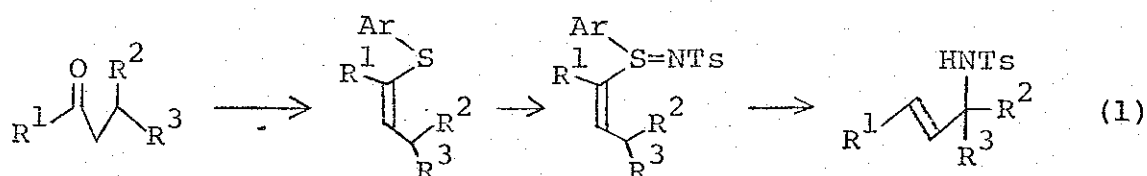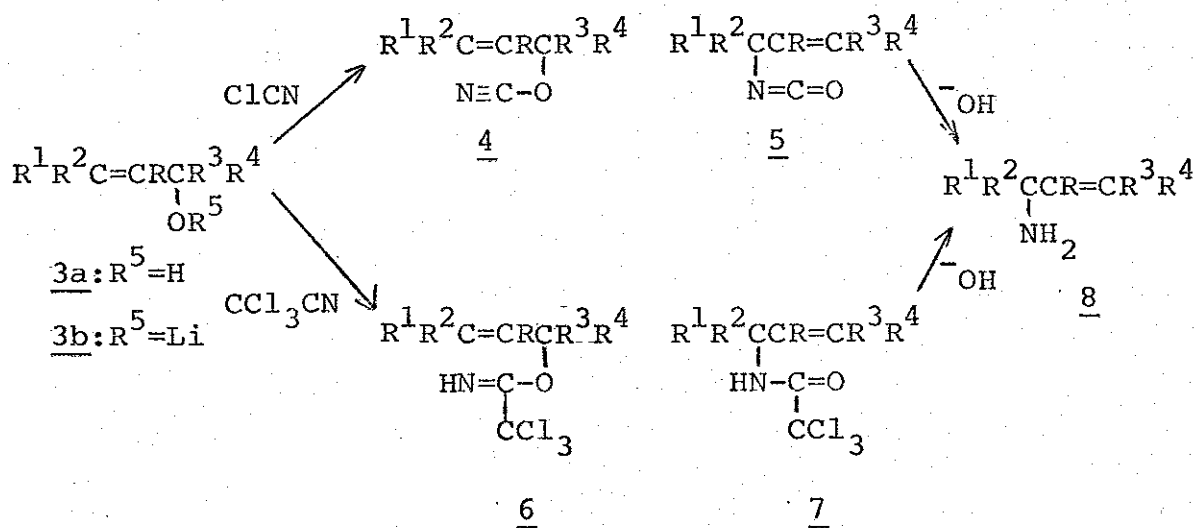
In Chapter 3, the study provides that the low temperature method for 1,3 transposition of hydroxyl and amine functions by means of the [3,3]-sigmatropic re-arrangement of allylic cyanates (Scheme I, $\underline{3} \gg \underline{4} \gg \underline{5} \gg \underline{8}$) has been demonstrated. The rearrangement in this

Scheme I

$$\begin{array}{c} R^1R^2C{=}CRCR^3R^4 \\ | \\ N{\equiv}C{-}O \\ \underline{4} \end{array} \qquad \begin{array}{c} R^1R^2CCR{=}CR^3R^4 \\ | \\ N{=}C{=}O \\ \underline{5} \end{array}$$

$$\overset{ClCN}{\nearrow} \qquad \qquad \qquad \searrow \overline{}OH$$

$$\begin{array}{c} R^1R^2C{=}CRCR^3R^4 \\ | \\ OR^5 \end{array}$$

$$\begin{array}{c} R^1R^2CCR{=}CR^3R^4 \\ | \\ NH_2 \end{array}$$

$$\begin{array}{l} \underline{3a}{:}R^5{=}H \\ \underline{3b}{:}R^5{=}Li \end{array} \qquad \overset{CCl_3CN}{\searrow} \qquad \qquad \nearrow \overline{}OH \qquad \underline{8}$$

$$\begin{array}{c} R^1R^2C{=}CRCR^3R^4 \\ | \\ HN{=}C{-}O \\ | \\ CCl_3 \\ \underline{6} \end{array} \qquad \begin{array}{c} R^1R^2CCR{=}CR^3R^4 \\ | \\ HN{-}C{=}O \\ | \\ CCl_3 \\ \underline{7} \end{array}$$

designed reaction proceeded at or below room temperature and the allylisocyanates $\underline{5}$ obtained were easily converted to the corresponding allylamines $\underline{8}$ by alkaline hydrolysis. The major problem of this method is that the reaction between rearranged isocyanate $\underline{5}$ and starting alkoxide $\underline{3b}$ competes with the desired reaction of $\underline{3b}$ and cyanogen chloride. However, in cases where the starting allylic
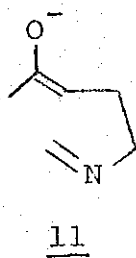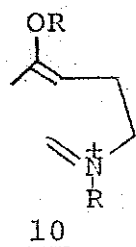
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alcohol is particularly prone to elimination and the
nitrogen is to be introduced at a highly hindered position,
the remarkable improvement has been achieved by the allylic
cyanate method ($\underline{3} \to \underline{4} \to \underline{5} \to \underline{8}$) compared with the previous
allylic trichloroacetimidate method ($\underline{3} \to \underline{6} \to \underline{7} \to \underline{8}$).

In chapter 4, the new pyrrolidine synthesis is des-
cribed. As shown in Scheme II, nitrogen-carbon bonding
(bond a) has been performed to synthesize pyrrolidine
ring system in the traditional methods. In contrast, the
formation of carbon-carbon bonding (bond b) has been
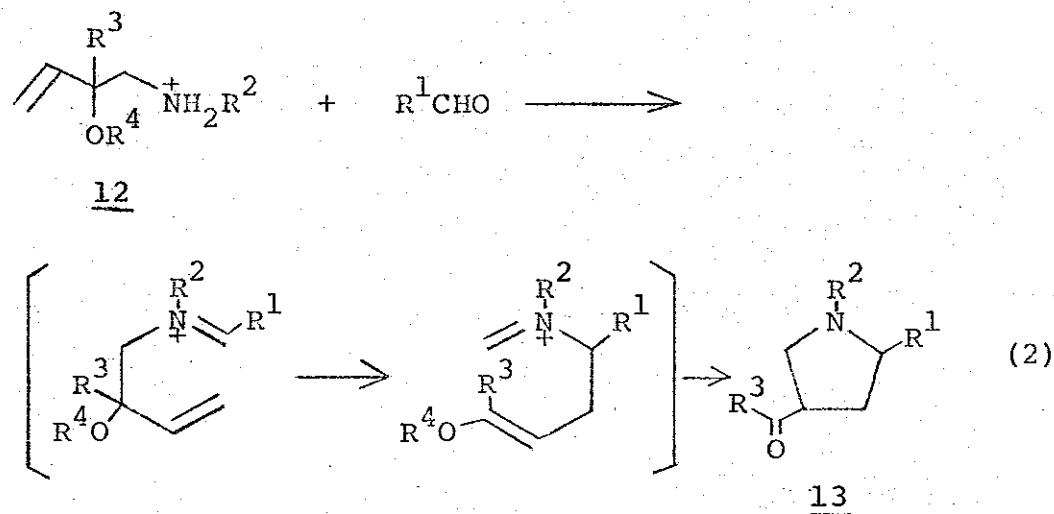achieved successfully in this work.

Scheme II
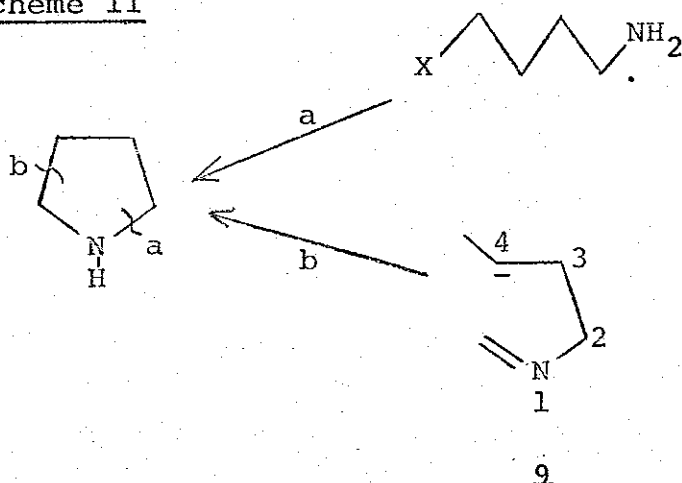
The author has assumed that $\underline{9}$ which has the electro-
phylic carbon (C=N) and the nucleophilic carbon at 4 posi-

tion should be the compounds composing from iminium ion and carbonyl (enolate) or imine and enolate anion functions (10, 11 respectively). The author's strategy to construct these structures (10, 11) was 2-aza-[3,3]-sigmatropic rearrangement in acidic or basic conditions. 3-Acetylpyrrolidines (13) can be synthesized in good yield by the simple reaction between the salt of 3-butenylamine 12 and the various aldehydes (eq.2). The

$$\underset{\underline{12}}{\overset{R^3}{\diagup\!\!\!\diagup\!\!\diagdown}\underset{OR^4}{\overset{}{\diagup}}\overset{+}{NH_2}R^2} \quad + \quad R^1CHO \quad \longrightarrow$$

$$\left[\quad \right] \longrightarrow \left[\quad \right] \longrightarrow \underset{\underline{13}}{\quad} \qquad (2)$$

major limitation of this method was that the carbonyl component should be unhindered aldehyde.

To improve the limitation, S-vinyloxazolidines 14, which can be conveniently synthesized from 1-amino-2-methyl-3-buten-2-ol and various carbonyl compounds, were used as the precursor of the sigmatropic rearrangement. Thus, the reaction of 14 with acid affords 3-acetyl-pyrrolidine 15 especially 1-azaspiro[4,5]decanes whose structure is hardly to synthesize by usual manners.

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15
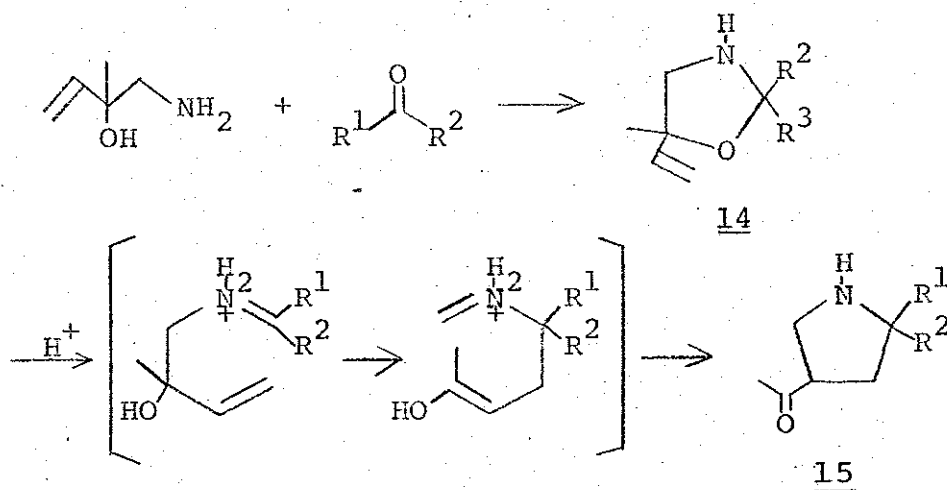
Furthermore, the author found that the structure of **11** could be also realized temporarily from 5-vinyloxazolidine **14** under basic condition. Thus, the reaction of **14** and potassium hydride in THF affords 3-acetylpyrrolidine **15** via 2-aza-4-oxy-Cope rearrangement (eq.3). The reaction

14   **15**   (3)
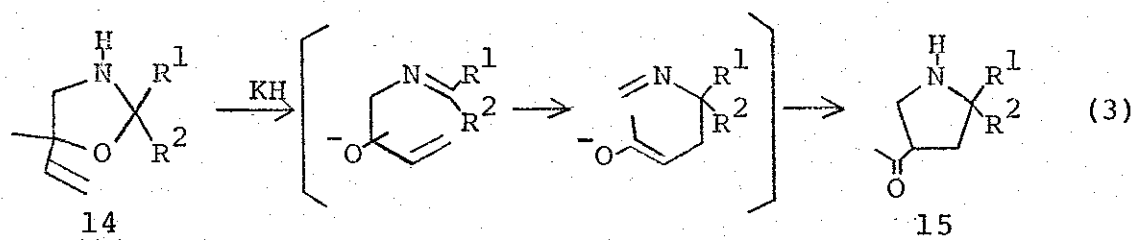
condition was dramatically improved being the reaction conducted at room temperature by the 2-aza-4-oxy-Cope method compared with the acid catalized 2-azonia-[3,3]-sigmatropic rearrangement (at 80°C). It is significant that 3-acetylpyrrolidines which could not be synthesized by the acid catalyzed reaction were prepared in good yield by the base catalyzed reaction.

Thus, it is found that pyrrolidine ring system can

be constructed under both the acidic and the basic conditions. The author assumes that the new pyrrolidine synthesis by means of 2-aza-[3,3]-sigmatropic rearrangement should have the wide applications to the synthetic chemistry employing the conditions at our discretion.

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