SYNTHETIC REACTIONS USING ISOXAZOLE COMPOUNDS

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Abstract — The activation of C-5 methyl group of 3,5-dimethylisoxazoles is discussed by MINDO/2 calculation and H-D exchange reaction. The regioselective substitution reaction of 5-methylisoxazoles with electrophiles such as alkyl halides, carbon dioxide, carbonyl compounds, Schiff bases, nitriles, nitrites and nitroso compounds is reviewed. Also the conversions of resulting isoxazole derivatives to β-diketones, enones and some heterocyclic compounds are reviewed.

In 1891, Claisen had succeeded to synthesize the isoxazole compound, which was an unsaturated five membered ring compound containing oxygen and nitrogen atoms.[1] Since then, many papers have been reported concerning to the isoxazole compounds.[2] The spectral data of isoxazoles such as IR, UV and NMR are similar to those of furans, pyridines and other azoles. From the microwave absorption spectral analysis, the structure of isoxazole ring was confirmed to be a planar pentagon showing in Fig. 1.[3] By the study of the heat of combustion, the resonance energy of

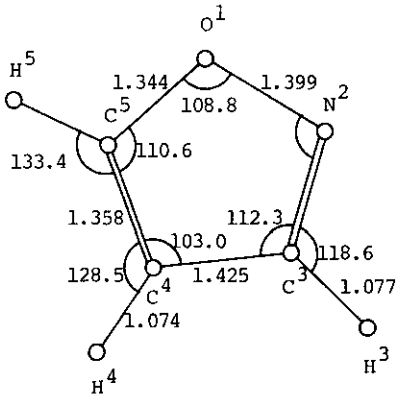


Fig. 1

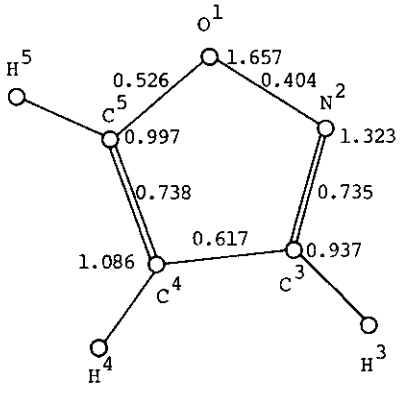


Fig. 2

isoxazole ring was estimated to be about 2 kcal/mol.[4] Further, the π-bond order and π-electron density by p.p.p. calculation method suggested that the π electron was delocalized on five membered ring showing in Fig. 2.[5] From these facts, isoxazole compounds are seemed to be a five membered aromatic compound containing oxygen and nitrogen atoms. The property of this oxygen is similar to that of furan, while nitrogen is similar to that of pyridine.

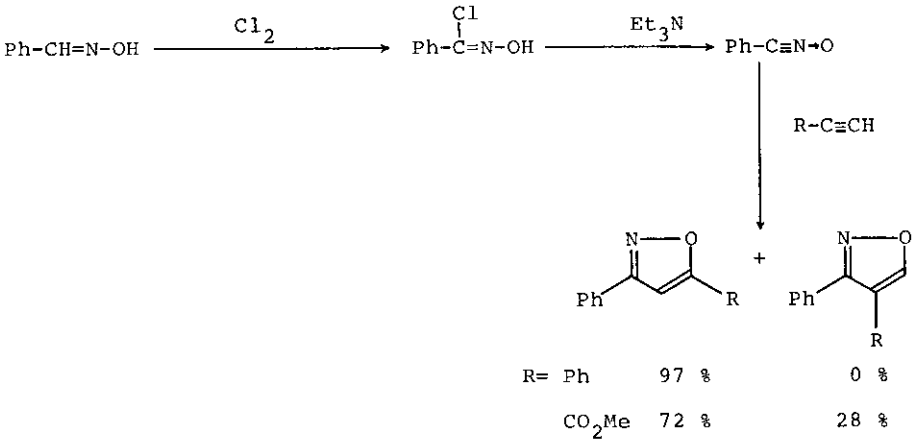
Chemically, isoxazole compounds show properties of typical aromatic compounds. That is, electrophilic substitution reactions such as nitration,[6] halogenation[7] and chloromethylation[8] on isoxazole ring are observed to give corresponding derivatives. The isoxazole ring is fairly stable against the oxidizing agents, acids or bases. Especially, 3,5-disubstituted isoxazole derivatives are quite stable to the oxidizing agents, acids and bases.

The basicity of isoxazole compounds is weaker than that of pyridines and pyrazoles. For example, the pK_a value of 3,5-dimethylisoxazole was reported to be 1.26.[9] However, isoxazole compounds afford the qurternary ammonium salts, isoxazolium salts, similar to the formation of pyridinium salts from pyridine derivatives. Although the isoxazole compounds chemically have a quite similar properties with other nitrogen containing heterocycles, isoxazole compounds have the N-O bond which causes the bond cleavage by catalytic hydrogenation to give a corresponding β-amino enones.[2]

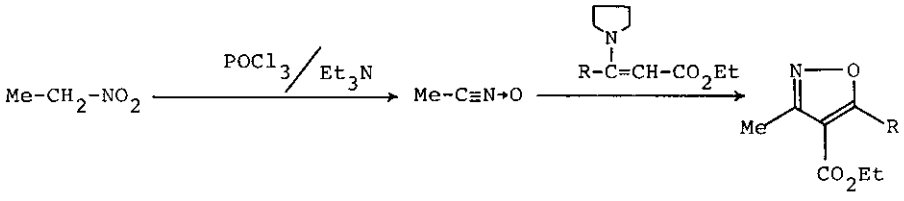
By these chemical properties, isoxazole compounds are applicable to the synthesis of various organic compounds such as terpenoids. Especially, 3,5-disubstituted isoxazoles are quite useful intermediate in the synthetic chemistry, because of its stability and reactivity to the various reagents. This paper will review the electrophilic substitution reaction of 3-substituted 5-methylisoxazoles in the presence of bases, and the conversion of the resulting isoxazole derivatives into various useful chain compounds by the effective ring opening reactions.

1. Synthesis of Isoxazole compounds.

There are two types of the preparations of isoxazole compounds. One is the 1,3-dipolar cycloaddition of nitrile oxides with olefins and acetylenes. The other is the condensation reaction of hydroxylamine with carbonyl compounds. Nitrile oxide for 1,3-dipolar cycloaddition is prepared by the dehydrogenation of aldoximes[10] and the dehydration of nitroalkanes.[11] In this 1,3-dipolar cyclo-



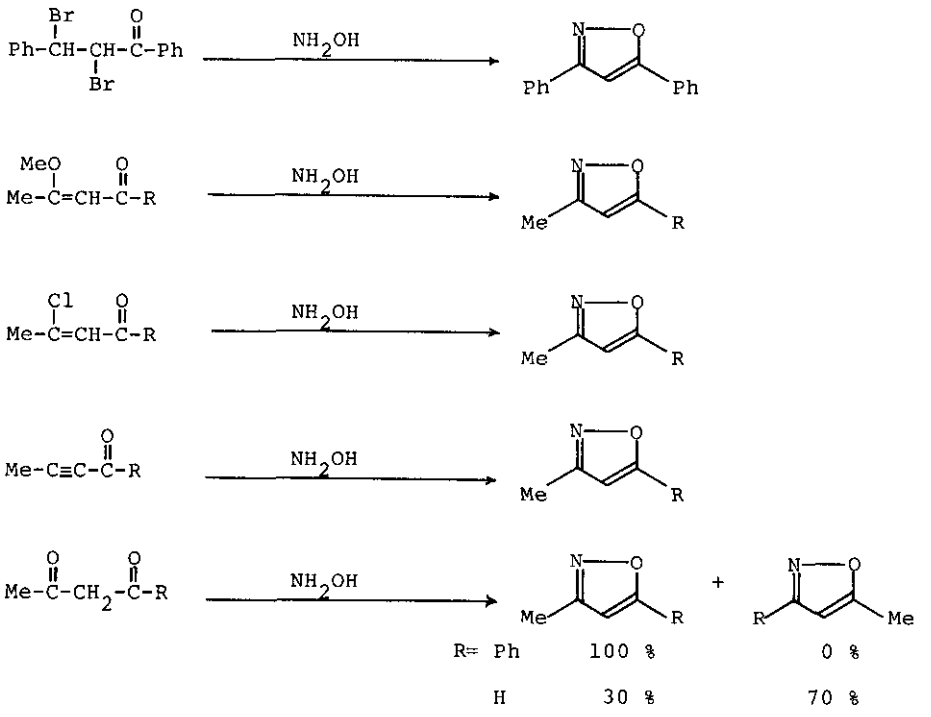
Scheme 1



Scheme 2

addition, nitrile oxide gives not only two isomeric mixtures, but also a cyclic dimer of nitrile oxide, floxane, as a by-product.[12]

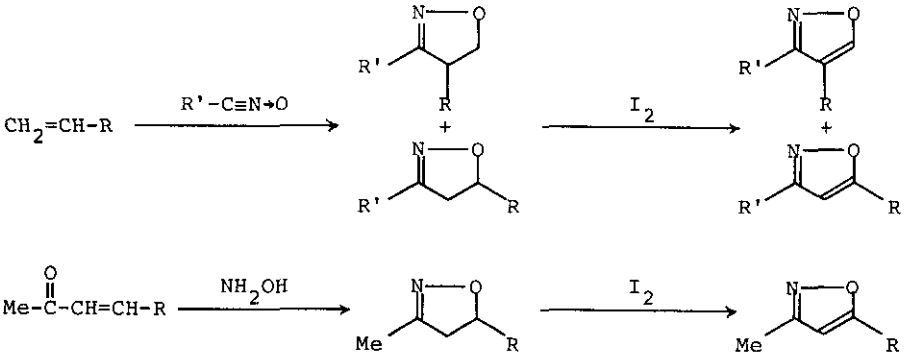
The condensation reaction of hydroxylamine with carbonyl compounds such as α,β-dihaloketones,[13] β-alkoxy enones,[14] β-chloro enones[15] and ynones[16] affords isoxazole compounds in good yield. In this reaction, alkylisoxazoles are regioselectively produced. However, these starting materials are limited in preparations. On the other hand, the synthesis of isoxazole compounds by the condensation reaction of β-diketones with hydroxylamine[17] is superior because of the cleaner reaction without any by-product, the simple procedure, the high yield and the easier preparation of β-diketones as the starting material. For example, by the treatment of 2,4-pentanedione with hydroxylamine hydrochloride in the presence of potassium carbonate, 3,5-dimethylisoxazole is obatined over 70 % yield without any by-product.[18] In this reaction, many β-diketones give the isomeric mixture having the two different substituent groups alternatively on 3 and 5 position.[19] In the case of the reaction giving the isoxazole compound



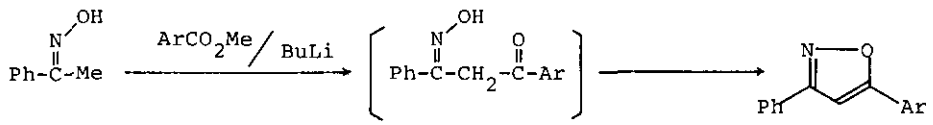
Scheme 3

without isomer, the preparation of opposite isomer is quite difficult.[20]

By the dehydrogenation with oxidizing agent such as iodine, isoxazoline compounds which are prepared from the 1,3-dipolar cycloaddition of nitrile oxide with alkene[21] or the condensation reaction of hydroxylamine with enones,[22] also give the isoxazole compounds.[23] However, this dehydrogenation reaction is not so broadly applicable for the synthesis of isoxazole compounds because of its various by-products. Further, the acylation of methylketoximes in the presence of base



Scheme 4

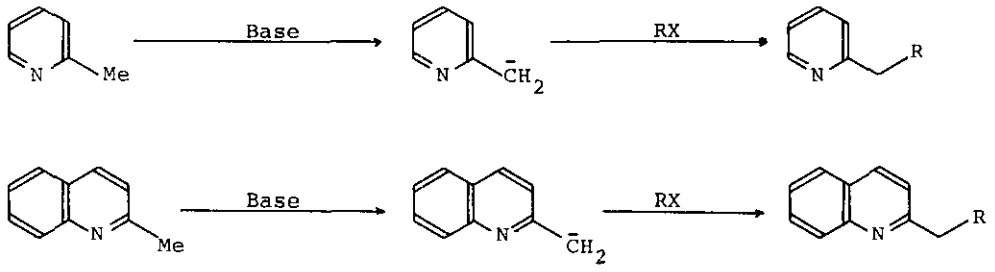


Scheme 5

gives the isoxazole compound in high yield with the high regioselectivity.[24] Although this preparative method is much applicable for the 3,5-diarylisoxazole, 3,5-disubstituted isoxazole compounds having the alkyl substituent groups can not be obtained. After all, it is concluded that there is no general method for the preparation of various isoxazole compound without isomers, especially for dialkyl substituted isoxazoles.[25]

2. Reactivity of 3,5-Dimethylisoxazoles.[26]

It is well-known that methyl groups are activated by the adjucent aromatic ring, especially nitrogen containing heteroaromatic ring. For example, a methyl group of 2-methylpyridine[27] or 2-methylquinoline[28] is easily deprotonated by base to give carbanion, which reacts with various electrophiles to give the substitution product on the methyl group. Similar substitution reaction with electrophiles can be expected on the methyl group of methylisoxazoles. However, the reaction of 3- or 5-unsubstituted isoxazoles in the presence of base could not give the expected products, because these isoxazoles are remarkably unstable to give acyclic nitriles. Therefore, author and co-workers studied the reactivity of methyl groups of 3,5-dimethylisoxazole.[26]

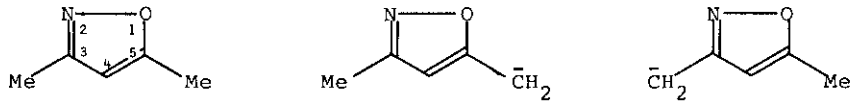


Scheme 6

2-1. Stability of Carbanion.

The mechanism of the reaction of 2-methylpyridine or 2-methylquinoline with electrophilic reagent in the presence of base is considered to be firstly the deprotonation to intermediate carbanion, which is attacked by an electrophilic reagent. In this reaction mechanism, the rate determining step is considered to be the formation of intermediate carbanion. Therefore, the reaction rate should depend on the stability of carbanion such as 2-pyridylmethyl and 2-quinolynylmethyl carbanion.

Since the methylisoxazole compounds can be assumed to react with electrophilic reagent in a similar reaction mechanism, the stability of the intermediate carbanion was studied by the quantum chemical calculation. In the case of 3,5-dimethylisoxazole (1), two carbanions, 3-methyl-5-isoxazolylmethyl (1-a) and 5-methyl-3-isoxazolylmethyl carbanion (1-b), can be assumed to form intermediately. By the MINDO/2 calculations of these two carbanions, the heats of formation of 1-a is about 8 kcal/mol smaller than that of 1-b. From this result, it is predicted that the 3-methyl-5-isoxazolylmethyl carbanion (1-a) is favorable to form thermodynamically by deprotonation from 1, and that the reaction with electrophilic reagent in the presence of base occurs predominantly on C-5 methyl group of 1.



(1) (1-a) (1-b)

Scheme 7

2-2. H-D Exchange Reaction.

For the confirmation of the prediction by MINDO/2 calculation, H-D exchange reaction of 1 is carried out by heating with sodium methoxide in deuterated methanol. As the result, protons on C-5 methyl group are exchanged to deuterium about 280 times faster than those on C-3 methyl group, and its activation energy is about 29 kcal/mol. From this result, even C-5 methyl group of 1 is seemed to be less reactive than the methyl group of 2-methylpyridine and 2-methylquinoline, which are reported to be 25 and 21 kcal/mol of activation energies, respectively,

for the H-D exchange reaction under same conditions.[29]

From the results of H-D exchange reaction of 4-substituted 3,5-dimethylisoxazoles, C-5 methyl groups are more reactive than C-3 methyl groups in any cases. Further, an electron-donating group on C-4 position of isoxazole ring retards the reaction on C-5 methyl group, while an electron-withdrawing group accelerates When these data are plotted with substituent constant of Hammett equation, σ, it seems to be almost linear showing in Fig. 3. Therefore, C-5 methyl groups on 3,5-dimethylisoxazoles are actually observed to react with some electrophiles regioselectively in the presence of base.

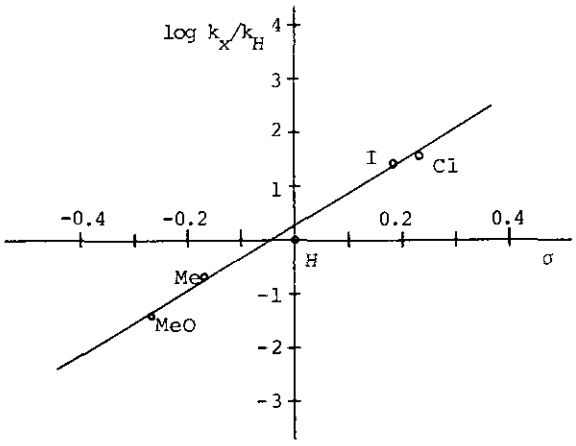
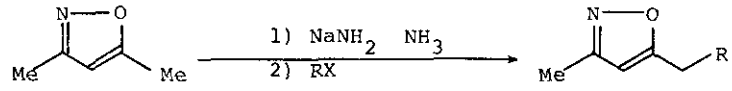


Fig. 3

3. Reactions of 5-Methylisoxazoles with Electrophilic Reagents.

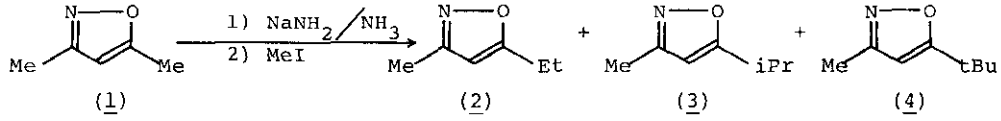
3-1. Alkylation

Since the H-D exchange rate of C-5 methyl group of 3,5-dimethylisoxazole (1) is 280 times larger than that of C-3 methyl group, it is expected that the alkylation of 1 occurs regioselectively on C-5 methyl group. After deprotonation with sodium amide in liquid ammonia, compound 1 is treated with alkyl halides. The product is actually the alkylated derivatives on C-5 methyl group, and no alkylated derivative on C-3 methyl group can be detected. This result shows that this alkylation reaction is quite regioselective. For example, compound 1 gives only 5-ethyl-3-methylisoxazole (2) in 70 % yield by the treatment with equimolar amount of methyl iodide in the presence of equimolar amount of sodium amide in liquid ammonia. When 2 molar amount of methyl iodide is used in the presence of



Scheme 8

2 molar amount of sodium amide, two methyl groups are substituted on C-5 methyl group to give 5-isopropyl-3-methylisoxazole (3). By the treatment with much excess amount of methyl iodide and sodium amide, 1 gives the further methylated product, 5-t-butyl-3-methylisoxazole (4). Under these conditions, any methylated product on C-3 methyl group can not be detected.

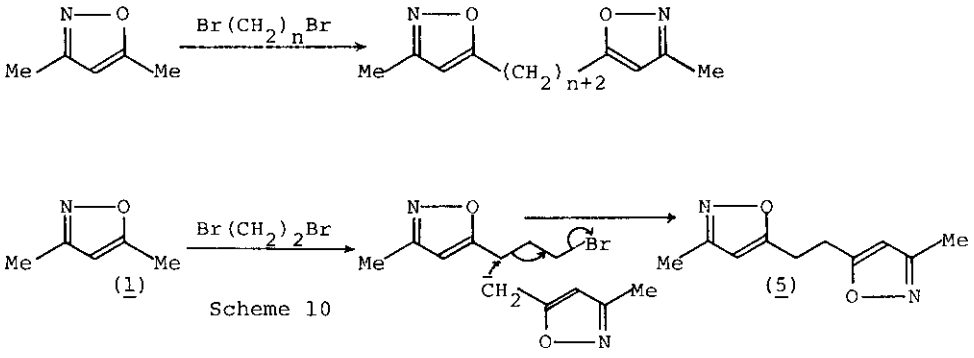


Scheme 9

Table 1

$NaNH_2$ (mol)	MeI (mol)	Yield (%)	Product Ratio 2 %	3 %	4 %
1	1	58	100	0	0
2	2	68	33	57	0
3	3	59	9	62	29
4	4	51	0	0	100

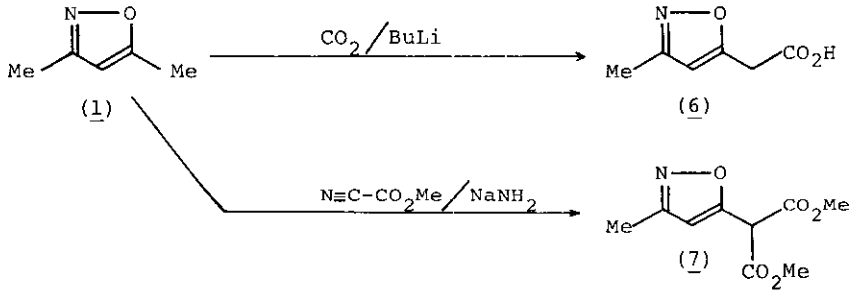
By the use of butyllithium in ether as the deprotonating agent, alkylation reaction also occurs on C-5 methyl group treating with alkyl halides.[31] When dihaloalkanes are used as the alkyl halide, diisoxazolylalkanes are yielded. In the case of 1,2-dibromoethane, compound 1 does not give the alkylated product, 1,4-di(3-methyl-5-isoxazolyl)butane, but the dimeric 1,2-di(3-methyl-5-isoxazolyl)-ethane (5). Compound 5 is also yielded from 1 by the treatment with iodine in the presence of butyllithium in ether.[31] Otherwise, by the treatment with iodine in the presence of nitric acid, 1 gives 4-iodo-3,5-dimethylisoxazole.[7]



Scheme 10

3-2. Carboxylation.

By the treatment with carbon dioxide (dry ice) in the presence of butyllithium, compound 1 gives 5-(3-methylisoxazolyl)acetic acid (6).[31] When cyanoformic ester was used as the carboxylating agent, 2 molar amount of ester reacts with 1 to give 3-methyl-5-isoxazolylmalonic ester (7).[32]

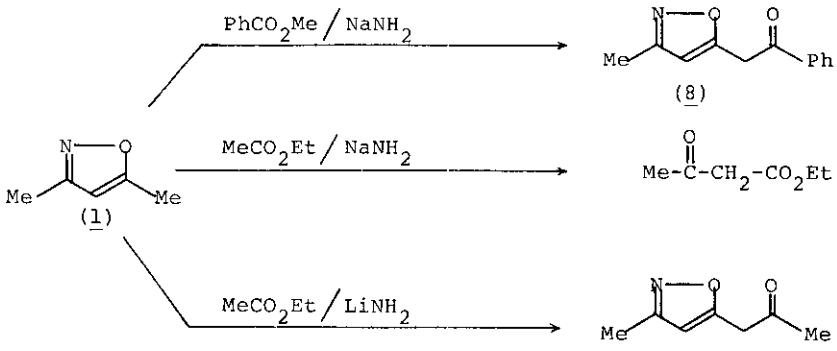


Scheme 11

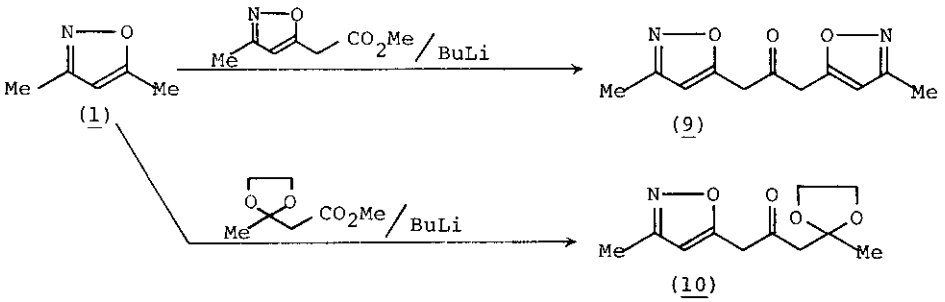
3-3. Reaction with Carbonyl Compounds.[33]

When compound 1 is treated with benzoic ester in the presence of sodium amide, acylation reaction occurs on C-5 methyl group to give 3-methyl-5-benzoylmethylisoxazole (8). Under same conditions, however, the treatment of 1 with ethyl acetate does not give the acetylated product on C-5 methyl group, but the self condensation product of ethyl acetate, ethyl 3-oxobutanoate. It is well-known that a methyl or a methylene group is activated by the strong electron-withdrawing effect of the adjacent carbonyl group. In the case of highly activated carbonyl

compound, the proton of methyl or methylene adjacent carbonyl group is transferred into the methyl carbanion of 5-methylisoxazoles, and the carbonyl compound is condensed by aldol type condensation reaction. Since ethyl acetate is superior in the deprotonation to give the carbanion than 5-methylisoxazoles, the production of ethyl 3-oxobutanoate by Claisen condensation of ethyl acetate is observed, and the starting isoxazole compound (1) is recovered. Meanwhile, C-Li bond of organolithium compound is rather covalent bond, and the proton transfer of organolithium compound is rather slow than that of organosodium or organopotassium compounds.[34] Therefore, 1 is acetylated on C-5 methyl group by ethyl acetate in the presence of lithium amide in liquid ammonia without any Claisen condensation product. By the use of butyllithium, acylation of 1 does not give an expected result. From this result, the optimal conditions of reaction of 5-methylisoxazoles with carbonyl compound having an active methyl or methylene group are concluded to be the use of lithium amide in liquid ammonia, while sodium amide is optimally used in the reaction with carbonyl compounds having no active methyl or methylene group.



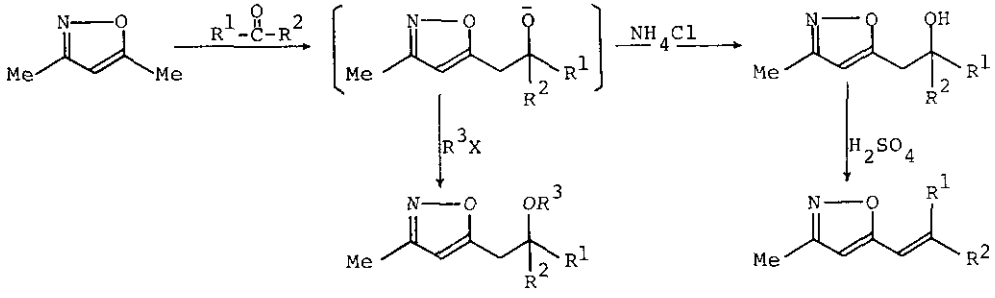
Scheme 12



Scheme 13

By the treatment with 3-methyl-5-isoxazoleacetic ester[35] or phosgene[36] and 3,3-ethylenedioxybutyric ester,[37] compound 1 gives compound 9 and 10, respectively. These derivatives are easily converted into the poly-β-ketides by the catalytic hydrogenation.

In the cases of ketones and aldehydes as the carbonyl compounds, 1 gives hydroxy derivatives of isoxazole compound by the nucleophilic addition of 3-methyl-5-isoxazolylmethyl carbanion on carbonyl group. When the resulting hydroxy derivatives are treated with sulfuric acid, the isoxazole derivatives having a conjugated double bond are obtained by the dehydration reaction. Furthermore, before the neutralization with acid in the formation of hydroxy derivatives, the treatment with alkyl halides gives the corresponding ether derivatives.

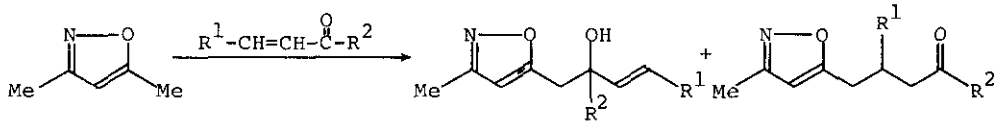


R^1= Me, Ph, p-Tol, p-Anis
R^2= H, Me, Ph
} $(CH_2)_5$
R^3= Me, Et, CH_2Ph, Allyl

Scheme 14

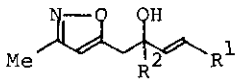
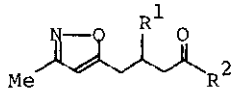
The chemical behaviors of 5-isoxazolylmethyl carbanion against the α,β-unsaturated carbonyl compounds are observed to be similar with Grignard reagents. That is, this carbanion attacks predominantly on the carbonyl carbon of enones and enals to give a corresponding alcohol derivative, while the α,β-unsaturated carboxylic acids and their esters mainly give Michael addition products.

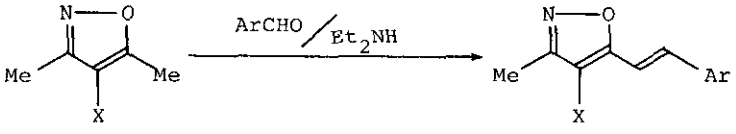
In the case of 5-methylisoxazoles having an electron-withdrawing group on C-4 position such as 4-nitro-, 4-cyano-, 4-acyl- and 4-carboxy- derivatives, the methyl group is activated even in the presence of diethylamine to condense with aromatic aldehydes.[38] This reaction seems to be very high regioselective to give only 5-styrylisoxazole derivatives.



Scheme 15

Table 2

R^1	R^2		
Ph	H	trace	38 %
H	Me	8 %	43 %
Ph	Ph	11 %	35 %
Ph	OMe	10 %	———
Ph	OH	4 %	———



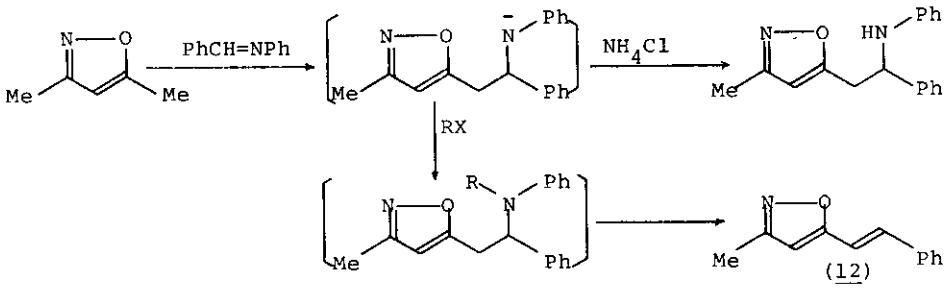
X= NO_2, CN, COPh, CO_2Et Ar= Ph, p-Tol, p-O_2N-C_6H_4

Scheme 16

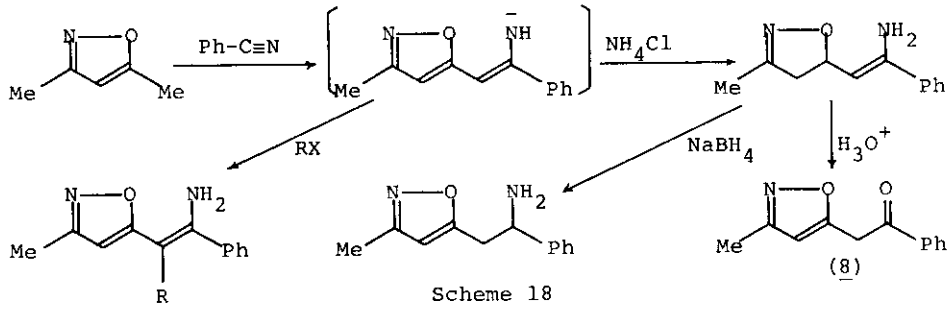
3-4. Reaction with Schiff Bases and Nitriles.[39]

As an analogy of carbonyl compounds, C=N and C≡N compounds react with 1 in the presence of base. For example, the reaction of 1 with benzylideneaniline gives 5-(2-anilino-2-phenyl)ethyl-3-methylisoxazole (11) in high yield, with the by-product which is resulted from one molar 1 and two molar amount of benzylideneaniline. When the reaction mixture of 1 and benzylideneaniline is treated with alkyl halides before neutralization, the formation of N,N-dialkylanilinium derivatives are expected. However, these compounds can not be isolated but 5-styryl-3-methylisoxazole (12) is isolated passing through the deamination reaction in the neutralization process.

In the reaction with benzonitriles, compound 1 gives the enamine derivative, which is easily hydrolyzed to give the corresponding carbonyl compound (8).[31] When this enamine derivative is reduced with sodium borohydride, amino derivative



Scheme 17

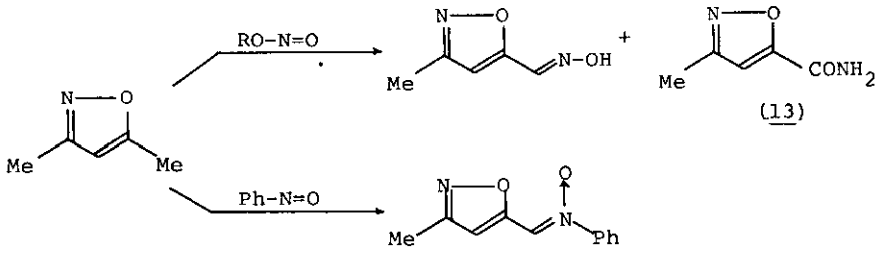


Scheme 18

is obtained. The alkylation of this enamine derivative occurs on olefinic carbon adjacent to isoxazole ring.

3-5. Reaction with Nitrite and Nitroso Compound.[40]

Similar nucleophilic addition reaction of 1 is observed even on the N=O compounds. The treatment of 1 with nitrite gives the nitrosation product, 5-(3-methyl)isoxazolealdoxime. Further, 3-methyl-5-isoxazolecarboxamide



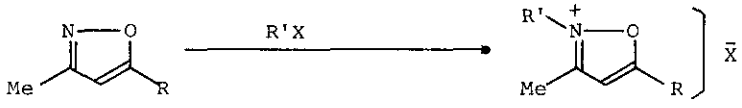
Scheme 19

(13) is isolated as the by-product through Beckmann rearrangement of this aldoxime. When compound 1 is treated with nitrosobenzene, the corresponding nitrone derivative is obtained in poor yield.

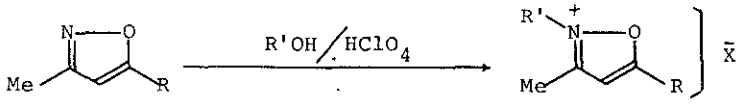
4. Conversion from Isoxazole Compounds.

4-1. Reactions of Isoxazolium Salts.

In a former section, the author summarized the regioselective synthesis of the isoxazole compounds having the various substituent groups on C-5 position by the treatment of 5-methylisoxazoles with various electrophilic reagents in a presence of base. These isoxazole derivatives are also able to form the isoxazolium salts similar to the formation of pyridinium salts from pyridines. By heating with alkyl halides in a sealed tube, isoxazole compounds afford the corresponding 2-alkylisoxazolium salts.[18] In the cases of the formation of 2-t-butyl or 2-benzhydrylisoxazolium salts, the treatment of isoxazoles with t-butanol or benzhydrol is applicable in the presence of perchloric acid at room temperature.[41] By the use of dialkyl sulfate[42] or Meerwein reagents,[43] the isoxazolium salts are also prepared from isoxazole compounds.



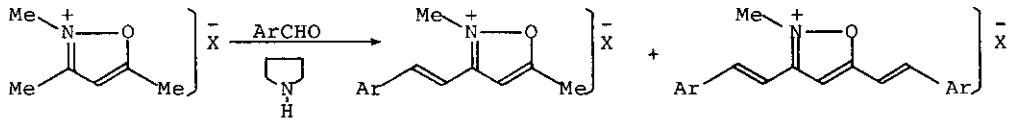
R'X= MeI, $Et_3O \cdot BF_4$, Me_2SO_4, EtI



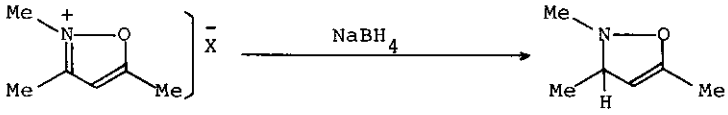
R'OH= t-BuOH, Ph_2CHOH

Scheme 20

The isoxazolium salts, easily derived from the isoxazoles by various methods, have the different electronic structure and reactivities from the original isoxazoles. Lampe reported that 2,3,5-trimethylisoxazolium salt gave 3-styryl-5-methylisoxazolium salt and 3,5-distyrylisoxazolium salt by the reaction with benzaldehyde in the presence of pyrrolidine.[44] This fact suggests that C-3 methyl group on isoxazolium salts is rather reactive with electrophilic reagents than C-5 methyl group, while isoxazole compounds react regioselectively on C-5



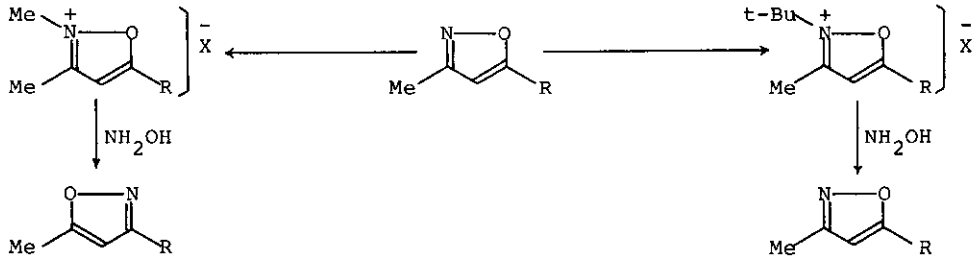
Scheme 21



Scheme 22

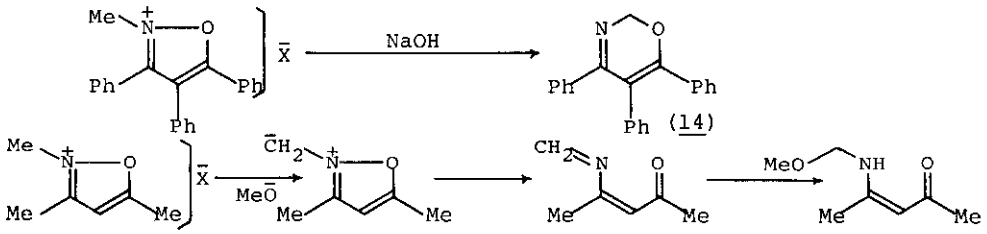
methyl group.

Although isoxazole compounds are fairly stable, 2-alkylisoxazolium salts react on C-3 carbon with various nucleophilic reagents such as sodium borohydride,[45] Grignard reagents[42,46] and organolithium compounds[47] to give the corresponding 2-alkyl-4-isoxazolines. When 2-alkylisoxazolium salts are treated with hydroxylamine in the presence of potassium carbonate, isoxazole compounds are reproduced via degenerate ring transformation.[48] By the detailed study of this degenerate ring transformation, 2-t-butyl or 2-benzhydrylisoxazolium salts give the original isoxazole by using hydroxylamine. On the contrary, in the reaction of 2-methylisoxazolium salts with hydroxylamine, the product is not a original isoxazole via degenerate ring transformation, but is isoxazole compound which has the alternative substituent groups on C-3 and C-5 position. Since this transformation of isoxazolium salts into isomeric isoxazoles is regioselective with high yield, the regioselective introduction of various substituent groups on either C-3 or C-5 position of isoxazole is accomplished by the combination with the reaction of isoxazole with electrophiles in the presence of base described former.



Scheme 23

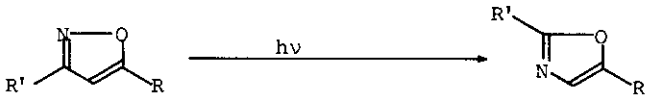
Ohashi reported that the ring of isoxazolium salts was opened and then recyclized intramolecularly by the treatment with sodium hydroxide to give phenol and aniline derivative.[49] King also reported that 2-methyl-3,4,5-triphenyl-isoxazolium salt was converted into oxazine compound (14) by the treatment with sodium hydroxide.[50] Similarly, 2-methylisoxazolium salts are converted to β-alkoxymethylamino enones in high yield by the treatment with sodium alkoxide in alcohol through the deprotonation from N-methyl group to form ylide.[51] The preparation of curcurmine derivative is accomplished by this reaction.



Scheme 24

4-2. Photoisomerization.[52]

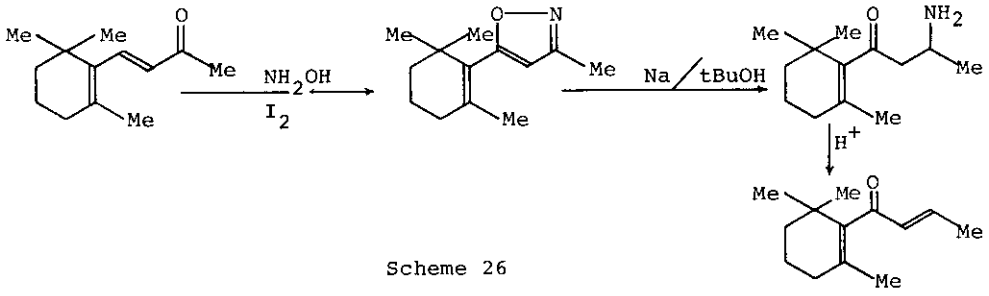
3,5-Disubstituted isoxazoles are photochemically isomerized into oxazole compounds in good yield. The resulting oxazoles are useful intermediate for a synthesis of various organic compounds such as carboxylic acid.



Scheme 25

4-3. Reduction of Isoxazole Compounds.

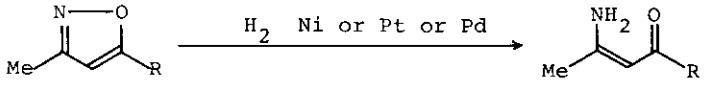
The isoxazole compounds are fairly stable to the reduction with sodium borohydride and lithium aluminum hydride. However, isoxazole compounds are cleaved to β-amino ketones by Birch reduction using sodium in liquid ammonia in the presence of t-butanol. The resulting β-amino ketones are easily deaminated to enones.[53] By this conversion, Büchi succeeded to afford



Scheme 26

β-damascone from α-ionone.

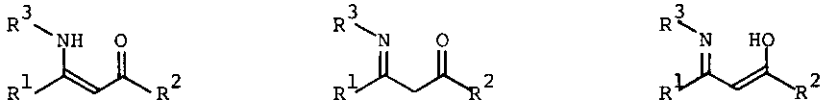
It is well-known that isoxazole ring easily opened by the catalytic hydrogenation to give β-amino enones.[2] Generally, Raney nickel, palladium or platinum black is used as the catalyst even under ordinary pressure and temperature. In this hydrogenation, the product is only β-amino enones in high yield and any by-product can not be detected.



Scheme 27

4-4. Regioselective Conversions of β-Amino Enones.

The isoxazole compounds are easily cleaved into β-amino enones by catalytic hydrogenation or alkylation to N-alkylisoxazolium salts followed by the ring opening with sodium alkoxide. Since these β-amino enones are isoelectronic with β-diketones, another two tautomers, β-imino ketone and β-imino enol, are considerable. However, the most stable form in this tautomerism is generally the β-amino enone form because of the larger electronegativity of oxygen than that of nitrogen.



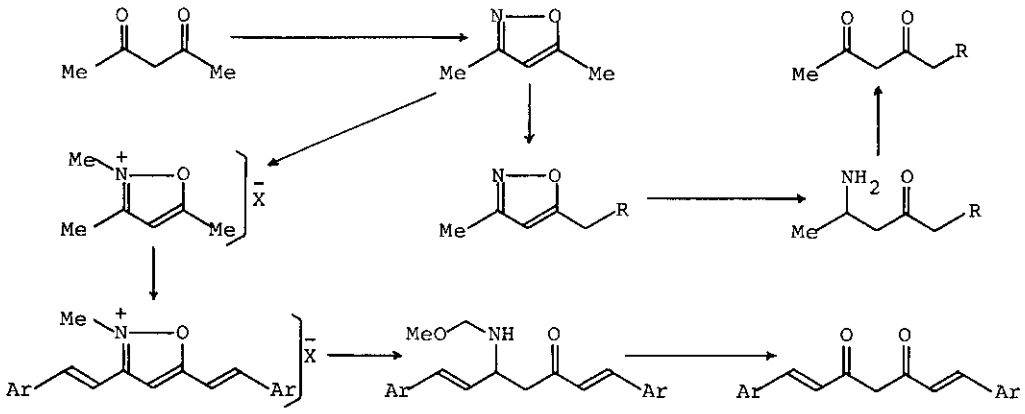
β-Amino Enone β-Imino Ketone β-Imino Enol

Scheme 28

Indeed, β-amino enones have the properties of enamines, ketones, enones and amines. Moreover, β-amino enones behave as the vinylogues of amides. Therefore, β-amino enones, easily prepared from isoxazole compound, are much useful intermediate for the synthesis of organic compounds.[54]

4-4-1. Conversion into β-Diketones.

Since β-amino enones are isoelectronic with β-diketones, β-amino enones are easily converted to β-diketones by the replacement of amino group into hydroxy group under the acid conditions at room temperature.[30] When this conversion is combined with the preparation of isoxazoles from β-diketones, isoxazole ring is useful protecting group of β-diketone group. Further, the chemical behaviors of isoxazoles and isoxazolium salts to electrophiles are enable to alkylate β-diketones at γ-position.[55] The preparation of naturally occuring curcurmin derivatives is accomplished by the use of this conversion into β-diketone.[51]

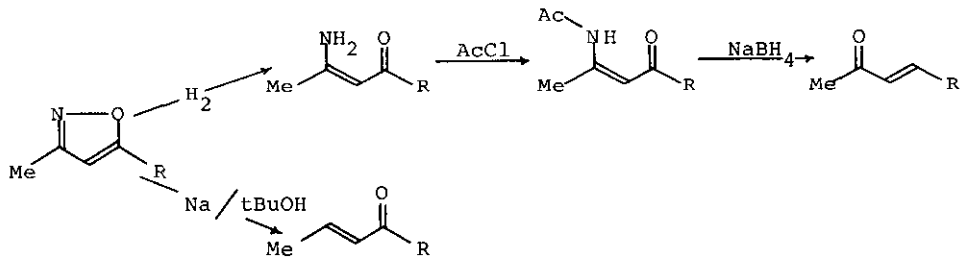


Scheme 29

Stork reported the preparation of cyclo enones from 1 by chloromethylation at C-4 position, the condensation with active methylene group adjacent to ketone, opening reaction of isoxazole ring, recyclization, and deamination.[56] This procedure, called isoxazole annulation, is extensively applied for the synthesis of various terpenoids.[57]

4-4-2. Conversion into Enones.

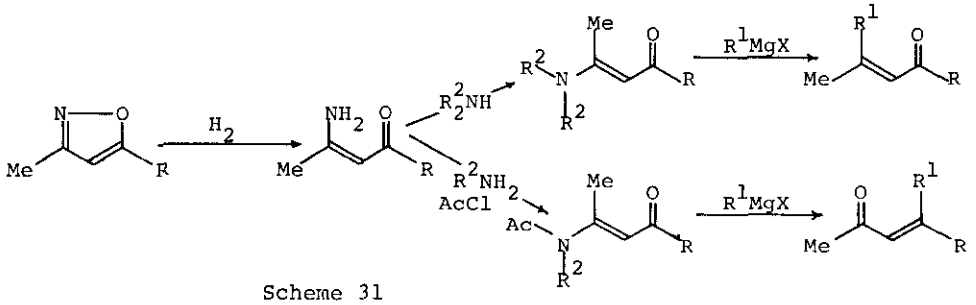
Although the ring opening of isoxazole compound is accomplished by the catalytic hydrogenation, the further hydrogenation of resulting β-amino enones can not be observed even in drastic conditions. Otherwise, unsubstituted β-amino enones are inert to sodium borohydride. However, N-acylated β-amino enones react with sodium borohydride to give enaminol compound, which is easily hydrolyzed and dehydrated to convert into enones by the treatment with acid.[58] In this conversion of isoxazole compound into enones through β-amino enones, the carbonyl carbon and olefinic β-carbon of the resulting enones are originated from C-3 and C-5 carbon of isoxazole ring, respectively. When isoxazoles are converted into enones by Birch reduction, on the contrary, the carbonyl carbon is originated from C-5 carbon of isoxazole ring.[53] By these two conversions of isoxazole into enones, two isomeric enones are possible to be prepared from an isoxazole compound regioselectively.[59] Furthermore, it is applicable protection method of enones in the synthesis to combine reactions of the preparation of isoxazoles from enones, catalytic hydrogenation, N-acylation, sodium borohydride reduction, and acidic hydration. In using lithium aluminum hydride, β-amino enones are reduced unselectively and give the many by-products.



Scheme 30

Although β-amino enones having hydrogen on nitrogen atom are inert to Grignard reagents, amino group of N,N-dialkylated β-amino enones is replaced to alkyl group by Grignard reagents to give β,β-dialkyl enones.[60] When N-acylated β-amino enones are treated with Grignard reagents, Grignard reagent attacks on the carbonyl carbon to give corresponding β-hydroxy enamines, which are easily hydrolyzed and dehydrated to form β,β-dialkyl enones. By the treatment with

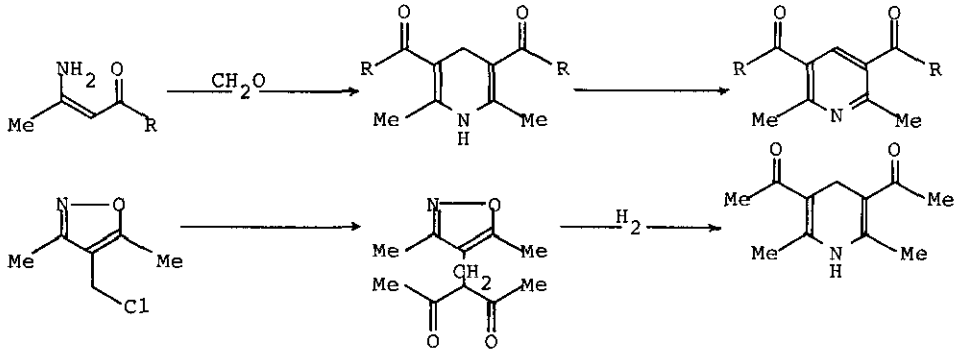
Grignard reagent, the regioselective preparation of β,β-dialkyl enones is accomplished from N,N-dialkyl or N-acyl-N-alkyl β-amino enones.[61] Both β-amino enone derivatives are easily obtained from isoxazole compound. After all, β-amino enones, which are easily derived from isoxazole compounds, are found to be very important intermediate for the reioselective synthesis of various isomeric enones by using dialkylation, acylation, Grignard reaction and sodium borohydride reduction.



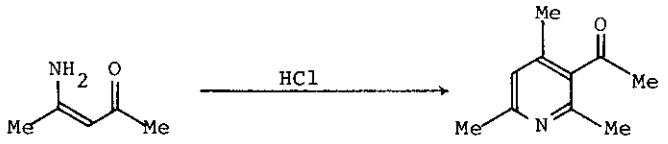
Scheme 31

4-4-3. Conversion into Pyridine Derivatives.

By the treatment with aldehydes, β-amino enones are converted into 1,4-dihydropyridine derivatives.[62] The condensation product from 4-chloromethylisoxazoles and 2,4-pentanedione is also found to be 1,4-dihydropyridine derivatives by catalytic hydrogenation and intramolecular condensation.[63] These 1,4-dihydropyridines are easily dehydrogenated to corresponding pyridines through enzyme like process. On the other hand, β-amino enones are dimerized by hydrogen chloride to give pyridine derivatives, as well as o-aminophenol derivatives.[64]



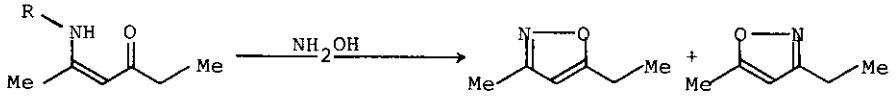
Scheme 32



Scheme 33

4-4-4. Conversion into Isoxazoles.[65]

Since β-amino enones are isoelectronic with β-diketones, β-amino enones easily condensed with hydroxylamine to give isoxazole derivatives similar to the formation from β-diketones. This reaction is initiated from the regioselective attack of hydroxylamine on β-carbon of β-amino enones. However, the electronic structure of β-amino enones is changed by N-acylation. Therefore, the first attack of hydroxylamine can be changed into carbonyl carbon. As the result, in the case of N-trichloroacetyl derivatives, the regioselective formation of the isomeric isoxazole can increase up to 75 % by the strong electron-withdrawing effect of acyl group.

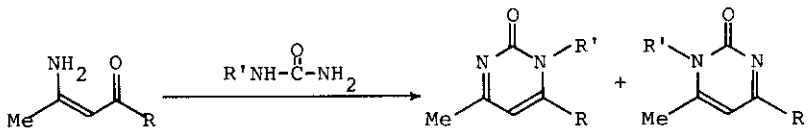


R=		
H	100 %	0 %
CO_2Me	67 %	33 %
$COCCl_3$	25 %	75 %

Scheme 34

4-4-5. Conversion into Pyrimidinones.[66]

Similar to the formation from β-diketones, 2(1H)-pyrimidinones are formed from β-amino enones and ureas. Though the high regioselectivity are also expected in this reaction, the result is rather undesiable owing to the low selectivity of ureas.



Scheme 35

5. Conclusion.

It is necessary to consider five points, when a heterocyclic compound is used as the useful intermediate for the synthesis of organic compounds. 1) The preparation of the heterocyclic compound is quite easy from the available starting materials. 2) The heterocyclic compound is quite stable under the various reaction conditions. 3) The heterocyclic compound does not inhibit the various reactions. 4) Under the specific reaction conditions, the heterocyclic compound reacts sensitively and selectively for introduction of useful functional groups in high yield. 5) The compound, which is derived from the heterocyclic compound by mild ring cleavage, is convertible to the various compounds. Meanwhile, 3,5-dimethylisoxazole (1) shows following behaviors. 1 is easily prepared from hydroxylamine and 2,4-pentanedione in high yield. 1 is quite stable against the oxidizing reagents, acids, bases and hydride compounds. 1 gives the various derivatives by the regioselective substitution on C-5 methyl group, which is activated by the isoxazole ring. 1 is almost neutral compound and shows no catalytic property as either acid or base. 1 is specifically cleaved to β-amino enones by catalytic hydrogenation. The resulting β-amino enones are converted into β-diketones, enones and some heterocyclic compounds. Considering the chemical behaviors, it is concluded that 3,5-disubstituted isoxazoles especially 1 are the useful intermediate for the synthesis of various organic compounds.

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