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THE REACTION OF 3,5-DIMETHYLISOXAZOLE WITH SOME ELECTROPHILES

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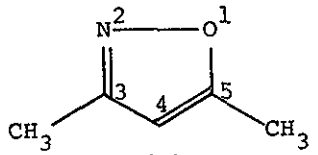
Contents

1. Introduction

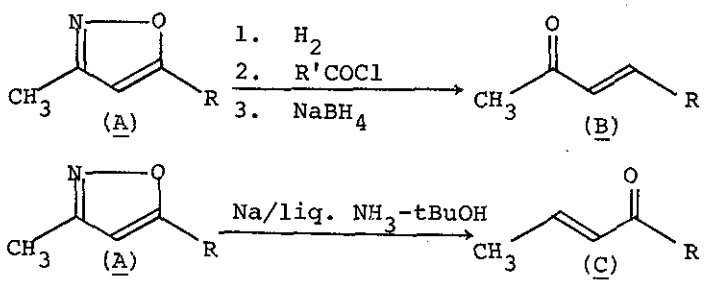
After reviews of the chemistry of the isoxazole ring compounds appeared in 1962[1] and 1969[2], we have not had any review about it. In the mean time, many papers concerning to the isoxazoles, especially of 3,5-dimethylisoxazole (1) with some electrophiles in the presence of bases.



(1)

The isoxazole compounds have long been interested in the pharmaceutical and synthetic chemistry. Kano[3] reported that antipyretic, analgesic, anti-inflammatory and antitussive activities have been observed on the isoxazole derivatives. The "Reagent K" in Woodward's peptide synthesis is also the isoxazole derivatives.[4] Furthermore, it is well-known that the nitrogen-oxygen linkage on an isoxazole ring is chemically labile and that isoxazole ring is easily cleaved to β-aminoenones by hydrolysis or hydrogenolysis. Thus many investigators have used the isoxazole compounds as the precursor in the synthesis of complex molecules. Stevens reported[5] that an appropriately substituted trisisoxazole compound was hydrogenated to give bispyrrole derivatives, which were converted to precorphin. Stork reported the isoxazole derivatives were used as the precursor in the synthesis of cyclohexenone and some steroids.[6,7] β-Diketones were easily synthesized in good yield by hydrolysis of β-aminoenones, which were produced from isoxazole derivatives.[8] In the reduction of "unsymmetric" 3,5-disubstituted isoxazoles (A), two types of enones were obtained. That is, when A was hydrogenated

followed by N-acylation and sodium borohydride reduction, some enoned (B) was obtained.[9] On the other hand, A was reduced by lithium in liquid ammonia to give the other enones (C).[10] Also the isoxazole derivatives were isomerized to the oxazole derivatives by photolysis.[11]



For the purpose of the research in laboratory, three type reactions are available to the synthesis of isoxazole derivatives.

1) The reaction of hydroxylamine with β-diketones,[12] α,β-unsaturated ketones,[13] or α,β-dihaloketones.[14]
2) The 1,3-dipolar addition of nitrile oxide with olefins[15] or acetylenes.[16]
3) The acylation of methyl ketoximes.[16]

In the type 1, the reaction proceeds very smoothly and gives the isoxazole derivatives in good yield. However, the starting α,β-unsaturated ketones and α,β-dihaloketones are sometimes very difficult to prepare. In the type 2, there are some limitation in the preparation of nitrile oxide. In the type 3, it has

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"Symmetric"isoxazole has the same substituent groups on C-3 and C-5 positions, and "Unsymmetric" isoxazole has the different groups on C-3 and C-5 positions.

never been reported to prepare 3-alkylisoxazoles. Therefore, in the case of symmetric isoxazole, the most useful preparative method is the treatment of β-diketones with hydroxylamine. For example, 3,5-dimethylisoxazole (1) is obtained in good yield from 2,4-pentanedione.[18] However, these methods usually give a mixture of two unsymmetric isoxazole isomers, whose separation is quite difficult.[19] When one unsymmetric isoxazole is apt to be formed, the other isomer is synthesized with much difficulties.[20]

It is well-known that the methyl group attached to the hetero-aromatic ring such as methyl groups of picoline[21] and quinaldine[22] is reactive to the electrophiles in the presence of bases. Since 3,5-dimethylisoxazole (1) has two methyl groups attached to the isoxazole ring, these methyl groups are expected to be activated by isoxazole ring. Here, the isoxazole ring has two kinds of hetero atoms. Therefore, the reactivities of methyl groups of 1 should differ on their positions in the presence of bases. From these hypothesis, the regioselective reactions of 1 with electrophiles will be expected.

2. The Reactivity of 3,5-Dimethylisoxazoles[23]

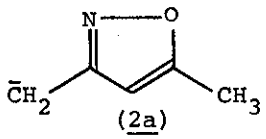
2-1 MINDO/2 Calculation

In the reaction of picoline and quinaldine with some electrophiles in the presence of bases, the rate determining step is supposed to be the formation of carbanion, which was derived by the proton abstraction. Similarly, 3,5-dimethyl-isoxazole (1) might conceivably be attacked by strong bases at a methyl hydrogen to form the carbanion. Therefore, it is considered that the reactivity of two methyl groups is comparable to the ease of the corresponding carbanion formation.

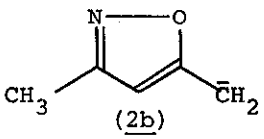
For the purpose of estimating the ease of the carbanion formation thermodynamically, the total energy and the heat of formation of 3-(5-methyl)isoxazolylmethyl carbanion(2a), which could be formed by proton abstraction from C-3 methyl, were calculated by MINDO/2 method. Similarly, 5-(3-methyl)isoxazolylmethyl carbanion (2b), which could be formed by proton abstraction from C-5 methyl, was also calculated as listed in Table 1. These calculations predict that carbanion 2b is more stable than carbanion 2a. The difference of heat of formation between carbanions 2a and 2b is about 7 kcal/mol. Thus, it is expected that the hydrogen of C-5 methyl on 1 is more easily abstracted by strong bases than that of C-3 methyl group under the thermodynamic control, and that C-5 methyl group is more reactive than C-3 methyl of 1.

Table 1.

MINDO/2 Calculation of 3,5-Dimethylisoxazole



(2a)



(2b)

Total Energy	-1252.149	-1252.483	ev
Heat of Formation	34.6	26.9	kcal/mol

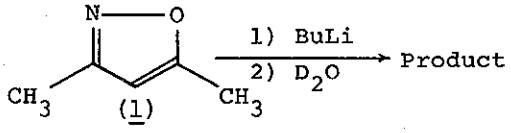
2-2 The Reaction of 3,5-Dimethylisoxazole with Deuterium Oxide

Along the above prediction, the compound 1 was treated with butyllithium in tetrahydrofuran to produce a carbanion, which

was quenched by deuterium oxide to give the deuterated products. Both mass spectra of 1 and the deuterated products were measured as listed in Table 2. Here, the report of the mass spectrum

Table 2.

Mass Spectral Data of 3,5-Dimethylisoxazole (1) and The Deuterated Product

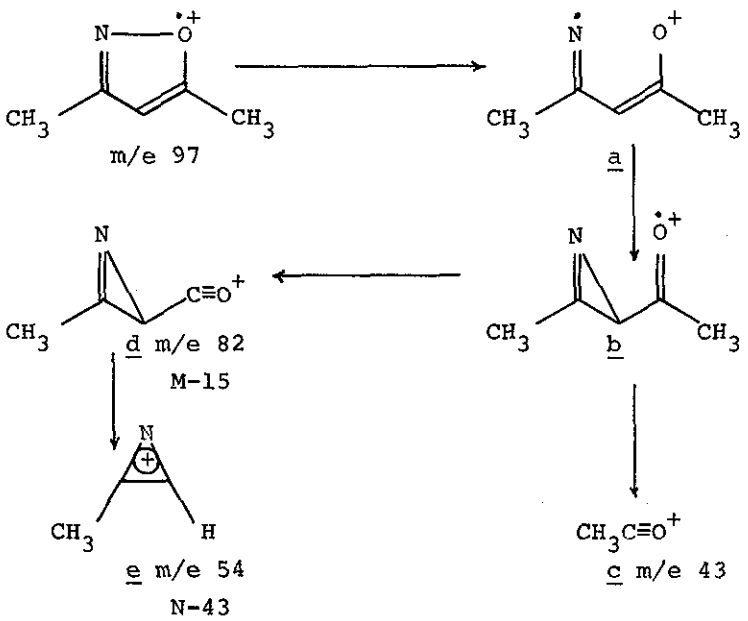


(1)

m/e	relative intensity	relative intensity
99	0.9	6.1
98	11.9	36.2
97	78.6	49.0
83	5.1	7.1
82	100.0	100.0
56	2.0	5.0
55	30.4	31.7
54	70.3	67.5

shows that 3,5-dimethylisoxazole (1) gives a strong molecular ion peak and the subsequent fragmentation is nicely formulated via an azirine intermediate (b) by the preferential cleavage of the nitrogen-oxygen linkage after electron-impact (Scheme 1).[24] The compound 1 gives a molecular ion peak at m/e 97. In the relative intensities of 1 and the deuterated products, the peak of the deuterated product at m/e 98 is much greater than that

Scheme 1.



of 1. Thus it is proved that 1 is mainly mono-deuterated. But the ratio of the peak of M-15 at m/e 82 to that at m/e 83, and the ratio of the peak of M-43 at m/e 54 to that at m/e 55 are unchanged in this deuteration reaction. While the compound 1 shows three singlet peaks at δ 2.21 (3H), 2.37 (3H), and 5.78 ppm (1H) in nmr spectrum, only the intensity of the peak of δ 2.37 is diminished after the deuteration reaction. Therefore, it is clear that 3,5-dimethylisoxazole (1) reacts regioselectively with deuterium oxide at C-5 methyl group in the presence of bases.

2-3 The Reactivity of 3,5-Dimethylisoxazole

The hydrogen-deuterium exchange rates of very weak acids

often parallel the acidities of this type of heteroaromatic compound.[25] This parallelism can be expected from the Brønsted catalysis law.[26] The relative reactivity of the methyl group of 1 was studied kinetically by means of a hydrogen-deuterium exchange reaction at 110°C in the presence of sodium methoxide in methanol-d_4. Actually, the hydrogen-deuterium exchange was monitored by the decreases in the nmr peaks of 1. The pseudo first-order rate constants of this reaction were found to be $k= 3.3 \times 10^{-4}\ s^{-1}$ at the C-5 methyl group and $k= 1.2 \times 10^{-6}\ s^{-1}$ at C-3 methyl group. That is,the C-5 methyl group was activated 280 times as much as the C-3 methyl group.

The reaction rates of the hydrogen-deuterium exchange on the C-5 methyl group of 1 were also measured at 80.1°, 89.0°, 100.0° and 121.2°C in methanol-d_4. The activation parameters for the C-5 methyl group of 1 were calculated to be $E_{act}= 28.7$ kcal/mol and log A= 12.76, while those for the methyl groups of 2-picoline and quinaldine were $E_{act}= 24.7$ kcal/mol; log A= 9.86 and $E_{act}= 20.8$ kcal/mol; log A= 9.77, respectively.[27] From these data, the C-5 methyl group of 1 is less reactive than those of 2-picoline and quinaldine.

2-4 The Effects of 4-Substituents

For the purpose of investigating the substituent effect on the reactivities of C-3 and C-5 methyl groups, the hydrogen-deuterium exchange reactions of 4-substituted 3,5-dimethylisoxazoles were carried out in methanol-d_4. The prepared compounds were 4-methoxyl- (3),[28] 4-methyl- (4),[29] 4-chloro- (5),[29] 4-iodo- (6),[30] 4-carbomethoxy- (7),[31] and 4-nitro-3,5-dimethylisoxazoles (8).[32] The results of these compounds, listed in

Table 3, show that the hydrogen-deuterium exchange was retarded by the electron-donating group at C-4 position of the isoxazole ring. However, the reactivity of C-5 methyl group is larger than that of C-3 methyl group and the C-5 methyl group was mainly deuterated in all of 4-substituted 3,5-dimethylisoxazoles.

Table 3.

Hydrogen-Deuterium Exchange Reaction Rates of 4-Substituted 3,5-Dimethylisoxazoles

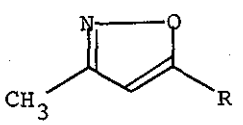
Substituent	Temp. (°C)	Reaction Rate (s^{-1}) 3-CH_3	5-CH_3
OCH_3	110.6	6.4×10^{-7}	1.3×10^{-5}
CH_3	110.6	4.1×10^{-7}	7.8×10^{-5}
H	110.6	1.2×10^{-6}	3.3×10^{-4}
	80.1	———	9.5×10^{-6}
Cl	80.1	———	5.5×10^{-4}
I	110.6	7.7×10^{-5}	8.0×10^{-3}
	80.1	———	9.4×10^{-4}
$COOCH_3$	34.2	———	2×10^{-3}

3. The Reaction with Electrophiles

3-1 The Alkylation [33]

Although 3,5-dimethylisoxazole (1) has three reaction sites in the electrophilic substitution reaction in the presence of bases, the results of deuterium exchange reaction of 1 show that 1 reacts with electrophiles regioselectively on C-5 methyl group. For determination of regioselectivity, 1 was treated with methyl

iodine in the presence of equimolar sodium amide in liquid ammonia. From the nmr spectrum data at δ 1.26, 2.18, 2.68 and 5.68 ppm, the reaction product is found to be 3-methyl-5-ethyl-isoxazole (9) which is identified by comparisons with authentic sample.[34] In this reaction, neither 3-ethyl-5-methylisoxazole nor 3,4,5-trimethylisoxazole can be detected at all by vpc and nmr spectrum. Similarly, 1 was treated with ethyl bromide, n-tropyl bromide, benzyl bromide and allyl bromide in the presence of sodium amide to give the corresponding products (10, 11, 12, and 13), alkylated on C-5 methyl group in good yields. Isopropyl bromide, one of the secondary alkyl halides, also gave 3-methyl-5-isobutylisoxazole (14). When butyllithium was used as the base in tetrahydrofuran, the alkylated products on C-5 methyl group was also obtained in good yield.[35]



9:	$R=CH_2CH_3$	14:	$R=CH_2CH(CH_3)_2$
10:	$R=CH_2CH_2CH_3$	15:	$R=CH(CH_3)_2$
11:	$R=CH_2CH_2CH_2CH_3$	16:	$R=C(CH_3)_3$
12:	$R=CH_2CH_2C_6H_5$	17:	$R=CH(CH_2C_6H_5)_2$
13:	$R=CH_2CH_2CH=CH_2$	18:	$R=CH(CH_3)CH_2CH_3$

For di- and tri-alkylation of the C-5 methyl group, the reaction of 1 with excess amounts of sodium amide and methyl iodide was tried. When 2 molar sodium amide and 2 molar methyl iodide were used, the products were 3-methyl-5-isopropyl- (15), 3-methyl-5-t-butylisoxazole (16) and 9. When 3 molar sodium amide and 3 molar methyl iodide were used, 9, 15 and 16 were also obtained. When 4 molar sodium amide and 4 molar methyl iodide were used, 16 was the sole product, and none of 9, 15, 5-ethyl-

5-t-butylisoxazole and 3,4-dimethyl-5-t-butylisoxazole could be detected by nmr spectrum and vpc. The product ratios in these reactions are summarized in Table 4. Similarly, 1 was treated with 2 molar sodium amide and 2 molar benzyl bromide to give a

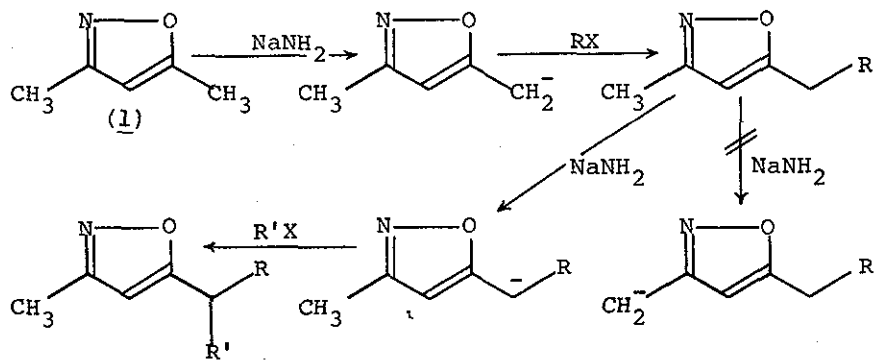
Table 4.

Product Ratios in the Reaction of 1 with Methyl Iodide

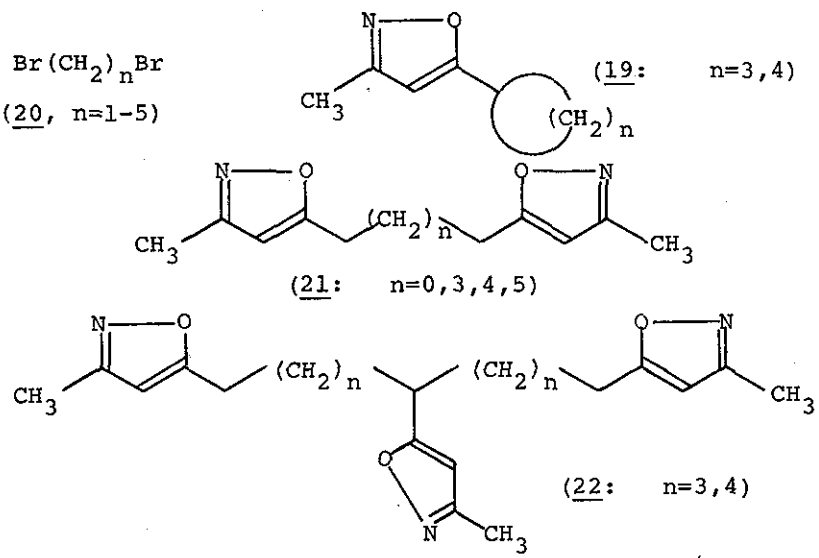
Molar Ratio			Total Yield	Product Ratio		
1	CH_3I	$NaNH_2$	(%)	9 %	15 %	16 %
1	1	1	58	100	0	0
1	2	2	68	33	57	10
1	3	3	59	9	62	29
1	4	4	51	0	0	100

dialkylation product, 3-methyl-5-(1,3-diphenyl-2-propyl)isoxazole (17). If two different alkyl halides are used in the presence of 2 molar sodium amide, 3-methyl-5-sec-alkylisoxazole might be obtained. When 1 was treated with methyl iodide followed by ethyl bromide, 3-methyl-5-sec-butylisoxazole (18) was obtained as well as 9, 10 and 15. These facts indicate that the di- and tri-alkylation reactions proceed in one step and could be controlled by the amount of sodium amide.

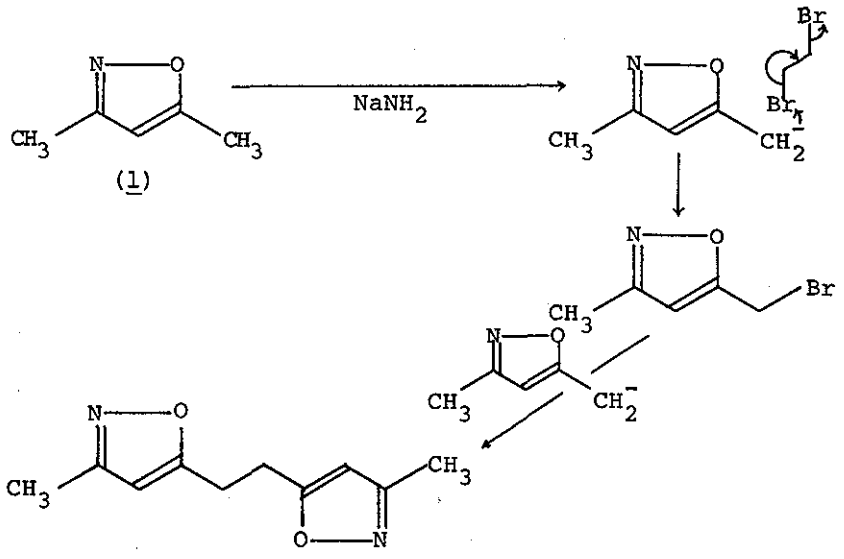
Thus, 3-methyl-5-cycloalkylisoxazoles (19) are expected in the case of α,ω-dibromoalkanes (20) and 1 in the presence of 2 molar sodium amide. When 1 was treated with a half molar α,ω-dibromoalkane (20, n=3,4,5), the corresponding α,ω-di(3-methyl-5-isoxazolyl)alkane (21, n=3,4,5) were obtained. When 1,3-dibromopropane (20, n=3) was treated with an equimolar 1



and 2 molar sodium amide, 1,5,9-tri(3-methyl-5-isoxazolyl)nonane (22, n=3) was obtained together with 21 (n=3), but no 3-methyl-5-cyclobutylisoxazole (19, n=3) was obtained. Similarly, 1,6,11-tri(3-methyl-5-isoxazolyl)undecane (22, n=4) was obtained from 1,4-dibromobutane (20, n=4) and 1, but no 3-methyl-5-cyclopentylisoxazole (19, n=4) was obtained.



In the case of 1,2-dibromoethane (20, n=2) with 2 molar 1 and sodium amide, the anomalous reaction product, 1,2-di(3-methyl-5-isoxazolyl)ethane (21, n=0), was obtained. When 1 was treated with sodium amide in liquid ammonia in the absence of 20 (n=2) followed by hydrolysis with ammonium chloride, the starting material was recovered. Thus 1,2-dibromoethane(20, n=2) apparently acted as an oxidative reagent in this anomalous reaction. Similar anomalous reaction was reported by Kofron.[36] That is, α-phenylacetonitrile dimerized to 1,2-diphenyl-1,2-dicyanoethane by the treatment with 1,2-dimethylbutane-1,2-dibromide in the presence of potassium amide in liquid ammonia. From these facts, the mechanism of this reaction of 1 with 1,2-dibromoethane to 21 (n=0) can be speculated as follows.

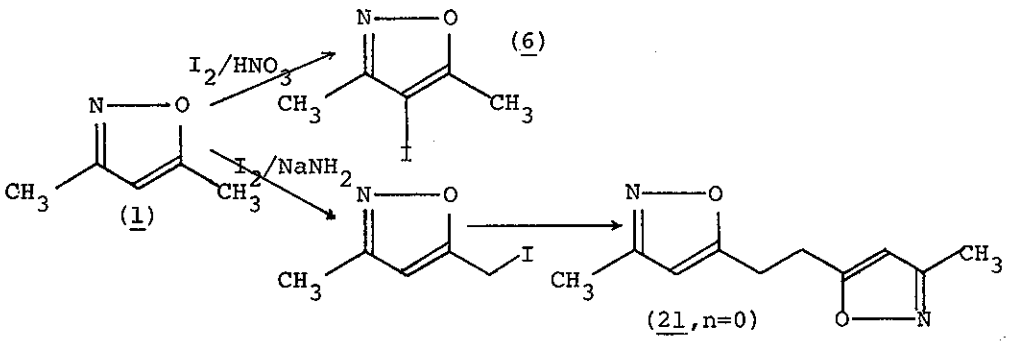


Thus, it is possible to alkylate the methyl group at the C-5 methyl group of 1 with sodium amide in liquid ammonia or butyllithium in THF. By di- and tri-alkylation reactions using

excess sodium amide in liquid ammonia, the isoxazole having secondary and tertiary alkyl groups at C-5 position can also be obtained regioselectively.

3-2 The Reaction with Iodine [35]

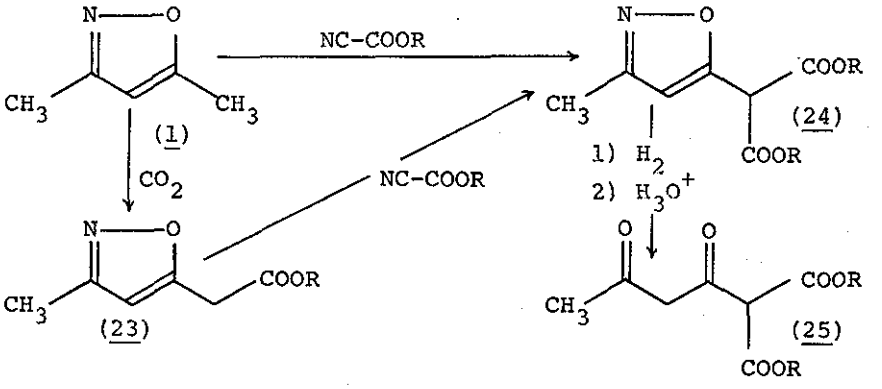
When 1 was treated with iodine in the presence of bases, 1,2-di(3-methyl-5-isoxazolyl)ethane (21, n=0) was obtained in good yield. In the presence of acid such as nitric acid, however, 1 was iodinated on C-4 position to give 3,5-dimethyl-4-iodoisoxazole (6).[30] Therefore, the mechanism of the oxidative coupling of 1 was speculated as follows. First, proton at C-5 methyl group of 1 was abstracted to give 3-methyl-5-isoxazolylmethyl carbanion (2-b), which is iodinated with iodonium cation. Second, the 3-methyl-5-iodomethylisoxazole was attacked with 2-b to give 21 (n=0).



3-3 The Carboxylation

The carbanion 2-b, prepared from 1 and butyllithium in THF, reacts with carbon dioxide to give 3-methyl-5-isoxazolylacetic acid (23) in good yield.[35] In the case of carboxylation with ethyl cyanoformate, mono-carboxylated product (23) can not be detected, and the product was found to be diethyl (3-methyl-

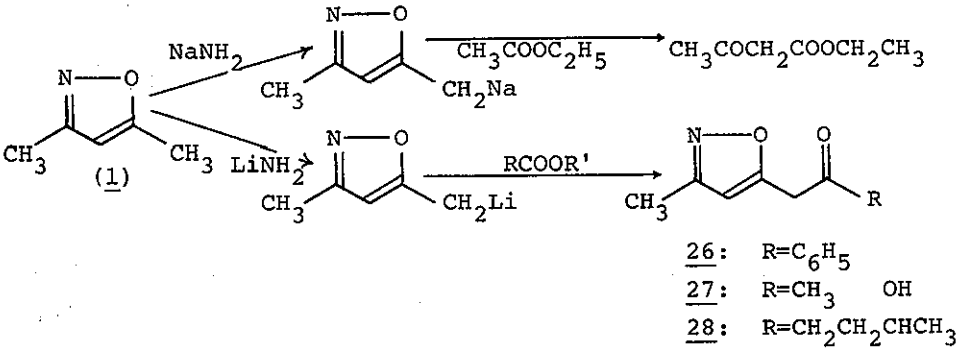
5-isoxazolyl)malonate (24).[37] These carboxylated isoxazole products were quite interested as the intermediates for the syntheses of poly-β-ketides. For example, 24 was hydrogenated and hydrolyzed to give ethyl 2-ethoxycarbonyl-3,5-dioxohexanoate (25).

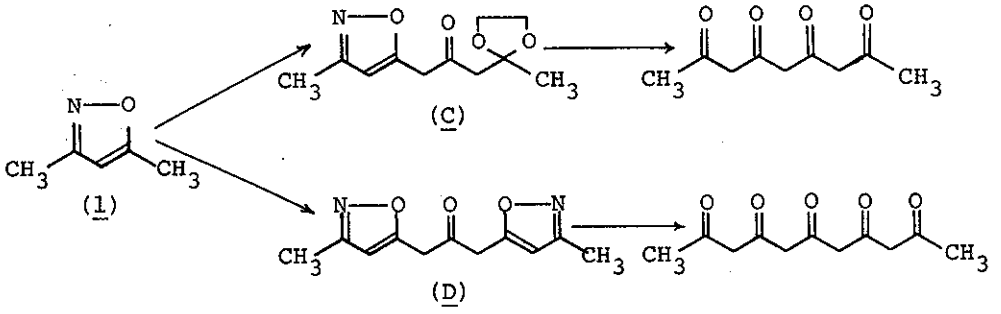


3-4 The Reaction with Carbonyl Compounds[38]

3-Methyl-5-(benzoylmethyl)isoxazole (26) was obtained by the reaction of 1 with methyl benzoate in the presence of sodium amide in liquid ammonia[38] or in the presence of butyllithium in THF.[35] Under the same conditions, 1 was treated with ethyl acetate. However, the expected product, 3-methyl-5-(2-oxopropyl)-isoxazole (27) could not be detected by vpc analysis. The sole product was identified as ethyl acetoacetate. This result suggested that sodium-hydrogen exchange occurred between the sodium salt of 1 and an active methyl of ethyl acetate. From the fact that lithium-hydrogen exchange is much slower than that of sodium-hydrogen,[39] it is expected that the lithium salt of 1 reacts ethyl acetate to give 27. Actually, a trace of 27 was obtained when 1 was treated with ethyl acetate in the presence

of butyllithium in THF. On the other hand, when lithium amide was used in liquid ammonia, 27 was obtained in a 40 % yield. No isomer of 27 could be detected by the vpc and nmr analysis. Also, 4-pentanolide with an active methylene, reacted with 1 to give 3-methyl-5-(5-hydroxy-2-oxohexyl)isoxazole (28). When the reaction of 1 with methyl 3-methyl-5-isoxazolylacetate[40] or ethyl 3,3-ethylenedioxybutyrate,[41] the key intermediate (C and D) for the synthesis of poly-β-ketide was obtained. From these results, the carbonyl compounds having an active methyl or methylene groups react with carbanion of 1 by the use of lithium amide in liquid ammonia.

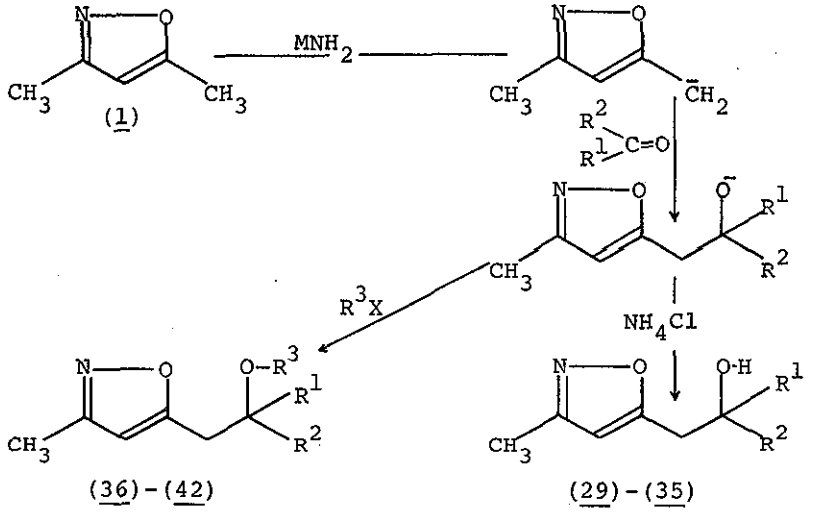




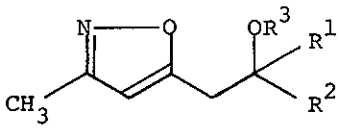
In the case of benzaldehyde, 1 gave 3-methyl-5-(2-hydroxy-2-phenylethyl)isoxazole (29) in the presence of sodium amide. The similar treatment of 1 with p-tolualdehyde, anisaldehyde,

and benzophenone gave the corresponding 2-hydroxy products 30, 31, and 32, respectively. In the presence of lithium amide instead of sodium amide, acetone, acetophenone, and cyclohexanone were also treated with 1 to produce the corresponding products, 33, 34, and 35. However, aliphatic aldehydes, such as butyraldehyde and acetaldehyde, did not still react with 1.

The mechanism of these reactions is speculated to be as is shown in the Scheme. Thus, if an oxide anion is treated with

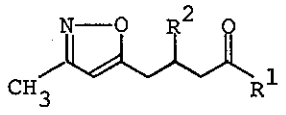


alkyl halides before neutralization, alkoxy derivatives are formed. The addition of methyl iodide to the mixture of 1, benzaldehyde, and sodium amide gave two products, namely, the expected alkoxy derivative, 3-methyl-5-(2-methoxy-2-phenylethyl)-isoxazole (36) and 29. Also, the alkylation with ethyl bromide, allyl bromide, and benzyl bromide gave the corresponding 2-alkoxy products 37, 38, and 39. Similarly, 40, 41, and 42 were prepared from p-tolualdehyde, anisaldehyde, and benzophenone, respectively.

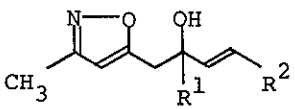


	R^1	R^2	R^3
29	C_6H_5	H	H
30	p-CH_3-C_6H_4	H	H
31	p-CH_3O-C_6H_4	H	H
32	C_6H_5	C_6H_5	H
33	CH_3	CH_3	H
34	C_6H_5	CH_3	H
35		$(CH_2)_5$	H
36	C_6H_5	H	CH_3
37	C_6H_5	H	CH_2CH_3
38	C_6H_5	H	$CH_2CH=CH_2$
39	C_6H_5	H	$CH_2C_6H_5$
40	p-CH_3-C_6H_4	H	CH_3
41	p-CH_3O-C_6H_4	H	CH_3
42	C_6H_5	C_6H_5	CH_3

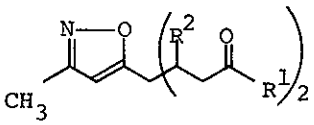
As an α,β-unsaturated carbonyl compound, chalcone was treated with 1. Two 1:1 addition products were found to be 1,3-diphenyl-3-hydroxy-4-(3-methyl-5-isoxazolyl)-1-butene (43) and 4-(3-methyl-5-isoxazolyl)-1,3-diphenyl-1-butanone (44). The treatment of butenone with 1 also gave two products, the 1,2-addition product 45 and Michael addition product 46. When 1 was treated with cinnamaldehyde, 1,2-addition product was obtained as well as trace amounts of a Michael addition product.



(A)



(B)



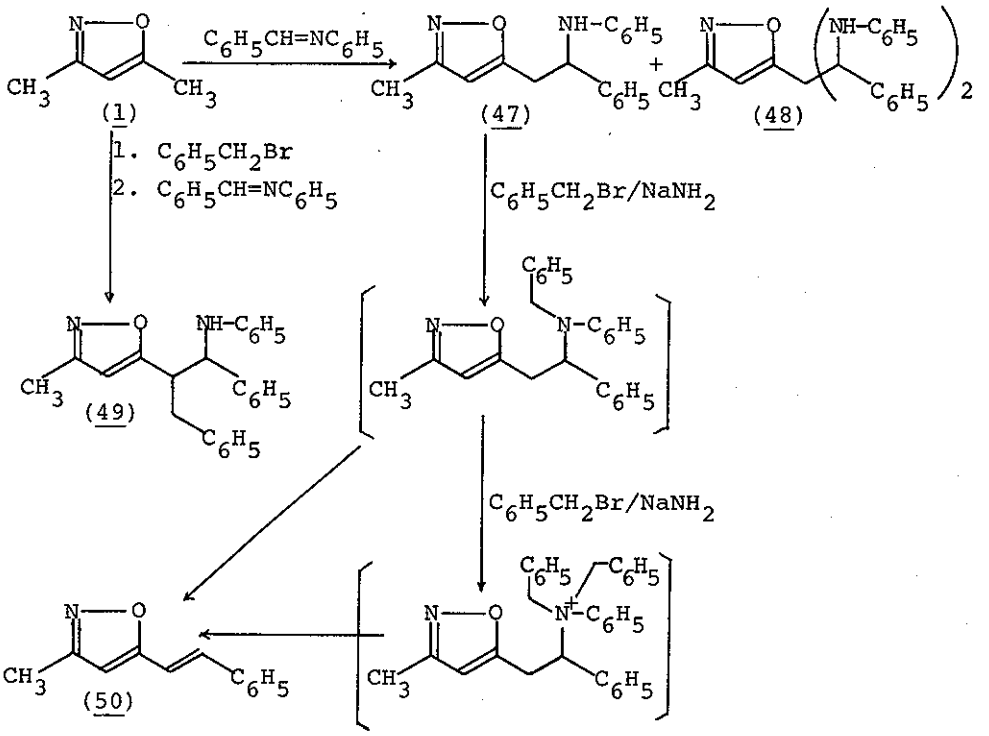
(C)

R^1	R^2	Yield of A	Yield of B	Yield of C
H	C_6H_5	trace	38 %	——
CH_3	H	8 % (46)	43 % (45)	——
C_6H_5	C_6H_5	11 % (44)	35 % (43)	——
OCH_3	C_6H_5	10 %	——	27 %
OH	C_6H_5	4 %	——	——

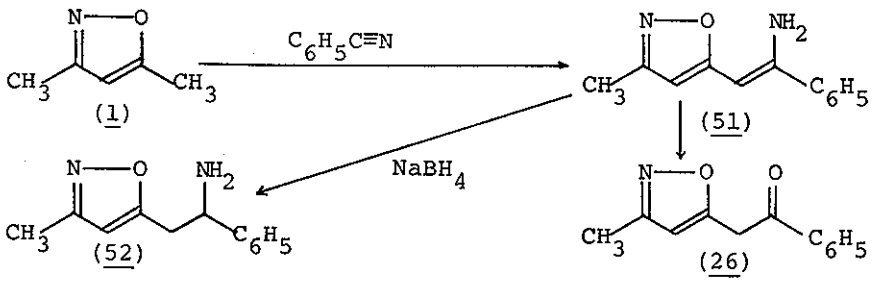
Similarly, 1 was treated with acrolein and crotonaldehyde to give the corresponding 1,2-addition products. In the case of methyl cinnamate, only a Michael addition product was obtained. These results show that the behavior of the anion of 1 is quite similar to the Grignard reagents.

3-5 The Reactions with Schiff Bases and Nitriles [42]

As one of the Schiff Bases, N-benzylideneaniline was treated with 1 in the presence of sodium amide to give 3-methyl-5-(2-anilino-2-phenylethyl)isoxazole (47) and 3-methyl-5-[2-(1,3-dianilino-1,3-diphenyl)propyl]isoxazole (48). Similarly, 1 was treated with N-benzylidene-p-toluidine and N,N'-bis(p-tolyl)-ethylenediimine to give the corresponding anilino derivatives. In the case of N-benzylidenebutylamine, 1 did not react under the condition of either butyllithium in THF or sodium amide in liquid ammonia. The reaction of 1 with benzyl bromide, followed by a reaction with N-benzylideneaniline, was carried out. By this reaction, 3-methyl-5-[2-(1-anilino-1,3-diphenyl)propyl]isoxazole (49) was obtained. However, the reaction of 1 with N-benzylidene-aniline, followed by a reaction with benzyl bromide, the expected product 49 was not obtained, and the product was found to be 3-methyl-5-styrylisoxazole (50). Similarly, the reaction products from 1, N-benzylideneaniline and ethyl bromide were found to be 48, N-ethylaniline, N,N-diethylaniline, and 50. These results suggested that the alkylation of 47 occurred on the N atom to give tertiary amines and quaternary ammonium compounds. However, these alkylated compounds were unstable in a basic solution and easily eliminate the amines to produce 50.

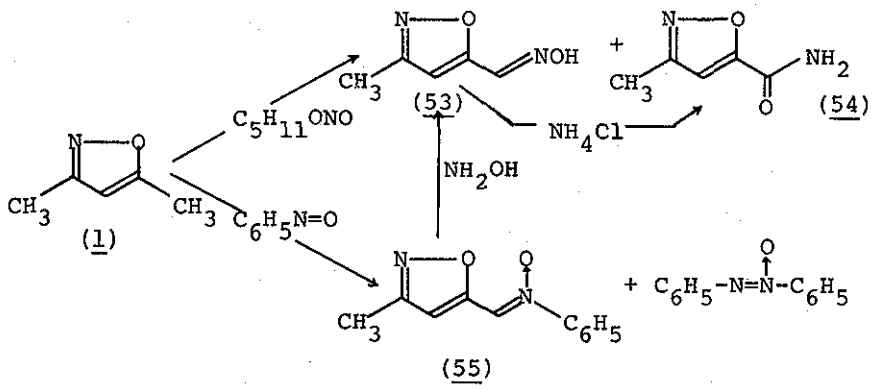


When the reaction mixture of 1 and benzonitrile was directly recrystallized from hexane-benzene mixture, 3-methyl-5-(2-aminostyryl)isoxazole (51) was obtained. Although 51 was easily hydrolyzed to 26 even by the silica gel chromatography,[35] 51 was reduced with sodium borohydride in methanol to give 3-methyl-5-(2-amino-2-phenylethyl)isoxazole (52).



3-6 The Reactions with Nitrites and Nitroso Compounds [43]

3,5-Dimethylisoxazole (1) upon treatment with amyl nitrite gave 3-methyl-5-isoxazolecarbaldoxime (53) and 3-methyl-5-isoxazolecarboxamide (54) in 19 and 15 % yield, respectively. In the case of the reaction with nitrosobenzene, 1 gave N-(3-methyl-5-isoxazolylmethylidene)aniline oxide (55) and azoxybenzene. Similarly, p-dimethylaminonitrosobenzene and 1 gave the corresponding p-dimethylamino derivatives.



4. Conclusion

Since 3,5-dimethylisoxazole (1), which is easily prepared from acetylacetone and hydroxylamine hydrochloride, is an unsymmetric five membered heteroaromatic compound, it is expected that two methyl groups of 1 are activated by bases, and also that the reactivities of two methyl groups differ from each other. From the results of calculation by MINDO/2 method and hydrogen-deuterium exchange reaction rate, 1 is concluded to be activated by bases regioselectively at C-5 methyl group. Actually, 1 reacts regioselectively with various electrophiles such as alkyl halides, iodine, carbon dioxide, carbonyl compounds,

Schiff bases, nitriles, nitrites and nitroso compounds. In connection with the transformation of isoxazole compounds into β-aminoenones, β-diketones, α,β-unsaturated ketones, isoxazolines, and isoxazolium salts, the regioselective synthesis of unsymmetric isoxazole derivatives is quite useful for the synthesis of various complex molecules such as terpenoids, steroids, alkaloids and others. Moreover, these isoxazoles having a various functional group would be interested in the medicinal chemistry as the antipyretic, antiinflammatory, analgestic, and antitussive substances.

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