RECENT ADVANCES IN THE CHEMISTRY OF 1,3-OXAZINES

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Abstract —— This review describes the advances reported since 1963 in the chemistry of single ring 1,3-oxazines, especially the syntheses and reactions of oxo-derivatives of 3,4-dihydro-2*H*-1,3-oxazine and 4*H*-1,3-oxazine.

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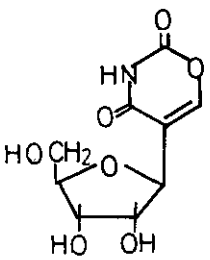
1. INTRODUCTION

The physical and chemical properties of pyrimidine, which is a representative of the class of six-membered heterocycles with two ring heteroatoms, are well known. Compared to pyrimidine, 1,3-oxazine, an isostere of pyrimidine, has until recently attracted little attention, mainly because most 1,3-oxazines have only marginal aromatic character and the ring system is much less important as a constituent of naturally occurring organic compounds.

The recent vigorous exploration for biologically and pharmacologically active compounds has found such activity in certain 1,3-oxazines and contributed to the development of 1,3-oxazine chemistry. For good example, oxazinomycin (minimycin) (1),[1-6] isolated from *Streptomyces tunashinesis*, and synthetic 2,3-dihydro-6*H*-1,3-oxazine-2,6-dione (2)[7] have antimetabolite activity in DNA biosynthesis, and reports concerning the synthesis and property of 1,3-oxazine (2) have increasingly been published.



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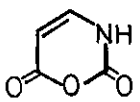

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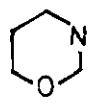
Scheme 1

Depending on the degree of saturation, the substituent-free 1,3-oxazine rings are classified as follows: tetrahydro-1,3-oxazine (I), dihydro-1,3-oxazines (II), 1,3-oxazines (III) and oxazinium salt (IV). Dihydro-1,3-oxazines (II) are conveniently divided into four subgroups according to the position of the double bond; 5,6-dihydro-2*H*-1,3-oxazine (or 5,6-dihydro-1,3,2-oxazine) (IIa), 5,6-dihydro-4*H*-1,3-oxazine (IIb), 3,4-dihydro-2*H*-1,3-oxazine (IIc), and 2,3-dihydro-6*H*-1,3-oxazine (IId). Similarly, 1,3-oxazines (III) are grouped into three types; 2*H*-1,3-oxazine (IIIa), 4*H*-1,3-oxazine (IIIb), and 6*H*-1,3-oxazine (IIIc).

Of these compounds, the tetrahydro derivatives (I) have often been prepared, chiefly for exploration of their biological activity. The two dihydro derivatives, 5,6-dihydro-4*H*- (IIb) and 3,4-dihydro-2*H*-1,3-oxazine derivatives (IIc), have long been well known. IIb has special interest as a potential precursor in a recent developed synthesis of aldehydes and ketones, which has been reviewed.[8-10] 4*H*-Derivatives (IIIb) have also been considerably investigated, and many papers concerning their syntheses and reactions have appeared. Also, oxazinium salts (IV) have become of interest because of their particular reactivity, as described in many recent reports.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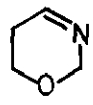
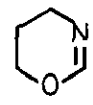

IIa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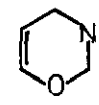
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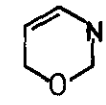
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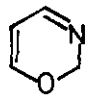
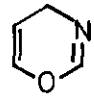
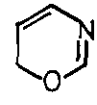

IIIa

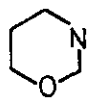

IIIb


IIIc


IV

Acknowledging that some excellent reviews have already been published,[11-13] this review concentrates its attention on the synthetically fascinating properties of single ring 1,3-oxazines, as developed since 1963, and especially on 4-oxo-derivatives (IIc) and IIIb which are easily available in our laboratory.

2. TETRAHYDRO-1,3-OXAZINES I

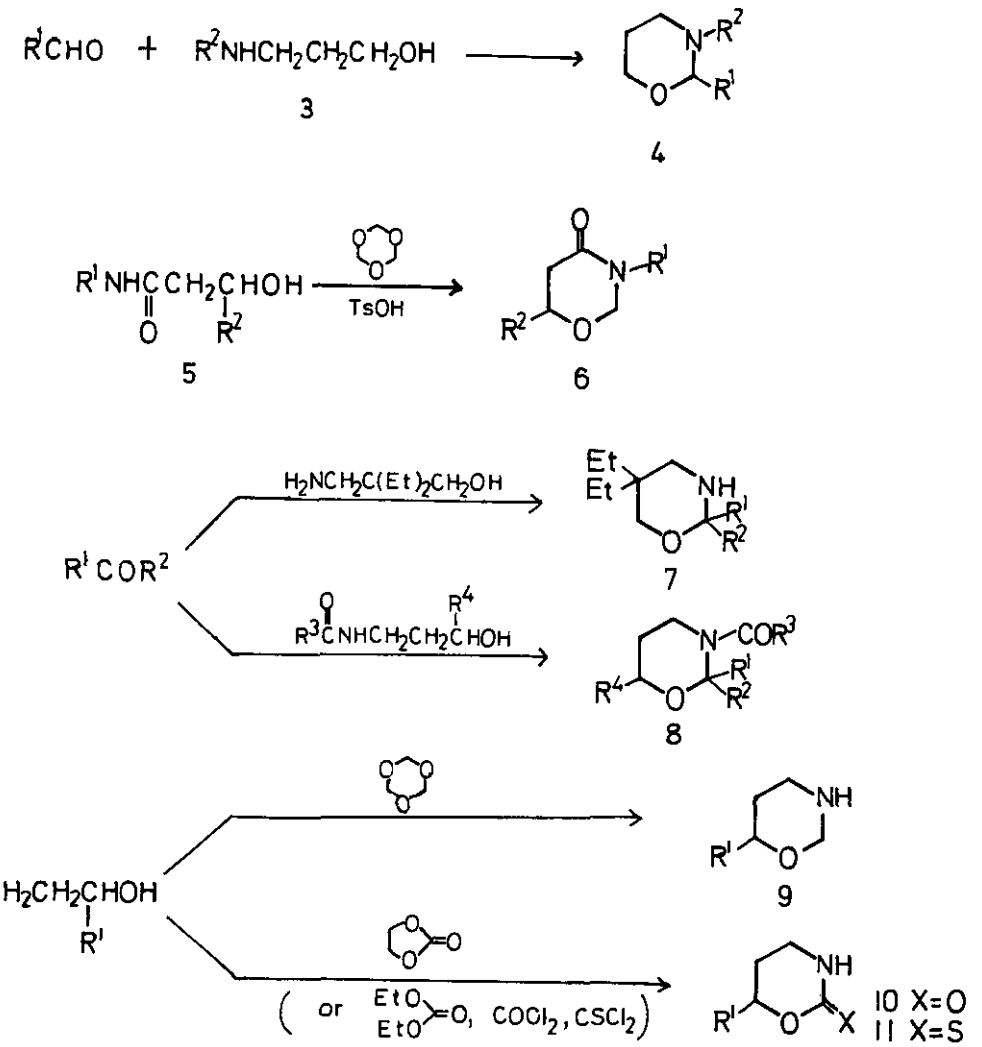

I

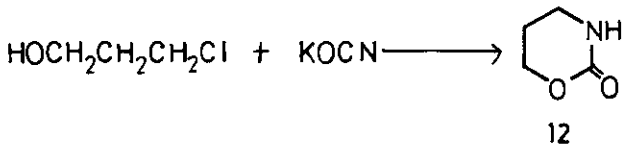
In 1963, Eckstein and Urbanski published a review regarding 1,3-oxazine, which mostly concerned tetrahydro-1,3-oxazine derivatives (including their oxo and dioxo derivatives).[12,217] Although tetrahydro-1,3-oxazines have long been familiar compounds, recent work with them has made significant contributions to the chemistry of 1,3-oxazine derivatives. Especially, many types of tetrahydro-1,3-oxazine have been synthesised in search for biologically or pharmacologically active compounds.

The most straightforward synthetic method for tetrahydro-1,3-oxazines (4) consists of the reaction of an aldehyde with 3-aminopropanol or a derivative thereof 3.[14-23]

Kametani *et al.* [24] obtained tetrahydro-1,3-oxazines (6) in good yield from the reactions of amide alcohols (5) with paraformaldehyde in the presence of acid as a catalyst. Ketones also react with 5 under the same conditions to give 2,2-disubstituted compounds.[25-27] Carbamate[28] and carbonate,[29-34] and phosgene[30-34] may be used in this reaction instead of aldehydes and ketones, furnishing 2-one derivatives (10). Likewise employment of thiophosgene[33] gives access to 2-thione derivatives (11).

Somewhat different in principle is the reaction of trimethylene chlorohydrin with potassium isocyanate to give tetrahydro-2*H*-1,3-oxazin-2-one (12).





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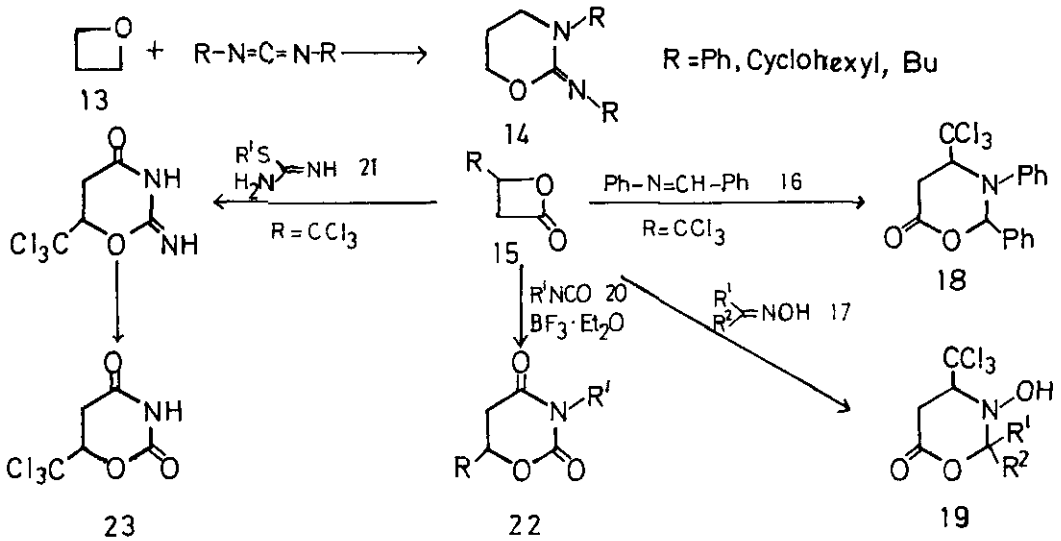
Scheme 2

Oxetane derivatives are often utilized in the preparation of 1,3-oxazines. For instance, oxetane (13) reacts with carbodiimides to give tetrahydro-1,3-oxazines (14).[35,36] Oxetanones (15) also add to a variety of C=N double bonds to give 4- or 6-oxo-tetrahydro-1,3-oxazines. In this case, different types of oxetanone ring cleavage (a; alkyl C-O cleavage, b; acyl C-O cleavage) result in a different products. For example, oxetanone (15, R = CCl_3) adds to the C=N double bond of Schiff base (16)[37] and of oxime (17)[38] by means of type a cleavage to give 6-ones (18) and 19, respectively. On the other hand, addition of 15 to isocyanates (20)[39] and *S*-alkylthioureas (21)[40] according to type b cleavage affords 2,4-diones (22) and 23, respectively.

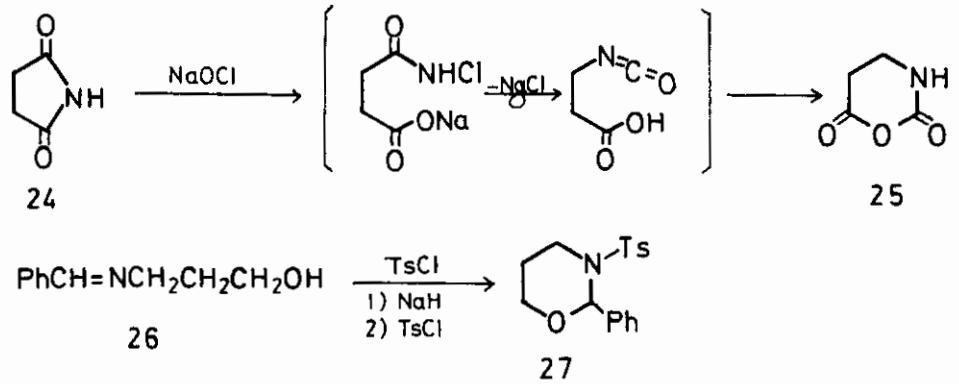


13 14 15 18 23 22 19

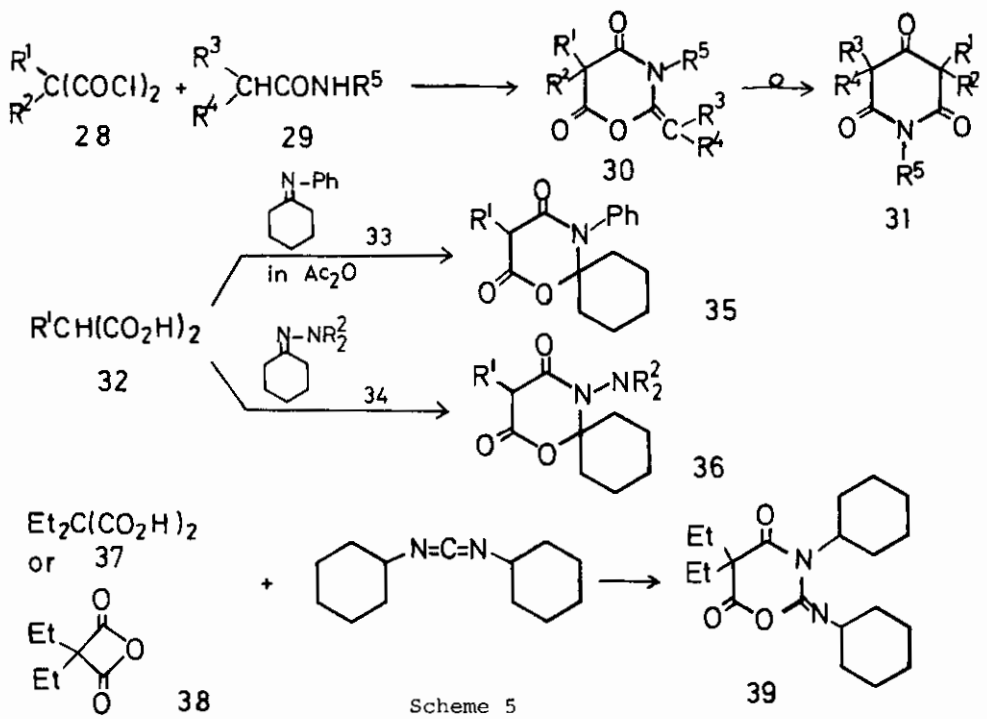
Scheme 3

When succinimide (24) is allowed to react with sodium hypochlorite (NaOCl), tetrahydro-1,3-oxazine-2,6-dione (25) is obtained.[41] In this reaction, the isocyanate generated by Hoffmann rearrangement is considered to be an intermediate. This reaction appears to proceed by the same mechanism as that of Rinkes' 2,3-dihydro-6*H*-1,3-oxazine-2,6-dione synthesis.[42]

Oxazine (27) is obtained from γ-hydroxyimine (26) in good yield.[43] Sodium hydride is an effective catalyst for this reaction.



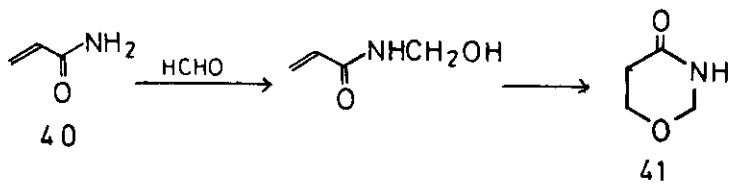
Scheme 4



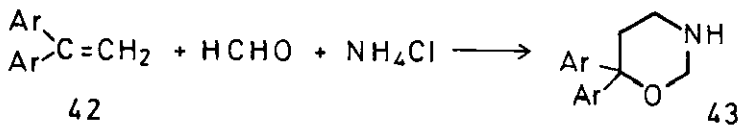
Scheme 5

Several 1,3-oxazine-2,6-diones have been synthesised from malonic acid derivatives. For example, reactions of malonyl dichlorides(28) with *N*-alkylamides (29) afford 2-alkylidene-2,6-dione derivatives (30), which are transformed into pyridone derivatives (31), by treatment with sodium methoxide.[44-46] Another approach is that of Ziegler *et al.*[47] who reported the synthesis of 1,3-oxazine-2,6-diones (35) and 36, possessing spiro structures, from the reaction of substituted malonic acids (32) with anil (33) and hydrazones(34) of cyclohexanone, respectively. Similarly, Resofszki *et al.*[48] obtained 39 from the reaction of diethyl malonic acid (37) or its anhydride (38) with carbodiimide.

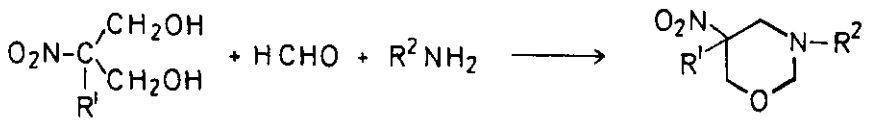
Formaldehyde is often utilized for the preparation of tetrahydro-1,3-oxazines without substituent at 2-position. For example, formaldehyde reacts with acrylamide (40)[49] and with ethylene derivatives (42)[50] to give tetrahydro-1,3-oxazine (41) and 43, respectively. Reactions of formaldehyde with 2-nitro-1,3-diols (44) in the presence of amines afford 5-substituted oxazine (45).[51-53] A variety of tetrahydro-1,3-oxazines possessing nitro group at 5-position can be synthesised by means of this method. Amino sugars, as amino derivatives, are sometimes used in this synthesis.[54] 4-Nitro-tetrahydro-1,3-oxazine derivatives (47, 48) are also obtained from the reaction of hexahydro-*s*-triazines (46) with nitro compounds.[55,56]



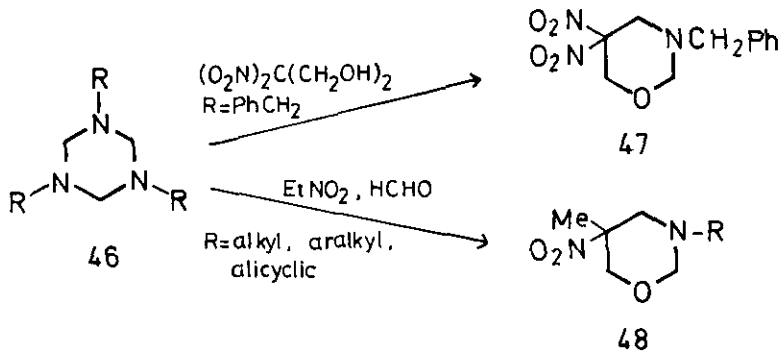
40 41



42 43



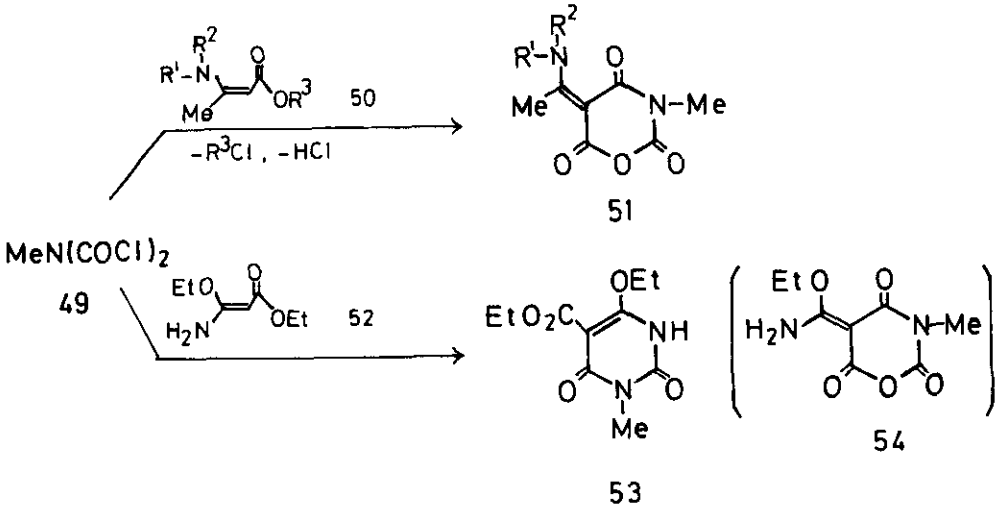
44 45

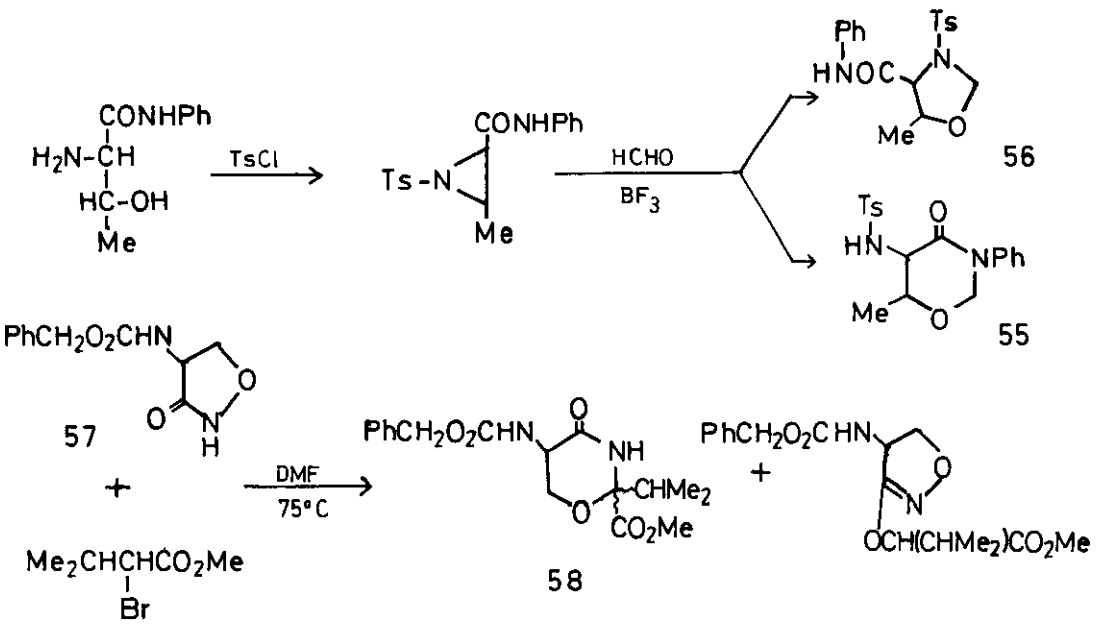


Scheme 6

Grohe *et al.*[57] have reported the synthesis of 1,3-oxazine-2,4,6-trione derivatives by a acylation-cyclization of β-amino esters. For instance, *N*-methylimino-dicarbonyl chloride (49) reacts with β-aminocrotonates(50) to give tetrahydro-1,3-oxazine-2,4,6-triones(51). When β-amino-β-ethoxyacrylate (52) is used, 54 is not isolated but pyrimidine-2,4-dione (53) obtained.

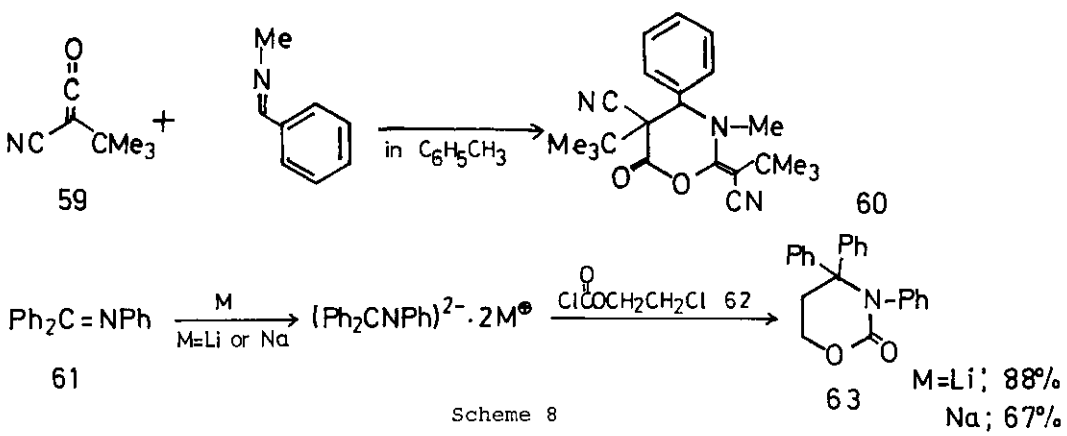
Synthesis of tetrahydro-1,3-oxazines (55) by reactions that open aziridine rings has been reported.[58] In this reaction, 1,3-oxazolidine (56) forms as a by-product. Cycloserine (57) was also transformed into tetrahydro-1,3-oxazine (58) by ring expansion.[59]





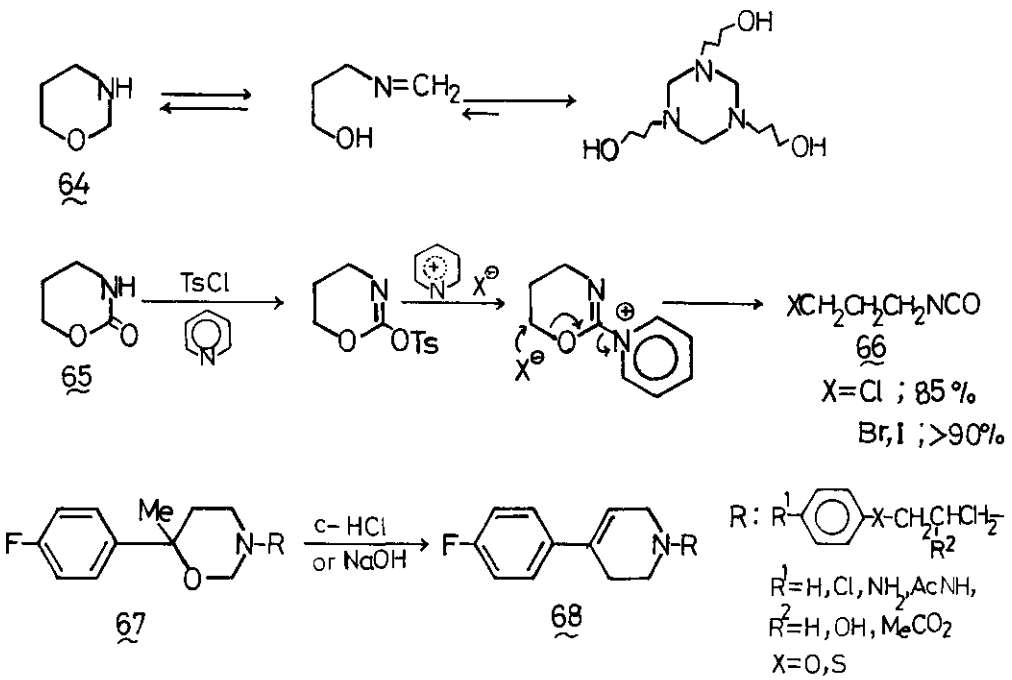
Scheme 7

Reactions of ketenes with imines can be conveniently utilized for the synthesis of 1,3-oxazines. Lusenko *et al.* [60] reported the reaction of *t*-butylcyanoketene (59) with *N*-benzylidenemethylamine to form tetrahydro-1,3-oxazine (60). Smith *et al.* [61] reported the synthesis of 2-one derivative (63) by metalation of imine (61), followed by treatment with 2-chloroethyl chloroformate (62).



Scheme 8

Though many reports concerning the synthesis of tetrahydro-1,3-oxazines are available, few publications dealing with the reactivity of these compounds are in hand. Tetrahydro-1,3-oxazine (64) has been reported to be transformed easily into its trimer by ring cleavage.[62] Kranz *et al.*[63] utilized 2-one derivative (65) in the synthesis of γ-halopropyl isocyanates. 6-Methyloxazines (67) are transformed into tetrahydropyridines (68) in the presence of acid or base as a catalyst.[64]



Scheme 9

3. DIHYDRO-1,3-OXAZINES II

As mentioned before, the 5,6-dihydro-1,3-oxazines are the best known of the four types of dihydro-1,3-oxazines.

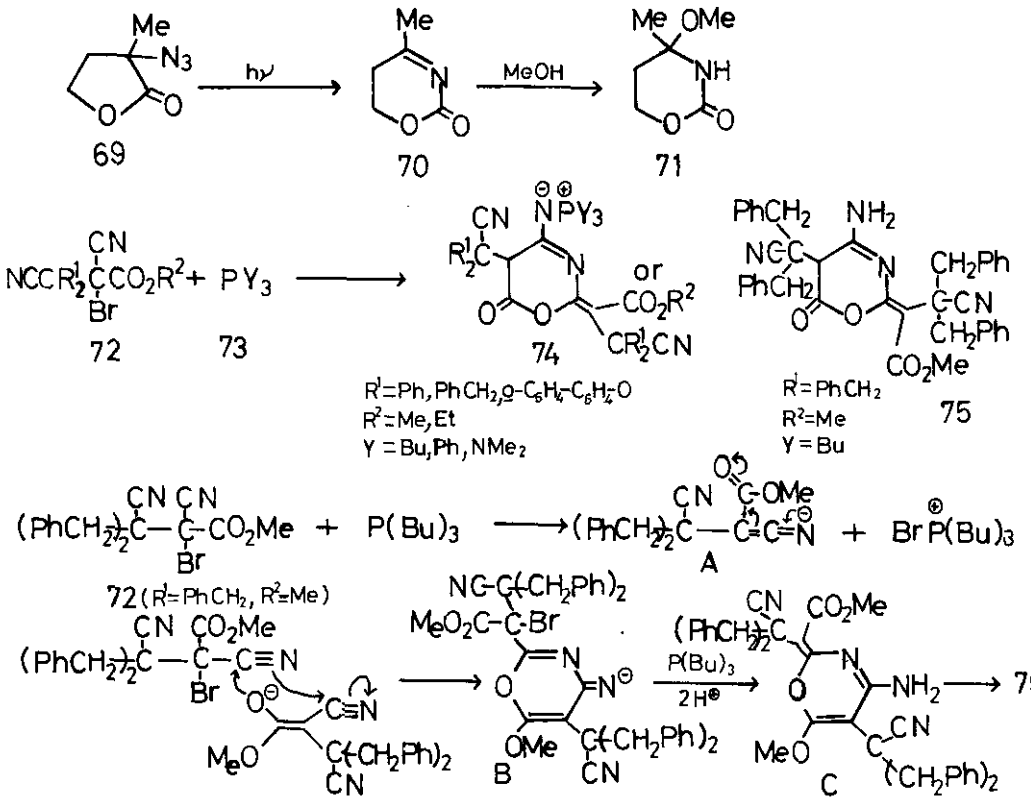
Recently, 3,4-dihydro-1,3-oxazines, especially as 4-oxo-derivatives, have become easily accessible.

3.1 5,6-Dihydro-2*H*-1,3-oxazines IIa

IIa

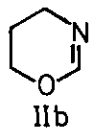
This type of compound was unknown for a long time. Recently, Edwards *et al.* [65] have achieved the synthesis of the 4-methyl-2-one derivative (70), which represents type IIa, by the photochemical Curtius rearrangement of γ-lactone azide (69). 70 is easily transformed into a tetrahydro-1,3-oxazine derivative (71) by addition of methanol. Foucaud *et al.* [66] have reported the reaction of 2-bromo-2,3-dicyanopropionates (72) with phosphines (73) to give 5,6-dihydro-2*H*-1,3-oxazines (74) or 75 in good yield.

The mechanism of formation of 75 could be speculated as follows: compound (72) initially reacts with phosphine (73) to give the intermediate (A), which adds to nitrile group of another molecule of 72 to afford (B). The intermediate (B) again reacts with phosphine (73) to give C. Demethylation of C gives compound (75).



Scheme 10

3.2 5,6-Dihydro-4*H*-1,3-oxazines IIb

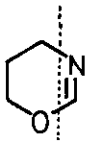


IIb

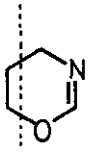
Type IIb oxazines are the most stable of the dihydro-1,3-oxazines, and many reports concerning their synthesis and reactivity have been published.

Especially, Meyers' synthesis of aldehydes and ketones using 5,6-dihydro-1,3-oxazines is noteworthy as a versatile synthetic method. Since Meyers' reaction has been ably reviewed,[9,10] the synthesis of type IIb oxazine is given principal attention in this Section.

Methods for synthesis of type IIb oxazine rings are classified into types a and b.



type α



type b

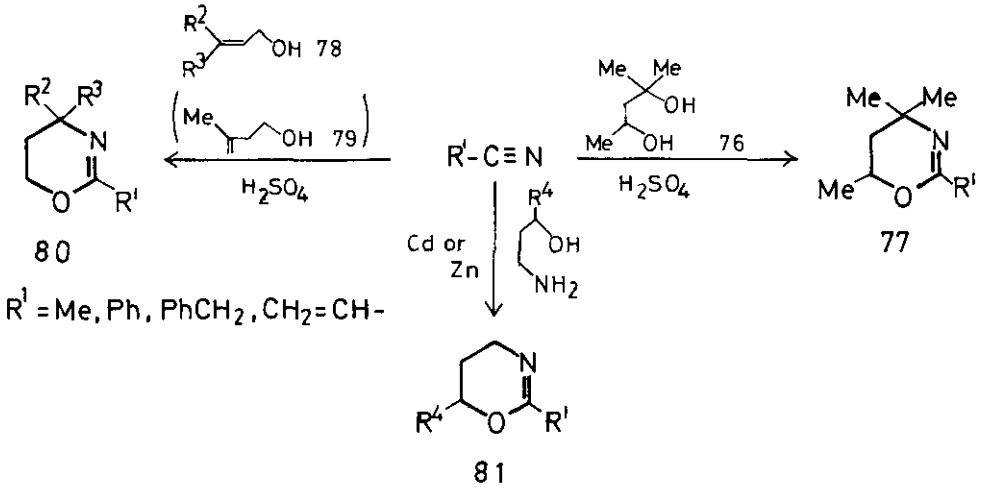
Both of them involve 2+4 cycloaddition reactions. The nonconcerted cycloaddition of appropriate 1,3-diols to nitriles, which is well known from many years ago, belongs to type a. Type b involves Diels-Alder cycloaddition of a 1,4-dipolar compound to an olefin, and has only recently been developed. As 1,4-dipolar compounds, acyl isocyanates and *N*-acylimines are mainly used.

The best representative of type a is the synthesis of oxazines (77) from 1,3-diol (76) and nitriles in the presence of sulfuric acid.[67-69] This reaction is used for the synthesis of intermediate in Meyers' aldehyde and ketone synthesis. Allyl alcohols (78) and 3-buten-1-ols (79) may also be used instead of a 1,3-diol.[70,71] 3-Aminopropyl alcohols react with nitriles to give 1,3-oxazines (81).[72] Metals such as Cd and Zn are effective catalysts in this reaction.[73]

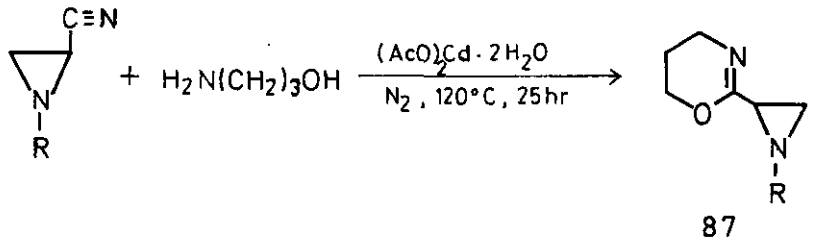
2-Cyanoaziridine derivatives also react with aminopropanol in the presence of cadmium acetate to give oxazine derivatives (87).[74]

Sasaki *et al.*[75] reported the synthesis of 2-ethynyl derivatives (84) by using RC≡CCN as a nitrile. Meschino *et al.*[76] obtained 2-amino-5,6-dihydro-1,3-oxazines (82) from the reactions of cyanogen bromide, a rather special nitrile, with 3-aminopropyl alcohol derivatives. Oxazine (82) ($R^1 = R^2 = H$) reacts with carbon suboxide to give pyrimidone (83).[77]

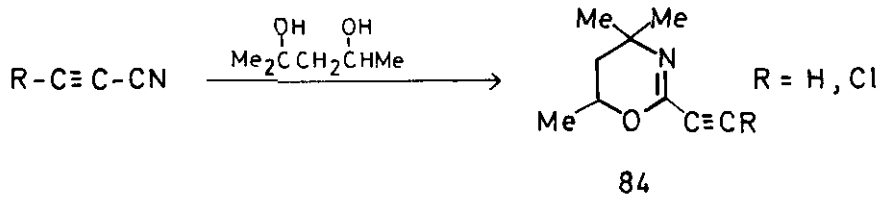
2-Vinyl-1,3-oxazine derivative (85) was synthesised from acrylonitrile *via* imido ester (86).[78]

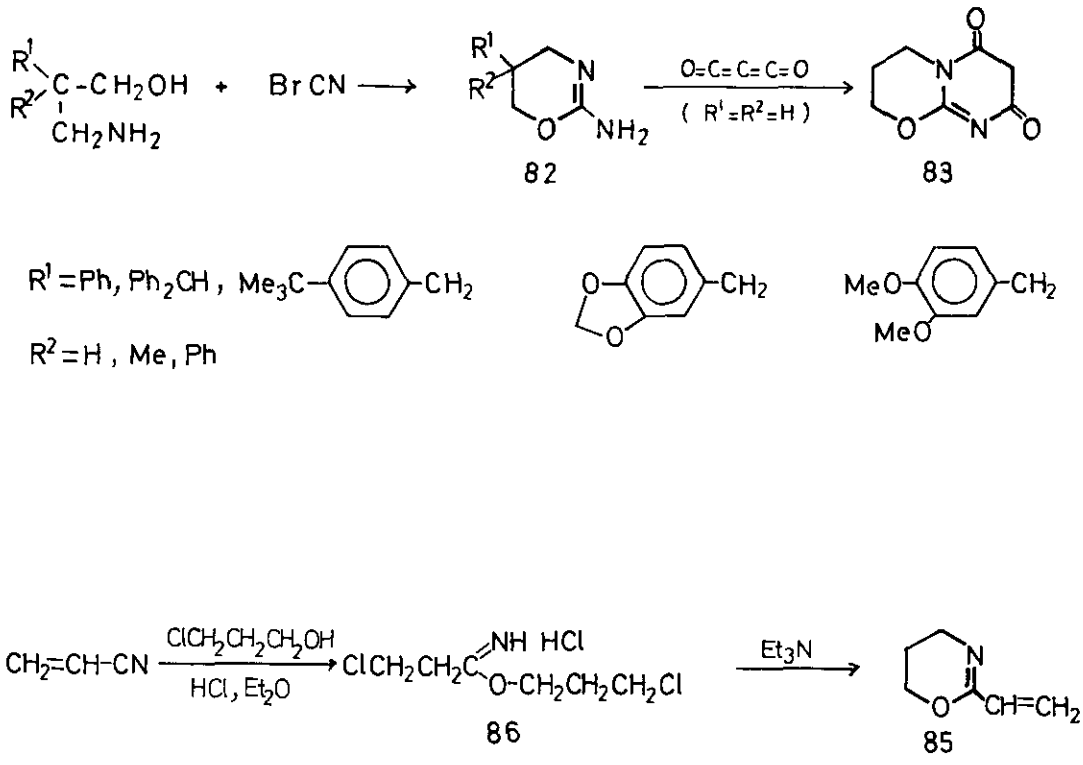


Scheme 11



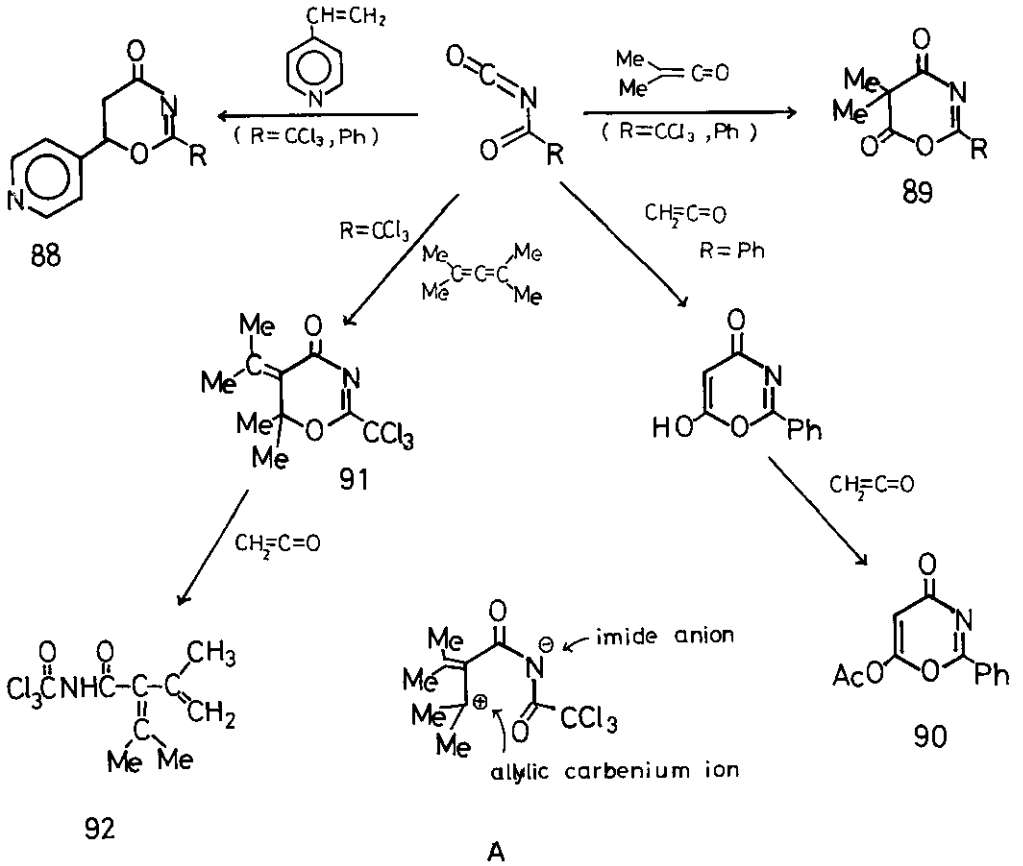
Scheme 12





Scheme 13

For type b syntheses, acyl isocyanates or *N*-acylimines are often utilized as the diene 1,4-dipolar reagent. Especially, 1,4-cycloaddition of acyl isocyanates to C=C double bonds is well known. Trichloroacetyl isocyanate and benzoyl isocyanate react with vinylpyridine to give 88.[79] Dimethylketene adds to acyl isocyanates giving 5,6-dihydro-1,3-oxazine-4,6-diones (89), but ketene itself affords 4*H*-1,3-oxazine (90), which is formed by acylation of the initial adduct, in an enol form, by a second molecule of ketene.[80] Similarly, acyl isocyanate reacts with tetramethylallene to form 91, which is transformed into 92.[81] This ring opening can be viewed as the ionization of a tertiary allylic ester to form a very favorable allylic carbenium ion and an imide anion (intermediate (A)), with ensuing proton transfer.

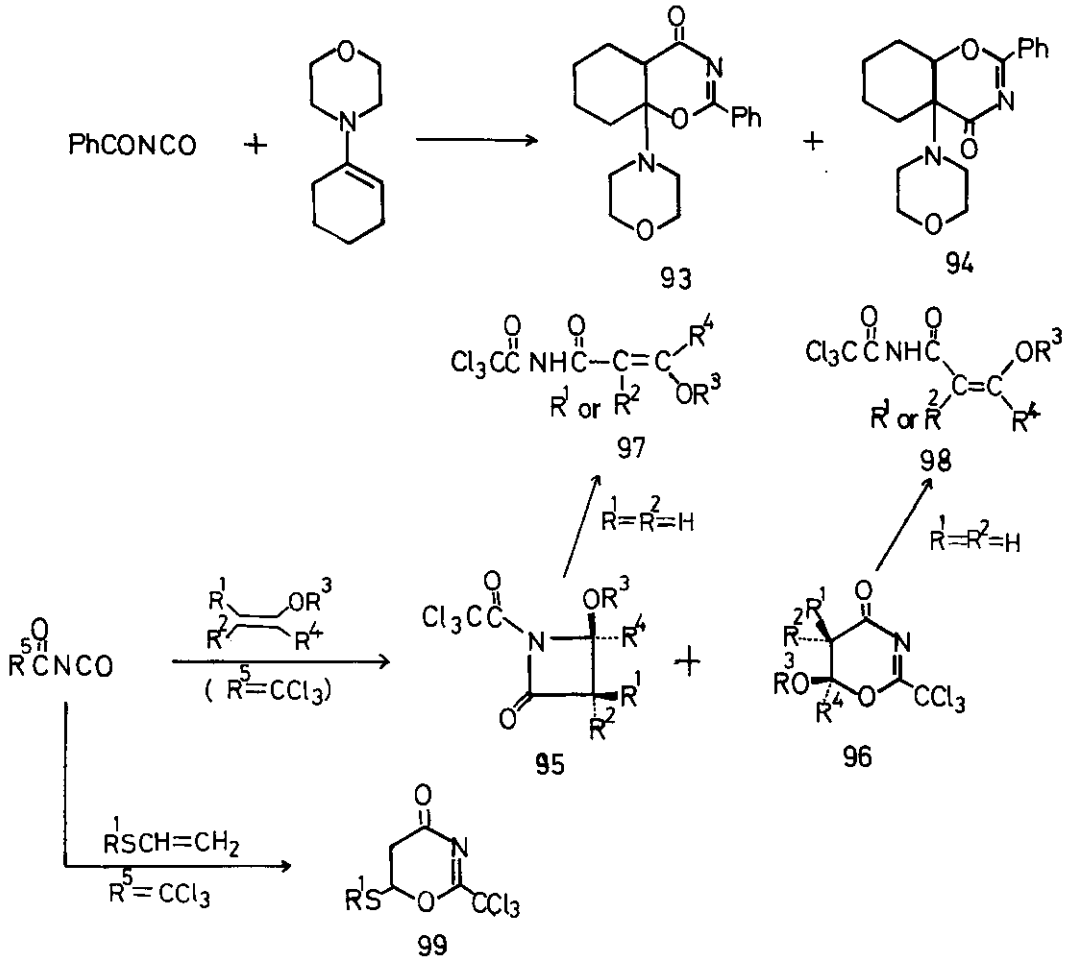


Scheme 14

Cycloaddition of acyl isocyanates to the C=C bond of enamines has also been reported. For example, benzoyl isocyanate reacts with 1-morpholino-cyclohexene, by 1,4-cycloaddition, to give two isomers, 93 and 94.[82]

1,2-Cycloaddition of trichloroacetyl isocyanate to vinyl ethers affords 2-azetidinones (95) and 1,3-oxazines (96).[83] These two compounds are generally unstable and are transformed into 97 and 98, respectively, again doubtless by ring-opening ionization.

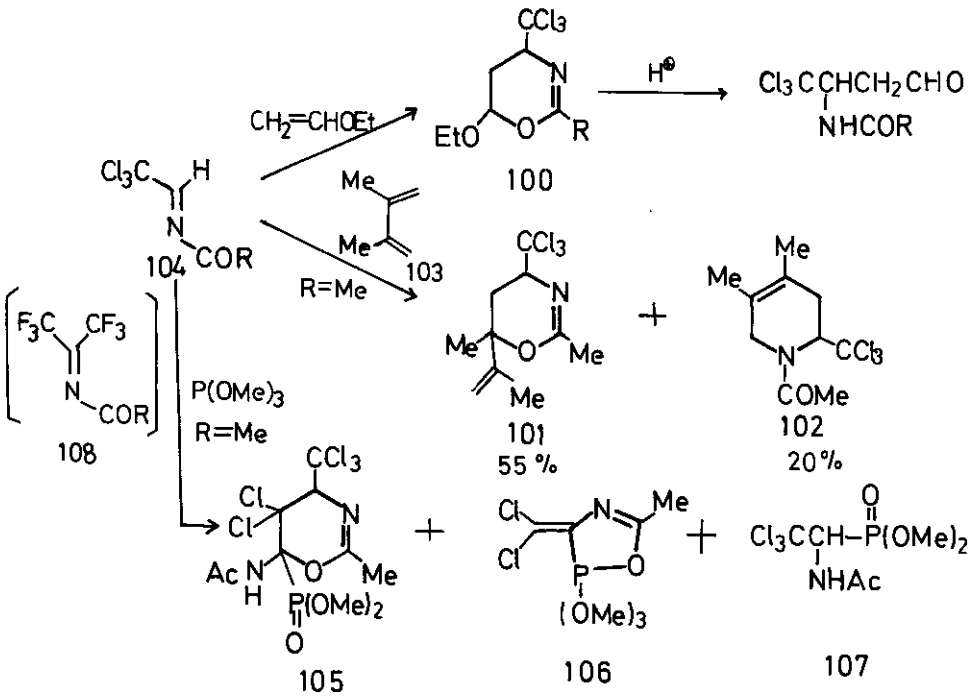
Dihydro-1,3-oxazines (99) were the sole products of the reactions of trichloroacetyl isocyanate with vinyl thioethers.[84]



Scheme 15

N-Acylimines of trichloroacetaldehyde, being activated by trichloromethyl group, possess strong 1,4-dipolar character, and their cycloadditions to vinyl ethers or diones have been investigated. For example, *N*-acylimines (104) react with vinyl ether to afford dihydro-oxazines (100).[85] When an *N*-acylimine reacts with 2,3-dimethyl-1,3-butadiene (103), either component can act as diene or dienophile, and both of the conceivable pathways are followed in part. Mainly, the *N*-acylimine acts as diene, giving oxazine (101). To a lesser extent, 103 acts as a diene, forming tetrahydropyridine derivative (102).[86] *N*-Acylimine (104: R = Me) reacts with trimethyl phosphite to give three products of 105, 106, and 107.[87]

Similar syntheses of 1,3-oxazines by the addition of perfluoroacylimines (108) instead of 104 have been reported.[88]

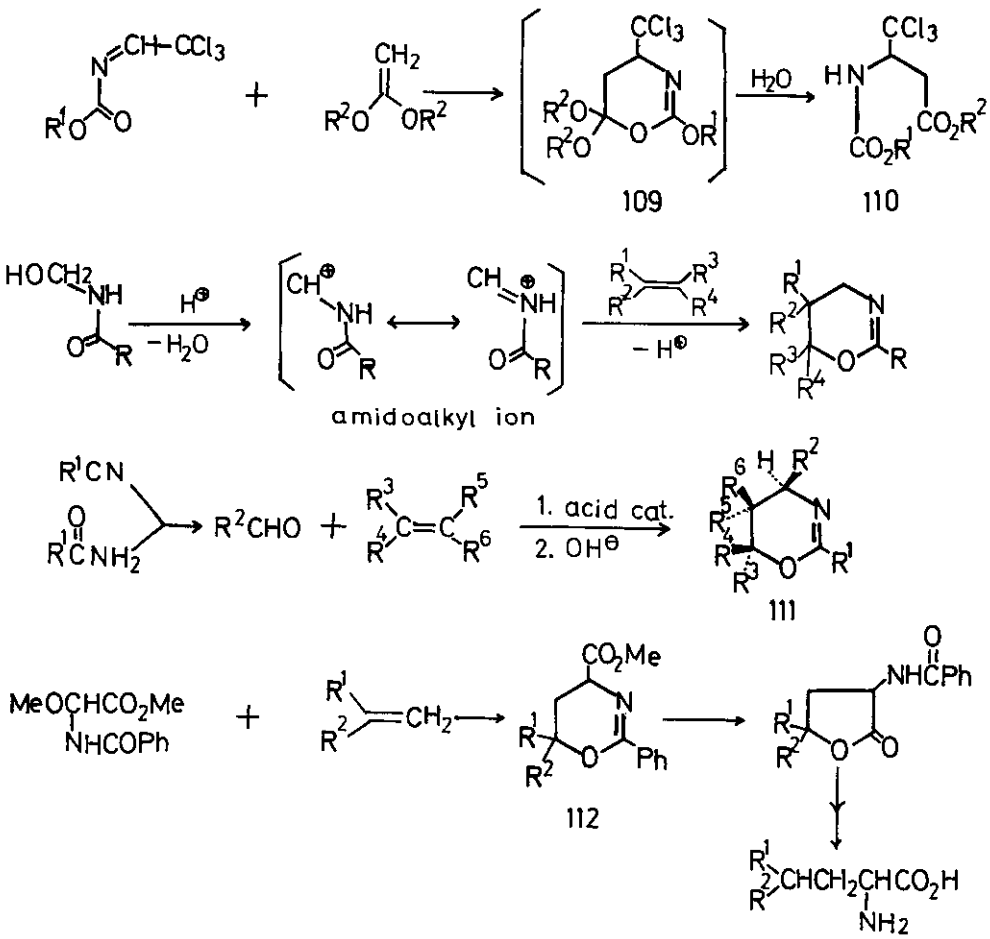


Scheme 16

Anhydrochloral urethane easily reacts with ketene acetals to give oxazines (109), which then undergo ring opening to give carbamate esters (110) in quantitative yield.[89]

The synthesis of an oxazine by cycloaddition of an amidoalkyl ion to an olefin is similar in principle to the acylimine cycloadditions. The amidoalkyl ion is derived by treatment of an *N*-hydroxymethylamide with acid (or by alkali treatment of an *N*-chloromethylamide). Seeligers' review[90] describes this reaction in detail. Giordano *et al.*[91,93-95] reported the reaction of amides (or nitriles) with aldehydes and olefins in the presence of acid catalyst to give oxazines (111). This reaction proceeds stereospecifically, regiospecifically and diastereogenically.

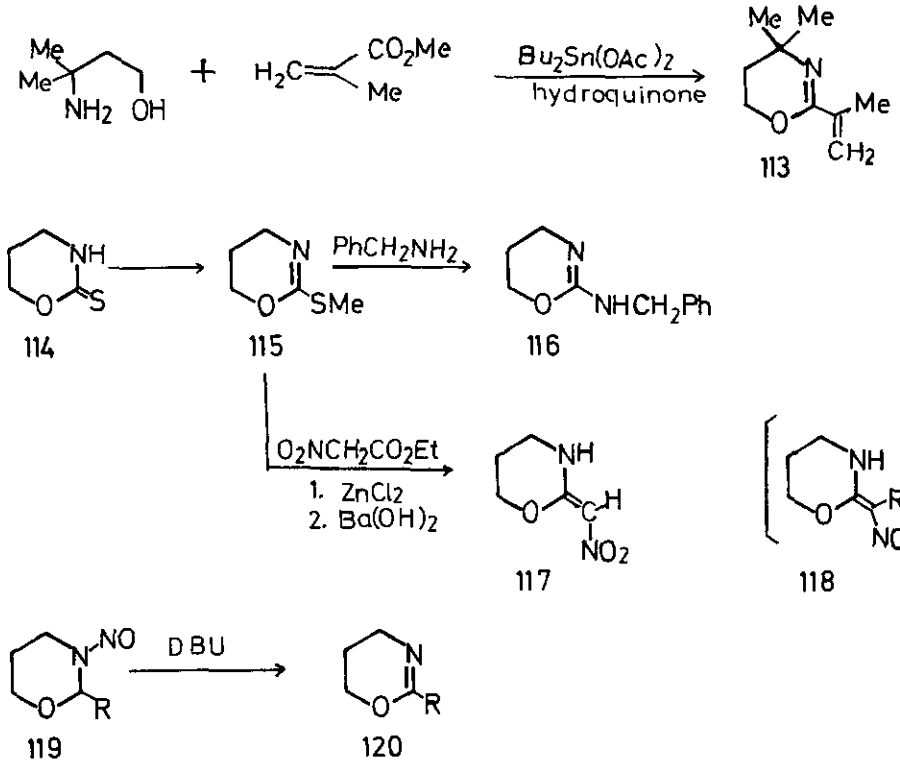
Ben-Ishai *et al.*[96] reported the synthesis of a variety of amino acids from oxazines (112) prepared by reactions of amides with olefins.



Scheme 17

1,3-Oxazine (113) is obtained when methyl methacrylate is allowed to react with 3-aminopropanol derivative in the presence of $Bu_2Sn(OAc)_2$. This synthetic approach is not concerned with both types a and b.[97] Some synthesis of 5,6-dihydro-1,3-oxazines by ring transformation method have been reported. Clapp *et al.*[98,99] obtained dihydro-1,3-oxazines (115) and 116 from tetrahydro-1,3-oxazine (114). An allied reaction is that of 115 with an active methylene compound to give tetrahydro-1,3-oxazines (117, 118).[100] Oediger *et al.*[101] reported the

synthesis of dihydro-1,3-oxazines (120) from *N*-nitroso-tetrahydro-1,3-oxazines (119).

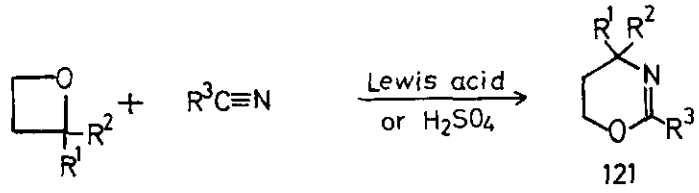


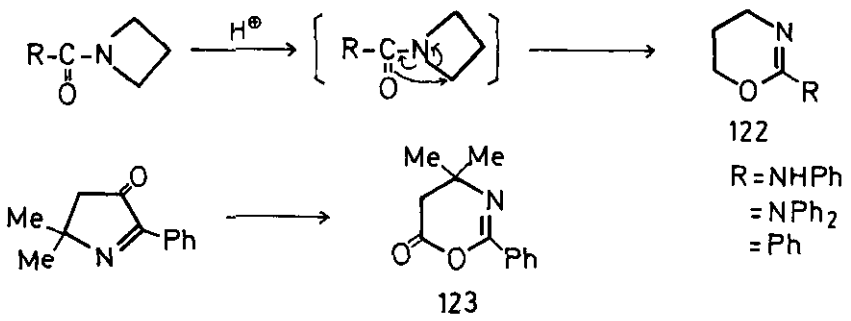
Scheme 18

Dihydro-1,3-oxazines (121) have been prepared by ring expansion of oxetane.[85,102-105] This synthetic method essentially belongs to category of type a.

It is well known that *N*-acylaziridines are transformed into isoxazolines by ring expansion. Under the similar fashion, *N*-acylazetidines are converted to dihydro-1,3-oxazines (122).[106]

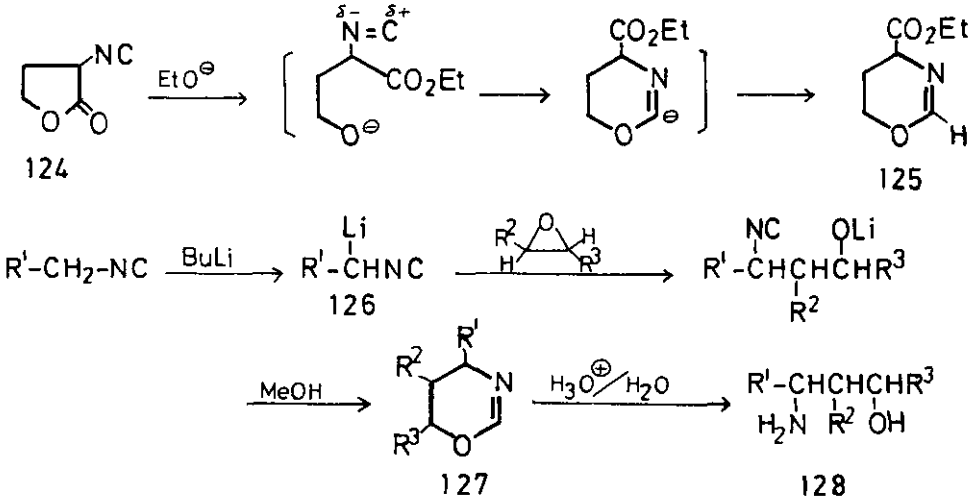
Ring expansion reaction of 3-oxo-1-pyrroline to oxazine (123) by oxidation with peracid, in an apparent Baeyer-Villiger oxidation, has also been reported.[107]

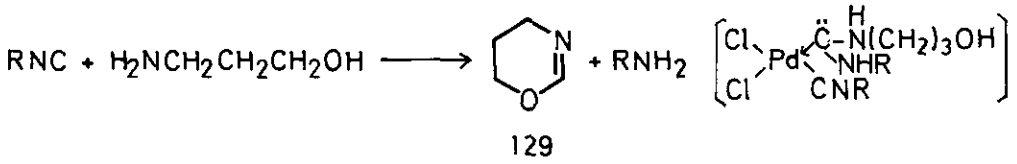




Scheme 19

Isonitriles are often used for the preparation of 1,3-oxazine without substituent at the 2-position. For example, Kraatz *et al.*[108] demonstrated that α-isocyano-γ-butyrolactone (124) undergoes ring expansion with sodium ethoxide to afford 1,3-oxazine (125). Isonitriles (126), metalated by butyllithium, react with epoxides to afford oxazines (127). This reaction is useful for the synthesis of γ-aminoalcohols since 127 is readily hydrolyzed with acid to give γ-aminoalcohols (128) in quantitative yield.[109] Saegusa *et al.*[110] obtained dihydro-1,3-oxazine (129) from the palladium-catalyzed reactions of isocyanides with 3-amino-1-propanol. In this reaction, metal-carbene complexes are considered to be reaction intermediates.

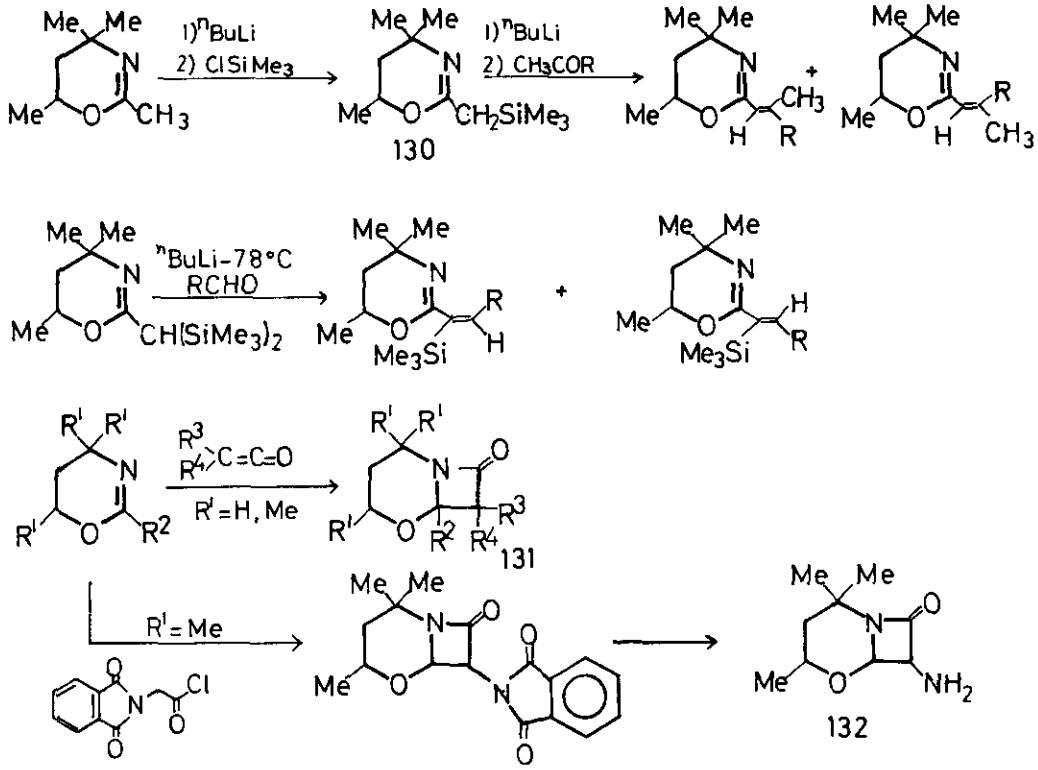




129

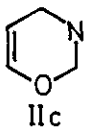
Scheme 20

As mentioned before, Meyers' synthesis of aldehydes and ketones is a well known synthetic reaction using dihydro-1,3-oxazines. Recently, Sachdev[111] has obtained 2-vinyloxazines stereoselectively from 2-silylmethyl-5,6-dihydro-1,3-oxazine (130).[112] Cepham analogs (131) have been synthesised by cycloaddition of ketene to 5,6-dihydro-1,3-oxazine.[113] The same oxazine reacts with phthaloylglycyl chloride in the presence of tertiary amine to form cepham analog (132) in a process that possibly involves a ketene intermediate.[114]



Scheme 21

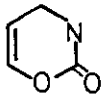
3.3 3,4-Dihydro-2*H*-1,3-oxazines IIc



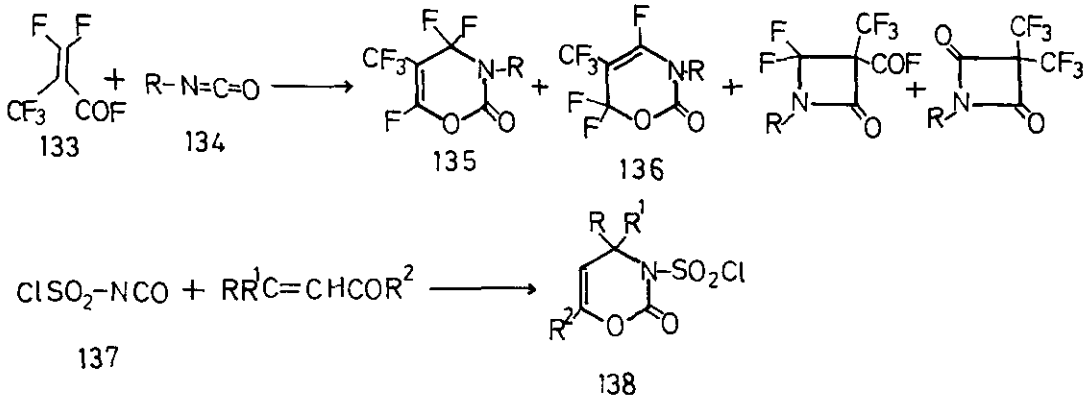
IIc

3,4-Dihydro-2*H*-1,3-oxazine itself is not recorded in the literature, but its oxo-derivatives are well known. Especially, a variety of 2,4-dione derivatives have been synthesised. Recently, 4-one derivatives have been easily obtained from diketene.[124]

3.3.1 3,4-Dihydro-2*H*-1,3-oxazin-2-ones

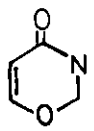


Only two examples of the preparation of this type of oxazine have been appeared in the literature. Perfluoromethacryloyl fluoride (133) undergoes [4+2] cycloaddition with isocyanates (134) to afford 3,4-dihydro-1,3-oxazin-2-ones (135). 2,3-Dihydro-1,3-oxazines (136), formed by anionotropic shift of fluorine, and two azetinone derivatives are also obtained from this reaction.[115] Similarly, the 1,4-cycloaddition of α,β-unsaturated ketones across chlorosulfonyl isocyanate (137) affords *N*-chlorosulfonyl-3,4-dihydro-2*H*-1,3-oxazin-2-ones(138).[116,117]

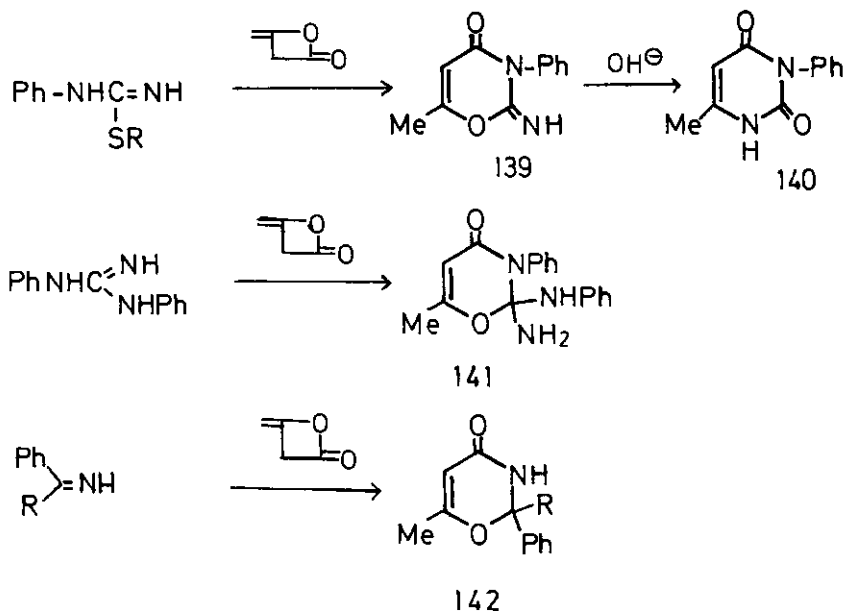


Scheme 22

3.3.2 3,4-Dihydro-2*H*-1,3-oxazin-4-ones

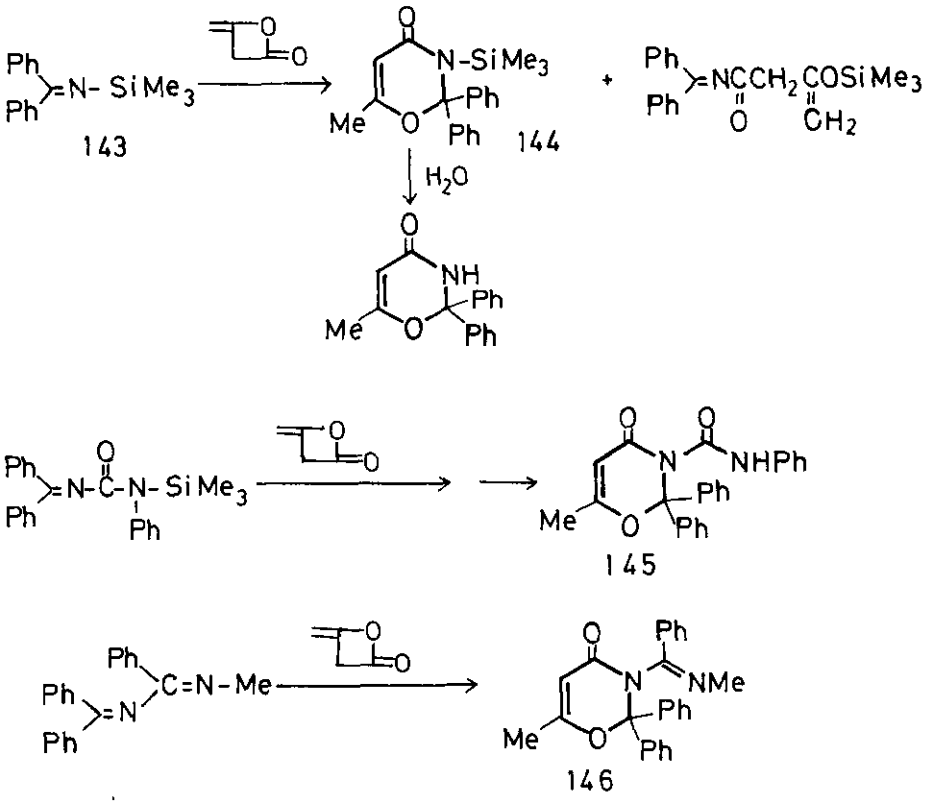


Diketene is the most versatile reagent for the preparation of oxazines of this type. It is well known that ethyl acetoacetate is an important synthetic precursor to *N*-heterocycles such as pyrimidines and pyridines.[124] Diketene, being an intramolecular anhydride of acetoacetic acid, is often used for the synthesis of pyrimidines. For example, diketene reacts with urea to give 6-methyluracil. On the other hand, Lacey[118] reported that reaction of diketene with *S*-alkylthioureas did not afford pyrimidine derivatives, but rather 1,3-oxazine (139), formed by cycloaddition of diketene to C=N bond, which on treatment with alkali was easily transformed into pyrimidine derivative (140). Similarly, guanidine derivative reacts with diketene to afford 1,3-oxazine (141).[118] The present authors[119] have observed that diketene undergoes 1,2-cycloaddition to the C=N double bond of ketimines to afford 1,3-oxazines (142) in good yields.



Scheme 23

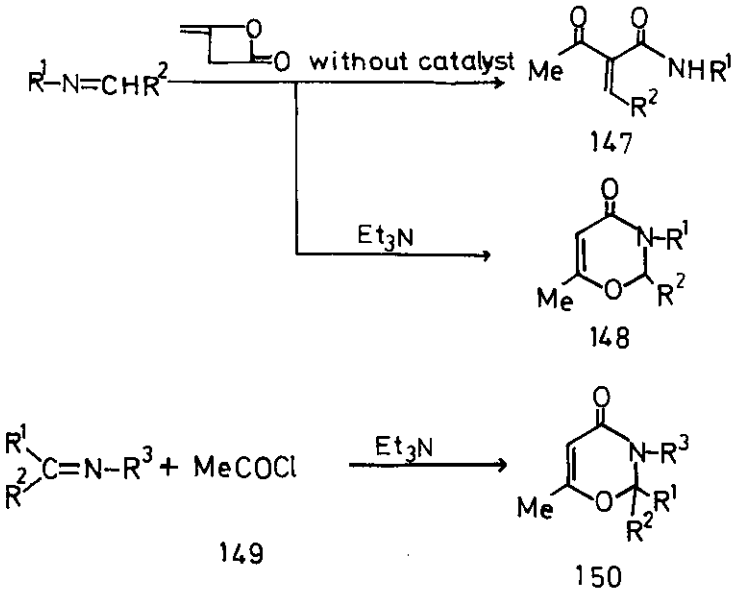
In the course of detailed and systematic investigations on organometallic compounds, Ishii *et al.*[120] observed that *N*-trimethylsilyl ketimine (143), similarly, reacts with diketene to form oxazine (144). *N*-Substituted oxazines (145) and 146 were obtained in the same fashion.



Scheme 24

Schiff bases react with diketene to afford 2-alkylideneacetoacetamides (147),[121] but in the presence of triethylamine oxazines (148) are obtained from this reaction.[122] On the other hand, reaction of Schiff bases with acetyl chloride (149) in the presence of triethylamine gives oxazines (150).[123] In this reaction, diketene would be formed by dimerization of ketene, generated from reaction of acetyl chloride with triethylamine. Probably, oxazines (150) would be formed by

1,4-cycloaddition of Schiff bases to diketene.

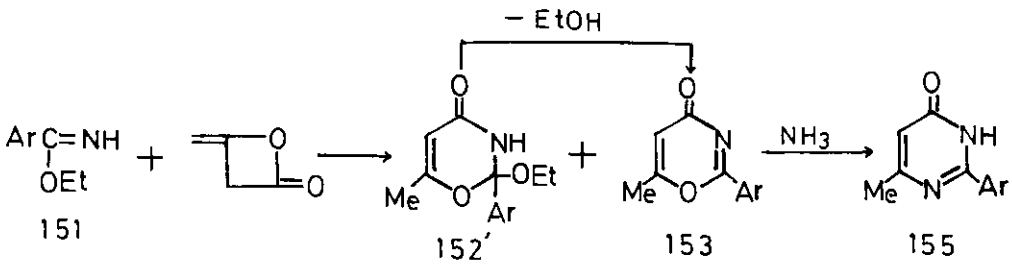


Scheme 25

The present authors demonstrated that diketene undergoes cycloaddition with the C=N double bond of imido esters to afford 1,3-oxazines, which possess unique reactivities different from those of other types of 1,3-oxazines. The synthetic method involves two advantages:

i) Imido esters are easily available from nitriles, and ii) 1,3-oxazines possessing a variety of substituents at the 2-position can be synthesised.

Both aliphatic (154) and aromatic imido esters (151) react with diketene to afford 3,4-dihydro-2*H*-1,3-oxazin-4-ones (152') and 152, respectively.[121,125] As shown in Table 1, in the case of aromatic imido esters compound (153) is also obtained as by-product. In the cases of 2-pyridyl and 2-quinolyl derivatives, compounds of type 152' were not isolated and compounds(153) were the sole product. 152' is easily transformed into 4*H*-1,3-oxazin-4-one (153) by elimination of ethanol. Both 152' and 153, on treatment with ammonia, are transformed into pyrimidones (155).



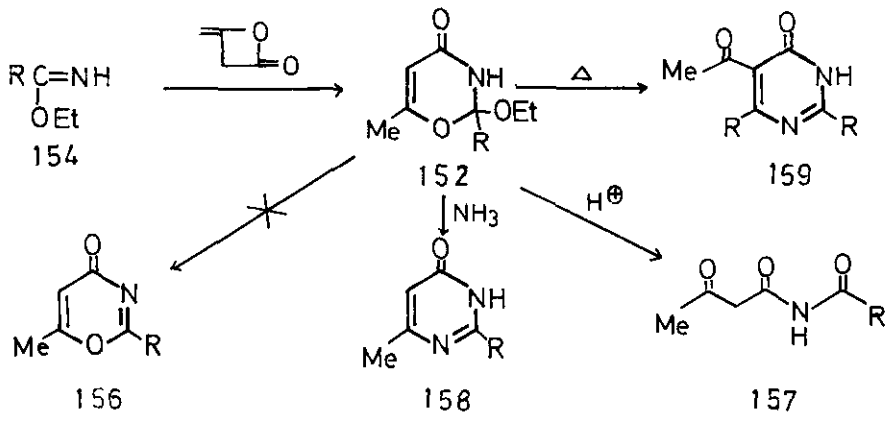
Scheme 26

Table 1.

	Ar	152'	153	155
a	Ph	21%	16% (81)	60%
b	2-Py	——	13% (41)	67%
c	3-Py	33%	31%*	25%
d	4-Py	40%	35%*	18%*
e	2-Qu	——	30% (49)	71%

* Yield is based on oxazine (152').
The yield shown in parenthesis is based on imido ester (151), and was obtained by the improved procedure.

In contrast, 1,3-oxazines (152) obtained from aliphatic imido esters (154) hardly eliminate ethanol, and transformation of 152 into 156 also fails to occur. Compounds of type 152 tend to be easily hydrolyzed to afford *N*-acylacetoacetamides (157). On treatment with ammonia, they afford pyrimidones (158). On heating oxazines of type (152), self condensation occurs to afford 5-acetylpyrimidones (159). Although the mechanism of this reaction is obscure, the formation of 159 can be explained as shown in Scheme 27 (2); heterolytic ring opening of 152, accompanied with elimination of ethanol, would give 160, which would self-condense to form 159.

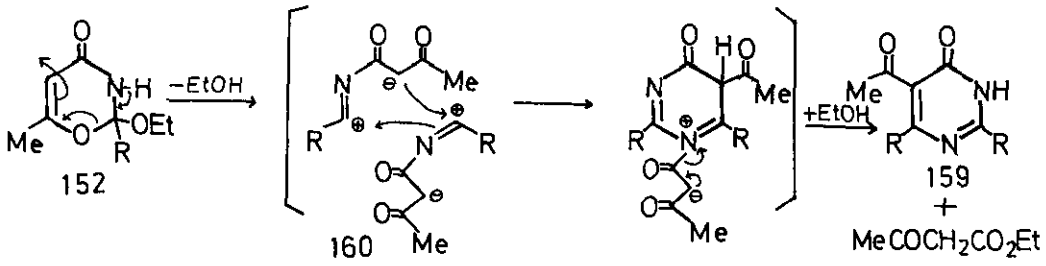


Scheme 27 (1)

Table 2.

	R	152	159	157	158
a	methyl	63	65	78	60
b	ethyl	91	81	60	89
c	isopropyl	93	65	63	97
d	benzyl	55*	64	72	43

* By using the improved procedure, oxazine (152d) was obtained as sole product in *ca.* 70% yield.

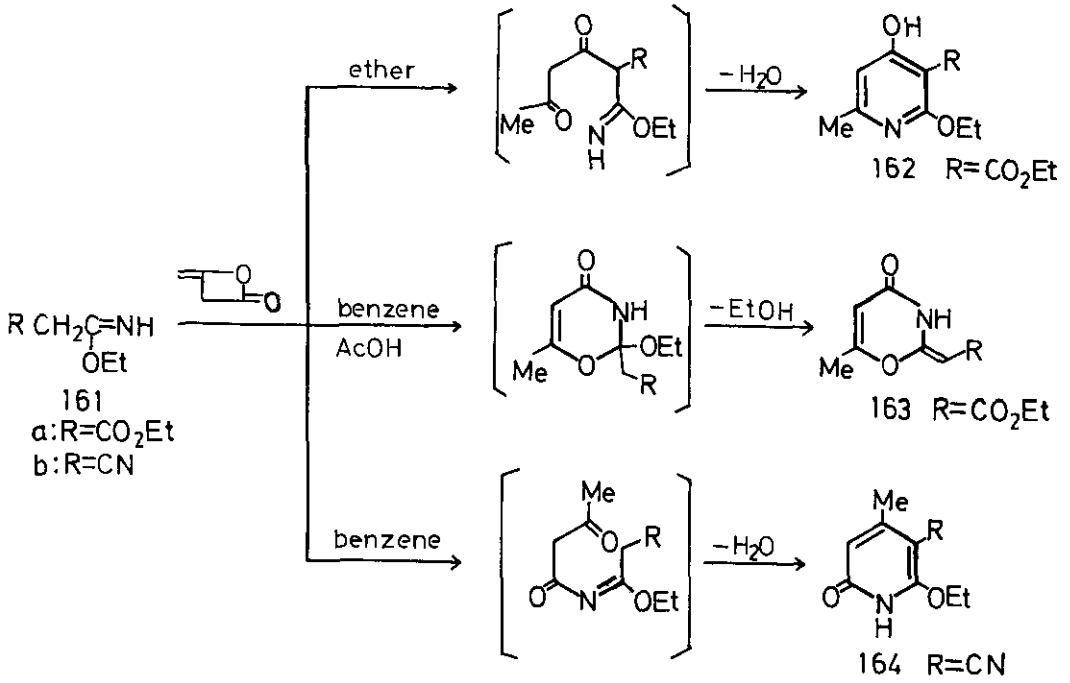


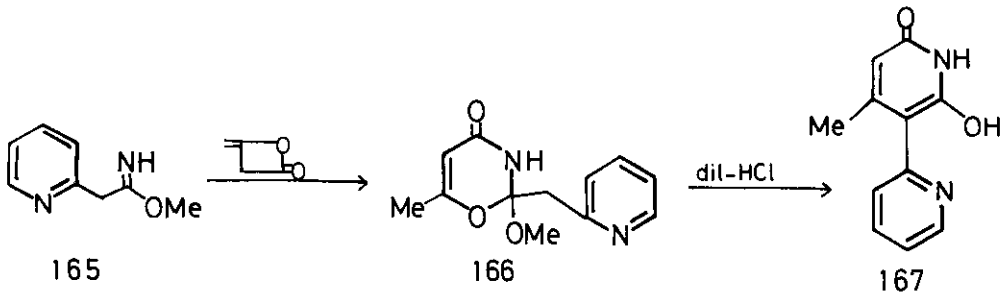
Scheme 27 (2)

Reactions of diketene with imido esters possessing active methylene groups are complicated, and do not always give 1,3-oxazines.[126] For example, ethyl ethoxycarbonylacetimide (161a) reacts with diketene in ether to afford pyridine derivative (162) while the reaction in benzene in the presence of a catalytic amount of acetic acid gives 1,3-oxazine (163). However, a 1,3-oxazine is not obtained from the reaction of diketene with ethyl cyanoacetimidate (161b), but rather pyridone derivative (164) is obtained as sole product.

Reactions of diketene with imido esters such as methyl 1-(2-pyridyl)acetimidate (165) do not give pyridone derivatives, but instead dihydro-1,3-oxazines (e.g., 166) in good yield.[126] 166 is transformed into pyridone derivative (167) by treatment with acid.

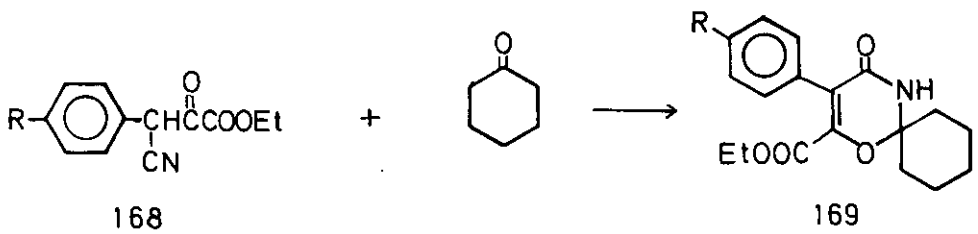
It is of interest that the reactivity of diketene toward imido ester is dependent on the structure of the utilized imido ester, so that a variety of products could be obtained using different types of imido ester.





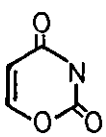
Scheme 28

A type of oxazine possessing a spiro structure was synthesised by Cordier *et al.*[127] They obtained oxazines of type 169 from the condensation of β-cyano-α-keto acid derivatives (168) with cyclohexanone.



Scheme 29

3.3.3 3,4-Dihydro-2*H*-1,3-oxazine-2,4-diones



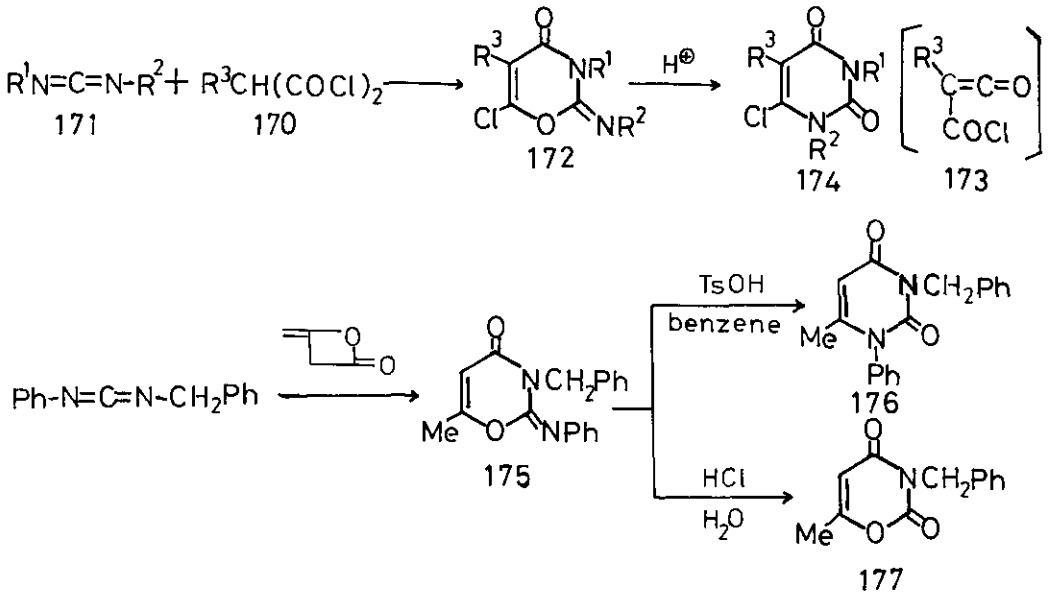
Most 3,4-dihydro-2*H*-1,3-oxazine-2,4-diones are synthesised by reaction of malonyl dichloride or diketene with hetero-cumulenes such as carbodiimides or isocyanates.

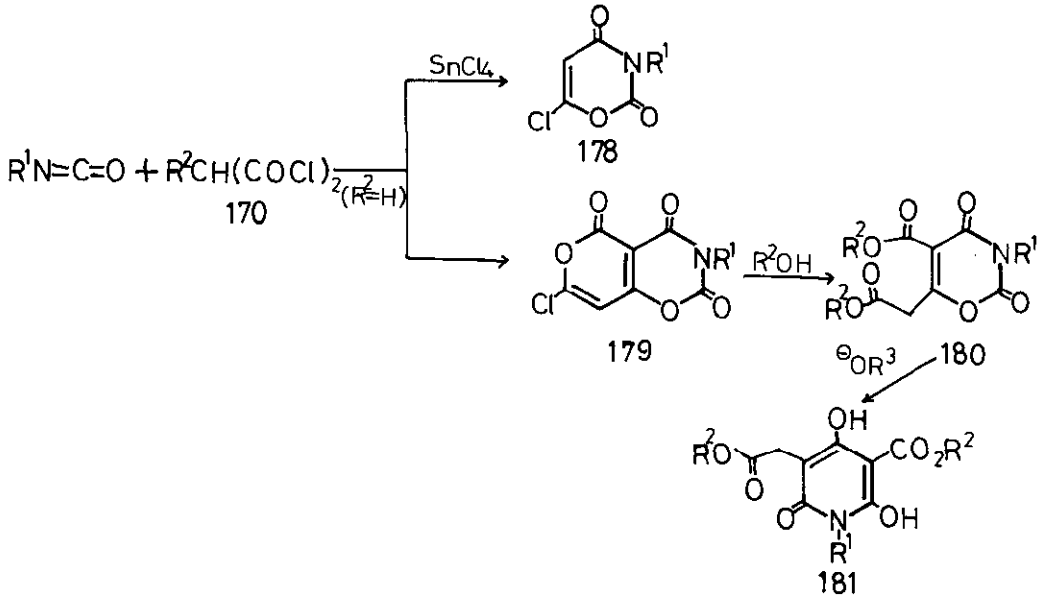
Mono-substituted malonyl dichlorides (170) react with carbodiimides (171) to give oxazines (172).[128] Probably, oxazines (172) are formed by 1,4-cycloaddition of 171 to intermediates, ketene derivatives (173), generated from

170. 172 undergoes ring transformation with acid catalyst into uracil derivatives (174). 2-Imino-1,3-oxazines such as 172 are also obtained from the reactions of diketene with carbodiimides.[118,129,130] In general, 2-imino-1,3-oxazine (175) is transformed into uracil derivative (176) by treatment with acid under anhydrous condition whereas 175 is easily hydrolyzed with dilute hydrochloric acid to afford 1,3-oxazine-2,4-dione (177).

Malonyl dichlorides (170) react with isocyanates in the presence of a Lewis acid catalyst such as stannic chloride to afford 6-chloro-2*H*-1,3-oxazine-2,4-diones (178).[131] However, when this reaction is carried out without catalyst, fused 1,3-oxazines (179), formed by reaction of isocyanate with two equivalents of 170, are obtained.[132]

Similarly, 170 also react with isothiocyanates to afford the corresponding 2-thione derivatives. 179 react with a variety of alcohols to afford oxazines (180), which on treatment with alkoxide ions are transformed into pyridone derivatives (181).



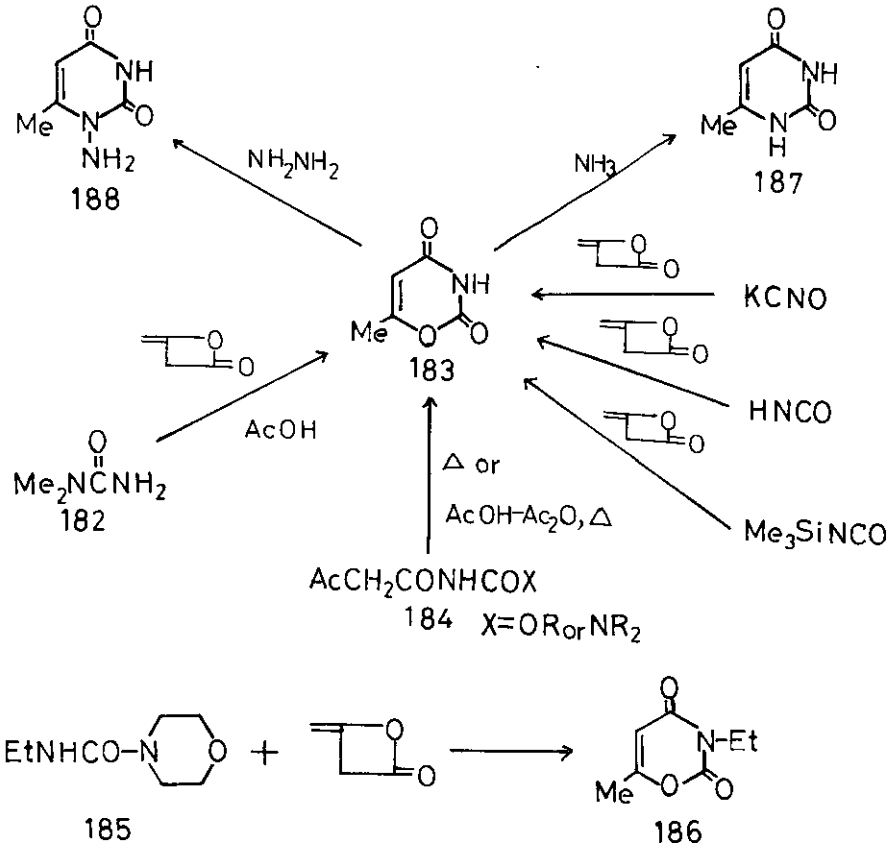


Scheme 30

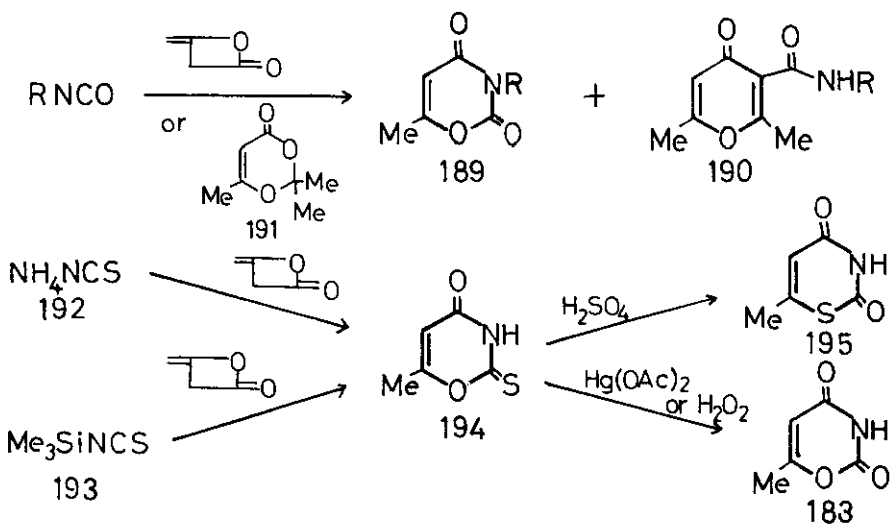
As described before, diketene reacts with urea to afford 6-methyluracil, while reactions of diketene with *N*,*N*-disubstituted ureas give 1,3-oxazines. For example, when *N*,*N*-dimethylurea was allowed to react with diketene in acetic acid, 6-methyl-3,4-dihydro-2*H*-1,3-oxazine-2,4-dione (183) was obtained.[133] Similarly, 183 is obtained when ethyl acetoacetate is used instead of diketene. 183 also can be synthesised by the reaction of diketene with potassium isocyanate,[134] isocyanic acid,[135] or trimethylsilyl isocyanate.[136] Ahmed *et al.*[137] obtained 183 by heating of acetoacetamide derivatives (184). *N*-Alkyl derivative (186) is obtained from 185 and diketene under the same conditions. 183 reacts with ammonia or hydrazine to afford 6-methyluracil (187) or *N*-aminouracil (188), respectively.[137]

The reactions of isocyanates with diketene were investigated in detail by Ozaki,[138] who obtained *N*-substituted oxazine-2,4-diones (189), with pyrone derivatives (190) as by products. In a similar fashion, isocyanates react with 1,3-dioxine derivative (191), which is the 1 : 1 adduct of diketene and acetone, to afford 189.[145] Both ammonium thiocyanate (192)[139] and trimethylsilyl isothiocyanate (193)[136] react with diketene to give 2-thione derivative (194), which on treatment with $Hg(OAc)_2$[134] (or H_2O_2)[139] or with sulfuric acid[130] is transformed into 183 or

thiazine (195), respectively.

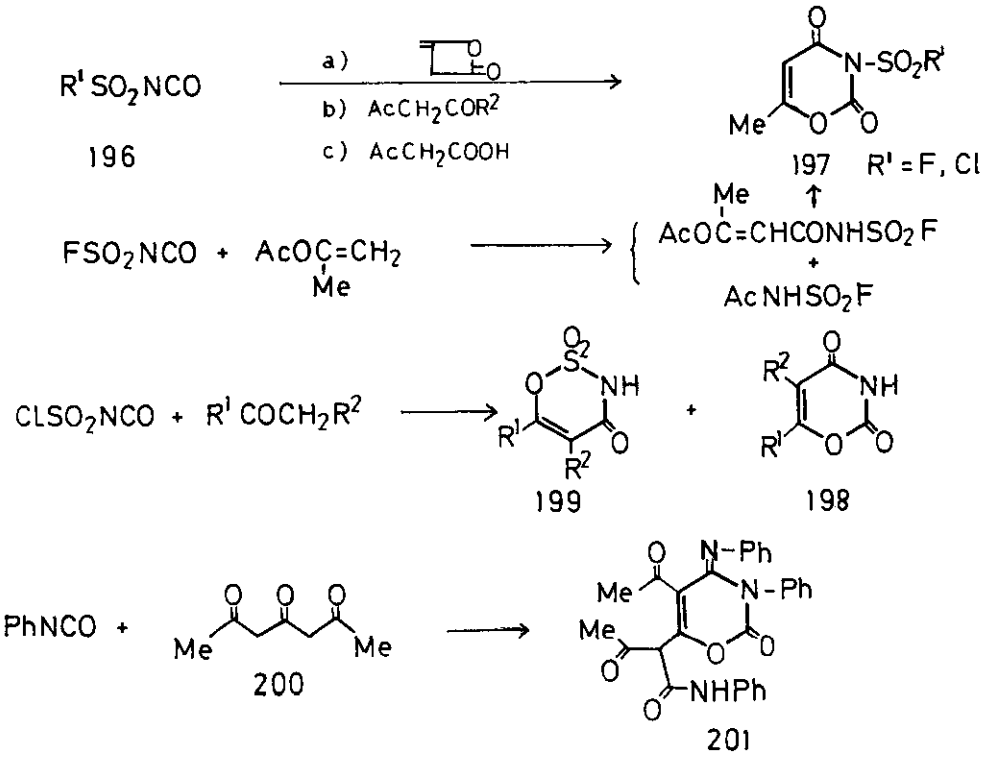


Scheme 31



Scheme 32

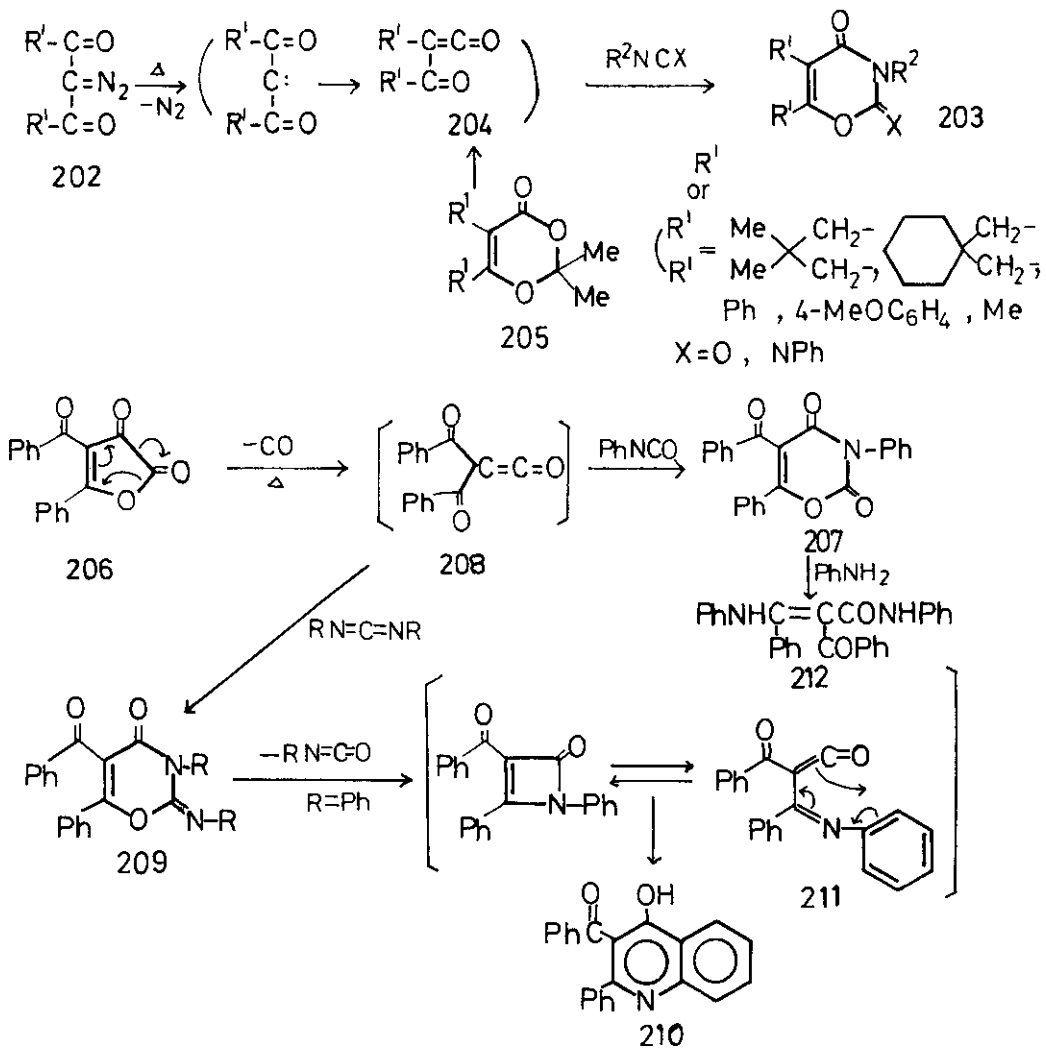
Sulfonyl isocyanates have become of interest in recent years for the synthesis of heterocycles. For example, Pietsch *et al.*[140] obtained *N*-substituted oxazine (197) from the reaction of 196 with diketene (or with acetoacetic acid or its derivatives). Hassner *et al.*[141] reported the synthesis of oxazines (198) from chlorosulfonyl isocyanate reacting with ketones. In this reaction, 199 also forms as a byproduct *via* 3+3 cycloaddition.[142] The reaction of diacetylacetone (200) with phenyl isocyanate to give oxazine (201) has been reported.[143]



Scheme 33

Capuano *et al.*[144] demonstrated an interesting synthesis of oxazines starting from 2-diazo-1,3-diketones (202). Heating of 202 with dienophiles such as isocyanates or carbodiimides affords oxazines (203). The acylketene intermediates (204), generated by thermolysis of 202, presumably undergo cycloaddition reactions with dienophiles to afford 203. Jaeger *et al.*[145] found that upon heating dioxinones (205) were transformed into acylketenes, and obtained 1,3-oxazines (203) by

similar cycloadditions to dienophiles.



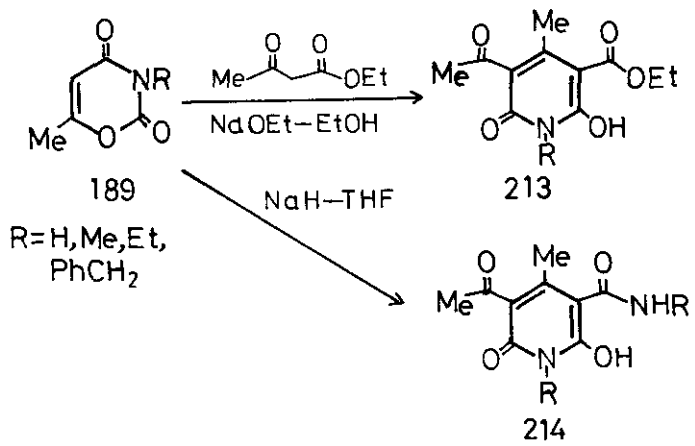
Scheme 34

On the other hand, Ziegler *et al.*[146] demonstrated that upon heating furanone derivative (206) eliminates carbon monoxide to form dibenzoylketene (208) as an intermediate which then reacts with phenyl isocyanate to give 5-benzoyl-3,6-diphenyl-2*H*-1,3-oxazine-2,4-dione (207). A similar reaction was reported by Andreichikov *et al.*[147] 206 likewise reacts with carbodiimides to afford 2-imino-1,3-oxazines (209). 209 (R = Ph) upon heating is transformed into quinoline derivative (210) via ketene (211).

Reaction of 207 with aniline does not afford a uracil derivative, but instead linear compound (212) formed by ring opening followed by decarboxylation. As compared with the ring transformation of 6-methyl-3,4-dihydro-2*H*-1,3-oxazine-2,4-dione (189) (described below), it is of interest that aniline attacks 6-position of 207 to give 212.

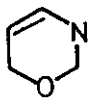
The present authors[148] obtained pyridone derivatives (213) from the reactions of 189 with ethyl acetoacetate in the presence of sodium ethoxide in ethanol. It is clear that attack of ethyl acetoacetate carbanion at 2-position of 189 results in ring opening and subsequent ring closure to pyridones 213.

When this reaction was carried out in the presence of sodium hydride in THF, 213 was not obtained. The product was 214 which was formed by ring opening of 189, followed by self condensation. (Such ring transformation reactions of 1,3-oxazines with active methylene compounds are discussed in Section 4.2.)



Scheme 35

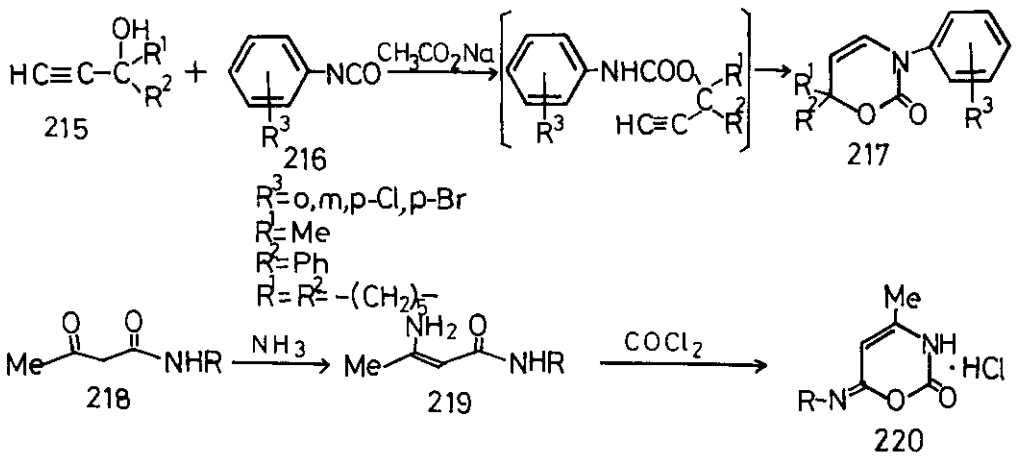
3.4 2,3-Dihydro-6*H*-1,3-oxazines IId



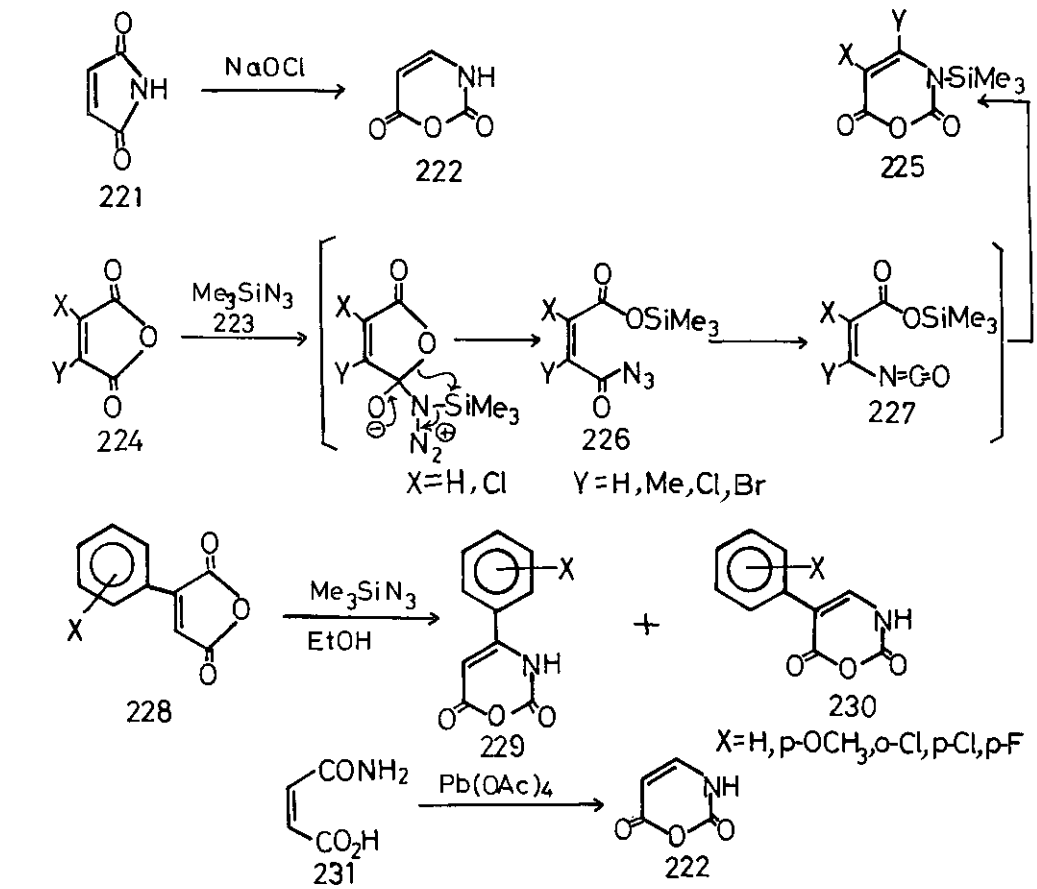
IId

This type of oxazine rarely appears in the literature, and only 2-oxo and 2,6-dioxo derivatives are known. *N*-Aryl-1,3-oxazin-2-ones (217) are synthesized by the reaction of ethynyl alcohols (215) with isocyanates (216) in the presence of sodium acetate.[149] β-Aminocrotonamide derivatives (219), easily obtained from acetoacetamides (218), on treatment with phosgene afford oxazine

hydrochlorides (220).[150]



Scheme 36



Scheme 37

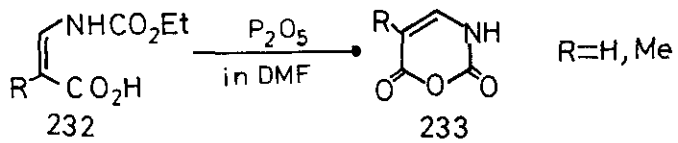
Rinkes' hypohalite oxazine synthesis is well known as a synthetic method of 2,3-dihydro-6*H*-1,3-oxazine-2,6-diones from long ago.[42] This reaction involves ring expansion of maleimide (221) with sodium hypochlorite to give oxazine-2,6-dione (222).

Recently, the synthesis of oxazine-2,6-dione and related compounds has become of interest because of their physiological activities. The synthesis of 2,6-diones from maleic anhydride or its derivatives was investigated in detail by Washburne *et al.*.[151] Trimethylsilyl azide (223) reacts with substituted maleic anhydrides (224) to afford oxazine-2,6-diones (225). The mechanism of this reaction is similar to that of Rinkes' synthesis. Thus, the adduct (226) from 223 and 224 undergoes Curtius rearrangement to afford isocyanate (227), which cyclizes to 225. In similar fashion, two isomers, with structures 229 and 230, are obtained from arylmaleic anhydrides (228).[152]

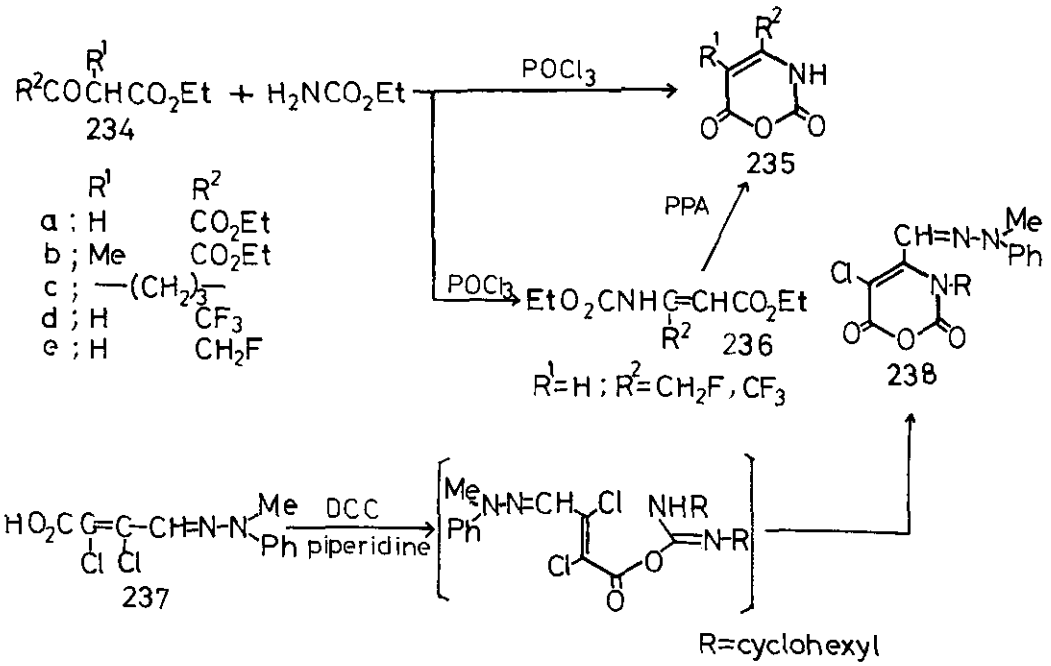
Farkes *et al.*[153] obtained 222 from maleic amide (231) and lead tetraacetate. This reaction proceeds *via* an isocyanate intermediate as do Rinkes' and Washburnes' syntheses.

The synthesis of 1,3-oxazine-2,6-diones (233) by cyclization of β-aminoacrylic acid derivatives (232) has been reported.[154] Closely related is a convenient synthesis of oxazine-2,6-diones (235) from β-keto esters (234) and urethane developed by Washburne *et al.*[155] However from γ-fluoro-β-ketoesters (234d,e), oxazines (235) are not obtained, but rather enamines (236). On treatment with polyphosphoric acid (PPA), these cyclize to fluorinated oxazines (235).

The cyclization reaction of hydrazone (237) with DCC giving oxazine (238) involves intramolecular nucleophilic substitution at a vinylic carbon.[156]



232 233

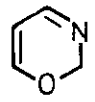


Scheme 38

4. 1,3-OXAZINES III

As described above, 1,3-oxazines are classified into three types, of which 4*H*-1,3-oxazines are the best known.

4.1 2*H*-1,3-Oxazines IIIa



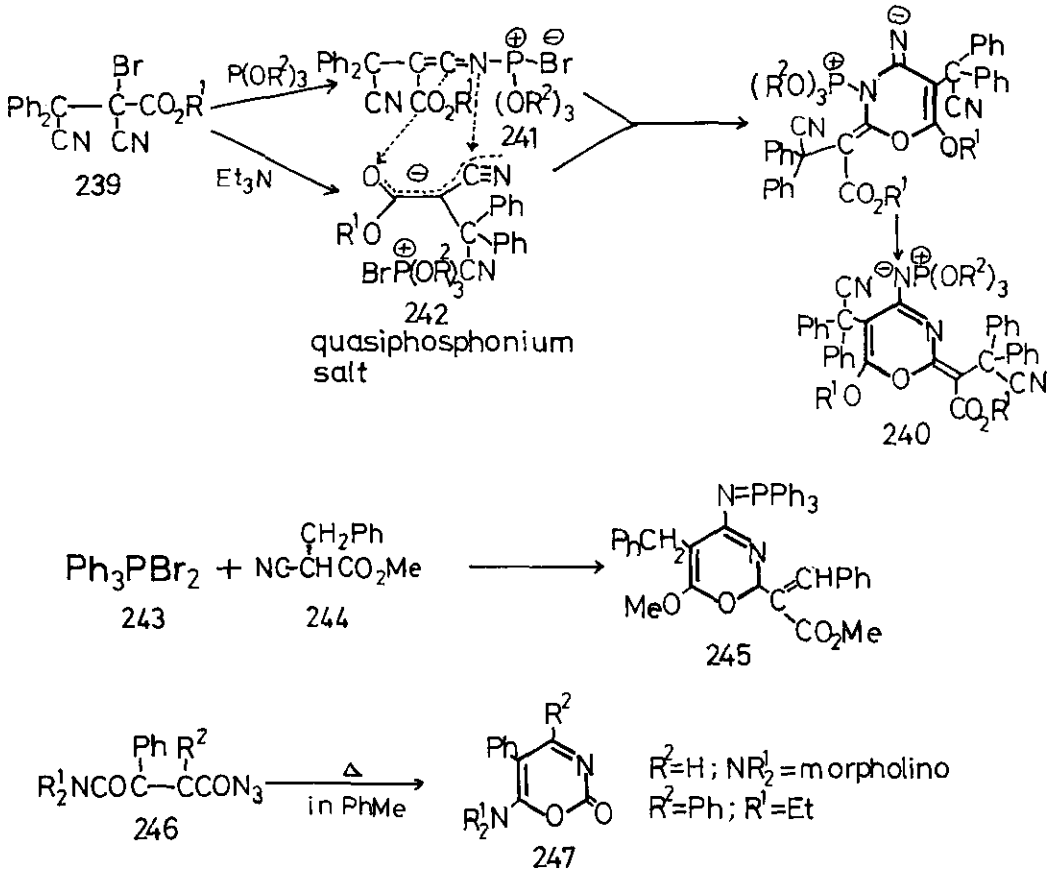
IIIa

Foucaud *et al.* have widely investigated the synthesis of heterocycles with use of phosphorus reagents. They obtained 2*H*-oxazines (240) from reaction of 2-bromo-2,3-dicyano-3,3-diphenylpropionates (239) and triisopropylphosphite in the presence of basic catalyst.[157] 240 would be formed by cycloaddition of ketenimine (241) derived from 239 to quasiphosphonium salt (242).

The formation of 2*H*-oxazine (245) from triphenylphosphine bromine (243) and cyanoacetic acid derivative (244) was observed.[158]

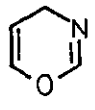
Bayder *et al.*[159] obtained 1,3-oxazin-2-ones (247) from thermolysis of azides (246).

King and Durst reported the reaction of the N-methyl triphenylisoxazolium salt with aqueous sodium hydroxide to give 4,5,6-triphenyl-2*H*-1,3-oxazine.[216]



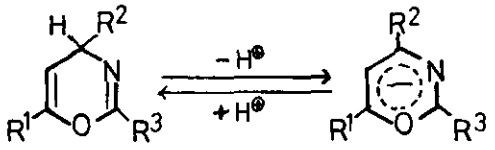
Scheme 39

4.2 4*H*-1,3-Oxazines IIIb



IIIb

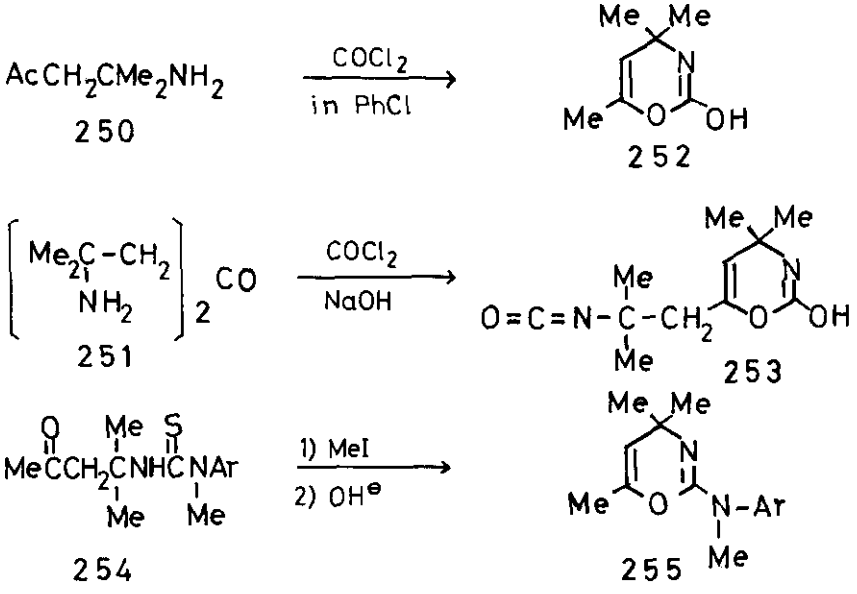
Most reports concerning IIIb type oxazines involve 4-one derivatives, and very few deal with 4*H*-1,3-oxazine itself. The syntheses and reactions of 4-substituted 4*H*-1,3-oxazines reported before 1970 are discussed in the review by Schmidt.[13] 4*H*-1,3-oxazine (248) on treatment with strong base eliminates a proton to produce 1,3-oxazininyl anion (249), which has an 8π electron system possessing interesting reactivity. The properties and reactions of 249 have been reviewed by Schmidt.[160]



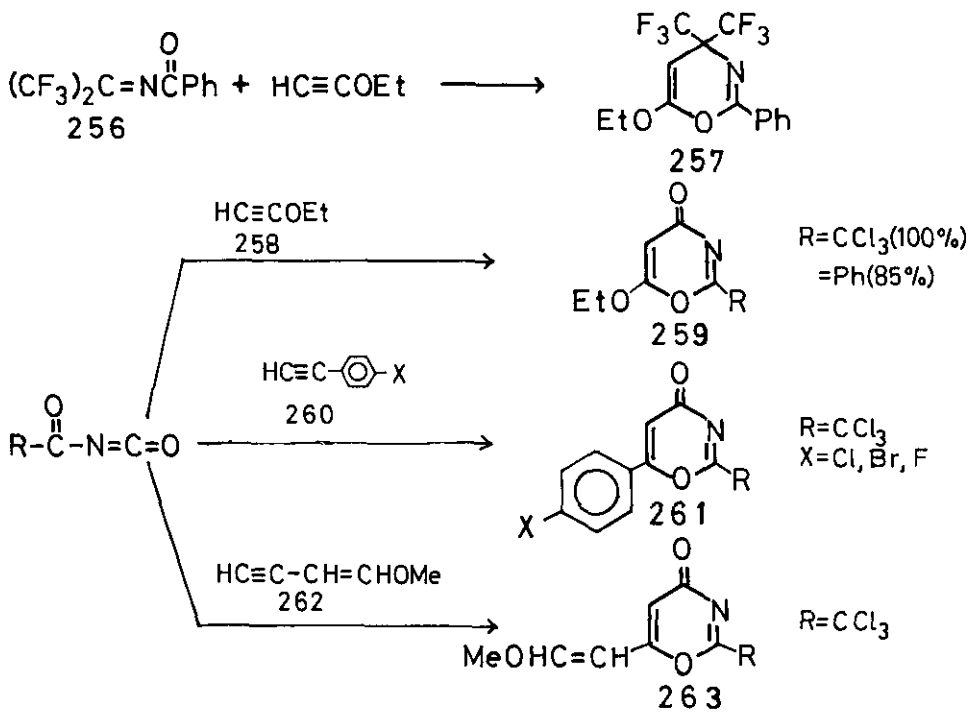
248 249

Lantzsch *et al.*[161] reported the synthesis of IIIb type oxazines. Aminoketone derivatives 250 and 251 react with phosgene to afford 2-hydroxy-4,4-dimethyl-4*H*-1,3-oxazines 252 and 253, respectively. Ignatova *et al.*[162] obtained 4*H*-1,3-oxazine (255) by cyclization of thiourea derivative (254).

The synthesis of 4*H*-1,3-oxazine (257) by 2+4 cycloaddition of ethoxyacetylene to 1,4-dipolar acylimine (256) was also reported. 4*H*-1,3-Oxazin-4-one derivatives can be prepared by 1,4-cycloaddition of acyl isocyanates to C≡C triple bonds. Thus, acyl isocyanates react with ethynyl ether (258) and arylacetylenes (260) to afford 4*H*-1,3-oxazin-4-ones of types 259 and 261, respectively. Acyl isocyanates selectively add to the C≡C bond of 1-buten-3-ynyl methyl ether (262) to afford 4*H*-1,3-oxazin-4-ones (263).



Scheme 40

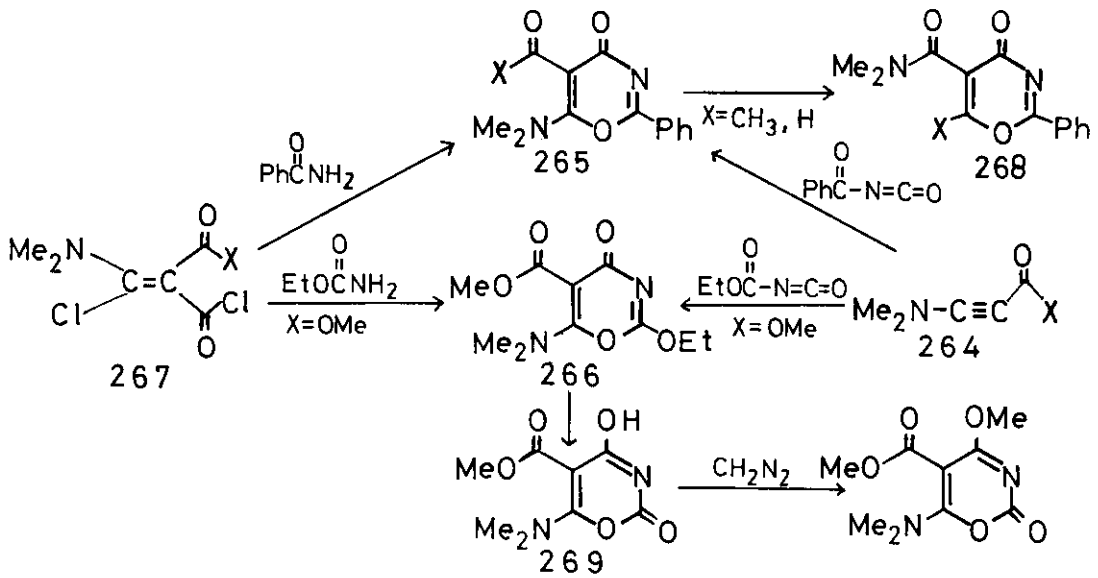


Scheme 41

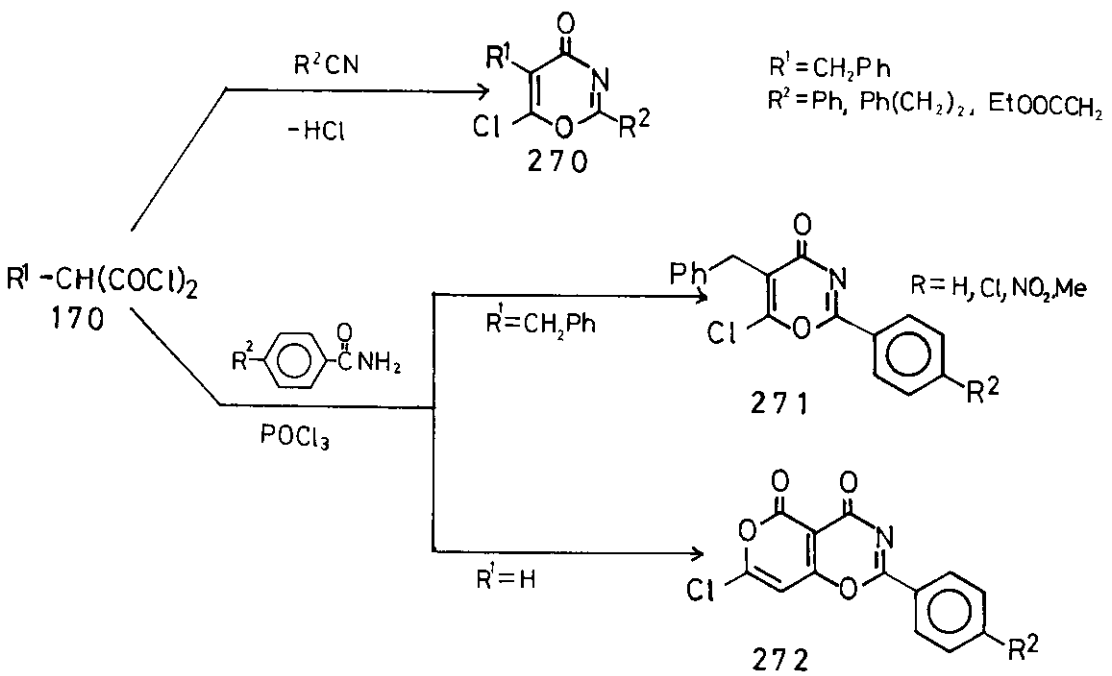
Hafner *et al.*[165,166] investigated in detail the reactivity of ynamines (264), as push-pull-acetylenes, and obtained 4*H*-1,3-oxazin-4-ones (265) and 266 by cycloaddition of acyl isocyanates (264). Adducts (267), from 264 and phosgene, react with amides and urethanes to afford 265 and 266, respectively. Upon treatment with hydrochloric acid, 265 and 266 are transformed into 268 and 269, respectively.

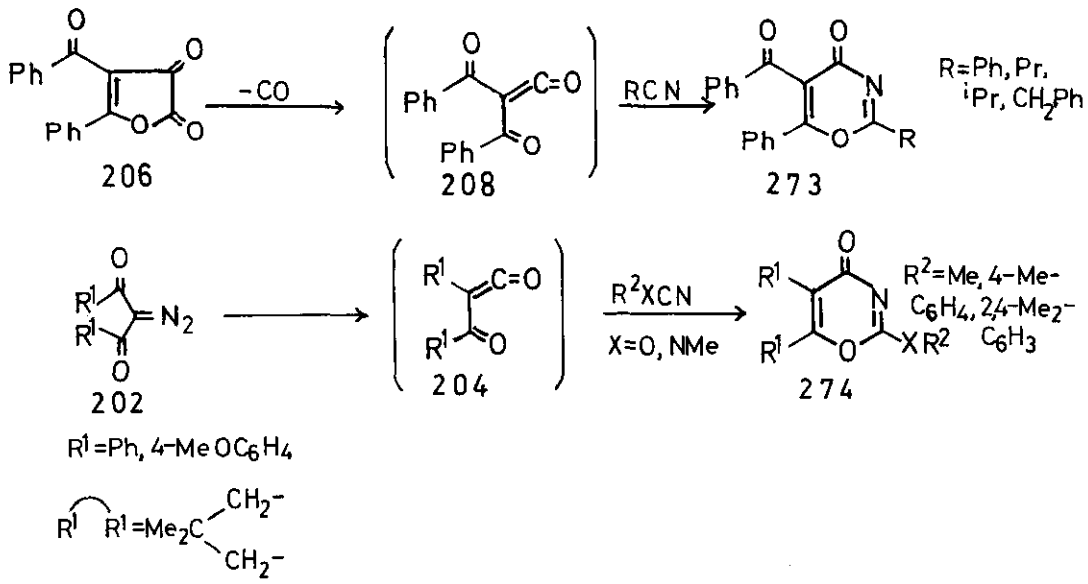
Ziegler *et al.*[167] obtained 6-chloro-4*H*-1,3-oxazin-4-ones (270 or 271) from mono-substituted malonyl dichlorides (170) and nitriles (or amides). From malonyl dichloride (170, R' = H) and amides, 271 is not obtained, but pyrano-1,3-oxazines (272) instead.

As described in Section 3.3.3, acylketene intermediates are often utilized for the synthesis of 1,3-oxazines. Dibenzoylketene (208), generated by the thermolysis of 206, reacts with nitriles to afford 4*H*-1,3-oxazin-4-ones (273).



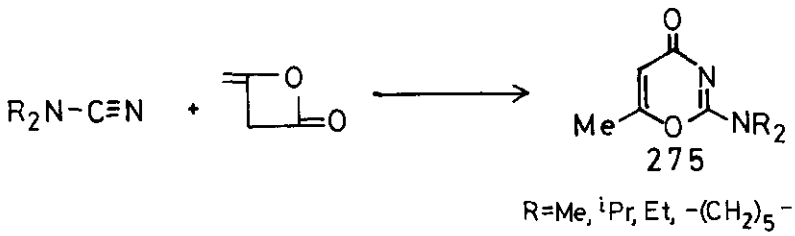
Scheme 42





Scheme 43

Capuano *et al.*[144] obtained oxazines (274) from 2-diazo-1,3-diketones (202) and cyanates (or cyanamides). Cyanamides also react with diketene to afford oxazines. In general, diketene does not add to the C≡N bonds of nitriles, but it does undergo 1,4-cycloaddition to activated nitriles such as cyanamides to afford 2-amino-1,3-oxazines (275).[169]



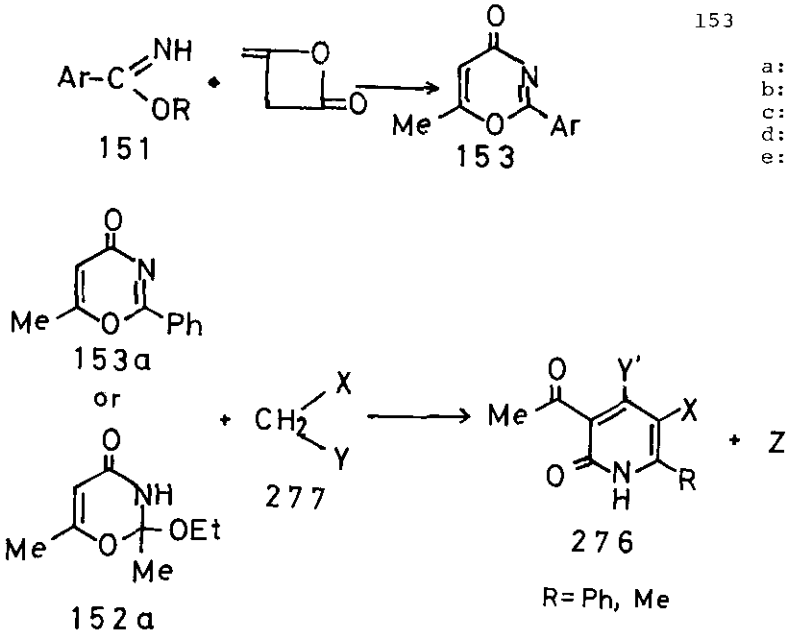
Scheme 44

As described in Section 3.3.2, diketene adds to the C=N bonds of imido esters to form oxazines (152) and 153, and this constitutes a useful synthesis of oxazin-4-ones from aromatic imido esters. The present authors obtained 4*H*-1,3-oxazin-4-ones (153) from the reactions of diketene with aromatic imido esters (151) such

as ethyl benzimidate, pyridine formimido ester, and quinoline formimido ester.[126] As discussed above in Section 3.3.2, dihydro-1,3-oxazin-4-ones (152) and 2,4-diones (183), prepared from diketene, undergo ring transformations to give pyrimidine and pyridine derivatives. The present authors investigated the reactivity of 4*H*-1,3-oxazin-4-one (153), especially its ring transformations, and found that this type of oxazine serves as a reagent for the synthesis of heterocycles such as azines and azoles.

The ring transformations of 4*H*-1,3-oxazin-4-ones and 3,4-dihydro-2*H*-1,3-oxazin-4-ones are summarized below.

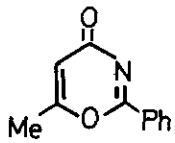
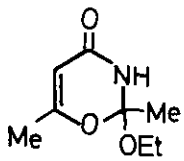
6-Methyl-2-phenyl-4*H*-1,3-oxazin-4-one (153a) reacts with a variety of active methylene compounds to give pyridone derivatives (276).[170] For example, when 153a was allowed to react with diethyl malonate in the presence of *t*-BuOK in *t*-BuOH, pyridone (276a) was obtained in 60% yield. Similarly, 3,4-dihydro-1,3-oxazine (152a) reacts with dimethyl malonate to afford pyridone (276b). Representative yields from the reactions of 153a (or 152a) with active methylene compounds (277) to give pyridone derivatives (276) are shown in Table 3.



153	Ar	Yield (%)
a:	Ph	81
b:	2-Py	41
c:	3-Py	31
d:	4-Py	35
e:	2-Qu	49

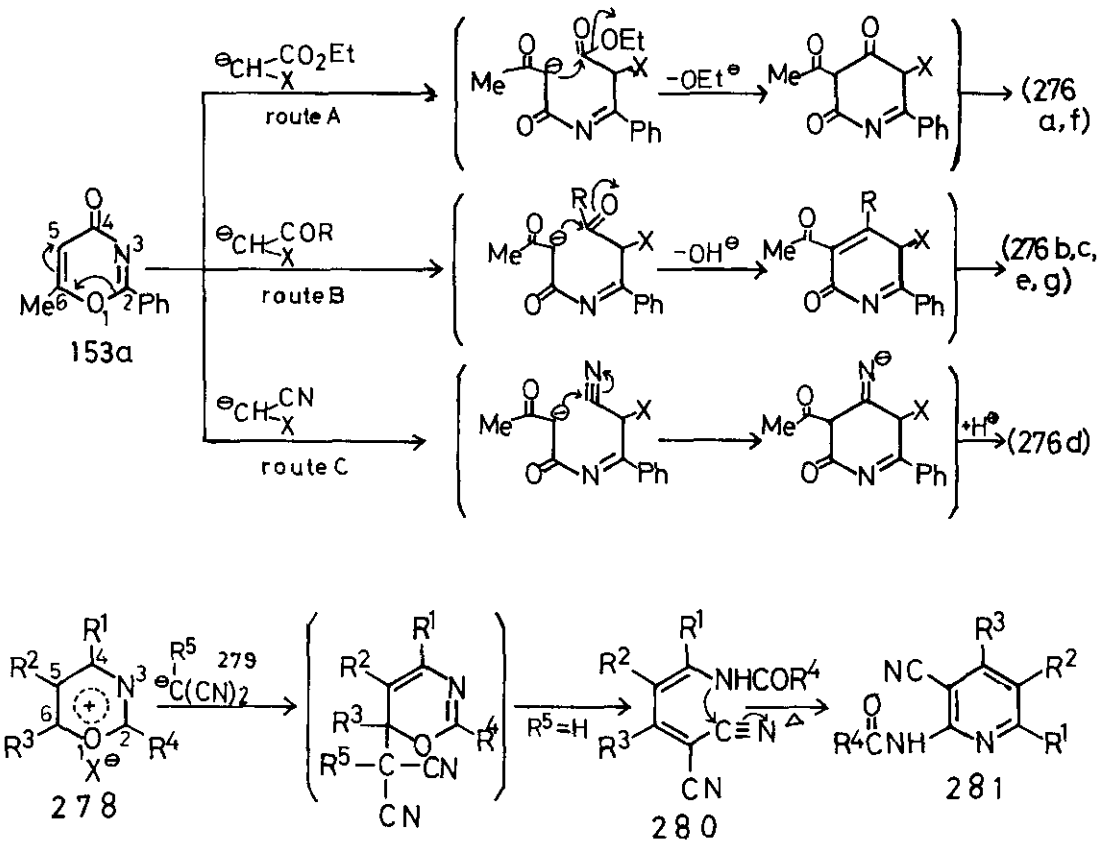
Scheme 45

Table 3

Oxazine	276	X	Y	Y'	Z	Yield (%)
 153a	a	CO_2Et	CO_2Et	OH	EtOH	60
	b	$COCH_3$	$COCH_3$	CH_3	H_2O	86
	c	$-CO(CH_2)_3CO-$		$-(CH_2)_3CO-$	H_2O	90
	d	CN	CN	NH_2		70
	e	CO_2Et	$COCH_3$	CH_3	H_2O	83
	f	CN	CO_2Et	OH	EtOH	80
	g	CN	COC_6H_5	C_6H_5	H_2O	90
 152a	h	$COCH_3$	$COCH_3$	CH_3	H_2O	35
	i	CO_2Et	CO_2Et	OH	EtOH	50
	j	$-CO(CH_2)_3CO-$		$-(CH_2)_3CO-$	H_2O	32
	k	CN	CN	NH_2		76
	l	CO_2Et	CO_2Et	CH_3	H_2O	80
	m	CN	CO_2Et	OH	EtOH	50
	n	CN	COC_6H_5	C_6H_5	H_2O	80

The mechanism of the ring transformation of oxazinones (153a or 152a) into pyridones (276) can be rationalized as shown in Scheme 46. The attack of the carbanion reagent at 2-position of oxazine (153a) causes ring opening to linear intermediates, which subsequently undergo ring closure through three routes such as Dieckmann condensation (route A), Knoevenagel condensation (route B) and addition to C≡N bond (route C) to afford pyridones (270). Since in general the ease of ring closure increase in order of route B, route A and route C, only one kind of pyridone is obtained even if an unsymmetrical active methylene compound (277, X ≠ Y) is used.

On the other hand, Schmidt *et al.*[171] obtained linear compounds of type (280) from reactions of oxazinium salts (278) with malononitriles (279). Upon heating 280 are transformed into pyridine derivatives (281). It is of interest that this ring transformation proceeds by the attack of carbanion (279) at 6-position of 278, in contrast to attack at C-2 of 153a in our studies.

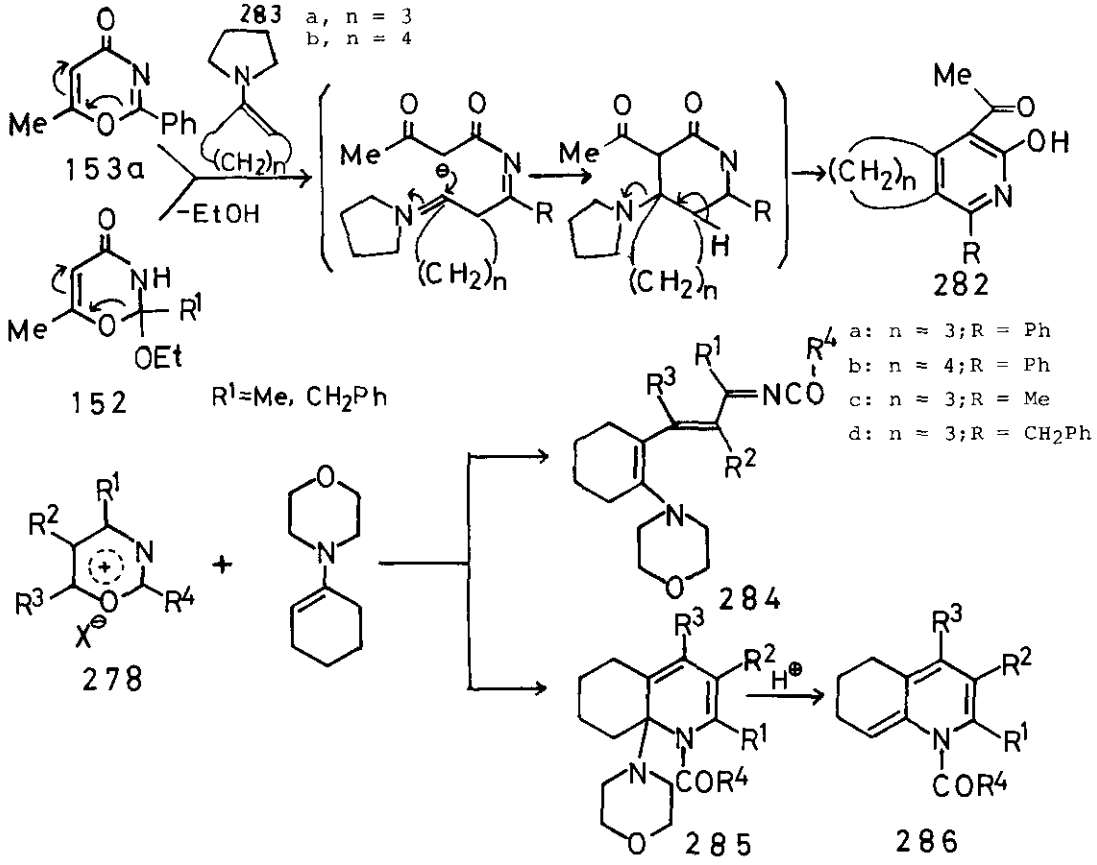


Scheme 46

Nucleophiles such as enamines react with 153a to afford double ring compounds of type (282).[172] For example, reaction of enamine (283a) with 153a in EtOH affords pyridine derivative (282a) whereas tetrahydroisoquinoline derivative (282b) is obtained from enamine (283b) and 153a. Similarly, 3,4-dihydro-1,3-oxazine (152) is transformed into 282c,d. As the reactions of active methylene compounds, this ring transformation takes place through nucleophilic attack of enamine at 2-position of the oxazine ring.

In contrast, two isomers (284, 285) are obtained from oxazinium salts (278) and enamines.[13] Upon treatment with acid 285 are easily transformed into tetrahydroquinolines (286). These two isomers are formed by selective nucleophilic attack at 6-position of oxazinium salts (278). This reaction involves a mechanism

definitely different from that of the ring transformations of 153a and 152 through the action of nucleophilic reagents.

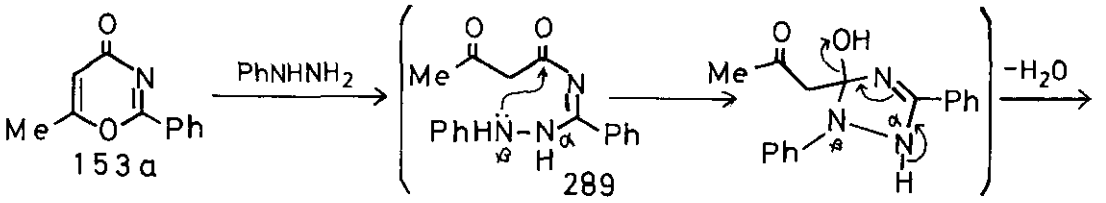


Scheme 47

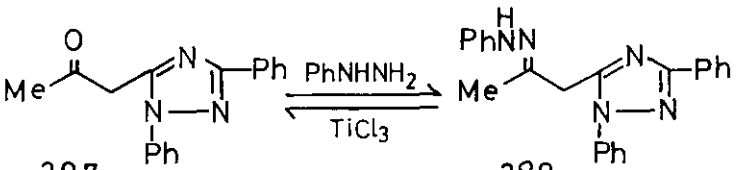
As discussed above in Section 3.3.3, 3,4-dihydro-1,3-oxazine-2,4-diones react with hydrazine to afford *N*-aminouracils. It is therefore noteworthy that reactions of 1,3-oxazin-4-one (153a) with hydrazines afford 1,2,4-triazole derivatives.[173] For example, when 153a was allowed to react with hydrazine hydrate or methyl hydrazine in EtOH, 3-acetonyl-1,2,4-triazoles (287a,b) were obtained. Reaction of 153a with phenylhydrazine affords phenylhydrazone (288), which is formed by the reaction of triazole (287c) with another equivalent of phenylhydrazine. 288 on treatment with $TiCl_3$ affords 287c in 66% yield.

Similarly, 2,3-dihydro-1,3-oxazine (152) reacts with phenylhydrazine to produce the corresponding triazoles (288). The mechanism of this ring transformation into triazoles can be explained as shown in Scheme 48. The attack of phenylhydrazine at 2-position of the oxazine produces acetoacetyl intermediate (289), subsequent dehydration of which gives 287c. Though the formation of an *N*-aminopyrimidine or triazepine by dehydration between the acetyl carbonyl group and *N*(α) or *N*(β) is possible, a five membered ring compound is formed preferentially by dehydration between the amide carbonyl group and *N*(β).

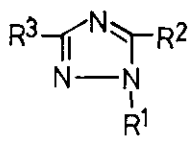
Hydroxylamine reacts much like hydrazine with 153 (or 152d) to afford 1,2,4-oxadiazoles 290 and 291.[174] 291 on treatment with sodium bisulphite ($NaHSO_3$) gives 290.



153a 289

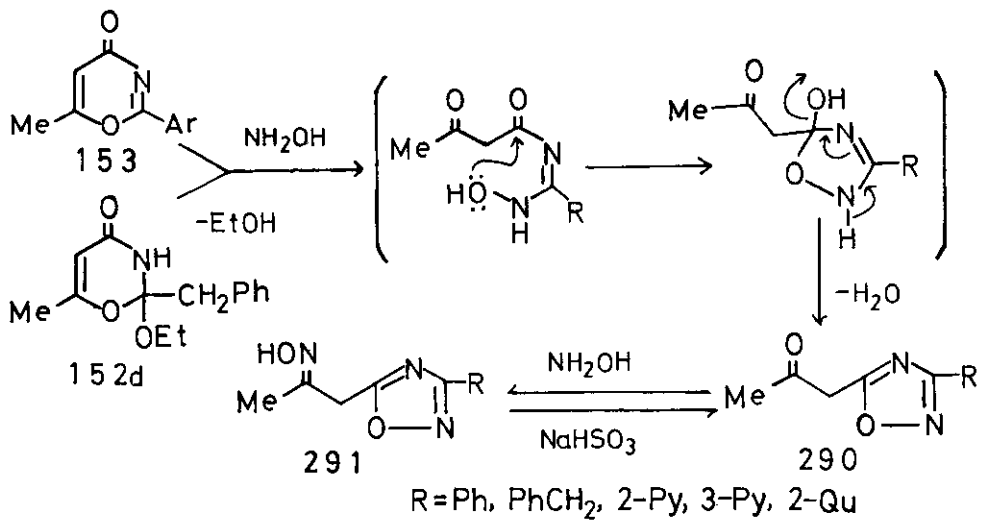


287c 288



287

287	R^1	R^2	R^3
a :	H	Ph	$MeCOCH_2$
b :	Me	Ph	$MeCOCH_2$
c :	Ph	$MeCOCH_2$	Ph
d :	Ph	$MeCOCH_2$	Me
e :	Ph	$MeCOCH_2$	$PhCH_2$

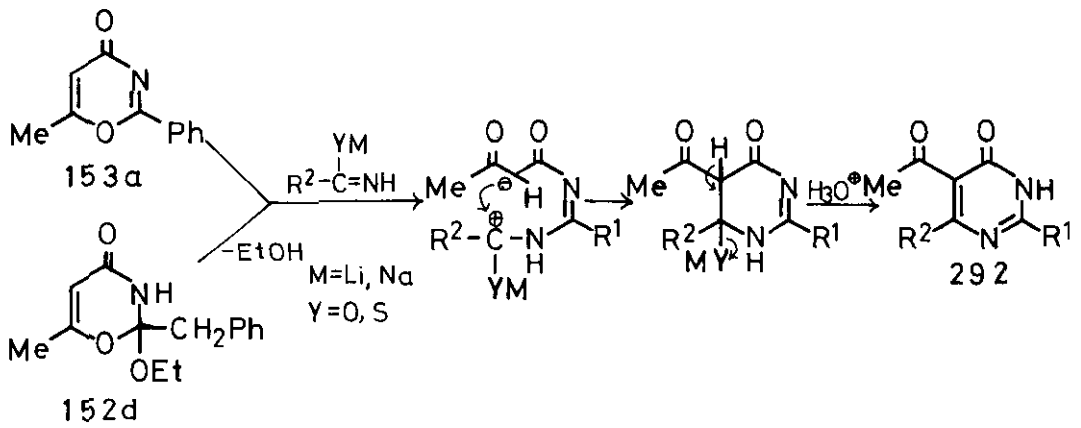


Scheme 48

As already mentioned before, oxazines are often used for the synthesis of pyrimidine derivatives. The present authors developed a versatile synthetic method using 1,3-oxazines.[175,176]

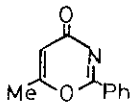
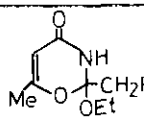
When 1,3-oxazine (153a) was allowed to react with an amide or thioamide in the presence of sodium hydride, a 5-acetylpyrimidine derivative (292) was obtained. Yields were considerably higher when thioamides were used. The yield from an amide can be improved by using *n*-butyllithium (*n*-BuLi) instead of sodium hydride as a metalating reagent. By means of our method, certain pyrimidine derivatives such as chloromethylpyrimidine (292g) and vinylpyrimidine (292i), which are difficult to prepare by conventional methods, can be synthesised.

In a similar fashion, 3,4-dihydro-1,3-oxazine (152d) reacts with amides or thioamides to afford pyrimidines (292). As shown in Scheme 49, pyrimidines (292) are visualized to form by the attack of amido anion at 2-position of oxazine (153a or 152d), followed by elimination of H_2O or H_2S.



Scheme 49

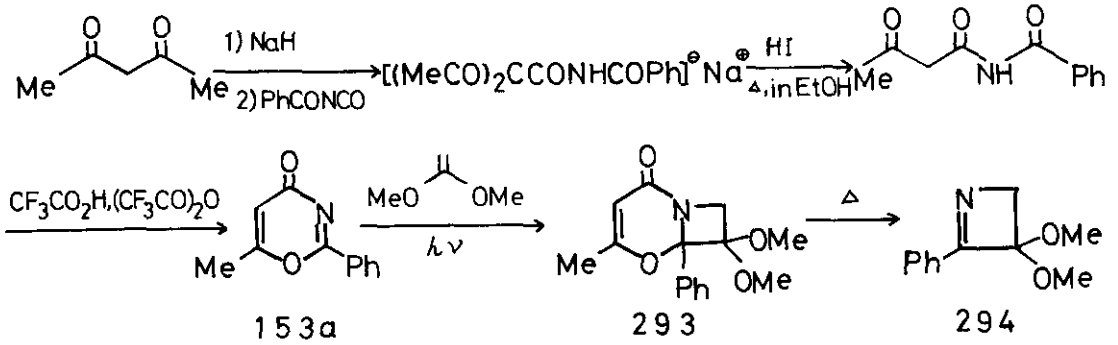
Table 4

Oxazine	Thioamide (amide)			Pyrimidine No.				
	R^2	X		292	R^2	R^1	Yield (%)	
	Me	S	(O)	a	Me	Ph	85	(8.3)
	Ph	S	(O)	b	Ph	Ph	52.6	(12.1)
	Et	S	(O)	c	Et	Ph	51.9	(10)
	$PhCH_2$	S	(O)	d	$PhCH_2$	Ph	85	(1.8)
	p-$MeOC_6H_4$	S		e	*p*-$MeOC_6H_4$	Ph	64.7	
	p-$MeOC_6H_4$	S		f	*p*-ClC_6H_4	Ph	54	
	CH_2Cl	S	(O)	g	CH_2Cl	Ph	12	(7.5, 50*)
	CCl_3	—	(O)	h	CCl_3	Ph	—	(—, 45*)
	$CH_2=CH$	—	(O)	i	$CH_2=CH$	Ph	—	(—, 50*)
	2-Py	S		j	2-Py	Ph	58	
	3-Py	S		k	3-Py	Ph	60	
	2-quinolyl	S		l	2-quinolyl	Ph	75	
	1-isoquinolyl	S		m	1-isoquinolyl	Ph	40	
	Me	S		n	Me	CH_2Ph	28	
	p-$MeOC_6H_4$	S		o	*p*-$MeOC_6H_4$	CH_2Ph	50	
	2-quinolyl	S		p	2-quinolyl	CH_2Ph	40	

* metalating reagent: *n*-BuLi

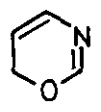
The yield in parenthesis is based on amide.

Though the photochemistry of 1,3-oxazines is considered to be an attractive field, the literature dealing with it is sparse. Recently, Koch *et al.*[123] isolated the novel adduct (293) from irradiation of 1,3-oxazine (153a) in the presence of dimethylketene acetal in dichloromethane. Upon heating 293 was transformed into azetine (294). The 153a used in this reaction was prepared by dehydration of *N*-benzoylacetoacetamide.



Scheme 50

4.3 6*H*-1,3-Oxazines IIIc

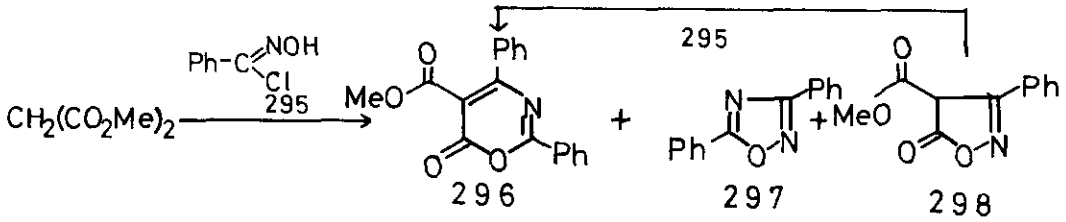


IIIc

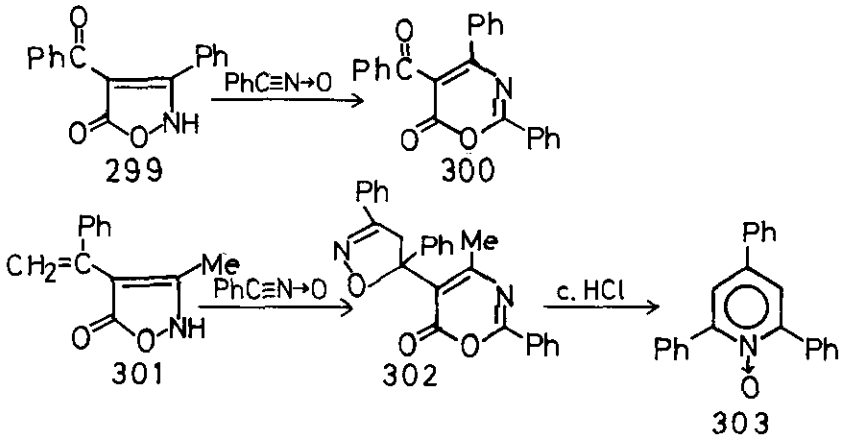
6*H*-1,3-Oxazine itself has not been synthesised. All of the 6*H*-1,3-oxazines prepared up to now are 6-oxo derivatives. Malonic acid derivatives are often utilized for the synthesis of 6-oxo-6*H*-1,3-oxazines.

D'Alcontres *et al.*[177] obtained 1,3-oxazin-6-one derivative (296) from dimethyl malonate and benzoyl chloride oxime (295). In this reaction 1,2,4-oxadiazole (297) and isoxazolone (298) are obtained as by products, and 298 is considered to be the precursor of 296. In fact, when isoxazolone (298) was allowed to react with oxime 295, oxazine (296) was obtained.

In a similar fashion, isoxazolones react with nitrile oxides to afford 1,3-oxazin-6-ones.[178] For example, 3-isoxazolin-5-one derivatives (299) and 301 react with benzonitrile oxide to give oxazine (300) and 302, respectively. On treatment with conc. hydrochloric acid, 302 undergoes ring opening and subsequent rearrangement to afford 2,4,6-triphenylpyridine 1-oxide (303).

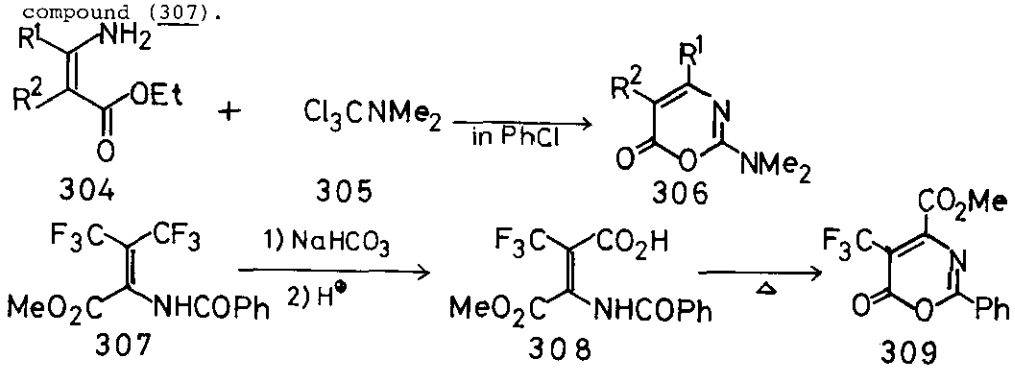


Scheme 51



Scheme 52

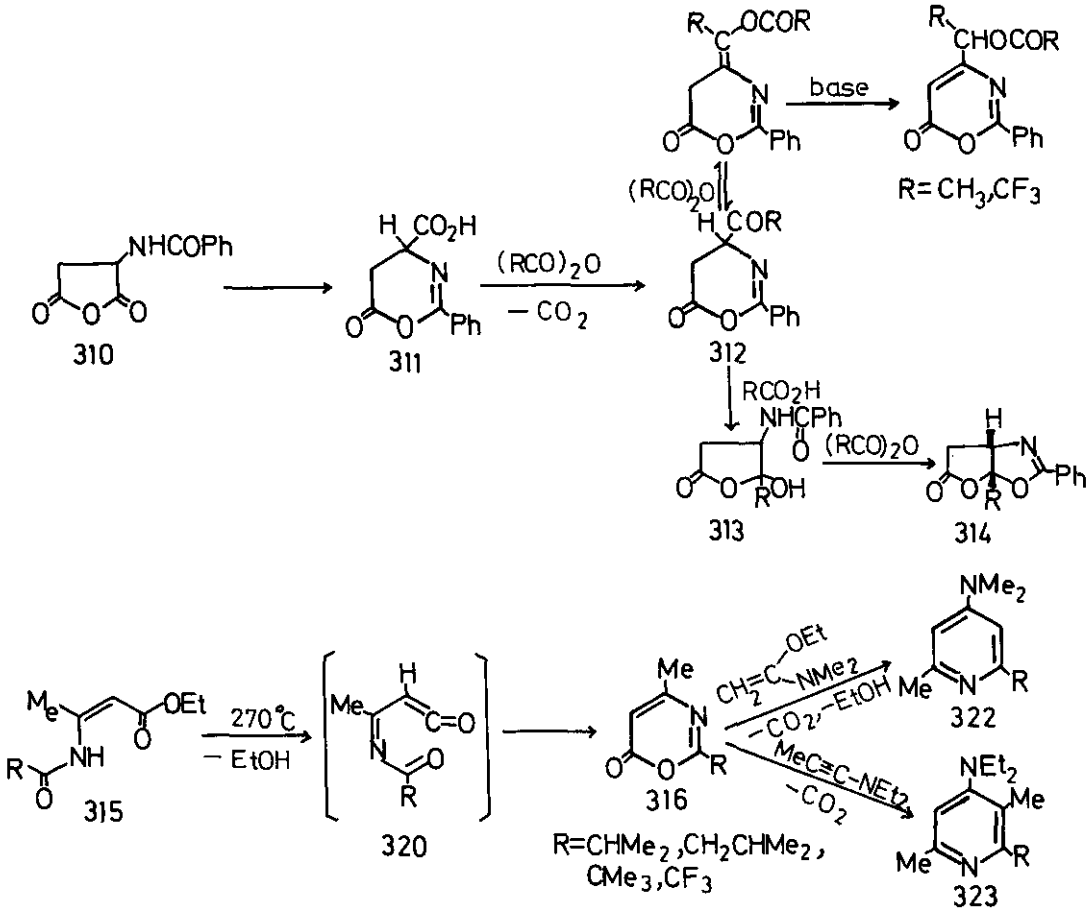
ß-Aminocrotonic acid derivatives also serve as reagents for the synthesis of 1,3-oxazines. Bodnarchuk *et al.*[179] obtained 1,3-oxazin-6-ones (306) from *N,N*-dimethyltrichloromethylamine (305) and ethyl ß-aminocrotonates (304). Rokhlin *et al.*[180] reported the synthesis of 1,3-oxazin-6-one (309) by heating carboxylic acid (308), which was prepared by the partial hydrolysis of perfluorinated compound (307).

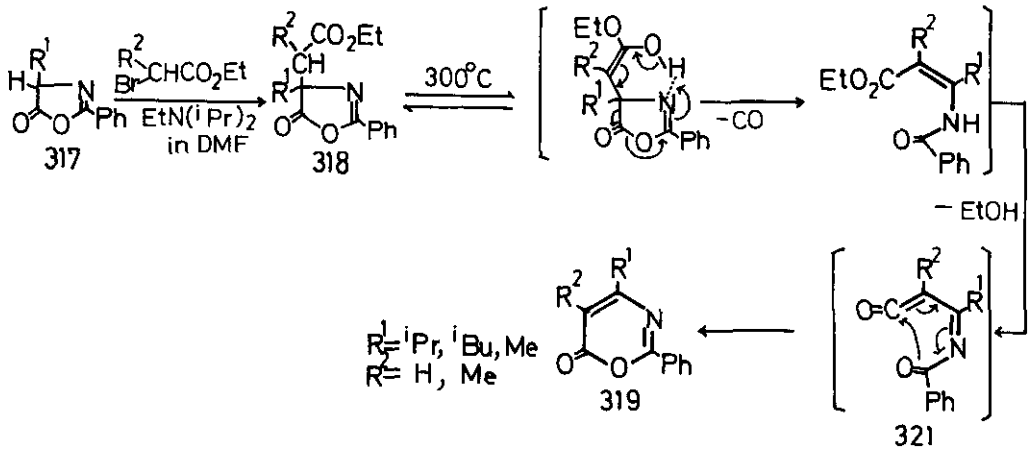


Scheme 53

Steglich *et al.*[181] demonstrated that *N*-benzoylaspartic anhydride (310) is transformed into 1,3-oxazin-6-one (311) in the presence of an acid anhydride and base. When only an acid anhydride is used, furo[3,2-*d*]oxazole (314) is obtained as sole product. This reaction proceeds through intermediates such as 5,6-dihydro-1,3-oxazin-6-ones (312) and γ-lactones (313).

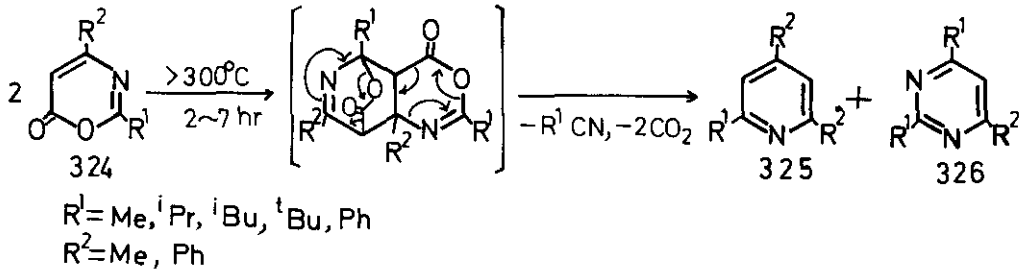
Further, Steglich *et al.*[182] reported the thermolysis of *N*-acyl-β-aminocrotonates (315) to give 1,3-oxazin-6-ones (316). Thermolysis of oxazolones may also afford 1,3-oxazin-6-ones. To illustrate, 4-(1-ethoxycarbonylalkyl)-2-oxazolin-5-ones (318), obtained from 2-oxazolin-5-ones (317) and α-bromo esters, on thermolysis at 300° eliminate carbon monoxide and ethanol to afford oxazines (319).[183] In both thermolyses, acyliminoketenes (320, 321) form as intermediates; their ring closure gives rise to oxazines (316, 319).





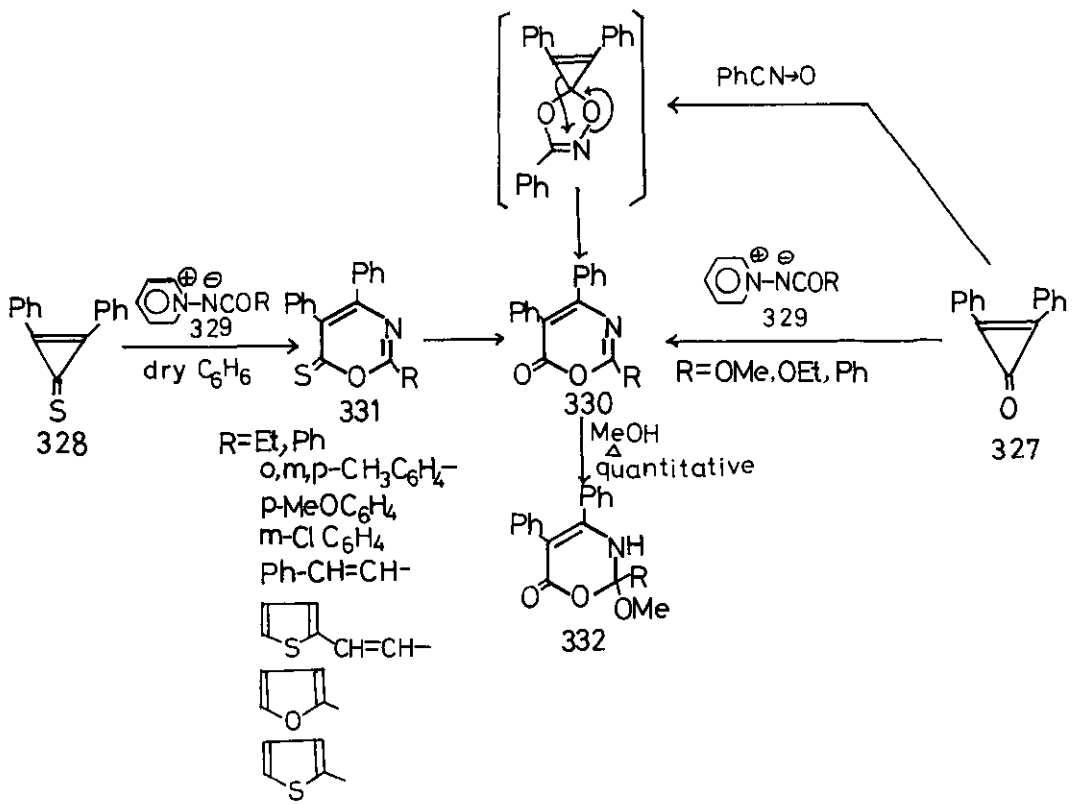
Scheme 54

Because of its diene character, 1,3-oxazin-6-one acts as a diene in Diels-Alder reaction to afford pyridine derivatives. For example, 316 reacts with an electron-rich ynamine and a ketene-*O*,*N*-acetal to afford pyridine derivatives (322) and 323, respectively. Similarly, dimerization of 1,3-oxazin-6-ones (324) by Diels-Alder type cycloaddition affords pyridine derivatives (325), accompanied by elimination of nitriles and carbon dioxide.[184] Pyrimidine derivatives (326) are also obtained as by-products.



Scheme 55

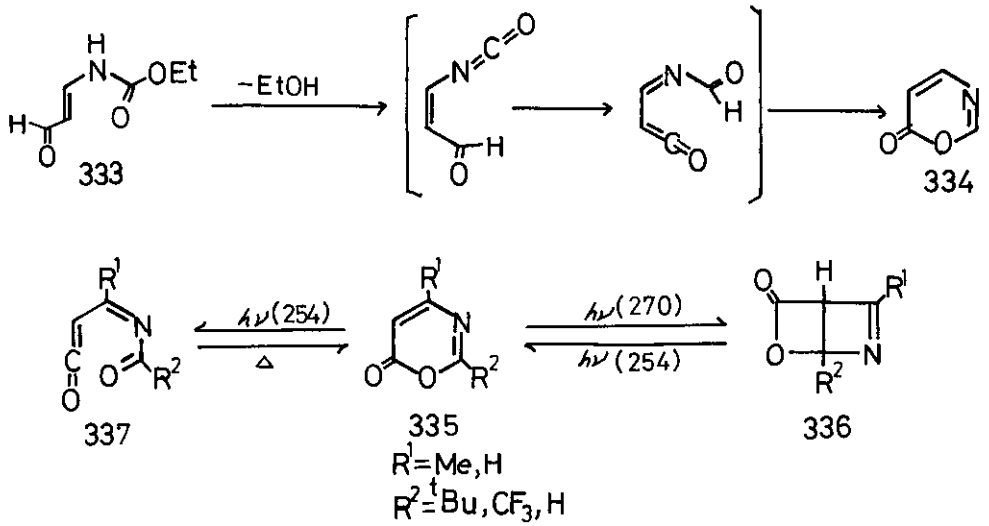
The synthesis of 1,3-oxazin-6-ones from *N*-iminopyridinium ylides and cyclopropenones has been reported.[185,186] Thus, cyclopropenone (327) and cyclopropenethione (328) undergo 2+3 cycloaddition reaction with ylides (329) and ensuing rearrangement to form oxazines (330) and 331, respectively. Upon treatment with sodium methoxide or peracid, thione derivatives (331) were transformed into 330. The refluxing of 330 in methanol affords 2,3-dihydro-1,3-oxazin-6-ones (332).



Scheme 56

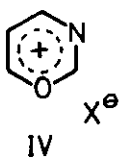
Krantz *et al.*[187] obtained 1,3-oxazin-6-one (334) by thermolysis of *trans*-3-ethoxycarbonylaminoprop-2-enal (333).

The photochemical behavior of 1,3-oxazin-6-one and its derivatives has been studied in detail by Maier *et al.*[188] 1,3-Oxazin-6-ones (335) were transformed into their valence isomers (336) and iminoketenes (337) under irradiation.



Scheme 57

5. 1,3-OXAZINIUM SALTS IV



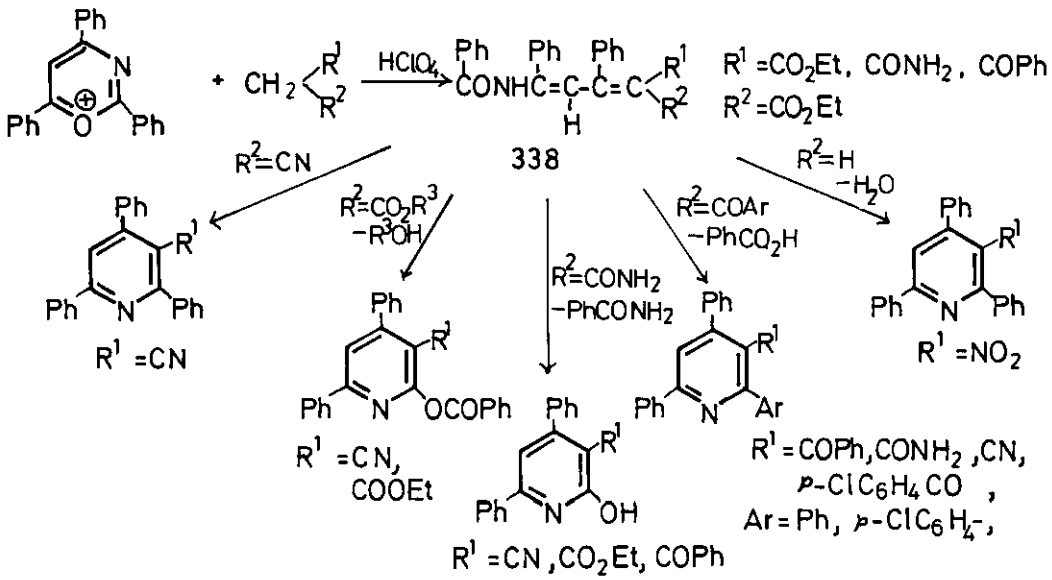
IV

1,3-Oxazinium salts (IV), like pyrylium salts, are 6π heteroaromatic compounds. Many interesting reports about them have been published.

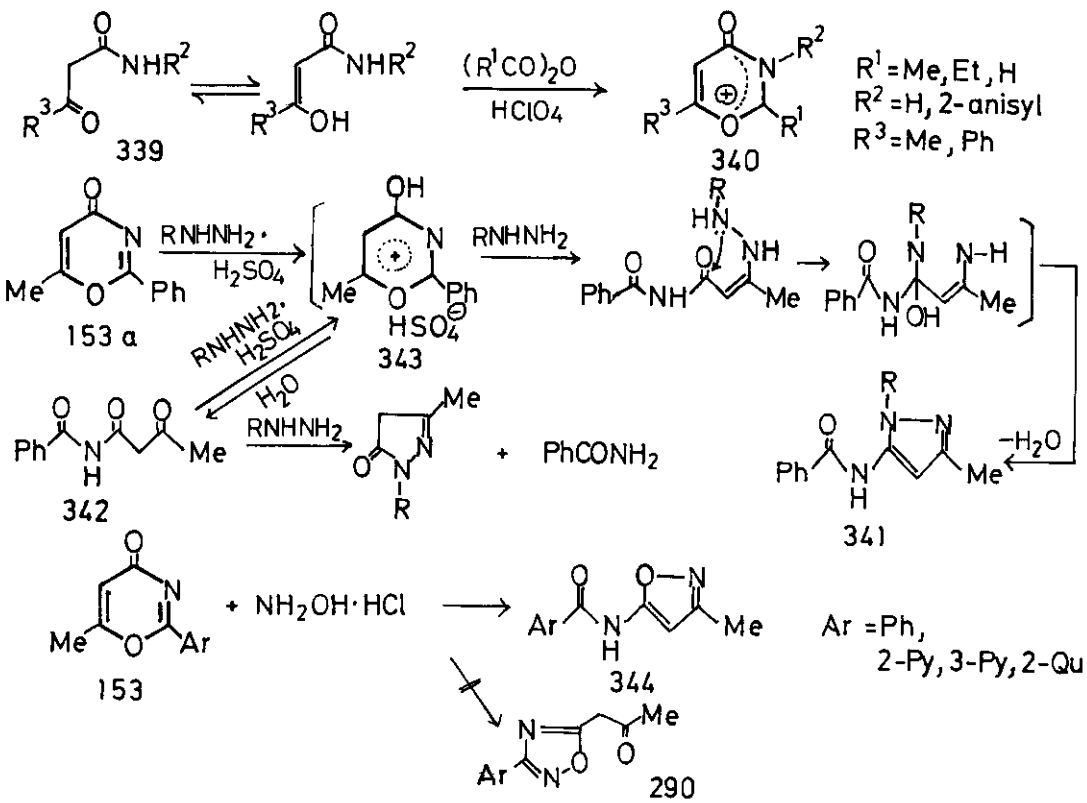
The ring transformations initiated by the selective attack of nucleophilic reagents at 6-position of 1,3-oxazinium salts are of special interest. The synthesis and reaction of 1,3-oxazinium salts have been reviewed by Schmidt.[13]

Schmidt *et al.* initially reported the ring transformation of 1,3-oxazinium salts into pyridine derivatives. Later, Shibuya *et al.*[189] investigated in detail the ring transformations that occur when 1,3-oxazinium salts react with a variety of active methylene compounds. They classified the patterns of ring closure of intermediates (338) to pyridine derivatives.

Dorofeenko *et al.*[190] obtained oxazinium salts (340) from the reactions of acetoacetamide derivatives (339) with carboxylic acid anhydrides in the presence of perchloric acid ($HClO_4$). The present authors have also observed that oxazinium salts form as intermediates in the reaction of 1,3-oxazin-4-one (153a) with hydrazine sulfates.[173] As described in Section 4.2 (Scheme 48), 153a reacts with



Scheme 58



Scheme 59

hydroxylamine or hydrazines to afford 1,2,4-oxadiazole (290; R = Ph) or 1,2,4-triazoles (287), respectively. When similar reactions were carried out using substituted hydrazine sulfates in place of hydrazines, triazoles (287) were not obtained; the sole products were pyrazole derivatives (341).

The reactions of substituted hydrazine sulfates with *N*-benzoylacetoacetamide (342), the product of hydrolysis of 153a, also afford pyrazoles (341). These facts suggest that oxazinium salt (343) is a common intermediate for these two reactions, being formed by interaction between a hydrazine sulfate and 153a, or 342.

Therefore, mechanism of the formation of 341 from 153a or 342 can be considered to be as follows: the hydrazine attacks at 6-position of oxazinium salt (343), opening the ring to form a linear compound which cyclizes to a pyrazole (341). Similarly, reactions of 153 with hydroxylamine hydrochloride did not afford oxadiazole derivatives (290), but rather isoxazole derivatives (344).[174]

6. THE BIOLOGICAL ACTIVITY OF 1,3-OXAZINES

The biological activity of 1,3-oxazines has long been of interest, and hence there is a considerable literature dealing with it, mostly involving tetrahydro-1,3-oxazines.

2-Substituted tetrahydro-1,3-oxazines are effective as bronchial dilators,[55] blood-pressure elevators,[55] central nervous system depressants,[191] and fungicides.[23,192] Many of the *N*-substituted (alkyl, acyl or aralkyl) tetrahydro-1,3-oxazines possess antiinflammatory,[193] and bactericidal activity.[194] In general, *N*-nitroso-tetrahydro-1,3-oxazines have carcinogenic activity.[195] *N*-Sulfonyl-tetrahydro-1,3-oxazines[196,197] serve as vasodilators, diuretics, herbicides and fungicides. 5-Nitro-tetrahydro-1,3-oxazines possess antitumor,[51, 198-201] antiprotozoal[202] and cytotoxic[203] activity, as well as oncostatic properties.[204]

Tetrahydro-1,3-oxazin-2-ones are effective as analgesics,[31,33a] spasmolytics,[33a] central nervous system-stimulants,[205] and barbiturate antagonists.[205] 1,3-Oxazine-2,4-diones such as 5,5-diethyl-1,3-oxazine-2,4-dione[206] have been widely studied for their pharmacological activity, and serve as barbiturate antagonists,

and anticonvulsants drugs. 5,6-Dihydro-4*H*-1,3-oxazines possess analgesic, spasmolytic, sedative, antiinflammatory and central nervous system stimulant activity.[74a,207-209] 3,4-Dihydro-2*H*-1,3-oxazine-2,4-diones are effective as agricultural chemicals, serving as insecticides and plant protective agents.[131] As already mentioned (see Introduction), *C*-nucleoside (oxazinomycin) (1) and 2,3-dihydro-6*H*-oxazine-2,6-dione[7] (2) possess nucleic acid antimetabolic activity. Hence the synthesis of these compounds and related derivatives has been a field of dynamic activity.[1-6,151,154,213-215]

7. CONCLUDING REMARKS

The literature relating to 1,3-oxazine during the recent fifteen years is summarized in this review. Our discussion has been limitted to single ring 1,3-oxazines, that is, fused 1,3-oxazines such as benzoxazine have been excluded. It is of interest that 450 references appeared in Chemical Abstracts during the period of 1963 - 1977. Many of them involve the synthesis of biologically active tetrahydro-1,3-oxazines, and appeared as patent literature. Since dihydro-1,3-oxazines, especially 3,4-dihydro-2*H*-1,3-oxazine derivatives, are easily available at present, new developments in their reactions and for synthetic purposes can be expected in the future.

ACKNOWLEDGEMENT

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