

## BASE-CATALYSED REARRANGEMENTS OF 5-OXODIHYDROISOXAZOLES

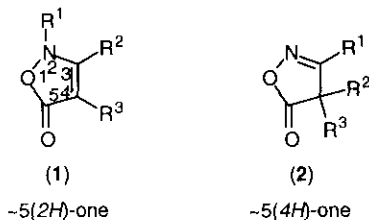
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**Abstract** - Five distinct pathways for the reaction of isoxazol-5(2*H*)-ones with bases or nucleophiles have been reported, and are detailed herein. That investigated in greatest detail, and of greatest application in heterocyclic synthesis, is that of isoxazolones unsubstituted at C-3, in which the sequentially formed ketenimine,  $\alpha$ -lactone and ketene may all react with a nucleophile.

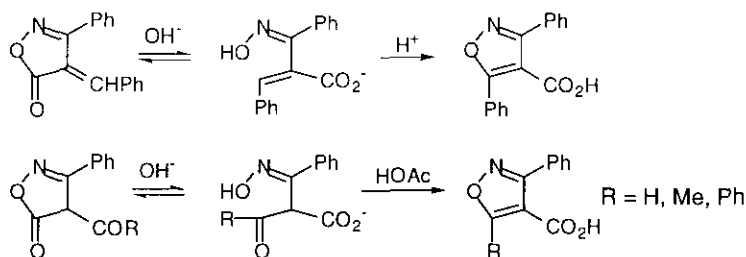
### I. INTRODUCTION

The tautomeric 5-oxodihydroisoxazoles, commonly known as either isoxazol-5(2*H*)-ones (**1**) or isoxazol-5(4*H*)-ones (**2**) have been known since the late 19th century.<sup>1</sup> A decade later both Ruhemann<sup>2</sup> and Claisen<sup>3</sup> reacted ethyl 2-methyl-2,5-dihydroisoxazole-4-carboxylate with aqueous hydroxide in order to establish the site of methylation of the parent compound. The rearrangements occurring in this reaction, while not fully understood until the work of Woodman,<sup>4-8</sup> are typical of those occurring with these systems. This review will cover both mechanistic investigations and synthetic applications, but while 5-oxodihydroisoxazoles are susceptible to a variety of base-induced reactions, this review will concentrate on the reactions of isoxazolones unsubstituted at C-3. However, other reactions will be treated briefly initially.

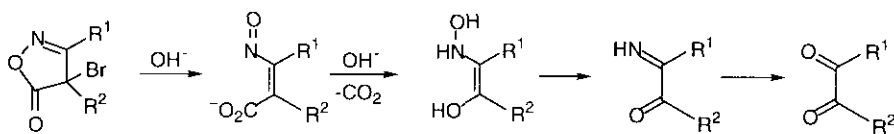


### II. REACTIONS INVOLVING LACTONE HYDROLYSIS

Speroni<sup>9</sup> clarified the earlier work of Betti<sup>10</sup> on the rearrangement of 4-benzylideneisoxazol-5(4*H*)-ones with hydroxide, which leads to the formation of isoxazole-4-carboxylic acids. This work shares a number of similarities with that of Korte<sup>11</sup> on the rearrangement of 4-acylisoxazolones to isoxazole-4-carboxylic acids, as both involve lactone hydrolysis and recyclisation (Scheme 1).

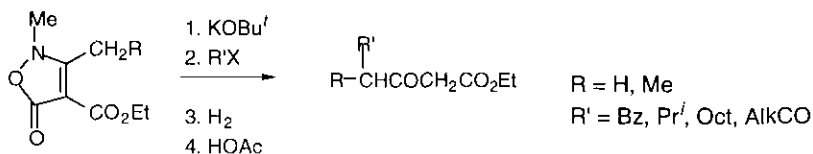
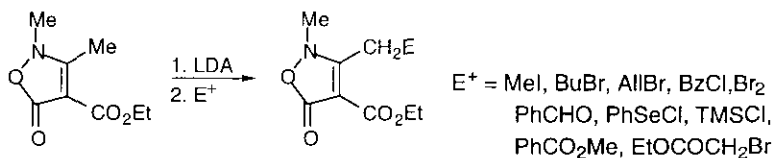


Similarly, Silveira<sup>12</sup> studied the reaction of 3,4-disubstituted 4-bromoisoxazol-5(4*H*)-ones with hydroxide, in which  $\alpha$ -diketones are unexceptionally obtained after lactone hydrolysis and decarboxylation (Scheme 2).



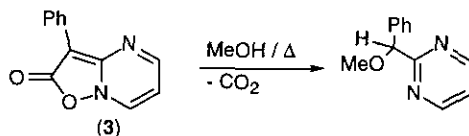
### III. BASE CATALYSED ALKYLATION AND ACYLATION OF 3-ALKYLISOXAZOL-5(2*H*)-ONES

Tishler and Weiler<sup>13</sup> showed that the alkyl group in 3-alkylisoxazolones could be converted by base to the anion which reacted smoothly with a number of electrophiles (Scheme 3). Doleschall<sup>14,15</sup> extended this work by subsequent hydrogenation and hydrolysis, leading to convenient syntheses of  $\gamma$ -alkylated acetoacetates and  $\beta,\delta$ -dioxo esters (Scheme 4).

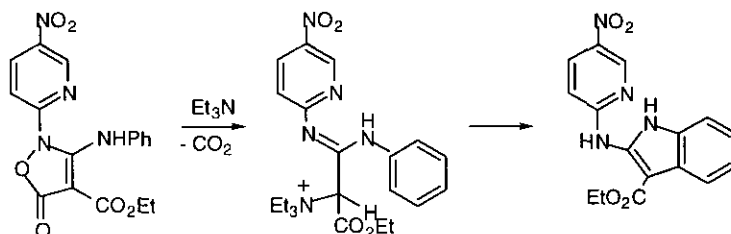


### IV. REACTIONS INVOLVING ADDITIONS TO C-4

Zvilichovsky<sup>16</sup> suggested that the ready decarboxylation of the annelated isoxazolone (**3**) by hot methanol involved ring opening initiated by nucleophilic addition to C-4 (Scheme 5). Similarly, Khalafy and Prager<sup>17</sup> showed that addition of base to C-4 was the most probable first step in the ring opening/decarboxylation of a series of 3-phenylaminoisoxazolones (Scheme 6).



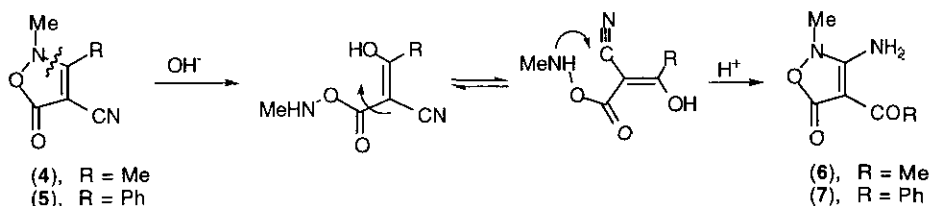
Scheme 5



Scheme 6

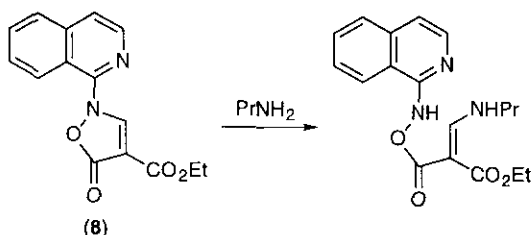
## V. REACTIONS INVOLVING ADDITIONS TO C-3

While the majority of amines and hydroxide react with 3-unsubstituted isoxazolones by the pathway shown in Section VI below, the presence of an additional electron withdrawing group at C-4 may promote reaction to occur by initial addition to C-3. Ponticelli<sup>18</sup> was able to isomerise the 4-cyanoisoxazolones (4) and (5) to the 3-amino-4-acyl isomers (6) and (7) by brief treatment with sodium hydroxide (Scheme 7).

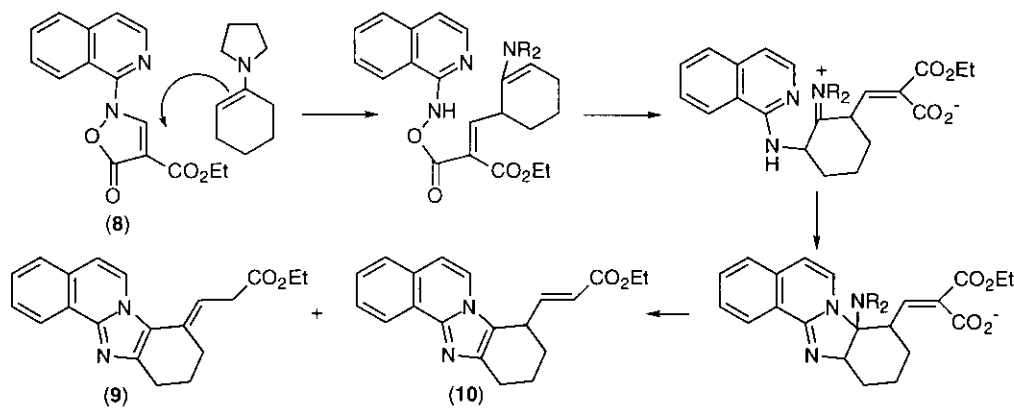


Scheme 7

Primary amines such as propylamine or aniline have been shown to add to C-3,<sup>19</sup> replacing the acyloxyamine (Scheme 8). We have shown that this process is reversible.<sup>20</sup> A more complex example of this mode of reaction came from a study of the reaction of isoxazolone (8) with pyrrolidinocyclohexene (Scheme 9).<sup>21</sup> The key steps leading to the isomeric tetracyclic products (9) and (10) were the displacement of the hydroxylamine from C-3, followed by electrophilic amination of the enamine by the resulting hydroxylamine ester.

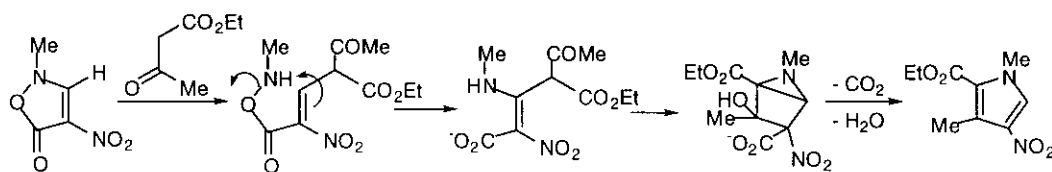


Scheme 8



Scheme 9

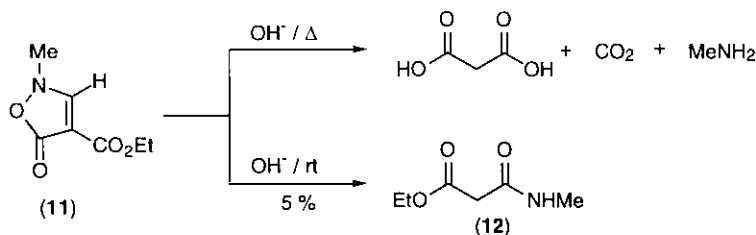
A recent synthesis of nitroindazoles by Ariga<sup>22a</sup> from the reaction of  $\beta$ -dicarbonyl compounds with 2-methyl-4-nitroisoxazol-5(2H)-one (Scheme 10) appears also to be initiated by addition to C-3, and the amination of the nucleophilic carbon is reminiscent of that reported by Prager's group.<sup>21</sup> More recent applications of 4-nitroisoxazol-5(2H)-one appear to involve cyano-*aci*-nitroacetate as an intermediate.<sup>22b</sup>



Scheme 10

## VI. REACTIONS WITH ISOXAZOL-5(2H)-ONES UNSUBSTITUTED AT C-3

The first 5-oxodihydroisoxazoles to be subjected to base treatment were the ester derivatives. Ruhemann<sup>2</sup> and Claisen<sup>3</sup> reported that ethyl 2-methyl-5-oxo-2,5-dihydroisoxazole-4-carboxylate (**11**) decomposed on boiling in alkaline solution to give methylamine, carbon dioxide and malonic acid. Much later Ulrich<sup>23</sup> repeated this work and isolated the amide (**12**) (Scheme 11).

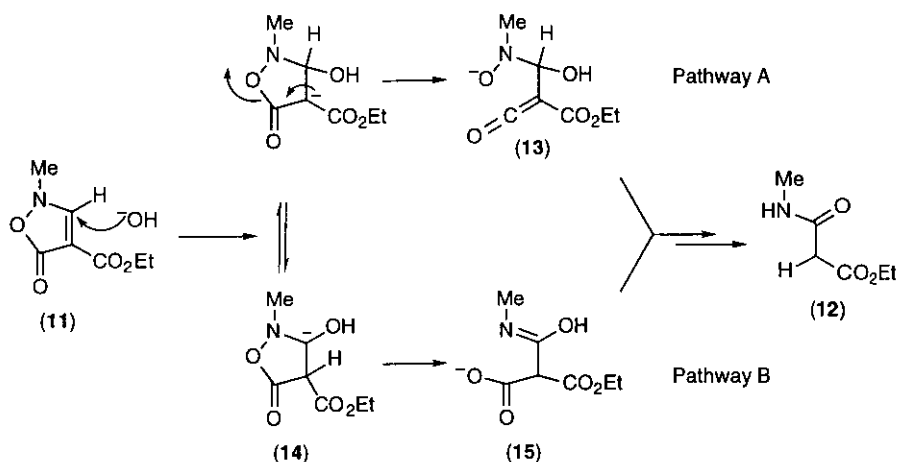


Scheme 11

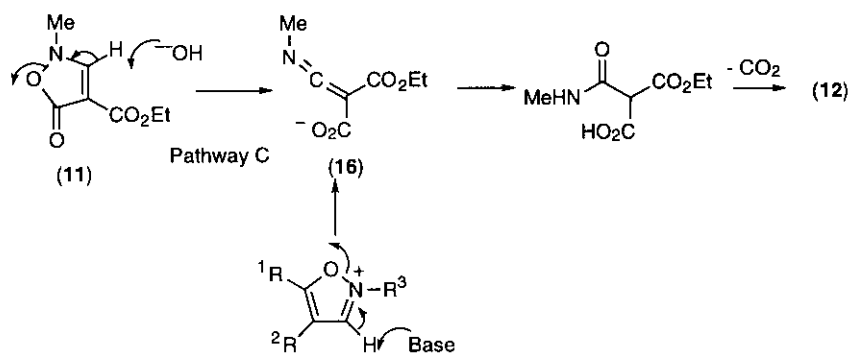
The work of Rupe<sup>24,25</sup> had been interpreted to suggest that hydrolysis of the lactone was the first step,<sup>26</sup> but this was based on misassignment of the structures of the products obtained. Ulrich<sup>23</sup> described three possible mechanistic pathways to account for the products obtained from **11**. The first (Pathway A) involves nucleophilic addition to C-3, forming an anion at C-4, which could undergo ring opening to form a ketene (**13**). Addition to the ketene followed by decarboxylation and dehydration would then lead to the

observed product (12).

The second (Pathway B) suggests that the initial anion could be in equilibrium with anion (14) which would form the imine (15), leading readily to the malonamide (12) (Scheme 12). It was also suggested by Ulrich that the products from the reaction of 11 with cyanide and azide provided evidence for pathway B because the first formed anion was then resonance stabilized.



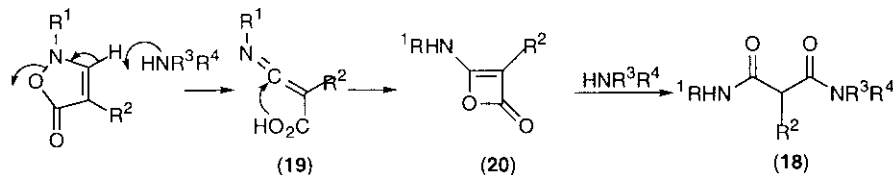
The third pathway (Pathway C) proposed by Ulrich involves the direct abstraction of the proton at C-3, affording a ketenimine intermediate (16), and was based on the accepted mode of ring opening of isoxazolium salts<sup>27-30</sup> (Scheme 13). However, Ulrich<sup>23</sup> favored Path B, as he was unable to detect any evidence for the ketene or ketenimine by IR spectroscopy.



Woodman clarified the mechanism of this process in a series of papers.<sup>4-8</sup> He first reinvestigated<sup>5</sup> the work of Ulrich with 11 and 2,4-diphenylisoxazol-5(2*H*)-one (17). He reassigned the structures of the malonamide esters obtained from 11 with sodium ethoxide, and from 17 with sodium acetate, correcting the work of Rupe<sup>25</sup> and Renzi.<sup>26</sup>

The reaction of a number of isoxazolones with primary and secondary amines gave not the expected amidines,<sup>6</sup> as required by the Ulrich pathway B (Scheme 12), but instead the diamides (18). A modification to the Ulrich pathway C, which had been rejected by Ulrich,<sup>25</sup> was now clearly supported. It

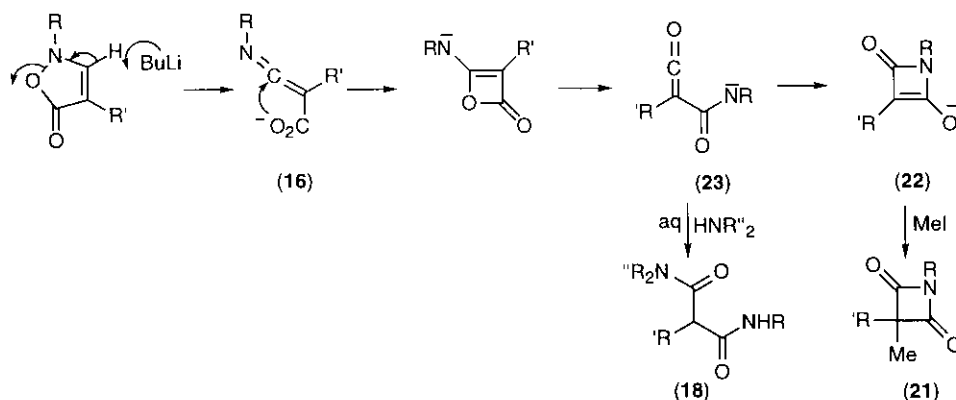
was proposed that the initially formed ketenimine (**19**) undergoes intramolecular cyclization to the  $\beta$ -lactone (**20**), which is opened by the amine to give the observed diamides (**18**) (Scheme 14). For the reaction with cyanide and azide, Woodman suggested that the nucleophiles reacted with the ketenimine (**19**) or  $\beta$ -lactone (**20**).



Scheme 14

Pepino<sup>31,32</sup> provided support for the Woodman mechanism, isolating diamides after reaction with a range of amines. He reported the reaction followed first order kinetics and their rate constants were in agreement with the proposed mechanism. Pepino<sup>33</sup> and Wicks<sup>34</sup> reported that alcohols followed the same rearrangement pathway as amines, but it is quite possible that they were observing photochemical reactions.<sup>35</sup>

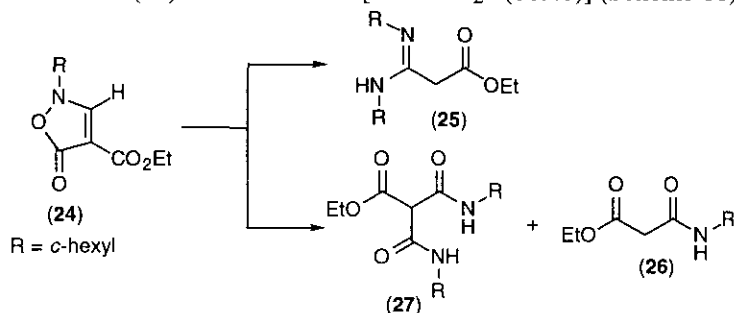
Woodman<sup>8</sup> was able to provide definitive IR spectral evidence for the formation of ketenimine carboxylates (**16**) (2020 and 1587  $\text{cm}^{-1}$  respectively). Even when methoxide was used as base, the ketenimine carboxylate (**16**) could be observed in the IR as a transient species. Moreover, when **16** was added to amines the previously observed diamides (**18**) were formed. When the solvent was changed from THF to HMPA a second intermediate was formed reversibly from the ketenimine carboxylate. This second anion also formed the diamide (**18**) when added to aqueous diethylamine and was trapped with methyl iodide, to afford the malonimide (**21**) (Scheme 15). While the second anion is probably the malonimide anion (**22**) rather than the ketene (**23**), the existence of the latter is inferred.



Scheme 15

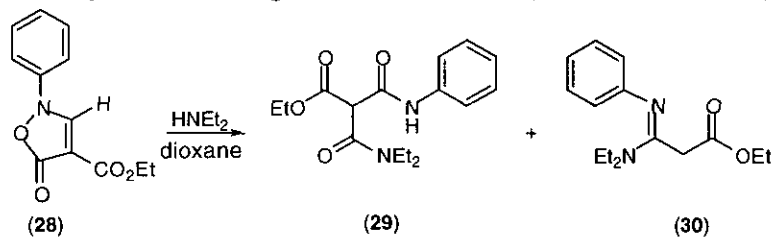
Using ethyl 2-cyclohexyl-5-oxo-2,5-dihydroisoxazole-4-carboxylate (**24**) and cyclohexylamine Wicks<sup>34</sup> demonstrated that by altering the solvent system, as Woodman had done, the reaction could be controlled to give either the amidine (**25**) from the ketenimine [ $\text{CCl}_4$ ,  $\text{MeCN}$ , or  $\text{Me}_2\text{SO}/\text{H}_2\text{O}$  (95:5)] or a mixture of

malonamide (26) and diamide (27) from the ketene [MeCN/H<sub>2</sub>O (60:40)] (Scheme 16).



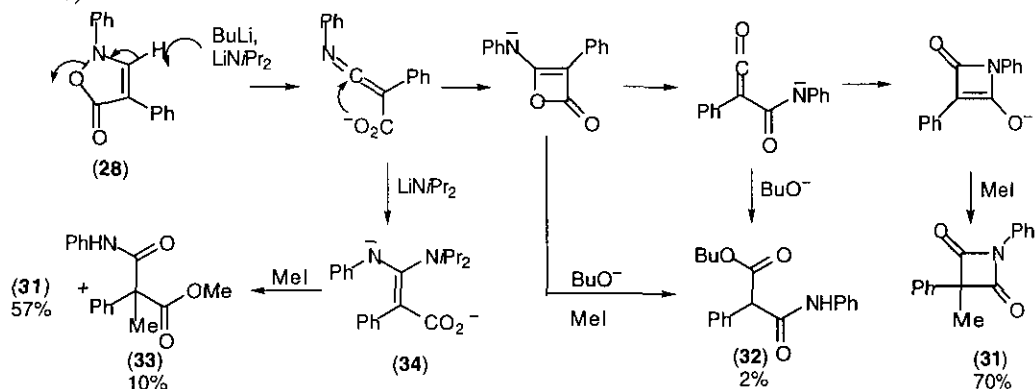
Scheme 16

The formation of the amidine (25) suggested that the more polar solvent increased the lifetime of the ketenimine carboxylate. This was supported by the work of Prager<sup>19</sup> in which 2-phenylisoxazol-5(2*H*)-one (28) was reacted with diethylamine affording both the malonamide (29) and the amidine (30) (Scheme 17).



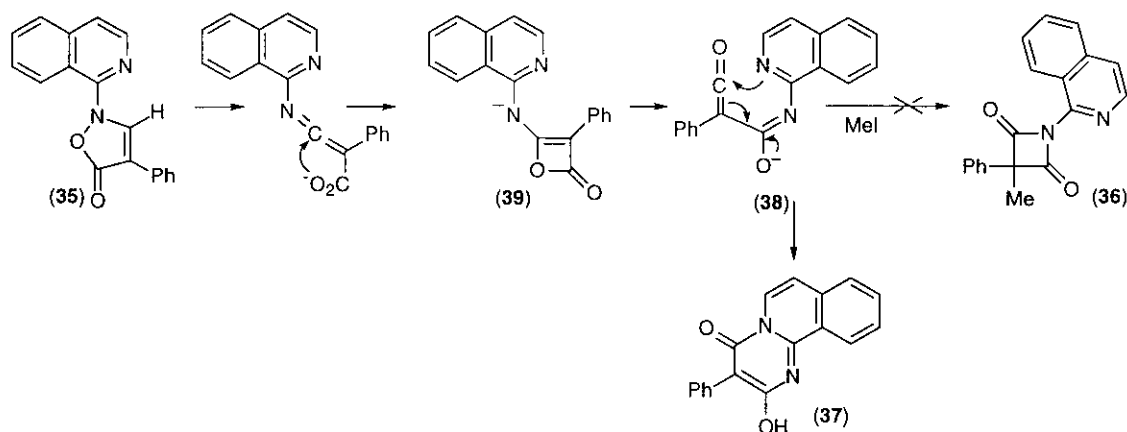
Scheme 17

Later, Prager and Razzino<sup>36</sup> were able to isolate products supporting each step of the Woodman mechanism. Treatment of 28 with *n*-BuLi, followed by trapping with methyl iodide, gave the azetidine-2,4-dione (31) in 70% yield. Replacement of butyllithium with LDA decreased the yield to 57% but two mechanistically significant minor products were obtained. The first was the butyl ester (32) which arises from the attack of the ketene or the β-lactone by LiOBu, present in trace amounts in the commercial reagent, followed by alkylation at the α position. A further by-product (33) arises from both carbon and carboxylate methylation of 34 which is the product resulting from reaction of LDA with the ketenimine (Scheme 18).



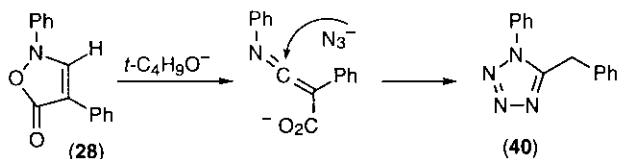
Scheme 18

The isolation of products **(32)** and **(33)** reinforces the proposed Woodman mechanism, but it was still not clear whether butoxide was reacting with the ketene or the  $\beta$ -lactone. However, when the 4-phenyl-2-quinolinylisoxazol-5(2*H*)-one **(35)** was reacted under similar conditions with butyllithium, no corresponding azetidine-2,4-dione **(36)** was isolated, but the pyrimidoquinoline **(37)** was isolated in 55% yield.<sup>36</sup> As shown in Scheme 19, this compound arises from an electrocyclic rearrangement of the ketene **(38)**. The corresponding  $\beta$ -lactone **(39)** cannot be the immediate precursor of **37** in this case, as steric constraints preclude attack by the quinoline N on the lactone carbonyl group.



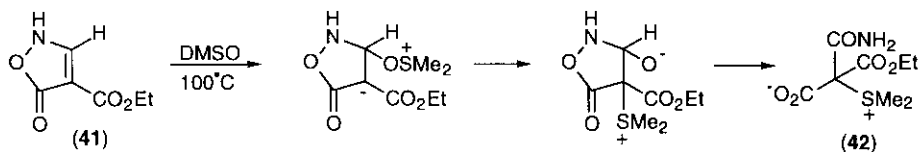
Scheme 19

Experimental work supporting the hypothesis that cyanide and azide reacted with the ketenimine was presented by Prager's group who confirmed a number of details of the proposed pathway.<sup>19,37</sup> When 2,4-diphenylisoxazol-5(2*H*)-one **(28)** was treated with lithium azide<sup>19,37</sup> no reaction occurred, but when it was reacted with one equivalent of potassium *t*-butoxide in the presence of lithium azide, the tetrazole **(40)** was obtained in 82% yield (Scheme 20).



Scheme 20

A number of unexploited observations or reaction by-products are also related to this base catalysed elimination process. For instance, when isoxazolone **(41)** is briefly heated in DMSO,<sup>19</sup> the major product (55%) is the betaine **(42)**, which possibly arises as shown in Scheme 21. In addition, the base frequently used to assist acylation of isoxazolones has been reported to lead to subsequent rearrangement.<sup>38</sup>

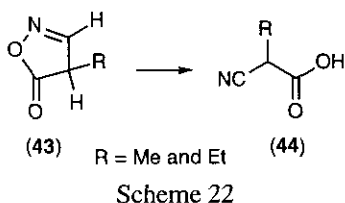


Scheme 21

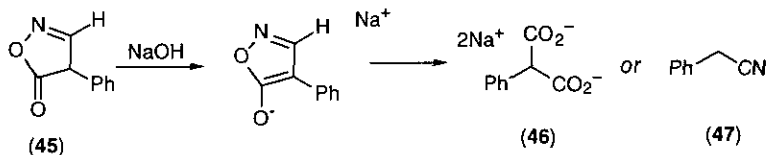


## VII. REACTIONS WITH ISOXAZOL-5(4*H*)-ONES

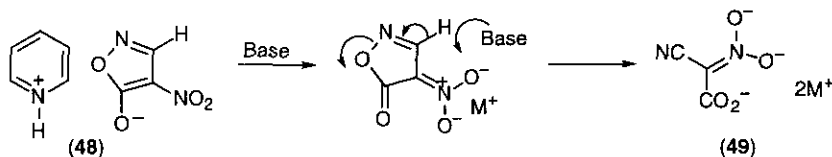
The base induced rearrangement of isoxazol-5(4*H*)-ones unsubstituted at position 3 has received far less attention than that of the 2*H* isomers. De Sarlo<sup>39</sup> reported that the 4-methyl- and 4-ethylisoxazol-5(4*H*)-one derivatives (**43**) were thermally unstable, rearranging to give  $\alpha$ -cyano acids, (**44**) (Scheme 22).



However, the phenyl derivative (**45**) was stable in aqueous sodium hydroxide solution, but ring opening occurred slowly on warming to give phenylmalonic acid (**46**) in aqueous sodium hydroxide or phenylacetonitrile (**47**) in alcoholic sodium ethoxide (Scheme 23).

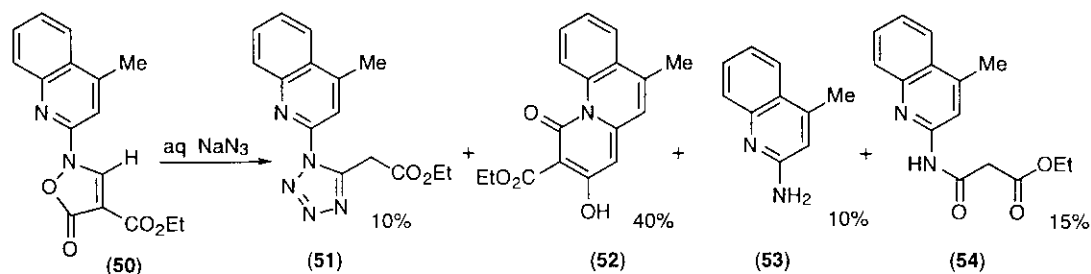


Although De Sarlo offered no mechanistic details, Quin<sup>40</sup> assumed deprotonation at C-3 was the key step, and Ariga<sup>41</sup> provided the most definitive evidence. It was shown that the pyridinium salt of 4-nitro-3-isoxazol-5-one (**48**) readily underwent rearrangement with a variety of bases affording cyanonitroacetate (**49**), a minimum of two equivalents of base being necessary to induce the rearrangement. The first equivalent deprotonates the pyridinium salt while the second equivalent was involved in proton abstraction from C-3, inducing N-O bond cleavage (Scheme 24).



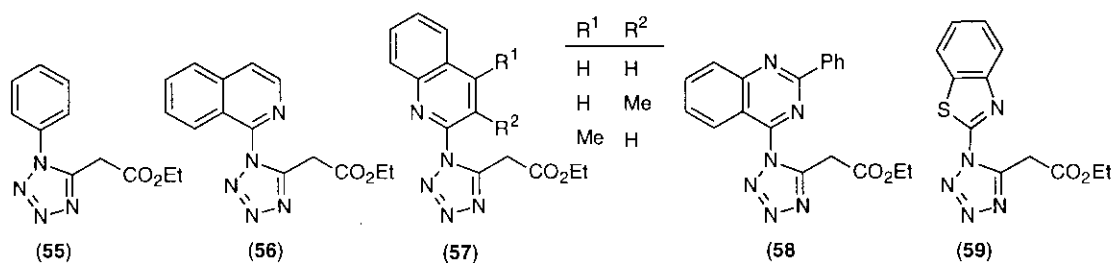
## VIII. SYNTHETIC APPLICATIONS

Prager's group<sup>19,37a</sup> developed the early work of Ulrich into a practical procedure for the synthesis of tetrazoleacetic acids, which were tested for potential antiinflammatory properties. For example, when the quinolinylisoxazol-5(2*H*)-one (**50**) and a number of other isoxazol-5(2*H*)-ones were reacted with sodium azide in aqueous THF at room temperature, a mixture of four compounds (**51-54**) were isolated in yields of 10, 40, 10 and 15% respectively (Scheme 25).



Scheme 25

The by-products (**52-54**) were formed by reactions involving the presence of water, and when lithium azide was used under anhydrous conditions, the tetrazoles (**55-59**) were obtained as the sole products in yields ranging from 82-20%. In the case of **55** and **58**, potassium *t*-butoxide was needed to generate the intermediate ketenimine. The acids (**55**), (**57**, R<sup>1</sup>=R<sup>2</sup>=H), (**58**) and (**59**) were assessed for their ability to inhibit prostaglandin PGE<sub>2</sub> synthesis, and on their affect on TNF<sub>α</sub> levels in human peripheral blood mononuclear cells.<sup>37b</sup> The most active was the quoline derivative (**57**, R<sup>1</sup>=R<sup>2</sup>=H) (30% inhibition of PGE<sub>2</sub> synthesis at 10<sup>-4</sup>M), but activities were deemed to be too low to follow up.



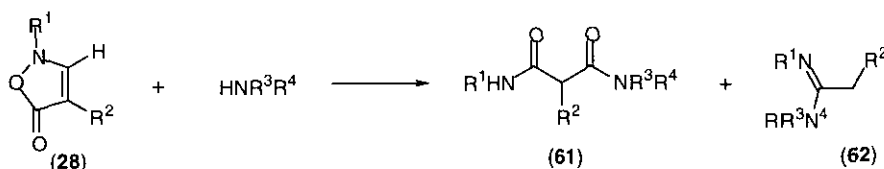
The base rearrangement of isoxazol-5(2H)-ones (**60**) is a convenient procedure for the synthesis of a variety of unsymmetrical malonamides (**61**), the advantage being that one can independently vary the substitution pattern of each amide unit as well as the substitution at C-2 of the malonamide. Pepino<sup>31,32</sup> showed that excess amine converted all ester containing derivatives into amides. Some examples are collected in Table 1.



Table I. Conversion of isoxazol-5(2*H*)-ones (60) into malonamides (61).

Isoxazol-5(2 <i>H</i> )-one	Product	Reference
$R^1, R^2 = \text{Ph}$	$R^3 = \text{H}, R^4 = \text{CMe}_3$	6
$R^1 = \text{CMe}_3, R^2 = \text{Ph}$	$R^3 = \text{H}, R^4 = \text{CMe}_3$	6
$R^1 = \text{Me}, R^2 = \text{Ph}$	$R^3, R^4 = \text{Et}$	6
$R^1 = \text{Me}, R^2 = \text{CO}_2\text{Et}$	$R^3 = \text{H}, R^4 = \text{CMe}_3$	6
$R^1 = \text{Me}, R^2 = \text{CO}_2\text{Et}$	$R^3, R^4 = \text{Et}$	6
$R^1 = \text{Ph}, R^2 = \text{CO}_2\text{Et}$	$R^3 = \text{H}, R^4 = \text{CMe}_3$	6
$R^1 = \text{Me}, R^2 = \text{CO}_2\text{Et}$	$R^3, R^4 = \text{H}$	31/32
	$R^3 = \text{H}, R^4 = \text{Me}$	31/32
	$R^3 = \text{H}, R^4 = \text{Et}$	31
	$R^3 = \text{H}, R^4 = (\text{CH}_2)_2\text{Me}$	31/32
	$R^3 = \text{H}, R^4 = \text{CMe}_3$	31/32
	$R^3 = \text{H}, R^4 = (\text{CH}_2)_2\text{Ph}$	31
	$R^3 = \text{H}, R^4 = \text{C}_6\text{H}_{11}$	31
	$R^3, R^4 = \text{Me}$	31/32
$R^1 = \text{Ph}, R^2 = \text{CO}_2\text{Et}$	$R^3, R^4 = \text{H}$	31/32
	$R^3 = \text{H}, R^4 = \text{Me}$	31/32
	$R^3 = \text{H}, R^4 = \text{Et}$	31
	$R^3 = \text{H}, R^4 = (\text{CH}_2)_2\text{Me}$	31/32
	$R^3 = \text{H}, R^4 = \text{CMe}_3$	31/32
	$R^3 = \text{H}, R^4 = (\text{CH}_2)_2\text{Ph}$	31
	$R^3 = \text{H}, R^4 = \text{C}_6\text{H}_{11}$	31
	$R^3, R^4 = \text{Me}$	31/32
$R^1 = \text{CH}_2\text{Ph}, R^2 = \text{CO}_2\text{Et}$	$R^3, R^4 = \text{H}$	31
	$R^3 = \text{H}, R^4 = \text{Me}$	31
	$R^3 = \text{H}, R^4 = \text{Et}$	31
	$R^3 = \text{H}, R^4 = (\text{CH}_2)_2\text{Me}$	31
	$R^3 = \text{H}, R^4 = \text{CMe}_3$	31
	$R^3 = \text{H}, R^4 = (\text{CH}_2)_2\text{Ph}$	31
	$R^3 = \text{H}, R^4 = \text{C}_6\text{H}_{11}$	31
	$R^3, R^4 = \text{Me}$	31

As previously mentioned, Wicks<sup>34</sup> and Prager<sup>19,20</sup> found that the formation of malonamides (61) or amidines (62) was strongly solvent dependent (Scheme 26).



Scheme 26

For isoxazolone (**28**,  $R^1 = \text{Ph}$ ,  $R^2 = \text{CO}_2\text{Et}$ ), the ratio of malonamide (**61**) to amidine (**62**) varied from dioxan (55 : 41), dichloromethane (50 : 50), ethyl acetate (72 : 25) and acetone (65 : 32). Traces of water raised the proportion of malonamide dramatically, for instance to 90% in dichloromethane. The product ratio was also highly dependent on the amine employed, as shown in Table 2.

Table 2. Product yields (%) from reactions of isoxazolone (**28**) and amines in dioxane

Amine	p <i>K</i> <sub>a</sub>	Amidine ( <b>62</b> )	malonamide ( <b>61</b> )
diethylamine	10.49	41	55
diisopropylamine <sup>a</sup>	10.96	36	10
piperidine	11.12	49	(7
morpholine	8.33	68	30
<i>n</i> -butylamine	10.77	0	100 <sup>b</sup>
<i>t</i> -butylamine	10.83	0	100

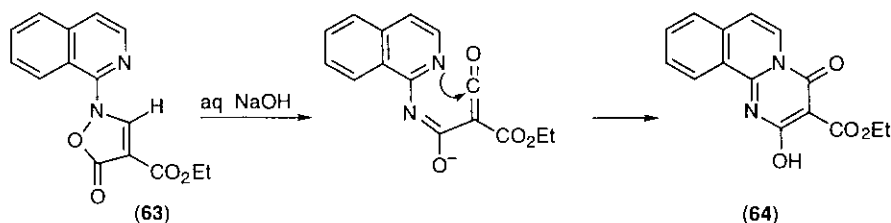
<sup>a</sup>) Considerable unreacted (**28**) was recovered; <sup>b</sup>) Ester undergoes amine/ester exchange.

The presence of  $\text{LiNR}_2$  it was generally found to improve yields<sup>42</sup> of amidines (**62**) as shown in Table 3.

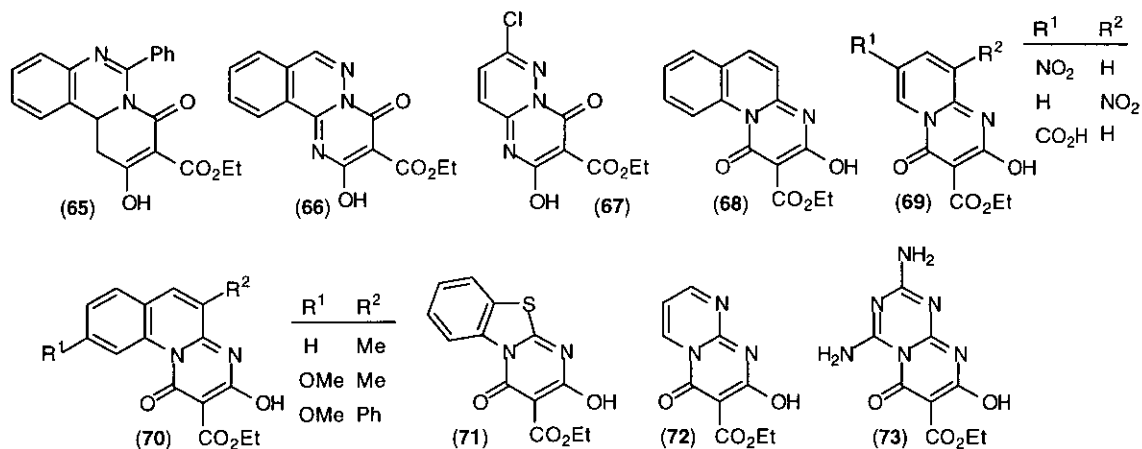
Table 3. Product yields (%) from reactions of isoxazolones (**28**) and lithium amides

Amide	Amidine ( <b>62</b> )	malonamide ( <b>61</b> )
Lithium diethylamide	52	47
Lithium diisopropylamide	87	13
Lithium piperidide	45	55
Lithium morpholinide	82	18
Lithium pyrrolidide	43	57

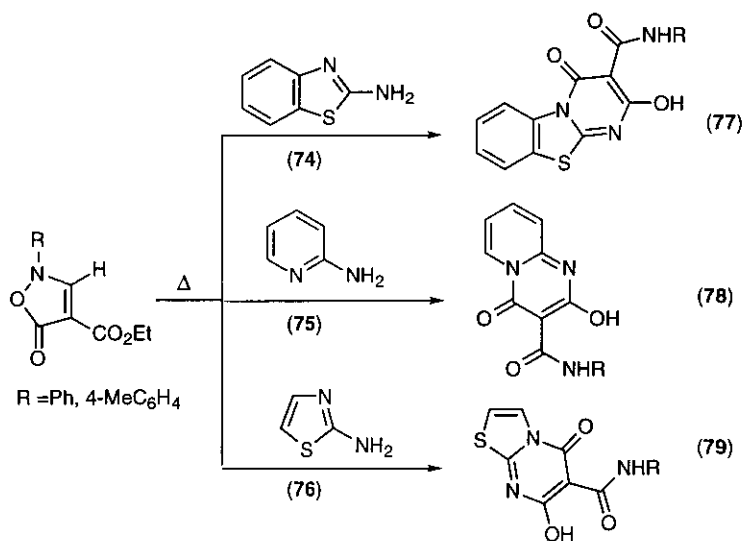
It was found that N-2 of an isoxazol-5(2*H*)-one is easily arylated with chlorohetarenes. Thus, the reaction of the isoxazolone (**41**) with 2-chloroisoquinoline gave the *N*-arylisoxazolone (**63**) in high yield,<sup>43</sup> and reaction of such compounds with aqueous sodium hydroxide afforded pyrimidine (**64**) in 96% yield (Scheme 27).<sup>44,45</sup> Many different derivatives (**65-73**), which are normally difficult to synthesize using conventional methods, were easily obtained in very high yields.



Scheme 27

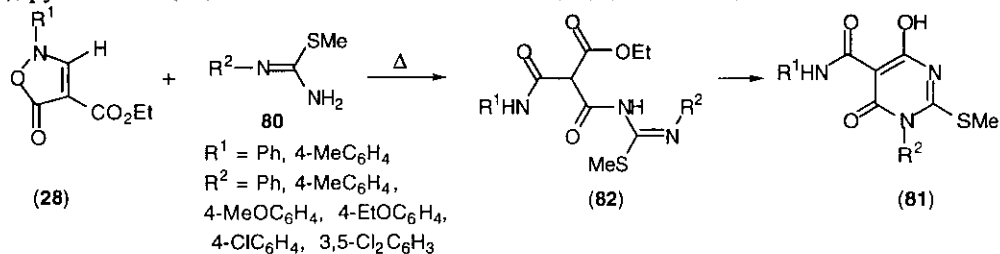


This sequence of reactions delivers annulated pyrimidines that have the same substitution pattern as those subsequently generated by Marcaccini,<sup>46</sup> who showed that when heteroaromatic amines (**74-76**) were used, both as base and nucleophile, the intermediate malonamides underwent cyclization to give fused pyrimidines (**77-79**) (Scheme 28).



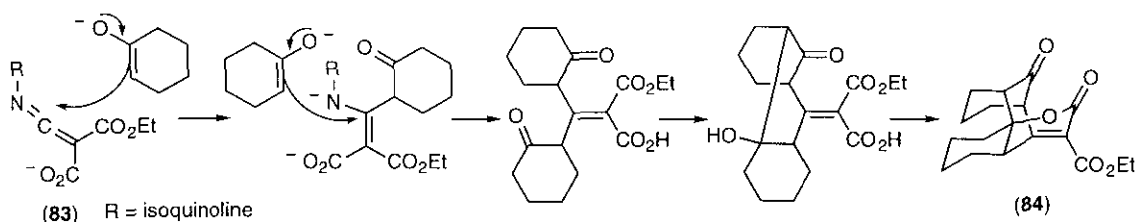
Scheme 28

Marcaccini<sup>47</sup> also showed that when 2-methyl-3-arylisothioureas (**80**) were reacted with isoxazol-5(2*H*)-one (**28**), pyrimidines (**81**) were formed *via* intermediate (**82**) (Scheme 29).



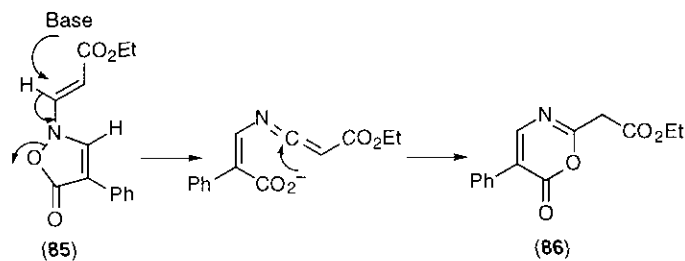
Scheme 29

While the enamine of cyclohexanone reacted with 4-ethoxycarbonylisoxazolones mainly by addition to C-3 of the isoxazolone as described in Section V,<sup>21</sup> the corresponding ketenimine (**83**) was trapped by the enolate of cyclohexanone, and the resulting alkylidenemalonate then reacted with a second equivalent of the enolate to give the lactone (**84**) (68%) (Scheme 30).<sup>21</sup>



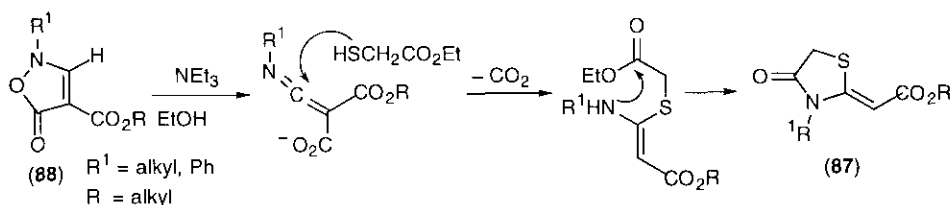
Scheme 30

The reaction of *N*-vinylisoxazolones with bases has not been explored in detail, but Prager and Razzino reported that the acrylate derivative (**85**) gave the 1,3-oxazin-6-one (**86**) on reaction with butyllithium at  $-80^{\circ}\text{C}$ .<sup>36</sup> In this case the formation of a ketenimine intermediate arises by proton elimination from the vinyl group, rather than from C-3 (Scheme 31).



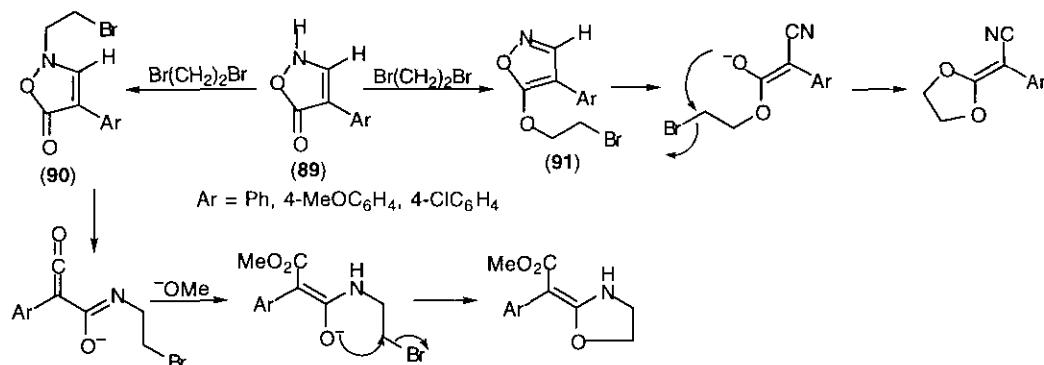
Scheme 31

Intermediates (**87**), for the synthesis of a number of antihypertensive agents were readily obtained from the reaction of isoxazol-5(2*H*)-ones (**88**) and ethyl thioglycolate after refluxing in ethanol containing triethylamine<sup>48</sup> (Scheme 32).



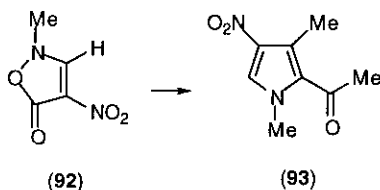
Scheme 32

The utility of the reaction of isoxazolone derivatives with bases is illustrated by the work of Beccali<sup>49</sup> who utilized both the *N*-alkylation product (**90**) of isoxazol-5(2*H*)-one (**89**), and the *O*-alkylation product (**91**), to synthesize ketene *O,O*-acetals and *N,O*-acetals (Scheme 33).



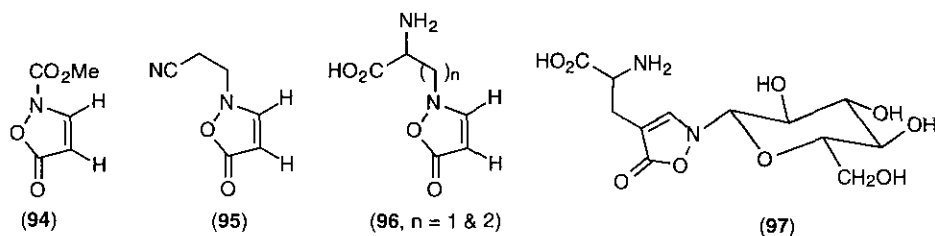
Scheme 33

Finally, as described in detail earlier, in 1997 Ariga reported<sup>22</sup> the synthesis of nitropyrroles (**93**) from 2-methyl-4-nitroisoxazol-5(2*H*)-one (**92**) and  $\beta$ -dicarbonyl enolates.

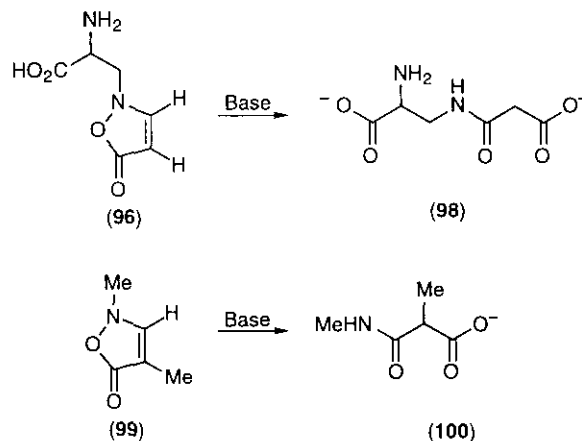


## IX. APPLICATION TO NATURAL PRODUCT DETERMINATION

A number of naturally occurring 3,4-unsubstituted isoxazol-5(2*H*)-ones (**94-97**) have been reported.<sup>50-54</sup>



The structure of **96**, isolated by Lambein from pea seedlings (*Pisum sativum*), was determined by a combination of NMR spectroscopy and degradation under basic conditions.<sup>53,55</sup> Base rearrangement of **96** ( $n = 1$ ) gave the amino acid (**98**) which was compared to the base rearrangement product (**100**) from 2,4-dimethylisoxazol-5(2*H*)-one (**99**)<sup>56</sup> (Scheme 34). This procedure has been adopted by subsequent workers in this field.<sup>51,52,54</sup>



Scheme 34

## X. CONCLUSION

The reaction of isoxazol-5-ones with nucleophiles has the potential to follow a number of different mechanistic pathways. Their potential in organic synthesis has not been fully exploited, and it is the hope of the reviewers that the clarification of the mechanisms involved in the reactions will lead to further applications.

## ACKNOWLEDGEMENTS

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