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# Annulation reactions of azoles and azolines with heterocumulenes

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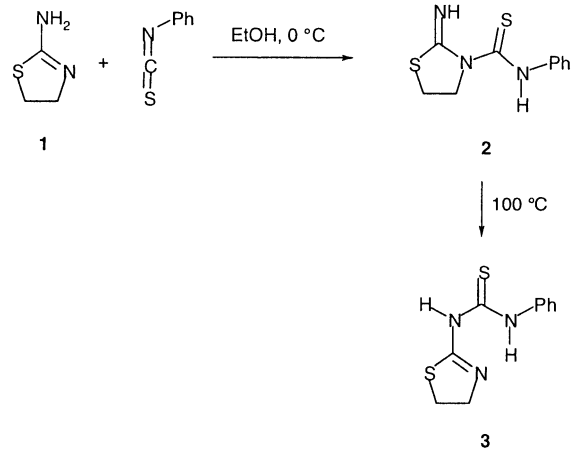
**Contents**



## 1. Introduction

Over the last 40 or so years a large number of reactions have been reported in which an azole or azoline (oxazole, thiazole, imidazole, and their reduced and/or fused analogues) has reacted with a heterocumulene (mainly and isocyanate or a ketene) to give an often bewildering range of heterocyclic products.[1] The literature on these compounds highlights the problems encountered in their characterisation, especially before the advent of high field NMR as a routinely available technique, and it is therefore hardly surprising to note that erroneous structural assignments have occurred. This review summarises the literature, and critically assesses the reaction mechanisms so that, hopefully, a reasonably unified pattern will emerge.

Although there are common mechanistic features between the various reactions, for convenience the reactions have been divided into simple acylations, [2+2], [2+2+2], [3+2], [3+3] and [4+2] annulations, and a number of reactions which do not fit into any of these categories. In most cases, the annulation reactions probably occur in a stepwise manner, with acylation of nitrogen often being the first step, so that while the simple acylation reactions do not result in ring formation, they have been included to allow a clearer understanding of the mechanisms of the latter reactions. Similarly, a number of related annulation reactions have been included which, while not involving both azolines and heterocumulenes, show the scope of some of the reactions and alternative preparations of related compounds. The vast amount of literature published makes comprehensive coverage impossible, especially for simple acylation reactions and reactions outside the main focus of the review, and it is unavoidable that the reviewers' interests will bias the choice of material. In particular, the use of carbon dioxide and carbon disulfide as heterocumulenes have been excluded since these reactions are usually straightforward and do not fit well with the rest of the subject matter.




1 2 3

**Scheme 1.**

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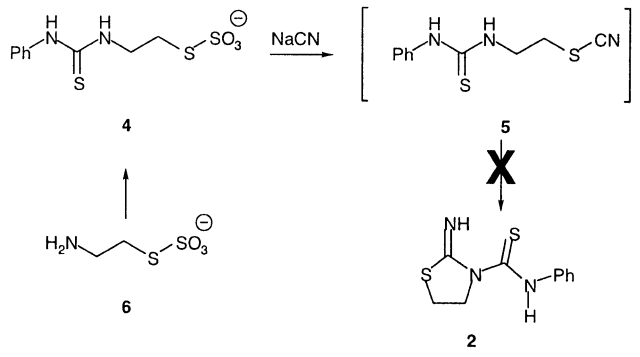


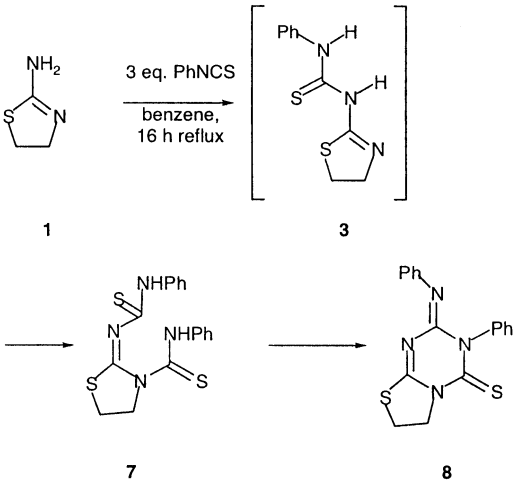

Scheme 2.

## 2. Acylation of azoles and azolines

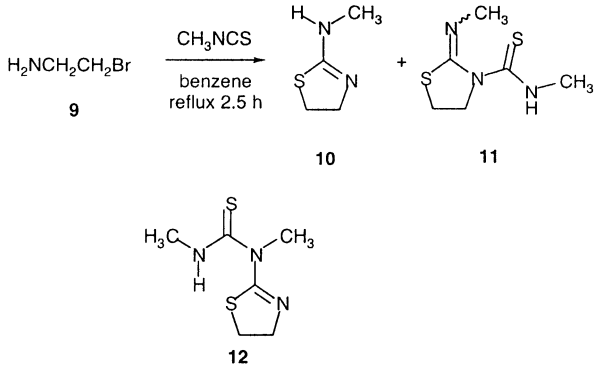
Isocyanates have long been used as derivatising agents. Henry and Dehn derivatised a wide range of nitrogen heterocycles with aryl isocyanates, but the structures of the products were not given. Most of the derivatives are presumably ureas, but, with compounds such as benzothiazole, acylation at the 2-position is more likely (vide infra).[2]

In the reactions of 2-aminothiazoline **1** with isothiocyanates, a number of erroneous structural assignments have been made, with a resulting amount of confusion in the literature. Surprisingly, in this example it appears that the initial report was correct in every detail. Thus, Fromm and Kapellen-Adler reported in 1928 that phenyl isothiocyanate reacts with 2-aminothiazoline **1** at 0°C at the endocyclic nitrogen to give **2** (mp 60°C; resolidified 80°C; second mp 129°C) followed by a migration to the exocyclic nitrogen giving **3** (mp 130°C) upon heating (Scheme 1).[3]

Klayman's re-investigation of this reaction highlights the problems in drawing conclusions from low yields of products. These workers were only able to isolate one product irrespective of the reaction temperature, the melting point of which was inconsistent with either product described in the earlier report.[3] In order to account for their results, an independent synthesis of **2** was attempted by reaction of **4** with cyanide (Scheme 2). Unfortunately,



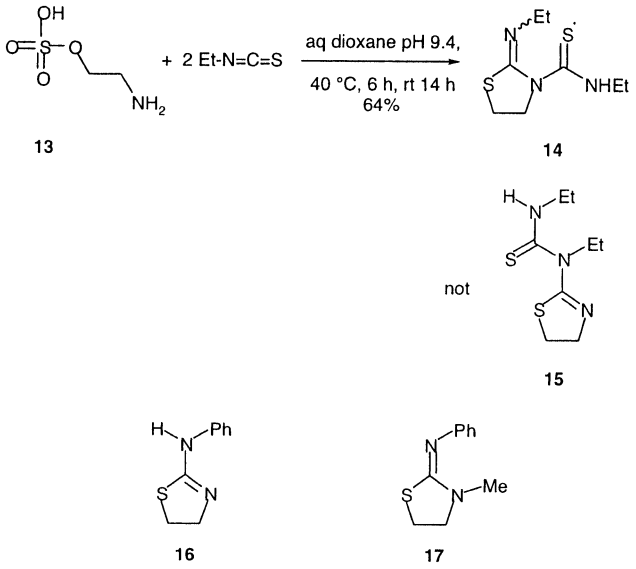

Scheme 3.



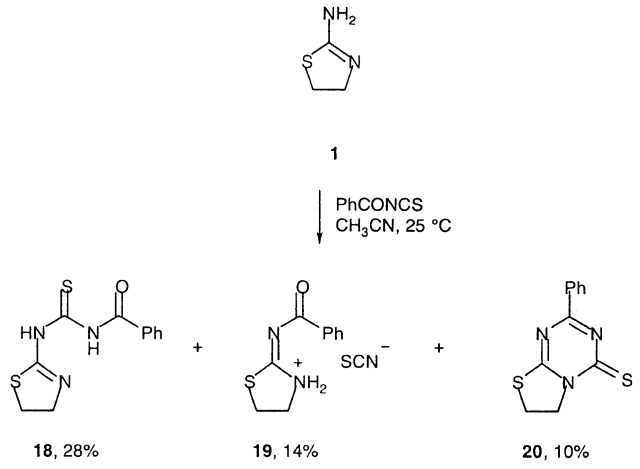

Scheme 4.

while a product was obtained with the same melting point (148–149°C) as that derived by these authors from the reaction of **1** with phenyl isothiocyanate,[4] it eventually became apparent[5] that this was formed by reaction of cyanide with unreacted **6** followed by reaction with phenyl isothiocyanate. Therefore, no conclusions could be reliably drawn. Tentative assignment of NMR and mass spectrometric data supported structure **3** for this product, but the structure was unequivocally established by Flippen and Karle by single crystal X-ray diffraction.[6] Surprisingly the crystallographic sample (supplied by Klayman) had the same melting point as compound **3** originally claimed by Fromm!

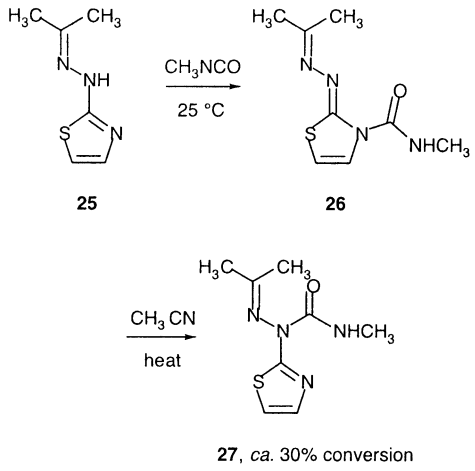
In a later re-investigation, Rasmussen et al.[7] observed the kinetic formation of **2** and thermodynamic formation of **3**, exactly as initially reported by Fromm. Again the melting point was higher than initially reported; this was attributed to formation of a polymorph due to rapid precipitation. Similar results were obtained in the reactions of 2-aminothiazoline with alkyl isothiocyanates.[8] Reaction of **3** with phenyl isothiocyanate, or reaction of **1** with an excess of the same, resulted in the formation of a double adduct **7** and subsequent cyclisation with loss of hydrogen sulfide gave **8**, the structure of which was confirmed by single crystal X-ray diffraction (Scheme 3).[9]




Scheme 5.



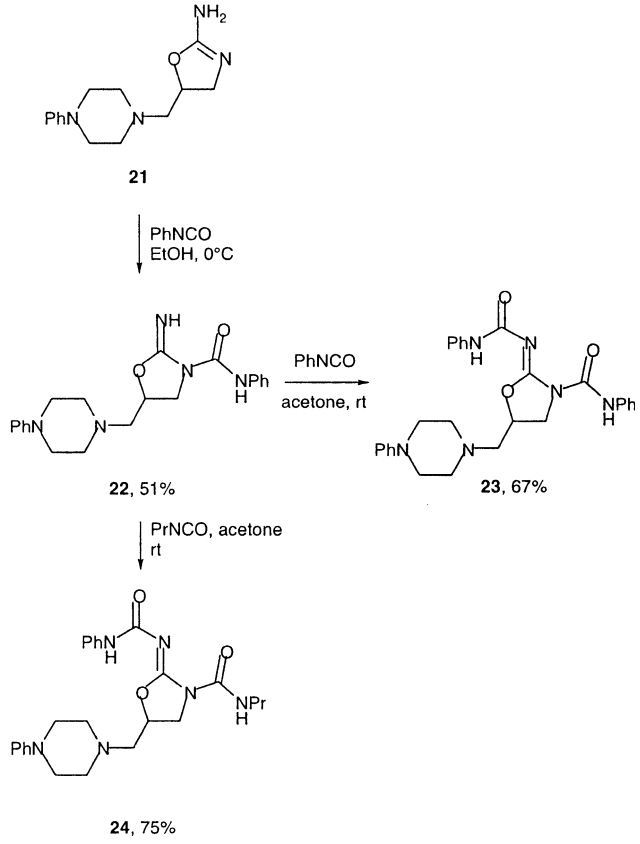

Scheme 6.




Scheme 8.

An acylated 2-aminothiazoline was isolated as a minor product in the formation of **10** from **9**. Under thermodynamic conditions we might expect this product to be **12**, as originally described.[10] Subsequent work, however, showed this to be incorrect,[11] and in fact it seems that while compounds similar to **11** have been shown to dissociate back to the iso(thio)cyanate, they do not subsequently recombine to give **12** unless there is a hydrogen on the imino nitrogen (Scheme 4).[12]

Similarly, the product derived from reaction of **13** with ethyl isothiocyanate was assigned structure **15** (the correct structure is **14**) on the basis of its NMR data bearing more similarity to **16** than to **17**.[13] In this case, Cherbuliez clearly underestimated the effect of acylation of the ring nitrogen on the chemical shift of the adjacent methylene group (Scheme 5).



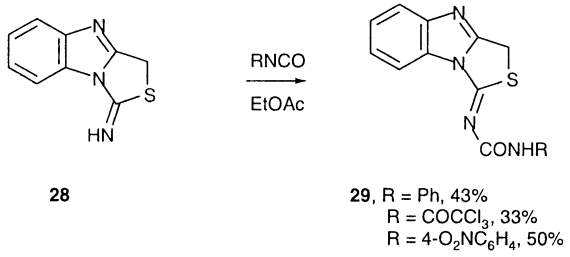

Scheme 7.

A further relatively early report describes the acylation of 2-aminothiazolines at only the exocyclic nitrogen, which is likely given the reaction conditions (benzene, reflux).[14] Meanwhile, reaction of 2-aminothiazoline with benzoyl isothiocyanate gave three products, **18**, **19** and **20**. The former products arise from acylation at the exocyclic nitrogen (**18** is converted into **19** upon heating) while **20** is presumably formed by initial acylation at the endocyclic nitrogen followed by cyclisation with concomitant dehydration. Clearly, although the kinetic/thermodynamic behaviour of such acylations has been well established, there are still surprises (Scheme 6).[15]

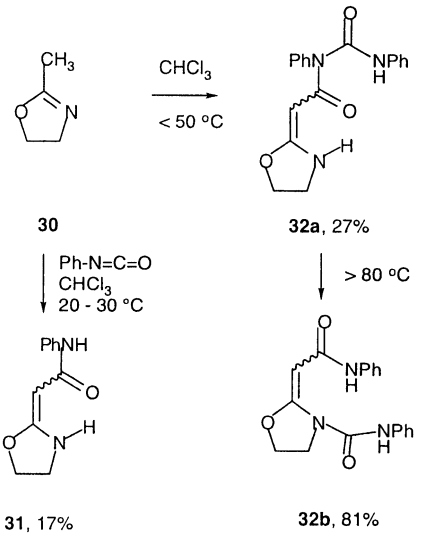
Oxazolines also show similar acylation behaviour towards isocyanates and isothiocyanates. Thus, reaction of **21** with phenyl isocyanate in dry ethanol gave **22** in 51% yield. Further reaction with the same isocyanate gave **23**. Reaction of **22** with propyl isocyanate, however, gave **24** in which the phenyl isocyanate has migrated prior to the second acylation (Scheme 7).[16]

Compound **26**, the kinetic acylation product from **25**, undergoes partial isomerisation to **27** upon heating, so that in this example there is clearly only a small energy difference between the two products (Scheme 8).[17]

Compound **28** is interesting, since there are two exocyclic (with respect to the thiazoline) nitrogens which could




Scheme 9.



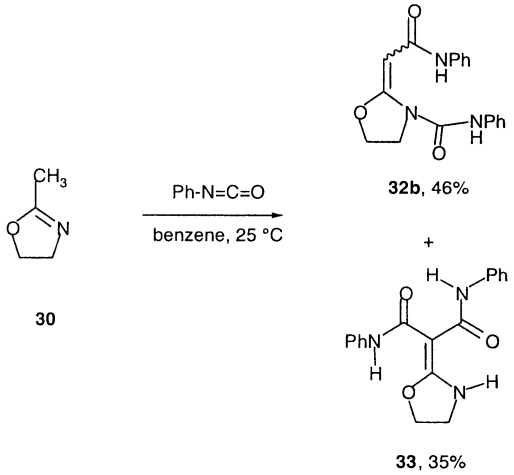

**Scheme 10.**

undergo acylation. Although the yields were modest, only ureas **29** were isolated (Scheme 9).[18]

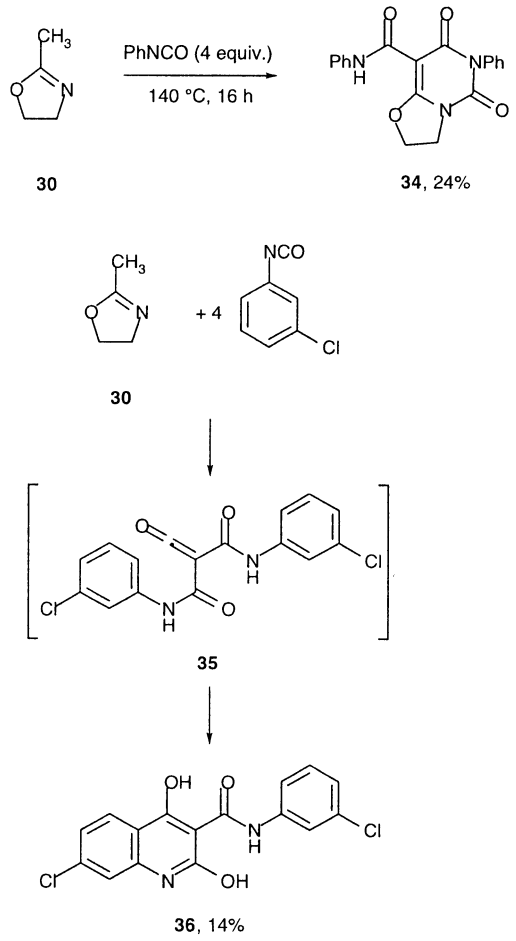
2-Methylazolines undergo a number of complex acylation reactions with isocyanates. A report in 1966 by Nehring and Seeliger[19] has been partially discredited by Richter and Ulrich.[20] The reaction of 2-methyloxazoline **30** with phenyl isocyanate was claimed to give a 1:1 adduct **31** at lower temperatures in chloroform, while at slightly higher temperatures a 2:1 adduct **32a** was formed which underwent isomerisation to **32b** on heating (Scheme 10).

Similar adducts were claimed for 2-ethyl and 2-undecyl-oxazoline, but no products were obtained with 2-isopropyl, 2-cyclohexyl or 2-phenyloxazolines. Richter and Ulrich re-assessed these reactions, and were unable to isolate either **31** or **32a**, and presented plausible data suggesting that the compound assigned structure **32a** by Seeliger is in fact **32b**, and that assigned as **32b** is actually **33** (Scheme 11).[20] Similar results were obtained with 2-methylthiazoline.

While these results are reasonable (and in fact we have obtained single crystal X-ray diffraction data for an ana-



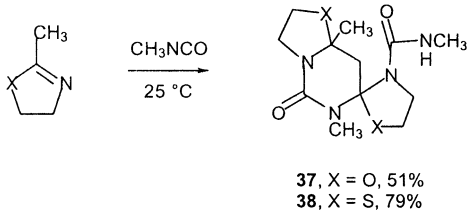

**Scheme 11.**



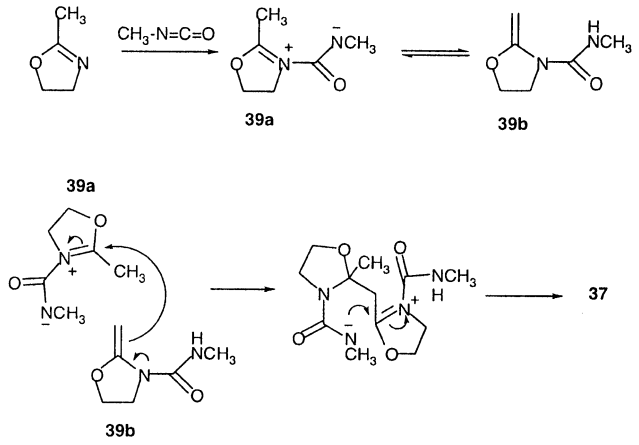

**Scheme 12.**

logue of **33** derived from 4-ethyl-2-methyloxazoline[21]), they do not account for the compounds obtained by Seeliger from 2-ethyl and 2-undecyloxazolines, which might reasonably be assumed to have structures related to **32b** as initially assigned. Under more vigorous conditions, 2-methyloxazoline and 2-methylthiazoline react further with isocyanates giving compounds of type **34**, with isoquinolines such as **36** being produced as minor by-products, presumably via the ketene **35** (Scheme 12).[22]

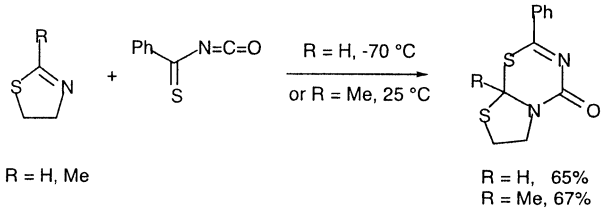
With methyl isocyanate, 2:2 adducts **37** and **38** were formed with 2-methyloxazoline and 2-methylthiazoline, respectively (Scheme 13). Similar adducts were only formed from 2-methyloxazoline and 2-ethyloxazoline and aryl isocyanates under the influence of boron trifluoride etherate, while even under these conditions 2-methylthiazoline gave only adducts similar to **33** with 4-methylphenylisocyanate.[23]




**Scheme 13.**




**Scheme 14.**

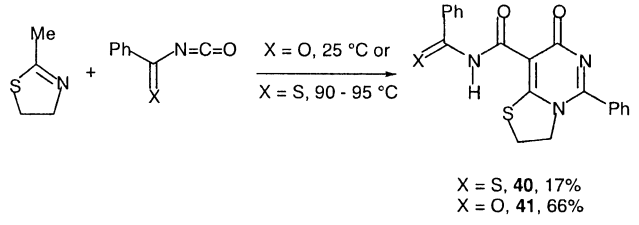



**Scheme 15.**

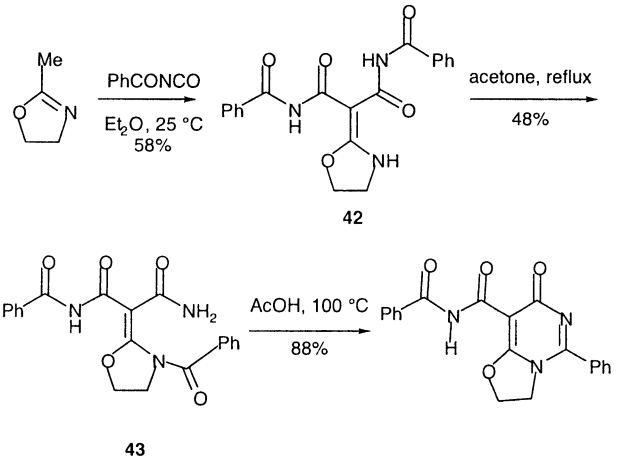
Presumably these 2:2 adducts are formed by initial acylation of the azoline, followed by a dimerisation in which one molecule reacts as the iminium ion tautomer **39a** with the enamine tautomer **39b** (Scheme 14).

Similar initial acylation was followed by an alternative mode of ring closure in the work of Tsuge and Kanemasa for benzoyl and thiobenzoyl isocyanates.[24] Benzoyl isocyanate did not react with 4,5-dihydro[1,3]thiazole, while thiobenzoyl isocyanate reacted as a 4π component in a formal hetero-Diels–Alder reaction with this compound and also with 2-methylthiazoline at room temperature (Scheme 15). This latter reaction proved temperature dependent, so that at elevated temperatures a 2:1 adduct **40** was obtained, which was readily hydrolysed (ammonium acetate/acetic acid) to **41**, the compound obtained from the reaction of 2-methylthiazoline with benzoyl isocyanate at room temperature (Scheme 16), confirming the relationship between these two products.

Similar results were obtained in the reactions of 2-methyloxazoline with benzoyl isocyanate, although in this case two intermediates were isolated. Clearly **42** is analogous to that obtained by Richter and Ulrich, and in this case can rearrange to **43** and cyclise as shown (Scheme 17).



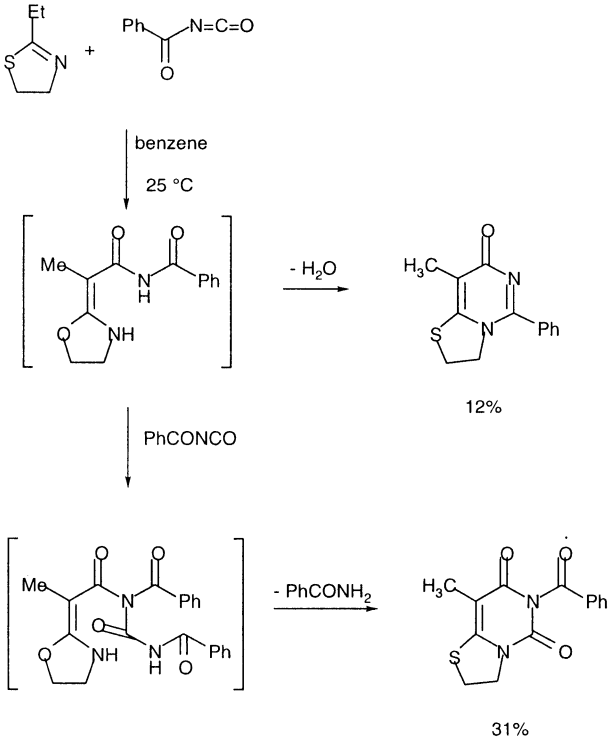

**Scheme 16.**



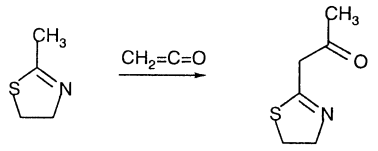

**Scheme 17.**

The reactions with 2-ethylthiazoline support our speculation about the work of Nehring and Seeliger,[19] in that a similar initial acylation was observed, again followed by cyclisation of the benzamide. Since with these compounds only a single acylation can occur at the carbon directly attached to the oxazoline ring, the major product is formed by a second acylation of the first isocyanate (Scheme 18). This is essentially the reaction proposed by Seeliger[19] and at least partially disproved by Richter and Ulrich.[20] In contrast, the reaction of 2-methylthiazoline with ketene is much more straightforward (Scheme 19).[25]

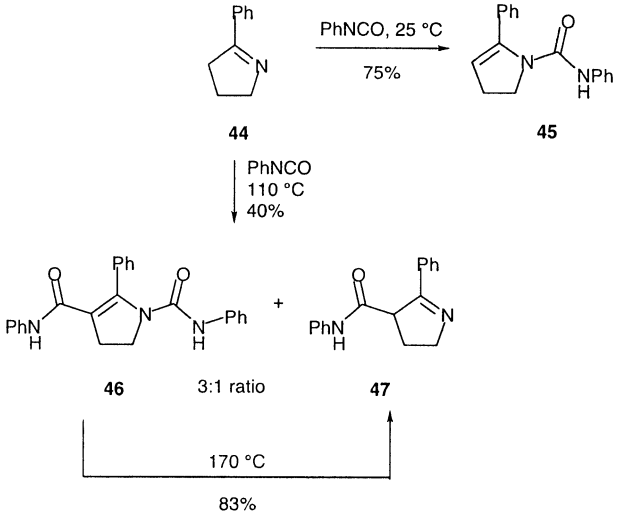
Pyrrolines also undergo acylation reactions, but the presence of a methylene group in place of the heteroatom in the azolines discussed thus far offers an alternative course of reaction. Treatment of **44** with phenyl isocyanate results




**Scheme 18.**



Scheme 19.

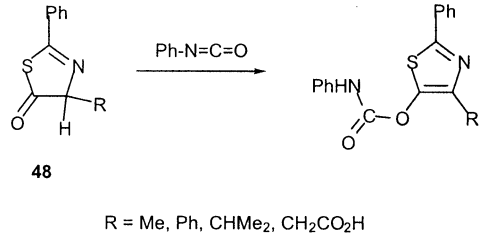


Scheme 20.

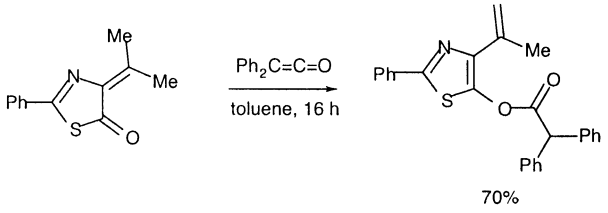
in the formation of *N*-acylenamine **45** by proton loss from the initial adduct. At elevated temperatures, a mixture of **46** and **47** was formed, while further heating of **46** formed **47** cleanly. The formation of **47** as the imine rather than the enamine tautomer is slightly surprising (Scheme 20).[26]

The types of reaction just discussed can be prevented by the presence of certain substituents on the azoline. Acylation of **48**, for example, takes place on the carbonyl oxygen to give the stable thiazole (Scheme 21).[27] A further related reaction is shown in Scheme 22.[28]

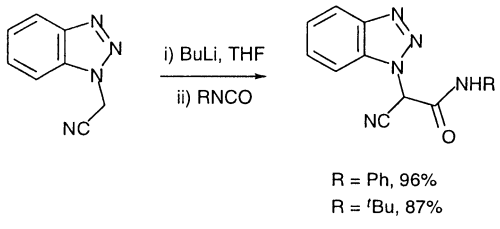
Benzotriazoles have been widely investigated as directing



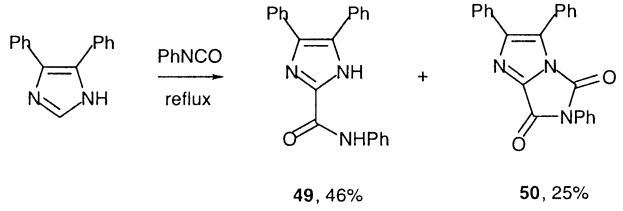
Scheme 21.



Scheme 22.



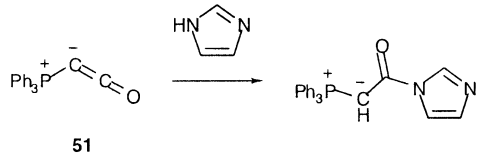
Scheme 23.



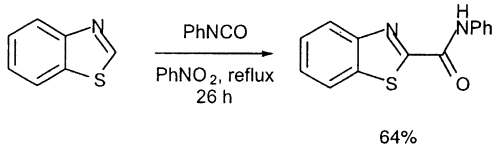
Scheme 24.

groups. Cyanomethylbenzotriazole reacts readily with alkyl and aryl isocyanates as shown in Scheme 23.[29]

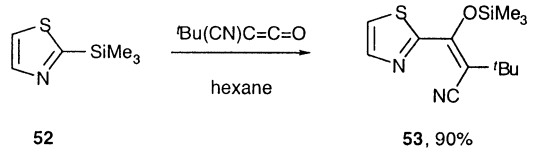
In other cases, acylation can take place directly onto the azoline ring. In what seems to be a common theme throughout this review, different products are obtained under kinetic and thermodynamic conditions. Staab and Seel observed the expected *N*-acylation of benzimidazole,[30] and an essentially identical reaction was observed with imidazole.[31] Gompper et al. were unable to reproduce the reaction under the exact conditions of Staab, but instead noted that *N*-acylation predominates at lower temperatures, while using phenyl isocyanate as solvent under reflux gave a mixture of **49** and **50** (Scheme 24).[32] Mitsuhashi et al. verified that acyl migration is possible, depending upon the substituents on the imidazole ring.[33]



Scheme 25.



Scheme 26.




52 53, 90%

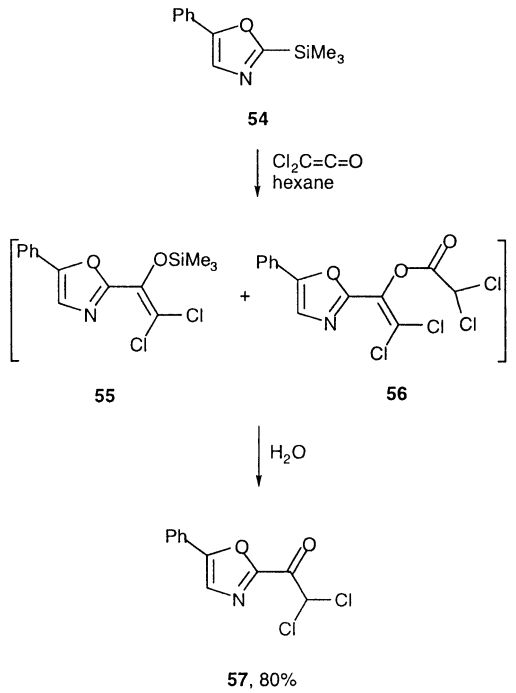
**Scheme 27.**

A further noteworthy example is the reaction of triphenylphosphoranylideneketene **51** with imidazole (Scheme 25).[34]

For benzothiazole, *N*-acylation does not lead directly to a stable product, so that *C*-acylation predominates as shown in Scheme 26. Similar products were obtained for imidazole and 1,2,4-triazole, but pyrazole gave only the *N*-acylated product. No reaction was observed with benzoxazole.[35]

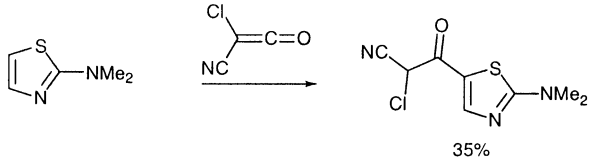
The related ketene adducts are conveniently prepared by reaction of 2-trimethylsilylthiazoles and 2-trimethylsilyloxazoles with the corresponding ketene. For instance, reaction of **52** with *t*-butylcyanoketene gave silyl enol ether **53** in 90% yield (Scheme 27). Diphenylketene and dichloroketene were also used with equal success.[36]

With compound **54**, reaction with 2 equiv. of dichloroketene gave a mixture of **55** and **56**, which, upon hydrolysis (silica gel), gave **57** in 80% yield (Scheme 28).[37]

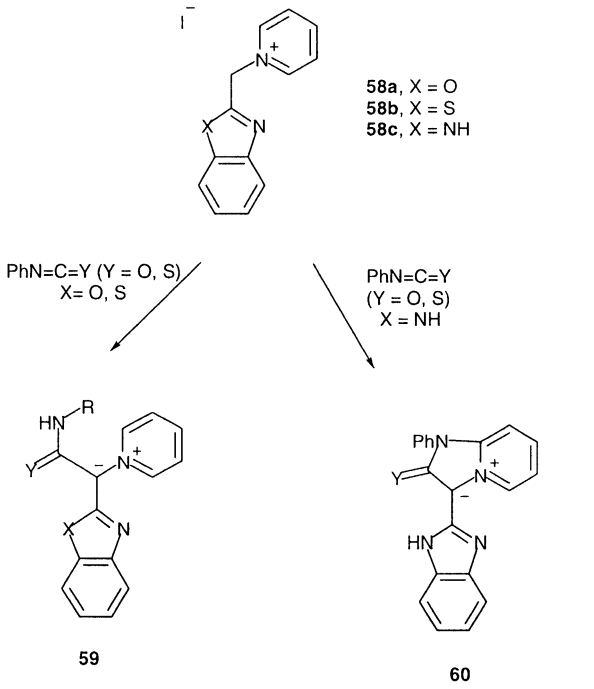



54 55 56 57, 80%

**Scheme 28.**




**Scheme 29.**



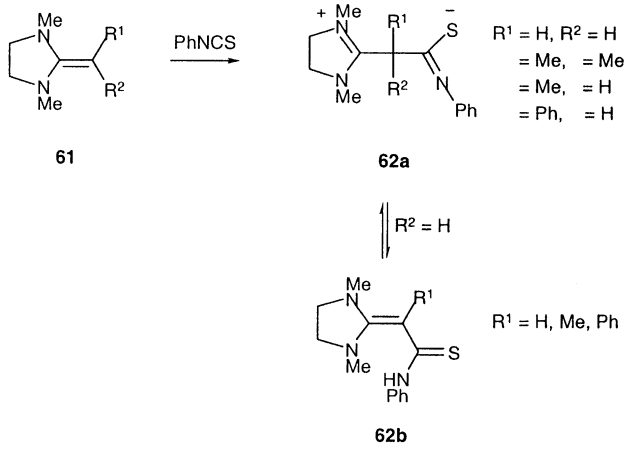

59 60

**Scheme 30.**

Analogous reactions of 2-dimethylaminothiazole (Scheme 29)[38] and a related oxazole[39] led to acylation at the 5-position, although if this position is blocked, acylation at the 4-position is possible.[40]

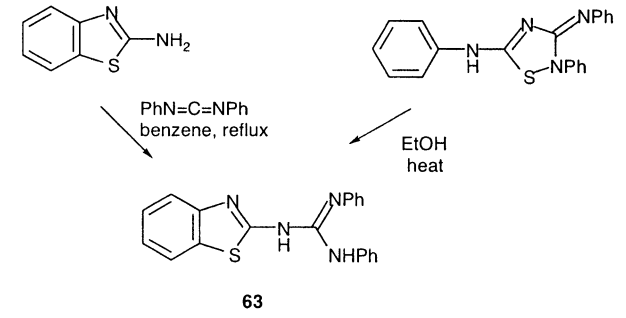
Stable ylides **59** were formed by reaction of isocyanates or isothiocyanates with benzoxazole **58a** or benzothiazole **58b**. With benzimidazole **58c**, however, ylides of general structure **60** were isolated (Scheme 30). It seems surprising that such a relatively minor change in the substrate would cause such a change to the product structure, but the authors present the results of a number of reactions on these products supporting their assigned structures.[41] These results with pyridinium ions should be contrasted with the work of Saczewski and co-workers.[42]

Related reactions take place with 2-methylene-1,3-dimethylimidazolidines **61** to give 1,4-dipoles **62a** in tautomeric equilibrium with thioamides **62b** (Scheme 31). When

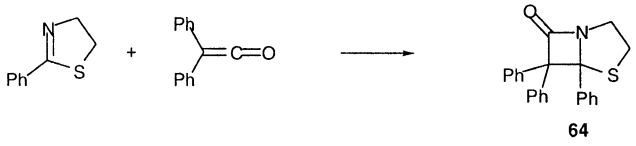



61 62a 62b

**Scheme 31.**



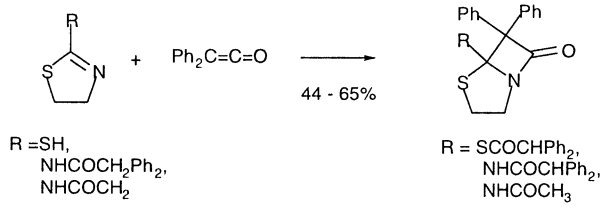

Scheme 32.



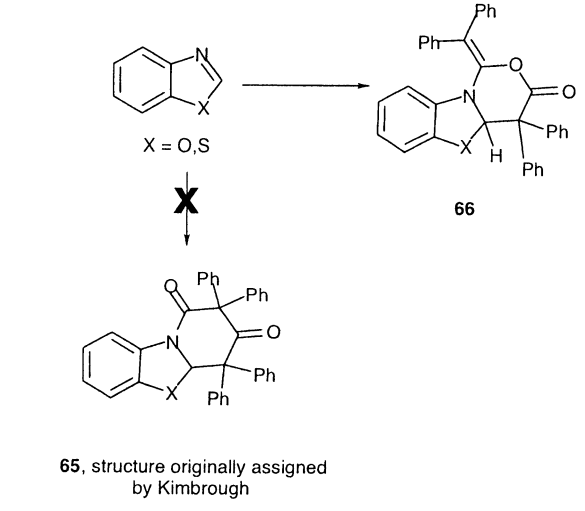

Scheme 33.

$R^1$=Ph, $R^2$=H, the thioamide tautomer is predominant, whilst with $R^1$=Me, $R^2$=H the dipolar tautomer is the major product; when both $R^1$=$R^2$=H, either tautomer can predominate depending on the solvent. Clearly, where $R^1$=$R^2$=Me, the thioamide tautomer is inaccessible, and this compound undergoes 1,4-dipolar cycloaddition with dimethyl acetylenedicarboxylate.[43]

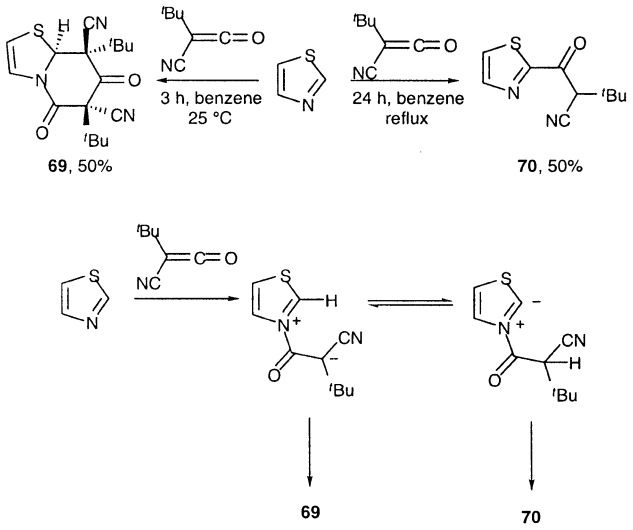
Simple acylation reactions of azoles with carbodiimides are less common, and **63** can be formed by the two routes shown in Scheme 32.[44]




Scheme 34.




Scheme 35.




Scheme 36.

## 3. [2+2] Annulations

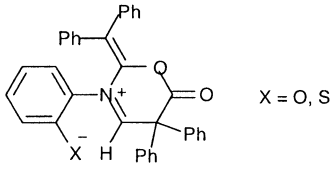
The reaction of ketenes with imines to form β-lactams has been known since the early part of the last century. With azolines, this reaction has particular applications to the β-lactam antibiotics, and has been thoroughly investigated. For example, reaction of 2-phenylthiazoline with diphenylketene gave the β-lactam **64** (Scheme 33).[45]

This reaction has been used successfully for a range of 2-substituted thiazolines (Scheme 34),[46] including a 2-methylselenylthiazoline.[47]

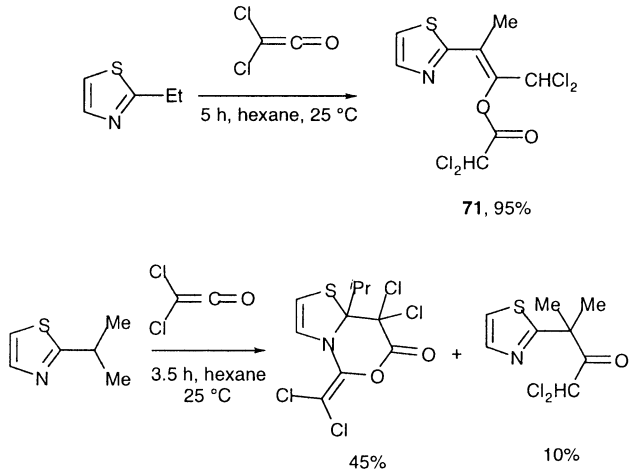
## 4. [2+2+2] Annulations

Early work from Kimbrough[48] had suggested that most simple azolines (2-methylthiazoline, 1-methylimidazole, benzoxazole, benzothiazole, 1-methylbenzimidazole) react with diphenylketene in a [2+2+2] manner to give **65** as shown in Scheme 35.

Other nitrogen heterocycles were found to give oxazinones with diphenylketene,[49] and so Haddadin and Hassner[50] re-examined the data presented for these compounds, since they felt that the high carbonyl infrared stretch (1770 $cm^{-1}$) was more consistent with structures **66**. Examination of the NMR spectra showed a difference between the oxazole and thiazole adducts compared to the imidazole adduct, and the betaine structure **67** was proposed to account for this data.



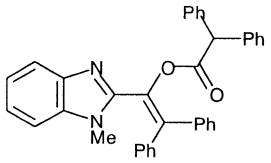

A further study showed that there was significant shielding of the proton at the benzoxazole or benzothiazole C-4




**Scheme 37.**

position, presumably due to the proximity of the aromatic rings of the diphenylmethylidene moiety, and that this would not be observed in the betaine due to free rotation of the C–N bond. On the basis of this investigation, Taylor considered that the betaine structures were unlikely, although no plausible explanantion for the position of the iminium hydrogen ($\delta$ 6.76 for the benzothiazole adduct compared to $\delta$ 5.1 for the analogous proton of the benzimidazole adduct) was provided.[51] It is worth noting, however, that reaction of **66/67** (X=S) with either methyl iodide or benzoyl chloride/pyridine returned only recovered starting material, so that an intermediate structure with some degree of charge separation and a lengthened C–S bond might account for the data without the need to postulate a full zwitterion.

In an additional complication to the story, Haddadin and Muradi returned to the problem in 1980, noting the differential reactivity of the three adducts to hydrazinolysis, and suggested a further alternative structure **68** for the benzimidazole adduct. The data presented are reasonable, so that the apparent discrepancy is due to initial attack of the ketene at carbon in this example but at nitrogen in the other two adducts.[52]

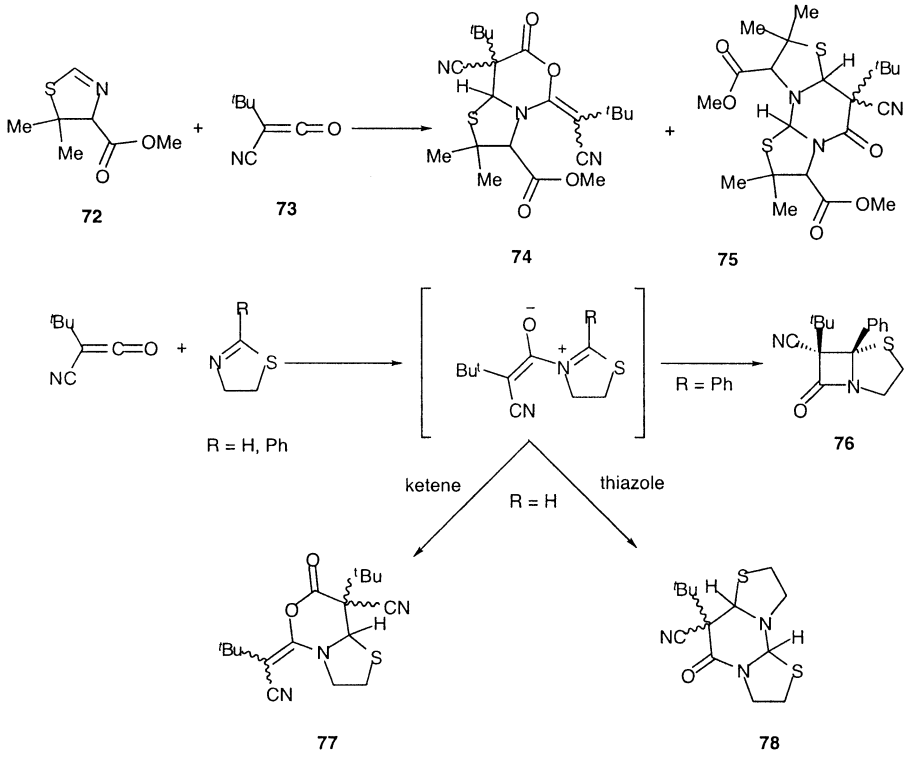


**68**

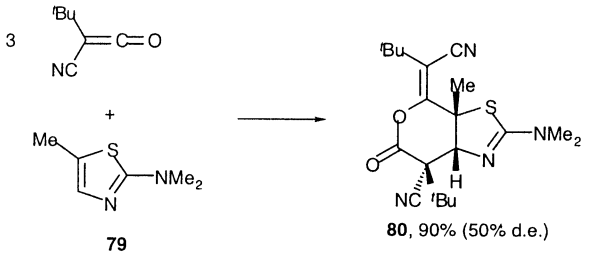
Dondoni and co-workers may have shed some light on this interesting result.[53] Reaction of thiazole with excess *t*-butylcyanoketene gave **69** as the major product. This proved to be unstable in solution (although an X-ray structure was obtained) and extended heating of the reaction gave **70** instead. The proposed mechanism for acylation at the 2-position involves activation by acylation of the nitrogen as shown in Scheme 36.

When the 2-ethylthiazole was allowed to react with dichloroketene, acylation of the ethyl group predominated to give **71**, presumably via an analogous mechanism. With the slightly more hindered 2-isopropylthiazole a third mode of reaction was observed, again by initial *N*-acylation, the initial adduct being *O*-acylated by the second equivalent of ketene prior to cyclisation (Scheme 37).[54]

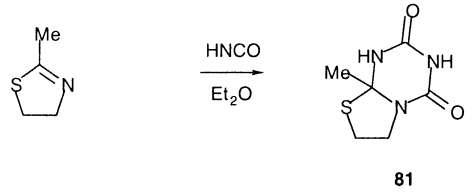
Clearly the fate of the initial adduct is very dependent on the




**Scheme 38.**




Scheme 39.

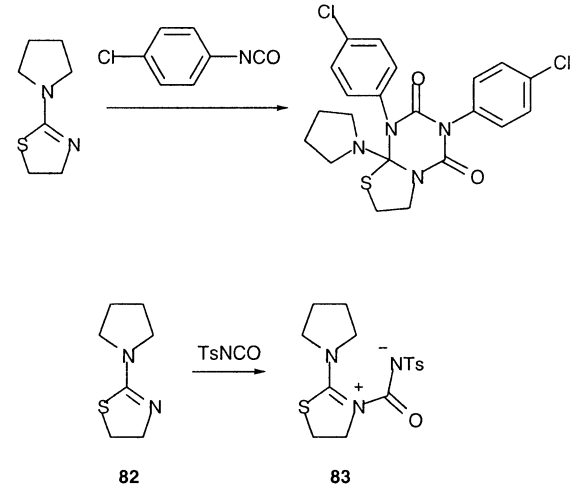



Scheme 40.

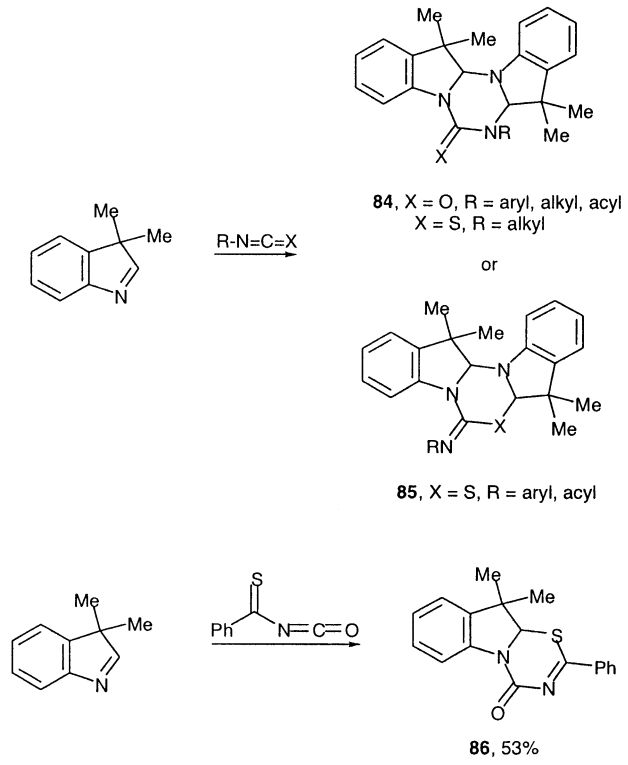
substrate and reaction conditions. In the work of Schaumann et al. for example, the order of addition and temperature is particularly important. Addition of **72** to **73** gave predominantly **74** (48% along with 14% **75**) at room temperature, while addition of **73** to **72** at 60°C gave only 6% of **74** and 36% of **75**. 2-Phenylthiazoline gave only the 1:1 adduct **76** (35%) upon addition of **73**, while thiazoline gave modest yields of **77** (20%) and **78** (31%), again depending on the temperature and order of addition (Scheme 38).[55]

With the structurally related 2-aminothiazole **79**, similar adducts were obtained by reaction at the 4,5-double bond, **79** giving a 3:1 mixture of diastereoisomers of which **80** was the major product (Scheme 39).[56]

The related reactions with isocyanates are less common. Simple thiazolines react with isocyanic acid to give triazine derivatives such as **81** (Scheme 40).[57] The substituent at the 2-position can be critical, since 2-aminothiazolines give similar products (Scheme 41), while 2-methylthiothiazolines do not react under these conditions. With 4-toluenesulfonyl isocyanate, however, **82** gave only the betaine **83**.[58]




Scheme 41.




Scheme 42.

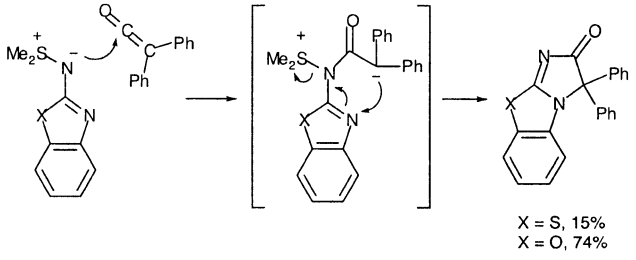
In the reactions of 3*H*-indoles with isocyanates and isothiocyanates, products were isolated arising from reaction of 2 equiv. of imine with one of heterocumulene. With aryl, alkyl and acyl isocyanates, however, the adducts were of type **84**, while with aryl and acyl isothiocyanates adducts of type **85** were formed, and, with thioacyl isocyanates, 1:1 adducts such as **86** were obtained (Scheme 42).[59]

## 5. [3+2] Annulations

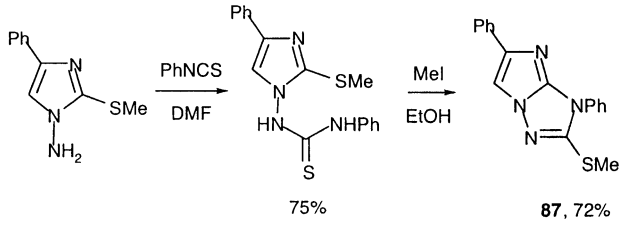
Much work from the Sakamoto group has focussed on [4+2] annulation reactions. By using the relatively unusual reactivity of sulfilimines, however, the same workers have demonstrated the use of 2-amino-1,3-azoles as a three-atom component in reactions with diphenylketene (Scheme 43).[60]

A slightly different use of sulfur leaving groups in this context is shown in Scheme 44 for the formation of [1,3]imidazo[1,2-*b*][1,2,4]triazole **87**.[61]

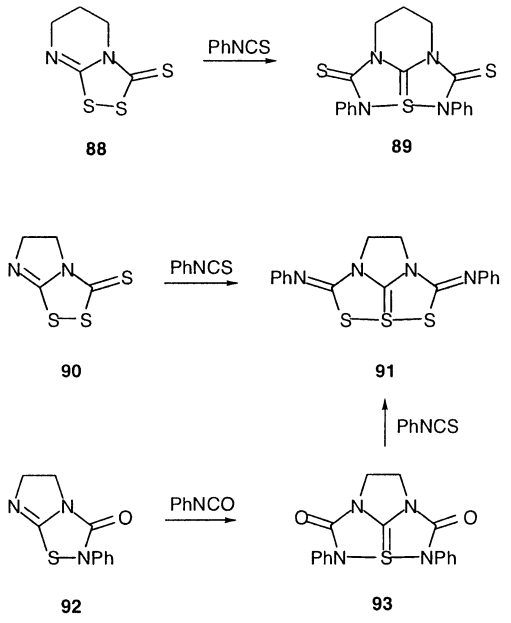
Striking differences in regioselectivity were observed in the formation of heteropentalene derivatives. The reaction of **88**




Scheme 43.



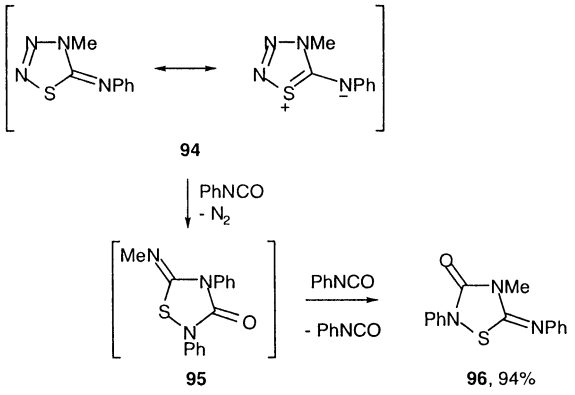

Scheme 44.



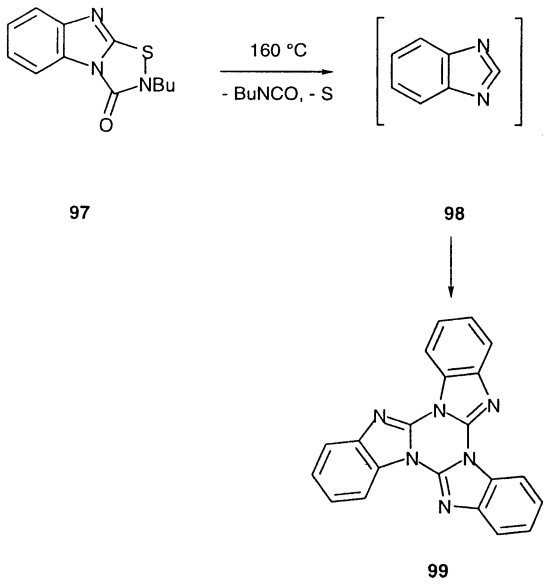

Scheme 45.

with phenyl isothiocyanate, for example, gave **89**, in which the heterocumulene has reacted via its C=N bond, while under similar conditions **90** gave **91**. This difference in reactivity has been attributed to the relief of strain in the 5-5-5 fused system as a result of the longer C–S bond and, indeed, with phenyl isocyanate, **92** gave **93**, which proved somewhat unstable and again gave **91** upon heating with phenyl isothiocyanate (Scheme 45).[62]

These reactions belong to a more general group of addition–elimination reactions. Similar reactions are possible with thiatriazolines **94**, although a number of mechanistic possi-




Scheme 46.

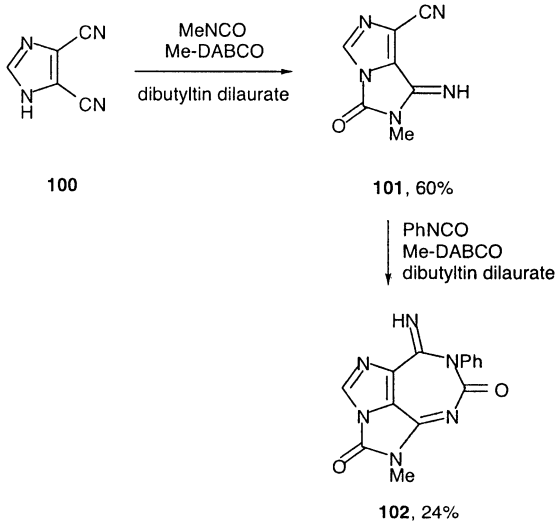



Scheme 47.

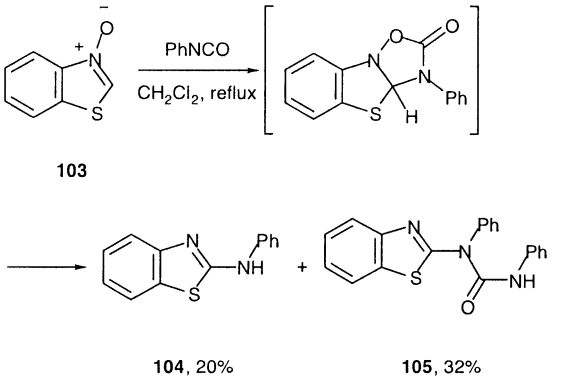
bilities exist. For this class of compounds, **94** reacts with phenyl isocyanate to give **96**, but there is strong evidence that this reaction proceeds through the intermediacy of **95**. The conversion of **95** into **96** is not a simple Dimroth rearrangement, but involves a further addition–elimination reaction (Scheme 46).[63]

A number of related reactions were reported by Martin and Tittelbach, who also observed that upon heating, **97** gave **99**, presumably via the highly strained carbodiimide **98** (Scheme 47).[64]

4,5-Dicyanoimidazoles undergo an interesting double addition with isocyanates in the presence of 2-methyl-DABCO and dibutyltin dilaurate. With methyl isocyanate, **100** gives **101** initially, which upon further reaction with phenyl isocyanate gave **102**. Reaction of **100** with aryl isocyanates gave only double adducts related to **102** (Scheme 48).[65]




Scheme 48.




**Scheme 49.**

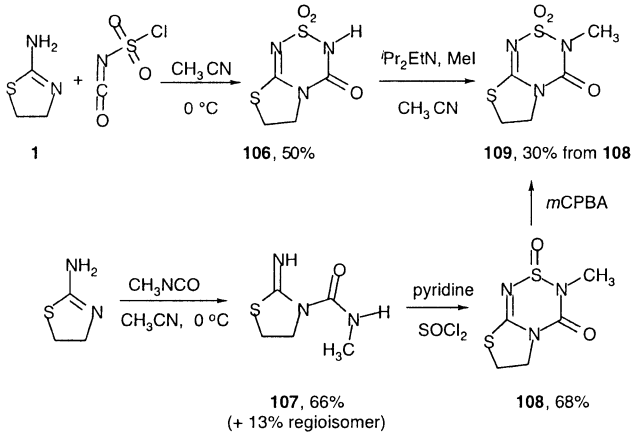
Heterocyclic *N*-oxides are frequently used in 1,3-dipolar cycloadditions. The benzothiazole *N*-oxide **103** underwent such a reaction with phenyl isocyanate, followed by loss of carbon dioxide to give **104**. Further reaction with phenyl isocyanate additionally provided **105** (Scheme 49).[66]

## 6. [3+3] Annulations

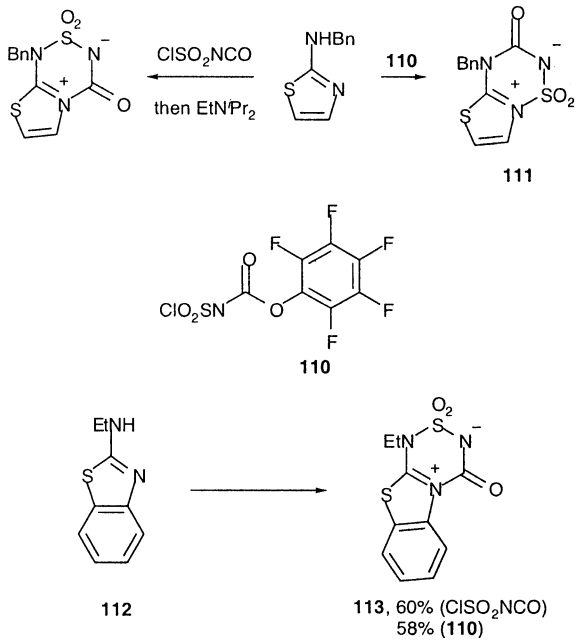
In a further report which sheds light on the regioselectivity of simple acylation reactions, **1** was shown to give only one of the possible isomeric products with chlorosulfonyl isocyanate.[67] Based on an independent synthesis of **109** from **107**, the product was shown to be **106** in accord with the previous work (Scheme 50).

2-Benzylaminothiazole reacts similarly, although the use of pentafluorophenylchlorosulfonyl carbamate **110** as a chlorosulfonyl isocyanate equivalent gave the regioisomeric product **111**, both this reagent and chlorosulfonyl isocyanate giving the same regioisomer **113** with benzothiazole **112** (Scheme 51).[68]

In another example of kinetic and thermodynamic products, **114** reacts with chloroacylketene **115** to give the betaine **116**. Thermolysis of this compound gives rise to a quantitative isomerisation to **117**.[69] A similar reaction involving 1-methylimidazole gave **118** (Scheme 52).[70]




**Scheme 50.**




**Scheme 51.**

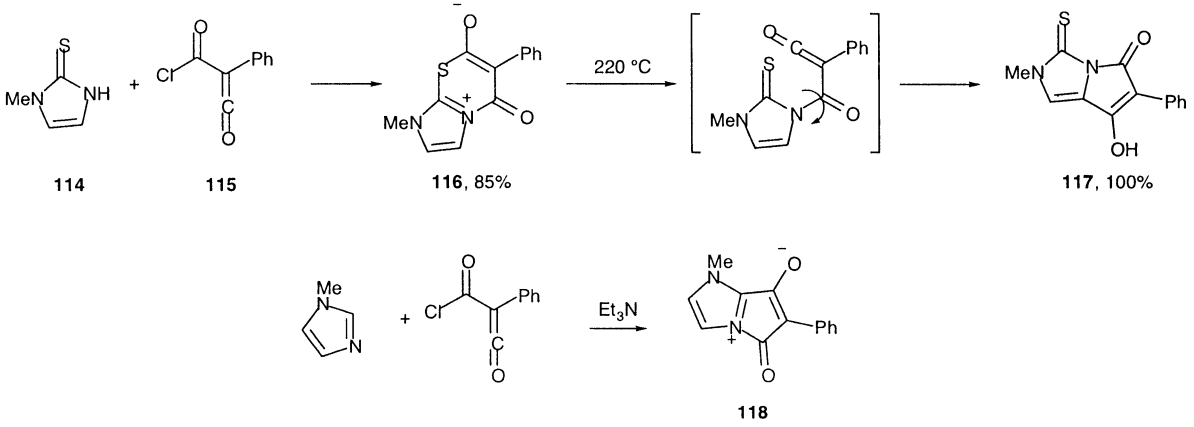
Ethoxycarbonyl isocyanates react similarly as bis-electrophiles, so that reaction of **119** gave **120**, which upon heating cyclised to **121**. Somewhat surprisingly, reaction of **122** with chlorosulfonyl isocyanate gave **123**.[71] Similar reactions are also undergone by 2-aminobenzothiazoles and 2-aminothiadiazoles (Scheme 53).[72]

Klayman and Woods[73] re-investigated earlier work by Capuano and Schrepfer,[74] and were able to assign the structure **124**[75] to the product of the reaction between 2-aminothiazoline and ethoxycarbonyl isothiocyanate, rather than the regioisomeric structure initially claimed. This is again in line with previous results in that initial attack is by the endocyclic nitrogen at the heterocumulene carbon. With the corresponding *gem*-dimethyl-substituted thiazoline **125**, the regioisomeric product **126** is claimed. This seems reasonable based on increased steric hindrance, but the data presented is hardly unequivocal (Scheme 54).

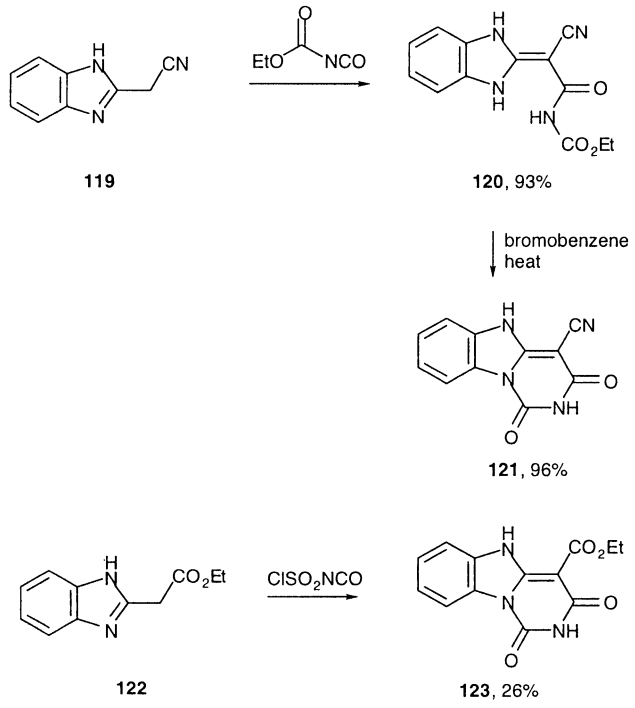
With indazole **127**, however, the alternative regioselectivity is proposed in a stepwise reaction (Scheme 55).[76]

A similar pattern of reactivity is observed with 2-aminooxazolines, as would be expected based on the studies of simple acylation reactions of these compounds (Section 2).[77] With *N*-substituted 2-aminothiazoles, such reactions lead to mesoionic compounds **128**. The initial site of attack is the ring nitrogen, reacting with the more electrophilic isocyanate carbon. Isothiocyanates are less reactive, so that with phenoxycarbonyl isothiocyanate the urethane carbonyl is attacked first, while the marginally less reactive ethoxycarbonyl isothiocyanate is attacked at the isothiocyanate carbon (Scheme 56).[78]

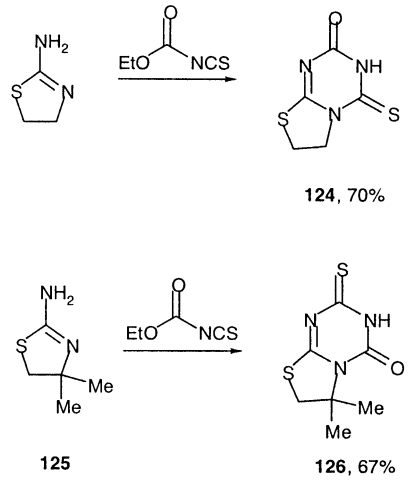
Related reactions were investigated by Nagano and co-workers, who isolated a number of by-products which indicate that the situation is slightly more complex. Various




Scheme 52.

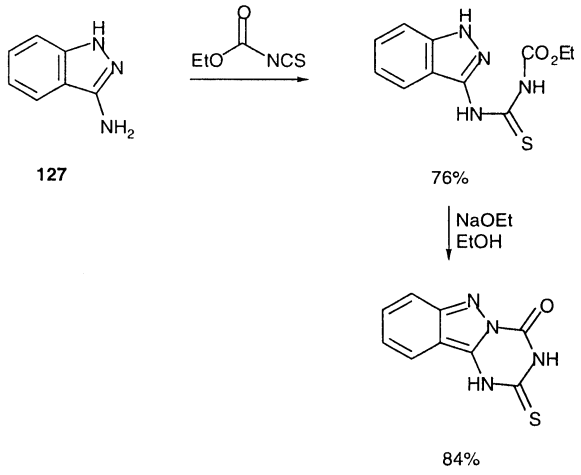



Scheme 53.

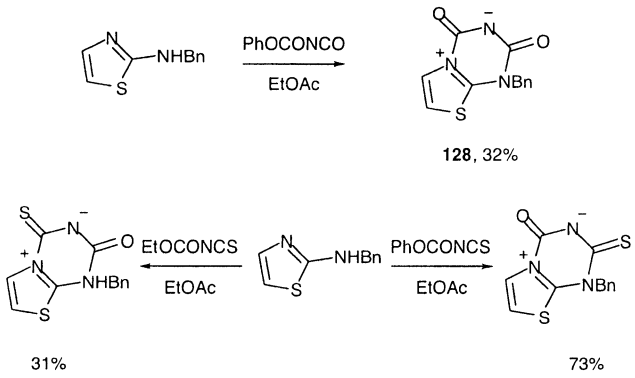



Scheme 54.

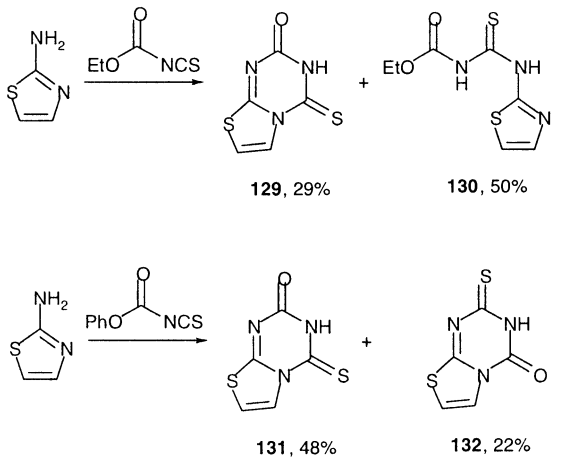
degradation studies showed that alkoxycarbonyl isothiocyanates give regioisomer **129** from 2-aminothiazole, along with significant amounts of thioureas **130** derived from attack at the amino nitrogen, while phenoxycarbonyl isothiocyanate only gave cyclised products **131** and **132** (along with the carbamate derived from loss of thiocyanic acid). It is therefore difficult to state which nitrogen is attacked preferentially since these reactions are doubtless reversible, and the regioisomer **130** is less prone to cyclisation.[79] With 4-substituted thiazoles, and with




Scheme 55.



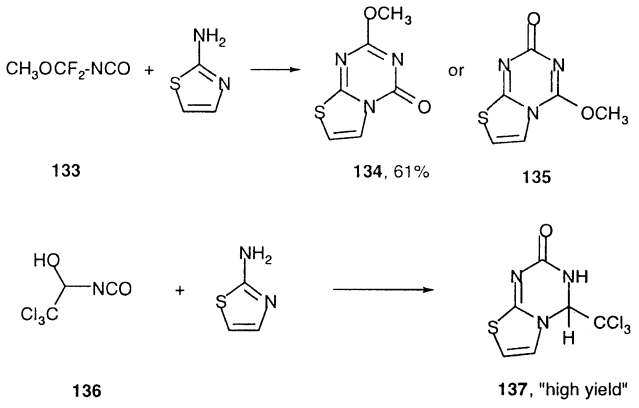

Scheme 56.




Scheme 57.

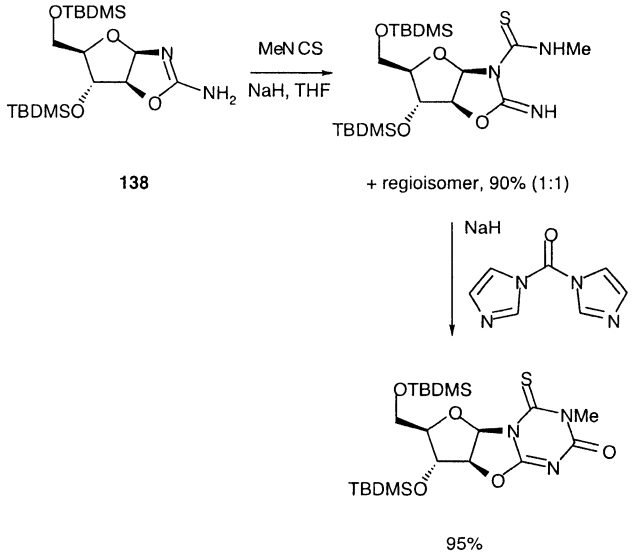
2-amino-5-phenylthiazole, cyclised products were not obtained (Scheme 57).[80]

Other substituted isocyanates have been used as 1,3-bis-electrophiles. 2-Aminothiazole reacts with **133**, for example, to give **134** (although the authors could not rule out regioisomeric structure **135**).[81] Similarly, 2-aminothiazole reacts with **136** (formed by reaction of isocyanic acid with chloral) to give **137**.[82] A regioisomeric structure is again possible, but without crystallographic data it would be non-trivial to distinguish between the isomers even with modern spectroscopic techniques (Scheme 58).



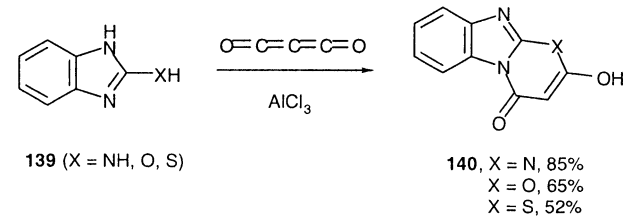

Scheme 58.

Similar annulation reactions were realised in a sequential manner by reaction of **138** with methyl isothiocyanate and then with carbonyldiimidazole. A 1:1 mixture of attack at the oxazoline and amino nitrogen atoms was observed under the conditions shown in Scheme 59, although surprisingly only attack at the oxazoline nitrogen was observed in the absence of base (THF, heat). Reaction with methyl isocyanate (NaH, THF) gives rise to acylation at only one of the two possible nitrogens, although the authors do not state which.[83]

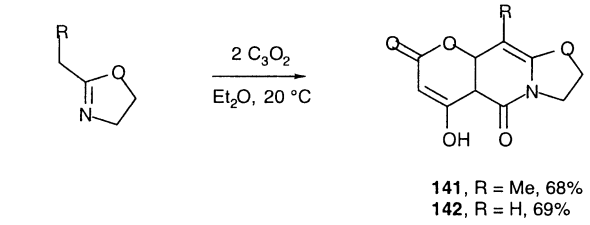



Scheme 59.

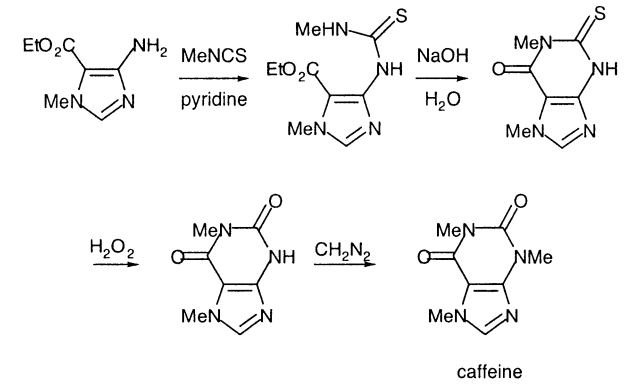
One further relatively uncommon bis-electrophile is carbon suboxide. Reaction of **139** (X=NH, O, S) gave cycloadducts **140** in moderate to good yields (Scheme 60), while use of malonyl dichloride gave 2:1 azoline:malonate adducts.[84] Ziegler and co-workers had prevously made similar observations,[85] and noted that the initial adducts react further,



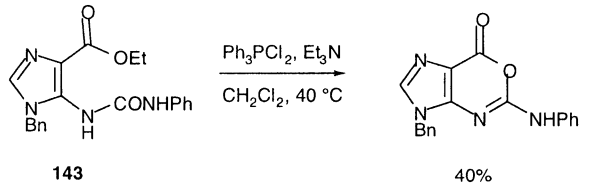

Scheme 60.



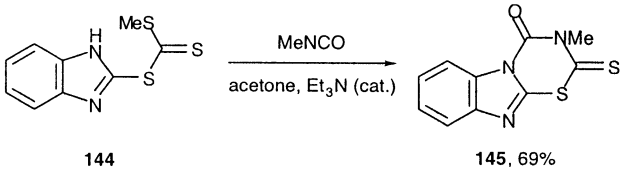

Scheme 61.




Scheme 62.




Scheme 63.




Scheme 64.

giving **141** and **142**, when an excess of carbon suboxide was used (Scheme 61).[86]

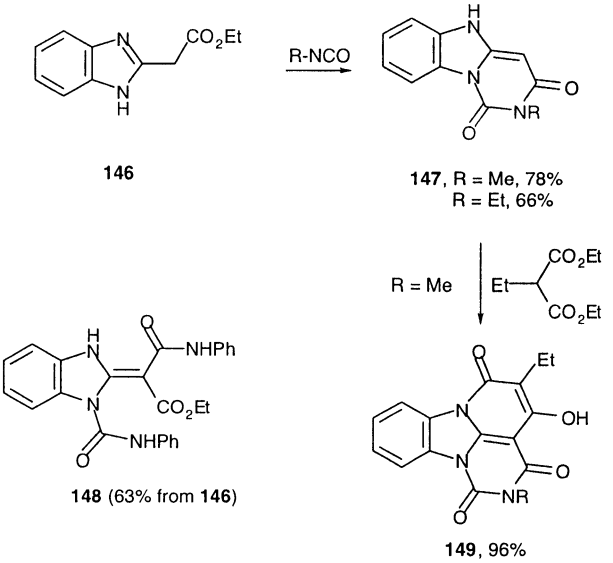
## 7. [4+2] Annulations

The importance of the purine ring system led to the development of a number of methods for the fusion of a pyrimidine ring onto an imidazole,[87] with much of the early work being pioneered by Cook, Heilbron and co-workers.[88] The example shown in Scheme 62 is from the synthesis of caffeine by Cook and Thomas.[89]

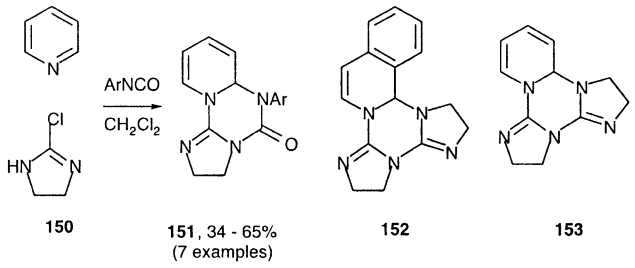
An alternative mode of ring closure is observed if the intermediate **143** is treated with dichlorotriphenylphosphorane (Scheme 63).[90]

Treatment of benzimidazole **144** with methyl isocyanate gave **145** in good yield (Scheme 64).[91]

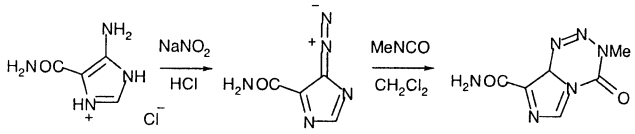
The related ethyl benzimidazol-2-ylacetate **146** reacted similarly with methyl and ethyl isocyanates, although, with phenyl isocyanate, **148** was obtained with no cyclisation (Scheme 65).[92] Further reactions of **147** have also been reported, giving **149**.[93]




Scheme 65.



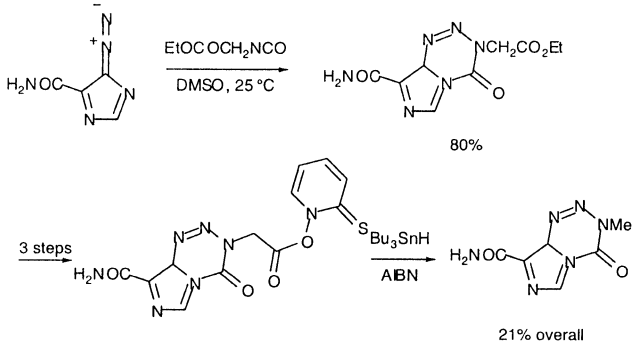

Scheme 66.



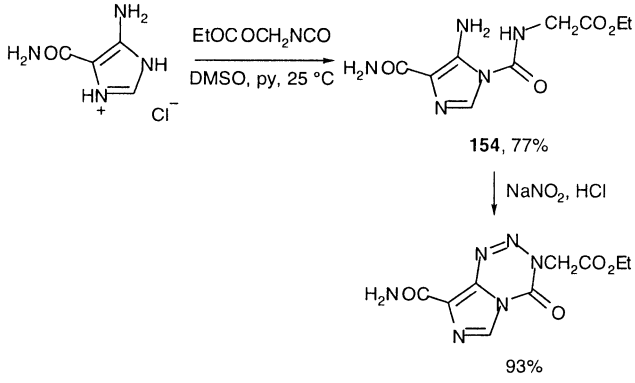

Scheme 67.

Such reactions are often extremely sensitive to the choice of reagent and reaction conditions. While **150** reacts with pyridine and aryl isocyanates to give compounds **151**, for example, attempted use of isoquinoline instead of pyridine, or isothiocyanates or alkyl isocyanates in place of aryl isocyanates, gave only compounds **152** or **153**, respectively (Scheme 66).[42]

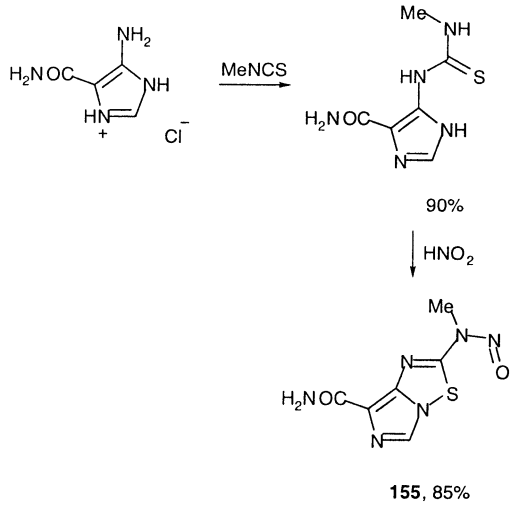
One important application of this type of chemistry is in the




Scheme 68.




Scheme 69.

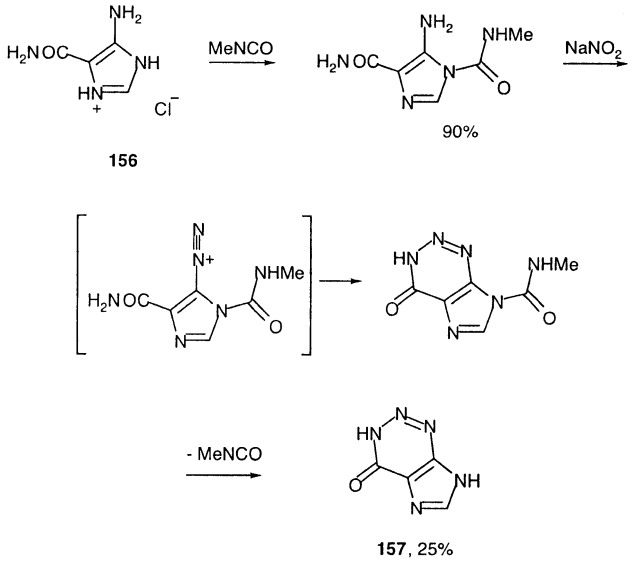



Scheme 70.

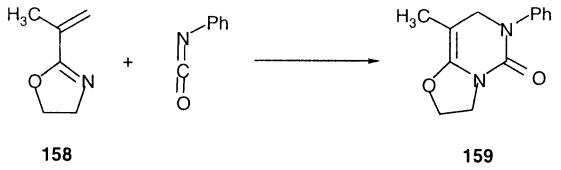
synthesis of the antitumour drug, temozolomide, which was originally synthesised as shown in Scheme 67,[94] although clearly the use of the highly volatile methyl isocyanate was less than ideal. A modified procedure used ethyl isocyanatoacetate in the key step, followed by Barton decarboxylation, to give the desired compound (Scheme 68).[95]

A further related route changes the order of the steps, so that cyclisation is by diazotisation of **154** (Scheme 69),[96] there being two possible sites for acylation, and methyl isothiocyanate gave exocyclic attack. Subsequent treatment with nitrous acid gave **155**, the structure of which was confirmed by single crystal X-ray diffraction (Scheme 70).[97]

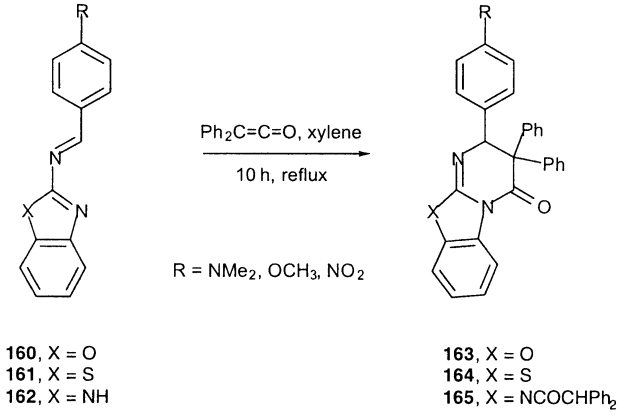
One further complication which is unique to these structures is the possibility of two different amides cyclising. When **156** was treated with methyl isocyanate prior to diazotisation, **157** was obtained. Other isocyanates, however, gave results in agreement with Scheme 69, and in higher yields (Scheme 71).[98]




Scheme 71.



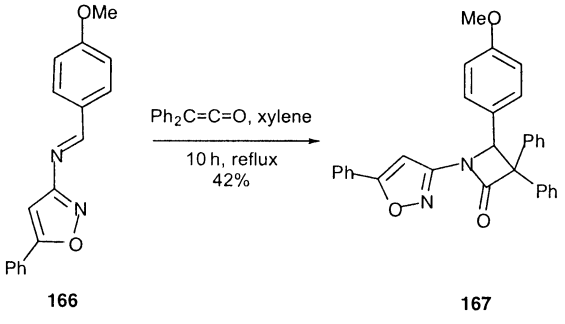

Scheme 72.



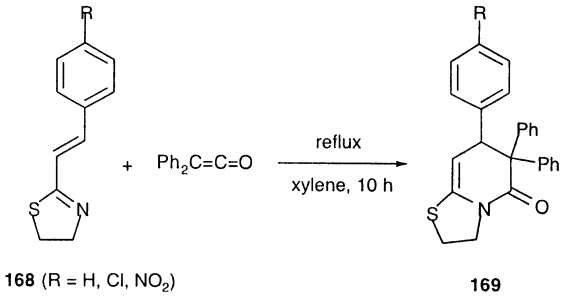

Scheme 73.

Our own studies in this area have centred on the use of alkenyloxazolines and alkenylthiazolines in formal aza-Diels–Alder reactions with isocyanates and ketenes and these have been inspired by the earlier work of Hellmann and by Sakamoto. In a 1966 review by Hellmann,[99] mention was made of the reaction of propenyloxazoline **158** with phenyl isocyanate to give the formal aza-Diels–Alder adduct **159**. Characterisation data for this compound were, however, sparse, and, after a detailed investigation into related reactions in our own laboratories (vide infra), we now believe this report to be in error, and suggest that the reported infrared stretch of 1760 $cm^{-1}$ is more likely due to the diazetidinedione formed by dimerisation of phenyl isocyanate (Scheme 72).

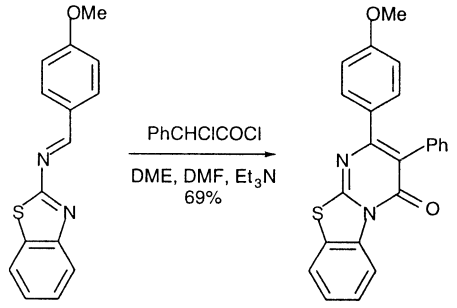
Sakamoto showed that a wide range of azoles react with diphenylketene to give [4+2] adducts.[100] In particular, benzo-fused azoles (oxazole, thiazole, imidazole) were used (Scheme 73), although oxa-, thia- and selenadiazoles also underwent analogous reactions. With the benzimidazole **162**, the free N–H was acylated under the reaction conditions, so that two equivalents of diphenylketene were required. Isoxazole **166**, however, gave β-lactam **167** (Scheme 74).




Scheme 74.




Scheme 75.



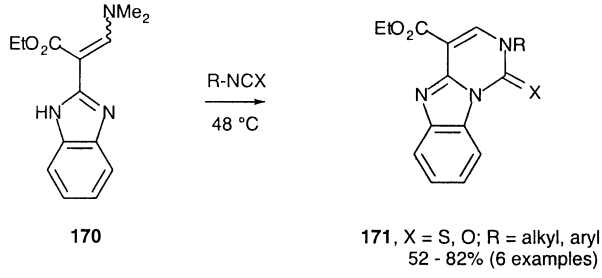

Scheme 76.

In a study on aza-dienes, three substituted styrylthiazolines **168** were used in reactions with diphenylketene to give thiazolo[3,2-*a*]pyridines **169** in good yield (Scheme 75).[101] Given the ready availability of homochiral oxazolines and thiazolines this approach would lend itself nicely to an asymmetric piperidine synthesis, and we have been fortunate to discover a number of highly diastereoselective reactions of this type (vide infra).

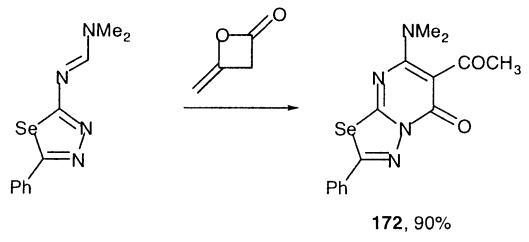
In related work with chloroketenes, as expected the initial cyclisation is followed by loss of HCl (Scheme 76).[102] In this case, reaction of a structurally related benzimidazole gave β-lactam formation as a competing (major) pathway, and with dichloroketene this was the only pathway observed. In this particular study, the ketenes were generated in situ by elimination of HCl from the corresponding acid chlorides.

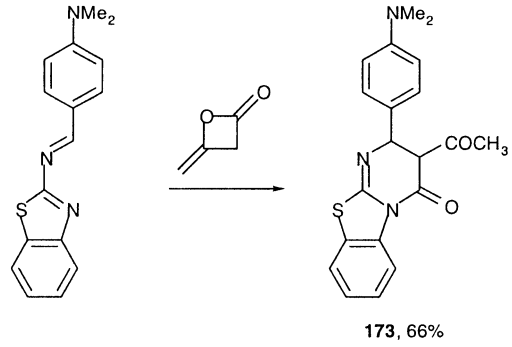
There are further permutations where elimination from the initial adduct is possible, including the reaction of aza-diene **170** with isocyanates or isothiocyanates under solvent-free conditions which gave adducts **171** (Scheme 77).[103]

All of these reactions presumably proceed via stepwise mechanisms (vide infra), and similar reactions have been




Scheme 77.



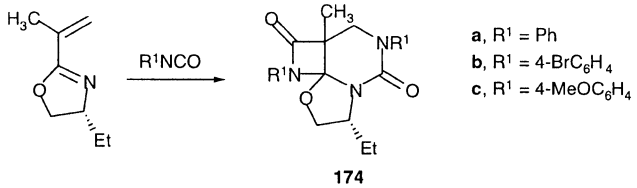




Scheme 78.

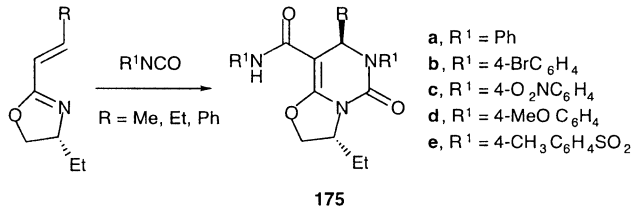
reported using diketene, giving compounds such as **172** and **173** (Scheme 78).[104]

Our attempts to repeat the reaction of Hellmann[99] were unsuccessful, but with the simple addition of an ethyl group at the 4-position of the oxazoline ring we were able to isolate tricyclic β-lactams **174**, formed by an initial formal aza-Diels–Alder reaction (as reported by Hellmann) followed by a subsequent [2+2] cycloaddition (Scheme 79).[105]

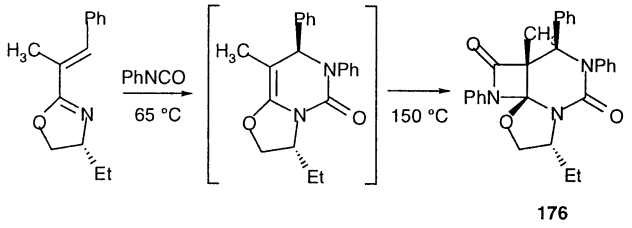
The diastereoselectivity in this reaction was modest (1.7:1), but with a simple modification to the structure of the substrate, single diastereoisomers of related compounds **175** were obtained (Scheme 80), with the relative stereochemistry being confirmed by single crystal X-ray diffraction of three representative compounds.[106] In this case, the



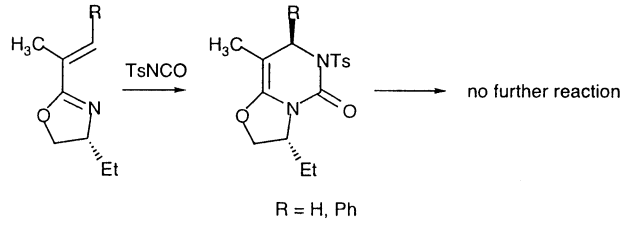

Scheme 79.




Scheme 80.




Scheme 81.

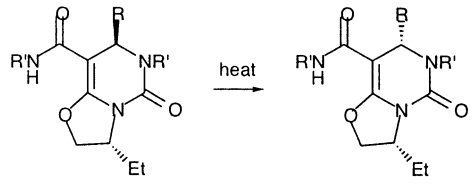



Scheme 82.

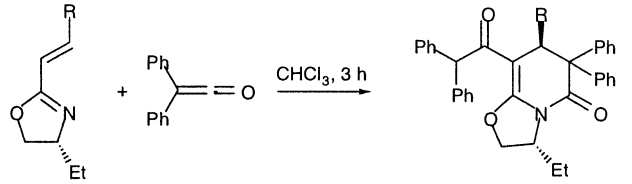
asymmetric induction occurs during the first addition of the isocyanate (Scheme 80).

Clearly, in all these examples, the double bond in the initial aza-Diels–Alder adduct is electron-rich, and so reacts faster with the isocyanate than does the starting material, although for some reactions we were able to obtain 1:1 adducts either by increased steric hindrance at this double bond (Scheme 81) or by decreasing the nucleophilicity of the double bond with an electron-withdrawing group at nitrogen (Scheme 82). In the former, we were able to prepare a single-isomer β-lactam **176** by using the stereogenic centre introduced during the first addition to direct the second addition.[107]

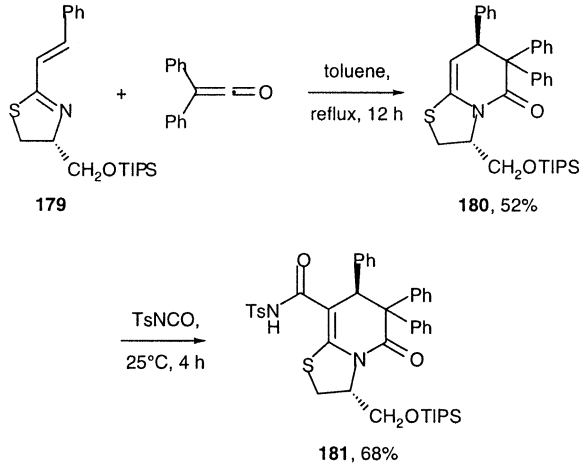
In all these examples, we believe the initial ring formation to occur in a stepwise manner, and have obtained calculated transition state structures which rationalise the stereochemical outcome of the reactions. Furthermore, we have found that extended heating of the adducts causes isomerisation with no evidence for complete loss of the isocyanate at any time (Scheme 83).[108]




Scheme 83.



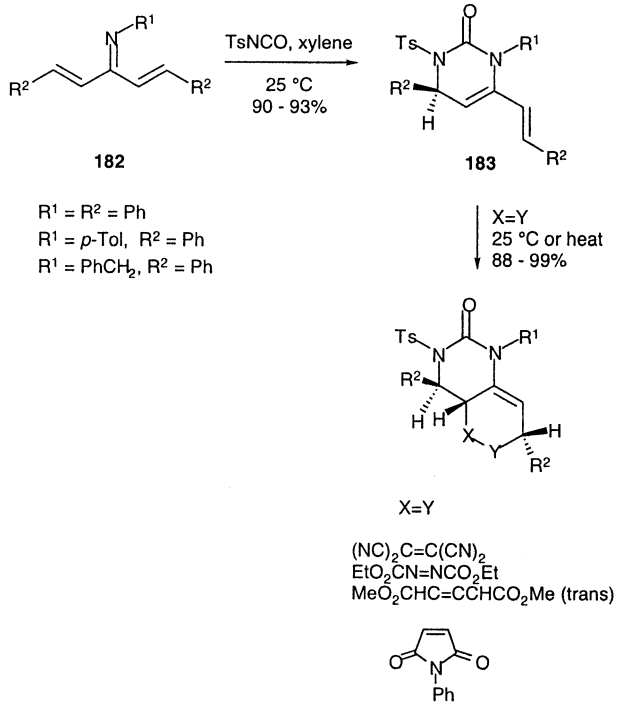

Scheme 84.



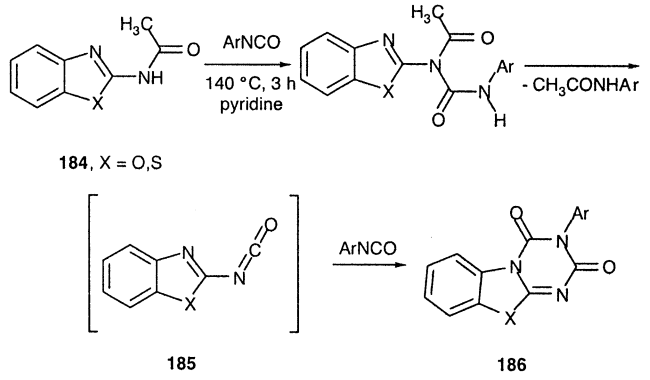

Scheme 85.

There is a clear difference between our results and those reported by Hellmann and by Sakamoto, in that both of these groups report only a single addition of the heterocumulene, whereas we have only seen double addition, with the exception of the easily understood systems highlighted above. In Hellmann's work we can see no justification in the results reported to support the structural assignment, but Sakamoto has presented excellent data which leave no doubt in our minds that either the lower reactivity of the ketene or the lower nucleophilicity of the thioenol ether in the 1:1 adduct are responsible. In the reactions between **177** and diphenylketene, we were only able to isolate 2:1 adducts **178**, these again being single diastereoisomers (Scheme 84).

Reaction of **179** with diphenylketene gave the 1:1 adduct **180**, although addition of tosyl isocyanate to this compound




Scheme 86.




**Scheme 87.**

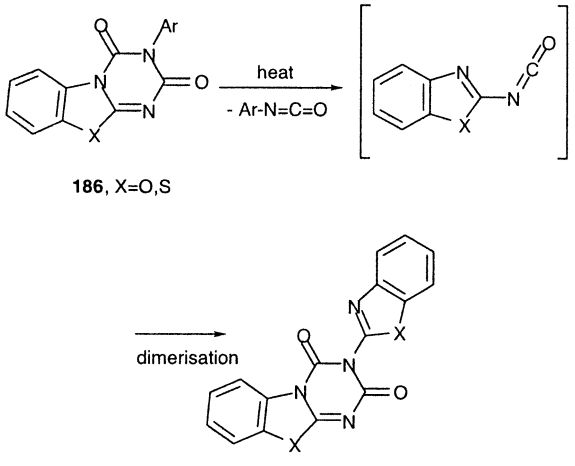
was possible, giving **181** (Scheme 85),[109] and clearly it is the lower nucleophilicity of the thioenol ether which is responsible for the isolation of 1:1 adducts.

In related work from Saito, although not involving azolines, divinylimines **182** have been used to give products **183** which contain a diene, which was further elaborated using conventional Diels–Alder reactions.[110] Similarly, the studies reported by Rossi[111] and others[112] describe the reactions of 1,3-diazabutadienes with ketenes. By analogy with our own investigations we might expect the initial reaction to occur in a stepwise manner (Scheme 86).

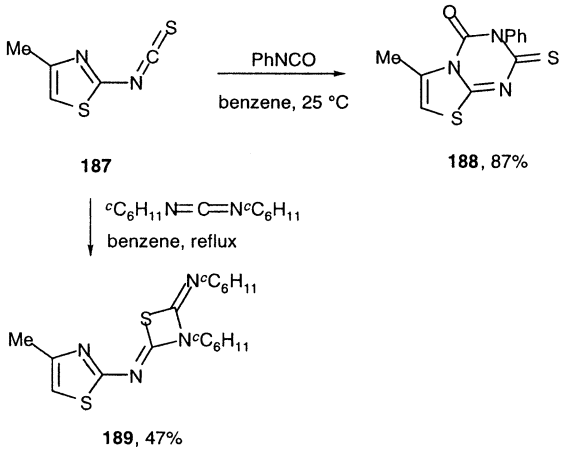
Reaction of 2-acetamidobenzothiazoles or benzoxazoles **184** with aryl isocyanates leads initially to the expected acylation reaction. Loss of *N*-arylacetamide then affords the 2-isocyanatoazole **185** which can undergo a formal hetero-Diels–Alder reaction with a second equivalent of the isocyanate to give **186** (Scheme 87).[113]

On further heating, **186** undergoes a formal retro-Diels–Alder reaction with loss of aryl isocyanate, followed by a formal aza-Diels–Alder dimerisation with the resulting isocyanate acting as both diene and dienophile (Scheme 88).[114] Similar observations were made by Tanaka and co-workers (Scheme 88).[115]

Isothiocyanatoazoles **187** are less reactive, and while [4+2] adducts **188** are obtained with isocyanates, [2+2] adduct **189** was formed by reaction of dicyclohexylcarbodiimide (Scheme 89).[116]

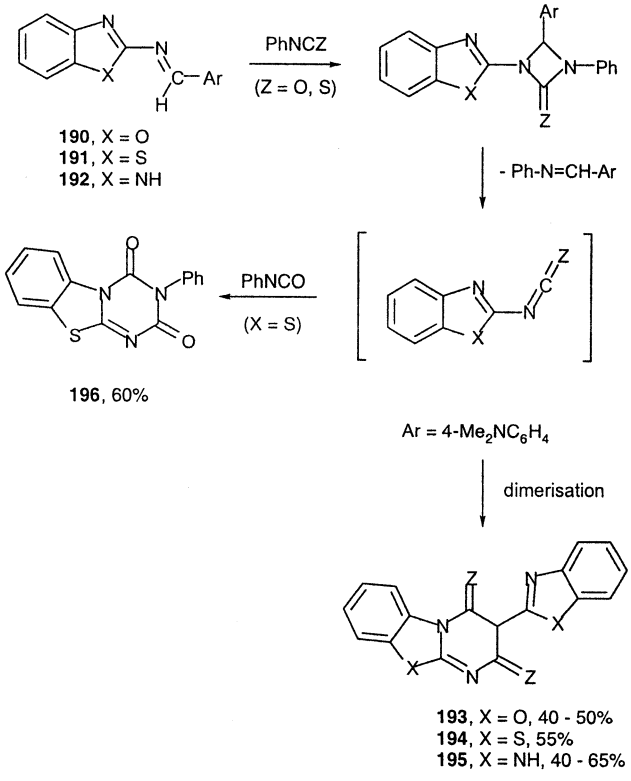



**Scheme 88.**

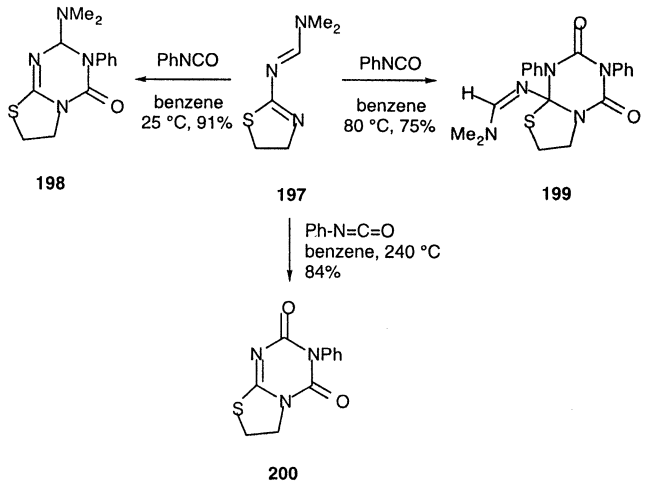



**Scheme 89.**

An essentially identical approach was reported by Abdel-Rahman in 1993, in which benzoxazoles, benzothiazoles and benzimidazoles **190**, **191** and **192** gave **193**, **194** and **195** by a process involving formal [2+2] cycloaddition–cycloreversion at the imine double bond, followed by dimerisation of the resulting isocyanato- or isothiocyanato-azoline (Scheme 90). This intermediate could also be trapped with phenyl isocyanate to give **196**.[117] When shorter reaction times were employed, however, normal aza-Diels–Alder adducts of **191** and **192** were obtained with phenyl isocyanate and phenyl isothiocyanate.[118]



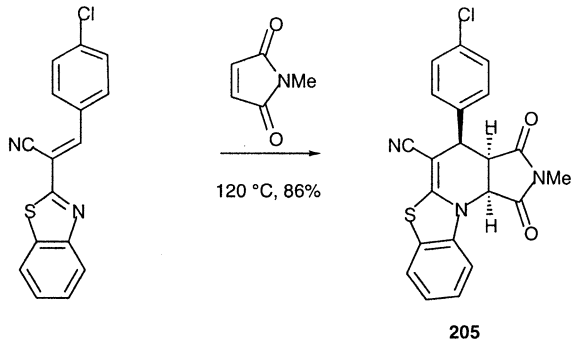

**Scheme 90.**




Scheme 91.

Such aza-Diels–Alder reactions were also observed by Richter and Ulrich in 1970, and these again highlighted the strong dependence of temperature on product distribution. While at room temperature, **198** was formed as the sole product, at 80°C and with an excess of isocyanate **199** was formed in high yield, while at even higher temperatures **200** was formed (Scheme 91).[119]

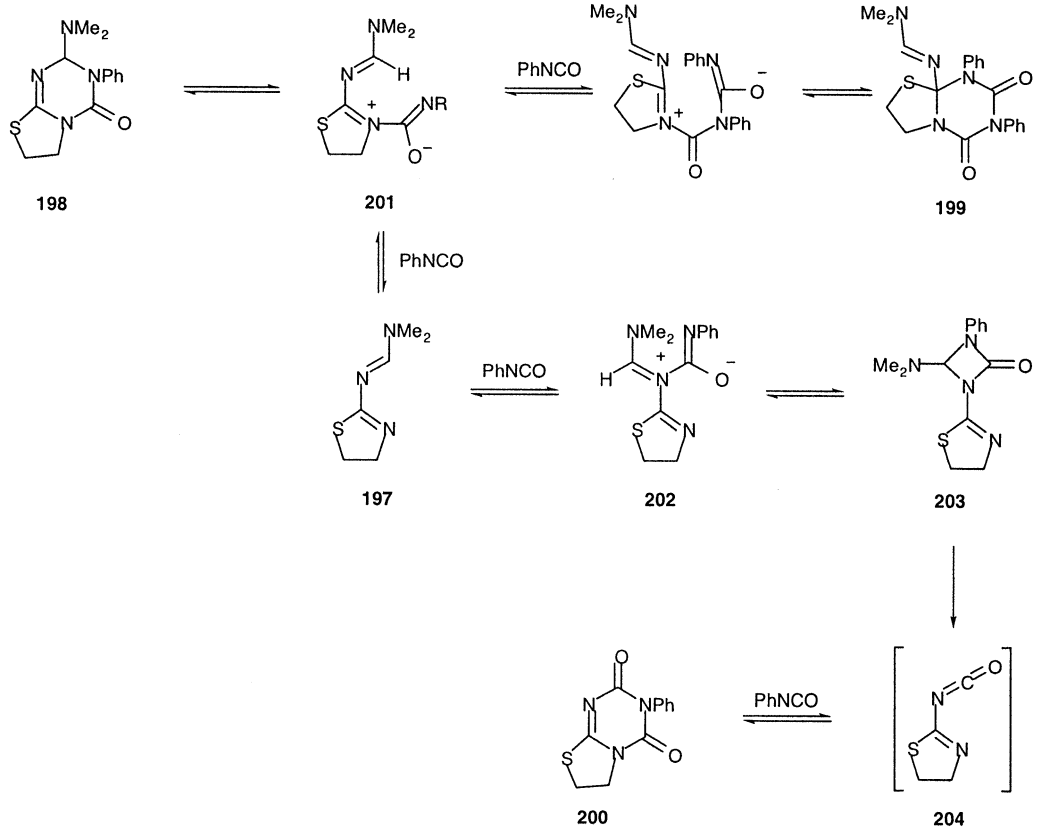
The formation of **198** can be readily rationalised as a formal aza-Diels–Alder reaction proceeding in a stepwise manner via **201**. If the ring closure of **201** to **198** is reversible (as seems likely based on our own work) then in the presence of excess isocyanate, this compound could form **199** as shown in Scheme 92. The formation of **200** presumably proceeds by acylation of the exocyclic nitrogen followed by formation of the diazetane **203**.



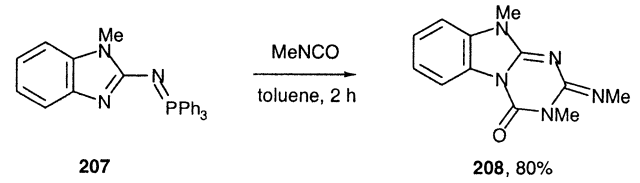

Scheme 93.

The aza-Diels–Alder reactions of alkenylazolines are not limited to those with heterocumulenes. In other work from Sakamoto, for example, benzothiazoles and benzoxazoles react with both electron-deficient and electron-rich dienophiles to give the cycloadducts such as **205**, presumably via a concerted cycloaddition (Scheme 93). Good regioselectivity was observed with unsymmetrical dienophiles.[120]

Using **206** as the aza-diene, the reactions with electron-rich dienophiles were higher yielding, and could be conducted at lower temperatures, but, not surprisingly, reactions with electron-deficient dienophiles were less efficient.

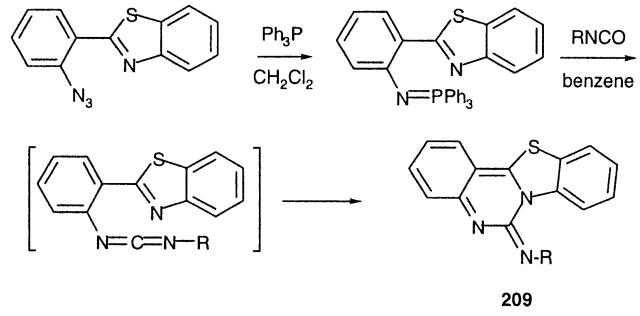



Scheme 92.




207 208, 80%

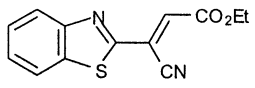
**Scheme 94.**




209

**Scheme 95.**

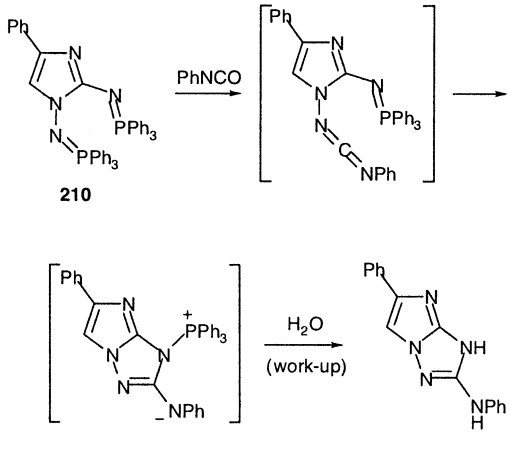
Transesterification of **206** allowed intramolecular aza-Diels–Alder reactions to take place.[121]




206

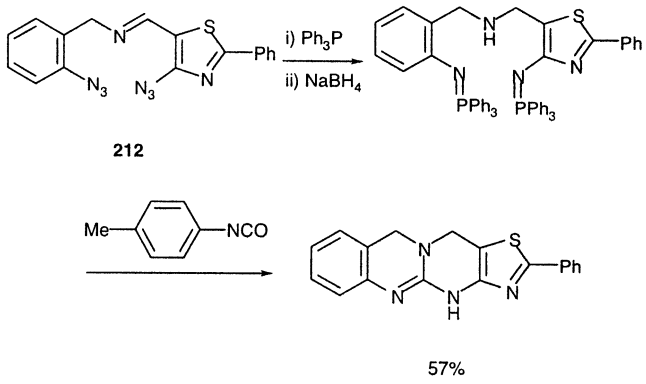
## 8. Miscellaneous reactions

One method for the formation of heterocumulenes, particularly carbodiimides, from azides has been developed by several research groups, the contribution of Molina being particularly prominent. The heterocyclic annulation reactions involving iminophosphoranes are staggering in number,[122] so that naturally some of these involve azoles and azolines. In the first example, which bears considerable similarity to some of the chemistry in the previous section, reaction of **207** with methyl isocyanate gave the intermediate carbodiimide (not shown in Scheme 94) which




210 211, 65%

**Scheme 96.**




212

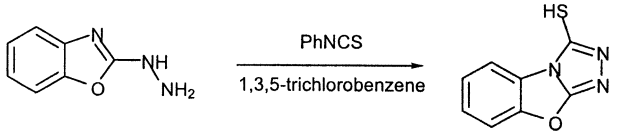
**Scheme 97.**

underwent a formal aza-Diels–Alder reaction with a second equivalent of the isocyanate to give **208**.[123]

A variety of fused quinazolines **209** were prepared by a tandem aza-Wittig/heterocumulene-mediated annulation strategy (Scheme 95). Similar reactions with benzimidazoles have also been described.[124]

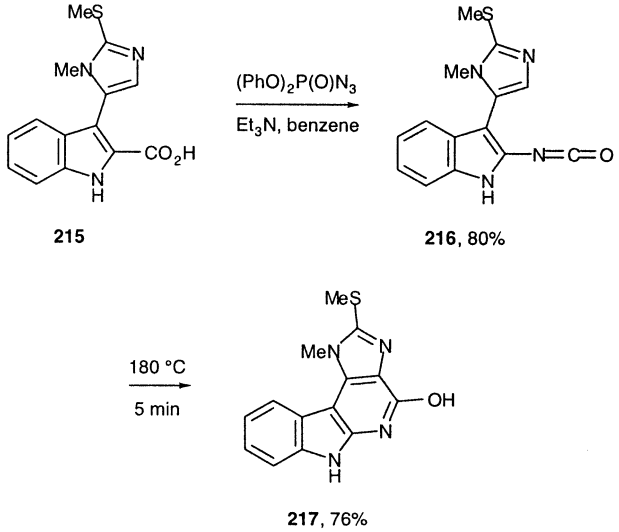
Reaction of bis-iminophosphorane **210** gave **211**. Reaction at only one iminophosphorane is shown in Scheme 96, although the same product would be formed by initial carbodiimide formation at either (or both).[125]

A final application of iminophosphoranes is demonstrated by the reaction of **212** in what is essentially a double metathesis (Scheme 97).[126]




213 214, 89%

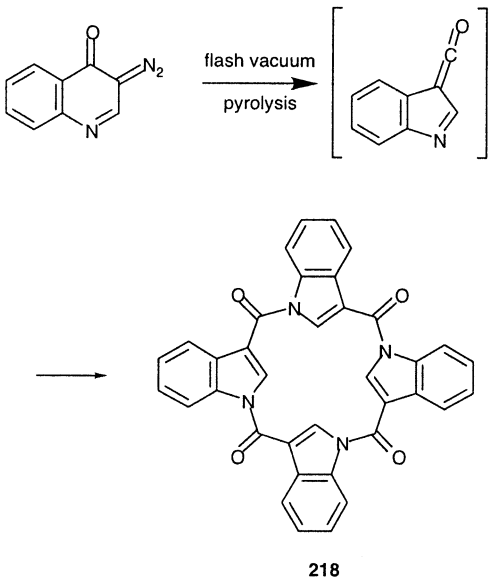
**Scheme 98.**




215 216, 80%

217, 76%

**Scheme 99.**

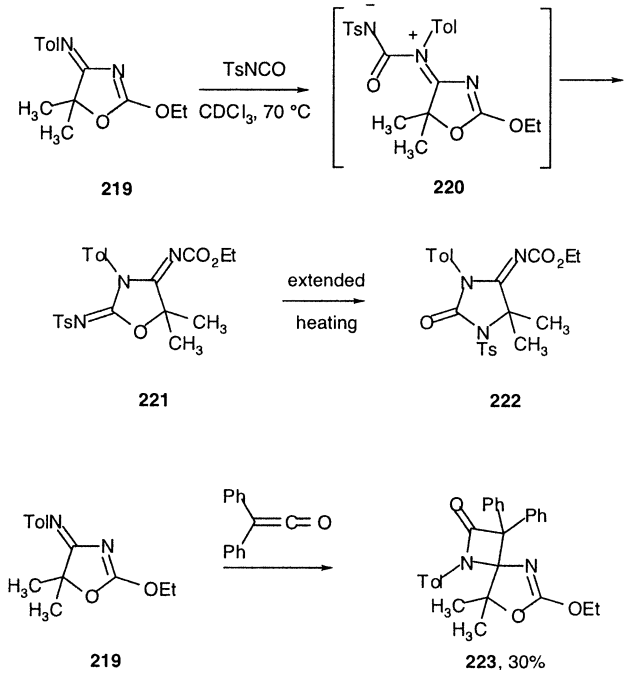



**Scheme 100.**

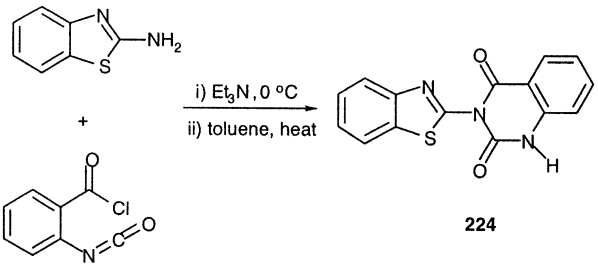
Isocyanates and isothiocyanates can react as one-carbon bis-electrophiles in selected reactions. With 2-hydrazinobenzoxazole **213**, for example, phenyl isothiocyanate gave **214** in 89% yield (Scheme 98).[127]

In the syntheses of grossularines **1** and **2**, Curtius rearrangement of the azide derived from **215** gave isocyanate **216**, thermolysis of which gave the fused 2-hydroxypyridine **217** (Scheme 99).[128]

The analogous Wolff rearrangement to give a ketene was used by Qiao and Wentrup in the preparation of **218** (Scheme 100).[129]




**Scheme 101.**




**Scheme 102.**

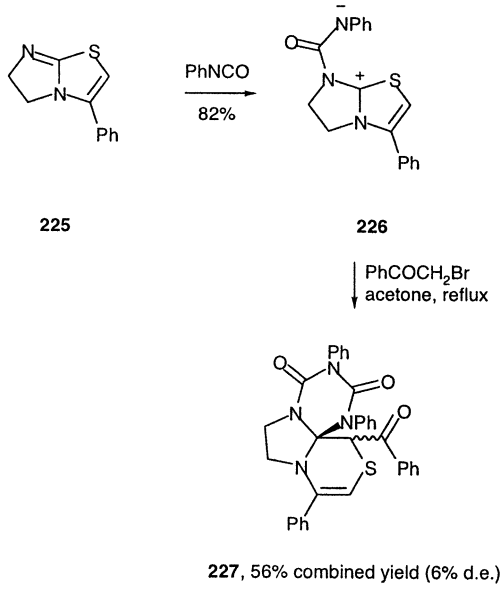
Compound **219** possesses a number of sites for initial acylation and, with 4-toluenesulfonyl isocyanate, the initial reaction forms the betaine **220**.[130] A Boulton–Katritzky type rearrangement[131] then leads to **221**, followed by rearrangement to the more stable **222** upon extended heating. With isothiocyanates, only the thermodynamic product was obtained, whereas with diphenylketene, the [2+2] adduct **223** was isolated (Scheme 101).

We have already seen cases where isomeric products may be formed, and the only way to confirm the identity of the product is independent synthesis. In the following example, isocyanate chemistry was used to confirm the structures of quinazolines such as **224** (Scheme 102).[132]

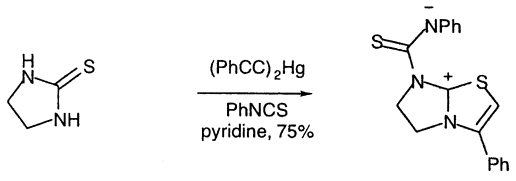
Betaine **226**, formed by the reaction of phenyl isocyanate with **225**, reacts in a relatively complex manner with phenacyl bromide to give a mixture of diastereoisomers of **227**, along with the hydrobromide salt of **225** (Scheme 103).[133]

While **225** was prepared by the reaction of imidazoline-2-thione with phenacyl bromide, an alternative route to betaines related to **226** involves reaction of imidazoline-2-thione with bis(2-phenylethynyl)mercury and phenyl isothiocyanate (Scheme 104).[134]

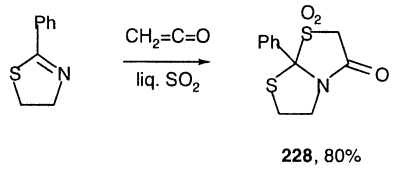
Unstable adducts such as **228** were obtained from the




**Scheme 103.**




Scheme 104.

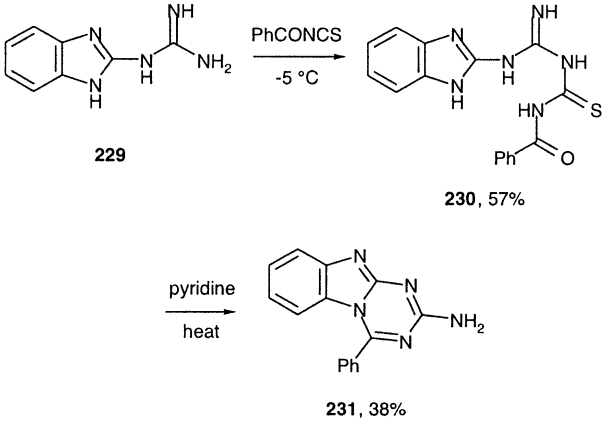



Scheme 105.

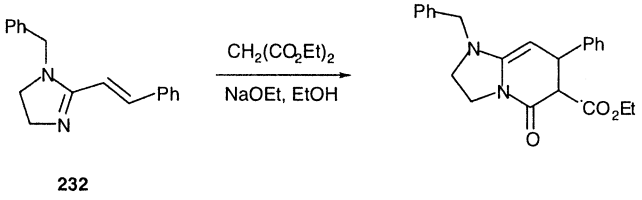
reaction of 2-phenylthiazoline with ketene in liquid sulfur dioxide (Scheme 105). Not surprisingly, these proved to be unstable and decomposed cleanly to starting material within one week.[135]

Finally, an example is shown in Scheme 106 in which the heterocumulene is not actually incorporated into the product. Reaction of **229** at low temperature with benzoyl isothiocyanate gives **230** which rearranges upon heating with loss of isothiocyanic acid followed by dehydration to give **231** in moderate yield.[136]

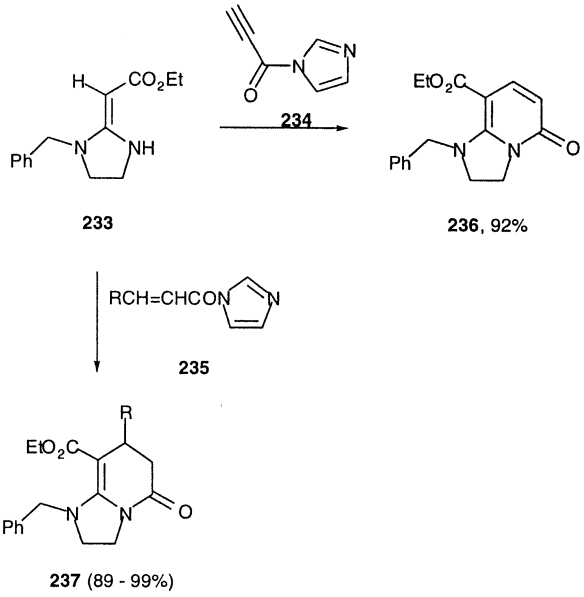
There are a number of annulation reactions of alkenylazolines which, while not involving heterocumulenes, warrant mention since they allow the formation of similar products to many of the other reactions covered within this review. Jones et al. for example, have demonstrated Michael




Scheme 106.




Scheme 107.

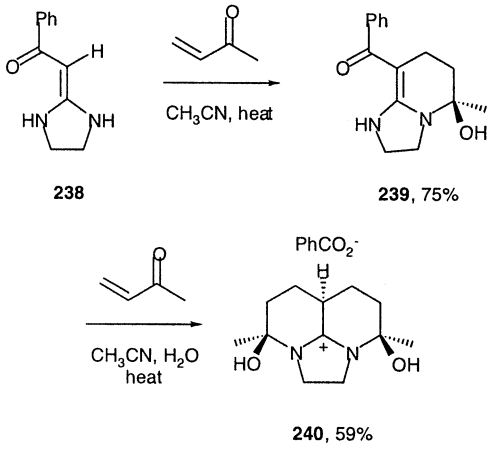



Scheme 108.

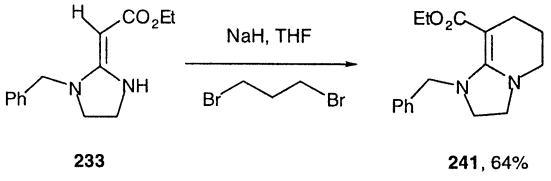
addition to styrylimidazoline **232** followed by cyclisation (Scheme 107).[137]

Alternatively, the azoline component **233** can be used as the Michael donor, in reactions with **234** or **235**, giving **236** and **237**, respectively.[138] Similar annulation reactions have been reported by Huang and Tzai (Scheme 108).[139]

Further reactions are possible, so that **238** reacts initially to give **239**, followed by a second such annulation to give, after debenzoylation, **240** (Scheme 109).[140]




Scheme 109.




Scheme 110.

Finally, 1,3-dibromopropane can also be used as a bis-electrophile with **233**, giving **241**, although 1,4-dibromobutane and 1,5-dibromopentane afforded only *C*-alkylated dihydroimidazoles (Scheme 110).[141]

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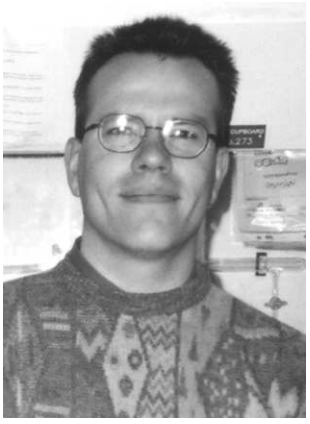
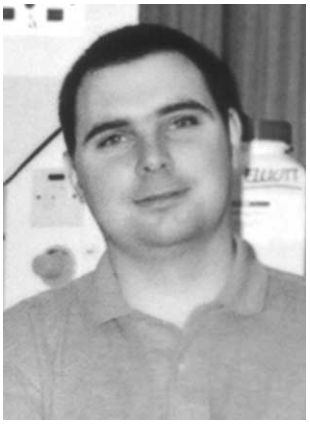
**Biographical sketch**

**Mark Elliott** studied chemistry at Loughborough University, where he was awarded his PhD in 1994 for research into transition metal catalysis in heterocyclic chemistry in the group of Professor C. J. Moody. After post-doctoral work with Professor A. Pfaltz (Basel and Mülheim) he joined the staff at Cardiff in 1996. His research centres on stoichiometric and catalytic asymmetric heterocyclic chemistry, with applications to total synthesis and materials chemistry.



**Elbertus Kruiswijk** received his MSc in organometallic chemistry from the University of Utrecht in 1996, and moved to Cardiff to undertake his PhD research in the group of Mark Elliott. In 1999 he joined the group of Professor B. L. Feringa at the University of Groningen to carry out post-doctoral work in collaboration with DSM Research, The Netherlands.



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