The azomethine ylide strategy for β-lactam synthesis: the structure of the key 1,3-dipolar intermediate

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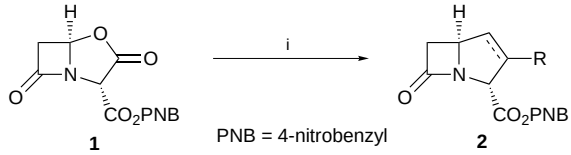
The thermolysis of the β-lactam-based oxazolidinone 1 leads to the formation of cycloadducts 2 and evidence is presented for the participation of the carboxylated azomethine ylide 4, rather than 3 (the more conventional product of oxazolidinone fragmentation), as the key 1,3-dipolar intermediate in this process.

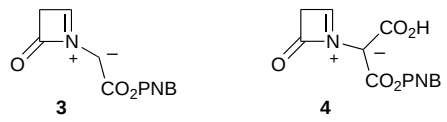
Recently, we disclosed a new and highly convergent cycloaddition strategy for the synthesis of bicyclic β-lactams **2**, encompassing carbapenems and Δ^1-carbapenems (Scheme 1),[1] as well as the sulfur-based penams and penems.[2] A critical step in this sequence involves the fragmentation of a β-lactam-based oxazolidinone **1** to release a reactive 1,3-dipole (a stabilised azomethine ylide); evidence for the structure of this key reaction intermediate is presented here.



1 **2**

Scheme 1 *Reagents and conditions*: i, $RCH{=}CH_2$ or $RC{\equiv}CH$, MeCN, 80 or 100 °C

Simpler oxazolidinones are known[3] to undergo a concerted and irreversible decarboxylation to produce azomethine ylides and this reaction has contributed significantly to the utility of 1,3-dipolar cycloaddition reactions within heterocyclic chemistry.[4,5] Extrapolating this established mechanism to the process shown in Scheme 1 points, in the first instance, towards participation of the ester-stabilised azomethine ylide **3** formed *via* direct decarboxylation of **1**. While production of cycloadducts **2** (which is usually the major regioisomer observed with monosubstituted alkenes/alkynes) can obviously be formulated in terms of the simple azomethine ylide **3**, we can now provide evidence that, under our usual reaction conditions, fragmentation of the β-lactam-based oxazolidinone **1** leads to the carboxylated azomethine ylide **4** as the key intermediate involved in the conversion of **1** to cycloadducts **2**.



3 **4**

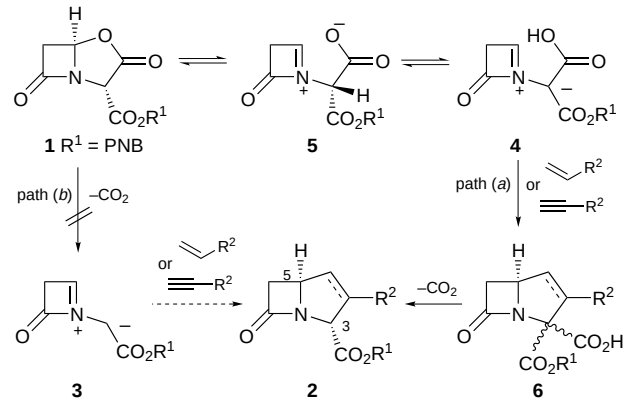
Thermolysis of the enantiomerically-pure oxazolidinone **1**[6] in the presence of an alkene or an alkyne provides the racemic carbapenams and Δ^1-carbapenems respectively. The rate of formation of cycloadducts **2** shows a significant dependence on the reactivity of the dipolarophile and, although this observation in of itself is not inconsistent with the 'concerted decarboxylation' pathway,[7] this would require participation of a relatively stable dipolar intermediate which has never been detected.‡ The more general fate of oxazolidinone **1** cannot, however, be reconciled with the established ('concerted decarboxylation') mechanism.[3] When oxazolidinone **1** was heated (as a 0.033 M solution in MeCN at 80 °C for 17 h) in the *absence* of a dipolarophile, decomposition (decarboxylation) of **1** was *not observed*. Moreover, the starting oxazolidinone **1**, which was recovered cleanly after this period of time, had undergone *complete racemisation* under these conditions, which correspond to those employed in the cycloaddition process shown in Scheme 1.§

A mechanistic rationale for the formation of cycloadducts **2**, which is consistent with our experimental observations and does not require involvement of the azomethine ylide **3**, is presented in Scheme 2.

We suggest that oxazolidinone **1** undergoes an initial fragmentation to generate the iminium intermediate **5** and this step is then followed by tautomerisation of the now highly activated malonyl proton to provide azomethine ylide **4**, a carboxylated variant of **3**. Azomethine ylide **4** is then the reactive species involved in the subsequent cycloaddition step but in the absence of a trap, collapse of **4** back to oxazolidinone **1** is facile and this provides an explanation for the observed thermal racemisation of **1**. The equilibrating steps linking **1** and **4** can, however, be intercepted by a dipolarophile (alkene or alkyne, or thiocarbonyl), displacing the equilibrium and leading, in what is likely to be the rate determining event, to cycloadduct **6** [path (*a*)]. Finally, decarboxylation of **6** serves to set the thermodynamically more stable relative *cis* configuration[9] between C(3) and C(5) of the bicyclic β-lactam product **2**.

The principal difference between path (*a*) (Scheme 2) and that normally associated[3] with the generation of azomethine ylides from oxazolidinones [path (*b*) *via* **3**] is that the decarboxylation step *follows, rather than precedes*, the cycloaddition event, although studies are still needed to establish all the details of this mechanism.

While no details are available for the positions of the two pre-cycloaddition equilibria shown in Scheme 2, displacing either of these to the right should increase the concentration of azomethine ylide **4** and accelerate the overall cycloaddition process. This acceleration has been achieved using LiBr as a

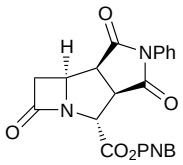


1 R^1 = PNB **5** **4**

3 **2** **6**

Scheme 2

mild Lewis acid¶ and thermolysis of **1** in the presence of *N*-phenylmaleimide (NPM) (0.040 M of **1**, 1.1 equiv. of NPM and 1.1 equiv. of LiBr in MeCN at 80 °C) led to complete consumption of **1** in 4 h and cycloadduct **7**[1] was isolated in 42% yield. This compares to a reaction time of 25 h (and 49% yield of **7**) when the same reaction was carried out in the absence of LiBr. Using thiobenzophenone as the dipolarophile, reaction time was cut (from 80 h to 1.5 h) using 1.1 equiv. of LiBr, although the yield of cycloadduct **8**[2] did decrease (30 *vs.* 51% without LiBr). The role played by the Lewis acid is not yet clear but it would be premature to exclude the intermediacy of an alternative dipolar component, for example **3**, under these modified conditions.



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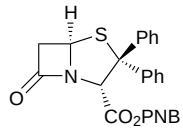

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The mechanism shown in Scheme 2 does not require any reassessment of the 1,3-dipolar cycloreversion mechanism which characterises the concerted fragmentation of simpler oxazolidinones.[3] When compared to the more usually encountered oxazolidinones, β-lactam derivatives such as **1** are different in a number of important respects that may favour the formation of azomethine ylide **4**: **1** is an *N*-acyl-, rather than an *N*-alkyl-oxazolidinone, which also incorporates a significant degree of strain and contains an unusual malonate moiety.‖ Nevertheless, we have uncovered an alternative pathway for expressing azomethine ylide reactivity from an oxazolidinone precursor and this unexpected pathway provides a method for generating cycloadducts carrying new and varied substitution patterns. These mechanistic concepts are currently being evaluated for a range of bicyclic oxazolidinones other than those based on a β-lactam, both to define the more general applicability and also to establish further details of this alternative 'cycloaddition-decarboxylation' sequence outlined in Scheme 2.

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Footnotes and References

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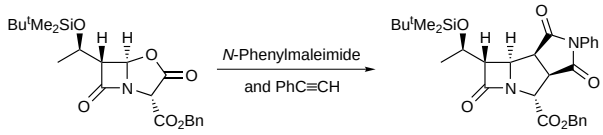
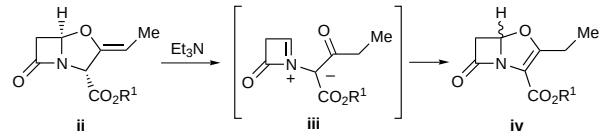
‡ Qualitative rate differences have been observed for the reaction of **1** with a variety of dipolarophiles and more detailed kinetic studies are underway. In addition, direct competition experiments have been carried using *N*-phenylmaleimide and PhC≡CH with a limiting quantity of the C(6) substituted β-lactam oxazolidinone **i** and only the maleimide cycloadduct (ref. 1), which is enantiomerically pure, was observed.



i only adduct observed

§ The racemisation of **1** was followed by both optical rotation and ^{1}H NMR spectroscopy using Eu(hfc)$_3$ and was shown to be a first order process ($t_{\frac{1}{2}}$ = 2.5 h, MeCN at 80 °C). After more prolonged heating (48 h), decomposition of **1** was observed. Workers at Glaxo (ref. 8) have reported that desoxyclavulanic acid **ii** undergoes both C=C bond isomerisation *and* racemisation to give (±)-**iv** when treated with Et_3N. The intermediacy of the stabilised azomethine ylide **iii**, which is structurally related to **4**, has been implicated in this study.



ii **iii** **iv**

¶ A wide variety of other, more conventional Lewis acids have been evaluated [*e.g.* AgOAc, $AgNO_3$, $ZnBr_2$, $Sc(OTf)_2$, $Ti(OPr^i)_4$] but all led to decomposition of oxazolidinone **1**.

‖ The strain associated with **1** may play an important activating role in the specific case of the β-lactam-based system and, for this reason, a stepwise cycloaddition pathway may intervene. Alkenes (dimethyl maleate and dimethyl fumarate) do undergo stereospecific cycloaddition (ref. 1), but the possibility that, for example, the iminium component of **5** is trapped by a direct nucleophilic addition (as the first step of a cycloaddition process) cannot be excluded, especially when more highly polarisable dipolarophiles, such as thiocarbonyls, are involved. Solvent effects are also apparent and the rate of formation of cycloadducts **2** is faster in MeCN than in toluene at comparable temperatures.

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