The azomethine ylide strategy for β-lactam synthesis. A comprehensive mechanistic evaluation

David Brown,[a] Giles A. Brown,[a] Sarah R. Martel,[a] Denis Planchenault,[a] Evelyn Turmes,[a] Kenneth E. Walsh,[a] Richard Wisedale,[a] Neil J. Hales,[b] Colin W. G. Fishwick[c] and Timothy Gallagher *[a]

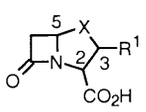
[a] *School of Chemistry, University of Bristol, Bristol, UK BS8 1TS*
[b] *AstraZeneca, Mereside, Alderley Park, Macclesfield, UK SK10 4TG*
[c] *School of Chemistry, University of Leeds, Leeds, UK LS2 9JT*

Received (in Cambridge, UK) 18th December 2000, Accepted 1st March 2001
First published as an Advance Article on the web 16th May 2001

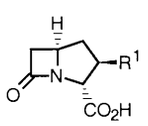
The release of azomethine ylide reactivity from oxazolidinones such as **4a/b** and **7** is proposed to involve a stepwise fragmentation *via* **12** and **13** followed by cycloaddition (to an alkene) leading to adduct **14**, which then undergoes decarboxylation under the reaction conditions to give the observed product **15**. In the case of C=C-based dipolarophiles, the cycloaddition is concerted and stereospecific, and the cycloaddition step is rate determining. Extensive experimental, together with computational data, including racemisation and kinetic studies, as well as the changes in reactivity associated with varying key structural features associated with the β-lactam based oxazolidinones is presented in support of the favoured mechanistic postulate. The fragmentation–cycloaddition–decarboxylation sequence is an alternative pathway for the release of an azomethine ylide from an oxazolidinone to that process already well established for *N*-alkyl oxazolidinones (concerted decarboxylation before cycloaddition). The *N*-acyl component associated with **4** may influence this change in mechanism, but specific structural features associated with the β-lactam system (ring strain and the presence of a malonyl moiety) are most likely responsible for the mechanistic divergence that is observed.

Introduction

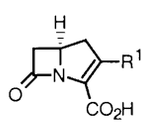
The bicyclic heterocyclic unit **1** represents a generic framework comprising the core of a diverse and commercially important group of β-lactam antibiotics. This group includes carbapenams and carbapenems, and heteroatom substituted variants, most notably the sulfur-based penams and penems. Such molecules have been the subject of intense synthetic interest and, given their clinical significance, new and particularly flexible entries to these targets remain important synthetic objectives.[1]



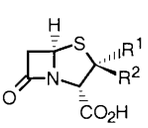
General structure **1**



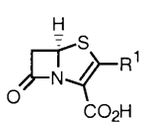
Carbapenam



Carbapenem

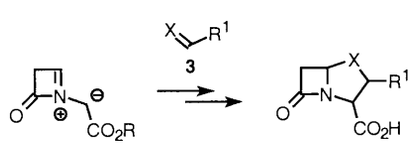


Penam



Penem

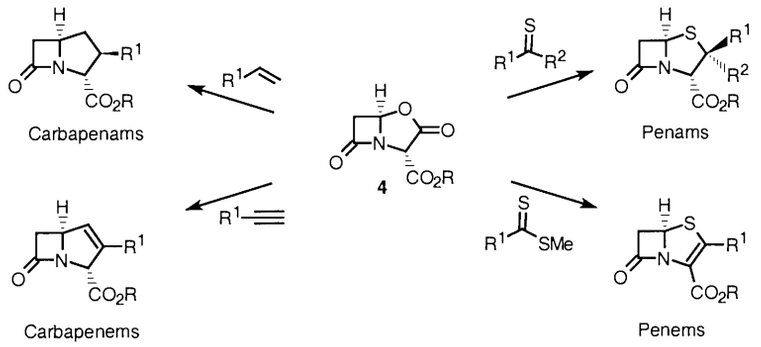
Our studies in this area focussed on the five-membered ring azacycle that is present within general structure **1**, which suggested a synthetic approach based on establishing this moiety using a 1,3-dipolar cycloaddition.[2] The ability of 1,3-dipolar cycloadditions to provide access to a variety of heterocyclic frameworks is already very well established, and azomethine ylides constitute an important class of dipole for constructing pyrrolidines and pyrrolines (*cf.* the carbapenam and carbapenem ring systems respectively).[3] Based on this precedent, it is possible to formulate an approach to general structure **1** that is based on the azomethine ylide **2**, where the 1,3-dipole is contained within the skeleton of the β-lactam component. Dipole **2** not only provides the reactivity that is needed to construct the five-membered ring present in **1**, but also carries within it those structural features (the β-lactam unit itself and the *C(2)* carboxy function) that are recognized as key requirements for viable antibacterial activity. Furthermore, this cycloaddition process is necessarily a two component process, and the dipolarophile **3** employed offers a powerful means of introducing additional flexibility and, above all, structural diversity. Azomethine ylides not only react well with a variety of alkenes and alkynes, but also with other 2π-components based on C=O,[4a] C=N[5] and C=S[6] containing dipolarophiles. With the ability to vary the nature of the dipolarophile (and thereby X and R^1), this approach offers the potential of a comprehensive entry into general structure **1**. A combination of this flexibility with the direct and highly convergent nature of the overall process represents a powerful tool that has particular attractions in the drug discovery process.



General structure **1**

Despite these apparent advantages, the successful implementation of a 1,3-dipolar cycloaddition based strategy for the construction of bicyclic β-lactams has only recently been achieved.[2a] The key to this success lies in an ability to generate the requisite azomethine ylide reactivity—the ester-stabilized 1,3-dipole **2** or its equivalent. We have developed a solution to this central issue whereby the necessary 1,3-dipolar reactivity

 DOI: 10.1039/b010046n

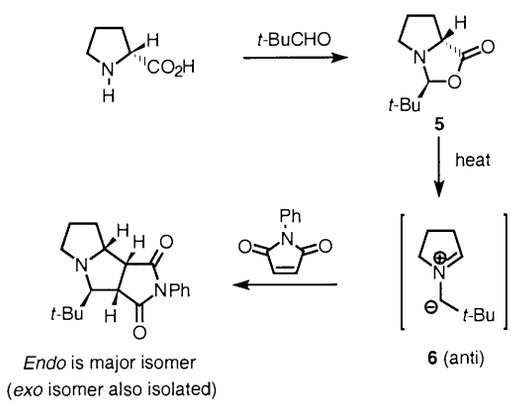


Scheme 1

equivalent but not identical to **2**—is available from an oxazolidinone precursor **4**. Thermolysis of **4** in the presence of a suitable dipolarophile provides an efficient route to racemic carbapenams and carbapenems, and to the thia analogues, penams and penems respectively (Scheme 1). Details of the synthetic aspects of this chemistry have been published[2a,b] but more recently, C=O,[2c] C=Se,[2e] and C=N[2f] based dipolarophiles have also been found to successfully partner the azomethine ylide generated from **4** to afford the corresponding heteroatom-containing bicyclic β-lactams.

Oxazolidinones as a source of azomethine ylides

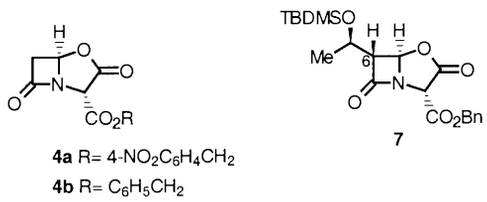
The formation of azomethine ylides by thermal decarboxylation of oxazolidinones is, in a more general sense, well established having been known for 30 years.[4a,7–10] Oxazolidinones **5**, which can be generated by condensation of an α-amino acid with an aldehyde, provide a versatile entry into azomethine ylide derived cycloadducts, illustrated for example in Scheme 2.



Scheme 2

Extensive studies, most significantly by Grigg,[10] have not only demonstrated the synthetic value of this process, but also established a number of important mechanistic characteristics. Stereochemical correlations between the starting oxazolidinone **5** and the final cycloadduct established that dipole formation involves a concerted decarboxylation (a 1,3-dipolar cycloreversion). For cyclic α-amino acids (lacking a benzylic carboxylic acid function) this leads stereospecifically to the *anti* azomethine ylide **6**, which is captured by cycloaddition to give mixtures of *endo* and *exo* cycloadducts.†

Quantitative kinetic information for the chemistry shown in Scheme 2 has not been reported, but it is reasonable that decarboxylation (azomethine ylide formation) is the rate-determining step.‡ In any event, oxazolidinones **5** and related derivatives are thermally unstable, and we have found that these derivatives undergo ready decomposition when heated in the absence of a dipolarophile. It is also pertinent to note that the systems studied by Grigg (such as **5**) incorporate an *N-alkyl* substituent, while the 1,3-dipole precursors used in the β-lactam series constitute *N-acyl* oxazolidinone derivatives. Nevertheless, our initial expectation was that the presence of an *N*-acyl, rather than *N*-alkyl moiety, would not have an overriding influence on the basic reaction mechanism involved, and that the β-lactam containing oxazolidinones *e.g.* **4** and **7** would follow a similar pathway.§ We expected to see a rate determining—and probably concerted—decarboxylation step, followed by a fast cycloaddition event.



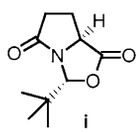
The following paper[11] describes work directed towards the generation of the "parent" β-lactam-based azomethine ylide **2**, and a number of avenues that were explored in order to achieve this objective. These results, as well as those derived from a series of related studies, have also contributed towards our appreciation of the scope and limitations of the cycloaddition chemistry associated with the oxazolidinone-derived pathways outlined in Scheme 1.

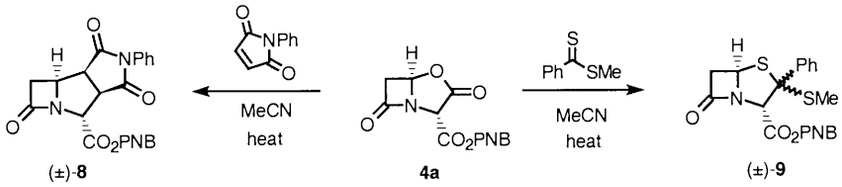
In this paper we deal with key aspects of the β-lactam based azomethine ylide cycloaddition strategy, focussing on the successful process for the synthesis of bicyclic β-lactams based on thermolysis of **4** in the presence of a dipolarophile. As this synthetic programme evolved, it became evident that the mechanism by which azomethine ylide reactivity was released from **4** did not conform to our initial expectations.[12] As a consequence, a more extensive mechanistic investigation has now been undertaken and the full results of this study are presented here.

† The stereospecificity of the decarboxylation step with respect to the geometry of the azomethine ylide does depend on the structure of the α-amino acid. Complete stereoselectivity (stereospecificity) is associated with cyclic amino acids but decreased stereoselectivity is observed with acyclic amino acids and for systems where the carboxylic acid resides at a benzylic centre.[10]

‡ The work of Tsuge and co-workers[9b] showed that different dipolarophiles react with the same azomethine ylide (derived from an amino acid and an aldehyde) and lead to similar yields of cycloadducts after comparable reaction times. This can be interpreted (albeit tentatively) to suggest that the rate of reaction is independent of the dipolarophile.

§ The pyrrolidinone-based *N*-acyloxazolidinone **i** has been reported (D. K. Dikshit, A. Maheshwari and S. K. Panday, *Tetrahedron Lett.*, 1995, **36**, 6131). No cycloaddition chemistry has been reported for this system.





Scheme 3

Results and discussion

β-Lactam containing oxazolidinones

To date, we have utilized two β-lactam based oxazolidinones **4a/b**[13] and **7**[14] as sources of azomethine ylide reactivity for the synthesis of carbapenams, carbapenems, penams, penems, and oxapenams.[2d] The chemistry described in this paper will focus on the more readily available derivatives **4a/b**, which are prepared on a multigram scale starting from natural clavulanic acid. Oxazolidinones **4a/b** are readily purified by crystallization but are sensitive to moisture and are not readily amenable to chromatography. Almost all of the chemistry described in this paper was carried out using the 4-nitrobenzyl ester derivative **4a**, although it should be appreciated that the corresponding benzyl ester **4b** behaves in an essentially identical fashion.

The enantiomerically pure oxazolidinone **4** gives *racemic* cycloadducts. In contrast, with the *C(6)* substituted variant **7**, the *O*-silyl protected (6*S*)-(1-hydroxyethyl) side chain is retained throughout the cycloaddition process, and this feature serves to maintain overall stereochemical integrity leading ultimately to enantiomerically pure cycloadducts. Nevertheless, the way in which oxazolidinones **4a/b** formed racemic products proved to be highly significant in our mechanistic investigations.

Synthetic and mechanistic experiments

It became clear that the reactivity of **4a** (and also **7**) was not consistent with the general mechanistic pathway established by Grigg[10] for *N*-alkyloxazolidinone derivatives (as outlined in Scheme 2). In particular, **4a** was relatively stable towards thermolysis and when unreactive (usually electron rich) dipolarophiles were employed, **4a** was recovered even after prolonged reaction times. Furthermore, when dipolarophiles of different reactivity *e.g.* *N*-phenylmaleimide (NPM) *vs.* PhC≡CH were used, a significantly longer reaction time was required for the less reactive PhC≡CH to achieve (*i*) a comparable conversion of **4a** and (*ii*) a similar yield of cycloadduct.¶ This suggested that it was the reactivity rather than the actual generation of the dipolarophile that was important and, in turn, raised the possibility of cycloaddition as the rate-determining step. We never observed (*e.g.* by ^{1}H NMR) the build-up of any intermediate dipolar species in reactions involving less reactive dipolarophiles and these results prompted a series of more detailed experiments designed to probe this mechanistic enigma.

A critical observation was made when thermolysis of **4a** was carried out *in the absence of a dipolarophile trap:* the anticipated decomposition of the oxazolidinone did *not* occur.‖ Instead **4a** was re-isolated (after *ca.* 17 h) in essentially quantitative yield but this recovered material was shown to be racemic. This observation was verified by using optical rotation measurements and chiral shift ^{1}H NMR experiments using Eu(hfc)$_3$ (hfc = heptafluoropropylhydroxymethylenecamphorate). A more controlled kinetic study, again using both α_D and ^{1}H NMR to follow the course of racemisation of **4a**, showed that this was a first order process with $t_{1/2}$ = *ca.* 2.5 h (in MeCN at 80 °C). Observation of this racemisation process was crucial to the development of an alternative mechanistic rationale to account for the reactivity of the β-lactam based oxazolidinones **4a/b** (and by inference the *C(6)* substituted variant **7**). Precedent for this type of racemisation process does exist within the β-lactam area,[15] and this is more appropriately discussed in detail in the accompanying paper.[11]

We have also probed the kinetic properties of two cycloaddition reactions using MeCN as solvent. The first involved a reactive dipolarophile (NPM) and the other using a significantly less reactive trap (methyl dithiobenzoate) (Scheme 3). In the case of NPM, the isolation method[16] was used in order to establish that the reaction leading to the racemic cycloadduct **8** was second order overall ($k = 17.8 \times 10^{-3}$ mol dm^{-1} s^{-1} at 98 °C), and first order in each of oxazolidinone **4a** and NPM. We were also able to determine the thermodynamic parameters for this cycloaddition reaction and these are shown in Table 1. Data from two related reactions (those shown in Equations 1 and 2)[17] are provided for purposes of comparison, and the values we have obtained, especially in respect of the strongly negative entropy of activation, are similar to these more typical 1,3-dipolar cycloaddition processes. There is a caveat that must be placed on the thermodynamic data obtained from **4a**. The fragmentation–cycloaddition reaction does not take place to a significant extent below 80 °C, at which temperature oxazolidinone **4a** is relatively stable. However, at higher temperatures (>110 °C), the rate of decomposition of **4a** complicated the kinetic analysis and, as a consequence, we were limited to using a narrow temperature range (85 to 98 °C) to obtain the parameters shown in Table 1.

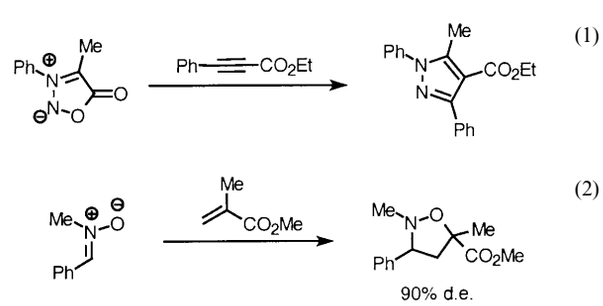


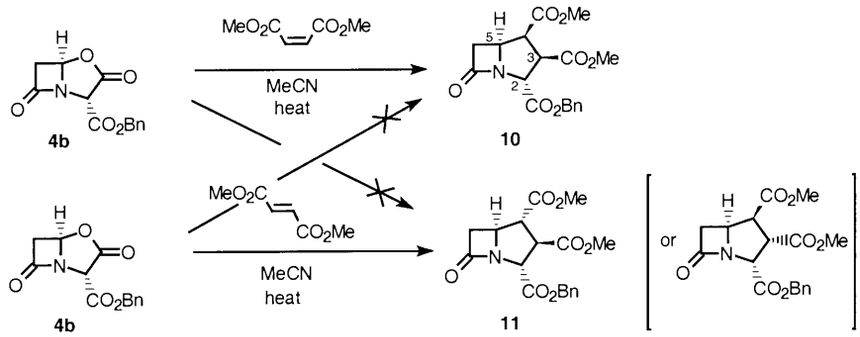
Table 1

	4a + NPM→**8**	*Equation 1*[a]	*Equation 2*[b]
$\Delta H^{\circ\ddagger}$	76.8 kJ mol^{-1}	76.6 kJ mol^{-1}	65.7 kJ mol^{-1}
$\Delta S^{\circ\ddagger}$	−76.8 J mol^{-1} K^{-1}	−121.4 J mol^{-1} K^{-1}	−133.9 J mol^{-1} K^{-1}
$\Delta G^{\circ\ddagger}$	107.6 kJ mol^{-1}	112.7 kJ mol^{-1}	105.6 kJ mol^{-1}
E_{ACT}	79.9 kJ mol^{-1}	79.1 kJ mol^{-1}[c]	68.2 kJ mol^{-1}[c]

[a] Ref. 17*a* and 17*b*. [b] Ref. 17*b* and 17*c*. [c] Calculated based on reported data.

¶ The higher reactivity of NPM as compared to PhC≡CH was easily demonstrated by a direct competition experiment. Also, a number of solvents have been successfully employed in the β-lactam cycloaddition process, including MeCN, PhMe, EtOAc, a range of chlorinated and ether solvents, DMF, DMSO, and CF_3CH_2OH. Acetonitrile proved to give consistently cleaner and faster reactions and higher yields.

‖ Oxazolidinone **4a** does decompose slowly on prolonged heating at 80 °C and more rapidly at temperatures in excess of 110 °C. Extended heating of **4a** (MeCN, >30 h) in the absence of a dipolarophile led to complete decomposition, and we have not been able to characterize any products (such as azomethine ylide dimer derived from the "parent" 1,3-dipole **2**) from this experiment.



Scheme 4

Similar results and limitations were associated with the reaction between **4a** and methyl dithiobenzoate to give the penem precursor **9**, again using MeCN as solvent. The reaction was first order with respect to both **4a** and the C=S based dipolarophile (second order overall; $k = 1.1 \times 10^{-3}$ mol dm^{-1} s^{-1} at 80 °C). In this slower reaction, partial decomposition of both reactants over the prolonged reaction time required made more detailed analysis of this process impractical. Additionally, the computational studies described below point to a possible complication associated with the kinetic analysis of the NPM reaction (see Scheme 9).

Useful conclusions can also be drawn from the stereochemical outcome of the cycloaddition process. Firstly, using dimethyl fumarate and dimethyl maleate with the benzyl ester derivative **4b**, we have demonstrated that the cycloaddition step is stereospecific (Scheme 4). A single cycloadduct **10** was isolated in 74% yield from dimethyl maleate, and dimethyl fumarate led to a major product **11** in 42% yield. A minor isomeric product (which was *not* **10**) was detected by NMR in this latter reaction but could not be isolated or further characterized. The relative stereochemistry of **10** has been determined by NOE experiments. We were not able to unambiguously assign the structure of **11** (the major adduct derived from fumarate) using NOE, and coupling constants ($^3J_{H(2)-H(3)}$, $^3J_{H(3)-H(4)}$) do not, in our experience, provide a reliable means for establishing relative stereochemistry in this type of β-lactam derivative. The structure shown for **11** is consistent with that observed in most cases examined, *i.e.* a *trans* relationship between the ring substituents at *C(2)* and *C(3)*, but this assignment must be regarded as provisional.

Importantly, the lack of any crossover products from these two reactions supports the participation of an azomethine ylide intermediate in an otherwise conventional and concerted [4π + 2π] cycloaddition step leading to the cycloadducts that we have observed. This statement can, of course, apply only to C=C-based dipolarophiles, since it is conceivable that cycloadditions involving highly polarized dipolarophiles, such as those incorporating C=X (where X = NR, O, S, Se), could proceed *via* a stepwise pathway.

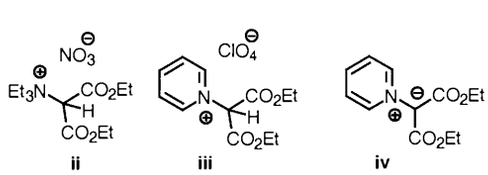
More significantly for our mechanistic proposals, we have only isolated products corresponding to the thermodynamically more stable stereochemical *trans* relationship[18] between *C(2)* and *C(5)*—see **8**–**11**. This places the *C(2)* carboxy moiety on the *exo* face of the 1-azabicyclo[3.2.0]heptane framework, an observation that not only applies to these examples but to all of the cycloadducts we have isolated to date. This particular stereochemical outcome does not conflict with the Grigg[10] mechanism (*cf.* Scheme 2) since a similar outcome would be expected if an *anti* dipole was involved in the cycloaddition step (see Computational studies described below). However, the stereochemical outcome in the β-lactam series may also be interpreted in another way that is consistent with the other observations that we have made.

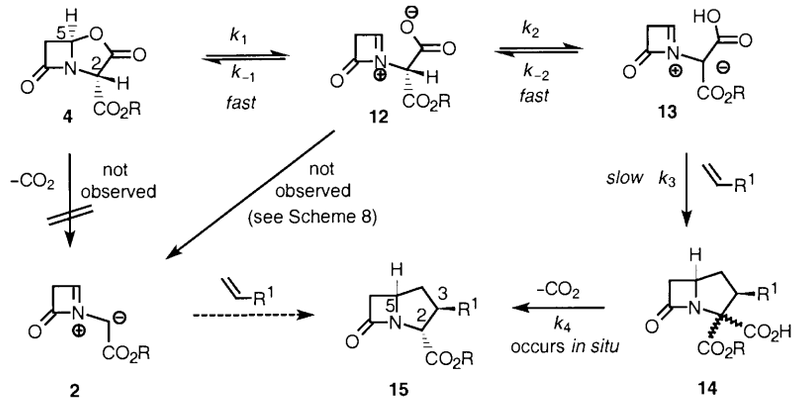
Clearly, the experimental results described above indicate that the mechanism by which azomethine ylide reactivity is released from **4** differs fundamentally from that associated with better known *N*-alkyloxazolidinones. 1. The simple β-lactam based oxazolidinone **4a** does not undergo spontaneous decarboxylation when heated—in the presence of an effective dipolarophile, **4a** is consumed but when heated for a similar period of time either alone or with an unreactive trap, **4a** is recovered. 2. Oxazolidinone **4a** does, however, undergo a first order racemisation under thermal conditions. 3. Kinetic analysis of the reaction of **4a** with *N*-phenylmaleimide has shown that this cycloaddition is a second order process overall, with a negative entropy of activation and we conclude that it is likely that the cycloaddition step is rate determining. 4. The stereochemistry of the dipolarophile is retained and we conclude from this that the cycloaddition involving alkenes is a concerted process. However, the (C2) carboxy stereochemistry is thermodynamically controlled and contains no information about the structure of reaction intermediates.

The mechanism already established for the fragmentation of *N*-alkyloxazolidinones, which would require the direct (concerted) decarboxylation of **4** to give azomethine ylide **2**, is not consistent with these observations, and an alternative explanation for the fate of the β-lactam-based oxazolidinones is required. Our proposal, shown in Scheme 5, has two key features: (*i*) the nature of the azomethine ylide species **13** involved and (*ii*) the suggestion that the (concerted and stereospecific) cycloaddition step *precedes* decarboxylation. The first phase of this process requires ring opening of oxazolidinone **4** to give **12**, followed by proton transfer to generate **13**, and it is this 'carboxylated' azomethine ylide intermediate—the *carboxylated* variant of our initial target 1,3-dipole **2**—that is postulated to participate in the crucial cycloaddition reaction. The ring strain associated with **4** is a likely contributor to the ease of ring opening and, based on related structures reported by Bordwell,[19] the malonyl proton present in **12** is anticipated to be of comparable acidity to that of a carboxylic acid.**

To account for the racemisation of **4**, formation of the 'carboxylated' azomethine ylide **13** must be reversible. In the absence of an effective dipolarophile, this equilibrium would result in the observed racemisation, but in the presence of a suitable trap, the azomethine ylide **13** is intercepted and under-

** Bordwell[19] has measured the acidity of both **iii** (pK_{HA} 11.8) and **ii** (pK_{HA}5.6). These measurements were made in DMSO (a non-hydrogen bond donor solvent), and it is of interest to compare these values to those obtained for carboxylic acids *e.g.* PhCO$_2$H: pK_{HA} 11.1 (in DMSO). The zwitterions **iv** derived from **iii** contain structural features—enolate of a β-dicarbonyl adjacent to an iminium moiety (albeit not *N*-acyl)—similar to those found in **13**.

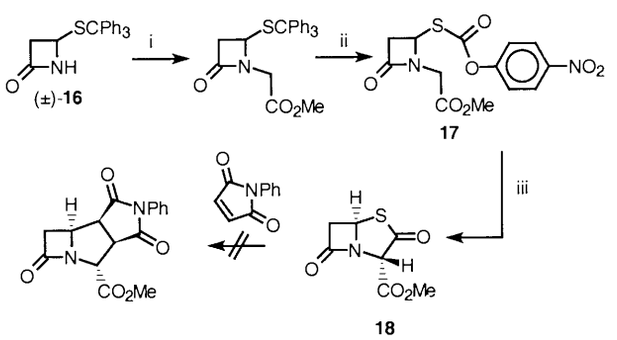




Scheme 5

goes a cycloaddition reaction. The final transformation would then require decarboxylation of the initially formed adduct **14**. If this pathway is followed, then decarboxylation must take place under the reaction conditions since we have been unable to detect adducts retaining the carboxylic acid function. This final step is also expected to give the (observed) thermodynamically more stable *trans* relationship between *C(2)* and *C(5)* in the final product **15**. Based on the kinetic data presented above, we suggest that the cycloaddition step is rate determining, *i.e.* k_3 is slow. An alternative scenario would involve decarboxylation of **14** to give **15** as the rate-limiting event ($k_3 > k_4$), but we regard this as less likely. We also consider decarboxylation of **12** to give **2** as unlikely (see Scheme 8). Under specific circumstances, this pathway can operate (see Scheme 7) but only when proton tautomerisation is unavailable.

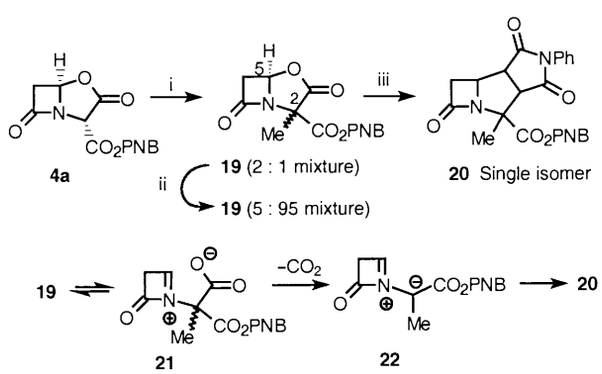
In order to probe further the proposal outlined in Scheme 5, two additional substrates have been investigated. We evaluated the thio analogue **18** as a precursor to an azomethine ylide, and the preparation of racemic **18** is outlined in Scheme 6,



Scheme 6 *Reagents and conditions*: i, K_2CO_3, $BrCH_2CO_2Me$, DMF (68%); ii, $AgNO_3$, py, MeOH, EtOAc, then 4-$NO_2C_6H_4OCOCl$, *i*-Pr_2NEt, DMAP, THF (83% overall); LiHMDS, THF (46%).

starting from the known S-protected 4-tritylthioazetidin-2-one **16**.[19] *N*-Alkylation of racemic **16**, followed by trityl cleavage and *S*-acylation gave the thiocarbonate **17**, which underwent base-mediated cyclization to give the thiazolidinone **18** as a crystalline solid. Thermolysis of **18** (MeCN, 100 °C, 23 h or 1,2-dichlorobenzene, 150 °C, 20 h) in the presence of NPM failed to produce a cycloadduct, and **18** was recovered unchanged. Subsequent heating of **18** and NPM in 1,2-dichlorobenzene at 200 °C (in a sealed tube) resulted in decomposition—no evidence for cycloaddition was detected. Loss of COS (*vs.* CO_2) does (ultimately) represent a thermodynamically less favourable process (see below) and the involvement of a more acidic thiol acid (the *S*-analogue of **12**) may also influence (disfavourably) the key proton transfer step [*cf.* **12** to **13**]. However, a significant factor accounting for the reduced reactivity of **18** is the comparative lack of strain associated with a sulfur (as opposed an oxygen) containing five-membered ring; the ring strain associated with this type of substrate is dealt with in the computational section of this paper.

The second substrate examined was the α-methylated oxazolidinone **19**. This substrate, which has proven to be particularly useful, lacks the acidic malonyl proton but otherwise closely mimics oxazolidinone **4**. The α-methylated variant **19** was prepared by direct alkylation of **4a** and isolated, albeit in low yield, as a 2 : 1 mixture of diastereoisomers; the sensitivity of **19** precluded separation of these isomers by chromatography and the mixture was used in subsequent experiments (Scheme 7). Thermolysis of **19** (MeCN, 100 °C, sealed tube) was then

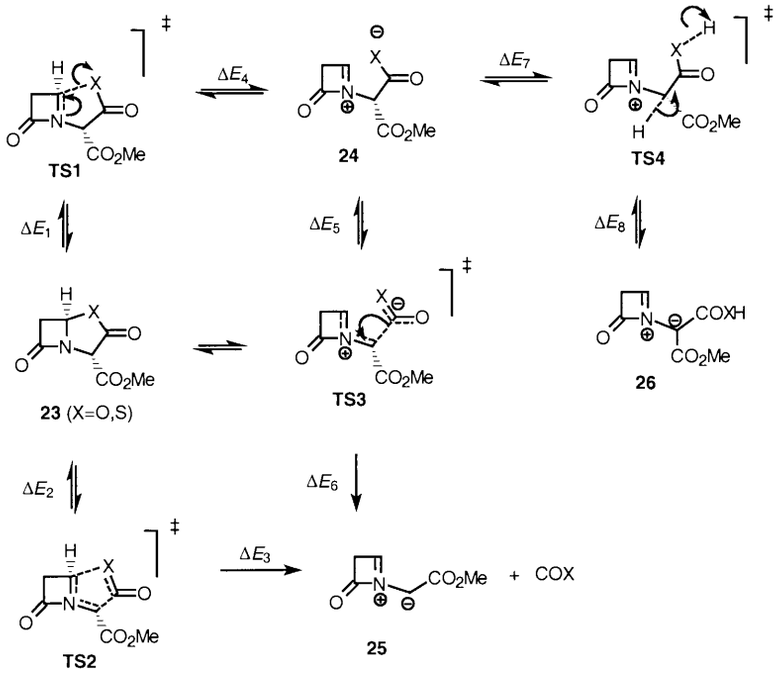


Scheme 7 *Reagents and conditions*: i, NaHMDS, −78 °C, MeI, THF (29% as a 2 : 1 mixture of isomers); ii, MeCN, 100 °C (sealed tube) 2 h; iii, *N*-phenylmaleimide, MeCN, 100 °C (sealed tube), 15 h (**20**: 78% yield).

studied. After 2 hours, the 2 : 1 mixture of isomers of **19** had undergone clean conversion to a 5 : 95 mixture (by ^{1}H NMR), favouring what had originally been the minor diastereomer. Heating **19** in the presence of *N*-phenylmaleimide (MeCN, 100 °C, sealed tube, 15 h) gave a single cycloadduct **20** in 78% isolated yield, and while the gross structure of **20** has been established, the detailed stereochemistry of this adduct was not pursued.††

Thermolysis of the α-methylated oxazolidinone **19** (MeCN, 100 °C, sealed tube, 15 h) but in the *absence* of NPM did result in significant decomposition, and we have correlated the pathways associated with decomposition and cycloaddition (leading to **20**). Solutions of **19** (in MeCN containing a small quantity of DMSO as an internal standard) were heated with and without NPM. After 14 hours, the extent of decay of **19** (as

†† Thermal epimerisation of **19** is presumed to involve *C(5)* rather than *C(2)* *via* **21**. We have not determined that the mixture corresponding to **19** is composed of enantiomerically pure isomers, and the structure of **19** (as shown in Scheme 7) is not intended to imply an absolute stereochemistry. Although the stereochemistry of cycloadduct **20** has not been pursued, it is noteworthy that the ^{1}H NMR spectrum of **20** is virtually superimposable (chemical shifts and *J* values) on the similar regions of the ^{1}H NMR spectrum of cycloadduct **8**, which has already been assigned as the *endo* adduct.[2a]



Scheme 8

judged by the amount of **19** remaining—*ca.* 20%) correlated almost exactly to the amount of cycloadduct **20** produced in the parallel experiment. This result indicates that the thermal decomposition of **19** and the subsequent cycloaddition reaction with NPM are both efficient processes.

Based on these observations, the mechanism associated with conversion of **19** to **20** most reasonably involves a stepwise (reversible) fragmentation *via* **21** and irreversible decarboxylation to yield azomethine ylide **22**. Isomerization of **19** (from a 2 : 1 mixture to a 5 : 95 mixture of isomers) under the conditions used provides support for this pathway.

This result does raise the possibility that a similar *nonconcerted* path is available to oxazolidinone **4** leading to azomethine ylide **2**, and these two processes have been compared computationally (see Scheme 8). However, given that we observe both racemisation of **4** (where both the *C(2)* and *C(5)* stereocentres have to be involved) and cycloadduct formation under conditions that otherwise do not lead to decomposition of **4**, this alternative stepwise decarboxylation can only play at best a minor role.

Computational studies

In order to gain further insight into the mechanistic possibilities outlined above, semi-empirical calculations were performed in order to estimate the relative energies of the intermediates and transition states involved in the generation of the two possible dipoles **2** and **13** as shown in Scheme 5. For simplicity, the calculations were carried out on the methyl (rather than PNB) ester **23**, but using a simulated solvent dielectric in order to closely match the calculation results to the actual reaction conditions used. Both the oxazolidinone (X = O) and thiazolidinone (X = S) series have been compared, and the results are summarised below (Scheme 8 and Tables 2 and 3).

Three discrete fragmentation pathways have been considered. 1. Stepwise fragmentation followed by decarboxylation to give azomethine ylide **25** (*via* **TS1** and **TS3**) (*cf.* **19**→**22**). 2. Stepwise fragmentation followed by tautomerisation (*via* **TS1** and **TS4**) to give carboxylated azomethine ylide **26** (which represents our favoured mechanistic pathway). 3. Concerted decarboxylation (*via* **TS2**) also to give azomethine ylide **25** which corresponds to the established[10] mechanism for the formation of azomethine ylides from *N*-alkyloxazolidinones.

Clearly, the data shown in Tables 2 and 3 indicate that cleavage of the C–O bond in oxazolidinone **23** (X = O) to yield zwitterion **24** (X = O) *via* transition state **TS1** (X = O) is favoured and reversible ($\Delta E_4 < \Delta E_1$) compared to concerted loss of carbon dioxide from **23** (X = O) *via* transition state **TS2**

Table 2 Heats of formation and transition state imaginary frequencies for Scheme 8

Structure	H_f[a] X = O	H_f[a] X = S	ν_i[b] X = O	ν_i[b] X = S
23	−163.05	−136.36	—	—
24	−144.83	−103.30	—	—
25	−141.82[d]	−76.68[d]	—	—
26	−149.93	−106.50	—	—
TS1	−136.87	−89.47	−355.93	−146.04
TS2	(−129.49)[c]	(−80.68)[c]	(−330.23)[c]	(−472.94)[c]
TS3	−128.67	−85.28	−568.50	−572.22

[a] Heats of formation in kcal mol^{-1}, obtained using AM1 (X = O) or PM3 (X = S) Hamiltonians and the COSMO[20] model to simulate a solvent field equivalent to that of acetonitrile. [b] All transition structures were characterized by observing them to have a single negative vibrational frequency corresponding to the reaction coordinate following a normal mode analysis (expressed in cm^{-1}). [c] Transition state could not be located in acetonitrile and energy is a single-point estimate (COSMO) on a gas-phase derived transition structure. [d] Energies are those of 1,3-dipole plus calculated heats of formation (COSMO) of CO_2 (H_f(MeCN) = −88.89 kcal mol^{-1}) and COS (H_f(MeCN) = −23.75 kcal mol^{-1}) respectively.

Table 3 Activation energies for Scheme 8

	value[a] X = O	value[a] X = S
ΔE_1	26.18	46.89
ΔE_2	(33.56)[b]	(55.68)[b]
ΔE_3	(−12.33)[b]	(−4.00)[b]
ΔE_4	−7.96	−13.83
ΔE_5	16.16	18.02
ΔE_6	−12.33	8.60

[a] Heats of formation in kcal mol^{-1}, obtained using AM1 (X = O) or PM3 (X = S) Hamiltonians and the COSMO[20] model to simulate a solvent field equivalent to that of acetonitrile. [b] Transition state could not be located in acetonitrile and energy is a single-point estimate (COSMO) on a gas-phase derived transition structure. [d] Energies are those of 1,3-dipole plus calculated heats of formation (COSMO) of CO_2 (H_f(MeCN) = −88.89 kcal mol^{-1}) and COS (H_f(MeCN) = −23.75 kcal mol^{-1}) respectively.

(X = O) to yield *anti* dipole **25** ($\Delta E_1 < \Delta E_2$). Indeed, transition state **TS2** (X = O) was not stable in a simulated acetonitrile environment when attempts at optimisation were made using the COSMO[20] model, and all measurements are single-point estimates on a transition structure optimised *in vacuo*.

Decarboxylation of zwitterion **24** (X = O) to yield anti-dipole **25** (X = O) *via* transition state **TS3** (X = O) is, however, predicted to be energetically reasonable. However, an alternative pathway involving formal (but stepwise) proton tautomerism of zwitterion **24** (X = O) *via* transition states approximated *via* **TS4** (X = O) to yield dipole **26** (X = O) would appear particularly favourable. Although the energetics and the structure(s) of **TS4** (X = O) have not been calculated in the present study, a number of previous reports[19,21] strongly indicate the extremely favourable nature of the transformation of zwitterion **24** (X = O) into dipole **26** (X = O). As mentioned above, Bordwell and co-workers[19] have found that malonyl-based systems which contain an iminium moiety attached to the malonyl carbon as present in zwitterion **24** (X = O) show the expected enhanced degrees of acidity when compared to simpler malonate-derived carbon acids.

Additionally for weak acids, including malonate derivatives, Dillon[21] has demonstrated an approximately linear relationship between measured pK_a's and measured rates (and thus activation energies) of ionisation. A weak carbon acid, such as 1-chloronitroethane, has a pK_a of around 7 with an activation energy for ionisation of 20 kcal mol^{-1}. Substituting the inductively anion-stabilising chlorine atom for a conjugating substituent (as in ethyl nitroacetate) decreases the pK_a to approx. 6 with a corresponding decrease in activation energy required for ionisation to 16 kcal mol^{-1}. It would be expected that C–H cleavage in zwitterion **24** (X = O) would be particularly favourable and this species is likely to have a pK_a of 5.6 or lower. This would require an energy barrier probably appreciably lower than 16 kcal mol^{-1} to induce C–H bond cleavage and carboxylate protonation to yield dipole **26** (X = O).

These calculations indicate that generation of *anti* dipole **25** *via concerted* thermal loss of carbon dioxide from oxazolidinone **23** (X = O) does not occur in acetonitrile. As suggested by the α-methylated variant **19**, formation of azomethine ylide **25** in acetonitrile is possible *via* stepwise decarboxylation with the intermediacy of zwitterion **24** (X = O).‡‡ However, tautomerism in zwitterion **24** (X = O) to yield dipole **26** (X = O) is even more favourable and, for this and the other reasons discussed above, remains the preferred reaction pathway for fragmentation of oxazolidinone **23** (X = O) to give an azomethine ylide.

The data in Tables 2 and 3 also shed light on the observed lack of reactivity of the thio variant **23** (X = S). The activation energies for both C–S cleavage of this substrate and the concerted loss of COS are in excess of 20 kcal mol^{-1} higher

n	H^a	ΔH^a
0	−21.03	
		42.87
1	−63.90	
		12.88
2	−76.78	

n	H^a	ΔH^a
0	14.50	
		33.94
1	−19.44	
		6.32
2	−25.76	

[a]Heats of formation in kcal mol^{-1}, obtained using the AM1 Hamiltonian.

Fig. 1

than those determined for **23** (X = O). Additionally, as with the oxazolidinone, the concerted fragmentation pathway could not be established in a simulated acetonitrile environment. As indicated previously, although a number of factors could contribute to the higher energies involved in the sulfur-containing substrates, the relative strain energies of oxygen *versus* sulfur ring systems appears to be an important factor. Comparison of the calculated heats of formation (*H*) and differences associated with ring size (ΔH) for a series of simple bicyclic *O*- and *S*-based heterocycles is shown in Fig. 1. As can be seen, decreasing ring size in the oxygen-containing ring system results in a considerable increase in energy compared to that for the thia analogues.

The viability of both 1,3-dipoles of the types **25** and **26** (Scheme 8) to undergo cycloaddition has also been investigated using a semi-empirical approach (Scheme 9 and Tables 4–6). Due to computational limitations, initial studies were performed in the gas phase as summarised below. These calculations were also extended to include solvent-based studies on the simplified (methyl ester containing) dipole species (see Table 5).

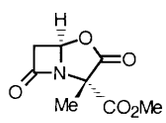
The energetics of these cycloaddition processes are shown in Table 6, and as can be seen, both the 'decarboxylated' 1,3-dipoles **27** (X = H), and the 'carboxylated' systems **27** (X = CO_2H) are predicted to undergo efficient cycloadditions to maleimide derivatives, cycloadditions *in vacuo* generally possessing activation energies in the range 7–14 kcal mol^{-1} (entries 1–4) and 12–24 kcal mol^{-1} for the solution-phase reactions (entries 5 and 6) respectively.

All cycloadditions favour formation of the *endo* adducts **29** (*i.e.* $\Delta E_9 < \Delta E_{10}$) with those resulting from cycloadditions of the 'non-carboxylated' dipoles (entries 1, 3, and 5) having around half the activation energy of the corresponding 'carboxylated' systems (entries 2, 4, and 6). In the 'carboxylated' series (X = CO_2H), however, the calculated preference associated with the *endo* pathway is marginal. It is particularly noteworthy that the value of the activation energy (ΔE_9 = 24.11 kcal mol^{-1}) for cycloaddition of the 'carboxylated' dipole model **27** (X = CO_2H, R = H) in acetonitrile is comparable with the largest of the calculated activation energies in the oxazolidinone fragmentation sequence (that of ΔE_1 = 26.18 kcal mol^{-1}, corresponding to C–O cleavage) which suggests that the rates of both steps may influence the overall reaction kinetics. The heats of formation of the cycloadducts **29** and **30** are generally much lower than those for the corresponding transition states **TS5** and **TS6**, such that the cycloadditions are essentially irreversible under these conditions (*i.e.*, $\Delta E_{11} \gg \Delta E_9$, and $\Delta E_{12} \gg \Delta E_{10}$).

Effect of Lewis acids

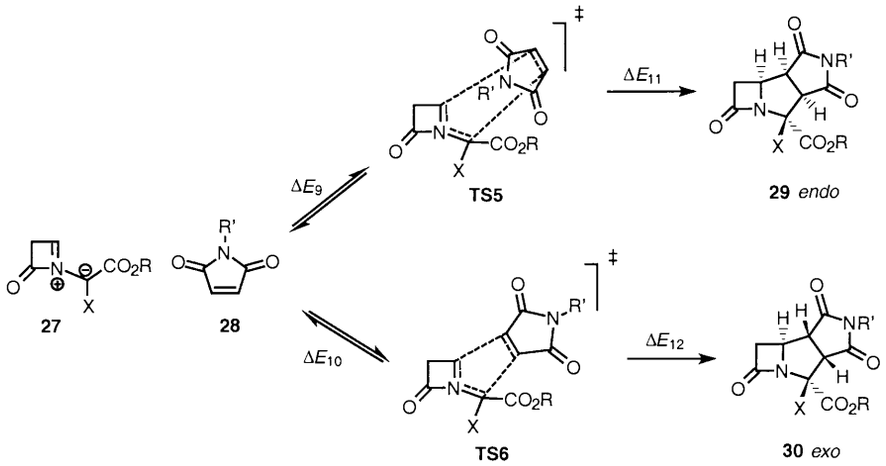
The mechanistic proposals presented here raise a number of other interesting issues. While we cannot determine experimentally the relative positions of the equilibria linking **12** and **13** (Scheme 5) or rates of these interconversions (k_1/k_{-1}, k_2/k_{-2}), increasing the concentration of the azomethine ylide **13** should accelerate the rate of formation of the final cycloadduct **15**.

‡‡ A parallel series of calculations relating to the transformations shown in Scheme 8 (X = O throughout) were performed based on the one diastereomer (of the possible two) of the α-methylated oxazolidinone **v**, and results are summarized here. Heats of formation and transition state imaginary frequencies for the methyl ester analogues of **23** −161.84; **24** −142.02; **25** −144.78; **TS1** −135.12 [−321.65]; **TS2** (−129.50)[a] [(−337.71)[a]]; **TS3** −128.52 [−535.36].



v

Activation energies for equivalent transformations involving **v** as shown in Scheme 8: ΔE_1 26.72; ΔE_2 (32.34)[a]; ΔE_3 (−15.28)[a]; ΔE_4 −6.9; ΔE_5 13.5; ΔE_6 −16.26. ([a] Transition state could not be located in acetonitrile and the energy is a single-point estimate (COSMO) on a gas-phase derived transition structure.)



Scheme 9

Table 4 Heats of formation, transition state imaginary frequencies and dipole moments for Scheme 9

Structure					Structure				
No.	R	R′	X	H_f[a] (ν_i)[b] [Dipole][c]	No.	R	R′	X	H_f[a] (ν_i)[b] [Dipole][c]
27	PNB	—	H	−2.38	**27**	Me	—	H	−33.47
28	—	Ph	—	5.83	**28**	—	Me	—	−28.88
29	PNB	Ph	H	−66.72	**29**	Me	Me	H	−134.61
30	PNB	Ph	H	−63.87	**30**	Me	Me	H	−131.97
TS5	PNB	Ph	H	10.79 (−334.5) [5.29]	**TS5**	Me	Me	H	−55.88 (−319.67) [2.45]
TS6	PNB	Ph	H	14.45 (−385.66) [6.63]	**TS6**	Me	Me	H	−52.64 (−381.95) [3.31]
27	PNB	—	CO_2H	−88.18	**27**	Me	—	CO_2H	−119.42
29	PNB	Ph	CO_2H	−137.06	**29**	Me	Me	CO_2H	−205.01
30	PNB	Ph	CO_2H	−137.83	**30**	Me	Me	CO_2H	−206.85
TS5	PNB	Ph	CO_2H	−68.70 (−506.43) [6.33]	**TS5**	Me	Me	CO_2H	−134.82 (−499.24) [2.86]
TS6	PNB	Ph	CO_2H	−67.38 (−503.28) [3.99]	**TS6**	Me	Me	CO_2H	−134.72 (−463.69) [3.58]

[a] Heats of formation (H_f) and energy differences (ΔH) in kcal mol^{-1}, obtained using AM1 Hamiltonian. [b] All transition structures were characterized by observing them to have a single negative vibrational frequency corresponding to the reaction coordinate following a normal mode analysis (expressed in cm^{-1}). [c] Expressed in Debyes.

One approach to this would be use of an oxaphilic Lewis acid that might serve to lower the barrier to the initial fragmentation of **4** (which corresponds to ΔE_1 in Scheme 8 and is the highest barrier in the formation of the carboxylated dipole) and also enhance the C–H acidity associated with **12**. Such interactions might then increase the effective concentration of the key azomethine ylide intermediate, and with this in mind a wide range of Lewis acids have been evaluated using the reaction between **4a** and NPM as a model system.§§

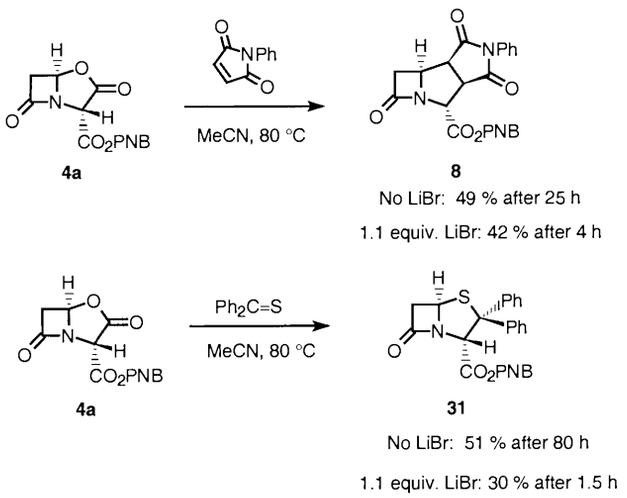
The general sensitivity of oxazolidinone **4a** precluded use of many of the more conventional Lewis acids, but LiBr did show a significant effect (Scheme 10). Using the same concentrations of reactants and the same reaction temperature, addition of 1.1 equivalents of LiBr resulted in a significant decrease in reaction time for a comparable level of conversion of **4a** and isolated yield of adduct (±)-**8**. A similar acceleration has also been observed when thiobenzophenone was employed, a process that leads directly to the diphenylpenam derivative (±)-**31**. In this case, however, use of the Lewis acid catalyst did cause some reduction in yield.¶¶

Conclusions

Evidence has been obtained pointing towards an alternative mechanism for the fragmentation of oxazolidinones to give azomethine ylides to that previously elucidated by Grigg.[10] In the β-lactam based derivatives exemplified by **4**, and based on the weight of evidence, we favour formation and participation of the carboxylated azomethine ylide **13**. This species can undergo concerted and stereospecific cycloaddition reactions, followed by decarboxylation of the initial adduct **14** to give

§§ A variety of Lewis acids were screened without success: Ti(O*i*-Pr)$_4$, AgX (X = OAc, NO_3), $MgBr_2$, $ZnBr_2$, $CeBr_3$, $Sc(OTf)_3$. Lithium salts ($LiClO_4$, LiBr, LiI) led to some acceleration, but LiBr was clearly superior. LiBr is similarly effective at accelerating the rate of reaction between the more substituted oxazolidinone **7** and NPM. We have also studied, without success, a range of acidic and basic catalysts with the aim of promoting, for example, the proton transfer step associated with the conversion of **12** to **13**. We have not attempted to promote ring opening–fragmentation of the thia analogue **18** or the α-methylated oxazolidinone **19** using a Lewis acid.

¶¶ The possibility that the carbonyl group of NPM or the thiocarbonyl moiety of thiobenzophenone interacts with LiBr and that this provides a mechanism for activation cannot be ignored. Attempts to catalyze the reaction of **4a** with PhC≡CH using LiBr as additive failed because the resulting cycloadduct underwent rapid decomposition in the presence of LiBr, a fact that was supported by a control experiment.



Scheme 10

the observed product **15**. A stepwise alternative operates in the case of the α-methylated oxazolidinone **19**, which undergoes a stepwise fragmentation and decarboxylation prior to cycloaddition. This system does, however, lack an acidic malonyl proton, which is a key feature of oxazolidinone **4**. If **4** does undergo a similar stepwise fragmentation to that proposed for the α-methylated oxazolidinone **19**, we suggest that this is a slower and (at best) minor pathway when compared to **4** ⟶ **12** ⟶ **13** (Scheme 5).

The observations presented in this paper do not invalidate the earlier mechanistic proposals developed for the *N*-alkyloxazolidinones such as **5**. In fact, it is more reasonable to suggest that it is the β-lactam series that shows the "anomalous" reactivity profile. This is a consequence of the particular and somewhat unusual structural features present in **4**—a very strained five-membered ring (which facilitates ring opening to give **12**) and the presence of an acidic proton associated with the malonyl moiety, which is activated by the adjacent iminium moiety. A combination of these features provides the means of generating the key 1,3-dipole critical to the success of the azomethine ylide strategy for β-lactam synthesis.

The following paper describes a series of related studies that were directed towards alternative methods and substrates for generating β-lactam-based azomethine ylides. These include efforts to generate the "parent" 1,3-dipole **2** by eliminating those structural features that appear to bias the fragmentation–cycloaddition–decarboxylation pathway which is favoured for **4**.

Table 5 Heats of formation, transition state imaginary frequencies and dipole moments for Scheme 9 in MeCN

Structure[a]				
No.	R	R′	X	H_f[a,b] (ν_i)[c] [Dipole][d]
27	Me	—	H	−52.93
28	—	Me	—	−42.85
29	Me	Me	H	−163.39
30	Me	Me	H	−161.69
TS5	Me	Me	H	−83.03 (−387.55) [4.46]
TS6	Me	Me	H	−80.16 (−375.07) [5.63]
27	H	—	CO_2H	−159.05
297	H	Me	CO_2H	−246.97
30	H	Me	CO_2H	−247.55
TS5	H	Me	CO_2H	−177.79 (−575.07) [6.12]
TS6	H	Me	CO_2H	−176.83 (−566.82) [4.52]

[a] These entries refer to calculations of reactions in acetonitrile using the COSMO[20] algorithm. [b] Heats of formation (H_f) and energy differences (ΔH) in kcal mol^{-1}, obtained using AM1 Hamiltonian. [c] All transition structures were characterized by observing them to have a single negative vibrational frequency corresponding to the reaction coordinate following a normal mode analysis (expressed in cm^{-1}). [d] Expressed in Debyes.

Experimental

General

Infrared spectra (ν_{max}) were recorded using a Perkin-Elmer 1715 FTIR spectrometer, in the range of 4000–600 cm^{-1} either as a neat film on NaCl plates or as a solution in CH_2Cl_2, using NaCl solution cells. Mass spectra *m/z* (E.I., C.I., FAB) were obtained using a Fisons/VG Analytical Autospec System. Nuclear magnetic resonance (NMR) spectra were recorded at the field strength shown and in $CDCl_3$, unless otherwise indicated using standard pulse sequences on an Alpha 500, JEOL GX400, Lambda 300, or Delta 270 with proton and carbon assignments made using a combination of $^1H/^1H$ and $^1H/^{13}C$ correlation spectroscopy. Flash column chromatography was carried out on either Silica Gel (Merck 1.09385) or 60H Silica Gel (Merck TLC, Merck 1.11695) and all commercially available reagents and solvents were purified and dried according to standard procedures.

Kinetic study

General procedures. A solution of oxazolidinone **4a**[13b] (60 mg, 0.196 mmol), 1,4-dibromobenzene (46.2 mg, 0.196 mmol) (which served as an internal standard) and NPM (33.9 mg, 0.159 mmol) in MeCN (6 cm^3) was divided into 6 × 1 cm^3 portions, and 5 × 1 cm^3 portions were placed in identical reseal-able tubes. The remaining portion provided the data point $t = 0$. The five tubes were heated in a temperature-controlled oil bath at the desired temperature (initial kinetic data was obtained at 98 °C) and tubes were removed at hourly intervals.

With each sample, the bulk of the solvent was removed carefully *in vacuo* and the residue was analysed by ^1H NMR (300 MHz). Using distinct signals associated with the individual components enabled the ratio of **4a** and **8**[2a] to be determined for each time point. The internal standard showed that negligible decomposition of **4a** occurred under the conditions employed. This reaction was also run under pseudo-first

Table 6 Energies of cycloadditions in Scheme 9

Entry	R	R′	X	ΔE_9	ΔE_{10}	ΔE_{11}	ΔE_{12}
1	PNB	Ph	H	7.34	11.00	−77.51	−78.32
2	PNB	Ph	CO_2H	13.65	14.97	−68.36	−70.45
3	Me	Me	H	6.47	9.71	−78.73	−79.33
4	Me	Me	CO_2H	13.48	13.58	−70.19	−72.13
5	Me	Me	H	12.75	15.62	−80.36	−81.53
6	H	Me	CO_2H	24.11	25.07	−69.18	−70.72

order conditions (*i.e.* 10 fold excess of NPM) and a plot of ln [**4a**] against time was linear ($R^2 = 0.99$).

Analysis of the alternative pseudo-first order plot (using an excess of **4a**) was complicated by slow but competitive decomposition of **4a**. The isolation method[16] was used to establish the overall second order of the reaction. This involved doubling the excess of NPM, which resulted in a doubling of the pseudo-first order rate constant. Thermodynamic parameters (Table 1) were obtained by determining second order rate constants at 358.2, 361.2, 363.9, 368.2 and 370.2 K, and a plot of ln *kr vs.* $1/T$ ($R^2 = 0.954$) was used to obtained E_{ACT} and ln kr/T ($R^2 = 0.951$) provided $\Delta H^{\circ\ddagger}$, and $\Delta S^{\circ\ddagger}$, and $\Delta G^{\circ\ddagger}$.

A similar procedure was followed to determine the order and rate constant for the reaction of **4a** with methyl dithiobenzoate, which was conducted at 80 °C. Further analysis of this reaction was complicated by decomposition of both reactants (and possibly the products) during the long reaction times that were required.

(±) Benzyl (2*R**,3*R**,4*S**,5*S**)-3,4-bis(methoxycarbonyl)-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate 10

A solution of oxazolidinone **4b**[13b] (100 mg, 0.38 mmol) and dimethyl maleate (66 mg, 0.46 mmol) in MeCN (2 cm^3) was heated under reflux for 60 h. Removal of solvent and purification of the residue by flash chromatography (40% EtOAc–60% petroleum ether 40–60 °C) gave cycloadduct **10** (102 mg, 74%) as a colourless oil. (Found: M + H^+, 362.1237. $C_{18}H_{20}NO_7$ requires *M*, 362.1240); ν_{max} (film)/cm^{-1} 2956, 1781 and 1742; δ_H (270 MHz) 2.71 (1 H, dd, *J* 16.3, 2.2, 6β-H), 3.25 (1 H, dd, *J* 16.3, 5.1, 6α-H), 3.60 (1 H, t, *J* 7, 4-H), 3.65 (3 H, s, CO_2*Me*), 3.71 (3 H, s, CO_2*Me*), 4.04 (1 H, dd, *J* 7.5, 7, 3-H), 4.12 (1 H, m, 5-H), 4.92 (1 H, d, *J* 7.5, 2-H), 5.18 (1 H, d, *J* 12.4, ArCH_2), 5.23 (1 H, d, *J* 12.4, ArCH_2), 7.36 (5 H, br s, Ar); *m*/*z* (C.I.) 362 (M + H^+, 2%).

NOE data for **10**: Irradiation of *H(2)* showed no enhancement of *H(3)*. Irradiation of *H(3)* showed enhancement of *H(4)* and irradiation of *H(4)* showed enhancement of both *H(3)* and *H(5)*. Irradiation of H(5) showed enhancements of both *H(6α)* and *H(6β)* and *H(4)*.

(±) Benzyl (2*R**,3*R**,4*R**,5*S**)- (or 2*R**,3*S**,4*R**,5*S**)-3,4-bis(methoxycarbonyl)-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate 11

A solution of the oxazolidinone **4b** (100 mg, 0.38 mmol) and dimethyl fumarate (67 mg, 0.47 mmol) in MeCN (2 cm^3) was heated under reflux for 60 h. Removal of solvent and purification of the residue by flash chromatography (20–40% EtOAc–petroleum ether 40–60 °C) gave **11** (58 mg, 42%) as a colourless oil. (Found: M + H^+, 362.1231. $C_{18}H_{20}NO_7$ requires *M*, 362.1240); ν_{max}(film)/cm^{-1} 2956, 1780 and 1740 (br); δ_H (270 MHz) 2.97 (1 H, dd, *J* 16.1, 2.0, 6β-H), 3.22 (1 H, dd, *J* 9.2, 7.7, 4-H), 3.40 (1 H, dd, *J* 16.1, 4.8, 6α-H), 3.69 (3 H, s, CO_2*Me*), 3.73 (3 H, s, CO_2*Me*), 4.05 (1 H, dd, *J* 9.2, 7.3, 3-H), 4.06 (1 H, m, 5-H), 4.70 (1 H, d, *J* 7.3, 2-H), 5.14 (1 H, d, *J* 12.3, ArCH_2), 5.24 (1 H, d, *J* 12.3, ArCH_2), 7.35 (5 H, m, Ar); *m*/*z* (C.I.) 362 (M + H^+, 1%).

(±)-Methyl 4-(triphenylmethylthio)-2-oxoazetidin-1-ylacetate

To a solution of 4-(triphenylmethylthioazetidin-2-one **16**[22] (5.03 g, 14.6 mmol) in DMF (25 cm^3) was added methyl bromoacetate (1.5 cm^3, 15.8 mmol) and K_2CO_3 (4.39 g, 31.8 mmol). The mixture was stirred at room temperature for 17.5 h and then partitioned between Et_2O (150 cm^3) and water (100 cm^3). The aqueous solution was further extracted with Et_2O (50 cm^3) and the combined ethereal solutions washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to a yellow oil. Purification by flash chromatography (10–40% EtOAc–petroleum ether) yielded a pale yellow oil, which, upon crystallisation from petroleum ether, afforded the *title compound* (4.14 g, 68%) as a colourless crystalline solid, mp 120–122 °C (MeOH) (Found: C, 71.65; H, 5.63; N, 3.44. $C_{25}H_{23}NO_3S$ requires C, 71.92; H, 5.55; N, 3.35%); ν_{max} (CH_2Cl_2)/cm^{-1} 1768 and 1748; δ_H (270 MHz) 3.05 (1 H, dd, *J* 15.1, 2.2, 3β-H), 3.26 (1 H, d, *J* 18.3), 3.31 (1 H, dd, *J* 15.1, 5.0, 3α-H), 3.64 (3 H, s, OMe), 3.91 (1 H, d, *J* 18.3), 4.51 (1 H, dd, *J* 5.0, 2.2, 4-H) and 7.20–7.39 (15 H, m, Ar); δ_C (75.5 MHz) 40.5 (CH_2), 48.0 (CH_2), 52.0 (OMe), 57.4 (CH), 67.7 (C), 127.3 (CH), 128.3 (CH), 129.6 (CH), 144.1 (C_{ipso}), 165.7 (C=O) and 167.9 (C=O); *m*/*z* (C.I.) 275 (Ph_3CS^+, 1%), 243 (Ph_3C^+, 100) and 142 ($M^+ - SCPh_3$, 9).

(±)-Methyl 4-(*p*-nitrophenoxycarbonylthio)-2-oxoazetidin-1-ylacetate 17

To an ice-cold solution of methyl 4-(triphenylmethylthio)-2-oxoazetidin-1-ylacetate (0.90 g, 2.2 mmol) in MeOH (10 cm^3) and EtOAc (10 cm^3) was added pyridine (0.3 cm^3) followed by a solution of $AgNO_3$ in methanol (0.12 mol dm^{-3}, 24 cm^3, 2.9 mmol), whereupon a colourless precipitate resulted. After stirring for a further 1 h at 0 °C, hydrogen sulfide was passed through the mixture at 0 °C until deposition of a dense black solid (Ag_2S) was complete, leaving a colourless solution. The solution was flushed with nitrogen, filtered, and concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 (40 cm^3) and aqueous HCl (1 mol dm^{-3}, 10 cm^3). The organic solution was washed with brine, dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless solid. ^{1}H NMR analysis showed a 6.5 : 1 mixture of the desired methyl 4-mercapto-2-oxoazetidin-1-ylacetate with starting material, which was used without further purification.

A solution of the crude thiol (prepared above) in THF (5 cm^3) was added to a solution of *p*-nitrophenyl chloroformate (0.43 g, 2.1 mmol), *N*,*N*-diisopropylethylamine (280 mg, 2.2 mmol) and catalytic DMAP in THF (5 cm^3) at 0 °C under an atmosphere of nitrogen. A colourless precipitate soon resulted and, after stirring for 40 min, the reaction mixture was partitioned between EtOAc (20 cm^3) and water (5 cm^3). The organic solution was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by flash chromatography (10–50% EtOAc–petroleum ether) afforded the thioacylated azetidinone **17** (338 mg, 83%) as a colourless solid, mp 119.5–120.5 °C (CCl_4) (Found: C, 45.52; H, 3.71; N, 8.55. $C_{13}H_{12}N_2O_7S$ requires C, 45.88; H, 3.55; N, 8.23%); ν_{max} (CH_2Cl_2)/cm^{-1} 1779, 1750 and 1727; δ_H (270 MHz) 3.15 (1 H, dd, *J* 15.2, 2.5, 3-H), 3.65 (1 H, dd, *J* 15.2, 5.5, 3-H), 3.75 (3 H, s, OMe), 3.80 (1 H, d, *J* 18.2), 4.28 (1 H, d, *J* 18.2), 5.57 (1 H, dd, *J* 5.5, 2.5, 4-H), 7.37 (2 H, part of AA′BB′, *J* 9.3, Ar) and 8.30 (2 H, part of AA′BB′, *J* 9.3, Ar); δ_C (75.5 MHz) 42.1 (CH_2), 44.2 (CH_2), 52.5 (CH_3), 56.5 (CH), 121.9 (CH), 125.4 (CH), 145.7 (C_{ipso}), 155.0 (C_{ipso}), 164.5 (C=O), 167.8 (C=O), 168.0 (C=O); *m*/*z* (E.I.) 281 ($M^+ - CO_2Me$, 15%).

(±)-Methyl (2*S**,5*R**)-3,7-dioxo-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylate 18

To a solution of LiHMDS (1.0 mol dm^{-3} in THF; 6.0 cm^3, 6.0 mmol) at −78 °C under a nitrogen atmosphere was added a solution of the 4-thioacylated azetidinone **17** (1.00 g, 2.9 mmol) in THF (10 cm^3). After stirring at −78 °C for 75 min, further LiHMDS solution (1.0 mol dm^{-3} in THF, 1 cm^3) was added and stirring continued for 15 min. The reaction mixture was diluted with EtOAc (30 cm^3) and quenched with aqueous HCl (1 mol dm^{-3}, 10 cm^3). The aqueous solution was further extracted with EtOAc (10 cm^3) and the combined organic solutions washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (50% EtOAc–50% petroleum ether) gave thiazolidinone (**18**) (270 mg, 46%) as a colourless oil (Found: M + H^+, 202.0174. $C_7H_8NO_4S$ requires *M*, 202.0174); ν_{max} (CH_2Cl_2)/cm^{-1} 1797, 1756 and 1726; δ_H (270 MHz) 3.43 (1 H, dd, *J* 16.4, 1.7, 6β-H), 3.84 (3 H, s, OMe), 3.94 (1 H, dd,

J 16.4, 4.2, 6α-H), 5.08 (1 H, s, 2-H) and 5.59 (1 H, dd, *J* 4.2, 1.7, 5-H); δ_C (75.5 MHz) 49.4 (CH_2), 53.5 (OCH_3), 60.6 (CH), 66.4 (CH), 164.1 (C=O), 168.6 (C=O) and 198.8 (C=O); *m*/*z* (C.I.) 202 ($M + H^+$, 1%).

4-Nitrobenzyl (2*S**,5*R**)-3,7-dioxo-2-methyl-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate 19

To a stirred solution of oxazolidinone **4a** (606 mg, 1.98 mmol) in THF (20 cm^3) at −78 °C under N_2 was added dropwise over 15 min a solution of NaHMDS (1.0 mol dm^{-3} in THF; 2.0 cm^3, 2.0 mmol). After stirring at −78 °C for 10 min, iodomethane (0.65 cm^3, 1.5 g, 10.4 mmol, 5 eq.) was added. Stirring was continued and the mixture was allowed to slowly warm to room temperature. After 3 h, AcOH (0.1 mol dm^{-3} in THF, 10 cm^3) was added and the solvent removed *in vacuo*. The residue was treated with CH_2Cl_2 (10 cm^3) and the resulting slurry was purified rapidly by filtration through a short column of silica (eluting with CH_2Cl_2) to give the α-methylated oxazolidinone **19** (185 mg, 29%) as a pale yellow oil as a 2 : 1 mixture of diastereoisomers (Found: $M + H^+$, 321.0737. $C_{14}H_{13}N_2O_7$ requires *M*, 321.0723); ν_{max}/cm^{-1} 1795 and 1760; δ_H (270 MHz, d_3-MeCN) 1.60 (3 H, s, Me, major isomer), 1.86 (3 H, s, Me, minor isomer), 3.32 (1 H, dd, *J* 17.5, 1, H(6), major isomer), 3.35 (1 H, dd, *J* 17.5, 3, H(6), minor isomer), 3.57 (1 H, dd, *J* 17.5, 3, H(6), major isomer), 5.21 (1 H, d, *J* 13.2, CH_2Ar, major isomer), 5.32 (2 H, s CH_2Ar, minor isomer), 5.42 (1 H, d, *J* 13.2, CH_2Ar, major isomer), 5.75 (1 H, dd, *J* 3.0, 1.0, H(5) minor isomer), 5.79 (1 H, dd, *J* 3.0, 1.0, H(5) major isomer), 7.60–7.54 (2 H, m, ArH *both isomers*) and 8.25–8.20 (2 H, m, ArH *both isomers*); δ_C (75.5 MHz) 16.6 (CH_3 minor), 18.9 (CH_3 major), 47.2 (C(6) major), 47.7 (C(6) minor), 66.9 (CH_2Ar minor), 67.1 (CH_2Ar major), 82.5 (C(5) major), 83.4 (C(5) minor), 123.9 (CH major), 124.1 (CH minor), 128.4 (CH minor), 128.7 (CH major), 141.3 (C_{ipso} major), 148.0 (C_{ipso} minor), 164.1 (CO major), 165.4 (CO minor), 169.9 (CO minor), 170.1 (CO major), 171.7 (CO minor), 172.3 (CO major); *m*/*z* (E.I.+) 321 ($[M + H]^+$, 2.5%), 292 (30), 248 (35), 140 (80), 136 ($[O_2NC_6H_4CH_2]^+$, 100).

4-Nitrobenzyl 2-methyl-9-phenyl-4,8,10-trioxo-3,9-diazatricyclo-[5.3.0.0^{3,6}]decane-2-carboxylate 20

To a solution of α-methylated oxazolidinone **19** (31 mg, 0.10 mmol) in degassed MeCN (2 cm^3) under N_2 was added *N*-phenylmaleimide (19 mg, 0.11 mmol, 1.1 eq.). The mixture was heated at 100 °C in a sealed tube for 15 h, before concentrating directly onto silica gel. Purification by flash column chromatography (98 : 2 CH_2Cl_2–Et_2O) gave cycloadduct **20** (34 mg, 78%) as a colourless oil and as a single diastereoisomer (Found: $M + H^+$, 450.1307. $C_{23}H_{20}N_3O_7$ requires *M*, 450.1301); ν_{max}/cm^{-1} 1770 and 1720; δ_H (270 MHz) 1.99 (3 H, s, Me), 3.12 (1 H, dd, *J* 2.3 and 16.5, H(5)), 3.36 (1 H, dd, *J* 5.0, 16.5, H(5)), 3.76 (1 H, t, *J* 8.3, C(7)), 4.11 (1 H, d, *J* 8.3, H(11)), 4.22 (1 H, ddd, *J* 2.3, 5.0, 8.3, H(6)), 5.32 (2 H, s, CH_2Ar), 7.22–7.18 (2 H, m, ArH), 7.57–7.44 (5 H, m, ArH), 8.29–8.25 (2 H, m, ArH); δ_C (75.5 MHz) 16.6 (Me), 40.9 (C(6)), 47.9, 54.1, 58.0, 66.5, 71.0 (C(2)), 124.1, 126.4, 128.5, 129.4, 129.45, 131.0, 141.75, 169.8, 170.4, 172.6, 174.0; *m*/*z* (C.I.+) 450 ($[M + H]^+$, 1%), 408 (7), 138 (100).

Acknowledgements

We thank AstraZeneca, EPSRC and the Royal Society for financial support, and SB Pharmaceuticals for a generous and continuing supply of clavulanic acid.

References

1 (*a*) R. B. Morin and M. Gorman, in *Chemistry and Biology of β-Lactam Antibiotics*, Academic Press, New York, 1982; (*b*) W. Dürckheimer, J. Blumbach, R. Lattrell and K. H. Scheunemann, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 180; (*c*) G. I. Georg, *The Organic Chemistry of β-Lactams*, VCH, New York, 1992; (*d*) G. I. Georg, in *Recent Advances in the Chemistry and Biology of β-Lactam and β-Lactam Antibiotics*, *Bioorg. Med. Chem. Lett.* (Symposia-in-Print no. 8), 1993, **3**, 2159–2313; (*e*) M. Gomez-Gallego, M. J. Macheno and M. A. Sierra, *Tetrahedron*, 2000, **56**, 5743; (*f*) M. J. Miller, in *Recent Aspects of the Chemistry of β-Lactams—II*, *Tetrahedron* (Symposia-in-Print no. 80), 2000, **56**, 5553–5742.

2 (*a*) S. R. Martel, R. Wisedale, T. Gallagher, L. D. Hall, M. F. Mahon, R. H. Bradbury and N. J. Hales, *J. Am. Chem. Soc.*, 1997, **119**, 2309; (*b*) D. Planchenault, R. Wisedale, T. Gallagher and N. J. Hales, *J. Org. Chem.*, 1997, **62**, 3438; (*c*) M. D. Andrews, G. A. Brown, J. P. H. Charmant, T. M. Peakman, A. Rebello, K. E. Walsh, T. Gallagher and N. J. Hales, *Chem. Commun.*, 1999, 249; (*d*) T. Gallagher, *J. Heterocycl. Chem.*, 1999, **36**, 1365; (*e*) G. A. Brown, K. M. Anderson, M. Murray, T. Gallagher and N. J. Hales, *Tetrahedron*, 2000, **56**, 5579; (*f*) G. A. Brown, Ph.D. Thesis, University of Bristol, 2000.

3 (*a*) J. W. Lown, in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley, New York, 1984; (*b*) R. Grigg, *Chem. Soc. Rev.*, 1987, **16**, 89; (*c*) W. H. Pearson, *Studies in Natural Products Chemisty*, ed. Atta-ur-Rahman, Elsevier, Amsterdam, 1988; (*d*) O. Tsuge and S. Kanemasa, *Adv. Heterocycl. Chem.*, 1989, **45**, 239.

4 (*a*) G. P. Rizzi, *J. Org. Chem.*, 1970, **35**, 2069; (*b*) M. Joucla and J. Mortier, *Tetrahedron Lett.*, 1987, **28**, 2973; (*c*) H. Ardill, R. Grigg, V. Sridharan, S. Surendrakumar, S. Thianpatanagul and S. Kanajun, *J. Chem. Soc., Chem. Commun.*, 1986, 602.

5 (*a*) R. Huisgen, W. Scheer, G. Szcimies and H. Huber, *Tetrahedron Lett.*, 1966, 397; (*b*) R. Huisgen, R. Grashey and E. Steingruber, *Tetrahedron Lett.*, 1963, 1441; (*c*) Z. Bende, I. Bitter, L. Toke, L. Weber, G. Toth and F. Janke, *Liebigs Ann. Chem.*, 1982, 2146; (*d*) D. M. B. Hickey, C. J. Moody and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1119.

6 A. Padwa and W. Dent, *J. Org. Chem.*, 1987, **52**, 235.

7 A. Eschenmoser, *Chem. Soc. Rev.*, 1976, **5**, 377.

8 K. Burger, A. Meffert and S. Bauer, *J. Fluorine Chem.*, 1977, **10**, 57.

9 (*a*) O. Tsuge, S. Kanemasa, M. Ohe, K. Yorozu, S. Takenaka and K. Ueno, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 4067; (*b*) O. Tsuge, S. Kanemasa, M. Ohe and S. Takenaka, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 4079; (*c*) S. Kanemasa, K. Sakamoto and O. Tsuge, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 1960.

10 (*a*) R. Grigg, S. Surendrakumar, S. Thianpatanagul and D. Vipond, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2693; (*b*) R. Grigg, J. Idle, P. McMeekin, S. Surendrakumar and D. Vipond, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2703.

11 G. A. Brown, S. R. Martel, R. Wisedale, J. P. A. Charmant, T. Gallagher, N. J. Hales and C. W. G. Fishwick, *J. Chem. Soc., Perkin Trans. 1*, 2001, following paper (DOI: 10.1039/b010050l).

12 S. R. Martel, D. Planchenault, R. Wisedale, T. Gallagher and N. J. Hales, *Chem. Commun.*, 1997, 1897.

13 (*a*) T. T. Howarth and I. Stirling, Ger. Offen. 2,655,675, (*Chem. Abstr.*, 1977, **87**, 102313); (*b*) A. G. Brown, D. F. Corbett, J. Goodacre, J. B. Harbridge, T. T. Howarth, R. J. Ponsford, I. Stirling and T. J. King, *J. Chem. Soc., Perkin Trans. 1*, 1984, 635.

14 E. J. J. Grabowski and P. J. Reider, European Patent 78 026 (*Chem. Abstr.*, 1983, **99**, 122171).

15 P. C. Cherry, C. E. Newall and N. S. Watson, *J. Chem. Soc., Chem. Commun.*, 1978, 469.

16 H. E. Avery, *Basic Reaction Kinetics and Mechanisms*, Macmillan, London, 1974.

17 (*a*) R. Huisgen, R. Grashey, H. Gotthardt and R. Schmidt, *Angew. Chem., Int. Ed. Engl.*, 1962, **1**, 48; (*b*) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 633; (*c*) R. Huisgen, H. Hauck, R. Grashey and H. Seidl, *Chem. Ber.*, 1968, **101**, 2568.

18 (*a*) A. G. Brown, D. F. Corbett and T. T. Howarth, *J. Chem. Soc., Chem. Commun.*, 1977, 359; (*b*) S. M. Schmitt, D. B. R. Johnston and B. G. Christensen, *J. Org. Chem.*, 1980, **45**, 1135; (*c*) T. C. Smale and R. Southgate, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2235; (*d*) S. Wolfe and R. Z. Sterzycki, *Can. J. Chem.*, 1987, **65**, 26; (*e*) A. G. M. Barrett and S. Sakadarat, *J. Org. Chem.*, 1990, **55**, 5110.

19 X. Zhang, F. G. Bordwell, M. Van Der Puy and H. E. Fried, *J. Org. Chem.*, 1993, **58**, 3060.

20 A. Klant and G. Schuurman, *J. Chem. Soc., Perkin Trans. 2*, 1993, 799.

21 W. J. Leanza, F. DiNinno, D. A. Muthard, R. R. Wilkening, K. J. Wildonger, R. W. Ratcliffe and B. G. Christensen, *Tetrahedron*, 1983, **39**, 2505.

22 R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, 1953, **75**, 2439.