# The azomethine ylide strategy for $\beta$ -lactam synthesis. An evaluation of alternative pathways for azomethine ylide generation

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Following the generation of azomethine ylide 3 from the  $\beta$ -lactam-based oxazolidinone 1, a series of alternative entries to this and related 1,3-dipoles have been explored. The first approach is based on the use of monocyclic azetidinones 6-12 and 14 carrying a leaving group at C(4) and an activated (acidic) proton adjacent to the ring nitrogen, structural moieties which are both associated with 1. These monocyclic substrates show no tendency towards azomethine ylide formation, which points towards the ring strain present in 1 as an important prerequisite for azomethine ylide formation. The reactivity associated with the racemic Glaxo betaine 17, the structure of which has now been confirmed by X-ray crystallography, appears to involve an azomethine ylide 19, which is very similar to 3. However, attempts to trap 19 using an intermolecular cycloaddition failed; the intramolecular process involving an enolate as a trapping agent to give oxapenem 18 is more effective. Two novel thia-substituted bicyclic oxazolidinones 22 and 23, as well as the unsubstituted variant 33, have been prepared. In the case of 22 and 23, products derived from an alternative mode of iminium ion formation are observed. This pathway is a consequence of C-S bond cleavage, and this reactivity profile has been evaluated computationally. The data suggest that relief of strain within the four-membered ring—as opposed to 1 in which five-membered ring cleavage leads to an iminium ion—provides a driving force for C-S bond cleavage. As a result, the ability of 22 and 23 to give a synthetically useful azomethine ylide is compromised by the siting of an alternative leaving group adjacent to the azetidinone nitrogen. The unsubstituted bicyclic oxazolidinone 33 is thermally unstable, and no cycloadducts have been characterized from this system. Again, computational studies suggest that both direct and stepwise decarboxylation of 33 are energetically demanding processes.

#### Introduction

In the preceding paper,<sup>1</sup> we described the application of the  $\beta$ -lactam based oxazolidinone **1** as a source of azomethine ylide reactivity providing an efficient and flexible entry to bicyclic  $\beta$ -lactams, including carbapenams, carbapenems, penams and penems.<sup>2</sup> The generation of azomethine ylides by decarboxylation of oxazolidinones is well established for simpler systems,<sup>3</sup> and the formation of cycloadducts **4** can be accounted for in a formal sense in terms of the "parent" azomethine ylide **2**, the product of a *concerted* decarboxylation of **1** (*path a*, Scheme 1). However, evidence has now been presented in support of an alternative and *stepwise* fragmentation of **1** (*path b*, Scheme 1) leading to the carboxylated azomethine

 $\bar{\bar{C}}O_2R$ 

ylide **3** as the key dipolar species.<sup>1,4</sup> As a result, and unlike the simpler and more established oxazolidinone fragmentations, the cycloaddition event in the  $\beta$ -lactam series takes place *before* loss of carbon dioxide. Provided that *path b* is available (see preceding paper which describes a 3,3disubstituted oxazolidinone which does not have access to this path), then available evidence also disfavours the participation of an alternative stepwise process as a means of generating azomethine ylide **2**: fragmentation to form an iminium ion, followed by decarboxylation (*path c*, Scheme 1). The important mechanistic features of the azomethine ylide strategy elucidated to date, which are based on the evidence presented in the preceding paper<sup>1</sup> and elsewhere,<sup>4</sup> are summarized in Scheme 1.

path c

3 CO2R

-CO2



Scheme 1

Τ5

ĊO₂R

path b

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Scheme 2 Reagents and conditions: i, R<sup>1</sup>SNa, EtOH, H<sub>2</sub>O (R<sup>1</sup> = Ph 88%; R<sup>1</sup> = Me 71%); ii, BrCH<sub>2</sub>CO<sub>2</sub>Me, NaH, DMF (R<sup>1</sup> = Ph 87%; R<sup>1</sup> = Me 71%); iii, heat, NPM, see text; iv, NaIO<sub>4</sub>, MeOH, H<sub>2</sub>O (78%); v, 2-pySNa, EtOH, H<sub>2</sub>O (72%), then BrCH<sub>2</sub>CO<sub>2</sub>Me, LHMDS (67%); vi, NaIO<sub>4</sub>, MeOH, H<sub>2</sub>O (79%); vii, BrCH<sub>2</sub>COO(CH<sub>2</sub>)<sub>2</sub>CH=CH<sub>2</sub>, NaH, DMF (65%); viii, NaIO<sub>4</sub>, MeOH, H<sub>2</sub>O (60%); ix, Ac<sub>2</sub>O, NPM, reflux (done in both the presence and absence of EtN*i*-Pr<sub>2</sub>); x, BrCH(CO<sub>2</sub>Me)<sub>2</sub>, NaH, THF, -50 °C (33%).

There are a number of issues associated with the reactivity of the different azomethine ylides 2 vs. 3. The stabilization of the 1,3-dipole intermediate inferred from the presence of the additional carboxy function present in 3 may place limitations on the scope of the cycloaddition process. Indeed, 3 reacts poorly with electron-rich dipolarophiles and use of even moderately hindered substrates can present problems. Access to a less stabilized (and more reactive) 1,3-dipole, such as the "parent"  $\beta$ -lactam-based azomethine ylide 2 could therefore enhance the potential of the basic azomethine ylide strategy, and the generation of 2 has remained a goal of this programme.

In this paper we outline a number of approaches to both the azomethine ylide **2** and a series of structurally related 1,3-dipoles, which were designed to explore and extend the range of  $\beta$ -lactam cycloadducts that can be made available using the basic cycloaddition strategy. All of these approaches have led to reaction pathways other than 1,3-dipole formation, and results obtained serve to underscore those key features associated with the success of the oxazolidinone-mediated pathway. In particular, with respect to dipole generation, the scope of the cycloaddition strategy has now been more fully defined and the observations presented below reinforce the notion that the ring strain and the 1,3-dicarbonyl (malonyl) component associated with **1** play a critical role in the expression of azomethine ylide reactivity, as in 1,3-dipole **3**.

## Studies directed towards the generation of the "parent" azomethine ylide 2

Our initial approach to generating the parent azomethine ylide **2** was based on a similar process to that successfully exploited

for the "carboxylated" azomethine ylide **3**. This involved positioning a suitable leaving group at C(4) of an *N*-alkylated azetidinone, which carries an acidic C–H adjacent to nitrogen. Substrates **6–12** and **14**, all of which incorporate this combination of structural features, were prepared starting from the commercially available 4-acetoxyazetidin-2-one **5**, and the routes employed, some aspects of which are based on earlier literature,<sup>5–8</sup> are outlined in Scheme 2.

These substrates were then screened for their ability to generate a viable azomethine ylide under thermal conditions, in a variety of solvents (MeCN, PhMe, 1,2-dichlorobenzene) and using N-phenylmaleimide (NPM) as a trap. The 4-thiosubstituted azetidinones 6 and 7 were thermally stable (up to approx. 180 °C), and attempts to induce iminium ion formation (using AgBF<sub>4</sub> as a thiophile) resulted only in decomposition. Enhancing the leaving group ability of sulfur via sulfoxide 8 was also unsuccessful; 8 was stable in both MeCN (at reflux) and PhMe (at reflux). Use of ZnI<sub>2</sub> (in MeCN at 50 °C) as a Lewis acid to promote ionization again led to decomposition of 8. The azetidinyl 2-pyridyl sulfide 9, which incorporates an internal base and the corresponding sulfoxide 10 (obtained as a 1:1.5 mixture of diastereoisomers) were prepared using similar methods. Again, these substrates proved to be remarkably stable and no evidence was obtained under a variety of thermal conditions for azomethine ylide formation.

Substrates carrying an intramolecular alkenyl trap were examined, but again, both sulfide **11** and sulfoxide **12** were thermally stable. When **12** was heated in acetic anhydride (with a view to promoting ionization *via O*-acylation of the sulfoxide entity), only the corresponding acetate **13** was isolated (as judged by <sup>1</sup>H NMR). In summary, all efforts to drive the formation of an azomethine ylide by initial *N*-acyl iminium ion



Scheme 3 Reagents and conditions: i, Et<sub>3</sub>N, EtOAc (62%); ii, heat, EtOAc (78%); iii, NEt<sub>3</sub>, EtOAc (87%).



Fig. 1 Solid state structure of 17. Hydrogen atoms and water molecules have been omitted for clarity.

formation from a simple but only monocyclic azetidinone precursor have been unsuccessful.<sup>†</sup>

Enhancing the acidity of the proton adjacent to nitrogen provided an alternative, but ultimately equally fruitless line of investigation. The *N*-malonyl derivative **14** was prepared and subjected to thermolysis (xylene at reflux, with and without a catalytic quantity of trifluoroacetic acid) in the presence of *N*-phenylmaleimide (NPM); no cycloadduct formation was observed. Fragmentation of this substrate would have led to a 1,3-dipole **15** similar to **3**, but **14** proved to be stable and was recovered unchanged even after prolonged heating (xylene at reflux for 3 hours). These same conditions would have resulted in complete consumption of the bicyclic variant **1**, and this again raises the issue of the viability of a monocyclic *vs.* a (more strained) bicyclic precursor to a  $\beta$ -lactam-based azomethine ylide.

#### Generation and reactivity of betaine 17

In the preceding paper, we discussed the ease with which the bicyclic oxazolidinone 1 undergoes thermal racemization, but not decarboxylation, when heated in the absence of a reactive dipolarophile. While this was a critical observation in terms of our mechanistic studies, it is not without precedent. Some years ago, Cherry *et al.*<sup>9</sup> reported that treatment of enantiomerically pure deoxyclavulanic acid 16 with triethylamine resulted in C=C migration to give the *racemic* oxapenem 18. Further, these workers were able to isolate the betaine intermediate 17 and showed that this species was converted to 18 on heating.

 Table 1
 Selected bond lengths (Å) and angles (°) for betaine 17

N(1)–C(4)	1.369(3)
N(1)-C(5)	1.441(2)
N(1)-C(2)	1.474(2)
C(2)–N(18)	1.527(3)
C(2)–C(3)	1.544(3)
C(3)–C(4)	1.518(3)
C(4)–O(4)	1.213(2)
C(5)–C(6)	1.393(3)
C(5)–C(9)	1.441(3)
C(4) - N(1) - C(5)	129.7(2)
C(4) - N(1) - C(2)	93.8(2)
C(5)-N(1)-C(2)	132.0(2)
N(1)-C(2)-N(18)	114.5(2)
N(1)-C(2)-C(3)	87.89(15)
N(18) - C(2) - C(3)	118.4(2)
C(4)-C(3)-C(2)	85.40(15)
N(1)-C(4)-C(3)	92.9(2)
C(6)-C(5)-C(9)	124.8(2)
C(6)-C(5)-N(1)	117.1(2)
C(9)-C(5)-N(1)	118.1(2)
O(6)–C(6)–C(5)	121.6(2)

In addition, exposure of 18 to triethylamine resulted in re-formation of betaine 17 (Scheme 3). The most likely intermediate involved in the formation of betaine 17 (and its subsequent conversion to 18) is the stablized azomethine ylide 19, though participation of a *C*-protonated variant of 19 on the pathway between 16 and 17 cannot be excluded. Azomethine ylide 19 bears a striking similarity to azomethine ylide 3 and, given the close relationship between the two processes involved  $(1\rightarrow 3\rightarrow 4 \text{ and } 16\rightarrow 18)$ , it was felt that this process merited further investigation as a potential source of azomethine ylide reactivity.

We have repeated the Glaxo work and isolated betaine intermediate 17. The structure of 17 (recrystallized from water) has now been confirmed by X-ray crystallographic analysis (Fig. 1 and Table 1).‡ Further, betaine 17 appears to be racemic, based on the crystallographic analysis and a lack of an optical rotation.§

Our aim was to attempt to intercept **19** using a reactive dipolarophile (NPM), but under a range of thermolysis conditions, betaine **17** gave *only* the conjugated oxapenem **18**. It is interesting to compare the reactivity of **1** to that of **17**. The

<sup>&</sup>lt;sup>†</sup> The selenide and selenoxide corresponding to **6** and **8** respectively were also prepared by analogous routes. The selenide was thermally stable but the selenoxide proved to be too unstable to merit further study. The sulfoxide-based substrates [**8**, **10**, **12**] were prepared with a view to promoting a concerted rather than stepwise fragmentation analogous to the well-known sulfoxide elimination process used in alkene synthesis. The possibility of a base assisting an alternative concerted pathway prompted incorporation of the pyridyl unit into **9** and **10**.

<sup>&</sup>lt;sup>‡</sup> Single crystals of C<sub>21</sub>H<sub>29</sub>N<sub>3</sub>O<sub>6</sub>·3H<sub>2</sub>O (17·3H<sub>2</sub>O) were obtained from water, coated in vacuum grease and mounted on a glass fibre. Crystal data. C<sub>21</sub>H<sub>35</sub>N<sub>3</sub>O<sub>9</sub>, M = 473.5, triclinic, a = 8.014(4), b = 8.438(4), c = 18.463(10) Å, a = 89.99(2),  $\beta = 82.22(4)$ ,  $\gamma = 78.06(4)^\circ$ , U = 1209.8(10) Å<sup>3</sup>, T = 173 K, space group  $P\overline{1}$  (no. 2), Z = 2,  $\mu$ (Mo-K $\alpha$ ) = 0.102 mm<sup>-1</sup>, 10221 reflections measured, 4224 unique ( $R_{int} = 4.1\%$ ). Final residuals: wR2 = 10.1% (all data), R1 = 4.3% (2719 observed data). Selected bond lengths and angles are shown in Table 1. CCDC 155747. See http://www.rsc.org/suppdata/p1/b0/b0100501/ for crystallographic files in .cif format.

<sup>§</sup> The Glaxo group<sup>9</sup> verified the racemic nature of 18 by correlation to an enantiomerically pure derivative. Oxapenem 18 is also opened by other nucleophiles (*e.g.* thiols), chemistry which is especially significant for providing an early entry to penems.

presence of a good (carboxylate) leaving group in 1 may provide a synthetically useful concentration of the reactive azomethine ylide *i.e.* 3. However, in the case of 17, the internal nucleophile (the oxygen of the ketone enolate) is an efficient trap for the iminium component of 19, and an intermolecular cycloaddition pathway cannot effectively compete.

#### Alternative oxazolidinone precursors

A series of other  $\beta$ -lactam based oxazolidinones **22**, **23** and **33** have also been prepared and evaluated as alternative sources of azomethine ylide reactivity. In the first instance the motivation to attempt to extend the scope of dipole precursors arose from problems that we had encountered in the application of the azomethine ylide strategy (based on **1**) for the synthesis of so-called  $\Delta^2$ -carbapenems. Thermolysis of oxazolidinone **1** in the presence of an alkyne does provide a versatile synthesis of the carbapenem isomers **20** (Scheme 4). However, the isomerization of **20** (a  $\Delta^1$ -carbapenem—classical penam numbering) to the biologically more important isomer **21** (a  $\Delta^2$ -carbapenem) is neither an efficient nor general process,<sup>10</sup> and a practical solution to this problem demanded an alternative approach.

Use of the sulfide or sulfoxide-based oxazolidinones 22 and 23 respectively in principle offered access to a number of interesting 1,3-dipoles. Decarboxylation of 22 or 23 would provide novel, functionalized  $\beta$ -lactam-based azomethine ylides (*e.g.* 1,3-dipole 35, *see* Scheme 6 below). Alternatively, a stepwise fragmentation and proton shift would offer access to azomethine ylide 24, which was anticipated to react with an alkene to give cycloadduct 25. This cycloadduct could then undergo thiol or sulfoxide elimination, rather than decarboxylation, to provide the desired  $\Delta^2$ -carbapenem directly. In this way we aimed to retain the carboxy function present in the starting oxazolidinones 22 or 23 as the carboxylic acid of the final target (Scheme 4).

The sulfide- and sulfoxide-containing oxazolidinones 22 and 23 respectively were both prepared starting from clavulanic acid 26 (Scheme 5). Using the procedures described by Hunt,<sup>11</sup> clavulanic acid was converted to diene 27. Addition of PhSH to 27 gave a 2 : 1 mixture of regioisomeric adducts 28 (40% yield as an inseparable 1 : 5 mixture of *E* and *Z* isomers) and 29 (19% yield). Chromatographic separation followed by controlled ozonolysis of 28 gave the sulfide-containing oxazolidinone 22 as an oil. Oxidation (MCPBA) of 28 followed again by controlled ozonolysis provided the sulfoxide derivative 23 as a mixture of diastereoisomers.¶

Thermolysis of 22 in the presence of NPM resulted in the formation of the thiol adduct **31** in 43% yield. A related fragmentation process was observed when 23 was heated in the presence of DMAD, and in this case the sulfenic acid adduct 32 was isolated in 35% yield. In each case, other sulfur-containing by-products (e.g. PhSSPh, PhSSO<sub>2</sub>Ph) were also isolated and characterized. In neither case could products retaining the  $\beta$ -lactam component be characterized and the fate of this unit remains unclear. Products 31 and 32 can be accounted for by loss of PhS- or PhSO- from the oxazolidinone precursors 22 and 23 respectively and subsequent capture of these nucleophiles by the electrophilic alkene/alkyne present. While no direct evidence has been obtained for the intermediacy of the *N*-acyl iminium component **30** (see also below, structure **36**, Scheme 6), it would appear that this pathway is preferred to formation of the alternative (and desired) N-acyl iminium species 24 (cf. Scheme 4) resulting from C–O bond scission. Further, a possible reason for the preference of 22 (and by



Scheme 4 Reagents and conditions: i,  $R_1C\equiv CH$ ; ii, DBU,  $CH_2CI_2$  (under these thermodynamic conditions, *ca.* 1 : 1 ratio of 20 to 21 is observed when  $R^1 = SPh$ ).

extrapolation 23) to undergo C–S cleavage to give 30 rather than C–O cleavage (which would lead to 24) has been identified, which is discussed in more detail below.

The isomeric thiol adduct **29** provided access to yet another oxazolidinone substrate. Careful oxidative cleavage of **29** gave the unsubstituted  $\beta$ -lactam-based oxazolidinone **33** (Scheme 5), a compound that has previously been prepared by a very similar procedure.<sup>12</sup> However, oxazolidinone **33** was very sensitive and could not be rigorously purified from the other ozone-derived product. We have examined the ability of **33** to generate an azomethine ylide, but without success: thermolysis of crude **33** (MeCN, 81 °C) in the presence of an excess NPM failed to generate an adduct and no characterizable products were isolated. The reactivity of **33** has also been examined computationally and compared to carboxylated variants (see Scheme 7).

#### **Computational studies**

The fragmentation of sulfide **22** and the fate of "parent" oxazolidinone **33** have also both been explored computationally. By analogy to the theoretical approach described in the preceding paper,<sup>1</sup> semi-empirical calculations were used to compare the hypothetical stepwise and concerted decarboxylation of sulfide **22** to yield an azomethine ylide **35** *vs.* a fragmentation pathway involving loss of PhS<sup>-</sup> (Scheme 6 and Tables 2 and 3).

These data confirm that fragmentation of oxazolidinone 22 via loss of phenylthiolate to yield cation 36 (activation energy  $\Delta E_7 = 26.13$  kcal mol<sup>-1</sup>) is considerably more favourable than decarboxylation to yield azomethine ylide 35 by either the stepwise pathway (involving transition states TS1 and TS2 with activation energies  $\Delta E_1 = 38.73$  and  $\Delta E_3 = 15.31$  kcal mol<sup>-1</sup> respectively) or a concerted pathway (involving transition state **TS3** with an activation energy  $\Delta E_5 = 48.27$  kcal mol<sup>-1</sup>) pathways. As with other calculations involving concerted decarboxylation to yield  $\beta$ -lactam based azomethine ylides (see preceding paper), the transition structure TS3 could not be obtained using calculations which simulate the presence of solvent, and all energies are derived from single-point estimates on a transition structure obtained in the gas-phase. A particularly interesting aspect of these studies relates to the mechanism of elimination of thiolate from oxazolidinone 22. Repeated attempts to identify the transition state for the cleavage of the C-S bond consistently produced structure TS4 in which the endocyclic N-C bond present within the fourmembered ring is partially cleaved. This bond is essentially antiperiplanar to the breaking C-S bond (assuming the C(2)

<sup>¶</sup> Though reported as such in the literature,<sup>11</sup> the stereochemistry at C(2) of **22** has not been rigorously determined. Placing the SPh residue on the *exo* face does, however, represent the thermodynamically more reasonable configuration. Nevertheless, and to avoid any confusion, it should be made clear that we have assumed the configurations shown in Scheme 5 and in the computational study associated with Scheme 6.



Scheme 5 *Reagents and conditions*: i, *N*,*N*-dimethylformamide dimethyl acetal; ii, PhSH, AIBN, heat; iii, O<sub>3</sub>, EtOAc (99% for 22; 97% for 23); iv, MCPBA, CH<sub>2</sub>Cl<sub>2</sub> (78%); v, NPM, MeCN, reflux, 120 h; vi, DMAD, MeCN, reflux, 48 h.



stereochemistry shown) such that this transition structure results from an E2 type elimination pathway to yield an acyl cation 36 (Scheme 6). The relative ease of this reaction compared to the hypothetical decarboxylative entry to azomethine ylide 35 may be due, in part, to the relief of ring strain associated with the formation of cation 36 via TS4. Clearly also, cation 36 is, in a broad sense, structurally equivalent to cation 30 (see Scheme 5).

Similar calculations involving the hypothetical decarboxylation of parent oxazolidinone 33 also tend to support the limited experimental observations concerning the behaviour of this substrate (Scheme 7 and Tables 4 and 5). The stepwise decarboxylation of oxazolidinone **33** via (i) cleavage of the ring C–O bond (through **TS5**) to yield zwitterion **37** followed by (ii) decarboxylation (through **TS6**) to yield parent  $\beta$ -lactam-based azomethine ylide **38** is predicted to require 27.49 kcal mol<sup>-1</sup> ( $\Delta E_9$ ) and 33.99 kcal mol<sup>-1</sup> ( $\Delta E_{11}$ ) respectively. Although the energy associated with the initial fragmentation ( $\Delta E_9$ ) is similar to that calculated for the corresponding transformation involving the ester-containing oxazolidinone **1** (R = Me), which

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Table 2Heats of formation and transition state imaginary frequenciesfor Scheme 6

Structure	$H_{\rm f}/{ m kcal}~{ m mol}^{-1a}$	$v_{\rm i}/{\rm cm}^{-1b}$
22	-71.82	_
34	-43.26	_
35	-49.18	_
36	-57.34	_
TS1	-33.09	-402.58
TS2	-27.95	-455.41
TS3	$(-23.55)^{c}$	$(-490.98)^{c}$
TS4	-45.69	-52.02

<sup>*a*</sup> Heats of formation obtained using PM3 Hamiltonian using the COSMO model to simulate a solvent field equivalent to that of acetonitrile. <sup>*b*</sup> All transition structures were characterized by having a single negative vibrational frequency. <sup>*c*</sup> Transition state unable to be located in acetonitrile and energy is a single-point estimate (COSMO)<sup>13</sup> on a gas-phase derived transition structure.

Table 3 Activation energies for Scheme 6

Energy	Value/kcal mol <sup>-1</sup>	Energy	Value/kcal mol <sup>-1</sup>
$ \frac{\Delta E_1}{\Delta E_2} \\ \Delta E_2 $	38.73 -10.17 15.31	$\Delta E_5$ $\Delta E_6$ $\Delta E_7$	$(48.27)^a$ -25.63 26.13
$\Delta E_4$	-21.23	$\Delta E_8$	11.65

<sup>*a*</sup> Transition state unable to be located in acetonitrile and energy is a single-point estimate (COSMO)<sup>13</sup> on a gas-phase derived transition structure.

requires 26.18 kcal mol<sup>-1</sup>, the energy barrier for the decarboxylation step (*via* **TS6**) is over twice that calculated (33.99 *vs*. 16.16 kcal mol<sup>-1</sup>) for the equivalent pathway involving **1** ( $\mathbf{R} = \mathbf{Me}$ ).<sup>1</sup> Similarly, the concerted decarboxylation of **33** (*via* **TS7**) is calculated to require nearly 10 kcal mol<sup>-1</sup> more energy than is calculated for **1** ( $\mathbf{R} = \mathbf{Me}$ ).

It would appear that for the simple, unsubstituted system 33, the stepwise decarboxylative generation of the corresponding azomethine ylide 38 is unfavourable due to the large barrier ( $\Delta E_{11}$ ) to loss of carbon dioxide. This is presumed to reflect the reduced ability of zwitterion 37 to stabilize the increasing electron density at the exocyclic methylene as the reaction enters into the transition state (TS6), when compared to the corresponding pathway starting with 1 (R = Me).

The need for caution regarding the calculated energies for the concerted decarboxylation pathway is underlined in the case of **TS7**. The single point estimate in a simulated solvent dielectric on the gas phase-derived structure yields an energy which is 0.22 kcal mol<sup>-1</sup> lower than the solution phase energy of the products (dipole **38** and CO<sub>2</sub>). However, comparing the gas phase energies for thiazolidinone **33** ( $E_{gas} =$ -63.90 kcal mol<sup>-1</sup>), **TS7** ( $E_{gas} = -8.65$  kcal mol<sup>-1</sup>) and **38** + CO<sub>2</sub> ( $E_{gas} = -28.79$  kcal mol<sup>-1</sup>) yields more reasonable relative energies.

To summarize, a combination of factors seem to predispose

structure.

the  $\beta$ -lactam based oxazolidinone 1 towards stepwise fragmentation to give the synthetically important azomethine ylide 3. Ring strain in the bicyclic framework plays an important role, and this is evident from the monocyclic azetidinones shown in Scheme 2 that do not give azomethine ylides despite the presence of similar structural components to those present in 1 *i.e.* a leaving group at C(4) and an acidic C–H bond adjacent to the ring nitrogen.

The Glaxo betaine 17 is interesting in this context because this species appears to undergo reversible ring closure *via* an azomethine ylide 19. However, we have not been able to capture this dipolar intermediate in a cycloaddition reaction, and it appears that the enolate oxygen associated with 19 is a highly efficient trap. In relation to the fragmentation of 1 to give 3, then the differences in reactivity seen with 17 (and by implication 19) may also involve differences in charge distribution a ketone enolate *vs*. a carboxy-based variant.

The sulfur-containing bicyclic oxazolidinones 22 and 23 again bear a close resemblance to 1, and were designed with a complementary synthetic role in mind. However in these cases, the preferred iminium species appears to be associated with C–S rather than C–O cleavage, although the fate of the  $\beta$ -lactam moiety remains unclear. In the case of 22, computational studies suggest that the ionization process involves participation and cleavage of the  $\beta$ -lactam ring, and this likely leads to even more relief of strain.

Table 4Heats of formation and transition state imaginary frequenciesfor Scheme 7

Structure	$H_{\rm f}$ /kcal mol <sup>-1 a</sup>	$v_{\rm i}/{\rm cm}^{-1b}$
33 37 38 TS5	-83.63 -66.10 -41.02 -56.14	
TS6 TS7	-32.11 (-41.24) <sup>c</sup>	-669.64 (-511.26) <sup>c</sup>

<sup>*a*</sup> Heats of formation obtained using PM3 Hamiltonian using the COSMO model to simulate a solvent field equivalent to that of acetonitrile. <sup>*b*</sup> All transition structures were characterized by having a single negative vibrational frequency. <sup>*c*</sup> Transition state unable to be located in acetonitrile and energy is a single-point estimate (COSMO)<sup>13</sup> on a gas-phase derived transition structure.

 Table 5
 Activation energies for Scheme 7

Energy	Value/kcal mol <sup>-1</sup>	Energy	Value/kcal mol <sup>-1</sup>
$\begin{array}{c} \Delta E_9 \\ \Delta E_{10} \\ \Delta E_{11} \end{array}$	27.49 -9.96 33.99	$\begin{array}{c} \Delta E_{12} \\ \Delta E_{13} \\ \Delta E_{14} \end{array}$	$-8.91 \\ (42.39)^{a} \\ (-0.22)^{a}$

<sup>*a*</sup> Transition state unable to be located in acetonitrile and energy is a single-point estimate (COSMO)<sup>13</sup> on a gas-phase derived transition

Fragmentation—either concerted or stepwise—of the simple, unsubstituted derivative **33** failed to yield a cycloadduct, apparently because this system lacks the electronic stablization that is associated with the carboxy function found in **3**. Calculations indicate that both of these pathways are energetically highly demanding, and we have been unable to isolate any 1,3-dipolar cycloadducts arising from **33**.

In conclusion, while the azomethine ylide strategy is of proven and general utility for the synthesis of a wide range of bicyclic  $\beta$ -lactams, oxazolidinones such as **1** remain the only viable source of the  $\beta$ -lactam based azomethine ylide to underpin this synthetic strategy. Less stabilized and more reactive variants, such as **2**, remain elusive, but we now know much more about those alternative reaction pathways that limit the range of oxazolidinones that are capable of generating synthetically useful  $\beta$ -lactam based azomethine ylides.

#### Experimental

For general details, see preceding paper.<sup>1</sup> Literature procedures were used to prepare intermediates  $6,^7 7^7$  and  $9^{12}$  (however, see below),  $14,^8 16,^9 17,^9 27-29.^{11}$ 

#### Methyl 4-phenylthio-2-oxoazetidin-1-ylacetate 8

A solution of methyl 4-phenylthio-2-oxoazetidin-1-ylacetate  $6^7$  (1.79 g, 7.1 mmol) in MeOH (20 cm<sup>3</sup>) was treated with a solution of NaIO<sub>4</sub> (1.78 g, 8.3 mmol) in water (10 cm<sup>3</sup>) and stirred for 17 h at room temperature. The mixture was filtered and the filtrate was concentrated in vacuo. The residual oil was partitioned between EtOAc (30 cm<sup>3</sup>) and water (10 cm<sup>3</sup>) and the aqueous solution further extracted with EtOAc (20 cm<sup>3</sup>). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and purified by flash chromatography (60% EtOAc-40% petroleum ether) to give 8 (1.48 g, 78%) as a 1:1 mixture of diastereoisomers and as a colourless oil (Found: M + H<sup>+</sup>. 268.0643.  $C_{12}H_{14}NO_4S$  requires *M*, 268.0644);  $v_{max}$  (film)/cm<sup>-1</sup> 1780 and 1750;  $\delta_{\rm H}$  (270 MHz–doubling of signals due to diastereoisomers is indicated) 2.86 and 3.15 (1 H, dd, J 14.9, 4.9 and J 15.2, 3.0, 3-H), 3.23 and 3.46 (1 H, dd, J 15.2, 4.6 and J 14.9, 2.0, 3-H), 3.65 and 3.78 (3 H, s, OMe), 3.74 and 3.88 (1 H, d, J 18.5), 4.29 and 4.44 (1 H, d, J 18.5), 4.76 and 4.80 (1 H, dd, J 4.9, 2.0 and J 4.6, 3.0, 4-H) and 7.50-7.68 (5 H, m, Ar);  $\delta_{\rm C}$  (75.5 MHz) 35.8 and 39.8 (CH<sub>2</sub>), 42.0 and 43.0 (CH<sub>2</sub>), 52.4 and 52.6 (OCH<sub>3</sub>), 71.1 and 71.4 (CH), 124.0 and 124.2 (CH), 129.6 (CH), 131.7 and 131.8 (CH), 139.4 and 140.3 ( $C_{ipso}$ ), 164.7 and 165.2 (C=O), and 168.0 and 168.3 (C=O); m/z (C.I., NH<sub>3</sub>) 285 (M + NH<sub>4</sub><sup>+</sup>, 100%), 268 (M + H<sup>+</sup>, 19).

#### 4-(2-Pyridylthio)azetidin-2-one

An ice-cold solution of 2-mercaptopyridine (1.11 g, 10 mmol) in 95% EtOH (15 cm<sup>3</sup>) was treated with a solution of NaOH (0.40 g, 10 mmol) in 95% EtOH (10 cm<sup>3</sup>) and water (2 cm<sup>3</sup>). The resultant solution was added to an ice-cold solution of 4-acetoxyazetidin-2-one 5 (1.29 g, 10 mmol) in 95% EtOH (20 cm<sup>3</sup>) dropwise over 15 min. After addition was complete, the ice-bath was removed and the yellow solution was stirred at room temperature overnight. After removal of solvents, the residual oil was partitioned between EtOAc (100 cm<sup>3</sup>) and brine (75 cm<sup>3</sup>). The aqueous solution was further extracted with EtOAc (50 cm<sup>3</sup>) and the combined organic extracts were dried  $(Na_2SO_4)$ , concentrated under reduced pressure and purified by flash chromatography (50% EtOAc-50% petroleum ether) to give the title compound (1.29 g, 72%) as a colourless crystalline solid, mp 82 °C (<sup>i</sup>Pr<sub>2</sub>O) (lit., <sup>14</sup> reported as an oil);  $\delta_{\rm H}$  (270 MHz) 2.98 (1 H, dd, J 15.0, 2.6, 3-H), 3.45 (1 H, dd, J 15.0, 5.1, 3-H), 5.49 (1 H, dd, J 5.1, 2.6, 4-H), 7.02–7.21 (2 H, m, Ar), 7.53 (1 H, m, Ar) and 8.41 (1 H, m, Ar).

#### Methyl 4-(2-pyridylthio)-2-oxoazetidin-1-ylacetate 9

To a solution of LiHMDS [prepared from addition of nbutyllithium (1.6 mol dm<sup>-3</sup> in hexanes; 18.0 cm<sup>3</sup>, 28.8 mmol) to a solution of 1,1,1,3,3,3-hexamethyldisilazane (6.1 cm<sup>3</sup>, 28.9 mmol) in THF (150 cm<sup>3</sup>) at -10 °C under nitrogen and maintained at this temperature for 15 min before cooling to -78 °C] at -78 °C was added a solution of 4-(2-pyridylthio)azetidin-2-one (5.11 g, 28.4 mmol) in THF (15 cm<sup>3</sup>). The mixture was stirred at -78 °C for 15 min, then methyl bromoacetate (3.0 cm<sup>3</sup>, 31.7 mmol) was added and the mixture was then allowed to warm to 15 °C over 2.5 h. Filtration and evaporation of the filtrate under reduced pressure followed by purification of the residue by flash chromatography (50% EtOAc-50% petroleum ether) gave azetidinone 9 (4.79 g, 67%) as a colourless crystalline solid, mp 80-81 °C (<sup>i</sup>Pr<sub>2</sub>O) (lit.,<sup>12</sup> reported as an oil);  $\delta_{\rm H}$  (270 MHz) 3.07 (1 H, dd, J 15.0, 2.9, 3-H), 3.57 (1 H, dd, J 15.0, 5.3, 3-H), 3.78 (3 H, s, OMe), 3.81 (1 H, d, J 18.0), 4.32 (1 H, d, J 18.0), 5.79 (1 H, dd, J 5.3, 2.9, 4-H), 7.04 (1 H, m, Ar), 7.22 (1 H, m, Ar), 7.53 (1 H, m, Ar) and 8.30 (1 H, m, Ar).

#### Methyl 4-(2-pyridylsulfinyl)-2-oxoazetidin-1-ylacetate 10

Using the same procedure as described for the preparation of sulfoxide 8, oxidation of 9 gave 10 in 71% yield as a colourless oil and as a 1:1.5 mixture of diastereoisomers (Found: C, 49.4; H, 4.75; N, 10.22. C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>S requires C, 49.25; H, 4.51; N, 10.44%) (Found: M + H<sup>+</sup>, 269.0606. C<sub>11</sub>H<sub>13</sub>N<sub>2</sub>O<sub>4</sub>S requires M, 269.0596);  $v_{\text{max}}$  (film)/cm<sup>-1</sup> 1780 and 1750;  $\delta_{\text{H}}$  (270 MHz) 3.35-3.45 (2 H, m, 3-H (both isomers)), 3.56 (1 H, d, J 18.0, major isomer), 3.64 (3 H, s, OMe, minor isomer), 3.80 (3 H, s, OMe, major isomer), 4.03 (1 H, d, J 18.0, minor isomer), 4.26 (1 H, d, J 18.0, minor isomer), 4.45 (1 H, d, J 18.0, major isomer), 5.15 (1 H, m, 4-H, both isomers), 7.43 (1 H, m, Ar), 7.96–8.00 (2 H, m, Ar) and 8.65 (1 H, m, Ar);  $\delta_{\rm C}$  (75.5 MHz) 35.7 (CH<sub>2</sub>), 40.2 (CH<sub>2</sub>), 42.1 (CH<sub>2</sub>), 42.58 (CH<sub>2</sub>), 52.0 (CH<sub>3</sub>), 52.3 (CH<sub>3</sub>), 69.5 (CH), 70.7 (CH), 120.0 (CH), 120.1 (CH), 124.8 (CH), 124.9 (CH), 138.0 (CH), 138.2 (CH), 149.5 (CH), 161.2 (C), 161.8 (C), 164.8 (C=O), 167.4 (C=O), 167.9 (C=O) (some doubling of signals due to diastereoisomers was observed).

#### But-3-enyl 4-phenylthio-2-oxoazetidin-1-ylacetate 11

To a suspension of NaH (60% dispersion in mineral oil, 270 mg, 6.75 mmol) in DMF (20 cm<sup>3</sup>) under nitrogen at -50 °C was added a solution of 4-phenylthioazetidin-2-one (1.13 g, 6.31 mmol) in THF (5 cm<sup>3</sup>). The temperature was allowed to rise to -30 °C over 40 min before cooling to -60 °C, and then a solution of but-3-envl bromoacetate<sup>15</sup> (1.26 g, 6.53 mmol) in THF (5 cm<sup>3</sup>) was added. After allowing to warm to 0 °C over 1 h, the mixture was further stirred for 2 h. Ether (30 cm<sup>3</sup>) and water (20 cm<sup>3</sup>) were added and the phases separated. The aqueous solution was extracted with Et<sub>2</sub>O (20 cm<sup>3</sup>) and the ethereal solutions combined, dried (Na2SO4) and concentrated in vacuo. Purification of the residue by flash chromatography (20% EtOAc-80% petroleum ether) gave 11 (1.19 g, 65%) as a pale yellow oil (Found:  $M^+$ , 291.0922.  $C_{15}H_{17}NO_3S$  requires M, 291.0929);  $\nu_{max}$  (film)/cm<sup>-1</sup> 1780–1750, 1642 and 1584;  $\delta_H$  (270 MHz) 2.23–2.31 (2 H, m), 2.77 (1 H, dd, J 15.0, 2.4, 3-H), 3.31 (1 H, dd, J 15.0, 5.0, 3-H), 3.65 (1 H, d, J 18), 3.98-4.12 (2 H, m), 4.20 (1 H, d, J 18), 4.97–5.05 (2 H, m), 5.12 (1 H, dd, J 5.0, 2.4, 4-H), 5.64 (1 H, m) and 7.17–7.36 (5 H, m, Ar);  $\delta_{\rm C}$  (75.5 MHz) 32.7 (CH<sub>2</sub>), 40.9 (CH<sub>2</sub>), 44.8 (CH<sub>2</sub>), 59.0 (CH<sub>2</sub>), 64.4 (CH), 117.5 (CH<sub>2</sub>), 128.7 (CH), 129.2 (CH), 130.0 (C<sub>ipso</sub>), 133.4 (CH), 133.9 (CH), 165.2 (C=O) and 167.7 (C=O); *m/z* (E.I.) 291  $(M^+, 1\%).$ 

#### But-3-enyl 4-phenylsulfinyl-2-oxoazetidin-1-ylacetate 12

To a solution of the 4-phenylthioazetidinone 11 (250 mg, 0.86

mmol) in MeOH (6 cm<sup>3</sup>) was added water (3 cm<sup>3</sup>) and NaIO<sub>4</sub> (240 mg, 1.13 mmol). The reaction mixture was stirred at room temperature for 19 h. The precipitate was removed by filtration, washed with Et<sub>2</sub>O, and the combined filtrate and washings were dried (Na<sub>2</sub>SO<sub>4</sub>) and then concentrated in vacuo. Purification of the residue by flash chromatography (50% EtOAc-50% petroleum ether) gave sulfoxide 12 (158 mg, 60%) as a 1:1 mixture of diastereoisomers and as a colourless oil (Found: C, 58.29; H, 5.42; N, 4.63. C<sub>15</sub>H<sub>17</sub>NO<sub>4</sub>S requires C, 58.62; H, 5.57; N, 4.57%);  $v_{max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 1780 and 1750;  $\delta_{H}$  (270 MHz) 2.31-2.47 (2 H, m), 2.86 and 3.15 (1 H, dd, J 15.0, 4.8 and J 15.2, 3.0, 3-H), 3.22 and 3.46 (1 H, dd, J 15.2, 4.6 and J 15.0, 2.0, 3-H), 3.65 and 3.84 (1 H, d, J 18.5), 4.02-4.16 (1 H, m), 4.19-4.28 (1 H, m), 4.29 and 4.44 (1 H, d, J 18.5), 4.76 and 4.81 (1 H, dd, J 4.8, 2.0 and J 4.6, 3.0, 4-H), 5.07–5.17 (2 H, m), 5.65–5.85 (1 H, m) and 7.54–7.68 (5 H, m, Ar);  $\delta_{\rm C}$  (75.5 MHz) 32.6 and 32.7 (CH<sub>2</sub>), 35.7 and 39.7 (CH<sub>2</sub>), 42.1 and 43.0 (CH<sub>2</sub>), 64.5 and 64.7 (CH<sub>2</sub>), 71.0 and 71.4 (CH), 117.5 and 117.6 (CH<sub>2</sub>), 124.0 and 124.2 (CH), 129.5 (CH), 131.6 and 131.8 (CH), 133.3 (CH), 139.3 and 140.2 ( $C_{ipso}$ ), 164.7 and 165.1 (C=O) and 167.5 and 167.7 (C=O); m/z (C.I., NH<sub>3</sub>) 325  $(M + NH_4^+, 100\%), 308 (M + H^+, 25).$ 

#### Thermolysis of sulfoxide 12 in acetic anhydride and NPM

A solution of sulfoxide **12** (23 mg, 0.8 mmol) in acetic anhydride (1 cm<sup>3</sup>) was heated at reflux for 1 h. Removal of solvent and analysis by <sup>1</sup>H NMR showed one major  $\beta$ -lactam product. This was not rigorously characterized, but tentatively assigned as the 4-acetoxyazetidinone **13** [ $\delta_{\rm H}$  (270 MHz) 2.16 (3 H, s), 2.25–2.35 (2 H, m), 3.04 (1 H, dd, *J* 15.0, 2.0, 3-H), 3.38 (1 H, dd, *J* 15.0, 5.0, 3-H), 3.75 (1 H, d, *J* 18), 3.95–4.10 (2 H, m), 4.20 (1 H, d, *J* 18), 4.97–5.05 (2 H, m), 5.65 (1 H, m) and 6.04 (1 H, dd, *J* 5.0, 2.0, 4-H)].

A solution of sulfoxide **12** (23 mg, 0.8 mmol), NPM (42 mg, 0.69 mmol) in acetic anhydride (1 cm<sup>3</sup>) was heated at reflux for 1 h. After this time, the solution was concentrated *in vacuo*, and <sup>1</sup>H NMR of the crude product showed no evidence of cycloaddition. The major  $\beta$ -lactam product evident in the crude product corresponded to **13** described above.

## (2*S*,5*R*)-2-Phenylthio-4-oxa-1-azabicyclo[3.2.0]heptane-3,7-dione 22

A solution of (E) and (Z)-(2S,5R)-3-ethylidene-2-phenylthio-4oxa-1-azabicylo[3.2.0]heptan-7-ones 28<sup>11</sup> (100 mg, 0.40 mmol) in EtOAc (10 cm<sup>3</sup>) was cooled to -78 °C under a stream of O<sub>2</sub> gas. An O<sub>2</sub>-O<sub>3</sub> stream was passed through the solution in short bursts until the starting materials were consumed, as judged by TLC. Dimethyl sulfide (slight excess) was introduced and the solution allowed to warm to room temperature. The colourless solution was then washed with  $H_2O$  (2 × 10 cm<sup>3</sup>) and saturated NaCl (10 cm<sup>3</sup>), dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated in vacuo to provide oxazolidinone 22 (90 mg, 95%) as a colourless oil, which was essentially pure by <sup>1</sup>H NMR and was used without further purification (Found: M<sup>+</sup>, 235.0306. C<sub>11</sub>H<sub>9</sub>NO<sub>3</sub>S requires *M*, 235.0303);  $v_{\text{max}}$  (film)/cm<sup>-1</sup> 1800;  $\delta_{\text{H}}$  (270 MHz) 3.16 (1 H, dd, J 17.2, 1.1, 6β-H), 3.50 (1 H, dd, J 17.2, 3.3, 6α-H), 4.81 (1 H, m, 5-H), 5.38 (1 H, s, 2-H), 7.34-7.48 (3 H, m, Ar), 7.63 (2 H, m, Ar); m/z (C.I.) 236 (M + H<sup>+</sup>, 42%).

# (2*S*,5*R*)-2-Phenylsulfinyl-4-oxa-1-azabicyclo[3.2.0]heptan-3,7-dione 23

A solution of **28** (204 mg, 0.826 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 cm<sup>3</sup>) was cooled to 0 °C under nitrogen and a solution of MCPBA (85% purity, 214 mg, 1.24 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 cm<sup>3</sup>) was added dropwise over 30 min. The solution was warmed to room temperature over 1 h, then washed with 10% NaHCO<sub>3</sub> (2 × 20 cm<sup>3</sup>), H<sub>2</sub>O (30 cm<sup>3</sup>) and sat. NaCl (30 cm<sup>3</sup>). The organic solution was dried (MgSO<sub>4</sub>), the solvent was removed *in vacuo* and the residue was purified by flash column chromatography [60 H silica gel, 15% EtOAc–85% petroleum ether] to give (Z)-(2S,5R)-3-ethylidene-2-phenylsulfinyl-4-oxa-1-azabicyclo-[3.2.0]heptan-7-one and (E)-(2S,5R)-3-ethylidene-2-phenylsulfinyl-4-oxa-1-azabicyclo[3.2.0]heptan-7-one (169 mg, 78%), an inseparable mixture of 4 diastereoisomers, as a colourless oil (Found: M + H<sup>+</sup>, 264.0693. C<sub>13</sub>H<sub>14</sub>NO<sub>3</sub>S requires M, 264.0694);  $v_{max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 1806;  $\delta_{\rm H}$  (300 MHz) 1.63–1.78 (12 H, m, 4 × CH<sub>3</sub>), 2.97–3.07 (4 H, m, 4 × 6β-H), 3.31–3.43 (4 H, m, 4 × 6α-H), 4.37 (1H, qd, J 7.0, 1.0), 4.76–4.91 (6 H, m), 5.20–5.28 (4 H, m), 5.32 (1 H, qd, J 7.5, 1.5), 7.30–7.74 (20 H, m, Ar); m/z (E.I.) 264 (M + H<sup>+</sup>, 0.5%).

A solution of the above sulfoxides (0.131 g, 0.43 mmol) in EtOAc (35 cm<sup>3</sup>) was cooled to -78 °C under a stream of O<sub>2</sub> gas. An O<sub>2</sub>-O<sub>3</sub> stream was passed through the solution for 20 min, after which time TLC analysis of the sky blue solution indicated the disappearance of starting material. The O2-O3 flow was interrupted and the mixture was slowly warmed to room temperature under a stream of nitrogen to provide a colourless solution, which was washed with  $H_2O$  (2 × 30 cm<sup>3</sup>) and then sat. NaCl (30 cm<sup>3</sup>). After drying (MgSO<sub>4</sub>), the solvent was removed in vacuo to provide sulfoxides 23 (0.1042 g, 97%), a 1:1 mixture of 2 diastereoisomers, as a colourless oil (Found: M + H<sup>+</sup>, 252.0328. C<sub>11</sub>H<sub>10</sub>NO<sub>4</sub>S requires M, 252.0331);  $v_{max}$ (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 1806 (br);  $\delta_{\rm H}$  (300 MHz: CD<sub>3</sub>CN—based on COSY analysis, signals due to one isomer are indicated by ') 3.24 (1 H, dd, J 17.5, 1.0, 6β-H), 3.28 (1 H, dd, J 17.5, 1.0, 6'β-H), 3.54 (1H, dd, J 17.5, 3.5, 6α-H), 3.55 (1 H, dd, J 17.5, 3.5, 6'a-H), 4.96 (1 H, ddd, J 3.5, 1.0, 0.5, 5-H), 5.19 (1 H, d, J 0.5, 2'-H), 5.42 (1H, d, J 0.5, 2-H), 5.51 (1 H, ddd, J 3.5, 1.0, 0.5, 5'-H) and 7.52–7.67 (10 H, m, Ar);  $\delta_{\rm C}$  (75.5 MHz, CD<sub>3</sub>CN) 48.8 (CH<sub>2</sub>), 49.2 (CH<sub>2</sub>), 76.7 (CH), 77.3 (CH), 85.9 (CH), 87.2 (CH), 125.3 (CH), 125.5 (CH), 129.8 (CH), 129.9 (CH), 132.8 (CH), 132.9 (CH), 139.2 (C<sub>ipso</sub>), 140.4 (C<sub>ipso</sub>), 169.2 (C=O), 173.7 (C=O) and 173.8 (C=O) (a signal due to one C=O carbon atom was not observed); m/z (E.I.) 250 (M – H<sup>+</sup>, 1.5%).

#### Thermolysis of 22 in the presence of NPM

A solution of oxazolidinone **22** (50 mg, 0.213 mmol) and NPM (40 mg, 0.234 mmol) in MeCN (2 cm<sup>3</sup>) [distilled and deoxygenated] was heated at 81 °C for 120 h in a sealed tube. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [60 H silica gel, 10% EtOAc–90% petroleum ether] to give **31** (23 mg, 43%) as a colourless solid, mp 143–145 °C (hexane) (lit.<sup>16</sup> 141–143 °C);  $\delta_{\rm H}$  (300 MHz) 2.90 (1 H, dd, *J* 19.0, 4.0, 4-H), 3.33 (1 H, dd, *J* 19.0, 9.5, 4-H), 4.15 (1 H, dd, *J* 9.5, 4.0, 3-H), 7.04–7.10 (2 H, m, Ar), 7.32–7.50 (6 H, m, Ar) and 7.56–7.62 (2 H, m, Ar).

Diphenyl disulfide (11 mg, 48%) was isolated as a colourless solid, mp 60–61 °C (hexane) and identified by direct comparison to an authentic sample.

#### Thermolysis of 23 in the presence of DMAD

A solution of oxazolidinone **23** (60 mg, 0.24 mmol) and DMAD (36 mg, 31.0 µl, 0.25 mmol) in MeCN (2 cm<sup>3</sup>) [distilled and deoxygenated] was heated at 81 °C for 48 h in a sealed tube. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [60 H silica gel, 1 : 9 $\rightarrow$ 1 : 4 EtOAc–hexane] to give **32**<sup>17</sup> (22 mg, 35%) as a colourless oil:  $\delta_{\rm H}$  (300 MHz) 3.65 (3 H, s, CH<sub>3</sub>), 3.81 (3 H, s, CH<sub>3</sub>), 7.00 (1 H, s, CH) and 7.48–7.70 (5 H, m, Ar). Diphenyl disulfide (8 mg, 32%) was isolated as a colourless solid, mp 59–60 °C (hexane), and (*S*)-phenyl benzenethiosulfonate (9 mg, 30%) was isolated as a colourless solid, mp 41–43 °C (hexane), and identified by direct comparison to an authentic sample.

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