β-Lactam-Based Azomethine Ylide Reactivity. Expedient Synthesis of Carbapenams and Carbapenems

Sarah R. Martel,[†] Richard Wisedale,[†] Timothy Gallagher,*[,†] Lee D. Hall,[‡] Mary F. Mahon,[§] Robert H. Bradbury,[⊥] and Neil J. Hales*[,⊥]

School of Chemistry, University of Bristol Bristol BS8 1TS, U.K. X-ray Crystallographic Unit, School of Chemistry University of Bristol, Bristol, BS8 1TS, U.K. X-ray Crystallographic Unit, School of Chemistry University of Bath, Bath, BA2 7AY, U.K. Zeneca Pharmaceuticals, Mereside, Alderley Park Macclesfield SK10 4TG, U.K.

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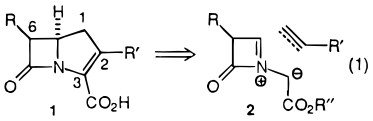
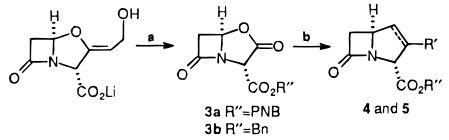
Carbapenems and carbapenams comprise a structurally diverse and clinically important class of *β*-lactam antibiotics that have been the focus of a sustained synthetic effort over the past 20 years.[1] While a variety of substitution patterns are known, for example at C(1), C(2), and C(6), the carbapenem skeleton **1** constitutes a modified pyrroline moiety fused to a *β*-lactam nucleus. As a consequence, synthesis of the carbapenem framework should be suited to a strategy based on 1,3-dipolar cycloaddition chemistry which would offer a direct method for assembling this strained and reactive bicycle. Such an approach does, however, require access to a stabilized azomethine ylide **2** (eq 1), and generating a species of this type represents a significant challenge.[2]



In this communication we disclose a method that expresses, for the first time, the reactivity of azomethine ylides that are equivalent to **2**. We also describe the synthesis of a representative series of carbapenams and carbapenems to exemplify the potential offered by the 1,3-dipolar cycloaddition strategy outlined in eq 1.

We have found that the requisite azomethine ylide reactivity[3] is available in a reaction involving decarboxylation[4] of a *β*-lactam-based oxazolidinone, **3**. Both the *p*-nitrobenzyl (PNB) and benzyl (Bn) esters **3a** and **3b**, respectively, are prepared from lithium clavulanate using an established two-step procedure[5] (Scheme 1).

Scheme 1[a]



[a] Reagents: (a) PNBBr or BnBr, then O_3; (b) MeCN, 80−100 °C, 1,3-dipolarophile (Tables 1 and 2).

Cycloaddition reactions were achieved by thermolysis of either **3a** or **3b** in acetonitrile (at reflux or in a sealed tube at 100 °C) in the presence of a dipolarophile: alkenyl dipolarophiles gave carbapenams **4a**−**f**, and alkynes produced the corresponding Δ^1-carbapenems **5a**−**d** directly. These products, which are racemic, are shown in Tables 1 and 2 with examples chosen to highlight the key features of this versatile cycloaddition process.

Several aspects merit specific comment. In the alkenyl series (Table 1), *endo* cycloadducts predominate and the cycloaddition step, which exhibits a high degree of regioselectivity for unsymmetrical 1,3-dipolarophiles, is also stereospecific.[6] Cycloalkenones provide access to the basic trinem[7] skeleton, as present in **4d**,[8] and use of benzoquinone gave the tricyclic adduct **4e** which has aromatized after cycloaddition.[9] A variety of other substitution patterns are tolerated, including heteroatoms (see **4f** and **4g**) to provide an important and effective level of functionality at C(2).[10] In the alkynyl series (Table 2), good regioselectivity was again observed and cycloaddition to sulfur-substituted dipolarophiles allows access to 2-(arylthio)- and 2-(alkylthio)-Δ^1-carbapenems **5c** and **5d**, respectively.

Base-mediated isomerization of Δ^1-carbapenems to the biologically more relevant Δ^2-carbapenem isomer, though achievable, is inefficient,[11] and we have sought to harness the 1,3-dipolar cycloaddition strategy to provide a direct entry to Δ^2-carbapenems. Thermolysis of **3a** (1,2-dichlorobenzene, reflux, 5 min) in the presence of phenyl vinyl selenide gave the *endo* adduct **4g** which, on oxidation (H_2O_2, −20 °C), gave the (±)-Δ^2-carbapenem **6**[12] in 45% overall yield (Scheme 2).

[†] School of Chemistry, University of Bristol.
[‡] X-ray Crystallographic Unit, School of Chemistry, University of Bristol.
[§] X-ray Crystallographic Unit, School of Chemistry, University of Bath.
[⊥] Zeneca Pharmaceuticals.

(1) (a) Dürchheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180. (b) *Recent Advances in the Chemistry and Biology of β-Lactams and β-Lactam Antibiotics*; Georg, G. I., Ed. *Bioorg. Med. Chem. Lett.* **1993**, *3*, (Symposia-in-Print No. 8), 2159−2313. The penam/carbapenam numbering scheme (see eq 1) is used in this paper.

(2) (a) Lown, J. W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, p 653. (b) Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89. (c) Pearson, W. H. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1. (d) Tsuge, O.; Kanemasa, S. In *Advances in Heterocyclic Chemistry*; Katritsky, A. R., Ed.; Academic Press, Inc.: San Diego, 1989; Vol. 45, p 231.

(3) An azomethine ylide related to **2** has been implicated in the base-mediated racemization of desoxyclavulanic acid. Newall, C. E. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Gregory, G. I., Ed.; Royal Society of Chemistry: London, 1981; Chapter 13, p 151.

(4) Simple oxazolidin-5-ones undergo thermal decarboxylation (1,3-dipolar cycloreversion) to give nonstabilized azomethine ylides. (a) Grigg, R.; Idle, J.; McMeekin, P.; Surendrakumar, S.; Vipond, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2703. (b) Kanesawa, S.; Sakamoto, K.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1960. See also: Burger, K.; Meffert, A.; Bauer, S. *J. Fluorine Chem.* **1977**, *10*, 57. Eschenmoser, A. *Chem. Soc. Rev.* **1976**, *5*, 377.

(5) (a) Brown, A. G.; Corbett, D. F.; Goodacre, J.; Harbidge, J. B.; Howarth, T. T.; Ponsford, R. J.; Stirling, I.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 635. (b) Howarth, T. T.; Stirling, I. Ger. Offen. 2,655,675; *Chem. Abstr.* **1977**, *87*, 102313. Also Campbell, M. M.; Jasys, V. J. *Heterocycles* **1981**, *16*, 1487.

(6) See the Supporting Information for experimental procedures. The regio- and stereochemical features of the cycloadducts described in Tables 1 and 2 were elucidated by NMR (2D and NOE). Structures of **4b** and **4f** were established by X-ray crystallographic analysis. Stereospecific reactions were observed using **3b** with (i) dimethyl maleate and (ii) dimethyl fumarate.

(7) Tamburini, B.; Perboni, A.; Rossi, T.; Donati, D.; Gaviraghi, G.; Tarzia, G. In *Recent Advances in the Chemistry of Anti-Infective Agents*; Bentley, P. H., Ponsford, R., Eds.; Royal Society of Chemistry: Cambridge, 1992; p 21. Camerini, R.; Panunzio, M.; Bonanomi, G.; Donati, D.; Perboni, A. *Tetrahedron Lett.* **1996**, *37*, 2467.

(8) Reaction of **3a** with 2-cyclopentenone gave a major product (in 26% yield) corresponding to an *endo*-adduct but with the opposite regiochemistry to that shown for **4d** (see the Supporting Information).

(9) Aryl-based tricyclic carbapenems analogous to **4e** have been described. Heck, J. V.; Christensen, B. G. *Tetrahedron Lett.* **1981**, *22*, 5027. Heck, J. V.; Szymonifka, M. J.; Christensen, B. G. *Tetrahedron Lett.* **1982**, *23*, 1519.

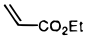
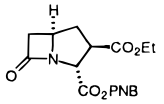
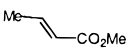
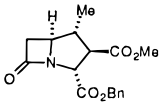
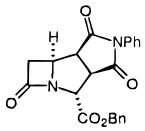
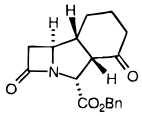
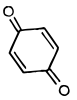
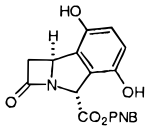
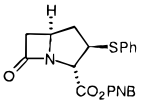
(10) Bateson, J. H.; Roberts, P. M.; Smale, T. C.; Southgate, R. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1541.

(11) Bateson, J. H.; Hickling, R. I.; Smale, T. C.; Southgate, R. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1793. Schmitt, S. M.; Johnston, D. B. R.; Christensen, B. G. *J. Org. Chem.* **1980**, *45*, 1135. Bateson, J. H.; Hickling, R. I.; Roberts, P. M.; Smale, T. C.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1980**, 1084. Ona, H.; Uyeo, S.; Motakowa, K.; Yoshida, T. *Chem. Pharm. Bull.* **1985**, *33*, 4346.

(12) Parker, W. L.; Rathnum, M. L.; Wells, J. S.; Trejo, W. H.; Principe, P. A.; Sykes, R. B. *J. Antibiot.* **1982**, *35*, 653.

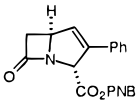
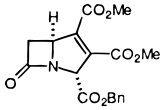
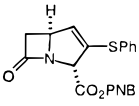
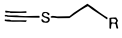
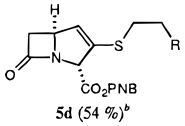
S0002-7863(96)03756-0 CCC: $14.00

Table 1. Carbapenam Cycloadducts Derived from Alkenes

Precursor	1,3-Dipolarophile	Cycloadduct (% yield)
3a		 **4a** (32 %)
3b		 **4b** (48 %)[a]
3b		 **4c** (57 %)
3b		 **4d** (18 %)[b]
3a		 **4e** (23 %)
3a		 **4f** (61 %)[a]

[a] Determined by X-ray crystallographic analysis. [b] *exo*-Adduct predominates.[8]

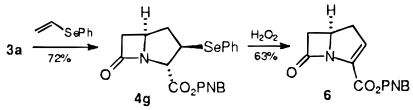
Table 2. Δ^1-Carbapenem Cycloadducts Derived from Alkynes

Precursor	1,3-Dipolarophile	Cycloadduct (% yield)
3a		 **5a** (41 %)
3b	E=CO_2Me	 **5b** (46 %)
3a		 **5c** (63 %)[a]
3a	 R = $NHCO_2$PNB	 **5d** (54 %)[b]

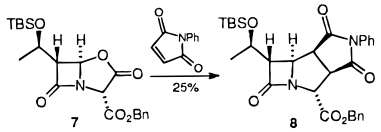
[a] Plus 10% of the regioisomer. [b] Plus 14% of the regioisomer.

Substituents at C(6) play a critical role in defining the biological profile of carbapenems.[13] Of these, the (*R*)-α-hydroxyethyl unit (as in thienamycin) is important, and the requisite azomethine ylide precursor, oxazolidinone **7**, is available in enantiomerically pure form.[14] Exposure of **7** to *N*-phenylmaleimide (MeCN, 100 °C) gave the *endo*-cycloadduct **8** in 25% yield, but unlike cycloadducts derived from **3a/b**, adduct **8** is produced in enantiomerically pure form; the C(6) substituent serves both to maintain enantiomeric purity and to control facial selectivity in the cycloaddition step (Scheme 3). We have, however, observed that reactions involving **7** are less efficient than those based on **3a/b** which is attributed to the sterically demanding silyl ether moiety.

Scheme 2



Scheme 3



In summary, we have realized a new strategy for the synthesis of carbapenams and carbapenems founded on the generation and exploitation of novel azomethine ylide reactivity.[16] This provides bicyclic β-lactams in a direct and convergent manner, with the dipolar reactivity also offering potential in the construction of other classes of β-lactam antibiotics. New opportunities for exploiting this methodology to provide efficient chemical and structural diversity are also now under evaluation.

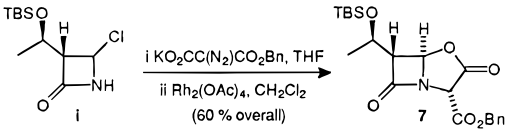
Acknowledgment. We thank Dr. R. Galt for advice and EPSRC and Zeneca Pharmaceuticals for financial support and acknowledge use of the EPSRC's Chemical Database Service at Daresbury.[17]

Supporting Information Available: Spectroscopic and analytical data for cycloadducts **4a**−**g**, **5a**−**d**, and **8** and ORTEP views and related structural details of **4b** and **4f** (26 pages). See any current masthead page for ordering and Internet access instructions.

JA9637560

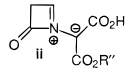
(13) Leanza, W. J.; Wildonger, K. L.; Hannah, J.; Shih, D. H.; Ratcliffe, R. W.; Barash, L.; Walton, E.; Firestone, R. A.; Patel, G. F.; Kahan, F. M.; Kahan, J. S.; Christensen, B. G. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Gregory, G. I., Ed.; Royal Society of Chemistry: London, 1981; Chapter 20, p 240. Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 8004.

(14) Synthesis of **7** was carried out by treatment of 4-chloroazetidinone **i** (Endo, M. *Can. J. Chem.* **1987**, *65*, 2140) with potassium benzyl diazomalonate followed by Rh(II)-mediated cyclization as described for a closely related derivative.[15]



(15) Grabowski, E. J. J.; Reider, P. J. Eur. Pat. 78 026; *Chem. Abstr.* **1983**, *99*, 122171.

(16) While cycloadducts **4** and **5** are formally derived from azomethine ylide **2**, the nature of the 1,3-dipole has not been established. Concerted decarboxylation to give an azomethine ylide (as with simple oxazolidinones[5a]) may occur. However, given the strain associated with **3a/b**, a pathway involving initial ring opening (to give an *N*-acyliminium species) followed by a proton transfer to provide the carboxylated variant **ii** of **2** cannot be excluded.[3] Cycloaddition may precede the decarboxylation event.



(17) Fletcher, D. A.; McMeeking, R. F.; Parkin, D. J. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746.