# A Direct and Convergent Approach to Penams and Penems

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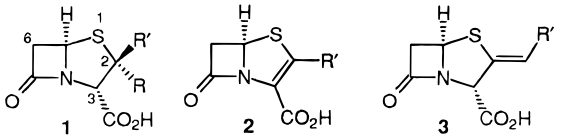
The sulfur-containing bicyclic $\beta$-lactams,[1] the naturally-occuring penams and the penems, a group of synthetic variants first described by Woodward,[2] have attracted a very substantial level of interest both for their potential as antibiotics and, more recently, as inhibitors of serine proteases.[3] Variation of both the structure and pattern of substitution associated with the five-membered ring plays an important role in defining biological profile, and penams **1**, together with penems **2** and thiaclavams **3** (the exocyclic penem isomer), are important target systems.



In this paper, we present concise and flexible routes to all three subgroups **1**−**3** of bicyclic sulfur-based $\beta$-lactams. The central feature of the chemistry described revolves around application of a versatile range of thiocarbonyl derivatives as 1,3-dipolarophiles[4] toward $\beta$-lactam-based azomethine ylides, which allows the penam/penem skeleton to be assembled in a single step.

The readily available oxazolidinone **4**[5] provides a convenient source of reactivity that is, in essence, equivalent to the stabilized azomethine ylide **5**.[6] Thermolysis of **4** (MeCN, 80 °C, 80 h) in the presence of the appropriate thioketone provided the 2,2-dialkyl and 2,2-diaryl penams **6a** and **6b** directly. Using dimethyl trithiocarbonate and dithiocarboxylates as the dipolarophile component gave, under similar reaction conditions (48−72 h), cycloadducts **7a**−**d** (Scheme 1). The range of products available, which are all racemic, are presented in Table 1, and in all cases, only the regioisomer shown was detected.[7]

**Scheme 1**

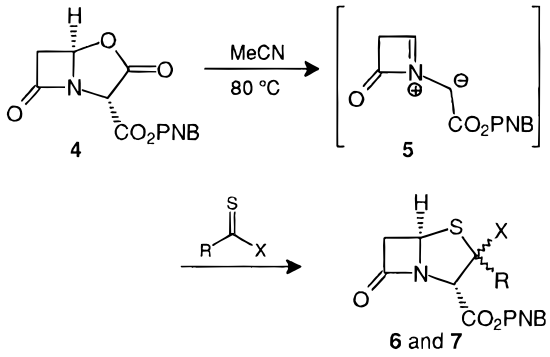
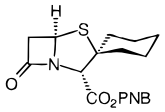
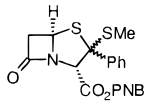
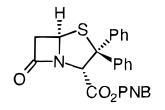
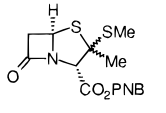
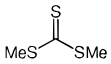
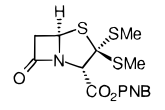
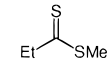
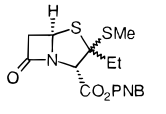


**Table 1**

| 1,3-Dipolarophile | Cycloadduct (%) | 1,3-Dipolarophile | Cycloadduct (%) |
|---|---|---|---|
|  |  **6a** (48 %) |  |  **7b** (71 %)[a] |
|  |  **6b** (51 %) |  |  **7c** (43 %)[a] |
|  |  **7a** (60 %) |  |  **7d** (44 %)[a] |

All products shown are racemic. [a] Isolated as a 4:1 mixture of diastereoisomers.

Conversion of the more highly functionalized cycloadducts **7a**−**d**, each carrying a potential leaving group at C(2), to the corresponding penem was straightforward (Scheme 2). Oxidation of **7a** gave a diastereomeric mixture of sulfoxides that underwent facile elimination on warming to room temperature to give the 2-(methylthio) penem **8a**.[8] Under similar conditions, cycloadducts **7b**−**d** provided the 2-phenyl,[2b] 2-methy,l[2bc,9] and 2-ethyl[10] penems **8b**−**d**, respectively. However, in these latter cases a base ($Et_3N$) was required to complete a two-step elimination sequence, the overall yields of which have not yet been optimized.

With the 2-alkyl variants **7c** and **7d**, the elimination process has a regiochemical option that can be exercised

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(1) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vols. 1−3. Dürchheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180. *Recent Advances in the Chemistry and Biology of β-Lactams and β-Lactam Antibiotics*; Georg, G. I., Ed.; VCH: New York, 1993.

(2) (a) Ernest, I.; Gosteli, J.; Greengrass, C. W.; Holick, W.; Jackman, D. E.; Pfaendler, H. P.; Woodward, R. B. *J. Am. Chem. Soc.* **1978**, *100*, 8214. (b) Lang, M.; Prasad, K.; Holick, W.; Gosteli, J.; Ernest, I.; Woodward, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 6296. (c) Ernest, I.; Gosteli, J.; Woodward, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 6301. (d) Pfaendler, H. R.; Gosteli, J.; Woodward, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 6306.

(3) Recent work in this area of $\beta$-lactam chemistry has been presented: *Bioorg. Med. Chem. Lett.* (Symposia-in-Print No. 8) **1993**, *3*, 2159−2313. The penam numbering scheme, see **1**, is used throughout this paper.

(4) (a) Campaigne, E. In *The Chemistry of the Carbonyl Group*; Patai, S., Ed.; Wiley: New York, 1966; p 918. (b) Schaumann, E. In *The Chemistry of Double-Bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, 1989; Vol. 2, p 1270. (c) Huisgen, R.; Langhals, E. *Tetrahedron Lett.* **1989**, *30*, 5369.

(5) Oxazolidinone **4** is most readily obtained from clavulanic acid, a component of Augmentin (SB Pharmaceuticals): (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*, 102 313. For other approaches to the synthesis of oxazolidinone **4** see: Bentley, P. H.; Berry, P. D.; Brooks, G.; Gilpin, M. L.; Hunt, E.; Zomaya, I. I. *J. Chem. Soc., Chem. Commun.* **1977**, 748. Campbell, M. M.; Jasys, V. J. *Heterocycles* **1981**, *16*, 1487.

(6) For the application of azomethine ylide reactivity to the synthesis of carbapenams and carbapenems, see: Martel, S. R.; Wisedale, R.; Gallagher, T.; Hall, L. D.; Mahon, M. F.; Bradbury, R. H.; Hales, N. J. *J. Am. Chem. Soc.* **1997**, *119*, 2309. While the precise nature of the 1,3-dipolar species involved in Scheme 1 has not been determined, azomethine ylide **5** offers a convenient way to rationalize the products available.

(7) The relative (and thermodynamically more stable) configuration between C(3) and C(5) of adducts **6a**,**b**, **7a**−**d**, and **11** (penicillin stereochemistry) is based on chemical shift comparisons to those observed in the diastereomeric series and on the absence of a long-range coupling (1−1.5 Hz) between H(3) and H(6$\beta$). Smale, T. C.; Southgate, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2235. Wolfe, S.; Sterzycki, R. Z. *Can. J. Chem.* **1987**, *65*, 26. Barrett, A. G. M.; Sakadarat, S. *J. Org. Chem.* **1990**, *55*, 5110.

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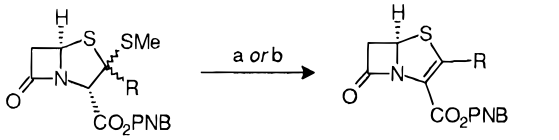
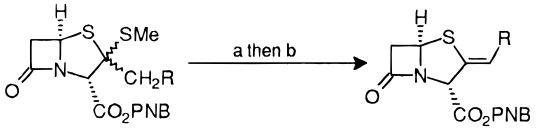
**Scheme 2**[a]




[a] Key: **7a**, (a) *m*-CPBA, $CH_2Cl_2$, 0 °C to rt; **7b**−**d**, (b) (i) *m*-CPBA, $CH_2Cl_2$, 0 °C to rt, (ii) $Et_3N$, $CH_2Cl_2$, reflux.

**Scheme 3**[a]

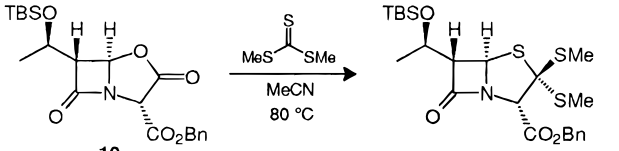



[a] Key: (a) *m*-CPBA, $CH_2Cl_2$, 0 °C to rt; (b) MeCN, 80 °C.

(Scheme 3).[11] Oxidation of **7c** and **7d** (*m*-CPBA) followed by thermolysis (MeCN, 80 °C) of the resulting mixture of diastereomeric sulfoxides gave the thiaclavams **9c** and **9d**, respectively; in the case of **9d** only the (*Z*)-isomer was observed.[12] In addition, isomerization ($Et_3N$, $CH_2Cl_2$) of the exo-isomer **9c** to the thermodynamically more stable penem **8c** has also been accomplished in 95% yield.[13,14]

Penems incorporating the (*R*)-α-hydroxyethyl substituent at C(6) are also important targets,[3] and thermolysis

**Scheme 4**




(MeCN, 110 °C, sealed tube, 24 h) of the enantiomerically pure oxazolidinone **10**[6] in the presence of dimethyl trithiocarbonate gave cycloadduct **11** in 20% isolated yield (Scheme 4); the presence of a bulky residue at C(6) does reduce the efficiency of the cycloaddition step, and this problem is being addressed. However, it is important to recognize that the C(6) substituent present in **10** serves not only to deliver enantiomeric integrity to adduct **11** but also controls facial selectivity in the cycloaddition step.

In summary, the azomethine ylide strategy for assembling bicyclic β-lactams constitutes a simple, versatile, and above all, direct synthesis of penams and penems. This chemistry permits access to a range of targets, some of which are difficult to prepare by conventional methods, and we are currently exploring ways of increasing the efficiency and diversity associated with the processes outlined in this paper.

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**Supporting Information Available:** Full experimental procedures and spectroscopic and physical data are available for **6a**,**b**, **7a**−**d**, **8a**−**d**, **9c**,**d**, and **11** (5 pages).

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(8) (a) Oida, S.; Yoshida, A.; Hayashi, T.; Takeda, N.; Ohki, E. *Chem. Pharm. Bull.* **1980**, *28*, 3232. (b) Oida, S.; Yoshida, A.; Hayashi, T.; Nakayama, E.; Sato, S.; Ohki, E. *Tetrahedron Lett.* **1980**, 619.

(9) (a) Beels, C. M. D.; Abu-Rabie, M. S.; Murray-Rust, P.; Murray-Rust, J. *J. Chem. Soc., Chem. Commun.* **1979**, 665. (b) Henderson, A.; Johnson, G.; Moore, K. W.; Ross, B. C. *J. Chem. Soc., Chem. Commun.* **1982**, 809. (c) Yoshida, A.; Hayashi, T.; Takeda, N.; Oida, S.; Ohki, E. *Chem. Pharm. Bull.* **1983**, *31*, 768.

(10) Cherry, P. C.; Newall, C. E.; Watson, N. S. *J. Chem. Soc., Chem. Commun.* **1979**, 663.

(11) For alternative syntheses of thiaclavams (exocyclic penems), see: (a) Cherry, P. C.; Evans, D. N.; Watson, N. S.; Murray-Rust, P.; Murray-Rust, J. *Tetrahedron Lett.* **1980**, 561. (b) Baldwin, J. E.; Forrest, A. K.; Ko, S.; Sheppard, L. N. *J. Chem. Soc., Chem. Commun.* **1987**, 81. (c) Tanaka, H.; Kameyama, Y.; Kosaka, A.; Yamauchi, T.; Torii, S. *Tetrahedron Lett.* **1991**, *32*, 7445. (d) Tanaka, H.; Kameyama, Y.; Yamauchi, T.; Torii, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1793. (e) Tanaka, H.; Sumida, S.; Sorajo, K.; Torii, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1461.

(12) Isomerization of penems to thiaclavams and structural assignment: Douglas, J. L.; Martel, A.; Caron, G.; Ménard, M.; Silveira, L.; Clardy, J. *Can. J. Chem.* **1984**, *62*, 2282. See also ref 11b.

(13) In reactions of **7a**−**d**, no evidence for oxidation of the endocyclic sulfur atom, which is presumably less reactive for both steric and electronic reasons, has been detected. For relatived observations: Hanessian, S.; Bedeschi, A.; Battistini, C.; Mongelli, N. *J. Am. Chem. Soc.* **1985**, *107*, 1438. Fahey, J. L.; Lange, B. C.; Van der Veen, J. M.; Young, G. R.; Bose, A. K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1117. Chemoselective oxidation of 2-thio-substituted penems has also been reported: Girijavallabhan, V. M.; McCombie, S. W.; Pinto, P.; Lin, S.-I.; Versace, R. *J. Chem. Soc., Chem. Commun.* **1987**, 691. Krahmwer-Seifert, U.; Emmer, G. *Heterocycles* **1984**, *22*, 375.

(14) The relative configuration between C(3) and C(5) of thiaclavams **9c** and **9d** (penicillin stereochemistry) is based on comparison with data available in the literature.[11] Assignment of (*Z*)-geometry of **9d** is based on NOE experiments involving the alkenyl proton and H(3) and isomerization of **9d** to the *endo* isomer **8d** took place under basic conditions. However, this is a slower and less efficient reaction than was observed for the formation of **8c** from **9c**.