Synthesis of Novel β-Lactam Core Structures Related to the Penam and Penem Antibiotics

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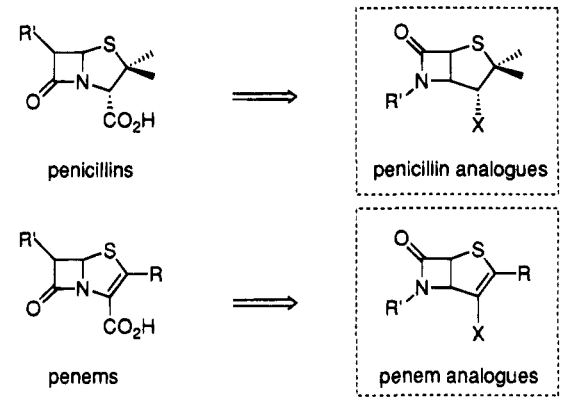
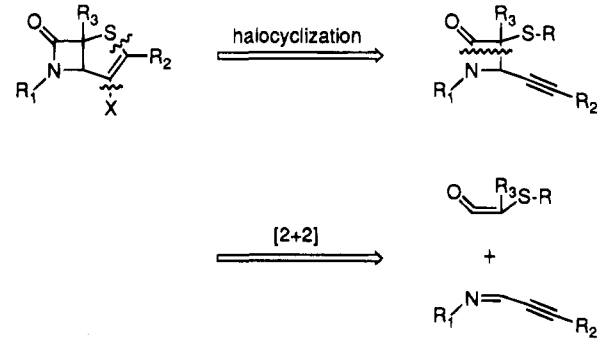
Summary: The synthesis of a structurally new class of penicillin- and penem-type ring systems is described which is based on a sequential imine–ketene cycloaddition reaction and halogen-induced sulfide cyclization process.

For several decades, the penicillins (and related antibiotics) have been widely used for the control and treatment of bacterial infections.[1] Efforts to improve upon the effectiveness of this class of antimicrobial agents has been an ongoing challenge, one which has continued to attract increasing attention because of the emergence of penicillin-resistant strains of bacteria.[2] Over the years, countless numbers of penicillin derivatives[3] have been prepared and tested, and a variety of new β-lactam ring systems have been introduced including the penems,[4] cephalosporins,[5] carbapenems,[6] oxapenams,[7] oxacephams,[8] as well as monocyclic,[9] spirocyclic,[10] and multicyclic[11,12] ring systems. Interestingly, all known classes of β-lactam antibiotics (with the exception of the monocyclic β-lactams) share a common structural feature in that the lactam nitrogen is at the ring fusion. It is rather surprising, given the enormous amount of research in the β-lactam field, that *no examples or studies of β-lactam antibiotics having a lactam group at other positions within the four-membered ring have been reported.*[13] As a result of ongoing work in our laboratory, we have recently become interested in the design and synthesis of unusual β-lactams that might provide potential leads in the search for new antibacterial agents. As entry into this area, we describe the synthesis of one such class of β-lactam structures resembling the penicillins and penems in which the azetidinone nitrogen has been moved off the ring fusion (see boxed structures below).



To construct the functionalized core of these bicyclic β-lactams, we devised a strategy which entails a sequential "double annulation" procedure, illustrated retrosynthetically in eq 1. This process involves the intermediacy of a 3-(alkylthio)-4-alkynyl (or alkenyl) azetidinone, which



(1)

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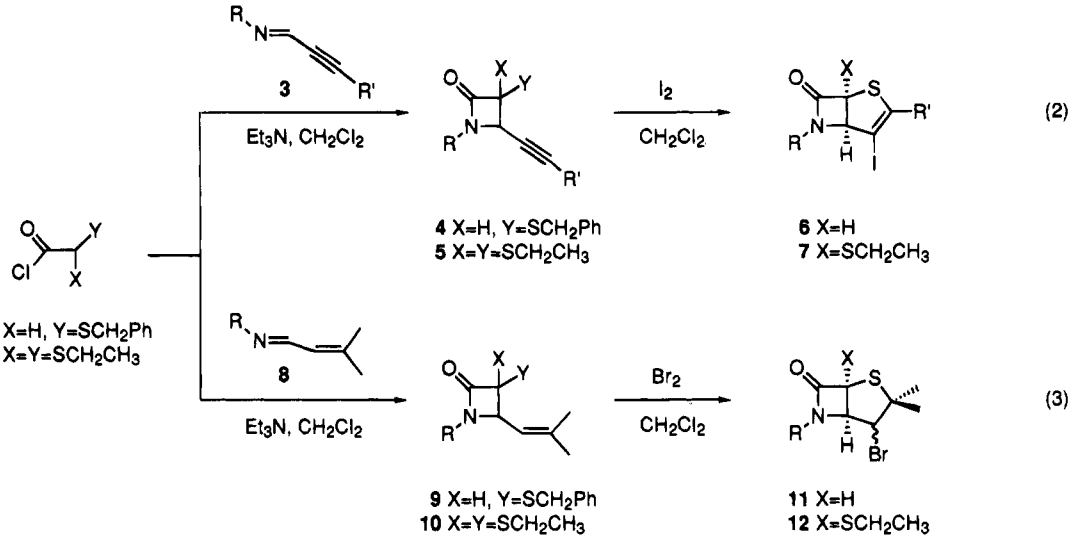
Scheme 1



can be prepared by a [2 + 2]-cycloaddition reaction[14] between an α-(alkylthio) ketene equivalent and an α,β-unsaturated imine. Formation of the fused-thiophene ring is achieved via a regiospecific halocyclization[15] of the thio group onto the distal end of the unsaturated substituent. This approach to the 4,5-fused β-lactam skeleton is not only expedient but also provides the opportunity to incorporate a variety of substituents (R_1, R_2, R_3, X) onto the bicyclic core.

We first applied this methodology to the synthesis of penem-type compounds **6**. Reaction of *S*-benzylthioacetyl chloride[16] (**1**) with propargylic imine **3**[17] (R = 4-MeOPh, R′ = Ph) in the presence of a stoichiometric amount of Et_3N, followed by treatment[18] of the crude product with *n*-butyllithium then aqueous acetic acid, yielded cycloadducts **4** (R = 4-MeOPh, R′ = Ph) in 87% yield as a 2:1 mixture of cis:trans isomers (Scheme 1, eq 2).[19] Upon treatment of this mixture with 1 equiv of I_2 in CH_2Cl_2 at room temperature, bicycloadduct **6** (R = 4-MeOPh, R′ = Ph) was produced in 95% yield (based on recovered *trans*-**4**).[20] In a similar manner, α-substituted penem-type derivatives **7**[21] could be synthesized in two steps from bis(ethylthio)acetyl chloride (**2**)[22] and propargyl imines **3**[17] (Scheme 1, eq 2). Azetidinone intermediates **5a** (88%, R = 4-MeOPh; R′ = Ph), **5b** (95%, R = CH_2Ph; R′ = Ph), and **5c** (98%, R = 4-MeOPh; R′ = $SiEt_3$) were each prepared by treating **2** with **3a** (R = 4-MeOPh; R′ = Ph), **3b** (R = CH_2Ph; R′ = Ph), and **3c** (R = 4-MeOPh; R′ = $SiEt_3$), respectively, in the presence of a stoichiometric quantity of Et_3N at room temperature. Reaction of the resulting azetidinones **5a**, **5b**, and **5c** with 1 equiv of I_2 produced bicycloadducts **7a** (98%, R = 4-MeOPh; R′ = Ph), **7b** (73%, R = CH_2Ph; R′ = Ph), and **7c** (92%, R = 4-MeOPh; R′ = $SiEt_3$), respectively. To our knowledge,

(12) Tetracyclic β-lactams: Wollmann, T.; Gerlach, U.; Horlein, R.; Krass, N.; Lattrell, R.; Limbert, M.; Markus, A. In *Recent Advances in the Chemistry of Anti-Infective Agents*; Bentley, P. H., Ponsford, R., Eds.; The Royal Society of Chemistry: Cambridge, 1993; pp 50–66.

(13) Isolated examples of bicyclic azetidinones having the lactam group *adjacent* to the ring fusion have been reported; however, the biological properties of these compounds do not appear to have been examined. See: (a) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbruggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852. (b) Baldwin, J. E.; Christie, M. A.; Haber, S. B.; Kruse, L. I. *J. Am. Chem. Soc.* **1976**, *98*, 3045. (c) Nakatsuka, S.-i.; Tanino, H.; Kishi, Y. *J. Am. Chem. Soc.* **1975**, *97*, 5008. (d) Nakatsuka, S.-i.; Tanino, H.; Kishi, Y. *J. Am. Chem. Soc.* **1975**, *97*, 5010. (e) Spitzer, W. A.; Goodson, T.; Lammert, S. R.; Kukolja, S. *J. Org. Chem.* **1981**, *46*, 3568. (f) Cooper, R. D. G.; Jose, F. L. *J. Am. Chem. Soc.* **1970**, *92*, 2576. (g) Barton, D. H. R.; Comer, F.; Sammes, P. G. *J. Am. Chem. Soc.* **1969**, *91*, 1529.

(14) (a) Staudinger, M. *Liebigs Ann. Chem.* **1907**, *356*, 51. (b) Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. E., Ed.; Verlag Chemie: New York, 1993; pp 295–368.

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(16) [2 + 2]-Cycloadditions of α-arylthioacetyl chlorides with imines have been reported previously. (a) Palomo, C.; Cossio, F. P.; Odiozola, J. M.; Oiarbide, M.; Ontoria, J. M. *Tetrahedron Lett.* **1989**, *30*, 4577. (b) Palomo, C.; Cossio, F. P.; Odiozola, J. M.; Oiarbide, M.; Ontoria, J. M. *J. Org. Chem.* **1991**, *56*, 4418. (c) Ishida, M.; Minami, T.; Agawa, T. *J. Org. Chem.* **1979**, *44*, 2069.

(17) The imines were prepared by stirring a CH_2Cl_2 solution containing an equimolar amount of the aldehyde and amine in the presence of 2 molar equiv of anhydrous $MgSO_4$.

(18) The crude product mixture, which is comprised mainly of the trans cycloadduct, is treated with nBuLi and then HOAc in order to increase the amount of cis isomer.

(19) All new compounds gave satisfactory ^1H NMR, ^{13}C NMR, infrared, and mass spectral analysis. The stereochemistry of the cycloadducts was assigned based on an observed proton coupling constant of 4.8 Hz for the vicinal protons of the *cis*-azetidinone and 2.0 Hz for these protons of the trans isomer.

(20) The *trans*-azetidinone was recovered after aqueous workup and flash chromatography.

(21) Our interest in these α-thio-substituted β-lactams stems from the fact that α-heterosubstitution can in certain instances make the β-lactam ring more resistant to hydrolysis by β-lactamases. 7α-Methoxylation of the cephalosporin ring system markedly enhances β-lactamase resistance. (a) Strominger, J. L.; Tipper, D. J. *Am. J. Med.* **1965**, *39*, 707. (b) Cama, L. D.; Leanza, W. J.; Beattie, T. R.; Christensen, B. G. *J. Am. Chem. Soc.* **1972**, *94*, 1408. (c) Stapley, E. O.; Birnbaum, J.; Miller, A. K.; Wallick, H.; Hendlin, D.; Woodruff, H. B. *Rev. Inf. Dis.* **1979**, *1*, 73 and references cited therein. (d) Nagarjan, R.; Boeck, L. D.; Gorman, M.; Hamill, R. L.; Higgens, C. E.; Hoehn, M. M.; Stark, W. M.; Whitney, J. G. *J. Am. Chem. Soc.* **1971**, *93*, 2308. However, analogous substitution on the penicillin core generally diminishes antibiotic activity (Bentley, P. H.; Clayton, J. P. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*, Elks, J., Ed.; Special Publication No. 28, The Chemical Society, London, 1977; pp 68–72), although the penicillin derivative temocillin seems to be an exception (Slocombe, B.; Basker, M. J.; Bentley, P. H.; Clayton, J. P.; Cole, M.; Comber, K. R. Dixon, R. A.; Edmondson, R. A.; Jackson, D.; Merrikin, D. J.; Sutherland, R. *Antimicrob. Agents Chemother.* **1981**, *20*, 38).

(22) The synthesis of 3-bis(ethylthio)azetidinones has been reported previously. Cossio, F. P.; Ganboa, I.; Garcia, J. M.; Lecea, B.; Palomo, C. *Tetrahedron Lett.* **1987**, *28*, 1945. Also see: Abramski, W.; Belzecki, C.; Chielewski, M. *Bull. Pol. Acad. Sci. Chem.* **1985**, *33*, 451.

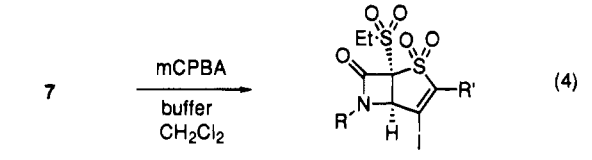
(23) The formation of an isomeric coproduct accounts for the lower yield of the desired [2 + 2]-cycloadduct in this reaction.

(24) NMR coupling constants for the vicinal protons at the nitrogen- and bromine-substituted centers of **11**, **12**, and **14** vary, depending on the oxidation state of the sulfur center and the lactam protecting group. Consequently, we have not been able to rigorously determine the relative stereochemistry of the bromine center in these compounds. Nevertheless, we are tentatively assigning the structures of the α-Br and β-Br epimers by assuming the halogen is preferentially incorporated from the more sterically accessible α-face during the halocyclization.

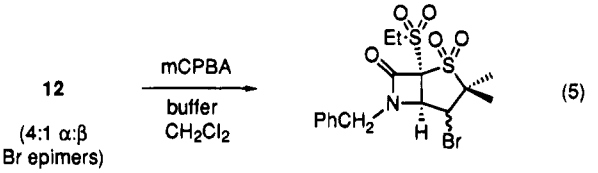
the conversion of **5** to **7** is the first example of a halocyclization involving an unsaturated thioketal.

Using an analogous procedure, we have prepared penicillin analogue **11** from acid chloride **1** and the *N*-arylimine of 3-methyl-2-butenal (**8a**, R = 4-MeOPh)[17] (Scheme 1, eq 3). Thus, after [2 + 2]-reaction of **1** with **8a** and treatment of the initial cycloadduct[18] with nBuLi then aqueous HOAc, azetidinone **9** (R = 4-MeOPh)[19] was obtained in 38% yield as a 1:2 mixture of cis:trans diastereomers.[23] Subsequently, reaction of **9** with Br_2 (1 equiv) in CH_2Cl_2 led to the isolation of **11** (R = 4-MeOPh, 100% based on *cis*-**9**) as a 5:1 mixture of α:β bromo epimers, as well as products arising from alkene bromination of trans-**9**.[24] α-Thio-substituted penam analogues **12** were likewise synthesized in two steps from the [2 + 2]-reaction of acid chloride **2** and *N*-benzylimine **8b** (R = $PhCH_2$) to give azetidinone **10** (R = $PhCH_2$)[19] in 58% yield, and bromination of **10** affords **12** (R = $PhCH_2$, 100%) as a 4:1 mixture of α:β bromo epimers (Scheme 1, eq 3).[24]

From inspection of their infrared spectra, bicyclic β-lactams **6**, **7**, **11**, and **12** ($\nu_{C=O}$ 1750–1760 cm^{-1}) appear to have a somewhat less electrophilic azetidinone ring than that of the penam or penem antibiotics ($\nu_{C=O}$ 1770–1790 cm^{-1}). Taking advantage of previous work[25] on the penicillins and cephalosporins, we thought that it would be possible to further enhance the electrophilicity of our β-lactam systems by sulfoxidation. We therefore decided to convert β-lactams **7** and **12** to their disulfone derivatives **13** and **14**, respectively, using *m*-chloroperoxybenzoic acid (*m*-CPBA)[26] in CH_2Cl_2 buffered with Na_2HPO_4–NaH_2PO_4 (eqs 4 and 5). Indeed, the strong electron-



13a R=4-MeOPh, R'=Ph (86%)
13b R=$PhCH_2$, R'=Ph (45%)
13c R=4-MeOPh, R'=$SiEt_3$ (72%)

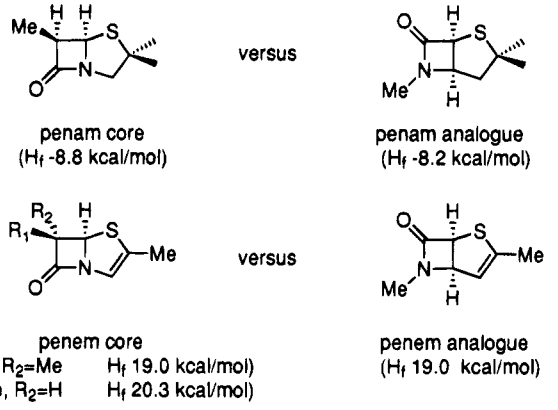


(73%) **14** (4:1 α:β Br epimers)

withdrawing influence of the twin α-disulfone groups on the β-lactam ring can be clearly observed from the shift of the C=O signal in the infrared spectrum from ν = 1750–1760 cm^{-1} (for sulfides **7** and **12**) to ν = 1780–1785 cm^{-1} (for disulfones **13** and **14**).

Since antibiotic activity among the β-lactams is in certain instances[27] related to the reactivity of the azetidinone ring, we wondered what effect moving the lactam off the ring fusion might have on the inherent stability of the four-membered ring. Previous structural studies[28] on fused bicyclic azetidinones have revealed that "N-fused" systems generally have a higher C=O stretching frequency than "C-fused" structures. Although these data suggest that the ring strain, and thus the stability and chemical reactivity, of the azetidinone ring may depend on the location of the ring fusion, other factors such as solvation, hydrogen-bonding, and substituent effects must also be considered. Indeed, semiemperical calculations[29] indicate that the thermodynamic stabilities of our C-fused structures are comparable to those of the corresponding N-fused penam and penem rings, based on their gas phase heats of formation (Table 1).[30]

Table 1. Calculated Heats of Formation



(25) Oxidation of penicillins and cephalosporins to their sulfoxides and sulfones increases the β-lactam carbonyl stretching frequency by 15 cm^{-1} and 45 cm^{-1}, respectively. (See: Demarco, P. V.; Nagarajan, R. In *Cephalosporins and Penicillins: Chemistry and Biology*; Flynn, E. H., Ed.; Academic Press: New York, 1972; pp 315–320.) Penicillin sulfones lack antibiotic activity but show β-lactamase inhibition. (For insight into their mechanism of action and lead references, see: Fink, A. L.; Ellerby, L. M.; Bassett, P. M. *J. Am. Chem. Soc.* **1989**, *111*, 6871.)

(26) (a) Cooper, R. D. G.; DeMarco, P. V.; Cheng, J. C.; Jones, N. D. *J. Am. Chem. Soc.* **1969**, *91*, 1408. (b) Cooper, R. D. G.; DeMarco, P. V.; Spry, D. O. *J. Am. Chem. Soc.* **1969**, *91*, 1528.

(27) For β-lactams within the same family, qualitative correlations exist between the reactivity of the azetidinone (as measured by its rate of base hydrolysis) and antimicrobial activity. However, in comparing β-lactams of different classes, there does not appear to be any direct correlation between reactivity and antimicrobial activity. Obviously, biological activity of a given β-lactam depends on a complex interplay of factors. For lead references and a discussion, see: Blaszczak, L. C.; Brown, R. F.; Cook, G. K.; Hornback, W. J.; Hoying, R. C.; Indelicato, J. M.; Jordon, C. L.; Katner, A. S.; Kinnick, M. D.; McDonald, J. H., III; Morin, J. M., Jr.; Munroe, J. E.; Pasini, C. E. *J. Med. Chem.* **1990**, *33*, 1656.

(28) (a) Sweet, R. M. In *Cephalosporins and Penicillins, Chemistry and Biology*; Flynn, E. H., Ed.; Academic Press: New York, 1972; p 280. (b) Dunn, G. L. In *Comprehensive Heterocyclic Chemistry*; Lwowski, W., Ed.; Pergamon Press: New York, 1984; Vol. 7, pp 341–362.

(29) These calculations were carried out using the semiempirical SPARTAN AM1 program. To preserve the tertiary nature of the lactam nitrogen, a methyl group was placed on each of the azetidinone rings, and the carboxylic acid group was omitted from each core structure to avoid discrepancies due to hydrogen-bonding effects.

(30) While the thermodynamic stabilities of our ring systems appear to be similar to those of the parent penam and penem rings, the kinetic properties (e.g., rate of base hydrolysis) or biological efficacy need not be comparable. We hope to obtain data on the hydrolysis rates and antimicrobial activities of appropriate derivatives to determine if the thermodynamic properties of these compounds can be correlated to their acylating abilities and biological properties.

(31) Halocyclization reactions of unsaturated sulfides and thiols have been employed to construct 5,5-fused bicyclic rings. See: (a) Shibasaki, M.; Ikegami, S. *Tetrahedron Lett.* **1978**, 559. (b) Nicolaou, K. C.; Barnette, W. E.; Magolda, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 3472; (c) **1981**, *103*, 3486. (d) Nicolaou, K. C.; Magolda, R. L.; Barnette, W. E. *J. Chem. Soc., Chem. Commun.* **1978**, 375. (e) Turos, E.; Parvez, M.; Garigipati, R. S.; Weinreb, S. M. *J. Org. Chem.* **1988**, *53*, 1116. This halocyclization procedure is somewhat reminiscent of the classical Morin isomerization of penicillin sulfoxides to cephams, a process thought to occur via intramolecular addition of an electrophilic sulfur group to an olefin. (Morin, R. B.; Jackson, B. G.; Mueller, R. A.; Lavagnino, E. R.; Scanlon, W. B.; Andrews, S. L. *J. Am. Chem. Soc.* **1963**, *85*, 1896.) For discussions and references, see: (a) Cooper, R. D. G.; Hatfield, L. D.; Spry, D. O. *Acc. Chem. Res.* **1973**, *6*, 32. (b) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. I. For related methodology involving an intramolecular sulfenylation of an allene, see: Farina, V.; Kant, J. *Tetrahedron Lett.* **1992**, *33*, 3559.

In summary, new methodology has been described for the synthesis of β-lactam ring systems related to the penicillin and penem families of antibiotics. The exclusive endo-regioselectivity and high chemical yield associated with the formation of the azetidinone-fused thiophene ring illustrates the efficiency of sulfide halocyclization reactions in the formation of highly strained ring systems.[31] Efforts are underway in our laboratory to prepare suitable derivatives for biological studies and to apply this methodology to the design and synthesis of additional classes of "nontraditional" β-lactam core structures.

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Supplementary Material Available: General experimental procedures as well as analytical (^1H and ^{13}C NMR, infrared, and mass spectral) data and copies of the ^1H and ^{13}C NMR spectra for compounds **4**–**7** and **9**–**14** (46 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.