New Synthesis of Penems, the Oxalimide Cyclization Reaction

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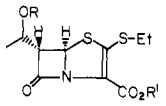
Among the nonclassical β-lactam antibiotics, penems are recognized as potent antimicrobial agents.[1] More recently, Sch 29482 (**1a**) has been reported to be an orally active penem.[2] The

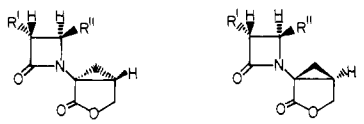


1a, R=R'=H
1b, R=-$CO_2CH_2CCl_3$(TCE)
R'=-$CH_2CH=CH_2$

methodology for the synthesis of this important class of compounds is limited, and the more widely used method involves an intramolecular thiocarbonyl Wittig cyclization developed by Woodward.[1,17] We were interested in devising a more efficient penem synthesis to be used for the large-scale preparation of **1a**.

In this communication we disclose a high-yielding one-step penem cyclization reaction starting from an azetidinone trithiocarbonate, which is based on the reaction of oxalimides with triethyl phosphite. The synthesis of **1b** is described below as a representative example of the new process.

The reactivity of the imidocarbonyl group of *N*-oxalylazetidinones[3] suggested to us that such systems would behave as α-keto ester equivalents and hence would have potential synthetic applications in β-lactam chemistry.[4] Accordingly, 4-acetoxy-*N*-allyloxalylazetidin-2-one (**2**)[6] was treated with 1 equiv of triethyl phosphite under high dilution conditions. The products from this reaction were characterized[9] as the cyclopropane compounds **3a**



4 3

a, R'=H; R''=-OAc
b, R'=(R)CH_3CH(OTCE)—
R''=—S—C(=S)—SEt

(1) (a) R. B. Woodward, "Recent Advances in the Chemistry of β-Lactam Antibiotics", J. Elks, Ed., Chemical Society, London, 1977, p 167. (b) S. Oida, A. Yoshida, T. Hayashi, N. Takeda, T. Nishimura, and E. Ohki, *J. Antibiot.*, **33**, 107 (1980). (c) H. R. Pfaendler, J. Gosteli, and R. B. Woodward, *J. Am. Chem. Soc.*, **102**, 2039 (1980).

(2) A. K. Ganguly, V. M. Girijavallabhan, S. McCombie, P. Pinto, R. Rizvi, P. D. Jeffrey, and S. Lin, *J. Antimicrob. Chemother.* (*Suppl. C*), **9** (1982), and other papers therein.

(3) Cf. reactions reported in (a) I. Ernst, J. Gosteli, C. W. Greengrass, W. Holick, D. E. Jackman, H. R. Pfaendler, and R. B. Woodward, *J. Am. Chem. Soc.*, **100**, 8215 (1978). (b) R. D. G. Cooper and F. L. Jose, *J. Am. Chem. Soc.*, **94**, 1021 (1972).

(4) For example, α-diketones and α-keto esters are known to form adducts with phosphorous esters, which in turn react with activated olefins to yield cyclopropanes.[5]

(5) (a) E. Corre and A. Foucad, *J. Chem. Soc., Chem. Commun.*, 570 (1971). (b) H. Faudet and R. Burgada, *Synthesis*, 642 (1980). (c) On the basis of our present work on oxalimides, we suggest that the reactions described in this reference do in fact involve carbene intermediates like R–C̈–COR[1] rather than ionic species as postulated.

(6) Prepared by adding diisopropylethylamine to a mixture of 4-acetoxyazetidinone[7] and allyloxalyl chloride[8] in dichloromethane.

(7) K. Clauss, D. Grimm, and G. Prossel, *Justus Liebigs Ann. Chem.*, 539 (1974).

(8) Obtained by reacting a solution of oxalyl chloride in ether, with 1 equiv of allyl alcohol.

(9) Data included in supplementary material.

(12%) and **4a** (30%). A single-crystal X-ray analysis confirmed the structure and relative stereochemistry of **4a** unequivocally.

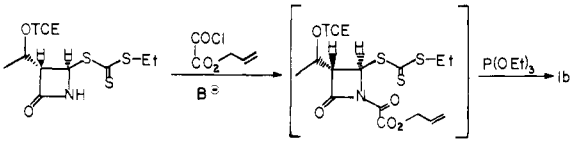
The formation of the cyclopropanes **3a** and **4a** as the sole isolatable products from this reaction requires the intermediacy of a carbene since an isolated olefinic bond is involved in the transformation. The initial reaction of **2** with triethyl phosphite would be expected to afford betaine **5a** by a two-electron transfer

5 6

from the phosphorous atom to the imide carbonyl oxygen. Analogous adducts have been demonstrated in the case of quinones[10] and α-keto esters.[5b] The betaine **5a**, under the thermal conditions of the reaction, generates the transitory carbene **6a** by eliminating triethyl phosphate. The carbene in **6a** adds intramolecularly[11] to the isolated double bond of the allyl group to afford the isomeric 2,3-cyclopropano-γ-lactones **3a** and **4a** in a ratio that favors the sterically less hindered **4a**.

If more than one carbene-reactive functional group is present in the oxalimide substrate, the ratio of the products arising from intramolecular competitive reactions will depend on the relative reactivity of the functional groups. An example of such a situation is observed in the application of the above reaction for the synthesis of penems.

Azetidinone trithiocarbonate **7**[12] is reacted with allyloxalyl chloride in the presence of diisopropylethylamine. The resulting allyloxalimide **8** is treated under high dilution conditions with



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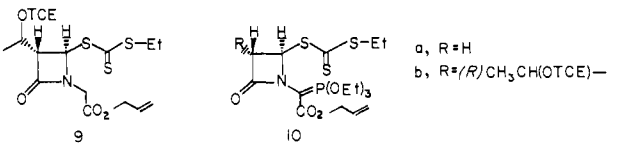
triethyl phosphite in boiling chloroform.[13] The desired penem **1b** is isolated in 50% yield by a simple silica gel filtration of the reaction mixture.

The stoichiometry of the reaction requires 2 equiv of triethyl phosphite, which has to be added at a slow rate in order to obtain optimum yields of **1b**; a fast addition of the phosphite favors byproduct formation. No C_5 epimer[12] of penem **1b** was detectable in the cyclization product.

Several byproducts are formed in this reaction. Thus, chromatography of the crude reaction product afforded the isomeric 2,3-cyclopropano-γ-lactones **3b** and **4b** (12%), the reduced product **9** (7%), and the phosphite ylide **10b** (30%). Triethyl thiophosphate



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a, R=H
b, R=(R)CH_3CH(OTCE)—

and triethyl phosphate are also formed in the reaction. The stereochemistry of the cyclopropane was assigned on the basis of the chemical shift of the methine proton; thus, the methine in **4b** is deshielded by 0.21 ppm by the thione group, relative to the methine in **3b**. In the pathway **8** → **5b** → **6b** the carbene intermediate inserts intramolecularly to form **3b** and **4b** or reacts

(10) F. Ramirez, *Acc. Chem. Res.*, **1**, 168 (1968).

(11) W. Kirmse, *Chem. Ber.*, 4027 (1965).

(12) V. M. Girijavallabhan, A. K. Ganguly, S. W. McCombie, P. Pinto, and R. Rizvi, *Tetrahedron Lett.*, **22**, 3485 (1981).

(13) In a typical experiment, a solution of **7** and allyloxalyl chloride[8] in CH_2Cl_2 containing $CaCO_3$ is treated with 1 equiv of *i*-Pr_2N-Et at 10–15 °C. The mixture is then quickly washed with water and dried, and the resulting solution of **8** is diluted 50–100-fold with EtOH-free $CHCl_3$. The solution is refluxed while 2 equiv of $P(OEt)_3$ is added over a period of 2 h by using a syringe pump.

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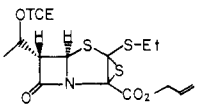
with excess triethyl phosphite to form the ylide **10b**. The reduction product **9** probably arises via reaction of **6b** with solvent.

Regarding the mechanism for the formation of penem **1b**, we propose that the carbene in **6b** adds intramolecularly to the thione group[14] to form an intermediate episulfide **11**. Since episulfides



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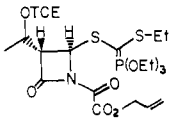
are readily desulfurized to olefins by triethyl phosphite,[15] the second molecule of the latter reagent used in the reaction desulfurizes **11** to form **1b**. The fact that **1b** is the major product when the reaction is run according to the conditions described earlier[13] implies that, among the pathways available for the carbene in **6b** to react, the rate of addition to the thione group is fast provided the intermolecular process leading to **10b** is physically controlled by adjusting the rate of addition of triethyl phosphite.

On the basis of precedents, there are two other possible mechanisms for the cyclization reaction. One of them involves an ylide intermediate **12**. Cyclic trithiocarbonates react quan-



12

titatively with triethyl phosphite to generate phosphite ylides.[16] Conceivably, if the oxalimide **3** had reacted according to this precedent to form **12**, the ylide could undergo an internal Wittig cyclization at the reactive oxalimido carbonyl to form **1b**. However, the intermediacy of **12** was ruled out on the basis of the stability of trithiocarbonates **3b**, **4b**, and **9** to further reaction with triethyl phosphite. The other mechanism is an intramolecular Wittig cyclization involving the phosphite ylide **10b**, which was isolated as a major byproduct of the reaction. No penem **1b** formation was detectable when a solution of **10b** was heated under the present reaction conditions.

In conclusion, the above described oxalimide cyclization reaction offers many advantages over Woodward's phosphorane cyclization for the synthesis of penems.[17]

Acknowledgment. We thank Professor J. Meinwald for helpful discussions on the mechanistic aspects of this work and Dr. M. Puar, R. Novotny, P. Bartner, and Dr. B. Pramanik for the spectral data.

Registry No. 1b, 80629-48-7; (±)**2**, 83248-84-4; (±)**3a**, 83248-85-5; **3b**, 83248-88-8; (±)**4a**, 83290-88-4; **4b**, 83290-89-5; **7**, 83248-86-6; **8**, 83248-87-7; **9**, 83248-89-9; **10b**, 83248-90-2; $P(OEt)_3$, 122-52-1; (allyloxy)oxalyl chloride, 74503-07-4.

Supplementary Material Available: Tables of atomic positional and thermal parameters, interatomic distances and angles, and crystal data, a view of the solid-state conformation of **4a**, and physical data of the compounds described (8 pages). Ordering information is given on any current masthead page.

(14) A. Schoenberg, B. Koenig, and E. Singer, *Chem. Ber.*, **100**, 767 (1967).
(15) N. P. Neureiter and P. G. Bordwell, *J. Am. Chem. Soc.*, **81**, 578 (1959).
(16) E. J. Corey and G. Markl, *Tetrahedron Lett.*, 3201 (1967).
(17) For example, the conversion of **2** to **1b** by the Woodward route[12] requires four separate intermediate steps, three chromatographies, and proceeds in approximately 25% overall yield. C_5 epimer formation and the number of days needed for completion of this reaction sequence are important drawbacks in the phosphorane route. The present oxalimide cyclization is essentially a one-step operation, since **8** need not be isolated, it proceeds in high yields with no epimer formation, and the process can be completed in a few hours.

An Ion Gate Membrane: Electrochemical Control of Ion Permeability through a Membrane with an Embedded Electrode

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Resistance to transport of ions across membranes, classically studied by dc resistance[1] and ac impedance methods,[2] is influenced by many factors, including the ion size, charge and concentration, the presence of carrier species (i.e., antibiotics in lipid bilayers), and of course the nature of the membrane. A membrane can be fabricated to have certain characteristics such as low resistance to transport of small ions and high resistance to large ions (dialysis), but once prepared, the membrane characteristics are fixed. Until now, no membrane has been devised whose resistance to ion transport between two contacting solutions could be varied in situ without altering the contacting solution conditions such as changing pH or adding carrier species. We report here development of a membrane in which the ionic resistance as measured by impedance methods can be dynamically varied by electrochemical control of redox states within the membrane.

Ion movement through membranes containing fixed ionic sites is dependent on the nature and number of such charged sites; changing these factors will change the membrane ionic resistance. If the charge on an ionic polymer site is altered by an electrochemical reaction, such an electrochemical reaction can be made the basis for changing the membrane resistance. The most drastic effect is expected on going between charged and neutral membranes. Poly(vinylferrocene), poly(tetrathiafulvalene), and poly(pyrrole) are examples of redox polymers whose films, deposited on solid electrodes, can be cycled electrochemically between charged-site and neutral states. All of these materials show electrochemical evidence of ion exclusion upon reduction to the neutral polymer.[3-6] Impedance measurements[5] of a film of poly(pyrrole) electrochemically polymerized onto platinum show that the neutral (reduced) polymer has a much higher resistance in 1.0 M aqueous KCl solution than the charged (oxidized) polymer.

The preceding films[3-6] were deposited on solid, nonporous electrodes. If a porous electrode is instead embedded *inside* a redox polymer membrane, and this membrane/electrode is used to separate two pools of electrolyte solution, control of the ion flow *through* the membrane can be achieved by control of the polymer redox state. To demonstrate this, we used a gold minigrid sheet (Buckbee-Mears 2000 lpi), epoxied between two glass slides predrilled with 0.24-cm^2 area holes, as the porous electrode and electropolymerized poly(pyrrole) as the redox membrane. Anodic polymerization of pyrrole as described by Diaz[6] (except with 0.1 M TEAP instead of 0.1 M $TEABF_4$ as supporting electrolyte) was carried out for ca. 6 min to fill the holes in the gold minigrid with polymer as seen by optical and scanning electron microscopy (total thickness ca. 15 μm). The resulting freshly prepared electrode/membrane was mounted in the cell (see Figure 1), and the change in its in-phase impedance at 2 Hz (which is proprotional to the ionic resistance) was monitored by using two large area Pt electrodes (a) and a PAR HR-8 lock-in amplifier. As shown by Buck and co-workers,[2] a cell like this with pools of non-redox-active ionic conductors (electrolyte solution) blocking

(1) Tiravanti, G. *J. Membr. Sci.* **1981**, *9*, 229.
(2) Buck, R. P. *Ion-Sel. Electrode Rev.* **1982**, *4*, 3-74.
(3) Daum, P.; Murray, R. W. *J. Electroanal. Chem.* **1979**, *103*, 289.
(4) Kaufman, F. B.; Schroeder, A. H.; Engler, E. M.; Kramer, S. R.; Chambers, J. Q. *J. Am. Chem. Soc.* **1980**, *102*, 483.
(5) Bull, R. A.; Fan, F. F.; Bard, A. J. *J. Electrochem. Soc.* **1982**, *129*, 1009.
(6) (a) Diaz, A. F.; Castillo, J. J.; Logan, J. A.; Lee, W. Y. *J. Electroanal. Chem.* **1981**, *129*, 115. (b) Diaz, A. F.; Vallejo, J. M.; Duran, A. M. *IBM J. Res. Develop.* **1981**, *25*, 42.

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