Silver-Assisted 1,2-Cleavage of Penicillins. A Three-Step Synthesis of Optically Active Penems

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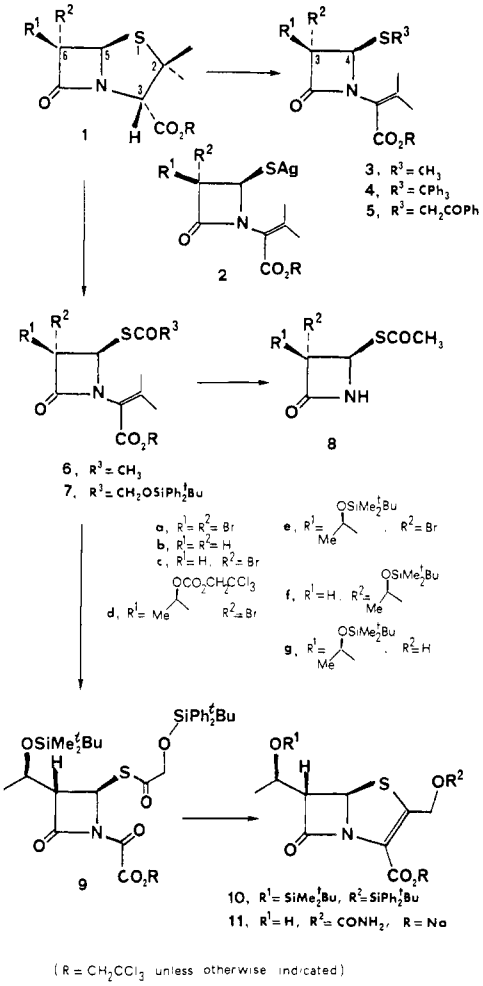
The use of penicillins as a cheap, natural source of optically active synthons for assembling new β-lactam antibiotics strongly relies on the sulfoxide–sulfenic acid thermal equilibration.[1] Ring-opening reactions at the sulfide level are comparatively few, and those entailing retention of the sulfur atom, i.e., the base-promoted S-alkylation and S-acylation, are severely limited in scope. Thus the former (Nayler reaction[2]) succeeds only on few substrates and with certain of the more reactive alkylating agents. The latter is embodied in the anhydropenicillin rearrangement,[3] and its intermolecular version has only a single, unattractive literature precedent.[4]

Since silver 2-oxoazetidine 4-mercaptides are stable compounds amenable to alkylation[5] and acylation,[6] we were intrigued by the potential feasibility of a direct conversion of penicillins **1** into salts **2**. It is known that the thiazolidine ring of penicillins is cleaved by mercuric acetate in hot acetic acid,[7] but the postulated sulfonium salt intermediate undergoes 1,5-fission, and an external nucleophile enters at C_5. We argued that such heavy-metal sulfonium intermediates could be led by a strong nonnucleophilic base to preferential 1,2-bond fission.

Treatment of the 6,6-dibromopenicillanate **1a** with $AgNO_3$ and DBN (MeCN, 3 h room temperature) resulted in the formation of a new, polar compound; **6a**, $[\alpha]_D$ +68.4° ($CHCl_3$), was obtained (82%) upon addition of acetyl chloride to the crude reaction mixture (Scheme I). The primary product **2a**, $[\alpha]_D$ +36°, could be isolated by aqueous workup and chromatography and proved identical with a sample obtained by silver-assisted methanolysis[8] of thio ester **6a**. An electron-withdrawing carboxylate was essential for a reasonably fast and clean ring-opening reaction, the observed reactivity order on varying R being trichloroethyl > *p*-nitrobenzyl > methyl > *tert*-butyl; i.e., **1a** → **2a**, approximate percent conversion, hours: TCE, 85%, 3; pNB, 45%, 3; Me, 20%, 3; *t*-Bu, 15%, 48.

Substitution of methyl iodide for acetyl chloride led to thioether **3a**, $[\alpha]_D$ +54° (56%), this new penicillin cleavage can duplicate Nayler's results; however, comparison with the latter reveals important differences. First, the silver-mediated reaction appears to be wider in scope, allowing a variety of substrates and alkylating agents to be combined. In fact, in addition to **1a**, the differently substituted penicillanates **1b–f** were successfully[9] cleaved ($AgNO_3$, DBN, MeCN) and the resulting products **2b–f** assessed after their in situ conversion (AcCl, 30 min) into thio esters **6** (diastereomerically pure by NMR spectroscopy; $[\alpha]_D$ 1% in $CHCl_3$ reported when enantiomers are possible): **6b**, $[\alpha]_D$ +79°, 60 h, 0 °C, 52%; **6c**, $[\alpha]_D$ +57°, 60 h, 0 °C, 86%; **6d**, 6 h, 20 °C, 88%; **6e**, 3 h, 20 °C, 85%; **6f**, 48 h, 0 °C, 55%. Alkylating agents reactive toward silver thiolate **2a** (MeCN, 20 °C) included trityl chloride and bromoacetophenone:[10] **4a**, $[\alpha]_D$ −25°, 62%; **5a**, $[\alpha]_D$ +49°, 48%.

Scheme I



Still, in view of the crucial role played by the azetidinone C_4 configuration upon antibacterial activity, the most relevant difference with Nayler reaction is that while the latter, as recently reported,[11,12] proceeds with loss of stereochemical integrity at this center, the new penicillin cleavage apparently does not. To better check this point, a 6-unsubstituted and a 6β-substituted substrate were closely examined. Starting from **1b**, **6b** was obtained as above indicated and its N-appendage conventionally removed; the optical activity observed on product **8a** well matched with the value reported by Woodward for an enantiomerically pure sample.[13] Full retention of configuration was observed even starting from the 5,6-cis arranged penicillin **1g**, wherefrom the 3,4-*cis* azetidinone **6g** was selectively obtained (60 h, 0 °C, 50%). Either a ring-opening–ring-closing process[11] or a trigonal thioaldehyde intermediate arising from a [3 + 2] cycloreversion[12] has been invoked to account for the loss of optical activity observed in Nayler's products; the stereoselectivity of the new reaction is suggestive of a different mechanism, presumably a β-eliminative pathway operating on a first-formed sulfonium salt which does not undergo reversible 1,5-dissociation.

A short, conservative route to FCE 22101 (**11**) and related penems[14] ensued from these findings. The protected 6-hydroxy-

(1) Cooper, R. D. G.; Koppel, G. A. In "Chemistry and Biology of β-Lactam Antibiotics"; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; pp 1–92.
(2) Brain, E. G.; McMillan, I.; Nayler, J. H. C.; Tolliday, P. *J. Chem. Soc., Perkin Trans. 1* **1975**, 562–567.
(3) Wolfe, S. *Can. J. Chem.* **1968**, *146*, 459–461.
(4) Mantovani, E.; Barbini, M.; Bassignani, L.; Brandt, A.; Re, L.; Settembri, L. *Gazz. Chim. Ital.* **1977**, *107*, 207–212.
(5) Lattrel, R. *Justus Liebigs Ann. Chem.* **1974**, 1361–1390.
(6) Longo, A.; Lombardi, P.; Gandolfi, G.; Franceschi, G. *Tetrahedron Lett.* **1981**, *22*, 355–358.
(7) Stoodley, R. J.; Whitehouse, N. R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 32–35.
(8) Lattrel, R. *Justus Liebigs Ann. Chem.* **1974**, 1937–1954.
(9) Under Nayler conditions, **1b** and **1c** underwent preferential β-elimination at 5,6, while **1e** is reported as unreactive.
(10) Bromo ketones failed to react under Nayler conditions: Nayler, J. H. C.; Pearson, M. J.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1973**, 57–58.
(11) Hirai, K.; Iwano, Y.; Fujimoto, K. *Heterocycles* **1982**, *117*, 201–207.
(12) Mak, C.-P.; Fliri, H. *Tetrahedron Lett.* **1985**, *26*, 1433–1436.
(13) Ernest, I.; Gosteli, J.; Woodward, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 6301–6305.

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ethyl penicillanate **1f** was added to a MeCN solution of $AgNO_3$ and DBN (1 mol equiv of each, 48 h, 0 °C in the dark, N_2) followed by [(*tert*-butyldiphenylsilyl)oxy]acetyl chloride (1 h, 20 °C), to yield thio ester **7f** (55%). Ozonolysis (CH_2Cl_2, −70 °C) and reductive workup (Me_2S) afforded the oxoamide **9** (92%); penem **10** was thence obtained by plain heating with triethyl phosphite (2 mol equiv, 9 h refluxing toluene, 80%),[15] thus completing a straightforward, three-step penam–penem conversion. Further manipulation of this key intermediate toward the target compound conformed to a well-established pattern.[16,17]

Supplementary Material Available: A listing of physical properties of new compounds **1–7**, **9**, and **10** (6 pages). Ordering information is given on any current masthead page.

(14) Franceschi, G.; Foglio, M.; Alpegiani, M.; Battistini, C.; Bedeschi, A.; Perrone, E.; Zarini, F.; Arcamone, F.; Della Bruna, C.; Sanfilippo, A. *J. Antibiot.* **1983**, *35*, 938–941.
(15) Battistini, C.; Scarafile, C.; Foglio, M.; Franceschi, G. *Tetrahedron Lett.* **1984**, *25*, 2395–2398.
(16) Alpegiani, M.; Bedeschi, A.; Perrone, E.; Franceschi, G. *Tetrahedron Lett.* **1984**, *25*, 4171–4174.
(17) FCE 22101 was obtained from its trichloroethyl ester by hydrolysis with activated Zn in THF–pH 4.2 phosphate buffer.

Effects of Molten Salts on Reactions. Nucleophilic Aromatic Substitution by Halide Ions in Molten Dodecyltributylphosphonium Salts[1]

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Organic molten salts have found limited use as solvents and reactants for organic reactions.[2-4] One should expect enhanced nucleophilicity in such media when the anionic portion is also a nucleophile[2,5,6] although the nature of the fused salts themselves could have a significant effect on relative reactivities.[7] A second potential advantage lies in the salts' apparent ability to stabilize charged intermediates or transition states by ion–ion interactions.[8] We report herein on studies of nucleophilic aromatic substitution reactions.

Table I (entries 1–4) contains rate constants measured for the reaction in eq 1.[9] The salts **2** were prepared from the commercially available tributyl phosphine and alkyl halides and were chosen simply because all of them melt below 40 °C.[10] Hammett plots give reasonable fits to straight lines and yield ρ values of +1.5 and 1.1 for σ and σ^-, respectively. Alternatively, one can postulate that the data represent a curved plot. Nonetheless, the small effects of the para groups G are substantially lower than those in the literature for reactions proceeding through the S_NAr mechanism.[11] These generally range from +3 to +5 with a few as high as +8 and are cases in which Meisenheimer complexes have been invoked. Our data suggest a transition state that is much earlier with respect to carbon–nucleophile bond formation in which only a small portion of the anionic charge can be interacting with the G group. If we assume a limiting ρ value of ~+4, our data suggest a transition state with about one-third C–X bond formation.

$$\text{G–Ph–OTs} + n\text{-dodecyl}(n\text{-Bu})\text{P}^+\text{X}^- \xrightarrow{100\ ^\circ\text{C}} \text{G–Ph–X} \quad (1)$$

1a, G = NO_2; **1b**, G = CO_2Et; **1c**, G = H; **1d**, G = OCH_3

2a, X = Cl; **2b**, X = Br; **2c**, X = I

3

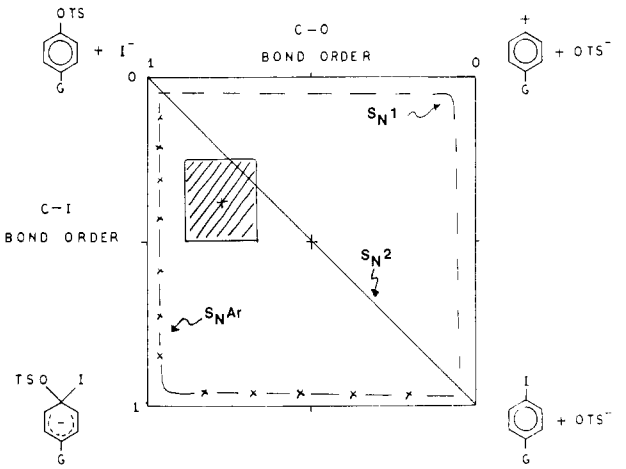

Figure 1. Projection of a three-dimensional potential energy surface for nucleophilic aromatic substitution. Limiting reaction pathways are indicated. The crosshatched rectangle represents the location of the transition state from this work.

Table I (entries 1, 5, 6) represent data from the reaction in eq 2 in which a substituent effect on the leaving group is probed.[9]

$$\text{NO}_2\text{–Ph–OSO}_2\text{–Ph–Y} + \mathbf{2c} \xrightarrow{100\ ^\circ\text{C}} \text{NO}_2\text{–Ph–I} \quad (2)$$

1a, Y = *p*-Me; **5**, Y = *p*-Br; **6**, Y = *m*-NO_2

The ρ value is +0.22 and thus implies that there is some sensitivity of the transition state to the substituent Y on the leaving group. We interpret it as the development of a partial negative charge on the leaving group that arises from some C–O bond breaking. The small magnitude of the ρ value makes its absolute certainty somewhat debatable because of the question of scatter in the rates, even though there is a good linear fit. Likewise, it is difficult to get unequivocal values for the limiting cases of ρ. We suggest $\rho \approx +1$ for the S_N1 equivalent (complete C–O bond scission) and $\rho \approx 0$ for the case of the addition complex in which we postulate

(1) Taken in part from the dissertation of S.E.F., 1985; preliminary results were reported at the National ACS Meeting: *Abstr. Pap.-Am. Chem. Soc.* **1985**, *189th*, ORGN 198.
(2) Gordon, J. E. In "Techniques and Methods of Organic and Organometallic Chemistry"; Denney, D. B., Ed.; Dekker: New York, 1969; pp 51–188.
(3) "Molten Salt Techniques"; Lovering, D. G., Gale, R. J., Eds.; Plenum Press: New York, 1983; Vol. 1.
(4) "Advances in Molten Salt Chemistry"; Braunstein, J., Mamantov, G., G. P. Smith, G. P., Eds.; Plenum Press: New York, 1971, 1973, 1975, 1981, 1984; Vols. 1–5.
(5) Gordon, J. E. "The Organic Chemistry of Electrolyte Solutions"; Wiley-Interscience: New York, 1975; pp 170–174, 440–441.
(6) Gordon, J. E.; Varughese, P. *J. Chem. Soc., Chem. Commun.* **1971**, 1160.
(7) Ford, W. T.; Hauri, R. J.; Smith, S. G. *J. Am. Chem. Soc.* **1974**, *96*, 4316.
(8) We saw little evidence for such an effect in a series of aliphatic substitution reactions conducted on neat oxyphosphonium salts where reactions, at primary and even at secondary carbons, occurred almost exclusively via a S_N2 pathway. Fry, S. E.; Pienta, N. J. *J. Org. Chem.* **1984**, *49*, 4877–4880.
(9) A 2-mL solution of 1–3 mol % of **1** in **2** was placed in a constant-temperature oil bath (100 ± 1 °C). Aliquots were removed by syringe and analyzed by liquid chromatography (C18 reversed-phase column, hexane–methanol–glyme mixtures as eluent) for the appearance of products. Detection was accomplished by absorption at 254 nm and converted to concentration using calibration samples. A single preparation of phosphonium salt generally served as solvent for three replicate runs each done for four different substrates (one substrate per vial). This was repeated 3 times for each entry, and, thus, the rate constants are an average of at least nine separate independent kinetics experiments. Rate constants were extracted as slopes from the linear regression analysis of the appropriate integrated rate expression using 5–8 samples at successive times.
(10) Beck, P. In "Organic Phosphorus Compounds"; Wiley: New York, 1972; Vol. 2, Chapter 4, p 189.
(11) Miller, J. "Aromatic Nucleophilic Substitutions"; American Elsevier: New York, 1968; (linear free energy relationships) p 65–75, (halide relative reactivity) pp 194–200, 316–8.
(12) "Advances in Linear Free Energy Relationships"; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1972.

0002-7863/85/1507-6399$01.50/0