Tetrahedron Letters,Vol.23,No.47,pp 4903-4906,1982 0040-4039/82/474903-04$03 00/0
Printed in Great Britain

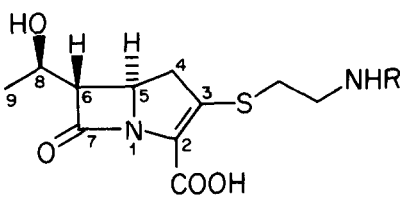
A DIRECT TRANSFORMATION OF BICYCLIC KETO ESTERS TO N-FORMIMIDOYL THIENAMYCIN

I Shinkai*, R A Reamer, F W. Hartner, T Liu and M. Sletzinger

Department of Process Research
Merck Sharp & Dohme Research Laboratories
Rahway, New Jersey 07065, U S A

Summary A convenient direct transformation of p-nitrobenzyl 6-(1'-hydroxyethyl)-1-azabicyclo-(3.2 0)heptane-3,7-dione-2-carboxylate to N-formimidoyl thienamycin utilizing the silylated derivative of N-formimidoyl cysteamine is described

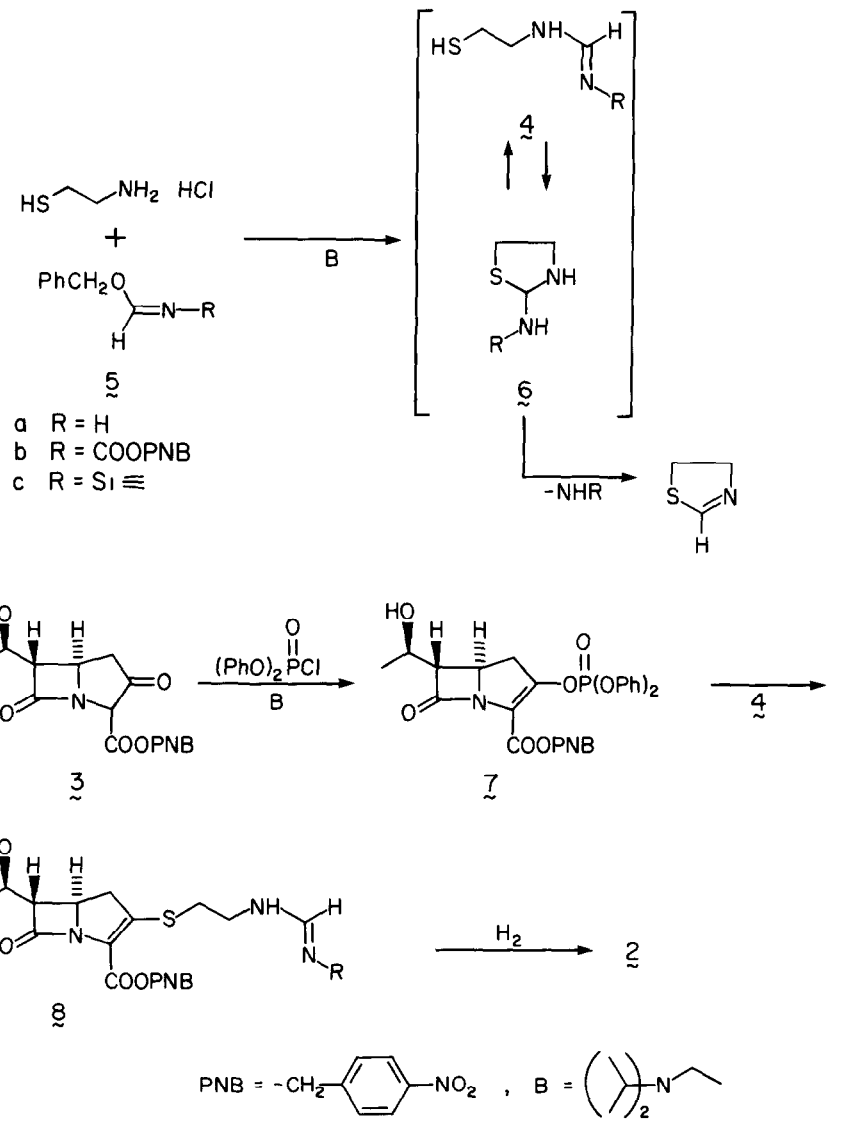
Derivatization of the amino group in thienamycin[1] (1) has resulted in the stable crystalline N-formimidoyl thienamycin[2] (2). The derivative (2) was selected for clinical studies on the basis of its improved *in vitro* and *in vivo* antibacterial activity and chemical stability versus thienamycin, as well as its enhanced *in vivo* activity against Pseudomonas aeruginosa[3] The current synthesis of 2 relies on the derivatization of unstable 1 with methyl formimidate in an aqueous solution at pH 8 2 followed by isolation using a Dowex 50 x 4 resin column We now wish to report a convenient direct transformation of p-nitrobenzyl 6-(1'-hydroxyethyl)-1-azabicyclo(3 2.0)heptane-3,7-dione-2-carboxylate (3)[4] to 2 without forming unstable thienamycin In principle, the direct transformation of 3 to 2 requires the prior preparation of N-formimidoyl cysteamine (4a) This proved to be a formidable task The attempted reaction of cysteamine with benzyl formimidate hydrochloride[5] (5) in acetonitrile in the presence of N,N-diisopropylethylamine afforded Δ^2-thiazoline and s-triazine as the only isolable products under various reaction conditions[6]. The formation of Δ^2-thiazoline indicates the formation of 4a with subsequent elimination of ammonia *via* the cyclic tautomer (6) To inhibit this elimination and maintain the stability of 4, the reaction of the N-protected benzyl formimidate with cysteamine was investigated The reaction of N-(N'-p-nitrobenzyloxycarbonyl)benzyl formimidate (5b), obtained *in situ* from the reaction of 5a with p-nitrobenzyl chloroformate in acetonitrile in the presence of N,N-diisopropylethylamine, with cysteamine gave crystalline 4b (mp 50-58°C) in 56% yield accompanied with Δ^2-thiazoline Although ^{1}H NMR of 4b at ambient temperature showed no SH signal, low temperature studies (-35°C) did show an SH triplet. In addition, the tlc of 4b (SiO_2/hexane ethyl acetate = 6 4 v/v, Rf = 0 36) indicated a positive test against Ellman's reagent suggesting the existence of an SH group



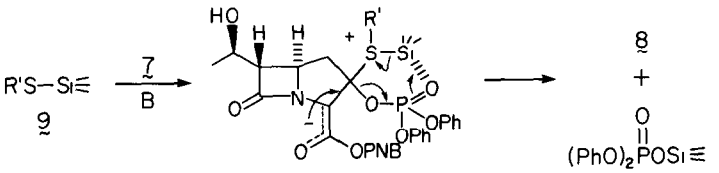
(8R,6S,5R)

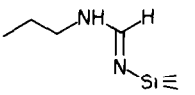
1 · R = -H
2 R = -CH=NH

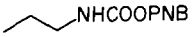
Based on carbon-13 NMR studies the product was tentatively assigned as an equilibrium mixture of N-(N'-p-nitrobenzyloxycarbonyl)formimidoyl cysteamine (4b) and 2-N-(p-nitrobenzyloxycarbonyl)-aminothiazolidine 6b This type of ring-chain tautomerism has previously been reported in the case of thiazolidines[7] and imidazolidines[8] It was reasoned that this equilibrium could be displaced by capturing the open chain form with enol phosphate (7) This was indeed the case. The reaction of the equilibrium mixture with 7 gave N-formimidoyl thienamycin (2) in 54% yield[9] after removal of the p-nitrobenzyl protecting group by catalytic hydrogenation. Unfortunately, decomposition of 4b due to the intramolecular elimination[10] of p-nitrobenzylcarbamate to form Δ^2-thiazoline is still significant



Our efforts were therefore directed at the protection of the sulfhydryl function with a trimethylsilyl group[11] in order to inhibit the cyclization of 4b to form the cyclic-intermediate (6b) Thus, the reaction of 5a with bis(trimethylsilyl)acetamide (BSA) gave a quantitative transformation to the N-trimethylsilyl iminoether (5c). The structure of 5c was confirmed by in situ ^{1}H- and ^{13}C-NMR studies In addition, it was found that 5c was reasonably stable at room temperature and only slowly trimerized to s-triazine. The reaction of 5c with monosilylated cysteamine, obtained from cysteamine and BSA, gave N,S-bistrimethylsilyl-N-formimidoyl cysteamine (9a). Indeed, a ^{13}C-NMR study indicated no evidence for the existence of the cyclic form of 9a. Since the silylated derivative (9a) was relatively stable the insertion reaction with 7 was studied However, no insertion reaction of 7 with 9a was observed in the absence of



a R' = 

b R' = 

base On the other hand, an excellent transformation of 7 to 8c was obtained when this reaction was carried out in the presence of N,N-diisopropylethylamine or 4-dimethylaminopyridine. In addition, N-formimidoyl thienamycin (2) was obtained in 63% yield after catalytic hydrogenation of the protecting group[12]. This result suggested that the base expanded the tetravalent silicon atom to a pentavalent bipyramidal hybridization thereby making the sulfur atom more nucleophilic Similarly, the reaction of 7 with 9b in acetonitrile gave an almost quantitative yield of bis-protected thienamycin[13]. This new process obviates both the formation of unstable thienamycin and the need for protection with p-nitrobenzyl chloroformate which is difficult to handle in a large scale operation

References and Notes

1 The structure and absolute configuration of thienamycin. Albers-Schonberg, G., Arison, B H , Hensens, O D , Hirschfield, J , Hoogsteen, K., Kaczka, E A , Rhodes, R E , Kahan, J. S , Kahan, F. M., Ratcliffe, R. W , Walton, E., Ruswinkle, L. J , Morin, R B , Christensen, B. G , J Am Chem Soc , 1978, 101, 6491

2 Leanza, W J , Wildonger, K J , Miller, T W , Christensen, B G., J Med Chem , 1979, 22, 1435

3 Kropp, H , Sundelof, J G., Kahan, J S , Kahan, F. M , Birnbaum, J , Antimicrob. Agents Chemother , 1980, 17, 993. Related activity of 2, see, Rolfe, R D., Finegold, S M , Antimicrob Agents Chemother , 1981, 20, 600

4 For a practical synthesis of 3 from diethyl 1,3-acetonedicarboxylate and its conversion to thienamycin, see, Melillo, D. G , Shinkai, I., Liu, T , Ryan, K M., Sletzinger, M , Tetrahedron Lett., 1980, 21, 2783, Melillo, D G , Liu, T , Ryan, K. M , Sletzinger, M., Shinkai, I , Tetrahedron Lett , 1981, 22, 913 Sletzinger, M., Liu, T , Reamer, R A , Shinkai, I., Tetrahedron Lett , 1980, 21, 4221 The preparation of optically active 3 (8R,6S,5R) via an acetonedicarboxylate route has been presented by Dr S H Pines of our laboratories at the Third International I U P A.C Symposium on Organic Synthesis, University of Wisconsin, Madison, June 1980 A stereocontrolled synthesis of (+)-thienamycin, see, Salzmann, T N , Ratcliffe, R W , Bouffard, F A , Christensen, B G , J Am. Chem Soc., 1980, 102, 6161 Karady, S , Amato, J. S , Reamer, R A , Weinstock, L. M ,J Am Chem Soc , 1981, 103, 6765 The stereochemical descriptors refer to the atoms that are to become 8, 6 and 5 of thienamycin, respectively

5 The use of benzyl formimidate hydrochloride during the derivatization of thienamycin, Volante, R , Wilson, K , and Hazen, G , submitted for publication

6 In situ ^{13}C NMR study suggested that s-triazine was formed as a result of oligomerization of benzyl formimidate free base in acetonitrile on standing. Similar oligomerizations of alkyl imidates have been previously reported See, Schaefer, F. C , Peters, G A , J. Org Chem , 1961, 26, 2778

7 Szilagyi, L , Gyorgydeak, Z., J Amer Chem Soc , 1979, 101, 427.

8 Witek, S , Bielawska, A., Bielawski, J , Heterocycles, 1980, 14, 1313

9. Yield of 2 was established by the HPLC, column, Waters' C-18-microbondapak, flow rate, 1 2 ml/min , U V detection, 299 nm, eluent, 5% acetonitrile in deionized water. We thank Mr M Davis and his group for the HPLC assay of 2.

10 Intramolecular elimination of p-nitrobenzylcarbamate can be envisioned to proceed via a six-membered transition state

11 For the use of trimethylsilyl in situ protection of the sulfhydryl group in the preparation of N-protected cysteamine, see, Sletzinger, M., Liu, T , Reamer, R A , Shinkai, I , Synthesis, 1980, 924

12 Recently, we found that this transformation can be carried out without the trimethylsilyl protecting groups to give N-formimidoyl thienamycin in 68% overall yield

13 Sletzinger, M., Liu, T Reamer, R A. Shinkai, I., Tetrahedron Lett., 1980, 21, 4221

14 All new compounds have been fully characterized and their spectral data are in accord with their assigned structure All chemical shifts are reported with respect to internal Me_4Si (δ=0) Selected C^{13} NMR data 8a, $\delta(CD_3)_2CO$, 22 2(C9), 31 2(SCH_2), 40.8(C_4), 42 2(CH_2N), 53 5(C_5), 65 4, 66 2(-OCH_2-), 65 7(C_8), 67 9(C_6), 124 3(C_2), 150 2(C_3), 161.4(CO_2R), 162.3 (CH=N), 164 7(NCOO) and 177 6(C_7). 4b, δ(DMSO-d_6), 22 6(CH_2S), 44 0(CH_2N), 65 1(OCH_2), 161 1 (CH=N, ^1J=178 Hz) and 163.7(-CO_2R). 6b, δ(DMSO-d_6), 35 6(CH_2S), 50 2(CH_2N), 64 3(OCH_2), 77.6 >CH-(^1J=167 Hz), 154 2(-CO_2R) Δ^2-thiazoline δ(DMSO-d_6), 30.7(CH_2S), 63.8(CH_2N), and 156 3 (CH=N, ^1J=206 Hz)

(Received in USA 19 August 1982)