Tetrahedron Letters No. 48, pp 4631 - 4634.
0040-4039/79/1122-4631$02.00/0

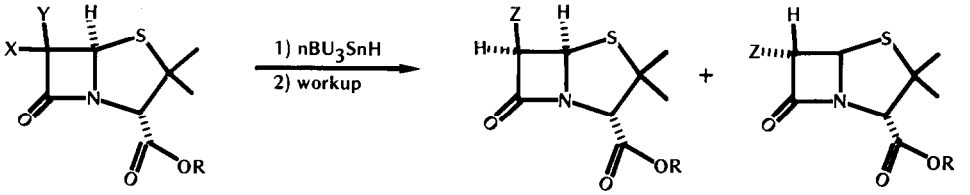
STEREOSELECTIVE SYNTHESIS OF 6β-SUBSTITUTED PENICILLANATES

Jules A. Aimetti, Ernest S. Hamanaka, David A. Johnson
and Michael S. Kellogg*
Pfizer Central Research,
Pfizer Inc.
Groton Connecticut 06340

Summary: Reduction of 6-substituted-6-halopenicillanates with tri-n-butyltin hydride can produce stereoselectively 6β-substituted derivatives.

Interest in the preparation of β-lactam antibiotics has been stimulated by the discovery of novel substances which maintain very interesting enzyme inhibitory properties in spite of the conspicuous absence of a 6β-amido side chain.[1] During an investigation of the biological properties of penicillanate congeners, we were confronted by the problem of stereoselective production of 6β- and 6α-substituted analogs. We, as well as others, have recently developed procedures which allow regio - and stereoselective aldolization at C-6 of the penicillin nucleus.[2] These methods yield adducts which retain a bromine atom at this position, a feature which we felt could be exploited to elicit stereocontrol at C-6. Preparation of the more hindered 6β-substituted isomers has proven a significant challenge to organic chemists. In fact, many of the more recent penicillin (and particularly cephalosporin) total syntheses[3] rely on a kinetic protonation scheme that Firestone and his coworkers developed several years ago in order to obtain the required stereochemistry at C-6(7).[4] Procedures useful for the synthesis of 6β-alkyl substituted penicillanates have generally relied on hydrogenation of the corresponding 6-alkylidene penam,[5] while reductive procedures involving catalytic hydrogenation or dissolving metals on derivatives featuring a 6-bromo substituent have consistently produced 6α-substituted penicillanates as the major isolated products.[2] We now wish to report that tri-n-butyltin hydride (n-Bu_3SnH) reduction of 6-halo penicillanates leads to the stereoselective production of 6β-substituted penicillanates in moderate to excellent yields.[6]

Kuivila has reviewed the use of n-Bu_3SnH as a selective reducing agent toward halogen.[7] Such reductions have proven selective in terms of functional group tolerance but are less predictable in stereoselectivity, although somewhat so for reductions of gem-dihalo cyclopropane derivatives.[8] We examined the reduction of trimethylsilyl 6,6-dibromo penicillanate 1[9] with tri-n-butyltin hydride. Stirring 1 with n-Bu_3SnH in benzene or toluene at room temperature gave, after hydrolysis of the ester and sodium salt formation, a 30% yield of the pure sodium salt of the potent β-lactamase inhibitor 6β-bromopenicillanic acid 2.[10] The course of the reduction could be monitored by pmr spectroscopy which indicated that less than 5% of the α-bromo epimer 3 was formed and that the major side reaction was overreduction to penicillanic acid 4.



	X	Y	R
1	Br	Br	$Si(CH_3)_3$
5	CH_3O	Br	CH_2Ph
8	Cl	I	$Si(CH_3)_3$
11	$(S)CH_3CHOH$	Br	CH_2Ph
13	Br	$(R)CH_3CHOH$	CH_2Ph

	Z	R	
2	Br	H	3
4	H	H	
6	CH_3O	CH_2Ph	7
9	Cl	H	10
12	$(S)CH_3CHOH$	CH_2Ph	
14	$(R)CH_3CHOH$	CH_2Ph	

More vigorous conditions were required to effect the transformation of benzyl-6β-bromo-6α-methoxy penicillate 5[11] to the dehalogenated product. In this instance refluxing a solution of 5 in benzene with an excess of n-Bu_3SnH produced a 3:1 mixture of 6β- to 6α-methoxy penicillanates (6 to 7) in nearly quantitative yield, the stereochemistry being deduced from the characteristic coupling constants of the β-lactam protons.[12]

Taking note that relative rates of halide reduction by n-Bu_3SnH follow the order of I>Br>Cl,[7,8] we also investigated the reduction of the trimethylsilyl ester of 6-iodo-6-chloropenicillanic acid 8. Preparation of 8 was accomplished through diazotization of 6-amino penicillanic acid in the presence of ICl.[9] Reduction of 8 with n-Bu_3SnH in benzene at reflux followed by hydrolytic workup produced 6β-chloropenicillanic acid 9[13] and substantial 6α-chloro epimer 10 (~25%) in 39% overall yield. This result suggested to us that perhaps reduction of 1 was not truly stereoselective but that the absence of the 6α-bromo epimer 3 might be due to its further rapid reduction to 4.

That this was not the case was proven by reduction of an equimolar mixture of 1 and 3 under the same conditions reported above. Monitoring of the reaction by pmr showed the rapid disappearance of 1 with production of 2 and 4 while 3 remained.

The capacity for excellent stereocontrol in the tin hydride reduction was best exemplified by extension of the reduction to benzyl 6-bromo-6-hydroxyethyl substituted penicillanates. Treatment of benzyl 6β-bromo-6α-[1(S)hydroxyethyl]penicillanate 11[2] with n-Bu_3SnH in benzene at reflux gave in 95% yield benzyl 6β-[1(S)-hydroxyethyl]penicillanate 12,[2] after chromatography on silica gel. In the same manner benzyl 6α-bromo-6β-[1(R)-hydroxyethyl]penicillanate 13 produced benzyl 6β-[1(R)-hydroxyethyl]penicillanate 14.[2] Neither reaction produced the α-epimer in detectable amounts. Regardless of the stereochemistry of bromine prior to reduction, hydrogen atom transfer takes place from the less hindered side of the molecule, even though significant non-bonded interactions are produced in the product.

These observations are consistent with approach of the very bulky n-Bu_3SnH at the unencumbered convex face of the cup-shaped penicillin molecule to trap the intermediate radical.

The excellent β-lactamase enzyme inhibitory properties of 2 have been disclosed by others,[10] however, these workers have not reported a preparation of material uncontaminated by the inactive epimer 3. The procedure described in this communication has proven quite general for the preparation of β-substituted penicillanates.

REFERENCE AND NOTES

1(a) Albers-Schonberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczku, E. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, R.; Ruswinkle, L. J.; Morin, R. B. and Christensen, B. G., J. Amer. Chem. Soc., 100, 6491 (1978).

(b) Brown, A. G.; Corbett, D. F.; Eglington, A. J. and Howarth, T. T., Chem. Commun., 523 (1977).

(c) Meada, K.; Takahashi, S.; Sezaki, M.; Iinuma, L.; Naganowa, H.; Kondo, S.; Ohno, M. and Umezawa, H., J. Antibiot., 30, 770 (1977).

(d) Johnston, D. B. R.; Schmidt, S. M.; Bouffard, F. A. and Christensen, B. G., J. Amer. Chem. Soc., 100, 313 (1978).

(e) Shih, P. H.; Hannah, J. and Christensen, B. G., J. Amer. Chem. Soc., 100, 8004 (1978).

(f) Cama, L. D. and Christensen, B. G., ibid., 100, 8006 (1978).

(g) Kahan, J. S.; Kahan, F. M.; Geogleman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H. B. and Birnbaum, J., J. Antibiot., 32, 1 (1979).

2(a) DiNinno, F.; Beattie, T. R. and Christensen, B. G., J. Org. Chem., 42, 2960 (1977).

(b) Aimetti, J. A.; Kellogg, M. S.; Tetrahedron Lett., in press (1979).

3(a) Christensen, B. G. and Ratcliffe, R. W., Annu. Rep. Med. Chem., 11, 271 (1976).

(b) Sammes, P. G., Chem. Rev., 76, 113 (1976).

4) Firestone, R. A.; Maziejewicz, N. S.; Ratcliffe, R. W. and Christensen, B. G., J. Org. Chem., 39, 437 (1974).

5(a) Sheehan, J. C.; Lo, Y. S., J. Org. Chem., 38, 3227 (1973).

(b) Sheehan, J. C.; Buku, A.; Chacko, E.; Commons, T. J.; Lo, Y. S.; Ponzi, D. R. and Shwarzel, W. L., J. Org. Chem., 42, 4045 (1977).

5(c) Applegate, H. E.; Cimarusti, C. M. and Slusarchyk, W. A., Tetrahedron Lett., 1637 (1979)

6) Subsequent to the completion of our work a report describing stereoselective production of 6β-substituted penicillanates through n-Bu_3SnH reduction of 6α-alkyl-6β-isocyanopenicillanates has appeared. Ivor John, D.; Thomas, E. J. and Tyrell, N. D., Chem. Commun., 345 (1979).

7(a) Kuivila, H. G., Adv. Organomet. Chem., 1, 47 (1964).

(b) Kuivila, H. G., Accounts Chem. Res., 1, 299 (1968).

(c) Kuivila, H. G., Synthesis, 499 (1970).

8) Seyferth, D.; Yamazaki, H.; Alleston, D. L., J. Org. Chem., 28, 703 (1963).

9) Clayton, J. P., J. Chem. Soc., C, 2123 (1969).

10(a) Loosemore, M. J.; Pratt, R. F., J. Org. Chem., 43, 3611 (1978).

(b) Pratt, R. F.; Loosemore, M. J., Proc. Natl. Acad. Sci

(c) Knott-Hunziker, B.; Orlek, B. S.; Sammes, P. G.; Waley, S., Biochem J., 177, 365 (1979).

(d) Knott-Hunziker, V.; Waley, S. G.; Orlek, B. S.; Sammes, P. G., FEBS Lett., 99, 59 (1979)

11) Cama, L. D.; Leanza, W. J.; Beattie, T. R. and Christensen, B. G., J. Amer. Chem. Soc., 94, 1408 (1972).

12) Compounds 6 and 7 were isolated as oils. 6: nmr (δ, $CDCl_3$) 7.42 (s, 5), 5.48 (d, 1, J=3.5 Hz), 5.23 (s, 2), 4.83 (d, 1, J=3.5 Hz), 4.60 (s, 1), 3.53 (s, 3), 1.65 (s, 3), 1.45 (s, 3); ir (neat) 1770, 1740 cm^{-1}. 7: nmr (δ, $CDCl_3$) 7.42 (s, 5), 5.35 (d, 1, J=1.5 Hz), 5.23 (s, 2) 4.6 (d, 1, J=1.5 Hz), 4.56 (s, 1), 3.53 (s, 3), 1.57 (s, 3), 1.45 (s, 3); ir ($CHCl_3$) 1775, 1740 cm^{-1}.

13) Roets, E.; Vlietinek, A.; Vanderhaeghe, J., J. Chem. Soc. Perkin I, 704, (1976). A 3% yield of the benzyl ester of 9 was reported by these workers.

(Received in USA 10 July 1979)