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PREPARATION AND REDUCTION OF 6-PHENYLSELENYLPENICILLANATES. A STEREOSELECTIVE SYNTHESIS OF 6β-SUBSTITUTED PENICILLANATES

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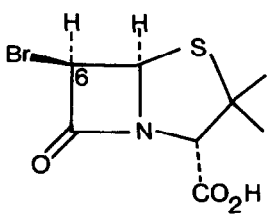
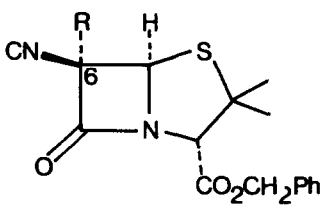
Abstract. The preparation and tri-n-butyltin hydride reduction of benzyl 6-chloro-6-phenylselenyl- and benzyl 6,6-bis(phenylselenyl)penicillanates, and related compounds, is discussed.

Since the discovery that 6β-bromopenicillanic acid (1) is an inhibitor of β-lactamase enzymes,[2] the synthesis of penicillanic acid derivatives with simple substituents in the 6β-position has become an area of considerable interest. Recently we demonstrated that the reduction of 6α-alkyl-6β-isocyanopenicillanates (2) by tri-n-butyltin hydride is stereoselective, and gives high yields of the corresponding 6β-alkylpenicillanates.[3] We here report on the use of 6-diazopenicillanates in the preparation of several 6-phenylselenylpenicillanates, and the reduction of these compounds, by tri-n-butyltin hydride,[4] to give several novel 6β-substituted penicillanic acid derivatives.

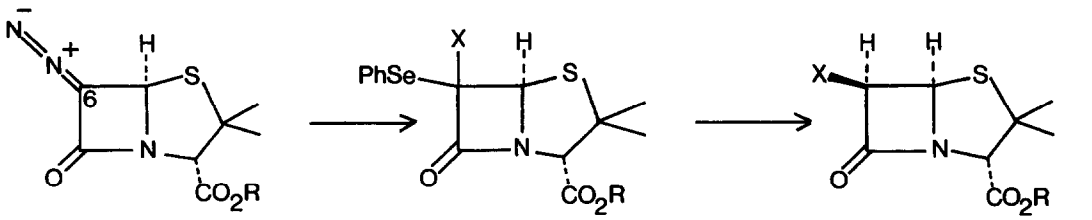


(1)



(2)

Reactions between diazo compounds and organoselenium compounds are scarcely mentioned in the literature.[5] However, it was found that 2,2,2-trichloroethyl and benzyl 6-diazopenicillanates (3) and (4) react rapidly with phenyl selenyl chloride in dichloromethane (no catalyst required) to give excellent yields of the corresponding 6-chloro-6-phenylselenylpenicillanates (5) and (6).[6] In each case, only one isomer of the 6-chloro-6-phenylselenylpenicillanate was obtained, and, although the configuration of these products at C-6 was not established, mechanistic considerations suggest that the phenylselenyl groups are in the 6β-position. The diazopenicillanates (3) and (4) also react with diphenyl diselenide in solution in dichloromethane, in the presence of $BF_3.Et_2O$ as catalyst, to give good yields of the corresponding 6,6-bis(phenylselenyl)penicillanates (7) and (8).[6] In contrast, preliminary investigations of reactions between 2,2,2-trichloroethyl 6-diazopenicillanate (3) and phenyl selenyl bromide were less successful. Complex reaction mixtures were obtained which would seem to contain several 6,6-disubstituted penicillanates, possibly including 6,6-dibromo-, 6,6-bis(phenylselenyl)-, and 6-bromo-6-phenylselenylpenicillanates, although these products could not be separated or formally characterized.



(3) R = CH_2CCl_3
(4) R = CH_2Ph

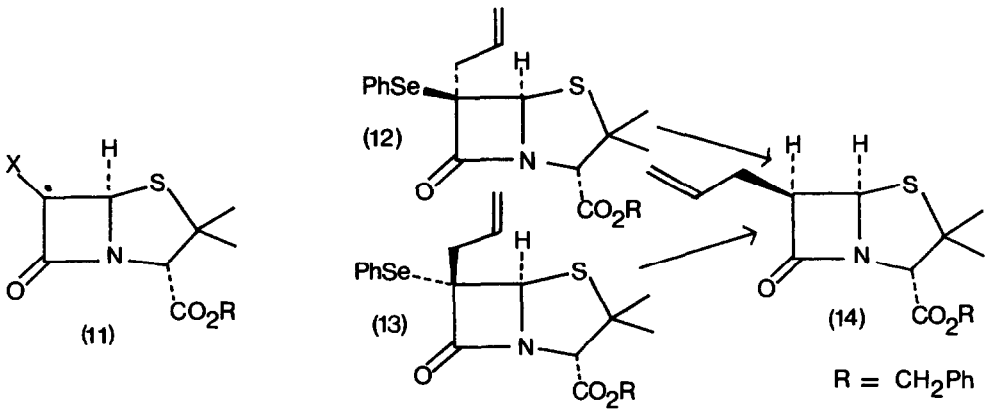
(5) X = Cl, R = CH_2CCl_3
(6) X = Cl, R = CH_2Ph
(7) X = PhSe, R = CH_2CCl_3
(8) X = PhSe, R = CH_2Ph

(9) X = Cl, R = CH_2Ph
(10) X = PhSe, R = CH_2Ph

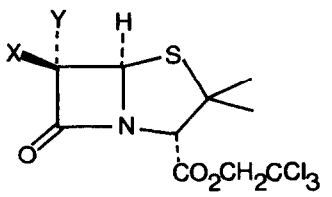
Preliminary investigations of the reduction of the 2,2,2-trichloroethyl penicillanate esters (5) and (7) using tri-n-butyltin hydride were complicated by competing reduction of the trichloroethyl ester groups. However reduction of the benzyl 6-phenylselenylpenicillanates (6) and (8) using a slight excess of tri-n-butyltin hydride in refluxing benzene in the presence of a catalytic amount of azobisisobutyronitrile was more successful, and, in each case, led to the formation of one major product which could be separated from the tri-n-butyltin residues by column chromatography on silica gel.[3] In this way, the 6-phenylselenylpenicillanates (6) and (8) were cleanly reduced to the 6β-chloro-, and 6β-phenylselenylpenicillanates (9) and (10), respectively. Both reductions were highly stereoselective; the 6β-substituted isomers were the only products isolated, and were characterized by spectroscopic methods.[6] In particular, the H(5)-H(6) coupling constants were both approximately 4Hz, consistent with the C-6 substituent being in the β-position.

The stereoselectivity of these reductions is similar to that reported for reduction of 6-alkyl-6-isocyanopenicillanates (2) by tri-n-butyltin hydride, and can be explained in terms of selective capture of an intermediate penicillanate radical (11) by tri-n-butyltin hydride from the less hindered α-face.[3] To test this explanation, both C-6 epimers of benzyl 6-allyl-6-phenylselenylpenicillanate (12) and (13) were prepared by treatment of benzyl 6-diazopenicillanate (4) with phenyl allyl selenide,[7] and their reduction by tri-n-butyltin hydride, studied. It was found that both epimers of benzyl 6-allyl-6-phenylselenylpenicillanate (12) and (13), were cleanly reduced by tri-n-butyltin hydride, in refluxing benzene containing a trace of azobisisobutyronitrile, to benzyl 6β-allylpenicillanate (14).[6] This result shows that these reductions are stereoselective, rather than stereospecific, and is consistent with the stereochemical explanation given above.

During the course of this work, the preparation of 6-phenylselenylpenicillanates directly from 6-diazopenicillanates was studied. Treatment of 2,2,2-trichloroethyl 6-diazopenicillanate (3) with phenyl selenol,[8] in dichloromethane, in the presence of $BF_3.Et_2O$, gave a single product which was isolated by column chromatography, and purified by recrystallization from ethyl acetate-light petroleum. It was identified as the 6α-phenylselenylpenicillanate (15) by spectroscopic methods; in particular the 6α-configuration was assigned on the basis of the small H(5)-H(6) coupling constant (1.76 Hz). This reaction was found to be subject to an unexpected solvent effect. When a mixture of dichloromethane and tetrahydrofuran (both rigorously dry), was used as the reaction solvent, a mixture containing both the 6α-

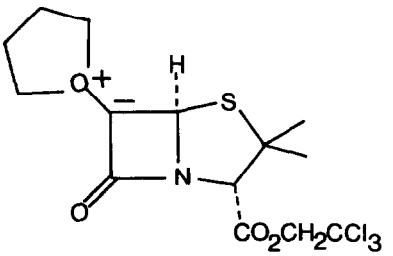


and 6β-phenylselenylpenicillanates (15) and (16), was obtained, in which the 6β-isomer (16) predominated. Typically the 6α- and 6β-isomers were formed in a 1:9 ratio, respectively, and the pure 6β-isomer (16) was isolated by crystallization from ethyl acetate-light petroleum.



(15) X = H, Y = PhSe

(16) X = PhSe, Y = H



(17)

The exclusive formation of 6α-phenylselenylpenicillanate (15) in the absence of tetrahydrofuran is consistent with the formation of the 6α-substituted product in reactions between 6-diazopenicillanates and alcohols and thiols in the presence of $BF_3.Et_2O$.[9] The inverted stereoselectivity in the presence of tetrahydrofuran may be due to participation of tetrahydrofuran in the reaction; possibly oxygen ylid (17) is involved, and this then reacts with phenyl selenol to give the 6β-phenylselenylpenicillanate (16). However, the precise origin of this stereoselectivity in the presence of tetrahydrofuran, has yet to be elucidated.[10]

Acknowledgements

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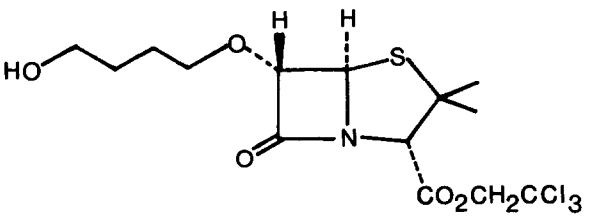
Notes and References

1. Present address: The Dyson Perrins Laboratory, South Parks Road, Oxford.
2. M.F. Loosemore and R.F. Pratt, J. Org. Chem., 1978, 43, 3611.
3. D.I. John, E.J. Thomas, and N.D. Tyrrell, J.C.S. Chem. Comm., 1979, 345.
4. D.L.J. Clive, G. Chittattu, and C.K. Wong, J.C.S. Chem. Comm., 1978, 41.

5. No such reactions are mentioned in recent reviews of diazo compound chemistry (B. Eistert, M. Regitz, G. Heck, and H. Schwall, in 'Methoden Der Organischen Chemie', Thieme Verlag, Stuttgart, 1968, vol 10/4, p. 482; D.S. Wulfman, G. Linstrumelle, and C.F. Cooper, in 'The Chemistry of Diazonium and Diazo Groups', ed. S. Patai, J. Wiley and Son, New York, 1968, p. 821), or organoselenium chemistry (D.L.J. Clive, Tetrahedron, 1978, 34, 1049). However, since our work was completed the reactions of ethyl diazoacetate and dimethyl diazomalonate with diphenyl diselenide have been reported, R. Pellicciari, M. Curini, P. Ceccherelli, and R. Fringuelli, J.C.S. Chem. Comm., 1979, 440.
6. Satisfactory spectroscopic, and analytical or accurate mass data were obtained for all new compounds.
7. P.J. Giddings, D.I. John and E.J. Thomas, preceding communication.
8. Prepared by reduction of diphenyl diselenide using hypophosphorous acid in aqueous tetrahydrofuran, and extraction of the phenyl selenol into dichloromethane. Repeated concentration in vacuo gave pure phenylselenol.
9. P.J. Giddings, D.I. John, and E.J. Thomas, Tetrahedron Letters, 1978, 995.
10. Treatment of 6-diazopenicillanate (3) with $BF_3.Et_2O$ in anhydrous tetrahydrofuran alone gives a low yield of the 6α-alkoxypenicillanate (i). This may have been formed by adventitious hydrolysis of the intermediate ylid (17).



(i)

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