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DIRECT C_6 EPIMERIZATION OF PENICILLIN V METHYL ESTER VIA THE VICINAL DIANION

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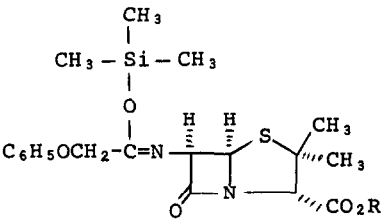
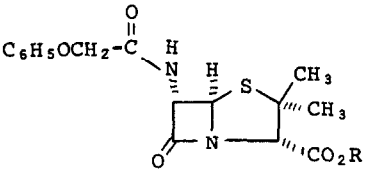
The direct base catalyzed C_6 epimerization of penicillins bearing a secondary amide side chain (1) has thus far not been reported. Presumably, the direct epimerization cannot occur in such a penicillin because of amide proton removal giving 1a, an intermediate which would prevent formation of 1b via C_6 proton extraction. A method of circumventing this problem was recently reported by Vlietinck et al.[1] They protected the secondary amide as the silyl imino ether (2) preventing amide anion formation and subsequently epimerized C_6 with a tertiary amine to give epipenicillin 3. I wish to disclose the direct C_6 epimerization of 1 by a method which suggests the intermediacy of the heretofore unreported vicinal dianion (1b).

Treatment of 1 with 2.5 equivalents of lithium-diisopropylamide in tetrahydrofuran at -80° followed by the addition of methanol and, subsequently, formic acid afforded upon workup an 80% yield of 4:1 ratio of 6-epipenicillin, 4, and penicillin, 1, respectively.[2a,b,c,d] In order to determine whether or not lithium diisopropylamide was effecting direct epimerization, 1 was treated with 2.5 equivalents of lithium-diisopropylamide in THF at -80° and then protonated directly with formic acid to give upon workup a 75% recovery of 1.[3] The possibility of direct kinetic protonation of dianion (1b) from the α-face was eliminated when the previously described experiment was quenched with deuterated-trifluoroacetic acid and no deuterium was incorporated into the C_6 position. If 1 was treated directly with 2.5 equivalents of lithium methoxide in THF at -80°, there was obtained only 1.

These data suggest a direct epimerization of 1 via dianion, 1b (Scheme 1).

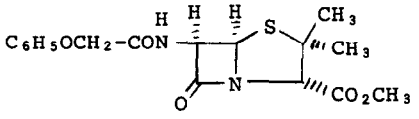


2



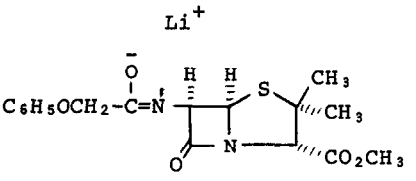
3

SCHEME 1



1

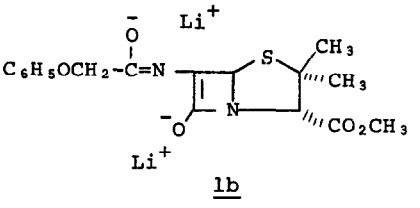
+ 2.5 eq Li-N(C_3H_7)$_2$



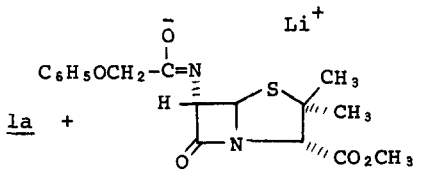
1a

+ Li-N(C_3H_7)$_2$

MeOH

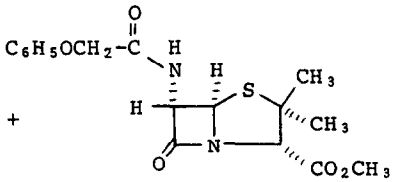


1b



1a +

Formic Acid



1 + 4

It is noteworthy that Kaiser et al.[4a] report that protic solvents facilitate formation of the enolate of the β-lactam, an intermediate implicated in the direct epimerization in this case.[4b]

An immediate consequence of this investigation which demonstrated the base stability of the β-lactam ring to methoxide at low temperature was the synthesi of the 7α-methoxycephalosporins.[5]

The author is currently investigating the synthetic utility of this unusual dianion and its application to other systems.

REFERENCES

1. A. Vlietinck, E. Roets, P. Claes, and H. Vanderhaeghe, Tetrahedron Lett., 285 (1972).

2. (a) The solvent system after addition is methanol-THF - 1:10. (b) The epimers were separated via preparative tlc on silica gel with 7:3 benzene-ethyl acetate as the solvent system. (c) The C_6-C_7 proton multiplet in the nmr is well separated for 1 and 4 so that the integration of the β-lactam proton multiplet could be used to determine the ratio of isomers. (d) All spectral data are consistent with the epipenicillin assignment.

3. There was no epipenicillin detectable from the nmr. If one makes the assumption that epipenicillin is as stable as penicillin, then the 25% of material unaccounted for should not be enriched by epipenicillin decomposition in water.

4. (a) G. V. Kaiser, C. W. Ashbrook, and J. E. Baldwin, J. Amer. Chem. Soc. 93, 2342 (1971). (b) The dianion is presumably short lived since methoxide ion itself is incapable of effecting epimerization.

5. G. A. Koppel and R. E. Koehler, J. Amer. Chem. Soc. 95, 2407 (1973).