Tetrahedron Letters No. 20, pp 1737 - 1740, 1978. 0040-4039/78/0508-1737. $02.00/0.

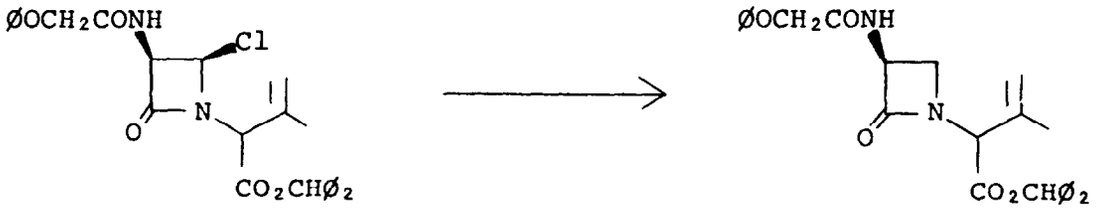
REACTIONS OF 4-CHLOROAZETIDINONES WITH TRIBUTYL TIN HYDRIDE

Celia A. Whitesitt* and David K. Herron

The Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, Indiana 46206

(Received in USA 28 December 1977; received in UK for publication 23 March 1978)

No efficient preparation of 4-unsubstituted monocyclic azetidinones from penicillins has been reported in the chemical literature. Before our work reported here, compounds of this type have been prepared by Raney nickel desulfurization of penicillins to yield mixtures of products requiring repeated recrystallizations or other separation techniques. Crystalline yields have been reported of 10% for derivatives of pen V[1] and up to 42% for pen G.[2] We have found that the title compounds can be prepared in good yield by the tri-n-butyl tin hydride reduction of 1[3] (m.p. 71-73°C); pmr ($CDCl_3$) δ 7.2 (broad, 16H, aromatic, $-CO_2CH-$), 6.17 (d, J=4, 1H, H4), 5.68 (q, J_1=4, J_2=10, 1H, H3), 5.12 (brs, 1H, $-N-\overset{|}{C}H-CO_2-$), 4.92 and 4.98 (2s, 2H, $=CH_2$), 4.55 (s, 2H, $-OCH_2CO-$), 1.88 (s, 3H, CH_3). Optical rotation of 1 was $[\alpha]_D^{MeOH} = -49.9°$.[4] Thus 2 is

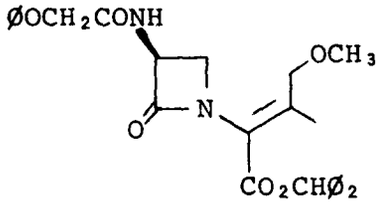


1 2

prepared by heating 10 mmoles of 1 with 10 mmoles of 2,2'-azobis-[2-methylpropionitrile] (AIBN) and 11 mmoles of $n\text{-}Bu_3SnH$ in 10 ml dry toluene at 65°C for 4 hr. Yields of 83% of 2 crystallized upon cooling and thorough washing with ether (m.p. 132-133°C); pmr ($CDCl_3$) δ 7.2 (broad, 16H, aromatic, $-CO_2CH-$), 5.08 (s, 2H, $=CH_2$), 4.82 (s, 1H, $-N-\overset{|}{C}H-CO_2$), 4.81 (m, 1H, H3), 4.45 (s, 2H, $-OCH_2CO-$), 3.85 (t, J=6, 1H, cis H4), 4.38 (q, J=3, 1H, trans H4),[5] 1.83 (s, 3H, CH_3).[4]

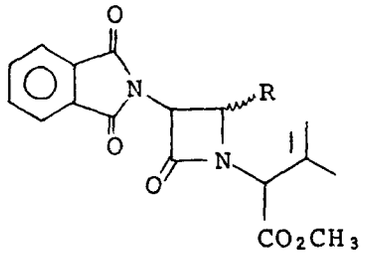
When n-Bu_3SnH was replaced by n-Bu_3SnD in the procedure above, the reduction gave an 80% yield of crystalline product which was shown by pmr to be a 1:1 mixture of the cis and trans 4-deuteroazetidinones. Thus the free radicals initially produced from 1 lost their stereochemical integrity before they were quenched.

The tin hydride method is generally useful for the reduction of chloro-azetidinones. For example, the method has been recently applied in a nocardicin synthesis,[6] and in a preparation of 3[7] from the corresponding 4-chloro compound.



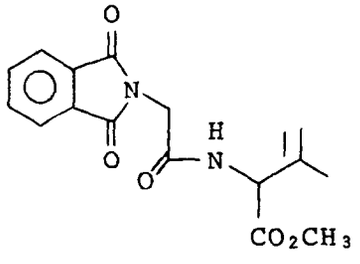
3

The cis 3-phthalimido derivative (4),[8] however, does not react in the same manner as 1. As the reaction temperature is raised, several other parts of the molecule are reduced before chlorine. The trans phthalimido compound (5)[8] upon reduction with n-Bu_3SnH gave the unexpected product 6 (m.p. 222-223°C); pmr



4: R = cis Cl

5: R = trans Cl

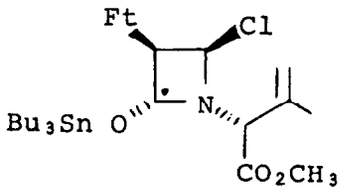


6

($CDCl_3$) δ 7.87 (broad, 4H, aromatic), 5.02 (s, 2H, $=CH_2$), 4.88 (d, J=8, 1H, $-N-\underset{|}{CH}-CO_2-$), 4.33 (s, 2H, $-N-CH_2CO-$), 3.70 (s, 3H, OCH_3), 2.83 (s, 3H, CH_3)[3]; mass spectrum m/e 316 (M), 284 ($M-OCH_3$), 257 ($M-CO_2CH_3$), 188 [$M-NHC-(CO_2CH_3)C(CH_3)CH_2$]. 10 mmoles of a 70:30 mixture of cis:trans phthalimido compounds (4:5) were heated with 10 mmoles AIBN and 11 mmoles n-Bu_3SnH in 10 ml dry toluene at 70°C for 4 hr. The solvents were removed under reduced pressure and ether was added. 6 precipitated and was filtered (1.2 mmoles, 40% yield from 5). After removing the ether, 4 was found to be unchanged. Upon heating 4 to

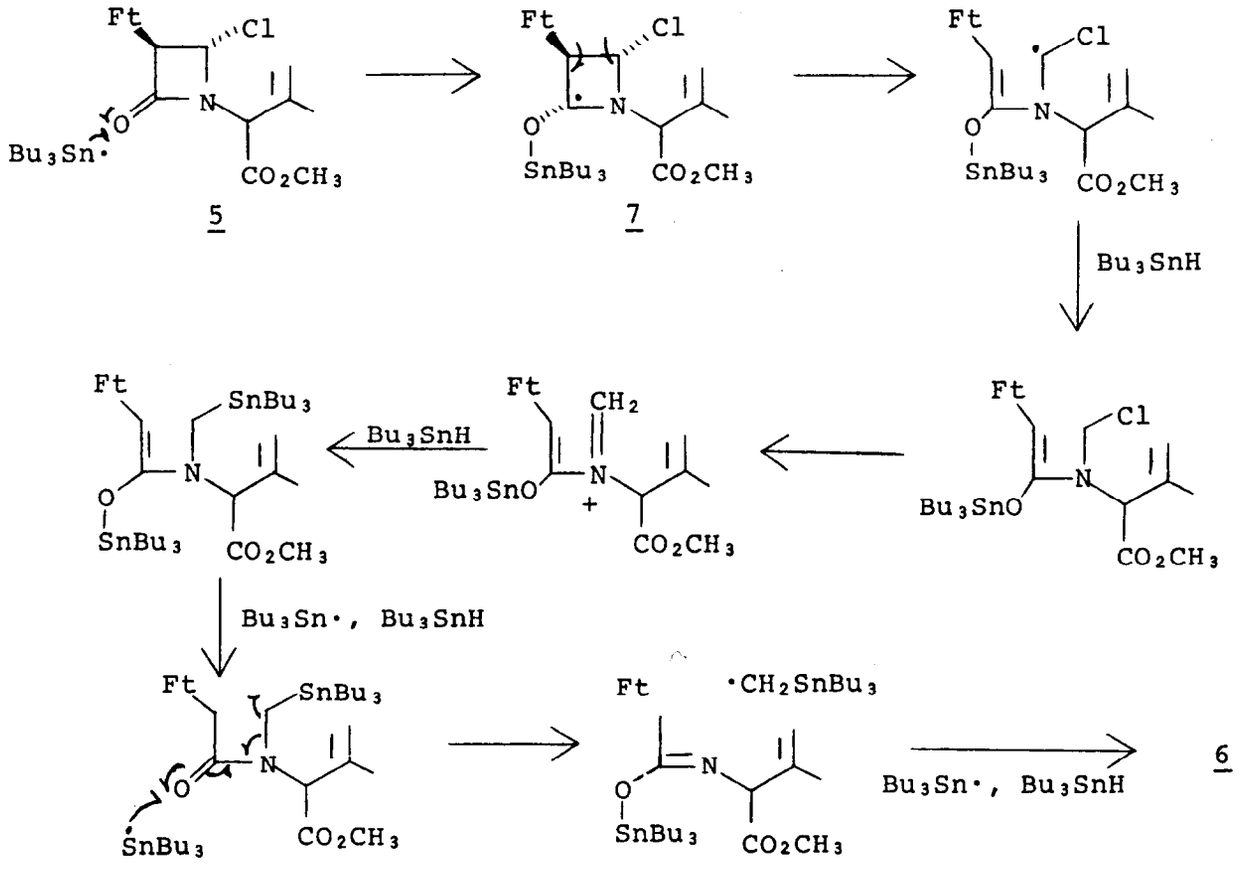
higher temperatures (90°C) with AIBN and n-Bu_3SnH, all products had the phthalimido side chain reduced, and several products had the chlorine reduced and the β-lactam opened.

The sensitivity of radical quenching by tributyl tin hydride to steric hindrance has been demonstrated,[9] and so it seems likely that the notorious bulk of the phthalimido group is responsible for the relatively drastic conditions required for the reduction of 4 as well as for the unusual course of the reduction of 5. In 4 the phthalimido group would directly hinder approach to the 4β-chlorine. In 5 the phthalimido group would indirectly hinder approach to the 4α-chlorine because the methyl ester group is forced to shield the α-face of the β-lactam. A mechanism for the formation of 6 from 5 is suggested below. There is ample precedent for each step in the mechanism.[10] The intermediate 8



8

corresponding to 7 is not formed readily from 4 because it suffers more severe steric compression than does 7.[11]



REFERENCES

1. E. Van Heyningen and L. K. Ahern, J. Med. Chem., 11, 933 (1968).
2. E. Kaczka and K. Folkers, in "The Chemistry of Penicillin," Princeton University Press, Princeton, New Jersey, 1949, p. 243.
3. Compounds of this type prepared by Saul Wolfe, Belgian Patent 832,174.
4. Satisfactory analytical data have been obtained for this compound.
5. The assignments of the cis 4H and trans 4H protons of 2 agree well with those of S. Wolfe and S. K. Hasan, Chem. Commun., 833 (1970).
6. G. A. Koppel, Lilly Research Laboratories, private communication.
7. Compound 3 was prepared from 1 by allylic bromination, methanolysis, and reduction.
8. Saul Wolfe, Jean-Bernard Ducep, Kam-Chung Tin, and Shui-Lung Lee, Can. J. Chem., 52, 3998 (1974).
9. J. T. Groves and S. Kittisapikul, Tetrahedron Lett., 4291 (1977).
10. P. G. Harrison, J. Organometal. Chem., 109, 241 (1976).
11. Examination of accurate molecular models support our steric argument.