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SOME LEWIS ACID CATALYSED REACTIONS OF 2,2,2-TRICHLOROETHYL 6-DIAZOPENICILLANATE

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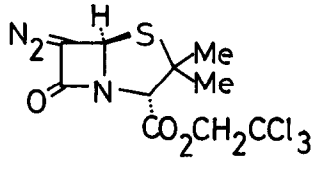
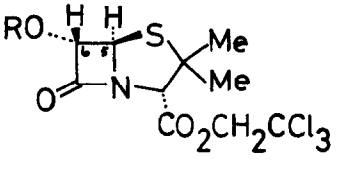
We have been interested in the preparation of penicillin analogues bearing novel substituents at C-6. The recent report by Sheehan and co-workers of the photochemical reactions of 6-diazopenicillanates with thiols and thioacids prompts us to describe some of our own complementary results in this area.[1] We wish to report $BF_3.Et_2O$ catalysed reactions of 2,2,2-trichloroethyl 6-diazopenicillanate (1) with alcohols, thiols, and related compounds, as a direct route to 6-oxy- and 6-thiopenicillanate derivatives.

The reaction of alcohols with α-diazocarbonyl compounds to give α-alkoxy substituted products is known to be catalysed by $BF_3.Et_2O$.[2] This reaction has now been found to be successful with 6-diazopenicillanates. Thus addition of $BF_3.Et_2O$ to a solution of the diazopenicillanate (1) and an alcohol in dichloromethane at room temperature, leads to the immediate evolution of nitrogen and to the formation of the corresponding 6α-alkoxypenicillanate (2). Following work-up of the reaction mixture and silica gel chromatography, pure 6α-alkoxypenicillanate can be isolated in greater than 60% yield.[3] In this manner, 6α-methoxy-, 6α-t-butoxy-, and 6α-benzyloxypenicillanates (2; R = Me, t-Bu, and $PhCH_2$) were obtained. The t-butoxy- and benzyloxypenicillanates were purified further by recrystallization from aqueous ethanol (2, R = t-Bu, mp = 85-86°; 2, R = $PhCH_2$, mp = 54-55°). The structures of products (2) were confirmed by spectroscopic methods,[4] the low values of the H(5)-H(6) coupling constants being consistent with the assigned α-configuration at C-6.



(1)

ROH
$BF_3.Et_2O$
CH_2Cl_2



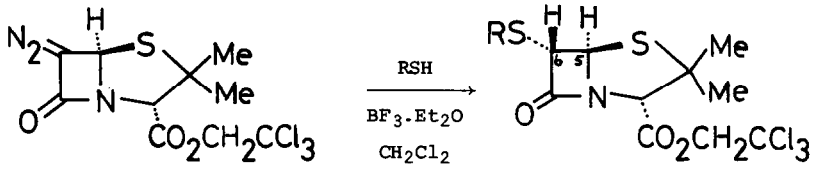
(2)

R = Me-
t-Bu-
$PhCH_2$-
$PhCH_2CO$-

Under the conditions used for the alcohol reactions, 6-diazopenicillanate (1) also reacted cleanly with phenylacetic acid to give the 6α-phenylacetoxypenicillanate (2; R = $PhCH_2CO$) which was isolated in 40% yield after chromatography. This is a new route to 6α-acyloxypenicillanates which have been prepared previously by acylation of 6α-hydroxypenicillanates and in low yield *via* thermal decomposition of N-nitroso derivatives of 6β-amidopenicillanates.[5]

Reactions between α-diazocarbonyl compounds and thiols are not well documented.[6] Nevertheless the 6-diazopenicillanate (1) was found to react cleanly at room temperature, in the presence of $BF_3.Et_2O$, with an excess of a thiol, to give a good yield of the corresponding 6α-alkylthiopenicillanate (3; R = $PhCH_2$, Me_2CH Et). These sulphide products were

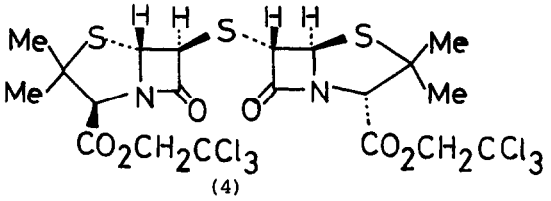
purified by silica gel chromatography (yields of chromatographed product were greater than 50%), and in the case of the benzyl compound (3; R = $PhCH_2$), by recrystallization from ether-light petroleum (mp = 60-61°).[3] Spectroscopic data established the structures of these products,[7] their 6α-configuration again being assigned on the basis of the low values of the H(5)-H(6) coupling constants. Under the conditions used for the thiol reactions, 6-diazopenicillanate (1) reacted with thioacetic acid to give the thioester (3; R = MeCO) which was isolated pure, but in only 11% yield, after chromatography,



(1) (3)

R = PhCH -
Me_2CHCH -
Et-
MeCO-

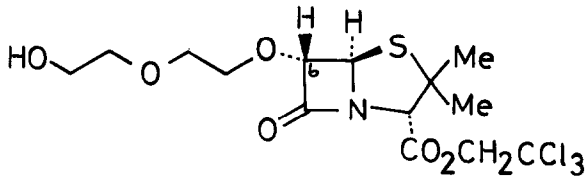
The above thiol reactions were carried out using an excess of the thiol. When 6-diazopenicillanate (1) was treated with one equivalent of benzyl thiol, in the presence of $BF_3.Et_2O$, in dichloromethane, a mixture of two products was obtained which was separated by silica gel chromatography. The less polar product, isolated in 39% yield, was identified as the expected benzyl sulphide (3; R = $PhCH_2$). The more polar product was isolated in 27% yield and has been assigned structure (4) on the basis of its spectroscopic data [ν_{max} (liquid film) 1750 cms^{-1}, δ($CDCl_3$) 5.27 (1H, d, J 1.7 Hz, H-5), 4.79 (2H, s, CH_2CCl_3), 4.66 (1H, s, H-3), 4.39 (1H, d, J 1.7 Hz, H-6), 1.67 and 1.55 (each 3H, s, CH_3-C-CH_3), m/e 692, 694, 696, 698 (M^+)].



(4)

Sulphide (4) was also prepared by treatment of the benzyl sulphide (3; R = $PhCH_2$) with the 6-diazopenicillanate (1) in the presence of $BF_3.Et_2O$. Presumably this is how it is formed in the thiol reaction too; the benzyl thiol and initially formed sulphide (3) compete for unchanged 6-diazopenicillanate. This side reaction can be avoided by using excess thiol and the excess thiol removed at the end of the reaction by extraction into aqueous base.

During the course of the work described above, a cleavage reaction of an oxygen ether was observed. Addition of $BF_3.Et_2O$ to a solution of 6-diazopenicillanate (1) in dioxan caused the immediate evolution of nitrogen and the formation of the dioxan cleavage product (5) which was isolated in 20% yield by chromatography. As before, the α-configuration was assigned to the substituent at C-6 because of the small H(5)-H(6) coupling constant. Diethyl ether was also cleaved by 6-diazopenicillanate (1) in the presence of $BF_3.Et_2O$ to give the 6α-ethoxypenicillanate (2; R = Et) in excellent yield.



(5)

The exclusive formation of the 6α-isomer in the $BF_3.Et_2O$ catalysed reactions reported here contrasts with the selective formation of the 6β-isomer in the photochemical reactions of thiols and 6-diazopenicillanates reported by Sheehan.[1] Several mechanisms have been proposed for $BF_3.Et_2O$ catalysis of reactions between alcohols and diazo compounds.[2] The $BF_3.Et_2O$ may co-ordinate with the alcohol or thiol which then protonates the 6-diazopenicillanate. Alternatively, the $BF_3.Et_2O$ may co-ordinate with the 6-diazopenicillanate so making it more electrophilic and more susceptible to attack by a nucleophile. A third possibility is the participation of a BF_3 complexed carbene formed by N_2 loss from BF_3 co-ordinated 6-diazopenicillanate. However, all three mechanisms are consistent with selective formation of the 6α-isomer as has been observed for proton acid catalysed reactions of 6-diazopenicillanates.[8]

Acknowledgements

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Notes and References

1. J.C. Sheehan, T.J. Commons, and Y.S. Lo, J. Org. Chem., 1977, 42, 2224.

2. G.W. Cowell and A. Ledwith, Quart. Rev., 1970, 24, 119.

3. Satisfactory analytical or accurate mass data were obtained for all new compounds.

4. For example; (2; R = Me) (chromatographed yield 60%), (Found: M^+, 360.9714. $C_{11}H_{14}Cl_3NO_4S$ requires M, 360.9709), ν_{max} (liquid film) 1760 (broad, C = 0) cm^{-1}, $\delta(CDCl_3)$ 5.30 (1H, d, J < 2 Hz, H-5), 4.75 (2H, s, CH_2CCl_3), 4.58 (1H, s, H-3), 4.58 (1H, d, J < 2 Hz, H-6), 3.48 (3H, s, OCH_3), 1.58 and 1.53 (each 3H, s, CH_3-C-CH_3), m/e 361, 363, 365 (M^+) and 290, 292, 294 (M^+ - 71).

5. D. Hauser and H.P. Sigg, Helv. Chim. Acta, 1967, 50, 1327; E. Roets, A. Vlietinck, and H. Vanderhaeghe, J.C.S. Perkin I, 1976, 704.

6. E. Eistert, M. Regitz, G. Heck, and H. Schwall, in 'Methoden Der Organischen Chemie (Houben-Weyl)', Thieme Verlag, Stuttgart, 1968, vol. 10/4.

7. For example; (3; R = Me_2CHCH_2) (chromatographed yield 50%), (Found: M^+ 418.9951. $C_{14}H_{20}Cl_3NO_3S_2$ requires M, 418.9950), ν_{max} (liquid film) 1770 (C = O) cms^{-1}, δ($CDCl_3$), δ 5.24 (1H, d, J 1.8 Hz, H-5), 4.84 (1H, d, J 11.7 Hz, $HCHCCl_3$), 4.72 (1H, d, J 11.7 Hz, $HCHCCl_3$), 4.66 (1H, s, H-3), 4.21 (1H, d, J 1.8 Hz, H-6), 2.57 (2H, d, J 7 Hz, CH_2CHMe_2), 1.78 (1H, m, $CHMe_2$), 1.67 and 1.55 (each 3H, s, CH_3CCH_3), and 1.00 (6H, d, J 7 Hz, CH_3CHCH_3), m/e 419, 421, 423 (M^+), and 290, 292, 294 (M^+ - 129).

8. J.C. Sheehan, Y.S. Lo, J. Löliger, and C.C. Podewell, J. Org. Chem., 1974, 39, 1444; I. McMillan and R.J. Stoodley, J. Chem. Soc.(C), 1968, 2533.