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SYNTHESIS OF OXA AND DITHIAZEPINE AZETIDINONES

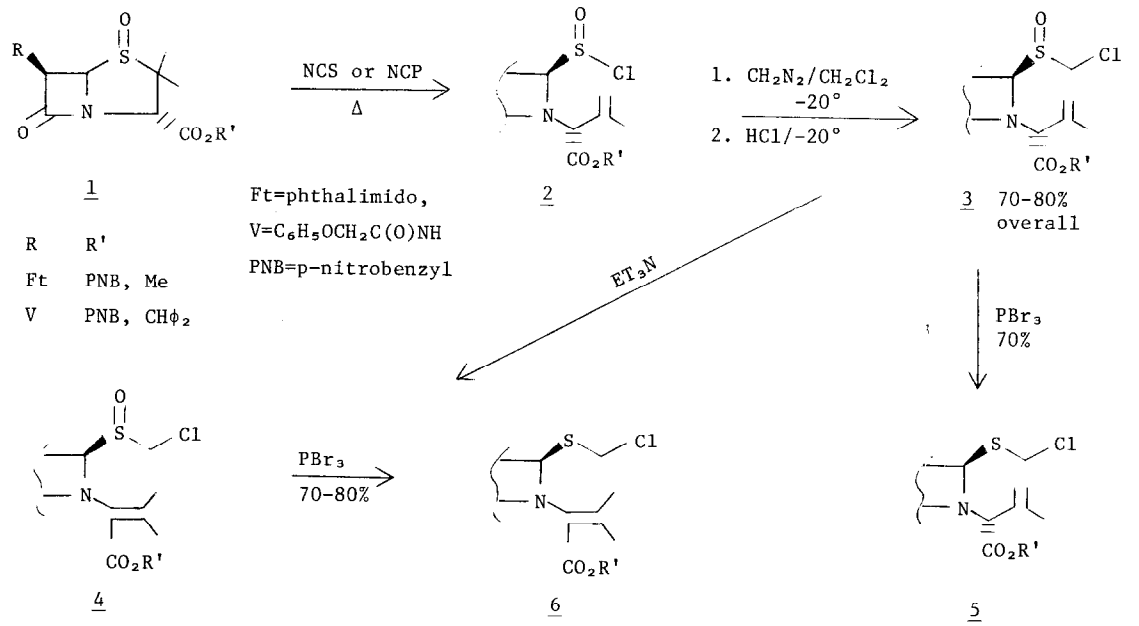
Douglas O. Spry

The Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, Indiana 46285

Abstract: Oxa and dithiazepine azetidinones are prepared from the versatile halomethyl sulfide intermediate 5.

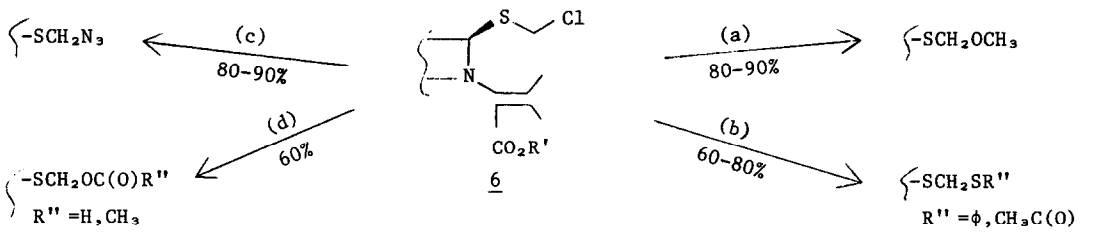
Lammert and Kukolja have described the reaction of the sulfinyl chloride 2 (R=FT, R'=PNB) with diazomethane to give 3 (R=Ft, R'=PNB) as one major isomer in 27% yield, along with the minor chiral sulfoxide isomer and various amounts of C(2) - C(3) methylene addition products (40%).[1,2]

Using a lower temperature (-20°) followed by the addition of excess anhydrous HCl we have isolated 3 (R=Ft, R'=PNB) in 76% overall yield from the penicillin 1 (R=Ft, R'=PNB). The product is a single isomer and is the minor isomer obtained by the previous workers. Other side chains and esters proved equally effective; however, in general, a mixture of sulfoxide isomers resulted with no detectable amounts of addition products.



Having achieved the synthesis of 3 in good overall yield, we hoped to use it in the synthesis of oxa and dithiazepine azetidinones 9 and 17.

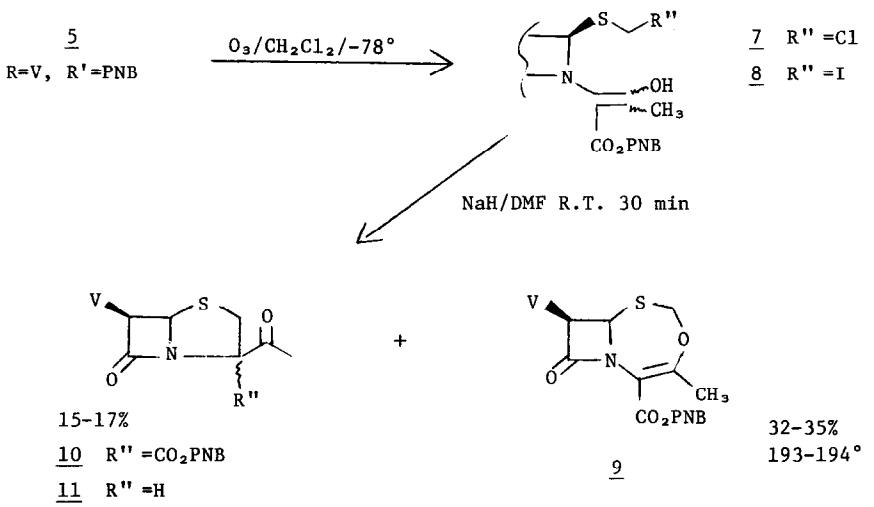
PBr_3[3] reduction of 3 and 4[4] gave the corresponding β-γ and α-β unsaturated sulfides 5[5] and 6 which appear to be quite stable. The reactivity of the chloromethyl sulfide with various nucleophiles (azides, alcohols, mercaptans, and substituted amides) is illustrated in the following scheme:



(a) MeOH/$AgClO_4$, (b) φSH or $CH_3C(O)SH$/DMF/DBU, (c) NaN_3/DMF, (d) AgOTs/DMF or DMAC

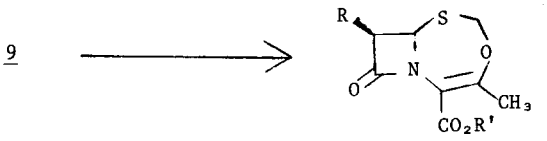
Ozonolysis of 5 (R=V, R'=PNB) went cleanly to give the corresponding enol 7 (65%) which could be alkylated with diazomethane to give cis/trans mixtures (30%, 17% isolated) of the O-methylated enol, thus illustrating the presence of the correct configuration for ring closure. Treatment of 7, however, with NaH/DMF failed to cause cyclization even though $AgClO_4$/MeOH led to cis/trans mixtures of the corresponding enol methoxymethyl sulfide.

The iodomethyl sulfide 8[6] was then prepared (90%) via the Finkelstein reaction (3.8 equiv NaI/acetone/R.T. 1 Hr) and this indeed undergoes the intramolecular cyclization to give both the C-alkylated product 10[7] (15-17%) as a mixture at C(3) and the O-alkylated product 9[8] (32-35%, mp 193-194°), the 3,1,6-oxathiazepine azetidinone.



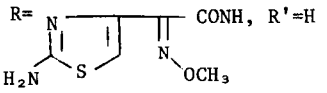
Hydrogenolysis[9] of the p-nitrobenzyl ester group of 9 gave the corresponding acid (mp 183°) in 65-70% yield while hydrogenolysis of the β-keto ester 10 resulted in ready decarboxylation to give 11 (30%).

Side chain cleavage (PCl_5)[10] of 9 gave the nucleus 12[11] (>90%) which was acylated and subsequently deblocked to give 13 and 14, neither of which showed significant microbiological activity.

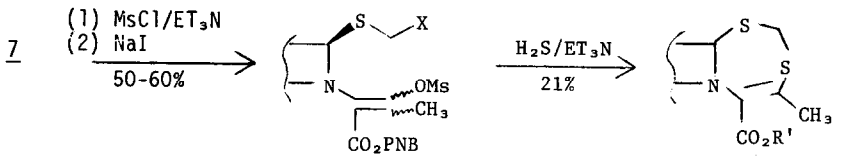


12 R=NH_2, R'=PNB

13 R=D-φCH(NH_2)CONH, R'=H

14 R=  CONH, R'=H

Synthesis of the 1,3,6-dithiazepine azetidinone 17[12] was accomplished via sulfide ring closure of the iodomethyl mesylate 16 in 21% yield. Its acid 18 (193°)[13] also proved to be rather inactive.



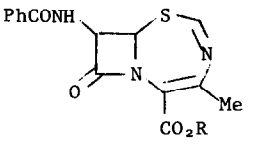
15 X=Cl

16 X=I

17 R'=PNB

18 R'=H

Other workers in the β-lactam area have shown interest in similar types of compounds. For example the synthesis of the 1,3,6-thiadiazepine azetidinone 19 has recently been reported.[14]



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It is obvious that 5 and 6 are readily available and appear to be very versatile intermediates in the synthesis of novel azetidinone derivatives.

References

1. S. R. Lammert and S. Kukolja, J. Am. Chem. Soc., 97, 5583 (1975).
2. U.S. Pat. 3,919,205 (1975).
3. G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, and E. M. Van Heyningen, J. Org. Chem., 35, 2430 (1970).
4. 4, R=Ft, R'=PNB, mp. 192-193°.
5. 5, R=V, R'=PNB: NMR: ($CDCl_3$) δ 1.93 (s, Me), 4.6 (s, ϕOCH_2 + SCH_2Cl), 4.97 (d, J = 4 Hz, $C{=}CH_2$), 5.17 (s, $CHCO_2PNB$), 5.30 (s, PNB), 5.4 (m, β-lactam protons); ir ($CHCl_3$) 1768 cm^{-1}.
6. 8, NMR ($CDCl_3$) δ 2.20 (s, Me), 4.07 (AB, J = 10 Hz, CH_2I), 4.57 (s, ϕOCH_2), 5.1-5.6 (m, β-lactam + PNB), 12.3 (s, OH); ir ($CHCl_3$) 1770 cm^{-1}.
7. 10, NMR ($CDCl_3$) δ 2.37, 2.42 (s, mixture of Me), 3.57 (AB, J = 12 Hz, SCH_2 one isomer), 3.67 (s, SCH_2 other isomer), 4.58 (s, ϕOCH_2), 5.37 (s, PNB), 5.47 (d, J = 4 Hz, H_5), 5.77 (q, J = 4, 9 Hz, H_6); ir ($CHCl_3$) 1790 cm^{-1}; mass spec. 499, 309.
8. 9, NMR ($CDCl_3$) δ 2.20 (s, Me), 4.57 (s, ϕOCH_2), 4.62, 6.13 (AB, J = 13 Hz, SCH_2O), 5.0-5.3 (m, PNB + H_8), 5.52 (d, J = 4 Hz, H_7); ir ($CHCl_3$) 1769 cm^{-1}; mass spec. 499, 309, 263; UV (ETOH) 267 nm, (ε = 21,925).
9. D. H. R. Barton, D. C. T. Greig, G. Lucente, P. G. Sammes, M. V. Tayler, M. C. Cooper, G. Hewitt, and W. G. E. Underwood, Chem. Commun., 1683 (1970).
10. B. Fechtig, H. Peter, H. Bickel, and E. Vischer, Helv. Chim. Acta, 51, 1108 (1968).
11. 12, NMR ($CDCl_3$) δ 2.20 (s, Me), 3.13 (br, NH_2), 4.85, 6.03 (AB, J = 13 Hz, SCH_2O), 5.22, 5.43 (d, J = 4 Hz, H_7 + H_8); ir ($CHCl_3$) 1765 cm^{-1}; mass spec. 365, 309, 263.
12. 17, NMR ($CDCl_3$) δ 2.27 (s, Me), 3.10, 5.02 (AB, J = 15 Hz, SCH_2S), 4.57 (s, ϕOCH_2), 5.20 (d, H_7) 5.25 (s, PNB), 5.43 (q, J = 4, 12 Hz, H_8); ir ($CHCl_3$) 1775 cm^{-1}; mass spec. 515, 325, 279.
13. All crystallizations were done from CH_2Cl_2/hexanes and all crystalline compounds analyzed correctly.
14. J. of Syn. Methods, 6, 77352v (1980).

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