Tetrahedron Letters,Vol.24,No.13,pp 1429-1432,1983 0040-4039/83/131429-04$03.00/0
Printed in Great Britain

A NEW REDUCTIVE ACETYLATION OF SULPHINIC ACIDS AND ITS APPLICATION TO THE SYNTHESIS OF 2-ACETYLTHIO-4-OXOAZETIDINES

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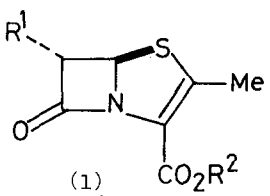
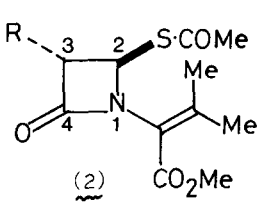
Summary: The sulphinic acid function of (4-oxoazetidin-2-yl)sulphinic acids is transformed into the acetylthio moiety by sequential reactions involving thionyl chloride, thioacetic acid and triphenylphosphine.

The substantial antibacterial activity associated with compound (1a)[1] has provided an impetus for the synthesis of penem-2-carboxylic acid derivatives. Thioesters of type (2) are expected to serve as precursors of penems of type (1), using Woodward's strategy.[2] We now report a novel procedure, operable under mild experimental conditions, for deriving such thioesters.



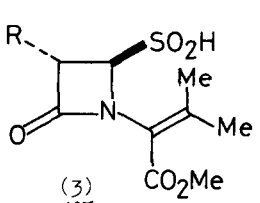
(1)

a; $R^1 = R^2 = H$



(2)

a; R = NH·CO·CH_2·OPh
b; R = NH·CO_2·CH_2Ph
c; R = Cl
d; R = phthalimido
e; R = NH·CO·CH_2Ph
f; R = H

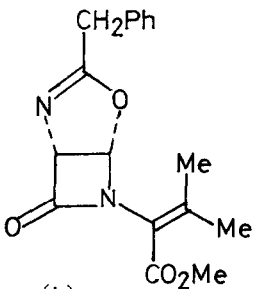


(3)

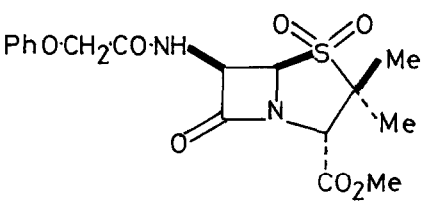
Reaction of sulphinic acid (3a)[3] in dichloromethane with thionyl chloride (1.1 mol. equiv.) was followed after 10 min by the addition at 0°C of thioacetic acid (3 mol. equiv.). The crude product, obtained by work-up after 30 min, was then treated in dichloromethane at 0°C with triphenylphosphine (1.5 mol. equiv.). Work-up after 30 min and purification of the product by silica-gel chromatography gave thioester (2a) [55% yield based upon (3a)], $[\alpha]_D$ +25° (EtOH).

Using a similar reaction sequence, sulphinic acids (3b-d)[3] were converted into thioesters (2b), $[\alpha]_D$ +81° (EtOH), (2c) $[\alpha]_D$ +80° (EtOH), and (2d), $[\alpha]_D$ +100° (EtOH), in respective yields

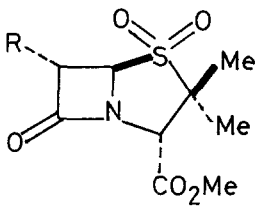
of 32%, 41% and 78% (after SiO_2 chromatography). In the case of sulphinic acid (3e),[3] a 2:1 mixture of thioester (2e) and epi-oxazoline-azetidinone (4)[4,5] was isolated (after SiO_2 chromatography); this mixture was transformed into thioester (2e)[6] [30% yield based upon (3e) after SiO_2 chromatography], m.p. 79-80°C, $[\alpha]_D$ +78° (EtOH), by neat thioacetic acid.



(4)



(5)

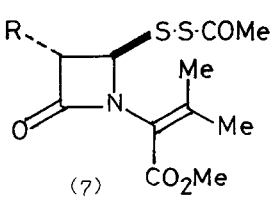


(6)

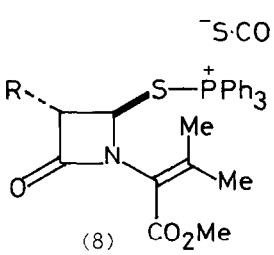
a; R = Cl
b; R = H

Since sulphinic acids of type (3) are prepared from esters of penicillanate sulphones by the action of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN),[3] it was of interest to determine whether it was necessary to isolate the acids before applying the reductive acetylation procedure. Accordingly, sulphones (5) and (6a) were reacted in dichloromethane with DBN.[7] The mixtures, after cooling in ice, were treated with thionyl chloride (2 mol. equiv.) followed, after 10 min, by thioacetic acid (3 mol. equiv.). Subsequent treatment with triphenylphosphine and work-up as before gave thioesters (2a,c) in respective yields of 58% and 45%.

Acetyl azetidinyl disulphides of type (7) intervene in the aforementioned reaction sequences. Thus disulphide (7a) (85% yield), $[\alpha]_D$ +19° (EtOH), and diacetyl disulphide were isolated, following silica-gel chromatography, from the reaction of sulphinic acid (3a) with thionyl chloride and thioacetic acid.[8] Compound (7a) reacted with triphenylphosphine (1 mol. equiv.) in dichloromethane to give, following silica-gel chromatography, triphenylphosphine sulphide (88% yield) and a 2:1 mixture of thioester (2e) and epi-oxazoline-azetidinone (4).

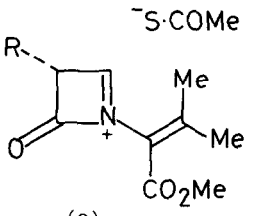


(7)



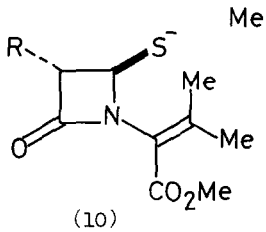
(8)

a; R = $NH{\cdot}CO{\cdot}CH_2Ph$



(9)

a; R = NH·CO·CH_2Ph



(10)

Two pathways warrant consideration for the transformation of disulphides of type (7) into thioesters of type (2). Thus phosphonium salts of type (8) may afford the products by way of azetinium salts of type (9); clearly, epi-oxazoline-azetidinone (4) must arise from a species of the foregoing type, i.e. either (8a) or (9a). Phosphonium salts of type (10) may also serve as precursors of thioesters of type (2).

If intermediates of type (9) are the exclusive precursors of thioesters of type (2), the high diastereoselectivity of the reactions must be attributed to the directing effect of the substituent R. In such an event, sulphone (6b) should afford the racemate of thioester (2f). Compound (6b), m.p. 105-107°C, $[\alpha]_D$ +221° (EtOH), when subjected to the β-elimination and reductive acetylation sequences, gave thioester (2f) (48% yield), m.p. 76-78°C, $[\alpha]_D$ +99° ($CHCl_3$). Since Woodward and his co-workers have shown[1] that thioester (2f), m.p. 81-82°C, $[\alpha]_D$ +149° ($CHCl_3$) is optically pure, it may be inferred that the thioester derived from sulphone (5c) possesses an optical purity of ca. 66%.

On the basis of the foregoing evidence, it appears that phosphonium salts of types (8) and (10) are implicated in the conversion of disulphides of type (7) into thioesters of type (2). Evidently, the nature of the substituent R plays a subtle role in influencing the reaction outcome.

Acknowledgements

We thank Dr. J.H.C. Nayler for his interest, the S.E.R.C. for a C.A.S.E. studentship (with Beecham Pharmaceuticals to J.R.I.) and Farmitalia Carlo-Erba for a research fellowship (to E.P.).

References and Footnotes

1 L. Ernest, J. Gosteli, and R.B. Woodward, J.Am.Chem.Soc., 1979, 101, 6301.

2 R.B. Woodward, "Recent Advances in the Chemistry of β-Lactam Antibiotics", Chem. Soc. Spec

Publ., 1977, No. 28, 1967; I. Ernest, J. Gosteli, C.W. Greengrass, W. Holick, D.E. Jackman, H.R. Pfaendler, and R.B. Woodward, J.Am.Chem.Soc., 1978, 100, 8214.

3 C.M. Pant, J. Steele, and R.J. Stoodley, J.Chem.Soc.,Perkin Trans 1, 1982, 595.

4 The enantiomer of this compound has been reported : J.C. Sheehan "Molecular Modification in Drug Design", A.C.S. Advances in Chemistry Series No. 45, Washington, D.C., 1964, p. 15; D.H.R. Barton, F. Comer, D.G.T. Greig, P.G. Sammes, C.M. Cooper, G. Hewitt, and W.G.E. Underwood, J.Chem.Soc.,(C), 1971, 3340.

5 The formation of these products is probably under kinetic control; thus epi-oxazoline-azetidinone (4) was recovered unchanged when treated under the reaction conditions with thioacetic acid (1 mol. equiv.).

6 A better route to this thioester [44% yield based upon (3e)] involved treating the epi-oxazoline-azetidinone (4), m.p. 124-126°C, $[\alpha]_D$ -84° ($CHCl_3$), prepared in 60% yield by oxidation of the sulphinic acid (3e) with lead(IV) acetate in dichloromethane (C.M. Pant and R.J. Stoodley, unpublished work), with neat thioacetic acid.

7 The base was added in drops until the reaction was complete by n.m.r. spectroscopy (as monitored by the downfield shift of the signals for the geminal dimethyl group).

8 This constitutes a new route to acetyl alkyl disulphides; for other syntheses see L. Field, W.S. Hanley, and I. McVeigh, J.Org.Chem., 1971, 36, 2735.

(Received in UK 10 January 1983)