Tetrahedron Letters,Vol.26,No.15,pp 1791-1794,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF 4-CARBOXY-2-THIABICYCLO [3.2.0] HEPTAN-6-ONES VIA 3-CARBOXY-2,3-DIHYDROTHIOPHENES: POTENTIAL β-LACTAMASE INHIBITORS

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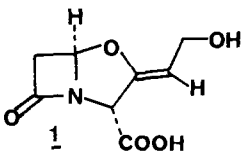
3-Carboalkoxy-2,3-dihydrothiophenes, available by Birch reduction of thiophene-3-carboxylic acid or more efficiently by deconjugation of 2,5-dihydrothiophene-3-carboxylic acid by reaction with ethyl chloroformate and triethylamine, undergo cycloaddition reactions with dichloroketene leading to 4-carboxy-7,7-dichloro-2-thiabicyclo[3.2.0]heptan-6-ones which are of interest as potential β-lactamase inhibitors.

During the past several years, there has been an intense interest in the development of potent inhibitors for the bacterial enzymes classified as β-lactamases largely stimulated by the need for an effective strategy for overcoming the penicillin resistance of β-lactamase producing pathogenic strains of microorganisms.[1] The effective natural and semi-synthetic inhibitors such as clavulanic acid **1** [2], 6-β-bromopenicillanic acid **2** [3] and the penicillanic acid sulfones **3** [4] have



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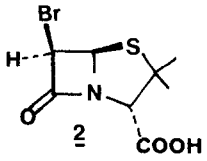

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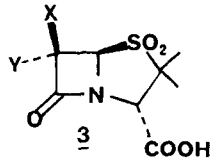
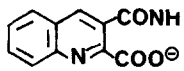


3

X	Y
H	H
H	Cl
CF_3SO_2NH	H

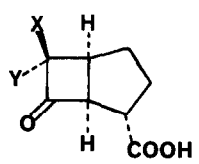


H

c

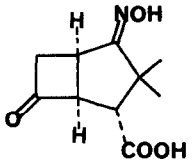
been studied in detail in several laboratories including our own[5] and found to function as enzyme activated irreversible inhibitors (so-called suicide substrates[6]). In our search for other effective strategies for inhibition of β-lactamases, we considered the possibility that a cyclobutanone analog **4** of the penicillins might inhibit β-lactamases by forming a stabilized hemi-acetal with the active-site serine side chain, thus functioning in the same way as certain aldehydopeptides which are inhibitors of serine and thiol proteases[7,8]. Several reports which have appeared in the literature since we began our studies in this area have revealed that our strategy was certainly not unique. Thus Gordon and coworkers[9] reported the synthesis of the carboxy substituted bicyclo[3.2.0]heptan-6-ones **4** while Roberts[10] and coworkers reported the preparation of the related system **5**. None of these compounds has been reported to have useful anti-β-lactamase activity. Most recently the 2-oxabicyclo[3.2.0]heptan-6-ones **6** have been prepared by Lowe and coworkers[11] and some β-lactamase inhibitory properties have been noted. We report herein in preliminary form our synthetic efforts towards the 4-carboxy-2-thiabicyclo[3.2.0]heptan-6-one system **7**.

Given the extensive literature[12] on the synthesis of cyclobutanones via ketene cycloaddition



X	Y
Cl	Cl
Cl	H
H	H

4



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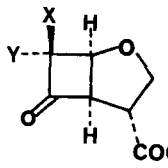
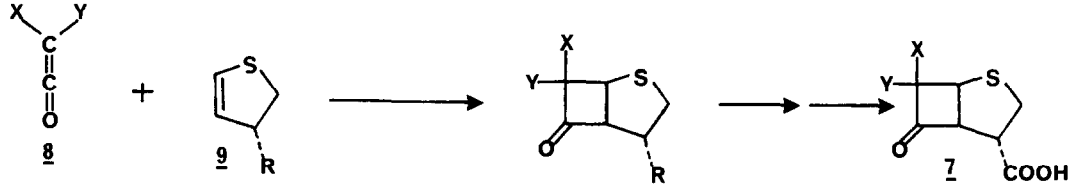


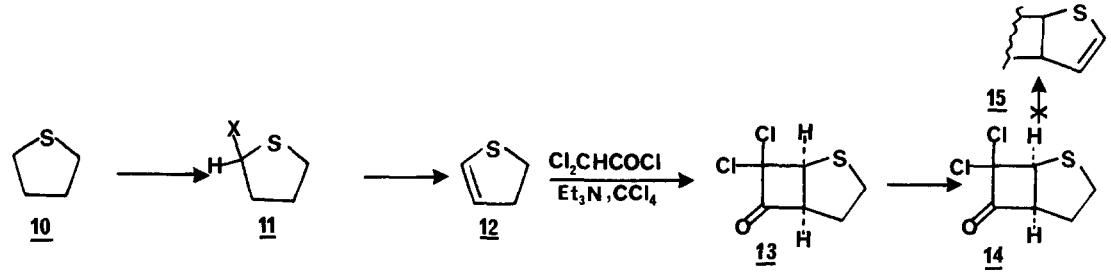
X	Y
Cl	H
$PhCH_2\overset{\overset{O}{\|}}{C}NH$	H

6

reactions, the most obvious approach to compounds such as **7** is such a $\pi^{2s}+\pi^{2a}$ reaction of a suitable ketene **8** with an appropriate 2,3-dihydrothiophene **9.** Since there was no report in the literature of a suitably substituted 2,3-dihydrothiophene such as **9** initial cycloaddition experiments were performed with the known 2,3-dihydrothiophene **12.**



8 9 7

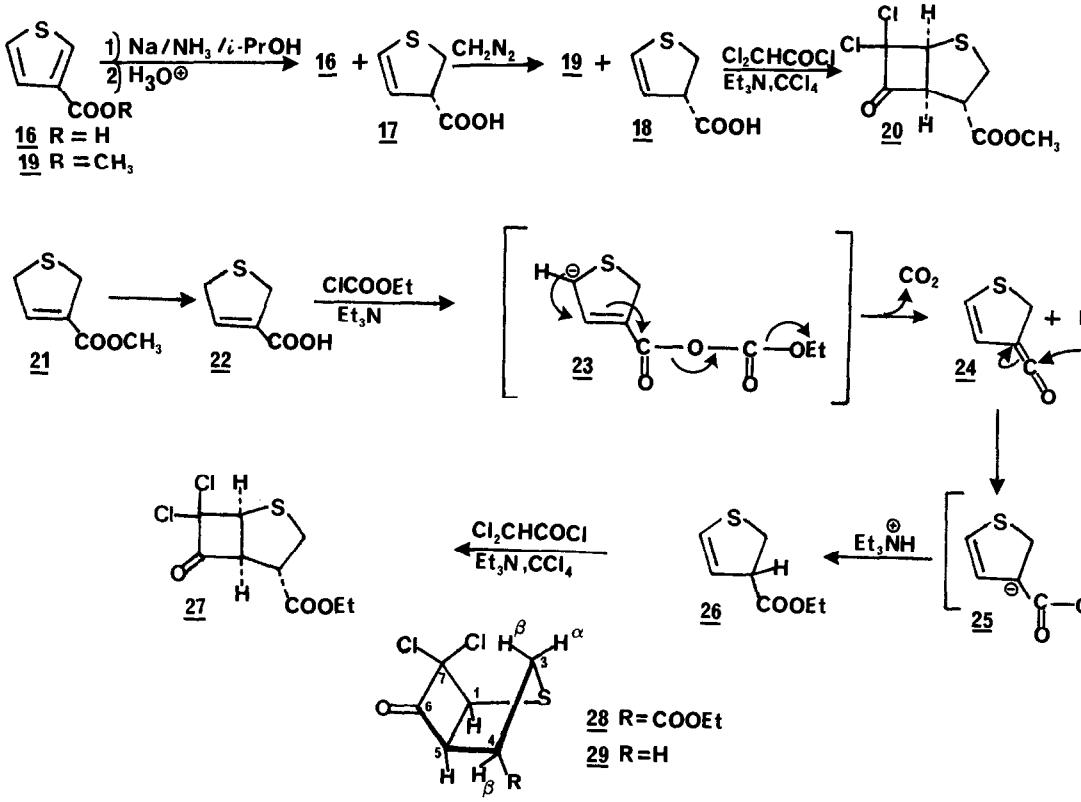


10 11 12 13 14 15

The unstable dihydrothiophene **12** *was generated by benzoyloxylation of tetrahydrothiophene* **10** followed by a thermal elimination of benzoic acid as described by Sosnovsky.[13] Reaction of **12** with dichloroketene generated in situ by reaction of dichloroacetylchloride with triethylamine gave the adduct **13** as a low melting solid (mp. 38-39°) in 13% overall yield from tetrahydrothiophene **10.** The structure of the adduct **13** was assigned on the basis of a detailed spectroscopic analysis[16] and confirmed by a single crystal X-ray diffraction study.[17] It was thought at first that the carboxysubstituted system **20** might be derived from **13** via the unsaturated system **15** through a suitable carboxylation reduction sequence. To this end **13** was chlorinated with sulfuryl chloride to give **14** in low yield (15%). However, all attempts to effect dehydrochlorination of **14** were unsuccessful.

Attention was then turned to the synthesis of a suitable 3-carboxy-substituted 2,3-dihydrothiophene **20.** Birch type reduction of thiophene-3-carboxylic acid with three equivalents of sodium in liquid ammonia containing isopropanol gave a complex mixture of products containing some of the desired reduction product.[18,19] It was found that by decreasing the amount of sodium employed to 2.5 equivalents the byproduct formation was eliminated and a clean mixture of **17** and **16** in a 3:2 ratio was obtained. The mixture of acids was readily esterified by treatment with diazomethane in ether. Although the esters **18** and **19** were not separable chromatographically, the mixture could be reacted with dichloroketene to give the adduct **20** in low

overall yield (3.7% from **16**). A much more efficient approach to this system was discovered when it was found that 2,5-dihydrothiophene-3-carboxylic acid **22** prepared from the known[20] methyl ester **21** could be readily deconjugated to ethyl 2,3-dihydrothiophene-3-carboxylate **26** by reaction with ethyl chloroformate in the presence of an excess of triethylamine for four hours at room temperature. This deconjugation process very likely proceeds via a kinetic protonation of the anion **25** generated by a decarboxylative elimination from the anion **23** followed by addition of ethoxide to the unsaturated ketene intermediate **24**.



The adduct **27** was obtained from the dihydrothiophene in 33% isolated yield. Analysis of the ^{1}H NMR spectrum of **27** ($J_{5,4\beta}$ = 0 implying a dihedral angle of $\phi_{5,4\beta}$ = 90°) indicated that the molecule possessed an endo-envelope conformation **28** with the carboalkoxy group attached to the exo face.[23] This route is potentially amenable to modification to allow the synthesis of analogs of **27** which bear an acylamido side-chain at C-7 and a gem-dimethyl grouping at C_3 and thus more closely resemble the natural penicillins. Such studies are being actively pursued. Biochemical evaluation of the anti-β-lactamase properties of the free acid available by treatment of the ester with iodotrimethylsilane in acetonitrile is in progress.[24]

Acknowledgements: This work was supported by the Natural Sciences and Engineering Research Council of Canada through individual operating grants (to G.I.D. and to T.V.) and a joint strategic grant. The authors would like to thank Professor John McIntosh (University of Windsor) for helpful discussions.

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11. Lowe, G. and Swain, S. J. Chem. Soc. Chem. Commun. (1983), 1279-1281.
12. Brady, W.T. (1980) in "The Chemistry of Ketenes, Allenes and Related Compounds"(S. Patai, ed.)
13. Sosnovsky, G. Tetrahedron (1962) 18, 903-908.
14. Alternatively, **13** could be prepared, more conveniently but in low yield (8% from **10**) by reaction of dichloroketene with **12** generated in situ by chlorination of **10** with SO_2Cl_2[15] followed by treatment with DBU.
15. Kruse, C.G.; Poels, E.K.; Jonkers, F.L. and van der Gen, A., J. Org. Chem. (1978), 43, 3548-3553.
16. ^1H nmr (400 MHz): 1.99 (dddd, 1, $J_{3\alpha,4\alpha}$ = 6.7, $J_{3\beta,4\alpha}$ = 12.2, $J_{4\alpha,4\beta}$ = 13.3, $J_{5,4\alpha}$ = 8.0, $H_{4\alpha}$), 2.65 (dd, 1, $J_{4\beta,4\alpha}$ = 13.3, $J_{3\beta,4\beta}$ = 5.2, $H_{4\beta}$), 2.84 (ddd, 1, $J_{3\alpha,4\alpha}$ = 6.7, $J_{3\alpha,3\beta}$ = 11.8, $H_{3\alpha,4\alpha}$ = 12.2, $J_{3\beta,4\beta}$ = 5.2, $H_{3\beta}$), 3.00 (dd, 1, $J_{3\alpha,4\alpha}$ = 6.7, $J_{3\alpha,3\beta}$ = 11.8, $H_{3\alpha}$), 4.50 (d, 1, $J_{1,5}$ = 8.4, H_1), 4.60 (dd, 1, $J_{1,5}$ = 8.4, $J_{5,4\alpha}$ = 8.0, H_5); ^{13}C nmr (20 MHz) CW: 33.34 (t, C3 or C4), 33.57 (t, C3 or C4), 59.50 (d, C1 or C5), 65.96 (d, C1 or C5), 89.64 (s, C7), 196.41 (s, C6), infrared ($CHCl_3$): 1809 (C = O, cyclobutanone). See structure 29.
17. The details of the X-ray diffraction study performed by Dr. N. Taylor of the Waterloo X-ray Diffraction Service, will be reported elsewhere.
18. These conditions were reported to yield 2,3-dihydro-3-furoic acid in good yield from furoic acid: Kinoshita, T.; Konischi, M.; and Miwa, T., Bull. Chem. Soc. Jpn. (1975), 48, 1865-1867.
19. The related reduction of thiophene itself was reported to yield 2,3-dihydrothiophene, 2,5-dihydrothiophene and various products produced by cleavage of C-S bond, S.F. Birch and D.T. McAllen J. Chem. Soc. (1951), 2556-2563.
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21. This procedure has been applied to a number of simple acyclic α,β-unsaturated acids and appears to have some generality. It also appears to have some advantages over the related deconjugation of α,β-unsaturated acids via the corresponding acid chlorides.[22] These studies will be reported in detail elsewhere.
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23. Examination of molecular models revealed that dihedral angles of $\phi_{5,4\alpha}$ = 130°, $\phi_{5,4\alpha}$ = 130°, $\phi_{5,4\alpha}$ = 45° and $\phi_{5,4\alpha}$ = 15° should be expected for an exo-envelope conformation of **27**, an endo envelope conformation of the C-4 epimer of **27** and an exo-envelope conformation of the C-4 epimer of **27** respectively.
24. Since the submission of this manuscript we have become aware of unpublished reports of the synthesis of **29** [25] and experiments which suggest that **29** binds to the active site of the D-Ala-D-Ala-Carboxypeptidase/transpeptidase from Streptomyces R61.[26] We thank a referee for bringing this work to our attention.
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(Received in USA 22 October 1984)