FREE RADICAL CYCLIZATION IN THE SYNTHESIS OF FUSED BICYCLIC β-LACTAMS

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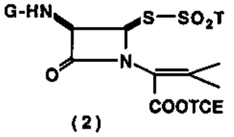
Abstract - Free radical cyclization is applied to cephalosporin synthesis. Fragmentation and deoxygenation reactions are observed.

Wittig condensations[1,2], carbene[3] and carbanion[4] cyclization reactions for the construction of fused bicyclic β-lactams are some of the well documented processes. But for a few recent reports,[5,6] radical reactions are seldom employed in β-lactam synthesis.

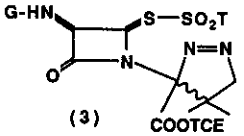
Addition of radicals to an acetylene directly attached to a sulfur atom has been elegantly utilized in the synthesis of biotins.[7] However, the course of radical cyclization is not so obvious when the substrate is a four-membered cyclic lactam as in structure (1), though ionic cyclization in a related system[8] is reported to have generated a 4,5 fused ring product. Whereas exo addition in (1) would lead to a penam (11), a "thioclavulanic" nucleus, the consequence of an endo addition would be a cephem system.

The thiosulfonate S-ester[9] (2), following reaction with diazomethane[10] in peroxide free THF afforded the diastereomeric adduct (3) as a foamy amorphous powder in 75% yield. Displacement at sulfur[9] with a protected propargylic carbanion cleanly yielded substance (4) as an oily residue, which was, without purification, reduced with zinc dust[10] to give, after filtration through a silica gel column, the azetidinone (5) (80%). It was then converted to the chloro compound (7) by reacting with t-butyl glyoxylate,[1,2] followed by mesyl chloride treatment.

Heating (7) with 1.1 equivalent of tri-n-butyltin hydride in dry toluene at 90°C for 0.5 h in presence of catalytic amount of AIBN afforded, after mild acidic (pH3) treatment, cephem (8) and the fragmentation product (9) [a 4:1 ratio of C_4 α and β isomers] along with traces of reduced product (10). No evidence of a penam/penem derivative was detected before or after the acidic work up, suggesting that an exo addition of the radical is not favored in this particular system, presumably due to relative ring strain (4/5 versus 4/6 fused ring system) considerations.



(2)



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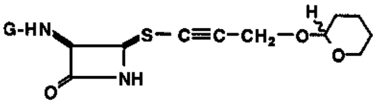

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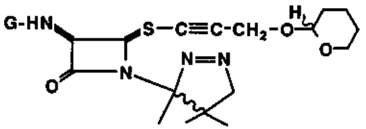

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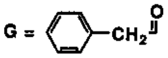
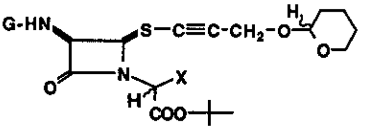
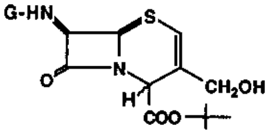


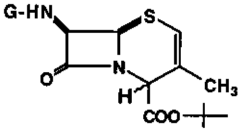
TCE = $-CH_2-CCl_3$



(1), X = •
(6), X = OH
(7), X = Cl
(10), X = H

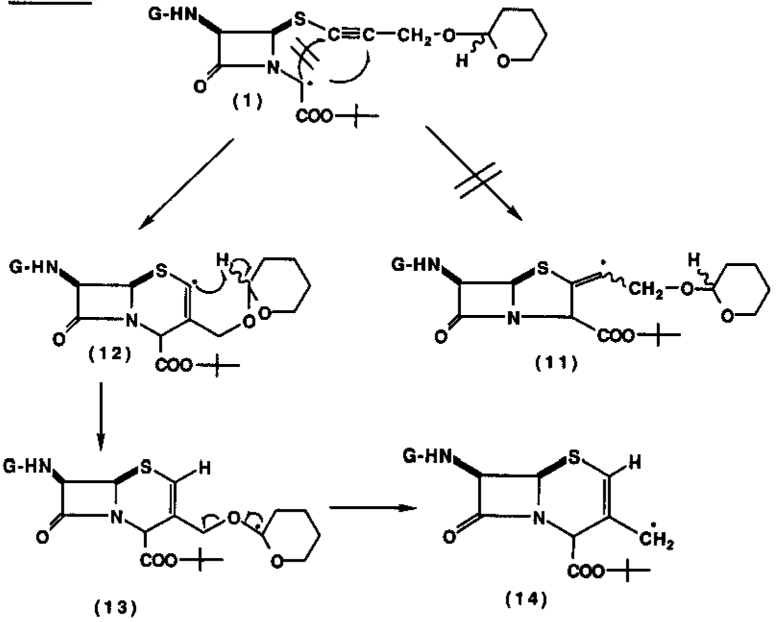


(8)



(9)

SCHEME:



Formation of (9) could be rationalized[11] as a result of hydrogen abstraction (as shown in the scheme) from the 'anomeric' position of the pyranyl ether by the transient C_2 cephem radical. The newly formed free radical (13) would then undergo fragmentation generating a stable allylic radical (14), which eventually gets quenched by the tin hydride to yield the deoxygenated product (9). Sufficient precedence exists for similar radical fragmentation reactions.[12,13]

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11. We thank Dr. S. McCombie for discussions.
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13. Prof. Dennis Curran, Dept. of Chemistry, Univ. of Pittsburg, Pittsburgh, PA, has observed similar hydrogen abstraction - private discussion.

Received, 25th July, 1988