1-(3-DIAZO-2-OXOPROPYL)-4-THIO-SUBSTITUTED AZETIDINE-2-ONES - VERSATILE INTERMEDIATES FOR THE PREPARATION OF BICYCLIC β-LACTAMS: SYNTHESIS OF NOVEL CEPHEM DERIVATIVES

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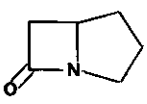
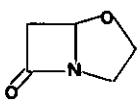
Abstract - Metal-catalyzed thermal decomposition of diazoketones 3c-3f afforded different substituted cephems, whose formation can be rationalized by assuming different reaction pathways. Possible mechanisms are proposed, and the effect of various 4-thio-substituents on the decomposition of these diazoketones are summarised.

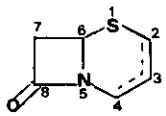
The exploitation of diazoketones 1 derived from 4-thioazetidin-1-ylacetic acids, for the preparation of novel β-lactam structures has been the subject of a number of recent reports from this and other laboratories. Depending upon the nature of the thio substituents, metal catalyzed thermal decomposition of these diazoketones afforded either carbapenams[1] and/or oxapenams[2,3], which possess interesting biological activities[4].



Carbapenam

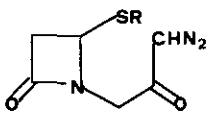


Oxapenam

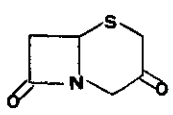


Cephem

R = aryl
heteroaryl
acrylate

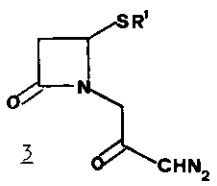


1



2

Oida and coworkers[2] reported the isolation of only 3-oxocepham 2, when diazoketone 3a, obtained from the corresponding 4-ethylthioazetidinon-1-ylacetic acid (4a), was subjected to similar decomposition conditions. Their observation confirmed our results of an analogous investigation undertaken with other S-alkyl and S-acyl substituents. It is the purpose of this communication to present our results on the carbene insertion reactions of 3b-3f here.



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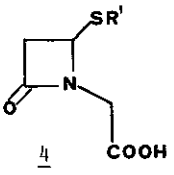
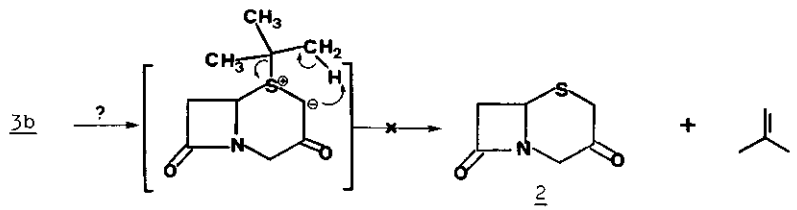


4

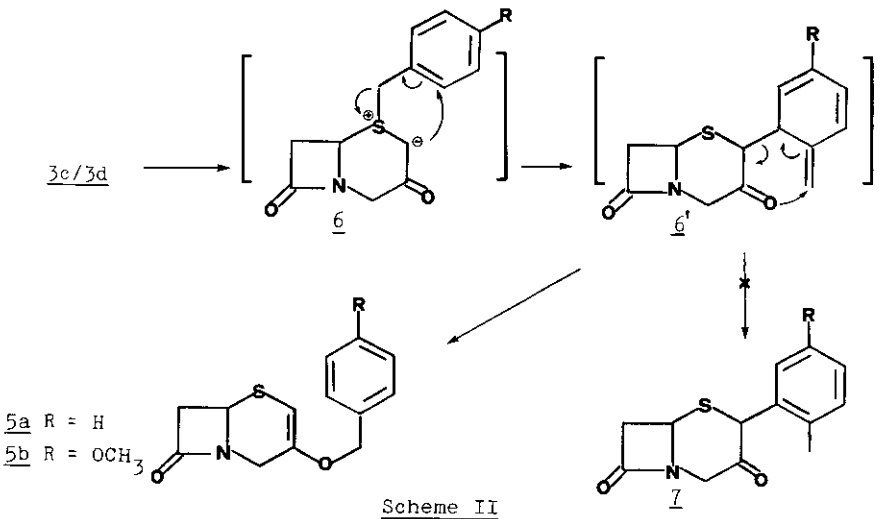
a R' = CH_2CH_3
b R' = $C(CH_3)_3$
c R' = CH_2Ph
d R' = CH_2Ph-p-OCH_3
e R' = $COCH_3$
f R' = $C(S)SCH_2CH_3$

Whereas the 4-ethylthio diazoketone 3a gave the cephem 2[5], the corresponding 4-tert-butylthio derivative 3b[6] failed to yield any identifiable products, despite the possibility of similar S-ylide formation with subsequent elimination of isobutene via a Retro-Ene reaction (Scheme I). However, treatment of the 4-benzylthio diazoketone 3c under the decomposition conditions did give a bicyclic ß-lactam[7] in 25 % yield.



Scheme I

The disappearance of the S-benzyl group together with the presence of an O-benzyl signal in the ^1H NMR spectrum suggested structure 5a for the product. Formation of 5a can best be explained by the initial reaction of the carbene with the sulfur atom to provide the ylide 6[2]; this undergoes a [2.3] sigmatropic rearrangement[8], yielding intermediate 6', which converts into 5a by yet another [3.3] shift (Scheme II).

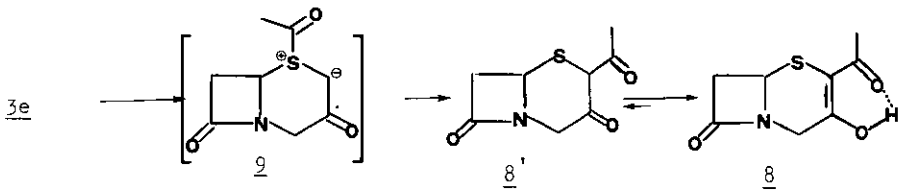


5a R = H
5b R = OCH_3

Scheme II

Compound 7, which could have been derived from 6' via prototropic aromatization, could not be isolated [9]. The presence of a p-methoxy group in the phenyl ring (3d), did not alter the course of the reaction and cephem 5b was obtained in similar yield.

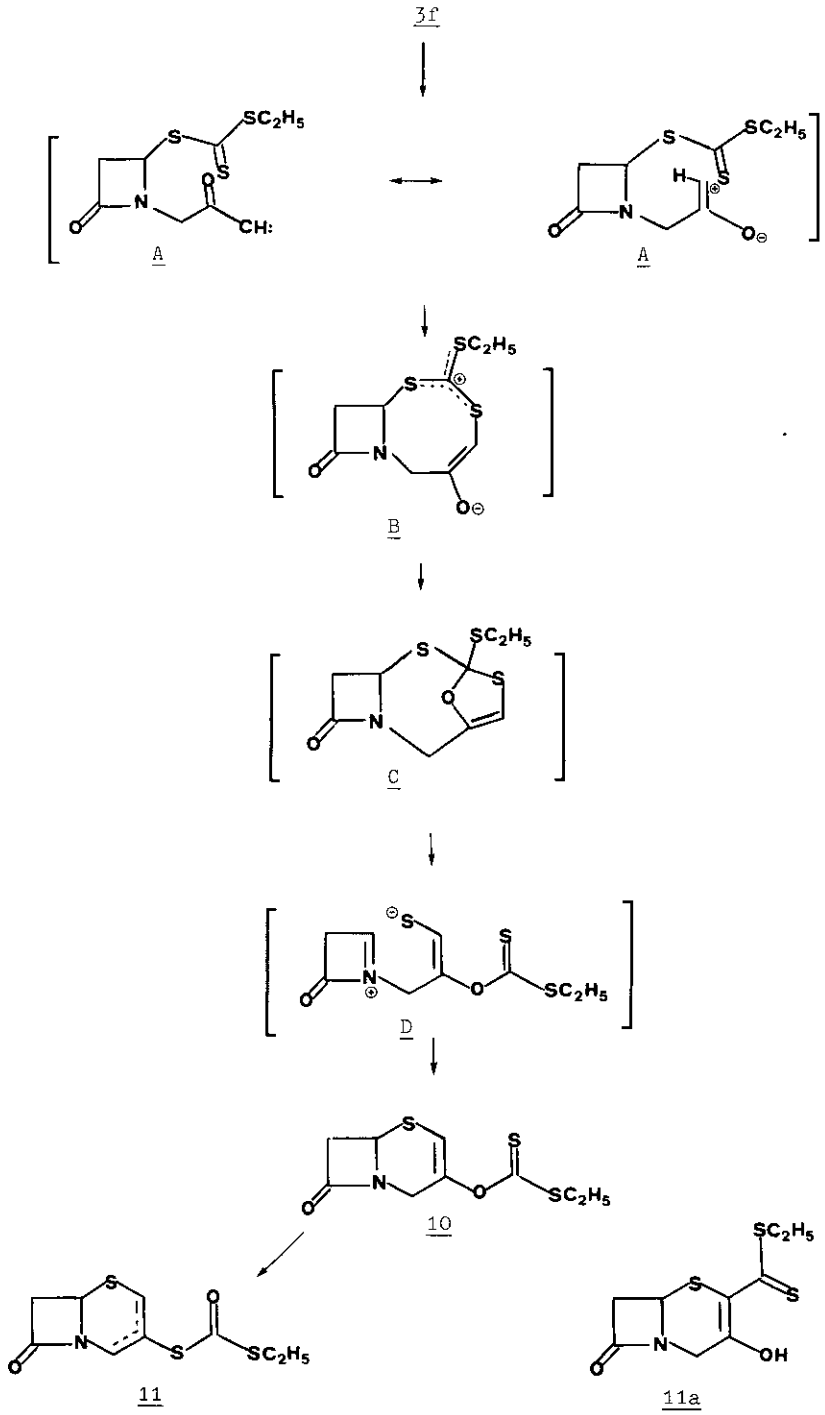
Our attention was then turned to the thioacyl substituents[6]. Heating diazoketone 3e in benzene gave a single isolable product (20 %). The ^{1}H NMR spectrum reveals the presence of a chelated hydroxyl proton at 16 ppm[7]. Structure 8 is proposed for the compound. Mechanistically, its formation could best be rationalized by direct acyl-migration of the ylide 9, followed by enolization (Scheme III).



Scheme III

When we examined the behaviour of diazoketone 3f under similar conditions, two isomeric products were isolated (17 % and 40 %). The ^{1}H NMR spectrum of the minor component is very similar to that of cephem 5, with the exception of an olefinic proton at lower field; its IR spectrum shows the characteristics of a dithiocarbonic O,S-ester, which is also evident from the presence of a signal at 212 ppm in the ^{13}C spectrum[10]. This would be in agreement with structure 10. The major isomer does not show any characteristic C=S absorption[11], and its ^{13}C spectrum is devoid of the down-field signal (as in 10). Instead, another signal appears at 196 ppm, which we attributed to the carbon of a dithiocarbonic S,S-ester. On the other hand, the ^{1}H NMR spectra of both isomers seem to be quite similar; we tentatively propose structure 11 for this compound which could be formed after rearrangement from 10 under the reaction conditions. Similar xanthate-dithiocarbonate transformations have been documented in the literature[12].

If decomposition of 3f proceeded similarly to that of 3c, one would expect 11a as the major product; this, however, was never observed. Consequently, a different mechnanism might be operative. For instance, attack of the carbene at the thione-sulfur atom could lead to a highly stabilized carbonium ion such as B. Formation of the C-O bond to give C not only establishes the enol-carbonate moiety as in the final product(s), but also would generate a bridgehead olefin. Subsequent dissociation would release strain and generate zwitterion D, which could collapse to give the 10 (Scheme IV).



Scheme IV

In summary, it has been shown that metal catalyzed decompositions of diazoketones derived from 4-thio-substituted azetidinon-1-ylacetic acids provide access to a large variety of functionalized bicyclic β-lactams, as shown in Scheme V.

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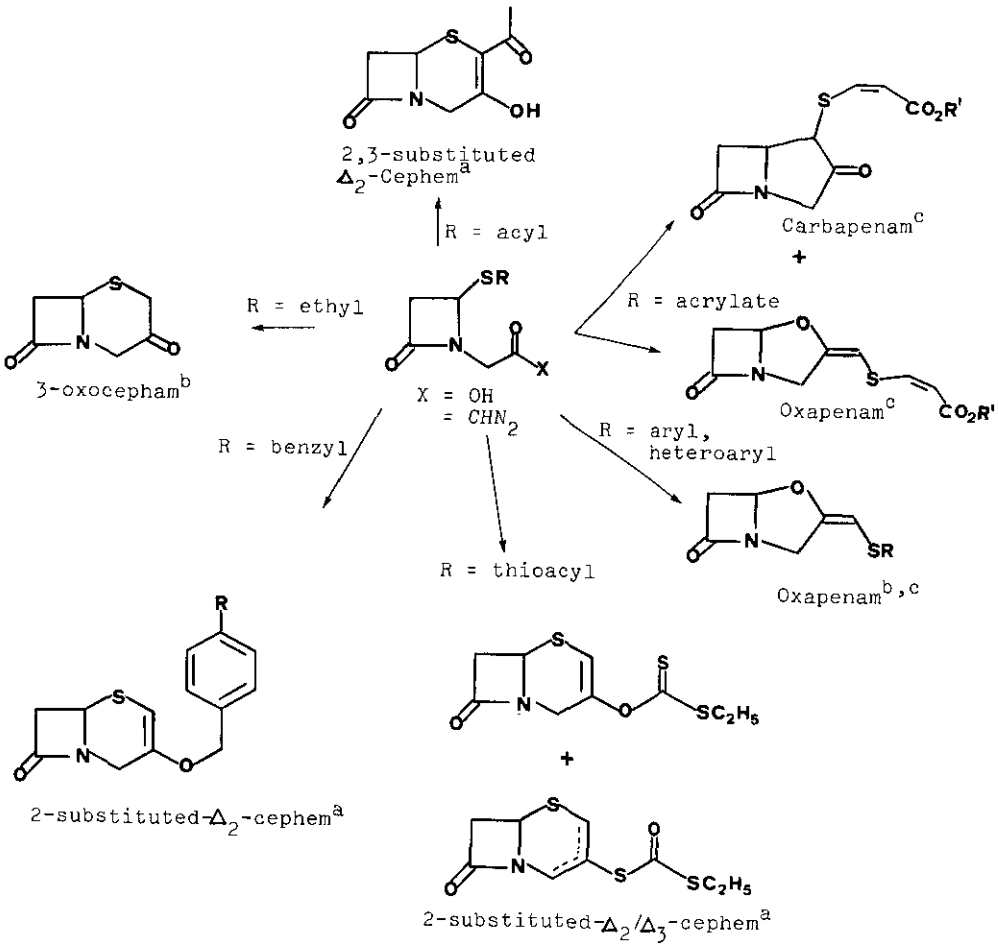
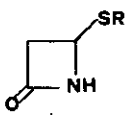


a. present communication
b. reference 2
c. reference 1 and 3

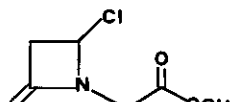
Scheme V

REFERENCES AND NOTES:

1. K. Prasad, G. Schulz, C.P. Mak, H. Hamberger, and P. Stutz, Heterocycles, 1981, 16, 1305.
2. S. Oida, A. Yoshida, and E. Ohki, Heterocycles, 1980, 14, 1999.
3. K. Prasad and P. Stütz, Heterocycles, 1982, 19, 1597.
4. C.P. Mak, K. Prasad, and F. Tumowsky, J. Antibiotics, submitted for publication.
5. Decomposition of the diazoketone 3 was routinely performed in hot benzene (~0.01 M), in the presence of a catalytic amount of copper acetylacetonate or rhodium acetate. The product was isolated by column chromatography of the crude reaction mixture.
6. Diazoketones 3a-3f were prepared according to previously employed conditions[1] from the corresponding azetidinon-1-ylacetic acid 4, which were either synthesized by direct alkylation of the thio-substituted azetidinone 1 with methyl bromacetate, followed by alkaline hydrolysis, or by introduction of the respective mercapto function via the chloroazetidinone 11[3].



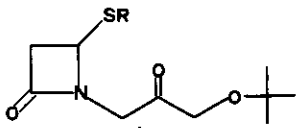
i



ii

7. Selected physical data: -5a: ir($CHCl_3$) 1765, 1625 cm^{-1}; nmr($CDCl_3$) δ 2.88 (dd, 1, J = 1.5, 15 Hz), 3.42 (ddd, 1, J = 2, 4, 15 Hz), 3.60 (dd, 1, J = 2, 17.5 Hz), 4.27 (dd, 1, J = 2, 17.5 Hz), 4.73 (dd, 1, J = 1.5, 4 Hz), 4.83 (s, 2), 5.30 (d, 1, J = 2 Hz), 7.35 (d, 5). 5b: ir(KBr) 1755, 1610 cm^{-1}; nmr($CDCl_3$) δ 2.87 (dd, 1, J = 1.5, 13.5 Hz), 3.38 (ddd, 1, J = 1.5, 4, 13.5 Hz), 3.58 (dd, 1, J = 2, 18 Hz), 3.80 (s, 3), 4.20 (dd, 1, J = 2, 18 Hz), 4.68 (dd, 1, J = 1.5, 4 Hz), 4.72 (s, 2), 5.28 (d, 1, J = 2 Hz), 6.90 (d, 2, J = 9 Hz), 7.26 (d, 2, J = 9 Hz). 8: ir(CH_2Cl_2) 1770 cm^{-1}; nmr($CDCl_3$) δ 2.30 (s, 3), 2.92 (dd, 1, J = 1.5, 16 Hz), 3.53 (ddd, 1, J = 1.5, 4, 16 Hz), 3.80 (dd, 1, J = 1.5, 19 Hz), 4.39 (d, 1, J = 19 Hz), 4.82 (dd, 1, J = 1.5, 4 Hz), 16.0 (br, 1). 10: ir(CH_2Cl_2) 1765, 1380, 1160, 1120, 1100, 1020 cm^{-1}; nmr($CDCl_3$) δ 1.37 (t, 3, J = 7.3 Hz), 2.97 (dd, 1, J = 1.5, 14.7 Hz), 3.16 (q, 2, J = 7.3 Hz), 3.46 (ddd, 1, J = 1.5, 4, 14.7 Hz), 3.72 (ddd, 1, J = 0.5, 1.5, 17.5 Hz), 4.36 (dd, 1, J = 2, 17.5 Hz), 4.84 (dd, 1, J = 1.5, 4 Hz), 6.08 (dd, 1, J = 0.5, 2 Hz); ^{13}C nmr($CDCl_3$) δ 12.9 (q), 31.3 (t), 38.9 (t), 45.7 (t), 46.8 (d), 110.5 (d), 140.4 (s), 164.4 (s), 213.5 (s). 11: ir(CH_2Cl_2) 1765, 1660, 1520 cm^{-1}; nmr($CDCl_3$) δ 1.34 (t, 3, J = 7.3 Hz), 2.90 (q, 2, J = 7.3 Hz), 3.15 (dd, 1, J = 2, 16 Hz), 3.50 (ddd, 1, J = 1, 4.5, 16 Hz), 3.91 (d, 1, J = 17 Hz), 4.28 (dt, 1, J = 2, 17 Hz), 4.91 (dd, 1, J = 2, 4 Hz), 6.20 (br, 1); ^{13}C nmr($CDCl_3$) δ 12.5 (q), 28.9 (t), 45.5 (t), 52.0 (d), 57.3 (t), 126.6 (d), 148.5 (s), 167.0 (s), 194.7 (s).
8. W. Ando, M. Yamada, E. Matsuzaki, and T. Migita, J. Org. Chem., 1972, 37, 3791.

9. When the reaction was performed in tert-butanol, only about 5 % of the cephem 5 was isolated and about 20 % of the tert-butyl ether 11i was also obtained.



11i

10. Sadtler Standard Carbon-13 NMR Spectra, Philadelphia, 1976.

11. D. Dolphin and A. Wick, 'Tabulation of Infrared Spectral Data', J. Wiley and Sons, New York, 1977.

12. I. Degani, R. Fochi, and V. Regondi, Synthesis, 1980, 375, and references cited therein.

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