# METAL CATALYZED DECOMPOSITION OF DIAZOKETONES AND DIAZOAMIDES OF ß-LACTAMS
## PART I: PENICILLIN ROUTE TO CARBAPENEMS ?

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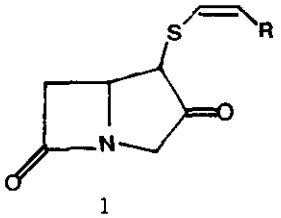
Abstract: Metal catalyzed decomposition of diazoketones and diazoamides derived from penicillanic acid were investigated as approaches towards the synthesis of the carbapenem nucleus. Diazoketones derived from C-3 gave products of insertion into the C-5/S bond with inversion of stereochemistry. Homologous diazoketones yielded the tricyclic amino-diketone 10, derived from carbene insertion into the amide bond exclusively. Attaching the diazo group to the amino function led either to insertion into solvent or gave decomposition products.

Since the discovery of several novel fused ß-lactam antibiotics such as thienamycin[1], clavulanic acid[2], etc., considerable interest in the synthesis of the "non-classical" ß-lactams is evident from the literature[3]. We have recently reported a new synthesis of the carbapenam 1 from diazoketone 2 via intramolecular carbene insertion[4].

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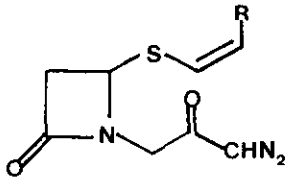
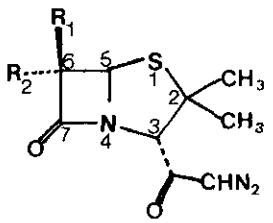
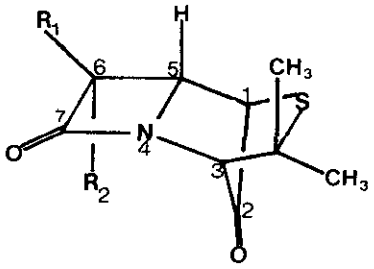



2

Our interest in the carbene approach was based on the earlier observation of Ernest[5], who reported that copper (II) catalyzed decomposition of diazoketones 3 resulted in the formation of tricyclic ketones 4. This could potentially be an entry to the carbapenam structure from readily available penicillin derivatives. Recently, Ponsford[6] has reported the isolation of an additional type of fused ß-lactam 5 from the decomposition of diazoketone 3. Intermediate structures, A — B — C — A , have been proposed.





3a $R_1 = R_2 = H$

3b $R_1 = H$, $R_2$ = phthalimido

3c $R_1$ = phthalimido, $R_2 = H$

4a $R_1 = R_2 = H$

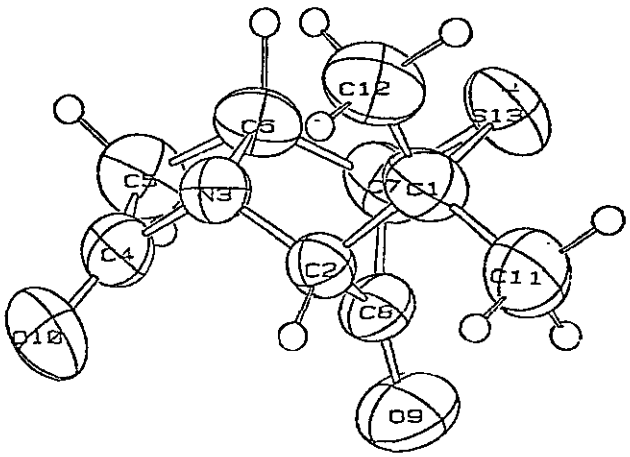
4b $R_1 = H$, $R_2$ = phthalimido

4c $R_1$ = phthalimido, $R_2 = H$

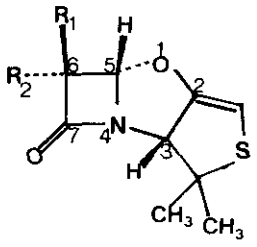
We felt that the sterochemical outcome of this reaction might be influenced by the substituents on C-6, since only 6β-substituted diazoketones (3, $R_2 = H$) have been studied, and these had all led to tricycles 4 with "underisable" stereochemistry at C-5. The C-6 unsubstituted product (4a, $R_1 = R_2 = H$) was reported by Ponsford[6] to be spectroscopically analogous to the 6β-substituted series. Our experiments also confirm these findings and we were able to obtain 4a by thermal decomposition of the diazoketone 3a, in the presence of copper (II) acetylacetonate in tetrahydrofuran or benzene at 80° C. Direct crystallization from the crude product mixture afforded 4a[7] in 60 % yield; clavam 5a (5 %) was isolated by column chromatography of the mother liquor. In order to confirm the structure of 4a, an X-ray diffraction study was performed[8]. A perspective view of the molecule is shown in figure 1; thus, the stereochemistry at C-5 was found to be consistent with the result of Ernest.

Figure 1

Perspective view of 4a showing the atomic numbering and the 50 % probability thermal vibration ellipsoids of the heavy atoms (ORTEP drawing).



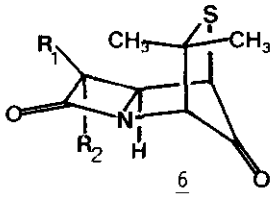
When the 6 α-phthalimido diazoketone 3b, prepared by triethylamine induced epimerization of the 6β-phthalimido diazoketone 3c[9], was treated similarly, decomposition of the compound proceeded smoothly to give the tricycles 4b (76 %) and 5b (7 %), which were separated by chromatography. Coupling constants of 5.9 Hz (4b) and 2.5 Hz (5b) are in agreement with the cis-pattern on the C-5/C-6 substituents.



5a $R_1 = R_2 = H$

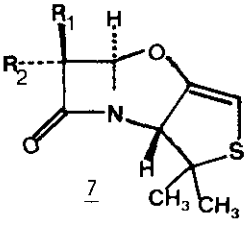
5b $R_1 = H$, $R_2$ = phthalimido

5c $R_1$ = phthalimido, $R_2 = H$



6

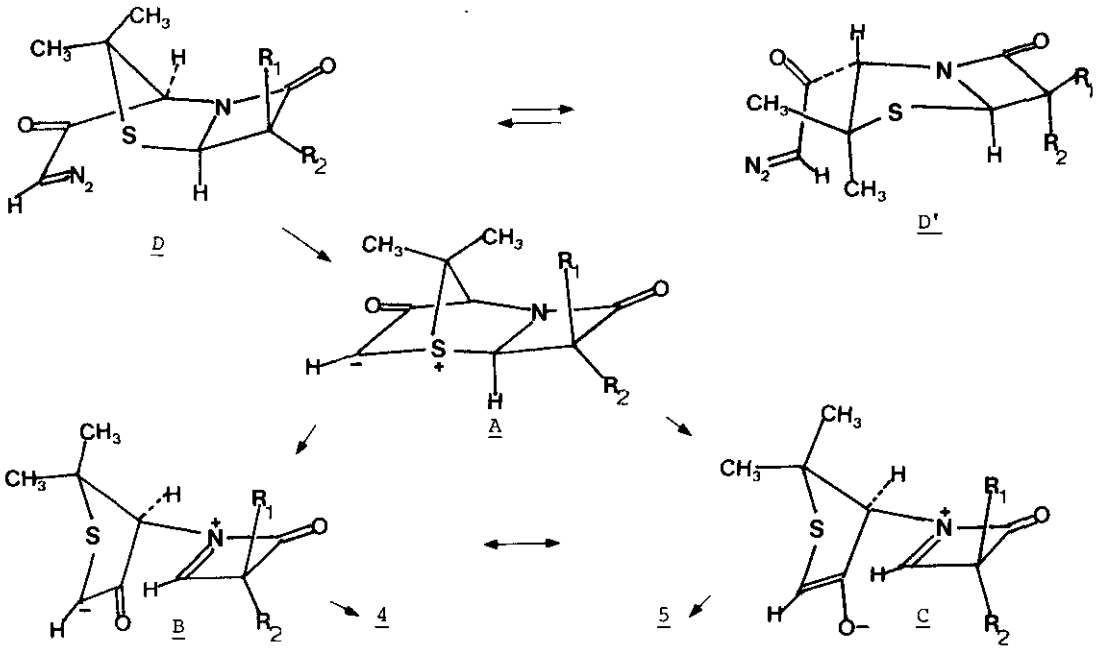
6 $R_1 = H$, $R_2$ = phthalimido



7

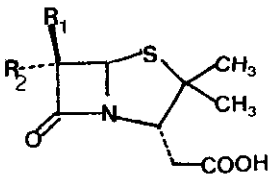
7 $R_1 = H$, $R_2$ = phthalimido

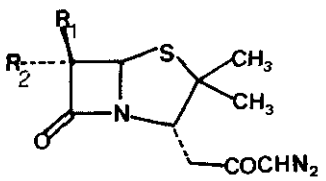
The exclusive stereochemical outcome of the observed product at C-5 is interesting in so far as the attack of the incoming nucleophile occurs only from the α-side of the proposed azetidinone intermediate B/C, despite considerable steric hindrance from the bulky group ($R_2$ = phthalimido). Inspection of molecular models suggests the required conformation of the diazoketone and/or the acyl carbene for the initial ylide formation to be D, which could easily be adopted by having bulky substituents on the α-side (e.g. 3b). With a bulky group on the β-side (3c), one should expect conformation D' as the more stable one, which would require ring inversion of the thiazolidine ring before ylide formation can take place. These assumptions are consistent with the observation that the decomposition of the α-phthalimido diazoketone 3b proceeds much more cleanly and gives better yields of the tricycle 4b than the β-isomer 3c. The ylide A should be very unstable due to an anomeric effect by the β-lactam nitrogen and formation of the immonium enolate intermediate B/C should be very facile. Subsequent C-C or C-O bond formation to 4b or 5b is kinetically controlled ("least motion" pathway), since formation of the new bonds from the β-side would require major conformational changes of B/C, although the corresponding products 6 or 7 should be expected to be thermodynamically much more stable.



Although the tricycle 4b seems to be quite stable to chromatographic conditions treatment of it with an excess of triethylamine in methylene chloride at room temperature resulted in an immediate and quantitative epimerization of the phthalimido group to the β-position, affording the trans-substituted tricycle 4c, identical in all respects to that described by Ernest ($J_{5,6}$ = 3.5 Hz).

However, base-catalyzed reaction of the clavam 5b proceeded more sluggishly. Pyridine failed to effect any epimerization while more potent bases (DBU, PMDBD) yielded no β-lactam products. Triethylamine treatment did give a cis ($J_{5,6}$ = 2.8 Hz)/trans ($J_{5,6}$ = 0.8 Hz) mixture of 5b/5c in a ratio of 5/95 (nmr integration) over a period of 40 h at room temperature. The structure 5c was assigned for the trans compound on the basis of $^1$H-nmr studies. A positive NOE was observed between H-3 and H-5 of 5c; this would be in disagreement with structure 7, (H-5/H-6 are trans) resulting from the attack of triethylamine at C-5, and subsequent recyclisation[10].





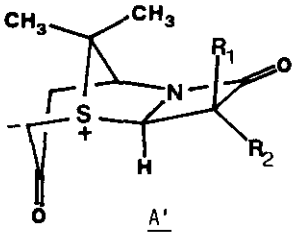
8a $R_1$ = H, $R_2$ = phthalimido

8b $R_1$ = phthalimido, $R_2$ = H

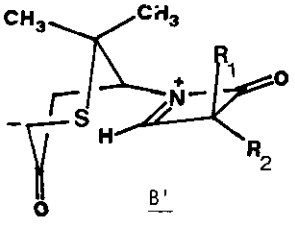
9a $R_1$ = H, $R_2$ = phthalimido

9b $R_1$ = phthalimido, $R_2$ = H

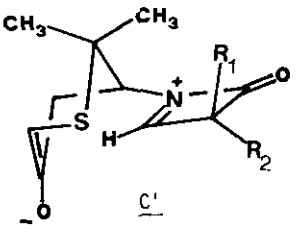
In order to explore the scope of this carbene insertion reaction we prepared homologous diazoketones 9a and 9b. It was hoped that the homologous immonium-enolate B'/C' resulting from ylide A' would adopt conformations less favourable to rapid ring closure from the α-face, thereby affording products such as 10'. Compounds 9a and 9b were prepared from acids 8a and 8b (mixed anhydride of isobutyl chloroformate, diazomethane, -70° C to room temperature), which in turn were obtained by photolysis (310 nm, dioxane/water) of 3b and 3c respectively. However the only product observed from reaction of either 9a or 9b was aminodiketone 10 (70 %). Rather than forming ylide A', the carbene inserted into the amide bond[11].



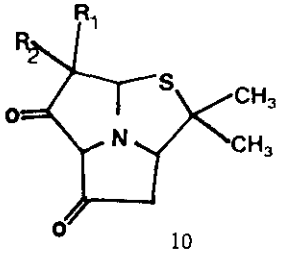
A'



B'



C'



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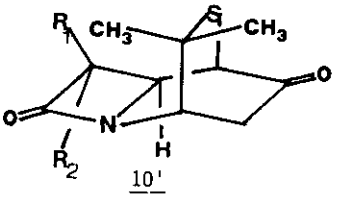
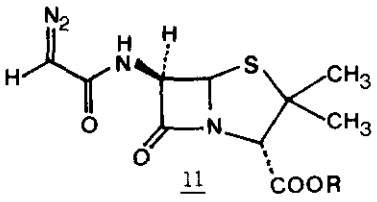
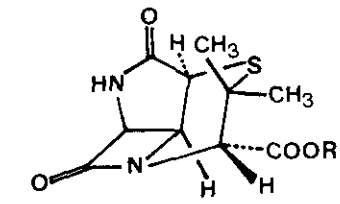


10'

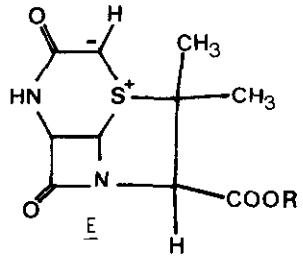
Since we had not been successful in achieving carbon-carbon bond formation at C-5 with "desired" chirality using diazoketones derived from C-3[12], we looked at the corresponding reaction with diazoamide 11 derived from C-6, in the hope that the carbene would add to the sulfur yielding ylide E, which could collapse only from the β-side to give tricycle 12. The diazoketone 11 was prepared by reaction of 6-aminopenicillanic acid pivaloyloxymethyl ester 13 with the acid chloride 14[13] (methylene chloride, excess triethylamine) in 70 % yield.



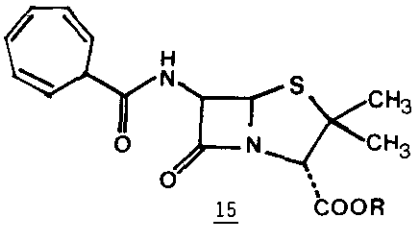
11



12



E



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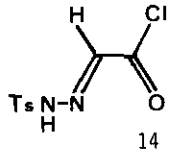

14

R = pivaloyloxymethyl

Decomposition of the diazoamide 11 in refluxing benzene, in the presence of copper (II) acetylacetonate or rhodium (II) acetate did not give the desired product 12 but the cycloheptatriene 15 (25 %) resulting from the insertion of the carbene into solvent [14]. When tetrahydrofuran or 1,2-dichloroethane was used as solvent, extensive decomposition took place.

Transformation of these tricycles into novel β-lactam compounds is presently being investigated.

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## REFERENCES AND NOTES


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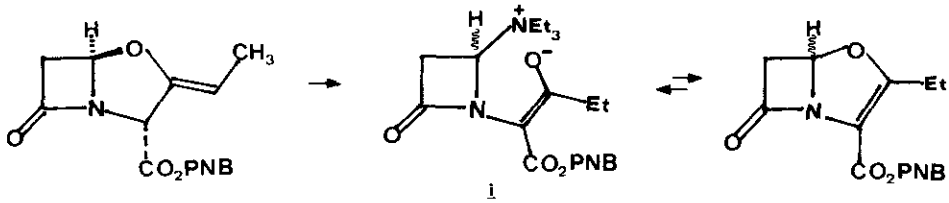
6. R.J. Ponsford, Tet. Lett., 1980, 21, 2451.

7. Satisfactory microanalytical and/or high resolution mass spectral data were obtained for all new compounds reported. Selected physical data: 3b: ir ($CHCl_3$) 2110, 1780, 1730, 1640 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 1.56 (s, 3), 1.73 (s, 3), 4.27 (s, 1), 5.32 (s, 2), 5.90 (s, 1), 7.75 - 8.05 (m, 4). 4b: ir ($CHCl_3$) 1780, 1730, 1390 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 1.56 (s, 3), 1.61 (s, 3), 3.53 (s, 1), 3.85 (s, 1), 4.34 (d, 1, J = 5.9 Hz), 5.89 (d, 1, J = 5.9 Hz), 7.75 - 8.05 (m, 4). 5b: ir ($CHCl_3$) 1810, 1785, 1730, 1390 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 1.54 (s, 3), 1.58 (s, 3), 5.26 (d, 1, J = 2.5 Hz), 5.50 (d, 1, J = 2.5 Hz), 5.66 (d, 1, J = 2.5 Hz), 5.78 (d, 1, J = 2.5 Hz), 7.75 -8.05 (m, 4). 5c: nmr ($CDCl_3$) $\delta$ 1.56 (s, 3), 1.58 (s, 3), 4.90 (d, 1, J = 2.5 Hz), 5.37 (d, 1, J = 0.8 Hz), 5.56 (d, 1, J = 2.5 Hz), 5.92 (d, 1, J = 0.8 Hz), 7.75 - 8.00 (m, 4). 9a: ir (KBr) 2110, 1770, 1720, 1630 $cm^{-1}$ nmr ($CDCl_3$) $\delta$ 1.42 (s, 3), 1.56 (s, 3), 2.30 - 2.80 (ABX, 2, J = 17, 8, 6 Hz), 4.50 (dd, 1, J = 8, 6 Hz), 5.32 (d, 1, J = 2 Hz), 5.38 (d, 1, J = 2 Hz), 5.58 (s, 1), 7.70 - 8.00 (m, 4). 9b: ir (KBr) 2100, 1790, 1770, 1720, 1640 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 1.45 (s, 3), 1.75 (s, 3), 2.30 - 2.80 (ABX, 2, J = 17, 8, 6 Hz), 4.50 (dd, 1, J = 8, 6 Hz), 5.36 (d, 1, J = 5 Hz), 5.42 (s, 1), 5.60 (d, 1, J = 5 Hz), 7.70 - 8.05 (m, 4). 10: nmr ($CDCl_3$) $\delta$ 1.59 (s, 3), 1.61 (s, 3), 2.33 (dd, 1, J = 15.3, 4.3 Hz), 2.41 (dd, 1, J = 15.3, 13.9 Hz), 3.20 (dd, 1, J = 13.9, 4.3 Hz), 4.33 (d, 1, J = 1.2 Hz), 4.90 (d, 1, J = 7.15 Hz), 4.98 (d, 1, J = 7.15 Hz), 7.70 - 8.00 (m, 4). 11: ir ($CHCl_3$) 2110, 1790, 1760, 1630 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 1.23 (s, 9), 1.54 (s, 3), 1.66 (s, 3), 4.44 (s, 1), 4.89 (s, 1), 5.46 (d, 1, J = 4.5 Hz), 5.70 - 5.95 (m, 1), 5.77 (d, 1, J = 5.8 Hz), 5.90 (d, 1, J = 5.8 Hz). 15: nmr ($CDCl_3$) $\delta$ 1.24 (s, 9), 1.54 (s, 3), 1.68 (s, 3), 2.77 (t, 1, J = 7 Hz), 4.47 (s, 1), 5.40 - 5.60 (m, 2), 5.58 (d, 1, J = 4.5 Hz), 5.77 (dd, 1, J = 9, 4.5 Hz), 5.80 (d, 1, J = 6.5 Hz), 5.92 (d, 1, J = 6.5 Hz), 6.25 -6.45 (m, 3), 6.65 -6.75 (m, 2).

8. In our opinion, the assignment of the stereochemistry at C-5 of the 6-unsubstituted tricycle 4a was inconclusive from $^1$H-nmr studies. Therefore an X-ray study of this compound was performed.

9. B.G. Ramsay and R.J. Stoodley, J. Chem. Soc. (C), 1969, 1320.

10. Similar reactions of clavams with triethylamine or pyridine have been reported to give betaine intermediate i, which would recyclize on heating; see C.E. Newall, "Recent advances in the chemistry of β-lactam antibiotics", ed. G.I. Gregory, Burlington House, London, 1981, pp 151-169.

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11. Details of this reaction will be reported in a forthcoming communication.

12. We believe that the decomposition of diazoketones derived from C-3β penicillanic acid would give C-C bond formation with the "desired" stereochemistry. We are at present investigating the epimerization of the acid.

13. C.J. Blankley, F.J. Sauter and H.O. House, Org. Syn., Coll. Vol. V, 1973, pp 258.

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