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Preliminary communication

THE SYNTHESIS OF α-HALO-β-LACTAMS BY THERMAL DECOMPOSITION OF DIETHYLTHALLIUM DIHALOAMIDES

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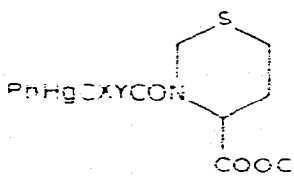
Summary

Fused α-halo-β-lactams are formed by the reaction of diethylthallium t-butoxide with dihaloacetamides in bromobenzene.

Diethylthallium t-butoxide is known to react with chloroform in the presence of cyclohexene to yield dichloronorcarane [1]. The reaction was assumed to proceed via the formation of diethyl(trichloromethyl)thallium, which by α-elimination afforded diethylthallium chloride and dichlorocarbene. Similar reactions have also been extensively studied by McKillop and co-workers [2].

We had earlier prepared penicillin analogues via halo-β-lactams, which were formed from halocarbenoids generated by the α-elimination of phenylmercury halide from phenylmercury dihaloamides [3—7]. Unfortunately, these reactions invariably produced very low yields of β-lactams fused to sulfur containing moieties [6, 7], presumably due to the strong affinity of mercury for sulfur, and the mercury compounds I, II, which are potential starting materials for the synthesis of cephalosporin analogues, could not be prepared in isolable amounts. We thus decided to see whether carbene generation via thallium compounds would yield the desired cephalosporin analogues. By treating diethylthallium t-butoxide [1] with the dihaloamides III or IV** we have prepared the cepham derivatives V and VI*, albeit in low yields (2—5%). With no sulfur present in the starting dihalo-



(I) X = Y = Br
(II) X = Br, Y = Cl

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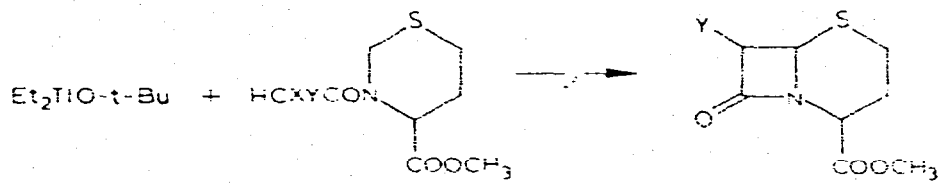
**The compounds III and IV are prepared from DL-1,3-thazane-4-carboxylic acid, which was obtained by the condensation of DL-homocysteine thiolactone with formaldehyde.

*The compounds were characterized by IR, NMR and mass spectroscopy.



(III) X = Y = Br
(IV) X = Br, Y = Cl

(V) Y = Br
(VI) Y = Cl

(VII) X = Y = Br
(VIII) X = Br, Y = Cl

(IX) Y = Br
(X) Y = Cl

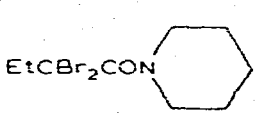
amides, greater yields of β-lactams are obtained. For instance, the yields of the β-lactams IX and X were 18 and 26%, respectively.

The general procedure was as follows. Diethylthallium t-butoxide was prepared from unsolvated potassium t-butoxide and diethylthallium bromide in diethyl ether or tetrahydrofuran (THF) solution at room temperature (with diethyl ether, potassium bromide precipitation was essentially quantitative). After filtration the solution was added to a bromobenzene solution of the appropriate dihaloamide, the solution being kept at 100° C during the addition to remove the diethyl ether or THF and t-butanol. The reaction was completed by heating during 30 min at 110°C for the thiazane derivatives III and IV and during 2.5 h at reflux for the simpler dihaloamides VII and VIII. The precipitated diethylthallium bromide was removed and the mixture worked up in the usual way.

The C-alkylated amide XI was isolated (ca. 2% yield) from the reaction of VII with diethylthallium t-butoxide. It is probably derived by reductive elimination of XI from an intermediate trialkylthallium compound. A similar reaction was observed by Gilman and Jones in the triarylthallium series [8].

In the choice between diethylthallium bromide and chloride the bromide was eliminated exclusively. The same feature is found in the mercury-promoted reaction [5]. These results reflect the "soft" acid character of thallium and mercury.

Both the *trans*- and *cis*-isomers of the halo-β-lactams (IX, X) were obtained in the thallium-promoted reaction, the *trans/cis* ratio being ca. 5.



(XI)

Several minor modifications of the procedure have been tried. For example: (i) the diethyl ether or THF was removed before treatment of diethylthallium t-butoxide with the appropriate dihaloamide, (ii) benzene was used as solvent for the cyclization step, (iii) attempts were made to synthesize the intermediate trialkylthallium compound by generating the anion of the dihaloamides and treating it with diethylthallium bromide. All these changes led to no or lower yields of the halo-β-lactams. An attempt to use diethylthallium methoxide instead of the t-butoxide was completely unsuccessful.

The fact that ca. 85% of the calculated amount of diethylthallium bromide separated from the cyclization reactions, taken along with the low recovery of the starting dihaloamides (10—25%) indicates that the carbene generation was efficient, and so it should be possible to improve the yields of the β-lactams. However, for dihaloamide VIII, the yields are the same in the thallium- and mercury-promoted reactions. Similarly, the yields of the halocephams V and VI from the amides III and IV by the thallium-induced synthesis are comparable with those obtained for halopenams [6, 7] by the mercury route. (The compounds V and VI could not be obtained by this method, see also above). A considerable advantage of the thallium-induced synthesis is that no steps corresponding to the isolation and purification of the phenylmercury amides are required.

Acknowledgement

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