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REGIOSELECTIVE RING EXPANSION OF 3,3-DIMETHYLAZIRIDIN-2-CARBOXYLATE AND A PHOTOCHEMICAL ENTRY TO THE PENEM NUCLEUS[1]

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Abstract – 3,3-Dimethylaziridin-2-carboxylates undergo ring expansion with thiocyanates to give a 4,4-dimethylthiazolidin-5-carboxylate as the major product. Irradiation of a *N*-cysteinyl-3,3-dimethylaziridin-2-carboxylate was found to give a penem in low yield, presumably via a transient thioaldehyde which added across the aziridine N-C(3) bond.

The aziridine ring is a valuable synthon for the preparation of larger heterocycles via ring expansion.[2] For an unsymmetrically substituted aziridine, ring enlargement can be programmed in a manner that results in scission of either of the C–N bonds (paths a or b), or in the special case of azomethine ylides, at the C–C bond (path c) (Figure 1). Our interest in aziridine ring expansion evolved from the proposition that they can lead to novel thiazolidine derivatives and can be used to construct a portion of the penem nucleus.[3] Herein, we report that 3,3-dimethylaziridin-2-carboxylate (**1**) undergoes regioselective ring expansion via either path a or path b with thiocyanates, a process which affords substituted thiazolidines. We have also found that a photochemical application of aziridine ring expansion provides access to the bicyclic nucleus of penems.

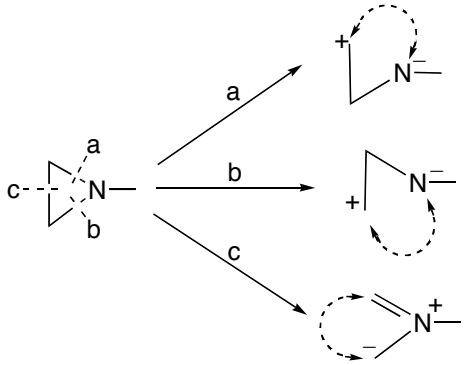
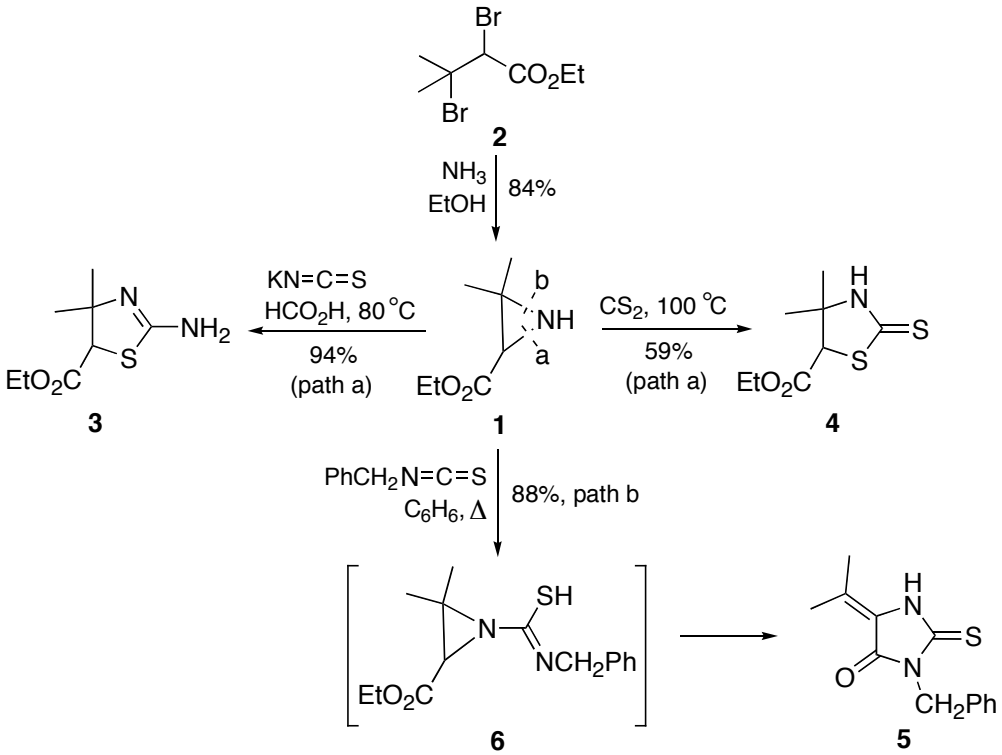


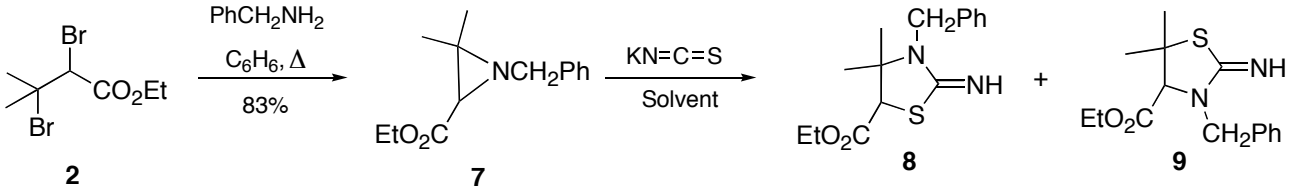
Figure 1. Ring expansion pathways of aziridines leading to heterocycles

Ethyl 3,3-dimethylaziridin-2-carboxylate (**1**) was prepared by reaction of ethyl 2,3-dibromo-3-methylbutanoate (**2**)[4] with ammonia-saturated ethanol[5] (Scheme 1). Exposure of **1** to potassium thiocyanate in hot formic acid led cleanly to crystalline thiazoline **3** (mp 103-104 °C), indicating that aziridine cleavage in this case followed path a. The same cleavage mode was observed when **1** was reacted with carbon disulfide and resulted in crystalline thiazolidinethione **4** (mp 99 °C).[6] On the other hand, treatment of **1** with benzyl isothiocyanate in benzene at reflux gave the hydantoin derivative **5**. The latter is believed to be formed via transient *N*-substituted aziridine **6** which undergoes internal acylation by the carboxylic ester. Aziridine fragmentation at bond b then generates the isopropylidene substituent.



Scheme 1

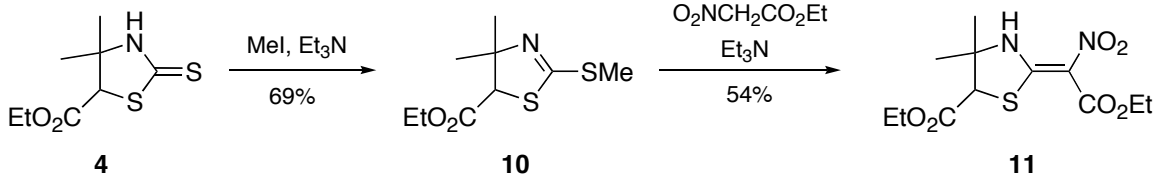
We also examined the reactivity of *N*-substituted aziridine **7** which was prepared by treatment of dibromo ester **2** with benzylamine in benzene at reflux[7] (Scheme 2). In contrast to **1**, which gave a single product **3** with potassium thiocyanate, the analogous reaction of **7** produced a mixture of regioisomeric thiazolidines **8** and **9**, the ratio of which depended upon polarity of the solvent. In a neutral solvent such as THF, the major product was **8**, but as the acidity of the reaction medium was increased the proportion of **9** also increased. This suggests that opening of the protonated aziridine from **7** increasingly favors path b of Figure 1, as would be expected on the basis of relative carbocation stabilization at C2 vs C3.



Solvent	Yield %	Ratio 8:9
THF	95	88:12
HOAc	88	74:26
HCO_2H	91	54:46

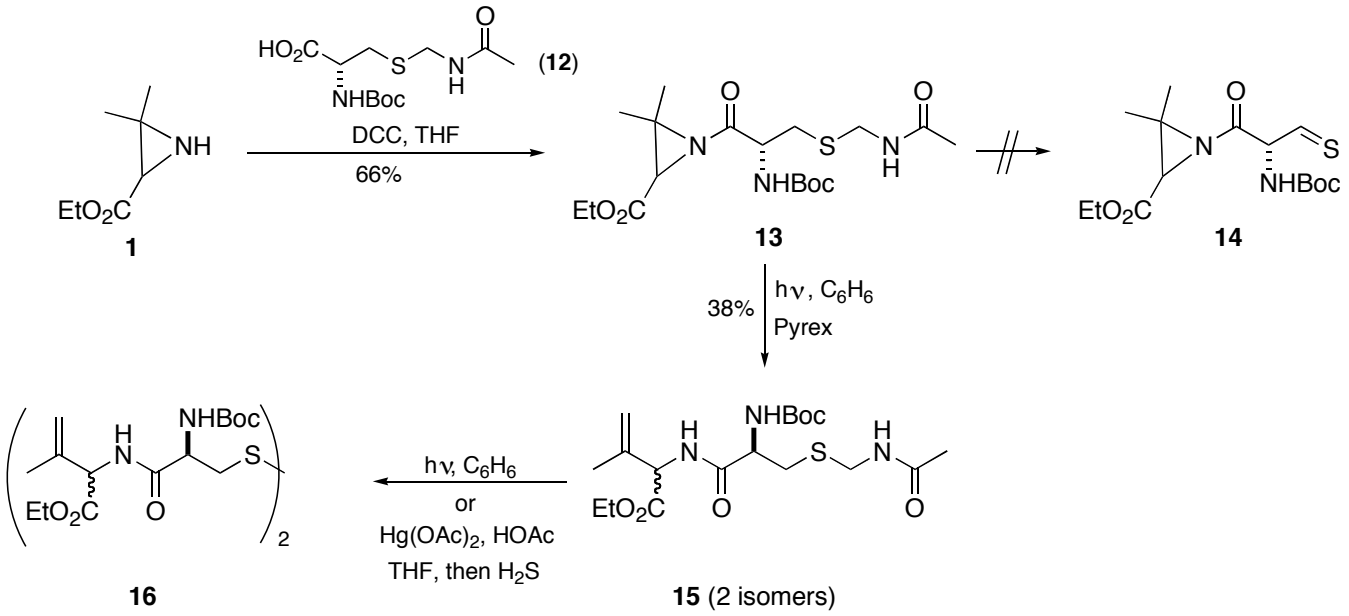
Scheme 2

Alkylation of 2-thionothiazolidines has been investigated,[8] and in concordance with previous results **4** was found to react with methyl iodide exclusively at the exo sulfur atom to yield **10** (Scheme 3). Thiazoline **10** provided an opportunity to test a strategy for appending functionality at C2 which could be used to build the isopenem nucleus, and it was found that condensation of **10** with the anion of ethyl α-nitroacetate led efficiently to **11**.[9] However, neither catalytic hydrogenation nor other reduction methods were successful in saturating the double bond of **11**.



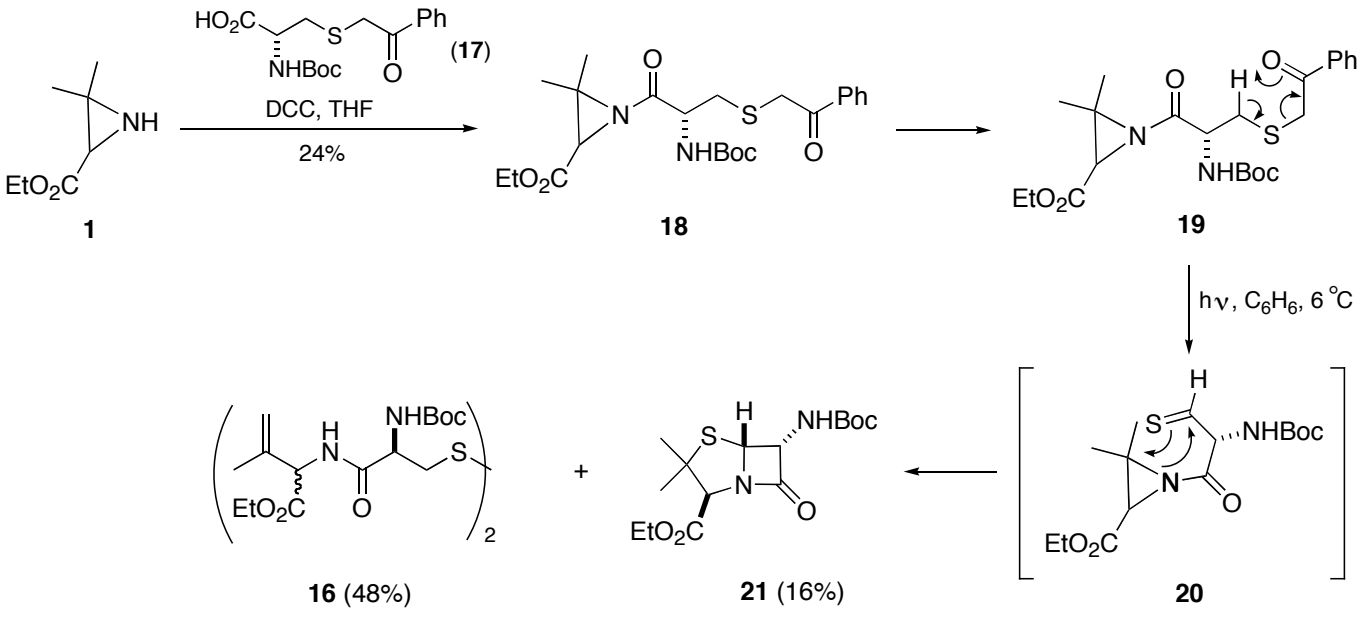
Scheme 3

The Arnstein postulate[10] as extended by Baldwin,[11] that the penicillin nucleus is formed in Nature via oxidation of a α-aminoadipoylcysteinylvaline tripeptide to a thioaldehyde has gained experimental support,[12] and in an attempt to simulate this pathway using aziridine **1** the latter was acylated with *S*-protected *N*-Boc cysteine derivative **12**.[13] Our hope was that photolysis of *N*-acylaziridine **13** would lead to cleavage of the acetamidomethyl appendage affording thioaldehyde **14** which would then add to the aziridine and yield a penem. However, the only product that could be isolated from this reaction was **15** resulting from Norrish type II cleavage of the acylaziridine. Further photolysis of **15** or treatment of **15** with mercuric acetate at pH 4 gave disulfide **16**, presumably via homolytic fracture of the C–S bond adjacent to the acetamide function followed by homocoupling of the sulfide radical.



Scheme 4

The formation of **16** upon extended photolysis of **15** and the failure of **13** to furnish a substance with the penem skeleton suggested that a more labile photocleavable group than the acetamidomethyl substituent was needed. Accordingly, **1** was acylated with *S*-benzoylmethyl-*N*-Boc cysteine derivative **17**[14] in the expectation that photolysis of sulfide **18** would result in activation via **19** to produce thioaldehyde **20**. In the event, irradiation[15] of a solution of **18** in benzene afforded known penicillanic ester **21**[16] as a single epimer. The major product was again disulfide **16** from homolytic cleavage of **18** and coupling, accompanied by Norrish type II cleavage of the acylaziridine.



Scheme 5

Although **18**, in which an aziridine serves as surrogate for dehydrovaline gave **21** in low yield, the formation of this penem lends circumstantial support to the Arnstein proposal for penicillin biosynthesis involving a thioaldehyde. Ring strain in **20** and the propensity for the aziridine to undergo expansion is probably responsible for the difference between our result and that of Scott.[14]

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