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RING CONTRACTION REACTIONS OF 2-AMINO PYRAZOLIDIN-3-ONES: A NEW SYNTHESIS OF MONO AND BICYCLO β-LACTAMS

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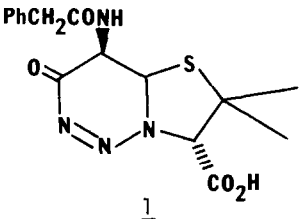
While approaches to penicillins involving formation of the β-lactam moiety using ring contraction reactions, such as the pyrolytic loss of nitrogen from triazine 1,[1] were considered by some of the earliest workers in the field, it has only been in the past several years that any successful β-lactam syntheses incorporating ring contraction steps have been reported.[2] The approach described here utilizes a valence tautomer of the triazene functionality found in 1, nitrene 2, which was generated by oxidation of the appropriate 2-aminopyrazolidin-3-one 3.



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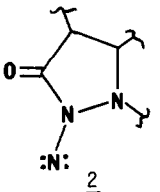

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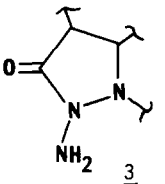

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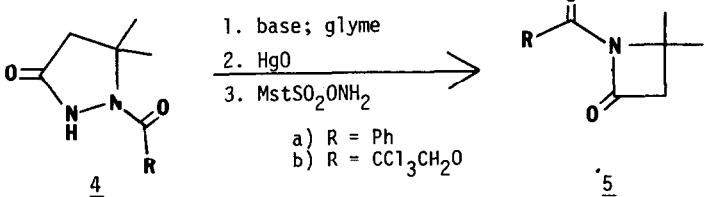
Our initial investigations in this area have focused on the ring contraction reactions of monocyclic 1-acyl-5,5-dimethylpyrazolidin-3-ones 4a and 4b. We have found that synthetically useful yields of β-lactams are formed when a solution of 1 equiv of O-mesitylenesulfonylhydroxyl amine[3] in CH_2Cl_2 is added at 25° to a mixture of 3 equiv of yellow HgO and the anion of the 1-acylpyrazolidin-3-one in glyme. Starting with the previously reported N-benzoyl compound 4a,[4] a 72% yield of the known lactam 5a[5] was isolated (mp 99.5-100° [lit[5] 99-101°], ir ($CHCl_3$) 1785, 1670 cm^{-1}, mass spectrum m/e 203 (M^+)). Likewise from 4b, [2a] a 39% yield of 5b was obtained (ir ($CHCl_3$) 1810, 1728 cm^{-1}, mass spectrum m/e 273 (M^+)).



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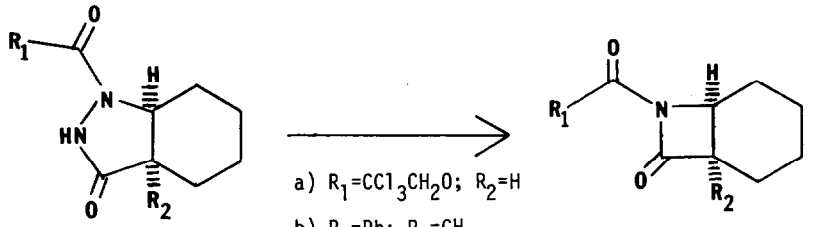
In an effort to investigate possible effects of ring strain on this reaction, two cephalo-

sporin-like model systems were synthesized and their chemistry studied. cis-Bicyclic 1-acyl pyrazolidin-3-one 6a was available from previous work[6] while 6b was obtained as one diastereomer after catalytic hydrogenation of the corresponding bicyclic acyl hydrazone[7] followed by benzoylation. The stereohomogeneity of 6b was demonstrated by ^{13}C NMR while the cis ring junction was inferred from its chemistry. β-Lactams 7a and 7b were obtained from 6a and 6b respectively in 30 - 50% isolated yields after purification by column chromatography. Their spectral properties were similar to those of the analogous monocyclic β-lactams 5a and 5b.[8]



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In the case of 4a a crude intermediate with properties consistent with those of an N-amino compound was isolated, but attempted purification led to its decomposition. Oxidation of the crude material, however, produced 5a in 50% yield. Attempted oxidation of 4a in the absence of aminating agent resulted in recovered starting meterial. These results tend to indicate that the N-amino compound is formed in situ and is subsequently oxidized by mercuric oxide to a N-nitrene (nitrenoid) intermediate.[9] Whether a triazine (e.g. 1) is an intermediate in β-lactam formation or whether the reaction proceeds by a dipolar mechanism[10] is not clear at this time. Further synthetic and mechanistic aspects of this reaction are presently under investigation.

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