

THE BASIC RING OPENING OF 3-UNSUBSTITUTED 3-ISOXAZOLIN-5-ONES *

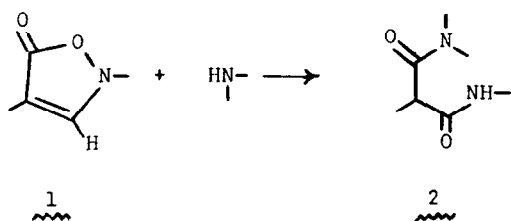
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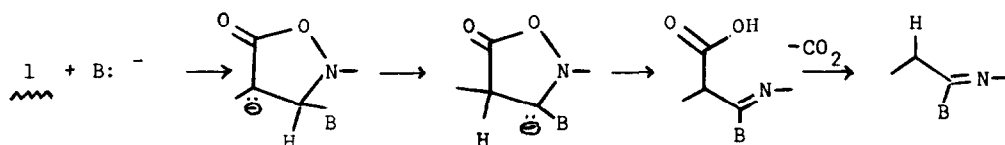
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We have found that the ring cleavage reaction of 3-unsubstituted 3-isoxazolin-5-ones (1) with amines follows a different pathway than previously observed with other nucleophiles to give diamide products (2).



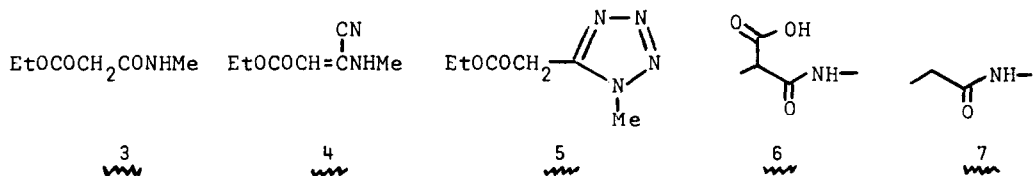
Ulrich, Tilley, and Sayigh demonstrated that facile ring cleavage required a proton in the 3-position of the isoxazalone ring and proposed the mechanism summarized in the scheme below to account for the formation of 3, 4, and 5,



from the reaction of aqueous hydroxide, cyanide, and azide, respectively, with 4-carbomethoxy-N-methyl-3-isoxazolin-5-one.¹ Subsequently the reaction of other isoxazolones with aqueous base was shown to give the amide 6 and, after

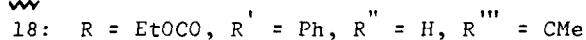
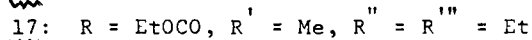
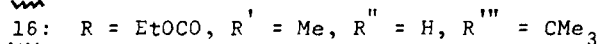
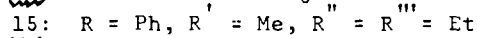
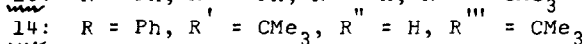
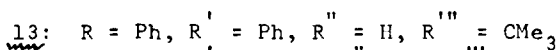
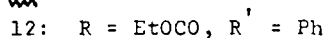
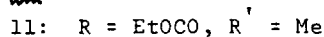
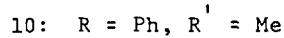
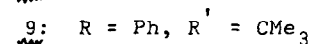
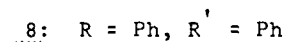
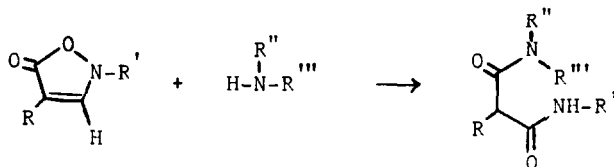
* These results were presented at the Northwest Regional Meeting of the American Chemical Society, Seattle, Washington, June (1970).

decarboxylation, 7, in accord with the above mechanism,² rather than the isomeric vinyl hydroxylamine structures incorrectly postulated by earlier workers.^{3,4}

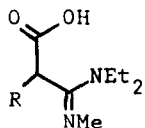


In our independent study of the latter compounds we found further that ring opening with ethoxide gave the carboxylic ester of 6 rather than the expected imido ester.⁵ That result, however, was rationalized on the basis of the mechanism proposed by Ulrich, Tilley, and Sayigh, since there exists the possibility of rearrangement of such an initially formed imido ester to the observed product.⁵

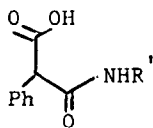
In our present investigation of the ring opening with amines we have now found the products to be diamides 2 rather than the expected amidines. For example treatment of the isoxazolones 8 - 12 with *t*-butylamine or diethylamine produces 13 - 18 as the sole products. In all cases the product ir and nmr



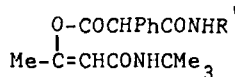
spectra are in complete accord with the diamide structures. The spectral data distinguish most clearly between the diamides and the anticipated amidines in the case of 15 and 17, where the presence of a sharp amide NH band near 3 μ in the infrared spectrum, an *N*-methyl doublet and a methine singlet in the nmr spectrum militate against any of the possible tautomers of the predicted product 19.



19



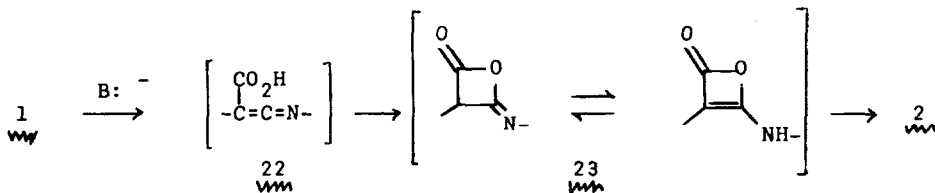
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21

Finally, confirmation of the structural assignments was obtained for 13 and 14 by independent synthesis from the corresponding phenylmalonamic acids (20) by aminolysis of the enol esters (21) prepared with N-t-butyl-5-methylisoxazolium perchlorate.⁶

The elucidation of the diamide product structures indicates that the reaction path followed in the ring opening with amines is different from that observed by Ulrich, Tilley, and Sayigh in their reactions with cyanide and azide ions. Here, in contrast to the case of the earlier-studied ring cleavage with sodium ethoxide, conversion in a subsequent reaction of an initial structure of the type predicted by the postulated mechanism to the products isolated may be ruled out since no reasonable rearrangement of amidines of the type 19 to the diamides 2 can be envisioned. Although it is not yet clear what factors determine which reaction path a given nucleophile will follow and mechanistic details remain to be established, it is apparent that the new reaction course cannot be accommodated on the basis of the scheme of Ulrich, Tilley, and Sayigh. Similarly, possible mechanisms involving attack at the isoxazolone carbonyl by bases fail to provide an explanation for oxidation of the carbon at the 3-position of the heterocyclic ring. However, formation of the diamides 2 could be rationalized by modification of a mechanism considered and rejected by the previous workers,¹ abstraction of a proton from the 3-position with ring opening to give a ketenimine 22 - similar eliminations have been observed with other N-O heterocycles.^{6,7} Since ketenimines are known to undergo additions with carboxylic acids,⁸ and an intramolecular addition to a ketenimine has been suggested in the case of the ring opening of furazanum salts,⁹ the intermediate 22 might well cyclize to 23,¹⁰ which could then ring open to give 2. Ulrich,



Sayigh, and Tilley concluded that the ring opening reaction must involve preliminary nucleophilic addition instead of proton abstraction since they did not observe cumulene absorption in the infrared spectrum of a basic aqueous reaction mixture. However even if the ketenimine 22 were favored at equilibrium relative to 23, hydration likely would be so rapid that 22 would not build up to a detectable concentration. Thus the spectral test does not exclude the simple elimination mechanism, and that mechanism might even provide a rationalization for both types of the observed ring opening products. The amides 6 and 7 as well as the ester of 6 could be obtained by the same pathway as for the reaction with amines. Only with cyanide and azide ions is the site of attachment established as the #3 carbon of the heterocycle, and with these nucleophiles there might be favored an alternate mode of attack upon 23, preferential addition to the ketenimine 22, or even decarboxylation prior to addition.

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