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AN UNUSUAL SYNTHETIC ROUTE TO MESOIONIC PYRIMIDINES

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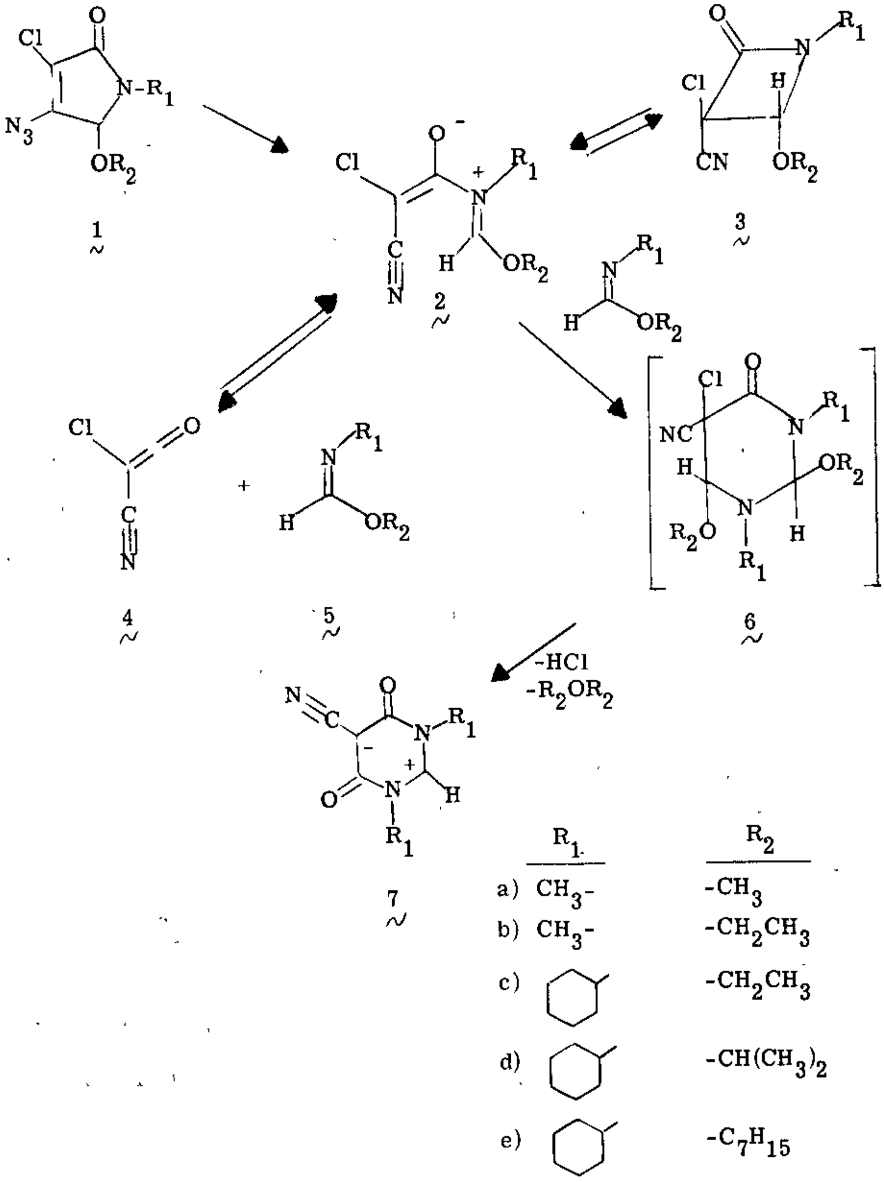
A new and novel synthetic route to the rare mesoionic pyrimidines is described. This involves the cycloaddition of formimidates to 1,4-dipolar zwitterions. The zwitterions themselves are generated from three independent pathways, i.e., 1) the thermolysis of 4-azido-2-pyrrolinones, 2) the thermolysis of of 3-cyano-2-azetidinones, and 3) from the cycloaddition of chlorocyanoketene to formimidates.

We have recently reported that 4-azido-2-pyrrolinones such as 1 readily ring contract to 3-cyano-2-azetidinones, 3, (β-lactams) upon thermolysis in refluxing benzene.[1] It was further established that this transformation involves the zwitterion 2 as the penultimate precursor to the β-lactams.[2,3] Reported here is a unique reaction which is intimately related to the above, but one that is of synthetic interest in its own right in that it gives the unusual mesoionic pyrimidines 7a,c rather than β-lactams. Specifically, when the 4-azido-2-pyrrolinones, 1a-e, were thermolyzed in refluxing benzene for 48 hrs, or when one equivalent each of chlorocyanoketene (4)[1] and the formimidates, 5a-e, were subjected to the same reaction conditions, in addition to the major β-lactam products, 3a-e, the mesoionic pyrimidines, 7a-c, were isolated in 5-20% yield. Such heterocyclic molecules, which represent further examples of a rare class of compounds,[4-8] are easily isolated since they precipitate from the reaction solution during the course of the thermolysis.

Syntheses of these mesoionic compounds on a more viable preparative scale can be accomplished by carrying out the thermolyses (96 hrs) in the presence of an excess (2-12 equivalents) of the formimidates which results in a marked increase in yields (> 70%). During the course of this reaction one can observe the initial formation of the β-lactams which slowly disappear as the pyrimidines form.

A mechanism describing the formation of the mesoionic pyrimidines, 7a-c, is outlined in Scheme I. Salient experimental points which are in agree-

Scheme I.



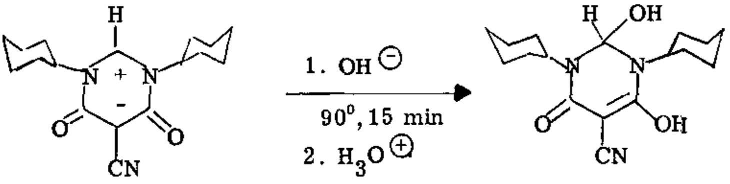
ment with this mechanism are: 1) the pyrimidines are generated from three independent starting materials, i.e., chlorocyanoketene/formimidate, 3-cyano-2-azetidinones and 4-azido-2-pyrrolinones. Thus, a common intermediate is strongly suggested; 2) a most reasonable intermediate which would be common to all three starting points would be the zwitterion 2. In fact, we have already shown that such zwitterions are formed in the cycloaddition of chlorocyanoketene to formimidates, the thermolysis of 4-azido-2-pyrrolinones and the thermolysis of 3-cyano-2-azetidinones. Thus the most consistent interpretation is one in which the zwitterion 2 is in equilibrium with the 3-cyanoazetidinone and also chlorocyanoketene and formimidate. The formimidate thus formed cycloadds to the zwitterion to give 6a-e. These then undergo loss of the equivalent of hydrogen chloride and dialkyl ether to give the observed products, 7a,c. It is worthy of note that when ketenes react with imines to form 2 : 1 adducts, it is normally an adduct composed of two molecules of the ketene and one of the imine. In the case at hand, the formation of 6 illustrates a reversal of this trend. Still another related exception has recently been reported for the cycloaddition of tert-butylcyanoketene (TBCK) to benzylidenemethylamine to give a functionalized hexahydropyrimidone analogous to 6.[9]

The structural assignments of the mesoionic pyridimines 7a,c are based upon analytical and mass spectra analysis as well as the spectral properties provided in Table I.

Table I

R_1	mp	ir (nujol)	nmr (DMSO-d_6)	cmr (DMSO-d_6)
CH_3 (7a)	300-302°	2208, 1693	3.24, s, 6 H	159.0, 154.5
			9.68, s, 1H	116.5, 73.9, 34.7
C_6H_{11} (7c)	329-331°	2220, 1706	1.55, M, 20 H	158.6, 150.6
			4.41, M, 2H	116.6, 74.6
			9.49, s, 1H	56.5, 30.5
				25.2, 24.3

Chemical confirmation of the structure of 7c comes from its expected hydrolysis (5% NaOH) to 5-cyano-1,3-dicyclohexyl-2,4-dihydroxy-6-oxo-1,2,3,6-tetrahydropyrimidine in 92% isolated yield: mp 139-140^0; Anal. calc. for $C_{17}H_{25}N_3O_3$: C, 63.89, H, 7.89; N, 13.15. Found: C, 64.20; H, 7.97; N, 13.10; ir (nujol, cm^{-1}) 2198 (CN), 1760, 1660 (CO), 3440 (0H); nmr (DMSO-d_6, δ) 0.8-2.1 multiplet.



In conclusion, the data presented here are of twofold significance. First, the formation of 7 provides additional evidence that zwitterions such as 2 are common intermediates in both the thermolysis of 4-azidopyrrolinones and in the cycloadditions of cyanoketenes to formimidates. Second, the results present a previously unprecedented route to an unusual heterocyclic ring system, mesoionic pyrimidines.

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10. Analytical and/or mass spectral data for the mesoionic pyrimidines were in complete accord with the formulations.
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