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BASE-CATALYZED CYCLIZATION OF AN OXOALKYLPYRIMIDINE

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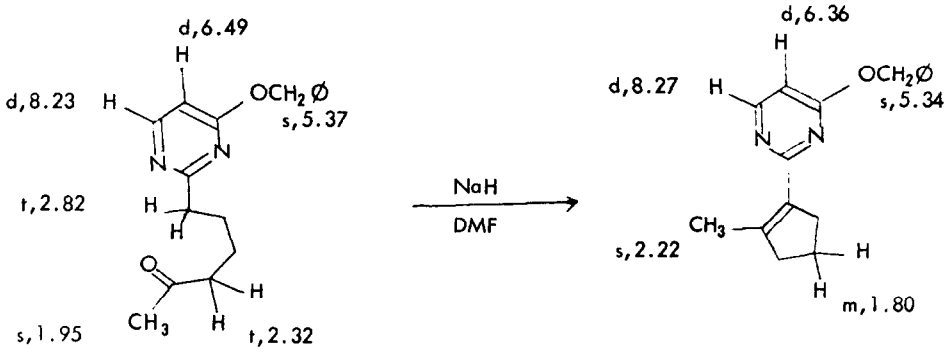
Developments concerning the fundamental role of nucleic acids in molecular biology have caused a dramatic increase of fundamental research into the chemistry of simple purine and pyrimidine[1,2] compounds. Even so, there are many areas where our chemical knowledge is scant. This paper deals with one such area, reactions of pyrimidine ketones.[3]

Methyl groups attached to the 2-, 4-, or 6-positions of a pyrimidine ring are activated for forming carbanion intermediates as evidenced by their ability to undergo base-catalyzed alkylations,[1,2] Mannich reactions,[2] Claisen-type condensations,[2,4,5] and Aldol-type reactions.[2,6] Examples of the latter type reaction have been limited to aldehydes having no alpha hydrogen atoms such as formaldehyde,[7] chloral,[8] and benzaldehydes.[2,6] For pyrimidines having alkyl side chains greater than methyl, no involvement of the side chain in condensations with aldehydes or with ketones have been previously described.[3] We wish to report the first example where a methylene group activated by a pyrimidinyl ring enters into such a condensation reaction. The intramolecular base-catalyzed reaction of the 2-(5-oxo-1-hexyl) pyrimidine I leads to formation of the cyclopentenyl pyrimidine II.[9,10]

Chemical Shifts in PPM Downfield from TMS



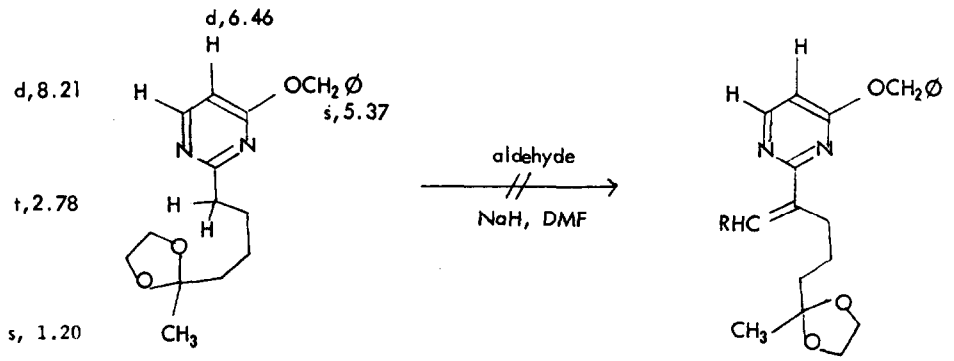
Allylic protons; m,2.49; m,2.86.

I II

The new cyclization reaction is not effectively catalyzed by nucleophilic bases such as hydroxide or alkoxide ions. These bases cause debenzylation. For generating anionic intermediates excess sodium hydride is the reagent of choice. Dry dimethylformamide seems to be an effective solvent. In a typical experiment, a solution of 1.5 mmole of I in five ml of DMF was added dropwise, under nitrogen, to ten ml of DMF containing 14.1 mmole of sodium hydride. After stirring at room temperature for seventeen hours, the mixture was quenched with water and extracted with an organic solvent. Chromatography on silica gel afforded pure II, eluted with 5% ether/pet ether (30-60°) in 41% yield.[9]

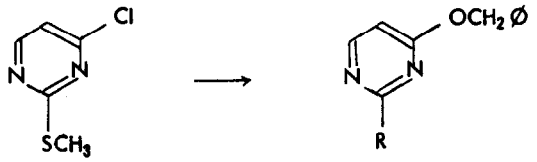
Spectral evidence indicates that the normal Aldol reaction of I is competing poorly with the cyclization of I to II. Typically the IR of the crude product shows very small bands for saturated and unsaturated ketones (Aldol?). It is known[11] that intramolecular versions of otherwise bimolecular reactions show an increased rate as a result of increased proximity of the reaction sites. This must be the predominant factor favoring the cyclization of I over the normal intermolecular Aldol reaction.

We wondered whether a methylene group next to a pyrimidine ring would condense with carbonyl compounds when the reaction was intermolecular. In order to test this, condensations of the ketal III with formaldehyde and with benzaldehyde were attempted. No adducts IV were obtained or even detected by spectral examinations of crude reaction mixtures. At this time, it is not known whether failure to effect an intermolecular condensation is due to special structural features of the ketal side chain or whether the intermolecular reaction is in general a poor one. Further experiments to clarify this point are in progress.



III IV

Substrates I and III were prepared from commercially available (Aldrich) 4-chloro-2-methylthiopyrimidine, V. The chloride was displaced with benzyloxy anion[12] to produce VI (83%), bp 140-141°/0.3 mm.[9] The sulfide VI was oxidized with m-chloroperbenzoic acid[13] to sulfone VII (98%), mp 76-76.5°,[9] and the resulting methylsulfonyl group was displaced with malonic ester anion to produce diester VIII (38%). With excess malonate ion the major product in this reaction was the monoester IX(58%).[14] Alkylation of IX with the dioxolane ketal[15] of 5-bromo-2-pentanone in DMF/benzene afforded X (48%). Base hydrolysis of X gave an acid which readily decarboxylated to III (66%). Acid hydrolysis of III gave I (98%). Except where noted above, all of these compounds were oils purified[9] by column chromatography on silica gel. I was characterized additionally as its semicarbazone, mp 123-126°.



V

VI R = SCH_3
VII R = SO_2CH_3
VIII R = $CH(CO_2Et)_2$
IX R = CH_2CO_2Et
X R = $CH-CO_2Et$
$CH_2CH_2-CH_2-C-CH_3$
O O

We are currently exploring reactions of other oxoalkylpyrimidines to see what size rings can be created by this method.

Acknowledgements

For support of this research, we are indebted to the Office of General Research at the University of Georgia and to the National Science Foundation (GP - 29587).

References and Footnotes

1. D. J. Brown, "The Pyrimidines", Interscience Publishers, New York, 1962.

2. D.J. Brown, "The Pyrimidines, Supplement I", Interscience Publishers, New York, 1970.

3. Reactions of pyrimidine ketones are rare. To quote from reference 2, Chapter XI, "It appears that most pyrimidine ketones must be used for biological testing or simply bottled, because few reactions are recorded."

4. H. R. Sullivan and W. T. Caldwell, J. Am. Chem. Soc. 77, 1559 (1955).

5. W. Pfleiderer and H. Mosthaf, Chem. Ber. 90, 728 (1957).

6. See reference 1, pages 125-126 and reference 2, Chapter IV.

7. C. G. Overberger and I. C. Kogon, J. Am. Chem. Soc. 76, 1879 (1954).

8. R. C. Jones, E. C. Kornfeld and K. C. McLaughlin, J. Am. Chem. Soc. 72, 3539 (1950).

9. All new compounds gave spectral data consistent with the structures assigned. Satisfactory analyses: I (semicarbazone), III, VI, VII, VIII, IX, and X. Analyses for percentage carbon in II have been just below the acceptable limit. However, the structure of II rests securely on spectral data: NMR (see structural formula II); IR, no $\geq C = O$, 1640 cm^{-1} ($\geq C = C \leq$); Mass spec. $(m/e)^+$, 175^+ = $(p\text{-benzyl})^+$, 108^+ = $(\text{methylcyclopentenyl-}C{=}NH)^+$, and 91^+ = $(\text{tropylium})^+$, intensities = 100, 32 and 19.

10. Assignments of pyrimidine protons follow the data summarized by L. M. Jackman and S. Sternhill, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd Edition, Vol. 5, p. 211.

11. J. B. Hendrickson, D.J. Cram and G. S. Hammond, "Organic Chemistry", 3rd Edition, McGraw-Hill, New York, 1970, p. 350.

12. See reference 1, pages 201-202.

13. Org. Syntheses 50, 15 (1970).

14. R. F. Koebel, results to be published.

15. Org. Syntheses, Coll. Vol. IV, 597; J. D. Cawley, Brit. 728, 446, April 20, 1955; C. A. 50: P5722 g.