$LiAlH_4$ REDUCTION - A FACILE ROUTE TO 2,5-DIHYDROPYRIMIDINES[1]

Alexander L. Weis* and Rosita Vishkautsan

Department of Organic Chemistry, The Weizmann Institute of Science
Rehovot 76100, Israel

Abstract - 2,5-Dihydropyrimidines stabilized by electron-donating groups at position 4 and 6 were prepared quantitatively by $LiAlH_4$ reduction of the corresponding pyrimidines.

Except for an isolated report by Mehta et al.,[2] 2,5-dihydropyrimidine compounds are unknown. This class of materials is of interest because it represents the remaining member of the five isomeric dihydropyrimidines, for which there is still no general synthesis.[3] These compounds are also of considerable theoretical interest as they enable the study of how nitrogen positioning affects the chemical and physical properties of the six membered ring (and to compare these with the known cyclohexadienes and dihydropyridines, as well as with other dihydrodiazines and -triazines). The 2,5-dihydropyrimidines also represent novel starting materials for new families of heterocycles and for natural products.

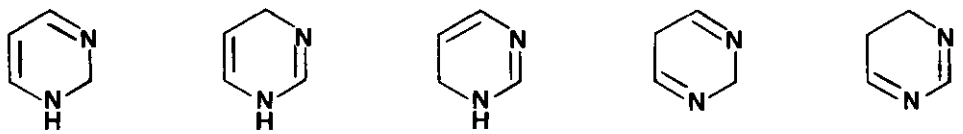
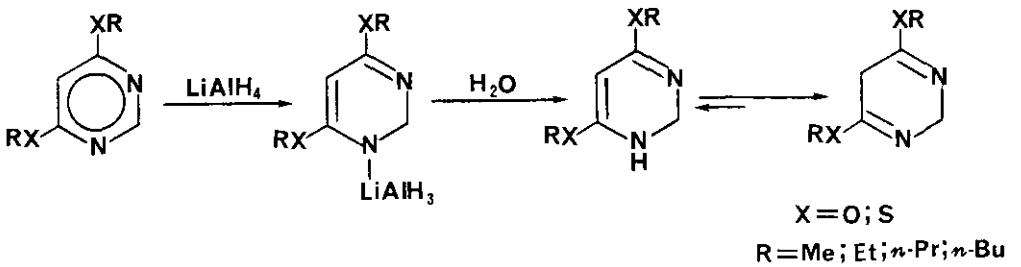


Figure I

Formally, dihydropyrimidines exist in the five isomeric structures given in Fig. I. However, most of the reported dihydropyrimidines have either the 1,2-(1) or the tautomeric 1,4-(2) and 1,6-(3) geometry.[4] Based on our experience and data available in the literature on dihydroazines, we can divide the dihydropyrimidines into two groups, within each of which interconversion between isomers is possible under thermal conditions, namely the 1,4-(2), 1,6-(3) and 4,5-(5) compounds, and the 1,2-(1) and 2,5-(4) isomers. It is worthwhile to note that while thermal interconversion between the two groups is not observed, photochemical rearrangement of 1,4- (or 1,6-) dihydropyrimidines to 1,2-isomers has been reported.[5]

It is known that, in contrast to acyclic compounds, the cyclic enamine is usually more stable than the corresponding imine. In order to stabilize the cyclic enamines, one substitutes electron-withdrawing groups in the β-position, whereas, to stabilize cyclic imines, electron-donating substituents in the α-position are required[3].

We have previously reported on the imine-enamine tautomerism between 1,2- and 2,5-dihydropyrimidines.[1] Since substitution of electron-donating groups at positions 4 and 6 should tend to stabilize the 2,5-dihydro structure, we chose to examine $LiAlH_4$ reduction of 4,6-di-substituted pyrimidines as a route for attaining the corresponding dihydropyrimidines. Herein we report on a highly efficient $LiAlH_4$ reduction of several pyrimidines bearing stabilizing groups at positions 4 and 6 to yield dihydropyrimidines.

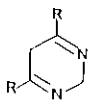


Scheme I

In a typical experiment, a solution of the starting pyrimidine 10 mmol in 15 ml dry tetrahydrofuran (THF) was slowly added to a preheated suspension of 15 mmol $LiAlH_4$ in 60 ml THF. The mixture was refluxed for 2 h, until the complete disappearance of pyrimidine. The progress of the reaction was monitored by TLC on silica gel plates (Kieselgel 60 F 254, Merck, mobile phase ethyl acetate). The solvent was evaporated to dryness, 100 ml of ether was added and excess of $LiAlH_4$ was destroyed by the usual procedure (subsequent addition of 1 ml H_2O, 1 ml 15% NaOH and 3 ml H_2O).[6] Filtration, drying over $MgSO_4$ and evaporation of the ether afforded the crude 2,5-dihydropyrimidine in near quantitative yield, which was further purified by column chromatography (SiO_2, ethyl acetate). Yields, melting points and some spectral data are given in Table 1. The structures of the prepared compounds were unambiguously determined by ^1H-NMR. Each new compound exhibited triplets in the δ 2.6-3.0 ppm (CH_2 at position 5) and δ 5.1-5.4 ppm (CH_2 at position 2) regions with a spin-spin coupling constant of 5.5 Hz. It should be noted that the results are in agreement with those we previously obtained for 4,6-diphenyl-2,5-dihydropyrimidine.[1] IR data are also informative, since 4,6-dialkoxy-2,5-dihydropyrimidines show the characteristic absorption peaks for alkoxy groups in the fingerprint region (~1180 cm^{-1}). Moreover two characteristic bands appear at 1600-1800 cm^{-1}, which can be attributed to the RO-C=N- stretching mode of the cyclic imino ethers. The use of the less electron-rich $-SC_2H_5$ group in positions 4- and 6- instead of -OR substituents produced a dihydropyrimidine whose absorption bands in the 1600-1800 cm^{-1} region were shifted to lower wave numbers. One might propose that electron donating substituents on the 2,5-dihydropyrimidine ring would shift the C=N absorption to higher wave numbers. Undoubtedly, this characteristic IR absorption is an excellent tool for differentiation between the five

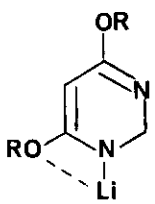
possible isomeric structures.[7] UV spectra of 4,6-dialkoxy-2,5-dihydropyrimidines show a single absorption maximum at ca. 202 nm. Particularly interesting information was obtained from mass spectroscopy, where in almost all cases a strong $(M-1)^+$ peak was obtained, presumably indicating abstraction of H from position 5 followed by formation of a stable homoaromatic system containing 6 π electrons.

Table 1. Selected data on 4,6-disubstituted 2,5-dihydropyrimidines

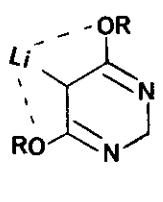
Compounds 	Yields* (%)	M.p. °C	UV(EtOH) λ_{max} nm(ε)	IR(KBr)** ν,cm^{-1}	^{1}H NMR ($CDCl_3$)*** δ ppm CH-2	CH-5
a. R=OCH_3	100(92)	72-73	202(2040)	1723, 1676	5.22(t)	2.67(t)
b. R=OC_2H_5	100(95)	49-50	202(2160)	1727, 1676	5.19(t)	2.65(t)
c. R=OC_3H_7	100(87)	oil	203(1930)	1719, 1677	5.19(t)	2.66(t)
d. R=OC_4H_9	100(85)	oil	203(2990)	1719, 1674	5.19(t)	2.65(t)
e. R=SC_2H_5	100(79)	39-40	-	1662, 1627	5.34(t)	2.86(t)

*In brackets are isolated yields of analytical samples; **Measured with a Nicolet MX-1 Fourier transform spectrometer; ***Measured on Varian-FT80 Fourier transform spectrometer.

The reduction, one can suppose, proceeds via nucleophilic attack of $LiAlH_4$ at the unoccupied N=C(2) double bond of the starting pyrimidine, forming, after hydrolysis, the corresponding 1,2-dihydropyrimidine, followed by fast enamine-imine tautomerism to the thermodynamically more stable 2,5-dihydropyrimidine (see Scheme I). The same mechanism probably operates in the reaction performed by Mehta et al.[2] However, one cannot exclude the formation of Li^+ complex (B) which can be formed by Li transfer. We prefer Scheme I,



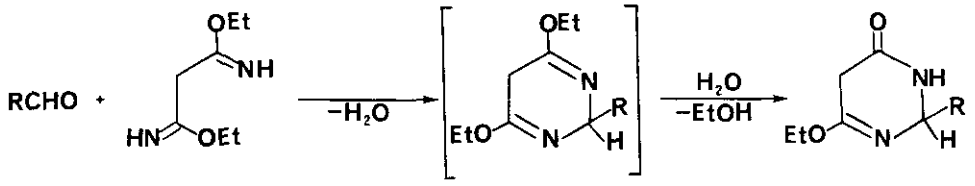
A



B

however, because [1,3] proton shift between the 1 (or 3) and 5 positions, characteristic of imine-enamine tautomerism, is energetically favourable as compared to Li^+ transfer. Certainly, the detailed mechanism of the process described needs further investigation.

2,5-Dihydropyrimidines with electron-donating substituents exist as stable solid or liquid compounds, which may be stored for long periods without deterioration. In this connection, it is worthwhile to note the work of Meyer,[8] who reacted diethyl malondiimidate with aldehydes to obtain 4-oxo-6-alkoxytetrahydropyrimidines, and in which they proposed a



dihydropyrimidine intermediate which they could not isolate. Our results indicate that this putative intermediate should be stable and if formed should be isolable under the appropriate conditions.

ACKNOWLEDGEMENT We thank Mrs. Z. Kustanovich for aid in obtaining mass-spectral data.

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3. A.L. Weis, Adv. Heterocycl. Chem., Vol. 38 (in press).

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