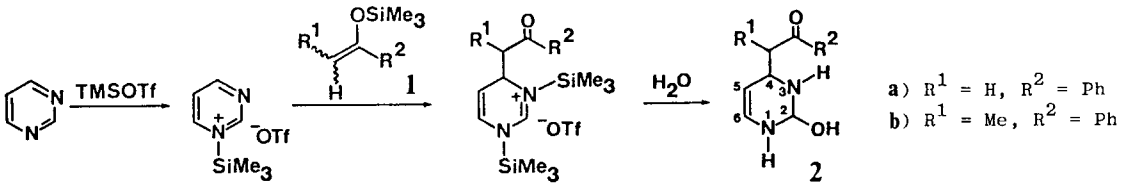
Tetrahedron Letters,Vol.27,No.46,pp 5651-5652,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

# FORMATION OF 2-OXA-8,9-DIAZABICYCLO[3.3.1]NONA-3,6-DIENE DERIVATIVES FROM PYRIMIDINE: UTILITY FOR TETRAHYDROPYRIMIDINE SYNTHESIS

Kin-ya Akiba,* Akira Sakaguchi, and Yohsuke Yamamoto
Department of Chemistry, Faculty of Science, Hiroshima University
Higashisenda-machi, Hiroshima 730, Japan

Abstract: The hydrate (2) of dihydropyrimidine obtained by the reaction of pyrimidine, $Me_3SiOTf$ and enol silyl ethers gave diazabicyclo[3.3.1]nona-3,6-diene derivatives (3) by acylation with excess chloroformate. 3 was reopened by protonation to give dihydropyrimidinium salts (A) and then tetrahydropyrimidines with nucleophiles of low basicity.

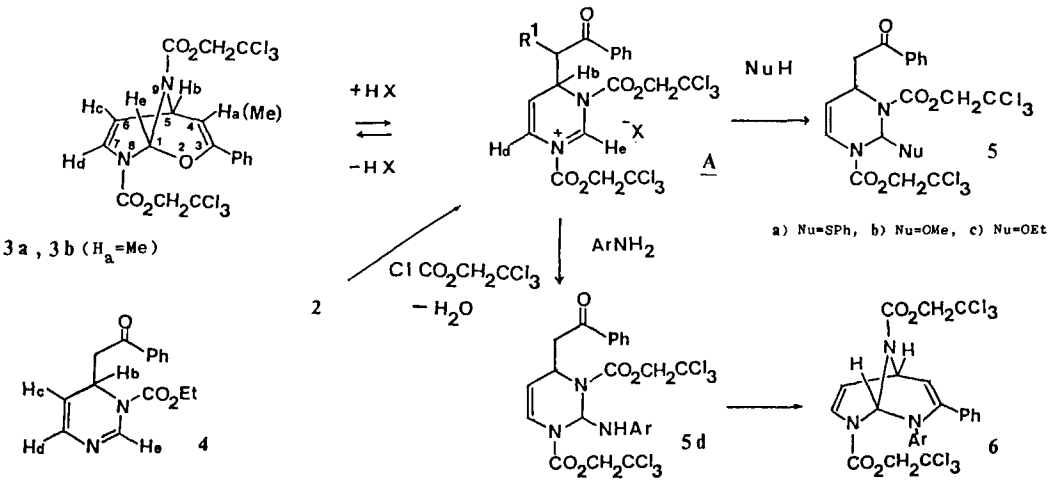
Di- and tetrahydropyrimidines have attracted attention based on their biological activity[1] and interest in amidinic tautomerism.[2] Synthesis of these derivatives has relied on conventional methods.[3] Related to the development of regioselective introduction of functional groups to pyridine via quaternization,[4] we activated pyrimidine with silyl triflate and reacted with enol silyl ethers (1) to obtain dihydropyrimidine hydrates (2) by one-pot procedure in moderate yields.[5] The hydrates are very polar and rather unstable to acid and base, hence it was impossible for us to obtain pure samples after recrystallization. In order to characterize 2, we acylated it with 8 equiv of 2,2,2-




trichloroethyl chloroformate (pyridine, room temp., 20 h) to give 8,9-bis-(2,2,2-trichloroethoxycarbonyl)-3-phenyl-2-oxa-8,9-diazabicyclo[3.3.1]nona-3,6-diene (3a) in 29 % yield. The structure was determined by $^1$H NMR.[6] The long range W letter coupling between $H_b$ and $H_e$ is characteristic in 3a.

3a is protonated cleanly at C-4 with 1 molar to excess trifluoroacetic acid in $CDCl_3$ to revert to A (X=$CF_3CO_2$). The W letter coupling between $H_b$ and $H_e$ disappears and two new long range couplings (J = 1.5 Hz) appear between $H_b$ and $H_d$ and also $H_d$ and $H_e$. This pattern is closely related to that (J = 1.5 Hz) of the dihydropyrimidine (4), although another small coupling (J = 0.9 Hz) is present between $H_b$ and $H_e$ in 4.[7,8]

A was found to be a convenient precursor for tetrahydropyrimidine synthesis. Thus, addition of trifluoroacetic acid to 3a in dichloromethane and subsequent trapping (room temp.) of the resulted A with thiophenol gave the dihydropyrimidine (5a, Nu = SPh) in 98 % yield as a mixture of diastereomers.




Similarly, methanol and ethanol gave 5b (Nu = OMe) and 5c (Nu = OEt) in 90 % and 88 % yield.[9] Anilines can also undergo the addition reaction to A, but in order to obtain the product in a reasonable yield, the reaction has to be performed at reflux ($CH_2Cl_2$, 23 h) in the presence of a drying agent, molecular sieves 4A. Furthermore the product (6) obtained in 53 % yield has a bicyclic structure similar to that of 3. Thus the hydrate 2 was disclosed to be a good synthetic intermediate for tetrahydropyrimidines (6), and the immediate precusor A can be stored as 3.

References and Notes

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5) Full description on the synthesis of 2 (mp 175.5-177.5 °C) is submitted to Bull. Chem. Soc. Jpn..
6) 3a: colorless solid, mp 110-111 °C; $^1$H NMR (DMSO-$d_6$, 100 °C) δ 4.92 (s, 2 H), 5.06 (s, 2 H), 5.16 (ddd, $H_b$, J = 6.0, 6.0, 1.7 Hz), 5.76 (dd, $H_c$, J = 6.0, 8.0 Hz), 5.89 (d, $H_a$, J = 6.0 Hz), 7.00 (d, $H_d$, J = 8.0 Hz), 7.20-7.60 (m, 5 H), 7.63 (d, $H_e$, J = 1.7 Hz). 3a gave correct elemental analysis.
3b: oil, 27 %.
7) H. Cho, K. Shima, M. Hayashimatsu, Y. Ohnaka, A. Mizuno, and Y. Takeuchi, J. Org. Chem., 50, 4227 (1985).
8) Almost pure 4 was obtained by the reaction of 2a with ethyl chloroformate in the presence of $Et_3N$ in MeCN. oil, 32 %.[7]
9) 5a-5c are oil. 5a and 5c gave correct elemental analysis.
10) 6, oil. $^1$H NMR can be explained similarly to 3a, but peaks are not so well resolved as 3a. 6 gave correct elemental analysis.

(Received in Japan 26 July 1986)