

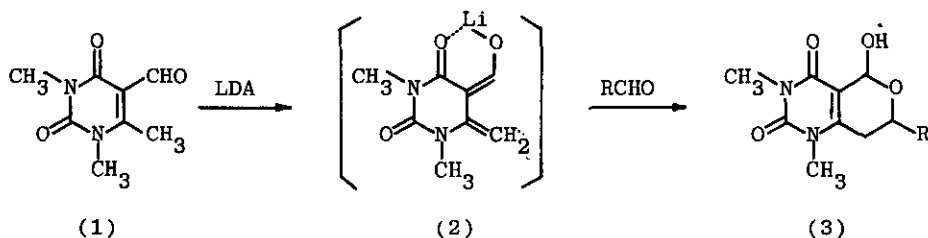
CYCLOADDITION REACTION OF 5-FORMYL-1,3,6-TRIMETHYLURACIL WITH ALDEHYDES. NEW SYNTHETIC APPROACH TO PYRANO[4,3-d]PYRIMIDINES

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Abstract — A new synthetic approach to pyrano[4,3-d]pyrimidine derivatives is described. Reaction of 5-formyl-1,3,6-trimethyluracil with aldehydes in the presence of lithium diisopropylamide affords pyrano[4,3-d]pyrimidines via a dienol intermediate.

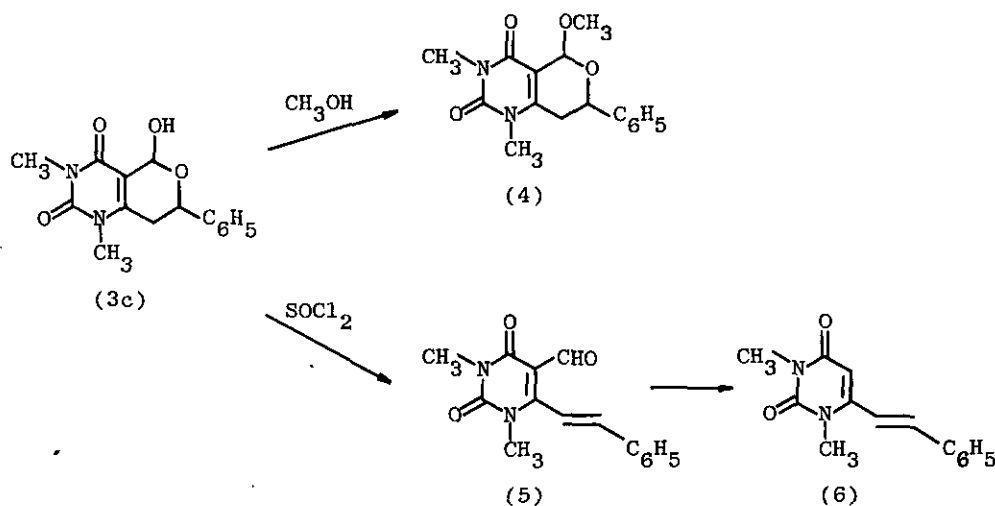
During studies directed toward the development of new synthetic routes to biologically interesting fused pyrimidines employing 6-methyluracils¹⁾, we have found²⁾ that 5-formyl-1,3,6-trimethyluracil(1) causes base-catalyzed isomerization to the dienol(2) which is a reactive and versatile heterocyclic diene in the Diels-Alder reaction. We here report the reaction of (1) with aldehydes in the presence of lithium diisopropylamide(LDA) to give the pyrano[4,3-d]pyrimidines(3) with high regio- and stereo-selectivity.

In a typical experiment a tetrahydrofuran(THF) solution of (1) (2.75 mmol) was stirred with LDA (4.13 mmol) under nitrogen at -70°C for 1 h. To the mixture was added benzaldehyde (4.13 mmol). The solution was gradually raised to room tempe-



Scheme I

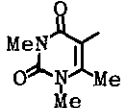
rature, stirred for 5 h and then evaporated in vacuo to dryness. Aqueous acid workup gave the pyrano[4,3-d]pyrimidine(3c) as a sole product (88%): m.p. 169-172 °C; m/e 288(M⁺); u.v. λ_{max} (EtOH) 270 nm ($\epsilon = 8.9 \times 10^3$); i.r.(KBr) 3450 cm⁻¹; ¹H-n.m.r. (DMSO-d₆) δ 2.74 (1H, d, J=10 Hz, A of ABX), 2.90 (1H, d, J=5 Hz, B of ABX), 3.22 (3H, s), 3.31 (3H, s), 5.22 (1H, dd, J=5 Hz and 10 Hz, X of ABX), 5.76 (1H, d, J=5.2 Hz, collapsing with D₂O to singlet), 6.69 (1H, d, J=5.2 Hz, vanishing with D₂O) and 7.22-7.54 (5H, m). The structure of (3c) was deduced from its spectroscopic properties as described above and following some chemical modifications. Thus, compound (3c) was slowly isomerized with trifluoroacetic acid in DMSO-d₆ to its epimer and attained equilibrium in the ratio 2:1 (3c/ its epimer) after 19 hr. Refluxing of (3c) in methanol afforded the acetal (4), m.p. 150-152 °C (74%)³. Treatment of (3c) with thionyl chloride at room temperature gave the 5-formyl-6-styryluracil(5), m.p. 155-156°C, which was converted to the 6-styryluracil(6), m.p. 208-210°C, by refluxing in 10% hydrochloric acid. Similar treatment of (3c) in 10% hydrochloric acid afforded (6).



Scheme II

Cycloaddition reaction of (1) with a variety of aldehydes were summarized in Table. In the absence of an aldehyde the reaction of (1) with half equivalent of LDA led to the dimerization to give (3f).

Table Formation of pyrano[4,3-d]pyrimidines (3) from (1) and aldehydes

Product	R	M.p. °C	Yield %
(3a)	H	189-191 (dec.)	22
(3b)	Et	204-206 (dec.)	16
(3c)	Ph	169-172	88
(3d)	PhCH ₂	181-183	13
(3e)		184-186	49
(3f)		200-203 (dec.)	22

The plausible mechanism for the formation of (3) is suggested as follows. Abstraction of the proton from the C-6 methyl group of (1) in basic medium would afford the pyrimidine-dienol (2), which is stabilized in the (Z)-form by intramolecular interaction between the hydroxy and the C-4 carbonyl group through a lithium ion. Subsequent cyclization of (2) with aldehydes by the thermal Diels-Alder reaction would occur in a disrotatory manner. Therefore, the stereochemistry between the hydroxy group and the R residue must be cis.

Although it is well known that ortho-alkyl substituted aromatic carbonyl compounds (e.g. o-tolualdehyde) undergo photo-enolization to give the (Z)-dienol⁴), our results are a rare example trapping the dienol derived by the base-catalyzed isomerization.

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