'UMPOLUNG' OF REACTIVITY AT C-5 POSITION OF URACIL : AN UNPRECEDENTED NUCLEOPHILIC REACTION OF THIOLATE ION AT C-5 OF 6-CYANO-1,3-DIMETHYLURACIL

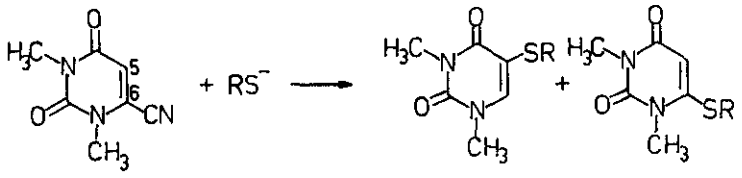
Subodh Kumar* and Swapandeep Singh Chimni
Department of Chemistry, Guru Nanak Dev University,
Amritsar - 143 005, India

Abstract - The soft thiolate ions react with 6-cyano-1,3-dimethyluracil at C-5 to give 5-alkylthio-1,3-dimethyluracil derivatives as major products.

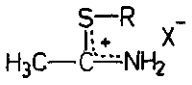
The relevance of model reactions of nucleophiles at C-6 of uracil derivatives arose from the biological significance of thymidylate synthase[1] catalysed conversion of uridylate (dUMP) to thymidylate (dTMP) and has been responsible for development of a variety of nucleophile induced ring transformations of uracil ring.[2] Except one report of nucleophilic attack of soft base ($^-$CN) at C-5 in 6-cyano-1,3-dimethyluracil[3] (1), nucleophiles have invariably been found to react at C-6 of uracil derivatives. Sulphur nucleophiles which are soft bases, like the enzyme (ESH), in inter[4] and intramolecular reactions[5] with uracil derivatives have been proposed to initially attack at C-6. Here, we present first report of reactions of thiolate ions at C-5 of 1 to form 5-alkylthiouracil derivatives as the major products. These results constitute a facile synthetic methodology as against the reported multistep low yield procedures.[6]

The reaction of 1 with benzyl thiolate ion generated *in situ* from benzyl ethanimidothiolate hydrochloride[7] (2a) under phase transfer conditions (PTC), using potassium carbonate as base and tetrabutylammonium hydrogensulphate ($TBAHSO_4$) as catalyst in dimethylformamide, gave two isomeric products M^+ m/z 262, R_f 0.4 and 0.3 (benzene:ethyl acetate :: 19:1). The first component (45% isolated yield) was assigned the structure, 1,3-dimethyl-5-benzylthiouracil (3a) as it showed C_6-H at δ 7.20 in its ^{1}H-nmr and the lower R_f component was assigned the structure, 1,3-dimethyl-6-benzylthiouracil (4a)(C_5-H, δ 5.47). Likewise, reaction of 1 with allyl thiolate ion, generated *in situ* from

2-propenyl ethanimidothiolate hydrobromide[7] (2b) gave only 5-allylthio-1,3-dimethyluracil (3c). Similarly, the reaction of 1 with propyl thiolate and phenyl thiolate ion generated from propylthiol and phenylthiol, respectively, under PTC conditions gave 3b along with 4b and 3d (55%) respectively.



(1) (3) (4)



(2)

(a) R= $CH_2C_6H_5$; X=Cl
(b) R= $CH_2CH=CH_2$; X=Br

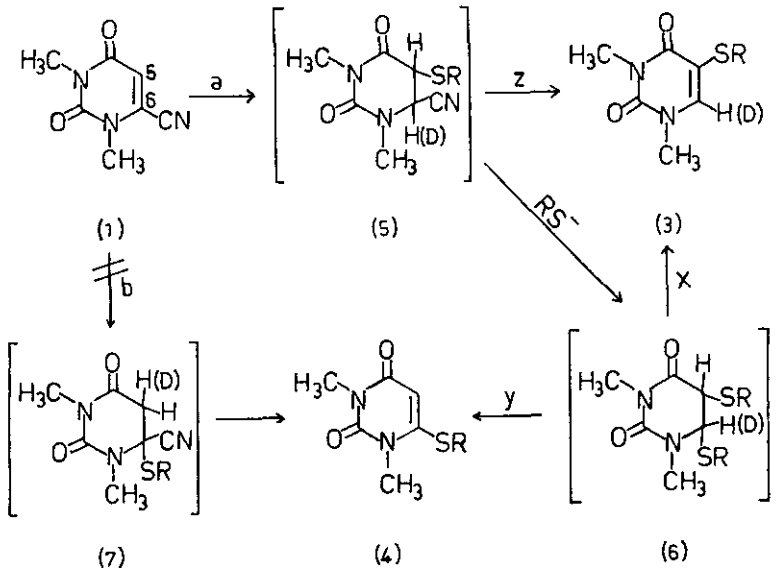
(a) R= $CH_2C_6H_5$
(b) R= $CH_2CH_2CH_3$
(c) R= $CH_2CH=CH_2$
(d) R= C_6H_5

Table: Physical and Spectral data of 3 and 4.

Product[m]	%yield	mp °C	Mass M^+ m/z	(δ) ^{1}H-NMR($CDCl_3$)
3a	45	105	262	3.17(s,3H,N-CH_3), 3.26(s,3H,N-CH_3), 3.78 (s,2H,CH_2), 7.2(s,1H,C_6-H), 7.00-7.20 (m,5H,ArH).
4a	5	143	262	3.26(s,3H,NCH_3), 3.39(s,3H,NCH_3), 4.06 (s,2H,SCH_2), 5.47(s,1H, C_5-H), 7.00-7.47 (m,5H,ArH).
3b	38	66-68	214	0.93(t,J=7Hz,3H,CH_3), 2.03(sext,J=7Hz,2H, CH_2-$\underline{CH}_2$-CH_3),3.30(s,3H,N-CH_3), 3.37(s,3H, N-CH_3), 2.70(t,J=7Hz,2H,SCH_2),7.23(s,1H,C_6-H).
4b	5	106-8	214	1.06(t,J=7Hz,3H,CH_3), 1.78(sext.,J=7Hz, 2H,$CH_2\underline{CH}_2CH_3$), 2.74(t,J=7Hz,2H,SCH_2), 3.27(s, 3H,N-CH_3),3.42(s,3H,N-CH_3),5.43(s,1H,C_5-H).
3c	52	Liquid[1]	212	3.20(d,J=7Hz,2H,SCH_2),3.23(s,3H,N-CH_3), 3.37(s,3H,N-CH_3), 4.67-5.90(m,3H,$CH=CH_2$), 7.33(s,1H,C_6-H).

(l) Elemental analysis of 3c, a liquid product was not performed.

(m) Structure of 3d was assigned by comparison with authentic sample.[9]



The formation of 3 may involve as in the case of the reaction of cyanide ion with 1,[3] the attack of thiolate ion at C-5 (path a) to give intermediate 5, which could lose HCN. Alternatively, nucleophilic substitution of CN^- of 5 with RS^- to 6, followed by elimination of HSR can also form 3 (path x) and 4 (path y). Alternatively, thiolate ion could attack at C-6 of 1 to form intermediate 7 followed by elimination of HCN (path b) to give 4.

On performing the reaction of 1 with propyl thiolate ion in dimethylformamide (15 ml)-D_2O (0.8 ml), 3b showed 60% exchange with deuterium[8] at C-6 position and 4b lacked the presence of any deuterium. The latter observation rules out the path b for the formation of 4b. Since, the intermediacy of both 5 and 6 would result in formation of deuterated 3b, it is likely both mechanisms (z and x) operate in forming 3. These observations showed that both normal and cine substitution had occurred through initial nucleophilic attack of thiolate ion at C-5.

Thus, in uracil, where both enamine (N_1-C_6 = C_5) and α,β-unsaturated ketone (C_6 = C_5-C_4 = O) chromophores involve nucleophilic character at C-5, The presence of strong electron-withdrawing group (^-CN) at C-6 has reversed the polarity at C-5. The potential of 1 to give 5-substituted uracil derivatives with carbon nucleophiles is under investigation.

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8. The amount of deuterium exchange was calculated by measuring integration of the enamine signal against NCH_3 and SCH_2 signals separately and results were within 2% difference.

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