Umpolung of Reactivity at the C-5 Position of Uracil:[1,2] Facile Nucleophilic Reactions of Thiolate Ions at C-5 of 6-Cyano-1,3-dimethyluracil to Procure 5-Alkyl or 5-aryl-thio-1,3-dimethyluracils

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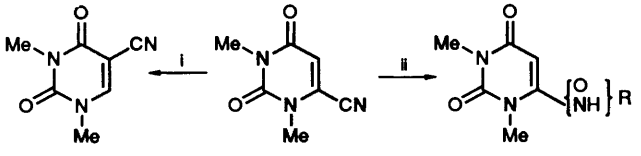
1,3-Dimethyluracil-6-carbonitrile **1** with thiolate ions generated *in situ* from thioiminium salts or thiols under phase transfer catalytic conditions undergoes umpolung of reactivity at C-5 to give 5-alkyl- or 5-aryl-thio-1,3-dimethyluracils as the major or sole products. However, propane-1,3-dithiol causes reductive decyanation of **1** to 1,3-dimethyluracil.

The relevance of model reactions[3,4] of nucleophiles at C-6 of uracil derivatives arose from the biological significance of thymidylate synthase-catalysed conversion of uridylate (dUMP) into thymidylate (dTMP) and has been responsible for the development of a variety of nucleophile-induced ring transformations of uracil derivatives.[5–7] Except for one report of nucleophilic attack of a soft base[8] ($^-$CN) at C-5 in 1,3-dimethyluracil-6-carbonitrile **1** to give **2**, the nucleophiles invariably react at C-6 of uracil derivatives. Even with amines[9] and alcohols,[9] compound **1** gives 6-amino- and 6-alkoxy-1,3-dimethyluracils **3** (Scheme 1). Here, we report the attack of thiolate ions at C-5 of **1** to form 5-alkyl- or 5-aryl-thio-1,3-dimethyluracils **5** as the major products.

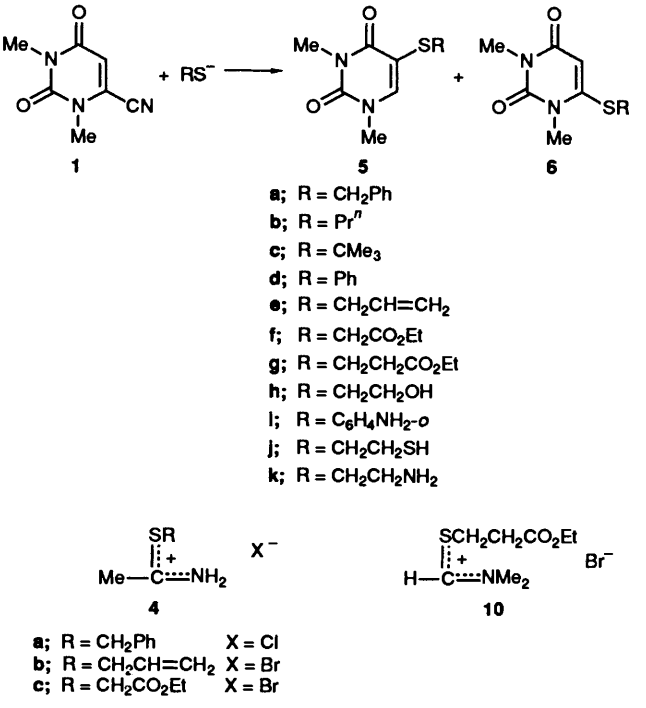


2 **1** **3**

Scheme 1 *Reagents and conditions:* i, DMF, $^-$CN, 80 °C; ii, ROH or RNH_2.

Results and Discussion

Compound **1**, treated with toluene-α-thiolate ion generated *in situ* from benzyl ethanimidothiolate hydrochloride[10] **4a** under phase transfer catalytic (PTC) conditions in DMF,† gave two isomeric products, *m/z* 262 (M^+), R_f 0.4 and 0.3 (benzene–ethyl acetate, 19:1). The higher R_f component (45%) was assigned the structure 5-benzylthio-1,3-dimethyluracil **5** as it showed a signal for 6-H at δ 7.20 in its ^{1}H NMR spectrum, and the lower R_f component was assigned the structure 6-benzylthio-1,3-dimethyluracil **6a** (5-H, δ 5.47).[11] Similarly, compound **1** with propanethiolate ion generated from propanethiol gave **5b** (35%) and **6b** (5%). However, the bulkier 1,1-dimethylethanethiolate and less nucleophilic benzenethiolate ions with **1** gave only **5c** (72%) and **5d** (55%) respectively (Scheme 2). However, 1,3-dimethyluracil-5-carbonitrile **2** (2–3%) could be isolated as a by-product. The formation of **2** along with **5** indicates the competition between liberated cyanide ion and thiolate ion in their attack at C-5 of **1**. Further, the reactions of **1** with prop-2-ene- (generated from **4b**), ethoxycarbonylethane- (generated from **10**) and ethoxy carbonylmethane-thiolate ions (generated from **4c**) gave **5e** (52%), **5g** (37%) and **5f** (10%), respectively. Therefore, the more nucleophilic thiols give both 5- and 6-substituted products but less nucleophilic thiols give only 5-substituted products. The yields of the products in general decrease with decrease in nucleophilicity of thiols. 1-Methyluracil-6-carbonitrile with propanethiolate ion under PTC conditions remains unaffected. Here, the generation of anions at N-3 probably inhibits the attack of negatively charged thiolate ions.

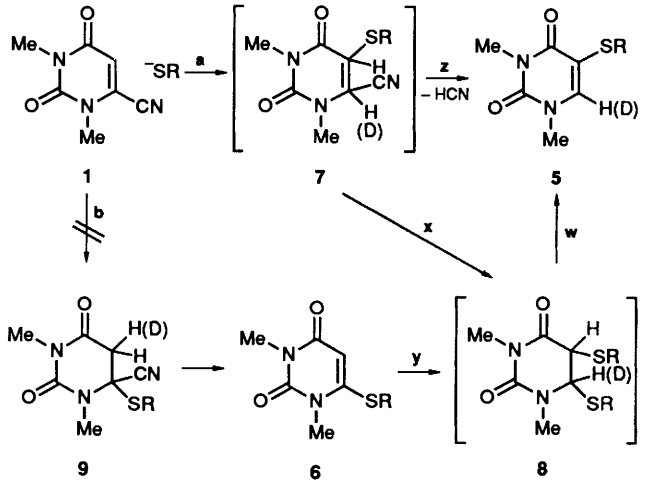


Scheme 2

The mechanism for the formation of **5** and **6** has been rationalised in a manner proposed for the reaction of cyanide ion[8] with **1**. The thiolate ion attacks at C-5 (path **a**) to give intermediate **7** which loses HCN to give **5** (path **z**) or undergoes nucleophilic substitution of $^-$CN with RS$^-$ to give **8**, followed by elimination of HSR to form **5** (path **w**) and **6** (path **y**). Alternatively, thiolate ion attacks at C-6 of **1** to form intermediate **9**, followed by loss of HCN to give **6** (path **b**) (Scheme 3). The reaction of **1** with propanethiolate ion in DMF (15 cm^3)–D_2O (0.8 cm^3), under PTC conditions, gave the product **5**; ^{1}H NMR showed 65% deuterium incorporation at the C-6 position, but **6** lacked the presence of deuterium at the C-5 position. Further, the reaction of **1** with methoxide ion in DMF (15 cm^3)–MeOD (1.5 cm^3) under PTC conditions gave 1,3-dimethyl-6-methoxy-

† The use of triethylbenzylammonium chloride or tetrabutylammonium bromide as catalyst and CH_2Cl_2. CH_3CN and toluene as solvent considerably slows down the reaction.

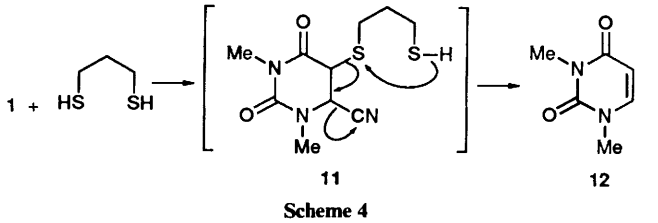
uracil (80%), m.p. 164–165 °C (lit.,[12] 165–166 °C), which showed 64% deuterium incorporation at the C-5 position and indicated the initial attack at C-6. These observations rule out path **b** for the formation of **6** and thus both direct- and *cine*-substitutions occur through initial nucleophilic attack of thiolate ion at C-5.



Scheme 3

Further, to investigate the effect of a second nucleophile placed on the thioalkyl chain, the reactions of **1** with 2-mercaptoethanol, ethane-1,2-dithiol, propane-1,3-dithiol, *o*-aminothiophenol, and cysteamine were performed. 2-Mercaptoethanol with **1** gave **5h** and 1,3-dimethyluracil-6-carboxamide (10%), m.p. 238–239 °C (lit.,[13] 238–239 °C) (TLC, ^{1}H NMR). The appearance of 6-H at δ 7.60 in the ^{1}H NMR spectrum and the presence of OH absorption (ν_{max}3400 cm^{-1}) and absence of SH absorption in the IR spectrum led to structure assignment as **5h**. Similarly, *o*-aminothiophenol and cysteamine with **1** gave **5i** and **5k** respectively. The possibility of other isomeric products was ruled out by the presence of 6-H in the ^{1}H NMR spectrum and NH_2 doublets in the IR spectrum. Ethane-1,2-dithiol with **1** at 0–10 °C gave **5j** (40%) along with 1,3-dimethyluracil **12** (5%); m.p. 123 °C (lit.,[14] 123–124 °C). In the reaction of **1** with propane-1,3-dithiol, only **12** (57%) could be isolated. Therefore, the second nucleophiles (OH or NH_2) present on the thiolate ion do not participate in the reaction but the second thiol groups of ethane-1,2-dithiol and propane-1,3-dithiol cause reductive decyanation of **1**.

The formation of **12** in the reaction of **1** with propane-1,3-dithiol occurs *via* initial attack of thiolate ion at C-5 to give intermediate **11** (Scheme 4), which undergoes facile



Scheme 4

elimination of a five membered 1,2-dithiolane ring. The corresponding loss of a four-membered ring from the similar intermediate obtained in the reaction of **1** and ethane-1,2-dithiol is less favourable. Therefore, the length of the intervening chain between the two thiols dictates the course of the reaction. This is a unique example of thiol-induced reductive decyanation of 6-cyanouracil derivative. The literature records only one reference for reductive decyanation of 5-cyanouracils.[15] However, 1,3-dimethyluracil-5-carbonitrile against propane-1,3-dithiol is stable under these conditions.

Thus, the presence of a cyano group at C-6 of 1,3-dimethyluracil invokes the umpolung of reactivity at C-5 against thiolate ions to provide a general methodology for 5-alkyl- or 5-aryl-thio-1,3-dimethyluracil derivatives.

Experimental

Reagent grade dimethylformamide (DMF) was dried over calcium oxide. ^{1}H NMR spectra were determined with a JEOL-JNM (60 MHz) instrument for solutions in $CDCl_3$, using TMS as internal standard. *J* Values are given in Hz. IR spectra were recorded with a Pye Unicam SP3-300 instrument. In UV data, ε values are given in dm^2 mol^{-1} cm^{-1}. Mass spectra were recorded on JEOL JMS-D-300 machine operating at 70 eV at CDRI, Lucknow. Melting points were determined in capillaries and are uncorrected. Thin layer chromatography was performed on precoated TLC plates (silica gel G or silica gel 60 HF_{254}). Column chromatography was carried out using silica gel (60–120).

Reactions of 1,3-*Dimethyluracil*-6-*carbonitrile* **1** *with Thiolate ions*: *General Procedure*.—The solution of thiol or α-thioiminium salt (1.5 equiv. 6.75 mmol) and 1,3-dimethyluracil-6-carbonitrile **1** (4.5 mmol) in DMF (15 cm^3) containing anhydrous potassium carbonate (3 equiv., 13.5 mmol) and tetrabutylammonium hydrogen sulfate (TBAHSO$_4$) (15–20 mg) was stirred under a nitrogen atmosphere. After completion of the reaction (TLC) (2–6 h), the solid was filtered off and washed with ethyl acetate. The combined filtrate was distilled under reduced pressure. The residue was column chromatographed on silica gel by using benzene and benzene–ethyl acetate mixtures as eluents.

5-*Benzylthio*-1,3-*dimethyluracil* **5a** (45%); m.p. 105 °C; *m*/*z* 262(M$^+$); δ_H 3.17 (s, 3 H, NCH_3), 3.26 (s, 3 H, NCH_3), 3.78 (s, 2 H, SCH_2), 7.20 (s, 1 H, 6-H) and 7.00–7.20 (m, 5 H, ArH); ν_{max}(KBr)/cm^{-1} 1710 (C=O), 1660 (C=O) and 1618 (C=C); λ_{max}(EtOH)/nm 285 (ε 7.9 × 10^3) and 215 (19.4 × 10^3) (Found: C, 59.2; H, 5.1; N, 10.6. $C_{13}H_{14}N_2O_2S$ requires C, 59.54; H, 5.34; N, 10.68%)

6-*Benzylthio*-1,3-*dimethyluracil* **6a** (5%); m.p. 143 °C; *m*/*z* 262 (M$^+$); δ_H 3.26 (s, 3 H, NCH_3), 3.39 (s, 3 H, NCH_3), 4.06 (s. 2 H, SCH_2), 5.47 (s, 1 H, 5-H) and 7.00–7.47 (m, 5 H, ArH); ν_{max}(KBr)/cm^{-1} 1690 (C=O), 1640 (C=O) and 1575 (C=O); λ_{max}(EtOH/nm 281 (ε 2.3 × 10^4), 220 (3.2 × 10^4) (Found: C, 59.4; H, 5.2; N, 10.5. $C_{13}H_{14}N_2O_2S$ requires C, 59.54; H, 5.34; N, 10.68%).

1,3-*Dimethyl*-5-*propylthiouracil* **5b** (38%); m.p. 66–68 °C; *m*/*z* 214 (M$^+$); δ_H 0.93 (t, *J* 7, 3 H, CH_3), 2.03 (sext, *J* 7, 2 H, CH_2), 2.70 (t, *J* 7, 2 H, SCH_2), 3.30 (s, 3 H, NCH_3), 3.37 (s, 3 H, NCH_3) and 7.23 (s, 1 H, 6-H); ν_{max}(KBr)/cm^{-1} 1700 (C=O), 1655 (C=C) and 1620 (C=C); λ_{max}(EtOH)/nm 285 (ε 6.9 × 10^3) (Found: C, 50.8; H, 6.2; N, 13.2. $C_9H_{14}N_2O_2S$ requires C, 50.47; H, 6.45; N, 13.08%).

1,3-*Dimethyl*-6-*propylthiouracil* **6b** (5%); m.p. 106–108 °C; *m*/*z* 214 (M$^+$); δ_H 1.06 (t, *J* 7, 3 H, CH_3), 1.78 (sext, *J* 7, 2 H, CH_2), 2.74 (t, *J* 7, 2H, SCH_2), 3.27 (s, 3 H, NCH_3), 3.42 (s, 3 H, NCH_3), 5.43 (s, 1 H, 5-H); ν_{max}(KBr)/cm^{-1} 1695 (C=O), 1645 (C=O) and 1575 (C=C); λ_{max}(EtOH)/nm 281 (ε 1.8 × 10^3), 221 (1.78 × 10^4) (Found C, 50.6; H, 6.1; N, 13.4. $C_9H_{14}N_2O_2S$ requires C, 50.47; H, 6.45; N, 13.08%).

5-(*tert*-*Butylthio*)-1,3-*dimethyluracil* **5c** (72%); m.p. 139–140 °C; *m*/*z* 228 (M$^+$); δ_H 1.30 (s, 9 H, Bu^t), 3.22 (s, 3 H, NCH_3), 3.37 (s, 3 H, NCH_3), 7.43 (s, 1 H, 6-H); ν_{max}($CHCl_3$)/cm^{-1} 1700 (C=O); λ_{max}(MeOH)/nm 274 and 221 (Found: C, 52.4; H, 6.9; N, 12.1. $C_{10}H_{16}N_2O_2S$ requires C, 52.63; H, 7.02; N, 12.28%).

1,3-*Dimethyl*-5-*phenylthiouracil* **5** (55%); m.p. 136 °C (lit.,[16] 136 °C).

5-*Allylthio*-1,3-*dimethyluracil* **5e** (52%), liquid, *m/z* 212 (M^+); δ_H 3.20 (d, *J* 7, 2 H, SCH_2), 3.23 (s, 3 H, NCH_3), 3.37 (s, 3 H, NCH_3), 4.67–5.90 (m, 3 H, $CH{=}CH_2$) and 7.33 (s, 1 H, 6-H); $\nu_{max}(CHCl_3)/cm^{-1}$ 1710 (C=O), 1660 (C=O) and 1625 (C=C); λ_{max}(EtOH)/nm 285 (ε 7.5 × 10^3) and 214 (12.8 × 10^3).

5-(*Ethoxycarbonylmethylthio*)-1,3-*dimethyluracil* **5f** (10%), m.p. 70–72 °C; *m/z* 258 (M^+); δ_H 1.23 (t, *J* 7, 3 H, CH_3), 3.26 (s, 3 H, NCH_3), 3.36 (s, 3 H, NCH_3), 3.40 (s, 2 H, SCH_2), 4.70 (q, *J* 7, 2 H, OCH_2), 7.67 (s, 1 H, 6-H); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 (C=O) and 1660 (C=O); λ_{max}(EtOH)/nm requires 283 (ε 19.9 × 10^3), 214 (12.1 × 10^3) (Found: C, 46.6; H, 5.2; N, 10.6. $C_{10}H_{14}N_2O_4S$ requires C, 46.51; H, 5.41; N, 10.85%).

5-[2-(*Ethoxycarbonyl*)*ethylthio*]-1,3-*dimethyluracil* **5g** (37%), m.p. 70–71 °C; *m/z* 272 (M^+); δ_H 1.25 (t, *J* 7, 3 H, CH_3), 2.58 (t, *J* 7, 2 H, SCH_2), 2.93 (t, *J* 7, 2 H, CH_2CO), 3.30 (s, 3 H, NCH_3), 3.37 (s, 3 H, NCH_3), 4.10 (q, *J* 7, 2 H, OCH_2), 7.47 (s, 1 H, 6-H); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 (C=O), 1705 (C=O) and 1655 (C=C); λ_{max}(MeOH)/nm 284 and 241 (Found: C, 48.4; H, 6.0; N, 10.1. $C_{11}H_{16}N_2O_4S$ requires C, 48.53; H, 5.88; N, 10.29%).

5-(2-*Hydroxyethylthio*)-1,3-*dimethyluracil* **5h** 42% (at 15 °C), 33% (at 30 °C), m.p. 126–128 °C; *m/z* 216 (M^+); δ_H 2.85 (t, *J* 5, SCH_2), 3.20 (s, 1 H, OH, exchanges with D_2O), 3.33 (s, 3 H, NCH_3), 3.40 (s, 3 H, NCH_3), 3.66 (t, *J* 5, 2 H, OCH_2) and 7.60 (s, 1 H, 6-H); $\nu_{max}(CHCl_3)/cm^{-1}$ 3440 (OH), 1705 (C=O), 1640 (C=O) and 1620 (C=C); λ_{max}(MeOH)/nm 284 and 212 (Found: C, 44.0; H, 5.6; N, 12.8, $C_8H_{12}N_2O_3S$ requires C, 44.44; H, 5.55; N, 12.96%).

5-(2-*Aminophenylthio*)-1,3-*dimethyluracil* **5i** (35%); m.p. 94–96 °C; *m/z* 263 (M^+); δ_H 3.30 (s, 6 H, 2 × NCH_3), 4.24 (s, 2 H, NH_2, exchanges with D_2O) and 6.36–7.43 (m, 5 H, ArH and 6-H); ν_{max}(KBr)/cm^{-1} 3480 and 3340 (NH_2), 1700 (C=O), 1650 (C=O) and 1610 (C=C); λ_{max}(MeOH)/cm^{-1} 279 and 223 (Found: C, 54.9; H, 5.0; N, 15.9. $C_{12}H_{13}N_3O_2S$ requires C, 54.75; H, 4.91; N, 15.97%).

5-(2-*Aminoethylthio*)-1,3-*dimethyluracil* **5k** (26%); m.p. 82 °C (hygroscopic); *m/z* 215 (M^+); δ_H (TFA + $CDCl_3$) 2.95 (t, 2 H, SCH_2), 4.00 (s, 6 H, 2 × NCH_3), 3.95 (t, 2 H, NCH_2), 6.38 (s, 1 H, 6-H) and 8.25–8.83 (br, 2 H, NH_2); ν_{max}(Nujol)/cm^{-1} 3280, 3160 (NH_2), 1700 (C=O), 1650 (C=O) and 1610 (C=C).

5-(2-*Mercaptoethylthio*)-1,3,*dimethyluracil* **5j** (40%); liquid; *m/z* 232 (M^+); δ_H 2.90 (s, 4 H, 2 × CH_2S), 3,37 (s, 3 H, NCH_3), 3.45 (s, 3 H, NCH_3), 7.60 (s, 1 H, 6-H); $\nu_{max}(CHCl_3)/cm^{-1}$ 1700 (C=O), 1650 (C=O) and 1620 (C=C); λ_{max}(MeOH)/nm 274 and 210.

Reaction of Compound **1** *with Propanethiol*–D_2O.—The solution of propanethiol (1.5 equiv., 6.75 mmol) and 1,3-dimethyluracil-6-carbonitrile **1** (4.5 mmol) in DMF (15 cm^3)–D_2O (0.8 cm^3) containing anhydrous potassium carbonate (3 equiv., 13.5 mmol) and tetrabutylammonium hydrogen sulfate (15–20 mg) was stirred under nitrogen. After completion of the reaction (2 h), the suspended solid was filtered off and washed with ethyl acetate. The combined filtrate was distilled under reduced pressure. The residue was column chromatographed on silica gel using benzene and benzene–ethyl acetate mixtures as eluents to isolate [6^{-2}H]-1,3-dimethyl-5-propylthiouracil **5b** and 1,3-dimethyl-6-propylthiouracil **6b**. The percentage of deuterium at C-6 of **5b** was determined by comparison of integration of the 6-H signal with NCH_3 and SCH_2 signals. The results were within ±2% error.

Acknowledgements

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