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Acid Catalysed Enamine Induced Transformations of 1,3-Dimethyl-5-formyluracil. A Unique Annulation Reaction with Enaminones.

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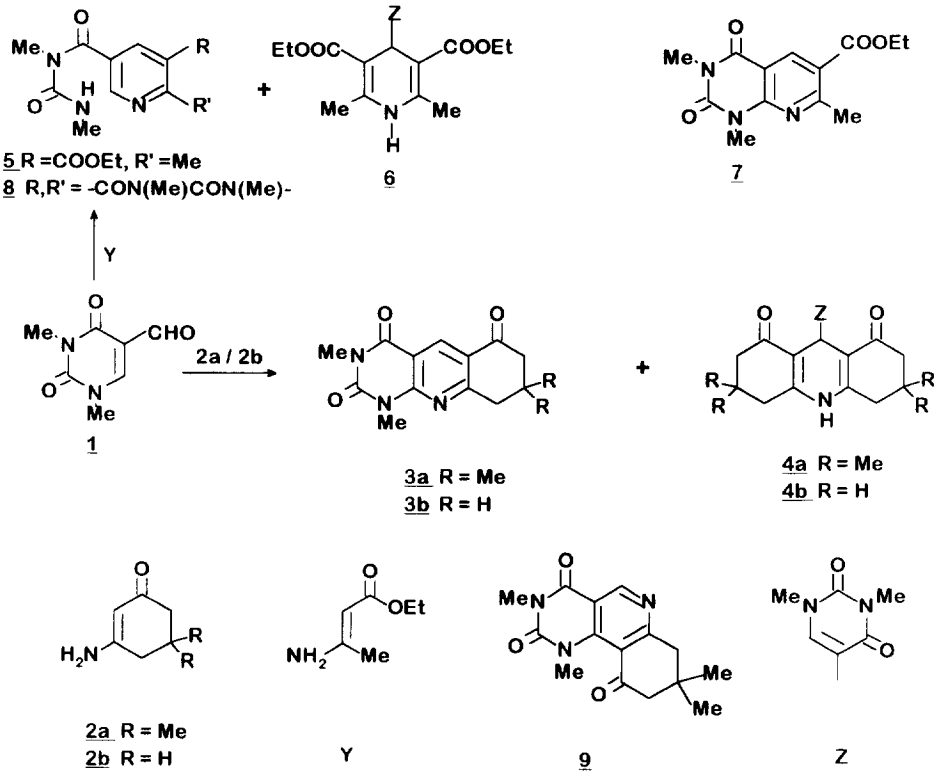
Abstract: 1,3-Dimethyl-5-formyluracil (**1**) with enaminones, 3-amino-5,5-dimethylcyclohex-2-enone and 3-aminocyclohex-2-enone in CH_3CN - TFA (10 : 0.1) gives annulation products - pyrimido[4,5-b]quinolin-2,4,6(*1H, 3H, 7H*)-trione derivatives along with Hantzsch type 1,4-dihydropyridine derivatives. However, **1** with ethyl β-aminocrotonate and 6-amino-1,3-dimethyluracil, enamine ester and amide respectively, provides subsequent transformation products.

Uracil derivatisation at each of its reactive sites has attained paramount significance in evolving medicinally potential target compounds[1]. The nucleophile induced modifications of uracil and its derivatives emanating from their reactions at C-5 and / or C-6[2-6] or at an electrophilic appendage at C-5, make use of relatively strong nucleophiles viz. amines, hydrazines, cyanide ion etc. or of strongly basic reaction conditions (NaOH, NaOEt, BuLi etc.). Recently, we have reported[3c] that under mild PTC conditions, 5-formyl-1,3-dimethyluracil (**1**) reacts with potential bisnucleophilic reagents - acetamides and acetones possessing α-electronwithdrawing group to provide novel pyridopyrimidines and quinazolines. Now, we report that under acidic conditions, biselectrophilic chromophore $-C_6H=C_5-CHO$ of **1**, reacts with binucleophilic unit -CH=CH-N< of enamine derivatives to undergo an unprecedented reaction to provide annulation or subsequent transformation products along with Hantzsch type 1,4-dihydropyridine derivatives.

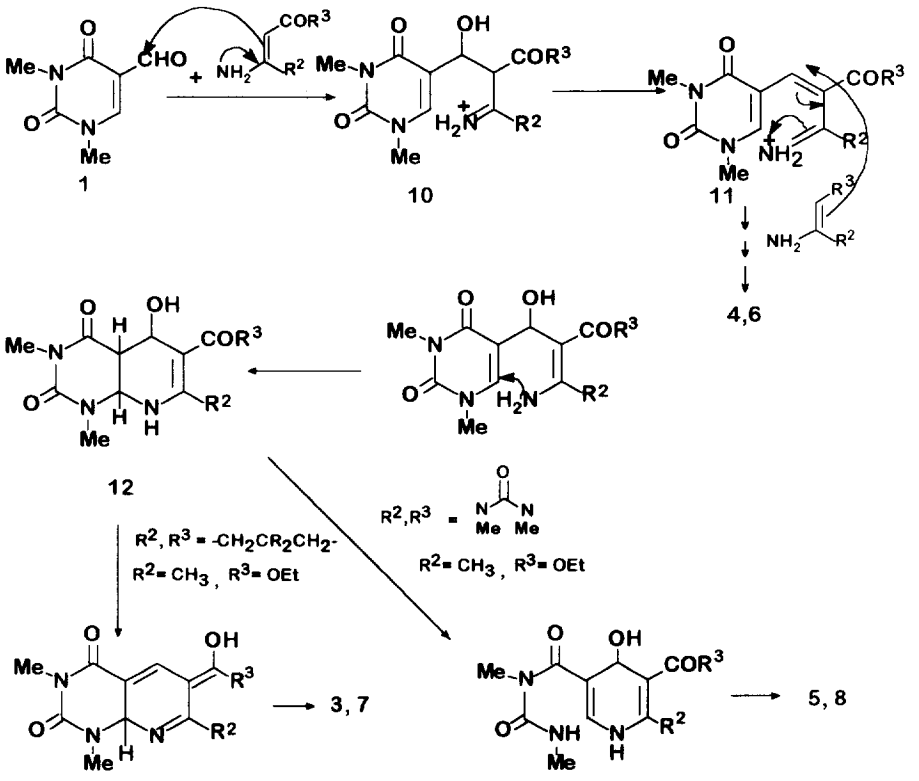
1 and 3-amino-5,5-dimethylcyclohex-2-enone (**2a**) in refluxing acetonitrile -TFA gave two products. The higher R_f component, (37%), m.p. 155°C, M^+ m/z 287, in its ^1H nmr spectrum shows gem dimethyl, methylene and N-methyl signals in 1:1 ratio along with a lowfield 1H signal at δ 8.95 and could be assigned any of two isomeric structures **3a** or **9** . The proximity of two N-Me signals in its ^1H nmr and the formation of 5-ketovinyluracil[7] derivative in case of the reaction of **1** with 1-morpholinocyclohexene favour the assignment of structure **3a** for this compound. The lower R_f component has been found to be a Hantzsch type product **4a** (43%), m.p. 145°C, M^+ m/z 411 Therefore, **2a** which normally should react with formyl

group of **1** in 2 : 1 stoicheiometry, to form 4-(1,3-dimethyluracil-5-yl)-1,4-dihydropyridines (**4a**), here induces novel transformation to provide additional annulation product **3a** through 1:1 stoicheiometric condensation[8]. However, on performing this reaction in dilute solutions using double the volume of solvent, only **4a** is formed. Similarly, **1** with 3-aminocyclohex-2-enone **(2b)** gave **3b** (30 %), m.p. 165°C, M^+ m/z 259 and 1,3-dimethyluracil[9](20%).



Further, to evaluate the scope of this reaction, the reactions of **1** with enamine - ester and enamine - amide were performed. **1** with ethyl β-aminocrotonate in acetonitrile - TFA gave Hantzsch type product **6**[10] (32%) along with a new product (34%), m.p. 185°C, M^+ m/z 279. The latter in its ^1H nmr spectrum shows one N-Me group as doublet at δ 2.93 which collapses to singlet on D_2O exchange and the second N-Me as singlet (δ 3.25) and two 1H doublets at δ 8.31 and 8.72 (Py) and could be assigned the structure **5**. In this reaction the corresponding annulation product **7** was not detected. However, on performing this reaction in DMF - TFA (10: 0.1), the annulation product **7**(4%), m.p. 85°C, M^+ m/z 277 was formed alongwith compounds **5** (12%) and **6** (20%). 6-Amino-1,3-dimethyluracil with **1** in CH_3CN - TFA gave only ring transformation product **8** (67%), m.p.175°C, M^+ m/z 305.

Therefore, enaminones **2** with **1** provide annulation products **3** but enamine - amide and enamine - ester provide ring transformation products **5, 8** . These reactions constitute unprecedented enamine induced transformations of 5-formyluracils. From these results, it is envisaged that a thorough understanding of role of structural variations in uracils and enamines would broaden the scope of this reaction for the synthesis of heterocyclic compounds.



The formation of all these products could be visualised to proceed through initial attack of enamine β-carbon at formyl group to give an intermediate **10,** which either reacts with another molecule of enamine to form dihydropyridine through **11** or undergoes intramolecular addition at C-6 of uracil unit to give intermediate **12.** The latter formed in reactions of **2** could undergo enolisation, dehydration and oxidation to give compounds **3** but in the case of amide and ester derivatives, where possibility of enolisation and consequent conjugative stabilisation of the intermediate is lowered, the elimination of urea moiety to give compounds **5** and **8** takes place. In these reactions, in contrast to the literature reports of initial attack of nucleophilic carbon of enamines at β-carbon of α,β-unsaturated carbonyl compounds[11], the attack of enamines at CHO of **1** takes precedence over β-carbon (C-6) of its α ,β -unsaturated aldehyde chromophore.

Experimental:

Melting points were determined in capillaries and are uncorrected. ^{1}HNMR and ^{13}CNMR spectra were recorded on Bruker 200 MHz instrument in $CDCl_3$, using TMS as internal standard. IR and mass spectra were recorded on Pye Unicam SP-300 and Shimadzu GC-MS QP2000 (at 70ev) instruments respectively. Reagent grade CH_3CN was freshly distilled over P_2O_5. Thin layer chromatography (TLC) was performed on precoated silica plates.

General Procedure:

The solution of 5-formyl-1,3-dimethyluracil (1.0g, 5.95mmol) and enamine (2eq., 11.9mmol) in CH_3CN (10 ml) containing TFA (0.1ml) was refluxed. After the completion of the reaction (TLC, 5-6h), the solvent was distilled off. The residue was column chromatographed on silica gel by using hexane-ethyl acetate mixtures as eluents.

1,3,8,8-Tetramethyl-6,7-dihydropyrimido[4,5-b]quinoline-2,4,6(1*H*,3*H*,7*H*)-trione (3a): (37%), m.p. 155°C ($CHCl_3$ - Hexane) , M^+ m/z 287; ^{1}Hnmr ($CDCl_3$): δ1.12 (s, 6H, CH_3), 2.26(s, 2H , CH_2), 3.03,(s, 2H, CH_2), 3.46(s, 3 H, NCH_3), 3.72 (s, 3H, NCH_3), 8.95(s,1H, C5-H); IR(KBr) 1680(br, C=O) cm^{-1}.

9-(1,3-Dimethyluracil-5-yl)-1,2,3,4,5,6,7,8,9,10-decahydro-3,3,6,6-tetramethylacridin-1,8-dione (4a): (43%), m.p.145°C (EtOH) ; M^+ m/z: 411; ^{1}Hnmr ($CDCl_3$): δ1.00 (s, 6H, 2 x CH_3), 1.09 (s, 6H, 2 x CH_3), 2.22(s, 4H, 2 x CH_2), 2.31(s, 4H, 2 x CH_2), 3.21 (s, 3H, NCH_3), 3.41(s, 3H, NCH_3), 4.78(s, 1H, Py 4-H), 6.50(br, 1H, NH), 7.52(s, 1H, U6-H); ^{13}C nmr($CDCl_3$): δ 27.02(q, CH3), 27.59(q, NCH3), 29.47(q, CH3), 30.67(q, NCH3), 32.67(s, >C<), 37.04(d, C-9), 41.20(t, CH2), 50.89(t, CH2), 109.34(s, UC-5), 112.68(s, C9a), 142.75(d, UC-6), 150.20, 151.77, 162.65 (s, C-4a / 10a, C=O), 196.10(s, C_1=O); IR (KBr): 1695(C=O), 1650(C=O), 1630(C=O) cm^{-1}. (Found C 67.46, H 6.71, N 9.82 %. $C_{23}H_{29}N_3O_4$ requires C 67.15, H 7.05, N 10.2)

1,3-Dimethyl-6,7-dihydropyrimido[4,5-b]quinoline-2,4,6(1*H*,3*H*,7*H*)-trione (3b): (30%), m.p 165°C ($CHCl_3$ - Hexane), M^+ m/z 259; ^{1}Hnmr ($CDCl_3$): δ 2.22(q, J 4.2, 2 H, CH_2), 2.72(t, J 4.2, 2 H, CH_2), 3.17(t, J 4.2, 2 H, CH_2), 3.48(s, 3H, NCH_3), 3.74(s, 3H, NCH_3), 9.02(s, 1 H, C5-H); ^{13}C nmr ($CDCl_3$): 21.30 (t, CH_2), 28.44 (q, CH_3), 29.76 (q, CH_3), 33.10 (t, CH_2), 38.17(t, CH_2), 109.58(s, C-5a), 124.25(s, C-4a), 137.63(d, CH), 151.22, 152.27, 160.54, 169.19 (s, C-9a, C-10a, C=O), 195.49(s, C=O); IR (KBr): 1710(C=O), 1690 (C=O),1665(C=O), 1600(C=C) cm^{-1}. (Found C 60.58, H 4.66, N 16.62 %. $C_{13}H_{13}N_3O_3$ requires C 60.23, H 5.02, N 16.21)

3-Ethoxycarbonyl-5-[(1,3-dimethylureido)carbonyl]-2-methylpyridine (5): (34%), m.p 185°C ($CHCl_3$ - Hexane), M^+ m/z 279; ^{1}Hnmr ($CDCl_3$): δ1.40 (t, J 3.6, 3 H, CH_3), 2.87(s, 3 H, CH_3), 2.93 (d, J 7.2, 3H, $NHCH_3$), 3.25 (s, 3 H, NCH_3), 4.41 (q, J 3.6, 2 H, OCH_2), 8.31 (d, J 2.2, C6-H), 8.72 (d, J 2.2, C4-H), 8.83 (b, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 14.25(q, CH_3), 24.91(q, CH_3), 27.19(q, NCH_3), 35.78(q, NCH_3), 61.85(t, CH_2), 125.51(s, PyC-3), 129.57(s, PyC-3), 136.99(d, PyC-4), 149.27(d, PyC-2), 155.42, 162.37, 165.45,

171.39 (s,CO / PyC-2); IR (KBr): 3310(NH),1710(C=O),1680(C=O), 1660(C=O),1600(C=C) cm^{-1} (Found C 55.51, H 5.84, N 15.06 %. $C_{13}H_{17}N_3O_4$ requires C 55.91, H 6.09, N 15.05).

2,6-Dimethyl-3,5-ethoxycarbonyl-4-(1,3-dimethyluracil-5-yl)-1,4-dihydropyridines (6): (32%), mp.85°C (EtOH); M^+ m/z 391; ^{1}Hnmr ($CDCl_3$): δ 1.23(t, J 7.2, 6H, 2 x CH_3), 2.24 (s, 6H, 2 x CH_3), 3.27 (s,3H, NCH_3), 3.38 (s, 3H, NCH_3), 4.15 (q, J 7.2, 4H, 2 x OCH_2), 4.73 (s, 1H, Py4-H), 7.21(s,1H, U6-H). ^{13}C nmr ($CDCl_3$): 14.29(q,CH3), 19.37(q,CH3), 27.63(q,CH3), 36.53(d,CH), 36.77(q,CH3), 59.36(t,CH2), 97.96(s,UC-5), 114.80(s,C-3), 141.73(d,UC-6), 147.07(s,C-2), 151.49(s,C=O), 162.42(s,C=O), 167.80(s, ester C=O); IR(KBr): 3500 (NH), 1740 (C=O of ester), 1700 (C=O), 1670(C=O) cm^{-1}.

6-Ethoxycarbonyl-7-methyl-1,3-dimethyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4(1*H*,3*H*)-dione (7): (4%), m.p. 85°C ($CHCl_3$ - Hexane); M^+ m/z 277; ^{1}Hnmr ($CDCl_3$): δ 1.42 (t, J 4.8, 3 H, CH_3), 2.9 (s, 3 H, CH_3), 3.48 (s, 3 H, NCH_3), 3.73(s, 3 H, NCH_3), 4.40 (q, J 4.8, 2H, OCH_2), 8.95, (s, 1H,CH). IR (KBr): 1710(C=O ester), 1700 (C=O), 1670(C=O) 1605(C=C) cm^{-1}. (Found C 56.19, H 5.34, N 15.06 %. $C_{13}H_{15}N_3O_4$ requires C 56.31, H 5.42, N 15.16).

6-[(1,3-dimethylureido)carbonyl]-1,3-dimethyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4(1*H*,3*H*)-dione (8): (67%), m.p. 175°C ($CHCl_3$ - Hexane); M^+ m/z 305; ^{1}Hnmr ($CDCl_3$) : δ 3.35 (s, 3H, NCH_3), 3.42 (d, J 10, 3H, NCH_3), 3.57(s, 3H, NCH_3), 3.83, (s, 3H, NCH_3), 8.77 (d, J 2.4, 1H, CH), 8.98 (d, J 2.4, 1H, CH). ^{13}C nmr ($CDCl_3$): δ 27.18 (q, CH3), 28.64 (q, CH3), 29.78(q, CH3), 35.69(q, CH3), 109.81(s, U-C3), 127.08(s, PyC-3), 136.61(d, PyCH), 151.07, 151.95(s, CO / PyC-2), 152.70(d, PyCH), 155.31, 160.51, 170.61(s, CO / PyC-2); IR (KBr): 3300(NH), 1700(C=O), 1665(C=O), 1600(C=C) cm^{-1}. (Found: C 50.76, H 4.04, N 22.88%. $C_{13}H_{15}N_5O_4$ requires C 51.14, H 4.09, N 22.9).

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