Enamine-induced Ring Transformations of 6-Substituted 5-Formyl-1,3-dimethyluracils†

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5-Formyl-1,3,6-trimethyluracil **1** undergoes facile ring transformation with enamines under acidic conditions to provide 1-heteroaroyl-1,3-dimethylurea derivatives.

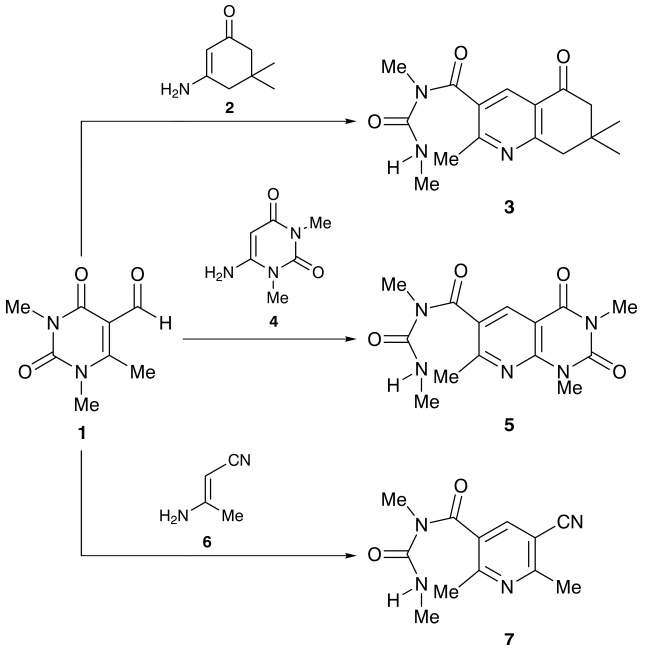
Uracil derivatisation at each of its reactive sites has attained paramount significance in potential medicinal target compounds.[1] The nucleophile-induced modifications of uracil and its derivatives emanating from their reactions at C(5) and/or C(6) or at an electrophilic appendage at C(5) make use of relatively strong nucleophiles, *viz*. amines, hydrazines, cyanide ion, *etc*. or of strongly basic reaction conditions (NaOH, NaOEt, BuLi, *etc*.).[2–6] The steric bulk of a methyl group at C(6) of uracil, in general, slows down or completely restricts nucleophilic addition at C(6) and causes alternative reactions due to generation of an anion[4b,7] at CCH_3. Recently, we have reported[8] that 5-formyl-1,3-dimethyluracil reacts with enamines, even under acidic conditions, to provide unique annulation products. We envisaged that in the reactions of enamines with 5-formyl-1,3,6-trimethyluracil under acidic conditions[9] the probability of generation of an anion at the 6-CH_3 carbon would be low and annulation might constitute the major mode of reaction. Hence, the reactions of 5-formyl-1,3,6-trimethyluracil **1** with enamines have been studied.

5-Formyl-1,3,6-trimethyluracil **1** on reaction with 3-amino-5,5-dimethylcyclohex-2-enone **2** in refluxing acetonitrile–TFA solution gives a product (50%), mp 92 °C. The parent ion peak at *m*/*z* 303 (M^+) in its mass spectrum shows it to be a condensation product of **1** and **2**. In its ^{1}H NMR spectrum the appearance of one Me signal as a doublet (δ 2.99, *J* 4.8 Hz) and other Me units as singlets points towards the N(1)—C(6) ring opening of the uracil moiety and a 1 H singlet at δ 8.07 shows the presence of the aromatic ring. From these spectral data and the elemental analysis the structure **3** is proposed for this compound. Therefore, **1** undergoes ring transformation with enamines and the 6-Me of **1** does not participate in the reaction (Scheme 1).

Similarly, compound **1** reacts with 6-amino-1,3-dimethyluracil **4** and 3-aminobut-2-enenitrile **6** in refluxing acetonitrile–TFA solution to give ring transformation products **5** (80%), mp 180–182 °C, M^+ at *m*/*z* 319 and **7** (8%), mp 120–125 °C, M^+ at *m*/*z* 246, respectively.

Therefore, despite the presence of a methyl group, compound **1** reacts with enamines through attack at CHO with subsquent annulation at C(6) but the area unit is eliminated and after annulation the uracil ring is opened. We argued that if uracil is substituted at C(6) with Cl, a leaving group, the formation of annulation products with intact uracil units could be facilitated.

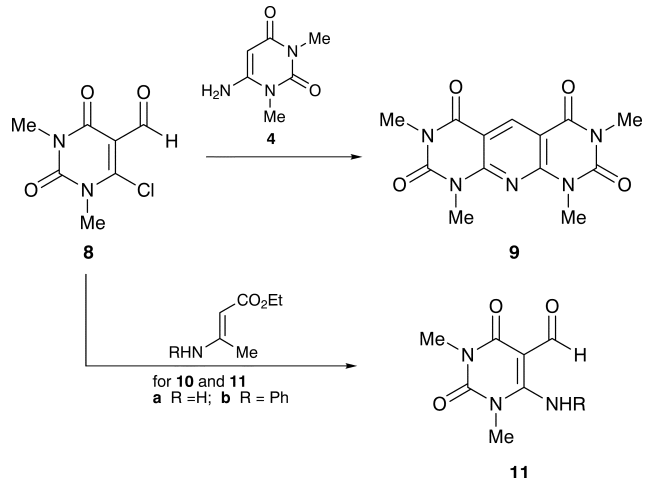
The reaction of compound **8** with **4** in refluxing acetonitrile–TFA solution gives annulation product **9**, mp 300–310 °C, M^+ at *m*/*z* 303. However, ethyl β-amino/anilino crotonates **10** with **8** provide respective 6-anilino-5-formyluracils **11a** (70%), mp 222 °C (lit.,[10] 225 °C) and **11b** (45%),



Scheme 1

mp 180 °C, M^+ at *m*/*z* 259 and corresponding ring-transformed products are not formed (Scheme 2).

The formation of compounds **3**, **5** and **7** could be rationalised through the initial nucleophilic attack of enamine at CHO to give intermediate **12** which subsequently through intramolecular attack of NH_2 at C(6) of uracil provides ring-transformed products[6,8] **3**, **5**, **7**. The well documented reversibility[11] of nucleophilic attack of amines, thiols, alcohols *etc*. at C(6) of uracil and higher reactivity of formyl than C(6) carbon rule out the possibility of alternative initial attack of amine nitrogen at C(6) of **1**. Also, as



Scheme 2

*To receive any correspondence.

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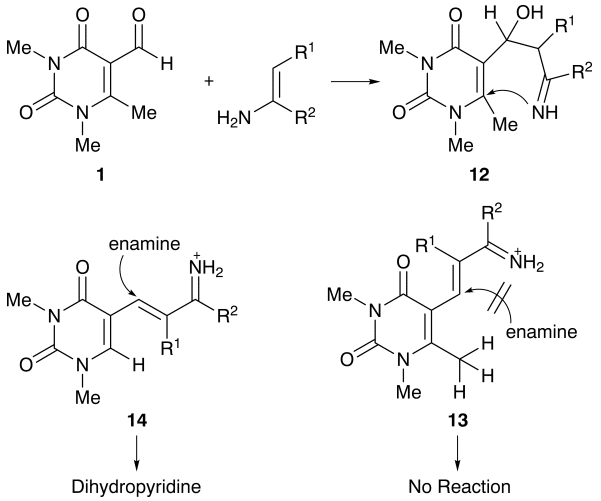

Scheme 3

the electron-withdrawing ability of the substituent (R^1) at the β position of the enamine increases, the nucleophilicity of enamine NH_2 and consequently the yield of the ring-transformation product [CON (80%), CO (50%), CN (8%)] decreases. Further in the case of reactions of 5-formyl-1,3-dimethyluracil with these enamines, the formation of dihydropyridines through intermediate **14** occurs[8] but when Me is present at C(6), the intermediate **13** does not form dihydropyridine derivatives. It has been found that 5-vinyluracil and 6-methyl-5-vinyluracils have *cis*- and *trans*-diene configurations, respectively, which the intermediates **13** and **14** would respectively acquire. In intermediate **13** the steric bulk of the Me group probably restricts the attack of enamine and respective dihydropyridine derivatives are not formed (Scheme 3).

Thus, 5-formyl-1,3,6-trimethyluracil **1** undergoes facile ring tranformations with enamines under acidic conditions to provide carbamoylpyridine derivatives, and the methyl at C(6) does not contribute 6-CH_2^- induced annulation reactions and rather restricts the usual Hantszch-type dihydropyridine formation reactions of the 5-formyl group.

Experimental

Melting points were determined in capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were run on a Bruker AC200 MHz instrument using TMS as an internal standard. Mass, infrared and UV spectra were recorded on Shimadzu GCMS-QP-2000, Philips Scientific SP3-300 and Shimadzu UV-240 spectrometers, respectively. Elemental analyses of solid samples were performed at the microanalytical laboratory of the Regional Sophisticated Instrumentation Centre, Chandigarh.

Reactions of 5-*Formyluracils* **1**, **8** *with Enamines: General Procedure*.—A solution of compound **1** or **8** (1.00 g, 5.95 mmol), enamine (2 equivalent, 12 mmol) in CH_3CN (10 ml) containing TFA (0.1 ml) was refluxed. The progress of the reaction was monitored by TLC and after completion (5–6 h) the solvent was distilled off. The residue was chromatographed on a silica gel column using hexane–ethyl acetate mixtures as eluents.

Compound **3**.—Yield 50%, mp 92 °C, M^+ at *m/z* 303 (EtOH); ^1H NMR ($CDCl_3$) δ 1.14 (s, 6 H, $2\times CH_3$), 2.58 (s, 4 H, $2\times CH_2$), 2.99 (d, $J = 4.8$ Hz, 3 H, $NHCH_3$), 3.02 (s, 3 H, CH_3), 3.09 (s, 3 H, CH_3), 8.07 (s, 1 H, C═CH), 9.03 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$) (Normal/DEPT-135) δ 22.72 (+ve, CH_3), 27.04 (+ve, CH_3), 26.23 (+ve, CH_3), 34.15 (+ve, CH_3), 46.22 (−ve, CH_2), 51.75 (−ve, CH_2), 131.52 (+ve, CH), 124.60 (absent), 131.53 (absent), 154.60 (absent), 156.42 (absent), 162.55 (absent), 172.15 (absent), 196.36 (absent); IR (KBr) $\tilde{\nu}_{max}$ 1660 (C═O), 1600 (C═O), 1700 cm^{-1} (C═O). (Found: C, 63.5; H, 6.6; N, 13.8. $C_{16}H_{21}N_3O_3$ requires C, 63.37; H, 6.93; N, 13.86%).

Compound **5**.—Yield 80%, mp 180–182 °C (EtOH), M^+ at *m/z* 319; ^1H NMR ($CDCl_3$) δ 2.56 (s, 3 H, CH_3), 3.10 (s, 3 H, CH_3), 3.30 (s, 3 H, CH_3), 3.47 (s, 3 H, NCH_3), 3.71 (d, $J = 4.63$ Hz, 3 H, $NHCH_3$), 8.25 (s, 1 H, ═CH); ^{13}C NMR ($CDCl_3$) (Normal/DEPT-135) δ 25.10 (+ve, CH_3), 28.43 (+ve, NCH_3), 29.49 (+ve, NCH_3), 34.38 (+ve, NCH_3), 39.36 (+ve, NCH_3), 134.93 (+ve, CH), 106.43 (absent), 107.95 (absent), 127.28 (absent), 134.97 (absent), 154.97 (absent), 160.17 (absent), 164.6 (absent), 171.17 (absent); IR (KBr) $\tilde{\nu}_{max}$ 1610 (C═O), 1700 cm^{-1} (C═O) (Found: C, 51.9; H, 5.24; N, 21.3. $C_{14}H_{17}N_5O_4$ requires C, 52.66; H, 5.37; N, 21.94%).

Compound **7**.—Yield 8%, mp 120–125 °C (EtOH), M^+ at *m/z* 246; ^1H NMR ($CDCl_3$) δ 2.58 (s, 3 H, CH_3), 2.79 (s, 3 H, CH_3), 2.96 (d, $J = 4.8$ Hz, 3 H, $NHCH_3$), 3.09 (s, 3 H, NCH_3), 7.72 (s, 1 H, ═CH); ^{13}C NMR ($CDCl_3$) (Normal/DEPT-135) δ 22.76 (+ve, CH_3), 23.58 (+ve, CH_3), 27.12 (+ve, NCH_3), 34.07 (+ve, NCH_3), 106.74 (absent), 115.99 (absent), 129.59 (absent), 136.67 (+ve, CH), 154.66 (absent), 157.41 (absent), 162.19 (absent), 171.02 (absent); IR (KBr) $\tilde{\nu}_{max}$ 1661 (C═O), 1690 (C═O), 2240 cm^{-1} (C≡N).

Compound **9**.—Yield 80%, mp 300–310 °C ($CHCl_3$–hexane), M^+ at *m/z* 303; ^1H NMR ($CDCl_3$) δ 3.49 (s, 6 H, $2\times NCH_3$), 3.75 (s, 6 H, $2\times NCH_3$), 9.18 (s, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 28.71 (q NCH_3), 30.15 (q, NCH_3), 96.20 (s, >C<), 106.52 (s, >C<), 139.73 (d, CH), 172.6 (s, C═O), 193 (s, C═O); IR (KBr) $\tilde{\nu}_{max}$ 1660 (C═O), 1600 cm^{-1} (C═C) (Found: C, 50.74; H, 4.02; N, 24.68%. $C_{13}H_{13}N_5O_4$ requires C, 51.48; H, 4.29; N, 23.10%).

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