SYNTHESIS OF 5-FORMYL-2,4,6-TRISUBSTITUTED PYRIMIDINES

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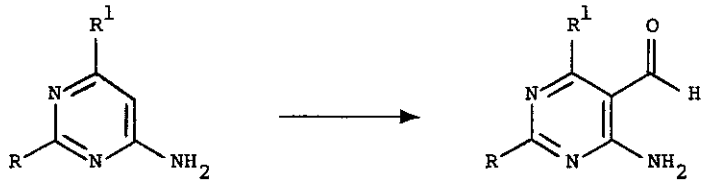
Abstract — A facile synthesis of 5-formyl-2,4,6-trisubstituted pyrimidines bearing amino and hydroxy groups is described. The Vilsmeier reagent, under mild conditions, gives good yields of products without accompanying chlorination of hydroxy groups.

Our recent synthesis of pyrimido[4,5-*d*]pyrimidines[1,2] utilized an aminomethylation reaction on the C-5 position of a suitably substituted pyrimidine. The main limitation of this route is the lack of opportunity to vary the substituents on the newly formed pyrimidine ring. We sought an alternate route which would allow additional substituents to be introduced, either prior to or subsequent to new ring formation. Pyrimidines bearing the formyl group at C-5 with an adjacent amino group would provide a suitable intermediate for this purpose.

The direct introduction of a formyl group into the C-5 position has not been extensively studied. Acetic formic anhydride[3], chloral[4], and the Reimer-Tiemann reaction[4] have been employed with limited success. The Vilsmeier reagent has been successfully used in the preparation of several 5-formyl derivatives of 2,4,6-trisubstituted pyrimidines.[5] However none of the examples possessed either a free amino or hydroxy group. Kloetzer and Herberz[6] were able to formylate pyrimidines with hydroxy groups using the Vilsmeier reagent. Unfortunately the yields were poor and formylation was accompanied by chlorination of the hydroxy groups.

Based on these previous studies we concluded that the Vilsmeier reagent would provide the best opportunity to introduce the formyl group into suitably substituted 2,4,6-trisubstituted pyrimidines. We wish to report on our initial

studies using this reagent in the successful formylation of pyrimidines bearing amino and hydroxy groups.



1 2

	R	R^1
a	NH_2	NH_2
b	NH_2	OH
c	OH	OH
d	Cl	Cl

Our studies began with an investigation of the conditions required for 1a → 2a. The presence of three strongly electron-donating groups should provide suitable activation for electrophilic attack[7] at C-5, barring any significant steric factor. Based on this reasoning we considered the normal Vilsmeier conditions of a large excess of $POCl_3$ and temperatures in excess of 70°C for long periods of time to be unwarranted, and possibly counterproductive. Allowing all of the components to mix below 0°C, followed by gentle warming to insure completeness of reaction, proved to be quite satisfactory. Indeed one can isolate the intermediate[8] in this case, after addition of the reaction mixture to ice and prior to treatment with base. However, better yields of 2a are obtained if this intermediate is heated in situ in the aqueous alkaline mixture without isolation. The most notable support for the structure of the product comes from the presence of an aldehydic proton in place of the C-5 proton in the ^1H nmr, the molecular ion (as determined by mass spectral analysis) and a positive aldehyde test using "Purpald".[9]

Concern for the reaction, 1b → 2b was based on the previously reported[6] chlorination accompanying formylation. However when 1b was treated as above very good yields of 2b were obtained without evidence of any significant chlorination. In this case the Vilsmeier intermediate was soluble in aqueous solution, and thus not isolable. The final structure was confirmed by the presence of an aldehyde

proton in the ^{1}H nmr spectrum replacing the C-5 proton, the correct molecular ion and, most importantly, no evidence of chlorine atoms in the mass spectrum. The "Purpald" test was again positive.

Since 1c was previously shown[6] to give 2d under more vigorous Vilsmeier conditions great care was taken in the conversion 1c → 2c. The second hydroxy group greatly enhanced the likelihood of some chlorination accompanying formylation. The reaction was carried out under essentially the same conditions as above. However, after heating with base (to pH 8-9) the product crystallized as the sodium salt. This salt was treated with concentrated HCl to pH 3. The free base was obtained, after cooling, filtering, washing with water and drying. Again, ^{1}H nmr and mass spectral data confirmed the structure as reported, eliminating the possibility of a chlorinated product.

These conditions should prove amenable to the formylation of many highly activated pyrimidines. We are presently determining the extent to which this reagent may be useful in formylating less activated pyrimidines.

EXPERIMENTAL

Microanalyses were performed by The Australian National University Analytical Service and the Galbraith Laboratories, Knoxville, TN, U.S.A. ^{1}H Nmr spectra were recorded on a JEOL FX90Q Fourier transform spectrometer using $(CD_3)_2SO$ as solvent with tetramethylsilane as the internal standard. The low resolution mass spectra were obtained on a Varian MAT-CH7. Uv spectra were measured on a Unicam SP800 spectrophotometer.

General Procedure for 1 → 2. –

Dimethylformamide (3.0 ml) was placed in a flask cooled below 0°C and protected from atmospheric moisture by means of a $CaCl_2$ drying tube. To this was added phosphorous oxychloride (1.5 ml; 0.016 mole) while maintaining the temperature below 0°C. To this stirred, cooled solution was added, portionwise, a suspension of the pyrimidine (ca 0.012 mole) in dimethylformamide (ca 15 ml). When addition was complete the temperature was allowed to rise to 40°C and maintained for one hour. The mixture was poured onto crushed ice (ca 50 g) and solid sodium hydroxide pellets added (ca 3 g) until alkaline (pH > 8). The mixture was heated to boiling until the evolution of dimethylamine ceased (as determined by measuring the vapors with pH paper). The products were collected by

filtration and purified as described below.

5-Formyl-2,4,6-triaminopyrimidine (2a). – Crystallized as fine, tan needles (1 N sodium hydroxide, 60% yield), mp dec. >250°C. ^{1}H Nmr showed resonances at δ 9.76 (CHO, sharp s), δ 7.19 (4-NH_2 and 6-NH_2, broad s) and δ 6.38 (2-NH_2, broad s). The mass spectrum gave m/e of 153 (100%) and other major peaks at 136 (10%), 125 (18%) and 110 (21%). The uv spectra gave the following: $\lambda_{max}^{pH\ 2}$ (nm) = 218, 238, 270(s), 291; $\lambda_{max}^{pH\ 7}$ (nm) = 220(s), 237, 300; $\lambda_{max}^{pH\ 13}$ (nm) = 237, 300. Anal. calc'd for $C_5H_7N_5O$: C, 39.21; H, 4.61; N, 45.73. Found: C, 38.96; H, 4.70; N, 45.56.

2,4-Diamino-5-formyl-6-oxo(1H)-pyrimidine (2b). – Crystallized as a tan solid (H_2O, 85% yield); does not melt below 300°C. ^{1}H Nmr showed resonances at δ 9.67 (CHO, sharp s), δ 8.86 (N_1-H, broad s), δ 7.63 (4-NH_2, broad s) and δ 6.91 (2-NH_2, broad s). The mass spectrum gave m/e of 154 (73%) and other major peaks at 153 (11%), 126 (100%), 98 (15%), 68 (27%) and 56 (16%). The uv spectra gave the following: $\lambda_{max}^{pH\ 2}$ (nm) = 230, 250(s), 292; $\lambda_{max}^{pH\ 7}$ (nm) = 229, 291; $\lambda_{max}^{pH\ 13}$ (nm) = 230, 299. Anal. calc'd for $C_5H_6N_4O_2 \cdot 0.5\ H_2O$: C, 36.81; H, 4.33; N, 34.35. Found: C, 37.21; H, 4.17; N, 34.22.

4-Amino-2,6-dioxo(1H,3H)-5-formylpyrimidine (2c). – The sodium salt obtained (88% yield) directly from the reaction mixture was suspended in H_2O and treated with conc. HCl until pH 3. The free base was obtained as a yellow solid. Recrystallized as a tan solid (H_2O); does not melt up to 300°C. ^{1}H Nmr showed resonances at δ 9.67 (CHO, sharp s), δ 8.95 and δ 8.49 (N_1-H and N_3-H, broad s) and δ 6.63 (4-NH_2, broad s). The mass spectrum gave m/e of 155 (35%) and other major peaks at 154 (49%), 127 (100%), 126 (50%), 84 (17%) and 68 (37%). The uv spectra gave the following: $\lambda_{max}^{pH\ 2}$ (nm) = 214, 245, 282; $\lambda_{max}^{pH\ 7}$ (nm) = 230, 242(s), 285; $\lambda_{max}^{pH\ 13}$ (nm) = 230, 288. Anal. calc'd for $C_5H_5N_3O_3$: C, 38.72; H, 3.25; N, 27.09. Found: C, 38.93; H, 3.24; N, 26.89.

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7. It is reasonable to assume that the active form of the Vilsmeier reagent is $R_2\overset{+}{N}=CHCl$.
8. Although not fully characterized, ^1H nmr evidence is consistent with 5-(1-chloro-1-dimethylaminomethyl)-2,4,6-triaminopyrimidine.
9. Purpald (Aldrich Chemical Co.) is added to 1 ml 1 N NaOH containing the aldehyde. Aeration and warming of the mixture gives a light purple color indicative of an aldehyde. See H.D. Durst and G.W. Gokel, J. Chem. Ed., 1978, 55, 206 for reactions involved.

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