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In a continuation of our studies involving the nucleophilic displacement of one of the chlorines from 2,4,6-trichloropyrimidine, we now report the initial displacement of one of the fluorine atoms from 2,4,6-trifluoropyrimidine using both aliphatic and aromatic amines. The monosubstitution products favor 2-substitution with ammonia and ethanolamine while aniline gave the 4-substituted derivative as the preferred product.

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Introduction.

Halogenated pyrimidines have long served as precursors to a variety of substituted pyrimidines. No other leaving group has enjoyed the popularity that the halogen atom has under conditions favoring nucleophilic displacement. Our own studies involving nitrogen nucleophilic species with 2,4,6-trichloropyrimidine (**1**) (Scheme 1) have afforded a wide variety of multisubstituted pyrimidines [1].

It is believed that 2,4,6-trifluoropyrimidine (**2**) (Scheme 1) is considerably more reactive than **1** in nucleophilic displacement reactions [2]. To ascertain the chemical behavior of **2** we chose to initiate studies involving the nucleophilic displacement reactions of **2** using a spectrum of amines. One of the earliest examples of this type of reaction is exemplified by the reaction of **2** with ammonia [3] in which the major monosubstituted product was 2-amino-4,6-difluoropyrimidine (**3**) (Scheme 1) with a minor amount of the 4-amino regioisomer **4**. A recent study involving the reaction of **2** with amino acids confirms the preference for 2-substitution versus 4-substitution by a 3:1 ratio [4]. These observations are in stark contrast to the order of reactivity between positions 2 and 4 observed for substitution on **1**. Quite interesting is the observation that the presence of a methyl group in position 5 of compound **2** completely reverses this ratio of products, favoring 4-substitution [4].

The overall lack of examples utilizing **2** in nucleophilic displacement reactions is likely due to the much higher cost of this pyrimidine and, perhaps, a belief that the chemistry would parallel that of **1**. Based on the literature and our own studies of the reaction of **1** we embarked on a preliminary investigation of the reaction of **2** with a variety of selected nitrogen nucleophiles. We chose representative nucleophilic reagents that had been used with **1** so that a comparison with **2** could be made.

Discussion.

Reactions with Ammonia.

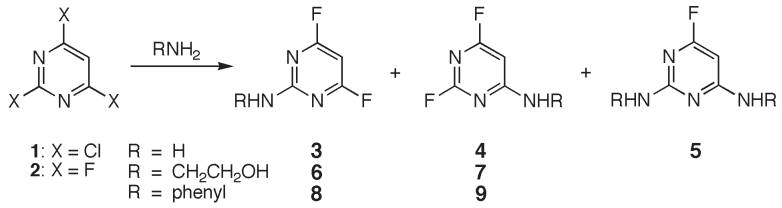
Previous work employing ammonia in ethanol at 0° afforded a mixture of **3** and **4** in an overall yield of 74 %. The 2-amino isomer **3** was isolated in 56% yield while the 4-isomer **4** was obtained as the minor component, in 8 % yield (Scheme 1) [3]. It was necessary to raise the temperature to ~ 100° in order to achieve disubstitution. This latter behavior is identical to that observed for reactions of **1** in which each successive substitution was made more difficult by the presence of an electron donating amino substituent. We conducted our experiment initially by bubbling ammonia into methanol containing **2** at ice bath temperature followed by stirring at room temperature overnight. Surprisingly only a 25 % mixture of **3** and **4** was obtained. The major component isolated was 67 % of 2,4-diamino-6-fluoropyrimidine (**5**). In this solvent it was not necessary to heat the contents to reflux in order to achieve disubstitution. The difference in the results obtained in these two solvents, ethanol versus methanol, is likely due to the increased polarity of methanol. Following the same procedure while changing the solvent to the considerably less polar dioxane, the reaction afforded a 4:1 ratio of **3** and **4**, as determined by ^{1}H nmr, in 81 % yield, with little or no disubstitution. Compounds **3** and **4** can be separated by column chromatography. Thus, it appears that using low polarity solvents can better control the formation of simple monoaminopyrimidines, as well as insure a significant preponderance of the 2-substituted isomer.

Reactions with Ethanolamine.

As an extension of the reactivity with ammonia we sought to explore the reaction of **2** with a simple alkyl amine. In a previous report [1a] compound **1**, upon treatment with ethanolamine, afforded a 3:1 mixture of 4-monosubstituted product and 2-monosubstituted product in 77 % overall yield. Based on our results in the reaction of **2** with ammonia it was of interest to compare the reaction of **2** with ethanolamine. Thus treatment of **2** with one equivalent of ethanolamine in ethanol, and stirring overnight at room temperature, gave a 91 % yield of a mixture of **6** and **7** in a ratio of ~ 2:1, as determined by ^{1}H nmr (Scheme 1). Although this ratio of isomers is not as high as that for ammonia, the preponderance of 2-substitution product is again observed. Column chromatography afforded pure **6** and this compound was characterized by ^{1}H and ^{13}C nmr spectroscopy.

Although the ^{1}H nmr spectrum was straightforward and consistent with the assigned structure, the ^{13}C nmr

Scheme 1



spectrum was less obvious. While the carbon at position five was, indeed, a triplet that indicated substitution had occurred at position two there were two sets of signals representing C-4 and C-6. Thus a doublet of doublets at 172.3 ppm is assigned to C-6 while the doublet of doublets at 171.7 ppm is attributed to C-4 [6]. Since we had good evidence for the ethanolamine substitution at C-2 we postulated that C-4 and C-6 were different due to intramolecular hydrogen bonding between the alcoholic proton and N-3 thereby creating different electronic environments at C-4 and C-6. As substantiation of this possibility the temperature of the nmr sample was raised to 100° whereupon the two sets of signals coalesced into one, a doublet of doublets at 172.1 ppm.

Because the ethanolamine derivative **6** was chosen in order to compare the chemistry with the analogous chloro derivatives previously reported [1a], we were interested in reexamining the ^{13}C nmr spectrum of the comparable chloro derivative, 4,6-dichloro-2-(2-hydroxyethyl)-pyrimidine. The ^{13}C nmr spectrum of this latter compound was found to have similar spectral behavior, though without the carbon-fluorine coupling. Two signals at 160.9 ppm and 160.6 ppm were found for C-4 and C-6 respectively. Again, intramolecular hydrogen bonding is offered as the explanation. Heating this sample to 90° coalesced these two signals into one signal at 160.5 ppm.

We were unable to obtain a complete separation of **7** from **6** in order to definitively characterize **7** however.

Reactions with Aniline.

Finally, we decided to explore the reaction of **2** with aniline. Recently we reported on the reaction of **1** with a variety of anilines [1d] and found that only monosubstitution was viable, primarily, if not exclusively, at position 4. The reaction of aniline with **2** would afford a good comparison between the reactivity of chlorine versus fluorine substituents. It has been suggested that fluorines on a pyrimidine ring are approximately 60-100 times more reactive towards nucleophilic substitution than the corresponding chlorines [2,5]. There is a paucity of nucleophilic displacement of fluorines on the pyrimidine ring, and none involving aromatic amines [2].

The initial reaction of **2** with aniline was conducted using sodium carbonate in ethanol, stirred at room temperature overnight or at reflux. Under reflux conditions a mixture of monosubstituted anilino products (corresponding to **8** and **9**) was obtained, although concomitant replacement of a second fluorine by an ethoxy group was observed [7]. However, the reaction conducted at room temperature afforded a mixture of the 4-substituted isomer **9** as the major component and the 2-substituted isomer **8** as the minor component. The ratio obtained was 2:1 as compared to a ratio of 9:1 for the analogous reaction with **1** [1d]. Undoubtedly the greater reactivity of the fluorine substituent has resulted in diminished selectivity.

^{13}C Nmr spectroscopy provides the best evidence for the structure assigned as **9**. Because of coupling with the nearby fluorine substituent at position 6 the C-5 carbon is strongly coupled and appears as a doublet (86 ppm). The 2-substituted isomer **8** should be represented as a triplet for the C-5 carbon, being adjacent to two C-F bonds at positions 4 and 6. Compound **2** has such a triplet for the C-5 carbon (92 ppm).

In an attempt to obviate the problem of solvolysis at elevated temperatures dioxane was employed as solvent. This resulted in reasonable yields of the mixture of isomers **8** and **9** without the accompanying solvolysis.

In conclusion, 2,4,6-trifluoropyrimidine (**2**) has been shown to react quite readily, even at low temperatures, with a variety of neutral nitrogen nucleophiles. The ratio of monosubstituted isomers representing 4-substitution and 2-substitution are not as large as those obtained in comparable reactions with 2,4,6-trichloropyrimidine (**1**).

EXPERIMENTAL

Melting points are uncorrected and were determined in open capillary tubes using a Thomas Hoover instrument. Most of the ^{1}H nmr and ^{13}C nmr spectra were obtained on a QE-300 NMR spectrometer or on a Varian Mercury Plus spectrometer at 300 MHz and 75 MHz, respectively. Some ^{13}C nmr spectra for compound **6** were obtained on a Varian Inova 500 MHz spectrometer at 125 MHz. All values are reported in ppm relative to TMS. Relative integrals of peak areas are in agreement with assigned structures. Galbraith laboratories, Knoxville, TN, performed elemental analyses. Column chromatography was carried out on silica gel (Mallinckrodt 60-200 mesh) using n-hexane/ethyl acetate mixtures as the eluant.

2-Amino-4,6-difluoropyrimidine (**3**) and 4-Amino-2,6-difluoropyrimidine (**4**).

(a) Using Methanol as Solvent.

To a flask containing 1 mmole of 2,4,6-trifluoropyrimidine (**2**) in methanol (10 mL) chilled in an ice bath is bubbled an excess of anhydrous ammonia. Upon complete addition of the ammonia the flask and its contents were allowed to warm to room temperature and stirred overnight. The residue obtained by evaporation of the solvent under reduced pressure was purified by column chromatography. The first fraction (25 %) was determined to be a mixture of **3** and **4** by ^{1}H nmr. The second fraction (67 %) was identified as 2,4-diamino-6-fluoropyrimidine (**5**) by comparison with reported mp and ^{1}H nmr [3].

(b) Using Dioxane as Solvent.

The same procedure as described above was employed except the solvent used was dioxane. Work up in a similar manner resulted in an 81 % yield of a mixture of **3** and **4** in a ratio of 4:1, as determined by ^{1}H nmr. Column chromatography afforded pure **3** and pure **4**. These assignments are based on comparison with ^{1}H nmr literature values [3].

4,6-Difluoro-(2-hydroxyethylamino)-4,6-difluoropyrimidine (**6**).

To a solution of 2,4,6-trifluoropyrimidine (**2**) (2.00 g; 14.9 mmoles) in ethanol (10 mL), cooled to –78°, 2-aminoethanol (0.92 g; 15.0 mmoles) in ethanol (10 mL) was added dropwise over 15 min. The mixture was allowed to warm to room temperature and stirred overnight. After evaporation of the solvent the residue was chromatographed. The major product **6** was obtained (1.7 g) in 65 % yield as a cream colored solid which melted at 102-3°; ^{1}H nmr (dimethylsulfoxide-d_6): δ 3.3 (t, 2H, -CH_2NH-), 3.5 (t, 2H, -O-CH_2-), 4.7 (t, 1H, HO-), 6.1 (s, 1H, pyrimidine C-5), 8.0 (t, 1H, -NH-); ^{13}C nmr (dimethylsulfoxide-d_6): δ 43.5, 59.1, 161.6 (t), 171.7 (dd), 172.3 (dd).

Anal. Calcd. For $C_6H_7F_2N_3O$• 0.1 $C_4H_8O_2$ (ethyl acetate): C, 41.78; H, 4.28; N, 22.85. Found: C, 42.02; H, 4.26; N, 23.01.

2,4-Difluoro-6-phenylaminopyrimidine (**9**).

Aniline (7.5 mmoles), 2,4,6-trifluoropyrimidine (**2**) (7.4 mmoles), and sodium carbonate (7.5 mmoles), in ethanol (20 mL) was allowed to stir at room temperature for 22 h. An equal volume of water was added and the resulting solid was collected by filtration, washed with water and dried to give a mixture of components. Column chromatography gave 2,4-difluoro-6-phenylaminopyrimidine (**9**) as the major product (50 %), mp 127-9°; ^{1}H nmr (dimethylsulfoxide-d_6): δ 6.3 (s, 1H, pyrimidine C-5), 7.2 (t, 1H, phenyl C-4), 7.4 (t, 2H, phenyl C-3,5), 7.6 (d, 2H, phenyl C-2,6), 10.4 (s, 1H, -NH); ^{13}C nmr (dimethylsulfoxide-d_6): δ 86 (d), 122, 125, 130, 139, 162.5 (dd), 166 (t), 171.5 (dd).

Anal. Calcd. For $C_{10}H_7F_2N_3$: C, 57.97, H, 3.41, N, 20.28. Found: C, 57.65, H, 3.44, N, 19.89.

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[6] This ^{13}C nmr spectrum at room temperature was run on the Varian Inova 500 MHz spectrometer.

[7] While the elemental analysis (for C,H, and N) confirmed the general structure the isomers could not be separated for complete characterization.