Pyrimidines. 9. Chlorination of 6-Trifluoromethyluracil with Phosphorus Oxychloride in the Presence of Trialkylamines

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Received April 16, 1987

Ring-chlorination of 6-trifluoromethyluracil in phosphorus oxychloride in the presence of triethyl, tri-*n*-propyl, and tri-*n*-butylamines was studied with respect to by-product formation. Comparisons were made with the results obtained by treating the preformed chlorinated pyrimidine with triethyl amine in boiling toluene.

Amination of chloropyrimidines by tertiary amines takes place by a Hofmann type reaction with substituent orientation generally in the 2 position of the ring. Yields of products depended on the base and reaction time. The rate of substitution in the 2 position is significantly enhanced by the presence of the trifluoromethyl group in the 6 position as compared with a methyl group.

Heating preformed chloropyrimidines with tertiary amines in toluene, offers a satisfactory approach for the preparation of 2-*N,N*-disubstituted aminopyrimidines. For the formation of ring-chlorinated pyrimidines in phosphorus oxychloride with a minimum of by-products, tri-*n*-propylamine, after a short reflux period is most useful.

J. Heterocyclic Chem., **24**, 1243 (1987).

In previous studies, we reported on the ring-chlorination of pyrimidines in the presence of phosphorus oxychloride and tertiary amines [1,2]. When *N,N*-dimethylaniline was the base employed [1], 6-methyluracil afforded high yields of the dichloropyrimidine, after 3 and 24 hours of heating, along with minor amounts of the 2-*N*-methylanilino by-product. After 48 hours, the formation of the 2-*N*-methylanilino product increased at the expense of the dichloro compound, the 2-chloro-4-methylanilino-6-methylpyrimidine and 2,4-*bis*(*N*-methylanilino)-6-methylpyrimidine were also formed in small amounts. With 6-trifluoromethyluracil, moderate yields of the dichloropyrimidine, accompanied by good yields of the 2-*N*-methylanilino by-product were obtained, after 3 hours of heating. After 24 hours, the 2-*N*-methylanilinopyrimidine was the primary product, along with low yields of 2,4-dichloro- and 2,4-*bis*-(*N*-methylanilino)-6-trifluoromethylpyrimidine. The mixture of products remained nearly the same over 188 hours of heating.

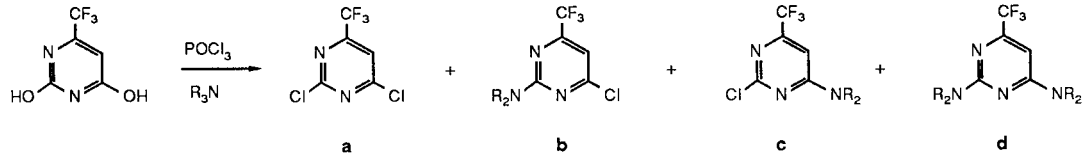
The effect of the tertiary bases triethylamine (TEA), tri-*n*-propylamine (TPA), and tri-*n*-butylamine (TBA) on the chlorination of 6-methyluracil by phosphorus oxychloride was studied and compared with the reaction of preformed 2,4-dichloro-6-methylpyrimidine and TEA in toluene [2]. The reaction in phosphorus oxychloride in the presence of TEA afforded high yields of 2,4-dichloro-6-methylpyrimidine and low yields of the 2-diethylamino derivative, after 3 and 24 hours of heating. After 188 hours of boiling, a high yield of the 2,4-*bis*(diethylamino) derivative was obtained and a small amount of the dichloropyrimidine remained. TPA in phosphorus oxychloride yielded solely the dichloropyrimidine, even after 188 hours of boiling, and TBA was the same after 48 hours, but 4% of 4-di-*n*-butylaminopyrimidine was found after 188 hours of boiling. Heating preformed 2,4-dichloro-6-methylpyrimidine in toluene along with TEA caused the formation of the 2-diethylamino derivatives (28%), after 8 hours. Further heating caused the gradual disappearance of the dichloropyrimidine with increase in yield of the 2-diethylamino compound, as well as the formation of the 4-diethylamino isomer. After 188 hours, the mixture of isomers was composed of 4-chloro-2-*N,N*-diethylamino-6-methylpyrimidine (87%) and 2-chloro-4-*N,N*-diethylamino-6-methylpyrimidine (13%).

With respect to the chlorination of 6-trifluoromethyluracil with phosphorus oxychloride in the presence of *N,N*-dimethylaniline [1], the orientation of the by-products was essentially the same as for 6-methyluracil, but the ratios of products were different after 3 hours, 33% of 2,4-dichloro-6-trifluoromethylpyrimidine, 62% of 4-chloro-2-*N*-methylanilino-6-trifluoromethylpyrimidine, and 5% of 2,4-*bis*-(*N*-methylanilino)-6-trifluoromethylpyrimidine were formed. Twenty-four hours of heating caused the composition of the mixture to change to 9%, 80%, and 11%, respectively, and remained nearly constant after 188 hours of heating. The course of the chlorination and by-product formation was explained on the basis of the π electron distribution, as influenced by substituents on the pyrimidine ring.

The purpose of the present work was to examine the chlorination of 6-trifluoromethyluracil by phosphorus oxychloride in the presence of the tertiary amines, TEA, TPA, and TBA, and to compare the results with those obtained with 6-methyluracil [2] and with *N,N*-dimethylaniline as the base [1]. It was further desired to compare the effect of TEA in preformed 2,4-dichloro-6-trifluoromethylpyrimidine with those of 2,4-dichloro-6-methylpyrimidine in boil-

Table 1

Reaction of 6-Trifluoromethyluracil with Phosphorus Oxychloride in the Presence of Triethylamine (TEA), Tri-*n*-propylamine (TPA), and Tri-*n*-butylamine (TBA)

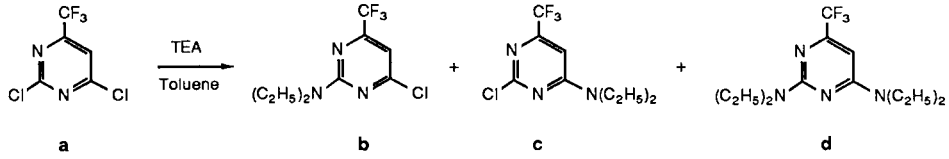


Amine	Reflux Time (hours) 3				24				48				188			
	Composition of Mixture, % [a]															
	a	**b**	**c**	**d**	**a**	**b**	**c**	**d**	**a**	**b**	**c**	**d**	**a**	**b**	**c**	**d**
TEA	89	11	0	0	87	10	3	0	86	10	4	0	74	16	10	0
TPA	96	4	0	0	91	6	3	0	81	12	7	0	71	17	12	0
TBA	97	3	0	0	82	11	7	0	76	14	10	0	36	30	34	0

[a] Quantitation by gas chromatography.

Table 2

Reaction of 2,4-Dichloro-6-Trifluoromethylpyrimidines with Triethylamine (TEA) in Toluene



Reflux Time (hours)	Composition of Mixture, % [a]			
	a	**b**	**c**	**d**
3	0	78	20	2
8	0	78	20	2
24	0	78	18	4
48	0	78	16	6
72	0	77	15	8
188	0	77	13	10

[a] Quantitation by gas chromatography.

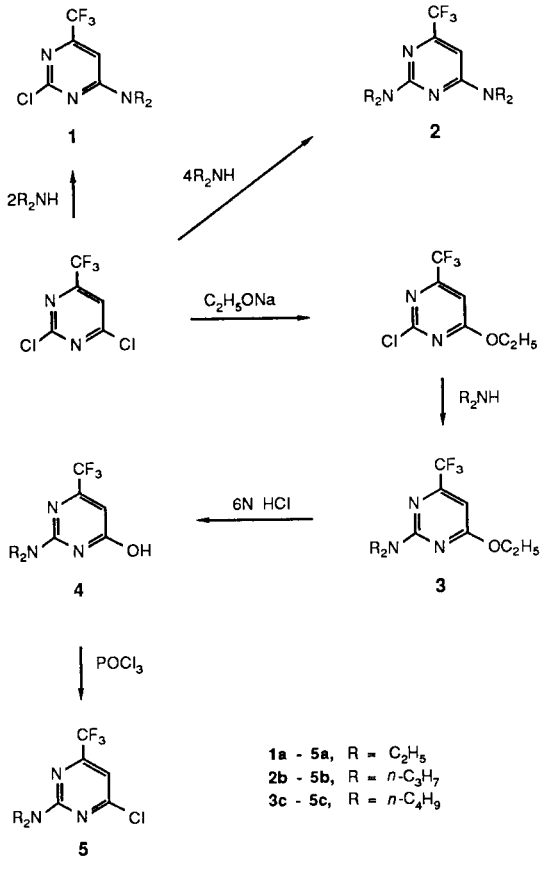
ing toluene. Also of interest was to determine if TPA would be the base of choice in the ring-chlorination of pyrimidines by means of phosphorus oxychloride, as was reported for 6-methyluracil [2].

A study was made of the products formed with respect to time, during the chlorination of 6-trifluoromethyluracil with phosphorus oxychloride in the presence of TEA, TPA, and TBA over 188 hours under reflux, and the results are summarized in Table 1. The reaction of 2,4-dichloro-6-trifluoromethylpyrimidine with TEA in boiling toluene was carried out similarly, and the results are summarized in Table 2. The reaction products were identified gas chromatographically by matching peaks with those obtained from authentic samples of compounds. Quantitation was done by integrating the areas under the peaks.

The preparation of the expected compounds are shown in Scheme 1 [3]. When 2,4-dichloro-6-trifluoromethyluracil was treated with 2 equivalents of TEA, TPA, and TBA, respectively in ethanol with ice cooling, the 4-dialkylamino derivatives **1a** (71%), **1b** (80%), and **1c** (80%) were obtained. Using double the amount of base in a sealed stainless steel pressure vessel at 70° overnight, the 2,4-*bis*-*N*,*N*-dialkylaminopyrimidines **2a** (83%), **2b** (95%), and **2c** (62%) were formed.

Amination of 2-chloro-4-ethoxy-6-trifluoromethylpyrimidine with TEA, TPA, and TBA, respectively in ethanol in the pressure vessel at 70° overnight, yielded **3a** (82%), **3b** (78%), and **3c** (84%). Upon hydrolysis of the ethoxy com-

Scheme 1



pounds with 6*N* hydrochloric acid for 80 hours, products **4a** (82%), **4b** (85%), and **4c** (48%) crystallized. Treating compounds **4** with phosphorus oxychloride, afforded **5a** (53%), **5b** (35%), and **5c** (11%). When 2,4-dichloro-6-trifluoromethylpyrimidine was heated with TBA in toluene, 79% of **5c** was obtained. All of the compounds were characterized by elemental analysis, uv, and ir spectra. The 100 MHz nmr spectra were consistent with the assigned structures.

After 3 hours of heating during the chlorination of 6-trifluoromethyluracil in phosphorus oxychloride containing trialkylamine, 2,4-dichloro-6-trifluoromethylpyrimidine was formed in the presence of TEA (89%), TPA (96%), and TBA (97%), with the respective 2-*N,N*-dialkylaminopyrimidine (**5**) as the sole by-product. At the end of 24 hours of reaction, the yield of dichloropyrimidine decreased in all cases with the appearance of 4-*N,N*-dialkylamino **1** along with the 2-*N,N*-dialkylamino isomer **5**. Further heating caused additional formation of both *N,N*-dialkylaminopyrimidines with decrease in the yield of the dichloropyrimidine. No *bis*(*N,N*-dialkylamino) derivative **2** was detected.

The results of the time study on the reaction of preformed 2,4-dichloro-6-trifluoromethylpyrimidine and TEA in boiling toluene indicated that no dichloropyrimidine was detected after 3 hours of reaction and **5a** (77-78%) remained constant over 188 hours of reaction time. Compound **1a** varied in yield from 20 to 13%, whereas **5a** varied from 2 to 10% at the end of the reaction.

Since previous experience had shown that TPA was superior as a base in the ring-chlorination of pyrimidines by phosphorus oxychloride [2] and it appeared equally effective in our time study with 6-trifluoromethyluracil, we carried out a preparative run for the formation of 2,4-dichloro-6-trifluoromethylpyrimidine, using a 3 hour reflux period. The yield of product was 83% as compared with 46% using *N,N*-dimethylaniline as the base [1] and 77% using phosphorus oxychloride in combination with phosphorus pentachloride followed by hydrogen chloride treatment [4].

When ring-chlorinated pyrimidines are aminated by tertiary amines either in phosphorus oxychloride or toluene, substitution takes place by a Hofmann type reaction, and the substituent is generally oriented to the 2 position of the ring [1,2]. The present results are consistent with these conclusions. The yields of products depend on the base and reaction times as well as the types of substituents present on the ring. The rate of this substitution in the 2 position is significantly enhanced by the presence of the trifluoromethyl group over that of the methyl group in the 6 position. To produce 2-*N,N*-disubstituted aminopyrimidines on a preparative basis, the reaction of the preformed chlorinated pyrimidine amine heated in toluene offers a satisfactory approach. For the formation of ring-chlorinated pyrimidines in phosphorus oxychloride with a minimum of by-products, TPA, after a short reflux period, is suggested as most useful.

EXPERIMENTAL

Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. Ultraviolet spectra were gotten with a Perkin-Elmer Lambda 5 uv/vis spectrophotometer, and refractive indices were taken with an Abbe-3L, B & L refractometer. Infrared spectra were obtained with a Perkin-Elmer Model 221 spectrophotometer, and 100 MHz nmr spectra were gotten with a Varian XL-100 spectrometer. The purity of samples and the course of reactions were established by gas chromatography which was performed on a Varian Aerograph Model 1400 gas chromatograph to which was attached a Varian Model 20 recorder. The column employed was 5 feet × 1/8 inch o.d. packed with 5% OV-101 on 80-100 mesh Gas Chrom Q.

2-Chloro-4-ethoxy-6-trifluoromethylpyrimidine.

A solution of sodium (1.06 g, 0.046 g-atom) in 100 ml of ethanol was added dropwise to a solution of 2,4-dichloro-6-trifluoromethylpyrimidine (10 g, 0.046 mole) [1] in 100 ml of ethanol with stirring below 5° over 2 hours. Stirring was continued for an additional hour, after which sodium chloride was removed by filtration. The solvent was evaporated under vacuum, and the residue was partitioned between water and ether. The ether layer was washed with water, dried over sodium sulfate, and the solvent was removed by evaporation and the residue distilled. The yield of product was 8 g (77%), bp 68° (1.7 mm), n_D^{25} 1.4433; uv (methanol): λ max 260 (ε 443), 217 (752); ir (neat): ν CF_3 1152 cm^{-1}; ^{1}H-nmr (deuterio-

chloroform, TMS): δ 1.45 (t, 3H, OCH_2CH_3); δ 4.58 (broad m, 2H, OCH_2CH_3); δ 6.93 (5-H).

Anal. Calcd. for $C_7H_6ClF_3N_2O$: C, 37.10; H, 2.67; Cl, 15.65; N, 12.36. Found: C, 37.11; H, 2.68; Cl, 15.48; N, 12.18.

2-Chloro-4-*N,N*-diethylamino-6-trifluoromethylpyrimidine (**1a**).

To a solution of diethylamine (7.4 g, 0.1 mole) in 30 ml of ethanol was added 2,4-dichloro-6-trifluoromethylpyrimidine (10.9 g, 0.05 mole) dropwise with stirring and ice cooling. The mixture was allowed to stand at room temperature for 3 hours. The solvent was removed by vacuum evaporation, and the residue was dissolved in ether and washed with water, and dried over sodium sulfate. After removal of the solvent, the product was distilled. The yield of compound was 9 g (71%), bp 97° (0.05 mm), mp 52-53°; uv (methanol): λ max 253 (ε 1756), 303 (457); ir (neat): ν CF_3 1158 cm^{-1}; ^{1}H-nmr (deuteriochloroform, TMS): δ 1.24 (t, 6H, $N(CH_2CH_3)_2$); δ 3.56 (broad m, 4H, $N(CH_2CH_3)_2$); δ 6.58 (5-H).

Anal. Calcd. for $C_9H_{11}ClF_3N_3$: C, 42.61; H, 4.37; Cl, 13.98; N, 16.56. Found: C, 42.37; H, 4.62; Cl, 13.85; N, 16.51.

2-Chloro-4-*N,N*-di-*n*-propylamino-6-trifluoromethylpyrimidine (**1b**).

Compound **1b** was prepared from 2,4-dichloro-6-trifluoromethylpyrimidine and di-*n*-propylamine in the same manner as **1a**. The yield of product was 80%, bp 108° (0.05 mm), mp 43-44°, n_D^{25} 1.4876; uv (methanol): λ max 254 (ε 1745), 304 (462); ir (neat); ν CF_3 1148 cm^{-1}; ^{1}H-nmr (deuteriochloroform, TMS): δ 6.26 (5-H).

Anal. Calcd. for $C_{11}H_{15}ClF_3N_3$: C, 46.89; H, 5.37; Cl, 12.59; N, 14.92. Found: C, 46.74; H, 5.61; Cl, 12.75; N, 14.77.

2-Chloro-4-*N,N*-di-*n*-butylamino-6-trifluoromethylpyrimidine (**1c**).

The title compound was prepared from 2,4-dichloro-6-trifluoromethylpyrimidine and di-*n*-butylamine in the same manner as for **1a**. The yield of **1c** was 80%, bp 122° (0.01 mm), n_D^{25} 1.4852; uv (methanol): λ max 255 (ε 1777), 304 (467); ir (neat): ν CF_3 1142 cm^{-1}; ^{1}H-nmr (deuteriochloroform, TMS): δ 6.29 (5-H).

Anal. Calcd. for $C_{13}H_{19}ClF_3N_3$: C, 50.41; H, 6.21; Cl, 11.44; N, 13.57. Found: C, 50.39; H, 6.21; Cl, 11.76; N, 13.48.

2,4-*bis*(*N,N*-Diethylamino)-6-trifluoromethylpyrimidine (**2a**).

A mixture of 2,4-dichloro-6-trifluoromethylpyrimidine (10.9 g, 0.05 mole) and diethylamine (17.5 g, 0.2 mole) in 70 ml of ethanol was prepared with ice cooling, sealed in a stainless steel pressure vessel, and kept at 70° overnight. After cooling, the solvent was removed in a rotary evaporator under vacuum, and the residue was partitioned between ether and water. The ether layer was washed with water, dried over sodium sulfate and vacuum distilled. The yield of product was 12 g (83%), bp 97-98° (0.01 mm), n_D^{25} 1.6892; uv (methanol): λ max 230 (ε 3666), 312 (734); ir (neat): ν CF_3 1138 cm^{-1}; ^{1}H-nmr (deuteriochloroform, TMS): δ 5.64 (5-H).

Anal. Calcd. for $C_{13}H_{21}F_3N_4$: C, 53.78; H, 7.29; N, 19.30. Found: C, 53.99; H, 7.51; N, 19.58.

2,4-*bis*(*N,N*-Di-*n*-propylamino-6-trifluoromethylpyrimidine (**2b**).

Compound **2b** was prepared from 2,4-dichloro-6-trifluoromethylpyrimidine and di-*n*-propylamine in a manner similar to that for **2a**. The product was obtained in 95% yield, bp 120-121° (0.01 mm), n_D^{25} 1.4807; uv (methanol): λ max 231 (ε 3167); 313 (740); ir (neat): ν CF_3 1138 cm^{-1}; ^{1}H-nmr (deuteriochloroform, TMS): δ 5.62 (5-H).

Anal. Calcd. for $C_{17}H_{29}F_3N_4$: C, 58.94; H, 8.44; N, 16.17. Found: C, 58.65; H, 8.60; N, 16.42.

2,4-*bis*(*N,N*-Di-*n*-butylamino-6-trifluoromethylpyrimidine (**2c**).

The title compound was obtained from 2,4-dichloro-6-trifluoromethylpymidine and di-*n*-butylamine by the same method as **2a** was prepared. The yield of product was 62%, bp 145° (0.01 mm), n_D^{25} 1.4791; uv (methanol): λ max 231 (ε 3069), 313 (740); ir (neat): ν CF_3 1140 cm^{-1}; ^{1}H-nmr (deuteriochloroform, TMS): δ 5.61 (5-H).

Anal. Calcd. for $C_{21}H_{37}F_3N_4$: C, 62.65; H, 9.27; N, 13.92. Found: C, 62.64; H, 9.58; N, 14.20.

2-*N,N*-Diethylamino-4-ethoxy-6-trifluoromethylpyrimidine (**3a**).

A solution of diethylamine (15.4 g, 0.176 mole) in 70 ml of ethanol was added in portions to a solution of 2-chloro-4-ethoxy-6-trifluoromethylpyrimidine (20 g, 0.088 mole) in 30 ml of ethanol in a stainless steel pressure vessel, cooled in an ice bath. The mixture was heated at 70° overnight. The alcohol was removed under vacuum, and the residue was partitioned between ether and water. The ether layer was further washed with water, dried over sodium sulfate, and the solvent removed under vacuum. The residue was distilled to yield 19 g (82%) of product, bp 62° (0.02 mm), n_D^{25} 1.4580; uv (methanol): λ max 265 (ε 379), 305 (2058); ir (neat): ν CF_3 1140 cm^{-1}; ^{1}H-nmr (deuteriochloroform, TMS): δ 6.10 (5-H).

Anal. Calcd. for $C_{11}H_{16}F_3N_3O$: C, 50.18; H, 6.13; N, 15.96. Found: C, 50.31; H, 6.00; N, 16.01.

2-*N,N*-Di-*n*-propylamino-4-ethoxy-6-trifluoromethylpyrimidine (**3b**).

Compound **3b** was prepared from di-*n*-propylamine and 2-chloro-4-ethoxy-6-trifluoromethylpyrimidine by a method similar to that for the preparation of compounds **3a**. A yield of 78% of product was obtained, bp 83° (0.02 mm), n_D^{25} 1.4568; uv (methanol): λ max 246 (ε 2772), 287 (600); ir (neat): ν CF_3 1146 cm^{-1}; ^{1}H-nmr (deuteriochlorform, TMS): δ 6.12 (5-H).

Anal. Calcd. for $C_{13}H_{20}F_3N_3O$: C, 53.60; H, 6.92; N, 14.42. Found: C, 53.73; H, 6.94; N, 14.32.

2-*N,N*-Di-*n*-butylamino-4-ethoxy-6-trifluoromethylpyrimidine (**3c**).

The title compound was prepared from 2-chloro-4-ethoxy-6-trifluoromethylpyrimidine and di-*n*-butylamine by an analogous method to that for compound **3a**. The yield of product was 84%, bp 101° (0.05 mm), n_D^{25} 1.4560; uv (methanol): λ max 245 (ε 2048), 306 (372); ir (neat): ν CF_3 1153 cm^{-1}; ^{1}H-nmr (deuteriochloroform, TMS): δ 6.07 (5-H).

Anal. Calcd. for $C_{15}H_{24}F_3N_3O$: C, 56.41; H, 7.57; N, 13.16. Found: C, 56.45; H, 7.48; N, 13.25.

2-*N,N*-Diethylamino-6-trifluoromethylpyrimidin-4-ol (**4a**).

A suspension of **3a** (15.8 g, 0.06 mole) in 120 ml of 6*N* hydrochloric acid was heated under reflux with stirring for 80 hours. After cooling, the crystalline material was removed by filtration, washed with water, and dried at 70° overnight. The product was obtained in 82% yield, and the analytical sample was crystallized from 70% aqueous ethanol, mp 105-107°; uv (methanol): λ max 230 (ε 1142), 308 (1012); ir (potassium bromide): ν CF_3 1152 cm^{-1}; ^{1}H-nmr (DMSO-d_6, TMS): δ 5.90 (5-H).

Anal. Calcd. for $C_9H_{12}F_3N_3O$: C, 45.95; H, 5.14; N, 17.86. Found: C, 46.25; H, 5.22; N, 18.05.

2-*N,N*-Di-*n*-propylamino-6-trifluoromethylpyrimidin-4-ol (**4b**).

The title compound was prepared from **4a** by the same procedure as employed for the preparation of **3b** from **3a**. The yield of product was 85%, and the analytical sample obtained by crystallization from ethanol, melted at 105°; uv (methanol): λ max 230 (ε 1146), 309 (986); ir (potassium bromide): ν CF_3 1132 cm^{-1}; ^{1}H-nmr (DMSO-d_6, TMS): δ 5.88 (5-H).

Anal. Calcd. for $C_{11}H_{16}F_3N_3O$: C, 50.18; H, 6.13; N, 15.96. Found: C, 50.31; H, 6.02; N, 16.23.

2-*N,N*-Di-*n*-butylamino-6-trifluoromethylpyrimidin-4-ol (**4c**).

Compound **4c** was obtained from **3c** in a manner similar to that for the preparation of **4a** from **3a**. The product was obtained in 48% yield, and the analytical sample, crystallized from ethanol, melted at 142-143°; uv (methanol): λ max 230 (ε 1178), 309 (1007); ir (potassium bromide): ν CF_3 1138 cm^{-1}; ^{1}H-nmr (DMSO-d_6, TMS): δ 5.87 (5-H).

Anal. Calcd. for $C_{13}H_{20}F_3N_3O$: C, 53.60; H, 6.92; N, 14.42. Found: C, 53.76; H, 6.80; N, 14.68.

4-Chloro-2-*N,N*-diethylamino-6-trifluoromethylpyrimidine (**5a**).

A suspension of **4a** (9.5 g, 0.04 mole) in 95 ml of phosphorus oxychloride was heated under reflux for 3 hours. The phosphorus oxychloride was removed under vacuum, and the residue was poured into an ice-water slurry. The aqueous material was extracted with ether, and the ether solution was washed with water and dried over sodium sulfate. After evaporation of the ether, the residue was distilled. The yield of product was

53%, bp 46° (0.03 mm), n_D^{25} 1.4765; uv (methanol): λ max 214 (ε 710), 251 (2307), 333 (220); ir (neat): ν CF_3 1148 cm^{-1}; ^{1}H-nmr (deuteriochloroform, TMS): δ 6.63 (5-H).

Anal. Calcd. for $C_9H_{11}ClF_3N_3$: C, 42.61; H, 4.37; Cl, 13.98; N, 16.57. Found: C, 42.45; H, 4.26; Cl, 14.24; N, 16.77.

4-Chloro-2-*N,N*-di-*n*-propylamino-6-trifluoromethylpyrimidine (**5b**).

The title compound was prepared from **4b** in the same manner as **5a** was prepared from **4a**. Compound **5b** was obtained in 35% yield, bp 64° (0.05 mm); mp 43-46°; n_D^{25} 1.4733; uv (methanol): λ max 215 (ε 206), 252 (2170), 330 (710); ir (neat): ν CF_3 1152 cm^{-1}; ^{1}H-nmr (deuteriochloroform, TMS): δ 6.62 (5-H).

Anal. Calcd. for $C_{11}H_{15}ClF_3N_3$: C, 46.90; H, 5.37; Cl, 12.59; N, 14.92. Found: C, 46.62; H, 5.29; Cl, 12.84; N, 15.13.

4-Chloro-2-*N,N*-di-*n*-butylamino-6-trifluoromethylpyrimidine (**5c**).

A. A suspension of **4c** (8.7 g, 0.03 mole) in 87 ml of phosphorus oxychloride was heated under reflux for 3 hours. The solution was poured onto ice and stirred intermittently until the phosphorus oxychloride decomposed. The aqueous material was extracted with ether, and the ether layer was washed with water and dried over sodium sulfate. Upon evaporation of the ether, a semisolid residue remained, which was slurried in hexane and filtered. The hexane solution was kept under refrigeration overnight and refiltered. The filtrate was evaporated under a stream of air, and the liquid residue was distilled. The yield of product was 1 g (11%), bp 101-103° (0.5 mm), n_D^{25} 1.4707; uv (methanol): λ max 218 (ε 718), 251 (2077), 320 (223); ir (neat): ν CF_3 1158 cm^{-1}; ^{1}H-nmr (deuteriochloroform, TMS): δ 6.65 (5-H).

Anal. Calcd. for $C_{13}H_{19}ClF_3N_3$: C, 50.41; H, 6.18; Cl, 11.66 N, 13.57. Found: C, 50.21; H, 6.00; Cl, 11.36; N, 13.48.

B. A solution of 2,4-dichloro-6-trifluoromethylpyrimidine (13.1 g, 0.06 mole) in 130 ml of dry toluene was heated under reflux with tri-*n*-butylamine (22.2 g, 0.12 mole) for 3 hours. The solvent was removed under vacuum, and the residue was distilled. The yield of product was 14.7 g (79%). The boiling point, refractive index, and ir spectrum were nearly the same as those for **5c**.

2,4-Dichloro-6-trifluoromethylpyrimidine.

To a suspension of 6-trifluoromethyluracil (18 g, 0.1 mole) in 100 ml of phosphorus oxychloride was added tri-*n*-propylamine (28.7 g, 0.2 mole) with stirring. The mixture was heated under reflux for 3 hours, and the material was poured onto ice. The slurry was stirred intermittently until the phosphorus oxychloride decomposed completely. The aqueous material was extracted with ether, and the ether extract was washed with water and dried over sodium sulfate. After removal of the solvent by distillation at atmospheric pressure, the residue was vacuum distilled. The yield of product was 18.1 g (83%), bp 52° (0.5 mm). The physical properties and spectra coincided with those of an authentic sample.

Products Identified by Heating 6-trifluoromethyluracil Under Reflux with Phosphorus Oxychloride in the Presence of TEA, TPA, and TBA. Respectively, for 3, 24, 48, and 188 hours.

To 36 ml of phosphorus oxychloride were added 6-trifluoromethyluracil (3.6 g, 0.02 mole) together with 2 molar equivalents of the respective tertiary amine. The mixtures were heated under reflux, and 1 ml aliquots were removed after each time period. The aliquots were poured onto ice and extracted with 10 ml of ether. After drying over calcium chloride, the solutions were assayed by gas chromatography. Quantitation was carried out by integrating the area under the curves. The results are summarized in Table 1.

Products Identified by Heating 2,4-Dichloro-6-trifluoromethylpyrimidine in Toluene under Reflux with Triethylamine for 3, 8, 24, 48, 72, and 188 Hours.

To a solution of 2,4-dichloro-6-trifluoromethylpyrimidine (10.9 g, 0.05) in 109 ml of dry toluene was added a solution of triethylamine in 30 ml of dry toluene. The mixture was heated under reflux, and 1 ml samples were drawn after each time period and assayed by gas chromatography without further workup. Quantitation was achieved as above. The results are summarized in Table 2.

REFERENCES AND NOTES

[1] H. Gershon and A. T. Grefig, *J. Heterocyclic Chem.*, **21**, 1161 (1984).

[2] H. Gershon, A. Grefig and D. D. Clarke, *J. Heterocyclic Chem.*, **24**, 205 (1987).

[3] The "hydroxy" pyrimidines will be shown as hydroxy derivatvies and not as oxo forms, irrespective of the evidence for the existence of a particular predominant tautomeric form.

[4] H. Gershon, A. T. Grefig, and A. A. Scala, *J. Heterocyclic Chem.*, **20**, 219 (1983).