Pyrimidines. 9. chlorination of 6-trifluoromethyluracil with phosphorus oxychloride in the presence of trialkylamines / Herman Gershon [ab], Anthony T. Grefig [a], and Donald D. Clarke [b] [a] Boyce Thompson Institute for Plant Research at Cornell University, Ithaca, New York 14853 [b] Department of Chemistry, Fordham University, Bronx, New York 10458

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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.


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 dichloropyrimidine, along with minor amounts of the 2-diethylamino derivative, after 24 hours. 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-methylpyrimidine, 62% of 4-chloro-2-N,N-dimethylanilino-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-
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-

Table 1
Reaction of 6-Trifluoromethyluracil with Phosphorus Oxychloride in the Presence of Triethylamine (TEA), Tri-n-propylamine (TPA), and Tri-n-butylamine (TBA)

<table>
<thead>
<tr>
<th>Amine</th>
<th>Reflux Time (hours)</th>
<th>Composition of Mixture, % [a]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>a</td>
</tr>
<tr>
<td>TEA</td>
<td>89</td>
<td>11</td>
</tr>
<tr>
<td>TPA</td>
<td>96</td>
<td>4</td>
</tr>
<tr>
<td>TBA</td>
<td>97</td>
<td>3</td>
</tr>
</tbody>
</table>

[a] Quantitation by gas chromatography.

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

<table>
<thead>
<tr>
<th>Reflux Time (hours)</th>
<th>Composition of Mixture, % [a]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>78</td>
</tr>
<tr>
<td>24</td>
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<td>48</td>
<td>78</td>
</tr>
<tr>
<td>72</td>
<td>77</td>
</tr>
<tr>
<td>188</td>
<td>77</td>
</tr>
</tbody>
</table>

[a] Quantitation by gas chromatography.
Pyrimidines. 9.

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 21 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), nD25 1.4433; uv (methanol): λ max 260 (ε 443), 217 (752); ir (neat): ν CF, 1152 cm⁻¹; 1H-nmr (deutero-

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chloroform, TMS): $\delta$ 1.45 (t, 3H, OCH$_2$CH$_3$); $\delta$ 4.58 (broad m, 2H, OCH$_2$CH$_3$); $\delta$ 6.93 (S-H).

$\text{Anal. Calcd. for }$ C$_4$H$_6$ClF$_3$N$_3$: C, 37.10; H, 2.67; Cl, 15.65; N, 12.36. Found: C, 37.11; H, 2.68; Cl, 15.45; N, 12.18.

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

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 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 83° (0.02 mm), n$_D$^20 1.4580; uv (methanol): $\lambda$ max 265 (e 379), 305 (2059); ir (neat): $\nu$ CF$_3$, 1146 cm$^{-1}$; $\nu$-nmr (deuteriochloroform, TMS): $\delta$ 6.10 (S-H).

$\text{Anal. Calcd. for }$ C$_{13}$H$_{16}$ClF$_3$N$_3$: C, 53.60; H, 6.21; Cl, 15.86. Found: C, 53.73; H, 6.94; N, 14.32.

2-Chloro-4-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 yield of compound was 9 g (71%), bp 97° (0.05 mm), n$_D$^20 1.4586; uv (methanol): $\lambda$ max 254 (e 1745), 304 (442); ir (neat): $\nu$ CF$_3$, 1148 cm$^{-1}$; $\nu$-nmr (deuteriochloroform, TMS): $\delta$ 6.26 (S-H).

$\text{Anal. Calcd. for }$ C$_{13}$H$_{20}$F$_3$N$_3$: C, 53.73; H, 6.94; N, 14.77.

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

The title compound was prepared from 2,4-dichloro-6-trifluoromethylpyrimidine and di-n-butylamine by the same method as 2a. The yield of compound was 9 g (71%), bp 108° (0.05 mm), n$_D$^20 1.4876; uv (methanol): $\lambda$ max 255 (e 1178), 309 (1012); ir (neat): $\nu$ CF$_3$, 1153 cm$^{-1}$; $\nu$-nmr (deuteriochloroform, TMS): $\delta$ 6.07 (S-H).

$\text{Anal. Calcd. for }$ C$_{21}$H$_{37}$F$_3$N$_4$: C, 62.64; H, 9.58; N, 13.92. Found: C, 62.64; H, 9.58; N, 13.92.
53%, bp 46° (0.03 mm), nD 1.4765; uv (methanol): λ max 214 (ε 710), 251 (2307), 333 (220); ir (neat): v CF 3 1148 cm⁻¹; 1H-nmr (deuteriochloroform, TMS): δ 6.63 (5-H).

Anal. Calcd. for C₈H₁₃ClF₃N₃: C, 46.90; H, 4.37; Cl, 13.98; N, 16.57.

A suspension of 6-trifluoromethyluracil (18 g, 0.1 mole) in 30 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.

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

A solution of 6-trifluoromethyluracil (18 g, 0.1 mole) in 30 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.

A. A suspension of 4e (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 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


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