2,4,6-Trichloropyrimidine. Reaction With Sodium Amide

Thomas J. Delia*, Bernard R. Meltsner, and Jennifer M. Schomaker

Malcolm H. Filson Laboratories, Department of Chemistry, Central Michigan University, Mt. Pleasant, MI 48859

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The first reaction between 2,4,6-trichloropyrimidine **1** and anionic nitrogen nucleophiles is described. Treatment of **1** with one equivalent of sodium amide gave mixtures of 4-amino-2,6-dichloropyrimidine **2** and 2-amino-4,6-dichloropyrimidine **3**. Additional quantities of sodium amide failed to provide either diamino- or triaminopyrimidines. Instead, the strongly basic nature of sodium amide led to higher molecular products that were not characterized.

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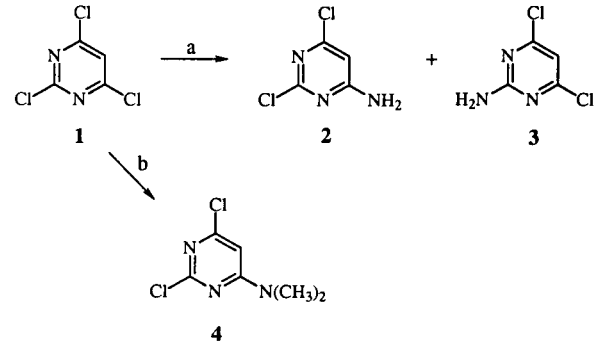
The reaction of 2,4,6-trichloropyrimidine **1** with a variety of nucleophiles has been the subject of considerable interest for more than ninety years. Since the early use of simple amines, such as ammonia [1], methylamine [2] and dimethylamine [3], other amines have been employed to prepare compounds designed to achieve a specific biological goal. These include pyrrolidine [4], aniline [5], and benzylamine [6]. Our own work in this area with ethanolamine and diethanolamine has recently been described [7].

There have been extensive studies using ammonia or substituted amines, including the factors that influence kinetic behavior, with other halogenated pyrimidines that have been described by Brown [8]. It is clear, however, that the conditions required to effect replacement of each subsequent halogen become increasingly vigorous. For example, the conversion of 2-amino- and 4-amino-dichloropyrimidines to 2,4-diamino-6-chloropyrimidine requires temperatures of greater than 100° [1,9].

However, there has not been comparable interest in the behavior of anionic nitrogen nucleophiles with **1**. As part of our continuing investigation of the reactivity of **1** with a variety of nucleophiles we have examined the reaction of **1** with sodium amide. Based on our previous experience with the reaction between **1** and phenoxides in which the 4-monosubstituted product was substantially preferred [10], we surmised that reactions between **1** and the amide ion would proceed under mild conditions and could provide us a means to selectively replace the halogen at the 4-position. Ultimately, we hoped, more gentle conditions could be employed to produce the diamino and triamino derivatives.

We first looked at the reaction of **1** with one equivalent of sodium amide. Treatment of **1** at room temperature in dimethylsulfoxide led to a good yield of a mixture of the known compounds 4-amino-2,6-dichloropyrimidine **2** (Scheme 1) and the 2-amino isomer **3**. The ratio of **2**:**3** was 3:1, as indicated by examining the C_5-proton signal of the ^1H nmr spectrum of the crude product [11]. The assignment of the major product as **2** and not **3** was initially based on comparison with commercially available **3**. ^1H nmr and mass spectral data of **2** supported this assignment, as well as melting point comparisons with those reported in the literature [1,9]. These results were not as favorable toward selective substitution as was encountered with phenolates [10].

Scheme 1

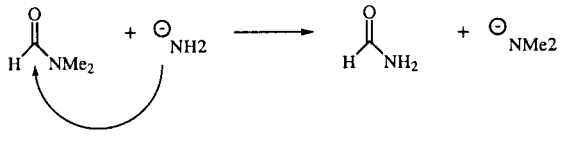


[a] : sodium amide in dimethylsulfoxide at room temperature
[b] : sodium amide in dimethylformamide at room temperature

During preliminary exploration of the conditions for this reaction we used dimethylformamide as the reaction solvent. In this case, formation of **2** (or **3**) was not observed. However, 4-dimethylamino-2,6-dichloropyrimidine **4** was isolated in 56% yield. This unexpected product was confirmed by ^{13}C nmr spectroscopy, mass spectrometry, and melting point comparison with a sample prepared according to the early literature citation [3]. The ^{13}C nmr spectrum showed four distinct carbon signals in the aromatic region, in addition to those attributed to the methyl groups. Only three aromatic carbon signals would be expected if the dimethylamino group was located at the carbon situated between the two ring nitrogen atoms. Assignments were based on heteronuclear nOe experiments where the C5-proton was saturated. Enhancement of the carbon signals at 160.0 ppm and 163.8 ppm were observed. The signal at 163.8 ppm is coupled to the substituent methyl protons nearby as well as the C5-proton,

thereby identifying this resonance as C_4, and that at 160.0 ppm as C_6. The signal at 159.6 ppm was unaffected by this process and was assigned to the C2 position because of the distance from the saturated C5 position. While we have not yet explored this observation fully, we speculate that the amide ion reacts with the solvent to generate the dimethylamine anion (Scheme 2). This suggestion is supported by the fact that treatment of **1** with dimethylamine in dimethylformamide, but without sodium amide, under the reaction conditions employed using sodium amide did not afford **4**. Investigations using the dimethylamine anion and other anionic nitrogen nucleophiles are in progress.

Scheme 2



The use of two equivalents of sodium amide in dimethylsulfoxide at room temperature gave essentially the same results as observed for the reaction involving one equivalent. However, two equivalents of sodium amide in dioxane alone or with 18-crown-6 added gave exclusively **3** in approximately 30% yield. The apparent selectivity of **3** over **2** under these conditions is being investigated further. Finally, treatment of **1** with more than three equivalents of sodium amide in dimethylsulfoxide, either at room temperature or at ~70°, failed to give even the monomeric compounds **2** or **3**.

It is clear from these observations that anionic nitrogen nucleophiles that are also strong bases cannot be used to provide diamino- or triaminopyrimidines under the conditions employed here. This limitation reduces the general utility of this reaction. Nevertheless, the possibility of forming one isomer exclusively over the other bears further investigation.

EXPERIMENTAL

Melting points are uncorrected and were determined in open capillary tubes using either a Thomas Hoover or MelTemp instrument. The ^1H nmr (at 300 MHz) and ^{13}C nmr (at 75 MHz) spectra were recorded on a QE-300 NMR Spectrometer in either deuteriochloroform or dimethy-d_6-sulfoxide, with tetramethylsilane as the internal standard. All values are reported in ppm relative to tetramethylsilane. Mass spectra were measured on a Hewlett Packard 5995A GC/MS instrument, using a direct insertion probe. An authentic sample of 2-amino-4,6-dichloropyrimidine was obtained from the Aldrich Chemical Company.

Reaction of 2,4,6-Trichloropyrimidine and One Equivalent of Sodium Amide

(a) In Dimethylsulfoxide.

A mixture of 2,4,6-trichloropyrimidine (2.50 g; 13.4 mmoles), sodium amide (0.520 g; 13.4 mmoles), and dimethylsulfoxide (~40 ml) was allowed to stir at room temperature for 5 days. A majority of the solvent was removed by vacuum distillation and the residue treated with ice/water (~40 ml) to give a light brown solid (2.00 g, 91% crude yield). A portion of this material (800 mg) was chromatographed on a silica gel column using ethyl acetate/hexane (2:3) to give a light yellow mixture (77%) of 4-amino-2,6-dichloropyrimidine **2** and 2-amino-4,6-dichloropyrimidine **3** in a ratio of 3:1 as determined by ^1H nmr spectroscopy. This material (~630 mg) was recrystallized from a mixed solvent containing ethyl acetate (15 ml) and hexane (45 ml) to afford **2** as a tan solid (244 mg), mp >270° dec. (lit mp 271° [1,9]); ^1H nmr (dimethyl-d_6-sulfoxide): 6.42 (C_5-H), 7.74 (NH_2); ms: m/z 164 (60), 163 (100).

The filtrate was evaporated and the residue heated with boiling ethyl ether, filtered, and allowed to cool. Filtration of the resulting solid gave **3** as a tan solid (55 mg), mp 215-17° (lit mp 219-22° [1,9] and mixed mp with a commercial sample showed no depression.); ^1H nmr (dimethyl-d_6-sulfoxide): 6.86 (C_5-H), 7.63 (NH_2).

(b) In Dimethylformamide.

A mixture of 2,4,6-trichloropyrimidine (2.60 g; 14.2 mmoles), sodium amide (0.550 g; 14.2 mmoles), and dimethylformamide (~40 ml) was allowed to stir at room temperature for 2 days. A majority of the solvent was removed by distillation and the residue treated with ice/water (~40 ml). The resulting light yellow solid (1.83 g; 67% crude yield) contained mainly 4-dimethylamino-2,6-dichloropyrimidine **4** as indicated by ^1H nmr spectroscopy and mass spectroscopy. Recrystallization (from hexane) gave a pale yellow solid, mp 107-9° (lit mp 113° [12] and mixed mp with a sample prepared according to the literature showed no depression); ^1H nmr (deuteriochloroform): 3.10, 3.20 (2 CH_3), 6.33 (C_5-H); ^{13}C nmr (deuteriochloroform): 37.6 (CH_3), 99.5 (C_5), 159.6 (C_2-Cl), 160.0 (C_6-Cl), 163.8 (C_4-NMe_2); ms: m/z 193 (50), 191 (80).

Reaction of 2,4,6-Trichloropyrimidine and Two Equivalents of Sodium Amide

(a) In Dimethylsulfoxide.

To a mixture of sodium amide (0.467 g; 12.0 mmoles) and dimethylsulfoxide (20 ml) was added 2,4,6-trichloropyrimidine (1.00 g; 5.50 mmoles). An exothermic reaction occurred (temperature of the mixture rose to ~48°) and the reaction mixture was allowed to stir at room temperature for two days. The solution was treated with ice/water (~50 ml). The resulting light brown solid was filtered and dried to give a mixture of **2** and **3** (400 mg; 45%) in a ratio of 2:1, as indicated by ^1H nmr. No evidence of a disubstituted aminopyrimidine was observed. Evaporation of the filtrate gave an intractible mixture which contained compounds with molecular weights considerably higher than any of the expected simple aminopyrimidine products.

(b) In Dioxane.

To a mixture of sodium amide (0.470 g; 12.0 mmoles) and dioxane (20 ml) was added 2,4,6-trichloropyrimidine (1.00 g; 5.50 mmoles). An exothermic reaction was not observed in this case. The reaction mixture was allowed to stir at room temperature for three hours, then heated at reflux for 16 hours. The solvent was removed on a rotary evaporator and ice/water (~20 ml) was added to the residue. The resulting yellow solid was filtered and dried to give **3** (258 mg; 29%), mp 216-220° (lit mp 219-222° [1,9]). ^{1}H nmr further supported the observation that **3** was the major compound isolated.

Evaporation of the filtrate, followed by column chromatography, gave several fractions (totalling 180 mg) which gave mass spectral data consistent with two pyrimidine rings joined by an amino group. These compounds were not further characterized.

Reaction of 2,4,6-Trichloropyrimidine and Three Equivalents of Sodium Amide

A mixture of 2,4,6-trichloropyrimidine (100 mg; 0.546 mmole), sodium amide (70.3 mg; 1.80 mmole), and dimethylsulfoxide (15 ml) was allowed to stir at room temperature for 23 hours. A majority of the solvent was removed by vacuum distillation and the residue treated with water (~20 ml). The resulting light brown solid (65.6 mg) contained no organic materials with molecular weight below 300 amu.

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