The Preparation of 2-Amino-6-chloropurine, A Safe Improved Procedure (1)

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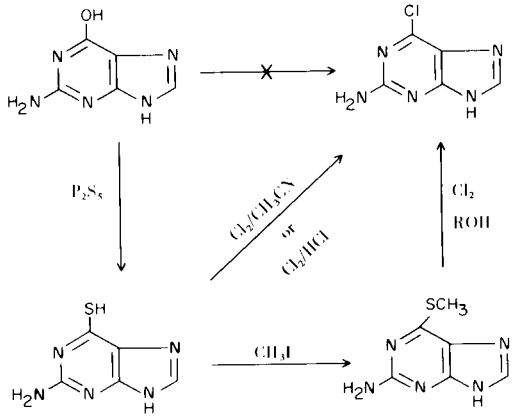
In association with a project for the preparation of a nucleoside, we needed to prepare 2-amino-6-chloropurine. Previously the compound had been prepared by Robins (2) from 2-amino-6-methylthiopurine and by Montgomery from 2-amino-6-mercaptopurine (3,4). In both instances, the chlorinations were conducted using chlorine gas in methanol or ethanol as solvent. Indeed this method is widely used for the preparation of heterocyclic chloro derivatives (5) particularly in the purine series. One of the reasons this method has found such widespread application is that other normal approaches to chloro compounds utilizing the action of phosphorous oxychloride, phosphorous pentachloride, thionyl chloride, phenyl phosphorodichloridite, sulfuryl chloride, dichlorotriphenylphosphorane, and phosgene on the appropriate intermediate fail. For example, the conversion of 2-amino-6-hydroxypurine (guanine) to 2-amino-6-chloropurine cannot be accomplished by the action of any of the reagents mentioned above.

This led us to the conclusion that we should also utilize the chlorine-methanol procedure. However, from some other observations as the project proceeded, we had reason to believe this reaction is hazardous. We were successful in finding one reference (6) to the possible explosion hazard with this procedure, and a personal communication with Dr. L. Townsend (7) revealed that he also had an explosion with this particular method.

Under the reaction conditions used, it appears evident that methyl hypochlorite could be formed readily. The chemistry of alkyl hypochlorites (8) has been studied and the associated explosive properties are documented. If the chlorinations are run at temperatures below 10°, there is every reason to believe methyl hypochlorite concentrations could build up and reach explosive levels. If the reaction is run at ambient temperature or above, the risk of explosion can be greatly diminished due to the inherent thermal instability of such alkyl hypochlorites, however, for other reasons, higher temperatures may not be convenient.

We have found that the risk can be completely avoided by using acetonitrile or concentrated hydrochloric acid as the solvent. Indeed in our hands these solvents offered several advantages over methanol for the preparation of 2-amino-6 chloropurine. We had consistently poor success in converting thioguanine directly to the desired chloro derivative in alcohols. However, with hydrochloric acid or acetonitrile 2-amino-6-chloropurine was obtained in good yields (55-90%). This procedure, therefore, has the added advantage that it eliminates the preparation of 2-amino-6-methylthiopurine as previously required to obtain 2-amino-6-chloropurine in good yield. Under these conditions, chlorination of acetonitrile does not take place.



In conclusion, we should like to recommend that methanol or ethanol be avoided as solvents for such chlorinations particularly when low temperatures are employed. We believe other solvents are more appropriate, with acetonitrile or concentrated hydrochloric acid being two excellent substitutes.

EXPERIMENTAL

Preparation of 2-Amino-6-chloropurine in Acetonitrile.

Thioguanine (9) (25 g.) was suspended in acetonitrile (500 ml.) in a three neck flask fitted with a mechanical stirrer. When chlorine was introduced, the temperature rose to 60° within ten minutes. The introduction of chlorine was continued for an additional 90 minutes with the temperature dropping slowly to 30°. The color of the reaction changed from a pale yellow to an intense bright yellow. The yellow salt was removed by filtration

to give 33 g. The salt was dissolved in cold water (200 ml.) containing sodium hydroxide (15 g.). Adjustment of the *p*H to 8.5-9 gave a thick white precipitate which was filtered and then resuspended in water and filtered again. This water wash was repeated again and then the product was dried at 80° in a vacuum oven; yield, 14 g., 55%, m.p. >275°.

Anal. Calcd. for $C_5H_4ClN_5$: C, 35.4; H, 2.4; Cl, 20.9; N, 41.3; S, 0. Found: C, 35.6; H, 2.2; Cl, 20.5; N, 41.4; S, 0.23.

Preparation of 2-Amino-6-chloropurine in 12*N* Hydrochloric Acid.

Thioguanine (100 g.) was added portionwise to one liter of 12*N* hydrochloric acid cooled to 0° with a dry ice bath. When chlorine was introduced to the stirred bright yellow suspension, the temperature quickly rose to 15°. However, during the 45 minute reaction time, the temperature was maintained at 0-10°. The color of the reaction changed from bright yellow to beige. The product was removed by filtration and the filter cake dissolved in one liter of water containing 2½ equivalents of sodium hydroxide (60 g.). The *p*H was adjusted to 6 with 6*N* hydrochloric acid and the product was isolated by filtration. It was necessary to wash the product several times with water to remove the trapped sodium chloride. The white solid was dried in a vacuum oven at 80° to yield 77 g., 76%, m.p. >275°.

Anal. Calcd. for $C_5H_4ClN_5$: C, 35.4; H, 2.4; Cl, 20.9; N, 41.3; S, 0. Found: C, 35.3; H, 2.6; Cl, 21.3; N, 4.12; S, 0.02.

The product showed only one spot on a thin layer chromatography silica gel plate using ethyl acetate-DMF-butanol 6:3:1, R_f 0.88.

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