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Facile and Practical Synthesis of 2,6-Dichloropurine

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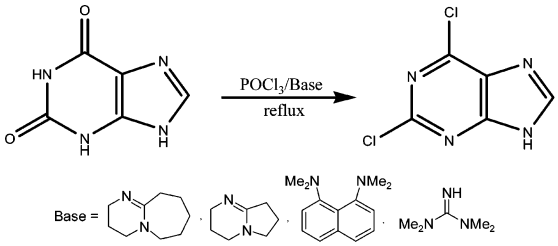
Abstract:

A facile and industrially viable process for preparation of 2,6-dichloropurine is reported. The process involves direct chlorination of xanthine with phosphorus oxychloride and a weak nucleophilic organic base, such as amidine, guanidine base, or Proton-Sponge.

Introduction

2,6-Dichloropurine is an important pharmaceutical intermediate.[1] It has been widely used in the preparation of purine nucleosides and purine nucleotides.[2] There are mainly two routes for the preparation of 2,6-dichloropurine. The first route is by chlorinating the purine ring structure, for example chlorinating xanthine (2,6-dihydroxypurine) with pyrophosphoryl chloride in a sealed tube at high temperature[3] or with phosphorus oxychloride at reflux in the presence of a phase transfer catalyst,[4] chlorinating 6-chloropurine, hypoxanthine or its *N*-oxide with phosphorus oxychloride,[5] chlorinating 2,6-dithiopurine with chlorine gas at low temperature.[6] The second route to prepare 2,6-dichloropurine is by building the purine ring with barbituric acid derivative[7] or 2,4-dichloro-5,6-diaminopyridmidine[8] as starting material. Unfortunately, neither of these routes is very practical in terms of industrial scale-up operations. They require either long preparation steps or complicated preparation procedures. Most of all, they all suffer from very low yields.

In this contribution, we present a new facile and practical procedure for the preparation of 2,6-dichloropurine by chlorinating xanthine with phosphorus oxychloride (Figure 1).



(1)

Figure 1. **Reaction of xanthine with $POCl_3$.**

Results and Discussion

A general method for the synthesis of chloropurines is by chlorination of the corresponding hydroxypurines with phosphorus oxychloride usually in the presence of a tertiary amine, such as triethylamine, *N*,*N*-dimethyl- or *N*,*N*-diethylaniline. 6-Chloropurine,[9] 6,8-dichloropurine,[10] and 2,6,8-trichloropurine[11] have been prepared in this manner. However, we could not succeed in the synthesis of 2,6-dichloropurine from xanthine by using this method. The addition of water into phosphorus oxychloride,[3] resulting in the formation of pyrophosphoryl chloride, does convert xanthine to 2,6-dichloropurine in a sealed tube at high temperature, but it is not viable on an industrial scale.

To ultilize the xanthine skeleton for preparing 2,6-dichloropurine, chlorination of xanthine with $POCl_3$ was examined in various solvents (*N*,*N*-dimethylformamide, dimethyl sulfoxide, or *N*-methylpyridinone), but none of them had promising results. When hexamethylphosphoric triamide (HMPA) or hexamethylphosphorus triamine (HMPT) was used, a moderate yield (ca. 20%) of 2,6-dichloropurine was obtained. However, HMPA and HMPT are strong carcinogenic reagents, which prevents application of this process in industrial scale.

Since xanthine is not very soluble in most organic solvents or even in $POCl_3$ under reflux conditions, facilitating dissolution of xanthine in $POCl_3$ became our focus. We figured that a strong base perhaps can remove the proton(s) in xanthine or form an ion pair, thus facilitating the dissolution and chlorination of xanthine.

We have found that xanthine can be successfully converted into 2,6-dichloropurine with phosphorus oxychloride in the presence of some amidine, guanidine bases, or Proton-Sponge. See Table 1.

Table 2 shows the effect of different molar ratios of DBU to xanthine on the yield of 2.6-dichloropurine ($POCl_3$ was used both as reagent and as solvent). It was observed that,

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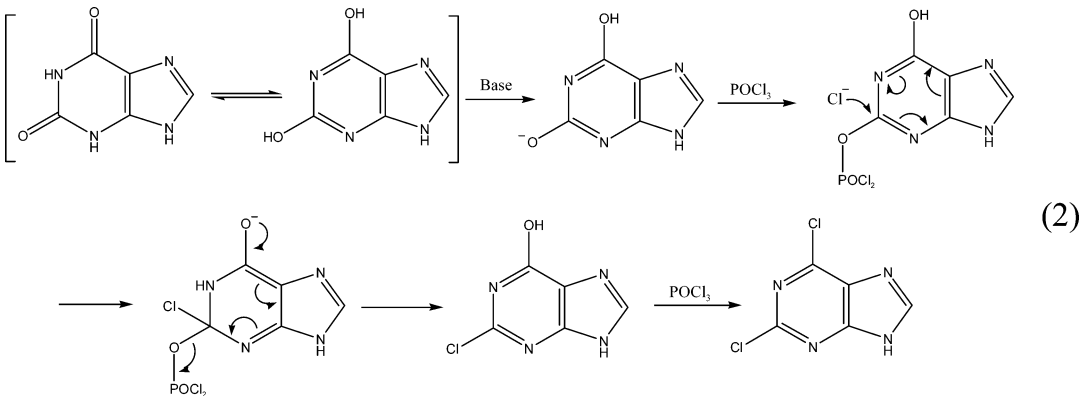

(2)

Figure 2. **Mechanism for the formation of 2,6-dichloropurine from xanthine.**

Table 1. **Base-catalyzed chlorination of xanthine**

entry	base[a]	yield (%)
1	DBU	47
2	DBN	40
3	Proton-Sponge	30
4	TMG	20
5	DABCO	0

[a] Note: DBU = 1,8-diazabicyclo[5,4,0] undec-7-ene; DBN = 1,5-diazabicyclo[4,3,0]non-5-ene; Proton-Sponge = 1,8-bis(dimethylamino)-naphthalene; TMG = 1,1,3,3-tetramethylguanidine; DABCO = 1,4-diaza-bicyclo[2,2,2]octane.

Table 2. **Effect of molar ratio of xanthine/$POCl_3$/DBU on the yield of 2,6-dichloropurine[a]**

entry	molar ratio of xanthine/$POCl_3$/DBU	yield (%) of 2,6-dichloropurine
1	1/10/1.5	8[b]
2	1/10/3.0	36[c]
3	1/10/6.0	47
4	1/10/8.0	52

[a] Reaction conditions: temperature, 105 °C (reflux); time, 6 h. [b] Reaction time was prolonged to 14 h. [c] 2,6-Dichloropurine obtained was yellow in color.

when the ratio of xanthine to DBU is 1 to 1.5, the reaction time was prolonged to 14 h, and the reaction still did not go to completion. Most of xanthine remained intact as original fine particles. When the ratio of xanthine to DBU is 1 to 3, the reaction took 8 h to complete. The crude product was brown powder. After recrystallization, the product was yellow in color. Although the yield increased from 47% to 52% when the ratio of xanthine to DBU was 1 to 8, the reaction mixture was very viscous and difficult for workup. The condition is also not as cost-effective as when the ratio of xanthine to DBU was 1 to 6.

The proposed mechanism for the first chlorination step is the following (Figure 2): With the proton being removed by the base, xanthine became anionic, dissolved in $POCl_3$, and then formed a phosphonate intermediate. It facilitated the chloride to attack on the ring.

The second chlorination may occur with the assistance of the base, which is similar to the above procedure, or without the help of the base, being directly chlorinated by $POCl_3$, since 2-chloro-6-hydroxypurine is much more soluble than xanthine in $POCl_3$.

Conclusions

With the utilization of the xanthine skeleton and inexpensive phosphorus oxychloride, this 2,6-dichloropurine preparation process is more economical (single-step reaction and relatively higher yield) compared to the literature methods mentioned above. This phosphorus oxychloride base catalysis method may be applicable to chlorination of some heterocyclic compounds which bear hydroxyl groups and are hard to dissolve in organic solvents or in phosphorus oxychloride. General applicability of this procedure to various heterocyclic compounds is under investigation.

Experimental Section

General Procedures. All melting points are uncorrected. NMR spectra were run at 400 MHz. All reactions were conducted under nitrogen.

2,6-Dichloropurine. Xanthine (6.08 g, 0.04 mol) and $POCl_3$ (61.5 g, 0.40 mol) were mixed at room temperauture and then slowly heated to 50 °C under nitrogen. DBU (36.5 g, 0.24 mol) was added dropwise under vigorous stirring. The mixture was heated to reflux (ca. 105 °C) for 6 h (around 100 min xanthine dissolved, and the reaction mixture formed a brown solution). The reaction mixture was cooled to 40 °C and slowly transferred to ice−water (300 g) under vigorous stirring. The brown solution obtained was neutralized to pH = 4 with 50% aqueous NaOH (80 mL) and then filtered through a pad of Celite. The yellow aqueous solution was extracted with ethyl acetate (2 × 150 mL). The organic extracts were combined and concentrated under vacuum on a rotavapor. A deep-yellow residue (6.0 g) was obtained which was dissolved in 100 mL of methanol at reflux, decolorized with 0.15 g of charcoal, filtered through a pad of Celite, and cooled to 5 °C for recrystallization. The off-white crystals were filtered and washed with 10 mL of methanol and then dried in a vacuum oven at 70 °C overnight. The obtained product weighed 3.56 g (47%). The product was characterized by comparison (HPLC, NMR, MS, etc.) with an authentic sample of 2,6-dichloropurine.

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