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Mild electrophilic halogenation of chloropyridines using CCl_4 or C_2Cl_6 under basic phase transfer conditions

Ashutosh V. Joshi, Mubeen Baidossi, Nida Qafisheh, Elsa Chachashvili and Yoel Sasson*

Casali Institute of Applied Chemistry, Hebrew University of Jerusalem, 91904 Jerusalem, Israel

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Abstract—Effective chlorination of 2,3,5,6-tetrachloropyridine to pentachloropyridine was realized under mild phase transfer conditions with carbon tetrachloride and 50% NaOH or solid K_3PO_4. Mechanistic study of this reaction indicated the possibility of an aromatic carbanionic intermediate. Hexachloroethane was established as a more selective electrophilic chlorination agent.

1. Introduction

A major contribution of phase transfer catalysis to the organic chemist's toolbox has been the replacement of anhydrous strong bases such as alkali metal alkoxides, amides or hydrides with the aqueous sodium hydroxide/quaternary ammonium catalyst combination (PTC/OH),[1] mainly in alkylation and related reactions. This was achieved by combining an acid–base equilibrium step with a biphasic anion exchange extraction step, which consequently allowed the deprotonation of exceedingly weak (mainly carbon) acids.[2] Thus, substrates with pK_a's as high as 23 could be smoothly alkylated with alkyl halides or sulfates.[3] Weaker acids could not be alkylated under PTC/OH conditions but there are reports on the oxidation of diphenylmethane[4] ($pK_a = 31$–32), isomerization of allyl benzene[5] ($pK_a = 34$) and H/D exchange of thiophene[6] ($pK_a = 38.4$). The latter is an example of a unique transformation most likely involving an aromatic carbanionic intermediate.

No other reaction, beside H/D exchange, was hitherto demonstrated to proceed via a putative aromatic carbanion intermediate generated under mild, aqueous PTC/OH conditions.

In this work we describe an aromatic chlorination process using carbon tetrachloride as a reagent and a solvent under PTC/OH conditions. The reaction is demonstrated using an electron poor 2,3,5,6-tetrachloropyridine as substrate, which is converted to pentachloropyridine. We assert a new aromatic chlorination mechanism where a chloronium cation attacks an aromatic carbanion to form a new C–Cl bond.

Formation of C–halogen bonds from C–H bonds is a fundamental reaction in organic synthesis.[7,8] Halogenation of C–H bonds has also been extensively studied in the presence of phase transfer catalysts.[3] Polyhalomethanes as a source of halogen have been utilized for halogenation, for example, for iodination of alkanes,[9] halogenation of terminal acetylenes[10] and of acidic hydrocarbons in the presence of tetrabutylammonium fluoride.[11] A recent review presents an account of reactions of practical significance of CCl_4 and CBr_4 with carbanions.[12] In this context, the synthesis of polychlorinated pyridines such as 2,3,6-trichloro-, 2,3,5-trichloro-, 3,4,5-trichloro-, 2,3,4,5-tetrachloro-, 2,3,5,6-tetrachloro- and 2,3,4,5,6-pentachloro pyridines, which are useful as intermediates for herbicides and insecticides[13] are of considerable interest. They are usually prepared by chlorination of pyridines[13] or picolines[14] at high temperatures, generally leading to a variety of products such as dichloro, trichloro, tetrachloro and pentachloropyridines. 2,3,5,6-Tetrachloropyridine has been selectively synthesized by the reaction of trichloroacetyl chloride and acrylonitrile[15] and also by selective reduction of pentachloropyridine with Zn dust in a basic medium.[16] A Dow patent claims high yields of pentachloropyridine by reaction of vapors of *n*-valeronitrile

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Keywords: Halogenation; Phase transfer; Polyhalomethane; Potassium phosphate; Aromatic carbanion.

* Corresponding author. Tel.: +972-2-6584530; e-mail: ysasson@huji.ac.il

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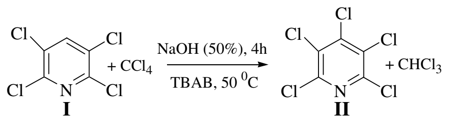
and chlorine at a temperature of about 600 °C.[17] Thus with this background in mind, where there are reports on the direct preparation of pentachloropyridine and 2,3,5,6-tetrachloropyridine, we thought it worthwhile to complete this reaction cycle by exploring the possibility of the chlorination of 2,3,5,6-tetrachloropyridine to pentachloropyridine with polyhalomethane under basic phase transfer conditions.

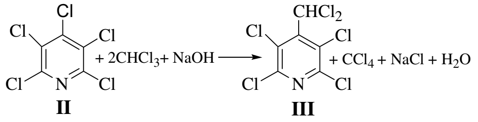
2. Results and discussion

In a typical reaction, a mixture of 0.5 mmol of 2,3,5,6-tetrachloropyridine, **I** (108 mg), 10 mL carbon tetrachloride (CCl_4, solvent and chlorinating agent), 6.0 mmol sodium hydroxide (240 mg, 50% w/w solution), 10 mol% tetra-*n*-butylammonium bromide (TBAB, 16 mg), was stirred at 50 °C in a round bottom flask equipped with an efficient condenser for 4 h. GC analysis of the reaction mixture after this time revealed 98% conversion. Pentachloropyridine, **II** was obtained with 80% selectivity (Eq. 1).

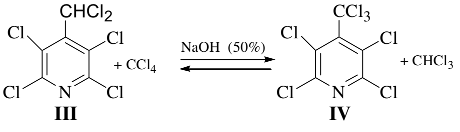


(1)

Two side products were also identified: 4-trichloromethyl-2,3,5,6-tetrachloropyridine (5%) **IV** and 4-dichloromethyl-2,3,5,6-tetrachloropyridine (13%), **III**,[18] the structures of which were confirmed by GC–MS analysis. Formation of the latter could be attributed to the reaction of chloroform with **II** [18a] (Eq. 2), which in turn could be converted in equilibrium to **IV** (Eq. 3) in the presence of excess CCl_4.[18b]



(2)

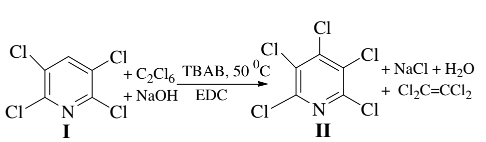


(3)

This type of equilibrium processes has been previously discussed by Orvik.[18a,b]

Indeed, when the reaction was continued further for a longer period (20 h) it was observed that formation of the side products increased with only 56% of **II** remaining and the rest being mainly **III** and **IV**. Moreover conducting the reaction of **II** with 8 equiv of $CHCl_3$ in dichloroethane and 50% NaOH confirmed the formation of **III** and even the formation of bis(dichloromethyl)-trichloropyridine. This is a unique instance where, in the presence of a base, chloroform forms a dichloromethyl anion and a chloronium cation rather than the obvious trichloromethyl anion.[19]

In order to attain a better selectivity for **II** in the chlorination of **I**, it is thus essential to avoid the formation of $CHCl_3$, which in turn will avert the generation of the side products. For this aim we applied hexachloroethane as a chlorinating agent[18c] in chlorination of **I**. Analysis of the product mixture indicated 80% conversion after 4 hours with 96% selectivity for **II** (Eq. 4). Tetrachloroethylene was also found as a reaction product. The latter has additional advantages since it can be recycled to hexachloroethane.



(4)

Surprisingly, only 30% conversion was achieved after 24 h when bromotrichloromethane was utilized as a halogen source under identical conditions. The product obtained was 4-bromo-2,3,5,6-tetrachloropyridine. This could probably be a result of the lower electrophilicity of the bromonium cation compared to the chloronium cation intermediate.

2,3,5-Trichloropyridine was also subjected to the chlorination reaction under identical conditions. Tetrachloropyridine was obtained (88% selectivity) with 33% conversion after 4 h. Formation of the 2,3,4,5-tetrachloropyridine isomer was confirmed by the facile formation of its corresponding sulfate salt.[20]

The presence of a phase transfer catalyst was proved to be critical. The reaction barely occurred when it was excluded. Tetra-*n*-butylammonium chloride was slightly inferior to TBAB.

There was an effect of the NaOH amount on the rate of reaction. By performing the reaction with 4 equiv instead of 12 equiv under identical conditions only 80% conversion was observed after 5.5 h. Evidently the excess of base was needed for kinetic reasons and could be recovered after the reaction was complete.

Shreiner has suggested that the pathway for the occurrence of halogenation reactions using polyhaloalkanes in basic conditions, for instance in the case of iodination of alkanes was via the formation of a tetrahalomethane anion radical formed by interaction of a hydroxide ion with carbon tetrahalide.[21] Proof for this mechanism was obtained from observations of the effect of addition of a radical anion scavenger such as *p*-dinitrobenzene.[22] When we added 15 mol% of *p*-dinitrobenzene under the reaction conditions, formation of pentachloropyridine was found to be greatly affected with only 50% conversion achieved after 4 h. This indicates the possibility of the reaction occurring via a similar radical anion mechanism proposed earlier. However, there are reports on H/D exchange of aromatic hydrogens even in the case of substrates such as thiophene, which has a very low pK_a of 38.4, in the presence of 60% $NaOH/D_2O$[6] suggesting that carbanion formation may also occur in the case of *p*-DNB. The latter can be compared in acidity to pentafluorobenzene, which has a pK_a of ca 25.8.[23]

Hence we decided to explore the other possibility, the reaction occurring via the formation of the tetrachloropyridine carbanion. Facile H/D exchange occurred when **I** was exposed to either D_2O or $CDCl_3$ in the presence of NaOH and 90% of deuterium exchange was determined by NMR analysis after 3 h at ambient temperature. The GC–MS analysis of the sample confirmed the formation of 4-deuterated **I** suggesting the formation of a carbanion intermediate. This was also substantiated by an earlier report where the complex base BuLi–LiDMAE reacted with pyridine to give a metallated species.[24]

In an extension of the above methodology we assessed the activity of the weaker base potassium phosphate. To our surprise we found that solid K_3PO_4 promoted both H/D exchange and chlorination of **I** to **II** with full conversion of **I** and 70% selectivity for **II** after 2 h at 90 °C. The byproducts **III** and **IV** were also detected in the reaction mixture.

To conclude, we have demonstrated that carbon tetrachloride can chlorinate 2,3,5,6-tetrachloropyridine and even 2,3,5-trichloropyridine under mild conditions in the presence of a base and phase transfer catalyst. Hexachloroethane also acts as a chlorinating agent to generate pentachloropyridine, where formation of side products can be avoided.

3. Procedure for the preparation of pentachloropyridine

Sodium hydroxide 120 mmol (4.8 g, 50% w/w solution), 50 mL dichloroethane, 10 mmol of 2,3,5,6-tetrachloropyridine (2.17 g), 25 mmol of hexachloroethane (5.92 g), and TBAB (5 mol %, 161 mg) were stirred together in a glass reactor equipped with a condenser at 55 °C. The progress of the reaction was monitored by GC. After completion of the reaction, 20 mL of water was added and the reaction mixture stirred for 5 min. The organic layer was separated from the aqueous layer, which was extracted twice with 10 mL of dichloromethane. The combined organic layers were washed with 20 mL of 2% HCl and the layers separated. The organic layer was dried over magnesium sulfate and was concentrated under reduced pressure to give a white powder. Absolute ethanol (40 mL) was added to the solid and stirred for 30 min. The slurry was filtered and the solid obtained was washed twice with 10 mL of absolute ethanol then dried. The weight of dried product, pentachloropyridine, was 1.78 g (71% of the theoretical yield) with 97% purity (GC analysis). The observed MP (125.4 °C) was in agreement with the literature. The nature of the product was also confirmed by GC–MS analysis.

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