The Specificity of Reductive Dechlorination in the Polychloropyridine Series. Synthesis of 2,3,5-Trichloro- and of 2,3,5,6-Tetrachloropyridine

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Received October 15, 1979

The high specificity of the reduction system zinc and ammonium salts in dimethyl methylphosphonate as solvent is demonstrated in several reductive dechlorination reactions of polychloropyridines. The reduction of pentachloropyridine with zinc/ammonium chloride system in dimethyl methylphosphonate yielded solely 2,3,5,6-tetrachloropyridine. Similarly, the reduction of 2,3,4,5-tetrachloropyridine with zinc and the tetramethylammonium salt of methyl methylphosphonate furnished exclusively 2,3,5-trichloropyridine. A synthetic procedure for the preparation of the new ammonium salts of methyl methylphosphonate is given.

J. Heterocyclic Chem., **17**, 493 (1980).

Technically feasible preparations of 2,3,5-trichloro- (**1**) and 2,3,5,6-tetrachloropyridine (**2**), respectively, have always encountered considerable problems. Each of these chloropyridines serves as a chemical basis for several important pesticides which have been developed during the last decade.

There are quite a number of pertinent patents (1a-f) and other publications (2a-e) describing the numerous attempts to overcome the experimental difficulties which arise during preparations on a large scale, and also the obstacles stemming from economic considerations in some of these processes.

Some of these difficulties can be traced either to the problems separating positional isomers formed in the synthesis simultaneously with the desired chloropyridines, or the reaction conditions for the preparation of these compounds are of such a nature as to make them of little or no industrial importance.

Largely for these reasons there has arisen a tendency during the last few years to develop new synthetic procedures not, however, by utilizing a method aimed directly at one of the title compounds by a specific chlorination of certain ring positions, but one which would rather start from easily accessible higher chlorinated pyridines and then apply specific reduction procedures upon them (2d,3). Thus, for example, the pentachloropyridine (**3**) can be obtained by vapor phase chlorination of a number of polychloro(trichloromethyl)pyridines (2d), from completely hydrogenated heterocycles such as piperidine (2d), or from caprolactam (4) in excellent yield.

Several examples of selective reductive dehalogenations of pentachloropyridine to 2,3,5,6-tetrachloropyridine have been reported using either catalytic hydrogenolysis or chemical reduction methods (2d).

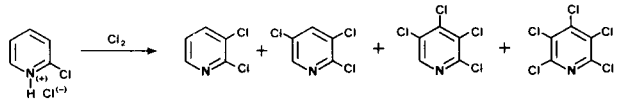
A recently described reductive dechlorination of **3** using metallic zinc and hydrochloric acid at 110° under autogenous pressure in an autoclave (3) gave the symmetrical tetrachloropyridine (**2**) in yields of over 90% accompanied by only 1.3% of 2,6-dichloropyridine and about 4% of a mixture of trichloropyridines.

Among the several procedures to prepare 2,3,4,5-tetrachloropyridine (**4**) which served as a starting material for the synthesis of 2,3,5-trichloropyridine, the most convenient method proved to be chlorination of 2-chloropyridine hydrochloride (**5**) (1c).

The chlorination of 2-chloropyridine hydrochloride according to the procedure described (1c) yielded a mixture of several chloropyridines representing different stages of chlorination (scheme I). Although the yield of **4** amounted only to 54%, the mono- or the dichloropyridine (**6**) may be subjected to further chlorination thus improving the overall yield of **4**. The separation of the mixture was performed by distillation through a column packed with glass helices.

Surprisingly, however, virtually no **2** was found to be present in the reaction mixture (less than 0.2% by gas chromatography), and this important result became the starting point for a new synthesis of **1**, easily amenable to large scale preparation, as described below.

SCHEME I



One of the most desirable goals, in particular from the technical point of view, is a direct and highly specific synthesis of **1** starting from **3**.

A recently reported process (5) described the reduction of pentachloropyridine and symmetrical tetrachloropyridine, respectively, in a benzene-water mixture using zinc in a strongly alkaline medium, *e.g.*, at a *p*H 11-14, yielding symmetrical tetrachloro- and 2,3,5-trichloropyridine, respectively, depending on reaction time.

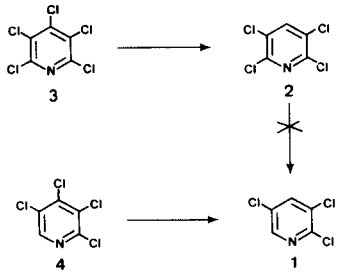
0022-152X/80/030493-04$02.25

The new feature of this process demonstrated the preferential formation of **1** in the reduction of higher chlorinated pyridines taking place in a strongly alkaline, aqueous solution. Representative examples of a mixture of the crystalline products obtained according to this procedure exhibited the following composition: 6.1% of an unknown compound, 6.6% of a mixture of dichloro-, 73.8% 2,3,5-trichloro-, 6.5% 2,3,6-trichloro-, 6.3% tetrachloro- and 0.75% of pentachloropyridine. There appears to be little deviation from these figures of whether reduction is carried out starting with **2** or with **3**. Although the process appears to be satisfactory, the number of by-products formed amount to a total of 26.2% in the crude reaction mixture.

This paper reports a simple, highly specific, reductive dechlorination procedure which can be carried out in inexpensive solvents without the aid of an autoclave. The same procedure with some slight modification served both for the synthesis of 2,3,5,6-tetrachloropyridine starting from the pentachloroanalogue and for that of 2,3,5-trichloropyridine from 2,3,4,5-tetrachloropyridine.

However, attempts to similarly prepare **1** starting with **2** which would be an easily accessible precurser, failed, and under more stringent reaction conditions only mixtures of partially dechlorinated pyridines were obtained in random distribution.

SCHEME II



To a solution of one mole of **3** in dimethyl methylphosphonate were added approximately 1.1 gramatoms of zinc dust followed by a saturated aqueous solution of an ammonium salt at a temperature of 85-90°. The reductive dechlorination took place almost exclusively at the 4-position of the pyridine ring. The resulting solution was then diluted with water and the crystalline product isolated by filtration.

The gas chromatographic analysis of the crude product indicated that it consisted of 97% of 2,3,5,6-tetrachloro-, 0.5% of 2,3,5-trichloro-, 0.6% of 2,3,6-trichloro- and 1.6% of unreacted pentachloropyridine (Scheme II). This mixture could easily be purified by recrystallization.

Since the commerically available **3** already contained 1.5% of **1**, any amount exceeding this value (Table I) should be corrected by 1.5%.

Several parameters of this reaction were modified. All the reductions listed in Table I were performed at 85-90° because in this temperature range the entire starting material was in solution and the reaction proceeded at a reasonable rate. Temperatures above 100° strongly favored the formation of mixtures of di- and trichlorinated pyridines at the expense of the desired **2**. One of the most critical parameters of the controlled reduction was the choice of a suitable solvent, since it should dissolve **3** sufficiently and preferably also be miscible with water in all proportions.

Dimethyl methylphosphonate (DMMP) in particular, and also trimethyl phosphate (TMP), proved to be exceptionally well suited for this purpose. The former is a by-product of Arbusov-reactions and can be isolated in substantial quantities when they are performed on large industrial scales. It is a very inexpensive solvent and in addition may be used without encountering any recovery

Table I

2,3,5,6-Tetrachloropyridine by Reduction of Pentachloropyridine

Solvent	Pentachloro pyridine (mole)	Ammonium Salt	mole	Zinc g.-atom	% Chloropyridines 2,3,5	2,3,6	2,3,5,6	2,3,4,5,6
DMMP (a)	1.0	NH_4Cl	1.6	1.2	1.0	0.9	97.6	0.5
DMMP	0.02	$(NH_4)_2CO_3$	0.025	0.028	2.1	2.2	93.4	0.8
DMMP	0.05	$(NH_4)_2SO_4$	0.075	0.06	3.3	1.3	92.0	2.9
DMMP	0.02	CH_3COONH_4	0.03	0.025	2.0	2.5	89.5	1.1
DMMP	0.02	NH_4HSO_4	0.03	0.025	2.5	0.6	76.6	20.0
DMMP	0.02	$(NH_4)_2HPO_4$	0.03	0.025	0.8	0.5	95.1	3.6
DMMP	0.02	$(NH_4)_3PO_4$	0.03	0.025	0.7	0.5	68.4	30.3
DMMP	0.05	$MMP^{\ominus}NH_4^{\oplus}$ (d)	0.075	0.07	2.5	1.9	94.1	0.17
DMMP	0.05	$MMP^{\ominus}{}^{\oplus}N(CH_3)_4$ (e)	0.075	0.06	1.6	0.9	96.9	0.6
DMMP	0.05	$MMP^{\ominus}{}^{\oplus}N(CH_3)_4$ (f)	0.075	0.052	2.7	2.6	91.3	0.5
DEEP (b)	0.1	NH_4Cl	0.265	0.11	1.2	2.2	92.7	2.8
TMP (c)	0.02	NH_4Cl	0.055	0.025	2.0	2.09	94.1	1.0

(a) Dimethyl methylphosphonate. (b) Diethyl ethylphosphonate. (c) Trimethyl phosphate. (d) Ammonium salt of methyl methylphosphonate. (e) Tetramethylammonium salt of methyl methylphosphonate. (f) Same salt as listed under (e) prepared *in situ*.

problems because of its extremely low toxicity (LD_{50}: 10,000 as tested on rats). Its outstanding qualities especially as a solvent for reactions involving organic with inorganic compounds, have been pointed out before on several occasions (6,7), and also its application as a mild selective methylating reagent has proven fruitful for synthetic purposes (4,6). Since the methylation properties of dimethyl methylphosphonate do not become apparent below a temperature of about 140° (6), no interference was to be expected with its use as a solvent in the reduction reaction.

Trimethyl phosphate was equally well suited in all respects as a solvent for the reductive dechlorination, however, it is considerably higher priced.

The influence of the choice of the anion of various ammonium salts was studied to some extent and stemmed largely from economic considerations.

The most prominent examples with regard to their specificity were ammonium chloride, -carbonate and the -diammonium phosphate. Furthermore, the ammonium, or in particular, the tetramethylammonium salt of the monoethyl ester of methylphosphonic acid gave products of excellent purity. Their seemed to be a slightly higher specificity as to the exclusive formation and final purity of **2** when the reaction was performed with the isolated tetramethylammonium salt rather than with the salt prepared *in situ* in an excess of dimethyl methylphosphonate. The prerequisite, however, in this latter case was addition of a little water to the reaction mixture before adding the zinc metal, as otherwise the reduction could not be carried to completion for unknown reasons.

The results of some reductions carried out under essentially the same conditions with diethyl ethylphosphonate and trimethyl phosphate, respectively, as solvents are also listed in Table I. The results indicated that there is no significant deviation in the compositions of products compared to the runs performed in dimethyl methylphosphonate.

While the cationic counterpart of the methyl methylphosphonate salts used did not generally influence the product composition to any large extent, quite the opposite results emerged from the investigation of the reduction of 2,3,4,5-tetrachloro- to 2,3,5-trichloropyridine.

Only the combination of zinc metal with the tetramethyl ammonium salt of methyl methylphosphonate ester gave a satisfactory result in respect to the purity of the product and the reaction time required. Other ammonium salts, such as ammonium chloride, -carbonate-, or the ammonium salt of methyl methylphosphonate favored the formation of other products which were assumed to be dichloropyridines (table II).

When methanol was used as solvent there was also good selectivity as to the formation of **1** with few by-products being formed, although extended reaction times were required and the yields obtained made further investigations unattractive.

Since the ammonium salts of the methylester of methylphosphonic acid (**8**) have not been described before, their preparation will be included in this paper.

The ammonium salt **8** (R = H) has been mentioned earlier as a likely intermediate in connection with a mechanistic investigation of the alkaline hydrolysis of dimethyl methylphosphonate, but no method as to its preparation was reported (8).

The synthesis of **8** (R = H, CH_3) was most easily achieved by heating a slurry of the respective ammonium chloride salt (**9**, R = H, CH_3) in an excess of dimethyl methylphosphonate at a temperature of 150° (Scheme III). The reaction proceeded with evolution of methyl chloride, which was collected in a cold trap and identified, and

SCHEME III

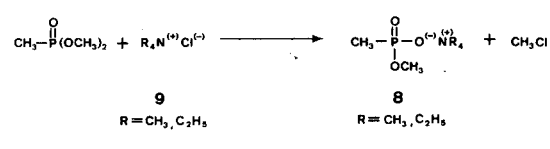


Table II

2,3,5-Trichloropyridine by Reduction of 2,3,4,5-Tetrachloropyridine

Solvent	Tetrachloropyridine (mole)	Ammonium Salt	mole	Zinc g.-atom	Product Composition, % Chloropyridines unknown	2,3,5	2,3,4,5	% yield 2,3,5
a) DMMP	0.05	$MMP^{\ominus}\,{}^{\oplus}N(CH_3)_4$ (c)	0.075	0.065	1.7	96.4	0.6	80
b) DMMP	0.05	$MMP^{\ominus}\,{}^{\oplus}NH_4$ (d)	0.075	0.065	–	68.0	13.5	- (a)
c) DMMP/H_2O	0.05	$MMP^{\ominus}\,{}^{\oplus}NH_4$ (d)	0.075	0.065	0.6	>8.8	2.5	(b)
d) DMMP	0.05	NH_4Cl	0.08	0.07	6.6	>9.2	11.8	? (b)
e) CH_3OH	0.05	NH_4Cl	0.08	0.06	5.7	92.7	1.0	62.5 (a)

(a) Yield after 22 hours. (b) Yield after 60 minutes reaction time. (c) Tetramethylammonium salt of methyl methylphosphonate. (d) Ammonium salt of methyl methylphosphonate.

final isolation of the product was completed by concentration of the solution.

The salts **8** were obtained as extremely hygroscopic, white crystals, and remained, however, singular examples as to their exceptional tendency to crystallize, which permitted an easy isolation, while all attempts to prepare the higher homologues yielded only oily products which did not conform with the expected analytical composition.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The separation of positional isomers of the different tri- tetra chloro-, and the pentachloropyridine and the determination of the percentage composition of the reaction mixtures was performed by gas chromatography (gc) using a column packed with carbowax 20 M, 3%, length 8 ft and diameter 2 mm, 100-240° program. The comparison of the different products was made with authentic samples prepared according to known procedures (9,1c).

Starting Materials.

Pentachloropyridine of commerical quality was obtained from Fluka Inc., Switzerland. Gas chromatography indicated that it contained 1.5% of 2,3,5-trichloropyridine.

2,3,4,5-Tetrachloropyridine was prepared by chlorination of 2-chloropyridine hydrochloride according to a reported method (1c). Gas chromatography indicated that the crude mixture obtained consisted of 8.8% of 2-chloro-, 14% of 2,3-dichloro- (**6**), 11.8% of 2,3,5-trichloro-, 54% of 2,3,4,5-tetrachloro-, and 11.1% of pentachloropyridine. Fractional distillation through a column (1.5 m, 1500 mm, packed with glass helices) yielded 2,3,4,5-tetrachloropyridine with a purity of 99.7% (gc), b.p. 108.5-110°/10 torr. From the foreruns were isolated 2,3-dichloropyridine, m.p. 64.5-66° (after recrystallization from methanol/water (9), and 2,3,5-trichloropyridine, m.p. 48-48.5° (after recrystallization from methanol) (9).

Dimethyl methylphosphonate (DMMP) was of commercial quality and contained 92% of dimethyl methylphosphonate, 2.3 % of trimethylphosphonate and 5.7% of dimethyl phosphite (gc) and was used as such (6).

2,3,5,6-Tetrachloropyridine (**2**).

Reduction with zinc/ammonium chloride. A suspension of 255.3 g. (1 mole) of pentachloropyridine in 1400 ml. of dimethyl methylphosphonate was heated to 90° resulting in a clear solution. Then 81.3 g. (1.2 g.-atom) of zinc dust (96.6%) was added with stirring, followed by the dropwise addition of an aqueous solution containing 85.5 g. (1.6 moles) of ammonium chloride, within a period of 45 minutes. Stirring was continued for an additional 30 minutes, the warm solution was filtered from metallic particles and washed on the filter with 50 ml. of dimethyl methylphosphonate. The filtrate was poured into 5 l. of water, acidified with 100 ml. of concentrated hydrochloric acid and stirred for 40 minutes. Crystals were filtered, washed with 1.5 l. of water and dried, yielding 208 g. (95.8%) of product, m.p. 86-88°. A sample was recrystallized from methanol yielding white crystals, m.p. 91.5-92° (2b). Gas chromatography indicated that the crude material consisted of 0.9% 2,3,6-trichloro-, 1.0% 2,3,5-trichloro-, 97.6% 2,3,5,6-tetrachloro- and 0.5% of pentachloropyridine.

2. Reduction with Zinc and Ammonium Methylphosphonic Acid Methyl Ester.

A soluton of 9.53 g. (0.075 mole) of ammonium methylphosphonic acid methyl ester in 44 ml. of water was added over a period of 25 minutes to a solution of 12.57 g. (0.05 mole) of pentachloropyridine in 150 ml. of dimethyl methylphosphonate containing 4.6 g. (0.07 mole) of zinc dust. The work-up procedure was the same as described in procedure 1, and yielded 8.72 g. of white crystals.

2,3,5-Trichloropyridine.

Reduction with zinc and tetramethylammonium methylphosphonic acid methyl ester. To a suspension of 11.0 g. (0.05 mole) of 2,3,4,5-tetrachloropyridine in 90 ml. of dimethyl methylphosphonate was added 4.4 g. (0.065 mole) of zinc dust (96.6%). Then a solution of 13.7 g. (0.075 mole) of the tetramethylammonium salt in 30 ml. of water was added dropwise with stirring at 85° over a period of 35 minutes. After the dilution had been completed stirring was continued for one hour. The work-up procedure followed the examples given above, yielding 7.3 g. (80%), m.p. 46.5-47.5°.

Ammonium Methylphosphonic Acid Methyl Ester.

A stirred slurry of 107 g. (2 moles) of ammonium chloride in 540 g. (4 moles) of dimethyl methylphosphonate was heated in a 1 l. round bottom flask to 110°. The reaction commenced with evolution of methyl chloride. The temperature was increased to 138° within 20 minutes and then to 151° within the same period of time. The excess of dimethyl methylphosphonate was distilled from the transparent, colorless solution at a pressure of 12 torr, and 500 ml. of acetone added to the residual oil. After stirring for 24 hours crystals were filtered from the cold solution (0°) and under exclusion of moisture washed with 150 ml. of anhydrous ether. The hygroscopic product was dried at 50°/12 torr yielding 118.6 g. (46%) of white crystals, m.p. 96-103° dec.; ir: cm^{-1} 1310, 1194, 1070, 1048, 893, 787.

Anal. Calcd. for $C_2H_{10}NO_3P$: C, 18.90; H, 7.93; N, 11.02; P. 24.38. Found: C, 18.82; H, 8.10; N, 10.80; P, 24.18.

Tetramethylammonium Methylphosphonic Acid Methyl Ester.

A stirred slurry of 219 g. (2 moles) of tetramethyl ammonium chloride in 540 g. (4 moles) of dimethyl methylphosphonate was heated to 130°. Then the temperature was increased to 150° within a period of 3 hours and kept at 160° for one additional hour. The excess of dimethyl methylphosphonate was distilled from the reaction flask at a pressure of 12 torr ad 400 ml. of acetone added to the dry crystalline residue. After stirring for 30 minutes, the product was filtered under exclusion of moisture and washed on the filter with 500 ml. of anhydrous ether. Traces of ether were removed by heating the product at 60°/12 torr yielding 312 g. (85%) of white crystals, m.p. 172-177° dec.; ir: cm^{-1} 1490, 1195, 1070, 1050, 960, 950, 785.

Anal. Calcd. for $C_2H_{10}NO_3P$: C, 39.34; H, 9.91; N, 7.65; P, 16.91. Found: C, 39.74; H, 10.23; N, 7.81; P, 16.45.

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