

Use of Chloride Ion as a Catalyst for Dehydrochlorination Reactions: The Synthesis of 3,5,6-Trichloropyridin-2-ol

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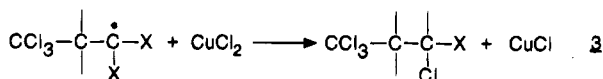
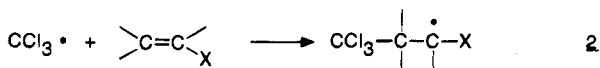
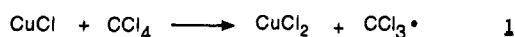
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The reaction conditions to prepare 2,2,4-trichloro-4-cyanobutanoyl chloride (**3**) in high yield via the CuCl addition of trichloroacetyl chloride (**1**) to acrylonitrile (**2**) are reported. A novel conversion of **3** to 3,5,6-trichloropyridin-2-ol (**6**) via 3,3,5,6-tetrachloro-3,4-dihydropyridin-2-one (**4**) under anhydrous conditions and without salt formation has been achieved in 90% yield using chloride ion as a dehydrochlorination catalyst.

Introduction

Nearly four decades ago, Kharasch and co-workers¹ showed that various halocarbons will add to olefins in a radical chain process to yield products wherein the polyhalocarbon moiety was attached to the primary carbon of the olefin and the halogen atom to the secondary carbon.² Later, it was observed that the reaction is catalyzed by a number of transition metal complexes.³ A redox-transfer chain mechanism was suggested in which the catalyst (e.g., CuCl) participates in the chain propagation as a chlorine atom transfer agent (eq 1-3).⁴



The products derived from CuCl-catalyzed addition are, in general, 1:1 adducts, whereas peroxide-initiated reactions often lead to considerable telomer formation. Extensive investigations on the transition metal catalyzed additions of polyhalogens have been carried out, and several reviews have been published on this area of chemistry.^{5,6} The utilization of this chemistry as a basis for the synthesis of substituted pyridines has been reported.^{7,8} Chlorinated and fluorinated pyridines are valuable intermediates for the preparation of various biologically active substances, particularly insecticides, herbicides, and fungicides. In the present study, we describe the CuCl-catalyzed addition of trichloroacetyl chloride (**1**) to acrylonitrile (**2**) and the subsequent conversion of the adduct to 3,5,6-trichloropyridin-2-ol (**6**), a valuable intermediate for the commercial production of Dursban insecticide⁹ and Garlon herbicide.⁹

Discussion of Results

The CuCl-catalyzed addition of trichloroacetyl chloride (**1**) to acrylonitrile (**2**) has been reported by Martin and others.¹⁰⁻¹² When **1** and **2** were allowed to react with an acetonitrile solution in the presence of CuCl at 180 °C in an autoclave, 2,3,5,6-tetrachloropyridine (**5**) and 3,5,6-trichloropyridin-2-ol (**6**) were isolated from the reaction mixture. The following series of reactions, illustrated in Scheme 1, are probably responsible for the products obtained by Martin.¹⁰ Although the series of reactions is advantageously carried out in a single operation and in a closed system under pressure, the combined yield of **5** and **6** is too low to be practical. Furthermore, the reaction typically produces a mixture of two products which must be separated or treated in subsequent operations to convert one product into the other. Hence, it is desirable to have a reaction sequence to prepare **6** in high yields and without byproduct **5**.¹³

The results of the present study demonstrate a high yield synthesis of **6** without formation of **5** as a byproduct by conducting the addition, cyclization, and dehydrochlorination reactions separately as shown in Scheme 2.

The results of the addition of **1** to **2** to give 2,2,4-trichloro-4-cyanobutanoyl chloride (**3**) are summarized in Table 1. The reactions were carried out at atmospheric pressure under reflux (see Experimental Section). These conditions permitted any trace amounts of HCl to escape from the reaction medium and prevented cyclization of the linear adduct, and hence the formation of water, etc., as outlined in Scheme 1.

In this manner, high yields of **3** (>90%) were obtained at the conversion indicated in Table 1. The results show that increasing the catalyst concentration, as expected, increases the rate of conversion (experiments 1 and 2). A further increase in catalyst concentration (experiment 3) has little effect, indicating that catalyst solubility may be a limiting factor. Addition of the catalyst in incremental amounts had little effect on the conversion (experiment 4). However, analysis of the catalyst showed

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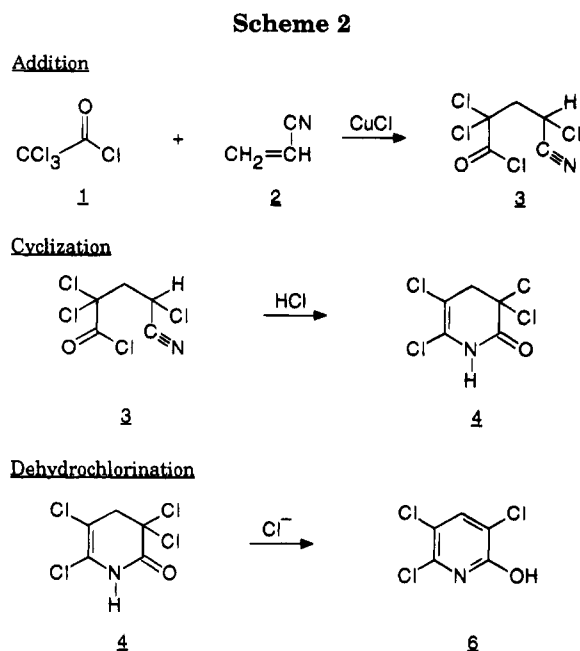
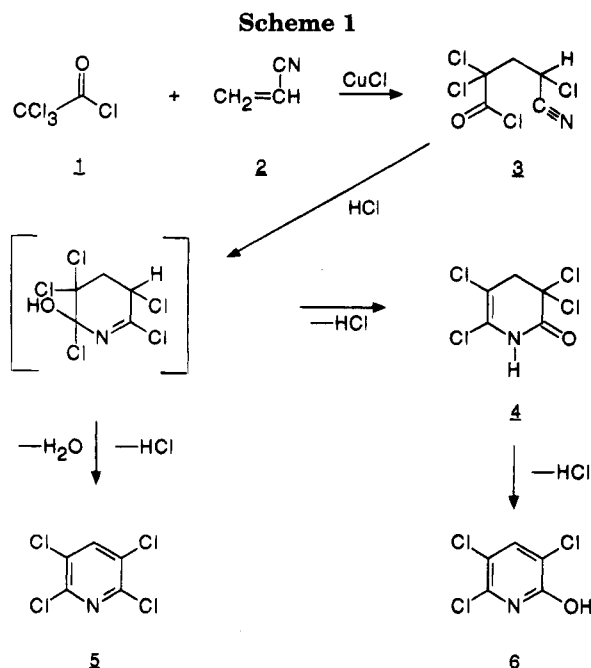
(9) Registered trademark of DowElanco.

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(13) After completion of the present study, the preparation of **4** from **1** and **2** was reported using nitrobenzene as the solvent.¹² Our results with nitrobenzene, perchloroethylene, and toluene as solvents were similar to those obtained in neat solution.



that approximately two-thirds of the CuCl had been converted to CuCl₂. The CuCl₂ is readily separated from the CuCl by dissolution in water (see Experimental Section). Further experimentation demonstrated that CuCl₂ is inactive as a catalyst for the addition reaction (experiment 5). Sparging gaseous reducing agents such as either carbon monoxide or hydrogen through the reaction medium had no effect on reducing the oxidation of CuCl to CuCl₂. However, the addition of elemental copper along with CuCl proved to be a very attractive system. Under these conditions (experiments 6 and 7), greater than 90% of the copper was recovered as CuCl that could be recycled. Furthermore, elemental copper can be utilized as the catalyst (experiment 8). The effect of the ratio of reactants was also investigated (experiments 9–12). Increasing the molar ratio of 2:1 from 0.82 to 1.36 increases the conversion as well as reduces the reaction time. This data has important commercial significance in that reactor capacity is increased sever-

Table 1. Addition of Trichloroacetyl Chloride to Acrylonitrile

$$1 + 2 \xrightarrow[80-105^\circ\text{C}]{\text{CuCl}} 3$$

expt	reactants (mol)		catalyst (mol)			time (h)	conversion ^a (%)	
	1	2	Cu	CuCl	CuCl ₂		NMR	Isol
1	1.00	0.50		0.011		25	43	
2	1.00	0.50		0.023		25	44	69
						48	95	
3	1.00	0.50		0.045 ^b		25	65	
						48	94	
4	1.00	0.40		0.045		24	65 ^c	65
5	1.00	0.40			0.050	24	0 ^d	0
6	1.00	0.40	0.023	0.023		24	65 ^e	65
7	1.00	0.40	0.046	0.045		24	74 ^e	76
8	1.00	0.40	0.046			10	45	45
9	0.50	0.41	0.023	0.023		10	45	45
10	0.50	0.52	0.023	0.023		10	51	48
11	0.50	0.61	0.023	0.023		10	65	62
12	0.50	0.68	0.023	0.023		10	67	66

^a Conversion of 2 to 3. ^b Catalyst added in increments over 12 h. ^c ~Two-thirds of CuCl → CuCl₂. ^d CuCl₂ is an inactive catalyst. ^e No Cu remains after 24 h.

Table 2. Cyclization of 2,2,4-Trichloro-4-cyanobutanoyl Chloride (3) to 3,3,5,6-Tetrachloro-3,4-dihydropyridin-2-one (4)

solvent	temp (°C)	time (h)	HCl pressure (psi)	yield of 4 (%)
none	25	3	1 atm (sparge)	no reaction
1,2-dichloroethane	25	16	200	93
1,2-dichloroethane	25	1.5	100	92
dichloromethane	25	2	100	97
perchloroethylene	50	2	150	95
ethyl acetate	25	2	100	97

alfold while the amount of material that is available for recycle (i.e., unreacted 1 and 2) is reduced.

The cyclization of the linear adduct 3 to the intermediate 3,3,5,6-tetrachloro-3,4-dihydropyridin-2-one, 4, is catalyzed by acidic reagents. From a practical point, the use of anhydrous HCl would be desirable. Results of the cyclization with anhydrous HCl are summarized in Table 2. At atmospheric pressure without a solvent, sparging anhydrous HCl through neat 3 does not produce cyclization. Since the melting point of the product is reasonably high, 127–128 °C, a solvent is necessary to facilitate handling the material. When allowed to react overnight under HCl pressure in 1,2-dichloroethane, cyclization occurred in near-quantitative yield. Further work demonstrated that the reaction was complete after ~1.5 h. Dichloromethane and perchloroethylene were also suitable solvents. However, the solubility of 4 in the chlorinated solvents was limited and ethyl acetate was found to be a better solvent, not only for 4, but also the final product 3,4,5,6-trichloropyridin-2-ol (6).

The dehydrochlorination of 4 to 6 has been reported by Martin¹⁰ via the addition of aqueous sodium hydroxide to an ethanolic solution of pyridinone (4). The results of our dehydrochlorination studies are described in Table 3. The thermolysis of 4 in refluxing *o*-dichlorobenzene results in partial dehydrochlorination. However, the rate is very slow (experiment 1). Under acidic conditions in refluxing chlorobenzene, both triflic acid and aluminum chloride catalyze the reaction (experiments 2 and 3). ZnCl₂ also exhibited good catalytic activity when heated without solvent to improve catalyst solubility. However, handling the high melting pyridinol was not practical

Table 3. Dehydrochlorination of 3,3-Tetrachloro-3,4-dihydropyridin-2-one (4) to 3,5,6-Trichloropyridin-2-ol (6)

expt	reagent (mol %)	time (h)	solvent	T (°C)	conversion (%)
1	none	20	<i>o</i> -dichlorobenzene	177	50
2	CF ₃ SO ₂ OH (2)	16	chlorobenzene	132	20
3	AlCl ₃ (10)	20	chlorobenzene	132	75
4	ZnCl ₂ (5)	2	none	170	90
5	NaOH (300)	20	1,2-dichloroethane/H ₂ O (1:1)	25	100
6	Na ₂ CO ₃ (300)	2	ethyl acetate/H ₂ O (1:1)	77	98
7	Na ₂ CO ₃ (300)	2	ethyl acetate/H ₂ O (1:1)	77	94
8	<i>n</i> -C ₄ H ₉) ₄ NX ^{a,b}	2	perchloroethylene	120	>90
9	18-crown-6, KCl ^b	2	perchloroethylene	120	96
10	poly-4-vinylpyridine ^b	2	perchloroethylene	120	93
11	MSA-1 Dow ion ^b exchange resin	2	perchloroethylene	120	94

^a X = F, Cl, Br, I, OAc, and CN. ^b Experiments 8–11 were carried out with 0.1 g of reagent (catalyst) per 25 g of 4.

without a solvent (experiment 4). Either an aqueous sodium hydroxide or an aqueous sodium carbonate solution in a two-phase system gave a high yield for **6** (experiments 5–7). However, environmentally and economically, a process that produces anhydrous HCl rather than salt is more desirable. This was achieved by utilizing chloride ion as the dehydrochlorination catalyst. For example, tetrabutylammonium chloride in refluxing perchloroethylene rapidly dehydrochlorinated **4** → **6**. The counteranion of the tetrabutylammonium anion does not appear to be critical as fluoride, bromide, iodide cyanide, and acetate all give comparable results (experiment 8). The analogous phosphonium salts were also good catalysts. From a practical point, poly-4-vinylpyridine and ion exchange resins were very useful as catalysts since they could be filtered from the hot perchloroethylene solution and reused (experiments 10 and 11).

The use of perchloroethylene has several advantages. First, perchloroethylene is the least expensive feedstock for the production of trichloroacetyl chloride,¹⁴ and second, both the cyclization and dehydrochlorination can be carried out in perchloroethylene. Hence, the cyclization and dehydrochlorination can be achieved in the same solvent and without isolation of the intermediate pyridin-2-one, **4**.

Conclusions

The present investigation of the addition of trichloroacetyl chloride to acrylonitrile followed by cyclization and dehydrochlorination has provided a commercially feasible route to 3,5,6-trichloropyridin-2-ol from inexpensive starting materials. In addition, the chemistry involves the use of a single solvent, which is also the feedstock for a starting material as well as avoiding the formation of byproduct salt.

Experimental Section

General. Trichloroacetyl chloride and acrylonitrile (Aldrich) were distilled prior to use. NMR spectra were recorded on either a Varian EM360 or a Varian Gemini 300-MHz spectrophotometer. Tetramethylsilane was used as an internal standard. The spectral and physical properties of the product and intermediates were identical to those reported by Martin.¹⁰

General Procedure for the Preparation of 2,2,4-Trichloro-4-cyanobutanoyl chloride (3) (See Table 1). Trichloroacetyl chloride (182.0 g, 1.0 mol), acrylonitrile (53.1

g, 1.0 mol), and anhydrous CuCl (1.12 g, .011 mol) were heated and stirred under reflux in a nitrogen atmosphere. The reflux temperature for the reaction mixture starts at ~80 °C and increases to ~100 °C at ~35% conversion. By utilizing a temperature controller, the maximum temperature was 105 °C. Percent conversion was determined by withdrawing, cooling, filtering, and analyzing samples by gas chromatography and nuclear magnetic resonance spectroscopy. The product was isolated by cooling the reaction mixture, evaporating the volatile starting materials on a rotary evaporator, diluting the residue with perchloroethylene, and filtering the spent catalyst. The catalyst was dried, weighed, washed with water to remove CuCl₂, dried, and weighed to determine the CuCl:CuCl₂ ratio. Evaporation of the perchloroethylene gave crude **3** (91% yield at ~50% conversion of **2**). Distillation of the crude material gave product with bp 90 °C (4mm): ¹H NMR (CDCl₃) δ 3.34 (q, 2H, CH₂), 4.89 (t, 1H, CH). Anal. Calcd for C₅H₃Cl₄NO: C, 60.05; H, 1.29; N, 5.96. Found: C, 60.26; H, 1.32; N, 6.28.

Preparation of 3,3,5,6-Tetrachloro-3,4-dihydropyridin-2-one (4) (See Table 2). The cyclizations were carried out in a 600 mL Hastelloy C Parr autoclave equipped with a magnetic drive. The 2,2,4-trichloro-4-cyanobutanoyl chloride (61 g, 0.26 mol) was diluted with the desired solvent (150 mL) and the bomb pressurized with anhydrous HCl to the desired pressure. After the mixture was stirred for the desired time, the bomb was vented, the contents were transferred to a round-bottom flask, and the solvent was evaporated on a rotary evaporator. The contents were slurried with hexane to facilitate isolation by filtration to give product with mp 127–28 °C (lit.¹⁰ mp 127–28 °C).

Preparation of 3,5,6-Trichloropyridin-2-ol (6). (a) **Aqueous Two-Phase System.** In a typical experiment, **4** (23.3 g, 0.1 mol), ethyl acetate (233 mL), water (233 mL), and 0.3 mol of base were stirred and refluxed for 2 h. After cooling, the reaction mixture was acidified with concentrated HCl and the organic phase separated and dried over MgSO₄. After filtration, the product was obtained by evaporation of the solvent from the filtrate. The results are summarized in Table 3.

(b) **Nonaqueous System.** 3,3,5,6-Tetrachloro-3,4-dihydropyridin-2-one (5 g, 0.02 mol), 0.1 g of catalyst, and solvent (25 mL) were heated to reflux and the reaction monitored by GC analysis. The product was recovered by filtration. Isolated yields were >90%. The results are summarized in Table 3.

(c) **Combined Cyclization and Aromatization.** The cyclization reaction was carried out as described above, and the contents from the Hastelloy C Parr reactor were transferred with the aid of an additional 100 mL of perchloroethylene to a round-bottom flask containing MSA-1 Dow ion exchange resin. The mixture was refluxed for 1.5 h, and the solid catalyst was removed by filtration from the hot solution. The filtrate was cooled to crystallize the 3,5,6-trichloropyridin-2-ol which was isolated and dried to give a 91% yield of product, mp 171–72 °C (lit.¹⁰ mp 171–72 °C).

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