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Safety Aspects of the Under-Pressure Reaction of Trichloroacetyl Chloride and Acrylonitrile in the Preparation of 3,5,6-Trichloro-2-pyridinol

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Abstract:

The under-pressure reaction of trichloroacetyl chloride (1) with acrylonitrile (2) in the preparation of 3,5,6-trichloro-2-pyridinol becomes explosive in certain circumstances. The studies of the reaction's enthalpy, the instability of the 2-chloropropionitrile (8), and the observation of the unexpected increase of pressure have helped us to point out that the above feature is due to the exothermic nature of the reactions and the HCl released by the 2-chloropropionitrile decomposition at elevated temperature. So, controlling the temperature and well-done stirring of the reaction mixture is very important in large-scale production to avoid the explosion nature of the reaction.

Introduction

The CuCl-catalyzed reaction of trichloroacetyl chloride (**1**) with acrylonitrile (**2**) is a well-known procedure for the large-scale production of 3,5,6-trichloropyridin-2-ol (**6**),[1−5] a valuable intermediate for the production of chlorpyrifos (insecticide) and triclopyr (herbicide).

The three-step mechanism (addition, cyclization and aromatization) was studied and proposed to prepare **6** in high yield[1] (Scheme 1). 2,2,4-Trichloro-4-cyanobutanoyl chloride (**3**) was produced under atmospheric pressure using nitrogen stream. The cyclization of **3** catalyzed by HCl under pressure has led to 3,3,5,6-tetrachloro-3,4-dihydropyridin-2(1*H*)-one (**4**), and the hydrolysis of **4** has afforded **6**.

The formations of the byproducts during the reaction have already been discussed.[6] They have been recognized as 3,3,5-trichloroglutarimide (**7**) and 2-chloropropionitrile (**8**) and have prevented the possibility of carrying out the under-pressure reaction with high yield and in safe conditions. The hydrolysis of 2,3,5,6-tetrachloropyridine (**5**), formed by the chlorination of **6** and **7**,[7,8] has afforded **6**.[9]

Table 1. **Proportional Composition (%)[a] of the Reaction Mixture of Trichloroacetyl Chloride and Acrylonitrile[b] Under Pressure Conditions**

expt	temp (°C)	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	110	40		31	1	1	2	25
2	150			3	26	29	16	26
3	180				35	25	25	15
4[c]	150			20	5	30		45

[a] Based on ^{1}H NMR spectroscopy. [b] Mol ratio of **2**:**1** was 1.5, and the reaction lasted for 5 h. [c] Experiment was performed in CH_3CN as solvent.

Nevertheless, the one-pot synthesis of **6** by the catalyzed reaction of **1** with **2** followed by the hydrolysis of the reaction mixture is a more attractive method, involving less separation and purification steps. It can be performed under both atmospheric and pressure conditions.

The reaction lasted for 5 h under pressure conditions because of the conversion rate dependency on the temperature and the possibility of reaching the elevated temperature (150 °C) in such conditions. Therefore, the same accomplishment of the reaction under atmospheric pressure would be achieved during 30−40 h.[6]

In this contribution, we describe the role of solvent and temperature on the reaction mixture composition, study the influence of temperature to increase the pressure during the reaction, and illustrate the causes of a sudden raise of pressure in certain circumstances.

Results and Discussion

The CuCl-catalyzed reaction of **1** with **2** was performed under pressure at 110, 150, and 180 °C during 5 h; the mixture constituents were determined by ^{1}H NMR spectroscopy and are outlined in the Table 1. Two byproducts (**7** and **8**) and three products (**4**, **5**, and **6**) are formed at different levels in four performed experiments. Under pressure conditions, we never observed **3**, because the reaction proceeded to the end of the cyclization step (i.e., formation of **4**).

At 110 °C, more than one-third of **2** was left unchanged; the reaction was halted at the end of the second step, and **4** was formed. At a more elevated temperature (150 °C), the conversion rate was increased and the reaction was performed until the end of the aromatization step. The products **5** and **6** were formed approximately at the same amount. At this stage, **5** was converted to **6** by hydrolysis of the reaction mixture via mineral base (e.g., NaOH) under pressure conditions during 2 h at 150 °C.

The comparison of the results obtained in experiments 2 and 4 illustrates the role of the solvent on the proportional

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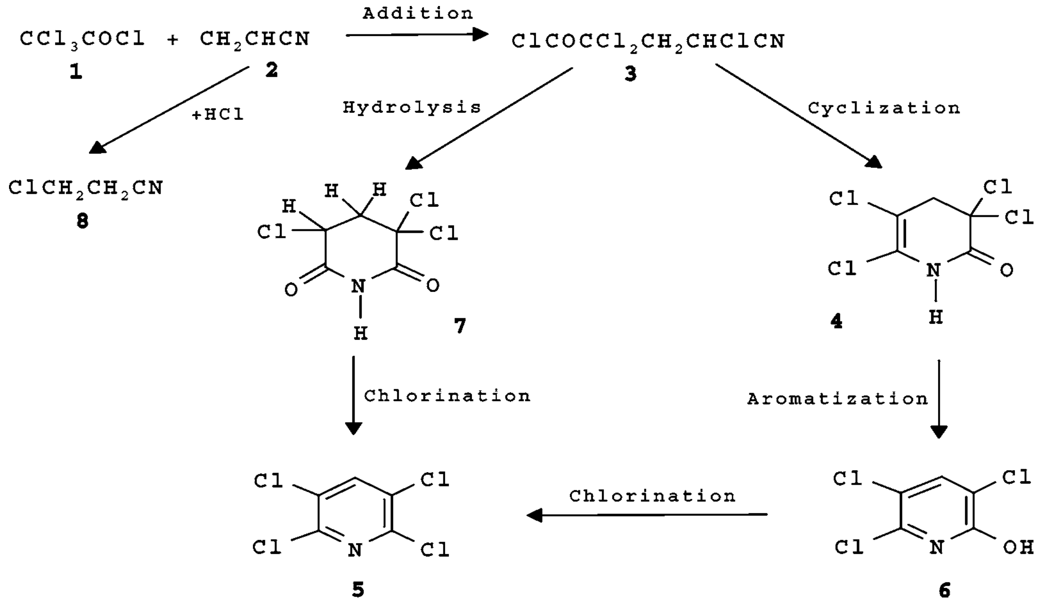
Scheme 1. **Mechanism Pathway for the Reaction of 1 with 2 in the Preparation of 6**



composition of the reaction mixture. The difference in the two experiments consisted of the quasi-absence of **5** and **7** and increase of **8**. This can be justified by the fact that, in the second experiment, the transformation of **4** to **6** released HCl that caused the formation of **5** via **6** by liberation of H_2O. The H_2O formed and induced the hydrolysis of **3** to **7**. In the fourth experiment, in which CH_3CN was used as solvent, the transformation of **4** to **6** and the release of HCl was followed by the hydrochlorination of **2** instead of **6**, so less **5** and H_2O were formed and the hydrolysis of **3** to **7** did not take place.

It seemed that **8** was not stable at 180 °C and was partly decomposed. The formation of **5** and **7** was favored at this temperature.

The results obtained from analysis of the reaction mixture by ^{1}H NMR and the small change of pressure at 110 °C during the reaction (Figure 1) indicate the least formation of **6** and HCl. At 150 °C, **6** was formed, the same amount of HCl was released, and the pressure was increased. At 180 °C, besides the HCl formed by the transformation of **4** to **6**, some part of **8** was decomposed to **2** and HCl. So, the pressure augmentation was remarkable at this temperature. Moreover, the observation of the pressure reduction at the first hour at 150 and 180 °C is due to the consumption of **2**.

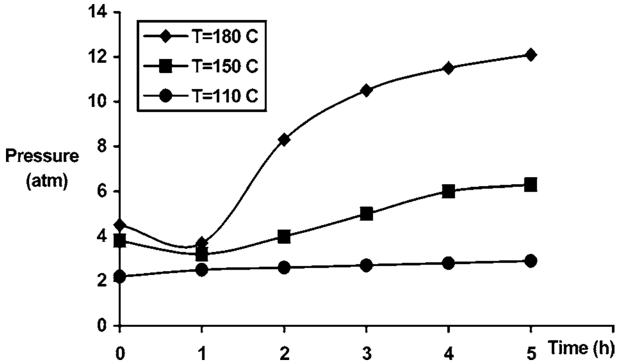


Figure 1. **Pressure change during the reaction of 1 with 2 (in 0.02 molar scale with 2:1 molar ratio of 1.5 and in a 25-mL glass autoclave) at different temperatures.**

Yet, carrying out the reaction under pressure at 150 °C and with **2** in excess (150 mol %) has afforded **5** and **6** with the yield of >80% (see Experimental Section) but with the risk of explosion in large-scale production. In fact, this proceeding is effective in small-scale production, where the magnetic stirrer is adequate and the internal temperature of the reaction could be taken the same as that of the bath. When the amounts of the starting materials were increased, the magnetic stirrer did not respond properly and the temperature was suddenly raised after 1 h, causing an appreciable amount of HCl to be released hence an increase of pressure. The ^{1}H NMR analysis of the residue after the explosion displayed the presence of a single compound (i.e., **6**).

The enthalpy calculation of the reactions in the three-step formation of **6** demonstrates the exothermic nature of the above reactions, particularly the aromatization step (i.e., the transformation of **4** to **6**).

$$\begin{aligned} \mathbf{1} + \mathbf{2} \rightarrow \mathbf{3} \qquad & \Delta H = -272 \text{ kJ/mol} \\ \mathbf{3} \rightarrow \mathbf{4} \qquad & \Delta H = -40 \text{ kJ/mol} \\ \mathbf{4} \rightarrow \mathbf{6} + \mathbf{HCl} \qquad & \Delta H = -474 \text{ kJ/mol} \end{aligned}$$

The first-order decomposition reaction of **8** above 140 °C is exothermic. The enhancement of the dehydrochlorination by the CN[10] and the thermodynamic data of **8**[11] were detailed.

$$\mathbf{8} \rightarrow \mathbf{2} + \mathbf{HCl} \qquad \Delta H = -245 \text{ kJ/mol}$$

The first and the second steps did not affect considerably the temperature of the reaction mixture because the first step was slow and the second was not exothermic enough. But, the transformation of **4** to **6**, occurring beyond 120 °C, was fast and very exothermic. In this condition, the temperature

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increased and caused the high rate conversion of **4** to **6** and rapid dissociation of **8**, both engendering HCl and the considerable raise of the pressure in the reaction vessel.

Knowing the mechanism of the formation of byproducts and the causes of the explosion occurrence of the reaction mixture, we performed the reaction in 0.1 molar scale of reactant under pressure conditions in a such manner preventing the risk of explosion. Initially, **2** was used in 110−120 mol % for minimizing the formation of **8** as the byproduct, exothermic decomposition of which being one of the causes of explosion. In the other part, the reaction temperature was controlled at 110−120 °C during 3 h, for the maximum transformation of **2** to **3** and **4**, after which, to accelerate the reaction rate, the temperature was elevated up to 150 °C for 3 h. In this manner, we diminished the risk of explosion and obtained the 61% yield.

So, controlling the temperature and well-done stirring of the reaction mixture is very important in large-scale production to avoid the explosion nature of the reaction.

Summary

The influence of temperature on the progress of the reaction of **1** with **2** and the formation of **6** is investigated. At 110 °C, the reaction resulted in the formation of **4**, and at 150 °C, **5** and **6** were formed.

In CH_3CN as solvent, the chlorination of **6** to **5** was minimized, whereas the formation of **8** was favored.

The explosive nature of the reaction of **1** with **2** was attributed to the lack of control of temperature and stirring items. Also, the exothermic reactions involved in the synthesis of **6** increased the temperature of the reaction mixture and caused the decomposition of **8** (byproduct) formed during the reaction that released HCl and increased the pressure in the reaction vessel.

Experimental Section

General. The reagent and the solvent are from the Merck Company and of high purity (>99%). Acrylonitrile was distilled prior to use. CuCl was produced in laboratory and was dried and preserved in a dark vessel free from humidity and air.

NMR spectra were recorded on a Bruker DPX-250 instrument (250 MHz for ^{1}H and 62.5 MHz for ^{13}C), and $CDCl_3$ was used as solvent; chemical shifts were reported in δ (ppm) from TMS (^{1}H and ^{13}C) that was used as internal standard. IR spectra were recorded on a Perkin-Elmer 783 instrument using KBr pellets (selected data given). Melting points were obtained on a Mettler FP61 apparatus. Elemental analysis was performed using a Carlo Erba analytical gas chromatograph.

Synthesis Procedure. Trichloroacetyl chloride (3.6 g, 0.02 mol), acrylonitrile (1.5 g, 0.03 mol), and anhydrous CuCl (0.1 g, 0.001 mol) were heated in a 25-mL glass autoclave equipped with a magnetic stirrer and pressure gauge. The mixture was stirred for 5 h in an oil bath at 150 °C. The pressure was started at 4 atm, diminished to 3.5 atm after 1 h, and increased to 6 atm after 5 h. The crude product was extracted 3 times with 10 mL of *n*-hexane. The evaporation of solvent afforded 1.64 g (0.0076 mol) of yellow crystals of **5**. ^{1}H NMR ($CDCl_3$): 7.9 (s) ppm. ^{13}C NMR ($CDCl_3$): 130, 140, 146 ppm. Mp = 90−91 °C (lit.[2] mp = 90−91 °C). IR (KBr pellet): 495(w), 637(s), 671(m), 708(w), 918(m), 1061(s), 1161(13), 1219(m), 1323(m), 1361(vs), 1387(s), 1506(m), 1719(m), 3010(m) cm^{-1}.

Residue was extracted 2 times with 10 mL of ether. The evaporation of the solvent lead to 1.9 g (0.0096 mol) of light yellow crystals of **6**. ^{1}H NMR ($CDCl_3$): 7.8 (s) ppm. ^{13}C NMR (DMSO): 116, 120, 141, 143, 158 ppm (in agreement to lit.[5]). Mp = 171−172 °C (lit.[2] mp = 171−172 °C). IR spectrum (KBr pellet): 541(w), 688(m), 750(m), 820(w), 893(w), 893(w), 954(w), 1021(w), 1078(s), 1155(m), 1211(s), 1273(w), 1315(s), 1382(m), 1452(vs), (1534(w), 1569(s), 1640(w), 2560(m), 2725(m), 2905(m), 3040(m) cm^{-1}.

The same procedure was carried out as precedent, and 10 mL of 10 M NaOH was added slowly to the crude product while controlling the temperature at 30−40 °C, after which the hydrolysis reaction was performed at 150 °C under 2 atm during 2 h. Filtration of the reaction mixture and washing the solid with 5 mL of cold H_2O gave the sodium salt of **6** that was dissolved in 100 mL of hot H_2O. Then, the solution was acidified to pH = 4 at 25 °C. The precipitate **6** was filtered and dried to afford 3.45 g (0.017 mol, 85%) of light yellow crystals of **6**.

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