Reaction Safety: A Critical Parameter in the Development of a Scaleable Synthesis of 2,3-Bis-chloromethylpyridine Hydrochloride

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Abstract:

This report describes the development of a scaleable process to prepare 2,3-bis(chloromethyl)pyridine hydrochloride, 2, that is safe, economical, and environmentally acceptable. On a small scale this material is prepared using thionyl chloride as the solvent. However, this reaction is not readily scaleable because of environmental and disposal issues. Reaction calorimetry is used to evaluate a number of potentially viable chlorination procedures. In the course of this investigation potentially hazardous reagent/solvent incompatibilities were identified. The use of thionyl chloride in MTBE is particularly hazardous owing to solvent decomposition in the presence of HCl and subsequent outgassing of large amounts of isobutylene. Reaction conditions employing thionyl chloride and 1% v/v DMF in toluene were found to be safe for scale-up. As a result, an environmentally acceptable, safe process has been developed and scaled to produce multikilogram amounts of material.

Introduction:

Recently, we required a safe, scaleable, and environmentally acceptable synthesis of 2,3-bis-(chloromethyl)pyridine hydrochloride, **2**, to support an ongoing project. Traditionally, chlorination of 2- or 3-hydroxymethylpyridines has been accomplished using thionyl chloride,[1–4] phosphorus trichloride,[5] phosphorus pentachloride,[6] or phosphorus oxychloride.[7,8] Indeed, chlorination of 2,3-bis(hydroxymethyl)pyridine, **1**, using thionyl chloride as the reactant and solvent is reported to afford **2** in excellent yield.[9–11]
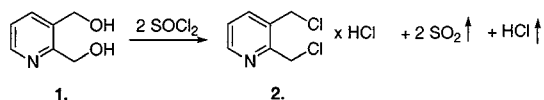
However, these classical reaction conditions can be drastic and often require evaporation and disposal of significant amounts of excess corrosive and environmentally harmful reagents or byproducts such as phosphorus oxychloride. Several alternatives using a slight excess of thionyl chloride in a reaction solvent were evaluated using reaction calorimetry to identify a safe, scaleable alternative to these reaction conditions.

Results and Discussion:

We repeated the literature procedure and treated **1** with 3.0 mol equiv of thionyl chloride as the reactant and solvent. As the reaction progressed to completion, the mixture became a thick, difficult-to-stir suspension from which isolation of **2** by filtration was clearly problematic. Addition of precooled *tert*-butyl methyl ether (MTBE) to the thick reaction suspension afforded an easily filtered mixture from which **2** was isolated in excellent yield. However, the difficulties encountered on small scale together with our concerns for safety and disposal of large volumes of excess thionyl chloride prompted us to investigate alternate approaches. Our goals were to prepare **2** in high yield and purity while minimizing the excess of thionyl chloride required and maintaining a convenient reaction time together with a simple and readily scaleable workup procedure.

Among the solvents we evaluated initially, most of our requirements could be met using MTBE as a diluent in the early research-scale work described above. This solvent was particularly advantageous for solubility and handling characteristics (e.g., filtration) during the reaction workup. In addition, we anticipated that the reaction could be run at ambient conditions. This would avoid the known cleavage of MTBE under acidic reaction conditions and elevated temperature. For example, a violent acid catalyzed decomposition of MTBE at elevated temperatures was reported wherein a fatal explosion and fire resulted when sulfuric acid accidentally entered a distillation vessel during removal of MTBE.[12]

Reaction of **1** with 1.6 equiv of thionyl chloride in MTBE at ambient temperature afforded **2** in excellent yield and purity. Product isolation was simple and straightforward, requiring only filtration and drying to afford **2** as a free flowing, granular, white solid. These results were confirmed and reproducible up to 2.0 mol scale. However, at this scale the reaction became very sluggish and required several hours

(1) Bell, I. M.; Erb, J. M.; Freidinger, R. M.; Gallicchio, S. N.; Guare, J. P.; Guidotti, M. T.; Halpin, R. A.; Hobbs, D. W.; Homnick, C. F.; Kuo, M. S.; Lis, E. V.; Mathre, D. J.; Michelson, S. R.; Pawluczyk, J. M.; Pettibone, D. J.; Reiss, D. R.; Vickers, S.; Williams, P. D.; Woyden, C. J. *J. Med. Chem.* **1998**, *41*, 2146.

(2) Kühler, T. C.; Swanson, M.; Shcherbuchin, V.; Larsson, H.; Mellgård, B.; Sjöström, J.-E. *J. Med. Chem.* **1998**, *41*, 177.

(3) Loukiala, S.; Ratilainen, J.; Airola, K.; Valkonen, J.; Rissanen, K. *Acta Chem. Scand.* **1998**, *58*, 593.

(4) Mosher, H. S.; Tessieri, J. E. *J. Am. Chem. Soc.* **1951**, *73*, 4925.

(5) Kobayashi, G.; Furukawa, S. *Chem. Pharm. Bull.* **1953**, *1*, 347.

(6) Rey-Bellet, G.; Spiegelberg, H. U.S. Patent 2,798,075, 1957; *Chem. Abstr.* **1957**, *52*, 2173.

(7) Itai, T.; Ogura, H. *J. Pharm. Soc. Jpn.* **1955**, *75*, 296.

(8) Kametani, T.; Fukumoto, K.; Nomura, Y. *Chem. Pharm. Bull.* **1958**, *6*, 467.

(9) Kim, D. Y.; Jung, I. C.; Lee, J. W.; Yoon, G. J. *J. Korean Chem. Soc.* **1998**, *42*, 102.

(10) Kim, W. J.; Park, T. H.; Kim, B. J.; Kim, M. H.; Pearson, N. Int. Pat. Appl. WO 94/15938, 1994; *Chem. Abstr.* **1994**, *121*, 205332.

(11) Armarego, W. L. F.; Milloy, B. A.; Sharma, S. C. *J. Chem. Soc. Perkin Trans. 1* **1972**, 2485.

(12) *Eur. Chem. News* **1995**, *64*(1678), 5.
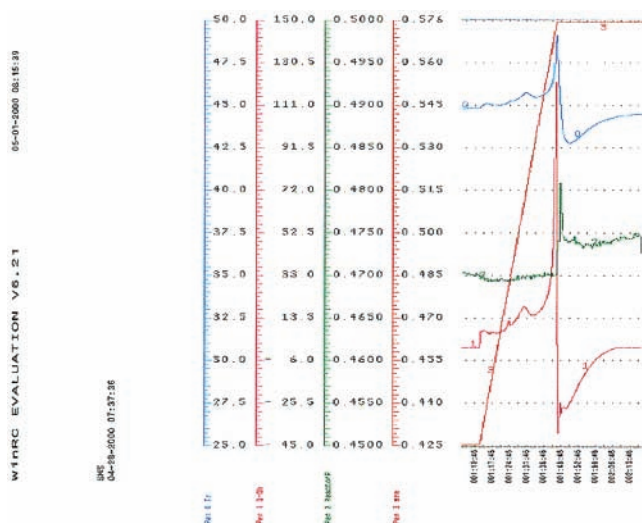
Figure 1. RC-1 heat flow curve for experiment in MTBE at 45 °C. (Blue) Reaction temperature T_r. (Red) Heat flow. (Green) Reactor pressure. (Orange) SOCl$_2$ addition.

for completion. We were concerned about prolonged exposure of MTBE to the acidic reaction conditions and further investigated this reaction using reaction calorimetry.

All experiments were carried out in a Mettler RC-1 reaction calorimeter. The instrument was equipped with the 1-L MP-10 pressure reactor or the SV01 1-L vessel and a propeller stirrer, temperature sensor, and calibration heater. Following the necessary calorimetric measurements, thionyl chloride was added via a dosing control loop using a Prominent diaphragm pump for all experiments. Only the addition time, solvent, and temperature were varied. These reactions were heterogeneous at all times.

To minimize the reaction time, we evaluated the reaction in MTBE at 45 °C anticipating that the chlorination would be complete before MTBE cleavage might occur. The MP10 pressure reactor was charged with MTBE and the starting diol **1** at 40 °C. Thionyl chloride was added over 30 min at 45 °C. The RC-1 heat flow results clearly indicate that the addition of thionyl chloride is exothermic under these conditions (red curve Figure 1).

The heat flow curve (in red) in Figure 1 indicates that the reaction is clearly not "feed controlled" as evidenced by the *en-masse* exotherm after a significant amount of thionyl chloride had accumulated in the reactor (estimated at 80% on the basis of the volume added to the reactor). This then reacted spontaneously and resulted in a serious, uncontrolled outgassing from the reaction mixture as shown by the pressure curve (in green) in Figure 1. The outgas was tentatively identified as a mixture of sulfur dioxide, the expected byproduct of the chlorination reaction and isobutylene resulting from acid-catalyzed decomposition of MTBE.

Support for this conclusion came from a separate experiment using the Omnical CRC90e calorimeter. Significant outgassing is observed when concentrated HCl is mixed with MTBE at 40 °C which strongly supports the presence of isobutylene as one of the components in the outgas. The calculated "worst-case temperature rise" (Tad) of 25 °C indicates that a final reaction temperature of 65 °C can be attained if the entire charge of thionyl chloride was ac-

cidentally added, coupled with loss of cooling and stirring. This exceeds the reflux temperature of MTBE (55−56 °C). These results, coupled with the uncontrollable outgassing of isobutylene and sulfur dioxide, represent a serious chemical reaction safety hazard and therefore were not scaled up. We were not able to conclusively establish the reason for the induction period observed during these and other similar reaction conditions. One possibility is that a change in the solubility of **1** in the presence of excess thionyl chloride could contribute to the observed induction period. Alternatively, the reaction of **1** with thionyl chloride could afford an intermediate cyclic sulfite **3** that is then converted to **2**.[13] Sharpless and co-workers have described the facile synthesis of cyclic sulfites from acyclic vicinal diols (<10 min), using thionyl chloride in the presence of a base, for example, triethylamine or pyridine, at 0 °C.[14,15] Cyclic sulfites can also be prepared from acyclic vicinal diols and thionyl chloride at room temperature in the absence of base.[14] In addition, O'Brien and co-workers[16] isolated the cyclic sulfite of *o*-xylene-α, α-diol **5** in excellent yield from **4** using thionyl chloride at 0 °C. However, Berridge and co-workers[17] reported that cyclic sulfites in general were unreactive as substrates in nucleophilic substitution reactions. The heterogeneous nature of the reaction mixture rendered attempts to monitor it by FTIR unsuccessful. We have not further studied the precise mechanism for conversion of **1** to **2**.
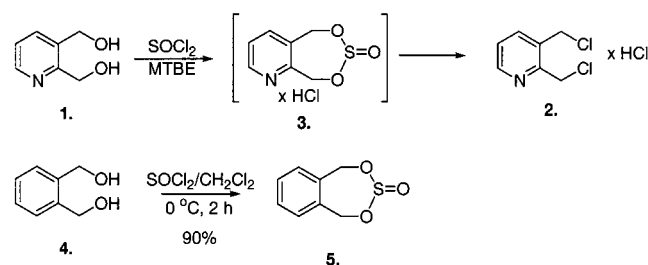
We next examined the reaction of **1** with thionyl chloride in MTBE at ambient temperature in an effort to control the vigorous outgassing. In this case the SVO1 reactor was charged with MTBE and the starting diol **1** at 20 °C. Thionyl chloride was added during 40 min at 25 °C. Once again the RC-1 heat flow results (green curve, Figure 2) shows an exothermic addition of thionyl chloride under these reaction conditions.

The heat flow curve in Figure 2 (green curve) indicates that the reaction is not "feed-controlled" and that unreacted thionyl chloride again accumulates in the reactor (red and orange curves in Figure 2). After approximately 20% of the thionyl chloride is added, the reaction initiates and exotherms. Two separate and distinct exothermic events are observed, with the second and major one initiating only after ca. two-thirds of the thionyl chloride is added. The calculated worst-case temperature rise (Tad) of 53 °C indicates that the final
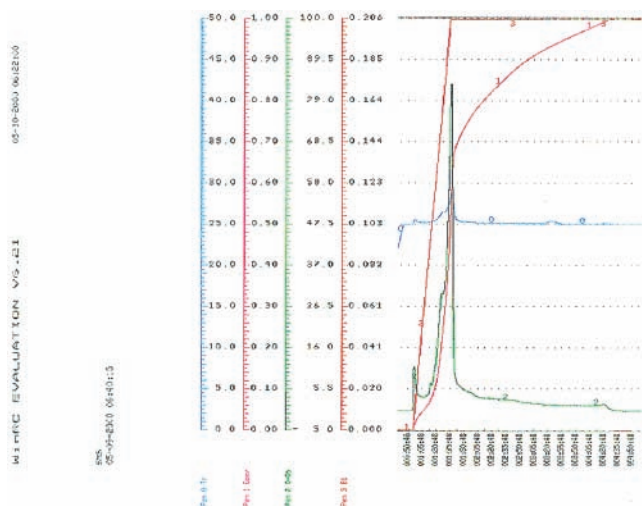
(13) We thank the editor for this suggestion.
(14) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538−7539.
(15) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 655−658.
(16) O'Brien, M. K.; Sledeski, A. W.; Truesdale, L. K. *Tetrahedron Lett.* **1997**, *38*, 509−512.
(17) Berridge, M. S.; Franceschini, M. P.; Rosenfeld, E.; Tewson, T. J. *J. Org. Chem.* **1990**, *55*, 1211−1217.

Figure 2. RC-1 heat flow curve for experiment in MTBE at 25 °C. (Blue) Reaction temperature T_r. (Red) Thermal conversion to product. (Green) Heat flow. (Orange) SOCl$_2$ addition.

reaction temperature can reach 78 °C if all of the thionyl chloride is charged with simultaneous loss of reactor cooling or stirring or both. This again significantly exceeds the reflux temperature of MTBE (55−56 °C). Additionally, under these conditions, the HCl generated from the reaction can result in isobutylene formation together with sulfur dioxide outgassing as observed previously. Therefore, a significant chemical reaction hazard still exists for these reaction conditions and they were not scaled up.

Substitution of toluene for MTBE would preclude any safety issues arising from solvent decomposition. In addition, we expected it to be inert under the reaction conditions and easily removed. We were gratified to find that the handling characteristics of **2** in toluene were comparable to those in MTBE and should permit ready scale-up of the reaction conditions. Therefore, toluene was selected as the solvent for the next reactions.

The SV01 reactor was charged with toluene and the starting diol **1** at 25 °C. Thionyl chloride was added during 40 min at 25 °C. Most surprisingly, there was no reaction at 25 °C as evidenced by the heat flow results from the RC-1 (green curve, Figure 3). Only after the entire charge of thionyl chloride had been added and the reaction mixture was warmed to 45 °C did the reaction initiate. Unfortunately, this batch process again occurs spontaneously and results in uncontrollable sulfur dioxide outgassing. Thus, these conditions were not acceptable for scale-up.

We then raised the reaction temperature to 45 °C in an attempt to initiate the reaction immediately upon addition of SOCl$_2$. In this case the SV01 reactor was charged with toluene and the starting diol **1** at 45 °C. Thionyl chloride was then added during 40 min, while maintaining the temperature at 45 °C. The RC-1 heat flow results (Figure 4) again indicate that the reaction still did not fully initiate after addition of 1 equivalent of thionyl chloride as evidenced by the heat flow exotherm (green curve in Figure 4).

Again, as the second equivalent of SOCl$_2$ was added, the reaction occurred spontaneously. The addition of thionyl chloride was exothermic under these conditions and was not
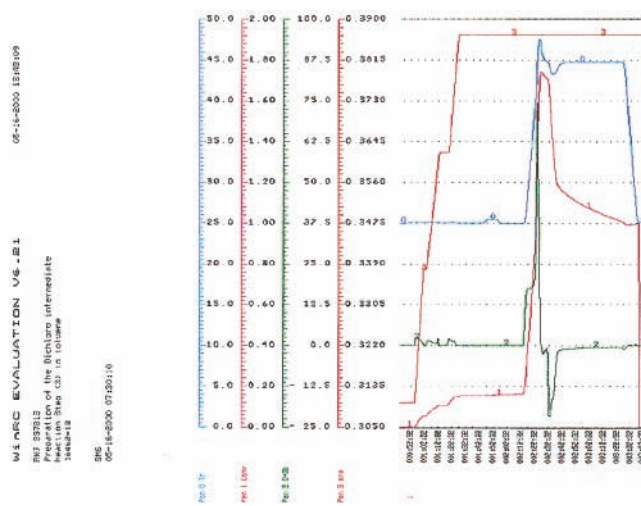
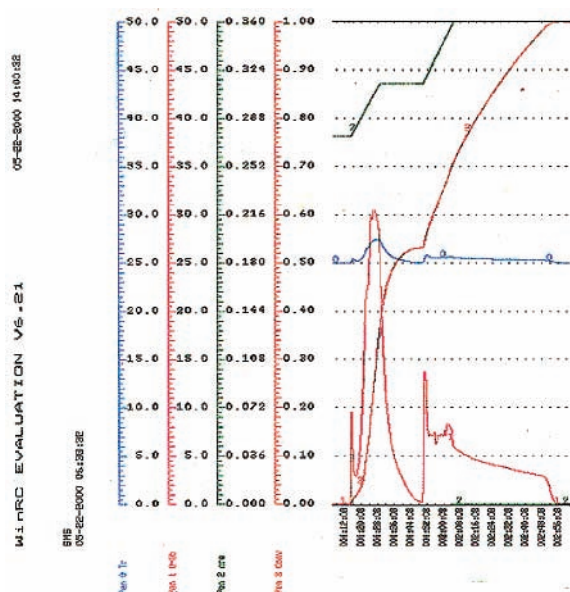**Figure 3.** RC-1 heat flow curve toluene experiment at 25 °C. (Blue) Reaction temperature T_r. (Green) Heat flow. (Orange) SOCl$_2$ addition. (Red) Thermal conversion to product.
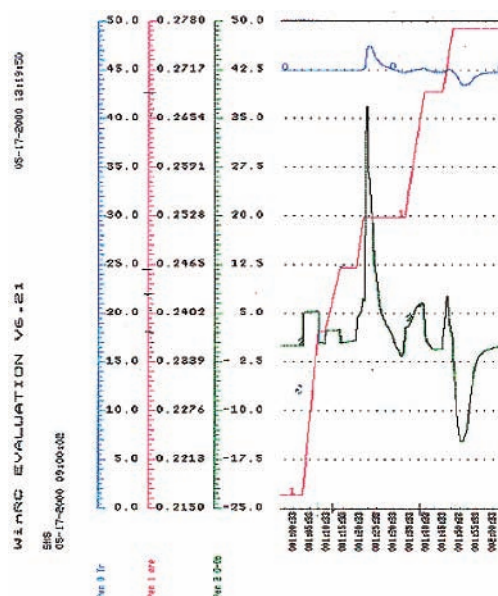
Figure 4. RC-1 heat flow curve toluene experiment at 45 °C. (Blue) Reaction temperature T_r. (Red) SOCl$_2$ addition. (Green) Heat flow.

feed-controlled. The calculated worst-case temperature rise (Tad) was 23 °C, suggesting that the final reaction temperature could reach 68 °C if there is a loss of cooling/stirring with full accidental charge of the thionyl chloride. This final Tad temperature was well below the reflux temperature of toluene (111 °C). However, this was still a batch process that occurs spontaneously at 40−45 °C. This concern together with the large volumes of sulfur dioxide that are generated spontaneously in an uncontrolled manner precluded scale-up of these reaction conditions as well.

We expected that a feed-controlled reaction profile for the addition of thionyl chloride would permit control of the expected exotherm and sulfur dioxide outgassing. In addition, we wanted to investigate the affects, if any, of a more reactive chlorinating reagent on the troublesome induction period we had encountered thus far in both MTBE and toluene. Therefore, we modified the reaction conditions to incorporate
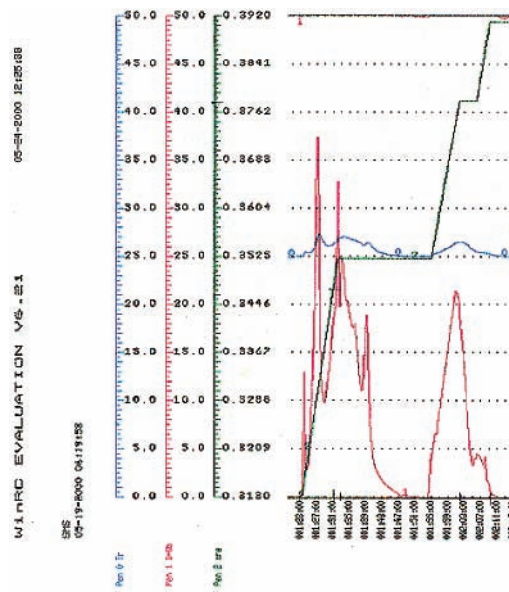
Figure 5. RC-1 heat flow curve for MTBE−DMF experiment at 25 °C. (Blue) Reaction temperature T_r. (Red) Heat flow. (Green) SOCl$_2$ addition. (Orange) Thermal conversion to product.

Figure 6. RC-1 heat flow curve toluene−DMF experiment at 45°C. (Blue) Reaction temperature T_r. (Red) Heat flow. (Green) SOCl$_2$ addition.

a catalytic amount of DMF to effect chlorination under mild conditions via the well-known Vilsmeier−Haack complex.[18,19] For example, *N,N*-dimethylchloromethaniminium chloride cleanly converts nucleosides to 5′-chloro-5′-deoxy-analogues.[20,21] Similarly, this same reagent chlorinates primary, secondary, and benzylic alcohols in very high yield at room temperature.[22] Recently, 4-cyano-2-fluorobenzyl chloride was prepared from the alcohol via this reagent.[23]

MTBE was used as the solvent but now containing 1% v/v dimethylformamide (DMF) to initiate chlorination via in situ generated *N,N*-dimethylchloromethaniminium chloride. The SV01 reactor was charged with MTBE, 1% v/v DMF, and the starting diol **1** at 25 °C. Thionyl chloride was added in two portions over 20 min at 25 °C. The RC-1 heat flow results (Figure 5) indicate that the addition of the first equivalent of thionyl chloride is exothermic as evidenced by the heat flow exotherm (red curve in Figure 5). The exotherm is somewhat feed-controlled and the reaction initiated once the thionyl chloride feed started. Here, use of a more reactive chlorinating reagent seemed to be effective to preclude the induction period we had encountered previously. Overall, we observed a more classically feed-controlled process for the addition of the of thionyl chloride which resulted in a more controlled heat generation and outgassing as the reaction progressed.

Visually, the outgassing (SO$_2$) appears to be much more controlled under these conditions. However, the calculated worst-case temperature rise (Tad) for the entire addition is

still 50 °C. As with the previous cases, an accidental charge of all of the thionyl chloride with concomitant loss of cooling/stirring would still significantly exceed the reflux temperature of MTBE. This, coupled with the HCl-catalyzed decomposition of MTBE above 45 °C poses the same significant safety concerns, and therefore, these conditions were also abandoned for scale-up.

On the basis of these results (vide supra) we concluded that MTBE is not an acceptable solvent for this chlorination reaction under any conditions we evaluated.

The last reaction conditions investigated employed toluene as the solvent containing 1% v/v dimethylformamide (DMF). The SV01 reactor is charged with toluene, 1% v/v DMF, and the starting diol **1** at 25 °C. Thionyl chloride is added in three portions at 25 °C during approximately 45 min. The RC-1 heat flow results indicate that the reaction does initiate at 25 °C (Figure 6).

Although the addition of the SOCl$_2$ is exothermic under these conditions, it is still not completely feed-controlled as the heat flow curve indicates (red curve in Figure 6). However, the calculated worst-case temperature rise (Tad) is only 20 °C, indicating that the final reaction temperature could reach 45 °C if there is a loss of cooling/stirring combined with an accidental charge of thionyl chloride. This final Tad temperature is well below the reflux temperature of toluene. In addition, the reaction is reasonably well controlled under these conditions, and a moderate evolution of sulfur dioxide is not observed visually until the second equivalent of SOCl$_2$ is added. As noted earlier, the use of toluene as the solvent completely precludes the complication of isobutylene formation. Therefore, these reaction conditions were recommended for and successfully scaled up to multikilogram quantities (see Experimental Section).

Conclusions

On the basis of the reaction calorimetry results the reaction conditions employing thionyl chloride and 1% v/v DMF in

(18) Vilsmeier, A.; Haack, A. *Chem. Ber.* **1927**, *60*, 119.
(19) Giles, P. R.; Marson, C. M. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995; Vol. 3, pp 2045−2047.
(20) Dods, R. F.; Roth, J. S. *Tetrahedron Lett.* **1969**, 165.
(21) Dods, R. F.; Roth, J. S. *J. Org. Chem.* **1969**, *34*, 1627.
(22) Yoshihara, M.; Eda, T.; Sakaki, K.; Maeshima, T. *Synthesis* **1980**, 746.
(23) Kimura, Y.; Suzuki, H.; Takao, Y. Jpn. Kokai Tokkyo Koho JP 2001172247, 2001; *Chem. Abstr.* **2001**, *135*, 61145.

toluene were found to be safe for scale-up. We also reduced the amount of thionyl chloride required to a slight excess, thereby minimizing disposal of excess reagent. As a result, we have identified an economical, environmentally acceptable, and safe process that has been scaled up to produce >3.0 kg of **2** in 89% yield.

Further, this "simple" chlorination is much more complex than initially believed. We have identified conditions using thionyl chloride in MTBE as particularly hazardous owing to solvent decomposition in the presence of HCl and subsequent outgassing of large amounts of isobutylene.

Experimental Section:

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All reagents and solvents were used as received from commercial sources. 2,3-Pyridinedicarboxylic acid dimethyl ester was purchased from Polycarbonate Industries. Nonaqueous reactions were performed under an atmosphere of nitrogen. NMR spectra were recorded on a Bruker 300 MHz spectrometer; chemical shifts are expressed on the δ scale and are in ppm downfield of the internal standard tetramethylsilane (TMS). Spectra were recorded in d_6-DMSO or CDCl$_3$. HPLC were obtained using a Hewlett-Packard HP 1100 equipped with a photodiode array detector. Mass spectra were recorded on a Hewlett-Packard series 1100 MSD. A Finnigan Navigator AQA LC/MS instrument was used to obtain LC/MS data. Elemental analyses were performed by QTI (Whitehouse, NJ).

2,3-Bis(hydroxymethyl)pyridine Hydrochloride, (1).[24] A 22-L (4N) flask was equipped with an air stirrer, nitrogen inlet, 2-L addition funnel, and a thermocouple. The flask was blanketed with nitrogen and sequentially charged at room temperature with 6.5 L of ethanol, 2,3-pyridinedicarboxylic acid dimethyl ester (890 gm, 4.56 mol) and sodium borohydride. The resulting thin yellow suspension was stirred and cooled to −5 to 0 °C. A solution of calcium chloride (447.5 gm, 4.03 mol) in ethanol (2.75 L) was added slowly, while maintaining the temperature at <5 °C. After the addition, the reaction mixture was allowed to slowly warm to ambient temperature and was judged to be complete after 2 h by HPLC analysis. The reaction mixture was quenched with 3.6 L of 50:50 aqueous ethanol after which it was evaporated to recover a yellow solid that was dried in a vacuum (28 in. Hg) overnight at room temperature. The crude product was ground to a powder and transferred to a 22-L (4N) flask. Ethanol (16 L) was added and the suspension heated to reflux and held for 1.0 h. Agitation was stopped and the suspension cooled to ambient temperature whereupon the slightly turbid ethanolic solution of crude diol was transferred to a 22-L (3N) flask. After this solution cooled to 10 °C, it was saturated with HCl$_{(g)}$ to precipitate **1** as a white solid. The product was collected by filtration and washed, first with a small volume of ethanol and then with MTBE. After air-drying for several hours the product was dried in a vacuum (28 in. Hg) at room-temperature overnight

to afford 2,3-bis(hydroxymethyl)pyridine·HCl, **1** (352.0 gm, 44.0%) as a white solid of 88.6 wt % purity (HPLC). A second crop of **1** (205 gm, 25%) was isolated as a white solid of 99.0 wt % purity by reworking the mother liquors from above. These crops were combined and used immediately without further purification.

2,3-Bis(chloromethyl)pyridine Hydrochloride, (2): Neat Thionyl Chloride. A 1-L three-neck Morton flask was equipped with a reflux condenser, nitrogen inlet, and thermocouple. Thionyl chloride (81.55 gm, 0.686 mol) was charged and cooled to 7.0 °C under nitrogen. 2,3-Bis(hydroxymethyl)-pyridine hydrochloride, **1** (39.59 gm, 0.227 mol), was added as a single portion with stirring. The temperature of the resulting thick, white paste quickly reached 29 °C. An ice bath was used to cool the suspension to 16 °C as all of the starting diol dissolved. The reaction mixture was stirred for an additional 35 min (post addition of the diol), at which time the reaction was judged complete by HPLC analysis. During this time the product precipitated as a white solid. The suspension was diluted with 100 mL of MTBE and was cooled to 2−3 °C in an ice bath. The suspension was filtered and the white filter cake was washed with 100−200 mL of MTBE. The filter cake was dried in a vacuum (28 in. Hg) at room temperature overnight to afford 2,3-bis(chloromethyl)-pyridine hydrochloride, **2** (46.01 gm, 96%), as a white solid of 97.0 wt % purity (HPLC). Mp 150.0−152.0 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 10.64 (1H, br s, NH$^+$), 8.68 (1H, dd, Ar H), 8.19 (1H, dd, Ar H), 7.65 (1H, dd, Ar H), 5.03 (2H, s, ArCH$_2$), 5.01 (2H, s, ArCH$_2$). HRMS: Calcd for C$_7$H$_8$Cl$_3$N: 176.0034; Found: 176.0034.

2,3-Bis(chloromethyl)pyridine Hydrochloride, (2): 1% (v/v) DMF in Toluene. A 12-L (4N) flask was equipped with an air stirrer, nitrogen inlet, reflux condenser, 1-L addition funnel, and a thermocouple. The flask was blanketed with nitrogen and charged at room temperature sequentially with toluene (5.85 L), 2,3-bis(hydroxymethyl)pyridine·HCl, **1** (972.5 g, 5.5 mol), and DMF (50 mL, 0.65 mol). The resulting mobile, white suspension was chilled to ca. 15 °C, and thionyl chloride (940 mL, 6.45 mol) was added via the addition funnel over 90 min, during which time the temperature rose to 26 °C. At this point the original suspension was now a white, somewhat tacky, heterogeneous mixture. As this mixture was heated to 45 °C, most of **1** dissolved to afford a cloudy solution. Heating was discontinued at this time, and the reaction mixture was cooled to ambient temperature during ca. 1.5 h. HPLC analysis of an aliquot at this time showed no residual **1**. The reaction mixture was chilled to 5 °C, and ethyl acetate (1500 mL) was added to aid in crystallization of the product. The solids were filtered, washed with MTBE (1500 mL), and air-dried overnight on the filter to afford 2,3-bis(chloromethyl)pyridine hydrochloride, **2** (1161 gm, 92.4%), as a white solid of 93.6 wt % analysis (HPLC). MS: [M + H]$^+$ = 176, 178. Anal. Calcd for C$_7$H$_8$Cl$_3$N: C, 39.56; H, 3.79; N, 6.59; Cl, 50.05, Found: C, 39.50; H, 3.77; N, 6.50; Cl, 48.72.

(24) This procedure was modified from that used for reduction of 2,3-pyridinedicarboxylic acid diethyl ester. See: Matsumoto, I.; Yoshizawa, J. Jpn. Kokai Tokkyo Koho JP 49020181, 1974; *Chem. Abstr.* **1974**, *81*, 120469.