Note

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A Method for Small-Scale Production of Deuterochloroform

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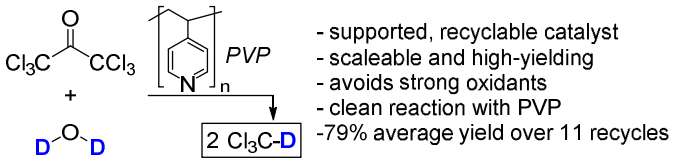
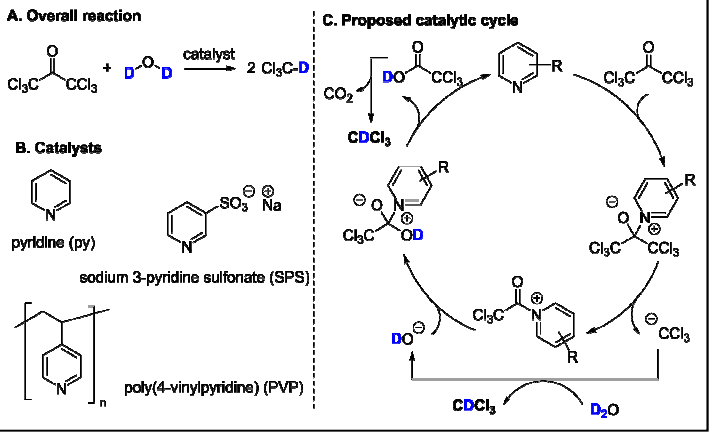


Abstract

Deuterochloroform ($CDCl_3$) is a common deuterated solvent for nuclear magnetic resonance (NMR) analyses. The synthesis of significant amounts of $CDCl_3$ for both research use and large undergraduate organic laboratories in a safe and inexpensive manner is appealing. Herein, we describe a convenient laboratory scale preparation of $CDCl_3$ that employs a reduction and decarboxylation of hexachloro-2-propanone (HCP) catalyzed by various pyridines. A PVP catalyst gives cleaner reaction and greater catalyst stability through multiple rounds of recycling, justifying its higher cost compared to pyridine.

Deuterochloroform ($CDCl_3$) is the primary solvent employed for NMR analyses and can constitute a significant expense for many organic laboratories. For institutions with large undergraduate organic lab courses, the cost associated with purchasing $CDCl_3$ may limit the quantity of experimentation or the extent of chemical analysis that can be used on a regular basis. In an industrial setting, $CDCl_3$ is typically produced through a haloform reaction between deuterated acetone/ethanol and an alkali metal hypochlorite,[1] or by treatment of chloral hydrate with sodium deuteroxide.[2] Previous reports of laboratory-scale synthesis of $CDCl_3$ using D_2O as an inexpensive deuterium source employ either Na metal or sodium peroxide, both of which have safety concerns for use on larger scales.[3,4] While convenient, the conversion of $CHCl_3$ to $CDCl_3$ with catalytic NaOD uses a large excess of D_2O and delivers only moderate yields.[5] We thus sought to develop an inexpensive and operationally simple protocol capable of producing $CDCl_3$ in a continuous, rather than batch, process. We also desired to utilize relatively non-toxic reagents with no major safety concerns, minimize the amount of the deuterium source required, have the capability to recycle the catalyst, and improve the overall yield of $CDCl_3$ compared to current methods.

Scheme 1. Reaction of hexachloro-2-propanone to $CDCl_3$ using pyridine-based catalysts.



In 1964, Paulson and Cooke reported the use of pyridine as an effective catalyst for the synthesis of $CDCl_3$ via the reduction and decarboxylation of hexachloro-2-propanone (HCP) using D_2O as the deuterium source (Scheme 1A).[6] We felt this system held promise for meeting our requirements for a simple and economical approach to the synthesis of $CDCl_3$ for common laboratory use if catalyst recycling could be employed.

Pyridine (py), sodium 3-pyridine sulfonate (SPS), and poly(4-vinylpyridine) (PVP) (Scheme 1B) were selected for comparison. SPS and PVP are the least expensive pyridine alternatives that are non-miscible

with $CDCl_3$, a useful feature for facile recycling. SPS is exclusively soluble in deuterium oxide (D_2O), while PVP is heterogeneous.

A benefit of utilizing SPS and PVP over pyridine is their relative safety and lower toxicity. The Globally Harmonized System of Classifications has noted the acute toxicity for pyridine in terms of oral, inhalation, and dermal contact.[7,8] In contrast, SPS and PVP have less specific or lower toxicity, with the exception of target organ toxicity by PVP (see the SI for details). The lower volatility of solid SPS and PVP, as compared to pyridine, allow these catalysts to be safely handled by less experienced researchers.

Reaction set-up. In these studies, the reaction vessel was charged with HCP, D_2O, and catalyst, as indicated in Table 1. The flask was slowly heated to the temperature specified; the three catalysts require three different reaction temperatures. Reaction with pyridine occurred at 65 °C, while SPS required heating to 105 °C, as the electron-withdrawing sulfonate group decreased the nucleophilicity of the catalyst. The heterogeneous PVP catalyst required a temperature of 85 °C, due to its lower solubility. The reaction was initiated when the vapor temperature reached 35° C and was concluded when the distillate temperature of the distillate returned to room temperature (25° C). The potential for recycling was assessed by running the reaction an additional seven times using the original catalyst. For each new run, a stoichiometric amount of D_2O was added, along with a fresh aliquot of HCP. Subsequent reactions were deemed complete when the vapor temperature dropped back to 25° C, or when the reaction time exceeded twice the initial batch time.

Table 1. Amounts of reagent and catalyst used.

Catalyst	Catalyst amount	HCP	Initial D_2O	2nd aliquot D_2O	temperature
pyridine	0.491 g (6.20 mmol)	13.25 g (50.05 mmol)	2.00 g (99.9 mmol)	1.00 g (50.0 mmol)	65 °C
SPS	1.124 g (6.20 mmol)	13.25 g (50.05 mmol)	3.00 g (150. mmol)	1.00 g (50.0 mmol)	105 °C
PVP	1.0 g (0.017 mmol)	13.25 g (50.05 mmol)	2.00 g (99.9 mmol)	1.00 g (50.0 mmol)	85 °C

A benefit to SPS and PVP over pyridine is the ease of removal of $CDCl_3$ from the reaction mixture. In the case of pyridine, an initial distillation is required to remove $CDCl_3$ from the vessel; however, if a convenient short-path distillation set-up is employed, a subsequent purification is required to remove residual pyridine. Due to their higher boiling points, neither SPS nor PVP co-distills with $CDCl_3$; thus, only a single distillation is needed to remove pure $CDCl_3$ from the mixture. The catalyst remains in the reaction vessel, where it can be charged with additional reagents for recycling. A simple Dean-Stark distillation could be employed with SPS and PVP to minimize the amount of D_2O required in the reaction. The potential for recycling these catalysts was assessed by running the reaction ten more times using the original catalyst, which remained in the flask, and simply adding a stoichiometric amount of D_2O and a fresh aliquot of HCP to the reaction vessel itself.

Depending on the identity of the pyridine-based catalyst, certain precautions were taken during to minimize by-product formation or exothermic reactions. Potential S_N2 reaction between the activated α-chlorines of HCP and pyridine were minimized by adding the catalyst slowly to a mixture of HCP and D_2O. The pyridine catalyst was injected slowly into the reaction mixture following assembly of the distillation apparatus. To preserve reagent usability for demonstrating catalyst recyclability, both the pyridine and SPS-catalyzed reaction mixtures were stored in the dark in the refrigerator at 10 °C until a fresh charge of HCP and D_2O could be added.

In the case of SPS (Table 1), additional D_2O was used for the reaction, as the catalyst is a salt that does not easily dissolve in HCP. The heterogeneous PVP also presented experimental challenges. In some cases, the temperature of the vapor phase dropped, even when the reaction was incomplete. This suggested the reaction promoted by PVP may happen in 'bursts', rather than in a continuous process,

perhaps due to the heterogeneous nature of the catalyst. The temperature in the reaction vessel was not allowed to exceed 90° C to prevent bumping. After completion of the reaction, the remaining PVP was cooled, removed from the reacting vessel, washed with acetone, and stored in an oven at ~100 °C.

Results. A control reaction using pyridine as the catalyst was conducted to establish the procedure necessary to collect the pure $CDCl_3$ in optimal yield,[6] and assess the possibilities for recycling the catalyst. Once these benchmark studies were completed, similar reactions were run employing SPS and PVP to compare and contrast the various catalyst systems.

In reactions catalyzed by pyridine (Figure 1A), the yield of $CDCl_3$ decreased as the catalyst was recycled in subsequent batches. By the time Batch 8 was reached, the experiment showed no production of $CDCl_3$ within 3 h. NMR characterization of the product $CDCl_3$ showed that some pyridine distilled over along with the desired $CDCl_3$ in the range of 2 mol % to 8 mol %. Thus, the losses in yield as the number of batches increases were attributed to loss of the catalyst due to co-distillation, as well as decomposition products resulting from undesired background reaction of the pyridine with the HCP.

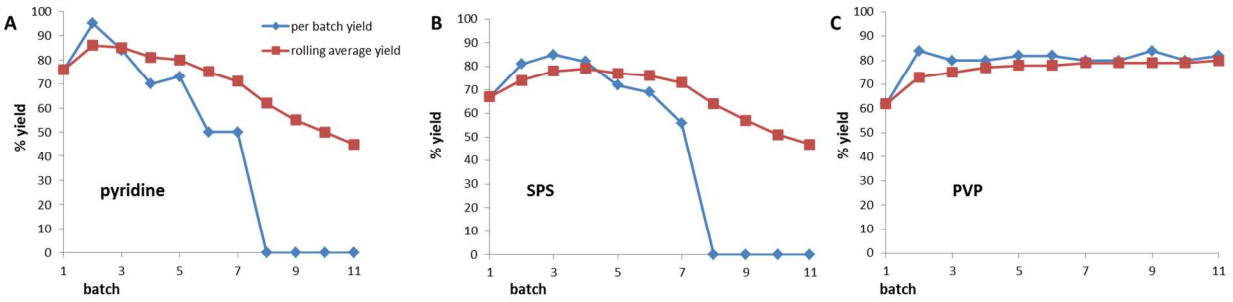


Figure 1. Yields per batch and rolling average yield using: **A**) pyridine as the catalyst; **B**) SPS as the catalyst; and **C**) PVP as the catalyst. Each catalyst was subjected to 11 recycles.

Reactions catalyzed by SPS (Figure 1B) exhibited a similar trend as the pyridine-catalyzed reaction (Figure 1A); however, SPS delivered a higher yield of $CDCl_3$ over the same number of batches. In contrast to reactions catalyzed by pyridine, no impurities were seen in the $CDCl_3$ product by either ^1H or ^{13}C NMR spectroscopy. The reason for the relatively quick drop in yield for the reactions catalyzed by either pyridine or SPS is hypothesized to be due to formation of a pyridinium salt resulting from the S_N2 reaction of the catalyst with HCP. This reasoning is supported by the formation of insoluble, dark brown solid, which accumulates as the batch number increases. Mixing stoichiometric amounts of HCP and pyridine resulted in the formation of a similar solid.

The use of the heterogeneous PVP catalyst (Figure 1C) resulted in the formation of no by-products as ascertained by NMR spectroscopy, similar to initial batches using SPS as the catalyst. However, in contrast to pyridine and SPS, PVP gave reproducibly high yields through 11 cycles!

Comparing the utility of the three catalysts. All three catalysts produce $CDCl_3$ in similar yield over a single batch; however, the catalysts differ in terms of their recyclability. The pyridine and SPS catalysts quickly lost their efficacy, becoming inactive after 7 batches. Impurities from side reactions were noted with both catalysts; in addition, a column was required for distillation of $CDCl_3$ formed using pyridine, while higher reaction temperatures were needed for reactions employing SPS. In contrast, the heterogeneous PVP was recycled multiple (11) times with little by-product formation, displays consistently higher overall yields and an overall yield of 79% over the 11 batches, and shows greater stability as compared to pyridine and SPS. Another advantage of PVP is the ease of operation, requiring only a Dean-Stark trap for the distillation; the periodic introduction of fresh reagents into the reaction vessel enables the continuous production of $CDCl_3$. While the costs of reagents will obviously change over time, a current cost-volume-profit (CVP, see the SI for details) analysis shows all three catalysts require recycling to beat the commercial price of $CDCl_3$. The pyridine-catalyzed reaction requires 2

recycles to be economically viable, while the SPS- and PVP-catalyzed reactions require 4 batches to be economically viable; the higher cost of PVP compared to pyridine is readily accommodated by its greater stability, recyclability and ability to be used for the continuous production of $CDCl_3$.

Experimental Section

General Information. All components of the reaction apparatus were washed first with deionized (DI) water, followed by acetone, and then dried overnight in an oven at 130 °C. If necessary, any grease present on the ground-glass joints was removed by washing with hexane prior to rinsing with DI and acetone. To ensure that no water is present in the reaction, the glassware was flame-dried immediately before use and cooled under nitrogen. Chemical reagents were purchased from Sigma-Aldrich. The D_2O was used fresh, the PVP dried overnight at 80 °C in an oven and the hexachloroacetone distilled over P_2O_5 into a flask containing 3 Å molecular sieves.[9] These precautions minimize the amount of protiated chloroform in the final product. ^{1}H NMR NMR spectra were obtained at 25 °C using a Bruker 400 MHz NMR spectrometer. For ^{1}H NMR, chemical shifts are reported relative to residual protiated solvent peaks (δ 7.26, 2.49, 7.15 and 4.80 ppm for $CDCl_3$, $(CD_3)_2SO$, C_6D_6 and CD_3OD respectively). ^{13}C NMR spectra were measured at 100 MHz on the same instrument noted above for recording ^{1}H NMR spectra. Chemical shifts were reported in accordance to residual protiated solvent peaks (δ 77.0, 39.5, 128.0 and 49.0 ppm for $CDCl_3$, $(CD_3)_2SO$, C_6D_6, and CD_3OD, respectively). Accurate mass measurements were acquired at the University of Wisconsin, Madison using a Micromass LCT (electrospray ionization, time-of-flight analyzer or electron impact methods).

Synthesis of $CDCl_3$ catalyzed by pyridine. A three-neck, 50-mL round bottom flask was charged with HCP (13.25 g, 50.05 mmol, 1.0 equiv), followed by D_2O (2.00 g, 100 mmol, 2.0 equiv, 99.9 atom%). A magnetic stir-bar was added to the reaction vessel and the central ground glass joint was equipped with a distillation head, fractionating column, Liebig condenser, thermometer and a cooled collection flask. The entire system was then flushed with nitrogen gas before the remaining two ground glass joints were stoppered with rubber septa. The flask was slowly heated to 65 °C, during which time, 12 mol % of pyridine (0.49 g, 6.20 mmol, 0.5 mL) was added through the rubber septum using a syringe. Bubbling was observed to occur shortly after the introduction of pyridine and the reaction solution turned a progressively darker brown color, due to formations of side products. The temperature was maintained at 65 °C as the distillation progressed. Distillation was continued until the vapor temperature of the distillate dropped back to 25 °C. The collected distillate could contain small amounts of pyridine and D_2O, depending on the height and type of distillation column. The immiscible D_2O was removed from the $CDCl_3$ using a separatory funnel and returned to the reaction vessel. Trace amounts of pyridine were removed through an additional distillation. The remaining material in the reaction vessel was allowed to cool and subsequent batches initiated by adding 1 equivalent of D_2O (1.00 g, 50.0 mmol) to the reaction vessel through the septum, followed by a stoichiometric amount of HCP (13.25 g, 50.05 mmol). The order of addition is critical to minimize impurity formation resulting from the SN2 reaction of pyridine with HCP. The yields for batches 1-7 were 76% (9.2 g, 76 mmol), 95%, 84%, 70%, 73%, 50%, and 50%, respectively, after which no further product was obtained, presumably due to catalyst decomposition.

Synthesis of $CDCl_3$ catalyzed by SPS. A 50-mL round bottom flask was charged with HCP (13.25 g, 50.05 mmol, 1.0 equiv), followed by D_2O (3.00 g, 150 mmol, 3.0 equiv). A magnetic stir-bar was added to the reaction vessel, followed by 12 mol % SPS (1.124 g, 6.20 mmol, 0.12 equiv). The central ground glass joint was equipped with a 10 mL Dean-Stark apparatus and a Liebig-condenser. To the Dean-Stark trap was added D_2O (1.00 g, 50.0 mmol, 1.0 equiv). The entire system was then flushed with nitrogen gas. The flask was slowly heated to 105 °C and maintained at that temperature throughout the distillation. The distillation was continued until no more $CDCl_3$ was being collected in the Dean-Stark trap. The collected distillate sometimes contained small amounts of D_2O, which were removed from the $CDCl_3$ using a separatory funnel and then returned to the reaction vessel. The organic phase was then dried over sodium sulfate to remove any remaining D_2O. The remaining material in the reaction vessel was allowed to cool

and subsequent batches initiated by adding 1 equivalent of D_2O (1.00 g, 50.0 mmol) to the reaction vessel, followed by a stoichiometric amount of HCP (13.25 g, 50.05 mmol). The yields for batches 1-7 were 67% (8.1 g, 67 mmol), 81%, 85%, 82%, 72%, 69%, and 56%, respectively, after which no further product was obtained, presumably due to catalyst decomposition.

Synthesis of $CDCl_3$ catalyzed by PVP. A 50-mL round bottom flask was charged with HCP (13.25 g, 50.05 mmol, 1.0 equiv), followed by D_2O (2.00 g, 100 mmol, 2.0 equiv). A magnetic stir-bar was added to the reaction vessel, followed by 19 mol % PVP (1.0 g, 0.017 mmol, 0.17 equiv). The central ground glass joint was equipped with a 10-mL Dean-Stark apparatus and a Liebig-condenser. To the Dean-Stark trap was added D_2O (1.00 g, 75.0 mmol, 1.0 equiv). The entire system was then flushed with nitrogen gas. The flask was slowly heated to 90°C and maintained at that temperature throughout the distillation. The distillation was continued until no more $CDCl_3$ was collected in the Dean-Stark trap. The collected distillate sometimes contained small amounts of D_2O, which were removed from the $CDCl_3$ using a separatory funnel and then returned to the reaction vessel. The organic phase was then dried over sodium sulfate to remove any remaining D_2O. The remaining material in the reaction vessel was allowed to cool and subsequent batches initiated by adding 1 equivalent of D_2O (1.00 g, 50.0 mmol) to the reaction vessel, followed by a stoichiometric amount of HCP (13.25 g, 50.05 mmol). The yields for batches 1-11 were 62%, 84% (10.1 g, 84 mmol), 80%, 80%, 82%, 82%, 80%, 80%, 84%, 80% and 82%.

Determining the purity of the $CDCl_3$ product. The purity of the $CDCl_3$ was determined to be 99.7% D by calculating the ratio of $CHCl_3$:$CDCl_3$ using a protiated internal standard via quantitative ^{1}H NMR, a deuterated internal standard via quantitative ^{2}H NMR, and ^{13}C-NMR spectroscopy.

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Supporting Information. Toxicity information, cost-volume-profit analysis and details for purity determination.

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