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# Iodobenzene Dichloride in the Esterification and Amidation of Carboxylic acids: In-Situ Synthesis of Ph<sub>3</sub>PCl<sub>2</sub>

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**Abstract:** A novel, in-situ synthesis of dichlorotriphenylphosphorane (Ph<sub>3</sub>PCl<sub>2</sub>) is accomplished upon combining PPh<sub>3</sub> and the easily prepared hypervalent iodine reagent iodobenzene dichloride, PhICl<sub>2</sub>. The phosphorane is selectively generated in the presence of carboxylic acid or alcohol residues to rapidly produce acid chlorides and alkyl chlorides in high yield. Addition of EtOH, PhOH, BnOH, Et<sub>2</sub>NH or CH<sub>2</sub>N<sub>2</sub> results in the direct synthesis of esters, amides and diazoketones from carboxylic acids.

#### Introduction

The conversion of carboxylic acids to acid chlorides is among the earliest transformations in organic synthesis, and remains a fundamental reaction. For over a century and a half, chemists have developed and employed organic (oxalyl chloride, (COCI)<sub>2</sub>) and inorganic (PCI<sub>5</sub>, SOCI<sub>2</sub>, etc.) reagents to effect this transformation. Curiously absent from the literature of acid chloride synthesis is PhICl<sub>2</sub> (1), the first hypervalent iodine reagent ever reported.<sup>[1]</sup> This easily prepared iodane has broad applicability in organic synthesis as an oxidant and chlorinating agent, and, like many hypervalent iodine reagents since reported, it enjoys a broad reactivity profile and mild, environmentally benign reaction conditions.<sup>[2]</sup> These favorable characteristics have resulted in strong interest in the synthetic community, with many new reports of its synthesis,<sup>[3]</sup> its use as an oxidant<sup>[3a,4,5]</sup> or a chlorinating agent,<sup>[6]</sup> and even its recyclability<sup>[7]</sup> within the last decade.

In addition to developing PhICl2-mediated chlorination reactions of diazo and hydrazone functional groups,<sup>[6b,c,g,h]</sup> we are also interested in using it in developing deoxygenative chlorination processes. Unlike oxalyl chloride, PCI<sub>5</sub> or SOCI<sub>2</sub>, iodane 1 does not engage in such chemistry; reactions with alcohols gives aldehydes<sup>[8]</sup> or ketones,<sup>[9]</sup> and reactions with carboxylic acids results in ligand metathesis on the iodane.<sup>[10]</sup> We were inspired by the recent work of Zhang and co-workers who showed that coupling reactions between carboxylic acids and alcohols or amines could be effected by the combination of iodosodilactone (2) and PPh<sub>3</sub> (Figure 1, a)).<sup>[11,12]</sup> Because 1 is so readily able to transfer chlorine to Lewis basic elements, we believed it should also do so with triphenylphosphine, which would constitute a novel synthesis of triphenylphosphine dichloride (3).<sup>[13]</sup> This phosphorane is a versatile deoxygenative chlorinating reagent popularized by Appel through the reaction that bears his name.  $^{\left[ 14\right] }$  Phosphorane 3 can be synthesized with Cl\_2, CCl\_4, COCl<sub>2</sub>, (COCl)<sub>2</sub> or  $C_2Cl_6$  etc,<sup>[13]</sup> but these reagents are either

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toxic, moisture sensitive or environmentally undesirable. Adapting the recyclable, hypervalent iodine-based chlorine gas surrogate to the synthesis of  $Ph_3PCl_2$  offers a mild and operationally simple means to access organic chlorides. We report here the in-situ synthesis of  $Ph_3PCl_2$  from  $Ph_3P$  and  $PhlCl_2$  that, in the presence of carboxylic acids and alcohols, results in smooth conversion to acid and alkyl chlorides.

#### Previous Work:

a) Esterification of carboxylic acids using iodosodilactone / PPh3



Figure 1. Esterification reactions based on hypervalent iodine /  $\mathsf{PPh}_3$  reagent mixtures.

#### **Results and Discussion**

We began our investigation by determining the feasibility and reaction rate of the chlorine transfer process in a time-lapse <sup>31</sup>P NMR experiment.<sup>[15]</sup> A mixture of PPh<sub>3</sub> (1.0 equiv), and PhICl<sub>2</sub> (1.2 equiv) was prepared in DCM; after 5 minutes we observed complete conversion to the phosphorane. Given the rate of the conversion, no competition was therefore expected from the carboxylic acid reacting with the iodane; however, since triphenylphosphine oxide was also observed so quickly, preventative measures to exclude atmospheric moisture were required.





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We investigated the feasibility of reacting the in situ-generated Ph<sub>3</sub>PCl<sub>2</sub> and carboxylic acids by screening a variety of reaction conditions using *p*-tolylacetic acid (4a) as the model substrate As the acid chloride was difficult to isolate, we (Table 1). trapped it by adding ethanol, giving ethyl p-tolylacetate (5a). The initial reaction combined phosphine, iodane and carboxylic acid in an equimolar ratio in DCM, which was stirred for 30 minutes at reflux, and afforded 5a in 81% yield (entry 1). Using a slight excess of the phosphorane caused the yield to increase to 92% (entry 2), and using a slight excess of 1 relative to phosphine and carboxylic acid gave a minor increase in product yield (entry 3). Maintaining this ratio of reagents and decreasing the temperature decreased product yield (entry 4); however when the reaction was repeated at reflux and terminated (by the addition of EtOH) after 10 minutes, the product was again recovered in excellent yield (entry 5). We tested the reaction in various common solvents and found that the reaction proceeded in high yield in toluene, THF, CHCl<sub>3</sub> and DCE, and proceeded poorly in DMF (entries 6-10). The rate and good to excellent vields observed demonstrate the ease and efficacy of the reaction, and confirm that there are no competitive side reactions between 1 and 4a.

Table 1. Optimization of the acid chloride synthesis.<sup>[a]</sup>

$\begin{array}{c} \begin{array}{c} \begin{array}{c} PhiCl_{2} (1) \\ PPh_{3} \\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ $						
Entry	Solvent	PPh₃ (equiv)	PhICl <sub>2</sub> (equiv)	Temp °C	Time (min)	Yield <sup>[b]</sup>
1	DCM	1	1	40	30	81%
2	DCM	1.2	1.2	40	30	92%
3	DCM	1	1.2	40	30	94%
4	DCM	1	1.2	rt	30	84%
5	DCM	1	1.2	40	10	93%
6	toluene	1	1.2	40	30	83%
7	$CHCl_3$	1	1.2	40	180	86%
8	DCE	1	1.2	40	120	77%
9	THF	1	1.2	40	30	84%
10	DMF	1	1.2	40	30	48%

[a] Reaction conditions: 1, PPh<sub>3</sub> and 4a are added to DCM and immersed in a 40 °C bath. The reaction is quenched by the addition of EtOH (1.5 mL). [b] Isolated yield.

We expanded the substrate scope of the reaction to investigate various carboxylic acid precursors and nucleophiles (Scheme 1). The aliphatic carboxylic acids (**4a-d**) all performed well in the reaction, whether they were trapped with EtOH, Et<sub>2</sub>NH, BnOH, PhOH or even (for **4a**) diazomethane. Pivalic acid (**4e**) was lower yielding, presumably due to steric hindrance. Two dicarboxylic acids were used in the reaction, and while **4f** was only moderately effective, **4g** underwent acid chloride formation

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**Scheme 1.** Substrate scope of esterification, amidation and diazoacylation reactions. [a] Isolated yields. [b] NMR yield based on internal standard HMDSO  $(O[Si(CH_3)_3]_2)$ .<sup>c</sup> 1.2 equiv of PPh<sub>3</sub> used.

and diesterification in 87% yield. The aryl carboxylic acids (**4h-j**) all performed well when trapped with EtOH, Et<sub>2</sub>NH or PhOH. Because PhICl<sub>2</sub> readily chlorinates alkenes, we were not surprised to find minor amounts of alkene chlorination product when excess **1** was used with **4k**.<sup>14</sup> Using an equimolar mixture of **1** and PPh<sub>3</sub> obviated this adventitious reactivity, and gave the esterification and amidation products (**5k**) in 72 – 81% yield.

Two additional carboxylic acids were investigated to determine the relative reactivity of alcohols and carboxylic acids (eq. 1, 2). Acid chloride formation on mandelic acid (4I) proceeded poorly, presumably due to competition with the alcohol. Conversely, COMMUNICATION

acid chloride formation on 4-hydroxybenzoic acid (4m) proceeded well, and gave 5m in 95% yield.



We also carried out chlorination reactions on benzylic and aliphatic alcohols (eq. 3-6). Both benzyl and *p*-methoxybenzyl alcohol reacted more slowly than did the carboxylic acids, but their conversion to the corresponding chlorides was clean and high yielding. Ethyl mandelate was converted to the chloride in excellent yield, supporting our suspicion that competition from the alcohol led to the decreased yield of **5I**, and (–)-menthol was converted to menthyl chloride in 72% yield.



#### Conclusions

In conclusion we have developed a novel, in-situ synthesis of Ph<sub>3</sub>PCl<sub>2</sub> from Ph<sub>3</sub>P and the hypervalent iodine reagent PhICl<sub>2</sub>. A time-lapse <sup>31</sup>P NMR experiment showed the chlorine transfer from iodane to phosphine to be rapid, though highly sensitive to atmospheric moisture. When synthesized in the presence of both saturated and unsaturated carboxylic acids, the ensuing acid chlorides underwent high-yielding esterification, amidation and diazoacylation reactions. Finally, when the phosphorane synthesis was carried out in the presence of benzylic alcohols, benzyl chlorides were observed in high yield.

#### **Experimental Section**

General procedure for acid chloride formation and trapping with EtOH: To an oven-dried 10 mL round bottom flask was added the carboxylic acid (1.0 eq) and dry DCM (1.5 mL), and the resulting solution was heated to reflux under nitrogen. PPh<sub>3</sub> (1.0 eq) was added, followed by PhICl<sub>2</sub> (1.2 eq), and the reaction was stirred for an additional 10 minutes at reflux. To this was then added ethanol (~10 eq) drop wise over 2 minutes, and the reaction was stirred for 30 minutes, by which time TLC analysis indicates the consumption of starting material. The crude reaction mixtures were concentrated by rotary evaporation and purified by column chromatography.

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**Keywords:** acid chloride • hypervalent iodine • Appel reaction • esterification • amidation

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Text: An in situ synthesis of dichlorotriphenylphosphorane  $(Ph_3PCl_2)$  was achieved via a chlorine transfer reaction between iodobenzene dichloride  $(PhICl_2)$  and  $PPh_3$ . When carried out in the presence of carboxylic acids, the resulting acid chlorides could be trapped with various nucleophiles. When carried out in the presence of alcohols, alkyl chlorides were produced.