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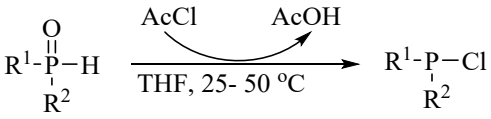

R^1, R^2 = aryl, alkyl

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Facial conversion of secondary phosphine oxides $R^1R^2P(O)H$ to chlorophosphines R^1R^2PCl by acetyl chloride

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ABSTRACT

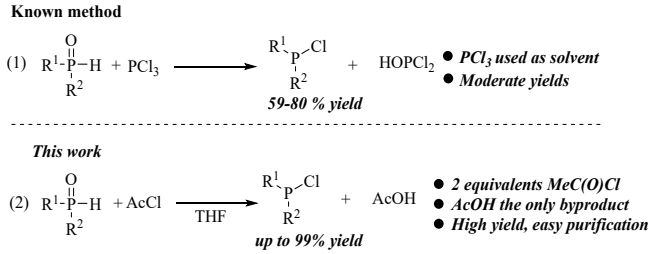
A practically useful protocol for the reductive transformation of secondary phosphine oxides $R^1R^2P(O)H$ to chlorophosphines R^1R^2PCl using acetyl chloride was disclosed. Various secondary phosphine oxides could be readily reduced to the corresponding chlorophosphines in high yields under mild conditions.

Keywords:
Chlorophosphines
Secondary phosphine oxides
Reductive conversion
Acyl chloride

Introduction

Chlorophosphines are key starting materials for the synthesis of trivalent phosphines, that have broad applications in organic synthesis as reagents and in metal-catalysis as ligands. For example, alkylation of chlorophosphines with organolithium or Grignard reagents was a general method for the preparation of a series of monodentate and bidentate phosphine ligands.[1] On the other hand, the corresponding phosphinoamine and phosphinites can also be easily obtained by the nucleophilic substitution reactions of chlorophosphines with amines[2] and alcohols.[3] Moreover, chlorophosphines can be also converted to the corresponding alkali metal phosphides R^1R^2PM, and subsequent substitution reactions with organic halides can generate a wide range of tertiary phosphines.[1c]

Among the chlorophosphines, perhaps diphenylphosphine chloride Ph_2PCl is one of the most frequently employed reagent for introducing a diphenylphosphino Ph_2P functionality to a molecular frame to generate the corresponding phosphine ligands. Industrially, Ph_2PCl is produced from benzene and PCl_3 in the presence of an equivalent of $AlCl_3$ under heating.[4] However, this process is inefficient because the generation of Ph_2PCl is accompanied by the formation of a lot of wastes such as HCl, $AlCl_3$ and a reagent used for deliberating Ph_2PCl from $AlCl_3$.[4a-d] Disproportionation reactions of $PhPCl_2$ with $ZnCl_2$ or Ph_3P also afford Ph_2PCl.[4e,f] However, heating at a very high temperature is required for this transformation. In addition, the preparation of $PhPCl_2$ also suffers from the same problems as mentioned for Ph_2PCl. Because of the rather severe conditions required for this disproportionation reaction, this method cannot be readily adopted in the laboratory synthesis.



Scheme 1. Preparation of chlorophosphines from secondary phosphine oxides.

Unlike tertiary phsophines R_3P that are easily oxidized under air, secondary phosphine oxides $R_2P(O)H$ can be easily handled under air without the need to pay attention to oxygen and moisture. Moreover, they are relatively easily prepared chemicals.[5] In particular, we very recently reported that

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Ph_2Pol) chemical waste $Ph_3P(O)$ at room temperature.[5d]

In this sense, using $R_2P(O)H$ as the substrate for R_2PCl preparation should be a convenient alternative laboratory method. Quin et al. reported that secondary phosphine oxides $R_2P(O)H$ could be converted into R_2PCl using PCl_3 as the chlorination reagent,[6] which has been widely used in the preparation of phosphine ligands.[7] However, this method has drawbacks such as the requirement of a large excess amount of PCl_3 (10 equivalents to P(O)H) and the difficult purification of the products (Scheme 1 (1)).

During our studies on the reactivity of secondary phosphine oxides, we accidently found that Ph_2PCl could be quantitatively generated by simply treating $Ph_2P(O)H$ with MesC(O)Cl (Mes: 2,4,6-trimethylphenyl). Eventually, we realized that, instead of the expensive MesC(O)Cl, the cheap and readily accessible acetyl chloride AcCl was an efficient reagent for this transformation. Herein, we disclose a facial transformation of secondary phosphine oxides $R^1R^2P(O)H$ to chlorophoshpines R^1R^2PCl by using acetyl chloride as the reductive chlorination reagent (Scheme 1 (2)). Compared to the literature method using PCl_3, this method using acetyl chloride AcCl possesses advantages such as low toxicity, corrosiveness and less amounts of the chlorination reagents as well as easy purification and high yield of the products.

Results and discussion

Initially, a mixture of diphenylphosphine oxide **1a** (0.05 mmol) and mesityl chloride (0.06 mmol) in THF (0.5 mL) in a sealed NMR tube was heated at 100 °C overnight. As indicated by ^{31}P NMR spectroscopy, a new signal at 82.8 ppm assignable to Ph_2PCl was observed and 85% yield of Ph_2PCl was generated (Table1, run 1). Under similar conditions, when we increased the amount of mesityl chloride to 0.1 mmol (2.0 equivalents to **1a**) (Table1, runs 2 and 3), Ph_2PCl was obtained in 94% yield. At low temperatures, however, only low yields of the product were obtained (Table1, runs 4–7). Then we decided to investigate the reactivity of other acyl chlorides (Table1, runs 8–10), and found that the simplest acetyl chloride showed highest reactivity for this reductive chlorination reaction (Table1, run 10). The effect of solvent was also investigated (Table1, runs 11–13). Solvents like 1,4-dioxane and toluene could also be used in this transformation. Dichloromethane gave 77% yield of the product under similar conditions (Table1, run 13). To avoid potential safety problems at high temperatures, we then tried to conduct the above reaction again under mild conditions. To our surprise, such a reductive transformation smoothly proceeded even at room temperature by using acetyl chloride AcCl (Table1, runs 14–15). The reaction could also take place smoothly with less loadings of acetyl chloride (Table1, runs 16-18) under room temperature. However, in order to obtain a high yield (over 90%) of the desired product Ph_2PCl, the use of a slightly higher temperature 50 °C was preferred. Therefore, after the above comprehensive evaluation on the reaction conditions, the reaction conditions by using THF as solvent and 2.0 equivalents of acetyl chloride were chosen as the optimized parameters for this reaction.

Table 1. Reaction condition optimization[a]

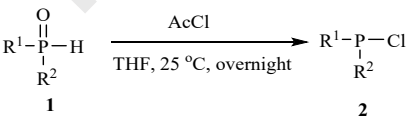
1a **2a**

Run	R	RC(O)Cl (equiv.)	Solvent	Tempt./°C	Yield/%
1	Mes	1.2	THF	100	85
2	Mes	1.6	THF	100	87
3	Mes	2.0	THF	100	94
4	Mes	2.0	THF	80	73
5	Mes	2.0	THF	70	48
6	Mes	2.0	THF	60	30
7	Mes	2.0	THF	50	8
8	Ph	2.0	THF	100	25
9	^{i}Pr	2.0	THF	100	90
10	Me	2.0	THF	100	97
11	Me	2.0	Dioxane	100	99
12	Me	2.0	Toluene	100	92
13	Me	2.0	CH_2Cl_2	100	77
14	Me	2.0	Dioxane	25	95
15	**Me**	**2.0**	**THF**	25	**95**
16	Me	1.5	THF	25	82(95)[b]
17	Me	1.2	THF	25	81(94)[b]
18	Me	1.0	THF	25	66(92)[b]

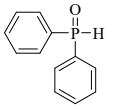
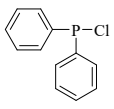
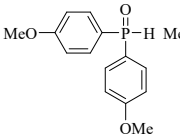
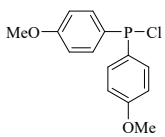
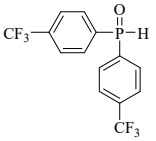
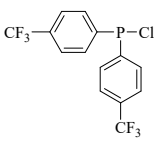
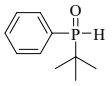
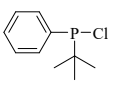
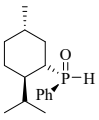
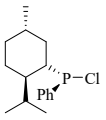
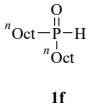
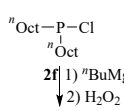
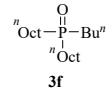
[a]Ph$_2$P(O)H (0.05 mmol) was dissolved in 0.5 mL solvent in an NMR tube. RC(O)Cl was added and the mixture was heated overnight at the temperature indicated. Yield refers to ^{31}P NMR yield based on **1a** used (Mes: 1,3,5-trimethylphenyl). [b]The yields in parenthesis were obtained at 50 °C.

As shown in Table 2, to explore its generality, a variety of representative secondary phosphine oxides (SPOs) were used as

Table 2. Ready conversion of secondary phosphine oxides by acetyl chloride to chlorophosphines.[a]



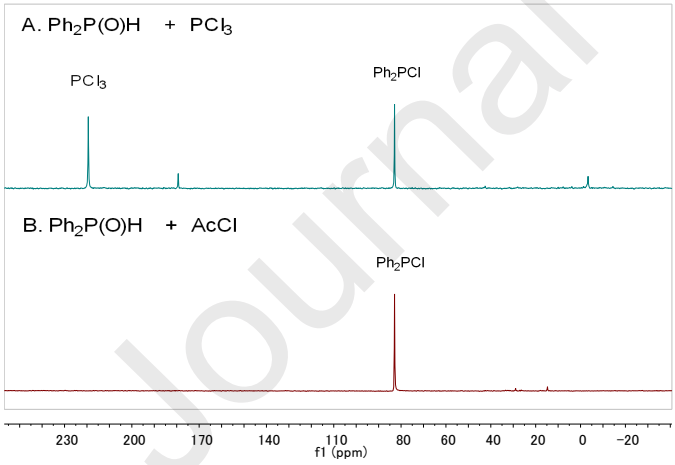
1 **2**

Run	$R^1R^2P(O)H$ (**1**)	R^1R^2PCl (**2**)	Yield
1	 **1a**	 **2a**	93%
2	 **1b**	 **2b**	87%
3[b]	 **1c**	 **2c**	96%
4	 **1d**	 **2d**	94%
5[c]	 **1e**	 **2e**	98%
6	 **1f**	 **2f** 1) ^{n}BuMgCl 2) H_2O_2  **3f**	70%[d] 66%[e]

[a]Rea… dissolved in 2.0 mL THF, and then MeC(O)Cl (2.0 mmol) was added to the solution. The mixture was stirred at room temperature overnight, and volatiles were removed under vacuum. Yields were based on **1** used. [b]50 °C. [c] A diastereomeric pure (-)menthylphenylphosphine oxide $R_{(P)}$-**1e** was used. 1 hour. **2e** obtained as a 74/26 mixture of diastereomers (SI). [d]0°C, 1 h. [e]Treating **2f** with ^{n}BuMgCl and then H_2O_2.

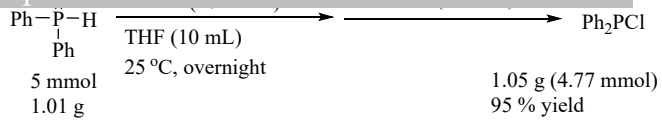
the reagents for this transformation. Both aromatic and aliphatic SPOs were all readily reduced to the corresponding phosphine chlorides with excellent yields under similar reactions. For example, in addition to $Ph_2P(O)H$ **1a** (Table 2, run 1**)**, aromatic SPOs bearing an electron-denoting group (p-MeO-$C_6H_4)_2P(O)H$ **1b** and an electron-withdrawing group (p-CF_3-$C_6H_4)_2P(O)H$ **1c**, all were reduced to the corresponding phosphine chlorides in high yields (Table 2, runs 2–3). The conversion of an alkylarylphosphine oxide like Ph*t*-BuP(O)H **1d** also could proceed smoothly to produce the corresponding P-Cl products in a nearly quantitative yield (Table 2, run 4**)**. Similarly, a chiral (R_P)-(-)menthylphenylphosphine oxide **1e** could also efficiently produce the corresponding chlorophosphine **2e** as a mixture of diastereomers (run 5) (SI ref. 10). Moreover, dioctyl phosphine oxide n-$Oct_2P(O)H$ also reacted with MeC(O)Cl quickly to give n-Oct_2PCl (Table1, run 6). Since the high reactivity of n-Oct_2PCl, the confirmation of its formation was carried out by quenching the reaction mixture using n-BuMgCl, following oxidation with hydrogen peroxide to produce the corresponding stable butyldioctylphosphine oxide **2f** (66% isolated yield). However, diethyl phosphite $(EtO)_2P(O)H$ and ethyl phenylphosphinate Ph(EtO)P(O)H sluggishly reacted with AcCl even at a high temperature (120 °C).

Although treating $Ph_2P(O)H$ with 2 equivalents of PCl_3 and AcCl in THF all can lead to the formation of Ph_2PCl (Scheme 2), the reaction with AcCl is cleaner than that of PCl_3 which is accompanied by the formation of a few phosphorus by-products. In addition, AcOH generated using AcCl, if necessary, can be easily pumped off from the chlorophosphines under vacuum to give highly pure chlorophosphines (Scheme 1 (2)).



Scheme 2. ^{31}P NMR spectroscopies of the reaction mixture of $Ph_2P(O)H$ with PCl_3 (**A**) and AcCl (**B**), respectively.

To further demonstrate the utility of the current reaction, as shown in Scheme 3, a gram-scale transformation of $Ph_2P(O)H$ to Ph_2PCl was conducted by stirring 1.01 g $Ph_2P(O)H$ with 2 equivalents of AcCl in 10 mL THF at room temperature overnight. After the reaction, volatiles were removed under a reduced pressure (100 Pa) to afforded spectroscopically pure Ph_2PCl in 95% yield.[8]



Scheme 3. Gram-scale preparation of Ph_2PCl from $Ph_2P(O)H$ and AcCl.

Conclusions

In summary, we have developed a convenient method for the synthesis of chlorophosphines from secondary phosphine oxides and acetyl chloride under mild conditions. After the reaction, a simple removal of the volatiles under vacuum affords the target R_2PCl in spectroscopically pure form as confirmed by ^{31}P and ^1H NMR spectroscopies. Various secondary phosphine oxides, diarylphosphine oxides, alkyl(aryl)phosphine oxides and dialkylphosphine oxides, all could be used as the substrates, and were reduced readily to the corresponding phosphine chlorides in high yields.

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Supplementary Material

Supplementary data was associated with this article.

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8. A bulb to bulb distillation of the resulted pale yellow oil (160 ^{o}C, 160 Pa) gave pure Ph_2PCl as a colorless oil in 70% yield (0.77 g, 3.50 mmol).