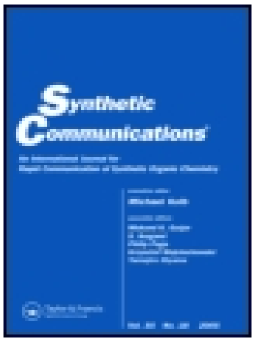

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PhPOCl$_2$ as A Potent Catalyst for Chlorination Reaction of Phenols with PCl$_5$

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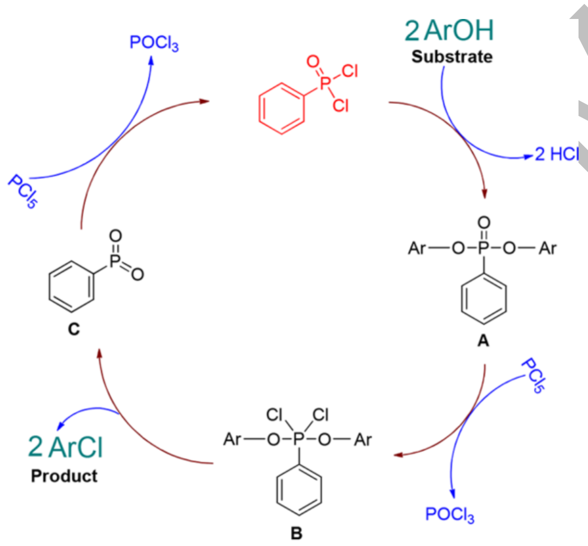
Abstract

Phenols are easily converted to the corresponding aryl chlorides by using phosphorus pentachloride (PCl$_5$) and the catalytic amount of phenylphosphonic dichloride (PhPOCl$_2$) , which is a new efficient method for synthesis of aryl chloride in good yields.

GRAPHICAL ABSTRACT:



◆ A rare example of PhPOCl$_2$ act as a catalyst
◆ A new efficient for synthesis of aryl chloride in good yields

KEYWORDS: chlorination reaction; phenols; aryl chloride; phosphorus pentachloride; phenylp-hosphonic dichloride

INTRODUCTION

A series of chlorinated aromatic hydrocarbons are important intermediates for synthesis of organic fine chemicals, such as dyes, drugs, and pesticides [1].They have versatile applications in carbon-carbon bond-forming reactions, such as cross-coupling reaction with organic boranes[2-4] and Grignard reaction with carbonyl compounds[5-7]. Very few methods have been reported in the literature for converting phenols directly into arylhalides. Bestmann's team[8] have observed that chlorobenzene can be obtained from phenol via a phenylchloroformate intermediate which produced by reaction with phosgene. This intermediate can be treated with triphenylphosphine , producing chlorobenzene in 67% yield by elimination of carbon dioxide. Moreover, Wiley[9] and Heinz[10] have found that halogenated benzene could be prepared from phenol by using triphenyl-phosphine dihalide. Recently, Bay and coworkers[11] have a discovery that phenylphosphorus tetrachloride (PPTC) is an excellent reagent for converting phenol into chlorobenzene. But in these above cases, expensive stoichiometric phosphorus-based halogenating agents are used, which reduce their atom efficiency and complicate the purification process. Since the generation of phenylphosphine oxides as a stoichiometric by-product is inevitable in the process, the development of a more efficient protocol still remains highly important and challenging. Now in our work, we have developed a novel system for chlorination to increase atom efficiency which is applicable to a wide range of phenols. In the process, PCl_5 is used as chlorination reagent under the catalysis of $PhPOCl_2$ to afford the target product. The amount of the $PhPOCl_2$ is around 10 mol% of the substrate. The reactions were described in Scheme 1.

RESULTS AND DISCUSSION

We began our study with 2-methoxyphenol as a model substrate. $POCl_3$, $SOCl_2$, PCl_5 or $PhPOCl_2$ was used as chlorination reagents which were cheap and generally available in laboratory, but the results showed that 2-chloroanisole was obtained in very poor yield. While Ph_3PCl_2, Ph_3PCl_4, Ph_3P/CCl_4 were used in this reaction, complex mixtures were formed in most cases. In the course of our trial, we were lucky enough to find 2-methoxyphenol could be converted 2-chloroanisole by treatment with the mixture of PCl_5 and $PhPOCl_2$. Moreover, in the late of our work we were surprised to find that a high yield for the chlorination of 2-methoxyphenol (Table 1) could be maintained when decreasing the molar ratio of the mixed reagent ($PhPOCl_2/PCl_5$), and the optimal catalyst loading was 10 mmol%. It seemed that the $PhPOCl_2$ plays a role as catalyst in the reacting system.

To validate this assumption, 2-Methoxyphenol was treated with PCl_5 alone (Table 1, entry 2), nothing was happened. When it was treated with $PhPOCl_2$ only (Table 1, entry 1), no target product was found, and yet a new substance appeared. The compound could then be isolated and proven to be phenylphosphonic acid diphenylester ($PhPO(OPhOMe\text{-}o)_2$). To our surprised, 2-chloroanisole was isolated in high yield while PhPO ($OphOMe\text{-}o)_2$ was heated with PCl_5. Base on the above experiments, a mechanism was proposed for the reaction of phenols with PCl_5 and $PhPOCl_2$ (Scheme 2). The $PhPOCl_2$ reacted with phenols to give phenyl phosphate diester(A), A was then reacted with PCl_5 to form the intermediate B, which can decomposed to yield the desired aryl chloride and phenylphosphineoxid(C). Finally, $PhPOCl_2$ was reformed from compound C by reaction with PCl_5. Meanwhile, we investigated the effects of the amount of chlorinating agent based on the above reaction mechanism. Taking 2-methoxyphenol as a model substrate, the results were showed in Table 2. The yield didn't improve dramatically by increasing the amount of chlorinateing agents. As a consequence, the optimal molar ratio for substrate/PCl_5/$PhOPOCl_2$ is (1 : 1.1 : 0.11).

Reaction condition: 2-methoxyphenol (100 mmol), Reaction temperature: 160℃, reaction time: 5h; ^{b} $n_1 : n_2 : n_{3=}$ n(Substrate) : n (PCl_5) : n ($PhPOCl_2$)

Then the optimized reaction conditions were tested on a variety of substrates, and our results showed that the substituted phenols readily undergone hydroxyl displacement. These data were recorded in Table 3.

Reaction condition: Substrate (100 mmol); Reaction temperature: 160℃, reaction time: 5h; The Molar ratio of Substrate/ $PhPOCl_2$ /PCl_5 is (1.0:0.11:1.1); ^{a} the molar ratio of Substrate/ $PhPOCl_2$ /PCl_5 is (1.0:0.33:3.3).

Phenols containing electron-withdrawing groups or electron-donating groups could be converted into the corresponding aryl chloride in high yield by our methods(entries 1-5). And the hydroxyl of pyridine derivatives (entries 8,9,10,11) were also effectively replaced by chloride group. In addition, the carboxyl group on the aromatic ring (entries 6,7,10,11) was easily converted into trichloromethyl group in the meantime, which were consistent with the results of H. B. Chen and Y.B. LIN's work in terms of carboxyl group[12].

CONCLUSION

In conclusion, the present investigation has demonstrated that the use of $PhPOCl_2$ /PCl_5 offers a simple, novel, efficient and convenient method for the conversion of phenols to their corresponding aryl chlorides.

EXPERIMENTAL

The ^{1}HNMR spectra were recorded on AVANCE AV (400MHz) FTNMR Digital spectrometer with $CDCl_3$ as the solvent, TMS as the internal standard; the IR spectra were measured on a Nicolet Vatar 370 spectrometer with KBr film; the mass spectra were obtained with Agilent GC: 6890N/MS:5973I. All the chemicals were of analytical grade or chemically pure. Products (a-j) are known compounds and their spectral data can be found in the literature[13-21].

General Procedure (Taking The Synthesis Of Compound I As An Example)

A mixture of 2-Hydroxypyridine-3-carboxylic acid (100.0 mmol), phenylphosphonic dichlo-ride (33.0 mmol) and phosphorus pentachloride (330.0 mmol) was slowly heated to 160 °C while distilled the by-product ($POCl_3$). Then the mixture was stirred at the same temperature for 5 hours. TLC analysis showed the reaction had been finished. The $POCl_3$ was evaporated in vacuum and the residue was poured into ice water, and it was neutralized with saturated aqueous sodium carbonate solution, and extracted with acetic ether. The organic layer was washed with water, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure , the obtained crude product was distilled or purified with silica gel chromatograph.

2-Chloro-3-Trichloromethylpyridine (Compound I)

R=COOH, X=N, yield:72.0%.^{1}HNMR (400 MHz, $CDCl_3$) δ: 8.51 (t, J = 6.6 Hz, 2H), 7.39 (dd, J = 7.9, 4.8 Hz, 1H). IR (KBr) ,ν,cm^{-1}: 1564.0 (C=C), 1074.6 (C-Cl). 759.6 (-C-Cl_3). GC-MS, m/z: 231.0 $[M]^+$, 194.0 $[M\text{- }Cl]^+$, 159.1$[M\text{-}2Cl]^+$, 124.1 $[M\text{-}3Cl]^+$, 97.1$[M\text{-}4Cl]^+$.

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Table 1. Effect of Phenylphosphonic dichloride on the reaction to aryl chlorides [a]

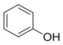
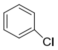
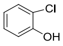
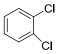
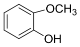
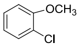
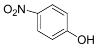
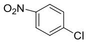
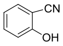
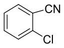
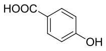
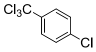
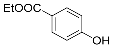
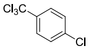
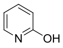
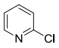
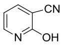
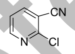
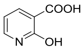
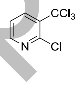
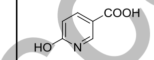
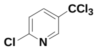
Entry	Substrate	molar ratio [e]	yield %
1	2-Methoxyphenol	0.0:1.0 [b]	0.0%
2	2-Methoxyphenol	1.0:0.0 [c]	0.0%
3	2-Methoxyphenol	1.0:0.05 [d]	42.1%
4	2-Methoxyphenol	1.0:0.1 [d]	73.0%
5	2-Methoxyphenol	1.0:0.2 [d]	72.7%
6	2-Methoxyphenol	1.0:0.5 [d]	73.5%
7	2-Methoxyphenol	1.0:1.0 [d]	72.8%

[a] Reaction condition: 2-methoxyphenol (100 mmol), reaction temperature: 160℃, reaction time: 5h; [b] PCl_5(0 mmol) , $PhPOCl_2$ (125 mmol); [c] PCl_5(125 mmol) , $PhPOCl_2$ (0 mmol); [d] PCl_5(125 mmol); [e] Molar ratio is PCl_5/ $PhPOCl_2$.

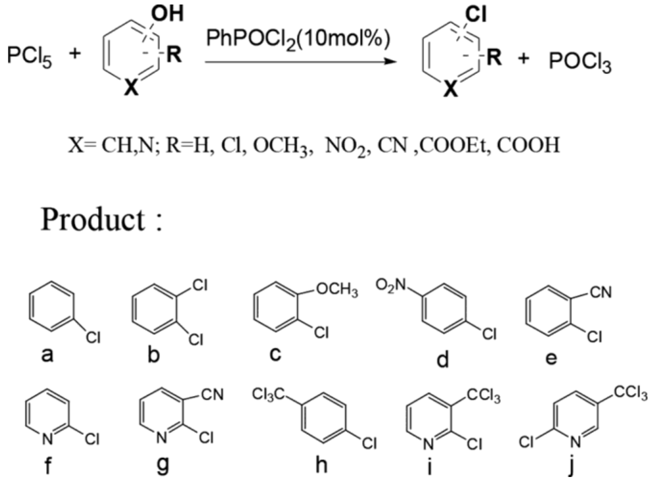
Table 2 Effect of chlorinating agent on the reaction

$n_1 : n_2 : n_3$ [b]	1:0.8:0.08	1:0.9:0.09	1:1:0.1	1:1.1:0.11	1:1.2:0.12
Yield/%	60.3	72.9	74.4	73.3	72.5

Table 3 Substrate Scope

Entry	Starting material	Product	yield %
1			75.4
2			76.3
3			73.3
4			79.4
5			76.3
6			64.9 [a]
7			54.6 [a]
8			96.5
9			94.6
10			72.0 [a]
11			70.5 [a]

Scheme 1. Synthesis of chloroaromatics from phenols catalyzed by $PhPOCl_2$.



Scheme 2. Possible mechanism of phosphorus-based catalytic reaction