http://dx.doi.org/10.5012/bkcs.2011.32.9.3486

Efficient Amidation and Esterification of Phosphoric Acid Using Cl_3CCN/ Ph_3P

Atthapol Kasemsuknimit, Apuri Satyender,† Warinthorn Chavasiri,* and Doo Ok Jang†,*

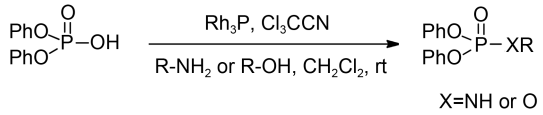
*Department of Chemistry, Faculty of Science and Center for Petroleum, Petrochemicals and Advanced Materials, Chulalongkorn University, Bangkok 10330, Thailand. *E-mail: warintho@yahoo.com*
*†Department of Chemistry, Yonsei University, Wonju 220-710, Korea. *E-mail: dojang@yonsei.ac.kr*
Received July 6, 2011, Accepted July 20, 2011

Key Words : Amidation, Esterification, Phosphoramides, Phosphates, Trichloroacetonitrile

In organophosphorous chemistry, phosphoryl amides and esters are important due to their broad ranges of biological properties and presence in bioactive molecules, such as natural products, amino acid analogues, pharmacological agents, and synthetic precursors.[1] These phosphate motifs are often used as prodrugs to enhance the water solubility[2a] or therapeutic potential of parent drugs.[2b-d] Phosphoramides play significant roles in modern organic chemistry, as they can be used in enantioselective catalytic processes that are activated by Lewis bases,[3] including aldol additions[4] and allylation reactions.[5] An important use of dialkyl, dibenzyl, and diphenyl phosphoramidates is protecting amino groups.[6] Phosphoric acid esters are among the most valuable substances in material and medicinal chemistry. Owing to their widespread use, general and convenient access to these compounds is desirable.

Numerous chemical approaches can synthesize phosphoramides, for example alcoholysis of phosphoramidic acid dichloride,[7] reacting *N*,*N*′-dialkyl phosphoramidic dichloride with sodium methoxide,[8] amidating phosphorochloridate[9] and *O*,*O*′-dialkyl phosphorocyanidate,[10] Lewis acid-catalyzed phosphorimidate rearrangement,[11] and reducing *N*-phosphoryl imines.[12] These methods, however, have intrinsic problems, including harsh reaction conditions, low yields, and hazardous materials. Typical methods for generating alkyl phosphates rely on reacting an alkyl halide with corresponding dialkyl/trialkyl phosphites,[13] directly esterifying phosphoric acid,[14] or treating phosphorochloridate with alcohol.[15] Although some of these methods are easy to carry out in a laboratory, most require long reaction times, strong bases, high temperatures, or tedious work-ups. Thus, there is a great demand to develop a practical method to synthesize phosphoryl amides and esters.

Combined used of trichloroacetonitrile and triphenylphosphine is a versatile chlorinating system that is used to prepare amides and esters *in situ* from aromatic carboxylic acids and sulfonic acids.[16] We hypothesized that this chlorinating agent could amidate and esterify phosphoric acids. To continue our previous work developing novel methodologies, we report a mild, efficient, one-pot procedure to synthesize of *N*-alkyl phosphoramides and alkyl phosphates using Ph_3P and Cl_3CCN (Scheme 1).



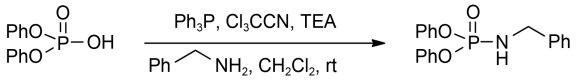
Scheme 1

Initially, we amidated diphenyl phosphoric acid, using benzyl amine as a model to establish optimal reaction conditions. To do so we chlorinated diphenyl phosphoric acid (1 equiv) using Ph_3P (2 equiv) and Cl_3CCN (3 equiv), and subsequently reacted with benzyl amine (1.15 equiv) and triethyl amine (TEA) (3 equiv) in dichloromethane at room temperature. This reaction generated an 81% yield of diphenyl benzylphosphoramidate (Table 1, entry 1). Increasing the reaction time increased the yield to 88% (Table 1, entry 2). The highest yield (93%) was obtained when we used 2 equivalents each of Ph_3P and Cl_3CCN for 1.5 h (Table 1, entry 4).

After establishing the optimal reaction conditions to amidate diphenyl phosphoric acid, we investigated the generality and scope of this reaction using various aliphatic amines, as summarized in Table 2. All aliphatic amines gave excellent phosphoramidate yields. Aniline, however, had low yield, likely because of its low nucleophilicity. Alicyclic and cyclic secondary amines had somewhat higher yields than primary amines. The relative reactivity of all aliphatic amines was consistent with a mechanism involving the –NH moiety attacking the phosphorous atom of the phosphate group.

This reaction can also amidate other phosphorylated compounds (Scheme 2). Diphenyl phosphine oxide and

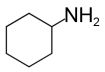
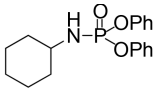
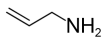
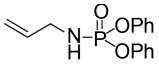
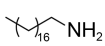
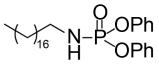
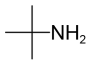
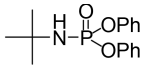
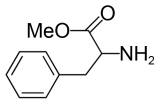
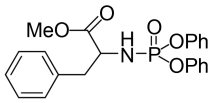
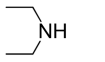
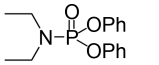
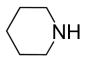
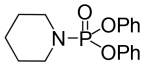
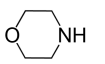
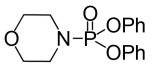
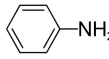
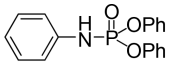
Table 1. Amidation of diphenyl phosphoric acid with benzyl amine under various reaction conditions[a]



Entry	Cl_3CCN (equiv)	Ph_3P (equiv)	Time (h)	Yield (%)[b]
1	3	2	1.5	81
2	3	2	2.0	88
3	2	2	2.0	89
4	2	2	1.5	93

[a]Reaction conditions: Diphenyl phosphoric acid (1 mmol), CH_2Cl_2 (6 mL), benzylamine (1.15 mmol) and TEA (3 mmol) at room temperature for 1.5 h. [b]Isolated yield.

Table 2. Syntheses of various *N*-alkyl phosphoramides from diphenyl phosphoric acid[a]

Entry	Amine	*N*-Alkyl phosphoramide	Yield (%)[b]
1			90
2			88
3			78
4			89
5			87
6			93
7			94
8			95
9			53

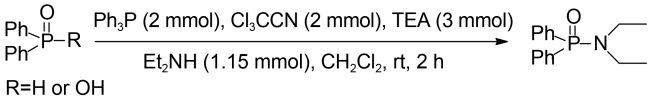
[a]All compounds were characterized by NMR, IR, and MS. [b]Isolated yield.

diphenyl phosphinic acid reacted with diethyl amine under these conditions, generating amides in 83% and 78% yields, respectively.

Next, we applied this methodology to the general synthesis of alkyl phosphates from diphenyl phosphoric acid. Firstly, we established the optimal reaction conditions by examining different mole ratios of reagents, bases, and reaction times (Table 3). Treating Ph_3P (2 equiv), Cl_3CCN (3 equiv) and *n*-butanol (1.5 equiv) with diphenyl phosphoric acid in the presence of pyridine generated the highest yield (92%) of ester (Table 3, entry 6). Other bases, such as TEA (Table 3, entry 4) and imidazole (Table 3, entry 7), were equally effective for affording esters.

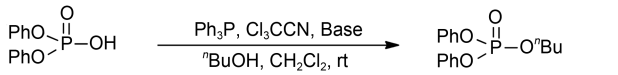
Based on our preliminary results, a number of other alcohols were tested under optimal reaction conditions to evaluate the scope and limitations of this reaction (Table 4). Primary and secondary alcohols reacted smoothly and produced high product yields, whereas tertiary alcohols were too bulky and did not react efficiently (Table 4, entry 10). All of the esters were characterized and confirmed with ^1H and ^{13}C NMR, IR, and mass spectrometry.

In conclusion, we developed a simple, convenient, one-pot



Scheme 2

Table 3. Esterifying diphenyl phosphoric acid with *n*-butanol under various reaction conditions[a]

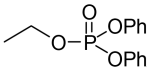
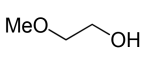
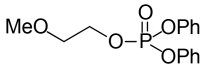
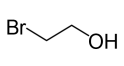
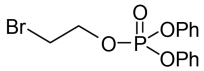
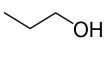
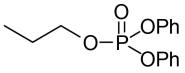
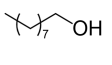
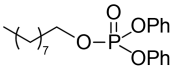
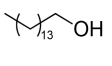
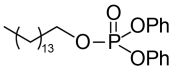
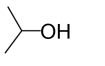
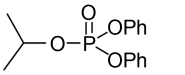
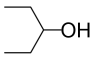
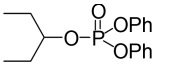
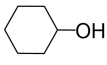
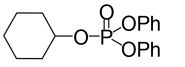
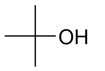
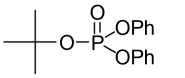


Entry	Cl_3CCN (equiv)	Ph_3P (equiv)	Time (h)	Base	Yield (%)[b]
1	2	2	2.0	TEA	50
2	3	2	3.0	TEA	70
3	3	2	4.0	TEA	78
4	3	2	5.5	TEA	86
5	2	2	5.5	pyridine	83
6	3	2	5.5	pyridine	92
7	3	2	5.5	imidazole	83
8	3	2	5.5	4-picoline	51

[a]Reaction conditions: Diphenyl phosphoric acid (1 mmol), CH_2Cl_2 (6 mL), *n*-butanol (1.3 mmol), and base (3 mmol) at room temperature. [b]Isolated yield.

synthetic method to synthesize phosphoramides and phosphates. This protocol has many attractive features, such as mild reaction conditions, short reaction times, and operational simplicity.

Table 4. Syntheses of various alkyl diphenyl phosphates from diphenyl phosphoric acid[a]

Entry	Amine	Alkyl phosphate	Yield (%)[b]
1			93
2			90
3			81
4			92
5			91
6			89
7			88
8			86
9			85
10			trace
11			78

[a]All compounds were characterized by NMR, IR, and MS. [b]Isolated yields.

Experimental Section

Typical Experimental Procedure for Phosphoramides. A solution of triphenylphosphine (530 mg, 2 mmol) in CH_2Cl_2 (3 mL) was added to a mixture of diphenyl phosphoric acid (250 mg, 1 mmol) and trichloroacetonitrile (200 mL, 2 mmol) in CH_2Cl_2 (3 mL) at room temperature. The mixture was stirred for 30 min. A mixture of amine (1.15 mmol) and triethylamine (0.42 mL, 3 mmol) was added to the above mixture. The reaction mixture was stirred for another 1 h at room temperature and monitored with TLC. When the reaction was complete, the organic layer was extracted with 1 M HCl and saturated $NaHCO_3$, dried over anhydrous $MgSO_4$, and evaporated in *vacuo*. The residue was purified by silica gel column chromatography, eluting the phosphoramide with hexane/EtOAc.

Acknowledgments. This work was supported by the Centre for Bioactive Molecular Hybrids at Yonsei University. W.C. is indebted to the partial financial support from NCRT.

References

1. (a) Eto, M. *Organophosphorus Pesticides, Organic and Biological Chemistry*; CRC Press: Boca Raton, 1974. (b) Van Wazer, J. R. *Phosphorus and its Compounds*; Wiley-Interscience: New York, 1961; Vol. II. (c) Kosolapoff, G. M. *Organic Phosphorus Compounds*; Wiley-Interscience: New York, 1950; Vol. 6, p 503. (d) Gryaznov, S.; Skorski, T.; Cucco, C.; Nieborowska-Skorska, M.; Chiu, C. Y.; Lloyd, D.; Chen, J. K.; Koziolkiewiez, M.; Calabretta, B. *Nucleic Acids Res*. **1996**, *24*, 1508. (e) Savignac, P.; Iorga, B. *Modern Phosphorus Chemistry*; CRC Press: New York, 2003; p 319. (f) Westheimer, F. H. *Science* **1987**, *235*, 1173. (g) Di Novi, M.; Trainor, D. A.; Nakanishi, K. *Tetrahedron Lett*. **1983**, *24*, 855.
2. (a) Fleisher, D.; Bong, R.; Stewart, B. H. *Adv. Drug Delivery Res*. **1996**, *19*, 115. (b) Chang, S.; Griesgraber, G. W.; Southern, P. J.; Wagner, C. R. *J. Med. Chem.* **2001**, *44*, 223. (c) Egron, D.; Imbach, J. L.; Gosselin, G.; Aubertin, A. M.; Perigaud, C. *J. Med. Chem.* **2003**, *46*, 4564. (d) Freel Meyers, C. L.; Borch, R. F. *J. Med. Chem*. **2000**, *43*, 4319.
3. Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed*. **2008**, *47*, 1560.
4. (a) Denmark, S. E.; Chung, W.-J. *Angew. Chem. Int. Ed*. **2008**, *47*, 1890. (b) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, *118*, 7404. (c) Denmark, S. E.; Stavenger, R. A.; Su, X.; Wong, K.-T.; Nishigaichi, Y. *Pure Appl. Chem.* **1998**, *70*, 1469.
5. (a) Denmark, S. E.; Coe, M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (c) Denmark, S. E.; Fu, J. *Chem. Commun.* **2003**, 167.
6. Wuts, P. G. M.; Greene, T. W. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley: New Jersey, 2006; p 844.
7. Corbridge, D. E. C. *Phosphorus: An Outline of its Chemistry, Biochemistry and Technology*, 4th ed.; Elsevier Science: Amsterdam, 1990; Ch 5, p 403.
8. Gupta, A. K.; Shakya, P. D.; Pardasani, D.; Dubey, D. K. *Rapid Commun. Mass Spectrom.* **2005**, *19*, 975.
9. Pourayoubi, M.; Eshtiagh-Hosseini, H.; Zargaran, P.; Divjakovic, V. *Acta Cryst.* **2010**, *E66*, o204.
10. Lopusinski, A. *Heteroatom Chem.* **2004**, *15*, 395.
11. Wilkening, I.; Signore, G.; Hackenberger, C. P. R. *Chem. Commun.* **2008**, 2932.
12. Ma, X.; Wang, C.; Xu, X.; Zhao, G.; Zhou, Z.; Tang, C. *Lett. Org. Chem.* **2007**, *4,* 51.
13. (a) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415. (b) Arbusov, B. A. *Pure Appl. Chem.* **1964**, *9*, 315. (c) *Methoden der Organischen Chemie (Houben-Weyl)*; Muller, E.; George Thieme: Stuttgart, 1964; *Vol. XII/I*, p 433.
14. Sathe, M.; Gupta, A. K.; Kaushik, M. P. *Tetrahedron Lett.* **2006**, *47*, 3107.
15. (a) Nilsson, J.; Kraszewski, A.; Stawinski, J. *J. Chem. Soc., Perkin. Trans 2* **2001**, 2263. (b) Dhawan, B.; Redmore, D. *J. Org. Chem.* **1986**, *51*, 179.
16. (a) Chantarasriwong, O.; Jang, D. O.; Chavasri, W. *Tetrahedron Lett.* **2006**, *47*, 7489. (b) Jang, D. O.; Cho, D. H.; Kim, J.-G. *Synth. Commun.* **2003**, *33*, 2885. (c) Kim, J.; Jang, D. O. *Synth. Commun.* **2001**, *31*, 395. (d) Jang, D. O.; Park, D. J.; Kim, J. *Tetrahedron Lett.* **1999**, *40*, 5323.