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A single-step one pot synthesis of *O*,*O*′-dialkyl *N*,*N*-dialkylphosphoramidates from dialkylphosphites

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ABSTRACT

An efficient synthetic method has been developed to obtain chemical weapons convention (CWC)-related *O*,*O*′-dialkyl-*N*,*N*-dialkylphosphoramidates from dialkylphosphites using inorganic reagents ($CuCl_2$ and Cs_2CO_3) at room temperature.

Organophosphorus compounds (OPCs) have attracted the attention of researchers because of their wide applications in industrial, agricultural, biochemical, and medicinal areas.[1,2] Phosphoramidates are abundant structural motifs widely present in natural and synthetic compounds of various applications.[3] Phosphoramidates are also important precursors for the synthesis of various bioactive compounds serving as a motif for natural products, phosphonopeptides, amino acid analogs, prodrugs and pharmacological agents.[4,5] One such class of OPCs is the *O*,*O*′-dialkyl *N*,*N*-dialkylphosphoramidates (DADAPs), bearing following general structures are included in the schedule 2B6 category of chemical weapons convention (CWC)[6,7] (Fig. 1).

DADAPs are often produced as side products during the synthesis of chemical warfare agents such as Tabun and its analogs (all of which belong to schedule 1A2 of CWC). Thus the phosphoramidates may be considered as indicators of production of 1A2 compounds. The identification of DADAPs in a suspected sample is an important component of the verification regime of the CWC.[8] Due to wide applications of DADAPs, their efficient synthesis is highly desirable. Several methods are reported in literature for the synthesis of DADAPs.[9–16] However, these methods have one or another drawback such as low yields, long reaction time, harsh reaction conditions, and use of hazardous materials.

Recently, Hayes et al. reported the use of CuI catalyst along with secondary amine for the synthesis of phosphoramidates.[17] However, this method was mostly applicable to aromatic phosphoramidates with limited success to aliphatic phosphoramidates related to CWC. Secondly, it involves tedious work-up procedure for the removal of excess amount of amine present in the reaction mixture, which leads to lower yields as well as the introduction of impurity to the desired product. Due to their wide utility and our interest to develop rapid and efficient synthetic methods for CWC related compounds, this study was aimed to develop an efficient synthetic procedure for the mild and efficient synthesis of *O*,*O*′-dialkyl *N*,*N*-dialkylphosphoramidates. Reactions that can be performed without elaborate procedure and in one-pot are highly desired.

Recently, we have explored the usage of the combination of two inorganic reagents such as $CuCl_2$ and CsF for the synthesis of dialkyl fluorophosphates.[18] Prompted by the efficiency and easy workup of inorganic reagents, here in we are reporting the synthesis of *O*,*O*′-dialkyl *N*,*N*-dialkylphosphoramidates from dialkylphosphites by $CuCl_2$ and cesium carbonate (Cs_2CO_3). There are several literature methods available for the use of Cs_2CO_3 as an inorganic base in different functional group transformations.[19–21] Cs_2CO_3 is not only soluble in various organic solvents, its efficiency is also high in comparison to other inorganic base due to unprecedented cesium effect.[22] We envisaged that combination of electrophilic substitution of hydrogen in dialkylphosphites by chlorine followed

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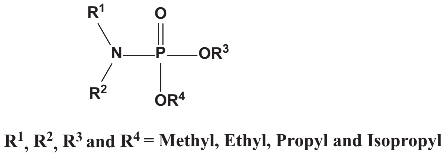


Figure 1. General structure of *O*,*O*′-dialkyl *N*,*N*-dialkylphosphoramidates.

by the nucleophilic addition of an amine to the resulting dialkyl chlorophosphate may lead to formation of DADAPs. By this procedure, by products could be removed from reaction mixture by filtration and desired products could be obtained without chromatographic purification process. To the best of our knowledge, combination of these reagents has not been reported for the one-pot conversion of dialkylphosphites to *O*,*O*′-dialkyl *N*,*N*-dialkylphosphoramidates using $CuCl_2$ and Cs_2CO_3 (Scheme 1).[23]

To optimize various reaction conditions such as solvent, temperature, metal salt and time, a model reaction was performed by treating diethylphosphite with $CuCl_2$ and inorganic base. Progress of the reaction was monitored by GC-MS and $^{31}P\{H\}$ NMR. Results are summarized in Table 1.

Reaction Conditions**:** Diethyl phosphite, secondary amine (*N*,*N*-diethyl amine), metal salt ($CuCl_2$) and inorganic base were used in the mole ratio of 1:2:2:2.

Among the various solvents screened, acetone, acetonitrile and ethyl acetate afforded good yields (entries 1–7, Table 1) and minimum time required for the completion of reaction was found to be 30 min (entries 7–9, Table 1). Highest yield of the desired product was obtained when Cs_2CO_3 was taken as inorganic base (entries 7 & 10–14, Table 1). Temperature also played an important role in this reaction; lower yields were observed when the temperature was increased to 50 °C (entries 14–16, Table 1). This may be due to the highly volatile nature of used secondary amine.

Although this reaction is performed in single pot, it proceeds in two successive steps.

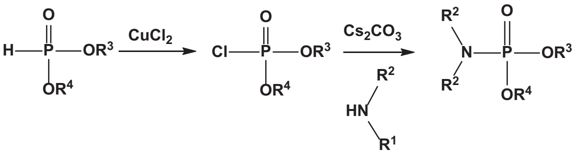
In the first step, hydrogen of dialkylphosphites is substituted by chlorine of $CuCl_2$ in an electrophilic displacement reaction. In the second step, the chloride of dialkylchlorophosphate is nucleophilically substituted by secondary amine to give the phosphoramidate. Putative reaction mechanism is depicted in Scheme 2.

The applicability of the method was tested on other analogs of dialkylphosphites. Results summarized in Table 2 confirm the applicability of the method to various dialkylphosphites for the synthesis of phosphoramidates.

Reaction Conditions**:** Dialkylphosphite, secondary amine, metal salt ($CuCl_2$) and inorganic base (Cs_2CO_3) were used in the mole ratio of 1:2:2:2 the reactions were carried out in acetone at room temperature (25 °C).

The major advantage of this method is the operational simplicity and product isolation. The desired product is isolated from the reaction mixture simply by filtration of reaction mixture followed by solvent evaporation. The use of inorganic reagents helps in delivering clean product without any organic impurities and thus the process required no chromatographic purification step.

In conclusion, we have developed an efficient method for the synthesis of *O*,*O*′-dialkyl *N*,*N*’-dialkylphosphoramidates at room temperature. Reactions are operationally simple, dispense hazardous reagents, give excellent yields and clean products. These virtues make this synthetic method an important contribution for the synthesis of CWC related phosphoramidates.

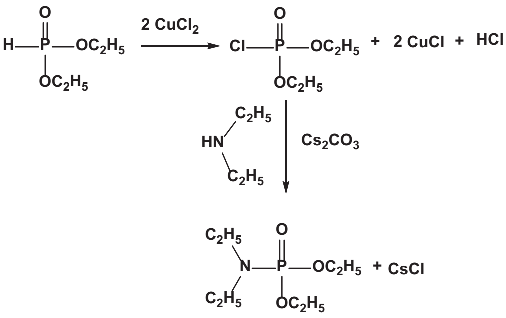


Scheme 1. Synthesis of *O*,*O*′-dialkyl *N*,*N*-dialkylphosphoramidates.

Table 1

Optimization of reaction conditions

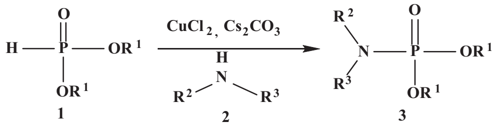
Entry	Time (min)	Solvent	Metal salt	Inorganic base	Temp. (°C)	Yield (%)
1	30	$CHCl_3$	$CuCl_2$	Cs_2CO_3	25	25
2	30	CH_2Cl_2	$CuCl_2$	Cs_2CO_3	25	12
3	30	CH_3CN	$CuCl_2$	Cs_2CO_3	25	70
4	30	Toluene	$CuCl_2$	Cs_2CO_3	25	40
5	30	THF	$CuCl_2$	Cs_2CO_3	25	45
6	30	Ethyl acetate	$CuCl_2$	Cs_2CO_3	25	75
7	30	Acetone	$CuCl_2$	Cs_2CO_3	25	93
8	10	Acetone	$CuCl_2$	Cs_2CO_3	25	30
9	20	Acetone	$CuCl_2$	Cs_2CO_3	25	75
10	30	Acetone	$CuCl_2$	Na_2CO_3	25	60
11	30	Acetone	$CuCl_2$	K_2CO_3	25	65
12	30	Acetone	$CuCl_2$	$NaHCO_3$	25	50
13	30	Acetone	$CuCl_2$	$KHCO_3$	25	48
14	30	Acetone	$CuCl_2$	MgO	25	72
15	30	Acetone	$CuCl_2$	Cs_2CO_3	40	53
16	30	Acetone	$CuCl_2$	Cs_2CO_3	50	32



Scheme 2. Reaction mechanism for the synthesis of *O*,*O*′-diethyl *N*,*N*-diethylphosphoramidate.

Table 2

Synthesis variety of *O*,*O*′-dialkyl *N*,*N*-dialkylphosphoramidates



Entry	R^1	R^2	R^3	Product	Time (min)	Yield (%)
1.	CH_3	CH_3	CH_3	3a	30	81
2.	CH_3	C_2H_5	C_2H_5	3b	30	87
3.	CH_3	i-C_3H_7	i-C_3H_7	3c	30	82
4.	CH_3	n-C_3H_7	n-C_3H_7	3d	30	80
5.	C_2H_5	n-C_3H_7	i-C_3H_7	3e	30	70
6.	C_2H_5	n-C_3H_7	n-C_3H_7	3f	30	86
7.	C_2H_5	i-C_3H_7	i-C_3H_7	3g	30	89
8.	C_2H_5	CH_3	i-C_3H_7	3h	30	84
9.	C_2H_5	C_2H_5	n-C_3H_7	3i	30	81
10.	C_2H_5	CH_3	C_2H_5	3j	30	75
11.	C_2H_5	CH_3	n-C_3H_7	3k	30	72
12.	n-C_3H_7	C_2H_5	C_2H_5	3l	30	83
13.	n-C_3H_7	n-C_3H_7	n-C_3H_7	3m	40	76
14.	i-C_3H_7	n-C_3H_7	n-C_3H_7	3n	40	74
15	i-C_3H_7	C_2H_5	C_2H_5	3o	40	82
16	i-C_3H_7	n-C_3H_7	C_2H_5	3p	40	85

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.07.019.

References and notes

1. Eto, M. *Organophosphorous Pesticides: Organic and Biological Chemistry*; CRC Press: USA, 1974.
2. Wazer, V.; John, R. *Phosphorous and its Compounds:*; Interscience: New York, 1961.
3. Engel, R. *Chem. Rev.* **1977**, *77*, 349–367.
4. Phillips, D. R.; Uramoto, M.; Isono, K.; McCloskey, J. A. *J. Org. Chem.* **1993**, *58*, 854–859.
5. Wittine, K.; Benci, K.; Rajić, Z.; Zorc, B.; Kralj, M.; Marjanović, M.; Pavelić, K.; De Clercq, E.; Andrei, G.; Snoeck, R.; Balzarini, J.; Mintas, M. *Eur. J. Med. Chem.* **2009**, *44*, 143–151.
6. Kostiainen, O. *Analysis of Chemicals Related to the Chemicals Weapons Conventions*; Elsevier Science: Amsterdam, 2000.
7. Convention on the Prohibition of the Development, Production, Stockpiling and use of Chemical Weapons and their Destruction; 1997; (O.P.C.W.: The Hague) http://www.opcw.org.
8. Palit, M.; Pardasani, D.; Gupta, A. K.; Shakya, P.; Dubey, D. K. *Anal. Bioanal. Chem.* **2005**, *381*, 477–486.
9. Cadogan, J. I. G.; Mackie, R. K.; Maynard, J. A. *J. Chem. Soc.* **1967**, 1356–1360.
10. Baumgarten, H. E.; Setterquist, R. A. *J. Am. Chem. Soc.* **1959**, *81*, 2132–2136.
11. Kers, I.; Stawinski, J. *Tetrahedron Lett.* **1998**, *39*, 1219–1222.
12. Adams, L. A.; Cox, R. J.; Gibson, J. S.; Mayo Martin, M. B.; Walter, M.; Whittingham, W. *Chem. Commun.* **2002**, 2004–2005.
13. Atherton, F. R.; Openshaw, H. T.; Todd, A. R. *J. Chem. Soc.* **1945**, 660–663.
14. Desmarchelier, J. M.; Fukuto, T. R. *J. Org. Chem.* **1972**, *37*, 4218–4220.
15. Kaboudin, B.; Kazemi, F.; Habibi, F. *Tetrahedron Lett.* **2015**, *56*, 6364–6367.
16. Shakya, P.; Dubey, D. K.; Pardasani, D.; Palit, M.; Gupta, A. K. *Catal. Commun.* **2005**, *6*, 669–673.
17. Fraser, J.; Wilson, L. J.; Blundell, R. K.; Hayes, C. J. *Chem. Commun.* **2013**, *49*, 8919–8921.
18. Purohit, A. K.; Pardasani, D.; Kumar, A.; Goud, R.; Jain, R.; Dubey, D. K. *Tetrahedron Lett.* **2015**, *56*, 4593–4595.
19. Cohen, R. J.; Fox, D. L.; Eubank, J. F.; Salvatore, R. N. *Tetrahedron Lett.* **2003**, *44*, 8617–8621.
20. Moeinpour, F.; Omidinia, R.; Ahmadi, N. D.; Khoshdeli, B. *Korean Chem. Soc.* **2011**, *6*, 2091–2092.
21. Flessner, T.; Doye, S. *J. Prakt. Chem.* **1999**, *2*, 341–345.
22. Flessner, T.; Doye, S. *J. Prakt. Chem.* **1999**, *341*, 186–190.
23. Typical experimental procedure: Diethyl phosphite, (0.10 mol) was added to a stirred suspension of $CuCl_2$ (0.20 mol) and Cs_2CO_3 (0.20 mol) in acetone (20 mL) at room temperature. Followed by addition of diethylamine (0.20 mol) in one shot. The reaction mixture was then stirred at room temperature for 30 min and reaction progress was monitored by GC–MS and ^{31}P NMR. After completion of the reaction the reaction mixture was filtered to remove the precipitate by using filter paper. The white solid residue was washed with 2×5 mL dichloromethane. The filtrate and washing were combined and excess solvent was removed by distillation followed by vacuum distillation to get the desired product. The reaction was carried out in an efficient fume hood and disposable latex gloves and safety goggles were worn as normal practice during the complete reaction work up.