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Trichloroisocyanuric acid: an efficient reagent for the synthesis of dialkyl chlorophosphates from dialkyl phosphites

J. Acharya, A. K. Gupta, P. D. Shakya and M. P. Kaushik*

Process Technology Development Division, Defence R&D Establishment, Jhansi Road, Gwalior 474 002, MP, India

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Abstract—A mild and operationally simple method for the synthesis of dialkyl chlorophosphates is described. Trichloroisocyanuric acid is used as an effective reagent for the rapid conversion of dialkyl phosphites to their corresponding dialkyl chlorophosphates under mild conditions.

Organophosphorus compounds are important both in living systems and in commercial applications such as pesticides, fungicides, fire retardants and lubricants. Dialkyl halophosphates are also important intermediates for the synthesis of various bioactive compounds such as phosphoramidates, phosphates, enol phosphates and phosphorohydrazides.[1–10] Recently, diethyl chlorophosphate has been used as an efficient reagent in cyclization reactions[8] and in regioselective ring opening of epoxides.[9] Because of their wide utility and our interest in their properties, we intended to reinvestigate their synthesis. A plethora of effective chemical approaches have been devised from the corresponding phosphites (dialkyl phosphates/trialkyl phosphates) with various reagents such as chlorine,[11] phosgene,[12] sulfuryl chloride,[13] sulfur monochloride and dichloride,[14,15] CCl_4,[16] chloramines,[17] $CuCl_2$[18] and *N*-chlorosuccinimide.[19] Among these methods, only a few can be carried out as convenient laboratory methods for the syntheses of the title compounds. Most of these reported methods use reagents that are either toxic or produce undesired by-products, which are difficult to remove from the sensitive chlorophosphates.[11–16] Another major drawback of these methods is that they require harsh reaction conditions, long reaction times[10–15] and also have limited scope in the synthesis of P–N compounds.[4d] Our aim in undertaking this work was to overcome the limitations and drawbacks of the reported methods.

Herein, we report a rapid, efficient, economic, and easy to scale-up method for the effective conversion of dialkyl phosphites to their corresponding dialkyl chlorophosphates at room temperature using trichloroisocyanuric acid as the chlorinating agent. The reagent is less toxic and within acceptable limits in comparison to that of other known chlorinating agents and is also an efficient chlorine releasing agent. This reagent is available commercially and has found infrequent application in synthetic organic chemistry. The developed method has allowed us to obtain quantitative yields of the products in reduced reaction times. The room temperature (20–25 °C) reaction of various dialkyl phosphites with trichloroisocyanuric acid afforded the corresponding dialkyl chlorophosphates in 10–15 min with excellent yields (Table 1).[20]

The important advantage of this reaction is its occurrence at room temperature. Further observation revealed that reaction completion is indicated by precipitation of cyanuric acid, within 10 min, from the homogeneous reaction medium. Another advantage is that the cyanuric acid **4** is formed in quantitative yields and can be recycled after reaction with elemental chlorine. Another positive feature of this reaction is that it requires only one mole of the reagent **2** to chlorinate three moles of the phosphites. Furthermore, the reaction does not require any base to scavenge the proton as it is picked up by the nitrogen of **2**. We also studied the reproducibility and scale-up feasibility of the developed protocol.

Keywords: Dialkyl phosphite; Dialkyl chlorophosphate; Trichloroisocyanuric acid; Cyanuric acid.
* Corresponding author. Tel.: +91 751 2343972; fax: +91 751 2341148; e-mail: mpkaushik@rediffmail.com

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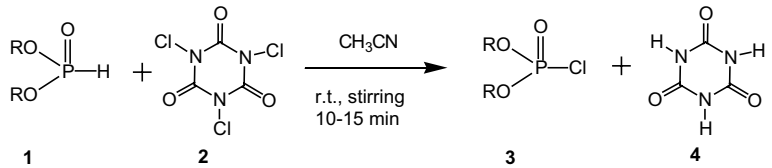
Table 1. Preparation of dialkyl chlorophosphates



1 2 3 4

Entry	R	Yield[a] (%)	Bp (°C/(mm/Hg))	^{31}P NMR[b] (ppm)
1	CH_3	96	75–77/20	6.34
2	C_2H_5	98	85–87/10	4.14
3	C_3H_7	94	102–103/10	5.48
4	*i*-C_3H_7	98	90–92/10	2.76
5	C_4H_9	95	120–122/9	4.58
6	*i*-C_4H_9	92	122–124/10	4.16
7	*sec*-C_4H_9	96	95–97/2	4.71
8	C_5H_{11}	95	129–132/1	4.59
9	*i*-C_5H_{11}	94	133–135/1	3.58
10	C_6H_{13}	96	Undistilled	4.25
11	C_6H_{11}	96	130–132/1	5.46
11	$C_6H_5CH_2$	94	Undistilled	4.7
12	C_6H_5	96	133–135/0.5	−6.2

All the products gave satisfactory IR, NMR and GC–MS data.
[a] Isolated yield of pure products.
[b] ^{31}P NMR spectra were recorded in $CDCl_3$ using 400 MHz instrument.

To prove the concept, 1 mol of diethyl phosphite was treated with 0.33 mol of the reagent **2** to give diethyl chlorophosphate in excellent yield (90%).

In conclusion we have described an efficient reagent for the rapid and convenient conversion of dialkyl phosphites to dialkyl chlorophosphates under mild conditions. Study of a further application of this reagent to detoxify chemical warfare agents is in progress. Preliminary experiments have confirmed that the reagent detoxifies sulfur mustard, a potential chemical warfare agent, completely, and the by-products produced are under investigation. Details of this study will be reported in due course.

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References and notes

1. Hinkle, P.; McCarty, R. Y. *Sci. Am.* **1978**, *104*, 238.
2. (a) Eto, M. *Organophosphorus Pesticides: Organic and Biological Chemistry*; CRC Press: USA, 1974, pp 18–19; (b) Van Wazer John, R. *Phosphorus and its Compounds*; Interscience: New York, 1961; Vol. II; (c) Engel, R. *Chem. Rev.* **1977**, *77*, 349; (d) Corbridge, D. E. C. *Studies in Inorganic Chemistry 10, Phosphorus, An outline of its Chemistry, Biochemistry, and Technology*, 4th ed., Elsevier Science Publishing Company: New York.
3. Kosolapoff, G. M. In *Organic Phosphorus Compounds*; Wiley-Interscience: New York, 1950; Vol. 6, p 503.
4. (a) Di Novi, M.; Trainor, D. A.; Nakanishi, K. *Tetrahedron Lett.* **1983**, *24*, 855; (b) Audrieth, L. E.; Smith, W. C. *J. Org. Chem.* **1953**, *18*, 1288; (c) Nilsson, J.; Stawinski, J. *Chem. Commun.* **2004**, 2566; (d) Atherton, F. R.; Openshaw, H. T.; Todd, A. R. *J. Org. Chem.* **1945**, *10*, 660; (e) Froehler, B. C. *Tetrahedron Lett.* **1986**, *27*, 5575.
5. Shi, E.; Pei, C. *Synthesis* **2004**, 2995.
6. (a) Larson, E.; Lining, B. *Tetrahedron Lett.* **1994**, *35*, 2737; (b) Xiao, Q.; Sun, J.; Sun, Q.; Ju, Y.; Zhao, Y-f; Cui, Y-x *Synthesis* **2003**, 107; (c) Zamyatina, A. Y.; Bushnev, A. S.; Shvets, V. I. *Bioorg. Khim.* **1994**, *20*, 1253.
7. Whitehead, A.; Moore, J. D.; Hanson, P. R. *Tetrahedron Lett.* **2003**, *44*, 4275.
8. Yarovenko, V. N.; Shirokov, A. V.; Zavarzin, I. V.; Krupinova, O. N.; Ignatenko, A. V.; Krayushkin, M. M. *Synthesis* **2004**, 17.
9. Ding, Y.; Hu, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1651.
10. Nicolaou, K. C.; Yang, Z.; Ouellette, M.; Shi, G. O.; Gaertner, P.; Gunzner, J. L.; Agrios, C.; Huber, R.; Chadha, R.; Huang, D. H. *J. Am. Chem. Soc.* **1997**, *119*, 8105.
11. (a) McCombie, H.; Saunders, B. C.; Stacey, G. J. *J. Chem. Soc.* **1945**, 380; (b) Hardy, E. E.; Kosolapoff, G. M. U.S. Patent 2,409,039, 1946, [*Chem. Abstr.* **1947**, *41*, 1233]; (c) Grosse-Ruyken, H.; Uhlig, K. *J. Prakt. Chem.* **1962**, *18*, 287; (d) Dennis, E. A.; Westheimer, F. H. *J. Am. Chem. Soc.* **1966**, *88*, 3432; (e) Walsh, E. N. *J. Am. Chem. Soc.* **1959**, *81*, 3023; (f) Steinberg, G. M. *J. Org. Chem.* **1950**, *15*, 637; (g) Atherton, F. R.; Openshaw, H. T.; Todd, A. R. *J. Chem. Soc.* **1945**, *36*, 4237.
12. Kabachnik, M. I.; Rossiiskaya, M. P. A. *Nauk SSSR, Izv. Akad.; Nauk, Otdel Khim.* **1958**, 1398, [*Chem. Abstr.* **1959**; *53*, 6988e].
13. (a) Fiszer, B.; Michalski, J. *Roczniki Chem.* **1952**, *26*, 688, [*Chem. Abstr.* **1955**; *49*, 2306c]; (b) Atherton, F. R.; Howard, H. T.; Todd, A. R. *J. Chem. Soc.* **1948**, 1106.
14. Ettel, V.; Zbirovsky, M. *Chem. Listy.* **1956**, *50*, 1261, [*Chem. Abstr.* **1956**; *50*, 16025f].

15. Poshkus, A. C.; Herweh, J. E. *J. Am. Chem. Soc.* **1962**, *84*, 555.
16. Stein, S. S.; Koshland, D. E. *Arch. Biochem. Biophys.* **1952**, *39*, 229.
17. Chawalinski, S.; Rypinska, W. *Roczniki Chem.* **1957**, *31*, 539, [*Chem. Abstr.* **1958**; *52*, 5284a].
18. (a) Smith, T. D. *J. Chem. Soc.* **1962**, 1122; (b) Kosolapaff, G. M. *Organic Phosphorus Compounds*; Wiley-Interscience: New York, 1950; Vol. 6, p 502.
19. (a) Goldwhite, M.; Saunders, B. C. *J. Chem. Soc.* **1955**, 3564; (b) Tichy, V.; Truchlik, S. *Chem. Zvesti.* **1958**, *12*, 345, [*Chem. Abstr.* **1958**; *52*, 18258a].
20. Typical experimental procedure: To a stirred solution of trichloroisocyanuric acid, **2** (0.76 g, 3.33 mmol) in dry acetonitrile (15 mL) at room temperature was added in one portion a solution of diisopropyl phosphite, (1.66 g, 10 mmol) in acetonitrile (5 mL). The resulting mixture was stirred at room temperature and monitored by GC and ^{31}P NMR. After 10 min, cyanuric acid precipitated indicating completion of the reaction. It was then further stirred for 5 min and filtered to remove the precipitate followed by removal of solvent and distillation under vacuum to afford the pure product.