N-tert-Butyl-*N*-chlorocyanamide: A Mild and Efficient Chlorinating Agent for the Synthesis of Dialkyl/Diaryl Chlorophosphates

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An efficient reagent for the synthesis of dialkyl/diaryl chlorophosphates has been developed. *N-tert*-Butyl-*N*-chlorocyanamide acts as a chlorinating agent both in polar as well in nonpolar medium and the transformation of dialkyl/diaryl phosphites to the dialkyl/diaryl chlorophosphates takes place rapidly under mild conditions in quantitative yields.

Dialkyl/diaryl chlorophosphates are versatile intermediates in the synthesis of various biologically active compounds. Many of the synthesis of phosphoramidates, phosphorohydrazides, and phosphoric acid esters[1–7] depend on the availability of such compounds having P–Cl bond which is easily replaced with amines, hydrazides, and alcohols. Consequently, majority of commercially known pesticides make use of the same synthetic strategy in their manufacturing process, and therefore, dialkyl/diaryl chlorophosphates occupies a unique place in organophosphorus chemistry. Recently, dialkyl chlorophosphates have also been used for cyclization reactions[8] and regioselective ring opening of epoxides.[9] Although, a myriad reagent[10] employed for the synthesis of dialkyl/diaryl chlorophosphates have been reported, there is still scope for improvement, as the exiting chlorinating methods suffer from one or more disadvantages, like use of toxic reagent, long reaction times, harsh reaction conditions, difficulties in isolation of products, and formation of the by-products leading to low yields. Advantages such as cleaner reactions, very short reaction time and easy work up have kindled a special interest in the synthesis of organophosphorus compounds of biological significance.

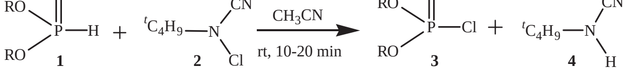
During the course of our study on chlorination of organophosphorous compounds,[11] we discovered a novel and even rather economic chlorinating agent than previously reported for efficient conversion of dialkyl/diaryl phosphites to dialkyl/diaryl chlorophosphates by using reagent **2** that overcomes the disadvantages and limitations associated with the methods/reagent developed so far. This reagent was conveniently prepared in our laboratory from easily and commonly available chemicals using known procedure.[12] Herein, we report the transformation of dialkyl/diaryl phosphites to their corresponding chlorophosphates by using newly discovered reagent that have already proven to bring about useful chemical transformation.[13,14] The reaction of dialkyl/diaryl phosphites with reagent **2** takes place in dry acetonitrile at room temperature within 10–20 min to give the corresponding dialkyl/diaryl chlorophosphates[15] in quantitative yields. The completion of the reaction was monitored by GC. Dialkyl/diaryl chlorophosphates **3** were isolated from the mixture by concentrating the reaction mixture and keeping it in refrigerator overnight. The scope and generality of this method is illustrated with respect to conversion of various phosphites to the corresponding chlorophosphates and the results are summarized in Table 1.

The reaction was carried out by taking equimolar ratio of phosphites to reagent in dry CH_3CN at room temperature for 10–20 min to give the desired products in excellent yields. Both dialkyl and diaryl phosphites react with reagent **2** without any significant difference in rate of reaction and yields of products. The method has advantages in terms of higher yields, simplicity, shorter reaction time and no by-products. The recovered *tert*-butyl cyanamide can be further chlorinated and reused many times. The noteworthy feature of this reagent is that the monitoring of the reaction is very easy; completion of reaction was confirmed by the disappearance of pale yellow color of the reagent in the reaction mixture. Moreover, the reaction does not require any base to scavenge the proton as it is picked up by the nitrogen of the reagent to give dechlorinated product.

Effect of solvents on the rate of reaction was also studied. The reaction of dimethyl phosphite and diethyl phosphite were carried out with reagent **2** in various polar and non-polar solvents viz. CCl_4, CH_2Cl_2, $CHCl_3$, and acetonitrile and it was observed that acetonitrile is the solvent of choice for this reaction and conversion was complete in 10 min.

In conclusion, we have exploited the chlorinating property of *N-tert*-butyl-*N*-chlorocyanamide for the conversion of dialkyl/diaryl phosphites to dialkyl/diaryl chlorophosphates. The striking features of the reagent are: short reaction time, no formation of the by-products, mild nature of the reagent, easy work up procedure, and quantitative yields.

Table 1. Synthesis of dialkyl/diaryl chlorophosphates from dialkyl/diaryl phosphites using **2**[a]



Entry	R	Yield/%[b]	bp(°C)/(mm/Hg)
1	CH_3	92	65–67/10
2	C_2H_5	95	90–92/12
3	C_3H_7	96	92–943/4
4	i-C_3H_7	95	80–82/4
5	C_4H_9	89	98–100/2
6	i-C_4H_9	92	100–102/3
7	C_5H_{11}	93	120–122/0.5
8	C_6H_{13}	88[c]	Not distilled
9	$C_6H_5CH_2$	90[c]	Not distilled
10	C_6H_5	92	130–132/0.5

[a] All the products gave satisfactory IR, NMR, and MS data.
[b] Isolated yield. [c] Crude yield.

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12 A dried solution containing 0.28 mol of cyanogen bromide in 350 mL of anhydrous ether was cooled at 0 °C and *tert*-butyl amine was added slowly with the help of dropping funnel. When 1.8 mol of amine/mol of cyanogen bromide have been added (2 h), a precipitate of amine hydrobromide was removed by filtration. This filtrate was washed with water (2 × 100 mL) and solution was evaporated to make one-half of its total volume. The resulting solution was diluted with 75 mL of carbon tetrachloride in flask cooled to 0 °C, treated with theoretical amount of *tert*-butyl hypochlorite in 30 mL of carbon tetrachloride and allowed to warm at room temperature. The yellow solution was evaporated, and residue was distilled to afford the product, bp 53.5 (8 mm), IR (KBr): 2216 cm^{-1} (NCN) and weak band at 2082 cm^{-1}. The positive chlorine of *N*-*tert*-butyl-*N*-chlorocyanamide[16] was checked by standard iodometric titration and it was found to be 26.54% (theoretical value 26.76%).

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15 Typical experimental procedure: A solution of *N*-*tert*-butyl-*N*-chlorocyanamide (5 mmol) in dry acetonitrile (5 mL) was added in one portion to the stirred solution of dialkyl phosphites (1.0 equiv.) in dry acetonitrile (10 mL). The resulting mixture was stirred at room temperature for 10–20 min. The reaction was monitored by GC and confirmed by the disappearance of pale yellow color of reaction mixture (color due to reagent). Dialkyl/diaryl chlorophosphates 3 were isolated from the mixture by concentrating the reaction mixture and keeping it in refrigerator overnight. Compound 4 precipitated (mp 12–13 °C) and was filtered off immediately. The filtrate was evaporated to give the crude product, which on distillation under vacuum afforded the pure product.

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