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Efficient and Convenient One-Pot Synthesis of Phosphoramidates and Phosphates

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Abstract: A simple and efficient one-pot method is described for the synthesis of phosphoramidates/phosphates in excellent yields from dialkylphosphites and trichloroisocyanuric acid in acetonitrile and subsequent treatment with dialkyl amines/alcohols. The procedure is operationally simple, has reduced reaction times, and uses a one-pot procedure.

Keywords: dialkylphosphites, phosphates, phosphoramidates, trichloroisocyanuric acid

Phosphoramidates and phosphates are important for the synthesis of various bioactive compounds serving as natural products, phosphates, phosphonopeptides, amino acids analogues, prodrugs, pharmacological agents and as important synthetic precursors.[1–6] Furthermore, O,O-dialkyl N,N′-dialkylphosphoraamidates (DADAPs) are also often produced when highly toxic chemical warfare agents such as tabun and its analogues are prepared. Amongst, the various procedures, two have been widely used in the laboratory. First is alcoholysis of phosphoramidic dichloride in presence of tertiary-amine.[2,7] The second method involves reaction of N,N′-dialkyl phosphoramidic dichloride with sodium alkoxide.[8]

Herein, we report a rapid, efficient, economic, environmentally benign, and easy to scale-up method for the effective conversion of O,O-dialkyl

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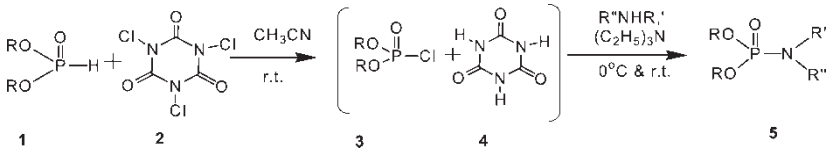


Scheme 1. One-pot synthesis of O,O-dialkyl N,N′-dialkyl phosphoramidates from dialkyl phosphites and dialkyl amines in, the presence of TCICA.

N,N′- dialkylphosphoraamidates (DADAPs) from dialkylphosphites in the presence of trichloroisocyanuric acid (TCICA) (Scheme 1) and Table 1.

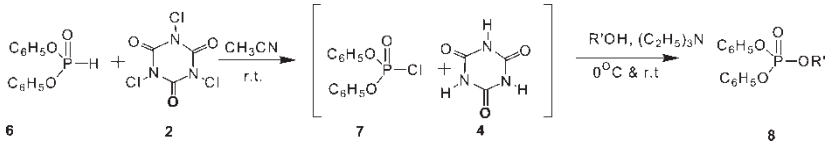
Dialkylphosphites were condensed with various dialkyl amines (symmetrical and unsymmetrical) in presence of trichloroisocyanuric acid at 0°C and at room temperature. The room temperature (20–25°C) reaction of dialkyl phosphites with various amines in the presence of TCICA afforded the corresponding phosphoramidates in 40–60 min with excellent yields (Table 1). The results of ^{31}P NMR studies indicated that signal of diethyl chlorophosphate appeared at δ 4.14. The ^{31}P NMR signal at δ 4.14 disappeared after the addition of dipropyl amine and a new signal re-appeared at

Table 1. Synthesis of O,O-dialkyl N,N′-dialkyl phosphoramidates[a]

Entry	Phosphoramidates R	R′	R″	^{31}P ppm	^{31}P ppm (lit)[9]	Bp (°C/ mm Hg)	Yield[b] (%)
1	CH_3	CH_3	CH_3	14.10	14.15	82/6	92
2	CH_3	CH_3	C_2H_5	11.42	11.48	84/5	86
3	CH_3	CH_3	$^nC_3H_7$	11.50	11.54	92/3	82
4	CH_3	CH_3	$^iC_3H_7$	9.35	9.32	92/1	85
5	C_2H_5	C_2H_5	CH_3	13.55	13.55	98/1	80
6	C_2H_5	C_2H_5	C_2H_5	10.80	10.73	110/1	82
7	C_2H_5	C_2H_5	$^nC_3H_7$	10.28	10.25	118/1	79
8	C_2H_5	C_2H_5	$^iC_3H_7$	8.30	8.30	116/1	84
9	$^nC_3H_7$	$^nC_3H_7$	CH_3	13.78	13.82	96/1	88
10	$^nC_3H_7$	$^nC_3H_7$	C_2H_5	11.11	11.50	110/2	
11	$^nC_3H_7$	$^nC_3H_7$	$^nC_3H_7$	11.20	11.20	114/1	86
12	$^nC_3H_7$	$^nC_3H_7$	$^iC_3H_7$	9.12	9.15	108/1	91
13	$^iC_3H_7$	C_3H_7	CH_3	11.45	11.50	96/1	89
14	$^iC_3H_7$	$^iC_3H_7$	C_2H_5	8.89	8.90	112/1	86
15	$^iC_3H_7$	$^iC_3H_7$	$^nC_3H_7$	8.82	8.80	124/1	87
16	$^iC_3H_7$	$^iC_3H_7$	$^iC_3H_7$	6.88	8.90	120/1	91

[a]Reactions were carried out at ambient temperature, and the products had satisfactory IR, NMR, and GC-MS data, which were compared with authentic samples and literature values.

[b]Reactions were monitored by ^{31}P NMR in $CDCl_3$ at 400 MHz NMR.



Scheme 2. One-pot synthesis of phosphates.

δ 10.28 within 30 min. It clearly demonstrated the conversion of diethylphosphite to diethyl chlorophosphate followed by the formation of corresponding O,O-diethyl N,N′-dipropyl phosphoramidates. Filtration of heterogeneous reaction mixture and concentration of the solvent provided the pure product in 79% isolated yield (entry 7, Table 1).

To study the versatility of the method, few reactions of diphenyl phosphite were also attempted (Scheme 2); corresponding phosphates were obtained in high yields (Table 2).

In conclusion, we have developed a simple, rapid, economical and efficient one-pot synthetic method for preparation of DADAPs and phosphates.

GENERAL EXPERIMENTAL PROCEDURE

In a typical experimental procedure, dialkylphosphite (0.01 mol) was added to a solution of TCICA (0.0034 mol) in 10 mL of acetonitrile, and the reaction mixture was stirred for 10–20 mins. The progress of the reaction mixture

Table 2. Synthesis of phosphates from diphenyl phosphite and alcohols in the presence of TCICA

Entry[a]	R′	Yield (%)[b]	Bp/ [DC(mmHg)]	^{31}P (ppm)[c]	^{31}P (ppm) (lit.)
1	CH_3	85	155(.2)	−15.2	−14.5
2	C_2H_5	84	157(.1)	−15.3	−14.3
3	*n*-C_3H_7	88	160(.1)	−14.6	−13.5
4	*i*-C_3H_7	89	161(.1)	−14.7	−13.9
5	*n*-C_4H_9	84	165(.1)	−12.5	−12.8
6	C_6H_{11}	85	172(.1)	−12.3	−11.4
7	C_5H_9	82	175(.2)	−12.2	−12.1
8	CH_2CHCH_2	79	160(.2)	−18.1	−18.3
9	Menthyl	78	190(.1)	−10.8	−10.8
10	$C_6H_5CH_2$	75	192(.1)	−17.5	−17.7

[a]Reaction completes at reflux temperature for entries 5–10. All compounds compared with authentic samples and characterized by IR, NMR, and MS.

[b]Isolated yield.

[c]^{31}P NMR spectra were recorded in $CDCl_3$ at 400 MHz.

was monitored by ^{31}P NMR by drawing a few milligrams of the reaction mixture in a NMR tube. The results of NMR studies indicate that the ^{31}P NMR signal of dialkylphosphites is exchanged by a corresponding dialkylchlorophosphate. It is also physically visualized by appearance of a white amorphous precipitate of cyanuric acid. The reaction mixture was diluted with 10 ml of dry ether and cooled at 0°C with stirring. A mixture of dialkyl amine and triethyl amine (0.02 mol each) was added slowly with stirring at room temperature. The progress of the reaction was further monitored by ^{31}P NMR. The results of NMR studies indicate that ^{31}P NMR signal of corresponding dialkylchlorophosphate completely disappeared, and a new signal of phosphoramidates appeared within 30 min. The reaction mixture was filtered; after removal of solvent, the product was distilled under vacuum to get pure DADAP.

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