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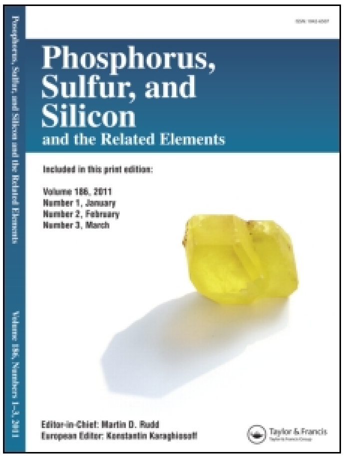

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An Efficient Synthesis of Dialkyl Phosphorocyanidates

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Dialkyl phosphorocyanidates ***2a–2g*** *were prepared in high yield from dialkyl phosphorochloridates and hydrogen cyanide in the presence of triethylamine in ether. The white precipitates formed in the reaction of diethyl phosphorochlorodates and triethylamine were verified as triethylammonium chloride, not the similar phosphoryltriethylammonium chloride by FAB-MS, ESI-MS, ^{31}P-NMR, and ^{1}H-NMR.*

Keywords Cyanation; phosphorochloridates; phosphorocyanidates; phosphoryltriethylammonium chloride

As a kind of important reagent in organic synthesis, diethyl phosphorocyanidate (DEPC) has been used widely to prepare amides, thiol esters, thiocyanates, a-aminonitriles, cyanophosphates, nitriles, a, β-unsaturated nitriles, and so on.[1]

Except for the conventional Arbuzov method,[2] we have recently developed two new methods in synthesis of phosphorocyanidates from phosphorochloridates.[3,4] Since it was reported that phosphonocyanidates can be obtained from the cyanation of phosphonochloridates by hydrogen cyanide,[5] we then examined the possibility of preparation of phosphorocyanidates in a similar way and received satisfactory results.

RESULTS AND DISCUSSION

Reaction of diethyl phosphorochloridate (DEPCl) with hydrogen cyanide in different solvents was studied detailedly (Table I). In contrast to the two-phase reaction of DEPCl with potassium cyanide,[3] the

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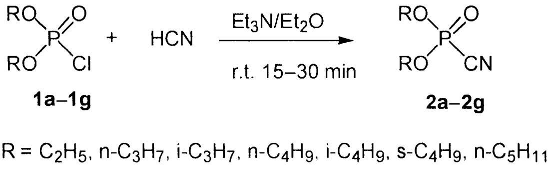
TABLE I Reaction Between DEPCl and HCN in Different Solvents

Entry	Solvent	$E_T(30)$	Yield (DEPC, %)[a]
1	C_6H_6	34.5	40
2	Et_2O	34.6	94
3	THF	37.4	54
4	CH_2Cl_2	41.1	73
5	DMF	43.8	22
6	CH_3CN	46.6	42

[a] GC yield %.

polarities (E_T (30)) of solvents showed no obvious effect on the homogeneous cyanation of DEPCl by hydrogen cyanide. However, there were more byproducts in the solvents containing an unsaturated bond such as DMF and methyl nitrile. Moreover, more anhydrides were generated with difficultly drying solvents, for example, THF and CH_2Cl_2. In ether, the yield of phosphorocyanidates was 94%. Thus, we employed ether as reaction solvent.

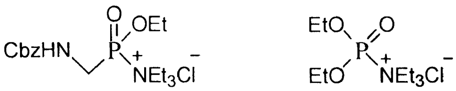
The complete cyanation of DEPCl by hydrogen cyanide in ether genearally took only 15 min and reaction temperature nearly had effects on cyanation. Considered convenient treatment, temperature of cyanation was kept 10–20°. Dialkyl phosphorocyanidates **2a–2g** were prepared in high yield (85–95%) from dialkyl phosphorochloridates **1a–1g** and hydrogen cyanide in presence of triethylamine in ether (Scheme 1).



SCHEME 1

It was found that the reaction mixture immediately became turbid and white precipitates appeared when triethylamine was added into DEPCl in ether. Moreover, it should be noted that DEPCl, without Et_3N, did not react with HCN. So Et_3N must play a key role in this cyanation and white precipitates may be possiblely powerful intermediate.

Hirschman argued[6] that phosphonochloridates could react with triethylamine to give phosphonyltriethylammonium chloride **3**, which were highly reactive phosphonylating agents, superior to phosphonochloridates, affording a higher yield of phosphonate esters and



3 **4a**

SCHEME 2

amides. Thus, the white solids would probably be novel diethyl phosphonyltriethylammonium chloride **4a** served as the intermediates in the above rapid cyanotion process (Scheme 2).

As for intermediate **4a**, we tested its probability by a fast atom bomb mass (FAB-MS) and electrospray ionization mass (ESI-MS). The FAB-MS and ESI-MS spectrums of the isolated white precipitates are shown in Figures 1 and 2.

It was unexpected, however, that characteristic position m/z 236 of the positive ion of the proposed intermediate **4a** was not detected by FAB-MS and ESI-MS as shown in Figures 1 and 2. On the contrary, the peak m/z 239, accompanied by a distinct chloride isotope, should be responsible for the fragment ion $(Et_3N)_2H^+Cl$. So the white solids may not be the predicted intermediates **4a**.

To verify our suspicion, the isolated white precipitates were added to ether and reacted with hydrogen cyanide. If cyanation proceeded via the intermediate **4a**, the corresponding phosphonates must be generated after cyanation. However, the result monitored by GC showed that there

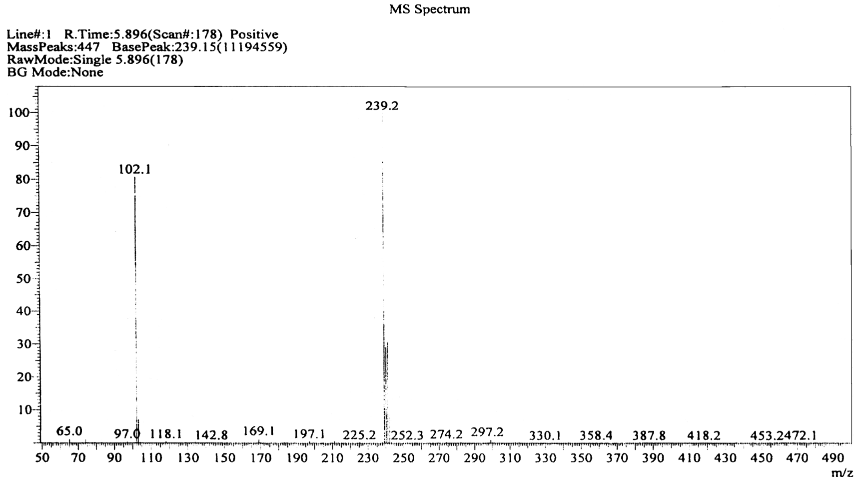


FIGURE 1 Positive ion FAB-MS spectrum of the white precipitates.

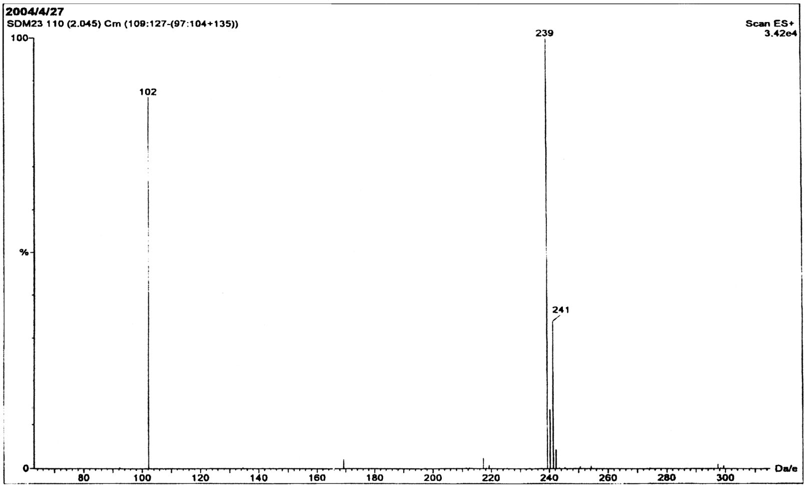


FIGURE 2 Positive ion ESI-MS spectrum of the white precipitates.

was nothing besides ether and triethylamine, which meant that the isolated white precipitates did not contain phosphorus ingredient.

In order to confirm our experimental result, further evidence for the structure of white solids came from the studies of ^{31}P-NMR and ^{1}H-NMR. Nothing was observed in the ^{31}P-NMR spectrum and the study of the ^{1}H-NMR showed that the white solids contained only Et_3N and a few ether (Figure 3). That is, the white solids were not the predicted phosphonyltriethylammonium salts, but the triethylammonium salts.

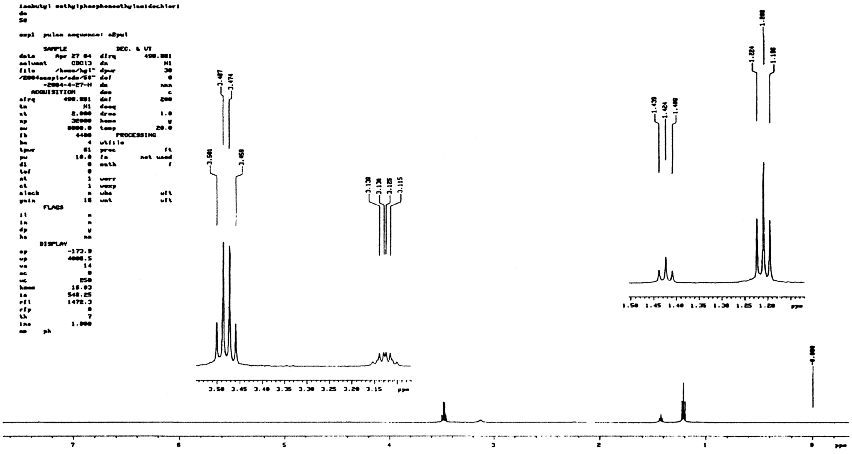


FIGURE 3 ^{1}H-NMR spectrum of the white precipitates.

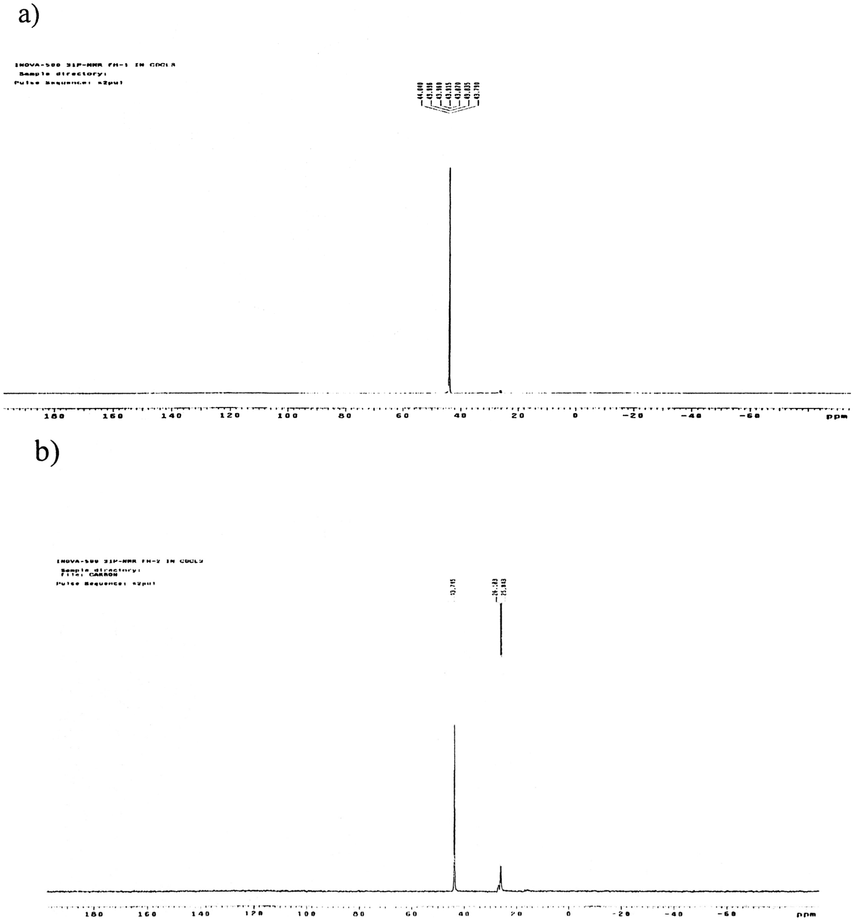


FIGURE 4 (a) ^{31}P-NMR spectrum of DEPCl. (b) ^{31}P-NMR spectrum of the filtrate filtrated out of the triethylammonium salts.

Since the white solids were not intermediates **4a**, whether the structure of phosphorochloridates had changed or not? As shown by Figure 4, the ^{31}P-NMR chemical shifts of the starting material DEPCl was 43.915 ppm, which was the same as the chemical shift of the filtrate (43.745 ppm), which was filtrated out of the triethylammonium salts. More important, no novel phosphorous compounds, unlike Hirschmann's studies, appeared by treatment DEPCl with triethylamine besides a few anhydrides (26.183 ppm). So we held that the structure of DEPCl kept unchanged after triethylamine added.

After all attempts to investigate the possibility of phosphoryltriethylammonium salts **4a** failed, we considered the role of triethylamine in this reaction. In many conventional phosphonate synthesis, triethylamine is added along with nucleophile as an acid scavenger. We investigated other typically organic base's effects on cyanation such as tributylamine and pyridine. However, no evidence for reaction of DEPCl and HCN was seen in the presence of tributylamine or pyridine. So the triethylamine acts as not only acid scavenger, but also as a catalyzer in this cyanation. Though the structure of DEPCl, in the presence of triethylamine, did not change, the reactivity of P—Cl bond had been enhanced by triethylamine, which was an impetus to the formation of phosphorocyanidates. The reason why tributylamine or pyridine could not catalyze this reaction might due to a steric effect. In addition, a few triethylammonium salts formed in the reaction of DEPCl and triethylammine might be a little water in the reaction system in result of the uncompleted drying.

Compared with Hirschman's experiment, otherwise, we cannot deny the viewpoint about intermediate resulting from different starting material and reactive conditions. Many assignments on the reaction mechanism need to be made.

In summary, we have given another efficient preparation of dialkyl phosphorocyanidates. The white precipitates, which were generated by diethyl phosphorochlorodates and triethylamide, were verified as triethylammonium salts, not the similar phosphoryltriethylammonium salts.

EXPERIMENTAL (CAUTION: ALL PROCEDURES MUST BE CARRIED OUT IN GOOD FUME CUPBOARDS)

GC was recorded on a Varian CP-3800 spectrometer, into IR, on a Bio-Rad FTS185 spectrometer, ^{31}P-NMR on a Varian UNITY500 spectrometer using 85% H_3PO_4 as external reference, MS on a Finnigan Mat TSQ70 spectrometer, and elemental anal. on Flash EA 1112 series.

General procedure for dialky phosphorocyanidates **2a–2g**:

To the mixture of dialky phosphorochloridate (5 mmole) and triethylamine (5 mmole) in ether (2 mL) was added the solution of hydrogen cyanide (6 mmol) in 0.5 mL ether at 10–20°. After stirring for 15 min, the mixture was filtrated, the filtrate was concentrated in *vacuo*, and distillation gave the product.

Diethyl Phosphorocyanidate 2a

Yield 94%; bp 52~54 (0.6 mm); IR 2206.5 ($\upsilon_{C\equiv N}$); ^{31}P-NMR ($CDCl_3$) −20.5; MS 164 (M+1); elemental anal.: Cacl. C, 36.82; H, 6.18; N, 8.59; Found: C, 36.76; H, 6.24; N, 8.75.

Dipropyl Phosphorocyanidate 2b

Yield 95%; bp 62~64 (0.4 mm); IR 2208.2 ($\upsilon_{C\equiv N}$); ^{31}P-NMR($CDCl_3$) −19.6; MS 192 (M+1); Elemental Anal.: Cacl. C, 43.98; H, 7.38; N, 7.33; Found: C, 43.88; H, 7.44; N, 7.37.

Diisopropyl Phosphorocyanidate 2c

Yield 88%; bp 53–55 (0.2 mm); IR 2208.4 ($\upsilon_{C\equiv N}$); ^{31}P-NMR ($CDCl_3$) −23.1; MS 192 (M+1); Elemental Anal.: Cacl. C, 43.98; H, 7.38; N, 7.33; Found: C, 44.12; H, 7.28; N, 7.41.

Dibutyl Phosphorocyanidate 2d

Yield 90%; bp 70~71 (0.2 mm); IR 2208.8 ($\upsilon_{C\equiv N}$); ^{31}P-NMR ($CDCl_3$) −20.1; MS 220 (M+1); Elemental Anal.: Cacl. C, 49.31; H, 8.28; N, 6.39; Found: C, 49.38; H, 8.33; N, 6.45.

Diisobutyl Phosphorocyanidate 2e

Yield 92%; bp 69–71 (0.1 mm); IR 2208.9 ($\upsilon_{C\equiv N}$); ^{31}P-NMR ($CDCl_3$) −19.5; MS 220 (M+1); Elemental Anal.: Cacl. C, 49.31; H, 8.28; N, 6.39; Found: C, 49.25; H, 8.24; N, 6.54.

Disecbutyl Phosphorocyanidate 2f

Yield 85%; bp 70~71 (0.2 mm); IR 2208.5 ($\upsilon_{C\equiv N}$), ^{31}P-NMR ($CDCl_3$) −22.1; MS 220 (M+1); Elemental Anal.: Cacl. C, 49.31; H, 8.28; N, 6.39; Found: C, 49.35; H, 8.17; N, 6.42.

Dianyl Phosphorocyanidate 2g

Yield 87%; bp 102~104 (0.5 mm); IR 2208.7 ($\upsilon_{C\equiv N}$); ^{31}P-NMR ($CDCl_3$) −19.9; MS 248 (M+1); Elemental Anal.: Cacl. C, 53.43; H, 8.97; N, 5.66; Found: C, 53.47; H, 8.94; N, 5.61.

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