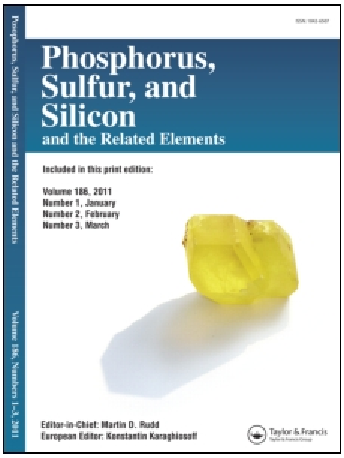
This article was downloaded by:
On: *28 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of Phosphorocyanidates via Phosphorochloridates

Enxue Shi[a]; Chengxin Pei[a]
[a] Beijing Insititute of Pharmceutic Chemistry, Beijing, China

Online publication date: 27 October 2010

To cite this Article Shi, Enxue and Pei, Chengxin(2003) 'Synthesis of Phosphorocyanidates via Phosphorochloridates', Phosphorus, Sulfur, and Silicon and the Related Elements, 178: 5, 1093 — 1099

To link to this Article: DOI: 10.1080/10426500307856

URL: http://dx.doi.org/10.1080/10426500307856

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Phosphorus, Sulfur and Silicon, 2003, Vol. 178:1093–1099
Copyright © 2003 Taylor & Francis
1042-6507/03 $12.00 + .00
DOI: 10.1080/10426500390208938

SYNTHESIS OF PHOSPHOROCYANIDATES VIA PHOSPHOROCHLORIDATES

Enxue Shi and Chengxin Pei
Beijing Insititute of Pharmceutic Chemistry, Beijing, China

(Received September 3, 2002; accepted October 31, 2002)

*Dialkyl phosphorocyanidates (**2**) were obtained from dialkyl phosphorochloridates (**1**) in high yield (80–86%) at room temperature in methyl cyanide. Reaction between diethyl phosphorochloridate and potassium cyanide was greatly influenced by the solvents used. Tetraethyl pyrophosphate also was found to react with potassium cyanide to give diethyl phosphorocyanidate in methyl cyanide.*

Keywords: Dialkyl phosphorochloridates; dialkyl phosphorocyanides; tetraealkyl pyrophosphates

The commonly known utility of diethyl phosphorocyanidate (DEPC) as a versatile coupling and phosphorylating reagent had stimulated considerable interest in peptide and organic synthesis over the last decades.[1–2] Recently derivatives of phosphorocyanidates also have been used as starting materials for the synthesis of the famous herbicide Roundup.[3]

The first reported synthesis of DEPC employed a reaction between cyanogen iodide and triethyl phosphite,[4] a variation of this was the use of cyanogen bromide.[5] An alternative approach reported by Tong[6] employed the reaction of diethyl phosphite and sodium cyanide using carbon tetrachloride as solvent, but Das[7] failed to repeat this procedure; so did we. On the other hand, phosphrochlridates were stated to be unreactive to sodium cyanide when used directly.[4] All of the attempts[7–10] to obtain phosphorocyanidates from phosphorochloridates had low yields (18–46%). Das[7] thought the reaction between dialkyl phosphorochloridates and cyanide in benzene involved the intermediacy of tetraalkyl pyrophosphates when catalytic sodium hydroxide was

We express our sincere thanks to Dr. J. H. Xiao for his keen interest and encouragement.

Address correspondence to Enxue Shi, Beijing Institute of Pharmaceutical Chemistry, Beijing, P.R. China 102205. E-mail: shienxue@yahoo.com.cn

used. Diflurophosphorocyanidate $F_2P(O)CN$ also was prepared by nucleophilic cleavage of pyrophosphonyl tetrafluoride $F_2P(O)OP(O)F_2$ by Roesky.[11] But Lennon[3] got a mixture of (EtO)(KO)P(O)CN (47.5%), $(EtO)_2(KO)P(O)$ (47.5%), and $(EtO)_3PO$ (5%) when using tetraethyl pyrophosphate and potassium cyanide as starting material reacting overnight in DMF at 50°C.

Here we report a new method for the synthesis dialkyl phosphorocyanidates (**2**) via dialkyl phosphorochloridates (**1**) under mild conditions.

RESULTS AND DISCUSSION

Since the reaction between diethyl phosphorochloridate (DEPCl) and KCN is a kind of two-phase reaction, it should be influenced greatly by the solvents used. But some polar aprotic solvents such as CH_3CN, DMF, and DMSO have been said to suppress the reaction in basic conditions.[7] However, the GC analysis of the course of the reaction between DEPCl and KCN in eight kinds of different aprotic solvents under different conditions gave unexpected results (Table I).

TABLE I Reactions Between DEPCl and KCN in Different Solvents

No.	Solvent	$E_T(30)$ (kcal/mol)	Condition	Time (h)	Yield[a] (%)
1	CH_3OH	55.5	r.t.*	3	0[b]
2	CH_3CN	46.0	r.t.	3	>90
3	DMSO	45.0	r.t.	3	0[c]
4	DMF	43.8	r.t.	3	0[d]
5[e]	CH_3COCH_3	42.2	r.t.	3	>90
6	$ClCH_2CH_2Cl$	41.9	r.t.	5	0
			Reflux	3	>90
7	$CHCl_3$	39.1	r.t	5	0
			Reflux	10	50–60
8	THF	37.4	Reflux		
			$^{cat.}$NaOH[f]	10	0
			NO NaOH	10	0
9	1,4-dioxane	36.0	The same to 5	10	0
10	C_6H_6	34.5	The same to 5	10	0
11	CCl_4	32.5	The same to 5	10	0

[a] Ratio in GC.

[b] Only $(EtO)_2P(O)OCH_3$ detected.

[c] Only $(EtO)_3PO$ detected.

[d] The final product was the mixture of $(EtO)_3PO$ (30%) and TEPP (70%).

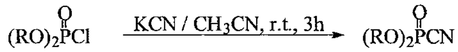
[e] The final product is **3**.

[f] 0.1eq. NaOH.

*r.t. = room temperature.

Whether heated to reflux or added to catalytic sodium hydroxide, DEPCl was unreactive with KCN in THF, 1,4-dioxane, benzene, or carbon tetrachloride. However, in those more polar solvents such as chloroform, 1,2-dichloroethane, acetone, and methyl cyanide (except DMSO and DMF), the reaction was accomplished more smoothly in the order of experiential polarity parameter $E_T(30)$. Larger solubility of KCN and more $ABCP^+{-}O^-$ formed in the equilibrium $ABCP{=}O \leftrightarrow ABCP^+{-}O^-$ in more polar solvents[12] probably led to the regular changes in different solvents in Table I. In the protic solvent of methanol, $(EtO)_2P(O)OCH_3$ was the only formed product due to the well-known reaction between DEPCl and CH_3OH. However, the negative results in DMSO and DMF suggested that some factors superior to the polarity of solvents severely affected the reaction.

In light of the above experiments, methyl cyanide seemed to be a good solvent to synthesize dialkyl phosphorocyanidates (**2**) from dialkyl phosphorochloridates (**1**) in the following procedure (Scheme 1).



$$(RO)_2\overset{O}{\overset{\Vert}{P}}Cl \xrightarrow{KCN\,/\,CH_3CN,\ r.t.,\ 3h} (RO)_2\overset{O}{\overset{\Vert}{P}}CN$$

1 **2**

SCHEME 1

Compounds **2a–2g** were prepared in high yield at room temperature (Table II). Diphenyl phosphorocyanidate (**2h**) also was prepared in the same procedure, yield 47%. But dimethyl phosphorochloridate seemed unreactive to KCN under the same conditions.

Dialkyl phosphorocyanidates **2a–2g** all showed sharp bands of medium intensity at *ca.* 2208–2210 cm^{-1}, but no 2085 cm^{-1} bands of the isomeric isocyanidates that Das reported.[7] The ^{31}P-NMR spectra (Table III) of **2a–2g** revealed that the chemical shift of **2c** and **2f** decreased 1–2 ppm mainly because of the changes of polarities among P—OR σ bonds.[13]

It should be mentioned that DEPC was found to change completely into acetone cyanohydrin O-phosphate (**3**) when using acetone as solvent. And when a mixture of equal mole of DEPCl, KCN in acetone was stirred at room temperature for 10 h, pure (**3**) was obtained in 91% yield.

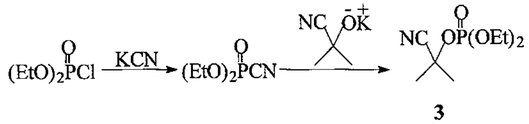
TABLE II Dialkyl Phosphorocyanidates **2a–2g**

No.	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**
R	C_2H_5	$^nC_3H_7$	$^iC_3H_7$	$^nC_4H_9$	$^iC_4H_9$	$^sC_4H_9$	$^nC_5H_{11}$
Yield (%)	81	86	86	80	82	82	83

TABLE III ^{31}P-NMR of Dialkyl Phosphorocyanidates **2a–2g** (in $CDCl_3$)

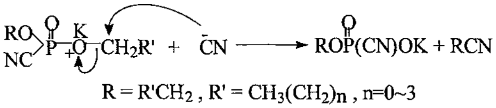
No.	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**
δ (ppm)	−20.583	−19.872	−23.366	−19.904	−19.591	−22.117	−19.913

GC analysis of the course of the reaction suggested a possible mechanism shown in Scheme 2, probably involving $Me_2C(OK)CN$ formed by acetone and KCN.



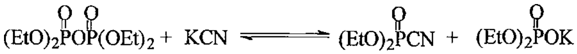
SCHEME 2

During the preparation of DEPC from DEPCl, another interesting phenomenon similar to what Lennon[3] reported was that when using tetraethyl pyrophosphate (TEPP) as starting material was found: When undertaken at high temperature, such as refluxing, DEPCl first went into DEPC, which then mainly changed into EtOPO(CN)OK ($\delta_P = -19.7$) and CH_3CH_2CN after about 10 h. The same side reactions also were observed among other dialkyl phosphorochloridates. A possible mechanism of this kind of side reaction may be expressed as in Scheme 3.



SCHEME 3

Studies also were undertaken on the course of the reaction between TEPP and KCN in methyl cyanide at room temperature. As expected, TEPP facilely reacted with potassium cyanide to give DEPC (Table IV), but only in about 50% yield probably because of the equilibrium between TEPP and $(EtO)_2P(O)(OK)$ as shown in Scheme 4.



$$(EtO)_2\overset{O}{\overset{\|}{P}}O\overset{O}{\overset{\|}{P}}(OEt)_2 + KCN \rightleftharpoons (EtO)_2\overset{O}{\overset{\|}{P}}CN + (EtO)_2\overset{O}{\overset{\|}{P}}OK$$

SCHEME 4

It also was observed that TEPP and DEPC in the mixture both changed into EtOPO(CN)OK when heated to reflux between 8–10 h.

TABLE IV Reaction Between TEPP and Potassium Cyanide[a]

Time (h)	0	2	4	6	8	10
Yield (%)	0	36	52	45	42	0

[a] 0–8 h, r.t.; 8–10 h, refluxing.

To sum up, in proper polar aprotic solvents such as methyl cyanide, dialkyl phosporochloridates, and tetraalkyl pyrophosphates, both xxx and xxx can react with potassium cyanide to yield dialkyl phosphorocyanidates under mild conditions. But phosphorochloridates seems to be a better choice not only because of the high yield (80–86%) in preparing phosphorocyanidates but also the convenience as starting material.

EXPERIMENTAL

Boiling points are uncorrected. Solvents were purified by standard methods. Dialkyl phosphorochloridates were prepared according to Steinberg.[14] GC were recorded on a Varian 3700 spectrometer, 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.

Dialkyl Phosphorocyanidate 2a–2g

To a 50 ml flask, anhydrous methyl cyanide (20 ml), potassium cyanide (0.4 mmol), and dialkyl phosphorochloridate (0.2 mmol) was added. The mixture was stirred vigorously at room temperature for 3 h, then filtered. After the solvent was removed, the residue was distilled under reduced pressure.

Diethyl phosphorocyanidate 2a. Yield 81%; b.p. 54–55° (0.7 mm); IR 2209.5 ($\nu_{C\equiv N}$), 1305.9 ($\nu_{P=O}$); ^{31}P-NMR ($CDCl_3$) $\delta = -20.583$ ppm; MS m/z(%) 164(M + 1, 4) 148(2) 136(30) 134(12) 120(35) 108(100) 91(5) 83(10) 65(5) 55(35) 45(14).

Dipropyl phosphorocyanidate 2b. Yield 86%; b.p. 76–78° (1.0 mm); IR 2209.2 ($\nu_{C\equiv N}$), 1300.1 ($\nu_{P=O}$); ^{31}P-NMR ($CDCl_3$) $\delta = -19.872$ ppm; MS m/z(%) 192(M + 1, 4) 162(2) 150(3) 134(5) 121(6) 108(100) 83(11) 69(3) 55(5) 43(32) 41(22) 27(6).

Diisopropyl phosphorocyanidate 2c. Yield 86%; b.p. 50–51° (0.2 mm); IR 2208.4 ($\nu_{C\equiv N}$), 1297.3 ($\nu_{P=O}$); ^{31}P-NMR ($CDCl_3$) $\delta = -23.366$ ppm; MS m/z(%) 192(M + 1, 3) 176(4) 150(12) 134(95) 108(100) 81(4) 69(22) 59(3) 43(28) 41(22).

Dibutyl phosphorocyanidate 2d. Yield 80%; b.p. 92–94° (0.8 mm); IR 2208.8 ($\nu_{C\equiv N}$), 1299.4 ($\nu_{P=O}$); ^{31}P-NMR (CDCl$_3$) $\delta = -19.904$ ppm; MS m/z(%) 220(M + 1, 5) 164(15) 134(5) 108(100) 83(10) 57(40) 41(58).

Diisobutyl phosphorocyanidate 2e. Yield 82%; b.p. 86–88° (1.0 mm); IR 2208.9 ($\nu_{C\equiv N}$), 1306.8 ($\nu_{P=O}$); ^{31}P-NMR (CDCl$_3$) $\delta = -19.591$ ppm; MS m/z(%) 220(M + 1, 2) 164(8) 148(7) 136(3) 121(12) 108(55) 96(4) 83(5) 57(100) 41(98).

Disecbutyl phosphorocyanidate 2f. Yield 81%; b.p. 68–69° (0.3 mm); IR 2208.0 ($\nu_{C\equiv N}$), 1299.4 ($\nu_{P=O}$); ^{31}P-NMR (CDCl$_3$) $\delta = -22.117$ ppm; MS m/z(%) 220(M + 1, 2) 190(4) 164(16) 148(18) 134(72) 108(100) 97(6) 83(43) 70(4) 57(32) 41(50) 29(60).

Diamyl phosphorocyanidate 2g. Yield 83%; b.p. 130–131° (1.2 mm); IR 2208.7 ($\nu_{C\equiv N}$), 1305.1 ($\nu_{P=O}$); ^{31}P-NMR (CDCl$_3$) $\delta = -19.913$ ppm; MS m/z(%) 248(M + 1, 2) 178(11) 148(5) 108(64) 96(5) 83(10) 71(100) 55(26) 43(50) 29(10).

Diphneyl phosphorocyanidate 2h. Yield 47%; b.p. 128–130° (0.4 mm); IR 2210.9 ($\nu_{C\equiv N}$), 1321.9 ($\nu_{P=O}$); ^{31}P-NMR (CDCl$_3$) $\delta = -29.159$ ppm; MS m/z(%) 259(M + 1, 75) 166(5) 140(100) 119(25) 94(90) 77(45) 65(22) 51(21).

Acetone Cyanohydrin O-phosphate (3)

To a 50 ml flask, 1.73 g diethyl phosphorochloridate (0.1 mmol), 1.3 g potassium cyanide (0.2 mmol), and 10 ml anhydrous acetone was added. The mixture was stirred vigorously at room temperature for 10 h, then filtered. After acetone was removed, distillation gave 2.0 g acetone cyanohydrin O-phosphate (**3**), b.p. 86–88° (0.5 mm), yield 91%. IR 2242.8 ($\nu_{C\equiv N}$), 1278.3 ($\nu_{P=O}$); ^{31}P-NMR (CDCl$_3$) $\delta = -4.732$ ppm; MS m/z(%) 222(M + 1, 6) 194(5) 179(7) 167(20) 155(21) 127(95) 99(100) 81(25) 68(22); ^{1}H-NMR (CDCl$_3$) δ 1.374(2t, 6H), 1.845(s, 6H), 4.177 (q, 4H).

Reaction Between Tetraethyl Pyrophosphate and Potassium Cyanide

To a 50 ml flask, methyl cyanide (20 ml), potassium cyanide (0.4 mmol), and tetraethyl pyrophosphate (0.2 mmol) was added. The mixture was stirred vigorously at room temperature for 8 h, then heated to reflux for 2 h. Samples for GC analysis were taken every 2 h during the course of the reaction.

REFERENCES

[1] T. Shioiri, *Yukai Gaosei Kaganku Kyokaishi*, **37**(10), 856 (1979).

[2] T. Kurihara, S. Harusawa, and R. Yoneda, *Yukai Gaosei Kaganku Kyokaishi*, **46**(12), 1164 (1988).

[3] P. J. Lonnon and S. G. Vulfson, U.S. Pat. 5,859,278 (1999).

[4] B. C. Saunders, G. T. Stacey, F. Wild, and I. G. E. Wiling, *J. Chem. Soc.*, 699 (1948).

[5] A. Takamizawa, Y. Sato, and S. Tanaka, *Yakugaku Zasshi*, **85,** 298 (1965).

[6] T. S. Tung and C. S. Tai, *Hua Hsuch Pao*, **31,** 199 (1965).

[7] S. K. Das and S. N. Balasubrahmanyam, *J. Org. Chem.*, **48,** 4232 (1983).

[8] R. Yoneda and T. Shioiri, Japan. Kakai 73 67,202 (1973).

[9] L. A. Lazuking, V. P. Kukhar, G. V. Romanov, et al., *Zh. Obshch. Khim.*, **50**(5), 985 (1980).

[10] T. R. Fukuto, R. S. Vetter, T. C. Baker, and M. S. Malik, U.S. Pat. 5,064,820 (1991).

[11] H. W. Roesky, *Chem. Ber.*, **100,** 2147 (1967).

[12] C. Reichardt, *Solvent Effects in Organic Chemistry* (Verlag Chemie Weinheim, New York, 1970), chap. 6, pp. 240–260.

[13] V. Mark and J. R. Van Wazer, *J. Org. Chem.*, **32,** 1187 (1967).

[14] G. M. Steinberg, *J. Org. Chem.*, **15**, 637 (1950).