Catalytic synthesis of phosphoryl isocyanates*,**

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A general efficient method for the synthesis of phosphoryl isocyanates was developed. The method involves reactions of phosphoryl chlorides with sodium cyanate in the presence of anhydrous magnesium chloride as a catalyst.

Key words: phosphoryl chlorides, sodium cyanate, catalysis, phosphoryl isocyanates, synthesis.

Phosphoryl isocyanates XYP(O)NCO are highly reactive and are used as starting reagents for the synthesis of various types of compounds of potential practical interest: phosphorylated urethans, ureas, heterocycles, etc. Although such isocyanates have been known since the midtwentieth century, none of the current methods for their synthesis combines versatility, efficiency, and use of accessible and inexpensive starting reagents. Reactions of phosphoryl chlorides XYP(O)Cl with sodium cyanate*** could serve as such a universal method; however, these reactions afford only isocyanates of some phosphonic and phosphinic acids in satisfactory yields, while reactions of NaOCN with phosphochloridates either give no corresponding isocyanates at all or their yields are low.^{2****} Most likely, such a result can be explained by the lower reactivities of phosphochloridates compared to phosphonochloridates and phosphinoyl chlorides in $S_N 2(P)$ -reactions.⁶ This problem could be solved by activation of the phosphorus-containing reagent, e.g., in the presence of an appropriate catalyst.

Earlier,⁷ we found that phosphorylation of weakly nucleophilic polyfluorinated alcohols with phosphoryl chlorides XYP(O)Cl is catalyzed by some metal salts exhibit-

** For the preliminary report, see Ref. 1.

ing the properties of Lewis acids. Most likely, the catalyst activates a phosphorylating agent by forming a complex of the metal cation with the O atom of the phosphoryl group. The formation of this complex increases the positive charge at the P atom, which promotes the corresponding nucleophilic displacement of the chlorine atom.

If such an activation really takes place, these metal salts should also catalyze other reactions of nucleophilic replacement of chlorine at the tetrahedral P atom, in particular, reactions of phosphoryl chlorides 1a-f with sodium cyanate. Indeed, it turned out that electrophilic catalysis by metal salts can be successfully employed for the synthesis of phosphoryl isocyanates 2a-f.

$$RR'P(O)CI + NaOCN \qquad \xrightarrow{MgCl_2} RR'P(O)NCO$$
1a-f
$$RR'P(O)NCO$$

 $\begin{array}{l} {\sf R} = {\sf R}^{\,\prime} = {\sf PhO}\left({\bf a} \right); \, m\text{-}{\sf MeC}_{6}{\sf H}_{4}{\rm O}\left({\bf b} \right); \, o\text{-}{\sf MeC}_{6}{\sf H}_{4}{\rm O}\left({\bf c} \right); \, {\sf CF}_{3}{\sf CH}_{2}{\rm O}\left({\bf d} \right); \\ {\sf R} = {\sf Me}, \, {\sf R}^{\,\prime} = {\sf PhO}\left({\bf e} \right); \, {\sf R} = {\sf R}^{\,\prime} = {\sf Ph}\left({\bf f} \right) \end{array}$

Anhydrous acetonitrile was used as a solvent for this reaction. This polar aprotic solvent possesses a high dissolving ability and is inert toward the starting phosphoryl chlorides and the resulting phosphoryl isocyanates 2a-f.

A metal salt combining a high efficiency and solubility in this reaction medium should be the best catalyst. We found that for catalytic phosphorylation of polyfluoroalkanols with phosphorus acid chlorides, anhydrous chlorides of Groups I and II metals (LiCl, CaCl₂, and MgCl₂) are the most efficient catalysts.⁷ These salts were tested for solubility in acetonitrile—phosphoryl chloride **1** and MgCl₂ proved to be substantially more soluble. For this reason, this salt was used as a catalyst.

We studied a reaction of diphenyl phosphochloridate (1a) with a double excess of NaOCN in boiling acetonitrile without a catalyst and in the presence of anhydrous

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^{***} According to data,² in reactions with phosphorus acid chlorides, commercial NaOCN is often even more efficient than much more expensive silver cyanate conventionally used in such reactions.

^{****} It should be noted that dialkoxyphosphoryl isocyanates can be alternatively obtained by reactions of the corresponding phosphoramidates with (COCl)₂;³ however, this method is unsuitable for the synthesis of diaryloxy-⁴ and bis(polyfluoroalkoxy)phosphoryl isocyanates⁵ because of low yields of the target products.

Entry	Starting reagent	Catalyst 1	Condi- tions*	τ/h	Content of 2 in the mixture** (%)	Yield of 2 (%)
1	a	_	A	70	34	25
2		MgCl ₂	A	4	70	59
3	b	MgCl ₂	A	4	65	49
4	c	MgCl ₂	A	6	61	46
5	d	_	A	3	50	29
6		MgCl ₂	A	1	72	58
7	e	_	A	3	72	52
8		MgCl ₂	В	3	93	73
9	f	_	A	1	93	70
10		$MgCl_2$	В	1	98	78

Table 1. Reactions of phosphoryl chlorides 1a-f with sodium cyanate

Table 2. Physicochemical constants and elemental analysis data for RR P(O)NCO 2a-f

* *A* refers to refluxing and *B* refers to room temperature.

** According to ³¹P{¹H} NMR spectra.

MgCl₂ (2.5 mol. %) (Table 1). According to ³¹P NMR data, this reaction in the absence of a catalyst (entry *1*) proceeded very slowly and was accompanied by side reactions, the yield of diphenoxyphosphoryl isocyanate (**2a**) being only 25%. The use of the catalyst (entry 2) reduced the reaction time from 70 to 4 h. In addition, the amounts of by-products were significantly lowered and, consequently, the yield of phosphoryl isocyanate **2a** was approximately doubled.

Introduction of a methyl substituent into the *meta*-position of the benzene ring of the starting phosphochloridate virtually did not change the rate of the catalytic process (entry 3), while the presence of an *ortho*-methyl group substantially reduced the reaction rate (entry 4), probably because of steric hindrances.

In the case of bis(2,2,2-trifluoroethyl) phosphochloridate (1d), the use of the catalyst (*cf.* entries 5, 6) also reduced the reaction time and appreciably increased the yield of the target isocyanate 2d.

We found that for both phenyl methylphosphonochloridate (1e) and diphenylphosphinoyl chloride (1f), the use of MgCl₂ as a catalyst allows the room-temperature synthesis of the corresponding phosphoryl isocyanates 2e,f (*cf.* entries 7 and 8 and entries 9 and 10, respectively). As with phosphochloridates, the use of this catalyst lowered the content of by-products in the reaction mixture and increased the yields of phosphoryl isocyanates. In the reaction of phosphinoyl chloride 1f with NaOCN in the presence of MgCl₂, the content of byproducts was only 2%, which allows isocyanate 2f to be used subsequently without additional purification.

In all the catalytic reactions studied, the resulting phosphoryl isocyanates 2a-f can be sufficiently easily separated from organophosphorus by-products by distillation *in vacuo*. The constants and elemental analysis data for

Com- pound	B.p./°C (<i>p</i> /Torr) [M.p./°C]	Found (%) Calculated				Molecular formula	
		С	Н	Ν	Р		
2a ⁸	149 (0.5)	_	_	_	_	_	
2b*	171 (1.0)	<u>59.34</u> 59.41	<u>4.44</u> 4.65	<u>4.58</u> 4.62	<u>10.18</u> 10.21	C ₁₅ H ₁₄ NO ₄ P	
2c*	177	<u>59.41</u> 59.41	<u>4.63</u> 4.65	<u>4.63</u> 4.62	<u>10.09</u> 10.21	C ₁₅ H ₁₄ NO ₄ P	
2d ⁵	64-65	_	_	—		—	
2e ⁹	(0.5) 115-117 (0.5)	_	_	_	_	—	
2f ¹⁰	(0.5) 158—160 (0.5)	—	_	_	_	_	
	[53-55]						

* Data of this study.

the isocyanates obtained are given in Table 2. The structures of phosphoryl isocyanates 2a-f were confirmed by ¹H, ¹⁹F, and ³¹P NMR spectroscopy (Table 3).

Thus, using electrophilic catalysis, we developed a general and efficient method for the synthesis of the corresponding isocyanates from phosphorus(v) oxo acid monochlorides and sodium cyanate.

Experimental

¹H and ³¹P NMR spectra were recorded on a Bruker AMX-400 instrument (400.13 (¹H) and 161.98 MHz (³¹P)). ¹⁹F NMR spectra were recorded on a Bruker WP-200SY instrument (188.31 MHz). Chemical shifts were referenced to signals for the residual protons of the deuterated solvent as the internal standard (¹H) and CF₃COOH (¹⁹F) and 85% H₃PO₄ (³¹P) as the external standards; C₆D₆ was used as a solvent.

Diphenylphosphinoyl chloride (1f) (Aldrich) was distilled *in vacuo* before use. Acetonitrile, benzene, and C_6D_6 were used freshly distilled over P_2O_5 . Sodium cyanate (Aldrich) was dried *in vacuo* over P_2O_5 at 120 °C for 4 h. All manipulations were carried out in an argon atmosphere. Phosphoryl chlorides 1a-ewere prepared according to known procedures.^{11–14}

Catalytic synthesis of phosphoryl isocyanates 2a-f (general procedure). Compound 1a-f (0.05 mol) was added to a suspension of finely divided anhydrous MgCl₂ (1.25 mmol) in MeCN (30 mL). The mixture was heated with stirring until the catalyst was completely dissolved. Then NaOCN (0.1 mol) was added and the reaction mixture was stirred until the starting compound 1 was completely consumed (³¹P NMR data). The precipitate of inorganic salts was filtered off (for 2a,d-f) or separated by centrifuging (2b,c) and washed with benzene (2×10 mL). The filtrate was concentrated and the residue was distilled *in vacuo*. The synthesis of phosphoryl isocyanates 2a,d-f in the absence of any catalyst was carried out analogously.

Com-	R	R´	¹ Η, δ (J	//Hz)	$^{19}F\{^{1}H\}$	$^{31}P\{^{1}H\}$
pound			R R'		δ (s)	
2a	PhO	PhO	6.90-7.2	_	-22.34	
2b	<i>m</i> -MeC ₆ H ₄ O	<i>m</i> -MeC ₆ H ₄ O	2.02 (s, 6 H, Me), 6.78-	_	-22.54	
2c	o-MeC ₆ H ₄ O	o-MeC ₆ H ₄ O	2.18 (s, 6 H, Me), $6.88-7.45$ (m, 8 H, C_6H_4)		_	-22.13
2d	CF ₃ CH _A H _B O	CF ₃ CH _A H _B O	$3.90 (m, H_A), 3.92 (m, H_B)$		2.03 ^a	-12.24^{b}
			$(^{2}J_{\rm H,H} = 12.4, ^{3}J_{\rm H,F})$	$= 8.0, {}^{3}J_{\rm H,P} = 9.8)$		
2e	Me	PhO	1.39 (d, 3 H,	6.94-7.30	—	15.31
			${}^{2}J_{\rm H,P} = 18.0$)	(m, 5 H)		
2f	Ph	Ph	7.02—7.15 (m, 6	H, <i>m</i> -, <i>p</i> -Ph);	_	17.60
			7.72—7.80 (m	, 4 H, <i>o</i> -Ph)		

Table 3. NMR spectra of phosphoryl isocyanates RR'P(O)NCO 2a-f

^{*a* ¹⁹F NMR, δ: 2.03 (t, ${}^{3}J_{H,F} = 8.0$ Hz). ^{*b* ³¹P NMR, δ: -12.24 (quint, ${}^{3}J_{H,P} = 9.5$ Hz).}}

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