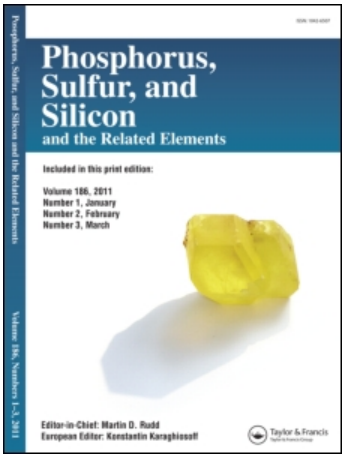

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Yu-Fen Zhao[a]; Gai-Jiao Ji[a]; She-Kang Xi[a]; Hue-Gong Tang[a]; Ai-Teng Song[a]; Shou-Zuo Wei[a]
[a] Institute of Chemistry, Academia Sinica, Beijing, China

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THE APPLICATION OF DIALKYLPHOSPHITE AS THE AMINO PROTECTION REAGENT IN ORGANIC SYNTHESIS

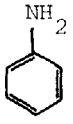
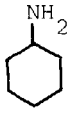
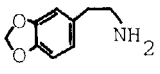
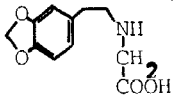
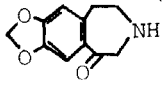
YU-FEN ZHAO*, GAI-JIAO JI, SHE-KANG XI, HUE-GONG TANG, AI-TENG SONG and SHOU-ZUO WEI
Institute of Chemistry, Academia Sinica, Beijing, China

Abstract The acid hydrolysis of N-phenyl-N-dialkylphosphoramidates was studied by HPLC, the N-phenyl-N-diisopropylphosphoramidate has half life 53 min in 6N HCl at 50°C. The P-N bonds of these phosphoryl derivatives also show a relative stability in organic and Lewis acids.

The protection of amino group is one of the most important problem in organic synthesis. The urethane-type acyl, sulfonyl, sulfenyl[1] and phosphinyl[2] protection reagents are often used in peptide synthesis. Among them, the deprotection of the sulfonamides has always been the problem. On the other hand, the phosphoryl group has rarely been used for the protection of amino group in general organic synthesis. This is due to the acid lability of the P-N bonds. In this communication, the acid tolerence of the dialkylphosphoramidate's derivatives and the persistence of their P-N bonds during Lewis acid catalyzed reaction were reported.

The dialkylphosphites were used as the amino protection reagents[3]. The deprotection of the dialkylphosphoryl groups was performed in the acid conditions[4], (TableI). The hydrolyzed products were identified by the m.p. of the amine·HCl salt or the IR and NMR as compared to the authentic sample. The N-β-phenylethyl-N-dialkylphosphoryl-

TABLE I. Acid degradation of the dialkylphosphoramidates and the corresponding sulfonamides

amine	protecting group	* P%	* D%	Deprotection cond.	reference
	$(CH_3O)_2\overset{O}{\overset{\|}{P}}-$	73	94	13%HCl, 70° 20 min.	
	$\phi-SO_2-$	-	26	25%HCl, reflux 7 hr.	5
n-Bu-NH_2	$(iPrO)_2\overset{O}{\overset{\|}{P}}-$	98	91	22%HCl, 50° 5 hr.	
	$\phi-\overset{O}{\overset{\|}{C}}-CH_2-SO_2-$	92	66	Zn/HAc, R.T. 1 hr.	6
	$(C_2H_5O)_2\overset{O}{\overset{\|}{P}}-$	90	88	13%HCl, 70°, 1 hr.	
	CF_3-SO_2-	95	94	$LiAlH_4$-ether, reflux	6
	$(iPrO)_2\overset{O}{\overset{\|}{P}}-$	98	83	22%HCl, 50°, 5 hr.	
	$\phi-\overset{O}{\overset{\|}{C}}-CH_2-SO_2-$	91	67	Zn/HAc, R.T. 1 hr.	6
	$(iPrO)_2\overset{O}{\overset{\|}{P}}-$	86	74	HCl(g)/THF, 15°, 24 hr	
	MBS-**	75	-	12N HCl/THF(1/1), 70°, 24 hr unreacted	
	$(iPrO)_2\overset{O}{\overset{\|}{P}}-$	80	70	HCl(g)/THF, 25°, 24 hr.	
	MBS-**	74	-	Na/NH_3, -50°, 2 hr gave complicated mixtures	
	$(iPrO)_2\overset{O}{\overset{\|}{P}}-$	73	85	HCl(g)/THF, 25°, 24 hr.	
	MBS-**	64	-	$NaBH_4$, then Na/NH_3 or $NaBH_4$ then CF_3COOH or H_2SO_4 gave complicated mixtures	

*. P%=the protection yield, D%=the deprotection yield.

** MBS- : $p-OCH_3-\phi-SO_2-$

glycine,1, and the N-dialkylphosphoryl-tetrahydro-3-benzazepine-1-one,2, prepared by the procedure outlined in the Scheme I, were quantitatively transformed into the amine·HCl salts[7]. For the corresponding N-tosyl or N-MBS ones[8] the deprotection of the sulfonyl group was not only complicated but oftenly unsuccessfully, (Table I).

For application to the organic synthesis, the protected amines, dialkylphosphoramidates, usually must have some degree of acid tolerence under the reaction conditions. Therefore, we used the HPLC to followed the acid hydrolysis of the N-phenyl-N-dialkylphosphoramidates in acidic media. And the first order rate constants[9] were calculated from the slope of the curve ln C versus time,(TableII). In $CF_3COOH/CHCl_3$ their degradation percentages were measured at specified time, (TableII). Among these three compounds the N-phenyl-N-diisopropylphosphoramidate has the greatest stability in acidic media. Also, as investigated by ^1H nmr a 0.086M compound 1 in $CF_3COOH/CHCl_3$(1/5) standing at 15° for 4 hr, there was no degradation. And a 0.103M compound 1 in pure CF_3COOH, there was 30% degradation after 4 hr at 15°.

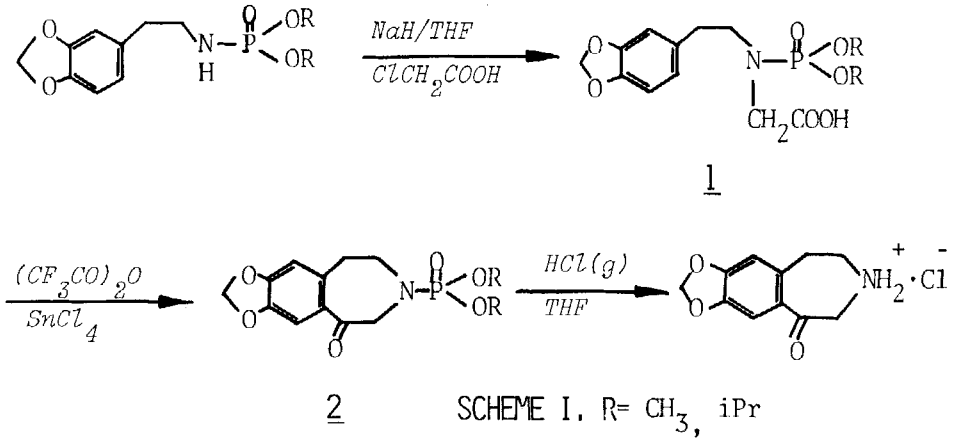
TABLE II. Acid degradation of the N-phenyl-N-dialkylphosphoramidates

compound	HCl[a]	T(°C)	rate const.($^{-1}$min) half life	$CF_3COOH/CHCl_3$[b] % degradation
$(CH_3O)_2\overset{O}{\overset{\|}{P}}NH\phi$	3N	50	0.084 (14 min)	19%/26 hr
$(C_2H_5O)_2\overset{O}{\overset{\|}{P}}NH\phi$	3N	50	0.028 (24 min)	22.6/23.5 hr
$(C_2H_5O)_2\overset{O}{\overset{\|}{P}}NH\phi$	6N	50	0.179 (4 min)	
$(iPrO)_2\overset{O}{\overset{\|}{P}}NH\phi$	6N	50	0.013 (53 min)	25.6/96 hr
	6N	25	(17 hr)	

(a). 0.2M phosphoramidates in HCl/CH_3OH, at regular interval, the remained conc.was measured by external standard in HPLC.

(b). 0.1M phosphoramidates in $CF_3COOH/CHCl_3$(1/5).

From the above results, it shows that the dialkylphosphoramidates have the great merit of acid tolerence,which will extend their potential as the general amino protecting groups in organic synthesis. For example, in Scheme I, the intramolecular Friedel-Crafts acylation of 1, catalyzed by Lewis acid, gave the stable compound 2. In conclusion, the P-N bonds of the phosphoryl derivatives show a relative stability in organic and Lewis acids. This property will be useful in general organic synthesis.



SCHEME I. R= CH_3, iPr

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