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Synthesis of Primary *sec*-Alkylamines *via* Nucleophilic Ring-opening of N-Phosphorylated Aziridines[1]

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Abstract: The novel ring-opening reaction of various 2-alkyl- and 2,2-dimethyl-N-(diethoxyphosphoryl)aziridines (**1**) and (**10**) with copper-modified Grignard reagents proceeds regiospecifically at the less hindered carbon. The diethyl N-*sec*-alkylphosphoramidates (**2**) thus obtained may efficiently be converted to primary *sec*-alkylamine hydrochlorides (**3**) by refluxing with 20% hydrochloric acid. 2,3-Disubstituted N-phosphorylated aziridines except N-phosphorylated cyclohexenimine (**4**) do not react under the described conditions. Copper-mediated reaction of 2-phenyl-N-(diethoxyphosphoryl)aziridine (**7**) with Grignard reagents affords a mixture of regioisomers (**8**) and (**9**) but still with the preference of ring-opening at the carbon of lesser substitution. © 1997 Elsevier Science Ltd.

INTRODUCTION

The ring-opening reaction of aziridines and subsequent transformations have found widespread application in the synthesis of biologically important cyclic and acyclic amines[2]. Activation of the aziridine, which is essential for effective ring-opening, can be achieved by the presence of an electron withdrawing protecting group on the ring nitrogen atom. The tosyl group serves as an excellent activator and has been widely employed[2,3], but no convenient detosylation procedures have been so far available due to the rather drastic conditions required for cleavage of the strong sulfonamide bond[4].Recently the diphenylphosphinyl (Dpp) group as a suitable activator for aziridine ring-opening reactions has been recommended[5] and some Dpp-aziridines were found useful 2-aminoethyl cation equivalents[5a,b]. The use of acid-labile Dpp protecting group in peptide chemistry is well known[6]. This group has been also extensively employed for other synthetic applications if easy deprotection of the nitrogen atom was required[7].

Looking for an easily available and relatively inexpensive substitute of the Dpp protecting group we turned recently our attention to the diethoxyphosphoryl residue as a potential aziridine activator. We describe herein the details of our studies on nucleophilic ring-opening of various N-(diethoxyphosphoryl)aziridines by means of copper-modified Grignard reagents.

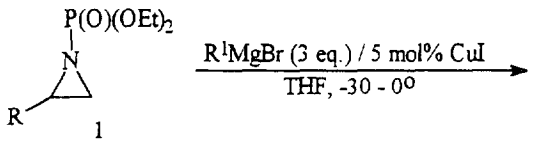
RESULTS AND DISCUSSION

It was envisaged that the diethoxyphosphoryl group linked to nitrogen atom of the aziridine ring would activate the C-N bonds to nucleophilic attack by organometallic reagents. Initial realization of this conjecture was demonstrated by the ring-opening of N-(diethoxyphosphoryl)aziridine with an excess of Grignard reagents in the presence of catalytic amounts of copper (I) iodide[8]. The extension of this work is the subject of this paper[1], which documents an investigation of the reactivity of various C-substituted N-(diethoxyphosphoryl)aziridines towards Grignard reagents and conversion of the initially obtained diethyl N-*sec*-alkylphosphoramidates (**2**) and (**5**) to *sec*-alkylamine hydrochlorides (**3**).

Preliminary studies proved that under a variety of conditions Grignard reagents were unreactive towards N-phosphorylated aziridines (**1**). Also initial attempts at ring-opening of (**1**) using organolithium compounds, not unexpectedly, resulted in preferential attack at phosphorus giving a complex mixture of products. These observations prompted us to check the possibility of copper mediation in nucleophilic ring-opening of N-phosphorylated aziridines (**1**). It was found that the use of 5 mole% of copper (I) iodide as catalyst allows ring-opening by Grignard reagents to proceed in high yield and with regiospecificity, thus making the reaction the first convenient and economic approach to *sec*-alkylamines from aziridines.

The reactions between N-phosphorylated aziridines (**1**) and an excess (typically 3 mole equivalents) of organomagnesium bromide were carried out in THF solution at -5° - 0°C. Copper (I) iodide used as catalyst (usually 5 mol%) was added to the freshly prepared solution of organomagnesium bromide at -30°C. The temperature of the reacting mixture was then slowly raised to 0°C and kept at -5° - 0°C for 2-3 hours. Progress of the reaction could be easily monitored by ^{31}P NMR spectroscopy. Vanishing signal at $\delta = 14\text{-}15$ ppm characteristic for N-phosphorylated aziridine (**1**) and appearance of the new signal at $\delta = 9\text{-}9.5$ ppm typical for diethyl N-*sec*-alkylphosphoramidate (**2**) could be observed. The use of an excess of Grignard reagent was found essential for complete disappearance of the starting aziridine from the reaction mixture. All ring-opening reactions of 2-alkyl-N-(diethoxyphosphoryl)aziridines (**1**) were regiospecific, always occuring with nucleophilic attack at the less substituted carbon atom of the aziridine ring. (Scheme 1). Diethyl N-*sec*-alkylphosphoramidates (**2**) could be easily isolated in pure state after quenching of the reaction mixture with aqueous ammonium chloride solution and no further purification was necessary before deprotection. In majority of cases (except compounds **11**) removal of the diethoxyphosphoryl group could be easily accomplished by refluxing crude phosphoramidates (**2**) with 20% hydrochloric acid to give *sec*-alkylamine hydrochlorides (**3**) in good to excellent yields. The reaction sequence (1)→(2)→(3) is of general utility and represents a simple, convergent construction of *sec*-alkylamine carbon skeleton from the respective aziridine and organomagnesium bromide.

The method suffers, however, from some serious limitations. 2,3-diethyl- and- 2,3-dipropyl-N-(diethoxyphosphoryl)aziridines were found completely unreactive towards Grignard reagents under standard conditions. Among bicyclic aziridines only N-(diethoxyphosphoryl)cyclohexeneimine



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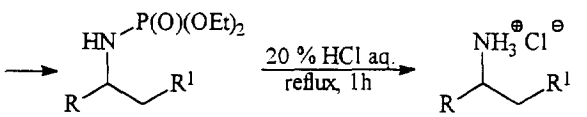
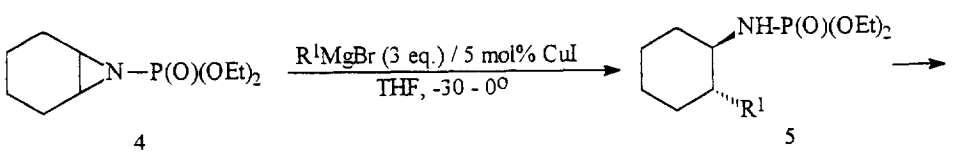


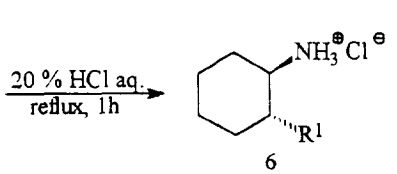
2 3

2, 3	R	R^1	2, 3	R	R^1
a	Me	Et	j	Me	$PhCH_2CH_2$
b	Me	*i*-Pr	k	Me	*c*-C_5H_9
c	Me	Pr	l	Pr	Et
d	Me	*s*-Bu	m	Pr	Bu
e	Me	*t*-Bu	n	Pr	*i*-Bu
f	Me	Ph	o	Bu	Et
g	Me	*p*-CH_3-C_6H_4	p	Bu	Bu
h	Me	*p*-CH_3O-C_6H_4	r	Bu	*i*-Bu
i	Me	2-naphthyl			

Scheme 1



4 5



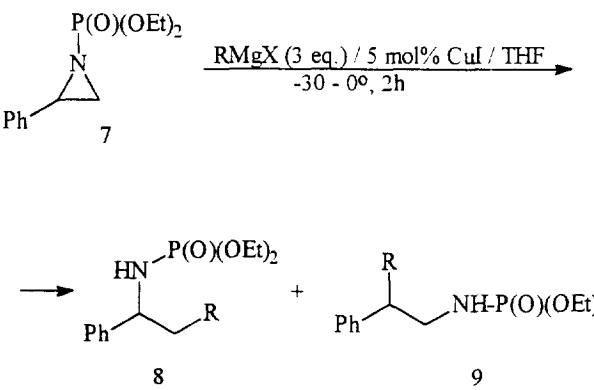
6

5, 6	R^1
a	Et
b	Bu
c	*i*-Bu

Scheme 2

(7-(diethoxyphosphoryl)-7-azabicyclo [4.1.0.]heptane) (**4**) could be easily converted into the respective 2-substituted cyclohexylamine hydrochlorides (**6a-c**). (Scheme 2). *Trans*-configuration has been tentatively ascribed to these compounds. In analogy with epoxides, fused bicyclic aziridine (**4**) may be expected to obey the Fűrst-Plattner rule[9] for *trans*-diaxial ring-opening leading to *trans*-1,2-disubstituted cyclohexanes (**5**) and (**6**). In contrast to (**4**) the homologous N-(diethoxyphosphoryl)cycloheptenеimine was found totally unreactive under a variety of experimental conditions.

Among the scattered reports on the ring-opening of phenyl-substituted N-tosyl aziridines by Grignard reagents it has been shown that the regioselectivity of such reactions depends on the amount of the Grignard reagent used[3f] and also on the nature of carbon residue of the Grignard reagent[10]. We have studied the reaction of 2-phenyl-N-(diethoxyphosphoryl)aziridine (**7**) with three mole equivalents of Grignard reagents in the presence of 5 mol% of copper (I) iodide under typical conditions. (Scheme 3). The regioselectivity of this reaction (the attack of Grignard reagent on the primary carbon atom to afford benzylic amine derivatives (**8**) *vs.* that on the benzylic carbon to give primary amine derivatives (**9**)) was found to be practically independent on the nature of the carbon residue of the Grignard reagent used (Table 1). The only exception was methylmagnesium iodide affording the mixture of (**8**+**9**) containing considerably more of (**9**) comparing to its regioisomer (**8**). In all cases the nucleophilic attack of Grignard reagent on the less hindered C-2 carbon atom prevailed. All structures of phosphoramidates (**8**) and of two phosphoramidates (**9**,R=Me,Et) have been unequivocally proved by comparing ^{31}P NMR spectra of the respective mixtures obtained by aziridine (**7**) ring-opening with those of authentic specimens prepared by independent synthetic procedures (see Experimental part.).



7 8 9

Scheme 3

Geminal disubstituted 2,2-dimethyl-N-(diethoxyphosphoryl)aziridine (**10**) reacted with organomagnesium bromides more slowly than compounds (**1**), (**4**), and (**7**). The ring-opening leading to diethyl N-*t*-alkylphosphoramidates (**11**) was completed (disappearance of the ^{31}P NMR signal of aziridine (**10**) at δ=12 ppm) only after 12 hours at room temperature in the presence of 10 mol% of copper (I) iodide. (Scheme 4).

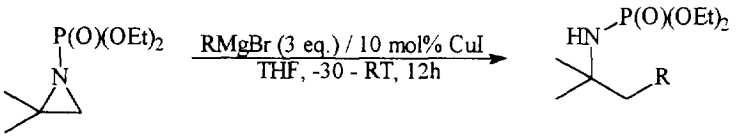
Table 1. Ring-opening of 2-phenyl-N-(diethoxyphosphoryl)aziridine **7** by Grignard reagents.

Entry	RMgX	Isolated yield of **8**+**9** (%)	^{31}P NMR($CDCl_3$) δ, ppm[a]		Ratio[b] **8:9**
			8	**9**	
1	MeMgI	96	8.24	9.58	58:42
2	EtMgBr	63	8.21	9.64	71:29
3	PrMgBr	73	8.22	9.62	72:28
4	BuMgBr	64	8.17	9.60	73:27

[a] Measured at 81 MHz with a Bruker AC 200 spectrometer.

[b] Determined by integrals of the ^{31}P-NMR spectrum.

The yields of diethyl N-*t*-alkylphosphoramidates (**11**), in all cases formed as the sole products, were reasonable (Table 2). According to expectations nucleophilic ring-opening occured always regioselectively on the primary less hindered C-3 carbon atom. Attempted dephosphorylation of phosphoramidates (**11**) could not be, however, accomplished under typical hydrolytic or acidolytic conditions. Deprotection with p-toluenesulphonic acid in refluxing ethanol was extremely slow leading to unresolvable mixtures of products in minute yields. Attempted cleavage of phosphorus-nitrogen bond with lithium aluminum hydride in refluxing ether[11] was also totally unsuccessful.



10 11

11	a	b	c	d	e	f	g
R	Et	Bu	*c*-C_5H_9	$PhCH_2CH_2$	Ph	*p*-CH_3-C_6H_4	*i*-Pr

Scheme 4

In conclusion only the use of 2-alkyl-N-(diethoxyphosphoryl)aziridines (**1**) and N-(diethoxyphosphoryl)cyclohexenimine (**4**) for nucleophilic ring-opening with Grignard reagents leads to the synthetically useful results. Such reactions allow the construction of *sec*-alkylamines with various carbon

Table 2. Diethyl N-t-Alkylphosphoramidates **11**.

Compd No.	Yield[a] %	n_D^{20}	^{1}H NMR($CDCl_3$) δ,ppm J,Hz	^{31}P NMR ($CDCl_3$) δ,ppm	IR (film) ϑ, cm^{-1}	FAB MS[b]
11a	88(60)	1.4374	0.87(t,3H,J=6.8);1.18(s,6H);1.24-1.45(m,4H);1.278,1.282 (2t,6H,J=7.1);2.46(d,1H,J=7.1);4.01,4.02(2qt,4H,J=7.1)	7.51	3212,2964,2884,2872,1236, 1040,962	238 (M+1)
11b	63(41)	1.4404	0.85(t,3H,J=6.8);1.18(s,6H);1.28,1.29(2t,6H,J=7.1);1.20-1.50(m,8H);2.47(d,1H,J=7.3);4.01,4.02(2qt,4H,J=7.1)	7.68	3212,2932,2864,1468,1386, 1238,1166,1032,960	266 (M+1)
11c	71(54)	1.4608	1.22(s,6H);1.29,1.30(2t,6H,J=7.1);1.36-1.65(m,8H);1.70-1.92(m,3H);2.49(d,1H,J=7.1);4.02,4.03(3qt,4H,J=7.1)	8.30	3200,2952,2884,2868,1468, 1386,1236,1034,962	278 (M+1)
11d	99(72)	1.4954	1.20(s,6H);1.283,1.287(2t,6H,J=7.1); 1.45-1.54(m,2H); 1.57-1.71(m,2H);2.52(d,1H,J=8.7);2.59(t,2H,J=7.1); 4.01,4.02(2qt,4H,J=7.1);7.12-7.31(m,5H)	7.70	3204,2976,2956,2940,1478, 1452,1386,1236,1034,962, 800,766,750,700	314 (M+1)
11e	84(30)	1.5362	1.25(s,6H);1.29,1.30(2t,6H,J=7.1); 2.51(d,1H,J=7.2); 2.76(s,2H);3.87-4.16(m,4H);7.12-7.48(m,5H)	8.05	3248,3060,3028,2980,1592, 1478,1384,1368,1226,1030, 970,740,702	286 (M+1)
11f	87(29)	1.4994	1.23(s,6H);1.20,1.30(2t,6H,J=7.1);2.31(s,3H);2.48(d,1H, J=7.2);4.02,4.03(2qt,4H,J=7.1);7.09(s,4H)	8.14	3208,3080,2984,2940,1512, 1496,1384,1366,1234,1164, 1032,966,816	300 (M+1)
11g	86(28)	1.4402	0.94(d,6H,J=6.6);1.24(s,6H);1.30,1.31(2t,6H,J=7.1); 1.38,1.39(dd,2H,J=5.4);1.551.87(m,1H); 2.46(d,1H,J=6.8);4.04,4.05(2qt,4H,J=7.1)	8.29	3213,2976,2884,1468,1386, 1366,1236,1040,962,800	252 (M+1)

[a] Yields of crude compounds 11. Yields of distilled samples are given in brackets.

[b] All compounds 11 have been satisfactorily analysed (C ±0.3%, H ±0.3%, N ±0.2%, P ±0.3%).

frameworks by the proper choice of both the carbon moiety of the Grignard reagent and the C-2 substituents of the aziridine.

EXPERIMENTAL

Solvents were purified in the usual way. Melting points (taken in capillaries) are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 200 MHz, using $CDCl_3$ solutions (unless otherwise stated) and TMS as internal standard. ^{31}P NMR spectra were taken on a Bruker AC 200 spectrometer at 81 MHz. Positive chemical shifts are downfield from 85% H_3PO_4 used as external reference. IR spectra were measured in liquid films using a Specord M 80 (C.Zeiss) instrument. FABMS were recorded on a PO Electron (Ukraine) Modell MI 1200 E mass spectrometer equipped with a FAB ion source (thioglycerol matrix). Xenon was used as ionizing gas. The beam energy was set to 5 keV. Mass spectra were recorded on a LKB 2091 mass spectrometer at 70 eV (direct inlet).

Materials and model compounds.

All starting materials including propyleneimine were purchased from Fluka and used without additional purification.

*2-Alkyl-N-(diethoxyphosphoryl)aziridines (**1**, R=Pr,Bu), 2-phenyl-N-(diethoxyphosphoryl)aziridine (**7**), and N-(diethoxyphosphoryl)cyclohexeneimine (**4**) were prepared as described previously*[19].

*2-Methyl-N-(diethoxyphosphoryl)aziridine (**1**, R=Me).*

A solution of diethyl phosphite (6.9 g, 0.05 mol) in CH_2Cl_2 (10 mL) was added dropwise with stirring at 10-15°C to the mixture of propyleneimine (3.19 g, 0.055 mol), potassium bicarbonate (10.0 g), potassium carbonate (13.8 g), tetrabutylammonium bromide (0.81 g, 0.0025 mol), CCl_4 (10 mL), and CH_2Cl_2 (40 mL). Stirring was then continued for 5hr at room temp. The resultant mixture was filtered, evaporated, and distilled under reduced pressure to give pure (**1**, R=Me) in 80% yield. Colorless oil; b.p. 78-80°/1.3 mmHg; n_D^{20}-1.4340; IR: ϑ = 2984, 2952, 2932, 1402, 1266, 1246,1238, 1158, 1040, 972, 912, 878 cm^{-1}; ^{1}H NMR: δ 1.26 (dd, 3H, J=5.4Hz, J=1.3Hz), 1.33 (t, 6H, J=7.1Hz), 1.85 (ddd, 1H, J=1.2Hz, J=3.5Hz), 2.31 (ddd, 1H, J=1.2Hz, J=5.9Hz, J=17.9Hz), 2.45-2.65 (m, 1H), 4.13 (dq, 4H, J=7.1Hz, J=7.6Hz); ^{31}P NMR: δ 14.99; FABMS: 194 (M+1). Anal.Calcd for $C_7H_{16}NO_3P$ (193.2): C, 43.52; H, 8.34; P, 16.03. Found: C, 43.49; H, 8.45; P, 15.90.

*2,2-Dimethyl-N-(diethoxyphosphoryl)aziridine (**10**).*

Isobutylene was slowly passed through the solution of crude diethyl N,N-dibromophosphoramidate[20] in CH_2Cl_2 (80 mL) at room temp. until pale-yellow coloration of the solution was acquired. The resultant mixture was cooled to 10°C and treated with a 20% aqueous solution of sodium bisulphite. The organic phase was separated, washed with water (50 mL), dried over $MgSO_4$, and evaporated. Crude diethyl N-(2-bromo-2-methylpropyl)-phosphoramidate thus obtained was added to the mixture of powdered potassium hydroxide (20.0 g), potassium carbonate (40.0 g), tetrabutylammonium hydrogen sulfate (3.4 g, 0.010 mol), and benzene (300 mL) and the mixture was efficiently stirred for 4hr at room temp. Solid inorganic salts were filtered off and washed with benzene (50 mL). Benzene solution was washed with water (2x50 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give crude aziridine (**10**) which was analytically pure. The compound is thermally unstable and should not be distilled. Yield - 21.8 g (52%); n_D^{20}-1.4420; IR: ϑ = 1250, 1140, 1040, 965, 853 cm^{-1}; ^{1}H NMR: δ 1.33, 1.34 (2t, 6H, J=7.0Hz), 1.41 (s, 6H), 2.18 (d, 2H, J=13.8Hz, J=13.8Hz), 4.12 (qt,4H,J=7.0Hz); ^{31}P NMR: δ 12.04; FABMS: 208(M+1). Anal.Calcd for $C_8H_{18}NO_3P$ (207.2): C, 46.40; H, 8.70; N, 6.77. Found: C, 46.50; H, 8.75; N, 6.60.

*Diethyl N-(1-phenylalkyl)phosphoramidates (**8a-d**)* were prepared by phase-transfer catalyzed phosphorylation of the respective 1-phenylalkylamines[21] with diethyl phosphite-CCl_4-$KHCO_3$-K_2CO_3 system according to the previously described procedure[22].

*Diethyl N-(1-phenylpropyl)phosphoramidate (**8a**).*

Yield - 99% (crude); colorless oil; ^{1}H NMR: δ 0.86 (t,3H,J=7.4Hz), 1.03, 1.29 (2t,6H,J=7.1Hz), 3.07 (bt,1H,J=9.9Hz), 3.50-3.63 (m,1H), 3.82-4.10 (m,4H), 7.19-7.35 (m,5H). Anal.Calcd for $C_{13}H_{22}NO_3P$ (271.3): C, 57.55: H, 8.17; N,5.16; P, 11.42. Found: C, 57.40, H, 8.02; N, 5.10; P, 11.20.

Diethyl N-(1-phenylbutyl)phosphoramidate (8b).

Yield - 62% (crude product washed with 10% NaOHaq.); colorless oil; ^{1}H NMR: δ 0.89 (t,3H,J=7.2Hz), 1.02, 1.29 (2t,6H,J=7.1Hz), 1.59-1.84 (m,4H), 3.03 (bt,1H,J=10.1Hz), 3.48-3.68 (m,1H), 3.75-4.17 (m,4H), 7.15-7.36 (m,5H). Anal.Calcd for $C_{14}H_{24}NO_3P$ (285.3): C, 58.93; H, 8.48; N, 4.91; P, 10.86. Found: C, 58.80; H, 8.59; N, 4.60; P, 10.65.

Diethyl N-(1-phenylpentyl)phosphoramidate (8c).

Yield - 67% (crude product washed with 10% NaOHaq.); colorless oil; ^{1}H NMR: δ 0.85 (dist.t,3H,J=6.75Hz), 1.03, 1.29 (2t,6H,J=7.1Hz), 1.61-1.78 (m,4H), 3.06 (bt,1H,J=10.5Hz), 3.52-3.66 (m,1H), 3.81-4.15 (m,4H), 7.17-7.37 (m,5H). Anal.Calcd for $C_{15}H_{26}NO_3P$ (299.3): C, 68.18; H, 8.76; N, 4.68; P, 10.35. Found: C, 67.90; H, 8.90; N, 4.51; P, 10.15.

Diethyl N-(1-phenylhexyl)phosphoramidate (8d).

Yield - 47% (crude product washed successively with aqueous oxalic acid and 10% NaOHaq.); colorless oil; ^{1}H NMR: δ 0.84 (dist.t,3H,J=6.8Hz), 1.02, 1.28 (2t,6H,J=7.1Hz), 1.69-1.79 (m,2H), 3.14 (br.t,1H,J=10.3Hz), 3.47-3.66 (m,1H), 3.76-4.15 (m,4H), 7.17-7.35 (m,5H). Anal.Calcd for $C_{16}H_{26}NO_3P$ (313.4): C, 61.32; H, 9.01; N, 4.47; P, 9.88. Found: C, 61.05; H, 9.25; N, 4.50; P, 9.70.

Diethyl N-(2-phenylpropyl)phosphoramidate (9a)

The compound was prepared by PTC phosphorylation[22] of 2-phenylpropylamine. Yield - 70%; colorless oil; ^{1}H NMR: δ 1.26 (d,3H,J=6.85Hz), 1.27, 1.29 (2t,6H,J=7.1Hz), 2.84 (m,1H), 2.95-3.16 (m,2H), 3.84-4.13 (m,4H), 7.17-7.33 (m,5H). Anal.Calcd for $C_{13}H_{22}NO_3P$ (271.3): C, 57.55; H, 8.17; N, 5.16; P, 11.42. Found: C, 57.60; H, 8.29; N, 5.30; P, 11.60.

Diethyl N-(2-phenylbutyl)phosphoramidate (9b).

The compounds was obtained by PTC phosphorylation[22] of 2-phenylbutylamine. Yield - 66%; colorless oil; ^{1}H NMR: δ 0.81 (t,3H,J=7.4Hz), 1.27, 1.29 (2t,6H,J=7.05Hz), 1.51-1.75 (m,2H), 2.52-2.66 (m,1H), 2.94-3.26 (m,2H), 3.79-4.06 (m,4H), 7.17-7.34 (m,5H). Anal.Calcd for $C_{14}H_{24}NO_3P$ (285.3): C, 58.93; H, 8.48; N, 4.91; P, 10.86. Found: C, 60.15; H, 8.60; N, 5.05; P, 10.58.

Diethyl N-(sec-alkylphosphoramidates (2a-r)(5a-c). General procedure.

Grignard reagent prepared from magnesium grit (0.73g,0.03 mol) and alkyl bromide (0.03 mol) in THF (40 mL) according to standard procedure was cooled to -30°C and CuI (0.95g, 0.0005 mol) was added at this temp. with stirring. Stirring was then continued for 15 min. at -30°C and the respective N-phosphorylated aziridine (**1**) or (**4**) (0.01 mol) dissolved in THF (5 mL) was added dropwise. The temperature of the reacting mixture was slowly raised to -5-0°C and kept at this temp. for 2-3hr. Saturated aqueous NH_4Cl solution (15 mL) was then added at 10-15°C. The organic phase was separated and the water layer was extracted with CH_2Cl_2 (2x20 mL) or with ether (2x20 mL), the extracts being combined with the organic phase after washing with water (2x15 mL). Evaporation of solvent from the dried ($MgSO_4$) solution left crude phosphoramidate (**2**) or (**5**) which was spectroscopically pure according to ^{31}P NMR.

Preparation of sec-alkyl amine hydrochlorides (3a-r)(6a-c). General procedure.

Crude phosphoramidate (**2**) or (**5**) (0.02 mol) was refluxed for 1hr with ca. 20% hydrochloric acid (15 mL). The resultant solution was cooled to room temp. and extracted with ether (20 mL). Ether extract was discarded and the solution was made strongly alkaline with solid NaOH. Amine was extracted with ether (2x20 mL), the extract was dried ($MgSO_4$) for 2hr and saturated with dry, gaseous hydrogen chloride at room temp. for 1hr. The mixture was left at room temp. for 24hr. Crystalline *sec*-alkylamine hydrochloride (**3**) or (**6**) was filtered off and purified by dissolving in EtOH (5-10mL) and precipitation with ether (50-100mL).

1-Methyl-butylamine hydrochloride (3a)

Yield - 66%; colorless solid; m.p. 152-153°C, lit.[12] m.p. 153-154°C; ^{1}H NMR (D_2O): δ 0.92

(bt,3H,J=6.6Hz), 1.27 (d,3H,J=6.6Hz), 1.32-1.81 (m,4H), 3.40 (sextet,1H). FABMS: 88 (M-Cl). Anal.Calcd for $C_5H_{14}ClN$ (123.6): C,48.58; H,11.42; N,11.33. Found: C,48.49; H,11.58; N,11.35.

*1,3-Dimethyl-butylamine hydrochloride (**3b**)*

Yield - 72%; colorless solid; m.p. 128-130°C, lit.[18] m.p. 137-139°C; ^{1}H NMR (D_2O): δ 0.91 (bd,6H,J=6.5Hz), 1.27 (d,3H,J=6.5Hz), 1.46 (t,2H,J=6.5Hz), 1.63 (m,1H), 3.45 (sextet,1H,J=6.5Hz). FABMS: 102 (M-Cl). Anal.Calcd for $C_6H_{16}ClN$ (137.6): C,52.35; H,11.72; N,10.18. Found: C,52.20; H,11.85; N,10.09.

*1-Methyl-pentylamine hydrochloride (**3c**)*

Yield - 87%; colorless solid; m.p. 134-137°C; ^{1}H NMR (D_2O): δ 0.88 (bt,3H,J=6.0Hz), 1.27 (d,3H,J=6.6Hz), 1.20-1.87 (m,6H), 3.36 (sextet,1H,J=6.6Hz). FABMS: 102 (M-Cl). Anal.Calcd for $C_6H_{16}ClN$ (137.6): C,52.35; H,11.72; N,10.18. Found: C,52.15; H,11.71; N,10.30.

*1,3-Dimethyl-pentylamine hydrochloride (**3d**)*

Yield - 73%; colorless solid; m.p. 132-134°C, lit.[17] m.p. 132-134°C; ^{1}H NMR (D_2O): δ 0.86 (t,3H,J=7.5Hz), 0.90 (d,3H,J=7.5Hz), 1.27 (d,3H,J=6.8Hz), 1.14-1.76 (m,5H), 3.47 (sextet,1H,J=6.8Hz). FABMS: 116 (M-Cl). Anal.Calcd for $C_7H_{18}ClN$ (151.7): C,55.43, H,11.96; N,9.23. Found: C,55.22; H,12.05; N,9.11.

*1,3,3-Trimethyl-butylamine hydrochloride (**3e**)*

Yield - 66%; colorless solid; m.p. 192-195°C; ^{1}H NMR (D_2O): δ 0.95 (s,9H), 1.34 (d,3H,J=6.6Hz), 1.55 (d,2H,J=5.6Hz), 3.49 (sextet,1H,J=5.6Hz). FABMS: 116 (M-Cl). Anal.Calcd for $C_7H_{18}ClN$ (151.7): C,55.43; H,11.96; N,9.23. Found: C,55.37; H,12.14; N,9.25.

*1-Methyl-2-phenyl-ethylamine hydrochloride (**3f**)*

Yield - 78%; colorless solid; m.p. 147-149°C, lit.[16] m.p. 146-147°C; ^{1}H NMR (D_2O): δ 1.31 (d,3H,J=6.5Hz), 2.95 (d,2H,J=7.3Hz), 3.67 (sextet,1H,J=6.5Hz), 7.38 (s,5H). FABMS: 136 (M-Cl). Anal.Calcd for $C_9H_{14}ClN$ (171.7): C,62.97; H,8.22; N,8.16. Found: C,62.89; H,8.30; N,8.02.

*1-Methyl-2-(p-methylphenyl)-ethylamine hydrochloride (**3g**)*

Yield - 81%; colorless solid; m.p. 155-157°C, lit.[15] m.p. 158-159°C; ^{1}H NMR (D_2O): δ 1.29 (d,3H,J=6.5Hz), 2.33 (s,3H), 2.90 (d,2H,J=7.2Hz), 3.65 (sextet,1H,J=6.5Hz), 7.23 (s,4H). FABMS: 150 (M-Cl). Anal.Calcd for $C_{10}H_{16}ClN$ (185.7): C,64.68; H,8.69; N,7.54. Found: C,64.55; H,8.91; N,7.41.

*1-Methyl-2-(p-methoxyphenyl)-ethylamine hydrochloride (**3h**)*

Yield - 90%; colorless solid; m.p. 204-206°C, lit.[14] m.p.210-211.5°C; ^{1}H NMR (D_2O): δ 1.30 (d,3H,J=6.6Hz), 2.89 (d,2H,J=6.9Hz), 3.61 (sextet,1H,J=6.9Hz), 3.84 (s,1H), 6.95-7.35 (4H,AA'XX' system). FABMS: 166 (M-Cl). Anal.Calcd for $C_{10}H_{16}ClN$ (201.7): C,59.55; H,8.00; N,6.94. Found: C,59.31; H,8.15; N,6.96.

*1-Methyl-2-(2-naphthyl)-ethylamine hydrochloride (**3i**)*

Yield - 82%; colorless solid; m.p.218-220°C, lit.[13] m.p. 207-208°C; ^{1}H NMR (D_2O): δ 1.36 (d,3H,J=6.5Hz), 3.43 (d,2H,J=6.6Hz), 3.86 (sextet,1H,J=6.5Hz), 7.45-8.37 (m,7H). FABMS: 186 (M-Cl).

Anal.Calcd for $C_{13}H_{16}ClN$ (221.7): C,70.42; H,7.27; N,6.32. Found: C,70.38; H,7.42; N,6.25.

1-Methyl-4-phenyl-butylamine hydrochloride (3j)

Yield - 73%; colorless solid; m.p. 130-132°C; ^1H NMR (D_2O): δ 1.27 (d,3H,J=6.6Hz), 1.50-1.90 (m,4H), 2.50-2.85 (m,2H), 3.35 (sextet,1H,J=6.6Hz), 7.33 (s,5H). FABMS: 164 (M-Cl). Anal.Calcd for $C_{11}H_{18}ClN$ (199.7): C,66.15; H,9.08; N,7.01. Found: C,66.02; H,9.22; N,7.08.

1-Methyl-2-cyclopentyl-ethylamine hydrochloride (3k)

Yield - 80%; colorless solid; m.p. 155-157°C; ^1H NMR (D_2O): δ 0.90-2.03 (m,11H), 1.29 (d,3H,J=6.6HZ), 3.35 (sextet,1H,J=6.6HZ). FABMS: 128 (M-Cl). Anal.Calcd for $C_8H_{18}ClN$ (163.7): C,58.70; H,11.08; N,8.56. Found: C,58.64; H,11.14; N,8.49.

1-Ethyl-pentylamine hydrochloride (3l)

Yield - 70 %; colorless solid; m.p. 240-242°C, lit.[7c] m.p. 238-240°C; ^1H NMR ($CDCl_3$): δ 0.96 (t,6H,J=7.2Hz), 1.31-1.82 (m,8H), 3.20 (br.s.,1H), 8.34 (br.s.,3H). MS: 72 ($PrCH{=}NH_2^+$,100%). Anal.Calcd for $C_7H_{18}ClN$ (151.7): C,55.43; N,11.96; N,9.23. Found: C,55.20; H,12.09; N,9.28.

1-Propyl-hexylamine hydrochloride (3m)

Yield - 77 %; colorless solid; m.p. 140-141°C, lit.[18] m.p.142-143°C; ^1H NMR ($CDCl_3$): δ 0.89 (t,3H,J=6.6Hz) 0.96 (t,3H,J=7.2Hz), 1.31-1.73 (m,12H), 3.10-3.25 (m,1H), 8.35 (br.s.,3H). MS: 72 ($PrCH{=}NH_2^+$,100%); 100 ($C_5H_{11}CH{=}NH_2^+$,52%). Anal.Calcd for $C_9H_{22}ClN$ (179.7): C,60.14; H,12.34; N,7.79. Found: C,59.92; H,12.47; N,7.82.

4-Methyl-1-propyl-pentylamine hydrochloride (3n)

Yield - 86 %; colorless solid; m.p. 178-180°C; ^1H NMR ($CDCl_3$): δ 0.91 (d,3H,J=6.5Hz), 0.92 (d,3H,J=6.5Hz), 0.96 (t,3H,J=7.2), 1.26-1.84 (m,9H), 3.06-3.25 (m,1H), 8.73 (br.s.,3H). MS: 72 ($PrCH{=}NH_2^+$,100%); 100 ($C_5H_{11}CH{=}NH_2^+$,38%). Anal.Calcd for $C_9H_{22}ClN$ (179.7): C, 60.14; H,12.34; N,7.79. Found: C,59.94; H,12.42; N,7.88.

1-Ethyl-hexylamine hydrochloride (3o)

Yield - 66 %; colorless solid; m.p. 202-203°C; ^1H NMR ($CDCl_3$): δ 0.87-0.99 (m,6H), 1.23-1.82 (m,10H), 3.10-3.25 (m,1H), 8.34 (br.s.,3H). MS: 72 ($PrCH{=}NH_2^+$,100%); 86 ($BuCH{=}NH_2^+$,77%). Anal.Calcd for $C_8H_{20}ClN$ (165.7): C,57.98; H,12.17; N,8.45. Found: C,57.78; H,12.31; N,8.51.

1-Butyl-hexylamine hydrochloride (3p)

Yield - 86 %; colorless solid; m.p. 176-178°C; ^1H NMR ($CDCl_3$): δ 0.84-0.97 (m,6H), 1.22-1.82 (m,14H), 3.10-3.20 (m,1H), 8.35 (br.s.,3H). MS: 86 ($BuCH{=}NH_2^+$,100%); 100 ($C_5H_{11}CH{=}NH_2^+$,79%). Anal.Calcd for $C_{10}H_{24}ClN$ (193.8): C,61.99; H,12.49; N,7.23. Found: C,61.80; H,12.61; N,7.14.

1-Butyl-4-methyl-pentylamine hydrochloride (3r)

Yield - 82 %; colorless solid; m.p. 176-177°C; ^1H NMR ($CDCl_3$): δ 0.86-0.97 (m,9H), 1.22-1.81 (m,11H), 3.08-3.18 (m,1H), 8.37 (br.s.,3H). MS: 86 ($BuCH{=}NH_2^+$,100%); 100 ($C_5H_{11}CH{=}NH_2^+$,56%). Anal.Calcd for $C_{10}H_{24}ClN$ (193.8): C,61.99; H,11.29; N,7.23. Found: C,61.81; H,12.59; N,7.18.

2-Ethyl-cyclohexylamine hydrochloride (6a)

Yield - 57 %; colorless solid; m.p. 253-255°C; ^{1}H NMR ($CDCl_3$): δ 0.93 (t,3H,J=7.4Hz), 1.40-1.95 (m,10H), 2.18-2.32 (m,1H), 2.77-2.95 (m,1H), 8.38 (br.s.,3H). MS: 127 (M-HCl, 22%). Anal.Calcd for $C_8H_{18}ClN$ (163.7): C,58.70; H,11.08; N,8.56. Found:C,58.55; H,11.19; N,8.49.

2-Butyl-cyclohexylamine hydrochloride (6b)

Yield - 55 %; colorless solid; m.p. 194-195°C; ^{1}H NMR ($CDCl_3$): δ 0.91 (t,3H,J=7.0Hz), 1.15-1.95 (m,16H), 2.18-2.32 (m,1H), 2.75-2.95 (m,1H), 8.41 (br.s.,3H). MS: 145 (M-HCl, 7%). Anal.Calcd for $C_{10}H_{22}ClN$ (191.7): C,62.64; H,11.57; N,7.31. Found: C,62.47; H,11.71; N.7.38.

2-Isobutyl-cyclohexylamine hydrochloride (6c)

Yield - 73 %; colorless solid; m.p. 216-217°C; ^{1}H NMR ($CDCl_3$): δ 0.91 (d,3H,J=8.5Hz), 0.94 (d,3H,J=8.5Hz), 1.05-1.85 (m,10H), 1.90-2.20 (m,1H), 2.20-2.32 (m,1H), 2.75-2.87 (m,1H), 8.43 (br.s., 3H). MS: 145 (M-HCl,8%). Anal.Calcd for $C_{10}H_{22}ClN$ (191.7): C.62.64; H,11.57; N,7.31. Found: C.62.41; H,11.73; N,7.34.

Nucleophilic ring-opening of 2-phenyl-N-(diethoxyphosphoryl)aziridine (7)

The reaction was carried out according to the standard procedure described for N-phosphorylated aziridines (**1**) and (**4**). Methylmagnesium iodide was prepared using the mixture of ether and THF (1:3 v/v). Crude mixtures of amides (**8**) and (**9**) were analyzed spectroscopically (^{31}P NMR) after washing with water and aqueous EDTA solution. The results are listed in Table 1.

Diethyl N-t-alkylphosphoramidates (11a-g). General procedure.

To the solution of organomagnesium bromide prepared from the respective bromide (0.09 mol) in THF (120 mL) and cooled to -30°C CuI (5.71g, 0.003 mol) was added with stirring. After 15 min. 2,2-dimethyl-N-(diethoxyphosphoryl)aziridine (**10**, 0.03 mol) was added dropwise, the solution was slowly heated to room temp., and left for 12hr.

Saturated aqueous NH_4Cl solution (25 mL) was then added dropwise at 10°C. The organic phase was separated and the water layer was extracted with ether (25 mL). The combined organic phases were evaporated, the residue dissolved in CH_2Cl_2 and washed with water (2x30 mL). Evaporation of the dried ($MgSO_4$) solution followed by "bulb to bulb" distillation of the residue under reduced pressure afforded pure phosphoramidates (**11a-g**). Yields, physical constants, and spectroscopic data of these compounds are summarized in Table 2.

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