Heteroatom Chemistry
Volume 4, Number 1, 1993

The Chemistry and Structure of the P(O)NC(O) System. Part 3. Preparation of O,O-diethyl-N-Acylphosphoramidates and Their Reactions with Electrophiles*

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Received 5 March 1992

ABSTRACT

*Six O, O-diethyl-N-acylphosphoramidates (**1a–f**) were synthesized. The reactions of their conjugate bases with haloalkanes were studied. The N/(phosphoryl)O/(carbonyl)O regioselectivity varied greatly, depending on the substrate, the haloalkane, the base, and other reaction conditions. The earlier [17] reaction of N-formyl substrate **1a** that led to the N-phosphorylated formamidine was extended to other substrates **1**. Again, the yields and the selectivity depended strongly on the structure of a substrate.*

INTRODUCTION

N-acylphosphoramidates (**1**) and their salts attract attention, because they show antiviral activity [1] and also some interesting complexing properties [2]. From the reactivity point of view, compounds **1** represent multifunctional systems, both in electrophilic and nucleophilic reactions. Solvolysis of **1** can proceed with the cleavage of the N—P(O) (phosphorylation) or the N—C(O) (acylation) bond; our earlier studies indicated that the selectivity in solvolysis is primarily the function of medium acidity [3]. In reactions with electrophiles, imides **1** can offer two oxygen atoms (the carbonyl and the phosphoryl) and the nitrogen atom as nucleophilic centers. Alkylation of the conjugate base of **1** can therefore lead to three isomeric products, **2**, **3**, **4**, one of which (**2**) can exist as a pair of syn/anti stereoisomers (Equation 1).

Alkylation of simple phosphoramidates, $(RO)_2P(O)NH_2$, $(RO)_2P(O)NHR'$, as well as of phosphinic hydrazides, $R_2P(O)NHNH_2$, was studied in detail [4] and was shown to occur at the nitrogen atom of the N—P(O) function; some evidence for the competitive alkylation of the phosphoryl oxygen is, however, also available [5].

N-acylation of a deprotonated phosphoramidate by acyl chlorides has also been reported [6] and offers a synthetic route to systems 1. Glidewell [7] demonstrated that O,O-diisopropyl-N-benzylphosphoramidate reacts with Me_3SiCl at nitrogen, but the possibility of the equilibration between the O- and N-trimethylsilylated tautomers of N,O,O-triphenylphosphoramidate had been considered [8].

Literature data on the nucleophilic reactivity of the mixed diacyl systems **1** are much more scarce. In our earlier work [9] on the ethylation of O,O-dimethyl-N-benzoylphosphoramidate (1, R = Me, R′ = Ph), we observed the reaction at both oxygen atoms (but not at the nitrogen), the selectivity being a function of the "hardness" of the ethylating agent. N-benzyloxyureas, on the other hand, undergo, after deprotonation, alkylation exclusively at nitrogen and thus offer a synthetic route to N-substituted-N-hydroxyureas [10]. Zabirov et al. [11]

*S. Bauermeister, T. A. Modro, P. K. Psotta, P. H. van Rooyen, The Chemistry and Structure of the P(O)NC(O) System. Part 2, *Phosphorus, Sulfur, and Silicon, 69*, 1992, 63.

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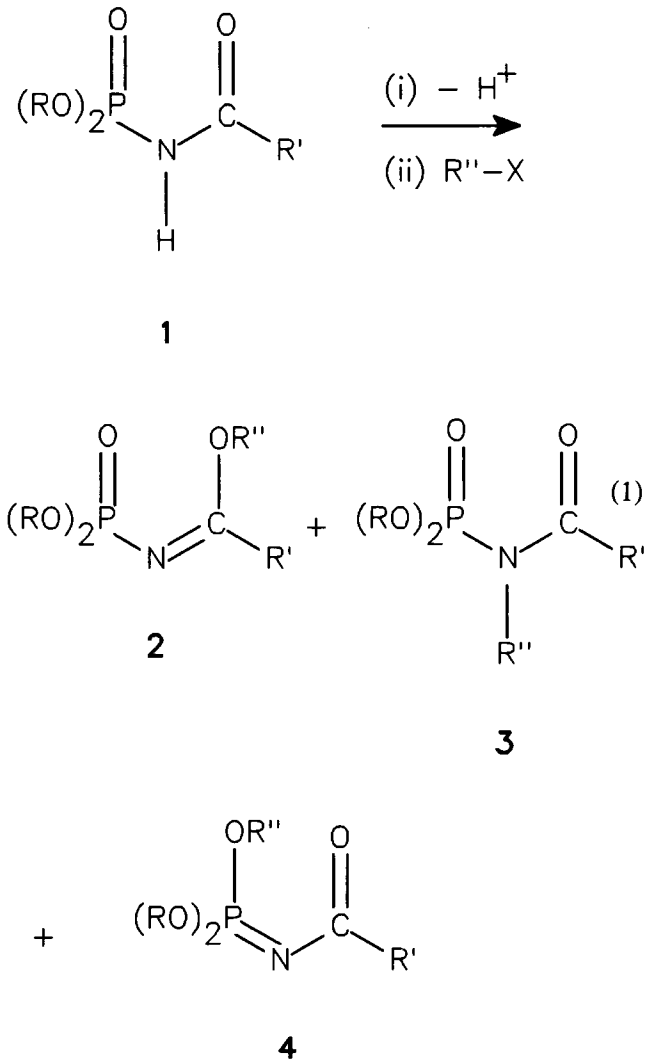
1042-7163/93/$5.00 + .25

recently reported that methylation of the potassium salt of O,O-diisopropyl-N-benzoylphosphoramidate (1, R = *i*-Pr, R′ = Ph) with iodomethane occurs selectively at the phosphoryl oxygen. Our results obtained for the O,O-diethyl analogue **1d** (vide infra) lead to the conclusion that Zabirov's structural assignments may be incorrect.



In this article, we report our studies on the alkylation (using haloalkanes) and silylation (using hexamethyldisilazane, HMDS) of a series of neutral O,O-diethyl-N-acylphosphoramidates (silylation) or their anions (alkylation). The N-acyl groups in substrates **1** were varied in order to establish the importance of both steric and electronic effects at the carbonyl center in the regioselectivity of the reaction. The structure of alkylating agents was also varied in such a way as to evaluate the effect of the increasing size of the Alkyl group on the product's structure. Finally, taking into account the well-known effect of a cation on the selectivity in reactions of ambident anions with electrophiles [12], we compared the alkylations of sodium salts of substrates **1** with those carried out in the presence of the phase transfer catalyst, tetrabutylammonium bromide (TBAB).

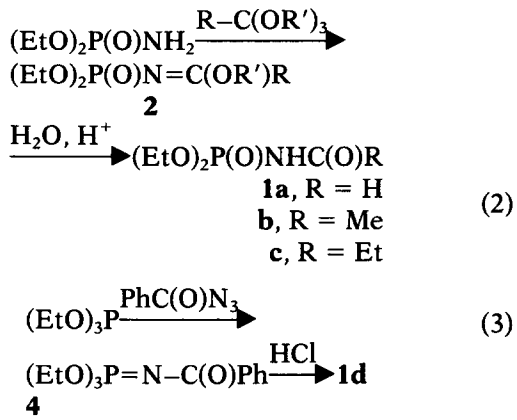
RESULTS AND DISCUSSION

Six O,O-diethyl-N-acylphosphoramidates (**1**, R = Et), **1a** (R′ = H), **1b** (R′ = Me), **1c** (R′ = Et), **1d** (R′ = Ph), **1e** (R′ = OEt), **1f** (R′ = NEt_2), were synthesized, and their base-promoted reactions with iodomethane and with five bromoalkanes, R″—Br (R″ = Et, *n*-Pr, *n*-Bu, *n*-C_6H_{13}, *i*-Pr), as well as their reaction with HMDS under neutral conditions, were studied.

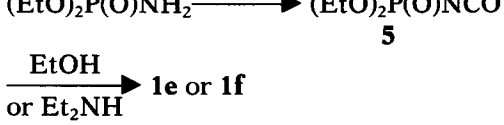
Substrates

N-acylphosphoramidates **1** were synthesized using three different procedures. Substrates **1a**, **1b**, and **1c** were prepared from diethylphosphoramidate [13] via the hydrolysis of the corresponding intermediate **2** [14] (Equation 2). It is worthy of note that in this procedure, intermediates **2** can also serve as standards for the identification of the alkylation products (see Equation 1).

Substrate **1d** was prepared as shown in Equation 3; again, the intermediate **4** represents the standard for the product of the ethylation of **1d** at the phosphoryl oxygen.



Finally, compounds **1e** and **1f** were synthesized by treating diethylphosphorisocyanatidate **5** [15] with ethanol or diethylamine (Equation 4).



Alkylation Reactions

Substrates **1** were converted into their sodium salts by treating them with sodium hydride in 1,2-dimethoxyethane (DME); the solution of the salt was

TABLE 1 δ ^{31}P for Compounds **1, 2, 3, 4** ($CDCl_3$, ppm Relative to Trimethyl Phosphate)

R'	*1*	*R''*	*3*	*2*	*4*
H	−4.46	Me	−0.49		8.05
		Et	−0.06	3.54	
		Pr	−0.20		
		Bu	−0.20	3.96	
		Hex	−0.08	4.20	
		i-Pr		3.40, 3.70	8.00
		Me_3Si		3.23	
Me	−4.50	Me	−0.03	0.73	
		Et	0.00	0.61	
		Hex	0.45	0.93	6.60
		Me_3Si	−0.26	2.34, 3.81	
Et	−4.90	Me	−0.02		
		Et	0.23	0.56	6.30
		Hex		0.56	6.60
		Me_3Si			
Ph	−4.50	Me	−0.88		
		Me_3Si		4.40	
OEt	−4.50	Me	−1.50		
		Et	−2.00		
		Hex	−1.50		
		Me_3Si	−2.70	4.50	7.90
NEt_2	−3.00	Me	0.20		
		Et	−0.20		
		Hex	−0.80		
		Me_3Si	−2.60	2.40, 4.60	7.80

then treated with the alkylating agent, and the reaction mixture was stirred at room temperature (for reactions with MeI), or under reflux, for several hours. The reaction products were identified mainly by the NMR (^{31}P, ^{1}H, ^{13}C) spectroscopy; in some cases, IR spectroscopy, MS, and elemental analysis were additionally used. ^{31}P NMR spectroscopy was found to be invaluable in both qualitative and quantitative identification of the reaction products. The types of phosphorus compounds involved in this work (**1**, **2**, **3**, **4**) are characterized by relatively narrow ranges of their ^{31}P chemical shift values, with the increasing deshielding of the ^{31}P nuclei in the order **1**<**3**<**2**<**4** (Table 1).

Alkylation reactions of substrates **1** (Equation 1) gave very diverse results from the point of view of the reactivity of the substrates, the purity of the products, and the regioselectivity of the alkylation. In some cases, reactions were regiospecific, yielding single products in high yield and purity, and thus offered useful synthetic routes to some alkyl derivatives of **1**. In other cases, the full conversion of a substrate into the product could not be achieved and/or the regioselectivity was low, so a mixture of isomeric alkyl derivatives was obtained. In these cases, it was not possible to separate individual components, and they were identified in a mixture of products by spectroscopic techniques. These reactions have little synthetic value and show that small changes in substrate structures can have a profound effect on the course of the alkylation. For that reason, it was difficult to arrive at any general description of the reaction represented by Equation 1, so the results are discussed below separately for individual substrates **1**.

Alkylation of **1a**. The results obtained for six haloalkanes are summarized in Table 2. It is clear that the sodium salt of **1a** behaves as a nitrogen nucleophile, yielding exclusively, or almost exclusively, the N-alkyl derivatives, **3a**. For methylation, ethylation, and *n*-propylation, the reaction is of practical value, since the products could be isolated in high yield and were fully characterized. For higher alkyl groups (*n*-butylation, *n*-hexylation), the reaction is, probably for steric reasons, slower and the competitive formation of the (carbonyl) O-alkylated products **2a** can be observed. The formation of **2a** is, in some cases, enhanced by use of the phase transfer catalyst. We have found, by examining the effect of the reaction time on the **3a**/**2a** ratio in *n*-hexylation, that this effect is mostly due to the TBAB—promoted subsequent rearrangement of **3a** to **2a**. The rearrangement is not a thermal reaction, since the *n*-hexylation product could, after the work-up, be distilled (bulb-to-bulb, oven temperature 115–120°C/2 Torr) without any change of the **3a**/**2a** ratio.

For the reaction with a secondary haloalkane (*i*-PrBr), we observed a dramatic change in the regioselectivity. In the absence of TBAB, only one product was formed which could not be purified by distillation or column chromatography without extensive decomposition. When the reaction work-up was carried out with rigorous exclusion of moisture, the crude product was identified by NMR spectroscopy as the phosphoryl O-*i*-Pr derivative **4a** (**4**, R' = H, R'' = *i*-Pr). In the presence of TBAB, the regioselectivity was again changed drastically: although the N-alkylation product was still absent, the alkylation occurred exclusively at the carbonyl oxygen, yielding two stereoisomers (syn/anti) of **2a** (**2**, R' = H, R'' = *i*-Pr). This remarkable change in the N vs. O regioselectivity observed for the secondary substrate as compared with primary haloalkanes suggests a change in the reaction mechanism. It is possible that for *i*-PrBr, the reaction has more of an S_N1 character, thus involving a "harder" electrophile of the 2-propylcarbonium ion type. Such an electrophile would be expected to show marked preference to react with "hard" nucleophilic centers (oxygen atoms) rather than with a "soft" nitrogen center.

The change in the orientation of the alkylation could also be achieved via the change of the counterion of the conjugate base of **1a**. While the sodium salt underwent methylation exclusively at nitrogen, the anion generated by LDA in THF

TABLE 2 Alkylation of the Conjugate Base of **1a**

Haloalkane R″—X	*Conditions*[a]	*TBAB*[b]	*Conversion (%)*	**2a** (%)[c]	**3a** (%)[c]	**4a** (%)[c]
MeI		No	87		87	
	In THF	No	92		92	
	LDA in Benzene	No	35		18	17
EtBr		No	50	Trace	>48	
		Present	64		64	
	LDA in Benzene	No	35			35
PrBr		Present	35		35	
BuBr		Present	27	2	25	
HexBr		No	66	12	54	
	2 h	Present	67	4	63	
	13.5 h	Present	67	31	36	
i-PrBr		No	22			22
		Present	26	26 (E/Z)		

[a]Unless otherwise stated, the conditions were NaH, DME, room temperature (for the methylation), or reflux; 16–24 h.
[b]"Present" denotes the addition of 5 mol % TBAB.
[c]Related to the percentage of conversion. The absence of a given product means that it was not detected by ^{31}P NMR spectroscopy.

yielded equal proportions of the N—Me derivative, **3a**, and the P—OMe derivative, **4a**. In the ethylation, the Li^+ counterion shifted the regioselectivity completely from the substitution at nitrogen to the reaction at the phosphoryl oxygen. In conclusion, with respect to primary haloalkanes, the Na^+ salt of **1a** behaves as a nitrogen nucleophile, although the N/O selectivity decreases in the order Me>Et>Bu>n-C_6H_{13}. This order most likely reflects the increasing steric hindrance for the reaction to occur at the congested nitrogen center. With respect to a secondary halide, the same sodium salt demonstrates its nucleophilic reactivity exclusively via its two oxygen atoms.

Alkylation of **1b–1f**. Table 3 lists the results of the alkylation of the remaining substrates by three primary haloalkanes (MeI, EtBr, HexBr). With respect to iodomethane, all substrates **1** behave as highly regiospecific nitrogen nucleophiles. The yields vary from medium (**1d**) to quantitative (**1c**, **1e**); the presence of TBAB usually improves the conversion to the corresponding **3**. For the N-acetyl substrate (**1b**), we observed in the methylation reaction the formation of two unexpected products, diethyl-N-methylphosphoramidate (**6**) and diethyl-N,N-dimethylphosphoramidate (**7**). These compounds, accompanying the major product **3b** (**3**, R′ = R″ = Me), could easily be identified by their ^{31}P chemical shift values (δ_P 7.30 and 7.90, respectively) and by the characteristic signals of their N—Me groups in the ^1H NMR spectra (δ_H 2.48, dd, J_{HP} 12.0, J_{HH} 5.0 Hz and δ_H 2.53, d, J_{HP} 10.2 Hz, respectively); those assignments were confirmed by the addition of the authentic samples of **6** and **7** and by the absence of any additional acetyl methyl signal in the ^1H NMR spectra. We do not believe that **6** and **7** are formed via the direct cleavage of the C(O)—N bond by sodium hydride, observed for some formates and formamides [16], as we did not observe these products in alkylations of **1a**. One can speculate that the formation of N-methylphosphoramidates results from the base-promoted deprotonation of one of the three α-hydrogens in **1b**, yielding ketene and the conjugate base of diethyl phosphoramidate, which can then undergo subsequent N-methylation [4].

With higher haloalkanes, **1b** and **1c** gave increasing proportions of the oxygen (both carbonyl and phosphoryl) alkylated products; this low selectivity limited synthetic applicability of the reaction. The N-benzoyl substrate **1d** proved to be the most unstable under the reaction conditions; extensive decomposition was observed in all alkylations, except for the methylation, which was carried out at room temperature. The latter reaction resulted in the formation, albeit in poor yield, of a single alkylation product, identified as the N-methyl derivative, **3d** (**3**, R′ = Ph, R″ = Me). The δ_P value (−0.88) obtained for this product is well within the range observed for other compounds **3**. Similarly, the methyl group signal in the ^1H NMR spectrum (δ_H 3.06, d, J_{HP} 7.7 Hz) is very typical for all N-methyl derivatives **3** obtained in this work (see the Experimental section). Zabirov et al. [11] identified the product of the methylation of O,O-diisopropyl-N-benzoylphosphoramidate as the corresponding P—OMe derivative of the type **4**. The NMR spectroscopic data reported for that product (δ_P −3; methyl group δ_H 3.10, d, J_{HP} 7 Hz) correspond closely to those observed by us for the N-methyl products **3**. We think therefore that Zabi-

TABLE 3 Alkylation of the Conjugate Bases of **1b–1f**[a]

Substrate	*Haloalkane R″—X*	*TBAB*	*Conversion (%)*	**2** (%)	**3** (%)	**4** (%)
1b	MeI	No	90		69[b]	
		Present	99		83[b]	
	EtBr	No	87	16	71	
		Present	58	19	39	
	HexBr	No	60	6	25	29
		Present	59	56	Trace	3
1c	MeI	No	100		100	
		Present	100		100	
	EtBr	No	51		38	13
		Present	68		54	14
	HexBr	No	43	19		24
		Present	51	45		6
1d	MeI	No	40		40	
		Present	43		43	
	EtBr	No	[c]			
		Present				
	HexBr	No	[c]			
		Present				
1e	MeI	No	100		100	
		Present	100		100	
	EtBr	No	79		79	
		Present	97		97	
	HexBr	No	47		47	
		Present	61		61	
1f	MeI	No	77		77	
		Present	99		99	
	EtBr	No	21[d]		21	
		Present	27[d]		27	
	HexBr	No	19[d]		19	
		Present	20[d]		20	

[a]In all reactions, the conditions were NaH, DME, room temperature (for the methylation), or reflux; 16–24 h. For other information, see footnotes b and c in Table 2.
[b]The remaining products were: diethyl N-methyl- and N, N-dimethylphosphoramidates; see the Discussion section.
[c]Extensive decomposition leading to a complex mixture of products.
[d]Partial decomposition during the course of reaction.

rov's product is, in fact, the O,O-diisopropyl analogue of compound **3d**, since for the P—OMe derivative, the ^{31}P NMR chemical shift would be expected to be in the range of +6 to +8 ppm (see Table 1).

The N-phosphorylated ethylcarbamate **1e** was shown to be the most regioselective among all substrates **1**. With all three haloalkanes, it gave exclusively N-alkyl derivatives **3** with good or excellent yields and in a high state of purity; the presence of TBAB increased the overall yield of the reaction. The substrate **1e** is, in fact, the only one capable of giving efficient and regiospecific results in the *n*-hexylation reaction. The urea derivative **1f** behaves very similarly to **1e**, the only difference being its lower stability, thus giving lower yields of alkylation and partial decomposition. It is clear, however, that both heteroatom-containing substituents R′ (OEt, NEt_2) markedly increase the regioselectivity of the corresponding conjugate base in favor of the nitrogen nucleophilicity.

Reactions of **1** *with HMDS*

We have recently studied in detail reactions of O,O-diethyl N-formylphosphoramidate (**1a**) with trimethylsilylating agents [17] and found that silylation occurred exclusively at the carbonyl oxygen atom. The most interesting result was obtained when HMDS was used as an electrophile, since the initial silylation product underwent a subsequent nucleophilic displacement with ammonia (released as a side product), yielding N-phosphorylated formamidine derivative, $(EtO)_2P(O)N{=}C(NH_2)H$ [18]. For this reason, we applied the reaction of HMDS to all substrates **1a–1f** in order to establish their reactivity toward a common, Si-containing electrophile.

In all cases, reactions with HMDS were reversible and the final product contained variable proportions of unreacted **1**. Only for **1a**, where the subsequent reaction with ammonia [16] removed the initial product from the reaction mixture, could

TABLE 4 Trimethylsilylation of **1a–1f** with HMDS[a]

Substrate	Conversion (%)	2[b] (%)	3[b] (%)	4[b] (%)
1a	100	100[c]		
1b	47	4	43	
1c	0[d]			
1d	71	71		
1e	95	25	48	22
1f	24	14	5	5

[a]Benzene, reflux, 3–6 h.
[b]For structures, see Equation 1; R″ = $SiMe_3$.
[c]Under reaction conditions converted quantitatively to $(EtO)_2P(O)N{=}C(NH_2)H$ [17].
[d]Only unreacted **1c** was observed in the ^{31}P NMR spectrum.

we achieve the full conversion. The reaction with ammonia was not, however, observed for any of the remaining substrates. It seems that the subsequent attack by a nucleophile is, for steric reasons, feasible only for the product with the unhindered, formamide center. As can be seen from Table 4, both conversion and selectivity vary widely for individual substrates. Compounds **1b–1f** react much more slowly than **1a**, indicating the importance of steric effects for the reaction involving a bulky electrophile. In conclusion, as for alkylation reactions, substrates **1** vary greatly with respect to HMDS in their reactivity and regioselectivity, with only some reactions being of real synthetic value.

EXPERIMENTAL

Solvents and commercially available substrates were purified by conventional methods immediately before use. All reactions were carried out in an atmosphere of dry argon. Mass spectra were recorded on a Varian MAT-212 double-focusing direct-inlet spectrometer at an ionization potential of 70 eV. IR spectra were recorded as neat liquids, with a Bruker IFS 113v FT-IR spectrometer. NMR spectra were recorded on a Bruker AC 300 MHz spectrometer for solutions in $CDCl_3$ (for alkylations) or in C_6D_6 (for silylations), and the chemical shifts are given relative to $SiMe_4$ (^1H, ^{13}C) and trimethyl phosphate (^{31}P). Elemental analysis (C/H/N) was carried out at the Council for Scientific and Industrial Research (Pretoria). Iodomethane and bromoethane were passed through a short column using Al_2O_3 (basic) as a stationary phase. Higher haloalkanes were purified by distillation. HMDS (Aldrich) was purified by distillation; bp 119–120°C.

Substrates

*Diethyl-N-formylphosphoramidate (**1a**).* The intermediate Ethyl-[N-(diethoxyphosphoryl)]-formimidate (**2a**) (**2**, R′ = H, R″ = Et) was prepared from diethylphosphoramidate and triethyl orthoformate according to the literature procedure [14]. δ_P ($CDCl_3$) 3.54; MS: m/z 209 (M^+, 14%), 182(13), 181(12), 153(35), 138(99), 126(59), 110(55), 109(83), 82(60), 81(100). Other data were in full agreement with those reported.

*Hydrolysis of **2a**.* A mixture of **2a** (34.0 g, 0.163 mol), water (5.85 g, 0.325 mol), and trifluoroacetic acid (a few drops) was stirred at room temperature for 3 hours. Volatile by-products were removed under reduced pressure, and crude **1a** was purified by distillation. Yield quantitative. Bp 119°C/0.15 Torr (Ref. [19], bp 135°C/0.25 Torr). ^1H NMR ($CDCl_3$) δ: 1.33 (6 H, t, J 7.1 Hz, 2 × Me of POEt), 4.15 (4 H, m, 2 × CH_2 of POEt), 8.45 (1 H, br s, C(O)H). ^{31}P NMR δ: −4.46. IR: $\nu_{(NH)}$ 3447, 3115; $\nu_{(CO)}$ 1718; $\nu_{(PO)}$ 1254; $\nu_{(POC)}$ 1099 cm^{-1}. MS: m/z 181 (M^+, 0.6%), 153(22), 126(77), 98(100), 81(92).

*Diethyl-N-acetylphosphoramidate (**1b**).* The intermediate Methyl-[N-(diethoxyphosphoryl)]-acetimidate (**2b**) (**2**, R′ = R″ = Me) was prepared in 88% yield from diethylphosphoramidate and trimethyl orthoacetate in the presence of catalytic amounts of trifluoroacetic acid; ^{31}P NMR δ: ($CDCl_3$) 0.73. ^1H NMR δ: 1.11 (6 H, t, J 7.2 Hz, 2 × Me of POEt), 2.10 (3 H, s, N=CMe), 3.51 (3 H, s, COMe), 3.88 (4 H, quintet, J 7.2 Hz, 2 × CH_2 of POEt). MS: m/z 209 (M^+, 4%), 149(4), 136(9), 95(27), 81(31), 42(100).

2b was hydrolyzed as described above; **1b**, 100%, mp 49–51°C (Ref. [20], mp 52–53°C). ^1H NMR ($CDCl_3$) δ: 1.32 (6 H, t, J 6.3 Hz, 2 × Me of POEt), 2.09 (3 H, s, C(O)Me), 4.15 (4 H, m, 2 × CH_2 of POEt), 8.99 (1 H, br s, NH). ^{31}P NMR δ: −4.50. MS: m/z 195 (M^+, 1%), 168(4), 127(72), 98(100), 81(97), 43(91).

*Diethyl-N-propionylphosphoramidate (**1c**).* The intermediate Ethyl-[N-(diethoxyphosphoryl)]-propionimidate (**2c**) (**2**, R′ = R″ = Et) was prepared as **2b**; 94%, bp 92–94°C/0.8 Torr. ^{31}P NMR δ: ($CDCl_3$) 0.56. ^1H NMR δ: 1.06 (3 H, t, J 7.7 Hz, Me of CEt) 1.16 (3 H, t, J 7.2 Hz, Me of COEt), 1.20 (6 H, t, J 7.0 Hz, 2 × Me of POEt), 2.57 (2 H, q, J 7.7 Hz, CH_2 of CEt), 3.96 (4 H, quintet, J 7.0 Hz, 2 × CH_2 of POEt), 4.08 (2 H, q, J 7.2, CH_2 of COEt). MS: m/z 238 (M + 1, 80%), 237 (M^+, 42), 208(9), 192(26), 164(100), 155(68), 138(79), 124(48), 109(56), 81(39), 56(72).

2c was hydrolyzed as described above; **1c**, 98%, viscous liquid. ^1H NMR ($CDCl_3$) δ: 0.95 (3 H, t, J 7.5 Hz, Me of CEt), 1.78 (6 H, t, J 6.5, 2 × Me of POEt), 2.21 (2 H, q, J 7.5 Hz, CH_2 of CEt), 4.03 (4 H, m, 2 × CH_2 of POEt), 9.05 (1 H, d, J 10.5 Hz, NH). ^{13}C NMR δ: 9.0 (Me of CEt), 16.0 (d, J 6.8 Hz, Me of POEt), 30.1 (d, J 9.7 Hz, CH_2 of CEt), 63.9 (d, J 5.6 Hz, CH_2 of POEt), 175.6 (d, J 8.2 Hz, CO). ^{31}P NMR δ: −4.90. MS: m/z 210 (M + 1, 100%), 209 (M^+, 6), 155(94), 137(48), 127(72), 109(70), 99(63), 81(48), 57(28).

Diethyl-N-benzoylphosphoramidate (**1d**). The intermediate N-benzoyl-O,O,O-triethylphosphorimidate **4d** was prepared as follows. A solution of sodium azide (15.6 g, 0.24 mol) in water (50 mL) was added dropwise with stirring and cooling at −5–0°C to the mixture of benzoyl chloride (27.5 g, 0.196 mol), dichloromethane (300 mL), and tetrabutylammonium bromide (TBAB, 0.2 g). The two-phase system was stirred vigorously at −5–+5°C for 2.5 hours and separated and the organic layer was washed with water (2 × 50 mL) and dried over [anhyd] $MgSO_4$. This solution was added dropwise with stirring at room temperature to the solution of triethyl phosphite (33.2 g, 0.20 mol) in benzene (500 mL). After the addition, the solution was stirred for an additional 5 hours at room temperature and evaporated under reduced pressure. Crude **4d** was purified by distillation; bp 110–115°C/0.05 Torr; 50.6 g (91%). ^{1}H NMR ($CDCl_3$) δ: 1.28 (9 H, t, J 6.9 Hz, 3 × Me of POEt), 4.19 (6 H, quintet, J 7.2 Hz, 3 × CH_2 of POEt), 7.26 (3 H, m, H-3, H-4, H-5 of Ph), 8.12 (2 H, d, J 6.6 Hz, H-2, H-6 of Ph). ^{31}P NMR δ: 11.50 (Ref. [7] δ: 10.66).

The product **4d** (50.0 g, 0.17 mol) was dissolved in benzene (80 mL), and dry HCl was passed through the solution at 15–20°C for 1.5 hours. The solution was washed with aq Na_2CO_3 until neutral, then with water, and then dried. The solvent was evaporated under reduced pressure yielding crude **1d** as a pale yellow solid, 29.3 g (67%). The product was purified by crystallization from cyclohexane, mp 72.6–75.6°C. ^{1}H NMR (C_6D_6) δ: 1.06 (6 H, t, J 7.2 Hz, 2 × Me of POEt), 4.13 (4 H, m, 2 × CH_2 of POEt), 7.17 (3 H, m, H-3, H-4, H-5 of Ph), 8.54 (2 H, d, J 8.2 Hz, H-2, H-6 of Ph), 10.61 (1 H, d, J 8.3 Hz, NH). ^{31}P NMR δ: −4.50. ^{13}C NMR δ: 16.1 (d, J 6.9 Hz, 2 × Me of POEt), 64.2 (d, J 5.8 Hz, 2 × CH_2 of POEt), 128.7, 129.1 (s, *o* and *m* C of Ph), 132.6 (s, *p* C of Ph), 133.5 (s, *ipso* C of Ph), 168.0 (s, CO). MS: *m/z* 257 (M^+, 7%), 180(4), 154(22), 127(38), 105(93), 81(17), 77(100), 51(28).

Diethyl-N-(ethoxycarbonyl)phosphoramidate (**1e**). The intermediate diethyl phosphorisocyanatidate **5** was prepared as described [15]; 72%, ^{31}P NMR δ: −15.5 (Ref. [15] δ: −17.6). This product was treated with anhydrous ethanol in tetrachloromethane in a manner analogous to that given for the preparation of the *t*-butoxycarbonyl derivative [15]. **1e**, 94%, colorless, viscous liquid which can be purified by distillation; bp 90–96°C/0.5 Torr. ^{1}H NMR ($CDCl_3$) δ: 1.18 (3 H, t, J 7.1 Hz, Me of COEt), 1.26 (6 H, t, J 7.2 Hz, 2 × Me of POEt), 4.11 (6 H, m, 3 × CH_2 of COEt and POEt), 7.79, (1 H, br s, NH). ^{31}P NMR (C_6D_6) δ: −4.50. ^{13}C NMR (C_6D_6) δ: 14.3 (s, Me of COEt), 16.0 (d, J 6.7 Hz, 2 × Me of POEt), 61.3 (s, CH_2 of COEt), 63.7 (d, J, 5.1 Hz, 2 × CH_2 of POEt), 154.0 (d, J 3.9 Hz, CO). MS: *m/z* 226 (M + 1, 100%), 225 (M^+, 34), 198(93), 180(41), 170(26), 154(36), 124(70), 109(62), 98(56), 81(65).

N-(Diethoxyphosphoryl)-N', N'-diethylurea (**1f**). A solution of diethylamine (10.4 g, 0.14 mol) in tetrachloromethane (15 mL) was added dropwise with cooling to a solution of freshly distilled **5** (25.2 g, 0.14 mol) in CCl_4 (30 mL) at such a rate as to maintain the temperature of the mixture below 5°C. The mixture was then stirred at 5°C for 45 minutes, warmed to room temperature, and stirred for an additional 3 hours. The solvent was removed under reduced pressure, yielding crude 1f as a pale yellow liquid, which was purified by bulb-to-bulb distillation (oven temperature 150°C/0.4 Torr), 30.0 g (84%). Pure **1f** crystallized upon standing; mp 37.8–41.5°C. ^{1}H NMR ($CDCl_3$) δ: 0.97 (6 H, t, J 7.0 Hz, 2 × Me of NEt), 1.17 (6 H, t, J 7.3 Hz, 2 × Me of POEt), 3.18 (4 H, q, J, 7.0 Hz, 2 × CH_2 of NEt), 4.04 (4 H, m, 2 × CH_2 of POEt), 7.79 (1 H, br s, NH). ^{31}P NMR δ: −3.00. ^{13}C NMR (C_6D_6) δ: 13.8 (s, 2 × Me of PNEt), 15.9 (d, J 7.0 Hz, 2 × Me of POEt), 41.4 (s, 2 × CH_2 of NEt), 63.5 (d, J 6.2 Hz, 2 × CH_2 of POEt), 154.0 (CO). MS: *m/z* 253 (M + 1, 81%), 252 (M^+, 16), 180(32), 152(36), 124(52), 81(17), 72(100), 58(84), 44(52).

Reactions of Phosphoramidates **1** *with Haloalkanes*

General Procedure. Sodium hydride (washed several times with petroleum ether) was added to DME (*ca.* 2.5 mL/mmol), and to this suspension, substrate 1 dissolved in DME (*ca.* 1.5 mL/mmol; molar ratio NaH:1 = 1.1) was added with stirring at room temperature. After the evolution of hydrogen had ceased, the solution of the haloalkane (R″X:1 = 1.5 for MeI and EtBr and 1.0 for other haloalkanes) in DME (*ca.* 0.8 mL/mmol) was added, and the mixture was either stirred overnight at room temperature (for MeI) or heated under reflux for 2–24 hours. For reactions carried out in the presence of TBAB, 5 mol% of the catalyst was added before the haloalkane was introduced to the mixture. A small volume of water was added, the mixture was evaporated under reduced pressure, ether or benzene (2 mL/mmol of 1) was added, and the solution was washed with water or dil aq NH_4Cl (for reactions with MeI, some $Na_2S_2O_3$ was also added) until neutral. After drying and evaporation of the solvent under reduced pressure, the alkylation product was identified. The following results were obtained (for ^{31}P chemical shifts, yields, and other details, see Tables 1–3).

Alkylation of **1a**

Methylation. O,O-Diethyl-N-formyl-N-methylphosphoramidate. Purified by bulb-to-bulb distillation; oven temperature 112°C/1.8 Torr. ^{1}H NMR δ: 1.21 (6 H, t, J 6.5 Hz, 2 × Me of POEt), 2.72 (3 H, d, J 8.1 Hz, NMe), 3.99 (4 H, m, 2 × CH_2 of POEt), 8.62 (1 H, s, C(O)H). MS: *m/z* 195 (M^+, 3%), 167(21),

139(35), 112(43), 110(80), 81(60), 65(42), 29(100). Anal. calcd. for $C_6H_{14}NO_4$ P: C, 36.9; H, 7.2; N, 7.2. Found: C, 36.4; H, 6.8; N, 6.4%.

Ethylation. O,O-Diethyl-N-formyl-N-ethylphosphoramidate. Purified by bulb-to-bulb distillation; oven temperature 115°C/2.5 Torr. ^{1}H NMR δ: 0.97 (3 H, t, J 7.1 Hz, Me of NEt), 1.16 (6 H, t, J 7.2 Hz, 2 × Me of POEt), 3.23 (2 H, 2 q, J 7.1, 7.4 Hz, CH_2 of NEt), 3.96 (4 H, m, 2 × CH_2 of POEt), 8.54 (1 H, s, C(O)H). MS: m/z 209 (M^+, 0.2%), 181(22), 166(72), 138(5)), 124(52), 110(100), 81(51), 56(15), 29(36). Anal. calcd. for $C_7H_{16}NO_4P$: C, 40.2; H, 7.7; N, 6.7. Found: C, 38.8; H, 7.8; N, 6.0%.

Propylation. O,O-Diethyl-N-formyl-N-propylphosphoramidate. Colorless oil. ^{1}H NMR δ: 0.79 (3 H, t, J 7.5 Hz, Me of NPr), 1.25 (6 H, t, J 7.4 Hz, 2 × Me of POEt), 1.49 (2 H, m, β-CH_2 of NPr), 3.22 (2 H, m, NCH_2 of NPr), 4.06 (4 H, m, 2 × CH_2 of POEt), 8.65 (1H, s, C(O)H).

Butylation. Colorless oil. Mixture: O,O-diethyl-N-formyl-N-butyl-phosphoramidate (major); ^{1}H NMR δ: 0.81 (3 H, t, J 7.3 Hz, Me of NBu), 1.21 (2 H, m, γ-CH_2 of NBu), 1.25 (6 H, t, J 7.4 Hz, 2 × Me of POEt), 1.46 (2 H, m, β-CH_2 of NBu), 3.26 (2 H, m, NCH_2 of NBu), 4.07 (4 H, m, 2 × CH_2 of POEt), 8.65 (1 H, s, C(O)H). Butyl-[N-(diethoxyphosphoryl)]-formimidate (minor); ^{1}H NMR δ: 1.04 (3 H, t, J 7.1 Hz, Me of COBu), 1.58 (2 H, m, β-CH_2 of COBu), 8.11 (1 H, d, J 15.3 Hz, N=CH); other signals of the minor product overlapping with those of the major.

Hexylation. Colorless oil, purified by distillation (see above). Mixture: O,O-diethyl-N-formyl-N-hexyl-phosphoramidate (major); ^{1}H NMR δ: 0.68 (3 H, t, J 6.9 Hz, Me of NHex), 0.94–1.28 (12 H, m, 2 × Me of POEt, 3 × CH_2 of NHex), 1.37 (2 H, m, β-CH_2 of NHex), 3.14 (2 H, m, NCH_2 of NHex), 3.85–4.05 (4 H, m, 2 × CH_2 of POEt), 8.55 (1 H, s, C(O)H). Hexyl-[N-(diethoxyphosphoryl)]-formimidate (minor); ^{1}H NMR δ: 0.80 (3 H, t, J 7.2 Hz, Me of COHex), 1.47 (2 H, m, β-CH_2 of COHex), 8.00 (1 H, d, J 15.2 Hz, N=CH); other signals of this product overlapping with those of the major. MS: m/z 266 (M + 1, 1.3%), 265 (M^+, 0.1), 237(1), 208(1), 182(9), 155(13), 126(12), 110(31), 99(20), 81(33), 43(57), 29(100).

Isopropylation. (i) No TBAB: crude product, glassy liquid, decomposing upon heating or exposure to moisture. O,O-diethyl-O-i-propyl-N-formylphosphorimidate. ^{1}H NMR δ: 1.06–1.36 (12 H, overlapping d and t, 2 × Me of POEt, 2 × Me of POi-Pr), 3.91 (4 H, q, J 7.0 Hz, 2 × CH_2 of POEt), 4.02 (1 H, d of sept, J 7.2, 8.7 Hz, CH of POiPr), 8.45 (1 H, d, J 21.1 Hz, C(O)H). No ^{13}C NMR spectrum was obtained, since the product was not stable over the period of data acquisition.

(ii) With TBAB: colorless oil, purified by washing with water. *i*-propyl[N-(diethoxyphosphoryl)]-formimidate (E/Z). ^{1}H NMR δ: 1.08 (d, J 6.2 Hz, 2 × Me of CO*i*-Pr of one stereoisomer), 1.11 (t, J 7.1 Hz, 2 × Me of POEt), 1.16 (d, J 6.9 Hz, 2 × Me of CO*i*-Pr of another stereoisomer) (all signals integrating for 12H), 3.80–3.94 (6 H, m, overlapping CH of CO*i*-Pr; both stereoisomers, 2 × CH_2 of POEt), 7.93 (1 H, d, 15.5 Hz, N=CH of one stereoisomer), 7.96 (1 H, d, J 15.3 Hz, N=CH of another stereoisomer). IR: $\nu_{(\text{vinylic CH})}$ 2983; $\nu_{(C=N)}$ 1635 [21]; $\nu_{(PO)}$ 1244; $\nu_{(POC)}$ 1103 cm^{-1}.

Alkylations of lithium salts of **1** were carried out as follows. Isopropylamine (1.1 mol-equivalent) was dissolved in THF (2 mL/mmol), the solution was cooled to −75°C, and BuLi (15% solution in hexane, 1.1 mol-equivalent) was added. After 10 minutes, a solution of 1 (1 mol-equivalent) in THF (2 ml/mmol) was added at −75°C, and the solution was stirred at this temperature for 45 minutes. Haloalkane (2 mol-equivalent) in THF (1 mL/mmol) was added to the solution, and the temperature was allowed to rise to −5°C. After having been stirred for 30 minutes, the mixture was warmed to room temperature and left overnight. Aqueous NH_4Cl was added, THF was removed under reduced pressure, and the neutral solution was extracted with ether. After drying and evaporation of the solvent, crude product was identified as described above.

Alkylation of **1b**

Methylation. Colorless oil. O,O-Diethyl-N-methyl-N-acetylphosphoramidate (major). ^{1}H NMR δ: 1.22 (6 H, t, J 7.2 Hz, 2 × Me of POEt), 2.23 (3 H, s, C(O)Me), 2.88 (3 H, d, J 7.5 Hz, NMe), 4.02 (4 H, m, 2 × CH_2 of POEt). ^{13}C NMR δ: 15.6 (d, J 6.9 Hz, 2 × Me of POEt), 24.2 (s, Me of C(O)Me), 29.3 (d, J 25.3 Hz, NMe), 63.2 (d, J 5.1 Hz, 2 × CH_2 of POEt), 172.7 (s, CO). O,O-Diethyl-N-methylphosphoramidate (minor). ^{1}H NMR δ: 1.17 (6 H, t, overlapping with that of the other phosphoramidate, 2 × Me of POEt), 2.43 (3 H, dd, J 5.0, 12.1 Hz, Me of PNHMe), 3.90 (4 H, m, overlapping with that of the other phosphoramidate, 2 × CH_2 of POEt). O,O-Diethyl-N,N-dimethylphosphoramidate (minor). ^{1}H NMR δ: 2.52 (6 H, d, J 10.2 Hz, 2 × Me of $PNMe_2$); other signals overlapping with those of the first phosphoramidate.

Ethylation. Oil. O,O-Diethyl-N-ethyl-N-acetylphosphoramidate (major). ^{1}H NMR δ: 0.85 (3 H, t, J 7.0 Hz, Me of NEt), 1.06 (6 H, t, J 7.2 Hz, 2 × Me of POEt), 2.02 (3 H, s, C(O)Me), 3.32 (2 H, 2 q, J, 7.2, 10.9 Hz, CH_2 of NEt) 3.71–3.93 (4 H, m, 2 × CH_2 of POEt, overlapping with those of the minor product). Ethyl-[N-(diethoxyphosphoryl)]-acetimidate (minor). ^{1}H NMR δ: 0.95 (3 H, t, J 7.0, Me of COEt), 2.08 (3 H, s, Me of N=CMe), 3.54 (2 H, q,

J 7.1 Hz, CH_2 of COEt); other signals overlapping with those of the major product.

Hexylation. Oil. O,O-Diethyl-N-hexyl-N-acetylphosphoramidate. ^{1}H NMR δ: 0.72 (3 H, Me of NHex, overlapping with corresponding signals of other isomers), 1.23 (6 H, 2 × Me of POEt, overlapping), 1.98 (3 H, s, C(O)Me), 1.30, 1.51, 2.75 (6 H, m, β-CH_2, γ-CH_2, δ-CH_2 of Hexyl, overlapping), 3.11 (2 H, m, α-CH_2 of NHex), 3.85–4.10 (4 H, m, 2 × CH_2 of POEt, overlapping). Hexyl-[N-(diethoxyphosphoryl)]-acetimidate. ^{1}H NMR δ: 1.87 (3 H, s, C(O)Me), 3.32 (2 H, m, CH_2 of COHex); other signals overlapping with those of other isomers. O,O-Diethyl-O-hexyl-N-acetylphosphorimidate. ^{1}H NMR δ: 1.83 (3 H, s, C(O)Me); other signals overlapping with those of other components.

Alkylation of **1c**

Methylation. Oil. O,O-Diethyl-N-methyl-N-propionylphosphoramidate. ^{1}H NMR δ: 0.94 (3 H, t, J 7.5 Hz, Me of C(O)Et), 1.17 (6 H, t, J 7.2 Hz, 2 × Me of POEt), 2.54 (2 H, q, J 7.3 Hz, CH_2 of C(O)Et), 2.85 (3 H, d, J 7.5 Hz, NMe), 3.92–3.99 (4 H, m, 2 × CH_2 of POEt). ^{13}C NMR δ: 9.0 (s, Me of C(O)Et), 15.6 (d, J 6.7 Hz, 2 × Me of POEt), 29.0 (d, J 19.6 Hz, NMe), 31.7 (s, CH_2 of C(O)Et), 63.1 (d, J 5.4 Hz, 2 × CH_2 of POEt), 176.3 (d, J 9.6 Hz, CO).

Ethylation. Oil. O,O-Diethyl-N-ethyl-N-propionylphosphoramidate (major). ^{1}H NMR δ: 0.86 (3 H, t, J 7.3 Hz, Me of NEt), 0.91 (3 H, t, J 6.9 Hz, Me of C(O)Et), 1.10 (6 H, 2 × Me of POEt, overlapping with signals of another isomer), 2.41 (2 H, q, J 7.3 Hz, CH_2 of C(O)Et), 3.38 (2 H, dq, J 7.0, 11, 1 Hz, CH_2 of NEt), 3.80–3.99 (4 H, m, 2 × CH_2 of POEt, overlapping with signals of another isomer). ^{13}C NMR δ: 8.8 (s, Me of C(O)Et), 14.3 (s, Me of NEt), 15.5 (d, J 6.7 Hz, 2 × Me of POEt), 29.2 (d, J 9.3 Hz, CH_2 of NEt), 40.1 (s, CH_2 of C(O)Et), 63.0 (d, 5.5 Hz, 2 × CH_2 of POEt), 175.4 (s, CO). O,O,O-Triethyl-N-propionylphosphorimidate (minor). ^{1}H NMR δ: 1.00 (3 H, t, J 8.0 Hz, Me of C(O)Et), 2.43 (2 H, q, J 8.0 Hz, CH_2 of C(O)Et); other signals overlapping with those of the major product. ^{13}C NMR δ: 8.3 (s, Me of C(O)Et), 13.5 (s, 3 × Me of POEt), 36.9 (s, CH_2 of C(O)Et), 61.9 (d, J 6.3 Hz, 3 × CH_2 of POEt), 176.5 (s, CO).

Hexylation. Oil. Hexyl-[N-(diethoxyphosphoryl)]-propionimidate and O,O-diethyl-O-hexyl-N-propionylphosphorimidate. ^{1}H NMR δ: the following signals of both compounds overlapped. 1.03 (3 H, t, J 7.4 Hz, Me of Hex), 1.10–1.27 (14 H, m, 2 × Me of POEt, β-,γ-,δ-,ϵ-CH_2 of Hex), 3.90–4.15 (4 H, m, 2 × CH_2 of POEt). The following signals could be observed for individual products: 2.55 (2 H, q, J 7.6 Hz, CH_2 of C(O)Et of compound **4c**), 2.74, 2.77 (2 H, 2 q, J 7.1 Hz, CH_2 of N=CEt of two stereoisomers of **2c**), 3.12 (2 H, m, CH_2 of POHex of **4c**), 3.43, 3.45 (2 H, 2 q, J 7.1 Hz, CH_2 of COHex of two stereoisomers of **2c**).

Alkylation of **1d**

Methylation. Colorless solid, unstable when exposed to air. O,O-Diethyl-N-methyl-N-benzoylphosphoramidate. ^{1}H NMR δ: 1.89 (6 H, t, J 6.4 Hz, 2 × Me of POEt), 3.11 (3 H, d, 7.7 Hz, NMe), 3.98 (4 H, dq, J 6.4, 7.1 Hz, 2 × CH_2 of POEt), 7.31–7.41 (3 H, m, H-3, H-4, H-5), 7.51 (2 H, dd, J 1.3, 7.9 Hz, H-2, H-6). ^{13}C NMR δ: 15.6 (d, J 6.9 Hz, 2 × Me of POEt), 29.7 (d, J 25.1 Hz, NMe), 63.5 (d, J 5.7 Hz, 2 × CH_2 of POEt), 128.3, 129.1 (s, *o* and *m* C of Ph), 132.1 (s, *p* C of Ph), 136.2 (s, *ipso* C of Ph), 173.1 (s, CO).

Alkylation of **1e**

Methylation Colorless oil. O,O-Diethyl-N-(ethoxycarbonyl)-N-methyl-phosphoramidate. ^{1}H NMR δ: 1.18 (3 H, t, J 7.1 Hz, Me of COEt), 1.22 (6 H, t, J 7.2 Hz, 2 × Me of POEt), 2.90 (3 H, d, J 7.9 Hz, NMe), 3.91 (4 H, dq, J 7.0, 8.3 Hz, 2 × CH_2 of POEt), 3.99 (2 H, q, J 7.1 Hz, CH_2 of COEt). ^{13}C NMR δ: 13.8 (s, Me of COEt), 15.5 (d, J 6.9 Hz, 2 × Me of POEt), 29.2 (d, J 25.1 Hz, NMe), 62.1 (s, CH_2 of COEt), 63.2 (d, J 5.7 Hz, 2 × CH_2 of POEt), 154.7 (d, J 6.6 Hz, CO).

Ethylation. Colorless oil. O,O-diethyl-N-(ethoxycarbonyl)-N-ethyl-phosphoramidate. ^{1}H NMR δ: 0.73 (3 H, t, J 6.9 Hz, Me of NEt), 0.83 (3 H, t, J 7.1 Hz, Me of COEt), 0.87 (6 H, t, J 7.1 Hz, 2 × Me of POEt), 3.15 (2 H, dq, J 6.9, 11.6 Hz, CH_2 of NEt), 3.66 (4 H, dq, J 7.1, 8.3 Hz, CH_2 of POEt), 3.75 (2 H, q, J 7.1 Hz, CH_2 of COEt). ^{13}C NMR δ: 13.3 (s, Me of NEt), 14.4 (s, Me of COEt), 15.1 (d, J 6.8 Hz, 2 × Me of POEt), 40.9 (s, CH_2 of NEt), 61.3 (s, CH_2 of COEt), 62.4 (d, J 5.7 Hz, 2 × CH_2 of POEt), 153.6 (d, J 6.3 Hz, CO).

Hexylation. Colorless oil. O,O-Diethyl-N-(ethoxycarbonyl)-N-hexyl-phosphoramidate. ^{1}H NMR δ: 0.62 (3 H, t, J 6.7 Hz, Me of NHex), 0.96–1.11 (17 H, m, Me of COEt, 2 × Me of POEt, 4 × CH_2 of NHex), 3.27 (2 H, dt, J 7.8, 11.5 Hz, NCH_2 of NHex), 3.89 (4 H, dq, J 7.0, 10.7 Hz, 2 × CH_2 of POEt), 3.96 (2 H, q, J 7.0 Hz, CH_2 of COEt). ^{13}C NMR δ: 13.4 (s, Me of NHex), 13.8 (s, ϵ-CH_2 of NHex), 15.5 (d, J 6.9 Hz, Me of POEt), 22.0 (s, Me of COEt), 25.7 (s, δ-CH_2 of NHex), 29.6 (s, γ-CH_2 of NHex), 30.9 (s, β-CH_2 of NHex), 46.4 (d, J 1.9 Hz, NCH_2 of NHex), 61.8 (s, CH_2 of COEt), 63.0 (d, J 5.7 Hz, 2 × CH_2 of POEt), 154.3 (d, J 6.7 Hz, CO).

Alkylation of **1f**

Methylation. Colorless oil. N-(Diethoxyphosphoryl)-N-methyl-N′,N′-diethylurea. ^{1}H NMR δ: 0.95

(6 H, t, J 7.1 Hz, 2 × Me of NEt), 1.13 (6 H, t, J 6.9 Hz, 2 × Me of POEt), 2.63 (3 H, d, J 9.7 Hz, NMe), 3.20 (4 H, q, J 7.1 Hz, 2 × CH_2 of NEt), 3.92 (4 H, quintet, J 6.9 Hz, 2 × CH_2 of POEt). ^{13}C NMR δ: 12.7 (s, 2 × Me of NEt), 15.6 (d, J 6.8 Hz, 2 × Me of POEt), 29.1 (d, J 25.3 Hz, NMe), 41.8 (s, 2 × CH_2 of NEt), 62.5 (d, J 5.2 Hz, 2 × CH_2 of POEt), 157.9 (J 6.5 Hz, CO).

Ethylation. Oil. N-(Diethoxyphosphoryl)-N-ethyl-N′,N′-diethylurea. ^1H NMR δ: 0.80 (3 H, t, J 7.0 Hz, Me of PNEt), 1.05 (6 H, t, 7.1 Hz, 2 × Me of CNEt), 1.20 (6 H, t, J 7.0 Hz, 2 × Me of POEt), 3.28 (2 H, m, CH_2 of PNEt), 3.41 (4 H, q, J 7.2 Hz, 2 × CH_2 of CNEt), 4.06 (4 H, quintet, J 7.6 Hz, 2 × CH_2 of POEt).

Hexylation. Oil. N-(Diethoxyphosphoryl)-N-hexyl-N′,N′-diethylurea. ^1H NMR δ: 0.80 (3 H, t, J 6.9 Hz, Me of NHex), 1.00–1.29 (20 H, m, 2 × Me of NEt, 2 × Me of POEt, 4 × CH_2 of NHex), 3.27 (2 H, m, NCH_2 of NHex), 3.37 (4 H, q, J 7.4 Hz, 2 × CH_2 of CNEt), 4.02 (4 H, quintet, J 7.4 Hz, 2 × CH_2 of POEt).

Reactions of Phosphoramidates **1** *with HMDS*

General Procedure. A solution of HMDS (0.6–1.1 mol-equivalent) in benzene (0.3 mL/mmol) was added to a solution of **1** (1 mol-equivalent) in the same solvent (0.2 mL/mmol), and the solution was heated under reflux for 3–6 hours. After having been cooled to room temperature, the solvent was evaporated under reduced pressure and the product was identified as given below. The following results were obtained (for ^{31}P chemical shifts, yields, and other details; see Tables 1 and 4).

Silylation of **1a**. *N-(diethoxyphosphoryl)-formamidine (see Ref. [17])*

Silylation of **1b**. Oil. O,O-Diethyl-N-acetyl-N-trimethylsilylphosphoramidate (major). ^1H NMR δ: 0.17 (9 H, s, Me_3SiN), 1.07 (6 H, t, J 6.5 Hz, 2 × Me of POEt), 2.22 (3 H, s, C(O)Me), 3.92 (4 H, quintet, J 6.1 Hz, 2 × CH_2 of POEt). ^{13}C NMR δ: −0.2 (s, Me_3Si), 16.2 (d, J 6.9 Hz, 2 × Me of POEt), 23.9 (d, J 9.7 Hz, Me of C(O)Me), 62.2 (d, J 5.6 Hz, 2 × CH_2 of POEt), 171.7 (s, CO). MS: *m/z* 268 (M + 1, 0.3%), 267(M^+, 0.1), 241(0.1), 211(0.6), 195(43), 168(7), 155(43), 137(12), 127(95), 109(55), 98(100), 81(80), 43(78). Trimethylsilyl-[N-(diethoxyphosphoryl)]-acetimidate (minor). ^1H NMR δ: 0.30 (9 H, s, Me_3SiO), 2.51 (3 H, s, N=CMe), signals of the POEt groups overlapping with those of the major product.

Silylation of **1d**. Oil. O,O-Diethyl-N-benzoyl-N-trimethylsilylphosphoramidate. ^1H NMR δ: 0.21 (9 H, s, Me_3SiN), 1.06 (6 H, t, J 7.1 Hz, 2 × Me of POEt), 4.06 (4 H, dq, J 7.1, 8.4 Hz, 2 × CH_2 of POEt), 7.24 (3 H, m, H-3, H-4, H-5), 8.54 (2 H, dd, J 3.4, 7.7 Hz, H-2, H-6). ^{13}C NMR δ: 0.7 (s, ME_3Si), 16.2 (d, J 6.9 Hz, 2 × Me of POEt), 64.5 (d, J 5.3 Hz, 2 × CH_2 of POEt), 128.0, 130.1 (s, *o* and *m* C of Ph), 131.1 (s, *p* C of Ph), 132.7 (s, *ipso* C of Ph), 174.2 (s, CO).

Silylation of **1e**. O,O-Diethyl-N-(ethoxycarbonyl)-N-trimethylsilylphosphoramidate (major). ^1H NMR δ: 0.04 (9 H, s, Me_3SiN), 1.04 (3 H, t, J 7.7 Hz, Me of COEt), 1.08 (6 H, t, J 6.5 Hz, 2 × Me of POEt), 3.94 (4 H, dq, J 7.2, 11.1 Hz, 2 × CH_2 of POEt). ^{13}C NMR δ: −0.6 (s, Me_3SiN), 16.0 (d, J 6.9 Hz, 2 × Me of POEt), 16.3 (s, Me of COEt), 61.6 (d, J 6.0 Hz, 2 × CH_2 of POEt), 63.4 (s, CH_2 of COEt), 158.9 (s, CO). O-Ethyl-O′-trimethylsilyl-N-(diethoxyphosphoryl)-carbimidate (minor). ^1H NMR δ: 0.24 (9H, s, Me_3SiO), signals of the COEt and POEt groups overlapping with those of the major product. ^{13}C NMR δ: −0.5 (s, Me_3SiO), 16.3 (d, J 5.3 Hz, 2 × Me of POEt), 16.4 (s, Me of COEt), 61.7 (d, J 6.3 Hz, 2 × CH_2 of POEt), 63.3 (s, CH_2 of COEt), 162.0 (s, CO). O,O-Diethyl-O-trimethylsilyl-N-(carboethoxy)phosphorimidate (minor). ^1H NMR δ: 0.20 (9 H, s, Me_3SiO), signals of the COEt and POEt groups overlapping with those of other isomers. ^{13}C NMR δ: 0.1 (s, Me_3SiO), 162.1 (s, CO), signals of the COEt and POEt groups overlapping with those of other isomers.

Silylation of **1f**. Oil. O-Trimethylsilyl-N-(diethoxyphosphoryl)-N′,N′-diethylisourea (major). ^1H NMR δ: 0.24 (9 H, s, Me_3SiO), other signals overlapping with those of other isomers and unreacted **1f**. ^{13}C NMR δ: 0.7 (s, Me_3SiO), 61.5 (d, J 4.6 Hz, 2 × CH_2 of POEt), other signals overlapping with those of other products. N,N-Diethyl-N′-(diethoxyphosphoryl)-N′-trimethylsilylurea (minor). ^1H NMR δ: 0.02 (9 H, s, Me_3SiN), other signals overlapping with those of other products. ^{13}C NMR δ: −0.6 (s, Me_3SiN), 63.3 (d, J 5.6 Hz, 2 × CH_2 of POEt), other signals overlapping with those of other products. O,O-Diethyl-O-trimethylsilyl-N-[(N′,N′-diethyl)carboxyamido]phosphorimidate (minor). ^1H NMR δ: 0.20 (9 H, s, Me_3SiO), other signals overlapping. ^{13}C NMR δ: 0.1 (s, Me_3SiO), 61.6 (d, J 5.6 Hz, 2 × CH_2 of POEt), other signals overlapping.

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