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A Convenient Synthetic Route to *N*-Aryl and *N*-Alkylamino(alkyl) Phosphonates and Phosphine Oxides

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Abstract: A variety of phosphorylated *N*-aryl and *N*-alkyl *N*-formyl and *N*-*tert*-butoxycarbonylaminomethyl derivatives have been efficiently prepared by treatment of the corresponding chloromethyl derivatives with a trialkyl phosphite or an alkyl diphenylphosphinite. These bifunctional compounds may be deprotonated with LDA and further submitted to electrophilic substitution. An acidic treatment of the resulting compounds gives rise to a range of *N*-aryl and *N*-alkylamino(alkyl) phosphonates and phosphine oxides.

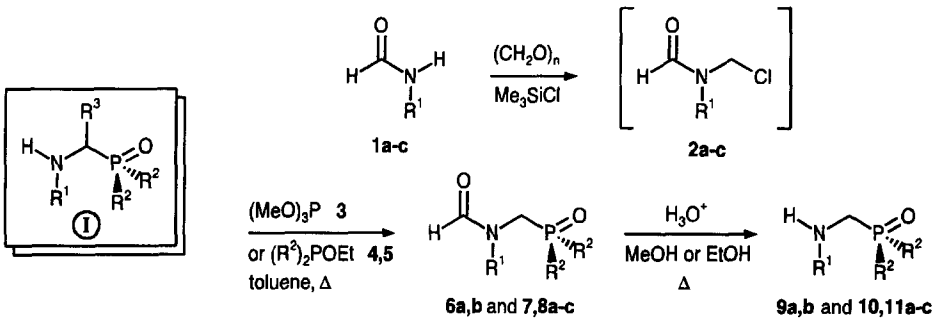
Over the years the synthesis of α-aminophosphorylated compounds of general form **I** has been an important area of research particularly due to their structural analogy with natural α-amino carboxylic acid derivatives.[1] Their presence in living matter, their diverse biological activity[2] as antibiotics,[3] enzyme inhibitors[4] and pesticides[5] and their role as key building blocks of phosphonopeptides[6] account for the impressive effort which have been devoted to the synthesis of these bifunctional compounds.

The α-amino phosphonates (**I**, R^3 = *O*-alkyl, *O*-aryl) may be synthesized in a number of different ways[7a] but the most common route involves the thermal addition of dialkyl phosphites to imines[7] which are either preformed or generated *in situ* from an aldehyde and an amine. The reactions are usually carried out in the presence of a metal alkoxide or a Lewis acid[8] at relatively high temperatures and various modifications have been introduced in the recent years with the aim of providing milder conditions.[9] This synthetically convenient route suffers however from several limitations. For example, in the three component condensation reaction involving a primary amine, the desired α-aminophosphorylated compound are invariably contaminated with the disubstitution products[10] and this problem may be only overcome by preliminary monosilylation of the primary amine.[11] For the elaboration of *C*-substituted compounds (**I**, $R^3 \neq H$) it has been demonstrated that dialkyl phosphites add efficiently to imines of aromatic aldehydes but the yields are low from Schiff bases of aliphatic aldehydes and ketones.[7a,12] On the other hand this strategy may not be applied to the synthesis of phosphorylated *N*-arylaminomethyl derivatives (**I**, R^1 = aryl, R^3 = H) which are only accessible by three methods: (1) substitution of chloromethylphosphonates with excess arylamine[13] (2) rearrangement of *P*-(halomethyl)-*N*-phenylphosphoramidates[14] (3) reaction of *N*-(methoxymethyl)arylamine with trialkyl phosphonates in the presence of titanium tetrachloride.[15] The corresponding *N*-arylaminoalkyl derivatives (**I**, R^1 = aryl, R^3 = alkyl) have been recently prepared by treatment of suitably substituted azomethines with phosphorus III chloride and an appropriate alcohol.[16] Paradoxically few efforts have been devoted to the synthesis of the α-amino diphenylphosphine oxides (**I**, R^1 = alkyl or aryl, R^2 = phenyl) although it has been established that, frequently, diphenylphosphine oxides show superior properties, particularly in the Horner reaction, compared to phosphonium salts and phosphonates.[17] Owing to the great sensitivity of dialkyl esters

of phosphonic acid with respect to nucleophilic attack a variety of α-aminodiphenylphosphine oxides were obtained by treatment of the corresponding phosphonates with phenyllithium but these conversions were always performed with *N,N*-disubstituted compounds.[18]

We looked therefore for a new and general synthetic approach to the α-aminophosphorylated compounds of general form **I** which could permit varying the nature of the terminal phosphoryl moiety (R^2) and of the substituent both on the nitrogen (R^1) and carbon atoms (R^3). The key to our route to α-aminophosphonic acid esters and phosphine oxides is the synthesis of diversely *N*-substituted-*N*-chloromethylcarboxamides. The connection of the appropriate phosphorylated entity may then be ensured by a classical Arbusov reaction and the subsequent removal of the carboxamide protective group completes the reaction thus providing an access to a wide variety of targeted α-aminophosphorylated compounds.

Depending on the degree of substitution at the carbon adjacent to the nitrogen two different models were required. For the *C*-unsubstituted compounds **9a,b** and **10, 11a-c** (Scheme 1, Table 1) *N*-methyl, *N*-benzyl and *N*-phenylformamide, **1a-c** respectively, (0.1 mol) were initially treated with paraformaldehyde (0.1 mol) and chloromethylsilane (0.3 mol) in boiling chloroform (100 mL)[19] for *c.a.* 2 h. NMR analysis of the crude reaction product clearly indicated that the resulting *N*-alkyl and *N*-aryl-*N*-chloromethylcarboxamides **2a-c** were not contaminated with other products so that they could be used directly in the next step. The synthesis of the phosphorylated formamides **6a,b** and **7,8a-c** was achieved by reacting the appropriate compounds **2a-c** (0.1 mol) with trimethyl phosphite **3** (R^2 = OMe), triethyl phosphite **4** (R^2 = OEt) or ethyl diphenylphosphinite **5**[20] (R^2 = Ph) (50 mmol) in boiling toluene (20 mL) for *c.a.* 1 h. The residue obtained after evaporation of the solvent was subjected to column chromatography on silica gel (eluent: acetone/hexane, 60:40) to furnish the parent phosphorylated amides **6a,b** and **7,8a-c** in good yields (Table 1).



Scheme 1

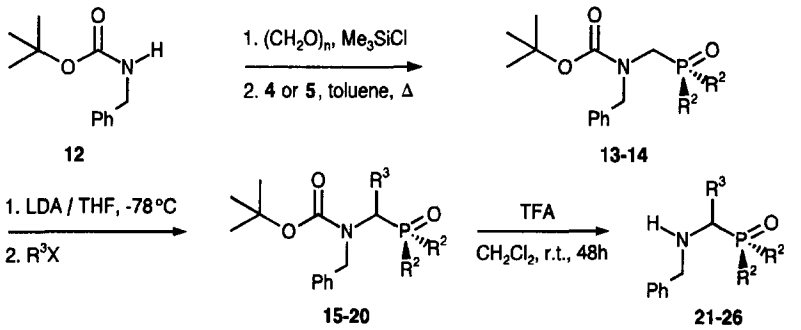
Table 1. Phosphorylated Formamides and Amines Prepared

	R^1	R^2	Yield (%)	m.p. (°C)		R^1	R^2	Yield (%)	m.p. (°C)
6a	Me	MeO	71	-	**9a**	Me	MeO	70	-
6b	CH_2Ph	MeO	70	-	**9b**	CH_2Ph	MeO	67	-
7a	Me	EtO	72	-	**10a**	Me	EtO	71	-
7b	CH_2Ph	EtO	75	-	**10b**	CH_2Ph	EtO	68	-
7c	Ph	EtO	70	-	**10c**	Ph	EtO	75	-
8a	Me	Ph	82	130-131[18]	**11a**	Me	Ph	85	77-78
8b	CH_2Ph	Ph	80	124-125	**11b**	CH_2Ph	Ph	82	101-102
8c	Ph	Ph	75	135-136	**11c**	Ph	Ph	83	136-137

The subsequent hydrolysis (10% HCl) in methanol (for **9a,b**) or ethanol (for **10, 11a-c**) induced the removal of the formamido protective group. The results of a representative series of dialkyl esters of *N*-aryl

and *N*-alkylaminomethylphosphonic acids and of diphenylphosphine oxides, **9a,b**, **10a-c** and **11a-c** respectively, obtained by this simple procedure are presented in Table1.

For the elaboration of *C*-substituted models we developed a noticeably different strategy which hinges upon the nucleophilicity of phosphorylated α-aminocarbanions.[21] This property has been thus far cleverly used by G. Lavielle,[22] J.P. Genet[23] and coll. for the electrophilic *C*-alkylation of free aminomethylphosphonates *via* their activated *N*-benzylidene and *N,N*-diphenylmethylene imines. To this aim, we chose to examine the carbamate as a protective group since formamides are known to be cleaved[24] or deprotonated[25] by lithiated bases while carbamates are known to stabilize nitrogen substituted organolithium compounds by dipole stabilization as well as internal lithium chelation.[26] For this purpose a number of diversely phosphorylated carbamates **13, 14** (Scheme 2, Table 2) was prepared by the two step sequence: (i) chloromethylation of the monosubstituted carbamate **12**, (ii) connection of the phosphoryl moiety. Deprotonation of the methylene linked to the two functional groups of **13, 14** (10 mmol) with LDA (1.1 equiv.) proceeded rapidly and efficiently at -78 °C in tetrahydrofuran. The nitrogen substituted carbanions[27] were then quenched with various electrophiles (1.5 equiv.) as reported in Table 2.[28] Deprotection of the adducts **15-20** was best accomplished by treatment with trifluoroacetic acid in dichloromethane. If purified adducts were used the deprotection produced analytically pure phosphorylated amines **21-26** in fairly good yields (Table 2).[29]

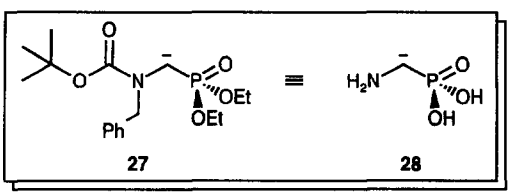


Scheme 2

Table 2. Phosphorylated Carbamates and Amines Prepared

	R^2	R^3	Yield (%)	^{31}P δ (ppm)		R^2	R^3	Yield (%)	m.p. (°C)	^{31}P δ (ppm)
13	EtO	-	65	21.6	**14**	Ph	-	68	118-119	34.7
15	EtO	Me	88	17.7	**18**	Ph	Me	92	152-153	30.2
16	EtO	CH_2Ph	81	19.5	**19**	Ph	CH_2Ph	90	169-170	33.8
17	EtO	$SiMe_3$	75	18.2	**20**	Ph	$SiMe_3$	85	120-121	31.3
21	EtO	Me	76	24.7	**24**	Ph	Me	81	135-136	32.9
22	EtO	CH_2Ph	79	22.8	**25**	Ph	CH_2Ph	80	152-153	30.5
23	EtO	$SiMe_3$	72	20.3	**26**	Ph	$SiMe_3$	75	104-105	21.8

In summary we have developed a general, simple and efficient procedure for the preparation of a wide array of variously substituted α-amino phosphorylated compounds. This protocol, which complements the existant methodologies, is applicable both to *N*-alkyl and *N*-arylamines and allows the connection of dialkoxyphosphoryl and diphenylphosphinyl groups indifferently in the targeted compounds. Furthermore the possibility of



the removal of *N*-benzyl protective group by transfer hydrogenolysis[26b,30] and the easy conversion of the esters to the phosphonic acids with trialkylsilyl halides[31] permits the metallated *N*-benzylcarbamate **27** to be considered as the synthetic equivalent of the carbanion of the free aminophosphonic acid **28**.

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