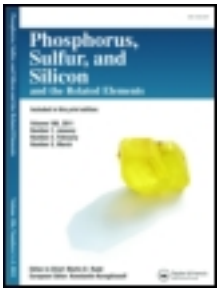

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A CONVENIENT DIRECT SYNTHESIS OF α-N,N-DIALKYLAMINOPHOSPHONATES UNDER APROTIC CONDITIONS

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Communication

A CONVENIENT DIRECT SYNTHESIS OF α-N,N-DIALKYLAMINOPHOSPHONATES UNDER APROTIC CONDITIONS

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A general one-pot synthesis of N,N-dialkylaminophosphonates under aprotic conditions is proposed using aromatic, heteroaromatic or aliphatic aldehydes and N,N-dialkyl-aminosilanes under trimethylsilyltriflate catalysis.

Key words: α-N,N-Dialkylaminophosphonates, dialkylaminosilanes, one-pot aprotic reaction.

INTRODUCTION

Aminophosphonic acids are well-known bioactive and useful chemical compounds as well as their esters (aminophosphonates) and N-mono or dialkyl derivatives.[1] Modification of the alkyl chain is also of interest, especially in case of aromatic or heteroaromatic substituents.[2]

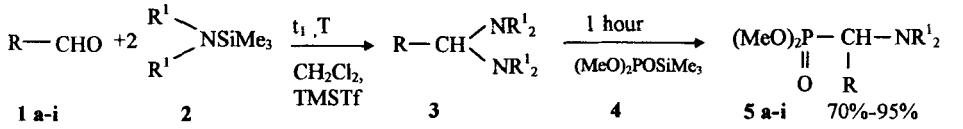
The main route to these compounds is a Mannich-type reaction first used by Fields[3] and recently extended to methods using amino derivatives of carbonyl compounds and silicon reagents.[4] Studies in this laboratory have demonstrated the utility of a new aminoalkylation system for the synthesis of β-dialkylaminoesters[5] and we propose here a direct and efficient synthesis of α-dialkylaminophosphonates under aprotic conditions.

RESULTS AND DISCUSSION

In a previous work, we described the reaction between dialkylaminosilanes **2** and aromatic aldehydes **1** at room temperature under trimethylsilyltriflate catalysis leading to corresponding aminals **3**.[5] Addition of trimethylsilyldimethyl phosphite to the mixture without isolation of **3** results in a smooth reaction that leads to dialkylaminophosphonates **5** (same results may be obtained after isolation, characterisation of **3** and reaction with TMS dimethylphosphite, but "direct" reaction of **1**, **2** and **4** does not give satisfactory results).

Using this procedure, even enolizable aldehydes may be reacted rapidly with good yields, under strict control of the temperature in the fist step of the reaction (enamine formation increases with higher temperature).

Scheme 1



T : reaction temperature t_1 : reaction time (first step of reaction : NMR disappearance of **1**)

TABLE I

Dialkylaminophosphonates **5**

	R	R^1	t_1 (h)	T	Yield % [1]	MW(g/mole)	MS [2]	^{31}P NMR
5a	C_6H_5	CH_3	0.5	RT	95	243	243 134 (100)	23.5 ppm
5b		CH_3	0.5	RT	95	286	244 135(100)	24.2 ppm
5c		CH_3	4	RT	95	233	233 124(100)	23.8 ppm
5d		CH_3	4	RT	92	249	249 140(100)	23.4 ppm
5e	C_6H_5		0.5	RT	95	285	285 176(100)	23.6 ppm
5f	CH_3		3.5	0°C	70	223	223 114(100)	29.4 ppm
5g	$(CH_3)_2CH$	CH_3	0.5	0°C	90	209	209 100(100)	30.1 ppm
5h	$C_6H_5CH_2$		1	-20°C	70	299	299/ 208(100) 190(70)	26.7 ppm
5i	ϕ-CH=CH	CH_3	1	RT	75	269	269 160(100)	23.6 ppm

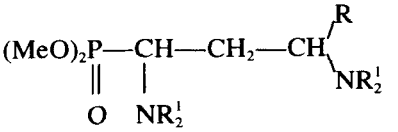
t_1 : reaction time (first step)

(1) After purification

(2) detected M^+ and most important fragment ions (see note 7)

Scheme 1 presents the sequence used in this new, simple and general one pot synthesis of aminophosphonates **5** and several examples are collected in Table I.[6]

Reaction with unsaturated aldehydes is more complicated and is under current investigation[8]: however expected **5i** is easily isolated from cinnamaldehyde but a mixture of **5** and bis dialkylaminophosphonate **6** is obtained from aliphatic α ethylenic aldehydes.[9]



6

EXPERIMENTAL

^1H, ^{13}C, ^{31}P NMR spectra were recorded on a BRUKER AC 200 spectrometer in $CDCl_3$ as solvent. All RMN spectra were measured with $SiMe_4$ or H_3PO_4 as internal standard.

Mass spectra were recorded on a GC/MS HEWLETT-PACKARD HP 5890/MSD 5970 at 70 eV.

General Procedure

All reactions are achieved under inert gas atmosphere. To a mixture of aldehyde (10^{-2} mole/10 cm^3 CH_2Cl_2) is added a solution of **2** (2.10^{-2} mole/10 cm^3 CH_2Cl_2). Stirring is kept during the indicated time (Table I), and a solution of TMS dimethyl phosphite is then added. After one hour, the solvent is evaporated and 20 cm^3 of water is added to the residue. The aqueous layer is extracted with diethylether. The solution is dried, evaporated under vacuum and the residue is purified by distillation or flash-chromatography (gradient $(CH_3)_2CO$—CH_2Cl_2).

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6. Satisfactory microanalysis (C ± 0.28, H ± 0.25, N ± 0.30) as well as spectroscopic data in good agreement with assigned structures obtained for all new products **5**. Data ^1H NMR (in ppm): **5a**: 2.25 (s, 6H), 3.30 (d, 3H, J = 10 Hz), 3.70 (d, 3H, J = 10 Hz), 3.75 (d, 1H, J = 24 Hz), 7.25 (m, 5H); **5b**: 2.40 (s, 6H), 3.50 (d, 3H, J = 10 Hz), 3.90 (d, 3H, J = 10 Hz), 3.95 (d, 1H, J = 24 Hz), 7.50 (m, 2H), 8.70 (m, 2H); **5c**: 2.30 (s, 6H), 3.55 (d, 3H, J = 10 Hz), 3.80 (d, 3H, J = 10 Hz), 3.95 (d, 1H, J = 24 Hz), 6.40 (m, 2H), 7.40 (m, 1H); **5d**: 2.35 (s, 6H), 3.50 (d, 3H, J = 10 Hz), 3.85 (d, 3H, J = 10 Hz), 4.10 (d, 1H, J = 24 Hz), 7.25 (m, 3H); **5e**: 2.70 (m, 4H), 3.40 (d, 3H, J = 10 Hz), 3.80 (d, 3H, J = 10 Hz), 3.65 (m, 5H), 7.30 (m, 5H); **5f**: 1.20 (dd, 3H, J = 7 Hz, 18 Hz), 2.75 (m, 5H), 3.60 (m, 4H), 3.70 (d, 3H, J = 11 Hz), 3.80 (d, 3H, J = 11 Hz); **5g**: 0.95 (d, 3H), 1.00 (d, 3H), 2.40 (d, 6H), 2.60 (dd, 1H, J = 7 Hz, 15 Hz), 3.60 (d, 3H, J = 11 Hz), 3.70 (d, 3H, J = 10 Hz); **5h**: 2.75 (m, 5H), 3.65 (m, 4H), 3.80 (d, 3H, J = 11 Hz), 3.90 (d, 3H, J = 11 Hz), 4.10 (d, 2H), 7.2 (m, 5H); **5i**: 2.50 (s, 6H), 3.75 (d, 3H, J = 11 Hz), 3.85 (d, 3H, J = 11 Hz), 3.80 (m, 1H), 6.35 (ddd, 1H, J = 15 Hz, 10 Hz, 7 Hz), 6.65 (dd, 1H, J = 16 Hz, 3 Hz), 7.40 (m, 5H).
7. All compounds exhibit analogous characteristic MS data with a major fragmentation path of molecular ion (loss of phosphorous group) leading to a iminium moiety (an easy loss of the benzyl group also occurs for **5h**); all other fragments are very weak with however molecular ion being always noticeable.
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