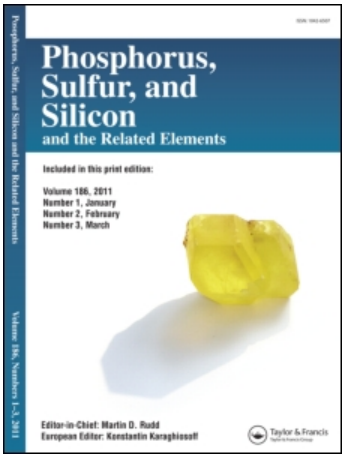

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Failla, Salvatore , Finocchiaro, Paolo and La Rosa, Giorgio(1996) 'FUNCTIONALIZATION OF 1-AMINO-1-ARYLMETHYL PHOSPHONIC ACID DIETHYL ESTERS AT THE NH GROUP', Phosphorus, Sulfur, and Silicon and the Related Elements, 113: 1, 225 — 230
To link to this Article: DOI: 10.1080/10426509608046392
URL: http://dx.doi.org/10.1080/10426509608046392

Phosphorus, Sulfur, and Silicon, 1996, Vol. 113, pp. 225–230
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FUNCTIONALIZATION OF 1-AMINO-1-ARYLMETHYL PHOSPHONIC ACID DIETHYL ESTERS AT THE NH GROUP

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(Received January 3, 1996; in final form January 29, 1996)

Functionalization at the NH group (s) of 1-amino-1-arylmethyl phosphonic acid diethyl esters with mono-isocyanates was performed in order to produce alkyl ureas bearing the phosphonate group. The condensation reaction is easily performed in dry toluene at 80°C using a catalytic amount of Et_3N, and the white crystalline products are obtained in satisfactory yields. Characterizations of these new compounds, of potential applications in agrochemistry, were performed by ^{1}H-NMR spectroscopy and by MS-FAB spectrometry, which reveals the presence of very diagnostic signals or peaks for structural assignments.

Key words: Alkyl ureas bearing phosphonic groups, ^{1}H-NMR and MS-FAB assignments, synthetic procedures.

INTRODUCTION

Recently we reported on the preparation and characterization of 1-amino-1-aryl-methylphosphonate dimethyl an diethyl esters, possessing *inter alia* free carboxylic groups in the aromatic moiety.[1–7] The interest of such compounds lies on the reactive groups which they possess i.e., the NH and —COOH moieties, which can be opportunely functionalized in order to obtain interesting derivatives of the amino-phosphonates, or, in turn, macrocycles and polycondensates bearing the —P(O)(OR)$_2$ group, when bifunctional substrates are used.

Therefore in order to test the possibility of obtaining pre-organized macrocycles and/or macromolecular composites by reacting our phosphonates with monomers bearing two functional groups capable of condensing with the NH or the carboxylic groups, we studied some model reactions aimed to produce alkyl ureas containing phosphonate moieties in the structure, by reacting our amino-phosphonates with mono isocyanates.

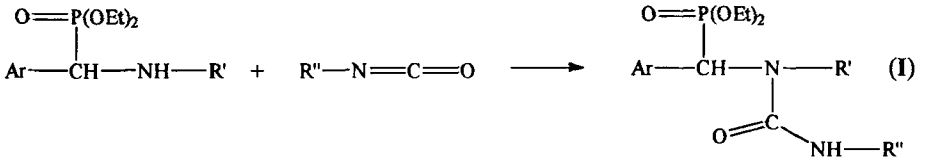
Furthermore, considering that aryl ureas are widely used in agrochemistry, our compounds could have relevant interest in such field of application because the phosphorus moiety could act both as metal carrier or as active principle.

RESULT AND DISCUSSION

Functionalizations at the NH group of our amino-phosphonates, in principle, could be performed by several electrophilic reagents, i.e., acyl halides, chloroformates, isocyanates,[8] etc.

As reported before,[9] the NH group directly attached to a phenyl ring in our phosphonates is of very low reactivity towards acyl chlorides and thus by using drastic reaction conditions and a large excess of the electrophile, amidophosphonic acids are formed by hydrolysis of the esters in situ; on the other hand, chloroformates and acyl chlorides are able to react in solution and in stoichiometric amount, without concomitant hydrolysis of the starting phosphonate ester, only with the NH group directly attached to an alkyl group.[10]

Therefore, having in mind the idea of preparing substituted alkyl ureas and polyureas outlined in the introductory part, we decided to react our amino-phosphonate ethyl esters with isocyanates in order to obtain the desired compounds, according to reaction I.



It is evident that using diamino-phosphonates and di-isocyanates reaction (I) will yield polycondensates possessing the $P(O)(OEt)_2$ pendant moieties.

Through reaction I, by using toluene as solvent, alkyl ureas containing the arylmethyl phosphonate group were obtained in satisfactory yields and they are listed in Table I. In order to improve yields a slight excess of isocyanate was employed. All products reported in Table I are white crystalline solids with high melting points. All compounds were characterized by ^{1}H-NMR and MS-FAB spectroscopy.

The ^{1}H-NMR chemical shifts are reported in Table I and the main features are the following:

i) The $P(O)(OEt)_2$ group still gives rise to two triplets at ca. 1.1 ÷ 1.3 ppm for the methyl signals, as in the precursor compounds;

ii) The CH—P signal appearing as a doublet or a quartet is very much downfield shifted by ca. 2.0 ppm when compared with the parent derivatives and thus this signal and its chemical shift is very diagnostic for assignment of the urethane structure;

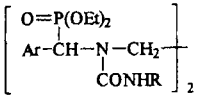
iii) The urea NH proton is resonating at ca. 6.90 ÷ 7.10 ppm as expected for such a functional group;

iv) In compounds **1**, **2** and **4** where *R"* = iso-propyl the methyl hydrogens appear at least as two doublets due to the proximity to the stereocenter. Small additional signals could be attributable, in some cases, to the presence of cis/trans isomers around the amide bond.

The characterization of the samples reported in Table I was also performed by the FAB-MS technique. First of all, we noticed that the FAB-MS spectrum of our compounds are rich in interesting and very diagnostic fragmentation pathways. For all compounds the protonated molecular ion $[M + H]^+$ was observed in high intensity, whereas the $[M + H - (HPO(OEt)_2 + \text{isocyanate})]^+$ and the $[M + H - 2(HPO(OEt)_2 + \text{isocyanate})]^+$ ions are always present also in high intensities. The $[M + H - (HPO(OEt)_2 + \text{isocyanate})]^+$ ion corresponding to the monophosphonate monourea molecule, was generated by the easy loss of diethyl phosphite and isocyanate molecules. The region at relatively low masses is characterized by the pres-

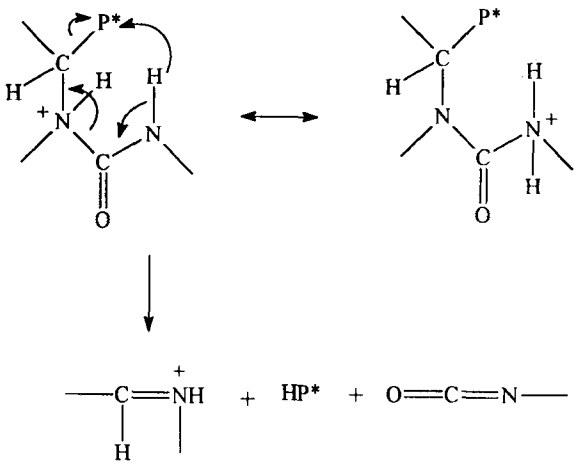
TABLE I

Physical properties of the synthesized alkyl ureas containing the arylmethyl phosphonate group possessing the general formula:



N.	Ar	R	Yield %	m.p. (°C)	^{1}H-NMR δ ($CDCl_3$) R	OCH_2CH_3	NCH_2	OCH_2	CHP	NH	ArH	Others
1 †	Ph-	$-CH(CH_3)_2$	64	189-192	1.14, 1.25 (d)	1.13, 1.24 (t)	3.36 (s)	3.95-4.15 (m)[a]	6.41 (d) J_{HP} = 23.5 Hz	7.08 (d) J_{HN} = 7 Hz	7.31, 7.56 (m)	-
2‡		$-CH(CH_3)_2$	53	204-207 (dec)	1.15, 1.27 (d)	1.15, 1.28 (t)	3.36 (br s)	3.96-4.10 (m)[a]	6.32 (d) J_{HP} = 23.5 Hz	7.07 (d) J_{HN} = 7 Hz	6.65, 7.45 (d)	2.95 (s) (NCH_3)
3		$-(CH_2)_2CH_3$	30	195-197	0.95 (t), 1.62 (m), 3.25 (m)	1.19, 1.24 (t)	3.35 (m)	4.07-4.24(m)	6.41 (d) J_{HP} = 22 Hz	6.92 (br s)	7.25 (d), 7.43 (s), 7.94 (d)	
4		$-CH(CH_3)_2$	44	174-176	1.15, 1.27 (d)	1.15, 1.27 (t)	3.35 (m)	4.01-4.36 (m)[a]	6.43 (d) J_{HP} = 21 Hz	6.75 (br s)	7.26 (d), 7.43 (s), 8,02 (d)	
5ζ		$-C_2H_5$	61	214-216	1.26(t)	1.19, 1.27 (t)	3.35 (m)[b]	4.04-4.27(m)	6.38 (d) J_{HP} = 21 Hz	6.90 (br s)	7.27 (m), 7.43 (m, 7.96 (d)	

[a] including $NHCH(CH_3)_2$ multiplet; [b] including $NHCH_2CH_3$ multiplet; † Calc. for $C_{32}H_{52}N_4O_8P_2$: C 56.30, H 7.68, N 8.21; found C 56.25, H 7.72, N 8.18; ‡ Calc. for $C_{36}H_{62}N_6O_8P_2$: C: 56.24, H 8.13, N 10.93; found C 56.20, H 8.18, N 10.88; ζ Calc. for $C_{30}H_{44}Cl_4N_4O_8P_2$: C: 45.47, H 5.60, N 7.07; found C 45.53, H 5.68, N 7.13.



where P* = $P(O)(OEt)_2$

SCHEME I

ence of the ion $[M + H - 2(HPO(OEt)_2 + \text{isocyanate})]^+$, which constitutes the base peak in relative intensity.

The fragment ions may originate from the protonated molecular ion $[M + H - (HPO(OEt)_2 + \text{isocyanate})]^+$ and form the fragment ion $[M + H - 2(HPO(OEt)_2 + \text{isocyanate})]^+$, respectively, by a hydrogen abstraction through a McLafferty like rearrangement (see Scheme I).

Reactions, in methanol as solvent, of 1-amino-1-arylmethyl phosphonic acid dimethyl esters bearing a free carboxyl group on the aryl moiety with an equimolar amount of a primary aliphatic amine produced the precipitation, in quantitative yield, of the corresponding ammonium salts (**6**, **7**), as judged by inspecting their ^{1}H-NMR and FAB-MS spectra and considering that the compounds obtained are extremely soluble in water but not in apolar organic solvents (see Experimental Section).

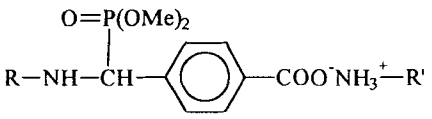
No evidences of the formation of the amido-amino-phosphonates were observed even when a large excess of neat primary amine was used. More interesting, in these conditions, no formation of the corresponding amino-phosphonic acid mono-methyl esters was detected contrary to what is generally observed when phosphonic acid dimethyl esters are allowed to react with an excess of *t*-butyl or primary amines.[11,12] This finding reveals that amino phosphonate dimethyl esters bearing a free carboxylic acid group are not hydrolysed in such conditions due to the formation of the corresponding amonium salts which, in turn, cannot further react with excess amine.

EXPERIMENTAL

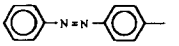
Amines, aldehydes, isocyanates, diethylphosphite as well as solvents and other chemicals used were high purity commercial products from Aldrich. All syntheses were performed under a dry N_2 atmosphere.

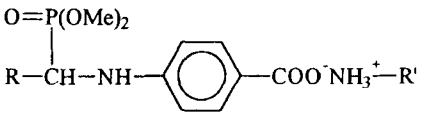
^{1}H-NMR spectra were recorded in $CDCl_3$, with TMS as an internal standard using a Bruker AC-200 instrument operating at 200 MHz.

Mass spectra were obtained using a double focusing Kratos MS 50S instrument equipped with a standard FAB source and DS 90 data system. 3-Nitro-benzylalcohol was used as matrix.

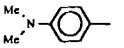
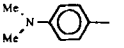


6

6	R	R'
a		
b	*t*-butyl	*i*-propyl
c		*i*-propyl



7

7	R	R'
a		
b		*i*-propyl
c		

Melting point were determined on a Büchi 530 melting point apparatus and are uncorrected.

The amino phosphonate diester precursors were all prepared in high yield by adding the diethylphosphite to the imine according to the following general procedure:

To a stirred solution of the imine precursor (0.1 mol) in EtOH (50 ml) were added dropwise 28 ml (0.3 mol) of $HP(O)(OEt)_2$ and a catalytic amount of NaH. After the addition was completed, the solution was heated and stirred for a few hours. The solvent was then evaporated and to the oily residue were added a few drops of ethylacetate. White crystal were formed on standing and were collected by filtration.

The compounds listed in Table I were synthesized by direct addition of isocyanate to the amino phosphonate precursors according to the following general procedure:

To a solution of the amino phosphonate precursor (0.01 mol) and a cataytic amount of Et_3N in dry toluene (50 ml) were added 0.025 mol of isocyanate and the solution heated to 80°C under a dry N_2 atmosphere for three hours. After cooling to room temperature the solid formed was filtered off. All the ureas synthesized are white solids and they were recrystallized from toluene.

Compound **7c**: to a stirred mixture of 3.42 g (0.01 mol) of 1-amiono-1-(*p*-benzoic acid)-cyclohexyl phosphonic dimethyl ester in 20 ml of methanol were added 1.3 g of cyclohexyl amine. During the cyclohexyl amine addition the hot mixture became homogeneous and after few minutes the precipitation of a white solid was observed. The reaction mixture was subsequently stirred at refluxing temperature for 15 min, concentrated, filtered, and the solid was washed with cold dioxane and ether to give 4.2 g of salt **7c** (yield 95%); m.p. 166–168°C; ^{1}H-NMR ($CDCl_3$, TMS): 1.04–1.98 (m, 22H, cyclohexyl moieties), 3.64 and 3.74 (two, d, 6H, OMe), 4.76 (ABX, 1H, CHP), 4.21 (ABX, 1H, NHC), 6.59 (d, 2H, ArH) and 7.84 (d, 2H, ArH); FAB-MS: 441 (M^+ 1), 341, 232 (base peak).

ACKNOWLEDGEMENTS

We thank C.N.R. and the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) for financial support.

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