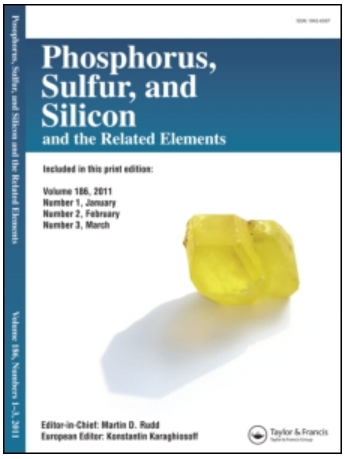

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

The Synthesis of Dialkoxyphosphorylcarboxamides

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To cite this Article Ye, Yong , Li, Ping , Hu, Xiao-lian , Ju, Zhi-yu and Zhao, Yu-fen(2008) 'The Synthesis of Dialkoxyphosphorylcarboxamides', Phosphorus, Sulfur, and Silicon and the Related Elements, 183: 2, 701 — 705
To link to this Article: DOI: 10.1080/10426500701807517
URL: http://dx.doi.org/10.1080/10426500701807517

Phosphorus, Sulfur, and Silicon, 183:701–705, 2008

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500701807517

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The Synthesis of Dialkoxyphosphorylcarboxamides

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The synthesis of dialkoxyphosphorylcarboxamides, which is difficult to monitor by TLC, was investigated by ESI-MS and ESI-MS^n. Their fragmentation pathways were rationalized and supported by tandem mass spectrometry. The characteristic ions in ESI-MS are useful for the structural determination of phosphorylcarboxamides.

Keywords Dialkoxyphosphorylcarboxamides; ESI-MS; fragment pathways; synthesis

INTRODUCTION

Aminoalkylphosphonic acid has received considerable attention because of their biological activity.[1–3] Several well-know reducing agents reported could be applied to selective reduction of the amide group of dialkoxyphosphorylcarboxamide, leading to aminoalkylphosphonic acids.[4,5] The dialkoxyphosphorylcarboxamides can be easily prepared from dialkyl phosphites through treatment with acrylamide according to known procedures.[6] However, the ESI-MS fragmentation characteristics of this type of compound has not been studied. Therefore, we synthesized a series of dialkoxyphosphorylcarboxamides and investigated their fragmentation processes. We found that ESI-MS/MSn is a powerful tool for tracing the addition reaction.

The authors would like to thank the financial support from the National Natural Science Foundation of China (No. 20602032 and 20572061).

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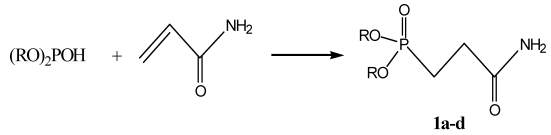
APPARATUS AND REAGENTS

Acrylamide was from Beibo (Zhengzhou, China). Dialkyl phosphites were synthesized as described previously.[7–9] Mass spectra were acquired in positive ion mode using a Bruker ESQUIRE-LCTM ion trap spectrometer equipped with a gas nebulizer probe that was capable of analyzing ions up to m/z 20000. Nitrogen was used as drying gas at a flow rate of 4 L/min. The nebulizer pressure was 7 psi. The capillary was typically held at 4 kV and the source temperature was maintained at 300°C. The instrument was operated at unit-mass resolution and calibration of m/z was performed using a standard ES-tuning-mix. The samples that were dissolved in methanol were ionized by ESI and continuously infused into the ESI chamber at a flow rate of 4 ul/min by a Cole-Parmer 74900 syringe pump (Cole Parmer Instrument Company).

RESULTS AND DISCUSSION

The Synthesis of Dialkoxyphosphorylcarboxamides

As shown in Scheme 1, compounds **1** are the key intermediate for the synthesis of the aminoalkylphosphonic acids and can be synthesized from dialkyl phosphite with acrylamide. It is impossible to monitor the reaction by TLC because there is no ultraviolet absorption for the products. Fortunately, we found that this reaction can be monitored by ESI-MS. After the reaction was complete (detected by ESI-MS) it was allowed to cool to room temperature and then was filtered. The propionamide was isolated by seeding the cooled solution and filtering off the precipitated crystals.



a-d: R= methyl, ethyl, propyl, butyl.

SCHEME 1 The synthetic route of dialkoxyphosphorylcarboxamides.

A solution of freshly prepared sodiun alkyloxide in MeOH was added slowly to a solution of acrylamide and dialkyl phosphite. When the reaction mixture was stirred at room temperature for 5 min, the reaction was checked by ESI-MS. The result showed that dialkyl phosphite but not the desired product was observed (Figure 1a), but not the desired product. The peak at m/z 111 and m/z 133 in the ESI-MS were identified as the dialkyl phosphite and its $[M^+Na]^+$. Consequently,

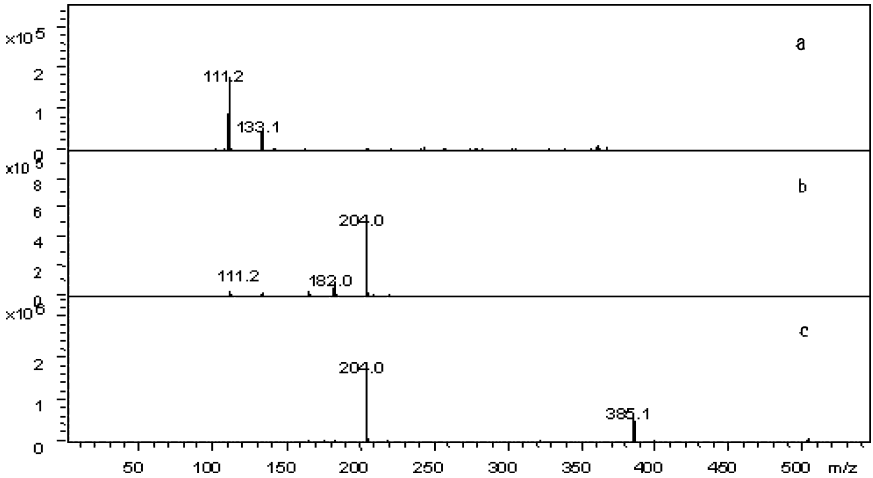


FIGURE 1 ESI-MS spectra of the components in the synthesis of compound 1a. (a) Spectrum of the reaction in 5 min; (b) MS analysis of the reaction in 40 min; and (c) reaction in 60 min.

we added a solution of sodiun alkyloxide in MeOH to the reaction mixture, which was warmed to 70°C and continuously stirred for 40 min. Then, the reaction was checked by ESI-MS. The resulting mixture showed quite a difficult pattern of spots on the TLC plate. In contrast, the reactants peak at m/z 111 was observed with quite low intensity from ESI-MS analysis, while a new peak at m/z 204 appeared in the spectrum, suggesting that the formation of the product had occurred, but in low yield (Figure 1b). Therefore, reaction time was prolonged 20 min, and the reactant was completely consumed (Figure 1c).

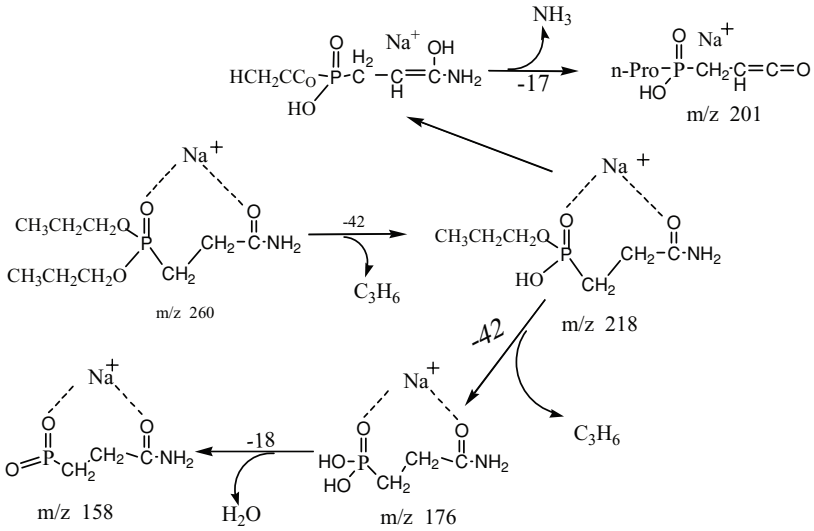
ESI MS/MS^n of Dialkoxyphosphoryl-carboxamides

ESI mass spectra for 1a–d showed both $[M^+H]^+$, $[M^+Na]^+$, and $[2M^+Na]^+$ ions, which were studied via multistage tandem mass spectrometry. It was found that all gave the $[2M+Na]^+$ ion as the base peak. Positive ion ESI-MS/MS of $[M^+Na]$ of 1a–d are shown in Table I.

The mass spectral fragment pathways of compound 1c are discussed as a typical example (shown in Scheme 2). The other compounds displayed similar fragment pattterns to 1c in ESI-MS. $[M^+Na]^+$ of 1c first gave the fragment ion at m/z 218 through the C_3H_6 extrusion pathway. Second, the fragmentation of m/z 218 gave peaks at m/z 176 by losing

TABLE I MS and MS^n Spectra of Compound 1 Cationized (Na^+) Ion

Comp.	Precursor	Fragment ions (relative, intensities)
1a	204(69)	187(30) 168(100)
1b	232(100)	204(34) 187(3) 158(56)
	204(12)	187(12) 176(3) 158(100)
1c	260(100)	218(46) 201(9) 176(4) 158(71)
	218(29)	201(9) 176(4) 158(100)
1d	288(32)	232(70) 215(5) 176(9) 158(100)
	232(53)	215(5) 176(6) 158(100)



SCHEME 2 Fragment pathway proposed for the compound **1c** cationized (Na^+) ion.

another C_3H_6 group. The m/z 176 fragment ion could generate the m/z 158 fragment ion by the losing water pathway.

CONCLUSIONS

The synthesis of dialkoxyphosphorylcarboxamides were investigated by ESI-MS and ESI-MS^n. Consequently, the reaction could be monitored successfully. The fragmentation pathways of those compounds were rationalized and supported by tandem mass spectrometry. These characteristic ions in ESI-MS are useful for the structural determination of phosphorylcarboxamides containing.

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