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Straightforward synthesis of *gem*-phosphonate-phosphate containing compounds *via* one-pot reaction of thioesters with diethyl phosphite†

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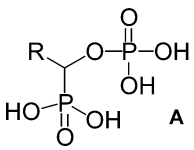
A convenient straightforward, three step, one-pot reaction of diethyl phosphite with thioesters in the presence of catalytic amounts of potassium *tert*-butoxide in toluene or DMF as solvent provided various phosphonate-phosphate containing compounds in excellent yields.

Phosphonic acids bearing heteroatoms in the α and β positions have attracted considerable interest because of their well recognized interesting biological properties.[1] Most importantly, they act as inhibitors of proteolytic enzymes, such as renin[2] and human immunodeficiency virus (HIV) protease,[3] as agents affecting the growth of plants,[4] or as haptens for the development of catalytic antibodies.[5] Further, 2-amino-4-phosphonobutanoic acid (AP4) has the ability to act as substrate mimic and to interfere with significant enzymatic and receptor mediated processes.[6] Recently, Nguyen *et al.*[7] studied the biological activity of *gem*-phosphonate-phosphate containing compounds of type **A** with specific high density lipoprotein inducing activity. Thus, it has been demonstrated that the methyl ester of *gem*-phosphonate-phosphate compound **17** (Table 1) possesses high activity compared to other substrates studied. Wiemann *et al.* incorporated 'phosphonate-phosphate' analogues (**A**) of phosphonoserine into synthetic peptides.[8]

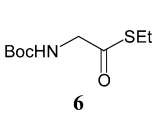
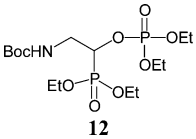
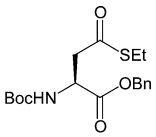
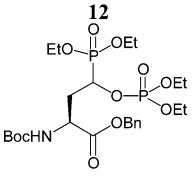
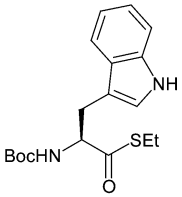
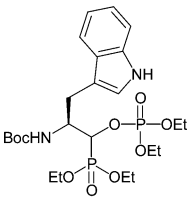
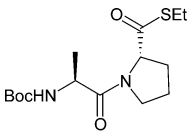
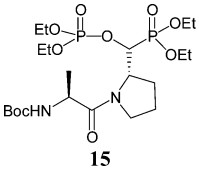
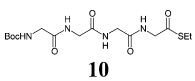
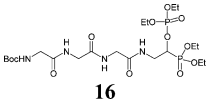
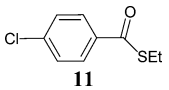
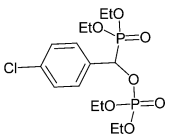


A R = aryl or aliphatic

Previously, this type of compounds were synthesised by two different well known strategies. The first method involves a reaction of acyl chloride derivatives with $P(OR)_3$ (Arbuzov reaction) followed by reaction with HPO_3R_2 (R = Me, Et, *etc.*) in the presence of 1 equivalent of base.[7] The second method is based on direct coupling of HPO_3R_2 with acyl chlorides in the presence of 1.2 equivalents of base (NaH).[8] Considering the low yields (10–23%) of the latter method, development of an efficient one-pot synthesis of this type of compounds from readily available acid derivatives is of general interest.

As a part of our ongoing work on enantiomerically pure α-hydroxyphosphonates[9] as key precursors for the asymmetric synthesis of potent sialyltransferase inhibitors,[10] we now wish to report a straightforward synthesis of phosphonate-phosphate containing compounds. We attempted to synthesize such compounds by mixing thioesters and diethyl phosphite in the presence of catalytic amounts of potassium *tert*-butoxide. With this procedure the desired products were obtained in excellent yields in 15 min. At first, we reacted *N*-Boc protected L-alanine thioester **1** with diethyl phosphite in dry toluene in the presence of 0.25 equivalents of *t*BuOK (Scheme 1), thus furnishing the compound **4** in 90% yield as a separable mixture of diastereomers (flash column chromatography 9 : 1 ratio). Obviously, the expected phosphonate-phosphate **4** is obtained in one-pot in three steps from thioester **1** *via* acyl phosphonate **2**, and hydroxy bis-phosphonate **3**. Compound **4** was deprotected in refluxing methanolic HCl to give **5** in quantitative yield.

Table 1 Synthesis of phosphonate-phosphate containing compounds[a]

Entry	Thioester	Product	Yield (%)
1	 **6**	 **12**	71
2	 **7**	 **13**	71
3	 **8**	 **14**	90
4	 **9**	 **15**	72
5	 **10**	 **16**	98
6	 **11**	 **17**	80

[a] For experimental details see ref. 14.

The presence of phosphonate-phosphate **4** was confirmed by the ^1H and ^{31}P NMR spectral data. In the ^1H NMR of the major diastereomer, N–C*H*–CH_3 appeared as a multiplet at δ 4.71 whereas in the minor diastereomer it appeared at δ 4.6. In the ^{31}P NMR of the major diastereomer, $-OPO_3Et_2$ appeared as a doublet at δ 1.36 and $-PO_3Et_2$ appeared as a doublet at δ 19.2 whereas in the minor diastereomer $-OPO_3Et_2$ appeared as a doublet at $\delta -0.34$ and $-PO_3Et_2$ appeared as a doublet at δ 18.4.

† Electronic supplementary information (ESI) available: physical data of new compounds. See http://www.rsc.org/suppdata/cc/b4/b401079e/

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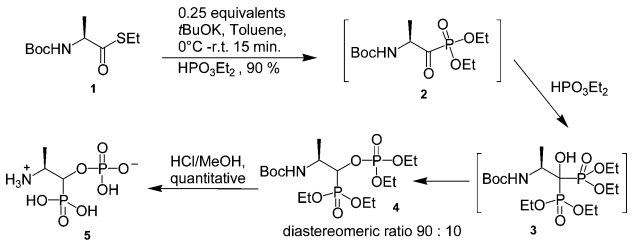

Scheme 1

Reaction of diethyl phosphite with thioester aminoacids **6–8** and peptides **9** and **10** worked very well under the same reaction conditions, providing **12**, **13**, **14** and **15**, **16** in 71, 71, 90 and 72, 98% yield, respectively. In the case of aminoacid thioesters **6–8** and dipeptide thioester **9** the reaction was performed in dry toluene and in the case of tetrapeptide **10** dry DMF was used as solvent. Compounds **13–15** were obtained as a mixture of inseparable diastereomers in the ratio of 66/34, 89/11, and 80/20, respectively.[11] Finally, reaction of *p*-chlorophenyl thioester **11** with HPO_3Et_2 also worked well under the same reaction conditions to give the corresponding product **17** in 80% yield. The required thioesters were prepared as we reported previously[12] by coupling of the corresponding carboxylic acids with EtSH in the presence of DCC/HOBt in DMF.

The procedure reported here has several advantages compared to the procedure previously reported using acid chloride derivatives as a starting material: i) The thioesters can be readily prepared and they are quite stable but at the same time very reactive towards phosphorus nucleophiles. As reported, peptide thioesters, which are starting materials for native chemical ligation, can also be easily prepared using solid phase peptide synthesis (SPPS).[13] On the other hand, the corresponding acid chloride derivatives can not be prepared for longer peptides and they are also not very stable. ii) Yields of the coupling products are high to excellent (71–98%).

In conclusion, we present herein a convenient straightforward, three step, one-pot synthesis of various phosphonate-phosphate containing compounds in excellent yields. To our knowledge, direct synthesis of phosphonate-phosphate containing compounds from thioesters was carried out for the first time.

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Notes and references

1 (*a*) V. P. Kukhar and H. R. Hudson, *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*, J. Wiley & Sons, New York, 2000; (*b*) C. Dejugnat, G. Etemad-Moghadam and I. Rico-Lattes, *Chem. Commun.*, 2003, 1858–1859.
2 (*a*) F. Dellaria, Jr., R. G. Maki, H. H. Stein, J. Cohen, D. Whittern, K. Marsh, D. J. Hoffman, J. J. Plattner and T. J. Perun, *J. Med. Chem.*, 1990, 534–542; (*b*) P. Kafarski and B. Lejczak, *Phosphorus Sulfur Silicon*, 1991, **63**, 193–215.
3 B. Stowasser, K. H. Budt, L. Jian-Qi, A. Peyman and D. Ruppert, *Tetrahedron Lett.*, 1992, **33**, 6625–6628.
4 P. Kafarski, P. Wieczorek, B. Lejczak, R. Gancarz and J. Zygmunt, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2989–2992.
5 B. A. Smith, M. Carol, S. J. Taylor, J. S. Benkovic and R. Hirschmann, *Tetrahedron Lett.*, 1994, **35**, 6853–6856.
6 M. C. Fernandez, J. M. Quintela, M. Ruiz and V. Ojea, *Tetrahedron: Asymmetry*, 2002, **13**, 233–237.
7 L. M. Nguyen, E. Niesor and C. L. Bentzen, *J. Med. Chem.*, 1987, **30**, 1426–1433.
8 A. Wiemann, R. Frank and W. Tegge, *Tetrahedron*, 2000, **56**, 1331–1337.
9 D. Skropeta and R. R. Schmidt, *Tetrahedron: Asymmetry*, 2003, **14**, 265–273.
10 B. Mueller, C. Schaub and R. R. Schmidt, *Angew. Chem.*, 1998, **110**, 3021–3024; B. Mueller, C. Schaub and R. R. Schmidt, *Angew. Chem., Int. Ed.*, 1998, **37**, 2893–2897.
11 Diastereomeric ratio was calculated on the basis of its ^{1}H NMR.
12 K. Pachamuthu and R. R. Schmidt, *Synlett*, 2003, 659–662.
13 P. E. Dawson and S. B. H. Kent, *Annu. Rev. Biochem.*, 2000, **69**, 923–960.
14 General experimental procedure: To a stirred solution of thioester (1 mmol) and diethyl phosphite (2.1 mmol), in dry toluene or dry DMF (5 mL), *t*BuOK (0.25 mmol) was added at 0 °C and the reaction mixture was allowed to stir at room temperature for 15 min. Evaporation of the solvent and purification of the crude material by flash column chromatography yielded the corresponding phosphonate-phosphate compounds **4**, **12–17**. Products **4**, **12**, **13**, **14** and **17** were purified by flash column chromatography using ethyl acetate and petroleum ether as eluent in the ratio of 7 : 3, 6 : 4, 7 : 3, 6 : 4, and 9 : 1, respectively, and products **15** and **16** using ethyl acetate and methanol as eluent in the ratio of 9 : 1 and 8 : 2, respectively.