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A General Method for the Synthesis of *N*-Protected α-Aminoalkylphosphinic Acids

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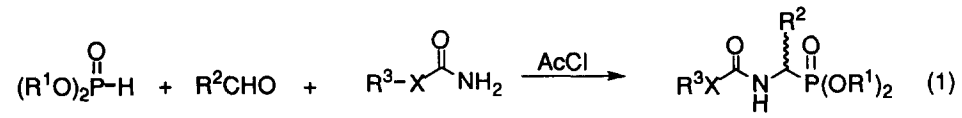
Abstract: A general and highly convenient method for the synthesis of *N*-protected α-aminophosphinic acids, suitable for side chain elongation either from *N*-, *P*-, or *C*- termini to form a variety of phosphinic peptides, has been developed. The desired phosphinic acids were obtained in moderate to satisfactory yield by a three-component condensation reaction of benzyl carbamate, an aldehyde, and an alkylphosphonous acid (or its 1-adamantanamine salt) in acetyl chloride under very mild conditions. Copyright © 1996 Elsevier Science Ltd

α-Aminophosphinic acids and the peptides derived therefrom (phosphinic peptides) have attracted increasing interest due to their usefulness both in the development of catalytic antibodies[1,2] and ligase or protease enzyme inhibitor research.[3-5] Various α-aminophosphinic acids and phosphinic peptides are potent inhibitors of a variety of enzymes such as aspartic peptidase,[6] D-alanine:D-alanine ligase,[7,8] collagenase,[5,9] glutamine synthetase,[10] glutathione synthetase,[11] glutathionylspermidine synthetase,[12] HIV protease,[13,14] leucine aminopeptidase,[15] matrix metalloproteinases,[16,17] renin,[18] and VanX.[19] Very recently, Dive et al.[20] found a most potent and specific phosphinic peptide inhibitor of endopeptidase 24-15 (thimetoligopeptidase) through combinatorial chemistry approach. However, despite their wide use as enzyme inhibitors, there are no general methods for the synthesis of α-aminophosphinic acids as far as we are aware. Several α-aminophosphinic acids have been synthesized from the corresponding α-aminophosphonous acids,[21,22] obtainable in poor to moderate yields by the method developed by Baylis[23] or its modifications,[24,25] via a cumbersome protection and deprotection process. The α-aminophosphinic analogue of aspartic acid was synthesized by Campbell and Carruthers[26] through the Arbuzov reaction of 4-acetyloxy azetidin-2-ones with O,O-dialkyl methylphosphonite. The corresponding analogue of statine was prepared by Bartlett and Kezer[6] by displacement of the phenylthio moiety of an *N*-protected α-aminophosphonic acid thiophenyl ester by *tert*-butyl lithioacetate. These methods are not suitable for the construction of a large number of diverse α-aminophosphinic acids for the purpose of combinatory chemistry research. The latter has proved to be a very useful tool in drug research discovery.[27-29]

As part of ongoing research concerning the syntheses of poly-functionalized phosphonates, phosphonamidates, and phosphinates as multisubstrate or transition-state analogue inhibitors[30] of glutathione spermidine (GSP) synthetase/amidase,[31,32] α-aminomethanephosphinic acids are required as building blocks for the construction of the final phosphinic peptides. Previous research has demonstrated the efficiency of several three-component reactions involving dialkyl or diaryl phosphites, alkyl or aryl aldehydes, and carbamates or carboxamides in the synthesis of a variety of α-aminophosphonic acids (eq. 1).[33-35]



We wish to report here a general and very convenient method for the direct synthesis of *N*-protected α-aminophosphinic acids through a similar three-component condensation reaction of an alkylphosphonous acid,[36-38] an aldehyde, and benzyl carbamate in acetyl chloride (eq. 2).

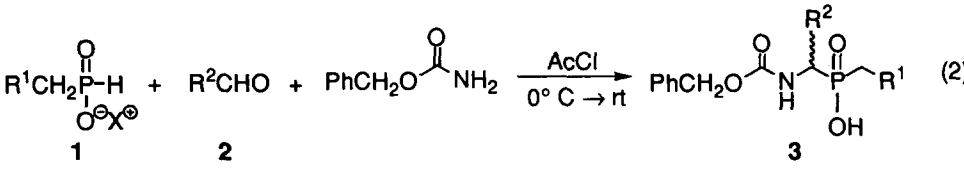
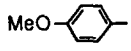
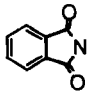
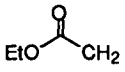
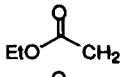
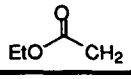
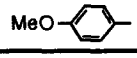


Table 1. Compound **3** Prepared[a]

Entry	**1**, R^1	**1**, $X^{\oplus}$	**2**, R^2	$\delta^{31}P$ (ppm)	MP (°C)	Yield **3** (%)
a	H		H	50.6	123-125[b]	67
b	H		*i*-Bu	54.2	162-164[b]	69
c	H			47.2	193-194[b]	61
d	H			42.6	188-190[b]	72
e	n-Pr	H	H	53.0	110-112[b]	50
f		H		36.6	194-195[b] (dec.)	73
g		H	Me	53.1	94-97[c]	75
h		H	Et	54.0	Oil[c]	48
i		H		51.5	186-188[b]	71

[a] All compounds were characterized by NMR, MS, HRMS and/or elemental analysis;

[b] Recrystallized from $CHCl_3$/hexane; [c] Purified by ion-exchange chromatography on DEAE cellulose followed by passing through a column of DOWEX^R 50W-X resin (H^+ form).

A typical procedure (Table 1, entry 'g') is as follows: To a stirred solution of 2-ethoxy-carbonylethylphosphonous acid (56 mg, 0.33 mmol) and benzyl carbamate (51mg, 0.34 mmol) in acetyl chloride (2 mL) was added acetaldehyde (15 mg, 0.34 mmol) at 0 °C. Stirring was continued at 0 °C for 30 min and then at rt for 6 h. Volatile components were removed under reduced pressure and the residue was partitioned between 5% $NaHCO_3$ solution (20 mL) and ether (10 mL). The aq solution was separated and acidified to pH 2 with conc. HCl and then extracted with EtOAc (4 x 20 mL). EtOAc extracts were combined and dried over Na_2SO_4. The crude product, 90 mg syrup, obtained after removal of the solvent was quite pure as indicated by NMR analysis. Further purification was carried out by ion-exchange chromatography on DEAE cellulose (eluting with 1 : 1 MeOH / 0.1M NH_4HCO_3 buffer) followed by cation exchange on DOWEX^R AG-8 resin (H^+ form); ^1H NMR (CD_3OD) δ 1.26 (t, 3H, J = 7 Hz), 1.35 (dd, 3H, J = 7, 14 Hz), 1.95-2.08 (m, 2H), 2.57-2.65 (m, 2H), 3.96-4.07 (m, 1H), 4.05-4.15 (q, 2H), 5.11 (s, 2H), 7.37 (s, 5H); ^{13}C NMR δ 172.6, 172.4, 156.2, 156.1, 136.3, 128.7, 128.4, 128.3, 67.4, 61.2, 45.15 (d, J =106.2 Hz), 26.54, 21.66 (d, 93.1 Hz), 14.30, 14.12; ^{31}P NMR (see Table 1, entry 'g') (CD_3OD): 53.1; MS (DCI/NH_3) m/z 344 (MH^+, 100), 326 (34), 257 (25), 236 (60), 210 (28), 195 (18), 167 (16), 134 (25), 108 (40), 91 (75); HRMS (DCI/NH3) calc for $C_{15}H_{22}NO_6PH$ (MH^+) 344.1263. Found: 344.1256.

Acting both as solvent and reagent, acetyl chloride is known to accelerate the condensation of an amide and an aldehyde with dialkylphosphite or phosphorus trichloride.[34] But the role of acetyl chloride in these reactions (eq. 1, 2) remains unclear. Considering the fact that acetic anhydride plus HCl or TsOH can also be used in place of acetyl chloride in some cases,[35] we suggest that acetyl chloride might act as a dehydration and acetylation reagent, leading to an O-acetyl intermediate during the condensation process.[39]

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