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A practical access to α-phosphonoenamides

Béatrice Quiclet-Sire [a,b], Samir Z. Zard [a,b,*], Haiwen Zhang [a]

[a] *Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette, France*
[b] *Laboratoire de Synthèse Organique associé au CNRS, Ecole Polytechnique, 91128 Palaiseau, France*

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This paper is dedicated with respect to Professor François Mathey, on the occasion of his 60th birthday

Abstract

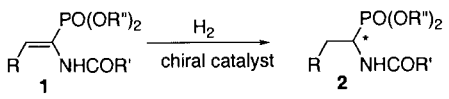
Reaction of α-oximinophosphonates first with acetic anhydride then with iron powder and acetic acid at 50–60 °C results in the clean formation of an *E*–*Z* mixture of α-phosphonoenacetamides, which are immediate precursors to α-aminophosphonic acids. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Enamides; Phosphonates; Iron metal; Reduction

1. Introduction

The synthesis of phosphonic acid analogues of amino acids remains an important endeavour since many of these derivatives exhibit interesting biological activity profiles. A few aminophosphonic acid derivatives have proved to be potent inhibitors of various enzymes [1], whereas *Alafosfalin* (*N*-alanyl-α-aminoethylphosphonic acid) has been reported to possess good antibacterial activity [2]. As a consequence, many synthetic routes to aminophosphonic acids have been developed over the past decades [3] but one especially attractive approach consists in the reduction of the corresponding enamides **1** (Scheme 1). Such a strategy allows access to optically active compounds through the use of asymmetric catalytic hydrogenation [4] and would directly benefit from the intense current research in chiral ligand design for enantioselective catalytic hydrogenation [5].

So far, the main limitation has been the preparation of the enamide precursors **1** since the commonly used



Scheme 1.

synthetic sequences, outlined in Scheme 2, are generally tedious and difficult to scale up. The first synthesis requires the chlorination of an unsaturated aminocarboxylic acid followed by heating with a trialkyl phosphite causing in situ decarboxylation [4]6a[6b]. This route seems to be limited to aromatic derivatives. The second, more flexible approach is an adaptation of the Wittig–Horner reaction; it requires the prior preparation of a suitable geminal bis-phosphonate [6c]. The special class of phosphonoeneformamides may be prepared by reaction of α-isocyanophosphonates with aldehydes or ketones, an elegant methodology developed by Schöllkopf et al. [6d]. Finally, the direct condensation of a primary amide with an acyl phosphonate has been reported. This last reaction is conceptually by far the simplest; unfortunately, the yields of the given examples are unacceptably low [6c]. In this letter, we describe a new, practical, and fairly direct route to enamides, also starting from acyl phosphonates. These precursors are readily made by an Arbusov reaction of an acid chloride with a trialkyl phosphite [7].

Our approach is displayed in Scheme 3. Thus, reduction by electron transfer from metallic iron of the oxime acetate **5** derived from acyl phosphonate **3** would result in the rupture of the weak N–O bond and the formation of an iminyl radical **6**. A second electron transfer would then lead to the iminyl anion **7** which would then be captured by acetic anhydride to give the desired enamide **8** and/or imide **9**. We had shown earlier that

* Corresponding author. Fax: +33-1-69333010.
E-mail address: sam.zard@icsn.cnrs-gif.fr (S.Z. Zard).

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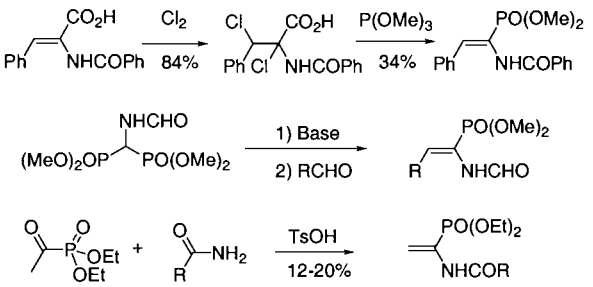
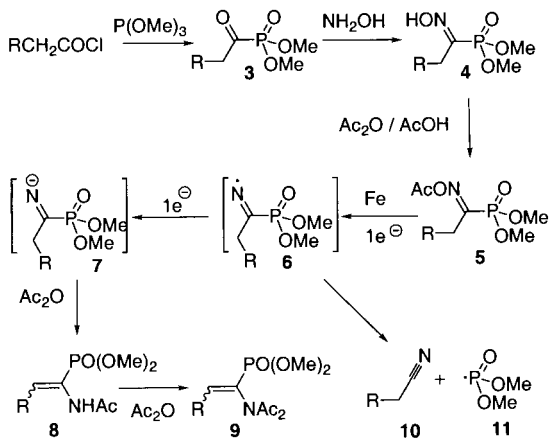


Scheme 2.



Scheme 3.

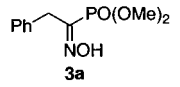
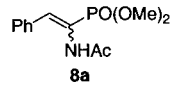
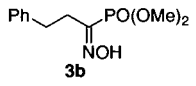
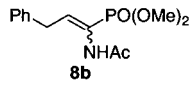
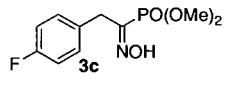
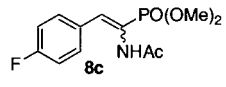
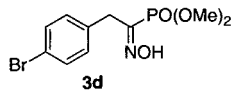
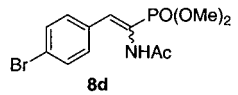
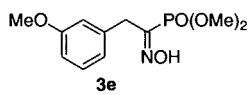
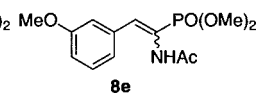
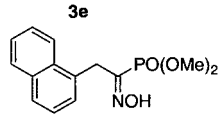
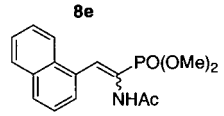
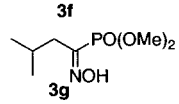
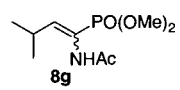
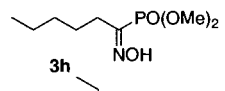
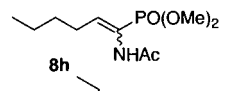
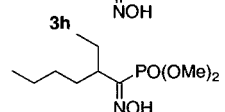
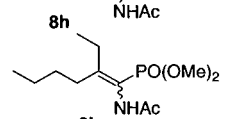
the combination of iron powder with acetic anhydride–acetic acid converted ketoximes or secondary nitro derivatives efficiently into the corresponding enamides [8]. In the present case, a potential complication could arise from a β-scission at the iminyl radical stage to give a nitrile and a phosphonyl radical **11**.

Indeed, in an encouraging first experiment, oxime **4a** derived from phenylacetic acid (R = Ph in Scheme 3) was heated with excess iron powder in a refluxing mixture of acetic anhydride and acetic acid. Work up of the reaction mixture and purification gave the corresponding imide **9a** in 54% yield. However, when these conditions were applied to the higher homologue **4b** (R = –CH_2Ph), little enamide **8b** (3%) or imide **9b** (14%) was observed. The main product turned out to be 3-phenylpropionitrile **10b**, isolated in 55% yield.

The fragmentation of iminyl radical **6** is a unimolecular process with a large positive entropy term; its rate is consequently very sensitive to a variation in the reaction temperature in comparison with the rate of the desired bimolecular electron transfer step, which should exhibit only a modest dependence on temperature. When the reaction with **4b** was conducted at 80 °C, the yield of enamide **8b** increased to 32% whereas that of imide **9b** and especially 3-phenylpropionitrile **10b** decreased to 3 and 7%, respectively. Lowering the reaction temperature to 50–60 °C increased dramatically the yield of the desired enamide **8a** (89%) and almost no imide or nitrile were formed. As can be seen by inspection of the results compiled in Table 1, this process is applicable to the synthesis of a variety of α-oximinophosphonates. A 1:1 mixture of *Z* and *E* isomers which could not be separated by simple chromatography and which presumably are in equilibrium under the mildly acidic conditions. Enamides are known to readily equilibrate [8].

We have thus developed a practical, flexible access to α-phosphonoenamides, using cheap and readily available starting materials and reagents. The mild experimental conditions should be compatible of many of the functional and protecting groups usually employed in organic synthesis. Last but not least, the process should be easily scaled up since the experimental procedure is straightforward and no toxic or hazardous components are involved.

Table 1
Formation of α-phosphonoenamides **8a–i** from a α-oximinophosphonates **3a–3i**

α-oximinophosphonate **3**	α-phosphonoenamide **8**	Yield (%)
 **3a**	 **8a**	77%
 **3b**	 **8b**	89%
 **3c**	 **8c**	71%
 **3d**	 **8d**	75%
 **3e**	 **8e**	72%
 **3f**	 **8f**	81%
 **3g**	 **8g**	75%
 **3h**	 **8h**	89%
 **3i**	 **8i**	76%

2. Experimental

2.1. General procedure for the preparation of α-oximinophosphonates

A drop of DMF is added to a solution of the carboxylic acid (0.02 mol) in dichloromethane (40 ml). Oxalyl chloride (0.06 mol) is then added dropwise at room temperature (r.t.). Half an hour after the evolution of gas has subsided, the reaction mixture is concentrated under partial vacuum, cooled in an ice bath and trimethylphosphite (0.02 mol) is added dropwise keeping the internal temperature below 40 °C.

After stirring overnight, the reaction mixture is concentrated under partial vacuum, diluted with methanol (10 ml) and cooled in an ice bath. Hydroxylamine hydrochloride (0.028 mol) is added, followed after a few minutes by pyridine (0.03 mol). After keeping overnight at r.t., the reaction mixture is concentrated under partial vacuum and the residue extracted with dichloromethane, washed successively with water, dilute HCl (2 M), and brine. The organic phase is dried over sodium sulfate, concentrated under partial vacuum, and the residue purified by column chromatography using silica gel. The oxime thus obtained is used without further purification for the next step. Some of these oximinophosphonates have been reported in the literature [7].

2.1.1. Dimethyl [2-(4-bromo-phenyl)-1-hydroxyimino-ethyl]-phosphonate (**3d**)

This compound was obtained as colourless oil from the corresponding carboxylic acid in 67% yield (eluent: AcOEt–pentane = 3/7, then AcOEt); IR (neat, ν cm^{-1}): 3168 (OH, broad); 1488; 1242 (P=O); 1036 (P–O–C); ^{1}H-NMR ($CDCl_3$, 250 MHz, δ ppm): 7.41–7.09 (4H, m, Ph); 3.85–3.61 (8H, m, $2OCH_3$ and CH_2).

2.1.2. Dimethyl [1-hydroxyimino-2-(3-methoxy-phenyl)-ethyl]-phosphonate (**3e**)

This compound was obtained as colourless oil from the corresponding carboxylic acid in 41% yield (eluent: AcOEt–pentane = 3/7, then AcOEt); IR (neat, ν cm^{-1}): 3169 (OH, broad); 1600 (C=N); 1260 (P=O); 1038 (P–O–C); ^{1}H-NMR ($CDCl_3$, 250 MHz, δ ppm): 10.99 (1H, broad s, OH); 7.22–7.13 (4H, m, Ph); 3.91–3.59 (11H, m, $3OCH_3$ and CH_2).

2.1.3. Dimethyl (1-hydroxyimino-2-naphthalen-1-yl-ethyl)-phosphonate (**3f**)

This compound was obtained as a yellowish oil from the corresponding carboxylic acid in 36% yield (eluent: AcOEt–pentane = 1/1, then AcOEt); IR (neat, ν cm^{-1}): 3165 (OH, broad); 1447; 1233 (P=O); 1036 (P–O–C); ^{1}H-NMR ($CDCl_3$, 200 MHz, δ ppm): 9.21 and 8.92 (1H, 2s, OH); 8.08–7.28 (7H, m, Ph); 4.33 (d, $^3J_{PH} = 14.3$ Hz) and 4.16 (d, $^3J_{PH} = 10$ Hz) (2H, CH_2); 3.59 and 3.35 (6H, 2d, $2OCH_3$, $^3J_{PH} = 11.6$ Hz).

2.1.4. Dimethyl (1-hydroxyimino-hexyl)-phosphonate (**3h**)

This compound was obtained as colourless oil from the corresponding carboxylic acid in 43% yield (eluent: AcOEt–pentane = 3/7, then AcOEt); IR (neat, ν cm^{-1}): 3179 (OH, broad); 1459; 1244 (P=O); 1036 (P–O–C); ^{1}H-NMR ($CDCl_3$, 200 MHz, δ ppm): 9.81 (1H, s, OH); 3.86; 3.83; 3.80; 3.77 (6H, 4s, $2OCH_3$); 2.48 (2H, m, CH_2); 1.58 (2H, m, CH_2); 1.31 (4H, m, $2CH_2$); 0.89 (3H, m, CH_3); ^{13}C-NMR ($CDCl_3$, 62.5 MHz, δ ppm): 155.7; 152.3 (C=N); 53.4; 53.3 ($2OCH_3$); 31.9; 26.6; 26.3; 25.3 and 22.3 (4C, $4CH_2$); 13.9 (CH_3).

2.1.5. Dimethyl (2-ethyl-1-hydroxyimino-hexyl)-phosphonate (**3i**)

This compound was obtained as colourless oil from the corresponding carboxylic acid in 43% yield (eluent: AcOEt–pentane = 1/1, then AcOEt); IR (neat, ν cm^{-1}): 3416 and 3236 (OH, broad); 1460; 1228 (P=O); 1050 (P–O–C); ^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm): 10.5 (1H, broad s, OH); 3.84 (6H, m, $2OCH_3$); 2.55 (1H, m, CH); 1.72–1.23 (11H, m, $3CH_2$ and C_2H_5); 0.88 (3H, m, CH_3).

2.2. General procedure for the synthesis of α-phosphonoenamides

A solution of the α-oximinophosphonate (1 mmol) in acetic anhydride (2.2 ml) is stirred at 45 °C until complete reaction (about 6 h; monitoring by TLC). Iron powder (0.56 g; 10 mmols) and acetic acid (0.17 ml) are added to the solution and the resulting mixture stirred at 55 °C for 1–2 h (TLC monitoring). After cooling, the reaction mixture is filtered through a pad of celite, the celite rinsed with EtOAc and toluene, and the filtrate concentrated in a rotary evaporator. The residue is finally purified by chromatography on silica gel to give the corresponding enamide.

2.2.1. Dimethyl (1-acetylamino-2-phenyl-vinyl)-phosphonate (**8a**)

This compound (Z–E cal/l) was obtained as colourless oil in 77% yield (eluent: AcOEt–pentane = 4/1, then AcOEt); IR (neat, ν cm^{-1}): 1672 (C=O); 1240 (P=O); 1030 (P–O–C); ^{1}H-NMR ($CDCl_3$, 200 MHz, δ ppm): 8.35 and 8.16 (1H, 2bs, NH), 7.69–7.25 (6H, m, Ph, CH = Z and E); 3.78 and 3.56 (6H, 2d, $^3J_{PH} = 11$ Hz, $2OCH_3$, Z and E); 2.14 and 2.10 (3H, 2s, CH_3 Z and E).

2.2.2. Dimethyl (1-acetylamino-3-phenyl-propenyl)-phosphonate (**8b**)

This compound (Z–E cal/l) was obtained as colourless oil in 89% yield (eluent: AcOEt–pentane = 4/1,

then AcOEt); IR (neat, ν cm^{-1}): 3435 (NH, broad); 1668 (C=O); 1240 (P=O); 1028 (P–O–C); ^{1}H-NMR ($CDCl_3$, 200 MHz, δ ppm): 7.24 (5H, m, Ph); 6.95 (1H, bs, HH), 6.64 (1H, two triplets, $J = 6$ Hz, =CH); 3.73 (6H, d, $^3J_{PH} = 11.1$ Hz, $2OCH_3$); 3.47 (2H, m, CH_2); 2.13 (3H, s, CH_3); ^{13}C-NMR ($CDCl_3$, 50 MHz, δ ppm): 168.4 (C=O); 144.5; 144.1; 138.4; 128.7; 126.6 (Ph, C=CH); 53.1 (d, $^2J_{PC} = 6.0$ Hz, $2OCH_3$); 35.3 (d, $^3J_{PC} = 15.1$ Hz, CH_2); 23.3 (CH_3); m/z (CI, NH_3): 284 [MH^+]; 252 [$MH^+ - MeOH$]. Anal. Calc. for $C_{13}H_{18}NO_4P$: C, 55.12; H, 6.41. Found: C, 55.21; H, 6.58%.

2.2.3. Dimethyl [1-acetylamino-2-(4-fluoro-phenyl)-vinyl]-phosphonate (**8c**)

This compound (Z–E cal/l) was obtained as colourless oil in 71% yield (eluent: AcOEt, then MeOH); IR (neat, ν cm^{-1}): 3436 and 3233 (NH); 1671 (C=O); 1234 (P=O); 1031 (P–O–C); ^{1}H-NMR ($CDCl_3$, 200 MHz, δ ppm): 7.89 (1H, s, NH); 7.53–6.97 (5H, m, Ph and =CH); 3.77; 3.58 (6H, 2d, $^3J_{PH} = 11.2$ Hz, $2OCH_3$, Z and E); 2.15 and 2.10 (3H, 2s, CH_3); ^{13}C-NMR ($CDCl_3$, 50 MHz, δ ppm): 168.7 (C=O); 160.7; 139.7; 139.3; 131.7; 131.5; 130.8; 130.7; 115.9; 115.5; 115.2 and 114.7 (Ph, C=CH); 53.2 (d, $^2J_{PC} = 5.5$ Hz); 52.9 (d, $^2J_{PC} = 4.5$ Hz) ($2OCH_3$, Z and E); 24.9; 23.4 (CH_3); m/z (CI, NH_3): 288 [MH^+]; 256 [$MH^+ - MeOH$]; 245 [$MH^+ - COCH_3$]. Anal. Calc. for $C_{12}H_{15}FNO_4P \cdot 1/2H_2O$: C, 48.65; H, 5.41. Found: C, 48.43; H, 5.31%.

2.2.4. Dimethyl [1-acetylamino-2-(4-bromo-phenyl)-vinyl]-phosphonate (**8d**)

This compound (Z–E cal/l) was obtained as colourless oil in 75% yield (eluent: AcOEt–pentane = 1/1, then AcOEt); IR (neat, ν cm^{-1}): 3437 and 3234 (NH); 1673 (C=O); 1240 (P=O); 1030 (P–O–C); ^{1}H-NMR ($CDCl_3$, 250 MHz, δ ppm): 7.72 (1H, s large, NH); 7.48–7.15 (5H, m, Ph and =NH); 3.78; 3.59 (6H, 2d, $^3J_{PH} = 11.3$ Hz, $2OCH_3$, Z and E); 2.14; 2.09 (3H, 2s, CH_3); ^{13}C-NMR ($CDCl_3$, 62.5 MHz, δ ppm): 168.6 (C=O); 139.2; 138.8; 131.8; 131.0; 130.9; 130.5 (Ph, C=CH); 53.2 and 52.9 (2d, $^2J_{PC} = 5.3$ Hz, $2OCH_3$, Z and E); 24.8 and 23.3 (CH_3). Anal. Calc. for $C_{12}H_{15}BrNO_4P \cdot \frac{1}{2}H_2O$: C, 40.34; H, 4.48. Found: C, 40.41; H, 4.59%.

2.2.5. Dimethyl [1-acetylamino-2-(3-methoxy-phenyl)-vinyl]-phosphonate (**8e**)

This compound (Z–E = 1/1) was obtained as colourless oil in 72% yield (eluent: AcOEt, then MeOH); IR (neat, ν cm^{-1}): 3437 and 3232 (NH); 1670 (C=O); 1239 (P=O); 1029 (P–O–C); ^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm): 7.63 (1H, broad s, NH); 7.30–6.82 (5H, m, Ph, =CH); 3.80 (3H, s, OCH_3); 3.81 and 3.60 (6H, 2d, $^3J_{PH} = 11.7$ Hz, $2OCH_3$, Z and E); 2.15 and 2.10 (3H, 2s, CH_3); ^{13}C-NMR ($CDCl_3$, 62.5 MHz, δ ppm): 168.8 (C=O); 159.6; 159.1; 140.9; 140.6; 134.9; 134.7; 129.6; 128.9; 122.1; 121.4; 115.6; 114.7; 114.1 and 114.0 (Ph, C=CH); 55.2 (OCH_3); 53.2 (d, $^2J_{PC} = 5.3$ Hz) 52.9 (d, $^2J_{PC} = 4.8$ Hz) ($2OCH_3$); 24.9; 23.3 (CH_3); m/z (CI, NH_3): 300 [MH^+]; 268 [$MH^+ - MeOH$]; 257 [$MH^+ - COCH_3$]. Anal. Calc. for $C_{13}H_{18}NO_5P \cdot 1/2H_2O$: C, 50.65; H, 6.17. Found: C, 50.74; H, 6.09%.

2.2.6. Dimethyl (1-acetylamino-2-naphthalen-1-yl-vinyl)-phosphonate (**8f**)

This compound (Z–E cal/l) was obtained as a yellowish oil in 81% yield (eluent: AcOEt–pentane = 1/1, then AcOEt); IR (neat, ν cm^{-1}): 3437 and 3237 (NH, broad); 1673 (C=O); 1241 (P=O); 1030 (P–O–C); ^{1}H-NMR($CDCl_3$, 250 MHz, δ ppm): 8.0–7.38 (8H, m, Ar, C=CH); 3.84; 3.35 (6H, 4d, $^3J_{PH} = 11.2$ Hz, $2OCH_3$); 2.18; 1.87 (3H, 2s, CH_3); ^{13}C-NMR ($CDCl_3$, 62.5 MHz, δ ppm): 169.6 and 168.9 (C=O); 133.5; 132.9; 132.2 and 131.4 (4C, Ar_q, C_q=CH); 130.9; 130.8; 129.5; 128.6; 128.5; 128.3; 126.8; 126.6; 126.2; 125.9; 125.2; 125.0; 124.9 and 124.0 (8C Ar, C=CH); 53.3; 52.8 (2C, 2d, $^2J_{PC} = 5.4$ Hz, $2CH_3$); 24.8 and 22.9 (CH_3); m/z (IC, NH_3): 320 [MH^+]; 288 [$MH^+ - MeOH$]. Anal. Calc. for $C_{16}H_{18}NO_4P \cdot H_2O$: C, 56.97; H, 5.93. Found: C, 56.94; H, 5.81%.

2.2.7. Dimethyl (1-acetylamino-3-methyl-but-1-enyl)-phosphonate (**8g**)

This compound (Z–E cal/l) was obtained as a colourless oil in 77% yield (eluent: AcOEt, then MeOH–CH_2Cl_2 = 1/4); IR (neat, ν cm^{-1}): 3449 and 3237 (NH, broad); 1670 (C=O); 1241 (P=O); 1031 (P–O–C); ^{1}H-NMR ($CDCl_3$, 200 MHz, δ ppm): 7.75 (1H, broad s, NH); 6.42 and 6.33 (1H, two doublets, $J = 12$ Hz, CH=); 3.73 (6H, d, $^3J_{PH} = 11.1$ Hz, $2OCH_3$); 2.62 (1H, m, CH); 2.09 (3H, s, CH_3CO); 1.05 (3H, s, CH_3); 1.02 (3H, s, CH_3); ^{13}C-NMR ($CDCl_3$, 62.5 MHz, δ ppm): 169.0 (C=O); 154.2 and 153.9 (CH=); 121.8; 118.4 (C_q); 52.6; 52.5 (OCH_3); 27.8; 27.6 (CH_3CO); 22.6 (CH); 21.1 ($2CH_3$); m/z (CI, NH_3): 236 [MH^+]; 204 [$MH^+ - MeOH$]. Anal. Calc. for $C_9H_{18}NO_4P \cdot 1/2H_2O$: C, 44.26; H, 7.79. Found: C, 43.85; H, 7.73%.

2.2.8. Dimethyl (1-acetylamino-hex-1-enyl)-phosphonate (**8h**)

This compound (Z–E cal/l) was obtained as a colourless oil in 89% yield (eluent: AcOEt–pentane = 1/1, then AcOEt); IR (neat, ν cm^{-1}): 3460 and 3239 (NH, broad); 1670 (C=O); 1241 (P=O); 1029 (P–O–C); ^{1}H-NMR ($CDCl_3$, 200 MHz, δ ppm): 7.63 (1H, broad d, NH); 6.54 (1H, apparent quintet, CH=); 3.74 (6H, d + d, $^3J_{PH} = 41.1$ Hz, $2OCH_3$); 2.11 (3H, bs, CH_3CO); 2.09; 1.38 (6H, m, $3CH_2$); 0.90 (3H, bt, $J = 7.5$ Hz, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm): 168.3 (C=O); 147.1 (CH=, d, $^2J_{PC} = 20.6$ Hz); 121.6; 52.8; 52.7 (2C, $2OCH_3$); 30.0 (CH_2); 28.6 and 28.4 (CH_2); 23.0 (CH_3CO); 22.4 (CH_2); 13.7 (CH_3); m/z (IC, NH_3): 250

[MH^+]; 218 [$MH^+ - MeOH$]. Anal. Calc. for $C_{10}H_{20}NO_4P \cdot H_2O$: C, 44.94; H, 8.24. Found: C, 45.34; H, 8.01%.

2.2.9. Dimethyl (1-acetylamino-2-ethyl-hex-1-enyl)-phosphonate (**8i**)

This compound (*Z*–*E* cal/l) was obtained as a colourless oil in 76% yield (eluent: AcOEt, then $MeOH–CH_2Cl_2 = 1/4$); IR (neat, ν cm^{-1}): 3432 and 3237 (NH, bande large); 1664 (C=O); 1243 (P=O); 1028 (P–O–C); ^{1}H-NMR ($CDCl_3$, 250 MHz, δ ppm): 7.53 (1H, d, $^3J_{PH} = 9.3$ Hz); 3.73 (6H, 2d, $^3J_{PH} = 11.3$ Hz, $2OCH_3$); 2.53 (2H, broad triplet, $J = 6.5$ Hz, CH_2); 2.18 (2H, broad triplet, $J = 9$ Hz CH_2); 2.07 (3H, s, CH_3CO); 1.36 (4H, m, $2CH_2$); 1.09 and 1.02 (3H, two triplets, $J = 6.5$ Hz, $2CH_3$), 0.90 and 0.88 (3H, two triplets, $2CH_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm): 169.6 (C=O); 118.7; 118.6; 115.9; 115.8 (2C, C=CH); 52.5 ($2OCH_3$); 31.7; 31.5; 31.3; 30.6; 29.5; 25.4; 25.3; 25.1; 22.8 ($4CH_2$); 22.9 (CH_3CO); 13.8; 13.7; 12.9 and 11.9 ($2CH_3$); m/z (CI, NH_3): 278 [MH^+]. Anal. Calc. for $C_{12}H_{24}NO_4P \cdot 1/2H_2O$: C, 50.35; H, 8.74. Found: C, 49.74; H, 8.73%.

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