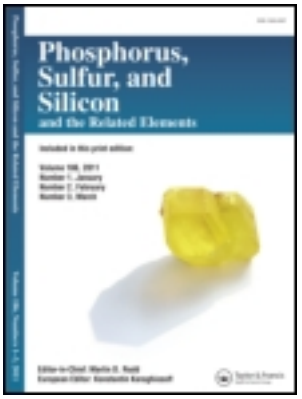


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

α-Ketiminophosphonates: Synthesis and Applications

Javier Vicario [a], Domitila Aparicio [a] & Francisco Palacios [a]

[a] Departamento de Química Orgánica I, Facultad de Farmacia, Universidad del País Vasco, Vitoria, Spain

Published online: 25 Apr 2011.

To cite this article: Javier Vicario , Domitila Aparicio & Francisco Palacios (2011): α-Ketiminophosphonates: Synthesis and Applications, Phosphorus, Sulfur, and Silicon and the Related Elements, 186:4, 638-643

To link to this article: http://dx.doi.org/10.1080/10426507.2010.521211

Phosphorus, Sulfur, and Silicon, 186:638–643, 2011

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2010.521211

α-KETIMINOPHOSPHONATES: SYNTHESIS AND APPLICATIONS

Javier Vicario, Domitila Aparicio, and Francisco Palacios
Departamento de Química Orgánica I, Facultad de Farmacia, Universidad del País Vasco, Vitoria, Spain

Abstract *The synthesis of α-iminophosphonates derived from ketones has been achieved by aza-Wittig reaction of P-trimethylphosphazenes with acylphosphonates. These unstable compounds can be used for the synthesis of chiral α-aminophosphonate derivatives through addition of nucleophiles to the C-N iminic double bond. Moreover, if α,β-unsaturated imines are used, regioselective Michael addition to the conjugated bond yields α-dehydroaminophosphonic acid derivatives functionalized at the γ-position.*

Keywords α-Aminophosphonates; α-dehydroaminophosphonates; α-iminophosphonates; α,β-unsaturated imines

INTRODUCTION

α-Aminophosphonic acids[1] **I** are structurally analogous to α-amino acids **II**, obtained by isosteric substitution of the carboxylic acid by a phosphonate moiety (Figure 1). As expected from this analogy, the single α-aminophosphonic acid molecules or their phosphonic esters as well as phosphapeptides containing α-aminophosphonic units show an assorted biological activity[2] as haptens of catalytic antibodies,[3a] peptide mimetics,[3b] enzyme inhibitors,[3c–e] and antibacterial agents.[3f] Moreover they are key compounds in agrochemistry and have found several applications as fungicides[4a] or herbicides.[4b]

α-Iminophosphonate derivatives **III** are direct precursors of α-aminophosphonic acid derivatives **IV** through the conversion of the imine moiety into amine through simple reduction of the C-N double bond or addition of nucleophiles to the electophilic imine carbon. In addition, α-iminophosphonates holding a β,γ-unsaturated double bond **III** (R═CH═CH-R′) are versatile compounds, which, owing to their ambident electrophilic character, can be excellent substrates for the preparation of a variety of cyclic and acyclic α-aminophosphorus derivatives.

Received 21 July 2010; accepted 1 September 2010.

The present work has been supported by the Dirección General de Investigación del Ministerio de Ciencia e Innovación (MICINN, Madrid DGI, CTQ2009-12156) and by the Departamento de Educación, Universidades e Investigación del Gobierno Vasco and Universidad del País Vasco (GV, IT 422-10; UPV, GIU-09/57). J. V. thanks the Ministerio de Ciencia e Innovación for a "Ramón y Cajal" contract.

Address correspondence to Francisco Palacios, Departamento de Química Orgánica I, Facultad de Farmacia, Universidad del País Vasco, P. O. Box 450, Vitoria-Gasteiz 01080, Spain. E-mail: Francisco.palacios@ehu.es

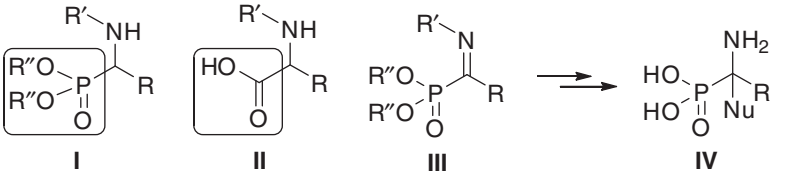
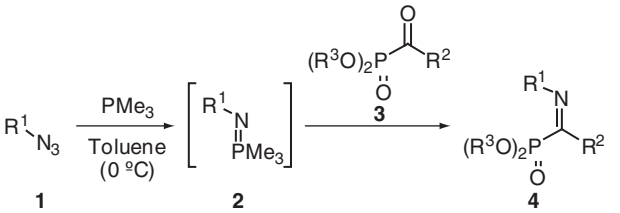


Figure 1 α-Aminoacids and their isosters α-aminophosphonates.

The simplest method for the synthesis of imines employs condensation of carbonyl compounds with amines. This condensation reaction becomes more complicated when electron-poor imines are sought, given the difficulty for the nucleophilic attack of the required deactivated amine to the carbonyl group. Besides, if α,β-unsaturated imines are the objective, this method is also often complicated by Michael addition reaction, especially when α,β-unsaturated ketones are used.[5] These preparative drawbacks can be sometimes avoided either by olefination reaction of β-phosphorylated imines or enamines with aldehydes to generate the conjugated C-C double bond,[6] or by the Aza-Wittig reaction[7,8] of phosphazenes, a strategy recently applied for the construction of α,β-unsaturated imines derived from α-aminoester derivatives.[9] In the past we have been involved in the synthesis and reactivity of phosphorylated oximes,[10] hydrazones,[11] and imines/enamines[6,12] and their transformation into different cyclic and acyclic aminophosphorus derivatives. In this article, we report the results on the synthesis and reactivity of α-ketiminophosphonate derivatives.

RESULTS AND DISCUSSION

Initially we attempted the direct condensation reaction between amines and carbonyl compounds. This reaction is proved successful for the synthesis of α-oxyminophosphonates[13] and α-hydrazonophosphonates,[14] but, in our case, the starting materials were recovered intact when the poorly nucleophilic amides, sulfonamides, or phosphinamides were heated with acylphosphonates in the presence of a dehydrating agent. The use of more nucleophilic amines is discarded in this case, since alkylamines have already been shown to afford amides through nucleophilic attack to the acylphosphonate followed by elimination of the phosphonate group.[15] For this reason, we explored the preparation of imines **4** by construction of the carbon-nitrogen double bond by aza-Wittig reaction of phosphazenes and carbonyl compounds (Scheme 1). The usefulness of phosphazenes species in the selective formation of imine bonds,[7,8] and the increased reactivity of phosphazenes when aromatic substituents at the phosphorus are replaced by alkyl substituents,[16] are well documented. Therefore, the synthesis of α-iminophosphonates **4**



Scheme 1 Synthesis of α-iminophosphonates **4** through aza-Wittig reaction.

Table 1 Synthesis of α-iminophosphonates **4**

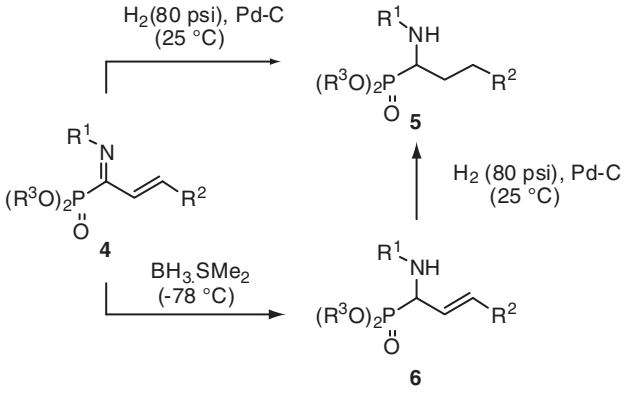
Entry	Compound	R^1	R^2	R^3	Conv. (%)	Yield[a] (%)
1	**4a**	*p*-Me-C_6H_4	Ph	Me	100	N.d.
2	**4b**	*p*-Me-C_6H_4	CH_3	Me	100	N.d.
3	**4c**	*p*-Me-C_6H_4	PhCH=CH	Me	100	89
4	**4d**	*p*-Me-C_6H_4	2-furyl−CH=CH	Me	100	89
5	**4e**	*p*-Me-C_6H_4	EtOCH=CH	Me	100	85
6	**4f**	*p*-NO_2-C_6H_4	MeCH=CH	Et	100	75
7	**4g**	*p*-MeO-C_6H_4	MeCH=CH	Et	100	73

[a]Isolated yield.

was achieved by the aza-Wittig reaction of the very reactive phosphazenes **2** derived from trimethyl phosphine and α-ketophosphonates **3** (Scheme 1).[17]

Phosphazenes **2** were readily prepared in situ by the addition of trimethylphosphine to azides **1** in dichloromethane, and, given the unstability of *P*-trialkyl phosphazene species **2**, their formation was monitored by ^{31}P NMR; they were used without purification for the following purposes. The formation of phosphazenes is evident from the visible nitrogen gas formation. The subsequent direct addition of the α-ketophosphonates **3** afforded, in a few minutes, α-iminophosphonates **4** in good yields (Scheme 1, Table 1). Simple α-iminophosphonates **4a,b** (Scheme 1, Table 1, entries 1 and 2) derived from benzoylphosphonate or acetylphosphonate showed very low stability. α-Iminophosphonates **4a,b** can be characterized in situ by ^1H, ^{13}C, and ^{31}P NMR, and they can be used from the resulting solution in the further steps. The reaction was successfully applied to the synthesis of aromatic (Scheme 1, Table 1, entry 1) aliphatic (Scheme 1, Table 1, entry 2) and unsaturated (Scheme 1, Table 1, entries 3–7) α-ketophosphonates **4a–g**.

With this successful methodology in hand, we tried to use α-ketiminophosphonates as substrates for the synthesis of several α-aminophosphonic acid derivatives. First, the selective reduction of α,β-unsaturated imines was explored. The synthesis of the saturated α-aminophosphonates **5** can be achieved in excellent yields (91–95%) by catalytic hydrogenation of the β,γ-unsaturated α-iminophosphonates **4c–g** (Scheme 2) in methanol at 80 psi.



Scheme 2 Selective reduction of β,γ-unsaturated α-iminophosphonates **4**.

Table 2 γ-Amino α-dehydroaminophosphonates **7** synthesized by aza-Michael reaction

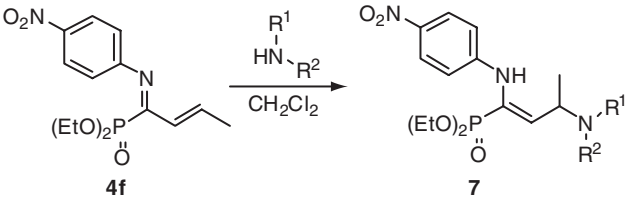
Entry	Compound	HNR^2R^3	E/Z[a]	Yield[b]
1	**7a**	NH_3	100/0	82%
2	**7b**	*p*-Me-C_6H_4-NH_2	100/0	83%
3	**7c**	Me-NH_2	100/0	88%
4	**7d**	^{n}Pr-NH_2	62/38	86%
5	**7e**	Bn-NH_2	0/100	79%
6	**7f**	CH_2=CH−CH_2−NH_2	0/100	85%
7	**7g**	Pyrrolidine	100/0	79%
8	**7h**	(*S*)-Pseudoephedrine[c]	100/0	81%

[a]Determined by integration of ^{31}P NMR signals of the crude.
[b]Yield after chromatography.
[c]D.r. = 1:1.

On the other hand, treatment of β,γ-unsaturated α-iminophosphonates **4c–g** with $BH_3{\cdot}SMe_2$ in toluene or THF at –78°C afforded exclusively vinylogous α-aminophosphonates **6** in very good yields (84–88%, Scheme 2) through selective reduction of the imine bond. It is remarkable that both reductions can be performed in a one-pot procedure directly with similar yields from the solutions generated after the aza-Wittig reaction, that is, starting from α-ketophosphonates **3**. This last aspect is of special importance, since this avoids problems of handling associated to the susceptibility of imines to undergo hydrolysis. Finally, the conversion of vinylogous α-aminophosphonates **6** into saturated α-aminophosphonates **5** is easily accomplished by simple catalytic hydrogenation (Scheme 2).

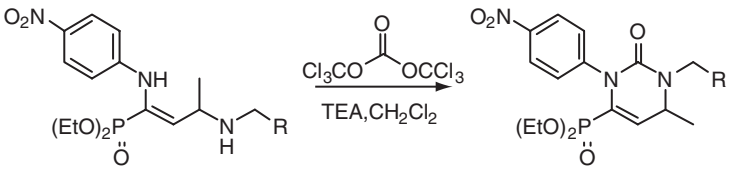
Moreover, aza-Michael reaction of amines with β,γ-unsaturated α-iminophosphonates **4f** affords α-dehydro aminophosphonates **7** in very good yields with a γ-stereogenic center bearing an amino group (Scheme 3, Table 2). It is remarkable that the conjugate addition of amines proceeds without any additional activation. The reaction of β,γ-unsaturated α-iminophosphonates **4f** with amines in dichloromethane at room temperature affords in a few minutes α-dehydroaminophosphonates **7** in good yields (Scheme 3, Table 2). The scope of the reaction is especially wide, since it tolerates the use of ammonia (Table 2, entry 1), aromatic amines (Table 2, entry 2), and primary and secondary aliphatic amines (Table 2, entries 3–8), including β-amino alcohol derivatives (Table 2, entry 8).

The resulting γ-amino enamines can be used for the preparation of phosphorylated pyrimidine derivatives. Thus, treatment of enamines **7e–f** at room temperature with



Scheme 3 Synthesis of α-dehydroaminophosphonates **7**.

triphosgene and two equivalents of triethylamine afforded phosporylated 3,4-dihydro-2-pyrimidones **8a**,**b** in very good yield (Scheme 4, 87–90%).



7e: R = Ph
7f: R = CH = CH_2

8a: R = Ph,87%
8b: R = CH = CH_2,90%

Scheme 4 Synthesis of pyrimidone derivatives **8a**,**b**.

CONCLUSION

The very reactive phosphazene species derived from trimethylphosphine constitute an excellent alternative for condensation (1,2-addition) with carbonyl groups, especially with α,β-unsaturated ketones avoiding undesirable Michael addition products. This methodology applied to α-ketophosphonates provides access to α-iminophosphonates and β,γ-unsaturated-α-iminophosphonates. Regioselective reduction of the imine carbon–nitrogen double bond of phosphorylated α,β-unsaturated imines provides access to vinylogous α-aminophosphonates, while total reduction of α,β-unsaturated imines gives saturated α-aminophosphonates. β,γ-Unsaturated-α-iminophosphonates can be also used as Michael acceptors in aza-Michael or conjugate addition of amines to give γ-amino-α-dehydroaminophosphonates. These amino α-dehydroaminophosphonates are also starting materials for the synthesis of phosphorylated pyrimidone derivatives.

REFERENCES

1. For an excellent book see: Kukhar, V. P.; Hadson, H. R., Eds. *Aminophosphonic and Aminophopshinic Acids. Chemistry and Biological Activity*; John Wiley: Chichester, UK, 2000.
2. For reviews see: (a) Kafarski, P.; Lejczak, B. *Curr. Med. Chem: Anti-Cancer Agent* **2001,** *1*, 301–312; (b) Gambecka, J.; Kafarski, P. *Mini-Rev. Med. Chem.* **2001,** *1*, 133–144.
3. (a) Hirschmann, R.; Smith III, A. B.; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengeler, P. A.; Venkovic, S. J. *Science* **1994,** *265*, 234–237; (b) Lejczak, B.; Kafarski, P.; Sztajer, H.; Masterlerz, P. *J. Med. Chem.* **1986,** *29*, 2212–2217; (c) Oleksyszyn, J.; Powers, J. C. *Biochemistry* **1991,** *30*, 485–493; (d) Bartlett, P. A.; Hanson, J. E.; Giannousis, P. G. *J. Org. Chem.* **1990,** *J. Org. Chem. 55*, 6268–6274; (e) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989,** *32*, 1652–1661; (f) Atherton, F. R.; Hassall, C. H.; Lambert R. W. *J. Med. Chem.* **1986,** *29*, 29–40.
4. (a) Smith, W. W.; Bartlett, P. A. *J. Am. Chem. Soc.* **1998,** *120*, 4622–4628; (b) Bonarska, D.; Kleszczyńska H.; Sarapuk, J. *Cell Mol. Biol. Lett.* **2002,** *7*, 929–935.
5. (a) Palacios, F.; Vicario, J.; Aparicio, D. *Eur. J. Org. Chem.* **2006,** 2843–2850; (b) Brady, W. T.; Shieh, C. H. *J. Org. Chem.* **1983,** *48*, 2499–2502.
6. (a) Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; Oyarzabal, J. *J. Org. Chem.* **2004,** *69*, 8767–8774; (b) Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; Oyarzabal, J. *Org. Lett.* **2002,** *4*, 769–772; (c) Palacios, F.; Aparicio, D.; Vicario, J. *Eur. J. Org. Chem.* **2002,** 4131–4136.

7. For reviews see: (a) Palacios, F.; Aparicio, D.; Rubiales, G.; Alonso, C.; de los Santos, J. M. *Tetrahedron* **2007,** *63*, 523–575; (b) Fresneda, P. M.; Molina, P. *Synlett* **2004**, 1–17; (c) Barluenga, J.; Palacios, F. *Org. Prep. Proced. Int.* **1991,** *23*, 1–65.
8. For contributions of creation of the C=N bouble bond by means of this process see: (a) Palacios, F.; Alonso, C.; Rubiales, G.; Villegas, M. *Tetrahedron* **2005,** *61*, 2779–2794; (b) Palacios, F.; Alonso, C.; Amezua, P.; Rubiales, G. *J. Org. Chem.* **2002,** *67*, 1941–1946; (c) Palacios, F.; Herrán, E.; Rubiales, G.; Ezpeleta, J. M. *J. Org. Chem.* **2002,** *67*, 2131–2135.
9. Palacios, F.; Vicario, J.; Aparicio, D. *J. Org. Chem.* **2006,** *71*, 7690–7696.
10. (a) Palacios, F.; Ochoa de Retana, A. M.; Alonso, J. M. *J. Org. Chem.* **2006,** *71*, 6141–6148; (b) Palacios, F.; Aparicio, D.; Ochoa de Retana, A. M.; de los Santos, J. M.; Gil, J. I.; Alonso, J. M. *J. Org. Chem.* **2002,** *67*, 7283–7288; (c) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Lopez de Munain, R. *Org. Lett.* **2002,** *4*, 2405–2408.
11. Palacios, F.; Aparicio, D.; Lopez, Y.; de los Santos, J. M.; Ezpeleta, J. M. *Tetrahedron* **2006,** *62*, 1095–1101; (b) Palacios, F.; Aparicio, Do.; de los Santos, J. M.; Vicario, J. *Tetrahedron* **2001,** *57*, 1961–1972; (c) Palacios, F.; Aparicio, D.; de los Santos, J. M. *Tetrahedron* **1996,** *52*, 4123–4132.
12. (a) Palacios, F.; Ochoa de Retana, A. M.; Oyarzabal, J.; Pascual, S.; Fernandez de Troconiz, G. *J. Org. Chem.* **2008,** *73*, 4568–4574; (b) Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; Lopez de Munain, R.; Oyarzabal, J.; Ezpeleta, J. M. *Tetrahedron* **2005,** *61*, 1087–1094; (c) Palacios, F.; Aparicio, D.; Garcia, J.; Vicario, J.; Ezpeleta, J. M. *Eur. J. Org. Chem.* **2001,** *66*, 3357–3365.
13. Breuer, E.; Karaman, R.; Goldblum, A.; Gibson, D.; Leader, H.; Potter, B. V. L.; Cummins, J. H. *J. Chem. Soc., Perkin Trans. 1* **1988,** 3047–3057.
14. Kudzin, Z. H.; Kotynski, A. *Synthesis* **1980,** 1028–1031.
15. Sekine, M.; Satoh, M.; Yamagata, H.; Hata, T. *J. Org. Chem.* **1980,** *45*, 4162–4167.
16. (a) Cossio, F. P.; Alonso, C.; Lecea, B.; Ayerbe, M.; Rubiales, G.; Palacios, F. *J. Org. Chem.* **2006,** *71*, 2839–2847; (b) Palacios, F.; Herran, E.; Rubiales, G. *J. Org. Chem.* **1999,** *64*, 6239–6246.
17. **General procedure for the synthesis of β,γ-unsaturated α-iminophosphonates 4.** To a solution of the corresponding azide **1** (2.0 mmol) in CH_2Cl_2 (10 mL) at 0°C, a 1.0 M solution of trimethylphosphine in toluene (2 mL) was added. The resulting solution was stirred for 30 min. until N_2 evolution stopped, which indicates the completion of the reaction, and phosphazene **2** formation and can be monitored by ^{31}P NMR. The corresponding neat β,γ-unsaturated α-ketophosphonate **3** (2.0 mmol) was then added, and the reaction was stirred for an additional 30 min at r.t. The solution was diluted with CH_2Cl_2 (40 mL) and washed with water (3 × 20 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford a yellow oily crude that was purified by chromatography (SiO_2, AcOEt:pentane 3:1).