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Conjugate Addition of Amines to an α,β-Unsaturated Imine Derived from α-Aminophosphonate. Synthesis of γ-Amino-α-dehydroaminophosphonates

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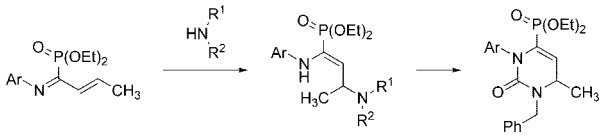
Received October 2, 2008



Aza-Michael reaction of ammonia, aliphatic, aromatic and optically active amines to an α,β-unsaturated imine derived from α-aminophosphonate affords α-dehydroaminophosphonates with a γ-stereogenic center bearing an amino group. Resulting γ-amino α-dehydroaminophosphonates can be used for the preparation of phosphorylated pyrimidine derivatives.

The aza-Michael reaction is one of the most powerful reactions in organic chemistry for the formation of C−N bonds.[1] Its simplicity makes it the most appropriate alternative for the preparation of functionalized γ-amino compounds. Conjugate addition of nitrogen nucleophiles to Michael acceptors can sometimes proceed without catalyst,[2] but, very often, deprotonation of the amine,[3] or activation of the conjugated system by the presence of Brönsted[4] or Lewis[5] acids or organocatalysts[6] is required, especially in the case of the addition of weakly nucleophilic aromatic amines. Despite the fact that conjugate addition of amines to α,β-unsaturated carbonylic compounds is well documented in the literature, to the best of our knowledge there are no examples reported about conjugate addition of amines to α,β-unsaturated imines. Moreover, the presence of a phosphonate group in the imine increases the synthetic interest of these substrates due to the applications of functionalized aminophosphonates in organic and medicinal chemistry.[7−10]

We have been involved in the chemistry of azabutadienes,[11] and we recently reported an efficient synthesis of α,β-unsaturated imines derived from α-aminoesters[12a] and α-aminophosphonates.[12b] These 1-azadienes have shown very assorted reactivity, and they have proved to be very useful intermediates for the synthesis of several heterocycles[13] as well as for the preparation of α-amino acid or α-aminophosphonic acid derivatives,[12] in some cases enantioselectively.[14] Following our interest in the chemistry of α-aminophosphonates[15] and 1-azabutadienes[11,12] and specifically in the reactivity of α,β-unsaturated imines derived from α-aminophosphonates, we report here the first example of a conjugate addition of amine nucleophiles to the β-carbon vinylogously attached to an imine group.

Conjugate addition of ammonia **2a** ($R^1 = R^2 = H$) to α,β-unsaturated imine **1** derived from α-aminophosphonate does not require any additional activation and can be performed in CH_2Cl_2 under mild conditions (procedure A, see the Experimental Section), affording exclusively the *E* isomer of γ-amino-α-dehydroaminophosphonate **3a** ($R^1 = R^2 = H$), in a stereose-

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10.1021/jo8022022 CCC: $40.75
Published on Web 11/19/2008

SCHEME 1. Nucleophilic Addition of Ammonia and Amines to α,β-Unsaturated Imine 1

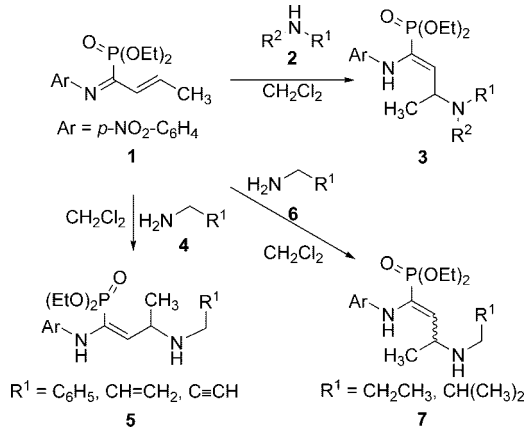
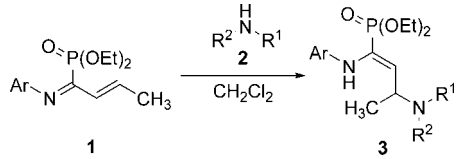


TABLE 1. (*E*)-γ-Amino α-Dehydroaminophosphonates 3 Synthesized by Aza-Michael Reaction of Ammonia and Amines 2 to Imine 1



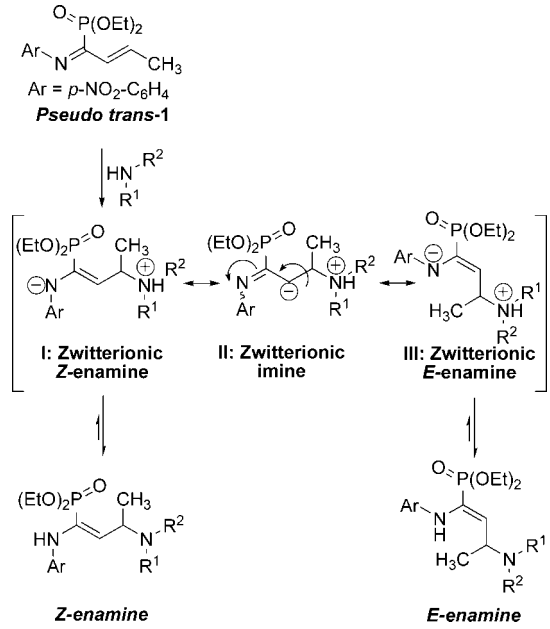
entry	compd	R^1	R^2	*E*/*Z*[a]	% yield[b]
1	**3a**	H	H	100/0	82, 80[d]
2	**3b**	H	*p*-CH_3-C_6H_4	100/0	83, 81[d]
3	**3c**	H	*p*-NO_2-C_6H_4	100/0	81, 80[d]
4	**3d**	H	CH_3	100/0	88
5	**3e**		$(CH_2)_4$	100/0	79, 77[d]
6	**3f**		(*S*)-methoxymethylpyrrolidine[c]	100/0	86
7	**3g**		(*S*)-pseudoephedrine[c]	100/0	81

[a] Determined by integration of ^{31}P NMR signals of the crude. [b] Yield after chromatography. [c] er = 1:1. [d] Yield using the multicomponent reaction, starting from but-2-(*E*)-enoylphosphonic acid diethyl ester **10** (procedure B).

lective fashion, with good yield (Scheme 1, Table 1, entry 1). γ-Amino-α-dehydroaminophosphonate **3a** was characterized on the basis of its ^1H, ^{31}P, and ^{13}C NMR, IR, and MS spectra. For example, the ^1H NMR spectrum of (*E*)-enamine **3a** presents a representative double doublet for the enaminic CH at $\delta_H = 6.46$ ppm, which shows coupling constants $^3J_{HH} = 8.6$ Hz, with the adjacent methyne, and $^3J_{PH} = 13.4$ Hz, typical for a *cis* relative configuration P−H in olefins.[16] ^{13}C NMR spectrum of (*E*)-enamine **3a** shows two doublets for the methyne and the quaternary carbon of the enamine double bond at $\delta_C = 145.9$ ppm, with a coupling constant $^2J_{PC} = 23.7$ Hz, and at $\delta_C = 128.2$ ppm, with a coupling constant $^1J_{PC} = 208.0$ Hz, respectively, and another doublet for the methyne at 44.1 ppm with a coupling constant $^3J_{PC} = 15.1$ Hz typical for the *trans* relative configuration P−C in alkenes.[16]

Aromatic amines showed a similar behavior, and conjugate addition of *p*-toluidine **2b** (R^1 = H, R^2 = *p*-Me-C_6H_4) and electron-deficient *p*-nitrophenylamine **2c** (R^1 = H, R^2 = *p*-NO_2-C_6H_4) to α,β-unsaturated imine **1** in CH_2Cl_2 gave only (*E*)-γ-amino-α-dehydroaminophosphonates **3b**,**c** with very good yields

SCHEME 2. Pathway for the Formation of *E*- and *Z*-Enamines by Addition of Amines to Imine 1



(Scheme 1, Table 1, entries 2 and 3). Likewise, the process was extended to methylamine **2d** (R^1 = H, R^2 = Me) (Table 1, entry 4), a secondary cyclic amine such as pyrrolidine ($R^1R^2 = (CH_2)_4$) (Table 1, entry 5) and optically active β-amino alcohol derivatives such as (*S*)-methoxymethylpyrrolidine or (*S*)-pseudoephedrine (Table 1, entries 6 and 7) with the formation the (*E*)-γ-amino-α-dehydroaminophosphonates **3d-g**.

The formation of the *E*-enamines could be explained taking into account a *pseudo-trans* conformation[17] of imine **1**. Nucleophilic addition of the amine could initially take place to afford the ionic intermediate **I**, with a *Z* configuration of the carbon−carbon double bond. If the γ-amine substituent is adequate, the zwitterionic (*Z*)-enamine **I** could evolve to the thermodynamically more stable zwiterionic *E*-enamine **III**[18] and the corresponding (*E*)-enamines can be obtained (Scheme 2).

A different behavior was observed by the conjugate addition of benzylamine **4a** ($R^1 = C_6H_5$), allylamine **4b** ($R^1 = CH{=}CH_2$), and propargylamine **4c** ($R^1 = C{\equiv}CH$) to α,β-unsaturated imine **1** in CH_2Cl_2 to give (*Z*)-γ-amino-α-dehydroaminophosphonates[19] **5a**−**c** in a stereoselective manner (Scheme 1, Table 2 entries 1−3). ^1H NMR spectrum of enamine **5a** shows the double doublet for the enaminic CH at $\delta_H = 6.11$ ppm with coupling constant values $^3J_{HH} = 10.3$ Hz with the adjacent methyne and $^3J_{PH} = 41.9$ ppm with the phosphonate, representative for a *trans* relative configuration P−H in the double bond. The ^{13}C NMR spectrum of enamine **5a** presents doublets at $\delta_C = 137.8$ ppm and $\delta_C = 127.2$ ppm, with coupling constants $^2J_{PC} = 20.3$ Hz and $^1J_{PC} = 200.3$ Hz, the first one for the methyne and the second one for the quaternary carbon of the enamine double bond as well as another doublet for the

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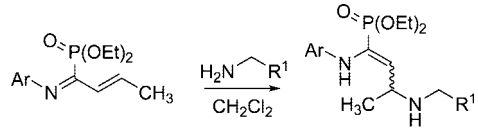
(17) The configuration and conformation in solution of α,β-unsaturated imine **1** was established on the basis of 2D NMR experiments. For the nuclear Overhauser enhancement spectroscopy (NOESY) spectrum, see the Supporting Information.

(18) Unlike enamine species **I**, in the iminic structures **II** there is free rotation around the C−C single bond, and if the energy barrier is small enough, the zwiterionic imine **II** can be converted into *E*-enamines **III**.

(19) *Z* Isomers compared to *E*-enamines showed a downfield shift of the signal corresponding to enaminic CH and an upfield shift of the signal assigned to the CH in the β-position.

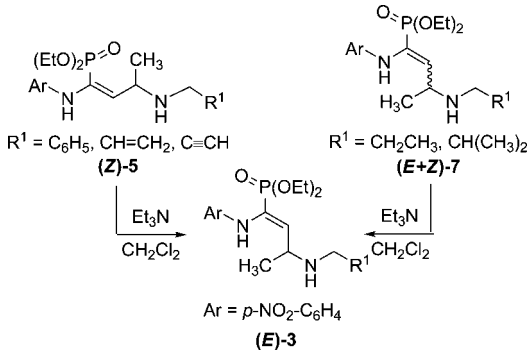
TABLE 2. γ-Amino α-Dehydroaminophosphonates 5 and 7 Synthesized



entry	compd	R^1	*E*/*Z*[a]	% yield[b]
1	**5a**	C_6H_5	0/100	79, 78[c]
2	**5b**	$CH{=}CH_2$	0/100	85
3	**5c**	$C{\equiv}CH$	0/100	91
4	**7a**	CH_2CH_3	62/38	86
5	**7b**	$CH(CH_3)_2$	63/37	89

[a] Determined by integration of ^{31}P NMR signals of the crude. [b] Yield after chromatography [c] Yield using the multicomponent procedure, starting from but-2-(*E*)-enoylphosphonic acid diethyl ester **10** (procedure B).

SCHEME 3. Base-Mediated Isomerization of *Z*-Enamines 5 and 7 to *E*-Enamines 3



β-methyne at $\delta_C = 51.4$ ppm and that shows a coupling constant $^3J_{PC} = 3.6$ Hz representative for a *cis* relative configuration P−C in the alkene bond.[16]

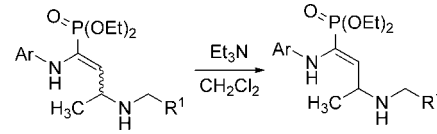
The formation of the *Z*-enamines could be explained by nucleophilic addition of the amine to afford the ionic intermediate **I**, with a *Z* configuration of the carbon−carbon double bond (Scheme 2). However, when a primary amine with sp^2 (benzyl or allyl amine) or sp (propargyl amine) β-carbon was used, this zwitterionic species **I** would undergo fast intermolecular interchange of the proton to afford the thermodynamically less favored *Z*-enamines.

On the other hand, when aliphatic amines such as *n*-propylamine **6a** ($R^1 = CH_2CH_3$) or isobutylamine **6b** ($R^1 = CH(CH_3)_2$) were treated with α,β-unsaturated imine **1**, mixtures of *E* and *Z*-enamines **7a**,**b** were obtained (Scheme 1, Table 2, entries 4 and 5). In these cases, *n*-propyl and isobutyl groups linked to the amino seems to favor the formation of mixtures of *E* and *Z* isomers.

With these results, we wanted to explore if the isomerization between *Z*- and *E*-enamines could be performed. In fact, heating *Z*-enamines **5a**−**c** in CH_2Cl_2 and in the presence of triethylamine afforded exclusively *E*-enamines **3h**−**j** in very good yields (Scheme 3, Table 3, entries 1−3).

In a similar way, heating mixtures of *E*- and *Z*-enamines **7a**,**b** in CH_2Cl_2 in the presence of triethylamine gave exclusively *E*-enamines **3k**,**l** (Scheme 3, Table 3, entries 4 and 5). This thermal isomerization is consistent with the higher stability of *E*-enamines toward the corresponding *Z*-enamines. It should be mentioned that the nucleophilic addition of amines to α,β-unsaturated imine **1** does not require the use of the isolated starting material, since the synthesis of enamines **3** can also be performed in very good yields in a multicomponent reaction (Scheme 4, Table 1, entries 1−3 and 5, Table 2, entry 1) by addition to α-ketophosphonate **10** of phosphazene **9**, generated "in situ" by addition of trimethylphosphine to *p*-nitrophenylazide **8**, with formation of β,γ-unsaturated iminophosphonate **1** and subsequent addition of the corresponding amine to the reaction mixture (procedure B, see the Experimental Section).

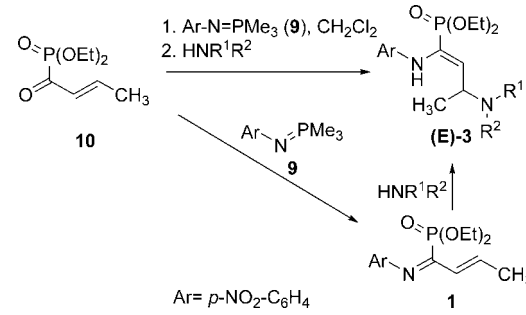
TABLE 3. Isomerization of *Z*-Enamines 5a−c and Mixtures of *E*- and *Z*-Enamines 7a,b to *E*-Enamines 3h−k



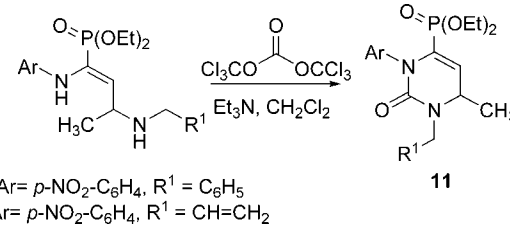
entry	compd	starting enamine	R^1	yield[a] (%)
1	**3h**	**5a**	C_6H_5	95
2	**3i**	**5b**	$CH{=}CH_2$	95
3	**3j**	**5c**	$C{\equiv}CH$	94
4	**3k**	**7a**[b]	CH_2CH_3	93
5	**3l**	**7b**[b]	$CH(CH_3)_2$	91

[a] Yield after chromatography [b] Mixtures of *E*- and *Z*-enamines.

SCHEME 4. Multicomponent Synthesis of (*E*)-γ-Amino-α-dehydroaminophosphonates 3



SCHEME 5. Synthesis of 4,5-Dihydro-2-pyrimidones 11a,b



Finally, given both the interest of azaheterocyclic phosphonates[20] and that it is well-known that molecular modifications involving the introduction of organophosphorus functionalities could increase biological activity,[21] enamines **3** were used as synthetic intermediates for the synthesis of 6-membered-ring phosphonylated heterocycles. Treatment of enamines **3h**,**i** at room temperature with triphosgene in the presence of 2 equiv of triethylamine afforded the phosphonylated 4,5-dihydro-2-pyrimidones **11a**,**b** in very good yield (87−90%) (Scheme 5). As far as we know, this strategy represents the first synthesis of 4,5-dihydropyrimidin-2-one-containing phosphorus substituents.

(20) For an excellent review of azaheterocyclic phosphonates, see: Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177.

(21) Toy, A. D. F.; Walsh, E. N. In *Phosphorus Chemistry in Everyday Living*; American Chemical Society: Washington DC., 1987.

In conclusion, we have shown here the first example of an aza-Michael reaction to α,β-unsaturated imines **1** to afford functionalized enamines **3**. The fact that a α,β-unsaturated imine derived from α-aminophosphonate is used as Michael acceptors makes this example of aza-Michael a suitable method for the preparation of chiral γ-amino α-dehydro aminophosphonates **3**. α-[7,8] and γ-aminophosphonate derivatives[10] as well as phosphapeptides containing α-aminophosphonic units show a variety of biological activities with interest in medicinal chemistry. Moreover, an application of γ-amino α-dehydro aminophosphonates **3** for the first synthesis of phosphorylated pyrimidone derivatives[20] is reported.

Experimental Section

Representative Example for the Aza-Michael Reaction of Amines 3 with the α,β-Unsaturated Imine-Derived from α-Aminophosphonate 4. Synthesis of [1-(4-Nitrophenylamino)-3-*p*-tolylaminobut-1-enyl]phosphonic Acid Diethyl Ester 3b. Procedure A: To a solution of α,β-unsaturated imine **1** (163 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) was added *p*-toluidine (64 mg, 0.6 mmol). The solution was stirred for 30 min, and the resulting mixture was concentrated under reduced pressure. The crude residue was purified by chromatography (SiO_2, AcOEt/MeOH 95:5) to afford 178 mg (83%) of **3b** as a pale yellow oil. **Procedure B:** multicomponent reaction procedure starting from but-2-(*E*)-enoylphosphonic acid diethyl ester **10**. To a solution of *p*-nitrophenyl azide **8** (82 mg, 0.5 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added a 1.0 M solution of trimethylphosphine in toluene (0.5 mL). The resulting solution was stirred for 30 min until N_2 evolution stopped, which indicates the completion of the reaction and phosphazene **9** formation. But-2-(*E*)-enoylphosphonic acid diethyl ester **10** (2.06 g, 10 mmol) was then added, and the reaction was stirred for an additional 30 min at rt. Neat *p*-toluidine (64 mg, 0.6 mmol) (0.6 mmol) was then added, and the reaction mixture was stirred for 30 min. The resulting solution was concentrated under reduced pressure, and the resulting yellow oily crude was purified by chromatography (SiO_2, AcOEt) to afford 175 mg (81%) of **3b** as a pale yellow oil. R_f (AcOEt/MeOH 95:5): 0.08. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11−1.29 (m, 6H, 2 × CH_3), 1.35 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3), 3.98−4.09 (m, 4H, 2 × CH_2O), 2.21 (s, 3H, CH_3), 4.22 (m, 1H, CHN), 6.18 (s, 1H, NH), 6.38 (dd, $^3J_{PH}$ = 14.2 Hz, $^3J_{HH}$ = 8.9 Hz, 1H, CH=), 6.77 (d, $^3J_{HH}$ = 9.0 Hz, 2 × CH_{ar}), 6.47 (d, $^3J_{HH}$ = 8.6 Hz, 2H, 2 × CH_{ar}), 6.93 (d, $^3J_{HH}$ = 8.6 Hz, 2H, 2 × CH_{ar}), 8.07 (d, $^3J_{HH}$ = 9.0 Hz, 2H, 2 × CH_{ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.1 (d,$^3J_{PC}$ = 5.5 Hz, 2 × CH_3), 19.6 (CH_3), 20.2 (CH_3), 47.2 (d, $^3J_{PC}$ = 15.1 Hz, CHN), 62.5 (d,$^2J_{PC}$ = 6.4 Hz, CH_2O), 62.6 (d,$^2J_{PC}$ = 6.1 Hz, CH_2O), 113.3 (2 × CH_{ar}), 114.5 (2 × CH_{ar}), 125.8 (2 × CH_{ar}), 126.2 (C_{quat}), 127.4 (d, $^1J_{PC}$ = 212.0 Hz), 129.6 (2 × CH_{ar}), 139.6 (C_{quat}), 143.6 (C_{quat}), 146.8 (d, $^2J_{PC}$ = 23.1 Hz, CH=), 151.7 (C_{quat}). ^{31}P NMR (120 MHz, $CDCl_3$): δ 13.0. FTIR (KBr) ν_{max} (cm^{-1}): 3343 (N−H st), 1239 (*P* = O st). CIMS *m*/*z* (amu): 433 ([M^+ + H], 87), 296 ([M^+] − $PO(OEt)_2$, 100). Anal. Calcd for $C_{21}H_{28}N_3O_5P$: C, 58.19; H, 6.51; N, 9.69. Found: C, 58.25; H, 6.47; N, 9.73.

Acknowledgment. The present work was supported by the Dirección General de Investigación del Ministerio de Ciencia y Tecnología (MCYT, Madrid DGI, CTQ2006-09323) and by the Departamento de Educación Universidades e Investigación del Gobierno Vasco (IT-277-07). J.V. thanks the Ministerio de Ciencia e Innovación for a Ramón y Cajal contract.

Supporting Information Available: Procedures and full characterization for compounds **3**, **5**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8022022