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Addition of amine derivatives to phosphorylated 1,2-diaza-1,3-butadienes. Synthesis of α-aminophosphonates

Francisco Palacios,* Domitila Aparicio, Yago López and Jesús M. de los Santos

Departamento de Química Orgánica I, Facultad de Farmacia, Universidad del País Vasco, Apartado 450, 01080 Vitoria Gasteiz, Spain

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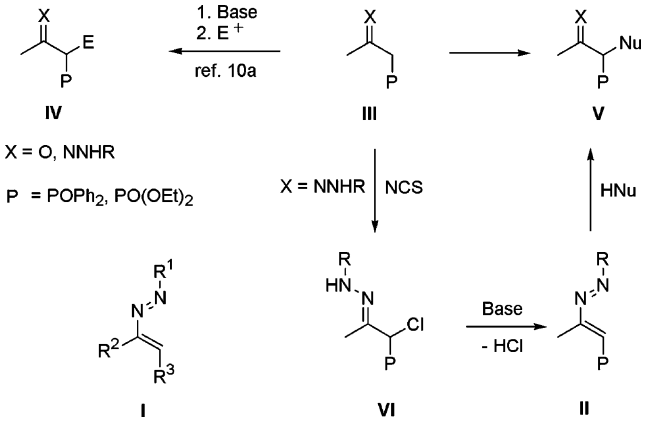
Abstract—Achiral and chiral 1,2-diaza-1,3-butadienes derived from phosphine oxides and phosphonates are obtained from hydrazonoalkyl-phosphine oxides and -phosphonates. Michael addition (1,4-addition) of ammonia, aminoesters and aminoalcohols to these azo-alkenes gives functionalized α-amino-phosphine oxides and -phosphonates.

1,2-Diaza-1,3-butadienes **I** (Scheme 1) are widely used intermediates in organic synthesis[1,2] because they offer easy access to a broad range of heterocycles.[3] Many of these heterodienes,[1,4] substituted on the terminal nitrogen (**I**, $R^1 = Me$, Ar, $ArSO_2$, COR) and on the terminal carbon (**I**, $R^3 = H$, Me, Cl, COR) have been described. However, only one example with phosphorus substituents **II** (Scheme 1, $R = POR_2$) was proposed as intermediate in the preparation of substituted aminopyrroles.[5] Furthermore, it is known that phosphorus substituents regulate important biological functions,[6] and that the introduction of organophosphorus functionalities in simple synthons may afford useful substrates for the preparation of biologically active compounds. However, as far as we know, neither the preparation of 1,2-diaza-1,3-butadienes containing phosphorus substituents nor the preparation of chiral phosphorylated diaza-alkenes[7] **II** (Scheme 1) has been described.



Scheme 1.

We have previously described the synthesis of 2-aza-1,3-butadienes[8] and the application of phosphorus substituted enamines[9] and hydrazones[10] as starting materials for the preparation of acyclic and cyclic compounds. In this context, the usefulness of carbanions derived from hydrazones for carbon–carbon bond formation reactions, has been well documented.[11] Besides enantioselective α-alkylations of aldehydes and ketones, the carbanion hydrazone method can be successfully applied to the introduction of electrophilic reagents in the Cα-carbon atom (Scheme 1) and we have used this strategy for the functionalization of hydrazonoalkyl-phosphine oxides and -phosphonates[10a] (**IV**, Scheme 1).

Taking into account that hydrazones can be considered as protected carbonyl compounds and that hydrazones can also be used as starting materials for the preparation of 1,2-diaza-1,3-butadienes,[1] and that these heterodienes react very easily with nucleophilic reagents through a conjugate addition (1,4-addition),[1] we envisaged the use of hydrazonoalkyl-phosphine oxides and -phosphonates (**III**, Scheme 1, $X = NNHR$, $P = POPh_2$, $PO(OEt)_2$) as starting materials for the preparation of functionalized hydrazones containing a nucleophilic substituent **V**

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* Corresponding author. Tel.: +34-945-013103; fax: +34-945-013049; e-mail: qoppagaf@vf.ehu.es

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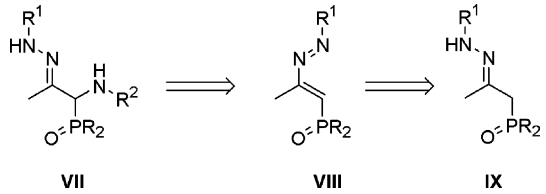
(X = NNHR), through a sequence involving halogenation with formation of an α-halogenated hydrazone **VI**, subsequent formation of aza-alkene **II**, and Michael addition of nucleophiles to the heterodiene (Scheme 1). Therefore, by means of this strategy the umpolung reaction in the Cα of the phosphonate (phosphine oxide) group could be achieved favouring the introduction of nucleophiles in order to prepare functionalized hydrazones or their synthetic equivalent carbonyl compounds **V** (Scheme 1).

This strategy could present special interest for the introduction of amino substituents (Scheme 1, NuH = RNH_2) in the Cα-carbon atom of hydrazones, because we could obtain azapeptides,[12] or α-aminophosphonates. It is noteworthy, that α-aminophosphonates[13,14] are important substrates in organic and medicinal chemistry because they can be considered as surrogates of α-aminoacids[15a] and have been used as haptens for the generation of catalytic antibodies,[15b] as antibacterial agents,[15c] or as phosphapeptide enzyme inhibitors.[15d]

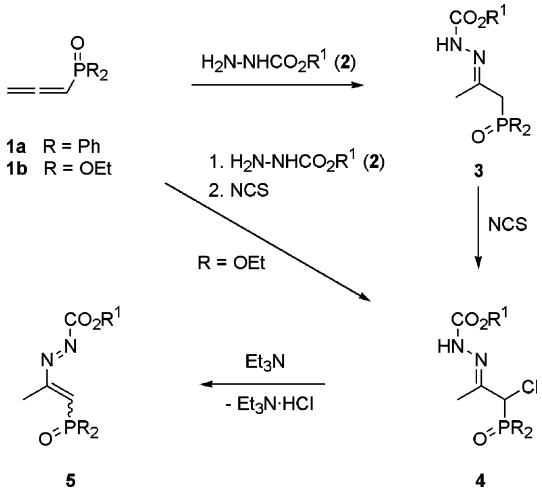
For this reason, in this communication we wish to describe a novel strategy for the preparation of functionalized α-aminophosphonates **VII** from hydrazones **IX**, involving nucleophilic addition of amines to 1,2-diaza-1,3-butadienes **VIII** as shown in Scheme 2. This Michael addition is also described for the first time in the case of phosphorus substituted aza-alkenes and, as far as we know, is the first reported example of conjugative addition of nucleophiles to chiral aza-alkenes.

The required functionalized β-hydrazones were prepared by the reaction of allenic phosphine oxide **1a** (R = Ph) or phosphonate **1b** (R = OEt) with carbazates **2**, in a similar way to that previously reported for simple hydrazines.[10c] Addition of ethoxycarbonylhydrazide **2a** (R^1 = Et) to allene **1a** in refluxing chloroform (*TLC* control) led to the formation of *anti*-β-hydrazono phosphine oxide **3aa** (Scheme 3, Table 1, entry 1). The process was extended to allene derived from phosphonate, and this allene **1b** reacted also with hydrazide **2a** and with (−)-menthyl carbazate **2b** (R^1 = (−)-menthyl)[16] to give β-hydrazono phosphonates **3ba** and **3bb** (Scheme 3, Table 1, entries 2 and 3).

Then, we used these hydrazones **3** for the preparation of 1,2-diaza-1,3-butadienes **5**. Chlorohydrazone **4aa** (R = Ph; R^1 = Et) was prepared from β-hydrazone **3aa** by treatment with 1 equiv of *N*-chlorosuccinimide (NCS) in carbon tetrachloride at room temperature (Scheme 3, Table 1, entry 4). In the case of chlorohydrazone derived from phosphonates, these hydrazones were directly prepared from allene **1b** and crude products **3ba** and **3bb** were treated without isolation with one equivalent of NCS in refluxing chloroform to give chlorohydrazone **4ba** and optically active hydrazone **4bb** (Scheme 3, Table 1, entries 5 and 6) in moderate yield.



Scheme 2.



Scheme 3.

Table 1. Synthesis of hydrazones **3** and **4**

Entry	Compound	R	R^1	Yield (%)
1	**3aa**	Ph	Et	92[a]
2	**3ba**	OEt	Et	76[b]
3	**3bb**	OEt	(−)-Ment	93[b]
4	**4aa**	Ph	Et	70[a]
5	**4ba**	OEt	Et	47[c]
6	**4bb**	OEt	(−)-Ment	43[c]

[a] Yield of isolated purified compounds **3** and **4**.
[b] Conversion calculated by ^{31}P NMR of the crude reaction mixture.
[c] Yield of isolated purified compounds **4** in a 'one pot' reaction from allene **1b**.

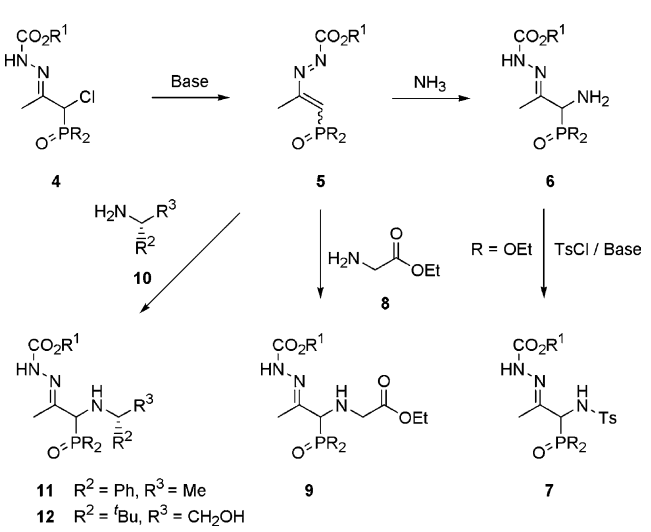
1,2-Diaza-1,3-butadienes **5** were synthesized from chlorohydrazones **4** in the presence of bases. The addition of an excess (1.2 equiv) of triethylamine to a solution of functionalized chlorohydrazones **4** in dichloromethane underwent 1,4-elimination of HCl and led to the formation of the highly coloured 4-phosphinyl- or 4-phosphonyl-1-alkoxycarbonyl-1,2-diaza-1,3-butadienes **5**[17] in almost quantitative yield (>99%) (Scheme 3). Diazaalkenes **5** proved to be unstable to chromatography, and were therefore not isolated. The presence of diazabutadienes **5** in the crude reaction mixtures was confirmed by NMR spectroscopy and showed that they were obtained as a mixture of the *E*- and *Z*-isomers (**5aa** in a ratio 85:15, **5ba** and **5bb** in 90:10). 1,2-Diaza-1,3-butadienes **5** were used 'in situ' without isolation in subsequent Michael additions.

The presence of electron-poor groups on terminal nitrogen atom of the azo-ene system of 1,2-diaza-1,3-butadienes favoured the Michael addition of nucleophilic reagents on the terminal carbon atom (1,4-addition), and electron-withdrawing groups enhance

the electrophilic character of this atom.[1] Some conjugative addition of amines to 1,2-diaza-1,3-butadienes has been reported.[18] However, neither Michael additions of nucleophiles to phosphorus substituted 1,2-diaza-1,3-butadienes nor nucleophilic additions to chiral 1,2-diazadienes have been reported. For these reasons, we explored the addition of amine derivatives to phosphorus-substituted 1,2-diaza-1,3-butadienes **5**. In addition, this strategy could be useful for the preparation of functionalized α-aminophosphonate derivatives **VII** (Scheme 2).

We explored the addition of ammonia to 1,2-diazadiene **5aa** (R = Ph, R^1 = Et) generated 'in situ' from chlorohydrazone **4aa**. When ammonia gas was bubbled through a solution of chlorohydrazone **4aa** in chloroform, the reaction mixture became red, showing the formation of 1,2-diazadiene **5aa**. The red colour disappeared very fast (<10 min) and TLC control showed the end of the reaction with the formation of only the *anti*-α-amino phosphine oxide **6aa** in good yield (Scheme 4, Table 2, entry 1). The formation of *anti*-α-amino phosphine oxide **6aa** could be explained by selective Michael addition (1,4-addition) of ammonia to conjugated diazaalkene **5aa** (Scheme 4). Then, the process was extended to 4-phosphonyl-1,2-diaza-1,3-butadiene **5bb**. However, in this case, after the addition of ammonia, α-amino phosphonate **6bb** (R = OEt; R^1 = (−)-Ment) was not isolated being very unstable, although its protection with tosyl chloride in the presence of base, made possible the isolation of the corresponding α-tosylamino phosphonate **7bb** as a 1:1 mixture of diastereisomers[19] (Scheme 4, Table 2, entry 2). Fast interconversion of the starting *E*- and *Z*-isomers could explain the formation of a 1:1 ratio of both diastereoisomers. This result suggests also that the chiral group on the nitrogen atom of the 1,2-diaza-diene is distant from the reaction centre (C-4 atom) with little influence on it.

We also studied the addition of primary amines to azoalkenes **5**. The addition of ethyl glycinate **8** to 1,2-diaza-1,3-butadienes **5**, generated 'in situ' from chlorohydrazones **4** and triethylamine, led to the formation of functionalized *anti*-α-aminophosphorus derivatives **9** in excellent yield[20] (Scheme 4, Table 2, entries 3–5). When chiral diazadiene **5bb** was used, a diastereoisomeric ratio 1:1 of *anti*-α-amino-phosphonate **9bb** (R = OEt; R^1 = (−)-Ment) was obtained. These new functionalized α-aminophosphonates **9ba** and **9bb** derived from α-aminoesters can be considered as 'phospha-depsipeptides' and could be interesting substrates in medicinal chemistry.[13b]



Scheme 4.

Table 2. Synthesis of functionalized α-aminophosphorus derivatives **6**, **7**, **9**, **11** and **12**

Entry	Compound	R	R^1	Yield
1	**6aa**	Ph	Et	68
2	**7bb**	OEt	(−)-Ment	43[b]
3	**9aa**	Ph	Et	89
4	**9ba**	OEt	Et	99
5	**9bb**	OEt	(−)-Ment	92
6	**11aa**	Ph	Et	79
7	**11bb**	OEt	(−)-Ment	83
8	**12aa**	Ph	Et	81
9	**12bb**	OEt	(−)-Ment	91

[a]Yield of isolated purified compounds.
[b]Yield of isolated purified compound **7bb** from hydrazone **5bb**.

Finally, we studied the diastereoselective addition of optically active amines **10** to phosphorylated 1,2-diaza-1,3-butadienes **5**. Very low diastereoselection (de <10%) was observed when (*R*)-benzylmethylamine **10a** (R^2 = Ph; R^3 = Me) was treated with azoalkenes **5aa** and **5bb**. Adducts **11** were obtained as nonseparable diastereoisomeric mixtures and very low diastereomeric excess (<10%) was observed (Scheme 4, Table 2, entries 6 and 7). However, a better diastereoselection was observed when a bulky aminoalcohol such as *tert*-leucinol was used. Reaction of (*S*)-*tert*-leucinol **10b** (R^2 = ^{t}Bu; R^3 = CH_2OH) with **5aa** and **5bb** gave compounds **12** obtained as before as nonseparable diastereoisomeric mixtures and quite good diastereoselective excess (>63%) was observed (Scheme 4, Table 2, entries 8 and 9). The bulky group and the presence of the hydroxyl group seem to control the diastereoselective addition of the aminoalcohol to the diaza-diene system.

In conclusion, the first synthesis of 1-alkoxycarbonyl-1,2-diaza-1,3-butadienes containing a phosphine oxide group **5aa** or a phosphonate group **5ba** in position 4, as well as of the chiral 1-(−)-menthyloxycarbonyl-4-phosphonyl-1,2-diaza-1,3-butadienes **5bb**, is described. The process implies 1,4-elimination of HCl from chlorohydrazones **4** in the presence of amines. Michael addition of ammonia, aminoesters and optically active amines on phosphorylated 1,2-diaza-1,3-butadienes **5** is reported also for the first time and functionalized α-aminophosphonates **6**, **7**, **9**, **11** and **12** are obtained in good yields. These hydrazonoalkyl-α-aminophosphonate derivatives may be important synthons in organic synthesis and for the preparation of biologically active compounds of interest to medicinal chemistry.[12–15]

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16. (−)-Menthyl carbazate was prepared by addition of a solution of (−)-menthyl chloroformate in dichloromethane to a solution of hydrazine hydrate in dichloromethane in the presence of CCl_4, K_2CO_3 and triethylbenzylammonium chloride.
17. General procedure for **5**: to a room temperature solution of chlorohydrazone **4** (5.00 mmol) in dry CH_2Cl_2 (25 mL), triethylamine (0.85 mL, 6.00 mmol) was added dropwise under a nitrogen atmosphere. The mixture was stirred at this temperature for 45 min. The crude mixture was diluted with CH_2Cl_2 (20 mL), washed with H_2O (2×20 mL) and the aqueous phase was extracted twice with CH_2Cl_2 (10 mL). The solvent was dried over $MgSO_4$ and evaporated under vacuum. Diaza-alkenes **5** proved to be unstable to chromatography and was then used in the next steps without further purification. The identity of products **5** was confirmed by NMR data.
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19. Diastereoisomeric excess were measured by ^{31}P NMR on the crude reaction mixture.
20. General procedure for the addition of amine derivatives to azo-alkenes **5**: to a stirred solution of chlorohydrazone **4** (1.00 mmol) in CH_2Cl_2 (5 mL), Et_3N (0.21 mL, 1.50 mmol) was added at room temperature and under nitrogen atmosphere. The mixture was stirred at room temperature for 15–45 min and a solution of primary amine (1.20 mmol) in CH_2Cl_2 (5 mL) was then added at the same temperature. The reaction mixture was stirred at room temperature for 20–120 min. The crude mixture was diluted with CH_2Cl_2 (10 mL), washed with H_2O (2×5 mL) and the aqueous phase was extracted twice with CH_2Cl_2 (5 mL). The organic layer was dried over $MgSO_4$ and evaporated under vacuum and the crude product was purified by flash-chromatography (silica gel). The identity of products **6**–**12** was confirmed by NMR data, IR, MS and elemental analyses.