Umpolung in Allylic Phosphonates. Regio- and Stereo-selective Synthesis of (*E*)-γ-Amino-α,β-unsaturated Phosphonates by Palladium-Catalysed Reaction of Allylic Acetoxy Phosphonates

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γ-Amino-α,β-unsaturated phosphonates have been synthesized regio- and stereo-selectively in high yield by the reaction of allylic α-acetoxy phosphonates with secondary amines catalysed by palladium.

The synthesis of a group of microbial metabolites containing γ-amino phosphonic acid functions has attracted increasing interest because of the unique biological properties of these substances.[1,2] Recently, we have studied the umpolung reactivity of allylic phosphonates and the use of allylic α-acetoxy phosphonates (readily obtained from α,β-unsaturated aldehydes)[3] as precursors of allylic phosphonate cations.[4] We now report the synthesis of γ-amino-α,β-unsaturated phosphonic acid derivatives (closely related to the naturally occurring microbial metabolites) from allylic α-acetoxy phosphonates.

The following procedure is typical. To a solution of piperidine (1.41 mmol), triethylamine (1 ml), and tetrakis(triphenylphosphine)palladium (0.04 mmol) in tetrahydrofuran (THF) (5 ml), diethyl α-acetoxyallylphosphonate (**1a**) (1.31 mmol) was added with a syringe under prepurified nitrogen. The mixture was stirred at room temperature for 2 h. After the usual work-up, the crude product was purified by column chromatography on silica gel (ethyl acetate–methanol), then distilled *in vacuo* (yield 330 mg, 97%).

Thus the electron-withdrawing phosphonyl group shows a decisive effect on the regioselectivity of this reaction; nucleophilic attack by the secondary amine takes place at the electron-deficient side, *i.e.* at the γ-position of the α,β-unsaturated phosphonate. Reactivities and yields were sensitive to the structure of the reactants and amines used. The yield was low when di-isopropylamine was used as nucleophile; furthermore, no amination product but only the rearrangement product, diethyl 3-acetoxyprop-1-enyl phosphonate, was obtained when hexamethyldisilazane was used. These observations may be due to the low nucleophilicity of the amines. High yields were obtained from the reaction of (**1a**) with piperidine even at room temperature, but a higher temperature was required for the reaction of (**1b**) and piperidine (*cf.* Table 1, entries 5 and 8). Only the *N*-allylation product was isolated from (**1a**) and (+)-(1*S*,2*R*)-ephedrine, indicating that the reaction is also chemoselective. From the reaction of (**1b**) and methyl prolinate at 65 °C for 2 h, a mixture of two diastereoisomers was obtained in the ratio 1 : 1, implying that no chiral induction was brought about by the

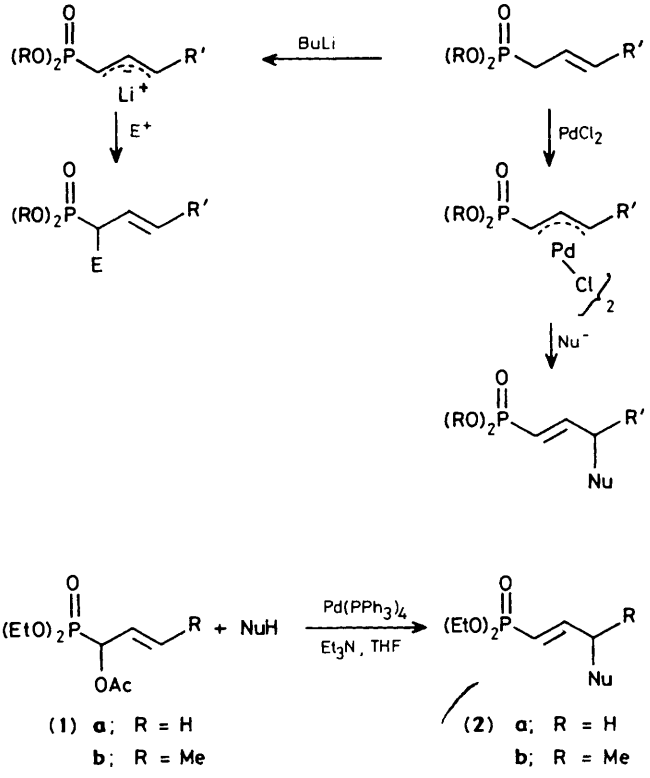

Table 1. γ-Amino-α,β-unsaturated phosphonates prepared.

Entry	Allylic acetoxy phosphonate	Amine (NuH)	*T*/°C (*t*/h)	Product (**2**)[a] *E* : *Z*[b]	Product (**2**)[a] Isolated yield (%)
1	(**1a**)	Et_2NH	25(2)	95 : 5	83
2	(**1a**)	Pr^i_2NH	25(12)	98 : 2	39
3	(**1a**)	Pr^i_2NH	65(5)	98 : 2	56
4	(**1a**)	$(Me_3Si)_2NH$	65(3)	100 : 0[c]	100[b]
5	(**1a**)	Piperidine	25(2)	95 : 5	97
6	(**1a**)	Pyrrolidine	25(12)	98 : 2	77
7	(**1a**)	Morpholine	25(15)	90 : 10	46
8	(**1b**)	Piperidine	25(10)		0[d]
9	(**1b**)	Piperidine	65(3)	85 : 15	65
10	(**1a**)	Ephedrine[e]	65(3)	98 : 2	83
11	(**1a**)	Methyl (−)-(*S*)-prolinate	65(8)	67 : 33[f]	62

[a] All products gave satisfactory ^1H n.m.r., i.r., and mass spectral data. [b] Determined by ^1H n.m.r. [c] Diethyl 3-acetoxyprop-1-enyl phosphonate. [d] Starting material was recovered. [e] (+)-(1*S*,2*R*)-Ephedrine. [f] Isolated ratio of the isomers.

chiral proline group. The products obtained were mainly of *E*-configuration; thus the reaction is regio- and stereo-selective and provides a convenient way to synthesize the title compounds.

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