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Aziridination of α,β-unsaturated phosphonic esters

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Abstract—Synthetic precursors of amino phosphonic acids are aziridinyl phosphonates. These compounds can be prepared through a reaction of phosphonates **2a–e** with $NsONHCO_2Et$ and inorganic bases involving addition of an (ethoxycarbonyl)amino group onto the double bond, via a new and easy procedure.

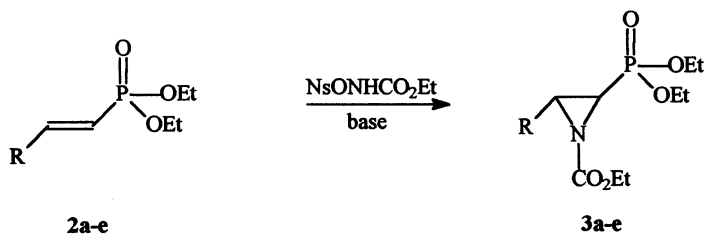
During the last few years, an increased interest has been shown in amino phosphonic acids and in their derivatives:[1] these compounds can be introduced into biologically active peptidic chains as antibacterial agents,[2] enzyme inhibitors[3] and as haptenes for catalytic antibodies.[4]

For many years our research group has been involved in a study of aziridination with a particular reagent: ethyl *N*-{[(4-nitrobenzene)sulphonyl]oxy}carbamate ($NsONHCO_2Et$) **1**. With Et_3N in homogeneous solutions of CH_2Cl_2[5] it shows good reactivity with electron-rich alkenes.[6] The use of **1** and inorganic insoluble bases such as CaO or K_2CO_3 permitted us to introduce the aziridine ring onto electrophilic olefins such as nitro olefins[7] and α,β-unsaturated esters,[8] obtaining in this last case aziridine-1,2-dicarboxylates.

Aziridine-2-carboxylates are important building blocks for the synthesis of α- or β-amino acids because they can undergo highly regiocontrolled ring-opening reactions.[9] Aziridine-2-phosphonates are expected to play a similar role in the synthesis of α- or β-amino phosphonates.[9] There are only a few reports of the synthesis of aziridinyl phosphonates starting from vinyl phosphonates.[10] In this communication we report the first results obtained from the aziridination of α,β-unsaturated phosphonic esters by **1**.

Substrates **2a–e** were obtained via Wittig–Horner reactions,[11] starting from the corresponding aldehyde. The aziridination reactions were carried out with generation of the (ethoxycarbonyl)nitrene by α-elimination of **1** with Et_3N, and gave only traces of aziridines **3**. Conversely, using **1** and CaO in excess, as in the procedures for aziridination of α,β-unsaturated esters[8] and nitro derivatives,[7] the expected aziridine derivatives **3a–e** were isolated (Scheme 1).

The products were easily separated by flash-chromatography on silica gel with hexane–ethyl acetate mixture in the yields reported in Table 1. Unreacted starting mate-



2a-e **3a-e**

Scheme 1.

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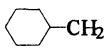
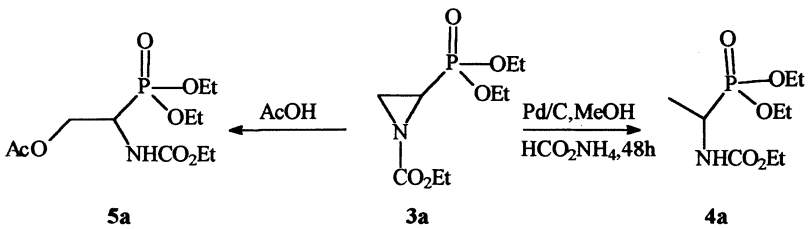
Table 1. Aziridination of phosphonates **2a–e**

2	R	Conditions	3 Yield %	^{1}H NMR aziridine protons
a	H	A[a]	40	δ 2.5–2.7 (m, 3H)
a	H	B[b]	45	
b	CH_3	A	20	δ 2.35 (dd, 1H, J=17.6, 3.5 Hz); 2.85 (m, 1H)
b	CH_3	B	25	
c	CH_3 $(CH_2)_4$	A	14	δ 2.34 (dd, 1H, J=18.0, 3.6 Hz); 2.78 (m, 1H)
c	CH_3 $(CH_2)_4$	B	24	
d	Ph	A	Traces	
d	Ph	B	N.r.	
e		A	20	δ 2.32 (dd, 1H, J=18.2, 3.6 Hz); 2.85 (m, 1H)

[a] A. Substrate:$NsONHCO_2Et$:CaO = 1:7:7, CH_2Cl_2 0.8 ml/mmol reagent, room temperature, 24 h.
[b] B. Substrate:$NsONHCO_2Et$:CaO = 1:4:4, in a mortar without solvent, room temperature, 5 h.



Scheme 2.

rial was partially recovered. Each aziridine was characterised by GC–MS, IR, ^{1}H and ^{13}C NMR analysis, and spectroscopic data are in agreement with the reported structures.[12] The stereochemistry of the vinyl phosphonate is retained in the products.

The results obtained compare to another example of aziridination via Michael addition[13] in reactions of electron-poor olefins with $NsONHCO_2Et$ and CaO. Furthermore, the method of synthesis proposed is a very simple one; it permits, starting from β-alkyl substituted vinyl phosphonates, in a few easy steps and with low cost reagents, one to obtain aziridine-2-phosphonates, useful intermediates in phosphonopeptide synthesis. This method appears to be complementary to that of Kim,[10] which is useful for aziridination of β-aryl substituted vinyl phosphonates.

As for aziridine-2-carboxylates,[9] aziridine 2-phosphonates **3** can give ring-opening reactions to form α- or β-amino phosphonic acid derivatives. Our first attempts at ring opening of **3a** by catalytic transfer hydrogenation in the presence of 10% Pd(0)/C and ammonium formate[10] gave the α-amino phosphonate **4a** and by using AcOH[14] (60°C, 8 h) the β-acetoxy-α-amino derivative **5a** was obtained in good yields (Scheme 2).

This method will be applied to vinyl phosphonates of chiral alcohols because of the importance of chiral aziridines in organic synthesis.[15]

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12. For example **3b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22–1.41 (m, 12H, CH_2CH_3 and $CHCH_3$); 2.35 (dd, 1H, CHP, $J_{HP}=17.6$ Hz, $J_{HH}=3.5$ Hz); 2.85 (m, 1H, $CHCH_3$); 4.10–4.28 (m, 6H, OCH_2). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.32 ($COCH_2CH_3$); 15.93 ($CHCH_3$); 16.41 ($POCH_2CH_3$, $J_{CCOP}=5.8$ Hz); 36.41(CHP, $J_{CP}=199$ Hz); 37.53 ($CHCH_3$, $J_{CCP}=3.4$ Hz; 62.51 ($POCH_2$ $J_{COP}=5.2$ Hz); 63.15 ($COCH_2$); 160.2 (CO); IR (CCl_4) 1707, 1738 cm^{-1}; GC–MS: m/z 265 [M$^+$] (3%), 56 (100%).
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