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Synthetic Applications of Vinyliminophosphoranes Based on the Reactivity of the Vinyl Side Chain. Preparation of Dihydropyridines

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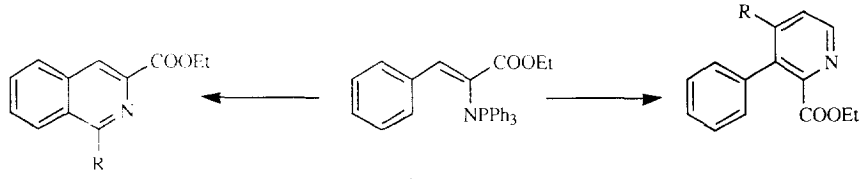
Abstract: New reactions of vinyliminophosphoranes with aldehydes involving an initial nucleophilic attack of the β-carbon atom of the vinyl side chain on the carbonylic carbon atom is reported. The resulting betaines undergo either intra- or intermolecular cyclization to give pyridines or dihydropyridines.

Vinyliminophosphoranes have been shown to be useful building blocks for the synthesis of nitrogen-containing heterocycles[1]. Vinyliminophosphoranes may be considered to be an equivalent of enamine and to contain two nucleophilic centers at the β-carbon atom of the vinyl side chain and the nitrogen atom of the iminophosphorane portion. Thus, unsubstituted vinyliminophosphoranes undergo a single step annulation with compounds containing two electrophilic centers such as α,β-unsaturated ketones[2], α,β-unsaturated aldehydes[3], and related Michael acceptors[4] to give several kinds of azaheterocycles by a Michael-type addition followed by proton transfer to generate an intermediate iminophosphorane, intramolecular aza-Wittig reaction, or by an aza-Wittig reaction lead to an intermediate azatriene, which undergoes a thermal 6π-electrocyclization[5]. Similarly, vinyliminophosphoranes of type **1** reacted with aliphatic, aromatic and heteroaromatic aldehydes to give the corresponding 2-azahexatriene, which underwent electrocyclic ring-closure followed by dehydrogenation to give pyridines[6] or isoquinoline derivatives[7] **2**. However, the reaction with α,β-unsaturated aldehydes provided 3-arylpyridines[8] **3**.



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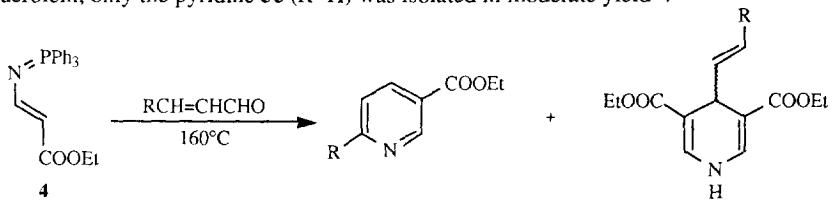
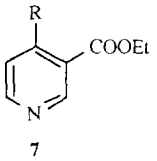
In this context, we wish to report herein that the behaviour of the vinyliminophosphorane **4**, bearing an ethoxycarbonyl group at the β-position, towards aldehydes is completely different from that previously reported for unsubstituted vinyliminophosphoranes and even for the closed related vinyliminophosphoranes **1**.

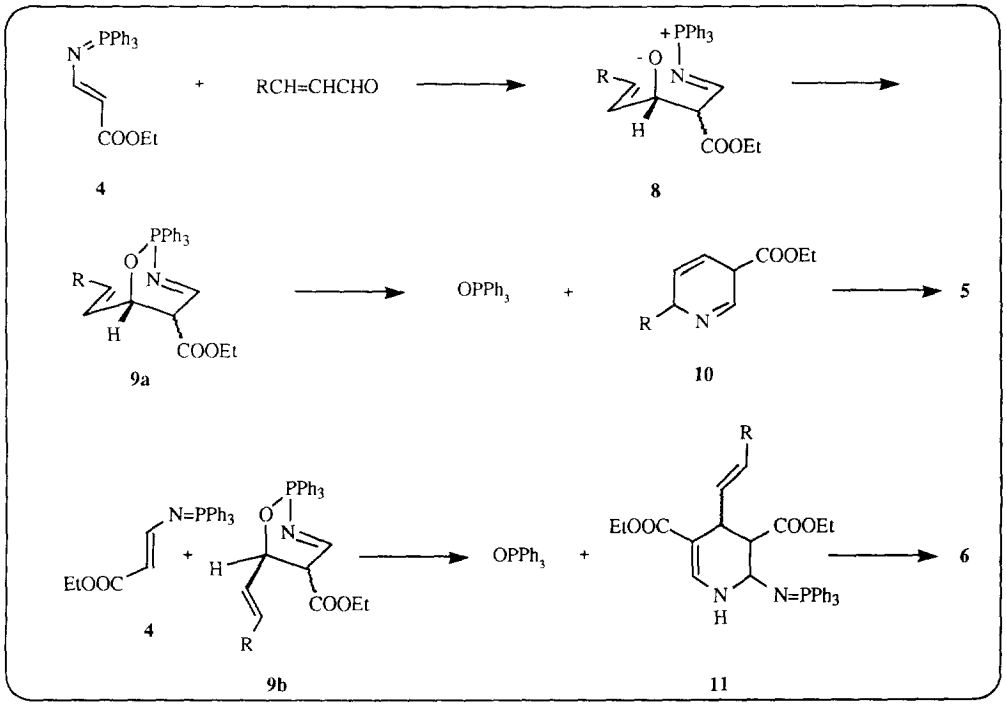
Vinyliminophosphorane **4** was readily prepared in 79% yield by Staudinger reaction of ethyl β-azidoacrylate[9] with triphenylphosphine at room temperature. In the ^{1}H n.m. r. spectrum, the chemical shifts of the vinylic protons and the vicinal H-H coupling constant ($^3J_{H\text{-}H}$=12.6 Hz) suggested that both protons were relatively *trans*[10]. Compound **4** reacted with α,β-unsaturated aldehydes in *o*-xylene at 160°C, in the presence of palladium on charcoal, in a sealed tube to give a mixture of pyridine **5** and dihydropyridine **6**, instead of the expected pyridine **7**. From the reaction with acrolein, only the pyridine **5e** (R=H) was isolated in moderate yield[11].





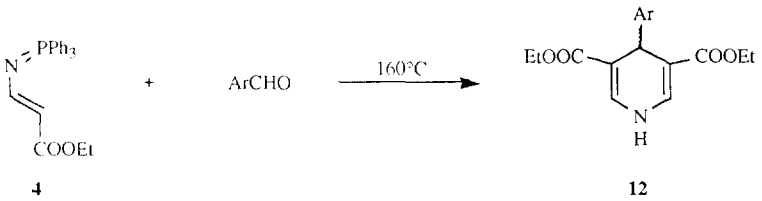
Compound	R	5 (%)	6 (%)
a	C_6H_5	33	44
b	4-ClC_6H_4	30	40
c	2-$O_2NC_6H_4$	30	46
d	2-$H_3COC_6H_4$	31	38
e	H	42	-

These findings are in clear contrast with the recently reported behaviour of this kind of vinyliminophosphoranes towards carbonyl compounds, such as ethyl glyoxalate, diethyl ketomalonate and pyruvonitrile, to give substituted 2-azadienes[12].



Formation of compounds **5** and **6** could be rationalised in terms of an initial addition of the β-carbon atom of the iminophosphorane **4** to the carbonyl carbon atom of the α,β-unsaturated aldehyde to give the betaine **8**, which cyclised to give the isomeric 1,2,5-oxaazaphosphanes **9**. The *endo* isomer **9a** underwent intramolecular cyclization with concomitant elimination of triphenylphosphine oxide to give the dihydropyridine **10**, which was dehydrogenated under the reaction conditions to give **5**. Regiospecific attack of a second molecule of the iminophosphorane **4** on the *exo* isomer **9b** with loss of triphenylphosphine oxide provided the tetrahydropyridine **11**. Subsequent elimination of triphenylphosphinimine afforded the dihydropyridine **6**, which was surprisingly stable under the reaction conditions.

Dihydropyridines were also formed from the reaction of iminophosphorane **4** with aromatic aldehydes. In this case, dihydropyridines **12** were prepared in moderate yields (40-43%), as the only reaction product, under the above-mentioned conditions[13]. Formation of compounds **12** could follow a pathway similar to the conversion **9**→**6**.



4 **12**

Compound	Ar	12 (%)
a	4-$H_3CC_6H_4$	43
b	4-ClC_6H_4	40
c	4-$H_3COC_6H_4$	40
d	2-$H_3COC_6H_4$	41

In conclusion, the reactivity of vinyliminophosphoranes, bearing an ethoxycarbonyl group as substituent, strongly depends on the relative position of the substituents on the vinylic chain. When both functionalities are placed at the same carbon atom, the reaction takes place via an aza-Wittig process. However, when they are placed on different carbon atoms, the reaction is initiated by nucleophilic attack of the β-carbon of vinylic side chain on the carbonyl group (charge-controlled reaction). This unprecedented behaviour of vinyliminophosphoranes towards aldehydes opens a new way to the preparation of a wide variety of dihydropyridines[14].

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11. General Procedure: A mixture of iminophosphorane **4** (0.75 g, 2 mmol) the appropiate α,β-unsaturated aldehyde (2 mmol), palladium on charcoal (0.053g) and dry *o*-xylene (35 ml) was heated at 160 °C in a sealed tube for 24 h. After cooling the mixture was filtered and the filtrate concentrated to dryness. The crude product was chromatographed on a silica gel column using ethyl acetate/ dicloromethane (1:7) as eluent to give the pyridine **5** and the dihydropyridine **6**, which were recrystallized from dichloromethane/ diethylether/ n-hexane (1:2:1).

    Compound **5d** (R=2-$H_3COC_6H_4$); 31% yield, m. p. 51-52°C colourless prisms. ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 1.41 (t, 3H, *J*=7.1 Hz, CH_3CH_2O), 3.86 (s, 3H, CH_3O), 4.42 (q, 2H, *J*=7.2 Hz, CH_3CH_2O), 7.01 (d, 1H, *J*=8.3 Hz, aromatic H-3), 7.09 (td, 1H, *J*=7.5, 0.9 Hz, aromatic H-5), 7.41 (td, 1H, *J*=8.3, 1.3 Hz, aromatic H-4), 7.86 (dd, 1H, *J*=7.7, 1.8 Hz, aromatic H-6), 7.95 (dd, 1H, *J*=8.4, 0.7 Hz, H-3), 8.29 (dd, 1H, *J*=8.3, 2.1 Hz, H-4), 9.29 (dd, 1H, *J*=1.9, 0.5 Hz, H-6); ^{13}C n.m.r. (50.3 MHz, $CDCl_3$) δ 14.3 (CH_3CH_2O), 55.6 (CH_3O), 61.2 (CH_3CH_2O), 111.5 (aromatic C-3), 121.1 (C-3), 124.0 (C-5), 124.5 (aromatic C-5), 128.1 (aromatic C-1), 130.8 (aromatic C-6), 131.3 (aromatic C-4), 136.6 (C-4), 150.5 (C-6), 157.2 (aromatic C-2), 159.7 (C-2), 165.5 (C=O); EI MS m/z (%): 257 (M^+, 33), 152 (100).

    Compound **6d** (R=2-$H_3COC_6H_4$); 38% yield, m. p. 119-121°C colourless prisms. ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 1.27 (t, 6H, *J*=7.1 Hz, CH_3CH_2O), 3.78 (s, 3H, CH_3O), 4.18 (m, 4H, CH_3CH_2O), 4.55 (d, 1H, *J*=6.5, H-4), 6.27 (dd, 1H, *J*=16.1, 6.5 Hz, vinylic H_α), 6.55 (t, 1H, *J*=5.0 Hz, NH), 6.66 (d, 1H, *J*=16.1 Hz, vinylic H_β), 6.79-6.90 (m, 2H, aromatic H-3+H-5), 7.15 (td, 1H, *J*=7.7, 1.5 Hz, aromatic H-4), 7.28 (d, 2H, *J*=5.4 Hz, H-2), 7.39 (dd, 1H, *J*=7.6, 1.5 Hz, aromatic H-6); ^{13}C n.m.r. (50.3 MHz, $CDCl_3$) δ 14.4 (CH_3CH_2O), 34.4 (C-4), 55.5 (CH_3O), 60.1 (CH_3CH_2O), 106.7 (C-3), 110.9 (aromatic C-3), 120.6 (aromatic C-5), 124.5 (C_β), 126.6 (aromatic C-6), 126.7 (aromatic C-1), 128.1(aromatic C-4), 132.7 (C_α), 134.3 (C-2), 156.6 (aromatic C-2), 167.3 (C=O); EI MS m/z (%): 357 (M^+, 23), 168 (100).
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13. Compound **12d** (R=2-$H_3COC_6H_4$); 40% yield, m. p. 135-138 °C colourless prisms. ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 1.08 (t, 6H, *J*=7.1 Hz, CH_3CH_2O), 3.76 (s, 3H, CH_3O), 3.83-4.07 (m, 4H, CH_3CH_2O), 5.14 (s, 1H, H-4), 6.72-6.81 (m, 3H, NH+ aromatic H-3+H-5), 7.05 (td, 1H, *J*=7.8, 1.7 Hz, aromatic H-4), 7.18-7.23 (m, 3H, H-2+ aromatic H-6); ^{13}C n.m.r. (50.3 MHz, $CDCl_3$) δ 14.2 (CH_3CH_2O), 32.4 (C-4), 55.6 (CH_3O), 59.8 (CH_3CH_2O), 107.9 (C-3), 110.8 (aromatic C-3), 120.3 (aromatic C-5), 127.6 (aromatic C-6), 131.1 (aromatic C-4), 134.4 (C-2), 135.6 (aromatic C-1), 157.1 (aromatic C-2), 167.6 (C=O); EI MS m/z (%): 331 (M^+, 13), 302 (100), 68 (80).
14. Satisfactory ^{1}H, ^{13}C n.m.r., mass spectra and elemental analysis were obtained for all new compounds.

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