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New Synthetic Applications of Vinyliminophosphoranes Based on the Reactivity of the Vinyl Side Chain

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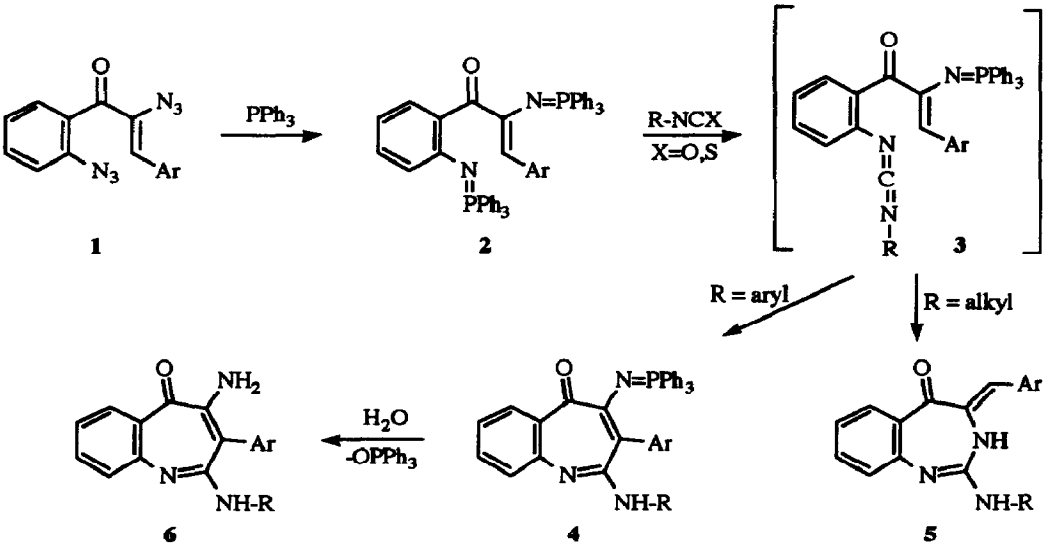
Abstract: New reactions of vinyliminophosphoranes involving either the β-carbon atom of the vinyl side chain as nucleophilic center or the α-carbon as electrophilic center are described

The utility of vinyliminophosphoranes for the synthesis of nitrogen-containing heterocycles has recently been demonstrated convincingly[1]. Spectroscopic and theoretical data of this sort of compounds revealed a high electron density on the β-carbon atom and enhanced nucleophilicity of the vinyl moiety[2]. On this basis, vinyliminophosphoranes may be considered to be an equivalent of enamine and to contain two nucleophilic centers at the β-carbon atom and the iminophosphorane portion. Thus, vinyliminophosphoranes undergo a single step annulation with compounds containing two electrophilic centers such as α,β-unsaturated ketones[3] and related Michael acceptors[4] to give several kinds of azaheterocycles through an enamine-type carbon-carbon bond formation and subsequent aza Wittig reaction. However, vinyliminophosphoranes react with iso(thio)cyanates across the iminophosphorane moiety in an aza Wittig-type fashion to give conjugated carbodiimides which undergo inter-[5] or intramolecular[6,7] [4+2] heteroDiels-Alder cycloadditions to give pyridine derivatives, some of them of valuable biological interest.

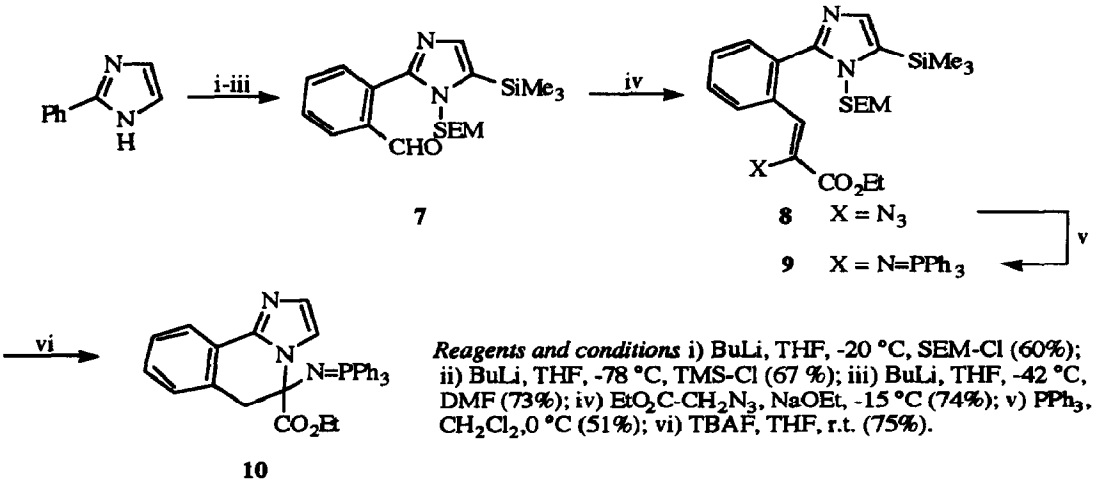
We wish to report herein some unprecedent reactions of vinyliminophosphoranes involving the vinyl side chain as the only reaction center, the iminophosphorane group remaining unaffected. These reactions, which involve either nucleophilic attack of the β-carbon atom of the vinyl side chain on the *sp*-hybridized carbon atom of a carbodiimide group or nucleophilic attack of nitrogen compounds on the α-carbon of the vinyl portion, in their intramolecular versions, have been found to be a useful method for the construction of highly functionalized six- and seven-membered nitrogen heterocycles. One especially noteworthy feature of these methodologies is that the iminophosphorane group, having served so well in the cyclization step, leaves the scene in the last step to provide amino-substituted nitrogen-containing heterocycles.

In order to explore the availability of the β-carbon atom of the iminophosphorane group to undergo electrophilic attack, the carbodiimide functionality was choosen as suitable electrophilic partner, due to the fact that this heterocumulenic system is able to undergo nucleophilic attack by the action of phosphonium ylides and related[8]. To this end a vinyliminophosphorane bearing a carbodiimide moiety placed at an appropriate position was selected as model. The requisite bisazide **1** was easily prepared by the following three-step sequence: a) aldol condensation between *o*-azidoacetophenone and *p*-tolualdehyde in the absence of solvent[9] provided the corresponding chalcone (68%); b) reaction with iodine azide[10] in acetonitrile lead to the iodine azide adduct (85%); and c) further treatment with sodium azide in DMF[11] furnished **1** (35%). Staudinger reaction of **1** with two equiv of triphenylphosphine in dry dichloromethane at room temperature gave the bis(iminophosphorane) **2** in 98% yield. Aza Wittig-type reaction of **2** with one equiv of aromatic isocyanates or isothiocyanates in dry dichloromethane at room temperature led to **4** whereas with aliphatic isocyanates under the same reaction

conditions provided **5**. In compounds **4** the remaining iminophosphorane group was easily removed by treatment with aqueous ethanol to give **6**[12]. This sequence provides direct access to the otherwise not readily available 5H-1-benzazepin-5-ones[13] in a one-step process. In general, this annulation reaction proceeded without complications for a range of aromatic isocyanates. Conversions **2** → **4** and **2** → **5** involve an initial aza Wittig-type reaction between the iminophosphorane moiety directly linked to the aromatic ring and the isocyanate to give a intermediate carbodiimide **3**, which undergoes cyclization by nucleophilic attack either of the β-carbon atom of the vinyliminophosphorane portion (R=aryl) or by the nitrogen atom of the iminophosphorane moiety (R=alkyl) on the central carbon atom of the carbodiimide, followed by hydrolytic cleavage of the phosphonium group during the workup[14]. Both conversions also showed the preferential reactivity of aryliminophosphorane groups with respect to vinyl iminophosphoranes in aza Wittig-type reactions towards isocyanates or isothiocyanates[15].

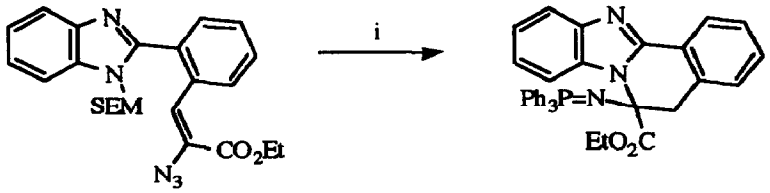


The other type of unusual reaction, namely an anomalous intramolecular conjugate addition, has been observed with vinyliminophosphoranes bearing an imidazole ring placed at an appropriate position. Preparation of the imidazole **7** was achieved from the commercially available 2-phenylimidazole by a three-step sequence: a)



Reagents and conditions i) BuLi, THF, -20 °C, SEM-Cl (60%); ii) BuLi, THF, -78 °C, TMS-Cl (67 %); iii) BuLi, THF, -42 °C, DMF (73%); iv) EtO_2C-CH_2N_3, NaOEt, -15 °C (74%); v) PPh_3, CH_2Cl_2,0 °C (51%); vi) TBAF, THF, r.t. (75%).

formation of the N-protected imidazole by reaction with BuLi and (trimethylsilyl)ethoxymethyl chloride (SEM-Cl); b) selective formation of the α-lithiated imidazole and subsequent reaction with chlorotrimethylsilane (TMS-Cl); and c) reaction of the sililated imidazole with BuLi and trapping of the lithiated intermediate with DMF. Conversion of the imidazole **7** into the vinyliminophosphorane **9** was conveniently carried out by condensation with ethyl azidoacetate and further Staudinger reaction with triphenylphosphine. Deblocking of both the SEM and TMS protecting groups on vinyliminophosphorane **9** using tetrabutylammonium fluoride led to the simultaneous removal of both groups with concomitant ring-closure by nucleophilic attack of the NH group of the imidazole ring on the α-carbon of the vinyliminophosphorane moiety *(6-endo-trig)* to give the iminophosphorane **10**[16], whose structure has been determined by X-Ray analysis and it will be published elsewhere in a near future. The success of this annulation reaction that ultimately led to iminophosphoranes derived from fused imidazoles prompted us to attempt this conversion in the related compound **11**, which was converted into the iminophosphorane **12** in 65% yield by sequential treatment with triphenylphosphine and TBAF. Both iminophosphoranes **10** and **12** showed the characteristic behaviour in aza Wittig-type reaction towards isocyanates, and the corresponding carbodiimides were thus obtained[17].



11 **12**

i) PPh_3, CH_2Cl_2, 0°C, then TBAF, THF, reflux.

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12. Compound **4** (Ar=4-H_3C-C_6H_4; R=4-H_3CO-C_6H_4),m.p.183-185°C;^{1}H-NMR (300 MHz, $CDCl_3$)δ 2.48(s,3H), 3.76(s,3H), 6.38(br s,1H), 6.78(d,2H,J=8.7Hz), 6.86-6.88(m,2H), 7.30-7.50(m,23H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.4 (CH_3), 55.6 (CH_3O), 113.8, 120.0(q), 122.2, 128.2 ($^3J_{P-C}$=12.0 Hz), 129.0, 129.4(q), 129.8, 131.0, 131.1($^4J_{P-C}$=3.0 Hz), 132.4, 132.5 (q, $^1J_{P-C}$=102.7 Hz), 132.6($^2J_{P-C}$=9.8 Hz), 133.9(q), 136.5(q), 138.0 (q), 148.0(br q), 152.9(br q), 155.3(br q), 156.0(br q), 189.3 (C=O, $^3J_{P-C}$=6.5 Hz), two CH carbons not observed. ^{31}P-NMR (125.5 MHz, $CDCl_3$) δ 7.40.

    Compound **5** (Ar=4-H_3C-C_6H_4; R=$(CH_3)_2CH$), m.p. 205-207°C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.21(d, 6H, J=6.3 Hz), 2.29(s,3H), 4.13(m,1H), 6.15(d,1H,J=8.1 Hz,NH), 6.18(s,1H,Ar-C*H*=), 6.98-7.03(m,2H), 7.12(d,2H,J=8.4 Hz), 7.47(t,1H), 7.75(d,2H,J=8.4 Hz), 7.96(d,1H,J=8.1 Hz), 8.76(s,1H,NH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.0, 23.1, 43.2, 115.1(Ar-*C*H=), 118.8, 120.8, 123.2(q), 128.7, 129.3, 130.2, 133.9(q), 134.1, 136.0(q), 143.8(q), 145.7(q), 147.1(q), 187.2(C=O); IR (Nujol) 3358(s), 1670(vs) cm^{-1}; EI mass spectrum m/z(%) 319(M^+,30), *55*(100).

    Compound **6** (Ar=4-H_3C-C_6H_4; R=4-H_3CO-C_6H_4), m.p. 144-146°C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.45 (s,3H), 3.77(s,3H), 5.00(br s,2H,NH_2), 6.16(s,1H,NH), 6.81(d,2H,J=8.7 Hz), 7.10-7.60(m,9H), 8.28(d, 1H,J=8.1 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.4 (CH_3), 55.6(CH_3O), 110.9(q), 113.7, 122.9, 123.3, 128.1(q), 129.7, 130.2, 131.4, 131.7, 133.2(q), 133.3(q), 133.8, 139.2(q), 148.4(q), 149.9(q), 151.5(q), 155.7(q), 182.8(C=O); IR(Nujol) 3499(m), 3410(m), 3353(m), 1555(vs) cm^{-1}; EI mass spectrum m/z (%) 383 (M^+,16), 130(100).
13. The only methods previously reported for the preparation of fully unsaturated 1-benzazepin-5-ones are based either on a carbene-mediated ring expansion of 1,2-dihydroquinolines (Cromarty, A.; Proctor, G.R. *J. Chem. Soc. Chem. Commun.* **1968**, 842. Cromarty, A.; Haque, K.E.; Proctor, G.R. *J. Chem. Soc. (C)* **1971**, 3536. Cromarty, A.; Proctor, G.R.; Shabbir, M. *J. Chem. Soc. Perkin Trans 1* **1972**, 2012), or by ring ex pansion of 1,4-naphthoquinones under Schmidt reaction conditions (Rees, A.H.; Simon, K. *Can. J. Chem.* **1969**, *47*, 1227. Moriconi, E.J.; Maniscalco, A. *J. Org. Chem.* **1972**, *37*, 208).
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16. Compound **10** (75%), m.p. 181-182°C (from dichloromethane/n-hexane); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.80(t,3H,J=7.1 Hz), 3.05(d,1H,J=15.0 Hz), 3.19(d,1H,J=15.0 Hz), 3.55(m,2H), 6.90(dd,1H,J=7.5 Hz), 7.09(dd,1H,J=7.5 Hz), 7.13(d,1H,J=1.3 Hz), 7.21(dd,1H,J=7.8,7.5 Hz), 7.48(m,9H), 7.71(d,1H,J=1.3 Hz), 7.77(m,6H), 7.95(d,1H,J=7.8 Hz); ^{13}C-NMR(75 MHz, $CDCl_3$) δ 13.5(CH_3), 43.2($^3J_{P-C}$=5.5 Hz), 60.6 (CH_3CH_2O), 77.5(q,$^2J_{P-C}$=5.4 Hz), 118.1, 123.1, 127.0(q), 127.2, 127.6, 127.7, 127.8, 128.3($^3J_{P-C}$=12.2 Hz), 131.3($^4J_{P-C}$=2.9 Hz), 131.4(q), 132.2(q,$^1J_{P-C}$=102.2 Hz), 132.4($^2J_{P-C}$=10.0 Hz), 143.6($^4J_{P-C}$=1.6 Hz), 171.2 (C=O, $^3J_{P-C}$=6.8 Hz);^{31}P-NMR (125.5 MHz, $CDCl_3$) δ -0.05; IR (Nujol) 1738(vs) cm^{-1}; EI mass spectrum m/z(%) 517(M^+, 5), 183(100).
17. Satisfactory ^{1}H-, ^{13}C-NMR, mass spectra and elemental analyses were obtained for all new compounds.

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