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Aza-Wittig Reaction of *N*-Vinylic Phosphazenes with Carbonyl Compounds. Azadiene-Mediated Synthesis of Dihydropyridines and Pyridines.

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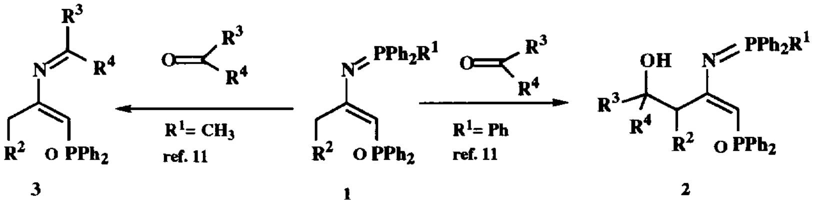
Abstract: Aza-Wittig reaction of *N*-vinylic phosphazenes derived from diphenylmethylphosphine **4** with carbonyl compounds leads to the formation of 2-azadienes derived from β-aminoacids **5**. Dimerization of 2-azadienes **5c,d** and reaction of compounds **5** with phosphazene **4** or enemine **6** affords substituted dihydropyridines **7** and **8**. Aza-Wittig reaction of phosphazenes **4** with α,β-unsaturated aldehydes gives 3-azatrienes **12**, which are easily converted into pyridines **13**.

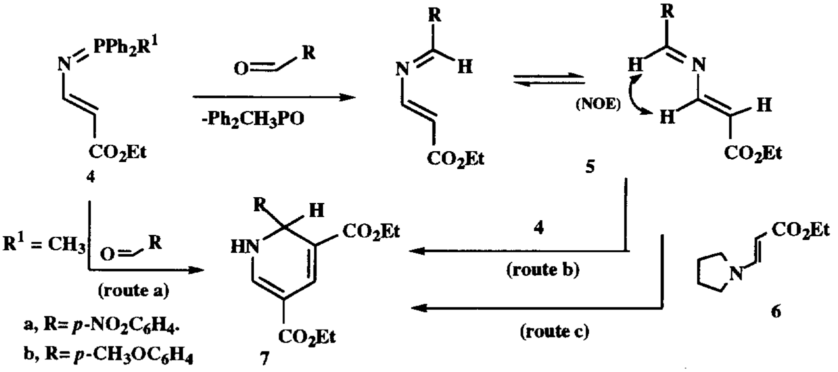
Phosphazenes[1], isoelectronic analogues of phosphorus ylides, represent an important class of compounds and have attracted a great deal of attention in recent years because of their broad range of applications. Furthermore, the utility of *N*-vinylic phosphazenes[2] has been recently demonstrated convincingly of in the synthesis of functionalized imine compounds such as 2-azadienes[3], and as key intermediates in the preparation of heterocycles such as pyridine derivatives[3a,e,4], polycyclic compounds[2,5], benzodiazepines[6] as well as in elegant routes to the preparation of biologically active natural products[7a] and for the construction of the framework of pharmacologically active alkaloids[7b,c].

In recent years, we have been involved in the study of simple and functionalized phosphazenes[1] as well as in the preparation of acyclic[3,8] and heterocyclic compounds[9]. In some cases the reaction involves the nitrogen-phosphorus double bond[3,8b,9] while in other examples the phosphazene group remains unaffected[8a]. Moreover, in the case of *N*-Vinylic phosphazenes an adjacent double bond in conjugation with the phosphazene moiety introduces the interesting problem of site selectivity; i.e. reaction at the nitrogen (1,2-addition) of the phosphazene group in a similar way to previously reported Aza-Wittig reactions[3] *versus* reactions at the γ-C-atom (1,4-addition), such as protected enamines[2,10]. In this context, it is noteworthy that recently we have even reported that the influence of substituents of the phosphorus atom in *N*-vinylic phosphazenes **1** can play an important role in the reactivity pattern observed with carbonyl compounds[11], since reaction of phosphazenes derived from triphenylphosphine (**1**, R^1=Ph) with carbonyl compounds gives the monoadduct **2** (1,4-addition), while phosphazene derived from diphenylmethylphosphine (**1**, R^1=CH_3) undergoes Aza-Wittig reaction with carbonyl compounds and leads to the formation of 2-azadienes **3** (Scheme 1). A recent publication[12], reporting that *N*-vinylic phosphazene **4** (R^1=Ph) bearing an ethoxycarbonyl group at the β- position and easy prepared[3a] by Staudinger reaction of β-azidocarboxylate[13] with phosphines, reacted with aldehydes involving an initial nucleophilic attack of the γ-C-atom (1,4-addition) of the vinyl side chain on the carboxylic atom, has prompted us to report our own results concerning the Aza-Wittig reaction (1,2-addition) of phosphazene **4** (R^1=CH_3) derived from diphenylmethylphosphine with aldehydes, which are consistent with the reported behaviour of this kind of phosphazene[3a]. Moreover, we report here that 2-azadienes **5** and 3-azatrienes **12** can be used in the synthesis of dihydropyridines **7** and **8** and pyridines **13** derived from β-aminoacids.



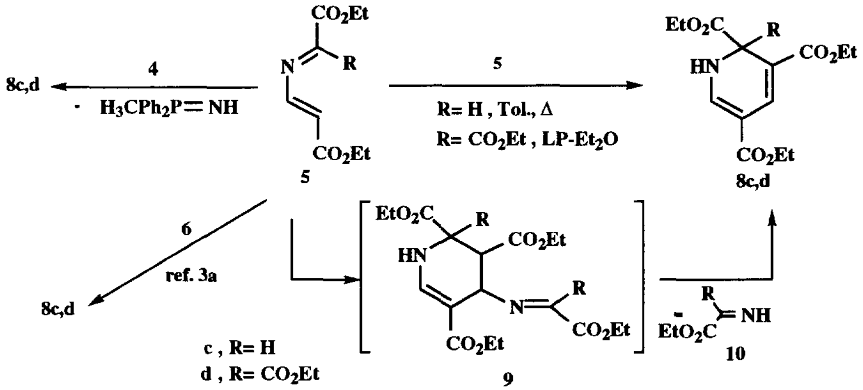
Scheme 1

Formation of 4-aryl-3,5-diethoxycarbonyldihydropyridines through reaction of phosphazenes derived from triphenylphosphine (**4**, R^1=Ph) and aromatic aldehydes has been reported[12]. However, treatment of two equivalents of phosphazene derived from diphenylmethylphosphine (**4**, R^1=CH_3) with one equivalent of aromatic aldehydes in refluxing $CHCl_3$ gave 2-aryl-3,5-diethoxycarbonyldihydropyridines[14] **7a,b** (Scheme 2, route a) in good yieds (72%) and in a regioselective fashion. These results suggest that the process could be initiated by an initial Aza-Wittig reaction of the phosphazene **4** (R^1=CH_3) and aldehydes to give azadienes **5a,b** which subsequently undergo regioselective [4+2] cycloaddition reaction of compounds **5** with a second molecule of phosphazene **4** yielding dihydropyridines **7**. In order to test whether azadienes **5a,b** are intermediates in this process, we try to stop the reaction at the first step, i.e. in the azadienes **5**. Thus, phosphazene **4** (R^1 =CH_3) was allowed to react with *p*-nitrobenzaldehyde at room temperature, affording very high yield (82%) of 2-azadiene **5a**[15,16]. Heating of compound **5a** in $CHCl_3$ at 60°C with a second molecule of phosphazene **4** led to dihydropyridine **7a** (Scheme 2, route b). Similary, heterocycle **7b** can be obtained through reaction of phosphazene **4** with *p*-methoxybenzaldehyde, followed by [4+2] cycloaddition reaction of azadiene **5b**[17], used "in situ" without isolation, with a second molecule of phosphazene **4**.



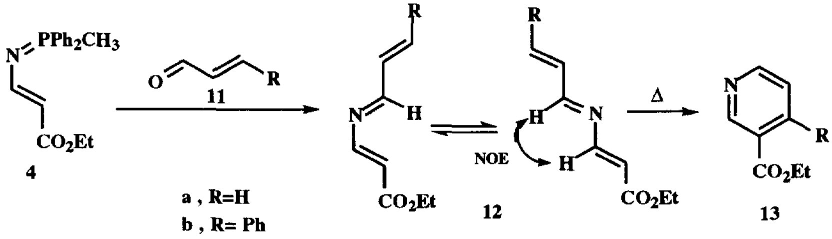
Scheme 2

These results prompted us to explore whether not only azadienes **5a,b** but also di- and tri-substituted azadienes **5c,d** could be key intermediates in the synthesis of dihydropyridines **8** in a similar way to that previously reported by the reaction of azadienes **5c,d** with enamine **6**[3a]. Dihydropyridine **8c** was formed from azadiene **5c** in refluxing of toluene (*TLC* control), while in the case of the trisubstituted azadiene **5d** heterocycle **8d**, was obtained when the reaction was performed in the presence of lithium perchlorate in a nonaqueous solvent such as diethyl ether (LP-Et_2O). Formation of dihydropyridines **8c,d** could be explained through dimerisation of azadienes **5c,d** by a cycloaddition in which one molecule acts as the dienophile and the other as a 2-azadiene (Scheme 3) in a similar way to that previously reported for azadienes derived from α-aminoacids[18]. Thermal elimination of the imine **10** from the initially formed dimer **9** could give dihydropyridines **8c,d**. Additionally azadienes **5c,d** reacted with phosphazene **4** (R^1=CH_3), leading also to the formation of dihydropyridines **8c,d**. These results suggest that from a preparative point of view dimerisation reaction of azadienes **5c,d** and the reaction of compounds **5c,d** with phosphazene **4** reacting as protected enamine is similar to that described[3a] for the reaction of azadienes **5c,d** with enamine **6**. Therefore, in an alternative way dihydropyridines **7** can also be obtained through reaction of azadienes **5a,b** with enamine **6**, which can be considered as a synthetic equivalent of phosphazene **4** (Scheme 2, route c).



Scheme 3

Likewise, Aza-Wittig reaction of phosphazene **4** can also be extended to α,β-unsaturated aldehydes **11**. Reaction of *N*-vinylic phosphazene **4** with acrylaldehyde **11** (R=H) and *trans*-cinnamaldehyde **11**(R=Ph) in $CHCl_3$ at room temperature gave very high yields of 3-azatrienes **12**[17] (Scheme 4). Heating of compounds **12** at 60°C in $CHCl_3$ led to pyridines **13**[19] derived from β-aminoacids. Formation of 3-azatrienes **12** could be explained through an Aza-Wittig reaction of phosphazene **4** with unsaturated aldehydes in a similar way to that previously reported in the synthesis of 2-[3e] and 3-azatrienes[3d] derived from α-aminoacids. From a preparative point of view, it is noteworthy that pyridines **13** can also be obtained when phosphazene **4** are directly heated in $CHCl_3$ at 60°C with aldehydes **11** (48 h).



Scheme 4

In conclusion we describe here an easy simple method for regioselective synthesis of dihydropyridines **7**,**8** and pyridines **13** derived from β-aminoacids from *N*-vinylic diphenylmethylphosphazenes **4**. In both cases an Aza-Wittig reaction of phosphazene with aldehydes takes place leading to the formation of acyclic 2-azadienes **5** and 3-azatrienes **12** in a regioselective fashion. Pyridine compounds derived from β-aminoacids are useful heterocycles not only for their biological activities[20] but also because the pyridine nucleus is a structural unit appearing in many natural products[21]. Further studies on compound **4** are now in progress in our laboratory.

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14. All new compounds reported here gave satisfactory elemental analysis. Spectral data for **7a**: ^{1}H NMR δ ($CDCl_3$, TMS, 300 MHz) 8.17 (d, 2H, $^{3}J_{H-H}$=9Hz, aromatic), 7.75 (s, 1H, H-3), 7.72 (d, 1H, $^{3}J_{H-H}$=7Hz, H-2), 7.58 (d, 2H, $^{3}J_{H-H}$=9Hz, aromatic), 6.26 (m, 1H, NH), 5.81 (d, 1H, $^{3}J_{H-H}$=3Hz, H-6), 4.23 (q, 2H, OCH_2), 4.13 (q, 2H, OCH_2), 1.31 (t, 3H, CH_3), 1.24 (t, 3H, CH_3); ^{13}C-NMR δ (75 MHz, $CDCl_3$) 165.7, 165.6, 149.7, 147.6, 146.4, 133.2, 127.6, 124.1, 112.2, 97.9, 60.54, 59.9, 54.7, 14.5, 14.2; IR (film)3314, 1682, 1526, 1349; MS (EI) m/z 346 (M^+, 10)
15. Compound **5a**, m.p. 161-162 °C. Spectral data for **5a**: ^{1}H NMR δ ($CDCl_3$, TMS, 300 MHz) 8.51 (s, 1H, N=CH), 8.32 (d, 2H, $^{3}J_{H-H}$=9Hz), 8.04(d, 2H, $^{3}J_{H-H}$=9Hz), 7.94 (d, 1H, $^{3}J_{H-H}$=13Hz, N-CH), 6.30 (d, 1H, $^{3}J_{H-H}$=13Hz, =CH), 4.26 (q, 2H, OCH_2), 1.34 (t, 3H, CH_3); ^{13}C-NMR δ (75 MHz, $CDCl_3$) 166.5, 164.7, 154.0, 149.8, 140.4, 130.0, 124.0, 121.2, 60.7, 14.2; IR (KBr) 1704, 1510, 1350; MS (EI) m/z 248 (M^+, 10)
16. From NOE experiments the stereochemistry of compounds **5** can be deduced, since the selective saturation of the singlet at 8.51 ppm afforded positive NOE over the adjacent vinylic proton and absence of interation with 4-H
17. Azadiene **5b** (R= *p*-CH_3O-C_6H_4) and azatrienes **12**, which proved to be unstable during distillation or chromatography, were therefore not isolated and the crude reaction mixture without purification was satisfactorily used for the following purposes. The presence of these azadienes **5b** and **12** in the crude reaction mixture was monitored by ^{1}H-NMR spectroscopy.
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19. Spectral data for **13b** : ^{1}H NMR δ ($CDCl_3$, TMS, 300 MHz) 9.28 (d, 1H, $^{4}J_{H-H}$=3Hz, H-2 Pyr.), 8.34 (dd, 1H, $^{3}J_{H-H}$=9Hz, H-6 Pyr.), 8.05 (d, 2H, $^{3}J_{H-H}$=Arom.), 7.80 (d, 1H, $^{3}J_{H-H}$=9Hz, H-5 Pyr.), 7.49-7.45 (m, 3H, Arom.), 4.42 (q, 2H, OCH_2), 1.42 (t, 3H, CH_3); ^{13}C-NMR δ (75 MHz, $CDCl_3$) 165.0, 160.8, 150.9, 137.8, 129.9-124.4 (m, 7C, Arom. + Pyr.), 119.8, 61.3, 14.25; IR (film) 1669; MS (EI) m/z 227 (M^+, 100)
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