Regioselective synthesis of dihydropyridines and pyridines derived from β-aminoacids from *N*-vinylic phosphazenes

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Abstract

Reaction of enamino-phosphonium salts derived from β-aminoacids with α,β-unsaturated aldehydes leads to the formation of symmetrical dihydropyridines. Moreover, no symmetrical dihydropyridines can be obtained by the reaction of enamino-phosphonium salts derived from of *N*-vinylic phosphazenes with α,β-unsaturated ketones.

Keywords: Aminophosphonium salts, *N*-vinylic phosphazenes, dihydropyridines, pyridines

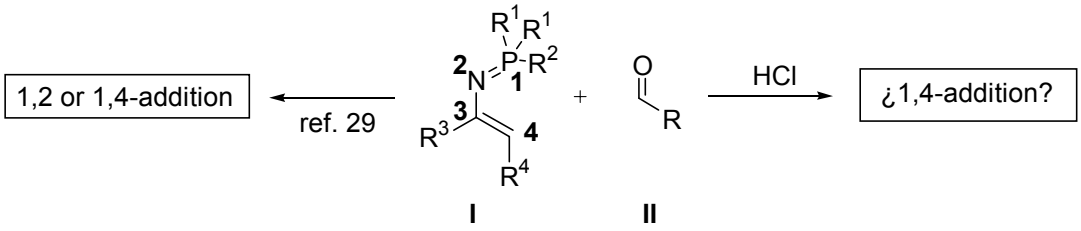
Introduction

Many natural products and bioactive agents such as nifedipine,[1] nitrendipine[2] and felodipine[3] are 1,4-dihydropyridine derivatives (1,4-DHPs). The coenzyme reduced nicotinamide adenine dinucleotide (NADH) is the cofactor used by many reductases in metabolism, and its reactive moiety is a 1,4-DHP unit. Compounds based on this heterocycle play key roles in therapeutic and bioorganic chemistry[4] for treatment of a variety of diseases, such as cardiovascular disorders,[4a] cancer[4b] and AIDS.[4c] Recent papers have reported novel 1,4-DHP derivatives as calcium channel modulators,[5] as Ca-blockers against endothelial cell oxidative injury,[6] with vasodilating activity[7] and as nonpeptide HIV-1 protease inhibitors.[8]

On the other hand, 1,4-DHPs are also used as versatile intermediates in organic synthesis.[9] Several groups have prepared diversely substituted 1,4-DHP derivatives, however, potential applications in the aforementioned fields remain elusive or unknown. Reduction of *N*-alkylpyridinium salts[10] or regioselective addition of nucleophilic reagents to *N*-acylpyridinium ions[11] are the most simple and reliable methods for the regioselective formation of the corresponding 1,4-DHP derivatives. Furthermore, few examples of 2,6-disubstituted

dihydropyridines have been described and most of them have been synthesized from the corresponding pyridine or pyridinium salt.[12]

N-Vinylic phosphazenes[13] have proved to be useful building blocks for the synthesis of electronically neutral 2-azadienes,[14] 3-fluoroalkyl-2-azadienes,[15] electron-poor 2-azadienes derived from aminophosphorus derivatives,[16] α-[17] or β-amino acids,[18] and as key intermediates in the preparation of glycosides,[19] cyclic compounds[14-18,20-23] as well as in the construction of the framework of pharmacologically active alkaloids.[24] Moreover, *N*-vinylic phosphazenes are ambident nucleophilic reagents, since the presence of an adjacent double bond in conjugation with the phosphazene moiety introduces a new site of reactivity towards electrophiles: either reaction at the nitrogen (1,2-addition) of the phosphazene[13,25] or reactions at the γ-carbon atom (1,4-addition).[13,21a,26,27]



Scheme 1

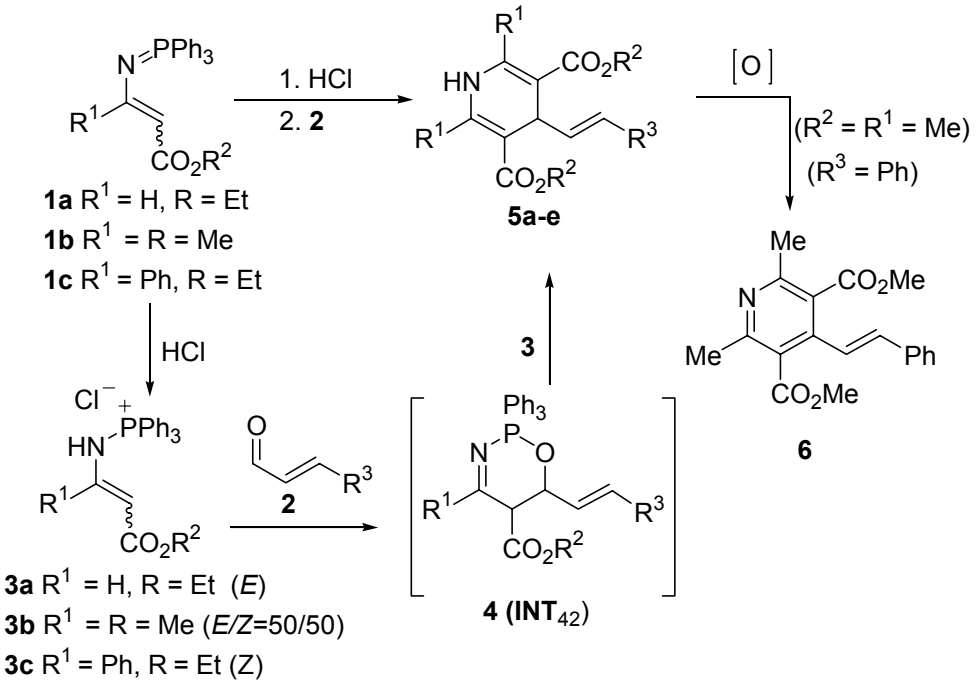
Continuing with our interest in the chemistry of simple phosphazenes[28] and *N*-vinylic phosphazenes,[14-18] we apply our approach to the synthesis of 1,4-dihydropyridine derivatives in mild conditions. The ambident behaviour (1,2- and 1,4-addition) observed for *N*-vinylic phosphazenes **I** (Scheme 1) against α,β-unsaturated aldehydes **II**[29] prompted us to establish, whether in the presence of acid (HCl) the reaction of these *N*-vinylic phosphazenes derived from triphenylphosphine gives the regioselective 1,4-addition. Therefore, we report here the use of β-enaminophosphonium salts of *N*-vinylic phosphazenes **I** derived from β-amino acids (R^2=H, Me, Ph, R^3=CO_2R) with α,β-unsaturated aldehydes and ketones, as key intermediates in the synthesis of dihydropyridine and pyridine compounds derived from β-aminoacids.

Results and Discussion

Reaction of enamino-phosphonium salts 3 with α,β-unsaturated aldehydes 2. Preparation of symmetrical dihydropyridines 5 and pyridine 6

We explored the reactivity of enaminophosphonium salts **3** derived from phosphazenes **1** with α,β-unsaturated aldehydes **2** (Scheme 2). The reaction of enaminophosphonium salt **3a**, prepared by hydrochloric acid treatment of *N*-vinylic phosphazene **1a** (R^1 = H, R^2 = Et), with cinnamaldehyde **2a** (R^3 = C_6H_5) or *p*-nitrocinnamaldehyde **2b** (R^3 = 4-NO_2-C_6H_4) in refluxing CH_2Cl_2 led to the formation of 4-(2-phenylethenyl)-3,5-diethoxycarbonyl-1,4-dihydropyridine

5a and 4-[2-(4-nitrophenyl)ethenyl]-3,5-diethoxycarbonyl-1,4-dihydropyridine **5b** (Table 1, entries 1 and 2), respectively. The formation of these dihydropyridines **5** could be explained by means of a formal [4+2]-cyclization process involving an initial 1,4-addition of the γ-carbon atom of the enaminophosphonium salt **3a** to the carbonyl group of the aldehydes **2** to give the cycloadduct intermediate 1,2,5-oxaazaphosphoranes **4** (**INT**$_{42}$) followed by regioselective attack[13,18b] of a second molecule of the phosphonium salt **3a** (Scheme 2). The structure of compound **5b** was assigned on the basis of the 1D and 2D NMR spectroscopy, including HMQC and HMBC experiments. Dihydropyridine **5a** was characterized, and its structure was consistent with reported symmetrical heterocycles.[29,30]



Scheme 2

This reaction can also be extended to 3-methyl or 3-phenyl substituted enaminophosphonium salts **3b**,**c** (R^1 = Me, Ph), with cinnamaldehyde **2a** (R^3 = C_6H_5) to obtain dihydropyridine **5c** (Table 1, entry 3) and 3-phenyl substituted symmetrical dihydropyridine **5d** (Table 1, entry 4) respectively. Moreover, enaminophosphonium salt **3c** (R^1 = Ph) reacted with 2-furanylacroleine **2c** (R^3 = 2-furyl) to give dihydropyridine **5e** in a similar process. The synthesis of dihydropyridines **5d** and **5e** does not require the isolation and purification of enaminophosphonium salt **3c** and it can be obtained when phosphazene **1c** is directly treated with acid followed by a subsequent addition of aldehydes **2a** or **2c** (Table 1, entries 4 and 5). Oxidation of dihydropyridine **5c** with quinone led to the formation of symmetrical pyridine **6** derived from β-aminoacids (Table 1, entry 6). Therefore, this strategy offers a new approach to the synthesis of symmetrical 1,4-dihydropyridines **5a-e** under mild reaction conditions.

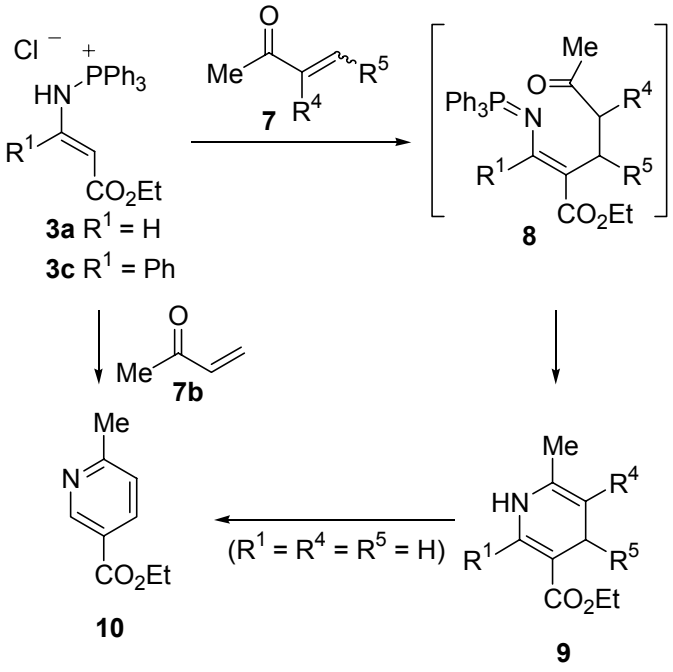
Reaction of enamino-phosphonium salts 3 with ketones

We tested also in a similar way to that reported for aldehydes,[17,29] the reactivity of enaminophosphonium salts **3** derived from phosphazenes with ketones (Scheme 3). The reaction of enaminophosphonium salts **3a** and **3c**, prepared by acid treatment of *N*-vinylic phosphazenes **1a** (R^1 = H) and **1c** (R^1 = Ph) respectively with methyl 2-(*p*-nitrophenyl)methyleneacetoacetate **7a** (R^4 = CO_2Me, R^5 = *p*-NO_2-C_6H_4) in refluxing CH_2Cl_2 led to the formation of asymmetrical 1,4-dihydro-3,5-pyridinedicarboxylates **9a,b** (Table 1, entries 7 and 8). Similarly, the reaction of enaminophosphonium salts **3a** (R^1 = H), with methylvinylketone **7b** (R^4 = R^5 = H) in refluxing CH_2Cl_2 led to the formation of pyridine **10** in low yield (Table 1, entry 9). Formation of dihydropyridines **9** can be explained by an enamine alkylation of enaminophosphonium salts **3** onto the β-carbon of the carbonyl compound **7** to give intermediates phosphazenes **8** which through an intramolecular aza-Wittig reaction give asymmetric dihydropyridines **9**. A similar process could explain the formation of pyridine **10**, since subsequent aromatization of dihydropyridine **9** when R^1 = R^4 = R^5 = H afforded pyridine **10**.

Table 1. 1,4-Dihydropyridines **5, 9** and pyridines **6** and **10** obtained

	Starting					Reaction conditions		
Entry	material	Products	R^1	R^2	R^3	T(°C)	time (h)	yield(%)[a]
1	**3a/2a**	**5a**	H	Et	C_6H_5	40	19	66
2	**3a/2b**	**5b**	H	Et	4-NO_2-C_6H_4	40	30	62
3	**3b/2a**	**5c**	Me	Me	C_6H_5	40	20	65
4	**3c/2a**	**5d**	Ph	Et	C_6H_5	40	25	51[b]
5	**3c/2c**	**5e**	Ph	Et	2-furyl	40	48	57[b]
6	**5c**	**6**	Me	Me	C_6H_5	100	18	89[c]
7	**3a/7a**	**9a**	H	Et	-	40	12	92
8	**3c/7a**	**9b**	Ph	Et	-	40	16	82[b]
9	**3a/7b**	**10**	H	Et	-	40	16	20

[a] Purified by chromatography. [b] Obtained in "one pot" process from phosphazene **1c**. [c] Obtained by oxidation with *p*-benzoquinone.



Scheme 3

In conclusion, symmetrical 1,4-dihydropyridines **5** are obtained by 1,4-addition of the γ-carbon atom of the enamino-phosphonium salt **3** to the carbonyl group of an α,β-unsaturated aldehyde **2**, through 1,2,5-oxaazaphosphorane **5** (**INT$_{42}$**) intermediate, followed by regioselective attack of a second molecule of the phosphonium salt **3** and cyclization. The efficient synthesis of symmetrical dihydropyridines **5** here described from enaminophosphonium salts **3** provides an easy approach to the preparation of these kind of compounds, avoiding the use of high temperatures (160 ºC).[30] Different behavior has been observed in the reaction of enaminophosphonium salts **3** with α,β-unsaturated ketones **7**. Dihydropyridines **9** are obtained by an enamine alkylation of enaminophosphonium salts **3** onto the β-carbon of the carbonyl compound and intramolecular aza-Wittig reaction of resulting phosphazenes. Subsequent aromatization affords pyridines **10** derived from β-aminoacids. It is worth noting 1,4-dihydropyridines are interesting compounds in synthetic, therapeutic and bioorganic chemistry.[1-12] Pyridine compounds derived from β-aminoacids are useful heterocycles not only for their biological activities[31] but also because the pyridine nucleus is a structural unit appearing in many natural products.[32]

Experimental Section

General Procedures. Solvents for extraction and chromatography were technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All

other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with silica gel 60 F_{254} and aluminum oxide N/UV_{254} plates. Visualization was accomplished by UV light. Flash chromatography was carried out using silica gel 60 (230–400 mesh ASTM) and aluminum oxide 90 active neutre (70–230 mesh ASTM). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. ^{1}H (300 MHz), ^{13}C (75 MHz) and ^{31}P NMR (120 MHz) spectra were recorded on a Varian VXR 300 MHz spectrometer using $CDCl_3$ solutions with TMS as an internal reference (δ = 0.00 ppm) for ^{1}H and ^{13}C NMR spectra, and phosphoric acid (85%) (δ = 0.00 ppm) for ^{31}P NMR spectra. Chemical shifts (δ) are reported in ppm. Coupling constants (J) are reported in Hertz (Hz). Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EIMS) on a Hewlett Packard 5971 or 5973 spectrometer. Data are reported in the form *m/z* (intensity relative to base = 100). Infrared spectra (IR) were taken on a Nicolet IRFT Magna 550 spectrometer, and were obtained as solids in KBr or as neat oils. Peaks are reported in cm^{-1}. Elemental analyses were performed in a LECO CHNS-932 apparatus. Phosphazenes **1**[18b,c] and enamino-phosphonium salts **3a**,**b**[18b] were synthesized according to literature procedures.

((2-Ethoxycarbonyl-1-phenyl)-1-ethenyl)amino)triphenylphosphonium chloride (3c). Hydrogen chloride was bubbled through a 0-10 ºC solution of phosphazene 1c (1.35 g, 3 mmol) in CH_2Cl_2 (10 mL)/ Et_2O (20 mL), and the mixture was stirred at 0-10 ºC for 30 min. Evaporation of solvent under reduced pressure afforded enamino phosphonium salt **3c**. The reaction product is unstable during distillation and/or chromatography and therefore was used without purification for the following reactions. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, $^3J_{(H,H)}$ = 7.1 Hz, 3H), 4.28 (q, $^3J_{(H,H)}$ = 7.1 Hz, 2H), 5.40 (d, $^4J_{(P,H)}$ = 2.6 Hz, 1H), 6.79-7.81 (m, 20 H), 11.26 (d, $^1J_{(P,H)}$ = 7.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 61.4, 103.9, 118.5 (d, $^1J_{(P,C)}$ = 100 Hz), 128.0-135.8 (m), 155.4, 169.6 ppm; ^{31}P NMR (120 MHz, $CDCl_3$) δ 34.91 ppm.

General procedure for the preparation of dihydropyridines 5

Aldehyde **2** (1.5 mmol) was added to a 0-10 ºC solution of phosphonium salt **3** (3 mmol) in CH_2Cl_2 (8 mL) under N_2, and the mixture was stirred and warmed at 40 ºC until TLC indicated the disappearance of aldehyde. Evaporation of solvent under reduced pressure afforded an oil that was chromatographied on silica gel to give the compounds **5**.

Diethyl 4-(2-phenylethenyl)-1,4-dihydro-3,5-pyridinedicarboxylate (5a). The general procedure was followed using phosphonium salt **3a** (3 mmol), prepared "in situ" and cynnamaldehyde **2a** (0.189 mL), for 19 h. Evaporation of solvent under reduced pressure afforded an oil which was chromatographied on silica gel (2:1 hexane/AcOEt) to give 0.328 g (66%) of **5a** as a white solid, m. p. 132-134ºC (*bibl*. reported: 133-135ºC). The spectroscopic data are identical to those reported previously.[30]

Diethyl 4-[2-(4-nitrophenyl)ethenyl]-1,4-dihydro-3,5-pyridinedicarboxylate (5b). The general procedure was followed using phosphonium salt **3a** (3 mmol), prepared "in situ" and *p*-

nitrocynnamaldehyde **2b** (0.266 g), for 30 h. Evaporation of solvent under reduced pressure afforded an oil which was chromatographied on silica gel (3:1 hexane/AcOEt) to give 0.346 g (62%) of **5b** as a yellow oil (R_f= 0.15, hexane/AcOEt 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, $^3J_{(H,H)}$ = 7.2 Hz, 6H), 4.16-4.24 (m, 4H), 4.60 (d, $^3J_{(H,H)}$ = 6.4 Hz, 1H), 6.35 (d, $^3J_{(H,H)}$ = 16 Hz, 1H), 6.48 (dd, $^3J_{(H,H)}$ = 16 Hz, $^3J_{(H,H)}$ = 6.4 Hz, 1H),7.21 (t, $^3J_{(H,H)}$ = 5.3 Hz, 1H), 7.34 (d, $^3J_{(H,H)}$ = 5.3 Hz, 2H), 7.43 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H), 8.09 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 34.4, 60.3, 105.3, 123.8, 127.8, 135.1, 137.2, 144.3, 146.5, 167.0 ppm; IR (NaCl) 3328, 1694, 1535; M/S (EI) *m/z* 372 (M^+, 24).

Dimethyl 2,6-dimethyl-4-(2-phenylethenyl)-1,4-dihydro-3,5-pyridinedicarboxylate (5c). The general procedure was followed using phosphonium salt **3b** (3 mmol), prepared "in situ" and cynnamaldehyde **2a** (0.189 mL), for 20 h. Evaporation of solvent under reduced pressure afforded an oil which was chromatographied on silica gel (5:1 hexane/AcOEt) to give 0.319 g (65%) of **5c** as a yellow solid: mp 169-170 ºC (recrystalized from hexane/AcOEt) . ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 6H), 3.66 (s, 6H), 4.54 (m, 1H), 5.59 (s, 1H), 6.10-6.17 (m, 2H), 7.09-7.27 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 36.2, 51.1, 101.4, 126.3-131.7, 137.7, 145.1, 167.9 ppm; IR (KBr) 3334, 1698, 1649; M/S (EI) *m/z* 327 (M^+, 56). Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.68; H, 6.49; N, 4.27.

Diethyl 2,6-diphenyl-4-(2-phenylethenyl)-1,4-dihydro-3,5-pyridinedicarboxylate (5d). The general procedure was followed using phosphonium salt **3c** (3 mmol), prepared "in situ" and cynnamaldehyde **2a** (0.189 mL), for 25 h. Evaporation of solvent under reduced pressure afforded an oil which was chromatographied on silica gel (10:1 hexane/AcOEt) to give 0.367 g (51%) of **5d** as a yellow solid: mp 152-153 ºC (recrystallized from hexane/AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, $^3J_{(H,H)}$ = 7.2 Hz, 6H), 3.91 (q, $^3J_{(H,H)}$ = 7.2 Hz, 4H), 4.79 (d, $^3J_{(H,H)}$ = 6.1 Hz, 1H), 5.94 (s, 1H), 6.36 (dd, $^3J_{(H,H)}$= 6.1 Hz, $^3J_{(H,H)}$ = 16.0 Hz, 1H), 6.49 (d, $^3J_{(H,H)}$ = 16.0 Hz, 1H), 7.11-7.57 (m, 15H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 37.0, 59.8, 101.8, 126.4-131.2, 136.6, 137.8, 146.3, 166.7 ppm; IR (KBr) 3285, 1681; M/S (EI) *m/z* 497 (M^+, 7). Anal. Calcd. for $C_{31}H_{29}NO_4$: C, 77.64; H, 6.10; N, 2.92. Found: C, 77.77; H, 6.13; N, 2.91.

Diethyl 2,6-diphenyl-4-(2-furylethenyl)-1,4-dihydro-3,5-pyridinedicarboxylate (5e). The general procedure was followed using phosphonium salt **3c** (3 mmol), prepared "in situ" and 2-furanylacroleine **2c** (0.183 g), for 48 h. Evaporation of solvent under reduced pressure afforded an oil which was chromatographied on silica gel (5:1 hexane/AcOEt) to give 0.402 g (57%) of **5e** as a white solid: mp 158-160 ºC (recrystallized from hexane/AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, $^3J_{(H,H)}$ = 7.2 Hz, 6H), 3.99 (q, $^3J_{(H,H)}$ = 7.2 Hz, 4H), 4.84 (d, $^3J_{(H,H)}$ = 5 Hz, 1H), 6.03 (s, 1H), 6.25 (d, $^3J_{(H,H)}$= 3.3 Hz, 1H), 6.38-6.40 (m, 3H), 7.36 (d, $^3J_{(H,H)}$ = 1.5 Hz, 1H), 7.39-7.44 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 36.9, 59.9, 101.7, 107.2, 111.3, 117.6, 128.3, 128.4, 129.3, 130.3, 136.6, 141.4 146.4, 153.4, 166.7 ppm; IR (KBr) 3335, 1682; M/S (EI) *m/z* 469 (M^+, 9). Anal. Calcd. for $C_{29}H_{27}NO_5$: C, 74.18; H, 5.80; N, 2.98. Found: C, 74.27; H, 5.93; N, 2.96.

Dimethyl 2,6-dimethyl-4-(2-phenylethenyl)-3,5-pyridinedicarboxylate (6). To a solution of dihydropyridine **5c** (0.654 g, 2 mmol) in dioxane (5 mL) was added 0.212 g (2 mmol) of *p*-benzoquinone, and the mixture was stirred at 100 ºC for 18 h under N_2. The solvent was evaporated under reduced pressure, and the resulting oil was purified by silica gel column chromatography (10:1 hexane/AcOEt) to give 0.579 g (89%) of **6** as a brown oil (R_f= 0.35, hexane/AcOEt 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50 (s, 6H), 3.79 (s, 6H), 6.72 (d, $^3J_{(H,H)}$ = 16.5 Hz, 1H), 7.02 (d, $^3J_{(H,H)}$ = 16.5 Hz, 1H), 7.24-7.40 (m, 5H) ppm; ^{13}C NMR (75Hz, $CDCl_3$) δ 23.0, 52.5, 122.7, 125.3, 126.9, 128.7, 136.1, 136.6, 150.1, 155.8, 168.7 ppm; IR (NaCl) 1731; M/S (EI) *m/z* 325 (M^+, 100).

General procedure for the preparation of dihydropyridines 9 and pyridine 10

Ketone **7** (2 mmol) was added to a 0-10 ºC solution of phosphonium salt **3** (2 mmol) prepared "in situ", in CH_2Cl_2 (6 mL) under N_2, and the mixture was stirred and warmed at 40 ºC until TLC indicated the disappearance of ketone. Evaporation of solvent under reduced pressure afforded an oil that was chromatographied on silica gel to give the compounds **9** or **10**.

3-Ethyl, 5-methyl 6-methyl-4-(4-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate (9a). The general procedure was followed using methyl 2-(4-nitrophenylmethylene)acetoacetate **7a** (0.498 g) and phosphonium salt **3a** (2 mmol), prepared "in situ", for 12h. Evaporation of solvent under reduced pressure afforded an oil that was chromatographied on aluminum oxide (10:1 hexane/AcOEt) to give 0.637 g (92%) of **9a** as a yellow solid: mp 48-49 ºC (recrystallized from AcOEt/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, $^3J_{(H,H)}$ = 7.2 Hz, 3H), 2.31 (s, 3H), 3.55 (s, 3H), 3.98-4.12 (m, 2H), 5.00 (s, 1H), 6.19 (s, 1H), 7.24 (d, $^3J_{(H,H)}$ = 5.5 Hz, 2H), 7.41 (d, $^3J_{(H,H)}$ = 8.7 Hz, 2H) 8.04 (d, $^3J_{(H,H)}$ = 8.7 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 19.7, 39.0, 51.1, 60.2, 102.9, 107.7, 123.4, 128.9, 133.9, 144.9, 146.4, 154.4, 166.4, 167.5 ppm; IR (KBr) 3327, 1698, 1514; M/S (EI) *m/z* 346 (M^+, 19). Anal. Calcd. for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.90; H, 5.25; N, 8.07.

3-Ethyl, 5-methyl 2-phenyl-6-methyl-4-(4-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate (9b). The general procedure was followed using methyl 2-(4-nitrophenylmethylene)acetoacetate **7a** (0.498 g) and phosphonium salt **3c** (2 mmol), prepared "in situ", for 16h. Evaporation of solvent under reduced pressure afforded an oil that was chromatographied on aluminum oxide (7:1 hexane/AcOEt) to give 0.693 g (82%) of **9b** as a yellow solid: mp 168-169 ºC (recrystallized from AcOEt/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (t, $^3J_{(H,H)}$ = 7.2 Hz, 3H), 2.33 (s, 3H), 3.60 (s, 3H), 3.71-3.81 (m, 2H), 5.16 (s, 1H), 5.89 (s, 1H), 7.19-7.34 (m, 5H), 7.51 (d, $^3J_{(H,H)}$ = 8.5 Hz, 2H), 8.07 (d, $^3J_{(H,H)}$ = 8.5 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 19.6, 40.2, 51.2, 59.9, 102.6, 103.8, 123.5-129.9, 136.6, 145.0, 146.2, 146.5, 154.6, 166.4, 167.4 ppm; IR (KBr) 3293, 1678, 1519; M/S (EI) *m/z* 422 (M^+, 28). Anal. Calcd. for $C_{23}H_{22}N_2O_6$: C, 65.39; H, 5.25; N, 6.63. Found: C, 65.42; H, 5.26; N, 6.62.

Ethyl 6-methyl-3-pyridinecarboxylate (10). The general procedure was followed using methylvinylcetone **7b** (0.167 mL) and phosphonium salt **3a** (2 mmol), prepared "in situ", for 16 h. Evaporation of solvent under reduced pressure afforded an oil that was chromatographied on

aluminum oxide (10:1 hexane/AcOEt) to give 0.066 g (20%) of **10** as a yellow oil (R_f= 0.30, hexane/AcOEt 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, $^3J_{(H,H)}$ = 7.1 Hz, 3H), 2.56 (s, 3H), 4.30 (q, $^3J_{(H,H)}$ = 7.1 Hz, 2H), 7.17 (d, $^3J_{(H,H)}$ = 8.1 Hz, 1H), 8.11 (d, $^3J_{(H,H)}$ = 8.1 Hz, 1H), 9.04 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 24.5, 61.0, 122.7, 123.4, 137.0, 150.2, 162.8, 165.2 ppm; IR (NaCl) 1730; M/S (EI) *m/z* 165 (M^+, 93).

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References and Footnotes

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