Synthesis of Pentasubstituted Pyridines. Cycloadditions of *N*-Vinylic Heterocumulenes with 1-(*N*,*N*-Diethylamine)prop-1-yne.

José Barluenga,* Miguel Ferrero

Instituto Universitario de Química Organometálica Enrique Moles, Universidad de Oviedo, 33071 Oviedo, Spain.

and Francisco Palacios.*

Departamento de Química Orgánica, Facultad de Farmacia, Universidad del País Vasco, Apdo. 450, 01080 Vitoria, Spain.

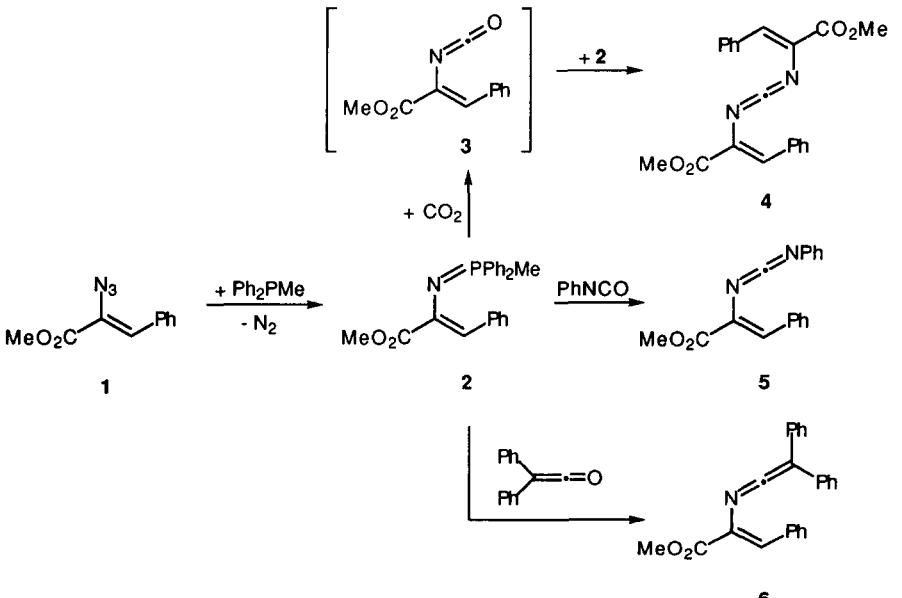
Abstract: The reactions of *N*-vinyl carbodiimides **4** and **5**, and *N*-vinyl ketenimine **6** with ynamine **7** in THF, chloroform, toluene, and xylenes at, respectively, 0 °C, 25 °C, 100 °C, and 140 °C is shown. Pentasubstituted pyridines **8**, **9**, **11**, and **12** are obtained in very high yields through thermally controlled [2+2] or [4+2] competitive processes. Additionally, when the temperature is raised, the *N*-vinyl heterocumulenes **5** and **6** undergo an electrocyclic ring closure of six electrons driving to isoquinolines **10** and **13**, respectively. © 1997 Elsevier Science Ltd.

Polyfunctionalised heteroaromatics, especially in the case of α-aminoacid derivatives, are biologically interesting molecules and their chemistry has received considerable attention. In particular, the pyridine nucleus is a structural unit appearing in many natural products.[1] Because pyridine derivatives occupy a unique position in medicinal chemistry and the pharmacological importance of functionalized pyridines, many synthetic pathways have been developed.[2] The convenient synthesis of substituted pyridines continues to attract attention and has resulted in the development of strategies for the preparation of these heterocycles including two main approaches: 1) modification of a preformed pyridine nucleus, or 2) formation from heterocycloaddition methodologies. In the latter, 2-azabutadiene systems have proved to be efficient Diels-Alder partners towards different dienophiles.[3,4] However, general synthetic applications of these cycloadditions encounter important limitations to the substitution patterns that may be accessed.[5] In addition, when the 2-azadiene skeleton belongs to a heterocumulenic system, such as *N*-vinyl heterocumulenes, which represent a new, highly reactive 2-azadiene species, these can react with electron-rich dienophiles affording different pyridine regioisomers due to two possible cycloaddition modes, [4+2] or [2+2]. This differential reactivity becomes a major problem when mixtures of isomers are obtained, usually in low yields.[6]

However, to the best of our knowledge, the study of cycloaddition reactions of *N*-vinyl heterocumulenes derived from α-aminoacids is restricted to isocyanates[7] and no results have been reported on the cycloaddition reactions of conjugated carbodiimides and ketenimines containing an alkoxycarbonyl group in position 3. The presence of the ester group in the substrate could provide these compounds derived from aminoacid useful applications as starting material in the preparation of heterocycles derived from aminoacids.

In connection with our interest in the synthesis and reactivity of 2-azadienes[3c] and the preparation of heterocyclic compounds derived from aminoacids we have developed a synthetic strategy for the preparation of heterodienes from *N*-vinyl phophazenes.[4,8,9] Furthermore, we have recently reported a new regioselective synthesis of pentasubstituted polyfunctionalized pyridines[7a] and studies on their NMR identification.[7b] The addition goes through domino reactions[10] of 1-(*N*,*N*-diethylamino)prop-1-yne and *N*-vinyl isothiocyanates derived from α-aminoacid compounds. We now study the reactivity of 1-(*N*,*N*-diethylamino)prop-1-yne with *N*-vinyl -carbodiimides and -ketenimines taking into account that these conjugated heterocumulenes can act not only as heterodienes in [4+2] cycloaddition reactions, but also as activated double bonds in heterocyclisation processes involving [2+2] cycloadditions.

N-Vinyl heterocumulenes were prepared very easily through aza-Wittig reaction[11] of *N*-vinyl-λ^5-phosphazenes with carbonyl compounds. This reaction leads to a very efficient and mild-reaction method for the construction of carbon-nitrogen double bonds, as we have reported in the synthesis of heterodienes derived from α-[12] and β-aminoacids.[4a,b] This methodology has been also recently used in elegant routes to the preparation of biologically active natural products such as the antibacterial alkaloids Eusdistomin U[13a] and Fascaplysin,[13b] the antitumor antibiotic Lavendamycin,[13c] and for the construction of the framework of pharmacologically active azafluoranthene,[13d] azacarboline,[13e] and aplysinopsine-type[13e,f] alkaloids.



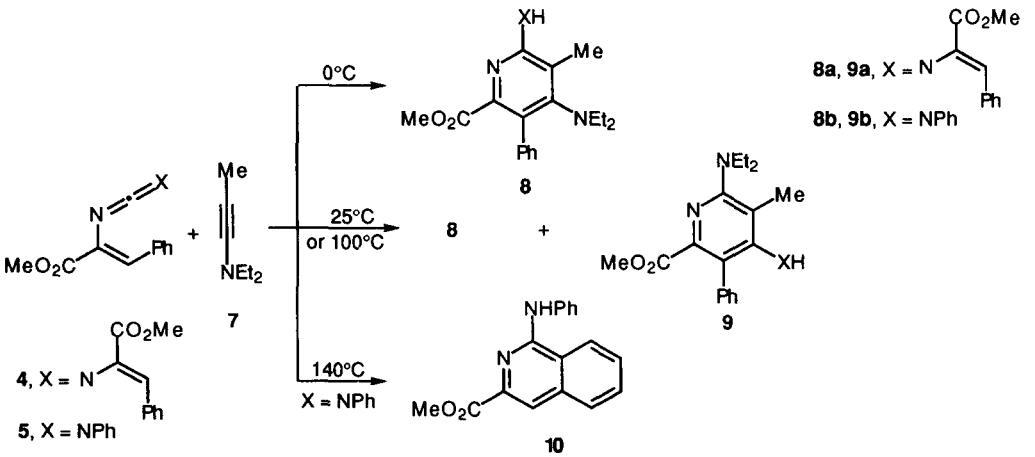
Scheme 1

Thus, symmetrical (**4**) and unsymmetrical[12] (**5**) *N*-vinyl carbodiimides, and *N*-vinyl ketenimine (**6**) were synthetized from *N*-vinyl-λ^5-phosphazenes and carbon dioxide, isocyanates, or diphenylketene respectively (Scheme 1). The key intermediate phosphazene **2** is obtained through a Staudinger reaction between azide **1** and

methyldiphenylphosphine. This phosphazene shows *Z*-isomerism in the configuration of carbon-carbon double bond as deduced from NOE experiments.[14]

Phosphazene **2** was allowed to react with carbon dioxide in THF, until no starting material remained (checked by ^{31}P-NMR), isocyanate **3** was not obtained,[15] but symmetric carbodiimide **4** was isolated instead. This result could be explained by invoking an initial aza-Wittig reaction between the phosphorous-nitrogen double bond of **2** and carbon dioxide. The intermediate *N*-vinyl isocyanate **3** formed, reacts further with a second molecule of phosphazene **2** affording *N*-vinyl carbodiimide **4**. Similarly, when compound **2** was treated with phenylisocyanate in methylene chloride at room temperature during 38 h, unsymmetrical *N*-vinyl carbodiimide **5** was isolated in 99% of yield. Treatment of *N*-vinyl-λ^5-phosphazene **2** with diphenylketene in THF at room temperature for 5 h led to ketenimine **6** in good yield. Interestingly, if the reaction is prolonged by more than 5 h, a by-product arising from a 6e$^-$ electrocyclic ring closure, begins to appear.

The azadiene system in the *N*-vinyl heterocumulenes is known to react easily with electron-rich dienophiles.[6] Therefore, taking into account the easy access to the *N*-vinyl heterocumulenes from λ^5-phosphazenes and following ousted interest in the preparation of six membered nitrogen heterocycles derived from aminoacids, we decided to explore the cycloaddition reactions of the above prepared *N*-vinyl heterocumulenes, such as carbodiimides **4**, **5** and ketenimine **6** with ynamine **7**.



Scheme 2

The reaction between carbodiimide **4** and ynamine **7** affords the pentasubstituted pyridines **8a** and **9a** in high yields (Scheme 2). Temperature plays an important role in the way of the reaction. The regioselectivity of the addition is noteworthy because when the process is run at 0 °C, exclusively, pyridine **8a** is formed; whereas at 100 °C only pyridine **9a** is formed (see Table 1, entries 1 and 3). However, when the reaction takes place at room temperature a mixture of pyridine **8a** and its isomer **9a** is observed in a ratio 3:1 (**8a**:**9a**) (Table 1, entry 2). The structures of the pentasubstituted pyridines **8a** and **9a** were assigned according to spectroscopic data.[16]

Similar behaviour has been observed when the asymmetrical carbodiimide **5** was used. Reaction of carbodiimide **5** with ynamine **7** at 0 °C for 84 hours affords the pentasubstituted pyridine **8b** with excellent yield (Scheme 2; Table 1, entry 4). However, when the reaction is carried out at room temperature, and independent

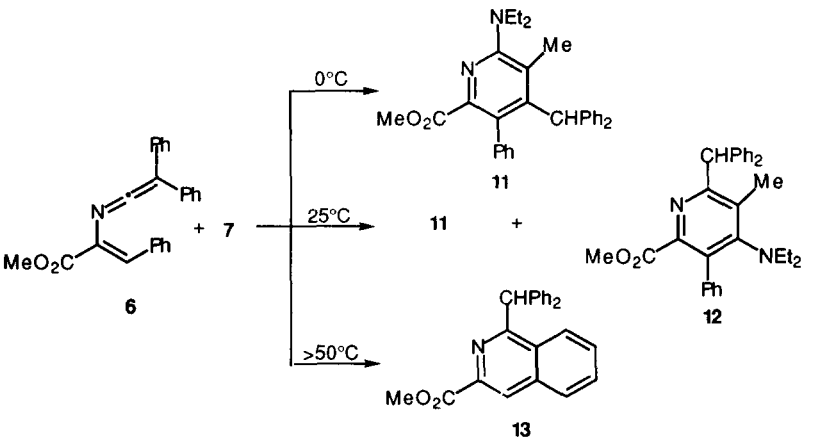
of the reaction time (from 2 to 6 days) (Table 1, entry 5), in addition to pyridine **8b** regioisomer **9b** appears (see Scheme 2) in a ratio of approximately 9:1 (**8b**:**9b**). The proportion of pyridine **9b** increases until about an equimolecular mixture of pyridines **8b** and **9b** (Table 1, entry 6) is observed if the reaction is performed at 100 °C. These two products can be easily separated by flash chromatography with silica gel. Meanwhile if the temperature of the reaction is raised above 140 °C the only product formed is isoquinoline **10**[17] (Table 1, entry 7), which corresponds to the electrocyclic ring closure of the starting material **5**.

Table 1. Reaction Conditions between Symmetrical Carbodiimides **4**, **5** and Ynamine **7**.

Entry	T (°C)	t (h)	Process[a]	Solvent	Product	RR[b]	Yield[c]
1	0	48	[4+2]	THF or $CHCl_3$	**8a**	100	94
2	25	72	[4+2]	THF or $CHCl_3$	**8a**	75	89
			[2+2]		**9a**	25	
3	100	96	[2+2]	Toluene	**9a**	100	88
4	0	84	[4+2]	THF or $CHCl_3$	**8b**	100	95
5	25	72	[4+2]	THF or $CHCl_3$	**8b**	90	94
			[2+2]		**9b**	10	
6	100	72	[4+2]	Toluene	**8b**	50	93
			[2+2]		**9b**	50	
7	140	48	6 e⁻ closure	Xylenes	**10**	100	100

a. Refers to initial process between carbodiimide and ynamine; b. %, Relative ratio; c. %, Total yield.

Both reactivity patterns observed in the reaction of carbodiimides with ynamine **7** can be extended to *N*-vinyl ketenimines derived from α-aminoacids, that also contain a 2-azadiene moiety in the molecular structure.



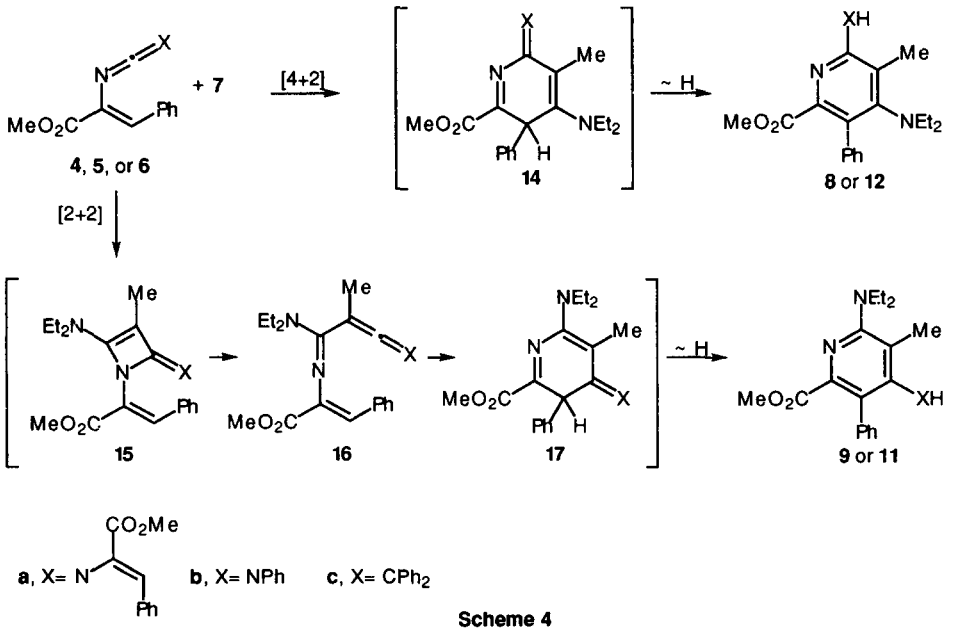
Scheme 3

The reaction of ketenimine **6** with ynamine **7** in THF or chloroform affords different results depending upon the temperature at which the reaction is run. At 0 °C the pentasubstituted pyridine **11** is observed as the unique product (Scheme 3; Table 2, entry 1). In contrast, at 25 °C a mixture is obtained, in an approximate ratio of 1:1 of pyridine **11** and its isomer **12** (Table 2, entry 2). At higher temperatures a new product, identified as the isoquinoline **13**, appears (Table 2, entry 3). Formation of this compound can be explained through electrocyclic closure of heterocumulene **6** in a similar way to that previously reported in the case of 3,4-diarylsubstituted *N*-vinyl ketenimines.[18] The products **11** and **12** are isolated and purified by column chromatography using silica gel as support. The experimental conditions and yields are shown in Table 2.

Table 2. Reaction Conditions between Ketenimine **6** and Ynamine **7**.

Entry	T (°C)	t (h)	Process[a]	Solvent	Product	RR[b]	Yield[c]
1	0	5	[2+2]	THF or $CHCl_3$	**11**	100	89
2	25	24	[2+2]	THF or $CHCl_3$	**11**	52	87
			[4+2]		**12**	48	
3	>50	20	6 e^- closure	THF, $CHCl_3$, toluene, or Xylenes	**13**	100	100

a. Refers to initial process between ketenimine and ynamine; b. %, Relative ratio; c. %, Total yield.



Scheme 4

Formation of pyridines **8** or **12** can be explained through the initial formation of a [4+2] Diels-Alder type cycloadduct **14** (Scheme 4). This intermediate could then undergo intramolecular [1,5] hydrogen migration to

the aromatic pyridine under the reaction conditions. Similarly, the pyridines **9** or **11** could arise from the initial formation of a [2+2] cycloadduct intermediate **15** regioselectively, in which the carbon-nitrogen double bond of the allene reacts with the triple bond of the ynamine. This compound rearranges to the cumulene **16**, which then undergoes an electrocyclical ring-closure affording the dihydropyridine **17**. This intermediate could then experience tautomerization to yield the pentasubstituted pyridines **9** or **11**.

In summary, heterocumulenes derived from α-aminoacids **4-6** are prepared from a common intermediate, *N*-vinyl-λ^5-phosphazene **2**, through an aza-Wittig reaction with carbon dioxide, phenylisocyanate, and phenylketene, respectively. At high temperatures the electrocyclic ring closure of the starting heterocumulenes **5** and **6** predominates and isoquinolines **10** and **13** are quantitatively obtained. When conjugated carbodiimides **4**, **5** and ketenimine **6** react with ynamine **7**, pentasubstituted pyridines **8**, **9**, **11**, and **12** containing a methoxycarbonyl group in the 6-position are easily and regioselectively synthesized with excellent yields. They originate from [2+2] or [4+2] cycloaddition processes governed by a small range of temperatures. It is noteworthy that pyridines derived from aminoacids are useful intermediates in the synthesis of biologically active compounds and natural products.[1]

EXPERIMENTAL SECTION

General. Melting points were taken on samples in open capillary tubes using a Büchi melting-point apparatus and are uncorrected. NMR spectra were obtained using a Bruker AC300 or AMX400 spectrometers with deuteriated chloroform as solvent; chemical shifts are reported downfield from internal tetramethylsilane for ^{1}H- and ^{13}C-NMR, or from H_3PO_4 85% in the case of ^{31}P-NMR spectra. IR spectra were recorded on a Phillips PU9716 or a Perkin-Elmer 1720-X FT spectrophotometers. Microanalyses were performed on a Perkin-Elmer model 240B instrument, and mass spectra were obtained using a Hewlett-Packard 5987A spectrometer. The solvents were dried by standard methods described in the literature. Vinyl azide **1**[19] and diphenylketene[20] were synthetized as has been reported previously. Ynamine **7** was obtained according to the method of Brandsma.[21]

3-Methoxycarbonyl-1-methyl-1,1,4-triphenyl-2-aza-1λ^5-phosphabuta-1,3-diene **2**. A solution of vinyl azide **1** (4.3 g, 20 mmol) in anhydrous Et_2O (15 ml) was added dropwise at 0 °C, to a solution of methyldiphenylphosphine (4.0 g, 20 mmol) in anhydrous Et_2O (15 ml) under nitrogen atmosphere. The mixture was stirred at room temperature until the evolution of nitrogen finished. The yellow solid was filtered and recrystallized from hexane/Et_2O to give phosphazene **2** (7.4 g, 99%). M.p.: 116-117 °C; IR (KBr): 1701 (C=O), and 1321 (P=N); ^{1}H-NMR: 2.25 (d, $^2J_{PH}$ 12.9 Hz, 3 H, Me), 3.58 (s, 3 H, OMe), 6.70 (d, $^4J_{PH}$ 7.4 Hz, 1 H, HC=), 7.10-7.85 (m, 13 H, Ph), and 8.17 (d, $^3J_{HH}$ 7.5 Hz, 2 H, H_{orto}); ^{13}C-NMR: 17.0 (d, $^1J_{PC}$ 67.3 Hz, Me), 51.8 (OMe), 116.0 (d, $^3J_{PC}$ 19.5 Hz, HC=), 125.6 (d), 127.9 (d, $^3J_{PC}$ 37.1 Hz, C_3), 128.8 (d, $^2J_{PC}$ 66.1 Hz, C_2), 130.1 (d), 130.7 (d), 131.6 (d), 134.5 (d, $^1J_{PC}$ 105.0 Hz, C_1), 135.9 (s), 138.4 (C_{ipso}), and 168.6 (d, $^3J_{PC}$ 7.6 Hz, C=O); ^{31}P-NMR: 7.42 ppm; MS (m/z): 375 (M^+, 79%), 316 (29), and 200 (100); Elemental analysis (%): calc. for $C_{23}H_{22}NO_2P$: C, 73.59; H, 5.91; N, 3.73. Found: C, 73.7; H, 5.8; N, 3.6.

3,5-Diaza-2,6-dimethoxycarbonyl-1,7-diphenyl-1,3,4,6-heptatetraene ***4***. To a solution of *N*-vinyl phophazene **2** (1.9 g, 5 mmol) in THF (150 ml), which was in a cool bath at -80 °C, was added a great excess of solid carbon dioxide. After 4 days the reaction was concentrated, and the crude, which were vinyl carbodiimide **4** and methyldiphenylphosphine oxide, was chromatographied on silica gel with Et_2O. The solid carbodiimide was recrystallized from hexane/Et_2O (1.4 g, 79%). M. p.: 120-121 °C; IR (KBr): 2115 (N=C=N), 1700 (C=O), and 1372 (N=C=N); ^{1}H-NMR: 3.89 (s, 6 H, OMe), 7.19 (s, 2 H, HC=), 7.30-7.53 (m, 6 H, Ph), and 8.01 (d, $^3J_{HH}$ 6.4 Hz, 4 H, H_{orto}); ^{13}C-NMR: 52.9, 124.6, 128.3, 128.4, 129.4, 130.5, 133.6, 134.7, and 164.9; MS (m/z): 362 (M^+, <1%) and 116 (100); Elemental analysis (%): calc. for $C_{21}H_{18}N_2O_4$: C, 69.61; H, 4.97; N, 7.73. Found: C, 69.6; H, 5.0; N, 7.6.

1,3-Diaza-4-methoxycarbonyl-1,5-diphenyl-1,2,4-pentatriene ***5***. Similarly to a procedure already described for carbodiimide **4** was obtained carbodiimide **5** (100% yield). M. p.: 63-64 °C; IR (KBr): 2124 (N=C=N), 1711 (C=O), and 1593 (C=N); ^{1}H-NMR: 3.86 (s, 3 H, OMe), 7.14 (s, 1 H, HC=), 7.22-7.48 (m, 8 H, Ph), and 7.92 (d, $^3J_{HH}$ 7.0 Hz, 2 H, H_{orto}); ^{13}C-NMR: 53.2, 124.3, 125.0, 125.2, 128.4, 128.4, 129.3, 129.5, 130.5, 133.5, 134.5, 138.1, and 165.0; MS (m/z): 278 (M^+, 47%), 219 (12), and 116 (100); Elemental analysis (%): calc. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.4; H, 5.1; N, 9.7.

3-Aza-4-methoxycarbonyl-1,1,5-triphenyl-1,2,4-pentatriene ***6***. The general procedure was similar to mention above for carbodiimide **4** (99% yield). M. p.: 114-115 °C; IR (KBr): 1983 (N=C=C), 1722 (C=O), and 1595 (C=N); ^{1}H-NMR: 3.80 (s, 3 H, OMe) and 7.10-8.00 (m, 16 H, Ph + HC=); ^{13}C-NMR: 52.8, 126.0, 126.4, 127.8, 128.2, 128.5, 128.6, 128.6, 130.1, 131.4, 133.0, 133.1, 134.2, and 163.9; MS (m/z): 353 (M^+, 93%), 352 (100), and 294 (16); Elemental analysis (%): calc. for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96. Found: C, 81.9; H, 5.2; N, 3.7.

4-(N,N-Diethylamino)-2-[(1-methoxycarbonyl-2-phenylethenyl)amino]-6-methoxycarbonyl-3-methyl-5-phenylpyridine ***8a***. To a solution of carbodiimide **4** (0.36 g, 1 mmol) in chloroform (3 ml) at 0 °C was added slowly ynamine **7** (0.12 g, 1.1 mmol). The mixture was allowed to react for 48 h at 0°C. Then, solvent was evaporated under reduced pressure and the crude was purified by means of a chromatographic column with silica gel and Et_2O/hexane (1:1) as eluent. Then, compound **8a** (0.45 g, 94%) was recrystallized from Et_2O/hexane. M. p.: 159-160 °C; IR (KBr): 3384 (N-H), 2968 (C-H), 1737 (C=O), and 1735 (C=O); ^{1}H-NMR: 0.87 (t, $^3J_{HH}$ 7.1 Hz, 6 H, Me), 2.10 (s, 3 H, Me), 2.66 (q, $^3J_{HH}$ 7.1 Hz, 4 H, NCH_2), 3.49 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 6.42 (s, 1 H, NH), 6.92 (s, 1 H, HC=), and 7.12-7.49 (m, 10 H, Ph); ^{13}C-NMR:13.7, 13.9, 46.1, 51.7, 52.4, 118.0, 121.6, 126.9, 127.3, 127.6, 127.8, 128.3, 128.8, 129.1, 129.9, 134.8, 137.3, 146.0, 153.1, 157.3, 167.0, and 167.3; MS (m/z): 473 (M^+, 1%), 413 (2), 176 (30), and 105 (100); Elemental analysis (%): calc. for $C_{28}H_{31}N_3O_4$: C, 71.02; H, 6.60; N, 8.87. Found: C, 71.0; H, 6.5; N, 8.9.

4-(N,N-Diethylamino)-6-methoxycarbonyl-3-methyl-5-phenyl-2-phenylaminopyridine ***8b***. Similar procedure to describe for **8a**. Pyridine **8b**: m. p.: 137-138 °C; IR (KBr): 3433 (N-H), and 1728 (C=O); ^{1}H-NMR: 0.91 (t, $^3J_{HH}$ 7.1 Hz, 6 H, Me), 2.18 (s, 3 H, Me), 2.75 (q, $^3J_{HH}$ 7.1 Hz, 4 H, NCH_2), 3.55 (s, 3 H, OMe), 6.36 (s, 1 H, NH), 6.98 (t, $^3J_{HH}$ 7.4 Hz, 1 H, *p*-PhNH), 7.24-7.38 (m, 7 H, ArH), and 7.51 (t, $^3J_{HH}$

8.6 Hz, 2 H, *o*-PhNH); ^{13}C-NMR: 13.7, 14.1, 46.3, 51.8, 118.6, 118.7, 121.4, 121.9, 126.9, 127.4, 127.6, 129.8, 137.3, 141.2, 146.2, 153.8, 157.0, and 167.9; MS (m/z): 389 (M^+, 55%), 360 (30), 330 (5), and 77 (100); Elemental analysis (%): calc. for $C_{24}H_{27}N_3O_2$: C, 74.01; H, 6.99; N, 10.79. Found: C, 74.1; H, 6.8; N, 10.6.

2-(N,N-Diethylamino)-4-[(1-methoxycarbonyl-2-phenylethenyl)amino]-6-methoxycarbonyl-3-methyl-5-phenylpyridine ***9a.*** This compound has been synthetized similarly to mention above. Pyridine **9a**: m. p.: 148-149 °C; IR (KBr): 3412 (N-H), 2965 (C-H), 1734 (C=O), and 1719 (C=O); ^{1}H-NMR: 0.96 (t, $^3J_{HH}$ 7.0 Hz, 6 H, Me), 1.75 (s, 3 H, Me), 2.73 (q, $^3J_{HH}$ 7.0 Hz, 4 H, NCH_2), 3.57 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 6.01 (s, 1 H, NH), 6.93 (s, 1 H, HC=), and 7.10-7.60 (m, 10 H, ArH); ^{13}C-NMR: 13.3, 17.0, 44.3, 51.9, 52.6, 114.2, 118.7, 120.9, 127.5, 127.7, 127.9, 128.2, 128.5, 128.8, 129.0, 133.4, 135.8, 143.9, 147.5, 161.7, 166.1, and 167.6; MS (m/z): 473 (M^+, 7%), 414 (21), and 59 (100); Elemental analysis (%): calc. for $C_{28}H_{31}N_3O_4$: C, 71.17; H, 6.40; N, 8.89. Found: C, 71.2; H, 6.3; N, 8.7.

2-(N,N-Diethylamino)-6-methoxycarbonyl-3-methyl-5-phenyl-4-phenylaminopyridine ***9b.*** Similar procedure to describe for **8a**. Pyridine **9b**: m. p.: 119-120 °C; IR (KBr): 3389 (N-H) and 1736 (C=O); ^{1}H-NMR: 1.19 (t, $^3J_{HH}$ 7.0 Hz, 6 H, Me), 1.99 (s, 3 H, Me), 3.32 (q, $^3J_{HH}$ 7.0 Hz, 4 H, NCH_2), 3.58 (s, 3 H, OMe), 5.52 (s, 1 H, NH), 6.65 (d, $^3J_{HH}$ 8.0 Hz, 2 H, *o*-PhNH), 6.90 (t, $^3J_{HH}$ 7.4 Hz, 1 H, *p*-PhNH), and 7.18-7.44 (m, 7 H, ArH); ^{13}C-NMR: 13.3, 16.7, 44.6, 51.7, 117.6, 117.6, 121.1, 122.6, 127.6, 128.6, 128.9, 129.4, 135.1, 143.4, 144.9, 147.6, 161.8, and 167.8; MS (m/z): 389 (M^+, 28%), 360 (100), 330 (11), and 77 (76); Elemental analysis (%): calc. for $C_{24}H_{27}N_3O_2$: C, 74.01; H, 6.99; N, 10.79. Found: C, 74.0; H, 7.0; N, 10.6.

3-Methoxycarbonyl-1-phenylaminoisoquinoline ***10***. To a solution of carbodiimide **5** (0.28 g, 1 mmol) in xylenes (3 ml) was heated at 140 °C for 48 h. Then, solvent was evaporated under reduced pressure given isoquinoline **10** (0.28 g, 100%). The latter was recrystallized from hexane. M. p.: 55-56 °C; IR (KBr): 3390 (N-H) and 1724 (C=O); ^{1}H-NMR: 3.99 (s, 3 H, OMe), 5.27 (s, 1 H, NH), 7.06 (t, $^3J_{HH}$ 7.4 Hz, 1 H, HC=), 7.36 (m, 2 H, HC=), 7.63 (t, $^3J_{HH}$ 7.4 Hz, 1 H, HC=), 7.69 (t, $^3J_{HH}$ 7.3 Hz, 1 H, HC=), 7.86 (d, $^3J_{HH}$ 8.3 Hz, 2 H, HC=), 7.97 (d, $^3J_{HH}$ 8.5 Hz, 2 H, HC=), and 8.06 (s, 1 H, HC=); ^{13}C-NMR: 52.5, 116.9, 119.3, 121.0, 121.7, 122.5, 128.7, 128.9, 129.0, 130.4, 136.9, 139.4, 140.3, 153.0, and 166.6; MS (m/z): 278 (M^+, 23%), 219 (13), and 77 (100); Elemental analysis (%): calc. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.4; H, 5.0; N, 10.0.

2-(N,N-Diethylamino)-6-methoxycarbonyl-3-methyl-5-phenyl-4-diphenylmethylpyridine ***11***. General procedure similar to described previously for pyridine **8a**. Compound **11**: m. p.: 185-186 °C; IR (KBr): 1737 (C=O); ^{1}H-NMR: 1.11 (t, $^3J_{HH}$ 7.0 Hz, 6 H, Me), 1.77 (s, 3 H, Me), 3.15 (q, $^3J_{HH}$ 7.0 Hz, 4 H, NCH_2), 3.54 (s, 3 H, OMe), 5.68 (s, 1 H, C*H*Ph_2), 6.94 (d, $^3J_{HH}$ 6.3 Hz, 4 H, H_{orto} $CHPh_2$), 6.99 (d, $^3J_{HH}$ 6.3 Hz, 2 H, H_{orto} Ph), 7.15-7.30 (m, 7 H, Ph), 7.49 (t, $^3J_{HH}$ 8.0 Hz, 1 H, H_{para} Ph), and 7.81 (d, $^3J_{HH}$ 6.7 Hz, 1 H, H_{para} Ph); ^{13}C-NMR: 13.2, 18.1, 45.0, 51.7, 52.2, 126.1, 127.3, 127.7, 128.0, 128.2, 129.1, 129.4, 131.0, 137.6, 141.5, 145.1, 151.0, 162.2, and 168.1; MS (m/z): 464 (M^+, 33%), 435 (100), 405 (12), and 167 (10); Elemental analysis (%): calc. for $C_{31}H_{32}N_2O_2$: C, 80.13; H, 6.95; N, 6.03. Found: C, 80.2; H, 6.8; N, 6.0.

4-(N,N-Diethylamino)-6-methoxycarbonyl-3-methyl-5-phenyl-2-diphenylmethylpyridine ***12***. Similar to described for **8a**. Pyridine **12**: oil, R_F (Et_2O-hexane): 0.7; IR (NaCl): 1732 (C=O); ^{1}H-NMR: 0.87 (t, $^3J_{HH}$ 7.1 Hz, 6 H, Me), 2.29 (s, 3 H, Me), 2.71 (q, $^3J_{HH}$ 7.1 Hz, 4 H, NCH_2), 3.48 (s, 3 H, OMe), 5.77 (s, 1 H, C*H*Ph_2), and 6.90-7-89 (m, 15 H, Ph); ^{13}C-NMR: 13.7, 15.3, 46.3, 51.8, 55.4, 126.1, 127.2, 127.8, 128.2, 129.5, 130.1, 132.2, 132.3, 137.5, 142.6, 143.5, 155.0, 160.5, and 168.1; MS (m/z): 464 (M^+, 25%), 435 (100), and 167 (20); Elemental analysis (%): calc. for $C_{31}H_{32}N_2O_2$: C, 80.13; H, 6.95; N, 6.03. Found: C, 80.0; H, 7.0; N, 5.9.

3-Methoxycarbonyl-1-diphenylmethylisoquinoline ***13***. Method A. In the standard conditions described above when ketenimine **6** was used, and the reaction time was more than 5 h started to appear a by-product which was isoquinoline **13**. At the end of 12 h all the ketenimine was transformed to isoquinoline. Moreover, if higher temperatures was aplied the reaction time was shorter. Method B. Other way to obtain isoquinoline **13** was starting from ketenimine **6**. To a solution of ketenimine **6** (1,4 g, 4 mmol) in THF, chloroform, methylene chloride, acetonitrile, toluene or bencene at room temperature or heating (the process was faster) was possible to aisolate in quantitative yield isoquinoline **13**. M. p.: 139-140 °C; IR (KBr): 1736 (C=O) and 1566 (C=N); ^{1}H-NMR: 3.98 (s, 3 H, OMe), 6.45 (s, 1 H, C*H*Ph_2), 7.64 (dd, $^3J_{HH}$ 6.2 Hz, $^3J_{HH}$ 8.5 Hz, 1 H, H-7), 7.71 (dd, $^3J_{HH}$ 6.7 Hz, $^3J_{HH}$ 8.2 Hz, 1 H, H-6), 7.97 (d, $^3J_{HH}$ 8.2 Hz, 1 H, H-5), 8.28 (d, $^3J_{HH}$ 8.5 Hz, 1 H, H-8), and 8.48 (s, 1 H, H-4); ^{13}C-NMR: 52.4, 55.4, 123.0, 125.5, 126.4, 127.3, 128.1, 128.5, 128.6, 129.4, 136.3, 138.0, 140.8, 142.1, 161.6, and 167.0; MS (m/z): 353 (M^+, 66%), 294 (9), 167 (31), and 77 (100); Elemental analysis (%): calc. for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96. Found: C, 81.3; H, 5.5; N, 3.8.

Acknowledgments. M. F. thanks the Ministerio de Educación y Ciencia for a Predoctoral Scholarship. We are also grateful to Dr. F. López-Ortiz for the helpful discussions.

REFERENCES AND NOTES

1. For recent reviews see: a) Schneider, M. J. *Alkaloids: Chemical and Biological Perspectives*, Pelletier, S. W. (Ed.), Pergamon Press, Oxford 1996, Vol. 10, p 155. b) Shipman, M. *Contemp. Org. Synth.* **1995**, *2*, 1.
2. a) For a review see: Jones, G. *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R.; Rees, C. W.; Boulton, A. J.; Mckillop, A. (Eds.), Pergamon Press, Oxford 1984, Vol. 2, p 395. b) Epsztajn, J.; Bieniek, A.; Kowalska, J. A. *Tetrahedron* **1991**, *47*, 1697-1706. c) Robinson, J. M.; Brent, L. W.; Chau, C.; Floyd, K. A.; Gillham, S. L.; McMahan, T. L.; Magda, D. J.; Motycka, T. J.; Pack, M. J.; Roberts, A. L.; Seally, L. A.; Simpson, S. L.; Smith, R. R.; Zalesny, K. N. *J. Org. Chem.* **1992**, *57*, 7352-7355, and literature therein cited. d) Barluenga, J.; Fustero, S.; Gotor, V. *Synthesis* **1975**, 191-192. e) Guzman, A.; Romero, M.; Maddox, M. L.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 5793-5797. f) Barluenga, J.; González, F. J.; Carlón, R. P.; Fustero, S. *J. Org. Chem.* **1991**, *56*, 6751-6754. g) Oikawa, T.; Kanomata, N.; Tada, M. *J. Org. Chem.* **1993**, *58*, 2046-2051. h) Molina, P.; Pastor, A.; Vilaplana, M. J. *Tetrahedron Lett.* **1993**, *34*, 3773-3776. i) Katritzky, A. R.; Mazurkiewicz, R.; Stevens, C. V.; Gordeev, M. F. *J. Org. Chem.* **1994**, *59*, 2740-2742.

3. For reviews see: a) Boger, D. L. *Comprehensive Organic Synthesis*, Trost, B. M.; Paquette, L. A.; (Eds.), Pergamon Press, Oxford 1991, Vol. 5, p. 451-512; b) Fringelli, F.; Tatichi, A. *Dienes in the Diels-Alder Reaction*, John Wiley, New York 1990; c) Barluenga, J.; Joglar, J.; González, F. J.; Fustero, S. *Synlett* **1990**, 129-138.
4. a) Palacios, F.; Perez de Heredia, I.; Rubiales, G. *J. Org. Chem.* **1995**, *60*, 2384-2390. b) Palacios, F.; Rubiales, G. *Tetrahedron Lett.* **1996**, *37*, 6379-6382. c) Palacios, F.; Aparicio, D.; de los Santos, J. M. *Tetrahedron* **1996**, *52*, 4857-4866.
5. a) Kelly, T. R.; Liu, H. T. *J. Am. Chem. Soc.* **1985**, *107*, 4998-4999. b) Khanapure, S. P.; Blehl, E. R. *Heterocycles* **1990**, *31*, 505-516.
6. Dondoni, A.; Kniezo, L.; Medici, A. *J. Org. Chem.* **1982**, *47*, 3994-3998.
7. a) Barluenga, J.; Ferrero, M.; Peláez-Arango, E.; López-Ortiz, F.; Palacios, F. *J. Chem. Soc., Chem. Commun.* **1994**, 865-866. b) Peláez-Arango, E.; López-Ortiz, F.; Barluenga, J.; Ferrero, M.; Palacios, F. *Magn. Reson. Chem.* **1994**, *32*, 646-651.
8. For a review see: Barluenga, J.; Palacios, F. *Org. Prep. Proc. Int.* **1991**, *23*, 1-65.
9. a) Barluenga, J.; Ferrero, M.; Palacios, F. *Tetrahedron Lett.* **1990**, *31*, 3497-3500. b) Barluenga, J.; Ferrero, M.; Palacios, F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2193-2197.
10. Tietze, L. F.; Beifus, U. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131-163.
11. For recent reviews of the aza-Wittig reaction see: a) Eguchi, S.; Matsushita, Y.; Yamashita, K. *Org. Prep. Proc. Int.* **1992**, *24*, 209. b) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353-1406. c) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197-1218.
12. Barluenga, J.; Ferrero, M.; Palacios, F. *Tetrahedron Lett.* **1988**, *29*, 4863-4864.
13. a) Molina, P.; Fresneda, P. M.; García-Zafra, S. *Tetrahedron Lett.* **1995**, *36*, 3581-3582. b) Molina, P.; Fresneda, P. M.; García-Zafra, S.; Almendros, P. *Tetrahedron Lett.* **1994**, *35*, 8851-8854. c) Molina, P.; Murcia, F.; Fresneda, P. M. *Tetrahedron Lett.* **1994**, *35*, 1453-1456. d) Molina, P.; García-Zafra, S.; Fresneda, P. M. *Synlett.* **1995**, 43-45. e) Chavignon, O.; Teulade, J. C.; Roche, D.; Madesclaire, M.; Blache, Y.; Gueiffier, A.; Chabard, J. L.; Dauphin, G. *J. Org. Chem.* **1994**, *59*, 6413-6418. f) Molina, P.; Almendros, P.; Fresneda, P. M. *Tetrahedron* **1994**, *50*, 2241-2254.
14. Ferrero, M. *Ph. D. Thesis*, Universidad de Oviedo, **1992**.
15. A synthesis of this compound through an alternative route using [(methylthio)carbonyl]amino derivatives has been reported: Alvarez-Ibarra, C.; Barbolla, M.; López-Ranz, M.; Quiroga, M. L.; Ruiz, M. P. *J. Org. Chem.* **1994**, *59*, 2648-2651.
16. Peláez-Arango, E.; Ferrero, M.; López-Ortiz, F. *Magn. Reson. Chem.* **1996**, *34*, 368-372.
17. Previously described by: Molina, P.; Tárraga, A.; Lidón, M. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1727-1731.
18. Capuano, L.; Braun, C.; Kühn, F. *Liebigs Ann. Chem.* **1992**, 15-18.
19. Knittel, D. *Synthesis* **1985**, 186-188.
20. Smith, L. I.; Hoehn, H. H. *Org. Synth.* **1955**, *Coll. Vol. III*, p. 356-358.
21. Brandsma, L. *Studies in Organic Chemistry 34. Preparative Acetylenic Chemistry*, 2nd ed., Elsevier, 1988.