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CYCLOADDITION REACTIONS OF NEUTRAL 2-AZADIENES WITH ACETYLENIC ESTERS[#]

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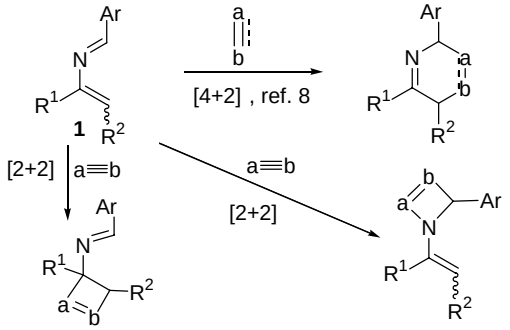
Abstract – A method for the preparation of functionalized polysubstituted dihydropyridine and pyridine derivatives is described, based on cycloaddition reactions of 2-aza-1,3-dienes with dimethyl acetylenedicarboxylate and ethyl propiolate.

INTRODUCTION

The Diels-Alder reaction has both enabled and shaped the art and science of synthesis in recent years and 2-azabutadiene systems have proved to be efficient heterodienes in Aza Diels-Alder processes.[1,2] The great majority of 2-azadienes studied are substituted with electron donating groups and are excellent reagents in Diels-Alder reactions with electron-poor dienophiles.[1,2c-f,3] Among them, azadienes have been used as heterodienes [1d,1g,4] for the preparation of nitrogen heterocyclic compounds. These experimental results are corroborated by theoretical studies,[4c] and the presence or absence of substituents especially in 3-position even seems to play an important role in the reactivity of 2-azadienes.[5]

Given the above, we have been involved in the synthesis of electron-poor azadienes derived from aminophosphorus derivatives[6] and β-amino esters[7] as well as of azadienes[8] and in the preparation of nitrogen heterocyclic compounds.[9] As a continuation of our work in the cycloaddition chemistry of neutral 2-azadienes,[8] here we aim to explore the behavior of azadienes (**1**) with acetylenes such as dimethyl acetylenedicarboxylate (DMAD) and ethyl propiolate, whether [4+2]-aza Diels-Alder and/or selective [2+2] cycloaddition processes could involve these substrates (Scheme 1), as well as the effect of substituents at C-3 and C-4 positions.[5] This strategy could open new entries for the preparation of substituted six membered heterocycles.

[#] Dedicated to Prof. Dr. Pierre Potier on the occasion of his 70th Birthday.

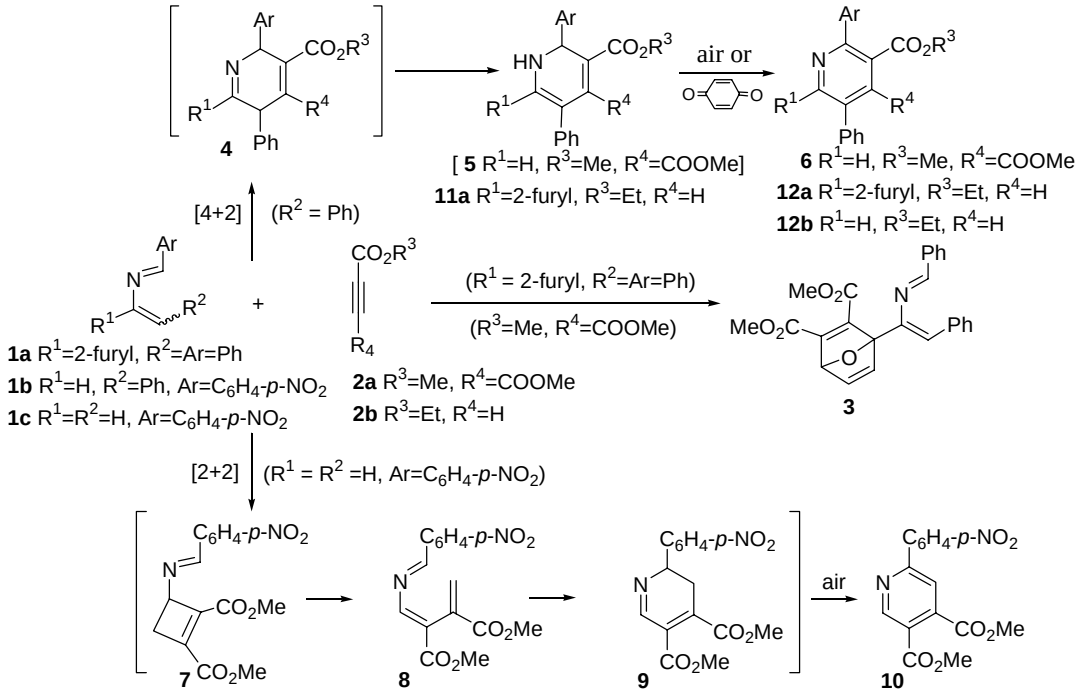


Scheme 1

RESULTS AND DISCUSSION

We first investigated the Diels-Alder reaction of 2-azadienes (**1**) with acetylenic diester (**2a**) (R^3 = Me, R^4 = COOMe). Thus, when azadiene (**1a**) (R^1 = 2-furyl, R^2 = Ar = Ph), easily prepared by Aza-Wittig treatment of *N*-vinylic phosphazenes and aldehydes,[8c] was treated with dimethyl acetylenedicarboxylate (DMAD) (**2a**) in refluxing toluene (110°C) for 2 days the expected dihydropyridine (**4**) (or its tautomers) was not obtained, and a cycloadduct (**3**) in low yield was isolated instead (Scheme 2, 30% yield) with several unrecognizable compounds. Molecular ion obtained in MS spectroscopy of compound (**3**) indicated that a molecule of DMAD was incorporated into the starting azadiene (**1a**). However, ^{1}H NMR spectroscopy showed two singlets at 6.40 and 8.42 ppm recognizables as 2-azadienic protons while furan hydrogens were not observed, suggesting that the furan heterocycle was involved in the process. These data are consistent with the proposed structure of cycloadduct (**3**), and its formation (Scheme 2) can be explained through a [4+2] cycloaddition reaction of furan as a diene with DMAD as dienophile in a similar way to previous cycloaddition reactions of furan derivatives.[10] Consistent with this fact, when azadienes without furan substituent in position 3, such as 1,3,4-triphenyl-2-aza-1,3-butadiene (**1**) (R^1= R^2= Ar =Ph), and 1-(3-pyridyl)-3-(2-thienyl)-4-phenyl -2-aza-1,3-butadiene (**1**) (R^1= 3-thi, R^2= Ph, Ar =3-pyr), were treated with DMAD (**2a**) in refluxing toluene (110°C) both reagents disappeared to give several unrecognizable compounds. Interestingly, 2-azadienes (**1**) with no substituent on 3-position (R^1 = H) have shown different behavior when they react with acetylenic diesters (**2a**) (R^3 = Me, R^4 = COOMe). In our hands, heterodiene (**1b**) (R^1 = H, R^2 = Ph, Ar = C_6H_4-*p*-NO_2) reacted with DMAD (**2a**) in a sealed tube at 110°C affording functionalized pyridine derived from β-amino acids (**6**) (Scheme 2, Table 1, Entry 2). The formation of pyridine (**6**) could be explained through a [4+2] cycloaddition reaction of 2-azadiene (**1**) with DMAD as dienophile to give dihydropyridine (**4**), which aromatization affords pyridine (**6**). Analogously, it has been previously reported[11] a [4+2] cycloaddition reaction between 1,4-diaryl-2-aza-1,4-butadienes and diethyl acetylenedicarboxylate, giving similar pyridines (**6**) (R^3 = Et,

R^4 = COOEt) containing two aryl groups in 2- and 5-positions as well as two carboxylic esters in 3- and 4-positions (Scheme 2).



Scheme 2

However, no substitution pattern on 3- and 4-position of 2-azadiene (**1**) (R^1 = R^2 = H) directed the reaction with acetylenic diesters in a different way. Reaction of DMAD (**2a**) with less substituted 2-azadiene (**1c**) (R^1 = R^2 = H, Ar = C_6H_4-*p*-NO_2) afforded pyridine (**10**) exclusively (Scheme 2, Table 1, Entry 3). Careful inspection of NMR spectral data led us to assign the substituent location in the pyridine ring. The ^{1}H NMR spectrum of compound (**10**) revealed no $^3J_{HH}$ coupling between pyridinic protons H-3 and H-6 appearing as singlets at δ 7.92 ppm and 9.11 ppm, respectively. Moreover, ^{1}H NMR NOE experiments of pyridine (**10**) were carried out at room temperature in $CDCl_3$, and selective saturation at δ = 7.92 (H-3) afforded significant NOEs (3 %) with the aromatic protons of the *p*-NO_2-phenyl substituent. Also, ^{1}H-^{13}C heteronuclear multiple-bond correlation NMR (HMBC) was achieved for the complete elucidation of this structure. Therefore, visible are HMBC signals of the two- or three-bond correlation between the pyridinic protons H-3 and H-6 and carboxylic carbon and there is no signal between pyridinic H-3 and C-6, and pyridinic H-6 and C-3, which means that respective H and C are more than two or three bond distance. The formation of this compound (**10**) can be explained through a [2+2] cycloaddition reaction, followed by cyclobutene (**7**) opening, heterocyclization and complete aromatization of intermediate (**9**) under the reaction conditions (Scheme 2).

With these results in hand, reaction of 2-azadienes (**1**) with monoacetylenic esters were also studied. When 2-azadiene (**1a**) (R^1 = 2-furyl, R^2 = Ar = Ph) was treated with ethyl propiolate (**2b**) (R^3 = Et, R^4 =

H) in refluxing toluene, dihydropyridine (**11a**) (R^1 = 2-furyl, R^2 = Ar = Ph, R^3 = Et, R^4 = H) (with the carboxylic ester on 3-position) was obtained in a regioselective fashion (Scheme 2, Table 1, Entry 4). ^{1}H-NMR spectrum of compound (**11a**) showed two double doublets at 5.34 and 6.08 ppm corresponding to two protons of the furan ring, a singlet at 4.63 ppm and a signal at 1.27 ppm which dissappeared when the sample was treated with deuterium oxide. Structural assignments were supported by NOE and ^{1}H-^{13}C heteronuclear multiple-bond correlation NMR spectral experiments (HMBC). The selective saturation at δ = 4.63 ppm afforded NOE with aromatic protons. Moreover, HMBC signals of the two- or three-bond correlation between H-1 and carboxylic carbon and H-2 and C-4 are visibles which confirmed the proposed structure for compound (**11a**). Aromatization of 1,2-dihydropyridine (**11a**) was performed by heating this compound at 80°C with benzoquinone to give tetrasubstituted pyridine (**12a**) (Scheme 2, Table 1, Entry 5).

Table 1: Cycloadducts (**3**, **6**, **10**, **11** and **12**) obtained.

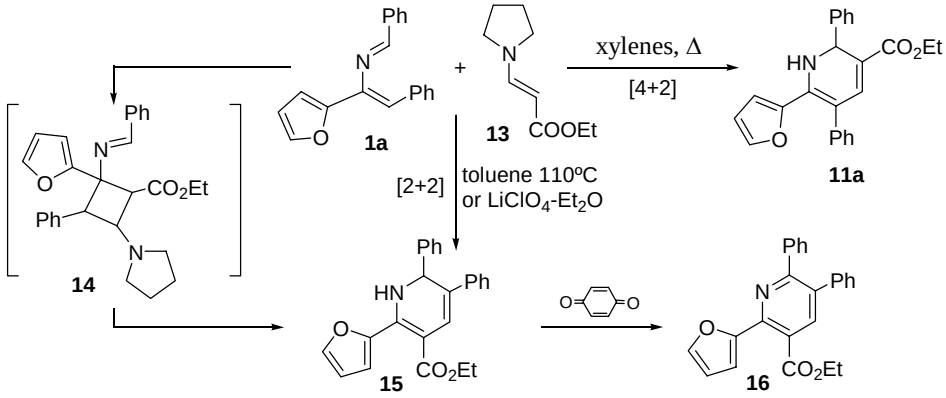
Entry	Compound	Ar	R^1	R^2	R^3	R^4	T(°C)	time (d)	yield(%)[a]
1	**3**	-	-	-	-	-	110	2	30
2	**6**	*p*-NO_2-C_6H_4	H	phenyl	Me	COOMe	110	6	35
3	**10**	-	-	-	-	-	110	5	45
4	**11a**	phenyl	2-furyl	phenyl	Et	H	110	6	62/60[b]
5	**12a**	phenyl	2-furyl	phenyl	Et	H	80	3	92[c]
6	**12b**	*p*-NO_2-C_6H_4	H	phenyl	Et	H	110	12	52

[a] Purified by chromatography. [b] Obtained by reaction of azadiene (**1a**) with enamine (**13**). [c] Yield from **11a**.

Similar behaviour was observed in the reaction of azadiene (**1b**) (R^1 = H, R^2 = Ph, Ar = C_6H_4-*p*-NO_2) with ethyl propiolate (**2b**) (in a sealed tube at 110°C). In this case, functionalized pyridine (**12b**) derived from β-amino acid (Scheme 2, Table 1, Entry 6) was obtained. Taking this into account, it could be assumed that the formation of compounds (**11**) and (**12**) can be rationalized by the reaction of 2-azadienes (**1a**,**b**) (R^2 = Ph) with ethyl propiolate (**2b**), through a [4+2] cyclization to yield compounds (**11**), whose aromatization give **12** (Scheme 2).

In this context, it is known that β-enamino ester (**13**) (Scheme 3) can be used as a synthetic equivalent[12] of ethyl propiolate (**2b**) and therefore we explored the reaction of enamine (**13**) with azadienes (**1**). Thus, reaction of **13** with 2-azadiene (**1a**) in refluxing xylenes (137-143°C) gave 1,2-dihydropyridine (**11a**) (60 % yield) in a regioselective fashion (Scheme 3, Table 1, Entry 4). However, when the reaction was

performed at refluxing toluene (110°C) or in the presence of lithium perchlorate in a nonaqueous solvent such as ether at room temperature the formation of 1,2-dihydropyridine (**15**) (60 % and 54 % yield, respectively) was observed. Regioselective formation of compound (**15**) may be explained by [2+2] cycloaddition reaction between enamine (**13**) and vinylic double bond of 2-azadiene (**1a**) to give an intermediate (**14**), followed by ring opening with loss of pyrrolidine and electrocyclic ring closure. The presence of lithium perchlorate seems to change the reactivity of heterodiene (**1a**) favouring its behavior as electron rich olefin. Compound (**15**) underwent aromatization with *p*-benzoquinone to give pyridine (**16**) (94 % yield).

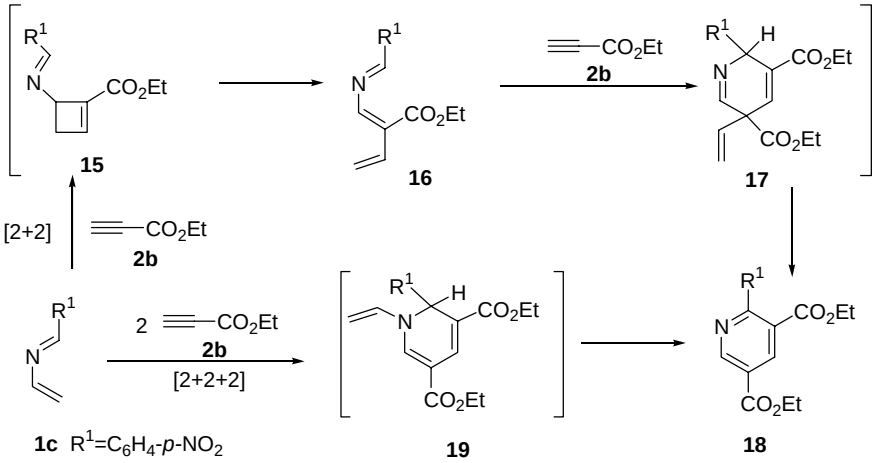


Scheme 3

In order to compare the obtained results, HMBC experiments were carried out for the elucidation of this new compound (**15**) obtained in the reaction with the enamine, whose ^{1}H and ^{13}C NMR spectra were different to those obtained for dihydropyridine (**11a**). Thus, in HMBC of 1,2-dihydropyridine (**15**) a two- or three-bond distance ^{1}H-^{13}C correlation is observed between H-2 and C-3 and between H-2 and the C at *p*-position respect to the nitrogen atom in the 1,2-dihydropyridine ring. These results confirm that both dihydropyridines (**11a**) and (**15**) are only different respect to the location of phenyl and ethylcarboxylate substituents and similar respect to the other substituents.

On the other hand, a surprising result was observed when 2-azadiene (**1c**) (R^1=R^2=H, Ar = C_6H_4-*p*-NO_2) with no substitutions at C-3 and C-4 positions was heated (8 h, 110ºC) with an excess of ethyl propiolate (**2b**) in a sealed tube. Spectroscopic analyses of the isolated product were consistent with the new pyridine (**20**) containing two carboxylic esters on position 3 and 5 (Scheme 4, 44% yield). ^{1}H NMR spectrum showed two doublets at 8.71 and 9.24 ppm, with a coupling constant of J_{HH} = 2.1 Hz, corresponding to two protons at C-2 and C-4 positions in the pyridine ring, and signals corresponding to two carboxylic ester groups were observed as well. Moreover, MS spectrometry showed a molecular ion at *m/z* 344 (7%). The formation of this compound (**20**) could be explained through a similar procedure to that observed before for reactions between 2-azadiene (**1c**) and DMAD: [2+2] cycloaddition to give cyclobutene (**17**), followed by ring opening to give azatriene (**18**), and [2+2] cycloaddition with a second

molecule of ethyl propiolate (**2b**) to give dihydropyridine (**19**) (Scheme 4). However, an alternative cascade [2+2+2] cycloaddition reaction between *N*-vinyl imine (**1c**) and two molecules of ethyl propiolate (**2b**), to give the intermediate (**21**) could also be involved, whose aromatization could afford pyridine (**20**) (Scheme 4). Similar domino [2+2+2] cycloadditions have been previously observed in the reaction of these neutral 2-azadienes (**1**) with enamines,[8b] or by other groups in reactions of imines with dimethyl acetylenedicarboxylate.[13]



Scheme 4

In summary, electronically neutral 2-aza-1,3-dienes (**1**) with aromatic and heteroaromatic substituents, are a class of heterodienes of great interest, owing to their remarkable Aza-Diels-Alder reactivity.[8] The substituent effects present in the starting heterodienes appear to play an important role in this new entry to the preparation of new substituted dihydropyridines and pyridines. While an aromatic substituent on 4-position (R^2 = Ph) allows [4+2] cycloaddition reactions with acetylenic esters, no substitution at 3- and 4-position (R^1 = R^2 = H) gives [2+2] reaction with acetylenic diesters and a formal [2+2+2] reaction with acetylenic monoester. Pyridine ring systems have received considerable attention not only for their widespread occurrence in nature[14] but also for their remarkable versatility in preparative organic synthesis[14] and in medicinal chemistry,[15] In addition, the furan substituent can be considered as a synthetic equivalent of carboxylic acid.[16] Therefore, through the strategies reported in this paper new access to polysubstituted pyridines derived from α- and β-amino acids can be designed.

EXPERIMENTAL

General. All melting points are uncorrected. Analytical TLC was performed on 0.25 mm silica gel plates. Visualization was accomplished by *UV* light and iodine. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: CH_2Cl_2 (P_2O_5); *n*-hexane and ether (sodium benzophenone ketyl); ethyl acetate (K_2CO_3). All solvents used in reactions were freshly distilled

from appropriate drying agents before use: $CHCl_3$ (P_2O_5); Toluene (CaH_2); Dioxane (Na, benzophenone). All other reagents were recrystallized or distilled as necessary. Column (flash) chromatography was carried out on silica gel (70-230 mesh). MS spectra (EI) were obtained with a ionization voltage of 70 eV. Data are reported in the form *m/z* (intensity relative to base = 100). IR spectra were taken as neat oils in NaCl, or as solids in KBr. Peaks are reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using tetramethylsilane (0.00 ppm) or chloroform (7.26 ppm) as an internal reference in $CDCl_3$ or D_2O solutions for ^1H NMR, or chloroform (77.0 ppm) as an internal reference in $CDCl_3$ or D_2O solutions for ^{13}C NMR. Chemical shifts are given in ppm *(δ)*. Coupling constants, *J*, are reported in hertz. All reactions were performed in oven (125 ºC) or flame-dried glassware under an inert atmosphere of dry N_2. Azadiene (**1a**) was prepared as described in the literature.[8c]

General procedure for preparation of azadienes (1b,c). Aldehyde (2 mmol) was added to a 0-10 ºC solution of phosphazene[17] (2 mmol) in $CHCl_3$ under N_2, and the mixture was stirred rt until TLC indicated the disappearance of phosphazene.

4-Phenyl-1-(4-nitrophenyl)-2-azabuta-1,3-diene (**1b**) The general procedure was followed using 4-phenyl-1,1,1-triphenyl-2-aza-1λ^5-phosphabuta-1,3-diene (0.94 g, 2 mmol) and 4-nitrobenzaldehyde (0.30 g, 2 mmol) for 5 h. Evaporation of solvent under reduced presure and chromatographic purification on neutral aluminium oxide (1/10, ethyl acetate/hexane) gave 0.32 g (63.5 %) of a 40/60 diastereomeric mixture of 1*E*/3*Z*, 1*E*/3*E* of **1b** as an orange solid, mp 138-139 °C. IR (KBr) ν 1513, 1348 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.23 (d, 1H, *J* = 8.3 Hz) for 3*Z*, 6.97 (d, 1H, *J* = 8.3 Hz) for 3*Z*, 7.07 (d, 1H, *J* = 13 Hz) for 3*E*, 7.20-7.69 (m, 11H), 7.92 (d, 2H, *J* = 8.8 Hz) for 3*Z*, 7.94 (d, 2H, *J* = 8.8 Hz) for 3*E*, 8,23 (d, 2H, *J* = 8.8 Hz) for 3*E*, 8.25 (d, 2H, *J* = 8.8 Hz) for 3*Z*, 8.29 (s, 1H) for 3*Z*, 8.34 (s, 1H) for 3*Z*;); ^{13}C NMR (75 MHz, $CDCl_3$) δ 124.4-130.9 (m,21C), 134.2 (for 3*E*), 135.6, 140.3 (for 3*Z)*, 141.0 (for 3*E)*, 141.8, 142.4, 148.9, 157.9 (for 3*E*), 158.7 (for 3*Z*); MS (EI) *m/z* 252 (M^+, 85). *Anal.* Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.40; H, 4.83; N, 11.11.

1-(4-Nitrophenyl)-2-azabuta-1,3-diene (1c) The general procedure was followed using 1,1,1-triphenyl-2-aza-1λ^5-phosphabuta-1,3-diene (0.76 g, 2 mmol) and 4-nitrobenzaldehyde (0.30 g, 2 mmol) for 2 h. The reaction product is unstable to distillation or chromatography and therefore was not isolated and used for the following reactions. ^1H NMR (300 MHz, $CDCl_3$) of crude reaction mixture (**1c**+Ph_3PO**)** δ 5.21 (d, 1H, *J* = 7.3 Hz), 5.64 (d, 1H, *J* = 14.6 Hz), 6.76 (dd, 1H, *J* = 7.3 Hz, *J* = 14.6 Hz), 7.59-7.89 (m, 15H), 7.91 (d, 2H, *J* = 8.8 Hz), 8.21 (d, 2H, *J* = 8.8 Hz), 8.26 (s, 1H).

General procedure for reactions of 2-azadienes (1) with acetylenic compounds (2a) and (2b). Acetylenic compound (5 mmol) was added to a 0-10 °C solution of azadiene (**1**) (5 mmol) in toluene (15

mL) under N_2, and the mixture was stirred at adequate temperature, until TLC indicated the disappearance of azadiene.

1-[1-(Benzylideneamino)-2-phenylvinyl]-2,3-bis(methoxycarbonyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene (**3**) The general procedure was followed using 1*E*/3*Z*-1,4-diphenyl-3-furan-2-yl-2-azabuta-1,3-diene (**1a**) (1.36 g, 5 mmol) and dimethyl acetylenedicarboxylate (**2a**) (0.62 mL, 5 mmol) in toluene (15 mL) at reflux temperature for 2 days. Evaporation of solvent under reduced pressure and chromatographic purification (5/1, hexane/ethylacetate) in Al_2O_3 of crude reaction gave 0.62 g (30%) of **3** as a yellow oil, t_R = 0.24 (1/5, ethyl acetate/hexane). IR (KBr) ν 1725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.78 (s, 3H), 5.82 (d, 1H, *J* = 2.0 Hz), 6.40 (s, 1H); 7.23-7.83 (m, 12H), 8.42 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.1, 83.8, 98.7, 118.9, 126.9-157.5 (m), 162.1, 163.7, 164.8; MS (EI) *m/z* 415 (M^++1, 100). *Anal.* Calcd for $C_{25}H_{21}NO_5$: C, 72.28; H, 5.10; N, 3.37. Found: C, 71.99; H, 5.07; N, 3.31.

3,4-Bis(methoxycarbonyl)-2-(*p*-nitrophenyl)-5-phenylpyridine (**6**) The general procedure was followed using 1*E*/3*E*-1-(*p*-nitrophenyl)-4-phenyl-2-azabuta-1,3-diene (**1b**) (1.27 g) and dimethyl acetylendicarboxylate (**2a**) (0.62 mL, 5 mmol) in toluene (15 mL) at reflux. Evaporation of solvent under reduced pressure and chromatographic separation (10/1, hexane/ethyl acetate) gave 0.69 g (35 %) of **6** as an orange solid, mp 146-148 °C (CH_2Cl_2/Hexane). IR (KBr) ν 1725, 1520 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (s, 3H), 3.66 (s, 3H), 7.32-8.27 (m, 9H), 8.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.8, 52.9, 123.5-153.9 (m), 166.5, 167.0; MS (EI) *m/z* 392 (M^+, 58). *Anal*. Calcd for $C_{21}H_{16}N_2O_6$: C, 64.28; H, 4.11; N, 7.14. Found: C, 64.29; H, 4.12; N, 7.10.

4,5-Bis(methoxycarbonyl)-2-(*p*-nitrophenyl)pyridine (**10**) The general procedure was followed using 1-(*p*-nitrophenyl)-2-azabuta-1,3-diene (**1c**) generated *in situ* and dimethyl acetylenedicarboxylate (**2a**) (0.62 mL, 5 mmol) in toluene (15 mL) at reflux. Evaporation of solvent under reduced presure and chromatographic separation (6/1, hexane/ethyl acetate) gave 0.71 g (45 %) of **10** as a yellow-orange oil, t_R = 0.34 (1/2, ethyl acetate/hexane). IR (KBr) ν 1712, 1513 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H), 3.98 (s, 3H), 7.92 (s, 1H), 8.19 (d, 2H, *J* = 9.0 Hz), 8.30 (d, 2H, *J* = 9.0 Hz), 9.11 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.0, 53.3, 119.2, 124.2-157.9 (m), 165.2, 166.6; MS (EI) *m/z* 316 (M^+, 100). *Anal*. Calcd for $C_{15}H_{12}N_2O_6$: C, 56.96; H, 3.82; N, 8.86. Found: C, 56.98; H, 3.83; N, 8.85.

3-Ethoxycarbonyl-6-furan-2-yl-2,5-diphenyl-1,2-dihydropyridine (**11a**) The general procedure was followed using 1*E*/3*Z*-1,4-diphenyl-3-furan-2-yl-2-azabuta-1,3-diene (**1a**) (1.36 g) and ethyl propiolate (**2b**) (0.5 mL, 5 mmol) in toluene (15 mL) at reflux. Evaporation of solvent under reduced pressure and chromatographic separation (5/1, hexane/ethyl acetate) gave 1.15 g (62 %) of **11a** as a yellow solid, mp 82-83 °C (CH_2Cl_2/Hexane). IR (KBr) ν 3363, 1692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, 3H, *J* = 7.2 Hz), 1.27 (s, 1H), 3.99-4.11 (m, 2H), 4.63 (s, 1H), 5.34 (dd, 1H, *J* = 3.4 Hz, *J* = 0.6 Hz), 6.08 (dd, 1H,

J = 3.4 Hz, *J* = 1.7 Hz), 6.85-7.52 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 45.4, 59.3, 103.0, 109,1, 111.4, 115.7, 123.3, 126.1-147.5 (m), 167.3; MS (EI) *m/z* 371 (M^+, 25). *Anal*. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.57; H, 5.68; N, 3.75.

When 1*E*/3*Z*-1,4-diphenyl-3-furan-2-yl-2-azabuta-1,3-diene (**1a**) (1.36 g, 5 mmol) reacted with 0.85 g of ethyl *trans*-3-pyrrolidin-1-yl-acrylate (5 mmol) (**13**) in refluxing xylene (10 mL) for 10 h evaporation of solvent under vacuum afforded an oil that was chromatographed on silica gel (15/1, hexane/ethyl acetate) to give 1.11 g (60 %) of **11a**.

5-Ethoxycarbonyl-2-furan-2-yl-3,6-diphenylpyridine (**12a**) *p*-Benzoquinone (0.216 g, 2 mmol) was added to a solution of compound (**11a**) (0.742 g, 2 mmol) in dioxane (5 mL), and the mixture was stirred at 105 °C for 72 h. The solvent was evaporated under reduced pressure, and the resulting oil was purified by silica gel column chromatography (10/1, hexane/ethyl acetate) to give 0.68 g (92 %) of **12a** as a white solid, mp 110-111 °C (CH_2Cl_2/Hexane). IR (KBr) ν 1725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H, *J* = 7.2 Hz), 4.05 (q, 2H, *J* = 7.2 Hz), 5.47 (d, 1H, *J* = 3.4 Hz), 6.21-6.23 (m, 1H), 6.71-7.48 (m, 11H), 9.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 61.1, 111.6, 114.1, 116.1-151.5 (m), 166.4; MS (EI) *m/z* 369 (M^+, 90). *Anal*. Calcd for $C_{24}H_{19}NO_3$: C, 78.03; H, 5.18; N, 3.79. Found: C, 77.96; H, 5.03; N, 3.72.

3-Ethoxycarbonyl-2-(*p*-nitrophenyl)-5-phenylpyridine (**12b**) The general procedure was followed using 1*E*/3*E*-1-(*p*-nitrophenyl)-4-phenyl-2-azabuta-1,3-diene (**1b**) (1.27 g) and ethyl propiolate (**2b**) (0.5 mL, 5 mmol) in refluxing toluene (15 mL) in a sealed tube. Chromatographic separation (15/1, hexane/ethyl acetate) gave 0.91 g (52 %) of **12b** as an orange solid, mp 122-124 °C (CH_2Cl_2/Hexane). IR (KBr) ν 1712, 1526 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, 3H, *J* = 7.2 Hz), 4.17 (q, 2H, *J* = 7.2 Hz), 7.41-8.25 (m, 9H), 8.33 (d, 2H, *J* = 2.1 Hz), 8.96 (d, 2H, *J* = 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 61.9, 123.3-155.3 (m), 166.9; MS (EI) *m/z* 348 (M^+, 100). *Anal*. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.97; H, 4.64; N, 8.03.

5-Ethoxycarbonyl-6-furan-2-yl-2,3-diphenyl-1,2-dihydropyridine (**15**) To a solution of 2-azadiene (**1a**) (1.36 g, 5 mmol) in Et_2O (10 mL) were added 5.32 g (0.050 mol) of $LiClO_4$ and 0.85 g of ethyl *trans*-3-pyrrolidin-1-yl-acrylate (**13**) (5 mmol). The mixture was stirred at rt for 24 h. The reaction mixture was poured on CH_2Cl_2 (20 mL), washed with a saturated solution of $NaHCO_3$, extracted with CH_2Cl_2 (3x20 mL) and dried ($MgSO_4$). Evaporation of solvent under vacuum afforded an oil that was chromatographied on silica gel (15/1, hexane/ethyl acetate) to give 1.00 g (54 %) of **15**. When 1*E*/3*Z*-1,4-diphenyl-3-furan-2-yl-2-azabuta-1,3-diene (**1a**) (1.36 g, 5 mmol) reacted with 0.85 g of ethyl *trans*-3-pyrrolidin-1-yl acrylate (5 mmol) (**13**) in toluene (10 mL) at 110ºC for 42 h evaporation of solvent under vacuum afforded an oil that was chromatographed on silica gel (15/1, hexane/ethyl acetate) gave 1.12 g (60 %) of **15** as an orange oil, t_R = 0.12 (1/2, ethyl acetate/hexane). IR (KBr) ν 3429 , 1722 ,

1253 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.2 Hz, 3 H), 4.10-4.50 (m, 2 H), 5.55 (br, 1 H, NH), 5.74-5.78 (m, 2H), 6.24 (dd, *J* = 4.0 Hz, *J* = 1.8 Hz, 1 H), 7.10-7.67 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7 , 52.9, 61.4, 111.5, 113.7, 126.2-147.9 (m), 166.4; MS (EI) *m/z* 371 (M^+ ,60). *Anal*. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found C, 77.05; H. 5.64; N 3.82.

3-Ethoxycarbonyl-2-furan-2-yl-5,6-diphenylpyridine (**16**) To a solution of compound (**15**) (2 mmol, 0.74 g) in dioxane (5 mL) was added 0.216 g (2 mmol) of *p*-benzoquinone, and the mixture was stirred at 105 °C for 12 h. The solvent was evaporated under reduced pressure, and the resulting oil was purified by silica gel column chromatography (2/1 hexane/ethyl acetate) affording 0.69 g (94 %) of **16** as a yellow solid, mp 117-118 °C (CH_2Cl_2/Hexane). IR (KBr) ν 1722, 1253; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, *J*= 7.2 Hz, 3 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 6.28-6.33 (m, 2 H), 7.34-7.67 (m, 11 H), 8.03 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 61.4, 111.5, 113.7, 124.5-147.7 (m), 152.0, 157.5, 167.7; MS (EI); *m/z* 369 (M^+,100). *Anal*. Calcd for $C_{24}H_{19}NO_3$: C, 78.03; H, 5.18; N, 3.79. Found C, 77.95; H, 5.24; N 3.82.

3,5-Bis(ethoxycarbonyl)-2-(*p*-nitrophenyl)pyridine (**20**) Ethyl propiolate (**2b**) in excess (1.5 mL, 15 mmol) was added to a 0-10ºC solution in toluene of 1-(*p*-nitrophenyl)-2-azabuta-1,3-diene (**1c**) (5 mmol) generated *in situ*. The mixture was heated at 110ºC in a sealed tube. Evaporation of solvent under reduced pressure and chromatographic separation (20/1, hexane/ethyl acetate) gave 0.76 g (44 %) of **20** as a yellow-orange oil, t_R = 0.41 (1/2, ethyl acetate/hexane). IR (KBr) ν 1727, 1520 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (t, 3H, *J* = 7.5 Hz), 1.21 (t, 3H, *J* = 7.5 Hz), 4.08-4.21 (m, 2H), 4.27-4.45 (m, 2H), 7.63-8.27 (m, 4H), 8.71 (d, 2H, *J* = 2.1 Hz), 9.24 (d, 2H, *J* = 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 13.8, 62.0, 62.1, 123.3-156.0 (m), 164.0, 165.9; MS (EI) *m/z* 344 (M^+, 7). *Anal*. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.32; H, 4.69; N, 8.10.

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