Synthesis of 2,5-*bis*-Arylpyridines by [4 + 2] Cycloaddition of 1,4-bis Aryl-2-aza-1,3-butadienes with Electron-Poor Dienophiles

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Tetrahydropyridines **4a**, **4b**, **4c** and pyridines **7a**, **7b**, **7c**, **9a**, **9b**, **9c** were synthesized by a [4 + 2] cycloaddition between 1,4-bis aryl-2-aza-1,3-butadienes and electron-poor dienophiles. Dimeric cycloadducts **6a**, **6b**, **6c**, were also isolated indicating a competition between the expected Hetero Diels-Alder and a dimerization process.

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Combinatorial chemistry is now actively used in the field of drug discovery [1] and consequently the need for new scaffolds that could be used to improve molecular diversity has been growing. Many compounds that display biological activity contain six-membered nitrogen heterocycles such as piperidines, di- or tetrahydropyridines or pyridines [2]. Therefore, we became interested in the synthesis of new six-membered nitrogen heterocycles containing two aryl groups at C_2 and C_5 positions and two functional groups at C_3 and C_4 (Figure 1) which can be used as scaffolds to build novel libraries.

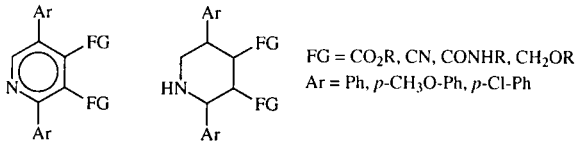
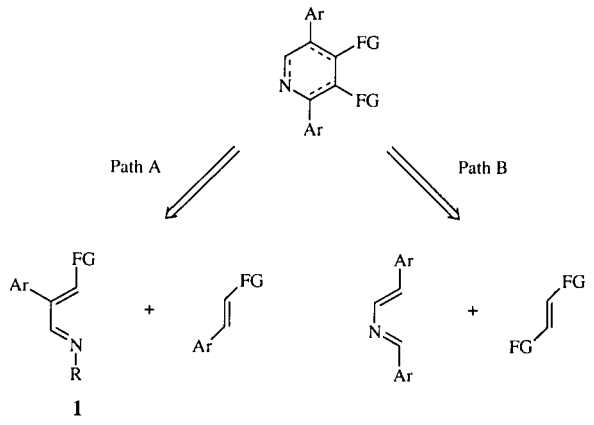


Figure 1

Such nitrogen heterocycles have not been reported in the literature and Hetero Diels-Alder of heterodienes would appear to be a straightforward approach to these compounds. Two analyses could be considered: reaction of either an 1-aza-1,3-butadiene (path A) or a 2-aza-1,3-butadiene (path B) with the corresponding dienophiles (Scheme 1).

The Aza Diels-Alder reaction of 1-aza-1,3-butadienes has received a great deal of attention [3]. Until relatively recently [4], it was thought that such derivatives usually fail to undergo [4 + 2] cycloaddition efficiently. However, in order to increase the nucleophilic character of the azadiene and to improve its reactivity in the normal (HOMO heterodiene controlled) Diels-Alder reaction, Ghosez [4] and Gilchrist [5] have attached a dialkyl- or an acylamino group to the nitrogen atom. Behforouz [6] has also activated 1-aza-1,3-butadienes with an *N*-silyloxy group.

Scheme 1



1

Reaction of the resulting hydrazones or silyloxyazadienes with electron-poor dienophiles produced pyridine derivatives in moderate to excellent yields.

On the other hand, Fowler and Grierson [7] increased the reactivity of such systems by incorporating electron withdrawing groups at a N and/or a C atom. Then *N*-acyl-α-cyano-1-azadienes and *N*-aryl-2-cyano-1-azadienes reacted with neutral, rich or poor dienophiles to give tetrahydropyridines with good yields while *N*-alkyl-2-cyano-1-azadienes reacted efficiently in intramolecular Hetero Diels-Alder reactions. Similarly, Boger [8] used 1-sulfonyl-1-aza-1,3-dienes to lower the LUMO of the azadiene in order to realize a successfull inverse electron demand Diels-Alder reaction with electron rich dienophiles.

This approach was not selected in our case since the synthesis of type **1** 1-azadienes (Scheme 1, R = NMe_2, or SO_2 R, FG = CO_2 R' or CONHR' or CN) seemed *a priori* uneasy.

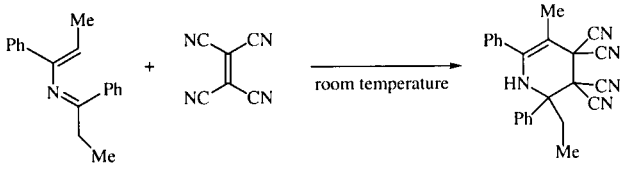
In the case of 2-aza-1,3-butadienes, the same two strategies have been largely investigated to increase the reactivity

in uncatalysed reactions. Ghosez [9a, 9b] and others [9c, 9d] reacted electron-donating group substituted azadienes (*e.g.* dimethylamino group in C_1 [9a] or *t*-butyldimethylsilyloxy group in C_1 and C_3 [9b]) with electron-poor dienophiles. This strategy has been the most extensively studied.

Barluenga [10] has increased the electrophilic character of 2-aza-1,3-butadienes by substituting them with electron-withdrawing groups (methoxycarbonyl groups in C_3 and C_4). Such compounds react with electron-rich dienophiles.

It has been generally accepted that electronically neutral 2-aza-1,3-butadienes are unable to undergo Hetero Diels-Alder reactions. Nevertheless, Barluenga [3,11] succeeded in doing the cycloaddition reaction of neutral azadiene **2** with several electron-poor dienophiles (Scheme 2) and Palacios [12] performed efficiently Hetero Diels-Alder reactions of neutral azadienes and hetero dienophiles such as ethyl glyoxalate.

Scheme 2



2

Ohshiro [13] reported the reaction of 1,4-diphenyl-2-aza-1,3-butadiene in an inverse electron demand way while Mariano [14] conducted the reaction of 1-phenyl-4-methyl-2-aza-1,3-butadiene with electron-rich dienophiles in a catalytic way. In each case the isolated yields were poor.

Overall, the reactivity of 1,4-bis aryl-2-aza-1,3-butadienes in Hetero Diels-Alder reactions has not been well studied and we report our results concerning the scope and limitations of the reaction of such dienes with several electron-poor dienophiles.

Results and Discussion.

We first prepared azadienes **3a**, **3b** and **3c** (Figure 2).

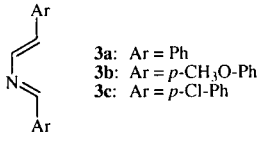


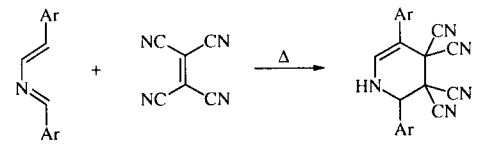
Figure 2

Only few methods have been reported for the preparation of 2-aza-1,3-butadienes. Recently, Katritzky [15] developped a new general synthesis of bis 1,4- and tetra-1,1,4,4-aryl-2-aza-1,3-butadienes. We used this methodology and isolated **3a**, **3b** and **3c**, however in lower yields (39% for **3a**, 23% for **3b** and 10% for **3c**). Having these three azadienes in hand we studied their reactivity towards five electron-poor dienophiles.

Reaction with Tetracyanoethylene (TCNE).

Azadienes **3a**, **3b** and **3c** reacted with TCNE at fairly high temperature to give substituted tetrahydropyridines **4a**, **4b** and **4c** (Scheme 3).

Scheme 3



3a: Ar = Ph
3b: Ar = *p*-CH_3O-Ph
3c: Ar = *p*-Cl-Ph

4a: Ar = Ph (15%) [a]
4b: Ar = *p*-CH_3O-Ph (83%) [b]
4c: Ar = *p*-Cl-Ph (13%) [c]

[a] Toluene, 5 hours, 80°. [b] Toluene, 4 hours, 60°. [c] Toluene, 24 hours, 90°.

It should be noticed that the Diels-Alder cycloaddition was followed by a prototropic rearrangement that gave enamines **4a**, **4b** and **4c**. These compounds were characterized on the basis of their spectroscopic data. In the case of **4b**, the nmr analysis was further confirmed by an X-Ray crystallographic analysis (Figure 3) [16].

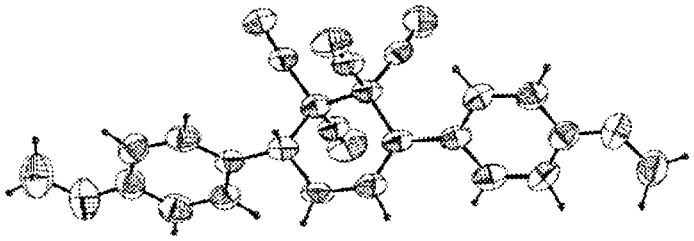


Figure 3

While compound **4b** was obtained in excellent yield, the formation of **4a** and **4c** was accompanied by the synthesis of many unidentified by-products. Moreover the low yields could be explained by loss of product during the purification on silica gel.

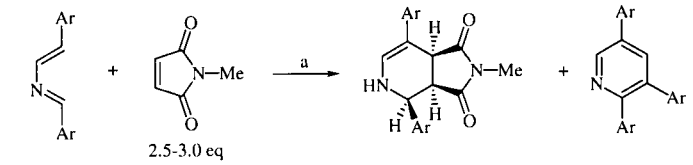
Reaction with *N*-methylmaleimide

Reaction of compounds **3a**, **3b** and **3c** with *N*-methylmaleimide at high temperature gave two main products, the expected tetrahydropyridines **5a**, **5b** and **5c** along with dimeric compounds **6a**, **6b** and **6c**. After purification on silica gel, unstable tetrahydropyridines **5a**, **5b** and **5c** were oxidized to yield corresponding pyridines **7a**, **7b** and **7c** (Scheme 4).

The structures of tetrahydropyridines **5a**, **5b** and **5c** were supported by ^1H, ^{13}C, COSY, HETCOR nmr and mass spectroscopy (Figure 4).

The data for compound **5c** are representative and examination of the molecular models indicates that for this type of bicyclic system, the J = 5.5 Hz coupling constant is indicative of a *cis* coupling. The Diels-Alder reaction thus

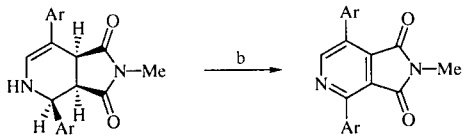
Scheme 4



3a: Ar = Ph
3b: Ar = *p*-CH_3O-Ph
3c: Ar = *p*-Cl-Ph

5a: Ar = Ph
5b: Ar = *p*-CH_3O-Ph
5c: Ar = *p*-Cl-Ph

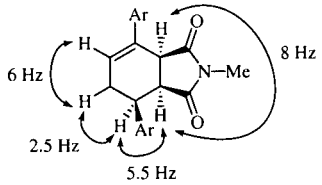
6a: 50%
6b: 16%
6c: 17%



5a: Ar = Ph
5b: Ar = *p*-CH_3O-Ph
5c: Ar = *p*-Cl-Ph

7a: 9%
7b: 15%
7c: 8%

[a] Xylene, 36 hours, 115° for **3a**; toluene, 60 hours, reflux for **3b**; toluene, 48 hours, reflux for **3c**. [b] DDQ for **5a** and **5b**; $CDCl_3$, 72 hours for **5c**.



5c

Figure 4

takes place *via* an endo transition state. This is in full agreement with previous results in similar reactions [17].

Unfortunately, yields of pyridines are very low, the main isolated products being dimeric compounds **6a**, **6b** and **6c**. The formation of compounds **6a**, **6b** and **6c** can be explained by a [4 + 2] cycloaddition reaction of two molecules of azadiene, one molecule acting as the diene and the other acting as an electron-rich dienophile (Scheme 5).

meta coupling constant (J = 2.5 Hz) between H_4 and H_6 demonstrates the regiochemistry. This has been further confirmed by an X-ray crystallographic analysis [16] of **6b** (Figure 5).

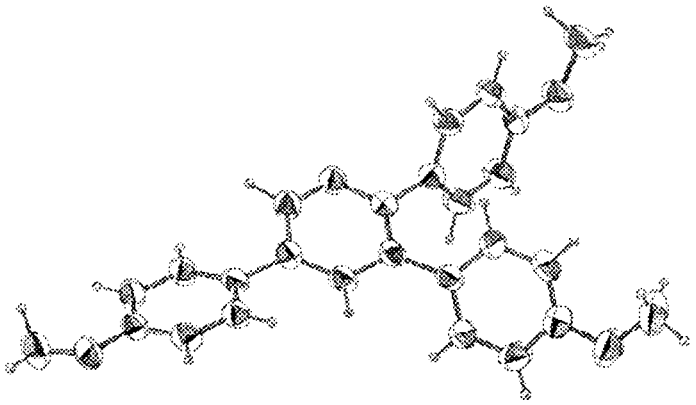
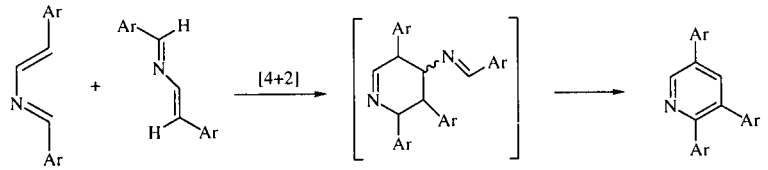


Figure 5

Scheme 5



3a: Ar = Ph
3b: Ar = *p*-CH_3O-Ph
3c: Ar = *p*-Cl-Ph

6a: Ar = Ph
6b: Ar = *p*-CH_3O-Ph
6c: Ar = *p*-Cl-Ph

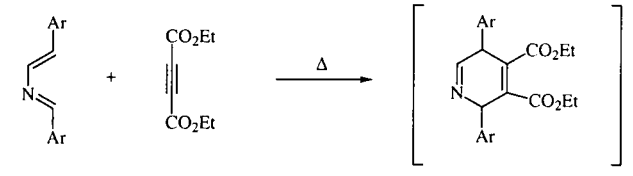
The cycloaddition is followed by a β-elimination of the imine [18a] and a subsequent aromatization (Scheme 5). Compounds **6a**, **6b** and **6c** were characterized on the basis of their ^1H and ^{13}C nmr spectra: the

Similar dimerisations of 2-aza-1,3-butadienes had already been observed by Palacios [18a], Wulff and Böhnke [18b] in thermal reactions and by Mariano [14] in Lewis acid catalyzed reactions.

Reaction with Diethyl Acetylenedicarboxylate.

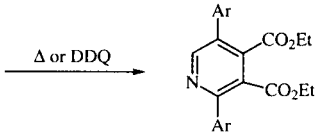
Reaction of azadienes **3a**, **3b** and **3c** with diethyl acetylenedicarboxylate at high temperature gave pyridines **9a**, **9b** and **9c** with moderate yields (Scheme 6).

Scheme 6



3a: Ar = Ph
3b: Ar = *p*-CH_3O-Ph
3c: Ar = *p*-Cl-Ph

8



9a: Ar = Ph (30%) [a]
9b: Ar = *p*-CH_3O-Ph (33%) [b]
9c: Ar = *p*-Cl-Ph (49%) [c]

[a] 1) Xylene, 25 hours, reflux 2) DDQ. [b] Toluene, 48 hours, reflux. [c] Xylene, 48 hours, reflux.

Pyridines **9a**, **9b** and **9c** probably result from oxidation of intermediate **8** as previously reported [9a, 19]. It is worth noting that formation of dimeric type compounds could not be detected in this case.

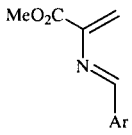
Reaction with Fumaronitrile and Methyl Fumarate.

Cycloaddition of **3b** with methyl fumarate and fumaronitrile was attempted, but even at high temperature no cycloadduct was isolated. However, dimeric pyridine **6b** was obtained in moderate yield (25-45%).

Additional Discussion and Conclusion.

The substituent effects on this type of Hetero Diels-Alder appear somewhat unusual and warrant some further comments. In order to determine whether a more electron-deficient (rich) aryl substituent would improve (decrease) the efficiency of the reaction, we performed the reaction with the more electron-rich 1,4-*bis*-(4-methoxyphenyl)-2-aza-1,3-butadiene **3b**, the more electron-poor 1,4-*bis*-(4-chlorophenyl)-2-aza-1,3-butadienediene **3c** and the neutral 1,4-diphenyl-2-aza-1,3-butadiene **3a**. The prediction would be that the presence of the methoxy group would serve to enhance the rate and the yield of the reaction. However, the effect of the substitution was not large except in the case of TCNE. This observation is consistent with some of the results published by Gilchrist [19, 20].

He compared the reactivity between azadienes **10a**, **10b** and **10c** (Figure 6) against various dienophiles.



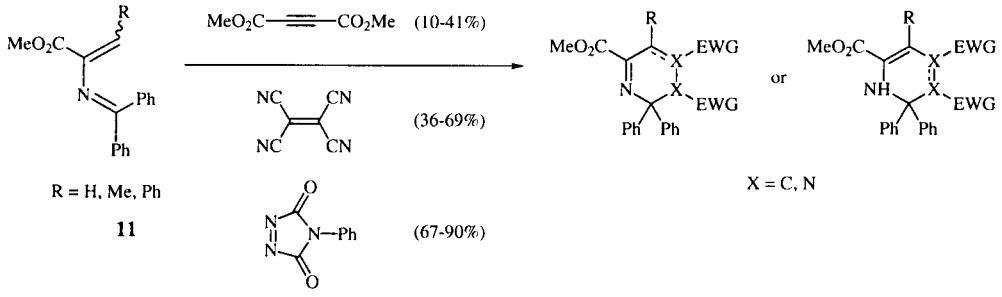
10a: Ar = Ph
10b: Ar = Ph-NO_2
10c: Ar = Ph-NMe_2

Figure 6

As expected, **10b** reacts only with electron-rich dienophiles while **10c** reacts only with electron-poor dienophiles. But, the authors did not observe a very important difference of reactivity between **10a** and **10b** when reacted with electron-rich dienophiles and between **10a** and **10c** when reacted with electron-poor dienophiles.

Moreover, the differences of reactivity between the azadienes are often uneasy to rationalize. For instance, Balsamini [21] showed that azadienes **11** underwent cycloaddition reaction with the most activated electron-poor dienophiles but were unreactive towards less electron-poor dienophiles and electron-rich dienophiles (Scheme 7). His results were different from those of Gilchrist [19,20] who observed that closely related compound **10a** (Figure 6) can participate in Hetero Diels-Alder reactions with strongly electron-rich dienophiles (*e.g. N*-cyclohex-1-enyl pyrrolidine) and various electron-poor dienophiles (*eg* but-3-en-2-one, methyl acrylate, ethylfumarate) but not all (no reaction was observed with *N*-phenylmaleimide or diethylazodicarboxylate).

Scheme 7



R = H, Me, Ph

11

(10-41%)

(36-69%)

(67-90%)

X = C, N

Very recently, Gilchrist and Rocha Gonsalves [22] performed molecular orbital calculations for some azadienes and so could rationalize the effect of substitution on their reactivity. For example, the AM1 calculations showed that the energy of the LUMO of **11** is higher than the energy

of the LUMO of **10a** thus explaining why **11** is less reactive than **10a** towards electron-rich dienophiles.

On the other hand, the HOMO of **10a** and **11** have similar energies. Therefore, steric effects must be introduced to explain the difference of reactivity between **10a** and **11** towards electron-poor dienophiles: the steric hindrance due to the two phenyl groups destabilizes the *s*-cisoide conformation [22].

Since we have neither a second phenyl group at C_1 that is present in **11** and causes steric hindrance, nor a carboxymethyl group at C_3 that is present in **11** and lowers the energy of the HOMO, we should have expected better results than Balsamini in the reactions with electron-poor dienophiles [21]. However this is not the case and this surprising result is not easily rationalized. Nevertheless, a low energy for the LUMO of our azadienes would explain the competitive formation of dimeric products **6a**, **6b**, **6c** observed in some cases. Otherwise, we could not observe any difference in reactivity between **1a**, **1b** and **1c**. A possible explanation is that, in our case, the effects of the substituents on the aromatic rings may be to small to be evidenced during the cycloaddition. However, it must be noticed that the isolated yields might not always be perfectly representative of the reactivity on account of the instability of the starting azadienes and the formation of many unidentified by-products during the reaction.

Thus, although the reactivity of our azadienes towards electron-poor dienophiles is relatively low, this reaction is a relatively straightforward way to obtain these new six-membered nitrogen heterocycles substituted at C_2 and C_5 by two aryl groups and at C_3 and C_4 by two connecting groups; these scaffolds can now be of use in combinatorial chemistry.

Table 1

Crystal Data for **4b**

Formula	$C_{23}H_{17}N_5O_2$
Mol. Wt	395.42
Cryst. Syst	Monoclinic
Space Group	$P2_1/c$
a	12.200(1)
b	21.167(3)
c	7.772(9)
α	---
β	94.88(3)
γ	---
V	2000(2)
Z	4
ρcalc g•cm^{-3}	1.313
F(000)	824
μ(MoKα) cm^{-1}	0.880
T(°K)	294
Crystal size (mm)	0.35*0.28*0.28
Radiation	MoKα
Max 2Θ (°)	54°
Scan	ω/2θ = 1
t_{max} (for one measure), s	60
Variance of standards	0.15%
Range of HKL	-15.15; 0.27; 0.9
Reflections measured	4679
Reflections obsrerved (I>σ(I))	1882 (2.0σ)
R_{int}(from merging equiv refl)	0.009
Fourier Difference	0.58-0.18
N(obs)/N(var)	1882/323
Final R	0.053
Rw	0.124
$w = 1/\sigma(F_o)^2=[\sigma^2(I) + (0.04F_o^2)^2]^{-1/2}$	
Sw	0.941
Max residual e.Å^{-3}	0.173

Table 2

Crystal Data for **6b**

Formula	$C_{26}H_{23}NO_3$
Mol. Wt	397.48
Cryst. Syst	Monoclinic
Space Group	P_21/c
a	8.822(3)
b	22.610(4)
c	10.930(2)
α	---
β	107.77(4)
γ	---
V	2076(4)
Z	4
ρcalc g•cm^{-3}	1.27
F(000)	840
μ(MoKα) cm^{-1}	0.774
T(°K)	294
Crystal size (mm)	0.35*0.12*0.12
Radiation	MoKα
Max 2Θ (°)	54°
Scan	ω/2θ = 1
t_{max} (for one measure), s	60
Variance fo standards	0.22%
Range of HKL	0.11; 0.28; -13.13
Reflections measured	4940
Reflections obsrerved (I>σ(I))	1985 (2.0σ)
R_{int}(from merging equiv refl)	0.033
Fourier Difference	0.52-0.21
N(obs)/N(var)	1985/341
Final R	0.054
Rw	0.050
$w = 1/\sigma(F_o)^2=[\sigma^2(I) = (0.04F_o^2)^2]^{-1/2}$	
Sw	1.11
Max residual e.Å^{-3}	0.16

EXPERIMENTAL

Melting points are uncorrected. IR spectra were determined on a Nicolet 205 FT-IR spectrophotometer and the bands are given in cm^{-1}. The nmr spectra were obtained at 400 MHz on a BRUKER ARX 400 using deuteriochloroform as solvent (unless specified otherwise). Chemical shifts (δ) are given in ppm relative to tetramethylsilane (δ = 0) for spectra run in deuteriochloroform, deuterobenzene (δ = 7.20 and 128.7) or deuteroacetone (δ = 2.05 and 205.1). C and H microanalyses were obtained from "Service de microanalyse" I.C.S.N.-C.N.R.S., Gif/Yvette, France. High Resolution Mass Spectra were obtained from the "Centre Régional de Mesures Physiques de l'Ouest" using a Varian MAT 311 spectrometer. Crystallographic data were

obtained using a CAD 4 ENRAF-NONIUS diffractometer. Crystal data are given in Table 1 (for **4b**) and 2 (for **6b**). Merck silica gel 60H was used for column chromatography. TLC were performed with Merck silica gel 60 F_{254} plates 0.25 mm (analytical). Compounds on chromatography plates were visualised by spraying with a solution of 5% *p*-anisaldehyde, 5% sulfuric acid and 0.1% acetic acid in ethyl alcohol followed by heating. Toluene and xylene were freshly distilled from sodium.

2,5-Diphenyl-3,3,4,4-tetracyano-1,2,3,4-tetrahydropyridine (**4a**).

1,4-Diphenyl-2-aza-1,3-butadiene [15] (200 mg, 0.96 mmole) and tetracyanoethylene (148 mg, 1.15 mmole) in toluene (3 ml) were stirred at 80° for 5 hours. The solvent was evaporated. The residue was purified by column chromatography on silica gel using toluene/petroleum ether (1:1 v/v) to toluene/ethylacetate (9:1 v/v) as eluent to give compound **4a** [23] (48 mg, 15%) that was crystallized from ethylacetate/hexane to give brown crystals: mp 182.5°; ir (methylene chloride): 3428, 1646, 1473; ^{1}H nmr (acetone): δ 7.88-7.81 (m, $2H_{Ar}$), 7.66-7.60 (m, $3H_{Ar}$), 7.56-7.46 (m, $4H_{Ar}$), 7.41-7.34 (m, 3H, $1H_{Ar}$ + HC=C + N-H), 5.39 (s, 1H, CH-Ph); ^{13}C nmr (acetone): 136.1, 134.9, 131.8, 131.1, 129.1, 128.8, 128.3, 127.3, 126.4, 111.8, 110.9, 110.6, 109.0, 92.5, 58.5, 45.3, 43.3; HRMS (m/z) Calcd. for $C_{21}H_{13}N_5$: 335.1171. Found: 335.1171.

2,5-*Bis*-(4-methoxyphenyl)-3,3,4,4-tetracyano-1,2,3,4-tetrahydropyridine (**4b**).

1,4-*Bis*-(4-Methoxyphenyl)-2-aza-1,3-butadiene [15] (90 mg, 0.33 mmole) and tetracyanoethylene (56 mg, 0.43 mmole) in toluene (4 ml) were stirred at 60° for 4 hours. Solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel using petroleum ether/ethylacetate (8:2 v/v) as eluent to give compound **4b** (110 mg, 83%) as a brown solid. Recrystallization (CH_2Cl_2/hexane/MeOH) gave brown crystals: mp 181°; ir (nujol): 3442, 1646, 1611, 1514; ^{1}H nmr (acetone): δ 7.78-7.71 (m, $2H_{Ar}$), 7.45-7.39 (m, $2H_{Ar}$), 7.20-7.08 (m, 4H, $2H_{Ar}$ + HC=C + N-H), 7.07-7.00 (m, $2H_{Ar}$), 5.27 (s, 1H, CH-PhOMe), 3.90 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); ^{13}C nmr (acetone): 161.7, 159.2, 135.4, 129.6, 128.4, 127.2, 123.4, 114.3, 114.1, 111.8, 110.9, 110.7, 109.1, 92.4, 58.2, 54.7, 54.5, 45.3, 43.7; HRMS (m/z) Calcd. for $C_{23}H_{17}N_5O_2$: 395.1382. Found: 395.1393.

Anal. Calcd. for $C_{23}H_{17}N_5O_2$: C, 69.86; H, 4.33; N, 17.71. Found: C, 69.97; H, 4.47; N, 17.61.

2,5-*Bis*-(4-Chlorophenyl)-3,3,4,4-tetracyano-1,2,3,4-tetrahydropyridine (**4c**).

1,4-*Bis*-(4-chlorophenyl)-2-aza-1,3-butadiene [15] (150 mg, 0.54 mmole) and tetracyanoethylene (139 mg, 1.08 mmole) in toluene (3 ml) were stirred at 90° for 24 hours. The solvent was evaporated. The residue was purified by column chromatography on silica gel using toluene/ethylacetate (8:2 v/v) as eluent to give compound **4c** [23] (27 mg, 13%) as a brown solid: ir (NaCl): 3416, 1641, 1478, 819; ^{1}H nmr (acetone): δ 7.91-7.85 (m, $2H_{Ar}$), 7.72-7.67 (m, $2H_{Ar}$), 7.56-7.52 (m, 5H, $4H_{Ar}$ + N-H), 7.46-7.43 (m, 1H, HC=C), 5.48 (s, 1H, CH-PhCl); ^{13}C nmr (acetone): 136.7 (2s), 133.7, 132.7, 130.6, 130.2, 129.3, 129.0, 128.1, 111.5, 110.7, 110.4, 108.8, 91.4, 57.8, 45.1, 43.1; HRMS (m/z) Calcd. for $C_{21}H_{11}N_5Cl_2$: 403.0391. Found: 403.0383.

2,5-Diphenyl-*N*-methyl-3,4-pyridinedicarboximide (**7a**) and 2,3,5-Triphenyl-pyridine (**6a**).

1,4-Diphenyl-2-aza-1,3-butadiene (185 mg, 0.89 mmole) and *N*-methyl maleimide (297 mg, 2.67 mmole) in xylene (4 ml) were stirred at 120° for 36 hours. Solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel using toluene to toluene/ethylacetate (10:1 v/v) as eluent to give 2,3,5-triphenyl-pyridine **6a** (68 mg, 49%) and crude imine **5a** (40 mg) that was not purified further. **6a** was crystallized in ethylacetate/hexane to give white crystals.

Crude 2,5-diphenyl-(*N*-methyl-3,4-carboximide)-2,3,4,5-tetrahydropyridine **5a** and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (60 mg, 0.26 mmole) were stirred in toluene (5 ml) for 3 hours. The solvent was evaporated and the residue was purified by column chromatography (petroleum ether/ether 7:3 v/v) to give the pyridine **7a** (25 mg, 9%) as a yellow solid.

Compound **6a**: mp 126°; ir (NaCl): 1450, 1431, 1391, 1009; ^{1}H nmr: δ 8.92 (d, 1H, J = 2.5 Hz, HC=N), 7.92 (d, 1H, J = 2.0 Hz, HC=C), 7.70-7.65 (m, $2H_{Ar}$), 7.53-7.46 (m, $2H_{Ar}$), 7.44-7.37 (m, $3H_{Ar}$), 7.31-7.21 (m, $8H_{Ar}$); ^{13}C nmr: 155.9, 146.7, 139.9, 139.8, 137.4, 136.9, 135.9, 135.0, 129.9, 129.6, 129.1, 128.4, 128.2, 127.9, 127.8, 127.3, 127.1; HRMS (m/z) Calcd. for $C_{23}H_{17}N$: 307.1361. Found: 307.1362.

Compound **5a**: ^{1}H nmr (C_6D_6): δ 7.53-7.47 (m, $2H_{Ar}$), 7.34-7.27 (m, $2H_{Ar}$), 7.25-7.19 (m, $2H_{Ar}$), 7.13-7.05 (m, $4H_{Ar}$), 6.47 (d, 1H, J = 6.6 Hz, C=CH), 4.00 (dd, 1H, J = 5.5 Hz, 2.3 Hz, CHPh), 3.38 (d, 1H, J = 8.1 Hz, C=C-CH), 3.15 (brm, 1H, NH), 2.80 (dd, 1H, J = 5.6 Hz, 8.1 Hz, CH-CO), 2.25 (s, 3H, N-Me); ^{13}C nmr (C_6D_6): 175.9, 175.5, 140.4, 140.3, 133.6, 129.3, 129.0, 128.6, 128.3, 126.0, 125.5, 104.4, 55.6, 47.0, 41.0, 24.4; HRMS (m/z) Calcd. for $C_{20}H_{18}N_2O_2$: 318.1368. Found: 318.1369.

Compound **7a**: ir (NaCl): 1774, 1717, 1450, 1436; ^{1}H nmr: δ 9.03 (s, 1H, HC=N), 8.00-7.95 (m, $2H_{Ar}$), 7.68-7.63 (m, $2H_{Ar}$), 7.59-7.54 (m, $6H_{Ar}$), 3.21 (s, 3H, N-Me); ^{13}C nmr: 167.1, 166.4, 156.2, 155.4, 136.3, 135.8, 132.8, 132.6, 130.2, 130.0, 129.7, 129.4, 128.5, 128.1, 122.1, 24.3; HRMS (m/z) Calcd. for $C_{20}H_{14}N_2O_2$: 314.1055. Found: 314.1043.

2,5-*Bis*-(4-Methoxyphenyl)-*N*-methyl-3,4-pyridinedicarboximide (**7b**) and 2,3,5-*Tris*-(4-Methoxyphenyl)pyridine (**6b**).

1,4-*Bis*-(4-Methoxyphenyl)-2-aza-1,3-butadiene (100 mg, 0.37 mmole) and *N*-methyl maleimide (125 mg, 0.75 mmole) in toluene (4 ml) were stirred at 110° for 60 hours. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel using toluene/ethylacetate (8:2 v/v) as eluent to give 2,3,5-tris (4-methoxyphenyl)-pyridine **6b** (12 mg, 16%) and crude imine **5b** (50 mg) that was not purifed further.

Crude 2,5-bis(4-methoxyphenyl)-(*N*-methyl-3,4-carboximide)-2,3,4,5-tetrahydropyridine **5b** and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (60 mg, 0.26 mmole) were stirred in toluene (5 ml) for 3 hours. The solvent was evaporated and the residue was purified by column chromatography (toluene/ether - 10:1 v/v) to give the expected pyridine **7b** (20 mg, 15%). Compounds **6b** and **7b** were crystallized from ethylacetate/hexane to give pale yellow crystals.

Compound **6b**: mp 163°; ir (carbon tetrachloride): 1610, 1518, 1513, 1290, 1249, 1176, 1039; ^{1}H nmr: δ 8.82 (d, 1H, J = 2.0 Hz, HC=N), 7.81 (d, 1H, J = 2.0 Hz, HC=C), 7.62-7.56 (m, $2H_{Ar}$), 7.37-7.32 (m, $2H_{Ar}$), 7.20-7.15 (m, $2H_{Ar}$), 7.05-6.99 (m, $2H_{Ar}$), 6.88-6.82 (m, $2H_{Ar}$), 6.82-6.76 (m, $2H_{Ar}$), 3.86 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3); ^{13}C nmr (deuteriobenzene): 160.8, 160.6, 160.1, 156.0, 147.2, 137.2, 136.1, 135.1, 134.2, 134.1, 132.7, 131.8, 131.2, 129.1, 115.5, 115.0, 114.4, 55.5, 55.4, 55.3.

Anal. Calcd. for $C_{26}H_{23}NO_3$: C, 78.57; H, 5.83; N, 3.52. Found: C, 78.39; H, 6.03; N, 3.45.

Compound **5b**: ^{1}H nmr: δ 7.42-7.36 (m, $2H_{Ar}$), 7.31-7.24 (m, $2H_{Ar}$), 6.93 (brd, 1H, J = 6.1 Hz, C=CH), 6.91-6.87 (m, $2H_{Ar}$), 6.85-6.81 (m, $2H_{Ar}$), 4.57 (bd, 1H, J = 5.1 Hz, CHPhOMe), 4.07 (brd, 2H, J = 8.1 Hz, C=C-CH), 4.06 (brs, 1H, NH), 3.80 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.53 (dd, 1H, J = 5.1 Hz, 8.1 Hz, CH-CO), 2.60 (s, 3H, N-Me); ^{13}C nmr: 176.2, 175.5, 159.2, 157.7, 132.2, 131.5, 131.0, 128.2, 125.6, 113.9, 113.6, 104.2, 55.3, 55.2, 54.7, 46.9, 40.9, 24.2.

Compound **7b**: mp 218°; ir (CH_2Cl_2): 1775, 1716, 1609, 1515, 1440, 1384; ^{1}H nmr: δ 8.98 (s, 1H, HC=N), 8.00-7.93 (m, $2H_{Ar}$), 7.61-7.55 (m, $2H_{Ar}$), 7.08-7.01 (m, $4H_{Ar}$), 3.90 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.16 (s, 3H, N-Me); ^{13}C nmr: 167.5, 166.7, 161.3, 160.5, 156.1, 154.4, 135.8, 131.8, 131.7, 131.0, 128.4, 125.1, 121.3, 113.9, 113.5, 55.4, 24.2; HRMS (m/z) Calcd. for $C_{22}H_{18}N_2O_4$: 374.1266. Found: 374.1275.

2,5-*Bis*-(4-Chloroxyphenyl)-*N*-methyl-3,4-pyridinedicarboximide (**7c**) and 2,3,5-*Tris*-(4-Chlorophenyl)pyridine (**6c**).

1,4-*Bis*-(4-chlorophenyl)-2-aza-1,3-butadiene (100 mg, 0.36 mmole) and *N*-methyl maleimide (100 mg, 0.90 mmole) in toluene (4 ml) were stirred at 110° for 48 hours. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel using toluene to toluene/ethylacetate (9:1 v/v) as eluent to give 2,3,5-*tris*-(4-methoxyphenyl)-pyridine **6c** [23] (17 mg, 17.5%) and crude imine **5c** (15 mg) that was not purified further. **6c** was crystallized from ethylacetate/hexane to give white crystals.

Crude 2,5-*bis*-(4-chlorophenyl)-(*N*-methyl-3,4-carboximide)-2,3,4,5-tetrahydropyridine **5c** was stirred 36 hours in deuteriochloroform. The solvent was evaporated and the residue was purified by column chromatography (toluene/dichloromethane 1:1 v/v) to give the pure pyridine **7c** (20 mg, 10%) as a pale yellow solid.

Compound **6c**: mp 160°; ir (methylene chloride): 1493, 1442, 1094, 1013, 830; ^{1}H nmr: δ 8.81 (d, 1H, J = 2.0 Hz, HC=N), 7.76 (d, 1H, J = 2.5 Hz, HC=C), 7.55-7.47 (m, $2H_{Ar}$), 7.43-7.37 (m, $2H_{Ar}$), 7.29-7.12 (m, $6H_{Ar}$), 7.12-7.01 (m, $2H_{Ar}$); ^{13}C nmr: 154.8, 146.8, 137.8, 137.7, 136.6, 135.4, 134.8, 134.6, 134.3, 134.2, 133.8, 131.2, 130.7, 129.4, 128.9, 128.4, 128.3.

Anal. Calcd. for $C_{23}H_{14}NCl_3$: C, 67.26; H, 3.44; N, 3.41. Found: C, 67.22; H, 3.79; N, 3.22.

Compound **5c**: ^{1}H nmr: δ 7.39-7.35 (m, $2H_{Ar}$), 7.30-7.24 (m, $6H_{Ar}$), 7.00 (dd, 1H, J = 1.0 Hz, 6.1 Hz, C=CH), 4.59 (dd, 1H, J = 2.5 Hz, 5.6 Hz, CHPhCl), 4.22 (bd, 1H, J ≈ 5.5 Hz, NH), 4.08 (d, 1H, J = 8.0 Hz, C=C-CH), 3.54 (dd, 1H, J = 5.6 Hz, 8.0 Hz, CH-CO), 2.58 (s, 3H, N-Me); ^{13}C nmr: 175.6, 175.1, 137.2, 137.1, 134.0, 133.3, 131.0, 128.6, 128.5, 125.6, 103.3, 54.4, 46.4, 40.4, 24.3.

Compound **7c**: ir (methylene chloride): 1776, 1718, 1598, 1445, 1382, 831; ^{1}H nmr: δ 8.98 (s, 1H, HC=N), 7.95-7.90 (m, $2H_{Ar}$), 7.60-7.48 (m, $6H_{Ar}$), 3.18 (s, 3H, N-Me); ^{13}C nmr: 166.9, 166.2, 155.9, 154.4, 136.7, 136.3, 135.9, 134.0, 131.6, 131.4, 131.0, 130.9, 128.8, 128.4, 122.1, 24.3; HRMS (m/z) Calcd for $C_{20}H_{12}Cl_2N_2O_2$: 382.0276. Found: 382.0275.

2,5-Diphenyl-3,4-carbomethoxypyridine (**9a**).

1,4-Diphenyl-2-aza-1,3-butadiene (200 mg, 0.96 mmole) and diethyl acetylenedicarboxylate (463 ml, 2.89 mmole) in xylene (4 ml) were stirred at 140° for 25 hours. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel using toluene to toluene/ether (15:1 v/v) as eluent to give compound **9a** (86 mg, 23%) then a complex mixture containing non-aromatized cycloadducts (95 mg).

The latter was stirred with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (60 mg, 0.26 mmole) in toluene (5 ml) for 2 hours. The solvent was evaporated and the residue was purified by column chromatography (toluene/diethyl ether 15:1 v/v) to give the expected pyridine **9a** (22 mg, 7%). **9a** (108 mg, 30%) was crystallized from ethylacetate/hexane to give white crystals: mp 143°; ir (methylene chloride): 1736, 1612, 1443, 1231, 1013; ^{1}H nmr: δ 8.78 (s, 1H, HC=N), 7.63-7.59 (m, $2H_{Ar}$), 7.49-7.38 (m, $8H_{Ar}$), 4.15 (q, 4H, J = 7.0 Hz, 2x CH_2O), 1.04 (t, 3H, J = 7.0 Hz, CH_3), 1.03 (t, 3H, J = 7.0 Hz, CH_3); ^{13}C nmr: 167.4, 166.5, 156.5, 151.3, 139.9, 139.2, 136.0, 133.1, 129.0, 128.7 (2s), 128.5, 128.4 (2s), 62.1, 62.0, 13.6, 13.5.

Anal. Calcd. for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.55 ; H, 5.75; N, 3.59.

2,5-*Bis*-(4-Methoxyphenyl)-3,4-carbomethoxypyridine (**9b**).

1,4-*Bis*-(4-methoxyphenyl)-2-aza-1,3-butadiene (102 mg, 0.38 mmole) and diethyl acetylene dicarboxylate (194 mg, 1.14 mmole) in toluene (5 ml) were stirred at 110° for 48 hours. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel using toluene/ethylacetate (9:1 v/v) as eluent to give compound **9b** (55 mg, 33%) that was crystallized from ethylacetate/hexane to give white crystals: mp 143°; ir (methylene chloride): 1736, 1611, 1519, 1451, 1031; ^{1}H nmr: δ 8.72 (s, 1H, HC=N), 7.60-7.54 (m, $2H_{Ar}$), 7.36-7.30 (m, $2H_{Ar}$), 7.01-6.95 (m, $4H_{Ar}$), 4.20 (q, 2H, J = 7.0 Hz, CH_2O), 4.17 (q, 2H, J = 7.0 Hz, CH_2O), 3.86 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 1.11 (t, 3H, J = 7.0 Hz, CH_3), 1.10 (t, 3H, J = 7.0 Hz, CH_3); ^{13}C nmr: 167.8, 166.8, 160.4, 159.9, 155.6, 151.3, 139.7, 132.2, 131.6, 129.9, 129.8, 128.3, 125.4, 114.1, 113.9, 62.05, 62.0, 55.4, 13.7, 13.6.

Anal. Calcd. for $C_{25}H_{15}NO_6$: C, 68.95; H, 5.79; N, 3.22. Found: C, 68.76; H, 5.81; N, 3.29.

2,5-*Bis*-(4-Chlorophenyl)-3,4-carbomethoxy-pyridine (**9c**).

1,4-*Bis*-(4-chlorophenyl)-2-aza-1,3-butadiene (120 mg, 0.44 mmole) and diethyl acetylene dicarboxylate (208 ml, 1.14 mmole) in xylene (4 ml) were stirred at 140° for 48 hours. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel using toluene/ethylacetate (20:1 v/v) as eluent to give compound **9c** (92 mg, 49%) that was crystallized from ethylacetate/hexane to give white crystals: mp 190-191°; ir (methylene chloride): 1737, 1600, 1450, 1013, 834; ^{1}H nmr: δ 8.73 (s, 1H, HC=N), 7.58-7.53 (m, $2H_{Ar}$), 7.48-7.42 (m, $4H_{Ar}$), 7.36-7.31 (m, $2H_{Ar}$), 4.18 (q, 2H, J = 7.0 Hz, CH_2O), 4.17 (q, 2H, J = 7.0 Hz, CH_2O), 1.11 (t, 3H, J = 7.0 Hz, CH_3), 1.10 (t, 3H, J = 7.0 Hz, CH_3); ^{13}C nmr: 167.1, 166.1, 155.6, 151.2, 140.0, 137.4, 135.5, 135.0, 134.3, 132.2, 130.0, 129.8, 129.0, 128.7, 126.0, 62.3 (2s), 13.7, 13.6.

Anal. Calcd. for $C_{23}H_{19}Cl_2NO_4$: C, 62.18; H, 4.31; N, 3.15; Cl, 15.96. Found: C, 62.15; H, 4.43; N, 3.04; Cl, 16.48.

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[23] Due to the formation of many by-products during the reaction this compound was isolated in very slightly impure form after column chromatography on silicagel. Nevertheless, pure form can be obtained after crystallization or trituration in diethyl ether. This was accomplished from the very small quantity isolated so yield obtained after this further purification is not representative and therefore is not given.