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[4+2] CYCLOADDITION REACTIONS OF NEUTRAL 2-AZADIENES WITH ELECTRON-DEFICIENT DIENOPHILES

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Abstract- A method for the preparation of functionalized tetrahydropyridine and triazine derivatives is described, based on aza Diels-Alder reaction of neutral 2-aza-1,3-dienes with electron-poor dienophiles as tetracyanoethylene and *N*-phenyl-1,2,4-triazoline-3,5-dione.

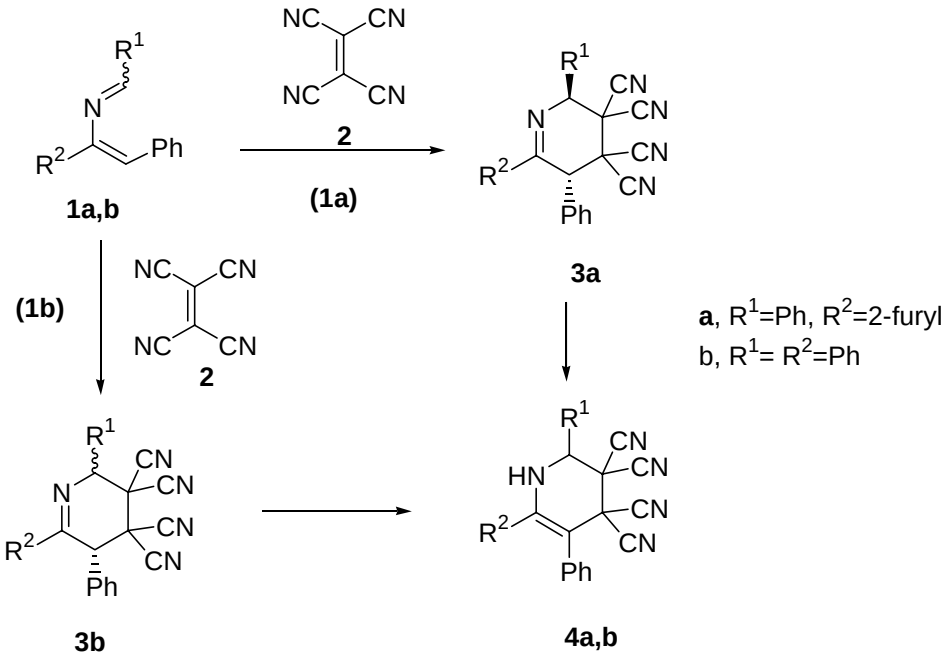
INTRODUCTION

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] Most 2-azadienes studied are substituted with electron donating groups and are excellent reagents in *normal* Diels-Alder reactions.[1,2b-e,3] Among them, neutral azadienes have been used as heterodienes, not only in *inverse*-electron demand Diels-Alder reactions with electron-rich dienophiles[4] but also in *normal* Diels-Alder reactions with electron-poor dienophiles[1c,f] and with heterodienophiles[5a] for the preparation of nitrogen containing heterocycles. These experimental results are corroborated by theoretical studies.[5b] The presence or absence of substituents especially in 3-position seems to play an important role in the reactivity of 2-azadienes.[6]

Given the above, we have been involved in the synthesis of electron-poor azadienes derived from aminophosphorus derivatives[7] and β-amino esters[8] as well as of neutral azadienes with electron-rich olefins and carbonyl compounds[9] and in the preparation of nitrogen containing heterocycles.[10] As a continuation of our work in the cycloaddition chemistry of neutral 2-azadienes,[9] here we aim to explore whether azadienes with aromatic substituents could react with electron-deficient dienophiles such as tetracyanoethylene (TCNE) and 4-phenyl-1,2,4-triazolin-3,5-dione (4-PTAD).

RESULTS AND DISCUSSION

Aza Diels-Alder Reaction of 2-Azadienes (1) with Tetracyanoethylene (2). We first investigated the Diels-Alder reaction of 1*E*-2-azadiene (**1a**) (R^1=Ph, R^2=2-furyl), easily prepared by aza-Wittig treatment of *N*-vinylic phosphazenes and aldehydes,[9c] with tetracyanoethylene (TCNE) (**2**) as electron-deficient alkene in $CHCl_3$ or toluene at room temperature, leading to the formation of only the polysubstituted tetrahydropyridine (**3a**) with substituents R^1 and Ph in *anti* configuration (Scheme 1, Table 1, Entry 1), in a stereoselective fashion. Compound (**3a**) was characterized on the basis of its spectroscopic data. Thus, the ^{13}C NMR spectrum for compound (**3a**) showed absorptions for the corresponding quaternary carbons substituted with two nitrile groups. In order to study the stereochemistry of the process, azadiene (**1b**) containing phenyl substituents (R^1=R^2=Ph) isolated as a mixture of *E*- and *Z*-imine isomers (1*E*/1*Z*=70/30),[9c] was used affording **3b** as a mixture of isomeric tetrahydropyridines (**3b$_1$**) and (**3b$_2$**) in similar proportion to those presented in the precursor azadiene (**1b**) (Scheme 1, Table 1, Entry 2).



Scheme 1

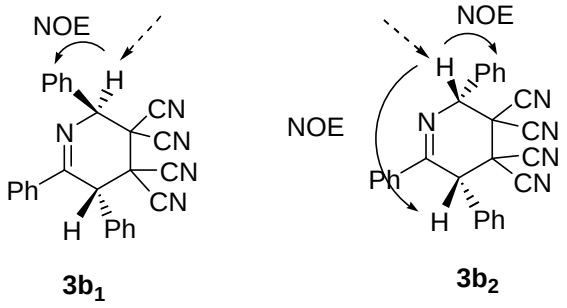


Figure 1

The relative configuration of hydrogens at C-3 and C-6 in both isomers was clarified by NOE difference experiments, which confirmed the proposed structure as no interaction was observed between hydrogens

at C-3 and C-6 in *trans* configuration in compound (**3b$_1$**) of higher abundance, and as a significant integral enhancement was seen between protons at C-3 and C-6 in *cis* configuration in the compound (**3b$_2$**) obtained in lower proportion (Figure 1).

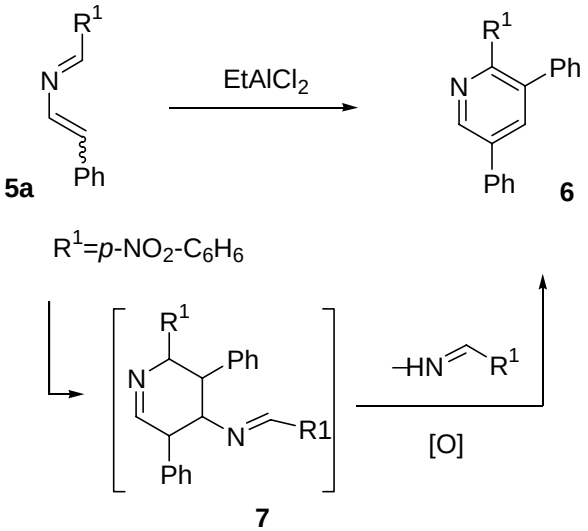
These results suggest that the formation of tetrahydropyridine derivatives (**3**) could be explained by [4+2] cycloaddition of the azadienes (**1**) and tetrasubstituted alkene (**2**). However, we were unable to obtain pure samples of compounds (**3**) by crystallization or by chromatographic purification on silica gel, given that when the purification of compounds (**3**) was attempted, tautomeric tetrahydropyridines (**4**) (Scheme 1, Table 1, Entries 3, 4) were isolated instead.

Table 1: Diels-Alder adducts (**3**) and (**4**) obtained.

				Reaction conditions			
Entry	Compound	R^1	R^2	T(°C)	time (h)	yield(%)	mp [°C]b
1	**3a**	phenyl	2-furyl	25	0.5	93	127-128
2	**3b**	phenyl	phenyl	25	0.5	89	-c
3	**4a**	phenyl	2-furyl	-	-	73a	130-131
4	**4b**	phenyl	phenyl	-	-	75a	154-155

a Purified by chromatography. b After recrystallization from CH_2Cl_2/Hexane. c Evaporation of solvent under reduced pressure and crystallization in hexanes gave a mixture of **3b$_1$** and **3b$_2$** (70/30) as a white solid

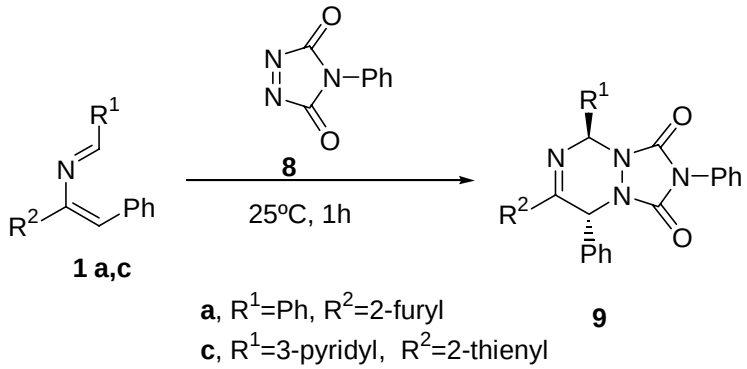
Next, the effect of absence of substituents in position 3 of the heterodiene was explored. No cycloaddition was observed when azadiene (**5a**) (R^1= *p*-NO_2-C_6H_6, 3*E*/3*Z* = 40/60) reacted with tetracyanoethylene



Scheme 2

at room temperature and over a long period (10 days), recovering the starting reagents, while in refluxing toluene a very complex reaction mixture was obtained, in a similar way to that reported for simple heterodienes.[11] Taking into account that Lewis Acids can activate Diels-Alder reactions,[8,12] we attempted the process in the presence of ethylaluminium dichloride ($EtAlCl_2$). However, the treatment of azadiene (**5a**)(120 h, room temperature) with this Lewis Acid ($EtAlCl_2$) gave pyridine (**6**) (Scheme 2, 63% yield). The formation of compound (**6**) can be explained by a [4+2] cycloaddition in which one molecule of 2-azadiene (**5a**) acts as the dienophile and the other as heterodiene to afford the dimeric tetrahydropyridine (**7**), which then loses a molecule of imine followed by aromatization, in a similar way to the dimerization of other neutral azadienes, previously observed by us[9a,b] and others.[2a,11,13]

Aza Diels-Alder Reaction of 2-Azadienes (1) and (5) with *N*-phenyl-1,2,4-triazoline-3,5-dione (8). The Diels-Alder methodology for the preparation of pyridine derivatives was further extended to a typical electron-poor dienophile such as *N*-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (**8**). The reaction of heterodienes containing aromatic and heteroaromatic substituents (**1a**) (R^1=Ph, R^2=2-furyl, 1*E*) and **1c** (R^1=3-pyridyl, R^2=2-thienyl, 1*E*), with the azodienophile (**8**) in mild conditions gave the corresponding Diels-Alder cycloadducts (**9a**,**c**) (Scheme 3, Table 2, Entries 1, 2) in a stereoselective fashion.



Scheme 3.

Table 2: Diels-Alder adducts (**9**) and (**10**) obtained.

Entry	Compound	R^1	R^2	Reaction conditions		yield(%)	mp [ºC]b
				T(°C)	time (h)		
1	**9a**	phenyl	2-furyl	25	1	69a	185-186
2	**9c**	3-pyridyl	2-thienyl	25	1	70a	147-149
3	**10**	*p*-NO_2-Ph	---	110	25	70a	oil

a Purified by chromatography. b After recrystallization from CH_2Cl_2/Hexane.

The compounds were characterized by their NMR spectral data, where ^{1}H NMR spectrum of **9a** showed two singlets at 6.29 and 7.06 ppm corresponding to hydrogens at 3 and 6 positions in bicyclic derivative respectively. The structure was finally determined by X-Ray study of **9a**[14] (Figure 2), confirming the stereochemistry proposed. The process could be explained through a [4+2] cycloaddition reaction, which is stereoselective and yields only one stereoisomer.

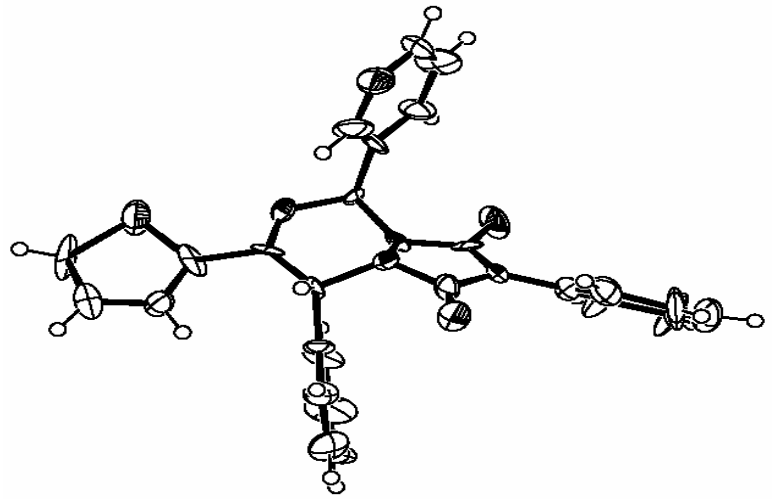
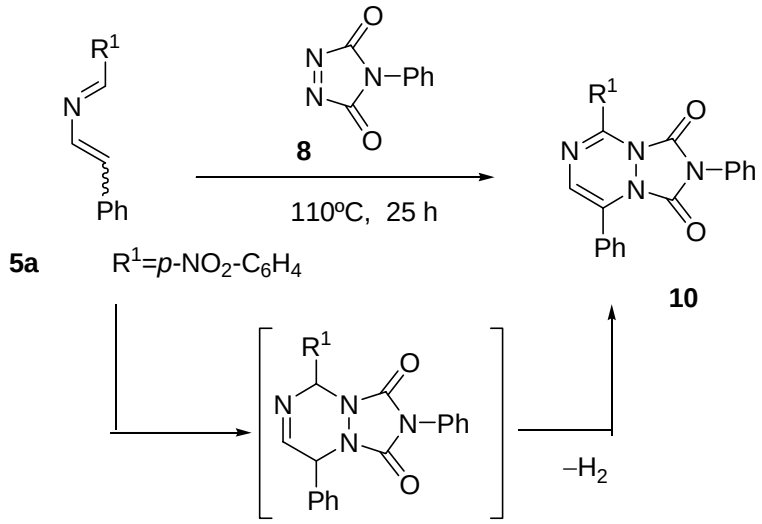


Figure 2. ORTEP view of compound (**9a**)

However, when 2-azadiene (**5a**) (R^1=*p*-NO_2-C_6H_6) with no substituent at C-3 position (Scheme 4) was used, very hard reactions conditions were necessary and in a sealed tube at refluxing toluene for 25 h, bicyclic product (**10**) was obtained directly (Scheme 4, Table 2, Entry 3). The formation of this compound (**10**) could be explained by [4+2] cycloaddition reaction followed by loss of an hydrogen molecule.



Scheme 4.

In summary, electronically neutral 2-aza-1,3-dienes (**1**) and (**5**) with aromatic and heteroaromatic substituents, are a class of heterodienes of great interest, owing to their remarkable aza Diels-Alder reactivity. With electron-deficient dienophiles such as tetracyanoethylene (TCNE) and

N-phenyl-1,2,4-triazoline-3,5-dione (PTAD) cycloadducts (**3, 4, 9, 10**) (*normal* Diels-Alder reaction) can be obtained while the presence of a Lewis acid ($EtAlCl_2$) catalyzes the dimerization of azadiene (**5a**), in which one molecule acts as electron-rich dienophile and the other as heterodiene (*inverse* electron demand Diels-Alder reaction) to give substituted pyridine (**6**). Pyridine ring systems have received considerable attention not only for their widespread occurrence in nature[15] but also for their remarkable versatility in preparative organic synthesis[15] and in medicinal chemistry,[16] In addition, the furan substituent can be considered as a synthetic equivalent of carboxylic acid. Therefore, through the strategies reported in this paper new access to polysubstituted pyridines 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 (EI) were obtained with a ionization voltage of 70 eV. Data are reported in the form *m/z* (intensity relative to base = 100). IR 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. ^{31}P NMR spectra were recorded at 120 MHz with 85% phosphoric acid as an external reference. 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. Azadienes (**1**) were prepared as described in the literature.[9c,d]

General procedure for preparation of azadienes (5). Aldehyde (2 mmol) was added to a 0-10 ºC solution of phosphazene[17] (2 mmol) in $CHCl_3$ under N_2. Then, the mixture was stirred at rt until TLC indicated the disappearance of phosphazene.

4-Phenyl-1-(4-nitrophenyl)-2-azabuta-1,3-diene (**5a**) 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 **5a** 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, $CDCl_3$) d 124.4-130.9 (m,11H), 134.2 (for 3*E*), 135.6, 140.3 (for 3*Z)*, 141.0 (for 3*E)*, 141.8, 142.4, 151.9, 157.9 (for 3*E*), 159.2 (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 (**5b**) 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 (**5a**+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 Aza Diels-Alder reactions. Dienophile (5 mmol) was added to a 0-10 °C solution of azadiene (**1**) or (**5**) (5 mmol) in $CHCl_3$ or toluene (15 mL) under N_2. Then, the mixture was stirred at adequate temperature until TLC indicated the disappearance of azadiene**.**

6-Furan-2-yl-2,5-diphenyl-2,5-dihydropyridine-3,3,4,4-tetracarbonitrile (**3a**). The general procedure was followed using 1,4-diphenyl-3-furan-2-yl-2-azabuta-1,3-diene (**1a**) (1.36 g, 5 mmol) and tetracyanoethylene (**2**) (0.64 g, 5 mmol) in toluene at rt for 0.5 h. Evaporation of solvent under reduced presure and crystallization of crude reaction in hexane gave 1.86 g (93 %) of **3a** as a green solid, mp 127-128 °C. IR (KBr) ν 2203, 1633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.01 (s, 1H), 5.78 (s, 1H), 6.33 (t, 1H, *J* = 1.7 Hz), 6.79 (d, 1H, *J* = 3.6 Hz), 7.13-7.63 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.3, 64.2, 107.7, 109.0, 111.0, 111.3, 112.2, 115.3, 125.1-152.9 (m); MS (CI) *m/z* 402 (M^++1, 100). Anal. Calcd for $C_{25}H_{15}N_5O$: C, 74.80; H, 3.77; N, 17.45. Found: C, 75.05; H, 4.31; N, 17.16.

6-Furan-2-yl-2,5-diphenyl-1,2-dihydropyridine-3,3,4,4-tetracarbonitrile (**4a**) After column chromatography (10/1, hexane/ethyl acetate) of compound (**3a**), compound (**4a**) was obtained as a green solid, 1.35 g (73 %), mp 130-131 °C (CH_2Cl_2/Hexane). IR (KBr) ν 3400, 1628, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.56 (s, 1H), 5.08 (s, 1H), 5.25 (d, 1H, *J* = 3.6 Hz), 6.17 (dd, 1H, *J* = 3.6 Hz, *J* = 1.5 Hz), 7.19-7.72 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 59.7, 108.9, 109.9, 110.0, 111.6, 112.7, 114.1, 122.1-152.1 (m); MS (EI) *m/z* 401 (M^+, 13). Anal. Calcd for $C_{25}H_{15}N_5O$: C, 74.80; H, 3.77; N, 17.45. Found: C, 74.85; H, 3.79; N, 17.44.

***trans*-Triphenyl-2,5-dihydropyridine-3,3,4,4-tetracarbonitrile (3b$_1$), *cis*-2,3,6-triphenyl-2,5-dihydro-pyridine-3,3,4,4-tetracarbonitrile** (**3b$_2$**) **and 2,5,6-triphenyl-1,2-dihydropyridine-3,3,4,4-tetra-**

carbonitrile (**4b**) The general procedure was followed using a 70/30 diastereomeric mixture of 1*E*/1*Z* isomers of 3*Z*-1,3,4-triphenyl-2-azabuta-1,3-diene (**1b**) (1.41 g) and tetracyanoethylene (**2**) (0.64 g) in $CHCl_3$ for 0.5 h. Evaporation of solvent under reduced pressure and crystallization in hexanes gave 1.83 g (89 %) of a mixture of **3b$_1$** and **3b$_2$** compounds (70/30) as a white solid, mp 165-168 °C (CH_2Cl_2/Hexane). IR (KBr) ν 2245, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.02 (d, 1H, *J* = 3.2 Hz) for **3b$_2$**, 5.12 (d, 1H, *J* = 1.8 Hz) for **3b$_1$**, 5.78 (d, 1H, *J* = 3.2 Hz) for **3b$_2$**, 5.84 (d, 1H, *J* = 1.8 Hz) for **3b$_1$**, 7.14-7.78 (m, 30H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.9 for **3b$_1$**, 48.5 for **3b$_2$**, 63.6 for **3b$_2$**, 64.6 for **3b$_1$**, 107.9 for **3b$_1$**, 108.4 for **3b$_2$**, 109.3 for **3b$_1$**, 109.5 for **3b$_2$**, 110.0 for **3b$_2$**, 110.4 for **3b$_2$**, 111.3 for **3b$_1$**, 111.5 for **3b$_1$**, 125.1-135.6 (m), 161.4 for **3b$_1$**, 164.1 for **3b$_2$**; MS (CI) *m/z* 412 (M^++1, 100). After column chromatography (10/1, hexane/ethyl acetate) of compound (**3b**), compound (**4b**) was obtained as a pink solid, 1.37 g (75 %), mp 154-155 °C (CH_2Cl_2/Hexane). IR (KBr) ν 2243, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (s, 1H), 5.21 (s, 1H), 7.20-7.77 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 59.7, 108.7, 109.7, 110.1, 111.8, 127.4-135.6 (m), 145.8; MS (CI) *m/z* 412 (M^++1, 100). Anal. Calcd for $C_{27}H_{17}N_5$: C, 78.81; H, 4.16; N, 17.02. Found: C, 78.88; H 4.08; N, 16.96.

2-(4-Nitrophenyl)-3,5-diphenylpyridine (6) The general procedure was followed using a 40/60 diastereomeric mixture of 3*Z*/3*E* isomers of 1*E*-1-(4-nitrophenyl)-4-phenyl-2-azabuta-1,3-diene (**5a**) (1.25 g) and $EtAlCl_2$ (0.5 mL, 97%, 5 mmol). After stirring at rt during 120 h, the mixture was neutralized with 6 mL of NaOH (3 N) and stirred at rt for 3 h. Filtration over Al_2O_3, extraction with CH_2Cl_2, dried ($MgSO_4$) and evaporation of solvent under reduced pressure afforded an oil which was chromatographied on silicagel (10/1, ethyl acetate/ hexane) giving 0.22 g (63%) of **6** as a yellow solid, mp 143-144 °C (CH_2Cl_2/Hexane). IR (KBr) ν 1520, 1347 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-7.49 (m, 10H), 7.52 (d, 2H, *J* = 8.8 Hz), 7.90 (d, 1H, *J* = 2.1 Hz) 8.04 (d, 2H, *J* = 8.8 Hz), 8.89 (d, 1H, *J* = 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 123.1-138.9 (m), 146.3, 147.0, 147.2, 153.2; MS (EI) *m/z* 352 (M^+, 72). Anal. Calcd for $C_{23}H_{16}N_2O_2$: C, 78.39; H, 4.58; N, 7.95. Found: C, 78.43; H, 4.50; N, 7.98.

7-Furan-2-yl-2,5,8-triphenyl-5,8-dihydro-[1,2,4]-triazolo[1,2-*a*][1,2,4]triazine-1,3-dione (**9a**) The general procedure was followed using 1*E*/3Z-1,4-diphenyl-3-furan-2-yl-2-azabuta-1,3-diene (**1a**) (1.36 g) and *N*-phenyl-1,2,4-triazoline-3,5-dione (**8**) (0.90 g, 5 mmol) in toluene at reflux for 1 h. Evaporation of solvent under reduced pressure and chromatographic separation (5/1, hexane/ethyl acetate) gave 1.54 g (69 %) of **9a** as a yellow solid, mp 185-186 °C (CH_2Cl_2/Hexane). IR (KBr) ν 1726 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (s, 1H), 6.40-6.43 (m, 1H), 6.87 (d, 1H, *J* = 3.5 Hz), 7.12-7.54 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.9, 73.3, 112.0, 114.3, 125.1-152.4 (m); MS (EI) *m/z* 448 (M^+, 50). Anal. Calcd for $C_{27}H_{20}N_4O_3$: C, 72.31; H, 4.49; N, 12.49. Found: C, 72.21; H, 4.37; N, 12.41.

2,8-Diphenyl-5-pyridin-3-yl-2-thien-2-yl-5,8-dihydro[1,2,4]triazolo[1,2-*a*][1,2,4]triazine-1,3-dione (**9c**) The general procedure was followed using 3-thien-2-yl-4-phenyl-1-pyridin-3-yl-2-azabuta-1,3-diene **1c** (1.45 g) and N-phenyl-1,2,4-triazoline-3,5-dione (**8**) (0.90 g, 5 mmol) in toluene at rt for 1 h. Evaporation of solvent under reduced presure and chromatographic separation (5/1, hexane/ethyl acetate) gave 1.63 g (70 %) of **9c** as a white solid, mp 147-149 °C (CH_2Cl_2/Hexane). IR (KBr) ν 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.29 (s, 1H), 6.97-7.00 (m, 1H), 7.06 (s, 1H), 7.13-7.56 (m, 13H), 7.78-7.82 (m, 1H), 8.65 (dd, 1H, *J* = 4.9 Hz, *J* = 1.2 Hz), 8.77 (d, 1H, *J* = 2.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.1, 71.2, 123.5-156.5 (m); MS (CI) *m/z* 466 (M^++1, 100). Anal. Calcd for $C_{26}H_{19}N_5O_2S$: C, 67.08; H, 4.11; N, 15.04. Found: C, 66.99; H, 4.00; N, 14.96.

2,8-Diphenyl-5-(*p*-nitrophenyl)[1,2,4]triazolo[1,2-*a*][1,2,4]triazine-1,3-dione (**10**) The general procedure was followed using 1-(*p*-nitro-phenyl)-4-phenyl-2-azabuta-1,3-diene (**5a**) (1.27 g) and *N*-phenyl-1,2,4-triazoline-3,5-dione (**8**) (0.90 g, 1 mmol) in toluene at reflux for 25 h. Evaporation of solvent under reduced presure and chromatographic separation (15/1, hexane/ethyl ether) gave 0.88 g (70 %) of **10** as an orange oil, *Rf* = 0.59 (1/2, ethyl acetate/hexane). IR (KBr) ν 1600, 1520 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18-7.69 (m, 10H), 8.01 (d, 2H, *J* = 8.8 Hz), 8.26 (d, 2H, *J* = 8.8 Hz), 8.49 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.9-150.9 (m), 157.3; MS (EI) *m/z* 425 (M^+, 11). Anal. Calcd for $C_{23}H_{15}N_5O_4$: C, 64.94; H, 3.55; N, 16.46. Found: C, 64.97; H, 3.50; N, 16.49.

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REFERENCES

1. For reviews see: a) K. C. Nicolau, S. A. Snyder, T. Montagnon, and G. Vassilikogiannakis, *Angew. Chem.,Int. Ed.*, 2002, **41**, 1669. b) S. Jayakumar, M. P. S. Ishar, and M. P. Mahajan, *Tetrahedron*, 2002, **58**, 379. c) P. Buonora, J.-C. Olsen, and T. Oh, *Tetrahedron*, 2001, **57**, 6099. d) L. F. Tietze and G. Kettschau, *Top. Curr. Chem.* 1997, **189**, 1. a) L. Ghosez in '*Stereocontrolled Organic Synthesis*', Backwell, Oxford, 1994, pp. 193-233. f) J. Barluenga and M. Tomás, *Adv. Heterocycl. Chem.*, 1993, **57**, 1.
2. For recent contributions, see: a) K. C. Nicolau, M. Nevalainen, B. S. Safina, M. Zak, and S. Bulat, *Angew. Chem., Int. Ed.*, 2002, **41**, 1941. b) C. J. Moody, R. A. Hughes, S. P. Thompson, and L. Alcaraz,

Chem. Commun., 2002, 1760. c) D. Ntirampebura and L. Ghosez, *Synthesis*, 2002, 2043. d) V. B. Genisson, P. Nebois, M. Domard, and H. Fillion, *Chem. Pharm. Bull.*, 2000, **48**, 893. e) E. Jnoff and L. Ghosez, *J. Am. Chem. Soc.*, 1999, **121**, 2617.

3. a) E. Bandini, G. Martelli, G. Spunta, A. Bongini, and M. Panunzio, *Synlett*, 1999, 1735. b) D. Ntirampebura and L. Ghosez, *Tetrahedron Lett.*, 1999, **40**, 7079. c) L. Ghosez, E. Jnoff, P. Bayard, F. Sainte, and R. Beaudegnies, *Tetrahedron*, 1999, **55**, 3387. d) A. Bongini, M. Panunzio, E. Bandini, G. Martelli, and G. Spunta, *J. Org. Chem.*, 1997, **62**, 8911. e) B. Mathieu and L. Ghosez, *Tetrahedron Lett.*, 1997, **38**, 5497. f) L. Ghosez, *Pure Appl. Chem.*, 1996, **68**, 15. g) A. Marchand, J. P. Pradere, and A. Guingant, *Tetrahedron Lett.*, 1997, **38**, 1033. h) M. Beres, G. Hajos, Z. Riedl, G. Timari, A. Messmer, S. Holly, and J. G. Schantl, *Tetrahedron*, 1997, **53**, 9393. i) G. Morel, E. Marchand, J. P. Pradere, L. Toupet, and S. Sinbandhit, *Tetrahedron*, 1996, **52**, 10095. j) V. Gouverneur and L. Ghosez, *Tetrahedron*, 1996, **52**, 7585.
4. Y. Cheng, E. Ho, P. S. Mariano, and H. L. Ammon, *J. Org. Chem.*, 1985, **50**, 5678.
5. a) A. Venturini, J. Joglar, S. Fustero, and J. González, *J. Org. Chem.*, 1997, **62**, 3919. b) J. González and K. N. Houk, *J. Org. Chem.*, 1992, **57**, 3031.
6. a) M. T. Barroso and A. Kascheres, *J. Org. Chem.*, 1999, **64**, 49. b) C. Balsamini, A. Bedini, G. Spadoni, M. Burdisso, and A. M. Capelli, *Tetrahedron*, 1994, **50**, 3773. c) K. J. Van Aken, G. M. Lux, G. G. Deroover, L. Meerpoel, and G. J. Hoorvaert, *Tetrahedron*, 1994, **50**, 5211. d) F. Sainte, B. Serckx-Poncin, A.-M. Hesbain-Frisque, and L. Ghosez, *J. Am. Chem. Soc.*, 1982, **104**, 1428.
7. a) F. Palacios, A. M. Ochoa de Retana, E. Martínez de Marigorta, M. Rodríguez, and J. Pagalday, *Tetrahedron*, 2003, **59**, 2617. b) F. Palacios, M. J. Gil, E. Martínez de Marigorta, and M. Rodríguez, *Tetrahedron Lett.*, 1999, **40**, 2411. c) F. Palacios, D. Aparicio, and J. M. de los Santos, *Tetrahedron*, 1996, **52**, 4857.
8. a) F. Palacios, E. Herrán, G. Rubiales, and J. M. Ezpeleta, *J. Org. Chem.*, 2002, **67**, 2131. b)) F. Palacios, M. Legido, I. Pérez de Heredia, and G. Rubiales, *Heterocycles*, 2000, **52**, 1657. c) F. Palacios, E. Herrán, and G. Rubiales, *J. Org. Chem.*, 1999, **64**, 6239. d) F. Palacios, I. Pérez de Heredia, and G. Rubiales, *J. Org. Chem.*, 1995, **60**, 2384.
9. a) F. Palacios, C. Alonso, P. Amezua, and G. Rubiales, *J. Org. Chem.*, 2002, **67**, 1941. b) F. Palacios, C. Alonso, G. Rubiales, and J. M. Ezpeleta, *Eur. J. Org. Chem.*, 2001, 2115. c) F. Palacios, C. Alonso, and G. Rubiales, *J. Org. Chem.*, 1997, **62**, 1146. d) F. Palacios, C. Alonso, and G. Rubiales, *Tetrahedron*, 1995, **51**, 3683.
10. For recent communications see: a) F. Palacios, D. Aparicio, A. M. Ochoa de Retana, J. M. de los Santos, J. I. Gil, and J. M. Alonso, *J. Org. Chem*,. 2002, **67**, 7283. b) F. Palacios, A. M. Ochoa de Retana, J. I. Gil, and R. López de Munain, *Org. Lett.*, 2002, **4**, 2405. c) F. Palacios, A. M. Ochoa de Retana, J. I. Gil,

and J. M. Alonso, *Tetrahedron: Asymmetry*, 2002, **13**, 2541. d) F. Palacios, E. Herrán, and G. Rubiales, *Heterocycles*, 2002, **58**, 89. e) F. Palacios, D. Aparicio, and J. Vicario, *Eur. J. Org. Chem.*, 2002, 4131. f) F. Palacios, D. Aparicio, J. García, J. Vicario, and J. M. Ezpeleta, *Eur. J. Org. Chem.*, 2001, 3357. g) F. Palacios, D. Aparicio, J. M. de los Santos and J. Vicario, *Tetrahedron*, 2001, **57**, 1961. h) F. Palacios, M. Legido, I. Pérez de Heredia, G. Rubiales, and J. M. Ezpeleta, *Heterocycles*, 2001, **55**, 1641.

11. J.L. Paparin, C. Crévisy, R. Grée, and L. Toupet, *J. Heterocycl. Chem*., 2000, **37**, 411.
12. a) A. Kumar, *Chem. Rev.*, 2001, **101**, 1. b) A. Kumar, *J. Org. Chem.*, 1994, **59**, 4612. c) P. A. Grieco, *Tetrahedron Lett.*, 1993, **34**, 7367.
13. a) J. V. Barkley, T. L. Gilchrist, A. M. d'A Rocha Gonzalves, and T. M. V. D. Pinho, *Tetrahedron*, 1995, **51**, 13455. b) H. Wulff and H. T. Klinken, *Tetrahedron*, 1992, **48**, 5985. c) H. Wulff and H. Böhnke, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 90.
14. CCDC-214529 contains the supplementary crystallographic data for this paper. These data can by obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat) +44-1223/336-033; Email: deposit@ccdc.cam.ac.uk].
15. For reviews see: a) N. Matzanke, R. J. Gregg, and S. M. Weinreb, *Org. Prep. Proc. Int.*, 1998, **30**, 1. b) W. H. Streng, *Drug Dis*. *Today*, 1997, **2**, 415. c) M. J. Schneider, in '*Alkaloids. Chemical and Biological Perspectives'*, ed. by S. W. Pelletier, Pergamon, Oxford, 1996, Vol. 10. p. 155. d) A. O. Plunkett, *Nat. Prod. Rep.*, 1994, **11**, 581. e) D. J. Triggle, in '*Comprehensive Medicinal Chemistry*', ed. by C. Hansch, Pergamon, Oxford, 1990; Vol. 3, p. 1070. f) A. Numata and T. Ibuka, in '*The Alkaloids'*, ed. by A. Brossi, Academic Press, New York, 1987, Vol. 31. g) J. L. Daly and T. F. Spande, in '*Alkaloids. Chemical and Biological Perspectives*, ed. By S. W. Pelletier, Wiley, New York, 1986, Vol. 4. p. 1.
16. For recent reviews see: a) W. S. Hamama and H. H. Zoorob, *Tetrahedron*, 2002, **58**, 6143. b) D. S. Coffey, S. A. May, and A. M. Ratz, *Prog. Heterocycl. Chem*., 2001, **13**, 238. c) F. Monguin and G. Queguiner, *Tetrahedron*, 2001, **57**, 4059. d) P. Espinet and K. Soulantica, *Coord. Chem. Rev.*, 1999, **195**, 499. e) L. F. Szczepura, L. M. Witham, and K. J. Takeuchi, *Coord. Chem. Rev.*, 1998, **174**, 5. f) G. Jones in '*Comprehensive Heterocyclic Chemistry II*', ed. by A. R. Katritzky, C. W. Rees, E. F. V. Scriven, A. McKillop, Pergamon, Oxford, 1996, Vol. 5, p. 217.
17. A.R. Katritzky, R. Mazurkiewicz, C.V. Stevens, and M.F. Gordeev, *J. Org. Chem.*, **1994**, *59*, 2740.