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Synthesis of Pyrazolo[3,4-*b*]pyridines by Cycloaddition Reactions under Microwave Irradiation

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Dedicated to Prof. José Elguero on the occasion of his 65th birthday

Abstract—Microwave irradiation induces the cycloaddition of pyrazolylimines with aromatic and aliphatic nitroalkenes to afford pyrazolo[3,4-*b*]pyridines in 5–20 min. Some of these reactions do not occur under classical heating. Tricyclic heterocycles can be synthesized from cycloalkenes. The reactivity and regiochemistry can be understood in terms of the energy and atomic coefficients of the frontier orbital, except in the case of compound **18**. Calculations at the HF/3-21G level predict an asynchronous transition structure for this cycloaddition with regiocontrol determined by Coulombic interaction.

Introduction

Pyrazolo[3,4-*b*]pyridines are very interesting compounds and have received considerable attention as a result of their biological activity and structural relationship to indoles. A number of pyrazolo[3,4-*b*]pyridines display interesting anxiolytic activity[1] (e.g. tracazolate[2]), are potentially biologically active compounds as new inhibitors of xantine oxidases,[3] have proved to be active against Gram positive and Gram negative bacteria[4] and as cholesterol formation-inhibiting compounds,[5] and are also promising for the treatment of cataracts associated with diabetes.[6]

Pyrazolo[3,4-*b*]pyridines have been prepared generally by cyclization reactions starting from different heterocyclic reagents.[7–11] Only two examples have been reported for the preparation of these compounds by cycloaddition reactions: in the first case, the title compounds were obtained by [4+2] cycloaddition of a 1,2,4-triazepine with dimethyl acetylenedicarboxylate (DMAD) and subsequent 1,3-sigmatropic rearrangement;[12] in the second case, pyrazolo[3,4-*b*]pyridines were prepared by 1,3-dipolar cycloaddition of cyclic ketene *N,O*-acetals with diphenylnitrilimine.[13]

Recently, we have reported a new, interesting and versatile approach to the preparation of pyrazolo[3,4-*b*]pyridines through a Diels–Alder cycloaddition of pyrazolyl imines with aromatic nitroalkenes under microwave irradiation.[14] This is the first example of a [4+2] cycloaddition of a 2-azadiene involving a pyrazole ring (Scheme 1).

The higher yields obtained and the mild reaction conditions used with azadiene **2** can be justified, in part, by the HOMO (diene)–LUMO (dienophile) energy gaps. These are 0.5 eV lower than those relating to the cycloadditions of **1** (see Table 1).

On the other hand, compounds **1** and **2** were modeled using the Hyperchem program.[15] The more stable conformation of 2-azadiene **2** has a torsion angle of 8.7° between the exocyclic double bond and the pyrazole ring, while in azadiene **1** this torsion angle has a value of 18.1°. This greater planarity in compound **2** partly justifies its higher reactivity as a diene.

Results and Discussion

In order to determine the scope of this reaction and its utility as a new synthetic approach to pyrazolo[3,4-*b*]pyridines, we have studied the cycloaddition of 2-azadienes **1** and **2** with aliphatic nitroalkenes and other dienophiles under microwave irradiation. All the cycloadditions were performed in the absence of solvent at atmospheric pressure in a focused microwave reactor with full control of the incident power and the reaction temperature. The reaction mixture was irradiated until complete consumption of the azadiene had been achieved. The pyrazolopyridines were directly isolated

Keywords: microwave heating; Diels–Alder reactions; nitrogen heterocycles; computed-assisted methods.
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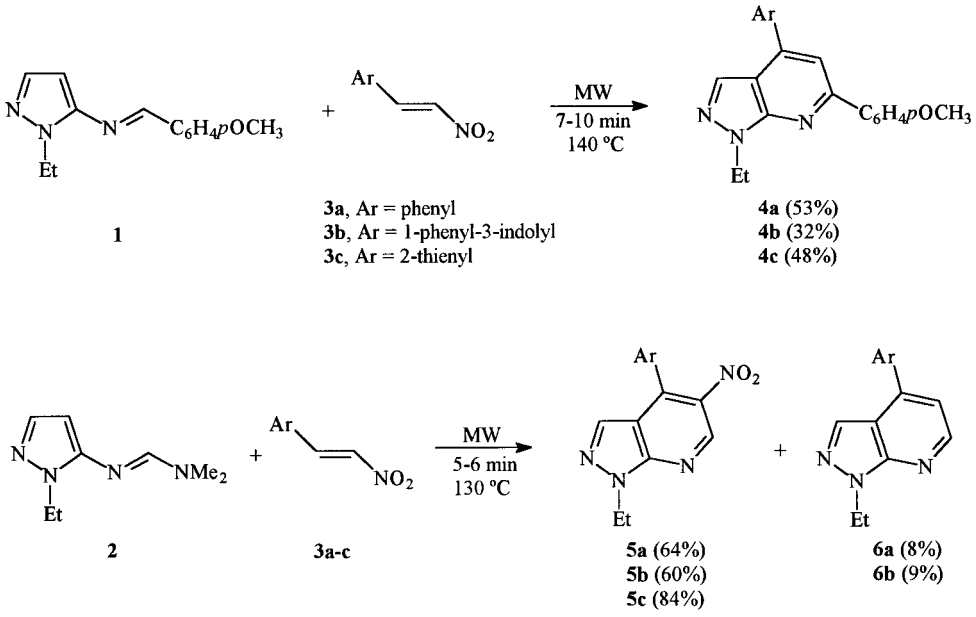


Scheme 1.

Table 1. HOMO–LUMO energies of Compounds **1**–**3** and energy gaps

Compound	E_{HOMO} (eV)	E_{LUMO} (eV)	E_{HOMO} **1**$-E_{LUMO}$	E_{HOMO} **2**$-E_{LUMO}$
1	−8.81	−0.66	–	–
2	−8.61	−0.13	–	–
3a	−10.05	−1.44	7.37	7.17
3b	−8.68	−1.29	7.52	7.32
3c	−10.09	−1.74	7.07	6.87

Table 2. Diels–Alder cycloadditions of 2-azadienes **1** or **2** with electron-poor dienophiles **7**–**12**

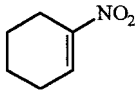
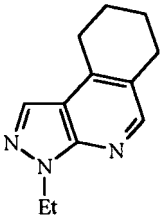
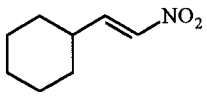
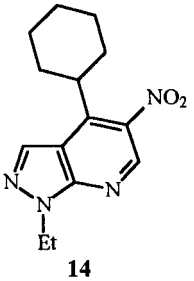
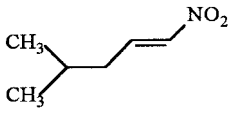
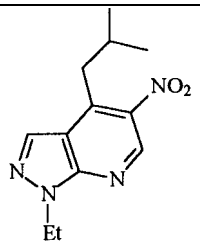
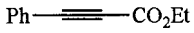
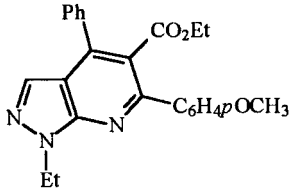
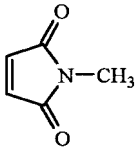
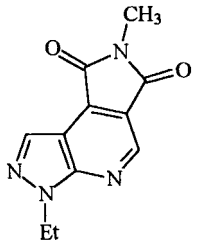
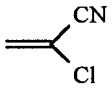
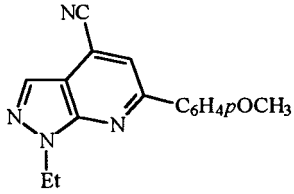
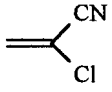
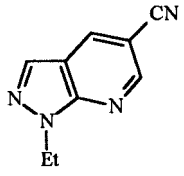
Diene	Dienophile	Reaction conditions	Product	Yield (%)
2	 **7**	180 W, 10 min, 100°C	 **13**	41
2	 **8**	90 W, 10 min, 130°C	 **14**	33

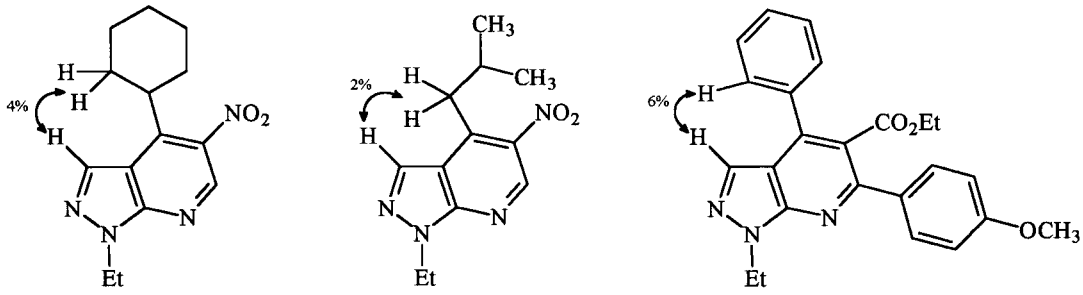
Table 2 (*continued*)

Diene	Dienophile	Reaction conditions	Product	Yield (%)
2	 **9**	90 W, 10 min, 120°C	 **15**	55
1	 **10**	285 W, 15 min, 140°C	 **16**	25
2	 **11**	210 W, 15 min, 170°C	 **17**	50
1	 **12**	150 W, 20 min, 85°C	 **18**	20
2	 **12**	150 W, 20 min, 85°C	 **19**	39

from the crude mixture by flash chromatography. Reaction conditions, products and yields are summarized in Table 2.

Microwave irradiation induced pyrazolyl 2-azadienes to undergo Diels–Alder cycloaddition with electron-poor dienophiles in 10–20 min to give the corresponding pyrazolo[3,4-*b*]pyridines.

This is a versatile synthetic procedure that permits the synthesis of several pyrazolopyridines by the introduction of various different substituents in the heterocyclic ring and



14 15 16

Figure 1. Selected NOEs for pyrazolopyridines **14**–**16**.

even allows the preparation of tricyclic derivatives such as **13** or **17**.

The moderate yields, in comparison with the results obtained from aromatic nitroalkenes, can be explained in terms of the LUMO energy of the dienophiles, ca. 1 eV higher than in the aromatic nitroalkenes, and the ease of polymerization of some of the reactants, such as **10** or **12**.

In all the reactions with unsymmetrical dienophiles only one regioisomer was obtained. The regiochemistry of the adducts has been inferred by NOE difference experiments (see Fig. 1).

Reaction of 2-azadiene **2** and aliphatic nitroalkenes **8** or **9** took place with loss of $HNMe_2$ and oxidation to yield the aromatic heterocycle. However, with 1-nitrocyclohexene (**7**) aromatization is possible only through loss of HNO_2.

In the case of 2-chloroacrylonitrile (**12**) aromatization took place with loss of HCl, a less usual process in cycloadditions. Owing to the low boiling point of the 2-chloroacrylonitrile, these reactions were performed with a large excess of dienophile (8 equiv.), in contrast with cycloadditions of the other dienophiles (only 2 equiv.).

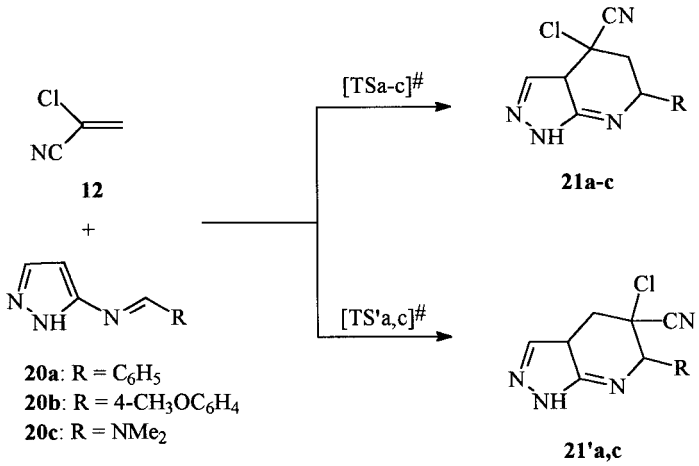
The regiochemistry of the adducts **18** and **19** was inferred by spectroscopic experiments. The ^1H NMR spectrum of **19** shows two doublets at 8.41 and 8.74 ppm (J=1.9 Hz) assigned to H-4 and H-6, respectively. In the case of **18**, an NOE (3%) between H-5 (δ 8.11) and *o*-H of *p*-$CH_3OC_6H_4$ (δ 7.74) could be observed.

In order to assess the efficiency of the microwave irradiation in inducing these processes, we studied the reaction of **1** or **2** with 2-chloroacrylonitrile by classical heating in an oil bath under the same reaction conditions (time and temperature). However, in this case the adducts **18** or **19** were not obtained and hydrolysis of the 2-azadiene took place.

The change in the regioselectivity of the cycloadditions of acrylonitrile on using **1** or **2** as the substrate is remarkable. Considering the LUMO of acrylonitrile, the atomic coefficient values could justify the regiochemistry of adduct **19** but not the regiochemistry of adduct **18**.

Computational Studies

In order to understand the reasons underlying the regiodivergent outcome of these cycloadditions, we performed several calculations on the model structures depicted in Scheme 2. Among the possible stereoisomers considered, those possessing *endo* cyano groups proved to be more stable and therefore only the corresponding reaction paths will be discussed. Given the size of the structures, geometry



20a: R = C_6H_5
20b: R = 4-$CH_3OC_6H_4$
20c: R = NMe_2

Scheme 2.

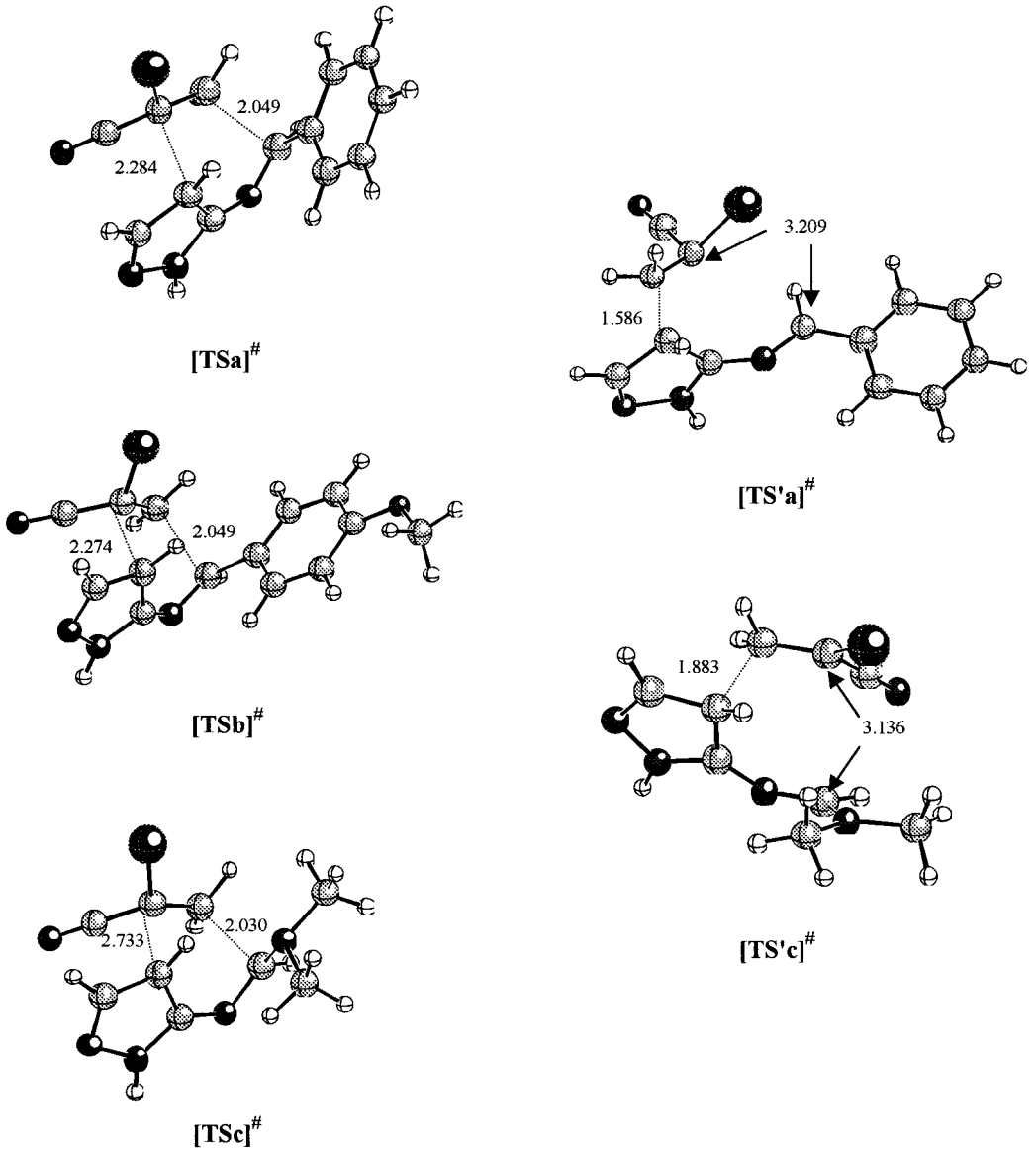


Figure 2. Chief geometric features of the transition structures. Bond distances are given in Å. Atoms are represented by increasing order of shading as follows: H, C, N.

optimizations were carried out at the relatively inexpensive HF/3-21G level, since previous calculations on related Diels–Alder reactions have shown that this level yields sufficiently accurate geometries.[16]

The chief geometric features of the transition structures are given in Fig. 2. It can be seen that the transition structures **Tsa**–**c** are significantly more synchronous than their regioisomeric analogues **TS′a**,**c**. In these latter transition structures the C2···C3 bond distances are larger than 3 Å, whereas the C4···C5 bond distances lie in the normal range for this kind of reaction.[17,18]

Relative energies were computed by means of the three parameter hybrid functional B3LYP, since this method has proved to yield accurate activation and reaction energies in thermal conditions.[19] Solvent effects were estimated by means of the Onsager model,[20,21] denoted as L1A1.[22] The computed activation and reaction energies are reported in Table 3.

Table 3. Computed activation energies[a,b] (ΔE_a, kcal/mol) and reaction energies[a,c] (ΔE_{rxn}, kcal/mol) for the transformations **20a**–**c**+**12**→**21a**–**c** and **20a**,**c**+**12**→**21′a**,**c** (see Scheme 2)

Series	R	ΔE_a		ΔE_{rxn}	
		ϵ=1.00	ϵ=36.64	ϵ=1.00	ϵ=36.64
20a–c+12→21a–c					
a	C_6H_5	39.31	40.62	−6.81	−4.40
b	*p*-$CH_3OC_6H_4$	39.68	41.33	−5.72	−2.43
c	NMe_2	45.17	47.51	+3.71	+8.97
20a,c+12→21′a,c					
a	C_6H_5	34.54	43.73	−4.56	−1.89
c	NMe_2	29.69	32.17	−5.11	−10.27

[a] Single-point energies computed at the B3LYP/G31G*//HF/3-21G*+ΔZPVE and B3LYP(L1A1)/G-31G*//HF/3-21G+ΔZPVE levels in the gas phase and in acetonitrile solution (ϵ=36.64), respectively.

[b] Computed as $\Delta E_a = E(TS) - E(\mathbf{20}) + E(\mathbf{12})]$ or $\Delta E_a = E(TS') - E(\mathbf{20}) + E(\mathbf{12})]$.

[c] Computed as $\Delta E_{rxn} = E(\mathbf{21}) - E(\mathbf{20}) + E(\mathbf{12})]$.

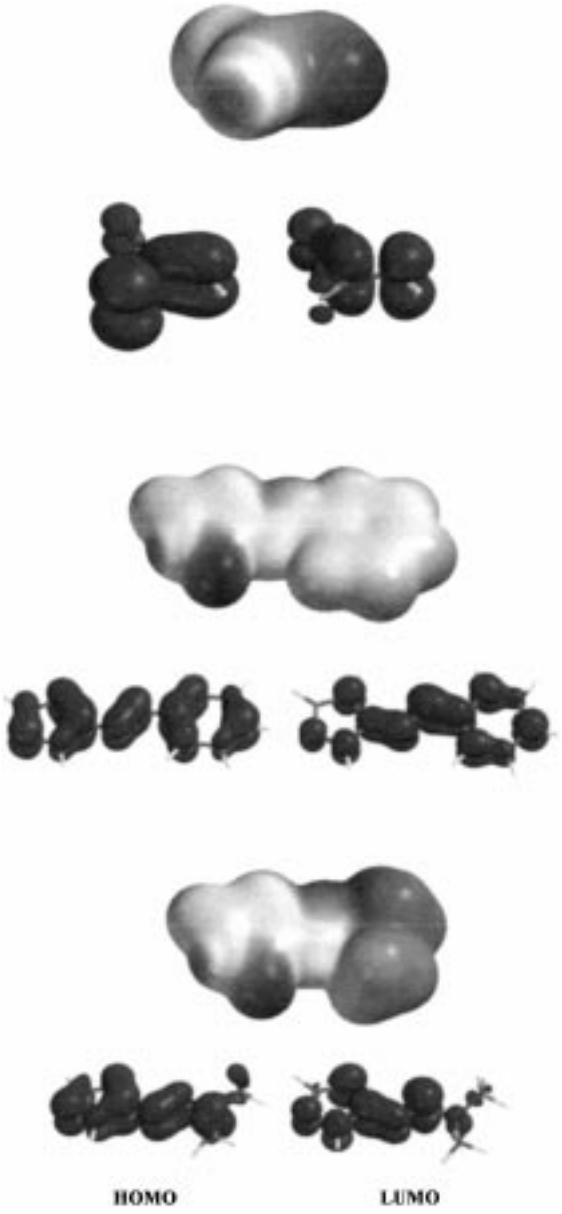


Figure 3. Frontier molecular orbitals (FMOs) of reactants **12**, **20a** and **20c**, respectively, as well as the electrostatic potentials mapped on the electron density surfaces.

Our results indicate that formation of cycloadducts **21a**,**b** is exothermic. In contrast, formation of compound **21c** is endothermic, especially in acetonitrile solution. Cycloadduct **21′a** lies only 1.89 kcal/mol below the reactants, whereas the energy of reaction for compound **21′c** is −10.27 kcal/mol in acetonitrile solution, a value ca. 20 kcal/mol more exothermic than for the formation of its analogue **21c**.

With respect to the activation energies, our calculations predict that formation of cycloadducts **21′** is always favored in the gas phase. However, the activation barriers computed in solution give different results depending upon the nature of the R group. If R is aromatic, virtually exclusive formation of cycloadducts **21** is predicted under kinetic control. However, if R is an amino group only formation of cycloadduct **21′** should be expected under the same conditions. These results agree very well with our experimental findings. However, it is noteworthy that this agreement is obtained only if solvent effects are taken into account. The explanation for this behavior can be found by examination of Fig. 3. In this figure we have included the frontier molecular orbitals (FMOs) of reactants **12** and **20a**,**c**, as well as the electrostatic potentials mapped on the electron density surfaces. From the shape of the FMOs it is clear that in both cases the formation of cycloadducts **21a**,**c** can be expected if only orbital control is considered, and this is in good agreement with our activation barriers computed in vacuo. In contrast, the electrostatic interactions between the reactants favor the formation of regioisomers **21a** and **21′c**, respectively. Therefore, if the electrostatic contribution of the solution energy is considered, the regiocontrol of the reaction is determined by Coulombic interaction rather than by FMO overlap.

Conclusions

Cycloaddition of pyrazolyl imines with electron-poor dienophiles under microwave irradiation provides a general procedure to synthesize substituted pyrazolo[3,4-*b*]pyridines. The procedure has been extended to aromatic and aliphatic nitroalkenes, cyclic electrondeficient dienophiles and reagents with a high tendency to polymerize, such as acrylonitrile. Some of these cycloadditions do not occur under classical heating.

Experimental

Computational methods

All calculations reported in this study were performed using the Gaussian 94[23] program suite, with either the 3-21G[24] or 6-31G*[25] basis sets. Electron correlation was partially taken into account by using the B3LYP[26–29] method. All stationary points were fully optimized with no symmetry constraints using analytical gradient techniques. Transition structures and local minima were conveniently characterized by harmonic analysis.[30] Zero-point vibrational energies (ZPVEs) computed at the HF/3-21G level were scaled by 0.92 as recommended.[31] Solvent effects were estimated by means of the Onsager model.[20,21] Only the electrostatic contribution was computed, since the cavitation and dispersion contributions are similar for stereoisomeric structures.[32] Electrostatic potentials were calculated by means of the SPARTAN package.[33]

General

Mp were determined on a Gallenkamp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 299.94 and 75.429 MHz, respectively, on a Varian Unity 300 spectrometer. Chemical shifts are reported in ppm (δ) using Me_4Si as the standard, and coupling constants J are given in Hz. Percentage NOE enhancements were obtained by integrating the affected resonance relative to the irradiated resonance in the difference spectrum in each case. Column chromatography was carried out with SiO_2 (silica gel, Merck type 60 230–400 mesh). Microwave irradiations

were conducted in a focused microwave reactor (Prolabo MX350) with measurement and control of power and temperature by infrared detection. Elemental analyses were determined on a Perkin–Elmer PE2400 CHN apparatus. Mass spectra were obtained on a VG Autospec instrument (70 eV).

General procedure

A mixture of the 2-azadiene and the corresponding dienophile (1:2 mole ratio) was irradiated at atmospheric pressure in a focused microwave reactor (Prolabo MX350) for the time and at the power indicated in Table 2. The crude product was purified by flash chromatography on silica gel (Merck type 60, 230–400 mesh).

1-Ethyl-6-(4-methoxyphenyl)-4-phenylpyrazolo[3,4-*b*]pyridine (4a). From azadiene **1** (200 mg, 0.87 mmol) and β-nitrostyrene (**3a**) (259 mg, 1.74 mmol) with irradiation at 285 W for 7 min (final temperature 140°C). Flash chromatography (hexane/ethyl acetate, 10:1) afforded the pyrazolopyridine **4a** (151 mg, 53%), mp 98–99°C (from methanol); ^{1}H NMR ($CDCl_3$) δ 1.61 (t, J=7.3 Hz, 3H, CH_3), 3.88 (s, 1H, OCH_3), 4.67 (q, J=7.3 Hz, 2H, CH_2), 7.03 (d, J=8.8 Hz, 2H, *m*-H *p*-$CH_3OC_6H_4$), 7.46–7.60 (m, 3H, *p*,*m*-H Ph), 7.63 (s, 1H, H-5), 7.79–7.82 (m, 2H, *o*-H Ph), 8.13 (s, 1H, H-3), 8.15 (d, J=8.8 Hz, 2H, *o*-H *p*-$CH_3OC_6H_4$); ^{13}C NMR ($CDCl_3$) δ 15.0 (CH_3), 42.0 (CH_2), 55.4 (OCH_3), 112.5 (C-5), 114.1 (*m*-C *p*-$CH_3OC_6H_4$), 128.3 (*o*-C Ph), 128.8 (*o*-C *p*-$CH_3OC_6H_4$), 129.0 (*m*-C Ph), 129.1 (*p*-C Ph), 131.2 (C-3), 160.7 (*C*-OCH_3), 112.4, 132.1, 137.9, 144.1, 150.9, 156.3 (other carbons). MS (EI) *m*/*z* 329 (M^+). Anal. calcd for $C_{21}H_{19}N_3O$: C, 76.55; H, 5.8; N, 12.75. Found: C, 76.4; H, 5.9; N, 12.8%.

1-Ethyl-6-(4-methoxyphenyl)-4-(1-phenylindol-3-yl)pyrazolo[3,4-*b*]pyridine (4b). From azadiene **1** (200 mg, 0.87 mmol) and 3-(2-nitrovinyl)-1-phenylindole (**3b**) (460 mg, 1.74 mmol) with irradiation at 285 W for 10 min (final temperature 140°C). Flash chromatography (hexane/ethyl acetate, 4:1) gave pyrazolopyridine **4b** (120 mg, 32%), mp 204–205°C (from methanol); ^{1}H NMR ($CDCl_3$) δ 1.63 (t, J=7.3 Hz, 3H, CH_3), 3.90 (s, 3H, OCH_3), 4.71 (q, J=7.3 Hz, 2H, CH_2), 7.07 (d, J=8.8 Hz, 2H, *m*-H *p*-$CH_3OC_6H_4$), 7.30–7.38 (m, 2H, H-5′ and -6′ indole), 7.59–7.61 (m, 5H, *N*–Ph), 7.63–7.67 (m, 1H, H-7′ indole) 7.86 (s, 1H, H-2′ indole), 7.89 (s, 1H, H-5), 8.06–8.09 (m, 1H, H-4′ indole), 8.17 (s, 1H, H-3), 8.18 (d, J=8.8 Hz, 2H, *o*-H *p*-$CH_3OC_6H_4$); ^{13}C NMR ($CDCl_3$) δ 15.1 (CH_3), 42.1 (CH_2), 55.4 (OCH_3), 111.2 (C-7′ indole), 112.2 (C-5), 114.1 (*m*-C *p*-$CH_3OC_6H_4$), 120.4 (C-4′ indole), 121.6 (C-5′ *indole*), 123.5 (C-6′ indole), 124.7 (*o*-C *N*–Ph), 128.1 (C-2′ indole), 128.9 (*o*-C *p*-$CH_3OC_6H_4$), 129.8 (*m*- and *p*-C *N*–Ph), 131.8 (C-3), 112.7, 115.4, 126.8, 136.9, 138.9, 156.4, 160.7 (other carbons). MS (EI) *m*/*z* 444 (M^+). Anal. calcd for $C_{29}H_{24}N_4O$: C, 78.35; H, 5.45; N, 12.6. Found: C, 78.45; H, 5.45; N, 12.6%.

1-Ethyl-6-(4-methoxyphenyl)-4-(2-thienyl)pyrazolo[3,4-*b*]pyridine (4c). From azadiene **1** (160 mg, 0.7 mmol) and 2-(2-nitrovinyl)thiophene (**3c**) (218 mg, 1.4 mmol) with irradiation at 285 W for 8 min (final temperature 140°C). Flash chromatography (hexane/ethyl acetate, 4:1) afforded the pyrazolopyridine **4c** (112 mg, 48%); ^{1}H NMR ($CDCl_3$) δ 1.60 (t, J=7.3 Hz, 3H, CH_3), 4.27 (q, J=7.3 Hz, 2H, CH_2), 7.04 (d, J=8.8 Hz, 2H, *m*-H *p*- $CH_3OC_6H_4$), 7.23 (dd, J=3.7 and 5.1 Hz, 1H, H-4′ thiophene), 7.52 (dd, J=1.2 and 5.1 Hz, 1H, H-5′ thiophene), 7.70 (s, 1H, H-5), 7.73 (dd, J=3.7 and 1.2 Hz, 1H, H-3′ thiophene), 8.12 (d, J=8.8 Hz, 2H, *o*-H *p*-$CH_3OC_6H_4$), 8.29 (s, 1H, H-3); ^{13}C NMR ($CDCl_3$) δ 15.0 (CH_3), 42.0 (CH_2), 55.4 (OCH_3), 110.9 (C-5), 114.1 (*m*-C *p*-$CH_3OC_6H_4$), 127.1 (C-4′ thiophene), 127.6 (C-3′ thiophene), 128.3 (C-5′ thiophene), 128.8 (*o*-C *p*-$CH_3OC_6H_4$), 131.3 (C-3), 114.3, 131.9, 136.4, 140.4, 151.0, 156.4, 160.8 (other carbons). MS (EI) *m*/*z* 335 (M^+). Anal. calcd for $C_{19}H_{17}N_3OS$: C, 68.0; H, 5.1; N, 12.5. Found: C, 68.1; H, 5.05; N, 12.55%.

1-Ethyl-5-nitro-4-phenylpyrazolo[3,4-*b*]pyridine (5a) and 1-ethyl-4-phenylpyrazolo[3,4-*b*]pyridine (6a). From azadiene **2** (200 mg, 1.2 mmol) and β-nitrostyrene (**3a**) (358 mg, 2.4 mmol) with irradiation at 240 W for 5 min (final temperature 130°C). Flash chromatography (hexane/ethyl acetate, 5:1) gave pyrazolopyridines **5a** (205 mg, 64%) and **6a** (21 mg, 8%).

Data for 5a. Mp 103–104°C (from *tert*-butanol); ^{1}H NMR ($CDCl_3$) δ 1.57 (t, J=7.3 Hz, 3H, CH_3), 4.63 (q, J=7.3 Hz, 2H, CH_2), 7.43–7.46 (m, 2H, *o*-H Ph), 7.51–7.55 (m, 3H, *m*- and *p*-H Ph), 7.96 (s, 1H, H-3), 9.12 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 14.7 (CH_3), 42.6 (CH_2), 127.9 (*o*-C Ph), 128.8 (*m*-C Ph), 129.6 (*p*-C Ph), 134.1 (C-3), 145.3 (C-6), 115.2, 132.6, 138.9, 140.4, 149.5 (other carbons). MS (EI) *m*/*z* 268 (M^+). Anal. calcd for $C_{14}H_{12}N_4O_2$: C, 62.65; H, 4.5; N, 20.9. Found: C, 62.7; H, 4.5; N, 20.95%.

Data for 6a. Yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.57 (t, J=7.3 Hz, 3H, CH_3), 4.64 (q, J=7.3 Hz, 2H, CH_2), 7.22 (d, J=4.9 Hz, 1H, H-5), 7.50–7.59 (m, 3H, *m*- and *p*-H Ph), 7.75–7.78 (m, 2H, *o*-H Ph), 8.18 (s, 1H, H-3), 8.58 (d, J=4.9 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 15.0 (CH_3), 42.3 (CH_2), 115.2 (C-5), 128.4 (*o*-C Ph), 129.1 (*m*-C Ph), 129.3 (*p*-C Ph), 131.4 (C-3), 148.7 (C-6), 112.4, 137.4, 144.1, 150.3 (other carbons). Anal. calcd for $C_{14}H_{13}N_3$: C, 75.3; H, 5.85; N, 18.8. Found: C, 75.4; H, 5.9; N, 18.8%.

1-Ethyl-5-nitro-4-(1-phenylindol-3-yl)pyrazolo[3,4-*b*]pyridine (5b) and 1-ethyl-4-(1-phenylindol-3-yl)pyrazolo[3,4-*b*]pyridine (6b). From azadiene **2** (200 mg, 1.2 mmol) and 3-(2-nitrovinyl)-1-phenylindole (**3b**) (634 mg, 2.4 mmol) with irradiation at 240 W for 6 min (final temperature 130°C). Flash chromatography (hexane/ethyl acetate, 4:1) afforded the pyrazolopyridines **5b** (275 mg, 60%) and **6b** (24 mg, 9%).

Data for 5b. Mp 138–139°C (from *tert*-butanol); ^{1}H NMR ($CDCl_3$) δ 1.57 (t, J=7.3 Hz, 3H, CH_3), 4.60 (q, J=7.3 Hz, 2H, CH_2), 7.21–7.26 (m, 1H, H-5′ indole), 7.30–7.36 (m, 1H, H-6′ indole), 7.43–7.48 (m, 2H, H-4′ indole and *p*-H *N–Ph*), 7.58–7.64 (m, 5H, *o*- and *m*-H *N*–Ph and H-7′ indole), 7.80 (s, 1H, H-2′ indole), 8.13 (s, 1H, H-3), 9.13 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 14.9 (CH_3), 42.7 (CH_2), 111.4 (C-7′ indole), 119.7 (C-4′ indole), 121.9 (C-5′ *indole*), 123.7 (C-6′ indole), 124.7 (*o*-C *N–Ph*), 127.6

(*p*-C *N*–Ph), 129.5 (C-2′ indole), 129.9 (*m*-C *N*–Ph), 134.9 (C-3), 145.8 (C-6), 109.3, 115.1, 126.7, 133.7, 136.5, 138.5, 136.7, 149.7 (other carbons). MS (EI) *m*/*z* 383 (M^+). Anal. calcd for $C_{22}H_{17}N_5O_2$: C, 68.9; H, 4.45; N, 18.25. Found: C, 68.8; H, 4.4; N, 18.25%.

Data for 6b. Mp 134–135°C (from methanol); ^{1}H NMR ($CDCl_3$) δ 1.59 (t, J=7.3 Hz, 3H, CH_3), 4.65 (q, J=7.3 Hz, 2H, CH_2), 7.28–7.37 (m, 2H, H-5′ and -6′ *indole*), 7.41–7.48 (m, 1H, *p*-H *N*–Ph), 7.46 (d, J=4.8 Hz, 1H, H-5), 7.57–7.64 (m, 5H, *m*- and *o*-H *N*–Ph and H-7′ indole), 7.82 (s, 1H, H-2′ indole), 8.02–8.05 (m, 1H, H-4′ indole), 8.21 (s, 1H, H-3), 8.59 (d, J=4.8 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 15.0 (CH_3), 42.2 (CH_2), 111.2 (C-7′ *indole*), 114.8 (C-5), 120.3 (C-4′ indole), 121.6 (C-5′ *indole*), 123.5 (C-6′ indole), 124.7 (*o*-C *N*–*Ph*), 127.4 (*p*-C *N*–Ph), 128.2 (C-2′ indole), 129.8 (*m*-C *N*–Ph), 131.8 (C-3), 148.8 (C-6), 114.0, 114.9, 126.7, 136.9, 137.8, 138.9, 150.4 (other carbons). Anal. calcd for $C_{22}H_{18}N_4$: C, 78.1; H, 5.35; N, 16.55. Found: C, 78.2; H, 5.3; N, 16.6%.

1-Ethyl-5-nitro-4-(2-thienyl)pyrazolo[3,4-*b*]pyridine (5c). From azadiene **2** (200 mg, 1.2 mmol) and 2-(2-nitrovinyl)thiophene (**3c**) (374 mg, 2.4 mmol) with irradiation at 240 W for 5 min (final temperature 110°C). Flash chromatography (hexane/ethyl acetate, 4:1) gave the pyrazolopyridine (278 mg, 84%), mp 79–80°C (from methanol); ^{1}H NMR ($CDCl_3$) δ 1.57 (t, J=7.3 Hz, 3H, CH_3), 4.66 (q, J=7.3 Hz, 2H, CH_2), 7.24 (dd, J=5.1 and 3.7 Hz, 1H, H-4′ thiophene), 7.41 (dd, J=3.7 and 1.2 Hz, 1H, H-3′ thiophene), 7.67 (dd, J=5.1 and 1.2 Hz, 1H, H-5′ thiophene), 8.22 (s, 1H, H-3), 9.00 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 14.8 (CH_3), 42.7 (CH_2), 128.1 (C-4′ thiophene), 129.8 (C-5′ thiophene), 130.1 (C-3′ thiophene), 134.3 (C-3), 145.0 (C-6), 114.7, 131.9, 132.4, 139.4, 149.5 (other carbons). MS (EI) *m*/*z* 274 (M^+). Anal. calcd for $C_{12}H_{10}N_4O_2S$: C, 52.55; H, 3.65; N, 20.4. Found: C, 52.5; H, 3.6; N, 20.5%.

1-Ethyl-4,5,6,7-tetrahydropyrazolo[3,4-*b*]isoquinoline (13). From azadiene **2** (200 mg, 1.2 mmol) and 1-nitrocyclohexene (**7**) (305 mg, 2.4 mmol) with irradiation at 180 W for 10 min (final temperature 100°C). Flash chromatography (hexane/ethyl acetate, 4:1) afforded the tricyclic heterocycle **13** (97 mg, 41%), yellow oil; ^{1}H NMR ($CDCl_3$), δ 1.51 (t, J=7.2 Hz, 3H, CH_3), 1.88–1.92 (m, 4H, H-5 and -6), 2.84–2.87 (m, 2H, H-7), 2.99–3.04 (m, 2H, H-4), 4.55 (q, J=7.2 Hz, 2H, CH_2–CH_3), 7.94 (s, 1H, H-3), 8.28 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ 15.0 (CH_3), 21.9, 22.8 (C-5 and -6), 26.0, 26.1 (C-4 and -7), 42.1 (*C*H_2–CH_3), 129.7 (C-3), 150.2 (C-8), 116.0, 125.1, 140.5 (other carbons). Anal. calcd for $C_{12}H_{15}N_3$: C, 71.6; H, 7.5; N, 20.85. Found: C, 71.55; H, 7.55; N, 20.9%.

4-Cyclohexyl-1-ethyl-5-nitropyrazolo[3,4-*b*]pyridine (14). From azadiene **2** (200 mg, 1.2 mmol) and 1-nitro-2-cyclohexylethylene [34] (**8**) (372 mg, 2.4 mmol) with irradiation at 90 W for 10 min (final temperature 130°C). Flash chromatography (hexane/ethyl acetate, 9:1) gave pyrazolopyridine **14** to be isolated (105 mg, 33%), mp 88–89°C (from methanol); ^{1}H NMR ($CDCl_3$), δ 1.25–1.51 (m, 3H, H *cyclohexyl*), 1.55 (t, J=7.1 Hz, 3H, CH_3), 1.88–2.04 (m, 7H, H *cyclohexyl*), 3.35–3.45 (m, 1H, H-1′ *cyclohexyl*), 4.59 (q, J=7.1 Hz, 2H, *C*$H_2$$CH_3$), 8.36 (s, 1H, H-3), 8.87 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 14.7 (CH_3), 25.9, 26.4, 32.9 (CH_2 *cyclohexyl*), 40.2 (C-1′ *cyclohexyl*), 42.5 (CH_2), 134.1 (C-3), 144.9 (C-6), 113.4 (C-3*a*), 141.1, 147.2, 149.7 (C-4, -5 and -7*a*). Anal. calcd for $C_{14}H_{17}N_4O_2$: C, 61.5; H, 6.25; N, 20.5. Found: C, 61.6; H, 6.3; N, 20.5%.

1-Ethyl-4-isobutyl-5-nitropyrazolo[3,4-*b*]pyridine (15). From azadiene **2** (200 mg, 1.2 mmol) and 4-methyl-1-nitro-1-pentene (**9**) (310 mg, 2.4 mmol) with irradiation at 90 W for 10 min (final temperature 120°C). Flash chromatography (hexane/ethyl acetate, 9:1) afforded the pyrazolopyridine **15** (165 mg, 55%) as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.99 (d, J=7.1 Hz, 6H, 2×*C*H_3CH), 1.56 (t, J=7.1 Hz, 3H, C$H_3$$CH_2$), 2.12 (m, 1H, CH), 3.23 (d, J=7.1 Hz, 2H, CH_2CH), 4.59 (q, J=7.1 Hz, 2H, C$H_2$$CH_3$), 8.20 (s, 1H, H-3), 9.16 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 14.7 (*C*$H_3$$CH_2$), 22.8 (2×$CH_3$), 30.0 (CH), 38.8 (*C*$H_2$CH), 42.6 (*C*$H_2$$CH_3$), 133.8 (C-3), 146.3 (C-6), 116.6, 139.9 (C-3*a* and -7*a*), 143.5, 149.3 (C-4 and -5). Anal. calcd for $C_{12}H_{14}N_4O_2$: C, 58.55; H, 5.75; N, 22.75. Found: C, 58.6; H, 5.8; N, 22.7%.

Ethyl 1-ethyl-6-(4-methoxyphenyl)-4-phenylpyrazolo[3,4-*b*]pyridine-5-carboxylate (16). From azadiene **1** (200 mg, 0.87 mmol) and ethyl phenylpropiolate (**10**) (454 mg, 2.61 mmol) with irradiation at 285 W for 15 min (final temperature 140°C). Flash chromatography (hexane/ethyl acetate, 15:1) gave pyrazolopyridine **16** as a yellow oil (87 mg, 25%); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J=7.1 Hz, 3H, C$H_3$$CH_2$), 1.56 (t, J=7.2 Hz, 3H, C$H_3$$CH_2$O), 3.86 (s, 3H, OCH_3), 3.96 (q, J=7.1 Hz, 2H, CH_2N), 4.64 (q, J=7.2 Hz, 2H, CH_2O), 6.99 (d, J=8.5 Hz, 2H, *m*-H *p*-$CH_3OC_6H_4$), 7.48–7.53 (m, 5H, Ph), 7.67 (d, J=8.5 Hz, 2H, *o*-H *p*-$CH_3OC_6H_4$), 7.90 (s, 1H, H-3); ^{13}C NMR ($CDCl_3$) δ 13.5 (*C*$H_3$$CH_2$N), 15.0 ($CH_2$O), 42.1 ($CH_3$O), 55.3 ($CH_2$N), 61.3 ($CH_2$O), 113.3 (C-3a), 113.7 (*m*-C *p*-$CH_3OC_6H_4$), 128.4, 128.6, 128.9 (*o*-, *m*- and *p*-C Ph), 130.0 (*o*-C *p*-$CH_3OC_6H_4$), 132.3 (C-3), 169.1 (COO), 122.3, 132.6, 135.9, 143.4, 149.2, 156.3, 160.2 (other carbons). Anal. calcd for $C_{24}H_{23}N_3O_3$: C, 71.8; H, 5.8; N, 10.45. Found: C, 71.8; H, 5.8; N, 10.5%.

1-Ethyl-5-methyl-1,2,5,8-tetraaza-1,4,5,6-tetrahydro-s-indacene-4,6-dione (17). From azadiene **2** (120 mg, 0.74 mmol) and *N*-methylmaleimide (**11**) (165 mg, 1.48 mmol) with irradiation at 210 W for 15 min (final temperature 170°C). Flash chromatography (hexane/ethyl acetate, 4:1) afforded the tricyclic heterocycle **17** (143 mg, 50%), mp 143–135°C (from methanol); ^{1}H NMR ($CDCl_3$) δ 1.58 (t, J=7.3 Hz, 3H, CH_3), 3.24 (s, 3H, *N*CH_3), 4.67 (q, J=7.3 Hz, 2H, CH_2), 8.43 (s, 1H, H-3), 8.99 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 14.7 (CH_3), 24.1 (*N*CH_3), 42.9 (CH_2), 108.2 (C-3*a*), 120.0 (C-5), 131.3 (C-3), 134.3 (C-4), 142.6 (C-6), 152.6 (C-7*a*), 166.6, 167.8 (2×CO). MS (EI) *m*/*z* 230 (M^+). Anal. calcd for $C_{11}H_{10}N_4O_2$: C, 57.4; H, 4.4; N, 24.35. Found: C, 57.4; H, 4.4; N, 24.4.

4-Cyano-1-ethyl-6-(4-methoxyphenyl)pyrazolo[3,4-*b*]pyridine (18). From azadiene **1** (200 mg, 0.87 mmol) and 2-chloroacrylonitrile (**12**) (609 mg, 6.96 mmol) with irradiation at 150 W for 20 min (final temperature 85°C).

Flash chromatography (hexane/ethyl acetate, 9:1) gave pyrazolopyridine **18** (44 mg, 20%), mp 93–94°C (from methanol); ^{1}H NMR ($CDCl_3$) δ 1.57 (t, J=7.3 Hz, 3H, CH_3), 3.92 (s, 3H, OCH_3), 4.62 (q, J=7.3 Hz, 2H, CH_2), 7.13 (d, J=6.8 Hz, 2H, *m*-H *p*-$CH_3OC_6H_4$), 7.74 (d, J=6.8 Hz, 2H, *o*-H *p*-$CH_3OC_6H_4$), 8.11 (s, 1H, H-5), 8.77 (s, 1H, H-3); ^{13}C NMR ($CDCl_3$) δ 14.9 (CH_3), 42.6 (CH_2), 55.5 (OCH_3), 100.1 (C-3*a*), 114.2 (C-4), 114.7 (*o*-C *p*-$CH_3OC_6H_4$), 118.2 (CN), 125.8 (*ipso*-C), 130.7 (*m*-C *p*-$CH_3OC_6H_4$), 133.2 (C-5), 148.9 (C-7*a*), 149.9 (C-6), 151.9 (C-3), 161.5 (*p*-C *p*-$CH_3OC_6H_4$). Anal. calcd for $C_{14}H_{14}ON_4$: C, 66.1; H, 5.55; N, 22.05. Found: C, 65.95; H, 5.5; N, 22.05%.

5-Cyano-1-ethylpyrazolo[3,4-*b*]pyridine (19). From azadiene **2** (200 mg, 1.2 mmol) and 2-chloroacrylonitrile (840 mg, 9.6 mmol) with irradiation at 150 W for 20 min (final temperature 85°C). Flash chromatography (hexane/ethyl acetate, 2:1) afforded the pyrazolopyridine **19** (79 mg, 39%), mp 93–94°C (from methanol); ^{1}H NMR ($CDCl_3$) δ 1.56 (t, J=7.4 Hz, 3H, CH_3), 4.62 (q, J=7.4 Hz, 2H, CH_2), 8.15 (s, 1H, H-3), 8.41 (d, J=1.9 Hz, 1H, H-4), 8.74 (d, J=1.9 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 14.8 (CH_3), 42.6 (CH_2), 132.9 (C-4), 135.0 (C-3), 150.2 (C-6), 102.1, 114.6, 117.7 (C-3*a*, -5 and CN), 136.1 (C-7*a*). Anal. calcd for $C_9H_8N_4$: C, 62.75; H, 4.70; N, 32.55. Found: C, 62.65; H, 4.7; N, 32.5%.

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