exo-Selective Peripheral Cycloaddition Reactions of Pyrido[2,1-*a*]isoindole

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Pyrido[2,1-*a*]isoindole cycloadds to olefinic dipolarophiles in a highly *exo*-selective fashion giving the kinetically controlled cycloadducts which gradually isomerize into the Michael adducts. With acetylenic dipolarophiles, the hydrogen-migrated cycloadducts are the only products. The mechanism of cycloadditions is discussed.

Some time ago the first example of stereochemical study on the peripheral cycloaddition reactions of indolizines to olefins was reported.[1] These cycloadditions are stereospecific and highly *exo*-selective. Nevertheless the stepwise mechanism through zwitterionic intermediates was proposed since Michael type adducts were formed in some cases.

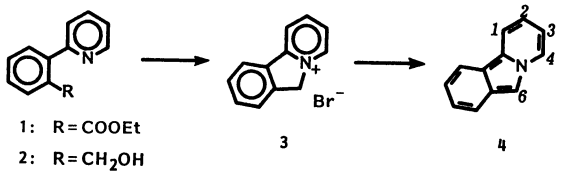
Thereafter a great number of cycloadditions of a variety of heteroaromatic *N*-ylides[2] and peripheral azomethine ylides[3-5] have been investigated, and these ylides were found to react with olefinic dipolarophiles in an exclusively *endo*-selective fashion. The high selectivity might be due to the positive interaction between the heteroaromatic plane and the unsaturated substituents of dipolarophiles.

We came to wonder why the indolizine cycloaddition showed such an exceptional *exo*-selectivety. Is it due to the stepwise reaction pathway?. If so, how? More informations on the stereoselectivity of the analogous cycloadditions are needed.

In the present paper, the cycloadditions of pyrido[2,1-*a*]isoindole with olefinic dipolarophiles were investigated and it was found that these reactions proceeded not *via* the zwitterionic intermediates but through synchronous cyclization pathway. The *exo*-selection might be a result from the $8\pi+2\pi$ concerted cycloaddition.

Results and Discussion

Pyrido[2,1-*a*]isoindole **4** is a known compound which was synthesized by the photoreaction between 2-bromopyridine and benzyl bromide.[6] Our approach to **4** starts with the reduction of ethyl 2-(2-pyridyl) benzoate **1** into 2-(2-pyridyl)benzyl alcohol **2** with lithium aluminum hydride, bromination of **2** into 6*H*-pyrido[2,1-*a*]isoindolium bromide **3** with hydrobromic acid, and the final step of dehydrobromination of **3** with aqueous sodium carbonate (Scheme 1).

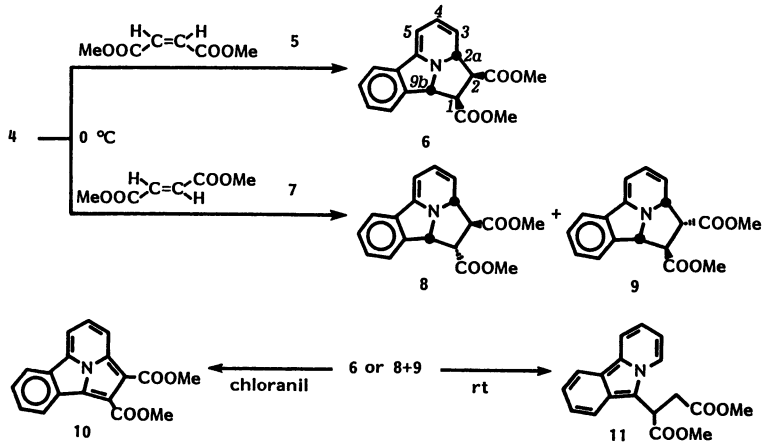


Scheme 1.

An advantage of this preparation is that the starting ester **1** is readily available in large quantities through the reaction of pyridine with 2-lithiotoluene and the subsequent several steps can be all performed in large scales. Furthermore, the salt **3** as the precursor of air-sensitive **4** can be safely stored without any serious decomposition.

Rapid cycloadditions were found to occur when **4** was allowed to react with electron-deficient olefins at 0 °C, but the cycloadducts formed were too labile to be isolated. They gradually changed into the corresponding Michael adducts. Accordingly, the structural analyses of the cycloadducts were based only on the ^{1}H-NMR spectra.

Equivalent amounts of **4** and dimethyl maleate **5**

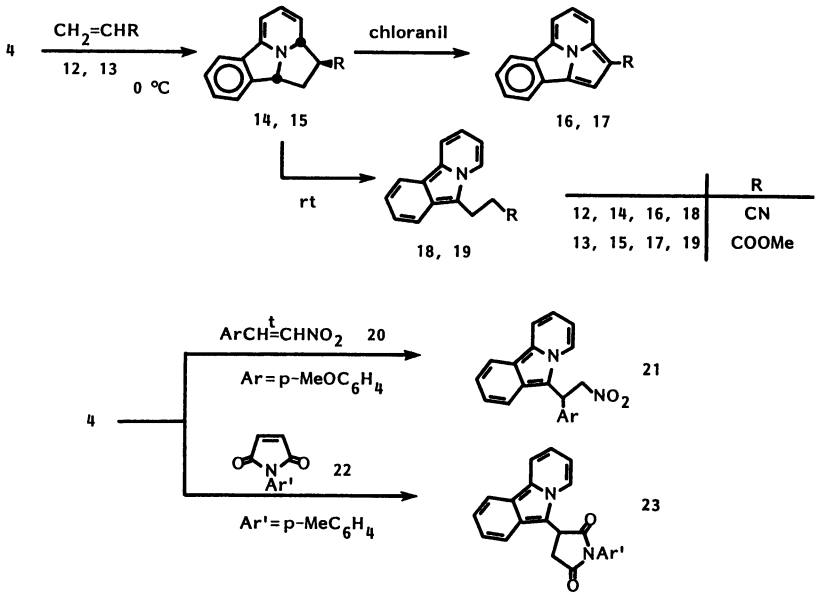


Scheme 2.

TABLE 1. ^{1}H-NMR SPECTRA OF THE OLEFIN CYCLOADDUCTS **6**, **8**, **9**, **14**, **15**

	Chemical shifts in δ and coupling constants in Hz																			
	9b-H		1-H		2-H		2a-H		3-H		4-H		5-H							
6	5.06[d]		2.57[dd]		3.12[dd]		4.57[dd]		5.85[dd]		6.25[dd]		5.58[d]		3.70[s] (2-COOMe),					
		5.3		10.5		10.0		5.5		9.6		5.8			3.80[s] (1-COOMe)					
8	5.23[d]		b)		b)		4.20[dd]		5.85[dd]		6.36[dd]		5.70[d]		3.35[s] (1-COOMe),					
		10.0		c)		9.8		5.6		9.6		6.0			3.72[s] (2-COOMe)					
9	4.92[d]		2.90[dd]		b)		4.89[dd]		5.65[dd]		6.34[dd]		5.49[d]		3.57[s] (2-COOMe),					
		7.0		5.6		9.0		5.5		10.0		6.0			3.79[s] (1-COOMe)					
14	4.79[dd]		1.52[ddd]		2.63[q]		4.14[dd]		5.66[dd]		6.16[dd]		5.45[d]							
		5.0		10.0		10.0		5.2		9.2		6.0								
			2.10[dt]																	
		10.0		10.0																
			13.5 (gem)																	
15	4.86[dd]		1.44[ddd]		2.86[ddd]		4.14[dd]		5.63[dd]		6.16[dd]		5.48[d]		3.66[s] (2-COOMe)					
		4.8		10.2		9.2		5.2		9.4		5.8								
			2.49[dt]																	
		9.5		9.5																
			13.5 (gem)																	

a) All the spectra were taken in $CDCl_3$ at 0°C. b) Overlapping with other signals. c) No clear coupling was given.



Scheme 3.

were dissolved in $CDCl_3$ at 0°C in an NMR sample tube and immediately subjected to the ^{1}H-NMR measurement. Only observed were the signals for the *exo*-selective and *cis*-specific cycloadduct **6**, indicating the quantitative formation of **6** (Scheme 2). On the other hand, the reaction of **4** with dimethyl fumarate **7** at 0°C formed the 7:3 mixture of two isomeric cycloadducts **8** and **9**. On standing at room temperature, these cycloadducts **6**, **8**, and **9** gradually isomerized into the same compound **11** which was isolated by the evaporation of the solvent and identified as the Michael adduct shown in Scheme 2.

The structural assignment of **6**, **8**, and **9** was based on the coupling constants among the methine hydrogens on the newly formed five-membered rings and the chemical shifts of ester methyls (Table 1). The stereochemistry of the starting olefins **5** and **7** must be retained in the cycloadducts and a molecular model inspection indicates that the only configuration for the points of fusion is cis (the methine hydrogens at the 2a- and 9b-positions are cis to each other). The 1—9b couplings of **6** and **9** are small to medium and the ester methyls at the 1-position of **8** and the 2-position of **9** are shielded. These informations are enough to determine the stereostructures of cycloadducts: **6**: 1-*exo*-2-*exo*-; **8**: 1-*endo*-2-*exo*-; **9**: 1-*exo*-2-*endo*-cycloadducts.

The cyclic structures of **6**, **8**, and **9** were confirmed by their dehydrogenation with chloranil at 0°C into dimethyl indolizino[3,4,5-*ab*]isoindole-1,2-dicarboxylate **10** which was no longer labile.

The regioselective and stereoselective cycloadducts **14** and **15** were formed also as unstable products in similar reactions of **4** with acrylonitrile **12** and methyl acrylate **13** (Scheme 3). They again isomerized into the

Table 2. Michael adducts **11**, **18**, **19**, **21**, **23** and indolizino[3,4,5-*ab*]isoindoles **10**, **16**, **17**

	Yield/%[a]	Mp(θ_m/°C)	IR/cm^{-1}	^{1}H-NMR in $CDCl_3$ (δ, ppm)	M$^+$(m/z)[b]
11	96[c] 93[d]	108—109	1730 (CO)	2.80 (1H, dd, J=17.5 and 6.0 Hz, one of CH_2), 3.60 (1H, dd, J=17.5 and 8.8 Hz, the other of CH_2), 3.58, 3.60 (each 3H, s, COOMe), 5.00 (1H, dd, J=6.0 and 8.8 Hz, CH)	311
18	82	136—137	2240 (CN)	2.61, 3.57 (each 2H, t, J=7.4 Hz, CH_2)	220
19	83	78—80	1735 (CO)	2.74, 3.62 (each 2H, t, J=7.6 Hz, CH_2), 3.66 (3H, s, COOMe)	253
21	83	140—143		3.58 (3H, s, *p*-OMe), 5.06 (1H, dd, J=16.0 and 8.0 Hz, one of CH_2), 5.18 (1H, dd, J=16.0 and 7.3 Hz, the other of CH_2), 5.50 (1H, dd, J=7.3 and 8.0 Hz, CH)	346
23	99	229—230	1770 (CO) 1710 (CO)	2.31 (3H, s, *p*-Me), 2.92 (1H, dd, J=19.0 and 5.4 Hz, one of CH_2), 3.24 1H, dd, J=19.0 and 9.5 Hz, the other of CH_2), 4.80 (1H, dd, J=5.4 and 9.5 Hz, CH)	
10	94[c] 92[d]	184—185	1730 (CO) 1700 (CO)	4.18, 4.30 (each 3H, s, COOMe)	307
16	74	162—163	2210 (CN)	7.60 (1H, s, 1-H)	216
17	60	119—120	1690 (CO)	4.12 (3H, s, COOMe), 8.20 (1H, s, 1-H)	249

a) Isolated yield. b) All as base peaks. c) From the maleate **5**. d) From the fumarate **7**.

Table 3. Hydrogen-migrated cycloadducts **27**—**29** to acetylenic dipolarophiles **24**—**26**

Acetylene	Conditions	Product Mp(θ_m/°C)	Yield %	Spectral data[a]
24	0.5 h at rt in C_6H_6	**27** (146—147)	71	IR (cm^{-1}): 1710 and 1700 (CO) ^{1}H-NMR: δ=2.31 (1H, dddd, J=16.5, 15.0, 3.0, and 2.0 Hz, one of 3-H), 2.88 (1H, dt, J=16.5, and 6.3 Hz, the other of 3-H), 3.84, 3.92 (each 3H, s, COOMe), 4.80 (1H, dd, J=15.0 and 6.3 Hz, 2a-H), 5.97 (1H, ddd, J=10.0, 6.3, and 2.0 Hz, 4-H), 6.88 (1H, dd, J=10.0 and 3.0 Hz, 5-H) MS (m/z): 309 (M$^+$)
25	3 h at 45°C in $CHCl_3$	**28** (129—130)	60	IR(cm^{-1}): 1690 (CO) ^{1}H-NMR: δ=2.25 (1H, ddt, J=16.5, 3.0, and 2.5 Hz, one of 3-H), 2.50 (3H, s, 1-Me), 2.75 (1H, dt, J=16.5 and 6.4 Hz the other of 3-H), 3.80 (3H, s, COOMe), 4.71 (1H, dd, J=16.5 and 6.4 Hz, 2a-H), 5.83 (1H, ddd, J=9.6, 6.4, and 2.5 Hz, 4-H), 6.97 (1H, dd, J=9.6 and 3.0 Hz, 5-H) MS (m/z): 265 (M$^+$)
26	1 h at rt in $CHCl_3$	**29** (83—85)	68	IR (cm^{-1}): 1700 (CO) ^{1}H-NMR: δ=2.30 (1H, dddd, J=17.2, 16.0, 3.2, and 2.5 Hz, one of 3-H), 2.80 (1H, dt, J=17.2 and 6.3 Hz, the other of 3-H), 3.84 (3H, s, COOMe), 4.79 (1H, dd, J=16.0 and 6.3 Hz, 2a-H), 5.90 (1H, ddd, J=9.8, 6.3, and 2.5 Hz, 4-H), 6.66 (1H, s, 1-H), 7.02 (1H, dd, J=9.8 and 3.2 Hz, 5-H) MS (m/z): 251 (M$^+$)

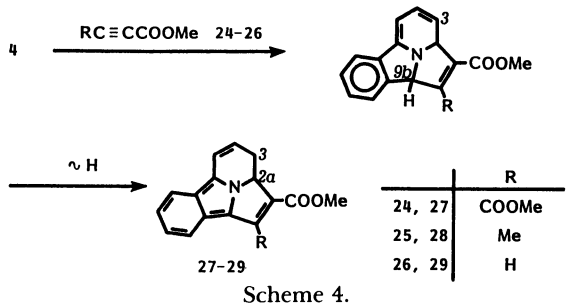
a) IR and ^{1}H-NMR spectra were measured as KBr disks and in $CDCl_3$, respectively.

Michael adducts **18** and **19** at room temperature and were dehydrogenated into the aromatized heterocycles **16** and **17** on treatment with chloranil at 0°C.

On the other hand, the reactions of **4** with (*E*)-1-(*p*-methoxyphenyl)-2-nitroethene **20** and *N*-(*p*-methylphenyl)maleimide **22** at 0°C provided no trace of the corresponding cycloadducts, only the Michael adducts **21** and **23** being observed in the reaction mixtures. By the evaporation of the reaction solvent, they were isolated as the sole products.

The spectral data of the Michael adducts **11**, **18**, **19**, **21**, and **23** as well as the indolizino[3,4,5-*ab*]isoindoles **10**, **16**, and **17** are summarized in Table 2. All the indolizino[3,4,5-*ab*]isoindoles show intense fluorescence in solution.

With acetylenic dipolarophiles such as dimethyl acetylenedicarboxylate **24**, methyl 2-butynoate **25**, and methyl propynoate **26** readily reacted **4** at room temperature giving the stable 1:1 adducts **27**—**29** all as yellow fluorescent materials (Scheme 4).



Scheme 4.

These regioselective products **27**—**29** were assigned as the hydrogen-migrated cycloadducts, from the 9b- to the 3-position, on the basis of the ^{1}H-NMR spectra shown in Table 3.

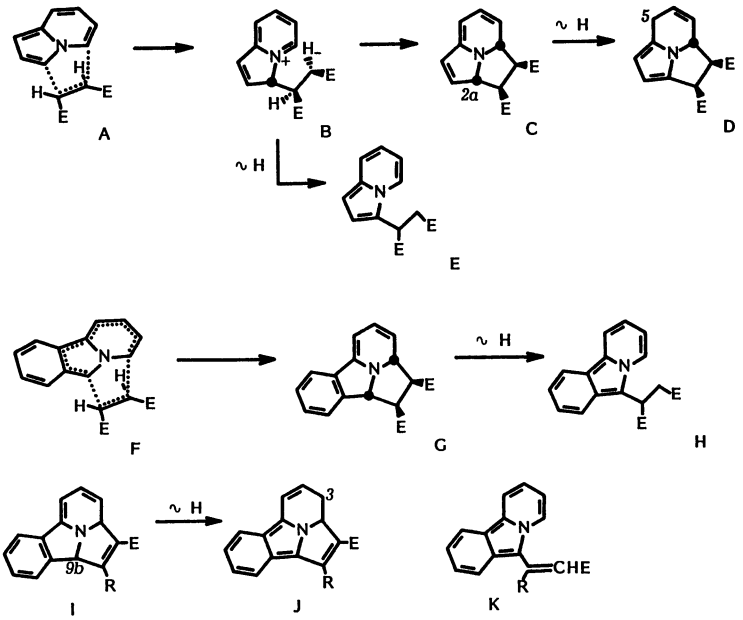
In the previous paper on the *exo*-selective cycloadditions of indolizines to olefinic dipolarophiles,[1] we proposed the stepwise mechanism *via* a zwitterionic intermediate **B**. This mechanism was based upon the formation of either the cycloadduct **D** or the Michael adduct **E** depending on the nature of dipolarophile and upon no interconversion between **D** and **E**. However, we would have to amend the reaction path because we now know that the Michael adduct **H** is the secondary product formed from the cycloadduct **G** (Scheme 5). The revised pathway is **A**→**C**→**D** or **A**→**C**→**E**.

In the cases of indolizines, two isomerization paths from **C**, the hydrogen migration from the 2a- to the 5-position leading to **D** and the bond cleavage into **B** (and hence **E**), presumably happened to compete. Once **D** and **E** are formed, there should be little chance of their interconversion. In the present cases, the similar hydrogen migration of **G** is suppressed by the influence of the additional fused benzo moiety, the cycloadduct **G** getting a chance of bond cleavage into **H**.

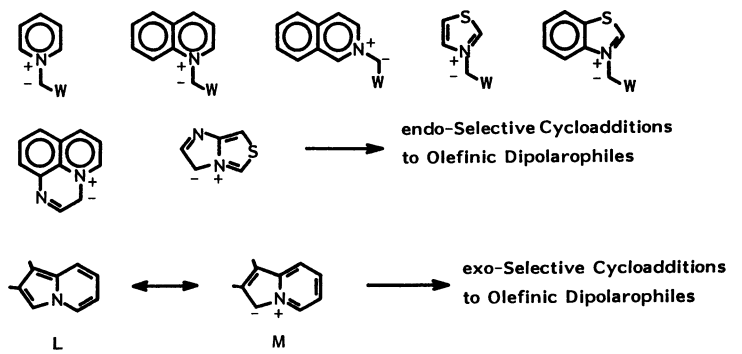
The acetylene cycloadduct **I** lies in a quite different situation. To accomplish the maximum extension of conjugation, the methine hydrogen at the 9b-position migrates long way to the 3-position giving **J** which was the isolated product. Since this migration may quickly occur, no Michael adduct **K** was obtained.

According to our study on the stereoselectivity of the cycloadditions of azomethine ylides involved as a part of heterocycles, all tested cases have shown the exclusive endo selectivity in the reactions with olefinic dipolarophiles[2-5] (Scheme 6); pyridinium, quinolinium, isoquinolinium, thiazolium, benzothiazolium methylides, anhydro-3*H*-pyrido[1,2,3-*de*]quinoxalinium hydroxide, thiazolo[4,3-*a*]isoindole, and imidazo[1,2-*c*]-thiazole.

Indolizine and pyrido[2,1-*a*]isoindole can be also regarded as the peripheral azomethine ylide 1,3-dipoles as illustrated with the charge-separated form **M** in Scheme 6. If the azomethine ylides participated in the $4\pi+2\pi$ cycloadditions, no satisfactory explanation for the high *exo*-selection would be available. We so far believe that the cycloadditions of indolizine and pyrido[2,1-*a*]isoindole to olefins belong to an $8\pi+2\pi$ synchronous cycloaddition.



Scheme 5.



Scheme 6.

Experimental

Melting and boiling points are all uncorrected. Spectral characterization was carried out with the following instruments: IR: JASCO IRA-1 spectrometer; ^{1}H-NMR: JEOL JNM-MH 100 spectrometer using tetramethylsilane as an internal standard; MS: JEOL JMS-100 mass spectrometer using a direct insertion probe at 70 eV of ionization energy. Elementary analyses were obtained on Shimadzu CHN-1A micro analyzer. Melting points were taken in capillaries on Mitamura Riken melting point measurement apparatus. Solvents were evaporated *in vacuo* using a rotary evaporator.

2-(2-Pyridyl)benzyl Alcohol **2**. To a suspension of lithium aluminum hydride (2.66 g, 0.07 mol) in dry ether (250 ml), was added slowly ethyl 2-(2-pyridyl)benzoate **1**[7] (10.59 g, 0.047 mol) in ether (200 ml) in 10 min. The mixture was stirred at room temperature for 1 h and poured into ice water. The ether separated was dried over $MgSO_4$, evaporated *in vacuo*, and the residual oil was distilled under vacuum to give **2** (8.13 g, 94%) as colorless liquid: Bp 159—164 °C/266 Pa; IR (Nujol) 3280 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$) δ= 4.46 (2H, s, CH_2), 6.10 (1H, br. s, OH), 7.14—7.86, and 8.52 (8H, m, ArH); MS *m/z* 185(M^+, base peak). Found: C, 77.7; H, 6.1; N, 7.4%. Calcd for $C_{12}H_{11}NO$: C, 77.8; H, 6.0; N, 7.6%.

6H-Pyrido[2,1-a]isoindolium Bromide **3**. A mixture of **2** (0.65 g, 3.5 mmol) and concd hydrobromic acid (48% content, d=1.48, 0.4 ml, 3.5 mmol) was warmed at 90 °C for 1.5 h. All the voratile materials were removed by evaporation *in vacuo* and the residue was treated with methanol to give **3** (0.77 g, 89%) which was purified by crystallization from ethanol: Colorless plates; mp 203—205 °C (lit,[6] mp 207.5—209.5 °C); ^{1}H-NMR (CF_3COOH) δ=5.53 (2H, s, CH_2), 7.30—8.32, and 8.70 (8H, m, ArH).

Pyrido[2,1-a]isoindole **4**. To a saturated aqueous solution of **3**, was added saturated aqueous solution of sodium carbonate at room temperature to give yellow precipitate of **4** in a quntitative yield: Yellow needles from ethanol; mp 221—223 °C (lit,[6] 225 °C).

General Procedure for the Cycloadditions of **4** *to Olefins.* Freshly prepared **4** (84 mg, 0.5 mmol) was added to a solution of olefins (0.5 mmol) in 1 ml of $CDCl_3$ at 0 °C. This mixture was transferred into an NMR sample tube and subjected to the ^{1}H-NMR measurement at 0 °C. In about 5 min, all the starting materials disappeared and instead very clean spectrum of the cycloadduct was observed. All the operations of integration, expansion, and decoupling were carried out at 0 °C. The ^{1}H-NMR spectra of **6**, **8**, **9**, **14**, and **15** are listed in Table 1.

General Procedure for the Michael Adduct Formation. The Michael adduct was obtained according to either of the following two procedures: 1) The solution of cycloadduct prepared above was allowed to stand at room temperature for 1 d and the solvent was evaporated *in vacuo* to give the Michael adduct. 2) An equivalent mixture of **3** (0.75 g, 3.0 mmol) and olefin in methanol (5 ml) was treated with triethylamine (5 mmol). The mixture was stirred at room temperature for 1 h and the solvent was evaporated *in vacuo*. The residue was triturated with cold 2-propanol or chromatographed over silica gel with chloroform to give the Michael adduct. The spectral data as well as melting points are summarized in Table 2. Other data are given below:

11: Yellow needles from methanol. Found: C, 69.6; H, 5.5; N, 4.3%. Calcd for $C_{18}H_{17}NO_4$: C, 69.4; H, 5.5; N, 4.5%.

18: Yellow needles from methanol. Found: C, 81.7; H, 5.6; N, 12.4%. Calcd for $C_{15}H_{12}N_2$: C, 81.8; H, 5.5; N, 12.7%.

21: Yellow prisms from methanol. Found: C, 72.7; H, 5.1; N, 8.2%. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.8; H, 5.2; N, 8.1%.

23: Pale yellow prisms from acetone–methanol. Found: C, 77.5; H, 5.1; N, 8.2%. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.9; H, 5.1; N, 7.9%.

General Procedure for the Indolizino[3,4,5-ab]isoindole Formation. A mixture of freshly prepared **4** (0.17 g, 1.0 mmol) and 1.2 equiv of olefin in dichloromethane (5 ml) was stirred at 0 °C for 15 min and chloranil (0.5 g, 2.0 mmol) was introduced. The resulting mixture was stirred at 0 °C for 1 h. The precipitate was removed by filteration and washed with boiling chloroform (15 ml×2). The combined filtrates were evaporated *in vacuo* and the residue was chromatographed over silica gel using chloroform as the eluent. The intensely fluorescent fraction gave the indolizino[3,4,5-*ab*]isoindoles, whose spectral data and melting points are given in Table 2. Other data are as follows:

10: Yellow plates from acetone. Found: C, 70.6; H, 4.3; N, 4.5%. Calcd for $C_{18}H_{13}NO_4$: C, 70.4; H, 4.3; N, 4.6%.

16: Yellow needles from methanol. Found: C, 83.3; H, 3.9; N; 13.0%. Calcd for $C_{15}H_8N_2$: C, 83.3; H, 3.7; N, 13.0%.

17: Yellow needles from petr. ether. Found: C, 77.0; H, 4.3; N, 5.8%. Calcd for $C_{16}H_{11}NO_2$: C, 77.1; H, 4.4; N, 5.6%.

General Procedure for the Cycloadditions of **4** *to Acetylenes.* An equimolar mixture of freshly prepared **4** and acetylene was allowed to react under the conditions shown in Table 3. After the solvent was evaporated *in vacuo*, the residue was chromatographed over silica gel with chloroform. The data of the product are listed in Table 3. Other data are as follows:

27: Yellow prisms from acetone. Found: C, 70.2; H, 4.8; N, 4.2%. Calcd for $C_{18}H_{15}NO_4$: C, 69.9; H, 4.9; N, 4.5%.

28: Yellow needles from petr. ether. Found: C, 77.1; H, 5.7; N, 5.5%. Calcd for $C_{17}H_{15}NO_2$: C, 77.0; H, 5.7; N, 5.3%.

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