Novel Syntheses of Indolizines and Pyrrolo[2,1-*a*]isoquinolines via Benzotriazole Methodology

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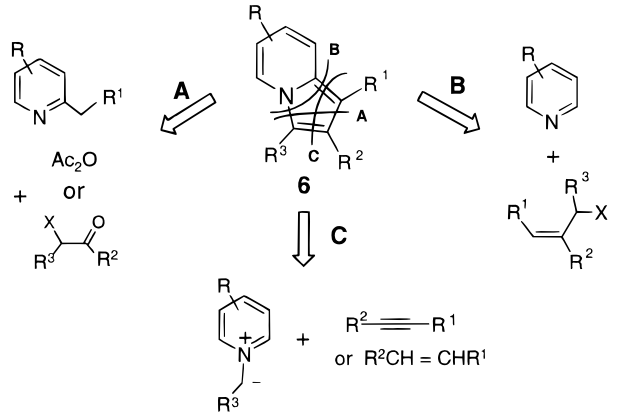
Indolizines and pyrrolo[2,1-*a*]isoquinolines are synthesized by 1,3-dipolar cycloadditions of pyridinium benzotriazolylmethylides or isoquinolinium benzotriazolylmethylides with ethylenes and acetylenes.

Introduction

Synthetic indolizines are important as potential central nervous system depressants,[1] calcium entry blockers,[2] cardiovascular agents,[3] spectral sensitizers,[4] and novel dyes.[5] They are also used for the treatment of angina pectoris[6] or as testosterone 5α-reductase inhibitors.[7] Furthermore, they are key intermediates for the syntheses of cycloazines.[8]

Typical molecular constructions of indolizines **6** (for a review, see ref 9) fall into three classes as shown in Scheme 1: (A) Condensation reactions of a 2-alkylpyridine with acid anhydrides (Scholtz reaction[10]) or α-halo ketones (Tschitschibabin reaction[11]); (B) reactions of an α-unsubstituted pyridine with a three carbon fragment such as an acyl- or aryl-substituted allyl halide or ester[12] and methyl propiolate;[13] (C) reactions of pyridinium *N*-methylides, generated from pyridinium salts under K_2CO_3,[14] pyridine and carbenes,[15] or *N*-(trimethylsilylmethyl)pyridinium triflates under fluoride ion,[16] with acetylenes; or reactions of pyridinium *N*-methylides with ethylenes in the presence of an oxidant.[17] While the third route has been widely utilized in the syntheses of indolizines,[9] there are some limitations. The reactions of pyridinium *N*-methylides with acetylenes require that the acetylenes bear two electron-withdrawing groups, e.g., ester groups, and thus limit the substituents (R^1, R^2) at the 1,2-positions of indolizines produced; furthermore, most of R^3 group are limited to acyl groups[14,15] or hydrogen.[16] When pyridinium ylides react with ethylenes, an oxidant is needed, otherwise di- and tetrahydroindolizines are obtained as byproducts, with correspondingly lower yields of the desired products.[17]

Scheme 1



We report here the direct formation of indolizines by 1,3-cycloadditions of pyridinium benzotriazolylmethylides with ethylenes or acetylenes. No oxidant is needed and substituents (R^2, R^3) at the 2,3-positions of the indolizine ring are not limited to electron-withdrawing groups.

Previous work showed *N*-bis(benzotriazol-1-ylmethyl)-hydroxylamine to be an effective 1,3-dipole synthon; subsequent reactions with dipolarphiles furnished substituted 2-(benzotriazol-1-ylmethyl)isoxazolidines.[18] α-(Benzotriazol-1-yl)arylmethylamines are also convenient sources of azomethine ylides which readily undergo 1,3-dipolar cycloaddition with dipolarophiles to produce 2,5-diarylpyrroles, 3,4-dihydro-2*H*-pyrroles and *c*-ring-fused 3,4-dihydro-2*H*-pyrroles.[19] Benzotriazolylmethylaminosilanes as azomethine ylide equivalents undergo stereospecific cycloadditions with dipolarophiles to produce sub-

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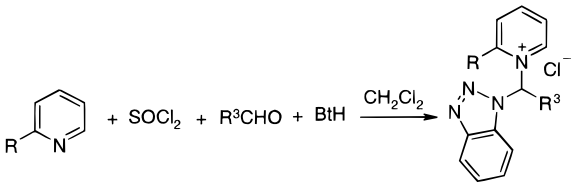
Scheme 2



	R	R^3	Yield (%)
1a	H	H	71
1b	H	C_2H_5	73
1c	H	*p*-tolyl	-
1d	C_2H_5	H	87

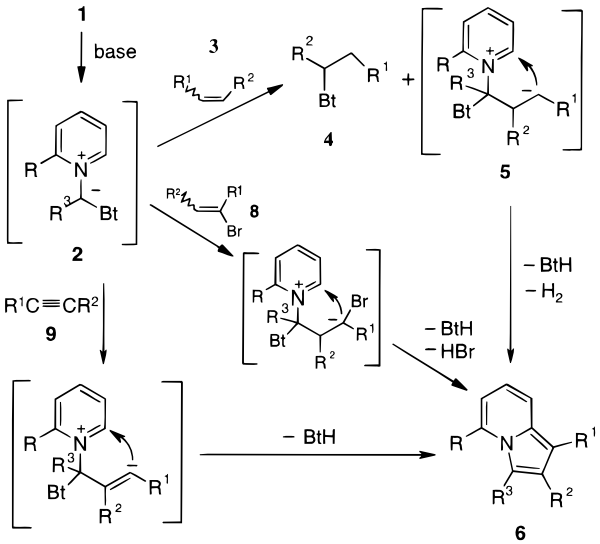
stituted pyrrolidines or 2,5-dihydropyrroles.[20] The formation of azomethine ylides in each of these systems relies on the ability of benzotriazole to stabilize negative charge at the α-position. In the present work, the benzotriazolyl group activates the methylene protons for easy deprotonation, stabilizes the resulting ylide by the delocalization of the negative charge, and serves as a good leaving group in the elimination step leading to indolizines **6**.

Results and Discussion

Preparation of *N*-[α-(Benzotriazol-1-yl)alkyl]pyridinium and *N*-[α-(Benzotriazol-1-yl)aryl]pyridinium Salts. An early report for the preparation of *N*-[α-(benzotriazol-1-yl)methyl]pyridinium chloride (**1a**) in 51% yield involved refluxing a mixture of pyridine and α-benzotriazol-1-ylmethyl chloride in nitromethane.[21] In the present work, *N*-[α-(benzotriazol-1-yl)alkyl]pyridinium and *N*-[α-(benzotriazol-1-yl)arylmethyl] pyridinium salts **1a**−**d** are readily prepared in 71−87% yield by the condensation of pyridine, thionyl chloride, benzotriazole, and the appropriate aldehyde in methylene chloride at 20 °C (Scheme 2). The crude products **1a**−**d** could be used for the subsequent preparation of indolizines without further purification.

Preparation of Indolizines. On the basis of our previous work,[18−20] the benzotriazolyl group can activate an α-proton for easy deprotonation and stabilize the subsequent α-carbanion. Accordingly, dark purple solutions of azomethine ylides **2** are readily formed from **1** with a mild base triethylamine (Scheme 3). Treatment of **2** with 1 equiv of an electron-deficient alkene **3** gave indolizines **6** in low yield along with the byproduct Michael adduct **4**, formed by the reaction of benzotriazole with the dipolarophiles. Therefore, 2 equiv of dipolarophile was used in subsequent reactions. The proposed mechanism is shown in Scheme 3. Azomethine ylide **2** reacts with electron-deficient alkene **3** to generate **5**, which subsequently eliminates benzotriazole and undergoes oxidative aromatization to give **6** in moderate yield. To avoid incomplete oxidation, an α-bromo-α,*β*-unsaturated ester or nitrile **8** was used instead of **3** (Scheme 3). The α-bromo-α,*β*-unsaturated ester and nitrile **8** were prepared by the bromination of alkene **3** to bromide **7**, followed by the elimination of hydrobromide with sodium hydroxide (Scheme 4). Treatment of ylides **2** with α-bromo-α,*β*-unsaturated esters or nitriles **8**, as expected, gave indolizines **6a**−**g** in good yields (Table 1). However, no cycloadduct was isolated when styrene was used as the dipolarophile, and the use of 4-vinylpyridine gave only a trace amount of the expected product **6**.

Scheme 3



Scheme 4

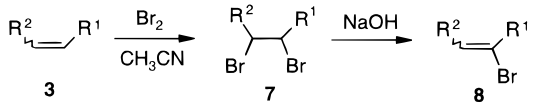


Table 1. Preparation of Indolizines 6[a]

no.	R	R^1	R^2	R^3	yield (%)[b]	mp (°C)[ref]
6a	H	COOEt	H	H	71	oil[22]
6b	H	COOEt	H	Et	74	65
6c	H	COOEt	H	*p*-tolyl	66[c]	96
6d	H	CN	H	H	71	53 (52[11b])
6e	H	CN	H	Et	73	73
6f	H	CN	H	*p*-tolyl	66[c]	107
6g	Et	CN	H	H	82	99
6h	H	$COOCH_3$	$COOCH_3$	H	66	90 (89[23])
6i	H	$COOCH_3$	$COOCH_3$	Et	69	47
6j	H	COOEt	COOEt	*p*-tolyl	69[c]	94
6k	Et	$COOCH_3$	$COOCH_3$	H	78	129
6l	H	$COOCH_3$	Ph	H	59	104 (106[24])

[a] **6a**-**g** were synthesized from ethylenes **8**; **6h**-**l** from acetylenes **9**. [b] Isolated yield based on **1** except for the preparation of **6c**, **6f** and **6j**. [c] Isolated yield based on benzotriazole.

When an acetylenic dipolarophile, i.e., dimethyl or diethyl acetylenedicarboxylate (**9**, $R^1 = R^2 = COOCH_3$ or COOEt), was used, compounds **6h**−**k** were obtained in 66−78% yields via 1,3-dipolar cycloadditions. Treatment of **1a** with ethyl phenylpropiolate produced **6l** in 59% yield.

Preparation of 2-(Benzotriazol-1-ylmethyl)isoquinolinium Chloride and Pyrrolo[2,1-*a*]isoquinolines. Pyrrolo[2,1-*a*]isoquinolines were also synthesized using benzotriazole methodology. 2-(Benzotriazol-1-ylmethyl)isoquinolinium chloride **10** was prepared in 89% yield by refluxing isoquinoline and (benzotriazol-1-yl)methyl chloride in acetonitrile (Scheme 5). Treatment of **10** with α-bromoacrylonitrile in the presence of triethylamine in acetonitrile gave pyrrolo[2,1-*a*]isoquinoline-1-carbonitrile (**11**) in 51% yield. Similarly, diethyl pyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**12**) was obtained in

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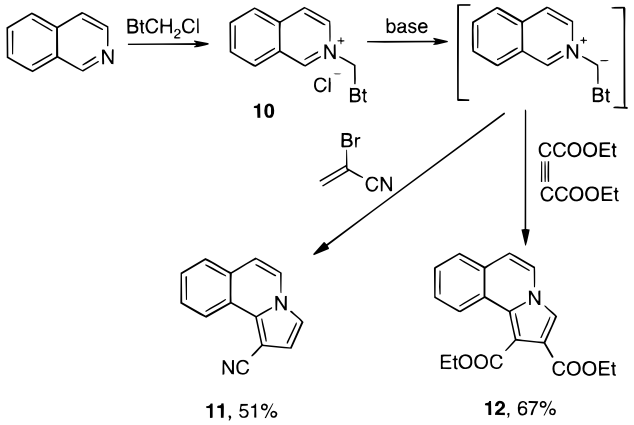
Scheme 5



67% yield by the reaction of **10** with diethyl acetylenedicarboxylate in the presence of sodium hydroxide.

In conclusion, we have described a convenient route to indolizines and pyrrolo[2,1-*a*]isoquinolines from readily prepared *N*-[(benzotriazol-1-yl)alkyl]pyridinium and 2-(benzotriazol-1-ylmethyl)isoquinolinium salts. Easy deprotonation by a mild base yields azomethine ylides, which are the presumed intermediates in 1,3-dipolar cycloadditions with electron-deficient dipolarophiles. The advantages of this method include (i) intermediates **1a**−**d** could be used directly for the next step without further purification; (ii) no oxidant is needed when 1-bromoethylenes are used as reactants; (iii) substituents at the 2,3-positions of the indolizines produced are not limited to electron-withdrawing groups; and (iv) the yields of indolizines and pyrrolo[2,1-*a*]isoquinolines are from good to excellent.

Experimental Section

General Procedure for the Preparation of *N*-[α-(Benzotriazol-1-yl)alkyl]pyridinium or *N*-[α-(Benzotriazol-1-yl)arylmethyl]pyridinium Chlorides 1a−d. A solution of thionyl chloride (0.9 mL, 12 mmol) in dry CH_2Cl_2 (12 mL) was cooled to 0 °C. Pyridine (1.0 mL, 12 mmol) in dry CH_2Cl_2 (6 mL) was added dropwise, followed by a solution of an appropriate aldehyde (10 mmol) in dry CH_2Cl_2 (5 mL). After the mixture was stirred for 1 h, benzotriazole (1.19 g, 10 mmol) in CH_2Cl_2 (50 mL) was added dropwise during 1 h. The mixture was stirred for another 24 h at room temperature. However, the time was reduced to 1 h for **1c** to avoid formation of undesired byproducts. The solvent was evaporated in vacuo, and the crude product could be used directly for the next step.

For the calculation of isolated yield and elemental analysis, the crude product was recrystallized from acetonitrile or converted into the pyridinium perchlorate by adding perchloric acid (70%) to the solution of the crude product in methylene chloride. However, no pure **1c** was obtained by these methods.

1-[(Benzotriazol-1-yl)methyl]pyridinium chloride (1a): white powder, mp 218−219 °C [lit.[21] mp 218−218.5 °C]; (1.75 g, 71%); ^{1}H NMR (DMSO) δ 7.53 (t, J = 7.5 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 8.02 (s, 2H), 8.17 (d, J = 8.4 Hz, 1H), 8.31 (t, J = 6.9 Hz, 2H), 8.61 (d, J = 8.4 Hz, 1H), 8.77 (t, J = 7.8 Hz, 1H), 9.66 (d, J = 6.3 Hz, 2H); ^{13}C NMR (DMSO) δ 67.3, 111.1, 119.6, 125.2, 128.7, 129.0, 132.7, 144.7, 145.2, 147.9.

1-[1-(Benzotriazol-1-yl)propyl]pyridinium perchlorate (1b): colorless crystal, mp 147−148 °C; (2.47 g, 73%); ^{1}H NMR (DMSO) δ 0.98 (t, J = 7.2 Hz, 3H), 2.95−3.08 (m, 1H), 3.10−3.25 (m, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.74 (t, J = 7.4 Hz, 1H), 7.92 (t, J = 7.4 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H), 8.21 (d, J = 8.3 Hz, 1H), 8.29 (t, J = 6.7 Hz, 2H), 8.75 (t, J = 7.7 Hz, 1H), 9.48 (d, J = 6.1 Hz, 2H); ^{13}C NMR (DMSO) δ 9.3, 27.1, 79.8, 110.3, 119.9, 125.4, 129.1, 132.8, 142.9, 145.2, 148.0. Anal. Calcd for $C_{14}H_{15}ClN_4O_4$: C, 49.64; H, 4.47; N, 16.54. Found: C, 49.73; H, 4.26; N, 16.49.

1-[Benzotriazol-1-yl(4-methylphenyl)methyl]pyridinium chloride (1c): crude intermediate; ^{1}H NMR δ 2.33 (s, 3H), 7.26 (d, J = 7.6 Hz, 2H), 7.41−7.50 (m, 1H), 7.63−7.67 (m, 1H), 7.68−7.73 (m, 1H), 7.78 (d, J = 7.6 Hz, 2H), 8.09 (d, J = 7.9 Hz, 1H), 8.18 (d, J = 7.9 Hz, 1H), 8.45 (t, J = 6.7 Hz, 2H), 8.81 (t, J = 7.7 Hz, 1H), 9.10 (s, 1H), 9.93 (d, J = 6.1 Hz, 1H).

1-(Benzotriazol-1-ylmethyl)-2-ethylpyridinium chloride (1d): white powder, mp 180−181 °C; (2.39 g, 87%); ^{1}H NMR δ 1.29 (t, J = 7.2 Hz, 3H), 3.57 (q, J = 7.2 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.74 (t, J = 7.5 Hz, 1H), 7.99 (s, 2H), 8.10−8.30 (m, 3H), 8.52 (d, J = 8.4 Hz, 1H), 8.72 (t, J = 7.8 Hz, 1H), 9.57 (d, J = 6.3 Hz, 1H); ^{13}C NMR δ 14.8, 25.3, 64.9, 111.1, 119.7, 125.1, 125.9, 128.4, 129.0, 132.8, 145.0, 145.7, 147.6, 160.6. Anal. Calcd. for $C_{14}H_{15}ClN_4$: C, 61.19; H, 5.51; N, 20.40. Found: C, 60.79; H, 5.43; N, 20.40.

General Procedure for the Preparation of Indolizines 6a−g. Bromine (0.64 g, 4 mmol) in acetonitrile (5 mL) was added slowly dropwise to a solution of an ethylene **3** (4 mmol) in acetonitrile (5 mL). The reaction mixture was stirred at room temperature until the color of bromine disappeared. NaOH (0.24 g, 6 mmol) was added, and then a solution of **1a**−**d** (2 mmol) in acetonitrile (15 mL) was added dropwise. The mixture was refluxed for 16 h. After cooling, H_2O and ethyl acetate were added. The organic phase was separated, washed with 1 M HCl and brine, and dried over Na_2SO_4. After removal of solvent in vacuo, the residue was separated by a column (silica gel) with hexanes−ethyl acetate (10:1) as eluent to give indolizines **6a**−**g**.

Ethyl 1-indolizinecarboxylate (6a):[22] a pale yellow oil; ^{1}H NMR δ 1.41 (t, J = 7.1 Hz, 3H), 4.37 (q, J = 7.1 Hz, 2H), 6.68 (t, J = 6.6 Hz, 1H), 7.02 (t, J = 7.9 Hz, 1H), 7.23 (dd, J = 11.3, 2.8 Hz, 2H), 7.98 (d, J = 6.9 Hz, 1H), 8.17 (d, J = 9.1 Hz, 1H); ^{13}C NMR δ 14.6, 59.4, 103.9, 112.3, 113.6, 116.1, 119.9, 122.1, 126.0, 135.7, 165.0.

Ethyl 3-ethyl-1-indolizinecarboxylate (6b): colorless flake; ^{1}H NMR δ 1.41 (t, J = 7.4 Hz, 6H), 2.79 (q, J = 7.4 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 6.75 (t, J = 6.7 Hz, 1H), 7.04 (t, J = 8.8 Hz, 1H), 7.06 (s, 1H), 7.82 (d, J = 6.9 Hz, 1H), 8.20 (d, J = 9.0 Hz, 1H); ^{13}C NMR δ 11.3, 14.7, 18.9, 59.3, 102.8, 112.1, 112.8, 120.0, 121.1, 122.6, 127.0, 135.7, 165.2. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.97; N, 6.45. Found: C, 71.62; H, 7.22; N, 6.75.

Ethyl 3-(4-methylphenyl)-1-indolizinecarboxylate (6c): colorless needles; ^{1}H NMR δ 1.41 (t, J = 7.1 Hz, 3H), 2.39 (s, 3H), 4.38 (q, J = 6.9 Hz, 2H), 6.63 (t, J = 6.7 Hz, 1H), 7.01 (t, J = 8.4 Hz, 1H), 7.25 (d, J = 7.7 Hz, 2H), 7.26 (s, 1H), 7.38 (d, J = 7.7 Hz, 2H), 8.19−8.29 (m, 2H); ^{13}C NMR δ 14.6, 21.2, 59.3, 104.0, 112.3, 115.7, 120.0, 121.9, 123.2, 126.3, 128.1, 128.4, 129.6, 136.1, 137.7, 164.9. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.15; N, 5.02. Found: C, 77.01; H, 6.20; N, 5.03.

1-Indolizinecarbonitrile (6d):[11b] colorless needles; ^{1}H NMR δ 6.73 (t, J = 6.8 Hz, 1H), 6.99 (d, J = 2.5 Hz, 1H), 7.03 (t, J = 7.3 Hz, 1H), 7.57 (d, J = 9.0 Hz, 1H), 8.02 (d, J = 6.9 Hz, 1H); ^{13}C NMR δ 81.2, 112.7, 113.8, 116.6, 116.8, 117.5, 122.2, 126.3, 137.6.

3-Ethyl-1-indolizinecarbonitrile (6e): colorless needles; ^{1}H NMR δ 1.38 (t, J = 7.4 Hz, 3H), 2.79 (q, J = 7.5 Hz, 2H), 6.78 (s, 1H), 6.78 (t, J = 6.5 Hz, 1H), 7.03 (t, J = 8.5 Hz, 1H), 7.61 (d, J = 9.1 Hz, 1H), 7.85 (d, J = 6.9 Hz, 1H); ^{13}C NMR δ 11.2, 18.8, 80.3, 112.5, 113.2, 117.3, 117.8, 121.2, 122.9, 127.6, 137.8. Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.61; H, 5.93; N, 16.46. Found: C, 77.31; H, 6.27; N, 16.31.

3-(4-Methylphenyl)-1-indolizinecarbonitrile (6f): colorless needles; ^{1}H NMR δ 2.43 (s, 3H), 6.72 (t, J = 6.9 Hz, 1H), 7.00 (s, 1H), 7.06 (t, J = 7.8 Hz, 1H), 7.31 (d, J = 7.9 Hz, 2H), 7.39 (d, J = 7.7 Hz, 2H), 7.67 (d, J = 8.8 Hz, 1H), 8.25 (d, J = 7.1 Hz, 1H); ^{13}C NMR δ 21.3, 82.0, 112.9, 115.9, 117.0, 118.1, 122.1, 123.7, 127.0, 127.2, 128.6, 129.9, 138.2, 138.6; HRMS calcd for $C_{16}H_{12}N_2$ 233.1078 (M + 1), found 233.1004.

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5-Ethyl-1-indolizinecarbonitrile (6g): colorless needles; ^{1}H NMR δ 1.44 (t, J = 7.4 Hz, 3H), 2.89 (q, J = 7.3 Hz, 2H), 6.64 (d, J = 6.7 Hz, 1H), 7.04−7.14 (m, 2H), 7.22 (d, J = 2.7 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H); ^{13}C NMR δ 10.3, 24.8, 81.9, 109.8, 110.6, 115.4, 116.8, 117.2, 122.7, 138.6, 139.8; HRMS calcd for $C_{11}H_{10}N_2$ 171.0922 (M + 1), found 171.0920.

General Procedure for the Preparation of Indolizines 6h−l. A solution of **1a**−**d** (2 mmol), acetylene **9** (4 mmol), and Et_3N (2.3 mL, 16 mmol) in acetonitrile (15 mL) was stirred at room temperature for 20 h. H_2O and ethyl acetate were added to the mixture. The organic phase was separated, washed with brine, and dried over Na_2SO_4. After removal of solvent in vacuo, the residue was separated by a column (silica gel) with hexanes−ethyl acetate (10:1) as eluent to give indolizines **6h**−**l**.

Dimethyl 1,2-indolizinedicarboxylate (6h):[23] white solid; ^{1}H NMR δ 3.91 (s, 6H), 6.75 (t, J = 6.6 Hz, 1H), 7.07 (t, J = 9.2 Hz, 1H), 7.63 (s, 1H), 7.94 (d, J = 6.9 Hz, 1H), 8.11 (d, J = 9.3 Hz, 1H); ^{13}C NMR δ 51.2, 52.1, 102.6, 113.6, 116.9, 120.4, 121.5, 123.2, 125.8, 136.0, 164.2, 165.0.

Dimethyl 3-ethyl-1,2-indolizinedicarboxylate (6i): white solid; ^{1}H NMR δ 1.26 (t, J = 7.4 Hz, 3H), 2.98 (q, J = 7.6 Hz, 2H), 3.88 (s, 3H), 3.95 (s, 3H), 6.79 (t, J = 6.8 Hz, 1H), 7.07 (t, J = 9.0 Hz, 1H), 7.86 (d, J = 7.1 Hz, 1H), 8.15 (d, J = 9.1 Hz, 1H); ^{13}C NMR δ 12.1, 17.8, 51.1, 52.3, 101.3, 113.2, 119.4, 120.5, 122.5, 122.7, 127.8, 135.0, 164.3, 167.0. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.80. Found: C, 64.07; H, 6.10.

Dimethyl 3-(4-methylphenyl)-1,2-indolizinedicarboxylate (6j): colorless cube; ^{1}H NMR δ 1.23 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 2.42 (s, 3H), 4.27 (q, J = 6.9 Hz, 2H), 4.37 (q, J = 6.9 Hz, 2H), 6.69 (t, J = 6.9 Hz, 1H), 7.09 (t, J = 6.9 Hz, 1H), 7.30 (d, J = 7.7 Hz, 2H), 7.40 (d, J = 7.9 Hz, 2H), 8.02 (d, J = 7.1 Hz, 1H), 8.24 (d, J = 9.1 Hz, 1H); ^{13}C NMR δ 14.0, 14.4, 21.4, 59.8, 61.2, 101.9, 113.2, 120.3, 122.1, 123.2, 123.5, 124.9, 125.9, 129.7, 129.8, 135.1, 138.9, 163.8, 166.4. Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.77; H, 6.04; N, 3.99. Found: C, 71.66; H, 6.04; N, 3.96.

Dimethyl 5-ethyl-1,2-indolizinedicarboxylate (6k): colorless needles; ^{1}H NMR δ 1.43 (t, J = 7.2 Hz, 3H), 2.88 (q, J = 7.4 Hz, 2H), 3.92 (s, 3H), 3.93 (s, 3H), 6.64 (d, J = 6.8 Hz, 1H), 7.10 (t, J = 7.1 Hz, 1H), 7.64 (s, 1H), 8.07 (d, J = 9.1 Hz, 1H); ^{13}C NMR δ 10.3, 24.6, 51.2, 52.1, 102.9, 110.5, 113.7, 118.1, 121.4, 123.6, 136.9, 139.1, 164.4, 165.4. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.80; N, 5.36. Found: C, 64.72; H, 6.17; N, 5.56.

Ethyl 2-phenyl-1-indolizinecarboxylate (6l):[24] colorless needles; ^{1}H NMR δ 1.23 (t, J = 7.2 Hz, 3H), 4.25 (q, J = 6.9 Hz, 2H), 6.72 (t, J = 6.6 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 7.25 (s, 1H), 7.28−7.41 (m, 3H), 7.51 (d, J = 6.6 Hz, 2H), 7.98 (d, J = 6.6 Hz, 1H), 8.24 (d, J = 9.3 Hz, 1H); ^{13}C NMR δ 14.3, 59.3, 101.6, 112.6, 113.6, 120.3, 122.4, 125.5, 127.0, 127.5, 129.9, 132.7, 134.9, 136.7, 163.0.

General Procedure for the Preparation of 11 and 12. To a solution of 1-(chloromethyl)benzotriazole (1.0 g, 6 mmol) in dry acetonitrile was added isoquinoline (0.77 g, 6 mmol). The mixture was refluxed with stirring for 20 h. After cooling, the mixture was diluted with Et_2O to give a crude salt, which was changed to perchlorate **10** (1.93 g, 89%) by addition of 70% perchloric acid.

A solution of **10** (0.72 g, 2 mmol) and 2,3-dibromopropanenitrile (1.28 g, 6 mmol) in dry acetonitrile (15 mL) was refluxed in the presence of NaOH (0.08 g, 2 mmol) for 16 h. After the mixture was cooled, H_2O and ethyl acetate were added to the reaction mixture. The organic phase was separated, washed with 1 M HCl and brine, and dried over Na_2SO_4. The solvents were evaporated in vacuo, and the residue was separated by column chromatography (silica gel) with hexanes−ethyl acetate (10:1) as eluent to give **11** (0.19 g, 51%).

A solution of **10** (0.72 g, 2 mmol) and diethyl acetylene dicarboxylate (1 mL, 6 mmol) in dry acetonitrile (15 mL) was stirred in the presence of triethylamine (2.3 mL, 16 mmol) at room temperature for 20 h. H_2O and ethyl acetate were added to the reaction mixture. The organic phase was separated, washed with brine, and dried over Na_2SO_4. The solvents were evaporated in vacuo, and the residue was separated by column chromatography (silica gel) with hexanes−ethyl acetate (5:1) as eluent to give **12** (0.42 g, 67%).

2-(1*H*-1,2,3-Benzotriazol-1-ylmethyl)isoquinolinium perchlorate (10): colorless crystal, mp 179−180 °C; ^{1}H NMR δ 7.54 (t, J = 7.9 Hz, 1H), 7.70−7.82 (m, 1H), 7.75 (s, 2H), 8.10−8.21 (m, 2H), 8.28−8.43 (m, 3H), 8.60−8.71 (m, 2H), 9.02 (d, J = 6.4 Hz, 1H), 10.47 (s, 1H); ^{13}C NMR δ 67.8, 110.7, 119.7, 125.1, 126.6, 127.2, 127.4, 129.0, 131.3, 131.6, 132.7, 134.0, 137.9, 138.1, 145.4. Anal. Calcd for $C_{16}H_{13}N_4$: C, 53.27; H, 3.64; N, 15.35. Found: C, 53.44; H, 3.47; N, 15.52.

Pyrrolo[2,1-*a*]isoquinoline-1-carbonitrile (11): colorless needles, mp 159−160 °C; ^{1}H NMR δ 6.96 (d, J = 4.3 Hz, 2H), 7.20 (d, J = 2.5 Hz, 1H), 7.47−7.70 (m, 3H), 7.76 (d, J = 7.1 Hz, 1H), 8.79 (d, J = 8.0 Hz, 1H); ^{13}C NMR δ 83.9, 113.8, 115.9, 116.0, 118.5, 123.0, 124.0, 124.8, 127.2, 128.0, 128.1, 128.4, 133.9; HRMS calcd for $C_{13}H_8N_2$ (M + 1) 193.0765, found 193.0729.

Diethyl pyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (12): colorless needles, mp 111−112 °C; ^{1}H NMR δ 1.36 (t, J = 7.1 Hz, 3H), 1.44 (t, J = 7.1 Hz, 3H), 4.34 (q, J = 7.1 Hz, 2H), 4.52 (q, J = 7.1 Hz, 2H), 6.76 (d, J = 7.4 Hz, 1H), 7.36−7.44 (m, 2H), 7.48 (t, J = 6.9 Hz, 1H), 7.57 (d, J = 7.4 Hz, 1H), 7.66 (s, 1H), 8.24 (d, J = 7.9 Hz, 1H); ^{13}C NMR δ 14.0, 14.2, 60.4, 61.5, 109.7, 114.1, 117.7, 118.7, 123.3, 123.6, 125.0, 127.2, 127.7, 127.8, 128.0, 163.6, 167.4. Anal. Calcd for $C_{18}H_{17}N$: C, 69.44; H, 5.51; N, 4.50. Found: C, 69.15; H, 5.60; N, 4.62.

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