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Regioselective Photocycloaddition of Pyridine Derivatives to Electron-Rich Alkenes

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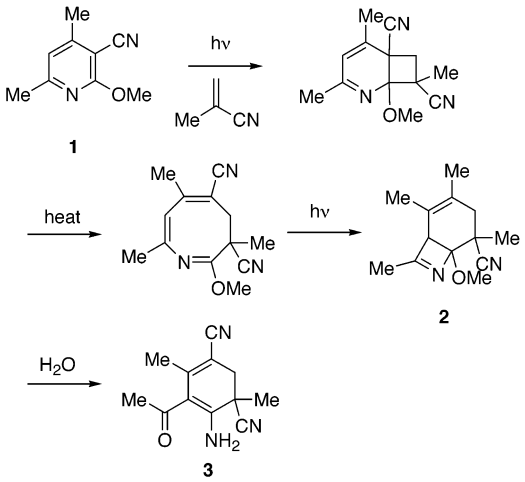
Irradiation of a benzene solution of 3-cyano-2,6-dimethoxypyridine in the presence of ethyl vinyl ether (EVE) gave 1:1 photoadducts, 3-cyano-5-ethoxy-2,8-dimethoxy-4,5-dihydroazocine, in good yields, whose structure was established by X-ray single-crystal analysis. The photoadduct was produced via cycloaddition between the C3−C4 position of the pyridine derivatives and an alkene chromophore. On the other hand, 3-cyano-2,6-dimethoxy-4-methylpyridine cycloadds to EVE at the C2−C3 position of the pyridine ring upon irradiation. The difference is explained on the basis of the steric effect.

Introduction

Photochemical cycloaddition of benzene derivatives toward several types of alkenes has been extensively studied, and 2 + 2, 3 + 2, and 4 + 2 cycloadditions were reported.[1−3] The reaction has received much attention from both mechanistic and synthetic perspectives because it is also a useful method of synthesizing natural products. On the other hand, while the valence isomerization of azaaromatic compounds, such as pyridines, was reported three decades ago,[4−11] only a few reports for the photochemical cycloaddition with alkenes are known.[12−14] New developments in the ring transformation of heteroaromatics will result in useful synthetic methodology of heterocyclic compounds.[15] Recently, we found that introduction of both electron-donating and -withdrawing substituents to the pyridine ring shows high reactivity toward dimerization and addition reaction.[16−20]

SCHEME 1



Previously, we reported the photocycloaddition of 2-alkoxy-3-cyanopyridine **1** with methacrylonitrile leading to cyclobutane, and ultimately, bicyclic azate **2** and aminoketone **3** were obtained as shown in Scheme 1.[13] Herein we found that the photoreaction of pyridine

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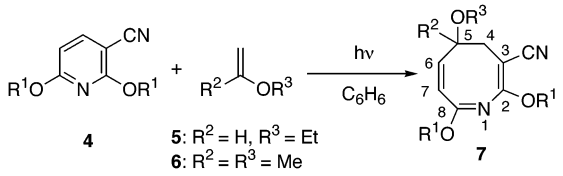
TABLE 1. Photoreaction of 4 in the Presence of Electron-Rich Alkenes[a]



entry	4	R^1	alkene	conv (%)	yields of 7 (%)
1	**a**	Me	**5**	95	83
2	**b**	Et	**5**	96	70
3	**c**	*i*-Pr	**5**	93	70
4	**a**	Me	**6**	64	60[b]

[a] A benzene solution of 0.02 M of pyridine derivatives **4** and 1.0 M of alkenes was irradiated with a high-pressure mercury lamp for 6 h. [b] Compound **7d**.

derivatives with electron-rich alkenes effected effective and regioselective cycloaddition leading to new heterocycles.

Results and Discussion

When a benzene solution of 2-alkoxy-3-cyanopyridine **1** was irradiated in the presence of ethyl vinyl ether (EVE), the ^{1}H NMR spectrum of the photolysate indicated the formation of some adducts; however, the adducts were too unstable to isolate. An attempted isolation of adducts by chromatography resulted in the formation of an intractable mixture. On the other hand, irradiation of a benzene solution of 2,6-dimethoxy-3-cyanopyridine **4a** (0.02 M) in the presence of EVE **5** (1.0 M) gave a 1:1 adduct, 5-ethoxy-2,8-dimethoxy-4,5-dihydroazocine-3-carbonitrile **7a**, in 83% yield (Table 1, entry 1). Photolysis of other nicotinates **4b**−**c** under the same conditions also gave the corresponding adducts **7b**−**c** in good yields (Table 1, entries 2 and 3). No other photoproducts, such as another type of adduct, transpositional isomer, or pyridine dimers, were isolated.[16,19] The adducts **7** were stable under usual conditions and were easily isolated by chromatography on silica gel and recrystallization from a mixture of chloroform and hexane.

The structure was determined on the basis of spectral data. For example, mass spectroscopy (FAB) of **7a** showed a molecular ion peak at 237 (MH^+), which supported that the product was a 1:1 adduct of **4a** and EVE **5**. Furthermore, the ^{1}H and ^{13}C NMR spectra strongly suggest the structure of the adduct **7a**. The ^{1}H NMR spectrum ($CDCl_3$) showed new protons at δ 2.19 (m, 1H, 4-CH), 2.40 (m, 1H, 4-CH), 4.07 (m, 1H, 5-CH), 5.83 (d, J = 13.2 Hz, 1H, 7-CH), 6.21 (dd, J = 3.7, 13.2 Hz, 1H, 6-CH) in addition to the alkoxy protons. The ^{13}C NMR also showed peaks at δ 29.2 (t, 4-C), 69.9 (s, 7-C), 77.0 (d, 3-C), 117.3 (d, 7-C), 139.7 (d, 6-C), 161.0 (s, 8-C), 166.4 (s, 2-C), ascribed to the azocine rings. The assignment was made using the COSY sequence.

Finally, the azocine structure of **7a** was unequivocally established by X-ray structural analysis.

Irradiation of **4a** in the presence of 2-methoxypropene **6** also gave azocine derivative **7d** (entry 4); however, the chemical yield slightly decreased (Table 1, entry 4). It seems that the steric hindrance caused by induction of one methyl group affected the addition reaction.

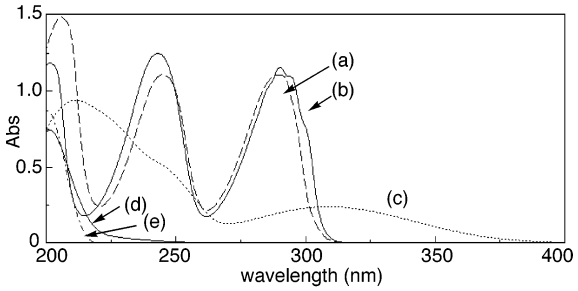
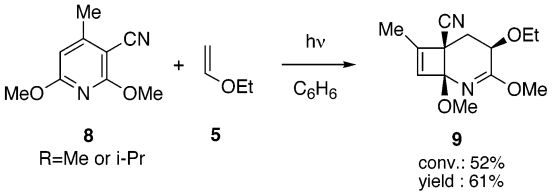


FIGURE 1. All UV spectra were measured at a concentration of 1.0×10^{-4} mol L^{-1} in C_6H_{12}: (a) UV spectrum of **4a**; (b) UV spectrum of **8**; (c) UV spectrum of the adduct **7a**; (d) UV spectrum of **9**; (e) UV spectrum of EVE **5**.

SCHEME 2



Next we tried the photoreaction of pyridine derivative **8**, which possesses another methyl group at the 4-position of **4a** (Scheme 2). When **8** was irradiated with EVE, a different type of adduct **9**, 6-cyano-4-ethoxy-1,3-dimethoxy-7-methyl-2-azabicyclo[4.2.0]octa-2,7-diene, was obtained in 61% yield at 52% conversion.

The structure was determined on the basis of spectral data. The mass spectroscopy (FAB) showed a molecular ion peak at 251 (MH^+), which supported that the product was a 1:1 adduct of **9** and EVE. The IR spectrum exhibited an absorption at 1655 cm^{-1} derived from the C═N bond. The ^{1}H and ^{13}C NMR spectra also strongly suggest a bicyclic structure. The ^{1}H NMR spectrum showed new peaks at δ 1.88 (d, J = 1.7 Hz, 3H, 7-CH_3), 2.11 (m, 1H, 5-CH), 2.33 (m, 1H, 5-CH), 3.57 (m, 1H, 4-CH), 6.04 (s, 1H, 8-CH) accompanied by peaks derived from the alkoxy group. The ^{13}C NMR also showed new peaks at δ 11.9 (q, 7-CH3), 31.9 (t, 5-C), 47.8 (s, 6-C), 68.6 (d, 4-C), 87.9 (s, 1-C), 119.2 (s, CN), 134.4 (d, 8-C), 145.7 (s, 7-C), 163.3 (s, 3-C). The assignment was made using the COSY sequence. Finally, the bicyclic structure of **9** was also established by X-ray structural analysis.

Figure 1 shows the UV spectra of pyridine **4a** and EVE **5** at the concentration of each 1.0×10^{-4} mol L^{-1} in cyclohexane. EVE has no absorption band above 250 nm. Since a high-pressure mercury lamp with a Pyrex filter was used as the irradiation source, light quantum of the 313 nm line was absorbed by the pyridine **4a** (ϵ 110 at 313 nm). The production of **7a** was not quenched by addition of 2,5-dimethylhexadiene (triplet quencher), and also the reaction was not sensitized by a triplet sensitizer such as 3-methoxyacetophenone. These results indicate that the photoaddition proceeds from the singlet-excited state of pyridine **4a**.

The adduct **9** has no absorption above 250 nm, and the azocine derivatives **7a** absorbs 313 nm line. It seems that azocine **7** is also able to transform to a bicyclic compound; however, the product is unstable and easily reverts to **7**. Therefore, **7** was apparently inert toward photolysis and was obtained in good chemical yields (Table 1).

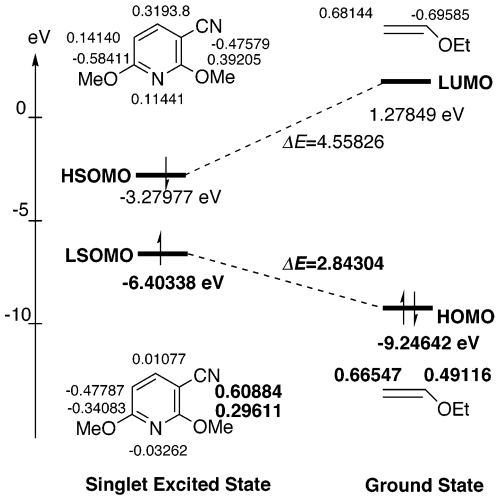
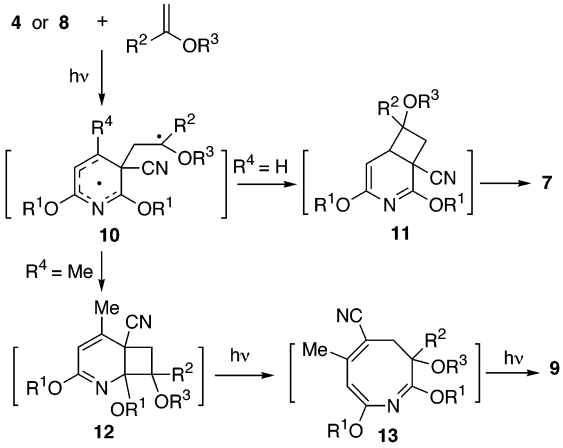


FIGURE 2. Estimated energies and coefficients of pyridine **4a** (singlet excited state) and the ground state of ethyl vinyl ether obtained from the PM3 Hamiltonian contained within the MOPAC program.

SCHEME 3



The regioselectivity and stereoselectivity in many singlet photoadditions can be explained by orbital interactions.[21,22] Frontier-MO calculations by the PM3 method help to explain the photocycloaddition.[23] The orbital surfaces of the H-SOMO and L-SOMO of **4a** were obtained from the PM3 Hamiltonian contained within the MOPAC program as shown in Figure 2. The $\Delta\Delta E$ value (2.84304 eV) between the L-SOMO of the excited state of the pyridine derivative and the HOMO of EVE is smaller than the value (4.55826 eV) between the H−SOMO of the excited state of the pyridine derivative and the HOMO of EVE. The coefficient value at the C-3 position of **4a** is bigger than those at other positions, and interaction between the C-3 position of **4a** and the C-2 position of EVE is suggested.

Scheme 3 shows a plausible mechanism for the formation of **7** and **9**. When R^3 is a hydrogen atom, C−C bond-formation between the C3-position of the pyridine ring and the C2 postion of EVE proceeds and results in formation of biradical intermediate **10**, which subsequently cyclizes to cyclobutane derivative **11**. However, cyclobutane-fused azacyclohexadiene is unstable and easily opens the cyclobutane ring leading to azocine derivative **7**.

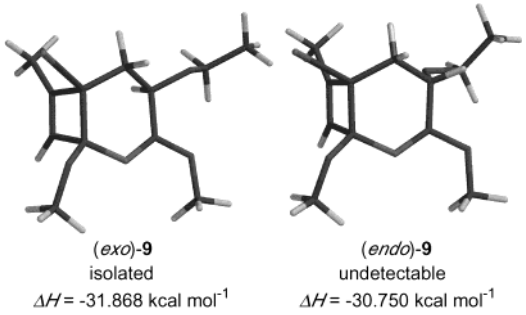


FIGURE 3. Left: energetically minimum conformation of the exo isomer. Right: energetically minimum conformation of the endo isomer.

On the other hand, the introduction of a methyl group at the 4-position of the pyridine ring (R^4 = Me) prevents the following bond formation at the C-4 position of the biradical intermediate **10** because of the steric repulsion between the alkoxy group and the methyl group at the C-4 position. Ultimately, the biradical recombines at the C-2 position to give cyclobutane **12**, which also easily opens the cyclobutane ring to yield azatriene **13**. The triene absorbs light quantum to effect the electrocyclization reaction and gives bicyclic cyclobutene **9**. To determine the proposed mechanism, the reaction was followed by ^{1}H NMR spectroscopy. A deuterated benzene solution containing 0.02 M of pyridine **4a** or **8** with 1.0 M of EVE was irradiated; however, the intermediates proposed in Scheme 3 were not detected, and the spectra assignable to the final photoproduct **7a** and **9** were exhibited.

There are two possible ways of electrocyclization from azatriene **13** to 2-azabicyclo[4.2.0]octa-2,7-diene **9**. Only one isomer was isolated from the photoreaction of **8** with EVE. The result was supported by computational calculations using the PM3 method with Mac-Spartan. The energetically more favorable *exo* isomer of **9** is 1.1 kcal mol^{-1} more stable than the endo isomer of **9** (Figure 3).

In conclusion, we have found a new example of the photochemical addition reaction of a pyridine ring with electro-rich alkenes leading to 1:1 cycloadducts. This reaction proceeds in a highly controlled regioselective manner and also provides a synthesis of new nitrogen-containing heterocycles.

Experimental Section

Melting points are uncorrected. FT-IR spectra are reported in cm^{-1}. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ solutions at 300 MHz. Chemical shifts are reported in delta (δ) units, parts per million (ppm) relative to the TMS as internal standard. Eikosya 500-W and 1000-W high-pressure mercury lamps were used as the irradiation source.

Preparation of 3-Cyano-2,6-dialkoxypyridines 4a−c and 3-Cyano-2,6-dialkoxy-4-methylpyridines 8. The pyridines were prepared by alkylation of 3-cyano-2,6-dihydroxypyridine or 3-cyano-2,6-dihydroxy-4-methylpyridine.[24−27] For

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example, the synthesis of **4a** is exemplified next. To 50 mL of benzene were added 3-cyano-2,6-dihydroxypyridine (25 mmol), silver carbonate (18 mmol), and methyl iodide (50 mmol), and the mixture was warmed at 50 °C for 24 h in the dark. Precipitated silver salts were filtered off through a Celite (545) column. After removal of the solvent in vacuo, the residual mixture was subjected to chromatography on silica gel. A colorless solid of **4a** was recrystallized from the chloroform−hexane mixture. Other pyridines **4b**,**c** and **8** were synthesized in the same manner.

3-Cyano-2,6-dimethoxypyridine 4a: mp 87−88 °C; UV (C_6H_{12}) 243 (ϵ 12 600), 290 (11 800), 294 (11 100); IR ($CHCl_3$) 2230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.98 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 6.37 (d, J = 8.2 Hz, 1H, 5-CH), 7.70 (d, J = 8.2 Hz, 1H, 4-CH); ^{13}C NMR ($CDCl_3$) δ 54.0, 54.2, 86.7, 102.7, 116.0, 144.1, 164.7, 165.6; MS (FAB) 165 (MH^+). Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.48; H, 4.86; N, 17.01.

3-Cyano-2,6-diethoxypyridine 4b: mp 40−41 °C; UV (C_6H_{12}) 244 (ϵ 12 200), 291 (11 200), 295 (10 700); IR ($CHCl_3$) 2230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3), 1.43 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 4.38 (q, J = 7.0 Hz, 2H, OCH_2), 4.46 (q, J = 7.1 Hz, 2H, OCH_2), 6.31 (d, J = 8.3 Hz, 1H, 5-CH), 7.68 (d, J = 8.3 Hz, 1H, 4-CH); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 62.7, 63.1, 86.6, 102.7, 116.3, 144.2, 164.4, 165.2; MS (FAB) 193 (MH^+). Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.57. Found: C, 62.65; H, 6.35; N, 14.75.

3-Cyano-2,6-diisopropoxypyridine 4c: mp 58−60 °C; UV (C_6H_{12}) 245 (ϵ 14 000), 293 (12 300), 297 (11 600); IR ($CHCl_3$) 2230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (d, J = 6.3 Hz, 6H, C(CH_3)$_2$), 1.40 (d, J = 6.3 Hz, 6H, C(CH_3)$_2$), 5.25 (sep, J = 6.3 Hz, 1H, OCH), 5.30 (sep, J = 6.3 Hz, 1H, OCH), 6.26 (d, J = 8.4 Hz, 1H, 5-CH), 7.66 (d, J = 8.4 Hz, 1H, 4-CH); ^{13}C NMR ($CDCl_3$) δ 21.9, 69.7, 70.3, 86.6, 103.0, 116.4, 144.2, 164.0, 164.8; MS (FAB) 221 (MH^+). Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.71. Found: C, 65.29; H, 7.11; N, 12.64.

3-Cyano-2,6-dimethoxy-4-methylpyridine 8: mp 106−107 °C; UV (C_6H_{12}) 245 (ϵ 11 100), 290 (11 000); IR ($CHCl_3$) 2220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H, 4-CH_3), 3.95 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 6.23 (s, 1H, 5-CH); ^{13}C NMR ($CDCl_3$) δ 20.1, 53.1, 54.2, 88.0, 103.2, 115.4, 155.7, 165.2, 165.2; MS (FAB) 179 (MH^+). Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.56; H, 5.57; N, 15.65.

General Procedure for the Photochemical Reaction of Pyridine Derivatives 4 and 8 in the Presence of Electron-Rich Alkenes. Twenty milliliters of a benzene solution containing 0.02 M of pyridine derivative **4** or **8** and 1.0 M of alkene in a test tube was deaerated by bubbling argon and was irradiated by Pyrex-filtered light with a 1000-W high-pressure mercury lamp at 15−20 °C. In the case of pyridine **4**, the solution was irradiated for 6 h, and phototolysis of pyridine **8** needed 2 h. After irradiation, the solvent was removed in vacuo, and the residual mixture was subjected to chromatography on silica gel (eluant: mixture of *n*-hexane and ethyl acetate). The crystalline photoproducts were recrystallized from a mixture of chloroform and hexane. The structure of the photoproducts was determined on the basis of the spectral data. Furthermore, the structures of **7a** and **9** were established by X-ray crystallographic analysis.

3-Cyano-5-ethoxy-2,8-dimethoxy-4,5-dihydroazocine 7a: mp 127−128 °C; UV (C_6H_{12}) 211 (ϵ 9400), 308 (2400); IR ($CHCl_3$) 1590, 1620, 2170, 2960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3), 2.19 (m, 1H, 4-CH), 2.40 (m, 1H, 4-CH), 3.55 (dq, J = 1.8, 7.0 Hz, 1H, OCH), 3.68 (s, 3H, 2-OCH_3), 3.71 (dq, J = 1.8, 7.0 Hz, 1H, OCH), 3.86 (s, 3H, 8-OCH_3), 4.07 (m, 1H, 5-CH), 5.83 (d, J = 13.2 Hz, 1H, 7-CH), 6.21 (dd, J = 3.7, 13.2 Hz, 1H, 6-CH); ^{13}C NMR ($CDCl_3$) δ 15.5, 29.2, 54.5, 55.1, 64.9, 69.9, 77.0, 117.3, 119.9, 139.7, 161.0, 166.4; HR-MS (FAB) calcd 237.1239 for $C_{12}H_{17}N_2O_3$ (MH^+), found *m*/*z* 237.1234.

X-ray Crystallographic Analysis of 7a. The cage product **7a** gave colorless prismatic crystals of $C_{12}H_{16}N_2O_3$: monoclinic space group *P*-1, a = 7.320(4) Å, b = 9.327(5) Å, c = 10.009(5) Å, α = 95.736(7)°, β = 107.392(5)°, γ = 94.547(7)°, V = 644.4-(5) Å^3, Z = 2, ρ = 1.217 g/cm^3, μ(Mo Kα) = 0.88 cm^{-1}. The structure was solved by the direct method and refined by the full-matrix least-squares method, where the final R and Rw were 0.080 and 0.086 for 1267 reflections.

3-Cyano-2,5,8-triethoxy-4,5-dihydroazocine 7b: yellowish oil; IR ($CHCl_3$) 1580, 1620, 2170, 2950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (m, 6H, OCH$_2$CH_3), 1.35 (m, 3H, OCH$_2$CH_3), 2.15 (m, 1H, 4-CH), 2.40 (m, 1H, 4-CH), 3.57 (m, 1H, 5-OCH), 3.68 (m, 1H, 5-OCH), 3.98 (m, 2H, 2-OCH_2), 4.06 (m, 1H, 5-CH), 4.26 (m, 2H, 8-OCH_2), 5.82 (d, J = 13.2 Hz, 1H, 7-CH), 6.19 (dd, J = 3.7, 13.2 Hz, 1H, 6-CH); ^{13}C NMR ($CDCl_3$) δ 14.0, 15.1, 15.5, 29.1, 63.4, 63.8, 64.9, 70.0, 77.4, 117.6, 120.1, 139.2, 160.3, 166.3; HR-MS (FAB) calcd 265.1552 for $C_{14}H_{21}N_2O_3$ (MH^+), found *m*/*z* 265.1545.

7-Cyano-5-ethoxy-2,8-diisopropoxy-1-azacycloocta-1,3,7-triene 7c: yellowish oil; IR ($CHCl_3$) 1580, 1620, 2170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3), 1.33 (d, J = 6.2 Hz, 12H, C(CH_3)$_2$), 2.19 (m, 1H, 4-CH), 2.37 (m, 1H, 4-CH), 3.52 (m, 1H, 5-OCH), 3.69 (m, 1H, 5-OCH), 4.06 (m, 1H, 5-CH), 4.54 (sep, J = 6.2 Hz, 1H, 2-OCH), 5.15 (sep, J = 6.2 Hz, 1H, 8-OCH), 5.78 (d, J = 13.2 Hz, 1H, 7-CH), 6.16 (dd, J = 3.7, 13.2 Hz, 1H, 6-CH); ^{13}C NMR ($CDCl_3$) δ 15.3, 21.4, 22.2, 29.0, 64.6, 70.4, 70.6, 70.9, 73.1, 117.8, 120.0, 138.5, 159.5, 165.8; HR-MS (FAB) calcd 293.1865 for $C_{16}H_{25}N_2O_3$ (MH^+), found *m*/*z* 293.1862.

3-Cyano-2,5,8-trimethoxy-5-methyl-4,5-dihydroazocine 7d: mp 93−94 °C; IR (KBr) 1650, 1690, 2410, 3160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 3H, 5-CH_3), 2.06 (d, J = 14.6 Hz, 1H, 4-CH), 2.39 (d, J = 14.6 Hz, 1H, 4-CH), 3.19 (s, 3H, 5-OCH_3), 3.70 (s, 3H, 2-OCH_3), 3.90 (s, 3H, 8-OCH_3), 5.89 (br, 2H, 6-CH and 7-CH); ^{13}C NMR ($CDCl_3$) δ 26.8, 32.8, 49.6, 54.3, 54.7, 69.3, 78.5, 117.5, 119.8, 142.2, 160.8, 165.9; HR-MS (FAB) calcd. 237.1239 for $C_{12}H_{17}N_2O_3$ (MH^+), found *m*/*z* 237.1235.

6-Cyano-4-ethoxy-1,3-dimethoxy-7-methyl-2-azabicyclo-[4.2.0]octa-2,7-diene 9: mp 81−82 °C; UV (C_6H_{12}) 201 (ϵ 7400); IR (KBr) 1655, 2250, 2970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (m, 3H, OCH$_2$CH_3), 1.88 (d, J = 1.5 Hz, 3H, 7-CH_3), 2.11 (dd, J = 10.7, 13.5 Hz, 1H, 5-CH), 2.33 (dd, J = 5.2, 13.5 Hz, 1H, 5-CH), 3.48 (s, 3H, 1-OCH_3), 3.57 (dd, J = 5.2, 13.5 Hz, 1H, 4-CH), 3.58 (m, 1H, 4-OCH), 3.76 (m, 1H, 4-OCH), 3.78 (s, 3H, 3-OCH_3), 6.04 (d, J = 1.5 Hz, 1H, 8-CH); ^{13}C NMR ($CDCl_3$) δ 11.9, 15.1, 31.9, 47.8, 52.0, 53.2, 66.8, 68.6, 87.9, 119.2, 134.4, 145.7, 163.3; HR-MS (FAB) calcd 251.1396 for $C_{13}H_{19}N_2O_3$ (MH^+), found *m*/*z* 251.1387.

X-ray Crystallographic Analysis of 9. The adduct **9** gave colorless prismatic crystals of $C_{13}H_{18}N_2O_3$: monoclinic space group $P2_1/n$, a = 10.184(1) Å, b = 11.459(1) Å, c = 11.709(1) Å, β = 93.629(9)°, V = 1363.8(3) Å^3, Z = 4, ρ = 1.219 g/cm^3, μ(Cu Kα) = 0.717 cm^{-1}. The structure was solved by the direct method and refined by the full-matrix least-squares method, where the final R and Rw were 0.072 and 0.081 for 2747 reflections.

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Supporting Information Available: Two X-ray crystallographic files (CIF) and ORTEP drawings for **7a** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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