Synthesis and Reactions of a Stable *o*-Quinoid 10-π-Electron System, Furo[3,4-*c*]pyridine

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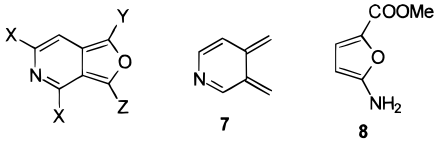
Methyl 4,6-dichloro-3-(diethylamino)furo[3,4-*c*]pyridine-1-carboxylate (**6**), an intermediate in the Hamaguchi−Ibata reaction involving the Rh^{II}-catalyzed intramolecular reaction of a diazo group with the carbonyl of an adjacent amido group, has been isolated and characterized. PM3 calculations reveal the heat of formation (ΔH_f) of this remarkably stable molecule to be −77.7 kcal/mol. Compound **6** undergoes a facile Diels−Alder cycloaddition with a variety of dienophiles to give polysubstituted isoquinoline derivatives via ring opening of initially formed cycloadducts. In each case the cycloaddition proceeds with high regioselectivity, with the electron-withdrawing group located *ortho* to the amino group. The most favorable FMO interaction is between the HOMO of the azaisobenzofuran **6** and the LUMO of the dienophile. The atomic coefficient at the ester carbon of the azaisobenzofuran **6** is larger than the amino center, and this nicely accommodates the observed regioselectivity.

Introduction

The *o*-quinoid 10-π-electron isobenzofuran system has remained the subject of intense theoretical, structural, and reactivity studies, but little work has been done with the analogous furo[*c*]pyridines.[1,2] The parent furo[3,4-*c*]-pyridine **1** was reported as early as 1977 as a white crystalline solid, stable only at low temperature, but undergoing rapid polymerization at about room temperature.[3] More recently, the 1,3-dimethyl derivative **2** was also made and was found stable enough to be characterized by ^{1}H NMR spectroscopy.[4] Although not isolated, substituted isobenzofurans[1] and azaisobenzofuran **3**[5] have been implicated as reactive intermediates in the synthesis of polyaromatic ring systems by tandem Hamaguchi−Ibata and Diels−Alder reactions.[6,7] In a preliminary communication, we described the synthesis of a remarkably stable azaisobenzofuran **6** by a Hamaguchi−Ibata reaction.[8] In this paper we report the full details of this work that shows that azaisobenzofuran **6** is simultaneously a functional analogue of labile pyridine *o*-quinodimethanes, e.g., **7**[9] as well as 2-amino-substituted furans, e.g., **8**[10] both of which have rejuvenated interest in recent years as reactive dienes in Diels−Alder reactions.



7 **8**

1, X=Y=Z=H
2, X=H; Y=Z=Me
3, X=Z=H; Y=NPr^i_2
4, X=Y=H; Z=NEt_2
5, X=H; Y=CO_2Me; Z=NEt_2
6, X=Cl; Y=CO_2Me; Z=NEt_2

Results and Discussion

Synthesis of 6. The synthesis began with readily available nitrile **9**[11] (Scheme 1) which on reduction with diisobutylaluminum hydride (DIBAL-H) gave aldehyde **10** in 66% yield. Oxidation[12] of **10** gave carboxylic acid **11** (78%) which was transformed to the amide **12** (64%) via the acid chloride. Treatment of **12** with excess lithium diisopropylamide (LDA) (2.2 equiv) followed by dimethyl carbonate yielded **13** (53%). It should be noted that use of 1 equiv of LDA did not give any lithiated product (burgundy color) from **12**. The substituted diazoacetic ester **14**, the substrate for Hamaguchi−Ibata reaction, was made from **13** by the Davies protocol via treatment with 4-acetamidobenzenesulfonyl azide (ABSA) in the presence of Et_3N.[13] When **14** was exposed to 1 mol % $Rh_2(OAc)_4$ in CH_2Cl_2 at room temperature for 1 h the azaisobenzofuran **6** was obtained in 50% yield as a bright orange air- and light-stable crystalline solid, which melted without decomposition at 110−112 °C. In addition to its ^{1}H- and ^{13}C NMR data, the structure of **6** is further supported by its high reactivity in a Diels−Alder reaction (Scheme 2). When a dichloromethane solution of 4-phenyl-3*H*-1,2,4-triazoline-3,5-dione (**15**) (1.2 equiv) was added

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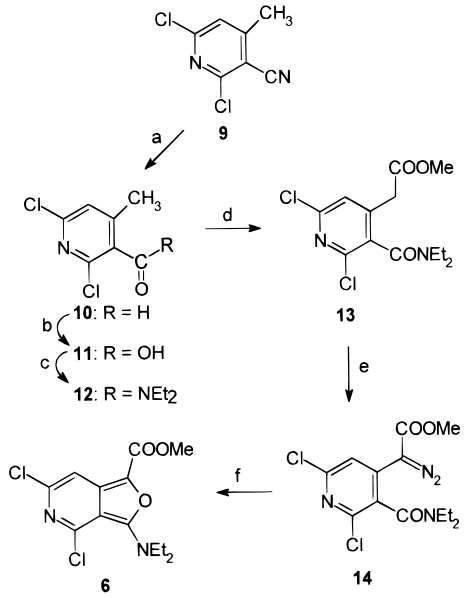
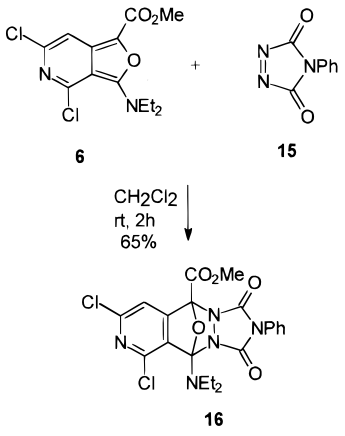
Scheme 1[a]



[a] (a) DIBALH, CH_2Cl_2, −78 °C → rt, 2 h, 66%; (b) $NaClO_2$, ^tBuOH, H_2O, 78%; (c) $(COCl)_2$, PhH, and then Et_2NH, py, 64%; (d) LDA, THF, and then $CO(OMe)_2$, 53%; (e) ABSA, Et_3N, 0 °C → rt, 85%; (f) $Rh_2(OAc)_4$, CH_2Cl_2, rt, 50%.

Scheme 2



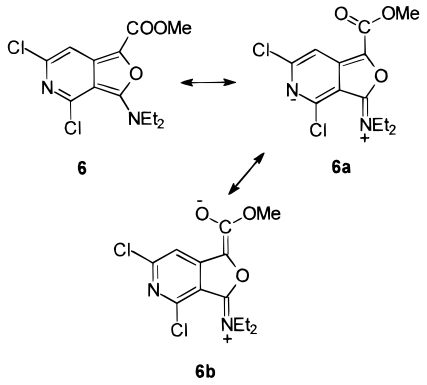
to crystalline **6**, a single adduct **16** (65%) was formed as a white crystalline solid.

The unusual stability of **6** is attributable to resonance involving the pyridine nitrogen and to electron withdrawal by that nitrogen as well as the ester group (Scheme 3). In fact, calculated heats of formation using the PM3 semiempirical molecular orbital method[14] reveal how thermodynamic parameters change in the series: **1** (27.2 kcal/mol) < **4** (12.9 kcal/mol) < **5** (−67.7 kcal/mol) < **6** (−77.7 kcal/mol).

Cycloaddition/Ring Opening Reactions of 6. Azaisobenzofuran **6** reacts with various dienophiles in an intermolecular fashion with high regio- and stereoselectivity (Scheme 4, Table 1). The resultant cycloadducts **17** undergo spontaneous ring opening followed by proton transfer to yield annulated products **18** as in the case of 2-amino-substituted furans, e.g., **8**.[10]

The structural assignment for **19**−**23** are based on interpretations of ^{1}H NMR spectra. For example the 200 MHz ^{1}H NMR spectrum of **19** shows a typical AB pattern for the allylic hydrogens at δ 2.81 Hz (J_{AB} = 14.62 Hz) and δ 2.98 (J_{AB} = 14.62 Hz). The alternative regioisomer is ruled out because the ^{1}H NMR spectrum of that

Scheme 3



Scheme 4

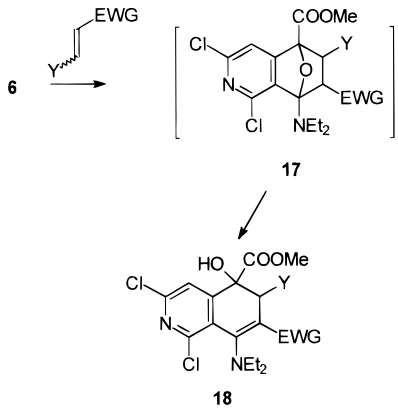
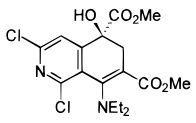
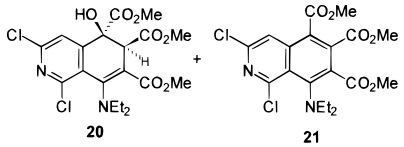
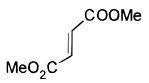
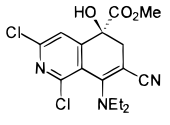
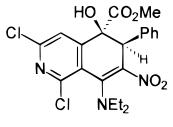


Table 1. Reaction of Methyl 4,6-Dichloro-3-diethylaminofuro[3,4-*c*]-pyridine-1-carboxylate (6) with Dienophiles

Dienophile	Product(s)	Combined Yield, %
	 **19**	92
	 **20** **21**	85[a]
	**20** **21**	80[b]
	 **22**	72
	 **23**	63

[a] **20:21** = ∼1:9 [b] **20:21** = ∼9:1

(14) All calculations were done using the semiempirical method PM3 implanted on Spartan with full geometry optimization. Stewart, J. J. P. *J. Comput.-Aided Mol. Des.* **1990**, *4*, 1.

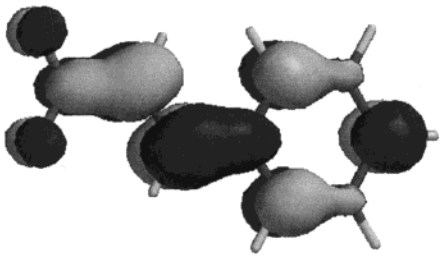


Figure 1. Orbital drawing for the LUMO of β-nitrostyrene.

compound should display a doublet vinylic hydrogen signal. The geometrically isomeric dienophiles dimethyl maleate and fumarate gave **20** and **21**. The major *endo*-adduct in the case of dimethyl maleate was unisolable as it simply eliminated a water molecule on standing to give the fully aromatic compound **21**, which is the minor product from dimethyl fumarate addition. Stereochemical assignment for **20**, where the two ester groups are trans-related, is based on an X-ray crystal structure determination.[15] The stereochemical profile of these reactions, i.e., formation of **20** and **21**, mirrors those observed in the cases of 1-amino-isobenzofurans.[5]

Similarly, the trans relationship of phenyl and carbomethoxy group in **23**, the single product from cycloaddition with *trans*-β-nitrostyrene was established on the basis of X-ray crystal structure determination.[16]

Unfortunately, the reaction of azaisobenzofuran **6** with 2-cyclohexenone or in situ-generated benzyne from 2-bromofluorobenzene[17] did not give any cycloaddition product.

Frontier Orbitals. The observed regioselectivity in the cycloaddition of **6** with methyl acrylate is similar to that of **8**[10] and may be rationalized by FMO theory.[10,18] This is a normal demand $\pi^4_s+\pi^2_s$ process with a HOMO−LUMO gap of 8.51 eV between the HOMO of **6** and LUMO of methyl acrylate. The analogous HOMO−LUMO gaps for **1**, **4**, and **5** are 8.62, 7.95, and 8.22 eV, respectively. In addition, the atomic coefficients of the interacting orbitals, e.g., 0.27 (ester carbon) and 0.10 (amino carbon) of the π^4 system, e.g., **6**, match with 0.43 and 0.25 of the π^2 acrylate system to provide the product as shown in Table 1, and the secondary orbital interaction which leads to assumed *endo* addition is also favorable. For *trans*-β-nitrostyrene, the regioselectivity is determined (mainly by primary orbital interactions) by the relative orbital coefficients on C_α and C_β of its LUMO, the MO coefficient plot of which is shown in Figure 1. The sum of squares of C_α is 0.27, and that of C_β is 0.20. Threfore, the larger end (C_α) of its LUMO will match with the larger end (ester carbon) of HOMO of **6**. It is, therefore, consistent with the observed result. As for dimethyl fumarate, the factor that decides which ester group should be oriented toward the *endo* side of **6** is the relative magnitude of C_{3a} and C_{7a} coefficients on HOMO of **6**. The sum of squares of C_{3a} coefficients is 0.039, and that of C_{7a} is 0.018 (Figure 2). This indicates that the secondary orbital effect between C_{3a} of **6** and the C(O) of dimethyl fumarate will be stronger than C_{7a} of **6** and the C(O) of dimethyl fumarate. In the transition state, one

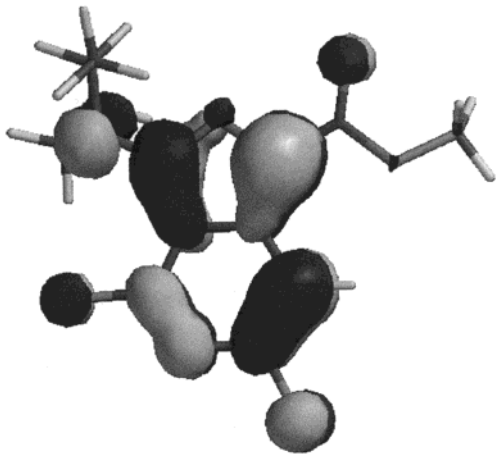


Figure 2. Orbital drawing for the HOMO of **6**.

of the ester groups of dimethyl fumarate is located on the *endo* side of **6**, and it will be oriented closer to the diethylamino group of **6**. A similar reasoning should also hold for the stereochemical results observed in the cases of 1-amino-isobenzofurans.[5] The *endo*-selectivity for dimethyl maleate has been well-analyzed as a result of secondary orbital interactions, i.e., between C_{3a} and C_{7a} of **6** and the C(O) of dimethyl maleate.

Conclusion

In conclusion, the product azaisobenzofuran **6** isolated from a Hamaguchi−Ibata reaction has been found to be stable and easily characterized. The Diels−Alder reactions of **6** proceed with various dienophiles to furnish [4 + 2]-cycloadducts that undergo spontaneous transformation into polysubstituted isoquinoline derivatives. In this respect, **6** mimics the functions of both aza *o*-quinodimethane **7** and 2-amino-substituted furan **8**, both of which have spurred vigorous research activities recently. Further application of this chemistry to intramolecular cycloadditions including the synthesis of conformationally restricted analogues of nicotine and anabasine[19] are in progress and will be reported in due course.

Experimental Section

Melting points were uncorrected. Unless otherwise noted, all reactions were carried out under argon atmosphere in flame-dried flasks. Solvents were dried by distillation from drying agents as follows: THF and benzene (sodium benzophenone ketyl), dichloromethane (P_2O_5), DMSO, Et_3N, acetonitrile, and pyridine (CaH_2). Solutions were evaporated under reduced pressure with a rotary evaporator, and the residue was flash chromatographed on silica gel (Acme's, particle size 230−400 mesh) using an ethyl acetate−petroleum ether (60−80 °C) mixture as eluent unless specified otherwise.

2,6-Dichloro-4-methyl-3-pyridinecarboxaldehyde (10). To a stirred solution of 3-cyano-2,6-dichloro-4-methylpyridine (**9**)[11] (6 g, 32.09 mmol) in 100 mL of CH_2Cl_2 cooled to −78 °C was added 32 mL of DIBAL-H (1.0 M solution in toluene) dropwise. Then the resulting solution was allowed to attain room temperature. It was stirred for another 2 h at room temperature and quenched by saturated aqueous NH_4Cl at 0 °C. This reaction mixture was stirred for another 1 h at 0 °C and then acidified with 1 N HCl. The organic layer was

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separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 3.96 g (66%) of aldehyde **10** as a snow white crystalline solid: mp 58−59 °C; IR (KBr) 1697, 1567 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.62 (s, 3H), 7.20 (s, 1H), 10.54 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.7, 126.0, 126.4, 153.3, 154.2, 154.9, 190.0. Anal. Calcd for $C_7H_5NOCl_2$: C, 44.21; H, 2.63; N, 7.37. Found: C, 44.23; H, 2.46; N, 7.48.

2,6-Dichloro-4-methyl-3-pyridinecarboxylic Acid (11). To a 10 °C solution of 2,6-dichloro-4-methyl-3-pyridinecarboxaldehyde (**10**) (3 g, 15.7 mmol) in 16 mL *tert*-butyl alcohol were added $NaClO_2$ (80%, technical, 4.6 g, 40.66 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (6.6 g, 47.14 mmol) in 11.9 mL of water over 25 min. The temperature was allowed to warm to 25 °C over 1 h. The reaction mixture was stirred at room temperature for 3 h, and then it was concentrated in vacuo to approximately half its volume. The concentrate was diluted to 20 mL with water and washed with pentane (2 × 10 mL). The water layer was acidified to pH 2.0 with 1 M HCl, saturated with NaCl, and extracted with ether (10 × 3 mL). The ether extracts were washed with brine, dried over Na_2SO_4, and concentrated. Heating to 40 °C at 0.03 mmHg (to remove the excess *tert*-butyl alcohol) afforded 2.54 g (78%) of acid **11** as an oil which solidified on standing as a white solid: mp 138−139 °C; IR (KBr) 1721, 1563 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.21 (s, 1H) and 7.50−7.70 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.7, 124.5, 127.7, 147.1, 150.8, 151.3, 169.5. Anal. Calcd for $C_7H_5NO_2Cl_2$: C, 40.78; H, 2.43; N, 6.79. Found: C, 40.75; H, 2.21; N, 6.52.

***N,N*-Diethyl-2,6-dichloro-4-methyl-3-pyridinamide (12).** To a stirred suspension containing 2,6-dichloro-4-methyl-3-pyridinecarboxylic acid (**11**) (2.5 g, 12.13 mmol) in benzene (25 mL) was added 1.5 mL (17.34 mmol) of oxalyl chloride. Then the solution was refluxed for 3 h and concentrated under reduced pressure. The crude acid chloride was dissolved in 20 mL of dry CH_2Cl_2, and to this solution was added dropwise 1.5 mL (14.54 mmol) of diethylamine followed by 1 mL (12.3 mmol) of pyridine at 0 °C under argon. After being stirred at room temperature for 2 h, the mixture was washed successively with water and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residual oil was purified by flash silica gel chromatography to give 2.02 g (64%) of amide **12** as a colorless oil: IR (neat) 1638 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.09 (t, 3H, J = 7.22 Hz), 1.25 (t, 3H, J = 7.09 Hz), 2.28 (s, 3H), 3.12 (q, 2H, J = 7.16 Hz), 3.43−3.69 (m, 2H) and 7.12 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.3, 13.9, 18.9, 38.9, 42.6, 124.3, 124.4, 131.4, 146.2, 149.7, 164.4.

Methyl 2,6-Dichloro-3-(*N,N*-diethylamido)pyridine-4-acetate (13). To a solution of LDA (16.7 mmol) (prepared from 11.9 mL of 1.4 M *n*-BuLi in hexane and 2.4 mL, 16.7 mmol of diisopropylamine) in THF (50 mL) at −78 °C under argon atmosphere was added by syringe injection a solution of *N,N*-diethyl-2,6-dichloro-4-methyl-3-pyridinamide (**12**) (2 g, 7.6 mmol) in THF (5 mL). After being stirred for 1 h, the burgundy red solution was treated with dimethyl carbonate (0.7 mL, 8.3 mmol) and HMPA (1.4 mL, 8.3 mmol). The cooling bath was removed after 2 h, and stirring was continued for 1 h at room temperature. Then the reaction mixture was quenched by saturated aqueous NH_4Cl and extracted with Et_2O. The combined ether extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give 1.27 g (53%) of acetate **13** as a colorless oil: IR (neat) 1743, 1636 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.12 (t, 3H, J = 7.17 Hz), 1.22 (t, 3H, J = 7.18 Hz), 3.07−3.20 (m, 2H), 3.45−3.64 (m, 4H), 3.69 (s, 3H) and 7.27 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.9, 13.3, 37.1, 38.5, 42.5, 52.2, 124.6, 131.3, 145.5, 146.1, 149.6, 163.6, 168.5.

Diazo Compound 14. To a stirred solution of methyl 2,6-dichloro-3-(*N,N*-diethylamido)pyridine-4-acetate (**13**) (1.2 g, 3.7 mmol) and *p*-acetamidobenzenesulfonyl azide (1.06 g, 4.4 mmol) in acetonitrile at 0 °C was added triethylamine (1.5 mL, 11.1 mmol). The reaction mixture was allowed to warm to room temperature and stirred for another 12 h. The solvent was evaporated under reduced pressure. The residue was triturated with ether/petroleum ether (1:1) and filtered, and the solvent was evaporated under reduced pressure. This gave the crude diazo product, which was further purified by chromatography over a short silica gel column with ether/petroleum ether (1:4) as eluent to give 1.1 g (85%) of diazo compound **14** as a light yellow crystalline solid: mp 112−114 °C; IR (KBr) 2113, 1714, 1634 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.09 (t, 3H, J = 7.18 Hz), 1.25 (t, 3H, J = 7.17 Hz), 3.11−3.29 (m, 3H), 3.66−3.80 (m, 1H), 3.84 (s, 3H), 7.93 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.0, 13.5, 39.1, 42.8, 52.5, 62.1, 119.6, 124.9, 136.8, 147.2, 150.1, 163.0, 163.2. Anal. Calcd for $C_{13}H_{14}N_4O_3Cl_2$: C, 45.23; H, 4.08; N, 16.23. Found: C, 45.31; H, 3.89; N, 16.27.

Methyl 4,6-Dichloro-3-(diethylamino)furo[3,4-*c*]pyridine-1-carboxylate (6). A mixture of diazo compound **14** (1 g, 2.9 mmol) and 1 mol % $Rh_2(OAc)_4$ in CH_2Cl_2 (3 mL) was stirred for 1 h at room temperature. Solvent was removed under reduced pressure, and the residue was purified by passing through a short silica column to give 450 mg (50%) of azaisobenzofuran **6** as a bright orange crystalline solid: mp 110−112 °C; IR (KBr) 1679, 1609, 1568 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, 6H, J = 7.0 Hz), 3.76 (q, 4H, J = 7.0 Hz), 3.90 (s, 3H), 7.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 46.3, 50.9, 102.1, 108.8, 122.6, 135.0, 144.6, 145.9, 157.1, 158.4; MS (EI) *m/e* (relative intensity) 318/316 (75/92, M^+), 289/287 (75/92, $M-C_2H_5$), 261/259 (15/22), 233/231 (23/47), 201/199 (88/100). Anal. Calcd for $C_{13}H_{14}N_2O_3Cl_2$: C, 49.23; H, 4.45; N, 8.83. Found: C, 49.38; H, 4.62; N, 8.66.

General Procedure for the Diels−Alder Cycloaddition Sequences. A dichloromethane (5 mL) solution of the methyl 4,6-dichloro-3-(diethylamino)furo[3,4-*c*]pyridine-1-carboxylate (**6**), and a 2-fold excess of dienophile was stirred at room temperature for 2−3 h. The mixture was then concentrated under reduced pressure to give the crude adducts, which was separated by column chromatography on silica gel (particle size 100−200 mesh) with various ratios of EtOAc/petroleum ether as eluant. Repeated recrystallization from EtOAc/petroleum ether was done to provide analytically pure products.

Dimethyl (5*SR*)-1,3-Dichloro-8-(*N,N*-diethylamino)-5,6-dihydro-5-hydroxy-5,7-isoquinolinedicarboxylate (19). The reaction was carried out with 200 mg (0.63 mmol) of **6** and 108 mg (1.26 mmol) of methyl acrylate. Column chromatography afforded 234 mg of **19** in 92% yield as a yellow crystalline solid: mp 150 °C; IR (KBr) 3408, 1742, 1674, 1571 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, 6H, J = 7.1 Hz), 2.81 (1H, J_{AB} = 14.62 Hz), 2.98 (1H, J_{AB} = 14.62 Hz), 2.93−3.05 (m, 3H), 3.15−3.26 (m, 2H), 3.52 (s, 1H), 3.66 (s, 3H), 3.72 (s, 3H), 7.47 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3, 37.9, 45.7, 51.5, 53.5, 74.2, 104.6, 119.0, 126.1, 147.3, 148.1, 150.1, 156.1, 167.4, 172.5; MS (EI) *m/e* (relative intensity) 404/402 (20/30, M^+), 389/387 (8/14, $M-CH_3$), 375/373 (9/27, $M-C_2H_5$), 369/367 (42/100, M − Cl), 345/343 (42/82, $M-CO_2Me$). Anal. Calcd for $C_{17}H_{20}N_2O_5Cl_2$: C, 50.63; H, 5.00; N, 6.95. Found: C, 50.62; H, 4.98; N, 6.97.

Trimethyl (5*SR*,6*SR*)-1,3-Dichloro-8-(*N,N*-diethylamino)-5,6-dihydro-5-hydroxy-5,6,7-isoquinolinetricarboxylate (20) and Trimethyl 1,3-Dichloro-8-(*N,N*-diethylamino)-5,6,7-isoquinolinetricarboxylate (21). The reaction was carried out with 200 mg (0.63 mmol) of **6** and 180 mg (1.25 mmol) of dimethyl maleate. Column chromatography afforded 25 mg of **20** (8.5%) and 214 mg of **21** (76.5%) as yellow crystalline solids: **20**: mp 150 °C; IR (KBr) 3361, 1742, 1674, 1569 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, 6H, J = 7.07 Hz), 3.04−3.29 (m, 4H), 3.56 (s, 3H), 3.66 (s, 3H), 3.74 (s, 3H), 4.22 (s, 1H), 7.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5, 46.6, 49.3, 51.6, 52.9, 53.4, 103.5, 120.1, 124.8, 147.8, 148.2, 150.9, 156.5, 166.0, 168.9, 172.9. Anal. Calcd for $C_{19}H_{22}N_2O_7Cl_2$: C, 49.47; H, 4.81; N, 6.07. Found: C, 49.50; H, 4.80; N, 6.10. **21**: mp 158 °C; IR (KBr) 1731, 1579, 1524 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, 6H, J = 4.7 Hz), 3.19−3.35 (m,

2H), 3.39−3.50 (m, 2H), 3.88 (s, 6H), 3.93 (s, 3H), 7.97 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8, 48.5, 53.0, 53.1, 53.2, 117.5, 121.6, 124.0, 128.1, 135.9, 140.2, 145.4, 149.3, 149.6, 165.9, 166.6, 167.2. Anal. Calcd for $C_{19}H_{22}N_2O_7Cl_2$: C, 51.48; H, 4.55; N, 6.32. Found: C, 51.50; H, 4.52; N, 6.30.

Diels−Alder Reaction of 6 with Dimethyl Fumarate. The reaction was carried out with 254 mg (0.80 mmol) of **6** and 230 mg (1.60 mmol) of dimethyl fumarate. Column chromatography afforded 266 mg of **20** (72%) and 28 mg of **21** (8%) as yellow crystalline solids.

Methyl (5*SR*)-7-Cyano-1,3-dichloro-8-(*N*,*N*-diethylamino)-5,6-dihydro-5-hydroxy-5-isoquinolinecarboxylate (22). The reaction was carried out with 300 mg (0.95 mmol) of **6** and 100 mg (1.9 mmol) of acrylonitrile. Column chromatography afforded 250 mg of **22** in (72%) yield as a yellow crystalline solid: mp 184 °C; IR (KBr) 3326, 2191, 1738, 1568 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.05−1.35 (bs, 6H), 2.69−2.87 (m, 2H), 3.25−3.50 (m, 4H), 3.83 (s, 3H), 7.50 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.5, 37.7, 45.8, 53.9, 73.6, 81.3, 119.4, 120.1, 124.6, 147.7, 151.0, 153.1, 155.2, 171.6. Anal. Calcd for $C_{16}H_{17}N_3O_3Cl_2$: C, 51.89; H, 4.59; N, 11.35. Found: C, 51.80; H, 4.61; N, 11.24.

Methyl (5*SR*,6*SR*)-1,3-Dichloro-8-(*N*,*N*-diethylamino)-5,6-dihydro-5-hydroxy-6-phenyl-7-nitro-5-isoquinolinecarboxylate (23). The reaction was carried out with 200 mg (0.63 mmol) of **6** and 188 mg (1.26 mmol) of *trans*-β-nitrostyrene. Column chromatography afforded 185 mg of **23** in (63%) yield as a yellow crystalline solid: mp 137 °C; IR (KBr) 3439, 2106, 1732, 1676, 1632 cm^{-1}; ^{1}H NMR δ 1.15 (t, 6H, J = 7.02 Hz), 3.10−3.30 (bs, 2H), 3.40−3.54 (m, 2H), 3.78 (s, 3H), 4.70 (s, 1H), 6.97−7.02 (m, 2H), 7.21−7.24 (m, 3H), 7.35 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 12.3, 46.6, 50.6, 52.5, 119.7, 123.7, 126.8, 127.3, 128.3, 128.5, 132.9, 143.0, 147.2, 150.5, 155.6, 170.8. Anal. Calcd for $C_{21}H_{21}N_3O_5Cl_2$: C, 54.09; H, 4.54; N, 9.01. Found: C, 54.10; H, 4.53; N, 9.04.

Compound 16. The reaction was carried out with 250 mg (0.79 mmol) of **6** and 175 mg (1.0 mmol) of 4-phenyl-3*H*-1,2,4-triazoline-3,5-dione. Column chromatography afforded 232 mg of **16** in (65%) yield as a white crystalline solid: mp 204−205 °C; IR (KBr) 1810, 1750, 1561 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.17 (t, 6H, J = 7.15 Hz), 2.77−3.03 (m, 4H), 3.82 (s, 3H), 7.44−7.56 (m, 5H), 7.96 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.1, 46.4, 54.5, 90.1, 118.5, 122.3, 126.3, 129.2, 129.3, 129.9, 145.6, 151.6, 152.2, 152.4, 154.5, 155.0, 164.9. Anal. Calcd for $C_{21}H_{19}N_5O_5Cl_2$: C, 51.23; H, 3.89; N, 14.22. Found: C, 51.30; H, 3.84; N, 13.90.

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